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From Synthetic Methodology to Biomimetic Target Assembly

Tetrahedron Prize for Creativity in Organic Chemistry 2003 D. Seebach

Guest editor: Léon A. Ghosez

Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac Cedex, France

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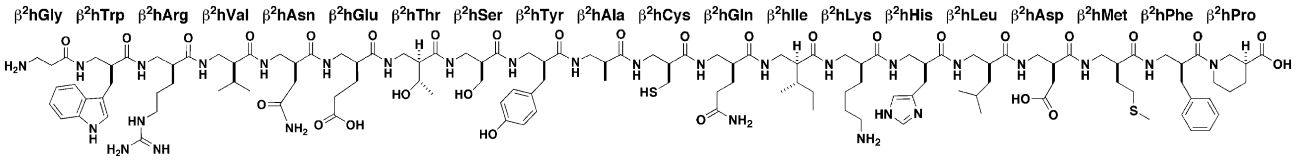
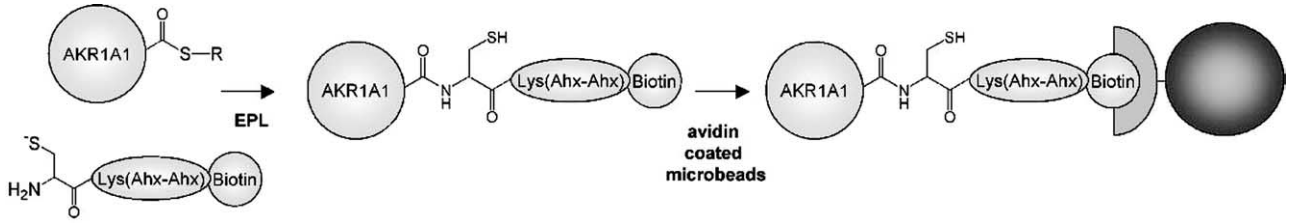
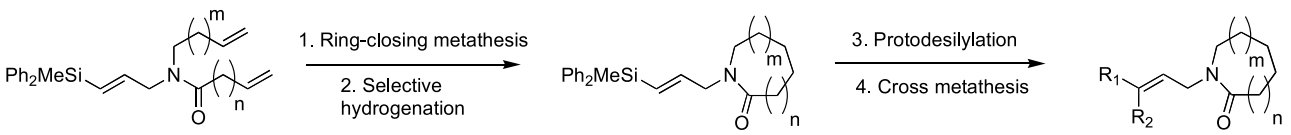
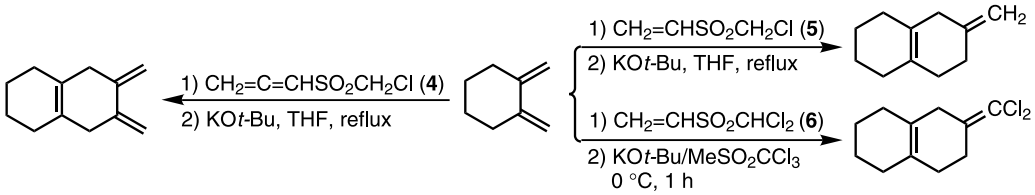
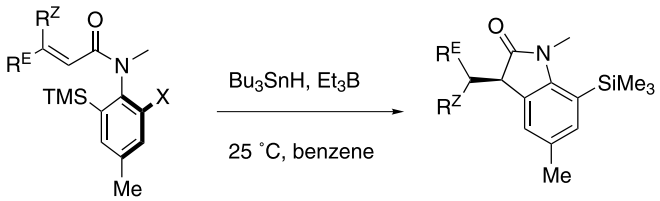


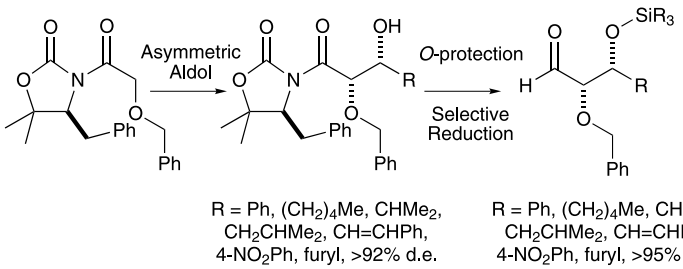


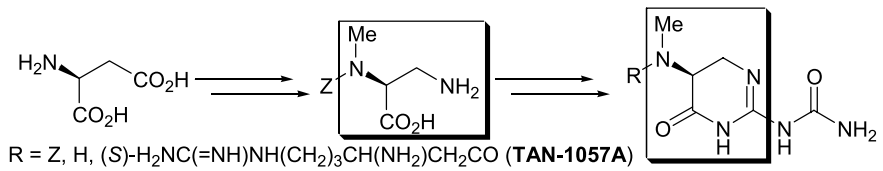


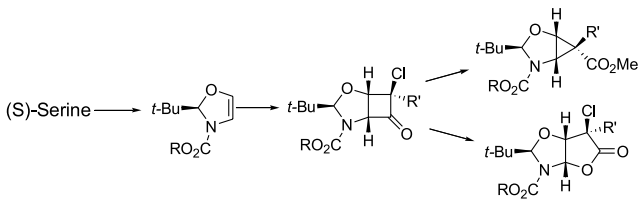


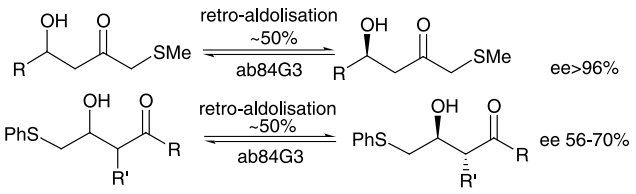
[(Chloromethyl)sulfonyl]-1,3-propadiene (**4**), [(chloromethyl)sulfonyl]ethene (**5**), and [(dichloromethyl)sulfonyl]ethene (**6**) serve as 'prepackaged' Ramberg–Bäcklund reagents, which following an appropriate first step, such as Diels–Alder addition, react with base giving Ramberg–Bäcklund products. Compounds **4**-**6** function as 1,2,3-butatriene, allene and 1,1-dichloroallene synthons, respectively.

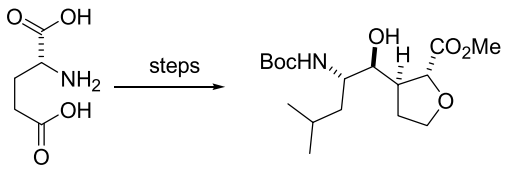


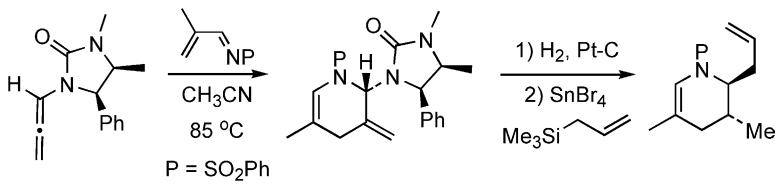




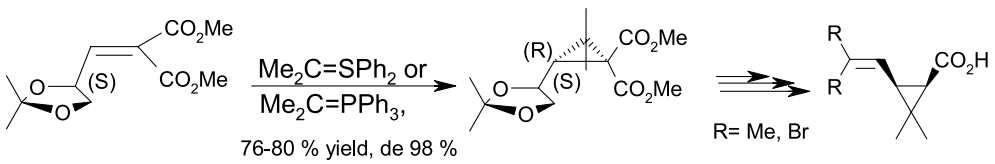


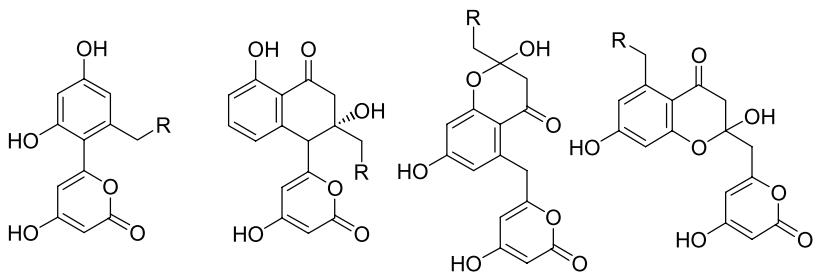


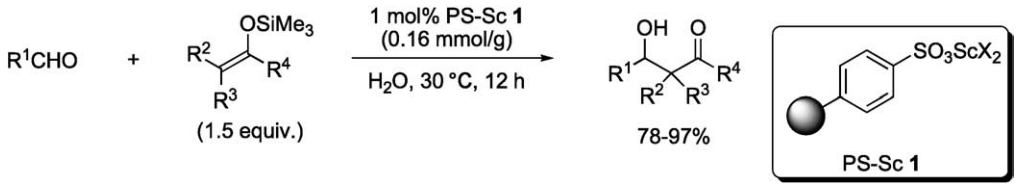




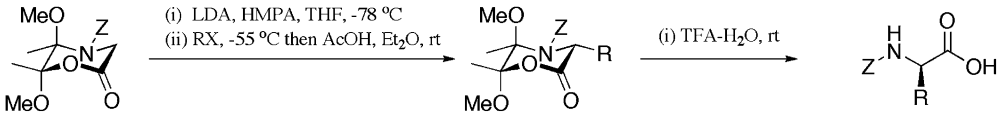
An inverse electron-demand aza-[4+2] cycloaddition reaction of allenamides with 1-azadiene is described here. This cycloaddition provides a unique chiral template for the synthesis of aza-glycoside related heterocycles.



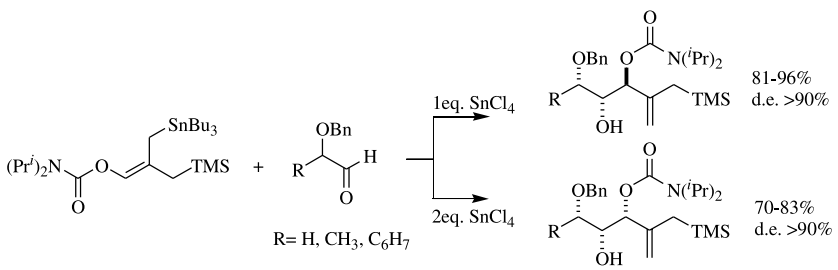


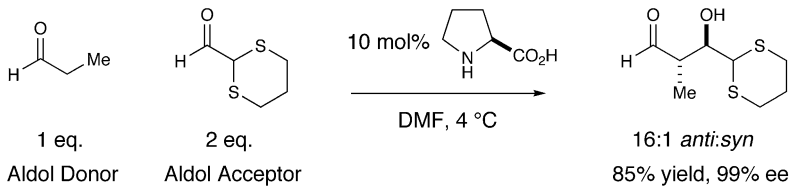


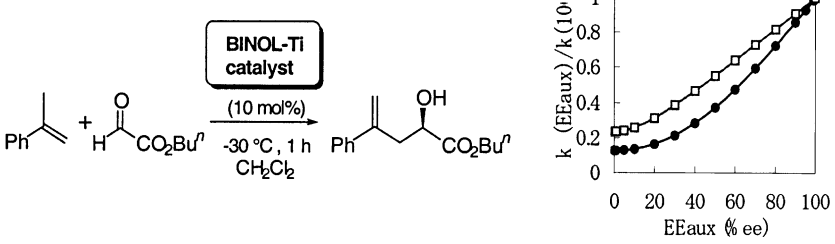
A hydrophobic polymer-supported scandium(III) catalyst (PS-Sc-**1**) prepared from sulfonated polystyrene resin is an effective catalyst for carbon–carbon bond-forming reactions such as Mukaiyama aldol reactions in water. According to studies on loading levels of scandium, hydrophobicity of the catalyst is a key for the efficient catalysis.

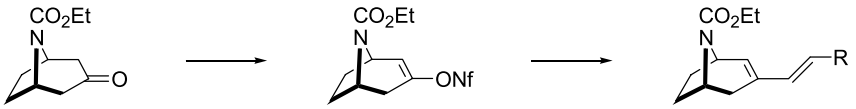


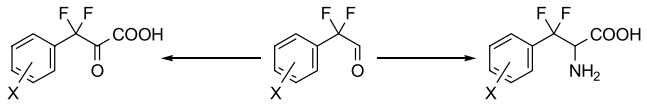
syn–anti and *syn–syn* Configured triol units are efficiently synthesized by the $SnCl_4$ mediated allylation of chiral α-benzyloxy-aldehydes. Remarkably, the stereochemistry of the adducts is solely governed by the amount of Lewis acid employed.

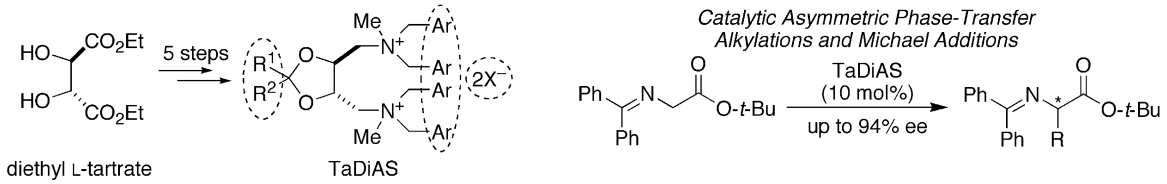


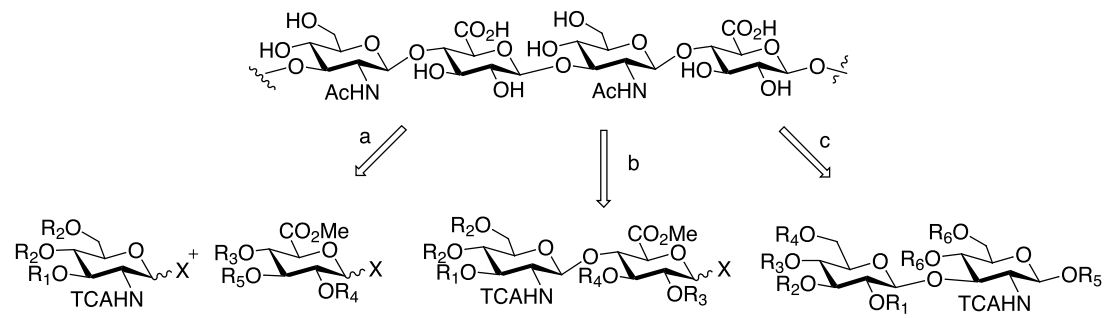


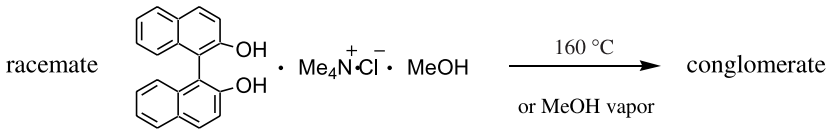


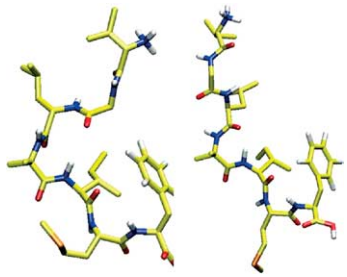




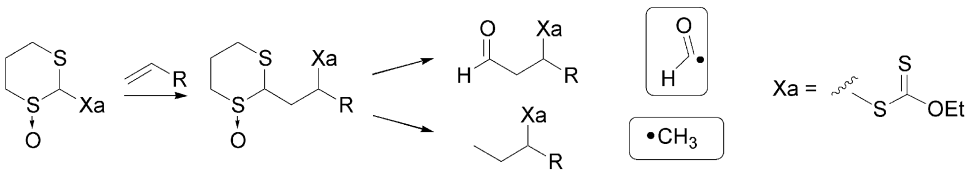








The most populated clusters of an MD simulation of an alpha-polypeptide do not show a helical secondary structure.



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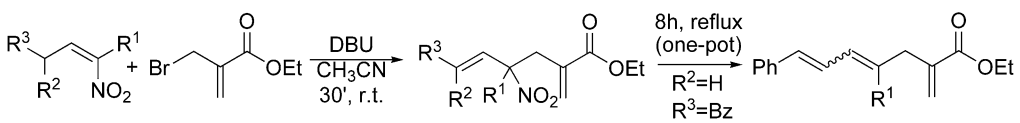

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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

On the cover of this Symposium-in-Print the way is sketched on which the Seebach group wandered into peptide chemistry (clockwise from *top left*). It started with backbone modifications of the cyclo-undecapeptide cyclosporin and the *in-silico* 3_1-helix of the polyester PHB which suggested that O/NH replacement in the backbone should lead to multiple hydrogen bonding and thus to an experimentally observable β-peptidic helix. This was indeed the case and led to the discovery that β-peptides fold to secondary structures with as few as four amino-acid residues in solution. One type of such secondary structures were protease-stable β-peptidic turn mimics of the α-peptidic hormon somatostatin (containing 14 amino acids). Larger β-peptides form tertiary structures by design of amphipatic helices. *Tetrahedron*, **2004**, *60*, 7439–7794.

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Preface

Tetrahedron Prize for Creativity in Organic Chemistry

The Executive Board of Editors for *Tetrahedron* Publications and Elsevier Ltd. is pleased to dedicate this special Symposium-in-Print to Professor Dieter Seebach of the Eidgenössischer Technischer Hochschule, Zürich, a co-recipient of the Tetrahedron Prize for 2003 with Professor Robert H. Grubbs. Professor Seebach is a leader in contemporary organic chemistry. He has made an exceptional number of seminal contributions to the development of synthetic methodology and to structure-based understanding of chemical reactivity. His career unfolded further with major advances in enzymatically mediated synthesis leading to a variety of polyketide-like natural products. His more recent studies on β-peptides have opened a whole new world for organic, physico-chemical and pharmaceutical research. In celebration of Professor Seebach's accomplishments, this special issue of *Tetrahedron* is entitled "From Synthetic Methodology to Biomimetic Target Assembly". This title is meant to reflect the wide domain of research covered by Professor D. Seebach's creative contributions.

In the first part of this Symposium-in-Print, Professor Dieter Seebach describes the history of peptide chemistry in his group which leads the reader through the avenues of his creative and intuitive thinking. Following this fascinating account is a series of original papers from colleagues and friends who were associated with him over the course of their career. The series of articles in this special Symposium-in-Print will walk the reader through several areas which are representative of what is organic chemistry in this 21st century.

Léon A. Ghosez
Institut Européen de Chimie et Biologie,
2 rue Robert Escarpit,
F-33607 Pessac Cedex, France
E-mail address: l.ghosez@iecb.u-bordeaux.fr

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Biographical sketch: Professor Dieter Seebach

Dieter Seebach was born in 1937 in Karlsruhe, Germany. He studied chemistry at the Technische Hochschule in Karlsruhe where he graduated in 1961. From 1961 to 1964, he completed a dissertation on small ring compounds and peroxides under the supervision of Professor R. Criegee and obtained a PhD degree. He then crossed the Atlantic to the United States and completed a postdoctoral appointment at Harvard University in the laboratory of Professor E. J. Corey. During this period he held a lectureship in the chemistry department of Harvard. He then returned to Karlsruhe to prepare a 'habilitation' which he earned in 1969 with a thesis on sulphur- and selenium-stabilized carbanions and carbenes. He then became Privatdozent at the University of Karlsruhe. In 1971, he was appointed Professor of Organic chemistry at the Justus Liebig University in Giessen, Germany. In 1977, he joined the faculty of the Eidgenössissche Technische Hochschule in Zürich where he is still now as Emeritus Professor. Dieter Seebach has held visiting professorships at the University of Wisconsin, the California Institute of Technology, the Max-Planck-Institut in Mülheim, the Université Louis Pasteur in Strasbourg, the Technische Universität München, the Universität of Kaiserslautern, the Universität Frankfurt, Cornell University, Harvard University as well as in Johannesburg, Canberra and as a fellow of JSPS in Japan.

For his scientific work, Professor Dieter Seebach has received many honours and awards, including the Havinga Medal (The Netherlands, 1985), the Karl Ziegler-Prize of the Gesellschaft des Deutscher Chemiker (1987), the Centenary Medal of the Royal Society of Chemistry (UK, 1991), the Award for Creative Work in Organic Synthesis (ACS, 1992), the King Faizal International Prize in Science (Saudi Arabia, 1999), the Roger Adams Award in Organic Chemistry (1999), the Yamada (Tokyo) and Marcel Benoist (Switzerland) Prizes in 2000, the Chirality Gold Medal and the Nagoya Gold Medal in 2002, the August-Wilhelm-von-Hofmann-Denkmünze (Germany, 2003) and the Vincent du Vigneaud Award 2004 of the American Peptide Society.

Dieter Seebach is a Fellow of the Royal Society of Chemistry (UK) and a member of the Deutsche Akademie der Naturforscher, Leopoldina (Halle), a corresponding member of the Akademie der Wissenschaften und Literatur in Mainz and of the Academia Mexicana de Ciencias (AMC) in México, a Founding Member of the Academia Europea and a 'Einzelmitglied' der Schweizerischen Akademie der Technischen Wissenschaften (1998). In 2004, he became a Honorary Member of the Swiss Chemical Society.

Professor D. Seebach is the author or co-author of over 760 research papers. He has supervised 150 PhD students. His original work has been presented in over 850 lectures in national and international meetings, in distinguished lectureships and in numerous seminars in universities or industries.

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How we drifted into peptide chemistry and where we have arrived at

Dieter Seebach,* Thierry Kimmerlin, Radovan Šebesta, Marino A. Campo and Albert K. Beck

Department für Chemie und Angewandte Biowissenschaften der Eidgenössischen Technischen Hochschule, ETH Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

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Abstract—The history of peptide chemistry in our group is described. It all started with the cyclic undecapeptide cyclosporin, the immunosuppressive compound, which is commercialised as Sandimmune®/Neoral® by Sandoz/Novartis, and which has revolutionized transplant medicine. The discovery that cyclosporin can be deprotonated to a hexalithio derivative, and thus *C*-alkylated on a sarcosine moiety, led us into a research project on *peptide modifications*. We defined structural prerequisites for the use of peptide enolates and for electrolytic decarboxylation of peptides. Parallel to these activities, the group was engaged in developing synthetic methodologies aimed at stereoselective preparations of α-, β-, and γ-amino acid derivatives (cf. diastereoselective alkylations, self regeneration of stereogenic centers, axially chiral enolates). A third avenue into peptide chemistry originated from our investigations on the biopolymer PHB (poly-3-hydroxybutanoic acid); the question arose 'what happens upon replacement of chain-bound O by NH in the polyester?' A brief summary is given of the results obtained in our ensuing discovery tour of β-peptides built of homologated proteinogenic amino acids. They form secondary structures with short chain lengths and they have unexpected physiological properties, rendering them candidates for peptidic drugs. The synthesis of β^3-peptides is straightforward, and in the meantime most of the Fmoc-protected building blocks are commercial. The β^2-homoamino acids are less readily available. Their preparation and the assembly of a β^2-eicosapeptide with the twenty proteinogenic side chains are discussed herein. The reasons for the chosen sequence and the strategy of what turned out to be a 159-step synthesis are described. Full experimental details are given for the preparation of the dimeric Fmoc-β^2hXaa(PG)-β^2hXaa(PG)-OH building blocks used, for their solid-phase coupling to two β^2-decapeptide segments, for the thioligation, and for the purification, isolation and spectroscopic characterization of the resulting 20mer. An outlook to future projects in the exciting field of β- and γ-peptide chemistry and biology is given.

1. Introduction

At the beginning of the senior author's (D. S.) journey through organic chemistry[1] he would never have expected to become a peptide chemist towards the end of his career. The lectures of his mentor in Karlsruhe, Rudolf Criegee, did not cover this subject at all. If asked, he would probably have answered, like most organic chemists at the time, that peptide chemistry is a highly specialized field, and that it is chemically boring to do nothing but create amide bounds. Thus, D. S. became a physical organic chemist studying the mechanism of peroxide decomposition and of cyclobutene ring-opening reactions. In the postdoctoral work with E. J. Corey in Cambridge and in the first steps into independent research back in Karlsruhe and later in Giessen with a growing group he was engaged in sulfur-, lithium-, nitroso-, and nitro-organic chemistry as a synthetic methodologist (umpolung of reactivity, pool of chiral building blocks). Later, in Zürich, the group moved into the areas of stereoselective transformations, self-regeneration of stereocenters, total synthesis of natural products (such as elaiophylidin and myxovirescin), structure and mechanisms of organolithium compounds, use of organotitanium reagents, TADDOL as a chiral auxiliary system of broad applicability, all the way to novel crosslinkers for polymerization and catalysts immobilized on controlled-pore glass.

The first encounter with peptide chemistry[2,3] occurred in one of the senior author's regular consulting visits at Sandoz in Basel. The issue was to find a more sensitive method of detection of their immunosuppressive drug cyclosporin A in plasma. With the experience of our group in organosulfur and -selenium chemistry[4] we treated cyclosporin with naphtylselenylchloride to induce a selenocyclization of the side chain in the unique C_9-amino acid of the peptide; the product has a much higher extinction coefficient than

Keywords: Cyclosporin; Chiral enolates; Peptide chemistry; β-Peptides.
* Corresponding author. Tel.: +41-1-632-2990; fax: +41-1-632-1144; e-mail address: seebach@org.chem.ethz.ch

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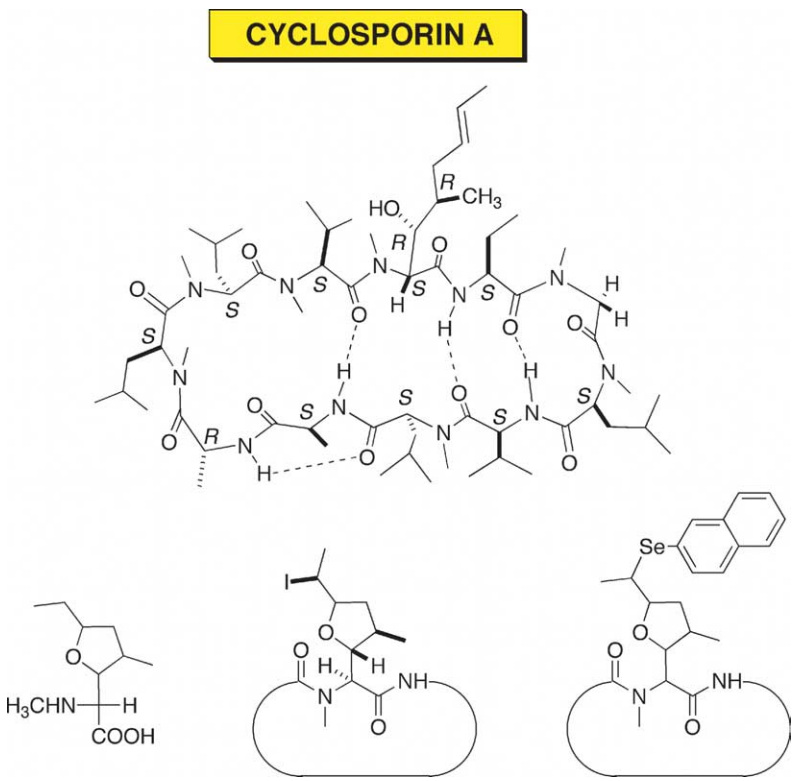

Figure 1. Formula of cyclosporin A and the THF derivatives formed with strong acid, iodine or $C_{10}H_7SeCl$.

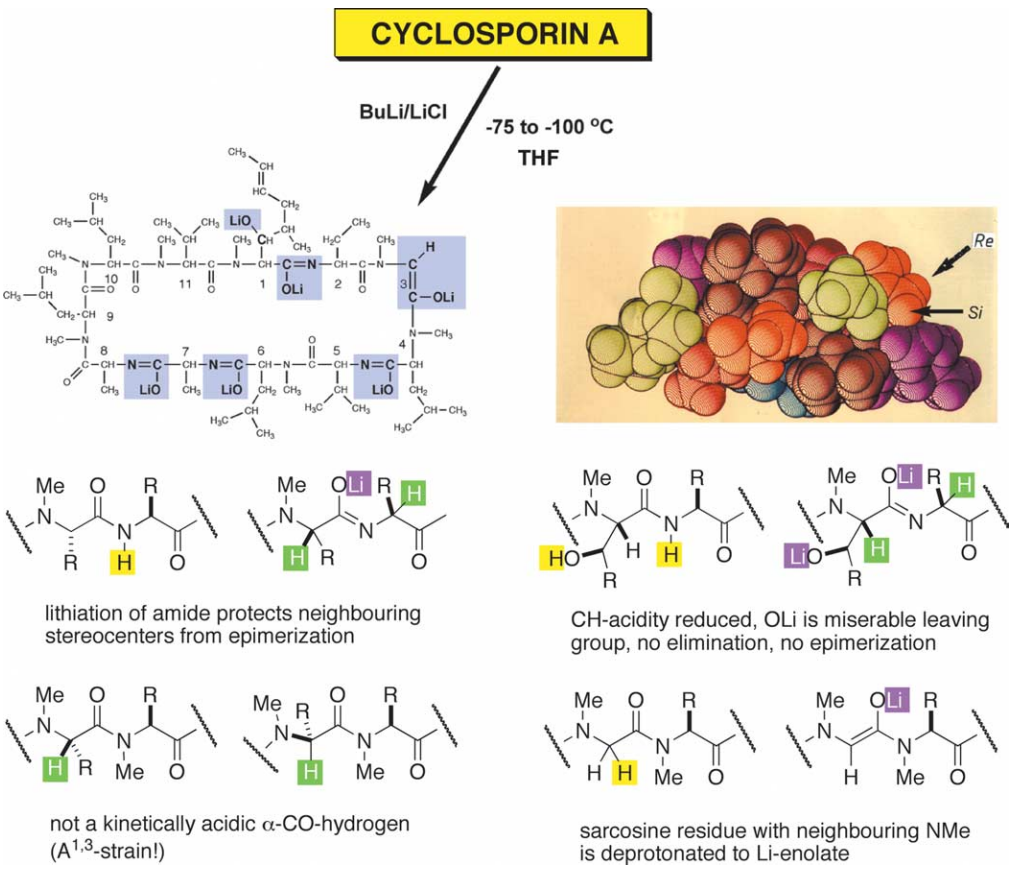

Figure 2. Hexalithiated cyclosporin A with a sarcosine enolate moiety that reacts selectively with electrophiles. Different types of amino-acid building blocks in cyclosporine and rationalization for lack of epimerization and elimination. The sarcosine CH_2-protons are the least acidic ones!

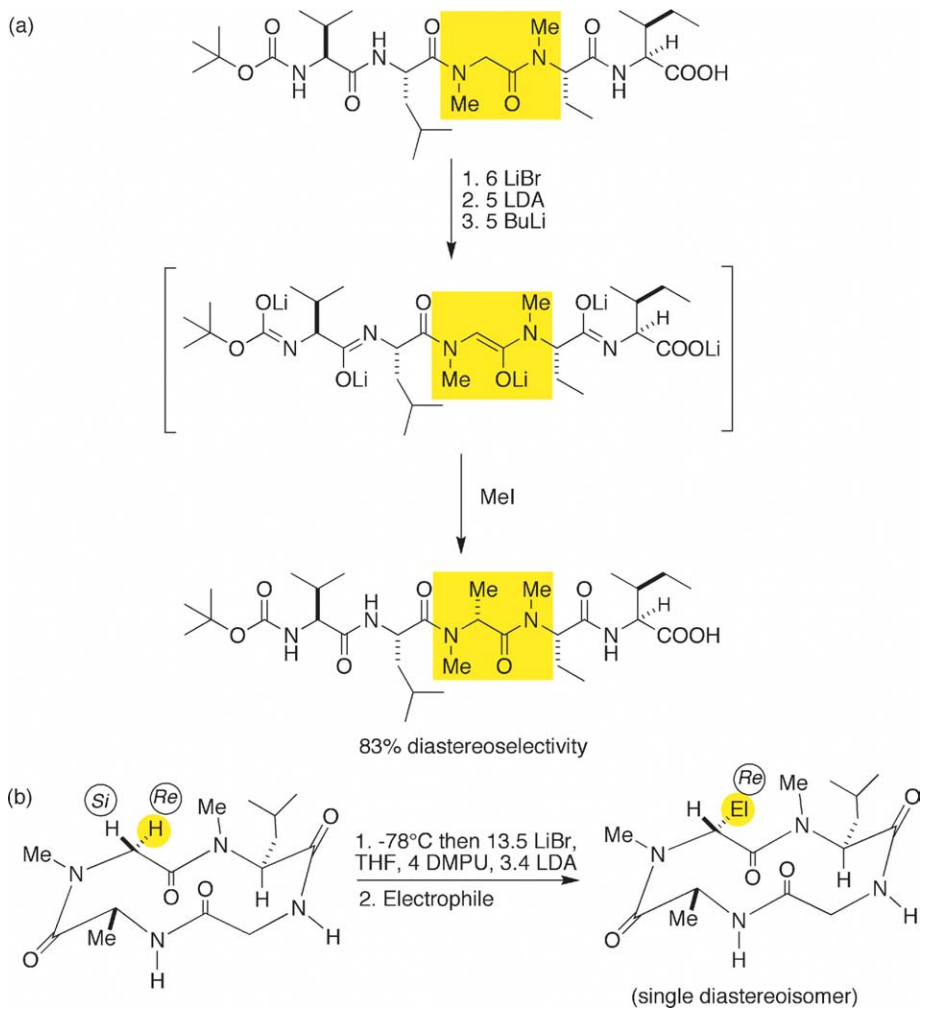

Figure 3. Li-Enolates of peptides and solubilization of peptides in THF; alkylation of open-chain (a) and of cyclic (b) peptides.

cyclosporin itself, which allowed for HPLC analysis with a detection limit of 5 ng (Fig. 1).[5]

The cyclic undecapeptide cyclosporin A containing one (*R*)-amino-acid and seven *N*-methyl-amino-acids has actually been seminal to our group's entry into the field of peptide chemistry. Returning from another visit to Sandoz in 1983, where there was a brain-storming session about possible chemical transformations of cyclosporin, D. S. carried a bottle of the peptide for an experiment he had proposed, causing shaking of heads among experts: why not generate a Li-enolate at the sarcosine residue and introduce side-chains by reactions with electrophiles? Indeed, treatment of cyclosporine with as strong bases/nucleophiles as butyl-lithium (in excess of six equivalents) and addition of typical electrophiles led to highly selective replacement of either the *Re*- or the *Si*-hydrogen in the sarcosine moiety, depending on the particular base and conditions employed;[6–10] an analysis of how this was possible is given in Figure 2.

Thus, we have excised a single proton from a peptide of molecular mass 1200 and replaced it by a side-chain substituent. The derivatives, in which the diastereotopic *Re*-hydrogen had been replaced are immunosuppressive like cyclosporin and have non-altered backbone structures. Those with H^{Si}-replacement have a different structure and exhibit different physiological activities.

The work on cyclosporin alkylations has triggered a series of investigations about peptide enolates,[6,11,12] about solubilization of peptides in THF by addition of Li salts[10,13,14] (Fig. 3), about direct thionations (C═O → C═S) of cyclosporin with Lawesson's reagent,[15] and about cyclosporin as a Li- and Ca-specific ionophor.[16]

We started a program entitled 'chemical modifications of peptides' which led to a number of dissertations in the group. One line of work was dedicated to the use of peptides containing amino-malonic-acid derivatives, which require only weak bases for alkylations[17] (Fig. 4). In a quite different investigation we used electrochemical oxidative decarboxylations of peptides containing up to ten amino-acid residues, a process leading to modifications of the *C*-termini[18] (Fig. 5). Yet another project was the in situ generation of ketenes for certain peptide couplings which enabled us to incorporate a single β-homoamino-acid unit into a larger peptide: activation of the *C*-terminal CO_2H-group, reaction with diazomethane, and decomposition of the resulting diazoketone in the

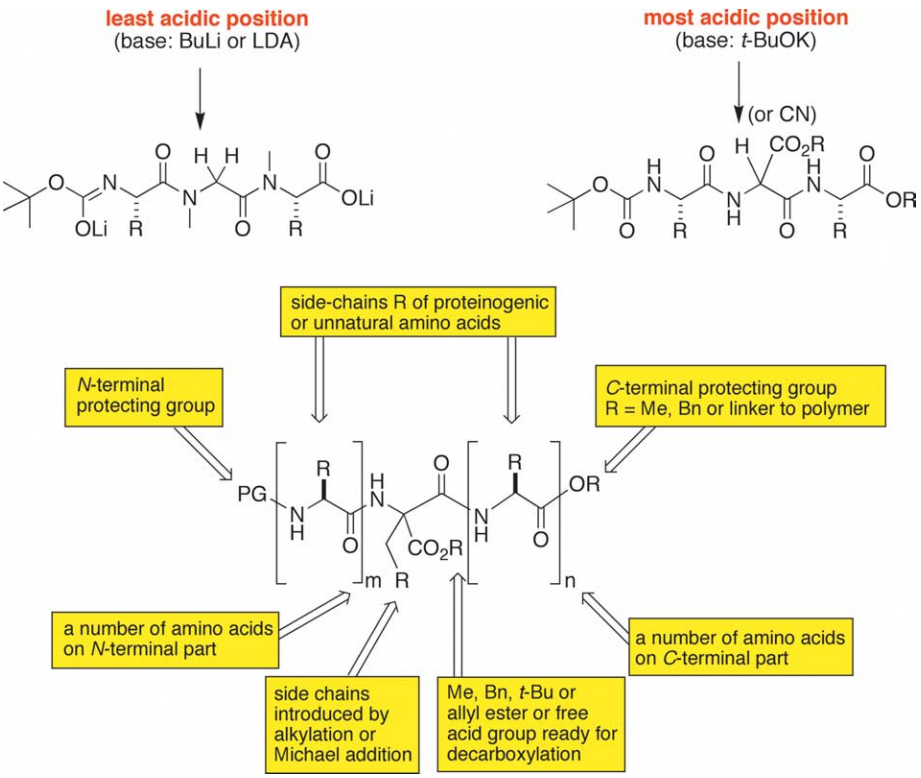

Figure 4. Peptide alkylation by going from the least to the most acidic CH group and application for peptide modification. The process is highly stereoselective in some cases and is amenable to combinatorial applications.

presence of a second peptide with unprotected *N*-terminus provides a homologative fragment coupling (Arndt–Eistert sequence of reactions, see Figure 6).[19] The intermediate activate β-homoamino-acid derivative can also be trapped with carbohydrates or nucleosides to give chimeric products.[20,21]

β-Homoamino acids had been part of our projects on synthetic methods for a long time. Following the work on dilithiated β-hydroxyesters, for instance malates,[22,23] we had generated aspartate-enolates[24,25] as early as 1981. A general method for the diastereoselective preparation of enantiopure $\beta^{2,3}$-homoamino acids involves formation of the Li_2-derivative and alkylation of the corresponding β^3-homoamino acids[26,27] (for nomenclature see an extensive review article on β-peptides[28]). A route to α-branched aspartates employs the principle of self-regeneration of stereocenters (SRS),[25,29,30] and chiral enolates of the achiral 3-amino-propanoic acid can be generated from suitable hydropyrimidines.[31] Formulae of some of these nucleophilic reagents are shown in Figure 7.

We actually conceived the idea of studying β-peptides in the course of our work on the biopolymer PHB (= poly(3-

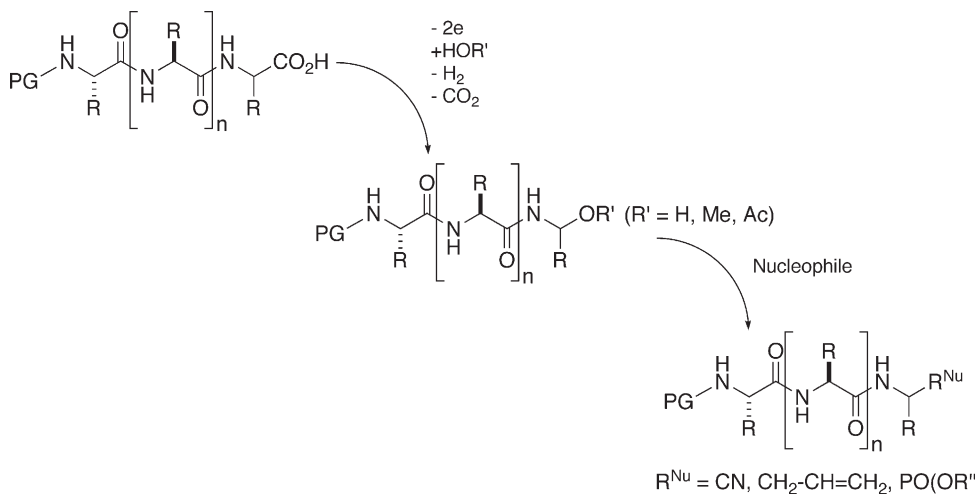

Figure 5. Hofer-Moest Electrolysis of peptides in a protic solvent (H_2O, MeOH, AcOH) and subsequent Lewis-acid-mediated nucleophilic substitution to *N*-terminally modified peptides.

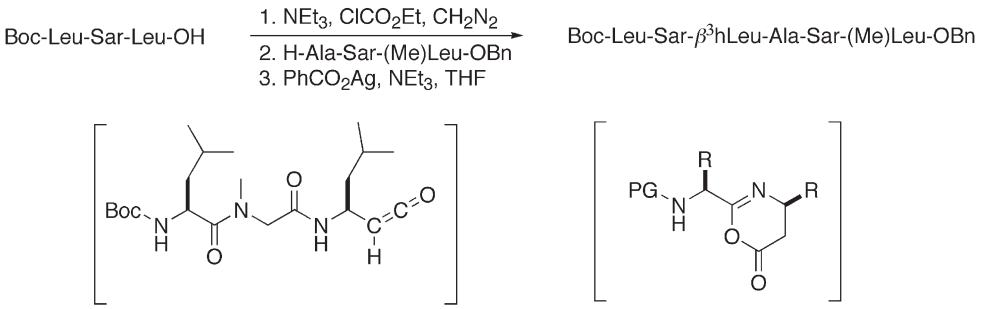

Figure 6. Homologative peptide-fragment coupling through a peptidic ketene intermediate. In the absence of an *N*-methyl-group the actual acylating reagent may be a di-dehydro-oxazinone. H-β^{3}hLeu-OH: (*S*)-3-amino-5-methyl-hexanoic acid.

hydroxybutyrate)): the backbones of cyclic oligo-((*R*)-3-hydroxybutanoates) were found to have a propensity to form (*P*)-helical conformations from which a helix could be modelled, containing chain-bound and carbonyl oxygens at such a distance and relative position that replacement of the former by an NH was expected to lead to hydrogen bonding, and thus stabilization of the helix[28,32] (Fig. 8, top). Exchange of O by NH in the backbone of a poly(3-hydroxyalkanoate) renders the same backbone structure as insertion of a CH_2-group in each and every amino-acid residue of a peptide (Fig. 8, bottom). The experimental test of these ideas led to many chemical, structural, and biological surprises, a full account of which is given in a review article[28] and in ca. 100 papers of our group since 1996 (see the attached complete list of publications of D. S.).

As expected, the additional tetrahedral carbon atom in each amino-acid residue of β-peptides leads to greater structural variety. There are not just two enantiomeric forms but also positional isomers (β^2- and β^3-homoamino acids), diastereoisomers (*l*- and *u*-β^{2,3}-homoamino acids with two side chains), and there can be heteroatoms on the backbone (cf. 2-halo- or 2-hydroxy-3-amino acids). As a consequence, five β-peptidic helices have been identified: an 8-,[28,33] 10-,[34] 10/12-,[35] 12-,[36] and 14-helix[37,38] (the numbers refer to the size of the hydrogen-bonded rings within the helix structures). Also, the β-peptidic backbone can be forced to adopt a pleated-sheet structure or to form a hairpin turn.[39] With two exceptions,[34,39] these structures are seen in solution with as few as six residues, they can be designed and found by molecular-modelling programs.[40] Thus, there are more secondary structures than in the 'α-world', but they can be predicted and constructed from a small number of β-homoamino acid residues. Some of the structures are shown in Figure 9.

Due to the different dimensions, geometries, and polarities of the β-peptidic structures the biological properties of β-peptides differ from those of α-peptides in those cases where exact fitting is mandatory: they do not bind to the active sites of peptidases and are proteolytically stable.[41] More surprisingly, they are even metabolically most stable in mammals, such as rats,[42,43] in insects, and in plant-cell cultures,[44] and very slow biodegradation by environmental microorganisms has been demonstrated in one case.[45] On the other hand, β-peptides can be used to mimic α-peptidic hairpin turns, motifs which are often decisive for so-called ligand–receptor recognitions. This was demonstrated by the design of *N*-acyl-β-tetrapeptide amides with specific nanomolar binding as agonists at one of the human receptors for the peptidic hormone somatostatin (Fig. 10).[46,47]

One of these peptides was recently shown to be orally bioavailable, to pass the blood-brain barrier and to regulate numerous genes in brain tissues.[43] Many other biological tests have been performed with β-peptides (for instance inhibition of an intestinal transport protein, antibiotic and hemolytic activities, binding to DNA and RNA; see references in a review article[28]). In recent investigations of β-oligoarginine derivatives,[48] it was shown that these polyelectrolytes enter mammalian cells in vitro and in vivo to end up in the nucleoli of cell nuclei (Fig. 11), where they remain located for longer periods of time (in contrast to corresponding α-oligoarginines, which are proteolytically degraded once having entered cells). There seem to be no toxic effects; the cell

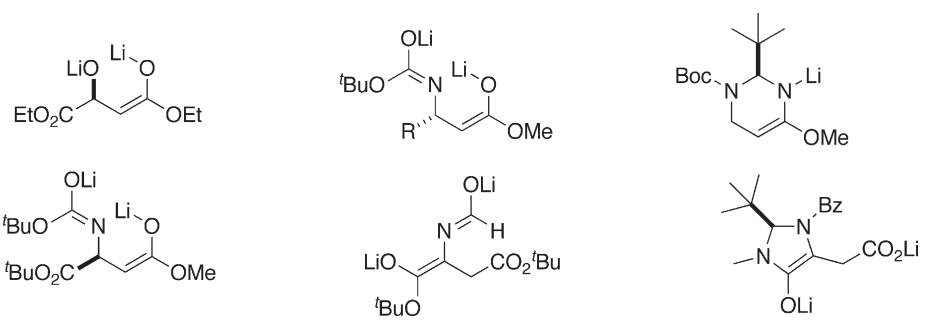

Figure 7. Chiral Li-enolates of β-heterosubstituted carboxylic acid esters. Malic acid, β-amino acids, aspartic acid.

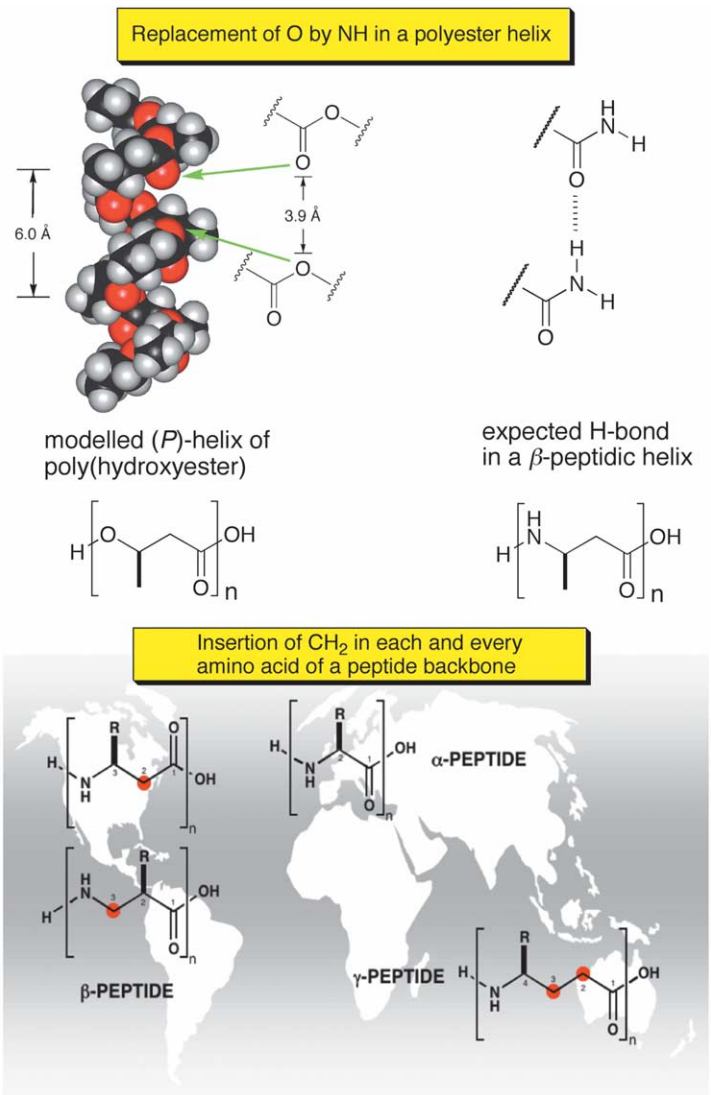

Figure 8. The question 'what happens upon replacement of O by NH in the modeled helix of PHB?' (top) is structurally equivalent to the question 'what happens upon CH_2-insertion in the amino acids of a peptide backbone?' (bottom).

culture of human keratinocytes keeps growing in the presence of the β-oligoarginines.

Thus we have gone a long way from the first experiments with cyclosporin A in 1980 to animal experiments with ^{14}C-labelled β-peptides in 2003.

So far, there was no mention made about synthesis of the β-peptides, which was actually the main occupation of everybody in the group! At the beginning, we prepared the β^3-homoamino acids from the corresponding α-amino acids by Arndt–Eistert homologation ourselves. In the meantime, 18 of the 20 β^3-homoamino acids with the side chains of the proteinogenic α-amino acid analogs are commercial (*N*-Fmoc- and acid labile side-chain protection); the exceptions are β^3hCys and β^3hHis.[49] The β^2-homoamino acids, on the other hand, have to be prepared enantioselectively. Since our research on β-peptides was focused on oligomers of homologs of the natural α-amino acids, we prepared the whole set of the 19 β^2-homoamino acids (β^2hGly = β^3hGly!). We use the chiral-auxiliary approach applying the modified Evans oxazolidinone DIOZ,[50,51] as outlined in Figure 12; for details see the original publications.[46,48,52–57]

Notably, it takes up to 13 steps to prepare some of the acids Fmoc-β^2hXaa(PG)-OH! Having the β-homoamino acids available for solid-phase synthesis by the Fmoc strategy (manual or in a synthesizer), we could make use of all the methods common in α-peptide synthesis, purification, analysis, structure determination, and modelling (Fig. 13), with certain adjustments (see discussion in a review article[28]).

For longer-chain β-peptides the thioligation method,[58] which works equally well for α-, β^2-, and β^3-peptide couplings,[59] turned out advantageous. We have recently addressed the issue, to which chain lengths a β-peptide might form the 3_{14}-helix: α-peptidic helices in proteins are typically only 15–20 residues long, one reason being a destabilization by the resulting macrodipole which increases with chain-length.[60] Thus, we have prepared a

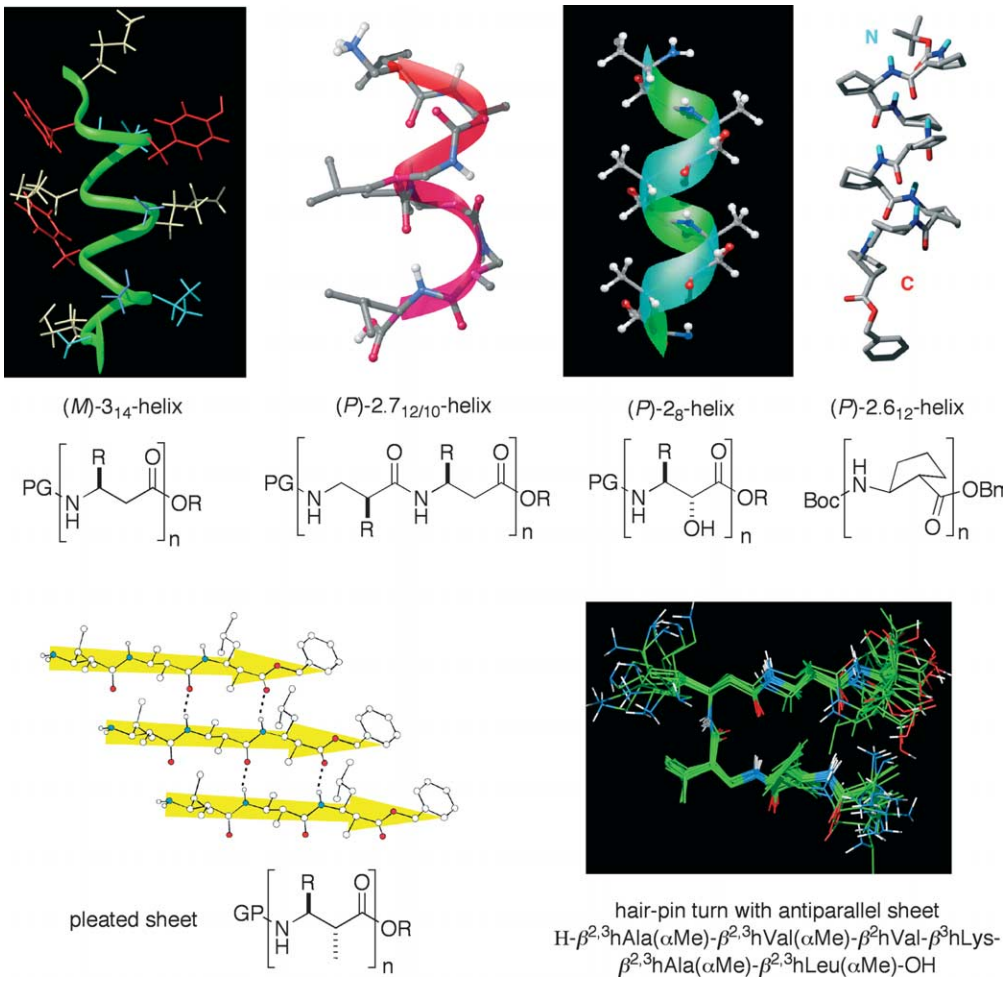

Figure 9. Helix, sheet, and turn structures of β-peptides. Except for the parallel pleated-sheet structure all secondary structures shown can be observed by NMR spectroscopy of solutions. This Figure has, in part, been reproduced by permission of the Verlag Helvetica Chimica Acta. [Rossi, F.; Lelais, G.; Seebach, D. *Helv. Chim. Acta*, **2003**, *86*, 2653. Etezady-Esfarjani, T.; Hilty, C.; Wüthrich, K.; Rueping, M.; Schreiber, J.; Seebach, D. *Helv. Chim. Acta*, **2002**, *85*, 1197.]

β^3-eicosapeptide consisting of the 20 different β^3-homoamino acids;[61] the sequence was chosen such that an amphiphatic helix would result, and stabilization by salt bridges between (*i*) and (*i*+3)-positions was part of its design, see the helical-wheel-type presentation in Figure 14. The CD spectra in methanol and water exhibit an intensive negative Cotton effect between 210 and 220 nm which we may consider typical of a 3$_{14}$-helical secondary structure, however without the usually more intensive short-wavelength maximum seen with short β^3-peptides. The NMR-solution structure determination of this 20mer is underway, and it looks like there is a helix in methanol over the full length of the 20 residues.[62]

As the last major project of our group before retirement of D. S. (with the concomitant necessary reduction of the research-group size) we joined forces and made essentially everybody (from advanced lab-course students, through master-thesis candidates, the last PhD students all the way to the post-doctoral co-workers) part of a team to synthesize the *all*-β^2-eicosapeptide **1** with the 20 proteinogenic amino-acid side chains (see below, Fig. 16).

The reason for embarking on this adventure, which eventually turned out to be a 159-step synthesis, was manifold. First of all, we wanted to demonstrate that we actually can synthesize all the necessary β^2-homoamino-acid building blocks with the chiral auxiliary DIOZ. Then, we decided to find ways of avoiding racemization/epimerization in β^2-homoamino-acid coupling, a problem we had noticed some time ago.[63] Also, the 3$_{14}$-helix of short-chain β^2-peptides has turned out to be less stable than that of isomeric β^3-peptides,[64,65] so that a comparison of larger β^2- and β^3-peptides was important, to find out, whether the former ones fold to other secondary structures. Finally, there was an atmosphere of sportive ambition in the group about getting it done!

The synthesis of the β^2-eicosapeptide **1** was designed to be as safe as possible. To make sure that there would not be insurmountable problems in the purification of the final product, we used a convergent synthesis for the β^2-peptide (Fig. 15), aware of the fact that there would be more danger of epimerization/racemization than with β^3-homoamino acids, and remembering that the isolation of the pure β ^{3}-eicosapeptide (Fig. 14), assembled in one stroke, had been quite cumbersome.[28,61]

For the choice of the sequence (there are more than 10^{18} possibilities) we applied several different criteria:

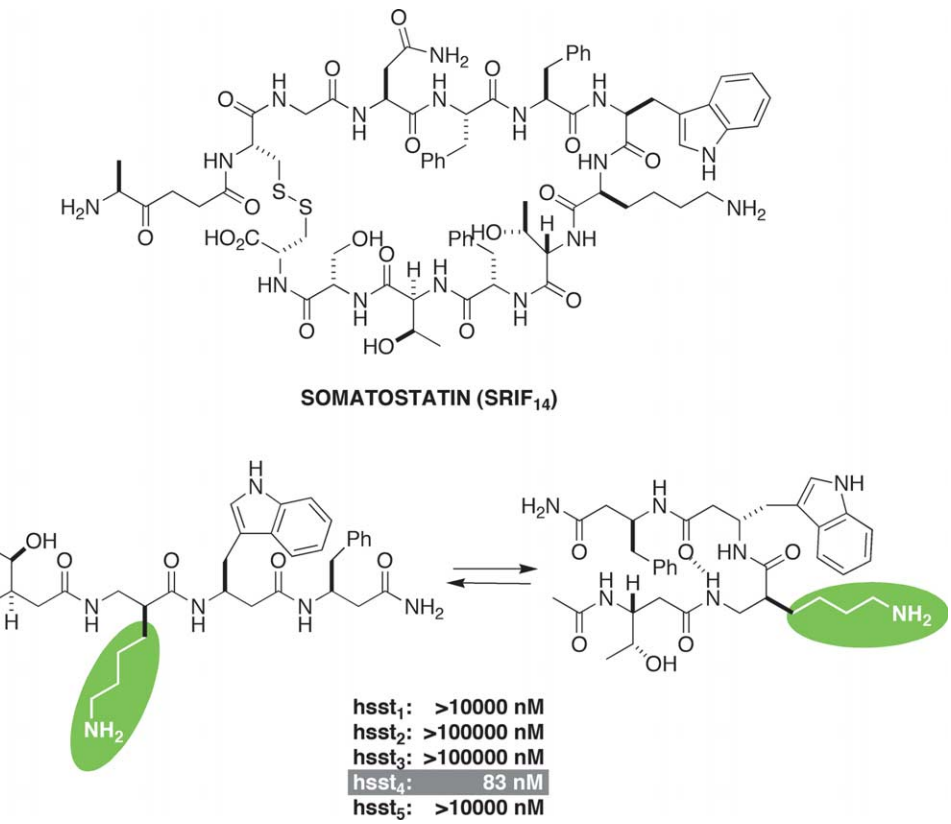

Figure 10. Formula of somatostatin and of a β-tetrapeptide derivative binding to one of the five human somatostatin receptors.

- The 3_{14}-helix of the eicosapeptide, should it be formed, was supposed to be amphipathic, with stripes of polar and non-polar side chains on its surface (Fig. 16).
- Also, the helix should experience salt-bridge stabilization, by putting the two pairs of positively and negatively charged side chains of Arg/Glu and Lys/Asp in (*i*)- and (*i*+3)-positions, that is, in juxtaposition on the helix at a distance of approximately 5 Å (cf. Fig. 9, 3_{14}-helix, top left).
- Next, we considered the well known 'capping effect',[60] according to which negative side chains near the positive and positive side chains near the negative end of a peptidic helix dipol[66] (Fig. 17) have a stabilizing effect, also in β-peptides,[67] thus we placed the β^{2}hArg in position 3 and the β^{2}hAsp in position 17 of the β^2-eicosapeptide **1**.
- The choice of β^{2}hCys in position 11 is dictated by the thioligation, and we put β^{2}hAla next to it (position 10) to reduce steric hindrance in the course of this coupling process.
- Also, the amino acids bearing the side chains of His and Met have been shown to be incompatible with the types of reactions (cf. treatment with CH_2N_2 or with I–CH_2CN) used for the solid-phase synthesis of peptide thioesters;[68] therefore the corresponding β^2-homoamino acids had to be incorporated in the decapeptide **3** with the terminal β^{2}hCys residue (Figs. 15 and 16).
- The β^{2}hPro residue was necessary to be placed in position 20 (i.e., first on the Wang resin), because this amino acid with its secondary piperidine-amino group does not fit into a 3_{14}-helix; rather it is a hairpin-turn structural element.[69]

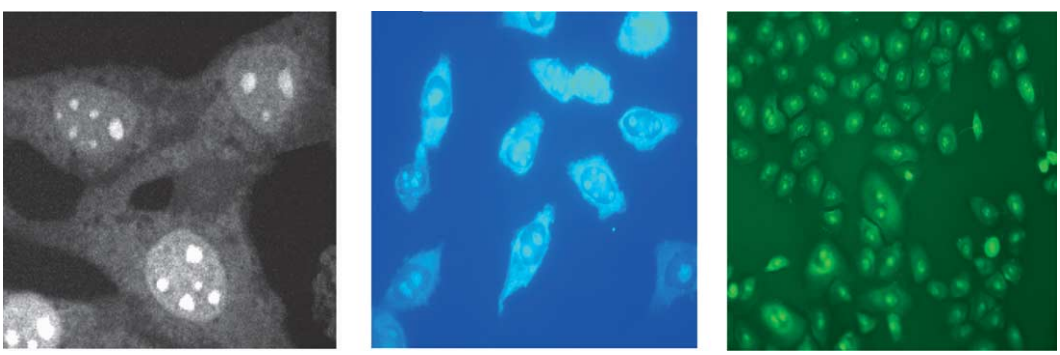

Figure 11. Fluorescence microscopy of mouse fibroblast (left), HeLa (center), and human keratinocyte cells (right) after treatment with fluoresceinylated β^3-oligoarginines consisting of 7, 8 or 10 β^{3}hArg residues. This Figure has, in part, been reproduced by permission of the Verlag Helvetica Chimica Acta. [Seebach, D.; Namoto, K.; Mahajan, Y. R.; Bindschädler, P.; Sustmann, R.; Kirsch, M.; Ryder, N. S.; Weiss, M.; Sauer, M.; Roth, C.; Werner, S.; Beer, H.-D.; Munding, C. *Chem. Biodiversity*, **2004**, *1*, 65.]

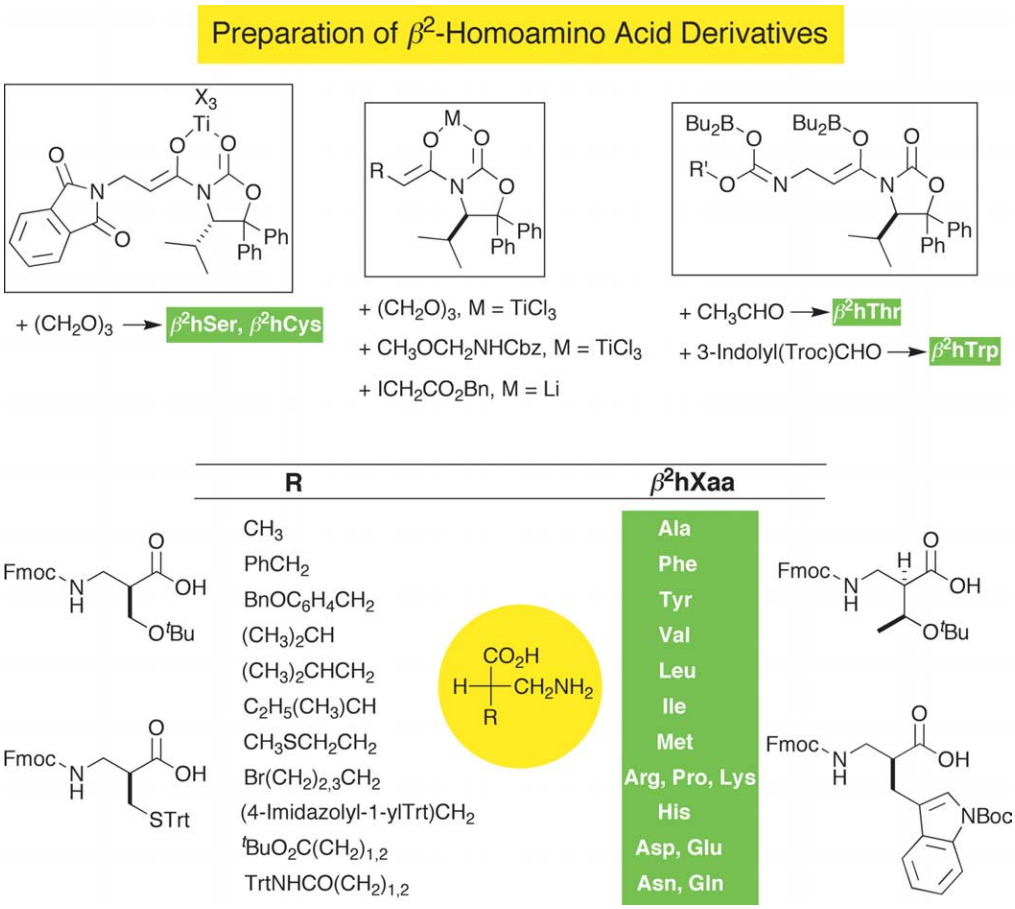

Figure 12. Preparation of 19 β[2]-homoamino acid derivatives with the proteinogenic side chains, using enolates derived from the chiral auxiliary DIOZ. For the preparation of Fmoc-(*S*)β[2]hTrp(Boc)-OH, the classical Evans auxiliary (without the geminal Ph groups) gives better results.

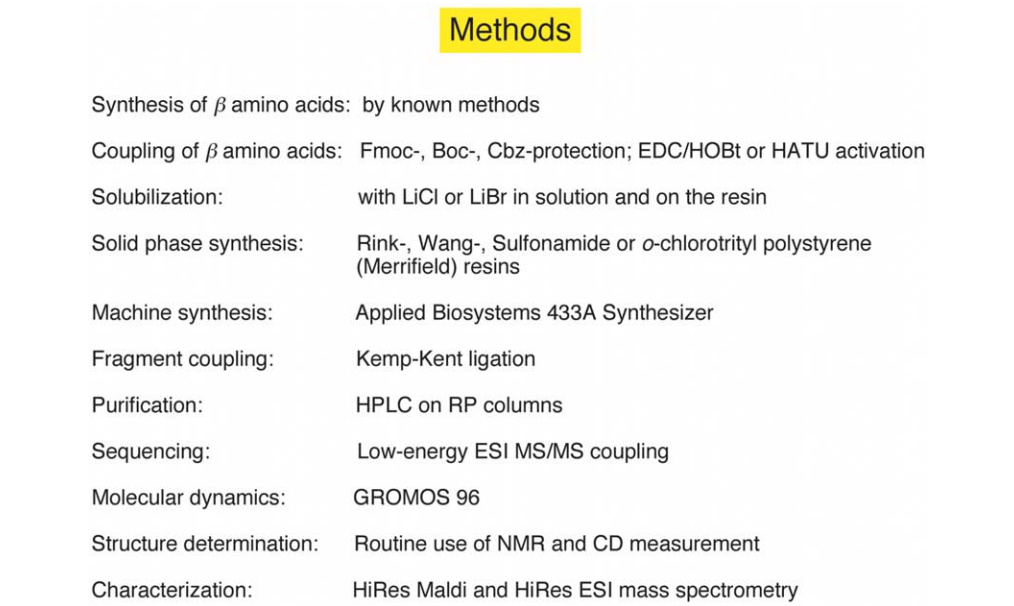

Figure 13. The synthesis and analysis of β-peptides from the Fmoc-β[2]- or -β[3]hXaa(PG)-OH is accomplished by the well established methods of α-peptide chemistry (see text books and monographs).

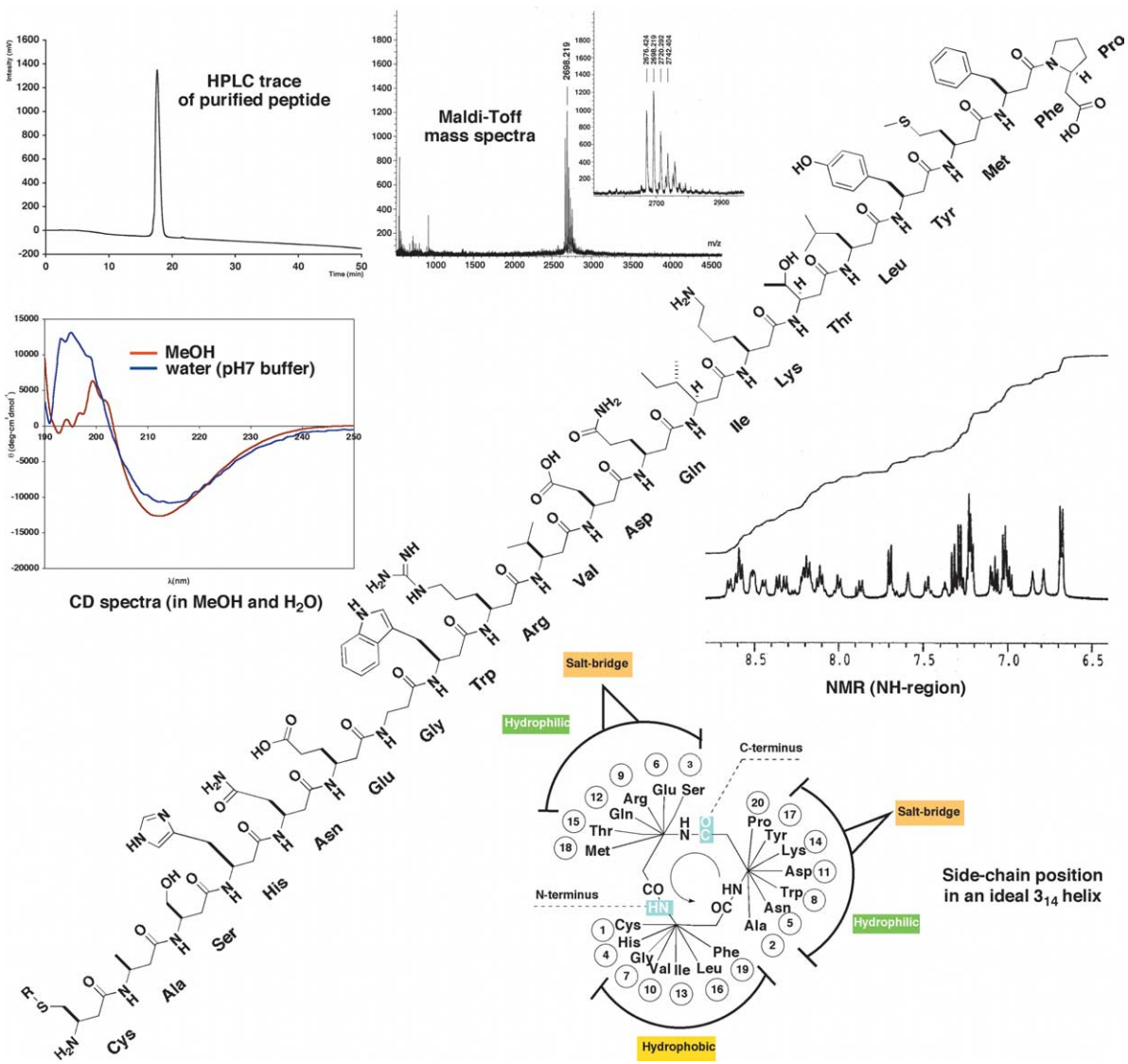

Figure 14. A β^3-eicosapeptide containing the 20 homologated proteinogenic amino acids. The compound was prepared on solid support and purified by preparative HPLC. MS, HPLC of purified sample, CD (normalized) and NMR spectra, and helical-wheel presentation of an (*M*)-3_{14}-helix, which might be formed by the β^3-eicosapeptide.

- The β^2hGly in position 1 was chosen in order to have a sterically unbiased *N*-terminus for derivatization.
- Furthermore, we employed β^2-dipeptide-fragment coupling, to make sure that the two β^2-decapeptide fragments **2** and **3** would be easy to purify in case of failure of a coupling step (a decamer is expected to be separated more easily from an octamer than from a nonamer); the β^2-dipeptide building blocks **4**–**12** could readily be isolated in diastereomerically pure form.
- The sequence of the dimer segments was, wherever possible, chosen such that the less epimerization-prone β^2-homoamino acid was at the *C*-, and the more 'dangerous' one (Phe, Asp, His, Cys, Tyr, Asn side chains) at the *N*-end; in this way, activation of the carboxylic acid group as active ester would involve less risk of epimerization.

The formulae of the suitably protected dipeptide derivatives are shown in Figure 18, and their preparations are outlined in the experimental part, where the not previously described intermediates **13**–**25**, are fully characterized, including specific references to their β^2hXaa-precursors. The dipeptide-coupling steps are preceded by numerous protection, deprotection and protective-group interchange operations. The enantiomer purities of all β^2hXaa starting materials were checked by HPLC analysis on chiral columns and/or by NMR spectroscopy of diastereomeric Pd-complexes.[70] Likewise, the diastereomer purity of the Fmoc-β^2-dipeptide acids was confirmed by NMR and RP-HPLC analysis before use in the solid-phase coupling steps, to make sure that no epimerization has occurred during dipeptide coupling or, else, that any epimer, which might have been formed, had actually been removed in the chromatographic purification procedure.

For the synthesis of β^2-decapeptide **3** bearing an *N*-terminal β^2hCys, by the Fmoc/^{t}Bu solid-phase strategy on Wang resin, the first dipeptide **4** was attached to the resin using the

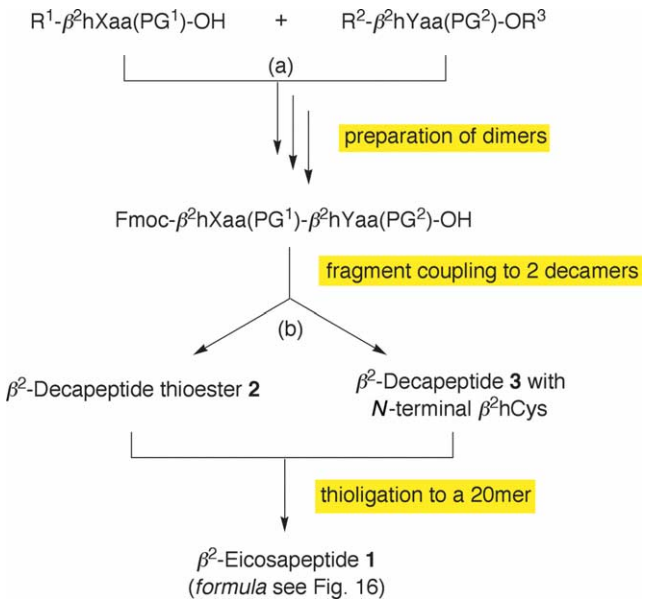

Figure 15. Strategy for the synthesis of a β^2-eicosapeptide through two β^2-decapeptides by dimer-fragment solid-phase coupling on sulfonamide (**2**) and Wang (**3**) resin, with subsequent thioligation.

MSNT/MeIm method[71] and the resin loading determined (after treatment with piperidine, 20% in DMF), by measuring the absorbance of the dibenzofulvene-piperidine adduct at 290 nm (we use the common abbreviations of peptide chemistry[72]). The unreacted OH groups were then 'capped' by acetylation (Ac_2O and DMAP). Chain elongation on solid support was performed with HATU and 3 equiv. of the Fmoc-protected β^2-dipeptides **5**–**8**, and with piperidine for Fmoc deprotection. After the last coupling, the peptide was cleaved from the resin and the side chains deprotected by treatement with CF_3COOH/EDT/TIS/H_2O. Finally purification by reverse-phase HPLC yielded the β^2-peptide **3**, which was analysed by high-resolution mass spectrometry (ESI HRMS).

The β^2-peptide **2** bearing a *C*-terminal thioester was prepared using the methodology developed by Ingenito et al.[68] and based on Kenner's acylsulfonamide safety-catch linker.[73,74] The loading of the resin was achieved with 4 equiv. of the Fmoc-protected β^2-dipeptide **9**, and DIPCDI/MeIm in DCM/DMF. The peptide was then assembled by the standard Fmoc protocol (HATU as coupling reagent and

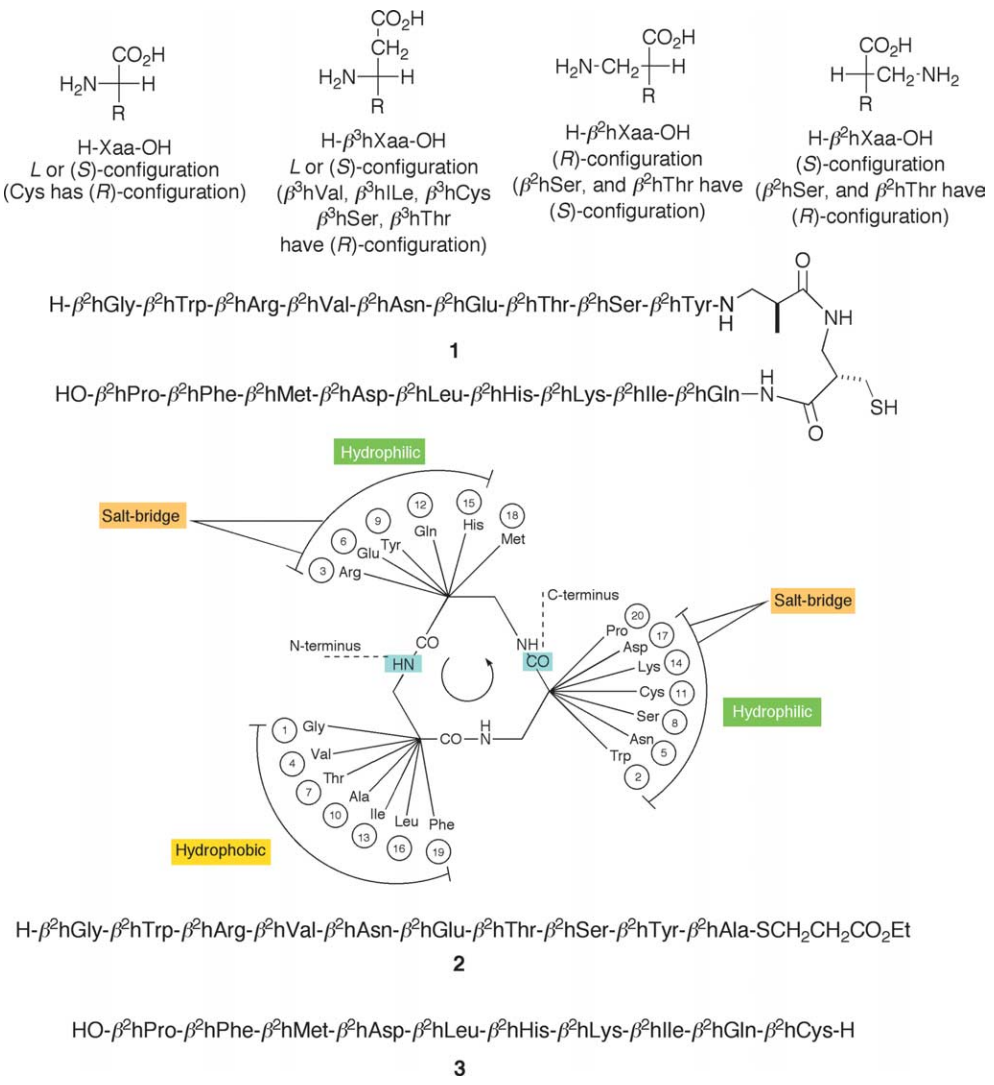

Figure 16. Configurational nomenclature of β-homoamino acids (top), and β^2-eicosapeptide **1** with central β^2hAla and β^2hCys segment, idealized helical-wheel-type presentation of its supposed (*M*)-3_{14}-helix secondary structure (middle), and the two β^2-decapeptide precursors **2** and **3** for thioligation (bottom).

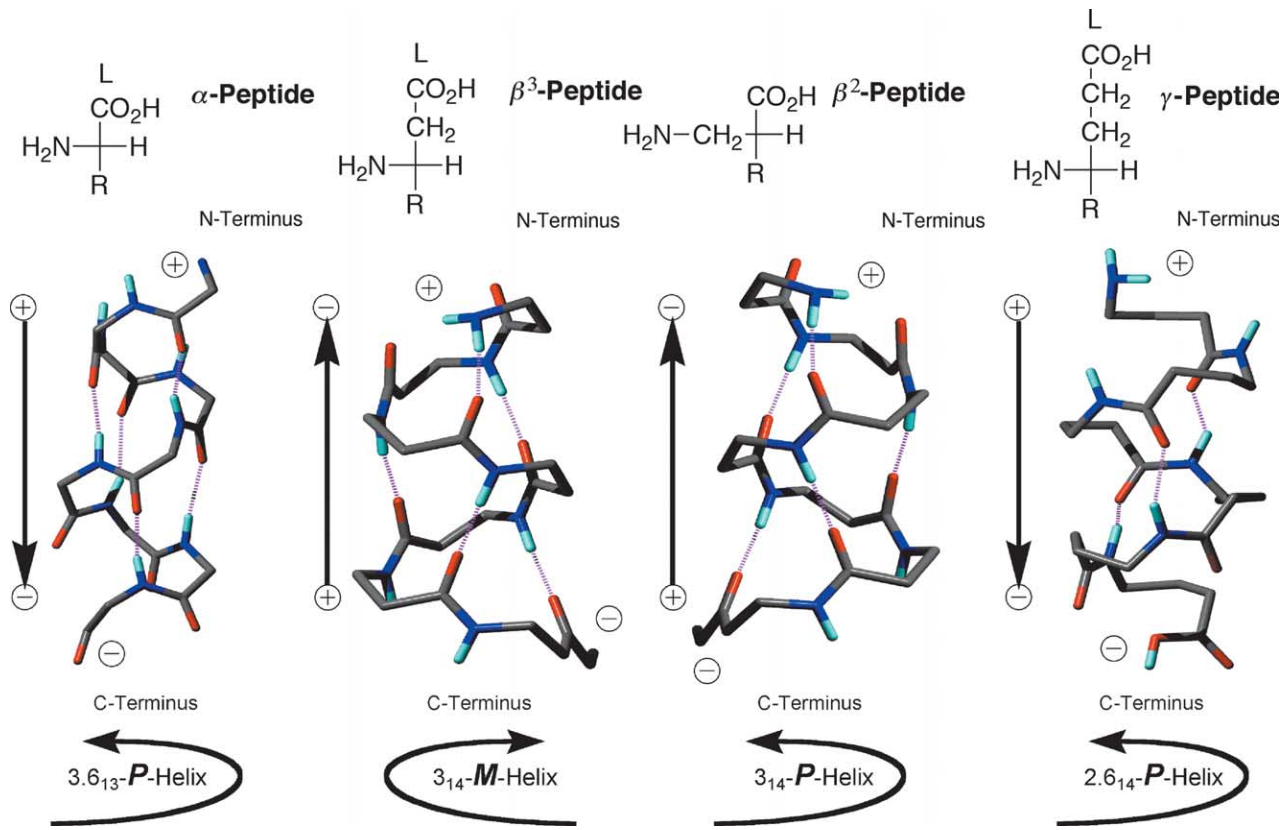

Figure 17. Helicity and direction of macrodipole reverse, as we go from α- to β^3- or β^2- to γ^4-peptides built of homochiral amino acids. The α- and γ-peptidic helices suffer from destabilizing pole-charge interaction, which is a stabilizing effect in the β-peptidic 3_{14}-helix. Furthermore, the resulting macrodipoles (increasing with chain lengths) destabilize the helices, which is counteracted by side chains with opposite charge (⊕ near ⊖ pole and vice versa). Note that helices built of β^2hXaa (shown here) and of the enantiomeric building blocks (Figure 12) have opposite helicity. This Figure has, in part, been reproduced by permission of the Verlag Helvetica Chimica Acta. [Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. *Helv. Chim. Acta*, **2000**, *83*, 34.]

piperidine for Fmoc deprotection). After the last coupling step, activation of the safety-catch linker, treatment with diazomethane followed by a displacement reaction involving $NaSPh/HS(CH_2)_2COOC_2H_5$ led to the still protected decapeptide. Finally, the side chain-protecting groups were removed in solution by treatment with TFA in the presence of an appropriate scavenger. In this way we obtained the β^2-peptide **2**. The displacement reaction did first not work, even in the presence of LiBr.[10,13,14,75,76] However, heating the reaction mixture at 80 °C overnight, and deprotection resulted in the formation of the desired thioester, which was purified by preparative reverse-phase HPLC and identified by high-resolution mass spectrometry. CD Spectra of the two β^2-decapeptides **2** and **3** are shown in Figure 19.

The chemical ligation-methodology, which allows the coupling of unprotected peptide fragment in aqueous solution, has made considerable advance in recent years. It offers a new route for the synthesis of larger peptides and proteins.[77,78] In the thioligation reaction the coupling process starts with a trans thioesterification reaction involving a peptide already bearing a *C*-terminal thioester and the sulfhydryl group of a second peptide bearing an *N*-terminal Cys. The thioester-linked intermediate undergoes a subsequent rapid intramolecular S → N acyl shift, forming the amide bond at the ligation site. In the case of peptides containing a β^2-homocysteine, the intramolecular S → N acyl shift in the ligation reaction proceeds through a 6-membered, rather than a 5-membered heterocycle, which is involved with Cys and β^3hCys as coupling components (Fig. 20).

We applied this method for the final step in the synthesis of the β^2-peptide **1** containing all the β^2-homoamino acids with proteinogenic side chains. The ligation was performed under standard conditions[79] (aqueous solution, pH 7.5 phosphate buffer and 4% (v/v) PhSH). After 4 h, more than 70% conversion had occurred and the reaction was essentially complete after 12 h as evident from the analytical RP-HPLC traces shown in Figure 21.

The crude product **1** was then purified by preparative reverse-phase HPLC and characterised by high-resolution mass spectrometry. The normalized CD spectrum of the β^2-eicosapeptide **1** in methanol shows the familiar negative Cotton effect between 210 and 220 nm with an intensity similar to that observed with the isomeric β^3-eicosapeptide (Fig. 14). However in water the negative Cotton effect (trough) almost vanishes, and an intensive positive Cotton effect (peak) appears at shorter wavelengths. Similar changes of β-peptidic CD patterns upon replacement of MeOH by H_2O as solvent had been observed previously,[58,80–82] and commented with awe ('miraculous');[81] they may suggest an alteration of the secondary structures, or unfolding to a 'totally disordered' backbone conformation. However, only a full NMR investigation will be able to elucidate what is going on (Fig. 22).[62,82]

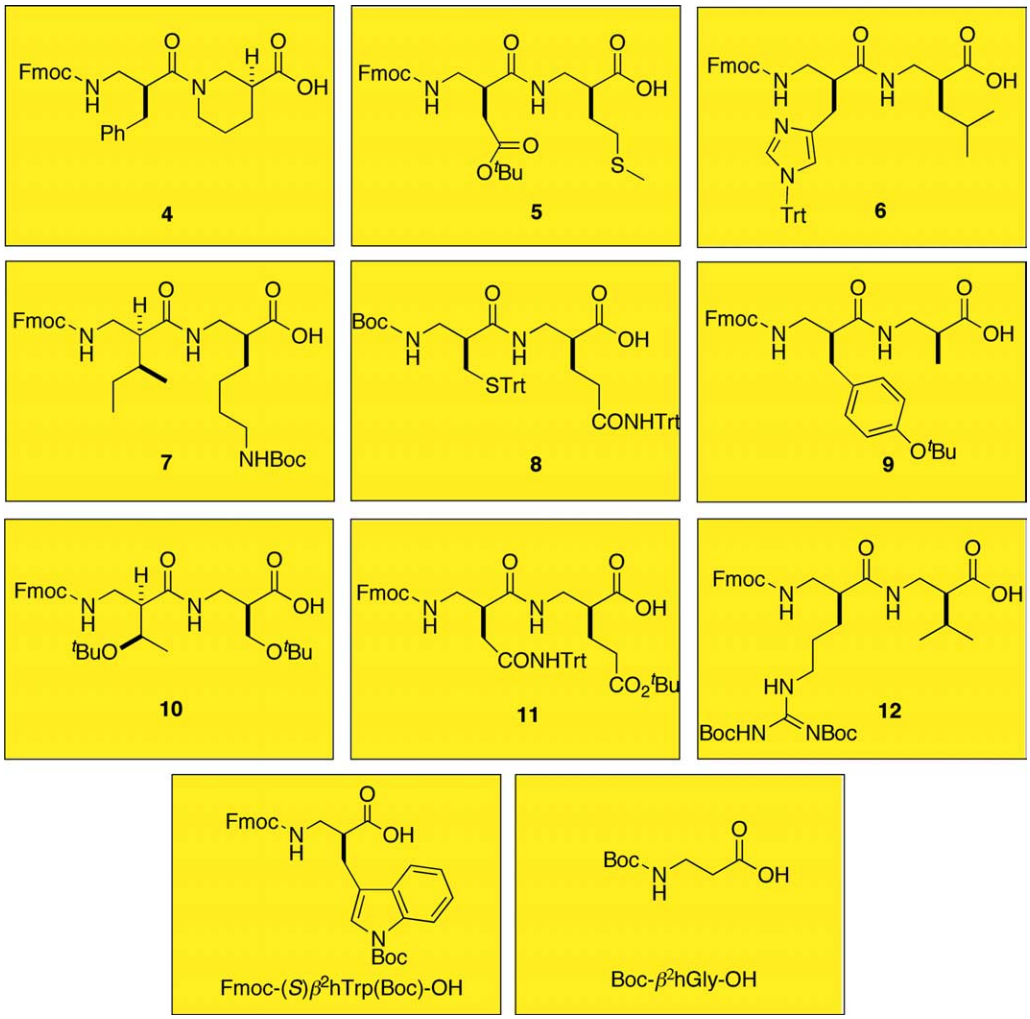

Figure 18. Nine β^2-dipeptide derivatives **4**-**12** and the Fmoc-(*S*)β^{2}hTrp(Boc) and β^{2}hGly components (*N*-terminal in **1** and **2**) for the solid-phase synthesis of the β^2-decapeptides **2** and **3** (Figure 16).

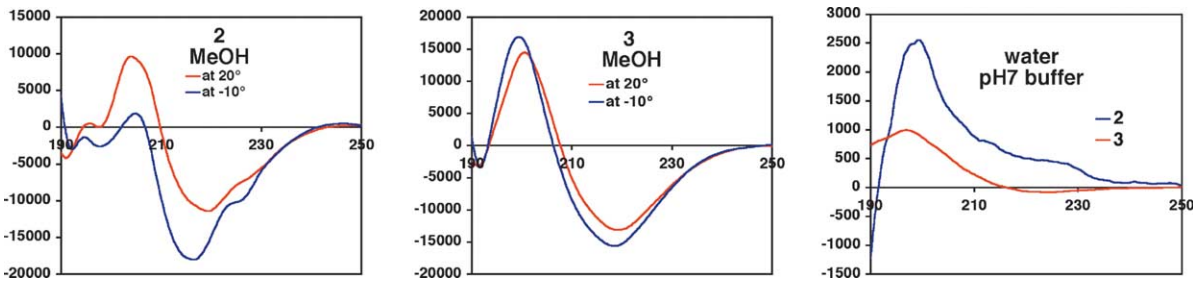

Figure 19. CD Spectra (normalized) of the two β^2-decapeptides **2** and **3** in MeOH at +20 and −10 °C, and in H_2O. The Cotton effect observed between 215 and 220 nm increases with decreasing temperature.[64,65] The pattern obtained with **3** we would consider typical of a 3_{14}-helix. The shoulder near 225 nm and the drastic reduction of intensity of the positive Cotton effect near 205 nm seen with the β^2-decapeptide **2**, however, is totally surprising and can not be interpreted at present. In aqueous pH 7 buffer the β^2-decapeptide **2** shows a positive Cotton effect at 200 nm albeit with low intensity; the β^2-decapeptide **3** does not show any significant Cotton effect. Compare the CD spectra of the β^2-eicosapeptide **1** in H_2O and MeOH in Figure 22 below.

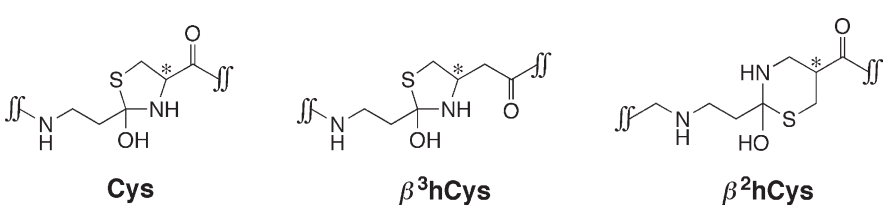

Figure 20. Formulae of the cyclic intermediates formed during the S → N acyl shift in the course of the thioligation reaction involving Cys, β^{3}hCys and β^{2}hCys.

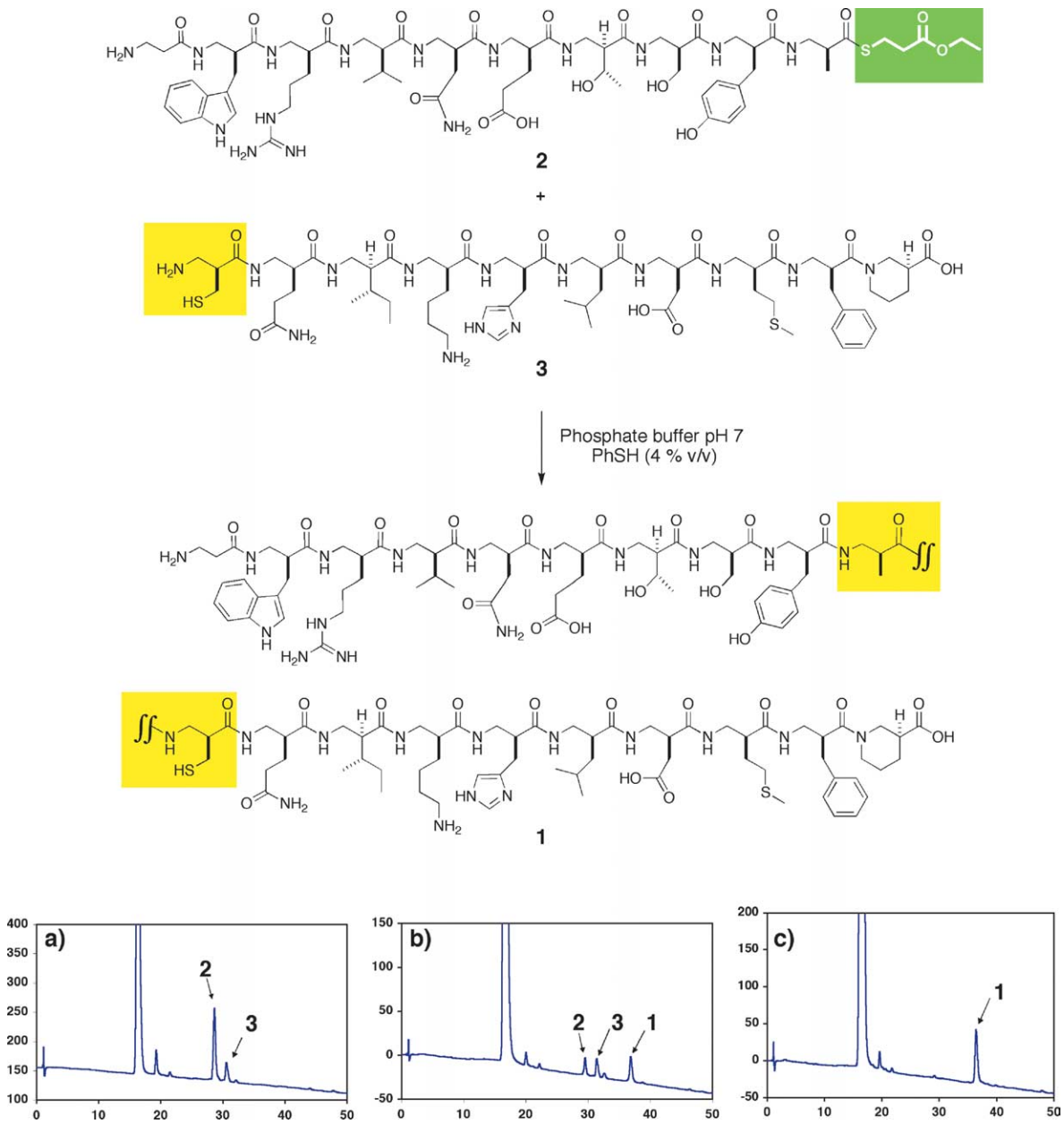

Figure 21. Analytical-HPLC traces of the ligation reaction between β^2-decapeptide **2** with a *C*-terminal thioester group and β^2-decapeptide **3** with an *N*-terminal β^2hCys residue. Samples taken from the reaction mixture at: (a) $t = 10$ min, (b) $t = 2$ h, and (c) $t = 12$ h (chromatographic conditions see Section 2).

The syntheses of the two β-eicosamers may be taken as a demonstration, that any sequence of β^2- or β^3-homoamino acid residues with the proteinogenic side chains can be assembled. This makes us confident that we will be able to construct–by design–β-peptides with tertiary and quaternary structures and, possibly, with catalytic activities. Some evidence for aggregation of long-chain β^3-peptides (consisting of homologated 'natural' α-aminoacid residues) has already emerged from concentration-dependent CD spectra.[58] Also, intramolecular helix–helix interaction has been deduced from CD spectra of a β^3-peptide with proteinogenic side chains.[83]

We should, however, not be too sure of our ability to synthesize any β-peptidic sequence: with the sheet-forming α-branched $\beta^{2,3}$-homoamino-acid residues we[39,84] and others[85] have observed difficulties in the solid-phase synthesis of corresponding β-peptides. On the other hand, we are optimistic, as synthetic organic chemists must be 'by definition', that there will be a solution to any synthetic problem, if we just try hard enough.

Besides construction of more complex architectures with function, the major goal in the field of β-peptides, and also γ-peptides,[86] is the exploitation of their biological, pharmacological, and biomedical potential.[28] Recent experiments with short-chain β-peptides (proteolytically and metabolitically stable!) have involved structure-dependent tissue-specific distributions, gene profiling in brain and lung tissues, affinity to MHC-type-I proteins,

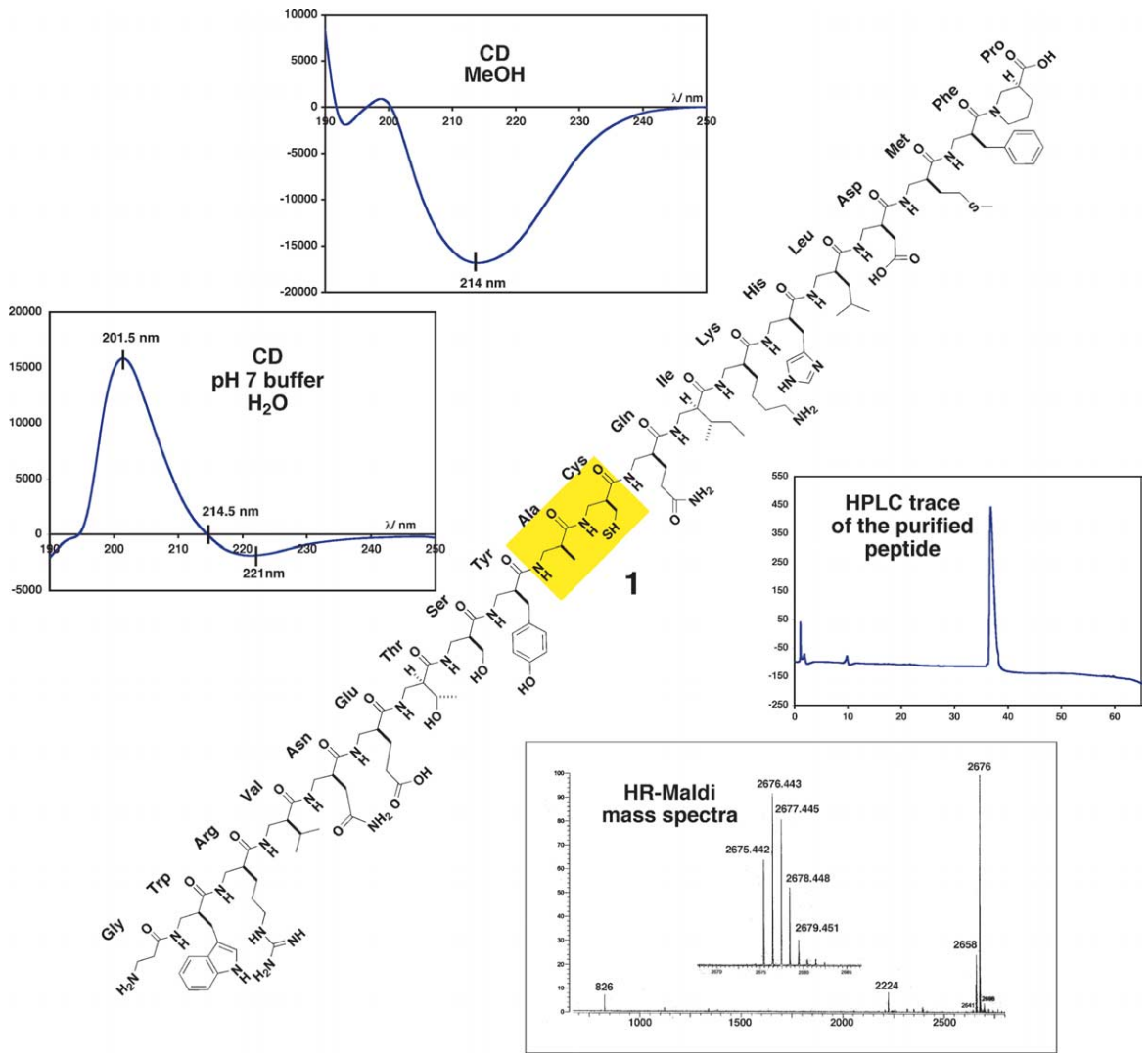

Figure 22. Formula, mass spectra, HPLC of a purified sample, CD spectrum (normalized) in MeOH and in H_2O of β^2-eicosapeptide **1**.

and human-leukocyte-antigen-mediated protection of pig cells against human natural-killer-cell cytotoxicity.[43]

2. Experimental

2.1. General

Abbreviations: The official abbreviations of Peptide Science[72] are used throughout this paper. DMAP (4-(dimethylamino)pyridine), DIPCDI (diisopropylcarbodiimide), DIPEA (diisopropylethylamine), EDC (*N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide hydrochloride), EDT (ethanedithiol), FC (flash chromatography), FmocOSu (*N*-(9-Fluorenylmethoxycarbonyloxy)succinimide), HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate), h.v. (high vacuum, 0.01–0.1 Torr), 1-MeIm (1-methylimidazole), NMM (*N*-methylmorpholine), MSNT (1-(mesitylene-2-sulphonyl)-3-nitro-1*H*-1,2,4-triazole), TBAF (tetra-*n*-butylammonium fluoride), TFA (trifluoroacetic acid), TIS (triisopropylsilane), TNBS (2,4,6-trinitrobenzensulfonic acid). Solvents for chromatography were distilled from Sikkon (anh. $CaSO_4$; Fluka), THF was distilled from Na, CH_2Cl_2 and NEt_3 from CaH_2. LiCl was dried in h.v. at 100 °C for 1 h. All other reagents were used as received from Fluka. TLC: Merck silica gel 60 F_{254} plates; detection with UV or 'Mo-stain' solution (25 g phosphormolybdic acid, 10 g $Ce(SO_4)_2{\cdot}H_2O$, 60 mL conc. H_2SO_4, 940 mL H_2O), FC: Fluka silica gel 60 (40–63 μm); at ca. 0.2 bar. Anal HPLC: Merck HPLC system (LaChrom, pump type L-7150, UV detector L-7400, Interface D-7000, HPLC Manager D-7000). Macherey-Nagel C_8-column (Nucleosil 100-5 C_8 250×4 mm); Waters HPLC system (pump type 515, data module type 746, tunable absorbance detector type 484). Chiralcel OD-H column. Prep. HPLC: Merck HPLC system (LaChrom, pump type L-7150, UV detector L-7400, Interface D-7000, HPLC Manager D-7000) Macherey-Nagel C_8 column (Nucleosil 100-7 C_8 (250×21 mm)). Circular dichroism (CD): CD spectra were recorded on a Jasco J-710 spectropolarimeter from 190 to 250 nm with a Jasco PTC-348 WI Peltier System at 20 °C or −10 °C in 1 mm rectangular cells. The optical system was flushed with N_2 at a flow rate of ca. 10 L/min. Parameters: band width 1.0 nm, resolution 0.2–1 nm, sensitivity 100 mdeg, response 0.5 s, speed 50 nm/min, 5 accumulations. All spectra were corrected for the corresponding solvent spectrum and normalized. Peptide concentrations were typically 0.2 mM. The molar ellipticity [θ] in

deg·cm^2·mol^{-1} (λ in nm). Smoothing was done by Jasco software. Solvents: MeOH (HPLC grade), aq. Buffer pH 7.0: 0.1 M KH_2PO_4/0.1 M NaOH. NMR: Bruker AMX 500 (^{1}H 500 MHz, ^{13}C 125 MHz), AMX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) and Varian Gemini (^{1}H 300 MHz, ^{13}C 75 MHz) chemical shifts δ in ppm downfield from internal $SiMe_4$ (0 ppm). Mass Spectra: IonSpec Ultima 4.7 T FT Ion Cyclotron Resonance (ICR, HR-MALDI, in a 2.5-dihydroxybenzoic acid matrix), or Finnigan MAT TSQ 700 (ESI) mass spectrometer; in *m*/*z* (% of basis peak). Melting points: Büchi-510 apparatus; uncorrected. Optical rotations: Perkin–Elmer 241 polarimeter (10 cm, 1 mL cell, room temperature). IR: Perkin–Elmer 1600 FT-IR spectrophotometer. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

2.2. General procedures

2.2.1. Peptide coupling to give dimers 4–12: general procedure 1 (GP1). The appropriate *N*-deprotected amino acid (1 equiv.) was dissolved in CH_2Cl_2 (0.1 M) and cooled in an ice-bath. To the mixture was successively added NMM (3 equiv.) and the *N*-protected amino acid (1 equiv.). To this solution either HATU (1.2 equiv.) (GP1a) or EDC (1.2 equiv.) and HOBt (1.2 equiv.) (GP1b) was added and the mixture allowed to warm up to 25 °C and stirred overnight. The mixture was then diluted with CH_2Cl_2 and washed with 1 M HCl, 10% aq. K_2CO_3 and brine solutions. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude dipeptide was purified by FC.

2.2.2. Hydrogenolysis of Cbz and Bn-ester groups: general procedure 2 (GP2). The corresponding substrate was dissolved in either MeOH or THF (0.02 M) and ca. 10% (w/w) Pd/C (10%) was added. The apparatus was evacuated and flushed with H_2 (3×), and the solution was stirred under an atmosphere of H_2 for the indicated amount of time (monitoring by TLC). Subsequent filtration through Celite and removal of solvent under reduced pressure yielded the product, which was used in the next step without further purification.

2.2.3. Saponifications: general procedure 3 (GP3). The appropriate ester (1 equiv.) was dissolved in MeOH/H_2O 3:1 (0.1 M) at 25 °C. To the resulting solution, LiOH·H_2O (2.5 equiv.) was added and the reaction mixture was stirred 3 h. The mixture was diluted with H_2O and extracted with Et_2O. The aqueous phase was acidified with 1 N HCl to pH~1 and extracted with AcOEt (3×). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by FC.

2.2.4. Fmoc-protection: general procedure 4 (GP4). To a solution of the *N*-deprotected dipeptide in 0.15 M Na_2CO_3 (2 equiv.) was added FmocOSu (1.2 equiv.) in acetone (0.1 M). If necessary, the pH was adjusted to 9–10 with additional aq. Na_2CO_3 solution and the mixture stirred at 25 °C for 4 h. The acetone was carefully removed under reduced pressure at 30 °C and the resulting mixture diluted with H_2O. At this point the pH of the solution was adjusted to 9–10 using 0.6 M aq. Na_2CO_3. The aq. mixture was then extracted with Et_2O (2×). The aq. phase was separated, cooled to 0 °C and AcOEt added. With continuous stirring of the biphasic system at 0 °C, the pH of the aq. phase was adjusted to 4–5 by slow addition of 10% aq. citric acid. The org. layer was separated and the aq. layer extracted with AcOEt (2×). The combined org. layers were washed with brine, then dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by FC.

2.2.5. Preparation of trimethylsilylethyl esters: general procedure 5 (GP5). To a solution of the *C*-unprotected amino acid (1 equiv.) in CH_2Cl_2 (0.1 M) at 0 °C under Ar, was added trimethylsilylethanol (1.5 equiv.), DMAP (0.2 equiv.), and EDC (1.2 equiv.). The resulting mixture was stirred at 0 °C for 16 h then diluted with AcOEt and the org. phase washed with 10% Na_2CO_3 (2×), and brine, then dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by FC.

2.2.6. Trimethylsilylethyl ester deprotection: general procedure 6 (GP6). To a solution of the corresponding Si-ester (1.0 equiv.) in THF (0.1 M) was added TBAF·3H_2O (4 equiv.) and the mixture stirred at 25 °C for 1 d. The reaction mixture was then diluted with AcOEt and the organic phase washed with sat. aq. NH_4Cl, and brine, then dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by FC.

2.2.7. Reversed-phase (RP) HPLC analysis and purification. RP-HPLC analysis was performed on a Macherey-Nagel C_8 column (Nucleosil 100-5 C_8 (250×4 mm)) by using a linear gradient of A (0.1% TFA in H_2O) and B (MeCN) at a flow rate of 1.2 mL/min with UV detection at 220 nm; t_R in min. RP-HPLC purification was performed on

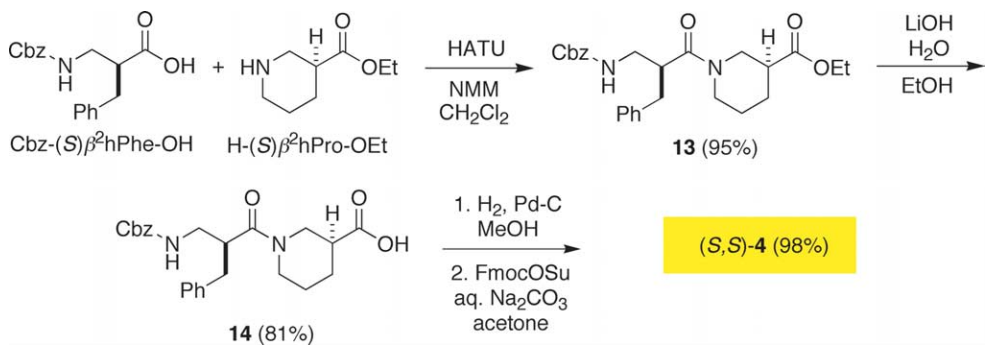

Figure 23. Preparation of Fmoc-(*S*)β^{2}hPhe-(*S*)β^{2}hPro-OH (**4**).

a Macherey-Nagel C_8 column (Nucleosil 100-5 C_8 (250×21 mm)) by using a linear gradient of A and B at a flow rate of 18 mL/min (Merck HPLC system).

2.3. Preparation of Fmoc-protected dipeptides 4–12

2.3.1. Cbz-(*S*)β²hPhe-(*S*)β²hPro-OEt (13). Amino acids Cbz-(*S*)β²hPhe-OH[87] (1.05 g, 3.35 mmol) and H-(*S*)β²hPro-OEt[88] (0.53 g, 3.35 mmol) were coupled according to GP1a. FC (AcOEt/hexane 1:1) gave **13** (1.44 g, 95%) as colorless oil; R_f=0.23 (AcOEt/hexane 1:1); $[\alpha]_D$=+27.5 (c=0.80, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450 (w), 3007 (m), 2944 (w), 1720 (s), 1626 (s), 1511 (s), 1454 (m), 1139 (m), 1085 (m), 1030 (m), 856 (w) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) **13**+rotamers δ 0.92–1.14 (m, 2H, CH_2), 1.17 (t, J=6.3 Hz, 3H, CH_3), 1.26–1.50 (m, 2H, CH_2), 1.66–1.84 (m, 2H, CH_2), 2.29 (m, 1H, CH), 2.51–2.90 (m, 4H, CH, CH_2, C*H*H), 3.06–3.19 (m, 2H, CH_2N), 3.67 (t, J=14.4 Hz, 1H, NH), 4.03 (m, 2H, OCH_2), 4.27 (d, J=11 Hz, 1H, CH*H*), 5.01 (m, 2H, OCH_2Ph), 7.07–7.49 (m, 10H, arom.); ^{13}C NMR (125 MHz, DMSO-d_6) **13**+rotamers δ: 13.9, 23.7, 24.4, 26.5, 26.7, 35.8, 36.3, 40.0, 40.5, 40.6, 41.4, 41.9, 42.2, 42.9, 43.1, 43.2, 45.0, 46.8, 59.8, 59.9, 65.1, 126.1, 127.6, 128.1, 128.2, 128.8, 137.2, 139.3, 156.1, 171.0, 172.2, 172.4; MALDI HRMS calcd for $C_{26}H_{32}N_2O_5Na$ $(M+Na)^+$: 475.2203, found: 475.2207. Anal. calcd for $C_{26}H_{32}N_2O_5$: C 69.01, H 7.13, N 6.19; found: C 69.01, H 7.16, N 5.93 (Fig. 23).

2.3.2. Cbz-(*S*)β²hPhe-(*S*)β²hPro-OH (14). Dipeptide ester **13** (1.34 g, 2.96 mmol) was hydrolyzed according to GP3. The resulting crude material was crystallized from $CHCl_3$/hexane to give **14** (1.02 g, 81%) as white crystals; mp 189–190 °C; R_f=0.32 (AcOEt/hexane/AcOH 10:10:1); $[\alpha]_D$=+2.4 (c=0.15, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3446 (w), 3008 (m), 1715 (s), 1627 (s), 1513 (m), 1454 (m), 1082 (m), 1046 (m), 1005 (w), 877 (w) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) **14**+rotamers δ 0.91–1.50 (m, 5H, 2×CH_2 and C*H*H), 1.68–1.91 (m, 2H, CH_2), 2.21–2.86 (m, 3H, NH, CH, CH*H*), 3.06–3.19 (m, 2H, CH_2), 3.54 (m, 1H, CH), 4.20 (d, J=12.9 Hz, 1H, C*H*H), 4.43 (d, J=10.7 Hz, 1H, CH*H*), 5.02 (m, 2H, OCH_2Ph), 7.06–7.39 (m, 10H, arom.), 12.32 (br s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) **14**+rotamers δ: 23.9, 24.6, 26.8, 26.9, 36.3, 40.6, 40.7, 41.5, 42.0, 42.1, 42.8, 43.1, 43.2, 45.0, 47.0, 65.1, 126.0, 126.1, 127.5, 126.6, 126.7, 128.1, 128.15, 128.22, 128.24, 128.6, 128.8, 137.1, 137.2, 139.2, 139.3, 156.1, 170.9, 171.1, 174.0, 174.2; MALDI HRMS calcd for $C_{24}H_{28}N_2O_5Na$ $(M+Na)^+$: 447.1890, found: 447.1887. Anal. calcd for $C_{24}H_{28}N_2O_5$: C 67.91, H 6.65, N 6.60; found: C 67.89, H 6.45, N 6.54.

2.3.3. Fmoc-(*S*)β²hPhe-(*S*)β²hPro-OH (4). Cbz-dipeptide **14** was hydrogenolyzed according to GP2 then Fmoc-protected according to GP4. The crude peptide was purified by FC (AcOEt/hexane/AcOH 10:10:0.1) to give **4** (1.13 g, 98%) as a white foam; mp 84–87 °C; R_f=0.35 (AcOEt/hexane/AcOH 10:10:1); $[\alpha]_D$=−1.6 (c=0.73, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450 (w), 3008 (m), 2949 (m), 2862 (w), 1713 (s), 1625 (s), 1514 (s), 1467 (m), 1450 (s), 1181 (m), 1144 (m), 1084 (m), 1008 (m), 990 (w), 856 (w) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) **4**+rotamers δ 1.02–1.99 (m, 4H, 2×CH_2), 2.27–2.93 (m, 4H, 2×CH and CH_2), 3.21–3.79 (m, 4H, 2×CH_2), 4.21 (m, 2H, CH_2), 4.30–4.53 (m, 3H, OCH_2CH), 7.08–7.79 (m, 13H, arom.); ^{13}C NMR (100 MHz, CD_3OD) **4**+rotamers δ 21.5, 25.35, 25.41, 25.7, 26.4, 28.4, 28.6, 37.8, 38.1, 42.39, 42.48, 42.54, 43.3, 43.5, 43.6, 44.1, 44.5, 44.6, 44.8, 44.83, 44.86, 44.93, 45.1, 45.3, 47.4, 67.6, 67.7, 67.8, 67.9, 121.0, 126.0, 126.1, 126.2, 126.3, 127.5, 127.6, 127.7, 128.2, 128.8, 129.3, 129.5, 129.6, 129.7, 130.0, 130.3, 140.3, 140.7, 142.7, 145.4, 158.9, 174.2, 174.3, 174.4, 176.2, 176.6, 176.9; MALDI HRMS calcd for $C_{31}H_{32}N_2O_5Na$ $(M+Na)^+$: 535.2203; found: 535.2199. Anal. calcd for $C_{31}H_{32}N_2O_5$: C 72.64, H 6.29, N 5.46; found: C 72.71, H 6.43, N 5.24 (Fig. 23).

2.3.4. Boc-(*S*)β²hMet-OCH_2CCl_3 (15). The crude H-(*S*)β²hMet-OH[55] (2.42 mmol) was dissolved in H_2O (2.5 mL) and aq. 1 M NaOH (5 mL) at 5 °C (ice bath). To the resulting solution Boc_2O (0.63 g, 2.90 mmol, 1.2 equiv.) in dioxane (5 mL), was added and the mixture stirred for 30 min at 25 °C. The solution was concentrated to half of its original volume, cooled again in an ice bath, covered with a layer of AcOEt and acidified with a dilute solution of $KHSO_4$ to pH 2–3. The aqueous phase was extracted with AcOEt (2×). The combined organic extracts were washed with H_2O, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product (0.45 g, 1.71 mmol)

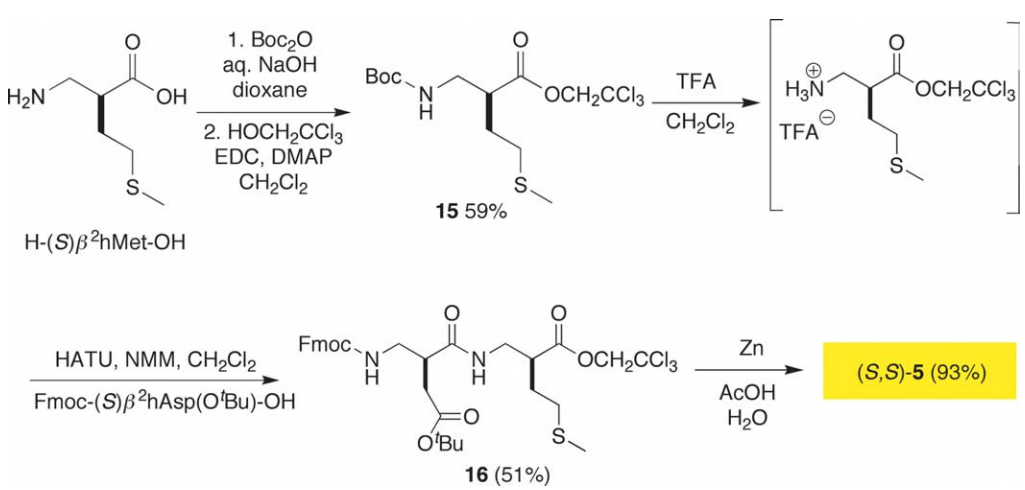

Figure 24. Preparation of Fmoc-(*S*)β²hAsp(O′Bu)-(*S*)β²hMet-OH (**5**).

and DMAP (42 mg, 0.34 mmol, 20 mol%) were dissolved in CH_2Cl_2 (20 mL) and Cl_3CCH_2OH (0.19 mL, 0.28 g, 1.88 mmol, 1.1 equiv.) was added. The resulting solution was cooled in an ice bath then EDC (0.39 g, 2.05 mmol, 1.2 equiv.) added and the reaction mixture stirred for 18 h at 25 °C. Sat. aq. NH_4Cl was added and the organic phase washed with 0.1 N HCl, 0.1 M K_2CO_3 and brine then dried ($MgSO_4$) and solvent removed under reduced pressure. The crude product was purified by FC (AcOEt/hexane 3:7) to give **15** (0.56 g, 59%) as colorless oil; R_f=0.61 (AcOEt/hexane 1:1); $[\alpha]_D$=+3.1 (c=0.26, $CHCl_3$); IR (neat) ν_{max} 3344 (w), 3054 (w), 2976 (w), 2140 (m), 1752 (s), 1710 (s), 1513 (m), 1445 (m), 1366 (m), 1272 (m), 1250 (m), 1167 (s), 789 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H, ^{t}Bu), 1.86 (m, 1H, C*H*HS), 2.03 (m, 1H, CH*H*S), 2.10 (s, 3H, SCH_3), 2.60 (t, J=7.5 Hz, 2H, CH_2), 2.95 (m, 1H, CHCO), 3.39 (m, 2H, CH_2N), 4.78 (s, 2H, OCH_2), 4.89 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 28.5, 28.6, 31.6, 41.3, 44.7, 74.0, 79.7, 94.8, 155.7, 172.6; MALDI HRMS calcd for $C_{13}H_{22}Cl_3NO_4SNa$ $(M+Na)^+$: 416.0227; found: 416.0233.

2.3.5. Fmoc-(*S*)β²hAsp(O^{t}Bu)-(*S*)β²hMet-OCH$_2$CCl$_3$ (16). To a solution of compound **15** (0.63 g, 1.60 mmol) in CH_2Cl_2 (6 mL), was added slowly TFA (6 mL) and the mixture stirred for 2 h at 25 °C. After removal of solvent under reduced pressure, the amino ester was coupled with Fmoc-(*S*)β²hAsp(O^{t}Bu)-OH[56] (0.68 g, 1.60 mmol) according to GP1a. FC (AcOEt/hexane 1:1) yielded **16** (0.57 g, 51%) as a white solid. R_f=0.33 (AcOEt/hexane 1:1); $[\alpha]_D$=+12.8 (c=0.49, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3445 (w), 3008 (w), 2974 (w), 2923 (w), 1720 (s), 1667 (m), 1513 (m), 1450 (m), 1368 (m), 1153 (s), 1077 (w), 1046 (w), 841 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H, ^{t}Bu), 1.80 (m, 1H, C*H*HS), 2.03 (m, 1H, CH*H*S), 2.08 (s, 3H, CH_3S), 2.37 (m, 1H, CH), 2.54 (m, 3H, CH and CH_2), 2.81–3.05 (m, 2H, CH_2), 3.29–3.57 (m, 4H, 2×CH_2N), 4.20 (t, J=6.2 Hz, 1H, C*H*CH_2O), 4.39 (d, J=6.2 Hz, 2H, CHC*H*$_2$O), 4.67–4.83 (m, 2H, CH_2CCl_3), 5.46 (br s, 1H, NH), 6.57 (br s, 1H, NH), 7.26–7.42 (m, 4H, arom.), 7.59 (d, J=7.1 Hz, 2H, arom.), 7.76 (d, J=7.2 Hz, 2H, arom.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 28.1, 28.7, 31.4, 35.7, 39.9, 42.2, 42.6, 44.1, 47.3, 66.7, 68.4, 74.1, 81.4, 119.9, 125.0, 126.9, 127.6, 141.2, 143.7, 156.4, 171.3, 172.2, 173.6; MALDI HRMS calcd for $C_{32}H_{39}Cl_3N_2O_7SNa$ $(M+Na)^+$: 723.1436; found: 723.1444.

2.3.6. Fmoc-(*S*)β²hAsp(O^{t}Bu)-(*S*)β²hMet-OH (5). Dipeptide ester **16** (0.86 g, 1.22 mmol) was dissolved in a mixture of AcOH (50 mL) and H_2O (5 mL). To the cooled solution (ice bath), Zn powder (3.99 g, 61 mmol, 50 equiv.) was added in portions over 2 h. The reaction mixture was allowed to warm up to 25 °C and stirred for 3 h. Zn was removed by filtration and the filtrate diluted with H_2O and extracted with AcOEt (3×). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. FC (AcOEt/hexane/AcOH 10:10:0.1) of the crude product yielded **5** (0.65 g, 93%) as a white solid; mp 143–144 °C; R_f=0.37 (AcOEt/hexane/AcOH 10:10:1); $[\alpha]_D$=+15.9 (c=0.43, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3436 (w), 3005 (m), 2974 (m), 1720 (s), 1667 (m), 1512 (m), 1450 (m), 1368 (m), 1154 (m), 1077 (w), 841 (w) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.43 (s, 9H, ^{t}Bu), 1.84 (m, 2H, CH_2S), 2.05 (s, 3H, CH_3S), 2.32 (m, 1H, CH); 2.47–2.58 (m, 3H, CH and CH_2), 2.77 (m, 2H, CH_2), 3.15–3.43 (m, 4H, 2×CH_2), 4.21 (t, J=6.6 Hz, 1H, C*H*CH_2O), 4.36 (d, J=6.5 Hz, 2H, CHC*H*$_2$O), 7.11 (m, 1H, NH), 7.28–7.40 (m, 4H, arom), 7.64 (d, J=7.2 Hz, 2H, arom.), 7.79 (d, J=7.5 Hz, 2H, arom.), 8.05 (br s, 1H, NH); ^{13}C NMR (75 MHz, CD_3OD) δ 15.0, 28.1, 29.9, 32.1, 36.0, 41.2, 43.6, 44.0, 45.3, 47.8, 67.5, 81.6, 120.5, 125.8, 127.7, 128.3, 142.1, 144.8, 144.9, 172.0, 175.0, 176.8; MALDI HRMS calcd for $C_{30}H_{38}N_2O_7SNa$ $(M+Na)^+$ 593.2292, found 593.2299 (Fig. 24).

2.3.7. Fmoc-(*S*)β²hHis(Trt)-(*S*)β²hLeu-OBn (17). Fmoc-(*S*)β²hHis(Trt)-OH[57] (0.72 g, 1.34 mmol) and *p*TsOH·H-(*S*)β²hLeu-OBn[65] (0.49 g, 1.41 mmol) were coupled according to GP1a in the presence of 4 equiv. of NMM. The crude product was purified by FC (AcOEt/hexane 3:1) to yield 0.96 g (84%) of **17** as an amorphous solid. R_f=0.12 (AcOEt/hexane 3:1). $[\alpha]_D$=−2.5 (c=0.75, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3734 (w), 3628 (w), 3063 (w), 2923 (w), 2853 (w), 1718 (s), 1652 (m), 1539 (m), 1495 (w), 1448 (s), 1169 (m), 1245 (m), 1139 (m), 1085 (w), 843 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.76 (d, J=6.3 Hz, 3H, Me); 0.77 (d, J=6.3 Hz, 3H, Me) 1.18–1.23 (m, 1H, CH*H*(*i*-Pr)), 1.37–1.47 (m, 2H, C*H*H(*i*-Pr), Me_2CH); 2.52–2.62 (m, 4H, 2×CHCO and CH_2Ar), 2.66–2.73 (m, 1H, CH*H*N); 2.97–3.06 (m, 1H, C*H*HN), 3.08–3.15 (m, 1H, C*H*HN), 3.20–3.26 (m, 1H, CH*H*N), 4.16–4.25 (m, 3H, OCH_2CH), 5.00–5.10 (m, 2H, CH_2Ph), 6.60 (s, 1H, arom.), 7.05–7.07 (m, 6H, arom.), 7.21 (s, 1H, arom.), 7.27–7.41 (m, 19H, 18 arom., NH), 7.66–7.68 (m, 2H, arom.), 7.88–7.99 (m, 2H, arom.), 8.02 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.7, 22.7, 25.5, 28.6, 38.3, 40.6, 42.1, 43.2, 45.7, 46.6, 65.5, 74.3, 118.3, 120.0, 125.1, 125.1, 126.9, 127.5, 127.8, 127.8, 128.0, 128.3, 129.1, 136.0, 137.2, 138.4, 140.6, 142.2, 143.7, 156.0, 173.0, 173.9. MALDI HRMS calcd for $C_{55}H_{54}N_4O_5Na$ $(M+Na)^+$: 873.3992; found: 873.3986.

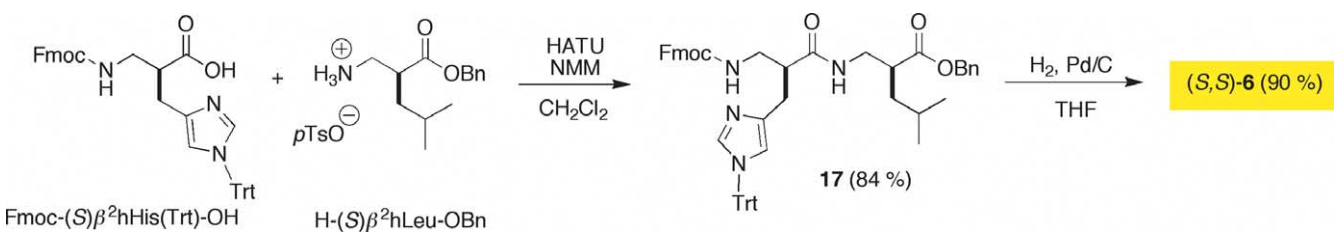

Figure 25. Preparation of Fmoc-(*S*)β²hHis(Trt)-(*S*)β²hLeu-OH (**6**).

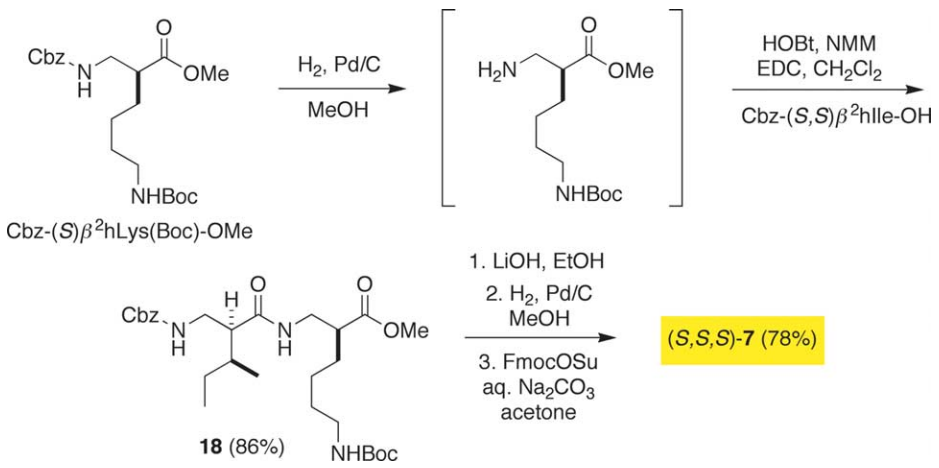

Figure 26. Preparation of Fmoc-(*S*,*S*)β^{2}hIle-(*S*)β^{2}hLys(Boc)-OH (**7**).

2.3.8. Fmoc-(*S*)β^{2}hHis(Trt)-(*S*)β^{2}hLeuOH (6). The *C*-terminus of the fully protected dipeptide **17** (0.96 g, 1.14 mmol) was deprotected according to GP2 in THF for 8 h. The crude product was purified by FC (CH_2Cl_2/MeOH 9:1) to yield 0.78 g (90%) of **6** as an amorphous solid. R_f=0.18 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$=+10.6 (*c*=0.43, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3297 (w), 3061 (w), 2922 (w), 2854 (w), 1719 (s), 1649 (s), 1551 (s), 1449 (s), 1245 (m), 1132 (m), 1001 (w), 842 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (d, *J*=6.4 Hz, 3H, Me); 0.79 (d, *J*=6.4 Hz, 3H, Me) 1.12–1.14 (m, 1H, C*H*H(*i*-Pr)); 1.36–1.44 (m, 1H, CH*H*(*i*-Pr)), 1.52–1.53 (m, 1H, Me_2CH), 2.40–2.46 (m, 1H, CHCO), 2.52–2.69 (m, 3H, CH_2Ar, CHCO), 2.96–3.17 (m, 4H, 2×CH_2N), 4.16–4.25 (m, 3H, OCH_2CH), 6.64 (s, 1H, arom.), 7.05–7.07 (m, 6H, arom.), 7.21 (s, 1H, arom.), 7.28–7.44 (m, 14H, 13 arom., NH), 7.67–7.68 (m, 2H, arom.), 7.86–7.88 (m, 2H, arom.), 7.97 (s, NH), 12.35 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.8, 22.8, 25.5, 28.4, 38.5, 40.9, 41.8, 45.4, 46.6, 54.8, 65.3, 74.4, 119.9, 121.3, 127.0, 127.2, 127.5, 127.8, 128.0, 128.8, 129.2, 138.1, 140.6, 140.6, 142.2, 143.8, 156.0, 172.8; MALDI HRMS calcd for $C_{48}H_{48}N_4O_5Na$ (M+Na)$^+$: 783.3523; found: 783.3517 (Fig. 25).

2.3.9. Cbz-(*S*,*S*)β^{2}hIle-(*S*)β^{2}hLys(Boc)-OMe (18). The Cbz-protecting group of Cbz-(*S*)β^{2}hLys(Boc)-OMe[54] (1.01 g, 2.47 mmol) was hydrogenated according to GP2 and the resulting crude H-(*S*)β^{2}hLys(Boc)-OMe was coupled with Cbz-(*S*,*S*)β^{2}hIle-OH[55] (0.69 g, 2.47 mmol) according to GP1b. The crude product was purified by FC (hexane/AcOEt 8:2→5:5) to yield **18** (1.13 g, 86%) as a colorless solid; mp 93–96 °C; R_f=0.18 (AcOEt/hexane 1:1); $[\alpha]_D$=+30.3 (*c*=1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450 (w), 3007 (w), 2968 (m), 2872 (w), 1713 (s), 1666 (m), 1509 (s), 1456 (m), 1367 (m), 1170 (m), 1064 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3H, Me), 0.91 (d, *J*=6.9 Hz, 3H, Me), 1.08–1.19 (m, 1H, CH), 1.30–1.37 (m, 2H, CH_2), 1.43 (s, 9H, ^{t}Bu), 1.42–1.51 (m, 2H, CH_2), 1.52–1.58 (m, 2H, CH_2),1.59–1.67 (m, 2H, CH_2), 2.22–2.26 (m, 1H, CH), 2.60–2.66 (m, 1H, CH), 3.07 (d, *J*=6.0 Hz, 2H, CH_2), 3.26–3.35 (m, 2H, CH_2), 3.42–3.54 (m, 2H, CH_2), 3.68 (s, 3H, MeO), 4.55 (br s, 1H, NH), 5.07 (q, *J*=12.4 Hz, 2H, CH_2Ph), 5.35 (br s, 1H, NH), 6.10 (br s, 1H, NH), 7.30–7.36 (m, 5H, arom.); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 15.9, 23.7, 27.2, 28.4, 28.9, 29.4, 29.7, 29.9, 35.2, 39.9, 40.2, 40.4, 44.8, 45.1, 51.9, 52.0, 58.5, 66.6, 72.3, 79.2, 128.0, 128.5, 136.6, 156.1, 156.5, 174.4, 175.4; MALDI HRMS calcd for $C_{28}H_{45}N_3O_7Na$ (M+Na)$^+$: 558.3150, found: 558.3157. Anal. calcd for $C_{28}H_{45}N_3O_7$: C 62.78, H 8.47, N 7.84; found: C 62.80, H 8.28, N 7.71.

2.3.10. Fmoc-(*S*,*S*)β^{2}hIle-(*S*)β^{2}hLys(Boc)-OH (7). The methyl ester- and the Cbz-protecting group of compound **18** (1.06 g, 1.98 mmol) were removed according to GP3 and GP2 respectively, and the resulting amino acid Fmoc-protected according to GP4. FC (CH_2Cl_2/MeOH 100:1→CH_2Cl_2/MeOH/AcOH 20:1:0.2) yielded **7** (0.94 g, 78%) colorless solid; mp 114–117 °C; R_f=0.30 (CH_2Cl_2/MeOH/AcOH 20:1:0.2); $[\alpha]_D$=+29.4 (*c*=1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3449 (w), 3344 (w), 3007 (w), 2969 (m), 2933

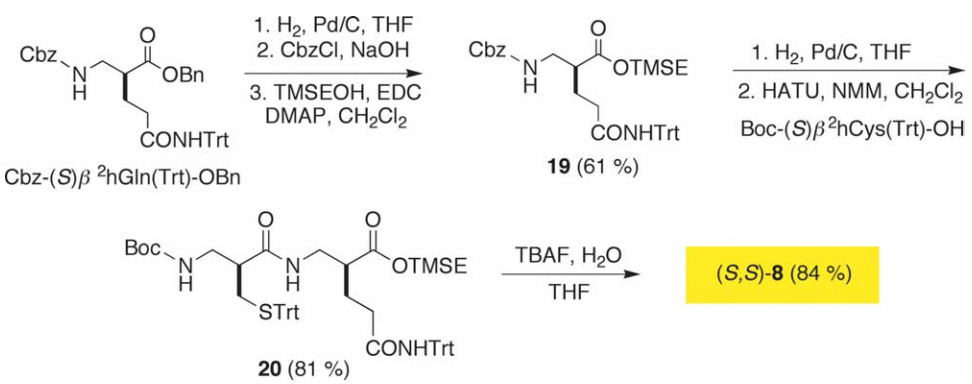

Figure 27. Preparation of Boc-(*S*)β^{2}hCys(Trt)-(*S*)β^{2}hGln(Trt)-OH (**8**).

(m), 2872 (w), 1710 (s), 1662 (m), 1510 (s), 1451 (m), 1368 (m), 1167 (m), 1078 (w), 990 (w) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.89 (t, J=7.4 Hz, 3H, Me), 0.94 (t, J=6.8 Hz, 3H, Me), 1.10–1.57 (m, 2H, CH_2), 1.29–1.39 (m, 2H, CH_2), 1.41 (s, 9H, ^{t}Bu), 1.42–1.49 (m, 2H, CH_2), 1.51–1.63 (m, 4H, 2×CH_2), 2.29–2.34 (m, 1H, CH), 2.58–2.62 (m, 1H, CH), 3.00 (d, J=6.9 Hz, 2H, CH_2), 3.20–3.28 (m, 2H, CH_2), 3.32–3.39 (m, 2H, CH_2), 4.19 (t, J=6.9 Hz, 2H, CH_2), 4.31 (d, J=7.1 Hz, 2H, CH_2), 6.89 (t, J=5.9 Hz, 1H, NH), 7.29–7.80 (m, 8H, arom.); ^{13}C NMR (125 MHz, CD_3OD) δ 11.7, 16.5, 25.3, 28.3, 28.8, 30.7, 30.9, 36.5, 41.1, 41.8, 42.0, 46.6, 48.5, 53.4, 67.9, 73.6, 79.8, 121.0, 126.2, 126.3, 128.2, 128.8, 142.6, 145.3, 145.4, 158.6, 158.7, 176.9, 178.2; MALDI HRMS calcd for $C_{34}H_{47}N_3O_7Na$ $(M+Na)^+$: 632.3306; found: 632.3313. Anal. calcd for $C_{34}H_{47}N_3O_7$: C 66.97, H 7.77, N 6.89; found: C 66.97, H 7.66, N 6.64 (Fig. 26).

2.3.11. Cbz-(*S*)β²hGln(Trt)-OTMSE (19). Cbz-(*S*)β²hGln(Trt)-OBn[56] (2.45 g, 3.9 mmol) was transformed to compound **19** in three steps. The first transformation involved hydrogenolysis in MeOH for 1.5 h according to GP2 to yield the amino acid (H-β²hGln(Trt)-OH), which without purification was *N*-Cbz protected using the following procedure: to an aqueous solution of the free amino acid in 0.5 M NaOH (1.1 equiv.) at 0 °C was added with continuous stirring BnO_2CCl (1.3 equiv.). The pH was kept basic by periodic addition of 1 M NaOH. After the addition was completed, the reaction mixture was stirred for one additional hour then extracted with AcOEt after adjusting the pH to 3 using 1 M HCl. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a yellow oil. Unreacted BnO_2CCl and BnOH were removed from the mixture by passing the mixture through a short column, and the crude product treated according to GP5. The purification by FC (Et_2O/pentane 1:3) yielded **19** (1.52 g, 61%) as a white solid; mp 135–136 °C; R_f=0.42 (Et_2O/pentane 1:3); $[\alpha]_D$=−6.8 (c=1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3439 (w), 3007 (w), 2956 (w), 1716 (s), 1516 (m), 1490 (m), 1448 (w), 860 (w), 839(w) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.01 (s, 9H, $SiMe_3$), 0.90–0.95 (m, 2H, CH_2Si); 1.56–1.65 (m, 2H, CH_2CH$_2$CON), 2.24–2.27 (m, 2H, CH_2CON), 2.44–2.47 (m, 1H, CHCO), 3.06–3.19 (m, 2H, CH_2N), 4.06–4.11 (m, 2H, OCH_2), 4.95–5.02 (m, 2H, CH_2Ph), 7.14–7.35 (m, 21H, 20 arom., NH), 8.53 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ−1.5, 16.8, 25.0, 33.2, 42.0, 44.9, 62.0, 65.2, 69.2, 126.2, 127.4, 127.6, 127.7, 128.3, 128.5, 137.1, 144.9, 156.1, 171.2, 173.5; MALDI HRMS calcd for $C_{38}H_{44}N_2O_5SiNa$ $(M+Na)^+$: 659.2917; found: 659.2912.

2.3.12. Boc-(*S*)β²hCys(Trt)-(*S*)β²hGln(Trt)-OTMSE (20). Compound **19** (1.00 g, 1.57 mmol) was hydrogenated in THF to give H-(*S*)β²hGln(Trt)-OTMSE according to GP2, then coupled with Boc-(*S*)β²hCys(Trt)-OH[57] (0.75 g, 1.57 mmol) according to GP1a. The crude product was purified by FC (CH_2Cl_2/*i*-PrOH 96:4) to yield **20** (1.22 g, 81%) as an amorphous solid; R_f=0.32 (CH_2Cl_2/*i*-PrOH 96:4); $[\alpha]_D$=+11.4 (c=1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3436 (w), 3026 (w), 1708 (s), 1681 (m), 1492 (s), 1446 (w), 1251 (m), 1164 (m), 1041 (w) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.00 (s, 9H, $SiMe_3$) 0.93 (t, J=8.5 Hz, 2H, CH_2Si), 1.31 (s, 9H, ^{t}Bu), 1.61–1.64 (m, 2H, CH_2CH$_2$CON), 2.01–2.03 (m, 1H,CH*H*S), 2.25–2.28 (m, 2H, CH_2CON), 2.30–2.33 (m, 2H, C*H*HS and CHCO), 2.47–2.50 (m, 1H, CHCO), 2.86–2.90 (m, 2H, CH_2N), 3.11–3.25 (m, 2H, CH_2N), 4.00–4.14 (m, 2H, OCH_2), 6.49 (s, 1H, NH), 7.15–7.30 (m, 30H, arom.), 7.93 (s, 1H, NH), 8.54 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ −1.6, 16.8, 25.1, 28.1, 31.1, 33.1, 39.9, 42.0, 44.3, 45.4; 61.9, 65.8, 69.1, 77.5, 126.2, 126.5, 127.3, 127.8, 128.4, 129.0, 144.3, 144.8, 155.2, 171.1, 171.6, 173.5; MALDI HRMS calcd for $C_{58}H_{67}N_3O_6SSiNa$ $(M+Na)^+$: 984.4418; found: 984.4400.

2.3.13. Boc-(*S*)β²hCys(Trt)-(*S*)β²hGln(Trt)-OH (8). The *C*-terminus of the fully protected dipeptide **20** (1.32 g, 1.37 mmol) was deprotected according to GP2. The crude product was purified by FC (AcOEt/Hexane/AcOH 20:10:0.1) to yield **8** (1.00 g, 85%) as an amorphous solid. R_f=0.10 (AcOEt/hexane/AcOH 20:10:0.1); $[\alpha]_D$=−6.3 (c=0.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3432 (w), 3058 (w), 3009 (w), 2980 (w), 1706 (s), 1667 (m), 1494 (s), 1445 (m), 1366 (w), 1228 (m), 1164 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 9H, ^{t}Bu), 1.62–1.66 (m, 2H, CH_2CH$_2$CON), 2.02–2.05 (m, 1H, CH*H*S), 2.28–2.33 (m, 4H, C*H*HS, CH_2CON, and CHCO), 2.37–2.43 (m, 1H, CHCO), 2.84–2.88 (m, 2H, CH_2N), 3.06–3.10 (m, 1H, CH*H*N), 3.25–3.31 (m, 1H, C*H*HN), 6.50 (t, J=5.8 Hz, 1H, NH), 7.15–7.32 (m, 30H, arom.), 7.89 (t, J=5.8 Hz, 1H, NH), 8.57 (s, 1H, NH), 12.30 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.1, 28.1, 31.1, 33.4, 41.3, 42.1, 44.3, 45.4, 65.8, 69.1, 77.5, 126.2, 126.5, 127.3, 127.8, 128.4, 129.0, 144.3, 144.8, 155.3, 171.3, 171.6, 175.2; MALDI HRMS calcd for $C_{53}H_{55}N_3O_6SNa$ $(M+Na)^+$: 884.3708; found: 884.3704 (Fig. 27).

2.3.14. Cbz-(*S*)β²hTyr(^{t}Bu)-(*S*)β²hAla-OBn (21). H-(*S*)β²hAla-OH[89] was dissolved in toluene, BnOH and *p*TsOH were added and the mixture was heated at reflux for 18 h using a Dean–Stark trap to azeotropically remove H_2O. The reaction mixture was cooled to 25 °C, toluene was evaporated and the residue washed several times with Et_2O. The resulting benzyl ester (0.92 g, 2.52 mmol) was coupled with Cbz-(*S*)β²hTyr(^{t}Bu)-OH[55] (0.97 g, 2.52 mmol) according to GP1a. FC (AcOEt/hexane 1:1) yielded **21** (1.17 g, 83%) as a white solid; mp 74–76 °C; R_f=0.18 (AcOEt/hexane 1:1); $[\alpha]_D$=+14.8 (c=0.54, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3443 (w), 2980 (m), 1719 (s), 1667 (m), 1507 (s), 1456 (m), 1367 (m), 1160 (m), 894 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.96 (d, J=7.1 Hz, 3H, Me), 1.28 (s, 9H, ^{t}Bu), 2.54 (q, J=7.0 Hz, 1H, CHCO), 2.66–2.93 (m, 3H, $CHCH_2Ph$), 3.11–3.29 (m, 4H, 2×CH_2N), 5.05 (s, 2H, OCH_2Ph), 5.07 (AB, J=12.6 Hz, 2H, OCH_2Ph), 6.85 (d, J=8.4 Hz, 2H, arom.), 7.04 (d, J=8.4 Hz, 2H, arom.), 7.26–7.34 (m, 10H, arom.); ^{13}C NMR (100 MHz, CD_3OD) δ 15.2, 29.2, 36.5, 40.8, 42.9, 44.1, 50.4, 67.4, 67.5, 79.4, 125.2, 128.8, 129.0, 129.1, 129.2, 129.5, 129.6, 130.4, 135.5, 137.6, 138.3, 155.0, 158.8, 176.0; MALDI HRMS calcd for $C_{33}H_{40}N_2O_6Na$ $(M+Na)^+$ 583.2779, found 583.2785. Anal. calcd for $C_{33}H_{40}N_2O_6$: C 70.69, H 7.19, N 5.00; found: C 70.52, H 7.34, N 5.14.

2.3.15. Fmoc-(*S*)β²hTyr(^{t}Bu)-(*S*)β²hAla-OH (9). The dipeptide derivative **21** was hydrogenated according to

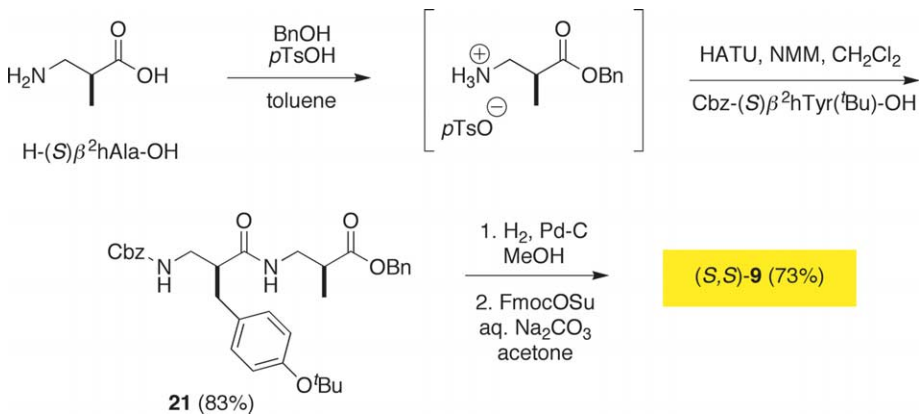

Figure 28. Preparation of Fmoc-(*S*)β^{2}hTyr(^{t}Bu)-(*S*)β^{2}hAla-OH (**8**).

GP2 and Fmoc-protected according to GP4. The crude peptide was purified by FC (AcOEt/hexane/AcOH 10:10:0.1) to give **9** (0.72 g, 73%) as a white solid; mp 143–144 °C; R_f=0.16 (AcOEt/hexane/AcOH 10:10:1); $[\alpha]_D$=+7.3 (*c*=0.55, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3442 (w), 3005 (m), 2980 (m), 1717 (s), 1683 (m), 1508 (s), 1467 (m), 1450 (m), 1368 (m), 1157 (m), 1082 (w), 891 (m) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.98 (d, *J*=7.1 Hz, 3H, Me), 1.29 (s, 9H, ^{t}Bu), 2.45 (q, *J*=7.1 Hz, 1H, CHMe), 2.67–2.80 (m, 3H, C*H*HN, CH_2Ph), 3.15 (dd, *J*=7.0, 13.4 Hz, 1H, CH), 3.26 (m, 3H, CH_2N, CH*H*N), 4.19 (t, *J*=6.8 Hz, 1H, C*H*CH_2O), 4.34 (d, *J*=6.9 Hz, 2H, CHCH_2O), 6.87 (d, *J*=8.5 Hz, 2H, arom.), 7.07 (d, *J*=8.4 Hz, 2H, arom.), 7.29 (m, 2H, arom.), 7.37 (m, 2H, arom.), 7.63 (d, *J*=7.5 Hz, 2H, arom.), 7.77 (m, 2H, arom.); ^{13}C NMR (100 MHz, CD_3OD) δ 15.4, 29.2, 36.5, 40.6, 43.0, 44.2, 48.5, 50.4, 67.8, 79.5, 121.0, 125.3, 126.2, 128.2, 128.8, 130.5, 135.7, 142.7, 145.4, 155.0, 158.9, 176.1, 178.4; MALDI HRMS calcd for $C_{33}H_{38}N_2O_6Na$ $(M+Na)^+$: 581.2622, found: 581.2629. Anal. calcd for $C_{33}H_{38}N_2O_6$: C 70.95, H 6.86, N 5.01; found: C 70.99, H 6.87, N 4.89 (Fig. 28).

2.3.16. Cbz-(*R*,*S*)β^{2}hThr(^{t}Bu)-(*R*)β^{2}hSer(^{t}Bu)-OBn (22). Cbz-(*R*,*S*)β^{2}hThr(^{t}Bu)-OH[57] (0.70 g, 2.16 mmol) and H-(*R*)β^{2}hSer(^{t}Bu)-OBn[57] (0.6 g, 2.27 mmol) were coupled according to GP1a. The crude product was purified by FC (AcOEt/hexane 3:4) to obtain 0.97 g (79%) of **22** as an amorphous solid. R_f=0.35 (AcOEt/hexane 3:4); $[\alpha]_D$=+27.6 (*c*=0.41, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3323 (w), 2972 (m), 2925 (w), 1726 (s), 1653 (m), 1534 (m), 1457 (m), 1233 (m), 1193 (m), 1091 (w) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.97 (d, *J*=4.8 Hz, 3H, Me); 1.05 (s, 9H, ^{t}Bu), 1.10 (s, 9H, ^{t}Bu), 2.36–2.40 (m, 1H, CHCO), 2.74–2.79 (m, 1H, CHCO), 3.10–3.27 (m, 3H, CH_2N, OCH*H*), 3.33–3.37 (m, 1H, OC*H*H), 3.44–3.51 (m, 2H, CH_2N), 3.68–3.70 (m, 1H, OCH), 4.95–5.17 (m, 4H, 2×CH_2Ph), 7.03 (t, *J*=4.6 Hz, 1H, NH) 7.27–7.37 (m, 10H, arom.); 7.72 (t, *J*=4.6 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.1, 27.0, 28.2, 37.3, 39.7, 46.1, 52.6, 60.3, 65.0, 65.2, 66.2, 72.0, 73.2, 127.4, 127.6, 127.6, 127.8, 128.2, 128.2, 136.1, 137.2, 155.9, 171.7, 172.2; MALDI HRMS calcd for $C_{32}H_{46}N_2O_7Na$: 593.3203; found: 593.3197.

2.3.17. Fmoc-(*R*,*S*)β^{2}hThr(^{t}Bu)-(*R*)β^{2}hSer(^{t}Bu)-OH (10). The fully protected dipeptide **22** (0.9 g, 1.58 mmol) was hydrogenolyzed in MeOH for 16 h according to GP2. The resulting amino acid was Fmoc-protected according to GP4. The crude product was purified by FC (AcOEt/Hexane/AcOH 10:10:0.1) to obtain 0.73 g (81%) of **22** as colorless oil. R_f=0.20 (AcOEt/hexane/AcOH 10:10:0.1). $[\alpha]_D$=+12.7 (*c*=0.52, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3312 (w), 2971 (m), 2925 (w), 1718 (s), 1653 (m), 1539 (m), 1450 (m), 1363 (m), 1249 (m), 1193 (m), 1091 (w) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00 (*d*, *J*=4.8 Hz, 3H, Me), 1.08 (s, 9H, ^{t}Bu), 1.12 (s, 9H, ^{t}Bu), 2.36–2.43 (m, 1H, CHCO), 2.53–2.60 (m, 1H, CHCO), 3.12–3.22 (m, 3H, CH_2N, OCH*H*), 3.35–3.41 (m, 1H, OC*H*H), 3.45 (d, *J*=4.6 Hz, 2H, CH_2N); 3.69–3.74 (m, 1H, OCH), 4.18–4.27 (m, 3H, OCH_2CH), 7.12 (t, *J*=4.5 Hz, 1H, NH), 7.30–7.34 (m, 2H, arom.), 7.39–7.43 (m, 2H, arom.), 7.62 (t, *J*=4.5 Hz, 1H, NH), 7.67 (d, *J*=5.8 Hz, 2H, arom.), 7.88 (d, *J*=6.1 Hz, 2H, arom.), 12.22 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.1, 27.1, 28.1, 37.4, 39.9, 46.0, 46.6, 52.4, 60.4, 65.4, 66.3, 72.2, 73.3, 120.0, 125.1, 126.9, 127.5, 140.6, 143.8, 155.9, 171.6, 173.8; MALDI HRMS calcd for $C_{32}H_{44}N_2O_7Na$: 591.3047; found: 591.3041 (Fig. 29).

2.3.18. Cbz-(*S*)β^{2}hGlu(O^{t}Bu)-OTMSE (23). Cbz-(*S*)β^{2}hGlu(O^{t}Bu)-OH[56] (0.9 g, 2.56 mmol) was treated according to GP5. Purification of the crude product by FC (Et_2O/pentane 1:1) gave **23** (1.06 g, 92%) as a colorless oil. R_f=0.43 (Et_2O/pentane 1:1). $[\alpha]_D$=+4.7 (*c*=0.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3446 (w), 3025 (w), 2954 (w), 1718 (s), 1508 (m), 1451 (w), 1364 (w), 1246 (m), 1148 (m), 1056

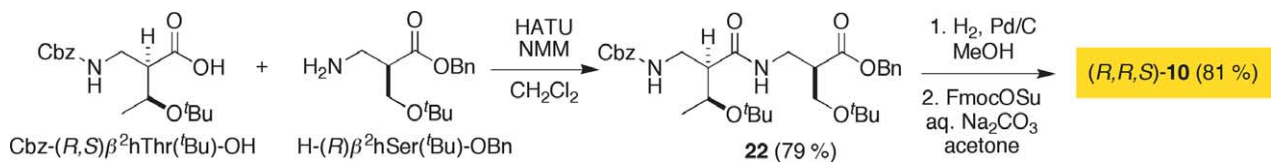

Figure 29. Preparation of Fmoc-(*R*,*S*)β^{2}hThr(^{t}Bu)-(*R*)β^{2}hSer(^{t}Bu)-OH (**10**).

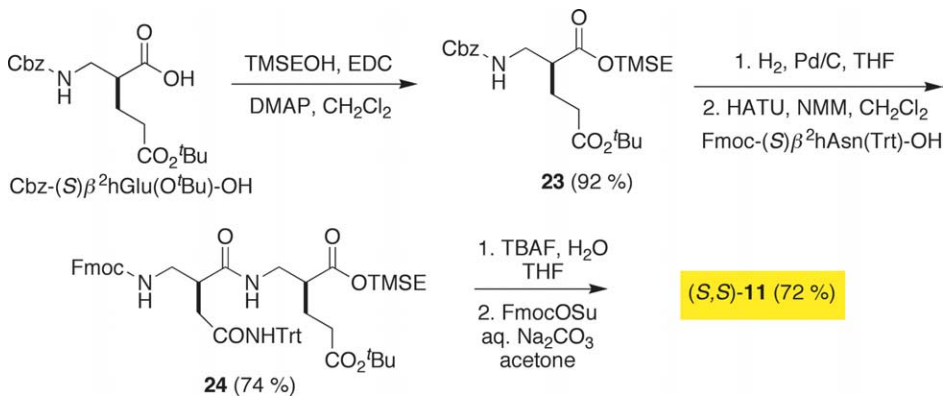

Figure 30. Preparation of Fmoc-(*S*)β^{2}hAsn(Trt)-(*S*)β^{2}hGlu(O^{t}Bu)-OH (**11**).

(w), 856 (w) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.02 (s, 9H, SiMe$_3$), 0.91–0.95 (m, 2H, CH$_2$Si), 1.39 (s, 9H, ^{t}Bu), 1.62–1.73 (m, 2H, C*H*$_2$CH$_2$CO), 2.11–2.26 (m, 2H, CH$_2$CO), 2.24–2.27 (m, 2H, CH$_2$CON), 2.51–2.55 (m, 1H, CHCO), 3.07–3.23 (m, 2H, CH$_2$N), 4.07–4.11 (m, 2H, OCH$_2$), 5.00 (s, 2H, CH$_2$Ph), 7.28–7.40 (m, 6H, 5 arom., NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ −1.6, 16.7, 24.2, 27.6, 32.1, 41.7, 44.4, 62.0, 65.1, 79.6, 127.5, 127.7, 128.2, 137.0, 156.0, 171.4, 173.2; MALDI HRMS calcd for $C_{23}H_{37}NO_6SiNa$ (M+Na)$^+$: 474.2388; found: 474.2382.

2.3.19. Fmoc-(*S*)β^{2}hAsn(Trt)-(*S*)β^{2}hGlu(O^{t}Bu)-OTMSE (24). Compound **23** (0.93 g, 2.06 mmol) was hydrogenated according to GP2 in THF. Coupling with Fmoc-(*S*)β^{2}hAsn(Trt)-OH[56] (1.26 g, 2.06 mmol) according to GP1a give a crude product, which was purified by FC (AcOEt/hexane 1:1) to yield **24** (1.39 g, 74%) as an amorphous solid. R_f=0.23 (AcOEt/hexane 1:1). $[\alpha]_D$=−16.0 (*c*=0.43, CHCl$_3$); IR (CHCl$_3$) ν_{max} 3436 (w), 3019 (w), 1716 (s), 1677 (m), 1504 (m), 1445 (w), 1248 (w), 1154 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.01 (s, 9H, SiMe$_3$), 0.89–0.94 (m, 2H, CH$_2$Si), 1.34 (s, 9H, ^{t}Bu), 1.64–171 (m, 2H, C*H*$_2$CH$_2$CO), 2.07–2.21 (m, 2H, CH$_2$CO), 2.27–2.33 (m, 1H, CHCO), 2.52–2.59 (m, 2H, CH*H*CON and CHCO), 2.71–2.75 (m, 1H, C*H*HCON), 2.99–3.05 (m, 1H, CH*H*N), 3.06–3.08 (m, 2H, CH$_2$N), 3.33–3.39 (m, 1H, C*H*HN), 4.03–4.13 (m, 2H, OCH$_2$), 4.18–4.29 (m, 3H, OCH$_2$CH), 7.13–7.41 (m, 20H, 19 arom., NH), 7.66 (d, *J*=7.5 Hz, 2H, arom.), 7.87 (d, *J*=7.6 Hz, 2H, arom.), 7.89 (s, 1H, NH), 8.52 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ −1.6, 16.7, 24.1, 27.6, 32.0, 33.1, 36.0, 40.1, 42.3, 42.4, 43.9, 46.6, 62.0, 65.4, 69.2, 79.5, 119.9, 121.3, 125.1, 126.9, 127.2, 127.3, 128.4, 140.6, 143.8, 144.8, 155.9, 170.1, 171.5, 172.7, 173.4; MALDI HRMS calcd for $C_{54}H_{63}N_3O_8SiNa$ (M+Na)$^+$: 932.4282; found: 932.4277.

2.3.20. Fmoc-(*S*)β^{2}hAsn(Trt)-(*S*)β^{2}hGlu(O^{t}Bu)-OH (11). The *C*-terminus of dipeptide derivative **24** (1.15 g, 1.27 mmol) was deprotected according to GP6; however, considerable amounts of Fmoc-deprotection took place during the reaction. For this reason, the crude reaction mixture was evaporated under reduced pressure and treated in situ with FmocOSu (1.2 equiv.) according to GP4. The crude product was purified by FC (AcOEt/CH$_2$Cl$_2$ 1:7→1:3) to give **11** (0.74 g, 72%) as an amorphous solid. R_f=0.23 (AcOEt/hexane 1:1); $[\alpha]_D$=−11.2 (*c*=0.75, CHCl$_3$); IR (CHCl$_3$) ν_{max} 3426 (w), 3343 (w), 3015 (w), 2985 (w), 1718 (s), 1677 (m), 1508 (m), 1492 (m), 1446 (w), 1369 (w), 1246 (m), 1154 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (s, 9H, ^{t}Bu), 1.62–1.74 (m, 2H, C*H*$_2$CH$_2$CO), 2.11–2.25 (m, 2H, CH$_2$CO), 2.28–2.32 (m, 1H, CHCO), 2.43–2.48 (m, 1H, CHCO), 2.55–2.60 (m, 1H, CH*H*CON), 2.72–2.78 (m, 1H, C*H*HCON), 2.99–3.06 (m, 1H, CH*H*N), 3.07–3.14 (m, 2H, CH$_2$N), 3.35–3.41 (m, 1H, C*H*HN), 4.19–4.29 (m, 3H, OCH$_2$CH), 7.13–7.42 (m, 21H, 19 arom., 2×NH), 7.68 (d, *J*=6.0 Hz, 2H, arom.), 7.88 (d, *J*=5.8 Hz, 2H, arom.),

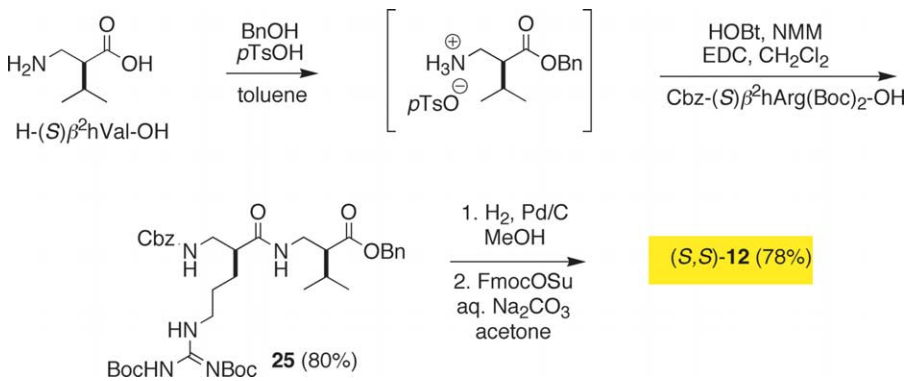

Figure 31. Preparation of Fmoc-(*S*)β^{2}hArg(Boc)$_2$-(*S*)β^{2}hVal-OH (**8**).

8.53 (s, 1H, NH), 12.30 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.2, 27.6, 32.2, 36.1, 40.0, 42.4, 42.4, 43.8, 46.6, 65.4, 69.2, 79.5, 120.0, 125.1, 126.2, 127.0, 127.3, 127.5, 128.4, 140.6, 143.8, 144.8, 156.0, 170.1, 171.6, 172.7, 175.0; MALDI HRMS calcd for $C_{49}H_{51}N_3O_8Na$ $(M+Na)^+$: 832.3598; found: 832.3568 (Fig. 30).

2.3.21. Cbz-(*S*)β^{2}hArg(Boc)$_2$-(*S*)β^{2}hVal-OBn (25). H-(*S*)β^{2}hVal-OH[89] was dissolved in toluene, BnOH and *p*TsOH were added and mixture was refluxed for 18 h using a Dean–Stark trap to azeotropically remove H_2O. The reaction mixture was cooled to 25 °C, and the toluene removed under reduced pressure. The crude product was purified by recrystallization from toluene/hexane to give the *p*TsOH-salt of H-(*S*)β^{2}hVal-OBn (0.72 g, 1.82 mmol) which was coupled with Cbz-(*S*)β^{2}hArg(Boc)$_2$-OH[48] (0.95 g, 1.82 mmol) according to GP1b. FC (AcOEt/hexane 3:7) yielded **25** (1.06 g, 80%) as white solid; mp 45–47 °C; R_f=0.22 (AcOEt/hexane 1:1); $[\alpha]_D$=+16.8 (c=0.37, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3446 (w), 3328 (w), 3007 (m), 2974 (m), 2933 (w), 1719 (s), 1636 (s), 1615 (s), 1574 (m), 1509 (m), 1418 (m), 1369 (m), 1332 (m), 1282 (m), 1136 (s), 1051 (m), 1027 (m), 872(w), 648(w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J=6.8 Hz, 3H, Me), 0.94 (d, J=6.8 Hz, 3H, Me), 1.41 (m, 2H, CH_2), 1.47 (s, 9H, ^{t}Bu), 1.49 (s, 9H, ^{t}Bu), 1.55 (m, 1H, C*H*H), 1.78 (m, 1H, CH*H*), 1.93 (m, 1H, C*H*(Me)$_2$), 2.47 (m, 1H, CHCO), 2.50 (m, 1H, CHCO), 3.21–3.38 (m, 5H, 2×CH_2 and C*H*H), 3.60 (m, 1H, CH*H*), 5.04 (d, J=12.2 Hz, 1H, OC*H*HPh), 5.08 (s, 2H, OCH_2Ph), 5.15 (d, J=12.2 Hz, 1H, OCH*H*Ph), 5.32 (br s, 1H, NH), 6.30 (br s, 1H, NH), 7.28–7.52 (m, 10H, arom.), 8.32 (br s, 1H, NH), 11.48 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.3, 26.6, 27.1, 28.1, 28.3, 28.9, 31.3, 38.8, 40.1, 42.8, 45.8, 51.9, 66.3, 66.6, 79.3, 83.2, 128.0, 128.1, 128.4, 128.5, 128.6, 135.8, 136.6, 153.3, 156.3, 156.6, 163.4, 174.2, 174.4; MALDI HRMS calcd for $C_{38}H_{55}N_5O_9Na$ $(M+Na)^+$: 748.3892; found: 748.3901. Anal. calcd for $C_{38}H_{55}N_5O_9$: C 62.88, H 7.64, N 9.65; found: C 62.92, H 7.68, N 9.51.

2.3.22. Fmoc-(*S*)β^{2}hArg(Boc)$_2$-(*S*)β^{2}hVal-OH (12). Dipeptide derivative **25** (1.06 g) was hydrogenated according to GP2. Subsequent Fmoc-protection according to GP4 and FC (AcOEt/hexane 1:1→1:0) yielded **12** (0.99 g, 78%) as white solid; mp 93–96 °C; R_f=0.46 (AcOEt/hexane/AcOH 10:10:1); $[\alpha]_D$=+29.3 (c=0.91, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3446 (w), 3326 (w), 3007 (m), 2972 (m), 2934 (m), 1719 (s), 1643 (s), 1615 (s), 1513 (m), 1450 (m), 1416 (m), 1369 (m), 1333 (m), 1282 (m), 1138 (s), 1053 (m), 872 (w), 650 (w) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (d, J=6.8 Hz, 3H, Me), 0.91 (d, J=6.8 Hz, 3H, Me), 1.35–1.61 (m, 4H, CH_2CH_2), 1.39 (s, 9H, ^{t}Bu), 1.46 (s, 9H, ^{t}Bu), 1.79 (m, 1H, C*H*(Me)$_2$), 2.30 (m, 1H, CHCO), 2.38 (br s, 1H, NH), 2.49 (m, 1H, CH), 2.99–3.10 (m, 3H, C*H*H, CH_2), 3.23 (m, 2H, CH_2), 3.35 (m, 1H, CH*H*), 4.17–4.28 (m, 3H, $CHCH_2O$), 7.13–7.36 (m, 3H, 2 arom., NH), 7.41 (t, J=7.4 Hz, 2H, arom.), 7.68 (d, J=7.4 Hz, 2H, arom.), 7.88 (d, J=7.5 Hz, 2H, arom.), 7.94 (br s, 1H, NH), 8.24 (br s, 1H, NH), 11.48 (br s, 1H, COOH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.5, 19.7, 20.2, 20.9, 26.1, 26.2, 26.8, 27.5, 27.9, 28.0, 31.2, 38.7, 42.6, 78.0, 82.8, 109.6, 119.9, 121.3, 127.2, 128.8, 137.3, 139.3, 142.5, 152.0, 155.1, 163.0, 173.1, 173.2; MALDI HRMS calcd for $C_{38}H_{53}N_5O_9Na$ $(M+Na)^+$: 746.3736, found: 746.3728. Anal. calcd for $C_{38}H_{53}N_5O_9$: C 63.05, H 7.38, N 9.67; found: C 63.17, H 7.40, N 9.44 (Fig. 31).

2.4. Solid-phase synthesis of 2 and 3 and their ligation to eicosapeptide 1

2.4.1. H-β^{2}hGly-(*S*)β^{2}hTrp-(*S*)β^{2}hArg-(*S*)β^{2}hVal-(*S*)β^{2}hAsn-(*S*)β^{2}hGlu-(*R*,*S*)β^{2}hThr-(*R*)β^{2}hSer-(*S*)β^{2}hTyr-(*S*)β^{2}hAla-*S*-Ethylpropionate (2). The loading of the sulfamylbutyryl resin was performed according to a procedure found in the literature.[90] A solution of Fmoc-(*S*)β^{2}hTyr(^{t}Bu)-(*S*)β^{2}hAla-OH (**9**) (502 mg, 0.9 mmol), DIPCDI (0.5 mL, 3.6 mmol) and 1-MeIm (0.2 mL, 3.6 mmol) in CH_2Cl_2/DMF (4:1) was added to the resin (205 mg, 0.225 mmol) that had been preswelled in CH_2Cl_2 for 1 h. The suspension was gently stirred using Ar bubbling for 18 h at 25 °C. Consequently, the resin was filtered off, washed with DMF (4 mL, 4×1 min), CH_2Cl_2 (4 mL, 4×1 min), and dried under h.v. overnight. Resin loading was measured using the absorbance of the benzofulvene–piperidine adduct according to Schreiber and Seebach[80] and was determined to be 0.66 mmol/g, which corresponds to 0.133 mmol of **9**. The Fmoc group was removed using 20% piperidine in DMF (4 mL, 4×10 min) under Ar bubbling. After filtration, the resin was washed with DMF (4mL, 4×1 min). Solid phase synthesis was continued by sequential incorporation of *N*-Fmoc-protected dipeptides or *N*-Fmoc protected β^2-homoamino acids building blocks (**10**, **11**, **12**, Fmoc-(*S*)β^{2}hTrp(Boc)-OH, Boc-β^{2}hGly-OH). For each coupling step, the resin was treated with a solution of Fmoc-protected building block (3 equiv.), HATU (2.9 equiv.) and DIPEA (6 equiv.) in DMF. The suspension was then gently stirred using Ar bubbling for 45–60 min. Monitoring of the coupling reaction was performed with TNBS.[91] In the case of a positive TNBS test (indicating incomplete coupling), the suspension was filtrated, and treated again with a freshly prepared solution of the same *N*-Fmoc protected building block (2 equiv.) and coupling reagents. The resin was then filtered off and washed with DMF (4 mL, 4×1 min) prior to the subsequent Fmoc deprotection step using 20% piperidine in DMF (4 mL, 4×10 min). After filtration, the resin was washed with DMF (4 mL, 3×1 min) and solid-phase synthesis was continued by sequential incorporation of *N*-Fmoc protected building blocks. For each coupling step, the resin was treated as described above. After the last coupling the resin was filtered off, washed with DMF (4 mL, 4×1 min), CH_2Cl_2 (4 mL, 4×1 min), and activated for the cleavage according to Ingenito et al.[68] After swelling the resin in THF (4 mL), a solution of TMS–CHN_2 (2 M in hexane) was added, and the suspension was gently stirred using Ar bubbling for 2 h. Subsequently, the resin was filtered off, washed with THF (4 mL, 4×1 min) and DMF (4 mL, 4×1 min), to prepare it for the displacement reaction. The activated *N*-acylsulfonamide resin was swollen in DMF and filtered off. A solution of ethyl-3-mercaptopropionate (0.86 mL, 6.65 mmol) and sodium thiophenolate (9 mg, 0.066 mmol) in DMF (5 mL) was added and the resulting mixture heated at 80 °C for 24 h. Removal of side-chain protecting groups was accomplished in solution by treating the protected β-peptide thioester with a solution of TFA/H_2O/TIS

(95/2.5/2.5). The solvents were removed under reduced pressure and the precipitate, which formed upon addition of cold Et_2O to the oily residue, was collected by centrifugation. Purification by RP-HPLC (10–50% B in 50 min, C_8) yielded **2** (10 mg, 10%) as a colorless fluffy solid. Anal. RP-HPLC: t_R 28.34 (10–40% B in 50 min, 40–95% B in 10 min C_8). CD (0.2 mM in MeOH, 20 °C): −11387.9 (219.5 nm); 0 (210 nm); +9643.96 (204 nm); CD (0.2 mM in MeOH, −10 °C): −17955.4 (216 nm); 0 (206.5 nm);+1895.45 (205 nm). ESI MS (positive mode): 1437.9 (15, $(M+H)^+$), 730.5 (40, $(M+Na+H)^{2+}$), 719.7 (100, $(M+2H)^{2+}$), 480.0 (32, $(M+3H)^{3+}$).

2.4.2. H-(*S*)β²hCys-(*S*)β²hGln-(*S*,*S*)β²hIle-(*S*)β²hLys-(*S*)β²hHis-(*S*)β²hLeu-(*S*)β²hAsp-(*S*)β²hMet-(*S*)β²hPhe-(*S*)β²hPro-OH (3). Esterification of the Wang resin was performed according to Chan and White.[71]To a soln. of Fmoc-(*S*)β²hPhe-(*S*)β²hPro-OH (**4**) (461 mg, 0.9 mmol) in dry CH_2Cl_2 (4 mL) was added 1-MeIm (0.05 mL, 0.675 mmol) followed by MSNT (267 mg, 0.90 mmol). The mixture was stirred until all MSNT had dissolved. The solution was then transferred to a vessel containing the preswelled resin (200 mg, 0.18 mmol), and mixed under Ar bubbling for 1 h at 25 °C. The resin was then filtered off, washed with DMF (4 mL, 4×1 min), CH_2Cl_2 (4 mL, 4×1min), and dried under h.v. overnight. The loading of the resin was determined by measuring the absorbance of the benzofulvene–piperidine adduct according to Schreiber and Seebach[80] and was found to be 0.61 mmol/g (68%), corresponding to 0.122 mmol of anchored **4**. The unreacted hydroxy groups were capped using Ac_2O (0.12 mL, 1.22 mmol) in DMF (4 mL) and DMAP (5 mg, 0.04 mmol, added in 0.5 mL DMF) for 30 min. The Fmoc group was removed using 20% piperidine in DMF (4 mL, 4×10 min) under Ar bubbling. After filtration, the resin was washed with DMF (4 mL, 4×1 min). Solid-phase synthesis was continued by sequential incorporation of *N*-Fmoc-protected dipeptides building blocks (**5**, **6**, **7**, **8**). For each coupling step, the resin was treated with a solution of Fmoc building block (3 equiv.), HATU (2.9 equiv.) and DIPEA (6 equiv.) in DMF. The suspension was then gently stirred using Ar bubbling for 45–60 min. Monitoring of the coupling reaction was performed with TNBS.[91] In the case of a positive TNBS test (indicating incomplete coupling), the suspension was filtered, and treated again with a freshly prepared solution of the same *N*-Fmoc protected building blocks (2 equiv.) and coupling reagents. The resin was then filtered off and washed with DMF (4 mL, 4×1 min) prior to the subsequent Fmoc deprotection step using 20% piperidine in DMF (4 mL, 4×10 min). After filtration, the resin was washed with DMF (4 mL, 3×1 min) and solid-phase synthesis was continued by sequential incorporation of *N*-Fmoc protected building block. For each coupling step, the resin was treated as described above. After the last coupling the resin was filtered off, washed with DMF (4 mL, 4×1 min), CH_2Cl_2 (4 mL, 4×1 min), MeOH (4 mL, 4×1 min) and dried under h.v. for 24 h. The dry peptide resin was treated for 2 h with a TFA/H_2-O/EDT/TIS (94:2.5:2.5:1) solution (10 mL). The resin was removed by filtration, washed with TFA, and the organic phase containing the peptide was concentrated under reduced pressure. The precipitate, which formed upon addition of cold Et_2O to the oily residue, was collected by centrifugation. The crude peptide was purified by RP-HPLC (15–50% B in 40 min, 50–95% B in 20 min, C_8) to yield the TFA salt of **3** (65 mg, 38%) as a colorless fluffy solid. Homogeneity >95% (RP-HPLC). Anal. RP-HPLC: t_R 28.44 (10–40% B in 40 min, 40–95% B in 5 min, C_8). CD (0.2 mM in MeOH, 20 °C): −13128.5 (219 nm); 0 (207.5 nm);+14495.7 (200.5 nm); CD (0.2 mM in MeOH, −10 °C): −15643.1 (218.5 nm); 0 (206 nm);+16894.2 (199.5 nm). ESI HRMS (positive mode): 708.3576 (100, $(M+2Na)^{2+}$, $C_{65}H_{106}N_{14}Na_2O_{14}S_2^{2+}$; calcd 708.3625), 697.3718 (70, $(M+H+Na)^{2+}$, $C_{65}H_{107}N_{14}NaO_{14}S_2^{2+}$; calcd 697.3715), 686.3795 (10, $(M+2H)^{2+}$, $C_{65}H_{108}N_{14}O_{14}S_2^{2+}$; calcd 686.3805).

2.4.3. H-β²hGly-(*S*)β²hTrp-(*S*)β²hArg-(*S*)β²hVal-(*S*)β²hAsn-(*S*)β²hGlu-(*R*,*S*)β²hThr-(*R*)β²hSer-(*S*)β²hTyr-(*S*)β²hAla-(*S*)β²hCys-(*S*)β²hGln-(*S*,*S*)β²hIle-(*S*)β²hLys-(*S*)β²hHis-(*S*)β²hLeu-(*S*)β²hAsp-(*S*)β²hMet-(*S*)β²Phe-(*S*)β²hPro-OH (1). β²-Peptide fragment **3** (5.2 mg, 3.1 μmol) and the *C*-terminal thioester β²-peptide **2** (4.8 mg, 3.1 μmol) were ligated in an aqueous buffer (100 mM phosphate, pH 7.5) (3 mL) containing thiophenol (4% v/v). The ligation reaction was performed at 25 °C and monitored using anal. RP-HPLC (see Fig. 21 above). Following completion of the ligation, the reaction mixture was diluted with H_2O (1 mL) containing 0.1% TFA and purified by preparative RP-HPLC (10–50% B in 40 min, 50–99% B in 10 min, C_8) to yield the TFA salt of **1** (5.12 mg, 54%) as a colorless fluffy solid. Anal. RP-HPLC: t_R 36.82 (10–50% B in 40 min, 50–99% B in 10 min, C_8). CD (0.2 mM in MeOH): −16849.8 (214 nm); 0 (200 nm); CD (0.2 mM in H_2O, pH 7): −1863.85 (220 nm); 0 (214.5 nm);+15824.65 (201.5 nm). MALDI HRMS: 2697.428 (10, $(M+Na)^+$, $C_{127}H_{199}N_{29}NaO_{30}S_2^+$; calcd 2697.428), 2675.442 (60, $(M+H)^+$, $C_{127}H_{199}N_{29}O_{30}S_2^+$; calcd 2675.445).

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Site specific biotinylation of the human aldo/keto reductase AKR1A1 for immobilization

Michael P. O. Richter, Kai Holland-Nell and Annette G. Beck-Sickinger*

Faculty of Biosciences, Institute of Biochemistry, Pharmacy and Psychology, University of Leipzig, Brüderstr. 34, D-04103 Leipzig, Germany

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Dedicated to Professor Seebach on the Occasion of Tetrahedron Prize for Creativity in Organic Chemistry

Abstract—New strategies for the specific monolabelling of enzymes play a key role in the development of artificial proteins. Especially for the emerging research field of nanobiotechnology and bioelectronics artificial monofunctionalized redoxproteins are of great interest. The human AKR1A1, an enzyme of the aldo/keto reductase superfamily, has been chosen as subject for the synthesis of an artificially mono biotinylated redoxprotein in order to selectively immobilize this enzyme for bioelectronic applications. To produce monofunctionalized enzyme we applied the strategy of Expressed Protein Ligation (EPL) in combination with solid phase peptide synthesis (SPPS). Accordingly, we used the IMPACT®-system and cloned the aldo/keto-reductase as fusion protein with an additional intein/chitin binding domain. Through intein mediated splicing we could produce the C-terminal thioester of the aldo/keto-reductase, which maintained its biological activity. Then, the thioester was coupled to Cys-Lys(Ahx-Ahx-biotin)-amide by Native Chemical Ligation, which led to mono-biotinylated protein. The enzyme activity was proven to be intact as shown by various kinetic investigations. Immobilization was performed on avidin coated silica microspheres. Accordingly, for the first time selectively modified AKR1A1 has been immobilized.

1. Introduction

The synthesis of monolabelled artificial redoxenzymes, which carry an appropriate single label that mediates specific interaction or unique molecular characteristics enables the engineering of macromolecules with new chemical properties and the construction of highly defined biomolecular monolayers on different surfaces. Artificially monolabelled oxidoreductases could have a great impact for a new generation of various biosensors, where immobilization problems might be circumvented by attaching a molecular immobilization tag at a unique site in the enzyme.[1–3] The major drawback of common immobilization methods for proteins, however, is the lack of any specific site directed position of the enzyme on a surface. This leads to randomly orientated enzymes, hindrance of the accessibility for the substrate and the cosubstrate to the active site of the enzyme and limited activity in consequence.[4–6] The aim of this work was to selectively label the oxidoreductase AKR1A1 at its C-terminus in order to allow specific immobilization. Enzymes modified at a unique position should keep their biological function much better than multilabelled ones and also favour a non random orientation of the active sites on the surface. The human AKR1A1, a member of the aldo/keto reductase superfamily, is an ideal enzyme for biosensor and nanobiolelectronic applications. It catalyzes the NADPH dependent reduction of a broad range of aliphatic and aromatic aldehydes to the corresponding alcohols[7] (Fig. 1). Accordingly, applications for the immobilized AKR1A1 have been suggested like the detection of ketones and aldehydes in analytical samples, or NADPH in sera or for the use in biofuel cells.[8,9]

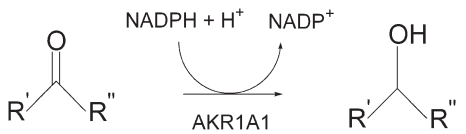

Figure 1. Scheme for the AKR1A1 catalyzed reaction. The enzyme catalyzes the NADPH dependent conversion of various aliphatic and aromatic ketones and aldehydes to the corresponding alcohols. For the enzymatic assay 4-nitrobenzaldehyde was used as substrate.

The enzyme is a monomer of 324 amino acids and has a well characterized $(\alpha/\beta)_8$—barrel structure;[10–12] (http://www.rcsb.org/pdb/; pdb: 2ALR). Monomeric proteins are of great interest for specific immobilization approaches because they do not need to assemble as multimers to maintain their activity. A single covalent attachment of every subunit on a

Keywords: Expressed protein ligation; Site specific mono labeling of proteins; Artificial redoxproteins; Aldo/keto reductase.
* Corresponding author. Tel.: +49-341-97-36-900; fax: +49-341-97-36-909; e-mail address: beck-sickinger@uni-leipzig.de

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certain surface in multimers might lead to a decrease in structural flexibility of the subunits and thereby to a great loss of activity. The X-ray structure of the human AKR1A1 clearly shows that the C-terminus of this enzyme is located in an optimal way for immobilization purposes. It is positioned backside to the active center and although it is said to be involved in determining the substrate specificity[13] it is ideal to attach a molecular spacer to the C-terminus because this favors an orientation of the active site towards the reaction mixture after immobilization (Fig. 2).

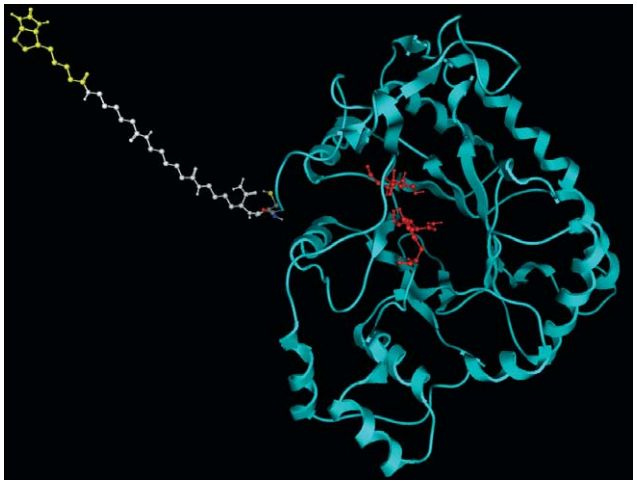

Figure 2. Model of the AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2 construct derived from the crystal structure of the human AKR1A1 (pdb: 2ALR). The blue colored part depicts the unmodified enzyme and the red highlighted residues indicate four key amino acids of the active site of the enzyme. On the left side the artificial peptide is shown (Lys, Ahx white, biotin yellow; the N-terminal cysteine residue is atom type coded), which was fused to the C-terminus of the oxidoreductase.

The aim of this work was to modify this enzyme at the C-terminus with a peptide by applying the Expressed Protein Ligation (EPL) to introduce a single specificity mediating immobilization tag.[14] By using this technique α-thioesters of proteins or peptides react with N-terminally Cys containing peptides to form a native amide bond at this site according to the reaction described by T. Wieland et al.[15] for amino acids. This method termed Native Chemical Ligation (NCL) was further applied to larger peptides by Dawson et al.[16,17] and recently by Muir et al. to proteins.[18] We used the IMPACT®-system to create a C-terminally activated enzyme as educt for the EPL to react with a peptide spacer molecule that was synthesized by solid phase peptide synthesis (SPPS). Expressed protein ligation, which is also known as intein-mediated protein ligation (IPL), is an extension of the NCL method. A recombinant C^{α}-thioester reacts with a chemically synthesized or expressed peptide or protein possessing an N-terminal cysteine under conditions of the Native Chemical Ligation to form a peptide bond. The suggested mechanism is shown in Figure 3. The advantage of this ligation method is the combination of the scopes of molecular engineering and chemical synthesis as reviewed in detail.[14,19] EPL allows the site specific introduction of non canonical amino acids and chemical or biophysical tags into large proteins.[20] Manifold applications have been reported such as segmental isotopic labeling of proteins,[21] introduction of fluorescence

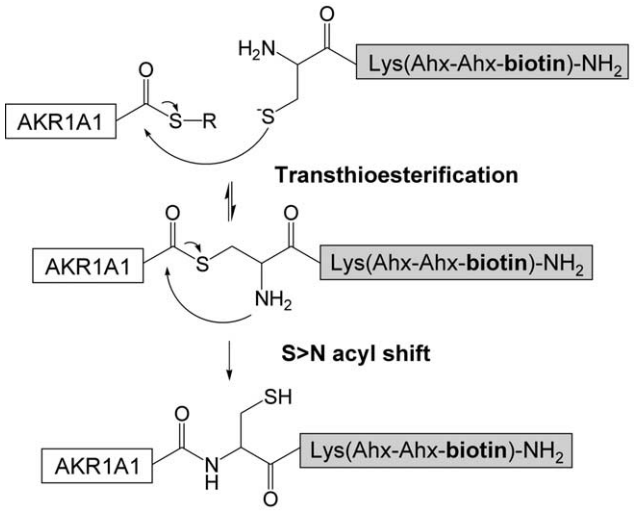

Figure 3. Reaction scheme of the Expressed Protein Ligation (EPL) of the AKR1A1 with the N-terminally Cys containing peptide Cys-Lys(Ahx_2-biotin). The recombinant thioester undergoes a transthioesterification with the cysteine residue followed by an S→N-acyl shift and leads to a native peptide bond.

tags into large peptides and proteins[22,23] as well as prenylation of proteins.[24] As this technique is not limited in size it solves the difficulties of the chemical preparation of peptide or protein C^{α}-thioesters.

2. Results and discussion

The IMPACT®-system allows the production of C^{α}-thioesters in large quantities and high purity by fusing the protein of interest to the N-terminus of an intein, a protein splicing element.[25,26] This intein is fused to a chitin binding domain for purification of the construct in a single step on chitin beads. The cleavage of the target protein α-thioesters can be induced by adding an excess of thiol. The well understood splicing mechanism of inteins used for the synthesis of protein α-thioesters starts with a transfer of the C-terminal amino acid residue of the target protein to the N-terminal side chain SH or OH of the cysteine/serine residue of the intein (N→S-acyl shift). Although this rearrangement seems to be thermodynamically highly unfavorable the molecular architecture of the intein forces the scissile peptide bond into a twisted conformation of higher energy and thereby pushes the equilibrium to the (thio)ester side. The second step is a transthioesterification and results in the protein α-thioester while the intein and the chitin binding domain remain on the resin. This thioester can subsequently be fused to an N-terminally Cys containing peptide. The standard peptides carrying Cys at their N-terminus for the fusion can easily be synthesized by the SPPS.

The ligation reaction occurs basically in the reverse way as the splicing does. The first step is a transthioesterification followed by a rearrangement (S→N-acyl shift), that forms the peptide bond (Fig. 3).

Furthermore, it is possible to synthesize N-terminally Cys containing proteins which can be attached to chemically synthesized α-thioesters of peptides. This approach enables

the selective monolabelling of the N-terminus of proteins for various applications.

The vector pET16b-AKR1A1 was used to amplify the human AKR1A1 cDNA through polymerase chain reaction (PCR). Primer were designed to introduce a *Nde*I and *Sap*I restriction site in the forward and the reverse primer, respectively, to allow an insertion of the restriction enzyme digested PCR fragment in the *Sap*I/*Nde*I treated target vector pTXB1. This vector allowed the C-terminally thiol mediated splicing of the target protein after expression. Molecular cloning and subsequent DNA sequencing confirmed the cDNA encoding for an AKR1A1-*Mxe*Intein/chitin binding domain (CBD) fusion protein. Accordingly, the C-terminus of the AKR1A1 is fused to the N-terminus of the intein protein splicing element attached to a chitin binding domain. After expression, the chitin binding domain allowed an affinity purification, while the intein part enabled the thiol mediated splicing of a C-terminally tagged AKR1A1-α-thioester in the presence of an excess of mercaptoethansulfonic acid (MESNA). The expression in Luria-Bertani media led to insoluble inclusion bodies of the target fusion protein. After solubilization in denaturing urea buffer, the urea concentration was reduced threefold and the protein was loaded onto the chitin column. Protein purification and the cleavage reaction were monitored by SDS-PAGE (Fig. 4).

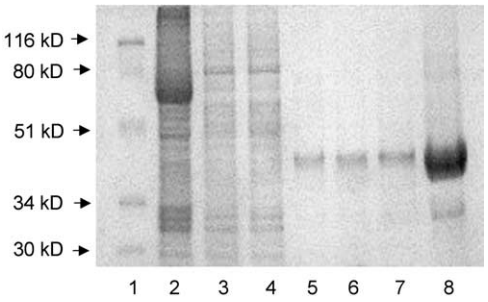

Figure 4. SDS-PAGE (12%) of the protein samples obtained during the production and purification process of AKR1A1-thioester. Lane 1 shows the protein marker, lane 2 depicts the solubilized protein fraction prior to column loading. Lanes 3 and 4 show the flow through. Lanes 5–8 show different fractions of the AKR1A1 α-thioester collected after MESNA induced splicing. A concentrated sample of the pooled fractions is shown on lane 8.

The analysis of the flow through revealed a complete binding efficiency of the fusion protein on the chitin beads and the intein cleavage finally led to 1–2 mg of highly pure AKR1A1-α-thioester.

Part of the AKR1A1 α-thioester was concentrated, desalted and subjected to MALDI mass spectrometry for further analysis. The mass spectra showed the expected mass (Fig. 5(A)) and only small amounts of a contamination by the intein/CBD protein.

Enzymatic activity was investigated by measuring the NADPH consumption at 340 nm as described.[27,28] The specific activity of the purified AKR1A1 α-thioester was A_{sp}=3000 nmol/(mg min); (Fig. 5(B)).

Peptide synthesis of the biotinylated Cys-Lys(Ahx-Ahx-biotin)-NH_2 was carried out by solid phase peptide

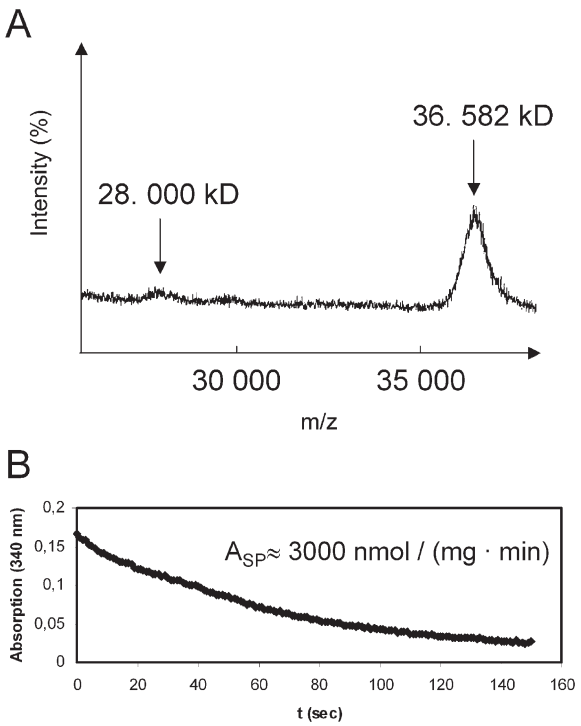

Figure 5. Characterization of AKR1A1 thioester. (A) MALDI mass spectrum of a desalted AKR1A1 α-thioester sample. The minor impurity corresponds to the intein/chitin binding domain. (B) Enzymatic activity of the AKR1A1 α-thioester measured by the decrease of the NADPH absorption at 340 nm. Enzyme was added to a solution containing 1 mM 4-nitrobenzaldehyde, 60 μM NADPH in 100 mM sodium phosphate, pH 7.0 at room temperature.

synthesis. Fmoc-Lys(Dde)-OH and Boc-Cys(Trt)-OH after Fmoc removal, was coupled to a Rinkamid resin. The Dde protecting group was removed by hydrazine. Subsequent coupling of Fmoc-aminohexanoic acid for spacing as well as biotin and final cleavage from the resin led to the desired product that was carefully analyzed and used for EPL.

Ligation of the AKR1A1 α-thioester with biotinylated peptide Cys-Lys(Ahx-Ahx-biotin)-NH_2 was carried out under mild conditions applying a high excess of peptide for 6 h. Excess of the biotinylated peptide was removed by size exclusion chromatography. The AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2 fractions were pooled, concentrated and the activity was proven to be intact. The specific activity of the combined fractions was A_{sp}=1700 nmol/(mg min). Analytical data of the chemically modified enzyme are shown in Figure 6.

Immobilization of the C-terminally biotinylated AKR1A1 was performed by using avidin coated silica beads with defined amounts of binding activity.

3. Conclusions

The synthesis of specifically labelled redoxproteins has become of great interest for structural elucidation of proteins, determinating protein-protein interactions, proteom research and especially for nanobioelectronic approaches.[3,8,29,30] For the construction of highly organized

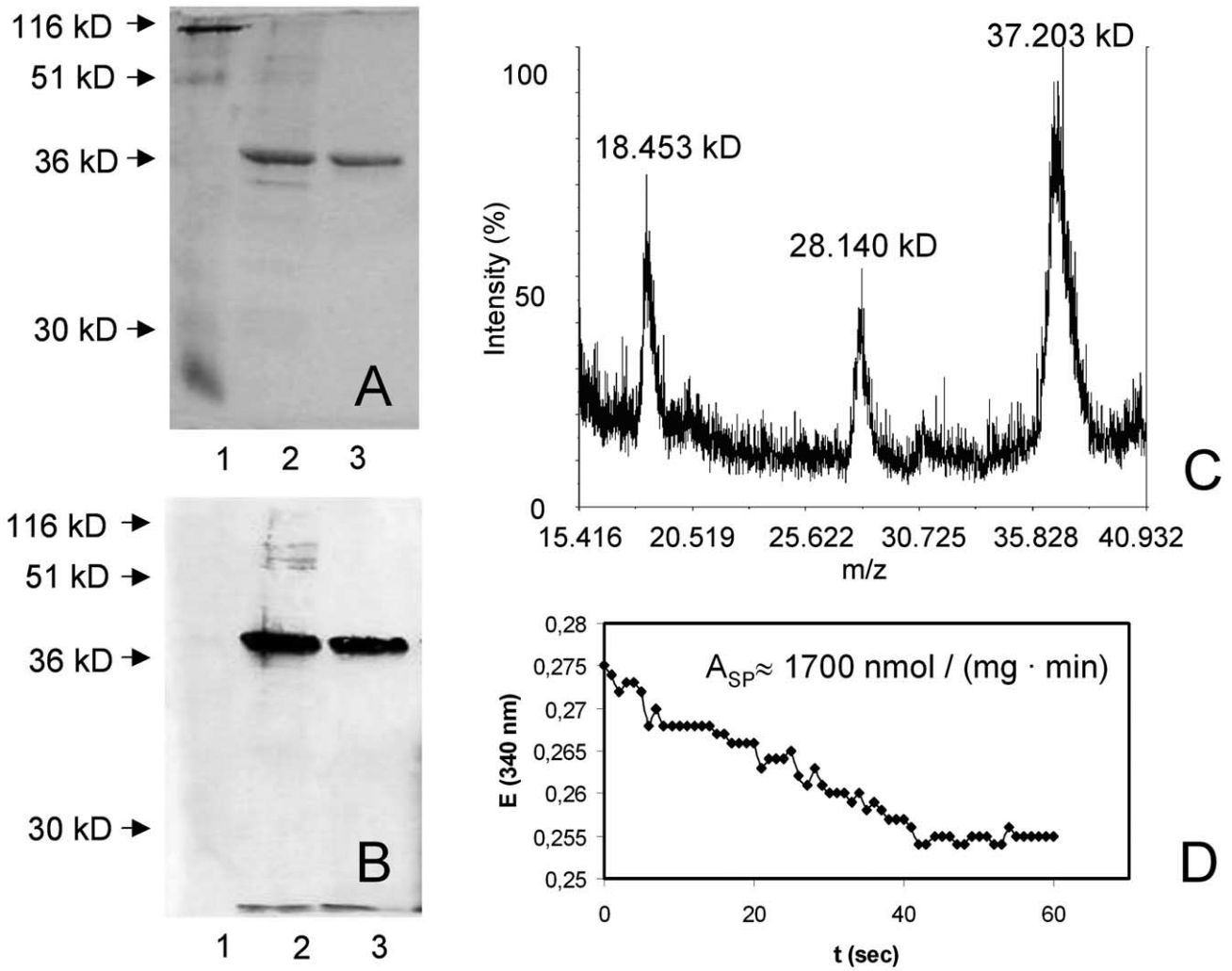

Figure 6. Analytical data of the AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2. (A) The Coomassie stained SDS-PAGE clearly shows single bands of the samples taken from ligation mixture after reduction with tris(carboxyethyl)phosphine (TCEP), after 2 h (lane 2) and 6 h (lane 3). (B) Successful ligation was proven by Western blot analysis of the same gel by using alkaline phosphatase labeled streptavidine. (C) The MALDI mass spectrum of the crude product after ligation shows the correct mass of the product M=37.203 kD [$M+K^+ +2Na^+$], M=18.453 kD [M^{2+}]. M=28.140 kD corresponds to the mass of the intein/chitin binding domain. (D) The enzyme activity of the purified enzyme samples is shown.

electrode architectures site specific monofunctionalization of proteins could have a great impact for the creation of well defined monolayers on different surfaces by attaching specificity mediating molecules for immobilization applications. Moreover this approach could lead to new artificial proteins with new chemical properties.[14,16,19,31] Expressed Protein Ligation of redoxproteins with molecular moieties facilitating the electron transfer to the enzyme and cofactors for example would eventually overcome the problem of sensor bleaching through covalent fixation of molecular electron transfer relais modules. Although numerous immobilization protocols are available for enzymes there is a lack in methods describing specific covalent attachment and the need of large protein quantities is necessary.[32,33] As a first step in this field we cloned the monomeric aldo/keto reductase to get recombinant AKR1A1 α-thioester by using the IMPACT®-system.[20] Peptide synthesis of a biotin carrying peptide with C16 spacer was achieved by manual solid phase peptide synthesis. The C16 spacer was selected to provide an improved fitting into the binding pocket of avidin. Expression of the human AKR1A1 in *E. coli* led to inclusion bodies, which had to be solubilized in a urea containing buffer. This procedure and the subsequent refolding through dilution might explain the twofold decrease in activity compared to the data in the literature where the protein is expressed in soluble form.[7] Expressed protein ligation was performed at pH 7.8 by using a large excess of N-terminally Cys containing peptide to shift the equilibrium of the reaction to the product side. Excess of peptide was removed by gelchromatography and eventually unlabelled AKR1A1 by thorough washing of the beads after avidin immobilization. The milky samples of the immobilized AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2 were easy to handle and no sedimentation was observed for minutes. In conclusion, EPL can be an efficient technique for the synthesis of modified AKR1A1 derived redoxproteins. The introduction of chemical modifications into the peptide sequence should enable the synthesis of valuable tools for nanobioeletronic approaches. Further studies with this construct by using avidin coated surfaces as well as various modifications will allow the elucidation of suitable applications for this redoxprotein.

4. Experimental

4.1. General

N-ethyldiisopropylamine (DIPEA), acetic anhydride, trifluoroacetic acid (TFA), thioanisol, thiocresole, 4-nitrobenzaldehyde, biotin, β-nicotinamide-adenin-dinucleotide-monophosphate tetrasodium salt (reduced form), hydrazine monohydrate solution as well as all other common salts were purchased from Fluka (Buchs, Switzerland), acetonitrile was obtained from Merck Eurolab (Bruchsal, Germany), Diethylether, dichloromethane (DCM) and dimethylformamide (DMF) was purchased from Biosolve (Valkenwaard, The Netherlands). Rinkamide resin, the N^{α}-Fmoc protected amino acids Lys(Dde)-OH and aminohexanoic acid as well as N^{α}-Boc-cysteine(Trt)-OH and hydroxybenzotriazole (HOBt) was obtained from Novabiochem (Läufelfingen, Switzerland), *N*,*N*′-diisopropylcarbodiimide (DIC), nitroblue tetrazolium and 5-bromo-4-chloro-indolylphosphate was purchased from Aldrich (Buchs, Switzerland). The plasmid pET16b-AKR1A1 vector was received as gift from Prof. Dr. T. M. Penning, University of Pennsylvania, USA, the pTXB1 vector was obtained from New England Biolabs (Beverly MA, USA), oligonucleotides for PCR experiments were purchased from MWG Biotech AG (München, Germany). MALDI mass spectra were recorded by using a Voyager II mass spectrometer (Perseptive Biosystems). Pipette tips for desalting and Amicon Ultra centrifugal filter devices were obtained from Millipore (Schwalbach, Germany). For UV/VIS measurements the UV/VIS-spectrophotometer LAMBDA EZ210 (Perkin Elmer, Germany) was used. Gel filtration was performed with an Econo System (BioRad).

4.2. DNA constructs

The cDNA of the human aldo/keto reductase AKR1A was amplified by PCR from the pET16b-AKR1A1 vector by using the forward 5′-GGG GGC CAT ATG GCG GCT TCC TGT GTT-3′ and reverse 5′-CGG CGG CGC TCT TCC GCAGTA CGG GTC ATT AAA GGG-3′ primer. Digested and purified PCR fragments were inserted into *Nde*I/*Sap*I-treated vector pTXB1. DNA sequencing was used to confirm in-frame cloning of the full length AKR1A1 gene.

4.3. Fusion protein expression in *E. coli*

E. coli BL21(DE3) or ER2566 cells transformed with pTXB1/AKR1A1 plasmid were grown in Luria-Bertani media containing Ampicillin (75 μg/ml) at 37 °C until they reached the mid-log phase. At this time the protein expression was induced by adding isopropylthiogalactosid (IPTG, 0.4 mM). After incubation at 30 °C for 5 h the cells were harvested by centrifugation. Lysis of the cells was performed within one hour at 4 °C in buffer A (4-(2-hydroxyethyl)-piperazinesulfonate sodium salt (HEPES) 20 mM, NaCl (500 mM); pH 8.0) in the presence of Tween-20 (0.1%), tris(carboxethyl)phosphine (TCEP, 0.7 mM), phenylmethylsulfonylfluoride (PMSF 20 μM) and lysozyme (15 μg/ml). To complete the lysis sonication pulses (5×45 s) were applied. Subsequently the viscosity of the lysate was reduced by adding DNaseI (10 μg/ml) as well as $MgCl_2$ (5 mM) and incubated for 1 h at room temperature. The insoluble fusion protein was then solubilized in buffer B (buffer A lacking Tween-20 but containing 6 M urea). Expression and isolation of the target protein was monitored by SDS-PAGE (12%, 200 mV, 180 mA, 60 min). GelCode® blue staining reagent (Perbio Science) was used for gel staining.

4.4. Purification and isolation of the protein α-thioester

An extract of a 1 l culture was loaded on a column filled with 15 ml chitin beads and equilibrated with 10 ml of buffer C (HEPES 20 mM, NaCl, 500 mM, 2 M Urea; pH 8.0). The sample containing the solubilized fusion protein was diluted 1:3 with buffer D (HEPES 20 mM, NaCl 500 mM; pH 8.0) prior to column loading. Loading proceeded at flow rate of 1 ml/min and the flow through was twice reloaded iteratively onto the column. After washing the column with 10 bed volumes of buffer C and additional 10 bed volumes of buffer B to get rid of non bound *E. coli* proteins the 'on column' cleavage of the absorbed intein-fusion protein was started by adding 20 ml of buffer B containing the sodium salt of mercaptoethansulfonic acid (MESNA, 0.2 M). The 'on column' cleavage proceeded for 40 h at 4 °C at pH 7.8. The AKR1A1 α-thioester was eluted at 4 °C and the protein content was determined according to Bradford.[34] Concentration of the protein samples was performed by using Amicon Ultra centrifugal filter devices (MWCO 10 kD). AKR1A1-MESNA α-thioester; MALDI Calcd: 36 561 D found: 36 582 D $[M+Na^+]$.

4.5. Enzymatic assay

The concentrated aldo/keto reductase was assayed based on the decrease at 340 nm owing to the conversion of NADPH to $NADP^+$. Assays were performed on a two channel spectrophotometer. The absorbance was taken over a period of 150 s. All assays were conducted at room temperature. A 200 μl reaction mixture contained 1 mM 4-nitrobenzaldehyde, 60 μM NADPH in 100 mM sodium phosphate, pH 7.0. The assay reaction was started by the addition of 1 μg AKR1A1-α-thioester or AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2.

4.6. Synthesis and analysis of the biotinylated peptide Cys-Lys(Ahx-Ahx-biotin)-NH_2

30 mg of Rinkamide resin with a binding capacity of 0.015 mmol was loaded in a syringe with a frit and incubated with 1 ml of DMF for 10 min at room temperature. Subsequently 500 μl reaction solution containing 0.15 mmol of HOBt, 0.15 mmol of N^{α}-Fmoc-Lys(Dde)-OH and 0.15 mmol DIC in DMF were added and the coupling was carried out twice for 3 h each. Completeness of the reaction was monitored with the Kaiser-Test.[35] The resin was washed with 10 ml of DMF, DCM and diethylether. A blocking step was performed by incubating the resin with 400 μl DCM, 50 μl DIPEA and 50 μl acetic anhydride for 1 h at room temperature. After further washing steps the Fmoc group was cleaved by adding 500 μl 20% piperidine in DMF for 30 min. Attachment of Boc-Cys(Trt)-OH was achieved by adding the reaction

solution consisting of 0.15 mmol protected amino acid, 0.15 mmol HOBt and 0.15 mmol DIC dissolved in 500 μl DMF. After 3 h at room temperature the reaction mixture was removed and the resin was washed thoroughly as described above and dried in a SpeedVac®. The Dde protecting group was removed from the Lys side chain by adding 10 times 1 ml of hydrazine monohydrate (20% in DMF, v/v). Side chain modification of Lys was performed as described above with Fmoc-6 aminohexanoic acid (Ahx) twice and biotin. Cleavage of the side chains of the biotinylated peptide and removal from the resin was conducted with 900 μl of TFA and 100 μl of the scavenger cocktail thioanisole and thiocresole (1:1, v/v) for 3 h at room temperature. Subsequently, the peptide was precipitated in diethylether. The peptide was dissolved in a mixture of water and *tert*-butanol (1:3, v/v) and lyophylized. HPLC analysis was carried out on C18 column (5 μm×3 Å; 4.5 μm, 250 mm, Vydac, USA) using 0.08% TFA in acetonitrile (v/v) and 0.1% TFA in water (v/v) with a gradient from 0% acetonitrile running up to 40% acetonitrile within 50 min. HPLC purity: >90%, MALDI: mass Calcd: 699 D, found: 701 D.

4.7. Monolabelling of AKR1A1 by attachment of the biotinylated peptide

The AKR1A1 α-thioester was eluted from the chitin column in a volume of 20 ml buffer D. Cys-Lys(Ahx-Ahx-biotin)-NH_2 was added (final concentration 1.5 mM) to one fraction of 10 ml containing 2.7×10^{-6} M AKR1A1-α-thioester in 10 mM TCEP, pH 7.8. Both samples were slightly shaken for 48 h at 4 °C. The other fraction was kept untreated at pH 8.0 to hydrolyze the protein α-thioester in order to obtain the free enzyme. The ligation sample was then transferred into a centrifugal filter device and centrifuged for 20 min at 4 °C.

4.8. SDS-PAGE and western blotting

Protein samples were mixed with gel loading buffer (pH 6.8, 10% glycerine, 2% SDS, 0.1% bromophenol blue) and heated for 10 min at 95 °C in a thermomixer before subjecting to SDS-PAGE on 12% SDS polyacrylamide gels at constant voltage of 200 V according to Lämmli.[36] Protein bands were visualized by staining with Gelcode® blue staining reagent. For Western blot analysis separated proteins were electrotransferred to a nitrocellulose membrane equilibrated in transfer buffer (25 mM Tris–HCl, pH 8.3, 150 mM glycine, 20% methanol, 1% SDS) for 60 min at constant 150 mA/cm^2 using a semi-dry apparatus. Membranes were blocked overnight at 4 °C in PBS-Tween (phosphate-buffered saline plus 0.1% Tween-20) containing 1% bovine serum albumine (BSA). Blocked membranes were washed three times in PBS-Tween, thereafter incubated with streptavidine coupled alkaline phosphatase in PBS-Tween containing 1% BSA for 1 h at room temperature while shaking. After three washes with PBS-Tween the biotinylated proteins were visualized by incubating the membranes with 10 ml Tris buffer, pH 9.6 containing 0.4 mM nitroblue tetrazolium, 0.5 mM 5-bromo-4-chloro-indolylphosphate and 0.4 mM $MgCl_2$. After 5 min the formation of the corresponding formazan was quenched by adding deionized water.

4.9. Purification and immobilization of the artificial protein

The crude reaction mixture was concentrated in Amicon Ultra Filter Devices (Millipore, Germany) with a MWCO of 10 kD at 4000 g at 4 °C. 500 μg protein solution were reduced with TCEP (0.1 mM) to cleave possible adducts of the biotinylated peptide onto the protein Cys residues for 30 min and subsequently loaded on 50 ml Sephadex®-G50 in an Econo column using phosphate buffer (0.5 M sodium phosphate, 0.1 M sodium chloride, pH 7.0) as solvent at a flow rate of 0.5 ml/min. The fractions containing biotinylated protein were pooled and concentrated. The activity was proven to be intact and mass spectrometry confirmed the correct mass of the identified product. MALDI; mass calcd: 37118 D, mass found: 37203 D [$M+K^+ +2Na^+$].

For immobilization avidin coated silica microspheres of 1 μm in diameter were used with a binding capacity for biotin of 9 nmol/mg. Bead samples were incubated with 0.16 U/ml AKR1A1-Cys-Lys(Ahx-Ahx-biotin)-NH_2 for 1 h at room temperature under reducing conditions. For negative controls the similar procedure was carried out using bead samples with 0.17 U/ml of unlabelled AKR1A1. After incubation, the samples were washed stepwise with 1 ml phosphate buffer for 15 times while gently shaking and additional centrifugation at 3000 g. All samples were kept in a final volume of 100 μl.

Acknowledgements

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Directed ring-closing metathesis of trienes by silyl substitution

Carsten Schultz-Fademrecht,[a] Prashant H. Deshmukh,[a] Karine Malagu,[a] Panayiotis A. Procopiou[b] and Anthony G. M. Barrett[a,*]

[a]*Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK*
[b]*Department of Medicinal Chemistry, GlaxoSmithKline Research and Development Ltd, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK*

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Abstract—A synthetic strategy for 'disarming' a terminal alkene by substitution with a bulky silyl blocking group has been developed. In a series of model studies, sequential selective ring-closing metathesis of trienes followed by selective mono-hydrogenation of the resulting diene is described. The bulky silylated alkene is activated for a subsequent cross-metathesis reaction with a range of diverse alkenes by protodesilylation.

1. Introduction

During the past decade, the synthetic potential of ring-closing metathesis (RCM) as a mild and catalytic C–C bond forming method has been well recognized, and as a result RCM has been widely used in the synthesis of various small, medium and large rings.[1] Recently, we have been pursuing the synthesis of macrocyclic compounds using selective RCM of dienes **1** to afford, after ring alkene hydrogenation, the macrocyclic core **2**. Selectivity in both the RCM step and hydrogenation are clearly prerequisites for this process. In this respect we envisaged the use of a sterically demanding, readily cleaved vinyl silane substituent, to 'disarm'[2] one of the alkene units by blocking both metathesis and hydrogenation at this position. Desilylation of **2** should afford the 'armed'[2] alkene **3**. Finally, cross-metathesis[3] and hydrogenation would provide the target analogues **4**, bearing a variety of functionalized 'R' groups. This method would therefore facilitate, by a synthetically convergent late stage diversification strategy, the synthesis of a range of macrocyclic analogues. The strategy has indirect precedent. Early studies by Schrock showed that metathesis of trialkylvinylsilanes were slow and inefficient.[4] It was later found that vinylsiloxanes are better metathesis substrates.[5] More recently, cross-metathesis of alkoxy- or silyloxy-vinylsilanes with alkenes in the presence of Grubbs I catalyst, $((Cy_3P)_2Ru(=CHPh)Cl_2)$, has also been reported.[6] Successful RCM reactions of $[Me_2(R^1O)Si]CR^2{=}CH_2$, with either R^1 or R^2 bearing a terminal alkene, has been recently described.[7] To the best of our knowledge, there are no examples of any metathesis of β-substituted vinylsilanes $(R_3Si)HC{=}CH_2R$ or even of the analogous alkoxysilanes. Additionally, there are a few examples of the use of Me_3Si as a blocking group for metathesis.[8] Tam has reported the selective ring opening-crossed metathesis of 2,3-bis-(trimethylsilyl)norbornadiene in which the two trimethylsilyl substituents completely block reaction at the more hindered alkene.[9] Additionally, Nelson and co-workers, in a total synthesis of (−)-laulimalide, have utilized a selective RCM of a trienyl-stannane to provide a dihydropyran derivative.[10] In this case, the selectivity was the result of the 'disarming' of an alkene by substitution with a tributylstannyl residue (Scheme 1). Finally, Hodgson has directed selectivity in the RCM of trienes with alkene disarming using an iodo-substituent.[11]

2. Results and discussion

2.1. Selective cross-metathesis of dienyl monosilanes

In a preliminary experiment, we studied the cross-metathesis of diene **5** with 3-methyl-2-butene, using the saturated imidazolylidene catalyst **7**[12] (Scheme 2). According to the Stoltz procedure, 3-methyl-2-butene acts as both solvent and alkene partner in the cross-metathesis reaction.[13] We successfully applied these conditions to the alkene **5** and obtained the desired product **6** in 82% yield. No metathetic desilylation of the 'disarmed' double bond was observed. This result demonstrated that the disarming of a terminal

Keywords: Ring-closing metathesis; Crossed metathesis; Ruthenium catalysts; Macrocyclization.
* Corresponding author. Tel.: +44-207-594-5766; fax: +44-207-594-5805; e-mail address: agmb@ic.ac.uk

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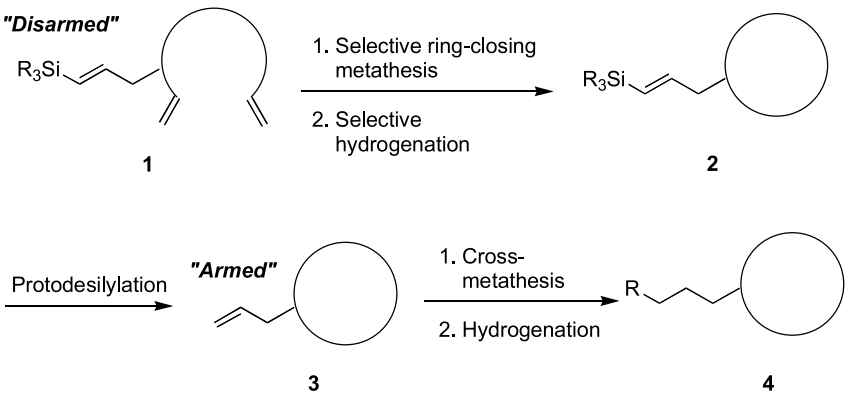
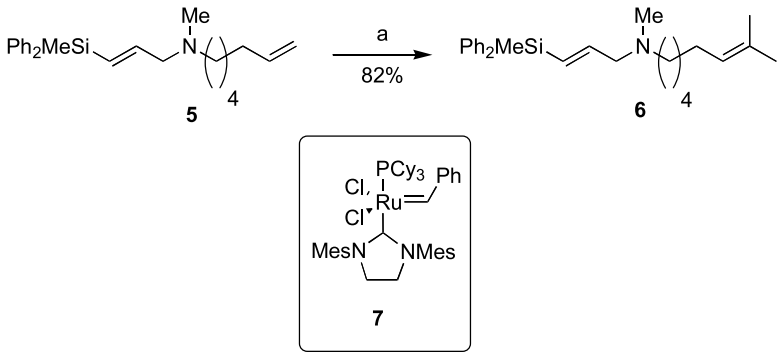


Scheme 1.



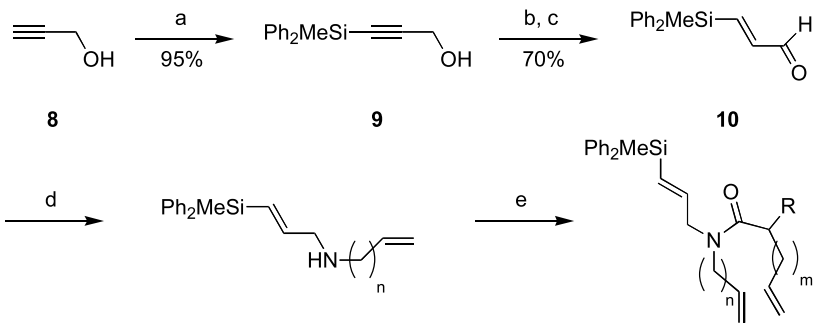
Scheme 2. Reagents and conditions: (a) excess 3-methyl-2-butene, **7** (10 mol%), 35 °C.

alkene could effectively be achieved via protection by terminal methyldiphenylsilylation.

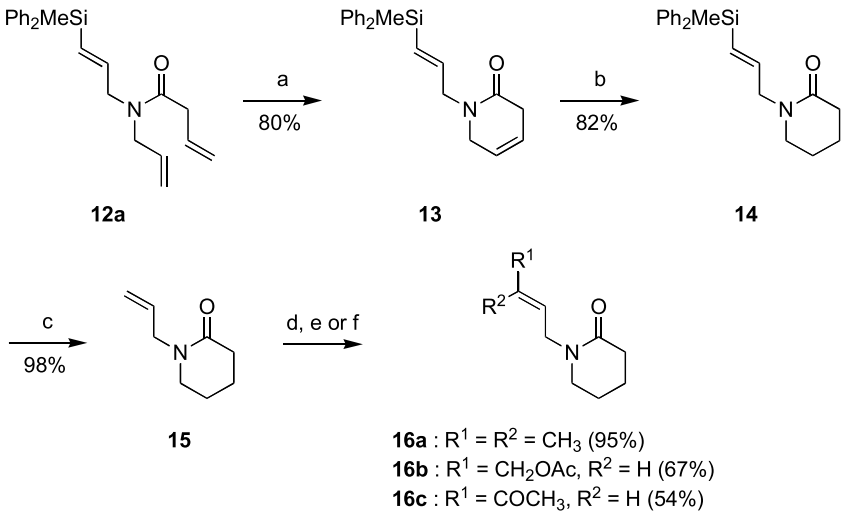
2.2. Selective ring-closing-metathesis of trienyl monosilanes

The encouraging result in Scheme 2 prompted us to prepare the series of amides **12a**-**d** as substrates to explore directed RCM. Thus, double deprotonation of propargyl alcohol (**8**) using methylmagnesium bromide, followed by reaction with methyl(diphenyl)chlorosilane (2 equiv.), and sulfuric acid-mediated monodeprotection afforded acetylene **9** in 95% overall yield, following the procedure by Denmark.[14] Stereospecific reduction using Red-Al® in toluene, followed by oxidation of the resulting allylic alcohol with manganese dioxide gave the key unsaturated aldehyde **10**. The stereochemistry of the alkene was determined to be exclusively *trans* by ^{1}H NMR spectroscopy. Reductive amination of **10** gave the secondary amines **11a** and **11b** in high yields, which were further derivatized by acylation to provide the amides **12a**-**d** (Scheme 3).

Our first application of the strategy involved the triene **12a** (Scheme 4). Reaction with catalyst **7** (5 mol%) in dichloromethane gave, after 12 h, selective conversion to the desired lactam **13** in 80% yield. No products of



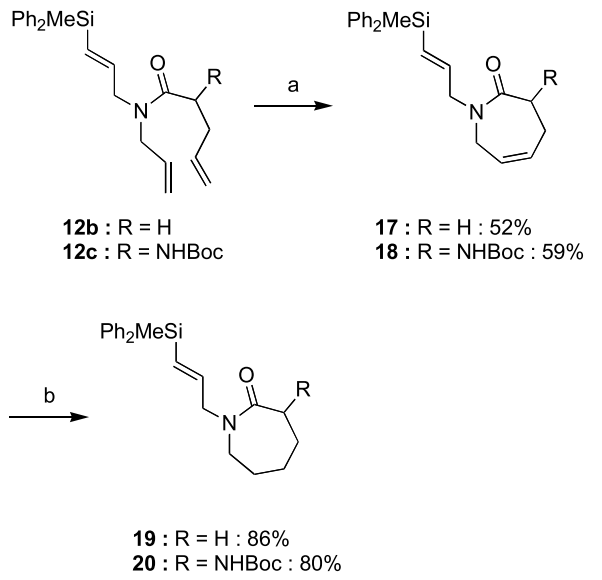
Scheme 3. Synthesis of ring-closing metathesis precursors **12a**-**d**. Reagents and conditions: (a) (i) MeMgBr (2.6 equiv.), THF, Et_2O, 0 °C; (ii) $Ph_2MeSiCl$ (2.6 equiv.), 40 °C; (iii) 1.4 M H_2SO_4, 0 °C; (b) 50% Red-Al®, PhMe, Et_2O, 0–25 °C; (c) MnO_2 (10 equiv.), CH_2Cl_2, 45 °C; (d) $CH_2{=}CH(CH_2)_nNH_2$, $NaBH_4$, MeOH, 25 °C; (e) $ClCOCH(R)(CH_2)_mCH{=}CH_2$, NEt_3, CH_2Cl_2, 25 °C.



Scheme 4. Arming–disarming strategy for the substituted 2-piperidinone series. Reagents and conditions: (a) **7** (5 mol%), CH_2Cl_2, 12 h; (b) H_2 (1 atm), $(Ph_3P)_3RhCl$ (10 mol%), THF, EtOH, 4 h; (c) Bu_4NF, DMSO, 80 °C, 1.5 h; (d) 3-methyl-2-butene, **7** (10 mol%), 45 °C, 20 h; (e) allyl acetate (2.0 equiv.), **7** (10 mol%), CH_2Cl_2, 25 °C, 16 h; (f) methyl vinyl ketone (3.0 equiv.), **7** (20 mol%), $CHCl_3$, 60 °C, 18 h.

desilylation were observed. Significantly reduced yields (23–33%) were obtained using the less reactive Grubbs I catalyst.[15] The endocyclic double bond in **13** was selectively hydrogenated using Wilkinson's catalyst ($(Ph_3P)_3RhCl$), in THF and ethanol at atmospheric pressure to afford the saturated lactam **14** (82%). The choice of solvent was critical, since other solvents resulted in competitive alkene migration or over-reduction of the silylalkene unit. When palladium on charcoal was used for the hydrogenation reaction at atmospheric pressure, no selectivity was observed. Both alkenes were hydrogenated giving the fully saturated product. Alternatively, ROMPgel supported Wilkinson's catalyst[16] was used for the selective hydrogenation, allowing a facile isolation of the product **14**. Hydrogenation over platinum oxide in benzene was irreproducible, whereas reaction using $(Ph_3P)_3RhCl$ in toluene resulted in double bond migration. The methyl(diphenyl)silyl blocking group in **14** was readily cleaved using tetrabutylammonium fluoride in DMSO, giving lactam **15**[17] (98%). Cross-metathesis of **15** following the Stolz procedure[13] yielded the desired product **16a** in 95% yield. Cross-metathesis was also successfully accomplished with allyl acetate and methyl vinyl ketone to afford the functionalized alkenes **16b** (67%) and **16c** (54%), respectively.

The promising results obtained for the 2-piperidinone series were extended to larger ring systems. Thus, we investigated various RCM conditions for the substituted 2-azepanone series precursors **12b** and **12c** (Scheme 5). Reaction of **12b** with catalyst **7** (5 mol%) at 25 °C gave the product **17** in very low yield, together with recovered starting material. Higher reaction temperatures increased the yield. Thus at 90 °C after 24 h, lactam **17** was obtained in 35% yield. In all reactions at higher temperature a minor unidentified side product(s) was also isolated. The silyl functionality was absent and the product appeared to be oligomeric with broad signals in the ^1H NMR spectrum. Trace amounts of methyl(diphenyl)vinylsilane were also detected (GCMS). These observations suggest that metathetic desilylation may have been a minor side reaction at elevated temperatures. Further improvements were obtained using microwave irradiation. After 15 min at 100 °C, the desired product **17** was isolated in 52% yield. RCM of triene **12c** using microwave heating at 100 °C for 15 min gave the lactam **18** in 59% yield. The lower yields observed in the seven-membered rings are not surprising, however, since studies by Grubbs et al. have shown that the synthesis of several seven- and eight-membered rings by RCM typically give only modest yields.[18] However, it is noteworthy to point out that the RCM in Scheme 5 selectively provided the ε-lactams **17** and **18** rather than the corresponding desilylated ε-lactams or *N*-acyl-pyrrolines. Selective hydrogenation of dienes **17** and **18** were accomplished in high yields (86 and 80%, respectively) using $(Ph_3P)_3RhCl$ in THF and ethanol.



Scheme 5. Application of the strategy to the substituted 2-azepanone series. Reagents and conditions: (a) **7** (5 mol%), CH_2Cl_2, microwave, 100 °C, 15 min; (b) H_2 (1 atm), $(Ph_3P)_3RhCl$ (10 mol%), THF, EtOH, 4 h.

2.3. Macrocyclization via selective ring-closing-metathesis of trienyl monosilanes

The use of the methyl(diphenyl)silyl blocking group to direct selective RCM to provide a macrocyclic alkene was next investigated (Scheme 6). When the metathesis precursor **12d** was allowed to react with catalyst **7** (10 mol%) under reflux for 24 h, the lactam **21** was obtained in 65% yield as a *cis*/*trans*-mixture. The mixture was carefully hydrogenated using $(Ph_3P)_3RhCl$ over 4 h, when **21** was converted into **22** and **23** (3.1:1; 89%). It is possible that the loss in selectivity here, in comparison with the 2-piperidinone series (Scheme 4) and the 2-azepanone series (Scheme 5) could stem from increased steric hindrance of the endocyclic alkene by the ring carbon skeleton. Additionally, the formation of *trans* as well as *cis* alkenes in the previous metathesis could lead to a loss of differentiation in reactivity between the macrocyclic alkene and the alkenylsilane. Nevertheless, it is important to note that the hydrogenation of **21** proceeds selectively with more rapid reduction of the macrocyclic alkene rather than the alkenylsilane. In any case, the mixture of lactams **22** and **23** were allowed to react with tetrabutylammonium fluoride in THF selectively to give the terminal alkene **24** in good yield (87%), based upon the quantity of **22** present in the reaction mixture. Cross-metathesis of **24** with 3-methyl-2-butene, allyl acetate or 5-hexene-2-one gave the modified alkenes **25a-c**, respectively.

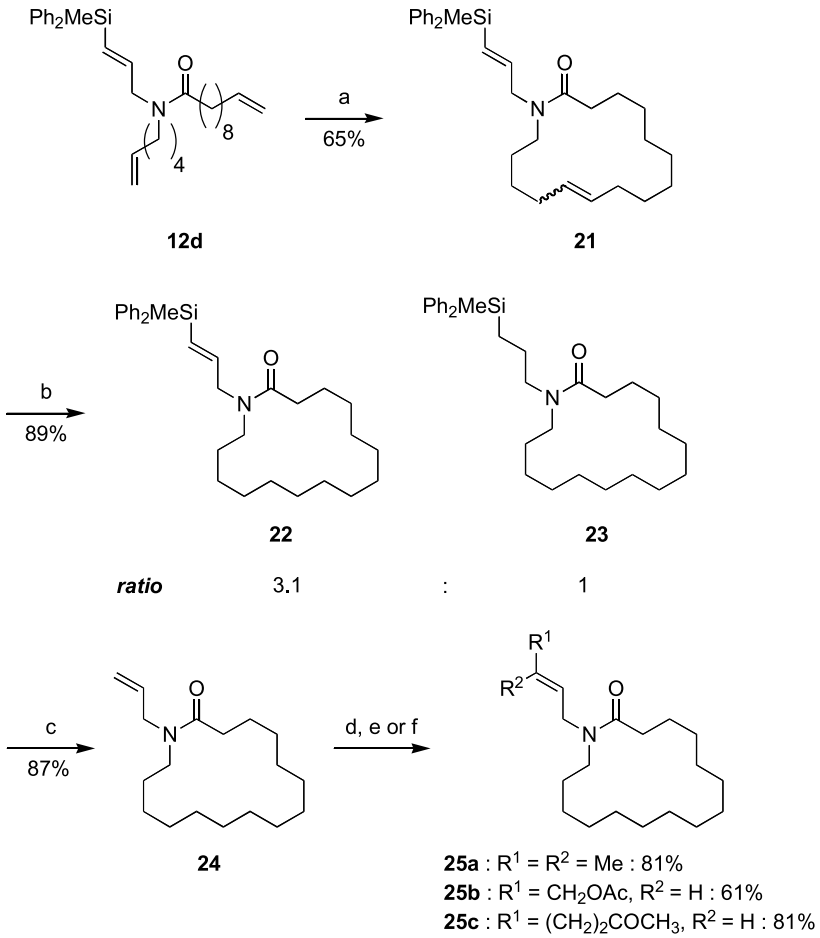
3. Conclusions

In conclusion, we have demonstrated the application of the methyl(diphenyl)silyl moiety to direct selectivity in both crossed and RCM. We have shown that RCM of a triene monosilane takes place selectively between the non-silylated alkenes and may be used to prepare six-, seven- and 16-membered lactams. Furthermore, selective hydrogenation of the diene products over $(Ph_3P)_3RhCl$ proceeded with good selectivity in the reduction of the ring alkene, whereas the alkenylsilane was not reduced. Application of this strategy to the synthesis of further macrocyclic systems will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out in an atmosphere of dry nitrogen. Where solvents have been described as dry or anhydrous, they have been vigorously dried over CaH_2



Scheme 6. Metathesis and selective hydrogenation of the 2-azacyclohexadecanone series. Reagents and conditions: (a) **7** (10 mol%), CH_2Cl_2, 45 °C; (b) H_2 (1 atm), $(Ph_3P)_3RhCl$ (10 mol%), THF, EtOH, 25 °C; (c) Bu_4NF, THF, DMSO, 80 °C; (d) **7** (10 mol%), 3-methyl-2-butene, 35 °C, 20 h; (e) allyl acetate (2.0 equiv.), **7** (10 mol%), CH_2Cl_2, 25 °C, 16 h; (f) 5-hexene-2-one (8.4 equiv.), **7** (20 mol%), $CHCl_3$; 60 °C, 18 h.

(CH_2Cl_2, PhMe), Na/K alloy (THF), and Na (Et_2O). All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Column chromatography was carried out on BDH silica gel, particle size 40–63 μm, using flash techniques (eluants are given in parenthesis). Analytical thin layer chromatography was performed on Merck pre-coated silica gel F_{254} plates.

4.1.1. Preparation of 3-(methyldiphenylsilyl)-2-propyn-1-ol (9). Propargyl alcohol (**8**) (2.5 mL, 43 mmol, 1.0 equiv.) was added dropwise to MeMgBr in dry Et_2O (3.0 M, 37 mL, 112 mmol, 2.6 equiv.) and dry THF (20 mL) at 0 °C under argon. The mixture was left overnight under argon at 0–4 °C, recooled to 0 °C and $Ph_2MeSiCl$ (23.5 mL, 112 mmol, 2.6 equiv.) was added dropwise. The mixture was heated under reflux at 40 °C for 2 h, cooled to 0 °C and dilute H_2SO_4 (1.4 M; 46 mL) was added slowly with stirring. After 5 min at 0 °C, Et_2O (35 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (2×20 mL). The combined Et_2O extracts were washed with H_2O (30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$) and concentrated. Chromatography (hexanes/EtOAc, 9:1) gave **9** (10.2 g, 95%) as a colorless oil: TLC R_f 0.50 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 3338, 2176, 1428, 1253, 1114, 1040, 793, 729, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.69 (m, 4H), 7.38–7.47 (m, 6H), 4.38 (s, 2H), 1.79 (br s, 1H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 134.6, 129.9, 128.1, 107.3, 87.1, 51.7, −2.1; MS (EI) *m/z* 252 ($M^{+\cdot}$, 4), 237 (38), 137 (100), 115 (43), 105 (14), 91 (21), 45 (22); HRMS (EI) *m/z* calcd for $C_{16}H_{15}OSi$: ($M^{+\cdot}$), 252.09704, found: ($M^{+\cdot}$), 252.09791. Anal. calcd for $C_{16}H_{16}OSi$: C, 76.14; H. 6.39. Found: C, 76.18; H, 6.43.

4.1.2. Preparation of 3*E*-(methyldiphenylsilyl)-2-propen-1-ol (26). Acetylene **9** (3.9 g, 15 mmol) in dry Et_2O (20 mL) was added dropwise over 1 h to Red-Al in PhMe (65% w/v, 7.5 mL, 24 mmol, 1.6 equiv.) in Et_2O (10 mL) at 0 °C. After 2 h at room temperature, the mixture was recooled to 0 °C when dilute H_2SO_4 (1.4 M, 50 mL) was added cautiously. The separated aqueous layer was further extracted with Et_2O (2×20 mL) and the combined phases were washed with H_2O (30 mL) and saturated aqueous NaCl (30 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes/EtOAc, 5:1) gave (*E*)-3-methyl(diphenyl)silyl-2-propen-1-ol (**26**) (3.9 g, 99%) as a colorless oil: TLC R_f 0.47 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 3338, 3069, 1620, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.63 (m, 4H), 7.42–7.48 (m, 6H), 6.34 (m, 2H), 4.27 (m, 2H), 2.11 (br s, 1H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 136.5, 134.9, 129.4, 128.0, 124.7, 65.3, −3.7; MS (CI, NH_3) *m/z* 272 ($(M+NH_4)^+$, 100), 256 (4), 232 (24), 216 (7), 214 (9), 194 (45), 179 (4), 154 (42), 173 (6); HRMS (CI, NH_3) *m/z* calcd for $C_{16}H_{22}NOSi$: $(M+NH_4)^+$, 272.1471, found: $(M+NH_4)^+$, 272.1478. Anal. calcd for $C_{16}H_{18}OSi$: C, 75.54; H, 7.13%. Found: C, 75.58; H, 7.24.

4.1.3. Preparation of 3*E*-(methyldiphenylsilyl)propenal (10). Powdered MnO_2 (8.8 g, 101 mmol, 10 equiv.) was added to (*E*)-3-methyl(diphenyl)silyl-2-propen-1-ol (**26**) (2.5 g, 9.8 mmol, 1.0 equiv.) in dry CH_2Cl_2 (15 mL) and the resulting suspension stirred under reflux for 3 h. The mixture was allowed to cool to room temperature and was filtered through silica, eluting with CH_2Cl_2. Rotary evaporation and chromatography (hexanes/EtOAc, 9:1) gave **10** (2.1 g, 85%) as a colorless oil: TLC R_f 0.31 (hexanes/EtOAc, 9:1; $KMnO_4$); IR (thin film) 1692, 1428, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, 1H, *J*=7.6 Hz), 7.56–7.42 (m, 11H), 6.63 (dd, 1H, *J*=18.6, 7.6 Hz), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 154.2, 146.6, 134.8, 133.9, 130.1, 128.3, −4.4; MS (EI) *m/z* 252 ($M^{+\cdot}$, 22), 237 (100), 197 (47), 183 (30), 174 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{16}OSi$: ($M^{+\cdot}$), 252.0970, found: ($M^{+\cdot}$), 252.0964. Anal. calcd for $C_{16}H_{16}OSi$: C, 76.14; H, 6.39. Found: C, 75.99; H, 6.38.

4.1.4. Preparation of propenyl-(3*E*-(methyldiphenylsilyl)propenyl)amine (11a). Allylamine (620 μL, 8.3 mmol, 1.1 equiv.) was added to aldehyde **10** (1.9 g, 7.5 mmol, 1.0 equiv.) in dry MeOH (30 mL) and the mixture was stirred at room temperature for 2 h. $NaBH_4$ (0.31 g, 8.3 mmol) was added and the mixture was stirred at room temperature for 18 h. H_2O (20 mL) was added and the combined solvents rotary evaporated. The residue was partitioned between Et_2O (30 mL) and H_2O (30 mL). The separated aqueous layer was further extracted with Et_2O (2×20 mL) and the combined ethereal phases were dried ($MgSO_4$) and rotary evaporated to give **11a** (1.5 g, 70%) as a colorless oil, which was used without purification: TLC R_f 0.09 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 3068, 3048, 1676, 1615, 1429, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.56 (m, 4H), 7.45–7.39 (m, 6H), 6.27–6.22 (m, 2H), 5.95 (ddt, 1H, *J*=17.2, 10.3, 6.0 Hz), 5.22 (dd, 1H, *J*=17.2, 1.2 Hz), 5.14 (d, 1H, *J*=10.3 Hz), 3.42 (d, 2H, *J*=4.1 Hz), 3.31 (d, 2H, *J*=6.0 Hz), 0.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 136.7, 136.6, 134.9, 129.3, 127.9, 126.6, 116.1, 54.0, 52.0, −3.7; MS (FAB, +ve) *m/z* 294 ($(M+H)^+$, 50), 197 (29), 159 (21), 121 (20), 109 (20), 55 (100); HRMS (FAB, +ve) *m/z* calcd for $C_{19}H_{24}NSi$: $(M+H)^+$, 294.1678, found: $(M+H)^+$, 294.1671. Anal. calcd for $C_{19}H_{23}NSi$: C, 77.76; H, 7.90; N, 4.77. Found: C, 77.69; H, 7.80; N, 4.70.

4.1.5. Preparation of (*E*)-hex-5-enyl-(3-(methyldiphenylsilyl)propenyl)-amine (11b). 5-Hexenyl-1-amine (300 mg, 3.02 mmol, 1.1 equiv.) was added to aldehyde **10** (699 mg, 2.75 mmol, 1.0 equiv.) in dry MeOH (6 mL) and the mixture was stirred at room temperature for 2 h, prior to the addition of $NaBH_4$ (114 mg, 3.02 mmol, 1.1 equiv.). The mixture was stirred at room temperature for 18 h, after which H_2O (20 mL) was added and the combined solvents evaporated. The residue was partitioned between Et_2O (30 mL) and H_2O (30 mL) and the separated aqueous layer was extracted further with Et_2O (2×20 mL). The combined ethereal phases were dried ($MgSO_4$) and rotary evaporated to give **11b** (846 mg, 92%) as a colorless oil, which was used without further purification: TLC R_f 0.47 (EtOAc; $KMnO_4$); IR (thin film) 1670, 1428, 791, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.53 (m, 4H), 7.49–7.33 (m, 6H), 6.24 (m, 2H), 5.86 (m, 1H), 5.07 (d, 1H, *J*=18 Hz), 5.01 (d, 1H, *J*=11 Hz), 3.42 (d, 2H, *J*=4 Hz), 2.68 (t, 2H, *J*=7 Hz), 2.12 (m, 2H), 1.53 (m, 4H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 138.8, 136.7, 134.9, 129.3, 127.9, 126.3, 114.6, 54.8, 49.5, 33.7, 30.2, 26.7, −3.7; MS (CI, NH_3) *m/z* 336 ($(M+H)^+$, 100), 257 (12); HRMS (CI,

NH_3) *m/z* calcd for $C_{22}H_{30}NSi$: $(M+H)^+$, 336.2148, found: $(M+H)^+$, 336.2144. Anal. calcd for $C_{22}H_{29}NSi$: C, 78.75; H, 8.71; N, 4.17. Found: C, 78.91; H, 8.86, N, 3.96.

4.1.6. Preparation of *N*-(5-hexen-1-yl)-*N*-methyl-*N*-(3*E*-(methyldiphenylsilyl)-propenyl)amine (5). Amine **11b** (0.7 g, 2.1 mmol, 1.0 equiv.) was added to HCO_2H (98% w/v; 0.2 mL, 5.2 mmol, 2.5 equiv.) at 0 °C and the resulting clear solution was stirred for 5 min prior to the addition of aqueous formaldehyde (37% w/v; 0.5 mL, 6.3 mmol, 3.0 equiv.). The cloudy solution was heated to 90 °C under reflux for 3 h, prior to the addition of 10% NaOH (10 mL) and extraction with CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2/MeOH, 19:1) to give **5** (0.6 g, 83%) as a clear colorless oil: TLC R_f 0.25 (CH_2Cl_2/MeOH, 19:1; UV, $KMnO_4$); IR (thin film) 1428, 1250, 1112, 791, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.36 (m, 10H), 6.29 (dt, 1H, *J*=18.5, 5.0 Hz), 6.22 (d, 1H, *J*=18.5 Hz), 5.87 (ddt, 1H, *J*=17.0, 10.0, 7.0 Hz), 5.07 (d, 1H, *J*=17.0 Hz), 5.02 (d, 1H, *J*=10.0 Hz), 3.19 (d, 2H, *J*=5.0 Hz), 2.42 (t, 2H, *J*=7.0 Hz), 2.29 (s, 3H), 2.13 (q, 2H, *J*=7.0 Hz), 1.62–1.41 (m, 4H), 0.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 138.8, 136.7, 134.9, 129.3, 128.7, 127.9, 114.6, 63.7, 57.4, 42.5, 33.7, 26.9, −3.7; MS (CI, NH_3) *m/z* 350 ($(M+H)^+$, 100), 288 (15), 280 (17); HRMS (CI, NH_3) *m/z* calcd for $C_{23}H_{32}NSi$: $(M+H)^+$, 350.2304, found: $(M+H)^+$, 350.2315. Anal. calcd for $C_{23}H_{31}NSi$: C, 79.02; H, 8.94; N, 4.01. Found: C, 79.13; H, 8.96; N, 4.13.

4.1.7. Preparation of *N*-(6-methylhept-5-en-1-yl)-*N*-(3*E*-(methyldiphenylsilyl)-propenyl)amine (6). Diene **5** (100 mg, 0.29 mmol, 1.0 equiv.), catalyst **7** (25 mg, 0.03 mmol, 0.1 equiv.) and 2-methyl-2-butene (3.0 mL) in CH_2Cl_2 (0.1 mL) were heated at reflux under N_2 for 18 h. Rotary evaporation and chromatography (CH_2Cl_2/MeOH, 39:1) gave **6** (88 mg, 82%) as a brown oil: TLC R_f 0.20 (CH_2Cl_2/MeOH, 39:1; UV, $KMnO_4$); IR (thin film) 1680, 1618, 1449, 1429, 1378, 792, 733, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.55 (m, 4H), 7.40–7.38 (m, 6H), 6.26 (dd, 1H, *J*=19.0, 4.5 Hz), 6.18 (d, 1H, *J*=19.0 Hz), 5.15 (t, 1H, *J*=6.0 Hz), 3.16 (d, 2H, *J*=4.5 Hz), 2.41–2.40 (m, 2H), 2.26 (s, 3H), 2.20–2.01 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.52–1.47 (m, 2H), 1.41–1.31 (m, 2H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 136.7, 134.8, 131.5, 129.3, 128.7, 127.8, 124.6, 63.7, 57.6, 42.4, 28.0, 27.8, 27.1, 25.8, 17.8, −3.7; MS (CI, NH_3) *m/z* 350 ($(M+H)^+$, 100), 288 (15), 280 (17); HRMS (CI, NH_3) *m/z* calcd for $C_{25}H_{36}NSi$: $(M+H)^+$, 378.2617, found: $(M+H)^+$, 378.2614. Anal. calcd for $C_{25}H_{35}NSi$: C, 79.51; H, 9.34; N, 3.71. Found: C, 79.35; H, 9.09; N, 3.61.

4.1.8. Preparation of *N*-propenyl-*N*-(3*E*-(methyldiphenylsilyl)propenyl)-3-butenamide (12a). Dicyclohexyl-carbodiimide (774 mg, 3.75 mmol, 1.1 equiv.) in DMF (5 mL) was added with stirring to amine **11a** (1.0 g, 3.4 mmol, 1.0 equiv.), 3-butenoic acid (320 μL, 3.75 mmol, 1.1 equiv.) and *N*,*N*-dimethylaminopyridine (458 mg, 3.75 mmol, 1.1 equiv.) in DMF (15 mL) at 0 °C. After 18 h at 30 °C, the mixture was filtered to remove dicyclohexylurea and the filtrate was evaporated. The residue in EtOAc (30 mL) was washed with saturated aqueous $NaHCO_3$ (20 mL) H_2O (30 mL), saturated aqueous NH_4Cl (20 mL) and H_2O (30 mL). The solution was dried ($MgSO_4$), rotary evaporated and chromatographed (hexanes/EtOAc, 9:1) to give **12a** (1.82 g, 64%) as an oily mixture of rotamers: TLC R_f 0.73 (EtOAc; $KMnO_4$); IR (thin film) 1624, 1461, 1428, 1199, 1112, 995, 917, 791, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.41–7.39 (m, 6H), 6.20–5.93 (m, 3H), 5.85–5.72 (m, 1H), 5.25–5.07 (m, 2H), 4.14–3.90 (m, 4H), 3.18–3.12 (m, 2H), 0.66 and 0.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 and 171.0, 144.8 and 143.8, 136.3 and 135.0, 134.8 and 134.7, 133.2 and 132.8, 131.8 (2C), 129.6 and 129.4, 128.3 and 127.8, 128.0 and 127.9, 117.8 (2C), 117.5 and 116.8, 51.4 and 50.1, 49.5 and 48.4, 38.5 and 38.4, −3.7 and −3.8; MS (FAB, +ve) *m/z* 362 ($(M+H)^+$, 100), 284 (12), 197 (48), 159 (17), 121 (18), 55 (16); HRMS (FAB, +ve) *m/z* calcd for $C_{23}H_{28}NOSi$: $(M+H)^+$, 362.1940, found: $(M+H)^+$, 362.1951.

4.1.9. Preparation of 1-[(*E*)-3-(methyldiphenylsilyl)propenyl]-3,6-dihydro-1*H*-pyridin-2-one (13). Diene **12a** (273 mg, 0.75 mmol, 1.0 equiv.) and catalyst **7** (51 mg, 0.075 mmol, 0.1 equiv.) in CH_2Cl_2 (3.0 mL) were stirred for 18 h at room temperature under N_2. Rotary evaporation and chromatography (PhMe/EtOAc, 19:1) afforded **13** (200 mg, 80%) as an oil: TLC R_f 0.42 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 1649, 1490, 1427, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 4H), 7.46–7.38 (m, 6H), 6.20–6.11 (m, 2H), 5.83–5.74 (m, 2H), 4.24 (d, 2H, *J*=3.6 Hz), 4.24 (d, 2H, *J*=3.6 Hz), 3.91 (m, 2H), 3.04 (m, 2H), 0.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 143.9, 136.2, 134.8, 129.5, 128.5, 128.0, 122.7, 120.9, 51.1, 48.6, 32.2, −3.7; MS (EI) *m/z* 333 (37), 332 ($M^{+\cdot}$), 318 (19), 256 (100), 216 (35), 197 (95), 136 (54), 105 (38); HRMS (EI) *m/z* calcd for $C_{21}H_{22}NOSi$: ($M^{+\cdot}$), 332.1471, found ($M^{+\cdot}$), 332.1464. Anal. calcd for $C_{21}H_{23}NOSi$: C, 75.63; H, 6.95; N, 4.20. Found: C, 75.42; H, 7.06; N, 4.12.

4.1.10. Preparation of 2-(3*E*-(methyldiphenylsilyl)propenyl)-2-piperidinone (14). Platinum oxide (6.8 mg, 0.03 mmol, 0.1 equiv.) and alkene **13** (100 mg, 0.3 mmol) in dry PhH (3.0 mL) were purged with H_2, cooled to −78 °C, evacuated, purged again with H_2, and the process repeated twice. The mixture was stirred under H_2 at room temperature for 18 h. Silica gel (200 mg) was added and the mixture was filtered. Rotary evaporation gave **14** (99 mg, 98%) as a clear colorless oil: TLC R_f 0.16 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 3067, 3047, 1642, 1492, 1427, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 4H), 7.44–7.39 (m, 6H), 6.09 (m, 2H), 4.16 (d, 2H, *J*=2.5 Hz), 3.26 (m, 2H), 2.44 (m, 2H), 1.83 (m, 4H), 0.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 144.5, 136.4, 134.8, 129.4, 128.4, 127.9, 51.5, 47.6, 32.3, 23.2, 21.5, −3.7; MS (EI) *m/z* 335 ($M^{+\cdot}$, 38), 320 (26), 258 (85), 218 (52), 197 (100), 181 (18), 138 (79), 121 (32), 105 (40), 55 (23); HRMS (EI) *m/z* calcd for $C_{21}H_{25}NOSi$: ($M^{+\cdot}$), 335.1705, found: ($M^{+\cdot}$), 335.1711. Anal. calcd for $C_{21}H_2NOSi$: C, 75.18; H, 7.51; N, 4.17. Found: C, 75.24; H, 7.63; N, 4.26.

4.1.11. Preparation of 1-propenyl-2-piperidinone (15). Bu_4NF in THF (1.0 M; 5.2 mL, 5.2 mmol, 5.2 equiv.) was

added to silylalkene **14** (350 mg, 1.0 mmol, 1.0 equiv.) in DMSO (5.0 mL) at room temperature. The reaction mixture was heated to 80 °C for 1.5 h, and was then partitioned between Et_2O (10 mL) and H_2O (10 mL). The separated aqueous layer was extracted further with Et_2O (2×10 mL) and the combined extracts were dried ($MgSO_4$) and rotary evaporated. Chromatography (hexanes/EtOAc, 4:1) gave **15**[17] (143 mg, 99%) as a clear colorless oil: TLC R_f 0.10 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 1639, 1495, 1466, 1416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddt, 1H, J=18.0, 9.0, 5.8 Hz), 5.16 (dd, 1H, J=9.0, 1.4 Hz), 5.14 (dd, 1H, J=18.0, 1.4 Hz), 4.99 (d, 2H, J=5.8 Hz), 3.24 (m, 2H), 2.39 (m, 2H), 1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 132.9, 117.1, 49.3, 47.3, 32.3, 23.2, 21.4; MS (CI, NH_3) m/z 140 ($(M+H)^+$ 100), HRMS (CI, NH_3) m/z calcd for $C_8H_{14}NO$: $(M+H)^+$, 140.10754, found: $(M+H)^+$, 140.10731.

4.1.12. Preparation of 1-(3-methylbut-2-enyl)piperidin-2-one (16a). Alkene **15** (5.0 mg, 0.036 mmol, 1.0 equiv.) and catalyst **7** (3.0 mg, 0.0036 mmol, 0.1 equiv.) in 3-methyl-2-butene (9.0 mL) were heated at reflux at 35 °C for 2 h, rotary evaporated and chromatographed (hexanes/EtOAc, 1:1) to give **16a** (6.0 mg, 95%) as a colorless oil: TLC R_f 0.27 (EtOAc; $KMnO_4$); IR (thin film) 1641, 1494, 1448, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (t, 1H, J=6.0 Hz), 4.02 (d, 2H, J=6.0 Hz), 3.23 (m, 2H), 2.40 (m, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 1.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 136.1, 119.7, 46.9, 44.2, 32.4, 25.7, 23.2, 21.4, 17.8; MS (CI, NH_3) m/z 168 ($(M+H)^+$, 100), 124 (6), 100 (10); HRMS (CI, NH_3) m/z calcd for $C_{10}H_{17}NO$: $(M+H)^+$, 168.13884, found: $(M+H)^+$, 168.13856. Anal. calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.81; H, 10.14; N, 8.27.

4.1.13. Preparation of 1-(4-acetoxy-2*E*-buten-1-yl)-2-piperidinone (16b). Catalyst **7** (62 mg, 0.07 mmol, 0.1 equiv.) was added to alkene **15** (0.1 mL, 0.7 mmol, 1.0 equiv.) and allyl acetate (155 μL, 1.4 mmol, 2.0 equiv.) in degassed CH_2Cl_2 at room temperature, under N_2. After 18 h, rotary evaporation and chromatography (EtOAc) gave **16b** (68 mg, 67%) as a colorless oil: TLC R_f 0.23 (EtOAc; $KMnO_4$); IR (thin film) 1739, 1640, 1448, 1355, 1235 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79–5.64 (m, 2H), 4.59–4.54 (m, 2H), 4.04–3.98 (m, 2H), 3.29–3.21 (m, 2H), 2.45–2.38 (m, 2H), 2.08 (s, 3H), 1.87–1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.6, 129.2, 126.8, 48.1, 47.4, 32.3, 23.1, 21.3, 20.9; MS (CI, NH_3) m/z ($(M+H)^+$, 212), 152 (38), 100 (10), 45 (9); HRMS (CI, NH_3) m/z calcd for $C_{11}H_{18}NO_3$ 212.1287, found 212.1289. Anal. calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: 62.47; H, 7.99; N, 6.61.

4.1.14. Preparation of 1-(4-oxo-2*E*-penten-1-yl)-2-piperidinone (16c). Methyl vinyl ketone (180 μL, 2.1 mmol) and catalyst **7** (125 mg, 0.14 mmol) were added to alkene **15** (100 mg, 0.7 mmol) in degassed dry $CHCl_3$ and the mixture was heated at reflux for 20 h and allowed to cool to room temperature. Rotary evaporation and chromatography (gradient elution, EtOAc/MeOH, 1:0 to 97:3) gave **16c** (70 mg, 54%) as a brown oil: TLC R_f 0.22 (EtOAc/MeOH, 97:3; $KMnO_4$); IR (thin film) 1677, 1641, 1418, 1355, 1257, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (dt, 1H, J=16.2, 5.3 Hz), 6.05 (d, 1H, J=16.2 Hz), 4.15 (d, 2H, J=5.3 Hz), 3.29–3.20 (m, 2H), 2.44–2.37 (m, 2H), 2.26–2.23 (m, 2H), 1.85–1.79 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 169.9, 141.7, 131.6, 48.2, 48.0, 32.2, 29.7, 27.0, 23.2, 21.3; MS (CI, NH_3) m/z 212 (3), 196 (13), 182 ($(M+H)^+$, 100), 138 (5); HRMS (CI, NH_3) m/z calcd for $C_{10}H_{16}NO_2$: $(M+H)^+$, 182.1182, found $(M+H)^+$, 182.1185.

4.1.15. Preparation of *N*-(3*E*-(methyldiphenylsilyl)propenyl)-*N*-propenyl-pent-4-enamide (12b). 4-Pentenoyl chloride (1.1 mL, 10 mmol, 1.4 equiv.) in dry CH_2Cl_2 (40 mL) was slowly added with stirring to amine **11a** (2.1 g, 7.2 mmol, 1.0 equiv.) and Et_3N (1.6 mL, 11 mmol, 1.5 equiv.) in CH_2Cl_2 (40 mL) at 0 °C. After standing at 0 °C for 30 min and at room temperature for 4 h, H_2O (50 mL) was added and the organic phase washed with H_2O (2×30 mL) and saturated aqueous NaCl (40 mL) and dried ($MgSO_4$). Rotary evaporation and chromatography (hexanes/EtOAc, 4:1) gave **12b** (2.1 g, 81%) as a clear yellow oil containing a mixture of rotamers: TLC R_f 0.66 (EtOAc; $KMnO_4$); IR (thin film) 1650, 1428, 1251, 1191, 1112, 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.45–7.40 (m, 6H), 6.18–6.00 (m, 2H), 5.91–5.72 (m, 2H), 5.24–4.98 (m, 4H), 4.19–3.88 (m, 4H), 2.42 (m, 4H), 0.67 and 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 and 172.3, 145.0 and 144.0, 137.6, 136.3 and 136.0, 134.8 and 134.7, 134.0, 133.4 and 132.9, 128.1 and 128.0, 127.9 and 127.6, 117.3 and 116.7, 115.2, 51.3 and 50.2, 49.4 and 48.5, 32.4 and 32.3, 29.4 and 29.3, −3.7 and −3.8; MS (CI, NH_3) m/z 375 ($M^{+\cdot}$, 37), 360 (20), 334 (24), 298 (74), 258 (15), 214 (24), 199 (100), 137 (17), 77 (10), 55 (10); HRMS (CI, NH_3) m/z calcd for $C_{24}H_{29}NOSi$: ($M^{+\cdot}$), 375.2018, found: ($M^{+\cdot}$), 375.2006. Anal. calcd for $C_{24}H_{29}NOSi$: C, 76.75; H, 7.78; N, 3.73. Found: C, 76.26; H, 7.74; N, 3.65.

4.1.16. Preparation of *N*-(3*E*-(methyldiphenylsilyl)propenyl)-2-((*t*-butyloxy-carbonyl)-amino)-*N*-propenyl-pent-4-enamide (12c). *N*,*N*-Dimethylaminopyridine (114 mg, 0.93 mmol, 1.2 equiv.), 2-((*t*-butyloxycarbonyl)amino)-4-pentenoic acid (225 mg, 0.85 mmol, 1.1 equiv.) and dicyclohexylcarbodiimide (192 mg, 0.93 mmol, 1.2 equiv.) in CH_2Cl_2 (1.5 mL) were added sequentially to amine **11a** (227 mg, 0.775 mmol) in CH_2Cl_2 (2 mL) at room temperature. The mixture was stirred at room temperature for 3 h when the precipitate of *N*,*N*-dicyclohexylurea was removed by filtration. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 mL) H_2O (2 mL), saturated aqueous NH_4Cl (1 mL) and H_2O (2×2 mL). The organic layer was dried ($MgSO_4$), rotary evaporated and chromatographed (gradient elution; hexanes/EtOAc, 99:1 to 95:5) to give **12c** (354 mg, 93%) as a pale yellow oil: TLC R_f 0.18 (hexanes/EtOAc, 4:1); IR (thin film) 1713, 1651, 1484, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.49 (m, 4H), 7.39–7.37 (m, 6H), 6.13–6.02 (m, 2H), 5.77–5.69 (m, 2H), 5.30–5.03 (m, 4H), 4.65–4.52 (m, 1H), 4.27–4.21 (m, 1H), 4.01–3.99 (m, 2H), 2.53–2.30 (m, 2H), 1.43 (s, 9H), 0.65 and 0.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 and 171.8, 155.2, 144.1 and 143.8, 136.2 and 135.8, 134.8, 132.8 and 132.6, 129.5 and 129.4, 128.7 and 128.5, 128.0 and 127.9, 118.6, 117.6, 79.6, 51.4 and 49.8, 49.5 and 48.4, 37.9, 28.3, −3.8; MS (EI) m/z 490 ($M^{+\cdot}$, 6), 339 (10), 197 (27), 170 (24), 159 (22), 114 (67), 70 (100), 57 (91); HRMS (EI) m/z calcd for

$C_{29}H_{38}N_2O_3Si$: ($M^{+\cdot}$), 490.2652, found: ($M^{+\cdot}$), 490.2661. Anal. calcd for $C_{29}H_{38}N_2O_3Si$: C, 70.98; H, 7.81; N, 5.71. Found: C, 71.06; H, 7.62; N, 5.86.

4.1.17. Preparation of 1-(3*E*-(methyldiphenylsilyl)propenyl)-1,3,4,7-tetrahydro-2-azepinone (17). Diene **12b** (100 mg, 0.26 mmol) and catalyst **7** (15 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) were heated for 15 min in the microwave at 100 °C. Rotary evaporation and chromatography (gradient elution; hexanes/EtOAc, 3:1 to 1:1) gave **17** (48 mg, 52%) as a pale yellow oil: TLC R_f 0.25 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 1650, 1481, 1427, 1112, 734, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 4H), 7.44–7.36 (m, 6H), 6.15 (d, 1H, J=18.0 Hz), 6.06 (dt, 1H, J=18.0, 4.0 Hz), 5.81–5.70 (m, 2H), 4.20 (d, 2H, J=4.0 Hz), 3.85 (d, 2H, J=4.0 Hz), 2.79 (t, 2H, J=6.5 Hz), 2.44 (m, 2H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 145.1, 136.3, 134.8, 131.6, 129.4, 128.0, 127.9, 124.5, 52.5, 45.5, 33.6, 25.2, −3.7; MS (EI) m/z 347 ($M^{+\cdot}$, 34), 332 (16), 270 (68), 230 (17), 197 (100), 150 (44), 137 (24), 121 (16), 105 (27), 91 (15), 84 (43), 67 (59), 55 (56); HRMS (EI) m/z calcd for $C_{22}H_{25}NOSi$: ($M^{+\cdot}$), 347.1705, found: ($M^{+\cdot}$), 347.1699. Anal. calcd for $C_{22}H_{25}NOSi$: C, 76.03; H, 7.25; N, 4.03. Found: C, 75.93; H, 7.27; N, 3.94.

4.1.18. Preparation of 1-(3*E*-(methyldiphenylsilyl)propenyl)-2-azepanone (19). Degassed dry THF (2.5 mL) and EtOH (2.5 mL) were added to $(Ph_3P)_3RhCl$ (21 mg, 0.23 mmol, 0.1 equiv.) and alkene **17** (80 mg, 0.23 mmol, 1.0 equiv.) under N_2. The mixture was purged once with H_2 and subsequently stirred under H_2 for 3 h, monitoring the progress of reaction by ^1H NMR spectroscopy. Rotary evaporation and chromatography (hexanes/EtOAc, 1:1) gave **19** (69 mg, 86%) as a clear colorless oil: TLC R_f 0.25 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 1644, 1482, 1444, 1428, 1354, 1195, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.51 (m, 4H), 7.46–7.35 (m, 6H), 6.14–6.05 (m, 2H), 4.15 (d, 2H, J=3.8 Hz), 4.32 (m, 2H), 3.32 (m, 2H), 2.57 (m, 2H), 1.72 (m, 4H), 1.61 (m, 2H), 0.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 145.4, 136.3, 134.8, 129.4, 128.3, 127.9, 52.6, 48.9, 37.1, 30.0, 28.4, 23.5, −3.7; MS (EI) m/z 349 ($M^{+\cdot}$, 40), 334 (20), 274 (55), 272 (50), 232 (35), 197 (100), 174 (22), 152 (45), 105 (31); HRMS (EI) m/z calcd for $C_{22}H_{27}NOSi$: ($M^{+\cdot}$), 349.1862, found: ($M^{+\cdot}$), 349.1877. Anal. calcd for $C_{22}H_{25}NOSi$: C, 75.59; H, 7.79; N, 4.01. Found: C, 75.49; H, 7.84; N, 3.87.

4.1.19. Preparation of 3-((*t*-butyloxycarbonyl)amino)-1-(3*E*-(methyldiphenyl-silyl)propenyl)-1,3,4,7-tetrahydro-2-azepinone (18). Diene **12b** (50 mg, 0.1 mmol) and catalyst **7** (9 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) were heated for 15 min in the microwave at 100 °C. Rotary evaporation and chromatography (hexanes/EtOAc, 10:1 to 4:1) gave **18** (28 mg, 59%) as a pale yellow oil containing a mixture of rotamers: TLC R_f 0.47 (hexanes/EtOAc, 2:1; $KMnO_4$); IR (thin film) 1712, 1658, 1480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.48 (m, 4H), 7.41–7.31 (m, 6H), 6.17 and 6.12 (m, 1H), 6.03 and 5.98 (m, 1H), 5.87 (d, 1H, J=7.0 Hz), 5.75 (m, 2H), 4.96 (m, 1H), 4.38 and 4.34 (m, 2H), 4.29 and 4.12 (dd, 2H, J=16.0, 5.0 Hz), 3.36 (dd, 1H, J=17.0, 7.0 Hz), 2.67 (dd, 1H, J=18.0, 4.0 Hz), 2.23 (m, 1H), 1.47 (s, 9H), 0.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 155.1, 144.2, 136.1, 134.8, 130.4, 129.4, 129.0, 127.9, 127.3, 79.6, 53.5, 50.0, 45.2, 33.5, 28.4, −3.7; MS (EI) m/z 462 ($M^{+\cdot}$, 43), 406 (38), 385 (63), 373 (35), 329 (60), 311 (46), 197 (64), 159 (21), 121 (20), 114 (21), 105 (22), 82 (18), 70 (29), 57 (100); HRMS (EI) m/z calcd for $C_{27}H_{34}N_2O_3Si$: ($M^{+\cdot}$), 462.2338, found: ($M^{+\cdot}$), 462.2357.

4.1.20. Preparation of 3-((*t*-butyloxycarbonyl)amino)-1-(3*E*-(methyldiphenyl-silyl)propenyl)-2-azepanone (20). Degassed dry THF (0.5 mL) and EtOH (0.5 mL) were added to $(Ph_3P)_3RhCl$ (5 mg, 0.005 mmol, 0.1 equiv.) and **18** (25 mg, 0.05 mmol, 1.0 equiv.) under N_2. The mixture was purged once with H_2 and stirred under H_2 for 3 h, monitoring reaction progress by ^1H NMR spectroscopy. Rotary evaporation and chromatography gave **20** (20 mg, 80%) as a clear, colorless oil: TLC R_f 0.73 (hexanes/EtOAc, 2:1; $KMnO_4$); IR (thin film) 1710, 1648, 1479, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.47 (m, 4H), 7.43–7.32 (m, 6H), 6.17 and 6.14 (m, 1H), 6.10 (m, 2H), 4.39 (m, 2H), 3.97 (dd, 1H, J=15.0, 4.0 Hz), 3.47 (m, 1H), 3.22 (dd, 1H, J=15.0, 4.0 Hz), 2.12–0.80 (m, 6H), 1.46 (s, 9H), 0.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 155.2, 144.4, 136.1, 134.9, 134.8, 134.0, 129.7, 129.4, 128.4, 79.4, 53.3, 52.9, 47.9, 32.7, 29.7, 27.9, 27.6, −3.7; MS (EI) m/z 464 ($M^{+\cdot}$, 7), 408 (7), 387 (8), 331 (9), 313 (18), 277 (12), 225 (11), 197 (33), 172 (20), 149 (19), 116 (63), 83 (30), 72 (63), 57 (100); HRMS (EI) m/z calcd for $C_{27}H_{36}N_2O_3Si$: ($M^{+\cdot}$), 464.2495, found: ($M^{+\cdot}$), 464.2515.

4.1.21. Preparation of *N*-5-hexenyl-*N*-(3*E*-(methyldiphenylsilyl)propenyl)-10-undecenamide (12d). 10-Undecenoyl chloride (264 mg, 1.3 mmol, 1.3 equiv.) in dry CH_2Cl_2 (1 mL) was added slowly to amine **11b** (335 mg, 1.0 mmol, 1.0 equiv.) and Et_3N (0.21 mL, 1.5 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL) at 0 °C. After 18 h at room temperature, the mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (10 mL) and the layers were separated. The aqueous layer was extracted further with Et_2O (2×20 mL). The combined ethereal phases were dried ($MgSO_4$) and rotary evaporated. Chromatography (hexanes/EtOAc, 20:1 to 5:1) gave **12d** (429 mg, 86%) as an oil: TLC R_f 0.63 (hexanes/EtOAc, 3:1; $KMnO_4$); IR (thin film) 1648, 1463, 1428, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.48 (m, 4H), 7.44–7.35 (m, 6H), 6.09 (m, 2H), 5.82 (m, 2H), 5.00 (m, 4H), 4.15 (d, 1H, J=3.0 Hz), 4.01 (d, 1H, J=3.0 Hz), 3.38 (t, 1H, J=7.0 Hz), 3.26 (t, 1H, J=7.0 Hz), 2.36 (t, 1H, J=7.0 Hz), 2.27 (t, 1H, J=7.0 Hz), 2.08 (m, 4H), 1.66 (m, 2H), 1.55 (m, 2H), 1.43–1.23 (m, 12H), 0.66 and 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.7, 145.5, 144.5, 139.2, 138.6, 138.0, 136.4, 136.0, 134.8, 134.7, 129.5, 129.3, 128.0, 127.9, 127.5, 127.3, 115.1, 114.6, 114.2, 52.3, 50.2, 47.5, 46.3, 33.9, 33.6, 33.4, 33.2, 33.1, 29.6, 29.5, 29.4, 29.2, 29.0, 28.4, 27.4, 26.3, 26.1, 25.6, 25.4, −3.8; MS (EI) 501 ($M^{+\cdot}$, 40), 460 (16), 424 (32), 390 (33), 362 (28), 304 (50), 266 (14), 197 (100), 159 (36), 138 (19), 121 (26), 112 (18), 83 (18), 69 (22), 55 (74); HRMS (EI) calcd for $C_{33}H_{47}NOSi$: ($M^{+\cdot}$), 501.3426, found: ($M^{+\cdot}$), 501.3449. Anal. calcd for $C_{33}H_{47}NOSi$: C, 78.98; H, 9.44; N, 2.79. Found: C, 78.74; H, 9.58; N, 2.82.

4.1.22. Preparation of 1-(3*E*-(methyldiphenylsilyl)propenyl)-1-azacyclohexadec-11-en-2-one (21). Diene **12d** (251 mg, 0.5 mmol, 1.0 equiv.) and catalyst **7** (44 mg,

0.05 mmol, 0.1 equiv.) in CH_2Cl_2 (25.0 mL) were stirred at reflux for 24 h under N_2. Rotary evaporation and chromatography (hexanes/EtOAc, 20:1 to 3:1) gave **21** (*cis*/*trans*, 1:1) (153 mg, 65%) as a pale yellow oil: TLC R_f 0.33 (hexanes/EtOAc, 3:1; $KMnO_4$); IR (thin film) 1642, 1461, 1428, 1112, 790, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.47 (m, 4H), 7.42–7.33 (m, 6H), 6.10 (m, 2H), 5.31 (m, 2H), 4.16 (m, 1H), 4.04 (m, 1H), 3.43 (t, 1H, J=7.0 Hz), 3.28 (t, 1H, J=7.0 Hz), 2.32 (m, 2H), 2.03 (m, 4H), 1.67 (m, 2H), 1.56 (m, 1H), 1.47 (m, 1H) 1.41–1.14 (m, 12H), 0.64 and 0.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 173.2, 145.6, 144.8, 136.4, 135.9, 134.8, 134.7, 131.4, 131.3, 130.9, 130.4, 130.2, 129.7, 129.5, 129.3, 127.9, 127.9, 127.5, 52.8, 50.9, 48.7, 46.1, 32.8, 32.3, 32.1, 31.0, 28.6, 28.5, 28.4, 28.0, 27.8, 27.6, 27.1, 26.9, 26.6, 26.2, 25.9, 25.1, −3.8; MS (CI, NH_3) m/z 474 ($(M+H)^+$, 100), 460 (10), 278 (19), 264 (22), 238 (21), 207 (14), 154 (10), 120 (11); HRMS (CI, NH_3) m/z calcd for $C_{31}H_{44}NOSi$: $(M+H)^+$, 474.3192, found: $(M+H)^+$, 474.3183. Anal. calcd for $C_{31}H_{43}NOSi$: C, 78.59; H, 9.15; N, 2.96. Found: C, 78.68; H, 9.29; N, 2.89.

4.1.23. Preparation of 1-(3*E*-(methyldiphenylsilyl)propenyl)-1-azacyclohexa-decan-2-one (22). Degassed dry THF (2.0 mL) and EtOH (2.0 mL) were added to $(Ph_3P)_3$-RhCl (8 mg, 8 μmol, 0.1 equiv.) and diene **21** (40 mg, 0.08 mmol, 1.0 equiv.) under N_2. The mixture was purged once with H_2, and stirred in a H_2 atmosphere for 4 h, whilst monitoring reaction progress by ^1H NMR spectroscopy. Rotary evaporation and chromatography gave **22** (35 mg, 89%) as a pale yellow oil. Analysis by ^1H NMR spectroscopy showed the product to be contaminated by **23** (**22/23** 3.1:1): TLC R_f=0.33 (hexanes/EtOAc, 3:1; $KMnO_4$); IR (thin film) 1642, 1458, 1427, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.48 (m, 4H), 7.43–7.33 (m, 6H), 6.11 (m, 2H), 4.17 (m, 1H), 4.05 (m, 1H), 3.54 and 3.45 (m, 1H), 3.30 and 3.19 (m, 1H), 2.38 (m, 2H), 1.78–1.27 (m, 24H), 0.67 and 0.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.8, 145.4, 144.5, 136.2, 135.7, 134.6, 134.5, 134.2, 129.3, 129.1, 129.0, 128.4, 127.8, 127.7, 127.3, 127.1, 52.2, 49.9, 47.8, 47.6, 45.0, 32.5, 32.3, 27.9, 27.8, 27.4, 27.3, 26.6, 26.5, 26.2, 26.0, 25.9, 25.7, 25.5, 25.4, 24.8, 24.4, 21.8, −3.9; MS (CI, NH_3) m/z 476 ($(M+H)^+$, 100), 462 (25), 414 (8), 400 (8), 387 (6), 282 (50), 279 (30), 249 (12), 240 (19), 214 (8), 52 (15); HRMS (CI, NH_3) m/z calcd for $C_{31}H_{46}NOSi$: $(M+H)^+$, 476.3349, found: $(M+H)^+$, 476.3350. Anal. calcd for $C_{31}H_{45}NOSi$: C, 78.26; H, 9.53; N, 2.94. Found: C, 78.12; H, 9.62; N, 2.99.

4.1.24. Preparation of 1-propenyl-azacyclohexadecan-2-one (24). Bu_4NF in THF (1.0 M; 0.6 mL, 0.6 mmol, 5 equiv.) was added to the mixture of silylalkenes **22** and **23** (61 mg, 0.13 mmol, 1.0 equiv.) in DMSO (2.6 mL) at room temperature. The reaction mixture was heated to 80 °C for 2 h, cooled and partitioned between Et_2O (10 mL) and H_2O (10 mL). The separated organic layer was washed further with H_2O (4×10 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (hexanes/EtOAc, 17:3) gave **24** (31 mg, 87%) as a clear, colorless, oily mixture of rotamers: TLC R_f 0.27 (hexanes/EtOAc, 15:1; $KMnO_4$); IR (thin film) 1646, 1460, 1415 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85–5.72 (m, 1H), 5.21–5.10 (m, 2H), 4.00 (d, 1.4H, J=5.6 Hz), 3.93 (d, 0.7H, J=2.3 Hz), 3.49 (t, 0.7H, J=5.3 Hz), 3.26 (t, 1.4H, J=7.6 Hz); 2.38–2.32 (m, 2H), 1.76–1.49 (m, 4H), 1.45–1.23 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 173.1, 133.8, 133.5, 116.7, 116.4, 50.1, 47.9, 47.4, 44.7, 32.7, 32.4, 27.9, 27.8, 27.7, 27.6, 27.4, 27.2, 26.8, 26.7, 26.5, 26.4, 26.2, 26.1, 26.0, 25.9, 25.7, 25.6, 25.0, 24.6; MS (CI, NH_3) m/z 560 ($(2M+H)^+$, 50), 280 ($(M+H)^+$, 100), 266 (10); HRMS (CI, NH_3) m/z calcd for $C_{18}H_{34}NO$: $(M+H)^+$, 280.2640, found: $(M+H)^+$, 280.2634. Anal. calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.48; H, 11.82; N, 4.94.

4.1.25. Preparation of 1-(3-methylbut-2-enyl)azacyclohexadecan-2-one (25a). 3-Methyl-2-butene (4.5 mL) and catalyst **7** (31 mg, 0.036 mmol, 0.1 equiv.) were added sequentially to lactam **24** (100 mg, 0.36 mmol, 1.0 equiv.) under N_2. The mixture was stirred at 35 °C for 18 h, and the solvent rotary evaporated. Chromatography (hexanes/EtOAc, 9:1) gave alkene **25a** (89 mg, 81%) as a light brown oily mixture of rotamers: TLC R_f 0.27 (hexanes/EtOAc, 9:1; $KMnO_4$); IR (thin film) 1643, 1446, 1421, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14–5.05 (m, 1H), 3.95 (d, 1.4H, J=6.3 Hz), 3.85 (d, 0.7H, J=5.9 Hz), 3.43 (t, 0.7H, J=5.0 Hz), 3.20 (t, 1.4H, J=7.6 Hz), 2.34–2.27 (m, 2H), 1.69 (s, 2.1H), 1.71–1.61 (m, 8H), 1.58–1.45 (m, 2H), 1.38–1.24 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.9, 135.2, 134.8, 121.0, 120.6, 47.2, 45.8, 44.4, 42.6, 32.7, 32.5, 28.0, 27.8, 27.6, 27.5, 27.1, 26.8, 26.5, 26.4, 26.2, 26.0, 25.9, 25.8, 25.7, 25.5, 25.2, 24.5; MS (CI, NH_3) m/z 616 ($(2M+H)^+$, 100), 308 ($(M+H)^+$, 95), 264 (13); HRMS (CI, NH_3) m/z calcd for $C_{20}H_{38}NO$: $(M+H)^+$, 308.2953, found: 308.2952. Anal calcd for $C_{20}H_{37}NO$: C, 78.11; H, 12.13; N, 4.55. Found: C, 78.29; H, 12.38, N, 4.64.

4.1.26. Preparation of 4-(2-oxo-azacyclohexadec-1-yl)-but-2-enyl acetate (25b). Allyl acetate (77 μL, 0.72 mmol, 2.0 equiv.) was added to lactam **24** (100 mg, 0.36 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL). The mixture was degassed with N_2 for 10 min and catalyst **7** (31 mg, 0.036 mmol, 0.1 equiv.) was added. The mixture was stirred under N_2 at 25 °C for 24 h before rotary evaporation. Chromatography (gradient elution; hexanes/EtOAc, 9:1 to hexanes/EtOAc, 4:1) gave alkene **25b** (77 mg, 61%) as a pale brown oil: TLC R_f 0.24 (hexanes/EtOAc, 1:1; $KMnO_4$); IR (thin film) 1743, 1643, 1459, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76–5.60 (m, 2H), 4.53 (d, 2H, J=5.0 Hz), 3.97 (d, 1.5H, J=4.3 Hz), 3.92 (bd m, 0.5H), 3.46 (bd m, 0.5H), 3.23 (t, 1.5H, J=7.6 Hz), 2.35–2.29 (m, 2H), 2.05 (s, 3H), 1.72–1.61 (m, 2H), 1.59–1.47 (m, 2H), 1.41–1.23 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 173.1, 170.7, 170.6, 130.4, 129.7, 126.3, 126.1, 64.3, 63.9, 48.9, 47.5, 46.5, 44.7, 32.6, 32.4, 29.7, 27.9, 27.8, 27.6, 27.4, 27.1, 26.7, 26.4, 26.2, 26.0, 25.9, 25.8, 25.6, 25.0, 24.5, 20.9; MS (CI, NH_3) m/z 369 ($(M+NH_4)^+$, 8), 352 ($(M+H)^+$, 100), 292 (28), 240 (15); HRMS (CI, NH_3) m/z calcd for $C_{21}H_{38}NO_3$: $(M+H)^+$, 352.2852, found: $(M+H)^+$, 352.2850. Anal. calcd for $C_{21}H_{37}NO_3$: C, 71.75; H, 10.61; N, 3.98. Found: C, 71.87; H, 10.52; N, 3.89.

4.1.27. Preparation of 1-(5-oxohex-2*E*-en-1-yl)azacyclohexadecan-2-one (25c). 5-Hexen-2-one (350 μL, 1.1 mmol, 3.0 equiv.) and catalyst **7** (62 mg, 0.07 mmol, 0.2 equiv.) were added sequentially under N_2 to lactam **24** (100 mg, 0.36 mmol, 1.0 equiv.) and the mixture refluxed

for 18 h. Rotary evaporation and chromatography (hexanes/EtOAc, 4:1) gave ketone **25c** (101 mg, 81%) as a brown oily mixture of rotamers: TLC R_f 0.15 (hexanes/EtOAc, 4:1; $KMnO_4$); IR (thin film) 1717, 1459, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57–5.47 (m, 1H), 5.43–5.34 (m, 1H), 4.02–3.80 (m, 2H), 3.43–3.38 (m, 0.5H), 3.18 (t, 1.5H, J=7.6 Hz), 2.48 (t, 2H, J=6.9 Hz), 2.35–2.20 (m, 4H), 1.68–1.44 (m, 4H), 1.41–1.17 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 207.7, 173.6, 173.0, 131.5, 131.2, 130.7, 126.9, 126.4, 126.1, 49.3, 47.2, 46.9, 44.4, 42.9, 42.8, 32.7, 32.5, 29.9, 29.7, 27.9, 27.7, 27.6, 27.4, 27.1, 26.7, 26.4, 26.3, 26.2, 26.0, 25.9, 25.8, 25.6, 25.0, 24.5; MS (CI, NH_3) m/z 367 ($(M+NH_4)^+$, 4), 350 ($(M+H)^+$, 100), 292 (11), 240 (10), 153 (5), 52 (2); HRMS (CI, NH_3) m/z calcd for $C_{22}H_{40}N_1O_2$: $(M+H)^+$, 350.3059, found: $(M+H)^+$, 350.3063. Anal. calcd for $C_{22}H_{39}NO_2$: C, 75.59; H, 11.25; N, 4.01. Found: C, 75.74; H, 11.18; N, 3.95.

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Prepackaged Ramberg–Bäcklund reagents: useful tools for organic synthesis

Eric Block,* Hak Rim Jeon, David Putman and Shao-Zhong Zhang

Department of Chemistry,University at Albany, State University of New York, Albany, NY 12222, USA

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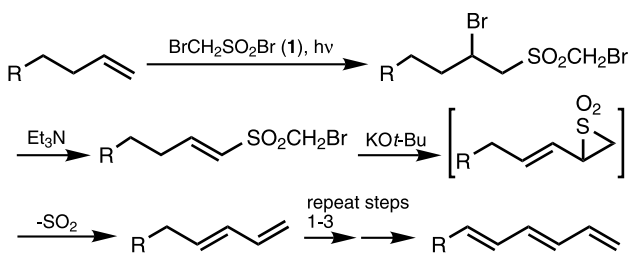
Dedicated to Professor Dieter Seebach on the occasion of the 2003 Tetrahedron Prize with admiration and respect for his many seminal contributions to chemistry, particularly his elegant work in the fields of organosulfur and organoselenium chemistry which has served as an inspiration for our own work

Abstract—The synthesis and reactions of several α,β-unsaturated chloromethyl sulfones is presented, for example [(chloromethyl)-sulfonyl]-1,3-propadiene (**4**), [(chloromethyl)sulfonyl]ethene (**5**), [(dichloromethyl)sulfonyl]ethene (**6**) and (*E*,*Z*)-1,2-bis[(chloromethyl)-sulfonyl]ethene (**7**). These compounds serve as 'prepackaged' Ramberg–Bäcklund reagents, which following an appropriate first step, such as Diels–Alder addition, react with base giving Ramberg–Bäcklund products.

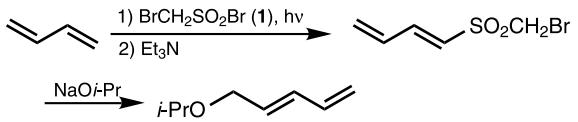
1. Introduction

'Prepackaged' Ramberg–Bäcklund reagents may be defined as compounds having sulfonyl and α-halogen groups which, following an appropriate first step, require only base to give by Ramberg–Bäcklund ('RB') reaction[1] olefinic end products with an increase in total number of carbon atoms. In 1983, we described the use of bromomethanesulfonyl bromide ($BrCH_2SO_2Br$, **1**) as a one-carbon example of such a prepackaged reagent (Scheme 1).[2] Reagent **1** readily undergoes light-induced free radical addition to alkenes. Dehydrobromination of the addition products followed by vinylogous RB reaction gives 1,3-dienes as *E*,*Z*-mixtures. Repetition of the process gives isomeric 1,3,5-trienes.

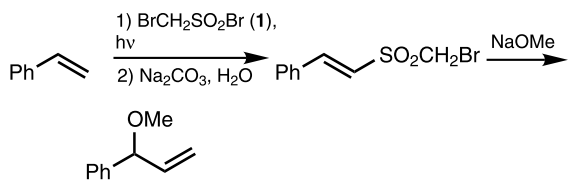
1-[(Bromomethyl)sulfonyl]-1,3-butadiene, from sequential reaction of 1,3-butadiene with **1** and triethylamine, undergoes vinylogous Michael-induced RB ('MIRB') reaction with sodium isopropoxide giving (*E*/*Z*)-1-isopropoxy-2,4-pentadiene (Scheme 2).[2e] A related sequence involving the adduct of **1** with styrene has been reported (Scheme 3).[3] Reagent **1** adds to reactive single bonds giving adducts which undergo the RB reaction (Scheme 4).[4]



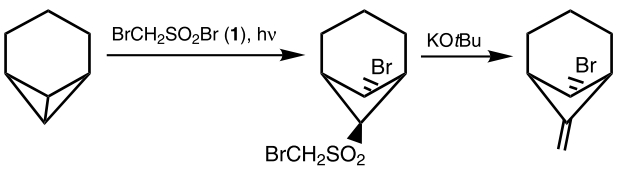
Scheme 1. Use of $BrCH_2SO_2Br$ (**1**) as a prepackaged RB reagent in an iterative process affording 1,3,5-trienes.



Scheme 2. Addition of **1** to 1,3-butadiene with dehydrobromination and Michael-induced Ramberg–Bäcklund (MIRB) reaction with NaO*i*-Pr.



Scheme 3. Addition of **1** to styrene followed by dehydrobromination and MIRB reaction with NaOMe.



Scheme 4. Addition of **1** to a strained single bond and then RB reaction.

Keywords: Ramberg–Bäcklund reaction; α-Halosulfones.
* Corresponding author. Tel.: +1-518-4424459; fax: +1-518-4423462; e-mail address: eb801@albany.edu

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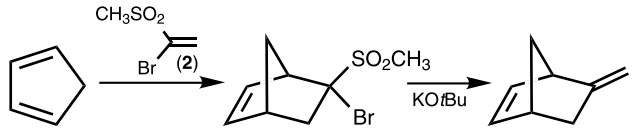
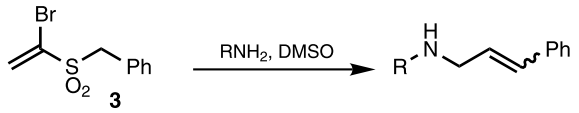


Scheme 5. Tandem Diels–Alder RB reaction of $CH_2{=}C(Br)SO_2CH_3$ (**2**).

An example of a three-carbon prepackaged RB reagent, 1-bromo-1-(methylsulfonyl)ethene ($CH_2{=}C(Br)SO_2CH_3$, **2**) was reported in 1972 (Scheme 5).[5] In this case, reagent **2** underwent Diels–Alder addition followed by RB reaction. A MIRB reaction (Scheme 6) involving benzyl 1-bromovinyl sulfone ($CH_2{=}C(Br)SO_2CH_2Ph$, **3**) with various nucleophiles has recently been described.[6] In a preliminary report in 1990 we showed that the four-carbon prepackaged RB reagent [(chloromethyl)sulfonyl]-1,2-propadiene ($CH_2{=}C{=}CHSO_2CH_2Cl$, **4**) upon tandem Diels–Alder RB reaction gives the formal Diels–Alder adducts of buta-1,2,3-triene.[7] In a more recent preliminary report we describe the syntheses and applications of the three- and four-carbon prepackaged RB reagents [(chloromethyl)-sulfonyl]ethene ($CH_2{=}CHSO_2CH_2Cl$, **5**), [(dichloromethyl)sulfonyl]ethene ($CH_2{=}CHSO_2CHCl_2$, **6**), and (*E*,*Z*)-1,2-bis[(chloromethyl)sulfonyl]ethene ($ClCH_2SO_2$-$CH{=}CHSO_2CH_2Cl$, **7**), respectively.[8] Our full experimental results on these and related studies on prepackaged RB reagents are reported here.



Scheme 6. MIRB reaction of $CH_2{=}C(Br)SO_2CH_2Ph$ (**3**).

2. Results and discussion

2.1. Synthesis of potential prepackaged Ramberg–Bäcklund reagents

Figure 1 gives a sampling of the α,β-unsaturated chloromethyl sulfones we wished to examine as possible prepackaged RB reagents. The examples include the above described allenyl (**4**) and ethenyl (**5**-**7**) chloromethyl sulfones, as well as chloromethyl ethynyl sulfone (**8**) and 1-[(chloromethyl)sulfonyl]-1-haloethenes ($CH_2{=}C(X)SO_2$-CH_2Cl, **9a**,**b**; X=I or F, respectively). While a single example of a dichloromethyl sulfone (**6**) is also included, in the other cases dichloromethyl and trichloromethyl groups could also replace the chloromethyl groups. None of these compounds were known at the inception of this work.

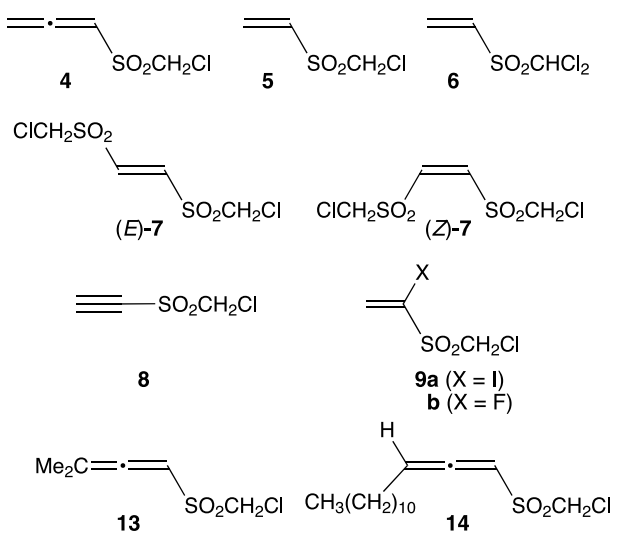
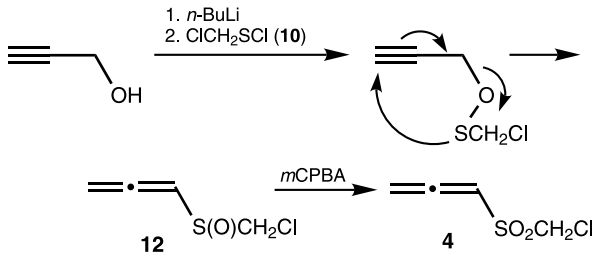


Figure 1. Potential prepackaged RB reagents.

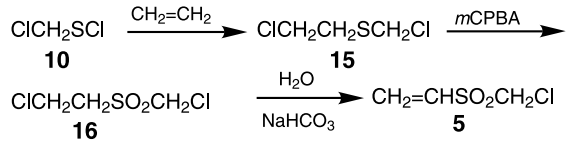
Compounds **4**-**9** should be powerful electron deficient Diels–Alder dienophiles as well as 1,3-dipolarophiles in 1,3-dipolar additions since it is known that sulfonyl groups, and in particular α-chloromethanesulfonyl groups, lower the level of the LUMO in such compounds.[9] It was anticipated that several of these compounds might also function as eneophiles in ene-reactions. Compound **9a** offers the possibility of replacing (by Stille/Heck type reactions) the iodine by sp^2- or sp-hybridized carbon functionalities, giving compounds which might find use in MIRB reactions, while **9b** could afford new fluoroolefins.

2.1.1. Synthesis of [(chloromethyl)sulfonyl]-1,2-propadienes 4 and homologues 13 and 14. It was anticipated that **4** could be prepared via a sequence involving coupling of chloromethanesulfenyl chloride ($ClCH_2SCl$, **10**) with propargyl alcohol giving *S*-chloromethyl propargyl sulfenate (**11**), [2,3]-sigmatropic rearrangement[10a] of **11** to [(chloromethyl)sulfinyl]-1,2-propadiene (**12**) and oxidation of **12** to **4** (Scheme 7). The success of our procedure depended in part on our discovery that Douglass' synthesis of **10** from the solid chlorination product of dimethyl disulfide, CH_3SCl_3,[10b] can be substantially improved if the latter is prepared and decomposed as a dilute solution in CH_2Cl_2. Under these conditions, pure **10** can be conveniently and safely prepared on a large scale in almost quantitative yield. Formation of the sulfenate ester is best conducted by reacting an ethereal solution of 1 equiv. of the lithium salt of the propargylic alcohol at −78 °C with **10** and then repeatedly filtering the mixture as it warms to remove LiCl (which otherwise catalyzes decomposition). Concentration affords **12**, which on oxidation (*m*CPBA) affords **4** as a low-melting, colorless solid.



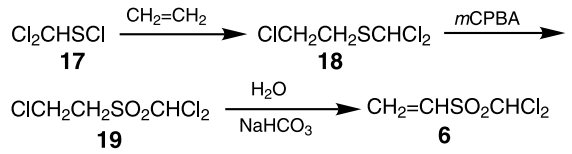
Scheme 7. Synthesis of reagent **4** from propargyl alcohol.

Commercially available 2-methyl-3-butyn-2-ol and tetradec-1-yn-3-ol (addition of ethynyl magnesium bromide[11] to dodecanal) were converted into 1-[(chloromethyl)sulfonyl]-3-methylbuta-1,2-diene ($Me_2C{=}C{=}CHSO_2CH_2Cl$, **13**) and [(chloromethyl)sulfonyl]-3-tetradeca-1,2-diene (CH_3-$(CH_2)_{10}CH{=}C{=}CHSO_2CH_2Cl$, **14**), respectively, by the method used to make **4**. Allenes **13** and **14** were less prone to decomposition than **4** and could be purified by column chromatography, although purification is not necessary as the crude compounds were at least 95% pure.



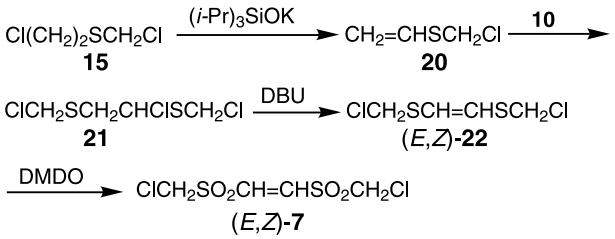
Scheme 8. Synthesis of reagent **5**.

2.1.2. Synthesis of [(chloromethyl)sulfonyl]ethene (5) and [(dichloromethyl)sulfonyl]ethene (6). Treatment of **10** with ethylene gives the known[12a] 1-chloro-2-[(chloromethyl)thio]ethane (**15**; 90%) which, without purification, is oxidized with 2 equiv. *m*CPBA (giving **16** (not isolated)) and stirred with aqueous $NaHCO_3$ giving **5** (99%), a colorless oil (Scheme 8). A similar sequence of steps can be used to convert Cl_2CHSCl (**17**; from chlorination of **10**)[10b] into **6** (78%) by way of 1-chloro-2-[(dichloromethyl)-thio]ethane (**18**) and 1-chloro-2-[(dichloromethyl)sulfonyl]-ethane (**19**), neither of which is isolated (Scheme 9).



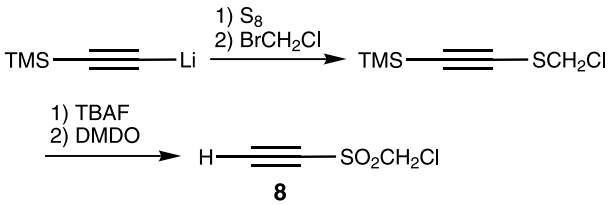
Scheme 9. Synthesis of reagent **6**.

2.1.3. Synthesis of (*E*/*Z*)-1,2-bis-[(chloromethyl)sulfonyl]-ethene ((*E*/*Z*)-7). Dehydrochlorination of **15** with $(i\text{-Pr})_3SiOK$[12b] gives [(chloromethyl)thio]ethene (**20**; 69%; Scheme 10). Compound **20** is converted into (*E*/*Z*)-1,2-bis-[(chloromethyl)sulfonyl]ethene ((*E*/*Z*)-**7**) by sequential addition of **10** (giving **21**; 96%), DBU dehydrochlorination of **21** to (*E*/*Z*)-**22** (58%; 1:3 *E*/*Z*), and oxidation with excess dimethyldioxirane (DMDO)[18b] (giving 28% (*E*)-**7** and 20% (*Z*)-**7**; Scheme 10).



Scheme 10. Synthesis of reagent **7**.

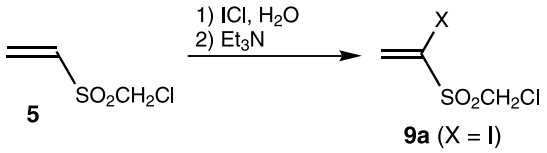
2.1.4. Synthesis of [(chloromethyl)sulfonyl]ethyne (8). Treatment of 2-(trimethylsilyl)ethynyllithium with sulfur followed by $BrCH_2Cl$ gave the known chloromethyl trimethylsilylethynyl sulfide, $TMSC{\equiv}CSCH_2Cl$.[13a,b] While this compound could be smoothly oxidized to the corresponding sulfone, efforts to desilylate this latter compound led to extensive decomposition. However, by reversing the sequence of reactions, namely by first desilylating and then oxidizing (2 equiv. DMDO), compound **8** could be directly prepared (Scheme 11). With less than 2 equiv. of DMDO, the corresponding sulfoxide, [(chloromethyl)sulfinyl]-ethyne, $HC{\equiv}CS(O)CH_2Cl$, was obtained instead of **8**. The series of compounds including the known[13a,b] $HC{\equiv}CSCH_2Cl$ and new $HC{\equiv}CS(O)CH_2Cl$ and $HC{\equiv}CSO_2CH_2Cl$ (**8**) showed interesting trends in their IR spectra, with ≡C–H at 3284, 3248 and 3242 cm^{-1}, and C≡C 2355/2332, 2050 and 2068 cm^{-1}, respectively, in



Scheme 11. Synthesis of **8** from the known 1-chloromethanesulfanyl-2-trimethylsilylethyne.

addition to the sulfoxide S=O at 1078 and the sulfone bands at 1343 and 1161 cm^{-1}.

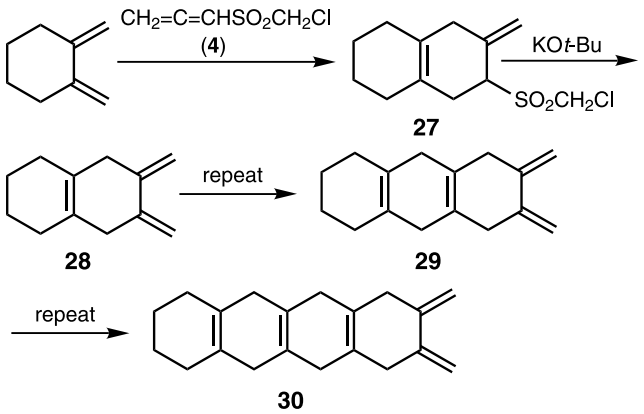
2.1.5. Synthesis of 1-iodo-1-[(chloromethyl)sulfonyl]-ethene (9a); attempted synthesis of 1-fluoro-1-[(chloromethyl)sulfonyl]ethene (9b). Treatment of aqueous solutions of **5** with iodine monochloride followed by triethylamine gave 1-iodo-1-[(chloromethyl)sulfonyl]ethene (**9a**) (Scheme 12). Efforts to prepare **9b** via addition of F_2 (as a 5% mixture with N_2)[13c] to **5** were unsuccessful.



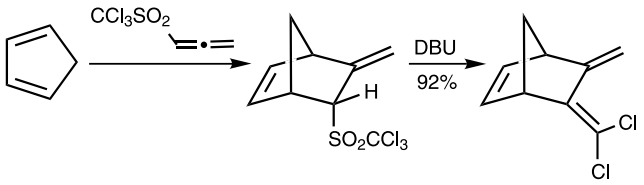
Scheme 12. Synthesis of **9a** from **5**.

2.2. Reactions of [(chloromethyl)sulfonyl]-1,2-propadienes

We examined the Diels–Alder reactivity of **4**, a potential 1,2,3-butatriene synthon. While (*Z*)-1,4-dichloro-2-butene may also be considered a 1,2,3-butatriene synthon, as a dienophile it requires "severe and carefully controlled reaction conditions [typically several days at 190–200 °C], was somewhat erratic", gave only moderate yields,



Scheme 13. Iterative cyclohomologation sequence using **4**.



Scheme 14. Tandem Diels–Alder RB reaction of [(trichloromethyl)sulfonyl]-1,2-propadiene.

Table 1. Tandem Diels–Alder Ramberg–Bäcklund products from compounds **4**–**6**, **13** and **14**

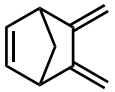
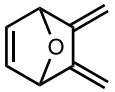
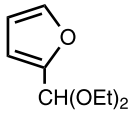
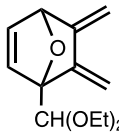
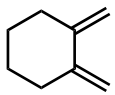
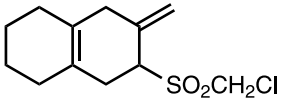
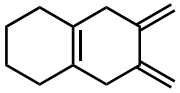
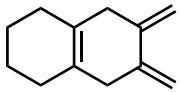
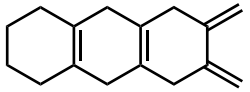
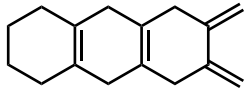
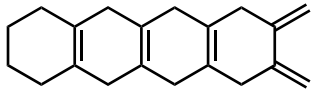
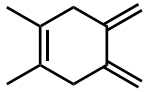
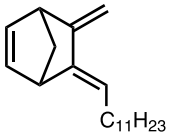
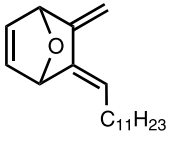
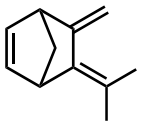
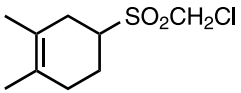
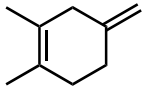
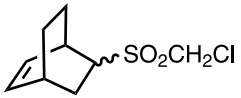
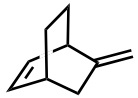
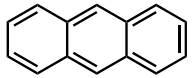
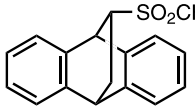
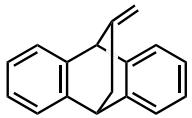
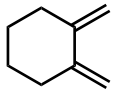
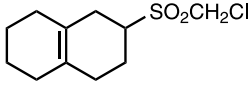
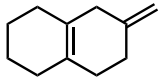
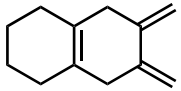
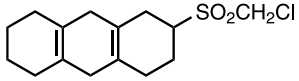
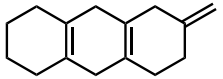
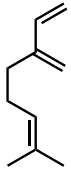
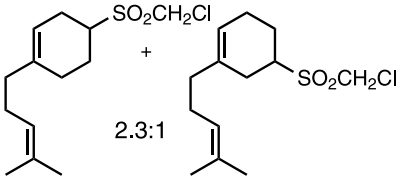
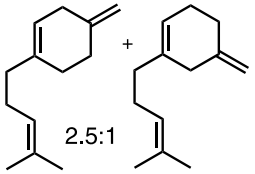
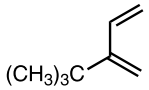
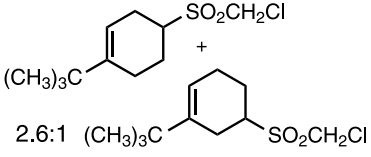
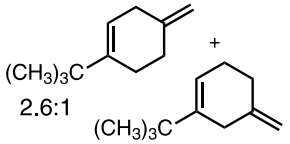
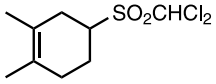
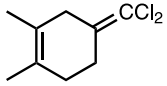
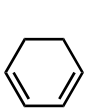
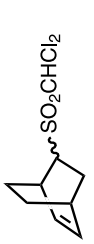
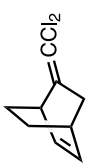
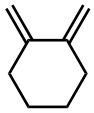
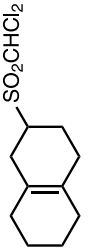
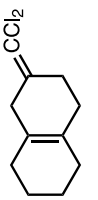
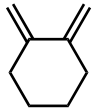
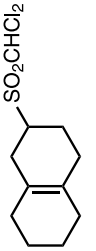
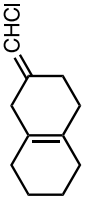
#	Diene	Dienophile	Diels–Alder adduct	Yield (%)	Ramberg–Bäcklund product	Yield (%)
1		**4**, 60 °C 30 min	—	—	 **23**	85
2		**4**, 60 °C 3 h	—	—	 **24**	85
3		**4**, 60 °C 2 h	—	—	 **25**	68
4		**4**, 60 °C 2 h	—	—	 **26**	60
5		**4**, 60 °C, 6 h	 **27**	76	 **28**	86
6	 **28**	**4**, 60 °C 3 h	—	—	 **29**	85
7	 **29**	**4**, 60 °C 3 h	—	—	 **30**	85
8		**4**, 80 °C 5 h	—	—	 **31**	57
9		**14**, 80 °C 5 h	—	—	 **32**	60
10		**14**, 80 °C 5 h	—	—	 **33**	49

Table 1 (*continued*)

#	Diene	Dienophile	Diels–Alder adduct		Yield (%)	Ramberg–Bäcklund product		Yield (%)
11		**13**, 80 °C 5 h	—		—		**34**	85
12		**5**, 120–130 °C 12 h		**35**	96		**36**	59[a]
13		**5**, 120–130 °C 12 h		**37**	95[b]		**38**	51[a]
14		**5**, 155 °C 7 h		**39**	96		**40**	89
15		**5**, 110 °C 16 h		**41**	97		**42**	79
16		**28** **5**, 60 °C 12 h		**43**	92		**44**	75
17		**5**, 145 °C 7 h			76			90
			45a	**45b**		**46a**	**46b**	
18		**5**, 150 °C 12 h		**47a** **47b**	74		**48a** **48b**	67
19		**6**, 80–100 °C 16 h		**50**	93		**51**	72[a]

(*continued on next page*)

Table 1 (*continued*)

#	Diene	Dienophile	Diels–Alder adduct	Yield (%)	Ramberg–Bäcklund product	Yield (%)
20		**6**, 80–100 °C 16 h	 **52**	92[c]	 **53**	72[a]
21		**6**, 80–100 °C 16 h	 **54**	94	 **55**	65[a]
22		**6**, 80–100 °C 16 h	 **54**	94	 **56**	55[d]

[a] 6.3:1 *endo*/*exo*.
[b] 3:1 *endo*/*exo*.
[c] $MeSO_2CCl_3$ (**49**) also required.
[d] Without **49**, **42** and **55** also formed (6% each).

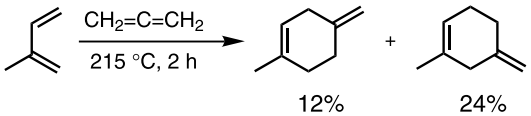
and does not react with either furan or 1,3-cyclohexadiene.[14]

When a 2:1 mixture of 1,2-bis(methylene)cyclohexane[2e,f] and **4** was warmed to 60 °C for 3 h and the product **27** (Scheme 13) was diluted with THF, treated with 1 equiv. of KO*t*-Bu at 0 °C, and worked up, triene **28** could be isolated in 57% overall yield via RB reaction of **27**. Repetition of the process twice gave tetraene **29** and then pentaene **30**, each in 85% overall yield. In these reactions **4** functions as a synthon for 1,2,3-butatriene. The sequence of reactions constitutes an iterative cyclohomologation approach to the synthesis of fused 1,4-cyclohexadienes. This protocol has been employed in syntheses of [*n*]beltenes.[15] Use of [(trichloromethyl)sulfonyl]-1,2-propadiene as a 1,1-dichloro-1,2,3-butatriene synthon has also been described (Scheme 14).[16a]

Table 1, entries 1–11, show the results of use of the above procedure with Diels–Alder adducts obtained from reaction of **4**, **13** and **14** with cyclopentadiene, furan, furfural diethyl acetal, 1,3-cyclohexadiene, 1,2-bis(methylene)cyclohexane, **28**, **29**, and 2,3-dimethyl-1,3-butadiene affording compounds **23**-**34**.

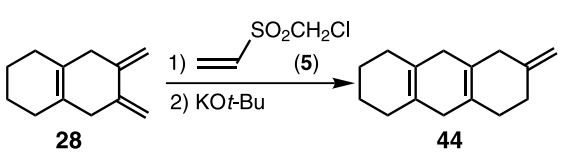
2.3. Reactions of [(chloromethyl)sulfonyl]ethene (5) and [(dichloromethyl)sulfonyl]ethene (6)

We examined the Diels–Alder reactivity of new compounds **5** and **6**, potential allene or chloroallene synthons. While Diels–Alder adducts of allene are useful synthetic intermediates, preparation of these compounds using allene itself is generally impractical because of its cost, low reactivity, lack of regioselectivity (Scheme 15) and the experimental difficulties associated with gaseous reagents.[16b] Because of the above problems, a variety of allene synthons have been devised, such as 1-bromo-1-(methylsulfonyl)ethene,[5] α-bromoacrolein,[17a] 2-(phenylsulfinyl)propene,[17b] ethenyl triphenylphosphonium bromide,[17c] α-methylene-β-propiolactone,[17d] and 1,2-[bis(phenylsulfonyl)]propene.[17e]

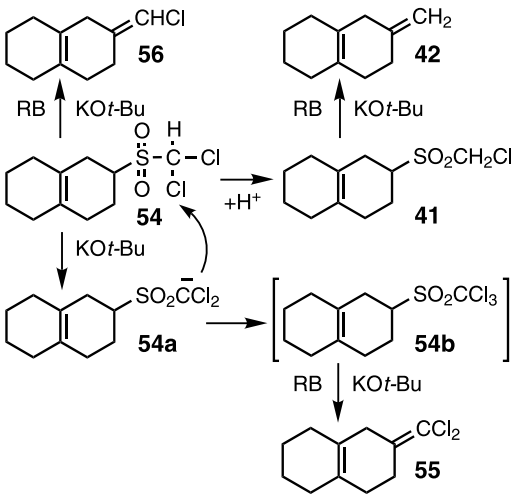


Scheme 15. Diels–Alder reaction of allene with isoprene.

Both **5** and **6** readily add to a variety of 1,3-dienes giving high yields of the corresponding Diels–Alder adducts, as shown in Table 1, entries 12–22, and Scheme 16. As anticipated, treatment of the Diels–Alder adducts of **5** with KO*t*-Bu/THF give good yields of the diene–allene adducts via Ramberg–Bäcklund reaction (entries 12–16). Analogous base treatment of adducts of **6** gave mixtures of the isomeric adducts of chloropropa-1,2-diene together with lesser amounts of the adducts of allene and 1,1-dichloropropa-1,2-diene



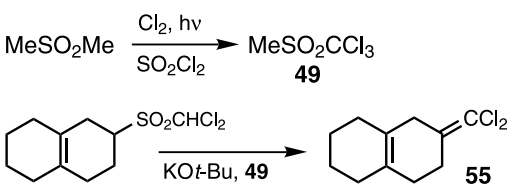
Scheme 16. Tandem Diels–Alder RB reaction of **5**.



Scheme 17. Proposed mechanism for the reaction of a Diels–Alder adduct of **6** with base.

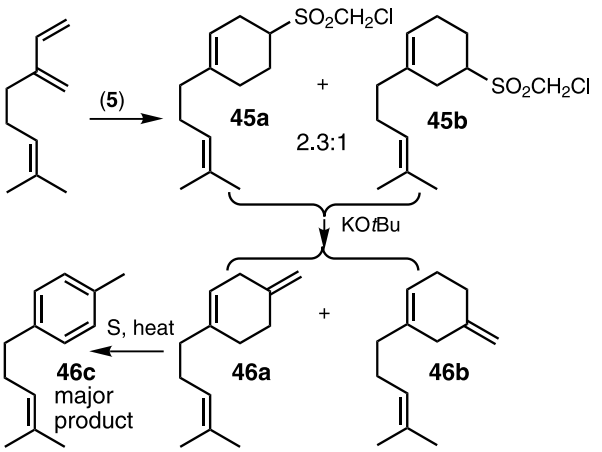
(**56**, **42**, **55**, respectively, Scheme 17). The latter two compounds are presumably formed by nucleophilic attack of the α-sulfonyl-α-chlorocarbanion **54a** of the Diels–Alder adduct **54** of **6** on the chlorine of a second adduct molecule giving [(trichloromethyl)sulfonyl]ethene adduct **54b**, which is not isolated.

We reasoned that if base treatment of Diels–Alder adducts of **6** were conducted in the presence of an excess of a suitably reactive source of chlorine, chlorine transfer might be possible prior to Ramberg–Bäcklund reaction leading to exclusive formation of Diels–Alder adducts of 1,1-dichloropropa-1,2-diene. To test this hypothesis, [(trichloromethyl)-sulfonyl]methane, $MeSO_2CCl_3$ (**49**), was used as a novel chlorine source. This little studied compound[18a] was conveniently prepared in 91% yield by bubbling Cl_2 into a refluxing, UV-irradiated solution of dimethyl sulfone in SO_2Cl_2 (Scheme 18). We were pleased to find that when Diels–Alder adducts of **6** were treated at 0 °C with KO*t*-Bu–THF in the presence of 2 equiv. of $MeSO_2CCl_3$, the corresponding Diels–Alder adducts of 1,1-dichloropropa-1,2-diene were formed in good yield (Table 1, entries 19–21), despite concerns about competing sulfonate formation sometimes seen in reactions involving base treatment of 1,1,1-trichloromethyl sulfones.[18c]



Scheme 18. Synthesis of [(trichloromethyl)sulfonyl]methane (**49**) and $CH_2{=}C{=}CCl_2$ Diels–Alder adduct **55**.

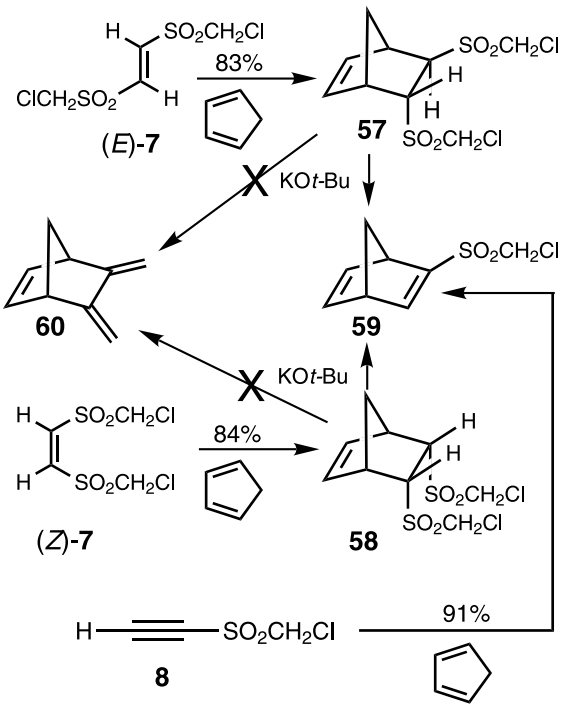
Mixtures of adducts were obtained on reaction of **5** or **6** with 2-substituted 1,3-dienes, for example, myrcene (76%; 2.3:1 *para*/*meta* mixture **45a**,**b** with **5**) and 2-*t*-butyl-1,3-butadiene (74%, 2.6:1 *para*/*meta* mixture **47a**,**b**). Individual adducts could not be separated chromatographically from the isomeric mixtures. Treatment of the mixtures of adducts with base afforded isomeric allene adducts **46a**,**b** and **48a**,**b** of myrcene and 2-*t*-butyl-1,3-butadiene, respectively. In the former case heating the **46a**,**b** mixture with sulfur let to aromatization affording 4-methyl-1-(4′methylpent-3′-enyl)-benzene **46c** as the major product, which in turn suggests that the *para* adduct **45a** of **5** with myrcene was the predominant adduct (Scheme 19).



Scheme 19. Reaction of **5** with myrcene, a 2-substituted 1,3-butadiene, gives a mixture of adducts.

2.4. Reactions of (*E*/*Z*)-1,2-bis-[(chloromethyl)sulfonyl]-ethene (7a/7b)

Both (*E*)- and (*Z*)-**7** readily form Diels–Alder adducts, for example, **57** and **58**, respectively, with 1,3-cyclopentadiene (Scheme 20), as confirmed by X-ray crystallography for **57**,[3] which also establishes the stereochemistry of (*E*)-**7**. The X-ray structure of **57** shows SCCS and HCCH (the two sulfur-bonded ring carbons) dihedral angles of −110.58(16)° and 124(3)°. Similarly, *cis* isomer **58** should

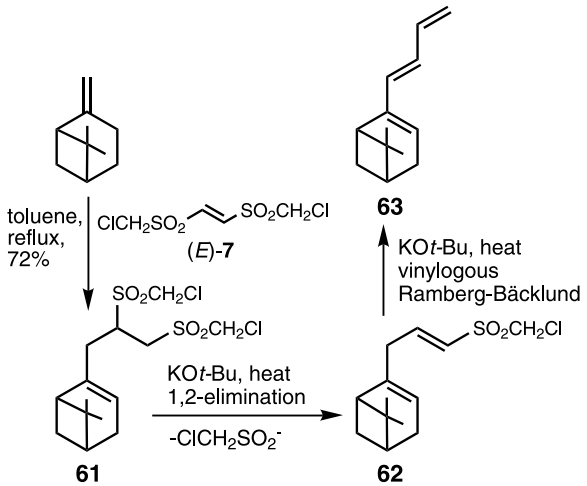


Scheme 20. Reaction of **57** and **58** with base; alternative synthesis of **59** via Diels–Alder addition of **8**.

have H on C(26) or C(27) far from *syn* or *anti*-periplanar with sulfur.

Base treatment of **57** or **58** gave unstable 2-[(chloromethyl)-sulfonyl]bicyclo[2.2.1]hepta-2,5-diene (**59**) rather than 5,6-bis(methylene)bicyclo[2.2.1]hept-2-ene (**60**), for example, 1,2-elimination from the activated α-sulfonyl carbanions is favored over 1,3-elimination (Ramberg–Bäcklund reaction), even with the adduct of (*Z*)-**7**, where a coplanar 1,2-elimination transition state is impossible. Compound **59** could be directly prepared in high yield from Diels–Alder addition of [(chloromethyl)sulfonyl]-ethyne (**8**) to cyclopentadiene (Scheme 20).

Since compound **7** showed good reactivity as a dienophile, we examined its reactivity in the ene reaction. When (*E*)-**7** was heated with 2 equiv. of β-pinene in toluene at 135 °C for 1.5 h, the ene product 2-{[(1′,2′-bis(chloromethyl)sulfo-nyl]propyl}-6,6-dimethylbicyclo[3.1.1]hept-2-ene (**61**) was formed in 72% yield as a crystalline solid. Base treatment (KO*t*-Bu) of **61** in refluxing THF afforded (*E*)-2-(buta-1,3-dienyl)-6,6-dimethylbicyclo[3.3.1]hept-2ene (**63**) in low yield. If treatment with base was conducted at 0 °C, low yields of 2-[(3-chloromethyl)sulfonyl]allyl-6,6-dimethyl-bicyclo[3.3.1]hept-2-ene (**62**) could be isolated, leading to the overall proposed mechanism shown in Scheme 21. While not of synthetic utility due to low yield, the reaction in Scheme 21 represents the first example of a tandem reaction sequence incorporating an ene-reaction with Ramberg–Bäcklund elimination.



Scheme 21. Ene-reaction of (*E*)-**7** with β-pinene followed by RB reaction of β-elimination product **62**.

Efforts to use easily prepared **8** as an eneophile with β-pinene did not appear to be promising due to the thermal instability of **8**. In addition, efforts to replace the iodine atom of **9a** with sp^2- or sp-hybridized carbon groups through Pd(0)-catalyzed reactions have not been successful thus far.

3. Conclusion

We have demonstrated that [(chloromethyl)sulfonyl]-1,3-propadiene (**4**), [(chloromethyl)sulfonyl]ethene (**5**), and [(dichloromethyl)sulfonyl]ethene (**6**) are new, easily prepared reagents which have considerable utility as pre-packaged Ramberg–Bäcklund reagents. When combined with Diels–Alder addition, these compounds conveniently afford in good yields the formal adducts of 1,2,3-butatriene (from **4**), allene (from **5**) and 1,1-dichloroallene (from **6**; when used in conjunction with a chlorine source such as [(trichloromethyl)sulfonyl]methane) **49**.

4. Experimental

4.1. Caution

β-Chlorosulfides may be toxic on inhalation, ingestion or skin contact. These compounds should only be handled in a well-ventilated hood using rubber gloves. All glassware used should be rinsed with bleach (‘Clorox’) immediately after use.

4.2. General methods

Reaction flasks were oven dried and cooled under nitrogen. Diethyl ether and THF were distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2. Propargyl alcohol was distilled prior to use. Unless otherwise noted, silica gel (Fisher Scientific Co., 200–425 mesh, 60 Å) was used as the chromatography solid phase and solutions were dried over anhydrous $MgSO_4$. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini at 300 and 75.1 MHz, respectively, in $CDCl_3$ unless otherwise noted, with all shifts referenced to TMS in ppm. IR spectra were recorded on a Perkin Elmer model 1600 FTIR or a Perkin Elmer 710B spectrophotometer. LR GC–MS was performed on a Hewlett Packard 5890 GC coupled to a Hewlett Packard 5970 MS (EI at 70 eV). Melting points were determined on a Buchi model 510 melting point apparatus and are uncorrected.

4.2.1. Chloromethanesulfenyl chloride (10). A magnetic stirrer-equipped flask was charged with CH_2Cl_2 (60 mL) and Me_2S_2 (9.16 g, 97 mmol), the mixture was cooled to −78 °C and Cl_2 gas was bubbled through slowly using a 9 mm glass tube (a solid was formed plugging smaller bore tubes). The mixture turned red-orange and a colorless solid (CH_3SCl_3) appeared. The mixture turned into a milky, yellow-white slurry, which continued to thicken and lighten until the solution became saturated with chlorine, at which time the mixture took on a yellow-green color. Addition of Cl_2 was stopped and a reflux condenser with drying tube was fitted to the flask. Decomposition of CH_3SCl_3 was promoted by warming the flask to room temperature. An orange liquid formed as HCl was evolved. Concentration in vacuo yielded the known **10**[10b] as a malodorous, lachrymatory oil (20 g, 88%) which was used without further purification; ^1H NMR δ 5.12 (s); ^{13}C NMR δ 54.8. If desired, **10** can be purified by distillation (bp 50–55 °C/115 mm).

4.2.2. 1-[(Chloromethyl)sulfonyl]-1,2-propadiene (4). To a solution of propargyl alcohol (4.8 mL, 80 mmol) in ether (240 mL) was added *n*-BuLi (2.5 M, 32 mL, 80 mmol, hexane) at −78 °C. The resultant thick colorless suspension was stirred for 20 min. Neat $ClCH_2SCl$ (**10**; 6.6 mL) was

added dropwise during 10 min. The mixture was stirred at −78 °C for 30 min, LiCl was removed by vacuum filtration through a silica gel pad, and the light yellow solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (80 mL). A solution of *m*-CPBA (77%, 26 g) in CH_2Cl_2 (200 mL) was added and the mixture was stirred at room temperature for 16 h. The colorless precipitate was removed by filtration, the filtrate was concentrated, and the residue was chromatographed (silica gel; 1:5 EtOAc/hexane) affording **4** as an oil or low melting solid, mp 39–39.5 °C (7.2 g, 59%); ^{1}H NMR δ 6.26 (t, J=6.3 Hz, 1H), 5.62 (d, J=6.3 Hz, 2H), 4.53 (s, 2H); ^{13}C NMR δ 212.3 (=C=), 95.2 (=CH), 84.3 (=CH_2), 58.3 (CH_2); IR 3000 (m), 1965 (m), 1328 (s), 1247 (m), 1148 (s), 1120 (s), 872 (m) cm^{-1}. EI HRMS calcd for $C_4H_5SO_2Cl$: 151.9698. Found: 151.9695. It is best to immediately oxidize the unstable intermediate **12**, which can be isolated, purified and characterized as colorless needles, mp 49–49.5 °C from ether/hexanes; ^{1}H NMR δ 6.00 (t, J=6 Hz, 1H), 5.30 (d, J=6 Hz, 2H), 4.40 (s, 2H); IR 3000 (m), 1925 (m), 1060 (s) cm^{-1}. It is also best to promptly purify the crude **4** by chromatography.

4.2.3. 1-[(Chloromethyl)sulfonyl]-3-methylbuta-1,2-diene (13). A 250 mL three-necked flask under N_2 was charged with diethyl ether (100 mL) and 2-methyl-3-butyn-2-ol (1 g, 11.9 mmol). The solution was cooled to −78 °C and *n*-BuLi (2.5 M, 4.76 mL, 11.9 mmol) was added dropwise. After 15 min **10** (1.38 g, 11.9 mmol) was added dropwise and the solution was stirred for 15 min. The solution was then continuously vacuum filtered as it warmed to room temperature. A sample of the product was concentrated in vacuo and analyzed: ^{1}H NMR δ 5.90 (m, 1H), 4.35 (m, 2H), 1.83 (m, 6H); ^{13}C NMR δ 203.4 (C), 105.5 (C), 95.5 (CH), 58.2 (CH_2), 20.0 (CH_3), 19.8 (CH_3); IR (ν_{max}) 3000 (s), 1950 (m), 1060 (vs) cm^{-1}. To the pale yellow solution was added CH_2Cl_2 (50 mL) and *m*-CPBA (50–60%) (3.75 g, 11.9 mmol). The solution was stirred overnight protected with a drying tube. The solution was then washed with saturated aqueous $NaHSO_3$ and $NaHCO_3$ (3× each). The organic layer was separated, dried and concentrated in vacuo to give **13** (1.31 g, 61%), a colorless oil: ^{1}H NMR δ 5.98 (m, 1H), 4.46 (s, 2H), 1.89 (d, J= 3.3 Hz, 3H); ^{13}C NMR δ 207.5 (C), 107.3 (C), 92.6 (CH), 57.7 (CH_2), 19.5 (CH_3); IR (ν_{max}) 3015 (m), 2950 (m), 1960 (m), 1320 (vs), 1115 (vs) cm^{-1}; mp ca. 10 °C; EI HRMS calcd for $C_6H_9SO_2Cl$: 180.0012. Found: 180.0018.

4.2.4. [(Chloromethyl)sulfonyl]-3-tetradeca-1,2-diene (14). A 250 mL three-necked flask under N_2 was charged with diethyl ether (100 mL) and tetradec-1-yn-3-ol (2 g, 9.5 mmol). The flask was cooled to −78 °C and *n*-BuLi (2.5 M, 3.8 mL, 9.5 mmol) was added dropwise. After 10 min **10** (1.1 g, 9.5 mmol) was added slowly with stirring. Workup and overnight oxidation (*m*-CPBA; 1.6 g, 9.5 mmol) as for **4** gave a yellow oil. Chromatography (5:1 CH_2Cl_2/hexane) gave **14** (2 g, 69% yield), a colorless low melting solid: mp 37 °C; ^{1}H NMR δ 6.15 (m, 1H), 5.99 (m, 1H), 4.48 (s, 2H), 2.23 (m, 2H), 1.47 (m, 2H), 1.24 (br s, 16H), 0.86 (t, J=7 Hz, 3H); ^{13}C NMR δ 208.9 (C), 101.3 (CH), 95.1 (CH), 57.9, 31.9, 29.5, 29.5, 29.4, 29.3, 29.3, 28.9, 28.4, 27.7, 22.7 (all CH_2), 14.1 (CH_3); IR (ν_{max}) 2924 (vs), 2853 (vs), 1954 (m), 1465 (m), 1330 (s), 1147 (s) cm^{-1}; EI HRMS calcd for $C_{14}H_{27}SO_2Cl$: 306.1420. Found: 306.1425.

4.2.5. 1-Chloro-2-[(chloromethyl)thio]ethane (15). A solution of $ClCH_2SCl$ (**10**; 19.2 g, 17.8 mmol) in CH_2Cl_2 (200 mL) was placed in a flask fitted with a gas inlet tube and a drying tube. Ethylene gas was slowly introduced at 0 °C until the starting material disappeared as indicated by ^{1}H NMR analysis. Concentration in vacuo afforded the known[12] **15** as a yellow oil (21.4 g, 90%) which was used directly for the next step without further purification; bp 99–100 °C (15 mm); ^{1}H NMR δ 4.75 (s, 2H), 3.76 (t, J=7.8 Hz, 2H), 3.11 (t, J=7.8 Hz, 2H); ^{13}C NMR δ 49.2, 42.4, 34.0; GC–MS *m/z* 146 (M^+, ^{37}Cl, 14%), 144 (M^+, ^{35}Cl, 20%), 111 (23%), 109 (63%), 95 (51%), 45 (100%).

4.2.6. [(Chloromethyl)sulfonyl]ethene (5). *m*-Chloroperbenzoic acid (77%, 107 g, 0.47 mol) was added to a solution of **15** (30.8 g, 0.21 mol) in CH_2Cl_2 (750 mL) over 30 min at room temperature and the mixture was stirred for 16 h. The colorless precipitate was removed by filtration and excess aqueous $NaHCO_3$ was added to the filtrate which was stirred for 16 h. The reaction mixture was washed with H_2O (3×200 mL) and brine (3×200 mL), and the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo affording **5** as a colorless oil (29.4 g, 99%); ^{1}H NMR δ 6.69 (dd, J=9.7, 16.6 Hz, 1H), 6.50 (d, J=16.6 Hz, 1H), 6.31 (d, J=9.7 Hz, 1H), 4.43 (s, 2H); ^{13}C NMR δ 56.6, 132.8, 134.1; IR ($CHCl_3$) 1149, 1325 (SO_2) cm^{-1}.

4.2.7. 1-Chloro-2-[(dichloromethyl)thio]ethane (18). A three-necked round bottom flask was charged with Me_2S_2 (10 mL, 113 mmol) and CH_2Cl_2 (120 mL). The solution was cooled to −78 °C and Cl_2 gas was bubbled through slowly for 3–5 min. The reaction mixture turned reddish orange and a colorless solid precipitated (CH_3SCl_3). The slurry continued to thicken until the solution had been saturated with Cl_2, at which time the mixture took on a yellow-green color and the addition of Cl_2 was stopped. The reaction mixture was warmed to room temperature and stirred for 1 h to give a bright orange solution with the release of HCl gas, which was absorbed with aqueous NaOH solution. The orange solution was cooled to −78 °C and Cl_2 gas was bubbled through again. As before, a colorless solid precipitated. The slurry continued to thicken until the solution had been saturated with Cl_2, at which time the mixture took on a yellow-green color and the addition of Cl_2 was stopped. The reaction mixture was warmed to room temperature, stirred for 1 h, concentrated in vacuo and diluted with CH_2Cl_2 (300 mL). The solution was cooled to 0 °C and ethylene gas was bubbled in through a glass tube until the color of the solution lightened. Concentration in vacuo afforded **18** as a yellow oil (37.2 g; 91%). The product was used directly for the next step without further purification; ^{1}H NMR δ 6.83 (s, 1H), 3.84 (t, J=7.3 Hz, 2H), 3.33 (t, J=7.3 Hz, 2H); ^{13}C NMR δ 73.9, 42.5, 34.1.

4.2.8. [(Dichloromethyl)sulfonyl]ethene (6). *m*-Chloroperbenzoic acid (77%, 27 g, 120 mmol) was added to a solution of **18** (9.0 g, 50 mol) in CH_2Cl_2 (200 mL) over 30 min at 20 °C and the mixture was stirred for 16 h. The colorless precipitate was removed by filtration. The filtrate was concentrated and the residue chromatographed (silica gel;

6:1 hexane/EtOAc). The so-purified **19** was dissolved in CH_2Cl_2 (200 mL), mixed with 1.1 equiv. of aqueous $NaHCO_3$ (excess $NaHCO_3$ is detrimental) and stirred for 16 h. The mixture was washed with H_2O (2×100 mL) and brine (2×100 mL), dried (Na_2SO_4), concentrated in vacuo, and chromatographed (5:1 hexane/EtOAc) to afford **6** as a low melting solid, mp 50–51 °C (7.5 g, 86%): ^{1}H NMR δ 6.86 (dd, J=9.8, 16.6 Hz, 1H), 6.69 (d, J=16.6 Hz, 1H), 6.55 (d, J=9.8 Hz, 1H), 6.26 (s, 1H); ^{13}C NMR δ 78.7, 129.8, 137.3; IR ($CHCl_3$) 1145, 1348 (SO_2), 948, 3020 cm^{-1} (C═C). Anal. Calcd for $C_3H_4Cl_2O_2S$: C, 20.59; H, 2.30. Found: C, 20.46; H, 2.07.

4.2.9. [(Chloromethyl)thio]ethene (20). Triisopropylsilanol (0.1 mL, 0.5 mmol) was added to a slurry of pulverized KOH (6.93 g, 0.12 mol) in tetraethyleneglycol dimethyl ether (150 mL) and the mixture was stirred at room temperature for 1 h. Compound **15** (2.91 g, 59 mmol) was added to the mixture and the color changed from yellow to dark brown. The mixture was stirred at 20 °C until the starting material had disappeared as indicated by TLC (7:1 hexane/EtOAc, ca. 1.5 h). The mixture was then distilled into a liquid nitrogen cooled trap (0.02 Torr). Compound **20** was separated as a colorless oil from the colorless precipitate using a syringe (4.38 g, 69%): ^{1}H NMR δ 6.39 (dd, J=10, 17 Hz, 1H), 5.40 (dd, J=2.4, 10 Hz, 1H), 5.39 (dd, J=2.4, 17 Hz, 1H), 4.78 (s, 2H); ^{13}C NMR δ 129.0, 115.4, 47.8; GC–MS m/z 110 (M^+, ^{37}Cl, 9%), 108 (M^+, ^{35}Cl, 27%), 73 (88%), 46 (27%), 45 (100%).

4.2.10. 1-Chloro-1,2-bis[(chloromethyl)thio]ethane (21). Compound **20** (3.03 g, 28 mmol) was added to $ClCH_2SCl$ (3.28 g, 28 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo affording the title compound as a yellow oil (5.78 g, 96%). The product was used directly without further purification; ^{1}H NMR δ 5.53 (t, J=7 Hz, 1H), 4.98 and 4.80 (AB_q, J=11 Hz, 2H), 4.78 (s, 2H), 3.41 (d, J=7 Hz, 2H); ^{13}C NMR: δ 64.4, 49.3, 46.7, 38.9; GC–MS m/z 227 (M^+, ^{37}Cl, 10%), 225 (M^+, ^{35}Cl, 29%), 108 (94%), 97 (43%), 95 (100%).

4.2.11. (*E*,*Z*)-1,2-Bis[(chloromethyl)thio]ethene ((*E*,*Z*)-22). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.66 mL, 11 mmol) was added to a solution of **21** (1.42 g, 5.5 mmol) in $CHCl_3$ (50 mL) at 0 °C and the reaction mixture was heated to reflux for 1 h. The reaction progress was monitored by GC. The organic layer was washed with 0.5 N HCl (2×25 mL), $NaHCO_3$ solution (2×25 mL), brine (2×25 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation gave (*E*,*Z*)-**22** as a light yellow oil (0.61 g, 58%; *E*/*Z* 1.3:1), bp 90–100 °C (0.02 Torr); ^{1}H NMR. δ 6.48 (s, 2H), 6.46 (s, 2H), 4.76 (s, 8H); ^{13}C NMR δ 124.1, 123.5, 48.7, 48.5; GC–MS m/z 190 (M^+, ^{37}Cl, 33%), 190 (M^+, ^{35}Cl, 45%), 106 (93%), 104 (100%), 103 (70%).

4.2.12. (*E*,*Z*)-1,2-Bis[(chloromethyl)sulfonyl]ethene ((*E*,*Z*)-7). Dimethyldioxirane[18b] (DMDO; 100 mL, 9.0 mmol) was added to a solution of **22** (0.4 g, 2.1 mmol) in $CHCl_3$ (5 mL) at room temperature and the reaction mixture was stirred at room temperature overnight. The resulting mixture was dried (Na_2SO_4), concentrated in vacuo, and the residue chromatographed (hexanes/EtOAc 3:2) affording both the (*E*)-**7** (R_f 0.8, 0.15 g, 28%) and the (*Z*)-**7** (R_f 0.6, 0.11 g, 20%) as colorless solids: (*E*)-**7**, mp 143–145 °C (EtOH); IR (film) 1389 (SO_2), 1124 (SO_2) cm^{-1}; ^{1}H NMR ($CD_3C(O)CD_3$) δ 7.82 (s, 2H), 5.22 (s, 4H); ^{13}C NMR ($CD_3C(O)CD_3$) δ 141.9, 57.2. Anal. Calcd for $C_4H_6Cl_2O_4S_2$: C, 18.98; H, 2.39. Found: C, 19.37; H, 2.06. (*Z*)-**7**, mp 113–115 °C (EtOH); IR (film) 1329 (SO_2), 1119 (SO_2) cm^{-1}; ^{1}H NMR ($CD_3C(O)CD_3$) δ 7.60 (s, 2H), 5.17 (s, 4H); ^{13}C NMR ($CD_3C(O)CD_3$) δ 141.8, 58.8.

4.2.13. [(Chloromethyl)sulfonyl]ethyne (8). A solution of 1-(chloromethyl)thio-2-(trimethylsilyl)ethyne (1.5 g, 8.4 mmol)[13a] in methanol (2 mL) at 0 °C was treated dropwise with Bu_4NF (3.75 mL, 9.2 mmol; 75% aqueous solution). The mixture was stirred at 0 °C for 2 h, and then diluted with ice water and extracted with pentane. The extracts were washed with cold water, dried (Na_2SO_4), cooled to 0 °C, and treated overnight with a solution of DMDO in acetone (18 mmol, 200 mL, 9 mmol/100 mL). Solvents were removed in vacuo and the residue was chromatographed (6:1 hexane/ethyl acetate), yielding the title compound (0.7 g, 60%) as a colorless oil: ^{1}H NMR δ 4.60 (s, 2H); 3.60 (s, 1H); ^{13}C NMR δ 91.7, 78.8, 60.6; IR (neat) 3242 (triple bond C–H), 1342, 1159 cm^{-1} (SO_2).

4.2.14. 1-[(Chloromethyl)sulfonyl]-1-iodoethene (9a). To a solution of **5** (1.41 g, 10 mmol) in 1:1 THF and water (30 mL) was added iodine monochloride (3.25 g, 20 mmol) at room temperature. The mixture was stirred overnight, concentrated in vacuo, the residue was extracted with CH_2Cl_2 (20×2 mL) and washed with aqueous sodium thiosulfate solution (20 mL) giving 2-chloro-1-[(chloromethyl)sulfonyl]-1-iodoethane (1.2 g, 40%). A portion of this latter compound (1.00 g, 3.3 mmol) in THF (15 mL) was treated with triethylamine (3 mL) which was added dropwise at room temperature. The mixture was stirred for 20 min, quenched with dilute HCl, extracted with CH_2Cl_2 (30×2 mL), dried, concentrated in vacuo and the residue chromatographed (5:1 hexane/ethyl acetate) to yield **9a** (862 mg, 89%) as colorless crystals, mp 49–50 °C; ^{1}H NMR δ 7.55 (d, J=2.9 Hz, 1H), 6.81 (d, J=2.9 Hz, 1H), 4.61 (s, 2H); ^{13}C NMR δ 144.1, 95.6, 52.6; IR (CH_2Cl_2) 1331, 1155 cm^{-1} (SO_2); EI-MS m/z 266 (M^+, 28%), 152 (100%), 126 (56%). Anal. Calcd for $C_3H_4ClIO_2S$: C, 13.52; H, 1.51. Found: C, 13.93; 2.53.

4.2.15. 5,6-Bis(methylene)bicyclo[2.2.1]hept-2-ene (23) [Table 1, entry 1]. A 2 mL screw capped vial was charged with **4** (0.5 g, 3.3 mmol), freshly distilled cyclopentadiene (0.65 g, 9.9 mmol), sealed and held at 60 °C. By GC, the reaction was found to be complete in 30 min (GC–MS m/z 218 (M^+, 0.77%), 105 (100%), 103 (25%), 79 (50%), 77 (42%), 39 (23%)). The product was placed in a 50 mL flask, dissolved in THF (10 mL) under N_2, cooled to 0 °C and a solution of KO*t*-Bu (0.57 g, 3.3 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 15 min and quenched with saturated aqueous NH_4Cl. Diethyl ether (10 mL) was added and the organic layer was removed, dried, and concentrated in vacuo. Chromatography (pentane) gave known compound **23**[14a,19] slightly contaminated with dicyclopentadiene (0.32 g, 85%): ^{13}C NMR δ 149.1 (C), 132.1 (CH), 101.2 (CH_2), 51.2 (CH), 50.3 (CH_2); GC–

MS *m/z* 118 (M^+, 54%), 117 (97%), 91 (40%), 66 (100%), 65 (36%), 51 (44%), 50 (29%), 39 (75%).

4.2.16. 5,6-Bis(methylene)-7-oxabicyclo[2.2.1]hept-2-ene (24) [Table 1, entry 2]. A 2 mL screw capped vial was charged with **4** (0.5 g, 3.3 mmol), furan (0.67 g, 9.9 mmol), sealed and maintained at 60 °C. The reaction was complete in 3 h according to GC analysis. The product was placed in a 50 mL flask, dissolved in THF (10 mL) under N_2, cooled to 0 °C and a solution of KO*t*-Bu (0.57 g, 3.3 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 15 min and quenched with saturated aqueous NH_4Cl. Diethyl ether (10 mL) was added, and the organic layer was separated, dried, concentrated in vacuo and chromatographed (pentane) giving known **24**[20] (0.34 g, 85%) as a colorless oil: ^{1}H NMR δ 6.74 (br s, 2H), 5.28 (br s, 2H), 5.16 (br s, 2H), 5.12 (br s, 2H); ^{13}C NMR δ 143.2 (C), 135.6 (CH), 102.6 (CH_2), 82.8 (CH); GC–MS *m/z* 120 (M^+, 2%), 92 (16%), 91 (100%), 68 (63%), 65 (36%), 63 (15%), 52 (28%), 51 (26%), 50 (19%), 39 (54%); EI HRMS calcd for C_8H_8O: 120.0575. Found: 120.0569.

4.2.17. 5,6-Bis(methylene)-7-oxabicyclo[2.2.1]hept-2-ene-1-carboxaldehyde diethylacetal (25) [Table 1, entry 3]. A 2 mL screw capped vial was charged with **4** (0.5 g, 3.3 mmol), 2-(bis(ethoxy)methyl) furan (1.2 g, 7.1 mmol) and sealed. The mixture was heated for 2 h at 60 °C. A 25 mL three-necked flask was charged with the product in THF (5 mL) under N_2. The flask was cooled to 0 °C and a solution of KO*t*-Bu (0.37 g, 3.3 mmol) in THF (5 mL) was added dropwise. The deep red solution was stirred for 15 min, quenched with saturated aqueous NH_4Cl, and the organic layer was separated, dried and concentrated in vacuo to yield a pale yellow oil. Chromatography (CH_2Cl_2/hexane (5:1)) gave **25** (0.5 g; 68%) as a colorless oil: ^{1}H NMR δ 6.51 (d, *J*=5.1 Hz, 1H), 6.34 (dd, *J*=5.1, 2.8 Hz, 1H), 5.34 (s, 1H), 5.24 (s, 1H), 5.16 (br s, 1H), 5.06 (s, 1H), 4.97 (s, 1H) 3.91 (m, 1H), 3.73 (m, 3H), 1.29 (t, *J*=6.7 Hz, 3H), 1.24 (t, *J*=6.7 Hz, 3H); ^{13}C NMR δ 150.1, 143.2 (both C), 135.6, 135.5, 103.0 (all CH), 101.7, 100.4 (both CH_2), 82.2, 71.7 (both CH), 63.9, 63.7 (both CH_2), 15.4, 15.3 (both CH_3); GC–MS *m/z* 222 (M^+, 0.1%), 125 (17%), 103 (50%), 97 (20%), 91 (30%), 75 (52%), 65 (19%), 47 (100%), 39 (23%); EI HRMS calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1253.

4.2.18. 5,6-Bis(methylene)bicyclo[2.2.2]oct-2-ene (26) [Table 1, entry 4]. A 2 mL screw capped vial, charged with **4** (0.5 g, 3.3 mmol) and 1,3-cyclohexadiene (0.79 g, 9.9 mmol) was sealed and kept at 60 °C. The reaction was complete in 2 h as determined by GC. The reaction gave two products in a 3:1 ratio: GC–MS *m/z* 232 (M^+, 0.06%), 119 (26%), 91 (100%), 65 (18%), 51 (8%), 41 (11%), 39 (13%). The products were placed in a 50 mL flask, dissolved in THF (10 mL) under N_2, cooled to 0 °C and a solution of KO*t*-Bu (0.57 g, 3.3 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 15 min and quenched with saturated aqueous NH_4Cl. Diethyl ether (10 mL) was added and the organic layer was separated, dried, concentrated in vacuo, and chromatographed (pentane) giving known **26**[14a,19] (0.26 g, 60%) as a colorless oil: ^{1}H NMR δ 6.2 (m, 2H), 5.1 (s, 2H), 4.7 (s, 2H), 3.2 (m, 2H), 1.6 (m, 2H), 1.4 (m, 2H); ^{13}C NMR δ 147.1 (C), 133.3 (CH), 102.2 (CH_2), 42.3 (CH), 26.1 (CH_2); GC–MS, *m/z* 132 (M^+, 11%), 105 (9%), 104 (100%), 91 (9%), 78 (34%), 77 (17%), 51 (18%), 50 (9%), 39 (20%).

4.2.19. 2-[(Chloromethyl)sulfonyl]-3-methylene-1,2,3,4,5,6,7,8-octahydronaphthalene (27) [Table 1, entry 5]. A 100 mL round-bottomed flask fitted with a reflux condenser was charged with 1,2-bis(methylene)cyclohexane (2.16 g, 20 mmol) and **4** (6.1 g, 40 mmol) under argon. The mixture was heated to 60 °C, stirred for 6 h, concentrated in vacuo, and chromatographed (6:1 hexane/EtOAc) giving **27** (3.95 g, 76%) as a colorless oil; ^{1}H NMR δ 5.23 (d, *J*=3.1 Hz, 2H); 4.48 (dd, *J*=12.6, 144 Hz, 2H), 2.90 (dd, *J*=18.9, 113 Hz, 2H), 2.40–2.65 (m, 2H), 1.73–2.00 (m, 4H), 1.41–1.73 (m, 4H); ^{13}C NMR δ 137.7, 127.1, 123.6, 117.3, 60.3, 52.3, 35.4, 29.6, 29.3, 28.1, 22.7, 22.5. GC–MS *m/e* 147 (49%), 146 (30%), 131 (100%), 118 (81%), 117 (38%), 105 (77%), 104 (35%), 103 (15%), 91 (68%), 79 (32%), 78 (19%), 77 (38%), 67 (17%), 65 (25%), 53 (15%), 51 (25%), 49 (32%), 41 (33%), 39 (33%).

4.2.20. 1,2,3,4,5,6,7,8-Octahydro-2,3-bis(methylene)-naphthalene (28) [Table 1, entry 5]. 2-[(Chloromethyl)-sulfonyl]-3-methylene-1,2,3,4,5,6,7,8-octahydronaphthalene (1.9 g, 7.29 mmol) in THF (10 mL) was cooled to 0 °C under argon. A solution of KO*t*Bu in THF (1 M, 16 mL, 16 mmol) was added dropwise. The mixture was stirred for 30 min and was quenched with saturated aqueous NH_4Cl. Diethyl ether was added and the organic layer was dried. The solvents were removed in vacuo and the residue was passed through a short column (5 cm; pentane) and the solution was concentrated again giving known **28**[21] as a colorless oil (1.0 g, 86%); ^{1}H NMR δ 5.08 (d, *J*=2 Hz, 2H), 4.75 (d, *J*=2 Hz, 2H), 2.81 (s, 4H), 1.91 (br s, 4H), 1.62 (quin., *J*=3.3 Hz, 4H); ^{13}C NMR δ 146.0, 126.7 (both C), 108.1, 38.6, 29.7, 23.0 (all CH_2); GC–MS *m/z* 160 (M^+, 64%), 145 (29%), 131 (32%), 117 (76%), 115 (36%), 92 (55%), 91 (100%), 77 (36%), 41 (37%), 39 (57%).

4.2.21. 1,2,3,4,5,6,7,8,9,10-Decahydro-2,3-bis(methylene)-anthracene (29) [Table 1, entry 6]. A 25 mL flask was charged with **28** (1.0 g, 6.25 mmol) and **4** (0.8 g, 5.26 mmol). The mixture was heated for 3 h at 60 °C, diluted with THF (5 mL), cooled to 0 °C and KO*t*-Bu (0.59 g, 5.26 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 15 min, quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, and the organic layer was removed, dried, concentrated in vacuo, and chromatographed (pentane) giving **29** (0.95 g; 85%) as a waxy solid: ^{1}H NMR δ 5.09 (d, *J*=2 Hz, 2H), 4.75 (d, *J*=2 Hz, 2H), 2.80 (m, 8H), 1.92 (br s, 4H), 1.62 (m, 4H); ^{13}C NMR δ 145.7, 125.5, 124.5 (all C), 108.3, 37.5, 36.7, 29.5, 23.2 (all CH_2); GC–MS *m/z* 212 (M^+, 80%), 197 (54%), 169 (60%), 155 (100%), 141 (52%), 129 (35%), 128 (37%), 115 (39%), 91 (40%), 77 (34%); EI HRMS calcd for $C_{16}H_{20}$: 212.1565. Found 212.1559.

4.2.22. 1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-2,3-bis-(methylene)naphthacene (30) [Table 1, entry 7]. Compounds **29** (0.5 g, 2.36 mmol) and **4** (0.36 g, 2.36 mmol) was kept in a screw capped vial maintained at 60 °C for 3 h. The product was then transferred to a 25 mL three-necked flask, dissolved in THF (10 mL), cooled to 0 °C and KO*t*-Bu

(0.26 g, 2.36 mmol) in THF (3 mL) was added dropwise. The solution was stirred for 15 min, quenched with saturated aqueous NH_4Cl, and the organic layer was separated, dried, concentrated in vacuo, and chromatographed (pentane) giving **30** (0.49 g, 85%) as a waxy solid: ^{1}H NMR δ 5.09 (d, J=2 Hz, 2H), 4.77 (d, J=2 Hz, 2H), 2.77 (m, 12H), 1.93 (br s, 4H), 1.61 (m, 4H); ^{13}C NMR, δ 146.1, 126.7, 125.6, 124.9 (all C), 108.3, 39.2, 38.5, 36.7, 29.7, 22.9 (all CH_2); GC–MS m/z 264 (M^+, 83%), 231 (57%), 203 (65%), 189 (100%); EI HRMS calcd for $C_{20}H_{24}$: 264.1878. Found: 264.1881.

4.2.23. 1,2-Dimethyl-4,5-bis(methylene)cyclohexene (31) [Table 1, entry 8]. A 2 mL screw capped vial was charged with **4** (0.1 g, 0.66 mmol), 2,3-dimethyl-1,3-butadiene (0.2 g, 2.4 mmol), sealed and maintained at 80 °C. The reaction was complete in 5 h, as verified by GC (GC–MS m/z 121 (26%), 120 (26%), 105 (100%), 93 (15%), 91 (32%), 79 (20%), 77 (25%), 65 (10%), 51 (13%), 49 (14%), 41 (16%), 39 (20%)). The product was placed in a 50 mL flask, dissolved in THF (10 mL) under N_2, cooled to 0 °C and a solution of KOt-Bu (0.114 g, 0.66 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 15 min, quenched with saturated aqueous NH_4Cl, diluted with diethyl ether (10 mL), and the organic layer was separated, dried, and concentrated in vacuo. Chromatography (pentane) gave **31** (0.05 g, 57%) as a colorless oil: ^{1}H NMR δ 5.08 (d, J=2.2 Hz, 2H), 4.74 (d, J=2.2 Hz, 2H), 2.85 (br s, 4H), 1.65 (br s, 6H); ^{13}C NMR δ 146.0 (C), 124.4 (C), 107.9 (CH_2), 39.7 (CH_2), 18.6 (CH_3); GC–MS m/z 134 (M^+, 38%), 119 (49%), 117 (17%), 105 (23%), 92 (18%), 91 (100%), 79 (20%), 77 (25%), 65 (17%), 51 (21%), 41 (37%), 39 (52%); EI HRMS calcd for $C_{10}H_{14}$: 134.1095. Found 134.1094.

4.2.24. (*E*,*Z*)-5-Methylene-6-(undecylidene)bicyclo-[2.2.1]hept-2-ene (32) [Table 1, entry 9]. A screw capped vial was charged with **14** (0.1 g, 0.3 mmol), and freshly distilled cyclopentadiene (0.07 g, 1.0 mmol). The tube was sealed and maintained at 100 °C for 30 min. The reaction was followed by TLC (CH_2Cl_2/hexane (5:1)). The product was dissolved in THF (5 mL), placed in a 50 mL three-necked flask under N_2, and cooled to 5 °C. A THF (5 mL) solution of KOt-Bu (0.033 g, 0.3 mmol) was added dropwise turning the solution a pale yellow color. The solution was stirred for 15 min, quenched with saturated aqueous NH_4Cl, treated with diethyl ether (10 mL), and the organic layer was separated, dried, concentrated in vacuo and chromatographed (hexane) giving **32** (0.048 g, 60%) as a colorless oil: ^{1}H NMR δ 6.26 (br s, 2H), 5.55 (t, J=4 Hz, 1H), 5.15 (d, J=4 Hz, 2H), 3.27 (br s, 1H), 3.18 (br s, 1H), 2.23 (m, 2H), 1.68 (dd, J=8, 4 Hz, 2H), 1.41 (m, 2H), 1.29 (s, 16H), 0.88 (t, J=4 Hz, 3H); ^{13}C NMR δ 150.3 (C), 137.5 (CH), 136.5 (CH), 125.4 (C), 124.6 (CH), 106.4 (CH_2), 53.6, 52.7 (both CH), 31.9, 29.8, 29.7, 29.5, 29.5, 29.4, 29.2, 29.0, 28.9, 28.7, 22.7 (all CH_2), 14.1 (CH_3); GC–MS m/z 272 (M^+, 0.2%), 131 (59%), 117 (57%), 91 (68%), 66 (61%), 43 (75%), 41 (100%); EI HRMS calcd for $C_{20}H_{32}$: 272.2504. Found 272.2501.

4.2.25. (*E*,*Z*)-5-Methylene-6-undecylidene-7-oxabicyclo-[2.2.1]hept-2-ene (33) [Table 1, entry 10]. A screw capped vial was charged with **14** (0.1 g, 0.33 mmol) and furan (0.068 g, 1.0 mmol). The vial was sealed and kept at 120 °C for 2 h. The product was dissolved in THF (5 mL) and placed in a 50 mL three-necked flask under N_2 at 5 °C. A THF (5 mL) solution of KOt-Bu (0.37 g, 0.33 mmol) was added dropwise giving a deep red color. Diethyl ether (10 mL) was added and the organic layer was separated, dried and concentrated in vacuo. Chromatography of the deep red oil (CH_2Cl_2/hexane (5:1)) gave **33** (0.45 g, 49%) as a colorless waxy solid: ^{1}H NMR δ 6.5 (d, J=2 Hz, 2H), 5.65 (t, J=4 Hz, 1H), 5.3 (m, 2H), 5.1 (m, 2H), 2.3 (m, 2H), 1.45 (m, 2H), 1.3 (s, 16H), 0.88 (t, J=4 Hz, 3H); ^{13}C NMR δ 143.2 (C), 142.1 (C), 136.4, 135.4, 125.7 (all CH), 107.2 (CH_2), 84.8 (CH), 84.5, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 28.4, 22.7 (all CH_2), 14.1 (CH_3); GC–MS m/z 274 (M^+, 0.6%), 133 (35%), 120 (33%), 105 (44%), 91 (100%), 55 (34%), 43 (66%), 41 (92%); EI HRMS calcd for $C_{17}H_{30}O$: 274.2297. Found 274.2293.

4.2.26. 5-Isopropylidene-6-(methylene)bicyclo[2.2.1]-hept-2-ene (34) [Table 1, entry 11]. A screw capped vial was charged with **13** (0.5 g, 2.78 mmol) and freshly distilled cyclopentadiene (0.25 g, 3.79 mmol). By GC, the reaction was complete after 1 h at room temperature. (GC–MS m/z 248 (M^+, ^{37}Cl, 0.65%), 246 (M^+, ^{35}Cl, 1.5%), 133 (80%), 105 (58%), 91 (100%), 77 (21%), 67 (23%), 66 (40%), 65 (27%), 55 (23%), 51 (21%), 49 (18%), 41 (43%), 39 (41%)). The product was dissolved in THF (25 mL) and transferred to a 50 mL three-necked round bottom flask. The solution was cooled to 0 °C and a THF (5 mL) solution of KOt-Bu (0.31 g, 2.78 mmol) was added dropwise, turning the solution a deep red-black color. The solution was then quenched with saturated aqueous NH_4Cl, the organic layer was separated, dried, concentrated in vacuo and the residue chromatographed (pentane) giving the **34** slightly contaminated with dicyclopentadiene (0.31 g, 85%) by GC: ^{13}C NMR δ 147.1 (C), 147.2 (C), 137.3 (CH), 137.4 (CH), 131.3 (C), 105.4 (CH_2), 65.3 (CH_2), 54.2 (CH), 52.1 (CH), 30.2 (CH_3); GC–MS m/z 146 (M^+, 54%), 131 (100%), 91 (74%), 80 (77%), 79 (85%), 77 (45%), 66 (42%), 65 (40%), 51 (38%), 41 (31%), 39 (83%); EI HRMS calcd for $C_{11}H_{14}$: 146.1096. Found 146.1099.

4.2.27. 4-[(Chloromethyl)sulfonyl]-1,2-dimethylcyclohexene (35) [Table 1, entry 12]. A mixture of 2,3-dimethylbutadiene (3.2 mL, 28.6 mmol) and **5** (2.05 g, 14.6 mmol) in toluene (4 mL) was heated in a sealed tube at 120–130 °C for 12 h. The product was concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) yielding the title compound (3.12 g, 96%) as a colorless solid, mp 69–70 °C; IR (film) 1309 (SO_2), 1146 (SO_2) cm^{-1}; ^{1}H NMR δ 4.43 (s, 2H), 3.47 (m, 1H), 2.41–2.07 (m, 5H), 1.71 (m, 1H), 1.60 (s, 3H), 1.57 (s, 3H); ^{13}C NMR δ 125.8, 122.0, 55.1, 53.6, 30.3, 29.5, 21.2, 18.8, 18.7. Anal. Calcd for $C_9H_{15}ClO_2S$: C, 48.53; H, 6.79 Found: C, 48.50; 7.44.

4.2.28. 1,2-Dimethyl-4-(methylene)cyclohexene (36) [Table 1, entry 12]. A solution of KOt-Bu (12.0 mL, 12.0 mmol, 1 M) in THF was added to 4-chloromethanesulfonyl-1,2-dimethylcyclohexene (1.34 g, 6.0 mmol) in THF (15 mL) at 0 °C. The mixture was heated at reflux for 1 h and then treated with CH_2Cl_2 (150 mL) and water (30 mL). The organic layer was washed with water (10×30 mL), dried, filtered through a silica gel pad, and

the solvent (CH_2Cl_2) was removed by distillation yielding known **36**[17a] as a colorless oil (429 mg, 59%); ^{1}H NMR δ 4.68 (s, 2H), 2.67 (s, 2H), 2.26 (t, J=6.5 Hz, 2H), 2.07 (m, 2H), 1.61 (s, 6H); ^{13}C NMR δ 147.0, 125.8, 124.9, 106.4, 39.7, 39.7, 33.9, 32.3, 18.8; GC–MS *m/z* (rel. intensity) 122 (M^+, 85), 107 (100), 91 (92), 79 (93).

4.2.29. 5-[(Chloromethyl)sulfonyl]bicyclo[2.2.2]oct-2-ene (37) [Table 1, entry 13]. A mixture of 1,3-cyclohexadiene (2.72 mL, 28.6 mmol) and **5** (2.09 g, 14.9 mmol) in toluene (1 mL) was heated in a sealed tube at 120–130 °C for 12 h. The product was concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) yielding **37** (3.1 g, 95%) as a colorless oil which by NMR was a 6.3:1 *endo*/*exo* mixture; *exo*: R_f 0.45 hexanes/EtOAc 5:1; IR (neat) 1319 (SO_2), 1146 (SO_2), 1120 (SO_2) cm^{-1}; ^{1}H NMR δ 6.39 (m, 2H), 4.45 and 4.35 (AB_q, J=12.6 Hz, 2H), 3.30 (m, 1H), 3.18 (br s, 1H), 2.75 (br s, 1H), 1.20–2.24 (m, 6H); ^{13}C NMR δ 136.1, 133.5, 56.5, 55.4, 29.3, 29.2, 27.3, 24.5, 20.4; *endo*: R_f 0.36 hexanes/EtOAc 5:1; IR (neat) 1319 (SO_2), 1147 (SO_2), 1122 (SO_2); ^{1}H NMR δ 6.41 (m, 1H), 6.28 (m, 1H), 4.35 (s, 2H), 3.60 (m, 1H), 3.17 (br s, 1H), 2.78 (br s, 1H), 1.24–2.04 (m, 6H); ^{13}C NMR δ 135.1, 130.4, 58.3, 54.3, 29.2, 29.0, 28.8, 26.1, 22.9.

4.2.30. 5-Methylenebicyclo[2.2.2]oct-2-ene (38) [Table 1, entry 13]. A solution of KO*t*-Bu in THF (12 mL, 12 mmol, 1 M) was added to **37** (1.32 g, 6.0 mmol) in THF (15 mL) at 0 °C. The mixture was heated at reflux for 1 h and then mixed with CH_2Cl_2 (150 mL) and water (30 mL). The organic layer was washed with water (10×30 mL), dried, and filtered through a silica gel pad. The solvent was removed by distillation yielding known **38**[17c] as a colorless oil (366 mg, 51%): ^{1}H NMR δ 6.26 (m, 2H), 4.74 (m, 1H), 4.55 (m, 1H), 3.00 (m, 1H), 2.65 (m, 1H), 2.25–2.18 (m, 2H), 1.66–1.54 (m, 4H); ^{13}C NMR δ 150.7, 134.1, 133.0, 103.8, 41.0, 34.9, 31.4, 29.7, 26.5; GC–MS *m/z* (rel. intensity) 120 (M^+, 35), 92 (100), 91 (92), 79 (38), 77 (37).

4.2.31. 11-[(Chloromethyl)sulfonyl]-9,10-dihydro-9,10-ethanoanthracene (39) [Table 1, entry 14]. A mixture of anthracene (1.35 g, 7.14 mmol) and **5** (0.5 g, 3.57 mmol) in toluene (1.5 mL) was heated in a sealed tube at 155 °C for 7 h. The reaction mixture was taken up in $CHCl_3$ (30 mL), anthracene (0.15 g) was removed by filtration, the filtrate was concentrated in vacuo and the residue chromatographed (1:1 pentane/$CHCl_3$, then $CHCl_3$) gave **39** as a colorless solid (1.12 g, 96%), mp 143–145 °C; IR (film) 1322 (SO_2), 1146 (SO_2), 1118 (SO_2) cm^{-1}; ^{1}H NMR δ 7.46–7.16 (m, 8H), 5.00 (d, J=2.1 Hz, 1H), 4.86 (*t*, J=2.7 Hz, 1H), 4.16 (AB_q, J=12.7, 2H), 3.74 (ddd, J=2.4, 6.3, 9.3 Hz, 1H), 2.30–2.26 (m, 2H); ^{13}C NMR δ 143.3, 143.2, 140.9, 137.9, 127.1, 127.0, 126.6, 126.5, 125.6, 124.0, 124.0, 123.6, 59.5, 55.6, 43.5, 43.3, 30.2.

4.2.32. 9,10-Dihydro-11-methylene-9,10-ethanoanthracene (40) [Table 1, entry 14]. A solution of KO*t*-Bu in THF (4.08 mL, 4.08 mmol, 1 M) was added to **39** (0.67 g, 2.04 mmol) in THF (10 mL) at 0 °C. The reaction mixture was heated at reflux for 1 h, concentrated in vacuo, and the residue was treated with ether (20 mL) and water (20 mL). The aqueous layer was extracted with ether (2×20 mL), organic phase washed with water (2×20 mL), dried, and concentrated in vacuo, affording known **40**[17a] as colorless crystals (0.39 g, 89%), mp 104–105 °C (lit. mp 101–102 °C[17a]); ^{1}H NMR δ 7.51–7.29 (m, 8H), 5.35 (br s, 1H), 4.94 (d, J=10.2 Hz, 2H), 4.55 (m, 1H), 2.65 (m, 2H); ^{13}C NMR δ 146.5, 143.4, 142.5, 126.2, 123.7, 123.6, 107.4, 107.4, 55.5, 45.0, 35.4; GC *m/z* (rel. intensity) 218 (M^+, 28), 178 (100).

4.2.33. 2-[(Chloromethyl)sulfonyl]-1,2,3,4,5,6,7,8-octahydronaphthalene (41) [Table 1, entry 15]. A mixture of 1,2-bis(methylene)cyclohexane (1.3 g, 12 mmol) and **5** (1.55 g, 11 mmol) in toluene (3 mL) was heated at 110–120 °C in a sealed tube for 16 h, the mixture concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) to afford **41** (2.41 g, 97%) as colorless crystals, mp 81–82 °C; ^{1}H NMR δ 4.44 (s, 2H); 3.49–3.61 (m, 1H), 1.65–2.42 (m, 12H), 1.41–1.54 (m, 2H); ^{13}C NMR δ 128.4, 124.6, 55.1, 53.3, 30.1, 29.8, 29.2, 28.6, 22.8, 21.2; IR (neat), 725 (C–Cl), 1156 (s), 1332 cm^{-1} (s, SO_2). Anal. Calcd for $C_{11}H_{17}ClO_2S$ C, 53.11; H, 6.89. Found, C, 52.78; H, 6.50 (see Scheme 18).

4.2.34. 1,2,3,4,5,6,7,8-Octahydro-2-methylenenaphthalene (42) [Table 1, entry 15]. A solution of KO*t*Bu in THF (1 M, 10.0 mL, 10.0 mmol) was added dropwise at 0 °C to **41** (1.24 g, 5.0 mmol) in THF (20 mL). The reaction mixture was refluxed for 1 h., concentrated in vacuo, and the residue was treated with ether (40 mL) and water (40 mL). The layers were separated and the aqueous layer was extracted with ether (3×40 mL). The combined ether layers were washed with water (2×30 mL), dried, concentrated in vacuo and chromatographed (pentane) to give **42** (584 mg, 79%) as a colorless oil; ^{1}H NMR δ 4.67 (s, 2H); 2.60 (s, 2H), 2.26 (t, J=6.6 Hz, 2H), 2.00 (t, J=6.1 Hz, 2H), 1.85 (br, 4H), 1.54–1.64 (m, 4H); ^{13}C NMR δ 147.0, 128.1, 127.3, 106.6, 38.6, 32.8, 32.1, 30.1, 30.0, 23.1, 23.0; EI MS: *m/z* 148 (M^+, 100), 133 (38), 119 (27), 105 (48), 91 (28); IR (neat) 2919 cm^{-1} (C=CH), 1649 (C=C), 1443 (C=CH), 885 cm^{-1} (C=CH).

4.2.35. 2-[(Chloromethyl)sulfonyl]-1,2,3,4,5,6,7,8,9,10-decahydroanthracene (43) [Table 1, entry 16]. Compound **5** (141 mg, 1.0 mmol) and **28** (320 mg, 2 mmol) were sealed in a tube and the mixture was heated to 60 °C and stirred for 12 h. The mixture was concentrated in vacuo and chromatographed (6:1 hexane/EtOAc) to yield the title compound (277 mg, 92%) as a colorless powder, mp 123–124 °C; ^{1}H NMR δ 4.45 (s, 2H); 3.54–3.64 (m, 1H), 2.31–2.60 (m, 5H), 2.10–2.30 (m, 4H), 1.80–1.90 (m, 5H), 1.60–1.65 (m, 4H); ^{13}C NMR δ 126.2, 125.5, 125.3, 122.5, 73.1, 55.0, 53.3, 36.8, 29.3, 28.3, 27.8, 23.9, 23.0, 21.1; IR ($CHCl_3$): 1161, 1322 cm^{-1} (SO_2). Anal. Calcd for $C_{15}H_{21}ClO_2S$: C, 59.88; H, 7.04. Found: C, 60.16; H, 6.65.

4.2.36. 1,2,3,4,5,6,7,8,9,10-Decahydro-2-methyleneanthracene (44) [Table 1, entry 16]. A solution of 2-[(chloromethyl)sulfonyl]-1,2,3,4,5,6,7,8,9,10-decahydroanthracene (301 mg, 1 mmol) in THF (5 mL) was cooled to −5 °C under Ar. A solution of KO*t*Bu in THF (1 M, 2.0 mL, 2.0 mmol) was added dropwise. The mixture was stirred for 30 min and was quenched with saturated aqueous NH_4Cl. Diethyl ether was added and the organic layer was dried.

The solvents were removed in vacuo, the residue was filtered through a short silica gel column (5 cm; pentane) and the solution was concentrated again. Compound **44** was obtained as a colorless oil (150 mg; 75%); ^{1}H NMR δ 4.70 (s, 2H), 2.64 (s, 2H), 2.41 (s, 4H), 2.31 (t, J=6.5 Hz, 2H), 2.03 (t, J=6.5 Hz, 2H), 1.86 (br, 4H), 1.54–1.64 (m, 4H); ^{13}C NMR δ 146.6, 126.0, 125.7, 125.6, 125.2, 107.0, 37.6, 37.2, 37.1, 32.1, 31.8, 29.4, 23.2; EIMS: m/z 200 (M^+, 100), 157 (18), 145 (63), 129 (15), 117 (13); IR (neat) 2926 (C═CH), 1653 (C═C), 1436 (C═CH), 881 (C═CH) (see Scheme 17).

4.2.37. 4-[(Chloromethyl)sulfonyl]-1-(4-methyl-1-pent-3-enyl)cyclohexene and 5-[(chloromethyl)sulfonyl]-1-(4-methyl-1-pent-3-enyl)cyclohexene (45a,b) [Table 1, entry 17]. A mixture of myrcene (0.97 g, 7.14 mmol) and **5** (0.5 g, 3.57 mmol) in toluene (1.5 mL) was heated in a sealed tube at 145 °C for 7 h; the mixture was concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) yielding a 2.3:1 **45a/45b** mixture (0.75 g, 76%; an oil); IR (neat) 1320 (SO_2), 1146 (SO_2), 1119 (SO_2) cm^{-1}; ^{1}H NMR **45a**, δ 5.37 (m, 1H), 5.04 (m, 1H), 4.44 (s, 2H), 3.60–3.44 (m 1H), 2.38–1.95 (m, 10H), 1.65 (s, 3H), 1.56 (s, 3H); **45b** had additional peaks at δ 5.47 (m, 1H), 4.67 (d, J=15 Hz, 1H), 4.45 (s, 2H), 1.69 (s, 3H), 1.54 (s, 3H), integrated relative to the minor component (**45b**) peaks; ^{13}C NMR (**45a**) 138.0, 131.9, 123.6, 116.7, 55.0, 53.4, 37.3, 27.4, 26.8, 25.8, 24.0, 20.9, 17.7. Anal. Calcd for $C_{13}H_{21}ClO_2S$: C, 56.40; H, 7.65. Found: C, 56.48; 8.34.

4.2.38. 4-Methylene-1-(4′-methylpent-3-enyl)-cyclohexene and 5-methylene-1-(4′-methylpent-3-enyl)-cyclohexene (46a,b) [Table 1, entry 17]. A solution of potassium *tert*-butoxide (1 M in THF, 6.3 mL, 6.3 mmol) was added dropwise to a solution of **45a**,**b** (830 mg, 3.0 mmol) in THF (15 mL). The mixture was refluxed for 1 h, quenched with NH_4Cl solution, concentrated in vacuo, and the residue taken up in ether (30 mL) and water (30 mL). The layers were separated and the aqueous layer was extracted with ether (3×40 mL). The combined ether layers were washed with water (3×20 mL) and dried ($MgSO_4$), concentrated in vacuo and the residue chromatographed (pentane) yielding 2.54:1 **46a/46b** (476 mg, 90%) as a colorless oil; **46a**: ^{1}H NMR δ 5.34 (br, 1H), 5.09 (t, J=6.9 Hz, 1H), 4.71 (s, 2H), 2.75 (br, 2H), 2.31–1.92 (m, 8H), 1.67 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 146.3, 137.8, 131.4, 124.3, 119.8, 107.2, 37.6, 33.5, 31.9, 30.8, 26.5, 25.7, 17.7; **46b**: ^{1}H NMR δ 5.43 (br, 1H), 5.09 (t, J=6.9 Hz, 1H), 4.71 (s, 2H), 2.68 (br, 2H), 2.31–1.92 (m, 8H), 1.67 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 146.5, 137.1, 131.5, 124.3, 120.6, 107.1, 37.4, 36.9, 31.9, 31.6, 27.4, 26.4, 17.7; EI GC–MS m/z 176 (M^+, 9%), 107 (26%), 91 (64%), 79 (45%), 69 (100%). The structure of the compound was established by heating a portion of **46a**,**b** (190 mg, 1.08 mmol) with sulfur (34.5 mg, 1.08 mmol) at 200 °C for 12 h. Chromatography (hexanes) of the product gave as the major product 4-methyl-1-(4′-methylpent-3′-enyl)benzene (**46c**; 50 mg, 26%) which could be identified by the simplicity of its ^{1}H and ^{13}C NMR spectra, compared to the spectra expected for the *meta* isomer; ^{1}H NMR δ 7.08 (s, 4H), 5.19 (m, 1H), 2.55–2.62 (m, 2H), 2.31 (s, 3H), 2.35–2.05 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 139.4, 135.1, 132.1, 129.0, 128.2, 123.9, 35.8, 30.2, 25.8, 21.1, 17.8.

4.2.39. 1-*tert*-Butyl-4-[(chloromethyl)sulfonyl]cyclohexene and 1-*tert*-butyl-5-[(chloromethyl)sulonyl]cyclohexene (47a,b) [Table 1, entry 18]. 2-*tert*-Butylbuta-1,3-diene (825 mg, 7.5 mmol) and **5** (703 mg, 5 mmol) were placed in a sealed tube and heated to 130–150 °C with stirring for 12 h. Volatiles were removed in vacuo and the residue was chromatographed (hexane/ethyl acetate, 6:1) to yield 2.6:1 **47a/47b** (962 mg, 74%) as a colorless oil; **47a**: ^{1}H NMR δ 5.40 (m, 1H), 4.44 (s, 2H), 3.38–3.48 (m, 1H), 1.60–2.40 (m, 6H), 1.00 (s, 9H); **47b** had additional peaks at δ 5.42–5.45 (m, 1H), 4.47 (d, J=3.21 Hz, 1H), 1.03 (s, 9H). Anal. Calcd for $C_{11}H_{19}ClO_2S$: C, 52.68; H, 7.64. Found: C, 52.10; H, 7.13.

4.2.40. 1-*t*-Butyl-4-(methylene)cyclohexene and 1-*t*-butyl-5-(methylene)cyclohexene (48a, 48b) [Table 1, entry 18]. A THF solution of KO*t*-Bu (1 M in THF, 4.4 mL, 4.4 mmol) was added dropwise to **47a**,**b** (501 mg, 2.0 mmol) in THF (10 mL). The mixture was refluxed for 1 h, quenched with NH_4Cl solution, concentrated in vacuo, and the residue mixed with ether (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with ether (3×40 mL). The combined ether layers were washed with water (3×15 mL), dried ($MgSO_4$), concentrated in vacuo, and the residue chromatographed (pentane) yielding a 2.5:1 **48a/48b** mixture (200 mg, 67%) as a colorless oil; **48a**: ^{1}H NMR δ 5.29 (t, J=3.6 Hz, 1H), 4.60 (s, 2H), 2.65–2.68 (m, 2H), 2.05–2.19 (m, 4H), 0.90 (s, 9H); ^{13}C NMR δ 146.6, 145.8, 116.6, 106.7, 35.3, 33.6, 31.6, 28.9, 27.0; **48b**: ^{1}H NMR δ 5.40 (m, 1H), 4.62 (s, 2H), 2.65–2.68 (m, 2H), 2.05–2.19 (m, 4H), 0.92 (s, 9H); ^{13}C NMR δ 147.2, 145.0, 128.3, 117.4, 34.7, 33.1, 31.6, 29.1, 27.5.

4.2.41. Trichloro(methylsulfonyl)methane (49). Dimethyl sulfone (1.5 g, 15.9 mmol) and SO_2Cl_2 (150 mL) were placed in a photoreactor fitted with a Hanovia 450 W UV lamp, wrapped with nichrome heating wire, and containing at the bottom a gas bubbling tube and topped by a condenser. The mixture was electrically heated to a gentle reflux as Cl_2 was slowly introduced. The refluxing solution was irradiated for 2.5 h while monitoring TLC. The mixture was then concentrated in vacuo, collecting the SO_2Cl_2 for further use. The residue was chromatographed (5:1 hexane/EtOAc) giving known **49**[18a] as colorless crystals (2.86 g, 91%), mp 163–165 °C; ^{1}H NMR δ 3.35 (s, 3H); ^{13}C NMR δ 103.1, 33.4.

4.2.42. 4-[(Dichloromethyl)sulfonyl]-1,2-dimethylcyclohexene (50) [Table 1, entry 19]. A solution of **6** (1.0 g, 5.7 mmol) and 2,3-dimethylbuta-1,3-diene (1.0 g, 11.4 mmol) in toluene (2 mL) was heated to 100 °C in a sealed tube overnight, the mixture concentrated in vacuo and chromatographed (5:1 hexane/ethyl acetate) giving **50** (1.36 g, 93%) as colorless crystals, mp 71–72 °C; ^{1}H NMR δ 6.28 (s, 1H), 3.70–3.82 (m, 1H), 2.47 (t, J=13.2 Hz, 1H), 2.20–2.32 (m, 2H), 2.10–2.20 (m, 2H), 1.80–1.90 (m, 1H), 1.64 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 126.0, 122.0, 55.6, 30.2, 19.0, 18.7; IR (neat): 777 (CCl_2), 1140, 1332 (SO_2), 1643, 1659 cm^{-1} (C═C). Anal. Calcd for $C_9H_{14}Cl_2O_2S$: C, 42.03; H, 5.49. Found C, 42.21; H, 5.16.

4.2.43. 4-(Dichloromethylene)-1,2-dimethylcyclohexene (51) [Table 1, entry 19]. A solution of **50** (300 mg,

1.17 mmol) and $MeSO_2CCl_3$ (300 mg, 1.62 mmol) in THF (12 mL) was cooled to −3 °C under Ar. A solution of KO*t*Bu in THF (1 M, 2.34 mL, 2.34 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with ether (2×20 mL). The combined ether layers were dried, concentrated in vacuo and chromatographed (hexane) to give the title compound (160 mg, 72%) as a colorless oil; ^{1}H NMR δ 2.85 (s, 2H), 2.50 (t, J=6.5 Hz, 2H), 2.09 (t, J=5.5 Hz, 2H), 1.66 (s, 6H); ^{13}C NMR δ 135.7, 126.1, 123.3, 111.5, 36.7, 31.6, 29.7, 28.7, 18.7; EI MS *m*/*z* 192 (M^++2, 63), 190 (M^+, 99), 177 (50), 175 (81), 155 (76), 139 (66), 119 (96), 91 (100), 77 (83), 51 (63); IR (neat): 1622 cm^{-1} (C═C).

4.2.44. 5-[(Dichloromethyl)sulfonyl]bicyclo[2.2.2]oct-2-ene (52) [Table 1, entry 20]. A mixture of cyclohexa-1,3-diene (800 mg mL, 10 mmol) and **6** (2.6 g, 15 mmol) in toluene (5 mL) was heated in a sealed tube at 120–130 °C for 12 h. The product was concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) yielding **52** (2.34 g, 92%) as colorless crystals, mp 121–122 °C which by NMR was found to be a 3:1 *endo*/*exo* mixture; ^{1}H NMR δ 6.41 (t, J=6.8 Hz, 1H), 6.27 (t, J=6.8 Hz, 1H), 6.10 (s, 1H), 3.80–3.85 (m, 1H), 3.20–3.3 (m, 1H), 2.70–2.80 (m, 1H), 1.90–2.20 (m, 2H), 1.55–1.67 (m, 2H), 1.31–1.43 (m, 2H); ^{13}C NMR δ 135.4, 130.1, 78.2, 57.9, 30.0, 29.9, 29.3, 25.7, 23.0; IR (CH_2Cl_2) 1147, 1336 cm^{-1} (SO_2). Anal. Calcd for $C_9H_{12}Cl_2O_2S$: C, 42.36; H, 4.74. Found: C, 42.41; H, 5.10.

4.2.45. 5-(Dichloromethylene)bicyclo[2.2.2]oct-2-ene (53) [Table 1, entry 20]. Compound **52** (255 mg, 1.0 mmol) and **49** (296 mg, 1.5 mmol) in THF (12 mL) were cooled to −3 °C under Ar and KO*t*-Bu (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, quenched with saturated aqueous NH_4Cl solution, extracted with ether (2×20 mL), the combined ether layers dried, concentrated in vacuo and the residue chromatographed (hexane) to yield **53** (136 mg, 72%) as a colorless oil; ^{1}H NMR δ 6.39 (t, J=6.7 Hz, 1H), 6.26 (t, J=6.7 Hz, 1H), 3.63–3.65 (m, 1H), 2.80–2.82 (m, 1H), 2.06–2.22 (m, 2H), 1.50–1.67 (m, 2H), 1.34–1.46 (m, 2H); ^{13}C NMR δ 140.0, 135.8, 131.1, 36.9, 31.2, 29.7, 24.6, 24.2; EI MS: *m*/*z* 190 (M^++2, 10), 188 (M^+, 16), 160 (54), 125 (100); IR (neat): 3048, 1626, 1444, 899 (C═C), 1463, 709 cm^{-1} (CCl_2).

4.2.46. 2-[(Dichloromethyl)sulfonyl]-1,2,3,4,5,6,7,8-octahydronaphthalene (54) [Table 1, entry 21]. A solution of **6** (1.0 g, 5.7 mmol) and 1,2-bis(methylene)cyclohexane (1.23 g, 11.4 mmol) in toluene (2 mL) was heated to 100 °C in a sealed tube overnight. The mixture was concentrated in vacuo and chromatographed (5:1 hexane/EtOAc) yielding **54** (1.52 g, 94%) as colorless crystals, mp 91–93 °C; ^{1}H NMR δ 6.27 (s, 1H), 3.75–3.85 (m, 1H), 2.42 (t, J=12.6 Hz, 1H), 2.15–2.30 (m, 2H), 2.03–2.11 (m, 2H), 1.80–1.90 (m, 5H), 1.62–1.75 (m, 2H), 1.40–1.52 (m, 2H); ^{13}C NMR δ 128.4, 124.5, 55.5, 30.0, 29.8, 29.1, 22.8, 21.8; IR ($CHCl_3$) 1140, 1322 cm^{-1} (SO_2). Anal. Calcd for $C_{11}H_{16}Cl_2O_2S$: C, 46.65; H, 5.69. Found: C, 46.81; H, 5.32.

4.2.47. 2-(Dichloromethylene)-1,2,3,4,5,6,7,8-octahydronaphthalene (55) [Table 1, entry 21]. A solution of **54** (566 mg, 2.0 mmol) and **49** (742 mg, 4.0 mmol) in THF (15 mL) was cooled to 0 °C under Ar. A solution of KO*t*Bu in THF (1 M, 4.0 mL, 4.0 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether (2×20 mL), dried, concentrated in vacuo and chromatographed (hexane) yielding **55** (150 mg, 65%) as a colorless oil; ^{1}H NMR δ 2.79 (s, 2H), 2.51 (t, J=6.5 Hz, 2H), 2.02 (t, J=6.5 Hz, 2H), 1.83–1.88 (m, 4H), 1.59–1.63 (m, 4H); ^{13}C NMR δ 135.5, 128.4, 125.7, 111.6, 35.7, 30.4, 29.9, 29.8, 29.7, 28.5, 22.9; EI MS: *m*/*z* 218 (M^++2, 62), 216 (M^+, 93), 181 (100), 145 (80), 117 (30), 91 (55); IR (neat): 715 (CCl_2), 1643, 1664 cm^{-1} (C═C).

4.2.48. Chloromethylene-1,2,3,4,5,6,7,8-octahydronaphthalene (56) [Table 1, entry 22]. To a solution of **54** (283 mg, 1.0 mmol) in 60 mL of THF KO*t*-Bu in THF (1 M, 1.5 mL, 1.5 mmol) was added dropwise. The mixture was stirred at 20 °C for 2 h and then warmed to 55 °C, and stirred for an additional 8 h. The mixture was quenched with saturated aqueous NH_4Cl solution, extracted with ether (2×20 mL), and the organic phase was dried, concentrated in vacuo and chromatographed (hexane) to afford a brown oil which by GC–MS consists of a 1:10:1 **42/56/55** mixture (120 mg, 66%).

4.2.49. 5-*exo*-6-*endo*-Bis[(chloromethyl)sulfonyl]bicyclo[2.2.1]hept-2-ene (57). Freshly distilled cyclopentadiene (0.21 mL, 2.6 mmol) was added to a suspension of (*E*)-**7** (0.33 g, 1.3 mmol) in CH_2Cl_2 (4 mL) and the reaction mixture was stirred at room temperature until a colorless clear solution was obtained (ca. 10 min). Concentration in vacuo followed by chromatography of the residue afforded **57** as a colorless solid (0.35 g, 83%), mp 144–145 °C; IR (film) 1322 (SO_2), 1149 (SO_2), 1121 (SO_2) cm^{-1}; ^{1}H NMR δ 6.44 (dd, J=3.00, 5.4 Hz, 1H), 6.39 (dd, J=3.00, 5.4 Hz, 1H), 4.75 (d, J=8.4 Hz, 1H), 4.71 (d, J=8.4 Hz, 1H), 4.57 (d, J=12.6 Hz, 1H), 4.44 (dd, J=3.3, 5.1 Hz, 1H), 4.42 (d, J=12.6 Hz, 1H), 3.73 (dd, J=2.1, 5.1 Hz, 1H), 3.52 (m, 2H), 2.03 and 1.71 (AB_q, J=9.6 Hz, 2H); ^{13}C NMR δ 136.8, 136.2, 61.1, 60.5, 56.4, 56.2, 47.6, 46.6, 45.2. Anal. Calcd for $C_9H_{12}Cl_2O_4S_2$: C, 33.86; H, 3.79. Found: C, 33.51; H, 3.09.

4.2.50. 5-*endo*-6-*endo*-Bis[(chloromethyl)sulfonyl]bicyclo[2.2.1]hept-2-ene (58). Freshly distilled cyclopentadiene (0.1 mL, 1.2 mmol) was added to a suspension of (*Z*)-**7** (0.15 g, 0.6 mmol) in CH_2Cl_2 (4 mL) and the reaction mixture was stirred at room temperature until a clear colorless solution was obtained (ca. 10 min). The product was concentrated in vacuo and the residue chromatographed (hexanes/EtOAc 5:1) affording **58** as a colorless solid (0.16 g, 84%), mp 184–186 °C; IR (film) 1331 (SO_2), 1152 (SO_2) cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ 6.50 (m, 2H), 5.14 and 4.98 (AB_q, J=12.6 Hz, 4H), 4.79 (m, 2H), 3.82 (m, 2H), 1.76 and 1.65 (AB_q, J=9.0 Hz, 2H); ^{13}C NMR (CD_3COCD_3) δ 130.9, 60.3, 53.4, 43.7, 42.8. Anal. Calcd for $C_9H_{12}Cl_2O_4S_2$: C, 33.86; H, 3.79. Found: C, 33.72; H, 3.48.

4.2.51. 2-[(Chloromethyl)sulfonyl]bicyclo[2.2.1]hepta-2,5-diene (59). *Method* 1. A solution of KO*t*-Bu in THF (1.88 mL, 1.88 mmol, 1 M) was added to **57** (0.3 g, 0.94 mmol) in THF (10 mL) at 0 °C. The reaction mixture

was stirred at room temperature for 1 h and the reaction was quenched with NH_4Cl solution. The mixture was extracted with ether (2×20 mL), washed with brine (2×20 ml), dried, concentrated in vacuo and the residue chromatographed (hexanes/EtOAc 5:1, R_f=0.31) yielding **59** as a colorless oil (40 mg, 2%): ^{1}H NMR δ 7.84 (d, J=3.4 Hz, 1H), 6.97 (dd, J=3.2, 5.0 Hz, 1H), 6.79 (dd, J=3.2, 5.0 Hz, 1H), 4.40 and 4.36 (d, J=6.6 Hz, 2H), 3.94 (m, 1H), 3.87 (m, 1H), 2.35 and 2.23 (AB_q, J=7.2 Hz, 2H); ^{13}C NMR δ 161.5, 153.2, 142.9, 141.8, 75.4, 56.6, 52.3, 51.8; IR (neat) 1319, 1161 cm^{-1} (SO_2); EI-MS *m/z*: 204 (M^+, 14%), 154 (28%), 91 (100%), 65 (98%). *Method* 2. A solution of KO*t*-Bu in THF (0.62 mL, 0.62 mmol, 1 M) was added to **58** (0.1 g, 0.31 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, quenched with NH_4Cl solution, extracted with ether (2×20 mL), washed with brine (2×20 ml), dried, concentrated in vacuo and the residue chromatographed (hexanes/EtOAc 5:1, R_f=0.31) yielding the title compound (10 mg, 16%). *Method* 3. [(Chloromethyl)sulfonyl]ethyne (**8**) (139 mg, 1.0 mmol) was placed in a 50 mL flask and cooled to 0 °C. Cyclopenta-1,3-diene (200 mg, 3.0 mmol) was added, then the mixture was stirred for 6 h at 0 °C. The reaction mixture was chromatographed (hexane/ethyl acetate=5:1) to yield **59** (186 mg, 91%) as a colorless oil. Compound **59** decomposes upon standing at room temperature.

4.2.52. 2-{2′,3′-Bis[(chloromethyl)sulfonyl]propyl}-6,6-dimethylbicyclo[3.1.1]hept-2-ene (61). A mixture of (*E*)-**7** (0.57 g, 2.25 mmol) and β-pinene (0.64 g, 4.67 mmol) in toluene (1.5 mL) were placed in a sealed tube and flushed with argon. The white slurry was heated at 135 °C for 1.5 h and then concentrated in vacuo at 60 °C and the residue chromatographed (hexanes/EtOAc 5:1) yielding **61** as a colorless solid (0.63 g, 72%), mp 108–110 °C; IR (film) 1323 (SO_2), 1122 (SO_2) cm^{-1}; ^{1}H NMR δ 5.09–5.51 (m, 1H), 4.63 and 4.77 (AB_q, J=12.6 Hz, 2H), 4.45 and 4.77 (AB_q, J=12.6 Hz, 2H), 4.01–4.13 (m, 2H), 3.29–3.35 (m, 1H), 2.74–2.82 (m, 1H), 2.40–2.50 (m, 2H), 2.26–2.28 (m, 2H), 2.01–2.12 (m, 2H), 1.88 (s, 3H), 1.15 (d, J=9 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR δ 141.9, 123.1, 57.2, 55.9, 52.0, 47.6, 45.3, 40.3, 38.2, 36.5, 31.7, 31.5, 26.0, 21.1. Anal. Calcd for $C_9H_{12}Cl_2O_4S_2$: C, 43.29; H, 5.70. Found: C, 43.39; H, 5.78.

4.2.53. 2-[(3-Chloromethyl)sulfonylallyl]-6,6-dimethylbicyclo[3.3.1]hept-2-ene (62). A solution of KO*t*-Bu in THF (3.14 mL, 3.14 mmol, 1 M) was added to ene adduct **61** (0.61 g, 1.57 mmol) in THF (15 mL) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with NH_4Cl solution, extracted with ether (2×20 mL), washed with H_2O (2×20 mL), dried, concentrated in vacuo and chromatographed (hexanes/EtOAc 5:1) to give (*E*)-2-buta-1,3-dienyl-6,6-dimethylbicyclo[3.3.1]hept-2-ene (**63**; see below) as a colorless oil (14 mg, 5%) and **62** (74 mg, 17%): IR (film) 1326 (SO_2), 1147 (SO_2), 1118 (SO_2) cm^{-1}; ^{1}H NMR δ 6.96 (ddd, J=15, 6.9, 7.2 Hz, 1H), 6.31 (d, J=15 Hz, 1H), 5.34 (m, 1H), 4.39 (s, 2H), 2.96 (d, J=6 Hz, 2H), 1.95–2.40 (m, 5H), 1.25 (s, 3H), 1.14 (d, J=8.7 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR δ 151.4, 142.7, 125.6, 120.5, 57.3, 45.7, 40.6, 39.3, 38.2, 31.7, 31.4, 26.2, 21.2; GC *m/z* (rel. intensity) 276 (M^+, ^{37}Cl, 1), 274 (M^+, ^{35}Cl, 3), 117 (100), 91 (65), 77 (36).

4.2.54. (*E*)-2-Buta-1,3-dienyl-6,6-dimethylbicyclo[3.3.1]-hept-2-ene (63). A solution of KO*t*-Bu in THF (3.1 mL, 3.1 mmol, 1 M) was added to β-pinene adduct **61** (0.57 g, 1.46 mmol) in THF (30 mL) at 0 °C. The reaction mixture was refluxed for 1 h, quenched with NH_4Cl solution, and extracted with $CHCl_3$ (5×30 mL). The organic layer was washed with brine (2×30 mL) and dried, concentrated in vacuo and the residue chromatographed (hexanes) yielding **63** (30 mg, 12%) as a colorless oil: ^{1}H NMR δ 6.39 (dd, J=9.9, 16.8 Hz, 1H), 6.23 (d, J=15.6 Hz, 1H), 6.01 (d, J=15.6 Hz, 1H), 5.58 (s, 1H), 5.16 (d, J=16.8 Hz, 1H), 5.01 (d, J=9.9 Hz, 1H), 2.56 (m, 1H), 2.45–2.28 (m, 3H), 2.01 (m, 1H), 1.32 (s, 3H), 1.12 (d, J=8.7 Hz, 1H), 0.78 (s, 3H); ^{13}C NMR δ 146.5, 137.7, 134.6, 125.9, 125.5, 115.9, 41.0, 37.8, 32.2, 31.4, 29.7, 26.4, 21.1; GC/MS (rel. intensity) *m/z* 174 (M+, 10), 131 (44), 91 (100), 77 (41); UV (CH_2Cl_2) λ_{max} 278 nm.

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Asymmetric reactions of axially chiral amides: use of removable *ortho*-substituents in radical cyclizations of *o*-iodoacrylanilides and *N*-allyl-*N*-*o*-iodoacrylamides☆

Marc Petit, Steven J. Geib† and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, 219 Parkman Ave, Pittsburgh, PA 15260, USA

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Abstract—Radical cyclizations of enantiomerically enriched *o*-iodoacrylanilides and *N*-allyl-*o*-iodoanilides bearing a removable *ortho*-substituent such as trimethylsilyl or bromine provide oxindoles and indoles in good yields and with good to excellent levels of chirality transfer from the N–Ar axis to the new stereocenter. Transition state models for the chirality transfer are suggested. Chemoselectivity of the radical cyclization in favor of the iodine in the case of 2-iodo-6-bromo-*N*-allylacrylamides has been exploited for the synthesis of chiral pyrroloquinolinones by a one-pot sequence of 5-*exo* and 6-*endo* cyclizations.

1. Introduction

Like biaryls, appropriately substituted amides, imides and related heterocycles exhibit axial chirality and have high rotation barriers due to hindered rotation around sp^2–sp^2 C–C or C–N bonds. Early studies on axially chiral amides and imides focused on structure, resolution and rotation barrier measurements,[1] but over the last decade a diverse assortment of asymmetric reactions of these classes of molecules have been identified.[2,3a] We and others have focused on asymmetric reactions of amides and imides where axial chirality emanates from a N–Ar bond.[3,4] Because of their high rates, radical reactions[5] can often occur much faster than N–Ar bond rotations, and asymmetric induction or transfer of chirality from the axis to a new stereocenter often results.

We have shown previously[6,7] that *o*-haloanilides such as M-**1** and M-**3** exist as stable atropisomers with rotation barriers for the N–Ar bond of 28–31 kcal/mol. Anilides M-**1** with a radical acceptor on the acyl group of the amide smoothly undergo 5-*exo* cyclizations to give substituted 1,3-dihydroindol-2-ones R-**2** with high levels of chirality transfer from the vanishing N–Ar axis to the forming stereocenter (Scheme 1).[6,7] Similarly high levels of transfer were observed during the cyclization of *N*-allyl-*o*-iodoanilides M-**3** with the radical acceptor on the *N*-substituent; these precursors produce chiral *N*-acyl dihydroindoles R-**4**.[7] However, in both cases a second *ortho*-substituent such as the methyl group is needed to increase the rotation barrier to obtain separable, stable atropisomers at room temperature. Related *o*-iodoanilides lacking the *o*-methyl substituent have rotation barriers of <20 kcal/mol.[1]

Oxindole alkaloids have generated a great deal of synthetic interest, and many syntheses in both racemic and enantioenriched forms have been achieved.[8,9] Like the representative natural products (−)-horsfiline[10] and spirotryprostatin B[8] shown below, most members of this family lack *ortho*-substituents and none have *ortho*-methyl groups. To extend this methodology to the synthesis of natural oxindole alkaloids, we sought to identify temporary *ortho*-substituents that met three requirements: (1) they should be large enough to ensure that the N–Ar rotation barrier is sufficiently high for resolution and radical cyclization at room temperature, (2) they should promote high levels of chirality transfer, and (3) they should be readily removed or replaced. Here we report that both a trimethylsilyl group and a bromine atom meet the needs of a temporary *ortho*-substituent and allow syntheses of unsubstituted oxindoles. We also report a new synthesis of chiral pyrroloindolone analogs by a cascade 5-*exo*-trig/6-*endo*-trig

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* Corresponding author. Tel.: +1-4126248240; fax: +1-4126249861; e-mail address: curran@pitt.edu
† Direct inquiries regarding the crystal structures to this author at geib@pitt.edu

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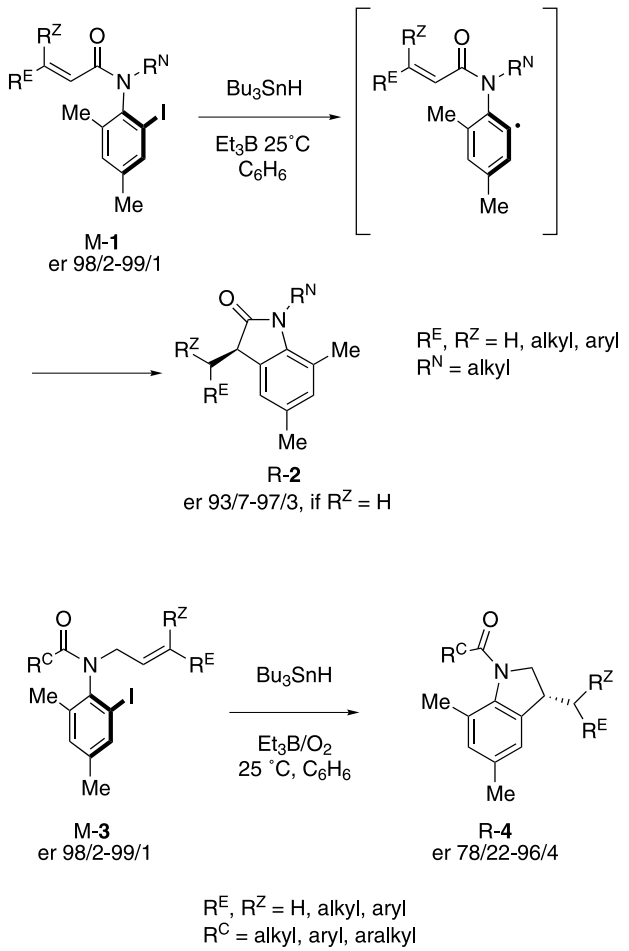
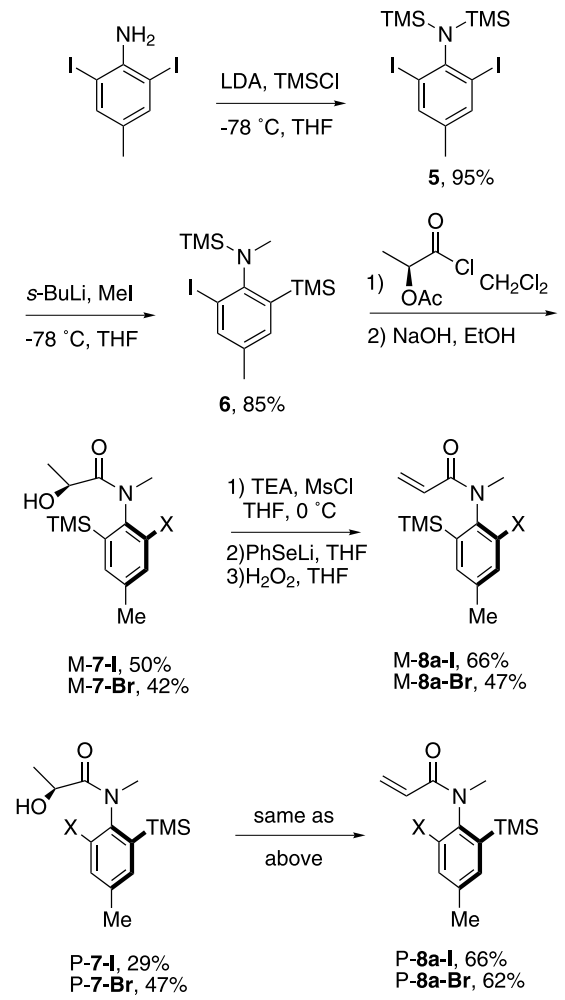
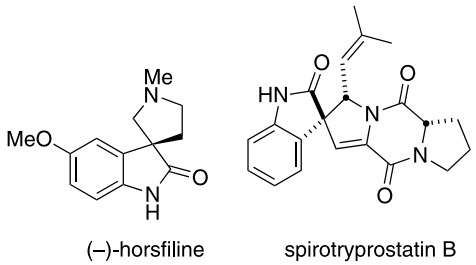


Scheme 1.



Scheme 2.

radical cyclization of *o*-iodo-*o*-bromoanilides.



(–)-horsfiline spirotryprostatin B

2. Results and discussion

We initially focused on using the trimethylsilyl (TMS) group as removable *ortho*-substituent. We prepared acrylanilide enantiomers M-**8a** and P-**8a**, measured their rotation barriers, and studied the cyclizations of the derived radicals. The synthesis of M-**8a**/P-**8a** is summarized in Scheme 2. Two successive protections of 2,6-diiodo-4-methylaniline[11] with trimethylsilyl chloride afforded *bis*-trimethylsilylaniline **5** in 95% yield. Metal–halogen exchange with *sec*-butyllithium induced the migration of one of the TMS groups to the *ortho* position,[12] and the resulting nitrogen anion was quenched with methyl iodide to give **6** in 85% yield. Acylation of **6** with (*S*)-(−)-2-acetoxypropionyl chloride provided an inseparable mixture of two diastereomeric acetates (not shown) that was used directly in the next step. Hydrolysis of the acetate with sodium hydroxide provided a mixture of M-**7**-**I** and P-**7**-**I** (1.7/1) that was readily separated into its two pure components by flash chromatography. The individual isomers were then subjected to a classic sequence described by Taguchi[13] involving substitution of the in situ-generated mesylate by lithium phenylselenide, oxidation and elimination to give M-**8a**-**I** and P-**8a**-**I** with enantiomeric ratios (er) of 94/6 and 98/2. A similar sequence of reactions starting from 2-bromo-6-iodo-4-methyl aniline provided the bromides M-**7**-**Br** and P-**7**-**Br** (1.2/1), which were separated and then converted to M-**8a**-**Br** and P-**8a**-**Br** (See Supporting information).

The absolute configurations of P-**8a**-**I** and P-**8a**-**Br** were assigned by solving the crystal structures of the intermediate alcohols P-**7**-**I** and P-**7**-**Br** (see Supporting information). Enantioenriched samples of M-**8a**-**I** and M-**8a**-**Br** (92/8 and 94/6 er) were racemized by heating at 95–100 °C in hexanes, and the decrease in er was measured as a function of time by chiral HPLC analysis. The rotation (enantiomerization) barrier was measured to be 30.8 kcal/mol for the 2-iodoanilide M-**8a**-**I** and 28.2 kcal/mol for the 2-bromoanilide M-**8a**-**Br**. The decreased rotation barrier of M-**8a**-**Br** relative to M-**8a**-**I** (about 2.6 kcal/mol) presumably reflects

the decreased size of bromine relative to iodine; however, both compounds are stable enantiomers at room temperature (25 °C). Interestingly, the measurements indicate that the TMS group has about the same effective size as a methyl group in this rotation since M-**8a**-**I** and compounds M-**1**[6] (R^E, R^Z=H) have about the same rotation barriers.

The rotational features of the amide N–CO bond (standard amide rotation) are also of interest in these molecules (Fig. 1). M/P-**8a**-**Br/I** exist as single rotamers according to ^{1}H NMR analysis, and crystal structures (see below) prove that this is the expected *E*-rotamer (C=O and Ar trans). Likewise P-**7**-**Br/I** exist as predominately the *E*-rotamer. In contrast, M-**7**-**Br/I** exists as approximately 1.7/1 mixtures of amide rotamers. The barriers to amide N–CO bond rotation have not been measured, but they must be significantly lower than the barriers to N–Ar bond rotation. This means that amide bond rotation occurs without racemization. The similarities of the chemical shift of the resonances of major rotamer of M-**7**-**I/Br** with the resonances of P-**7**-**I/Br** suggest that the major rotamer of M-**7**-**I/Br** is *E*, as shown in Figure 1.

Radical cyclizations were conducted by a standard procedure.[14] Benzene solutions (0.005 M) of M-**8a**-**I** (94/6 er) and P-**8a**-**I** (98/2 er), Bu_3SnH (1.1 equiv.) and Et_3B (1.0 equiv.) were stirred at room temperature for 30–60 min, during which time oxindole **9a** formed. The enantiomer ratios of **9a** were measured by HPLC with an analytical (*S*,*S*)-Whelk-O1[15] column and found to be 88/12 and 96/4 (see Table 1, entries 1 and 2). Taking into account the enantiopurity of the precursors, this corresponds to a 94–96% transfer of chirality from the axis in **8a** to the stereocenter in **9a**. Isolated yields of R-**9a** and S-**9a** were 76 and 78% after flash chromatographic purification. Bromide M-**8a**-**Br** cyclized to give R-**9a** with about the same level of chirality transfer as the iodide (95%), but the conversion was very low (10% isolated yield), and most of the precursor was recovered unreacted (entry 3). Due to the poor conversion, the er measurement of P-**8a**-**Br** was not conducted, and subsequent work was focused on the more reactive iodides.

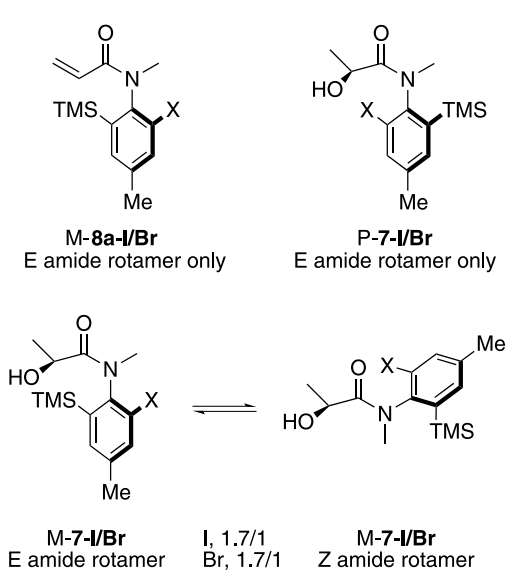
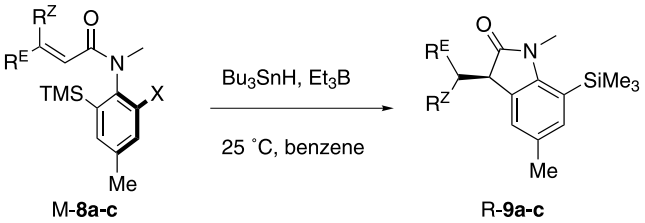


Figure 1. Amide Rotamer Preferences of **7** and **8a**.

Table 1. Chirality transfer in radical cyclizations of M/P**8a–c**



Entry	Precursor-X[a]	R^E	R^Z	Product	%Yield[b]	er_{SM}[c]	er_P[d]	%ct[e]
1	M-**8a**-**I**	H	H	R-**9a**	76	94/6	88/12	94
2	P-**8a**-**I**	H	H	S-**9a**	78	98/2	94/6	96
3	M-**8a**-**Br**	H	H	R-**9a**	10	95/5	91/9	96
4	P-**8a**-**Br**	H	H	S-**9a**	10	95/5	nd	nd
5	M-**8b**-**I**	Me	H	R-**9b**	76	96/4	87/13	91
6	P-**8b**-**I**	Me	H	S-**9b**	77	99/1	91/9	92
7	M-**8c**-**I**	Me	Me	R-**9c**	90	>99/1	73/27	73
8	P-**8c**-**I**	Me	Me	S-**9a**	92	>99/1	73/27	73

[a] Under the standard HPLC conditions, the first eluting enantiomer (M) of the precursor gives the second eluting enantiomer (R) of the product.
[b] Isolated yield after chromatography.
[c] Enantiomeric ratio of precursor **8**.
[d] Enantiomeric ratio of product **9**.
[e] % Chirality transfer = yield (not excess) of the major enantiomer expected from an enantiopure precursor; (% major enantiomer SM)/(%major enantiomer product).

The generality of this chirality transfer was probed by synthesizing and cyclizing two more pairs of enantiomers. Racemic crotonoyl anilide **8b** and 3,3-dimethylacryloyl anilide **8c** (Table 1) were obtained in 79 and 82% yield by mixing **6** with the appropriate acyl chloride. The racemates were resolved on semi-preparative column ((*S*,*S*)-Whelk-O1, 25 cm×21.1 mm I.D., 2–10% *i*PrOH in hexanes, 10 ml/min, 25–50 mg per injection) to give the individual enantiomeric components.

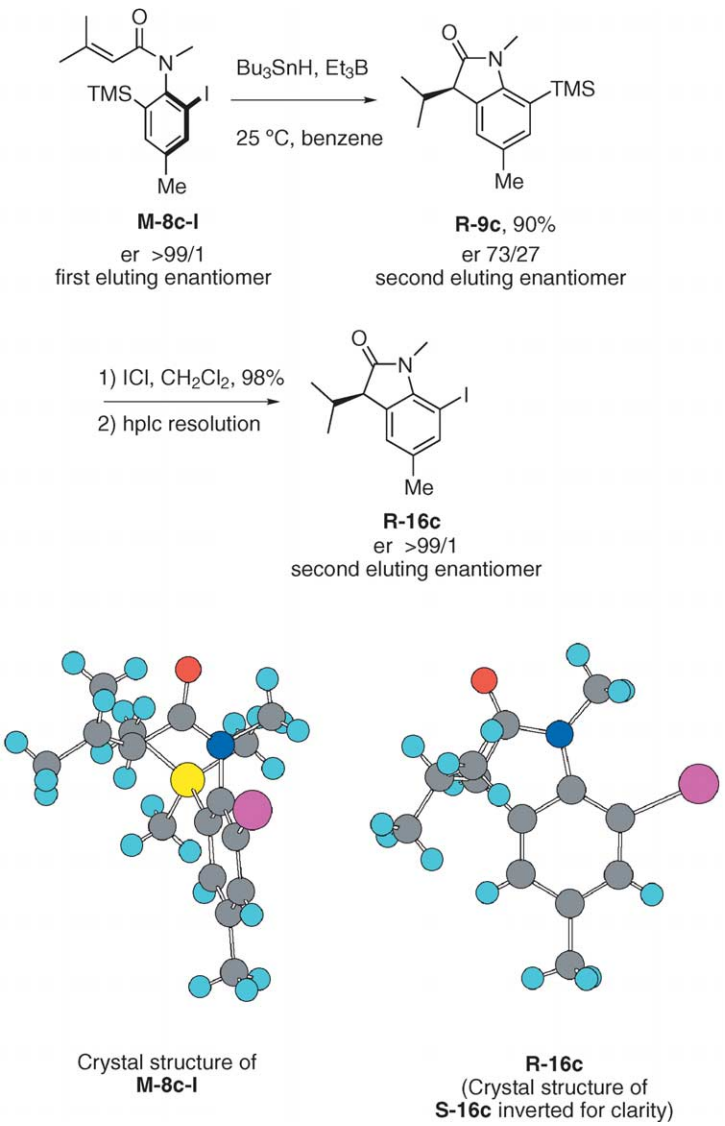
Highly enantioenriched compounds M-**8b**,**c** and P-**8b**,**c** were cyclized by using the standard conditions, and the results of these experiments are shown in Table 1, entries 5–8. Isolated yields of cyclized products ranged from 76–92%.[16] Crotonoyl precursors M/P-**8b** gave levels of chirality transfer (91–92%) similar to the acryloyl analogs (compare entries 1–4 with 5 and 6), while the 3,3-dimethylacryloyl precursors **8c** gave a lower but still significant level of chirality transfer (73%, entries 7/8). This is the same trend that was observed with the *o*-methyl substituted acrylanilides: precursors with R^Z=H give higher levels of chirality transfer (>90%), while those with R^Z=Me are less selective (70–75%).[6]

To date, the absolute configurations of all products from *N*-acryloyl radical cyclizations[6] have been assigned by analogy to a single optical rotation calculation[17] and by using the trend that the first eluting enantiomer precursor in HPLC always gave the second eluting enantiomer of cyclized compound. This HPLC trend held for all the examples in Table 1, and we were able to confirm the computational assignment of absolute configuration by solving two key crystal structures by the anomalous

dispersion method. The structures and associated chemistry for this assignment are shown in Scheme 3.

First, we solved the crystal structure of the first eluting enantiomer of the precursor with the 3,3-dimethylacryloyl group and showed that this was M-**8c**-**I**. Next, we cyclized this as above (Table 1, entry 7) to provide **9c** in a 73/27 ratio with the second eluting enantiomer predominating. The enriched mixture **9c** was then treated with ICl to provide a 73/27 mixture of aryl iodide **16c** with the second eluting enantiomer again predominating. The minor (first eluting) enantiomer of this mixture was isolated by semi-preparative chiral HPLC, was crystallized, and its structure was shown by X-ray to be S-**16c**. In turn, this means that the major enantiomeric product from the radical cyclization of M-**8c**-**I** must be R-**9c**. This is the first example where crystal structures of both a precursor and a product have been solved to secure configuration assignment, and this assignment agrees with our existing model derived from rotation calculations and retention trends.[6,7] Thus, we can now with good confidence conclude that the first eluting M-enantiomers of the precursors **8** give the second eluting R-enantiomers of the products **9**.

Based on the low reactivity of the bromides **9**-**Br**, we hypothesized that radical cyclization of an *o*-iodo *o′*-bromoanilide would occur selectivity at the iodide-bearing carbon, leaving the bromine atom intact for a subsequent reaction.[18] To test this hypothesis, we prepared 2-bromo-6-iodo-4-methylaniline **10** from 2,6-dibromo-4-methylaniline by iodination with BTMA·ICl_2 in presence of calcium carbonate (see Supporting information). A one-pot sequence of deprotonation of **10**, *N*-methylation with iodomethane, deprotonation again, and subsequent *N*-acylation with acryloyl chloride gave **11** in racemic form. Resolution by semi-prep HPLC (Chiralcel OD 25 cm×2 cm, 4% *i*PrOH in hexanes, 10 ml/min, 30 mg per injection) gave 2-bromo-6-iodo-4-methylaniline anilides **M**-**11** and **P**-**11** with good er (96/4 and 99/1). The absolute configuration of the first eluting enantiomer of **11** was determined to be P by X-ray crystallography (see Supporting information). **M**-**11** was racemized by heating at 78–82 °C in hexanes, and the

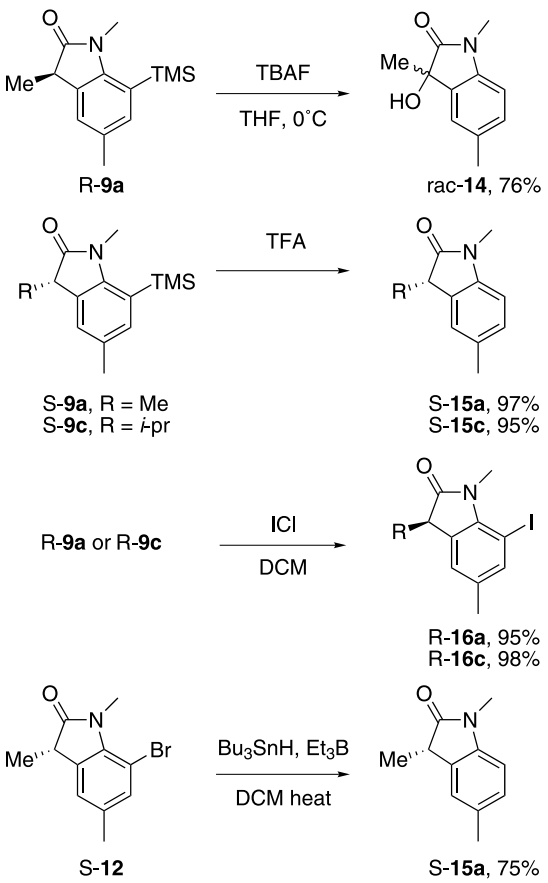


Scheme 3.

decrease in er was measured as a function of time by chiral HPLC analysis. The rotation barrier was measured to be 30.4 kcal/mol, indicating that these are stable enantiomers at room temperature.

The two enantiomers of **11** were then submitted to the usual cyclization conditions to give oxindolones R-**12** and S-**12** in 47 and 45% yield after flash chromatography (Scheme 4). We also isolated lesser amounts (20–22%) of the phenylated compound **13** from both reactions. This compound must arise because radical addition to the solvent benzene competes with the cyclization. Such additions are well known for aryl radicals.[19] The reaction progress was followed by gas chromatography and no formation of the oxindole **16** was observed, confirming that the abstraction reaction is totally chemoselective for iodine. Compounds R-**12** and S-**12** were obtained with good transfer of chirality of 96% from M-**11** and 95% for P-**11**. In this case, the first eluting enantiomer P-**11** on HPLC (Chiralcel-OD) gave the first eluting enantiomer S-**12**. The absolute configuration of R-**12** was confirmed by exposure of silane R-**9a** to bromine in dichloromethane to provide bromide R-**12** (not shown). This sample matched the retention time of the product from the cyclization of M-**11** on chiral HPLC analysis.

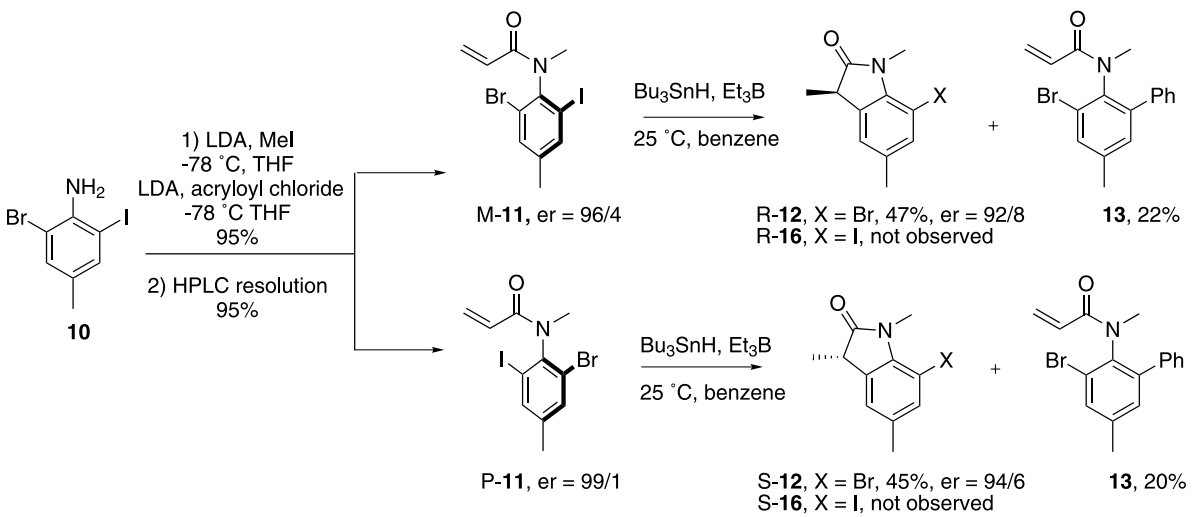
With a good understanding of how to make and cyclize the *o*-silyl and *o*-bromoacrylanilides, we next investigated ways to remove and replace the substituents. In the case of the silicon, we initially tried the standard methods of desilylation by using fluoride reagents. We first submitted oxindole R-**9a** to TBAF, but the only isolated compound (76% yield) was racemic 3-hydroxy-1,3-dihydroindol-2-one **14a**. This must arise from base-promoted air oxidation during desilylation.[20] When R-**9a** was reacted with an excess of HF/pyridine, the expected desilylated compound **15a** was obtained but in low conversion (50%). Finally, exposure of S-**9a**,**c** to trifluoroacetic acid gave the oxindoles S-**15a**,**c** in 97 and 95% yield, respectively, without racemization of the stereocenter (Scheme 5). The silicon group can also serve as a precursor for new functionality. For example, exposure of R-**9a** and R-**9c** to ICl induced clean exchange between the silicon and the iodine, and 6-iodo-oxindoles R-**16a** and R-**16c** were formed in 95 and 98% yields. This exchange opens



Scheme 5.

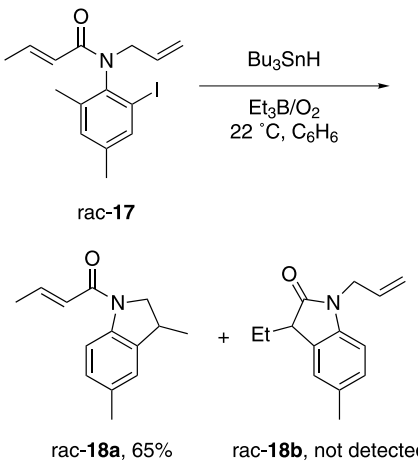
the possibility of introducing different substituents by using standard organometallic coupling reactions. On the other hand, the bromine in S-**12** was removed by reduction with an excess of tributyltin hydride in refluxing dichloromethane to give S-**15a** in 75% yield. These representative transformations open the door to a diverse assortment of enantioenriched oxindoles.

Previous work in our laboratory[7] has also shown that radical cyclizations of enantiomerically enriched *N*-allyl-*o*-iodoanilides (Scheme 1, **3**→**4**) occur in good yields with good to

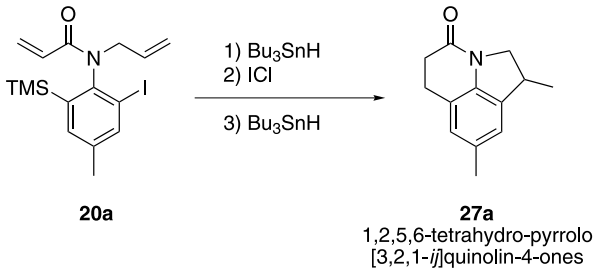


Scheme 4.

previous regioselective cyclization

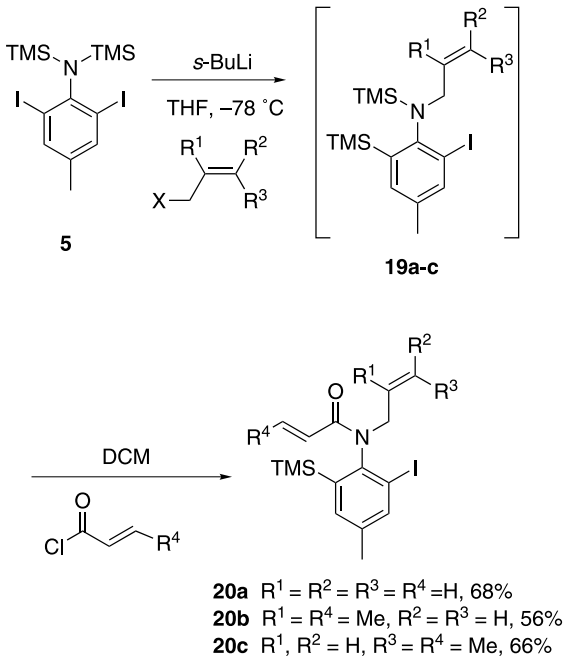


proposed sequential double cyclization



Scheme 6.

excellent levels of chirality transfer. Furthermore, competitive cyclization of compound *rac*-**17** bearing both *N*-crotonoyl and *N*-allyl groups produced exclusively *rac*-**18a** resulting from the cyclization to the *N*-allyl group (Scheme 6).[7] The regioisomer *rac*-**18b** was not observed. We hypothesized that this regioselectivity could be

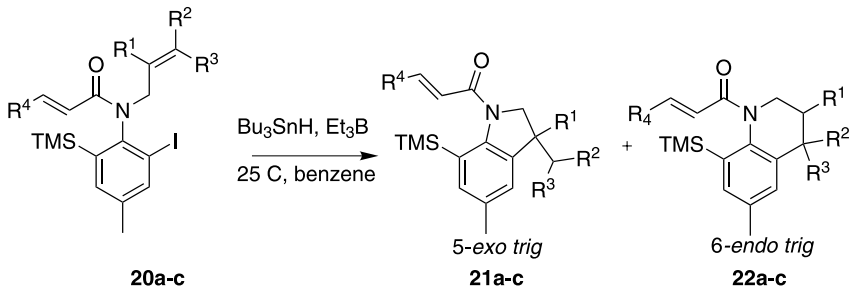


Scheme 7.

combined with the above conversion of the trimethylsilyl to iodine followed by a second radical cyclization to give direct access to tetrahydropyrroloquinolones **27a** from **20a**. Because of ring strain in the forming tricyclic system, we expected the second radical cyclization to occur in a 6-*endo* fashion.[21] As it turned out, the first cyclization also provided minor amounts of 6-*endo* product, depending on the substitution pattern of the double bond.

Precursors **20a**-**c** were prepared starting from 2,6-diiodo-4-methylaniline **5** by the silyl migration route shown in Scheme 2. Treatment of **5** with *sec*-BuLi followed by the appropriate allyl halide provided intermediates **19a**–**c** (Scheme 7). These were not purified but were directly

Table 2.



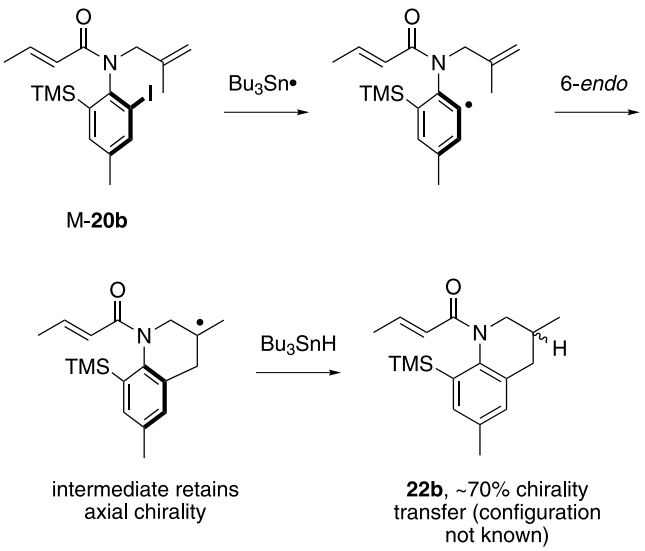
Entry	Precursor	R^1	R^2	R^3	R^4	er_{SM}[a]	**5**-*exo*	Yield	er_P[b]	ct[c]	**6**-*endo*	Yield	er_P[d]	ct[c]
1	**M-20a**	H	H	H	H	>99/1	R-**21a**	47	97/3	97	**22a**	22	—	—
2	**P-20a**	H	H	H	H	95/5	S-**21a**	48	90/10	95	**22a**	21	—	—
3	**M-20b**	Me	H	H	Me	>99/1	**21b**	21	—	—	R-**22b**	57	73/27	73
4	**P-20b**	Me	H	H	Me	>99/1	**21b**	21	—	—	S-**22b**	55	70/30	70
5	**M-20c**	H	Me	Me	Me	>99/1	R-**21c**	88	86/14	86	**22c**	0	—	—
6	**P-20c**	H	Me	Me	Me	>99/1	S-**21c**	90	82/18	82	**22c**	0	—	—

[a] Enantiomeric ratio of precursor **20**.
[b] Enantiomeric ratio of product **21**.
[c] Chirality transfer = yield (not excess) of the major enantiomer calculated for a 100% conversion from a starting material with an er >99/1.
[d] Enantiomeric ratio of product **22**.

acylated to provide **20a**–**c**, which were isolated in pure form by flash chromatography in 56–68% overall yield.

Racemic precursors **20a**–**c** were resolved on a semi-preparative HPLC column ((*S*,*S*)-Whelk-O1, 25 cm× 21.1 mm I.D., 2–10% *i*PrOH in hexanes, 10 ml/min). The enantioenriched compounds were then subjected to the usual conditions for radical cyclization, and the results of this series of experiments are shown in Table 2. Cyclization of unsubstituted M-**20a** (R^1–R^4=H) followed by flash chromatography provided the 5-*exo* product R-**21a** in 47% yield alongside the 6-*endo* product **22a** in 22% yield (entry 1). The level of chirality transfer to the 5-*exo* product was excellent (97%), while the 6-*endo* product is achiral. Similar results were obtained with enantiomer P-**20a** (entry 2). Increasing the terminal substitution on the *N*-allyl group suppressed the 6-*endo* cyclization. Cyclization of *N*-(3,3-dimethylallyl)-*N*-crotonoyl precursor M-**20c** provided exclusively the 5-*exo* product R-**21c** (R^1=H, R^2-R^4=Me) in 88% yield with 86% chirality transfer. Again, enantiomer P-**20c** behaved similarly (entries 5 and 6).

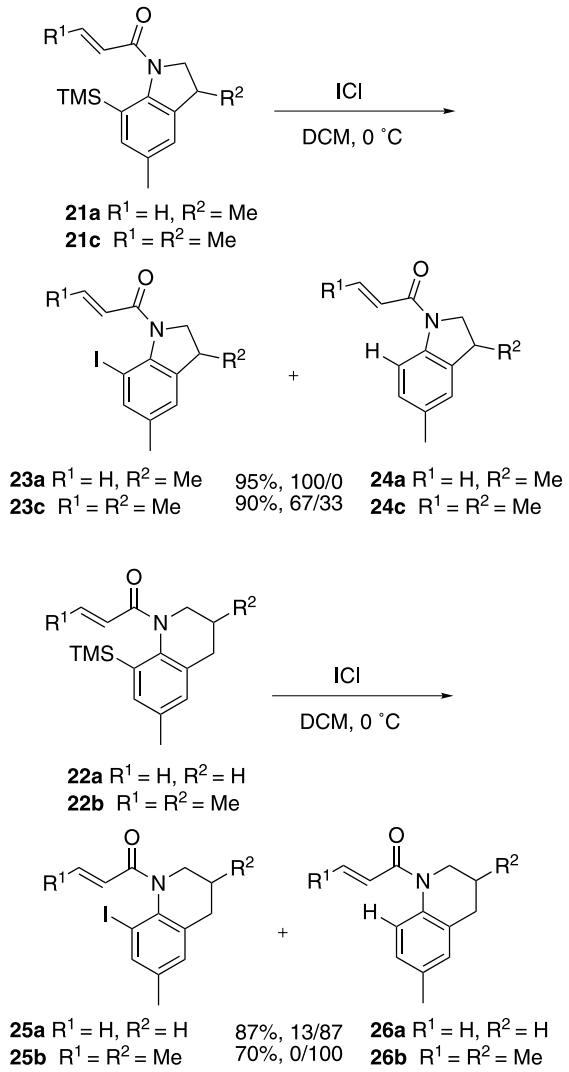
Cyclization of *N*-crotyl, *N*-crotonoyl derivatives M/P-**20b** gave achiral 5-*exo* product **21b** in 21% yield alongside the 6-*endo* product **22b** in 55–57% yield (entries 3 and 4). Interestingly, the 6-*endo* products are significantly enantioenriched, and the level of chirality transfer of the methyl bearing stereocenter is 70–73% (entries 3 and 4). There is no opportunity for chirality transfer from the N–Ar axis in the 6-*endo* cyclization process, but instead the transfer occurs during the bimolecular hydrogen abstraction reaction with Bu_3SnH (see Eq. 1). This is the first example of this type of transfer from a chiral axis to a stereocenter in a radical hydrogen transfer reaction. The configuration of the 6-*endo* compound **22b** is not known.



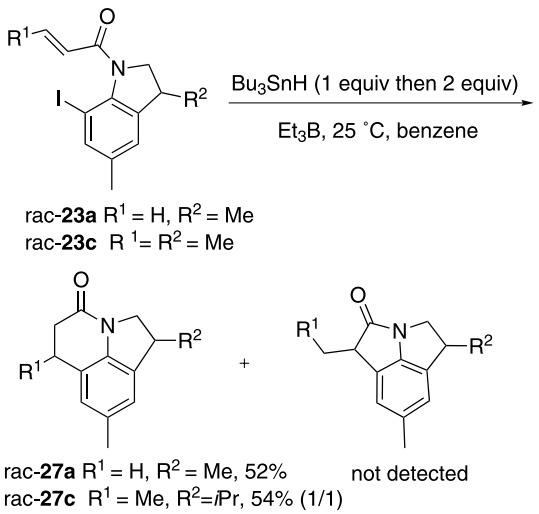
(1)

We were not able to fully resolve the cyclized enantiomers of **21a** and **21c** by using an analytical (*S*,*S*)-Whelk-O1 column but the enantiomer ratio was accurately measured by using an analytical Chiralcel OD column. The ratio of enantiomers **22b** was determined after desilylation (TFA) by using a (*S*,*S*)-Whelk-O1 column. The absolute configuration of compound R-**21c** (first eluting enantiomer) was determined by X-ray crystallography using the anomalous dispersion method (see Supporting information), and the configurations of **21a**,**b** were assigned by assuming that their enantiomers elute in the same order. In these cyclizations, the first eluting enantiomers of **20** ((*S*,*S*)-Whelk-O1 column) again gave the second eluting enantiomer by using the (*S*,*S*)-Whelk-O1 column (poor resolution) and gave the first eluting enantiomer **21** by using the Chiralcel OD column (good resolution). That both pairs of enantiomers switch elution order on the two columns increases the level of confidence in the use of elution order to assign configuration. We currently have no firm assignment of the configuration of any of the precursors **20**, so these were tentatively assigned as shown in Table 2 by using the transition state model described in scheme (see below).

As in the previous study,[7] the three cyclizations are totally regioselective and occurred only on the allyl group. The levels of chirality transfer in the 5-*exo* cyclizations are good to excellent (entries 1/2 and 5/6) and always a little lower for precursors with a *Z* substituent on the allyl group. This trend with *N*-allyl acceptors is similar to that exhibited by the



Scheme 8.



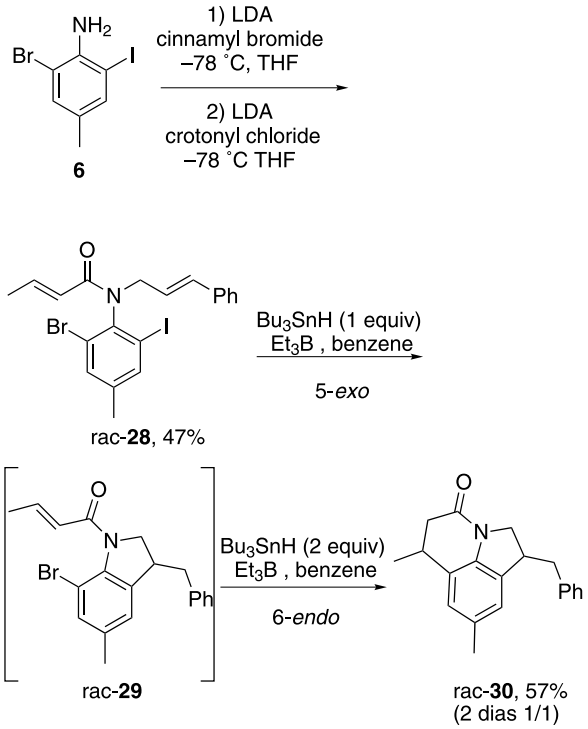
Scheme 9.

previously studied methyl *ortho*-substituted class of compounds.[7]

To obtain precursors for the tricyclic compounds, we submitted compounds **21a**, **21c**, **22a** and **22b** to silicon/iodine exchange reaction with ICl. Results varied depending upon the ring size, as shown in Scheme 8. The dihydroindoles gave the expected iodides as the exclusive or major products. Iodide **23a** was formed from **21a** in 95% yield, while **21c** provided a mixture 67/33 of the iodinated compound **23c** and the desilylated compound **24c**. These were separated on a semi-preparative column ((*S*,*S*)-Whelk-O1, 25 cm×21.1 mm I.D, 10% *i*PrOH in hexanes, 10 ml/min, 50 mg per injection). In contrast, the tetrahydroquinolines **22a** and **22b** provided the desilylated compounds as the major (**26a**) or exclusive (**26b**) products.

We then submitted iodides *rac*-**23a** and *rac*-**23c** to the standard cyclization conditions to provide the pyrroloquinolones *rac*-**27a** and *rac*-**27c** in 52 and 54% yields after flash chromatographic purification (Scheme 9). Tricycle **27c** was characterized as an inseparable 1/1 mixture of diastereomers. These tricyclic quinolinones result from regioselective 6-*endo* cyclization, and products of 5-*exo* cyclization were not observed. Related observations have been made by Dankwardt and co-workers who studied the regioselectivity of an intramolecular Heck reaction. In this work, a preformed five membered ring directed the formation of a six membered ring for the second cyclization.[22]

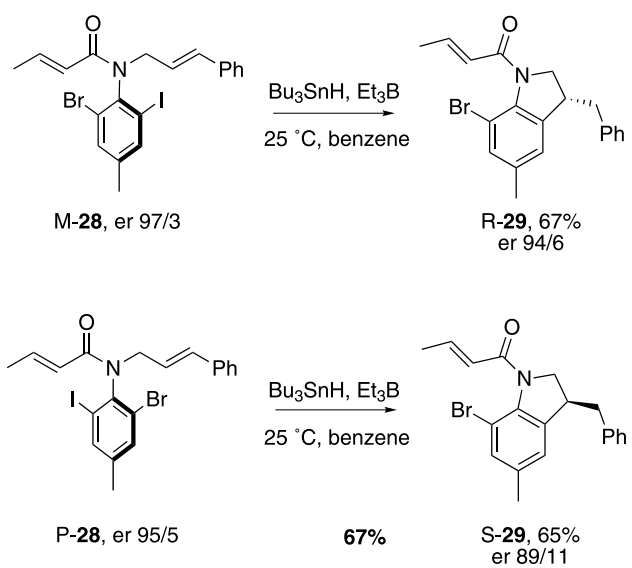
Finally, to eliminate the need for silicon/iodine exchange, we studied both the sequential and one-pot cyclizations of two *o*-iodo *o′*-bromo anilides. Precursor *rac*-**28** was synthesized from **6** by a one-pot sequence of deprotonation, *N*-alkylation with *trans*-cinnamyl bromide, deprotonation, and subsequent *N*-acylation with *trans*-crotonoyl chloride (Scheme 10). When *rac*-**28** was exposed to 1 equiv. of tributyltin hydride, a single new product was formed whose mass spectrum was consistent with *rac*-**29**. Upon addition of two more equivalents of tin hydride, **29** was consumed and a single new product was formed. This was isolated in 57% yield and identified as pyrroloquinolone *rac*-**30**. These results confirm the earlier observations (Scheme 4) showing



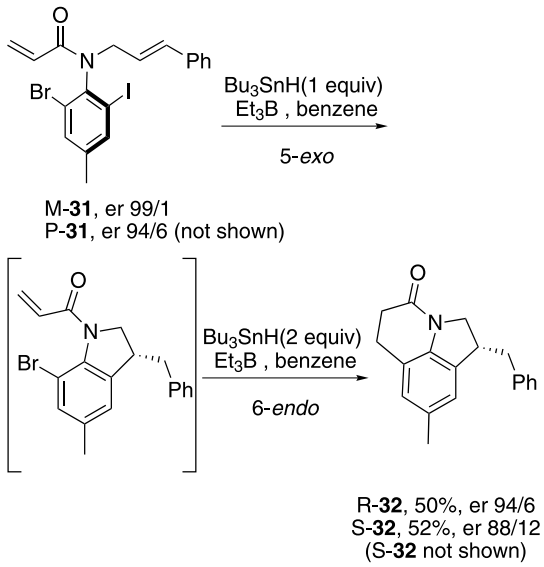
Scheme 10.

that iodine abstraction is highly favored over bromine abstraction. This is crucial for chirality transfer, since iodine and bromine abstraction give quasienantiomeric radicals that will ultimately result in enantiomeric tricyclic products.

Resolution of *rac*-**28** by semi prep HPLC (Chiralcel OD 25 cm×2 cm, 4% *i*PrOH in hexanes, 10 ml/min, 30 mg per injection) gave 6-bromo-2-iodo-4-methyl-anilides M-**28** and P-**28** with 97/3 and 95/5 er. These compounds were then subjected to the usual conditions of radical cyclization, and the results are shown in Scheme 11. Bromodihydrole indoles R/S-**29** were the only isolated products from these reactions in good yields (67 and 65%) and enantiomer ratios (94/6 and 89/11, corresponding to chirality transfer levels of



Scheme 11.

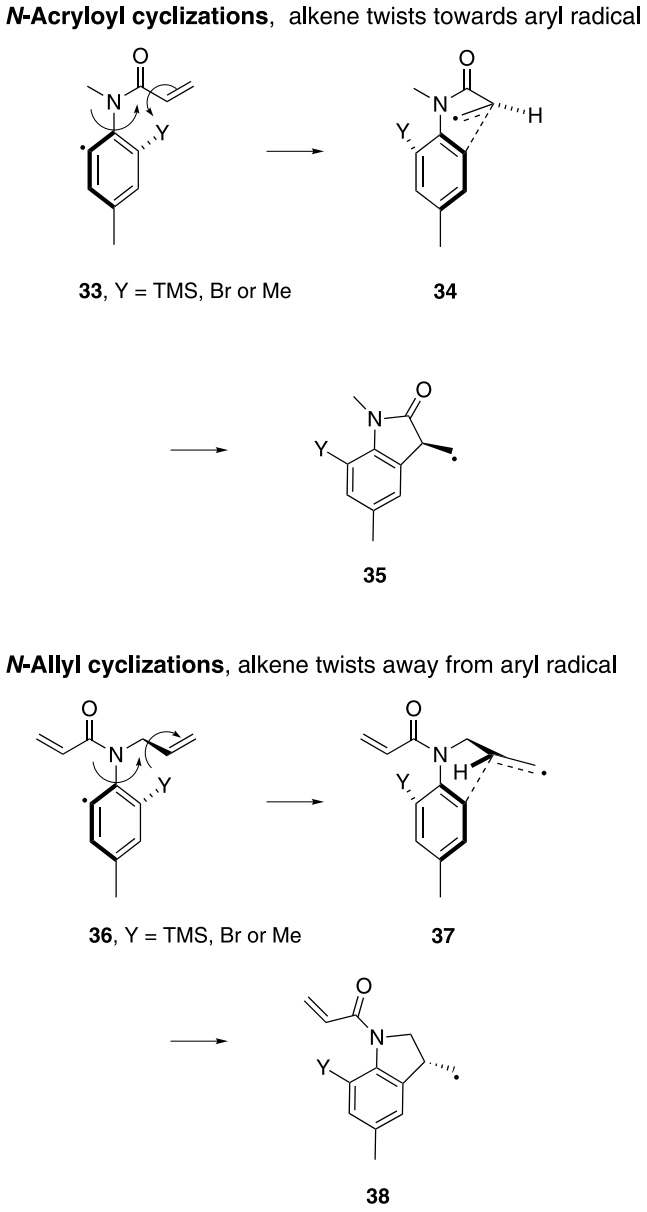


Scheme 12.

97 and 95%). We have no crystal structures in this series, and the absolute configurations of the precursors were assigned by the elution order trend in HPLC.

To complete this study, we needed only to conduct this sequence starting from a resolved precursor to form an enriched product quinolinone. For that, we choose, 2-bromo-6-iodo-4-methyl-anilide **31**. This has an acryloyl group in place of the crotonoyl group in **28**, and accordingly can only give a single enantiomer in the second cyclization. Anilide *rac*-**31** was prepared by using the method described for **28** (see Supporting information). After resolution by preparative HPLC (Chiralcel OD), we obtained the M-**31** and P-**31** with 99/1 and 94/6 er. These two enantiomers were submitted to the double cyclization conditions to give the two quinolines **R-32** and **S-32** in 50 and 52% isolated yields (Scheme 12, only the M/R enantiomer series is shown). Again, the double cyclization was regioselective and the only compound isolated was the quinoline arising from the sequence 5-*exo* then 6-*endo* radical cyclizations. The chirality transfer levels were 95 and 94% as ascertained by the usual chiral HPLC analysis on the (*S*,*S*)-Whelk-O1 column, and absolute configurations were assigned by HPLC elution orders.

Models for chirality transfer for both *N*-acryloyl and *N*-allyl cyclizations of *o*-iodo anilides bearing *o*′-methyl groups have been previously proposed,[6,7] and the straightforward applications of these models to the *o*′-silyl and *o*′-bromo substrates **33** and **36** are shown in Scheme 13. Both models **34** and **37** involve twisting of the aryl ring bearing the radical and the alkene acceptor towards each other, but the alkene acceptor twists in opposite directions. This is surprising because the two cyclizations only differ by the presence of a CH_2 (*N*-allyl) or C=O (*N*-acryloyl) group along the connecting chain between the radical and the acceptor. We have suggested that the increased flexibility of the *N*-allyl group allows it to reach out to the aryl radical and this alters significantly the geometry of cyclization transition state **37**.[7] In contrast, the *N*-acryloyl group of **34** resists reaching out to the radical because amide resonance



Scheme 13.

would be sacrificed, and the transition state geometry is reached mainly by twisting of the two key bonds only (see arrows).

In this work, the structures of several precursors and products in the *N*-acryloyl series have been rigorously determined by a combination of X-ray analysis and interconversion. Since the original model was based on tentative assignments,[6] this greatly increases the confidence that the original structure assignments were correct and that the model can now be used to assign absolute configuration of products from precursors. In contrast, in the *N*-allyl series, the stereochemical model was already based on prior crystal structure work,[7] and the configuration of the products in Table 2 were primarily assigned based on the model. These assignments are fully consistent with the assignments made based on the trends in order of elution of the precursors and products on chiral HPLC, thereby further increasing the confidence that the assignments are correct.

3. Conclusions

In summary, we have shown that a removable *ortho*-substituent can be used for radical cyclizations of axially chiral *N*-acryloyl-*o*-iodoanilides and *N*-allyl-*o*-iodoanilides. High levels of chirality transfer are observed in many cases and an *ortho*-substituent such as bromine or silicon can be easily removed or replaced with retention of the enantiopurity. In the case of 6-bromo-2-iodoanilide, we observed total chemoselectivity in favor of the iodine in the tin hydride reduction. The regioselectivity of the competitive cyclization to the *N*-allyl group over the *N*-acryloyl group discovered in previous work was extended. For axially chiral *N*-acryloyl-*o*-iodoanilides, we proved the sense of chirality transfer by obtaining several X-ray structures of precursors and cyclized compounds. Finally, we demonstrated that the cyclization of axially chiral *N*-acryloyl-*o*-iodoanilides and *N*-allyl-*o*-iodoanilides can be applied toward the synthesis of chiral dihydrooxindoles and dihydroindoles, and can also be extended to the synthesis of chiral pyrroloquinolinones by using a chemo-, regio- and stereoselective double radical cyclization.

Supporting information available

Full experimental details of the synthesis, separation, cyclization, and characterization of all compounds described in this paper are available (part 1, pages 1–42) along with complete details of all the crystal structures (part 2, pages 43–111) and copies of representative spectra (part 3, pages 112–155).

Acknowledgements

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N-α-Benzyloxyacetyl derivatives of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one for the asymmetric synthesis of differentially protected α,β-dihydroxyaldehydes

Stephen G. Davies,* Ian A. Hunter, Rebecca L. Nicholson, Paul. M. Roberts, Edward D. Savory and Andrew D. Smith

Department of Organic Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, UK

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Abstract—α-Dibenzylamino- and α-benzyloxy- derivatives of *N*-acetyl-(*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one readily undergo highly stereoselective boron mediated *syn*-aldol reactions with a range of aromatic and aliphatic aldehydes, generating the *syn*-aldol products in good to excellent yields as single diastereoisomers after purification. In the α-dibenzylamino series, deprotection of the functionalised aldol fragments to the corresponding α-amino-β-hydroxy methyl ester or α-amino-β-hydroxyaldehyde proved problematic, with a range of *N*- and *O*-protecting groups giving mixtures of products arising from endocyclic and exocyclic cleavage pathways. However, in the α-benzyloxy series, *O*-silyl protection of the aldol products, and subsequent DIBAL reduction gives stereoselectively the corresponding *N*-1′-hydroxyalkyloxazolidin-2-ones, which undergo base promoted fragmentation to the desired highly functionalised and differentially protected α,β-dihydroxyaldehydes in good yields and without loss of stereochemical integrity.

1. Introduction

Enantiomerically pure aldehydes are versatile synthetic intermediates that are utilised widely for a range of complex synthetic transformations. As only limited structural variations of such species are available indirectly from the chiral pool, the majority of enantiomerically enriched aldehydes are synthesised using chiral auxiliary techniques.[1] In this area, we have demonstrated previously that diastereoselective enolate alkylation of (*S*)-*N*-acyl-4-benzyl-5,5-dimethyloxazolidin-2-ones, or conjugate addition to (*S*)-*N*-acryloyl-4-phenyl-5,5-dimethyloxazolidin-2-ones and reduction of the resulting α- or β-substituted-*N*-acyl-5,5-dimethyloxazolidin-2-ones, respectively, with DIBAL afford non-racemic aldehydes directly without loss of stereochemical integrity (Fig. 1).[2] This approach offers significant advantages over the two stage reduction and selective oxidation protocol typically used[3] to generate aldehydes from *N*-acyl oxazolidinones.[4]

As part of a research programme directed toward the de novo asymmetric synthesis of carbohydrates and amino sugars,[5] the extension of this strategy to the synthesis of polyfunctionalised *O*- and *N*-containing aldehydes was

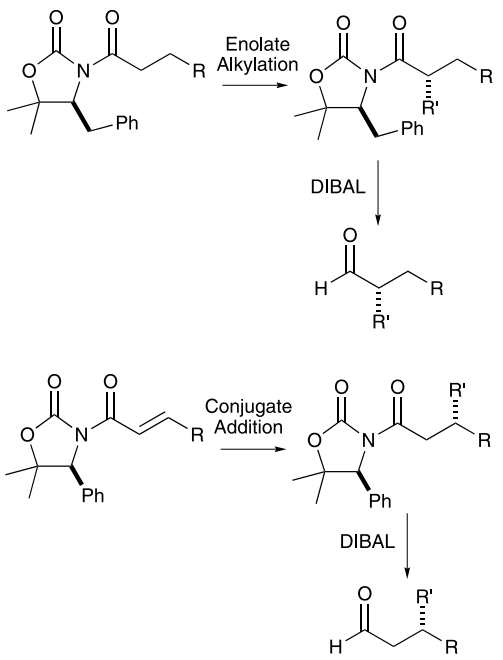

Figure 1. Synthetic route to enantiomerically enriched α-alkyl and β-alkyl aldehydes.

Keywords: Asymmetric aldol; α,β-Dihydroxyaldehydes.
* Corresponding author. Tel.: +44-1865-275695; fax: +44-1865-275633; e-mail address: steve.davies@chem.ox.ac.uk

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investigated. It was predicted that the combination of an asymmetric aldol reaction of an α-alkoxy or α-amino oxazolidinone **1**, combined with subsequent selective DIBAL reduction of the resulting aldol product **2**, would allow direct access to differentially protected, highly functionalised *syn*-α,β-dihydroxy- and *syn*-α-amino-β-hydroxy-aldehydes **3** (Fig. 2). Glycolate enolate aldol and alkylation reactions have been reported in the literature,[6] with *N*-acyl oxazolidinones previously shown to impart high levels of asymmetric induction in these processes.[7] The generality of the glycolate aldol protocol has yet to be fully realised, however, and in particular the direct synthesis of homochiral differentially protected α,β-dihydroxyaldehydes via this procedure has not been previously described. In the α-amino series, Caddick et al. have recently evaluated the utility of *N*-acyl-α-aminoimidazolin-2-one derivatives to undergo boron mediated diastereoselective *syn*-aldol reactions for the synthesis of β-substituted α-phenylserine derivatives, although the diastereoselectivity of the aldol protocol was found to be highly sensitive to both the reaction temperature and nature of the boron reagent used.[8] We report herein our investigations on *N*-α-aminoacetyl and *N*-α-methylbenzyloxyacetyl derivatives of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one for the asymmetric synthesis of differentially protected α-amino-β-hydroxy- and α,β-dihydroxyaldehydes.

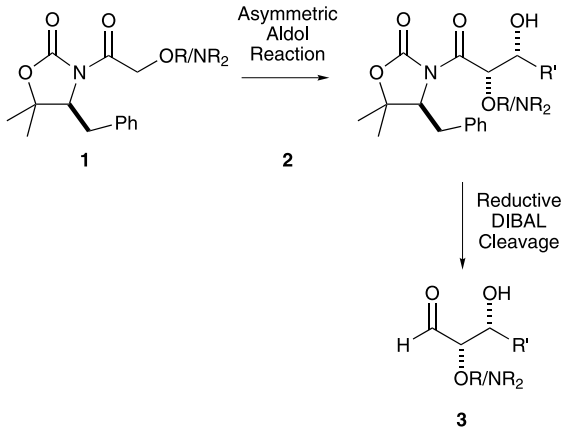
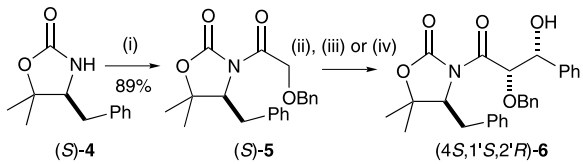


Figure 2. Proposed synthetic route to α-amino-β-hydroxy- and α-alkoxy-β-hydroxyaldehydes.

2. Results and discussion

2.1. The development of asymmetric aldol protocols for *N*-α-benzyloxyacetyl and *N*-α-aminoacetyl derivatives of (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one

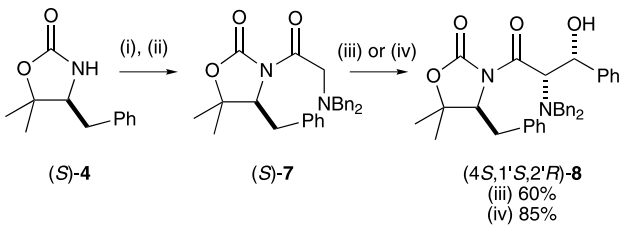
The development of an efficient glycolate *syn*-aldol protocol was chosen as the initial goal, with the asymmetric aldol reaction of (*S*)-3-benzyloxyacetyl-4-benzyl-5,5-dimethyloxazolidin-2-one-**5** with benzaldehyde used as a model system for reaction optimisation. Glycolate oxazolidinone (*S*)-**5** was prepared by treatment of the lithium anion of (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one-**4** with benzyloxyacetyl chloride, giving the desired product (*S*)-**5** in 89% yield. Treatment of *N*-acyl-oxazolidin-2-one (*S*)-**5** with either Et_2BOTf or 9-BBNOTf, followed by triethylamine or Hünig's base afforded the corresponding (*Z*)-boron enolates,[9] while treatment of (*S*)-**5** with titanium tetrachloride and Hünig's base furnished the (*Z*)-titanium enolate.[10] Subsequent reaction with benzaldehyde gave the *syn*-aldol adduct (4*S*,1′*S*,2′*R*)-**6** as the major product in >63% yield in each case, and in >85% d.e. The relative configuration of the newly formed stereogenic centres within **6** were assigned as *syn*- using ^1H NMR ($J_{C(2')H-C(3')H}$ 5.3 Hz), on the basis of the well precedented assumption that the C(3′)-hydroxycarbonyl aldol product **6** exists in solution predominantly in an intramolecularly hydrogen bonded form,[11] with the absolute configuration following from the known stereodirecting preference of oxazolidinone auxiliaries in simple glycolate aldol reactions.[12] The boron aldol reaction using the combination of Et_2BOTf and Hünig's base proved optimal in terms of both yield and stereocontrol, affording the *syn*-aldol adduct **6** in 96% d.e. and in 77% yield as a single diastereoisomer after chromatographic purification (Scheme 1).



Conditions	Base	Lewis Acid	Yield (%)	d.e. (%)
(ii)	$^iPr_2NEt$	Et_2BOTf	77	96
(ii)	NEt_3	Et_2BOTf	76	93
(iii)	$^iPr_2NEt$	9-BBNOTf	63	86
(iii)	NEt_3	9-BBNOTf	67	91
(iv)	$^iPr_2NEt$	$TiCl_4$	74	85

Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C then benzyloxyacetyl chloride; (ii) Et_2BOTf, base, DCM, 0 °C then PhCHO, −78 °C to 0 °C; (iii) 9-BBNOTf, base, DCM, 0 °C then PhCHO, −78 °C to rt; (iv) $TiCl_4$, $^iPr_2NEt$, PhCHO, DCM, −78 °C.

Having established an efficient synthetic procedure for the *syn*-glycolate aldol reaction of (*S*)-**5** with benzaldehyde, the aldol reaction using (*S*)-*N*,*N*-dibenzylaminoacetyl-5,5-dimethyloxazolidin-2-one **7** as a chiral glycine enolate equivalent with benzaldehyde was investigated. Treatment of the lithium anion of (*S*)-benzyl-5,5-dimethyl-oxazolidin-2-one-**4** with bromoacetylbromide gave the corresponding *N*-α-bromoacetyloxazolidinone in 73% yield, which upon displacement with dibenzylamine gave the desired α-dibenzyloxazolidin-2-one **7** in 76% yield. Treatment of **7** with Et_2BOTf and Hünig's base and subsequent reaction with benzaldehyde proceeded to only 70% conversion, and gave the *syn*-aldol product (4*S*,1′*S*,2′*R*)-**8** in >95% d.e. and in 60% yield after chromatographic purification, with starting material (*S*)-**7** being returned in 29% yield. However, the use of 9-BBNOTf and Hünig's base and subsequent reaction with benzaldehyde proceeded to completion, giving (4*S*,1′*S*,2′*R*)-**8** in >95% d.e. and in 85% yield as a single diastereoisomer after purification (Scheme 2).[13] The *syn*-relative configuration within (4*S*,1′*S*,2′*R*)-**8** was proven unambiguously via single crystal X-ray analysis, with the absolute configuration determined relative to the known (*S*)-configuration of the auxiliary (Fig. 3). ^1H NMR analysis ($J_{C(2')H-C(3')H}$ 9.8 Hz) indicated a larger coupling constant for the *syn*-configuration within **8** than expected upon the basis of intramolecular hydrogen bonding between the C(3′)-hydroxyl and the β-carbonyl. In



Scheme 2. Reagents and conditions: (i) *n*-BuLi (1.5 equiv.), THF, −78 °C then bromoacetyl bromide (1.2 equiv.), −78 °C to rt; (ii) dibenzylamine (2.2 equiv.), DCM, rt; (iii) Et_2BOTf, base, DCM, 0 °C then PhCHO, −78 °C to 0 °C; (iv) 9-BBNOTf, DCM, 0 °C; $^iPr_2NEt$, 0 °C; PhCHO, −78 °C to rt; MeOH, $H_2O_{2(aq)}$.

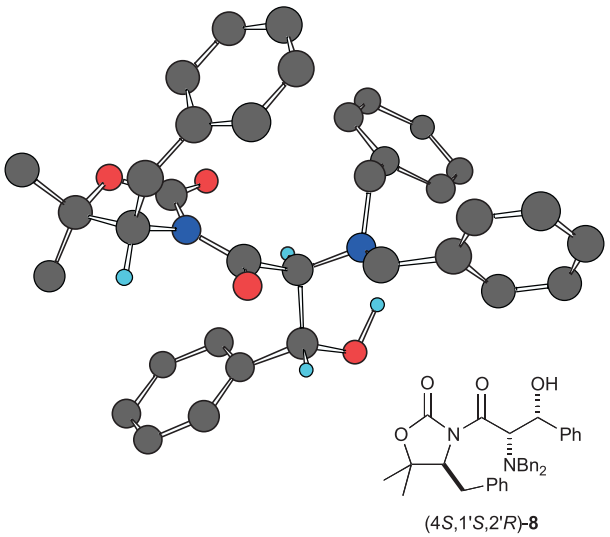
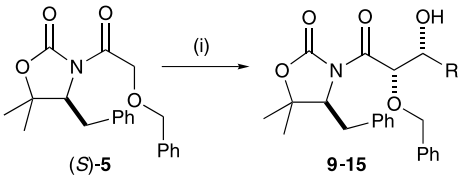


Figure 3. Chem 3D representation of the X-ray crystal structure of (4*S*,1′*S*,2′*R*)-**8** (some H omitted for clarity).

this case, preferential hydrogen bonding in solution between the C(2′)-amino and C(3′)-hydroxyl functionalities, as found in the X-ray crystal structure of (4*S*,1′*S*,2′*R*)-**8**, will result in an approximately *anti*-periplanar arrangement of C(2′)H and C(3′)H, giving the larger coupling constant.

With asymmetric aldol protocols with benzaldehyde established in both the α-benzyloxy- and α-dibenzylamino-*N*-acetyloxazolidinone series, the generality of these processes was tested. Treatment of α-benzyloxy-oxazolidinone (*S*)-**5** with Et_2BOTf and Hünig's base and subsequent reaction with pentanal, 2-methyl-propanal, 3-methyl-butanal, cinnamaldehyde, 4-nitrobenzaldehyde, furfural and pyridine-2-carboxaldehyde gave the *syn*-aldol products **9**-**15** in >92% d.e. in each case. Chromatographic purification gave the α-benzyloxyaldol products **9**-**15** as single diastereoisomers and in good isolated yield (64–83%) (Scheme 3). The *syn*-configuration within α-alkoxyaldol products **9**-**15** was assigned by analogy to that observed in the benzaldehyde derived aldol product **6**. In support of this configurational assignment, ^1H NMR spectroscopic analysis indicated that the coupling constant $J_{C(2')-C(3')}$ was <5.0 Hz in each case.

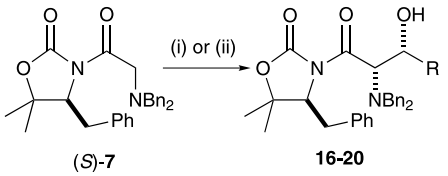
In a similar fashion, further application of the glycine enolate aldol protocol was investigated. Boron mediated aldol reaction of α-dibenzylamino-oxazolidinone **7** with acetaldehyde, pentanal, 2-methyl-propanal, 3-methyl-butanal and



	R	Yield (%)	d.e. (%)	$J_{C(2')-C(3')}$ (Hz)
9	$(CH_2)_4CH_3$	79	>95	2.6
10	$CHMe_2$	77	92	4.5
11	CH_2CHMe_2	96	>95	2.9
12	CH=CHPh	83	>95	5.0
13	4-NO_2Ph	82	>95	2.8
14	furyl	81	92	4.9
15	2-pyridyl	64	>95	3.0

Scheme 3. Reagents and conditions: (i) Et_2BOTf, $^iPr_2NEt$, DCM, 0 °C then RCHO, −78 °C to 0 °C.

cinnamaldehyde using Hünig's base and either 9-BBNOTf or Et_2BBOTf as a Lewis acid gave the *syn*-aldol products **16**-**20** in >95% d.e. in each case, giving **16**-**20** as single diastereoisomers in generally good isolated yields (up to 81%) upon purification. In each case, the reaction with commercially available 9-BBNOTf proceeded to >90% completion and proved optimal in terms of isolated yield, as the reaction with in situ-formed Et_2BBOTf consistently returned between 20 and 30% starting material. Furthermore, in support of the assigned *syn*-configuration, ^1H NMR spectroscopic analysis indicated that the coupling constant $J_{C(2')-C(3')}$ was >9.1 and <9.6 Hz in each case, consistent with that observed in the benzaldehyde derived aldol **8** (Scheme 4).



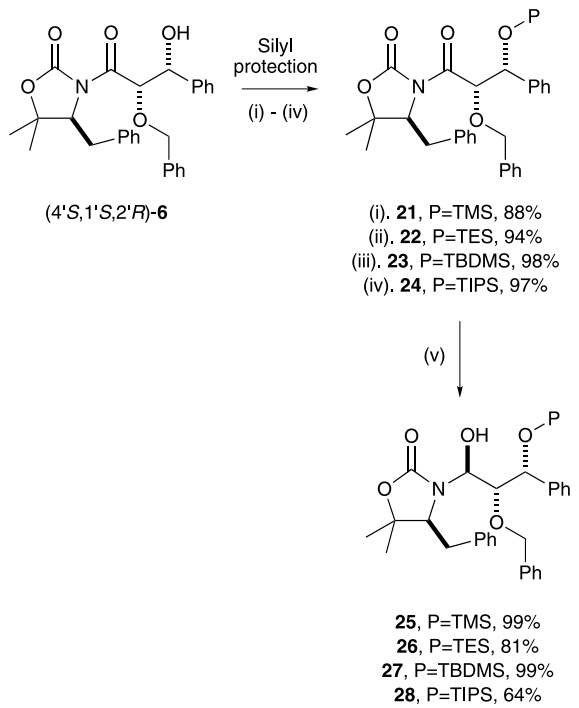
	R	Yield (%) and Conditions	d.e. (%)	$J_{C(2')-C(3')}$ (Hz)
16	Me	(i) 82; (ii) 61	>95	9.2
17	$(CH_2)_4CH_3$	(i) 62; (ii) ---	>95	9.1
18	$CHMe_2$	(i) 41; (ii) 28	>95	9.4
19	CH_2CHMe_2	(i) 62; (ii) 60	>95	9.3
20	CH=CHPh	(i) 73; (ii) 31	>95	9.6

Scheme 4. Reagents and conditions: (i) 9-BBNOTf, DCM, 0 °C; $^iPr_2NEt$, 0 °C; RCHO, −78 °C to rt; MeOH, $H_2O_{2(aq)}$; (ii) Et_2BOTf, $^iPr_2NEt$, DCM, 0 °C then RCHO, −78 °C to 0 °C.

2.2. Asymmetric synthesis of α-alkoxy-β-hydroxy- and α-amino-β-hydroxy-carbonyls

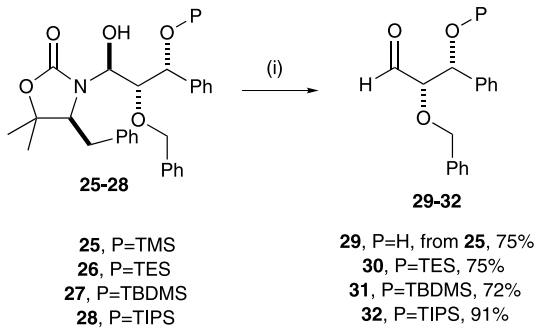
With the generality of the asymmetric aldol reaction upon α-benzyloxy- and α-dibenzylamino-oxazolidinones **5** and **7** demonstrated, the cleavage of the functionalised fragment from the auxiliary to the corresponding aldehyde via reduction with DIBAL was investigated, with the benzaldehyde aldol products **6** and **8** used as model systems for reaction optimisation. Attempted direct cleavage of glycolate aldol product **6** to the α,β-dihydroxy aldehyde with DIBAL or Red-Al®[4] gave a complex mixture of products, suggesting that *O*-protection of the free C(3′)-hydroxyl functionality was required. *O*-Silyl protection of **6** was readily achieved by treatment with either TMSCl, TESCl,

TBDMSOTf or TBDMSCl and TIPSOTf, giving a range of *O*-silyl ethers **21**-**24** in excellent yields after chromatographic purification (Scheme 5). Treatment of the *O*-TMS, *O*-TES and *O*-TBDMS protected aldols **21**-**23** with DIBAL furnished in each case the corresponding stable *N*-1′-hydroxyalkyloxazolidin-2-ones **25**-**27** as single diastereoisomers in 99, 81 and 99% yields, respectively.[14] Although the configuration at C(1′)-within **25**-**27** was not established unambiguously, it was assigned as (*S*) in each case, by analogy to that proven by X-ray crystal structure analysis on an analogous *N*-1′-hydroxy-2′-benzyloxy-oxazolidin-2-one (vide infra). Similar treatment of the *O*-TIPS protected aldol **24** proceeded to only 80% conversion and gave a mixture of products, from which the stable *N*-1′-hydroxyalkyloxazolidin-2-one **28** was isolated as a single diastereoisomer in 64% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) TMSCl, imidazole, DMAP, DMF, rt; (ii) TESCl, imidazole, DMAP, DMF, rt; (iii) TBDMSCl, imidazole, DMAP, DMF, rt or TBDMSOTf, DMAP, DCM, 0 °C; (iv) TIPSOTf, DMAP, DCM, 0 °C; (v) DIBAL, DCM, −78 °C.

Previous studies from this laboratory have demonstrated that stable 1′-hydroxyalkyloxazolidin-2-ones such as **25**-**28** may be considered as masked aldehyde equivalents due to their controlled fragmentation to the corresponding aldehyde upon treatment with base.[2] Although treatment of *O*-TBDMS-protected-1′-hydroxyalkyloxazolidin-2-one **27** with DBU in THF/H_2O[15] resulted in the formation of a mixture of aldehyde products, presumably due to epimerisation and partial *O*-silyl deprotection upon fragmentation, treatment of either the *O*-TES, *O*-TBDMS- or *O*-TIPS-protected 1′-hydroxyalkyloxazolidin-2-ones **26**-**28** with K_2CO_3 in methanol/water gave the corresponding *O*-silyl protected aldehydes **30**-**32** in 75, 72 and 91% yield, respectively, and in >95% d.e. in each case. Similar treatment of the *O*-TMS-protected 1′-hydroxyalkyloxazolidin-2-one **25** gave the unprotected C(3′)-hydroxy aldehyde **29** in 75% yield and >95% d.e. (Scheme 6).

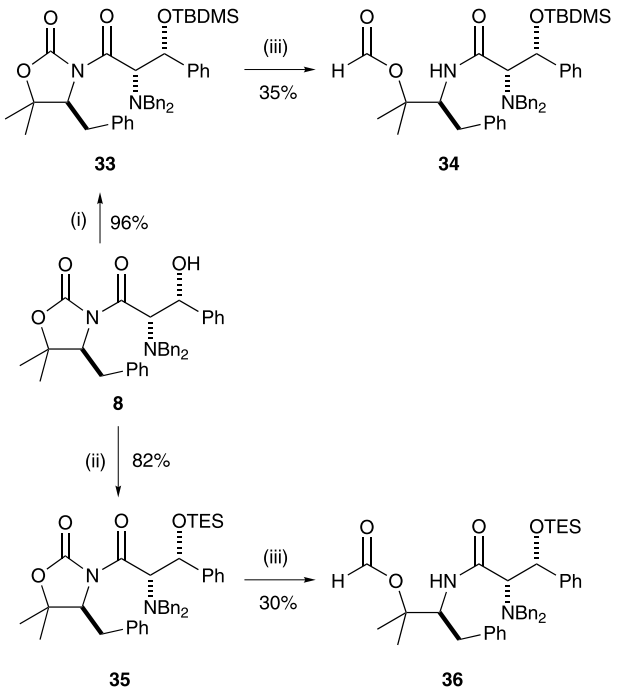


Scheme 6. Reagents and conditions: (i) K_2CO_3, MeOH, H_2O, rt.

With a synthetic protocol established for the synthesis of differentially protected α,β-dihydroxy aldehydes, derivatisation of α-dibenzylamino-β-hydroxyaldol **8** to its corresponding aldehyde was evaluated. Attempted direct cleavage of aldol **8** to the corresponding aldehyde with either DIBAL, $LiAlH_4$ or Red-Al® gave a complex mixture of products, while reduction with $LiBH_4$ returned only starting material. The effect of *O*-silyl protection upon the product distribution of these cleavage reactions was next investigated, with TBDMS or TES protection of aldol **8** giving **33** and **35** in good yields. Subsequent direct reduction of *O*-TBDMS protected aldol **33** with $LiAlH_4$ returned starting material at −78 °C, with reduction at −20 or 0 °C giving a mixture of products, with only a trace of the desired aldehyde by ^1H NMR spectroscopic analysis. Reduction with $LiBH_4$, BH_3, $NaBH_4$ or SuperHydride only returned starting material, while DIBAL reduction returned 20% starting material and gave the formate ester product of endocyclic cleavage **34** in 35% yield as the only other isolable reaction product. Similarly, DIBAL cleavage of *O*-TES protected aldol **35** proceeded to only 40% conversion under standard conditions, returning starting material in 53% yield and giving formate ester **36** in 30% upon chromatographic purification (Scheme 7).

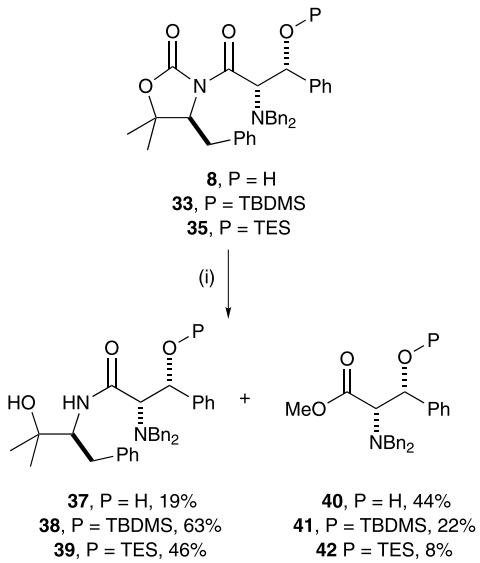
As an alternative strategy for the release of the functionalised fragment from the auxiliary, the cleavage of α-aminoaldol products **8**, **33** and **35** to the corresponding carboxylic ester was probed. Direct treatment of unprotected aldol **8** with LiOMe in MeOH gave a 66:34 mixture of the desired α-amino-β-hydroxyester **40**[16] and (2*R*,3*S*)-3-phenyl-propionamide **37** (the product of endocyclic cleavage) in 44 and 19% isolated yield, respectively. Treatment of *O*-TBDMS protected aldol **33** with LiOMe in THF furnished a 23:77 mixture of methyl ester **41** and amide **38**, isolated in 22% yield and 63% yield, respectively, and in 98% d.e. in each case. Similar treatment of *O*-TES protected aldol **35** gave a 17:66:17 mixture of methyl ester **42**, *O*-TES protected amide **39** and C(3′)-hydroxy amide **37** in 8, 46 and 11% yield, respectively, and as single diastereoisomers in each case (Scheme 8).

In contrast to the selective exocyclic reduction observed upon treatment of α-benzyloxyaldols **21**-**24** with DIBAL, the product distribution upon attempted cleavage of α-dibenzylaminoaldols **8**, **33** and **35** with either DIBAL or LiOMe indicates that competitive exo- and endocyclic cleavage pathways are available in this series. This product distribution is consistent with the exocyclic C(1′)-dibenzyl



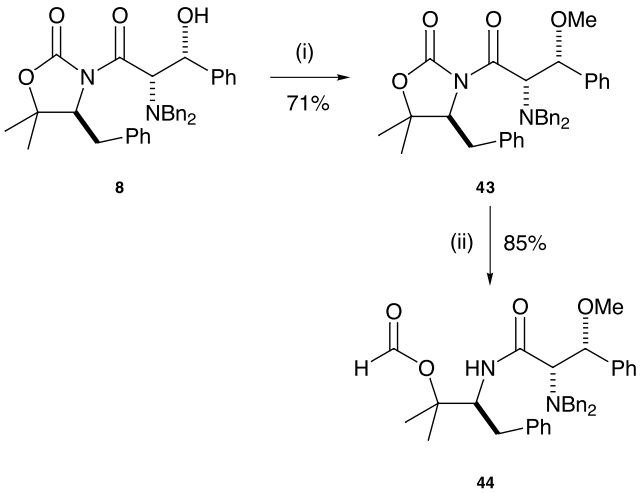
Scheme 7. Reagents and conditions: (i) TBDMSOTf, DMAP, DCM, 0 °C; (ii) TESOTf, DMAP, DCM, 0 °C; (iii) DIBAL (2 equiv.), DCM, −78 °C.

amino group having an enormous steric and conformational bias, which, when combined with the preferred conformation of the C(4)-alkyl group within the oxazolidinone,[17] effectively shields both faces of the exocyclic carbonyl from nucleophilic attack. This steric shielding promotes endocyclic cleavage to compete effectively with the exocyclic cleavage manifold that is encouraged by incorporation of the *gem*-dimethyl group within the oxazolidinone.[18] With the less sterically encumbered C(1′)-alkoxy group within **21**-**24**, the exocyclic cleavage pathway that is favoured by the auxiliary predominates, giving the desired C(1′)-hydroxyalkyloxazolidin-2-ones selectively.



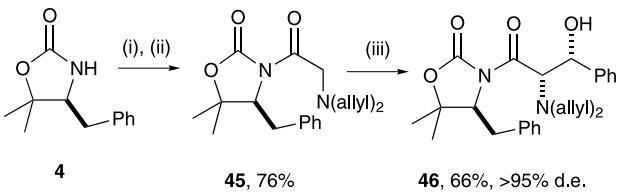
Scheme 8. Reagents and conditions: (i) LiOMe, THF, rt.

In an attempt to solve the regioselective cleavage problem of α-dibenzylaminoaldols **8**, **33** and **35**, the effect of systematically changing the stereodirecting group of the auxiliary and the *N*- and *O*-protecting groups upon the product distribution upon DIBAL reduction was investigated. The effect of altering the size and nature of the *O*-protecting group of aldol product **8** upon DIBAL reduction was first attempted, with *O*-methylation with trimethyloxonium tetrafluoroborate giving *O*-Me **43** in 71% yield at 83% conversion. Reduction of **43** with DIBAL gave formate ester **44** as the exclusive reaction product, giving **44** in 85% isolated yield as a single diastereoisomer (Scheme 9).



Scheme 9. Reagents and conditions: (i) $Me_3O^+BF_4^-$, proton sponge, DCM, rt; (ii) DIBAL (2 equiv.), DCM, −78 °C.

Altering the nature of the *N*-protecting groups was next investigated, with *N*,*N*-diallyl-oxazolidinone **45** prepared by standard protocols. Boron mediated aldol reaction with benzaldehyde gave the *syn*-aldol product **46** ($J_{C(2')-C(3')}$=9.7 Hz) in >95% d.e., giving **46** as a single diastereoisomer in 66% yield after purification (Scheme 10). The *syn*-relative configuration within **46** was established via single crystal X-ray analysis, with the absolute (4*S*,1′*S*,2′*R*)-configuration determined relative to the known (*S*)-configuration of the auxiliary (Fig. 4).



Scheme 10. Reagents and conditions: (i) *n*-BuLi (1.5 equiv.), THF, −78 °C then bromoacetyl bromide (1.2 equiv.), −78 °C to rt; (ii) diallylamine (2.2 equiv.), DCM, rt; (iii) 9-BBNOTf, DCM, 0 °C; $^iPr_2NEt$, 0 °C; PhCHO, −78 °C to rt then MeOH, $H_2O_{2(aq)}$.

TES-protection of the hydroxyl functionality within *N*,*N*-diallyl **46** gave *O*-TES-aldol **47**, with DIBAL reduction under standard conditions returning predominantly starting material (40% isolated yield), and giving poor conversion to the formate ester product of endocyclic cleavage **48** in 20% isolated yield (Scheme 11).

Lastly, the effect of changing the (*S*)-4-benzyl oxazolidinone **4** to the alanine derived (*S*)-4-methyl oxazolidinone **49** in the aldol and reduction procedure was evaluated, with the

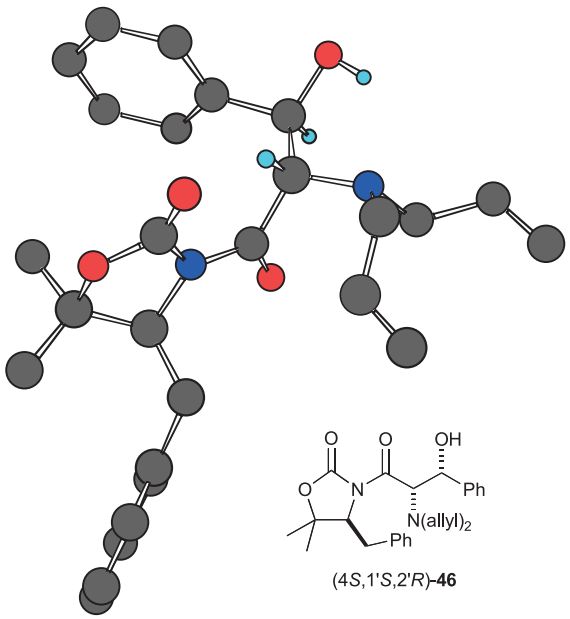
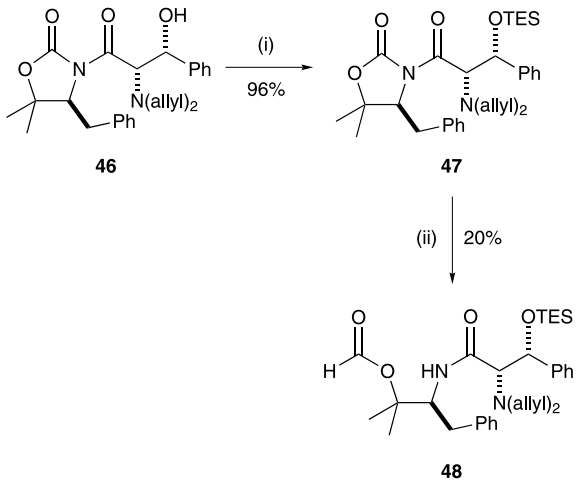


Figure 4. Chem 3D representation of the X-ray crystal structure of (4*S*,1′*S*,2′*R*)-**46** (some H omitted for clarity).

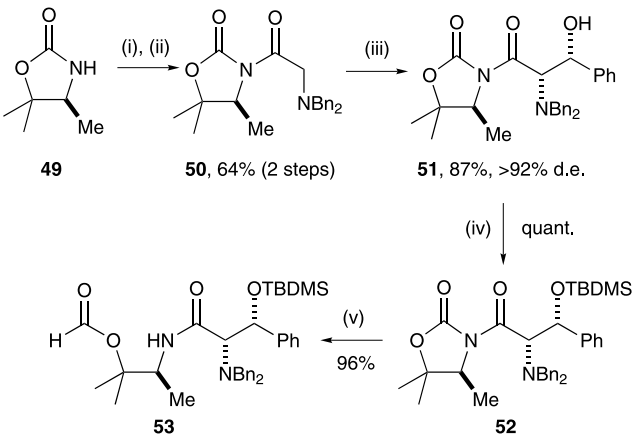


Scheme 11. Reagents and conditions: (i) TESCl (2.5 equiv.), imidazole (5 equiv.), DMAP (1 equiv.), DMF, rt; (ii) DIBAL (2 equiv.), DCM, −78 °C.

syn-aldol product **51** ($J_{C(2')-C(3')}$=9.6 Hz) being formed in high yield as a single diastereoisomer after purification from reaction with the oxazolidinone **50**. *O*-Silyl protection to give **52** and reduction with DIBAL gave formate ester **53** as the exclusive reaction product in 96% isolated yield (Scheme 12).

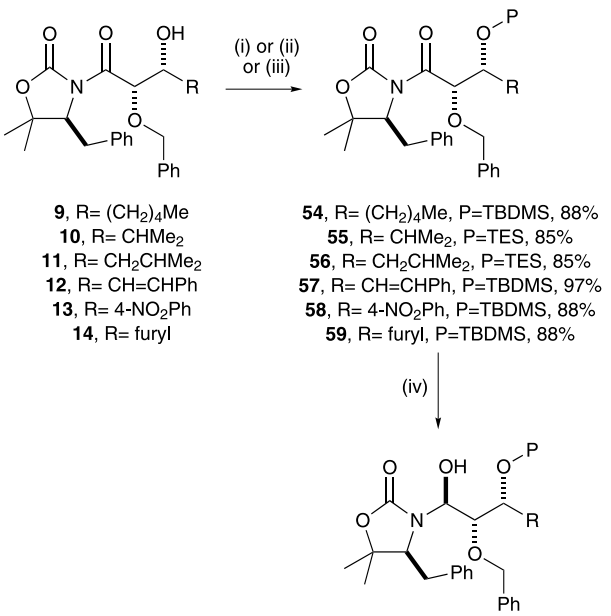
2.3. Diastereoselective preparation of a range of α,β-dihydroxyaldehydes

Although not applicable to the preparation of α-amino-β-hydroxyaldehydes, the efficiency and generality of this asymmetric aldol and reduction methodology for the synthesis of a range of *O*-protected α,β-dihydroxyaldehydes was demonstrated. The glycolate *syn*-aldol products **9** and **12**-**14** were treated with either TBDMSOTf or TBDMSCl, giving the corresponding *O*-TBDMS ethers **54** and **57**-**59** in



Scheme 12. Reagents and conditions: (i) *n*-BuLi (1.5 equiv.), THF, −78 °C then bromoacetyl bromide (1.2 equiv.), −78 °C to rt; (ii) dibenzylamine (2.2 equiv.), DCM, rt; (iii) 9-BBNOTf, DCM, 0 °C; $^{i}Pr_2NEt$, 0 °C; PhCHO, −78 °C to rt then MeOH, $H_2O_{2(aq)}$; (iv) TBDMSOTf, DMAP, DCM, 0 °C; (v) DIBAL (2 equiv.), DCM, −78 °C.

excellent yield; no reaction was observed with the C(4′)- or C(5′)-branched alkyl aldol products **10** and **11** under these conditions. *O*-TES protection of **10** and **11** was achieved via treatment with TESCl, giving **55** and **56** in good yield (Scheme 13). Treatment of the *O*-silyl protected aldols **54**-**59** with DIBAL gave, in each case, the corresponding stable *N*-1′-hydroxyalkyloxazolidin-2-ones **60**-**65** as single diastereoisomers and in excellent yield in each case. The C(2′)–C(3′)-*syn*- and C(1′)–C(2′)-*anti*-relative configuration within 3′-4-nitrophenyl-1′-hydroxyalkyloxazolidin-2-one **64** was established unambiguously by single crystal



Scheme 13. Reagents and conditions: (i) TBDMSCl, imidazole, DMAP, DMF, rt; (ii) TBDMSOTf, DMAP, DCM, 0 °C; (iii) TBDMSCl, imidazole, DMAP, DMF, rt; (iv) DIBAL, DCM, −78 °C.

X-ray structural analysis, with the absolute (4*S*,1′*S*,2′*S*,3′*S*)-configuration confirmed relative to the known (*S*)-configuration of the auxiliary (Fig. 5).[19] The configuration at C(1′)-within *N*-1′-hydroxyalkyloxazolidin-2-ones **60**-**63** and **65** was assigned by analogy to that observed in the crystal structure of **64** (Scheme 13).[20]

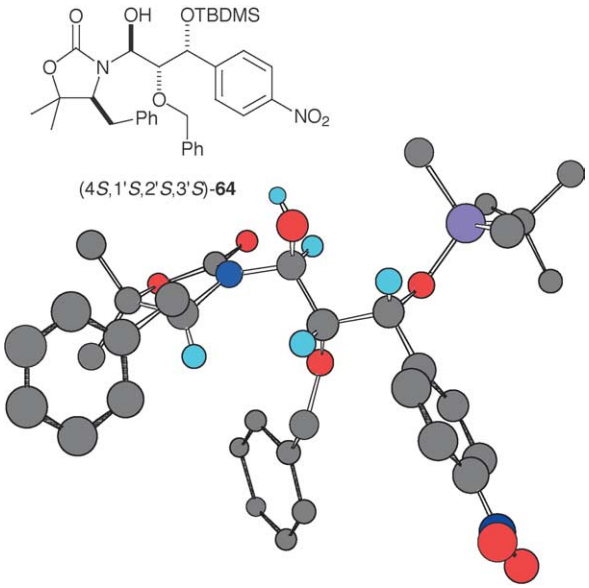
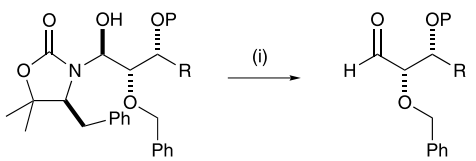


Figure 5. Chem 3D representation of the X-ray crystal structure of (4*S*,1′*S*,2′*S*,3′*S*)-**64** (some H omitted for clarity).

Treatment of *O*-TES protected *N*-1′-hydroxyalkyloxazolidin-2-ones **61** and **62** with K_2CO_3 in MeOH/H_2O returned the auxiliary (*S*)-**4** and gave the corresponding aldehydes **67** and **68**, respectively, as the major reaction products, although in each case an unidentified minor product was apparent in the crude reaction mixture. Chromatographic purification gave homogenous **67** and **68** in 61 and 69% isolated yield, respectively, as single diastereoisomers. Base promoted fragmentation of *O*-TBDMS protected *N*-1′-hydroxyalkyloxazolidin-2-ones **60** and **63**-**65** under the same conditions gave auxiliary (*S*)-**4** and furnished the corresponding aldehydes **66** and **69**-**71**, respectively, in good yields and in >95% d.e. after purification.[21] In each case the desired aldehyde was obtained as a single diastereoisomer, indicating that no epimerisation occurs during fragmentation or purification (Scheme 14).



60, R= $(CH_2)_4Me$, P=TBDMS
61, R= $CHMe_2$, P=TES
62, R= CH_2CHMe_2, P=TES
63, R= CH=CHPh, P=TBDMS
64, R= 4-NO_2Ph, P=TBDMS
65, R= furyl, P=TBDMS

66, R= $(CH_2)_4Me$, P=TBDMS, 89%
67, R= $CHMe_2$, P=TES, 61%
68, R= CH_2CHMe_2, P=TES, 69%
69, R= CH=CHPh, P=TBDMS, 64%
70, R= 4-NO_2Ph, P=TBDMS, 76%
71, R= furyl, P=TBDMS, 85%

Scheme 14. Reagents and conditions: (i) K_2CO_3, MeOH, H_2O, rt.

In conclusion, we have demonstrated that α-benzyloxy and α-dibenzylamino derivatives of *N*-acetyl-(*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one readily undergo highly stereoselective boron mediated *syn*-aldol reactions with a range of aromatic and aliphatic aldehydes, generating the aldol products with high diastereoselectivity and in good to excellent yields. In the α-dibenzylamino series, deprotection of the functionalised aldol fragments to the corresponding α-amino-β-hydroxy methyl esters or α-amino-β-hydroxyaldehydes proved problematic, with competitive exo- and endocyclic cleavage pathways providing a mixture of products. However, in the α-benzyloxy series, *O*-silyl protection of the aldol products, and subsequent DIBAL reduction gives stereoselectively the corresponding *N*-1′-hydroxyalkyloxazolidin-2-ones, which undergo base promoted fragmentation to the desired α-alkoxy-β-hydroxyaldehydes in good yields and without loss of stereochemical integrity. These investigation suggest that while the glycolate aldol reaction, protection and reduction strategy is efficient for the production of α,β-hydroxyaldehyde derivatives, the generation of α-amino-β-hydroxycarbonyl derivatives is limited using this protocol. The application of this methodology to the asymmetric synthesis of a range of natural products, including carbohydrate and amino-sugar derivatives, and alternative strategies for the production of α-amino carbonyl derivatives are currently under investigation within our laboratory.

3. Experimental

3.1. General experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques, using glassware that was flame dried and cooled under nitrogen. THF was distilled from sodium/benzophenone ketyl; DCM was distilled from calcium hydride prior to use. *n*-Butyllithium was used as a solution in hexanes and was titrated against diphenylacetic acid prior to use. DIBAL was used as supplied (Aldrich) as a 1 M solution in hexanes. All other reagents were used as supplied without further purification. Flash column chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infra red spectra were recorded as thin films or KBr discs using a Perkin–Elmer PARAGON 1000 FT-IR spectrometer with only selected peaks reported. ^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz), Bruker DPX-200 (200 MHz), Bruker DPX-400 (400 MHz), Bruker AV400 (400 MHz) or Bruker AM-500 (500 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak and coupling constants (*J*) are measured in Hertz. ^{13}C spectra were recorded at 50.31 MHz on the Varian Gemini 200 or the Bruker DPX-200 spectrometers, at 100.62 MHz on the Bruker DQX-400 or the Bruker DPX-400 spectrometers and at 125.77 MHz on the Bruker AM-500 spectrometer. Chemical shifts (δ_C) are quoted in ppm and referenced using residual solvent peaks. Low resolution mass spectra (*m*/*z*) were recorded on either a VG Masslab 20-250 instrument (CI, NH_3) or Platform instrument

(APCI). MALDI spectra were recorded on a Micromass MALDI TOF SPEC 2E spectrometer. Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a VG Autospec and a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 full width half height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly-DL-alanine with leucine enkephalin as the internal lock mass. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter, using a path length of 10 cm, in spectroscopic grade solvents (Aldrich), with concentrations (*c*) given in g/100 cm^3, solvent and temperature as recorded. Elemental analyses were obtained by Mrs A. Douglas of the Inorganic Chemistry Analytical Department using an Elementar Vario EL combustion elemental analyser. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected.

3.2. Representative procedure 1 for the *N*-acylation of 5,5-dimethyl-oxazoldin-2-ones

n-BuLi (1.1 equiv.) was added to a stirred solution of the oxazolidin-2-one (1.0 equiv.) in THF at −78 °C. After 15 min, the acid chloride (1.3 equiv.) was added dropwise via syringe or via cannula as a solution in THF and stirred at −78 °C for 15 min before being warmed to ambient temperature. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and acetic acid, extracted with EtOAc, washed sequentially with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.3. Representative procedure 2 for the preparation of 2′-(dialkylamino)acetyl 5,5-dimethyl-oxazolidin-2-ones

Dialkylamine (2.2 equiv.) was added to a stirred solution of the *N*-acyl-oxazolidin-2-one (1.0 equiv.) in CH_2Cl_2 at rt and the reaction mixture stirred for 18 h. The resulting mixture was partitioned between CH_2Cl_2 and H_2O, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.4. Representative procedure 3 for the Et_2BOTf mediated aldol addition of *N*-acyl-oxazolidin-2-ones

CF_3SO_3H (1.2 equiv.) was added to Et_3B (1 M in hexanes; 1.2 equiv.) at rt then warmed to 40 °C. After stirring for 10 min, the resultant solution was cooled to 0 °C and added to a solution of *N*-acyl-oxazolidin-2-one (1.0 equiv.) in CH_2Cl_2 via cannula. After stirring for 10 min, *i*-Pr_2NEt (1.4 equiv.) was added and the reaction mixture was stirred for a further 20 min. The reaction was then cooled to −78 °C and freshly distilled aldehyde (1.1 equiv.) was added via syringe. After stirring for 30 min, the resultant mixture was warmed to 0 °C and stirred for a further hour. The reaction was quenched with MeOH/H_2O_2 (v:v 1:1), extracted with CH_2Cl_2, washed with brine, dried and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.5. Representative procedure 4 for the 9-BBNOTf mediated aldol additions of *N*-acyl-oxazolidin-2-ones

9-BBNOTf (1.5 equiv.) was added to a stirred solution of the *N*-acyl-oxazolidin-2-one (1.0 equiv.) in CH_2Cl_2 at 0 °C. After stirring for 10 min, *i*-Pr_2NEt (1.4 equiv.) was added and the reaction mixture was stirred for a further 20 min. The reaction was then cooled to −78 °C and freshly distilled aldehyde (1.1 equiv.) was added via syringe. After stirring for 30 min, the resultant mixture was warmed to 0 °C and stirred for a further hour. The reaction was quenched with MeOH/H_2O_2 (v:v 1:1), extracted with CH_2Cl_2, washed with brine, dried and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.6. Representative procedure 5 for the DIBAL reduction of *N*-acyl-oxazoldin-2-ones

DIBAL (2.0 equiv.) was added dropwise to a stirred solution of *N*-acyl-oxazolidin-2-one (1.0 equiv.) in CH_2Cl_2 at −78 °C. The reaction was quenched at −78 °C after 20 min with saturated aqueous NH_4Cl solution, warmed to rt and stirred for a further 20 min. The resultant mixture was filtered through Celite® (eluent: CH_2Cl_2), dried over $MgSO_4$ and concentrated in vacuo.

3.7. Representative procedure 6 for the protection of aldol adducts with TMSCl, TESCl, TBDMSCl or TBDPSCl

Imidazole (5.0 equiv.), TMSCl, TESCl, TBDMSCl or TBDPSCl (2.5 equiv.) and DMAP (0.1 equiv.) were added sequentially to a solution of *N*-acyl-oxazolidin-2-one (1.0 equiv.) in DMF at ambient temperature. After stirring for 18 h, the reaction was quenched with MeOH, diluted with Et_2O, washed with water, dried and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.8. Representative procedure 7 for the protection of aldol adducts with TBDMSOTf or TIPSOTf

DMAP (1.5 equiv.) and TBDMSOTf (2.0 equiv.) were added sequentially to a solution of *N*-acyl-oxazolidin-2-one (1.0 equiv.) in CH_2Cl_2 at 0 °C. After stirring for 18 h, the reaction was quenched with MeOH, extracted with CH_2Cl_2, washed with brine, dried and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.9. Representative procedure 8 for the fragmentation of *N*-1′-hydroxyalkyloxazolidin-2-ones with K_2CO_3

K_2CO_3 (1.4 equiv.) was added to a suspension of the *N*-1′-hydroxyalkyloxazolidin-2-one (1.0 equiv.) in MeOH/H_2O (v:v 4:1) at ambient temperature. After stirring for 15 min, the reaction mixture was diluted with CH_2Cl_2, washed with water and brine and dried. The crude product was purified by flash column chromatography on silica gel.

3.10. Representative procedure 9 for the preparation of esters from *N*-acyl-oxazolidin-2-ones

A solution of *n*-BuLi (5 equiv.) in MeOH prepared at 0 °C was added via canula to a stirred solution of *N*-acyl-oxazolidin-2-one (1 equiv.) in THF at −78 °C and stirred for 10 min before warming to ambient temperature. After 18 h the reaction mixture was quenched with pH 7 buffer, extracted with Et_2O, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel.

3.10.1. Preparation of (*S*)-4-benzyl-3-(2′-benzyloxyacetyl)-5,5-dimethyl-oxazolidin-2-one 5. Following representative procedure 1, *n*-BuLi (4.30 mL, 10.73 mmol), (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **4** (2.00 g, 9.76 mmol) and $PhCH_2OCH_2COCl$ (2.00 mL, 12.69 mmol) in THF (80 mL) furnished **5** as a pale yellow oil (3.06 g, 8.68 mmol, 89%) after flash column chromatography.

R_f 0.1 [3:1 pentane/Et_2O]; $[\alpha]_D^{22}=-33.9$ ($c=1.0$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.41 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.90 [1H, dd, $J=14.4$, 9.6 Hz, $CHCH_AH_B$-Ph], 3.22 [1H, dd, $J=14.4$, 3.9 Hz, $CHCH_AH_BPh$], 4.53 [1H, dd, $J=9.6$, 3.9 Hz, $CHCH_2Ph$], 4.62 [2H, s, CH_2OCH_2Ph], 4.62–4.76 [2H, ABq, $J=17.9$ Hz, CH_2OCH_2Ph], 7.23–7.41 [10H, m, Ph*H*]; δ_C (50 MHz, $CDCl_3$) 22.8, 29.1 [$C(CH_3)_2$], 35.6 [$CHCH_2Ph$], 63.8 [$CHCH_2Ph$], 70.2 [CH_2OCH_2Ph], 73.9 [CH_2OCH_2Ph], 84.1 [$C(CH_3)_2$], 127.4, 128.4 [*p-Ph*], 128.5, 129.0, 129.2, 129.6 [*m/o-Ph*], 137.2, 137.7 [*i-Ph*], 153.0 [*C*=O exocyclic], [*C*=O endocyclic]; ν_{max} (thin film, cm^{-1}) 1774, 1716 [*C*=O]; $C_{21}H_{23}NO_4$ requires C, 71.37; H, 6.56; N, 3.96%. Found C, 71.11; H, 6.54; N, 3.90%; *m/z* APCI+ 376 [100%, MNa^+].

3.10.2. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-hydroxy-3-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 6. Following representative procedure 3, CF_3SO_3H (0.90 mL, 10.20 mmol), Et_3B (10.20 mL, 10.20 mmol), **5** (3.00 g, 8.50 mmol), *i*-Pr_2NEt (1.92 mL, 11.05 mmol) and PhCHO (0.95 mL, 9.35 mmol) in CH_2Cl_2 (50 mL) furnished **6** (3.01 g, 6.56 mmol, 77%) as a white solid after flash column chromatography.

R_f 0.15 [1:1 pentane/Et_2O]; mp 99–101 °C [pentane/Et_2O]; $[\alpha]_D^{24}=+1.5$ ($c=1.0$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.27 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.73 [1H, dd, $J=14.5$, 9.6 Hz, $CHCH_AH_BPh$], 2.90 [1H, dd, $J=14.5$, 3.7 Hz, $CHCH_AH_BPh$], 3.08 [1H, d, $J=5.6$ Hz, CH(O*H*)], 4.28 [1H, dd, $J=9.6$, 3.7 Hz, $CHCH_2Ph$], 4.51 [2H, s, $CHOCH_2Ph$], 4.98 [1H, t, $J=5.3$ Hz, C*H*(OH)], 5.57 [1H, d, $J=5.3$ Hz, $CHOCH_2Ph$], 7.19–7.44 [15H, m, Ph*H*]; δ_C (50 MHz, $CDCl_3$) 22.1, 27.8 [$C(CH_3)_2$], 35.1 [$CHCH_2Ph$], 63.7 [$CHCH_2Ph$], 73.3 [$CHOCH_2Ph$], 75.1 [*C*H(OH)], 80.8 [$CHOCH_2Ph$], 83.0 [$C(CH_3)_2$], 126.9, 127.1, 128.1 [*p-Ph*], 128.2, 128.3, 128.4, 128.7, 129.0 [*m/o-Ph*], 136.7, 137.0, 138.7 [*i-Ph*], 152.3 [*C*=O endocyclic], 170.7 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1775, 1703 [C=O]; $C_{28}H_{29}NO_5$ requires 73.18, H, 6.36; N, 3.05%. Found C, 73.13; H, 6.38; N, 3.06%; *m/z* ES+ 482 [100%, MNa^+].

3.10.3. Preparation of (*S*)-4-benzyl-3-(2′-dibenzylamino-acetyl)-5,5-dimethyl-oxazolidin-2-one 7. Following representative procedure 1, **4** (4.00 g, 19.51 mmol), *n*-BuLi (8.59 mL, 21.46 mmol) and bromoacetyl bromide (2.21 mL, 25.36 mmol) in THF (80 mL) furnished (*S*)-4-benzyl-3-(2′-bromo-acetyl)-5,5-dimethyl-oxazolidin-2-one (5.52 g, 16.93 mmol, 87%) as an orange oil after flash column chromatography.

R_f 0.23 [3:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-26.7$ ($c=1.0$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.40 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.91 [1H, dd, $J=9.8$, 14.5 Hz, $CHCH_AH_BPh$], 3.19 [1H, dd, $J=3.7$, 14.5 Hz, $CHCH_AH_BPh$], 4.45 [1H, d, $J=12.4$ Hz, CH_AH_BBr], 4.58 [1H, d, $J=12.4$ Hz, CH_AH_BBr], 4.51 [1H, dd, $J=3.7$, 9.8 Hz, $CHCH_2Ph$], 7.24–7.34 [5H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 22.3, 28.6 [$C(CH_3)_2$], 28.4 [CH_2Br], 34.9 [$CHCH_2Ph$], 64.0 [$CHCH_2Ph$], 83.3 [$C(CH_3)_2$], 127.0, 128.8, 129.0 [*p*- and *m/o-Ph*], 136.4 [*i-Ph*], 152.1 [*C*=O endocyclic], 166.2 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1778 [C=O]; HRMS $C_{14}H_{17}NO_3Br$ [MH^+] requires 326.0392. Found 326.0391; *m/z* APCI+ 326 [100%, MH^+].

Following representative procedure 2, (*S*)-4-benzyl-3-(2′-bromo-acetyl)-5,5-dimethyl-oxazolidin-2-one (1.64 g, 5.03 mmol) and $(PhCH_2)_2NH$ (2.12 mL, 11.07 mmol) in CH_2Cl_2 (80 mL) furnished **7** (1.87 g, 4.23 mmol, 84%) as an orange oil after flash column chromatography.

R_f 0.21 [3:1 60–80 °C petrol/Et_2O]; $[\alpha]_D^{25}=-15.7$ ($c=1.0$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.35 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.38 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.89 [1H, dd, $J=4.1$, 14.4 Hz, $CHCH_AH_BPh$], 3.16 [1H, dd, $J=9.3$, 14.4 Hz, $CHCH_AH_BPh$], 3.87 [4H, s, $CH_2N(CH_2Ph)_2$], 3.85–3.98 [2H, ABq, $J=18.6$ Hz, $CH_2N(CH_2Ph)_2$], 4.54 [1H, dd, $J=4.1$, 9.3 Hz, $CHCH_3$], 7.25–7.43 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 22.3, 28.5 [$C(CH_3)_2$], 35.3 [$CHCH_2Ph$], 55.5 [$CH_2N(CH_2Ph)_2$], 57.5 [$CH_2N(CH_2Ph)_2$], 63.1 [$CHCH_2Ph$], 82.8 [$C(CH_3)_2$], 126.8, 127.1, 128.3, 128.7, 128.8, 129.1 [*p*-and *m/o-Ph*], 136.8, 139.2 [*i-Ph*], 152.5 [*C*=O endocyclic], 171.7 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1776 [C=O]; HRMS $C_{28}H_{31}N_2O_3$ [MH^+] requires 443.2335. Found 443.2334; *m/z* ES+ 443 [100%, MH^+].

3.10.4. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-3-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 8. Following representative procedure 4, 9-BBNOTf (5.43 mL, 2.71 mmol), **7** (1.00 g, 2.26 mmol), *i*-Pr_2NEt (0.55 mL, 3.16 mmol) and PhCHO (0.25 mL, 2.49 mmol) in CH_2Cl_2 (50 mL) furnished **8** (1.05 g, 1.92 mmol, 85%) as a white solid after flash column chromatography.

R_f 0.22 [2:1 30–40 °C petrol/Et_2O]; mp 130 °C [hexane/Et_2O]; $[\alpha]_D^{23}=-36.5$ ($c=0.80$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.59 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.28 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.84 [2H, m, $CHCH_AH_BPh$], 3.45 [2H, d, $J=14.2$ Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.87 [1H, s, O*H*], 4.05 [2H, d, $J=14.2$ Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 4.31 [1H, app. t, $J=7.3$ Hz, $CHCH_2Ph$], 4.78 [1H, d, $J=9.7$ Hz, C*H*(OH)], 5.26 [1H, d, $J=9.7$ Hz, $CHN(CH_2Ph)_2$], 7.18–7.40 [20H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 21.7, 26.9 [$C(CH_3)_2$], 36.1 [$CHCH_2Ph$], 54.6 [$CHN(CH_2Ph)_2$], 62.6 [$CHCH_2Ph$], 66.2 [*C*H(OH)], 71.8 [$CHN(CH_2Ph)_2$], 81.9 [$C(CH_3)_2$], 127.0,

127.3, 128.1, 128.3, 128.4, 128.7, 129.2, 129.4 [*p*- and *m*/*o*-*Ph*], 136.5, 138.7, 139.0 [*i*-*Ph*], 151.8 [*C*=O endocyclic], 169.9 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1777, 1691 [C=O]; *m*/*z* APCI+ 549 [100%, MH^+]; HRMS $C_{35}H_{37}N_2O_4$ [MH^+] requires 549.2753. Found 549.2778.

X-ray crystal structure determination for **8**. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[22] X-ray crystal structure data for **8** [$C_{35}H_{36}N_2O_4$]: M=548.68, orthorhombic, space group $P2_12_12_1$, a=10.0206(1) Å, b=29.1014(4) Å, c=10.3865(2) Å, V=3028.8 $Å^3$, Z=4, μ=0.078 mm^{-1}, colourless block, crystal dimensions=0.4×0.4×0.4 mm^3. A total of 3899 unique reflections were measured for $1<\theta<27$ and 3012 reflections were used in the refinement. The final parameters were wR_2=0.054 and R_1=0.057 [$I>1\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC234754. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.10.5. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-hydroxy-octanoyl)-5,5-dimethyl-oxazolidin-2-one 9. Following representative procedure 3, CF_3SO_3H (0.22 mL, 2.55 mmol), Et_3B (2.60 mL, 2.60 mmol), **5** (750 mg, 2.12 mmol), *i*-Pr_2NEt (0.52 mL, 2.97 mmol) and $Me(CH_2)_4CHO$ (0.28 mL, 2.33 mmol) in CH_2Cl_2 (30 mL) furnished **9** (754 mg, 1.66 mmol, 79%) as a pale yellow oil after flash column chromatography.

R_f 0.16 [1:1 pentane/Et_2O]; $[\alpha]_D^{25}=-53.5$ (c=2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 [3H, t, J=6.8 Hz, $CH_2CH_2CH_2CH_2CH_3$], 1.28–1.35 [4H, m, $CH_2CH_AH_BCH_AH_BCH_2CH_3$] 1.39 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.40 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.39–1.42 [1H, m, $CH_2CH_AH_BCH_2CH_3$], 1.45–1.51 [1H, m, $CH_2CH_AH_BCH_2CH_2CH_3$], 1.55–1.66 [2H, $CH_2CH_2CH_2CH_2CH_3$], 2.19 [1H, s, CH(O*H*)], 2.90 [1H, dd, J=9.3, 14.5 Hz, $CHCH_AH_BPh$], 3.10 [1H, dd, J=4.0, 14.5 Hz, $CHCH_AH_BPh$], 3.84 [1H, app. s, C*H*(OH)], 4.38 [1H, d, J=11.4 Hz, $CHOCH_AH_BPh$], 4.53 [1H, dd, J=4.0, 9.3 Hz, C*H*CH_2Ph], 4.58 [1H, d, J=11.4 Hz, $CHOCH_AH_BPh$], 5.17 [1H, d, J=2.6 Hz, C*H*OCH_2Ph], 7.22–7.36 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 14.0 [$CH_2CH_2CH_2CH_3$], 22.1, 28.4 [$C(CH_3)_2$], 22.5, 25.2, 31.7, 34.0 [$CH_2CH_2CH_2CH_2CH_3$], 35.3 [$CHCH_2Ph$], 63.9 [$CHCH_2Ph$], 72.7 [*C*H(OH)], 72.8 [$CHOCH_2Ph$], 79.4 [$CHOCH_2Ph$], 83.5 [$C(CH_3)_2$], 126.9, 128.1 [*p*-*Ph*], 128.4, 128.4, 128.7, 129.1 [*m*/*o*-*Ph*], 136.8, 137.2 [*i*-*Ph*], 152.8 [*C*=O endocyclic], 171.0 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1775, 1709 [C=O]; $C_{27}H_{35}NO_5$ requires C, 71.50; H, 7.78; N, 3.09%. Found C, 71.09; H, 7.78; N, 3.28%; HRMS $C_{27}H_{35}NO_5Na$ [MNa^+] requires 476.2413. Found 476.2409; *m*/*z* ES+ 454 [20%, MH^+], 476 [60%, MNa^+].

3.10.6. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-hydroxy-4′-methyl-butryryl)-5,5-dimethyl-oxazolidin-2-one 10. Following representative procedure 3, CF_3SO_3H (0.13 mL, 1.50 mmol), Et_3B (1.5 mL, 1.50 mmol), **5** (440 mg, 1.25 mmol), *i*-Pr_2NEt (0.30 mL, 1.75 mmol) and Me_2CHCHO (0.13 mL, 1.38 mmol) in CH_2Cl_2 (20 mL) furnished **10** (407 mg, 0.96 mmol, 77%) as a clear colourless oil after flash column chromatography.

R_f 0.16 [2:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{22}=-73.4$ (c=2.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.96 [3H, d, J=6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 1.03 [3H, d, J=6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 1.40 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.42 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.86–1.98 [1H, m, $CH(CH_3)_2$], 2.95 [1H, dd, J=14.4, 9.2 Hz, $CHCH_AH_BPh$], 3.15 [1H, dd, J=14.4, 4.2 Hz, $CHCH_AH_BPh$], 3.43 [1H, d, J=8.2 Hz, C*H*(OH)], 4.32 [1H, d, J=11.2 Hz, $CHOCH_AH_BPh$], 4.52 [1H, dd, J=9.2, 4.2 Hz, C*H*CH_2Ph], 4.57 [1H, d, J=11.2 Hz, $CHOCH_AH_BPh$], 5.29 [1H, d, J=1.8 Hz, C*H*OCH_2Ph], 7.16–7.41 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 18.7, 19.1 [$CH(CH_3)_2$], 22.0, 28.4 [$C(CH_3)_2$], 31.8 [$CH(CH_3)_2$], 35.4 [$CHCH_2Ph$], 63.9 [$CHCH_2Ph$], 72.6 [$CHOCH_2Ph$], 77.8, 78.1 [*C*H(OH) and *C*HOCH_2Ph], 83.6 [$C(CH_3)_2$], 126.9, 128.1 [*p*-*Ph*], 128.3, 128.4, 128.7, 129.2 [*m*/*o*-*Ph*], 136.8, 137.2 [*i*-*Ph*], 152.7 [*C*=O endocyclic], 171.1 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1774, 1705 [C=O]; HRMS $C_{25}H_{32}NO_5$ [MH^+] requires 426.2280. Found 426.2279; *m*/*z* ES+ 426 [60%, MH^+], 448 [100%, MNa^+].

3.10.7. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-hydroxy-5′-methyl-hexanoyl)-5,5-dimethyl-oxazolidin-2-one 11. Following representative procedure 3, CF_3SO_3H (0.15 mL, 1.70 mmol), Et_3B (1.70 mL, 1.70 mmol), **5** (500 mg, 1.41 mmol), *i*-Pr_2NEt (0.34 mL, 1.98 mmol) and Me_2CHCH_2CHO (0.17 mL, 1.55 mmol) in CH_2Cl_2 (30 mL) furnished **11** (593 mg, 1.35 mmol, 96%) as a cream solid after flash column chromatography.

R_f 0.18 [1:1 pentane/Et_2O]; mp 91–92 °C [pentane/Et_2O]; $[\alpha]_D^{25}=-55.3$ (c=1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 [3H, d, J=6.7 Hz, $CH(CH_3)_A(CH_3)_B$], 0.95 [3H, d, J=6.7 Hz, $CH(CH_3)_A(CH_3)_B$], 1.36–1.43 [1H, m, $CH_AH_BCH(CH_3)_2$], 1.38 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.41 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.56–1.64 [1H, m, $CH_AH_BCH(CH_3)_2$], 1.73–1.82 [1H, m, $CH_2CH(CH_3)_2$], 2.26 [1H, s, CH(O*H*)], 2.89 [1H, dd, J=9.3, 14.4 Hz, $CHCH_AH_BPh$], 3.10 [1H, dd, J=4.1, 14.4 Hz, $CHCH_AH_BPh$], 3.96 [1H, s, C*H*(OH)], 4.40 [1H, d, J=11.4 Hz, $CHOCH_AH_BPh$], 4.53 [1H, dd, J=4.1, 9.3 Hz, C*H*CH_2Ph], 4.57 [1H, d, J=11.4 Hz, $CHOCH_AH_BPh$], 5.16 [1H, d, J=2.9 Hz, C*H*OCH_2Ph], 7.16–7.41 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 22.0, 28.3 [$C(CH_3)_2$], 22.1, 23.3 [$CH(CH_3)_2$], 24.5 [$CH_2CH(CH_3)_2$], 35.3 [$CHCH_2Ph$], 42.7 [$CH_2CH(CH_3)_2$], 63.9 [$CHCH_2Ph$], 70.8 [*C*H(OH)], 72.9 [$CHOCH_2Ph$], 80.0 [$CHOCH_2Ph$], 83.4 [$C(CH_3)_2$], 126.9, 128.0 [*p*-*Ph*], 128.3, 128.4, 128.7, 129.1 [*m*/*o*-*Ph*], 136.8, 137.3 [*i*-*Ph*], 152.8 [*C*=O endocyclic], 171.0 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1754, 1715 [C=O]; $C_{26}H_{33}NO_5$ requires C, 71.05; H, 7.57; N, 3.19%. Found C, 71.06; H, 7.43; N, 3.23%; HRMS $C_{26}H_{33}NO_5Na$ [MNa^+] requires 462.2256. Found 462.2249; *m*/*z* ES+ 462 [100%, MNa^+].

3.10.8. Preparation of (2′*S*,3′*R*,4*S*)-benzyl-3-(2′-benzyloxy-3′-hydroxy-5′-phenyl-pent-4′-enoyl)-5,5-dimethyloxazolidin-2one 12. Following representative procedure 3, CF_3SO_3H (0.09 mL, 1.02 mmol), Et_3B (1.02 mL, 1.02 mmol), **5** (300 mg, 0.85 mmol), *i*-Pr_2NEt (0.19 mL, 1.11 mmol) and PhCH=CHCHO (0.12 mL, 0.94 mmol) in CH_2Cl_2 (10 mL) furnished **12** (343 mg, 0.71 mmol, 83%) as a pale yellow oil after flash column chromatography.

R_f 0.11 [3:2 40–60 °C petrol/Et_2O]; $[\alpha]_D^{25}$=+40.6 (*c*=0.63, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.12 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.31 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.76–2.82 [2H, m, $CHCH_AH_BPh$ and CH(O*H*)], 2.966 [1H, dd, *J*=14.5, 3.9 Hz, $CHCH_AH_BPh$], 4.45 [1H, dd, *J*=9.5, 3.9 Hz, C*H*CH_2Ph], 4.50–4.60 [3H, m, $CHOCH_2Ph$ and C*H*(OH)], 5.42 [1H, d, *J*=5.0 Hz, C*H*OCH_2Ph], 6.29 [1H, dd, *J*=6.9, 16.0 Hz, CH=CHPh], 6.66 [1H, d, *J*=15.9 Hz, CH=C*H*Ph], 7.19–7.38 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 22.1, 28.6 [$C(CH_3)_2$], 35.3 [$CHCH_2Ph$], 63.7 [$CHCH_2Ph$], 73.2 [$CHOCH_2Ph$], 74.1 [*C*H(OH)], 79.9 [*C*$HOCH_2Ph$], 83.3 [$C(CH_3)_2$], 126.7 [CH=*C*HPh], 126.9, 126.9, 128.2 [*p-Ph*], 128.4, 128.5, 128.5, 128.7, 128.8, 129.1 [*m*/*o-Ph*], 132.9 [*C*H=CHPh], 136.1, 136.7, 137.0 [*i-Ph*], 152.6 [*C*=O endocyclic], 170.5 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1769 [C=O endocyclic], 1713 [C=O exocyclic]; HRMS $C_{30}H_{31}NO_5Na$ [MNa^+] requires 508.2100. Found 508.2093; *m*/*z* ES+ 508 [50%, MNa^+].

3.10.9. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-hydroxy-3′-(4″-nitro-phenyl)-propionyl)-5,5-dimethyl-oxazolidin-2one 13. Following representative procedure 3, CF_3SO_3H (0.09 mL, 1.02 mmol), Et_3B (1.02 mL, 1.02 mmol), **5** (300 mg, 0.85 mmol), *i*-Pr_2NEt (0.19 mL, 1.11 mmol) and ArCHO (141 mg, 0.94 mmol) in CH_2Cl_2 (20 mL) furnished **13** (350 mg, 0.69 mmol, 82%) as a peach foam after flash column chromatography.

R_f 0.18 [1:2 30–40 °C petrol/Et_2O]; $[\alpha]_D^{22}$=−24.9 (*c*=0.55, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.40 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.91 [1H, dd, *J*=14.4, 9.3 Hz, $CHCH_AH_BPh$], 3.07 [1H, dd, *J*=14.4, 4.3 Hz, $CHCH_AH_BPh$], 3.30 [1H, d, *J*=8.0 Hz, CH(O*H*)], 4.21 [1H, d, *J*=11.7 Hz, $CHOCH_AH_BPh$], 4.456 [1H, d, *J*=11.7 Hz, $CHOCH_AH_BPh$], 4.52 [1H, dd, *J*=9.2, 4.3 Hz, C*H*CH_2Ph], 5.13 [1H, d, *J*=4.6 Hz, C*H*(OH)], 5.38 [1H, d, *J*=2.8 Hz, C*H*OCH_2Ph], 6.99–7.02 [2H, m, Ar*H*], 7.16–7.35 [8H, m, Ar*H*], 7.604 [2H, m, Ar*H*], 8.15–8.18 [2H, m, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 22.1, 28.3 [$C(CH_3)_2$], 35.2 [$CHCH_2Ph$], 63.8 [$CHCH_2Ph$], 72.9 [$CHOCH_2Ph$], 73.4 [*C*H(OH)], 79.9 [*C*$HOCH_2Ph$], 83.9 [$C(CH_3)_2$], 127.0, 127.2 [*p-Ph*], 123.3, 128.2, 128.4, 128.8, 129.1 [*m*/*o*-Ph and *m*/*o-Ar*], 136.2, 136.4 [*i-Ph*], 147.4, 147.6 [*i-Ar* and *p-Ar*], 152.8 [*C*=O endocyclic], 169.7 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1771, 1710 [C=O]; $C_{28}H_{28}N_2O_7$ requires C, 66.66; H, 5.59; N, 5.55%. Found C, 66.64; H, 5.71; N, 5.44%.

3.10.10. Preparation of (2′*S*,3′*S*,4*S*)-4-benzyl-3-(2′-benzyloxy-3-furan-2-yl-3-hydroxy-propionyl)-5,5-dimethyl-oxazolidin-2-one 14. Following representative procedure 3, CF_3SO_3H (0.75 mL, 8.50 mmol), Et_3B (8.50 mL, 8.50 mmol), **5** (2.50 g, 7.08 mmol), *i*-Pr_2NEt (1.73 mL, 9.91 mmol) and ArCHO (0.64 mL, 7.79 mmol) in CH_2Cl_2 (40 mL) furnished **14** (2.59 g, 5.77 mmol, 81%) as a white solid after flash column chromatography.

R_f 0.15 [1:1 pentane/Et_2O]; mp 83–84 °C [pentane/Et_2O]; δ_H (400 MHz, $CDCl_3$) 1.232 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.33 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.77 [1H, dd, *J*=14.5, 9.6 Hz, $CHCH_AH_BPh$], 2.96 [1H, dd, *J*=14.5, 3.7 Hz, $CHCH_AH_BPh$], 3.06–3.10 [1H, m, CH(O*H*)], 4.41 [1H, dd, *J*=9.6, 3.7 Hz, C*H*CH_2Ph], 4.536–4.59 [2H, ABq, *J*=11.7 Hz, $CHOCH_2Ph$], 5.04 [1H, dd, *J*=6.9, 5.0 Hz, C*H*(OH)], 5.67 [1H, d, *J*=4.9 Hz, C*H*OCH_2Ph], 6.34–6.39 [2H, m, Ar*H*], 7.21–7.39 [11H, m, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 22.1, 28.1 [$C(CH_3)_2$], 35.1 [$CHCH_2Ph$], 63.8 [$CHCH_2Ph$], 69.06 [*C*H(OH)], 73.3 [$CHOCH_2Ph$], 78.7 [*C*$HOCH_2Ph$], 83.3 [$C(CH_3)_2$], 108.0, 110.5 [*C*H furan], 126.9, 128.1 [*p-Ph*], 128.3, 128.7, 128.8, 129.0, 129.1 [*m*/*o-Ph* and *C*H furan], 136.7, 137.0 [*i-Ph*], 152.2 [*i-Ar* furan], 152.3 [*C*=O endocyclic], 170.0 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1770, 1704 [C=O]; $C_{26}H_{27}NO_6$ requires C, 69.47; H, 6.05; N, 3.12%. Found C, 69.35; H, 6.05; N, 3.01%; $[\alpha]_D^{20}$=+31.9 (*c*=1.0, $CHCl_3$); *m*/*z* ES+ 432 [30%, MH^+-H_2O], 472 [100%, MNa^+].

3.10.11. Preparation of (2′*S*,3′*S*,4*S*)-benzyl-3-(2′-benzyloxy-3′-hydroxy-3′-pyridin-2″-yl)-5,5-dimethyl-oxazolidin-2one 15. Following representative procedure 3, CF_3SO_3H (0.09 mL, 1.02 mmol), Et_3B (1.02 mL, 1.02 mmol), **5** (300 mg, 0.85 mmol), *i*-Pr_2NEt (0.19 mL, 1.11 mmol) and ArCHO (0.09 mL, 0.94 mmol) in CH_2Cl_2 (10 mL) furnished **15** (251 mg, 0.55 mmol, 64%) as a clear colourless oil after flash column chromatography.

R_f 0.1 [3:2 Et_2O/40–60 °C petrol]; δ_H (400 MHz, $CDCl_3$) 1.39 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.41 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.91 [1H, dd, *J*=14.5, 9.7 Hz, $CHCH_AH_BPh$], 3.17 [1H, dd, *J*=14.5, 3.5 Hz, $CHCH_AH_BPh$], 4.24 [1H, d, *J*=12.1 Hz, $CHOCH_AH_BPh$], 4.53 [1H, d, *J*=12.1 Hz, $CHOCH_AH_BPh$], 4.58 [1H, dd, *J*=9.7, 3.5 Hz, C*H*CH_2Ph], 4.65 [1H, br s, CH(O*H*)], 5.17 [1H, d, *J*=1.8 Hz, C*H*(OH)], 5.51 [1H, d, *J*=3.0 Hz, C*H*OCH_2Ph], 6.94–8.57 [14H, m, Ar*H*]; δ_C (100 MHz, $CDCl_3$) 22.2, 28.5 [$C(CH_3)_2$], 35.1 [$CHCH_2Ph$], 64.0 [$CHCH_2Ph$], 72.7 [$CHOCH_2Ph$], 72.8 [*C*H(OH)], 80.1 [*C*$HOCH_2Ph$], 83.6 [$C(CH_3)_2$], 120.9, 122.6, 126.8 [*p-Ph* and *p-Ar*], 127.9, 128.2, 128.7, 129.1 [*m*/*o-Ph*], 127.8, 136.7, 147.8 [*m*/*o-Ar*], 136.7, 137.0 [*i-Ph*], 152.9 [*i-Ar*], 157.5 [*C*=O endocyclic], 170.1 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1772, 1714 [C=O]; HRMS $C_{27}H_{29}N_2O_5$ [MH^+] requires 461.2076. Found 461.2072; $[\alpha]_D^{25}$=−40.0 (*c*=0.6, $CHCl_3$); *m*/*z* APCI+ 206 [25%, SQH^+], 461 [100%, MH^+].

3.10.12. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-propionyl)-5,5-dimethyl-oxazolidin-2-one 16. Following representative procedure 4, 9-BBNOTf (2.71 mL, 1.36 mmol), **7** (500 mg, 1.13 mmol), *i*-Pr_2NEt (0.28 mL, 1.58 mmol) and MeCHO (0.06 mL, 1.24 mmol) in CH_2Cl_2 (30 mL) furnished **16** (447 mg, 0.92 mmol, 81%) as a white solid after flash column chromatography.

R_f 0.35 [1:1 petrol/Et_2O]; mp 100 °C [hexane/Et_2O]; $[\alpha]_D^{23}$=−94.9 (*c*=0.96, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.13 [3H, d, *J*=7.9 Hz, $CHCH_3$], 1.34 [3H, s, $C(CH_3)_A$

($CH_3)_B$], 1.45 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.88 [1H, dd, J=9.1, 14.3 Hz, $CHCH_AH_BPh$], 3.08 [1H, dd, J=4.9, 14.3 Hz, $CHCH_AH_BPh$], 3.38 [1H, s, O*H*], 3.48 [2H, d, J=14.2 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.99–4.06 [1H, m, C*H*(OH)], 4.01 [2H, d, J=14.2 Hz, $N(CH_AH_BPh)(CH_CH_D$-Ph)], 4.65 [1H, dd, J=5.0, 9.0 Hz, $CHCH_2Ph$], 4.90 [1H, d, J=9.2 Hz, $CHN(CH_2Ph)_2$], 7.18–7.40 [15H, m, Ph]; δ_C (100 MHz, $CDCl_3$) 18.2 [$CHCH_3$], 22.2, 28.4 [$C(CH_3)_2$], 35.8 [$CHCH_2Ph$], 54.6 [$CHN(CH_2Ph)_2$], 63.4, 64.5, 66.0 [$CHCH_2Ph$, *C*H(OH) and $CHN(CH_2Ph)_2$], 82.0 [$C(CH_3)_2$], 127.1, 127.3, 128.4, 128.8, 129.1, 129.2 [*p*- and *m*/*o*-*Ph*], 136.5, 138.8 [*i*-*Ph*], 152.3 [*C*=O endocyclic], 171.6 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1777, 1678 [C=O]; $C_{30}H_{34}N_2O_4$ requires C, 74.05; H, 7.04; N, 5.76%. Found C, 74.19; H, 7.31; N, 5.68%; *m*/*z* APCI+ 487 [100%, MH^+].

3.10.13. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-octanoyl)-5,5-dimethyl-oxazolidin-2-one 17. Following representative procedure 4, 9-BBNOTf (4.40 mL, 2.20 mmol), **7** (650 mg, 1.46 mmol), *i*-Pr_2NEt (0.36 mL, 2.04 mmol) and $Me(CH_2)_4CHO$ (0.22 mL, 1.61 mmol) in CH_2Cl_2 (30 mL) furnished **17** (490 mg, 0.90 mmol, 62%) as a white solid after flash column chromatography.

Mp 86 °C [hexane/Et_2O]; $[\alpha]_D^{23}$=−61.3 (*c*=0.93, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.85 [3H, t, J=6.9 Hz, CH_2CH_2-$CH_2CH_2CH_3$], 1.17–1.57 [8H, m, $CH_2CH_2CH_2CH_2CH_3$], 1.33 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.44 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.88 [1H, dd, J=9.0, 14.3 Hz, $CHCH_AH_BPh$], 3.09 [1H, dd, J=4.9, 14.3 Hz, $CHCH_AH_BPh$], 3.38 [1H, s, CH(O*H*)], 3.44 [2H, d, J=13.9 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.83–3.90 [1H, m, C*H*(OH)], 4.01 [2H, d, J=13.9 Hz, $N(CH_AH_B$-Ph)(CH_CH_DPh)], 4.65 [1H, dd, J=4.9, 9.0 Hz, $CHCH_2Ph$], 4.91 [1H, d, J=9.1 Hz, $CHN(CH_2Ph)_2$], 7.22–7.40 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 14.0 [CH_2CH_2 $CH_2CH_2CH_3$], 22.3, 28.3 [$C(CH_3)_2$], 22.5, 25.5, 31.6, 33.0 [$CH_2CH_2CH_2$-CH_2CH_3], 35.7 [$CHCH_2Ph$], 54.6 [$CHN(CH_2Ph)_2$], 63.4, 64.8, 68.3, [$CHCH_2Ph$, *C*H(OH), $CHN(CH_2Ph)_2$], 82.0 [$C(CH_3)_2$], 127.1, 127.3 [*p*-*Ph*], 128.4, 128.8, 129.1, 129.2 [*m*/*o*-*Ph*], 136.5, 138.8 [*i*-*Ph*], 152.2 [*C*=O endocyclic], 171.6 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 3425 [O–H] 1775, 1700 [C=O] $C_{34}H_{42}N_2O_4$ requires C, 75.25; H, 7.8; N 5.2%. Found C, 75.5; H, 8.0; N, 5.1%; *m*/*z* APCI+ 543 [100%, MH^+].

3.10.14. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-4-methyl-pentanoyl)-5,5-dimethyl-oxazolidin-2-one 18. Following representative procedure 4, 9-BBNOTf (2.71 mL, 1.36 mmol), **7** (500 mg, 1.13 mmol), *i*-Pr_2NEt (0.18 mL, 1.58 mmol) and Me_2CHCHO (0.11 mL, 1.24 mmol) in CH_2Cl_2 (30 mL) furnished **18** (240 mg, 0.47 mmol, 41%) as a pale yellow oil and returned **7** (168 mg, 0.38 mmol, 34%) as a pale yellow oil after flash column chromatography.

R_f 0.23 [2:1 pentane/Et_2O]; $[\alpha]_D^{25}$=−88.9 (*c*=0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 [3H, d, J=6.8 Hz, $CH(CH_3)_A$ $(CH_3)_B$], 0.99 [3H, d, J=6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 1.34 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.45 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.52–1.59 [1H, m, C*H*$(CH_3)_2$], 2.97 [1H, dd, J=9.0, 14.3 Hz, $CHCH_AH_BPh$], 3.21 [1H, dd, J=5.0, 14.3 Hz, $CHCH_AH_BPh$], 3.31 [1H, s, CH(O*H*)], 3.44 [2H, d, J=14.0 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.85 [1H, dd, J=2.9, 9.4 Hz, C*H*(OH)], 4.01 [2H, d, J=14.0 Hz, $N(CH_A$-$H_BPh)(CH_CH_DPh)$], 4.69 [1H, dd, J=5.0, 8.9 Hz, $CHCH_2$-Ph], 4.97 [1H, d, J=9.4 Hz, $CHN(CH_2Ph)_2$], 7.18–7.34 [10H, m, Ph*H*], 7.36–7.42 [5H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 15.6, 20.6 [$CH(CH_3)_2$], 22.3, 27.4 [$C(CH_3)_2$], 30.2 [$CH(CH_3)_2$], 35.9 [$CHCH_2Ph$], 54.7 [$CHN(CH_2Ph)_2$], 62.6 [$CHN(CH_2Ph)_2$], 63.6 [$CHCH_2Ph$], 72.3 [C*H*(OH)], 82.2 [$C(CH_3)_2$], 127.1, 127.2 [*p*-*Ph*], 128.4, 128.8, 129.1, 129.3 [*m*/*o*-*Ph*], 136.5, 138.9 [*i*-*Ph*], 152.4 [*C*=O endocyclic], 171.2 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1775, 1690 [C=O]; HRMS $C_{32}H_{39}N_2O_4$ [MH^+] requires 515.2910. Found 515.2933; *m*/*z* ES+ 515 [100%, MH^+], 537 [20%, MNa^+].

3.10.15. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-5-methyl-hexanoyl)-5,5-dimethyl-oxazolidin-2-one 19. Following representative procedure 4, 9-BBNOTf (2.71 mL, 1.36 mmol), **7** (500 mg, 1.13 mmol), *i*-Pr_2NEt (0.18 mL, 1.58 mmol) and Me_2CHCH_2CHO (0.13 mL, 1.24 mmol) in CH_2Cl_2 (30 mL) furnished **19** (372 mg, 0.70 mmol, 62%) as a pale yellow oil and returned **7** (99 mg, 0.22 mmol, 20%) as a pale yellow oil after flash column chromatography.

R_f 0.19 [3:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}$=−53.5 (*c*=1.15, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92–1.34 [7H, m, $CH(CH_3)_2$ and $CH_AH_BCH(CH_3)_2$], 1.34 [3H, s, $C(CH_3)_A$ $(CH_3)_B$], 1.40–1.50 [1H, m, $CH_AH_BCH(CH_3)_2$], 1.45 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.81–1.90 [1H, m, $CH_2CH(CH_3)_2$], 2.89 [1H, dd, J=9.0, 14.3 Hz, $CHCH_AH_BPh$], 3.10 [1H, dd, J=5.0, 14.3 Hz, $CHCH_AH_BPh$], 3.34 [1H, s, CH(O*H*)], 3.44 [2H, d, J=14.0 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.89–3.9 [1H, m, C*H*(OH)], 4.00 [2H, d, J=14.0 Hz, $N(CH_AH_B$-Ph)(CH_CH_DPh)], 4.70 [1H, dd, J=5.0, 9.0 Hz, $CHCH_2Ph$], 4.90 [1H, d, J=9.3 Hz, $CHN(CH_2Ph)_2$], 7.23–7.51 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 21.4, 22.3 [$CH_2CH(CH_3)_2$], 23.8, 24.7 [$C(CH_3)_2$], 28.4 [$CH_2CH(CH_3)_2$], 35.8 [$CHCH_2$-Ph], 42.1 [$CH_2CH(CH_3)_2$], 54.7 [$CHN(CH_2Ph)_2$], 63.4 [$CHCH_2Ph$], 65.3 [$CHN(CH_2Ph)_2$], 66.4 [C*H*(OH)], 82.0 [$C(CH_3)_2$], 127.1, 127.3 [*p*-*Ph*], 128.4, 128.8, 129.1, 129.3 [*m*/*o*-*Ph*], 136.5, 138.9 [*i*-*Ph*], 152.3 [*C*=O endocyclic], 171.6 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1775, 1692 [C=O]; $C_{33}H_{40}N_2O_4$ requires C, 74.97; H, 7.63; N, 5.30%. Found C, 75.09; H, 7.20; N, 5.15%; HRMS $C_{33}H_{41}N_2O_4$ [MH^+] requires 529.3066. Found 529.3036; *m*/*z* ES+ 529 [100%, MH^+], 551 [35%, MNa^+].

3.10.16. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-hydroxy-5′-phenyl-pent-4′-enoyl)-5,5-dimethyl-oxazolidin-2-one 20. Following representative procedure 4, 9-BBNOTf (2.71 mL, 1.36 mmol), **7** (500 mg, 1.13 mmol), *i*-Pr_2NEt (0.18 mL, 1.58 mmol) and PhCH=CHCHO (0.13 mL, 1.24 mmol) in CH_2Cl_2 (30 mL) furnished **20** (474 mg, 0.83 mmol, 73%) as a white solid and returned **7** (124 mg, 0.27 mmol, 24%) as a pale yellow oil after flash column chromatography.

R_f 0.24 [2:1 30–40 °C petrol/Et_2O]; mp 141–142 °C [petrol/Et_2O]; $[\alpha]_D^{25}$=+81.3 (*c*=0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.86 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.30 [3H, s, $C(CH_3)$-$_{A(CH3)_B}$], 2.84 [1H, dd, J=8.4, 14.3 Hz, $CHCH_AH_BPh$], 2.91 [1H, dd, J=5.7, 14.3 Hz, $CHCH_AH_BPh$], 3.51 [2H, d,

J=14.1 Hz, N(CH_AH$_B$Ph)(CH_CH$_D$Ph)], 3.79 [1H, s, CH(OH)], 4.07 [2H, d, J=14.1 Hz, N(CH$_A$$H_B$Ph)(CH$_C$$H_D$Ph)], 4.42–4.54 [2H, m, CHCH$_2$Ph and CH(OH)], 5.21 [1H, d, J=9.6 Hz, CHN(CH$_2$Ph)$_2$], 6.13 [1H, dd, J=8.3, 15.9 Hz, CH=CHPh], 6.64 [1H, d, J=15.9 Hz, CH=CHPh], 7.18–7.59 [20H, m, PhH]; δ_C (100 MHz, CDCl$_3$) 22.0, 27.6 [C(CH_3)$_2$], 36.0 [CHCH$_2$Ph], 54.4 [CHN(CH_2Ph)$_2$], 63.0 [CHCH$_2$Ph], 64.6 [CHN(CH$_2$Ph)$_2$], 71.0 [CH(OH)], 82.0 [C(CH$_3$)$_2$], 126.7 [CH=CHPh], 127.3, 127.4, 128.0 [p-Ph], 128.5, 128.7, 129.2, 129.3 [m/o-Ph], 134.2 [CH=CHPh], 136.0, 136.6, 138.7 [i-Ph], 152.2 [C=O endocyclic], 171.0 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1638, 1617 [C=O]; HRMS $C_{37}H_{39}N_2O_4$ [MH$^+$] requires 575.2910. Found 575.2901; m/z ES+ 575 [100%, MH$^+$].

3.10.17. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-trimethylsilanoxy-3′-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 21. Following representative procedure 6, **6** (1.24 g, 2.71 mmol), trimethylsilyl chloride (0.86 mL, 6.78 mmol), imidazole (921 mg, 13.55 mmol) and DMAP (33 mg, 0.27 mmol) in DMF (5 mL) furnished **21** (1.27 g, 2.38 mmol, 88%) as a white solid after flash column chromatography.

R_f 0.21 [5:1 30–40 °C petrol/Et$_2$O]; mp 100–101 °C [pentane/Et$_2$O]; $[\alpha]_D^{25}$=+14.9 (c=0.85, CHCl$_3$); δ_H (400 MHz, CDCl$_3$) 0.05 [9H, s, Si(CH_3)$_3$], 0.77 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.20 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.61 [1H, dd, J=9.9, 14.6 Hz, CHCH_AH$_B$Ph], 2.80 [1H, dd, J=3.2, 14.6 Hz, CHCH$_A$$H_B$Ph], 4.10 [1H, dd, J=3.2, 9.9 Hz, CHCH$_2$Ph], 4.57 [1H, d, J=12.1 Hz, CHOCH_AH$_B$Ph], 4.71 [1H, d, J=12.1 Hz, CHOCH$_A$$H_B$Ph], 5.01 [1H, d, J=6.6 Hz, CHOCH$_2$Ph], 5.63 [1H, d, J=6.6 Hz, CH(OTMS)], 7.19–7.30 [13H, m, PhH], 7.38–7.40 [2H, m, PhH]; δ_C (100 MHz, CDCl$_3$) 0.16 [Si(CH$_3$)$_3$], 22.2, 27.7 [C(CH$_3$)$_2$], 35.0 [CHCH$_2$Ph], 63.6 [CHCH$_2$Ph], 73.6 [CHOCH$_2$Ph], 76.6 [CH(OTMS)], 81.2 [CHOCH$_2$Ph], 82.2 [C(CH$_3$)$_2$], 126.7, 127.7, 128.0 [p-Ph], 127.7, 128.1, 128.2, 128.6, 129.0 [m/o-Ph], 136.9, 137.9, 139.8 [i-Ph], 151.9 [C=O endocyclic], 171.0 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1771, 1694 [C=O]; HRMS $C_{31}H_{37}NO_5Na$ [MNa$^+$] requires 554.2339. Found 554.2349; m/z ES+ 554 [100%, MNa$^+$].

3.10.18. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(triethyl-silanyloxy)-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 22. Following representative rrocedure 6, **6** (470 mg, 1.02 mmol), TESCl (0.43 mL, 2.56 mmol), imidazole (348 mg, 5.12 mmol) and DMAP (12 mg, 0.10 mmol) in DMF (5 mL) furnished **22** (550 mg, 0.96 mmol, 94%) as a white solid after flash column chromatography.

R_f 0.15 [9:1 pentane/Et$_2$O]; mp 70–72 °C [pentane/Et$_2$O]; $[\alpha]_D^{24}$=+26.8 (c=1.0, CHCl$_3$); δ_H (400 MHz, CDCl$_3$) 0.45–0.58 [6H, m, Si(CH_2CH$_3$)$_3$], 0.63 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 0.85 [9H, t, J=7.9 Hz, Si(CH$_2$CH_3)$_3$], 1.15 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.51 [1H, dd, J=14.6, 10.0 Hz, CHCH_AH$_B$Ph], 2.70 [1H, dd, J=14.6, 2.9 Hz, CHCH$_A$$H_B$Ph], 4.00 [1H, dd, J=10.0, 2.9 Hz, CHCH$_2$Ph], 4.58 [1H, d, J=12.0 Hz, CHOCH_AH$_B$Ph], 4.79 [1H, d, J=12.0 Hz, CHOCH$_A$$H_B$Ph], 4.97 [1H, d, J=7.2 Hz, CH(OTES)], 5.66 [1H, d, J=7.2 Hz, CHOCH$_2$Ph], 7.17–7.39 [15H, m, PhH]; δ_C (100 MHz, CDCl$_3$) 4.7 [Si(CH$_2$CH$_3$)$_3$], 6.6 [Si(CH$_2$$CH_3$)$_3$], 22.1, 27.5 [C($CH_3$)$_2$], 34.9 [CH$CH_2$Ph], 63.5 [$CHCH_2$Ph], 73.8 [CHO$CH_2$Ph], 77.0 [$C$H(OTES)], 81.5 [$C$HOCH$_2$Ph], 82.0 [$C$(CH$_3$)$_2$], 126.7, 127.7, 127.9 [$p$-$Ph$], 128.0, 128.1, 128.2, 128.3, 128.6, 128.9 [m/o-Ph], 136.9, 138.0, 139.9 [i-Ph], 151.7 [C=O endocyclic], 171.3 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1778, 1700 [C=O]; HRMS $C_{34}H_{47}N_2O_5Si$ [MNH$_4^+$] requires 591.3264. Found 591.3254; m/z ES+ 442 [100%, MH$^+$−OTES], 591 [55%, MNH$_4^+$].

3.10.19. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-3″-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 23. Following representative procedure 6, **6** (210 mg, 0.46 mmol), TBDMSCl (173 mg, 1.14 mmol) imidazole (156 mg, 2.30 mmol) and DMAP (6 mg, 0.05 mmol) in DMF (3 mL) furnished **23** (258 mg, 0.45 mmol, 98%) as a white solid after flash column chromatography.

R_f 0.15 [10:1 pentane/Et$_2$O]; mp 85–86 °C [pentane/Et$_2$O]; $[\alpha]_D^{24}$=+30.4 (c=1.0, CHCl$_3$); δ_H (400 MHz, CDCl$_3$) −0.10 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.07 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.57 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 0.83 [9H, s, SiC(CH_3)$_3$], 1.13 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.48 [1H, dd, J=14.6, 10.0 Hz, CHCH_AH$_B$Ph], 2.67 [1H, dd, J=14.6, 2.8 Hz, CHCH$_A$$H_B$Ph], 3.97 [1H, dd, J=10.0, 3.0 Hz, CHCH$_2$Ph], 4.57 [1H, d, J=12.0 Hz, CHOCH_AH$_B$Ph], 4.81 [1H, d, J=12.0 Hz, CHOCH$_A$$H_B$Ph], 4.94 [1H, d, J=7.4 Hz, CH(OTBDMS)], 5.67 [1H, d, J=7.4 Hz, CHOCH$_2$Ph], 7.18–7.37 [15H, m, PhH]; δ_C (50 MHz, CDCl$_3$) −5.0, −4.7 [Si(CH$_3$)$_2$], 18.2 [SiC(CH$_3$)$_3$], 25.7 [SiC(CH$_3$)$_3$], 22.1, 27.4 [C(CH$_3$)$_2$], 34.9 [CHCH$_2$Ph], 63.4 [CHCH$_2$Ph], 73.9 [CHOCH$_2$Ph], 77.3 [CH(OTBDMS)], 81.6 [CHOCH$_2$Ph], 82.0 [C(CH$_3$)$_2$], 126.7, 127.7 [p-Ph], 127.9, 128.1, 128.3, 128.3, 128.6, 128.9 [m/o-Ph], 136.9, 137.9, 139.6 [i-Ph], 151.6 [C=O endocyclic], 171.4 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1778, 1699. [C=O]; $C_{34}H_{43}NO_5Si$ requires C, 71.17; H, 7.55; N 2.44%. Found C, 71.19; H, 8.01; N, 2.37%; m/z CI+ (NH$_3$) 442 [87%, MH$^+$−OTBDMS], 530 [20%, MH$^+$−CO$_2$], 591 [3%, MNH$_4^+$].

3.10.20. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(triisopropylsilanyloxy)-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 24. Following representative procedure 7, **6** (300 mg, 0.65 mmol), TIPSOTf (0.35 mL, 1.31 mmol) and DMAP (119 mg, 0.98 mmol) in CH$_2$Cl$_2$ (20 mL) furnished **24** (388 mg, 0.63 mmol, 97%) as a white solid after flash column chromatography.

R_f 0.31 [9:1 30–40 °C petrol/Et$_2$O]; mp 94–95 °C [petrol/Et$_2$O]; δ_H (400 MHz, CDCl$_3$) 0.96 [8H, app. d, J=4.2 Hz, Si(CH(CH_3)$_2$], 1.01–1.08 [13H, m, Si(CH(CH_3)$_2$], 0.50 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.22 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.14 [1H, dd, J=14.7, 10.2 Hz, CHCH_AH$_B$Ph], 2.60 [1H, dd, J=14.7, 2.6 Hz, CHCH$_A$$H_B$Ph], 3.91 [1H, dd, J=10.2, 2.6 Hz, CHCH$_2$Ph], 4.59 [1H, d, J=12.0 Hz, CHOCH_AH$_B$Ph], 4.87 [1H, d, J=12.0 Hz, CHOCH$_A$$H_B$Ph], 5.07 [1H, d, J=7.8 Hz, CH(OTIPS)], 5.73 [1H, d, J=7.8 Hz, CHOCH$_2$Ph], 7.16–7.31 [9H, m, PhH], 7.38–7.40 [4H, m, PhH]; δ_C (100 MHz, CDCl$_3$) 12.6 [Si(CH(CH$_3$)$_2$)$_3$], 17.8 [Si(CH(CH$_3$)$_2$)$_3$], 22.1, 27.4

[C(*C*H$_3$)$_2$], 34.8 [CH*C*H$_2$Ph], 63.5 [*C*HCH$_2$Ph], 73.9 [CHO*C*H$_2$Ph], 77.6 [*C*H(OTIPS)], 81.9 [*C*(CH$_3$)$_2$], 82.2 [*C*HOCH$_2$Ph], 126.6, 127.7, [2×*p-Ph*], 128.1, 128.2, 128.2, 128.3, 128.4, 128.6, 129.9 [1×*p-Ph* and *m*/*o-Ph*], 137.0, 138.0, 140.0 [*i-Ph*], 151.6 [*C*=O endocyclic], 171.7 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1779, 1699 [C=O]; HRMS $C_{37}H_{49}NO_5SiNa$ [MNa$^+$] requires 638.3278. Found 638.3295; $[\alpha]_D^{24}$=+26.8 (*c*=1.0, $CHCl_3$); *m*/*z* ESI+ 638 [100%, MNa$^+$].

3.10.21. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-benzyl-3-[2′-benzyloxy-3′-(trimethyl-silanyloxy)-1′-hydroxy-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 25. Following representative procedure 5, **21** (500 mg, 0.94 mmol) and DIBAL (2.85 mL, 1.88 mmol) in CH_2Cl_2 (20 mL) furnished **25** (496 mg, 0.93 mmol, 99%) as a white solid.

Mp 103–104 °C [pentane/Et$_2$O]; $[\alpha]_D^{24}$=−48.3 (*c*=0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.08[9H, s, Si(C*H*$_3$)$_3$], 1.14 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.20 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.57 [1H, dd, *J*=9.7, 14.7 Hz, CHC*H*$_A$H$_B$Ph], 3.09 [1H, dd, *J*=4.7, 14.7 Hz, CHCH$_A$*H*$_B$Ph], 4.08 [1H, dd, *J*=4.7, 9.7 Hz, C*H*CH$_2$Ph], 4.12 [1H, s, CH(O*H*)], 4.15 [1H, d, *J*=11.1 Hz, CHOC*H*$_A$H$_B$Ph], 4.22 [1H, dd, *J*=3.0, 8.3 Hz, C*H*OCH$_2$Ph], 4.41 [1H, d, *J*=11.1 Hz, CHOCH$_A$*H*$_B$Ph], 4.76 [1H, app. t, *J*=8.3 Hz, C*H*(OH)], 5.06 [1H, d, *J*=3.0 Hz, C*H*(OTMS)], 7.05–7.10 [2H, m, Ph*H*], 7.17–7.44 [13H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 0.0 [Si(*C*H$_3$)$_3$], 22.1, 27.6 [C(*C*H$_3$)$_2$], 35.2 [CH*C*H$_2$Ph], 66.0 [*C*HCH$_2$Ph], 74.0 [*C*H(OTMS)], 74.6 [CHO*C*H$_2$Ph], 79.1 [*C*H(OH)], 81.8 [*C*HOCH$_2$Ph], 82.0 [*C*(CH$_3$)$_2$], 126.6, 127.4, 127.6 [*p-Ph*], 126.8, 128.0, 128.1, 128.2, 128.6, 128.9 [*m*/*o-Ph*], 136.8, 138.0, 140.9 [*i-Ph*], 157.4 [*C*=O]; ν_{max} (KBr disc, cm^{-1}) 1727 [C=O]; HRMS $C_{31}H_{39}NO_5SiNa$ [MNa$^+$] requires 556.2495. Found 556.2491; *m*/*z* ES+ 556 [100%, MNa$^+$]

3.10.22. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-benzyl-3-[2′-benzyloxy-3′-(triethyl-silanyloxy)-1′-hydroxy-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 26. Following representative procedure 5, **22** (200 mg, 0.35 mmol) and DIBAL (0.70 mL, 0.70 mmol) in CH_2Cl_2 (5 mL) furnished **26** (164 mg, 0.29 mmol, 81%) as a white solid.

Mp 80–81 °C [pentane/Et$_2$O]; $[\alpha]_D^{24}$=−23.5 (*c*=1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.50–0.57 [6H, m, Si(C*H*$_2$CH$_3$)$_3$], 0.88 [9H, t, *J*=7.9 Hz, Si(CH$_2$C*H*$_3$)$_3$], 1.11 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.18 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.55 [1H, dd, *J*=14.8, 9.9 Hz, CHC*H*$_A$H$_B$Ph], 3.06 [1H, dd, *J*=14.8, 4.5 Hz, CHCH$_A$*H*$_B$Ph], 4.05 [1H, dd, *J*=9.9, 4.5 Hz, C*H*CH$_2$Ph], 4.26–4.29 [2H, m, C*H*OCH$_2$Ph and CH(O*H*)], 4.35 [1H, d, *J*=11.3 Hz, CHOC*H*$_A$H$_B$Ph], 4.53 [1H, d, *J*=11.3 Hz, CHOCH$_A$*H*$_B$Ph], 4.71 [1H, app. t, *J*=8.1 Hz, C*H*(OH)], 5.024 [1H, d, *J*=3.5 Hz, C*H*(OTES)], 7.00–7.43 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 4.6 [Si(*C*H$_2$CH$_3$)$_3$], 6.7 [Si(CH$_2$*C*H$_3$)$_3$], 22.1, 27.6 [C(*C*H$_3$)$_2$], 35.2 [CH*C*H$_2$Ph], 65.9 [*C*HCH$_2$Ph], 74.1 [*C*HOCH$_2$Ph], 74.2 [CHO*C*H$_2$Ph], 79.0 [*C*H(OH)], 80.9 [*C*H(OTES)], 81.8 [*C*(CH$_3$)$_2$], 126.5, 126.9, 127.5 [*p-Ph*], 127.6, 127.9, 128.0, 128.3, 128.6, 128.8 [*m*/*o-Ph*], 136.9, 138.1, 140.4 [*i-Ph*], 157.22 [*C*=O endocyclic]; ν_{max} (KBr disc, cm^{-1}) 1727 [C=O]; HRMS $C_{34}H_{45}NO_5NaSi$ [MNa$^+$] requires 598.2965. Found 598.2970; *m*/*z* ES+ 598 [55%, MNa$^+$].

3.10.23. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-benzyl-3-[2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-1′-hydroxy-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 27. Following representative procedure 5, **23** (3.20 g, 5.58 mmol) and DIBAL (11.2 mL, 11.17 mmol) in CH_2Cl_2 (70 mL) furnished **27** (3.19 g, 5.54 mmol, 99%) as a white solid.

Mp 115–117 °C [pentane/Et$_2$O]; $[\alpha]_D^{23}$=−35.0 (*c*=1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.12 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.06 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.91 [9H, s, SiC(C*H*$_3$)$_3$], 1.08 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.17 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.52 [1H, dd, *J*=14.8, 10.3 Hz, CHC*H*$_A$H$_B$Ph], 3.06 [1H, dd, *J*=14.8, 4.3 Hz, CHCH$_A$*H*$_B$Ph], 4.04 [1H, dd, *J*=10.3, 4.3 Hz, C*H*CH$_2$Ph], 4.23–4.27 [2H, m, C*H*(OH) and C*H*(OTBDMS)], 4.31 [1H, d, *J*=11.4 Hz, CHOC*H*$_A$H$_B$Ph], 4.52 [1H, d, *J*=11.4 Hz, CHOCH$_A$*H*$_B$Ph], 4.73 [1H, app. t, *J*=8.3 Hz, O*H*], 5.02 [1H, d, *J*=3.3 Hz, C*H*OCH$_2$Ph], 6.99–7.01 [2H, m, Ph*H*], 7.18–7.35 [11H, m, Ph*H*], 7.42–7.43 [2H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) −4.7 [Si(*C*H$_3$)$_2$], 18.2 [Si*C*(CH$_3$)$_3$], 22.1, 27.6 [C(*C*H$_3$)$_2$], 25.8 [SiC(*C*H$_3$)$_3$], 35.1 [CH*C*H$_2$Ph], 65.9 [*C*HCH$_2$Ph], 74.1 [CHO*C*H$_2$Ph], 74.2 [*C*H(OTBDMS)], 79.0 [*C*HOCH$_2$Ph], 81.0 [*C*H(OH)], 81.9 [*C*(CH$_3$)$_2$], 126.6, 127.0, 127.5, 127.6, 127.8, 128.0, 128.3, 128.6, 128.8 [*p*- and *m*/*o-Ph*], 136.8, 138.1, 140.4 [*i-Ph*], 157.2 [*C*=O endocyclic]; ν_{max} (KBr disc, cm^{-1}) 3362 [O–H broad], 1726 [C=O]; $C_{34}H_{45}NO_5Si$ requires C, 70.92; H, 7.88; N, 2.43%. Found C, 70.84; H, 7.86; N, 2.68%; *m*/*z* ES+ 598 [40%, MNa$^+$].

3.10.24. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-benzyl-3-[2′-benzyloxy-3′-(trimethyl-silanyloxy)-1′-hydroxy-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 28. Following representative procedure 5, **24** (300 mg, 0.49 mmol) and DIBAL (0.98 mL, 0.98 mmol) in CH_2Cl_2 (10 mL) furnished **24** (41 mg, 0.07 mmol, 14%) as a white solid, **28** (194 mg, 0.31 mmol, 64%) as a white solid and an unidentified compound (29 mg) as a white solid after flash column chromatography.

R_f 0.39 [1:1 30–40 °C petrol/Et$_2$O]; $[\alpha]_D^{25}$=+30.0 (*c*=0.24, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.97–1.09 [21H, m, Si(C*H*(CH$_3$)$_2$)$_3$], 1.12 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.18 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.52 [1H, dd, *J*=14.8, 9.9 Hz, CHC*H*$_A$H$_B$Ph], 2.96 [1H, dd, *J*=14.8, 4.6 Hz, CHCH$_A$*H*$_B$Ph], 3.98 [1H, dd, *J*=9.9, 4.6 Hz, C*H*CH$_2$Ph], 4.50–4.57 [2H, m, C*H*OCH$_2$Ph and C*H*(OH)], 4.63 [1H, s, CH(O*H*)], 4.65 [1H, d, *J*=11.6 Hz, CHOC*H*$_A$H$_B$Ph], 4.72 [1H, d, *J*=11.6 Hz, CHOCH$_A$*H*$_B$Ph], 5.08 [1H, app. s, C*H*(OTIPS)], 6.95 [2H, m, Ph*H*,], 7.13–7.21 [3H, m, Ph*H*], 7.25–7.45 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 12.1 [Si(*C*H(CH$_3$)$_2$)$_3$], 17.8 [Si(CH(*C*H$_3$)$_2$)$_3$], 22.1, 27.6 [C(*C*H$_3$)$_2$], 35.2 [CH*C*H$_2$Ph], 65.7 [*C*HCH$_2$Ph], 73.7 [CHO*C*H$_2$Ph], 75.0 [*C*H(OTIPS)], 78.7, 79.2 [*C*H(OH) and *C*HOCH$_2$Ph], 81.4 [*C*(CH$_3$)$_2$], 126.5, 127.3, 127.8, 127.9, 128.0, 128.4, 128.6, 128.7 [*p-Ph* and *m*/*o-Ph*], 136.9, 138.1, 139.3 [*i-Ph*], 157.0 [*C*=O]; ν_{max} (thin film, cm^{-1}) 1728 [C=O]; HRMS $C_{37}H_{51}NO_5SiNa$ [MNa$^+$] requires 640.3434. Found 640.3422; *m*/*z* ESI+ 640 [70%, MNa$^+$].

3.10.25. Preparation of (2*S*,3*R*)-2-benzyloxy-3-hydroxy-3-phenyl-propionaldehyde 29. Following representative

procedure 8, **25** (230 mg, 0.43 mmol) and K_2CO_3 (83 mg, 0.60 mmol) in MeOH/H_2O (v:v 4:1; 50 mL) furnished **29** (83 mg, 0.32 mmol, 75%) as a clear colourless oil and **4** (87 mg, 0.42 mmol, 99%) as a white solid after flash column chromatography.

R_f 0.18 [1:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-101.43$ (c=0.35, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.98 [1H, dd, J=1.5, 4.6 Hz, C*H*OCH$_2$Ph], 4.49 [1H, d, J=11.7 Hz, CHOC*H*$_A$H$_B$Ph], 4.63 [1H, d, J=11.7 Hz, CHOCH$_A$*H*$_B$Ph], 5.02 [1H, d, J=4.6 Hz, C*H*(OH)], 7.18–7.41 [10H, m, Ph*H*], 9.65 [1H, d, J=1.5 Hz, C*H*O]; δ_C (100 MHz, $CDCl_3$) 73.4 [*C*H(OH)], 73.5 [CHO*C*H$_2$Ph], 86.9 [*C*HOCH$_2$Ph], 126.37 [*p-Ph*], 128.2, 128.3, 128.6 [*m/o-Ph*], 136.5, 139.3 [*i-Ph*], 201.96 [*C*HO]; ν_{max} (thin film, cm^{-1}) 1732 [C=O]; HRMS $C_{16}H_{20}NO_3$ [MNH_4^+] requires 274.1443. Found 274.1439; *m/z* CI+ 168 [100%, MNH_4^+−PhCHO], 274 [15%, MNH_4^+].

3.10.26. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(triethylsilanyloxy)-3-phenyl-propionaldehyde 30. Following representative procedure 8, **26** (345 mg, 0.60 mmol) and K_2CO_3 (116 mg, 0.84 mmol) in MeOH/H_2O (50 mL) furnished **30** (167 mg, 0.45 mmol, 75%) as a clear colourless oil and **4** (112 mg, 0.54 mmol, 90%) as a white solid after flash column chromatography.

R_f 0.18 [12:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-78.5$ (c=0.35, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.47–0.57 [6H, m, Si(C*H*$_2$CH$_3$)$_3$], 0.84–0.88 [9H, m, Si(CH$_2$C*H*$_3$)$_3$], 3.85 [1H, dd, J=4.3, 1.5 Hz, C*H*OCH$_2$Ph], 4.459 [1H, d, J=12.3 Hz, CHOC*H*$_A$H$_B$Ph], 4.56 [1H, d, J=12.3 Hz, CHOCH$_A$*H*$_B$Ph], 5.05 [1H, d, J=4.3 Hz, C*H*(OTES)], 7.13–7.16 [2H, m, Ph*H*], 7.17–7.44 [8H, m, Ph*H*], 9.65 [1H, t, J=1.5 Hz, C*H*O]; δ_C (100 MHz, $CDCl_3$) 4.6 [Si(*C*H$_2$CH$_3$)$_3$], 6.7 [Si(CH$_2$*C*H$_3$)$_3$], 73.1 [CHO*C*H$_2$Ph], 75.2 [*C*HOTES], 87.0 [*C*HOCH$_2$Ph], 126.7, 127.9, 128.1, 128.4 [*m/o-Ph*], 128.7, 130.4 [*p-Ph*], 137.1, 140.2 [*i-Ph*], 203.0 [*C*HO]; ν_{max} (thin film, cm^{-1}) 1732 [C=O]; HRMS $C_{22}H_{34}NO_3Si$ [MH^+] requires 388.2308. Found 388.2317; *m/z* CI+ 221 [80%, MNH_4^+−HOTBDMS], 388 [100%, MNH_4^+].

3.10.27. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-3-phenyl-propionaldehyde 31. Following representative procedure 8, **27** (2.3 g, 4.00 mmol) and K_2CO_3 (774 mg, 5.60 mmol) in MeOH/H_2O (v:v 4:1; 50 mL) furnished **31** (1.06 g, 2.88 mmol, 72%) as a clear colourless oil and **4** (824 mg, 4.00 mmol, 100%) as a white solid after flash column chromatography.

R_f 0.15 [12:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{26}=-67.0$ (c=0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.10 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.01 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.88 [9H, s, SiC(C*H*$_3$)$_3$], 3.86 [1H, dd, J=4.5, 1.6 Hz, C*H*OCH$_2$Ph], 4.45 [1H, d, J=12.2 Hz, CHOC*H*$_A$H$_B$Ph], 4.57 [1H, d, J=12.2 Hz, CHOCH$_A$*H*$_B$Ph], 5.03 [1H, d, J=4.5 Hz, C*H*(OTBDMS)], 7.16–7.44 [10H, m, Ph*H*], 9.63 [1H, d, J=1.6 Hz, C*H*O]; δ_C (50 MHz, $CDCl_3$) −5.4, −4.8 [Si(*C*H$_3$)$_2$], 18.0 [Si*C*(CH$_3$)$_3$], 25.6 [SiC(*C*H$_3$)$_3$], 73.1 [CHO*C*H$_2$Ph], 75.4 [*C*HOCH$_2$Ph], 87.2 [*C*H(OTBDMS)], 127.0, 127.1 [*p-Ph*], 127.9, 128.3, 128.5 [*m/o-Ph*], 130.0, 136.6 [*i-Ph*], 140.2 [*C*HO]; ν_{max} (thin film, cm^{-1}) 1733 [C=O]; HRMS $C_{22}H_{34}NO_3Si$ [MNH_4^+] requires 388.2308. Found 388.2306; *m/z* GCMS (NH_3) 239 [55%, MH^+−OTBDMS], 256 [40%, MNH_4^+−OTBDMS], 388 [60%, MNH_4^+].

3.10.28. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(triisopropyl-silanyloxy)-3-phenyl-propionaldehyde 32. Following representative procedure 8, **28** (100 mg, 0.16 mmol) and K_2CO_3 (32 mg, 0.23 mmol) in MeOH/H_2O (v:v 4:1; 10 mL) furnished **32** (60 mg, 0.15 mmol, 91%) as a clear colourless oil and **4** (32 mg, 0.15 mmol, 97%) as a white solid after flash column chromatography.

R_f 0.44 [9:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-15.6$ (c=0.85, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95–1.10 [21H, m, Si(C*H*(CH$_3$)$_2$)$_3$], 3.98 [1H, dd, J=1.7, 5.2 Hz, C*H*OCH$_2$Ph], 4.50 [1H, d, J=12.2 Hz, CHOC*H*$_A$H$_B$Ph], 4.69 [1H, d, J=12.2 Hz, CHOCH$_A$*H*$_B$Ph], 5.08 [1H, d, J=5.2 Hz, C*H*(OTIPS)], 7.27–7.38 [10H, m, Ph*H*], 9.63 [1H, d, J=1.7 Hz, C*H*O]; δ_C (100 MHz, $CDCl_3$) 12.2, 17.8 [Si(*C*H(*C*H$_3$)$_2$)$_3$], 72.7 [CHO*C*H$_2$Ph], 75.3 [*C*H(OTIPS)], 86.5 [*C*HOCH$_2$Ph], 126.9, 127.9 [*p-Ph*], 127.9, 128.0, 128.1, 128.4 [*m/o-Ph*], 137.3, 139.9 [*i-Ph*], 202.0 [*C*HO]; ν_{max} (thin film, cm^{-1}) 1733 [C=O]; HRMS $C_{25}H_{40}NO_3Si$ [MNH_4^+] requires 430.2777. Found 430.2787; *m/z* CI+(NH_3) 430 [5%, MNH_4^+].

3.10.29. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-(*N*,*N*-dibenzylamino)-3′-(*tert*-butyl-dimethyl-silanyloxy)-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 33. Following representative procedure 7, **8** (200 mg, 0.36 mmol), TBDMSOTf (0.17 mL, 0.73 mmol) and DMAP (66 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) furnished **33** (229 mg, 0.35 mmol, 96%) as a white solid after flash column chromatography.

R_f 0.22 [9:1 pentane/Et_2O]; mp 125 °C [petrol/Et_2O]; $[\alpha]_D^{25}=-22.7$ (c=1.15, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.28 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.16 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.75 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.021 [9H, s, SiC(C*H*$_3$)$_3$], 1.25 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.84 [1H, dd, J=9.6, 14.4 Hz, CHC*H*$_A$H$_B$Ph], 3.10 [1H, dd, J=3.5, 14.4 Hz, CHCH$_A$*H*$_B$Ph], 3.95 [2H, d, J=14.4 Hz, N(C*H*$_A$-H$_B$Ph)(C*H*$_C$H$_D$Ph)], 4.26 [2H, d, J=14.4 Hz, N(CH$_A$*H*$_B$-Ph)(CH$_C$*H*$_D$Ph)], 4.27–4.30 [1H, m, C*H*CH$_2$Ph], 5.36 [1H, d, J=8.2 Hz, C*H*(OTBDMS)], 5.45 [1H, d, J=8.2 Hz, C*H*N(CH$_2$Ph)$_2$], 7.20–7.41 [20H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) −4.6, −4.2 [Si(*C*H$_3$)$_2$], 18.1 [Si*C*(CH$_3$)$_3$], 22.3, 27.7 [C(*C*H$_3$)$_2$], 26.1 [SiC(*C*H$_3$)$_3$], 35.5 [CH*C*H$_2$Ph], 55.6 [CHN(*C*H$_2$Ph)$_2$], 63.0 [C*H*CH$_2$Ph], 65.6 [*C*HN(CH$_2$Ph)$_2$], 74.9 [*C*H(OTBDMS)], 81.3 [*C*(CH$_3$)$_2$], 126.6, 126.8, 127.9 [*p-Ph*], 128.0, 128.1, 128.3, 128.6, 128.7, 129.2 [*m/o-Ph*], 137.1, 140.3, 141.3 [*i-Ph*], 151.3 [*C*=O endocylic], 171.6 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1772, 1695 [C=O]; HRMS $C_{41}H_{51}N_2O_4Si$ [MH^+] requires 663.3618. Found 663.3625; *m/z* ES+ 663 [100%, MH^+].

3.10.30. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-(*N*,*N*-dibenzylamino)-3′-(triethyl-silanyloxy)-3′-phenyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 35. Following representative procedure 6, **8** (415 mg, 0.76 mmol), TESCl (0.32 mL, 1.89 mmol), imidazole (257 mg, 3.79 mmol) and DMAP (10 mg, 0.08 mmol) in DMF

(2 mL) furnished **35** (411 mg, 0.62 mmol, 82%) as a white solid after flash column chromatography.

R_f 0.17 [9:1 pentane/Et_2O]; mp 92 °C [pentane/EtOAc]; $[\alpha]_D^{24}=-19.3$ (c=0.94, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.50 [6H, m, $Si(CH_2CH_3)_3$], 0.68 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.21 [3H, s, $C(CH_3)_A(CH_3)_B$], 0.90 [9H, t, J=7.9 Hz, $Si(CH_2CH_3)_3$], 2.79 [1H, dd, J=9.6, 14.6 Hz, $CHCH_AH_BPh$], 3.00 [1H, dd, J=3.7, 14.6 Hz, $CHCH_AH_BPh$], 3.87 [2H, d, J=14.5 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.17 [2H, d, J=14.5 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.21 [1H, m, $CHCH_2Ph$], 5.30 [1H, d, J=8.6 Hz, CH(OTES)], 5.37 [1H, d, J=8.6 Hz, $CHN(CH_2Ph)_2$], 7.16–7.36 [20H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 5.0 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)_3$], 22.1, 27.5 [$C(CH_3)_2$], 35.5 [$CHCH_2Ph$], 55.4 [$CHN(CH_2Ph)_2$], 62.9, 65.3, 74.7 [$CHCH_2Ph$, $CHN(CH_2Ph)_2$, CH(OTES)], 81.3 [$C(CH_3)_2$], 126.5, 126.8, 127.9, 128.0, 128.1, 128.6, 128.6, 129.1 [*p*- and *m*/*o*-*Ph*], 137.0, 140.3, 141.2 [*i*-*Ph*], 151.3 [*C*=O endocyclic], 171.5 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1779, 1688 [C=O]; HRMS $C_{41}H_{51}N_2O_4Si$ requires 663.3618. Found 663.3639; *m*/*z* APCI+ 663 [MH^+, 100%].

3.10.31. Preparation of (2*S*,2′*S*,3′*R*)-formic acid 2-(3′-(*tert*-butyl-dimethyl-silanoxy)-2′-dibenzylamino-3′-phenyl-propionylamino)-1,1-dimethyl-2-benzyl-ethyl ester 34. Following representative procedure 5, **33** (175 mg, 0.26 mmol) and DIBAL (0.80 mL, 053 mmol) in CH_2Cl_2 (10 mL) furnished **33** (38 mg, 0.06 mmol, 22%) as a white solid, **34** (60 mg, 0.09 mmol, 35%) as a pale yellow oil and unidentified compounds (63 mg) as a white solid after flash column chromatography.

Compound **34**. R_f 0.14 [5:1 pentane/Et_2O]; $[\alpha]_D^{25}=-76.6$ (c=3.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.37 [3H, s, $Si(CH_3)_A(CH_3)_B$], −0.08 [3H, s, $Si(CH_3)_A(CH_3)_B$], 0.88 [9H, s, $SiC(CH_3)_3$], 1.02 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.47 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.45 [1H, dd, J=11.0, 14.7 Hz, $CHCH_AH_BPh$], 3.12 [1H, dd, J=3.4, 14.7 Hz, $CHCH_AH_BPh$], 3.40 [1H, d, J=6.1 Hz, CH(OTBDMS)], 3.60 [2H, d, J=14.4 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 3.74 [2H, d, J=14.4 Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 4.32–4.38 [1H, m, $CHCH_2Ph$], 5.42 [1H, d, J=6.1 Hz, $CHN(CH_2Ph)_2$], 6.81 [1H, d, J=10.4 Hz, N*H*], 7.04–7.05 [2H, m, Ph*H*], 7.17–7.33 [18H, m, Ph*H*], 8.050 [1H, s, CHO]; δ_C (100 MHz, $CDCl_3$) −4.9, −4.8 [$Si(CH_3)_2$], 18.1 [$SiC(CH_3)_3$], 22.9, 24.9 [$C(CH_3)_2$], 26.1 [$SiC(CH_3)_3$], 35.8 [$CHCH_2Ph$], 54.5 [$CHN(CH_2Ph)_2$], 56.6 [$CHCH_2Ph$], 67.6 [CH(OTBDMS)], 74.4 [$CHN(CH_2Ph)_2$], 85.4 [$C(CH_3)_2$], 126.5, 126.9, 127.4 [*p*-*Ph*], 127.7, 128.0, 128.2, 128.3, 128.5, 128.9 [*m*/*o*-*Ph*], 137.9, 139.7, 143.3 [*i*-*Ph*], 160.1 [*C*HO], 169.8 [*C*=O amide]; ν_{max} (thin film, cm^{-1}) 1725, 1674 [C=O]; HRMS $C_{41}H_{53}N_2O_4Si$ [MH^+] requires 665.3775. Found 665.3774; *m*/*z* ES+ 665 [100%, MH^+].

3.10.32. Preparation of (2*S*,2′*S*,3′*R*)-formic acid 2-(2′-dibenzylamino-3′-phenyl-3′-(triethyl-silanoxy)-propionylamino)-1,1-dimethyl-2-benzyl-ethyl ester 36. Following representative procedure 5, **35** (114 mg, 0.17 mmol) and DIBAL (0.34 mL, 0.34 mmol) in CH_2Cl_2 (5 mL) furnished **35** (60 mg, 0.09 mmol, 53%) as a white solid and **36** (34 mg, 0.05 mmol, 30%) as a clear colourless oil after flash column chromatography.

$[\alpha]_D^{23}=-88.0$ (c=0.47, $CHCl_3$); δ_H (40 MHz, $CDCl_3$) 0.31–0.46 [6H, m, $Si(CH_2CH_3)_3$], 0.83 [9H, t, J=7.9 Hz, $Si(CH_2CH_3)_3$], 1.10 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.51 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.44 [1H, dd, J=11.4, 14.5 Hz, $CHCH_AH_BPh$), 3.12 [1H, dd, J=3.4, 14.5 Hz, $CHCH_AH_BPh$], 3.41 [1H, d, J=5.8 Hz, CH(OTES)], 3.64 [4H, s, $CHN(CH_2Ph)_2$], 4.34 [1H, m, $CHCH_2Ph$], 5.44 [1H, d, J=5.8 Hz, $CHN(CH_2Ph)_2$], 6.98–7.01 [3H, m, N*H* and 2×Ph*H*], 7.18–7.33 [18H, m, Ph*H*], 8.09 [1H, s, $OCHO$]; δ_C (100 MHz, $CDCl_3$) 4.7 [$Si(CH_2CH_3)_3$], 6.9 [$Si(CH_2CH_3)_3$], 22.9, 24.8 [$C(CH_3)_2$], 35.7 [$CHCH_2Ph$], 54.5 [$CHN(CH_2Ph)_2$], 56.8, 67.2, 74.4 [$CHCH_2Ph$, $CHN(CH_2Ph)_2$, CH(OTES)], 85.4 [$C(CH_3)_2$], 126.4, 126.9, 127.3, 128.0, 128.1, 128.3, 128.4, 129.0 [*p*- and *m*/*o*-*Ph*], 137.9, 139.8, 143.3 [*i*-*Ph*], 160.2 [*C*=O amide], 169.9 [*C*=O ester]; ν_{max} (thin film, cm^{-1}) 1727, 1669 [C=O]; HRMS $C_{41}H_{53}N_2O_4Si$ requires 665.3775. Found 665.3781; *m*/*z* APCI+ 619 [25%, MH^+-CO_2], 665 [100%, MH^+].

3.10.33. Preparation of (2*S*,3*R*)-2-dibenzylamino-3-hydroxy-3-phenyl-propionic acid methyl ester 40 and (1′*S*,2*S*,3*R*)-*N*-(1′-benzyl-2′-hydroxy-2′-methyl-propyl)-2-dibenzylamino-3-hydroxy-3-phenyl-propionamide 37. Following representative procedure 9, **8** (50 mg, 0.09 mmol), *n*-BuLi (0.18 mL, 0.46 mmol) in MeOH (2 mL) and THF (2 mL) furnished **40**[8] (15 mg, 0.04 mmol, 44%) as a clear colourless oil, **37** (9 mg, 0.02 mmol, 19%) as a clear colourless oil and **4** (11 mg, 0.05 mmol, 60%) as a white solid after flash column chromatography.

Compound **40**. R_f 0.24 [8:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-180.3$ (c=0.35, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.42 [1H, d, J=9.9 Hz, $CHN(CH_2Ph)_2$], 3.46 [2H, d, J=13.2 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 3.64 [3H, s, CO_2CH_3], 4.15 [2H, d, J=13.2 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.95 [1H, d, J=9.9 Hz, CH(OH)], 7.12–7.42 [15H, m, Ph*H*].

Compound **37**. R_f 0.11 [1:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-69.9$ (c=1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.67 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.11 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.55 [1H, dd, J=12.2, 14.7 Hz, $CHCH_AH_BPh$], 2.69 [2H, d, J=14.0 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 2.87 [1H, d, J=9.2 Hz, CH(OH)], 3.19 [1H, dd, J=3.7, 14.7 Hz, $CHCH_AH_BPh$], 3.81 [2H, d, J=14.0 Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.07 [1H, s, CH(O*H*)], 4.30–4.36 [1H, m, $CHCH_2Ph$], 4.98 [1H, d, J=9.2 Hz, $CHN(CH_2Ph)_2$], 5.27 [1H, d, J=9.8 Hz, N*H*], 7.11–7.43 [20H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 26.8, 27.2 [$C(CH_3)_2$], 35.6 [$CHCH_2Ph$], 54.0 [$CHN(CH_2Ph)_2$], 56.6 [$CHCH_2Ph$], 69.1 [CH(OH)], 70.3 [$CHN(CH_2Ph)_2$], 72.4 [$C(CH_3)_2$], 126.7, 127.4, 127.6, 128.3, 128.7, 129.3 [*p*- and *m*/*o*-*Ph*], 138.4, 138.6, 140.4 [*i*-*Ph*], 167.7 [*C*=O]; ν_{max} (thin film, cm^{-1}) 1654 [C=O]; HRMS $C_{34}H_{39}N_2O_3$ [MH^+] requires 523.2961. Found 523.2970; *m*/*z* ESI+ 523 [100%, MH^+].

3.10.34. Preparation of (2*S*,3*R*)-3-(*tert*-butyl-dimethyl-silanoxy)-2-dibenzylamino-3-phenyl-propionic acid methyl ester 41 and (1′*S*,2*S*,3*R*)-*N*-(1′-benzyl-2′-hydroxy-2′-methyl-propyl)-3-(*tert*-butyl-dimethyl-silanoxy)-2-dibenzylamino-3-phenyl-propionamide 38. Following representative procedure 9, **35** (150 mg, 0.23 mmol), *n*-BuLi (0.45 mL, 1.13 mmol) in MeOH (5 mL) and THF

(5 mL) furnished **35** (16 mg, 0.02 mmol, 11%), **41** (24 mg, 0.05 mmol, 33%) as a clear colourless oil, **38** (92 mg, 0.14 mmol, 63%) as a clear colourless oil and **4** (5 mg, 0.02 mmol, 11%) as a white solid after flash column chromatography.

Compound **41**. R_f 0.48 [9:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-34.0$ ($c=1.0$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.26 [3H, s, $Si(CH_3)_A(CH_3)_B$], 0.03 [3H, s, $Si(CH_3)_A(CH_3)_B$], 0.90 [9H, s, $SiC(CH_3)_3$], 3.64 [1H, d, $J=5.5$ Hz, $CHN(CH_2Ph)_2$], 3.66 [3H, s, CO_2CH_3], 3.85 [2H, d, $J=14.5$ Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.21 [2H, d, $J=14.5$ Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 5.33 [1H, d, $J=5.5$ Hz, C*H*(OTBDMS)], 7.11–7.29 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) −5.4, −4.4 [$Si(CH_3)_2$], 18.0 [$SiC(CH_3)_3$], 25.8 [$SiC(CH_3)_3$], 51.0 [CO_2CH_3], 55.4 [$CHN(CH_2Ph)_2$], 67.5 [$CHN(CH_2Ph)_2$], 75.9 [CHOTBDMS}, 126.5, 127.7 [*m/o-Ph* (CHPh)], 127.1 [*p-Ph* ($CHN(CH_2Ph)_2$], 127.3 [*p-Ph* (CHPh)], 128.0, 128.4 [*m/o-Ph* ($CHN(CH_2Ph)_2$], 140.0 [*i-Ph* ($CHN(CH_2Ph)_2$], 141.7 [*i-Ph* (CHPh)], 171.7 [C=O]; ν_{max} (thin film, cm^{-1}) 1746 [C=O]; HRMS $C_{30}H_{40}NO_3Si$ [MH^+] requires 490.2777. Found 490.2768; *m/z* ESI+ 490 [100%, MH^+].

Compound **38**. R_f 0.21 [1:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-67.8$ ($c=2.75$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.35 [3H, s, $Si(CH_3)_A(CH_3)_B$], −0.03 [3H, s, $Si(CH_3)_A(CH_3)_B$], 0.89 [9H, s, $SiC(CH_3)_3$], 0.90 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.04 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.45 [1H, dd, $J=11.0$, 14.8 Hz, $CHCH_AH_BPh$], 3.079[1H, dd, $J=3.3$, 14.8 Hz, $CHCH_AH_BPh$], 3.40 [1H, d, $J=6.2$ Hz, C*H*(OTBDMS)], 3.65 [2H, d, $J=14.5$ Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 3.75 [2H, d, $J=14.5$ Hz, $CHN(CH_AH_BPh)(CH_CH_DPh)$], 4.08–4.14 [1H, m, $CHCH_2Ph$], 5.46 [1H, d, $J=6.2$ Hz, $CHN(CH_2Ph)_2$], 6.38 [1H, d, $J=9.5$ Hz, N*H*], 7.02–7.04 [2H, m, Ph*H*], 7.15–7.35 [18H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) −4.8, −4.7 [$Si(CH_3)_2$], 18.0 [$SiC(CH_3)_3$], 26.1 [$SiC(CH_3)_3$], 26.3, 27.3 [$C(CH_3)_2$], 35.9 [$CHCH_2Ph$], 54.5 [$CHN(CH_2Ph)_2$], 58.1 [$CHCH_2Ph$], 67.8 [$CHN(CH_2Ph)_2$], 73.2 [$C(CH_3)_2$], 74.5 [C*H*(OTBDMS)], 126.4, 126.9, 127.5 [*p-Ph*], 127.6, 128.1, 128.3, 128.3, 128.5, 128.8 [*m/o-Ph*], 138.5, 139.8, 143.2 [*i-Ph*], 170.8 [C=O]; ν_{max} (thin film, cm^{-1}) 1652 [C=O]; HRMS $C_{40}H_{53}N_2O_3Si$ [MH^+] requires 637.3825. Found 637.3827; *m/z* ESI+ 637 [100%, MH^+].

3.10.35. Preparation of (2*S*,3*R*)-2-dibenzylamino-3-phenyl-3-(triethyl-silanoxy)-propionic acid methyl ester 42, (1′*S*,2*S*,3*R*)-*N*-(1′-benzyl-2′-hydroxy-2′-methyl-propyl)-2-dibenzylamino-3-phenyl-3-(triethyl-silanoxy)-propionamide 39 and(1′*S*,2*S*,3*R*)-*N*-(1′-benzyl-2′-hydroxy-2′-methyl-propyl)-2-dibenzylamino-3-hydroxy-3-phenyl-propionamide 37. Following representative procedure 9, **35** (150 mg, 0.23 mmol), *n*-BuLi (0.45 mL, 1.13 mmol) in MeOH (5 mL) and THF (5 mL) furnished **42** (9 mg, 0.02 mmol, 8%) as a white solid, **39** (67 mg, 0.11 mmol, 46%) as a pale yellow oil, **35** (16 mg, 0.02 mmol, 10%) as a white solid, **37** (13 mg, 0.025 mmol, 11%) as a clear colourless oil and **4** (6 mg, 0.03 mmol, 13%) as a white solid after flash column chromatography.

Compound **42**. R_f 0.48 [9:1 30–40 °C petrol/Et_2O]; mp 61 °C [pentane/Et_2O]; $[\alpha]_D^{23}=-54.4$ ($c=0.50$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.50 [6H, q, $J=8.0$ Hz, $Si(CH_2CH_3)_3$], 0.87 [9H, t, $J=8.0$ Hz, $Si(CH_2CH_3)_3$], 3.64 [1H, d, $J=5.6$ Hz, $CHN(CH_2Ph)_2$], 3.66 [3H, s, CO_2CH_3], 4.02 [4H, ABq, $J=14.4$ Hz, $CHN(CH_2Ph)_2$], 5.37 [1H, d, $J=5.6$ Hz, C*H*(OTES)], 7.14–7.30 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 4.8 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)_3$], 51.0 [CO_2CH_3], 55.4 [$CHN(CH_2Ph)_2$], 67.4, 75.7 [$CHN(CH_2Ph)_2$ and C*H*(OTES)], 126.5, 127.0, 127.3, 127.8, 128.0, 128.4 [*p-* and *m/o-Ph*], 140.0, 141.8 [*i-Ph*], 171.8 [C=O]; ν_{max} (KBr disc, cm^{-1}) 1733 (C=O); HRMS $C_{30}H_{40}NO_3Si$ requires 490.2777. Found 490.2768; *m/z* APCI+ 490 [MH^+, 100%].

Compound **39**. R_f 0.22 [1:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-62.2$ ($c=1.65$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.35–0.49 [6H, m, $Si(CH_2CH_3)_3$], 0.81–0.87 [9H, m, $Si(CH_2CH_3)_3$], 0.93 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.10 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.44 [1H, dd, $J=11.2$, 14.7 Hz, $CHCH_AH_BPh$], 3.08 [1H, dd, $J=3.4$, 14.7 Hz, $CHCH_AH_BPh$], 3.40 [1H, d, $J=6.2$ Hz, C*H*(OTES)], 3.65–3.72 [4H, m, $CHN(CH_2Ph)_2$], 4.08–4.14 [1H, m, $CHCH_2Ph$], 5.47 [1H, d, $J=6.2$ Hz, $CHN(CH_2Ph)_2$], 6.49 [1H, d, $J=9.6$ Hz, N*H*], 6.99–7.02 [2H, m, Ph*H*], 7.16–7.37 [18H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 4.8 [$Si(CH_2CH_3)_3$], 6.9 [$Si(CH_2CH_3)_3$], 26.3, 27.3 [$C(CH_3)_2$], 35.8 [$CHCH_2Ph$], 54.6 [$CHN(CH_2Ph)_2$], 58.1 [$CHCH_2Ph$], 67.5 [$CHN(CH_2Ph)_2$], 73.2 [$C(CH_3)_2$], 74.6 [C*H*(OTES)], 126.3, 127.4, 127.5 [*p-Ph*], 126.9, 128.1, 128.2, 128.3, 128.4, 128.8 [*m/o-Ph*], 138.5, 139.9, 143.2 [*i-Ph*], 170.9 [C=O]; ν_{max} (thin film, cm^{-1}) 1644 [C=O]; HRMS $C_{40}H_{53}N_2O_3Si$ [MH^+] requires 637.3825. Found 637.3821; *m/z* ESI+ 637 [100%, MH^+].

3.10.36. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2′-dibenzylamino-3′-methoxy-3-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 43. $Me_3O^+BF_4^-$ (133 mg, 0.90 mmol) was added to a stirred solution of **8** (100 mg, 0.18 mmol) and Proton Sponge® (193 mg, 0.90 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. After stirring for 72 h, the reaction mixture was filtered through Celite® and concentrated in vacuo. Purification by flash column chromatography furnished **43** (72 mg, 0.13 mmol, 71%) as a pale yellow oil and returned **8** (14 mg, 0.03 mmol, 14%) as a white solid.

R_f 0.33 [3:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-4.8$ ($c=0.38$, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.76 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.24 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.77 [1H, dd, $J=9.7$, 14.5 Hz, $CHCH_AH_BPh$], 3.00 [1H, dd, $J=3.7$, 14.5 Hz, $CHCH_AH_BPh$], 3.22 [3H, s, $CHO(CH_3)$], 3.94 [2H, d, $J=14.5$ Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 4.12 [2H, d, $J=14.5$ Hz, $N(CH_AH_BPh)(CH_CH_DPh)$], 4.24 [1H, dd, $J=3.7$, 9.7 Hz, $CHCH_2Ph$], 4.71 [1H, d, $J=8.5$ Hz, $CHN(CH_2Ph)_2$], 5.43 [1H, d, $J=8.5$ Hz, $CH(OCH_3)$], 7.16–7.35 [20H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 22.1, 27.6 [$C(CH_3)_2$], 35.4 [$CHCH_2Ph$], 55.4 [$CHN(CH_2Ph)_2$], 56.9 [$CH(OCH_3)$], 63.1 [$CHCH_2Ph$], 65.0 [$CH(OCH_3)$], 81.6 [$C(CH_3)_2$], 82.9 [$CHN(CH_2Ph)_2$], 126.6, 126.7 [*p-Ph*], 128.0, 128.2, 128.3, 128.7, 128.7, 129.1 [*m/o-Ph*], 137.0, 138.0, 140.2 [*i-Ph*], 151.5 [C=O endocyclic], 171.5 [C=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1776, 1689 [C=O]; HRMS $C_{36}H_{39}N_2O_4$ [MH^+] requires 563.2910. Found 563.2919; *m/z* ES+ 563 [100%, MH^+].

3.10.37. Preparation of (1′*S*,2*S*,3*R*)-*N*-(1′-benzyl-2′-hydroxy-2′-methyl-propyl)-2-dibenzylamino-3-methoxy-3-phenyl-propionamide 44. Following representative procedure 5, **43** (50 mg, 0.09 mmol) and DIBAL (0.18 mL, 0.18 mmol) in CH_2Cl_2 (5 mL) furnished **44** (43 mg, 0.08 mmol, 85%) as a pale yellow oil after flash column chromatography.

R_f 0.28 [1:1 pentane/Et_2O]; $[\alpha]_D^{25}=-72.1$ (c=2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.54 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.49 [1H, dd, J=11.6, 14.6 Hz, $CHCH_AH_BPh$], 3.13 [3H, s, $CH(OCH_3)$], 3.13–3.18 [1H, m, $CHCH_AH_BPh$], 3.45 [1H, d, J=6.0 Hz, $CH(OCH_3)$], 3.51–3.59 [4H, m, $N(CH_2Ph)_2$], 4.38–4.45 [1H, m, $CHCH_2Ph$], 4.82 [1H, d, J=6.0 Hz, $CHN(CH_2Ph)_2$], 7.00 [1H, d, J=10.1 Hz, NH], 7.05–7.07 [2H, m, PhH], 7.20–7.34 [18H, m, PhH], 8.09 [1H, s, CHO]; δ_C (100 MHz, $CDCl_3$) 23.1, 24.7 [$C(CH_3)_2$], 35.5 [$CHCH_2Ph$], 54.7 [$CHN(CH_2Ph)_2$], 56.3 [$CHCH_2Ph$], 57.5 [$CH(OCH_3)$], 66.4 [$CH(OCH_3)$], 82.9 [$CHN(CH_2Ph)_2$], 85.2 [$C(CH_3)_2$], 126.3, 126.9 [*p-Ph*], 127.5, 128.2, 128.3, 129.0 [*m/o-Ph*], 137.7, 139.8, 140.0 [*i-Ph*], 160.1 [CHO], 170.0 [C=O amide]; ν_{max} (thin film, cm^{-1}) 1725, 1674 [C=O]; HRMS $C_{36}H_{41}N_2O_4$ [MH^+] requires 565.3066. Found 565.3061; m/z ES+ 565 [100%, MH^+].

3.10.38. Preparation of (*S*)-2′-*N*-(*N*′-*N*′-diallylaminoacetyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one 45. Following representative procedure 2, (*S*)-4-benzyl-3-(2′-bromoacetyl)-5,5-dimethyl-oxazolidin-2-one (4.71 g, 14.4 mmol) and $(CH_2{=}CHCH_2)NH$ (3.09 g, 3.93 mL) in CH_2Cl_2 (100 mL) furnished **45** as a yellow oil (3.76 g, 11.0 mmol, 76%) after flash column chromatography.

$[\alpha]_D^{24}=-24.6$ (c=0.79, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.33 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.84 [1H, dd, J=9.5, 14.4 Hz, $CHCH_AH_BPh$], 3.11 [1H, dd, J=4.0, 14.4 Hz, $CHCH_AH_BPh$], 3.23 [4H, d, J=6.8 Hz, $N(CH_2CH{=}CH_2)_2$], 3.87 [2H, ABq, J=18.6 Hz, $CH_2N(CH_2CH{=}CH_2)_2$], 4.46 [1H, dd, J=4.0, 9.5 Hz, $CHCH_2Ph$], 5.08–5.17 [4H, m, $N(CH_2CH{=}CH_2)_2$], 5.78–5.88 [2H, m, $N(CH_2CH{=}CH_2)_2$], 7.16–7.28 [5H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 22.2, 28.4 [$C(CH_3)_2$], 35.2 [$CHCH_2Ph$], 55.4 [$CH_2N(CH_2CH{=}CH_2)_2$], 57.1 [$CH_2N(CH_2CH{=}CH_2)_2$), 63.2 [$CHCH_2Ph$], 82.7 [$C(CH_3)_2$], 117.8 [$CH_2N(CH_2CH{=}CH_2)_2$) 126.7 [*p-Ph*], 128.6, 129.0 [*m/o-Ph*], 135.5 [$CH_2N(CH_2CH{=}CH_2)_2$), 136.8 [*i-Ph*], 152.5 [C=O endocyclic], 171.5 [C=O endocyclic]; ν_{max} (thin film, cm^{-1}) 2978 [C–H], 1777, 1707 [C=O]; HRMS $C_{20}H_{27}N_2O_3$ requires 343.2022. Found 343.2014; m/z APCI+ 343 [MH^+, 100%].

3.10.39. Preparation of (4*S*,2′*S*,3′*R*)-*N*-(2′-(*N*′-*N*′-diallylamino)-3′-hydroxy-3′-phenyl-1′-oxopropyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one 46. Following representative procedure 4, **45** (200 mg, 0.584 mmol), 9-BBNOTf (1.75 mL, 0.83 mmol), *i*-Pr_2NEt (0.14 mL, 0.81 mmol), PhCHO (0.073 mL,0.64 mmol) and CH_2Cl_2 (5 mL) furnished **46** (172 mg, 0.191 mmol, 66%) as a white crystalline solid after purification by flash column chromatography followed by recrystallisation from hexane/ether solution.

Mp 73 °C [hexane/Et_2O]; $[\alpha]_D^{23}=+82.6$ (c=0.94, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.58 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.21 [3H, s, $C(CH_3)_A(CH_3)_B$], 2.80 [1H, dd, J=9.4, 14.3 Hz, $CHCH_AH_BPh$], 2.97 [1H, dd, J=4.5, 14.3 Hz, $CHCH_AH_BPh$], 3.17 [2H, dd, J=7.6, 15.1 Hz, $N(CH_AH_BCH{=}CH_2)_2$], 3.61 [2H, dd, J=5.1, 15.1 Hz, $N(CH_AH_BCH{=}CH_2)_2$], 4.05 [1H, s, OH], 4.22 [1H, dd, J=4.5, 9.4 Hz, $CHCH_2Ph$], 4.74 [1H, d, J=9.7 Hz, CH(OH)] 5.17–5.27 [5H, m, $CHN(CH_2CH{=}CH_2)_2$ and $CHN(CH_2CH{=}CH_2)_2$), 5.81–5.89 [2H, m, $N(CH_2CH{=}CH_2)_2$] 7.22–7.38 [10H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 21.8, 26.9 [$C(CH_3)_2$], 35.5 [$CHCH_2Ph$], 52.5 [$CHN(CH_2CH{=}CH_2)_2$], 63.1 [$CHCH_2Ph$], 66.3 [CH(OH)], 71.7 [$CHN(CH_2CH{=}CH_2)_2$], 81.7 [$C(CH_3)_2$], 118.0 [$CHN(CH_2CH{=}CH_2)_2$], 126.8, 127.9 [*p-Ph*], 128.3, 128.3, 128.6, 129.0 [*m/o-Ph*], 135.1 [$CHN(CH_2CH{=}CH_2)_2$], 136.6, 138.7 [*i-Ph*], 151.7 [C=O endocyclic], 170.8 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 3407 [O–H], 1770, 1684 [C=O]; $C_{27}H_{32}N_2O_4$ requires C, 72.3; H, 7.2; N, 6.25%. Found C, 72.5; H, 7.5; N, 6.2%; m/z APCI+ 449 [MH^+, 58%], 343 [100%].

X-ray crystal structure determination for **46**. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[22] X-ray crystal structure data for **46** [$C_{27}H_{32}N_2O_4$]: M=448.56, orthorhombic, space group P 21 21 21, a=11.0817(3) Å, b=14.9551(4) Å, c=15.1422(5) Å, V=2509.5 $Å^3$, Z=4, μ=0.080 mm^{-1}, colourless block, crystal dimensions=0.6×0.6×0.8 mm^3. A total of 3092 unique reflections were measured for $1<\theta<27$ and 2381 reflections were used in the refinement. The final parameters were wR_2=0.051 and R_1=0.040 [$I>3\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC234753. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.10.40. Preparation of (4*S*,2′*S*,3′*R*)-*N*-(2′-(*N*′-*N*′-diallylamino)-3′-triethylsiloxy-3′-phenyl-1′-oxopropyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one 47. Following representative procedure 6, **46** (342 mg, 1.12 mmol), TESCl (288 mg, 0.32 mL, 2.80 mmol), imidazole (260 mg, 5.60 mmol) and DMAP (93 mg, 1.12 mmol) in DMF (10 mL) furnished **47** (604 mg, 1.073 mmol, 96%) as a colourless oil after purification by flash column chromatography.

$[\alpha]_D^{24}=+8.8$ (c=0.99, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.43–0.50 [6H, m, $Si(CH_2CH_3)_3$], 0.66 [3H, s, $C(CH_3)_A(CH_3)_B$], 1.21 [3H, s, $C(CH_3)_A(CH_3)_B$], 0.86 [9H, t, J=7.7 Hz, $Si(CH_2CH_3)_3$], 2.80 [1H, dd, J=9.4, 14.3 Hz, $CHCH_AH_BPh$], 2.99 [1H, dd, J=3.6, 14.3 Hz, $CHCH_AH_BPh$], 3.41 [2H, dd, J=6.3, 15.0 Hz, $CHN(CH_AH_BCH{=}CH_2)_2$), 3.59 [2H, dd, J=5.8, 15.0 Hz, $N(CH_AH_BCH{=}CH_2)_2$], 4.15 [1H, dd, J=3.6, 9.4 Hz, $CHCH_AH_BPh$], 5.06–5.23 [5H, m, $CHN(CH_2CH{=}CH_2)_2$), 5.33 [1H, d, J=8.9 Hz, CH(OTES)], 5.79–5.89 [2H, m, $N(CH_2CH{=}CH_2)_2$], 7.17–7.38 [10H, m, PhH]; δ_C (400 MHz, $CDCl_3$) 4.9

[Si(CH_2CH_3)$_3$], 6.8 [Si(CH_2CH_3)$_3$], 22.0, 27.4 [C(CH_3)$_2$], 35.3 [CHCH_2Ph], 53.9 [CHN(CH_2CH=CH_2)$_2$], 63.0, 66.5, 74.1 [CHCH$_2$Ph, CHN(CH$_2$CH=CH$_2$)$_2$, CH(OTES)], 81.4 [C(CH$_3$)$_2$], 116.0 [CHN(CH$_2$CH=CH_2)$_2$], 126.7, 127.8, 128.0, 128.1, 128.6, 129.1 [*p-Ph* and *m/o-Ph*], 137.3 [CHN(CH$_2$$CH$=CH$_2$)$_2$], 137.0, 141.6 [*i-Ph*], 151.7 [C=O endocyclic], 171.3 [C=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1779, 1689 [C=O]; HRMS $C_{33}H_{47}N_2O_4Si$ requires 563.3305. Found 563.3323; *m/z* APCI+ 563 [MH$^+$, 100%].

3.10.41. Preparation of (2*S*,2′*S*,3′*R*)-formic acid 2-(2′-diallylamino-3′-hydroxy-3′-phenyl-propionylamino)-1,1-dimethyl-(2*S*)-benzyl-ethyl ester 48. Following representative procedure 5, **47** (50 mg, 0.089 mmol) and DIBAL (0.34 mL, 0.34 mmol) in DCM (3 mL) furnished **47** (20 mg, 0.036 mmol, 40%) as a white solid and **48** (12 mg, 0.018 mmol, 20%) as a colourless oil.

$[\alpha]_D^{23}$=−91.9 (c=0.14, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.29–0.42 [6H, m, Si(CH_2CH$_3$)$_3$], 0.78 [9H, t, J=7.9 Hz, Si(CH$_2$CH_3)$_3$], 1.27 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.56 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.49 [1H, dd, J=11.0, 14.3 Hz, CHCH_AH$_B$Ph], 2.92 [2H, m, CHN(CH_AH$_B$CH=CH$_2$)$_2$], 3.07–3.16 [3H, m, CHCH$_A$$H_B$Ph, CHN(CH$_A$$H_B$CH=CH$_2$)$_2$], 3.53 [1H, d, J=4.9 Hz, CH(OTES)], 4.34 [1H, m, CHCH$_2$Ph], 4.97–5.08 [4H, m, N(CH$_2$CH=CH_2)$_2$], 5.40 [1H, d, J=4.9 Hz, CHN(CH$_2$CH=CH$_2$)$_2$], 5.60–5.70 [2H, m, N(CH$_2$CH=CH$_2$)$_2$], 7.18–7.36 [11H, m, NH, PhH], 8.03 [1H, s, OCHO]; δ_C (100 MHz, $CDCl_3$) 4.6 [Si(CH_2CH$_3$)$_3$], 6.9 [Si(CH$_2$$CH_3$)$_3$], 23.0, 25.1 [C($CH_3$)$_2$], 35.8 [$CHCH_2$Ph], 53.5 [CHN($CH_2$CH=CH$_2$)$_2$], 56.8 [CH$CH_2$Ph], 67.5 [$C$H(OTES)], 74.2 [$C$HN(CH$_2$CH=CH$_2$)$_2$], 85.5 [$C$(CH$_3$)$_2$], 116.6 [CHN(CH$_2$CH=$CH_2$)$_2$], 126.4, 126.9 [*p-Ph*], 127.1, 127.8, 128.3, 129.1 [*m/o-Ph*], 137.2 [CHN(CH$_2$$CH$=CH$_2$)$_2$], 138.1, 143.6 [*i-Ph*], 160.3 [OCHO], 170.5 [C=O]; ν_{max} (thin film, cm^{-1}) 2922 [C–H], 1732, 1674 [C=O]; HRMS $C_{33}H_{49}N_2O_4Si$ requires 565.3462. Found 565.3459; *m/z* APCI+ 565 [MH$^+$, 100%].

3.10.42. Preparation of (*S*)-4-methyl-3-(2′-dibenzylamino-acetyl)-5,5-dimethyl-oxazolidin-2-one 50. Following representative procedure 1, **49** (1.70 g, 13.18 mmol), *n*-BuLi (5.8 mL, 14.50 mmol) and bromoacetyl bromide (1.5 mL, 17.13 mmol) in THF (80 mL) furnished (*S*)-4-methyl-3-(2′-bromo-acetyl)-5,5-dimethyl-oxazolidin-2-one (2.57 g, 10.32 mmol, 78%) as an orange solid after flash column chromatography.

R_f 0.26 [2:1 30–40 °C petrol/Et_2O]; mp 53–54 °C [petrol/Et_2O]; $[\alpha]_D^{25}$=+33.29 (c=0.85, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.288 [3H, d, J=6.6 Hz, CHCH_3], 1.410 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.443 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 4.175 [1H, q, J=6.6 Hz, CHCH$_3$], 4.434 [1H, d, J=12.5 Hz, CH_AH$_B$Br], 4.536 [1H, d, J=12.5 Hz, CH$_A$$H_B$Br]; δ_C (100 MHz, $CDCl_3$) 14.3 [CHCH$_3$], 21.5, 27.8 [C(CH$_3$)$_2$], 28.5 [CH$_2$Br], 59.4 [CHCH$_3$], 82.6 [C(CH$_3$)$_2$], 152.2 [C=O endocyclic], 166.3 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1769, 1706 [C=O]; HRMS $C_8H_{13}NO_3Br$ [MH$^+$] requires 250.0079. Found 250.0067; *m/z* GCMS 250 [100%, MH$^+$].

Following representative procedure 2, (*S*)-4-methyl-3-(2′-bromo-acetyl)-5,5-dimethyl-oxazolidin-2-one (2.10 g, 8.46 mmol) and (PhCH$_2$)$_2$NH (3.57 mL, 18.61 mmol) in CH_2Cl_2 (100 mL) furnished **50** (2.53 g, 6.91 mmol, 82%) as an orange oil after flash column chromatography.

R_f 0.43 [1:1 30–40 °C petrol/Et_2O]; mp 78–79 °C [petrol/Et_2O]; $[\alpha]_D^{25}$=+33.2 (c=0.85, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.28 [3H, d, J=6.5 Hz, CHCH_3], 1.38 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.402 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 3.87 [4H, s, CH$_2$N(CH_2Ph)$_2$], 3.91 [2H, s, CH_2N(CH$_2$Ph)$_2$], 4.16 [1H, q, J=6.5 Hz, CHCH$_3$], 7.22–7.55 [10H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 14.7 [CHCH$_3$], 21.6, 27.8 [C(CH$_3$)$_2$], 55.6 [CH$_2$N(CH$_2$Ph)$_2$], 57.7 [CH$_2$N(CH$_2$Ph)$_2$], 58.7 [CHCH$_3$], 82.0 [C(CH$_3$)$_2$], 127.1 [*p-Ph*], 128.3, 128.8 [*m/o-Ph*], 139.1 [*i-Ph*], 152.6 [C=O endocyclic], 171.9 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1761, 1700 [C=O]; HRMS $C_{22}H_{27}N_2O_3$ [MH$^+$] requires 367.2022. Found 367.2022; *m/z* ES+ 367 [100%, MH$^+$], 389 [100%, MNa$^+$].

3.10.43. Preparation of (2′*S*,3′*R*,4*S*)-4-methyl-3-(2′-dibenzylamino-3′-hydroxy-3-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 51. Following representative procedure 4, 9-BBNOTf (5.90 mL, 2.95 mmol), **50** (720 mg, 1.97 mmol), *i*-Pr$_2$NEt (0.51 mL, 2.95 mmol) and PhCHO (0.23 mL, 2.17 mmol) in CH_2Cl_2 (40 mL) furnished **51** (722 mg, 1.53 mmol, 78%) as a pale yellow solid after flash column chromatography.

R_f 0.3 [1:1 30–40 °C petrol/Et_2O]; mp 89–90 °C [petrol/Et_2O]; $[\alpha]_D^{25}$=+7.1 (c=1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.71 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.15 [3H, d, J=6.6 Hz, CHCH_3], 1.26 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 3.76 [2H, d, J=14.1 Hz, CHN(CH_AH$_B$Ph)(CH_CH$_D$Ph)], 3.83 [1H, q, J=6.6 Hz, CHCH$_3$], 3.89 [1H, s, CH(OH)], 4.25 [2H, d, J=14.1 Hz, CHN(CH$_A$$H_B$Ph)(CH$_C$$H_D$Ph)], 4.87 [1H, d, J=9.6 Hz, CHN(CH$_2$Ph)$_2$], 5.33 [1H, d, J=9.6 Hz, CH(OH)], 7.19–7.39 [15H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 15.0 [CHCH$_3$], 21.3, 26.7 [C(CH$_3$)$_2$], 54.8 [CHN(CH$_2$Ph)$_2$], 58.7 [CHCH$_3$], 66.6 [CH(OH)], 72.2 [CHN(CH$_2$Ph)$_2$], 80.9 [C(CH$_3$)$_2$], 127.3, 128.0 [*p-Ph*], 128.3, 128.5, 129.1 [*m/o-Ph*], 138.8, 138.9 [*i-Ph*], 151.7 [C=O endocyclic], 170.8 [C=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1771, 1668 [C=O]; HRMS $C_{29}H_{33}N_2O_4$ [MH$^+$] requires 473.2440. Found 473.2455; *m/z* ES+ 473 [100%, MH$^+$], 495 [80%, MNa$^+$].

3.10.44. Preparation of (2′*S*,3′*R*,4*S*)-4-methyl-3-(3′-(*tert*-butyl-dimethyl-silanoxy)-2′-dibenzylamino-3-phenyl-propionyl)-5,5-dimethyl-oxazolidin-2-one 52. Following representative procedure 7, **51** (100 mg, 0.21 mmol), TBDMSOTf (0.10 mL, 0.42 mmol) and DMAP (38 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) furnished **52** (124 mg, 0.21 mmol, 99%) as a pale yellow oil after flash column chromatography.

R_f 0.13 [5:1 30–40 °C petrol/Et_2O]; [petrol/Et_2O]; $[\alpha]_D^{25}$=+20.1 (c=0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.29 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.10 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.95 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 0.96 [9H, s, Si(CH_3)$_3$], 1.21 [3H, d, J=6.5 Hz, CHCH_3], 1.28 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 3.89 [1H, q, J=6.6 Hz, CHCH$_3$], 4.02 [2H, d, J=14.3 Hz, CHN(CH_AH$_B$Ph)(CH_CH$_D$Ph)], 4.26 [2H, d, J=14.3 Hz, CHN(CH$_A$$H_B$Ph)(CH$_C$$H_D$Ph)], 5.27

[1H, d, J=7.4 Hz, CHN($CH_2Ph)_2$], 5.34 [1H, d, J=7.4 Hz, CH(OTBDMS)], 7.15–7.27 [13H, m, PhH], 7.318–7.342 [2H, m, PhH]; δ_C (100 MHz, $CDCl_3$) −4.8, −4.3 [Si($CH_3)_2$], 14.7 [CHCH_3], 18.1 [SiC($CH_3)_3$], 21.5, 27.2 [C($CH_3)_2$], 26.0 [SiC($CH_3)_3$], 55.9 [CHN($CH_2Ph)_2$], 58.5 [CHCH$_3$], 65.5 [CH(OTBDMS)], 75.0 [CHN($CH_2Ph)_2$], 80.5 [C($CH_3)_2$], 126.6, 127.6 [*p-Ph*], 127.8, 127.9, 128.5, 128.5 [*m/o-Ph*], 140.3, 141.2 [*i-Ph*], 151.4 [C=O endocyclic], 171.9 [C=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1780, 1706 [C=O]; HRMS $C_{35}H_{47}N_2O_4Si$ [MH^+] requires 587.3305. Found 587.3306; *m/z* ES+ 587 [100%, MH^+], 609 [5%, MNa^+].

3.10.45. Preparation of (1′*S*,2*S*,3*R*)-*N*-(1′-methyl-2′-hydroxy-2′-methyl-propyl)-2-dibenzylamino-3-phenyl-3-(*tert*-butyl-dimethyl-silanoxy)-propionamide 53. Following representative procedure 5, **52** (120 mg, 0.20 mmol) and DIBAL (0.60 mL, 0.40 mmol) in CH_2Cl_2 (5 mL) furnished **53** (113 mg, 0.19 mmol, 96%) as a pale yellow oil after flash column chromatography.

R_f 0.5 [1:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}$=−73.3 (c=1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.16 [3H, s, Si(C$H_3)_A$($CH_3)_B$], 0.14 [3H, s, Si($CH_3)_A$(C$H_3)_B$], 0.96 [9H, s, Si(C$H_3)_3$], 1.15 [3H, d, J=6.8 Hz, CHCH_3], 1.171 [3H, s, C(C$H_3)_A$($CH_3)_B$], 1.46 [3H, s, C($CH_3)_A$(C$H_3)_B$], 3.53 [1H, d, J=5.0 Hz, CHN($CH_2Ph)_2$], 3.69 [2H, d, J=14.0 Hz, CHN(CH_AH$_B$Ph)(CH_CH$_D$Ph)], 3.95–3.99 [1H, m, CHCH$_3$], 4.09 [2H, d, J=14.0 Hz, CHN(C$H_A$$H_B$Ph)(C$H_C$$H_D$Ph)], 5.73 [1H, d, J=5.0 Hz, CH(OTBDMS)], 7.21–7.30 [12H, m, Ph$H$and NH], 7.33–7.37 [2H, m, PhH], 7.45 [2H, d, J=7.2 Hz, PhH], 8.04 [1H, s, CHO]; δ_C (100 MHz, $CDCl_3$) −5.0, −4.4 [Si($CH_3)_2$], 15.8 [CHCH_3], 18.2 [SiC($CH_3)_3$], 23.1, 24.0 [C($CH_3)_2$], 26.1 [SiC($CH_3)_3$], 52.1 [CHCH$_3$], 54.9 [CHN($CH_2Ph)_2$], 67.2 [CHN($CH_2Ph)_2$], 75.0 [CH(OTBDMS)], 84.8 [C($CH_3)_2$], 127.1, 127.2 [*p-Ph*], 127.4, 128.1, 128.4, 128.5 [*m/o-Ph*], 139.7, 143.2 [*i-Ph*], 160.0 [OCHO], 170.2 [C=O amide]; ν_{max} (thin film, cm^{-1}) 1728, 1674 [C=O]; HRMS $C_{35}H_{49}N_2O_4Si$ [MH^+] requires 589.3462. Found 589.3437; *m/z* ES+ 589 [60%, MH^+], 611 [100%, MNa^+].

3.10.46. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-octanoyl)-5,5-dimethyl-oxazolidin-2-one 54. Following representative procedure 6, **9** (720 mg, 1.59 mmol), TBDMSCl (600 mg, 3.97 mmol), imidazole (540 mg, 7.94 mmol) and DMAP (20 mg, 0.16 mmol) in DMF (10 mL) furnished **54** (791 mg, 1.40 mmol, 88%) as a pale yellow oil after flash column chromatography.

R_f 0.18 [10:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}$=−4.9 (c=1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.04 [3H, s, Si(C$H_3)_A$($CH_3)_B$], 0.06 [3H, s, Si($CH_3)_A$(C$H_3)_B$], 0.84–0.88 [3H, m, $CH_2CH_2CH_2CH_2CH_3$], 0.88 [9H, s, SiC(C$H_3)_3$], 1.20–1.29 [4H, m, $CH_2CH_2CH_2CH_2CH_3$], 1.32 [3H, s, C(C$H_3)_A$($CH_3)_B$], 1.35 [3H, s, C($CH_3)_A$(C$H_3)_B$], 1.37–1.43 [3H, m, CH_AH$_B$CH_2CH$_2$CH$_2$CH$_3$], 1.53–1.57 [1H, m, CH$_A$$H_B$-CH$_2CH_2CH_2CH_3$], 2.71 [1H, dd, J=10.0, 14.6 Hz, CHCH_A-H$_B$Ph], 2.95 [1H, dd, J=2.9, 14.6 Hz, CHCH$_A$$H_B$Ph], 3.97–4.00 [1H, m, C$H$OTBDMS], 4.39 [1H, dd, J=2.9, 10.0 Hz, CHCH$_2$Ph], 4.58–4.58 [2H, ABq, J=11.9 Hz, CHOCH_2-Ph], 5.29 [1H, d, J=5.1 Hz, CHOCH$_2$Ph], 7.21–7.37 [10H, m, PhH]; δ_C (100 MHz, $CDCl_3$) −4.4, −4.1 [Si($CH_3)_2$], 14.0 [$CH_2CH_2CH_2CH_2CH_3$], 18.2 [SiC($CH_3)_3$], 22.3, 28.5 [C($CH_3)_2$], 22.5, 25.2, 32.0, 33.6 [$CH_2CH_2CH_2CH_2CH_3$], 26.0 [SiC($CH_3)_3$], 34.9 [CHCH_2Ph], 64.2 [CHCH$_2$Ph], 73.1 [CHOCH_2Ph], 73.9 [CHOTBDMS], 79.9 [CHOCH_2Ph], 82.6 [C($CH_3)_2$], 126.8, 127.8 [*p-Ph*], 128.3, 128.4, 128.7, 129.0 [*m/o-Ph*], 137.0, 137.8 [*i-Ph*], 152.2 [C=O endocyclic], 171.8 [C=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1778, 1703 [C=O]; HRMS $C_{33}H_{50}NO_5Si$ [MH^+] requires 568.3458. Found 568.3455; *m/z* ES+ 568 [30%, MH^+], 585 [100%, MNH_4^+], 590 [70%, MNa^+].

3.10.47. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2-benzyloxy-4-methyl-3-triethylsilanoxy-pentanoyl)-5,5-dimethyl-oxazolidin-2-one 55. Following representative procedure 6, **10** (360 mg, 0.85 mmol), TESCl (0.36 mL, 2.11 mmol), imidazole (288 mg, 4.23 mmol) and DMAP (10 mg, 0.09 mmol) in DMF (5 mL) furnished **55** (388 mg, 0.72 mmol, 85%) as a pale yellow oil after flash column chromatography.

R_f 0.31 [9:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}$=−5.32(c=0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.64 [6H, q, J=7.9 Hz, Si(CH_2CH$_3)_3$], 0.91 [3H, d, J=6.7 Hz, CH(C$H_3)_A$($CH_3)_B$], 0.97 [9H, t, J=7.9 Hz, Si(CH_2C$H_3)_3$], 0.95–0.99 [3H, m, CH($CH_3)_A$(C$H_3)_B$], 1.31 [3H, s, C(C$H_3)_A$($CH_3)_B$], 1.34 [3H, s, C($CH_3)_A$(C$H_3)_B$], 1.62–1.69 [1H, m, CH($CH_3)_2$], 2.62 [1H, dd, J=10.2, 14.6 Hz, CHCH_AH$_B$Ph], 2.86 [1H, dd, J=2.6, 14.6 Hz, CHCH$_A$$H_B$Ph], 3.937 [1H, dd, J=3.2, 6.5 Hz, CH(OTES)], 4.37 [1H, dd, J=2.6, 10.2 Hz, CHCH$_2$-Ph], 4.56 [1H, d, J=11.9 Hz, CHOCH_AH$_B$Ph], 4.67 [1H, d, J=11.9 Hz, CHOCH$_A$$H_B$Ph], 5.33 [1H, d, J=6.5 Hz, CHOCH$_2$Ph], 7.19–7.38 [10H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 5.3 [Si(CH_2CH$_3)_3$], 7.0 [Si(CH_2C$H_3)_3$], 16.7, 20.7 [CH(C$H_3)_2$], 22.3, 28.3 [C(C$H_3)_2$], 30.7 [CH($CH_3)_2$], 34.7 [CHCH_2Ph], 64.3 [CHCH$_2$Ph], 73.2 [CHOCH_2Ph], 78.3 [CHOTES], 79.8 [CHOCH_2Ph], 82.5 [C($CH_3)_2$], 126.7, 127.7 [*p-Ph*], 128.2, 128.3, 128.7, 129.0 [*m/o-Ph*], 137.0, 138.0 [*i-Ph*], 152.2 [C=O endocyclic], 172.4 [C=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1778, 1699 [C=O]; $C_{31}H_{45}NO_5Si$ requires C, 68.98; H, 8.40; N, 2.59%. Found C, 68.93; H, 8.63; N, 2.58%; HRMS $C_{31}H_{46}NO_5Si$ [MH^+] requires 540.3145. Found 540.3149; *m/z* ES+ 562 [100%, MNa^+].

3.10.48. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-(2-benzyloxy-5-methyl-3-triethylsilanoxy-hexanoyl)-5,5-dimethyl-oxazolidin-2-one 56. Following representative procedure 6, **11** (375 mg, 0.85 mmol), TESCl (0.36 mL, 2.13 mmol), imidazole (290 mg, 4.28 mmol) and DMAP (11 mg, 0.09 mmol) in DMF (6 mL) furnished **56** (400 mg, 0.72 mmol, 85%) as a pale yellow oil after flash column chromatography.

R_f 0.23 [9:1pentane/Et_2O]; $[\alpha]_D^{25}$=−4.6 (c=0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.52 [6H, q, J=7.9 Hz, Si(CH_2CH$_3)_3$], 0.86 [3H, d, J=6.6 Hz, CH(C$H_3)_A$($CH_3)_B$], 0.90 [3H, d, J=6.6 Hz, CH($CH_3)_A$(C$H_3)_B$], 0.93 [9H, t, J=7.9 Hz, Si(CH_2C$H_3)_3$], 1.30–1.37 [1H, m, CH_AH$_B$CH($CH_3)_2$], 1.35 [3H, s, C(C$H_3)_A$($CH_3)_B$], 1.39 [3H, s, C($CH_3)_A$(CH_3)$_B$], 1.42–1.48 [1H, m, CH$_A$$H_B$CH($CH_3)_2$], 1.63–1.69 [1H, m, CH_2CH($CH_3)_2$], 2.75 [1H, dd, J=9.9, 14.5 Hz, CHCH_AH$_B$-Ph], 2.98 [1H, dd, J=3.2, 14.5 Hz, CHCH$_A$$H_B$Ph], 4.07–

4.11 [1H, m, C*H*(OTES)], 4.41 [1H, dd, *J*=3.2, 9.9 Hz, C*H*CH$_2$Ph], 4.48 [1H, d, *J*=11.9 Hz, CHOC*H*$_A$H$_B$Ph], 4.56 [1H, d, *J*=11.9 Hz, CHOCH$_A$*H*$_B$Ph], 5.31 [1H, d, *J*=4.8 Hz, C*H*OCH$_2$Ph], 7.19–7.36 [10H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) 5.1 [Si(*C*H$_2$CH$_3$)$_3$], 7.0 [Si(CH$_2$*C*H$_3$)$_3$], 22.3, 22.4 [CH(*C*H$_3$)$_2$], 23.3, 28.4 [C(*C*H$_3$)$_2$], 24.0 [CH$_2$*C*H(CH$_3$)$_2$], 35.1 [CH*C*H$_2$Ph], 42.7 [*C*H$_2$CH(CH$_3$)$_2$], 64.2 [C*H*CH$_2$Ph], 71.8 [*C*H(OTES)], 72.9 [CHO*C*H$_2$Ph], 79.9 [C*H*OCH$_2$Ph], 82.6 [*C*(CH$_3$)$_2$], 126.7, 127.8 [*p-Ph*], 128.2, 128.4, 128.6, 129.1 [*m*/*o-Ph*], 137.0, 137.7 [*i-Ph*], 152.3 [*C*=O endocyclic], 171.5 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1778, 1702 [C=O]; $C_{32}H_{47}NO_5Si$ requires C, 69.40; H, 8.55; N, 2.53%. Found C, 69.43; H, 8.59; N, 2.55%; HRMS $C_{32}H_{48}NO_5Si$ [MH$^+$] requires 554.3302. Found 554.3298; *m*/*z* ES+ 576 [100%, MNa$^+$].

3.10.49. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-5-phenyl-pent-4-enoyl]-5,5-dimethyl-oxazolidin-2-one 57. Following representative procedure 6, **12** (300 mg, 0.62 mmol), TBDMSCl (375 mg, 2.48 mmol), imidazole (337 mg, 4.96 mmol) and DMAP (7 mg, 0.06 mmol) in DMF (5 mL) furnished **57** (361 mg, 0.60 mmol, 97%) as a pale yellow oil after flash column chromatography.

R_f 0.17 [9:1 30–40 °C petrol/Et$_2$O]; $[\alpha]_D^{25}$=+54.8 (*c*=0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.11 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.14 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.94 [9H, s, SiC(C*H*$_3$)$_3$], 0.95 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.24 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.65 [1H, dd, *J*=10.0, 14.6 Hz, CHC*H*$_A$H$_B$Ph], 2.87 [1H, dd, *J*=3.2, 14.6 Hz, CHCH$_A$*H*$_B$Ph], 4.32 [1H, dd, *J*=3.2, 9.9 Hz, C*H*CH$_2$Ph], 4.60 [1H, d, *J*=12.0 Hz, CHOC*H*$_A$H$_B$Ph], 4.60–4.63 [1H, m, C*H*(OTBDMS)], 4.71 [1H, d, *J*=12.0 Hz, CHOCH$_A$*H*$_B$Ph], 5.57 [1H, d, *J*=6.8 Hz, C*H*OCH$_2$Ph], 6.29 [1H, dd, *J*=7.5, 16.0 Hz, CH=CHPh], 6.56 [1H, d, *J*=16.0 Hz, CH=C*H*Ph], 7.19–7.42 [15H, m, Ph*H*]; δ_C (100 MHz, $CDCl_3$) −4.6, −4.5 [Si(*C*H$_3$)$_2$], 15.3 [Si*C*(CH$_3$)$_3$], 18.4, 28.0 [C(*C*H$_3$)$_2$], 25.9 [SiC(*C*H$_3$)$_3$], 35.1 [CH*C*H$_2$Ph], 63.7 [C*H*CH$_2$Ph], 73.7 [CHO*C*H$_2$Ph], 76.0 [*C*H(OTBDMS)], 80.6 [C*H*OCH$_2$Ph], 82.4 [*C*(CH$_3$)$_2$], 126.7 [*C*H=CHPh], 126.8, 127.8, 128.3, 128.5, 128.6, 128.7, 129.0 [*p*- and *m*/*o-Ph*], 132.3 [CH=*C*HPh], 136.4, 137.0, 137.8 [*i-Ph*], 152.2 [*C*=O endocyclic], 171.3 [*C*=O exocyclic]; ν_{max} (thin film, cm^{-1}) 1776, 1702 [C=O]; HRMS $C_{36}H_{45}NO_5SiNa$ [MNa$^+$] requires 622.2965. Found 622.2986; *m*/*z* ES+ 622 [100%, MNa$^+$].

3.10.50. Preparation of (2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-3″-(4‴-nitrophenyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 58. Following representative procedure 7, **13** (114 mg, 0.23 mmol), TBDMSOTf (0.31 mL, 1.36 mmol) and DMAP (134 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) furnished **58** (126 mg, 0.20 mmol, 88%) as a white solid after flash column chromatography.

R_f 0.26 [5:1 30–40 °C petrol/Et$_2$O]; mp 118–119 °C [petrol/Et$_2$O]; $[\alpha]_D^{22}$=+31.4 (*c*=0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.05 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.07 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.91 [9H, s, SiC(C*H*$_3$)$_3$], 0.92 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.21 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.59 [1H, dd, *J*=14.6, 10.0 Hz, CHC*H*$_A$H$_B$Ph], 2.79 [1H, dd, *J*=14.6, 2.9 Hz, CHCH$_A$*H*$_B$Ph], 4.17 [1H, dd, *J*=10.0, 2.9 Hz, C*H*CH$_2$Ph], 4.51 [1H, d, *J*=12.0 Hz, CHOC*H*$_A$H$_B$Ph], 4.60 [1H, d, *J*=12.0 Hz, CHOCH$_A$*H*$_B$Ph], 5.12 [1H, d, *J*=7.4 Hz, C*H*(OTBDMS)], 5.58 [1H, d, *J*=6.0 Hz, C*H*OCH$_2$Ph], 7.19–7.29 [10H, m, Ph*H*], 7.58 [2H, d, *J*=8.7 Hz, Ar*H*], 8.15 [2H, d, *J*=8.7 Hz, Ar*H*]; δ_C (100 MHz, $CDCl_3$) −5.0, −4.8 [Si(*C*H$_3$)$_2$], 18.2 [Si*C*(CH$_3$)$_3$], 22.2, 27.8 [C(*C*H$_3$)$_2$], 25.7 [SiC(*C*H$_3$)$_3$], 34.8 [CH*C*H$_2$Ph], 63.7 [*C*HCH$_2$Ph], 73.7 [CHO*C*H$_2$Ph], 75.7 [*C*H(OTBDMS)], 80.6 [*C*HOCH$_2$Ph], 82.5 [*C*(CH$_3$)$_2$], 126.9, 128.0 [*p-Ph*], 123.2, 128.3, 128.4, 128.6, 128.7, 128.9 [*m*/*o-Ph* and *m*/*o-Ar*], 136.6, 137.2 [*i-Ph*], 147.5, 147.6 [*p-Ar* and *i-Ar*], 151.9 [*C*=O endocyclic], 170.4 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1765, 1691 [C=O]; HRMS $C_{34}H_{46}N_3O_7Si$ [MNH$_4^+$] requires 636.3105. Found 636.310645; *m*/*z* CI+ (NH_3) 487 [80%, MH$^+$−OTBDMS], 636 [100%, MNH$_4^+$].

3.10.51. Preparation of (2′*S*,3′*S*,4*S*)-4-benzyl-3-(2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-furan-2″-yl-propionyl)-5,5-dimethyl-oxazolidin-2-one 59. Following representative procedure 6, **14** (1.78 g, 3.97 mmol), TBDMSCl (1.5 g, 9.93 mmol), imidazole (1.35 g, 19.85 mmol) and DMAP (52 mg, 0.4 mmol) in DMF (15 mL) furnished **59** (1.98 g, 3.51 mmol, 88%) as a white solid after flash column chromatography.

R_f 0.1 [10:1 pentane/Et$_2$O]; mp 76–77 °C [pentane/Et$_2$O]; $[\alpha]_D^{23}$=−17.0 (*c*=1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.04 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.11 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.84 [9H, s, SiC(C*H*$_3$)$_3$], 1.04 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.24 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 2.59 [1H, dd, *J*=14.6, 10.0 Hz, CHC*H*$_A$H$_B$Ph], 2.81 [1H, dd, *J*=14.6, 3.0 Hz, CHCH$_A$*H*$_B$Ph], 4.20 [1H, dd, *J*=10.0, 3.0 Hz, C*H*CH$_2$Ph], 4.65 [1H, d, *J*=11.9 Hz, CHOC*H*$_A$H$_B$Ph], 4.84 [1H, d, *J*=11.9 Hz, CHOCH$_A$*H*$_B$Ph], 5.07 [1H, d, *J*=7.8 Hz, C*H*(OTBDMS)], 5.75 [1H, *J*=7.8 Hz, C*H*OCH$_2$Ph], 6.28–6.32 [2H, m, Ar*H*], 7.19–7.38 [11H, m, Ar*H*]; δ_C (50 MHz, $CDCl_3$) −5.2, −4.9 [Si(*C*H$_3$)$_2$], 14.1 [Si*C*(CH$_3$)$_3$], 22.2, 28.0 [C(*C*H$_3$)$_2$], 25.7 [SiC(*C*H$_3$)$_3$], 34.9 [CH*C*H$_2$Ph], 63.7 [*C*HCH$_2$Ph], 70.5 [*C*H(OTBDMS)], 74.0 [CHO*C*H$_2$Ph], 79.3 [*C*HOCH$_2$Ph], 82.3 [*C*(CH$_3$)$_2$], 108.3, 110.4, 142.1 [*C*H furan], 126.7, 127.7 [*p-Ph*], 128.2, 128.6, 129.0 [*m*/*o-Ph*], 136.9, 137.9 [*i-Ph*], 157.7 [*i-Ar* furan], 153.0 [*C*=O endocyclic], 170.7 [*C*=O exocyclic]; ν_{max} (KBr disc, cm^{-1}) 1777 [C=O endocyclic], 1699 [C=O exocyclic]; $C_{32}H_{41}NO_6Si$ requires C, 68.18; H, 7.33; N, 2.48%. Found C, 68.11; H, 7.37; N, 2.51%; *m*/*z* ES+ 432 [80%, MH$^+$−OTBDMS], 586 [100%, MNa$^+$].

3.10.52. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-4-benzyl-3-[2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-1-hydroxy-octyl)-5,5-dimethyl-oxazolidin-2-one 60. Following representative procedure 5, **54** (775 mg, 1.37 mmol) and DIBAL (2.75 mL, 2.75 mmol) in CH_2Cl_2 (20 mL) furnished **60** (777 mg, 1.37 mmol, 100%) as a pale yellow oil.

$[\alpha]_D^{24}$=+11.1 (*c*=1.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 [3H, s, Si(C*H*$_3$)$_A$(CH$_3$)$_B$], 0.10 [3H, s, Si(CH$_3$)$_A$(C*H*$_3$)$_B$], 0.83 [9H, s, SiC(C*H*$_3$)$_3$], 0.84–1.03 [3H, m, CH$_2$CH$_2$CH$_2$-CH$_2$C*H*$_3$], 1.03 [3H, s, C(C*H*$_3$)$_A$(CH$_3$)$_B$], 1.16–1.35 [5H, m, CH$_2$C*H*$_A$H$_B$C*H*$_2$C*H*$_2$CH$_3$], 1.33 [3H, s, C(CH$_3$)$_A$(C*H*$_3$)$_B$], 1.40–1.49 [2H, m, C*H*$_A$H$_B$CH$_A$*H*$_B$CH$_2$CH$_2$CH$_3$], 1.68–1.77 [1H, m, CH$_A$*H*$_B$CH$_2$CH$_2$CH$_2$CH$_3$], 2.73 [1H, dd,

J=9.8, 14.8 Hz, CHCH_AH$_B$Ph], 3.23 [1H, dd, J=4.8, 14.8 Hz, CHCH$_A$$H_B$Ph], 3.87–3.91 [1H, m, C$H$OTBDMS], 4.00 [1H, dd, J=4.8, 9.8 Hz, CHCH$_2$Ph], 4.20 [1H, dd, J=3.7, 8.8 Hz, CHOCH$_2$Ph], 4.57 [1H, d, J=4.2 Hz, CH(OH)], 4.64–4.73 [2H, ABq, J=11.9 Hz, CHOCH_2Ph], 5.00 [1H, dd, J=4.2, 8.8 Hz, CH(OH)], 7.10 [2H, d, J=7.1 Hz, PhH], 7.20–7.39 [8H, m, PhH]; δ_C (100 MHz, $CDCl_3$) −4.9, −4.5 [Si(CH_3)$_2$], 14.0 [CH$_2$CH$_2$CH$_2$CH$_2$-CH_3], 17.9 [SiC(CH$_3$)$_3$], 22.2, 25.9 [C(CH_3)$_2$], 22.5, 25.9, 30.7, 31.8 [$CH_2CH_2CH_2CH_3$], 25.7 [SiC(CH_3)$_3$], 35.6 [CHCH_2Ph], 65.1 [CHCH$_2$Ph], 72.9 [CHOTBDMS], 73.0 [CHOCH_2Ph], 76.6 [CHOCH$_2$Ph], 79.5 [CH(OH)], 81.1 [C(CH$_3$)$_2$], 126.7, 127.9 [p-Ph], 128.0, 128.5, 128.7, 128.9 [m/o-Ph], 137.0, 138.1 [i-Ph], 157.0 [C=O]; ν_{max} (thin film, cm^{-1}) 1731 [C=O]; HRMS $C_{33}H_{51}NO_5SiNa$ [MNa$^+$] requires 592.3434. Found 592.3434; m/z ES+ 592 [100%, MNa$^+$], 452 [100%].

3.10.53. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(triethyl-silanoxy)-1-hydroxy-4′-methyl-pentyl)-5,5-dimethyl-oxazolidin-2-one 61. Following representative procedure 5, **55** (172 mg, 0.32 mmol) and DIBAL (0.64 mL, 0.64 mmol) in CH_2Cl_2 (10 mL) furnished **61** (168 mg, 0.31 mmol, 97%) as a clear colourless oil.

$[\alpha]_D^{25}$=+4.75 (c=0.61, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.67–0.71 [6H, m, Si(CH_2CH$_3$)$_3$], 0.90–1.00 [15H, m, Si(CH$_2$CH_3)$_3$ and CH(CH_3)$_2$], 1.09 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.26 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 1.94–2.02 [1H, m, CH(CH$_3$)$_2$], 2.69 [1H, dd, J=10.1, 14.9 Hz, CHCH_AH$_B$-Ph], 3.25 [1H, dd, J=4.5, 14.9 Hz, CHCH$_A$$H_B$Ph], 3.72 [1H, dd, J=3.6, 7.0 Hz, CH(OTES)], 4.06 [1H, dd, J=4.5, 10.1 Hz, CHCH$_2$Ph], 4.22 [1H, dd, J=3.6, 8.5 Hz, CHOCH$_2$Ph], 4.34 [1H, d, J=5.6 Hz, CH(OH)], 4.69–4.75 [2H, m, CHOCH_2Ph], 5.08 [1H, dd, J=5.6, 8.5 Hz, CH(OH)], 7.10 [2H, d, J=7.1 Hz, PhH], 7.18–7.39 [8H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 5.0 [Si(CH_2CH$_3$)$_3$], 6.9 [Si(CH$_2$$CH_3$)$_3$], 19.5, 20.2 [CH($CH_3$)$_2$], 22.2, 27.6 [C($CH_3$)$_2$], 30.0 [$CH$(CH$_3$)$_2$], 35.5 [CH$CH_2$Ph], 65.2 [$CHCH_2$Ph], 73.2 [CHO$CH_2$Ph], 77.3 [$CH$(OTES)], 78.3 [$CHOCH_2$Ph], 79.5 [$CH$(OH)], 81.3 [$C$(CH$_3$)$_2$], 126.6 [$p$-$Ph$], 127.7, 128.4, 128.6, 128.8 [1×p-Ph and m/o-Ph], 137.0, 138.2 [i-Ph], 157.1 [C=O]; ν_{max} (thin film, cm^{-1}) 1728 [C=O]; HRMS $C_{31}H_{51}N_2O_5Si$ [MNH$_4^+$] requires 559.3567. Found 559.3594; m/z ES+ 564 [100%, MNa$^+$].

3.10.54. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(triethyl-silanoxy)-1-hydroxy-5′-methyl-hexyl)-5,5-dimethyl-oxazolidin-2-one 62. Following representative procedure 5, **56** (340 mg, 0.61 mmol) and DIBAL (1.23 mL, 1.23 mmol) in CH_2Cl_2 (10 mL) furnished **62** (338 mg, 0.60 mmol, 99%) as a clear colourless oil.

$[\alpha]_D^{25}$=+11.0 (c=1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.53–0.62 [6H, m, Si(CH_2CH$_3$)$_3$], 0.85 [3H, d, J=6.4 Hz, CH$_2$CH(CH_3)$_A$(CH$_3$)$_B$], 0.90–0.96 [12H, m, Si(CH$_2$CH_3)$_3$ and CH$_2$CH(CH$_3$)$_A$(CH_3)$_B$], 1.12 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.28 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 1.33–1.40 [1H, m, CH_AH$_B$CH(CH$_3$)$_2$], 1.42–1.52 [1H, m, CH$_A$$H_B$-CH(CH$_3$)$_2$], 1.64–1.68 [1H, m, CH$_2CH$(CH$_3$)$_2$], 2.72 [1H, dd, J=9.3, 14.4 Hz, CHCH_AH$_B$Ph], 3.19 [1H, dd, J=4.4, 14.4 Hz, CHCH$_A$$H_B$Ph], 4.00–4.04 [2H, m, C$H$(OTES) and C$HCH_2$Ph], 4.21 [1H, dd, J=2.2, 7.8 Hz, CHOCH$_2$Ph], 4.55 [1H, s, CH(OH)], 4.62–4.71 [2H, ABq, J=11.9 Hz, CHOCH_2Ph], 4.93–4.96 [1H, m, CH(OH)], 7.11–7.38 [10H, m, PhH]; δ_C (100 MHz, $CDCl_3$) 4.8 [Si(CH_2CH$_3$)$_3$], 6.8 [Si(CH$_2$$CH_3$)$_3$], 22.0, 24.1 [C($CH_3$)$_2$], 22.2, 23.8 [CH$_2$CH($CH_3$)$_2$], 27.5 [CH$_2$-$CH$(CH$_3$)$_2$], 35.6 [CH$CH_2$Ph], 40.2 [$CH_2$CH(CH$_3$)$_2$], 65.2 [$CHCH_2$Ph], 70.6 [$CH$(OTES)], 73.0 [CHO$CH_2$Ph], 77.3 [$CHOCH_2$Ph], 79.6 [$CH$(OH)], 81.2 [$C$(CH$_3$)$_2$], 126.7, 127.9 [$p$-$Ph$], 128.1, 128.5, 128.7, 128.9 [m/o-Ph], 137.0, 138.0 [i-Ph], 157.0 [C=O]; ν_{max} (thin film, cm^{-1}) 1732 [C=O]; HRMS $C_{32}H_{49}NO_5Si$ [MH$^+$] requires 578.3278. Found 578.3278; m/z ES+ 578 [100%, MH$^+$].

3.10.55. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-4-benzyl-3-[2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-1-hydroxy-5-phenyl-pent-4-enyl]-5,5-dimethyl-oxazolidin-2-one 63. Following representative procedure 5, **57** (287 mg, 0.48 mmol) and DIBAL (0.96 mL, 0.96 mmol) in CH_2Cl_2 (10 mL) furnished **63** (280 mg, 0.47 mmol, 97%) as a pale yellow oil.

$[\alpha]_D^{25}$=+5.5 (c=1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.06 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.11 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.93 [9H, s, SiC(CH_3)$_3$], 1.13 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.26 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.69 [1H, dd, J=9.5, 14.8 Hz, CHCH_AH$_B$Ph], 3.18 [1H, dd, J=4.8, 14.8 Hz, CHCH$_A$$H_B$-Ph], 4.04 [1H, dd, J=4.8, 9.5 Hz, CHCH$_2$Ph], 4.30 [1H, dd, J=3.8, 8.4 Hz, CHOCH$_2$Ph], 4.31 [1H, s, CH(OH)], 4.59 [1H, app. t, J=4.6 Hz, CH(OTBDMS)], 4.72–4.79 [2H, ABq, J=11.8 Hz, CHOCH_2Ph], 4.93 [1H, d, J=8.1 Hz, CH(OH)], 6.30 [1H, dd, J=6.0, 16.1 Hz, CH=CHPh], 6.60 [1H, d, J=16.1 Hz, CH=CHPh], 7.07–7.42 [15H, m, PhH]; δ_C (100 MHz, $CDCl_3$) −5.1, −4.6 [Si(CH_3)$_2$], 18.1 [SiC(CH$_3$)$_3$], 22.1, 27.5 [C(CH_3)$_2$], 25.8 [SiC(CH_3)$_3$], 35.4 [CHCH_2Ph], 65.6 [CHCH$_2$Ph], 73.5 [CH(OTBDMS)], 73.7 [CHOCH_2Ph], 79.2 [CHOCH$_2$Ph], 79.5 [CH(OH)], 81.4 [C(CH$_3$)$_2$], 126.6 [CH=CHPh], 126.7, 127.4, 127.7 [p-Ph], 127.9, 128.1, 128.4, 128.5, 128.6, 128.8 [m/o-Ph], 131.8 [CH=CHPh], 136.6, 136.9, 137.1 [i-Ph], 157.1 [C=O]; ν_{max} (thin film, cm^{-1}) 1728 [C=O]; HRMS $C_{36}H_{47}NO_5$-SiNa [MNa$^+$] requires 624.31215. Found 624.3225; m/z ES+ 624 [100%, MNa$^+$].

3.10.56. Preparation of (1′*S*,2′*S*,3′*R*,4*S*)-benzyl-3-[2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-1′-hydroxy-3′-(4″-nitro-phenyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 64. Following representative procedure 5, **58** (75 mg, 0.12 mmol) and DIBAL (0.24 mL, 0.24 mmol) in CH_2Cl_2 (5 mL) furnished **64** (74 mg, 0.12 mmol, 99%) as a yellow solid.

Mp 82 °C [pentane/CH_2Cl_2]; $[\alpha]_D^{22}$=+14.8 (c=0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.14 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.07 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.91 [9H, s, SiC(CH_3)$_3$], 1.13 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.26 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 2.59 [1H, dd, J=14.8, 9.4 Hz, CHCH_AH$_B$Ph], 3.00 [1H, dd, J=14.8, 5.0 Hz, CHCH$_A$$H_B$Ph], 4.05 [1H, dd, J=9.4, 5.1 Hz, CHCH$_2$Ph], 4.24 [1H, d, J=11.5 Hz, CHOCH_AH$_B$-Ph], 4.28 [1H, d, J=9.6 Hz, CH(OH)], 4.28–4.30 [1H, m, CHOCH$_2$Ph], 4.58 [1H, d, J=11.5 Hz, CHOCH$_A$$H_B$Ph], 4.56–4.61 [1H, m, C$H$(OH)], 5.07 [1H, d, J=2.8 Hz, CH(OTBDMS)], 7.01–7.03 [2H, m, ArH], 7.16–7.33 [8H,

m, Ar*H*], 7.54 [2H, d, *J*=8.6 Hz, Ar*H*], 8.08–8.12 [2H, m, Ar*H*]; δ_C (100 MHz, $CDCl_3$) −5.3, −4.8 [Si(CH_3)$_2$], 18.2 [Si*C*(CH_3)$_3$], 22.1, 27.5 [C(*C*H_3)$_2$], 25.8 [SiC(*C*H_3)$_3$], 35.1 [CH*C*H_2Ph], 66.0 [*C*HCH_2Ph], 73.7 [*C*H(OTBDMS)], 74.1 [CHO*C*H_2Ph], 79.1 [*C*H(OH)], 80.4 [*C*HOCH_2Ph], 82.2 [*C*(CH_3)$_2$], 126.8, 127.8 [*p-Ph*], 123.1, 127.8, 128.4, 128.7 [*m/o-Ph*], 136.4, 137.4 [*i-Ph*], 147.3, 148.3 [*p-Ar* and *i-Ar*], 157.5 [*C*=O endocyclic]; ν_{max} (KBr disc, cm^{-1}) 3362 [O–H broad], 1718 [C=O].

X-ray crystal structure determination for **64**. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[22]

X-ray crystal structure data for **64** [$C_{34}H_{46}N_2O_8Si$]: *M*=638.83, orthorhombic, space group *P* 21 21 21, *a*=7.3881(1) Å, *b*=14.5390(3) Å, *c*=32.6682(7) Å, *V*=3509.07(11) Å^3, *Z*=4, μ=0.117 mm^{-1}, colourless plate, crystal dimensions=0.1×0.2×0.5 mm^3. A total of 9588 unique reflections were measured for $5<\theta<30$ and 4715 reflections were used in the refinement. The final parameters were wR_2=0.051 and R_1=0.040 [$I>3\sigma(I)$], Flack enantiopole=0.01(19).

The X-ray crystal structure of **64** showed that disorder was present within the crystal. The OTBDMS group was best modelled as disordered over two sites in a ratio of 0.62:0.38. The *O*-benzyl and 4-benzyl-5,5-dimethyloxazolidin-2-one fragments of the structure also contain some disorder which is reflected in the prolated ADPs for the atoms contained within these fragments.

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC234755. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.10.57. Preparation of (1′*S*,2′*S*,3′*S*,4*S*)-4-benzyl-3-[2′-benzyloxy-3′-(*tert*-butyl-dimethyl-silanyloxy)-1′-hydroxy-3′-furan-2-yl-propionyl]-5,5-dimethyl-oxazolidin-2-one 65. Following representative procedure 5, **59** (2.00 g, 3.55 mmol) and DIBAL (7.10 mL, 7.10 mmol) in CH_2Cl_2 (50 mL) furnished **65** (1.80 g, 3.18 mmol, 90%) as a very viscous pale yellow oil.

$[\alpha]_D^{23}$=−20.8 (*c*=0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.06 [3H, s, Si(CH_3)$_A$(CH_3)$_B$], 0.06 [3H, s, Si(CH_3)$_A$(CH_3)$_B$], 0.89 [9H, s, SiC(CH_3)$_3$], 1.12 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 1.19 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 2.62 [1H, dd, *J*=14.9, 10.4 Hz, CHCH_AH$_B$Ph], 3.25 [1H, dd, *J*=14.9, 4.1 Hz, CHCH_AH$_B$Ph], 4.10 [1H, dd, *J*=10.4, 4.1 Hz, C*H*CH_2Ph], 4.20 [1H, d, *J*=7.5 Hz, CH(O*H*)], 4.33 [1H, dd, *J*=7.5, 4.4 Hz, C*H*(OH)], 4.58–4.68 [2H, ABq, *J*=11.3 Hz, CHOCH_2Ph], 4.98–5.02 [2H, m, C*H*(OTBDMS) and C*H*OCH_2Ph], 6.30–6.35 [2H, m, C*H* furan], 7.04–7.38 [11H, m, Ar*H*]; δ_C (100 MHz, $CDCl_3$) −5.0, −5.3 [Si(*C*H_3)$_2$], 18.1 [Si*C*(CH_3)$_3$], 22.2, 27.7 [C(*C*H_3)$_2$], 25.7 [SiC(*C*H_3)$_3$], 35.3 [CH*C*H_2Ph], 35.4 [*C*H*C*H_2Ph], 69.2 [*C*H(OTBDMS)], 74.1 [CHO*C*H_2Ph], 78.6 [*C*HOCH_2Ph], 79.8 [*C*H(OH)], 81.8 [*C*(CH_3)$_2$], 108.1, 110.4, 141.8 [*C*H furan], 126.5, 127.7 [*p-Ph*], 128.1, 128.3, 128.6, 128.8 [*m/o-Ph*], 138.1, 137.0 [*i-Ph*], 153.4 [*i-Ar* furan], 157.2 [*C*=O endocyclic]; ν_{max} (thin film, cm^{-1}) 3402 [O–H broad], 1702 [C=O]; $C_{32}H_{43}NO_6Si$ requires C, 67.93; H, 7.66; N, 2.48%. Found C, 67.25; H, 7.31; N, 2.67%; *m/z* ES+ 452 [65%, MH^+−TBDMS], 583 [100%, MNH_4^+].

3.10.58. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-octanal 66. Following representative procedure 8, **60** (687 mg, 1.21 mmol) and K_2CO_3 (234 mg, 1.70 mmol) in MeOH/H_2O (v:v 4:1; 100 mL) furnished **66** (390 mg, 1.08 mmol, 89%) as a clear colourless oil and **4** (242 mg, 1.18 mmol, 98%) as a white solid after flash column chromatography.

R_f 0.38 [9:1 pentane/Et_2O]; $[\alpha]_D^{25}$=−4.4 (*c*=1.55, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 [3H, s, Si(CH_3)$_A$(CH_3)$_B$], 0.03 [3H, s, Si(CH_3)$_A$(CH_3)$_B$], 0.85–0.88 [3H, m, $CH_2CH_2CH_2$-CH_3], 0.87 [9H, s, SiC(CH_3)$_3$], 1.07–1.16 [1H, m, CH_2-CH_2CH_AH$_B$CH_2CH_3], 1.20–1.36 [6H, m, CH_AH$_B$CH_2CH_AH$_B$CH_2CH_3], 1.69–1.77 [1H, m, CH$_A$H$_B$-$CH_2CH_2CH_2CH_3$], 3.77 [1H, dd, *J*=1.3, 4.6 Hz, C*H*OCH$_2$-Ph], 3.90–3.94 [1H, m, C*H*(OTBDMS)], 4.50 [1H, d, *J*=12.1 Hz, CHOCH_AH$_B$Ph], 4.78 [1H, d, *J*=12.1 Hz, CHOCH$_A$H$_B$Ph], 7.31–7.37 [5H, m, Ph*H*], 9.78 [1H, d, *J*=1.3 Hz, C*H*O]; δ_C (100 MHz, $CDCl_3$) −4.7, −4.6 [Si(*C*H_3)$_2$], 14.0 [$CH_2CH_2CH_2CH_2$*C*H_3], 18.0 [Si*C*(CH_3)$_3$], 22.5, 25.3, 31.7, 33.1 [*C*H_2*C*H_2*C*H_2*C*H_2CH_3], 25.8 [SiC(*C*H_3)$_3$], 72.7 [CHO*C*H_2Ph], 73.2 [*C*H(OTBDMS)], 85.0 [*C*HOCH$_2$Ph], 128.0, 128.5 [*m/o-Ph*], 128.1 [*p-Ph*], 137.4 [*i-Ph*], 203.7 [*C*=O]; ν_{max} (thin film, cm^{-1}) 1734 [C=O]; *m/z* ES+ 91 [70%], 215 [100%], 257 [15%].

3.10.59. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(triethyl-silanoxy)-4-methyl-pentanal 67. Following representative procedure 8, **61** (168 mg, 0.31 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in MeOH/H_2O (v:v 4:1; 20 mL) furnished **67** (64 mg, 0.19 mmol, 61%) as a clear colourless oil and **4** (59 mg, 0.29 mmol, 93%) as a white solid after flash column chromatography.

R_f 0.42 [9:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}$=−28.8 (*c*=0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.54–0.61 [6H, m, Si(CH_2-CH_3)$_3$], 0.88 [3H, d, *J*=1.2 Hz, CH(CH_3)$_A$(CH_3)$_B$], 0.89 [3H, d, *J*=1.2 Hz, CH(CH_3)$_A$(CH_3)$_B$], 0.913–0.96 [9H, m, Si(CH_2CH_3)$_3$], 1.86–1.91 [1H, m, C*H*(CH_3)$_2$], 3.75–3.79 [2H, m, C*H*OCH$_2$Ph and C*H*(OTES)], 4.54 [1H, d, *J*=11.9 Hz, CHOCH_AH$_B$Ph], 4.73 [1H, d, *J*=11.9 Hz, CHOCH$_A$H$_B$Ph], 7.26–7.36 [5H, m, Ph*H*], 9.77 [1H, d, *J*=1.5 Hz, C*H*O]; δ_C (100 MHz, $CDCl_3$) 5.0 [Si(*C*H_2-CH_3)$_3$], 6.9 [Si(CH_2*C*H_3)$_3$], 17.7, 19.6 [CH(*C*H_3)$_2$], 30.9 [*C*H(CH_3)$_2$], 72.9, 85.5 [*C*HOCH$_2$Ph and *C*H(OTES)], 77.6 [CHO*C*H_2Ph], 128.1 [*p-Ph*], 128.3, 128.4 [*m/o-Ph*], 137.2 [*i-Ph*], 204.0 [*C*HO]; ν_{max} (thin film, cm^{-1}) 1732 [C=O]; HRMS $C_{19}H_{36}NO_3Si$ [MNH_4^+] requires 354.2464. Found 354.2465; *m/z* CI+ 354 [15%, MNH_4^+].

3.10.60. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(triethylsilanoxy)-5-methyl-hexanal 68. Following representative procedure 8, **62** (227 mg, 0.50 mmol) and K_2CO_3 (97 mg, 0.70 mmol) in MeOH/H_2O (v:v 4:1; 30 mL) furnished **68** (120 mg, 0.34 mmol, 69%) as a clear colourless oil and **4** (87 mg, 0.42 mmol, 85%) as a white solid after flash column chromatography.

R_f 0.23 [12:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-18.6$ (c=0.75, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.53–0.59 [6H, m, Si(CH_2CH$_3$)$_3$], 0.85 [3H, d, J=6.5 Hz, $CH_2CH(CH_3)_A(CH_3)_B$], 0.88 [3H, d, J=6.5 Hz, $CH_2CH(CH_3)_A(CH_3)_B$], 0.90–0.95 [9H, m, Si(CH$_2$CH_3)$_3$], 1.25–1.32 [1H, m, CH_AH_BCH(CH$_3$)$_2$], 1.47–1.54 [1H, m, CH$_2$CH(CH$_3$)$_2$], 1.57–1.64 [1H, m, CH$_A$$H_B$CH(CH$_3$)$_2$], 3.72 [1H, dd, J=1.4, 4.1 Hz, CHOCH$_2$Ph], 4.03–4.07 [1H, m, CH(OTES)], 4.51 [1H, d, J=12.1 Hz, CHOCH_AH_BPh], 4.79 [1H, d, J=12.1 Hz, CHOCH$_A$$H_B$Ph], 7.26–7.38 [5H, m, PhH], 9.78 [1H, d, J=1.4 Hz, CHO]; δ_C (100 MHz, $CDCl_3$) 4.9 [Si(CH$_2$CH$_3$)$_3$], 6.8 [Si(CH$_2$$CH_3$)$_3$], 22.1, 23.0 [CH$_2$-CH($CH_3$)$_2$], 24.1 [CH$_2$$C$H(CH$_3$)$_2$], 42.4 [$CH_2$CH(CH$_3$)$_2$], 71.4 [$C$H(OTES)], 72.8 [CHOC$H_2$Ph], 84.9 [$C$HOCH$_2$Ph], 128.1 [*p-Ph*], 128.2, 128.5 [*m*/*o-Ph*], 137.2 [*i-Ph*], 204.3 [CHO]; ν_{max} (thin film, cm^{-1}) 1734 [C=O]; *m*/*z* CI+ 368 [10%, MNH$_4^+$].

3.10.61. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(*tert*-butyl-dimethyl-silanoxy)-5-phenyl-pent-4-enal 69. Following representative procedure 8, **63** (270 mg, 0.45 mmol) and K_2CO_3 (87 mg, 0.63 mmol) in MeOH/H_2O (v:v 4:1; 30 mL) furnished **69** (114 mg, 0.29 mmol, 64%) as a clear colourless oil and **4** (86 mg, 0.42 mmol, 93%) as a white solid after flash column chromatography.

R_f 0.19 [12:1 30–40 °C petrol/Et_2O]; $[\alpha]_D^{25}=-24.8$ (c=0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 [6H, s, Si(CH_3)$_2$], 0.92 [9H, s, SiC(CH_3)$_3$], 3.84 [1H, dd, J=1.8, 4.9 Hz, CHOCH$_2$-Ph], 4.61 [1H, d, J=12.3 Hz, CHOCH_AH_BPh], 4.64–4.67 [1H, m, CH(OTBDMS)], 4.80 [1H, d, J=12.3 Hz, CHOCH$_A$$H_B$Ph], 6.33 [1H, dd, J=6.0, 16.0 Hz, CH=CHPh], 6.62 [1H, dd, J=0.9, 16.0 Hz, CH=CHPh], 7.26–7.39 [5H, m, PhH], 9.742 [1H, d, J=1.7 Hz, CHO]; δ_C (100 MHz, $CDCl_3$) −5.0, −4.5 [Si(CH$_3$)$_2$], 18.2 [SiC(CH$_3$)$_3$], 25.8 [SiC(CH$_3$)$_3$], 73.1 [CHOCH$_2$Ph], 73.8 [CH(OTBDMS)], 86.0 [CHOCH$_2$Ph], 126.6, 127.8, 128.0, 128.5, 128.6 [CH=CHPh, *p*-and *m*/*o-Ph*], 131.5 [CH=CHPh], 136.4, 137.3 [*i-Ph*], 202.6 [CHO]; ν_{max} (thin film, cm^{-1}) 1734 [C=O]; *m*/*z* CI+ 414 [15%, MNH$_4^+$].

3.10.62. Preparation of (2*S*,3*R*)-2-benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-3-4′-nitrophenyl-propional-dehyde 70. Following representative procedure 8, **64** (460 mg, 0.74 mmol) and K_2CO_3 (144 mg, 1.04 mmol) in MeOH/H_2O (v:v 4:1; 50 mL) furnished **70** (218 mg) as a yellow foam contaminated with <2% of an unknown compound and **4** (128 mg, 0.62 mmol, 84%) as a white solid after flash column chromatography.

R_f 0.25 [2:1 30–40 °C petrol/Et_2O]; δ_H (400 MHz, $CDCl_3$) −0.10 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.02 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.88 [9H, s, SiC(CH_3)$_3$], 3.85 [1H, dd, J=1.5, 4.1 Hz, CHOCH$_2$Ph], 4.40 [1H, d, J=12.2 Hz, CHOCH_AH$_B$Ph], 4.62 [1H, d, J=12.2 Hz, CHOCH$_A$$H_B$Ph], 5.13 [1H, d, J=4.1 Hz, CH(OTBDMS)], 7.10–7.13 [2H, m, PhH], 7.26–7.27 [3H, m, PhH], 7.53 [2H, d, J=8.8 Hz, ArH], 8.16–8.19 [2H, m, ArH], 9.701 [1H, d, J=1.5 Hz, CHO]; δ_C (100 MHz, $CDCl_3$) −5.3, −4.8 [Si(CH$_3$)$_2$], 18.1 [SiC(CH$_3$)$_3$], 25.6 [SiC(CH$_3$)$_3$], 65.8 [CHOCH$_2$Ph], 74.6 [CH(OTBDMS)], 85.9 [CHOCH$_2$Ph], 123.3 [*p-Ph*], 127.9, 128.2, 128.5, 128.6 [*m*/*o-Ph* and *m*/*o-Ar*], 136.5, 147.5 [*i-Ph* and *i-Ar*], 202.5 [CHO]; ν_{max} (KBr disc, cm^{-1}) 1734 [C=O]; HRMS $C_{22}H_{33}N_2O_5Si$ [MNH$_4^+$] requires 433.2159. Found 433.2166; *m*/*z* CI+ 433 [12%, MNH$_4^+$].

3.10.63. Preparation of (2*S*,3*S*)-2-benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-3-furan-2-yl-propionaldehyde 71. Following representative procedure 8, **65** (1.9 g, 3.39 mmol) and K_2CO_3 (656 mg, 4.75 mmol) in MeOH/H_2O (50 mL) furnished **71** (1.04 g, 2.88 mmol, 85%) as a clear colourless oil and **4** (625 mg, 3.05 mmol, 90%) as a white solid after flash column chromatography.

$[\alpha]_D^{25}=-92.4$ (c=0.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) −0.07 [3H, s, Si(CH_3)$_A$(CH$_3$)$_B$], 0.03 [3H, s, Si(CH$_3$)$_A$(CH_3)$_B$], 0.87 [9H, s, SiC(CH_3)$_3$], 4.03 [1H, dd, J=5.4, 1.5 Hz, CHOCH$_2$Ph], 4.57–4.70 [2H, ABq, J=12.1 Hz, CHOCH_2Ph], 5.02 [1H, d, J=5.4 Hz, CH(OTBDMS)], 6.31–6.36 [2H, m, ArH], 7.27–7.39 [6H, m, ArH], 9.69 [1H, d, J=1.5 Hz, CHO]; δ_C (100 MHz, $CDCl_3$) −5.3, −5.1 [Si(CH$_3$)$_2$], 18.2 [SiC(CH$_3$)$_3$], 25.6 [SiC(CH$_3$)$_3$], 69.1 [CHOCH$_2$Ph], 73.1 [CHOCH$_2$Ph], 85.3 [CH(OTBDMS)], 108.5, 110.4, 142.2 [CH (furan)], 128.0 [*p-Ph*], 128.4 [*m*/*o-Ph*], 137.2 [*i-Ph*], 152.6 [*i-Ar* furan], 201.4 [CHO]; ν_{max} (thin film, cm^{-1}) 1735 [C=O]; HRMS $C_{20}H_{32}NO_4Si$ [MNH$_4^+$] requires 378.2101. Found 378.2100; *m*/*z* CI+(NH$_3$) 246 [22%, MH$^+$−TBDMS,], 378 [100%, MNH$_4^+$].

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20. The ^{1}H NMR coupling constant $J_{C(1')H-C(2')H}$ in all *N*-1′-hydroxy-2′-benzyloxyoxazolidin-2-ones **25**-**28** and **60**-**65** arising from DIBAL reduction of the corresponding *O*-silyl protected aldol products was of a similar magnitude (J>7.5 Hz but <8.8 Hz where it could be established).
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First enantioselective synthesis of the novel antiinfective TAN-1057A via its aminomethyl-substituted dihydropyrimidinone heterocycle

Vladimir N. Belov,[a,b] Michael Brands,[c] Siegfried Raddatz,[d] Jochen Krüger,[d] Sofia Nikolskaya,[a,e] Viktor Sokolov[a,e] and Armin de Meijere[a,b,*]

[a]*Institut für Organische und Biomolekulare Chemie, Georg-August Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany*
[b]*KAdemCustomChem GmbH, Brombeerweg 13, D-37077 Göttingen, Germany*
[c]*BAYER Corporation, Pharmaceutical Division, 400 Morgen Lane-B 27, West Haven, CT 06516-4175, USA*
[d]*Pharma Research Center, Bayer HealthCare AG, D-42096 Wuppertal, Germany*
[e]*Department of Chemistry, St. Petersburg State University, Universitetskii Pr. 26, 198504 St. Petersburg, Petrodvorets, Russian Federation*

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Dedicated to Professor Dieter Seebach

Abstract—Enantiomerically pure N^2-*Z*-N^2-MeAsnOH [(*S*)-**14**], prepared in 8 steps (23% overall yield) from asparaginic acid, was first subjected to a Hofmann degradation with $PhI(OCOCF_3)_2$ yielding (*S*)-N^2-*Z*-N^2-methyl-2,3-diaminopropanoic acid [N^2-*Z*-N^2-Me-*L*-A_2pr, (*S*)-**15**], and this in turn was protected to give N^2-*Z*-N^3-Boc-N^2-Me-*L*-A_2pr [(*S*)-**17**]. Condensation of (*S*)-**17** with HN=C(SMe)NHCONH$_2$ followed by removal of the *tert*-butoxycarbonyl protecting group, cyclization and hydrogenolytic removal of the Z-group gave the heterocycle of TAN-1057A [(*S*)-**1**] with an e.e. of 87 in 36% yield [from (*S*)-**14**]. Coupling of (*S*)-**1** with (*S*)-tris-Z-β-homoarginine (**20a**) in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and iPr_2NEt in *N*,*N*-dimethylacetamide followed by hydrogenolysis afforded the most active A-diastereomer of the natural antibiotic TAN-1057 in 52% yield (from (*S*)-**1** and **20a**). Similarly, starting from (*S*)-**1**, a single diastereomer of the potent, less toxic TAN-1057A analogue **22b** with a β-lysine side chain has been prepared. All described synthetic steps do not require column chromatography for purification of the products.

1. Introduction

A mixture of diastereomers of the very potent antibiotics TAN-1057A/B was first isolated by Japanese scientists at the Takeda company from the culture broth of *Flexibacter* sp. PK-74.[1] These compounds were found to be highly active against methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[1,2] Both main components of this mixture were found to be dipeptides with an (*S*)-β-homoarginine side chain attached to a dihydropyrimidinone heterocyclic moiety.[2] The Takeda group succeeded in separating the natural diastereomeric mixture of TAN-1057A/B (6.0 g) into two fractions and isolated TAN-1057A (1.56 g) and TAN-1057B (5 mg) as dihydrochlorides.[2]

The absolute configurations at C-5 for both epimers of TAN-1057A/B were assigned on the basis of the similarities in the CD spectra which were recorded for the product obtained by mild hydrolysis (2% aq. Na_2CO_3, 70 °C, 1 h) of TAN-1057A (acyclic dipeptide **2**), and the model compound **3** with its known (*S*)-configuration at C-2 (Fig. 1).[2]

(*S*)-Configuration of C-5 in the heterocyclic portion of the molecule was assigned to TAN-1057A, while (*R*)-configuration of C-5 was attributed to TAN-1057B. Epimerization at C-5 in TAN-1057A occurs in MeOH in the presence of MeONa, or during heating in aqueous HCl. Acidic degradation of the molecule yields derivatives of *N*-methyl-2,3-diaminopropionic acid, a constituent amino acid of the TAN-1057 heterocycle.

The first successful synthesis of TAN-1057A/B in which an attempt to prepare TAN-1057A as a single diastereomer was made, instead resulted in a diastereomeric mixture of TAN-1057A and B due to the lability of the 2,3-diaminopropionic acid to epimerization.[3] Before embarking on the present study, it was not clear, whether this stereogenic center is configurationally stable enough to allow for a total synthesis of the enantiomerically pure material in vitro.

Keywords: Total synthesis; Amino acids; Chiral pool; Nitrogen heterocycles; Natural products.
* Corresponding author. Tel.: +49-551-393231; fax: +49-551-399475; e-mail address: armin.demeijere@chemie.uni-gottingen.de

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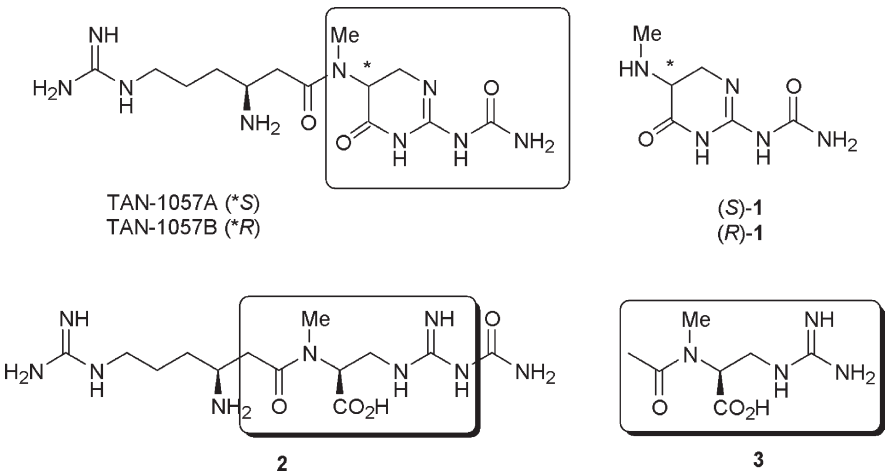


Figure 1. Structures and absolute configurations of TAN-1057A/B and the dihydropyrimidinone derivative **1** contained therein.

Up to now, most of the unique biological activity data have been determined for the diastereomeric mixture of TAN-1057A,B. For example, no cross-resistance between TAN-1057A,B and methicillin, erythromycin and gentamycin was found. TAN-1057A was shown to be by a factor of 2–4 more potent against Gram-positive and Gram-negative bacteria than TAN-1057B.[1,2] TAN-1057A is efficient against all of the MRSA strains evaluated, and was found to compare very favorably to vancomycin in an in vivo infection model.[1] Therefore, for further tests it was deemed necessary to elaborate a stereoselective access to either diastereomer of TAN-1057. This synthetic procedure should also be applicable for the facile preparation of diastereomerically pure analogues of TAN-1057[4] with improved properties (more active, less toxic) and therefore might lead to the discovery of new therapeutically useful drugs. We have reported convenient, convergent syntheses of TAN-1057 A/B and its analogues with various side chains[4b–e] utilizing the heterocycle **1** as a starting material.[5]

In designing a synthetic strategy towards the enantiomerically pure heterocycle (*S*)-**1**, the known facile racemization of N^2-methyl-2,3-diaminopropionic acid derivatives had to be taken into account,[3] therefore a reliable approach to the suitably protected N^2-methyl-2,3-diaminopropionic acid (N^2-Me-*L*-A_2pr) in enantiomerically pure form was the key issue.

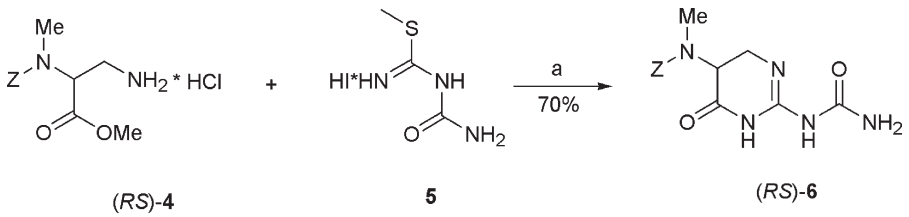
2. Results and discussion

2.1. Enantioselective synthesis of the heterocycle in TAN-1057A

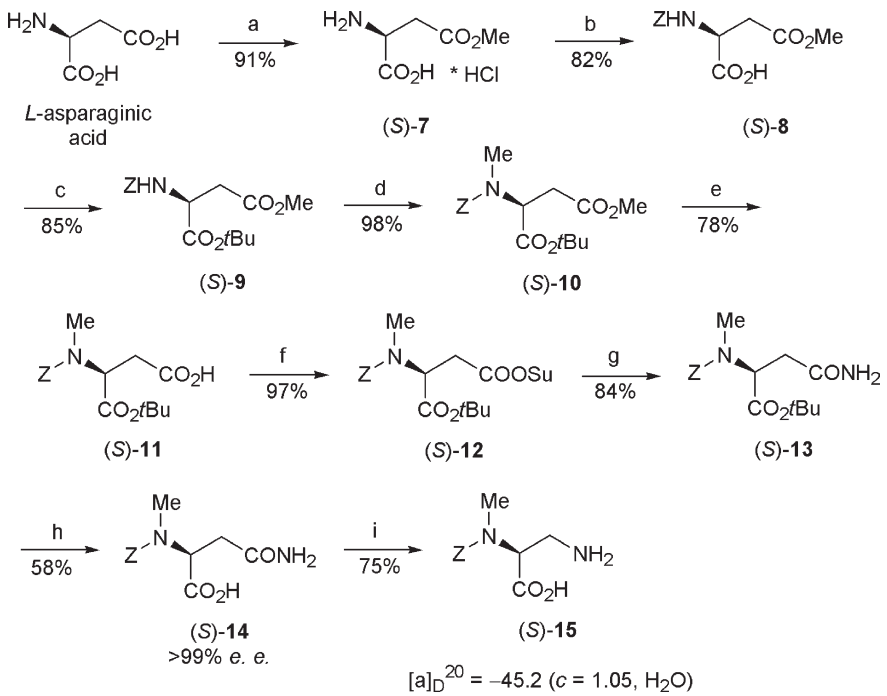
The racemic heterocycle (*RS*)-**1** was prepared by condensation of N^2-Z-N^2-Me-A_2prOMe [(*RS*)-**4**] with 2-methyl-2-thiopseudobiuret hydroiodide (**5**) and subsequent removal of the Z-protecting group from the resulting (*RS*)-**6** (Scheme 1) by hydrogenolysis.[5]

With a similar approach to the enantiomerically pure heterocycle (*S*)-**1** in mind, optically pure N^2-Z-*L*-A_2pr and N^2-Boc-*L*-A_2pr were prepared from the correspondingly protected asparagines.[7] In order to be able to create the 2,3-diaminopropionic acid fragment at a later step of the synthesis, N^2-Z-N^2-Me-*L*-AsnOH was needed. Selective N^2-methylation of asparagine is not possible, unless the amido group ($CONH_2$) is blocked. Therefore, the simplest way to overcome this difficulty was to use the aspartic acid with an appropriate protection which discriminates the two carboxyl groups, and then, after performing the mono *N*-methylation, to transform the terminal carboxyl group into its corresponding amide. Thus, *L*-aspartic acid was first converted into Z-*L*-Asp(OMe)OH [(*S*)-**8**][8] which was then protected by the formation of the *tert*-butyl ester (*S*)-**9** (Scheme 2).[9]

N-Methylation of (*S*)-**9** was achieved with methyl iodide in DMF in the presence of silver(I) oxide as a base according to the known method.[10] As stated in the original publication, no racemization was detected under these conditions. Nevertheless, due to the strong basicity of Ag_2O, this step as well as the next one, are the most dangerous in this respect. Saponification of the methyl ester (*S*)-**10** was performed carefully by slow addition of a slight excess of lithium hydroxide solution at +5 °C. The acid (*S*)-**11** may be converted into the amide (*S*)-**13** in a one pot operation by treatment first with *N*-hydroxybenzotriazole (HOBt) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) in THF at 0 °C, and then with conc. aq. NH_3. However, it is



Scheme 1. Improved conditions of the one-step cyclization to the racemic heterocycle (*RS*)-**10**: (a) AcONa, MeCN, 55 °C, 48 h.[6]



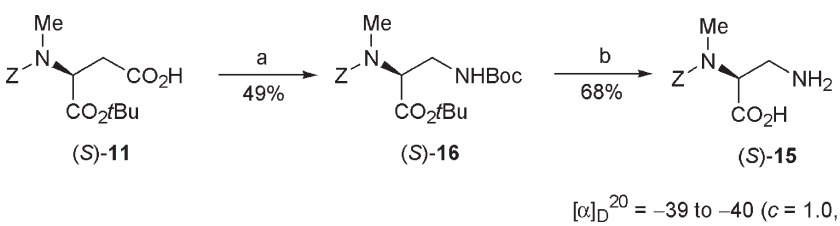
Scheme 2. Stereoselective synthesis of N^2-benzyloxycarbonyl-N^2-methyl-*L*-asparagine (N^2-Z-N^2-Me-*L*-AsnOH, (*S*)-**14**) and (*S*)-3-amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)aminopropionic acid (N^2-Z-N^2-Me-*L*-A_2pr, (*S*)-**15**): (a) $SOCl_2$, MeOH, −10→+20 °C, 25 min; (b) ZCl, MgO, H_2O/ether, +5 °C, 6 h; (c) isobutene, conc. H_2SO_4, CH_2Cl_2, 20 °C, 48 h; (d) MeI (7 equiv.), Ag_2O (1.02 equiv.), DMF, 20 °C, 7 h; (e) LiOH (1.0 equiv.), MeOH/H_2O, +5→20 °C; (f) *N*-hydroxysuccinimide (1.1 equiv.), EtOAc, DCC (1.1 equiv.) in dioxane, +5 °C, overnight; (g) aq. NH_3, THF, 0 °C; (h) TFA, CH_2Cl_2, 20 °C, 4 h; (i) $PhI(OCOCF_3)_2$, DMF/H_2O, pyridine, 20 °C, 16 h.

better to first transform (*S*)-**11** into the crystalline *O*-succinimidyl ester (*S*)-**12**. With this, two goals were achieved: firstly, the ester (*S*)-**12** could be easily purified by recrystallization from a dioxane/ether mixture, and, secondly, the ω-carboxyl group was activated for subsequent conversion to the amide. Afterwards, the α-carboxyl group in (*S*)-**13** was deprotected under standard conditions, and the key intermediate N^{α}-Z-N^{α}-MeAsnOH [(*S*)-**14**] was isolated. In several experiments the enantiomeric excess of the crude (*S*)-**14** was always found to be about 77% (HPLC analysis on a chiral stationary phase; see Section 4 for details). Therefore, considerable racemization must have taken place at an earlier stage. Luckily, the optical purity could easily be restored after recrystallization from an *i*PrOH/EtOAc mixture. The racemic mixture (*RS*)-**14** (mp 160–162 °C) is much less soluble in *i*PrOH and water, and therefore the soluble fraction contains mostly the material with high enantiomeric excess. By this procedure, optically pure (*S*)-**14** (>99% e.e.) was obtained in 58% yield after one or two recrystallizations (mp 129 °C). When this work was completed, a general approach to *N*-methylamino acids by way of intermediate 5-oxazolidinones appeared in print.[11]

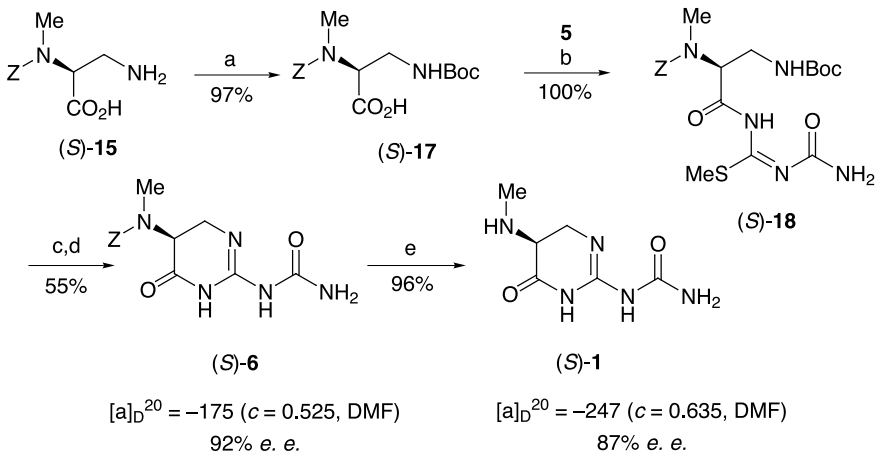
By this published approach, compound (*S*)-**14** has been prepared in only 4 steps.[11a] However, two of these four steps require column chromatography, certainly a drawback, when scale-up would be required.[12]

Direct amidation of the methyl ester (*S*)-**10** with methanolic ammonia was found to be difficult, as it required prolonged heating at about 100 °C, or the reaction with liquid ammonia at room temperature.[13] Due to the high probability of racemization, these reactions were not tried on a preparative scale. Hofmann degradation of the amide (*S*)-**14** proceeded under the same conditions as for the racemic compound[5] and for N^2-Z(Boc)-*L*-AsnOH,[7] and thus the 2,3-diaminopropionic acid fragment in the target compound (*S*)-**15** was created.

An attempt to synthesize (*S*)-**15** along a shorter route was made (Scheme 3). Curtius degradation of the azide which was generated from the acid (*S*)-**11** and *O*,*O*-diphenylphosphoryl azide (DPPA) in the presence of *t*BuOH led to the Boc-protected amino ester (*S*)-**16**. After purification by chromatography on silica gel, it was isolated in moderate



Scheme 3. Preparation of N^2-Z-N^2-Me-*L*-A_2pr [(*S*)-**15**] through Curtius degradation of (*S*)-**11**: (a) DPPA (1.1 equiv.), Et_3N (1 equiv.), *t*BuOH, 80 °C, 17 h; (b) TFA, 0 °C.



Scheme 4. Enantioselective synthesis of the heterocycle (*S*)-**1**: (a) 1.3 M aq. NaOH, Boc_2O, *t*BuOH; (b) HOBt, EDC, *N*,*N*-diisopropylethylamine (DIEA), CH_2Cl_2; (c) TFA, anisole, CH_2Cl_2, 20 °C; (d) Et_3N, AcOH (pH 8–9); (e) H_2, Pd/C, *N*,*N*-dimethylacetamide (DMAA).

yield and transformed directly to the amino acid (*S*)-**15** by simultaneous removal of both *tert*-butyl-containing protecting groups.

The optical purity of (*S*)-**15** obtained along this route was lower: it was necessary to recrystallize it twice from an EtOH/H_2O mixture in order to get an optical rotation value which was similar to that obtained earlier ($[\alpha]_D^{20}=-43.5$ versus −45.2 (Scheme 2), $c=1$, H_2O). Lower optical purity, higher losses during recrystallizations, the moderate yield of the intermediate (*S*)-**16**, and the necessity to purify it by column chromatography render this route inappropriate.

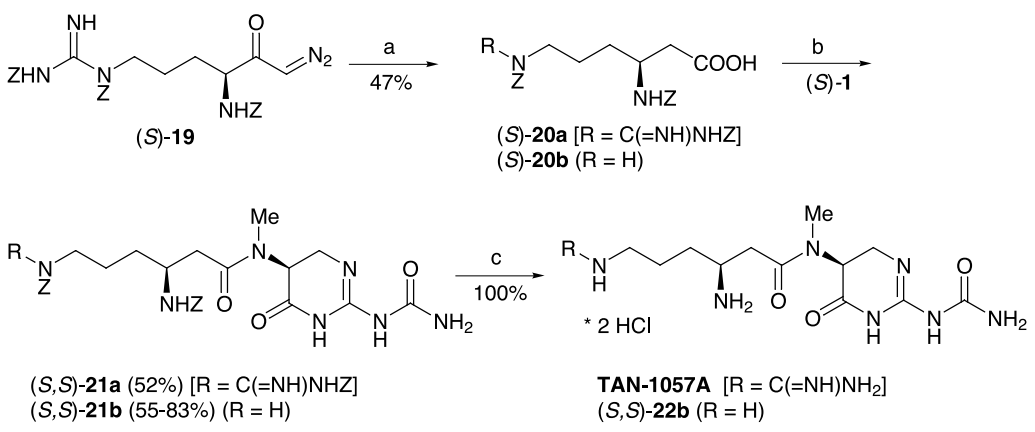
Surprisingly, esterification of (*S*)-**15** in methanol with thionyl chloride (HCl and $(MeO)_2SO$) was accompanied by considerable epimerization, and the e.e. of the amino ester (*S*)-**4** was found to be only 30–50%. Probably, the strongly electron-withdrawing properties of the protonated primary amino group enhance the α-CH acidity at the stereogenic center adjacent to the ester group (which may also be protonated in the strongly acidic medium), and therefore, rapid racemization occurs.[14]

Since the preparation of the amino ester (*S*)-**4** with high enantiomeric excess failed, the direct one-step cyclization as worked out for the preparation of the racemic heterocycle (*RS*)-**6** could not be used (Scheme 1). Therefore, a two-step cyclization was employed (Scheme 4, cf.[3]).

The monoprotected diamino acid (*S*)-**15** was first orthogonally bisprotected, and then coupled with easily available *S*-methylisothiobiuret hydroiodide (**5**) to give the intermediate (*S*)-**15**. In **8** the nitrogen next to the methylthio group turned out to be more nucleophilic than any of the other two, thus it is not necessary to use a protected equivalent of the compound **5**, as reported by Williams et al.[3] In monothiobiuret **5**, the nucleophilicity of the nitrogen atom next to the MeS-group proved to be much higher than that of the other two nitrogens, and the selectivity of the coupling was very high. Removal of the Boc-protecting group from the coupling product (*S*)-**18** followed by cyclization under very mild basic conditions afforded (*S*)-**6** (e.e.=92%). Hydrogenolysis under ordinary conditions gave the desired heterocycle (*S*)-**1** with an enantiomeric excess of 87%. This means that in the six synthetic steps the enantiomeric excess did decrease, but not drastically.

2.2. Diastereoselective synthesis of TAN-1057A as well as an analogue with lower acute toxicity

The last task to complete the synthesis of TAN-1057A was



Scheme 5. Diastereoselective synthesis of TAN-1057A*2HCl and its analogue with a β-lysine side chain: (a) hν, dioxane/water, 30 °C, 2 h; (b) HATU, DIEA, DMAA, 20 °C; (c) MeOH, H_2, $PdCl_2$, 25 °C.

to connect the (*S*)-tris-Z-β-homoarginine (**20a**) with the enantiomerically enriched heterocycle (*S*)-**1** (Scheme 5). Towards this goal, the tris-Z-protected diazoketone **19**,[5] precursor to **20a**, was irradiated with a daylight lamp in a dioxane/water mixture to yield the acid **20a** (47%).[15]

Several coupling reagents were tried. Treatment with EDC (alone or in the presence of HOBt or 7-aza-1-hydroxybenzotriazole) failed to give the coupling product (*S*,*S*)-**21a**. The desired compound was prepared in high crude yield (84%) by using of 2 equiv. of HATU and DIEA. The coupling reaction was not accompanied by any detectable epimerization: the diastereomeric ratio of TAN-1057A/B in the crude product was about 93:7, virtually the same as the enantiomeric ratio of the starting heterocycle (*S*)-**1** with an e.e.=87%. The minor epimer was removed completely by recrystallization from dichloromethane. However, recrystallization was accompanied by considerable losses, so that the isolated yield of the pure A-diastereomer dropped to 52% from about 79% calculated from the crude yield of the 93:7 mixture. The purity of the recrystallized coupling product (*S*,*S*)-**21a** was confirmed by LC–MS and the elemental analysis.

Compound (*S*,*S*)-**21a** exists as a mixture of two amide rotamers which (in [D_6]DMSO) display two singlets of *N*-methyl groups in the ^{1}H NMR spectrum (600 MHz): a low-field broad resonance with higher intensity at 2.85 ppm, and another (sharp) resonance at 2.66 ppm. The 1:1 epimeric mixture (C-5) of the coupling product **21a** prepared from the racemic heterocycle (*RS*)-**1**[5] shows three singlets of *N*-methyl groups in the ^{1}H NMR spectrum: a low field resonance (2.85 ppm) and two closely positioned sharp singlets with δ=2.65 and 2.66 ppm. Each of them is ca. two times less intensive than the high-field singlet (2.66 ppm) for the A-diastereomer. Therefore, the degree of diastereomeric purity may easily be estimated by ^{1}H NMR spectroscopy. An attempted separation of **21a** by HPLC failed.

The final deprotection of (*S*,*S*)-**21a** by catalytic hydrogenation with $PdCl_2$ as a (pre)catalyst and a source of HCl necessary for the salt formation, was also found to occur without epimerization. The CD-spectrum of this sample was identical to that of HPLC-purified TAN-1057A reported earlier.[2] This rigorously proves the assignment of the absolute configuration at C-5 initially made by the Takeda group.[2] The absolute value of the optical rotation of pure TAN-1057A*2HCl found here is lower than that previously reported ($[\alpha]_D^{22}=-22.7$ versus -39.1,[2] c=0.53, H_2O).[16] However, this lower value cannot be explained with epimerization, though the B-epimer has $[\alpha]_D^{22}=+72.6$ (c=0.53, H_2O).[2] The diastereomeric purity of this current sample was established unequivocally by comparison of its ^{1}H NMR spectrum (600 MHz) with that of the epimeric mixture. There is a striking contrast between them. The synthetic sample has one set of signals; only the *N*-methyl group displays two sharp singlets of the two rotamers: at 3.12 ppm and a much less intensive one at 2.88 ppm. In the case of the epimeric mixture of TAN-1057A,B, nearly all the signals are doubled. The most convenient way to estimate the diastereomeric purity is by measuring the relative intensities of the two resolved singlets of the *N*-methyl group (near 3.1 ppm), as there is one signal for each epimer.

As has been reported previously,[4b–e] several novel analogues of TAN-1057A,B showed lower acute toxicity compared to the natural product, yet with concomitant retention of excellent anti-microbial activity. For example, the analogue of the compound (*S*,*S*)-**22b** (Scheme 5) first prepared from the racemic heterocycle (*RS*)-**6** and bis-Z-β-(*S*)-lysine (**20b**) as a 1:1 mixture of two diastereomers was shown to be at least 4 times less toxic than TAN-1057A/B (mice, i. p.), while in vivo anti-staphylococcal activity was nearly the same.[4b,d] Therefore the pure diastereomer (3′*S*,5*S*)-**21b** was synthesized by coupling the enantiomerically enriched heterocycle (*S*)-**1** (e.e.=75–87%) with bis-Z-β-(*S*)-lysine (**20b**). After recrystallization, the obtained product **21b** (55% yield) had de=85–90%. Final deprotection of (*S*,*S*)-**21b** was performed under the same conditions as for TAN-1057A. The CD-spectrum of (3′*S*,5*S*)-**22b** is very similar to that of TAN-1057A. The diastereomeric purity of this sample was also confirmed by ^{1}H NMR spectroscopy. As for TAN-1057A, there is only one set of signals including well-resolved sharp singlets of the *N*-Me group at 3.16 and 2.89 ppm (the latter is much less intense and indicates the presence of a small amount of the second amide rotamer).

3. Conclusion

The first synthesis of the chiral heterocycle of TAN-1057A with high enantiomeric purity has been accomplished. The overall yield was about 9% over 14 steps, starting from *L*-aspartic acid. The same methodology is in principle applicable for the synthesis of the (*R*)-enantiomer (*R*)-**1**. Starting from (*S*)-**1**, diastereomerically pure TAN-1057A was synthesized (5% yield over 16 steps), and thus the absolute configurations at C-5 in both natural diastereomers of TAN-1057 were rigorously confirmed. No chromatographic separations were necessary, therefore these synthetic procedures may easily be scaled-up. In addition, the route to numerous analogues with various side-chains is feasible (for example, compound (*S*,*S*)-**22b**). Enantiomerically pure orthogonally protected (*S*)-N^2-methyl-2,3-diaminopropionic acid (*S*)-**17** also is a valuable intermediate for the synthesis of other biologically active compounds.[17]

4. Experimental

4.1. General

Melting points (uncorrected) were determined in capillaries using a Büchi 510 apparatus. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets. ^{1}H NMR: Bruker AM 250 instrument (250 MHz), and VARIAN INOVA-600 spectrometer (600 MHz); ^{13}C (and DEPT) NMR: Bruker AM 250 at 62.9 MHz and Varian UNITY 300 at 75.5 MHz. All spectra are calibrated against tetramethylsilane as an internal standard (δ=0) or the signals of residual protons of deuterated solvents: 7.26 for $CHCl_3$, 2.50 for [D_5]DMSO and 3.30 for [D_3]MeOH. Multiplicities of signals are reported as follows: s=singlet, d=doublet, t=triplet,

q=quartet, quint=quintet, m_c=centrosymmetrical multiplet. Coupling constants (*J*) are given in Hz. EI-MS: Finnigan MAT 95 and Varian CH 5 spectrometers (70 eV). HPLC-MS: Hewlett–Packard 1100 instrument (Micromass Platform LCZ). HRMS: Micromass LCT (TOF MS, electrospray ionization, positive and negative modes). HPLC-MS parameters: column: Kromasil C 18; 50×2.1 mm; eluent A: 5 mL 70% $HClO_4$ in 1 L H_2O; eluent B. MeCN; 0–0.5 min: 98% A+2% B, 0.5–4.5 min: 2–90% B, 4.5–6.5 min: 10% A+90% B; UV-detection at 210 nm; column temp. 30 °C, flow rate 0.75 mL/min. Analytical TLC: Macherey-Nagel ready-to-use plates AluGram Sil G/UV_{254}. Detection under a UV-lamp at 254 nm, development with molybdatophosphoric acid solution (5% in EtOH) or 0.5% aq. $KMnO_4$. Column chromatography: Merck silica gel, grade 60, 230–400 mesh. Optical rotations were measured with a Perkin–Elmer polarimeter, and CD-spectra were recorded with a *J*-810 instrument (JASCO). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Georg-August Universität Göttingen. Solvents were purified according to standard procedures. Organic solutions were dried over $MgSO_4$. All reactions were carried out with magnetic stirring, unless otherwise stated.

4.1.1. *L*-Aspartic acid 3-methyl ester [(*S*)-7] and *N*-benzyloxycarbonyl-*L*-asparaginic acid 3-methyl ester [(*S*)-8]. The title compounds were prepared as described in the literature.[8] Unlike the authors of the original publication, we were not able to obtain a crystalline sample of (*S*)-**8** (reported mp 98 °C). Diester (*S*)-**9** was synthesized as reported,[9] $[\alpha]_D^{20}=-2.3$ (*c* 1.75, EtOAc); lit.:[9] $[\alpha]_D^{20}=-1.7$ (*c* 1.75, EtOAc). In the latter publication compound (*S*)-**8** is also described to be a colorless oil. The isothiuronium salt **5** was synthesized according to the known procedure.[18] Bis-Z-β-(*S*)-lysine **20b** was purchased from EMKA Chemical Enterprise, Ltd.

4.1.2. 1-*tert*-Butyl methyl (*S*)-*N*-benzyloxycarbonyl-*N*-methylaspartate (*N*-Z-*N*-MeAsp(OMe)O*t*Bu, (*S*)-10). To a solution of diester (*S*)-**9** (21.4 g, 63.4 mmol) and MeI (28.0 mL, 63.6 g, 448 mmol) in anhydrous DMF (100 mL), was added 15.0 g (64.7 mmol) of Ag_2O, and the black suspension was vigorously stirred at room temperature for 7 h. A small amount of the reaction mixture was worked-up (see below) and analyzed by means of TLC (eluent EtOAc/hexane, 1:4) or, better, NMR spectroscopy to determine, whether the reaction was complete; compound (*S*)-**9**: R_f=0.53; compound (*S*)-**10**: R_f=0.57. Dichloromethane (700 mL) was added to the reaction mixture, and it was filtered through Celite®. The filter cake was washed with dichloromethane (2×100 mL), and the combined organic solutions were washed with saturated aq. $Na_2S_2O_3$ or 10% aq. NaCN solution (2×100 mL) and water (8×100 mL). After drying, they were concentrated in vacuo, and the oily residue was kept at 0.01 mm Hg to remove traces of DMF, and compound (*S*)-**10** was isolated as a yellowish oil (21.8 g, 98%) and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.35/1.40∗ (s, 9H), 2.63–2.80 (m, 1H, C*H*H), 2.93/2.94∗ (s, 3H, *N*Me), 2.91–3.10 (m, 1H, CH*H*), 3.64/3.66∗ (s, 3H, OMe), 4.75 (m_c, 1H, CH), 5.03–5.25 (m, 2H, OCH_2), 7.28 (br. s, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.7∗/27.8 (Me), 33.5/34.4∗ (*N*Me), 34.9∗/36.3 (CH_2), 51.7∗/51.8 (OMe), 57.6/58.2∗ (CHN), 67.1/67.4∗ (OCH_2), 81.9∗/82.1 (C–O), 127.7 (CH), 127.9 (CH), 128.3 (CH), 136.5 (C), 156.01/156.07∗ (NC=O), 168.85∗/168.91 (C=O), 171.1/171.3∗ (C=O).

4.1.3. 1-*tert*-Butyl (*S*)-*N*-benzyloxycarbonyl-*N*-methylaspartate (*N*-Z-*N*-MeAspO*t*Bu, (*S*)-11). To a solution of diester (*S*)-**10** (102 g, 0.29 mol) in MeOH (0.8 L) kept in an ice-bath, was added dropwise within 4 h a solution of $LiOH^*H_2O$ (12.2 g, 0.29 mol) in water (200 mL). The mixture was left to warm up to room temperature. Most of the MeOH was evaporated in vacuo (bath temp. ≤35 °C), the residue was diluted with water (0.5 L) and extracted with ether (3×150 mL). The aqueous layer was acidified with cold 6 M HCl up to pH 3–4, and extracted with ether (3×200 mL). The organic layers were washed with brine, dried and evaporated to give 75.9 g (78%) of (*S*)-**11** as an oil. ^{1}H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.34/1.40∗ (s, 9H), 2.66–2.89 (m, 1H, C*H*H), 2.96 (s, 3H, *N*Me), 3.00–3.17 (m, 1H, CH*H*), 4.71 (q, 1H, *J*=6.6 Hz, CH), 5.04–5.21 (m, 2H, OCH_2), 7.31–7.39 (m, 5H), ~9.9 (br. s, 1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.7 (Me), 33.7 (*N*Me), 34.4∗/34.9 (CH_2), 57.5/58.2∗ (CHN), 67.4∗/67.6 (OCH_2), 82.3∗/82.4 (C–O), 127.7 (CH), 127.9 (CH), 128.5 (CH), 130.4/136.4∗ (C), 155.9/156.3∗ (NC=O), 168.7/168.8∗ (C=O), 176.2/176.5∗ (C=O).

4.1.4. (*S*)-3-*tert*-Butoxycarbonyl-3-[(*N*-benzyloxycarbonyl-*N*-methyl)amino]propanoylsuccinimide (*N*-Z-*N*-MeAsp(OSu)O*t*Bu, (*S*)-12). To a solution of the ester (*S*)-**11** (8.94 g, 26.5 mmol) in EtOAc (50 mL) was added at +5 °C *N*-hydroxysuccinimide (3.35 g, 29.2 mmol) and then dropwise with ice-cooling a solution of *N*,*N*′-dicyclohexylcarbodiimide (6.00 g, 29.1 mmol) in 50 mL of dioxane. The reaction mixture was kept overnight at +5 °C. *N*,*N*-Dicyclohexylurea was removed by filtration, washed with dioxane (15 mL), and the filtrate was concentrated in vacuo to give 11.2 g (97%) of (*S*)-**12** as a solid. An analytical sample was recrystallized from dioxane–ether, mp 120–122 °C. Found C 57.81, H 6.19; calcd for $C_{21}H_{26}N_2O_8$ (434.43) C 58.06, H 6.03; ^{1}H NMR ($CDCl_3$, the signals of the major isomer are marked with ∗) δ 1.37/1.41∗ (s, 9H, Me), 2.81 (br. s, 3H, *N*Me), 3.00 (s, 4H, CH_2), 2.91–3.41 (m, 2H, CH_2), 4.61–4.75 (m, 1H, CH), 5.02–5.28 (m, 2H, CH_2O), 7.30–7.39 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major isomer are marked with ∗) δ 25.5 (CH_2), 27.7 (Me), 31.7∗/32.2 (CH_2), 34.2/34.4∗ (Me*N*), 57.5/58.3∗ (CHN), 67.4∗/67.6 (CH_2O), 82.7∗/82.9 (C–O), 127.8 (CH), 127.9 (CH), 128.4 (CH), 136.4 (C), 155.6/156.1∗ (NCO), 166.2/166.6∗ (CO), 167.9/168.0∗ (CO), 168.7/168.8∗ (CO).

4.1.5. N^2-Benzyloxycarbonyl-N^2-methyl-*L*-asparagine *tert*-butyl ester (N^2-Z-N^2-Me-*L*-AsnO*t*Bu, (*S*)-13). To a suspension of compound (*S*)-**12** (11.05 g, 25.4 mmol) in THF (100 mL) was added dropwise at 0 °C 4 mL of 25% aq. NH_3. The reaction mixture was stirred at room temperature overnight, filtered, and the filtrate was evaporated in vacuo.

The residue was dissolved in ether (200 mL), the solution was washed with 0.5 M aq. HCl (20 mL), H_2O (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). After drying and evaporation of the solvent, 7.15 g (84%) of the title compound was obtained as an oil which was used in the next step without further purification. ^1H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.38 (s, 9H, Me), 2.48–3.04 (m, CH_2), 2.96/2.99* (s, *N*Me, total intensity 5H), 4.49* (dd, J=5.8, 8.4 Hz, CH) and 4.68 (t, J=7.1 Hz, total intensity 1H, CH), 4.98–5.23 (m, 2H, CH_2O), 5.82/5.93*/6.00/6.22* (br. s, total intensity 2H, NH_2), 7.38 (br. s, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major isomer are marked with ∗) δ 27.8 (Me), 34.7*/35.2 (CH_2), 36.0*/36.5 (Me*N*), 58.3/59.5* (CHN), 67.2*/67.4 (CH_2O), 82.0*/82.8 (C–O), 127.7 (CH), 128.0 (CH), 128.5 (CH), 136.4 (C), 156.4 (NCO), 169.4 (CO), 172.7 (CO).

4.1.6. N^2-Benzyloxycarbonyl-N^2-methyl-*L*-asparagine (N^2-Z-N^2-Me-*L*-AsnOH, (*S*)-14). To a solution of N^2-Z-N^2-Me-*L*-AsnO*t*Bu (16.0 g, 47.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C TFA (30 mL), and the solution was stirred at room temperature for 4 h. Volatiles were evaporated in vacuo, the residue was triturated with anhydrous ether (200 mL) and kept at 0 °C overnight, until it solidified completely. After washing with anhydrous ether (3×100 mL) and drying in vacuo, 11.0 g of a colorless solid was obtained; $[\alpha]_D^{20}=-47.0$ (c 0.99, MeOH), e.e.= 77% (HPLC on a chiral stationary phase: poly(*N*-acyloyl-*L*-leucid-*d*-methylamide) grafted silica gel; column 250×20 mm, isohexane/THF=3:7, 1 mL/min; (*S*)-isomer: 7.75 min, (*R*)-isomer: 9.77 min). The solid was powdered and stirred in 2-propanol (100 mL) at 50–60 °C for 30 min with occasional sonification. The suspension was left overnight at room temperature and filtered through a sintered glass filter (No. 4). The filter cake was washed with EtOAc (20 mL), and the clear solution was evaporated in vacuo. The residue was recrystallized from 2-propanol and EtOAc mixture, and the solid which formed was collected by filtration to give 7.71 g (58%) of the title compound with $[\alpha]_D^{20}=-59.2$ (c 0.95, MeOH), e.e. ≥99%, mp 129 °C (dec.). An analytical sample was recrystallized once more from 2-propanol. Found C 56.08, H 5.75, N 9.84; calcd for $C_{13}H_{16}N_2O_5$ (280.27): C 55.71, H 5.75, N 9.99; $[\alpha]_D^{20}=-60.9$ (c 1.0, MeOH); lit.:[11a] $[\alpha]_D^{20}=-60.8$ (c 1.0, MeOH), mp 134–136 °C. The other spectra of (*S*)-**18** are identical to those of the racemate[5] and to the previously published ones.[11a]

4.1.7. (*S*)-3-Amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)-aminopropionic acid (N^2-Z-N^2-Me-*L*-A_2pr, (*S*)-15). The title compound was prepared in 75% yield from (*S*)-**14** as described for the racemate (*RS*)-**14**;[5] $[\alpha]_D^{20}=-45.2$ (c 1.05, water), mp 204 °C (dec., aq. EtOH). Found C 57.43, H 6.40, N 10.95; calcd for $C_{12}H_{16}N_2O_4$ (252.26) C 57.13, H 6.39, N 11.10. The spectra of (*S*)-**14** were identical to those of the racemate.[5]

4.1.8. *tert*-Butyl(*S*)-2-(*N*-benzyloxycarbonyl-*N*-methyl)-amino-3-(*tert*-butoxycarbonyl)amino-propionate (N^2-Z-N^2-Me-N^3-Boc-*L*-A_2pr*O*t*Bu, (*S*)-16). To a solution of compound **11** (1.69 g, 5.01 mmol) and Et_3N (0.51 g, 5.0 mmol) in 20 mL of anhydrous *t*BuOH was added under nitrogen DPPA (1.19 mL, 5.50 mmol). The reaction mixture was stirred at 80 °C for 17 h, diluted with ethyl acetate (200 mL), washed with 1% aq. solution of citric acid (30 mL), sat. aq. $NaHCO_3$ (50 mL), dried and evaporated. Chromatography on SiO_2 (60 g) eluting with an EtOAc/hexane mixture (1:4) gave 1.00 g (49%) of (*S*)-**16** as a colorless oil; R_f=0.75 (CH_2Cl_2/MeOH, 20:1). ^1H NMR ($CDCl_3$, the signals of the major rotamer are marked with ∗) δ 1.40 (s, 18H, 2×*t*Bu), 2.92 (s, 3H, *N*Me), 3.37/3.58* (m, 2H, CH_2), 4.42 (m, 1H, CH), 4.79/4.83* (m, 1H, NH), 5.00–5.23 (m, 2H, CH_2O), 7.29–7.35 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, the signals of the major rotamer are marked with ∗) δ 27.8 (Me), 28.2 (Me), 32.9*/33.2 (*N*Me), 39.2*/39.5 (CH_2), 59.9/60.4* (CH), 67.2*/67.4 (CH_2O), 79.3*/79.5 (CO), 82.0*/82.1 (CO), 127.6 (CH), 127.7 (CH), 128.4 (CH), 136.1 (C), 136.5 (C),155.8 (C), 155.9 (C), 156.2 (C), 157.0 (C), 168.7 (CO).

4.1.9. Reaction of compound (*S*)-16 with trifluoroacetic acid. A solution of (*S*)-**16** (1.00 g, 2.45 mmol) in TFA (5 mL) prepared at 0 °C, was stirred at room temperature for 1.5 h. Volatiles were evaporated in vacuo at room temperature, the residue was dissolved in water (10 mL), and 25% aq. NH_3 was added carefully until the pH value reached 7. The suspension was evaporated to dryness, and the solid residue was recrystallized from EtOH to give 0.423 g (68%) of (*S*)-**15** with $[\alpha]_D^{20}=-38.8$ (c 0.98, H_2O). In another run the $[\alpha]_D^{20}$ was found to be −40.2° (c 0.99, H_2O). A second recrystallization from aq. EtOH afforded 0.280 g (45%) of (*S*)-**19** with $[\alpha]_D^{20}=-43.5°$ (c 1.00, H_2O).

4.1.10. Methyl (−)-3-amino-2-(*N*-benzyloxycarbonyl-*N*-methyl)aminopropionate hydrochloride [(*S*)-4]. The title compound was prepared from 0.475 g (1.88 mmol) of (*S*)-**15** in anhydrous MeOH (5.6 mL) in the presence of 0.49 mL $SOCl_2$ as described before.[5] The reaction mixture was stirred at room temperature for 1.5 h and kept at +5 °C overnight. Crystallization from MeOH (5 mL) and ether (20 mL) gave 0.490 g of (*S*)-**4** (86%) with mp 171–172 °C (the racemate has mp 175–176 °C[5]) and $[\alpha]_D^{20}=-51.8$ (c 0.92, MeOH); e.e.≈55%. HPLC on Gromchiral AD; heptane/EtOH/TFA, 82:17:0.2, 0.2 mL/min; column 250×2 mm, R_t=11.82 min (*S*-isomer) and 14.87 min (*R*-isomer). The spectral data were found to be identical to these of the racemic compound.[5]

4.1.11. (*S*)-2-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-3-(*tert*-butoxycarbonylamino)propionic acid [(*S*)-17, N^2-Z-N^2-Me-N^3-Boc-*L*-A_2pr].[19] A suspension of (*S*)-**15** (0.660 g, 2.62 mmol) in 10 mL of water was cooled to 0 °C, and 2.0 mL of 1.3 M aq. NaOH was added dropwise followed by *t*BuOH (5 mL) and Boc_2O (0.661 g, 3.02 mmol). The cold bath was removed, and stirring was continued at room temperature. Gas evolution started after about 15 min, and the pH value gradually decreased. It was kept at about 9 by careful addition of sat. aq. Na_2CO_3 solution. The reaction was complete within 3.5 h. The reaction mixture was diluted with H_2O (20 mL), extracted with hexane (2×20 mL), and acidified at +5 °C with 5% aq. $KHSO_4$ (pH ≈2). Then it was extracted with ether (4×20 mL); the combined ether layers were washed with brine, dried, and evaporated to yield 0.90 g (97%) of (*S*)-**17** as a glass-like foam. The racemate (*RS*)-**17** was obtained

analogously from (*RS*)-**15**[5] and had mp 133–134 °C (EtOAc/PE). IR: ν=3384, 3328, 2940, 2863, 1690, 1634, 1540, 1518, 1450, 1382, 1363, 1319, 1271, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, signals of the major isomer are marked with *) δ 1.41* s/1.44 br. s ($\sum$ 9H, *t*Bu), 2.91/2.94* (s, $\sum$ 3H, Me*N*), 3.40 br. m/3.62* m ($\sum$ 2H, CH_2N), 4.48* t/4.60 br. m ($\sum$ 1H, CHN), 4.89/5.02* (br. t, $\sum$ 0.5H, NHCO), 5.12 br. s/5.16* s ($\sum$ 2H, CH_2O), 6.16*/6.23 (br. s, $\sum$ 0.5H, NHCO), 7.23–7.39 m (5H), 9.63 br. s (1H, COOH); ^{13}C NMR (62.9 MHz, $CDCl_3$, signals of the major isomer are marked with *) δ 28.3 (Me in *t*Bu), 33.1/33.4* (Me*N*), 39.2/39.5* (CH_2N), 59.6/60.1* (CHN), 61.7*/67.8 (CH_2O), 79.8 (C–O), 127.7, 127.9, 128.1, 128.5 (CH), 136.0/136.1* (C), 156.0, 156.9 (CONMe), 172.8 (COOH); ESI-MS (positive mode), *m/z* (rel. int., %) 727 (100) [2M+Na^+], 375 (24) [M+Na^+]. (*S*)-**17***DCHA salt was prepared from (*S*)-**17** and dicyclohexylamine in EtOAc and precipitated at +5 °C by addition of hexane; mp 120–121 °C; found C 64.98, H 8.76, N 7.61; calcd for $C_{29}H_{47}N_3O_6$ (533.71) C 65.26, H 8.88, N 7.87; $[\alpha]_D^{27}$=−3.9 (*c* 1.24, $CHCl_3$).

4.1.12. (*S*)-5-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-3,4,5,6-tetrahydro-2-ureidopyrimidin-4-one [(*S*)-6]. *Coupling product* **18**. To a suspension of (*S*)-**17** (0.900 g, 2.55 mmol) in CH_2Cl_2 (15 mL), was added *N*-hydroxybenzotriazole hydrate (0.430 g, 2.81 mmol), and the mixture was cooled to 0 °C. EDC (0.434 g, 490 μL, 3.16 mmol) was added dropwise, and the precipitate disappeared. Stirring was continued for 20 min at 0 °C, DIEA (645 mg, 825 μL, 4.99 mmol) was added dropwise followed by the compound **5** (1.30 g, 4.98 mmol). Stirring at 0 °C was continued for 15 min, and the clear solution was kept at +5 °C overnight. Then, CH_2Cl_2 (200 mL) was added, and the solution was washed with water (20 mL), 5% aq. $KHSO_4$ (20 mL), water (20 mL), 1% aq. $NaHCO_3$ (20 mL), and brine (20 mL). After drying and evaporation of the solvent, a semi-crystalline mass of the crude coupling product **18** was obtained (1.19 g, quantitative yield); R_f~0.5 (CH_2Cl_2/MeOH, 20:1, UV-active spot). $[\alpha]_D^{20}$=−17.0 (*c* 1.14, $CHCl_3$); IR: ν=3353, 2978, 1700, 1570, 1456, 1400, 1366, 1230, 1165, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, signals of the major isomer are marked with *) δ 1.39 (s, 9H, *t*Bu), 2.28/2.32* (s, $\sum$ 3H, Me*N*), 3.01 (s, 3H, Me*S*), 3.43/3.65* (m, 2H, CH_2N), 4.40 (br. t, 1H, CHN or NH), 4.57 (br. t, 1H, NH or CHN), 4.98 (m, 2H, NH_2), 5.08/5.20* (m, 2H, CH_2O), 5.42*/5.58 (br. s, 1H, NH), 7.32–7.39 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, the signals of the major isomer are marked with *) δ 14.3 (*S*Me), 28.26*/28.32 (Me), 33.2*/34.1 (br. Me*N*), 38.8*/39.2*/39.7 (br. *N*CH_2), 61.4*/63.3 (br. CHN), 67.2/67.9*/68.0* (br. CH_2O), 79.7/79.8 (br. C–O), 127.84, 127.9, 128.0, 128.2, 128.5*, 128.8 (CH), 135.8/136.2* (C), 155.5/155.7*, 156.8 (NCO), 163.3, 168.2/168.6/169.2* (CO). ESI-MS (positive mode), *m/z* (rel. int., %) 957 (100) [2M+Na^+], 490 (29) [M+Na^+].

*Deprotection and cyclization of the coupling product **18** to (S)-**6***

To a suspension of the semi-solid **18** (1.18 g, 2.55 mmol) in anisole (5 mL), was added at room temperature a mixture of CH_2Cl_2 (10 mL) and TFA (7.5 mL), and the solution was stirred for 2.5 h. When the deprotection reaction was complete (TLC), the solvents were evaporated in vacuo (0.1 mm Hg) at room temperature, the residue was triturated with anhydrous ether (2×15 mL, with decantation) and dried in vacuo (0.01 Torr). Then it was suspended in CH_2Cl_2, and Et_3N (399 mg, 550 μL, 3.95 mmol) was added at 0 °C. Slow gas evolution was observed, and a precipitate started to form. A sheet of wet indicator paper introduced into the head space of the reaction flask indicated that the pH was about 11. A few small drops of glacial AcOH were added, until the pH value (measured in the same way) reached 8–9. Stirring at room temperature was continued overnight. The solvent was evaporated in vacuo, 10 mL of water was added, and the suspension was sonificated in an ultra-sound bath (30 s). The precipitate was removed by filtration, washed with H_2O (10 mL), cold MeOH (2×5 mL), ether (5 mL), and dried in vacuo to give 447 mg (55%) of (*S*)-**6**, $[\alpha]_D^{20}$=−175 (*c* 0.525, DMF), e.e.=92%; column: Chiralpak AS (250×4.6 mm), eluent: heptane/ethanol (1:1), 1 mL/min; (*R*)-isomer: 6.82 min, (*S*)-isomer: 8.78 min. The spectral data were identical to those of the racemate.[5] In another run a product with $[\alpha]_D^{20}$=−157 (*c* 0.545, DMF) was obtained in 65% yield. A sample of this product (464 mg) was suspended in 15 mL of DMAA with sonification and warming at 30 °C. The insoluble fraction was removed by filtration (35 mg after washing with ether and drying), and the solution was used in the next step (see below). (*S*)-**1** was obtained with practically the same e.e. (86%). This simple way to increase the e.e. is based on the fact that the solubility of the racemate (*RS*)-**6** is much lower than that of (*S*)-**6**.

4.1.13. (*S*)-3,4,5,6-Tetrahydro-5-methylamino-2-ureidopyrimidin-4-one [(*S*)-1]. To a solution of (*S*)-**6** (360 mg, 1.62 mmol, e.e.=92%) in 15 mL of anhydrous *N*,*N*-dimethylacetamide (DMAA) was added 200 mg of 10% Pd/C. (Merck, oxidized form). The reaction mixture was flushed with N_2, then with hydrogen, and stirred at room temperature. A rapid consumption of H_2 (from a balloon attached to the reaction flask) was observed. After 1.5 h, the reaction was complete (detection by TLC (CH_2Cl_2/MeOH, 1:1); R_f of (*S*)-**6**~0.9, R_f of (*S*)-**1**~0.5). The suspension was filtered through Celite®, the filter cake was washed with DMAA (3×3 mL), and the filtrate was evaporated in vacuo (bath temp. 30–40 °C, 0.01 mm Hg). The residue was triturated with anhydrous ether (10 mL), the solid residue was filtered off, washed with anhydrous ether (10 mL), and dried to give 200 mg (96%) of (*S*)-**1**, $[\alpha]_D^{20}$=−247 (*c* 0.635, DMF), e.e.=87%; column: Chiral AS (250×2 mm); heptane/EtOH/Et_2NH, 65:34.8:0.2; 0.25 mL/min; (*S*)-isomer: 6.63 min, (*R*)-isomer: 8.78 min.

4.1.14. (*S*)-N^{β},N^{ε},N^{ω}-Tris(benzyloxycarbonyl)-β-homoarginine [(*S*)-20a].[15] To a solution of the diazoketone (*S*)-**19** (22.2 g, 37.0 mmol) in 250 mL of dioxane was added 18 mL of water. The solution was cooled in an ice bath and irradiated for 2 h with a 300 W daylight lamp (the internal temp. was about 30 °C). The solvents were removed in vacuo, and the semi-solid residue was crystallized from acetone/ether mixture to give a first crop (5.6 g) as a colorless solid. The mother liquors were concentrated, and the residue was purified by passing it through a short silica gel pad (100 g) eluting with a gradient of CH_2Cl_2/EtOAc (1:1) to CH_2Cl_2/EtOAc/MeOH (8:8:1). After evaporation, the main fraction was crystallized from acetone/ether

yielding another 4.6 g of the title compound, total yield 10.2 g (47%). An analytical sample was recrystallized once more from EtOH. Found C 62.28, H 6.29; calcd for $C_{31}H_{34}N_4O_8^*1/2H_2O$ (599.62) C 62.09, H 5.88; $[\alpha]_D^{20}=+0.8$ (*c* 1.21, $CHCl_3$); lit.[20] $[\alpha]_D^{20}=-2.5$ (*c* 1.1, CH_2Cl_2/MeOH); 30.4 (CH_2), ^{1}H NMR ($CDCl_3$) δ 1.42–1.65 (m, 4H, H-4 and H-5), 2.55 (m, 2H, H-2), 3.88 (m, 3H, H-3 and H-6), 5.05 s, 5.17s and 5.25 s (6H, $PhCH_2O$), 5.58 (d, *J*=5 Hz, 1H, NH), 7.34–7.39 (m, 15H), 9.27 and 9.41 (br. s, 2H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3 (CH_2), 30.4 (CH_2), 38.7 (CH_2), 44.3 (CH_2), 47.7 (CH), 66.6, 67.0 68.9 (CH_2O), 127.8, 127.88, 127.94, 128.02, 128.11, 128.35, 128.4, 128.77, 128.82 (CH), 134.6, 136.4, 136.8 (C), 155.8, 156.0 (NCO), 160.5, 163.7 (CO), 175.9 (br. COOH); ESI-MS (positive mode), *m*/*z* (rel. int., %) 1203 (64) [2M+Na^+], 613 (39) [M+Na^+], 591 (39) [M+H^+]; (negative mode), 1201 (34) [2M−2H+Na^+], 589 (100) [M−H^+].

4.1.15. (3′*S*,5*S*)-5-[*N*-Methyl-*N*-[*N*$^{\beta}$,*N*$^{\varepsilon}$,*N*$^{\omega}$-tris(benzyloxycarbonyl)-β-homoarginyl]amino]-5,6-dihydro-2-ureidopyrimidin-4(1*H*)-one [(*S*,*S*)-21a]. To a suspension of the acid (*S*)-**20a** (495 mg, 0.84 mmol) and (*S*)-**1** (155 mg, 0.84 mmol) in anhydrous DMAA (4 mL) was added HATU (646 mg, 1.70 mmol) in one portion at room temperature followed by DIEA (0.29 mL, 227 mg, 1.75 mmol) which was added dropwise without external cooling. A slightly exothermic reaction was observed, and the solid heterocycle (*S*)-**1** gradually dissolved. After 4.5 h at room temperature, the solvent was evaporated in vacuo (0.01 mm Hg, bath temp. 30–40 °C), and the residue was dissolved in dichloromethane (50 mL). The solution was washed with water, 5% aq. $KHSO_4$, water, sat aq. $NaHCO_3$, brine (10 mL each), and dried. The solvent was evaporated, and the semi-solid residue was triturated with 10 mL of a mixture of EtOAc and ether (1:1). After keeping this suspension overnight at +5 °C, the solid crude coupling product (*S*,*S*)-**21a** was collected on a filter and washed with ether (10 mL). After drying, the crude product (0.53 g, 84% yield) was recrystallized from dichloromethane (45 mL). The fraction, which was insoluble in boiling dichloromethane, was removed by filtration (0.10 g after drying), the filtrate was diluted with EtOAc (1:1), and kept at +5 °C overnight. The colorless solid of (*S*,*S*)-**21a** (0.33 g, 52%) was collected, washed on a filter with ether (10 mL) and dried in vacuo (0.01 Torr). Found C 58.16, H 5.81, N 16.28; calcd for $C_{37}H_{43}N_9O_9^*1/4H_2O$ (761.8) C 58.30, H 5.75, N 16.54; $[\alpha]_D^{20}=-51$ (*c* 0.26, DMF); HPLC-MS: R_t=4.52 min (peak area 100%); IR: ν=3388, 3266, 3133, 2946, 1718, 1610, 1575, 1507, 1456, 1377, 1257, 1097, 1029 cm^{-1}; ^{1}H NMR ([D_6]DMSO, 600 MHz, signals of the major rotamer are marked with ∗) δ 1.32, 1.42, 1.51 and 1.58 (4 m, 4H, H-4′ and H-5′), 2.22 (dd, *J*=16.2, 6.6 Hz, A-part of an AB-system, H-2′), 2.40* (dd, *J*=15.3, 6.6 Hz, A-part of an AB-system, H-2′), 2.48* (dd, *J*=[masked by the solvent] and 6.1 Hz, B-part of an AB-system, H-2′), 2.56 (dd, *J*=16.2, 6.6 Hz, B-part of an AB-system, H-2′), 2.66/2.85* (s, 3H, *N*Me), 3.35* (dd, *J*=11, 8 Hz, H-6), 3.52* (t, *J*=13.1 Hz, H-6), 3.56–3.63 [m, 2H (together with 3.35 and 3.52), H-6], 3.83 (m, 3H, H-3′ and H-6′), 4.73 (m, H-5), 4.95* [m, 3 H (together with 4.73), H-5 and CH_2O], 5.05 (s, 2H, CH_2O), 5.22 (s, 2H, CH_2O), ≈6. 8 (br. s, 1H, NH), 6.98/7.08* (d, 1H, *J*=5.5 Hz, ZNH–C-3′), 7.23–7.40 (m, 15H), 9.11 (br. s, 2H, NH) and ≈9.6 (br. s, 2H, NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO, signals of the major rotamer are marked with ∗) δ 25.2 (CH_2), 29.5/33.0 (*N*Me), 31.3 (CH_2), 44.6 (CH_2), other signals of CH_2-groups are masked by the signals of [D_6]DMSO, 47.8*/47.9 (CH), 52.1*/54.2 (CH), 65.1, 66.2, 68.2 (CH_2O), 127.53, 127.66, 127.71, 127.79, 127.82, 127.88, 128.27, 128.32, 128.5 (CH), 135.3, 137.1, 137.2 (C), 155.0*/155.5, 155.6 (NCO), 159.7, 162.9, 170.9*/171.1 (CO); ESI-MS (positive mode), *m*/*z* (rel. int., %) 780 (100) [M+Na^+], 758 (84) [M+H^+].

4.1.16. (3′*S*,5*S*)-3,4,5,6-Tetrahydro-5-[*N*-methyl-*N*-(β-homoarginyl)amino]-2-ureidopyrimidin-4-one dihydrochloride (TAN-1057A*2HCl). A suspension of the coupling product (*S*,*S*)-**21a** (205 mg, 0.271 mmol) and $PdCl_2$ (48.5 mg, 0.274 mmol) in anhydrous MeOH (7 mL) was flushed with nitrogen and then with hydrogen, and was vigorously stirred under hydrogen (a balloon with H_2 was attached). Gradually, the light-brown suspension turned gray, and then the starting material dissolved. After stirring for about 3–4 h at room temp. (28 °C), the reaction was complete. After flushing with N_2, the reaction mixture was filtered through Celite® to remove the Pd-black. The filter-cake was washed with MeOH (3×3 mL), and the filtrate was evaporated in vacuo. The colorless solid residue was triturated with anhydrous ether (10 mL), collected on a filter under ether, quickly washed with ether once more (10 mL), and dried in vacuo (0.01 mm Hg) overnight to give 122 mg of the title compound (106% yield, 6% w/w of MeOH) as an amorphous white powder. $[\alpha]_D^{22}=-22.7$ (*c* 0.6, water);[16] lit.:[2] $[\alpha]_D^{22}=-39.1$ (*c* 0.53, water); CD spectrum θ (λ, nm, water)=+12,500 (215), −12,600 (233), −7500 (253), −14,200 (269); lit.[2] θ (λ, nm, water)=+13,300 (215), −13,500 (231), −13,500 (267); IR: ν=3340, 3156, 1747, 1653, 1615, 1420, 1378, 1277, 1218, 1135, 1013 cm^{-1}; ^{1}H NMR ([D_4]MeOH, 600 MHz) δ 1.71, 1.80 (2 m, 4H, H-4′ and H-5′), 2.79 (dd, *J*=17.4, 9 Hz, 1H, H-2′), 2.97 (dd, *J*=17.4, 3.8 Hz, 1H, H-2′), 2.88/3.12 (2 s, $\sum$ 3H, *N*Me), 3.25 (t, *J*=6.8 Hz, 2H, H-6′), 3.61 (m, 1H, H-3′), 3.81 (dd, *J*=12.9, 7.9 Hz, 1H, H-6), 3.95 (t, *J*=12.9 Hz, 1H, H-6), 5.19 (dd, *J*=8.7, 12.7 Hz, 1H, H-5); ^{13}C NMR (75.5 MHz [D_4]MeOH,) δ 25.8 (C-5′), 30.8 (C-4′), 35.1 (*N*Me), 36.1 (C-2′), 40.2 (C-6), 42.0 (C-6′), 49.6 (C-3′), 54.9 (C-5), 156.3, 156.7, 156.8 (NCO), 170.5, 173.0 (CO); ESI-MS (positive mode), *m*/*z* (rel. int., %) 356 (100) [M+H^+].

4.1.17. (3′*S*,5*S*)-5-[*N*-Methyl-*N*-[3′,6′-bis(benzyloxycarbonylamino)hexanoyl]amino]-5,6-dihydro-2-ureidopyrimidin-4(1*H*)-one [(*S*,*S*)-21b]. The title compound was obtained from the acid (*S*)-**20b** (317 mg, 0.77 mmol) and (*S*)-**1** (142 mg, 0.77 mmol; e.e.=87%) in anhydrous DMF (4 mL) with HATU (585 mg, 1.54 mmol) and DIEA (199 mg, 1.54 mmol) as described for the coupling product (*S*,*S*)-**21a**. After recrystallization from a mixture of CH_2Cl_2 and EtOAc, 370 mg (83%) of the title compound with de=90% was obtained; $[\alpha]_D^{20}=-93$ (*c* 1.03, DMF). In another experiment, (*S*)-**1** (1.20 g, 6.48 mmol) of lower optical purity ($[\alpha]_D^{20}=-213$ (*c* 0.48, DMF), e.e.≈75%), acid (*S*)-**20b** (2.69 g, 6.49 mmol), HATU (4.90 g, 12.9 mmol) and DIEA (2.22 mL, 1.74 g, 13.5 mmol) in 15 mL of DMAA gave 2.74 g (73%) of the crude (*S*,*S*)-**21b**, which was twice recrystallized from a mixture of CH_2Cl_2 and EtOAc to afford 2.09 g (55%) of the title compound with de=85%; (3′*S*,5*R*)-isomer: R_t=14.38 min, (3′*S*,5*S*)-isomer:

R_t=20.77 min (Chiracel OD-H, column 250×2 mm, heptane/isopropanol, 1:1, 0.2 mL/min); (3′*S*,5*R*)-isomer: R_t=15.99 min, (3′*S*,5*S*)-isomer: R_t=26.52 min (Chiralpak OD-H, column 250×4.6 mm, methanol, 0.5 mL/min). Found C 57.63, H 6.14, N 16.49; calcd for $C_{28}H_{35}N_7O_7$ (581.6) C 57.82, H 6.06, N 16.86; IR: ν=3335, 3148, 2940, 1716, 1698, 1643, 1610, 1576, 1528, 1455, 1404, 1347, 1271, 1141, 1069, 1026 cm^{-1}; ^1H NMR ([D$_6$]DMSO, 600 MHz, signals of the major rotamer are marked with ∗) δ 1.37 and 1.45 (2 m, 4H, H-4′ and H-5′), 2.24 (dd, *J*=14.5, 6.4 Hz, A-part of an AB-system, H-2′), 2.43∗ (dd, *J*=15.6, 6.4 Hz, A-part of an AB-system, H-2′), 2.52∗ (dd, *J*=15, 6 Hz, B-part of an AB-system, H-2′), 2.58 (dd, *J*=15.7, 6 Hz, B-part of an AB-system, H-2′), 2.67/2.90∗ (s/br. s∗, 3H, *N*Me), 2.97 (br. s, 2H, H-6′), 3.40∗ (dd, *J*=12.3, 7.8 Hz, H-6), 3.56∗ (t, *J*=12.9 Hz, H-6), 3.59–3.65 [m, 2H (together with 3.40 and 3.56), H-6], 3.80/3.84∗ (br. s, 1H, H-3′), 4.78 (m, H-5), 5.05 [br. s, 5H (together with 4.78), 2×CH_2O], ≈6.8 (br. s, 1H, NH), 6.99/7.09∗ (d, 1H, *J*=5.5 Hz, ZNH-C-3′), 7.23–7.40 (m, 10H), ≈9.8 (br. s, 2H, NH). ^{13}C NMR (75.5 MHz, [D$_6$]DMSO, signals of the major rotamer are marked with ∗) δ 26.3 (C-5′), 29.5/33.1∗ (*N*Me), 31.6 (C-4′), 47.8∗/48.2 (C-3′), 52.1∗/54.1 (C-5), 65.2 (CH_2O), 127.6, 127.7, 128.3 (CH), 137.3 (C), 155.7, 156.1 158.5 (br.) (NCO), 171.0∗/171.2, 173.1∗/174.0 (CO). ESI-MS (positive mode), *m*/*z* (rel. int., %) 1185 (100) [2M+Na$^+$], 604 (92) [M+Na$^+$]; (positive mode) 580 (100) [M−H$^+$].

4.1.18. (3′*S*,5*S*)-3,4,5,6-Tetrahydro-5-[*N*-methyl-*N*-(3,6-diaminohexanoyl)amino]-2-ureidopyrimidin-4-one dihydrochloride [(*S*,*S*)-22b]. The coupling product (*S*,*S*)-**21b** (268 mg, 0.461 mmol, de=90%) with added $PdCl_2$ (81.7 mmol, 0.461 mmol) in anhydrous MeOH (15 mL) was hydrogenated and worked-up as described above for the preparation of TAN-1057A∗2HCl to give 193 mg (108% yield, 8% w/w of MeOH) of the title compound as an amorphous powder. HRMS *m*/*z* (ESI) found 314.1913, calcd for $C_{12}H_{24}N_7O_3$ [M+H$^+$] 314.1941; found 627.3810, calcd for $C_{24}H_{47}N_{14}O_6$ [2M+H$^+$] 627.3810; $[\alpha]_D^{22}$=+0.6 (*c* 1.0, water); CD spectrum θ (λ, nm, water)=+13,800 (215), −11,700 (235), −6900 (254), −12,000 (266); IR: ν=3343, 3127, 3010 sh, 2893, 1778, 1747, 1683, 1623, 1576, 1490, 1380, 1284, 1212, 1123, 1085, 1012 cm^{-1}; ^1H NMR ([D$_4$]MeOH, 600 MHz) δ 1.81 (br. s, 4H, H-4′ and H-5′), 2.81 (dd, *J*=17.6, 8.5 Hz, 1H, H-2′), 2.98 (dd, *J*=17.1, 4.1 Hz, H-2′), 2.99 (br. s, $\sum$ 3H, H-6′), 2.89/3.16 (2 s, $\sum$ 3H, *N*Me), 3.62 (br. s, 1H, H-3′), 3.89 (dd, *J*=13.5, 7.9 Hz, 1H, H-6), 4.02 (t, *J*=12.9 Hz, 1H, H-6), 5.17 (dd, *J*=7, 12 Hz, H-5); ^{13}C NMR ([D$_4$]MeOH, 75.5 MHz) δ 24.5 (C-5′), 30.6 (C-4′), 35.6 (*N*Me), 36.0 (C-2′), 40.2 (C-6/C-6′), 40.0 (C-6/C-6′), 49.4 (C-3′), 55.4 (C-5), 154.1, 155.3 (NCO), 166.6, 172.8 (CO). ESI-MS (positive mode), *m*/*z* (rel. int., %) 627 (18) [2M+H$^+$], 314 (100) [M+H$^+$]; (negative mode) 348 (50) [M+Cl$^-$], 312 (100) [M−H$^+$].

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15. An alternative synthesis of the β-amino acid (*S*)-**20a** by Wolff-rearrangement of the diazoketone (*S*)-**19** catalyzed by silver benzoate was described in the Supporting Information of Ref. 3.
16. Our sample of TAN-1057A*2HCl contains ca. 1 mol of MeOH per 1 mol of the hydrochloride salt. This corresponds to ca. 7% (w/w) of MeOH. Corrected $[\alpha]_D^{22}=-24$ (*c* 0.6, H_2O). As reported in Ref. 5 the residual amount of MeOH could not be removed even by prolonged drying in high vacuum.
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19. This compound (with an unknown degree of racemization and an unknown optical rotation value) was also found to be an oil: see Supporting Information of Ref. 3.
20. Data for the monohydrate of the title compound from the Supporting information to Ref. 3. Relative amounts of the solvents are not given.

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Synthesis of enantiomerically pure α-amino-β-hydroxy-cyclobutanone derivatives and their transformations into polyfunctional three- and five-membered ring compounds

Léon Ghosez,[a,b,*] Gaoqiang Yang,[a] José Renato Cagnon,[a] Franck Le Bideau[a] and Jacqueline Marchand-Brynaert[a]

[a]*Department of Chemistry, University of Louvain, Place L. Pasteur 1, B-1348 Louvain-la-Neuve, Belgium*
[b]*Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac Cedex, France*

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Dedicated to Professor Dieter Seebach in recognition of his seminal contributions to organic chemistry

Abstract—Ketenes readily cycloadded to (*R*)-*tert*-butyldihydrooxazole **2a**–**d** to yield enantiomerically pure bicyclic cyclobutanones. The cycloadditions proceeded with unusual regiochemistry giving predominantly or exclusively protected α-amino-β-hydroxycyclobutanone derivatives. The adducts could be converted into a variety of interesting enantiopure intermediates equipped with many functional groups: α-amino-β-hydroxy cyclopropane carboxylic acid derivatives, α-amino-β-hydroxy succinic acid derivatives, α-amino-β-hydroxy lactones and lactams derivatives.

1. Introduction

The growing resistance of bacterial strains to antibiotics is a major concern of our society.[1] β-Lactam antibiotics are the most often prescribed class of antibacterial agents and, as a result, bacteria have developed efficient resistance mechanisms to these antibiotics. For instance the microorganisms produce β-lactamases which are able to cleave the ester linkage formed by acylation of D,D-peptidases by the antibiotics, thus regenerating the free enzyme which can again exercise its biological function.[2] For several years, we have been interested in the design, synthesis and biological evaluation of new inhibitors of penicillin binding proteins.[3–5] Our approach was to design molecules which would make an ether link with the serine protease, thus suppressing the regeneration of the free enzyme by a hydrolytic mechanism. In this context, the replacement of the acylating lactam function of penicillins or cephalosporins by a reactive hydroxyalkylating carbonyl group could lead to stable adducts with bacterial serine proteases. General structure **1** (Fig. 1) or its stereoisomers were regarded as potential alkylating inhibitors of these enzymes: (a) the carbonyl group is part of a strained ring and more

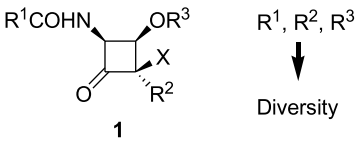
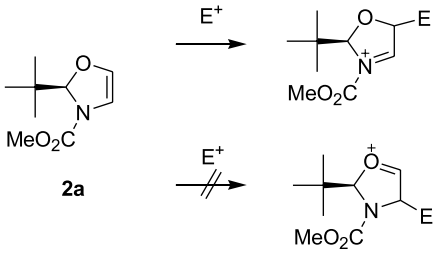


Figure 1.

susceptible to undergo addition reactions; (b) the X atom (H, F, Cl) could be used to modulate the electrophilic reactivity of the neighbouring carbonyl group; (c) the carboxyl and acylamino groups are properly placed to mimic the β-lactam antibiotics.

Clearly such an endeavour required an easy access to enantiomerically pure 2-aminocyclobutanones with appropriate functional groups at C-3 and C-4. Methyl (2*R*)-2-*tert*-butyldihydrooxazole **2a** first studied in Seebach's group[6]



Scheme 1.

Keywords: Asymmetric synthesis; (2+2) Cycloaddition; Ketene; Cyclobutanone; Cyclopropane; Amino acid; Serine protease.
* Corresponding author. Tel: +33-5-4000-2217; fax: +33-5-4000-2222; e-mail address: l.ghosez@iecb.u-bordeaux.fr

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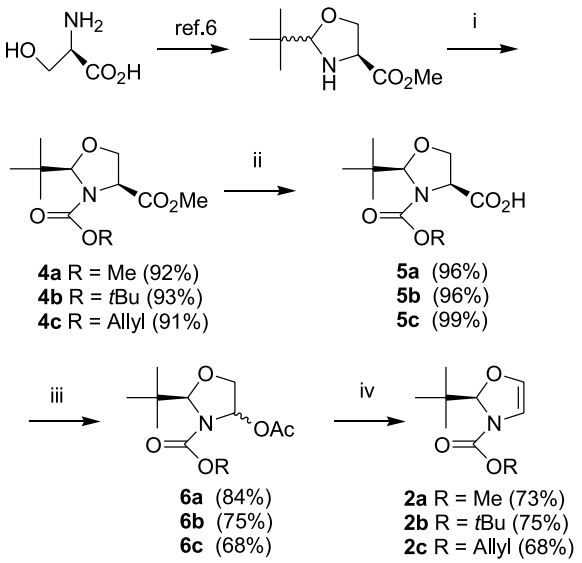
was regarded as an interesting olefinic building-block which should selectively cycloadd with ketenes from the face opposite to the *tert*-butyl substituent (Scheme 1). However Seebach et al. had shown that electrophilic additions to **2a** always occurred at C-5 as a result of the lower energy of an acyl iminium intermediate relative to that of an oxonium ion.[7] Thus ketenes were expected to react with **2** to yield an adduct with the carbonyl group α to the oxygen. Additional steps would then be needed to move the carbonyl group to the right position. Gratifyingly our initial studies showed that the theoretical predictions were not fulfilled: the cycloaddition of **2a** with diphenylketene led to the unpredicted, yet desired cycloadduct.[8] We now report the full details of the cycloaddition of ketenes to (2*H*)oxazoles as well as illustrative examples of the synthetic potential of the cycloadducts.



Scheme 2. Reagents and conditions: (i) MeOCOCl, Et_3N (**4a**), $(Boc)_2O$, $NaHCO_3$, MeOH (**4b**), AllylOCOCl, $NaHCO_3$, MeOH (**4c**); (ii) KOH, MeOH–H_2O, RT; (iii) $Pb(OAc)_4$, benzene, reflux, (iv) NH_4Br, 1,2-dichloroethane, reflux.

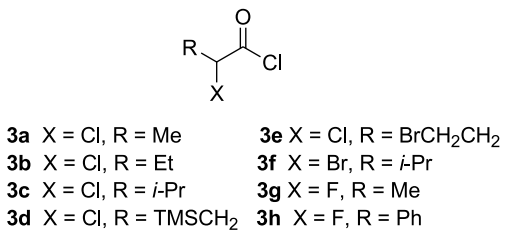


Figure 2.

2. Results and discussion

2.1. Synthesis of (2*H*)oxazoles

Methyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate **2a**,**b** were prepared from l-serine following the procedure described by Seebach[6] except for the electrochemical oxidative decarboxylation step (Scheme 2). We found that a thermal oxidative decarboxylation with lead tetraacetate was more practical and gave better yields (84 and 82%) than the described electrochemical method (33%). The new (2*H*)oxazoles **2c** and **2d** (enantiomer of **2b**, prepared from d-serine) were also synthesized by this modified procedure. These optimized sequences of reactions allowed us to prepare up to 50 g of enantiopure (2*H*)oxazoles in 35–45% overall yield.

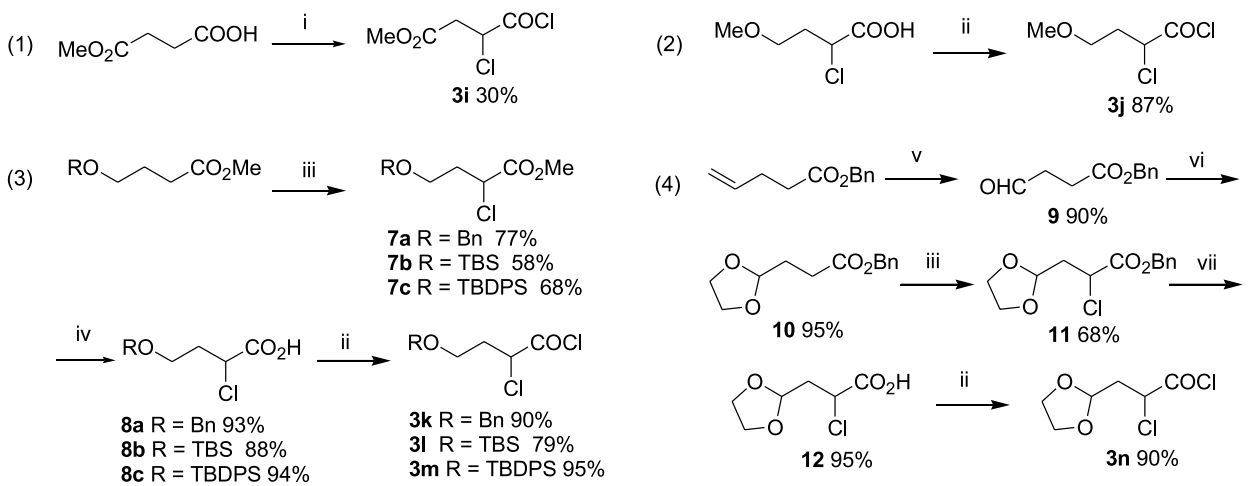
2.2. Synthesis of acyl chlorides

Ketenes were conveniently generated by dehydrochlorination of the corresponding acid chlorides. α-Chloroacyl chlorides **3a**–**h** were readily prepared following literature procedures (Fig. 2).[9]

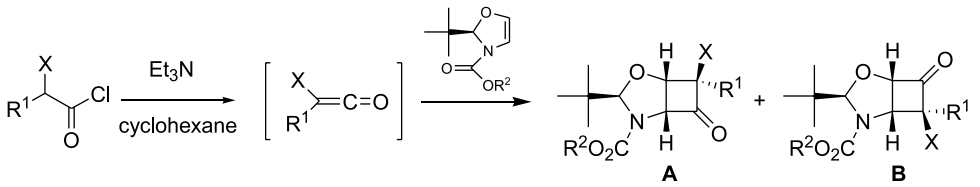
Acyl chlorides **3i**–**n** was synthesized by the sequences of reaction shown in Scheme 3.

2.3. Cycloaddition reactions

2.3.1. Cycloadditions to α-haloketenes. α-Haloketenes were generated in situ from the corresponding acid chlorides **3** and triethylamine. In most cases cycloadditions were performed in cyclohexane at 60 °C to give high yields of adducts (Scheme 4, Table 1). No cycloadduct was obtained



Scheme 3. Reagents and conditions: (i) $SOCl_2$, 70 °C, then NCS, $SOCl_2$, HCl, 85 °C; (ii) $(COCl)_2$, DMF, DCM; (iii) LDA, −78 °C, then CCl_4; (iv) LiOH, THF–H_2O, H_2O_2; (v) O_3, DCM; (vi) ethylene glycol, TsOH, benzene; (vii) H_2, Pd/C.



Scheme 4.

Table 1. Cycloadditions of oxazolines **2a–c** to haloketenes

Entry	R^1	R^2	X	Adduct	Yield (%)	**A/B**
1	Me	Me	Cl	**13**	80[a]	>98:2
2	*t*-Bu	Me	Cl	**14**	75[a]	>98:2
3	Allyl	Me	Cl	**15**	78	Only **A**
4	Me	Et	Cl	**16**	80	Only **A**
5	Me	*i*Pr	Cl	**17**	62[a]	10:1
6	*t*-Bu	*i*Pr	Cl	**18**	65[b]	4:1
7	Me	Ph	Cl	**19**	87[a]	10:1
8	*t*-Bu	Ph	Cl	**20**	60[a]	6:1
9	Me	CH_2TMS	Cl	**21**	86	Only **A**
10	*t*-Bu	CH_2TMS	Cl	**22**	82	Only **A**
11	Me	CH_2CH_2Br	Cl	**23**	80[b]	6:1
12	*t*-Bu	CH_2CH_2Br	Cl	**24**	72[b]	8:1
13	Allyl	CH_2CH_2Br	Cl	**25**	77[a]	20:1
14	Me	CH_2CH_2OMe	Cl	**26**	76[b]	8:1
15	Me	CH_2CH_2OSi*t*$BuMe_2$	Cl	**27**	54[a]	8/1
16	Me	CH_2CH_2OSi*t*$BuPh_2$	Cl	**28**	80[a]	19:1
17	*t*-Bu	CH_2CH_2OSi*t*$BuPh_2$	Cl	**29**	75[a]	20:1
18	Allyl	CH_2CH_2OSi*t*$BuPh_2$	Cl	**30**	77[b]	10:1
19	Me	CH_2CH_2OBn	Cl	**31**	72[b]	6:1
20	*t*-Bu	CH_2CH_2OBn	Cl	**32**	56	Only **A**
21	Me	$CH_2CH(OCH_2CH_2O)$	Cl	**33**	62[b]	10:1
22	Me	$CH_2CO_2CH_3$	Cl		0	
23	Me	*i*Pr	Br	**34**	74[b]	4:1
24	Me	Me	F		0	
25	Me	Ph	F		0	

[a] Pure isomer **A**.
[b] Purified mixture of **A** and **B**.

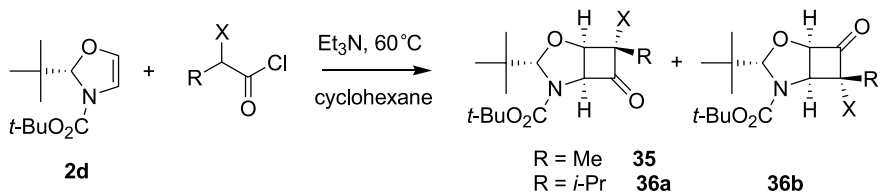
with the acid chloride derived from methyl monochlorosuccinate (entry 22). In this case, the ketene was probably not formed since a facile competitive β-elimination of HCl could occur. Also we did not get any adduct from the α-fluoroacyl chlorides (entries 24 and 25). It is also highly probable that the corresponding fluoroketenes were not formed. As in the model reaction with diphenylketene, the cycloaddition was regioselective, yielding predominantly or exclusively the isomer with the carbonyl group α to the nitrogen substituent.

The cycloadditions were remarkably stereoselective. In all cases, the addition took place from the face opposite to the *t*-butyl group and the halogen atom was always *exo*. Thus the reaction produced enantiomerically pure adducts. The configuration of the stereogenic centers of the adducts results from the selection of the serine enantiomer (here l-serine) and the stereochemical course of the reaction.

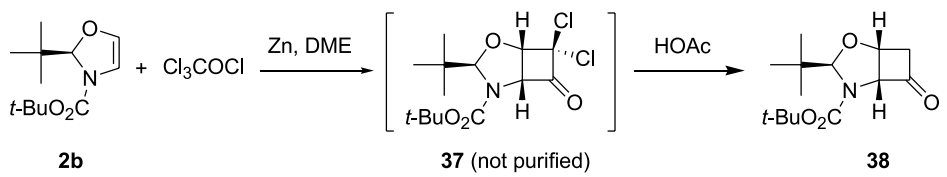
(2*H*)Oxazole **2d**, the enantiomer of **2b** was prepared from d-serine. It also reacted with ketenes derived from acid chlorides **3a** and **3c** to give good yields of adducts **35** and **36a-b** (Scheme 5).

The cycloaddition of **2b** with dichloroketene was less successful as a result of the instability of the adduct **37** which was therefore dechlorinated in situ to give a modest 30% yield of **38**. The best conditions are described in Scheme 6.

The structure and configuration of adducts were established by a detailed analysis of their ^1H and ^{13}C NMR spectra and the use of NOE effects (Section 4). The assignments were confirmed by X-ray diffraction analyses of a 'minor' adduct **20B** and a 'major' adduct **29A**.[10] The regioselectivity of the cycloaddition excluded a two-step pathway involving a zwitterionic intermediate since an electrophilic addition to (2*H*)oxazoles should predominantly lead to isomer **B** in agreement with the earlier observations of Seebach's group.[6] Both the regio- and stereoselectivity of the cycloaddition can be accounted for by a concerted cycloaddition involving an orthogonal approach of the ketene to the less-hindered face (away from the *t*-butyl substituent) of the (2*H*)oxazole and with the larger



Scheme 5.



Scheme 6.

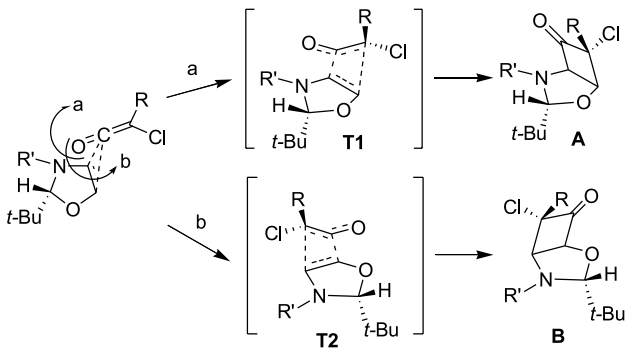
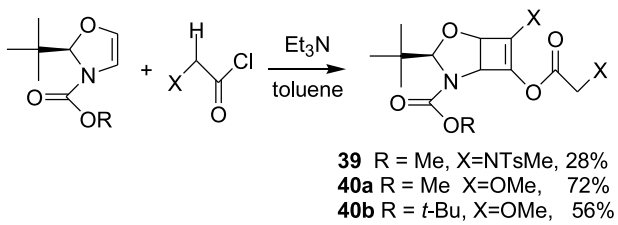


Figure 3.

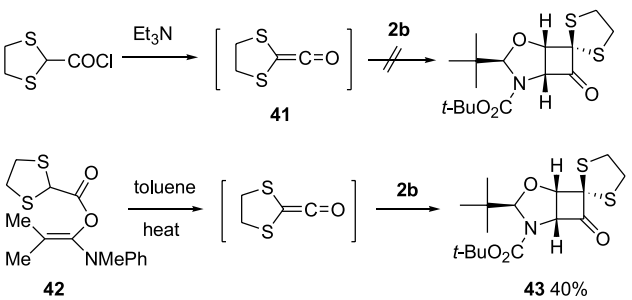
substituent R away from the double bond (Fig. 3). It can be readily seen that rotation *b* which is favoured by electronic factors would create an interaction between R and the nitrogen substituent. No such steric repulsion results from rotation *a* which places the carbonyl group α to the nitrogen atom. Thus, in all cases, steric effects superseded electronic effects.



39 R = Me, X=NTsMe, 28%
40a R = Me X=OMe, 72%
40b R = *t*-Bu, X=OMe, 56%

Scheme 7.

2.3.2. Cycloadditions to other ketenes. Scheme 7 describes the [2+2] cycloadditions of (2*H*)oxazoles **2a** and **2b** with *N*-methyl-*N*-tosyl- or methoxyketene.[11] Surprisingly we could not isolate the cyclobutanone adducts which were acylated in situ to give enol esters **39** and **40**. The high temperature (110 °C) required for these cycloadditions probably accounted for the acylation of the adducts. Of special interest to us was the cycloaddition of **2b** to dithiolanoketene **41**, a synthetic equivalent of the unknown dimer of CO (Scheme 8).[12] In this case, the cycloaddition did not occur when the ketene was generated from the acid chloride. However the thermolysis of **42** in refluxing toluene slowly generated ketene **41** which was trapped by olefin **2b** to give adduct **43** in moderate yields.

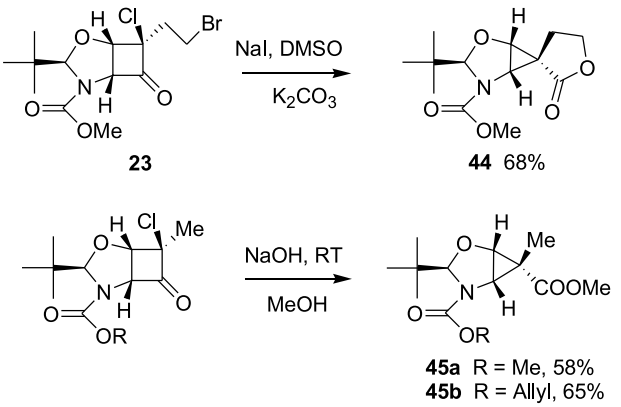


Scheme 8.

2.4. Selected transformations of the cycloadducts

The concatenation of many functional groups in these readily accessible cyclobutane derivatives make them interesting enantiopure synthetic intermediates. It was out of the scope of this work to investigate in detail the synthetic potential of these cyclobutanones. We just performed a selected number of transformations showing that the four-membered ring could readily be transformed into three- and five-membered rings or be cleaved to generate functionalized α-amino acid derivatives.

2.4.1. Synthesis of enantiopure α-aminocyclopropane carboxylic acid derivatives. In the course of our studies on the total synthesis of bacterial peptidase inhibitors, we observed that the treatment of cyclobutanone **23** with NaI in DMSO containing potassium carbonate did not yield the desired iodide but rather led to a cyclopropane carboxylic acid derivative **44** resulting from a Favorskii rearrangement (Scheme 9). The same ring contraction could be more classically effected by sodium hydroxide in methanol.[13]

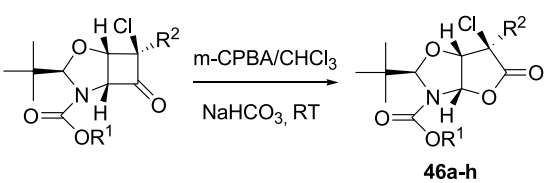


45a R = Me, 58%
45b R = Allyl, 65%

Scheme 9.

Thus the sequential cycloaddition-Favorskii rearrangement represents a potentially useful route towards highly functionalized enantiopure α-aminocyclopropane carboxylic acid derivatives.

2.4.2. Synthesis of enantiopure bicyclic γ-lactones and γ-lactams. A number of cyclobutanones could be readily oxidized to the corresponding γ-butyrolactones **46a–h** (Scheme 10, Table 2). The reaction was totally regiospecific giving the expected isomer resulting from the insertion of the oxygen atom into the carbon–carbon bond adjacent to the acylamino substituent. Yields were excellent.

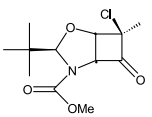
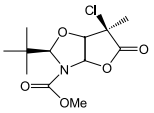
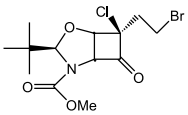
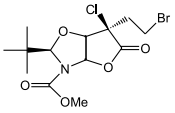
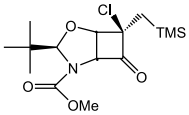
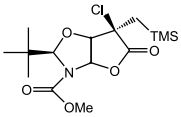
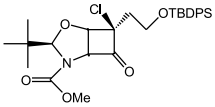
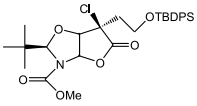
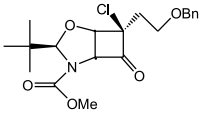
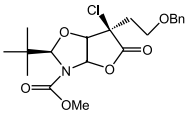
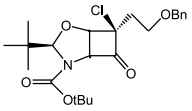
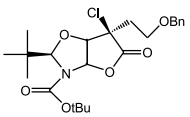
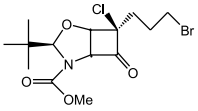
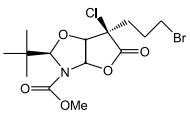
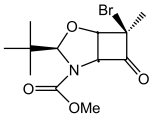
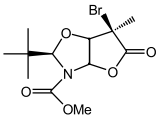


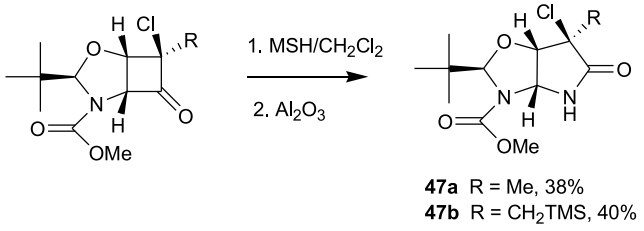
Scheme 10.

Similarly treatment of cyclobutanones **13** and **21** by an excess of *o*-mesitylsulfonylhydroxylamine,[14] followed by absorption on basic alumina and elution with methanol gave a moderate yield of bicyclic γ-lactam **47a–b** and but in moderate yields (Scheme 11).

2.4.3. Synthesis of enantiomerically pure α-amino-β-hydroxysuccinic acid derivatives. Based on previous

Table 2. Bayer–Villiger oxidations

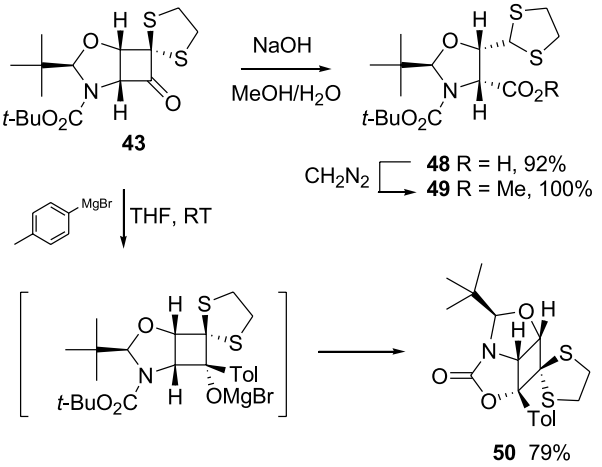
Substrates	Products		Yield (%)
		**46a**	90
		**46b**	85
		**46c**	92
		**46d**	90
		**46e**	88
		**46f**	86
		**46g**	85
		**46h**	80



Scheme 11.

observations, it was anticipated that cyclobutanone **43** should be readily cleaved by nucleophilic reagents. Indeed treatment of **43** with sodium hydroxide in methanol–water or with sodium methoxide at room temperature led to the selective cleavage of the four-membered ring in very high yield (Scheme 12). Compound **48** corresponds to a product of vicinal acylation of (2*H*)oxazole **2b**.

Interestingly the reaction of cyclobutanone **43** with tolyl magnesium bromide yielded the tricyclic structure **50** resulting from a stereoselective addition of the Grignard reagent from the *exo*-face of the bicyclic cyclobutanone



Scheme 12.

followed by nucleophilic attack of the resulting alkoxide ion on the carbamate group.

3. Conclusions

In conclusion, we have described the unique capacity of (2*H*)oxazole to react with ketenes to yield enantiopure α-amino-cyclobutanone derivatives. The stereochemistry of the cycloadditions is controlled by the large *t*-butyl group. Steric factors in an orthogonal transition state readily account for the unusual regiochemistry of these reactions. The rich functionality of the adducts should make them very useful for further transformations. These intermediates thus appeared to be well suited for the synthesis of our target inhibitors **1** of bacterial peptidases (Fig. 1). We have also shown in selected experiments that the four-membered ring could be contracted or expanded to generate enantiopure three- or five-membered ring derivatives. They could also be used for the preparation of new α-amino acids.

4. Experimental

4.1. General

NMR spectra were recorded on a Varian Gemini 300BB (300 MHz for ^{1}H and 75 MHz for ^{13}C). High resolution spectra were recorded on a Brucker AM-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are given in ppm relative to the internal reference. Coupling constants (*J* values) are reported in Hertz (Hz), and multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). The MS spectra were recorded on a Varian MAT-44 or FINNIGAN MAT-TSQ 70 apparatus. Infrared spectra were recorded on a BIORAD FTS-135. The optical rotation values were measured on a PERKIN–ELMER 241 polarimeter. Concentrations are given in g/100 ml. Melting points were measured with a BUCHI apparatus (oil bath) and are uncorrected. Flash chromatography separations were performed using MERCK 60 40–63 μm silica and pre-distilled technical grade solvents. Triethylamine, CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled on CaH_2.

Cyclohexane and toluene were distilled on Na with benzophenone as indicator. DMF was dried over 3 Å MS.

4.1.1. 3-(*tert*-Butyl)4-methyl (2*R*,4*S*)-2-(*tert*-butyl)-1,3-oxazolane-3,4-dicarboxylate 4b. Into a 1 l three-necked flask equipped with a condenser, methyl (2*R*,4*S*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (38.0 g, 0.2 mol), sodium bicarbonate (41.72 g, 0.5 mol), di-*t*-butyl dicarbonate (44.7 g, 0.2 mol,) and methanol (550 ml) were added, the mixture was allowed to stay in an ultrasonic bath at 50 °C for 5 h. After cooling, the mixture was filtered, and the filtrate was concentrated under the reduced pressure. The resulting residue was diluted with diethyl ether, and washed with brine, dried over $MgSO_4$ and concentrated to give **4b** as a colourless oil (86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H, NCHO), 4.70 (dd, J=8.3, 6.1 Hz, 1H, CH_2O), 4.30 (dd, J=8.4, 6.0 Hz, 1H, CH_2O), 4.12 (t, J=8.4 Hz, 1H, CHN), 3.75 (s, 3H, MeO), 1.47 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C=O), 155.2 (C=O), 97.8 (NCHO), 81.4 (O*t*Bu), 68.7 (CH_2O), 59.6 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 28.4 (O*t*Bu), 25.6 (*t*Bu). IR (neat) ν 2976, 1764, 1709. $[\alpha]_D^{20}=-33.1$ (*c* 1.14 $CHCl_3$). MS (CI) *m*/*z* 287 (M^+), 230, 174, 130, 57. Anal. Calcd for $C_{14}H_{25}NO_5$ C 58.52, H 8.76, N 4.87; found C 58.85, H 8.53, N 4.25.

4.1.2. 3-Allyl 4-methyl (2*R*,4*S*)-2-(*tert*-butyl)-1,3-oxazolane-3,4-dicarboxylate 4c. Into a 500 ml three-necked flask equipped with an additional funnel, methyl (2*R*,4*S*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (38 g, 0.2 mol) and dichloromethane (250 ml) were added, the mixture was cooled to 0 °C, and then allyl chloroformate (25 g, 0.21 mol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. After filtration, the filtrate was washed with 1 N HCl and brine, then dried over $MgSO_4$ and concentrated to give the product as a colourless oil, yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 1H, =CH), 5.32 (ddd, J=17.2, 3.1, 1.5 Hz, 1H, CH_2=), 5.24 (ddd, J=10.4, 2.7, 1.3 Hz, 1H, CH_2=), 5.1 (s, 1H, NCHO), 4.77 (dd, J=8.0, 4.9 Hz, 1H, CH_2O), 4.64 (dd, J=5.4, 1.4 Hz, 2H, CH_2OCO), 4.35 (dd, J=8.6, 4.9 Hz, 1H, CH_2O), 4.12 (t, J=8.4 Hz, 1H, CHN), 3.72 (s, 3H, MeO), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C=O), 155.8 (C=O), 132.2 (CH=), 117.9 (CH_2=), 97.8 (NCHO), 68.2 (CH_2OCO), 66.7 (CH_2O), 59.6 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 25.6 (*t*Bu).

4.1.3. *tert*-Butyl (2*S*,4*R*)-4-methoxycarbonyl-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate (4d). Into a 250 ml flask equipped with a condenser, methyl (2*S*,4*R*)-2-(*t*-butyl)-1,3-oxazolane-4-carboxylate (15.7 g, 83.85 mmol), sodium bicarbonate (17.6 g, 209.6 mmol) and di-*t*-butyl dicarbonate (18.86 g, 83.85 mmol) in methanol (234 ml) were added. The mixture was stirred at 50 °C in an ultrasonic bath for 5 h. The solution was filtered and the MeOH was evaporated. The residue was diluted with ether and washed with brine, dried over $MgSO_4$ and concentrated to give the product (22.6 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H, NCHO), 4.7 (m, 1H, CH_2O), 4.28 (dd, J=8.6, 5.75 Hz, 1H, CH_2O), 4.14 (t, J=8.6 Hz, 1H, CHN), 3.76 (s, 3H, MeO), 1.48 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C=O), 155.9 (C=O), 97.5 (NCHO), 81.8 (O*t*Bu), 68.3 (CH_2O), 59.7 (CHN), 52.4 (OMe), 37.5 (*t*Bu), 28.3 (O*t*Bu), 25.8 (*t*Bu).

4.2. General procedure for the preparation of 5a–5d

Into a 500 ml three-necked flask equipped with an additional funnel, **4a–4d** (1 equiv.) and methanol (2 ml/mmol) was added, the mixture was cooled to 0 °C and then 3 N KOH (1.5 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed, and the residue was diluted with ether, then acidified with 3 N HCl till pH 1–2, and then extracted with ether. The combined organic layers were washed with 2 N NaCl, dried and concentrated to give the product **5a–5d**.

4.2.1. (2*R*,4*S*)-4-(*tert*-Butoxycarbonyl)-2-(*tert*-butyl)-1,3-oxazolane-4-carboxylic acid 5b. White solid, yield 94%, mp 106–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (b, 1H, OH), 5.06 (s, 1H, NCHO), 4.69 (dd, J=9.0, 6.4 Hz, 1H, CH_2O), 4.40 (dd, J=9.0, 6.4 Hz, 1H, CH_2O), 4.23 (t, J=9.0 Hz, 1H, CHN), 1.49 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C=O), 155.8 (C=O), 97.6 (NCHO), 82.4 (O*t*Bu), 67.8 (CH_2O), 59.4 (CHN), 37.8 (*t*Bu), 28.2 (O*t*Bu), 25.6 (*t*Bu). IR (neat) ν (cm^{-1}) 3180, 2979, 1765, 1681. $[\alpha]_D^{20}=-64$ (*c* 1.0 $CHCl_3$). MS (CI) *m*/*z* 216 (M^+), 160, 116, 57. Anal. Calcd for $C_{14}H_{25}NO_5$ C 57.12, H 8.48, N 5.12; found C 57.56, H 8.20, N 5.68.

4.2.2. (2*R*,4*S*)-4-(Allyloxycarbonyl)-2-(*tert*-butyl)-1,3-oxazolane-4-carboxylic acid 5c. White solid, yield 96%, mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H, =CH), 5.34 (ddd, J=17.2, 3.0, 1.5 Hz, 1H, CH_2=), 5.25 (ddd, J=10.5, 2.7, 1.3 Hz, 1H, CH_2=), 5.12 (s, 1H, NCHO), 4.78 (dd, J=8.5, 5.5 Hz, 1H, CH_2O), 4.66 (ddd, J=15.7, 2.7, 1.4 Hz, 2H, CH_2OCO), 4.41 (dd, J=8.8, 5.5 Hz, 1H, CH_2O), 4.2 (t, J=8.6 Hz, 1H, CHN), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C=O), 156.5 (C=O), 131.8 (CH=), 118.6 (CH_2=), 97.9 (NCHO), 68.0 (CH_2OCO), 67.2 (CH_2O), 59.6 (CHN), 37.5 (*t*Bu), 25.6 (*t*Bu).

4.2.3. *tert*-Butyl (2*S*,4*R*)-4-hydroxycarbonyl-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate (5d). White solid, yield 89%, mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H, OH), 5.07 (s, 1H, NCHO), 4.65 (dd, J=8.7, 6.4 Hz, 1H, CH_2O), 4.47 (dd, J=8.7, 6.3 Hz, 1H, CH_2O), 4.24 (t, J=8.8 Hz, 1H, CHN), 1.50 (s, 9H, O*t*Bu), 0.94 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C=O), 155.9 (C=O), 97.4 (NCHO), 83.5 (O*t*Bu), 67.7 (CH_2O), 59.4 (CHN), 37.8 (*t*Bu), 28.1 (O*t*Bu), 26.7 (*t*Bu).

4.3. General procedure for the preparation of 6a–6d

Into a 1 l three-necked flask equipped with an additional funnel, lead tetraacetate (1.5 equiv.) and benzene (3 ml/mmol) were added. After stirring for 30 min, **5a–5d** (1 equiv.) in benzene (1 ml/mmol) was added dropwise. The mixture was allowed to heat to reflux for 8 h. After cooling, the mixture was filtered through a small column of 6–7 cm celite, washed with cyclohexane. The solvent was removed under the reduced pressure; the residue was diluted with

pentane, then filtered through a pad of silica gel. The filtrate was concentrated to give the product **6a–6d**.

4.3.1. *tert*-Butyl (2*R*,4*R*)-4-acetyloxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6b. Colorless oil, yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (dd, J=5.2, 2.2 Hz, 1H, CHOAc), 5.08 (s, 1H, NCHO), 4.15 (dd, J=10.2, 5.2 Hz, 1H, CH_2O), 3.98 (dd, J=10.0, 2.2 Hz, 1H, CH_2O), 2.08 (s, 3H, CH_3CO), 1.48 (s, 9H, O*t*Bu), 0.98 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 154.5 (C=O), 97.7 (NCHO), 82.9 (CHOAc), 81.4 (O*t*Bu), 66.8 (CH_2O), 38.0 (*t*Bu), 28.4 (O*t*Bu), 25.2 (*t*Bu), 21.2 (Me). IR (film) ν 2978, 1719, 1480, 1360. $[\alpha]_D^{20}$=+25.7 (*c* 1.07 $CHCl_3$). MS (EI) *m*/*z* 287 ($M^{+\cdot}$), 230 (M−*t*Bu)$^+$, 130. Anal. Calcd for $C_{14}H_{25}NO_5$ C 58.51, H 8.76, N 4.87; found C 58.75, H 8.87, N 4.97.

4.3.2. Allyl (2*R*,4*R*)-4-acetyloxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6c. Colourless oil, yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J=4.94, 1.92 Hz, 1H, CHOAc), 5.93 (m, 1H, =CH), 5.33 (ddd, J=17.2, 3.0, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.6, 2.7, 1.4 Hz, 1H, CH_2=), 5.12 (s, 1H, NCHO), 4.64 (dt, J=15.7, 1.4 Hz, 2H, CH_2OCO), 4.13 (dd, J=10.0, 5.0 Hz, 1H, CH_2O), 4.01 (dd, J=10.0, 1.9 Hz, 1H, CH_2O), 2.01 (s, 3H, CH_3CO), 0.98 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 154.5 (C=O), 131.8 (CH=), 118.4 (CH_2=), 97.7 (NCHO), 82.9 (CHOAc), 72.65 (CH_2OCO), 66.8 (CH_2O), 37.2 (*t*Bu), 25.6 (*t*Bu).

4.3.3. *tert*-Butyl (2*S*,4*R*)-4-acetoxy-2-(*tert*-butyl)-1,3-oxazolane-3-carboxylate 6d. Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (dd, J=5.3, 1.9 Hz, 1H, CHOCO), 5.08 (s, 1H, NCHO), 4.15 (dd, J=10.0, 5.3 Hz, 1H, CH_2O), 3.97 (dd, J=10.0, 2.4 Hz, 1H, CH_2O), 2.1 (s, 3H, Me), 1.48 (s, 9H, O*t*Bu), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C=O), 153.6 (C=O), 97.4 (NCHO), 83.3 (CHOCO), 81.8 (O*t*Bu), 72.7 (CH_2O), 37.1 (*t*Bu), 28.1 (O*t*Bu), 25.6 (*t*Bu), 21.0 (Me).

4.4. General procedure for the preparation of 2a–2d

Into a 500 ml three-necked flask equipped with an extractor connected with a condenser, **6a–6d** (1 equiv.), ammonium bromide (2.5 equiv.) and toluene (2 ml/mmol) were added. In the extractor toluene (150 ml) and 3 N KOH (150 ml) were added. The mixture was allowed to warm to reflux for 6 h. After cooling, the mixture was filtered and the filtrate was washed with a solution of saturated $NaHCO_3$ and brine, then dried and concentrated. The residue was flash chromatographied to give the product **2a–2d**.

4.4.1. *tert*-Butyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate 2b. White solid, yield 68%, mp 45–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J=13.7 Hz, 2H, CHO, CHN), 5.60 (s, 1H, NCHO), 1.44 (s, 9H, O*t*Bu), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 (C=O), 133.5 (CHO), 109.5 (CHN), 98.2 (NCHO), 81.2 (O*t*Bu), 38.3 (*t*Bu), 28.2 (O*t*Bu), 26.1 (*t*Bu). $[\alpha]_D^{20}$=+352 (*c* 1.01, $CHCl_3$). MS (CI) *m*/*z* 227 (M^+), 170, 114, 70. Anal. Calcd for $C_{12}H_{21}NO_3$ C 63.40, H 9.31, N 6.16; found C 63.10, H 9.22, N 5.91.

4.4.2. Allyl (2*R*)-2-(*tert*-butyl)-1,3-oxazole-3(2*H*)-carboxylate 2c. White solid, yield 85%, mp 38–40 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J=13.7 Hz, 2H, CHO, CHN), 5.93 (m, 1H, =CH), 5.62 (s, 1H, NCHO), 5.33 (ddd, J=17.2, 3.1, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.4, 2.7, 1.4 Hz, 1H, CH_2=), 4.64 (dd, J=5.7, 1.4 Hz, 2H, CH_2), 0.97 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1 (C=O), 133.7 (CHO), 132.3 (CH=), 118.1 (CH_2=), 109.5 (CHN), 98.2 (NCHO), 66.4 (CH_2O), 38.3 (*t*Bu), 24.1 (*t*Bu). $[\alpha]_D^{20}$=+432 (*c* 1.05, $CHCl_3$). MS (EI) *m*/*z* (%) 211 (M+1, 74), 154 (M−*t*Bu, 100), 110 (74), 70 (19). Anal. Calcd for $C_{11}H_{17}NO_3$ C 62.86, H 8.08, N 6.42; found C 62.54, H 8.11, N 6.63.

4.4.3. *tert*-Butyl (2*S*)-2-(*tert*-butyl)-1,3-oxazole-3-carboxylate 2d. White solid, yield 74%, mp 45–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (se, 2H, NCHO, CH=), 5.56 (s, 1H, CH=), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9 (C=O), 133.1 (CH=), 101.0 (CH=), 97.9 (NCHO), 81.0 (O*t*Bu), 38.2 (*t*Bu), 28.2 (O*t*Bu), 24.1 (*t*Bu). MS (APCI) *m*/*z* (%) 172 (M−*t*Bu, 10), 126 (M−Boc, 80). $[\alpha]_{20}^{D}$=−3.6 (*c* 1.3, $CHCl_3$), Anal. Calcd for $C_{12}H_{21}NO_3$ C 63.41, H 9.31, N 6.16; found C 63.72, H 9.08, N 6.29.

4.4.4. 2-Chloro-3-methoxycarbonylpropanoyl chloride 3i. Mono-methyl succinate (6.23 g, 44.79 mmol) and thionyl chloride (13.1 ml, 179.1 mmol) were placed in a 50 ml flask equipped with a magnetic bar and a condenser with a drying tube. The reaction mixture was stirred and heated in a 70 °C oil bath. After 0.5 h, the flask was removed from the oil bath and cooled to room temperature. The finely powdered *N*-chlorosuccinimide (12 g, 89.6 mmol), thionyl chloride (9 ml, 122.9 mmol) and hydrochloric acid (conc. 270 μl) were added consecutively. The flask was heated again to 85 °C for 3 h. The solvent was removed under the reduced pressure and the solid (succinimide) was washed with CCl_4. The filtrate was fractionally distilled to give the product (2.5 g, 30%), bp 30–32 °C/0.1 mm Hg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (dd, J=7.1, 6.5 Hz, 1H, CHCl), 3.76 (s, 3H, OCH_3), 3.04–3.29 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C=O), 167.8 (C=O), 66.4 (CHCl), 52.2 (OCH_3), 35.2 (CH_2).

4.5. General procedure for α-chlorination of ester

Methyl 4-benzyloxybutanoate (10 g, 48.0 mmol) in THF (25 ml) was added dropwise at −78 °C to a LDA solution that was prepared by adding *n*-butyllithium (2.4 M in hexane, 20 ml, 48.0 mmol) to diisopropylamine (7.1 ml, 50.4 mmol) in THF (250 ml) at 0 °C and stirring for 30 min. After stirring for a further 20 min, CCl_4 (5.0 ml, 52.8 mmol) was added rapidly and the resulting solution was stirred for 5 min at −78 °C, then a solution of saturated NH_4Cl (160 ml) was added and the mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give the product. Purification by flash chromatography gave pure product.

4.5.1. Methyl 4-benzyloxy-2-chlorobutanoate 7a. Colourless oil, yield 77%, R_f=0.3 (PE/AcOEt=9/1,) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5H, Ph), 4.55 (dd, J=8.35, 5.55 Hz, 1H, CHCl), 4.50 (s, 2H, $PhCH_2$), 3.71 (s,

3H, OMe), 3.65 (m, 2H, OCH_2), 2.16–2.37 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 138.0 (C_{arom}), 128.4, 128.3, 127.6 (CH_{arom}), 73.1 ($PhCH_2$), 65.7 (OCH_2), 54.3 (CHCl), 52.7 (OMe), 35.1 (CH_2). MS (APCI) *m/z* (%) 243 (M+1, 5), 91 (100). Anal. Calcd for $C_{12}H_{15}ClO_3$ C 59.39, H 6.23, Cl 14.60; found C 59.68, H 6.14, Cl 15.39.

4.5.2. Methyl 2-chloro-4-*tert*-butyldimethylsilyloxy butanoate 7b. Colorless oil, yield 58%, R_f=0.42 (PE/AcOEt=16/1) ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, *J*=9.0, 5.1 Hz, 1H, CHCl), 3.78 (s, 3H, OMe), 3.76 (m, 2H, OCH_2), 2.0–2.3 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 58.7 (OCH_2), 54.1 (CHCl), 52.9 (OMe), 37.5 (CH_2), 25.8 (*t*Bu), 18.2 (*t*Bu), −5.5 (SiMe).

4.5.3. Methyl 2-chloro-4-*tert*-butyldiphenylsilyloxy butanoate 7c. Yield 68%, R_f=0.3 (PE/Et_2O=16/1), ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.76 (m, 10H, 2Ph), 4.77 (dd, *J*=8.8, 4.94 Hz, 1H, CHCl), 3.9 (m, 2H, OCH_2), 3.8 (s, 3H, OMe), 2.15–2.45 (m, 2H, CH_2), 1.15 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (C=O), 133.5 (C_{arom}), 135.5, 129.6, 127.6 (CH_{arom}), 59.7 (OCH_2), 54.1 (CHCl), 52.8 (OMe), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.2 (CH_2). MS (APCI) *m/z* (%) 391 (M+1, 5), 313 (M−Ph, 100). Anal. Calcd for $C_{21}H_{27}ClO_3Si$ C 64.51, H 6.96, Cl 9.07; found C 65.19, H 6.86, Cl 9.24.

4.5.4. General procedure for the hydrolysis of methyl esters. Into a 100 ml flask, methyl 2-chloro-4-benzyloxy-butanoate (3.65 g, 15.0 mmol) was dissloved in THF (90 ml), then a solution of lithium hydroxide monohydrate (947 mg, 22.55 mmol) in water (40 ml) was added at 0 °C. The mixture was stirred overnight, acidified with H_2SO_4 to pH 3, and then extracted with CH_2Cl_2. The combined dichloromethane was dried and evaporated to afford the product.

4.5.5. 4-Benzyloxy-2-chlorobutanoic acid 8a. Yield 93%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.7 (s, 1H, OH), 7.27–7.37 (m, 5H, Ph), 4.56 (dd, *J*=8.6, 5.2 Hz, 1H, CHCl), 4.51 (s, 2H, $PhCH_2$), 3.65 (m, 2H, OCH_2), 2.12–2.41 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C=O), 137.8 (C_{arom}), 128.4, 128.3, 127.6 (CH_{arom}), 73.1 ($PhCH_2$), 65.7 (OCH_2), 54.4 (CHCl), 34.8 (CH_2). MS (APCI) *m/z* (%) 229 (M+1, 45), 136 (10), 91 (100). Anal. Calcd for $C_{11}H_{13}ClO_3$ C 57.78, H 5.73, Cl 15.50; found C 58.10, H 5.89, Cl 16.75.

4.5.6. 2-Chloro-4-*tert*-butyldimethylsilyloxybutanoic acid 8b. Yield 88%. ^1H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H, OH), 4.50 (dd, *J*=8.5, 5.1 Hz, 1H, CHCl), 3.80 (m, 2H, OCH_2), 2.0–2.3 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (C=O), 58.7 (OCH_2), 54.3 (CHCl), 37.5 (CH_2), 25.8 (*t*Bu), 18.3 (*t*Bu), −5.5 (SiMe).

4.5.7. 2-Chloro-4-*tert*-butyldiphenylsilyloxybutanoic acid 8c. White solid, yield 94%. ^1H NMR (300 MHz, $CDCl_3$) δ 10.45 (s, 1H, OH), 7.38–7.72 (m, 10H, 2Ph), 4.68 (dd, *J*=8.7, 5.0 Hz, 1H, CHCl), 3.8 (m, 2H, OCH_2), 2.07–2.36 (m, 2H, CH_2), 1.05 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (C=O), 133.2 (C_{arom}), 135.5, 129.6, 127.6 (CH_{arom}), 59.6 (OCH_2), 54.3 (CHCl), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.1 (CH_2). MS (APCI) *m/z* (%) 377 (M+1, 100), 299 (M−Ph, 30), 209 (30). Anal. Calcd for $C_{20}H_{25}ClO_3Si$ C 63.72, H 6.68, Cl 9.41; found C 63.02, H 6.69, Cl 9.62.

4.6. General procedure for the preparation 3j–n

Into a 100 ml flask, 4-methoxy-2-chloro-3-butanoic acid (1 equiv.), catalytical amount of DMF and CH_2Cl_2 (10 ml/mmol) were added, the mixture was cooled to 0 °C, then oxalyl chloride (5 equiv.) was added dropwise. The mixture was allowed to warm slowly to 15 °C for 30 min. The solvent was removed under the reduced pressure, and the residue was diluted with benzene and concentrated one more time to give the product.

4.6.1. 4-Methoxy-2-chloro-3-butanoyl chloride 3j. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (dd, *J*=8.0, 5.0 Hz, 1H, CH), 3.60 (m, 2H, OCH_2), 3.35 (s, 3H, OMe), 2.2–2.48 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C=O), 67.3 (OCH_2), 62.4 (CH), 58.8 (OMe), 34.7 (CH_2).

4.6.2. 4-Benzyloxy-2-chlorobutanoylchloride 3k. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.38 (m, 5H, Ph), 4.81 (dd, *J*=8.0, 5.2 Hz, 1H, CHCl), 4.50 (s, 2H, $PhCH_2$), 3.66 (m, 2H, OCH_2), 2.22–2.51 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C=O), 137.8 (C_{arom}), 128.4, 127.8, 127.6 (CH_{arom}), 73.3 ($PhCH_2$), 64.9 (OCH_2), 62.5 (CHCl), 34.9 (CH_2).

4.6.3. 2-Chloro-4-*tert*-butyldimethylsilyloxybutanoyl chloride 3l. Yield 79%, ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (dd, *J*=8.0, 4.9 Hz, 1H, CHCl), 3.84 (m, 2H, OCH_2), 2.17–2.46 (m, 2H, CH_2), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C=O), 62.5 (OCH_2), 58.0 (CHCl), 38.5 (CH_2), 25.9 (*t*Bu), 18.3 (*t*Bu), −5.5 (SiMe).

4.6.4. 2-Chloro-4-*tert*-butyldiphenylsilyloxybutanoyl chloride 3m. Yield 95%. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.70 (m, 10H, 2Ph), 4.90 (dd, *J*=8.0, 4.9 Hz, 1H, CHCl), 3.84 (m, 2H, OCH_2), 2.17–2.46 (m, 2H, CH_2), 1.06 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C=O), 133.0 (C_{arom}), 135.5, 129.6, 127.7 (CH_{arom}), 62.5 (OCH_2), 59.0 (CHCl), 37.3 (*t*Bu), 26.7 (*t*Bu), 19.2 (CH_2).

4.6.5. 2-Chloro-3-(1,3-dioxolan-2-yl)propanoyl chloride 3n. Yield 90%. ^1H NMR (300 MHz, $CDCl_3$) δ 5.1 (dd, *J*=4.65, 3.3 Hz, 1H CHCl), 4.72 (dd, *J*=7.5, 6.15 Hz, 1H, OCHO), 3.89–4.04 (m, 4H, OCH_2CH_2O), 2.34–2.61 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 100.5 (OCHO), 65.1 (OCH_2CH_2O), 60.1 (CHCl), 38.7 (CH_2).

4.6.6. 4-Oxo-butyric acid benzyl ester 9. Ozone was passed through a solution of benzyl 4-pentenoate (21 g, 110.3 mmol) in dichloromethane (160 ml) in a 250 ml three-necked flask at −78 °C until the solution became blue. Then triethylamine (30.7 ml, 220.7 mmol) was added and the mixture was warmed gradually to room temperature. The mixture was washed with 1N HCl (100 ml), then 5% $NaHCO_3$ (50 ml). The organic layer was dried and evaporated. The residue was flash chromatographied (PE/

AcOEt=6/1) to give pure product as a colourless oil, yield 90%, R_f=0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H, CHO), 7.31–7.37 (m, 5H, Ph), 5.12 (s, 2H, OCH_2), 2.61–2.8 (m, 4H, CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5 (C=O), 171.6 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 127.9 (CH_{arom}), 68.6 (OCH_2), 37.5 (CH_2CHO), 26.5 (CH_2).

4.6.7. Benzyl 3-(1,3-dioxolan-2-yl)propanoate 10. Into a 500 ml flask equipped with a Dean-Stark dried with flame under argon, benzyl 4-oxobutanoate (23 g, 119.6 mmol), ethylene glycol (13.3 ml, 239.3 mmol), anhydrous *para*-toluenesulfonic acid (2.06 g, 11.96 mmol) and benzene (690 ml) were mixed and heated to reflux until 2 ml water was collected. After cooling, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$, then dried and evaporated to give the product which is pure enough for the next reaction, yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.37 (m, 5H, Ph), 5.12 (s, 2H, OCH_2), 4.95 (t, J=4.1 Hz, 1H, OCHO), 3.80–3.95 (m, 4H, OCH_2CH_2O), 2.49 (t, J=7.36 Hz, 2H, CH_2CO), 2.04 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 127.9 (CH_{arom}), 110.1 (OCHO), 68.2 (OCH_2), 367.5 (OCH_2CH_2O), 26.4 (CH_2CO), 25.9 (CH_2).

4.6.8. Benzyl 2-chloro-3-(1,3-dioxolan-2-yl)propanoate 11. Colourless oil, yield 68%, R_f=0.3 (PE/AcOEt=8/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.37 (m, 5H, Ph), 5.21 (s, 2H, OCH_2), 5.04 (dd, J=5.22, 3.4 Hz, 1H CHCl), 4.51 (t, J=7.1 Hz, 1H, OCHO), 3.81–3.95 (m, 4H, OCH_2CH_2O), 2.27–2.50 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C=O), 135.8 (C_{arom}), 128.6, 128.2, 128.0 (CH_{arom}), 110.1 (OCHO), 67.6 (OCH_2), 65.1 (OCH_2CH_2O), 52.4 (CHCl), 38.9 (CH_2).

4.6.9. 2-Chloro-3-(1,3-dioxolan-2-yl)propanoic acid 12. Benzyl 2-chloro-3-(1,3-dioxolan-2-yl) propanoate (3.65 g, 13.48 mmol), palladium on activated carbon (10% Pd, 1.3 g; 1.2 mmol) and ethyl acetate (110 ml) were added to a 250 ml flask at room temperature, then hydrogen was flushed through a balloon. After 12 h, the mixture was passed through a pad of celite, washed with ether, dried over $MgSO_4$ and evaporated to give the product as a white solid, yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.1 (s, 1H, OH), 5.1 (dd, J=5.2, 3.4 Hz, 1H CHCl), 4.51 (t, J=7.1 Hz, 1H, OCHO), 3.89–4.0 (m, 4H, OCH_2CH_2O), 2.29–2.51 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (C=O), 101.1 (OCHO), 65.1 (OCH_2CH_2O), 52.4 (CHCl), 38.7 (CH_2).

4.7. General procedure for the [2+2] cycloaddition of oxazolines to haloketenes

Into a 250 ml three-necked flask dried by flame under the argon, oxazoline **2** (1 equiv.), triethylamine (1.2 equiv.) and cyclohexane (5 ml/mmol) were added, then acyl chloride (1.0–1.2 equiv.) in cyclohexane (2 ml/mmol) was added dropwise by a syringe pump at 60 °C. After the addition, the mixture was stirred at 60 °C for another 4 h, then cooled to room temperature. The mixture was allowed to stay at room temperature overnight, then filtered. The filtrate was evaporated to give the crude cycloadduct, which was purified by flash chromatography.

4.7.1. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 13. White solid, yield 77%, mp 103–105 °C, R_f=0.27 (3% isopropanol in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.34 (d, J=5.5 Hz, 1H, CHN), 4.90 (d, J=5.5 Hz, 1H, CHO), 3.76 (s, 3H, OMe), 1.62 (s, 3H, Me), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9 (C=O), 154.6 (C=O), 102.1 (NCHO), 81.3 (CHO), 75.0 (CCl), 74.2 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.2 (*t*Bu), 17.3 (Me). $[\alpha]_D^{20}$=+0.97 (1.03, $CHCl_3$). IR (KBr) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (EI) m/z (%) 276 ($M^{+\cdot}$, 6), 248 (27), 246 (66), 220 (24), 218 (74), 164 (36), 162 (93), 128 (88), 126 (100). Anal. Calcd for $C_{12}H_{18}ClNO_4$ C 52.27, H 6.58, Cl 12.86, N 4.77; found C 51.87, H 6.46, Cl 13.03, N 4.77.

4.7.2. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 14. Yield 75%, R_f=0.28 (3% isopropanol in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (s, 1H, NCHO), 5.23 (d, J=5.5 Hz, 1H, CHN), 4.88 (d, J=5.5 Hz, 1H, CHO), 1.62 (s, 3H, Me), 1.47 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.0 (C=O), 153.2 (C=O), 101.8 (NCHO), 81.6 (O*t*Bu), 81.5 (CHO), 75.3 (CCl), 74.4 (CHN), 39.1 (*t*Bu), 28.1 (O*t*Bu), 25.3 (*t*Bu), 17.5 (Me). $[\alpha]_D^{20}$=+1.0 (c 1.1, $CHCl_3$). IR (KBr) ν 1803 (C=O), 1715 (C=$O_{carbamate}$). MS (EI) m/z (%) 318 ($M^{+\cdot}$, 7), 290 (24), 288 (60), 262 (20), 224 (69), 168 (100). Anal. Calcd for $C_{15}H_{24}ClNO_4$ C 56.7, H 7.61, Cl 11.16, N 4.40; found C 57.77, H 7.70, Cl 10.27, N 4.27.

4.7.3. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 15. Yield 78%, R_f=0.27 (petroleum ether/AcOEt=4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H, CH=), 5.39 (s, 1H, NCHO), 5.37 (d, J=5.5 Hz, 1H, CHN), 5.36 (ddd, J=17.2, 3.2, 1.5 Hz, 1H, CH_2=), 5.26 (ddd, J=10.3, 2.8, 1.4 Hz, 1H, CH_2=), 4.92 (d, J=5.5 Hz, 1H, CHO), 4.63 (dt, J=5.8, 1.4 Hz, 2H, CH_2O), 1.64 (s, 3H, Me), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 154.1 (C=O), 132.2 (CH=), 118.5 (=CH_2), 102.1 (NCHO), 81.3 (CHO), 75.0 (CH_2O), 74.2 (CHN), 66.8 (CCl), 39.0 (*t*Bu), 25.3 (*t*Bu), 17.3 (Me). IR (film) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (CI) m/z (%) 302 (M+1, 5), 244 (M−*t*Bu, 69), 216 (M−Alloc, 44), 188 (100), 152 (88), 108 (71).

4.7.4. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 16. Yield 82%, R_f=0.29 (3% isopropanol in petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (s, 1H, NCHO), 5.31 (d, J=5.56 Hz, 1H, CHO), 4.90 (d, J=5.56 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 1.97 (q, J=7.3 Hz, 2H, CH_2), 1.10 (t, J=7.3 Hz, 3H, CH_3), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (C=O), 154.2 (C=O), 102.0 (NCHO), 81.1 (CHO), 80.0 (CCl), 73.6 (CHN), 62.8 (OMe), 39.0 (*t*Bu), 25.4 (*t*Bu), 23.5 (CH_2), 8.1 (Me). IR (KBr) ν 1802 (C=O), 1714 (C=$O_{carbamate}$). MS (APCI) m/z (%) 290 (M+1, 66), 251 (M−COOMe, 16), 222 (16), 186 (20), 144 (30). HRMS (ESI) Calcd for $C_{13}H_{20}ClNO_4$ 290.1159, found 290.1148.

4.7.5. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 17. Colorless oil, yield 68%, R_f=0.20 (PE/Et_2O=10/1). ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H, NCHO), 5.31 (d, J=5.26 Hz, 1H, CHO), 4.90 (d, J=5.26 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 2.50 (m, 1H, $CHMe_2$), 1.10 (d, J=6.75 Hz, 3H, CH_3), 1.0 (d, J=6.75 Hz, 3H, CH_3), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1 (C=O), 154.3 (C=O), 101.9 (NCHO), 84.3 (CCl), 81.3 (CHO), 73.3 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 28.1 ($CHMe_2$), 25.4 (*t*Bu), 16.8 (Me), 16.7 (Me). IR (KBr) ν 1800 (C=O), 1716 (C=$O_{carbamate}$). MS (ESI) *m*/*z* (%) 304 (M+1, 16).

4.7.6. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 18. White solid, yield 58%, mp 114–116 °C, R_f=0.30 (PE/Et_2O=20/1). ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H, NCHO), 5.20 (d, J=5.7 Hz, 1H, CHO), 4.86 (d, J=5.7 Hz, 1H, CHN), 2.50 (m, 1H, $CHMe_2$), 1.49 (s, 9H, O*t*Bu), 1.10 (d, J=6.6 Hz, 3H, CH_3), 1.0 (d, J=6.6 Hz, 3H, CH_3), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 154.3 (C=O), 101.6 (NCHO), 84.7 (O*t*Bu), 81.5 (CHO), 77.9 (CCl), 73.6 (CHN), 39.1 (*t*Bu), 28.6 (O*t*Bu), 28.1 ($CHMe_2$), 25.4 (*t*Bu), 16.9 (Me), 16.8 (Me). $[\alpha]_D^{20}$=+1.25 (*c* 0.62, $CHCl_3$). IR (KBr) ν 1800 (C=O), 1716 (C=$O_{carbamate}$). MS (APCI) *m*/*z* (%) 290 (M−*t*Bu, 60), 126 (100). Anal. Calcd for $C_{17}H_{28}ClNO_4$ C 59.04, H 8.15, Cl 10.25, N 4.05; found C 59.08, H 7.92, Cl 10.03, N 3.93.

4.7.7. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-phenyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 19A. White solid, yield 76%, mp 159–162 °C. R_f=0.27 (PE/Et_2O=95/5), ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5H, Ph), 5.41 (d, J=5.3 Hz, 1H, CHN), 5.23 (d, J=5.4 Hz, 1H, CHO), 5.08 (s, 1H, NCHO), 3.76 (s, 3H, OMe), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9 (C=O), 154.2 (C=O), 132.7 ($C_{arom.}$), 129.4, 128.7, 128.2 (CH_{arom}), 102.0 (NCHO), 82.0 (CHO), 81.0 (CCl), 74.1 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.4 (*t*Bu). $[\alpha]_{20}^{D}$=+1.90 (*c* 0.5, $CHCl_3$). IR (KBr) ν 2990, 1800 (C=O), 1720 (C=$O_{carbamate}$), 1360. MS (CI) *m*/*z* 337 (M+1), 306, 280, 188. Anal. Calcd for $C_{17}H_{20}ClNO_4$ C 60.44, H 5.96, N 4.14; found C 59.96, H 6.32, N 3.88.

4.7.8. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-phenyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 20A. White solid, yield 76%, mp 101–103 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5H, Ph), 5.30 (d, J=5.2 Hz, 1H, CHN), 5.21 (d, J=5.2 Hz, 1H, CHO), 5.01 (s, 1H, NCHO), 1.49 (s, 9H, O*t*Bu), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (C=O), 153.2 (C=O), 133.0 (C_{arom}), 129.2, 128.5, 128.3 (CH_{arom}), 101.3 (NCHO), 82.0 (CHO), 81.5 (O*t*Bu), 77.6 (CCl), 74.3 (CHN), 39.0 (*t*Bu), 28.8 (O*t*Bu), 25.4 (*t*Bu). IR (neat) ν 2920, 1810 (C=O), 1720 (C=$O_{carbamate}$), 1364. MS (CI) *m*/*z* 351 (M^+−CO), 295, 251, 222, 164. Anal. Calcd for $C_{20}H_{26}ClNO_4$ C 63.23, H 6.89, N 3.68; found C 63.39, H 7.00, N 3.19.

4.7.9. *tert*-Butyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-phenyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 20B. White solid, yield 76%, mp 121–125 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.6–7.30 (m, 5H, Ph), 5.63 (d, J=6.1 Hz, 1H, CHN), 5.55 (d, J=5.9 Hz, 1H, CHN), 5.44 (s, 1H, NCHO), 5.17 (s, 1H, NCHO), 4.91 (d, J=5.9 Hz, 1H, CHO), 4.79 (d, J=6.1 Hz, 1H, CHO), 1.11 (s, 9H, O*t*Bu), 1.09 (s, 9H, O*t*Bu), 0.93 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0 (C=O), 152.2 (C=O), 129.1, 128.8 (C_{arom}), 128.6, 128.4, 128.3, 128.2, 128.1, 127.9 (CH_{arom}), 102.1, 101.3 (NCHO), 91.9, 90.7, 66.5, 66.1, 40.0, 39.9, 27.7, 27.5, 25.7. 82.0 (CHO), 81.5 (O*t*Bu), 77.6 (CCl), 74.3 (CHN), 39.0 (*t*Bu), 28.8 (O*t*Bu), 25.4 (*t*Bu).

4.7.10. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-trimethylsilylmethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 21. White solid, yield 86%, mp 127–129 °C, R_f=0.30 (3% isopropanol in petroleum ether). ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, J=5.5 Hz, 1H, CHO), 5.33 (s, 1H, NCHO), 4.87 (d, J=5.5 Hz, 1H, CHN), 3.76 (s, 3H, OMe), 1.36 (d, J=1.5 Hz, 2H, CH_2), 0.93 (s, 9H, *t*Bu), 0.14 (s, 9H, 3Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7 (C=O), 154.8 (C=O), 102.0 (NCHO), 81.9 (CHO), 79.0 (CCl), 73.9 (CHN), 52.8 (OMe), 39.0 (*t*Bu), 25.5 (*t*Bu), 18.6 (CH_2), −0.04 ($SiMe_3$). $[\alpha]_D^{20}$=+1.16 (*c* 1.09, $CHCl_3$). IR (KBr) ν 2959, 1804 (C=O), 1716 (C=$O_{carbamate}$), 1367, 844. MS (CI) *m*/*z* (%) 348 (M+1, 19), 312 (12), 262 (19), 240 (24), 208 (12), 144 (39), 112 (35), 73 (100). Anal. Calcd for $C_{15}H_{26}ClNO_4Si$ C 51.78, H 7.53, N 4.03; found C 51.26, H 7.66, N 4.64.

4.7.11. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-trimethylsilylmethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 22. Yield 82%, R_f=0.29 (PE/Et_2O/*i*PrOH=100/3/3), mp 135–138 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H, NCHO), 5.26 (d, J=5.5 Hz, 1H, CHO), 4.85 (d, J=5.5 Hz, 1H, CHN), 1.49 (s, 9H, O*t*Bu), 1.36 (d, J=1.5 Hz, 2H, CH_2), 0.93 (s, 9H, *t*Bu), 0.14 (s, 9H, 3Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7 (C=O), 153.4 (C=O), 101.6 (NCHO), 82.0 (CHO), 81.4 (O*t*Bu), 79.1 (CCl), 74.1 (CHN), 39.0 (*t*Bu), 28.3 (O*t*Bu), 25.7 (*t*Bu), 18.8 (CH_2), −0.05 ($SiMe_3$). IR (KBr) ν 2960, 1805 (C=O), 1715 (C=$O_{carbamate}$), 1367, 845.

4.7.12. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromo)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 23. Yield 80%, R_f=0.26 (PE/Et_2O/*i*PrOH=100/4/3). ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (d, J=5.5 Hz, 1H, CHO), 5.35 (s, 1H, NCHO), 4.92 (d, J=5.5 Hz, 1H, CHN), 3.72 (s, 3H, OMe), 3.51 (m, 2H, CH_2Br), 2.50 (m, 2H, CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4 (C=O), 154.3 (C=O), 102.2 (NCHO), 80.8 (CHO), 77.0 (CCl), 74.3 (CHN), 52.9 (OMe), 39.0 (*t*Bu), 33.1 (CH_2Br), 25.2 (*t*Bu), 25.2 (CH_2). IR (film) ν 2972, 1804 (C=O), 1715 (C=$O_{carbamate}$), 1366, 1223. MS (EI) *m*/*z* (%) 368 ($M^{+\cdot}$, 5), 254 (11), 144 (15), 87 (100). Anal. Calcd for $C_{13}H_{19}BrClNO_4$ C 42.35, H 5.19, N 3.79; found C 41.87, H 4.97, N 3.59.

4.7.13. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromoethyl)-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 24A. Yield 72%, two inseparable regioisomers with a ratio of 8/1. R_f=0.30 (PE/AcOEt/*i*PrOH=100/5/3). ^1H NMR (200 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.29 (d, J=5.46 Hz, 1H, CHO), 4.92 (d, J=5.46 Hz, 1H, CHN), 3.55 (m, 2H, CH_2Br), 2.52 (m, 2H, CH_2), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR

(50 MHz, $CDCl_3$) δ 195.8 (C═O), 153.1 (C═O), 101.2 (NCHO), 83.4 (CHO), 82.6 (O*t*Bu), 77.4 (CCl), 74.5 (CHN), 39.1 (*t*Bu), 37.5 (CH_2Br), 28.5 (O*t*Bu), 26.1 (CH_2), 25.6 (*t*Bu). IR (film) ν 2982, 1800 (C═O), 1698 (C═$O_{cabamate}$), 1362, 1172. MS (FAB) *m*/*z* (%) 412 (M+1, 4), 356 (27), 154 (89), 136 (64).

4.7.14. *tert*-Butyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-(2-bromoethyl)-7-oxo-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 24B. ^{1}H NMR (200 MHz, CDCl3) δ 5.36 (s, 1H, NCHO), 4.65 (d, *J*=6.7 Hz, 1H, CHN), 4.41 (d, *J*=6.7 Hz, 1H, CHO), 3.55 (m, 2H, CH_2Br), 2.52 (m, 2H, CH_2), 1.50 (s, 9H, O*t*Bu), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, CDCl3) δ 194.8 (C═O), 153.1 (C═O), 101.2 (NCHO), 90.3 (CHO), 82.2 (O*t*Bu), 77.4 (CCl), 63.5 (CHN), 39.1 (*t*Bu), 37.5 (CH_2Br), 28.5 (O*t*Bu), 26.1 (CH_2), 25.6 (*t*Bu).

4.7.15. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromo)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 25. Yield 77%, R_f=0.3 (PE/AcOEt/*i*PrOH=100/5/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 1H, CH═), 5.42 (d, *J*=5.4 Hz, 1H, CHN), 5.40 (s, 1H, NCHO), 5.37 (ddd, *J*=17.1, 3.1, 1.5 Hz, 1H, CH_2═), 5.26 (ddd, *J*=10.3, 2.9, 1.4 Hz, 1H, CH_2═), 4.96 (d, *J*=5.5 Hz, 1H, CHO), 4.63 (dt, *J*=5.8, 1.4 Hz, 2H, CH_2O), 3.57 (m, 2H, CH_2Br), 2.50 (m, 2H, CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6 (C═O), 154.0 (C═O), 132.2 (CH═), 118.6 (═CH_2), 102.2 (NCHO), 80.9 (CHO), 77.0 (CH_2O), 74.2 (CHN), 66.9 (CCl), 39.6 (CH_2Br), 39.0 (*t*Bu), 25.5 (*t*Bu), 25.3 (CH_2). IR (film) ν 2942, 1792 (C═O), 1711 (C═O), 1140. MS (APCI) *m*/*z* (%) 394 (M+1, 3), 338 (5), 282 (100). Anal. Calcd for $C_{15}H_{21}BrClNO_4$ C 45.64, H 5.36, N 3.55; found C 43.97, H 5.17, N 3.45.

4.7.16. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-methoxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 26A. Yield 76%, R_f=0.24 (3% isopropanol in petroleum ether), two regioisomers inseparable with a proportion of 6/1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H, NCHO), 5.35 (d, *J*=5.45 Hz, 1H, CHN), 4.90 (d, *J*=5.45 Hz, 1H, CHO), 3.75 (s, 3H, OMe), 3.62 (m, 2H, CH_2O), 3.32 (s, 3H, OMe), 2.25 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1 (C═O), 154.5 (C═O), 102.0 (NCHO), 81.3 (CHO), 77.2 (CCl), 74.4 (CHN), 67.5 (CH_2O), 58.6 (OMe), 52.8 (OMe), 39.0 (*t*Bu), 29.7 (CH_2), 25.4 (*t*Bu). IR (KBr) ν 1804 (C═O), 1715 (C═$O_{carbamate}$). MS (EI) *m*/*z* (%) 320 ($M^{+\cdot}$, 22), 284 (31), 210 (30), 208 (100), 176 (72), 88 (76). Anal. Calcd for $C_{14}H_{22}ClNO_5$ C 52.58, H 6.93, N 4.38; found C 49.34, H 6.84, N 4.29.

4.7.17. Methyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-chloro-6-(2-methoxy)ethyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 26B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H, NCHO), 5.0 (d, *J*=6.7 Hz, 1H, CHN), 4.95 (d, *J*=6.7 Hz, 1H, CHO), 3.75 (s, 3H, OMe), 3.62 (m, 2H, CH_2O), 3.32 (s, 3H, OMe), 2.25 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0 (C═O), 154.5 (C═O), 102.0 (NCHO), 94.0 (CHO), 77.3 (CCl), 67.1 (CH_2O), 65.2 (CHN), 58.6 (OMe), 52.8 (OMe), 39.0 (*t*Bu), 29.7 (CH_2), 25.4 (*t*Bu).

4.7.18. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldimethylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 27. Yield 54%, R_f=0.29 (PE/AcOEt/*i*PrOH=100/4/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (d, *J*=5.2 Hz, 1H, CHN), 5.35 (s, 1H, NCHO), 4.88 (d, *J*=5.2 Hz, 1H, CHO), 3.85 (m, 2H, CH_2O), 3.74 (s, 3H, OMe), 2.37 (m, 1H, 1/2CH_2), 1.96 (m, 1H, 1/2CH_2), 0.98 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu), 0.05 (s, 6H, $SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (C═O), 154.2 (C═O), 102.0 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.7 (CHN), 66.3 (CH_2O), 52.9 (OMe), 38.9 (*t*Bu), 30.6 (CH_2), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu), −5.4 (SiMe). IR (film) ν 2959, 1803 (C═O), 1733 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 420 (M+1, 14), 384 (8), 280 (20), 154 (39), 73 (100). Anal. Calcd for $C_{19}H_{34}ClNO_5Si$ C 54.33, H 8.16, N 3.33; found C 52.63, H 8.14, N 2.87.

4.7.19. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 28. Yield 80%, R_f=0.28 (PE/AcOEt/*i*PrOH=100/4/3), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.71 (m, 10H, 2Ph), 5.41 (d, *J*=5.2 Hz, 1H, CHN), 5.32 (s, 1H, NCHO), 4.92 (d, *J*=5.2 Hz, 1H, CHO), 3.78–3.97 (m, 2H, CH_2O), 3.73 (s, 3H, OMe), 2.42 (ddd, *J*=15.0, 7.3, 7.3 Hz, 1H, 1/2CH_2), 2.0 (ddd, *J*=15.0, 6.4, 4.6 Hz, 1H, 1/2CH_2), 1.04 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9 (C═O), 154.2 (C═O), 133.3 (C_{arom}), 135.6, 130.0, 129.7, 127.8, 127.7 (CH_{arom}), 102.1 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.8 (CHN), 59.2 (CH_2O), 52.9 (OMe), 38.9 (*t*Bu), 30.6 (CH_2), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu). IR (film) ν 2958, 1803 (C═O), 1733 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 544 (M+1, 6), 486 (10), 217 (15), 197 (41), 135 (100). Anal. Calcd for $C_{29}H_{38}ClNO_5Si$ C 64.01, H 7.04, N 2.43; found C 63.85, H 7.05, N 2.43.

4.7.20. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 29. Yield 80%, R_f=0.25, (PE/Et_2O/*i*PrOH=100/3/3), mp129–131 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.72 (m, 10H, 2Ph), 5.34 (d, *J*=5.1 Hz, 1H, CHN), 5.32 (s, 1H, NCHO), 4.91 (d, *J*=5.1 Hz, 1H, CHO), 3.78–3.97 (m, 2H, CH_2O), 2.45 (ddd, *J*=14.8, 8.2, 6.3 Hz, 1H, 1/2CH_2), 1.97 (ddd, *J*=14.8, 6.3, 3.6 Hz, 1H, 1/2CH_2), 1.49 (s, 9H, O*t*Bu), 1.06 (s, 9H, Si*t*Bu), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3 (C═O), 153.2 (C═O), 133.4 (C_{arom}), 135.6, 130.0, 129.7, 127.8, 127.7 (CH_{arom}), 101.7 (NCHO), 81.7 (CHO), 81.4 (O*t*Bu), 75.0 (CHN), 74.5 (CCl), 59.2 (CH_2O), 39.0 (*t*Bu), 30.8 (CH_2), 28.0 (O*t*Bu), 26.8 (Si*t*Bu), 25.2 (*t*Bu), 19.1 (Si*t*Bu). IR (KBr) ν 2959, 1804 (C═O), 1726 (C═$O_{carbamate}$), 1363, 1112. MS (FAB) *m*/*z* (%) 586 (M+1). Anal. Calcd for $C_{32}H_{44}BrClNO_5S$ C 65.56, H 7.57, N 2.38, Cl 6.04; found C 65.85, H 7.68, N 2.31, Cl 5.70. $[\alpha]_{20}^{D}$=+0.99 (*c* 1.06, $CHCl_3$), X-Ray diffraction analysis wavelength: 0.71069 Å, Crystal system: orthorhombic unit cell dimensions, *a*=9.738 (3) Å, α=90°, *b*=10.205 (4) Å, β=90°, *c*=33.446 (8) Å, γ=90°.

4.7.21. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-*tert*-butyldiphenylsilyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 30. Yield 77%, two inseparable regioisomers with a ratio of 10/1. R_f=0.27 (3%

isopropanol in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.69 (m, 10H, 2Ph), 5.98 (m, 1H, CH═), 5.43 (d, J=5.5 Hz, 1H, CHN), 5.37 (s, 1H, NCHO), 5.35 (ddd, J=17.4, 3.0, 1.5 Hz, 1H, CH_2═), 5.25 (ddd, J=10.3, 3.0, 1.5 Hz, 1H, CH_2═), 4.93 (d, J=5.5 Hz, 1H, CHO), 4.64 (dt, J=6.1, 1.5 Hz, 2H, CH_2OCO), 3.95 (ddd, J=10.1, 8.2, 6.7 Hz, 1H, CH_2OSi), 3.87 (ddd, J=10.1, 7.6, 4.0 Hz, 1H, CH_2OSi), 2.43 (ddd, J=14.6, 8.2, 7.6 Hz, 1H, CH_2), 2.03 (ddd, J=14.6, 6.7, 4.0 Hz, 1H, CH_2), 0.90 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, CDCl3) δ 195.3 (C═O), 156.1 (C═O), 133.6 (C_{arom}), 132.3 (CH═), 135.5, 129.5, 127.7 (CH_{arom}), 118.3 (═CH2), 102.1 (NCHO), 81.5 (CHO), 77.3 (CH_2OCO), 74.8 (CHN), 66.7 (CCl), 59.3 (CH_2OSi), 39.0 (*t*Bu), 31.2 (CH_2), 25.3 (*t*Bu). IR (film) ν 2962, 1800 (C═O), 1709 (C═O). MS (APCI) *m*/*z* (%) 570 (M+1, 18), 534 (80), 492 (62), 314 (24). Anal. Calcd for $C_{31}H_{40}ClNO_4Si$ C 65.30, H 7.07, N 2.45; found C 63.95, H 7.49, N 2.20.

4.7.22. Allyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-6-chloro-7-oxo-6-(2-{[*tert*-butyl (diphenyl)silyl]oxy}ethyl)-2-oxa-4-aza-bicyclo[3.2.0]heptane-4-carboxylate 30B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.7 (m, 10H, 2Ph), 5.98 (m, 1H, CH═), 5.37 (s, 1H, NCHO), 5.38 (ddd, J=17.5, 3.0, 1.5 Hz, 1H, CH_2═), 5.22 (ddd, J=10.3, 3.0, 1.5 Hz, 1H, CH_2═), 4.68 (dt, J=6.1, 1.5 Hz, 2H, CH_2OCO), 4.64 (d, J=6.1 Hz, 1H, CHN), 4.48 (d, J=6.1 Hz, 1H, CHO), 3.65–3.97 (m, 2H, CH_2OSi), 1.70–2.79 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C═O), 156.1 (C═O), 133.6 (C_{arom}), 132.3 (CH═), 135.5, 129.5, 127.7 (CH_{arom}), 118.3 (═CH_2), 102.1 (NCHO), 81.5 (CHO), 77.3 (CH_2OCO), 74.8 (CHN), 66.7 (CCl), 59.3 (CH_2OSi), 39.0 (*t*Bu), 31.2 (CH_2), 25.3 (*t*Bu).

4.7.23. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-benzyloxyethyl)-2-oxa-4-aza bicycle[3.2.0]heptane-4-carboxylate 31. Yield 72%, two inseparable regioisomers with a ratio of 6/1. R_f=0.26 (PE/Et_2O/*i*PrOH=100/3/3). ^{1}H NMR (500 MHz, $CDCl_3$, 47 °C) δ 7.2–7.4 (m, 5H, Ph), 5.36 (s, 1H, NCHO), 5.35 (d, J=5.2 Hz, 1H, CHN), 4.90 (d, J=5.2 Hz, 1H, CHO), 4.45–4.55 (ab, J=12.2 Hz, 2H, CH_2Ph), 3.75 (m, 2H, CH_2O), 3.73 (s, 3H, OMe), 2.42 (ddd, J=15.0, 7.3, 7.3 Hz, 1H, 1/2CH_2), 2.14 (ddd, J=15.0, 6.4, 4.6 Hz, 1H, 1/2CH_2), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$, 47 °C) δ 195.1 (C═O), 154.6 (C═O), 138.3 (C_{arom}), 128.2, 127.4, 127.3 (CH_{arom}), 102.0 (NCHO), 81.4 (CHO), 77.4 (CCl), 74.6 (CHN), 72.8 (CH_2Ph), 65.1 (CH_2O), 52.7 (OMe), 38.9 (*t*Bu), 29.6 (CH_2), 25.2 (*t*Bu). IR (film) ν 1804 (C═O), 1715 (C═$O_{carbamate}$). MS (CI) *m*/*z* (%) 396 (M+1, 4), 362 (5), 306 (9), 288 (15), 254 (11), 211 (100), 184 (11), 91 (51).

4.7.24. *tert*-Butyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-benzyloxy)ethyl-2-oxa-4-azabicyclo[3.2.0]-heptane-4-carboxylate 32. Yield 56%, R_f=0.26 (PE/AcOEt/*i*PrOH=100/4/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5H, Ph), 5.33 (s, ^{1}H, NCHO), 5.29 (d, J=5.2 Hz, 1H, CHO), 4.87 (d, J=5.2 Hz, 1H, CHN), 4.47–4.59 (ab, J=12.2 Hz, 2H, CH_2Ph), 3.75 (m, 2H, CH_2O), 2.14–2.42 (m, 2H, CH_2), 1.48 (s, 9H, O*t*Bu), 0.91 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C═O), 154.3 (C═O), 138.3 (C_{arom}), 128.2, 127.4, 127.3 (CH_{arom}), 102.0 (NCHO), 82.4 (O*t*Bu), 81.6 (CHO), 77.4 (CCl), 74.3 (CHN), 72.8 (CH_2Ph), 65.1 (CH_2O), 39.0 (*t*Bu), 29.6 (CH_2), 28.6 (O*t*Bu), 25.2 (*t*Bu). IR (film) ν 1792 (C═O), 1706 (C═$O_{carbamate}$), 1368. MS (APCI) *m*/*z* (%) 438 (M+1, 12), 380, 316, 184 (11), 91 (51).

4.7.25. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(1,3-dioxolan-2-ylmethyl)-2-oxa-4-azabicyclo-[3.2.0]heptane-4-carboxylate 33. Yield 62%, R_f=0.26 (PE/AcOEt/*i*PrOH=100/5/3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.36 (s, 1H, NCHO), 5.32 (d, J=5.4 Hz, 1H, CHN), 4.95 (d, J=5.4 Hz, 1H, CHO), 4.45 (dd, J=5.9, 4.5 Hz, 1H, OCHO), 3.86–3.98 (m, 4H, OCH_2CH_2O), 3.76 (s, 3H, OMe), 2.32 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.2 (C═O), 153.6 (C═O), 101.9 (NCHO), 101.2 (OCHO), 81.6 (CHO), 75.8 (CCl), 74.5 (CHN), 65.0 (OCH_2CH_2O), 52.6 (OMe), 38.9 (*t*Bu), 34.5 (CH_2), 27.2 (*t*Bu). IR (film) ν 2960, 1803 (C═O), 1724 (C═$O_{carbamate}$), 1363, 1115. MS (APCI) *m*/*z* (%) 348 (M+1, 23), 312 (17).

4.7.26. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-bromo-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 34A. Yield 76%, R_f=0.27 (3% isopropanol in petroleum ether), two regioisomers inseparable with a ratio of 4/1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 5.31 (d, J=5.3 Hz, 1H, CHN), 5.0 (d, J=5.3 Hz, 1H, CHO), 2.24 (m, 1H, $CHMe_2$), 1.47 (s, 9H, O*t*Bu), 1.09 (d, J=6.6 Hz, 3H, Me), 0.99 (d, J=6.5 Hz, 3H, Me), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (C═O), 153.6 (C═O), 101.6 (NCHO), 81.4 (CHO), 80.7 (O*t*Bu), 77.3 (CBr), 73.3 (CHN), 39.1 (*t*Bu), 28.2 (O*t*Bu), 25.4 ($CHMe_2$), 25.2 (*t*Bu), 18.2 (Me). IR (film) ν 2942, 1793 (C═O), 1696 (C═$O_{carbamate}$), 1368. MS (CI) *m*/*z* (%) 390 (M+1, 5), 334 (100), 290 (51), 256 (24).

4.7.27. Methyl (1*S*,3*R*,5*R*,6*S*)-3-(*tert*-butyl)-6-bromo-6-isopropyl-7-oxo-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 34B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 4.84 (d, J=6.2 Hz, 1H, CHN), 4.1 (d, J=6.2 Hz, 1H, CHO), 2.25 (m, 1H, $CHMe_2$), 1.47 (s, 9H, O*t*Bu), 1.09 (d, J=6.6 Hz, 3H, Me), 0.99 (d, J=6.5 Hz, 3H, Me), 0.90 (s, 9H, *t*Bu).

4.7.28. *tert*-Butyl (1*R*,3*S*,5*S*,7*S*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-methyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 35. White solid, yield 72%, R_f=0.16 (EP/Et_2O=20/1), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H, NCHO), 5.23 (d, J=5.26 Hz, 1H, CHO), 4.88 (d, J=5.26 Hz, 1H, CHN), 1.63 (s, 3H, Me), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2 (C═O), 153.6 (C═O), 101.7 (NCHO), 82.2 (O*t*Bu), 81.2 (CCl), 81.0 (CHO), 74.4 (CHN), 39.1 (*t*Bu), 28.3 (O*t*Bu), 25.3 (*t*Bu), 24.2 (Me). $[\alpha]_D^{20}$=−0.95 (*c* 0.44, $CHCl_3$). MS (APCI) *m*/*z* (%) 318 (M+1, 7), 260 (M−*t*Bu, 6), 218 (100). Anal. Calcd for $C_{15}H_{24}ClNO_4$ C 56.68, H 7.61, N 4.41; found C 55.69, H 7.37, N 4.34.

4.7.29. *tert*-Butyl (1*R*,3*S*,5*S*,7*S*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-isopropyl-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 36A. White solid, yield 66%, mp 110–113 °C, R_f=0.40 (PE/Et_2O=20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1H, NCHO), 5.20 (d, J=5.5 Hz, 1H, CHO), 4.87 (d, J=5.5 Hz, 1H, CHN), 2.48 (m, 1H, $CHMe_2$), 1.49 (s, 9H,

O*t*Bu), 1.09 (d, *J*=6.7 Hz, 3H, CH_3), 1.0 (d, *J*=6.7 Hz, 3H, CH_3), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2 (C=O), 153.6 (C=O), 101.5 (NCHO), 84.2 (O*t*Bu), 81.0 (CHO), 76.9 (CCl), 73.5 (CHN), 39.1 (*t*Bu), 28.4 (O*t*Bu), 28.0 ($CHMe_2$), 25.3 (*t*Bu), 16.9 (Me), 16.8 (Me). $[\alpha]_D^{20}$=−1.14 (*c* 1.25, $CHCl_3$). MS (APCI) *m*/*z* (%) 290 (M−*t*Bu, 46), 246 (100). Anal. Calcd for $C_{17}H_{28}ClNO_4$ C 59.03, H 8.16, Cl 10.25, N 4.05; found C 58.77, H 8.00, Cl 9.46, N 4.28.

4.7.30. *tert*-Butyl (1*R*,3*S*,5*S*,6*R*)-3-(*tert*-butyl)-6-chloro-6-isopropyl-7-oxo-2-oxa-4-aza bicyclo[3.2.0]heptane-4-carboxylate 36b. R_f=0.34 (PE/E_2O=20/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (d, *J*=6.0 Hz, 1H, CHO), 5.29 (s, 1H, NCHO), 4.66 (d, *J*=6.0 Hz, 1H, CHN), 2.32 (m, 1H, $CHMe_2$), 1.50 (s, 9H, O*t*Bu), 1.15 (d, *J*=6.7 Hz, 3H, CH_3), 1.12 (d, *J*=6.7 Hz, 3H, CH_3), 0.94 (s, 9H, *t*Bu).

4.7.31. (1*R*,3*R*,5*R*)-4-(*tert*-Butoxycarbonyl)-6-(*tert*-butyl)-2-oxa-4-azabicyclo[3.2.0]heptane-6-one 38. Mp 90–91 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.07 (ddd, *J*=5.0, 5.0, 2.3 Hz, 1H), 4.92–4.85 (m, 1H), 3.18 (ddd, *J*=17.5, 5.0, 3.5 Hz, 1H), 3.08 (ddd, *J*=17.5, 2.3, 2.3 Hz), 1H), 1.48 (s, 9H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 153.1, 101.1, 81.2, 76.2, 71.3, 52.6, 39.0, 28.0, 25.5; $[\alpha]_D^{20}$=+116 (*c* 1.00, $CHCl_3$). IR (KBr) ν 2960, 1790, 1700. MS (CI) *m*/*z* (%) 227, 170, 57. Anal. Calcd for $C_{14}H_{23}NO_4$ C 62.03, H 8.60, N 5.2; found C 61.72, H 8.57, N 4.95.

4.8. General procedure for the [2+2] cycloaddition of oxazolines to methoxyketene and *N*-methyl-*N*-tosyl-aminoketene

Into a 25 ml three-necked flask dried by flame under the argon, (2*H*)oxazole **2** (1 equiv.), triethylamine (1.2–2.2 equiv.) and toluene (10 ml/mmol) were added, then acetyl chloride (1.2–2.2 equiv.) in toluene (2 ml/mmol) was added dropwise by a syringe pump at 110 °C. After the addition (2 h), the mixture was stirred at 110 °C for 8 h then 10 h at room temperature and filtered. The filtrate was evaporated to give crude product. Flash chromatography gave the pure product.

4.8.1. Methyl (3*R*)-3-(*tert*-butyl)-7-{methyl[(4-methylphenyl) sulfonyl]amino}-6-[(2-{methyl[(4-methylphenyl) sulfonyl]amino}acetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]-hept-6ene-4-carboxylate 39. White solid, yield 29%, mp 127–129 °C, R_f=0.35 (hexane/*i*PrOH/AcOEt=100/8/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.81 (m, 8H, 2Ph), 5.35 (s, 1H, NCHO), 5.31 (d, *J*=4.12 Hz, 1H, CHN), 5.03 (d, *J*=4.12 Hz, 1H, CHO), 4.05 (d, *J*=4.67 Hz, 2H, CH_2), 3.67 (s, 3H, OMe), 3.05 (s, 3H, NMe), 2.89 (s, 3H, NMe), 2.45 (s, 3H, Me), 2.43 (s, 3H, Me), 0.89 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (C=O), 155.3 (C=O), 144.3, 143.8, 134.9, 134.7 (C_{arom}), 129.8, 129.7, 127.8, 127.7, 127.4 (CH_{arom}), 128.3 (OC=), 127.7 (=CN), 104.0 (NCHO), 74.3 (CHO), 61.5 (CHN), 52.7 (OMe), 50.6 (CH_2), 38.8 (*t*Bu), 35.5 (NMe), 34.7 (NMe), 25.0 (*t*Bu), 21.6 (Me), 21.5 (Me). $[\alpha]_D^{20}$=+0.98 (*c* 0.62, $CHCl_3$). IR (KBr) ν 2959, 1726 (C=O), 1710 (C=$O_{carbamate}$), 1654, 1259, 1172. MS (CI) *m*/*z* (%) 635 (M−Me, 17), 480 (18), 410 (36), 298 (20), 242 (59), 190 (86), 155 (100). Anal. Calcd for $C_{30}H_{39}N_3O_9S_2$ C 55.45, H 6.04, N 6.46; found C 53.85, H 5.69, N 6.37.

4.8.2. Methyl (3*R*)-3-(*tert*-butyl)-7-methoxy-6-[(2-methoxy acetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]hept-6ene-4-carboxylate 40a. Yield 72%, R_f=0.33 (hexane/MeOH/AcOEt=100/7/20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H, NCHO), 5.07 (d, *J*=4.4 Hz, 1H, CHO), 4.96 (d, *J*=4.4 Hz, 1H, CHN), 4.11 (s, 2H, CH_2), 3.79 (s, 3H, OMe), 3.64 (s, 3H, $OMe_{carbamate}$), 3.48 (s, 3H, $MeOCH_2$), 0.86 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C=O), 155.3 (C=O), 142.4 (OC=), 120.7 (=COMe), 104.5 (NCHO), 77.7 (CHO), 69.0 (OCH_2), 59.6 (CHN), 59.4 ($MeOCH_2$), 58.0 (OCH_3), 52.3 ($OMe_{carbamate}$), 38.7 (*t*Bu), 24.8 (*t*Bu). IR (KBr) ν 2959, 2931, 1780 (C=O), 1716 (C=$O_{carbamate}$), 1447, 1367, 1117. MS (CI) *m*/*z* (%) 330 (M+1, 16), 272 (M−*t*Bu, 32), 240 (M−$OCOCH_2OCH_3$, 54), 216 (38), 202 (22), 172 (100), 144 (75). Anal. Calcd for $C_{15}H_{23}NO_7$ C 54.7, H 7.03, N 4.25; found C 54.29, H 6.77, N 4.35.

4.8.3. *tert*-Butyl (3*R*)-3-(*tert*-butyl)-7-methoxy-6-[(2-methoxyacetyl)oxy]-2-oxa-4-azabicyclo[3.2.0]hept-6ene-4-carboxylate 40b. Yield 56%, R_f=0.27 (hexane/*i*PrOH/AcOEt=100/8/8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 1H, NCHO), 5.41 (d, *J*=4.12 Hz, 1H, CHN), 4.63 (d, *J*=4.12 Hz, 1H, CHO), 4.13 (s, 2H, CH_2), 3.83 (s, 3H, OMe), 3.48 (s, 3H, $MeOCH_2$), 1.46 (s, 9H, O*t*Bu), 0.88 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C=O), 153.8 (C=O), 142.4 (OC=), 120.8 (=COMe), 103.1 (NCHO), 80.2 (CHO), 79.3 (O*t*Bu), 69.2 (OCH_2), 59.8 (CHN), 59.5 ($MeOCH_2$), 58.0 (OCH_3), 39.0 (*t*Bu), 28.2 (O*t*Bu), 25.1 (*t*Bu). IR (KBr) ν 2959, 2931, 1780 (C=O), 1716 (C=$O_{carbamate}$), 1447, 1367, 1117. MS (CI) *m*/*z* (%) 372 (M+1, 12), 314 (M−*t*Bu, 25), 282 (M−$OCOCH_2OCH_3$, 23), 270 (M−CO_2*t*Bu, 5), 258 (15), 187 (67), 83 (100). HRMS (CI) Calcd for $C_{18}H_{29}NO_7$ 372.20235, found 372.20223.

4.8.4. *tert*-Butyl (1*S*,3*R*,5*R*)-3-(*tert*-butyl)-6-oxo-7,7-(ethylene dithio)-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate 43. Into a 25 ml three-necked flask dried by flame under the argon, oxazoline **2b** (0.37 g, 1.6 mmol) and toluene (3 ml) were added and heated to reflux. 2,2-dimethyl-1-(*N*-methylphenylanilino)vinyl-1,3-dithiolane-2-carboxylate (1.34 g, 4.3 mmol) in toluene (2 ml) was added dropwise by a syringe pump during a period of 6 h. After the addition, the mixture was stirred for another 1 h. The solvent was evaporated, and the resulting residue was flash chromatographied to give product 0.23 g, 40%, R_f=0.47 (cyclohexane/AcOEt=4/1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.28 (s, 1H, NCHO), 5.03 (d, *J*=5.4 Hz, 1H, CHO), 4.96 (d, *J*=5.4 Hz, 1H, CHN), 3.38 (m, 4H, CH_2CH_2), 1.49 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.8 (C=O), 153.02 (C=O), 101.5 (NCHO), 81.4 (CHO), 80.9 (O*t*Bu), 78.6 (CS), 74.4 (CHN), 39.7 (CH_2), 39.4 (CH_2), 28.1 (O*t*Bu), 25.3 (*t*Bu). IR (KBr) ν 1796 (C=O), 1714 (C=$O_{cabamate}$). MS (EI) *m*/*z* (%) 359 (M^+), 331, 230, 174, 57. Anal. Calcd For $C_{16}H_{25}NO_4S_2$ C 53.45, H 7.0, N 3.89, S 17.83; found C 53.45, H 7.01, N 3.82, S 18.08.

4.8.5. Favorskii rearrangement of 23. Into a 25 ml two-necked flask dried by flame under argon, sodium iodide

(56.9 mg, 0.38 mmol), potassium carbonate (53 mg, 0.38 mmol) and methyl sulfoxide (4 ml) were heated to 120 °C under argon, then methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-(2-bromoethyl)-2-oxa-4-aza bicyclo [3.2.0]heptane-4carboxylate **23** (140 mg, 0.38 mmol) in DMSO (1 ml) was added. After stirring for an additional 1 h, the mixture was rapidly cooled and then poured into ice-cold brine (5 ml). The mixture was extracted with ether (2×5 ml). The combined extracts were washed with water, brine, 5% $NaHCO_3$ and brine, then dried and evaporated. The residue was chromatographied (PE/AcOEt=6/1, R_f=0.3) to give a Favorskii rearrangement product **44** (70 mg, 68%), mp 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 1H, NCHO), 4.49 (d, *J*=6.8 Hz, 1H, CHO), 4.46 (t, *J*=7.62 Hz, 2H, CH_2O), 3.78 (d, *J*=6.8 Hz, 1H, CHN), 3.77 (s, 3H, OMe), 2.12 (m, 2H, CH_2), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$, APT) δ 174.1 (C=O), 156.1 (C=O), 104.6 (NCHO), 66.3 (CH_2O), 66.0 (CHO), 53.2 (OMe), 42.4 (CHN), 38.0 (*t*Bu), 37.1 (CCO), 24.3 (*t*Bu), 20.8 (CH_2). IR (film) ν 2971, 1754 (C=O), 1718 (C=$O_{carbamate}$), 1351, 1021. MS (CI) *m*/*z* (%) 270 (M+1, 29), 211 (M−*t*Bu, 17), 144 (15), 184 (100), 144 (32), 89 (33). Anal. Calcd for $C_{13}H_{19}NO_5$ C 57.98, H 7.11, N 5.20; found C 57.74, 6.92, N 4.95.

4.8.6. Dimethyl (1*R*,3*R*,5*S*,6*R*)-3-(*tert*-butyl)-6-methyl-2-oxo-4-azabicyclo[3.1.0]hexane-4,6-dicarboxylate 45. Methyl (1*S*,3*R*,5*R*,7*R*)-3-(*tert*-butyl)-7-chloro-6-oxo-7-[2-(benzyloxy)ethyl]-2-oxa-4-azabicyclo[3.2.0]heptane-4-carboxylate **13** (280 mg, 1.0 mmol) and sodium hydroxide (426 mg, 1.1 mmol) in MeOH/H_2O (5:1, 5 ml) were mixed and stirred at room temperature for 4 h, then solvent was removed under reduced pressure. The residue was diluted with ether (20 ml), washed with 1 N HCl (2 ml) and water (5 ml), dried over $MgSO_4$ and evaporated. Flash chromatography (PE/AcOEt/*i*PrOH=100/5/5, R_f=0.45) gave the product (0.16 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 1H, NCHO), 4.37 (d, *J*=5.8 Hz, 1H, CHO), 3.73 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.62 (d, *J*=5.8 Hz, 1H, CHN), 1.16 (s, 3H, CH_3), 0.95 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (C=O), 157.1 (C=O), 105.0 (NCHO), 67.8 (CHO), 53.0 (OMe), 52.0 (OMe), 44.5 (CHN), 38.0 (*t*Bu), 35.5 (CCO), 24.5 (*t*Bu), 6.3 (CH_3). IR (film) ν 2957, 1734 (C=O), 1708 (C=$O_{carbamate}$), 1361, 1121. MS (FAB+) *m*/*z* (%) 272 (M+1, 25), 214 (M−*t*Bu, 28), 154 (100), 136 (67), 89 (30).

4.9. General procedure for the Baeyer–Villiger oxidation

Into a 25 ml two-necked flask dried by flame under the argon, cyclobutanones (1 equiv.) and chloroform (5 ml/mmol) were added, then 3-chloroperoxybenzoic acid (1 equiv.) and sodium bicarbonate (1 equiv.) were added consecutively. The mixture was stirred at room temperature under argon overnight, then washed with sodium sulphite solution (10%) and saturated $NaHCO_3$ solution. The organic fraction was dried and evaporated. Flash chromatography (PE/Et_2O=8/1) gave pure product (**46a**–**h**).

4.9.1. Methyl (2*R*,6*R*)-6-methyl-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46a. 95% yield, R_f=0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, *J*=3.02 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.82 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.8 (s, 3H, CH_3), 0.96 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.7 (CHN), 85.0 (CHO), 66.0 (CCl), 53.5 (OMe), 38.9 (*t*Bu), 25.6 (*t*Bu), 18.9 (CH_3). IR (film) ν 2960, 1800 (C=$O_{lactone}$), 1740 (C=O), 1359, 1112. MS (APCI) *m*/*z* (%) 292 (M+1, 14).

4.9.2. Methyl (2*R*,6*R*)-6-(2-bromoethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46b. 85% yield, R_f=0.34. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, *J*=3.02 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 5.0 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 3.65 (m, 2H, CH_2Br), 2.67 (m, 2H, CH_2), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9 (C=O), 154.2 (C=O), 99.5 (NCHO), 89.2 (CHN), 83.6 (CHO), 66.0 (CCl), 53.5 (OMe), 39.1 (*t*Bu), 33.5 (CH_2Br), 25.7 (CH_2), 25.6 (*t*Bu). IR (film) ν 2958, 1799 (C=$O_{lactone}$), 1742 (C=O), 1365, 1124. MS (FAB) *m*/*z* (%) 384 (M+1, 8), 307 (21), 154 (100), 136 (82).

4.9.3. Methyl (2*R*,6*R*)-6-(trimethylsilyl)methyl-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46c. 96% yield, R_f=0.37. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (d, *J*=3.02 Hz, 1H, CHN), 5.28 (s, 1H, NCHO), 4.86 (d, *J*=3.02 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.56 (ab, *J*=15.3 Hz, 2H, CH_2), 0.96 (s, 9H, *t*Bu), 0.18 (s, 9H, $SiMe_3$). ^{13}C NMR (75 MHz) δ 171.6 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.4 (CHN), 84.7 (CHO), 67.3 (CCl), 53.5 (OMe), 39.1 (*t*Bu), 25.6 (*t*Bu), 20.2 (CH_2), −0.1 ($SiMe_3$). IR (film) ν 2959, 1798 (C=$O_{lactone}$), 1743 (C=O), 1360, 1160. MS (APCI) *m*/*z* (%) 364 (M+1, 32), 328 (44), 282 (88), 256 (100), 196 (19). Anal. Calcd for $C_{15}H_{26}ClNO_5Si$ C 49.51, H 7.20, N 3.82; found C 48.80, H 7.24, N 4.19.

4.9.4. Methyl (2*R*,6*R*)-6-(2-{[*tert*-butyl(diphenyl)silyl]-oxy}ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46d. 92% yield. R_f=0.3 (PE/Et_2O=10/1), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.70 (m, 10H, 2Ph), 6.18 (d, *J*=3.0 Hz, 1H, CHN), 5.23 (s, 1H, NCHO), 4.82 (d, *J*=3.0 Hz, 1H, CHO), 3.98 (m, 2H, OCH_2), 3.80 (s, 3H, OMe), 2.44 (m, 2H, CH_2), 1.07 (s, 9H, Si*t*Bu), 0.86 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz) δ 170.6 (C=O), 154.3 (C=O), 133.4 (C_{arom}), 135.5, 129.8, 127.8 (CH_{arom}), 99.5 (NCHO), 89.3 (CHN), 84.1 (CHO), 65.4 (CCl), 59.7 (CH_2O), 53.5 (OMe), 39.0 (*t*Bu), 32.8 (Si*t*Bu), 26.9 (CH_2), 25.6 (*t*Bu), 19.2 (Si*t*Bu). IR (film) ν 2960, 1798 (C=$O_{lactone}$), 1735 (C=O), 1360, 1168, 760. MS (APCI) *m*/*z* (%) 560 (M+1, 12), 446 (17).

4.9.5. Methyl (2*R*,6*R*)-6-(2-[benzyloxy]ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46e. 88% yield, R_f=0.33. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.35 (m, 5H, Ph), 6.17 (d, *J*=2.8 Hz, 1H, CHN), 5.21 (s, 1H, NCHO), 4.88 (d, *J*=2.8 Hz, 1H, CHO), 4.52 (s, 2H, CH_2Ph), 3.82 (m, 2H, CH_2O), 3.79 (s, 3H, OMe), 2.23–2.54 (m, 2H, CH_2), 0.84 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8 (C=O), 154.3 (C=O), 137.8 (C_{arom}), 128.5, 128.2, 127.8 (CH_{arom}), 99.2 (NCHO), 89.3 (CHN), 84.4 (CHO), 73.4 (CH_2Ph), 66.2 (CCl), 65.1 (CH_2O), 53.3 (OMe), 38.8 (*t*Bu), 31.9 (CH_2), 25.5 (*t*Bu). IR (film) ν 2927, 1796 (C=$O_{lactone}$), 1738

(C=O), 1360, 1109. MS (APCI) *m/z* (%) 412 (M+1, 12), 394 (74), 326 (63), 304 (100), 246 (72).

4.9.6. *tert*-Butyl (2*R*,6*R*)-6-(2-[benzyloxy]ethyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46f. 89% yield, R_f=0.36. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.37 (m, 5H, Ph), 6.11 (d, *J*=2.8 Hz, 1H, CHN), 5.21 (s, 1H, NCHO), 4.84 (d, *J*=2.8 Hz, 1H, CHO), 4.54 (ab, *J*=15.4 Hz, 2H, CH_2Ph), 3.81 (m, 2H, CH_2O), 2.54 (ddd, *J*=15.1, 9.6, 6.1 Hz, 1H, CH_2), 2.23 (ddd, *J*=15.1, 4.7, 3.3 Hz, 1H, CH_2), 1.47 (s, 9H, O*t*Bu), 0.85 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6 (C=O), 156.0 (C=O), 137.5 (C_{arom}), 128.7, 128.2, 128.0 (CH_{arom}), 99.1 (NCHO), 90.2 (CHN), 84.7 (CHO), 82.2 (O*t*Bu), 73.6 (CH_2Ph), 69.2 (CCl), 65.5 (CH_2O), 39.2 (*t*Bu), 30.3 (CH_2), 28.4 (O*t*Bu), 25.9 (*t*Bu). IR (KBr) ν 2977, 1799 ($C=O_{lactone}$), 1734 (C=O), 1361, 1163. MS (APCI) *m/z* (%) 454 (M+1, 14), 282 (100), 144 (12). Anal. Calcd for $C_{23}H_{32}ClNO_6$ C 60.85, H 7.10, N 3.08, Cl 7.81; found C 60.68, H 6.95, N 2.97, Cl 8.01. X-ray diffraction analysis Wavelength: 0.71069 Å, Crystal system: orthorhombic; unit cell dimensions: *a*=9.560 (3) Å, α=90°; *b*=10.468 (3), β=90°; *c*=23.952 (9), γ=90°.

4.9.7. Methyl (2*R*,6*R*)-6-(3-bromopropyl)-2-(*tert*-butyl)-6-chloro-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46g. 90% yield, R_f=0.3. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, *J*=3.0 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.82 (d, *J*=3.0 Hz, 1H, CHO), 3.80 (s, 3H, OMe), 3.47 (m, 2H, CH_2Br), 2.21–2.33 (m, 4H, CH_2CH_2), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2 (C=O), 154.1 (C=O), 99.5 (NCHO), 88.9 (CHN), 83.9 (CHO), 66.4 (CCl), 53.5 (OMe), 39.0 (*t*Bu), 32.2 (CH_2Br), 30.2 (CH_2), 27.2 (CH_2), 25.6 (*t*Bu). IR (film) ν 2960, 1798 ($C=O_{lactone}$), 1738 (C=O), 1360, 1143. MS (APCI) *m/z* (%) 398 (M+1, 9), 282 (100), 220 (32), 144 (12). Anal. Calcd for $C_{14}H_{21}BrClNO_5$ C 42.17, H 5.31, N 3.51, Cl 8.89; found C 42.07, H 5.44, N 3.58, Cl 9.29.

4.9.8. Methyl (2*R*,6*R*)-6-methyl-2-(*tert*-butyl)-6-bromo-5-oxotetrahydrofuro[2,3-*d*][1,3]oxazole-3(2*H*)-carboxylate 46h. 91% yield, R_f=0.34. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21 (d, *J*=2.9 Hz, 1H, CHN), 5.29 (s, 1H, NCHO), 4.97 (d, *J*=2.9 Hz, 1H, CHO), 3.81 (s, 3H, OMe), 1.94 (s, 3H, CH_3), 0.95 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5 (C=O), 154.3 (C=O), 99.5 (NCHO), 88.6 (CHN), 85.2 (CHO), 62.8 (CBr), 53.5 (OMe), 39.0 (*t*Bu), 25.6 (*t*Bu), 19.8 (CH_3). IR (film) ν 2960, 1797 ($C=O_{lactone}$), 1739 (C=O), 1360, 1110. MS (APCI) *m/z* (%) 336 (M+1, 9), 282 (100).

4.10. General procedure for the Beckmann rearrangement

To a solution of cyclobutanones (1 equiv.) in dichloromethane (1 ml/mmol) was added with stirring O-mesitylenesulfonylhydroxylamine (1.2 equiv.) in dichloromethane (1 ml/mmol) dropwise at room temperature. After stirring for another 70 min, the solvent was removed under reduced pressure to yield a colourless oil which was then dissolved in benzene–methanol (3:1, 1 ml/mmol) and the resulting mixture was added dropwise to a stirring suspension of alumina (5 g/mmol) in methanol (5 ml/mmol). The mixture was stirred for 4 h and filtered. The alumina was washed with methanol. The combined methanolic solution was concentrated. The residue was dissloved in $CHCl_3$ (2 ml/mmol) and the insoluble material was removed. After evaporation of the solvent, the residue was chromatographied on silica gel to give the product (**47a–b**).

4.10.1. Methyl (2*R*,3a*R*,6*R*,6a*R*)-2-(*tert*-butyl)-6-chloro-6-methyl-5-oxotetrahydro-2*H*-pyrrolo[2,3-*d*][1,3]oxazole-3(3a*H*)-carboxylate 47a. 38% yield, R_f=0.25 (PE/Et_2O=5/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (s, 1H, NH), 6.21 (d, *J*=3.0 Hz, 1H, CHN), 5.28 (s, 1H, NCHO), 4.81 (d, *J*=3.0 Hz, 1H, CHN), 3.81 (s, 3H, OMe), 1.76 (s, 3H, CH_3), 0.96 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2 (C=O), 153.4 (C=O), 100.2 (NCHO), 85.7 (CHN), 75.9 (CHO), 69.5 (CCl), 54.6 (OMe), 39.1 (*t*Bu), 25.3 (*t*Bu), 17.6 (CH_3). IR (KBr) ν 2964, 1741 ($C=O_{lactam}$), 1728 (C=O), 1361, 1112. MS (CI) *m/z* (%) 291 (M+1, 12), 253 (10), 199 (86), 183 (100).

4.10.2. Methyl (2*R*,3a*R*,6*R*,6a*R*)-2-(*tert*-butyl)-6-chloro-6-(trimethylsilylmethyl)-5-oxotetrahydro-2*H*-pyrrolo[2,3-*d*][1,3]oxazole-3(3a*H*)-carboxylate 47b. 40% yield, R_f=0.25 (PE/Et_2O=6/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.76 (s, 1H, NH), 5.36 (d, *J*=4.8 Hz, 1H, CHN), 5.01 (s, 1H, NCHO), 4.48 (d, *J*=4.8 Hz, 1H, CHN), 3.66 (s, 3H, OMe), 0.86 (s, 9H, *t*Bu), 0.14 ($SiMe_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3 (C=O), 154.5 (C=O), 98.6 (NCHO), 84.7 (CHN), 69.3 (CCl), 68.5 (CHO), 53.2 (OMe), 39.2 (*t*Bu), 25.6 (*t*Bu), 19.6 (CH_2), 0.1 ($SiMe_3$). IR (film) ν 3237, 2942, 1744 (C=O), 1723 (C=O), 976. MS (CI+Q1MS) *m/z* (%): 363 (M+1, 35), 347 (100), 327 (32), 313 (14), 89 (10). MS (CI−Q1MS) *m/z* (%) 361 (M−1, 22), 240 (24), 168 (100). Anal. Calcd for $C_{15}H_{27}ClN_2O_4Si$ C 49.64, H 7.50, N 7.71; found C 50.27, H 7.60, N 6.76.

4.10.3. (2*R*,4*R*,5*S*)-2-*tert*-Butyl-5-[1,3]dithiolan-2-yl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 48. Into a suspension of **43** (0.3 g, 0.83 mmol) and NaOH (60 mg, 1.5 mmol) in H_2O (10 ml) was added acetone until a clear solution was formed. The mixture was stirred overnight, then diluted phosphoric acid was added to pH 1. The mixture was extracted with ether (4×10 ml). The combined ether was evaporated to give crude product which was recrystallized in *n*-hexane–CH_2Cl_2 to afford pure product 0.29 g, 92%, mp 148.7–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (s, 1H, NCHO), 4.48–4.35 (m, 3H), 3.22–3.19 (m, 4H), 1.43 (s, 9H, O*t*Bu), 0.92 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C=O), 154.5 (C=O), 97.1 (NCHO), 84.6 (CHN), 81.7 (O*t*Bu), 64.3 (CH_2O), 51.9 (SCHS), 39.1 (CH_2), 38.5 (CH_2), 28.1 (O*t*Bu), 26.5 (*t*Bu). IR (film) ν 3340, 2960, 1720 (C=O). MS (EI) *m/z* (%) 334 $(M-CO_2)^+$, 320 (M−*t*Bu), 264, 220, 175 (100). Anal. Calcd for $C_{16}H_{27}NO_5S_2$ C 50.80, H 7.20, N 3.71, S 16.98; found C 50.45, H 7.18, N 3.47, S 16.70.

4.10.4. (2*R*,4*R*,5*S*)-2-*tert*-Butyl-5-[1,3]dithiolan-2-yl-oxazolidine-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-methyl ester 49. Into a solution of **48** (91 mg, 0.24 mmol) in ether (15 ml) was added CH_2N_2 in ether at 0 °C. After stirring for 15 min, acetic acid was added to neutralize excess CH_2N_2. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 ml), dried over $MgSO_4$ and concentrated. Recrystallization in *n*-hexane gave pure product 0.31 g,

94%, mp 118.9–119.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (s, 1H, NCHO), 4.56–4.37 (m, 2H), 4.15 (m, 1H), 3.77 (s, 3H), 3.27–3.12 (m, 4H), 1.40 (s, 9H, O*t*Bu), 0.96 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (C═O), 154.3 (C═O), 96.7 (NCHO), 84.6 (CHN), 81.4 (O*t*Bu), 64.4 (CH_2O), 52.1 (OMe), 51.9 (SCHS), 39.0 (CH_2), 38.8 (CH_2), 28.1 (O*t*Bu), 26.5 (*t*Bu). IR (film) ν 3055, 2987, 1747 (C═O), 1719 (C═O). MS (EI) *m*/*z* 335 $(M-C_4H_8)^+$, 278, 234, 189 (100%). Anal. Calcd for $C_{17}H_{29}NO_5S_2$ C 52.14, H 7.46, N 3.57, S 16.37; found C 51.99, H 7.48, N 3.36, S 15.74.

4.10.5. 5-*tert*-Butyl-1a-(*p*-tolyl)1a,6b-dihydrospiro{1*H*,3*H*,5*H*-cyclobuta[*gh*]oxazolo[3,4-*c*]oxazole-1,2′-[1,3]-dithiolan}-3-one 50. Into a solution of **43** (100 mg, 0.29 mmol) in THF (3 ml) was added 1 M para-tolylmagnesium bromide in ether at room temperature. After stirring for 2 h, saturated aqueous NH_4Cl (1 ml) was added. The mixture was extracted with ether (3×5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography (c-hexane/AcOEt=4/1) gave pure product 86 mg, 79%, mp 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 4H), 5.36 (s, 1H), 4.85 (d, 1H, *J*=4.6 Hz), 4.79 (d, 1H, *J*=4.6 Hz), 2.40 (s, 3H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 139.1, 131.8, 129.1, 125.8, 105.0, 87.9, 83.6, 77.4, 66.2, 39.9, 39.5, 36.3, 24.9, 21.3. IR (film) ν 2990, 1760 (C═O), 1610, 1486, 1455, 1320. MS (EI) *m*/*z* 377 $(M)^+$, 321, 277, 91, 57; HRMS Calcd for $C_{19}H_{23}NO_3S_2$ 377.111, found 377.113.

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A biocatalytic route to enantioenriched, sulfanyl aldol products

C. Baker-Glenn,[a] R. Ancliff[b] and V. Gouverneur[a,*]

[a]*Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b]*GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK*

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Abstract—The aldol products derived from sulfur- or selenium containing acceptors were prepared by kinetic resolution in the presence of antibody 84G3 with enantiomeric excesses ranging from 56 to 70%. Much higher level of enantioselectivity was obtained (enantiomeric excesses all superior to 96%) for sulfanyl aldol products derived from thiomethoxyacetone with three different acceptors.

1. Introduction

The development of strategies for the preparation of enantiomerically pure heterocycles remains a very important area of research. Recently, Warren and House have reviewed the effectiveness of using the sulfanyl group as a tool for the construction of various heterocyclic compounds with in most cases total control over the product stereochemistry.[1] The sulfanyl migration of several enantiopure 1,3-diols has been studied and allowed the preparation of various heterocycles, including heavily substituted tetrahydrofurans with excellent level of diastereo- and enantiocontrol.[2] In addition, sulfanyl 1,3-diols have been transformed into the corresponding β,γ-epoxy alcohols upon methylation of the sulfide functionality followed by cyclization under basic conditions.[3] Therefore, numerous strategies are reported in the literature for the synthesis of sulfanyl-based cyclization precursors, including organometallic addition to aldehydes, Sharpless asymmetric dihydroxylation or asymmetric aldol reaction.[4] In this contribution, we report the first abzymatic route to various enantioenriched sulfanyl aldols that are direct precursors of sulfanyl 1,3-diols and the corresponding heterocyclic targets. We recently described aldolase antibody 84G3 as a highly efficient catalyst for the regio- and enantioselective aldol reaction of various unsymmetrical methyl ketones with *para*-nitrobenzaldehyde.[5,6] This study revealed that in the presence of this antibody, the catalysed reaction of thiomethoxyacetone with *para*-nitrobenzaldehyde was highly regioselective with the preferential formation of the otherwise disfavoured linear regioisomer resulting from an addition at the less substituted carbon. Both linear aldol enantiomers could be accessed through aldol or retro-adol reactions using the same antibody. Herein, we report that antibody 84G3 has also the ability to catalyse aldol reactions involving sulfur containing acceptors and the corresponding retroaldolisation processes. In addition, we have investigated the sense and level of regioselectivity for the antibody-mediated aldol reactions of thiomethoxyacetone with two acceptors other than *para*-nitrobenzaldehyde and the corresponding retroaldolisations. We have also determined the enantioselectivity for the forward and reverse aldol reactions allowing the preparation of various sulfanyl aldols and the assignment of their absolute configurations. Finally, we are reporting the kinetic parameters for selected reactions.

2. Results and discussion

2.1. Antibody-catalysed forward aldol reactions of acetone, 2-pentanone and 3-pentanone with various sulfur and selenium containing aldehydes and antibody-mediated retroaldolisation of the corresponding racemic aldols

First, we set out to study the ability of ab84G3 to catalyse the forward aldol reactions of three representative donors with sulfur- and selenium containing acceptors, and for the unsymmetrical donor 2-pentanone, the degree of regiocontrol that antibody 84G3 could exercise on the aldol process (Table 1).

For all experiments, the product assignment and the product distribution were proven unambiguously by comparison of the retention times with independently chemically synthesized standards using high performance liquid chromatography (HPLC).[7] To screen for catalytic activity,

Keywords: Catalytic antibodies; Aldol additon; Sulfur.
* Corresponding author. Tel./fax: +44-1865-275-644;
e-mail address: veronique.gouverneur@chem.ox.ac.uk

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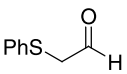
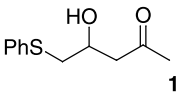
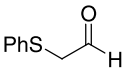
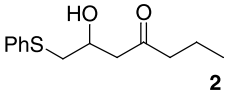
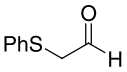
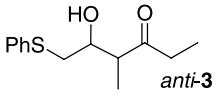
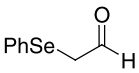
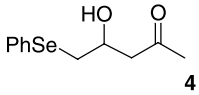
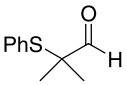
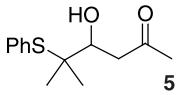
Table 1. Aldol reactions of S- and Se-containing acceptors with acetone, 2-pentanone and 3-pentanone

Entry	Acceptor and donor		Conditions[a]	Conversion (%)	Product
1 2		+acetone	PBS, 20 h Ab84G3, 20 h	0 24	 **1**
3 4		+2-pentanone	PBS, 3 h Ab84G3, 3 h	0 48	 **2**
5 6		+3-pentanone	PBS, 20 h Ab84G3, 20 h	0 3	 *anti*-**3**
7 8		+acetone	PBS, 20 h Ab84G3, 20 h	0 27	 **4**
9 10		+acetone	PBS, 18 h Ab84G3, 18 h	0 0	 **5**

[a] All reactions at pH=7.4, rt.

we performed the reactions under the following defined conditions: 90 mM of donor, 130 μM of acceptor and 9 mol% antibody in PBS (pH=7.4) at room temperature. Control experiments revealed that, in the absence of antibody, no reactions take place under these conditions (entries 1, 3, 5, 7, 9). For the antibody-mediated reactions, we found that all the reactions were taking place in the presence of ab84G3 with the exception of the reaction of acetone with 2-phenylthiobutyraldehyde[8] (entry 10). Indeed, this latter reaction did not produce any detectable amount of aldol product after 18 h in the presence of up to 9 mol% ab84G3 suggesting that 2-phenylthiobutyraldehyde is not a suitable donor for this antibody. The data collected in Table 1 revealed that the best-catalysed antibody transformation is the aldol reaction of phenylthioacetaldehyde[9] with 2-pentanone (entry 4). For this reaction, only the linear regioisomer was formed with no trace of the branched regioisomer detectable by HPLC. The reaction of phenylthioacetaldehyde with acetone was less efficient with 24% of the desired aldol product formed after 20 h at room temperature (entry 2). The aldol reaction of phenylselenoacetaldehyde[10] was also successfully catalysed by antibody 84G3 but the use of the selenoaldehyde did not present any significant advantage in comparison with the 'thioanalogue' (entry 8). Finally, we have found that only 3% of the branched *anti* regioisomer was detected by HPLC for the antibody-mediated aldol reaction involving 3-pentanone, suggesting that this antibody-mediated transformation has no synthetic utility. For all the antibody-catalysed reactions (entries 2, 4, 6, 8), another compound was detected by HPLC in addition to the desired aldol product. The structure of this side product is unclear but we hypothesised that this compound is arising from a self-condensation aldol reaction of the S- or Se-containing aldehyde, which are both prone to enolisation. This hypothesis is supported by the observation that the retention time (HPLC analysis) of this side-product was the same for all aldol reactions involving phenylthioacetaldehyde independent of the structure of the donors examined herein. In addition, a control experiment revealed that this same product was formed upon incubation of phenylthioacetaldehyde as the sole substrate in the presence of ab84G3.[11]

In addition to these experiments, we also assessed the ability of ab84G3 to catalyse the retroaldolisation of racemic sulfanyl aldols **1**-**5** all prepared according to standard literature procedures (Table 2).[7] The racemic aldols (228 μM) were treated with ab84G3 (10 mol%) in aqueous buffer (PBS, pH=7.4, at room temperature). Analysis by high-performance liquid chromatography (HPLC) indicated that no reaction takes place in the absence of the antibody. In contrast, the antibody-mediated retro-aldolisation reactions of compounds **1**, **2** and **4** halted at approximately 50% conversion, auguring an efficient kinetic resolution for these substrates. As expected from our results on the corresponding forward aldol reactions, the antibody-catalysed retroaldolisation of the *anti*-**3** was slow with 26% conversion of the starting material after 90 h and no reaction was observed for the *syn*-**3** stereoisomer. No retroaldolisation was observed with compound **5** suggesting that the binding pocket of 84G3 does not tolerate the presence of the quaternary carbon.

Table 2. Retro-aldolisation of compounds **1**-**4** in the presence of antibody 84G3

Entry	Substrate	Conditions	Conversion
1	(±)-**1**	PBS, rt, 20 h	0
2	(±)-**1**	10 % ab84G3, rt, 20 h	49
3	(±)-**2**	PBS, rt, 3.5 h	0
4	(±)-**2**	10 % ab84G3, rt, 3.5 h	45
5	(±)-*anti*-**3**	PBS, rt, 90 h	0
6	(±)-*anti*-**3**	10 % ab84G3, rt, 90 h	26
7	(±)-*syn*-**3**	PBS, rt, 90 h	0
8	(±)-*syn*-**3**	10 % ab84G3, rt, 90 h	0
9	(±)-**4**	PBS, rt, 20 h	0
10	(±)-**4**	10 % ab84G3, rt, 20 h	47

2.2. Antibody-catalysed forward aldol reactions of thiomethoxyacetone with benzaldehyde and *para*-methoxycinnamaldehyde and the antibody-mediated retro-aldolisations of the corresponding racemic aldols

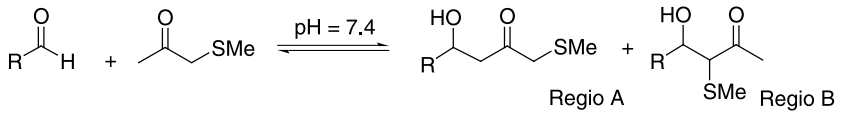
Previous work from our laboratory has shown that the reaction of thiomethoxyacetone with *para*-nitrobenzaldehyde **6** catalysed by ab84G3 is highly regioselective with the preferential formation of the linear regioisomer **9** resulting from an addition at the less substituted carbon (entry 2) (Table 3).[5,6] We have now further investigated the scope of this reaction and we have found that, in the presence of antibody 84G3, thiomethoxyacetone also undergoes the aldol condensation with benzaldehyde to afford predominantly the linear regioisomer **10** with a conversion of 12% after 3 h at room temperature (entry 4). The sense and level of regioselectivity of these antibody-mediated transformations suggest that in the presence of the donor thiomethoxyacetone, ab84G3 catalyses predominantly the formation of the linear regioisomers independent of the structure of the acceptors. We have also found that no reaction was observed with the less reactive acceptor *para*-methoxycinnamaldehyde **8** (entry 6). In contrast to the forward aldol reactions, the corresponding antibody-mediated retroaldolisations were much more efficient with a rapid reaction taking place with the three racemic linear aldol products **9**-**11** (entries 8, 10, 12). The reactions were halting at approximately 50% as expected for a kinetic resolution. The retroaldolisation of compounds **10** and **11** derived from the less reactive acceptors were the best-catalysed transformations as reflected by the shorter reaction time required to reach 50% conversion.

2.3. Enantioselectivity of the aldol and retro-aldol products and assignment of absolute configurations

To probe further the synthetic scope of these antibodies, we studied the enantioselectivity of selected forward aldol and retroaldol reactions. The enantiomeric excesses of the products were determined by HPLC using chiral stationary phases and are collected in Table 4.

The data showed that the enantiomeric excesses of all aldol products derived from sulfur- and selenium containing acceptors ranged from 56% to 70%. As expected the ee values of the forward aldol reaction correlate well with the ee values of the corresponding retroaldolisations. Gratifyingly, the catalyst was highly enantioselective and allowed the recovery of the unreacted aldols **9**-**11** with ee values typically greater than 96% for the retroaldolisation of the racemic aldol products **9**-**11** derived from the reactions of *para*-benzaldehyde, benzaldehyde or *para*-methoxycinnamaldehyde with thiomethoxyacetone. These results suggest that for antibody 84G3, the highest enantioselectivities (>96%) were observed for aldol reactions where conjugated aldehydes served as acceptors. Lower enantioselectivities were obtained when aldol acceptors containing an sp^3 center in the α-position are selected as reaction partners. All the enantioenriched aldol products formed via an antibody-mediated forward aldol reactions possess the (*R*)-configuration and the recovered aldols resulting from a retroaldolisation process possess the (*S*)-configuration. To assign the absolute configurations unambiguously, products **1**, **2**, **9** and **10** were prepared independently by asymmetric synthesis or catalysis. The absolute configurations of all other aldol products were

Table 3. Aldolisation of thiomethoxyacetone with various acceptors and retro aldolisations



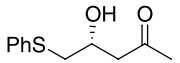
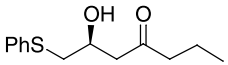
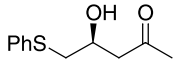
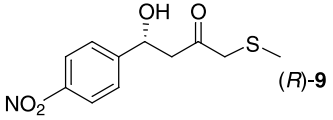
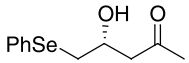
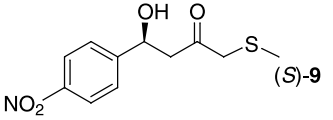
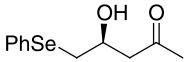
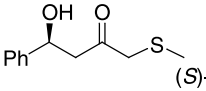
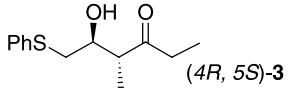
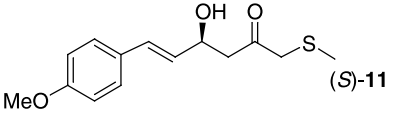
6 R = *para*-NO_2Ph
7 R = Ph
8 R = *para*-MeOPhCH=CH-

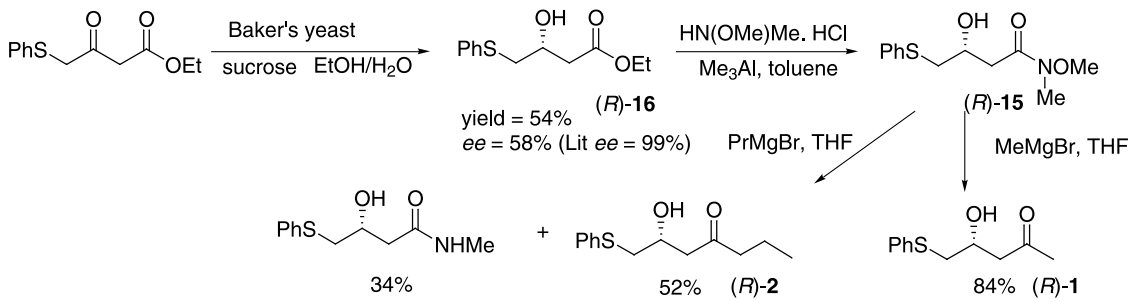
9 R = *para*-NO_2Ph
10 R = Ph
11 R = *para*-MeOPhCH=CH-

12 R = *para*-NO_2Ph
13 R = Ph
14 R = *para*-MeOPhCH=CH-

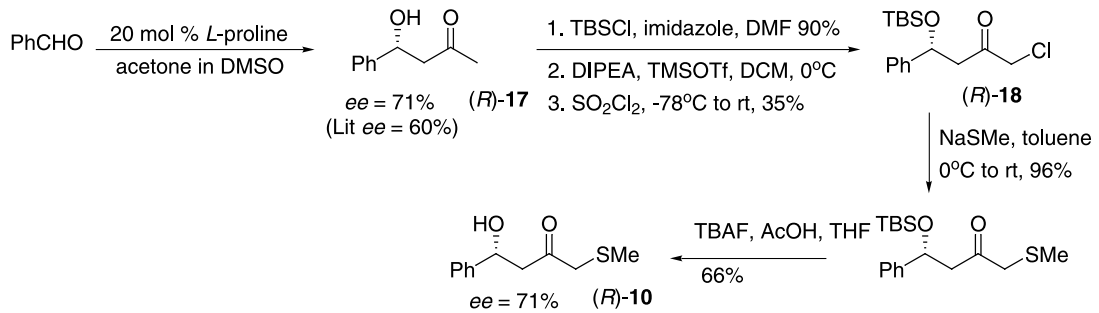
Entry	Acceptor and donor	Conditions[a]	Conversion (%)	Ratio A/B
Aldolisation				
1	**6**	PBS, 0 °C, 1 h 40	9	10:90
2	**6**	25% ab84G3, 0 °C, 1 h 40	56	98:2
3	**7**	PBS, rt, 3 h	1	0:100
4	**7**	9% ab84G3, rt, 3 h	12	92:8
5	**8**	PBS, 40 h	0	—
6	**8**	9% ab84G3, rt, 24 h	0	—
Retroaldolisation				
Entry	Substrate	Conditions	Conversion (%)	
7	(±)-**9**	PBS, rt, 2 h	0	
8	(±)-**9**	10 % ab84G3, rt, 2 h	51	
9	(±)-**10**	PBS, rt, 1 h	0	
10	(±)-**10**	10 % ab84G3, rt, 1 h	50	
11	(±)-**11**	PBS, rt, 1 h	0	
12	(±)-**11**	10 % ab84G3, rt, 1 h	50	

Table 4. ee Values for antibody-catalysed aldol and retro-aldol reactions

Entry	Product	Method conversion (%)	ee (%)	Entry	Product	Method conversion (%)	ee (%)
1	 (*R*)-**1**	Aldol (30%)	60	6	 (*S*)-**2**	Retro-aldol (50%)	60
2	 (*S*)-**1**	Retro-aldol (50%)	56	7	 (*R*)-**9**	Aldol (10%)	97
3	 (*R*)-**4**	Aldol (65%)	64	8	 (*S*)-**9**	Retro-aldol (50%)	96
4	 (*S*)-**4**	Retro-aldol (54%)	66	9	 (*S*)-**10**	Retro-aldol (50%)	98
5	 (*4R, 5S*)-**3**	Retro-aldol (37%)	70	10	 (*S*)-**11**	Retro-aldol (50%)	99



Scheme 1. Independent asymmetric syntheses of enantioenriched aldols **1** and **2**.



Scheme 2. Independent asymmetric syntheses of enantioenriched aldol **10**.

assigned by analogy. It was anticipated that compounds **1** and **2** could be prepared in enantiomerically pure form from a common precursor, the Weinreb amide **15** by functional group manipulation of the methoxy-N-methylamide group (Scheme 1).

The absolute configuration of the Weinreb amide **15** could be easily secured through Bakers' yeast reduction of the corresponding ketoester according to a procedure described in the literature.[12] Although the Bakers' yeast reduction of the ethyl 4-phenylthio-3-oxobutanoate is reported to produce the corresponding (*R*)-hydroxy ester **16** in 99% ee, in our hands, this reaction gave the desired product with a lower enantiomeric excess of 58% as determined by chiral HPLC. Transamination of this enantioenriched compound to give the N-methoxy-N-methylamide **15**, followed by addition of the Grignard reagent afforded the desired enantioenriched compounds **1** and **2** with respective yields of 84% and 52%. For the addition of *n*-PrMgBr on compound **15**, a side product resulting from elimination of formaldehyde was observed and isolated with a chemical yield of 34%.[13] This side reaction was not observed when compound **15** was treated with MeMgBr. Analysis of these compounds by chiral HPLC revealed that no epimerisation has occurred converting the Weinreb amide into the desired ketones as these two compounds were obtained with an ee of 58%. Comparison of the retention times of these enantioenriched independently synthesised reference compounds with the antibody-products established the (*R*) configuration of the stereogenic center of the enantioenriched antibody aldol products, which is consistent with preferential addition of the ketone to the Si face of the aldehyde. For the retro-aldol reactions, HPLC analysis confirmed that at approximately 50% conversion, the major enantiomer for the recovered enantioenriched aldol products **1** and **2** possess the (*S*)-configuration. For the aldol compounds derived from thiomethoxyacetone, the absolute configuration of compound **9** was already established correlating the absolute configuration of the antibody-product with the enantiopure sample prepared according to the Evans's asymmetric aldol methodology.[14] Herein, we suggest an alternative route for the preparation of enantioenriched **10** using *L*-proline as the organocatalyst (Scheme 2).[15] The (*R*)-aldol product **17** (ee=71%) derived from acetone and benzaldehyde was prepared in DMSO, in the presence of 20 mol% *L*-proline at room temperature. Chlorination of the corresponding protected terminal silyl enol ether followed by nucleophilic substitution of the chlorine group of **18** with sodium thiomethoxide in toluene at 0 °C proceeded smoothly to afford, after deprotection, the enantioenriched compound **10** in 96% yield and with an ee of 71%. HPLC analysis revealed that the retention time of the minor (*S*)-enantiomer of this sample is identical to the retention time of the antibody-product resulting from the retro-aldolisation process, confirming that the antibody-product possess the (*S*)-configuration.

2.4. Kinetic studies

The results of the kinetic studies of several retro-aldol reactions are provided in Table 5. The kinetic parameters are reported per antibody active site assuming that both active sites of the antibody function independently. All the

Table 5. Kinetic parameters for selected retro-aldol reaction

Entry	Substrates	k_{cat} (min^{-1})	K_M (μM)	k_{cat}/k_{uncat}	$(k_{cat}/K_M)/k_{uncat}$ (M^{-1})
1	(±)-**1**	0.031	474	—	—
2	(±)-**2**	0.604	148	—	—
3	(±)-*anti*-**3**	0.006	390	—	—
4	(±)-**4**	0.053	584	—	—
5	(±)-**9**	0.81	69	4.3×10^5	6.2×10^9
6	(±)-**10**	3.17	56	1.9×10^6	3.3×10^{10}

retro-aldol reactions followed typical Michaelis–Menten kinetics. The determination of k_{cat}/k_{uncat} was not determined for compounds **1**-**4** as no product resulting from a retro-aldolisation process was observed to be formed for the uncatalysed reaction under our essay conditions, even after prolonged reaction times. For compounds **1**-**4**, the kinetic data suggest that the linear aldol product **2** derived from 2-pentanone was processed by the antibody more efficiently (k_{cat}=0.6 min^{-1}) than the aldol products **1** or **4** derived from acetone. A similar trend was reported in the literature as it was found that the retroaldolisation of a linear aldol product derived from butanone was processed approximately 20 times more efficiently by antibody 84G3 than the corresponding aldol product derived from acetone.[16] We have also found that the presence of the additional methyl group of the branched aldol product *anti*-**3** slowed down considerably the antibody-mediated retroaldolisation of this racemic substrate as reflected by the much lower rate constant (k_{cat}=0.006 min^{-1}). The data also revealed that the antibody-mediated retro-aldolisation of the aldol product derived from the less reactive acceptor (benzaldehyde) is significantly more efficient than the catalysed retroaldolisation of compounds derived from the more electron deficient acceptor (*para*-nitrobenzaldehyde). The high catalytic proficiencies of ab84G3 for both the retro-aldolisation of aldols (±)-**9** and (±)-**10** suggest that these reactions are synthetically valuable processes as the recovered aldol products resulting from these kinetic resolutions were formed with enantiomeric excesses superior to 98%.

3. Conclusion

Two major issues were under consideration. First was the critical issue as to whether aldolase antibody 84G3 could catalyse aldol reactions of all carbon donors with sulfur or selenium-containing acceptors. Second, the possibility of controlling simultaneously the regio- and enantioselectivity of aldol reactions of thiomethoxyacetone with three electronically and structurally different acceptors had to be determined as well as the ability of ab84G3 to catalyse the corresponding retro-aldolisations. It was found that the antibody-aldol products derived from sulfur- or selenium containing acceptors were obtained with enantiomeric excesses ranging from 56 to 70%. In contrast, various enantiopure (ee >96%) sulfanyl aldol products derived from thiomethoxyacetone with three different acceptors were obtained using antibody-catalysed aldolisation and retro-aldolisations. The retro-aldolisations are synthetically superior as reflected by the catalytic proficiency of ab84G3 for these reactions. Further exploration of ab84G3 to produced enantioenriched precursors of various heterocyclic systems is in progress in our laboratory.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) was obtained by distillation over sodium and benzophenone, dry methylene chloride (CH_2Cl_2) was obtained by distillation over calcium hydride. Yields refer to chromatography and spectroscopically (^{1}H NMR) homogeneous materials. Commercially available reagents were used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck aluminum foil backed sheets precoated with Kieselgel 60 F-254 using UV light as visualizing agent and an ethanolic solution of potassium permanganate and heat as developing agent. Merck Silica gel C60 (40–60 μM) was used for flash column chromatography. NMR spectra were recorded on a Bruker DPX-400 or Bruker AMX-500 spectrometer and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain multiciplicities: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, b=broad. The coupling constants *J* are given in hertz. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Mass spectra (*m*/*z*) and HRMS were recorded on Micromass GCT using Chemical Ionisation (NH_3, CI), Electronic Impact (EI+) or Field Ionization (FI). Microanalyses were performed by 'Elemental Microanalysis Limited', Devon. Melting points were determined in a capillary and are uncorrected.

HPLC information. Analytical HPLC and semi-preparative HPLC were performed on a Waters HPLC system (626 Pump, 600 S Controller, 996 Photodiode Array Detector, Millenium^{32} Software). Reactions were followed by analytical RP-HPLC: Nova-pak Waters column, C-18, 60 Å pore size, 4 μm particle size, 3.9×150 mm, flow rate 1.0 ml/min. Enantiomeric excesses (ee) were determined by chiral normal phase HPLC: Daicel Chiralpak AD or Daicel Chiracel OJ, OD or OJ-H columns (4.6×250 mm), flow rate 1.0 ml/min. The solvent systems used for the retention times provided for the donors, acceptors and aldol products studied are defined as: solvent A: hexane; solvent B: *i*PrOH; solvent C: EtOH.

4.2. Antibody assays

All antibody-catalysed reactions were performed in phosphate buffered saline (10 mM phosphate, 16 mM NaCl, pH 7.4). All antibody-catalysed reactions and background reactions were monitored by high-pressure liquid chromatography (HPLC; Waters HPLC system (626 Pump, 600 S Controller, 996 Photodiode Array Detector, Millenium^{32} Software) using a Nova-pak Waters column (C-18, 60 Å pore size, 4 micrometer particle micrometer size, 3.9×150 mm) and acetonitrile/water or methanol/water mixtures (containing 0.1% trifluoroacetic acid) as eluents at a flow rate of 1.0 ml/min.

4.3. Michaelis–Menten kinetics

Product formation or percent conversion of antibody-catalysed reaction mixtures was monitored by HPLC. The points were determined experimentally and the best fit value of V_{max} and K_m were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression. All data are reported per antibody active site. An IgG antibody possesses 2 active sites per MW of ~150,000 g/mol.

4.4. Determination of enantiomeric excesses: forward aldol reaction

Antibody (64 nmol) was added to a stock solution containing the aldehyde (10 ml of 66 mM in 10% acetonitrile, 90% PBS, 660 nmol), the ketone (100 ml of 65 mM in PBS, 6.5 mmol) and PBS (amount required to make the final volume up to 2.11 ml). The reactions were monitored by RP-HPLC using a Nova-pak Waters column. After reaching a suitable conversion, the unreacted aldol was isolated by semi-preparative reversed-phase HPLC, Hypersil ODS column, 5 micrometer particle size, 7×250 mm, flow rate 2.0 ml min^{-1} or Phenomenex Luna C18 column, 8.8 micrometer particle size, 15×250 mm, flow rate 8.0 ml min^{-1}. The fractions were freeze-dried, the residue was redissolved in 200 ml of dichloromethane/hexane (50:50) and the ee was determined by chiral normal-phase HPLC.

Retro-aldol reactions. Antibody (32 nmol) was added to racemic stock solution of aldol (10 ml of 80 mM in acetonitrile, 800 nmol). The reactions were monitored by RP-HPLC using using a Waters Nova-pak column. After reaching 50% conversion, the unreacted aldol was isolated by semi-preparative reversed-phase HPLC, Hypersil ODS column, 5 micrometer particle size, 7×250 mm, flow rate 2.0 ml min^{-1} or Phenomenex Luna C18 column, 8.8 micrometer particle size, 15×250 mm, flow rate 8.0 ml min^{-1}. The fractions were freeze-dried, the residue was redissolved in 200 ml of dichloromethane/hexane (50:50) and the ee was determined by normal-phase HPLC.

4.5. General procedure 1: aldol reactions

To a solution of LDA [prepared by dropwise addition of *n*-butyllithium (11.2 mmol, 2 M) to a solution of diisopropylamine (11.3 mmol) in dry THF (15 ml) at 0 °C] at −78 °C was added the donor ketone (11.3 mmol) in dry THF (7.5 ml) via cannula. The reaction was allowed to stir at −78 °C for 30 min. The aldehyde acceptor (7.5 mmol) in dry THF (7.5 ml) was then added via cannula, and the mixture allowed to stir at −78 °C for 15 min. The reaction was then quenched with saturated NH_4Cl and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.6. General procedure 2: formation of Weinreb amide from the corresponding ester

To N,O-dimethylhydroxylamine hydrochloride (43 mmol) in dry toluene (50 ml) at 0 °C was added $AlMe_3$ (39 mmol, 2 M in hexanes) dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min before being cooled to 0 °C and ester (10.4 mmol) in dry toluene (35 ml) added dropwise via cannula. The mixture was allowed to warm to room temperature and stir for 2 h, then poured in to aqueous tartaric acid and allowed to stir for a further 1.5 h. The mixture was extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed in vacuo.

4.7. General procedure 3: formation of Weinreb amide from the corresponding ester

To N,O-dimethylhydroxylamine hydrochloride (4 mmol) in THF (13 ml) at 0 °C was added $AlMe_3$ (2 M in DCM, 4 mmol). The mixture was stirred at 0 °C for 30 min and room temperature for 20 min. The reaction mixture was then cooled to −15 °C and ester (1.3 mmol) in THF (10 ml) was added dropwise. The mixture was warmed to 0 °C and stirred for a further 4 h. The reaction was then quenched with 0.5 M HCl and the mixture extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo.

4.8. General procedure 4: Grignard addition to the Weinreb amide

The Grignard reagent (8.5 mmol) was added to a solution of Weinreb amide (1.6 mmol) in THF (15 ml) at −40 °C. The mixture was allowed to warm to 0 °C over 30 min and stirred for a further 3–48 h. Sat. NH_4Cl was added, and the mixture allowed to warm to room temperature. The mixture was extracted with DCM, dried over $MgSO_4$ and the solvent removed in vacuo.

4.9. General procedure 5: TBS protection

To the aldol product (20 mmol) in DMF (80 ml) at 0 °C was added imidazole (98 mmol) and TBSCl (48 mmol). The mixture was allowed to warm to room temperature and stir for 18 h. The reaction was quenched with water. The mixture was extracted with DCM, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.10. General procedure 6: TBS-deprotection of aldol product

A stock solution was prepared by the addition of AcOH (0.3 ml) to a solution of TBAF (5 ml, 1 M in THF). TBS protected aldol (0.37 mmol) in THF (3.7 ml) was treated with a portion of this stock solution (4 ml) and allowed to stir at room temperature for 15 h. The reaction was then quenched by addition of sat. $NaHCO_3$ (10 ml). The mixture was extracted with EtOAc, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.11. General procedure 7: substitution of chloride with sodium thiomethoxide

To the chlorinated aldol (1.6 mmol) in toluene (35 ml) at 0 °C was added sodium thiomethoxide (3.2 mmol). The mixture was allowed to slowly warm to room temperature, stirred for 18 h and then quenched with saturated NH_4Cl. The mixture was extracted with DCM, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.11.1. 4-Hydroxy-5-phenylsulfanyl-pentan-2-one (±)-1. Synthesised from (phenylthio)-acetaldehyde (2 g, 13 mmol) and dry acetone (1 ml, 14.5 mmol) using general procedure 1. Purification by column chromatography (1:1 hexane/

EtOAc) afforded **1** (1.9 g, 70%) as an oil. R_F (1:1 hexane/EtOAc): 0.25; δ ^{1}H NMR (400 MHz): 2.12 (3H, s, CH_3), 2.67 (1H, dd, J=8.0, 17.5 Hz, CH_AH$_B$CHO), 2.75 (1H, dd, J=4.0, 17.5 Hz, CH$_A$$H_B$CHO), 3.04 (1H, dd, J=6.5, 14.0 Hz, CH_AH$_B$S), 3.05 (1H, dd, J=6.0, 14.0 Hz, CH$_A$$H_B$S), 3.40 (1H, br s, O$H$), 4.10–4.18 (1H, m, C$H$), 7.1.5–7.38 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 30.7 (*C*H$_3$), 40.0 (*C*H$_2$S), 48.4 (*C*H$_2$CO), 66.2 (*C*H), 126.4 (Ar–*C*), 129.1 (Ar–*C*, 2C), 129.5 (Ar–*C*, 2C), 135.3 (Ar–*C*, quarternary), 208.7 (*C*=O); ν_{max} (neat): 3418.0 (br, O–H), 1710.9 (s, C=O); *m/z* (autospec, CI$^+$): 207 ([M−OH]$^+$, 100%), 225 ([M+H]$^+$, 51%), 242 ([M+NH$_4$]$^+$, 26%); (HRMS, autospec CI$^+$): found 211.0800 ([M+H]$^+$), $C_{11}H_{15}SO_2$ requires 211.0793.

4.12. Synthesis of the two aldol regioisomers derived from 2-pentanone and phenylthioacetaldehyde

4.12.1. (±)-3-Hydroxy-4-phenylsulfanyl-butyric acid ethyl ester. Synthesised from (phenylthio)acetaldehyde (4.365 g, 28.7 mmol) and ethyl acetate (4.17 ml, 43 mmol) using general procedure 1. Purification by column chromatography (4:1 hexane/EtOAc) afforded the desired compound (5.6 g, 82%) as an oil. R_f (4:1 hexane/EtOAc): 0.50; δ ^{1}H NMR (500 MHz): 1.27 (3H, t, J=7.2 Hz, CH_3), 2.58 (1H, dd, J=16.4, 8.1 Hz, CH_AH$_B$CHO), 2.67 (1H, dd, J=16.4, 4.1 Hz, CH$_A$$H_B$CHO), 3.07 (1H, dd, J=13.8, 7.0 Hz, CH_AH$_B$S), 3.11 (1H, dd, J=13.8, 5.7 Hz), 3.21 (1H, d, J=3.9 Hz, OH), 4.11–4.17 (1H, m, CHOH), 4.17 (2H, q, J=7.0 Hz, CH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 14.0 (*C*H$_3$), 39.8 (*C*H$_2$CHO), 40.1 (*C*H$_2$S), 60.8 (*C*H$_2$CH$_3$), 66.5 (*C*HOH), 126.5 (Ar–*C*), 129.0 (Ar–*C*, 2C), 129.7 (Ar–*C*, 2C), 135.1 (Ar–*C*, quarternary), 172.0 (*C*=O); ν_{max} (neat): 3458.4 (br, O–H), 1729.5 (s, C=O); *m/z* (autospec, CI$^+$): 223 ([M−OH]$^+$, 100%), 241 ([M+H]$^+$, 21%), 258 ([M+NH$_4$]$^+$, 34%); (HRMS, GCT, FI): found 240.0821 ([M·]), $C_{12}H_{16}SO_3$ requires 240.0820.

4.12.2. (±)-3-Hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide. Synthesised from 3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester (2.5 g, 10.4 mmol) using general procedure 2. Purification by column chromatography (1:1 hexane/EtOAc) afforded the desired compound (2.1 g, 78%) as a white solid. R_f (1:1 hexane/EtOAc): 0.16; δ ^{1}H NMR (500 MHz): 2.65 (1H, dd, J=16.8, 8.5 Hz, CH_AH$_B$CHO), 2.86 (1H, dd, J=16.8, 2.2 Hz CH$_A$$H_B$CHO), 3.09 (1H, dd, J=13.4, 6.7 Hz, CH_AH$_B$S), 3.17 (1H, dd, J=13.4, 5.0 Hz), 3.19 (3H, s, CH_3N), 3.67 (3H, s, CH_3O), 3.97 (1H, d, J=3.0 Hz, OH), 4.14–4.22 (1H, m, CHOH), 7.18–7.22 (1H, m, Ar), 7.27–7.32 (2H, m, Ar), 7.39–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 31.7 (*C*H$_3$N), 36.6 (*C*H$_2$CO), 39.6 (*C*H$_2$S), 61.2 (*C*H$_3$O), 66.9 (*C*HOH), 126.2 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.3 (Ar–*C*, 2C), 135.5 (Ar–*C*, quarternary), 172.9 (*C*=O); ν_{max} (neat): 3430.1 (br, O–H), 1643.7 (s, C=O); *m/z* (autospec, CI$^+$): 238 ([M−OH]$^+$, 52%), 256 ([M+H]$^+$, 100%); (HRMS, GCT, CI$^+$): found 256.1018 ([M+H]$^+$), $C_{12}H_{18}SO_3N$ requires 256.1007. Analysis for $C_{12}H_{17}SO_3N$: calculated C: 56.45, H: 6.71, N: 5.49; found C: 56.61, H: 6.87, N: 5.53.

4.12.3. 2-Hydroxy-1-phenylsulfanyl-heptan-4-one (±)-2. Magnesium turnings (1.75 g, 72 mmol) were stirred vigorously in a round-bottomed flask overnight under argon. Dry THF (12 ml) was added. A single crystal of iodine was added and a solution of propyl bromide (2.2 ml, 2.95 g, 24 mmol) in dry THF (12 ml) was added dropwise. The mixture was allowed to stir until it cooled to room temperature. The mixture was then added to a solution of Weinreb amide (1.02 g, 4 mmol) in dry THF (8 ml) at −40 °C via cannula. The mixture was allowed to warm to 0 °C over 30 min and allowed to stir for a further 1.5 h. Saturated ammonium chloride solution (25 ml) was added and the mixture extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (5:1 hexane/EtOAc) afforded **2** (520 mg, 55%) as an oil. R_f (1:1 hexane/EtOAc): 0.16; δ ^{1}H NMR (400 MHz): 0.91 (3H, t, J=7.6 Hz, CH_3), 1.59 (2H, tq, J=7.6, 7.6 Hz, CH_2CH$_3$), 2.39 (2H, t, J=7.6 Hz, CH_2CH$_2$CH$_3$), 2.67 (1H, dd, J=17.4, 7.9 Hz, CH_AH$_B$CHO), 2.76 (1H, dd, J=17.4, 3.9 Hz, CH$_A$$H_B$CHO), 3.05 (1H, dd, J=13.9, 6.4 Hz, CH_AH$_B$S), 3.06 (1H, dd, J=13.9, 6.4 Hz, CH$_A$$H_B$S), 3.28 (1H, d, J=2.2 Hz, OH), 4.11–4.20 (1H, m, CHOH), 7.18–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.36–7.41 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 13.6 (*C*H$_3$), 17.0 (*C*H$_2$CH$_3$), 40.0 (C*H*$_2$S), 45.5 (*C*H$_2$CH$_2$CH$_3$), 47.3 (CH(OH)*C*H$_2$CHO), 66.4 (*C*HOH), 126.5 (Ar–*C*), 129.1 (2C, Ar–*C*), 129.6 (2C, Ar–*C*), 135.3 (Ar–*C*, quarternary), 211.2 (*C*=O); ν_{max} (neat): 3445.5 (br, O–H), 1706.7 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 87%), 256 ([M+NH$_4$]$^+$, 45%); (HRMS, GCT, FI): found 238.1026 ([M·]), $C_{13}H_{18}SO_2$ requires 238.1028.

4.12.4. (±)-2-Ethyl-3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester. Synthesised from (phenylthio)acetaldehyde (88 mg, 6.5 mmol) and ethyl butanoate (1.2 ml, 9.8 mmol) using general procedure 1. Purification by column chromatography afforded the desired compound (1.1 g of a mixture of diastereomers, 64% yield, 44% de) as an oil. Major diastereomer (isomer 1): δ ^{1}H NMR (500 MHz): 0.92 (3H, t, J=7.7 Hz, CH_3CH$_2$CH), 1.27 (3H, t, J=7.2 Hz, CH_3CH$_2$O), 1.69–1.80 (2H, m, CHCH_2CH$_3$), 2.40 (1H, ddd, J=5.1, 6.8, 9.0 Hz, CHEt), 2.87 (1H, br s, OH), 2.95 (1H, dd, J=13.8, 8.5 Hz, CH_AH$_B$S), 3.18 (1H, dd, J=13.8, 3.4 Hz, CH$_A$$H_B$S), 3.87–3.91 (1H, m, C$H$OH), 4.12–4.24 (2H, m, OCH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.6 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$O), 21.1 (CH*C*H$_2$CH$_3$), 39.1 (*C*H$_2$S), 51.7 (*C*HEt), 60.5 (*C*H$_2$O), 69.5 (*C*HOH), 126.5 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.6 (Ar–*C*, 2C), 134.9 (Ar–*C*, quarternary), 174.2 (CO); minor diastereomer: δ ^{1}H NMR (500 MHz): 0.92 (3H, t, J=7.7 Hz, CH_3CH$_2$CH), 1.28 (3H, t, J=7.3 Hz, CH_3CH$_2$O), 1.60–1.69 (2H, CHCH_2CH$_3$), 2.60 (1H, ddd, J=5.4, 5.4, 8.9 Hz, CHEt), 2.87 (1H, br s, OH), 3.05 (1H, dd, J=13.7, 7.7 Hz, CH_AH$_B$S), 3.12 (1H, dd, J=13.7, 5.0 Hz, CH$_A$$H_B$S), 3.82–3.86 (1H, m, C$H$OH), 4.12–4.24 (2H, OC$H_2CH_3$), 7.19–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.6 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$O), 22.3 (CH*C*H$_2$CH$_3$), 39.6 (*C*H$_2$S), 50.9 (*C*HEt), 60.5 (*C*H$_2$O), 70.4 (*C*HOH), 126.5 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.9 (Ar–*C*, 2C), 135.2 (Ar–*C*, quarternary), 174.6 (CO); ν_{max} (neat): 3468.3 (br, O–H), 1725.7 (s, C=O); *m/z* (HRMS, GCT, FI): found 268.1146 ([M·]), $C_{14}H_{20}O_3S$ requires 268.1133.

4.12.5. (±)-2-Ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide. To N,O-dimethylhydroxylamine hydrochloride (840 mg, 8.6 mmol) in dry toluene (10 ml) at 0 °C was added trimethylaluminium (3.9 ml, 7.8 mmol, 2 M in hexanes) dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was then cooled to 0 °C and 2-ethyl-3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester (500 mg of mixture of diastereomers, 2.1 mmol) in dry toluene (7 ml) was added dropwise via cannula. The mixture was heated to reflux for 2.5 h. The mixture was then allowed to cool, and poured into aqueous tartaric acid (250 ml, 1 M) and allowed to stir for 1.5 h. The mixture was extracted with Et_2O. The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded *anti*-isomer (254 mg, 43%) and *syn*-isomer (96 mg, 16%) as oils (46% de). Analysis *syn*-isomer: R_f (1:1 hexane/EtOAc): 0.32; δ ^{1}H NMR (400 MHz): 0.88 (3H, t, J=7.6 Hz, CH_3CH$_2$), 1.62–1.85 (2H, m, CH_2CH$_3$), 3.07 (1H, dd, J=13.8, 7.5 Hz, CH_AH$_B$S), 3.13 (1H, dd, J=13.8, 5.8 Hz, CH$_A$$H_B$S), 3.15–3.24 (1H, m, C$H$Et), 3.21 (3H, s, C$H_3$N), 3.49 (1H, br s, O$H$), 3.68 (3H, s, C$H_3$O), 3.88–3.95 (1H, m, C$H$OH), 7.16–7.21 (1H, m, Ar), 7.26–7.31 (2H, m, Ar), 7.35–7.39 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 11.9 (CH_3CH$_2$), 20.1 (CH_2CH$_3$), 31.9 (CH_3N), 37.8 (CH_2S), 45.1 (CHEt), 61.5 (*C*H$_3$O), 70.5 (CHOH), 126.3 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.3 (2C, Ar–*C*), 135.3 (Ar–*C*, quaternary), 176.1 (CO); ν_{max} (neat): 3426.5 (br, O–H), 1643.6 (s, C=O); *m/z* (autospec, ESI$^+$): 589 ([2M+Na]$^+$, 78%), 306 ([M+Na]$^+$, 100%);*m/z* (HRMS, autospec, ESI$^+$): found 306.1131 ([M+Na]$^+$): $C_{14}H_{21}NO_3SNa$ requires 306.1140. Analysis for *anti*-isomer: (1:1 hexane/EtOAc): 0.28; δ ^{1}H NMR (400 MHz): 0.91 (3H, t, J=7.6 Hz, CH_3CH$_2$),1.68–1.82 (2H, m, CH_2CH$_3$),2.99–3.26 (3H, m, CH_2S and OH), 3.22 (3H, s, CH_3N), 3.76 (3H, s, CH_3O), 3.80–3.90 (1H, m, CHOH), 4.11–4.17 (1H, m, CHEt), 7.17–7.22 (1H, m, Ar), 7.27–7.31 (2H, m, Ar), 7.35–7.39 (2H, m, Ar); δ ^{13}C NMR (100 MHz):11.9 (CH_3CH$_2$), 22.7 (CH_2CH$_3$), 31.8 (CH_3N), 39.3 (CH_2S), 44.3 (CHEt), 61.6 (*C*H$_3$O), 70.8 (CHOH), 126.4 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.5 (2C, Ar–*C*), 135.5 (Ar–*C*, quaternary), 176.4 (CO); ν_{max} (neat): 3415.8 (br, O–H), 1635.2 (s, C=O); *m/z* (autospec, ESI$^+$): 589 ([2M+Na]$^+$, 42%), 306 ([M+Na]$^+$, 100%); *m/z* (HRMS, autospec, ESI$^+$): found 306.1131 ([M+Na]$^+$): $C_{14}H_{21}NO_3$-SNa requires 306.1140.

4.12.6. (±)-3-Ethyl-4-hydroxy-5-phenylsulfanyl-pentan-2-one. *syn*-Isomer synthesised from the corresponding 2-ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (120 mg, 0.42 mmol) using general procedure 4 and a reaction time of 1.5 h. Purification by column chromatography afforded the product (69 mg, 69%) as an oil. R_f (1:1 hexane/EtOAc): 0.46; δ ^{1}H NMR (400 MHz): 0.87 (3H, t, J=7.6 Hz, CH_3CH$_2$), 1.59–1.69 (1H, m, CH_AH$_B$Me), 1.71–1.84 (1H, m, CH$_A$$H_B$Me), 2.17 (3H, s, C$H_3$CO), 2.76–2.81 (1H, m, C$H$Et), 2.89 (1H, dd, J=11.1, 2.4 Hz, CH_AH$_B$S), 2.90 (1H, br s, OH), 3.14 (1H, dd, J=11.1, 3.9 Hz, CH$_A$$H_B$S), 3.87–3.92 (1H, m, C$H$OH), 7.17–7.22 (1H, m, Ar), 7.26–7.31 (2H, m, Ar), 7.35–7.40 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 11.7 (CH_3CH$_2$), 22.6 (CH_2CH$_3$), 31.6 (CH_3CO), 39.1 (CH_2S), 57.5 (CHEt), 69.1 (CHOH), 126.7 (Ar–*C*), 129.1 (2C, Ar–*C*), 129.8 (2C, Ar–*C*), 134.8 (Ar–*C*, quaternary), 212.1 (CO); ν_{max} (neat): 3437.5 (br, O–H), 1784.3 (s, C=O); *m/z* (HRMS, GCT, FI): found 238.1038 ([M·]), $C_{13}H_{18}O_2S$ requires 238.1028; *anti*-isomer synthesised from the corresponding 2-ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (30 mg, 0.1 mmol) using general procedure 4 with a reaction time of 6 h. Purification by column chromatography (4:1 hexane/EtOAc) afforded the product (10 mg, 42%) as an oil. R_f (1:1 hexane/EtOAc): 0.44; δ ^{1}H NMR (500 MHz): 0.91 (3H, t, J=7.7 Hz, CH_3CH$_2$), 1.57–1.73 (2H, m, CH_2Me), 2.18 (3H, s, CH_3CO), 2.71–2.77 (1H, m, CHEt), 3.01 (1H, dd, J=13.7, 7.7 Hz, CH_AH$_B$S), 3.13 (1H, dd, J=13.7, 5.1 Hz, CH$_A$$H_B$S), 3.15 (1H, br s, O$H$), 3.78–3.85 (1H, m, C$H$OH), 7.21–7.25 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.7 (CH_3CH$_2$), 21.8 (CH_2CH$_3$), 31.3 (CH_3CO), 39.8 (CH_2S), 56.9 (CHEt), 70.4 (CHOH), 126.6 (Ar–*C*), 129.0 (2C, Ar–*C*), 130.0 (2C, Ar–*C*), 134.9 (Ar–*C*, quaternary), 213.2 (CO); ν_{max} (neat): 3413.9 (br, O–H), 1704.7 (s, C=O); *m/z* (GCT, FI): 238 ([M·], 100%); *m/z* (HRMS, autospec, CI$^+$): found 239.1106 ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.7. (±)-5-Hydroxy-4-methyl-6-phenylsulfanyl-hexan-3-one 3. Formed from (phenylthio)-acetaldehyde (447.5 mg, 2.9 mmol) and 3-pentanone (0.45 ml, 376 mg, 4.4 mmol) using general procedure 1. Purification by column chromatography (2:1 40–60 petrol/Et_2O) afforded the two diastereomers: *anti*-**3**: oil, (70 mg, 10.1%); R_f (2:1 40–60 petrol/Et_2O): 0.27; δ ^{1}H NMR (500 MHz): 1.04 (3H, t, J=7.2 Hz, CH_3CH$_2$), 1.15 (3H, d, J=7.3 Hz, CH_3CH), 2.38–2.47 (1H, m, CH_AH$_B$CH$_3$), 2.50–2.59 (1H, m, CH$_A$$H_BCH_3$), 2.88 (1H, dq, J=7.0, 7.2 Hz, CHMe), 2.98 (1H, dd, J=13.9, 8.5 Hz, CH_AH$_B$CHOH), 3.17 (1H, dd, J=13.9, 5.0 Hz, CH$_A$$H_B$CHOH), 3.18 (1H, d, J=5.5 Hz, OH), 3.76–3.83 (1H, m, CHOH), 7.20–7.54 (1H, m, Ar), 7.26–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 7.3 (*C*H$_3$CH$_2$), 13.8 (*C*H$_3$CH), 35.9 (CH$_3$*C*H$_2$), 39.3 (*C*H$_2$S), 48.8 (CH$_3$*C*H), 71.9 (*C*HOH), 126.6 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.8 (2C, Ar–*C*), 135.0 (Ar–*C*, quaternary), 215.6 (*C*=O); ν_{max} (KBr disk): 3339.6 (br, O–H), 1708.4 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 48%), 256 ([M+NH$_4$]$^+$, 15%); (HRMS, autospec, CI$^+$): found 239.1104 ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106; HPLC OD: 80% solvent A/20% solvent B: 7.4 min (5*R*, 4*S*), 8.4 min (5*S*, 4*R*); *syn*-**3**: oil, 375 mg, 54.3%); R_f (2:1 40–60 petrol/Et_2O): 0.23; δ ^{1}H NMR (500 MHz): 1.04 (3H, t, J=7.3 Hz, CH_3CH$_2$), 1.17 (3H, d, J=7.0 Hz, CH_3CH), 2.40–2.50 (1H, m, CH_AH$_B$CH$_3$), 2.52–2.61 (1H, m, CH$_A$$H_BCH_3$), 2.84 (1H, dq, J=4.5, 7.0 Hz, CHCH$_3$), 2.98 (1H, dd, J=13.9, 7.5 Hz, CH_AH$_B$CH$_3$S), 3.04 (1H, dd, J=13.9, 5.5 Hz), 3.00 (1H, d, J=3.0 Hz, OH), 3.98–4.02 (1H, m, CHOH), 7.20–7.25 (1H, m, Ar), 7.25–7.33 (2H, m, Ar), 7.37–7.40 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 8.0 (*C*H$_3$CH$_2$), 11.4 (*C*H$_3$CH), 35.7 (CH$_3$*C*H$_2$), 38.5 (*C*H$_2$S), 49.2 (CH$_3$*C*H), 70.0 (*C*HOH), 127.0 (Ar–*C*), 129.6 (2C, Ar–*C*), 130.1 (2C, Ar–*C*), 135.5 (Ar–*C*, quaternary), 215.8 (*C*=O); ν_{max} (neat): 3437.4 (br, O–H), 1704.0 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 60%); (HRMS, autospec, CI$^+$): found 239.1110, ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.8. 4-Hydroxy-5-phenylselenyl-pentan-2-one (±)-4. Formed from (phenylselenyl)-acetaldehyde (100 mg,

0.53 mmol) and acetone (0.06 ml, 0.80 mmol) using general procedure 1. Purification by column chromatography (1:1 hexane/EtOAc) afforded **4** (95 mg, 70%) as an oil. R_f (1:1 hexane/EtOAc): 0.30; δ ^{1}H NMR (400 MHz): 2.14 (3H, s, CH_3), 2.71 (1H, dd, J=17.5, 7.9 Hz, CH_AH$_B$CHO), 2.77 (1H, dd, J=17.5, 4.0 Hz, CH$_A$$H_B$CHO), 3.02 (1H, dd, J=12.7, 6.8 Hz, CH_AH$_B$Se), 3.06 (1H, dd, J=12.7, 5.9 Hz, CH$_A$$H_B$Se), 3.25 (1H, br s, O$H$), 4.12–4.21 (1H, m, C$H$) 7.25–7.30 (3H, m, Ar) 7.50–7.55 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 30.7 (*C*H$_3$), 34.5 (*C*H$_2$Se), 48.8 (*C*H$_2$CO), 66.8 (*C*H), 127.3 (Ar–*C*, quaternary), 127.3 (Ar–*C*), 129.2 (2C, Ar–*C*), 132.7 (2C, Ar–*C*), 208.7 (*C*=O); ν_{max} (neat): 3422.8 (br, O–H), 1710.7 (s, C=O); *m*/*z* (HRMS, autospec, ESI$^+$) found 281.0061 ([M+Na]$^+$), $C_{11}H_{14}O_2SeNa$ requires 281.0057; HPLC OJ–H: 93% solvent A/7% solvent C: 24.2 min (*S*), 23.2 min (*R*).

4.12.9. 4-Hydroxy-5-methyl-5-phenylsulfanyl-hexan-2-one (±)-5. 2-Methyl-2-phenylsulfanyl-propionaldehyde (200 mg, 1.1 mmol) and acetone (0.22 ml, 3.2 mmol) using general procedure 1. Purification by column chromatography (2:1 hexane/EtOAc) afforded **5** (250 mg, 95%) as an oil. R_f (1:1 hexane/EtOAc): 0.34; δ ^{1}H NMR (400 MHz): 1.21 (3H, s, CH_3CMe) 1.26 (3H, s, CH_3CMe), 2.23 (3H, s, CH_3CO), 2.65 (1H, dd, J=16.5, 10.1 Hz, CH_AH$_B$CHO), 2.80 (1H, dd, J=16.5, 1.9 Hz, CH$_A$$H_B$CHO), 3.19 (1H, d, O$H$), 3.91 (1H, ddd, J=2.4, 2.4, 10.1 Hz, CHOH), 7.30–7.40 (3H, m, Ar), 7.50–7.55 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 23.9 (*C*H$_3$CMe), 24.7 (*C*H$_3$CMe), 31.0 (*C*H$_3$CO), 44.9 (*C*H$_2$CO), 53.1 (*C*H$_2$S), 72.1 (*C*H), 128.8 (2C, Ar–*C*), 129.2 (Ar–*C*), 130.4 (Ar–*C*, quaternary), 137.5 (2C, Ar–*C*), 185.8 (*C*O); ν_{max} (neat): 3418.0 (br, O–H), 1710.9 (s, C=O); *m*/*z* (autospec, CI$^+$): 239 ([M+H]$^+$, 12%), 221 ([M−OH]$^+$, 100%); *m*/*z* (HRMS, autospec, CI$^+$): found 239.1109 ([M+H]$^+$) $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.10. 4-Hydroxy-1-methylsulfanyl-4-phenyl-butan-2-one (±)-10. Formed from benzaldehyde (1 ml, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (linear regioisomer **10**/branched-*syn* **13**/branched-*anti* **13** 15:15:14). Purification by column chromatography (4:1 hexane/EtOAc) afforded **10** (622 mg of 1:1 mix with *anti* regioisomer **13**, 15%) as an oil; linear isomer:R_f (1:1 hexane/EtOAc): 0.43; δ ^{1}H NMR (400 MHz): 2.04 (3H, s, SCH_3), 3.00 (1H, dd, J=17.2, 3.4 Hz, CH_AH$_B$CH), 3.09 (1H, dd, J=17.2, 9.0 Hz, CH$_A$$H_B$CH), 3.16 (2H, s, C$H_2$S), 3.19 (1H, br s, O$H$), 5.18 (1H, dd, J=3.4, 9.0 Hz, CHOH), 7.24–7.41 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 15.6 (S*C*H$_3$), 43.6 (*C*H$_2$S), 48.6 (*C*H$_2$CH), 70.3 (*C*H), 125.7 (2C, Ar–*C*), 127.8 (Ar–*C*), 128.6 (2C, Ar–*C*), 142.7 (Ar–*C*, quaternary), 205.3 (*C*O); ν_{max} (neat): 3430.0 (br, O–H), 1700.5 (s, C=O); *m*/*z* (GCT, FI): found 209.0640 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636.

4.12.11. 4-Hydroxy-3-methylsulfanyl-4-phenyl-butan-2-one (±)-13. Formed from benzaldehyde (1 ml, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (linear/*syn*/*anti* 15:15:14). Purification by column chromatography (4:1 hexane/EtOAc) afforded *anti*-**13** (622 mg of 1:1 mix with linear regioisomer **10**, 15%) as an oil and *syn*-**13** (301 mg, 14%) as an oil. *anti*-**13** (from mixture with linear regioisomer): R_f (1:1 hexane/EtOAc): 0.43; δ ^{1}H NMR (400 MHz): 1.82 (3H, CH_3S), 2.34 (3H, s, CH_3CO), 3.43 (1H, d, J=9.7 Hz, CHS), 3.46 (1H, br s, OH), 4.91 (1H, d, J=9.7 Hz, CHOH), 7.24–7.38 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 13.3 (*C*H$_3$S), 28.0 (*C*H$_3$CO), 59.6 (*C*HS), 73.2 (*C*HOH), 126.9 (2C, Ar–*C*), 128.3 (Ar–*C*), 128.4 (2C, Ar–*C*), 140.8 (Ar–*C*, quaternary), 204.7 (CO); ν_{max} (neat): 3436.1 (br, O–H), 1700.2 (s, C=O); *m*/*z* (GCT, FI): found 209.0640 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636; *syn*-**13**: R_f (1:1 hexane/EtOAc): 0.46; δ ^{1}H NMR (400 MHz): 2.06 (3H, CH_3S), 2.13 (3H, s, CH_3CO), 3.28 (1H, br s, OH), 3.51 (1H, d, J=8.6 Hz, CHS), 4.97 (1H, d, J=8.6 Hz, CHOH), 7.25–7.40 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 12.3 (*C*H$_3$S), 29.1 (*C*H$_3$CO), 60.5 (*C*HS), 69.8 (*C*HOH), 126.9 (2C, Ar–*C*), 128.2 (Ar–*C*), 128.4 (2C, Ar–*C*), 140.4 (Ar–*C*, quaternary), 202.7 (CO); ν_{max} (neat): 3448.3 (br, O–H), 1700.4 (s, C=O); *m*/*z* (GCT, FI): found 209.0634 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636.

4.12.12. 4-Hydroxy-6-(4-methoxy-phenyl)-1-methylsulfanyl-hex-5-en-2-one (±)-11. Formed from 4-methoxycinnamaldehyde (1.62 g, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (**11**/*syn*-**14**/*anti*-**14** 69:8:23). Purification by column chromatography afforded **11** (1.1 g of mix with *anti* product, 37%) as an oil; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 2.06 (3H, s, CH_3S), 2.89 (1H, dd, J=15.2, 4.8 Hz, CH_AH$_B$CH), 2.93 (1H, dd, J=15.2, 7.3 Hz, CH$_A$$H_B$CH), 3.20 (2H, s, C$H_2$S), 3.79 (3H, s, C$H_3$O), 4.71–4.76 (1H, m, C$H$OH), 6.07 (1H, dd, J=6.3, 15.9 Hz, CH=CHAr), 6.57 (1H, d, J=15.9 Hz, CHAr), 6.80 (2H, d, J=8.7 Hz, Ar), 7.26 (2H, d, J=8.8 Hz, Ar); δ ^{13}C NMR (100 MHz): 15.6 (*C*H$_3$S), 43.7 (*C*H$_2$S), 46.9 (*C*H$_2$CH), 55.2 (*C*H$_3$O), 69.0 (*C*H), 114.0 (2C, Ar–*C*), 127.7 (2C, Ar–*C*), 127.9 (*C*H=CHAr), 129.2 (Ar–*C*, quaternary), 129.9 (*C*HAr), 159.3 (Ar–*C*, quaternary), 204.9 (*C*O); ν_{max} (neat):1700.4 (s, C=O), 1606.3 (s, C=C); *m*/*z* (GCT, FI): 266.0987 ([M·]), $C_{14}H_{18}O_3S$ requires 266.0977; HPLC OD: 85% solvent A/15% solvent C: 17.3 min (*S*), 19.1 min (*R*).

4.12.13. 4-Hydroxy-6-(4-methoxy-phenyl)-3-methylsulfanyl-hex-5-en-2-one (±)-14. Formed from 4-methoxycinnamaldehyde (1.62 g, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (**11**/*syn*-**14**/*anti*-**14** 69:8:23). Purification by column chromatography afforded *anti*-**14** (1.1 g of mix with linear regioisomer, 4%) as an oil and *syn*-**14** (213 mg, 8%) as an oil; *anti*-**14**; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 1.99 (3H, s, CH_3S), 2.36 (3H, s, CH_3CO), 3.29 (1H, d, J=9.1 Hz, CHS), 3.79 (3H, s, CH_3O), 4.61 (1H, app t, J=7.9 Hz, CHOH), 6.20 (1H, dd, J=6.8, 15.8 Hz, CHCHAr), 6.63 (1H, d, J=15.9 Hz, CHAr), 6.84 (2H, d, J=8.7 Hz, Ar), 7.33 (2H, d, J=8.7 Hz, Ar); δ ^{13}C NMR (100 MHz): 12.9 (*C*H$_3$S), 28.0 (*C*H$_3$C), 55.3 (*C*H$_3$O), 58.1 (*C*HS), 71.3 (*C*HOH), 114.0 (2C, Ar–*C*), 125.9 (*C*H=CHAr), 128.0 (2C, Ar–*C*), 129.2 (Ar–*C*, quaternary), 131.8 (*C*HAr), 159.4 (Ar–*C*, quaternary), 204.5 (*C*O); ν_{max} (neat):1700.1 (s, C=O), 1606.8 (s, C=C); *m*/*z* (GCT, FI): 266.0965 ([M·]), $C_{14}H_{18}O_3S$ requires 266.0977; *syn*-**14**: R_f (1:1 hexane/EtOAc): 0.40; δ ^{1}H NMR (400 MHz): 2.06 (3H, s, CH_3S), 2.32 (3H, s, CH_3C),

3.34 (1H, d, J=8.3 Hz, C*H*S), 3.79 (3H, s, CH_3O), 4.58 (1H, app t, J=6.8 Hz, C*H*OH), 6.04 (1H, dd, J=6.6, 15.9 Hz, C*H*=CHAr),6.65 (1H, d, J=15.8 Hz, C*H*Ar), 6.84 (2H, d, J=8.8 Hz, Ar), 7.31 (2H, d, J=8.7 Hz, Ar); δ ^{13}C NMR (100 MHz): 12.4 (*C*H_3S), 29.0 (*C*H_3C), 55.3 (*C*H_3O), 59.4 (*C*HS), 68.8 (*C*HOH), 113.9 (2C, Ar–*C*), 125.1 (*C*H=CHAr), 127.8 (2C, Ar–*C*), 129.1 (Ar–*C*, quarternary), 132.3 (*C*HAr), 159.5 (Ar–*C*, quarternary), 203.0 (*C*O); ν_{max} (neat):1699.7 (s, C=O), 1606.7 (s, C=C); *m/z* (HRMS, autospec, ESI$^-$): 265.0894 ([M−H]$^-$), $C_{14}H_{17}O_3S$ requires 265.0898.

4.12.14. (*R*)-3-Hydroxy-4-phenylsulfanyl-butyric acid ethyl ester 16. To baker's yeast (42 g) in distilled water (420 ml) was added sucrose (50.4 g). The mixture was allowed to stir for 30 min and then 3-oxo-4-phenylsulfanyl-butyric acid ethyl ester (2 g, 8.3 mmol) in EtOH (42 ml) added. The mixture was allowed to stir for 18 h and then the mixture was filtered through celite. The celite was washed with EtOAc (100 ml) and the layers separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**16** (1.08 g, 54%) as an oil. R_f (4:1 hexane/EtOAc): 0.50; δ ^{1}H NMR (500 MHz): 1.27 (3H, t, J=7.2 Hz, CH_3), 2.58 (1H, dd, J=16.4, 8.1 Hz, CH_AH$_B$CHO), 2.67 (1H, dd, J=16.4, 4.1 Hz, CH$_A$$H_B$CHO), 3.07 (1H, dd, J=13.8, 7.0 Hz, CH_AH$_B$S), 3.11 (1H, dd, J=13.8, 5.7 Hz), 3.21 (1H, d, J=3.9 Hz, O*H*), 4.11–4.17 (1H, m, C*H*OH), 4.17 (2H, q, J=7.0 Hz, CH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 14.0 (*C*H$_3$), 39.8 (*C*H$_2$CHO), 40.1 (*C*H$_2$S), 60.8 (*C*H$_2$CH$_3$), 66.5 (*C*HOH), 126.5 (Ar–*C*), 129.0 (Ar–*C*, 2C), 129.7 (Ar–*C*, 2C), 135.1 (Ar–*C*, quarternary), 172.0 (*C*HO); ν_{max} (neat): 3458.4 (br, O–H), 1729.5 (s, C=O); *m/z* (autospec, CI$^+$): 223 ([M−OH]$^+$, 100%), 241 ([M+H]$^+$, 21%), 258 ([M+NH$_4$]$^+$, 34%); (HRMS, GCT, FI): found 240.0821 ([M·]), $C_{12}H_{16}SO_3$ requires 240.0820; $[\alpha]_D$=+5.8 (c=10, CHCl$_3$); ee=58%.

4.12.15. 3-Hydroxy-N-methoxy-N-methyl-4-phenyl-sulfanyl-butyramide (*R*)-15. Synthesised from 3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester **16** (1 g, 4.16 mmol) using general procedure 2. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**15** (863 mg, 81%) as an oil. R_f (1:1hexane/EtOAc): 0.16; δ ^{1}H NMR (500 MHz): 2.65 (1H, dd, J=16.8, 8.5 Hz, CH_AH$_B$CHO), 2.86 (1H, dd, J=16.8, 2.2 Hz CH$_A$$H_B$CHO), 3.09 (1H, dd, J=13.4, 6.7 Hz, CH_AH$_B$S), 3.17 (1H, dd, J=13.4, 5.0 Hz), 3.19 (3H, s, CH_3N), 3.67 (3H, s, CH_3O), 3.97 (1H, d, J=3.0 Hz, O*H*), 4.14–4.22 (1H, m, C*H*OH), 7.18–7.22 (1H, m, Ar), 7.27–7.32 (2H, m, Ar), 7.39–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 31.7 (*C*H$_3$N), 36.6 (*C*H$_2$CO), 39.6 (*C*H$_2$S), 61.2 (*C*H$_3$O), 66.9 (*C*HOH), 126.2 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.3 (Ar–*C*, 2C), 135.5 (Ar–*C*, quarternary), 172.9 (*C*=O); ν_{max} (neat): 3430.1 (br, O–H), 1643.7 (s, C=O); *m/z* (autospec, CI$^+$): 238 ([M−OH]$^+$, 52%), 256 ([M+H]$^+$, 100%); (HRMS, GCT, CI$^+$): found 256.1018 ([M+H]$^+$), $C_{12}H_{18}SO_3N$ requires 256.1007. Analysis for $C_{12}H_{17}SO_3N$: calculated C: 56.45, H: 6.71, N: 5.49; found C: 56.61, H: 6.87, N: 5.53; $[\alpha]_D$=+39.3 (c=10, CHCl$_3$). ee=58%.

4.12.16. 4-Hydroxy-5-phenylsulfanyl-pentan-2-one (*R*)-1. Synthesised from 3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (*R*)-**15** (255 mg, 1 mmol) using general procedure 4. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**1** (176 mg, 84%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+8.6 (c=10, CHCl$_3$). ee=58%; HPLC OD: 93% solvent A/7% solvent B: 15.5 min (*S*), 16.7 min (*R*).

4.12.17. 2-Hydroxy-1-phenylsulfanyl-heptan-4-one (*R*)-2. Magnesium turnings (438 mg, 18 mmol) were stirred vigorously overnight. Dry THF (3 ml) was added. Iodine (a single crystal) was added and a solution of propyl bromide (0.55 ml, 6 mmol) in dry THF (3 ml) was added dropwise. The mixture was allowed to stir until it cooled to room temperature. The mixture was then added to a solution of amide (**22**) (255 mg, 1 mmol) in dry THF (2 ml) at −40 °C via cannula. The mixture was allowed to warm to 0 °C over 30 min and allowed to stir for a further 1.5 h. Saturated ammonium chloride solution (15 ml) was added and the mixture extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-(**c4**) (123 mg, 52%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+14.4 (c=10, CHCl$_3$). ee=58%; HPLC OD: 85% solvent A/15% solvent B: 12.2 min (*S*), 10.2 min (*R*).

4.12.18. 4-Hydroxy-4-phenyl-butan-2-one (*R*)-17. To benzaldehyde (2 ml, 20 mmol) in DMSO (160 ml) and acetone (40 ml) was added (*L*)-proline (690 mg, 6 mmol). The mixture was allowed to stir for 3 h. Water (100 ml) was added and the mixture extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**17** (920 mg, 28%) as an oil; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 2.20 (3H, s, CH_3), 2.83 (1H, dd, J=17.3, 3.3 Hz, CH_AH$_B$), 2.89 (1H, dd, J=17.3, 9.1 Hz, CH$_A$$H_B$), 3.33 (1H, br s, O*H*), 5.16 (1H, dd, J=3.3, 9.1 Hz, C*H*), 7.26–7.37 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 30.8 (*C*H$_3$), 52.0 (*C*H$_2$), 69.8 (*C*H), 125.6 (2C, Ar–*C*), 127.7 (Ar–*C*), 128.6 (2C, Ar–*C*), 142.7 (Ar–*C*, quarternary), 209.1 (*C*O); ν_{max} (neat): 3448.9 (br, O–H), 1708.1 (s, C=O); *m/z* (HRMS, GCT, FI): found: 164.0833 ([M·]), $C_{10}H_{12}O_2$ requires 164.0837; $[\alpha]_D$=+45.1 (c=10, CHCl$_3$). ee=71%.

4.12.19. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-4-phenyl-butan-2-one. Synthesised from 4-hydroxy-4-phenyl-butan-2-one (850 mg, 5.2 mmol) using general procedure 5. Purification by column chromatography (4:1 hexane/DCM) afforded the desired compound (1.29g, 90%) as an oil. R_f (1:1 hexane/Et$_2$O): 0.70; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.85 (9H, s, C(CH_3)$_3$), 2.55 (1H, dd, J=14.9, 4.0 Hz, CH_AH$_B$), 2.95 (1H, dd, J=14.9, 8.9 Hz, CH$_A$$H_B$), 5.16 (1H, dd, J=4.0, 8.8 Hz, C*H*), 7.22–7.36 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.3 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 25.7 (3C, C(*C*H$_3$)$_3$), 31.8 (*C*H$_3$CO), 54.4 (CH_2), 71.9 (*C*H), 125.8 (2C, Ar–*C*), 127.4 (Ar–*C*), 128.3 (2C, Ar–*C*), 144.4

(Ar–*C*, quarternary), 207.3 (CO); ν_{max} (neat): 1720.6 (s, C=O); *m/z* (GCT, CI$^+$): 279 ([M+H]$^+$, 7%), 221 ([M−C_4H_9]$^+$, 15%), 164 ([M−OTBS+NH_3]$^+$, 33%), 147 ([M−OTBS]$^+$, 100%); $[\alpha]_D$=+65.9 (*c*=10, $CHCl_3$).

4.12.20. 4-(*tert*-Butyl-dimethyl-silanyloxy)-1-chloro-4-phenyl-butan-2-one (*R*)-18. To 4-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butan-2-one (556 mg, 2 mmol) in dry DCM (30 ml) at 0 °C was added DIPEA (1.7 ml, 12 mmol). To this was added TMSOTf (1.5 ml, 4 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1.5 h. The reaction was then cautiously quenched with sat. NH_4Cl (50 ml). The mixture was extracted with hexane, the organic fractions combined, dried over Na_2SO_4, filtered under suction and the solvent removed in vacuo. The residue was taken up in dry DCM (2 ml) and added dropwise to a solution of SO_2Cl_2 (0.19 ml, 2.4 mmol) in DCM (10 ml) at −78 °C. The mixture was allowed to warm to room temperature over 30 min and allowed to stir at room temperature for 30 min. The reaction was then quenched with ice-cold water (15 ml). The mixture was extracted with DCM, the organic layers combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/DCM) afforded (*R*)-**18** (221 mg, 35%) as an oil. R_f (1:1 hexane/DCM): 0.32; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 2.65 (1H, dd, *J*=14.6, 3.8 Hz, CH_AH$_B$CH), 3.05 (1H, dd, *J*=14.6, 9.2 Hz, CH$_A$-H_BCH), 4.10 (1H, dd, *J*=16.0 Hz, CH_AH$_B$Cl), 4.19 (1H, dd, *J*=16.0 Hz, CH$_A$$H_B$Cl), 5.17 (1H, dd, *J*=3.8, 9.1 Hz, C*H*), 7.24–7.37 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.3 (Si*C*H$_3$), −4.8 (Si*C*H$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 25.7 (3C, SiC(*C*H$_3$)$_3$), 50.0 (*C*H$_2$Cl), 50.7 (*C*H$_2$CH), 72.2 (*C*H), 125.7 (2C, Ar–*C*), 127.7 (Ar–*C*), 128.4 (2C, Ar–*C*), 143.7 (Ar–*C*, quarternary), 200.3 (CO); ν_{max} (neat):1736.5 (s, C=O); *m/z* (autospec, CI$^+$): 315 ([M+H]$^+$ ^{37}Cl, 1%) 313 ([M+H]$^+$ ^{35}Cl, 2.5%), 257 ([M−C(CH$_3$)$_3$]$^+$ ^{37}Cl, 18%), 255 ([M−C(CH$_3$)$_3$]$^+$ ^{35}Cl, 49%), 183 ([M−OTBS]$^+$ ^{37}Cl, 35%), 181 ([M−OTBS]$^+$ ^{35}Cl, 100%); *m/z* (autospec, CI$^+$): 313.1389 ([M+H]$^+$(^{35}Cl)), $C_{16}H_{26}O_2SiCl$ requires 313.1391; $[\alpha]_D$=+78.7 (*c*=10, $CHCl_3$).

4.12.21. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methylsulfanyl-4-phenyl-butan-2-one. Synthesised from 4-(*tert*-butyl-dimethyl-silanyloxy)-1-chloro-4-phenyl-butan-2-one (130 mg, 0.44 mmol) using general procedure 7. Purification by column chromatography (4:1 hexane/DCM) afforded the desired compound (137 mg, 96%) as an oil. R_f (1:1 hexane/DCM): 0.25; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 2.00 (3H, s, CH_3S), 2.73 (1H, dd, *J*=15.0, 4.2 Hz, CH_AH$_B$CH), 3.13 (1H, dd, *J*=15.0, 8.8 Hz, CH$_A$-H_BCH), 3.14 (1H, d, *J*=13.9 Hz, CH_AH$_B$S), 3.21 (1H, d, *J*=13.9 Hz, CH$_A$$H_B$S), 5.18 (1H, dd, *J*=4.2, 8.8 Hz, C*H*), 7.21–7.40 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.2 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), 15.4 (S*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), 25.7 (3C, C(*C*H$_3$)$_3$), 44.5 (*C*H$_3$SMe), 51.1 (*C*H$_2$CH), 72.1 (*C*H), 125.8 (2C, Ar–*C*), 127.5 (Ar–*C*), 128.4 (2C, Ar–*C*), 144.2 (Ar–*C*, quarternary), 203.4 (*C*O); ν_{max} (neat):1708.7 (s, C=O); *m/z* (GCT, FI): 324.1592 ([M·]), $C_{17}H_{28}O_2SiS$ requires 324.1579; $[\alpha]_D$=+77.5 (*c*=10, $CHCl_3$).

4.12.22. 4-Hydroxy-1-methylsulfanyl-4-phenyl-butan-2-one (*R*)-10. Synthesised from 4-(*tert*-butyl-dimethyl-silanyloxy)-1-methylsulfanyl-4-phenyl-butan-2-one (130 mg, 0.37 mmol) using general procedure 6. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**10** (40 mg, 66%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+43.7 (*c*=10, $CHCl_3$); HPLC OD: 90% solvent A/10% solvent B: 15.6 min (*S*), 16.7 min (*R*).

Acknowledgements

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Stereoselective synthesis of constrained oxacyclic hydroxyethylene isosteres of aspartyl protease inhibitors. Nitroaldol methodology toward 2,3-substituted tetrahydrofurans☆

Stephen Hanessian* and Martin Brassard

Department of Chemistry, Université de Montréal, C.P. 6128, Station Centre-ville, Montréal, Que., Canada H3C 3J7

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Dedicated to Dieter Seebach, chemist extraordinaire, scholar and friend

Abstract—The Shibasaki heterobimetallic Binol lanthanide, and Trost dinuclear zinc catalysts were studied in a nitroaldol reaction of 3-methyl-1-nitrobutane with a chiral non-racemic tetrahydrofuran aldehyde. Other methods utilized KF, Amberlyst A-21, and *t*-BuOK as bases for the same nitroaldol reaction. The major isomer in the Binol lanthanide and dinuclear zinc catalyzed reactions was the *syn/syn*-nitroaldol product. Structures were confirmed by single-crystal X-ray crystallography. The major nitroaldol isomer was converted to a 2,3-substituted tetrahydrofuran 2-carboxylic acid containing a γ,δ-amino alcohol branch, corresponding to a constrained oxacyclic analogue of a hydroxyethylene isostere of aspartyl protease inhibitors.

1. Introduction

The synthesis of functionalized tetrahydrofurans has been an area of long-standing interest in conjunction with natural product synthesis harboring such motifs.[1] Numerous methods have been reported covering a wide range of strategies, depending on the pattern, and nature of the substituents on the tetrahydrofuran ring. An obvious choice in some instances has been to manipulate the appropriate furanoid sugar,[2] or the elaboration of γ-butyrolactones.[3] Asymmetric methods of synthesis under catalytic or non-catalytic conditions have also been reported.[4]

Several synthetic inhibitors of aspartyl proteases include a hydroxyethylene isostere subunit corresponding to a 2-alkyl-4-hydroxy-5-amino-1-carboxylic acid or to the truncated statine-type variant[5] (Fig. 1A). We envisaged an oxacyclic, conformationally constrained variant of an acyclic hydroxyethylene isostere in which the requisite functional groups had the correct absolute configurations for

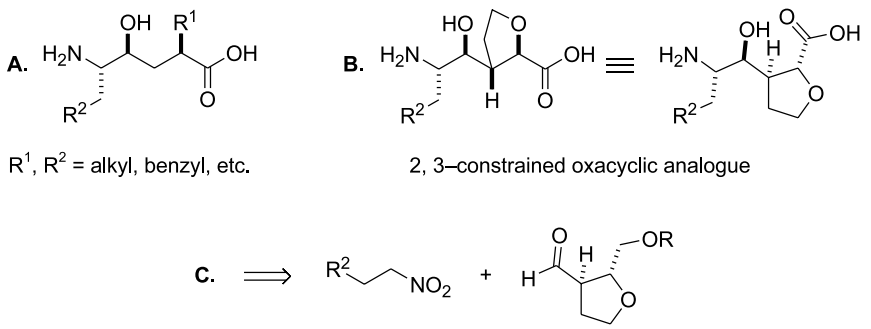

Figure 1. Oxacyclic hydroxyethylene peptide isostere core subunits.

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* Corresponding author. Tel.: +1-514-343-6738; fax: +1-514-343-5728; e-mail address: stephen.hanessian@umontreal.ca

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effective interactions with aspartyl residues of a given enzyme.[5] In essence, the space encompassed by the C-2 alkyl group and the adjacent methylene in the acyclic chain, could be occupied by the five membered oxacycle as depicted in perspective drawings in Figure 1B. Consideration of various approaches to such a motif having four contiguous stereogenic centers, led us to explore the nitroaldol reaction between suitable 1-nitroalkanes and a 3-aldehydo-2-hydroxymethyl tetrahydrofuran of known absolute configuration (Fig. 1C).

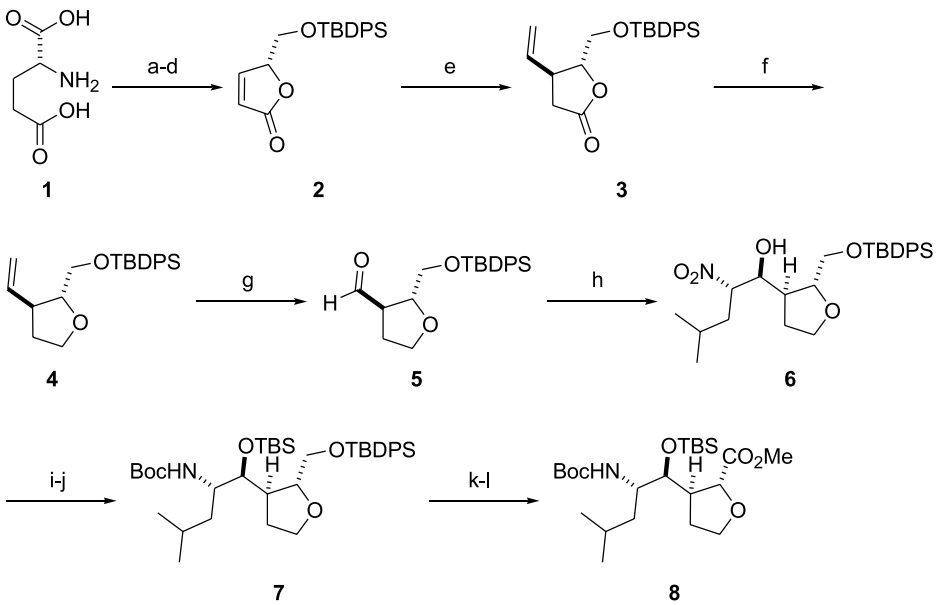
The venerable nitroaldol (Henry) reaction[6] has been a classical method for the synthesis of α-hydroxy nitroalkanes for over a century.[7] Important applications can be found, in the synthesis of natural products and medicinally important compounds.[7] α-Hydroxy nitroalkanes are easily converted to α-hydroxy aldehydes (Nef reaction),[8] nitroolefins, α-amino alcohols and related functionalities. In the original report, Henry described the reaction of nitromethane with acetaldehyde to give 1-nitro-2-hydroxypropane, and compared it to the cyanohydrin reaction.[6] Nearly a century later, Seebach and co-workers[9] showed that bis-lithiated nitronates and silylnitronates were excellent nucleophiles for the reaction. *Syn*- or *anti*-α-hydroxy nitroalkanes could be obtained as major or minor diastereomers depending on the quench method, the reaction conditions, and the presence of additives. In 1983, Rosini and co-workers,[10] reported the synthesis of α-hydroxy nitroalkanes in good yields simply by bringing the nitroalkane and the aldehyde in contact with chromatography-grade alumina. The method was successfully applied for the synthesis of aminodeoxy sugars.[11] Subsequently, the condensing medium was changed to the tetraalkylammonium resin Amberlyst A-21 by Ballini and co-workers[12] with improved yields of adducts. Potassium fluoride has been used as a mild base in asymmetric nitroaldol condensations of aldehydo esters of 8-phenylmenthol by Solladié-Cavallo.[13] Tetrabutylammonium fluoride was the promoter of choice in the condensation of primary nitroalkanes with α,α-*N*,*N*-dibenzylamino aldehydes.[14] Nitrogen bases such as tetramethylguanidine[15] have also found, many uses in nitroaldol reactions. Extension to chiral guanidines have been explored in diastereoselective nitroaldol reactions.[16] Condensations in the presence of catalytic amounts of proazaphosphatranes were described by Kisanga and Verkade.[17]

Recently, several groups have reported catatylic asymmetric versions of the nitroaldol reaction, especially with nitromethane. Thus, Shibasaki[18] has utilized chiral non-racemic Binol lanthanides in nitroaldol reactions with nitromethane, and extended the methodology to simple primary nitroalkanes affording *syn*-nitroaldol products with unsubstituted aldehydes.[19] Trost[20] has used a dinuclear zinc catalyst, while Jørgensen[21] and Evans[22] have exploited bis-oxazoline copper catalyst. Finally, chiral quaternary ammonium salts have been described in the catalytic asymmetric synthetis of nitroaldol reactions by Corey[23] and Maruoka,[24] respectively. With three exceptions,[19,21,24] all nitroaldol reactions were done with nitromethane, leading to enantioenriched 1-nitro-2-hydroxy adducts.

With a plethora of methods to prepare α-hydroxynitroalkanes relying on diastereoselective methods with various additives, and the possibility to extend such reactions to catalytic asymmetric variants, we embarked on the synthesis of the intended oxacyclic hydroxyethylene α-amino alcohol isostere (Fig. 1B and C).

2. Results

Our initial studies were focused on the use of 3-methyl-1-nitrobutane as the nucleophile. The requisite aldehyde



Scheme 1. Reagents and conditions: (a) $NaNO_2$, H_2SO_4, H_2O, 0 °C (55%); (b) $BH_3{\cdot}Me_2S$, THF, 0 °C (80%); (c) TBDPSiCl, Et_3N, DMAP, CH_2Cl_2 (85%); (d) 1. LiHMDS, PhSeBr, THF, −78 °C; 2. H_2O_2, CH_2Cl_2, 0 °C (60%, 2 steps); (e) CuI, $CH_2{=}CHMgBr$, Me_2S, THF, −78 °C (80%); (f) 1. DIBAL, CH_2Cl_2, −78 °C; 2. Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −45 °C (85%, 2 steps); (g) O_3, PPh_3, CH_2Cl_2, −78 °C (90%); (h) 3-methyl-1-nitrobutane, $LaLi_3$(R-Binol)$_3{\cdot}$LiOH, THF, −40 °C (46%, major isomer); (i) TBSOTf, 2,6-Lutidine, CH_2Cl_2 (90%); (j) 1. H_2 (5 atm), Raney-Ni, H_2PtCl_6, MeOH; 2. Boc_2O, THF/Et_3N (9:1) (90%, 2 steps); (k) TBAF/AcOH (1:1), THF, 40% (l) 1. PDC, DMF; 2. CH_2N_2, CH_2Cl_2 (57%, 2 steps).

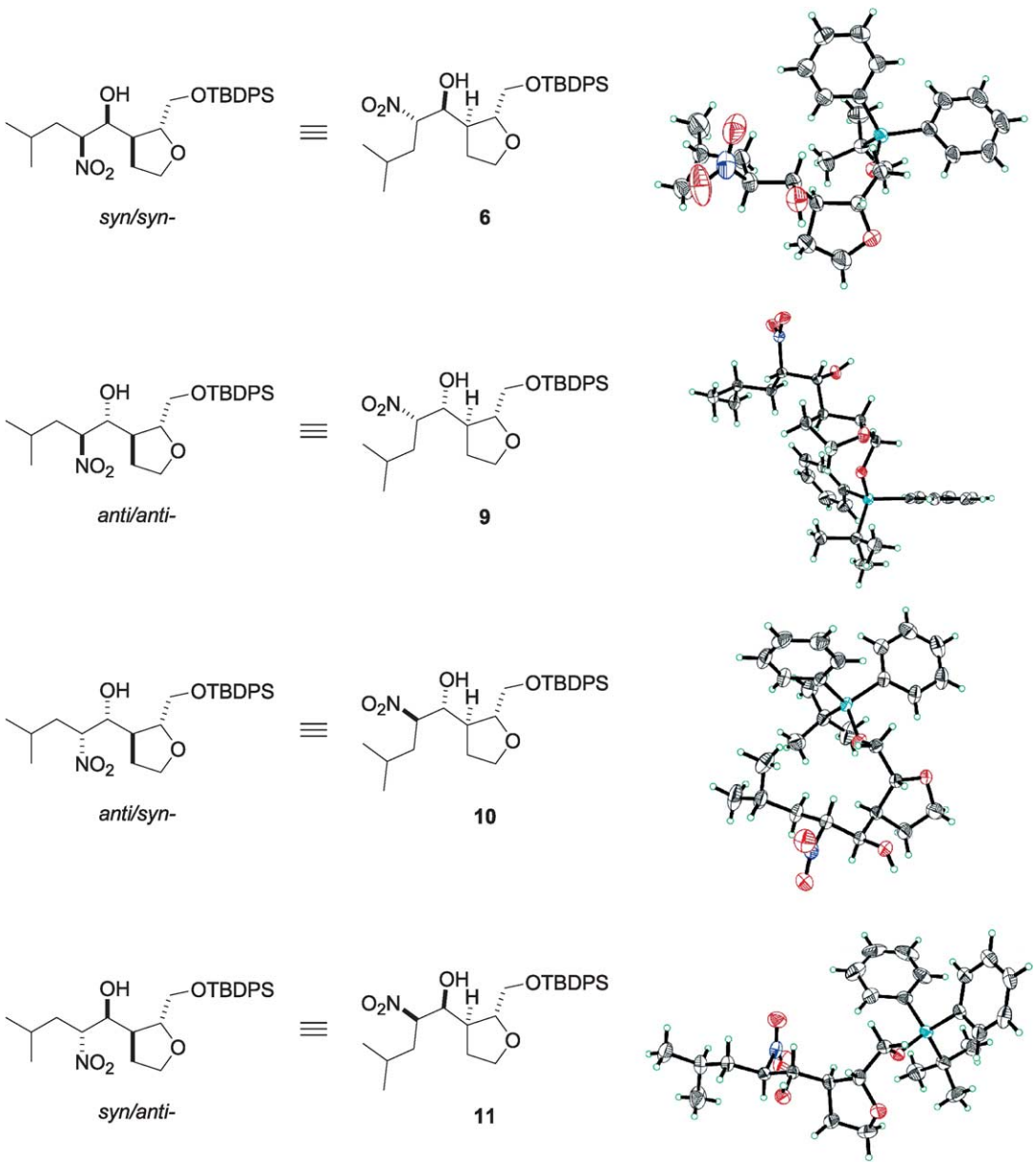


Figure 2. Ortep representations of X-ray crystal structures of nitroaldol products **6**, **9**, **10** and **11**.

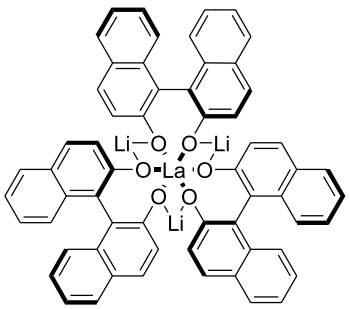
(Fig. 1C, R=TBDPS), was prepared in eight steps from *R*-glutamic acid **1** using previously developed methodology in the enantiomeric series[25] (Scheme 1). Thus, addition of a mixed vinylmagnesium cuprate to the unsaturated lactone **2** afforded the vinyl adduct **3** in excellent yield. Treatment with Dibal followed by triethylsilane and $BF_3{\cdot}Et_2O$ afforded the corresponding 3-vinyl tetrahydrofuran **4**. Finally, oxidative cleavage of the double bond by ozonolysis led to the desired aldehyde **5** in 13% yield for eight steps.

The nitroaldol reaction was first done in the presence of several promoters using 3-methyl-1-nitrobutane as a representative precursor of the amino moiety, and 3-phenylpropanal as a model aldehyde. Attempted condensation with the guanidinium nitronate or in the presence of alumina gave only starting aldehyde. Formation of the lithium nitronate with butyl lithium gave the expected mixture of nitroaldol products. Since preliminary results had shown promising selectivity with the key aldehyde **5** utilizing the Shibasaki Binol lanthanide catalyst,[18] we proceeded to optimize the reaction further utilizing the second generation catalyst.[18c] Thus, reaction at −40 °C for 80 h led to a mixture of all four diastereomers of which the desired *syn/syn*-isomer **6** was preponderant (46% isolated). The structure and absolute stereochemistry was confirmed by a single crystal X-ray structure. The structures of the other diastereomers were also confirmed by X-ray crystallographic analysis (Fig. 2). The crystalline nitroaldol products are shown in their order of elution by column chromatography. Thus, isomers **9** and **10** were followed by **11**, and the desired **6** which was the most polar. A small quantity of unreacted aldehyde **5** (10–15%) was also isolated. With the desired diastereomer **6** in hand, we proceeded with its elaboration to the intended δ-amino acid motif (Fig. 1B).

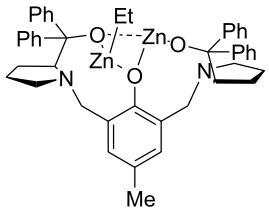
Thus, protection of the hydroxyl group as a TBS ether, reduction of the nitro group in the presence of Raney-Ni and H_2PtCl_6,[26] followed by treatment with Boc anhydride, gave

Table 1. Nitroaldol reaction conditions

Entry	Catalyst	Conditions	Yield (%)[a]	Ratio and % yield[b]			
				9	**10**	**11**	**6**
1	Amberlyst A-21	THF, rt	60	1, 10%	1.6, 17%	1.1, 12%	1.9, 20%
2	KF	*i*-PrOH, rt	52	1, 10%	1, 10%	1.3, 12%	2, 20%
3	*t*-BuOK	*t*-BuOH/THF (1:1), −25 °C	70	1.4, 13%	2, 18%	1, 9%	3.5, 30%
4	*t*-BuOLi	*t*-BuOH/THF (1:1), −25 °C	70	1, 11%	1.4, 16%	1.2, 13%	2.7, 30%
5	$LaLi_3$(*R*-Binol)$_3$·LiOH (Shibasaki)[18c]	THF, −40 °C	65[c]	1.5, 3%	5.5, 13%	1, 3%	20, 46%
6	$LaLi_3$(*S*-Binol)$_3$·LiOH (Shibasaki)	THF, −40 °C	65	2.3, 11%	5.6, 26%	1, 5%	5, 23%
7	Dinuclear Zn catalyst (Trost)[20]	THF, rt	60[c]	4.4, 15%	3.9, 14%	1, 4%	8.7, 29%



Shibasaki heterobimetallic catalyst[18]



Trost dinuclear Zn catalyst[20]

[a] Total yield of all isomers.
[b] Yield percentage of isomers based on weights of isolated products.
[c] Starting aldehyde **5** could be recovered (10–15%).

the N-Boc derivative **7** in excellent overall yield (Scheme 1). Several other reduction conditions were tried but were not satisfactory or led to decomposition (Pd/C, Raney-Ni, PtO_2, SmI_2,[27] Al–Hg,[28] $NaBH_4$, $NiCl_2$).[29] Selective desilylation and oxidation of the primary alcohol with PDC in DMF led to the corresponding carboxylic acid which was characterized as the ester **8**.

Other promoters and catalysts were also tried for the nitroaldol reaction shown in Table 1. In the presence of Amberlyst A-21 or KF, the diastereomeric ratios favoring **6** were disappointing (Table 1, entry 1,2). Some improvement could be seen in the presence of Li or *t*-BuOK as the base (Table 1, entry 3, 4). With Trost's dinuclear zinc catalyst,[20] the reaction was slow even at room temperature. However, the desired isomer **6** was formed in a 2:1:1 ratio with respect to the diastereomeric compounds **9** and **10** (Table 1). Unreacted aldehyde **5** was also recovered in this case (~15%).

With the Shibasaki *R*-Binol catalyst,[18c] the second significant diastereomer was found to be the *anti/syn*-adduct **10**, while the *anti/anti*- and *syn/anti*-isomers **9** and **11**, respectively, were formed in negligible quantities (Table 1, entry 5, Fig. 2). It is also of interest that the *S*-Binol lanthanide catalyst gave a quasi-equivalent ratio of isomers **6** and **10** (Table 1, entry 6) reflecting a mismatched pairing. The preponderance of *syn*-nitroaldol products with nitroethane and hexanal for example has been rationalized based on steric hinderance.[19] Control experiments showed that the products **6**, **9**, **10** and **11** were configurationally stable under the Shibasaki reaction conditions.

As previously mentioned the majority of intermolecular catalytic asymmetric nitroaldol reactions reported so far have utilized nitromethane and relatively simple aldehydes. The successful application of the Shibasaki catalytic reaction to higher primary nitroalkanes and an oxacyclic carbaldehyde with a bulky ether appendage such as **5**, is a useful extension that warrants further investigation. The incorporation of the oxacyclic hydroxyethylene isostere in structure-based designed potential inhibitors of aspartyl proteases will be reported in due course.

3. Experimental

3.1. General

3.1.1. (*R*)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-(*S*)-4-vinyldihydrofuran-2-one (3). To a suspension of CuI (1.6 g, 8.4 mmol) in THF (40 ml) at −78 °C was added vinylmagnesium bromide (1.6 M/THF) (10.5 ml, 16.8 mmol). The mixture was stirred for 10 min, Me_2S was added, and stirring was continued at −78 °C for 2 h 30 min, after which, a solution of **2** (1.0 g, 2.8 mmol) in THF (20 ml) was added dropwise. After 2 h, reaction was quenched by adding a 1:1 mixture (100 ml) of saturated aqueous NH_4Cl solution and aqueous ammonium hydroxide. Ether was added and the resulting mixture was stirred vigorously for 1 h. The combined organic phases were washed with a 1:1 mixture of saturated aqueous NH_4Cl, aqueous ammonium hydroxide, and brine. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (10% AcOEt/hexanes) gave **3**

(852 mg, 2.2 mmol, 80%); $[\alpha]_D^{20}$ −28.7° (*c* 3.1, $CHCl_3$), reported[30] $[\alpha]_D^{20}$ +33.1° (*c* 0.7, $CHCl_3$); (film) (cm^{-1}) 1794 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.70–7.67 (m, 4H), 7.48–7.39 (m, 6H), 5.81–5.72 (ddd, *J*=8.0, 10.6, 16.7 Hz, 1H), 5.15 (s, 1H), 5.13–5.11 (d, *J*=7.1 Hz, 1H), 4.28–4.25 (td, *J*=3.3, 6.8 Hz, 1H), 3.97–3.93 (dd, *J*=2.8, 11.7 Hz, 1H), 3.76–3.72 (dd, *J*=3.4, 11.7 Hz, 1H), 3.26–3.18 (qu, *J*=8.0 Hz, 1H), 2.88–2.81 (dd, *J*=9.0, 17.6 Hz, 1H), 2.50–2.43 (dd, *J*=8.5, 17.6 Hz, 1H), 1.08 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 176.5, 136.8, 136.1, 136.0, 133.3, 133.0, 130.4, 128.3, 117.9, 85.0, 63.7, 41.2, 35.5, 27.2, 19.7; HRMS: calcd 380.1808; found, 380.1751.

3.1.2. (*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-(*S*)-3-vinyltetrahydrofuran (4). To a solution of **3** (1.0 g, 2.6 mmol) in CH_2Cl_2 (10 ml) at −78 °C was added DIBAL (1.5 M/toluene) (2.1 ml, 31.5 mmol) dropwise. After stirring for 3 h, few drops of water were added and stirring was continued for another hour. Temperature was raised to 0 °C, ether (10 ml) and water (0.5 ml) were added and the resulting mixture was stirred 20 min at room temperature. The resulting gel was filtered through Celite and washed with hot AcOEt. After evaporation of the solvents under vacuum, the residue was dissolved in CH_2Cl_2 (10 ml) and Et_3SiH (648 mg, 3.9 mmol) was added. The resulting solution was cooled to −45 °C and $BF_3{\cdot}Et_2O$ (412 mg, 2.9 mmol) was added dropwise. After stirring for 3 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and phases were separated. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (5% AcOEt/hexanes) gave **4** (809 mg, 2.2 mmol, 85%);. $[\alpha]_D^{20}$ −8.7° (*c* 0.9, $CHCl_3$); IR (film) (cm^{-1}) 2932; NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.78–7.75 (m, 4H), 7.49–7.40 (m, 6H), 5.83–5.74 (ddd, *J*=8.1, 10.2, 17.1 Hz, 1H), 5.10–5.05 (ddd, *J*=1.0, 1.6, 17.1 Hz, 1H), 5.05–5.02 (ddd, *J*=0.7, 1.7, 10.2 Hz, 1H), 4.01–3.71 (m, 5H), 2.88–2.80 (qu, *J*=8.0 Hz, 1H), 2.19–2.12 (m, 1H), 1.90–1.80 (m, 1H), 1.12 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 138.9, 135.6, 133.5, 129.5, 127.5, 115.3, 84.0, 67.9, 64.7, 45.0, 33.2, 26.7, 19.1.

3.1.3. (*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-carbaldehyde (5). Through a solution of **4** (591 mg, 1.6 mmol) in CH_2Cl_2 (16 ml) at −78 °C was passed a stream of ozone during 30 min until a blue color persisted. The solution was stirred under argon for another 30 min and the ozonide was reduced with PPh_3 (420 mg, 1.6 mmol). The mixture was stirred for 4 h at room temperature. Evaporation under vacuum and purification by flash chromatography (5% AcOEt/hexanes) gave **5** (531 mg, 1.4 mmol, 90%); $[\alpha]_D^{20}$ −21.0° (*c* 1.25; $CHCl_3$); IR (film) (cm^{-1}) 1727.3 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 9.72–9.71 (d, *J*=2.3 Hz, 1H), 7.74–7.66 (m, 4H), 7.47–7.38 (m, 6H), 4.27–4.21 (m, 1H), 3.98–3.82 (m, 2H), 3.80–3.75 (dd, *J*=4.3, 10.6 Hz, 1H), 3.74–3.69 (dd, *J*=5.5, 10.6 Hz, 1H), 3.15–3.07 (m, 1H), 2.31–2.08 (m, 2H), 1.06 (s, 9H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 201.3, 136.0, 136.0, 133.5, 133.5, 130.3, 130.2, 128.2, 128.2, 79.7, 68.8, 65.5, 54.5, 27.6, 27.2, 19.6; MS (*m*/*z*) 291.2 (M−C_6H_5); HRMS: calcd 368.1808; found, 368.1801.

3.1.4. (*S*)-1-[(*R*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-yl]-4-methyl-(*S*)-2-nitropentan-1-ol (6). *Method A: heterobimetallic catalyst (Shibasaki).*[18c] The catalyst was prepared as follows: to a solution of (*R*)-(+)-1,1′-bi(2-naphthol) (100 mg, 0.35 mmol) in THF (10 ml) was added a solution of La(O*i*-Pr)$_3$ (37 mg, 116 μmol) in THF (1.5 ml) at 0 °C. To this mixture was added BuLi (2.5 M/hexanes) (140 μl). The ice bath was removed and mixture was stirred for 12 h. Water (1 M/THF) (116 μl) and BuLi (2.5 M/hexanes) (42 μl) were added and the catalyst was used as such. To a solution of catalyst (3.7 ml) at −40 °C was added 3-methyl-1-nitrobutane[31] (1.3 ml, 11 mmol) and the mixture was stirred 30 min. A solution of **5** (400 mg, 1.1 mmol) in THF (3.3 ml) was added and the reaction mixture was stirred for 80 h. The mixture was quenched with HCl 1.2 M (2 ml), the aqueous phase was extracted with ether (3×10 ml) and the organic phase was washed with brine. Drying with Na_2SO_4, concentration under vacuum, and purification by flash chromatography (1% AcOEt/CH_2Cl_2 to isolate **9** and **10** and a gradient to 5% AcOEt/CH_2Cl_2 to isolate **11** and **6**) gave the four isomers **9** (17 mg, 35 μmol, 3%), **10** (69 mg, 142 μmol, 13%), **11** (14 mg, 29 μmol, 3%) and **6** (246 mg, 507 μmol, 46%), by order of elution, respectively.

For isomer **9**, mp 84–86 °C; $[\alpha]_D^{20}$ −19.4° (*c* 0.82, $CHCl_3$); IR (film) (cm^{-1}) 3392 (OH), 1551 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.70–7.67 (m, 4H), 7.46–7.41 (m, 6H), 4.58–4.55 (m, 1H), 4.08–4.03 (m, 2H), 3.93–3.89 (m, 1H), 3.83–3.73 (m, 2H), 3.64–3.60 (m, 2H), 2.33–2.23 (m, 2H), 2.00–1.97 (m, 1H), 1.75–1.50 (m, 3H), 1.08 (s, 9H), 1.00–0.99 (d, *J*=6.5 Hz, 3H), 0.96–0.95 (d, *J*=6.4 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 135.5, 133.5, 132.4, 132.3, 129.8, 127.7, 89.4, 82.3, 75.5, 67.6, 66.2, 45.9, 35.5, 30.1, 26.6, 24.9, 23.2, 21.1, 19.0; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2592.

For isomer **10**, mp 145–147 °C; $[\alpha]_D^{20}$ −10.4° (*c* 0.68, $CHCl_3$); IR (film) (cm^{-1}) 3392 (OH), 1551 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.65 (m,4H), 7.48–7.39 (m, 6H), 4.68–4.64 (dt, *J*=3.4, 9.9 Hz, 1H), 4.10–4.02 (m,1H), 3.93–3.88 (m,H), 3.80–3.72 (m,2H), 3.68–3.62 (m,1H), 3.55–3.51 (m, 2H), 2.34–2.22 (m, 3H), 1.71–1.61 (m, 3H), 1.07 (s, 9H), 0.98 (d, *J*=2.8 Hz, 3H), 0.96 (d, *J*=2.7 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 132.8, 130.4, 128.3, 89.1, 82.2, 75.6, 68.3, 66.5, 46.6, 39.3, 31.3, 27.2, 25.5, 23.1, 22.1, 19.5; MS (*m*/*z*) 486 (M+1); HRMS: calcd. 485.2598; found, 485.2589.

For isomer **11**, mp 104–107 °C; $[\alpha]_D^{20}$ −10.8° (*c* 0.98, $CHCl_3$); IR (film) (cm^{-1}) 3401 (OH), 1549 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.69–7.65 (m, 4H), 7.47–7.39 (m, 6H), 4.55–4.50 (ddd, *J*=2.6, 5.9, 11.5 Hz, 1H), 4.04–4.01 (m, 1H), 3.91–3.81 (m, 3H), 3.71–3.67 (dd, *J*=4.5, 10.8 Hz, 1H), 3.66–3.62 (dd, *J*=5.1, 10.8 Hz, 1H), 2.37 (m, 1H), 2.28–2.22 (m, 1H), 2.14–1.94 (m, 3H), 1.67–1.48 (m, 2H), 1.07 (s, 9H), 0.95–0.93 (d, *J*=6.5 Hz, 3H), 0.92–0.90 (d, *J*=6.4 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.6, 130.2, 130.2, 128.2, 89.9, 81.6, 73.1, 68.6, 65.9, 44.0, 38.4, 27.2, 26.6, 25.5, 23.6, 21.5, 19.6; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2594.

For isomer **6**, mp 128–131 °C; $[\alpha]_D^{20}$ −30.6° (*c* 1.73,

$CHCl_3$); IR (film) (cm^{-1}) 3346 (OH), 1558 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.66 (m, 4H), 7.47–7.39 (m, 6H), 4.59–4.54 (ddd, J=3.2, 8.0, 11.2 Hz, 1H), 4.04–4.01 (dd, J=2.1, 7.7 Hz, 1H), 3.92–3.78 (m, 4H), 3.72–3.68 (dd, J=5.4, 10.7 Hz, 1H), 2.38–2.28 (m, 2H), 2.08–1.94 (m, 2H), 1.84–1.76 (m, 1H), 1.60–1.50 (m, 1H), 1.46–1.39 (m, 1H), 1.09 (s, 9H), 0.98–0.97 (d, J=6.4 Hz, 3H), 0.95–0.93 (d, J=6.6 Hz, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.6, 130.3, 130.3, 128.2, 128.2, 91.2, 81.2, 72.5, 68.6, 65.9, 43.8, 39.8, 27.3, 25.5, 25.5, 23.6, 21.5, 19.6; MS (*m*/*z*) 486 (M+1); HRMS: calcd 485.2598; found, 485.2594.

The procedure with (*S*)-(−)-1,1′-bi(2-naphthol) and **5** (37 mg, 100 μmol) was the same and gave the four isomers: **9** (5.4 mg, 11 μmol, 11%), **10** (12.8 mg, 26 μmol, 26%), **11** (2.2 mg, 5 μmol, 5%) and **6** (11.5 mg, 23 μmol, 23%).

Method B: dinuclear Zn catalyst (Trost).[20] To a solution of **5** (60 mg, 163 μmol) and 3-methyl-1-nitrobutane[31] in THF (0.5 ml) at −78 °C was added dinuclear Zn catalyst (82 μl) (0.1 M prepared as follows: Et_2Zn (1 M/hexanes) (0.4 ml) was added dropwise to a solution of the ligand precursor (synthesized in 3 steps from *p*-cresol and (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol)[20] (128 mg, 0.2 mmol) in THF (2 ml) at 0 °C. The ice bath was removed and the mixture was stirred 4 days. Reaction was quenched with 0.5 M HCl and the aqueous phase was extracted with ether. The organic phase was washed with water and brine, dried with Na_2SO_4, evaporated under vacuum, then purified by flash chromatography (see method A) to give the four isomers: **9** (11.6 mg, 24 μmol, 15%), **10** (10.7 mg, 22 μmol, 14%), **11** (2.9 mg, 6 μmol, 4%) and **6** (23 mg, 47 μmol, 29%).

Method C: potassium fluoride. To a solution of product **5** (500 mg, 1.5 mmol) and 3-methyl-1-nitrobutane[31] in *iso*-PrOH (30 ml) was added KF (174 mg, 3 mmol). The mixture was stirred for 24 h and poured in water. The aqueous phase was extracted with ether (3×20 ml), dried with Na_2SO_4, evaporated under vacuum and the residue was purified by flash chromatography (see method A) to give **9** (72 mg, 148 μmol, 10%), **10** (72 mg, 148 μmol, 10%), **11** (91 mg, 187 μmol, 12%) and **6** (144 mg, 296 μmol, 20%).

Method D: t-BuOK. To a solution of **5** (37 mg, 0.1 mmol) and 3-methyl-1-nitrobutane[31] (21 mg, 0.18 mmol) in *t*-BuOH/THF (1:1) (1 ml) was added *t*-BuOK (1 M/*t*-BuOH) (0.01 ml, 0.01 mmol). The reaction mixture was stirred at −25 °C during 2 days. Water was added and aqueous phase was extracted with ether (3×20 ml). Combined organic phases were dried with Na_2SO_4, filtered and evaporated under vacuum. Purification by flash chromatography (see method A) gave the four isomers **9** (6.1 mg, 13 μmol, 13%), **10** (8.5 mg, 18 μmol, 18%), **11** (4.4 mg, 9 μmol, 9%) and **6** (15 mg, 30 μmol, 30%).

The procedure with *t*-BuOLi and **5** (37 mg, 0.1 mmol) was the same and gave the four isomers: **9** (5.4 mg, 11 μmol, 11%), **10** (7.5 mg, 16 μmol, 16%), **11** (6.5 mg, 13 μmol, 13%)and **6** (14.5 mg, 30 μmol, 30%).

Method E: Amberlyst A-21. To a solution of **5** (37 mg, 0.1 mmol) and 3-methyl-1-nitrobutane (21 mg, 0.18 mmol) in THF was added Amberlyst A-21 (excess). The suspension was stirred 48 h, filtered and the resin was washed with THF. Evaporation under vacuum and purification by flash chromatography (see method A) gave the four isomers: **9** (4.9 mg, 10 μmol, 10%), **10** (8.4 mg, 17 μmol, 17%), **11** (5.8 mg, 12 μmol, 12%) and **6** (9.9 mg, 20 μmol, 20%).

3.1.5. ((*S*)-1-{(*S*)-(*tert*-Butyldimethylsilanyloxy)-[(*R*)-2-(*tert*-butyldiphenylsilanyloxymethyl)-tetrahydrofuran-(*R*)-3-yl]-methyl}-3-methylbutyl)-carbamic acid *tert*-butyl ester (7). To a solution of **6** (229 mg, 0.47 mmol) in CH_2Cl_2 (4.7 ml) at 0 °C was added 2,6-lutidine (164 μl, 1.41 mmol) and TBSOTf (216 μl, 0.94 mmol) and reaction was stirred for 24 h at room temperature. After addition of ether, the organic phase was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. Drying with Na_2SO_4, evaporation under vacuum and purification by flash chromatography (5% AcOEt/hexanes) gave the TBS ether derivative (259 mg, 433 μmol, 90%); $[\alpha]_D^{20}$ −24.5° (*c* 1.32, $CHCl_3$); IR (film) (cm^{-1}) 1556 (NO_2); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.72–7.68 (m, 4H), 7.48–7.41 (m, 6H), 4.61–4.55 (ddd, J=11.5, 8.6, 2.7 Hz, 1H), 4.31–4.29 (d, J=8.3 Hz, 1H), 3.95–3.82 (m, 3H), 3.79–3.75 (dd, J=3.9, 10.6 Hz, 1H), 3.74–3.70 (dd, J=5.2, 10.6 Hz, 1H), 2.49–2.43 (q, J=8.4 Hz, 1H), 2.22–2.13 (m, 1H), 2.01–1.94 (m, 1H), 1.84–1.76 (m, 1H), 1.54–1.39 (m, 2H), 1.10 (s, 9H), 0.99–0.97 (d, J=6.2 Hz, 3H), 0.95–0.94 (d, J=6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 136.1, 136.0, 133.5, 130.3, 130.2, 128.2, 128.2, 92.3, 80.4, 73.6, 68.8, 65.7, 43.8, 39.6, 27.3, 26.4, 25.6, 25.6, 23.9, 21.3, 19.7, 18.8, −4.0, −4.3; MS 522.3 ($M-C_6H_5$); HRMS: calcd 599.3462; found, 599.3459.

To a solution of the above compound (200 mg, 0.33 mmol) in MeOH (3.3 ml) was added Raney-Ni (catalytic amount) and H_2PtCl_6 (ca 5 mg) and the mixture was stirred under H_2 (5 atm) for 16 h. After filtration through Celite and evaporation under vacuum, the residue was dissolved in MeOH and the reduction was continued for 3 days. After filtration through Celite and evaporation under vacuum, the residue was dissolved with THF/Et_3N (9:1) (3.3 ml) and Boc_2O (87 mg, 0.4 mmol) was added. After 5 h of stirring, the solvents were removed under vacuum and the residue was purified by chromatography (5% AcOEt/hexanes) to give **7** (199 mg, 297 μmol, 90%); IR (film) (cm^{-1}) 1715 (C=O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 7.71–7.70 (m, 4H), 7.43–7.38 (m, 6H), 4.54–4.52 (d, J=9.3 Hz, 1H), 3.86–3.61 (m, 7H), 2.27–2.25 (m, 1H), 2.15–2.07 (m, 1H), 1.86 (m, 1H), 1.70–1.58 (m, 1H), 1.42 (s, 9H), 1.33–1.23 (m, 2H), 1.08 (s, 9H), 0.93 (m, 15H), 0.14–0.09 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 155.9, 136.1, 133.9, 133.8, 130.0, 128.1, 82.1, 79.4, 73.7, 68.7, 66.5, 53.6, 45.7, 42.3, 28.9, 27.8, 27.5, 27.3, 26.6, 25.2, 23.9, 22.5, 19.6, 18.8, −3.3, −3.6; MS 670.5 (M+1); HRMS: calcd 669.4245; found, 669.4240.

3.1.6. (*R*)-3-[(*S*)-2-*tert*-Butoxycarbonylamino-(*S*)-1-(*tert*-butyldimethylsilanyloxy)-4-methylpentyl]-tetrahydrofuran-(*R*)-2-carboxylic acid methyl ester (8). To a solution of **7** (104 mg, 155 μmol) in THF (1.5 ml) was added a TBAF/AcOH solution (1:1) (0.5 M) (340 μl) and the mixture was stirred 16 h, then poured in water (5 ml).

After extraction of the aqueous phase with ether (3×15 ml), the organic phase was washed with saturated aqueous $NaHCO_3$, and brine. Drying with Na_2SO_4, evaporation under vacuum and purification by flash chromatography (20% AcOEt/hexanes) gave the free alcohol (27 mg, 62 μmol, 40%); $[\alpha]_D^{20}$ −48.3° (*c* 1, $CHCl_3$); IR (film) (cm^{-1}) 3336 (OH), 1702 (C═O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 4.57–4.55 (d, *J*=9.2 Hz, 1H), 3.83–3.80 (m, 2H), 3.74–3.68 (m, 3H), 3.62–3.49 (m, 1H), 2.37–2.34 (t, *J*=6.0 Hz, 1H), 2.18–2.12 (m, 1H), 2.08–1.98 (m, 1H), 1.93–1.85 (m, 1H), 1.66–1.56 (m, 1H), 1.44 (s, 9H), 1.31–1.25 (m, 2H), 0.93–0.92 (m, 15H), 0.13–0.10 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 156.1, 82.4, 79.7, 73.9, 68.2, 64.2, 52.6, 44.1, 32.3, 28.8, 28.7, 26.5, 25.2, 23.8, 22.4, 18.8, −3.2, −3.6; MS 432.3 (M+1); HRMS: calcd 431.3067; found, 431.3061.

To a solution of the above compound (20 mg, 46 mmol) in DMF (0.46 ml) was added PDC (87 mg, 230 mmol) and the mixture was stirred 2 days, then quenched with saturated aqueous $NaHCO_3$. After extraction with ether (3×15 ml), the aqueous phase was acidified with 1 N HCl to pH 4. A second extraction with ether (2×15 ml) was followed by acidification with 1 N HCl to pH 1. Drying of the combined organic phases and evaporation under vacuum gave the acid that was dissolved in MeOH and cooled to 0 °C. A solution of CH_2N_2 in ether was added dropwise until the yellow color persisted for several minutes. A few drops of AcOH were added to neutralize excess CH_2N_2. Evaporation under vacuum, and purification by flash chromatography (10% AcOEt/hexanes) gave **8** (12 mg, 26 μmol, 57%); $[\alpha]_D^{20}$ −46.8° (*c* 0.6, $CHCl_3$); IR (film) (cm^{-1}) 1711 (C═O); NMR ^1H ($CDCl_3$, 400 MHz) δ (ppm) 4.66–4.64 (d, *J*=9.0 Hz, 1H), 4.24–4.23 (d, *J*=7.3 Hz, 1H), 3.99–3.90 (m, 3H), 3.78 (s, 3H), 3.74 (m, 1H), 2.52–2.45 (m, 1H), 2.09–2.02 (m, 1H), 2.00–1.90 (m, 1H), 1.67–1.62 (m, 1H), 1.45 (s, 9H), 1.42–1.36 (m, 1H), 1.30–1.23 (m, 1H), 0.96–0.94 (m, 15H), 0.19–0.14 (2s, 6H); NMR ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) 174.3, 155.8, 79.5, 73.5, 69.7, 53.3, 52.5, 48.1, 41.3, 28.8, 28.2, 26.5, 25.3, 23.8, 22.4, 18.7, −3.3, −3.9; MS 460.4 (M+1); HRMS: calcd 459.3016; found, 459.3011.

4. Supporting Information

X-ray structure data for compounds **6**, **9**, **10**, **11**. See also Cambridge Data Base.

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Inverse electron-demand aza-[4+2] cycloaddition reactions of allenamides

Craig R. Berry and Richard P. Hsung*,†

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

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Abstract—An inverse electron-demand aza-[4+2] cycloaddition reaction of allenamides with 1-azadiene is described here. Effects of solvents on diastereoselectivity along with synthetic scopes and mechanistic insights are illustrated. Despite some synthetic limitations, this aza-[4+2] cycloaddition does provide a useful template for the synthesis of aza-glycoside related heterocycles.

1. Introduction

Allenamides have emerged as attractive building blocks in organic synthesis.[1–6] With vastly improved stability and comparable reactivity relative to traditional allenamines, allenamides can be utilized in a diverse array of stereoselective methodologies.[3–6] We reported [4+2] cycloadditions of chiral allenamide **1** with vinyl ketones **2** that led to pyrans **3** in a highly stereoselective manner,[3a] representing a rare account of an inverse demand hetero [4+2] cycloaddition involving a chiral enamide [Fig. 1].[7–9] We have also been focusing on applications of this cycloaddition method as a new approach for stereoselective constructions of *C*-glycoside derivatives **4** [W=O].[4,10] Given such synthetic potential, we examined [4+2] cycloadditions of 1-azadienes **5** with allenamides **6** to access nitrogen heterocycles **7**.

1-Azadienes are known to be poor dienes in Diels–Alder cycloadditions in general because of competing 1,2-additions to imines along with problems related to tautomerization to energetically favored enamines prior to cycloadditions.[7] However, elegant efforts from Boger[11–13] and Fowler,[14–15] by placing electron-withdrawing substituents on the nitrogen atom, have rendered 1-azadienes highly useful for inverse demand hetero [4+2]

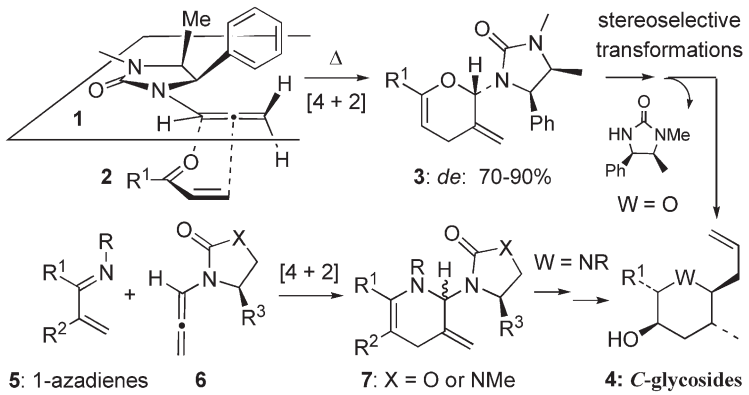

Figure 1.

Keywords: Allenamides; Diels–Alder; Cycloaddition; Inverse Demand; 1-Azadiene; Aza-glycoside.
* Corresponding author. Tel.: +1-612-625-3045; fax: +1-612-626-7541; e-mail address: hsung@chem.umn.edu
† A recipient of 2001–2003 Camille Dreyfus Teacher-Scholar Award.

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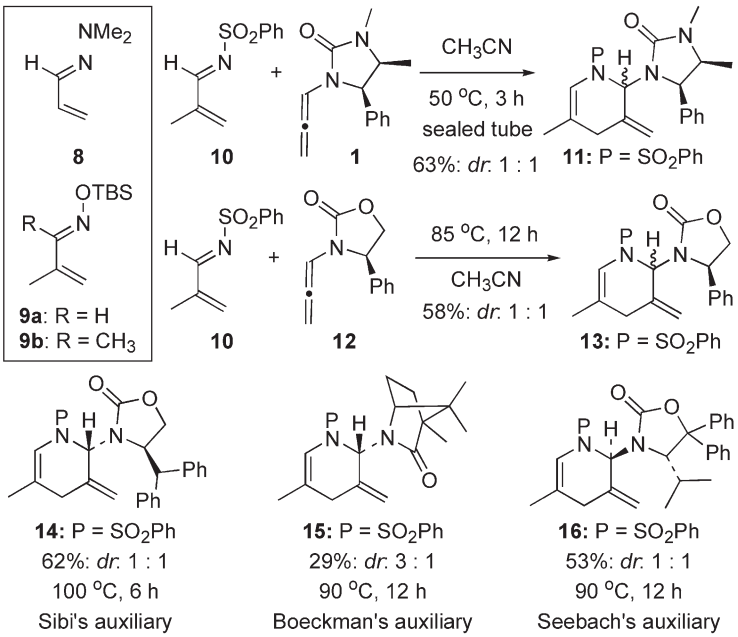


Scheme 1.

cycloadditions with electron rich dienophiles. While Boger[12] has demonstrated that allenol ethers can be used in such cycloadditions, nitrogen-substituted allenes have not been examined.[1,16] Success in this endeavor could provide an opportunity for constructing highly functionalized aza-sugars and related heterocycles [see also **4**: W=NR], a concept that we have already demonstrated using pyrans **3**.[4] We report here our findings in the feasibility and limitation of inverse electron-demand aza-[4+2] cycloadditions of allenamides with 1-azadienes.

2. Results and discussion

2.1. Feasibility of the aza-[4+2] cycloaddition

We quickly demonstrated that more electron-rich 1-azadeines,[17,18] such as **8** and **9a/b** [Scheme 1], did not match well electronically with an allenamide, leading to no observable hetero cycloadducts. On the other hand, 1-*N*-sulfonyl vinyl aldimine **10**[11] was a feasible 1-azadiene to give the desired hetero cycloadducts **11** and **13**[19] in good yields, respectively, from chiral allenamides **1** and **12**. However, the diastereoselectivity was not encouraging with chiral allenamides **1** and **12** substituted with the Close's auxiliary[20] and Evans' auxiliary,[21] respectively, providing virtually no stereoselectivity, although **1** appeared to be more reactive for the reaction could be carried out at a lower temperature.

We then examined chiral allenamides substituted with other well known chiral auxiliaries such as Sibi's[22] and Boeckman's auxiliaries,[23] but neither gave better selectivity as evident in their respective cycloadducts **14** and **15**. The allenamide substituted with the Boeckman's auxiliary was much less stable, and thus, under the same thermal conditions, much decomposition occurred to give **15** in a lower yield. Finally, the use of Seebach's chiral auxiliary[24] unfortunately also did not lead to any improvement in the diastereoselectivity, as evident with cycloadduct **16**.

2.2. Stereochemical and mechanistic issues

2.2.1. Solvent effect. We did observe some interesting solvent effect on the stereochemical outcome of the cycloaddition. As shown in Table 1, a very diverse range of different solvents could be used for the aza-[4+2] cycloaddition of allenamide **1** [entries 1–9]. The temperature could be lowered to 35 °C in some solvents [entries, 4, and 6–8]. More importantly, there is a small but noticeable increase in the diastereoselectivity with increasing in the

Table 1.

Entry	Allenamide[a]	Solvent	Temp (°C)	Time (h)	Cycloadd	Yield (%)[b]	Ratio[c]
1	**1**	Hexane	50	15	**11**	67	2.3:1
2	**1**	PhH	50	15	**11**	75	2.3:1
3	**1**	EtOAc	50	15	**11**	75	1.7:1
4	**1**	Et_2O	35	12	**11**	71	1.7:1
5	**1**	THF	50	15	**11**	75	2.4:1
6	**1**	CH_2Cl_2	35	12	**11**	70	3.5:1
7	**1**	$CHCl_3$	35	12	**11**	71	4.4:1
8	**1**	Acetone	35	12	**11**	67	1.4:1
9	**1**	MeOH	50	15	**11**	59	3.6:1
10	**12**	$CHCl_3$	35	50	**13**	53	1:1
11	**12**	$CHCl_3$	55	24	**13**	50	1:1
12	**12**	$CHCl_3$	65	24	**13**	52	1:1
13	**12**	CH_2Cl_2	35	50	**13**	52	1:1
14	**12**	CH_2Cl_2	55	24	**13**	60	1:1
15	**12**	MeOH	65	72	**13**	62	1:1
16	**12**	THF	65	72	**13**	25	1:1
17	**12**	EtOAc	65	72	**13**	34	1.5:1
18	**12**	PhH	65	72	**13**	52	1.5:1

[a] Reactions were carried out using anhydrous solvent in a sealed tube and 1.0 equiv. of 1-azadiene **10** were used.
[b] Isolated yields.
[c] Diastereomeric ratios [*dr*] were assigned by using ^{1}H NMR and represent ratios of **11/13a** : **11/13b** with **a** being the major isomer.

solvent polarity, with the best ratio being 4.4:1 when the reaction was run in $CHCl_3$ at 35 °C [entry 7]. This modest solvent effect suggests that the cycloaddition could proceed through a stepwise process that involves perhaps ionic intermediates. However, we are not clear how exactly the polarity of the solvent impacts the stereoselectivity of this cycloaddition, especially when the reaction in CH_3CN [see Scheme 1] did not give a good ratio. Stereochemistry of the major isomer **11a** was assigned using an X-ray structure [Fig. 2].

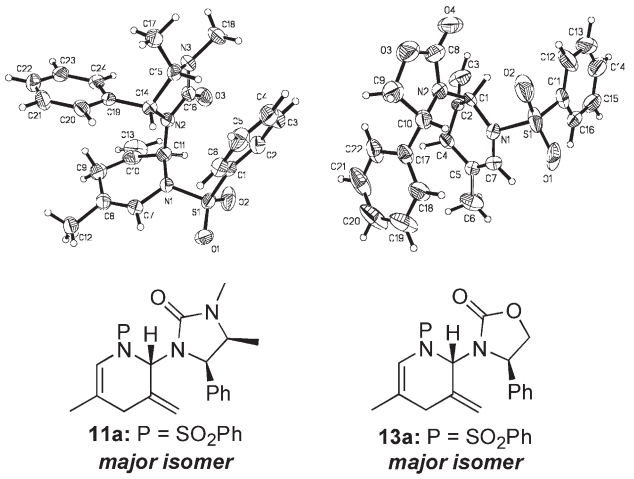


Figure 2. X-ray structures of **11a** [left] and **13a**.

For allenamide **12**, while a range of solvents could also be used [entries 10–18], in most cases, there was no observable increase in stereoselectivity [entries 10–16], even in $CHCl_3$ at various different temperatures [entries 10–13]. An exception would be that we did observe a very small but noticeable selectivity when the reaction was carried out in EtOAc and PhH. The major isomer **13a** was isolated with its stereochemistry being resolved using X-ray analysis [Fig. 2].

2.2.2. A mechanistic model. Although we did not observe any solvent effect on the stereoselectivity of *oxa*-[4+2] cycloadditions of allenamides with acrolein or various vinyl ketones,[3] the overall stereochemical outcome observed here in these aza-[4+2] cycloadditions illustrate a similar trend. That is, chiral allenamide **1** containing an imidazolidinone auxiliary provides better stereoselectivity than any of the oxazolidinone-based allenamides. This trend could be rationalized using the following proposed mechanistic model.

ChemDraw reproductions of the minimized structures of chiral allenamides **1**, **12**, and *ent*-**17** [containing the enantiomer of Seebach's auxiliary[24] for ease of comparison] using Spartan™ AM1-calculations are shown in Figure 3. The allene fragment is essentially co-planar with the imidazolidinone or oxazolidinone ring, thereby suggesting that the observed diastereoselectivity is likely due to a preferred addition of 1-azadienes from the less crowded bottom face of all allenamides.

The phenyl group of the imidazolidinone ring in allenamide **1** appears to be much closer to the allene fragment in the minimized model, thereby providing the best steric presence or facial differentiation and leading to the highest diastereoselectivity. The phenyl group in **12** actually tilts away from the allene moiety, thereby diminishing a significant amount of facial steric bias. This difference between **1** and **12**, however, is likely not a result of the methyl group present in the imidazolidinone ring of **1**, which could contribute toward pushing the phenyl ring closer to the allene fragment. However, if true, *ent*-allenamide **17** with Seebach's auxiliary would have provided an improved stereoselectivity relative to **12**.

Finally, although this mechanistic model accounts for the overall stereochemical outcome, it does not account at this time for the solvent effect that we have observed.

2.3. Synthetic limitations

An apparent limitation of this aza-[4+2] cycloaddition in this study is the accessibility of 1-*N*-sulfonyl vinyl imines. Although there are several accounts in describing their preparations,[11] we were only able to prepare a few,

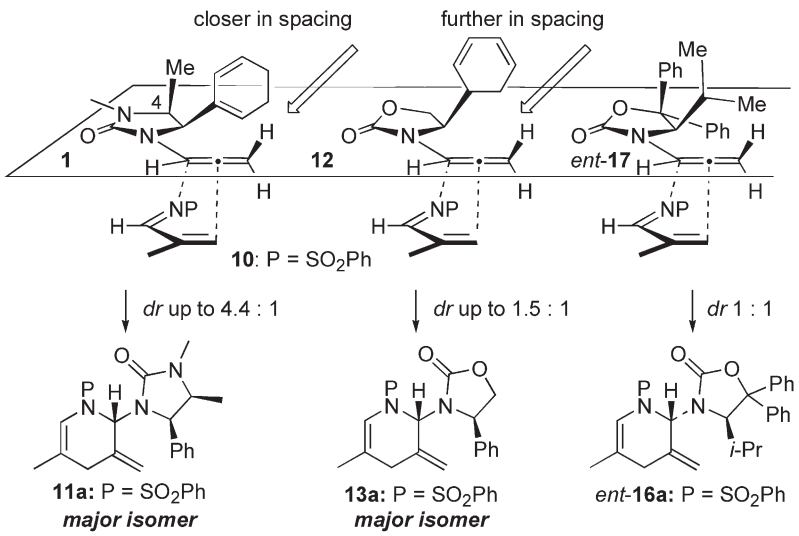
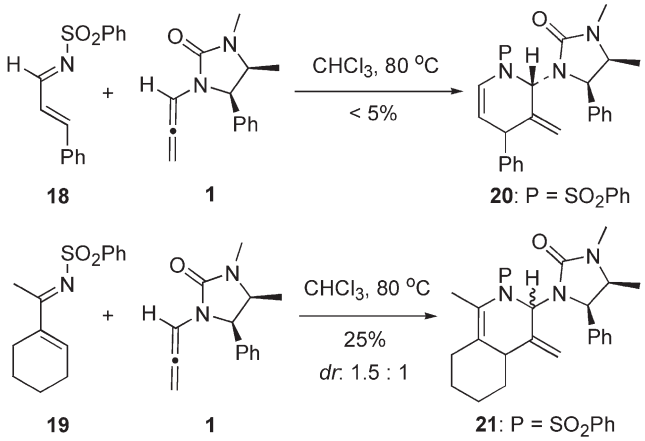


Figure 3.

including 1-azadiene **10**, consistently. The other two successful preparations afforded 1-*N*-sulfonyl vinyl aldimine **18** and ketimine **19** [Scheme 2]. However, cycloaddition of **18** with allenamide **1** did not produce the desired cycloadduct **20** in a synthetically useful manner, although we were able to isolate **21** in 25% yield from the reaction of **19** with **1**. In addition, **21** was isolated as a mixture of only two diastereomers [out of a possible four] with a moderate ratio of 1.5:1. Their relative stereochemistry was not assigned vigorously.



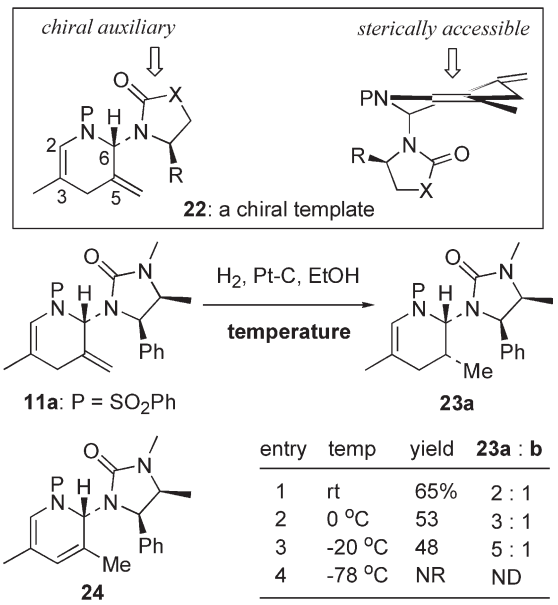
Scheme 2.

We are currently exploring improved preparations of 1-*N*-sulfonyl vinyl imines to access a broader range of aza-cycles through this aza-[4+2] cycloaddition.

2.4. Functionalizations of the aza-[4+2] cycloadduct and removal of the auxiliary

With the aza-cycles **11**, **13**, and **14**–**16** in hand, we examined the concept of employing them as a template for constructing aza-glycoside related heterocycles. X-ray analysis of the major isomer of **11** [Fig. 2] reveals that the chiral imidazolidinone group at C6 is oriented *pseudo*-axially and situated beneath the two olefins: The electron-rich *endo*-cyclic at C2/C3, and the accessible *exo*-cyclic at C5. Based on this analysis, we envisioned that in a manner analogous to our work using pyran **3**,[4] azacycle **22** can also be utilized as a chiral template with the C6 imidazolidinone of **22** being the chiral auxiliary, and that transformations of the two well-differentiated olefins can proceed selectively from the sterically less congested top face [Scheme 3].

To support this concept, the C5 *exo*-cyclic olefin in **11a** was hydrogenated under standard conditions at rt to give **23a** as the major isomer with a modest ratio of 2:1 [entry 1]. The assignment of relative stereochemistry in **23a** using NOE confirmed that the addition of hydrogen occurred at the less congested top face. While the overall selectivity was not as high as we had expected, we did see a much better selectivity [entry 3] at lower temperature. In addition, we consistently isolated 10–15% of dihydropyridine **24**, resulting from isomerization of the *exo*-cyclic olefin. The formation of **24** could be related to the erosion of diastereoselectivity during the hydrogenation.

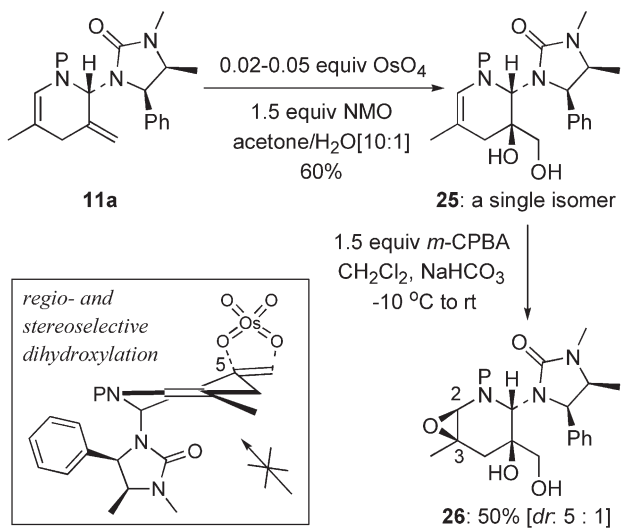


Scheme 3.

A more solid support of the template concept was obtained when azacycle **11a** was dihydroxylated in a highly regio- and stereoselective manner using cat OsO_4 to give diol **25** as a single isomer in 60% yield [Scheme 4]. NOE assignment of relative stereochemistry confirmed that the dihydroxylation occurred exclusively at the top less congested face of the more accessible C5 *exo*-cyclic olefin [lower left box]. An ensuing epoxidation of the C2-3 *endo*-cyclic olefin was also stereoselective, leading to a surprisingly stable epoxide **25** in 50% yield with an isomeric ratio of 5:1.

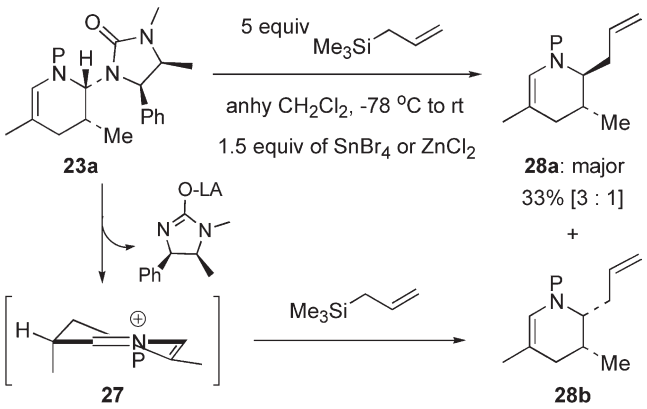
These studies suggest that the aza-[4+2] cycloadduct **22** can be employed as a template with the imidazolidinone group at C6 serving as a chiral auxiliary [or blocking one face] for constructing aza-glycoside related heterocycles.

2.4.1. Removal of the chiral auxiliary. To complete the concept of the C6 imidazolidinone of **22** serving as a chiral auxiliary, we carried out its removal and recovery using related conditions reported for *oxa*-[4+2] cycloadducts,[4a]



Scheme 4.

but it proved to be quite difficult. As shown in Scheme 5, after screening through a variety of Lewis acids, only $SnBr_4$ and $ZnCl_2$ appeared to be suitable Lewis acids that would facilitate a proper departure of the C6 imidazolidinone group in **23a**. An ensuing addition of allyltrimethylsilane to the presumed aza-carbenium intermediate **27** did give azacycle **28a/b** as an isomeric mixture in only 33% yield with a ratio of 3:1. The major isomer was again assigned using NOE experiments.



Scheme 5.

3. Conclusions

We have described here an inverse electron-demand aza-[4+2] cycloaddition reaction of allenamides with 1-aza-dienes. Effect of solvents on diastereoselectivity, along with synthetic scopes and mechanistic insights are reported. Despite some of the current synthetic limitations, this aza-[4+2] cycloaddition does provide cycloadducts that can be employed as a template for the synthesis of aza-glycoside related hetereocycles.

4. Experimental

All reactions performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separation were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VX-300, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Midac M2000 FTIR. TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and vanillin or $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD and are APCI. High-resolution mass spectral analyses performed at Department of Chemistry Mass Spectrometry Laboratory, University of Minnesota. X-ray analyses performed at University of Minnesota Department of Chemistry X-ray facility. All spectral data obtained for new compounds are reported here.

4.1. General procedure for the aza-[4+2] cycloadditions

To a solution of 0.83 g of allenamide **1** (3.6 mmol, 1.0 equiv.) in freshly distilled CH_3CN (36 mL, 0.10 M) was added 0.76 g of sulfonyl imine **10** (3.6 mmol, 1.0 equiv.). The reaction mixture was sealed under a blanket of nitrogen, and the mixture was stirred for 3 h at 50 °C. After which, the solution was allowed to cool to room temperature, and solvent was removed under reduced pressure. Silica gel flash column chromatography (gradient eluent: 0–25% EtOAc in hexanes) afforded both the major and minor cycloadduct **11a** and **11b** in 63% yield (1.00 g) of as a foamy solid. The two isomers could be separated via subsequent column chromatography.

4.1.1. Major isomer 11a. R_f=0.35 [50% EtOAc/hexane]; mp 148–150 °C; $[\alpha]_D^{20}$ −66.3° [*c* 4.1, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 0.65 (d, 3H, *J*=6 Hz), 1.22 (d, 1H, *J*=20.5 Hz), 1.31 (s, 3H), 1.94 (d, 1H, 20.5 Hz), 2.69 (s, 3H), 3.52 (dq, 1H, *J*=6, 9 Hz), 4.59 (s, 1H), 4.60 (d, 1H, *J*=9 Hz), 5.04 (s, 1H), 6.24 (s, 1H), 6.44 (s, 1H), 7.20–7.24 (m, 4H), 7.47–7.56 (m, 4H), 7.82 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 19.8, 28.7, 32.0, 56.8, 59.1, 65.4, 114.9, 116.5, 117.9, 126.4, 127.0, 127.9, 128.6, 129.1, 132.9, 138.1, 138.3, 138.9, 161.1; IR (film) cm^{-1} 3212m, 3063s, 2933s, 2882s, 1712s, 1168s; mass spectrum (LRMS): *m/e* (% relative intensity) 438 (100) M^++H, 296 (50), 248 (100), 203 (80), 191 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1664.

4.1.2. Minor isomer 11b. R_f=0.30 [50% EtOAc/hexane]; mp 84–87 °C; $[\alpha]_D^{20}$ +29.8° [*c* 1.7, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 0.74 (d, 3H, *J*=6 Hz), 1.60 (s, 3H), 2.35 (d, 1H, *J*=20 Hz), 2.71 (s, 3H), 3.01 (d, 1H, *J*=20 Hz), 3.69 (dq, 1H, *J*=6, 9 Hz), 4.67–4.70 (m, 3H), 5.80 (s, 1H), 5.93 (s, 1H), 7.31–7.42 (m, 4H), 7.46–7.51 (m, 4H), 7.63 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9, 20.0, 28.7, 33.8, 56.1, 61.7, 66.2, 114.0, 118.5, 120.2, 126.9, 127.0, 127.9, 128.0, 128.7, 132.5, 136.5, 138.0, 138.7, 159.7; IR (film) cm^{-1} 3190m, 3090s, 2915s, 2930m, 1722s, 1209m; mass spectrum (LRMS): *m/e* (% relative intensity) 438 (100) M^++H, 296 (50), 248 (100), 203 (80), 191 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1678.

4.1.3. Cycloadduct 13a. R_f=0.30 [50% EtOAc/hexane]; mp 105–108 °C; $[\alpha]_D^{20}$ −88.1° [*c* 5.1, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.40 (d, 1H, *J*=20 Hz), 1.99 (d, 1H, *J*=20 Hz), 4.07 (dd, 1H, *J*=6, 9 Hz), 4.51 (t, 1H, *J*=9 Hz), 4.08 (d, 1H, *J*=2.5 Hz), 4.88 (dd, 1H, *J*=6, 9 Hz), 5.07 (d, 1H, *J*=2.5 Hz), 5.98 (s, 1H), 6.28 (s, 1H), 7.24–7.36 (m, 4H), 7.48–7.54 (m, 4H), 7.81 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 31.6, 57.6, 67.0, 71.2, 116.1, 116.7, 117.6, 127.0, 127.3, 128.6, 128.7, 129.2, 133.2, 136.8, 138.2, 140.0, 158.5; IR (film) cm^{-1} 3010s, 2905s, 2877m, 1709s, 1552m; mass spectrum (LRMS): *m/e* (% relative intensity) 411 (100) M^++H, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1198, found 433.1193.

4.1.4. Cycloadduct 13b. R_f=0.22 [50% EtOAc/hexane]; mp 121–123 °C; $[\alpha]_D^{20}$ +59.0° [*c* 2.7, CH_2Cl_2]; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 2.36 (d, 1H, *J*=20 Hz), 2.96 (d, 1H, *J*=20 Hz), 4.10 (dd, 1H, *J*=6, 8.5 Hz), 4.56 (t, 1H, *J*=9 Hz), 4.71 (d, 1H, *J*=2.5 Hz), 4.77 (d, 1H, *J*=2.5 Hz), 4.93 (dd,

1H, *J*=6.5, 9 Hz), 5.67 (s, 1H), 5.95 (s, 1H), 7.36–7.44 (m, 6H), 7.50–7.54 (m, 2H), 7.48 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.0, 59.6, 66.4, 67.1, 70.3, 112.4, 115.4, 118.0, 127.0, 127.2, 128.8, 128.9, 129.0, 132.9, 136.7, 138.6, 148.0, 156.6; IR (film) cm^{-1} 2997m, 2912m, 2815m, 1689s, 1541m; mass spectrum (LRMS): *m/e* (% relative intensity) 411 (100) M^++H, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{22}H_{22}N_2O_4SNa$ 433.1198, found 433.1190.

4.1.5. Cycloadducts 14a/b as a mixture. R_f=0.22 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **14a** δ 1.23 (s, 3H), 2.35 (d, 1H, *J*=20 Hz), 2.55 (d, 1H, *J*=20 Hz), 4.05 (s, 1H), 4.26–4.31 (m, 2H), 4.45 (d, 1H, *J*=5 Hz), 4.52 (s, 1H), 4.79 (m, 1H), 5.86 (s, 1H), 6.38 (s, 1H), 7.22–7.38 (m, 8H), 7.49–7.62 (m, 4H), 7.86 (d, 2H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); **14b**: δ 1.63 (s, 3H), 2.14 (d, 1H, *J*=21 Hz), 3.04 (d, 1H, *J*=21 Hz), 4.15 (dd, 1H, *J*=2, 8 Hz), 4.24 (dd, 1H, *J*=2, 8 Hz), 4.57 (d, 1H, *J*=8 Hz), 4.86 (s, 1H), 4.90 (dt, 1H, *J*=2, 8 Hz), 5.03 (s, 1H), 6.27 (s, 1H), 6.42 (s, 1H), 7.22–7.38 (m, 8H), 7.49–7.62 (m, 4H), 7.86 (d, 2H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); IR (film) cm^{-1} 3060m, 2914m, 1755s, 1347s, 1166s; mass spectrum (LRMS): *m/e* (% relative intensity) 501 (20) M^++H, 359 (50), 266 (100), 193 (10); *m/e* calcd for $C_{29}H_{28}N_2O_4SNa$ 523.1668, found 523.1640.

4.1.6. Cycloadducts 15a/b as a mixture. R_f=0.25 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **15a**: δ 0.83 (s, 3H), 0.86 (s, 3H), 1.00 (s, 3H), 1.48–1.60 (m, 2H), 1.72 (s, 3H), 1.86–1.96 (m, 2H), 2.43 (d, 1H, *J*=20 Hz), 2.77 (d, 1H, *J*=20 Hz), 3.40 (d, 1H, *J*=2 Hz), 4.68 (d, 1H, *J*=2 Hz), 4.80 (d, 1H, *J*=2 Hz), 5.89 (s, 1H), 6.49 (s, 1H), 7.47–7.60 (m, 3H), 7.77 (d, 2H, *J*=7 Hz); **15b**: δ 0.97 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.21–1.29 (m, 2H), 1.58–1.62 (m, 2H), 1.65 (s, 3H), 3.45 (d, 1H, *J*=2 Hz), 3.76 (d, 1H, *J*=13 Hz), 4.01 (d, 1H, *J*=13 Hz), 4.68 (d, 1H, *J*=2 Hz), 4.80 (d, 1H, *J*=2 Hz), 6.08 (s, 1H), 6.40 (s, 1H), 7.47–7.60 (m, 3H), 7.77 (d, 2H, *J*=7 Hz); IR (film) cm^{-1} 3045m, 2905m, 2900m, 1710s, 1600m; mass spectrum (LRMS): *m/e* (% relative intensity) 400 (100) M^+, 273 (20), 154 (15); *m/e* calcd for $C_{22}H_{28}N_2O_3SNa$ 423.1718, found 423.1725.

4.1.7. Cycloadducts 16a/b as a mixture. R_f=0.30 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **16a**: δ 0.73 (d, 6H, *J*=6.5 Hz), 1.32 (d, 1H, *J*=11.5 Hz), 1.62 (s, 3H), 1.81–1.95 (m, 1H), 2.32 (d, 1H, *J*=15 Hz), 2.43 (d, 1H, *J*=15 Hz), 4.57 (d, 1H, *J*=2.5 Hz), 4.60 (d, 1H, *J*=2.5 Hz), 6.15 (t, 1H, *J*=2 Hz), 6.41 (s, 1H), 7.22–7.38 (m, 5H), 7.41–7.59 (m, 6H), 7.82 (d, 2H, *J*=8 Hz), 9.62 (d, 2H, *J*=9 Hz); **16b**: δ 0.69 (d, 6H, *J*=6 Hz), 1.32 (d, 1H, *J*=11.5 Hz), 1.66 (s, 3H), 1.81–1.95 (m, 1H), 3.72 (d, 1H, *J*=15 Hz), 3.86 (d, 1H, *J*=15 Hz), 4.60 (d, 1H, *J*=1 Hz), 4.89 (d, 1H, *J*=1 Hz), 6.07 (t, 1H, *J*=2 Hz), 6.12 (s, 1H), 7.22–7.38 (m, 5H), 7.41–7.59 (m, 6H), 7.82 (d, 2H, *J*=8 Hz), 9.62 (d, 2H, *J*=9 Hz); IR (film) cm^{-1} 3034m, 2945m, 2815m, 1708s, 1514m; mass spectrum (LRMS): *m/e* (% relative intensity) 529 (100) M^++H, 485 (22), 387 (60), 248 (32); *m/e* calcd for $C_{31}H_{32}N_2O_4SNa$ 551.1980, found 551.1988.

4.1.8. Cycloadducts 21a/b as a mixture. R_f=0.28 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) **21a**: δ 0.67 (d, 3H, *J*=7 Hz), 0.80–1.08 (m, 4H), 1.31–1.54 (m, 4H), 2.04 (s, 3H), 2.32 (m, 1H), 2.78 (s, 3H), 3.76 (dq, 1H, *J*=7, 9 Hz), 4.64 (s, 1H), 4.75 (d, 1H, *J*=9 Hz), 5.01 (s, 1H), 6.56 (s, 1H), 7.02–7.26 (m, 3H), 7.38–7.58 (m, 3H), 7.61 (d, 2H, *J*=8 Hz), 7.67 (d, 2H, *J*=8 Hz); **21b**: δ 0.64 (d, 3H, *J*=7 Hz), 0.80–1.08 (m, 4H), 1.31–1.54 (m, 4H), 1.81 (s, 3H), 2.28 (m, 1H), 2.73 (s, 3H), 3.76 (dq, 1H, *J*=7, 9 Hz), 4.54 (s, 1H), 4.64 (s, 1H), 4.75 (d, 1H, *J*=9 Hz), 6.43 (s, 1H), 7.02–7.26 (m, 3H), 7.38–7.58 (m, 3H), 7.61 (d, 2H, *J*=8 Hz), 7.67 (d, 2H, *J*=8 Hz); IR (film) cm^{-1} 3354m, 3024m, 2912m, 1715s, 1498m; mass spectrum (LRMS): *m/e* (% relative intensity) 492 (100) M^++H, 351 (20), 302 (15); *m/e* calcd for $C_{28}H_{33}N_3O_3SNa$ 514.2140, found 514.2124.

4.2. Synthesis of mono-hydrogenated product 23a

To a solution of 130.0 mg of cycloadduct **11a** (0.29 mmol) in EtOH (3.0 mL, 0.01 *M*) was added 10% Pt–C (25 mg). After purging the system with H_2 gas, the mixture was allowed to stir at rt for 2 h. Filtration through celite and removal of the solvent under reduced pressure provided the crude mono-hydrogenated product. Silica gel flash column chromatography (gradient eluent: 0–25% EtOAc in hexanes) provided the pure mono-hydrogenated **23a** [ratio of **a/b**: 2:1 at rt] in 65% yield (82.0 mg) along with 10–15% of the byproduct **24**.

4.2.1. Compound 23a. R_f=0.41 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −116.2° [*c* 2.6, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.19–0.25 (m, 1H), 0.71 (d, 3H, *J*=7 Hz), 0.84 (d, 3H, *J*=7 Hz), 1.22–1.31 (m, 1H), 1.38–1.45 (m, 1H), 1.40 (s, 3H), 2.74 (s, 3H), 3.73 (dq, 1H, *J*=7, 10 Hz), 4.50 (d, 1H, *J*=10 Hz), 5.70 (d, 1H, *J*=4 Hz), 6.62 (s, 1H), 6.95 (d, 1H, *J*=9 Hz), 7.21–7.31 (m, 4H), 7.53–7.62 (m, 3H), 7.87 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2, 16.6, 20.4, 29.0, 30.9, 32.1, 57.6, 59.1, 65.8, 116.2, 117.6, 127.1, 127.9, 128.3, 128.6, 129.1, 129.3, 132.9, 138.8, 163.5; IR (film) cm^{-1} 3478w, 3061m, 2931s, 2877s, 1715s, 1288s; mass spectrum (LRMS): *m/e* (% relative intensity) 440 (100) M^++H, 310 (10), 250 (10), 191 (15); *m/e* calcd for $C_{24}H_{29}N_3O_3SNa$ 462.1827, found 462.1835.

4.2.2. Byproduct dihydropyridine 24. R_f=0.37 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −420.7° [*c* 2.1, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.60 (d, 3H, *J*=6.5 Hz), 1.50 (m, 3H), 1.60 (s, 3H), 2.69 (s, 3H), 3.09 (dq, 1H, *J*=6.5, 9 Hz), 4.20 (d, 1H, *J*=9 Hz), 4.94 (s, 1H), 6.44 (s, 1H), 6.58 (s, 1H), 7.17–7.23 (m, 4H), 7.51–7.65 (m, 4H), 7.94 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 17.6, 19.8, 28.6, 55.9, 59.5, 63.1, 66.9, 115.1, 116.9, 123.3, 126.0, 127.1, 127.8, 129.1, 132.9, 137.3, 139.8, 146.3, 160.0; IR (film) cm^{-1} 3063w, 2969m, 2872w, 1699s, 1353m, 1165s; mass spectrum (LRMS): *m/e* (% relative intensity) 437 (100) M^+, 270 (50), 248 (100), 163 (45); *m/e* calcd for $C_{24}H_{27}N_3O_3SNa$ 460.1671, found 460.1701.

4.3. Synthesis of diol 25

To a solution of 0.47 g of cycloadduct **11a** (1.1 mmol, 1 equiv.) in 10:1 acetone/water mixture (22 mL, 0.05 M) was added NMO (0.19 g, 1.6 mmol, 1.5 equiv.) followed by addition of a solution of OsO_4 (5.0–13 mg, 0.02–0.05 mmol, 0.02–0.05 equiv.) in *t*-BuOH (1.5 mL). The mixture was allowed to stir for 3 h at rt after which sodium

bisulfite (1.0 g) and sodium *meta*-bisulfite (1.0 g) were added in large excess. The mixture was allowed to stir for an additional 5 h, after which gravity filtration followed by removal of solvent under reduced pressure provided crude diol **25**. Silica gel flash column chromatography (gradient eluent: 0–40% EtOAc in hexanes) provided the pure diol **25** in 60% yield (303.0 mg).

4.3.1. Compound 25. R_f=0.20 [50% EtOAc/hexane]; $[\alpha]_D^{20}$ −149.2° [*c* 0.7, CH_2Cl_2]; ^{1}H NMR ($CDCl_3$) δ 0.32 (d, 1H, *J*=18 Hz), 0.78 (d, 3H, *J*=7 Hz), 1.13 (d, 1H, *J*=18 Hz), 1.31 (s, 3H), 2.40 (brs, 1H, –O*H*), 2.80 (s, 3H), 3.67 (dd, 1H, *J*=5, 12 Hz), 4.02 (dq, 1H, *J*=7, 9 Hz), 4.64 (d, 1H, *J*=9 Hz), 4.86 (brs, 1H, –O*H*), 5.13 (dd, 1H, *J*=5, 12 Hz), 5.32 (s, 1H), 6.93 (s, 1H), 7.01 (d, 1H, *J*=7 Hz), 7.24–7.38 (m, 4H), 7.48–7.61 (m, 3H), 7.89 (d, 1H, *J*=8 Hz), 7.94 (d, 1H, *J*=8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 20.1, 28.6, 31.3, 57.9, 59.2, 65.5, 67.4, 71.4, 112.7, 117.0, 127.1, 127.4, 128.1, 129.0, 129.2, 133.2, 138.1, 138.5, 164.1; IR (film) cm^{-1} 3507m, 3354m, 3062m, 2932m, 1679s, 1433s; mass spectrum (LRMS): *m/e* (% relative intensity) 472 (100) M^++H, 331 (58), 282 (50), 191 (20); *m/e* calcd for $C_{24}H_{29}N_3O_5SNa$ 494.1726, found 494.1724.

4.4. Preparation of epoxide 26

To solution of diol **25** (95.0 mg, 0.20 mmol, 1.0 equiv.) in freshly distilled CH_2Cl_2 (20 mL, 0.01 M) was added 51.0 mg $NaHCO_3$ (0.60 mmol, 3.0 equiv.). The mixture was cooled to −10 °C after which 1.5 equiv. of *m*-CPBA (52.0 mg, 0.30 mmol) was added. The mixture was allowed to stir under N_2 for 8 h. Gravity filtration followed by removal of solvent under reduced pressure and silica gel flash column flash chromatography (gradient eluent: 0–10% EtOAc in hexanes) afforded epoxide **26** in a 50% yield (49.0 mg).

4.4.1. Compound 26. R_f=0.62 [50% EtOAc/hexane]; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, 1H, *J*=15 Hz), 0.91 (d, 3H, *J*=8 Hz), 1.10 (s, 3H), 1.14 (d, 1H, *J*=15 Hz), 2.86 (s, 3H), 2.90 (d, 1H, *J*=8.5 Hz), 3.65 (d, 1H, *J*=12 Hz), 4.26 (dq, 1H, *J*=8, 12 Hz), 5.18 (brm, 1H, –O*H*), 5.31 (t, 1H, *J*=5 Hz), 5.65 (d, 1H, *J*=1 Hz), 5.70 (d, 1H, *J*=8.5 Hz), 6.91 (s, 1H), 7.39–7.64 (m, 6H), 7.97–8.11 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2, 25.1, 28.3, 33.9, 58.0, 66.7, 69.9, 70.6, 73.9, 84.7, 105.3, 127.8, 128.0, 128.1, 128.6, 129.0, 129.7, 133.6, 133.7, 169.6; IR (film) cm^{-1} 3522m, 3317m, 3117m, 2958m, 1684s, 1421s; mass spectrum (LRMS): *m/e* (% relative intensity) 488 (100) M^++H, 191 (10); *m/e* calcd for $C_{24}H_{29}N_3O_6SNa$ 510.1675, found 510.1661.

4.5. Removal of the chiral auxiliary

To a solution of 35.0 mg of **23a** (0.08 mmol, 1.0 equiv.) in freshly distilled CH_2Cl_2 (8.4 mL, 0.01 M) was added at −78 °C 52.0 mg of $SnBr_4$ (0.12 mmol, 1.5 equiv.) followed by allyltrimethylsilane (0.05 mL, 4.0 equiv.) in dropwise manner via a syringe. The reaction mixture was allowed to gradually warm up to rt over 12 h under N_2 to give the crude mixture **28a/b** after removal of solvent under reduced pressure. Silica gel flash column chromatography (gradient eluent: 0–10% EtOAc in hexanes) provided the isomeric mixture **28a/b** in 33% yield (8.0 mg) as clear oil.

4.5.1. Compound 28a. R_f=0.45 [15% ethyl acetate/hexane]; ^{1}H NMR ($CDCl_3$) δ 0.85–0.91 (m, 1H), 1.01 (d, 3H, *J*=6.5 Hz), 1.24–1.36 (m, 1H), 1.72–1.79 (m, 1H), 2.05 (s, 3H), 2.61–2.79 (m, 2H), 3.70–3.82 (m, 1H), 4.99–5.18 (m, 2H), 5.91–6.11 (m, 1H), 6.42 (s, 1H), 7.40–7.61 (m, 3H), 7.87 (d, 2H, *J*=9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.1, 31.8, 36.9, 37.5, 53.8, 57.3, 112.2, 115.7, 126.9, 127.8, 129.0, 132.4, 134.3, 138.1; IR (film) cm^{-1} 3190m, 3022m, 2952m, 1274m; mass spectrum (LRMS): *m/e* (% relative intensity) 292 (100) M^++H, 250 (20), 151 (30), 110 (10); *m/e* calcd for $C_{16}H_{21}NO_2SNa$ 314.1191, found 314.1218.

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Hemisynthesis of methyl pyrethroates from γ-alkoxy-alkylidene malonates and isopropylidenediphenylsulfurane and isopropylidenetriphenylphosphorane

Alain Krief[a,*] and Alexandre Froidbise[a,b]

[a]*Laboratoire de Chimie Organique de Synthèse, Département de Chimie, Facultés Universitaires N.D de la Paix, 61 rue de Bruxelles, 5000 Namur, Belgium*
[b]*Fonds pour la Formation à la Recherche dans l'Industrie et l'Agriculture, 5 rue d'Egmont, 1000 Bruxelles, Belgium*

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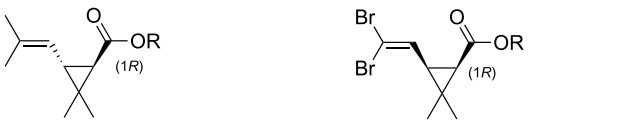
Dedicated to Professor Dieter Seebach at the occasion of the 2003 Tetrahedron Prize with admiration for his extremely important contribution to Organic Chemistry

Abstract—Hemisynthesis of methyl pyrethroates from γ-alkoxy-alkylidene malonates and isopropylidenediphenylsulfurane and isopropylidenetriphenylphosphorane is disclosed. It takes advantage of the high degree of stereocontrol observed in the cyclopropanation of γ-alkoxy-alkylidene malonates by the above mentioned ylides.

1. Introduction

We have been interested over the last fifteen years to develop new synthetic routes to chrysanthemic **1** and deltamethrinic acid and related esters **2** (Scheme 1).[1]



1a R= H; Chrysanthemic acid
2a R=Alkyl; Alkyl chrysanthemate

1b R= H; Deltamethrinic acid
2b R=Alkyl; Alkyl deltamethrinate

Scheme 1. Structure of chrysanthemic and deltamethrinic compounds.

One of our strategy involves the use of chiral γ-alkoxy-α,β-unsaturated esters as starting materials and isopropylidene-diphenylsulfurane or isopropylidenetriphenylphosphorane as cyclopropanating agents.[1e,2–6] This interest arose from our original work which involves the synthesis of methyl (*d*,*l*)-*trans*-chrysanthemate in a single step from methyl 4-oxobutenoate and isopropylidenetriphenylphosphorane (Scheme 2, entry a)[2a] and from the work of Mulzer[7] who described the diastereoselective cyclopropanation of ethyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate which produces, after some functional group manipulation, the enantio-enriched methyl (*d*)-*trans*-chrysanthemate with a 74% ee (Scheme 2, entry b). In such transformation ethyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate has played the role of chiral masked methyl 4-oxobutenoate.

We have subsequently found that the cyclopropanation reaction takes place from either the *Re* or the *Si*-face of the electrophilic olefin depending not only on the stereochemistry at its allylic carbon bearing the alkoxy group and of its [C,C] double bond but also on the nature of the heteroatomic moiety present on the α-heterosubstituted organometallic (Scheme 3).[5,7]

Important features of the reactions involving methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate, are collected in Scheme 3.

Isopropylidenetriphenylphosphorane adds from the *Si*-face of the *E*-stereoisomer (Scheme 3, entry a) whereas it adds from the *Re*-face of its *Z*-stereoisomer (Scheme 3, entry c) providing in both cases stereoselectively the *trans*-cyclopropane derivatives.[5a,b,7]

Its sulfur ylide analogue however reacts by the *Re*-face of methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate, irrespective of its stereochemistry. Furthermore the reaction proved to be completely stereospecific since it leads to the *trans*-cyclopropane carboxylate from the *E*-diastereoisomer of methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate

Keywords: Asymmetric induction; Insecticide; γ-Alkoxy enoates; Deltamethrinic acid; Chrysanthemic acid.
* Corresponding author. Tel.: 32-81-724539; fax: +32-81-724536; e-mail address: alainkrief@fund.ac.be

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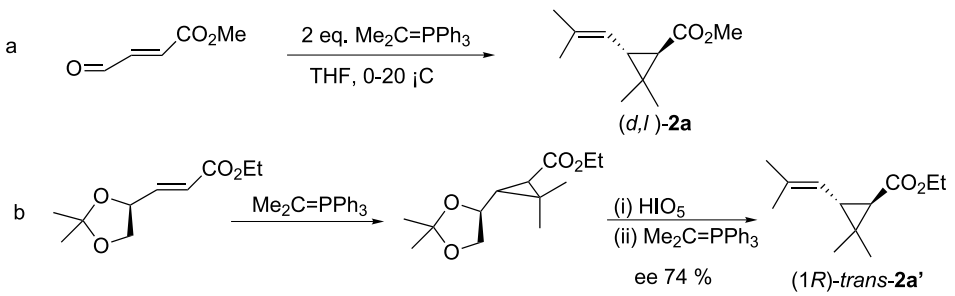
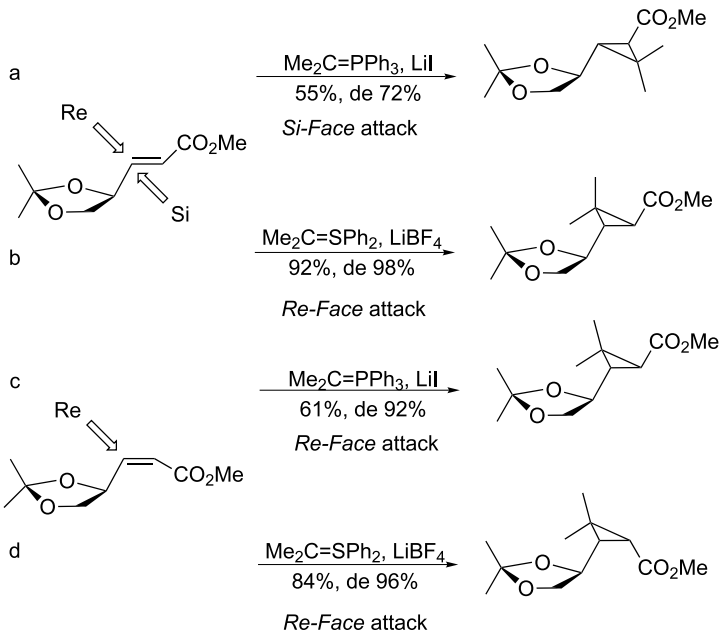


Scheme 2. Previous syntheses of *trans*-chrysanthemates.



Scheme 3. Stereocontrolled addition of P- and S-ylides to γ-alkoxy enoates.

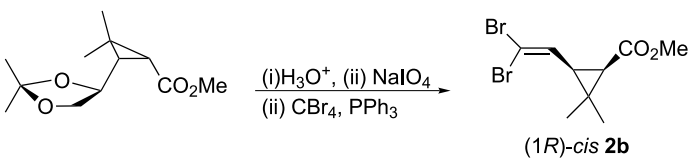
(Scheme 3; entry b) and to the *cis*-cyclopropane carboxylate from its *Z*-diastereoisomer (Scheme 3; entry d).[5b–f]

Asymmetric induction is as expected dependant on the stereochemistry of the allylic carbon to which the alkoxy group is attached. Enoates whose structures are described above belong to the (*S*)-series. Their syntheses have been selectively achieved using well established protocols from the acetonides of D-glyceraldehyde derived from (*d*)-mannitol.[1e,5a–d]

The strategy used to produce the required vinylcyclopropane carboxylates from the above mentioned adducts involves (i) acid hydrolysis of the acetal moieties, (ii) sodium periodate cleavage of the resulting diol and (iii) Wittig olefination reaction. An even shorter approach involves periodic acid which performs, in the same pot, the transformation of the acetal moiety to methyl hemicaronates.[7]

The synthesis of methyl *trans*-chrysanthemate implies isopropylidenetriphenylphosphorane ($Ph_3P{=}CMe_2$, THF, 20 °C, Scheme 2, entry b)[5c,7] whereas that of methyl deltamethrinate requires instead the use of dibromomethylenetriphenylphosphorane (CBr_4, PPh_3, THF, 20 °C, *cis*: 81% yield, Scheme 4).[5b,c]

The most important substrates are those which possess the appropriate stereochemistry to produce, without any stereochemical modification, either methyl (1*R*)-*trans*-chrysanthemate **2a** or methyl (1*R*)-*cis*-deltamethrinate **2b**. Thus starting from the (*S*)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylate derived from D-glyceraldehyde, the *E*-α,β-unsaturated carboxylates and isopropylidenetriphenyl-



Scheme 4. Synthesis of methyl deltamethrinate.

phosphorane must be used for the synthesis of the former compound (Scheme 2, entry b; Scheme 3, entry a)[2k,3] and *Z*-α,β-unsaturated carboxylates and isopropylidene-diphenylsulfurane for the latter (Scheme 3, entry d; Scheme 4).[5a,b]

The synthesis of methyl (1*R*)-*cis*-deltamethrinate works fine.[2i,k] Not only the *cis*-content (100%) and the enantiomeric excess (98%) are excellent, but also the strategy which requires the introduction of the dibromomethylene moiety at the end of the synthesis is reasonably good. This is not the case of methyl (1*R*)-*trans*-chrysanthemate which suffers both from quite poor enantiomeric excess (74–72%) and quite lengthy functional group manipulation to produce the vinyl side chain.[5,7]

We have therefore designed two new routes to methyl (1*R*)-*trans*-chrysanthemate which use both isopropylidene-diphenylsulfurane as cyclopropanating agent (Scheme 5).[2t,u] The latter is known to provide much better asymmetric induction than the related phosphorus ylide (Scheme 3). This choice requires using as partner *E*-α,β-unsaturated carboxylates possessing the inverted (*R*)-stereochemistry on the chiral carbon bearing the alkoxy moiety.

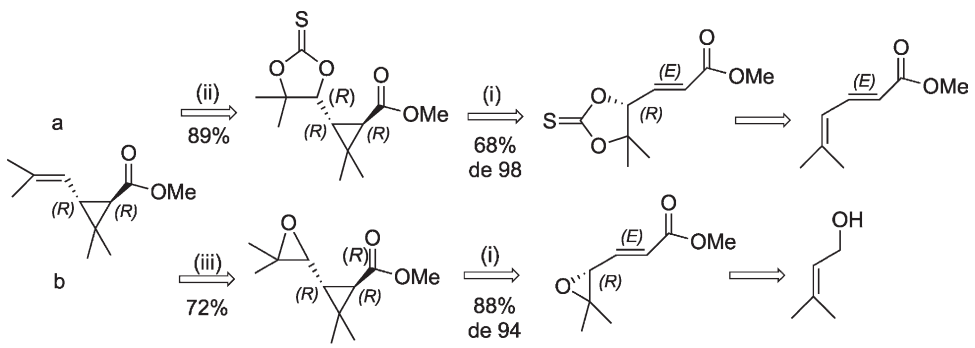
In order to increase the diastereoselection and to shorten the number of steps leading to methyl (1*R*)-*trans*-chrysanthemate, we have performed the cyclopropanation on methyl γ-alkoxy-α,β-unsaturated carboxylates whose hydrocarbon content provides, after sequential cyclopropanation ($Me_2C{=}SPh_2$–$LiBF_4$, DME, −78 °C, 2 h, −78 to 20 °C, 1 h) and reductive decomposition, directly the desired compound. Methyl (*R*)-3-(5,5-dimethyl-2-thioxo-[1,3]dioxolan-4-yl)-[5g] and (*R*)-3-(3,3-dimethyl-oxiranyl)-[5h] acrylates (Scheme 5, entries a and b, respectively) proved to be the perfect candidates: (i) they are readily prepared from methyl 5-methyl-hexa-2,4-dienoate and AD-mix β using Sharpless catalytic asymmetric dihydroxylation reaction (AD reaction, Scheme 5, entry a)[8a] and 3-methyl-but-2-en-1-ol, titanium tetraisopropoxide, *tert*-butylhydroperoxide and l-diisopropyl tartrate according to Sharpless catalytic asymmetric epoxidation of allyl alcohols (AE reaction, Scheme 5, entry b)[9] respectively, (ii) after cyclopropanation has been achieved the thionocarbonate substructure present on the former product can be efficiently reduced according to the Hopkins[10] variation of the Corey–Winter reaction ($(CH_2NMe)_2P$–Ph, neat, 40 °C, 6 h, 89%; Scheme 5, entry a)[5g] whereas the epoxy[5h] substructure present on the latter adduct has been transformed to the corresponding tri-substituted C,C double bond on reaction with P_2I_4 (CS_2, pyridine, 5 h, reflux, 72%; Scheme 5, entry b).[11]

In the examples reported above the control of the stereochemistry (1*R*)/(1*S*), *cis*/*trans* on the cyclopropane ring depends on (i) the nature of the ylide (S or P) and (ii) the stereochemistry (*R* or *S*) at [C-3] and also the stereochemistry (*Z* or *E*) of the [C,C] double bond of the γ-alkoxy-α,β-unsaturated carboxylates.[5] Therefore the stereochemistry of the [C,C] double bond has to be perfectly controlled for successful enantioselective synthesis of pyrethroic acids.

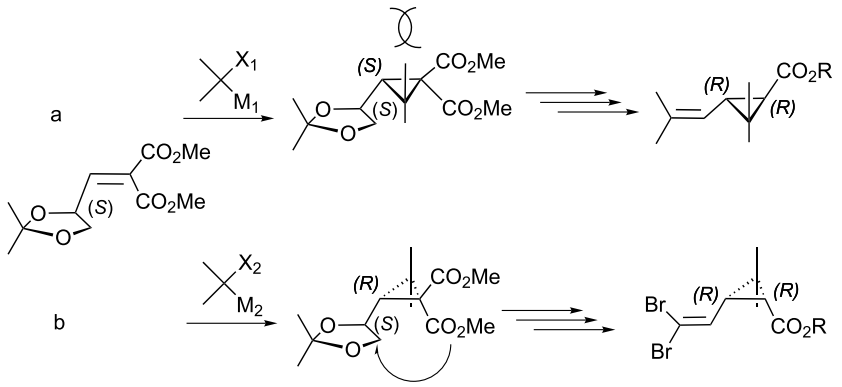
Use of γ-alkoxy-alkylidene malonates in place of the corresponding α,β-unsaturated carboxylates should avoid the latter constraint for the control of the face of attack and therefore for the control of the stereochemistry at [C-2] on the methyl chrysanthemate.[6] This strategy nevertheless introduces other constraints since the stereochemistry at [C-1] on the cyclopropane carboxylate is no longer related to the stereochemistry of the [C,C] double bond of the starting material and will be created at the time the tandem decarboxylative-dealkylation is achieved. We expected that the production of the *trans*-stereochemistry will take advantage of steric hindrance between the group at [C-2] and the carboxy group at [C-1] (Scheme 6, entry a) whereas the *cis*-stereochemistry will derive from lactone ring formation (Scheme 6, entry b).

In order to achieve the two approaches leading to each of the two epimeric cyclopropane moieties at [C-2] present in chrysanthemates **2a** and deltamethrinates **2b**, we had to find cyclopropanating agents able to react with complete stereocontrol but divergently on the same methyl γ-alkoxy-alkylidene malonate (Scheme 6).[6]

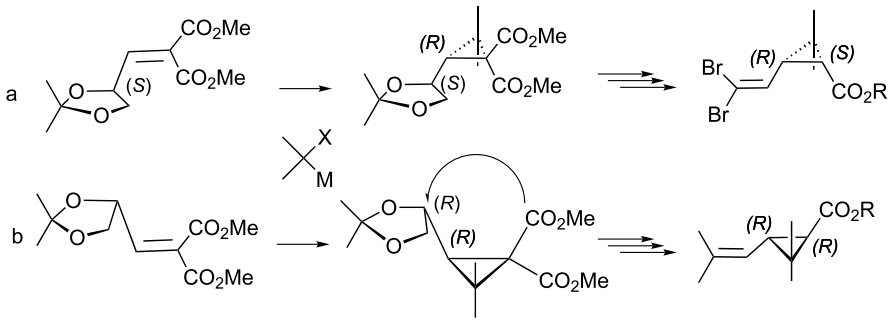
Another less constraining approach uses the same reagent but requires the synthesis of each of the two enantiomers of methyl γ-alkoxy-alkylidene malonate such as 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester (Scheme 7).



Scheme 5. Straightforward synthesis of methyl (1*R*)-*trans*-chrysanthemate.



Scheme 6. Planned enantioselective syntheses of pyrethroates using different ylides.



Scheme 7. Planned enantioselective syntheses of pyrethroates pyrethroates using different enoates.

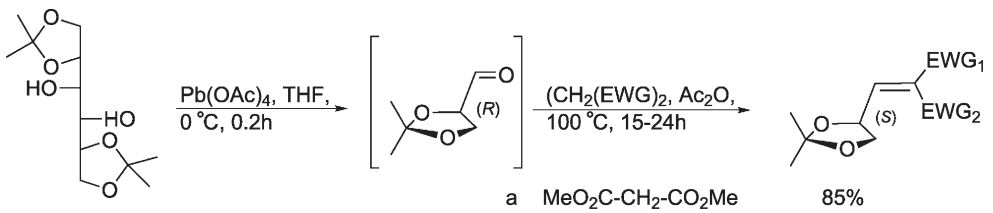
We have successfully performed each of the two approaches[6] but will present only the latter in this paper.[6a]

2. Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid esters, related malononitriles and malonodinitrile

When we started this work 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid diethyl ester was already known. It was produced in modest yield (24–30%), via a Knoevenagel reaction[12] from (*R*)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde (the acetonide of D-glyceraldehyde)[13] and diethyl malonate using piperidine as the catalyst (toluene, 20 °C, 1–24 h)[14] but its stereochemical integrity was not described. Piperidinium acetate which was successfully used by Tietze[12] for related cases does not lead to the desired compound using dimethyl malonate. Titanium tetrachloride in the presence of pyridine[15] proved the most suitable combination at the condition that the ingredients are mixed at low temperature (dimethyl malonate, $TiCl_4$, pyridine, THF, −78 to 20 °C, 72 h, 70% yield on 10 g scale; 20 °C, 72 h, 24–41% yield).[6a]

It was later found that even better results could be obtained if both the oxidative cleavage of central diol of the terminal diacetonide of D-mannitol ($Pb(OAc)_4$, THF, 0 °C, 0.2 h) and the Knoevenagel reaction (dimethyl malonate, acetic anhydride, reflux, 24 h, 85% yield, $[\alpha]_D^{20}=+20.1$, $c=1.05$; ee >96%, Scheme 8, entry a) were carried out in the same pot according to the procedure described for the corresponding methyl malononitrile[16] (Scheme 8, entry d).

The same process was successfully used for the synthesis of methyl tertiobutyl and di-tertiobutyl-alkylidene malonates ((i) $Pb(OAc)_4$, THF, 0 °C, 0.2 h, (ii) malonate, acetic anhydride, reflux, 24 h, 96 and 87% yield, respectively, Scheme 8, entries b and c). Those conditions do not work with malonodinitrile. The corresponding alkylidene malonodinitrile has been however prepared in almost

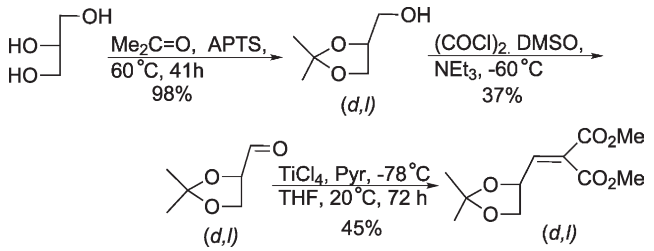


a	$MeO_2C\text{-}CH_2\text{-}CO_2Me$	85%
b	$t\text{-}BuO_2C\text{-}CH_2\text{-}CO_2Me$	96% (Z/E: 45/55)
c	$t\text{-}BuO_2C\text{-}CH_2\text{-}CO_2t\text{-}Bu$	87%
d	$MeO_2C\text{-}CH_2\text{-}CN$	77%
e	$NC\text{-}CH_2\text{-}CN$	00%

Scheme 8. Synthesis of alkylidene malonates and alkylidene malononitriles derived from (*R*)-2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde.

quantitative yield, on reaction of the acetonide of D-glyceraldehyde and malonodinitrile in the presence of 4-*N*,*N*-dimethylaminopyridine (CH_2Cl_2, 0 °C, 1 h, 20 °C, quantitative yield) but its isolation from 4-*N*,*N*-dimethylaminopyridine was unsuccessful and it has been used without purification in the next step.

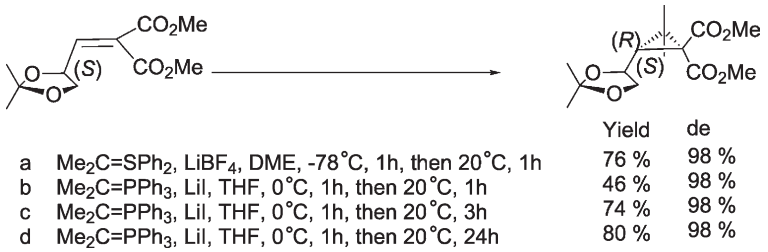
We have checked the stereochemical purity of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester just prepared by comparison on HPLC (Diacel, Chiracel, ODH, isopropanol/hexane: 3/7 (v/v) 1 ml/min; 47 bar; λ_{DET} 254 nm) of an authentic racemic sample prepared on reaction of acetonide of *rac*-glyceraldehyde, obtained from glycerol on acetalization (acetone, APTS, pentane, 60 °C, 41 h, 98%)[17] and Swern oxidation (1.2 equiv. $(COCl)_2$, 2.5 equiv. DMSO, 5 equiv. NEt_3, −60 °C, 37%),[18a] using the procedure we already disclosed ($TiCl_4$, pyridine, THF, −78 to 20 °C, 72 h, 45% yield, Scheme 9).[6a] The latter reaction does not work if PCC is used instead of Swern oxidation.[18b,c]



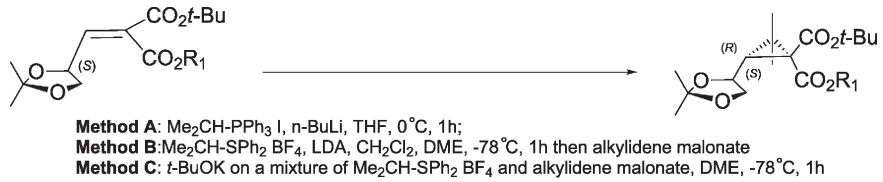
Scheme 9. Synthesis of *rac*-2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester.

3. Synthesis of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dialkyl esters, related ester, nitriles and dinitriles

Isopropylidenetriphenylphosphorane generated from the corresponding isopropyltriphenylphosphonium iodide and *n*-butyllithium (THF, 0 °C, 0.2 h)[19] and isopropylidene-diphenylsulfurane synthesized from isopropyldiphenyl-sulfonium tetrafluoroborate, LDA and dichloromethane (DME, −78 °C, 0.5 h)[20] have been successfully reacted with 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl-ene)-malonic acid dimethyl ester and provide both 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester in extremely good yield and enantioselectivity (Scheme 10).[6a] The two ylides react by the same *Re*-face of the alkylidene malonate as it has been described from the reaction of these two ylides with 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid methyl ester.



Scheme 10. Cyclopropanation of-2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester.

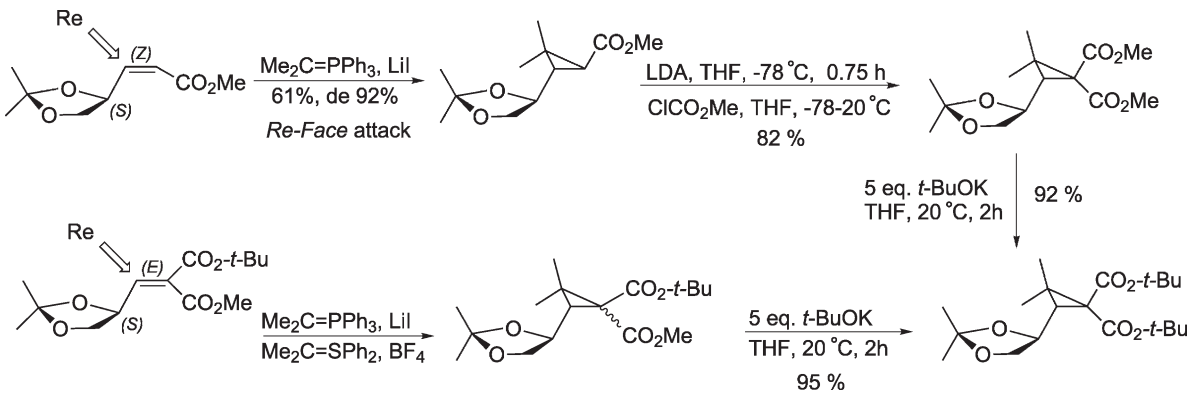


Entry	R_1	X	Method	Yield %	*Re/Si*
a	*t*-Bu	PPh_3	A	90	> 99/1
b	*t*-Bu	SPh_2	B	78	> 99/1
c	*t*-Bu	SPh_2	C	58	> 99/1
d	Me	PPh_3	A	69	> 99/1
e	Me	PPh_3	A	75	> 99/1
f	Me	PPh_3	A	84	> 99/1
g	Me	SPh_2	B	77	> 99/1

Scheme 11. Cyclopropanation of alkylidenemalonates.

Entry	X	EWG	Method	Yield %	*Re/Si*
a	PPh_3	CO_2Me	A	75	80/20
b	SPh_2	CO_2Me	B	75	80/20
c	PPh_3	CN	A	29	52/48
d	SPh_2	CN	B	33	59/41

Scheme 12. Cyclopropanation of alkylidene malononitriles.



Scheme 13. Structure determination of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester.

Isopropylidenediphenylsulfurane (DME, −78 °C, 2 h, 20 °C, 1 h, 76% yield, de 98%, Scheme 10, entry a) proved be more reactive than its phosphorus analogue (THF, 0 °C, 24 h, 80%, de 98%, Scheme 10, entry d, compare to entries b and c).[6a]

Similar results were obtained when instead the reactions are carried out on the related di-tertiobutyl malonate (Scheme 11, entries a–c) or on a 45/55 *Z*/*E* diastereomerize mixture of tertiobutyl methyl malonates (Scheme 11, entry a) in this case the reaction proceeds with complete facial control but leads to about a 45/55 mixture of *cis*/*trans* cyclopropane derivatives (Scheme 11, entries d–g).

The reaction still proceeds with complete control of the relative stereochemistry on the cyclopropane ring when instead performed on the related alkylidene malononitrile possessing the *E*-stereochemistry since the cyclopropane derivatives belong both to the *trans*-series. Reaction by the Re face is now predominant but no longer exclusive (de 60; Scheme 12, entries a and b) whatever the nature of the ylide is. And interestingly, almost no stereocontrol is found with alkylidene malonodinitrile (de 4–18%; (Scheme 12, entries c and d). In such case the reaction has been carried out on the crude mixture of the electrophilic derivative whose enantiomeric integrity has not been ascertained, just after its synthesis due to its instability.

The structure of all the cyclopropane derivatives has been ascertained by physical methods and in the case of cyclopropane dicarboxylates has been in complement achieved by comparison with authentic samples (Scheme 13). Thus 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester resulting from the reaction of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester with isopropylidenediphenylsulfurane (Scheme 13) has been compared to an authentic sample prepared in a multistep sequence from methyl 3-(2,2-dimethyl-[1,3]-dioxolan-4-yl)-acrylate and isopropylidenetriphenylphosphorane followed by a tandem metalation–carboxylation

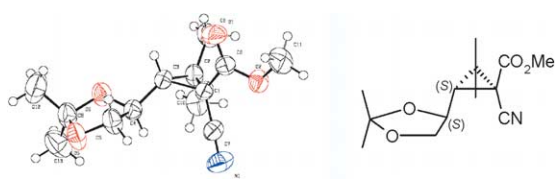
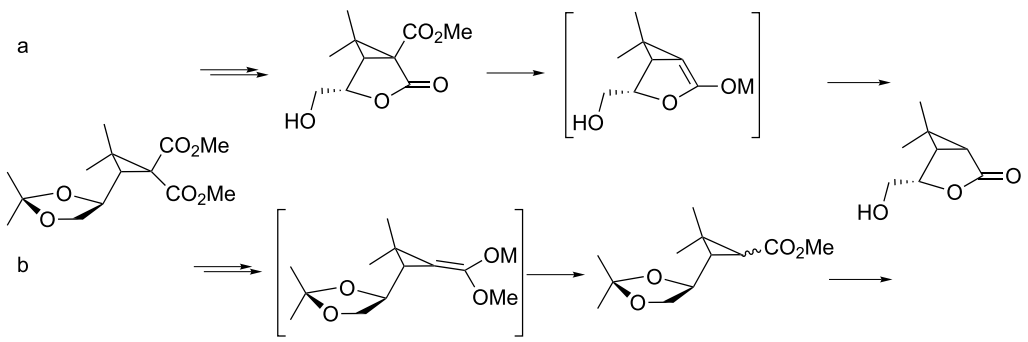


Figure 1. Structure of methyl 1-cyano-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate.



Scheme 14. Strategies for deltamethrinic acid synthesis.

reaction of the resulting methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxate ((i) LDA, THF, −78 °C, 0.75 h, (ii) $ClCO_2Me$, THF, −78 to 20 °C, Scheme 13).

Furthermore, 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester as well as the stereoisomeric mixture of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,carboxylic acid methyl ester-1-carboxylic acid tertiobutyl ester have been both transformed to the 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid ditertiobutyl ester (Scheme 13) on reaction with potassium *t*-butoxide in THF, −78 to 20 °C, 2 h, 92 and 95% yield, respectively).

Finally, the structure of the major stereoisomer of methyl 1-cyano-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate has been unambiguously accessed by X-ray crystallography (Fig. 1).[6c]

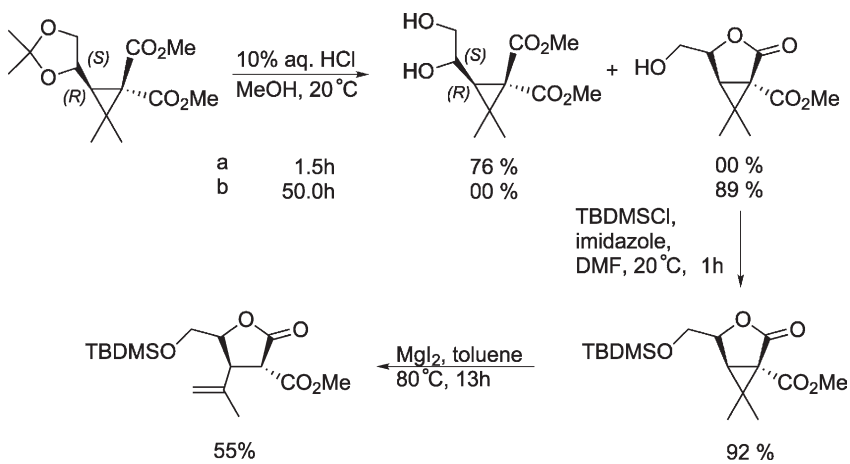
4. Synthesis of deltamethrinic acid from 3(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester

The (3*R*) stereochemistry at [C-3] of 3(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester suggests that it could be a valuable precursor of deltamethrinic acid. The strategy used for that purpose requires the lactone ring formation. The most suitable approach would have been ideally to generate at first the lactone ring then to perform the demethylation–decarboxylation reaction (Scheme 14, entry a). This should avoid the extra *trans*/*cis*-epimerisation which should be otherwise required (Scheme 14, entry b).

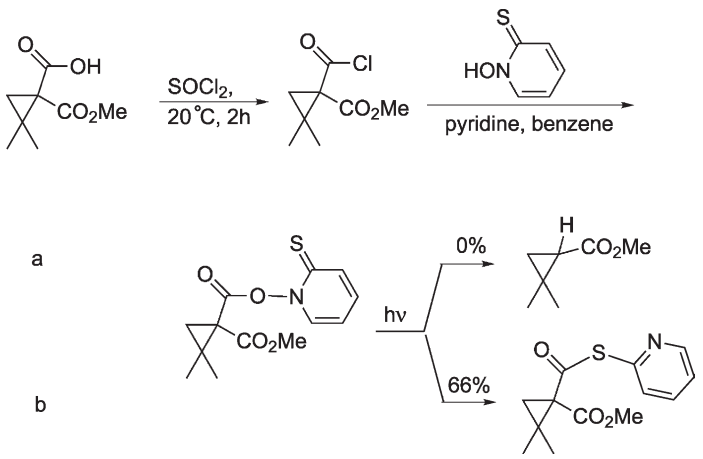
In fact the decarboxylation reaction of dimethyl cyclopropane dicarboxylates is not as easy as that of dimethyl malonates missing the cyclopropane ring probably because the enol or enolate intermediate has a lower propensity to be formed due to the extra strain induced by the three-membered ring (Scheme 14, entry b). This effect is at its paroxysm when decarboxylation is carried out on 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one because the enol or enolate intermediate is at a bridgehead position (Scheme 14, entry a).

We tried the first route because it was the most challenging one. We planned to perform the decarboxylation reaction through a Barton reaction[21] involving a radical process as it was described in a related series.[22a]

Acid catalyzed dioxolane ring opening was successfully achieved using aqueous hydrochloric acid (Scheme 16). Careful monitoring of this reaction shows however that methyl 3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylate is efficiently obtained if the reaction is performed within a few hours (10% aq. HCl, 20 °C, 1.5 h, 76% yield, Scheme 15, entry a). Otherwise,



Scheme 15. Unsuccessful decarboxylation reaction.



Scheme 16. Radical promoted decarboxylation reaction.

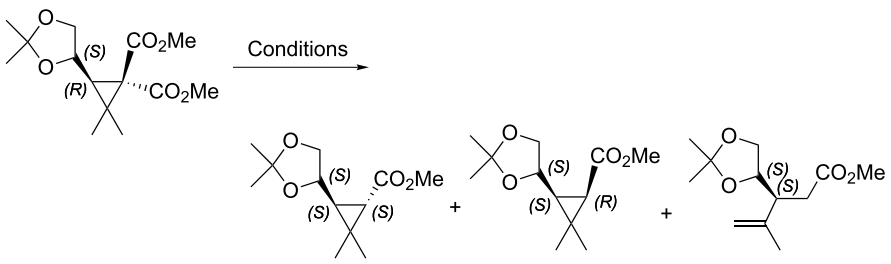
cyclization of the diol on the *cis*-carbomethoxy group takes place and leads to methyl 4-hydroxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylate in very good yield (10% aq. HCl, 20 °C, 50 h, 89% yield, Scheme 16, entry b). Protection as *tert*-butyl dimethylsilylether of the hydroxyl group of the resulting lactone has been achieved on reaction with *tert*-butyl dimethylsilylchloride (TBSCl, imidazole, DMF, 20 °C, 1 h, 92%, Scheme 15, entry b). We however gave up this approach because the milder conditions used which involves magnesium diiodide,[22] as reported above, induces the cyclopropane ring opening rather than the desired dimethylation–carboxylation reaction (MgI_2, 110 °C, 10 h, 54% or 80 °C, 13 h, 55%, Scheme 15).

We have also unsuccessfully tried to perform the decarboxylation of 2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid methyl ester as model using the Barton[21] procedure since the end-product proved to be mainly 2,2-dimethyl-1-(pyridin-2-ylsulfanylcarbonyl)-cyclopropane-carboxylic acid methyl ester (Scheme 16, entry b) instead of the expected methyl cyclopropanecarboxylate (Scheme 16, entry a).[22]

We therefore turned our attention to the second approach in which the decarboxylation of 3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester has to be achieved first but this was not a simple task.

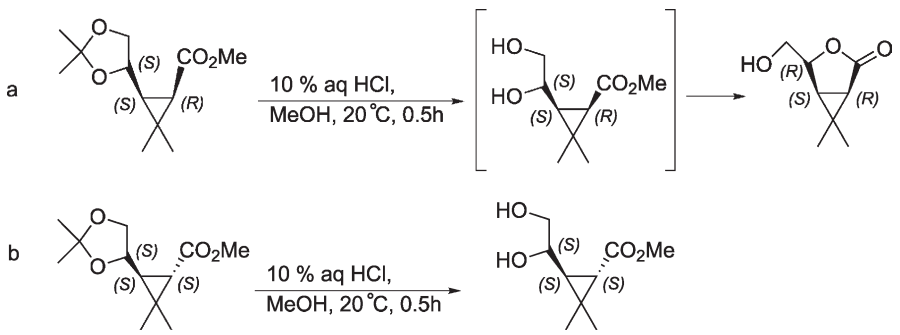
We decided not to use acidic conditions to avoid competing deacetalisation which would favor lactone ring formation and tried to use almost neutral conditions which are known for allowing a tandem dealkylation–decarboxylation by substitution at the methyl of the methoxy group of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester.

The most usual conditions which use metal halides or



Entry	Reagents	Temp (° C)	Time (h)	Yield (%)	*trans*/*cis* ring fission ratio
a	NaCl-aq. DMSO	160	6	73	27/21/52
b	1 NaCN, aq. DMF	120	48	88	50/34/16
c	*p*(H_2N)PhS Cs, DMF	90	26	68	61-39/0
d	Me_4NOAc, HMPA	95	4	90	70/30/0

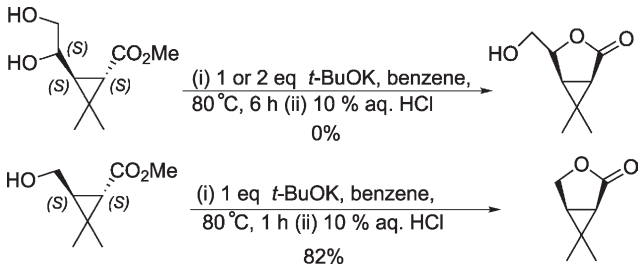
Scheme 17. Decarboxylation of alkylidene malonates.



Scheme 18. Acid catalyzed ring opening of dioxolane moiety. Potential lactone ring formation.

sodium cyanide in DMF or DMSO required too drastic conditions (160–140 °C, 6–60 h, Scheme 17, entries a and b).[4a,23] They in fact leads to the formation of substantial amount of methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-4-methyl-pent-4-enoate resulting from cyclopropane ring opening. Other conditions which used instead metal chalcogenides in DMF[24] proceed at lower temperature but require too longer time to go to completion and methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-cyclopropanecarboxylate is obtained in quite modest yields (90 °C, 26–30 h, 54–68%, Scheme 17, entry c). Tetramethyl ammonium acetate in anhydrous polar solvents, which was used by Trost,[25] proved to be the best compromise since the desired compound, methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropanecarboxylate is obtained, in extremely high yield, as a mixture of diastereoisomers, under relatively mild conditions and without competing cyclopropane ring opening (Scheme 17, entry d).

Acid hydrolysis of the 70/30 *trans*/*cis*-mixture of diastereoisomeric methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-2,2-dimethyl-cyclopropanecarboxylate (Scheme 17, entry d) leads to a 70/30 mixture of methyl *trans*-3-(2,3-dihydroxy-propyl)-2,2-dimethyl-cyclopropanecarboxylate and 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one resulting from lactonization of the *cis*-diastereoisomer (10% aq. HCl, MeOH, 20 °C, 0.5 h, $[\alpha]_D^{20}=-68.7$ ($CHCl_3$, $c=1.27$), Scheme 18).



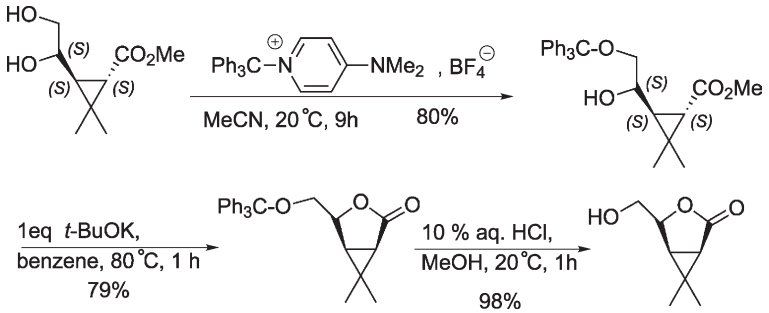
Scheme 19. Lactones synthesis by cyclization of γ-hydroxy esters.

It was also found that lactonization of methyl *cis*-3-(2,3-dihydroxy-propyl)-2,2-dimethyl-cyclopropanecarboxylate, occurs even faster than that of 3-(2,3-dihydroxy-propyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (compare Scheme 15 to Scheme 18, entry a).

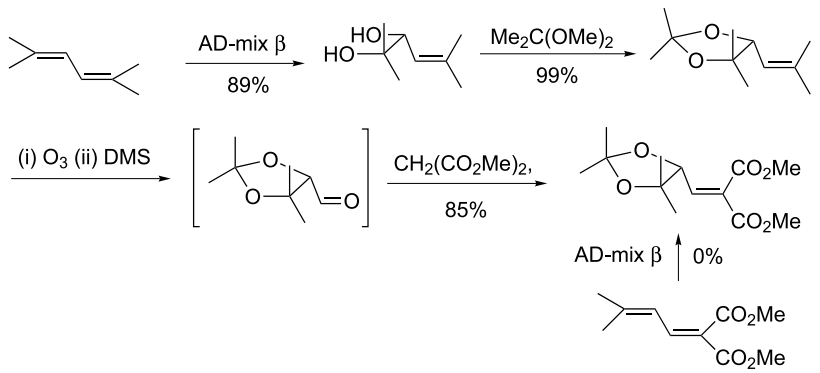
Lactonization of the remaining methyl *trans*-3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate to 4-hydroxymethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one, which is required to reach the *cis*-cyclopropane derivative, was problematic. No reaction takes place under conditions which successfully allow lactonization of methyl 3-hydroxymethyl-2,2-dimethyl-cyclopropanecarboxylate[2f] (i) 1 or 2 equiv. *t*-BuOK, benzene, 80 °C, 6 h; (ii) 10% aq. HCl, Scheme 19) and other conditions which use lithium hydride to protect each of the two hydroxyl groups as their lithium alcoholates and potassium *t*-butoxide to perform the epimerization reaction fail too.

Successful contrathermodynamic *trans*/*cis*-isomerisation has been finally achieved on reaction of methyl 3-(1-hydroxy-2-trityloxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate, which possesses a trityloxy group at its terminus, with potassium *t*-butoxide in benzene (Scheme 20).

The trityl protecting group which was selectively introduced on reaction of methyl *trans*-3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate with *N*,*N*-4-dimethyl-amino-*N*-triphenylmethylpyridinium chloride (prepared



Scheme 20. The lactone ring formation requires the protection of the primary hydroxyl group present on the diol, as a trityl ether.



Scheme 21. AD-mix is able to oxidize 2,5-dimethyl-hexadiene but not 2-(3-methyl-but-2-enylidene)-malonic acid dimethyl ester.

from dimethylaminopyridine and triphenylmethyl-chloride)[26] was then easily removed from 6,6-dimethyl-4-trityloxymethyl-3-oxa-bicyclo[3.1.0]hexan-2-one on acid hydrolysis (10% aq. HCl, MeOH, 20 °C, 1 h, Scheme 20).[27] The synthesis of deltamethrinic acid from this compound has been already disclosed.[28]

5. Synthesis of methyl *trans*-chrysanthemate from 3(*R*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester

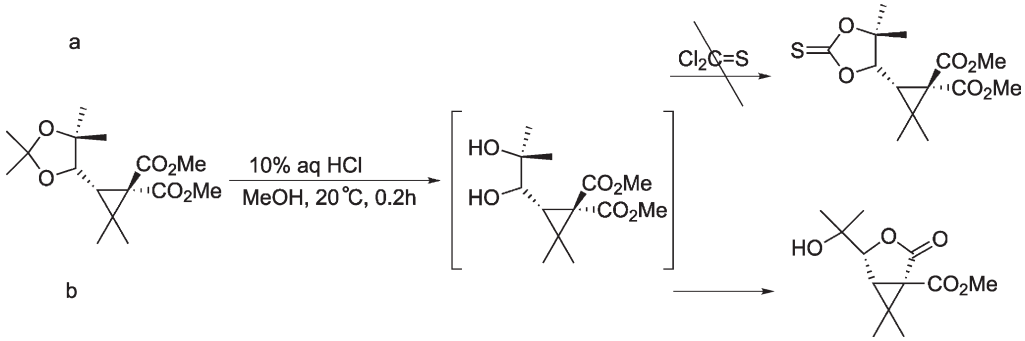
The synthesis of methyl *trans*-chrysanthemate has been performed, as outlined in Schemes 23 and 24 from 2,5-dimethyl-hexadiene using Sharpless AD reaction[8a] (AD-mix β, $K_2OsO_2(OH)_4$, DHQD, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), $MeSO_2NH_2$, 20 °C, 2 h, 89% yield). Protection of the resulting diol ($Me_2C(OMe)_2$, acetone, *p*TSA, 99% yield) leads to 2,2,4,4-tetramethyl-5-(2-methyl-propenyl)-[1,3]dioxolane. Its ozonolysis followed by reduction of the resulting ozonide ((i) O_3, CH_2Cl_2, −78 °C, 2 h (ii) DMS, 20 °C, 12 h) leads to 2,2,5,5-tetramethyl-[1,3]dioxolane-4-carbaldehyde which has been subjected without purification to the Knoevenagel reaction ($CH_2(CO_2Me)_2$, $TiCl_4$, pyridine, THF, −78 to 20 °C, 72 h, 85%, Scheme 23).

A much straightforward approach to 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester which instead would have implied 2-(3-methyl-but-2-enylidene)-malonic acid dimethyl ester and AD-mix β proved to be unsuccessful (20 °C, 140 h, 0% yield, Scheme 21).

Cyclopropanation of 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester using isopropylidenetriphenylphosphorane or isopropylidene-diphenylsulfurane proved to be excellent ($Me_2C{=}PPh_3$, LiI, 0 °C, 1 h then 20 °C, 24 h; 82% yield, de 90%, Scheme 22, entry a; $Me_2C{=}SPh_2$, BF_4, −78 °C, 2 h, 20 °C, 1 h, 76%, de 98%, Scheme 22, entry b).

We have been unable to produce alkyl *trans*-chrysanthemates from 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester by the route disclosed in Scheme 23, entry a which involves acetonide deprotection and thionocarbonate reduction. We have been unable to isolate the expected

Scheme 22. Cyclopropanation of 2-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester.



Scheme 23. Unsuccessful deoxygenation of a diol moiety.

3-(1,2-dihydroxy-2-methyl-propyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester due to the extreme ease with which it cyclizes to 4-(1-hydroxy-1-methyl-ethyl)-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]-hexane-1-carboxylic acid methyl ester (Scheme 23, entry b).

It is interesting to compare the ease of that lactone ring formation (Scheme 25, entry b) to that of the related desdimethylated analogue disclosed in Scheme 15 or the *cis*-cyclopropanecarboxylate disclosed in Scheme 19, entry a) which all possess the same relative diastereoisomeric relationship around the stereogenic centers.

In order to achieve the desired transformation leading to (1*R*)-*trans*-chrysanthemic we used a more lengthy route which requires to perform at first the decarboxylation of 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester and to effect the deoxygenation of the side chain at the end of the sequence (Scheme 24). Almost all the reactions which have been used for such purpose have already used but in another order for the synthesis of deltamethrin acid disclosed above.

6. Conclusion

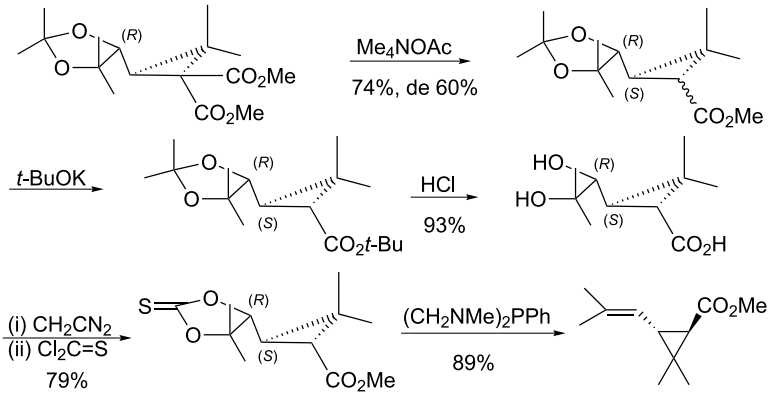
Addition of various reagents to alicyclic electrophilic olefins bearing an alkoxy group in γ-position has been the subject of intensive work over the last twenty years.[29] Most of these reactions involve γ-alkoxy-α,β-unsaturated esters whose C,C double bond is either *E* or *Z* and γ-alkoxy-malonates possessing a stereogenic centre at C-γ. Those can be attacked either by one or the other face producing compounds possessing the *syn*- or *anti*-stereochemistry between Cβ and C-γ (Scheme 25).

These belong to different class of 'reagents' and are involved in a large variety of organic reaction implying polar or radical type of additions, concerted and non concerted cycloadditions and performed under different conditions, for example, in different solvents.[5c,7,29–48] Although several explanations and calculations,[36,46b,c,49] often based on the Felkin–Anh model[50–55] have been disclosed, till now there is no model which explain all these results and it is therefore impossible to predict, unless very closely related examples are available, the stereochemical course of addition reaction to *E*-γ-alkoxy-α,β-unsaturated esters, their *Z*-stereoisomers and related γ-alkoxy-alkylidene malonates. We are working towards this end.

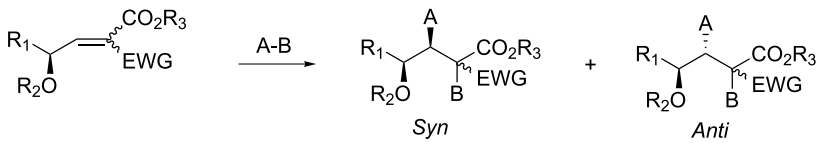
7. Experimental

7.1. General

NMR spectra were recorded on a JEOL JNM EX-400 (400 and 100.6 MHz, for ^{1}H and ^{13}C, respectively) or JEOL JNM EX-90 (90 and 22.5 MHz, for ^{1}H and ^{13}C, respectively). All spectra were carried out in $CDCl_3$ unless otherwise stated using TMS as internal standard. IR spectra reported in cm^{-1} were recorded on a BIO-RAD FTS-165 spectrometer. Melting points were recorded on a Tottoli–Büchi apparatus and are uncorrected. Optical rotations were measured on a Helwett–Packard digital polarimeter, the concentration being expressed as *c*: g/100 ml. Mass spectra were recorded on a HP 5989B spectrometer. Elemental analyses were performed by the Service d'Analyse de l'Université Pierre et Marie Curie, 75252 Paris Cedex 05, France. X-ray diffraction measurements were carried out at the 'Laboratoire de Chimie Moléculaire Structurale des FUNDP-Namur-Belgium'. |GC^2| were recorded on a HP 5890A chromatograph using a capillary SE30 column (25 m×0.25 mm×0.2 μm) in the following standard conditions: T detector: 250 °C, T injector: 250 °C, He pressure (1 ml/min). The oven temperatures were, respectively: program A (heating from 100 to 220 °C with a temperature increase of 10 °C/min), program B (heating from 60 to 220 °C with a temperature increase of 10 °C/min). Enantio-



Scheme 24. Synthesis of 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester.



Scheme 25. *syn*- or *anti*-adducts produced on addition of various reagents to γ-alkoxy-α,β-unsaturated esters.

meric excess (e.e.) were determined by |GC²| using a chiral capillary β-cyclodextrine column (Diacel, Chiracel, ODH, 25 m×0.25 mm×0.2 μm) in the following standard conditions: T detector: 250 °C, T injector: 250 °C, He pressure (1 ml/min).TLC was performed on pre-made commercial glass-backed plate SiO_2 (Merck 5719, 250 mesh) $60PF_{254}$ as fluorescent indicator. Compounds were visualized by UV illumination (254 nm) and by heating to 150 °C after spraying 20% phosphomolybdic acid in ethanol. Preparative layer chromatography (PLC) was performed on SiO_2 plates from silica gel $60PF_{254}$ (Merck 5719) All reactions were carried under Ar, unless stated otherwise. Solvents were freshly distilled from Na/benzophenone (THF, Et_2O), Na (toluene), $LiAlH_4$ (DME), Calcium hydride (DMSO, HMPA) or P_2O_5 (CH_2Cl_2). Column chromatography was performed using silica gel 60 under usual techniques. 1,2-5,6-Diisopropylidene-D-mannitol,[55] 2,3-*O*-isopropylidene-D-glyceraldehyde,[55] and 3,4-isopropylidene-D-mannitol[12c] were prepared following the procedures described in the literature.

7.1.1. Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester. *Procedure A*. Titanium (IV) chloride (140 mmol, 26.6 g) was added dropwise under an atmosphere of argon, to 420 ml of anhydrous THF maintained at −78 °C. The resulting yellow suspension was kept at this temperature for 0.25 h. A mixture of dimethyl malonate (200 mmol, 26.1 g), 2,3-*O*-isopropylidene-D-glyceraldehyde (70 mmol, 9.1 g) and pyridine (280 mmol, 22.1 g) was then added dropwise to the yellow suspension. The resulting mixture was stirred at 20 °C for 120 h before the reaction was quenched with a saturated ammonium chloride solution (200 ml). The aqueous phase was extracted with ether (7×100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 33.5 g of brown oil. The crude product (33.3 g) was purified by distillation (bp 95 °C, 0.2 mm Hg) to yield the pure alkylidene malonate (12.0 g, 70%) as a yellow oil.

Procedure B. Lead tetracetate (12.4 mmol, 5.5 g) was added under an atmosphere of argon, in small portions to a solution of 1,2-5,6-diisopropylidene-D-mannitol (11.4 mmol, 3.0 g) in anhydrous THF (200 ml) maintained at 0 °C. The mixture was stirred at 0 °C for 10 min and dimethyl malonate (30 mmol, 3.96 g) and freshly distilled acetic anhydride (4.65 ml) were added. The resulting mixture was then heated under reflux for 24 h. After cooling, the solution was filtered and the solvents eliminated under reduced pressure. The residue was dissolved in dichloromethane (100 ml), washed with a saturated aqueous sodium bicarbonate solution (1×20 ml) and brine (1×20 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give an orange oil which was purified by distillation (bp 95 °C, 0.2 mm Hg) to yield the pure alkylidene malonate (4.73 g, 85%) as a yellow oil. $[\alpha]_D^{20}$=+20.4 (*c* 1.0, $CHCl_3$); TLC, SiO_2: R_f 0.5 (pentane/ether: 70/30). |GC²|, program A, 5.3 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.02 (d, 1H, *J*=6.9 Hz, C*H*=C(CO_2-Me)$_2$), 4.90 (m, 1H, C*H*−O), 4.27 (m, 1H, C*H*−O), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.72 (m, 3H, C*H*−O), 1.44 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 164.6, 163.6, 148.4, 128.1, 110.3, 73.1, 68.8, 52.4, 52.3, 26.1, 25.3; IR (film, KBr) 2989, 2956, 2883, 1733, 1655, 1438, 1373, 1258, 1224, 1155, 1060, 1033, 986, 942, 840, 794, 765, 647 cm^{-1}; GC/MS *m/z* 244 (M^+), 229, 214, 182, 169, 156, 138, 123, 85, 59. Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found C, 53.96; H, 6.62.

7.1.2. Synthesis of (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol. Glycerol (109 mmol, 10.0 g), acetone (ACS reagent, 30 ml), pentane (30 ml) and *p*-toluenesulfonic acid (1.57 mmol, 300 mg) were successively introduced into a vessel fitted with a Dean−Stark. The mixture was then stirred at reflux for 41 h. After cooling, sodium acetate (1.83 mmol, 150 mg) was added. The mixture was filtered and the solvents were evaporated under reduced pressure to give the pure alcohol (14.1 g, 98%) as alight yellow oil. |GC²|, program B, 2.5 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.28−3.57 (br, 3H, C*H*−OH+C*H*−O), 2.6 (br, 3H, CH_2−OH+O*H*), 1.45 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); IR (film, KBr) 3435, 2988, 2937, 1458, 1381, 1372, 1257, 1214, 1157, 1118, 1074, 1053, 971, 845, 793 cm^{-1}. Spectral and analytical data are in agreement with the reported data.[17a]

7.1.3. Synthesis of 2,3-*O*-isopropylidene-(*d,l*)-glyceraldehyde. Freshly distilled DMSO (48 mmol, 3.75 g), diluted in 5 ml of anhydrous dichloromethane, was added dropwise to a well stirred solution of oxalyl chloride (22 mmol, 2.79 g) in anhydrous dichloromethane (50 ml) maintained at −60 °C. The mixture became yellow and (2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (20 mmol, 2.64 g), diluted with 10 ml of anhydrous dichloromethane, was introduced dropwise to the solution which was then stirred for 15 min. Triethylamine (100 mmol, 10.1 g) was added dropwise and the mixture was then heated to room temperature. Water (50 ml) and dichloromethane (50 ml) were added. Organic layer was washed with water (25 ml) and the combined aqueous layers were extracted with dichloromethane (3×50 ml). Organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure to give 1.60 g of crude material which was rapidly purified by distillation (40 °C, 20 mm Hg) to yield the aldehyde (893 mg, 37%) as colorless oil. |GC²|, program A, 1.6 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.71 (d, 1H, *J*=2.2 Hz, C*H*=O), 4.61−3.91 (br, 3H, 3C*H*−OH), 1.49 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); IR (film, KBr) 3423, 2989, 2938, 2893, 1737, 1457, 1375, 1256, 1217, 1154, 1154, 1074, 848 cm^{-1}. Spectral data are in agreement with those from the enantiopure 2,3-*O*-isopropylidene-(*d*)-glyceraldehyde.[55]

7.1.4. Synthesis of (*d,l*) 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester. Has been achieved on 2,3-*O*-isopropylidene-(*d,l*)-glyceraldehyde (10 mmol, 1.30 g) according to the procedure described for 2,3-*O*-isopropylidene-D-glyceraldehyde (see above).

7.1.5. Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene) malonic di-*tert*-butyl ester. It has been performed according to the Procedure B described above for the related dimethyl ester using lead tetracetate (18.6 mmol, 8.4 g) and di-*tert*-butyl malonate (45 mmol, 9.6 g) to yield pure alkylidene malonate (10.7 g, 96%) as a colorless oil.

$[\alpha]_D^{20}$=+15.8 (*c* 2.37, $CHCl_3$); TLC, SiO_2: R_f 0.7 (pentane/ether: 90/10). |GC²|, program A, 10.9 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 6.76 (d, 1H, *J*=7.5 Hz, C*H*=C(CO_2-*t*Bu)$_2$), 4.88 (m, 1H, C*H*–O–), 4.26 (m, 1H, C*H*–O–), 3.72 (m, 1H, C*H*–O–), 1.53 (s, 9H, C(CH_3)$_3$), 1.51 (s, 9H, C(CH_3)$_3$), 1.46 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 164.0, 162.8, 144.3, 139.0, 132.3, 110.2, 82.3, 82.0, 73.1, 72.3, 68.9, 27.7, 26.3, 25.5; IR (film, KBr) 2982, 2937, 2877, 1725, 1654, 1479, 1457, 1393, 1371, 1273, 1251, 1162, 1063, 1024, 904, 851, 787 cm^{-1}; GC/MS *m/z* 328 (M^+), 273, 217, 199, 187, 159, 138, 123, 85, 59. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found C, 62.15; H, 8.67.

7.1.6. Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid *tert*-butyl ester methyl ester. It has been performed according to the Procedure B described above for the related dimethyl ester using lead tetracetate (18.6 mmol, 8.4 g) and *tert*-butyl-methyl malonate (45 mmol, 7.8 g) to give an orange oil (16.3 g) which was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield pure alkylidene malonate (8.5 g, 87%) as a colorless oil (45/55 mixture of two isomers); TLC, SiO_2: R_f 0.63 (pentane/ether: 70/30). |GC²|, program A, 9.2 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 6.90 (d, *J*=7.1 Hz, C*H*=C(CO_2R)$_2$ *E*), 6.88 (d, *J*=7.0 Hz, C*H*=C(CO_2R)$_2$ *Z*), 4.91 (m, C*H*–O *E*), 4.87 (m, C*H*–O *Z*), 4.26 (br, C*H*–O *Z*+*E*), 3.82 (s, OCH_3 *Z*), 3.80 (s, OCH_3 *E*), 3.75–3.70 (br, C*H*–O *Z*+*E*), 1.53 (s, C(CH_3)$_3$ *E*), 1.50 (s, C(CH_3)$_3$ *Z*), 1.45 (s, CH_3 *Z*+*E*), 1.40 (s, CH_3 *E*), 1.39 (s, CH_3 *Z*); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 165.4, 164.7, 163.6, 162.5, 146.3, 140.4, 139.8, 130.5, 130.3, 110.5, 82.9, 82.5, 79.4, 76.4, 73.3, 73.2, 72.4, 69.0, 66.3, 52.4, 52.3, 27.9, 27.4, 26.7, 26.4, 25.8, 25.5; IR (film, KBr) 2986, 2955, 2939, 2881, 1731, 1656, 1478, 1457, 1438, 1372, 1329, 1256, 1225, 1160, 1062, 1032, 967, 905, 847, 754, 645 cm^{-1}; GC/MS *m/z* 287 (M^++1), 244, 229, 215, 201, 177, 169, 143, 115, 101, 85, 72, 59. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.72; 7.74. Found C, 58.65; H, 7.79.

7.1.7. Synthesis of 2-cyano-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)acrylic acid methyl ester. It has been performed according to the Procedure B described above for the related dimethyl ester using lead tetracetate (12.4 mmol, 5.5 g) and methyl cyanoacetate (30 mmol, 2.97 g). It give an orange oil (6.9 g) which was rapidly purified by column chromatography (pentane/ethyl acetate: 85/15 (v/v)) to yield the pure alkylidene malonate (3.49 g, 74%) as a light yellow oil. $[\alpha]_D^{20}$=+17.0 (*c* 1.88, $CHCl_3$); TLC, SiO_2: R_f 0.51 (pentane/ether: 70/30). |GC²|, program A, 6.8 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.58 (d, 1H, *J*=7.6 Hz, C*H*=C(CO_2Me)(CN)), 5.07 (m, C*H*–O), 4.34 (m, 1H, C*H*–O), 3.90 (s, 3H, OCH_3), 3.80 (m, 1H, C*H*–O), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 161.0, 159.7, 112.7, 111.5, 109.9, 73.6, 68.2, 53.5, 26.3, 25.3 IR (film, KBr) 2992, 2959, 2889, 2235, 1740, 1637, 1439, 1376, 1329, 1309, 1261, 1225, 1151, 1060, 1034, 963, 921, 843, 762, 513 cm^{-1}; GC/MS *m/z* 212 (M^++1), 196, 181, 154, 136, 123, 108, 94, 72, 59, 52. The analytical data are in agreement with that reported in the literature.[16]

7.1.8. Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malononitrile. Malononitrile (5.5 mmol, 360 mg) was added under an atmosphere of argon, to a solution of 4-*N*,*N*-dimethylaminopyridine (0.5 mmol, 60 mg) and 2,3-*O*-isopropylidene-D-glyceraldehyde (5 mmol, 655 mg) in anhydrous dichloromethane (10 ml) maintained at 0 °C. The orange mixture was then stirred at 0 °C for 1 h and at 20 °C for 2 h. The solvents were then evaporated under reduced pressure to give the crude compound (1.11 g), as an orange glue which could not be purified and was used directly in the next reactions. This compound decomposes rapidly on alumina, silica gel and by heating. ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.26 (d, 1H, *J*=7.6 Hz, C*H*=C(CN)$_2$), 5.34 (m, 1H, C*H*–O), 4.35 (m, 1H, C*H*–O), 3.86 (m, 1H, C*H*–O), 1.51 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); IR (film, KBr) 3348, 3332, 3055, 2992, 2941, 2899, 2241, 2202, 2169, 2112, 1757, 1720, 1650, 1617, 1570, 1481, 1457, 1379, 1345, 1264, 1217, 1153, 1122, 1064, 966, 919, 840, 738 cm^{-1}.

7.1.9. Synthesis of 2,4-dimethyl-hex-4-ene-2,3-(*R*)-diol. AD-mix β (15 g) was added in small portions to a well stirred mixture of water (50 ml) and *tert*-butanol (50 ml) at 20 °C. Methane sulfonamide (10 mmol, 950 mg) was added and the mixture was stirred at 20 °C for 10 min. 2,5-Dimethyl-2,4-hexadiene (10 mmol, 1.1 g) was added dropwise to the solution and the mixture was stirred vigorously at 20 °C for 2 h. Sodium bisulfite (15 g) was added in small portions and the resulting grey mixture was kept at room temperature for 1 h, extracted with ethyl acetate (3×70 ml). Organic layers were washed with brine (2×10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 2.3 g of crude material which was purified by column chromatography (pentane/ether: 0/100 (v/v)) to yield the pure 2,4-dimethyl-hex-4-ene-2,3-(*R*)-diol (1.17 g, 89%) as a colorless oil. $[\alpha]_D^{20}$=+9.57 (*c* 0.94, $CHCl_3$); TLC, SiO_2: R_f 0.61 (pentane/ethyl acetate: 0/100). |GC²|, program A, 3.2 min; chiral |GC²| (β-Dextrine column, 110 °C isotherm) 13,2 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.22 (d, 1H, *J*=9.2 Hz, C*H*=CMe_2), 4.16 (d, 1H, *J*=9.3 Hz, C*H*–O), 2.19 (br, 2H, 2O*H*), 1.79 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.16 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 137.1, 123.6, 74.9, 73.4, 26.0, 25.9, 23.1, 18.4; IR (film, KBr) 3399, 2977, 2933, 2917, 1677, 1449, 1379, 1303, 1265, 1222, 1160, 1116, 1040, 1027, 989, 963, 898, 849, 775, 733 cm^{-1}; GC/MS *m/z* 144 (M^+), 127, 111, 97, 93, 86, 77, 71, 59, 55. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found C, 66.38; H, 11.39.

7.1.10. Synthesis of 2,2-dimethyl-4-(2-methyl-propenyl)-[1,3]dioxolane. *p*-Toluenesulfonic acid (50 mg) and 2,2-dimethoxypropane (50 ml) were added under an atmosphere of argon to a solution of 2,4-dimethyl-hex-4-ene-2,3-(*R*)-diol (12 mmol, 1.74 g) in acetone (A.C.S reagent, 50 ml) maintained at 20 °C. The mixture was stirred at 20 °C for 12 h. A saturated sodium bicarbonate solution (5 ml) was then added and the mixture was extracted with diethyl ether (3×70 ml). Organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the pure acetonide (2.2 g, 99%) as a colorless oil. $[\alpha]_D^{20}$=−3.14 (*c* 2.96, $CHCl_3$); TLC, SiO_2: R_f 0.33 (pentane/ether: 90/10). |GC²|, program A, 3.3 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.21 (d, 1H, *J*=8.8 Hz, C*H*=CMe_2), 4.50 (d, 1H, *J*=8.9 Hz, C*H*–O), 1.80 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.46 (s, 3H,

CH_3), 1.39 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.13 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 139.0, 119.4, 80.9, 80.0, 28.3, 26.8, 26.0, 25.5, 23.2, 18.3; IR (film, KBr) 2982, 2935, 2889, 1779, 1679, 1454, 1376, 1372, 1311, 1266, 1234, 1217, 1202, 1145, 1121, 1048, 1035, 995, 962, 933, 916, 866, 829, 806, 654 cm^{-1}; GC/MS *m/z* 169 (M^+-CH_3), 126, 111, 109, 97, 84, 67, 59, 51. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found C, 71.56; H, 11.14.

7.1.11. Synthesis of 2,2-5,5-tetramethyl-[1,3]dioxolane-4-carbaldehyde. 2,2-Dimethyl-4-(2-methyl-propenyl)-[1,3]-dioxolane (9.8 mmol, 1.8 g) was dissolved in anhydrous dichloromethane (40 ml) and the mixture was cooled to −78 °C. Ozone was then bubbled for 1 h in the solution. Methyl sulfide (4 ml) was then added, the mixture was stirred at room temperature overnight and the solvents were removed under reduced pressure to give aldehyde (2.34 g) as a light yellow oil. This product was used directly without purification in the Knoevenagel condensation with dimethyl malonate. ^1H NMR δ (400 MHz, $CDCl_3$) 9.70 (d, 1H, *J*=2.11 Hz, C*H*=O), 4.10 (d, 1H, *J*=2.03 Hz, C*H*–O), 1.57 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 200.3, 102.1, 86.6, 80.8, 40.4, 27.9, 27.0, 26.7, 23.6; IR (film, KBr) 3268, 2985, 2938, 2882, 2731, 2593, 1735, 1465, 1438, 1406, 1374, 1313, 1259, 1233, 1221, 1198, 1130, 1071, 1025, 1004, 953, 916, 893, 862, 828, 813, 735, 701, 666 cm^{-1}; GC/MS *m/z* 143 (M^+-CH_3), 129, 110, 95, 85, 59, 55.

7.1.12. Synthesis of 2-(2,2-5,5-tetramethyl-[1,3]dioxolane-4-ylmethylene)-malonic acid dimethyl ester. Titanium (IV) chloride (18 mmol, 2.03 g) was added dropwise under an atmosphere of argon, to anhydrous THF (57 ml) maintained at −78 °C. The resulting yellow suspension was kept at this temperature for 0.25 h. A mixture of dimethyl malonate (27 mmol, 3.6 g), 2,2-5,5-tetramethyl-[1,3]dioxolane-4-carbaldehyde (9 mmol, 2.3 g) and pyridine (36 mmol, 2.85 ml) was then added dropwise to the yellow suspension. The resulting orange mixture was stirred at 20 °C for 48 h before the reaction was quenched with a saturated ammonium chloride solution (50 ml). The aqueous phase was extracted with diethyl ether (3×80 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 5.11 g of brown oil. The crude product (4.98 g) was purified by distillation (bp 110 °C, 0.1 mm Hg) to yield the pure alkylidene malonate (2.11 g, 88%) as a yellow oil. $[\alpha]_D^{20}=-2.66$ (*c* 1.43, $CHCl_3$); TLC, SiO_2: R_f 0.43 (pentane/ether: 80/20). |GC^2|, program A, 8.3 min; ^1H NMR δ (400 MHz, $CDCl_3$) 6.89 (d, 1H, *J*=6.6 Hz, C*H*=C(CO_2Me)$_2$), 4.56 (d, 1H, *J*=6.7 Hz, C*H*–O), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 1.47 (s, 3H, CH_3), 1.37 (m, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 165.4, 163.7, 142.0, 129.5, 109.0, 82.0, 80.7, 52.6, 52.3, 28.1, 27.0, 26.1, 23.9; IR (film, KBr) 2985, 2957, 2850, 1735, 1659, 1559, 1438, 1372, 1338, 1252, 1224, 1199, 1147, 1119, 1075, 1040, 1017, 1001, 944, 904, 862, 672 cm^{-1}; GC/MS *m/z* 257 (M^+-CH_3), 225, 214, 197, 183, 156, 139, 125, 110, 95, 73, 59, 53. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found C, 56.55; H, 7.38.

7.1.13. Cyclopropanation of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester. *Typical procedure C, using isopropylidene triphenylphosphorane*. To a well stirred suspension of isopropyltriphenylphosphonium iodide (3.6 mmol, 1.55 g) in anhydrous THF (8 ml) was added under an atmosphere of argon, dropwise *n*-butyllithium (1.6 N in hexane, 3.0 mmol, 1.84 ml) maintained at 0 °C. The dark red mixture was then stirred at room temperature for 0.25 h before addition of the alkylidene malonate (2.0 mmol, 488 mg) to the solution at 0 °C. After stirring at this temperature for 1 h, the mixture was stirred at 20 °C for 24 h. Water was added and the mixture was extracted with diethyl ether (3×50 ml), washed with water (1×10 ml), with brine (1×10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give orange oil (1.16 g). The crude material (1.09 g) was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield the pure cyclopropane-1,1-dicarboxylate (432 mg, 80%) as a colorless oil.

Typical procedure D, using isopropylidene diphenylsulfurane. A solution of LDA 0.55 N (2.10 ml) was added dropwise under an atmosphere of argon, to a well stirred mixture of isopropyldiphenylsulfonium tetrafluoroborate (1.2 mmol, 380 mg) and freshly distilled dichloromethane (1.2 mmol, 102 mg) in anhydrous DME (7 ml) maintained at −78 °C. The yellow solution was then stirred for 0.3 h at −78 °C. The alkylidene malonate (1.0 mmol, 244 mg), diluted in DME (1 ml), was added. After stirring for 2 h at −78 °C and 1 h at 20 °C, the mixture was hydrolyzed by the addition of a saturated aqueous ammonium chloride solution (5 ml), extracted with diethyl ether (3×50 ml), washed with brine (1×10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give an orange oil (442 mg). The crude material (370 mg) was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield the pure cyclopropane-1,1-dicarboxylate (180 mg, 76%) as a colorless oil. $[\alpha]_D^{20}=+0.93$ (*c* 1.01, $CHCl_3$); TLC, SiO_2: R_f 0.6 (pentane/ether: 70/30). |GC^2|, program A, 6.3 min; ^1H NMR δ (400 MHz, $CDCl_3$) 4.16 (m, 1H, C*H*–O), 3.98 (m, 1H, C*H*–O), 3.79 (m, 1H, C*H*–O), 3.73 (s, 6H, 2OCH_3), 1.81 (d, 1H, *J*=9.8 Hz, *H* cyclopropane), 1.45 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 168.7, 167.6, 109.2, 73.3, 69.1, 52.6, 52.3, 38.8, 30.9, 26.9, 25.5, 22.0, 18.0; IR (film, KBr) 2998, 2956, 2878, 1733, 1437, 1380, 1291, 1250, 1159, 1123, 1112, 1067, 1032, 996, 947, 917, 852, 823, 791, 735, 649 cm^{-1}; GC/MS *m/z* 271 (M^+-CH_3), 211, 185, 153, 125, 101, 59. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found C, 58.62; H, 7.97.

7.1.14. Cyclopropanation of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid di-*tert*-butyl ester. *According to procedure C*. Using isopropyltriphenylphosphonium iodide (3.6 mmol, 1.55 g) and the alkylidene malonate (2.0 mmol, 656 mg), gives an orange oil (1.56 g) purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield the pure cyclopropane-1,1-dicarboxylate (638 mg, 90%).

According to procedure D. Using isopropyldiphenylsulfonium tetrafluoroborate (1.2 mmol, 380 mg). The alkylidene malonate (1.0 mmol, 328 mg) to give an orange oil

(629 mg) purified by column chromatography (pentane/ether: 90/10 (v/v)) to yield the pure cyclopropane-1,1-dicarboxylate (261 mg, 78%) as a colorless oil.

According to procedure E. A solution of potassium *tert*-butoxide (0.7 mmol, 79 mg) in anhydrous THF was added dropwise under an atmosphere of argon, to a well stirred mixture of isopropyldiphenylsulfonium tetrafluoroborate (0.75 mmol, 237 mg) and alkylidene malonate (0.5 mmol, 164 mg) in anhydrous THF maintained at −78 °C. After stirring the light yellow solution for 1 h at −78 °C and 1 h at 20 °C, the mixture was hydrolyzed by the addition of water (10 ml), extracted with diethyl ether (3×30 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give orange oil (308 mg). The crude material (272 mg) was purified by column chromatography (pentane/ether: 85/15 (v/v)) to yield the pure cyclopropane-1,1-dicarboxylate (96 mg, 58%) as a colorless oil. $[\alpha]_D^{20}=+3.00$ (*c* 1.40, $CHCl_3$); TLC, SiO_2: R_f 0.42 (pentane/ether: 80/20). |GC^2|, program A, 11.4 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.15 (m, 1H, C*H*–O), 3.95 (m, 1H, C*H*–O), 3.80 (m, 1H, C*H*–O), 1.68 (d, 1H, *J*=9.8 Hz, *H* cyclopropane), 1.46 (s, 18H, 2O(CH_3)$_3$), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 167.7, 166.6, 109.1, 81.7, 81.4, 73.7, 69.3, 37.2, 29.6, 28.0, 27.0, 26.9, 25.6, 22.1, 17.8; IR (film, KBr) 2994, 2978, 2939, 2873, 2362, 1726, 1464, 1395, 1370, 1338, 1291, 1258, 1218, 1156, 1129, 1113, 1066, 1018, 978, 947, 921, 909, 859, 815, 790, 737, 667 cm^{-1}; GC/MS *m*/*z* 339, 315, 299, 287, 259, 229, 215, 201, 183, 165, 157. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found C, 64.83; H, 9.19.

7.1.15. Cyclopropanation of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid *tert*-butyl ester dimethyl ester. *According to procedure C*. Using isopropyltriphenylphosphonium iodide (2.7 mmol, 1.17 g) and the alkylidene malonate (1.5 mmol, 429 mg) to give orange oil (923 mg). The crude material (867 mg) was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield a intractable 59/41 mixture of cyclopropane-1,1-dicarboxylates (388 mg, 84%) as a colorless oil.

According to procedure D. Using isopropyldiphenylsulfonium tetrafluoroborate (1.2 mmol, 380 mg) and the alkylidene malonate (1.0 mmol, 286 mg), gives an orange oil (627 mg). The crude material (583 mg) purified by column chromatography (pentane/ether: 80/20 (v/v)) to yield a intractable 55/45 mixture of cyclopropane-1,1-dicarboxylates (235 mg, 77%) as a colorless oil. TLC, SiO_2: R_f 0.8 (pentane/ether: 80/20). |GC^2|, program A, 9.8 and 9.9 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.21–4.14 (m, C*H*–O *Z*+*E*), 4.02–3.94 (m, C*H*–O *Z*+*E*), 3.84–2.78 (m, C*H*–O *Z*+*E*), 3.73 (s, OCH_3 *E*), 3.72 (s, OCH_3 *Z*), 1.79–1.74 (d, *J*=9, 4, 9.0 Hz, *H* cyclopropane *Z*+*E*), 1.47 (s, OC(CH_3)$_3$ *E*), 1.46 (s, 2CH_3), 1.45 (s, OC(CH_3)$_3$ *Z*), 1.36 (s, CH_3), 1.35 (s, 2CH_3), 1.34 (s, CH_3), 1.30 (s, CH_3), 1.28 (s, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.4, 168.3, 167.3, 166.2, 109.2, 81.9, 81.8, 73.6, 73.4, 69, 3, 69.2, 52.4, 52.1, 42.7, 30.3, 30.2, 27.9, 27.8, 27.0, 26.9, 25.5, 22.1, 22.0, 18.1, 17.8; IR (film, KBr) 2985, 2956, 2937, 2877, 1347, 1731, 1458, 1437, 1393, 1371, 1291, 1253, 1222, 1209, 1160, 1125, 1112, 1067, 997, 949, 917, 849, 809, 791, 740, 588, 515 cm^{-1}; GC/MS *m*/*z* 313 (M^+-CH_3), 257, 227, 215, 197, 171, 153, 139, 101, 93, 73, 57. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.60. Found C, 62.24; H, 8.56.

7.1.16. Cyclopropanation of 2-cyano-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid methyl ester. *According to procedure C*. Using isopropyltriphenylphosphonium iodide (2.7 mmol, 1.17 g) and the α-cyanoacrylate (1.5 mmol, 317 mg) gives an orange oil (721 mg). The crude material (704 mg) purified by column chromatography (pentane/ether: 80/20 (v/v)) yields two pure cyclopropane derivatives: *Re* compound (colorless oil, 240 mg, 67%) and *Si* compound (white solid, 29 mg, 8%). Overall yield: 75%.

According to procedure D. Using isopropyldiphenylsulfonium tetrafluoroborate (1.2 mmol, 380 mg) and the α-cyanoacrylate (1.0 mmol, 211 mg), gives an orange oil (612 mg). The crude material (582 mg) was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield two pure cyclopropane derivatives. *Re compound* (colorless oil, 161 mg, 67%) and *Si* compound (white solid, 19 mg, 8%). Overall yield: 75%. *Re compound*: $[\alpha]_D^{20}=+11.13$ (*c* 0.72, $CHCl_3$); TLC, SiO_2: R_f 0.33 (pentane/ether: 80/20). |GC^2|, program A, 8.0 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.23 (m, 1H, C*H*–O), 4.05 (m, 1H, C*H*–O), 3.83 (s, 1H, OCH_3), 3.81 (m, 1H, C*H*–O), 2.12 (d, 1H, *J*=10.4 Hz, *H* cyclopropane), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 165.8, 115.9, 109.8, 72.8, 68.3, 53.2, 39.9, 36.4, 27.8, 26.6, 25.2, 20.2, 18.4; IR (film, KBr) 2982, 2938, 2865, 2245, 1740, 1460, 1436, 1295, 1233, 1167, 1113, 1073, 1046, 999, 936, 915, 871, 844, 786, 689, 613, 552 cm^{-1}; GC/MS *m*/*z* 238 (M^+-CH_3), 196, 178, 164, 152, 137, 120, 101, 93, 73, 59, 53. Anal. Calcd for $C_{13}H_{19}O_4N$: C, 61.,64; H, 7.56; N, 5.53. Found C, 61.64; H, 7.58; N, 5.55. *Si compound*: $[\alpha]_D^{20}=-12.13$ (*c* 0.80, $CHCl_3$); TLC, SiO_2: R_f 0.19 (pentane/ether: 80/20). |GC^2|, program A, 8.1 min; mp 97 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.13 (m, 1H, C*H*–O), 4.07 (m, 1H, C*H*–O), 3.82 (s, 1H, OCH_3), 3.74 (m, 1H, C*H*–O), 2.16 (d, 1H, *J*=9.6 Hz, *H* cyclopropane), 1.46 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 166.2, 116.1, 110.0, 73.1, 68.2, 53.4, 41.0, 35.2, 29.6, 26.7, 25.4, 20.5, 19.2; IR (film, KBr) 3034, 2998, 2982, 2938, 2865, 2369, 2345, 2245, 1740, 1460, 1436, 1380, 1375, 1325, 1294, 1233, 1167, 1113, 1073, 1046, 999, 936, 915, 871, 844, 786, 689, 613, 552 cm^{-1}; *GC/MS m*/*z* 238 (M^+-CH_3), 196, 178, 164, 152, 137, 120, 101, 93, 72, 59, 53. Anal. Calcd for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found C, 61.60; H, 7.75; N, 5.49.

7.1.17. Cyclopropanation of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylene)-malononitrile. *According to procedure C*. Using isopropyltriphenylphosphonium iodide (18.0 mmol, 7.8 g) and the alkylidene malononitrile (prepared just before as previously described from 10.0 mmol of 2,3-*O*-isopropylidene-D-glyceraldehyde, gives an brown oil (3.2 g). The crude material was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield two pure cyclopropane derivatives as white solids. *Re* compound (246 mg, 11%) and *Si* compound (396 mg, 18%). Overall yield over two steps: 29%.

According to procedure D. Using isopropyldiphenylsulfonium tetrafluoroborate (6.0 mmol, 1.9 g) and the alkylidene malononitrile (prepared just before as previously described from 5.0 mmol of 2,3-*O*-isopropylidene-D-glyceraldehyde, gives an brown oil (1.31 g). The crude material was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield two pure cyclopropane derivatives as white solids: *Re* compound (145 mg, 13%) and the *Si* compound (218 mg, 20%). Overall yield over two steps: 33%. *Re compound*: $[\alpha]_D^{20}=-7.75$ (*c* 0.96, $CHCl_3$); TLC, SiO_2: R_f 0.38 (pentane/ether: 50/50). |GC^2|, program A, 7.5 min; mp 118 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.15 (m, 1H, C*H*–O), 3.99 (m, 1H, C*H*–O), 3.77 (m, 1H, C*H*–O), 1.90 (d, 1H, *J*=9.7 Hz, *H* cyclopropane), 1.51 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 114.1, 112.5, 110.5, 72.3, 67.8, 43.3, 33.8, 26.7, 25.2, 24.1, 17.4, 14.9; IR (film, KBr) 2997, 2943, 2904, 2870, 2243, 1477, 1457, 1421, 1383, 1338, 1263, 1226, 1210, 1153, 1113, 1063, 1048, 1003, 978, 916, 839, 791, 638 cm^{-1}; GC/MS *m/z* 221 (M^++1), 205, 190, 175, 163, 145, 120, 118, 73, 59, 53. Anal. Calcd for $C_{12}H_{16}O_2N_2$: C, 65.43; H, 7.32; N, 12.72. Found C, 65.33; H, 7.47; N, 12.53. *Si compound*: $[\alpha]_D^{20}=+6.9$ (*c* 0.81, $CHCl_3$); TLC, SiO_2: R_f 0.4 (pentane/ether: 50/50). |GC^2|, program A, 6.5 min; mp 117 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.22 (m, 1H, C*H*–O), 3.93–3.86 (m, 2H, 2C*H*–O), 1.82 (d, 1H, *J*=9.3 Hz, *H* cyclopropane), 1.46 (s, 6H, 2CH_3), 1.40 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 113.9, 112.6, 110.5, 72.5, 68.3, 42.5, 35.2, 26.9, 25.2, 24.0, 17.0, 13.2; IR (film, KBr) 3034, 2986, 2937, 2884, 2244, 1481, 1456, 1378, 1260, 1222, 1164, 1075, 1055, 992, 974, 931, 858, 834, 793, 720, 691, 649 cm^{-1}; *GC/MS m/z* 205, 190, 175, 163, 145, 128, 118, 101, 73, 59, 53. Anal. Calcd for $C_{12}H_{16}O_2N_2$: C, 65.43; H, 7.32; N, 12.72. Found C, 65.93; H, 7.52; N, 12.11.

7.1.18. Cyclopropanation of 2-(2,2-5,5-tetramethyl-[1,3]dioxolan-4-ylmethylene)-malonic acid dimethyl ester. *According to procedure C*. Using isopropyltriphenylphosphonium iodide (1.94 mmol, 838 mg) and the alkylidene malonate (1.08 mmol, 293 mg), gives yellow oil (1.41 g). The crude material (1.37 g) was purified by column chromatography (pentane/ether: 70/30 (v/v)) to yield a mixture of cyclopropane-1,1-dicarboxylates (269 mg, 82%) as a colorless oil (95/5 *Si*/*Re* compounds).

According to procedure D. Using isopropyldiphenylsulfonium tetrafluoroborate (1.2 mmol, 380 mg) and the alkylidene malonate, gives brown oil (639 mg). The crude material (602 mg) was purified by column chromatography (pentane/ether: 80/20 (v/v)) to yield the pure *Si* compound (224 mg, 76%) as a colorless oil. *Si compound*: $[\alpha]_D^{20}=+23.90$ (*c* 0.70, $CHCl_3$); TLC, SiO_2: R_f 0.47 (pentane/ether: 80/20). |GC^2|, program A, 9.3 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.88 (d, 1H, *J*=10.2 Hz, C*H*–O), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 1.84 (d, 1H, *J*=10.4 Hz, *H* cyclopropane), 1.44 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.2, 168.2, 79.1, 52.6, 52.2, 35.1, 30.6, 28.9, 27.2, 26.4, 23.8, 23.7, 16.7; IR (film, KBr) 2982, 2956, 2938, 2878, 1733, 1461, 1437, 1377, 1346, 1291, 1250, 1216, 1201, 1169, 1126, 1109, 1077, 1052, 1032, 1001, 962, 937, 912, 891, 861, 824, 800, 753 cm^{-1}; GC/MS *m/z* 299 (M^+-CH_3), 256, 225, 185, 153, 139, 73, 59. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found C, 60.97; H, 8.54. *Re compound*: $[\alpha]_D^{20}=-9.05$ (*c* 1.21, $CHCl_3$); TLC, SiO_2: R_f 0.48 (pentane/ether: 80/20). |GC^2|, program A, 9.1 min; mp 56 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.82 (d, 1H, *J*=9.5 Hz, C*H*–O), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.89 (d, 1H, *J*=9.7 Hz, *H* cyclopropane), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.1, 80.2, 79.2, 52.6, 52.2, 35.6, 30.3, 28.5, 26.8, 26.5, 23.7, 23.5, 18.2; IR (film, KBr) 2985, 2957, 2938, 1729, 1462, 1440, 1429, 1380, 1370, 1350, 1301, 1246, 1215, 1192, 1109, 1182, 1168, 992, 962, 935, 914, 889, 861, 828, 815, 752 cm^{-1}; GC/MS *m/z* 299 (M^+-CH_3), 225, 185, 153, 139, 100, 73, 59. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found C, 60.98; H, 8.37.

7.1.19. Synthesis of the authentic sample of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester from methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1-carboxylate.[5c] To a well stirred solution of diisopropylamine (1.5 mmol, 151 mg) in anhydrous tetrahydrofuran (2 ml) was added under an atmosphere of argon, *n*-butyllithium (1.6 N in hexane, 1.2 mmol, 0.75 ml) maintained at 0 °C. The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C before addition of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1-methylcarboxylate (1.0 mmol, 228 mg) previously prepared as the well known procedure.[5c] The yellow solution was stirred at −78 °C for 45 min and methyl chloro formate (1.5 mmol, 142 mg) was then added dropwise. After stirring at this temperature for 2 h, the mixture was hydrolyzed by addition of water (5 ml), extracted with diethyl ether (4×20 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 313 mg of crude material. 173 mg were purified by column chromatography (pentane/ether: 80/20) to yield the pure 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (131 mg, 82%). Spectral and analytical data are in agreement with the authentic sample previously described in this paper.

7.1.20. Transesterification of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid *tert*-butyl ester methyl ester with potassium *tert*-butoxide. To a well stirred solution of potassium *tert*-butoxide (2.8 mmol, 314 mg) in anhydrous THF (3.7 ml) was added under an atmosphere of argon, the 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (0.91 mmol, 300 mg) maintained at 20 °C. The mixture was then stirred 2 h at room temperature. Water was added (5 ml) and the mixture was extracted with diethyl ether (3×30 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 392 mg of crude material. 337 mg were purified by thin layer chromatography (pentane/ether: 90/10) to yield the pure 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester (274 mg, 95%). Spectral and analytical

data are in agreement with the authentic sample previously described in this paper.

7.1.21. Bis-transesterification of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester with potassium *tert*-butoxide. To a well stirred solution of potassium *tert*-butoxide (20.0 mmol, 2.24 g) in anhydrous THF (16 ml) was added under an atmosphere of argon, 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid *tert*-butyl ester methyl ester (4 mmol, 1.15 g) maintained at 20 °C. The mixture was then stirred for 1.5 h at room temperature. Water was added (7 ml) and the mixture was extracted with diethyl ether (3×50 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 1.52 g of crude material. 1.47 g were purified by column chromatography (pentane/ether: 90/10) to yield the pure 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester (1.21 g, 92%). Spectral and analytical data are in agreement with the authentic sample previously described in this paper. Acid cleavage of the dioxolane ring of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester: (HCl 10%) which exist at the smaller/MeOH, 1.5 h at 20 °C. 10% Aqueous hydrochloric acid (3.0 ml) was added to a solution of cyclopropane-1,1-dicarboxylate (2.0 mmol, 572 mg) in methanol (10 ml). The mixture was then stirred for 1.5 h at room temperature and the solvents were rapidly removed under reduced pressure. The residue was then solved with ethyl acetate (100 ml) and the solution was filtered through a mixture of sodium bicarbonate and magnesium sulfate. The solvents were removed under reduced pressure to give 556 mg of crude material. 433 mg were purified by column chromatography (ethyl acetate) to yield the pure methyl 3-(1,2-dihydroxy-ethyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylate (291 mg, 76%) as a colorless oil. $[\alpha]_D^{20}=-14.2$ (*c* 2.43, $CHCl_3$); TLC, SiO_2: R_f 0.25 (pentane/ether: 0/100). ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.73 (s, 6H, 2OCH_3), 3.84–3.63 (br, 3H, 3CH–O), 1.79 (d, 1H, *J*=9.8 Hz, *H* cyclopropane), 1.37 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.0, 168.0, 69.3, 66.1, 52.8, 52.5, 37.6, 30.5, 22.7, 17.8; IR (film, KBr) 3404, 2956, 2882, 1728, 1438, 1382, 1298, 1256, 1201, 114, 1120, 1033, 993, 950, 923, 874, 823, 804, 747, 722, 695, 600 cm^{-1}; GC/MS *m*/*z* 247 (M^+ +1), 229, 215, 199, 185, 179, 153, 137, 122, 109, 95, 73, 67, 55. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.70; H, 7.04. Found C, 53.46; H, 7.15.

7.1.22. Acid cleavage of dioxolane ring of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester. 10% HCl/MeOH, 50 h at 20 °C. 10% Aqueous hydrochloric acid (3.0 ml) was added to a solution of cyclopropane 1,1-dicarboxylate (2.0 mmol, 572 mg) in methanol (10 ml). The mixture was then stirred for 50 h at room temperature and the solvents were rapidly removed under reduced pressure. The residue was then solved with ethyl acetate (100 ml) and the solution was filtered through a mixture of sodium bicarbonate and magnesium sulfate. The solvents were removed under reduced pressure to give 463 mg of crude material. 382 mg were purified by column chromatography (ethyl acetate) to yield the pure methyl 4-hydroxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylate (316 mg, 89%) as a colorless oil. $[\alpha]_D^{20}=-21.86$ (*c* 2.20, $CHCl_3$); TLC, SiO_2: R_f 0.51 (pentane/ether: 0/100). $|GC^2|$, program A, 6.1 min; δ_H (400 MHz, $CDCl_3$) 4.81 (m, 1H, CH–O), 3.98–3.73 (br, 2H, 2CH–OH), 3.82 (s, 3H, OCH_3), 2.52 (d, *J*=4.4 Hz, 1H, *H* cyclopropane), 2.40 (br, 1H, O*H*), 1.41 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.4, 166.0, 79.5, 61.4, 52.8, 42.1, 36.1, 33.4, 22.0, 19.5; IR (film, KBr) 3440, 2999, 2958, 2883, 1770, 1730, 1639, 1441, 1320, 1233, 1196, 936, 897, 871, 804, 730, 638 cm^{-1}; GC/MS *m*/*z* 215 (M^++1), 199, 197, 183, 165, 153, 151. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found C, 55.03; H, 6.87.

7.1.23. Protection as *tert*-butyl dimethylsilylether of the hydroxyl group of methyl 4-hydroxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylate. Imidazole (18.0 mmol, 1.21 g) was added under an atmosphere of argon, to a solution of 4-hydroxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylate (7.2 mmol, 1.55 mg) in anhydrous DMF (10 ml) maintained at room temperature. The mixture was then stirred for 1 h at room temperature. Water (10 ml) was added and the mixture was extracted with ethyl acetate (3×30 ml). Organic layer was dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 2.6 g of crude material which were purified by thin layer chromatography (pentane/ether: 70/30 (v/v)) to yield the pure lactone (2.2 g, 92%) as a colorless oil. TLC, SiO_2: R_f 0.48 (pentane/ether: 70/30). $|GC^2|$, program A, 13.5 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.81 (m, 1H, CH–O), 3.98–3.73 (br, 2H, 2CH–OTBS), 3.82 (s, 3H, OCH_3), 2.49 (d, 1H, *J*=4.4 Hz, *H* cyclopropane), 1.36 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.4, 166.3, 78.6, 61.5, 52.8, 41.8, 36.4, 33.3, 25.7, 25.6, 21.9, 19.1, 18.1, −5.2, −5.6; IR (film, KBr) 2955, 2932, 2886, 2858, 2363, 1786, 1731, 1464, 1439, 1407, 1391, 1363, 1318, 1276, 1256, 1229, 1195, 1106, 1078, 1051, 1020, 991, 960, 939, 902, 840, 780, 713, 666 cm^{-1}; GC/MS *m*/*z* 329 (M^++1), 313, 297, 271, 253, 239, 225, 197, 179, 159, 153. Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found C, 58.44; H, 8.64.

7.1.24. Attempted demethoxycarbonylation of methyl 4-*tert*-butyl-dimethylsilyloxymethyl-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylate with magnesium iodide. To a mixture of magnesium turnings (0.67 mmol, 16 mg) in anhydrous diethyl ether (3 ml) was added under an atmosphere of argon, portion wise iodine (0.54 mmol, 138 mg) maintained at room temperature. When the color of the iodine disappeared, the ether was evaporated, the residue was dissolved in anhydrous toluene (3 ml) and the lactone (0.54 mmol, 176 mg) was added. After 13 h at 80 °C, the mixture was cooled at room temperature, a saturated aqueous bicarbonate solution (10 ml) was added and the layers were separated. The aqueous layer was acidified with 10% aqueous HCl and was extracted with diethyl ether (3×30 ml). Organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give cyclopropane ring opening compound (93 mg, 55%) as a brown solid (purity ~90%). ^{1}H NMR δ (400 MHz, $CDCl_3$) 5.11 (s, *H* olefinic), 4.96 (s, *H* olefinic), 4.69 (m, *H* vinylic), 4.11 (d, 1H, *J*=13 Hz,

C*H*(CO_2H) cyclopropane), 3.86–3.69 (br, 3H, 2C*H*–OTBS+C*H*–O), 1.87 (s, 3H, CH_3), 0.89 (s, 9H, SiC(CH_3)$_3$). 0.08 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3); IR (film, KBr) 2957, 2932, 2860, 1720, 1655, 1390, 1335, 1256, 1161, 1112, 1061, 1037, 1006, 997, 911, 868, 837, 808, 781, 734 cm^{-1}.

7.1.25. Decarboxylation of 2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid methyl ester using the Barton procedure. Thionyl chloride (1 ml) was added dropwise under an atmosphere of argon, to a well stirred solution of carboxylic acid[X] (1.37 mmol, 250 mg) in benzene (1 ml) maintained at 0 °C. One drop of anhydrous DMF was added and the mixture was stirred at room temperature for 2 h. The solvents were removed under reduced pressure. The residue (in 5 ml of benzene) was then added to a solution of thione[21a] (1.51 mmol, 189 mg) in benzene (4 ml) before introduction of pyridine (0.12 ml). The resulting mixture, sheltered from sunlight, was stirred at room temperature for 2 h at room temperature, was filtered and the solvents were removed under reduced pressure. After exposition to sunlight, the mixture was purified by thin layer chromatography (pentane/ether: 60/40) to yield 169 mg of the pure 2,2-dimethyl-1-(pyridine-2-ylsulfanylcarbonyl)-cyclopropanecarboxylic acid methyl ester (169 mg, 66%) as a colorless liquid. TLC, SiO_2: R_f 0.93 (pentane/ether: 60/40). |GC^2|, program A, 9.8 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.41 (m, *H* aromatic), 7.55 (m, *H* aromatic), 7.30 (s, *H* aromatic), 7.01 (m, *H* aromatic), 3.71 (s, 3H, OCH_3), 2.05 (d, 1H, *J*=4.77 Hz, *H* cyclopropane), 1.48 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.07 (d, 1H, *J*=5.34 Hz, *H* cyclopropane); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 160.7, 149.2, 136.7, 120.9, 119.5, 52.8, 36.0, 30.1, 22.9, 21.1, −0.1; IR (film, KBr) 3047, 2990, 2953, 2931, 2877, 1723, 1605, 1576, 1561, 1452, 1435, 1419, 1377, 1329, 1283, 1243, 1191, 1149, 1128, 1106, 1046, 1017, 998, 986, 966, 944, 874, 854, 759, 726, 667, 619 cm^{-1}; GC/MS *m/z* 237 (M$^+$), 222, 205, 204, 178, 162, 151, 136, 122, 111, 99, 78, 67, 5. Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found C, 60.57; H, 6.59; N, 5.78.

7.1.26. Demethoxycarbonylation of 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester. (i) *Using NaCl in wet DMSO at 180 °C*. A mixture of sodium chloride (4.0 mmol, 236 mg), water (6.0 mmol, 108 mg) and cyclopropane-1,1-dicarboxylate (3.0 mmol, 858 mg) in DMSO (3 ml) was stirred at 180 °C for 6 h. After cooling to room temperature, the mixture was hydrolyzed with water (10 ml) and extracted with diethyl ether (4×25 ml). Organic layers were washed with water (10 ml), with brine (10 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 591 mg of crude material. 522 mg were purified by column (pentane/ether: 70/30 (v/v)) to yield a mixture (449 mg, 73%) of three compounds (*trans*/*cis*/*open*: 27/21/52) as a colorless oil.

trans-Cyclopropane carboxylate. $[\alpha]_D^{20}$=−17.8 (*c* 0.91, $CHCl_3$); TLC, SiO_2: R_f 0.78 (pentane/ether: 70/30). |GC^2|, program A, 4.1 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.55 (m, 1H, C*H*–O), 4.05 (m, 1H, C*H*–O), 3.66–3.60 (s+m, 4H, OCH_3+C*H*–O), 1.56 (d, *J*=8.8 Hz, 1H, C*H*(CO_2Me), 1.45 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.24 (s+m, 4H, CH_3+*H* cyclopropane); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 172.0, 109.2, 72.4, 69.2, 68.0, 66.4, 51.5, 35.2, 29.3, 28.2, 27.2, 25.7; IR (film, KBr) 2988, 2955, 2872, 1728, 1458, 1440, 1378, 1320, 1236, 1205, 1149, 1124, 1097, 1060, 1012, 938, 855, 790, 742 cm^{-1}; GC/MS *m/z* 213 (M$^+$−CH_3), 153, 139, 127, 111, 101, 72, 71, 55. Spectral and analytical data are in agreement with those reported.[5]

cis-Cyclopropyl ester. $[\alpha]_D^{20}$=+32.6 (*c* 12.0, $CHCl_3$); TLC, SiO_2: R_f 0.68 (pentane/ether: 70/30). |GC^2|, program A, 3.6 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.06 (m, 1H, C*H*–O), 3.76–3.68 (br, 2H, 2C*H*–O), 3.67 (s, 3H, OCH_3), 1.55 (m, 1H, *H* cyclopropane), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.27 (2s, 4H, CH_3+C*H*(CO_2Me)), 1.26 (s, 3H, CH_3); IR (film, KBr) 2987, 2954, 2876, 1730, 1449, 1377, 1349, 1284, 1234, 1214, 1175, 1117, 1067, 999, 941, 909, 852, 792, 736, 646 cm^{-1}; GC/MS *m/z* 213 (M$^+$−CH_3), 197, 127, 93, 59. Spectral and analytical data are in agreement with that reported.[5c]

Opened form. TLC, SiO_2: R_f 0.78 (pentane/ether: 70/30). |GC^2|, program A, 3.9 min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.91 (s, 1H, *H* olefinic), 4.81 (s, 1H, *H* olefinic), 4.20 (m, 1H, C*H*–O), 3.97 (m, 1H, C*H*–O), 3.83 (s, 3H, OCH_3), 3.80 (m, 1H, C*H*–O), 2.82 (br, 1H, *H* vinylic), 2.46 (m, 2H, CH_2(CO_2Me), 1.80 (s, 3H, CH_3 olefinic), 1.45 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); IR (film, KBr) 2988, 2952, 2937, 2876, 1727, 1660, 1503, 1384, 1256, 1234, 1213, 1175, 1155, 1093, 1063, 1001, 939, 908, 854, 792, 736, 659 cm^{-1}; GC/MS *m/z* 228 (M$^+$), 213, 197 (M$^+$−OCH_3), 169, 127, 95, 59. Spectral and analytical data are in agreement with those reported.

(ii) *Using PATP in DMF with a catalytic amount of cesium carbonate*. A solution of PATP (2.0 mmol, 250 mg), cyclopropane-1,1-dicarboxylate (1.0 mmol, 286 mg) and cesium carbonate (0.32 mmol, 105 mg) in anhydrous DMF (9 ml) was stirred under an atmosphere of argon, maintained at 90 °C for 26 h, then cooled, hydrolyzed with water (10 ml), extracted with diethyl ether (3×20 ml), washed with water (10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 910 mg of crude material which were purified by column chromatography (pentane/ether: 80/20 (v/v)) to yield a mixture (155 mg, 68%) of the two desired cyclopropyl carboxylates (*trans*/*cis*: 61/39).

(iii) *Using Me_4NOAc in DMPU*. Tetramethylammonium acetate (1.1 g) was added under an atmosphere of argon, to a solution of the cyclopropane-1,1-dicarboxylate (1.0 mmol, 286 mg) in anhydrous DMPU (9 ml) maintained at 20 °C. The mixture was then stirred for 6 h at 95 °C, cooled, hydrolyzed with water (10 ml), extracted with diethyl ether (3×20 ml), washed with water (10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 850 mg of crude material which were purified by column chromatography (pentane/ether: 80/20 (v/v)) to yield a mixture (180 mg, 79%) of the two desired cyclopropyl carboxylates (*trans*/*cis*: 68/32).

7.1.27. Acidic cleavage of dioxolane ring of methyl 3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-cyclopropane-1-carboxylate. *cis-Compound*. 10% aqueous

hydrochloric acid (3 ml) was added to a solution of cyclopropane (2.41 mmol, 456 mg) in methanol (10 ml). The mixture was then stirred for 30 min at room temperature and the solvents were rapidly removed under reduced pressure. The residue was then solved with ethyl acetate (50 ml) and the solution was filtered through a mixture of sodium bicarbonate and magnesium sulfate. The solvents were removed under reduced pressure to give 503 mg of crude material. 481 mg were purified by column chromatography (pentane/ether: 0/100 (v/v)) to yield the pure lactone (257 mg, 89%) as a colorless oil. $[\alpha]_D^{20}=-68.7$ (*c* 1.27, $CHCl_3$). ^{1}H NMR δ (400 MHz, $CDCl_3$) 4.78 (m, 1H, C*H*–O), 3.98 (m, 1H, CH_2–OH), 3.77 (m, 1H, CH_2-OH), 2.07 (d, 1H, *J*=5.4 Hz, C*H*–C=O), 1.97 (m, 1H, *H* cyclopropane), 1.75 (s, 1H, O*H*), 1.32 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 172.2, 68.0, 66.3, 51.4, 33.9, 29.1, 28.6, 25.1; IR (film, KBr) 3421, 2960, 1755, 1648, 1456, 1383, 1353, 1313, 1291, 1201, 1119, 1086, 1050, 990, 940, 883, 845, 784 cm^{-1}; GC/MS *m*/*z* 152, 139, 126, 115, 111, 97, 93, 81, 69, 67, 55. The spectral and analytical data agree with those previously reported.[28]

trans-Compound. 10% aqueous hydrochloric acid (3 ml) was added to a solution of cyclopropane (2.41 mmol, 456 mg) in methanol (12 ml). The mixture was then stirred for 30 min at room temperature and the solvents were rapidly removed under reduced pressure. The residue was then solved with ethyl acetate (50 ml) and the solution was filtered through a mixture of sodium bicarbonate and magnesium sulfate. The solvents were removed under reduced pressure to give 491 mg of crude material which was purified by column chromatography (ethyl acetate) to yield the pure diol (417 mg, 92%) as colorless oil. $[\alpha]_D^{20}=+45.0$ (*c* 2.91, $CHCl_3$). ^{1}H NMR δ (400 MHz, $CDCl_3$) 3.67 (s, 3H, OCH_3), 3.74–3.57 (br, 2H, 2C*H*–O), 3.40 (m, 1H, C*H*–O), 2.69 (br, 2H, 2O*H*), 1.51 (m, 1H, *H* cyclopropane), 1.40 (d, 1H, *J*=9.7 Hz, C*H*(CO_2Me)), 1.30 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 172.5, 72.4, 66.2, 51.7, 34.2, 30.9, 26.7, 21.2, 20.7; IR (film, KBr) 3407, 2954, 2932, 2877, 2745, 1731, 1449, 1381, 1357, 1288, 1214, 1171, 1117, 1090, 1039, 1014, 998, 969, 938, 909, 874, 843, 778, 733, 653 cm^{-1}; GC/MS *m*/*z* 127, 97, 95, 79, 73, 67, 59, 51. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found C, 56.53; H, 8.76.

7.1.28. Selective tritylation of the primary hydroxyl group of methyl *trans*-3-(2,3-dihydroxy-propyl)-2,2-dimethyl-cyclopropanecarboxylate. *N*,*N*-4-dimethyl-amino-*N*-triphenylmethylpyridinium chloride[26] (1.28 mmol, 512 mg) was added under an atmosphere of argon, to a solution of the diol (1.06 mmol, 200 mg) in anhydrous CH_2Cl_2 (6 ml) maintained at 20 °C. The mixture was then stirred for 22 h at reflux, cooled, hydrolyzed with water (5 ml), extracted with dichloromethane (3×20 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 821 mg of crude material which were purified by column chromatography (pentane/ethyl acetate: 80/20 (v/v)) to yield the pure tritylether (405 mg, 89%) as a white solid. TLC, SiO_2: R_f 0.85 (pentane/ethyl acetate: 80/20). Mp 61 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.46–7.24 (br, 15H, OC(C_6H_5)$_3$), 3.64 (s, H, OCH_3), 3.31–3.26 (br, 3H, 3C*H*–O), 2.27 (br, 1H, O*H*), 1.50 (m, 1H, *H* cyclopropane), 1.27 (d, 1H, *J*=5.5 Hz, C*H*(CO_2Me)), 1.23 (2s, 6H, 2CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 172.3, 143.8, 128.7, 128.0, 127.1, 87.0, 71.0, 67.3, 51.5, 34.6, 30.9, 26.6, 21.2, 20.7; IR (film, KBr) 3468, 3088, 3060, 3027, 2982, 2952, 2928, 2874, 2742, 2081, 1963, 1893, 1816, 1731, 1716, 1598, 1492, 1448, 1375, 1244, 1213, 1171, 1115, 1048, 986, 944, 903, 845, 766, 748, 707, 647, 633, 608 cm^{-1}; GC/MS *m*/*z* 258, 243, 229, 215, 183, 165, 152, 127, 105, 77, 67, 55. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found C, 78.00; H, 7.16.

7.1.29. Contrathermodynamic lactonisation of methyl *trans*-3-(1-hydroxy-2-trityloxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate using potassium *tert*-butoxide in benzene. Potassium *tert*-butoxide (0.44 mmol, 51 mg) was added under an atmosphere of argon, to a solution of methyl *trans*-3-(1-hydroxy-2-trityloxy-ethyl)-2,2-dimethyl-cyclopropanecarboxylate (0.44 mmol, 169 mg) in anhydrous benzene (2 ml) maintained at 20 °C. The resulting yellow mixture was then stirred for 6 h at 80 °C, cooled and dichloromethane was added (10 ml). The solution was hydrolyzed with a saturated aqueous ammonium chloride solution (5 ml), extracted with dichloromethane (2×10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 181 mg of crude material. 152 mg were purified by thin layer chromatography (pentane/ether: 60/40 (v/v)) to yield the pure 6,6-dimethyl-4-trityloxy-methyl-3-oxa-bicyclo[3.1.0]hexan-2-one (138 mg, 79%) as a white solid. $[\alpha]_D^{20}=-57.3$ (*c* 1.24, $CHCl_3$); TLC, SiO_2: R_f 0.40 (pentane/ether: 70/30). |GC^2|, program A, 13.7; mp 101 °C; min; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.49–7.25 (m, 15H, OC(C_6H_5)$_3$), 4.84 (m, H, C*H*–O), 3.50 (m, 1H, C*H*–O), 3.50 (m, 1H, C*H*–O), 2.27 (br, 1H, O*H*), 2.00 (br, 2H, 2*H* cyclopropane), 1.11 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 174.4, 143.6, 128.7, 128.0, 127.3, 86.8, 78.9, 62.4, 31.4, 30.9, 26.0, 24.1, 17.4; IR (film, KBr) 3087, 3058, 3031, 2997, 2982, 2960, 2928, 2901, 2873, 1966, 1921, 1875, 1766, 1596, 1561, 1446, 1399, 1380, 1366, 1348, 1314, 1290, 1253, 1217, 1189, 1155, 1134, 1117, 1076, 1028, 991, 937, 899, 864, 848, 820, 771, 755, 703, 647, 631 cm^{-1}; GC/MS *m*/*z* 253, 251, 235, 233. Anal. Calcd for $C_{27}H_{26}O_3$: C, 81.38; H, 6.58. Found C, 81.33; H, 6.61.

7.1.30. Removal of trityl group from 6,6-dimethyl-4-trityloxymethyl-3-oxa-bicyclo[3.1.0]hexan-2-one. 10% Aqueous hydrochloric acid (0.5 ml) was added to a solution of lactone (0.25 mmol, 100 mg) in methanol (2 ml). The mixture was then stirred for 50 min at room temperature, extracted with diethyl ether (3×10 ml), dried ($MgSO_4$). The solvents were removed under reduced pressure to yield the pure lactone (39 mg, 98%) as a colorless oil. Spectral and analytical data are in agreement with the product synthesized previously and the reported data.[28]

7.1.31. Acid cleavage of dioxolane ring of 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester. 10% Aqueous hydrochloric acid (3 ml) was added to a solution of cyclopropane (2 mmol, 628 mg) in methanol (10 ml). The mixture was then stirred for 15 min at room temperature and the solvents were rapidly removed under reduced pressure. The residue was then solved with ethyl acetate (30 ml) and the solution was filtered through a mixture of sodium

bicarbonate and magnesium sulfate. The solvents were removed under reduced pressure to give 589 mg of crude material which was purified by column chromatography (pentane/ether: 0/100 (v/v)) to yield pure 4-(1-hydroxy-1-methyl-ethyl)-6,6-dimethyl-2-oxo-3-oxa-bicyclo[3.1.0]hexane-1-carboxylic acid methyl ester (393 mg, 81%) as a glue. $[\alpha]_D^{20}=-25.7$ (*c* 1.43, $CHCl_3$); TLC, SiO_2: R_f 0.59 (pentane/ether: 0/100). |GC[2]|, program A, 9.9 min; ^1H NMR δ (400 MHz, $CDCl_3$) 4.00 (s, 1H, C*H*–O), 3.82 (s, 3H, OCH_3), 2.50 (s, 1H, *H* cyclopropane), 1.82 (br, 1H, O*H*), 1.32 (s, 3H, CH_3), 1.30 (s, 6H, 2CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 169.7, 166.2, 100.6, 81.8, 71.6, 52.9, 36.5, 31.8, 25.0, 23.9, 21.2, 16.2; IR (film, KBr) 3500, 3066, 2979, 2936, 2885, 2750, 2106, 1770, 1731, 1646, 1440, 1383, 1334, 1306, 1278, 1234, 1179, 1126, 1106, 1086, 1056, 1027, 1000, 967, 932, 913, 885, 829, 800, 775, 731 cm^{-1}; *GC/MS m/z* 243 (M^++1), 225, 211 (M^+−OCH_3), 185, 169, 153, 137, 125, 95, 84, 59, 55. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found C, 57.88, H, 7.69.

7.1.32. Demethoxycarbonylation of 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester. Tetramethylammonium acetate (1.6 g) was added under an atmosphere of argon, to a solution of the 2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (1.6 mmol, 502 mg) in anhydrous HMPA (14 ml) maintained at 20 °C. The mixture was then stirred for 6 h at 95 °C, cooled, hydrolyzed with water (10 ml), extracted with diethyl ether (4×30 ml). Organic layers were washed with water (2×10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 655 mg of crude material. 612 mg were purified by column chromatography (pentane/ether: 80/20 (v/v)) to yield a mixture of the desired cyclopropyl carboxylates (81/19 *trans*/*cis*, 301 mg, 74%) as a colorless oil. $[\alpha]_D^{20}=-25.7$ (*c* 1.43, $CHCl_3$); TLC, SiO_2: R_f 0.51 and 0.47 (pentane/ether: 0/100). |GC[2]|, program A, 6.6 and 6.7 min; ^1H NMR δ (400 MHz, $CDCl_3$) 4.30 (s, C*H*–O *cis*), 3.70 (s, OCH_3 *trans*), 3.68 (s, OCH_3 *trans*), 3.56 (d, *J*=5.2 Hz, C*H*–O *trans*), 1.72 (d, *J*=8.8 Hz, C*H*(CO_2Me) *cis*), 1.70 (d, *J*=5.2 Hz, C*H*(CO_2Me) *trans*), 1.51 (mult, *H* cyclopropane *trans*), 1.44–1.21 (br, 4CH_3 *trans*+4 CH_3 *cis*+*H* cyclopropane *trans*); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 98.1, 89.1, 82.3, 51.6, 51.3, 31.9, 31.7, 30.8, 28.9, 28.7, 28.5, 27.0, 26.7, 26.3, 26.2, 23.8, 23.6, 22.1, 20.7; IR (film, KBr) 2979, 2933, 2871, 1722, 1445, 1433, 1377, 1314, 1268, 1230, 1220, 1190, 1151, 1129, 1118, 1095, 1070, 1039, 1006, 934, 729 cm^{-1}; GC/MS *m/z* 241, 198, 181, 149, 139, 100, 84, 59. Anal. Calcd for $C_{14}H_{25}O_4$: C, 65.60; H, 9.44. Found C, 65.52; H, 9.61.

7.1.33. Synthesis of *tert*-butyl *trans*-2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate. To a well stirred solution of potassium *tert*-butoxide (1.6 mmol, 180 mg) in anhydrous THF (4 ml) was added under an atmosphere of argon, the mixture of cyclopropanes and (0.8 mmol, 204 mg) maintained at 20 °C. The mixture was then stirred for 2 h at room temperature. Water was added (5 ml) and the mixture was extracted with diethyl ether (3×30 ml), washed with water (10 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 394 mg of crude material which is purified by column chromatography (pentane/ether: 90/10) to yield the pure *tert*-butyl *trans*-2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate (222 mg, 93%) as a white solid. $[\alpha]_D^{20}=+15.3$ (*c* 0.51, $CHCl_3$); TLC, SiO_2: R_f 0.65 (pentane/ether: 90/10). |GC[2]|, program A, 8.0 min; mp 66 °C. ^1H NMR δ (400 MHz, $CDCl_3$) 3.56 (d, 1H, *J*=7.1 Hz, C*H*–O), 1.62 (d, 1H, *J*=5.8 Hz, C*H*–O). 1.46 (s, 9H, O(CH_3)$_3$), 1.43 (s, 3H, OCH_3), 1.40 (m, 1H, *H* cyclopropane), 1.33 (s, 1H, CH_3), 1.29 (s, 1H, CH_3), 1.23 (s, 1H, CH_3), 1.22 (s, 1H, CH_3), 1.21 (s, 1H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 220.4, 82.0, 31.8, 31.0, 29.6, 28.5, 28.2, 27.1, 26.3, 25.8, 23.5, 22.1, 20.6; IR (film, KBr) 2981, 2935, 2871, 1719, 1460, 1368, 1289, 1268, 1234, 1219, 1201, 1151, 1117, 1067, 1041, 1019, 1002, 917, 844, 772 cm^{-1}; GC/MS *m/z* 283 (M^+−CH_3), 242, 225, 184, 149, 139, 123, 100, 83, 59.57. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found C, 67.55; H, 10.15.

7.1.34. Synthesis of thionocarbonate from *tert*-butyl *trans*-2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate. 10% Aqueous hydrochloric acid (2 ml) was added to a solution of *tert*-butyl *trans*-2,2-dimethyl-3-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-cyclopropanecarboxylate (0.54 mmol, 166 mg) in THF (3 ml). The mixture was then stirred 4 h at room temperature and extracted with diethyl ether (4×10 ml). Organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 178 mg of crude diol as a white solid (115 °C). The diol (0.4 mmol, 81 mg) was dissolved in anhydrous diethyl ether (2 ml). Diazomethane, freshly prepared, was then added dropwise to the solution of until disappearance of the yellow color. The mixture was stirred for 1 h at 20 °C and the solvents were then removed under reduced pressure to give 98 mg of crude ester which is used directly in the next step. *N*,*N*-Dimethylaminopyridine (0.41 mmol, 50 mg) and the previous synthesized ester (0.34 mmol, 74 mg) were dissolved under an atmosphere of argon, in anhydrous dichloromethane (2 ml) maintained at 0 °C. Thiophosgene (0.82 mmol, 94 mg), diluted by 1 ml of dichloromethane, was added dropwise to the solution and the orange mixture was stirred at 0 °C for 12 h. Silicagel (2 g) was added to the solution and the solvents were removed under reduced pressure. The resulting solid was placed on a silicagel column and eluted with a mixture of pentane/ether (2/8 (v/v)) to give 69 mg of pure thionocarbonate (69 mg, 79% over three steps) as a white solid. $[\alpha]_D^{20}=+33.5$ (*c* 0.90, $CHCl_3$); TLC, SiO_2: R_f 0.40 (pentane/ether: 60/40). Mp 108 °C; ^1H NMR δ (400 MHz, $CDCl_3$) 4.10 (d, 1H, *J*=10.7 Hz, C*H*–O), 3.73 (s, 3H, OCH_3); 1.71 (m, 1H, *H* cyclopropane); 1.57 (s, 3H, CH_3); 1.50 (s, 3H, CH_3); 1.48 (d, 1H, *J*=5.6 Hz, C*H*(CO_2Me)); 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR δ (100.4 MHz, $CDCl_3$) 190.1, 170.7, 89.3, 89.0, 52.1, 30.6, 28.9, 26.3, 21.6, 21.1, 19.6; IR (film, KBr) 2989, 2963, 2932, 1733, 1465, 1385, 1326, 1299, 1275, 1251, 1221, 1196, 1180, 1113, 1003, 975, 934, 914, 865, 842, 807, 774, 735, 664 cm^{-1}; GC/MS *m/z* 127, 121, 105, 99, 91, 85, 79, 73, 67. Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.79; H, 7.02. Found C, 55.72; H, 7.13.

7.1.35. Synthesis of (1*R*) *trans*-chrysanthemate by reduction of thionocarbonate. Thionocarbonate (0.027 mmol, 69 mg) was heated for 6 h at 40 °C in the presence of diazaphospholidine (0.80 mmol, 155 mg). After cooling to room temperature, the crude mixture was purified by thin layer chromatography (pentane/ether: 90/10 (v/v)) to yield the pure methyl chrysanthemate (44 mg, 89%) as colorless liquid. $[\alpha]_D^{20}$=+19.7 (*c* 1.12, $CHCl_3$) ($[\alpha]_{D\,lit}^{20}$=+20.7 (*c* 1.1, $CHCl_3$)); TLC, SiO_2: R_f 0.80 (pentane/ether: 95/05); |GC[2]|, program A, 4.4 min; ^1H NMR δ (400 MHz, $CDCl_3$) 4.90 (d, 1H, *J*=4.8 Hz, *H* olefinic), 3.69 (s, 3H, OCH_3); 2.07 (m, 1H, *H* cyclopropane); 1.72 (s, 3H, CH_3 olefinic); 1.71 (s, 3H, CH_3 olefinic); 1.40 (d, 1H, *J*=5.4 Hz, $CH(CO_2Me)$); 1.28 (s, 3H, CH_3), 1.15 (s, 3H, CH_3); IR (film, KBr) 2952, 2926, 2881, 1730, 1440, 1411, 1379, 1322, 1285, 1235, 1198, 1165, 1142, 1117, 1083, 1065, 995, 919, 854, 782, 729 cm^{-1}. Spectral and analytical data are in agreement with the published data.[56]

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Exploring the biosynthetic potential of bimodular aromatic polyketide synthases

Yi Tang,[†] Taek Soon Lee, Ho Young Lee and Chaitan Khosla*

Departments of Chemistry and Chemical Engineering, Stanford University, Stanford, CA 943055025, USA

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Abstract—Polycyclic aromatic polyketides such as actinorhodin and tetracenomycin are synthesized from acetate equivalents by type II polyketide synthases (PKS). Their carbon chain backbones are derived from malonyl-CoA building blocks through the action of a minimal PKS module consisting of a ketosynthase, a chain length factor, an acyl carrier protein (ACP) and a malonyl-CoA/ACP transacylase. In contrast to these acetogenic polyketides, the backbones of a few aromatic polyketide natural products, such as the R1128 antibiotics, are primed by non-acetate building blocks. These polyketides are synthesized by bimodular PKSs comprising of a dedicated initiation module, which includes a ketosynthase, acyl transferase and ACP, as well as a minimal PKS module. Recently we showed that regioselectively modified polyketides could be synthesized through the genetic recombination of initiation modules and minimal PKS modules from different polyketide biosynthetic pathways (Tang et al. *PLoS Biol.* 2004, *2*, 227–238). For example, the actinorhodin and tetracenomycin minimal PKSs could accept and elongate unnatural primer units from the R1128 initiation module. In this report we provide further examples of using heterologous bimodular PKSs for the engineered biosynthesis of new aromatic polyketides. In addition to providing insights into the biosynthetic mechanisms of aromatic PKSs, our findings also highlight considerable potential for crosstalk between amino acid catabolism and aromatic polyketide biosynthesis. For example, exogenously supplied unnatural amino acids are efficiently incorporated into bioactive anthraquinone antibiotics.

1. Introduction

Polyketides are produced as secondary metabolites by many bacteria and fungi.[1] A large number of polyketide natural products are important drugs, including many antibacterial and antitumor agents. Polyketides are biosynthesized by polyketide synthases (PKSs) through repeated Claisen-like condensations between malonyl or substituted malonyl extender units.[2] PKSs can be classified into three categories (Types I, II and III) based on their biosynthetic mechanisms.[3] Type I PKSs are large, multidomain megasynthases that synthesize macrolides, such as erythromycin A and rifamycin. Catalytic domains within type I PKSs are arranged in a linear, modular fashion that resemble an assembly line.[4] Type III PKSs synthesize small aromatic metabolites such as flaviolin from free CoA thioesters directly without the use of acyl carrier proteins.[5]

Type II PKSs (also known as aromatic PKSs) are involved in the biosynthesis of polycyclic aromatic polyketides such as actinorhodin and tetracenomycin (Fig. 1).[6] In contrast to type I PKSs, catalytic components of type II PKSs are dissociated monofunctional enzymes. Genes encoding individual type II PKS enzymes are clustered on the chromosomes of different producers.[2] The organization and sequences of type II PKS genes between different actinomyces hosts are highly similar (Fig. 2). Genetic analysis of type II PKSs has revealed that each PKS consists of a minimal PKS[7] and a collection of auxiliary enzymes.[8] The minimal PKS (Fig. 2) consists of four enzymes that can synthesize a full-length poly-β-ketide chain from malonyl-CoA.[9] The ketosynthase (KS) and the chain length factor (CLF) form a heterodimer that catalyzes carbon–carbon bond formation between successive malonyl units and the growing polyketide chain, until a defined chain length is reached. An acyl-carrier protein (ACP) shuttles malonyl extender units to the active site of the KS-CLF.[10] Acyl transfer between malonyl-CoA and ACP is catalyzed by malonyl-CoA:ACP acyltransferase (MAT), which is shared between fatty acid synthases (FAS) and PKSs in a polyketide producing host cell.[11] For example, the minimal PKS of the 16-carbon actinorhodin[12] (act) PKS synthesizes an octaketide from 8 equiv. of malonyl-CoA, whereas the minimal PKS of the 20-carbon tetracenomycin[13] (tcm) PKS synthesizes a decaketide from 10 equiv. of malonyl-CoA. ACPs can be interchanged between different minimal PKSs

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* Corresponding author. Tel.: +1-650-723-6538; fax: +1-650-723-9780; e-mail address: ck@chemeng.stanford.edu
† Present address: Department of Chemical Engineering, University of California, Los Angeles, CA 90095.

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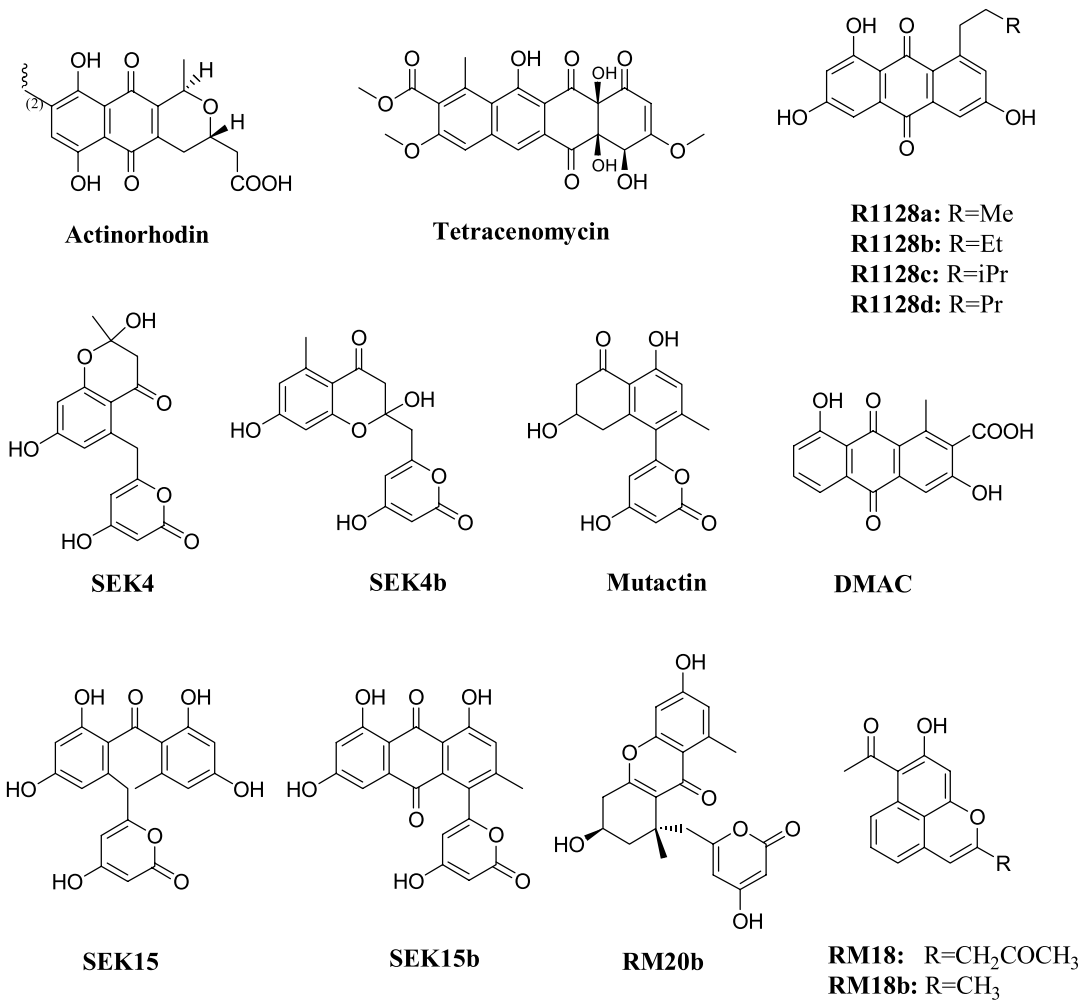


Figure 1. Examples of natural (first row) and engineered (second and third rows) aromatic polyketides.

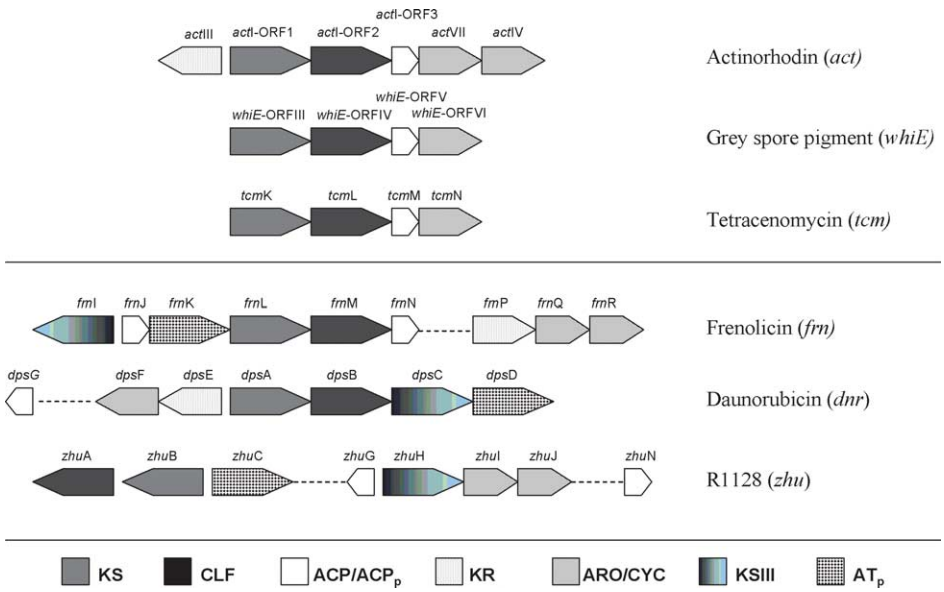


Figure 2. Gene cluster organization of various type II polyketide synthases. Top half: acetate-primed PKSs; bottom half: nonacetate-primed PKSs. The minimal PKS (KS-CLF and ACP) and auxiliary enzymes (such as CYC and KR) are found in all type II PKS clusters. In nonacetate-primed PKSs, an initiation module is also present. For the daunorubicin (dnr), frenolicin (fren) and R1128 (zhu) PKSs, the common initiation module components are homologs of ketosynthase III (KSIII) and acyltransferase (AT_p). For the fren and R1128 PKSs, a second ACP (termed ACP_p) is also present. The R1128 compounds are selective estrogen receptor antagonists (Hori et al, *J. Antibiot*. **1993**).

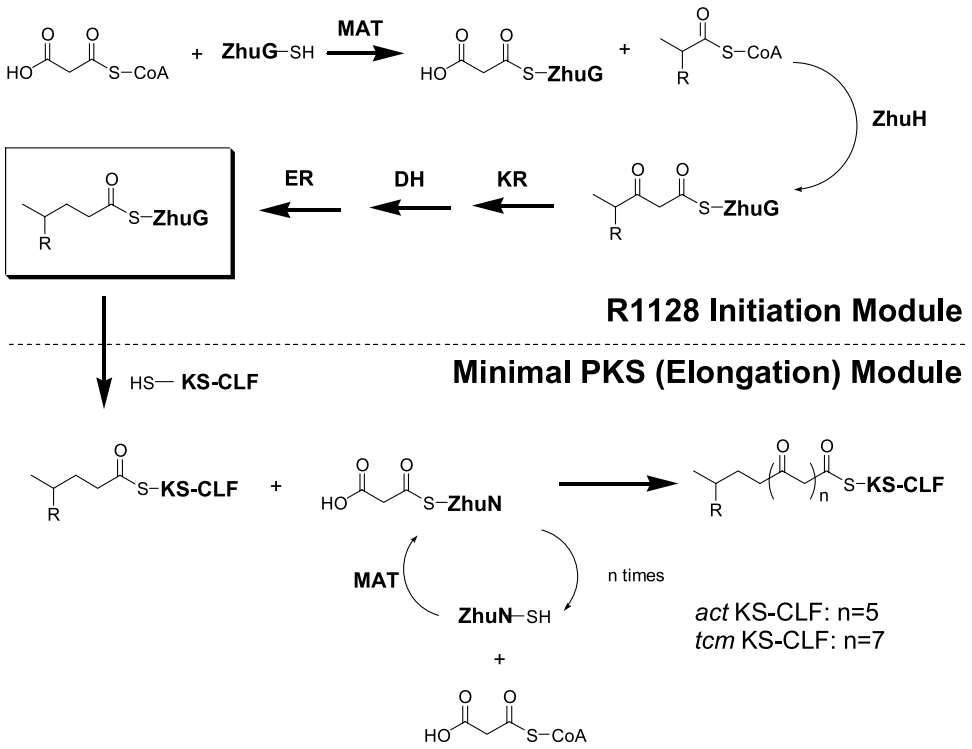


Figure 3. Mechanisms of bimodular polyketide synthases. The R1128 initiation module mechanism is shown in the top half. The final product of the initiation module is an acyl-ZhuG species. The acyl group carried by ZhuG is shuttled to the KS-CLF of the minimal PKS. The acyl-primed KS-CLF is then able to elongate the starter unit into a full length polyketide.

without affecting the overall kinetics of the KS-CLF.[14,15] In the absence of tailoring enzymes, an octaketide spontaneously rearranges to form SEK4[16] or SEK4b,[17] while a decaketide backbone is converted into either SEK15[16] or SEK15b[18] (Fig. 1).

Ketoreductases (KR), bifunctional aromatases (ARO) and cyclases (CYC) are auxiliary PKS enzymes that interact directly with a nascent polyketide. The KR from the act PKS (act III) regioselectively reduces the carbonyl moiety at C-9 of both an octaketide and a decaketide[7] (we have adopted the conventional numbering of carbon atoms in the polyketide literature, where C-1 corresponds to the carboxyl carbon attached to the enzyme). A reduced octaketide spontaneously forms mutactin, while a reduced decaketide spontaneously forms either RM20, RM20b (major product) or RM20c[7,19] (Fig. 1). The bifunctional act ARO/CYC (actVII) cyclizes and aromatizes the first ring of a C-9 reduced octaketide; subsequent second-ring cyclization catalyzed by act CYC (actIV), followed by spontaneous third-ring cyclization, and C-6 oxidation generates the anthraquinone 3,8-dihydroxy-1-methylanthraquinone-2-carboxylic acid (DMAC)[7,20] (Fig. 1). Cyclases specific for reduced or unreduced decaketides are also known.[6] Other tailoring enzymes such as oxygenases and methylases[21] are present in different PKS clusters, contributing to the diverse structures observed among aromatic polyketides.

An attractive site in the polyketide scaffold for introducing unnatural building blocks is via the primer unit.[22] Most aromatic PKSs, including the act and the tcm PKSs initiate polyketide biosynthesis with an acetyl primer unit, which arises through decarboxylation of malonyl-ACP.[23,24] A few aromatic PKSs utilize primer units other than acetate.[22] For example, daunorubicin (dnr) is primed by a propionate unit,[25] frenolicin (fren) is primed by a butyrate unit[26] and R1128 (zhu) is primed by a variety of alkyl units[27] (Fig. 1). Common to the nonacetate-primed PKSs is a dedicated PKS module responsible for chain initiation[27] (Fig. 2). The initiation module consists of a ketosynthase III (KSIII), an acyltransferase (AT_p) of unknown function, and in the fren and R1128 PKSs, an additional ACP (ACP_p). The proposed priming mechanism of the R1128 PKS is shown in Figure 3. MAT transfers a malonyl unit from malonyl-CoA to ACP_p (ZhuG) to generate malonyl-ZhuG. KSIII (ZhuH) catalyzes the condensation of a short chain electrophile (derived from acetyl-CoA, propionyl-CoA, isobutyryl-CoA or isovaleryl-CoA) to the malonyl-ZhuG derived nucleophile to yield β-ketoacyl-ZhuG.[28] Thus, primer unit specificity is determined by ZhuH, which exhibits strong preference for propionyl-CoA and isobutyryl-CoA.[28] The β-ketoacyl-ZhuG is then reduced to an alkylacyl-ZhuG by a ketoreductase (KR), dehydratase (DH), and enoylreductase (ER) associated with the FAS.[27] Finally, the alkylacyl group is transacylated from ZhuG to the active site cysteine of R1128 KS-CLF (ZhuB-ZhuA), and serves as the primer unit for further chain elongation.

Using the genetically engineered *Streptomyces coelicolor* strain CH999 as a biosynthetic host, we have shown that the R1128 initiation module can be genetically recombined with minimal PKS modules from act and tcm PKSs to produce regioselectively modified aromatic polyketides.[29] For example, when the act KS-CLF is co-expressed with the R1128 initiation module in the presence of the act KR, polyketides YT46 (**1**) and YT46b (**2**) are produced

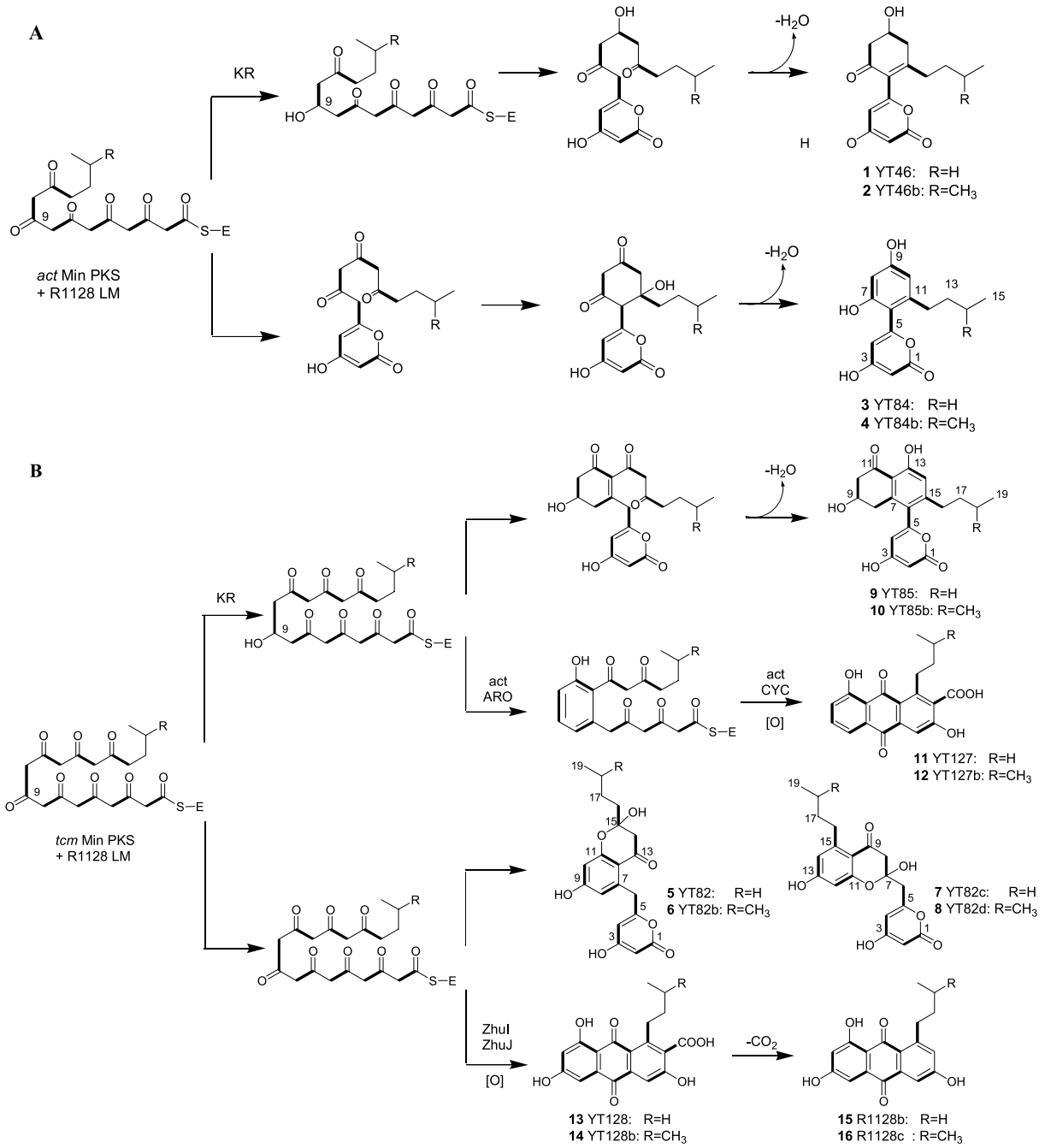


Figure 4. Novel polyketides produced by act (A) and tcm (B) minimal PKSs in the presence of the R1128 initiation module. Compounds **1**, **2**, **11**, **12**, **13**–**16** are described in the previous paper. Compounds **3**–**10** are presented in this work. ^{1}H and ^{13}C NMR data of novel compounds are presented in Tables 2 and 3.

(Fig. 4(A)). YT46 and YT46b both contain extended alkyl side chains, which are derived from propionyl-CoA and isobutyryl-CoA, respectively. Similarly, co-expression of the R1128 initiation module, the tcm KS-CLF and appropriate cyclases resulted in the biosynthesis of YT127 (**11**), YT127b (**12**), YT128 (**13**) and YT128b (**14**) (Fig. 4(B)). We were also able to reconstitute the biosynthesis of R1128b (**15**) and R1128c (**16**) using the bimodular PKSs. The engineered biosynthesis of the above compounds showed that:

(1) KS-CLFs normally primed by acetate groups through decarboxylative priming of malonyl-ACP can be efficiently primed with an alkylacyl-ACP_p in vivo. For both act and tcm KS-CLFs, the alkylacyl-primed polyketides were the major products isolated, indicating that nonacetate primer units are preferred over decarboxylative priming;

(2) KS-CLFs determine polyketide chain length by monitoring the overall number of carbons in the polyketide backbone instead of the number of extension cycles. Thus, when primed with a five-carbon starter unit, the act KS-CLF effectively becomes a hexaketide synthase, whereas the tcm KS-CLF becomes an octaketide synthase.

In this report, we further examine the biosynthetic capacity of the bimodular PKS constructs. Specifically, we studied (i)

the effects of removing downstream auxiliary enzymes on the cyclization patterns of the alkylacyl-primed polyketides; (ii) whether the R1128 initiation module can interact with the dual chain length specific frenolicin PKS;[30] and (iii) whether polyketides containing novel primer units could be realized by feeding of unnatural amino acids.

2. Results

We used the heterologous host/vector pair first described by McDaniel et al.[7] to study the biosynthesis of aromatic polyketides. The host is the aforementioned *S. coelicolor* strain CH999, which contains chromosomal deletions of the entire act gene cluster. The vectors are derived from the *E. coli*/*S. coelicolor* shuttle vector pRM5. The different vectors constructed for this study are shown in Table 1. Genes of interest are cloned under the control of the actII-ORF4 activator, which activates transcription during stationary phase of CH999 life cycle.[31] Polyketides produced by the host/vector pairs are extracted after 10 days of growth on solid R5 media and subjected to analysis by LC-MS and HPLC. Novel polyketides are purified and analyzed by proton and carbon NMR.

2.1. Biosynthesis of YT84 (3) and YT84b (4)

In the absence of the act KR, the act minimal PKS (CH999/pSEK24) produces the octaketides SEK4[16] and SEK4b.[17] The plasmid pYT84 encodes act KS-CLF, zhuN (as the ACP for the minimal PKS) and the R1128 initiation module (zhuH, zhuC and zhuG). Upon transformation of pYT84, two new compounds with masses of 294 (15 mg/L) and 308 (10 mg/L), respectively, were produced by CH999 in addition to SEK4 (10 mg/L) and SEK4b (10 mg/L). When L-valine was supplemented at 1 g/L to the growth media, the yield of the second compound (m/z=308) doubled, indicating that the compound is derived from isobutyryl-CoA, the primary catabolite of valine. Based on our previous characterization of compounds synthesized by CH999/pYT46, we expect that the first compound (m/z=294) is derived from propionyl-CoA;[29] this compound was not purified for NMR analysis. During purification of the second compound, the polyketide underwent dehydration, as observed by mass analysis on the purified compound (m/z: 290). The chemical formula of $C_{16}H_{18}O_5$ was assigned to the dehydrated compound (YT84b, **4**) and its structure was established through ^{13}C and ^{1}H NMR (Fig. 4(A), Table 2). The results of sodium [1,2-^{13}C]acetate feeding experiments were consistent with the incorporation of six acetate units in **4** (Table 2). The α-pyrone and isohexanoyl side chains were readily identified from ^{1}H NMR analysis. The connectivity between the dihydroxyphenyl and α-pyrone rings were determined with the aid of HMBC and HSQC experiments. The novel C-6/C-11 cyclization regiospecificity present in **4** is similar to that found in the compound **2**[29] and is thus generally associated with hexaketides. The parent compound (observed mass 308) is proposed to have the structure shown in Figure 4(A). Under HPLC purification conditions, this compound readily dehydrates to **4**. The bicyclic structure of **3** and **4** has not been observed in natural or engineered polyketides and illustrates the potential of using bimodular PKSs to generate completely new polyketide scaffolds.

Table 2. Proton and Carbon NMR Data for YT84b (**4**)[a]

No.[b]	^{13}C δ (ppm), (J_{cc} (Hz))	^{131}H δ (ppm) (m, area, J_{HH} (Hz))
1	169.2 (78.6)	—
2	89.7 (78.6)	5.47 (d, 1H, 2)
3	173.2 (58.1)	—
4	106.5 (58.1)	6.18 (d, 1H, 2)
5	162.4 (69.1)	—
6	112.9 (69.1)	—
7	158.2 (66.6)	—
8	101.2 (66.6)	6.22 (d, 1H, 2)
9	161.0 (64.6)	—
10	109.0 (64.6)	6.20 (d, 1H, 2)
11	145.9 (42.6)	—
12	32.6 (43.1)	2.47–2.51 (m, 2H)
13	41.8	1.32–1.40 (m, 2H)
14	29.1	1.44–1.52 (m, 1H)
15	22.8	0.86 (d, 6H, 6.5)

[a] Spectra were obtained at 500 MHz for proton and 125 MHz for carbon and were recorded in CD_3OD. 1,2-^{13}C-acetate labeling experiments were performed and the observed carbon–carbon coupling constants are shown in parenthesis.
[b] Carbons are labeled as shown in Figure 4.

2.2. Biosynthesis of YT82 series (5–8) of compounds

To investigate the cyclization patterns of an alkylacyl-primed octaketide in the absence of octaketide-specific cyclases and KR, we constructed the plasmid pYT82, which contains the genes of tcm KS/CLF, zhuN, and the R1128 initiation module. Upon transformation of this plasmid, CH999 produced four new compounds in addition to SEK15[16] (12 mg/L) and SEK15b[18] (1 mg/L). Compounds YT82 (**5**) and YT82c (**7**) eluted in the first doublet have the masses of 360 and are derived from propionyl-CoA.

Table 1. Plasmids constructions and resulting polyketide products[a]

Plasmid	Minimal PKS[b]	KR (actIII)	Aromatase, cyclase	Polyketide products	Reference
PYT46	act	+	−	**1**, **2**, Mutactin	29
PYT84	act	−	−	**3**, **4**, SEK4, SEK4b	This work
PYT82	tcm	−	−	**5**–**8**, SEK15, SEK15b	This work
PYT85	tcm	+	−	**9**, **10**, RM20, RM20b, RM20c	This work
PYT87	fren	+	−	**1**, **2**, **17**, **18**, Mutactin, etc	This work
PYT127	tcm	+	actVII, actIV	**11**, **12**, RM20, RM20b, RM20c	29
PYT128	tcm	−	ZhuI, ZhuJ	**13**–**16**, SEK15, SEK 15b	29

[a] The *Streptonmyces coelicolor* strain CH999 is used as the host for polyketide biosynthesis. Each plamid is derived from pRM5. Each construct contains genes for the minimal PKS, cyclases and the R1128 initiation module, which consists of zhuG, zhuH and zhuC. Products are analyzed by LC/MS and NMR.
[b] The minimal PKS consists of the indicated KS-CLF, ZhuN and the endogenous MAT.

Table 3. Proton NMR data for YT82 (**5**), YT82b (**6**), YT82d (**8**), YT85 (**9**) and YT85b (**10**); carbon NMR data for YT82b (**6**) and YT85b (**10**)[a]

	YT82 (**5**)	YT82b (**6**)		YT82d (**8**)	YT85 (**9**)	YT85b (**10**)	
No.[b]	^{1}H δ (ppm) (m, area, J_{HH} (Hz))	^{13}C δ (ppm)	^{1}H δ (ppm) (m, area, J_{HH} (Hz))	^{1}H δ (ppm) (m, area, J_{HH} (Hz))	^{1}H δ (ppm) (m, area, J_{HH} (Hz))	^{13}C δ (ppm)	^{1}H δ (ppm) (m, area, J_{HH} (Hz))
1	—	164.1	—	—	—	164.6	—
2	5.29 (d, 1H, 2)	88.5	5.29 (d, 1H, 2)	5.26 (d, 1H, 2)	5.51 (d, 1H, 2)	89.5	5.51 (d, 1H, 2)
3	—	174.3	—	—	—	173.0	—
4	5.70 (d, 1H, 2)	104.5	5.70 (d, 1H, 2)	6.14 (d, 1H, 2)	6.22 (d, 1H, 2)	107.1	6.23 (d, 1H, 2)
5	—	168.7	—	—	—	161.7	—
6	4.14 (d, 1H, 16.4) 4.23 (d, 1H, 16.4)	39.4	4.14 (d, 1H, 16.4) 4.23 (d, 1H, 16.4)	3.04 (d, 1H, 14) 3.11 (d, 1H, 14)	—	125.6	—
7	—	140.1	—	—	—	143.0	—
8	6.39 (d, 1H, 2.4)	114.8	6.39 (d, 1H, 2.4)	2.74 (d, 1H, 16) 3.03 (d, 1H, 16)	2.72 (dd, 1H, 16.0, 7) 2.94 (dd, 1H, 17.0, 3.5)	36.2	2.72 (dd, 1H, 16.0, 7) 2.94 (dd, 1H, 17.0, 3.5)
9	—	165.2	—	—	4.29–2.35 (m, 1H)	66.5	4.29–2.35 (m, 1H)
10	6.32 (d, 1H, 2.4)	103.5	6.32 (d, 1H, 2.4)	—	2.84 (dd, 1H, 17, 6.5) 3.07 (dd, 1H, 16.5, 3.5)	47.0	2.84 (dd, 1H, 17, 6.5) 3.07 (dd, 1H, 16.5, 3.5)
11	—	167.4	—	—	—	204.7	—
12	—	113.0	—	6.33 (d, 1H, 2.4)	—	116.1	—
13	—	193.8	—	—	—	168.1	—
14	2.88 (d, 1H, 16) 2.60 (d, 1H, 16)	49.5	2.88 (d, 1H, 16) 2.60 (d, 1H, 16)	6.27 (d, 1H, 2.4)	6.77 (s, 1H)	117.2	6.77 (s, 1H)
15	—	102.4	—	—	—	153.2	—
16	1.82–1.91 (m, 2H)	39.7	1.81–1.92 (m, 2H)	2.92–3.0 (m, 2H)	2.40–2.47 (m, 2H)	41.5	2.48–2.56 (m, 2H)
17	1.42–1.50 (m, 2H)	29.4	1.34–1.41 (m, 2H)	1.30–1.40 (m, 2H)	1.50–1.57 (m, 2H)	29.2	1.39–1.46 (m, 2H)
18	1.36–1.42 (m, 2H)	33.6	1.53–1.61 (m, 1H)	1.54–1.66 (m, 1H)	1.28–1.35 (m, 2H)	33.4	1.49–1.58 (m, 1H)
19	0.96 (t, 3H, 7)	22.9	0.94 (d, 6H, 6.4)	0.93 (dd, 6H, 6.8, 2)	0.88 (t, 3H, 7)	22.7	0.87 (d, 6H, 6.8)

[a] Spectra were obtained at 500 MHz for proton and 125 MHz for carbon and were recorded in CD_3OD except for YT82d (**8**), which was recorded in acetone-d_6.
[b] Carbons are labeled as shown in Figure 4.

Compounds YT82b (**6**) and YT82d (**8**) eluted in the second doublet have the masses of 374 and are derived from isobutyryl-CoA, as confirmed through L-valine feeding experiments. The combined titers of **5**–**8** is ~ 20 mg/L. ^{1}H and ^{13}C NMR spectroscopy (Table 3) confirmed that **5** and **6** are alkyl-primed analogs of the unreduced octaketide SEK4, while proton NMR showed that **7** and **8** are alkyl-primed analogs of SEK4b. SEK4 and SEK4b are synthesized at similar titers by strains harboring the act minimal PKS. This result shows that cyclization regiospecificity of an alkyl-primed octaketide remains unchanged as compared to an acetate-primed octaketide, regardless of the PKS used to make the products.

2.3. Biosynthesis of YT85 (9) and YT85b (10)

From the above analysis for a unreduced alkyl-octaketide, a C-9 reduced alkyl-octaketide should cyclize to give the alkyl-primed analog of mutactin, a product of the act minimal PKS outfitted with KR. The plasmid pYT85 was constructed to test this hypothesis. The tcm KS-CLF gene cassette was moved from pYT82 to pYT46 to yield pYT85. CH999/pYT85 produced two major compounds in addition to RM20, RM20b and RM20c (combined yield ~20 mg/L), which are reduced decaketides primed with acetate units. The two new compounds YT85 (**9**, 20 mg/L) and YT85b (**10**, 20 mg/L) have masses of 344 and 358, respectively, which correspond to mass increases of 42 (3 CH_2) and 56 (4 CH_2) from that of mutactin (m/z=302). Both ^{1}H and ^{13}C NMR spectra (Table 3) were nearly identical to those of mutactin, except for the benzylic protons (at C-16) and the appearance of alkyl protons/carbons in **9** and **10**. The dehydrated analogs of both compounds, which result from non-enzymatic dehydration of **9** and **10**, are also found using LC-MS, consistent with the detection of dehydromutactin from mutactin producing hosts (CH999/pSEK21).[18]

2.4. Biosynthesis of YT87 (17) and YT87b (18)

The fren KS-CLF has been shown to produce both octaketides and nonaketides.[30] In the presence of act KR, the minimal fren PKS synthesizes mutactin, RM18 and RM18b (Fig. 1). Mutactin and RM18 are an octaketide and nonaketide, respectively, both reduced at the C-9 position. RM18b is an octaketide reduced at C-7. The relaxed substrate specificity of the act KR in the presence of fren KS-CLF has been attributed to a 'slippage' mechanism, in which the octaketide substrate can be oriented in two conformations in the KS-CLF active site.[30]

Unlike the act and tcm PKSs, the fren PKS from *Streptomyces roseofulvus* is equipped with an endogenous initiation module.[26] The proteins FrenJ, FrenK and FrenI are close homologs of ZhuG, ZhuC and ZhuH, respectively. Combined with the FAS KR, DH and ER, the fren initiation module synthesizes butyryl-FrenJ as the primer unit, which is incorporated into the scaffold of frenolicin. However, *S. roseofulvus* synthesizes nanaomycin, the acetate-primed version of frenolicin as the dominant product.[32] Thus the fren KS-CLF appears to be more efficient at acetate priming compared to alkylacyl priming. To examine the chain initiation properties of the fren KS-CLF in a heterologous host, we construct the vector pYT87, which encodes KR, fren KS-CLF, ZhuN, and the R1128 initiation module. The

polyketide products of CH999/pYT87 were extracted and analyzed as above.

As expected from the relaxed chain-length specificity of the fren KS-CLF, the HPLC trace of the crude extract showed a complex product distribution. A majority of compounds are produced at levels lower than 1 mg/L, of which mutactin, RM18, RM18b, **1** and **2** were identified based on LC-MS analysis in comparison with authentic reference standards. Two major compounds (7 mg/L each) with masses of 276 (YT87, **17**) and 290 (YT87b, **18**) were observed in the extracts and were analyzed further. The levels of **18** increased significantly upon L-valine feeding. The structure of **18** is shown in Figure 5. From the ^{1}H NMR, it is apparent that this compound is indeed primed with an isohexanoyl unit. In addition, the common α-pyrone moiety observed in YT46/b, YT82/b/c/d, YT84/b and YT85/b is absent in **18**. Protons at C-14 were assigned to the multiplet at δ=2.85 using COSY, which is indicative of its connectivity to an aromatic ring (as seen in YT84). The 1H singlet at δ=6.63 (assigned to the proton at C-12) resembles the single proton at C-14 in **10**. The 3H singlet at δ=2.51 is assigned to an acetyl group at one terminus of the polyketide, which can arise from decarboxylation at C-1 (also seen in RM20 and RM18), and is consistent with the absence of the pyrone moiety. A proposed mechanism for the biosynthesis **18** is shown in Figure 5. **18** is derived from an alkylacyl-primed heptaketide with 17 backbone carbons in the nascent polyketide. Analogous to that observed in RM18b,[30] the C-7 carbonyl in **18** is reduced instead of the C-9 carbonyl. The C-5/C-10 cyclization must therefore take place rapidly before a possible O-1/C-5 cyclization that forms the α-pyrone. The second cyclization takes place between C-4 and C-13, and is followed by dehydration of the second ring and the subsequent decarboxylation at C-1.

The biosynthesis of **17** and **18** at appreciable amounts by CH999/pYT87 further proves that heterologous minimal PKSs and initiation modules can be combined to generate new polyketide scaffolds. We have now shown that alkyl-primed hexaketide, heptaketides and octaketides can be synthesized from octaketide-, nonaketide- and decaketide-synthases, respectively. The accumulation of **17** and **18** by this strain also shows that the fren KS-CLF favors chain initiation by an alternative primer unit over acetate-ACP in *S. coelicolor*. The low titers of frenolicin produced by *S. roseofulvus* may be attributed to low expression levels of the fren initiation module, high intracellular concentration

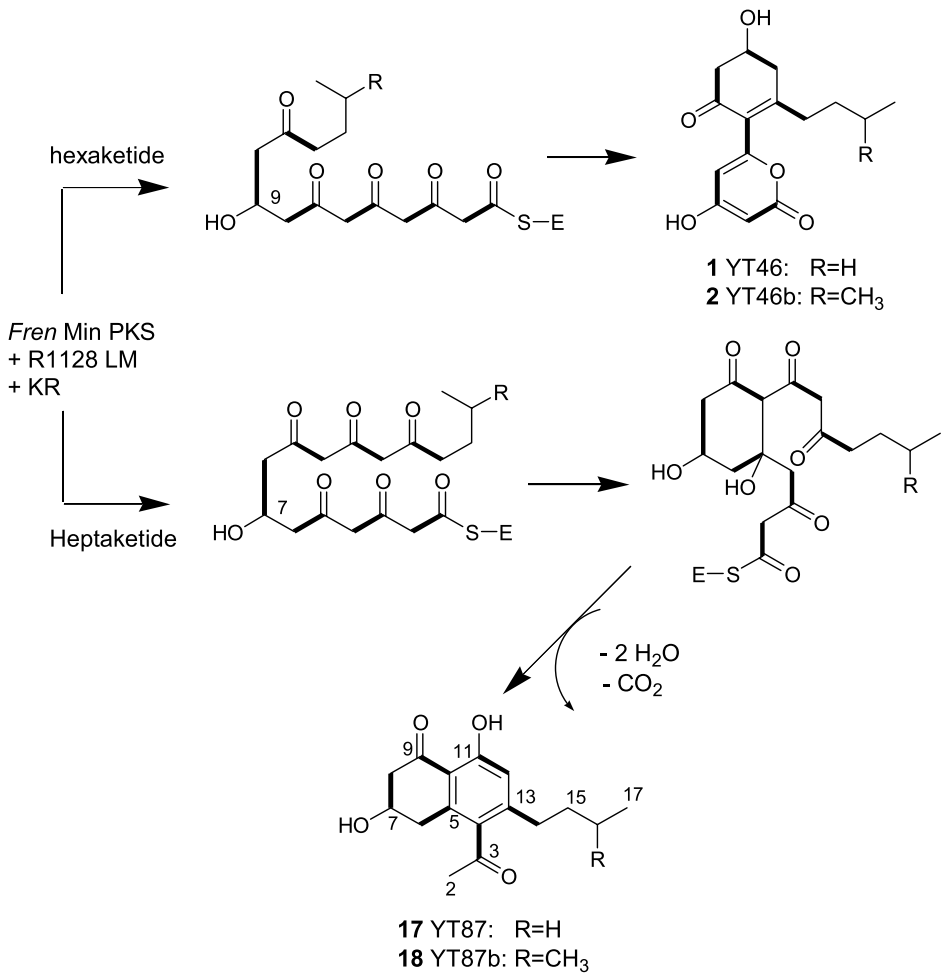
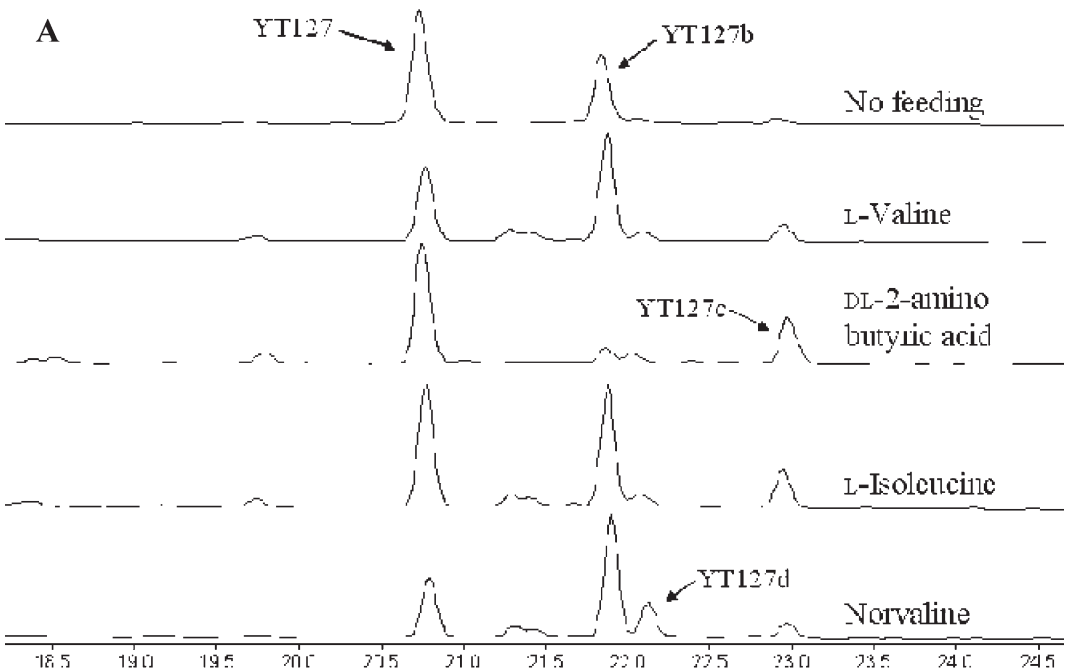


Figure 5. Novel polyketides produced by fren minimal PKS in the presence of the R1128 initiation module. When presented with the alkylacyl-ZhuG, the fren minimal PKS is able to synthesize the alkyl-heptaketides YT87(**17**) and YT87b(**18**). YT87/b are reduced at C-7 instead C-9. ^{1}H and ^{13}C NMR data for YT87b is shown in Table 4. The fren minimal PKS is also able to synthesize YT46 and YT46b, although at much lower titers (<1 mg/L).



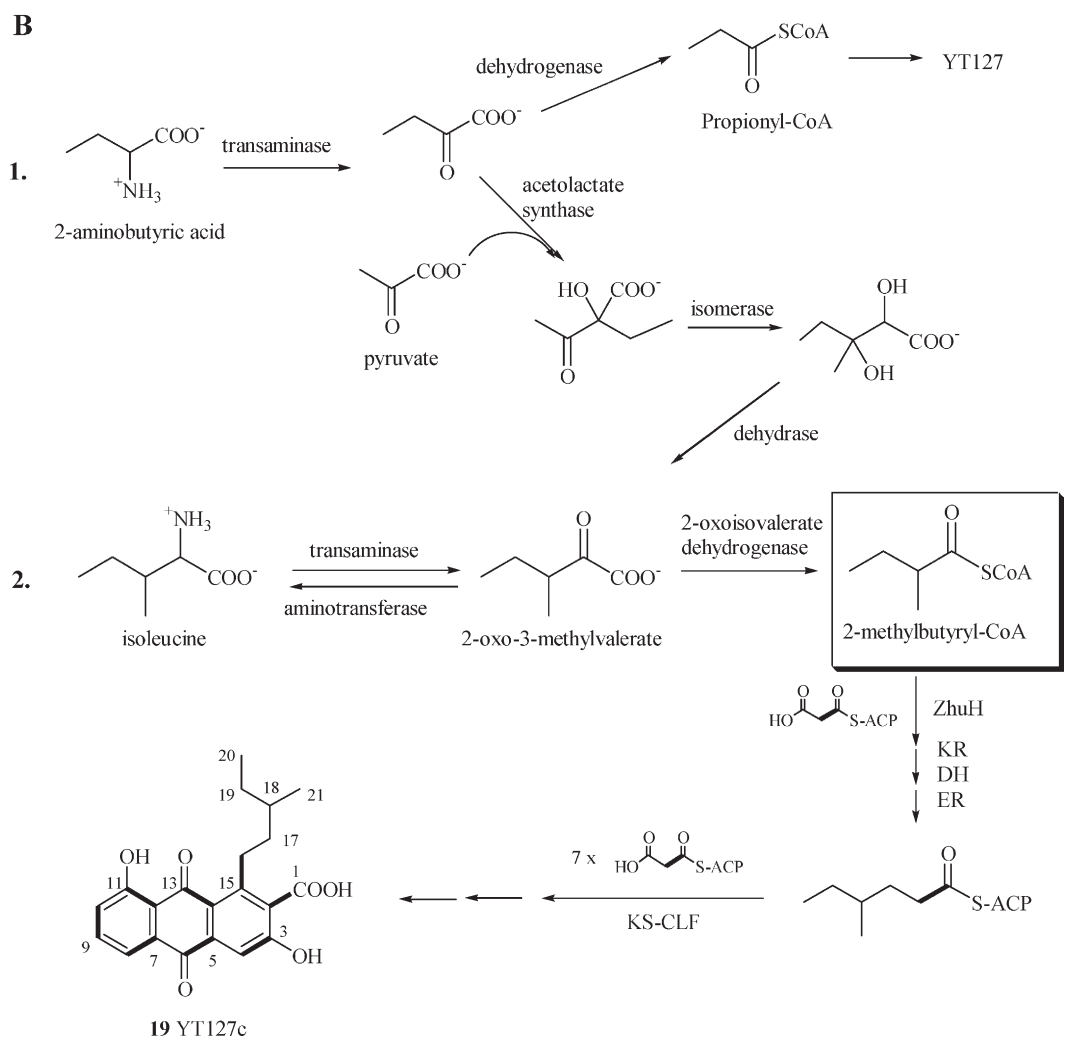


Figure 6. New YT127 derivatives synthesized through unnatural amino acid feeding of CH999/pYT127. (A) All amino acids are fed at 1 g/L. YT127c (**19**) is biosynthesized when DL-2-aminobutyric acid (2-AB) is supplemented. Supplementation of norvaline resulted in accumulation of YT127d. (B) Possible mechanisms of 2-AB utilization.

of acetyl-FrenN (fren minimal ACP) or other host-dependent factors. We could not detect any alkyl-primed heptaketides that are reduced at C-9, or any alkyl-primed hexaketide that is reduced at C-7. These compounds may be synthesized at much lower levels by CH999/pYT87.

2.5. Biosynthesis of new YT127 analogs through unnatural amino acid feeding

Short chain acyl-CoA substrates utilized by the R1128 initiation module are derived mainly through the catabolism of amino acids (Fig. 6(B)).[33] The amino acid is first converted into the α-ketoacid by branched-chain amino acid transaminase. The α-ketoacid is then decarboxylated by acyl-CoA dehydrogenase (AcdH) to yield the corresponding acyl-CoA.[33] The intracellular concentration of this acyl-CoA may thus be elevated by feeding *S. coelicolor* the corresponding amino acid. Furthermore, novel biosynthetic precursors for the R1128 initiation module may be introduced via feeding of nonproteinogenic amino acids, given the catabolic enzymes can recognize the unnatural substrates. We fed several natural and unnatural amino acids to the growth media of strain CH999/pYT127 and screened for the biosynthesis of YT127 analogs via HPLC and LC-MS (Fig. 6(A)).

Table 4. Proton and carbon NMR data for YT87b (**18**)[a]

No.[b]	^{13}C δ (ppm)	^{1}H δ (ppm) (m, area, J_{HH} (Hz))
1	—	—
2	30.1	2.47 (s, 3H)
3	198.9	—
4	132.1	—
5	145.6	—
6	40.1	2.60 (dd, 1H, 16.5, 8) 2.82 (dd, 1H, 16, 3.5)
7	66.7	4.22–4.24 (m, 1H)
8	50.3	2.90 (dd, 1H, 16, 7.5) 3.15 (dd, 1H, 16, 3.5)
9	207.9	—
10	124.1	—
11	159.0	—
12	114.8	6.63 (s, 1H)
13	147.5	—
14	41.5	2.82–2.89 (m, 2H)
15	30.7	1.31–1.38 (m, 2H)
16	32.8	1.60–1.65 (m, 1H)
17, 17′	22.7	0.92 (d, 6H, 6.5)

[a] Spectra were obtained at 500 MHz for proton and 125 MHz for carbon and were recorded in CD_3OD.
[b] Carbons are labeled as shown in Figure 5.

Without supplementation of any amino acid, propionate-derived **11** (*m*/*z*=340) and isobutyryl-derived **12** (*m*/*z*=354) are the only anthraquinones produced by CH999/pYT127 at detectable levels. As expected, the level of **12** doubled and the level of **11** decreased when L-valine (1 g/L) is included in the growth media. Upon feeding 1 g/L of the unnatural amino acid DL-2-aminobutyric acid (2-AB), the opposite change in product distribution was observed: level of **11** was elevated while level of **12** was significantly decreased. This is consistent with the conversion of 2-AB into propionyl-CoA through the amino acid catabolic pathway. Unexpectedly, a third anthraquinone (YT127c, **19**) was biosynthesized at appreciable levels by this host. The mass (*m*/*z*=368) of the compound indicated incorporation of one additional methylene unit in the primer unit of **19** compared to that of **12**. NMR (^{1}H, ^{13}C and COSY, Table 5) analysis of purified **19** revealed that the compound is derived from 2-methylbutyryl-CoA, a primary catabolite of isoleucine. Feeding L-isoleucine (1 g/L) to the same strain also increased the titers of **19**. When norvaline was added to the growth media, the amount of the corresponding anthraquinone, YT127d, was significantly higher. Mass analysis confirmed that YT127d (*m*/*z*=354) is derived from butyryl-CoA (which is converted to hexanoyl-ZhuG). Amino acid feeding experiments were also performed with CH999/pYT46 and CH999/pYT85. New analogs of **1** and **9** were detected using LC-MS upon 2-AB and norvaline supplementation.

Table 5. Proton and carbon NMR data for YT127c (**19**)[a]

No.[b]	^{13}C δ (ppm)	^{1}H δ (ppm) (m, J_{HH} (Hz), area)
1	174.3	—
2	134.3	—
3	161.7	—
4	113.8	7.49 (s, 1H)
5	137.8	—
6	184.2	—
7	135.4	—
8	119.3	7.59 (dd, 10, 2, 1H)
9	136.5	7.53 (t, 10, 1H)
10	125.4	7.16 (dd, 10, 2, 1H)
11	163.5	—
12	123.8	—
13	191.2	—
14	118.6	—
15	149.2	—
16	38.6	3.27–3.42 (m, 2H)
17	30.5	1.54–1.72 (m, 2H)
18	31.4	1.47–1.53 (m, 1H)
19	36.9	1.12–1.28 (m, 2H)
20	11.9	0.85 (t, 9, 3H)
21	19.5	0.93 (d, 9, 3H)

[a] Spectra were obtained at 500 MHz for proton and 125 MHz for carbon and were recorded in CD_3OD.
[b] Carbons are labeled as shown in Figure 6(B).

The formation of **19** upon 2-AB supplementation is surprising. The first catabolite of 2-AB, 2-oxobutanoate, can be directly converted to propionyl-CoA, which leads to the higher titers of **11** as observed. The other likely catabolic fate of 2-oxobutanoate is being channeled through the isoleucine biosynthetic pathway (Fig. 6(B)). Sequential transformations catalyzed by acetolactate synthase, ketol-acid reductoisomerase and dihydroxyacid dehydratase result in the formation of 2-oxo-3-methylvalerate, which can be subsequently converted into 2-methylbutyryl-CoA by 2-oxoisovalerate dehydrogenase. Alternatively, increased amounts of 2-oxo-3-methylvalerate, which is an immediate biosynthetic precursor of isoleucine, may possibly activate isoleucine catabolic enzymes and lead to further accumulation of 2-methylbutyryl-CoA in vivo.

The low titers of **19** and YT127d produced by CH999/pYT127 in the presence of the corresponding amino acids are consistent with the substrate specificities of ZhuH determined in vitro: the k_{cat}/K_m value of ZhuH towards butyryl-CoA is 5-fold lower compared to those of propionyl-CoA and isobutyryl-CoA.[28] Supplementation of leucine did not result in the formation of the isovaleryl-CoA

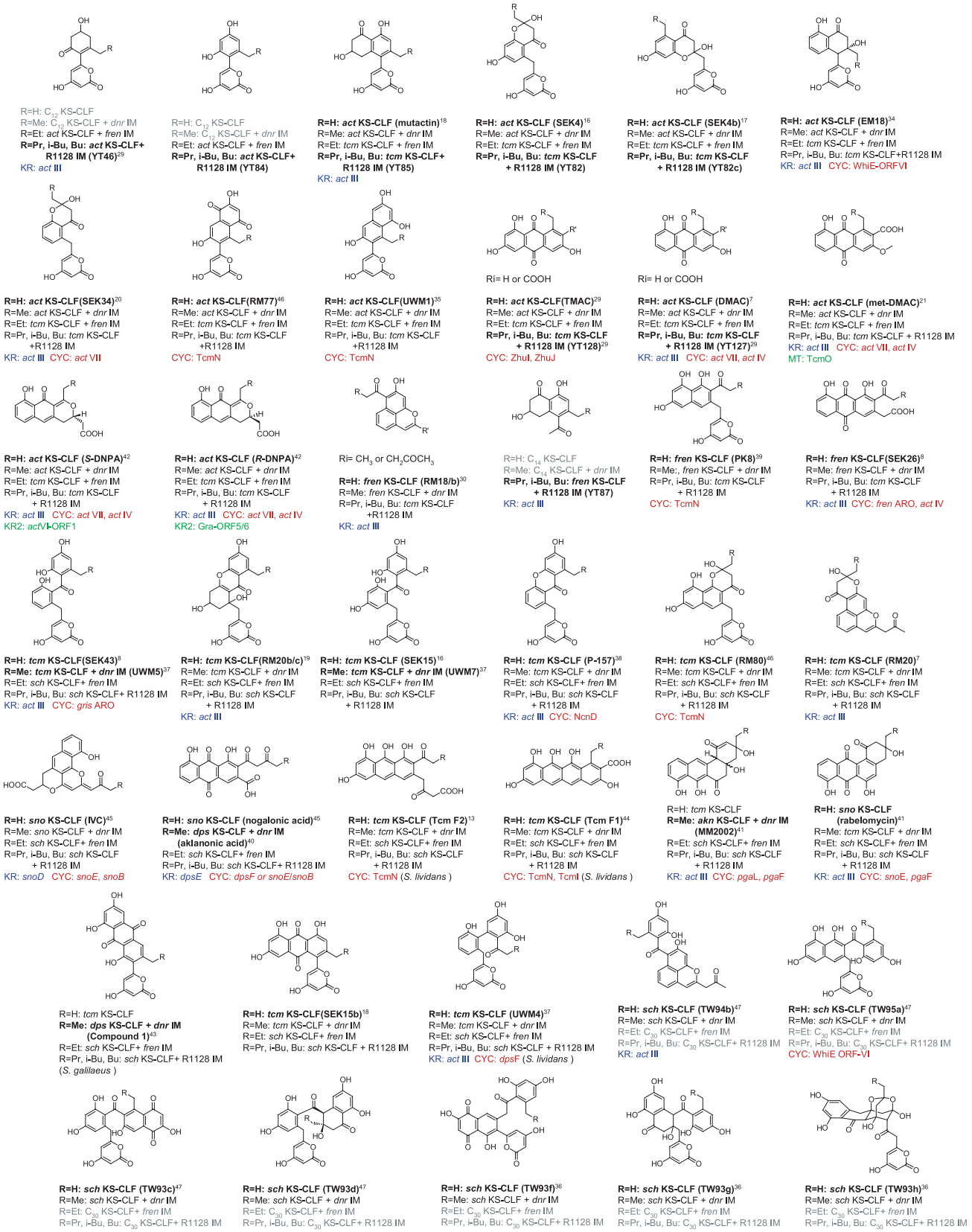


Figure 7. Genetically combining initiation modules (IM), minimal PKSs, KR and cyclases allows access to numerous scaffolds with varying primer unit chain length (acetate to hexanoate/isohexanoate). Shown in bold are compounds that have been reported (with name in parenthesis). Shown in plain text are the predicted combinations. Shown in grey are KS-CLFs that have not been identified (C_{12}, C_{14} and C_{30} PKSs). KR requirements are shown in blue and cyclase requirements are shown in red. Other enzymes such as methyltransferases (MT) and additional KRs are shown in green.

primed YT127 analog (within our detection limits), presumably due to the 40-fold decrease in the catalytic efficiencies of ZhuH towards isovaleryl-CoA compared to that of propionyl-CoA.[28] Supplementation of the growth media with unnatural amino acids such as allylglycine, propargylglycine and 2-amino-3-fluorobutyric acid did not lead to the biosynthesis of YT127 analogs. The failure of incorporating the more unusual starter units may be due to substrate intolerance of catabolic enzymes, ZhuH and/or KS-CLF. Further understanding of the substrate specificities of these three classes of enzymes could lead to the biosynthesis of more diverse set of polyketide analogs.

3. Discussion

In this report we have presented further evidence for using genetically recombined initiation modules and elongation modules towards biosynthesis of regioselectively modified aromatic polyketides. We showed that (1) in the absence of tailoring enzymes, alkylacyl-primed (reduced) octaketides synthesized by decaketide synthases cyclize with exactly the same regioselectivity as an acetate-primed (reduced) octaketide synthesized by an octaketide synthase. (2) In addition to octaketide synthases (act) and decaketide synthases (tcm), a nonaketide synthase such as that from the fren PKS can also be primed with an alkylacyl starter unit and becomes an alkylacyl-primed heptaketide synthase; and (3) although limited by the substrate specificity of the initiation module selectivity filter KSIII, supplementing the growth media of engineered strains with unnatural amino acids can lead to the biosynthesis of novel alkylacyl polyketides.

During the past decade, we and others have derived a set of programming rules for the type II PKSs.[8,13,21,34–45] The programming rules specify the carbon chain length of the polyketide, degree and location (C-7 or C-9) of ketoreduction, and cyclization regioselectivity based on the combination of KS-CLF, KR and cyclases. Many engineered polyketide scaffolds can be predicatively biosynthesized using these empirical rules. Together with another recent study from our laboratory,[29] this work further expands these rules to include primer unit choice. A comprehensive list of accessible polyketide scaffolds is shown in Figure 7. In each scaffold, the primer unit can be an acetate (R=H), propionate ($R=CH_3$), butyrate ($R=CH_2CH_3$) or between three to four carbons in length ($R=CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH_2(CH_2)_2CH_3$). Combined with the appropriate ketoreductase and cyclases, a specific pair of initiation and minimal PKS module can be expected to generate the polyketide scaffold with a primer unit of choice. One or more compounds in each scaffold has been characterized, and is shown in bold along with the associated names. For example, a pentanoate ($R=CH_2CH_2CH_3$) primed version of RM80[46] (a C9/C14 cyclized decaketide) can be biosynthesized from a dodecaketide synthase such as the sch KS-CLF from *Streptomyces halstedii* spore pigment PKS,[47] combined with the R1128 initiation module and TcmN.

Some of the KS-CLFs shown in Figure 7 are currently not accessible in the type II PKS family. For example, in order to make an acetate primed versions of **3** (a reduced alkyl hexaketide) or **17** (a reduced alkyl heptaketide), a C_{12}^- or C_{14}- specific KS-CLF is required. Furthermore, in order to access an alkylacyl (R=C3–C4) primed TW93c (a dodecaketide),[47] a C_{30}- specific KS-CLF combined with the R1128 initiation module is necessary. These novel chain-length specific KS-CLF enzymes can either be discovered from new PKS clusters, or by engineering existing KS-CLFs. We have previously demonstrated the use of rational mutagenesis to inter-convert between an octaketide and a decaketide synthase.[47] The same approach may potentially be applied to generate a hexaketide synthase or a C_{30} specific synthase.

The polyketide library proposed in Figure 7 is limited to the exploitation of only the daunorubicin, frenolicin and R1128 initiation modules. The library could potentially be expanded through the use of other initiation modules, such as the oxytetracycline (otc) initiation module[48] which produces a malonamate starter unit and the enterocin (enc) initiation module,[5,49] which produces a benzoate starter unit. Malonamate primed version of SEK4 and SEK4b have been generated from *Streptomyces rimosus* by deleting the cyclase genes associated with oxytetracycline biosynthesis,[50] suggesting that the initiation module can be potentially combined with other type II PKS genes to generate novel compounds. At this time, the exact mechanism of the malonamate unit formation has remains unresolved. Benzoate primed versions of mutactin (Wailupemycin D) has also been generated by Moore and co-workers,[5] although the chain length specificity of the enc KS-CLF remains unknown (no acetate primed polyketide produced by the enc KS-CLF has been reported).

The full extent of aromatic polyketide structural diversity is of course significantly greater than that shown in Figure 7. Other tailoring enzymes such as oxidoreductases, cyclases, methylases, oxygenases and glycosyl transferases can further transform and decorate the nascent polyketide into more complex structures.[51] In most cases these tailoring enzymes are unlikely to be affected by the presence of a foreign primer unit. If so, it should be possible to generate analogs of many medicinally important polyketides such as daunorubicin and tetracycline by co-expressing the desired KS-CLF/initiation module pair in the presence of the full set of tailoring enzymes.

4. Experimental

4.1. Bacterial strains and general methods for DNA manipulation

S. coelicolor strain CH999 was used as the host for transformation by shuttle vectors. Protoplast preparation and PEG-assisted transformation were performed as described by Hopwood et al.[52] All cloning steps were performed in *E. coli* strain XL-1 Blue. PCR was performed using the pfuTurbo polymerase (Strategene). Unmethylated DNA was obtained by using the methylase deficient strain GM2163 (New England Biolabs). Amino acids were

purchased from Sigma and all other chemicals were from standard sources.

4.2. Construction of plasmids

The R1128 initiation module was constructed as a XbaI/EcoRI cassette as described in our previous paper.[29] The 2.8 kb cassette contains genes arranged in the following order: ZhuC, ZhuN, ZhuG and ZhuH. The initiation module cassette was transferred to pSEK24 and pSEK33 to yield pYT84 and pYT82, respectively. The 2.5 kb PacI/XbaI fragment containing the tcm KS-CLF was transferred from pYT82 to pYT46 (which containing the act KR upstream of PacI) to yield pYT85. The 2.5 kb PacI/XbaI fragment containing the fren KS-CLF was transferred from pSEK22 to pYT46 to yield pYT87. The construction of pYT127 was described previously. All shuttle plasmids were transformed into *E. coli* strain GM2163 by electroporation. Unmethylated plasmids recovered from GM strain were used to transform *S. coelicolor* strain CH999.

4.3. Culture conditions, extraction and small scale analysis

The strains were grown on R5 plates containing 50 mg/L thiostrepton at 30 °C for 7~10 days. Amino acids were fed at 1 g/L in feeding experiments. For LC/MS and analytic HPLC analysis, one plate was chopped into fine pieces and extracted with 30 mL of ethyl acetate (EA)/methanol/acetic acid (89:10:1). The solvent was removed in vacuo and the residue was redissolved in 1 mL of methanol. The polyketide products were separated and detected by analytical reverse phase HPLC using a diode array detector at 280 and 410 nm (Alltech Econosphere C18 column (50 mm×4.6 mm); linear gradient: 10% acetonitrile (ACN) in water (0.1% TFA) to 60% ACN in water (0.1% TFA) over 30 min; 1 mL/min). HPLC retention times (t_R, minutes): **3**: 11.2; **4**: 12.4, **5**: 17.4; **6**: 17.6; **7**: 19.2; **8**: 19.4; **9**: 19.6; **10**: 20.8; **17**: 16.2; **18**: 18.4; **19**: 25.9. LC/MS was performed at the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University using a ThermoFinnigan quadrupole ion trap LC-MS system and electrospray ionization (both positive and negative ionization).

4.4. Large scale production and isolation

Sufficient number of R5 plates (20–60 plates, depending on the yield of the product) streaked with the desired CH999 strains were grown at 30 °C for one week. The plates were chopped into fine pieces and extracted with a minimum of 1 L of EA/methanol/acetic acid (89:10:1). The organic solvents were removed and the residuals were dissolved in 5 mL of methanol. The solution was filtered and fractioned with normal phase silica gel. Fractions containing the desired compounds were combined, concentrated and injected into a preparative reversed-phase HPLC column (250×22.5 mm C-18 column, Alltech Econosil). An 10–40% ACN in water (0.1% TFA) gradient (50 min, 5 mL/min) was used to separate the polyketide products except for **3** and **4**, for which a 0–20% gradient was used. Fractions containing the desired polyketides were combined and concentrated in vacuo. The residuals were redissolved in acetone and applied to a preparative TLC plate (20 cm×20 cm, 0.25 mm E. Merck silica gel plates (60F-254)). The desired bands were excised from the TLC plates and stirred in EA/methanol (10 mL, 9:1) for 2 h. The compounds were eluted from silica using the same solvent and dried in vacuo.

4.5. NMR and MS characterization of novel compounds

NMR spectra were recorded on Varian Inova 500 or Mercury 400 instruments and calibrated using residual undeuterated solvent as an internal reference. ^{1}H and ^{13}C NMR spectra data are shown in Tables 2–5.

Acknowledgements

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Hydrophobic polymer-supported scandium catalyst for carbon–carbon bond-forming reactions in water

Shinya Iimura, Kei Manabe and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—It has been revealed that a hydrophobic polymer-supported scandium(III) catalyst prepared from sulfonated polystyrene resin is an effective catalyst for carbon–carbon bond-forming reactions such as Mukaiyama aldol reactions in water. According to studies on loading levels of scandium, hydrophobicity of the catalyst is a key for the efficient catalysis. The scandium catalyst was successfully recovered and reused. Several ketones instead of aldehydes were also used as substrates in the aldol reactions. Some 1,4-addition reactions also occurred using the scandium catalyst in water.

1. Introduction

Due to the increasing importance of green chemistry in organic synthesis, development of more efficient and environmentally friendly processes for chemical transformations is desired.[1] One of the ideal methodologies is the development of organic reactions using highly active, reusable solid catalysts in water.[2,3] Although use of amphiphilic polymer-supported catalysts has received much attention, we have recently found that a hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H) is an effective catalyst for several organic reactions such as formation of esters, hydrolysis of thioesters, and Mannich-type reactions in water.[4] In addition, as a result of continuous studies on the loading levels and the structures of the catalyst, it is suggested that hydrophobicity of the catalyst is a key for efficient catalysis in water.[5] We then envisaged that hydrophobic polymer-supported Lewis acids would also work effectively in water. While some solid-supported Lewis acids which work well in aqueous media have been reported so far,[2] there are still limitations in the types of reactions and substrates. It is strongly required to develop more effective, solid-supported Lewis acid catalysts for organic transformations in water. Here, we report that a novel hydrophobic polystyrene-supported scandium(III) is a powerful catalyst for carbon–carbon bond-forming reactions in pure water.

2. Results and discussion

The aldol-type reactions of silicon enolates with carbonyl compounds (Mukaiyama aldol reactions) have been recognized as one of the most important tools for carbon–carbon bond formation that afford synthetically useful β-hydroxy carbonyl compounds.[6] Thus, we performed the reaction of benzaldehyde with the thioketene silyl acetal (1.5 equiv.) derived from ethyl 2-methylthiopropionate in water. First, we tested PS-SO_3H, a polymer-supported Brønsted acid prepared by sulfonation of DVB cross-linked polystyrene with a loading level of 0.21 mmol/g (Table 1, entry 1). It was found that the desired product was obtained in a low yield due to rapid hydrolysis of the silicon enolate. Then, we tested polymer-supported Lewis acids. Among the Lewis acids, we focused on scandium(III) because we have already revealed that it is a water-compatible, strong Lewis acid.[7] While several solid-supported scandium(III) catalysts have been used for aldol reactions in water,[2a,i,j] wide substrate generality has not been demonstrated. Moreover, in the previous example of the same combination of substrates,[2a] an excess amount (3.6 equiv.) of the thioketene silyl acetal was required to obtain the desired adduct in high yield. Thus, we decided to develop a more effective polymer-supported scandium. A hydrophobic catalyst, PS-Sc **1**, was readily prepared from hydrophobic PS-SO_3H, and ICP analysis verified that 0.16 mmol/g of Sc was present in the catalyst. It was exciting to find that the reaction proceeded smoothly to give the β-hydroxy thioester in excellent yield when PS-Sc **1** was used as a catalyst (entry 6). Next, we carried out the reaction with other Lewis acids to compare the catalytic activities. $Sc(O_3SOC_{12}H_{25})_3$,[8] which we previously developed as a Lewis acid-surfactant-combined catalyst, gave the aldol product in 75% yield (entry 2). It is

Keywords: Lewis acid; Scandium; Aldol reaction; 1,4-Addition; Water.
* Corresponding author. Tel.: +81-3-5841-4790; fax: +81-3-5684-0634; e-mail address: skobayas@mol.f.u-tokyo.ac.jp

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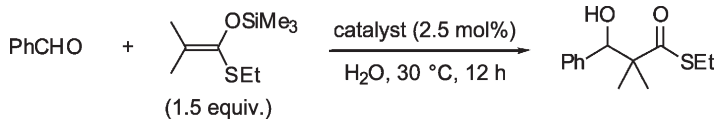
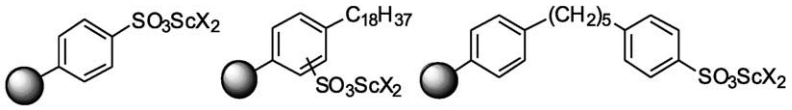
Table 1. Mukaiyama aldol reaction in water with various catalysts



Entry	Catalyst	Loading (mmol/g)[a]	Yield (%)
1	PS-SO_3H	0.21 (S)	35
2	$Sc(O_3SOC_{12}H_{25})_3$	—	75
3	$Sc(OTf)_3$	—	0
4[b]	PS-Sc	0.64 (Sc)	0
5[b]	PS-Yb	0.80 (Yb)	0
6	PS-Sc **1**	0.16 (Sc)	97 (97)[c]
7	PS-Sc **1**	0.67 (Sc)	16[c]
8	PS-Sc **2**	0.11 (Sc)	37[c]
9	PS-Sc **3**	0.11 (Sc)	21[c]

[a] The value is of the element shown in the parenthesis.
[b] Commercially available polymer-supported Lewis acid catalysts.
[c] The catalyst (1 mol%).

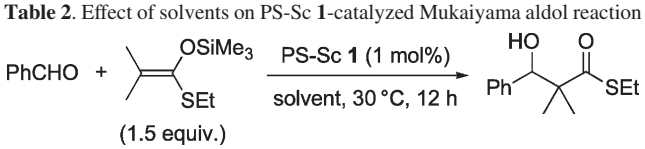


PS-Sc **1** PS-Sc **2** PS-Sc **3**

noteworthy that hydrophobic PS-Sc **1** is superior to the surfactant-type catalyst ($Sc(O_3SOC_{12}H_{25})_3$), which has been one of the best catalysts for Mukaiyama aldol reactions in water. Furthermore, only 1 mol% of the catalyst is enough to complete the reaction (entry 6). On the other hand, $Sc(OTf)_3$ and commercially available polymer-supported Lewis acid catalysts (PS-Sc and PS-Yb)[9] did not catalyze the reaction at all in every case (entries 3–5). While PS-Sc **1** did not seem to swell, these commercially available polymer-supported Lewis acids swelled significantly in water, suggesting that the hydrophobicity of the polymer-supported catalysts is a key to exhibit high activity in water. The reaction did not proceed at all in the presence of the cross-linked polystyrene which is the parent polymer of PS-Sc **1**, revealing the critical role of the scandium. We also investigated the effects of the loading levels and the polymer structures on catalytic activity (entry 7–9). It was revealed that the lower loading PS-Sc **1** (entry 6) gave better results.

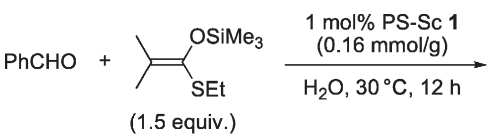
Next, we examined the effect of solvents in the PS-Sc **1**-catalyzed Mukaiyama aldol reaction (Table 2). Interestingly, it turned out that PS-Sc **1** worked well only in water (entry 6). This unique solvent effect might be mainly attributed to the following two factors: (1) hydrophobic interactions in water to concentrate the catalyst and the substrates; (2) hydration of the Sc(III) ion and counteranion by water molecules lead to dissociation of the catalyst to form a highly Lewis acidic species.[8]

Table 2. Effect of solvents on PS-Sc **1**-catalyzed Mukaiyama aldol reaction

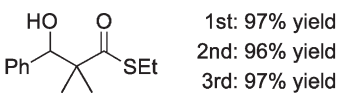


Entry	Solvent	Yield (%)
1	Neat	10
2	CH_2Cl_2	Trace
3	MeOH	9
4	THF	0
5	THF/H_2O (9/1)	23
6	H_2O	97

We then examined reusability of PS-Sc **1**, and it was found that the catalyst was easily recovered and reused without any loss of catalytic activity (Eq. 1).

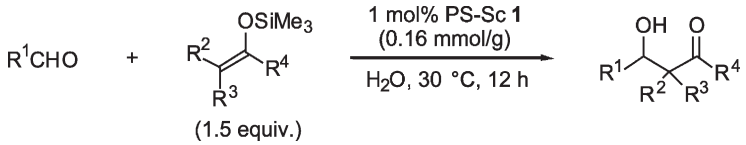


(1)



Various substrates were successfully used in the present PS-Sc **1**-catalyzed Mukaiyama aldol reactions as shown in Table 3. As for aldehydes, aromatic as well as α,β-unsaturated, and aliphatic aldehydes worked well to give the corresponding β-hydroxy thioesters in good to excellent yields (entries 1–8). While *p*-chlorobenzaldehyde is solid (mp 47–50 °C), it also reacted smoothly in water. In addition, it was revealed that silicon enolates derived from not only a thioester but also an ester and ketones reacted smoothly to afford the corresponding aldol adducts in good yields (entries 9–11). It should be noted that highly water-sensitive silicon enolates were successfully used in water under these conditions. These results suggest that a hydrophobic environment created by the catalyst in water suppresses the hydrolysis of water-sensitive silicon enolates but accelerates the desired reactions. To the best of our knowledge, there are no examples of reusable solid catalysts, which catalyze Mukaiyama aldol reactions in

Table 3. PS-Sc **1**-catalyzed Mukaiyama aldol reaction in water

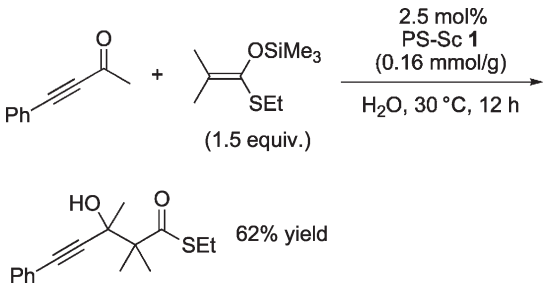


Entry	R^1	R^2	R^3	R^4	Yield (%)
1	Ph	Me	Me	SEt	97
2	4-$MeOC_6H_4$	Me	Me	SEt	96
3	4-ClC_6H_4	Me	Me	SEt	88
4	2-HOC_6H_4	Me	Me	SEt	91[a]
5	(*E*)-PhCH=CH	Me	Me	SEt	95
6	$Ph(CH_2)_2$	Me	Me	SEt	93
7[b]	*n*-C_5H_{11}	Me	Me	SEt	84
8[b]	*c*-C_6H_{11}	Me	Me	SEt	78
9[c]	Ph	Me	Me	OMe	81
10[d]	Ph	Me	H	Ph	89[e]
11[d]	Ph	H	$-(CH_2)_4-$		85[f]

[a] Yield of the cyclized, six-membered lactone which was obtained after purification.
[b] The aldehyde was slowly added to the reaction mixture over 8 h, and then the whole was stirred for 16 h.
[c] At 0 °C. The sillicon enolate was slowly added to the reaction mixture over 8 h, and then the whole was stirred for 16 h.
[d] The catalyst (2.5 mol%).
[e] *syn*/*anti*=54/46.
[f] *syn*/*anti*=68/32.

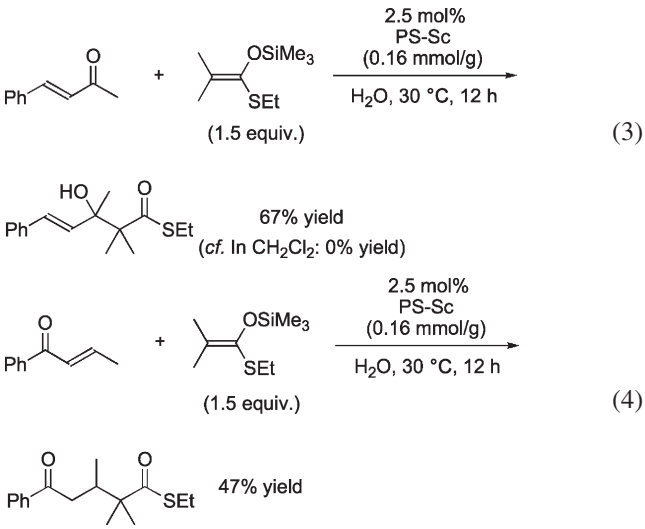
water with wide substrate generality. This reaction system would provide an ideal Mukaiyama aldol reaction with respect to efficiency and environmental friendliness for chemical transformations.

The wide substrate generality mentioned above encouraged us to investigate catalytic Mukaiyama aldol reactions of ketones in water. This type of reactions has not been reported previously. As results, it was found that the reaction of an alkynyl ketone with the thioketene silyl acetal proceeded in good yield using the present catalytic system (Eq. 2), although the yield was 36% in the case of simple acetophenone under the same conditions.



(2)

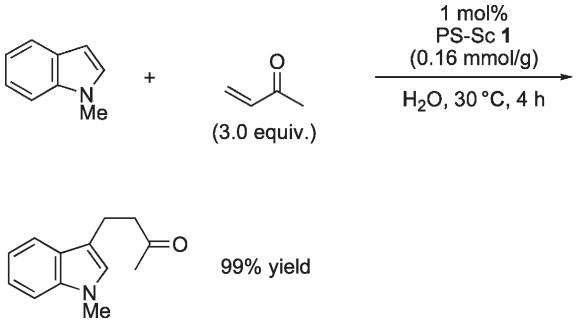
Furthermore, the reaction of benzalacetone gave the desired 1,2-adduct (Eq. 3). This result is remarkable, not only because the aldol reaction with the ketone proceeded smoothly but also because the 1,2-adduct was obtained without the 1,4-adduct.[10] This regioselectivity is contrary to that of $Sc(OTf)_3$-catalyzed reaction performed in organic solvents where the corresponding 1,4-adduct was obtained as the sole product.[11] On the other hand, the corresponding 1,4-adduct was obtained in 47% yield without the 1,2-adduct when phenyl 1-propenyl ketone was used as a substrate (Eq. 4). While the yield was still unsatisfactory, this is the first example of Mukaiyama–Michael reaction[12] in water. Although the origin of this unique regioselectivity is not clear at this stage, these results suggest that both 1,2- and 1,4-adducts could be obtained by simply switching the reaction systems.[13]



(3)

(4)

Finally, Michael addition of an indole in water using this catalytic system was carried out (Eq. 5).[14] It was found that the reaction proceeded smoothly in the presence of only 1 mol% of the catalyst to give the product in excellent yield.



(5)

In summary, we have developed a novel hydrophobic

polystyrene-supported scandium catalyst for carbon–carbon bond-forming reactions in water. This work will not only expand our concept related to hydrophobic Brønsted acid catalysts but also provide new possibilities for organic reactions in water. Detailed mechanistic studies of the unique regioselective reaction in Mukaiyama–Michael reaction in water and application of the concept of hydrophobic polymer-supported catalysts to other Lewis acid catalysis are now in progress.

3. Experimental

3.1. General

Melting points were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-610 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-LA300 or JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (δ=0) was used as an internal standard for ^1H NMR and $CDCl_3$ (δ=77.0) for ^{13}C NMR. Mass spectra (MS) were measured with a JEOL JMS-MS700V or Burker BIO TOF-II spectrometer. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography (TLC) was carried out using Wakogel B-5F. Distilled water was used as a solvent for aqueous reactions. Polystyrene resin (1% DVB cross-linked) was purchased from Advanced ChemTech Co., Inc. All other reagents were purified based on standard procedures unless otherwise noted. Starting materials are commercially available or were synthesized by the reported procedure. The structures of the known compounds were confirmed by comparison with published data.

3.2. Preparation of polymer-supported sulfonic acid catalysts

Various types of polystyrene-supported sulfonic acid catalysts (PS-SO_3H, ALPS-SO_3H, PS-spacer-SO_3H) were prepared according to the our previous report.[5a]

3.3. Preparation of polymer-supported scandium catalyst

To a suspension of hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H **1**, 0.20 mmol/g, 2.00 g, 0.41 mmol) in THF/H_2O (3/1, 25 mL) was slowly added 1 N aq. NaOH (2.0 mL, 2.00 mmol) at rt, and stirred for 24 h at the temperature. The resin was collected on a glass filter, rinsed with water, water/THF, THF, and dichloromethane, and dried in vacuo to give the sodium salt of PS-SO_3H. Scandium triflate was immobilized into the resin in the following step. $Sc(OTf)_3$ (536 mg, 1.01 mmol) was added to a suspension of PS-SO_3Na (1.82 g, ca. 0.37 mmol) in THF (35 mL) at rt. After being stirred for 72 h at the same temperature, the resin was collected on a glass filter, rinsed with water, water/THF, THF, and dichloromethane, and dried in vacuo to give the hydrophobic polymer-supported scandium catalysts (PS-Sc). From a result of ICP analysis (found: Sc, 0.74%; Na, 0.01%), the scandium content was estimated as 0.16 mmol/g. PS-Sc **1** with another loading level was similarly prepared by changing the loading of the starting PS-SO_3H (1.55 mmol/g). PS-Sc **2** was also similarly prepared from ALPS-SO_3H (0.37 mmol/g). PS-Sc **3** was also similarly prepared from PS-spacer-SO_3H (0.57 mmol/g).

3.4. A typical experimental procedure for PS-Sc-catalyzed Mukaiyama aldol reactions in water (Table 1, entry 6)

Benzaldehyde (26.5 mg, 0.25 mmol) and the thioketene silyl acetal (76.4 mg, 0.374 mmol) derived from ethyl 2-methylthiopropionate were successively added to a mixture of PS-Sc (0.16 mmol/g, 38.8 mg, 0.0064 mmol) in degassed water (1.5 mL) at 30 °C. The reaction mixture was stirred for 12 h at the same temperature. The polymer was filtered and washed with water and ethyl acetate. After extraction with ethyl acetate, the organic layer was dried over anhydrous Na_2SO_4, and evaporated. The mixture was purified by preparative TLC on silica gel to give the desired product (57.8 mg, 97%).

3.4.1. Ethyl 3-hydroxy-2,2-dimethyl-3-phenylthiopropionate.[15] Colorless oil; ^1H NMR ($CDCl_3$) δ 1.12 (3H, s), 1.22 (3H, s), 1.26 (3H, t, J=7.4 Hz), 2.89 (2H, q, J=7.4 Hz), 2.96 (1H, br s), 4.94 (1H, s), 7.27–7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.0, 23.3, 23.7, 54.3, 78.9, 127.78, 127.80, 139.9, 208.0.

3.4.2. *S*-Ethyl 3-hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropanethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.09 (3H, s), 1.20 (3H, s), 1.25 (3H, t, J=7.4 Hz), 2.88 (2H, q, J=7.4 Hz), 2.94 (1H, br d, J=3.7 Hz), 3.79 (3H, s), 6.81–6.88 (2H, m), 7.20–7.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 18.9, 23.3, 23.6, 54.5, 55.2, 78.5, 113.1, 128.8, 132.0, 159.1, 208.0; IR (neat) 3502, 2974, 1670, 1512, 1248, 1038, 945 cm^{-1}; MS (ESI-TOF) m/z 291 (M^++Na). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 62.40; H, 7.50.

3.4.3. *S*-Ethyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.11 (3H, s), 1.19 (3H, s), 1.25 (3H, t, J=7.4 Hz), 2.88 (2H, q, J=7.4 Hz), 3.10 (1H, br s), 4.90 (1H, s), 7.20–7.31 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.1, 23.3, 23.4, 54.2, 78.2, 127.9, 129.1, 133.5, 138.4, 207.9.

3.4.4. 4-Hydroxy-3,3-dimethyl-2-chromanone.[16] Colorless needles. Mp 101.6–101.9 °C; ^1H NMR ($CDCl_3$) δ 1.19 (3H, s), 1.39 (3H, s), 2.16 (1H, br s), 4.49 (1H, s), 7.06 (5H, d, J=7.7 Hz), 7.14–7.20 (1H, m), 7.31–7.39 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.7, 22.5, 43.5, 74.0, 116.6, 124.4, 124.7, 127.9, 130.2, 150.5, 172.7.

3.4.5. (*E*)-*S*-Ethyl 3-hydroxy-2,2-dimethyl-5-phenylpent-4-enethioate. Colorless oil; ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, J=7.5 Hz), 1.27 (3H, s), 1.30 (3H, s), 2.72 (1H, d, J=5.4 Hz), 2.88 (2H, q, J=7.4 Hz), 4.38–4.43 (1H, m), 6.19 (1H, dd, J=15.9, 7.1 Hz), 6.63 (1H, d, J=15.8 Hz), 7.22–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.2, 23.2, 54.0, 78.1, 126.6, 127.3, 127.8, 128.6, 132.9, 136.6, 207.4; IR (neat) 3485, 2972, 2931, 1668, 1462, 945 cm^{-1}; MS (FAB) m/z 265 (M^++1). Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.62. Found: C, 68.13; H, 7.63.

3.4.6. *S*-Ethyl 3-hydroxy-2,2-dimethyl-5-phenylpentanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, s), 1.225 (3H, s), 1.231 (3H, t, J=7.5 Hz), 1.56–1.67 (1H, m), 1.73–1.81 (1H, m), 2.50 (1H, d, J=6.6 Hz), 2.59–2.68 (1H, m), 2.85 (2H, q, J=7.4 Hz), 2.90–2.98 (1H, m), 3.67 (1H, ddd, J=10.6, 6.7, 2.0 Hz), 7.16–7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.9, 22.7, 23.1, 32.9, 33.7, 54.1, 76.6, 125.9, 128.4, 128.5, 142.0, 207.8; IR (neat) 3492, 2974, 1672, 1456, 1076, 937 cm^{-1}; MS (FAB) *m/z* 267 (M^++1). Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.37; H, 8.27.

3.4.7. *S*-Ethyl 3-hydroxy-2,2-dimethyloctanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J=6.8 Hz), 1.21–1.35 (15H, m), 1.40–1.47 (1H, m), 1.54–1.63 (1H, m), 2.27 (1H, d, J=6.6 Hz), 2.86 (2H, q, J=7.5 Hz), 3.62–3.68 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.5, 20.9, 22.5, 22.6, 23.1, 26.4, 31.7, 31.8, 54.2, 77.2, 207.8; IR (neat) 3477, 2929, 1672, 1464, 939 cm^{-1}; MS (FAB) *m/z* 233 (M^++1). Anal. Calcd for $C_{12}H_{24}O_2S$: C, 62.02; H, 10.41. Found: C, 61.75; H, 10.26.

3.4.8. *S*-Ethyl 3-cyclohexyl-3-hydroxy-2,2-dimethylpropanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.11–1.71 (20H, m), 2.84 (2H, d, J=7.3 Hz), 2.85 (1H, br s), 3.40 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.7, 23.0, 24.1, 26.2, 26.3, 26.7, 27.4, 32.1, 40.4, 53.2, 82.6, 208.6; IR (neat) 3465, 2933, 2852, 1674, 1450, 943 cm^{-1}; MS (FAB) *m/z* 245 (M^++1). Anal. Calcd for $C_{13}H_{24}O_2S$: C, 63.89; H, 9.90. Found: C, 63.70; H, 9.99.

3.4.9. Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate.[17] Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, s), 1.15 (3H, s), 3.05 (1H, br s), 3.73 (3H, s), 4.90 (1H, s), 7.27–7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 23.1, 47.8, 52.2, 78.8, 127.4, 127.7, 127.8, 140.0, 178.3.

3.4.10. 3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one.[18] Colorless oil; (*syn*/*anti*=54/46): ^{1}H NMR ($CDCl_3$) δ 1.06 (1.38H, d, J=7.1 Hz), 1.19 (1.62H, d, J=7.1 Hz), 3.03 (0.46H, br s), 3.64–3.75 (1.08H, m), 3.83 (0.46H, quint, J=7.3 Hz), 4.99 (0.46H, br d, J=8.1 Hz), 5.23 (0.54H, br d, J=3.1 Hz), 7.23–7.62 (8H, m), 7.90–7.99 (2H, m); ^{13}C NMR ($CDCl_3$) δ 11.2, 15.7, 47.1, 48.0, 73.1, 76.8, 126.0, 126.7, 127.3, 127.9, 128.2, 128.45, 128.48, 128.54, 128.6, 128.8, 128.9, 133.3, 133.6, 135.7, 136.8, 141.8, 142.2, 204.9, 205.7.

3.4.11. 2-(Hydroxy(phenyl)methyl)cyclohexanone.[18] Colorless crystals; (*syn*/*anti*=68/32): ^{1}H NMR ($CDCl_3$) δ 1.23–1.38 (0.32H, m), 1.43–1.89 (4.68H, m), 2.01–2.14 (1H, m), 2.31–2.68 (3H, m), 3.02 (0.68H, br s), 3.98 (0.32H, br s), 4.78 (0.32H, d, J=8.8 Hz), 5.39 (0.68H, m), 7.21–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 24.7, 24.9, 26.0, 27.8, 28.0, 30.9, 42.7, 57.2, 57.5, 70.6, 74.8, 125.8, 126.98, 127.03, 127.9, 128.2, 128.4, 141.0, 141.5, 214.8, 215.6.

3.4.12. *S*-Ethyl 3-hydroxy-2,2-dimethyl-3-phenylbutanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, s), 1.22 (3H, s), 1.22 (3H, t, J=7.3 Hz), 1.61 (3H, s), 2.84 (2H, q, J=7.3 Hz), 4.57 (1H, br s), 7.19–7.35 (3H, m), 7.42–7.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.8, 21.9, 23.5, 25.0, 56.1, 77.8, 126.9, 127.3, 127.4, 143.4, 210.9; IR (neat) 3481, 2976, 2933, 1641, 1450, 1375, 962, 704 cm^{-1}; MS (FAB) *m/z* 253 (M^++1). Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.65; H, 7.97.

3.4.13. *S*-Ethyl 3-hydroxy-2,2,3-trimethyl-5-phenylpent-4-ynethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ1.24 (3H, t, J=7.4 Hz), 1.39 (3H, s), 1.51 (3H, s), 1.53 (3H, s), 2.79–2.97 (2H, m), 4.50 (1H, br s), 7.25–7.43 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 20.9, 22.1, 23.5, 24.8, 56.2, 72.9, 83.9, 91.2, 122.7, 128.2, 128.3, 131.7, 209.8; IR (neat) 3469, 2978, 2933, 1645, 1387, 960 cm^{-1}; MS (FAB) *m/z* 277 (M^++1). Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.27; H, 7.44.

3.4.14. *S*-Ethyl 2,2,3-trimethyl-5-oxo-5-phenylpentanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d, J=6.3 Hz), 1.18–1.27 (9H, m), 2.62–2.75 (2H, m), 2.87 (2H, q, J=7.4 Hz), 3.02 (1H, br d, J=14.6 Hz), 7.42–7.59 (3H, m), 7.91–7.98 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.6, 14.9, 21.2, 23.1, 23.5, 36.8, 41.4, 52.7, 128.2, 128.6, 133.0, 137.1, 199.5, 206.8; IR (neat) 2972, 1680, 1450, 1292, 957 cm^{-1}; MS (FAB) *m/z* 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 68.93; H, 8.13.

3.4.15. (*E*)-*S*-Ethyl 3-hydroxy-2,2,3-trimethyl-5-phenylpent-4-enethioate. Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, J=7.3 Hz), 1.34 (9H, s), 2.73–2.88 (2H, m), 4.09 (1H, br s), 6.29 (1H, d, J=15.9 Hz), 6.66 (1H, d, J=15.9 Hz), 7.18–7.39 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.4, 23.4, 23.7, 56.1, 76.4, 126.5, 127.4, 128.5, 129.4, 132.4, 137.1, 210.1; IR (neat) 3486, 2973, 1642, 961 cm^{-1}; MS (FAB) *m/z* 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 69.09; H, 8.12.

3.4.16. *S*-Ethyl 2,2-dimethyl-5-oxo-3-phenylhexanethioate. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, s), 1.19 (3H, s), 1.23 (3H, t, J=7.3 Hz), 1.98 (3H, s), 2.68 (1H, dd, J=16.3, 3.6 Hz), 2.84 (2H, q, J=7.3 Hz), 3.01 (1H, dd, J=16.3, 11.2 Hz), 3.64 (1H, dd, J=11.2, 3.6 Hz), 7.17–7.29 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.5, 20.5, 23.3, 25.6, 30.2, 44.8, 48.2, 52.7, 127.0, 128.0, 129.6, 139.2, 206.6, 206.8; IR (neat) 2972, 1718, 1668, 1456, 1360, 958 cm^{-1}; MS (FAB) *m/z* 279 (M^++1). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.02; H, 7.96. Found: C, 68.73; H, 7.96.

3.4.17. 4-(1-Methyl-1*H*-indol-3-yl)butan-2-one. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.12 (3H, s), 2.82 (2H, t, J=7.3 Hz), 3.03 (2H, t, J=7.3 Hz) 3.71 (3H, s), 6.83 (1H, s), 7.07–7.12 (1H, m), 7.19–7.28 (2H, m), 7.6 (1H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.2, 30.0, 32.5, 44.3, 109.2, 113.6, 118.69, 118.73, 121.6, 126.3, 127.5, 137.0, 208.7; IR (neat) 3055, 2925, 1714, 1475, 1159, 741 cm^{-1}; MS (FAB) *m/z* 202 (M^++1). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.54; H, 7.72; N, 6.96.

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The preparation and alkylation of a butanedione-derived chiral glycine equivalent and its use for the synthesis of α-amino acids and α,α-disubstituted amino acids

Christopher I. Harding, Darren J. Dixon and Steven V. Ley*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

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Dedicated to Dieter Seebach with congratulations on receipt of the 2003 Tetrahedron Prize

Abstract—A benzyloxycarbonyl protected glycine equivalent **2** has been prepared in enantiopure form and has been used in the synthesis of both α-substituted amino acids and α,α-disubstituted amino acids. The process involved deprotonation to form the corresponding enolates which underwent stereoselective alkylation with various electrophiles and upon hydrolysis gave the corresponding amino acid derivatives as enantiomerically pure products.

1. Introduction

Owing to the importance of α-amino acids in organic synthesis, innumerable methods for their preparation have been developed over the years.[1] However, based on extensive knowledge of metal enolate formation as well as the diversity of electrophiles available to quench the anions, chiral glycine anion equivalents form the basis of one of the more commonly used synthetic procedures to α-amino acids.[2] Whilst many chiral glycine equivalents are reported, in terms of practicality, molecular weight, atom economy, solubility and reactivity, issues remain that still need to be addressed for their general use in synthesis programmes. In addition, the ability of a chiral glycine equivalent to deliver amino acids with useful *N*-protection as well as allowing access to α,α-diaminoacids in enantiopure form still remains a challenge.

Our group has been interested in the synthesis of various chiral building blocks, and recently we developed a butane diacetal protected (BDA) glycolic acid derivative **1** that was used in the preparation of α-hydroxy acids.[3] This auxiliary was utilised in a range of reactions, including alkylation,[3a] aldol[3b,c] and Michael reactions[4] which generally proceeded in excellent yields and with high diastereoselectivity. Compound **1** has also been used as the starting point for the synthesis of the natural product Herbarumin II (Fig. 1).[3e,5]

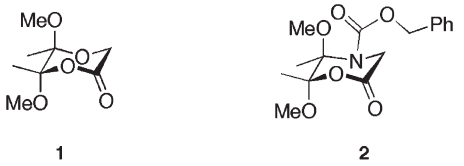

Figure 1.

In a logical extension of this glycolate chemistry and in the hope of addressing some of the important issues related to amino acid synthesis, we have recently reported benzyloxycarbonyl (*Z*)-protected glycine equivalent **2** and its use in the synthesis of α-amino acid derivates.[6] Here we report in detail on the preparation of **2** in enantiopure form, and discuss its use in the synthesis of a range of mono- and α,α-di-substituted amino acids.

2. Results and discussion

Our favoured route to compound **2** begins from (*S*)-glycidol **3**, this is commercially available in enantiomerically pure form and was readily converted to the (*S*)-amino alcohol **4** in 54% yield over three straightforward steps. A Mitsunobu reaction with phthalimide mediated by di-*tert*-butyl azidodicarboxylate (DTBAD) and triphenylphosphine[7] installed the required nitrogen atom. Subsequent treatment of **5** with aqueous hydrobromic acid facilitated *N*-deprotection and epoxide ring opening and gave salt **6**.[8] This was then

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* Corresponding author. Tel.: +44-1223-336402; fax: +44-1223-336442; e-mail address: svl1000@cam.ac.uk

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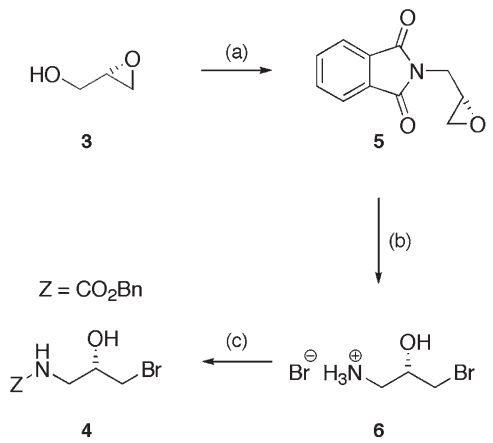
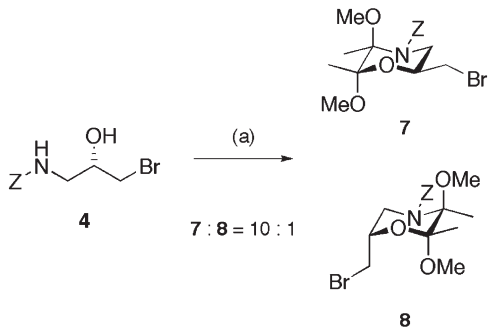


Scheme 1. (a) 1.1 equiv. Phthalimide, 1.1 equiv. PPh_3, 1.1 equiv. DTBAD, THF, reflux, 16 h; (b) 48% aq. HBr, reflux, 16 h, 73%; (c) 1.1 equiv. benzyl chloroformate, MeOH, then 2 equiv. DIPEA, 0 °C to rt, 2h, 74%; 54% from **3**.

protected as the benzyloxy carbamate to give **4**. The benzyloxy carbamate was chosen due to its perceived acid stability in the subsequent Lewis acid mediated butane diacetal protection step (Scheme 1).

Treatment of **4** with 2,2,3,3-tetramethoxybutane and catalytic boron trifluoride tetrahydrofuran complex in dichloromethane at 30 °C gave the desired cyclic precursor as a mixture of diastereoisomers, **7** and **8**, in an approximate 10:1 ratio in favour of the desired diastereoisomer **7** (Scheme 2). After column chromatography and recrystallization from petroleum ether it was possible to isolate **7** in 69% yield as a white crystalline solid.



Scheme 2. (a) 5 equiv. 2,2,3,3-tetramethoxybutane, 0.1 equiv. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 30 °C, 2 h; 69% of **7**.

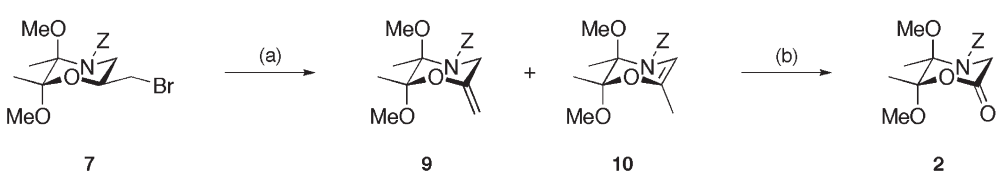
The approach to compound **7** makes use of a chiral memory protocol[9] where the chirality of the suitably protected amino alcohol **4** was used to control the configurations of the newly formed acetal stereocentres[10] during protection with 2,2,3,3-tetramethoxybutane. The reaction makes use of the known preference of alkyl substituents for equatorial positions and the favoured formation of axial methoxyl groups in the acetal owing to maximum anomeric (*exo* anomeric) stabilisation.

Treatment of **7** with potassium bis(trimethylsilyl)amide (KHMDS) in tetrahydrofuran afforded the *exo*-enol ether **9** in a 64% yield preferentially over the *endo*-enol ether **10** (>20:1). The *exo*-enol ether **9** was subsequently oxidatively cleaved to give the desired chiral glycine equivalent **2** (Scheme 3). Initially ozone was employed as the oxidant; however with a view to ease of synthesis and possible scale-up, oxidative cleavage using ruthenium trichloride with sodium periodate to generate ruthenium tetroxide in situ was employed. This was buffered with sodium hydrogen carbonate (1.5 equiv.) to prevent the build-up of significant acidic side products. The best yield was achieved using the Sharpless conditions (carbon tetrachloride, water and acetonitrile)[11] and the crystalline product **2** was isolated in an 85% yield, representing a 24% overall yield from (*S*)-glycidol. The conditions of Yoshifuji et al.[12] using ethyl acetate in place of carbon tetrachloride were also investigated which gave a 69% yield in the presence of benzyl triethyl ammonium chloride (as a phase transfer catalyst). On larger scales the last two steps could be performed without any intermediate purification, to provide **2** in 52% yield over the two steps.

The enantiomeric auxiliary **11** was also synthesised in an analogous manner from (*R*)-glycidol **12** (Scheme 4). This material aided in the determination of the enantiopurity of the new building blocks using chiral HPLC.[13] For both enantiomers the enantiomeric excess was shown to be greater than 99%. Eventually we hope these building blocks will be available from commercial compound supply sources.

Scheme 4. Synthesis of enantiomer **11** from (*R*)-glycidol **12**.

With the new glycine equivalent (**2**) in hand we next investigated its conversion to an enolate by deprotonation and its subsequent reaction with various electrophiles. In initial experiments with allyl bromide as the electrophile, the best results were observed with lithium diisopropylamide (LDA), which give an 14:1 diastereoisomeric ratio in favour of the pseudo-equatorial diastereoisomer: diastereoselection was not affected by the quantity of base included in the reaction. The reactivity of the lithium enolate was however low, presumably due to the formation of lithium enolate aggregates, but the use of 1.1 equiv. of

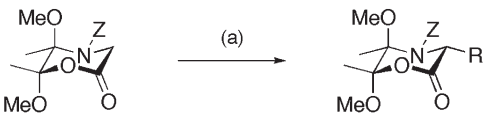


Scheme 3. (a) 2 equiv. KHMDS (1 M in PhMe), THF, −78 °C to rt, 64% (>20:1 **9**:**10**); (b) 4 equiv. $NaIO_4$, 0.02 equiv. $RuCl_3$, 1.5 equiv. $NaHCO_3$, H_2O/MeCN/CCl_4 (1:1:2), rt, 85%.

hexamethylphosphoramide (HMPA) in the mixture increased reactivity and the reactions were complete in around 22 h at temperatures between −55 and −50 °C. The results of the alkylations with a range of alkyl halides, following the optimal conditions, to give monosubstituted products **13** are summarised below (Scheme 5, Table 1). A particularly attractive aspect of these auxiliaries is the methyl and methoxy signals in the NMR spectra which greatly facilitate structural assignments. Moreover, these units often impart crystallinity to the products again aid product purification and characterisation.

In general the reactions proceeded with good to excellent yields and usually exhibited high diastereoselectivities. The lower diastereoselectivities observed with propargyl bromide **13f** and *tert*-butyl bromoacetate **13d** are difficult to rationalise, but may arise through secondary chelation effects in the transition state. In the majority of cases, a simple recrystallization or trituration with petrol, facilitated the isolation of the major equatorial diastereoisomer. In a number of cases these were additionally characterised via single crystal X-ray analysis. In all the cases the major product arises from attack of the alkyl halide from the opposite face to the hindering axial methoxy group (Fig. 2).

The requirement for HMPA to improve reactivity in these reactions was not ideal so we briefly investigated alternative additives for the alkylation reaction with allyl bromide (Table 2). The conversion with the addition of DMPU was poorer than HMPA, however *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA) showed a similar kinetic enhancement to HMPA and has since been used in the subsequent alkylations. In all the cases the diastereoselectivity of the reaction was not significantly affected by the different additives.



Scheme 5. (a) 1.1 equiv. LDA, 1.1 equiv. HMPA, THF, −78 °C, 1 h, then RX, −55 °C, 22 h, then 1.1 equiv. AcOH, Et_2O, to rt.

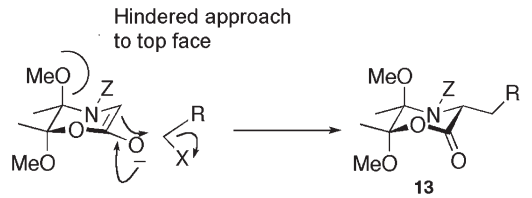


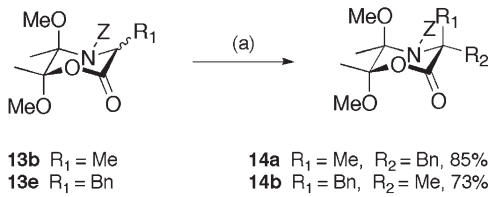
Figure 2. Proposed approach model leading to the major diastereomeric product.

Table 2. Comparison of additives on the alkylation reaction with allyl bromide

Additive	Conversion[a] (%)	Additive	Conversion[a] (%)
None	55	TMEDA	75
HMPA	74	PMDETA	64
DMPU	68	12-Crown-4	63

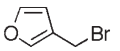
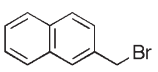
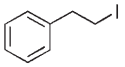
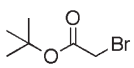
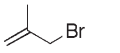
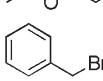
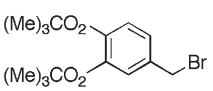
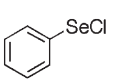
[a] Conversion by ^{1}H NMR after 22 h at −50 to −55 °C.

In the next experiments we investigated the feasibility of performing a second diastereoselective alkylation on the mono-alkylated products **13**. In the initial reaction, **13b** was alkylated with benzyl bromide in an 85% yield giving **14a**



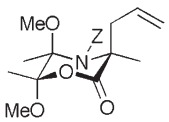
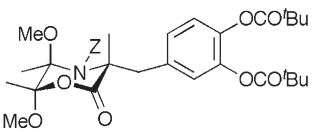
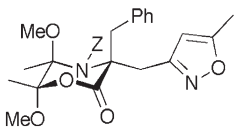
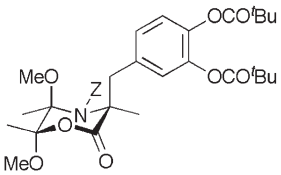
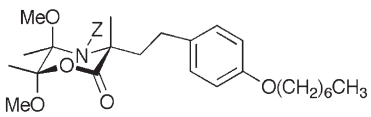
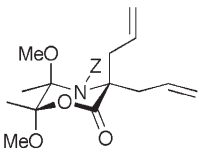
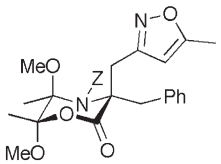
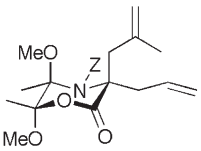
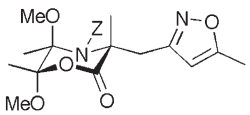
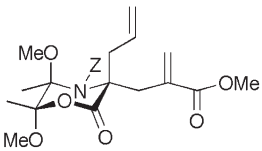
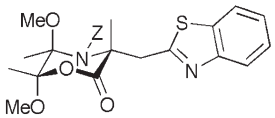
Scheme 6. (a) 1.1 equiv. LDA, 1.1 equiv. HMPA, THF, −78 °C, 1 h, then R_2X, −55 °C, 22 h, then 1.1 equiv. AcOH, Et_2O, to rt.

Table 1. Results of the monoalkylation reactions of **2**

RX	Product	d.r.[a]	Yield (%)[b]	RX	Product	d.r.[a]	Yield (%)[b]
	**13a**	14:1	73		**13g**[c]	13:1	81
	**13b**	22:1	82		**13h**	10:1	89
	**13c**	19:1	72		**13i**[d]	11:1	37
	**13d**	3:1	68		**13j**	11:1	70
	**13e**	14:1	74		**13k**[e]	12:1	49
	**13f**	2:1	92		**13l**	8:1	25

[a] Ratio of diastereoisomers in crude ^{1}H NMR.
[b] Yield of reaction after purification by column chromatography.
[c] Bromide synthesised from corresponding alcohol using PPh_3Br_2.[14]
[d] Iodide synthesised via Finklestein reaction from corresponding bromide.[15]
[e] 4-(Bromomethyl)-2-[(2,2-dimethylpropanoyl)oxy]phenyl pivalate synthesised from 3,4-dihydroxybenzaldehyde in 3 steps: (i) pyridine, −15 °C, 16 h, 51%; (ii) sodium borohydride, IPA, 0 °C, 2 h, 48%; (iii) PPh_3, CBr_4, MeCN, 0 °C, 1.5 h, 64%.

Table 3. Results of second alkylation reactions to give disubstituted products **14**

Product		Yield (%)[a,b]	Product		Yield (%)[a,b]
	**14c**	41		**14i**	15
	**14d**	36		**14j**	44
	**14e**	30		**14k**	72
	**14f**	31		**14l**	38
	**14g**	62		**14m**	79
	**14h**	25			

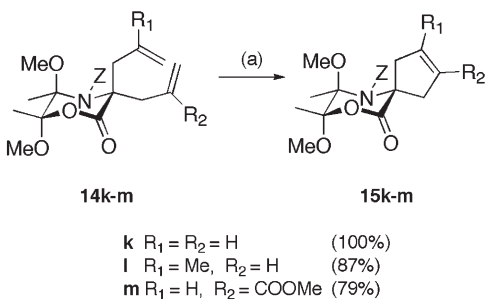
[a] Only single diastereoisomers were observed in the crude reaction mixtures by ^{1}H NMR spectroscopy.
[b] Yield of reaction after purification by column chromatography.

as the only observable product by ^{1}H NMR spectroscopy of the crude reaction mixture (Scheme 6). In the complementary alkylation of **13e** with methyl iodide, **14b** was produced in a 73% yield again as the only observable product.

In both cases single crystal X-ray diffraction studies unambiguously established the stereochemistry of the products. The pseudo-equatorial placement of the new group suggests again that the electrophile was approaching from the least hindered face. Additionally, the outstanding diastereoselection was independent of the diastereomeric excess of the starting material.

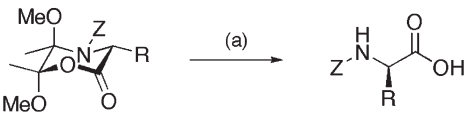
A number of other α,α-disubstituted products (**14a**-**m**) were obtained in an analogous manner (Scheme 6, Table 3) and in all cases only a single diastereomeric product was observed in the reaction mixture by ^{1}H NMR spectroscopy.

The possible synthesis of cyclic α-amino acid precursors was investigated using a ring closing metathesis strategy with disubstituted products **14k**-**m** in a similar method to Undheim.[16] In all three cases the cyclic products **15k**-**m** were obtained in good yields after treatment with the Grubbs second generation catalyst (Scheme 7).[17]



Scheme 7. (a) Grubbs-II catalyst, THF, reflux.

In a few examples we studied the conversion of the mono-alkylated products **13a**, **b** and **e** to the corresponding α-amino acids **16** using aqueous TFA (1:9) at room temperature (rt) (Scheme 8 and Table 4). In all the cases the yields of the amino acids were good to excellent and the products could be purified by either column chromatography or preparative HPLC. The cleavage of a single diastereoisomer was shown to lead to a single enantiomer of the α-amino acid (confirmed by chiral HPLC) showing that there was no racemisation of the α-centre in the cleavage step.



13 16

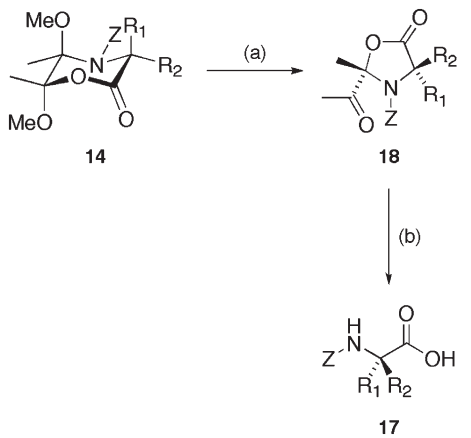
Scheme 8. (a) 9:1 TFA–H_2O, rt, 30 min.

Table 4. Results of the cleavage reactions of the mono-substituted products to give α-amino acids

R	Amino acid	Yield (%)	ee (%)
Allyl	**16a**	77	>99[a]
Me	**16b**	71	>99[a]
Bn	**16c**	85	>99[b]

[a] Determined on Chiralcel OD column, 9:1 hexane–IPA, 1 mL/min.
[b] Determined on Chiralcel OD column, 95:5 hexane–IPA, 1 mL/min.

Similarly, the corresponding α,α-disubstituted amino acids **17** were produced by treating the disubstituted products **14** with aqueous TFA (2:1 TFA–water) followed by neutralisation with 1 N sodium hydroxide in methanol. The neutralisation was required to release the desired free acids from the cyclic intermediates **18** (Scheme 9).[18] As before, the α,α-amino acids **17** could be purified by either column chromatography or preparative HPLC and the results are shown in Table 4.



14 18 17

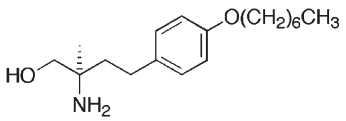
Scheme 9. (a) 9:1 TFA–H_2O, rt, 30 min. (b) 1 N NaOH–MeOH (1:1), rt, 30 min.

In order to extend the use of the chiral auxiliary **2** towards the preparation of a biologically relevant α-branched amine **19**, designed as an analogue of the powerful amino alcohol immuno-suppressant FTY-720 (**20**), we have prepared the amino acid **21** from the dialkylated precursor **14e** (Table 3) by hydrolytic cleavage in 97% yield (Scheme 10, Table 5, Fig. 3).

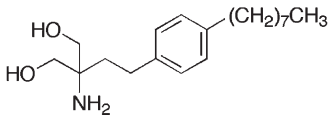
Table 5. Results of the cleavages of the disubstituted products **14** to give α,α-amino acids **17**

Starting material	Amino acid	Yield[a] (%)
14b	**17b**	76
14d	**17d**	52
14e	**17e**	97
14g	**17g**	81
15l	**17l**	84

[a] As the starting materials had >99:1 d.r. and racemisation is not possible, the amino acids are assumed to have >98% ee.



19



20 FTY-720

Figure 3. Structure of FTY-720 20 and the biologically active (*R*) chiral analogue **19**.

This β-hydroxy amine **19** had been identified by Kiuchi et al.[19] and was recently synthesised by Hinterding et al.[20]

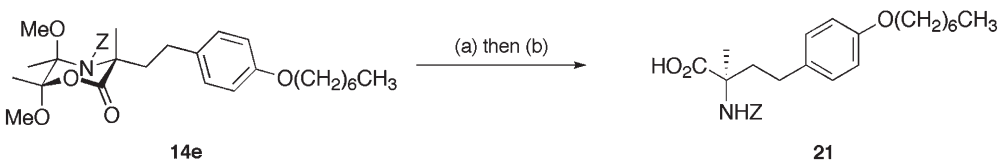
3. Conclusion

In summary, we have described in full the preparation of a new chiral glycine equivalent **2**. It undergoes lithium enolate mediated monoalkylation reactions in good to excellent yields and good diastereoselectivities and the corresponding dialkylation reactions in good yields and outstanding diastereoselectivities. These products can be readily deprotected under mild conditions to yield *N*–*Z* α-amino acids **5** and disubstituted *N*–*Z* α,α-amino acids **17** in generally excellent yields, with no evidence of racemisation of the α-centre. We hope that this glycine equivalent will become more generally useful in amino acid synthesis when the more traditionally used equivalents are unsatisfactory.

4. Experimental

4.1. General

2,2,3,3-Tetramethoxybutane was synthesised and purified according to the method of Frost et al.[21]



14e 21

Scheme 10. (a) 9:1 TFA/H_2O, rt, 30 min; (b) 1 N NaOH–MeOH, rt, 30 min. 97% from **14e**.

3-(Bromomethyl)furan was prepared with phosphorous dibromide according to the method of Sandri et al.[14b] Phenethyl iodide was prepared according to the method of Mendenhall et al.[15] 1-Heptyloxy-4-(2-iodo-ethyl)-benzene was prepared according to the method of Kiuchi et al.[19] All other reagents were used as obtained from commercial sources. Column chromatography was carried out using Merck Kieselgel (230–400 mesh) and analytical tlc was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F254). Filtration of crude reaction mixtures through silica was carried out in fritted plastic tubes (1 or 2 cm diameter, 2–3 cm silica depth) washing through with the indicated solvents. Chiral HPLC was performed on an Agilent 1100 series HPLC or a Gilson HPLC. Melting points were performed on a Reichert hot stage apparatus and are uncorrected. Boiling points were measured during distillation. Optical rotations were measured using a Perkin–Elmer Model 343 polarimeter and values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. Infra-red spectra were recorded on a Perkin–Elmer Spectrum-One spectrometer. Microanalyses were determined using a CE-440 Elemental Analyser. Mass spectra were obtained on Kratos Concept 1H, Micromass Q-TOF or Bruker BIOAPEX 4.7E T FTICR spectrometers, using electron impact (EI) or electrospray techniques (ESI). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 600, 500 or 400 spectrometers in $CDCl_3$ at 300 K unless otherwise stated.

4.1.1. (2*S*)-3-Bromo-2-hydroxypropan-1-ammonium bromide (6).[8] Triphenyl phosphine (68.8 g, 0.47 mol) was added to a stirred solution of phthalimide (38.6 g, 0.47 mol) in THF (400 mL) at 0 °C, followed by (*S*)-(−)-glycidol (22.4 g, 0.53 mol). Di-*tert*-butyl azodicarboxylate (60.4 g, 0.47 mol) was added dropwise and the solution stirred for 5 h at rt. The solvent was removed under reduced pressure, dissolved in methanol (200 mL) and cooled to 0 °C. Hydrobromic acid (48% aq.) was added slowly to the rapidly stirred solution until no further effervescence was observed and a white precipitate formed. The solution was diluted with water (200 mL) and filtered. The aqueous layer extracted with CH_2Cl_2 (3×300 mL) and the solvent was removed under reduced pressure. The residue was dissolved in hydrobromic acid (48% aq., 500 mL) and heated at reflux overnight. The solvent was removed under reduced pressure and the residue dissolved in toluene (100 mL). The solvent was removed under reduced pressure and the residue washed with ether (3×100 mL), chloroform (3×100 mL), ether (50 mL) and isopropanol (50 mL) before drying over KOH and P_2O_5 to give hydrobromide salt **6** (45.1 g, 73%) as white needles. Mp 134–140 °C (*i*PrOH, lit. 115–117 °C, ethanol);[8] IR (neat) 3327 (OH), 2999 (br N^+H_3) cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 3.85 (m, 1H), 3.48 (dd, *J*=10.6, 4.7 Hz, 1H) 3.42 (dd, *J*=10.6, 5.9 Hz, 1H), 3.29 (dd, *J*=13.8, 5.0 Hz, 1H), 3.16 (dd, *J*=13.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 71.3, 36.5, 28.7. −12.7 (*c* 2.0, H_2O). HRMS (+EI) Calcd for C_3H_9NOBr $[M-Br]^+$ 153.9868, found 153.9869.

4.1.2. Benzyl (2*S*)-3-bromo-2-hydroxypropylcarbamate (4). Benzyl chloroformate (7.98 g, 46.8 mmol) was added to a solution of **6** (10.0 g, 42.6 mmol) in methanol (100 mL) at 0 °C, followed by DIPEA (11.0 g, 85.2 mmol) and the solution was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1–1:1) to give amino alcohol **4** (9.03 g, 74%) as white needles. Mp 33–34 °C (petrol/ether). IR (neat) 3329 (OH), 1691 (NC═O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.37 (m, 5H, Ph), 5.17 (br s, 1H, NH), 5.11 (s, 2H, PhCH_2), 3.94 (br s, 1H), 3.50 (m, 1H), 3.46 (dd, *J*=10.4, 5.1 Hz, 1H), 3.40 (dd, *J*=10.4, 6.3 Hz, 1H), 3.33 (m, 1H), 3.07 (d, *J*=3.4 Hz, 1H, OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8 (C═O), 138.1, 128.6, 128.3, 128.1, 70.7, 67.2 (Ph*C*H_2), 44.9, 35.8. −12.1 (*c* 5.0, $CHCl_3$). Anal Calcd for $C_{11}H_{14}O_3N$ C, 45.9; H, 4.9; N, 4.9%; found C, 46.0; H, 4.9; N, 4.8%. HRMS (+ESI) Calcd for $C_{11}H_{14}O_3NBr$ $[M+Na]^+$ 310.0063, found 310.0055.

4.1.3. Benzyl-(2*S*,3*R*,6*S*)-6-(bromomethyl)-2,3-dimethoxy-2,3-dimethylmorpholine-4-carboxylate (7). Amino alcohol **4** (4.0 g, 13.9 mmol) was dissolved in CH_2Cl_2 (40 mL) and 2,2,3,3-tetramethoxybutane (12.36 g, 69.5 mmol) was added to the stirred solution. The solution was warmed to 30 °C and BF_3.THF (0.152 mL, 1.39 mmol) added dropwise. After 2 h, the reaction was cooled to rt, triethylamine (1 mL) was added to quench the reaction and the resulting solution was stirred for 1 h. The solution was then diluted with CH_2Cl_2 (50 mL), washed with $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (petrol/ether, 5:1 to neat ether) to leave a mixture of bromides **7** and **8** (10:1 d.r.). The mixture was recrystallized (petrol/ether) to give the bromide **7** (3.84 g, 69%) as white needles. Mp 67–69 °C (ether). IR (neat) 1718 (NC═O) cm^{-1}. ^{1}H NMR (600 MHz, $CHCl_3$) δ 7.36–7.31 (m, 5H, Ph), 5.17–5.12 (m, 2H, OCH_2Ph), 4.11 (dd, *J*=13.2, 2.6 Hz, 1H), 4.00 (m, 1H), 3.31–3.25 (m, 2H), 3.24 (s, 3H, CH_3O), 3.18 (s, 3H, CH_3O), 3.02 (dd, *J*=13.2, 11.4 Hz, 1H), 1.55 (s, 3H, CH_3C), 1.35 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CHCl_3$) δ 156.2 (NC═O), 136.6, 128.5, 127.9, 127.7, 101.3, 90.2, 67.9 (O*C*H_2Ph), 67.1, 48.5 (*C*H_3OC), 48.2 (*C*H_3OC), 44.1, 31.5 (*C*H_2Br), 18.9 (*C*H_3C), 17.8 (*C*H_3C). $[\alpha]_D^{25}$=+62.6 (*c* 2.1, $CHCl_3$). Anal Calcd for $C_{17}H_{24}NO_5Br$ C, 50.8; H, 6.0; N, 3.5; Br, 19.9%; found C, 50.8; H, 6.1; N, 3.4; Br, 19.8%. HRMS (+ESI) Calcd for $C_{17}H_{24}NO_5BrNa$ $[M+Na]^+$ 424.0748, found 424.0736. Structure and absolute stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.1.4. (2*S*,3*R*)-2,3-Dimethoxy-2,3-dimethyl-6-methylene-4-(3-phenylpropanoyl)morpholine (9). Potassium bis(trimethylsilyl)amide (1 M in toluene, 96.4 mL, 48.2 mmol) was added dropwise to a solution of bromide **7** (9.69 g, 24.1 mmol) in THF (96.4 mL) at −78 °C. The solution was allowed to warm to rt overnight and stir at rt for 4 h. The reaction was quenched by addition of water (100 mL) and the aqueous layer was extracted with ether (3×100 mL) and the combined organics washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by column chromatography (ether/petrol+1% Et_3N, 5:1–1:1) to give enol ether **9** (4.97 g, 64%) as a colourless oil. IR (neat) 1718 cm^{-1} (NC═O). ^{1}H NMR (600 MHz, $CHCl_3$) δ 7.37–7.29 (m, 5H, Ph), 5.16 (s, 2H, OCH_2Ph), 4.35 (s, 1H, C═C$H_A$$H_B$), 4.26–4.17 (2H, br m, NCH_2), 4.09 (s, 1H, C═C$H_A$$H_B$), 3.27 (s, 3H, C$H_3$OC), 3.25 (s, 3H, C$H_3$OC), 1.74 (s, 3H, C$H_3$C), 1.47 (s, 3H,

CH_3C). ^{13}C NMR (150 MHz, $CHCl_3$) δ 155.2 (NC═O), 152.5 (C═CH_2), 136.4, 128.4, 127.9, 127.7, 103.7, 89.7, 89.2 (C═CH_2), 67.2 (OCH_2Ph), 50.3 (CH_3OC), 48.8 (CH_3OC), 43.4, 17.8. $[\alpha]_D^{25}$=+60.0 (*c* 4.24, $CHCl_3$). HRMS (+ESI) Calcd for $C_{17}H_{23}NO_5Na$ $[M+Na]^+$ 344.1479, found 344.1474.

4.1.5. Benzyl (2*S*,3*R*)-2,3-Dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (2). Enol ether **9** (0.41 g, 1.27 mmol) was dissolved in water (4 mL), carbon tetrachloride (2.6 mL) and acetonitrile (2.6 mL). Ruthenium trichloride (5.8 mg, 0.28 mmol) was added followed by sodium periodate (1.11 g, 5.22 mmol) and the reaction was stirred for 2 h. The reaction was diluted with water (20 mL) and dichloromethane (20 mL) and the aqueous layer extracted with dichloromethane (2×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was dissolved in ether and filtered through a silica plug (eluting with ether). The solvent was removed under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1) to give lactone **2** (351 mg, 85%) as white needles. Mp 41–43 °C (ether/petrol). IR 1755 (OC═O), 1725 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.36–7.32 (m, 5H, Ph), 5.14 (d, *J*=12.4 Hz, 1H, OCH_AH_BPh), 5.13 (d, *J*=12.4 Hz, 1H, OCH_AH_BPh), 4.45 (d, *J*=18.2 Hz, 1H), 3.97 (d, *J*=18.2 Hz, 1H), 3.40 (s, 3H, CH_3OC), 3.23 (s, 3H, CH_3OC), 1.81 (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CHCl_3$) δ 166.4 (OC═O), 154.8 (NC═O), 135.9, 128.6, 128.3, 127.9, 106.6, 88.9, 67.5 (OCH_2Ph), 50.5 (CH_3OC), 49.9 (CH_3OC), 45.6, 17.9; $[\alpha]_D^{25}$=+86.4 (*c* 2.9, $CHCl_3$). Anal Calcd for $C_{16}H_{21}NO_6$ C, 59.4; H, 6.6; N, 4.3%, found C, 59.6; H, 6.7; N, 4.5%. HRMS (+ESI) Calcd for $C_{16}H_{21}NO_6Na$ $[M+Na]^+$ 346.1267, found 346.1253. Enantiomeric excess determined by chiral HPLC analysis (Chiralcel AD column, 95:5 hexane/IPA, 1 mL min^{-1}) to be greater than 99%. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.2. General method A for the deprotonation of the glycinate

Diisopropyl amine (1.15 equiv.) was dissolved in THF (5 mL per 200 mg of substrate) at −78 °C and butyl lithium (1.6 or 2.5 M in hexanes, 1.1 equiv.) was added and the solution was allowed to warm to rt. Upon reaching rt, the solution was cooled back down to −78 °C, a solution of the lactone (1 equiv.) in THF (1 mL) added via cannula followed by HMPA (1.1 equiv.) and stirred at −78 °C for 1 h. The alkyl halide (3 equiv.) was added, the reaction was stirred at −55 °C for 21 h. The reaction was quenched by the addition of glacial acetic acid (1.1 equiv.) at −55 °C followed by the addition of ether (5 mL per 200 mg of substrate) and the solution stirred at rt for 2 h. The turbid mixture was filtered through silica (ether), concentrated under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1).

4.3. General method B for the deprotonation of the glycinate

Diisopropyl amine (1.15 equiv.) was dissolved in THF (5 mL per 200 mg of lactone) at −78 °C and butyl lithium (1.6 or 2.5 M in hexanes, 1.1 equiv.) was added and the solution was warmed up to rt. Upon reaching rt, the solution was cooled back down to −78 °C, a solution of the lactone (1 equiv.) in THF (1 mL) added via cannula followed by TMEDA (1.1 equiv.) and the solution stirred at −78 °C for 1 h. The alkyl halide (3 equiv.) was added, the reaction stirred at −55 °C for 21 h. The reaction was quenched by the addition of glacial acetic acid (1.1 equiv.) at −55 °C followed by the addition of ether (5 mL per 200 mg of substrate) and the solution stirred at rt for 2 h. The turbid mixture was filtered through silica (ether), concentrated under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1).

4.4. General method C for the deprotonation of the glycinate

Lithium diisopropylamide (0.125 M in THF/hexanes, 1.1 equiv.) was added to a solution of the lactone (1 equiv.) in THF (1 mL) at −78 °C, followed by HMPA (1.1 equiv.) and the solution was stirred at −78 °C for 1 h. The alkyl halide (3 equiv.) was added and the reaction stirred at −55 °C for 21 h. The reaction was quenched by the addition of glacial acetic acid (1.1 equiv.) at −55 °C followed by the addition of ether (5 mL per 200 mg of substrate) and the solution stirred at rt for 2 h. The turbid mixture was filtered through silica (ether) and concentrated under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1).

4.5. General method D for the deprotonation of the glycinate

Lithium diisopropylamide (0.125 M in THF/hexanes, 1.1 equiv.) was added to a solution of the lactone (1 equiv.) in THF (1 mL) at −78 °C, followed by TMEDA (1.1 equiv.) and the solution was stirred at −78 °C for 1 h. The alkyl halide (3 equiv.) was added and the reaction was stirred at −55 °C for 21 h. The reaction was quenched by the addition of glacial acetic acid (1.1 equiv.) at −55 °C followed by the addition of ether (5 mL per 200 mg of lactone) and the solution stirred at rt for 2 h. The turbid mixture was filtered through silica (ether), concentrated under reduced pressure and the residue purified by column chromatography (petrol/ether, 3:1).

4.5.1. Benzyl (2*S*,3*R*,5*R*)-5-allyl-2,3-dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (13a). Lactone **2** (196 mg, 0.61 mmol) was alkylated with allyl bromide (220 mg, 1.82 mmol) according to method A to give lactone **13a** (161 mg, 73%, 14:1 crude d.r.) as a white solid. Recrystallization (petrol/ether) gave only the major diastereoisomer as white needles. Mp 53–54 °C (petrol/ether). IR (neat) 1754 (OC═O), 1718 (NC═O), 1694 and 1642 (C═C) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H, Ph), 5.82–5.75 (m, 1H, CH_2CH═CH_2), 5.18 (s, 2H, OCH_2Ph), 5.02 (d, *J*=10.1 Hz, 1H, CH═C$H_{cis}H_{trans}$), 4.98 (d, *J*=17.0 Hz, 1H, CH═C$H_{cis}H_{trans}$), 4.49 (dd, *J*=9.4, 4.7 Hz, 1H), 3.41 (s, 3H, CH_3OC), 3.15 (s, 3H, CH_3OC), 2.79–2.74 (m, 1H), 2.59–2.55 (m, 1H), 1.85 (s, 3H, CH_3C), 1.59 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2 (OC═O), 155.1 (NC═O), 135.6, 133.5, 128.6, 128.4, 128.3, 117.6, 107.1, 89.2, 67.8 (OCH_2Ph), 57.5, 50.6

(CH_3OC), 49.6 (CH_3OC), 38.9, 19.6 (CH_3C), 18.7 (CH_3C). $[\alpha]_D^{25}=+14.3$ (c 0.7, $CHCl_3$). Anal Calcd for $C_{19}H_{25}NO_6$ requires C, 62.8; H, 6.9; N, 3.9%; found C, 62.5; H, 6.8; N, 3.8%. HRMS (+ESI) Calcd for $C_{19}H_{25}NO_6Na$ $[M+Na]^+$ 386.1580, found 386.1577. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.5.2. Benzyl (2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3,5-trimethyl-6-oxomorpholine-4-carboxylate (13b). Lactone **2** (188 mg, 0.58 mmol) was alkylated with methyl iodide (273 mg, 1.75 mmol) according to method A to give lactone **13b** (160 mg, 82%, 22:1 crude d.r.) as a yellow oil which crystallized on standing. Recrystallization (petrol/ether) gave only the major diastereoisomer as white needles. Mp 78–79 °C (ether). IR (neat) 1754 (OC═O), 1718 (NC═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.33 (m, 5H, Ph), 5.18 (s, 2H, OCH_2Ph), 4.55 (q, J=6.8 Hz, 1H), 3.41 (s, 3H,CH_3OC), 3.16 (s, 3H, CH_3OC), 1.85 (s, 3H, CH_3C), 1.58 (d, J=6.8 Hz, 3H, CH_3C), 1.54 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7 (OC═O), 155.1 (NC═O), 135.8, 128.6, 128.3, 128.1, 106.9, 89.1, 67.6 (OCH_2Ph), 53.2, 50.6 (CH_3OC), 49.6 (CH_3OC), 20.3 (CH_3C-3), 19.5 (CH_3C), 18.1 (CH_3C). $[\alpha]_D^{25}=+37.2$ (c 2.24, $CHCl_3$). Anal Calcd for $C_{17}H_{23}NO_6$ C, 60.5; H, 6.9; N, 4.2%; found C, 60.5; H, 6.8; N, 4.1%. HRMS (+ESI) Calcd for $C_{17}H_{23}NO_6Na$ $[M+Na]^+$ 360.1423, found 360.1418. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.5.3. Benzyl (2*S*,3*R*,5*R*)-5-ethyl-2,3-dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (13c). Lactone **2** (181 mg, 0.56 mmol) was alkylated with ethyl iodide (262 mg, 1.68 mmol) according to method A to give lactone **13e** (142 mg, 72%, 19:1 crude d.r.) as a white solid. Mp 61–62 °C (petrol/ether). IR (neat) 1751 (OC═O), 1718 (NC═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.33 (m, 5H, m), 5.17 (ap q, 2H, OCH_2Ph), 4.27 (dd, J=9.8, 3.7 Hz, 1H), 3.38 (s, 3H, CH_3OC), 3.15 (s, 3H, CH_3OC), 1.99 (m, 1H), 1.88–1.84 (m, 4H), 1.58 (s, 3H, CH_3C), 0.98 (t, J=7.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8 (OC═O), 155.2 (NC═O), 135.8, 128.6, 128.3, 128.2, 107.0, 89.2, 67.7 (OCH_2Ph), 59.2, 50.6 (CH_3OC), 49.6 (CH_3OC), 28.1 (CH_2CH_3), 19.4, 18.3, 10.9. $[\alpha]_D^{25}=+41.0$ (c 0.21, $CHCl_3$). HRMS (+ESI) Calcd for $C_{18}H_{25}NO_6Na$ $[M+Na]^+$ 374.1580, found 374.1575. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.5.4. Benzyl-(2*S*,3*R*,5*R*)-5-*tert*-butoxycarbonylmethyl-2,3-dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (13d). Lactone **2** (195 mg, 0.60 mmol) was alkylated with *tert*-butyl bromoacetate (351 mg, 1.80 mmol) according to method A to give lactone **13d** (177 mg, 68%, 3:1 crude d.r.) as a white solid. Mp 52–56 °C (ether). IR (neat) 1753 (OC═O lactone), 1722 (NC═O, OC═O ester) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H, Ph), 5.19 (s, 2H, OCH_2Ph), 5.02 (dd, J=9.1, 4.1 Hz, 1H), 3.42 (s, 3H, CH_3OC), 3.16 (s, 3H, CH_3OC), 2.87 (dd, J=15.1, 4.1 Hz, 1H), 2.68 (dd, J=15.1, 4.1 Hz, 1H), 1.82 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C), 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 168.1, 154.8 (NC═O), 135.7, 128.6, 128.3, 128.1, 107.1, 89.0, 81.1 ($OC(CH_3)_3$), 67.7 (OCH_2Ph), 54.3, 50.8 (CH_3OC), 49.7 (CH_3OC), 41.4, 27.9 ($C(CH_3)_3$), 19.7, 17.9. $[\alpha]_D^{25}=-1.1$ (c 0.75, $CHCl_3$, 6:1 d.r.). HRMS (+ESI) Calcd for $C_{22}H_{31}O_8NNa$ $[M+Na]^+$ 460.1947, found 460.1959.

4.5.5. Benzyl (2*S*,3*R*,5*R*)-5-benzyl-2,3-dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (13e). Lactone **2** (182 mg, 0.56 mmol) was alkylated with benzyl bromide (287 mg, 1.68 mmol) according to method A to give lactone **13e** (174 mg, 74%, 14:1 crude d.r.) as a white solid. Recrystallization (petrol/ether) gave only the major diastereoisomer as white needles. Mp 141–142 °C (ether). IR (neat) 1756 (OC═O), 1718 (NC═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.35 (m, 5H, Ph(carbamate)), 7.21–7.19 (m, 3H), 7.08 (d, J=6.4 Hz, 2H), 5.19 (d, J=11.9 Hz, 1H, OCH_AH_BPh), 5.03 (d, J=11.9 Hz, 1H, OCH_AH_BPh), 4.65 (dd, J=9.3, 4.4 Hz, 1H), 3.50 (s, 3H, CH_3OC), 3.32 (dd, J=13.7, 4.4 Hz, 1H), 3.16 (s, 3H, CH_3OC), 3.05 (dd, J=13.7, 9.3 Hz, 1H), 1.91 (s, 3H, CH_3C), 1.62 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8 (OC═O), 155.1 (NC═O), 137.1, 135.5, 129.3, 128.6, 128.5, 128.4, 128.3, 126.7, 107.2, 89.3, 67.9, 59.5, 50.7, 49.6, 40.6, 19.6, 18.3. $[\alpha]_D^{25}=+63.0$ (c 0.3, $CHCl_3$). Anal Calcd for $C_{23}H_{27}NO_6$ C, 66.8; H, 6.6; N, 3.4%, found C, 66.1; H, 6.6; N, 3.3%. HRMS (+EI) Calcd for $C_{23}H_{27}NO_6$ $[M]^+$ 413.183, found 413.1831. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.5.6. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3-dimethyl-6-oxo-5-prop-2-ynyl-morpholine-4-carboxylate (13f). Lactone **2** (180 mg, 0.58 mmol) was alkylated with propargyl bromide (80% in toluene, 259 mg, 1.75 mmol) according to method A to give lactone **13f** (194 mg, 92%, 2:1 d.r.) as a yellow oil. IR (neat) 1751 (OC═O), 1722 (NC═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H, Ph), 5.20 (d, J=12.3 Hz, 1H, OCH_AH_BPh), 5.11 (d, J=12.3 Hz, 1H, OCH_AH_BPh), 4.97 (ap t, J=6.8 Hz, 1H), 3.37 (s, 3H, CH_3OC), 3.34 (s, 3H, CH_3OC), 2.97 (ddd, J=17.1, 6.1, 2.6 Hz, 1H), 2.66 (ddd, J=17.1, 7.7, 2.7 Hz, 1H), 1.97 (ap t, J=2.7 Hz, 1H), 1.80 (s, 3H, CH_3C), 1.51 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7 (OC═O), 160.3 (NC═O), 135.8, 128.5, 128.2, 128.1, 106.9, 89.8, 80.4, 70.5, 67.9 (OCH_2Ph), 54.2, 50.6 (CH_3OC), 50.5, 24.2, 18.6, 18.0. $[\alpha]_D^{25}=+79.5$ (c 0.42, $CHCl_3$). HRMS (+EI) Calcd for $C_{19}H_{23}NO_6$ $[M]^+$ 361.1525, found 361.1525.

4.5.7. Benzyl (2*S*,3*R*,5*R*)-5-furan-3-ylmethyl-2,3-dimethoxy-2,3-dimethyl-6-oxomorpholine-4-carboxylate (13g). Lactone **2** (180 mg, 0.56 mmol) was alkylated with 3-(bromomethyl)furan (268 mg, 1.67 mmol) according to method A to give lactone **13g** (182 mg, 81%, 13:1 crude d.r.) as a white solid. Mp 38–40 °C ($CHCl_3$). IR (neat) 1758 (OC═O), 1720 (C═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37–7.35 (m, 5H, Ph), 7.29 (s, 1H), 7.11 (s, 1H), 6.17 (s, 1H), 5.18 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.14 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 4.54 (dd, J=9.4, 3.8 Hz, 1H), 3.45 (s, 3H, CH_3OC), 3.17 (s, 3H, CH_3OC), 3.05 (dd, J=14.7, 3.8 Hz, 1H), 2.94 (dd, J=14.7, 9.4 Hz, 1H), 1.89 (s, 3H, CH_3C), 1.61 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0 (OC═O), 142.7, 140.3, 135.5, 128.7, 128.5, 128.5, 111.2, 107.1, 89.2, 67.9 (OCH_2Ph), 58.6, 50.7, 49.6, 30.3, 19.4, 18.3. $[\alpha]_D^{25}=-15.4$ (c 0.45, $CHCl_3$). HRMS

(+ESI) Calcd for $C_{21}H_{25}NO_7Na$ $[M+Na]^+$ 426.1529, found 426.1516. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction.

4.5.8. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3-dimethyl-5-naphthalen-2-ylmethyl-6-oxomorpholine-4-carboxylate (13h). Lactone **2** (184 mg, 0.57 mmol) was alkylated with 2-(bromomethyl)napthalene (378 mg, 1.71 mmol) according to method A to give lactone **13h** (236 mg, 89%, 10:1 crude d.r.) as a white solid. Mp 87–89 °C (ether). IR (neat) 1756 (OC═O), 1719 (C═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.78–7.76 (m, 1H), 7.68 (d, J=8.2 Hz, 1H), 7.66 (d, J=5.9 Hz, 1H), 7.50 (br s, 1H), 7.43–7.40 (m, 2H), 7.36–7.32 (m, 5H, Ph), 7.22 (d, J=8.2 Hz, 1H), 5.18 (d, J=11.9 Hz, 1H, OCH_AH$_B$Ph), 5.01 (d, J=11.9 Hz, 1H, OCH$_A$$H_B$Ph), 4.76 (dd, J=9.3, 4.4 Hz, 1H), 3.54 (s, 3H, CH_3OC), 3.50–3.46 (m, 1H), 3.22 (dd, J=18.6, 9.3 Hz, 1H), 3.18 (s, 3H, CH_3OC), 1.94 (s, 3H, CH_3C), 1.65 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8 (OC═O), 155.1 (NC═O), 135.5, 134.6, 133.4, 132.4, 128.7, 128.6, 128.5, 127.9, 127.8, 127.7, 127.6, 127.5, 125.8, 125.4, 107.2, 89.3, 68.0 (OCH$_2$Ph), 59.4, 50.7, 49.7, 40.8, 18.3, 15.2. $[\alpha]_D^{25}$=−2.2 (c 0.32, $CHCl_3$). HRMS (+EI) Calcd for $C_{27}H_{29}NO_6$ $[M]^+$ 463.1995, found 463.1993.

4.5.9. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3-dimethyl-6-oxo-5-phenethyl-morpholine-4-carboxylate (13i). Lactone **2** (98 mg, 0.30 mmol) was alkylated with phenethyl iodide (209 mg, 0.90 mmol) according to method A for 3.5 days to give lactone **13i** (48 mg, 37%, 11:1 crude d.r.) as a white solid. Mp 75–78 °C ($CHCl_3$). IR (neat) 1752 (OC═O), 1720 (NC═O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H, OCH$_2$*Ph*), 7.26–7.22 (m, 2H), 7.18–7.14 (m, 1H), 7.09–7.04 (m, 2H), 5.13 (d, J=12.0 Hz, 1H, OCH_AH$_B$Ph), 5.11 (d, J=12.0 Hz, 1H, OCH$_A$$H_B$Ph), 4.42 (dd, J=9.8, 3.5 Hz, 1H), 3.39 (s, 3H, CH_3OC), 3.16 (s, 3H, CH_3OC), 2.75 (td, J=12.6, 5.1 Hz, 1H), 2.65 (td, J=12.6, 6.3 Hz, 1H), 2.27–2.04 (m, 2H), 1.85 (s, 3H, CH_3C), 1.60 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (OC═O), 155.1 (NC═O), 141.1, 135.7, 128.7, 128.4, 128.3, 107.1, 89.2, 67.7 (OCH$_2$Ph), 57.4, 50.7, 49.7, 36.6, 32.6, 19.2, 18.3. $[\alpha]_D^{25}$=−2.0 (c 0.57, $CHCl_3$). HRMS (+ESI) Calcd for $C_{24}H_{29}NO_6Na$ $[M+Na]^+$ requires 450.1893, found 450.1899.

4.5.10. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3-dimethyl-5-(2-methylprop-2-enyl)-6-oxomorpholine-4-carboxylate (13j). Lactone **2** (79 mg, 0.24 mmol) was alkylated with 3-bromo-2-methylpropene (99 mg, 0.73 mmol) according to method B (for 35 h) to give lactone **13j** (160 mg, 70%, 11:1 crude d.r.) as a yellow oil. Recrystallization (petrol/ether) gave only the major diastereoisomer as white prisms. Mp 51–53 °C (ether/petrol). IR (neat) 1758 (OC═O), 1720 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 5H, Ph), 5.16 (s, 2H, OCH_2Ph), 4.78 (s, 1H, C═CH_AH$_B$), 4.66 (s, 1H, C═CH$_A$$H_B$), 4.63 (dd, J=10.0, 4.7 Hz, 1H), 3.41 (s, 3H, CH_3OC), 3.15 (s, 3H, CH_3OC), 2.72 (dd, J=13.4, 4.7 Hz, 1H), 2.55 (dd, J=13.4, 10.0 Hz, 1H), 1.84 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C), 1.56 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5 (OC═O), 155.1 (NC═O), 141.1 (C═CH$_2$), 135.6, 128.6, 128.5, 128.5, 114.3 (C═CH$_2$), 107.1, 89.3, 67.9 (OCH$_2$Ph), 56.3, 50.7, 49.5, 42.7, 21.4, 19.8, 18.3. $[\alpha]_D^{25}$=+16.2 (c 1.0, $CHCl_3$). Anal Calcd for $C_{20}H_{27}NO_6$ C, 63.6; H, 7.2; N, 3.7%, found C, 63.3; H, 7.2; N, 3.7%. Structure and relative stereochemistry were confirmed by single crystal X-ray diffraction studies.

4.5.11. Benzyl-(2*S*,3*R*,5*R*)-5-[3,4-bis-(2,2-dimethyl-propionyloxy)-benzyl]-2,3-dimethoxy-2,3-dimethyl-6-oxo-morpholine-4-carboxylate (13k). Lactone **2** (135 mg, 0.42 mmol) was alkylated with 4-(bromomethyl)-2-[(2,2-dimethylpropanoyl)oxy]phenyl pivalate (465 mg, 1.25 mmol) according to method D to give lactone **13k** (125 mg, 49%, 12:1 crude d.r.) as a colourless foam. IR (neat) 1756 (OC═O), 1722 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H, OCH$_2$*Ph*), 6.96–6.90 (m, 3H), 5.16 (d, J=12.0 Hz, 1H, OCH_AH$_B$Ph), 5.01 (d, J=12.0 Hz, 1H, OCH$_A$$H_B$Ph), 4.65 (dd, J=8.5, 4.7 Hz, 1H), 3.45 (s, 3H, CH_3OC), 3.26 (dd, J=14.1, 4.7 Hz, 1H), 3.13 (s, 3H, CH_3OC), 3.03 (dd, J=14.1, 8.5 Hz, 1H), 1.88 (s, 1H, CH_3C), 1.60 (s, 3H, CH_3C), 1.32 (s, 9H, C(CH_3)$_3$), 1.31 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 175.7, 168.0 (OC═O), 155.0 (NC═O), 142.1, 141.1, 135.7, 135.6, 128.6, 128.6, 128.4, 127.1, 124.2, 123.0, 107.2, 89.3, 67.8 (OCH$_2$Ph), 59.0, 50.7 (CH$_3$OC), 49.7 (CH$_3$OC), 40.1, 39.1, 39.0, 27.2, 27.2, 19.5, 18.2. $[\alpha]_D^{25}$=+21.6 (c 0.57, $CHCl_3$). HRMS (+ESI) Calcd for $C_{33}H_{43}NO_{10}Na$ $[M+Na]^+$ 636.2784, found 636.2781.

4.5.12. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3-dimethyl-6-oxo-5-phenylselanyl-morpholine-4-carboxylate (13l). Lactone **2** (84 mg, 0.260 mmol) was alkylated with phenylselenium chloride (149 mg, 0.780 mmol) according to method D to give lactone **13l** (31 mg, 25%, 8:1 crude d.r.) as yellow needles. Mp 39–42 °C ($CHCl_3$). IR (neat) 1745 (OC═O), 1724 (NC═O) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.66–7.60 (m, 3H, Se*Ph*), 7.39–7.19 (m, 7H, OCH$_2$*Ph*, Se*Ph*), 5.61 (1s, 1H), 5.21 (d, J=12.1 Hz, 1H, OCH_AH$_B$Ph), 5.08 (d, J=12.1 Hz, OCH$_A$$H_B$Ph), 3.55 (s, 3H, C$H_3$OC), 3.17 (s, 3H, C$H_3$OC), 1.87 (s, 3H, C$H_3$C), 1.65 (s, 3H, C$H_3$C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0 (OC═O), 154.0 (NC═O), 135.4, 134.7, 131.5, 129.0, 128.6, 128.4, 107.2, 89.4, 68.2, 57.2, 51.2, 50.7, 17.8. $[\alpha]_D^{25}$=+32.3 (c 1.4, $CHCl_3$). HRMS (+ESI) Calcd for $C_{22}H_{25}O_6NSe$ $[M+Na]^+$ 502.0745, found 502.0721.

4.5.13. Benzyl (2*S*,3*R*,5*R*)-5-benzyl-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14a). Lactone **13b** (160 mg, 0.47 mmol) was alkylated with benzyl bromide (239 mg, 1.41 mmol) according to method A to give lactone **14a** (171 mg, 85%) as white needles. Mp 72–74 °C (petrol/ether). IR (neat) 1751 (OC═O), 1718 (NC═O) cm^{-1}. ^1H (600 MHz, $CDCl_3$) δ 7.46–7.36 (m, 5H), 7.19, (m, 3H), 6.98 (m, 2H), 5.57 (d, J=12.1 Hz, 1H, OCH_AH$_B$Ph), 5.24 (d, J=12.1 Hz, 1H, OCH$_A$$H_B$Ph), 3.67 (d, J=13.7 Hz, 1H), 3.37 (d, J=13.7 Hz, 1H), 3.26 (s, 3H, CH_3OC), 3.25 (s, 3H, CH_3OC), 1.79 (s, 3H, CH_3C), 1.59 (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2 (OC═O), 155.5 (NC═O), 136.2, 135.6, 130.7, 128.7, 128.6, 128.5, 127.9, 126.7, 106.5, 90.5, 67.7 (OCH_2Ph), 66.0, 50.3, 49.7, 43.6, 22.2, 19.4, 18.9. $[\alpha]_D^{25}$=+66.7 (c 3.6, $CHCl_3$). HRMS Calcd for $C_{24}H_{29}NO_6$ $[M]^+$ 427.1995, found 427.1996. Structure and relative stereochemistry confirmed by single crystal X-ray diffraction studies.

4.5.14. Benzyl (2*S*,3*R*,5*S*)-5-benzyl-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14b). Lactone **13e** (30 mg, 0.073 mmol) was alkylated with methyl iodide (31 mg, 0.22 mmol) according to method A to give lactone **14b** (23 mg, 73%) as white plates. Mp 116–118 °C (petrol/ether). IR (neat) 1749 (OC═O), 1711 (C═O) cm^{-1}. ^1H MR (600 MHz, $CDCl_3$) δ 7.46–7.40 (m, 5H), 7.20–7.13 (m, 5H), 5.28 (d, J=11.9 Hz, 1H, OCH_AH$_B$Ph), 5.19 (d, J=11.9 Hz, 1H, OCH$_A$$H_B$Ph), 3.62 (d, J=14.0 Hz, 1H), 3.49 (d, J=14.0 Hz, 1H), 3.42 (s, 3H, CH_3OC), 2.31 (s, 3H, CH_3OC), 1.80 (s, 3H, CH_3C), 1.68 (s, 3H, CH_3C), 1.50 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3 (OC═O), 155.3 (NC═O), 137.8, 135.6, 131.4, 128.9, 128.7, 128.5, 128.0, 126.5, 106.0, 89.4, 67.6 (O*C*H$_2$Ph), 65.4, 49.6, 49.2, 42.1, 27.7, 19.5, 18.6. $[\alpha]_D^{25}$=+102.1 (*c* 1.23, $CHCl_3$). HRMS Calcd for $C_{24}H_{29}NO_6$ $[M+Na]^+$ 450.1893, found 450.1905. Structure and relative stereochemistry confirmed by single crystal X-ray diffraction studies.

4.5.15. Benzyl-(2*S*,3*R*,5*S*)-5-allyl-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14c). Lactone **13a** (150 mg, 0.41 mmol) was alkylated with methyl iodide (176 mg, 1.24 mmol) according to method A to give lactone **14c** (61 mg, 41%) as white needles. Mp 52–54 °C ($CHCl_3$). IR (neat) 1748 (OC═O), 1712 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.39–7.33 (m, 5H), 5.78 (m, 1H, C*H*═CH$_2$), 5.14 (s, 2H, OCH_2Ph), 4.92 (d, J=9.8 Hz, 1H, CH═CH_AH$_B$), 4.84 (d, J=16.6 Hz, 1H, CH═CH$_A$$H_B$), 3.41 (s, 3H, C$H_3$OC), 3.27 (s, 3H, C$H_3$OC), 2.90 (dd, J=14.3, 6.1 Hz, 1H), 2.87 (dd, J=14.3, 8.7 Hz, 1H), 1.79 (s, 3H, CH_3C), 1.70 (s, 3H, CH_3C), 1.56 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CHCl_3$) δ 172.4 (OC═O), 155.4 (NC═O), 136.6, 135.0 (*C*H═CH$_2$), 128.7, 128.6, 128.4, 117.7 (CH═*C*H$_2$), 106.1, 89.7, 67.5 (O*C*H$_2$Ph), 62.7, 51.5, 49.7, 42.2, 26.8, 19.5, 18.3. $[\alpha]_D^{25}$=+82.2 (*c* 0.48, $CHCl_3$). HRMS (+ESI) Calcd for $C_{20}H_{27}NO_6Na$ $[M+Na]^+$ 400.1736, found 400.1740.

4.5.16. Benzyl-(2*S*,3*R*,5*R*)-5-benzyl-2,3-dimethoxy-2,3-dimethyl-5-(5-methyl-isoxazol-3-ylmethyl)-6-oxo-morpholine-4-carboxylate (14d). Lactone **13e** (82 mg, 0.199 mmol) was alkylated with in 3-bromomethyl-5-isoxazole (105 mg, 0.517 mmol) according to method D to give lactone **14d** (35 mg, 36%) as a yellow oil. IR (neat) 1752 (OC═O), 1712 (C═O), 1693 (C═N) cm^{-1}. ^1H NMR (600 MHz, $CHCl_3$) δ 7.46 (m, 2H), 7.43–7.37 (m, 3H), 7.14–7.08 (m, 5H), 5.83 (d, J=0.7 Hz, 1H), 5.32 (d, J=11.9 Hz, 1H, OCH_AH$_B$Ph), 5.23 (d, J=11.9 Hz, 1H, OCH$_A$$H_B$Ph), 4.09 (d, J=14.2 Hz, 1H), 3.65 (d, J=13.9 Hz, 1H), 3.59 (d, J=13.9 Hz, 1H), 3.58 (d, J=14.2 Hz, 1H), 3.50 (s, 3H, CH_3OC), 2.36 (d, J=0.7 Hz, 3H, CH_3C), 2.12 (s, 3H, CH_3OC), 1.64 (s, 3H, CH_3C), 1.50 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CHCl_3$) δ 169.0 (OC═O), 168.5 (C═N), 159.6, 155.4 (NC═O), 137.1, 135.4, 131.5, 129.0, 128.7, 128.6, 128.2, 126.7, 106.5, 102.9, 89.6, 68.7, 67.9 (O*C*H$_2$Ph), 50.0, 49.1, 39.5, 35.7, 19.9, 18.6, 12.3. $[\alpha]_D^{25}$=+34.2 (*c* 3.49, $CHCl_3$). HRMS (+ESI) Calcd for $C_{28}H_{32}N_2O_7Na$ $[M+Na]^+$ 531.2107, found 531.2097.

4.5.17. Benzyl-(2*S*,3*R*,5*R*)-5-(4-Heptyloxy-benzyl)-2,3-dimethoxy-2,3,5-trimethyl-6-oxomorpholine-4-carboxylate (14e). Lactone **13b** (60 mg, 0.18 mmol) was alkylated with 1-heptyloxy-4-(iodo-ethyl)-benzene (173 mg, 0.54 mmol) according to method C for 36 h to give lactone **14e** (30 mg, 30%) as a colourless oil. IR (neat) 1749 (OC═O), 1713 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.33 (m, 5H), 6.83 (d, J=2.0 Hz, 2H), 6.73 (d, J=2.0 Hz, 2H), 5.13 (ap q, 2H, OCH_2Ph), 3.90 (t, J=6.6 Hz, 2H), 3.41 (s, 3H, CH_3OC), 3.26 (s, 3H, CH_3OC), 2.47–2.33 (m, 4H), 1.80 (s, 3H, CH_3), 1.79–1.73 (m, 2H), 1.65 (s, 3H, CH_3C), 1.56 (s, 3H, CH_3OC), 1.44–1.41 (m, 2H), 1.35–1.24 (m, 6H), 0.88 (t, J=6.8 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8 (OC═O), 157.3, 155.4 (NC═O), 135.6, 133.5, 129.1, 128.6, 128.5, 128.3, 114.4, 106.5, 90.4, 68.0 (O*C*H$_2$Ph), 67.5, 64.8, 50.4, 49.9, 41.7, 31.7, 30.6, 29.3, 29.1, 26.0, 23.1, 22.6, 19.3, 18.9, 14.1. $[\alpha]_D^{25}$=+2.0 (*c* 0.9 $CHCl_3$). HRMS (+ESI) Calcd for $C_{32}H_{45}NO_7Na$ $[M+Na]^+$ 578.3094, found 578.3094.

4.5.18. Benzyl-(2*S*,3*R*,5*S*)-5-benzyl-2,3-dimethoxy-2,3-dimethyl-5-(5-methyl-isoxazol-3-ylmethyl)-6-oxo-morpholine-4-carboxylate (14f). Lactone **2** (119 mg, 0.37 mmol) was alkylated with 3-bromomethyl-5-isoxazole (176 mg, 1 mmol) according to method D to give an intermediate lactone as a colourless oil, a portion of which (33 mg, 0.079 mmol) which was alkylated with benzyl bromide (41 mg, 0.237 mmol) according to method A to give lactone **14f** (47 mg, 31%) as a white solid. Mp 156–160 °C (ether). IR (neat) 1752 (OC═O), 1712 (C═O) cm^{-1}. ^1H NMR (600 MHz, $CHCl_3$) δ 7.57–7.56 (m, 2H), 7.47–7.41 (m, 3H), 7.18–7.14 (m, 4H), 6.89–6.87 (m, 1H), 5.87 (s, 1H), 5.33 (d, J=11.5 Hz, 1H, OCH_AH$_B$Ph), 5.32 (d, J=11.5 Hz, 1H, OCH$_A$$H_B$Ph), 3.89 (d, J=13.8, 1H), 3.68 (d, J=14.3, 1H), 3.51 (s, 3H, CH_3OC), 3.45 (d, J=13.8 Hz, 1H), 3.02 (d, J=14.3 Hz, 1H), 2.92 (s, 3H, CH_3OC), 2.60 (s, 3H, CH_3OC), 1.80 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CHCl_3$) δ 171.4 (OC═O), 168.3 (C═N), 160.3 (C═*C*–O), 155.4 (NC═O), 140.1, 135.7, 135.5, 130.8, 129.3, 128.7, 128.6, 128.5, 128.2, 128.1, 107.1, 103.9, 89.6, 68.6 (O*C*H$_2$Ph), 67.9, 49.9, 49.7, 44.0, 33.3, 28.5, 20.0, 18.2. $[\alpha]_D^{25}$=+104.8 (*c* 0.5, $CHCl_3$).

4.5.19. Benzyl-(2*S*,3*R*,5*R*)-2,3-dimethoxy-2,3,5-trimethyl-5-(5-methyl-isoxazol-3-ylmethyl)-6-oxo-morpholine-4-carboxylate (14g). Lactone **13b** (62 mg, 0.19 mmol) was alkylated with 3-bromomethyl-5-isoxazole (99 mg, 0.56 mmol) according to method C to give lactone **14g** (50 mg, 62%) as a colourless oil. IR (neat) 1754 (OC═O), 1713 (C═O), 1608 (C═N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.33 (m, 5H), 5.72 (d, J=0.6 Hz, 1H), 5.23 (d, J=12.1 Hz, 1H, CH_AH$_B$Ph), 5.20 (d, J=12.1 Hz, 1H, CH$_A$$H_B$Ph), 3.80 (d, J=14.2 Hz, 1H, CH_AH$_B$C═N), 3.40 (s, 3H, CH_3OC), 3.35 (d, J=14.2 Hz, 1H, CH$_A$$H_B$C═N), 3.24 (s, 3H, C$H_3$OC), 2.33 (d, J=0.6 Hz, 3H), 1.77 (s, 3H, CH_3C), 1.68 (s, 3H, CH_3C), 1.54 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (OC═O), 168.8 (C═N), 159.4, 155.3 (NC═O), 135.6, 128.7, 128.5, 128.4, 106.5, 102.8, 90.6, 67.7 (O*C*H$_2$Ph), 64.3, 50.4, 50.0, 34.9, 22.4, 19.4, 18.8, 12.5 (C═CO–*C*H$_3$). $[\alpha]_D^{25}$=+33.6 (*c* 1.0, $CHCl_3$). HRMS (+ESI) Calcd for $C_{22}H_{28}N_2O_7Na$ $[M+Na]^+$ 455.1794, found 455.1787.

4.5.20. Benzyl-(2*S*,3*R*,5*R*)-5-benzothiazol-2-ylmethyl-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14h). Lactone **13b** (49 mg, 0.151 mmol) was

alkylated with 2-bromomethyl-1,3-benzathiazole (103 mg, 0.453 mmol) according to method C to give lactone **14h** (18 mg, 25%) as a brown solid. Mp 82–84 °C (petrol/ether). IR (neat) 1754 (OC═O), 1716 (NC═O), 1693 (C═N) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, J=8.1 Hz, 1H) 7.79 (d, J=7.9 Hz, 1H), 7.46–7.31 (m, 7H), 5.33 (d, J=12.1 Hz, 1H, OCH_AH_BPh), 5.29 (d, J=12.1 Hz, 1H, OCH_AH_BPh), 4.13 (d, J=14.1 Hz, 1H), 3.99 (d, J=14.1 Hz, 1H), 3.26 (s, 3H, CH_3OC), 3.09 (s, 3H, CH_3OC), 1.84 (s, 3H, CH_3C), 1.76 (s, 3H, CH_3C), 1.50 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (OC═O), 165.1 (C═N–C), 155.4 (NC═O), 153.7 (C═N–C), 135.9, 135.7, 128.7, 128.5, 128.4, 125.7, 124.8, 123.2, 121.3, 106.5, 90.6, 67.8 (OCH_2Ph), 65.1, 50.4, 50.3, 43.1, 23.6, 19.2, 18.9. $[\alpha]_D^{25}$=+2.0 (c 0.9, $CHCl_3$). HRMS (+ESI) Calcd for $C_{25}H_{28}N_2O_6SNa$ $[M+Na]^+$ 507.1567, found 507.1566.

4.5.21. Benzyl-(2*S*,3*R*,5*R*)-5-[3,4-bis-(2,2-dimethyl-propionyloxy)-benzyl]-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14i). Lactone **13b** (98 mg, 0.29 mmol) was alkylated with 4-(bromomethyl)-2-[(2,2-dimethylpropanoyl)oxy]phenyl pivalate (323 mg, 0.87 mmol) according to method D to give lactone **14i** (27 mg, 15%) as a colourless oil. IR (neat) 1760, 1715 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 6.90 (d J=8.9 Hz, 1H), 6.70–6.77 (m, 2H), 5.22 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.21 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 3.39 (d, J=10 Hz, 1H, CH_ACH_BAr), 3.24 (d, J=10 Hz, 1H, CH_ACH_BAr), 3.23 (s, 3H, CH_3OC), 3.17 (s, 3H, CH_3OC), 1.73 (s, 3H, CH_3C), 1.59 (s, 3H, CH_3C), 1.48 (s, 3H, CH_3OC), 1.30 (s, 18H, $C(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9 (OC═O^{t}Bu), 175.7 (OC═O^{t}Bu), 170.8 (OC═O), 155.5 (NC═O), 141.9, 141.5, 135.5, 134.8, 128.7, 128.65, 128.62, 128.5, 127.8, 125.4, 106.4, 90.5, 67.7 (OCH_2Ph), 65.8, 50.4, 49.9, 43.2, 39.1, 39.0, 27.24, 27.20, 22.9, 19.2, 19.0. $[\alpha]_D^{25}$=+15.0 (c 0.4, $CHCl_3$). HRMS (+ESI) Calcd for $C_{34}H_{45}NO_9Na$ $[M+Na]^+$ 650.2941, found 650.2940.

4.5.22. Benzyl-(2*S*,3*R*,5*S*)-5-[3,4-bis-(2,2-dimethyl-propionyloxy)-benzyl]-2,3-dimethoxy-2,3,5-trimethyl-6-oxo-morpholine-4-carboxylate (14j). Lactone **13k** (80 mg, 0.13 mmol) was alkylated with methyl iodide (55 mg, 0.39 mmol) according to method A to give lactone **14j** (36 mg, 44%) as a colourless oil. IR (neat) 1758 (OC═O), 1714 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.42–7.21 (m, 5H), 7.08 (d, J=2.0 Hz, 1H), 7.00 (dd, J=8.3, 2.0 Hz, 1H), 6.83 (d, J=8.3 Hz, 1H), 5.32 (d, J=7.3 Hz, 1H, OCH_AH_BPh), 5.18 (d, J=7.3 Hz, 1H, OCH_AH_BPh), 3.59 (d, J=14.0 Hz, 1H), 3.51 (d, J=14.0 Hz, 1H), 3.40 (s, 3H, CH_3OC), 2.47 (s, 3H, CH_3OC), 1.79 (s, 3H, CH_3C), 1.63 (s, 3H, CH_3C), 1.47 (s, 3H, CH_3C), 1.30 (6×CH_3). ^{13}C NMR (125 MHz, $CHCl_3$) δ 176.1 (OC═O^{t}Bu), 175.9 (OC═O^{t}Bu), 172.3 (OC═O), 155.2 (NC═O), 142.2, 141.1, 136.5, 135.6, 129.3, 128.8, 128.7, 128.6, 128.4, 126.2, 106.2, 86.7, 67.7 (OCH_2Ph), 65.4, 49.7 (CH_3OC), 49.6 (CH_3OC), 41.1, 39.1, 39.0, 27.3, 27.2, 19.6, 18.7, 15.3. $[\alpha]_D^{25}$=+43.0 (c 1.5, $CHCl_3$). HRMS (+ESI) $C_{34}H_{45}NO_{10}Na$ $[M+Na]^+$ 650.2941, found 650.2961.

4.5.23. Benzyl-(2*S*,3*R*)-5,5-diallyl-2,3-dimethoxy-2,3-dimethyl-6-oxo-morpholine-4-carboxylate (14k). Lactone **13a** (30 mg, 0.083 mmol) was alkylated with allyl bromide (30 mg, 0.249 mmol) according to method A to give lactone **14k** (24 mg, 72%) as white needles. Mp 88–90 °C. IR (neat) 1751 (OC═O), 1710 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 5H), 5.82–5.73 (m, 1H, CH═CH_2), 5.70–5.62 (m, 1H, CH═CH_2) 5.17 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.12 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.05–4.88 (m, 4H, 2×CH═CH_2), 3.42 (s, 3H, CH_3OC), 3.31 (s, 3H, CH_3OC), 3.17 (ddt, J=14.2, 8.1 Hz, 1H, $C_AH_AH_BCH$═CH_2), 3.02 (ddt, J=14.5, 5.1, 1.7 Hz, 1H, $C_BH_AH_BCH$═CH_2), 2.93 (ddt, J=14.2, 7.1, 1.2 Hz, 1H, $C_AH_AH_BCH$═CH_2), 2.84 (dd, J=14.5, 9.5 Hz, 1H, $C_BH_AH_BCH$═CH_2), 1.81 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (OC═O), 155.5 (NC═O), 135.5, 134.9, 133.4, 128.7, 128.7, 128.5, 118.2, 117.9, 106.6, 89.9, 67.8, 67.3, 51.9, 49.7, 43.1, 40.0, 19.8, 18.3. $[\alpha]_D^{25}$=+28.5 (c 2.0, $CHCl_3$). HRMS (+ESI) Calcd for $C_{22}H_{29}NO_6Na$ $[M+Na]^+$ 426.1893, found 426.1912. Structure and relative stereochemistry confirmed by single crystal X-ray diffraction studies.

4.5.24. Benzyl-(2*S*,3*R*,5*S*)-5-allyl-2,3-dimethoxy-2,3-dimethyl-5-(2-methyl-allyl)-6-oxo-morpholine-4-carboxylate (14l). Lactone **13j** (198 mg, 0.53 mmol) was alkylated with allyl bromide (193 mg, 1.59 mmol) according to method D to give lactone **14l** (85 mg, 38%) as white needles. Mp 62–64 °C (petrol/ether). IR (neat) 1749 (OC═O), 1710 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.35 (m, 5H), 5.65 (dddd, J=16.9, 10.1, 8.1, 7.0 Hz, 1H), 5.19 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.11 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.01 (d, J=10.1 Hz, 1H), 4.93 (d, J=16.9 Hz, 1H), 4.76 (s, 1H), 4.65 (s, 1H), 3.41 (s, 3H, CH_3OC), 3.33 (dd, J=14.2, 8.1 Hz, 1H, CH_3OC), 3.10 (s, 3H, CH_3OC), 2.98 (d, J=13.9 Hz, 1H), 2.96 (d, J=13.9 Hz, 1H), 2.87 (dd, J=14.2, 7.0 Hz, 1H), 1.80 (s, 3H, CH_3C), 1.72 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (OC═O), 155.5 (NC═O), 142.5, 135.4, 133.5, 128.8, 128.7, 128.6, 118.1, 116.6, 106.3, 89.5, 67.8 (OCH_2Ph), 66.7, 51.1, 49.6, 43.6, 42.3, 23.9, 19.7, 18.5. $[\alpha]_D^{25}$=+39.0 (c 1.0, $CHCl_3$). HRMS (+ESI) Calcd for $C_{23}H_{31}NO_6Na$ $[M+Na]^+$ 440.2049, found 440.2051. Structure and relative stereochemistry confirmed by single crystal X-ray diffraction studies.

4.5.25. Benzyl-(2*S*,3*R*,5*R*)-5-allyl-2,3-dimethoxy-5-(2-methoxycarbonyl-allyl)-2,3-dimethyl-6-oxo-morpholine-4-carboxylate (14m). Lactone **13a** (91 mg, 0.25 mmol) was alkylated with methyl (2-bromomethyl)-acrylate (149 mg, 0.83 mmol) according to method D to give lactone **14m** (92 mg, 79%) as white needles. Mp 124–126 °C ($CHCl_3$). IR (neat) 1746 (OC═O), 1714 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.34 (m, 5H), 6.16 (d, J=1.5 Hz, 1H), 5.67–5.5.61 (m, 1H), 5.38 (s, 1H), 5.18 (d, J=11.8 Hz, 1H, OCH_AH_BPh), 5.13 (d, J=11.8 Hz, 1H, OCH_AH_BPh), 4.91 (dd, J=10.1, 1.5 Hz, 1H), 4.84 (dd, J=17.1, 1.5 Hz, 1H), 3.69 (s, 3H, CH_3OC), 3.55 (d, J=13.6 Hz, 1H), 3.52 (s, 3H, CH_3OC), 3.30 (s, 3H, CH_3OC), 3.29 (d, J=13.6 Hz, 1H), 2.90–2.83 (m, 2H), 1.81 (s, 3H, CH_3C) 1.58 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (OC═O), 167.3 (OC═O), 155.6 (NC═O), 136.4, 135.4 (C═CH_2), 134.8 (CH═CH_2), 129.7, 128.9, 128.7, 128.6, 117.7 (CH═CH_2), 106.5, 89.6, 67.9 (OCH_2Ph), 66.8, 52.2, 51.8, 50.1, 39.4, 38.5, 19.8, 18.3. $[\alpha]_D^{25}$=+70.2 (c 1.2, $CHCl_3$).

HRMS (+ESI) Calcd for $C_{24}H_{31}NO_8Na$ $[M+Na]^+$ 484.1947, found 484.1948. Structure and relative stereochemistry confirmed by single crystal X-ray diffraction studies.

4.5.26. Benzyl-(7*R*,8*S*)-7,8-dimethoxy-7,8-dimethyl-10-oxo-9-oxa-6-aza-spiro[4.5]dec-2-ene-6-carboxylate (15k). 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)-ruthenium (5.9 mg, 6.9 μmol) was added to a solution of lactone **14k** (28 mg, 6.9 μmol) was dissolved in dichloromethane (5 mL) and the solution heated at reflux for 2 h. The solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was purified by column chromatography (petrol/ether, 3:1) to give cyclopentene **15k** (23 mg, 89%) as white needles. IR (neat) 1752 (OC═O), 1714 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.33–7.31 (m, 5H), 5.61 (m, 1H, CH_A═CH_B), 5.43 (m, 1H, CH_A═CH_B), 5.10 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 5.09 (d, J=12.0 Hz, 1H, OCH_AH_BPh), 3.41 (s, 3H, CH_3OC), 3.26 (dq, J=16.3, 2.5 Hz, 1H), 3.20 (s, 3H, CH_3OC), 3.07 (dm, J=17.7 Hz, 1H, CH_AH_BC), 2.64 (dq, J=17.7, 2.5 Hz, 1H, CH_AH_BC), 2.57 (dqn, J=16.3, 2.2 Hz, 1H, CH_AH_BC), 1.79 (s, 3H, CH_3C), 1.55 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CHCl_3$) δ 172.3 (OC═O), 154.9 (NC═O), 135.5, 129.3 (C_A═C_B), 128.7, 128.4, 128.3, 126.3 (C_A═C_B), 106.0, 90.1, 67.4 (OCH_2Ph), 66.3, 50.0, 49.6, 47.6, 45.1, 18.9, 17.9. $[\alpha]_D^{25}$=+4.0 (c 0.25, $CHCl_3$). HRMS (+ESI) $C_{20}H_{25}NO_6Na$ $[M+Na]^+$ 398.1580, found 398.1579. Structure and relative stereochemistry confirmed by single crystal X-ray diffractions studies.

4.5.27. Benzyl-(5*R*,7*R*,8*S*)-7,8-dimethoxy-2,7,8-trimethyl-10-oxo-9-oxa-6-aza-spiro[4.5]dec-2-ene-6-carboxylate (15l). 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium (12 mg, 0.014 mmol) was added to a solution of lactone **14l** (60 mg, 0.14 mmol) in tetrahydrofuran (5 mL) and the solution heated at reflux for 2 h. The solution was allowed to cool and the solvent removed under reduced pressure. The residue was purified by column chromatography (petrol/ether, 3:1) to give cyclopentene **15l** (49 mg, 87%) as white needles. Mp 129–132 °C (ether). IR (neat) 1747 (OC═O), 1710 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.33–7.30 (m, 5H), 5.12 (d, J=11.9 Hz, 1H, OCH_AH_BPh), 5.03 (d, J=11.9 Hz, 1H, OCH_AH_BPh), 4.98 (d, J=1.7, 1H), 3.41 (s, 3H, CH_3OC), 3.20 (s, 3H, CH_3OC), 3.06 (d, J=16.0 Hz, 1H), 3.00 (dqn, J=17.4, 2.0 Hz, 1H), 2.61 (dq, J=17.4, 2.2 Hz, 1H), 2.46 (d, J=16.0 Hz, 1H), 1.79 (s, 3H, CH_3C), 1.54 (br s, 3H, CH_3C═C), 1.53 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CHCl_3$) δ 172.3 (OC═O), 154.9 (NC═O), 138.7, 135.5, 128.7, 128.4, 128.3, 120.1, 105.9, 90.1, 67.4 (OCH_2Ph), 66.8, 49.9 (CH_3OC), 49.6 (CH_3OC), 48.7, 47.9, 18.9, 18.0, 16.2 (CH═CCH_3). $[\alpha]_D^{25}$=+12.2 (c 0.58, $CHCl_3$). HRMS (+ESI) Calcd for $C_{21}H_{27}NO_6$ $[M+Na]^+$ 412.1736, found 412.1729.

4.5.28. 6-Benzyl-2-methyl-(5*R*,7*R*,8*S*)-7,8-dimethoxy-7,8-dimethyl-10-oxo-9-oxa-6-aza-spiro[4.5]dec-2-ene-2,6-dicarboxylate (15m). 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium (11 mg, 13 μmol) was added to a solution of lactone **14m** (59 mg, 0.13 mmol) in dichloromethane (10 mL) and the solution heated at reflux for 2 days. The solution was allowed to cool and the solvent removed under reduced pressure and the residue was purified by column chromatography (petrol/ether, 3:1) to give cyclopentene **15m** (44 mg, 79%) as a yellow oil. IR (neat) 1749 (OC═O) and 1713 (NC═O) cm^{-1}. ^1H NMR (500 MHz, $CHCl_3$) δ 7.32–7.30 (m, 3H), 7.26–7.24 (m, 2H), 6.50 (qn, J=2.1 Hz, 1H), 5.06 (d, J=11.7 Hz, 1H, OCH_AH_BPh), 5.05 (d, J=11.7 Hz, 1H, OCH_AH_BPh), 3.62 (s, 3H, CH_3OC), 3.45–3.41 (m, 4H), 3.24 (ddt, J=17.8, 3.2, 1.6 Hz, 1H), 3.20 (s, 3H, CH_3OC), 2.84 (dt, J=17.8, 2.4 Hz, 1H), 2.69 (dq, J=18.9, 2.5 Hz, 1H), 1.80 (s, 3H, CH_3C), 1.57 (s, 3H, CH_3C). ^{13}C NMR (125 MHz, $CHCl_3$) δ 171.7 (C═$OOCH_3$), 164.3 (OC═O), 154.7 (NC═O), 141.2, 134.9, 132.0 (C-8), 128.9, 128.5, 128.4, 106.2, 90.2, 67.9 (OCH_2Ph), 66.0, 51.3, 50.2, 49.7, 46.2, 45.9, 18.8, 17.8. $[\alpha]_D^{25}$=−46.8 (c 0.98, $CHCl_3$). HRMS (+ESI) $C_{22}H_{27}NO_8Na$ $[M+Na]^+$ 456.1634 found 456.1648.

4.6. Cleavage method A for the preparation of mono substituted α-amino acids

The lactone was treated with aqueous trifluoroacetic acid (9:1 TFA–H_2O, 1 mL per 10 mg) and the solution stirred for 30 min. The solvent was removed under reduced pressure and the residue purified by column chromatography (petrol/ether, 2:1–2:1+5% acetic acid) or preparative HPLC to give the amino acid.

4.7. Cleavage method B for the preparation of disubstituted α,α-amino acids

The lactone (1 equiv.) was treated with aqueous trifluoroacetic acid (2:1 TFA–H_2O, 1 mL per 10 mg) and the solution stirred for 30 min. The solvent was removed under reduced pressure and the residue treated with 1 N NaOH–MeOH (1 mL per 10 mg) for 30 min. The solvent was removed under reduced pressure and the residue purified by column chromatography (petrol/ether, 1:1–1:1+5% acetic acid) or prep-HPLC to give the amino acid.

4.7.1. (2*R*)-2-Benzyloxycarbonylamino pent-4-enoic acid (16a). Lactone **13a** (20.6 mg, 0.044 mmol) was treated according to method A to yield amino acid **16a** (12 mg, 77%) as a colourless oil. IR (neat) 3400 (OH), 1671 (br 2×C═O) cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 7.36–7.26 (m, 5H, Ph), 5.83–5.74 (m, 1H), 5.13–5.04 (m, 4H), 4.19 (dd, J=8.2, 4.9 Hz, 1H, NHCH), 2.60–2.52 (m, 1H), 2.46–2.40 (m, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 175.6 (C═OOH), 158.4 (NC═O), 138.3, 134.8, 129.4, 129.0, 128.8, 118.5, 67.6 (OCH_2Ph), 55.5, 37.4. $[\alpha]_D^{25}$=−9.3 (c 0.8, $CHCl_3$). HRMS (+ESI) Calcd for $C_{13}H_{15}NO_4Na$ $[M+Na]^+$ 272.0899, found 272.0903.

4.7.2. (2*R*)-2-Benzyloxycarbonylamino propanoic acid (16b). Lactone **13b** (25.7 mg, 0.076 mmol) was treated according to cleavage method A to yield amino acid **16b** (12 mg, 71%) as white plates. Mp 71–73 °C (H_2O). IR (neat) 1701 (br, 2×C═O) cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 7.36–7.26 (m, 5H, Ph), 5.08 (s, 2H, OCH_2Ph), 4.17 (q, J=7.3 Hz, 1H, NHCH), 1.37 (d, J=7.3 Hz, 3H,

CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 176.5 (C═OOH), 158.4 (NC═O), 138.2, 129.4, 129.0, 128.8, 67.5 (OCH_2Ph), 51.1 (NHCH), 17.9 (CH_3). $[\alpha]_D^{25}$=+12.1 (*c* 0.9, $CHCl_3$). HRMS (+ESI) Calcd for $C_{11}H_{13}NO_4Na$ $[M+Na]^+$ 246.0742, found 246.0732.

4.7.3. (2*R*)-2-Benzyloxycarbonylamino-3-phenylpropanoic acid (16e). Lactone **13e** (21 mg, 0.051 mmol) was treated according to method A to yield amino acid **16e** (13 mg, 85%) as a white solid. Mp 85–88 °C (H_2O). IR (neat) 1691 (br, 2×C═O) cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) δ 7.32–7.19 (m, 10H), 5.03 (d, *J*=12.5 Hz, 1H, OC$H_A$$H_B$Ph), 5.01 (d, *J*=12.5 Hz, 1H, OCH$_A$$H_B$Ph), 4.39 (dd, *J*=9.0, 4.9 Hz, 2H, CHCH$_2$), 3.18 (dd, *J*=13.8, 4.9 Hz, 1H, CHC$H_A$$H_B$Ph), 2.92 (dd, *J*=13.8, 9.0 Hz, 1H, CHCH$_A$$H_B$). ^{13}C NMR (125 MHz, CD_3OD) δ 158.3 (NC═O), 138.7, 138.3, 130.3, 129.4, 129.37, 128.9, 128.7, 127.7, 67.4 (OCH_2Ph), 57.1, 38.7 (*C*OOH not observed). $[\alpha]_D^{25}$=+4.1 (*c* 1.0. MeOH). HRMS (+ESI) Calcd for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$ 322.1055, found 322.1042.

4.7.4. (2*S*)-2-Benzyloxycarbonylamino-2-methyl-3-phenylpropanoic acid (17b). Lactone **14b** (15 mg, 0.035 mmol) was treated according to cleavage method B to obtain amino acid **17b** (10 mg, 76%) as a colourless oil. IR (neat) 3333 (OH), 1714 (br, 2×C═O) cm^{-1}. ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.38–7.32 (m, 5H), 7.22–7.19 (m, 3H), 7.03–7.02 (m, 2H), 5.33 (s, 1H, NH), 5.15 (d, *J*=12.3 Hz, 1H, OC$H_A$$H_B$Ph), 5.11 (d, *J*=12.3 Hz, 1H, OCH$_A$$H_B$Ph), 3.34 (d, *J*=13.6 Hz, 1H), 3.27 (d, *J*=13.6 Hz, 1H), 1.63 (s, 3H, CH_3C). ^{13}C NMR (150 MHz, $CHCl_3$) δ 176.9 (C═OOH), 155.0 (NC═O), 136.3, 135.6, 130.0, 128.5, 128.3, 128.2, 127.0, 66.7 (OCH_2Ph), 60.3, 41.3, 23.5 (CH_3C). $[\alpha]_D^{25}$=−25.8 (*c* 1.5, $CHCl_3$). HRMS (+ESI) Calcd for $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ 336.1206, found 336.1214.

4.7.5. (2*R*)-2-Benzyloxycarbonylamino-2-(5-methylisoxazol-3-ylmethyl)-3-phenyl-propionic acid (17d). Lactone **14d** (10 mg, 19.7 μmol) was treated according to cleavage method B to obtain amino acid **17d** (4 mg, 52%) as a colourless oil. IR (neat) 3367 (OH), 1711 (br 2×C═O) cm^{-1}. ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.39–7.34 (m, 5H, OCH$_2$*Ph*), 7.21–7.17 (m, 3H, Ph), 7.08–7.07 (m, 2H, Ph), 5.69 (s, 1H, N*H*), 5.57 (s, 1H, C*H*═CCH$_3$), 5.17 (d, *J*=12.3 Hz, 1H, OC$H_A$$H_B$Ph), 5.15 (d, *J*=12.3 Hz, 1H, OCH$_A$$H_B$Ph), 3.82 (d, *J*=13.9 Hz, 1H, C$_A$$H_AH_B$C), 3.66 (d, *J*=13.4 Hz, 1H, C$_B$$H_AH_B$C), 3.41 (d, *J*=13.9 Hz, 1H, C$_A$H$_A$$H_B$C), 3.31 (d, *J*=13.4 Hz, 1H, C$_B$H$_A$$H_B$C), 2.26 (s, 3H, C$H_3$). ^{13}C NMR (125 MHz, $CHCl_3$) δ 172.3 (C═OOH), 169.6 (C═N), 154.7 (NC═O), 136.6, 135.3, 129.8, 128.5, 128.4, 128.3, 128.2, 127.1, 125.5, 103.2 (*C*H═CCH$_3$), 66.4 (OCH_2Ph), 40.8, 34.3, 12.2. $[\alpha]_D^{25}$=+3.0 (*c* 0.4, $CHCl_3$). HRMS (+ESI) Calcd for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ 417.1426, found 417.1425.

4.7.6. (2*R*)-2-Benzyloxycarbonylamino-4-(4-heptyloxyphenyl)-2-methyl-butyric acid (17e). Lactone **14e** (13.5 mg, 23 μmol) was treated according to cleavage method B to obtain amino acid **17e** (9.8 mg, 97%) as a colourless oil. IR (neat) 1711 (br 2×C═O) cm^{-1}. 1H NMR (500 MHz, $CHCl_3$) δ 7.35–7.29 (m, 5H, OCH$_2$*Ph*), 7.00 (d, *J*=8.1 Hz, 2H), 6.78 (d, *J*=8.1 Hz, 2H), 5.55 (s, 1H, N*H*), 5.09 (s, 2H, OCH_2Ph), 3.89 (t, *J*=6.6 Hz, 2H), 2.55 (dd, *J*=11.2, 8.8 Hz, 1H), 2.43 (m, 2H), 2.13 (m, 1H), 1.74 (ap qn, *J*=7.0 Hz, 2H), 1.64 (s, 3H, CH_3), 1.43–1.21 (m, 8H), 0.87 (t, *J*=6.2 Hz, 3H). $[\alpha]_D^{25}$=−4.0 (*c* 0.5, $CHCl_3$). HRMS (+ESI) Calcd for $C_{26}H_{35}NO_5Na$ $[M+Na]^+$ 464.2413, found 464.2393.

4.7.7. (2*R*)-2-Benzyloxycarbonylamino-2-methyl-3-(5-methylisoxazol-3-yl)propanoic acid (17g). Lactone **14g** (26 mg, 61.4 μmol) was treated according to cleavage method B to obtain amino acid **17g** (16 mg, 81%) as a colourless oil. IR (neat) 1717 br (2×C═O) cm^{-1}. ^{1}H NMR (600 MHz, $CHCl_3$) δ 7.38–7.26 (m, 5H), 5.79 (s, 1H, NH), 5.62 (s, 1H), 5.18 (d, *J*=12.2 Hz, 1H, OC$H_A$$H_B$Ph), 5.07 (d, *J*=12.2 Hz, 1H, OCH$_A$$H_B$Ph), 3.46 (d, *J*=14.2 Hz, 1H), 3.34 (d, *J*=14.2 Hz, 1H), 2.65 (s, 3H, CH_3), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CHCl_3$) δ 174.1 (OC═O), 169.6 (C═N), 159.4, 155.2 (NC═O), 136.2, 128.5, 128.3, 128.2, 103.1, 66.8 (OCH_2Ph), 59.1, 32.4, 23.7, 12.2. $[\alpha]_D^{25}$=−4.1 (*c* 0.8, $CHCl_3$). HRMS (+ESI) Calcd for $C_{16}H_{18}N_2O_5Na$ $[M+Na]^+$ 341.1113, found 341.1115.

4.7.8. (1*S*)-1-Benzyloxycarbonylamino-3-methylcyclopent-3-ene-1-carboxylic acid (17l). Lactone **15l** (22 mg, 56 μmol) was treated according to cleavage method B to obtain amino acid **17l** (13 mg, 84%) as a colourless oil. IR (neat) 1709 (br, 2×C═O) cm^{-1}. ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.37–7.30 (m, 5H, Ph), 5.36 (s, 1H, C*H*═C), 5.23 (s, 1H, N*H*), 5.10 (s, 2H, OCH_2Ph), 3.07 (br d, *J*=16.2 Hz, 2H, C$_A$$H_AH_BC, C_B$$H_AH_B$C), 2.58 (ap t, *J*=17.0 Hz, 2H, C$_A$H$_A$$H_BC, C_BH_A$$H_B$C), 1.72 (s, 3H, C$H_3$). ^{13}C NMR (125 MHz, $CHCl_3$) δ 155.9 (NC═O), 137.6 (CH═*C*CH$_3$), 135.9, 128.5, 128.2, 128.1, 120.7 (*C*H═CCH$_3$), 67.1 (OCH_2Ph), 64.9, 48.3, 44.8, 16.1. $[\alpha]_D^{25}$=−3.2 (*c* 0.5, $CHCl_3$). HRMS (+ESI) Calcd for $C_{15}H_{17}NO_4Na$ $[M+Na]^+$ 298.1055, found 298.1042.

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Stereoselective synthesis of functionalised triol units by $SnCl_4$ promoted allylation of α-benzyloxyaldehydes: crucial role of the stoichiometry of the Lewis acid

Christophe Dubost,[a] Bernard Leroy,[a] Istvan E. Markó,[a,*] Bernard Tinant,[b] Jean-Paul Declercq[b] and Justin Bryans[c]

[a]*Unité de chimie organique et médicinale, Département de Chimie, Université catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la Neuve, Belgium*
[b]*Unité de chimie structurale, Département de Chimie, Université catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la Neuve, Belgium*
[c]*Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*

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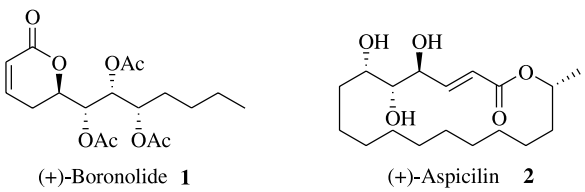
Dedicated with deep respect to Professor Dieter Seebach

Abstract—Enantiomerically pure *syn–anti* and *syn–syn* configured triol units are efficiently synthesized by the $SnCl_4$ mediated allylation of chiral α-benzyloxyaldehydes with the uniquely functionalised allylstannane **9**. Remarkably, the stereochemistry of the adducts is solely governed by the amount of Lewis acid employed.

1. Introduction

Numerous natural products, exhibiting interesting biological activities, contain a polyhydroxylated subunit in their structures. These fragments are present, for example, in molecules such as (+)-boronolide[1] **1** or (+)-aspicilin[2] **2**, which possess a *syn–syn* and *syn–anti* triol sequence, respectively (Fig. 1).



(+)-Boronolide **1** (+)-Aspicilin **2**

Figure 1.

In views of the ubiquitousness of these polyol entities, it is not surprising that numerous synthetic methods have been developed to assemble these structures with excellent levels of relative and absolute stereocontrol.[3] Among others, the reaction of allylic organometallic species with aldehydes has emerged as one of the most synthetically useful procedures for acyclic stereoselection. Over the past few years, the allylation of chiral alkoxyaldehydes has been extensively studied and has become a particularly valuable tool for the construction of homoallylic alcohols. Numerous allylic derivatives such as allylborons,[4] allylchromiums,[5] allyltins,[6] etc. were found to be efficient reagent in this transformation, leading to the desired adducts with high stereoselectivity for this process (Fig. 2).

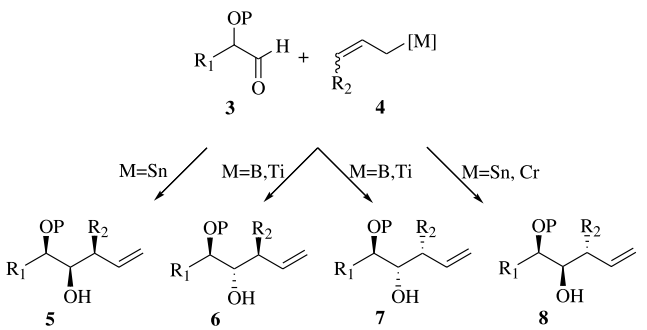


Figure 2. R_1=Me, Et, *n*Bu; R_2=OR, Me, SR P=Bn, TBDMS, MOM.

All four possible diastereoisomers of the triol subunit can be obtained by varying the nature of the allylic metal, the

Keywords: Allylation; Allylstannane; Chelation; Triols; Stereocontrol; Lewis acid.
* Corresponding author. Tel.: +32-10-47-8773; fax: +32-10-47-2788; e-mail address: marko@chim.ucl.ac.be

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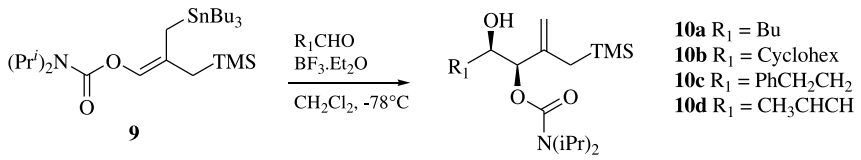


Figure 3.

conditions of the reaction (Lewis acid catalysed, high pressure or thermal), or the geometry of the double bond[7] present in the allylating agent. Roush et al.[4a–c] showed that β-substituted allylborons provided access to **5**, **6** and **7** but each isomer corresponds to a specific combination of the double bond geometry of **4** and the nature of the ligand on the boron. Chromium[5] derivatives were found to be less flexible, giving access only to isomer **8**. In sharp contrast, allyltin species afford isomers **5** and **8**, depending upon the type of transition states involved in the condensation.[8] Thus Lewis acids such as $BF_3{\cdot}Et_2O$ give rise to isomer **8** through a non chelating Felkin–Anh process whilst $MgBr_2$ a chelating Lewis acid provides access to isomer **5** as described by Keck.[8a–d] Furthermore, Marshall[8f–g] has reported complementary examples of this transformation by using enantioenriched (γ-alkoxyallyl) stannanes, which provide well defined (E) configured alkenes. Therefore, the use of β-alkoxyallylstannanes has become an efficient method for the assembly of stereodefined triols by modulating the experimental parameters.

Recently, we became interested in the reactivity of the uniquely functionalised allylstannane **9** and studied its condensation with various aldehydes. In the presence of $BF_3{\cdot}Et_2O$, the *syn* diols[9] **10a–d** were stereoselectively produced (Fig. 3).

Extension of this methodology to α-alkoxyaldehydes should increase its scope by giving access to stereodefined, protected, triols. In this article, we wish to report in full our results on the successful implementation of this approach.

Allylic alcohol **12** was prepared in good yield according to the procedure described by Trost[10] and starting from methallylalcohol **11** (Fig. 4). Allylsilane **12** was then condensed with isopropylcarbamoylchloride to afford allylcarbamate **13** in 93% yield. The use of NaH as the base and of Et_2O as the solvent proved essential to obtain high yields of the desired products. Deprotonation of **13** with *sec*BuLi,[11] followed by transmetallation with $Ti(O^iPr)_4$, generated the allyltitanium species **14a**, which subsequently reacted with tributyl tin chloride to give the allylating agent **9** in high yields.

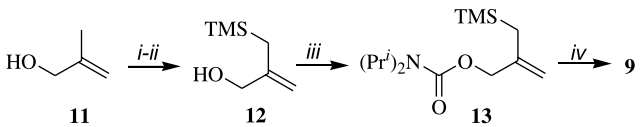


Figure 4. (i) *n*BuLi, TMEDA, TMSCl, Et_2O/THF, −78 °C; (ii) H_2SO_4, THF rt (47% 2 steps); (iii) $(^iPr)_2NCOCl$, NaH, Et_2O, 0 °C to rt (93%); (iv) *sec*BuLi, TMEDA, $Ti(O^iPr)_4$, Bu_3SnCl, Et_2O, −78 °C (80%).

This reaction proceeded efficiently at −78 °C and gave only the (*Z*)-isomer of allylstannane **9**. The observed stereoselectivity can be explained by the preferential pseudo-axial configuration adopted by the carbamate substitutent in the chair-like transition state **14b** leading to a better chelation of the titanium (Fig. 5). This preferred configuration is in agreement with previous observations reported by Yamamoto.[12]

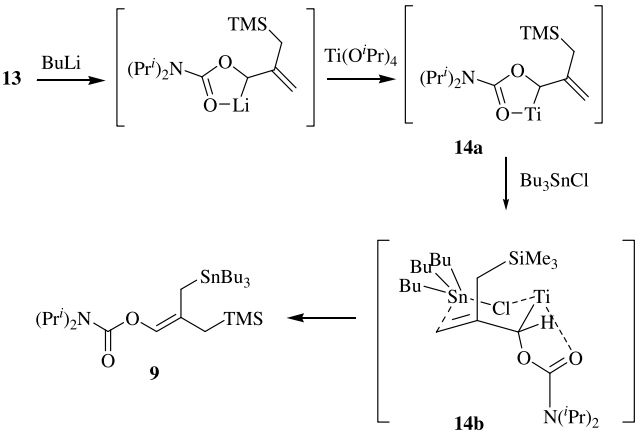
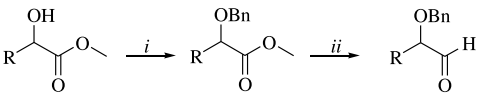


Figure 5. Synthesis of allystannane **9**.

Having access to large quantities of **9**, we next turned our attention to its condensation with various aldehydes. In the presence of $BF_3{\cdot}Et_2O$ simple aldehydes reacted smoothly with **9** to afford selectively the *syn* diol[9] products **10a–d** (Fig. 3). In order to extend the scope of this allylation protocol, we decided to study the Lewis acid catalysed addition of **9** to various α-alkoxyaldehydes.

The desired aldehydes were prepared from the corresponding racemic or enantiomerically pure α-hydroxy esters **15(b–d)**, by protection of the alcohol function with a benzyl substitutent followed by reduction of the ester group (Fig. 6). The benzyl protection was introduced using benzyltrichloroacetimidate under acidic catalysis.[13] This protocol suppressed some undesired transesterification problems we have encountered with the classical procedure using benzylbromide.[14] The α-benzyloxyesters **16(b–d)** were then submitted to controlled reduction with DIBAL-H to afford the expected aldehydes **17(b–d)** in good yields.



15b R= *rac*-Me
15c R=(*S*)-Me
15d R=(*R*)-Cyclohex

16b R=R= *rac*-Me (99%)
16c R=(*S*)-Me (99%)
16d R=(*R*)-Cyclohex (47%)

17a R=H
17b R= *rac*-Me (82%)
17c R=(*S*)-Me (82%)
17d R=(*R*)-Cyclohex (80%)

Figure 6. (i) Benzyl-2,2,2-trichloroacetimidate, TfOH cat., Hex/CH_2Cl_2, rt; (ii) DIBALH, CH_2Cl_2, −78 °C.

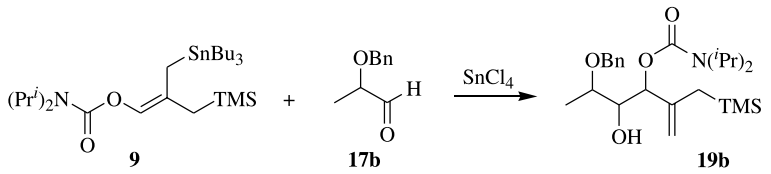


Figure 7.

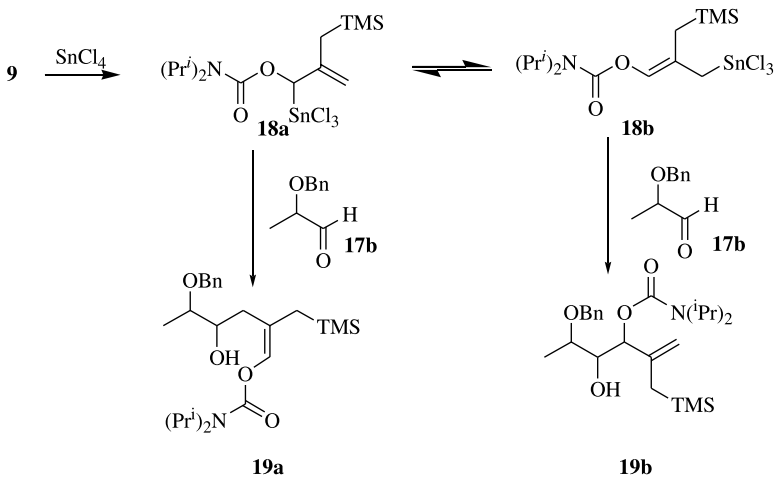


Figure 8. proposed allylation mechanism.

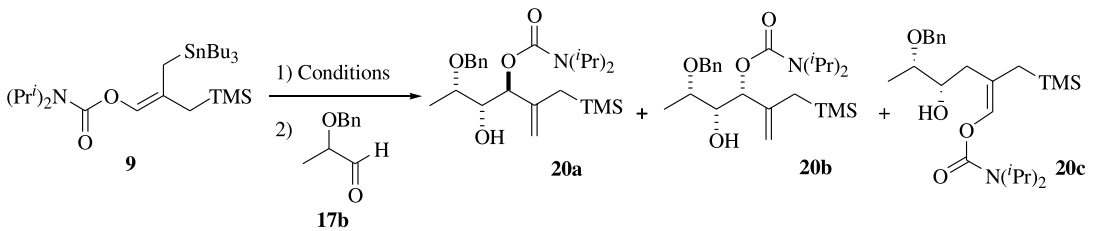
The enantiomeric purity of the optically active aldehydes was controlled by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as resolving agent or by HPLC whenever possible. In all cases, the freshly prepared aldehydes exhibited an enantiomeric purity greater than 95%.

Surprisingly, under these conditions that proved successful with simple aldehydes, α-alkoxyaldehydes such as **17b** did not give rise to the desired products.

Several Lewis acids were then screened and tin tetrachloride was found to be the reagent of choice for this transformation (Fig. 7).

This methodology takes advantage of the rapid transmetallation[15] that occurs between an allyltrialkylstannane and tin tetrachloride, producing an allylic trichlorometal species **18a** that exhibits a higher reactivity and a stronger coordinating power as compared to the parent allylic trialkyltin reagent. The α-isomer **18a** is in dynamic equilibrium with its γ-form **18b** either through an intramolecular transposition of tin or by reaction of **18a** with tin tetrachloride still available in the reaction medium. The condensation of intermediate **18a** with an aldehyde then leads to the α-adducts **19a**, whilst reaction with **18b** produces the δ-addition product **19b** (Fig. 8).

Table 1. Conditions optimisation[a]



Entry	Eq. of $SnCl_4$	T (°C)	Solvent	Equilibration time	Ratio **20a/20b/20c**[b]
1	1	−60	CH_2Cl_2	1 h 30 min	85/15/0
2	1	−76	CH_2Cl_2	2 h 30 min	97/3/0
3	1	−76	CH_2Cl_2	1 h	96/4/0
4	1	−96	CH_2Cl_2	1 h	97/3/0
5	2	−60	CH_2Cl_2	1 h 30 min	16/31/53
6	2	−76	CH_2Cl_2	1 h 30 min	7/57/36
7	2	−96	CH_2Cl_2	1 h	1/83/16
8	2	−102	1,2 dichloropropane	1 h	20/80/0
9	2	(±)-120	$CClF_3/CH_2Cl_2$ 9/1	1 h	7/45/48

[a] The isolated yields were equal to the NMR yields.
[b] Determined by integration of the ^{1}H NMR signal belonging to the vinylic protons.

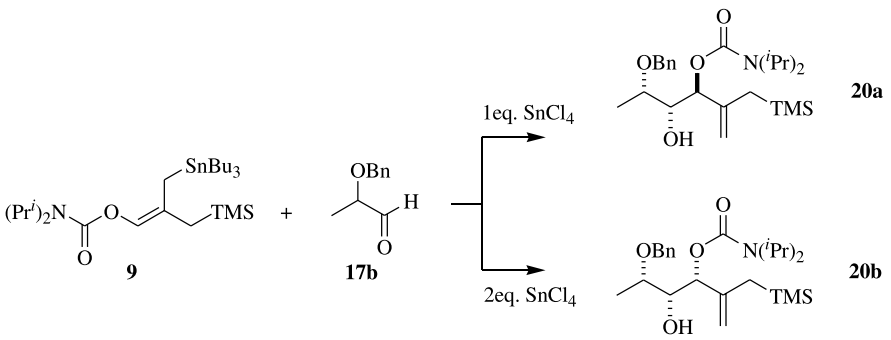


Figure 9.

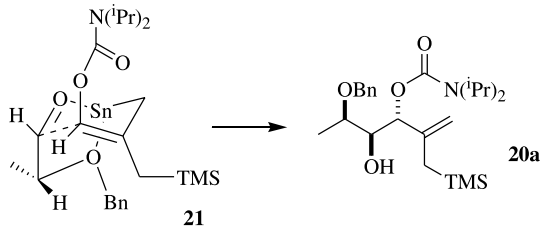


Figure 10. Cyclic transition state.

Such a transmetallation also occurs with allylsilanes, though it has been shown to proceed more slowly.[16]

Since a mixture of α- and δ-adducts are produced under these initial conditions, and taking into account the proposed transmetallation mechanism, we reasoned that by changing the temperature of the reaction, it might be possible to alter the position of the equilibrium and hence produce either **19a** or **19b** at will. Our first attempts were carried out by mixing **9** and $SnCl_4$ at low temperature followed, after a period of equilibration of one hour, by the addition of **17b**. We were delighted to observe that under these conditions the γ-adduct **19b** largely predominated (Table 1). Lowering the temperature even further resulted in a significant improvement of the diastereoselectivity and, at −96 °C, a d.r. of 97:3 in favour of the *syn–anti* isomer **20a** was observed. In order to further improve this procedure, two equivalents of $SnCl_4$ were added instead of one. Much to our surprise, an inversion of diastereoselectivity occurred, leading to the preferential formation of the previously minor *syn–syn* diastereoisomer **20b**.

Again, lowering the temperature resulted in the overwhelming generation of **20b** (d.r.=83:1). Thus, in the presence of one equivalent of $SnCl_4$, allylstannane **9** reacts quantitatively with **17b** to afford the *syn–anti* diastereoisomer **20a** whilst the use of two equivalents of the same Lewis acid resulted in a complete inversion of selectivity, leading to the *syn–syn* isomer **20b** (Fig. 9).

To the best of our knowledge, such inversions related to the stoichiometry of the Lewis acid employed have never been reported in the literature and this parameter seems, in most of the cases, to have been largely underestimated. Examples of allylation by similar γ-substituted allyltin compounds, mediated by magnesium dibromide or titanium tetrachloride and affording *syn–syn* alcohols with high stereoselectivity have already been described.[8d–g] However, in these cases, the amount of Lewis acid has never been considered as a key parameter to influence the stereochemical outcome of the reaction.

To rationalise these results, we propose the involvement of two different transition states. When one equivalent of $SnCl_4$ is used, the transmetallated species **18b** would react with the aldehyde through a bicyclic transition state **21** as depicted in Figure 10. This transition state has been postulated for thermal and high pressure reactions of allyltrialkyltin reagents. In these cases, the tin plays the role of a weak Lewis acid.[17] In contrast the trichlorotin generated under our conditions, possesses a greater chelating ability. The carbamate would thus adopt a pseudo-axial orientation in order to interact with the tin which is already chelated to the benzyl ether and to the carbonyl of the aldehyde. Allyl transfer through this rigid, hydrindane-like, transition state then leads to the observed *syn–anti* selectivity.

In contrast, when 2 equiv. of $SnCl_4$ are used, one equivalent reacts with the aldehyde to form the chelate **22** whilst the second equivalent of Lewis acid transmetallates the allylating agent **9**.[18,19] The allyl transfer now takes place through an open transition state such as **23**, leading to the *syn–syn* diastereoisomer **20b** (Fig. 11). Such a reaction pathway has been proposed by Keck et al.[8a–d] to rationalize the selectivities observed during the allylation of aldehydes with crotyl tin derivatives. In this case, the carbamate will occupy the less hindered quadrant.

The choice of the protecting group present on the

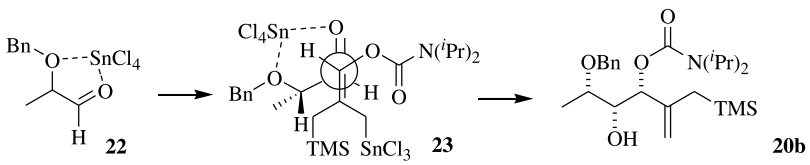
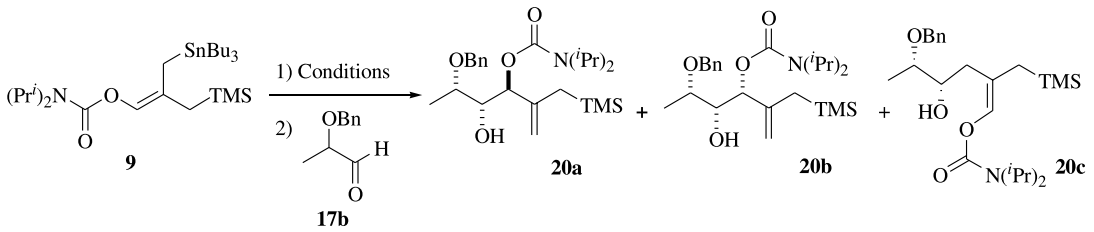


Figure 11. Open transition state.

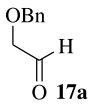
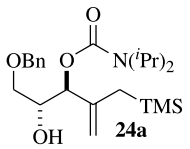
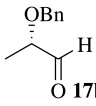
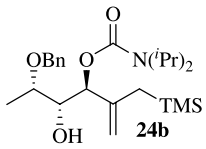
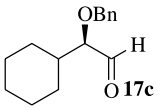
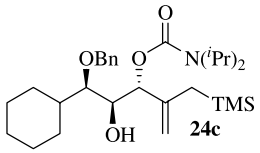
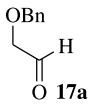
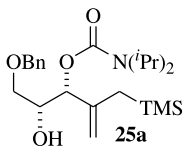
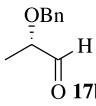
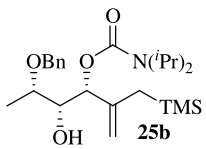
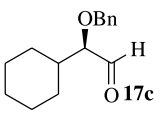
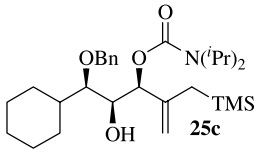
Table 2. Effect of the order of addition[a]



Entry	Eq. of $SnCl_4$	T (°C)	Solvent	Equilibration time (h)	Ratio **20a/20b/20c**[b]
1	2	−96	CH_2Cl_2	1	1/78/21
2	2	−102	1,2 dichloropropane	1	15/75/5

[a] The isolated yields were equal to the NMR yields.
[b] Determined by integration of the ^1H NMR signal belonging to the vinylic protons.

Table 3. Allylation of chiral aldehydes

Entry	Aldehyde	Product	Yield[a] (%)	de[b] (%)	ee[c]
1[d]	 **17a**	 **24a**	84	90	n.a[e]
2[d]	 **17b**	 **24b**	96	94	>95%
3[d]	 **17c**	 **24c**	81	94	>95%
4[f]	 **17a**	 **25a**	70	91	n.a[e]
5[f]	 **17b**	 **25b**	83	97	>95%
6[f]	 **17c**	 **25c**	81	90	>95%

[a] Isolated yields.
[b] Determined by integration of the ^1H NMR signal belonging to the vinylic protons.
[c] Determined by chiral HPLC.
[d] Using 1 equiv. of $SnCl_4$.
[e] Diol obtained as a racemic mixture.
[f] Using 2 equiv. of $SnCl_4$.

alkoxyaldehyde is of paramount importance for the success of this reaction. The use of benzyl ether, exhibiting a high Lewis basicity on the oxygen, enables the formation of a strong chelate. In sharp contrast, the use of a silicon-based protecting group such as a TBDMS which prevents efficient coordination by the Lewis acid leads to poor selectivities.

In order to lend further support to the postulated open-transition state pathway, it was decided to effect the transmetallation first and then to add to the in situ generated allyltrichlorotin species **18b**, one equivalent of the pre-complexed aldehyde. As can be seen from Table 2, the same ratios are obtained, at two different temperatures, either using this 'inverse' protocol or the 'normal' addition procedure described previously. (Vide supra). This observation lends further credit to our proposed transition states.

Having demonstrated that the addition of the allylating agent **9** onto a variety of racemic α-benzyloxyaldehydes proceeded with excellent levels of diastereocontrol, we turned our attention to the use of optically pure substrates with a view to generate enantioenriched triols. Our results are summarised in Table 3.

In all cases, the triols were formed in good to excellent yields (70–96%) and with high diastereoselectivities. (90–97%). Gratifyingly, no erosion of the enantiopurity of the starting α-benzyloxyaldehydes was observed and the final adducts were isolated in essentially optically pure form (Table 3, entries 2, 3, 5 and 6). It thus transpires that racemisation is a slower process than addition of the allylating agent.

At this stage, it is important to note that each oxygen function of the triol unit present in adducts **24a–c** and **25a–c** is differently substituted. Such orthogonal protection allows subsequent chemoselective transformations to be readily effected on adducts **20a–b** as shown in Figure 12.

The stereochemistry of both *syn–anti* and *syn–syn* triol units was determined by synthesizing the acetonides derived from each pair of vicinal diols, themselves obtained by chemoselective deprotection of either the carbamate or the benzylether function. Analysis of the ^{1}H NMR coupling constants between the adjacent protons at C2, C3 and C3, C4 is a reliable method to determine the stereochemistry of these two stereogenics centres.[20]

Initially, treatment of **20a** and **20b** by $BF_3{\cdot}Et_2O$ removed the allylic silane which proved to be troublesome at times. Substrates **26(a–b)** were then hydrogenated in order to cleave the benzyl ether. This reaction occurred with concomitant reduction of the C–C double bond. Alternatively, reduction of the carbamate moiety with $LiAlH_4$ afforded diols **27b** and **27d**. Finally, the reaction of the resulting diols **27(a–d)** with acetone under acidic conditions produces the desired acetonides **28(a–d)** (Fig. 12).

The ^{1}H NMR data clearly revealed that in all cases, the vicinal diols were *syn* configured (^3J>8 Hz) except in the case of **28b** where an *anti* configuration (^3J<7 Hz) was

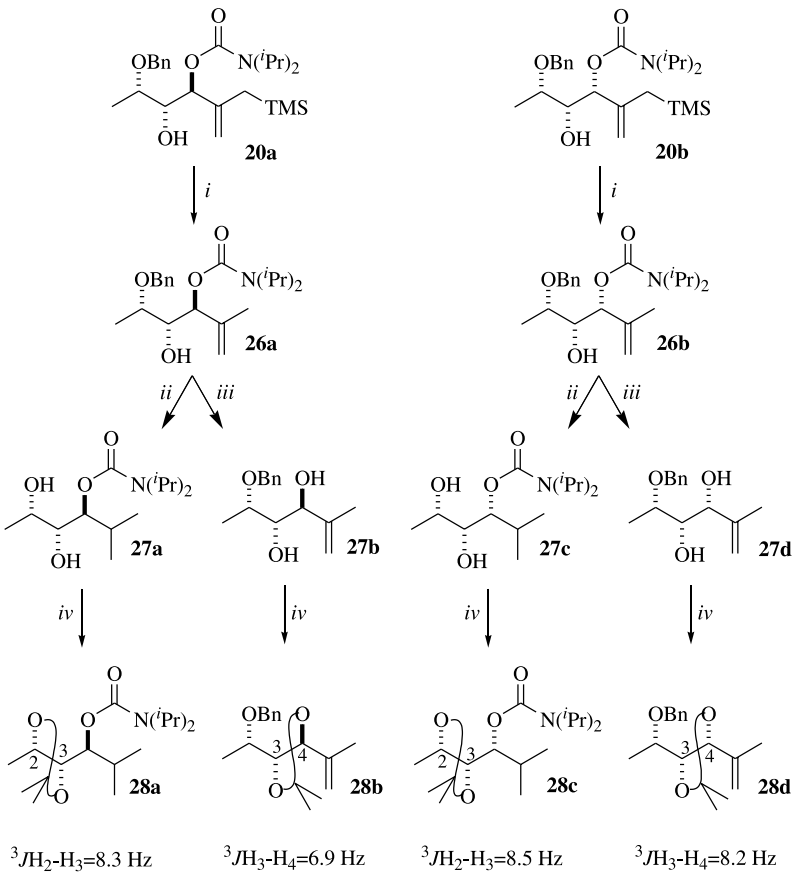


Figure 12. (i) $BF_3{\cdot}Et_2O$, DCM, −15 °C; (ii) H_2, Pd/C cat., AcOEt, 40 °C; (iii) $LialH_4$, THF, reflux; (iv) Acetone, APTS, reflux.

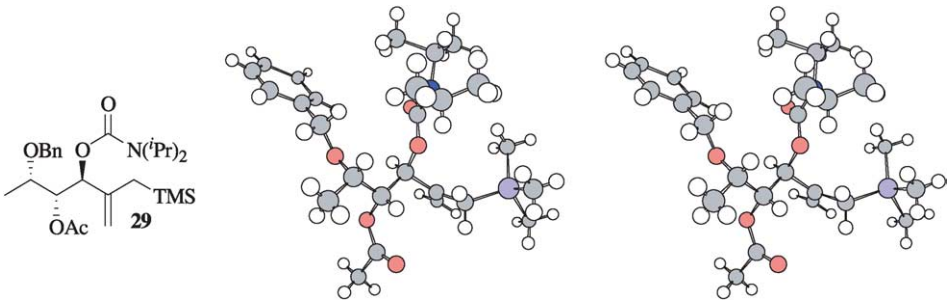


Figure 13. Cross-eyed stereo view of X-ray analysis of acetate derivative **29**.

observed. Finally, having access to the enantiomerically pure, chemoselectively protected compounds **24b** and **25b**, we attempted to derivatize the free alcohol function in order to obtain suitable crystals for an X-ray diffraction analysis. Gratifyingly, the acetate **29**, derived from the *syn–anti* triol **24b** eventually crystallised upon standing. A three-dimensional view of compound **29** clearly reveals the *syn–anti* relationship between the three oxygenated functions, thus fully corroborating our previous assignments (Fig. 13).

In summary, we have developed an efficient methodology for the rapid assembly of consecutive triols arrays in good yields (70–96%) and high diastereoselectivities (de. 90–97%). A remarkable and complete inversion of stereochemistry is observed when the amount of Lewis acid is varied. Thus, 1 equiv. of $SnCl_4$ leads to the *syn–anti* triol whilst two equivalents give access to the *syn–syn* triol. This stereodivergent behaviour has been rationalized by invoking the participation of two different transition states. This convenient procedure allows a ready access to stereocomplementary, orthogonally protected triol subunits present in a variety of interesting natural products. The scope and limitations of this protocol and its application to the preparation of highly oxygenated natural products are currently under active investigation. The results of these studies will be reported in due course.

2. Experimental

2.1. Generalities

Unless otherwise stated all the reactions were carried out using anhydrous conditions and in an atmosphere of argon. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200, 300 and 2000 instruments. Chemical shifts are expressed as parts per million (ppm) down-field from tetramethylsilane or calibrated from $CDCl_3$. Mass spectra were obtained using Varian MAT-44 and Finnigan MAT-TSQ 70 spectrometers with electron impact (70 eV) and chemical ionisation (100 eV, ionisation gas, isobutane). IR spectra were taken with a BIO-RAD FTS 135 spectrometer. Microanalysis were performed in Professor V. Jäger's analytical laboratory (Institut für Organishe Chemie, Universität Stuttgart, Germany). High resolution mass spectra were recorded in Professor R. Flamant's laboratory (Université de Mons, Belgium).

(*S*)-Methyl 2-hydroxypropanoate **15b** is commercially available from Sigma-Aldrich and was used as received.

2-(Benzyloxy)acetaldehyde **17a** is commercially available from Acros and was used as received.

2.2. Synthesis of allylstannane 9

2.2.1. 2-((Trimethylsilyl)methyl)prop-2-en-1-ol 12. In a 2 l round bottom flask equipped with a mechanical stirrer were added TMEDA (140 ml, 107.73 g, 0.92 mol, 2.6 equiv.) and freshly distilled Et_2O (440 ml). At 0 °C, a solution of *n*BuLi (10 M in hexane, 100 ml, 1 mol, 2.8 equiv.) is added via a large diameter canula. Then, methallylic alcohol **7** (30 ml, 25.71 g, 0.35 mol, 1 equiv.) was added dropwise to the solution, at 0 °C. (300 ml) Dry THF was added and the resulting orange solution was allowed to reach room temperature and was stirred for 24 h to afford a red gum. The mixture was cooled to −30 °C and TMSCl (204 ml, 1.60 mol, 4.5 equiv.) was added slowly. The cooling bath was removed and the white suspension was stirred 15 min at room temperature to give a brown suspension. After dilution with Et_2O (1.2 l), the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (1.2 l). The organic phase was separated and washed with a saturated aqueous solution of $CuSO_4$ (1.2 l), water (1.2 l) and dried with $MgSO_4$. The solvent was then removed under reduced pressure and the resulting viscous oil is distilled (90–120 °C at 20 mbar) to give 36.51 g (47%) of allylsilane **12**. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.90 (1H, bs), 4.62 (1H, bs), 3.94 (2H, s), 1.48 (2H, s), 0.13 (9H, s), 0.01 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 145.92, 106.62, 66.49, 22.77, −0.47, −1.37; IR (neat, NaCl) 2957, 1647, 1636, 1251, 1085 cm^{-1}; MS (CI) *m/z*: 216.0 ($M^{\cdot+}$).

2.2.2. 2-((Trimethylsilyl)methyl)allyl diisopropylcarbamate 13. Allylsilane **12** (3 g, 13.85 mmol, 1 equiv.) was dissolved in 50 ml of THF and a 1 N aqueous solution of sulfuric acid (6 ml, 3 mmol, 0.21 equiv.) was added. The mixture was stirred for 1 h 30 min and then neutralised with solid K_2CO_3 until pH 7 was reached. After dilution with water (50 ml) and extraction with Et_2O, the organics were combined and dried over $MgSO_4$. Removing of the solvent under reduced pressure afforded a viscous oil. This oil, diluted in 12 ml of Et_2O, was poured dropwise over a suspension of NaH (60% in mineral oil, prewashed with Et_2O (833 mg, 20.83 mmol, 1.5 equiv.) in Et_2O (12 ml) at 0 °C. A solution of diisopropylcarbamoyl chloride (4.54 g, 27.77 mmol, 2 equiv.) in Et_2O (12 ml) was added slowly.

The mixture was then allowed to reach room temperature and to stir for 18 h. The reaction was quenched by adding slowly a saturated aqueous solution of NH_4Cl (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×30 ml). The organics were combined, dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography (PE/EA=30/1, Et_3N 5%) to give pure allylcarbamate **13** (3.48 g, 93%) as a colourless oil; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.85 (1H, q, J=1.6 Hz), 4.66 (1H, bs), 4.43 (2H, s), 3.61–4.19 (2H, m), 1.52 (2H, s), 1.18 (12H, d, J=6.2 Hz), 0.02 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.93, 143.45, 109.21, 68.64, 46.56, 24.35, 21.70, −0.75; IR (neat, NaCl) 3084, 2998, 2967, 2894, 1699, 1645, 1439, 1368, 1314, 1296, 1249, 1219, 1158, 1134, 1067, 843, 770 cm^{-1}; MS (CI) m/z: 271.2 ($M^{\cdot+}$); Anal. calcd for $C_{14}H_{29}NO_2Si$ C, 61.94; H, 10.77 N, 5.16; found C, 61.97; H, 10.88; N, 5.10.

2.2.3. (*Z*)-3-(Tributylstannyl)-2-((trimethylsilyl)methyl)-prop-1-enyl diisopropylcarbamate 9. In a 100 ml round bottom flask were introduced TMEDA (1.11 ml, 858 mg, 7.38 mmol, 2 equiv.) and Et_2O (15 ml). At −78 °C a solution of *sec*BuLi (1.3 M in hexanes, 5.67 ml, 7.38 mmol, 2 equiv.) was added dropwise and the mixture allowed to stir 30 min at −78 °C. A solution of allylcarbamate **13** in Et_2O (15 ml) was added quickly and the orange-brown media was stirred 30 min at −78 °C. A solution of tributyltin chloride (3.00 ml, 3.60 g, 11.07 mmol, 3 equiv.) in Et_2O (15 ml) was added quickly at −78 °C and the dry ice/acetone cooling bath was replaced immediately with an Ice/Water cooling bath. The yellow solution was stirred for 15 min at 0 °C, poured over an aqueous solution of HCl (50 ml, 1 N) and diluted with Et_2O (20 ml). The layers were separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated. The crude oil was purified by column chromatography (PE/EA=30/1) to give pure allylstannane **9** (1.61 g, 80%) as a colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.53 (1H, s), 3.91–3.95 (2H, m), 1.73 (2H, s), 1.17–1.63 (14H, m), 1.24 (12H, d, J=6.8 Hz), 0.88 (9H, t, J=7.2 Hz), 0.74–0.96 (6H, m), 0.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.05, 126.19, 120.34, 45.91, 29.15, 27.38, 22.94, 21.43, 13.95, 13.69, 9.68, −1.08; IR (neat, NaCl) 3084, 2956, 2928, 2875, 2857, 1696, 1594, 1461, 1428, 1338, 1302, 1285, 1247, 1152, 1079, 1046, 857, 761 cm^{-1}; MS (EI) m/z: 561.4 ($M^{\cdot+}$); Anal. calcd for $C_{26}H_{55}NO_2SiSn$: C, 55.72; H, 9.89 N, 2.50; found C, 55.98; H, 9.95; N, 2.45.

2.2.4. (*R*)-Methyl 2-cyclohexyl-2-hydroxyacetate 15d. (*R*)-hexahydromandelic acid (900 mg, 5.68 mmol, 1 equiv.) was dissolved in methanol (50 ml) and $SOCl_2$ (4.14 ml, 6.75 g, 56.8 mmol, 10 equiv.) was added dropwise at room temperature. After 30 min the mixture was evaporated to dryness and dissolved in CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was obtained in 99% yield was essentially pure ester **15c**. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.03 (1H, d, J=3.3 Hz), 3.79 (3H, s), 2.70 (1H, bs), 1.9–1 (11H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.17, 74.84,52.38, 41.94, 29.10, 26.37, 26.262, 26.02, 25.97; IR (neat, NaCl) 3495, 2998, 2927, 2854, 2665, 1736, 1450, 1261, 1220, 1117, 986 cm^{-1}; MS (CI) m/z: 172.9 ($M+H^+$).

2.3. General procedure for the preparation of the α-benzyloxy esters

The corresponding α-hydroxyester was dissolved in CH_2Cl_2 (0.5 ml/mmol of ester). At room temperature, were added sequentially a solution of 2,2,2-trichlorobenzylacetimidate (2 equiv.) in hexane (1.5 ml/mmol) and triflic acid (5% mol). The white suspension that formed was stirred for 16 h at room temperature. The white solid was filtered off and rinsed with hexane. The filtrate was then washed with a saturated aqueous solution of $NaHCO_3$, the layers separated and the aqueous phase extracted with hexane. The combined organics were dried over $MgSO_4$ and concentrated. The resulting oil was purified by column chromatography to give pure α-benzyloxyesters.

2.3.1. (*S*)-Methyl 2-(benzyloxy)propanoate 16c. The title compound obtained as a colourless oil in 99% yield following the general procedure; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.23 (5H, m), 4.69 (1H, d, J=11.7 Hz), 4.44 (1H, d, J=11.7 Hz), 4.21 (2H, q, J=7.1 Hz), 4.04 (2H, q, J=6.9 Hz), 1.43 (3H, d, J=6.9 Hz), 1.29 (3H, t, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.15, 137.49, 128.31, 127.87, 127.73, 79.96, 71.88, 60.75, 18.64, 14.17; IR (neat, NaCl) 3058, 2984, 2937, 2902, 2872, 1751, 1449, 1264, 1133, 1065, 1026, 737 cm^{-1}; MS (EI) m/z: 209.0 ($M+H^+$).

2.3.2. (*R*)-Methyl 2-(benzyloxy)-2-cyclohexylacetate 16d. The title compound as a colourless oil in 49% yield following the general procedure; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.30 (5H, m), 4.68 (1H, d, J=11.7 Hz), 4.35 (1H, d, J=11.7 Hz), 3.74 (H, s), 3.72 (1H, d, J=6 Hz), 1.85–1.60 (5H, m), 1.35–1.05 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.85, 137.52, 128.22, 127.88, 127.66, 82.93, 72.49, 51.65, 41.14, 29.11, 28.30, 26.19, 26.07, 25.97; IR (neat, NaCl) 3031, 2927, 2854, 2669, 1735, 1452, 1268, 1120, 1012, 737 cm^{-1}.

2.4. General procedure for the preparation of the α-benzyloxy aldehydes

A solution of the corresponding ester in dry CH_2Cl_2 (5 ml/mmol of ester) was cooled to −78 °C. Cold DIBAL-H (1.5 M in Tol, 1 equiv.) was added dropwise and the mixture was allowed to stir at −78 °C for an hour. Then, small portions of DIBAL-H were added every 15 min until all the starting material disappeared by TLC (~1 more equiv.). After completion of the reaction, a saturated aqueous solution of NH_4Cl was poured directly in the cold reaction mixture and vigorous stirring was maintained until the mixture reached rt. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was either purified by column chromatography, to give pure α-alkoxyaldehydes required for analysis, or used directly in the subsequent step to avoid degradation.

2.4.1. (*S*)-2-(Benzyloxy)propanal 17c. The title compound obtained as a colourless oil in 75% yield following the

general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.67 (1H, d, J=1.7 Hz), 7.38–7.26 (5H, m), 4.66 (1H, d, J=11.7 Hz), 4.60 (1H, d, J=11.7 Hz), 3.90 (1H, qd, J=7.0, 1.7 Hz), 1.34 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.4, 137.23, 128.51, 128.02, 127.97, 79.35, 71.95, 15.26; IR (neat, NaCl) 3031, 2981, 2869, 1735, 1496, 1454, 1374, 1094, 1047, 737 cm^{-1}; MS (EI) m/z: 165.1 (M+H$^+$).

2.4.2. (*S*)-2-(Benzyloxy)-2-cyclohexylacetaldehyde 17d. The tile compound obtained as a colourless oil in 80% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.66 (1H, d, J=2.7 Hz), 7.35–7.32 (5H, m), 4.67 (1H, d, J=11.7 Hz), 4.47 (1H, d, J=11.7 Hz), 3.49 (1H, dd, J=5.7, 2.7 Hz), 1.85–1.6 (5H, m), 1.35–1.05 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.43, 137.38, 128.36, 127.83, 87.67, 72.80, 39.57, 28.774, 28.03, 26.17, 26.04, 25.96; IR (neat, NaCl) 3031, 2928, 2854, 1729, 1497, 1452, 734 cm^{-1}; MS (CI) m/z: 231.2 (M−H$^+$).

2.5. General procedure for the allylation of α-benzyloxyaldehydes with 1 equiv. of $SnCl_4$

Allylstannane **9** was dissolved in freshly distilled CH_2Cl_2 (30 ml/mmol of stannane) and cooled to −78 °C with a dry ice–acetone bath. $SnCl_4$ (1 M in CH_2Cl_2, 1 equiv.) was added and the mixture allowed to stir at −78 °C for 1 h. A solution of aldehyde in CH_2Cl_2 (10 ml/mmol of aldehyde), cooled to −78 °C, was added dropwise with a canula over 5 min. The resulting mixture was stirred at −78 °C for 1 h. The reaction bulk was then diluted with CH_2Cl_2 (2×volume) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase extracted 3× with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to give pure triols.

2.5.1. 1-(Benzyloxy)-2-hydroxy-4-((trimethylsilyl)-methyl)pent-4-en-3-yl diisopropylcarbamate 24a. The tile compound obtained as a colourless oil in 84% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24–7.35 (5H, m), 5.16 (1H, d, J=4.8 Hz), 4.96 (1H, s), 4.82 (1H, s), 4.57 (1H, d, J=12.0 Hz), 4.53 (1H, d, J=12.0 Hz), 3.76–4.08 (3H, m), 3.62 (1H, dd J=10.0, 2.9 Hz), 3.50 (1H, dd, J=9.9, 7.7 Hz), 2.99 (1H, d, J=5.3 Hz), 1.61 (1H, d, J=14.4 Hz), 1.50 (1H, d, J=14.4 Hz), 1.17 (12H, d, J=6.7 Hz), 0.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl^3$) δ: 154.39, 143.04, 137.76, 128.12, 127.57, 127.41, 110.25, 78.28, 73.23, 70.69, 70.68, 45.54, 23.31, 20.52–20.94, −1.30; IR (neat, NaCl) 3447, 3029, 2965, 2931, 2875, 1700, 1636, 1435, 1368, 1317, 1248, 1133, 1048, 850 cm^{-1}; MS (CI+) m/z: 422.3 (M+H$^+$); HRMS (CI+, M+H$^+$) calcd for $C_{23}H_{40}NO_4Si$, 422.2734; found 422.2726.

2.5.2. (3*S*,4*R*,5*S*)-5-(Benzyloxy)-4-hydroxy-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 24b. The tile compound obtained as a colourless oil in 97% yield following the general procedure; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38–7.27 (5H, m), 5.24 (1H, d, J=7.0 Hz), 5.04 (1H, s), 4.88 (1H, d, J=1.2 Hz), 4.61 (1H, d, J=11.1 Hz), 4.46 (1H, d, J=11.1 Hz), 3.90 (2H, hept, J=6.9 Hz), 3.67 (1H, qd, J=6.3, 3.0 Hz), 3.56 (1H, td, J=7.4, 3.1 Hz), 2.44 (1H, d, J=7.4 Hz), 1.58 (2H, bs), 1.28 (3H, d, J=6.3 Hz), 1.19 (12H, m), 0.05 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 153.98, 144.33, 138.34, 128.33, 128.01, 127.61, 111.99, 77.7, 75.06, 73.62, 71.40, 45.92, 22.56, 20.94, 16.76, −1.05; IR (neat, NaCl) 3488, 3067, 3032, 2966, 2928, 2876, 1699, 1636, 1432, 1367, 1298, 1133, 1071, 1048, 848 cm^{-1}; MS (EI) m/z: 435.3 (M−H$^+$). $[\alpha]_{20}^{D}$=2.7 (c 1.0, CH_2Cl_2); Anal. calcd for $C_{24}H_{41}NO_4Si$: C, 66.17; H, 9.49; N, 3.21; found: C, 65.48; H, 9.46; N, 3.09.

2.5.3. (1*R*,2*S*,3*R*)-1-(Benzyloxy)-1-cyclohexyl-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-3-yl diisopropylcarbamate 24c. The tile compound obtained as a colourless oil in 81% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.26 (5H, m), 5.15 (1H, d, J=8.7 Hz), 5.04 (1H, s), 4.89 (1H, d, J=1 Hz), 4.64 (1H, d, J=11 Hz), 4.59 (1H, d, J=11 Hz), 3.90 (2H, bs), 3.75 (1H, bd, J=8.7 Hz), 3.28 (1H, d, J=7 Hz), 2.52 (1H, bs),1.92–0.8 (25H, m), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.69, 144.37, 138.22, 128.25, 127.95, 127.58, 112.26, 81.39, 78.01, 74.374, 70.435, 45.92, 40.53, 29.61, 29.35, 26.60, 26.34, 26.30, 22.30, 21.41, 17.58, 13.703, −0.92; IR (neat, NaCl) 3489, 3031, 2959, 2928, 2854, 1700, 1636, 1436, 1305, 1048, 851 cm^{-1}; MS (CI) m/z: 504.5 (M−H$^+$); HRMS (CI+, M+H$^+$) calcd for $C_{29}H_{50}NO_4Si$, 504.3509; found 504.3519. $[\alpha]_{20}^{D}$=8.7 (c 1.0, CH_2Cl_2).

2.6. General procedure for the allylation of α-benzyloxyaldehydes with 2 equiv. of $SnCl_4$

Allylstannane **9** was dissolved in freshly distilled CH_2Cl_2 (30 ml/mmol of stannane) and cooled to −78 °C with a dry ice–acetone bath. $SnCl_4$ (1 M in CH_2Cl_2, 2 equiv.) was added and the mixture allowed to stir at −78 °C for 1 h. The solution was cooled to −97 °C with a MeOH/N_2 bath and a solution of aldehyde in CH_2Cl_2 (10 ml/mmol of aldehyde), cooled to −97 °C, was added dropwise with a canula over 5 min. The resulting mixture was stirred at −97 °C for 1 h. The reaction bulk was then diluted with CH_2Cl_2 (2×volume) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase extracted 3× with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to give pure triols.

2.6.1. 1-(Benzyloxy)-2-hydroxy-4-((trimethylsilyl)-methyl)pent-4-en-3-yl diisopropylcarbamate 25a. The tile compound obtained as a colourless oil in 70% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19–7.31 (5H, m), 5.13 (1H, d, J=4.3 Hz), 4.89 (1H, s), 4.76 (1H, s), 4.49 (2H, s), 3.91 (1H, dt J=5.7, 4.3 Hz), 3.76–3.95 (2H, m), 3.50 (1H, dd J=9.6, 4.8 Hz), 3.45 (1H, dd, J=9.6, 6.2 Hz), 2.30–2.52 (1H, m), 1.54 (1H, d, J=14.4 Hz), 1.43 (1H, d, J=13.9 Hz), 1.15 (6H, d, J=7.2 Hz), 1.14 (6H, d, J=7.2 Hz), 0.01 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.47, 143.60, 137.87, 128.28, 127.72, 127.58, 110.08, 76.99, 73.49, 71.36, 70.93, 45.97, 23.71, 20.70–21.58, −1.18; IR (neat, NaCl): 3457, 3065, 3032, 2965, 2930, 2866, 1699, 1630, 1437, 1368, 1300, 1248, 1126, 1050, 850 cm^{-1}; MS (EI) m/z: 421.5 (M$^{\cdot+}$); HRMS (EI+, M$^+$) calcd for $C_{29}H_{39}NO_4Si$, 421.2650; found 421.2648.

2.6.2. (3*R*,4*R*,5*S*)-5-(Benzyloxy)-4-hydroxy-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 25b. The tile compound obtained as a colourless oil in 83% yield following the general procedure; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.37–7.30 (5H, m), 5.29 (1H, d, J=3.3 Hz), 4.98 (1H, s), 4.85 (1H, s), 4.71 (1H, d, J=11.4 Hz), 4.48 (1H, d, J=11.4 Hz), 4.03–3.87 (2H, m), 3.68–3.60 (2H, m), 2.71 (1H, d, J=3.9 Hz), 1.63 (1H, d, J=14.1 Hz), 1.51 (1H, d, J=14.1 Hz), 1.29 (3H, d, J=5.8 Hz), 1.24 (12H, d, J=6.3 Hz), 0.09 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.54, 143.64, 138.17, 128.27, 127.61, 127.49, 110.03, 76.36, 75.51, 75.12, 70.72, 45.58, 23.35, 20.44, 15.52, −1.39; IR (neat, NaCl) 3457, 2967, 2931, 1694, 1635, 1431, 1300, 1248, 1135, 1048, 851 cm^{-1}; MS (EI) m/z: 435.3 ($M-H^+$). $[\alpha]_{20}^{D}$=42.3 (c 1.0, CH_2Cl_2); Anal. calcd for $C_{24}H_{41}NO_4Si$: C, 66.17; H, 9.49; N, 3.21; found: C, 65.62; H, 9.51; N, 3.09.

2.6.3. (1*R*,2*S*,3*S*)-1-(Benzyloxy)-1-cyclohexyl-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-3-yl diisopropylcarbamate 25c. The tile compound obtained as a colourless oil in 81% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.26 (5H, m), 5.20 (1H, d, J=4.8 Hz), 4.96 (1H, s), 4.84 (1H, s), 4.66 (2H, s), 3.95 (2H, bs), 3.90 (H, q, J=4.8 Hz), 3.30 (1H, t, J=4.8 Hz), 2.55 (1H, d, J=4.8 Hz),1.92–0.8 (25H, m), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.42, 143.83, 138.57, 128.28, 127.52, 127.45, 110.82, 83.23, 77.69, 74.18, 71.77, 45.97, 40.00, 30.21, 28.01, 27.90, 26.919, 26.576, 26.34, 23.40, 21.52, 20.71, 17.59, 13.688, −1.08; IR (neat, NaCl) 3547, 3032, 2926, 2853, 1698, 1451, 1432, 1311, 1157, 1048, 849 cm^{-1}; MS (CI) m/z: 504.4 ($M-H^+$); HRMS (CI+, $M+H^+$) calcd for $C_{29}H_{50}NO_4Si$, 504.3509; found 504.3494. $[\alpha]_{20}^{D}$=32.9 (c 1.0, CH_2Cl_2).

2.7. Determination of stereochemistry

2.7.1. *Syn–anti* 5-(benzyloxy)-4-hydroxy-2-methylhex-1-en-3-yl diisopropylcarbamate 26a. Allylsilane **20a** (822 mg, 1.89 mmol, 1 equiv.) was dissolved in 25 ml of CH_2Cl_2. At −15 °C, $BF_3.Et_2O$ (233 μl, 269 mg, 1.89 mmol, 1 equiv.) was added and the mixture allowed to stir 18 h at −15 °C. The mixture was diluted with CH_2Cl_2 (20 ml) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=6/1) to give pure alcohol **26a** as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.37 (5H, m), 5.27 (1H, d, J=7.7 Hz), 5.08 (1H, s), 5.05 (1H, t, J=1.8 Hz), 4.62 (1H, d, J=11.3 Hz), 4.48 (1H, d, J=11.3 Hz), 3.72–4.08 (2H, m), 3.65 (1H, qd J=6.0, 3.0 Hz), 3.57 (1H, bd, J=7.8 Hz), 2.35 (1H, m), 1.82 (3H, s), 1.29 (3H, d, J=6.3 Hz), 1.13–1.25 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.95, 142.14, 137.90, 128.16, 127.82, 127.46, 115.20, 77.02, 74.31, 73.06, 71.06, 46.08, 20.49, 18.62, 16.23; IR (neat, NaCl) 3472, 2971, 2934, 2879, 1695, 1437, 1298, 1136, 1088, 1049, 851, 738 cm^{-1}; MS (EI) m/z: 363.3 ($M^{\cdot+}$); HRMS for $C_{21}H_{33}NO_4$ (CI+, $M+H^+$): Calcd 364.2488; found 364.2492.

2.7.2. *Syn–syn* 5-(benzyloxy)-4-hydroxy-2-methylhex-1-en-3-yl diisopropylcarbamate 26b. Allylsilane **20b** (277 mg, 0.63 mmol, 1 equiv.) was dissolved in 10 ml of CH_2Cl_2. At −15 °C, $BF_3.Et_2O$ (79 μl, 91 mg, 0.63 mmol, 1 equiv.) was added and the mixture allowed to stir 18 h at −15 °C. The mixture was diluted with CH_2Cl_2 (20 ml) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=7/1) to give pure alcohol **26b** as colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27–7.36 (5H, m), 5.30 (1H, d, J=5.2 Hz), 4.98 (2H, s), 4.66 (1H, d, J=11.5 Hz), 4.42 (1H, d, J=11.5 Hz), 3.74–4.12 (2H, m), 3.55–3.65 (2H, m), 1.79 (3H, s), 1.28 (3H, d, J=6.0 Hz), 1.21 (12H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.14, 141.79, 138.17, 128.43, 127.76, 127.67, 114.04, 77.61, 75.57, 74.54, 70.81, 46.34, 21.44, 19.32, 15.73; IR (neat, NaCl) 3474, 2970, 2932, 2872, 1686, 1438, 1297, 1132, 1053, 903, 737 cm^{-1}; MS (EI) m/z: 363.3 ($M^{\cdot+}$); HRMS for $C_{21}H_{33}NO_4$ (CI+, $M+H^+$): Calcd 364.2488; found 364.2492.

2.7.3. *Syn–anti* 4,5-dihydroxy-2-methylhexan-3-yl diisopropylcarbamate 27a. Carbamate **26a** (17 mg, 0.046 mmol, 1 equiv.) was mixed with Pd/C (10 mol%) in AcOEt (5 ml). The flask was purged 4 times with nitrogen and 5 times with hydrogen. The mixture was heated to 40 °C under hydrogen pressure (1 atm) for 48 h. The crude mixture was filtered through celite, rinsed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=3/1) to give pure diol **27a** as a colourless oil (10 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.56 (1H, dd, J=9.6, 2.4 Hz), 4.03–3.82 (2H, m), 3.66 (1H, qd, J=6.6, 1.2 Hz), 3.30 (1H, bd, J=9.9 Hz), 2.30 (1H, hept d, J=7.2, 2.4 Hz), 1.32–1.22 (15H, m), 1.00 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.64, 77.90, 73.22, 65.01, 46.60–45.78, 27.84, 21.28–20.01, 20.65, 18.39, 15.76; IR (neat, NaCl) 3421, 2969, 2937, 2877, 1674, 1443, 1295, 1051, 936, 770 cm^{-1}; MS (CI+) m/z: 276.1 ($M+H^+$); HRMS (CI+, $M+H^+$) calcd for $C_{14}H_{29}NO_4$, 276.2175; found 276.2178.

2.7.4. *Syn–syn* 4,5-dihydroxy-2-methylhexan-3-yl diisopropylcarbamate 27c. Carbamate **26c** (45 mg, 0.12 mmol, 1 equiv.) was mixed with Pd/C (10 mol%) in AcOEt (5 ml). The flask was purged 4 times with nitrogen and 5 times with hydrogen. The mixture was heated to 40 °C under hydrogen pressure (1 atm) for 48 h. The crude mixture was filtered through celite, rinsed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=2/3) to give pure diol **27c** as a colourless oil (17 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.56 (1H, dd, J=7.1, 4.1 Hz), 4.03–3.81 (2H, m), 3.71 (1H, qd, J=6.3, 5.2 Hz), 3.47 (1H, dd, J=5.2, 4.1 Hz), 2.20 (1H, oct, J=6.8 Hz), 1.26–1.21 (15H, m), 0.99 (3H, d, J=6.6 Hz), 0.95 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.21, 80.49, 75.54, 68.56, 46.43–45.82, 29.12, 21.41, 20.38, 19.35, 18.04; IR (neat, NaCl) 3414, 2968, 2931, 1688, 1440, 1298, 1136, 1050, 768 cm^{-1}; MS (EI) m/z: 275.1 ($M^{\cdot+}$).

2.7.5. *Syn–anti* 5-(benzyloxy)-2-methylhex-1-ene-3,4-diol 27b. To a solution of carbamate **26b** (178 mg,

0.49 mmol, 1 equiv.) in THF (20 ml) was added dropwise a solution of $LiAlH_4$ (1 M in Et_2O, 1.96 ml, 1.96 mmol, 4 equiv.). After completion the mixture was heated at reflux for 3 h. After cooling to room temperature, the solution was diluted with 20 ml of Et_2O and 30 ml of water. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE 3/EA 1) to give pure diol **21b** as a colourless oil (75 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.28 (5H, m), 5.03 (1H, bs), 4.98 (1H, bs), 4.64 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 4.17 (1H, d, J=5.8 Hz), 3.83 (1H, qd, J=6.1, 3.1 Hz), 3.53 (1H, dd, J=5.8, 3.1 Hz), 1.75 (3H, s), 1.31 (3H, d, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.72, 137.70, 128.48, 127.93, 112.72, 77.00, 74.64, 73.46, 70.85, 18.48, 15.69; IR (neat, NaCl) 3439, 3069, 3028, 2975, 2924, 1451, 1131, 1067, 1022, 995, 901, 737 cm^{-1}; MS (EI) m/z: 236.3 (M$^{\cdot+}$); Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 71.13; H, 8.71.

2.7.6. *Syn–syn* 5-(benzyloxy)-2-methylhex-1-ene-3,4-diol 27d. To a solution of carbamate **26d** (84 mg, 0.231 mmol, 1 equiv.) in THF (17 ml) was added dropwise a solution of $LiAlH_4$ (1 M in Et_2O, 0.926 ml, 0.926 mmol, 4 equiv.). After completion the mixture was heated at reflux for 5 h. After cooling to room temperature, the solution was diluted with 20 ml of Et_2O and 30 ml of water. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated to give pure diol **27d** as a colourless oil (55 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.27 (5H, m), 5.00 (1H, bs), 4.96–4.93 (1H, m), 4.68 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.5 Hz), 4.08 (1H, d, J=3.8 Hz), 3.70 (1H, qd, J=6.3, 4.1 Hz), 3.46 (1H, bt, J=4.1 Hz), 3.11–2.99 (1H, m), 2.69–2.60 (1H, m), 1.74 (3H, s), 1.31 (3H, d, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.31, 137.75, 128.52, 127.91, 112.73, 75.60, 74.58, 74.84, 70.84, 18.59, 15.79; IR (neat, NaCl) 3428, 3063, 3024, 2975, 2922, 1452, 1137, 1069, 1020, 901, 733 cm^{-1}; MS (CI−) m/z: 235.2 (M−H$^-$).

2.7.7. *Syn–anti 2*-methyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl diisopropylcarbamate 28a. Diol **27a** (54 mg, 0.19 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 10 ml of acetone. The mixture was heated at reflux for 5 h. After cooling, 20 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=5/1, Et_3N 5%) to give pure acetonide **28a** as a colourless oil (55 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.91 (1H, dd, J=8.5, 3.6 Hz), 4.13 (1H, dq, J=7.7, 6.0 Hz), 4.02–3.80 (2H, m), 3.61 (1H, t, J=8.3 Hz), 2.08 (1H, hept d, J=6.9, 3.6 Hz),1.40 (3H, s), 1.37 (3H, s), 1.32–1.19 (15H, m), 0.98 (3H, d, J=6.9 Hz), 0.94 (3H, d, J=6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.60, 108.03, 26.86, 21.48–20.57, 19.28, 18.86, 16.43; IR (neat, NaCl) 2968, 2936, 2882, 1701, 1430, 1369, 1293, 1215, 1154, 1090, 1048, 985, 858, 766 cm^{-1}; MS (CI+) m/z: 316.2 (M−H$^+$); Anal. calcd for $C_{17}H_{33}NO_4$: C, 64.73; H, 10.54; N, 4.44; found: C, 64.94; H, 10.51; N, 4.37.

2.7.8. *Syn–syn* 2-methyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl diisopropylcarbamate 28c. Diol **27c** (29 mg, 0.10 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 15 ml of acetone. The mixture was heated at reflux for 3 h. After cooling, 15 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated to give pure acetonide **28c** as a colourless oil (30 mg, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.65 (1H, dd, J=8.5, 1.9 Hz), 4.02–3.88 (2H, m), 3.77 (1H, dq, J=8.5, 5.8 Hz), 3.68 (1H, dd, J=8.5, 1.9 Hz), 2.08 (1H, hept d, J=8.4, 6.6 Hz), 1.39 (3H, s), 1.37 (3H, s), 1.22 (3H, d, J=5.8 Hz), 1.22 (12H, m), 0.99 (3H, d, J=6.9 Hz), 0.95 (3H, d, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.27, 107.69, 81.83, 74.75, 72.93, 46.12–45.55, 30.40, 27.21, 26.91, 29.67–20.56 −19.29, 19.16, 17.25; IR (neat, NaCl) 2969, 2933, 2876, 1695, 1435, 1370, 1310, 1221, 1097, 1048, 935, 874, 767 cm^{-1}; MS (EI) m/z: 316.3 (M+H$^+$).

2.7.9. *Syn–anti* 4-(1-(benzyloxy)ethyl)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane 28b. Diol **27b** (16 mg, 0.066 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 5 ml of acetone. The mixture was heated at reflux for 18 h. After cooling, 20 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=8/1, Et_3N 5%) to give pure acetonide **28b** as a colourless oil (7 mg, 39%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.23 (5H, m), 4.97 (1H, t, J=0.8 Hz), 4.94 (1H, t, J=1.6 Hz), 4.67 (1H, d, J=12.1 Hz), 4.62 (1H, d, J=12.1 Hz), 4.52 (1H, d, J=6.9 Hz), 4.20 (1H, dd, J=8.0, 6.9 Hz), 3.51 (1H, dq, J=8.0, 6.0 Hz), 1.73 (3H, s), 1.58 (3H, s), 1.57 (3 h, s), 1.14 (3H, d, J=6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 141.94, 139.01, 128.20, 127.67, 127.31, 115.12, 108.63, 82.41, 81.12, 72.99, 71.43, 26.57, 25.12, 19.66, 17.27; IR (neat, NaCl) 2983, 2930, 1451, 1374, 1260, 1212, 1159, 1088, 1045, 874, 735 cm^{-1}; MS (EI) m/z: 276.3 (M$^{\cdot+}$).

2.7.10. *Syn–syn* 4-(1-(benzyloxy)ethyl)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane 28d. Diol **27d** (54 mg, 0.23 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 20 ml of acetone. The mixture was heated to reflux for 3 h. After cooling, 10 ml of Et_2O were added followed by a saturated solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=15/1) to give pure acetonide **28d** as a colourless oil (52 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.24 (5H, m), 4.93–4.91 (2H, m), 4.70 (1H, d, J=12.1 Hz), 4.55 (1H, d, J=12.1 Hz), 4.35 (1H, d, J=8.1 Hz), 3.80 (1H, dd, J=8.3, 4.4 Hz), 3.55 (1H, qd, J=6.4, 4.5 Hz), 1.75 (3H, s), 1.45 (3H, s), 1.44 (3 h, s), 1.23 (3H, d, J=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.97, 139.57, 128.31, 127.85, 127.52, 115.22, 108.91, 82.07, 81.07, 73.33, 71.08, 27.09, 27.03, 17.07, 16.25; IR (neat, NaCl) 3068, 3033, 2986, 2935, 2871, 1652, 1454, 1372, 1244, 1214, 1154, 1091, 1070, 883, 737 cm^{-1}; MS (EI) m/z: 276.2 (M$^{\cdot+}$).

2.7.11. (3*R*,4*R*,5*S*)-4-Acetoxy-5-(benzyloxy)-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 29. Alcohol **24b** (1.1 g, 2.52 mmol, 1 equiv.) was dissolved in 25 ml of pyridine and cooled to 0 °C. Acetic anhydride (700 μl, 743 mg, 7.58 mmol, 3 equiv.) was added slowly. Then the mixture was allowed to reach room temperature within 1 h and was stirred another 12 h. The solution was poured over a saturated solution of $NaHCO_3$ (50 ml) and diluted with Et_2O (50 ml). The organic phase was washed with a saturated solution of $CuSO_4$ (50 ml), water (50 ml) and a saturated solution of NaCl (50 ml). After drying over $MgSO_4$, the solution was filtered and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=10/1) to give pure acetate **29** as a colourless oil (1.02 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.22 (5H, m), 5.30 (1H, d, J=3.6 Hz), 5.21 (1H, t, J=3.6 Hz), 4.89 (1H, s), 4.73 (1H, s), 4.61 (1H, d, J=12 Hz), 4.41 (1H, d, J=12 Hz), 3.99 (2H, bs), 3.70 (1H, m), 2.03 (3H, s), 1.58 (1H, d, J=14.4 Hz), 1.47 (1H, d, J=14.4 Hz), 1.18 (15H, m), 0.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.25, 153.77, 142.92, 138.34, 128.16, 127.41, 127.32, 110.38, 75.259, 73.96, 71.00, 45.43, 23.05, 21.56, 20.95, 15.98, −1.14; IR (neat, NaCl) 2966, 2875, 1744, 1701, 1434, 1370, 1306, 1234, 1046, 848 cm^{-1}; MS (CI) m/z: 478.4 ($M+H^+$); Anal. calcd for $C_{26}H_{43}NO_5Si$: C, 65.43; H, 9.08; N, 2.93; found: C, 65.43; H, 9.09; N, 2.90. $[\alpha]_{20}^{D}$=57.1 (c 1.0, CH_2Cl_2).

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Enantioselective organocatalytic aldehyde–aldehyde cross-aldol couplings. The broad utility of α-thioacetal aldehydes

R. Ian Storer and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E California Blvd; Pasadena, CA 91125, USA

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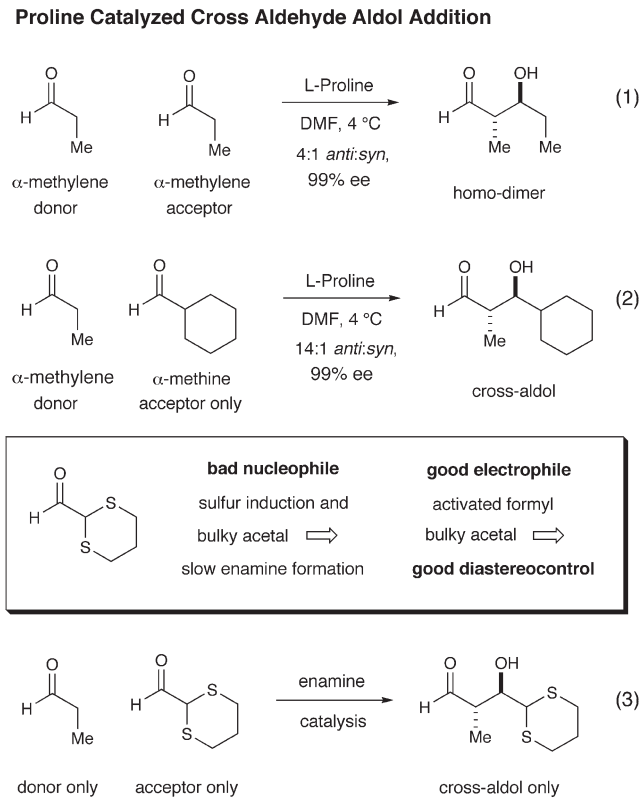
This manuscript is dedicated to Professor D. Seebach for his pioneering work in the area of asymmetric synthesis

Abstract—An asymmetric proline catalyzed aldol reaction with α-thioacetal aldehydes has been developed. Thioacetal bearing aldehydes readily participate as electrophilic cross-aldol partners with a broad range of aldehyde and ketone donors. High levels of reaction efficiency as well as diastereo- and enantiocontrol are observed in the production of *anti*-aldol adducts.

1. Introduction

The aldol reaction is widely considered to be one of the most important technologies for carbon–carbon bond formation in chemical synthesis.[1] Over the last thirty years, seminal research from the laboratories of Evans,[2] Heathcock,[3] Masamune[4] and Mukaiyama[5] have established this venerable reaction as the principal chemical method for the stereoselective construction of complex polyol architecture. Recently, studies by Barbas,[6] Evans,[7] List,[8] Shair,[9] Shibasaki,[10] and Trost[11] have outlined the first examples of enantioselective direct aldol reactions, an important class of metal or proline catalyzed transformation that does not require the pregeneration of enolates or enolate equivalents. With these remarkable advances in place, a fundamental goal for asymmetric aldol technology has become the development of catalytic methods that would allow the direct coupling of aldehyde substrates.[12] In this context, our laboratory has recently reported the first example of a direct enantioselective aldehyde–aldehyde cross-aldol reaction using small molecule catalysts (Scheme 1).[13] Subsequently, we described the enantioselective dimerization and cross coupling of α-oxygenated aldehydes to provide erythrose architecture of broad utility for the construction of hexose carbohydrates.[14] In this report, we further advance this enamine catalysis concept to describe a highly stereoselective protocol for the cross coupling of aldehydes and ketones with α-thioacetal aldehydes. Importantly, the successful introduction of α-thioacetal functionality in this enantioselective cross coupling allows access to highly oxidized, stereodefined synthons of broad versatility. Moreover, the observed reactivity profile of 'viable-electrophile, non-nucleophile' has established α-thioacetal aldehydes as



Scheme 1. Proline-catalyzed cross aldehyde aldol.

Keywords: Aldol; Catalysis; Diastereoselection; Enantioselective; Organocatalysis; Proline.
* Corresponding author. Tel.: +1-626-395-6044; fax: +1-626-795-3658; e-mail address: dmacmill@caltech.edu

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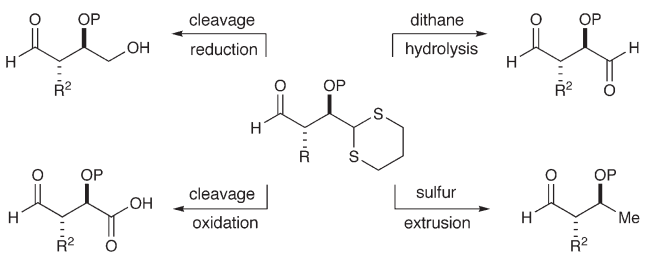
preeminent substrates for highly selective cross aldol reactions with prototypical aldehyde and ketone donors.

Traditionally, the enantioselective aldol coupling of non-equivalent aldehydes has been viewed as a formidable synthetic challenge on account of (i) the propensity of aldehydes to polymerize under metal catalyzed conditions and (ii) the mechanistic requirement that non-equivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. In our recent studies, however, we have established that enamine catalysis can provide good levels of chemo-differentiation and stereocontrol with non-equivalent aldehydes, thereby establishing the aldehyde cross-aldol as an operationally useful transformation. More specifically, we have found that aldehydes containing a methylene carbon (CH_2R_2) adjacent to the carbonyl have a strong propensity to dimerize, via participation as both nucleophile and electrophile (Scheme 1, Eq. 1).[13] In contrast, aldehydes that incorporate an α-methine carbon (CHR_3) generally do not homo-dimerize when exposed to proline, instead behaving as electrophilic acceptors exclusively (Scheme 1, Eq. 2). In this latter case, it is presumed that the kinetic inaccessabilty of the α-methine proton and the thermodynamic instability of the corresponding enamine effectively prohibit nucleophile formation. As a consequence, chemoselective partitioning of α-methylene and α-methine aldehydes into nucleophilic and electrophilic partners respectively can be accomplished via slow addition of the enamine precursor to the α-methine aldehyde in the presence of catalyst. With respect to stereoselectivity, it should be noted that the bulky α,α-disubstituted aldehyde acceptors consistently provide superior levels of *anti*-diastereocontrol in crossed aldehyde aldol reactions in comparison to their α-methylene counterparts (Scheme 1, cf. Eqs. 1 and 3). This improvement in diastereocontrol as a function of increasing steric demand of the electrophile is in accord with a chair-like Zimmerman–Traxler transition state that has been proposed for enamine aldol reactions.

Based on our knowledge of the chemo- and stereo-differentiating features of the enamine cross aldol, we recently sought to devise a new and generally useful class of aldehyde cross coupling partner. Specifically we focused upon the design of aldehydic reagents that would (i) selectively function as aldol donors or acceptors, (ii) engender high levels of diastereocontrol, and (iii) contain chemical functionality that is readily elaborated and synthetically versatile. In this context, we selected α-thioacetal aldehydes with the expectation that they would be highly electrophilic yet sterically and electronically deactivated towards enamine formation (Scheme 1 Eq. 3). Moreover, the substantial steric demand of the α-dithane was expected to enforce high levels of absolute and relative stereocontrol in the aldol event. Lastly, the synthetic utility of thioacetals as latent carbonyl and alkyl equivalents has been widely established.[15] Indeed, a variety of conditions have been elucidated to transform dithianes to aldehydes, alcohols or carboxylic acids. Alternatively, the reductive extrusion of sulfur using transition metals is commonly utilized for the conversion of thioacetals to saturated alkyl substituents (Scheme 2).[15] With regard to operational advantages, it is important to note that α-thioacetal aldehydes are readily accessible on large scale and can be easily handled and stored.[16]

Dithiane Aldol Adducts: Latent Functionality

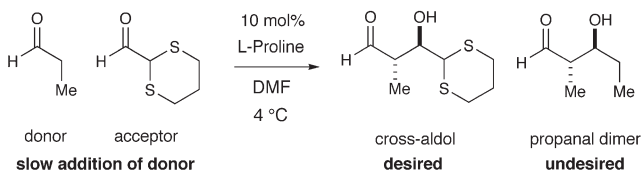


Scheme 2. Manipulation of dithianes.

2. Results and discussion

The proposed organocatalytic cross aldol was first examined using equimolar quantities of propanal and [1,3]-dithane-2-carbaldehyde[16] in the presence of catalytic proline (Table 1, entry 1). Preliminary studies revealed that this aldol reaction was indeed possible to provide the cross aldehyde adduct in 99% ee, however small quantities of the propanal dimer were observed. Gratifyingly, the aldol union can be

Table 1. Enantioselective direct cross-aldol reaction: preliminary studies



Entry	Donor (equiv.[a])	Acceptor (equiv.)	% Cross[b] (desired)	% Dimer[b] (undesired)	% ee Cross
1	1.0	1.0	90	10	99
2	2.0	1.0	65	35	99
3	1.0	2.0	100	0	99
4	1.0	4.0	100	0	99
5[c]	1.0	2.0	90	10	99
6	0	1.0	no thioacetal dimer	—	—

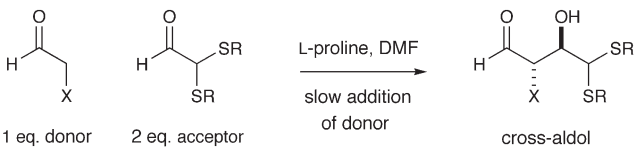
[a] Donor added by syringe pump over 24 h.
[b] Ratio of products determined by ^{1}H NMR integration of reaction crude.
[c] Donor and acceptor premixed.

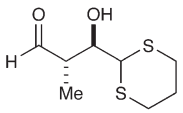
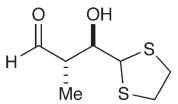
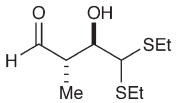
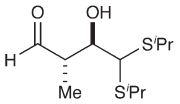
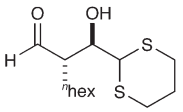
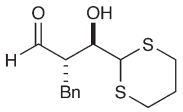
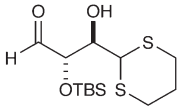
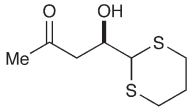
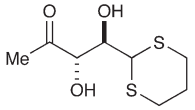
comprehensively partitioned to a cross aldol mechanism via the slow addition of propanal to an excess of the electrophilic aldehyde (entries 3 and 4).

In these cases the corresponding cross aldol adduct was obtained with excellent levels of *anti* diastereoselectivity and enantiocontrol (entry 3, 16:1 *anti–syn*, 99% ee) without production of dimeric propanal. As revealed in entries 3 and 5, the slow addition of the donor component is critical to the kinetic circumvention of the undesired dimerization pathway. The superior levels of cross-aldol selectivity, asymmetric induction and efficiency obtained via slow addition of the donor with excess dithiane acceptor (2 equiv.) prompted us to select these catalytic conditions for further exploration.

Experiments that probed the scope of the dithiane moiety and the donor aldehyde are summarized in Table 2. In all cases, slow addition of the donor aldehyde to a series of thioacetal aldehydes in the presence of proline effectively suppressed homodimerization, whilst providing good to excellent yields of the desired cross-aldol products (entries

Table 2. Enantioselective direct cross-aldol reaction: scope studies



Entry	Temperature (°C)	Mol% cat.	Product	% Yield	*anti–syn*[a]	% cc
1	4	10		85	16:1	>99[b]
2	4	10		77	8:1	99[b]
3	23	10		70	10:1	97[b]
4	23	10		41	8:1	98[b]
5[c]	4	10		75	>20:1	97[b]
6	23	10		73	>20:1	97[b]
7	23	20		52	13:1	70[b]
8[d]	23	20		91	—	96[e]
9[d,f]	23	10		88	>20:1	>99[e]

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixtures.
[b] Enantiomeric excess determined by chiral HPLC analysis of the 2,2-dimethyl-1,3-propanediol acetal derivatives.
[c] Ratio of donor–acceptor was 1:1.5.
[d] An excess of ketone donor was used.
[e] Enantiomeric excess determined by chiral HPLC analysis.
[f] Relative and absolute stereochemistry was confirmed by X-ray analysis.[17]

1–7). Considerable variation in the steric demand of the thioacetal substituent is possible without loss in enantiocontrol (entries 1–4, 97 to 99% ee).[16] However, couplings performed with cyclic thioacetal aldehydes (Table 1, entries 1–2) were found to proceed more efficiently than with the acyclic examples (Table 1, entries 3–4). In these cases, we presume that the inherent reactivity of the acceptor decreases with the relative steric demands of the proximal acetal. To our delight, this chemo- and enantioselective cross aldol is also tolerant to a wide range of donor systems (entries 5–9, 97–99% ee). In the context of aldehyde donors, propanal, octanal and hydrocinnamaldehyde provide cross coupled adducts with [1,3]-dithane-2-carbaldehyde in 70–85% yield, >20:1 dr and 95–99% ee (Table 2, entries 1,5,6). Moreover, the silyloxy glycoaldehyde donor enables the rapid construction of latent erythrose architecture (entry 7, 95% yield, 13:1 *anti*–*syn*, 70% ee).

In accord with the studies of Hajos–Parrish[18] and Barbas[6]–List,[7] ketone donors can also be accommodated without loss in reaction efficiency or stereocontrol (Table 2, entries 8 and 9). More specifically, the rapid addition of acetone to [1,3]-dithane-2-carbaldehyde in the presence of proline at room temperature resulted in the corresponding cross aldol adduct in 91% yield and 96% ee (entry 8). Of particular note was the coupling of acetol in 88% yield, >20:1 dr, >99% ee (entry 9) and the silyloxy glycoaldehyde donor (entry 7). The successful implementation of these α-oxy substrates in this cross aldol sequence should allow facile and rapid access to biologically important polyol architectures, such as hexose carbohydrates.

Lastly, it is important to note that this dithiane-aldehyde class provides the highest levels of diastereocontrol that have been observed in aldehyde–aldehyde couplings to date. As revealed in Table 2, formation of the *anti*-isomer is accomplished with excellent selectivity for a range of aldehyde donors and thio-acetal acceptors (entries 1–7, 8 to 20:1 *anti*–*syn*). The relative and absolute stereochemistry observed is in accord with the previously proposed models for proline catalyzed reactions.[14,19]

In summary, we have shown α-thioacetal aldehydes to be versatile acceptor units for direct proline catalyzed aldol reactions with a range of aldehyde and ketone donors. Significantly, this reaction permits highly diastereoselective and enantioselective access to β-hydroxy and α,β-dihydroxy aldehydes and ketones. Work is continuing to apply these units in the synthesis of desymmetrized *meso*-tartrate derivatives, hexose and pentose carbohydrates, and to the total synthesis of polypropionate and polyacetate natural products. A full account of these studies will be presented in due course.

3. Experimental

3.1. General

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[20] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. dimethylformamide (DMF) was purified according to the method of Grubbs.[21] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63 according to the method of Still.[22] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or stained using anisaldehyde or aqueous acidic ammonium molybdate. ^{1}H NMR spectra were recorded in $CDCl_3$, at ambient temperature on a Varian 300 spectrometer, at 300 MHz, with residual protic solvent $CHCl_3$ as the internal reference (δ_H=7.26 ppm); Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: chemical shift (δ/ppm) (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sept=septet, m=multiplet), coupling constant (J/Hz), number of protons, assignment). ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on the same spectrometer at 75 MHz, with the central peak of $CHCl_3$ as the internal reference (δ_C=77.3 ppm). Data for ^{13}C NMR are reported in terms of chemical shift. Two dimensional COSY and HMQC NMR spectroscopy were used where appropriate, to aid in the assignment of signals in the ^{1}H NMR spectra. Where a compound has been characterized as an inseparable mixture of diastereoisomers, the NMR data for the major isomer has been reported. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} deg cm2 g^{-1}; concentration (c) is in g/100 mL. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm), a Chiralcel OJ column (25 cm) and OJ guard (5 cm), a Chiralcel AS column (25 cm) and AS guard (5 cm), or a Chiralcel ODH column (25 cm) and ODH guard (5 cm) as noted. Syringe pump additions were made using a 10 syringe parallel pump (in all cases the syringe needle tip was submerged below the surface of the liquid in the receiver vessel to ensure continuous mixing).

3.2. Synthesis and characterization

3.2.1. [1,3]Dithiane-2-carbaldehyde. The title compound was obtained from 1,3-dithiane and ethyl formate using the procedure outlined by Page.[16b] The product was initially purified by flash chromatography (3:1 pentane–diethyl ether) to remove any residual 1,3-dithiane and yield a pale yellow oil. The aldehyde was then purified by distillation in vacuo (78 °C, 0.15 mm Hg, 135 °C bath temp.)[16a] to yield a colorless oil. The aldehyde could be successfully stored under anhydrous conditions at ca. −20 °C (mp <0 °C) as a white crystalline solid.

3.2.2. (2*S*,3*R*)-3-[1,3]Dithiane-2-yl-3-hydroxy-2-methylpropionaldehyde (Table 2, entry 1). A solution of freshly

distilled propionaldehyde (100 μL, 1.35 mmol) in 1.35 mL DMF pre-cooled to 4 °C was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (400 mg, 2.70 mmol), L-proline (16 mg, 0.139 mmol) and 1.35 mL DMF at 4 °C. After 46 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a 16:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (1:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 85% yield (236 mg, 1.15 mmol). The enaniomeric excess (ee) was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3456, 2902, 1717, 1422, 1277, 986, 908, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, J=1.2 Hz, 1H, C*H*O), 4.24 (dd, J=7.2, 4.8 Hz, 1H, C*H*OH), 3.87 (d, J=7.2 Hz, 1H, SC*H*S), 3.05–2.78 (m, 3H, C*H*CH_3, SC$H_2$$CH_2CH_2$S), 2.74–2.60 (m, 2H, SC$H_2$$CH_2CH_2$S), 2.15–1.95 (m, 2H, SCH_2C$H_2$$CH_2$S), 1.25 (d, J=7.5 Hz, 3H, CH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 73.7, 48.5, 47.9, 27.7, 26.9, 25.4, 10.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_2S_2$) requires m/z 206.0435, found m/z 206.0432; $[\alpha]_D$=−15.3 (c=1.0, $CHCl_3$).

3.2.3. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (21.0 mg, 0.202 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-3-[1,3]dithiane-2-yl-3-hydroxy-2-methyl-propionaldehyde (17.0 mg, 0.083 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 16 h before filtration through a pad of silica (2:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (5:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 82% yield (20 mg, 0.068 mmol) 99% ee. The product ee was measured by chiral HPLC (OJ column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=39.3 min, (1*S*,2*R*) *anti* isomer t_r=33.7 min, *syn* isomers t_r major=25.1 min, t_r minor=21.4 min. IR (film) 3446, 2954, 1471, 1394, 1108, 1081, 1040, 983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, J=3.6 Hz, 1H, OC*H*O), 4.17 (d, J=4.2 Hz, 1H, SC*H*S), 4.00–3.90 (m, 1H, C*H*OH), 3.63 (d, J=11.1 Hz, 2H, OCH_2C$(CH_3)_2$CH_2O), 3.42 (d, J=11.1 Hz, 2H, OCH_2C$(CH_3)_2$CH_2O), 3.02–2.70 (m, 4H, SC$H_2$$CH_2CH_2$S), 2.21 (qdd (app. pd), J=7.2, 7.2, 4.2 Hz, 1H, C*H*CH_3), 2.15–1.86 (m, 2H, SCH_2C$H_2$$CH_2$S), 1.18 (s, 3H, C$H_3$$CCH_3$), 0.87 (d, J=7.2 Hz, 3H, CHCH_3), 0.72 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 77.7, 77.5, 76.2, 51.9, 40.1, 30.7, 30.6, 29.8, 26.4, 23.3, 22.1, 12.0; HRMS (FAB+) exact mass calcd for $[M-H]^+$ ($C_{13}H_{23}O_3S_2$) requires m/z 291.1089, found m/z 291.1098; $[\alpha]_D^{22}$=−13.5 (c=1.0, $CHCl_3$).

3.2.4. [1,3]Dithiolane-2-carbaldehyde.[16c] A solution of DIBAL-H (1.0 M hexanes, 14.1 mL, 14.0 mmol) was added dropwise to a stirred solution of [1,3]dithiolane-2-carboxylic acid ethyl ester (2.5 g, 14.0 mmol) in CH_2Cl_2 (21 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, quenched with MeOH (2 mL) and allowed to slowly warm to room temperature. A solution of Rochel salts (20 mL) and CH_2Cl_2 (30 mL) were added and stirring continued for 3 h. The mixture was extracted three times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield a pale yellow oil. Purification by flash chromatography (4:1 pentane–diethyl ether) yielded a colorless clear oil in 85% yield (1.59 g, 11.9 mmol). The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage).

3.2.5. (2*S*,3*R*)-[1,3]Dithiolane-2-yl-3-hydroxy-2-methyl-propionaldehyde (Table 2, entry 2). A solution of freshly distilled propionaldehyde (123 μL, 1.69 mmol) in 1.75 mL DMF pre-cooled to 4 °C was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiolane-2-carbaldehyde (453 mg, 3.38 mmol), L-proline (19.5 mg, 0.169 mmol) and 1.75 mL DMF at 4 °C. After 28 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed an 8:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (2:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 77% yield (251 mg, 1.31 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3440, 2972, 2928, 2877, 2730, 1715, 1456, 1423, 1380, 1279, 1101, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=2.1 Hz, 1H, C*H*O), 4.71 (d, J=5.7 Hz, 1H, SC*H*S), 3.74 (ddd, J=5.7, 5.7, 4.5 Hz, 1H, C*H*OH), 3.40–3.14 (m, 4H, SC$H_2$$CH_2$S), 2.85 (d, J=4.4 Hz, 1H, O*H*), 2.78–2.66 (m, 1H, C*H*CH_3), 1.19 (d, J=7.2 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 76.6, 57.3, 50.3, 39.3, 38.5, 11.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_7H_{12}O_2S_2$) requires m/z 192.0279, found m/z 192.0279; $[\alpha]_D^{22}$=−2.4 (c=1.0, $CHCl_3$).

3.2.6. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl-1-[1,3]dithiolan-2-yl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (10.8 mg, 0.104 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-[1,3]dithiolane-2-yl-3-hydroxy-2-methyl-propionaldehyde (10.0 mg, 0.052 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 26 h before filtration through a pad of silica (2:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (4:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 76% yield (11 mg, 0.04 mmol) 99% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=22.2 min, (1*S*,2*R*) *anti* isomer t_r=40.6 min, *syn* isomers t_r major=16.6 min, t_r minor=18.7 min. IR (film) 3487, 2954, 2860, 1471, 1394, 1108, 1017, 990, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, J=5.7 Hz, 1H, SC*H*S), 4.63 (d, J=3.3 Hz, 1H, OC*H*O), 3.64 (m, 1H, C*H*OH), 3.62 (d,

J=11.0 Hz, 2H, $CH_2C(CH_3)_2CH_2$), 3.42 (d, J=11.0 Hz, 2H, $CH_2C(CH_3)_2CH_2$), 3.34–3.13 (m, 4H, SCH_2CH_2S), 2.09 (qdd, J=6.9, 6.6, 3.0 Hz, 1H, $CHCH_3$), 1.17 (s, 3H, CH_3CCH_3), 1.06 (d, J=6.9 Hz, 3H, $CHCH_3$), 0.71 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 77.5, 77.4, 57.8, 41.6, 39.2, 38.8, 30.5, 23.3, 22.0, 12.0, one signal obscured; HRMS (EI+) exact mass calcd for $[M-H]^+$ ($C_{12}H_{22}O_3S_2$) requires m/z 277.0932, found m/z 277.0919; $[\alpha]_D^{24}$=+17.6 (c=1.0, $CHCl_3$).

3.2.7. Bis-ethylsulfanyl-acetaldehyde (Table 2, entry 3). The title compound was obtained from glyoxal and ethane thiol using the procedure outlined by Bates.[16d] The product can be purified by flash chromatography (40:1 pentane–diethyl ether) or by vacuum distillation (60 °C, 0.1 mm Hg) to yield a colorless clear oil. The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage).

3.2.8. (2*S*,3*R*)-4,4-Bis-ethylsulfanyl-3-hydroxy-2-methyl-butyraldehyde. A solution of freshly distilled propionaldehyde (98 mg, 123 μL, 1.69 mmol) in 1.75 mL DMF was added slowly over the course of 24 h to a stirring suspension of bis-ethylsulfanyl-acetaldehyde (554 mg, 3.38 mmol), L-proline (19.5 mg, 0.17 mmol) and 1.75 mL DMF room temperature. After 38 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 10:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 70% yield (262 mg, 1.18 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3468, 2970, 2929, 2872, 2728, 1722, 1455, 1455, 1377, 1266, 1108, 1051, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=1.5 Hz, 1H, CHO), 3.93 (d, J=6.3 Hz, 1H, $CH(SEt)_2$), 3.86 (dd, J=6.3, 7.2 Hz, 1H, $CHOH$), 3.17 (br s, 1H, $CHOH$), 2.93 (qdd, J=7.2, 7.2, 1.5 Hz, 1H, $CHCH_3$), 2.80–2.50 (m, 4H, $S(CH_2CH_3)_2$), 1.27 (t, J=7.2 Hz, 3H, SCH_2CH_3), 1.26 (t, J=7.2 Hz, 3H, SCH_2CH_3), 1.19 (d, J=7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 74.5, 56.3, 48.8, 25.8, 24.7, 14.9, 14.7, 11.1; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_9H_{18}O_2S_2$) requires m/z 222.0748, found m/z 222.0758; $[\alpha]_D^{21}$=+23.3 (c=1.0, $CHCl_3$).

3.2.9. (2*R*,3*S*)-3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1,1-bis-ethylsulfanyl-butan-2-ol. A solution of 2,2-dimethyl-propane-1,3-diol (20.0 mg, 0.193 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-4,4-bis-ethylsulfanyl-3-hydroxy-2-methyl-butyraldehyde (21.4 mg, 0.096 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 36 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 81% yield (24 mg, 0.078 mmol) 97% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (2*R*,3*S*) *anti* isomer t_r=8.0 min, (2*S*,3*R*) *anti* isomer t_r=13.6 min, *syn* isomers t_r major=5.4 min, t_r minor=6.5 min. IR (film) 3490, 2957, 2929, 2870, 2852, 1455, 1393, 1265, 1154, 1108, 1080, 1018, 976, 923 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, J=3.0 Hz, 1H, $OCHO$), 3.94 (d, J=3.3 Hz, 1H, $CH(SEt)_2$), 3.91–3.83 (m, 1H, $CHOH$), 3.62 (d, J=11.1 Hz, 2H, CH_2O), 3.44 (d, J=10.8 Hz, 1H, CH_2O), 3.43 (d, J=10.5 Hz, 1H, CH_2O), 2.80–2.60 (m, 4H, $(SCH_2CH_3)_2$), 2.28 (qdd, J=7.2, 7.2, 3.0 Hz, 1H, $CHCH_3$), 1.27 (t, J=7.8 Hz, 6H, $(SCH_2CH_3)_2$), 1.18 (s, 3H, CH_3CCH_3), 0.99 (d, 3H, J=7.2 Hz, $CHCH_3$), 0.71 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.7, 77.6, 77.5, 75.4, 55.9, 40.6, 30.6, 25.8, 25.3, 23.3, 22.0, 14.9, 14.8, 11.3; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{14}H_{28}O_3S_2$) requires m/z 308.1480, found m/z 308.1490; $[\alpha]_D$=−33.2 (c=1.0, $CHCl_3$).

3.2.10. Bis-isopropylsulfanyl-acetaldehyde (Table 2, entry 4). A biphasic mixture of an aqueous 40% solution of glyoxal (12.5 g solution, ca. 5 g glyoxal, 86 mmol), isopropanethiol (13.1 g, 16.0 mL, 172 mmol) and 2 N HCl (10 mL) in CH_2Cl_2 was stirred vigorously for 24 h. The phases were separated and the aqueous phase extracted two times with CH_2Cl_2. The organic phases were combined, washed once with an aqueous solution of Na_2CO_3, dried over $MgSO_4$, and concentrated to yield a pale yellow oil. The product was purified by flash chromatography (10:1 pentane–diethyl ether) to yield the title compound as a colourless clear oil in 38% yield (6.4 g, 33 mmol). The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage). IR (film) 2963, 2927, 2867, 2813, 2707, 1715, 1590, 1455, 1384, 1367, 1247, 1155, 1128, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (d, J=5.6 Hz, 1H, CHO), 4.18 (dd, J=5.6, 0.6 Hz, 1H, $CH(S^iPr)_2$), 3.05 (sep, J=6.9 Hz, 2H, $(CH(CH_3)_2)_2$), 1.32 (d, J=6.6 Hz, 6H, $CH_2(CH_3)_2$), 1.28 (d, J=6.6 Hz, 6H, $CH_2(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 53.6, 36.2, 23.8, 23.6; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{16}OS_2$) requires m/z 192.0643, found m/z 192.0636.

3.2.11. (2*S*,3*R*)-3-Hydroxy-4,4-bis-isopropylsulfanyl-2-methyl-butyraldehyde. A solution of freshly distilled propionaldehyde (20 mg, 25 μL, 1.69 mmol) in 0.35 mL DMF was added slowly over the course of 24 h to a stirring suspension of bis-isopropylsulfanyl-acetaldehyde (130 mg, 0.68 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF room temperature. After 40 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 8:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 41% yield (34.2 mg, 0.14 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3470, 2962,

2927, 2864, 1723, 1454, 1367, 1243, 1154, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=1.8 Hz, 1H, C*H*O), 4.01 (d, J=5.4 Hz, 1H, C*H*(S^iPr)$_2$), 3.86 (dd (app. t), J=5.7, 5.7 Hz, 1H, C*H*OH), 3.23 (br s, 1H, CHO*H*), 3.22–3.04 (m, 2H, (SC*H*(CH_3)$_2$)$_2$), 2.93 (qdd, J=7.5, 5.7, 1.8 Hz, 1H, C*H*CH_3), 1.32 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.31 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.30 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.27 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.17 (d, J=7.5 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 74.7, 54.5, 48.7, 35.6, 35.3, 24.1, 24.0, 23.7, 23.5, 11.0; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{11}H_{22}O_2S_2$) requires m/z 250.1061, found m/z 250.1071; $[\alpha]_D^{22}$=−8.2 (c=1.0, $CHCl_3$).

3.2.12. (2*R*,3*S*)-3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1,1-bis-isopropylsulfanyl-butan-2-ol. A solution of 2,2-dimethylpropane-1,3-diol (14.2 mg, 0.136 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-3-hydroxy-4,4-bis-isopropylsulfanyl-2-methyl-butyraldehyde (17.0 mg, 0.068 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 51 h before filtration through a pad of silica (5:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 83% yield (19.1 mg, 0.057 mmol) 98% ee. The product ee was measured by chiral HPLC (ODH column, 2% ^{i}PrOH in hexanes) relative to a racemic sample; (2*R*,3*S*) *anti* isomer t_r=10.2 min, (2*S*,3*R*) *anti* isomer t_r=11.7 min, *syn* isomers t_r major=8.4 min, t_r minor=9.7 min. IR (film) 3494, 2957, 2928, 2867, 1461, 1393, 1365, 1244, 1154, 1107, 1040, 989, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (d, J=3.3 Hz, 1H, OC*H*O), 4.03 (d, J=3.0 Hz, 1H, SC*H*S), 3.82 (dd, J=8.5, 3.0 Hz, 1H, C*H*OH), 3.61 (d, 2H, CH_2O), 3.51–3.37 (m, 2H, CH_2O), 3.18 (sept, J=6.6 Hz, 1H, SC*H*(CH_3)$_2$), 3.10 (sept, J=6.9 Hz, 1H, SC*H*(CH_3)$_2$), 2.33–2.19 (m, 1H, C*H*CH_3), 1.31 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.30 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.28 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.25 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.18 (s, 3H, CH_3CCH$_3$), 1.00 (d, J=7.2 Hz, 3H, CHCH_3), 0.71 (s, 3H, CH$_3$CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.2, 77.53, 77.47, 74.7, 53.9, 40.3, 35.1, 34.9, 30.6, 24.1, 23.9, 23.5, 23.4, 23.3, 22.0, 10.6; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{16}H_{32}O_3S_2$) requires m/z 336.1793, found m/z 336.1794; $[\alpha]_D^{22}$=−42.9 (c=1.0, $CHCl_3$).

3.2.13. (2*S*,2′*R*)-2-([1,3]Dithian-2-yl-hydroxy-methyl)-octanal (Table 2, entry 5). A solution of freshly distilled octanal (65 mg, 79 μL, 0.34 mmol) in 0.35 mL DMF was added slowly over the course of 15 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (50 mg, 0.34 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF at room temperature. After 36 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a >20:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 75% yield (70 mg, 0.25 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3460, 2927, 2856, 1718, 1465, 1422, 1378, 1277, 1244, 1051, 910, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, J=2.1 Hz, 1H, C*H*O), 4.20 (ddd, J=8.1, 2.7, 2.1 Hz, 1H, C*H*OH), 3.86 (d, J=8.1 Hz, 1H, SC*H*S), 3.02–2.60 (m, 6H, C*H*C_6H_{13}, O*H*, SCH_2CH_2CH_2S), 2.14–1.94 (m, 2H, SCH$_2$CH_2CH$_2$S), 1.88–1.60 (m, 2H, CH_2(CH$_2$)$_4$CH$_3$), 1.46–1.22 (m, 8H, (CH_2)$_4$CH$_3$), 0.88 (t, J=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 72.9, 53.3, 48.2, 31.9, 29.6, 27.8, 27.5, 26.7, 26.3, 25.4, 22.8, 14.3; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{24}O_2S_2$) requires m/z 276.1218, found m/z 276.1224; $[\alpha]_D^{22}$=−16.3 (c=1.0, $CHCl_3$).

3.2.14. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-octan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (20.4 mg, 0.20 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,2′*R*)-2-([1,3]dithian-2-yl-hydroxy-methyl)-octanal (27 mg, 0.098 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 49 h before filtration through a pad of silica (5:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (4:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 95% yield (33.5 mg, 0.092 mmol) 97% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=24.7 min, (1*S*,2*R*) *anti* isomer t_r=16.7 min, *syn* isomers t_r major=27.6 min, t_r minor=31.5 min. IR (film) 3490, 2953, 2928, 2855, 1469, 1422, 1394, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J=3.3 Hz, 1H, OC*H*O), 4.25 (d, J=6.8 Hz, 1H, SC*H*S), 4.00 (dd, J=6.8, 5.4 Hz, 1H, C*H*OH), 3.63 (d, J=11.0 Hz, 2H, OCH_2C(CH$_3$)$_2$CH_2O), 3.42 (d, J=11.0 Hz, 2H, OCH_2C(CH$_3$)$_2$CH_2O), 2.99–2.72 (m, 4H, SCH_2CH$_2$-CH_2S), 2.19–2.01 (m, 2H, C*H*(C_6H_{13}), CH_2(CH$_2$)$_4$CH$_3$), 2.00–1.85 (m, 1H, CH_2(CH$_2$)$_4$CH$_3$), 1.62–1.46 (m, 2H, SCH$_2$CH_2CH$_2$S), 1.36–1.22 (m, 8H, (CH_2)$_4$CH$_3$), 1.18 (s, 3H, CH_3CCH$_3$), 0.87 (t, J=6.6 Hz, 3H, (CH$_2$)$_5$CH_3), 0.72 (s, 3H, CH$_3$CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.4, 77.7, 77.5, 74.0, 51.7, 43.6, 32.0, 30.6, 29.9, 29.8, 29.3, 27.5, 26.4, 26.2, 23.4, 22.9, 22.0, 14.4; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{18}H_{34}O_3S_2$) requires m/z 362.1950, found m/z 362.1937; $[\alpha]_D^{22}$=+0.71 (c=1.0, $CHCl_3$).

3.2.15. (2*S*,3*R*)-2-Benzyl-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (Table 2, entry 6). A solution of freshly distilled hydrocinnamaldehyde (45 mg, 45 μL, 0.34 mmol) in 0.35 mL DMF was added slowly over the course of 24 h to a stirring suspension of [1,3]Dithiane-2-carbaldehyde (100 mg, 0.68 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF at room temperature. After 46 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a >20:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (1:1 pentane–diethyl ether) afforded the title compound as a

mixture of diastereoisomers as a clear, colorless oil in 75% yield (71 mg, 0.25 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3436, 2903, 1719, 1496, 1422, 1049, 747, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=0.6 Hz, 1H, C*H*O), 7.34–7.16 (m, 5H, Ph), 4.11 (dd, J=9.3, 2.7 Hz, 1H, C*H*OH), 3.88 (d, J=9.3 Hz, 1H, SC*H*S), 3.28 (m, 1H, C*H*Bn), 3.17 (dd, J=13.6, 7.5 Hz, 1H, CH_2Ph), 3.04 (dd, J=13.6, 7.8 Hz, 1H, CH_2Ph), 2.86 (ddd, J=13.1, 8.7, 2.7 Hz, 1H, SCH_2), 2.64–2.50 (m, 3H, SCH_2, SCH_2), 2.10–1.85 (m, 2H, $SCH_2CH_2CH_2S$), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 138.6, 129.4, 129.0, 126.9, 71.5, 54.0, 47.8, 32.6, 26.7, 26.1, 25.3; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{14}H_{18}O_2S_2$) requires m/z 282.0748, found m/z 282.0762; $[\alpha]_D$=+29.5 (c=1.0, $CHCl_3$).

3.2.16. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-3-phenyl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (25.0 mg, 0.24 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-2-benzyl-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (26 mg, 0.092 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 65 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (5:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 90% yield (31 mg, 0.084 mmol) >99% ee. The product ee was measured by chiral HPLC (AD column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=40.7 min, (1*S*,2*R*) *anti* isomer t_r=66.7 min, *syn* isomers t_r major=59.6 min, t_r minor=54.0 min. IR (film) 3480, 2955, 2867, 1472, 1422, 1394, 1131, 1096, 1024, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.15 (m, 5H, Ph), 4.61 (d, J=3.0 Hz, 1H, OC*H*O), 4.18 (d, J=6.9 Hz, 1H, SC*H*S), 3.92 (m, 1H, C*H*OH), 3.83 (br s, 1H, O*H*), 3.65 (m, 2H, CH_2O), 3.39 (d, J=11.4 Hz, 1H, CH_2O), 3.38 (d, J=11.4 Hz, 1H, CH_2O), 3.00–2.79 (m, 3H, CH_2Ph, SCH_2), 2.74–2.64 (m, 3H, $SCH_2CH_2CH_2S$), 2.08–1.95 (m, 1H, $SCH_2CH_2CH_2S$), 1.94–1.78 (m, 1H, $SCH_2CH_2CH_2S$), 1.21 (s, 3H, CH_3), 0.71 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 128.7, 126.4, 102.5, 77.5, 77.3, 72.6, 51.3, 45.5, 33.2, 32.6, 30.6, 29.4, 28.8, 26.2, 23.4, 22.0; HRMS (FAB+) exact mass calcd for $[M-H]^+$ ($C_{19}H_{27}O_3S_2$) requires m/z 367.1402, found m/z 367.1416; $[\alpha]_D^{22}$=+16.7 (c=1.0, $CHCl_3$).

3.2.17. (2*S*,3*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (Table 2, entry 7). A solution of freshly purified (*tert*-butyl-dimethyl-silanyloxy)-acetaldehyde (294 mg, 1.69 mmol) in 0.88 mL DMF was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (500 mg, 3.38 mmol), L-proline (39 mg, 0.34 mmol) and 0.88 mL DMF at room temperature. After 44 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a 13:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 52% yield (283 mg, 0.88 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol and confirmed by analysis of the corresponding diol, obtained by reduction of the aldehyde (see below). IR (film) 3468, 2945, 2910, 2892, 2847, 1714, 1466, 1422, 1373, 1253, 1129, 1005, 872, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 9.53 (s, 1H, C*H*O), 4.37 (ddd, J=9.5, 2.1, 1.9 Hz, 1H, C*H*OH), 4.33 (d, J=2.1 Hz, 1H, C*H*OTBS), 3.59 (d, J=9.5 Hz, 1H, SC*H*S), 3.07–2.83 (m, 2H, SCH_2), 2.76 (s, 1H, O*H*), 2.55–2.42 (m, 1H, SCH_2), 2.37–2.25 (m, 1H, SCH_2), 2.13–1.88 (m, 2H, $SCH_2CH_2CH_2S$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.092 (s, 3H, $SiCH_3$), 0.089 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 78.7, 73.7, 42.7, 26.0, 24.8, 24.7, 24.1, 18.4, −4.5, −4.8; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{26}O_3SiS_2$) requires m/z 322.1063, found m/z 322.1070; $[\alpha]_D^{24}$=−9.9 (c=1.0, $CHCl_3$).

3.2.18. (1*R*,2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-ethanol. A solution of 2,2-dimethylpropane-1,3-diol (102 mg, 0.975 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) in acetonitrile (0.3 mL) were added to a solution of (2*S*,3*R*)-3-[1,3]dithiane-2-yl-3-hydroxy-2-methyl-propionaldehyde (31.4 mg, 0.098 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 16 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 46% yield (18.2 mg, 0.045 mmol) 70% ee. The product ee was measured by chiral HPLC (AD column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=6.3 min, (2*S*,3*R*) *anti* isomer t_r=7.7 min, *syn* isomers t_r major=9.8 min, t_r minor=11.7 min. IR (film) 3485.7, 2954, 2927, 2900, 2856, 1470, 1395, 1249, 1124, 1100, 1027, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, J=4.4 Hz, 1H, OC*H*O), 4.27 (d, J=3.0 Hz, 1H, SC*H*S), 4.15 (dd, J=7.9, 3.0 Hz, 1H, C*H*OH), 3.87 (dd, J=7.9, 4.4 Hz, 1H, C*H*OTBS), 3.72–3.58 (m, 2H, CH_2O), 3.45–3.35 (m, 2H, CH_2O), 3.10–2.95 (m, 2H, $SCH_2CH_2CH_2S$), 2.90–2.63 (m, 2H, $SCH_2CH_2CH_2S$), 2.12–1.90 (m, 2H, $SCH_2CH_2CH_2S$), 1.19 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.73 (s, 3H, $C(CH_3)_2$), 0.14 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 77.5, 76.5, 72.8, 48.4, 30.7, 30.2, 29.3, 26.3, 26.2, 23.4, 22.1, 18.6, −4.0, −4.5, 1 signal obscured; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{18}H_{36}O_4SiS_2$) requires m/z 408.1824, found m/z 408.1827; $[\alpha]_D^{24}$=−21.2475 (c=1.0, $CHCl_3$).

3.2.19. (1*R*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-[1,3]dithian-2-yl-propane-1,3-diol. (A reduction method was used to provide an alternative enantiomeric excess assay). A solution of (2*S*,3*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (19.0 mg, 0.16 mmol) was added dropwise to a stirring suspension of sodium borohydride (15.0 mg, 0.39 mmol) in ethanol at 0 °C. The effervescing mixture was slowly warmed to room temperature and stirred for 30 min. A saturated solution of ammonium chloride was added to quench the reaction, followed by dilution with CH_2Cl_2 and water. The aqueous

layer was washed three times with portions of CH_2Cl_2, and the combined organics dried over $MgSO_4$, filtered and concentrated to yield a colourless oil. Purification by flash chromatography (2:1 pentane–diethyl ether) gave the title product as a colorless oil in 89% yield (17.0 mg, 0.052 mmol), 72% ee. The product ee was measured by chiral HPLC (AD column, 4% EtOH in hexanes) relative to a racemic sample; (1*R*,2*R*) *anti* isomer t_r=23.3 min, (1*S*,2*S*) *anti* isomer t_r=29.1 min. IR (film) 3405, 2954, 2929, 2892, 2847, 1461, 1422, 1253, 1253, 1091, 1040, 836, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (br s, 1H, SC*H*S), 3.99–3.94 (m, *J*=1.8 Hz, 2H, C*H*OH, C*H*OTBS), 3.86–3.66 (m, 2H, CH_2OH), 2.99–2.88 (m, 3H, SCH_2CH$_2$C*H*HS), 2.84–2.72 (m, 1H, SCH$_2$CH$_2$CH_2S), 2.16–1.85 (m, 2H, SCH$_2$-CH_2CH$_2$S), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.17 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.0, 72.1, 64.3, 50.0, 30.3, 29.4, 26.1, 26.0, 18.3, −4.2, −4.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{28}O_3SiS_2$) requires *m*/*z* 324.1249, found *m*/*z* 324.1252.

3.2.20. (*R*)-4-[1,3]Dithian-2-yl-4-hydroxy-butan-2-one (Table 2, entry 8). Acetone (395 mg, 0.5 mL, 6.80 mmol) was added to a suspension of [1,3]dithiane-2-carbaldehyde (37 mg, 0.25 mmol) and L-proline (5.8 mg, 0.05 mmol) in 2.0 mL DMF at room temperature. After stirring at room temperature for 65 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:2 pentane–diethyl ether) afforded the title compound as a clear, colorless oil in 91% yield (47 mg, 0.23 mmol) 96% ee. The product ee was measured by chiral HPLC (ODH column, 5% EtOH in hexanes) relative to a racemic sample; *R*-isomer t_r=28.9 min, *S*-isomer t_r=26.5 min. IR (film) 3438, 2901, 1713, 1422, 1361, 1277, 1164, 1072, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41–4.32 (m, 1H, C*H*OH), 3.86 (d, *J*=6.0 Hz, 1H, SC*H*S), 3.23 (d, *J*=2.7 Hz, 1H, CHO*H*), 3.00–2.65 (m, 6H, SCH_2CH$_2$CH_2S, CH_2CHOH), 2.19 (s, 3H, CH_3), 2.11–1.87 (m, 2H, SCH$_2$CH_2CH$_2$S); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 68.8, 51.0, 47.5, 31.1, 28.3, 27.9, 25.7; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_2S_2$) requires *m*/*z* 206.0435, found *m*/*z* 206.0429; $[\alpha]_D^{21}$=+34.2 (*c*=1.0, $CHCl_3$).

3.2.21. (3*S*,4*R*)-4-[1,3]Dithian-2-yl-3,4-dihydroxy-butan-2-one (Table 2, entry 9). Acetol (541 mg, 0.50 mL, 7.30 mmol) was added to a suspension of [1,3]dithiane-2-carbaldehyde (37 mg, 0.25 mmol) and L-proline (2.9 mg, 0.025 mmol) in 2.0 mL DMF at room temperature. After stirring at room temperature for 12 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield a waxy white solid. Analysis of the crude reaction mixture by ^1H NMR revealed an >20:1 *anti*–*syn* mixture of diastereoisomers. The crude white solid was triturated twice with diethyl ether. Syringe removal of the ether yielded the title compound as a dry white solid 88% yield (46 mg, 0.22 mmol), >20:1 dr, >99% ee. Product ee was measured by chiral HPLC (AD column, 12% EtOH in hexanes) relative to a racemic sample; (3*S*,4*R*) *anti* isomer t_r=108.0 min, (3*R*,4*S*) *anti* isomer t_r=128.3 min, *syn* isomers not detected. The product was recrystallized from boiling acetone. The resulting crystals were analyzed by X-ray crystallogrphy to obtain confirmation of both relative and absolute stereochemistry. IR (film) 3370, 3304, 1673, 1386, 1357, 1262, 1222, 1126, 1060, 1005, 913 cm^{-1}; ^1H NMR (300 MHz, C_2D_6SO) δ 5.81 (d, *J*=5.1 Hz, 1H, C(O)CHO*H*), 5.56 (d, *J*=6.0 Hz, 1H, CH(O*H*)C(S)S), 4.23 (d, *J*=3.6 Hz, 1H, SC*H*S), 4.00 (m, 1H, C(O)C*H*OH), 3.90 (m, 1H, C*H*(OH)CS), 3.00–2.68 (m, 4H, SCH_2CH$_2$CH_2S), 2.16 (s, 3H, CH_3), 1.98 (m, 1H, SCH$_2$CH_2CH$_2$S), 1.82 (m, 1H, SCH$_2$CH_2CH$_2$S); ^{13}C NMR (75 MHz, C_2D_6SO) δ 210.7, 77.9, 76.0, 49.5, 29.5, 28.8, 27.6, 26.7; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_3S_2$) requires *m*/*z* 222.0385, found *m*/*z* 222.0382; $[\alpha]_D$=+13.0 (*c*=1.0, EtOH).

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Kinetic analysis of positive nonlinear effects ((+)-NLE) for dimeric rather than trimeric nature of binaphthol-derived titanium (BINOL–Ti) catalyst

Koichi Mikami* and Yousuke Matsumoto

Department of Applied Chemistry, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan

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It is our great honor to dedicate this manuscript to Professor Dieter Seebach for his receipt of the Tetrahedron Prize for Creativity in Organic Chemistry

Abstract—Kinetic analysis of nonlinear effect in enantioselectivity is employed to show that the rate of glyoxylate–ene reaction is a function of catalyst enantiomeric excesses and oligomeric nature of the binaphthol-titanium (BINOL–Ti) catalyst and that the BINOL–Ti catalyst exists as dimeric species.

1. Introduction

Nonlinear effects (NLE) in asymmetric catalysis are mechanistically informative and practically important as the relationship between product enantioselectivity versus catalyst enantiomeric excess.[1] The NLE has been uncovered by Kagan first experimentally and then theoretically.[2–6] We have already reported that a binaphthol-derived titanium (BINOL–Ti) catalyst prepared from $Ti(OPr^i)_2Cl_2$ (Method A) using wet MS 4A shows remarkable level of positive nonlinear effect ((+)-NLE) in glyoxylate–ene reactions (Fig. 1).[7] We have also reported that the NLE curve experimentally obtained with the BINOL–Ti catalyst (Method A) fits well with the curve calculated for dimeric species (Fig. 1).[7d,8] In the model that a homochiral dimer is more active than the heterochiral dimer, (+)-NLE can be observed (line 2). In the opposite case that the heterochiral dimer is more active than the homochiral dimer, negative NLE ((−)-NLE) can be observed (line 3).

Blackmond has simulated kinetic behavior of NLE and has shown that kinetic information is useful for detailed analysis of NLE phenomena.[9] In the case of (+)-NLE, the reaction rate should be increased with increasing % ee of a catalyst (Fig. 2). Kagan and Blackmond have independently simulated the dimeric case of our BINOL–Ti catalyst prepared from BINOL and $Ti(OPr^i)_2Cl_2$ in the presence of MS 4A (Method A).[2a,10] Blackmond has reported that the predicted result shows a smaller suppression in catalytic activity of the racemic catalyst than our experimental result.[10] We have also reported that ^{17}O NMR analysis of BINOL–Ti catalyst shows the presence of μ^3-oxo or -hydroxo structure.[11] This result may suggest the possible involvement of trimeric active BINOL–Ti catalyst.

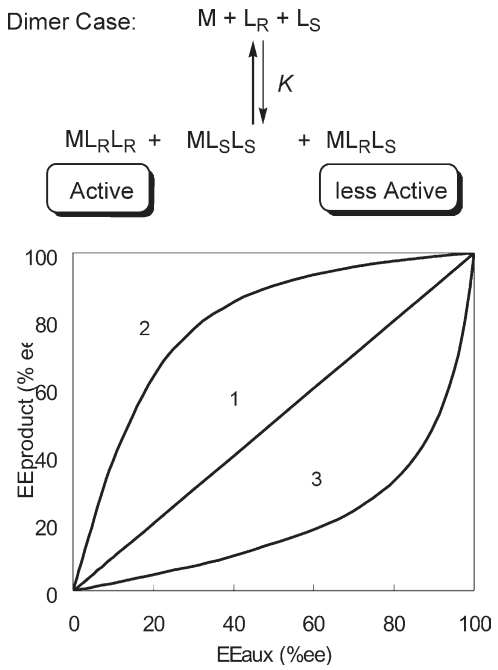

Figure 1. The general situations. Relationships between EEs of a chiral auxiliary to the EEs of the product.

Keywords: Asymmetic catalyst; Nonlinear effect; Kinetic analysis; Titanium catalyst.
* Corresponding author. Tel.: +81-3-5734-2142; fax: 81-3-5734-2776; e-mail address: kmikami@o.cc.titech.ac.jp

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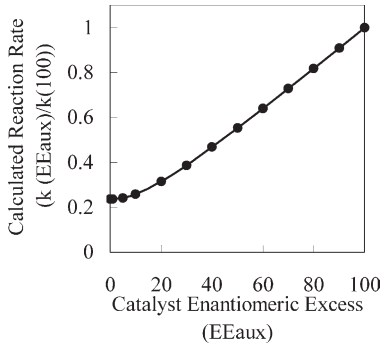
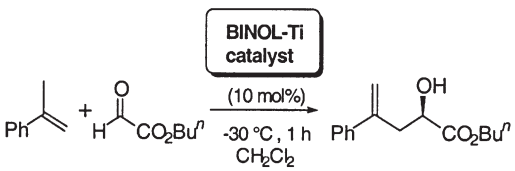


Figure 2. The overall reaction rate for each data (ee_{aux}, ee_{prod}) of (+)-NLE.

Furthermore, a tetranuclear oxo complex was isolated as a pre-catalyst to imply the tetrameric or dimeric active species.[12] We report here the detail kinetic analysis of NLE exemplified by BINOL–Ti catalyst prepared from Ti(BINOLato)(OPr^i)$_2$ and wet MS 4A or H_2O (Method B) and comparison of reaction rates experimentally obtained with the simulated ones for monomeric, dimeric, trimeric, and tetrameric systems.

2. Results

The carbonyl–ene reactions of α-methylstyrene (1 mmol) and butyl glyoxylate (1 mmol) were performed in the presence of BINOL–Ti catalyst (0.1 mmol based on BINOL) prepared by the Method B in CH_2Cl_2 (4 mL) as a solvent (Eq. 1). The BINOL–Ti catalyst can be prepared by the following two methods:



(1)

Method A. To BINOL (0.1 mmol) in CH_2Cl_2 (4 mL) was added Ti(OPr^i)$_2Cl_2$ (0.1 mmol) and wet MS 4A (0.5 g) and the mixture was stirred for 1 h. Solvents and Pr^iOH formed were then removed under reduced pressure.

Method B. To BINOL (0.1 mmol) in CH_2Cl_2 (4 mL) was added Ti(OPr^i)$_4$ (0.1 mmol) and followed by the addition of wet MS 4A (0.5 g) or H_2O/Et_2O solution. After stirring for 1 h, solvents and Pr^iOH formed were removed under reduced pressure.

The ene reaction product of the highest enantiomeric excess (97% ee) was obtained by using 100% ee of the catalyst. As expected, EE_{prod} was decreased but only gradually with decreasing EE_{aux} and hence (+)-NLE was observed.

In order to determine the degree of oligomerization (trimer vs. dimer, in particular) of BINOL–Ti catalyst, the dimeric and trimeric catalyst cases were simulated.

2.1. Dimeric catalyst case

Following Kagan's equations, the dimeric catalyst case was simulated to determine the relative reactivity (g) of racemic and enantiopure catalysts, and equilibrium constant (K) for kinetic analysis.

$$(K\mathrm{EE}_{aux}^2 + 4)\beta^2 + 2K\mathrm{EE}_{aux}^2\beta + K(\mathrm{EE}_{aux}^2 - 1) = 0 \quad (2)$$

$$\mathrm{EE}_{prod} = \mathrm{EE}_1\mathrm{EE}_{aux}(1+\beta)/(1+g\beta) \quad (3)$$

Thus, the relationships of EE_{prod} and EE_{aux} were simulated on the basis of β and g values. In turn, the values K=110, g=0.09 were determined by fitting the simulated curve with the experimental one. High K value ($K \gg 1$) suggests that the heterochiral catalyst is thermally more stable than the homochiral catalyst and the low g value suggests the heterochiral catalyst is of lower catalytic activity than the homochiral one. Thus, BINOL–Ti catalyst prepared from Method B shows (+)-NLE and good fits are observed with the simulated curve (K=110, g=0.09) (Fig. 3).

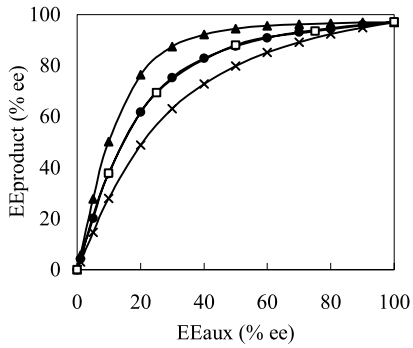


Figure 3. Relationships between EEs of BINOL and EEs of the products obtained from reactions catalyzed by BINOL–Ti catalyst prepared by Method B. experimental data (□), calculated for dimer: K=110, g=0.01 (▲), K=110, g=0.09 (●), K=110, g=0.20 (×).

2.2. Trimeric catalyst case

Next, trimeric catalyst case was also simulated following Kagan's equations and compared with the experimental result. α value was calculated based on K for each EE_{aux}. Only one possible answer ($0<\alpha<1$) was obtained from Eq. 4.

$$(3\mathrm{EE}_{aux} + 3)\alpha^3 + K(3\mathrm{EE}_{aux} + 1)\alpha^2 + K(3\mathrm{EE}_{aux} - 3)\alpha + (3\mathrm{EE}_{aux} - 3) = 0 \quad (4)$$

Then, EE_{prod} was calculated based on K and g values for each EE_{aux}.

$$\mathrm{EE}_{prod} = \{\mathrm{EE}_1(1-\alpha^3) + \mathrm{EE}_0 gK(\alpha - \alpha^2)\}/\{1 + \alpha^3 + gK(\alpha + \alpha^2)\} \quad (5)$$

Figure 4 shows the comparison of experimental and simulated curves for trimeric species. As in the case of dimeric system, the values K=10 and g=0.04 were set by fitting the simulated curve with experimental one. Again, large K value ($K \gg 1$) suggests that the heterochiral complex is more stable than the homochiral one and small g ($g \ll 1$) value suggests that the heterochiral catalyst is less active. The effect of EE_1 value was only faint (~0).

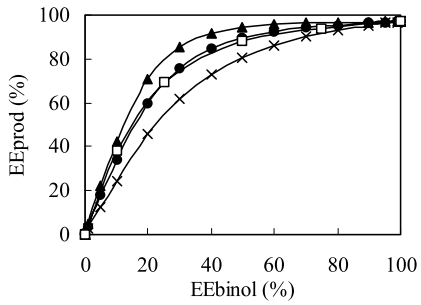


Figure 4. Relationships between EE of BINOL and EE of products obtained in reactions catalyzed by BINOL–Ti catalyst prepared by Method B. Experimental data (□), calculated for trimer: K=10, g=0.01 (▲); K=10, g=0.04 (●); K=10, g=0.1 (×) (EE_1=0.001).

3. Discussion

With the β and g values for dimeric and trimeric cases in hand, we executed Blackmond's kinetic analysis in order to determine the degree of oligomerization of BINOL–Ti catalyst (trimer vs. dimer, in particular). The relationships between ee(ligand) and k/k_{RRR}, the ratio between the reaction rates catalyzed by complexes of certain % ee and 100% ee respectively, were thus examined.

3.1. Monomeric catalyst case

In the case of monomeric catalyst, only one active species exists to catalyze a reaction. Catalytic activity is thus not dependent on EE_{aux} and horizontal line ($k(n)/k_{RRR}$=1) should be observed. Apparently, the experimental curve does not fit with the horizontal and straight line simulated for a monomeric catalyst.

3.2. Dimeric catalyst case

In the case of dimeric catalyst, the ratios of k_{RRR} (with BINOL of % ee=100) and $k(n)$ (with BINOL of % ee=n) were calculated on each EE_{aux} (EE of BINOL). β value was calculated from EE_{aux}.

$$k(n)/k_{RRR} = (1 + g\beta)/(1 + \beta) \quad (6)$$

The relationships between $k(n)/k_{RRR}$ and EE_{aux} were simulated based on the K and g values (K=110, g=0.09).

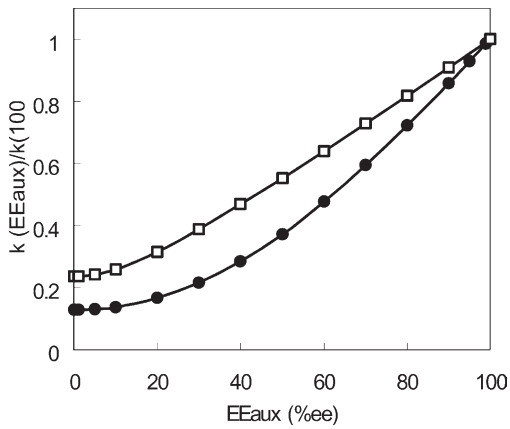


Figure 5. Simulation of relationships between k/k_{RRR} and EE of BINOL. Calculated for dimer (K=110, g=0.09 (□)) and trimer (K=10, g=0.04 (●)).

3.3. Trimeric catalyst case

In a similar way, $k(n)/k_{RRR}$ value was calculated in trimer case on the basis of the K and g values (K=10, g=0.04).

$$k(n)/k_{RRR} = (1 + gK\alpha + gK\alpha^2 + \alpha^3))/(1 + K\alpha + K\alpha^2 + \alpha^3) \quad (7)$$

Figure 5 shows the relationships of EE_{aux} and k/k_{RRR} values for dimer and trimer cases. The $k(0)/k_{RRR}$ values, the ratio of reaction rates (k) by racemic (0% ee) and enantiopure (100% ee) BINOL–Ti catalysts were calculated for the dimer (0.236) and trimer (0.127) cases. Higher oligomeric species turned out to have smaller $k(0)/k_{RRR}$ value.

$k(0)/k_{RRR}$ for monomer: 1.0 (Method A)
$k(0)/k_{RRR}$ for dimer: 0.236 (Method A)
$k(0)/k_{RRR}$ for trimer: 0.127 (Method A).

The estimation of the degree of oligomerization was thus performed by comparison of the calculated $k(0)/k_{RRR}$ value and the experimental $k(0)/k_{RRR}$ value. Figure 6 shows the kinetic feature of carbonyl–ene reactions; Reactions of α-methylstyrene (0.5 mmol) and butyl glyoxylate (0.5 mmol) were performed in the presence of the racemic (0% ee) or enantiopure (100% ee) BINOL–Ti catalysts (0.05 mmol).

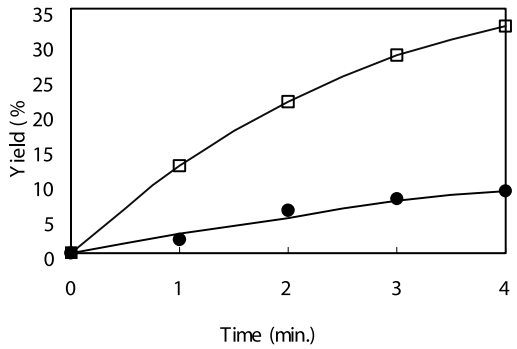


Figure 6. Time dependence of ene-reaction catalyzed by 100% ee and 0% ee of catalyst (□: 100% ee of catalyst ●: 100% ee of catalyst).

4. Conclusion

The $k(0)/k_{RRR}$ value (0.223) actually obtained by the experiment above was found to well match with the value simulated for the dimer (0.236) rather than the trimer (0.127). Therefore, the dimeric structure of BINOL–Ti catalyst to show the simulated value (0.236) is highly likely. Higher oligomeric species such as trimer and further tetramer species to show the smaller simulated value (e.g., trimer: 0.127) is thus unlikely.

5. Experimental

5.1. General

All experiments were carried out under argon atmosphere otherwise noted. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N

(spherical, neutral), employing hexane ethyl acetate mixture as eluent unless otherwise noted. Liquid chromatographic analysis (LC) were conducted on a JASCO LG-980-02, DG-980-50 and CO-966 instrument equipped with model UV-975 spectrimeters as an ultra violet light. Molecular Sieves (MS 4A, activated powder and pelets) were purchased from Aldrich Chemical Co. Dichloromethane (dehydrate) and chloroform-d_3 were purchased from Kanto chemical Co., Inc and dried from Molecular Sieves (MS 4A, pelets).

5.1.1. General procedure for carbonyl–ene reaction (Method B). To the CH_2Cl_2 (4 mL) solution of BINOL (28.6 mg, 0.1 mmol) was added $Ti(OPr^i)_4$ (0.24 mL, 0.1 mmol) at room temperature. After stirring for 1 h at that temperature, the solution was added MS 4A (0.5 g). After stirring for 1 h, dried α-methylstyrene (118 mg, 1.00 mmol) and a solution of freshly-distilled *n*-butyl glyoxylate (156 mg, 1.20 mmol) in toluene (0.4 mL) at −30 °C in this order. After stirring for 1 h at −30 °C, the reaction mixture was quenched with a solution of triethylamine (0.1 mL) in hexane (10 mL). The MS 4A was filtered off through a pad of Celite and the filtrate was concentrated under vacuum. The crude material was purified by silica gel chromatography (hexane/ethyl acetate=20:1) to give *n*-butyl 2-hydroxy-4-phenyl-4-pentenoate. The enantiomeric purity was determined by HPLC.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.2 Hz, 3H), 1.34 (m, 2H), 1.56 (m, 2H), 2.72 (d, *J*=6.0 Hz, 1H), 2.83 (ddd, *J*=14.4, 7.5, 0.9 Hz, 1H), 3.06 (ddd, *J*=14.4, 4.5, 1.2 Hz, 1H), 3.96–4.15 (m, 2H), 4.26 (br, 1H), 5.20 (d, *J*=1.2 Hz, 1H), 5.39 (d, *J*=1.2 Hz, 1H), 7.25–7.43 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 30.4, 40.5, 65.4, 69.2, 113.6, 116.5, 126.4, 127.6, 128.3, 140.3, 143.6, 174.5.

IR (neat) 3470, 2970, 1740, 1450, 1270, 1210, 1090, 780, 710 cm^{-1}.

HPLC (CHIRALPAK-AS column, hexane/Pr^{i}OH=3/1, frow rate 0.5 mL/min).

t_R=(*R*)-isomer: 9.5 min, (*S*)-isomer: 12.6 min.

5.2. Simulation of nonlinear effect and relative reaction rate for dimeric catalyst

Chiral auxiliary (L_R, L_S) of enantiomeric excess Ee_{aux} is engaged in the formation of complexes ML_RL_R, ML_SL_S, ML_RL_S. At the steady state of the catalytic reaction the relative amounts are X_0, X_1 and X_2 respectively. k_{RR}=k_{SS} and k_{RS} are the pseudo first-order rate constants. EE of product obtained from reaction catalyzed by ML_RL_R and ML_RL_S is EE_1 (measurable) and 0 respectively.

$$M + L_R + L_S \leftrightarrow ML_RL_R + ML_RL_S + ML_SL_S$$

	X_0	X_1	X_2
kinetic constant	k_{RR}	k_{RS}	k_{SS}=k_{RR}
EE of product	E_1 (for *R*)	0 (for *R*)	E_1

The relative amount (β) and the relative reactivities (g) of meso and chiral catalysts, equilibrium constant (*K*) were expressed as follows.

$$K = X_1^2/X_0X_2 \tag{8}$$

$$\beta = X_1/(X_0 + X_2) \tag{9}$$

$$g = k_{RS}/k_{RR} \tag{10}$$

here, EE_{aux} (EE of ligand) is expressed

$$EE_{aux} = (X_0 - X_2)/(X_0 + X_1 + X_2) \tag{11}$$

The amount of *R* and *S* product can be expressed following Eqs. 12 and 13.

$$R \text{ product}: \; k_{RR}X_0t(1 + EE_1)/2 + k_{RS}X_1t/2 + k_{RR}X_2t(1 - EE_1)/2 \tag{12}$$

$$S \text{ product}: \; k_{RR}X_0t(1 - EE_1)/2 + k_{RS}X_1t/2 + k_{RR}X_2t(1 + EE_1)/2 \tag{13}$$

From 12 and 13, ee of product is calculated 14

$$\begin{aligned} EE_{prod} &= (k_{RR}X_0EE_1 - k_{RR}X_2EE_1)/(k_{RR}X_0 + k_{RS}X_1 + k_{RR}X_2) \\ &= EE_1(X_0 - X_2)/(X_0 + gX_1 + X_2) \\ &= EE_1EE_{aux}(1 + \beta)/(1 + g\beta) \end{aligned} \tag{14}$$

EE_{prod} can be simulated based on *g* and *K*.

β can be calculated based on *K* for each EE_{aux} from Eqs. 8, 9 and 11.

$$(KEE_{aux}^2 + 4)\beta^2 + 2KEE_{aux}^2\beta + K(EE_{aux}^2 - 1) = 0 \tag{15}$$

here, $k_{(n)}$ (pseudo-first order kinetic constant in the case of EE_{aux}=*n*) is

$$\begin{aligned} k(n) &= (k_{RR}X_0 + k_{RS}X_1 + k_{RR}X_2)/(X_0 + X_1 + X_2) \\ &= (k_{RR} + k_{RS}\beta)/(1 + \beta) \end{aligned}$$

$$k_{(100)}X_0/k_{(n)} = k_{RR}(1 + \beta)/(k_{RR} + k_{RS}\beta) = (1 + \beta)/(1 + g\beta)$$

This equation suggests linear relationship between EE_{prod} and $EE_{aux}k_{RR}X_0/k(n)$

$$EE_{prod} = EE_1EE_{aux}(1 + \beta)/(1 + g\beta) = EE_1EE_{aux}k_{RR}X_0/k_{(n)}$$

EE_{prod} can be simulated based on *g*, EE_1, *K* and β.

5.3. Simulation of nonlinear effect and relative reaction rate for trimeric catalyst

Chiral auxiliary (L_R, L_S) of enantiomeric excess Ee_{aux} is engaged in the formation of complexes $ML_RL_RL_R$, $ML_RL_RL_S$, $ML_RL_SL_S$ and $ML_SL_SL_S$. k_{RRR}=k_{SSS} and k_{RSS}=k_{RRS} are the pseudo first-order rate constants.

$$M + L_R + L_S \leftrightarrow ML_RL_RL_R + ML_RL_RL_S + ML_RL_SL_S + ML_SL_SL_S$$

	X_0=$X0$	X_1=αKX	X_2=$\alpha^2 KX$	X_0=$\alpha^3 X$
kinetic constant	k_{RRR}	k^{RRS}	k_{RSS}=k_{RRS}	k_{SSS}=k_{RRR}
EE of product	E_1 (for R)	E_0 (for R)	$-E_0$	$-E_1$

$$K_0 = X_1^2/X_0X_2 = X_2^2/X_1X_3$$

here, EE_{aux} (EE of ligand) is expressed as follows.

$$\begin{aligned} EE_{aux} &= \{3(1-\alpha^3) + K(\alpha-\alpha^2)\}/ \\ &\quad \{3(1+\alpha^3) + 3K(\alpha+\alpha^2)\} \\ &(3EE_{aux}+3)\alpha^3 + K(3EE_{aux}+1)\alpha^2 \\ &+K(3EE_{aux}-3)\alpha + (3EE_{aux}-3) = 0 \end{aligned} \tag{16}$$

From 16, α can be calculated based on K for each EE_{aux}. α value was calculated by Cardano method.

$$\begin{aligned} R \text{ product}: \; & k_{RRR}X_0t(1+EE_1)/2 + k_{RRS}X_1t(1+EE_0)/2 \\ & + k_{RRS}X_2t(1-EE_0)/2 + k_{RRR}X_3t(1-EE_1)/2 \\ S \text{ product}: \; & k_{RRR}X_0t(1-EE_1)/2 + k_{RRS}X_1t(1-EE_0)/2 \\ & + k_{RRS}X_2t(1+EE_0)/2 + k_{RRR}X_3t(1+EE_1)/2 \end{aligned}$$

$$\begin{aligned} EE_{prod} &= (k_{RRR}X_0EE_1 + k_{RRS}X_1EE_0 - k_{RRS}X_2EE_0 \\ &\quad - k_{RRR}X_3EE_1)/(k_{RRR}X_0 + k_{RRS}X_1 + k_{RRS}X_2 \\ &\quad + k_{RRR}X_3) \\ &= \{EE_1(1-\alpha^3) + EE_0gK(\alpha-\alpha^2)\}/ \\ &\quad \{1+\alpha^3 + gK(\alpha+\alpha^2)\} \end{aligned} \tag{17}$$

EE_{prod} can be simulated based on g, EE_0, K and α.

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Synthesis of new tropinone derivatives by palladium-catalyzed couplings of 8-azabicyclo[3.2.1]oct-2-enyl nonaflates

Ilya M. Lyapkalo,[a,b] Jens Högermeier[a] and Hans-Ulrich Reissig[a,*]

[a]*Institut für Chemie, Freie Universität Berlin, Takustr. 3, D-14195 Berlin, Germany*
[b]*Institute of Chemical and Engineering Sciences Ltd, Ayer Rajah Crescent, Singapore, Singapore 139959*

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Dedicated to Professor Dieter Seebach

Abstract—Whereas tropinone derived nonaflate **3** was no suitable precursor for Heck-reactions, the related carbamate **7** was an excellent substrate for palladium-catalyzed processes. Nonaflate **7** was either isolated in excellent yield by LDA treatment of ketone **5** followed by trapping with NfF (nonafluorobutanesulfonyl fluoride) or generated in situ by fluoride-catalyzed reaction of silyl enol ether **6** with NfF. The desired 1,3-diene **8** was prepared by conventional Heck-reaction of nonaflate **7** with methyl acrylate in almost quantitative yield. Alternatively, the one-pot nonaflation-Heck protocol starting from silyl enol ether **6** provided **8** in good yield. The couplings of acrylonitrile or phenyl vinyl sulfone were also performed with in situ generated **7** and they afforded the expected 1,3-dienes **9** and **10** in good yields. The Sonogashira-reaction with phenylacetylene also started from silyl enol ether **6** and provided enyne **11** via **7** in good yield. A Diels–Alder reaction of 1,3-diene **8** with *N*-phenyl maleimide at 100 °C furnished tetracyclic adduct **12** in good yield, with excellent diastereofacial selectivity, but with low *endo*–*exo*-selectivity. Nonaflate **14** was easily obtained from the corresponding unsaturated bicyclic ketone **13**. It behaved differently in an attempted Heck-reaction and mainly led to fragmentation products **15** and **16**, whereas the expected 1,3-diene **17** was formed only as minor component. However, **14** could successfully be used in a Sonogashira-reaction with phenylacetylene to afford compound **18**. These transformations demonstrate the great potential of tropinone derived alkenyl nonaflates for diversity oriented syntheses of interesting compounds containing an 8-azabicyclo[3.2.1]octane scaffold.

1. Introduction

Due to their influence on neurotransmitters, compounds with tropinone structure or related 8-azabicyclo[3.2.1]octane skeletons have attracted considerable attention in medicinal chemistry.[1] With this general structure, they are of interest as analogues of cocaine (Scheme 1) and other physiologically active compounds and are considered as candidates for drug development, for example, for treatment of cocaine addiction or neurodegenerative diseases such as Alzheimer and Parkinson, but also for other indications. A variety of new synthetic approaches to this class of bicyclic nitrogen heterocycles has been reported.[2] In this report, we describe our results employing tropinone derived alkenyl nonaflates (nonafluorobutanesulfonates) in palladium-catalyzed reactions[3] leading to compounds which may be further transformed into interesting products, for example, by Diels–Alder reaction to polycyclic systems.

We have recently demonstrated that easily available alkenyl nonaflates are excellent coupling partners in a variety of palladium-catalyzed reactions, in particular in Heck, Suzuki and Sonogashira couplings, leading to interestingly functionalized 1,3-dienes, aryl-substituted alkenes or enynes.[4,5] The required alkenyl nonaflates were either conventionally prepared by deprotonation of the corresponding ketones with LDA and trapping of the generated enolates with NfF (nonafluorobutanesulfonyl fluoride) or alternatively via their silyl enol ethers by a fluoride-catalyzed version. This later method has particular advantages, when aldehydes have to be transformed into alkenyl nonaflates, and it could successfully be applied in one-pot nonaflation-Heck reaction sequences without isolation of the intermediate alkenyl nonaflates.[4d] We also demonstrated that after enantioselective deprotonation of ketones alkenyl nonaflates and finally coupling products are accessible with high enantiomeric excess.[4e]

We examined both methods for the preparation of the desired bicyclic nonaflate **3** starting from commercially available tropinone **1**. A mixture of silyl enol ether **2**[6] and NfF was treated with tetra-*n*-butylammonium fluoride in the presence of dry potassium fluoride under the conditions

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* Corresponding author. Tel.: +49-30-83855366; fax: +49-30-83855367; e-mail address: hans.reissig@chemie.fu-berlin.de

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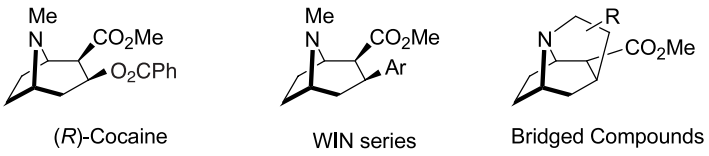
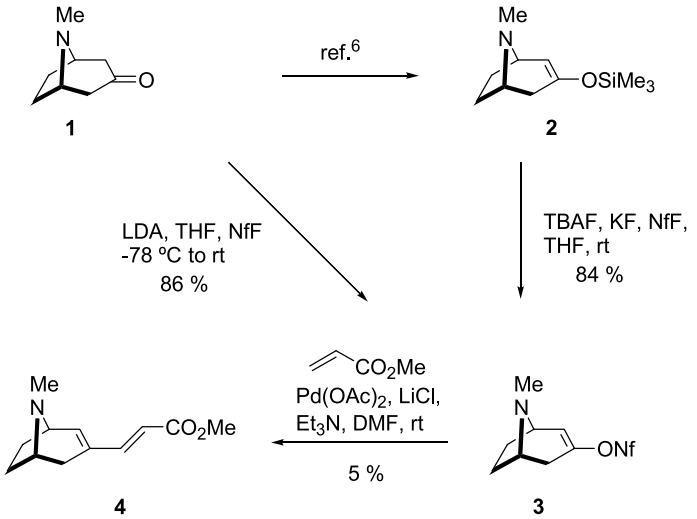


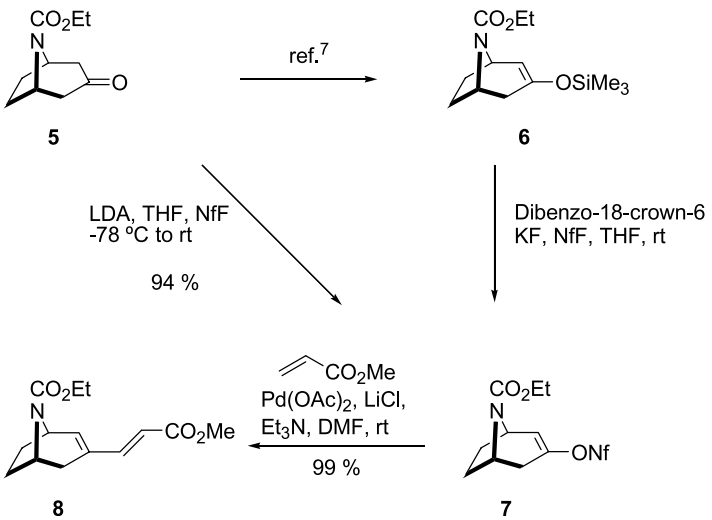
Scheme 1. (*R*)-Cocaine and selected analogues.

developed by us earlier.[4d] This method provided **3** in 84% yield after aqueous workup. The alternative route to **3** by deprotonation of **1** with LDA and quench with NfF gave the desired nonaflate in 86% yield, demonstrating that the direct method is slightly more efficient in this case (Scheme 2). Unfortunately, all attempts to couple **3** with methyl acrylate or acrylonitrile were not very successful. Only one experiment of **3** with methyl acrylate provided the expected diene **4** in very low 5% yield. The reasons for these failures are not completely clear. Since no starting material **3** was recovered in these reactions and no other definite products could be isolated, we have to conclude that the coupling products undergo mainly oligomerization or polymerization under the reaction conditions employed. Actually, brownish high molecular, insoluble material was isolated, though not characterized. This behaviour of **3** or its subsequent products may be due to the nucleophilic tertiary amine present in these compounds, which can induce polymerization.

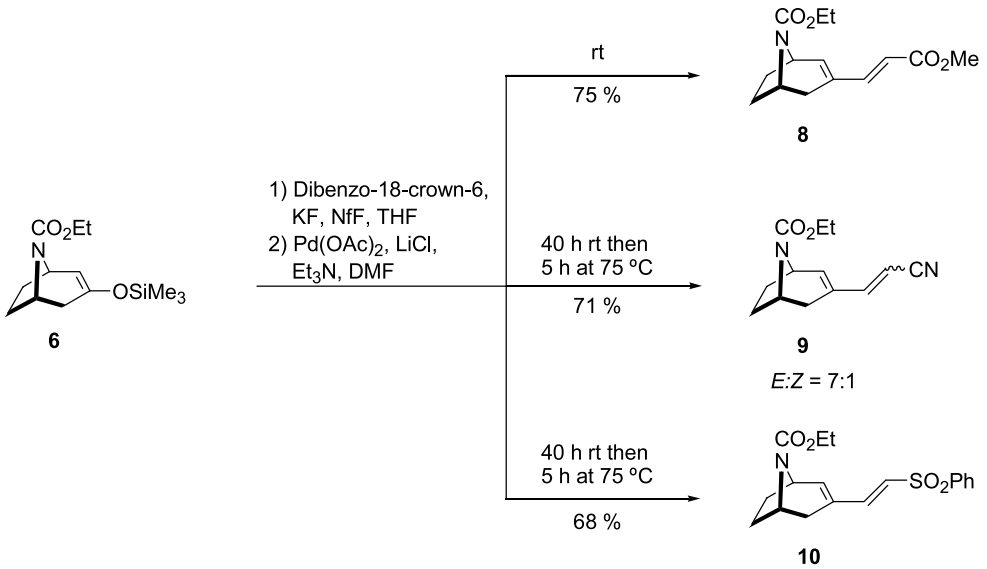
To decrease the reactivity we switched to starting materials lacking this basic and nucleophilic unit and subsequently used *N*-ethoxycarbonyl-substituted nortropin-3-one **5** as precursor. The direct nonaflation of this compound proceeded excellently delivering **7** in 94% yield (Scheme 3). Alternatively, silyl enol ether **6** was prepared according to a literature procedure[7] and smoothly converted into the required nonaflate **7** under fluoride catalysis. In this case, **7** was not isolated but directly used for the palladium-catalyzed reactions (see below). Gratifyingly, nonaflate **7**



Scheme 2. Synthesis of bicyclic nonaflate **3** and its attempted Heck-reaction with methyl acrylate.



Scheme 3. Synthesis of bicyclic nonaflate **7** and its Heck-reaction with methyl acrylate.

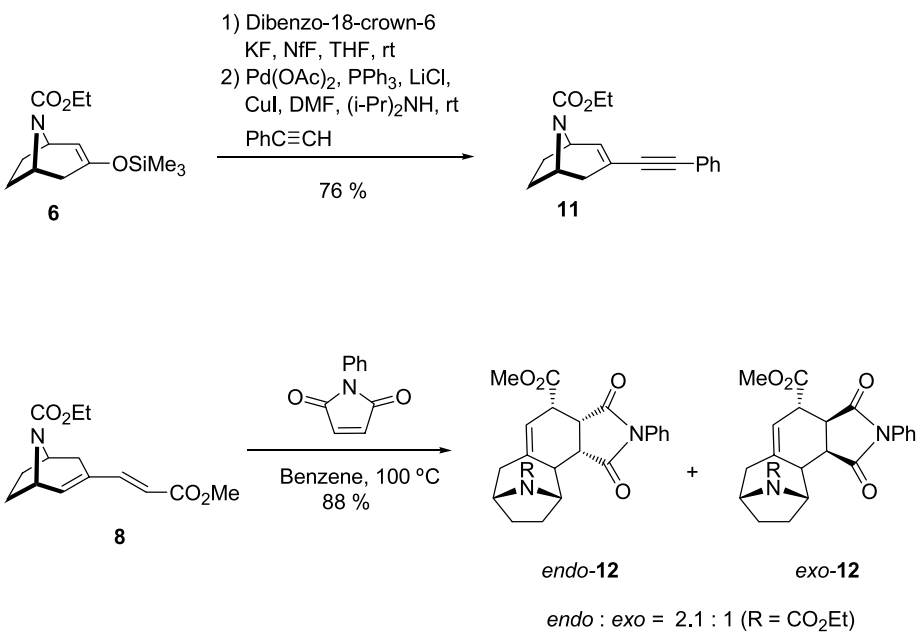


Scheme 4. One-pot nonaflation-Heck couplings of silyl enol ether **6** leading to 1,3-dienes **8**, **9**, and **10**.

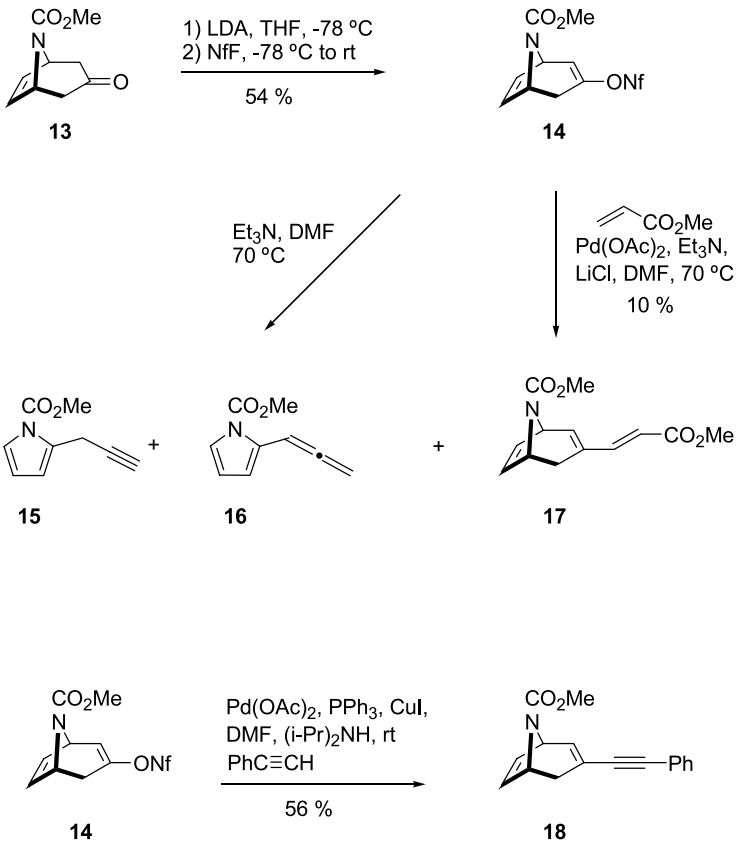
was an excellent substrate for the anticipated palladium-catalyzed coupling reactions. As first example, the Heck-reaction of isolated **7** with methyl acrylate was executed under very mild conditions and the expected 1,3-diene **8** was formed almost quantitatively.

With silyl enol ether **6**, we explored the scope of our earlier developed one-pot nonaflation-Heck coupling protocol.[4d] By in situ conversion of **6** into **7** under fluoride catalysis and subsequent addition of all ingredients required for the Heck reaction, we could synthesize the expected 1,3-dienes **8**, **9**, and **10** in good overall yield (Scheme 4). Whereas methyl acrylate and phenyl vinyl sulfone provided exclusively the *E*-isomers, acrylonitrile reacted less stereoselective, affording a 7:1 *E*/*Z* mixture of **9**.

As second palladium-catalyzed process we checked the ability of nonaflate **7** to undergo a Sonogashira-reaction.[8] Again **7** was generated in situ from silyl enol ether **6** by fluoride/NfF treatment. Subsequent addition of phenylacetylene and the catalyst cocktail furnished the expected enyne **11** under mild conditions and in good overall yield (Scheme 5). Since 1,3-dienes are substrates for Diels–Alder reactions we heated compound **8** with *N*-phenyl maleimide in benzene (7 d, 100 °C) and after column chromatography two stereoisomers of tetracyclic compound **12** were isolated in 59 and 29% yield.[9] The coupling constants observed in the ^{1}H NMR spectra allow highly probable assignments for the two isomers. Both compounds result from an approach of the dienophile to the 'bottom-side' of **8**. Apparently, the N–CO_2Et moiety effectively shields the 'top-side' of the bicyclic diene **8**. Major cycloadduct is *endo*-**12** whereas the minor isomer is *exo*-configured. We can conclude that the diastereofacial discrimination of this Diels–Alder



Scheme 5. Sonogashira-reaction leading to enyne **11** and Diels–Alder reaction of diene **8** furnishing *endo*/*exo*-**12**.



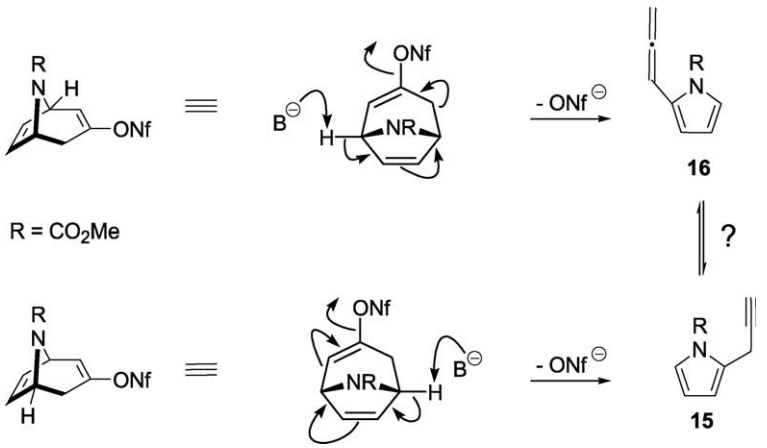
Scheme 6. Synthesis of nonaflate **14**, its fragmentation to **15** and **16** during an attempted Heck-reaction and its Sonogashira-reaction providing enyne **18**.

reaction is high whilst the *endo–exo* selectivity is only moderate. However, we did not prove so far whether our observed product ratio is the result of kinetic or thermodynamic control.

We finally investigated a dehydro derivative of **5** and **7**, the unsaturated bicyclic ketone **13** and nonaflate **14** derived thereof. This comparison was of interest because the corresponding oxygen containing bicyclic compounds revealed remarkable differences between the saturated and unsaturated systems.[10] Compound **13** was available by literature methods[11] and by deprotonation with LDA followed by trapping with NfF it afforded desired nonaflate **14** in 54% yield; this transformation has not been optimized so far (Scheme 6). The attempt to perform a Heck-reaction with this precursor provided only a small amount of the expected 1,3-diene **17**. As major reaction pathway we observed the base-promoted fragmentation of **14** into 2-propargylpyrrole derivative **15** together with its allenylic isomer **16** (9:1). In a control experiment **14** was treated with triethylamine and it also delivered a mixture of **15** and **16** in good yield. We were not able to perform the Heck-reaction of **14** under similarly mild conditions as those starting with the dihydro derivative **7** to avoid this fragmentation process.[12] The mechanism of the fragmentation is currently ambiguous. Deprotonation at bridge-head C-1 accompanied by (synchronous) aromatization, C–C bond cleavage and displacement of the nonaflates anion would lead to allene **16**, whereas the alternative deprotonation at bridge-head C-4 would give by analogous processes the alkyne **15**. It is possible that both pathways occur or that compounds **15** and **16** interconvert under the applied reaction conditions (Scheme 7). Control experiments with specifically labelled compounds are required to investigate the mechanism of this fragmentation in detail.[13] Gratifyingly, the Sonogashira reaction of **14** with phenylacetylene could be performed under very mild conditions and the expected enyne **18** was isolated in moderate yield.

2. Conclusion

We could demonstrate that tropinone derived alkenyl nonaflates such as **7** and **14** are suitable precursors for palladium-catalyzed reactions. Whereas for the Heck-reactions with **14** milder conditions will be required to avoid fragmentation of the bicyclic compound the reactions with the saturated counterpart **7** proceeded with broad scope and good yields. However, smooth Sonogashira-couplings were possible with both nonaflates. It should be mentioned that the in situ nonaflation of silyl enol ether **6** efficiently generated nonaflate **7** which could be used in the palladium-catalyzed reactions without isolation. The Diels–Alder reaction of bicyclic 1,3-diene **8** proceeded with excellent yield and diastereofacial selectivity, but with only moderate *endo*-preference. All reactions reveal that a variety of compounds containing the interesting 8-azabicyclo[3.2.1]-octane scaffold are available via nonaflates and their coupling reactions. The resulting products offer several functional groups as tools for diversity orientated syntheses of complex and highly substituted polycyclic compounds.[14]



Scheme 7. Mechanism of the fragmentation of **14**.

3. Experimental

3.1. General informations

NMR spectra were recorded on *Bruker* WH 270, *Bruker* AC 500 and *Joel Eclipse* 500 (500 MHz) instruments at various temperatures (many signals show significant broadening due to hindered rotation of the carbamate moieties). ^{1}H and ^{13}C chemical shifts are expressed as ppm downfield from tetramethylsilane (δ=0) used as an internal standard. ^{13}C NMR signals of $CF_3(CF_2)_3$ groups are not given since unambiguous assignment is not possible due to strong splitting by coupling with the ^{19}F nuclei. Mass spectra were registered with *Varian* MAT 711 spectrometer. IR spectra were measured with a spectrometer 5 SXC Nicolet. TLC-analysis was performed using *Merck* silica gel *60 F_{254}* plates. Column chromatography was conducted on silica gel 60 (40–63 μm, *Fluka*). The lithiation and nonaflation reactions were carried out under an atmosphere of argon in heat-gun dried reaction flasks by adding the components via syringes. Solvents for reactions were dried by standard procedures. Nonafluorobutane-1-sulfonyl fluoride was obtained from *Bayer AG*; it can also be purchased from *Aldrich*. Commercially available 2.5 M *n*-BuLi solution (*Aldrich*) was used.

3.2. General procedure for Heck-reactions with isolated nonaflates (GP 1)

A mixture of the corresponding nonaflate (1 equiv), base (3 equiv), additive (2 equiv), olefin (1.5 equiv) and $Pd(OAc)_2$ (4–8 mol %) in the solvent was stirred under conditions described in the individual experiments. After aqueous workup and extraction with EtOAc or *n*-pentane the pure product was isolated by column chromatography or Kugelrohr distillation unless stated otherwise. The base triethylamine and the additive LiCl were used in different combinations as described below.

3.3. General procedure for one-pot Heck-coupling protocol starting from silyl enol ether (GP 2)

The corresponding nonaflate **7** was generated from silyl enol ether **6** (1 equiv), NfF (1.3 equiv) and substoichiometric amounts of *n*-Bu_4NF or dibenzo-18-crown-6 (db-18-c-6) (0.15 equiv)/KF (1.05 equiv) as described earlier.[4b,d] To this mixture were added—according to the GP 1—base (1.3 equiv), additive (1 equiv), olefin (1.3 equiv) and $Pd(OAc)_2$ (4–8 mol%), and the resulting solution was stirred under conditions indicated in the individual experiments. After aqueous workup and extraction with EtOAc or *n*-pentane the product was isolated by column chromatography or Kugelrohr distillation.

3.3.1. 8-Methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl nonaflate (3). *Method A, via silyl enol ether* **2**. According to the general procedure published,[6] a mixture of silyl enol ether **2** (0.950 g, 4.00 mmol), NfF (1.57 g, 5.20 mmol), dry KF (0.20 g, 3.44 mmol), and *n*-$Bu_4NF{\cdot}0.5H_2O$ (0.14 mL of a 1.05 M solution in THF) dissolved in 0.7 mL of THF provided after aqueous workup with satd aq $NaHCO_3$ solution crude nonaflate **3**. Kugelrohr distillation (105–108 °C/0.31 mbar) furnished 1.42 g (84%) of **3** as colorless oil.

Method B, direct method. An LDA solution in THF (12 mL) was generated by adding *n*-butyllithium (5.6 mL, 2.5 M in hexane, 14.0 mmol) to diisopropylamine (1.54 g, 15.0 mmol). A solution of tropinone **1** (1.43 g, 10.2 mmol) in THF (10 mL) was added at −78 °C, the mixture was allowed to warm up to −50 °C for 30 min, then recooled to −78 °C and treated with neat NfF (6.06 g, 20.0 mmol). After 2 h at this temperature the mixture was slowly warmed up to room temperature and stirred for 15 h. The resulting brown solution was poured into a vigorously stirred mixture of hexane (100 mL) and ice/satd aq $NaHCO_3$ solution (100 mL), the aqueous phase was extracted with hexane (3×30 mL), and the combined organic phases were dried ($MgSO_4$). Filtration and evaporation followed by column chromatography on silica gel (hexane then hexane/Et_2O 20:1 then hexane/Et_2O/Et_3N 8:2:1) afforded pure nonaflate **3** (3.72 g, 86%) as colorless oil. IR (film) ν 2950 (C–H), 2875, 2805, 1675 (C=C), 1420 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.71 (dt, J=5.4, 1.5 Hz, 1H, 2-H), 3.49–3.38 (m, 2H, 1-H, 5-H), 2.88–2.76 (m, 1H, 4-H), 2.41 (s, 3H, NCH_3), 2.25–2.14, 2.13–1.99, 1.98–1.87, 1.62–1.52 (4 m, 5H, 4-H, 6-H, 7-H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 146.1 (s, C-3), 120.8 (d, C-2), 58.2, 57.4 (2 d, C-1, C-5), 35.0, 34.3, 33.0 (3 d, C-4, C-6, C-7) 29.9 (NCH_3); MS (EI, 80 eV) *m/z* (%) 421 (M^+, 4), 138 ($M^+-SO_3C_4F_9$, 11), 110 (138

$-CH_2-CH_2$, 23), 96 (15), 42 (16), 18 (100); Anal. calcd for $C_{12}H_{12}F_9NO_3S$ (421.3): C, 34.21; H, 2.87; N, 3.32. Found: C, 33.93; H, 2.87; N, 3.50%.

3.3.2. Methyl (*E*)-3-(8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)propenoate (4). According to GP 1, a suspension of **3** (0.420 g, 1.00 mmol) in DMF (1 mL), LiCl (0.085 g, 2.00 mmol), triethylamine (0.303 g, 3.00 mmol), methyl acrylate (0.14 mL, 0.129 g, 1.50 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) was vigorously stirred under an argon atmosphere for 48 h at room temperature. Aqueous workup and chromatography on silica gel yielded 0.010 g (5%) of **4** as yellowish oil which was only characterized by a ^{1}H NMR spectrum. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24, 5.76 (2 d, J=15.6 Hz, 1H each, CH=CH), 6.25 (br. d, J=5.4 Hz, 1H, 2-H), 3.75 (s, 3H, CO_2CH_3), 3.43–3.35 (m, 2H, 1-H, 5-H), 2.35 (s, 3H, NCH_3), 2.65–2.62, 2.24–2.02, 1.88–1.74, 1.56–1.46 (4 m, 6H, 4-H, 6-H, 7-H).

3.3.3. (8-Ethoxycarbonyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)nonaflate (7). An LDA solution in THF (14 mL) was generated by adding *n*-butyllithium (5.3 mL, 2.5 M in hexane, 11.9 mmol) to diisopropylamine (2.17 g, 14.3 mmol). A solution of nortropinone derivative **5** (1.87 g, 9.50 mmol) in THF (12 mL) was added at −78 °C, the mixture was allowed to warm up to −50 °C for 30 min, then recooled to −78 °C and treated with neat NfF (4.72 g, 14.3 mmol). After 2 h at this temperature the mixture was slowly warmed up to room temperature and stirred for 15 h. The resulting brown solution was poured into a vigorously stirred mixture of hexane (100 mL) and ice/satd aq $NaHCO_3$ solution (100 mL), the aqueous phase was extracted with hexane (3×30 mL), and the combined organic phases were dried ($MgSO_4$). Filtration and evaporation followed by column chromatography on silica gel (hexane then hexane/Et_2O 20:1 then hexane/Et_2O/Et_3N 8:2:1) afforded pure nonaflate **7** (4.27 g, 94%) as colorless oil. IR (film) ν 3075 (=C–H), 2985–2880 (C–H), 1710 (C=O), 1670 (C=C), 1420 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.09 (d, J=5.4 Hz, 1H, 2-H), 4.62–4.45 (m, 2H, 1-H, 5-H), 4.13 (q, J=7.0 Hz, 2H, $NCO_2CH_2CH_3$), 3.14–2.92 (m, 1-H, 4-H), 2.32–2.18, 2.16–1.98, 1.82–1.68 (3 m, 5H, 6-H, 7-H, 4-H), 1.24 (t, J=7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.1 (s, C-3), 123.3 (d, C-2), 61.4 ($NCOCH_2CH_3$), 51.9, 51.8 (2 d, C-1, C-5), 36.5 34.7, 28.9 (3 t, C-4, C-6, C-7), 14.5 (q, $NCO_2CH_2CH_3$), the C=O signal could not be observed; MS (EI, 80 eV) m/z (%) 479 (M^+, 40), 196 ($M^+-SO_3C_4F_9$, 21), 168 (196 $-CH_2CH_3$, 28), 154 (168 $-CH_2$, 100), 96 (17), 82 (19), 69 (17), 28 (20); Anal. calcd for $C_{14}H_{14}F_9NO_5S$ (479.3): C, 35.08; H, 2.94; N, 2.92. Found: C, 35.07; H, 2.74; N, 2.72%.

3.3.4. Methyl (*E*)-3-(8-ethoxycarbonyl-8-azabicyclo[3.2.1]oct-2-en-3-yl)propenoate (8). According to GP 1, a mixture of nonaflate **7** (0.479 g, 1.00 mmol), LiCl (0.064 g, 1.50 mmol), triethylamine (0.202 g, 2.00 mmol), methyl acrylate (0.112 g, 1.30 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) in DMF (1 mL) was stirred at room temperature for 36 h. After aqueous workup (30 mL Et_2O/10 mL satd aq $NaHCO_3$ and ice) and extraction with Et_2O (3×10 mL), the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). The volatile components were removed and the residue was purified by column chromatography on silica gel (hexane/Et_2O 4:1 then 1:1) providing 0.262 g (99%) of **8** as a viscous yellowish oil.

One pot procedure. According to GP 2, nonaflation of silyl enol ether **6** (0.270 g, 1.00 mmol) with NfF (0.395 g, 1.30 mmol) was performed in DMF (1 mL) with dry KF (0.060 g, 1.03 mmol) and dibenzo-18-crown-6 (0.054 g, 0.15 mmol) at room temperature for 40 h. Then LiCl (0.042 g, 1.00 mmol), triethylamine (0.132 g, 1.30 mmol), methyl acrylate (0.112 g, 1.30 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) were added, and the mixture was stirred at room temperature for 36 h. After aqueous workup (30 mL Et_2O/10 mL satd aq $NaHCO_3$ and ice) and extraction with Et_2O (3×10 mL), the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). The volatile components were removed and the residue was purified by column chromatography on silica gel (hexane/Et_2O 4:1 then 1:1) furnishing 0.198 g (75%) of **8** as viscous yellowish oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.22, 5.77 (2 d, J=15.8 Hz, 1H each, CH=CH), 6.44–6.37 (m, 1H, 2-H), 4.53 (m_c, 2H, 1-H, 5-H), 4.12 (br. q, J=7.1 Hz, 2H, $NCO_2CH_2CH_3$), 3.75 (s, 3H, CO_2CH_3), 2.84 (m_c, 1H, 4-H), 2.29–2.15, 2.09–1.88, 1.71–1.56 (3 m, 5H, 4-H, 6-H, 7-H), 1.24 (br. t, J=7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, 55 °C) δ 167.3 (s, CO_2CH_3), 154.2 (s, $NCO_2CH_2CH_3$), 145.9 (d, =CH), 140.5 (br. d, C-2), 131.9 (br. s, C-3), 116.7 (d, =CH), 61.0 (t, $NCO_2CH_2CH_3$), 51.3, 51.6, 53.4 (q, 2 d, CO_2CH_3, C-1, C-5), 29.6, 33.5, 33.9 (3 br. t, C-4, C-6, C-7), 14.5 (q, OCH_2CH_3); MS (EI, 80 eV) m/z (%) 265 (M^+, 23), 236 (M^+-Et, 56), 192 (M^+-CO_2Et, 4), 164 ($M^+-CO_2Et-CH_2CH_2$, 100); Anal. calcd for $C_{14}H_{19}NO_4$ (265.3): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.33; H, 7.14; N, 5.26%.

3.3.5. Ethyl 3-(2-cyanoethenyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (9). According to GP 2, nonaflation of silyl enol ether **6** (0.270 g, 1.00 mmol) with NfF (0.395 g, 1.30 mmol) was performed in DMF (1 mL) with dry KF (0.060 g, 1.03 mmol) and dibenzo-18-crown-6 (0.054 g, 0.15 mmol) at room temperature for 40 h. Then LiCl (0.042 g, 1.00 mmol), triethylamine (0.132 g, 1.30 mmol), acrylonitrile (0.080 g, 1.50 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) were added, and the mixture was stirred at 75 °C for 5 h. These conditions led to complete conversion of intermediate nonaflate **7** into the expected coupling product (*E*/*Z* ratio 7:1 according to ^{1}H NMR spectrum). After aqueous workup (30 mL *t*-BuOMe/10 mL satd aq $NaHCO_3$ and ice) and extraction with *t*-BuOMe (3×10 mL), the combined organic phase was washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane:*t*-BuOMe 3:1 then 2:1 then 1:1 then 0:1) affording pure *E*-**9** (0.125 g) and an *E*/*Z* mixture, which provided after a second column chromatography an additional amount of *E*-**9** (22 mg) and pure *Z*-**9** (18 mg). Overall yield: 0.165 g (71%), both isomers are yellowish viscous oils. (*E*)-**9** IR (film) ν 2960, 2930, 2870 (C–H), 1735 (C=O), 1470 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.94, 5.21 (2 d, J=16.4 Hz, 1H each, CH=CH), 6.42 (br. s, 1H, 2-H), 4.54 (m_c, 2H, 1-H, 5-H), 4.13 (br. q, J=7.1 Hz, 2H, $NCO_2CH_2CH_3$), 2.80 (m_c, 1H, 4-H), 2.32–2.16, 2.11–1.86, 1.69–1.55 (3 m, 5H, 4-H, 6-H, 7-H), 1.25 (t, J=7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (67.5 MHz,

$CDCl_3$) δ 154.1 (s, $NCO_2CH_2CH_3$), 151.6 (d, =CH), 141.7 (br. d, C-2), 131.4 (br. s, C-3), 118.1 (s, CN), 94.9 (d, =CH), 61.2 (t, $NCO_2CH_2CH_3$), 51.3, 53.2 (2 d, C-1, C-5), 29.6, 32.6, 33.8 (3 br. t, C-4, C-6, C-7), 14.6 (q, OCH_2CH_3); Anal. calcd for $C_{13}H_{16}N_2O_2$ (232.2): C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 6.71; N, 12.00%.

(*Z*)-**9** ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.58, 5.17 (2 d, J=12.0 Hz, 1H each, CH=CH), 6.44 (br. s, 1H, 2-H), 4.53 (m_c, 2H, 1-H, 5-H), 4.12 (br. q, $J\approx$7.1 Hz, 2H, $NCO_2CH_2CH_3$), 2.84 (m_c, 1H, 4-H), 2.29–2.15, 2.09–1.88, 1.71–1.56 (3 m, 5H, 4-H, 6-H, 7-H), 1.24 (t, $J\approx$7.1 Hz, 3H, OCH_2CH_3); MS (EI, 80 eV) *m*/*z* (%) 232 (M^+, 7), 203 (M^+-Et, 19), 159 (M^+-CO_2Et, 2), 131 ($M^+-CO_2Et-CH_2=CH_2$, 100).

3.3.6. Ethyl 3-[(*E*)-2-(phenylsulfonyl)ethenyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (10). According to GP 2, nonaflation of silyl enol ether **6** (0.270 g, 1.00 mmol) with NfF (0.395 g, 1.30 mmol) was performed in DMF (1 mL) with dry KF (60 mg, 1.03 mmol) and dibenzo-18-crown-6 (54 mg, 0.15 mmol) at room temperature for 40 h. Then LiCl (42 mg, 1.00 mmol), triethylamine (0.132 g, 1.30 mmol), phenyl vinyl sulfone (0.219 g, 1.30 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added, and the mixture was stirred at 75 °C for 5 h. After aqueous workup (30 mL Et_2O/10 mL satd aq $NaHCO_3$ and ice) and extraction with Et_2O (3×10 mL), the combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane/Et_2O 4:1 then 3:2 then 1:1 then 0:1) providing 0.236 g (68%) of **10** as glassy yellow oil. IR (film) ν 3055 (=C–H), 2980–2870 (C–H), 1690, 1620 (C=O), 1590 (C=C), 1450 (SO_2) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.90–7.84, 7.68–7.48 (2 m, 2H, 3H, Ph), 6.94, 5.21 (2 d, J=16.4 Hz, 1H each, CH=CH), 6.42 (br. s, 1H, 2-H), 4.54 (m_c, 2H, 1-H, 5-H), 4.13 (br. q, J=7.1 Hz, 2H, OCH_2CH_3), 2.76 (m_c, 1H, 4-H), 2.32–2.16, 2.11–1.86, 1.69–1.55 (3 m, 5H, 4-H, 6-H, 7-H), 1.23 (t, J=7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (s, $NCO_2CH_2CH_3$), 143.4, 126.0 (2 d, CH=CH), 140.6 (s, Ph), 133.1, 129.1, 127.7 (3 d, Ph), 60.9 (t, $NCO_2CH_2CH_3$), 53.1, 51.2 (2 d, C-1, C-5), 33.8, 33.2, 28.9 (3 br. t, C-4, C-6, C-7), 14.4 (q, $NCO_2CH_2CH_3$), the signal for C-3 could not be observed; Anal. calcd for $C_{18}H_{21}NO_4S$ (347.4): C, 62.23; H, 6.09; N, 4.03. Found: C, 61.92; H, 5.89; N, 3.95%.

3.3.7. Ethyl 3-(2-phenylethynyl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (11). According to GP 2, nonaflation of silyl enol ether **6** (0.270 g, 1.00 mmol) with NfF (0.395 g, 1.30 mmol) was performed in DMF (1 mL) with dry KF (0.060 g, 1.03 mmol) and dibenzo-18-crown-6 (0.054 g, 0.15 mmol) at room temperature for 40 h. Then (i-Pr)$_2$NH (2 mL), LiCl (0.064 g, 1.50 mmol), phenylacetylene (0.143 g, 1.40 mmol), CuI (0.019 g, 0.1 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol) were added, and the mixture was stirred at room temperature for 7 h. After aqueous workup (30 mL Et_2O/10 mL satd aq $NaHCO_3$ and ice) and extraction with Et_2O (3×10 mL), the combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane/*t*-BuOMe 8:1 then 5:1) providing 0.214 g (76%) of **11** as orange oil. IR (film) ν 3080, 3055 (=C–H), 2980–2840 (C–H), 2205 (C≡C), 1700 (CO), 1600 (C=C), 1490, 1420, 1380 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.41–7.37, 7.30–7.26 (2 m, 2H, 3H, Ph), 6.40 (d, J=4.7 Hz, 1H, 2-H), 4.48, 4.42 (2 m_c, 1H each, 1-H, 5-H), 4.14 (m_c, 2H, $NCO_2CH_2CH_3$), 2.93 (br. d, J=15.1 Hz, 1H, 4-H), 2.25–2.15, 2.00–1.95, 1.78–1.70 (3 m, 4H, 6-H, 7-H), 2.01 (d, J=15.1 Hz, 1 H, 4-H), 1.26 (t, $J\approx$7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C) δ 154.2 (s, $NCO_2CH_2CH_3$), 138.2 (d, C-2), 131.8 (s, C-3), 131.5, 128.2, 128.1, 122.0 (3 d, s, Ph), 89.0, 88.9 (2 s, C≡C) 61.0 (t, $NCO_2CH_2CH_3$), 53.2, 51.9 (2 d, C-1, C-5), 38.1 (t, C-4), 34.4 (t, C-6), 29.6 (t, C-7), 14.6 (q, $NCO_2CH_2CH_3$); MS (EI, 80 eV) *m*/*z* (%) 281 (M^+, 90), 253 ($M^+-CH_2CH_3$, 100), 226 (62), 210 (30), 193 (9), 180 ($M^+-PhC\equiv C$, 90), 165 (16), 153 (16), 115 (13), 29 (50); HRMS calcd for $C_{18}H_{19}NO_2$: 281.14158. Found: 281.14149.

3.3.8. 15-Ethyl 8-methyl 4,6-dioxo-5-phenyl-5,15-diazatetracyclo[10.2.1.0^{2,10}.0^{3,7}]pentadec-9-ene-8,15-dicarboxylate (12). Bicyclic diene **8** (0.111 g, 0.42 mmol) and *N*-phenyl maleimide (0.087 g, 0.50 mmol) were dissolved in benzene (1.5 mL) and stirred for 6 days at 100 °C in a sealed tube. The solvent was removed in vacuo and the crude mixture was purified by column chromatography on silica gel (*t*-BuOMe/hexane 1:4 then 1:2 then 1:1) to yield 0.110 g (59%) *endo*-**12** and 0.052 g (29%) *exo*-**12** as colorless solids. *endo*-**12** mp: 89–91 °C; IR (KBr) ν 2980–2870 (C–H), 1740, 1720, 1690 (C=O), 1500, 1435, 1380 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 70 °C) δ 7.30–7.28, 7.13–7.09, 6.98–6.94 (3 m, 2H, 2H, 1H, Ph), 6.24 (s, 1H, 9-H), 4.91 (d, J=6.7 Hz, 1H, 1-H), 4.43 (t, J=6.1 Hz, 1H, 12-H), 4.20–4.14 (m, 2H, $NCO_2CH_2CH_3$), 3.65 (s, 3H, CO_2CH_3), 3.29 (dd, J=8.5, 4.8 Hz, 1H, 7-H), 2.68 (dd, J=8.5, 6.7 Hz, 1H, 3-H), 2.55 (t, J=4.6 Hz, 1H, 8-H), 2.52 (br. d, J=17.0 Hz, 1H, 11-H), 1.99 (d, J=17.0 Hz, 1H, 11-H), 1.80–1.75, 1.70–1.60 (2 m, 2H, 14-H, 13-H), 1.56 (d, J=6.7 Hz, 1H, 2-H), 1.27 (ddd, J=12.2, 9.1, 2.9 Hz, 1H, 14-H), 1.16 (t, J=6.9 Hz, 3H, $NCO_2CH_2CH_3$), 1.20–1.10 (m, 1H, 13-H); ^{13}C NMR (126 MHz, C_6D_6, 70 °C) δ 175.2, 174.1, 170.8 (3 s, CO), 155.9 (s, $NCO_2CH_2CH_3$), 134.7, 133.1 (2 s, C-10, Ph), 128.9, 126.5, 125.0 (3 d, Ph), 119.9 (d, C-9), 56.3 (t, $NCO_2CH_2CH_3$), 54.2 (d, C-1), 52.3 (d, C-12), 51,8 (q, CO_2CH_3), 44.9† (d, C-8, C-7), 44.8 (d, C-2), 41.3 (d, C-3), 37.8 (t, C-11), 32.9, 28.5 (2 t, C-13, C-14), 14.8 (q, $NCO_2CH_2CH_3$); MS (EI, 80 eV) *m*/*z* (%) 454 (M^++16, 5), 438 (M^+, 19), 299 (100), 267 (31), 252 (11), 239 (34), 180 (10), 156 (13), 143 (11), 140 (84), 130 (11), 119 (12), 117 (15), 115 (10), 11 (10), 93 (30), 78 (13), 68 (82), 28 (71); HRMS calcd for $C_{24}H_{26}N_2O_6$: 438.17909. Found: 438.17744. *exo*-**12** mp: 94–96 °C; IR (KBr) ν 2970–2850 (C–H), 1740, 1710, 1690 (CO), 1500, 1430, 1380 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 70 °C) δ 7.37–7.33, 7.15–7.12, 7.05–7.01 (3 m, 2H, 2H, 1H, Ph), 5.49 (t, J=2.5 Hz, 1H, 9-H), 5.40 (d, J=7.4 Hz, 1H, 1-H or 12-H), 4.36–4.30 (m, 1H, 1-H or 12-H), 4.13 (q, J=7.1 Hz, 2H, $NCO_2CH_2CH_3$), 3.52 (s, 3H, CO_2CH_3), 3.25 (t, J=9.4 Hz, 1H, 7-H), 3.08–3.03 (m, 2H, 3-H, 7-H), 2.74 (ddt, J=17.2, 5.7, 1.6 Hz, 1H, 11-H), 1.86 (dd, J=17.2, 1.6 Hz, 1H, 11-H), 1.85–1.80 (m, 1H, 14-H), 1.75 (d, J=11.0 Hz, 1H, 2-H), 1.66–1.58 (m,

† The signal has doubled intensity.

1H, 13-H), 1.33–1.26 (m, 1H, 14-H), 1.16–1.11 (m, 1H, 13-H), 1.22 (t, J=7.1 Hz, 3H, $NCO_2CH_2CH_3$); ^{13}C NMR (126 MHz, C_6D_6, 70 °C) δ 175.8, 175.0, 172.2 (3 s, CO), 153.8 (s, $NCO_2CH_2CH_3$), 129.9, 137.3 (2 s, C-10, Ph), 128.9, 128.1, 126.6 (3 d, Ph), 124.9 (d, C-9), 60.3 (t, $NCO_2CH_2CH_3$), 53.3 (q, CO_2CH_3), 51.2, 50.3 (2 d, C-1, C-12), 45.1 (d, C-2), 42.5 (d, C-7), 41.8, 41.5 (2 d, C-8, C-3), 36.2 (t, C-11), 30.1, 29.5 (2 t, C-13, C-14), 13.9 (q, $CO_2CH_2CH_3$); Anal. calcd for $C_{24}H_{26}N_2O_6$ (438.5): C, 65.47; H, 5.98; N, 6.39. Found: C, 65.44, H, 5.79, N, 6.00%.

3.3.9. (8-Methoxycarbonyl-8-azabicyclo[3.2.1]octa-2,6-dien-3-yl)nonaflate (14). An LDA solution in THF (10 mL) was generated by adding *n*-butyllithium (1.32 mL, 2.5 M in hexane, 3.30 mmol) to diisopropylamine (0.360 g, 3.55 mmol). Ketone **13** (0.460 g, 2.54 mmol) was slowly added at −78 °C, the resulting brown solution was stirred for 1 h and NfF (1.23 g, 4.06 mmol). The mixture was allowed to warm up to room temperature within 17 h. The solvent was removed in vacuo and the resulting brown residue was taken up in EtOAc and extracted with water. The aqueous layer was reextracted with EtOAc and the combined organic layers were washed with brine and then dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (pentane/EtOAc 60:40) to yield 0.629 g (54%) of **14** as colorless oil. IR (film) ν 3085–2830 (=C–H, C–H), 1710 (C=O), 1660 (C=C), 1450–1350, 1300–1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ 6.32–6.26 (m, 1H, 2-H), 6.44, 5.96 (2 dd, J=5.8, 2.5 Hz, J=5.8, 2.1 Hz, 1H each, 6-H, 7-H), 4.90-4.70 (m, 2H, 1-H, 5-H), 3.68 (s, 3H, NCO_2CH_3), 3.10–2.90 (m, 1H, 4-H), 2.06 (d, J=17.7 Hz, 1H, 4-H); ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C) δ 153.9 (s, C-3), 146.5‡ (br. s, NCO_2CH_3), 128.3, 137.3 (2 d, C-6, C-7), 123.3 (d, C-2), 54.9, 56.6 (2 d, C-1, C-5), 52.4 (q, NCO_2CH_3), 30.8‡ (br. t, C-4); MS (EI, 80 eV) m/z (%) 463 (M^+, 47), 180 ($M^+-C_4F_9SO_2$, 86), 164 (180 $-CH_3$, 100), 161 (10), 153 (26), 149 (32), 138 (99), 136 (17), 132 (23), 121 (22), 120 (15), 109 (10), 108 (13), 105 (10), 104 (22), 96 (71), 81 (25), 69 (54), 67 (24), 66 (23), 60 (19), 59 (80), 55 (22), 42 (62); Anal. calcd for $C_{13}H_{10}F_9NO_5S$ (463.3): C, 33.70; H, 2.18; N, 3.02. Found: C, 34.18; H, 2.12; N, 2.87%.

3.3.10. Methyl (*E*)-3-[8-(methoxycarbonyl)azabicyclo[3.2.1]octa-2,6-dien-3-yl]propenoate (17). According to GP 1, nonaflate **14** (0.234 g, 0.51 mmol) was dissolved in DMF (2 mL). LiCl (0.034 g, 0.81 mmol), triethylamine (0.153 g, 1.52 mmol), methyl acrylate (0.065 g, 0.76 mmol) and $Pd(OAc)_2$ (0.006 g, 0.03 mmol) were added and the reaction mixture was stirred for 24 h at room temperature. $Pd(OAc)_2$ (0.006 g, 0.03 mmol) was added again and the mixture was stirred at 70 °C for 24 h. The resulting brown mixture was taken up in EtOAc (20 mL) and washed with water (2×20 mL). The organic phase was then washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (hexane/EtOAc 9:1 then 5:1 then 3:1) yielding 13 mg (10%) of **17** as yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 7.14, 5.79 (2 d, J=15.9 Hz, 1H each, CH=CH), 6.56§ (br. s, 1H, 2-H), 6.46–6.38§, 6.04–5.95§ (2 m, 2H, 6-H, 7-H), 4.89–4.68 (m, 2H, 1-H, 5-H), 3.73 (s, 3H, CO_2CH_3), 3.69§ (br. s, 3H, NCO_2CH_3), 2.90–2.68§ (m, 1H, 4-H), 1.94 (d, J=17.7 Hz, 1H, 4-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9 (s, CO_2CH_3), 153.9 (s, NCO_2CH_3), 146.7 (s, C-3), 139.8, 139.3, 136.5, 129.2, 115.5 (5 d, C-2, C-6, C-7, CH=CH), 56.5, 56.4 (2 q, CO_2CH_3, NCO_2CH_3), 52.5, 51.5 (2 d, C-1, C-5), 25.6 (t, C-4).

3.3.11. Methyl 2-(prop-2-ynyl)pyrrole-1-carboxylate (15) and methyl 2-(propa-1,2-dienyl)pyrrole-1-carboxylate (16). Nonaflate **15** (0.279 g, 0.602 mmol) was dissolved in DMF (2 mL), triethylamine (0.081 g, 0.602 mmol) was added and the mixture was stirred at 70 °C for 24 h. Pentane was added and the mixture was washed with water and brine. The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. Column chromatography on silica gel (hexane then hexane/EtOAc 98:2) yielded 34 mg (35%) of **15** and 9 mg (10%) of **16** as colorless liquids. **15**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.22 (m, 1H, 5-H), 6.32 (td, J=3.2, 1.4 Hz, 1H, 4-H), 6.14 (t, J=3.3 Hz, 1H, 3-H), 3.94 (s, 3H, CO_2CH_3), 3.84–3.83 (m, 2H, 2-CH_2), 2.14 (t, J=2.7 Hz, 1H, ≡CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3 (s, CO_2CH_3), 130.0 (s, C-2), 121.3, 112.8, 110.8 (3 d, C-3, C-4, C-5), 80.6 (s, C≡CH), 69.6 (d, C≡CH), 53.8 (q, CO_2CH_3), 19.4 (t, 2-CH_2); MS (EI, 80 eV) m/z (%) 163 (M^+, 48), 148 (M^+-CH_3, 100), 118 (17), 117 (16), 104 ($M^+-CO_2CH_3$, 43), 91 (13), 78 (19), 59 (20), 51 (37), 50 (15). **16:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.25 (m, 1H, 5-H), 6.99–6.95 (m, 1H, 2-CH), 6.31–6.29 (m, 1H, 4-H), 6.18 (d, J=3.4 Hz, 1H, 3-H), 5.07 (d, J=7.0 Hz, 2H, =CH_2), 3.95 (s, 3H, CO_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0 (s, =C=), 128.5 (s, C-2), 121.6, 112.3, 111.8 (3 d, C-3, C-4, C-5), 77.7 (t, CH_2), 58.5 (d, 2-CH), 53.9 (q, CO_2CH_3); the signal for CO_2CH_3 could not unambiguously be detected.

3.3.12. Methyl 3-(2-phenylethynyl)-8-azabicyclo[3.2.1]octa-2,6-diene-8-carboxylate (18). Nonaflate **14** (66 mg, 0.142 mmol), phenylacetylene (16 mg, 0.157 mmol), PPh_3 (7 mg, 0.028 mmol), CuI (2 mg, 0.007 mmol) and $Pd(OAc)_2$ (2 mg, 0.007 mmol) were dissolved in a mixture of $(i\text{-Pr})_2NH$ (1 mL) and DMF (2 mL). The reaction mixture was stirred at room temperature for 18 h, then taken up with Et_2O and washed with water and brine. The organic phase was then dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 90:10 then 85:15) to yield 21 mg (56%) of **18** as yellow solid. Mp: 77–78 °C; ^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.39–7.36, 7.29–7.26 (2 m, 2H, 3H, Ph), 6.56 (br. s, 1H, 2-H), 6.43, 5.98 (2 m_c, 1H each, 6-H, 7-H), 4.80–4.60 (m, 2H, 1-H, 5-H), 3.72 (s, 3H, CO_2CH_3), 3.00–2.80 (m, 1H, 4-H), 1.93 (d, J=17.8 Hz, 1H, 4-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.9 (s, C-3), 136.9¶‖ (s, C-2, NCO_2CH_3, C-6, C-7), 131.5** (d, Ph), 128.3, 128.2 (2 d, Ph), 128.1 (s, Ph), 89.4, 87.8 (2 s, C≡C), 56.7, 56.1 (2 d, C-1, C-5), 52.4 (q, CO_2CH_3), 30.4¶ (t, C-4); MS (EI, 80 eV) m/z (%) 265 (M^+,

‡ The signals for C-4 and NCO_2CH_3 are very broad due to hindered rotation of the N–CO_2CH_3 moiety.

§ The marked signals are very broad because of hindered rotation of the N–CO_2CH_3 moiety.

¶ The marked signals are very broad because of hindered rotation of the N–CO_2CH_3 moiety.

‖ The signal contains probably 4 C concerning 2D correlation spectra.

** The signal shows doubled intensity.

24), 206 ($M^+-C_2H_3O_2$, 29), 204 (23), 179 (29), 178 (206–C_2H_2, 43), 165 ($M^+-C_8H_4$, 6), 152 (10), 139 (16), 138 (100), 94 (20), 86 (12), 77 (11), 59 ($C_2H_3O_2^+$, 20); HRMS calcd for $C_{17}H_{15}NO_2$: 265.11211. Found: 265.11029.

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β,β-Difluoro analogs of α-oxo-β-phenylpropionic acid and phenylalanine

Manfred Schlosser,[a,*] Nadia Brügger,[a] Werner Schmidt[b] and Nikolaus Amrhein[b]

[a]*Institut de Chimie moléculaire et biologique, Ecole fédérale polytechnique, CH-1015 Lausanne, Switzerland*
[b]*Institut für Pflanzenwissenschaften, ETH, CH-8092 Zürich, Switzerland*

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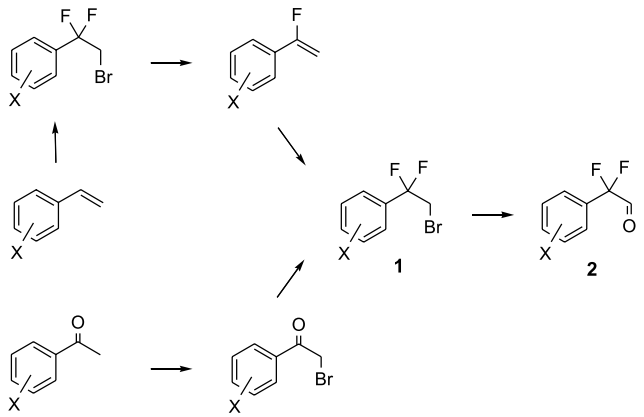
To Dieter Seebach with congratulations and best wishes

Abstract—A simple three-step procedure converted the readily accessible (2-bromo-1,1-difluoroethyl)arenes (**2**) into α-aryl-α,α-difluoroacetaldehydes (**1**). Subsequent hydrocyanation, hydrolysis, oxidation and again hydrolysis afforded β-aryl-β,β-difluoro-α-oxopropionic acids (**3**). Reductive amination transformed the oxoacids **3** into a separable mixture of α-hydroxyacids **11** and racemic β,β-difluoro-β-phenylalanine derivatives (**4**). Enantiomerically pure β,β-difluorophenylalanine (L-**4a**) was obtained when α,α-difluoro-α-phenylacet-aldehyde (**1a**) was condensed with homochiral 1-phenylethylamine, hydrogen cyanide added to the resulting imine, the diastereomeric mixture thus produced hydrolyzed to the carboxamides (**15**) which were found to be separable by fractional crystallization or chromatography. The pK_a values of the β-aryl-β,β-difluoroalanines (**4**) were measured and biological profile of the latter probed. 3-(4-Chlorophenyl)-3,3-difluoro-2-oxopropionic acid (**4c**) proved to be a potent (K_i 27 μM) and selective inhibitor of arogenate dehydratase, a key enzyme catalyzing the last step of the phenylalanine biosynthesis.

1. Introduction

Years ago, we have disclosed a convenient access to aryldifluoroacetaldehydes (**2**). If not commercial, the starting material, a styrene or a ring-substituted congener, was usually made by Wittig methylenation of the corresponding benzaldehyde. It was then consecutively subjected to a *vic*-bromofluorination, a base-promoted dehydrobromination and a second *vic*-bromofluorination. The resulting (2-bromo-1,1-difluoroethyl)arene[1] (**1**) was eventually oxidized by applying the Pummerer method.[1] As we have recognized in the meantime, the bromo compounds **1** are also readily obtained by the bromination of the corresponding acetophenone and the subsequent treatment of the α-bromoketone with diethylaminosulfur trifluoride ('DAST') or sulfur tetrafluoride (see Section 6) (Scheme 1).

We wanted to explore now how the aldehydes **2** might be converted into the 3,3-difluoro analogs of 3-aryl-2-oxopropionic acids (3-arylpyruvic acids, 2-hydroxycinnamic acids; **3**) and 3-arylalanines (**4**). Both types of compounds are physiologically relevant intermediates (Scheme 2).



Scheme 1.

The *erythro*- and *threo*-β-fluorophenylalanines have been extensively investigated in the past.[2–6] β,β-Difluoro-β-phenylalanine, one of the few difluorinated amino acids known so far, was synthesized by R. Guedj et al. in a fairly laborious multistep sequence.[7,8] Biological studies accomplished with this compound have not been reported. We felt, suitably *para* substituted derivatives of β,β-difluorophenylalanine might exhibit a potential as inhibitors of tyrosine hydroxylase,[9] decarboxylase[9] and ammonia lyase.[10] We decided to investigate the ring-unsubstituted parent

Keywords: Cyanhydrines; Fluoroanalogs; Oxidation; Reductive amination; Separation of diastereomers; Transition state analogs.
* Corresponding author. Fax: +41-21-692-39-65;
e-mail address: manfred.schlosser@epfl.ch

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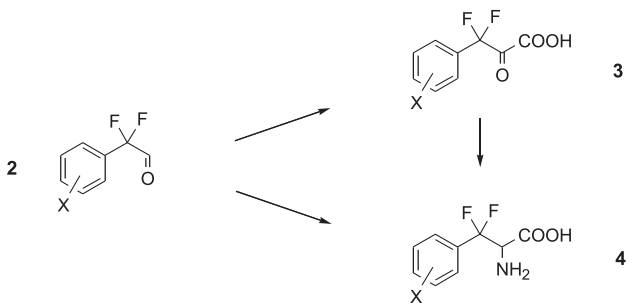
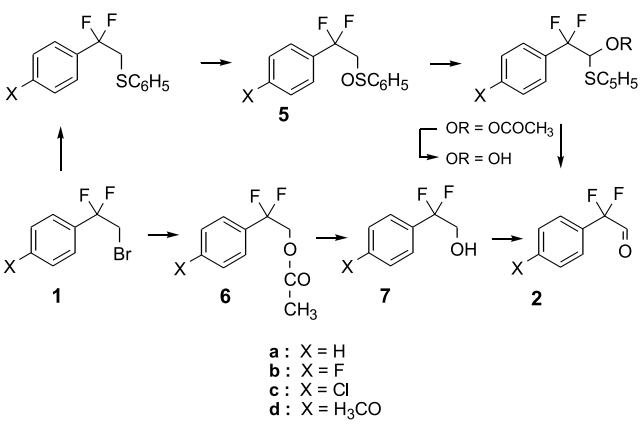


Scheme 2.

structure, along with three analogs carrying fluorine, chlorine and methoxy at the *para* position.

2. 2-Aryl-2,2-difluoroacetaldehydes

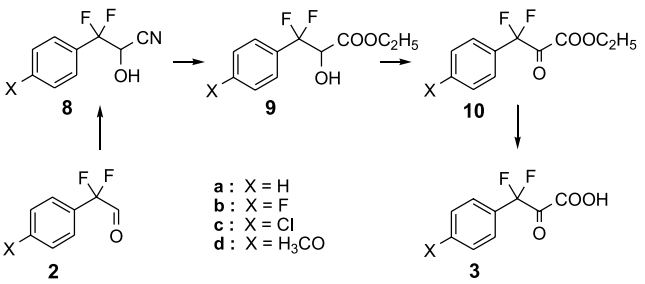
The (2-bromo-1,1-difluoroethyl)arenes (**1**) were prepared in the standard way described above.[1] However, their transformation into the α-aryl-α,α-difluoroacetaldehydes (**2**) no longer relied on the Pummerer isomerization of the sulfoxide **5** but was based on a simplified sequence consisting of a nucleophilic acetate/bromide displacement, hydrolysis of the resulting ester **6** to the alcohol **7** and treatment of the latter with the Swern[11,12] or Dess–Martin[13,14] reagent. Under such conditions the aldehydes **2** could be isolated in almost quantitative yield although they showed a pronounced tendency to form the hydrate or to polymerize (Scheme 3).



Scheme 3.

3. 3-Aryl-3,3-difluoro-2-oxopropionic acids

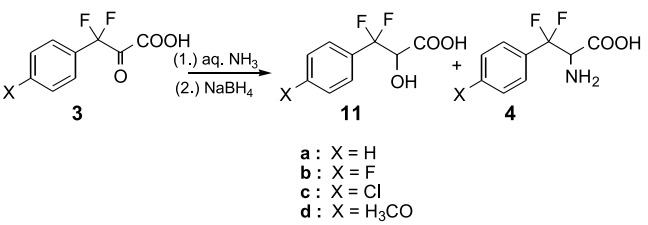
The cyanhydrines **8** were obtained in satisfactory yield (62–74%) when the hydrogen sulfite adducts of the aldehydes **2** were dissolved in an aqueous solution of sodium cyanide. The hydrolysis was accomplished by passing gaseous hydrogen chloride into an ethanolic solution of the cyanhydrines **8** before pouring the mixture into water. The resulting ethyl 3-aryl-3,3-difluoro-2-hydroxypropionates (**9**; 77–78%) were oxidized to the ethyl 3-aryl-3,3-difluoro-2-oxopropionates (**10**; 89–98%) using the Dess–Martin reagent.[13,14] Saponification of the esters **10** with sodium hydrogen carbonate in aqueous isopropanol eventually gave the oxoacids **3** (87–96%) (Scheme 4).



Scheme 4.

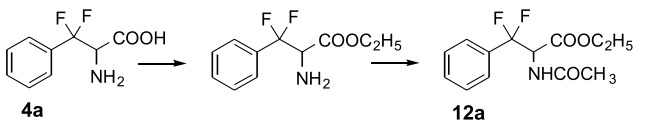
4. 3-Aryl-3,3-difluoroalanines

The consecutive treatment of an oxoacid **3** with 25% aqueous ammonia and sodium borohydride invariably led to a mixture of the α-hydroxyacid **11** and the α-aminoacid **4**. The product separation required the use of an ion exchange column. The product ratios 11:4 depend critically on the imine generating step. For example, 62% of the α-hydroxyacid **11a** and only 1% of the α-aminoacid **4a** were formed when the oxo precursor **3a** was exposed to 25% aqueous ammonia at 100 °C under atmospheric pressure, whereas the product composition changed to 29% of **11a** and 67% of **4a** when the treatment with ammonia was performed at 60 °C in a hermetically closed pressure vessel under otherwise identical conditions. In contrast, to shorten the standard reaction time of 5–3 h or to extend it to 19 h had little effect on the combined yields of products, nor on the product ratios (Scheme 5).



Scheme 5.

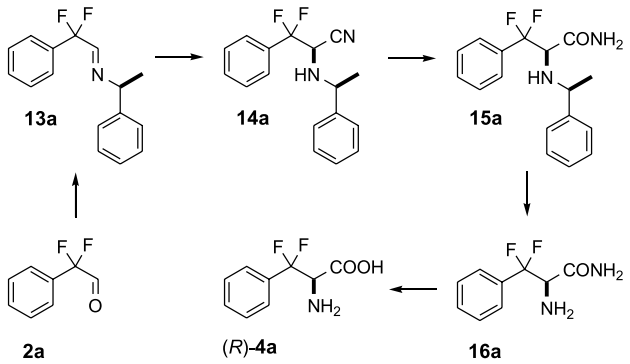
Both the α-aminoacids **4** and their chlorohydrates decompose upon heating above 150 °C. In order to record at least one reproducible melting range, compound **4a** was converted into the *N*-acetyl ethyl ester **12a** (mp 92–93 °C) (Scheme 6).



Scheme 6.

It was never a main objective of the present work to make enantiomerically pure fluoro analogs of α-aminoacids available, the more as the kinetic racemate resolution by enzymatic hydrolysis of methyl phenylalaninates[8] appears to be a generally applicable method. Thus, it was merely for curiosity if we wanted to explore a new approach. The aldehyde **2a** was condensed with (*S*)-1-phenylethylamine and the resulting imine **13a** was heated with trimethylsilyl cyanide in the presence of zinc iodide.[15,16] The aminonitrile

14a, existing as a roughly 1:1 diastereomeric mixture, was immediately hydrolyzed to provide the carboxamide **15a**, one component of which crystallized readily. Removal of the chiral auxiliary by catalytic hydrogenation to afford **16a** and acid-mediated hydrolysis of the carboxamide **16a** to the free amino acid (L)- or (*R*)-β,β-difluoroalanine (**4a**), concluded the reaction sequence. Unfortunately, the hydrolysis was accompanied by extensive racemization. We should have searched for a milder amide cleavage method but ran out of time (Scheme 7).



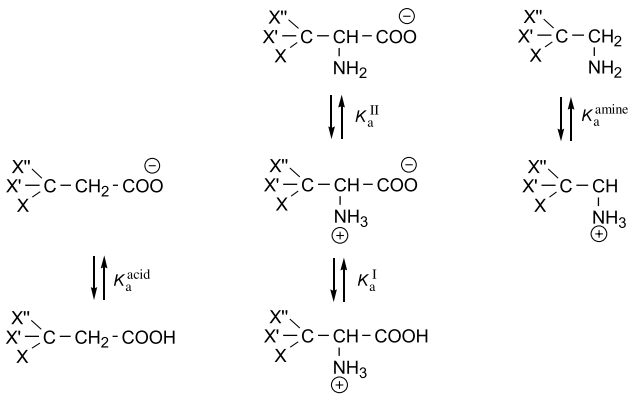
Scheme 7.

5. Physical and biological properties

The introduction of fluorine atoms into organic lead compounds is a favorite tool for the modulation of molecular properties in the life science arena.[17,18] The change of the pK_a value caused by such a halogen substituent is of course a key issue in this respect. It is plausible to expect the inductive effect to level off with distance, decreasing for example to one third of the former magnitude with each additional methylene group inserted between the substituent-produced perturbation and the monitoring functional group. One might further suppose fluorine effects to be cumulative, in other words to increase proportionally if there are two or three halogen atoms in the same chemical environment rather than a single one. At least the last assumption is naive and invalid, as we shall see in a minute.

β-Fluoroamino acids are particularly instructive model compounds to test the additivity or non-additivity of substituent effects on acidity.[19] Ideally, they would behave as a super-position of 3-fluorinated propanoic acids and 2-fluorinated ethylamines. This means, the first dissociation constant of the amino acid (K_a^I) should approximate that of the corresponding propanoic acid (K_a^{acid}) and the second one (K_a^{II}) should mirror that of the corresponding promoted amine (K_a^{amine}) (Scheme 8).

This view is oversimplified and not supported by the reality. Due to cross-interactions between the two functional groups, the pK_a values of amino acids deviate considerably from that of their structural subcomponents (Tables 1–3). More importantly, the acidity does not increase monotonously with the number of fluorine substituents. In fact, the first one does little or even may slightly raise the pK_a value. In this context, it should be recalled that halogen effects on the acidity of acetic acids in aqueous solution,[20,21] but not in the gas phase,[22,23] are rather entropy than enthalpy



Scheme 8.

dictated. The introduction of a geminal pair of fluorine atoms into the β-position of alanine lowers the pK_a^I and pK_a^{II} values by 0.8 and 1.5 units, whereas the same structural modification of phenylalanine does hardly affect the pK_a^I value (+0.1), but decreases the pK_a^{II} number by 2.4 units (Table 3), as potentiometric measurement have now revealed. The acidity differences between the *p*-chloro and *p*-methoxy substituted phenylalanines and their β,β-difluoro congeners are quite similar (ΔpK_a^I +0.2 to +0.3; ΔpK_a^I −2.3 to −2.5).

A preliminary screening of the β-aryl-β,β-difluoroalanines **5** as inhibitors of the tyrosine metabolism ended disappointingly. No binding appeared to occur at low concentrations.

Table 1. Negative logarithmic of dissociation constants (pK_a^{acid}) of propanoic acid and its 3-fluoro substituted derivatives[24–29] X″X′XC–CH_2–COOH

X″	X′	X	(pK_a^{acid})
H	H	H	4.8
F	H	H	2.6
F	F	H	1.3
F	F	F	0.2

Table 2. Negative logarithmic of dissociation dissociation constants (pK_a^{amine}) of the *N*-protonated ethylamine and 2-fluoro substituted derivatives[30–33] X″X′XC–CH_2–NH_2

X″	X′	X	(pK_a^{amine})
H	H	H	10.7
F	H	H	8.8
F	F	H	7.1
F	F	F	5.6

Table 3. Negative logarithmic of dissociation constants (pK_a^I and pK_a^{II}) of alanine, phenylalanine and its β-fluoro substituted derivatives[24,30,34–36] X″X′XC–CH(NH_2)–COOH

X″	X′	X	pK_a^I	pK_a^{II}
H	H	H	2.3	9.9
F	H	H	2.4	9.8
F	F	H	1.5	8.4
F	F	F	1.2	5.3
H_5C_6	H	H	2.2	9.2
H_5C_6	F	H	n.r	n.r
H_5C_6	F	F	2.3	6.8

n.r., not yet reported.

On the other hand, the 3-aryl-3,3-difluoro-2-oxopropionic acids display all the structural features of a successful 'transition state analog'.[37–39] The keto group being flanked by two electron-withdrawing entities, the carboxy function and the difluoromethylene unit, is exceptionally electrophilic. If water is not rigorously excluded, the oxo compound spontaneously metamorphoses to the corresponding hydrate. This held the promise of 3-aryl-3,3-difluoro-2-oxopropionic acids to act as potential inhibitors of plant metabolism. Its structure suggesting possible interference with the biosynthesis of phenylalanine, the oxoacid **3c** was considered to be particularly attractive and was, therefore, selected for a series of tests. Only bacteria, fungi and plants are capable of synthesizing the three proteinogenic aromatic amino acids, that is, phenylalanine, tyrosine, and tryptophan, along the shikimate pathway,[40] and phenylalanine in particular is the biosynthetic precursor of a large number of aromatic natural plant products, such as flavonoids, lignins, coumarins, etc. En route to these compounds, phenylalanine is deaminated by phenylalanine ammonia-lyase (PAL) to yield (*E*)-cinnamic acid. Among the flavonoids, anthocyanins are coloured intensely red or blue, and inhibitors of the synthesis of phenylalanine and cinnamic acid can be easily identified by their interference with anthocyanin pigment formation in vivo. When testing the effect of oxoacid **3c** on light-induced anthocyanin synthesis in buckwheat hypocotyls,[41] we found inhibition with an IC_{50} value of ca. 200 μM. Unlike known inhibitors of PAL, oxoacid **3c** did not cause an increase, but rather a decrease in the concentration of the endogenous soluble phenylalanine, suggesting an interference of oxoacid **3c** with phenylalanine biosynthesis. The number of potential sites of interference of oxoacid **3c** with phenylalanine biosynthesis was narrowed down by experiments in which oxoacid **3c** was applied simultaneously with the herbicidal compound glyphosate (*N*-[phosphonomethyl]-glycine), which is known to inhibit the shikimate pathway at the level of the enzyme 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, thereby causing the accumulation of large amounts of shikimate in planta. As oxoacid **3c** did not affect glyphosate-induced shikimate accumulation in buckwheat hypocotyls, we suspected one of the enzymes catalyzing a step between EPSP and phenylalanine as the target of oxoacid **3c**. As we had, for the first time, succeeded in the cloning and heterologous expression of the ultimate enzyme in phenylalanine biosynthesis, that is, arogenate dehydratase, from the higher plant *Arabidopsis thaliana*, we tested oxoacid **3c** as a potential inhibitor of this enzyme and found it to be strongly inhibitory (K_i=27 μM, mixed-type inhibition). Reduction of the 2-oxo group of oxoacid **3c** led to the loss of the inhibitory action on arogenate dehydratase. Thus, a presumably specific inhibitor of this poorly characterized plant enzyme has been uncovered and may serve as a lead in the identification of more potent compounds with possible herbicidal activity.

6. Experimental

6.1. Generalities

Details regarding standard operations and abbreviations can be found in previous publications from this laboratory.[42–44] ^{1}H, (^{1}H-decoupled) ^{13}C and ^{19}F NMR spectra were recorded at 400, 101 and 376 MHz, respectively, chemical shifts being given relative to tetramethylsilane and trichlorofluoromethane as the internal standards. The samples were dissolved in deuterochloroform or, if marked by an asterisk, in hexadeuteroacetone unless stated otherwise. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was applied. Whenever no molecular peak was observed under such conditions, chemical ionization ('c.i.') in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundant information, only the [^{35}Cl] and [^{79}Br] containing fragments, and not the [^{37}Cl] or [^{81}Br] isotopomers, are listed. For the pK_a measurements, an automatic titrator model PCA101 (Sirius Analytical Instruments Ltd, East Sussex, UK) was employed.

6.2. (2-Bromo-1-fluoroethyl)benzenes

6.2.1. (2-Bromo-1-fluoroethyl)benzene. At 0 °C, triethylamine tris(hydrofluoride) (46 mL, 45 g, 0.28 mol) was added dropwise over 30 min to a solution of styrene (28 mL, 25 g, 0.24 mol) and *N*-bromosuccinimide (50 g, 0.28 mol) in dichloromethane (0.15 L). The mixture was stirred for 15 h at 25 °C before being washed with water (3×50 mL), a saturated aqueous solution of sodium hydrogen carbonate (3×50 mL) and brine (2×50 mL). Distillation afforded a colorless oil; bp 69–72 °C/2 mm Hg; (Ref. 45: bp 53 °C/0.05 mm Hg); n_D^{20} 1.5433; d_4^{20} 1.473; yield: 39.5 g (81%). ^{1}H NMR: δ 7.5 (5H, m), 5.60 (1H, ddd, *J*=47.1, 7.8, 4.1 Hz), 3.66 (1H, ddd, *J*=15.3, 11.3, 7.8 Hz), 3.58 (1H, ddd, *J*=26.0, 11.3, 4.2 Hz). ^{13}C NMR: δ 137.1 (d, *J*=20 Hz), 129.2 (s), 128.7 (s), 125.7 (d, *J*=6 Hz), 92.7 (d, *J*=126 Hz), 34.3 (d, *J*=28 Hz). ^{19}F NMR: δ −175.0 (ddd, *J*=47.0, 26.0, 15.4 Hz). MS: 202 (3%, M^+), 127 (3%), 109 (100%), 89 (1%).

6.2.2. 1-(2-Bromo-1-fluoroethyl)-4-fluorobenzene. Analogously from 4-fluorostyrene (29 mL, 29 g, 0.24 mol); colorless oil; bp 70–72 °C/2 mm Hg; mp 11–13 °C; n_D^{20} 1.5223; d_4^{20} 1.552; yield: 44.0 g (83%). ^{1}H NMR: δ 7.33 (2H, dd, *J*=8.4, 5.7 Hz), 7.09 (2H, t, *J*=8.4 Hz), 5.60 (1H, ddd, *J*=46.5, 7.5, 4.5 Hz), 3.67 (1H, ddd, *J*=15.2, 11.3, 7.5 Hz), 3.58 (1H, ddd, *J*=24.2, 11.3, 4.5 Hz). ^{13}C NMR: δ 163.1 (d, *J*=248 Hz), 133.0 (dd, *J*=21, 3 Hz), 127.8 (t, *J*=7 Hz), 115.8 (d, *J*=22 Hz), 92.1 (d, *J*=178 Hz), 34.0 (d, *J*=29 Hz). ^{19}F NMR: δ −112.4 (symm. m), −172.2 (ddd, *J*=46.3, 24.2, 15.3 Hz). MS: 220 (10%, M^+), 201 (3%), 140 (9%), 127 (100%). Anal. Calcd for $C_8H_7BrF_2$ (221.04) C 43.47, H 3.19; found C 43.64, H 2.88%.

6.2.3. 1-(2-Bromo-1-fluoroethyl)-4-chlorobenzene. Analogously from 4-chlorostyrene (31 mL, 33 g, 0.24 mol); slightly yellow oil; bp 92–98 °C/2 mm Hg; mp 9–11 °C; n_D^{20} 1.5564; d_4^{20} 1.576; yield: 45.7 g (80%). ^{1}H NMR: δ 7.41 (2H, dm, *J*=7.3 Hz), 7.32 (2H, dm, *J*=7.3 Hz), 5.62 (1H, ddd, *J*=46.6, 7.3, 4.5 Hz), 3.68 (1H, ddd, *J*=16.2, 11.3, 7.3 Hz), 3.61 (1H, ddd, *J*=24.4, 11.3, 4.4 Hz). ^{13}C NMR: δ 135.5 (d, *J*=21 Hz), 135.1 (s), 128.9 (s), 127.1 (d, *J*=6 Hz), 91.9 (d, *J*=179 Hz), 33.9 (d, *J*=29 Hz). ^{19}F NMR: δ −174.5 (1 F, ddd, *J*=46.6, 23.8, 15.8 Hz). MS: 236 (42%, M^+), 219 (2%), 157 (3%), 143 (100%). Anal. Calcd for C_8H_7BrClF (237.50) C 40.46, H 2.97; found C 40.43, H 2.84%.

6.3. (1-Fluorovinyl)benzenes

6.3.1. 1-(Fluorovinyl)benzene. 1-(2-Bromo-1-fluoroethyl)-benzene (26 mL, 39 g, 0.19 mol) was added to a solution of potassium *tert*-butoxide (21 g, 0.19 mol) in tetrahydrofuran (80 mL). The mixture was stirred 2 h at 25 °C and filtered. The solvent was evaporated and the residue distilled; colorless liquid; bp 61–64 °C/40 mm Hg (Ref. 46: bp 45.0–45.4 °C/14 mm Hg); mp −29 to −27 °C; n_D^{20} 1.5223; d_4^{20} 1.026; yield: 18.9 g (81%). ^{1}H NMR: δ 7.6 (5H, m), 5.02 (1H, dd, *J*=49.8, 3.4 Hz), 4.84 (1H, dd, *J*=17.9, 3.4 Hz). ^{13}C NMR: δ 163.0 (d, *J*=250 Hz), 132.0 (d, *J*=29 Hz), 129.4 (s), 128.5 (s), 124.6 (d, *J*=7 Hz), 89.5 (d, *J*=26 Hz). ^{19}F NMR: δ −108.5 (1 F, dd, *J*=49.8, 17.8 Hz). MS: 122 (100%, M^+), 109 (50%), 96 (20%).

6.3.2. 1-Fluoro-4-(1-fluorovinyl)benzene. Analogously from 1-(2-bromo-1-fluoroethyl)-4-fluoro-benzene (27 mL, 42 g, 0.19 mol); colorless liquid; bp 144–146 °C; mp −30 to −28 °C; n_D^{20} 1.4976; d_4^{20} 1.126; yield: 21.3 g (80%). ^{1}H NMR: δ 7.52 (2H, dd, *J*=8.9, 5.2 Hz), 7.05 (2H, t, *J*=8.9 Hz), 4.95 (1H, dd, *J*=49.6, 3.6 Hz), 4.82 (1H, dd, *J*=17.9, 3.6 Hz). ^{13}C NMR: δ 163.4 (d, *J*=249 Hz), 162.2 (d, *J*=250 Hz), 128.53 (dd, *J*=30, 3 Hz), 126.6 (t, *J*=8 Hz), 115.6 (d, *J*=22 Hz), 89.3 (d, *J*=23 Hz). ^{19}F NMR: δ −107.5 (1F, dd, *J*=49.6, 17.9 Hz), −119.9 (1F, symm. m). MS: 140 (100%, M^+), 120 (17%), 114 (18%), 96 (11%). Anal. Calcd for $C_8H_6F_2$ (140.13) C 68.57, H 4.32; found C 68.60, H 4.40%.

6.3.3. 1-Chloro-4-(1-fluorovinyl)benzene. Analogously from 1-(2-chloro-1-fluoroethyl)-4-chloro-benzene (29 mL, 45 g, 0.19 mol); colorless liquid; bp 72–73 °C/12 mm Hg; mp −29 to −28 °C; n_D^{20} 1.5442; d_4^{20} 1.189; yield: 25.0 g (84%). ^{1}H NMR: δ 7.42 (2H, dm, *J*=8.7 Hz), 7.33 (2H, dm, *J*=8.7 Hz), 5.00 (1H, dd, *J*=49.4, 3.7 Hz), 4.86 (1H, dd, *J*=17.8 Hz, 3.7).^{13}C NMR: δ 162.0 (d, *J*=250 Hz), 135.3 (s), 130.5 (d, *J*=30 Hz), 128.7 (s), 125.9 (d, *J*=7 Hz), 90.1 (d, *J*=22 Hz). ^{19}F NMR: δ −108.6 (1F, dd, *J*=49.4 Hz, 17.6). MS: 156 (100%, M^+), 136 (2%), 121 (39%), 101 (28%), 91 (8%). Anal. Calcd for C_8H_6ClF (156.59) C 61.36, H 3.86; found C 61.49, H 3.99%.

6.4. (2-Bromo-1,1-difluoroethyl)benzenes

The (2-bromo-1,1-difluoroethyl)benzenes were made from (1-fluorovinyl)benzenes following exactly the same protocol as described for the preparation of (2-bromo-1-fluoroethyl)-benzenes from styrenes. Due to the chemical lability of 1-(2,bromo-1-fluoroethyl)-4-methoxy-benzene, the *p*-methoxy derivative **1d** was prepared on a different route (see below).

6.4.1. (2-Bromo-1,1-difluoroethyl)benzene (1a). From (1-fluorovinyl)benzene (18 mL, 18 g, 0.15 mol) using *N*-bromosuccinimide (32 g, 0.18 mol) and triethylamine tris(hydrofluoride) (49 mL, 48 g, 0.30 mol) in dichloromethane (0.12 L). Upon distillation a faintly yellow oil was collected; bp 55–56 °C/2 mm Hg (Ref. 1: bp 62–63 °C/5 mm Hg); mp −26 to −24 °C; n_D^{20} 1.5131; d_4^{20} 1.534; yield: 30.2 g (91%). ^{1}H NMR: δ 7.5 (5H, m), 3.75 (2H, t, *J*=13.9 Hz). ^{13}C NMR: δ 134.4 (t, *J*=26 Hz), 130.6 (s), 128.6 (s), 125.4 (t, *J*=6 Hz), 118.5 (t, *J*=244 Hz), 33.8 (t, *J*=35 Hz). ^{19}F NMR: δ −98.2 (2F, t, *J*=13.8 Hz). MS: 220 (45%, M^+), 169 (19%), 127 (100%), 109 (37%), 77 (25%).

6.4.2. 1-(2-Bromo-1,1-difluoroethyl)-4-fluorobenzene (1b). Analogously from 1-fluoro-4-(1-fluorovinyl)benzene (19 mL, 21 g, 0.15 mol); slightly yellow liquid; bp 82–84 °C/15 mm Hg; mp −5 to −3 °C; n_D^{20} 1.4943; d_4^{20} 1.602; yield: 27.9 g (78%). ^{1}H NMR: δ 7.50 (2H, dd, *J*=8.6, 5.1 Hz), 7.13 (2H, t, *J*=8.5 Hz), 3.74 (2H, t, *J*=13.5 Hz). ^{13}C NMR: δ 164.0 (d, *J*=251 Hz), 130.4 (td, *J*=27, 3 Hz), 127.7 (q, *J*=6 Hz), 118.4 (t, *J*=245 Hz), 115.8 (d, *J*=22 Hz), 33.6 (t, *J*=36 Hz). ^{19}F NMR: δ −96.9 (2F, t, *J*=13.4 Hz), −110.2 (1F, symm. m). MS: 238 (13%, M^+), 220 (2%), 145 (100%), 125 (2%), 109 (9%), 95 (4%). Anal. Calcd for $C_8H_6BrClF_2$ (255.49) C 40.20, H 2.53; found C 40.12, H 2.89%.

6.4.3. 1-(2-Bromo-1,1-difluoroethyl)-4-chlorobenzene (1c). Analogously from 1-chloro-4-(1-fluorovinyl)benzene (20 mL, 24 g, 0.15 mol); colorless liquid; bp 82–84 °C/2 mm Hg; mp −4 to −2 °C; n_D^{20} 1.5287; d_4^{20} 1.621; yield: 31.8 g (83%). ^{1}H NMR: δ 7.44 (4H, s), 3.74 (2H, t, *J*=13.5 Hz). ^{13}C NMR: δ 136.8 (s), 132.8 (t, *J*=26 Hz), 128.9 (s), 126.9 (t, *J*=6 Hz), 118.4 (t, *J*=245 Hz), 33.4 (t, *J*=35 Hz). ^{19}F NMR: δ −97.7 (2F, t, *J*=13.6 Hz). MS: 254 (34%, M^+), 237 (4%), 161 (100%), 125 (15%), 111 (9%). Anal. Calcd for $C_8H_6BrClF_2$ (255.49) C 37.61, H 2.37; found C 37.59, H 2.14%.

6.4.4. 1-(2-Bromo-1,1-difluoroethyl)-4-methoxybenzene (1d). A solution of 2-bromo-1-(4-methoxyphenyl)ethanone (80 g, 0.35 mol) and diethylaminosulfur trifluoride (46 mL, 56 g, 0.35 mol) in dichloromethane (0.35 L) was heated under reflux for 50 h. The mixture was cautiously poured onto ice (0.10 L) and the organic phase washed with a saturated aqueous solution of sodium hydrogen carbonate (3×0.10 L), water (2×0.10 L) and brine (0.10 L). Distillation in the presence of some potassium carbonate (0.1 g) gave a yellow oil; bp 92–94 °C/2 mm Hg; mp 15–17 °C; n_D^{20} 1.5253; d_4^{20} 1.516; yield: 33.2 g (38%). ^{1}H NMR: δ 7.42 (2H, d, *J*=7.7 Hz), 6.94 (2H, d, *J*=7.7 Hz), 3.73 (2H, t, *J*=13.8 Hz). ^{13}C NMR: δ 161.2 (s), 126.9 (t, *J*=6 Hz), 126.4 (t, *J*=27 Hz), 118.4 (t, *J*=244 Hz), 113.9 (s), 55.4 (s), 34.0 (t, *J*=36 Hz). ^{19}F NMR: δ −96.7 (2F, t, *J*=13.8 Hz). MS: 250 (75%, M^+), 233 (53%), 157 (100%), 135 (62%). Anal. Calcd for $C_9H_9BrF_2O$ (251.07) C 43.06, H 3.61; found C 43.11, H 3.63%.

6.5. 2-Aryl-2,2-difluoroethyl acetates

6.5.1. 2,2-Difluoro-2-phenylethyl acetate (6a). A mixture containing (2-bromo-1,1-difluoroethyl)benzene (**1a**; 17 mL, 27 g, 0.12 mol), anhydrous potassium acetate (47 g, 0.48 mol) and 1,4,7,10,13,16-hexaoxacyclooctadecane (3.2 g, 12 mmol) in anhydrous *N*,*N*-dimethylformamide (0.12 L) was heated to 150 °C for 15 h. The mixture was diluted with water (0.10 L) and extracted with diethyl ether (3×50 mL). The combined organic layers were evaporated and the product was isolated by distillation as a colorless liquid; bp 57–59 °C/1 mm Hg; mp −32 to −30 °C; n_D^{20} 1.4655; d_4^{20} 1.188; yield: 20.6 g (86%). ^{1}H NMR: δ 7.5 (5H, m), 4.50 (2H, t, *J*=13.3 Hz), 2.09 (3H, s). ^{13}C NMR: δ 169.9

(s), 134.1 (t, J=25 Hz), 130.5 (s), 128.6 (s), 125.4 (t, J=6 Hz), 119.2 (t, J=244 Hz), 65.1 (t, J=33 Hz), 20.5 (s). ^{19}F NMR: δ −105.0 (2F, t, J=13.4 Hz). MS: 200 (13%, M^+), 158 (2%), 140 (6%), 127 (100%), 109 (6%). Anal. Calcd for $C_{10}H_{10}F_2O_2$ (200.19) C 60.00, H 5.04; found C 59.89, H 4.93%.

6.5.2. 2,2-Difluoro-2-(4-fluorophenyl)ethyl acetate (6b). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-fluorobenzene (**1b**; 18 mL, 29 g, 0.12 mol); colorless liquid; bp 40–42 °C/0.5 mm Hg; mp 8–9 °C; n_D^{20} 1.4529; d_4^{20} 1.260; yield: 21.2 g (81%). ^{1}H NMR: δ 7.51 (2H, dd, J=8.8, 5.1 Hz), 7.13 (2H, t, J=8.8 Hz), 4.47 (2H, t, J=13.1 Hz), 2.07 (3H, s). ^{13}C NMR: δ 169.8 (s), 164.0 (d, J=250 Hz), 130.2 (td, J=26, 3 Hz), 127.8 (q, J=7 Hz), 119.0 (t, J=244 Hz), 115.8 (d, J=22 Hz), 65.0 (t, J=34 Hz), 20.5 (s). ^{19}F NMR: δ −103.8 (2F, t, J=13.0 Hz), −110.4 (1F, symm. m). MS: 218 (28%, M^+), 215 (7%), 199 (5%), 158 (16%), 145 (100%), 109 (8%). Anal. Calcd for $C_{10}H_9F_3O_2$ (218.17) C 55.05, H 4.16; found C 55.37, H 3.91%.

6.5.3. 2-(4-Chlorophenyl)-2,2-difluoroethyl acetate (6c). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-chlorobenzene (**1c**; 19 mL, 31 g, 0.12 mol); colorless liquid; bp 90–92 °C/2 mm Hg; mp −7 to −5 °C; n_D^{20} 1.4851; d_4^{20} 1.298; yield: 22.1 g (78%). ^{1}H NMR: δ 7.42 (4H, symm. m), 4.47 (2H, t, J=13.0 Hz), 2.08 (3H, s). ^{13}C NMR: δ 169.6 (s), 136.7 (s), 132.6 (t, J=26 Hz), 128.8 (s), 127.0 (t, J=6 Hz), 118.9 (t, J=244 Hz), 64.8 (t, J=34 Hz), 20.3 (s). ^{19}F NMR: δ −104.7 (2F, t, J=13.0 Hz). MS: 234 (100%, M^+), 215 (7%), 174 (7%), 161 (70%), 125 (14%), 111 (7%). Anal. Calcd for $C_{10}H_9ClF_2O_2$ (234.63) C 51.19, H 3.87; found C 51.13, H 3.97%.

6.5.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethyl acetate (6d). Analogously from 1-(2-bromo-1,1-difluoroethyl)-4-methoxybenzene (**1d**, 20 mL, 30 g, 0.12 mol); bp 102–104 °C/1 mm Hg; mp 11–13 °C; n_D^{20} 1.4914, d_4^{20} 1.226; yield: 22.3 g (81%). ^{1}H NMR: δ 7.43 (2H, d, J=7.7 Hz), 6.94 (2H, d, J=7.7 Hz), 4.46 (2H, t, J=13.2 Hz), 3.82 (3H, s), 2.08 (3H, s). ^{13}C NMR: δ 169.6 (s), 161.2 (s), 127.0 (t, J=6 Hz), 126.2 (t, J=26 Hz), 119.4 (t, J=244 Hz), 113.9 (s), 65.1 (t, J=34 Hz), 55.3 (s), 20.5 (s). ^{19}F NMR: δ −103.3 (2F, t, J=13.2 Hz). MS: 230 (83%, M^+), 211 (17%), 157 (100%), 114 (38%). Anal. Calcd for $C_{11}H_{12}F_2O_3$ (230.21) C 57.39, H 5.25; found C 57.35, H 5.30%.

6.6. 2-Aryl-2,2-difluoroethanol

6.6.1. 2,2-Difluoro-2-phenylethanol (7a). A solution of 2,2-difluoro-2-phenylethyl acetate (**6a**; 15 mL, 28 g, 90 mmol) and sodium hydroxide (7.2 g, 0.18 mol) in 80% aqueous ethanol (0.10 L) was left for 2 h at 25 °C. The mixture was diluted with water and the product extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (3×50 mL) and evaporated. The product was isolated by distillation; colorless liquid; bp 69–72 °C/2 mm Hg; mp 19–21 °C; n_D^{20} 1.4890; d_4^{20} 1.232; yield: 13.8 g (97%). ^{1}H NMR: δ 7.5 (5H, m), 3.98 (2H, t, J=13.6 Hz), 2.68 (1H, broad s). ^{13}C NMR: δ 134.5 (t, J=26 Hz), 130.3 (s), 128.5 (s), 125.5 (t, J=6 Hz), 120.7 (t, J=244 Hz), 65.7 (t, J=32 Hz). ^{19}F NMR: δ −107.9 (t, J=13.6 Hz). MS: 158 (7%, M^+), 127 (100%), 109 (2%), 91 (10%), 77 (28%). Anal. Calcd for $C_8H_8F_2O$ (158.15) C 60.76, H 5.10; found C 60.61, H 5.11%.

6.6.2. 2,2-Difluoro-2-(4-fluorophenyl)ethanol (7b). Analogously from 2,2-difluoro-2-(4-fluorophenyl)ethyl acetate (**6b**; 16 mL, 20 g, 90 mmol); the product was purified by crystallization rather than distillation; colorless needles (from diethyl ether and hexanes); mp 41–42 °C; yield: 14.7 g (93%). ^{1}H NMR: δ 7.50 (2H, dd, J=8.8, 5.4 Hz), 7.12 (2H, t, J=8.8 Hz), 3.93 (2H, t, J=13.3 Hz), 2.40 (1H, broad s). ^{13}C NMR: δ 163.9 (d, J=250 Hz), 130.5 (t, J=25 Hz), 127.8 (q, J=7 Hz), 120.3 (t, J=244 Hz), 115.7 (d, J=22 Hz), 65.9 (t, J=33 Hz). ^{19}F NMR: δ −106.5 (2F, t, J=13.0 Hz), −110.9 (1F, symm. m). MS: 176 (9%, M^+), 157 (1%), 145 (100%), 125 (4%), 109 (7%), 95 (6%). Anal. Calcd for $C_8H_7F_3O$ (176.14) C 54.55, H 4.01; found C 54.42, H 3.87%.

6.6.3. 2-(4-Chlorophenyl)-2,2-difluoroethanol (7c). Analogously from 2-(4-chlorophenyl)-2,2-di-fluoroethyl acetate (**6c**; 16 mL, 21 g, 90 mmol); colorless needles (from chloroform and hexanes); mp 38–39 °C; yield: 16.2 g (94%). ^{1}H NMR: δ 7.42 (4H, symm. m), 3.92 (2H, t, J=13.4 Hz), 2.48 (1H, broad s). ^{13}C NMR: δ 136.5 (s), 132.9 (t, J=26 Hz), 128.9 (s), 127.1 (t, J=6 Hz), 120.3 (t, J=244 Hz), 65.7 (t, J=33 Hz). ^{19}F NMR: δ −107.5 (t, J=13.4 Hz). MS: 192 (45%, M^+), 161 (100%), 125 (21%), 111 (10%). Anal. Calcd for $C_8H_7ClF_2O$ (192.59) C 49.89, H 3.66; found C 49.60, H 3.90%.

6.6.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethanol (7d). Analogously from 2,2-difluoro-2-(4-methoxyphenyl)ethyl acetate (**6d**; 17 mL, 21 g, 90 mmol); colorless needles (from diethyl ether and hexanes); mp 57–58 °C; bp 122–125 °C/4 mm Hg; yield: 16.1 g (95%). H NMR: δ 7.44 (2H, d, J=7.7 Hz), 6.95 (2H, d, J=7.7 Hz), 3.94 (2H, td, J=13.4, 6.5 Hz), 3.83 (3H, s), 2.09 (1H, broad t, J=6.1 Hz). ^{13}C NMR: δ 161.0 (s), 127.0 (t, J=6 Hz), 126.6 (t, J=26 Hz), 120.8 (t, J=243 Hz), 113.9 (s), 66.0 (t, J=33 Hz), 55.4 (s). ^{19}F NMR: δ −106.1 (2F, t, J=13.4 Hz). MS: 188 (21%, M^+), 169 (1%), 157 (100%), 142 (4%), 114 (16%). Anal. Calcd for $C_9H_{10}F_2O_2$ (188.18) C 57.45, H 5.36; found C 57.96, H 5.32%.

6.7. 2-Aryl-2,2-difluoroacetaldehydes

6.7.1. 2,2-Difluoro-2-phenylethanal (2a). At −75 °C, anhydrous dimethyl sulfoxide (13 mL, 14 g, 0.18 mol) was added to a solution of oxalyl chloride (7.6 mL, 11 g, 88 mmol) in dichloromethane (0.30 L). The mixture was kept at −60 °C for 30 min, before 2,2-difluoro-2-phenylethanol (**7a**; 10 mL, 13 g, 80 mmol) in dichloromethane (0.10 mL) was added, then stirred vigorously at −60 °C for 30 min, before triethylamine was added (50 mL, 36 g, 0.36 mol). After having waited 6 h at 25 °C, the mixture was washed with water (5×0.10 L), dried and evaporated. The residue cannot be stored for a longer period of time, undergoing polymerization or decomposition; yellow oil; bp 60–64 °C/5 mm Hg (Ref. 1: bp 66–69 °C/5 mm Hg); yield: 12.4 g (99%). ^{1}H NMR: δ 9.55 (1H, t, J=3.2 Hz), 7.4 (5H, m). ^{19}F NMR: δ −111.7 (2F, t, J=3.1 Hz), −113.0 (2F, t, J=5.5 Hz).

6.7.2. 2,2-Difluoro-2-(4-fluorophenyl)ethanal (2b). Analogously from 2,2-difluoro-2-(4-fluoro-phenyl)ethanol (**7b**; 14 g, 80 mmol); yellowish oil; bp 49–54 °C/1 mm Hg; n_D^{20} 1.4668; d_4^{20} 1.276; unstable compound; yield: 23.8 g (99%). ^{1}H NMR: δ 7.56 (2H, dd, *J*=8.6, 5.1 Hz), 7.17 (2H, t, *J*=8.5 Hz), 4.79 (1H, t, *J*=8.4 Hz), 3.67 (1H, broad s). ^{13}C NMR: δ 165.5 (d, *J*=252 Hz), 128.5 (q, *J*=7 Hz), 127.1 (t, *J*=26 Hz), 117.7 (t, *J*=251 Hz), 116.0 (t, *J*=22 Hz), 115.2 (s), 65.7 (t, *J*=38 Hz). ^{19}F NMR: δ −104.7 (1F, dd, *J*=253.5, 7.5 Hz), −106.4 (1F, dd, *J*=253.5, 8.5 Hz), −108.8 (1F, symm. m). MS: 201 (1%, M^+), 155 (1%), 145 (100%), 127 (3%), 95 (4%). Anal. Calcd for $C_8H_5F_3O$ (174.12) C 55.19, H 2.89; found C 55.87, H 3.09%.

6.7.3. 2-(4-Chlorophenyl)-2,2-difluoroethanal (2c). Analogously from 2-(4-chlorophenyl)-2,2-difluoroethanol (**7c**; 15 g, 80 mmol); yellow oil; bp 49–51 °C/1 mm Hg; n_D^{20} 1.4995; yield: 15.0 (99%). ^{1}H NMR: δ 9.56 (1H, t, *J*=2.7 Hz), 7.44 (4H, s). ^{13}C NMR: δ 188.0 (t, *J*=40 Hz), 137.9 (s), 129.4 (s), 128.6 (t, *J*=25 Hz), 127.4 (t, *J*=6 Hz), 114.3 (t, *J*=251 Hz). ^{19}F NMR: δ −110.8 (2F, t, *J*=2.7 Hz). MS: 190 (8%, M^+), 171 (2%), 161 (100%), 143 (5%), 125 (13%), 111 (10%). Anal. Calcd for $C_8H_5ClF_2O$ (190.58) C 50.42, H 2.64; found C 50.02, H 2.92%.

6.7.4. 2,2-Difluoro-2-(4-methoxyphenyl)ethanal (2d). A solution containing 2,2-difluoro-2-(4-methoxyphenyl)-ethanol (**7d**; 15 g, 80 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[13,14] ('Dess–Martin reagent'; 34 g, 80 mmol) in dichloromethane (0.16 L) was kept at 25 °C for 4 h. The suspension formed was diluted with diethyl ether (0.60 L) before being slowly poured into a saturated solution of sodium hydrogen carbonate (0.60 L) in which beforehand sodium thiosulfate pentahydrate (40 g, 0.16 mol) had been dissolved. After 15 min of vigorous stirring, the organic phase was collected and the aqueous one extracted with diethyl ether (3×0.10 L). The combined organic layers were dried and evaporated. Distillation of the residue provided an unstable colorless oil; bp 49–51 °C/1 mm Hg; n_D^{20} 1.4995; d_4^{20} 1.280; yield: 11.0 g (74%). ^{1}H NMR: δ 9.52 (1H, t, *J*=3.4 Hz), 7.45 (2H, d, *J*=8.7 Hz), 6.97 (2H, d, *J*=8.7 Hz), 3.82 (3H, s). ^{13}C NMR: δ 188.2 (t, *J*=41 Hz), 162.0 (s), 127.6 (t, *J*=6 Hz), 122.0 (t, *J*=26 Hz), 115.0 (t, *J*=251 Hz), 114.5 (s), 55.4 (s). ^{19}F NMR: δ −110.6 (2F, s). MS (c.i.): 204 (5%, M^++NH_4), 186 (29%, M^+), 167 (53%), 157 (100%), 114 (62%). Anal. Calcd for $C_9H_8ClF_2O_2$ (186.16) C 58.07, H 4.33; found C 58.07, H 4.24%.

6.8. Cyanhydrines

6.8.1. 3,3-Difluoro-2-hydroxy-3-phenylpropionitrile (8a). 2,2-Difluoro-2-phenylethanal (**2a**; 9.4 g, 60 mmol) was added to a solution of sodium metabisulfite (11 g, 60 mmol) in water. The mixture was vigorously stirred for 2 h at 25 °C and, after the addition of a solution of sodium cyanide (5.9 g, 0.12 mol) in water (25 mL), again for 1 h. The mixture was extracted with diethyl ether (3×50 mL). The product was absorbed on silica gel (30 mL) and eluted from a column filled with more silica (0.35 L) with a 1:4 (v/v) mixture of diethyl ether and hexanes to afford a yellowish oil, bp 99–100 °C/1 mm Hg (Ref. 47: bp 109–110 °C/1.3 mm Hg); n_D^{20} 1.4875; d_4^{20} 1.312; yield: 7.82 g (71%). ^{1}H NMR: δ 7.5 (5H, m), 4.81 (1H, dd, *J*=9.6, 8.0 Hz), 3.87 (1H, broad s). ^{13}C NMR: δ 131.4 (s), 131.2 (t, *J*=25 Hz), 128.7 (s), 126.1 (t, *J*=6 Hz), 118.0 (t, *J*=251 Hz), 115.2 (s), 65.6 (t, *J*=37 Hz). ^{19}F NMR: δ −105.7 (1F, dd, *J*=252.2, 7.8 Hz), −107.7 (1F, dd, *J*=252.2, 9.6 Hz). MS: 183 (1%, M^+), 127 (100%), 109 (5%), 77 (18%). Anal. Calcd for $C_9H_7F_2NO$ (183.16) C 59.02, H 3.85; found C 58.96, H 4.00%.

6.8.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-hydroxypropionitrile (8b). Analogously from 2,2-difluoro-2-(4-fluorophenyl)ethanal (**2b**; 10.4 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.4769; d_4^{20} 1.388; yield: 7.51 g (62%). ^{1}H NMR: δ 7.56 (2H, dd, *J*=8.6, 5.1 Hz), 7.17 (2H, t, *J*=8.5 Hz), 4.79 (1H, t, *J*=8.4 Hz), 3.67 (1H, broad s). ^{13}C NMR: δ 165.5 (d, *J*=252 Hz), 128.5 (q, *J*=7 Hz), 127.1 (t, *J*=26 Hz), 117.7 (t, *J*=251 Hz), 116.0 (t, *J*=22 Hz), 115.2 (s), 65.7 (t, *J*=38 Hz). ^{19}F NMR: δ −104.7 (1F, dd, *J*=253.5, 7.5 Hz), −106.4 (1F, dd, *J*=253.5, 8.5 Hz), −108.8 (1F, symm. m). MS: 201 (1%, M^+), 155 (1%), 145 (100%), 127 (3%), 95 (4%). Anal. Calcd for $C_9H_6F_3NO$ (201.15) C 53.74, H 3.01; found C 53.76, H 2.94%.

6.8.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-hydroxypropionitrile (8c). Analogously from 2-(4-chlorophenyl)-2,2-difluoroethanal (**2c**; 11.4 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.5055, d_4^{20} 1.595; yield: 8.55 g (69%). ^{1}H NMR: δ 7.49 (4H, symm. m), 4.79 (1H, dd, *J*=8.9, 7.9 Hz), 3.70 (1H, broad s). ^{13}C NMR: δ 137.8 (s), 129.5 (t, *J*=25 Hz), 129.1 (s), 127.7 (t, *J*=6 Hz), 117.6 (t, *J*=251 Hz), 114.8 (s), 65.5 (t, *J*=37 Hz). ^{19}F NMR: δ −105.4 (1F, dd, *J*=253.8, 7.6 Hz), −107.4 (1F, dd, *J*=253.8, 9.0 Hz). MS: 217 (1%, M^+), 190 (2%), 161 (100%), 143 (5%), 125 (10%), 111 (6%). Anal. Calcd for $C_9H_6ClF_2NO$ (206.62) C 49.68, H 2.78; found C 49.40, H 3.09%.

6.8.4. 3,3-Difluoro-2-hydroxy-3-(4-methoxyphenyl)propionitrile (8d). Analogously from 2,2-difluoro-2-(4-methoxyphenyl)ethanal (**2d**; 11.2 g, 60 mmol); yellow oil; bp 99–102 °C/2 mm Hg; n_D^{20} 1.5043, d_4^{20} 1.272; yield: 9.46 g (74%). ^{1}H NMR: δ 7.48 (2H, d, *J*=8.6 Hz), 6.97 (2H, d, *J*=8.6 Hz), 4.76 (1H, t, *J*=8.3 Hz), 3.83 (3H, s), 4.7 (1H, broad m). ^{13}C NMR: δ 161.8 (s), 127.7 (t, *J*=6 Hz), 123.1 (t, *J*=25 Hz), 118.2 (t, *J*=250 Hz), 115.2 (s,), 114.2 (s), 65.9 (t, *J*=38 Hz), 55.5 (s). ^{19}F NMR: δ −104.8 (1F, dd, *J*=250.4, 8.6 Hz), −105.9 (1F, dm, *J*=250 Hz). MS (c.i.): 231 (4%, M^++NH_4), 213 (6%, M^+), 186 (6%), 164 (100%), 157 (47%). Anal. Calcd for $C_{10}H_9F_2NO_2$ (213.19) C 56.32, H 4.26; found C 56.31, H 4.27%.

6.9. Ethyl 3-aryl-3,3-difluoro-2-hydroxypropionates

6.9.1. Ethyl 3,3-difluoro-2-hydroxy-3-phenylpropionate (9a). Gaseous hydrogen chloride was slowly bubbled into a mixture of 3,3-difluoro-2-hydroxy-3-phenylpropionitrile (**8a**; 6.4 g, 35 mmol) and ethanol (4.1 mL, 3.2 g, 70 mmol), whereupon a precipitate formed. After 4 h at 25 °C, water (20 mL) was added and the suspension was stirred until it became clear. The product was extracted with diethyl ether (4×25 mL) and, after washing (2×25 mL of brine), drying and evaporation of the combined organic

layers, crystallized from diethyl ether and hexanes; colorless needles; mp 59–60 °C (Ref. 47: mp 59–60 °C); yield: 6.76 g (84%). ^{1}H NMR: δ 7.5 (5H, m), 4.56 (1H, dt, J=12.8, 7.8 Hz), 4.28 (2H, q, J=7.2 Hz), 3.29 (1H, broad d, J=8.2 Hz), 1.27 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.5 (s), 133.5 (t, J=25 Hz), 130.5 (s), 128.3 (s), 125.8 (t, J=6 Hz), 119.3 (t, J=251 Hz), 73.7 (t, J=33 Hz), 62.8 (s), 13.9 (s). ^{19}F NMR: δ −104.0 (1F, dd, J=252.8, 7.6 Hz), −108.3 (1F, dd, J=252.8, 13.0 Hz). MS: 230 (3%, M^+), 210 (1%), 149 (3%), 127 (100%), 109 (15%), 91 (12%), 77 (18%).

6.9.2. Ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionate (9b). Analogously from 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionitrile (**8b**; 7.0 g, 35 mmol); colorless needles; mp 43–44 °C; yield: 7.12 g (82%). ^{1}H NMR: δ 7.49 (2H, dd, J=8.7, 5.2 Hz), 7.11 (2H, t, J=8.6 Hz), 4.51 (1H, dt, J=13.1, 7.5 Hz), 4.27 (2H, q, J=7.1 Hz), 3.37 (1H, broad d, J=7.9 Hz), 1.27 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 169.4 (s), 164.0 (d, J=250 Hz), 129.5 (t, J=25 Hz), 128.1 (q, J=7 Hz), 118.9 (t, J=251 Hz), 115.5 (d, J=22 Hz), 73.6 (t, J=33 Hz), 63.0 (s), 14.0 (s). ^{19}F NMR: δ −102.5 (1F, dd, J=253.5, 7.1 Hz), −107.3 (1F, dd, J=253.4, 13.1 Hz), −110.6 (1F, symm. m). MS: 248 (2%, M^+), 145 (100%), 127 (26%), 107 (4%). Anal. Calcd for $C_{11}H_{11}F_3O_3$ (248.20) C 53.23, H 4.47; found C 53.36, H 4.89%.

6.9.3. Ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionate (9c). Analogously from 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionitrile (**8c**; 7.2 g, 35 mmol); colorless needles; mp 45–46 °C; yield: 7.14 g (77%). ^{1}H NMR: δ 7.44 (4H, symm. m), 4.51 (1H, dt, J=13.4, 6.8 Hz), 4.29 (2H, q, J=7.1 Hz), 3.75 (1H, broad d, J=6.9 Hz), 1.28 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 169.4 (s), 136.9 (s), 132.1 (t, J=26 Hz), 128.7 (s), 127.5 (t, J=6 Hz), 118.9 (t, J=251 Hz), 73.5 (t, J=33 Hz), 63.0 (s), 14.0 (s). ^{19}F NMR: δ −103.1 (1F, dd, J=253.8 Hz, 6.8), −108.4 (1F, dd, J=253.8 Hz, 13.4). MS: 264 (5%, M^+), 244 (1%), 161 (100%), 143 (10%), 125 (4%), 111 (3%). Anal. Calcd for $C_{11}H_{11}ClF_2O_3$ (264.66) C 49.92, H 4.19; found C 49.81, H 4.30%.

6.9.4. Ethyl 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionate (9d). Analogously from 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionitrile (**8d**; 7.5 g, 35 mmol); colorless needles; mp 54–55 °C; yield: 7.93 g (87%). ^{1}H NMR: δ 7.42 (2H, d, J=8.8 Hz), 6.93 (2H, d, J=8.8 Hz), 4.51 (1H, dt, J=12.6 Hz, 7.4), 4.27 (2H, q, J=7.2 Hz), 3.83 (3H, s), 3.25 (1H, broad d, J=8.0 Hz), 1.27 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.6 (s), 161.1 (s), 127.4 (t, J=6 Hz), 125.6 (t, J=26 Hz), 119.3 (t, J=251 Hz), 113.7 (s), 73.8 (t, J=33 Hz), 62.8 (s), 55.3 (s), 14.0 (s). ^{19}F NMR: δ −102.0 (1F, dd, J=251.5, 7.1 Hz), −106.8 (1F, dd, J=251.5, 12.6 Hz). MS (c.i.): 278 (100%, M^++NH_4), 260 (12%, M^+), 238 (100%), 157 (75%), 114 (8%). Anal. Calcd for $C_{12}H_{14}F_2O_4$ (260.24) C 55.39, H 5.42; found C 55.49, H 5.36%.

6.10. Ethyl 3-aryl-3,3-difluoro-2-oxopropionates

6.10.1. Ethyl 3,3-difluoro-2-oxo-3-phenylpropionate (10a) hydrate. Ethyl 3,3-difluoro-2-hydroxy-3-phenylpropionate (**9a**; 5.8 g, 25 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[13,14] (16 g, 38 mmol) were conjointly dissolved in dichloromethane (0.12 L) and kept at 25 °C for 5 h. After dilution with diethyl ether (0.30 L), the mixture was slowly poured into a concentrated aqueous solution of sodium hydrogen carbonate (0.30 L), which also contained sodium thiosulfate pentahydrate (19 g, 75 mmol). After 15 min of vigorous stirring, the organic phase was collected and the aqueous one extracted with diethyl ether (3×0.10 L). The combined organic layers were evaporated and the residue absorbed on silica gel (30 mL). The product was eluted from a column filled with more silica (0.32 L) using a 1:1 (v/v) mixture of diethyl ether and hexanes. The product was recrystallized from the same mixture; colorless needles; mp 48–50 °C (Ref. 47 mp 55–56 °C); yield: 5.85 g (95%). ^{1}H NMR: δ 7.6 (2H, m), 7.5 (3H, m), 4.37 (2H, q, J=7.2 Hz), 1.37 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 168.9 (s), 131.6 (t, J=25 Hz), 130.7 (s), 128.0 (s), 127.2 (t, J=6 Hz), 118.6 (t, J=254 Hz), 93.0 (t, J=34 Hz), 64.0 (s), 13.9 (s). ^{19}F NMR: δ −110.2 (2F, s). MS: 228 (2%, M^+), 200 (1%), 127 (100%), 109 (6%), 91 (1%), 77 (6%).

6.10.2. Ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionate (10b) hydrate. Analogously from ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-hydroxypropionate (**9b**; 6.2 g, 25 mmol); colorless needles; mp 44–45 °C; yield: 6.47 g (98%). ^{1}H NMR: δ 7.57 (2H, dd, J=8.8, 5.2 Hz), 7.09 (2H, t, J=8.6 Hz), 4.37 (2H, s), 4.34 (2H, q, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz). ^{13}C NMR: δ 168.9 (s), 164.2 (d, J=250 Hz), 129.5 (q, J=7 Hz), 127.8 (t, J=26 Hz), 118.4 (t, J=253 Hz), 115.1 (d, J=22 Hz), 93.0 (t, J=35 Hz), 64.1 (s), 13.9 (s). ^{19}F NMR: δ −109.3 (2F, s), −110.4 (1F, symm. m). MS: 246 (2%, M^+), 218 (3%), 171 (7%), 145 (100%), 125 (11%), 95 (22%). Anal. Calcd for $C_{11}H_{11}F_3O_4$ (264.20) C 50.01, H 4.20; found C 50.24, H 4.31%.

6.10.3. Ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionate (10c) hydrate. Analogously from ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-hydroxypropionate (**9c**; 6.6 g, 25 mmol); colorless needles; mp 65–67 °C; yield: 6.26 g (89%). ^{1}H NMR: δ 7.53 (2H, d, J=7.7 Hz), 7.40 (2H, d, J=7.7 Hz), 4.39 (2H, q, J=7.2 Hz), 4.12 (2H, broad m), 1.37 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 168.8 (s), 136.9 (s), 130.2 (t, J=26 Hz), 128.7 (t, J=6 Hz), 128.2 (s), 118.2 (t, J=253 Hz), 92.8 (t, J=33 Hz), 64.1 (s), 13.8 (s). ^{19}F NMR: δ −110.0 (2F, s). MS: 262 (5%, M^+), 234 (4%), 161 (100%), 143 (4%), 125 (8%), 111 (6%). Anal. Calcd for $C_{11}H_{11}ClF_2O_4$ (280.66) C 47.08, H 3.95; found C 47.13, H 4.16%.

6.10.4. Ethyl 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)-propionate (10d) hydrate. Analogously from ethyl 3,3-difluoro-2-hydroxy-3-(4-methoxyphenyl)propionate (**9d**; 6.5 g, 25 mmol); colorless needles; mp 69–70 °C; yield: 6.38 g (92%). ^{1}H NMR: δ 7.50 (2H, d, J=8.9 Hz), 6.91 (2H, d, J=8.9 Hz), 4.34 (2H, q, J=7.2 Hz), 4.25 (2H, s), 3.80 (3H, s), 1.34 (3H, t, J=7.2 Hz). ^{13}C NMR: δ 169.1 (s), 161.3 (s), 128.7 (t, J=6 Hz), 123.8 (t, J=26 Hz), 118.8 (t, J=253 Hz), 113.4 (s), 93.1 (t, J=35 Hz), 64.0 (s), 55.3 (s), 13.9 (s). ^{19}F NMR: δ −109.1 (2F, s). MS (c.i.): 276 (32%, M^++NH_4), 258 (8%, M^+), 239 (72%), 157 (100%), 114 (23%). Anal. Calcd for $C_{11}H_{11}ClF_2O_4$ (280.66) C 52.18, H 5.11; found C 52.20, H 5.10%.

6.11. 3-Aryl-3,3-difluoro-2-oxopropionic acids

Upon heating or even simple storage, these compounds may loose partially or completely hydrate water. Thus melting ranges and analytical data may be a bit fortuitous.

6.11.1. 3,3-Difluoro-2-oxo-3-phenylpropionic acid (3a) hydrate. Ethyl 3,3-difluoro-2-oxo-3-phenylpropionate (**10a**; 4.92 g, 20 mmol) and sodium hydrogen carbonate (5.0 g, 60 mmol) in 50% aqueous isopropanol (40 mL) were heated to 50 °C for 24 h. The solvents were evaporated. The residue was taken up in water (10 mL), washed with diethyl ether and acidified with 1.0 M hydrochloric acid (50 mL), which had beforehand been saturated with sodium chloride. The product was extracted with diethyl ether (3×50 mL) and, after drying and evaporation of the solvent, crystallized from a mixture of ethyl acetate and hexanes; colorless needles; mp 116–118 °C (Ref. 47: mp 90–91 °C); yield: 4.09 g (94%). ^{1}H NMR*: δ 7.62 (2H, dm, J=7.8 Hz), 7.5 (3H, m). ^{13}C NMR*: δ 170.1 (s), 133.4 (t, J=25 Hz), 129.9 (s), 127.4 (s), 127.3 (t, J=7 Hz), 119.3 (t, J=252 Hz), 93.1 (t, J=34 Hz). ^{19}F NMR*: δ −107.9 (2F, s). MS: 199 (2%, M^+), 127 (100%), 109 (5%), 91 (2%).

6.11.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-oxopropionic acid (3b) hydrate. Analogously from ethyl 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionate (**10b**; 5.3 g, 20 mmol); colorless needles; mp 135–137 °C; yield: 4.52 g (96%). ^{1}H NMR*: δ 7.68 (2H, dd, J=9.0, 5.4 Hz), 7.21 (2H, t, J=9.0 Hz), 6.23 (2H, broad s). ^{13}C NMR*: δ 170.7 (s), 164.7 (d, J=247 Hz), 130.7 (q, J=7 Hz), 130.1 (t, J=26 Hz), 119.9 (t, J=252 Hz), 115.3 (d, J=22 Hz), 94.0 (t, J=34 Hz). ^{19}F NMR*: δ −107.4 (2F, s), −111.9 (1F, symm. m). MS: 218 (1%, M^+), 199 (2%), 145 (100%), 125 (20%), 95 (31%). Anal. Calcd for $C_9H_7F_3O_4$ (236.14) C 45.78, H 2.99; found C 45.82, H 3.20%.

6.11.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-oxopropionic acid (3c) hydrate. Analogously from ethyl 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionate (**10c**; 5.6 g, 20 mmol); colorless needles; mp 156–158 °C (hydrate); mp 167–169 °C (without hydrate water); yield: 4.40 g (87%). ^{1}H NMR*: δ 7.63 (2H, d, J=8.4 Hz), 7.48 (2H, d, J=8.4 Hz), 6.22 (2H, s). ^{13}C NMR*: δ 170.5 (s), 136.5 (s), 132.9 (t, J=26 Hz), 130.0 (t, J=6 Hz), 128.5 (s), 119.8 (t, J=252 Hz), 93.8 (t, J=33 Hz). ^{19}F NMR*: δ −108.2 (2F, s). MS: 234 (1%, M^+), 189 (1%), 161 (100%), 143 (3%), 125 (9%), 111 (6%). Anal. Calcd for $C_9H_7ClF_2O_4$ (252.60) C 42.80, H 2.79; found C 42.92, H 2.73%.

6.11.4. 3,3-Difluoro-2-oxo-3-(4-methoxyphenyl)propionic acid (3d) hydrate. Analogously from ethyl 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)propionate (**10d**; 5.5 g, 20 mmol); colorless needles; mp 122–124 °C; yield: 4.52 g (91%). ^{1}H NMR*: δ 7.54 (2H, d, J=9.0 Hz), 6.97 (2H, d, J=9.0 Hz), 6.09 (2H, broad s), 3.83 (3H, s). ^{13}C NMR*: δ 170.9 (s), 162.0 (s), 129.8 (t, J=6 Hz), 126.2 (t, J=26 Hz), 120.3 (t, J=252 Hz), 113.7 (s), 94.1 (t, J=34 Hz), 55.6 (s). ^{19}F NMR*: δ −106.9 (2F, s). MS: 230 (12%, M^+), 211 (10%), 186 (7%), 157 (100%), 139 (43%). Anal. Calcd for $C_{10}H_{10}F_2O_5$ (248.19) C 48.40, H 4.06; found C 48.60, H 4.16%.

6.12. 3-Aryl-3,3-difluoroalanines

6.12.1. 2-Amino-3,3-difluoro-3-phenylpropionic acid (4a). 3,3-Difluoro-2-oxo-3-phenylpropionic acid (**3a**; 2.2 g, 10 mmol) was dissolved in a 25% aqueous solution of ammonia (20 mL) placed in a pressure-resistant vessel, which was hermetically closed. After heating to 60 °C for 5 h, sodium borohydride (1.1 g, 30 mmol) was added to the mixture through which a gentle current of nitrogen was bubbled for 30 min at 25 °C. At 0 °C, the mixture was acidified with 37% hydrochloric acid (5.0 mL) before being poured into a column filled with an ion exchange resin (Dowex 50W-X8, acid form, 50–100 mesh, 110 mL) and which was eluted consecutively with 50% aqueous isopropanol (0.50 L) and neat water (0.50 L). These eluents were combined and evaporated. The residue was suspended in a 2.0 M aqueous solution of sodium hydroxide (50 mL) and washed with diethyl ether (3×25 mL). The aqueous phase was acidified with 5.0 M hydrochloric acid which was beforehand saturated with sodium chloride. Extraction with diethyl ether (3×25 mL) and evaporation of the dried organic phases left a residue behind, the crystallization of which provided the 3,3-difluoro-2-hydroxy-3-phenylpropionic acid **11a** as described below (Section 6.13). Finally the ion exchange column was eluted with a 1.0 M aqueous solution of ammonia. Evaporation of the solvents afforded the aminoacid **4a**; colorless needles crystallized as the chlorhydrate from hydrogen chloride-containing ethanol; mp 176–177 °C (decomp.; Ref. 8: mp 178–179 °C); yield: 1.34 g (67%). ^{1}H NMR (CD_3OD): δ 7.6 (5H, m), 4.95 (1H, dd, J=20.7, 5.4 Hz). ^{13}C NMR (CD_3OD): δ 165.8 (s), 133.6 (t, J=24 Hz), 132.4 (s), 129.8 (s), 126.9 (t, J=6 Hz), 120.1 (t, J=250 Hz), 59.6 (t, J=29 Hz). ^{19}F NMR (CD_3OD): δ −90.4 (1F, dd, J=250.3, 4.8 Hz), −109.3 (1F, dd, J=250.3, 21.1 Hz). MS: 202 (4%, M^++1), 156 (4%), 137 (24%), 127 (100%), 109 (24%), 91 (4%). Anal. Calcd for $C_9H_{10}ClF_2NO_2$ (237.64) C 45.49, H 4.24; found C 45.81, H 4.10%.

6.12.2. 2-Amino-3,3-difluoro-3-(4-fluorophenyl)propionic acid (4b). Analogously from 3,3-difluoro-3-(4-fluorophenyl)-2-oxopropionic acid (**3b**; 2.4 g, 10 mmol); colorless needles; mp 174–176 °C (decomp.); yield: 0.46 g (21%). ^{1}H NMR (CD_3OD): δ 7.67 (2H, dd, J=8.6, 5.1 Hz), 7.27 (3H, t, J=8.6 Hz), 5.01 (1H, dd, J=21.6, 5.0 Hz). ^{13}C NMR (CD_3OD): δ 165.9 (d, J=250 Hz), 165.7 (s), 129.9 (t, J=25 Hz), 129.6 (q, J=7 Hz), 119.9 (t, J=250 Hz), 116.9 (d, J=23 Hz), 59.5 (t, J=29 Hz). ^{19}F NMR (CD_3OD): δ −89.1 (1F, d, J=250.8 Hz), −108.4 (1F, dd, J=250.8, 21.6 Hz), −109.3 (1F, symm. m). MS (c.i.): 237 (8%, M^++NH_4), 220 (100%, M^++1), 176 (14%), 156 (41%), 145 (49%), 127 (17%), 95 (6%). Anal. Calcd for $C_9H_{10}ClF_2NO_2$ (237.64) C 42.29, H 3.55; found C 42.82, H 4.16%.

6.12.3. 2-Amino-3-(4-chlorophenyl)-3,3-difluoropropionic acid (4c). Analogously from 3-(4-chlorophenyl)-3,3-difluoro-2-oxopropionic acid (**3c**; 2.5 g, 10 mmol); colorless needles; mp 186–188 °C (decomp.); yield: 0.76 g (32%). ^{1}H NMR (CD_3OD): δ 7.61 (2H, d, J=8.3 Hz), 7.56 (2H, d, J=8.3 Hz), 5.03 (1H, dd, J=22.0, 4.8 Hz). ^{13}C NMR (CD_3OD): δ 165.6 (s), 138.7 (s), 132.4 (t, J=25 Hz), 130.1 (s), 128.8 (t, J=6 Hz), 119.8 (t, J=250 Hz), 59.3 (t, J=28 Hz). ^{19}F NMR (CD_3OD): δ

−89.7 (1F, d, *J*=252.0 Hz), −109.3 (1F, dd, *J*=252.0, 22.0 Hz). MS (c.i.): 253 (6%, M^++NH_4), 238 (6%, M^++1), 183 (79%), 166 (100%). Anal. Calcd for $C_9H_9Cl_2F_2NO_2$ (272.08) C 39.73, H 3.33; found C 40.10, H 3.06%.

6.12.4. 2-Amino-3,3-difluoro-3-(4-methoxyphenyl)propionic acid (4d). Analogously from 3,3-difluoro-2-oxo-3-(4-methoxyphenyl)propionic acid (**3d**; 2.5 g, 10 mmol); colorless platelets; mp 168–170 °C (decomp.); yield: 1.11 g (48%). ^{1}H NMR (CD_3OD): δ 7.52 (2H, d, *J*=8.9 Hz), 7.05 (2H, d, *J*=8.9 Hz), 4.89 (1H, dd, *J*=20.5, 5.5 Hz), 3.85 (3H, s). ^{13}C NMR (CD_3OD): δ 167.6 (s), 164.5 (s), 130.0 (t, *J*=6 Hz), 127.0 (t, *J*=25 Hz), 121.8 (t, *J*=249 Hz), 116.6 (s), 61.2 (t, *J*=30 Hz), 57.5 (s). ^{19}F NMR (CD_3OD): δ −88.8 (1F, dd, *J*=248.8, 5.1 Hz), −107.4 (1F, dd, *J*=248.8, 20.5 Hz). MS (c.i.): 249 (22%, M^++NH_4), 232 (100%, M^++1), 188 (20%), 168 (86%), 157 (53%), 114 (10%). Anal. Calcd for $C_{10}H_{12}ClF_2NO_3$ (267.66) C 44.87, H 4.52; found C 44.61, H 4.74%.

6.13. 3-Aryl-3,3-difluoro-2-hydroxypropionic acids

The 3-aryl-3,3-difluoro-2-hydroxypropionic acids **11** were the first components to be eluted from the ion exchange column as described in the preceding section. They were purified by crystallization from diethyl ether and hexanes.

6.13.1. 3,3-Difluoro-2-hydroxy-3-phenylpropionic acid (11a). Colorless needles; mp 100–102 °C; yield: 0.59 g (29%). ^{1}H NMR*: δ 7.5 (5H, m), 5.17 (1H, broad s), 4.64 (1H, dd, *J*=13.7, 6.6 Hz). ^{13}C NMR*: δ 170.3 (s), 135.1 (t, *J*=25 Hz), 131.1 (s), 129.0 (s), 126.9 (t, *J*=6 Hz), 120.7 (t, *J*=249 Hz), 74.2 (t, *J*=32 Hz). ^{19}F NMR*: δ −102.7 (1F, dd, *J*=253.6, 6.4 Hz), −108.7 (1F, dd, *J*=253.6, 13.6 Hz). MS: 202 (1%, M^+), 138 (4%), 127 (100%), 109 (17%), 91 (3%). Anal. Calcd for $C_9H_8F_2O_3$ (202.16) C 53.57, H 3.99; found C 53.27, H 4.04%.

6.13.2. 3,3-Difluoro-3-(4-fluorophenyl)-2-hydroxypropionic acid (11b). Colorless needles; mp 109–110 °C; yield: 1.49 g (68%). ^{1}H NMR*: δ 7.65 (2H, dd, *J*=9.0, 5.3 Hz), 7.24 (2H, t, *J*=9.0 Hz), 4.72 (1H, dd, *J*=14.0 Hz, 7.8). ^{13}C NMR*: δ 170.2 (s), 164.6 (d, *J*=248 Hz), 131.1 (t, *J*=26 Hz), 129.4 (q, *J*=26 Hz), 120.4 (t, *J*=249 Hz), 115.9 (d, *J*=22 Hz), 74.1 (t, *J*=32 Hz). ^{19}F NMR*: δ −99.7 (1F, dd, *J*=252.5, 7.4 Hz), −105.5 (1F, dd, *J*=252.5, 14.0 Hz), −111.3 (1F, symm. m). MS: 220 (1%, M^++1), 201 (1%), 156 (2%), 145 (100%), 127 (14%), 95 (7%). Anal. Calcd for $C_9H_7F_3O_3$ (220.15) C 49.10, H 3.21; found C 49.32, H 2.85%.

6.13.3. 3-(4-Chlorophenyl)-3,3-difluoro-2-hydroxypropionic acid (11c). Colorless needles; mp 128–129 °C; yield: 1.51 g (64%). ^{1}H NMR*: δ 7.60 (2H, d, *J*=8.5 Hz), 7.52 (2H, d, *J*=8.5 Hz), 4.71 (1H, dd, *J*=14.0, 7.9 Hz). ^{13}C NMR*: δ 170.1 (s), 136.7 (s), 134.0 (t, *J*=26 Hz), 128.9 (s), 128.8 (t, *J*=6 Hz), 120.4 (t, *J*=249 Hz), 74.0 (t, *J*=32 Hz). ^{19}F NMR*: δ −100.5 (1F, dd, *J*=252.8, 7.8 Hz), −106.4 (1F, dd, *J*=252.8, 14.0 Hz). MS (c.i.): 254 (11%, M^++NH_4), 236 (6%, M^+), 216 (1%), 161 (100%), 143 (11%), 111 (10%). Anal. Calcd for $C_9H_7ClF_2O_3$ (236.60) C 45.69, H 2.98; found C 45.78, H 3.03%.

6.13.4. 3,3-Difluoro-2-hydroxy-3-(4-methoxyphenyl)propionic acid (11d). Colorless needles; mp 104–105 °C; yield: 0.74 g (32%). ^{1}H NMR*: δ 7.50 (2H, d, *J*=8.9 Hz), 7.00 (2H, d, *J*=8.9 Hz), 4,65 (1H, dd, *J*=13.7, 7.7 Hz), 3.83 (3H, s). ^{13}C NMR*: δ 170.4 (s), 162.0 (s), 128.4 (t, *J*=6 Hz), 127.2 (t, *J*=26 Hz), 120.9 (t, *J*=249 Hz), 114.3 (s), 74.3 (t, *J*=33 Hz), 55.7 (s). ^{19}F NMR*: δ −99.1 (1F, dd, *J*=250.9, 7.7 Hz), −104.8 (1F, dd, *J*=250.9, 13.7 Hz). MS: 232 (9%, M^+), 213 (9%), 168 (14%), 157 (100%), 139 (22%), 114 (14%). Anal. Calcd for $C_{10}H_{10}F_2O_4$ (232.19) C 51.73, H 4.34; found C 52.08, H 4.30%.

6.14. 3,3-Difluorophenylalanine derivatives

6.14.1. Ethyl 2-amino-3,3-difluoro-3-phenylpropionate hydrochloride. A solution of 2-amino-3,3-difluoro-3-phenylpropionic acid (**4a**; 1.0 g, 5.0 mmol) and concentrated sulfuric acid (1.0 mL) in ethanol (10 mL) was heated under reflux for 24 h. The mixture was concentrated by evaporation and, after addition of a 2.0 M solution of sodium hydroxide (20 mL), was extracted with diethyl ether (3×25 mL). The combined organic layers were dried and evaporated. The residue was crystallized from ethanol saturated with hydrogen chloride; colorless needles; mp 158–160 °C; yield: 0.73 g (55%). ^{1}H NMR (CD_3OD): δ 7.6 (5H, m), 5.08 (1H, dd, *J*=21.2, 5.0 Hz), 4.09 (2H, q, *J*=7.1 Hz), 0.99 (3H, t, *J*=7.1 Hz). ^{13}C NMR (CD_3OD): δ 164.8 (s), 133.4 (t, *J*=24 Hz), 132.7 (s), 130.0 (s), 126.8 (t, *J*=6 Hz), 119.9 (t, *J*=250 Hz), 64.3 (s), 59.6 (t, *J*=28 Hz), 13.9 (s). ^{19}F NMR (CD_3OD): δ −90.6 (1F, dd, *J*=248.4, 4.6 Hz), −110.2 (1F, dd, *J*=248.4, 21.2 Hz). MS: 230 (7%, M^++1), 210 (4%), 189 (6%), 156 (5%), 127 (15%), 102 (100%). Anal. Calcd for $C_{11}H_{14}ClF_2NO_2$ (265.69) C 49.79, H 5.31; found C 49.57, H 5.36%.

6.14.2. Ethyl 2-acetamido-3,3-difluoro-3-phenylpropionate (12a). Ethyl 2-amino-3,3-difluoro-3-phenylpropionate hydrochloride (see preceding paragraph; 0.73 g, 2.8 mmol), acetic anhydride (5.0 mL) and pyridine (5.0 mL) were combined and stored at 25 °C for 24 h. The mixture was absorbed on silica gel (5 mL) and eluted with diethyl ether from a column filled with more silica (0.10 L); colorless needles (from diethyl ether and hexanes); mp 92–93 °C; yield: 0.24 g (32%). ^{1}H NMR: δ 7.5 (5H, m), 6.44 (1H, d, *J*=9.3 Hz), 5.36 (1H, ddd, *J*=13.6, 12.5, 9.5 Hz), 4.10 (2H, q, *J*=7.2 Hz), 2.01 (3H, s), 1.10 (3H, t, *J*=7.2 Hz). ^{13}C NMR: δ 169.7 (s), 167.0 (s), 133.7 (t, *J*=25 Hz), 130.6 (s), 128.4 (s), 125.5 (t, *J*=6 Hz), 119.5 (t, *J*=251 Hz), 62.2 (s), 57.4 (t, *J*=30 Hz), 23.0 (s), 13.7 (s). ^{19}F NMR: δ −101.2 (1F, dd, *J*=247.4, 12.4 Hz), −105.2 (1F, dd, *J*=247.4, 13.7 Hz). MS: 271 (11%, M^+), 231 (3%), 198 (6%), 156 (18%), 127 (76%), 102 (100%). Anal. Calcd for $C_{13}H_{15}F_2NO_3$ (271.26) C 57.56, H 5.57; found C 56.83, H 5.42%.

6.15. Resolution of the 3,3-difluorophenylalanine racemate

6.15.1. *N*-[(*S*)-1-Phenylethyl]-2,2-difluoro-2-phenylethylideneamine (13a). A solution of 2,2-difluoro-2-phenylethanal (**2a**; 9.4 g, 60 mmol) and *N*-[(*S*)-1-phenylethyl]amine (9.2 mL, 8.7 g, 72 mmol) in toluene (20 mL) was heated under reflux for 4 h and the water formed was collected in a

Dean-Stark trap. Fractional distillation afforded the product as a colorless oil; bp 116–118 °C/1 mm Hg; mp 14–16 °C; n_D^{20} 1.5318, d_4^{20} 1.115; yield: 8.57 g (55%). ^{1}H NMR: δ 7.83 (1H, t, J=5.2 Hz), 7.5 (2H, m), 7.4 (3H, m), 7.2 (5H, m), 4.51 (1H, q, J=6.3 Hz), 1.51 (3H, d, J=6.3 Hz). ^{13}C NMR: δ 155.6 (t, J=33 Hz), 143.5 (s), 134.4 (t, J=29 Hz), 130.4 (s), 128.5 (s), 128.4 (s), 127.3 (s), 126.7 (s), 125.8 (t, J=6 Hz), 116.7 (t, J=239 Hz), 69.0 (s), 24.1 (s). ^{19}F NMR: δ −100.1 (2F, dd, J=13.9 Hz, 5.0). MS: 260 (61%, M^++1), 232 (4%), 169 (3%), 127 (9%), 105 (100%). Anal. Calcd for $C_{16}H_{15}F_2N$ (259.30) C 74.11, H 5.83; found C 74.09, H 6.29%.

6.15.2. 3,3-Difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]-propionitrile (14a). *N*-[(*S*)-1-Phenyl-ethyl]-2,2-difluoro-2-phenylethylideneamine (**13a**; 7.0 mL, 7.8 g, 30 mmol), cyanotrimethylsilane (4.0 mL, 3.0 g, 30 mmol) and zinc diiodide (0.96 g, 3.0 mmol) were heated in a closed vessel at 50 °C for 3 days. The mixture was absorbed on silica gel (30 mL) and eluted from a column filled with more silica (0.30 L) using a 1:9 (v/v) mixture of diethyl ether and hexanes; faintly yellow oil; n_D^{20} 1.5301, d_4^{20} 1.145; yield: 7.90 g (92%). ^{1}H NMR: δ 7.5 (5H, m), 7.3 (4H, m), 7.0 (1H, m), 4.05 (0.5H, dd, J=10.5 Hz, 8.2), 4.03 (0.5H, q, J=6.5 Hz), 3.94 (0.5H, q, J=6.5 Hz), 3.72 (0.5H, dd, J=14.7, 6.0 Hz), 1.79 (1H, broad s), 1.32 (1.5H, d, J=6.5 Hz), 1.27 (1.5H, d, J=6.5 Hz). ^{13}C NMR: δ 143.2 (s), 141.9 (s), 132.6 (t, J=25 Hz), 132.5 (t, J=25 Hz), 131.0 (s), 130.8 (s), 128.8 (s), 128.6 (s), 128.4 (s), 127.9 (s), 126.7 (s), 125.9 (t, J=6 Hz), 119.0 (t, J=250 Hz), 118.5 (t, J=250 Hz), 115.8 (s), 56.5 (s), 56.2 (s), 55.2 (t, J=34 Hz), 55.0 (t, J=34 Hz), 24.9 (s), 22.6 (s). ^{19}F NMR: δ −98.6 (0.5F, dd, J=250.3 Hz, 6.0), −101.1 (0.5F, dd, J=248.1, 8.1 Hz), −103.6 (0.5F, dd, J=248.0, 10.4 Hz), −107.2 (0.5F, dd, J=250.4, 14.6 Hz). MS: 286 (1%, M^+), 271 (5%), 159 (12%), 127 (9%), 105 (100%), 91 (1%). Anal. Calcd for $C_{17}H_{16}F_2N_2$ (286.32) C 71.31, H 5.63; found C 71.19, H 5.80%.

6.15.3. 3,3-Difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]-propionamide (15a). At 0 °C, the mixture of 3,3-difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]propionitrile (**14a**; 6.3 mL, 7.2 g, 25 mmol) in dichloromethane (25 mL) and 97% sulfuric acid (40 mL) were stirred for 3 h. The mixture was poured on ice (0.10 L) and a 25% solution of ammonia (0.10 L) was cautiously added. The organic layer was collected and the aqueous one was extracted with dichloromethane (3×50 mL). The combined organic layers were evaporated and the residue was absorbed on silica gel (30 mL). Elution with a 1:1 (v/v) mixture of diethyl ether and hexanes provided first a small amount of unconsumed starting material **14a** (0.22 g, 3%) and then the product **15a** as a colorless oil; yield: 4.87 g (64%). ^{1}H NMR: δ 7.4 (5H, m), 7.2 (4H, m), 7.0 (1H, m), 6.36 (0.5H, broad s), 6.27 (0.5H, broad s), 6.16 (0.5H, broad s), 5.95 (0.5H, broad s), 3.65 (0.5H, q, J=6.7 Hz), 3.60 (0.5H, q, J=6.8 Hz), 3.59 (0.5H, dd, J=13.2, 10.2 Hz), 3.39 (0.5H, dd, J=16.3, 8.4 Hz), 2.12 (1H, broad s), 1.28 (3H, d, J=6.6 Hz), 1.25 (3H, d, J=6.6 Hz). ^{13}C NMR: δ 170.7 (s), 170.2 (s), 144.4 (s), 143.7 (s), 134.4 (t, J=26 Hz), 130.2 (s), 130.1 (s), 128.6 (s), 128.5 (s), 128.1 (s), 127.3 (s), 127.2 (s), 126.7 (s), 126.6 (s), 126.0 (t, J=6 Hz), 125.9 (t, J=6 Hz), 121.6 (t, J=250 Hz), 120.6 (t, J=249 Hz), 65.3 (t, J=29 Hz), 64.7 (t, J=29 Hz), 57.3 (s), 56.7 (s), 24.8 (s), 23.8 (s). ^{19}F NMR: δ −98.4 (0.5F, dd, J=248.3, 8.2 Hz), −99.6 (0.5F, dd, J=246.8, 10.1 Hz), −101.9 (0.5F, dd, J=246.8, 13.0 Hz), −106.9 (0.5F, dd, J=248.3, 16.2 Hz). MS: 305 (4%, M^++1), 260 (7%), 177 (18%), 127 (5%), 120 (40%), 105 (100%), 91 (3%). Anal. Calcd for $C_{17}H_{18}F_2N_2O$ (304.34) C 67.09, H 5.96; found C 67.04, H 5.82%.

This oil crystallized from a mixture of diethyl ether and hexanes at −20 °C; colorless needles; mp 75–78 °C; $[\alpha]_D^{20}$=−6.9 (dichloromethane; c=0.51); yield: 1.67 g (34%). ^{1}H NMR: δ 7.5 (5H, m), 7.2 (3H, m), 7.0 (2H, m), 6.26 (1H, broad s), 5.97 (1H, broad s), 3.68 (1H, q, J=6.6 Hz), 3.42 (1H, dd, J=16.2, 8.6 Hz), 2.22 (1H, broad s), 1.31 (3H, d, J=6.6 Hz). ^{13}C NMR: δ 170.5 (s), 143.6 (s), 134.3 (t, J=26 Hz), 130.1 (s), 128.5 (s), 128.1 (s), 127.2 (s), 126.7 (s), 125.9 (t, J=6 Hz), 120.6 (t, J=249 Hz), 65.3 (t, J=29 Hz), 56.7 (s), 24.8 (s). ^{19}F NMR: δ −98.3 (1F, dd, J=248.4, 8.4 Hz), −106.9 (1F, dd, J=248.4, 16.3 Hz).

6.15.4. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionamide (16a). A slurry containing the crystallized 3,3-difluoro-3-phenyl-2-[(*S*)-1-phenylethylamino]propionamide (see above; **15a**; 4.6 g, 15 mmol) and 10% palladium on charcoal (0.69 g) in ethanol (50 mL) was stirred at 25 °C for 2 h under a blanket of hydrogen (1 atm.). The solvent was evaporated and the product absorbed on silica gel (20 mL). Elution from a column filled with more silica (0.23 L) with diethyl ether gave a yellowish oil which crystallized from a mixture of chloroform and hexanes; colorless prisms; mp 77–78 °C; $[\alpha]_D^{20}$=+17.1 (dichloromethane; c=0.52); yield: 2.91 g (91%). ^{1}H NMR: δ 7.5 (5H, m), 6.41 (1H, broad s), 6.06 (1H, broad s), 3.97 (1H, t, J=11.6 Hz), 1.84 (2H, broad s). ^{13}C NMR: δ 170.6 (s), 133.8 (t, J=26 Hz), 130.4 (s), 128.4 (s), 125.8 (t, J=6 Hz), 120.9 (t, J=248 Hz), 60.9 (t, J=29 Hz). ^{19}F NMR: δ −102.3 (1F, dd, J=248.0, 11.2 Hz), −103.1 (1F, dd, J=248.0, 11.8 Hz). MS: 201 (100%, M^++1), 181 (24%), 156 (14%), 136 (13%), 127 (16%), 109 (21%). Anal. Calcd for $C_9H_{10}F_2N_2O$ (200.19) C 54.00, H 5.04; found C 54.14, H 5.13%.

6.15.5. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionic acid (L-3,3-difluorophenylalanine) (*R*-4a) hydrochloride. (*R*)-2-Amino-3,3-difluoro-3-phenylpropionamide (**16a**; 2.4 g, 10 mmol) and 20% aqueous sulfuric acid (10 mL) were heated under reflux for 4 h. After addition of a 5.0 M aqueous solution of sodium hydroxide (50 mL), the mixture was extracted with diethyl ether (3×50 mL). In this way a major amount of the starting material **16a** (1.54 g, 65%) was recovered. The aqueous phase was acidified with 37% hydrochloric acid (10 mL) before being loaded in a column filled with an ion exchange resin (Dowex 50W-X8, acid form, 50–100 mesh, 0.11 L). The column was washed consecutively with 50% aqueous isopropanol (0.50 L) and water (0.50 L). The product was eluted with a 1.0 M aqueous solution of ammonia and isolated, after evaporation of the solvent and crystallization from ethanol saturated with hydrogen chloride, as colorless needles; mp 176–177 °C (decomp.); $[\alpha]_D^{20}$=+1.0 (HCl 1.2 N; c=0.52) (Ref. 8: $[\alpha]_D^{20}$=+14.5 (HCl 1.2 N; c=0.15)); yield: 0.44 g (22%).

6.16. Determination of the acidity constants

The samples were dissolved in a 0.10 M aqueous solution of

potassium chloride and the pH of the solution was adjusted to 2.5 by addition of 0.50 M hydrochloric acid. The sample concentrations fell in the range between 5×10^{-4} and 2×10^{-3} M. Using a automatic titrator equipment (model PCA 101) and working under argon, the sample was titrated with a 0.50 M solution of potassium hydroxide until pH 10 was attained, the change in pH being monitored with a glass electrode.[48,49] This electrode was calibrated in the pH range of 1.8–12.2 by means of a 0.10 M aqueous solution of potassium chloride following the instructions of the supplier. The pK_a value was calculated as a function of the change in shape of the titration curve in comparison with a blank titration carried out without any sample present. The data were processed with the *pKaLOGP* software.[48] To check the reproducibility, all measurements were performed three-fold.

Acknowledgements

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Catalytic asymmetric phase-transfer reactions using tartrate-derived asymmetric two-center organocatalysts

Takashi Ohshima, Tomoyuki Shibuguchi, Yuhei Fukuta and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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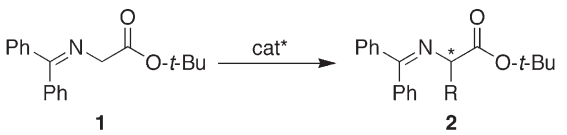
Abstract—A new highly versatile asymmetric two-center catalyst, tartrate-derived diammonium salt (TaDiAS), was designed and a catalyst library containing more than 70 new two-center catalysts was constructed. A variety of (*S*,*S*)- and (*R*,*R*)-TaDiAS were easily synthesized from diethyl L- and D-tartrate, respectively, using common and inexpensive reagents under operationally simple reaction conditions. TaDiAS was used in phase-transfer alkylations and Michael additions to afford various optically active α-amino acid equivalents in up to 93% yield. Moreover, dramatic counter anion effects were observed in phase-transfer catalysis (PTC) for the first time, making it possible to further improve reactivity and selectivity. These findings validate the usefulness of three-dimensional fine-tuning of the catalyst (acetal, Ar, and counter anion) for optimization. Recovery and reuse of the catalyst was also possible using simple procedures. The present asymmetric PTC was successfully applied to enantioselective syntheses of serine protease inhibitor aeruginosin 298-A and its analogues.

1. Introduction

In contrast to the natural subtle balance between metal-free and metal-mediated conditions, asymmetric catalysis has been advanced mainly by the development of chiral metal complexes.[1] In recent years, asymmetric organocatalysis has become of great interest as a new catalytic method to introduce chirality into a molecule.[2] Among them, phase-transfer catalysis (PTC) is one of the most important and useful methods in synthetic organic chemistry because of its preparative advantages, such as simple reaction procedures, mild conditions, inexpensive and environmentally friendly reagents, and the ease in scaling-up the reaction.[3] An asymmetric version of PTC utilizing chiral phase-transfer catalysts is a highly attractive method in terms of atom economy; however, it has not been as extensively studied as metal-mediated asymmetric catalysis. The first efficient asymmetric PTC was reported in 1984 by the Merck group, where cinchonidine-derived quaternary ammonium salt catalyzed methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone with 92% enantioselectivity (1 example).[4] In 1989, O'Donnell and co-workers developed a very useful method for the syntheses of α-alkyl-α-amino acids by asymmetric phase-transfer mono-alkylation of the Schiff base of *tert*-butyl glycinate **1** (Scheme 1) using similar *Cinchona* alkaloid-derived catalysts.[5a] Later, Corey et al.[6] and Lygo et al.[7] independently greatly improved this catalyst system by changing the *N*-alkyl moiety from *N*-benzyl to *N*-anthracenylmethyl.[8] Although many types of phase-transfer catalysts have been used as chiral catalysts in PTC, *Cinchona* alkaloid derivatives provide greater enantioselectivity for a wider range of reactions than do other catalysts. Several efficiently designed chiral phase-transfer catalysts such as *N*-spiro binaphtyl derivatives[9] were recently developed.[10] The major drawback of these catalysts is the difficulty in modifying the catalyst structure for further improvement of selectivity and reactivity or further application to other types of catalytic asymmetric reaction systems.[3]



1 2

Scheme 1. Syntheses of α-alkyl-α-amino esters **2** by asymmetric phase-transfer mono-alkylation of the Schiff base of *tert*-butyl glycinate **1**.

To address this issue, we developed a new versatile asymmetric phase-transfer catalyst. The design of our new asymmetric catalyst was based on a two-center catalyst and structural diversity. Herein, we describe our efforts towards

Keywords: Phase-transfer catalysis; Asymmetric two-center catalyst; Alkylation; Michael addition; Aeruginosin 298-A; Serine protease inhibitor.

* Corresponding author. Tel.: +81-3-5684-0651; fax: +81-3-5684-5206; e-mail address: mshibasa@mol.f.u-tokyo.ac.jp

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the development of a novel two-center catalyst: tartrate-derived diammonium salt (TaDiAS **3**) (Fig. 1)[11] and present a brief introduction of its application for the syntheses of serine protease inhibitor aeruginosin 298-A and its analogues.[12]

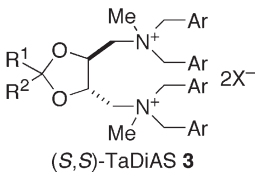


Figure 1. Structure of a new two-center asymmetric organocatalyst, TaDiAS **3**.

2. Results and discussion

2.1. Design and synthesis of TaDiAS[11]

We developed a wide variety of metal-mediated asymmetric two-center catalyses based on a multifunctional catalyst concept.[13] To extend this concept to asymmetric organocatalysis, we introduced two ammonium salt moieties in the catalyst, keeping an appropriate distance (two-center organocatalyst), where the substrate can be fixed in a chiral environment by two cationic moieties. To achieve ideal complexation of the two-center catalyst and the substrate (glycine Schiff base **1**), we selected a 1,4-diammonium salt, rather than a 1,2-diammonium salt or a 1,3-diammonium salt, based on the spatial environment created by two cationic moieties and several preliminary investigations. Thus, we designed a new two-center catalyst, TaDiAS **3**, both enantiomers of which can be synthesized from commercially available and relatively inexpensive[14] L- or D-tartrate. Preliminary molecular mechanics simulations using the Monte Carlo method on Cerius[2] (Accelrys Inc.)[15] supported our hypothesis (Fig. 2). Although a naked enolate is thought to form *E*-enolate preferentially,[6a] we expect that the two-center catalyst TaDiAS **3** might form a tight complex with the *Z*-enolate of ketimine **1** through several hydrogen bonds (see Section 2.7).

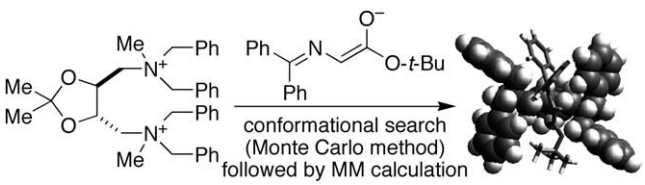


Figure 2. The results of molecular mechanics simulations (right).

As in the success of TADDOLs, many chiral catalysts and chiral ligands were synthesized from tartaric acid, which provides a proper C_2 symmetric framework and structural diversity.[16,17] TaDiAS **3** (Fig. 1) has remarkable structural diversity because a wide variety of catalysts can be easily synthesized by changing acetal moieties (R^1 and R^2), aromatic parts (Ar), and counter anions (X^-), making it possible to three-dimensionally fine-tune the catalyst (vide infra).

Other candidates, such as **4**, **5**, and **6** (Fig. 3), produced unsatisfactory results (<10% ee) during preliminary catalyst screening of *N*-substituents. Thus, we hypothesized that the combination of two large *N*-substituents and one small *N*-substituent like TaDiAS **3** would be best for the phase-transfer alkylation of **1**.

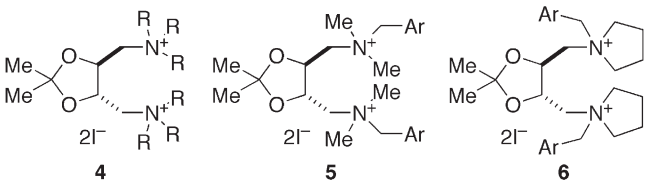
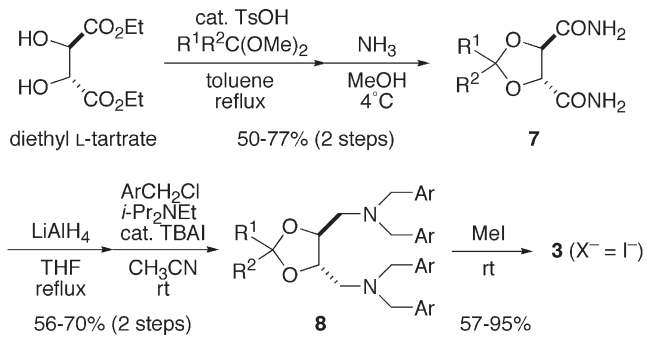


Figure 3. Other candidates for the two-center catalyst.

Scheme 2 summarizes the synthesis of (*S*,*S*)-TaDiAS **3** from diethyl L-tartrate. Several synthetic processes were examined, and the present five-step synthesis, which needs only common and inexpensive reagents under operationally simple reaction conditions, was selected. The ketone (R^1COR^2) was first converted to the corresponding dimethoxy acetal, which was then directly reacted with diethyl tartrate to afford an acetal compound (mixture of ethyl and methyl esters). Introduction of ammonia gas to a methanol solution of the acetal compound gave diamide **7** in 50–77% yield (two steps) after purification by recrystallization. Reduction of the diamide moiety of **7** to diamine with $LiAlH_4$ following arylmethylation provided di-*tert*-amine **8** in 56–70% yield (two steps). Finally, treatment with iodomethane furnished the synthesis of diammonium salt TaDiAS **3** ($X^-=I^-$) (57–95% yield). A potentially large-scale reaction, starting from 0.1 mol (20.6 g) of diethyl tartrate, can also be performed with the same efficiency; thus, this process is suitable for industrial-scale reactions.[18] Using this synthetic process, a variety of catalysts with versatility on the acetal moiety and aromatic part (more than 70) were produced.

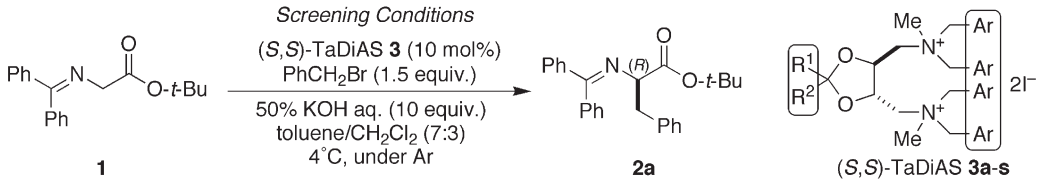


Scheme 2. Preparation of TaDiAS **3** ($X^-=I^-$) from diethyl tartrate.

2.2. Catalytic asymmetric phase-transfer alkylation[11,12a]

We then examined a variety of TaDiAS **3** in phase-transfer alkylation under screening conditions and selected results are shown in Table 1.[19] This condition is very convenient for high throughput screening of catalysts because the reaction can be performed with a common disposable test tube and a rubber septum without any special care to avoid contamination by moisture or air. Moreover, the reaction was usually complete in 1–4 h at 4 °C (ice-cold water bath). Although the reactions were performed under an argon atmosphere to prevent partial decomposition of **1** under

Table 1. Catalytic asymmetric phase-transfer alkylations: catalyst screening under screening conditions

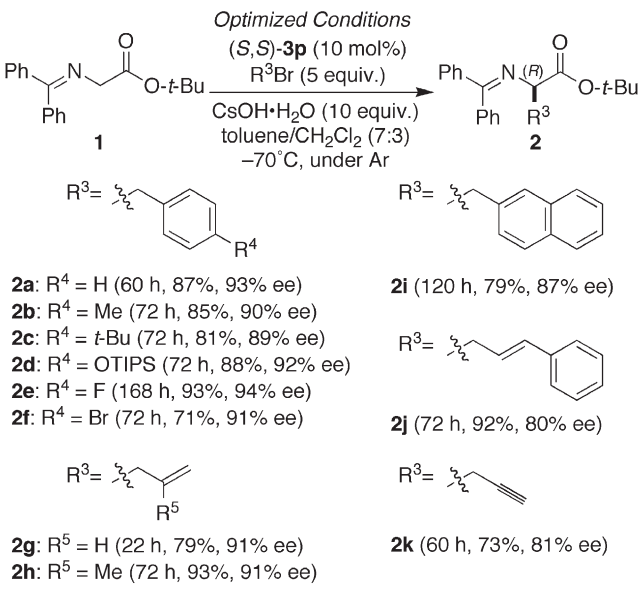


Entry	R^1	R^2	Ar	(*S*,*S*)-TaDiAS **3**	Time (h)	Yield (%)[a]	ee (%)[b]
1[c]	Me	Me	$-C_6H_5$	**3a**	4.0	67	47
2	Me	Me	$-C_6H_5$	**3a**	2.0	87	47
3	Et	Et	$-C_6H_5$	**3b**	2.0	94	37
4	Pr	Pr	$-C_6H_5$	**3c**	2.5	92	40
5	Bu	Bu	$-C_6H_4$-4-OMe	**3d**	4.0	91	38
6	*i*-Bu	*i*-Bu	$-C_6H_4$-4-OMe	**3e**	4.0	87	39
7	$-(CH_2)_5-$		$-C_6H_5$	**3f**	2.5	92	38
8	*t*-Bu	H	$-C_6H_5$	**3g**	2.0	90	48
9	*i*-Pr	Me	$-C_6H_4$-4-OMe	**3h**	2.0	92	57
10	Bu	Me	$-C_6H_4$-4-OMe	**3i**	2.0	94	57
11	*i*-Bu	Me	$-C_6H_4$-4-OMe	**3j**	2.0	91	54
12	*t*-Bu	Me	$-C_6H_5$	**3k**	2.0	89	52
13	*t*-Bu	Me	$-C_6H_4$-4-Me	**3l**	2.0	92	63
14	*t*-Bu	Me	$-C_6H_4$-4-(*i*-Pr)	**3m**	2.0	89	67
15	*t*-Bu	Me	$-C_6H_4$-4-(*t*-Bu)	**3n**	2.0	87	62
16	*t*-Bu	Me	2-Naphthyl	**3o**	2.0	84	49
17	*t*-Bu	Me	$-C_6H_4$-4-OMe	**3p**	2.0	92	70
18[d]	*t*-Bu	Me	$-C_6H_4$-4-OMe	**3p**	3.0	91	71
19	*t*-Bu	Me	$-C_6H_4$-4-OEt	**3q**	1.5	93	67
20	*t*-Bu	Me	$-C_6H_4$-4-OPr	**3r**	1.5	89	68
21	$C_{14}H_{29}$	Me	$-C_6H_4$-4-OMe	**3s**	2.5	92	60

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was performed under aerobic conditions.
[d] The reaction mixture was completely degassed by the freeze-pump-thaw cycle.

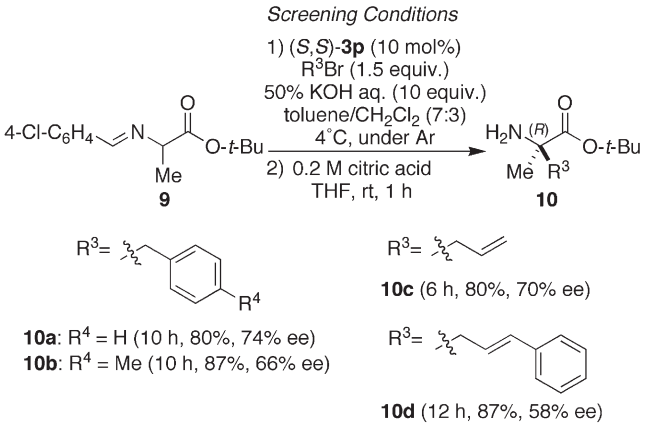
aerobic conditions (Table 1, entry 1),[9d] simple replacement of the reaction atmosphere with flowing argon was enough to obtain high yield (entry 2) and degassed conditions were not necessary (entry 18). Starting from the original TaDiAS **3a**, the effect of an acetal moiety was examined.[20] On the contrary to our expectation, better phase-transfer alkylation was obtained when un-C_2-symmetric catalysts ($R^1 \neq R^2$) were used. Among them, *tert*-butyl methyl acetal had the highest selectivity (entry 12). Keeping the acetal moiety as a *tert*-butyl methyl acetal, the effect of the aromatic part was examined (entries 12–20). Screening of the aromatic part revealed that TaDiAS **3p** (Ar=4-methoxyphenyl) gave the best result (92% yield and 70% ee, entry 17). In all entries, when (*S*,*S*)-TaDiAS **3** was used as a catalyst, the absolute configurations were *R*.[21]

Using the best catalyst **3p**, the reaction conditions were further optimized to improve selectivity. Because lower temperature conditions cannot be applied to liquid–liquid phase-transfer reactions, liquid–solid phase-transfer reactions were investigated. Although the reactivity significantly dropped when NaOH (pellet) or KOH (pellet) was used as a base in organic solvent (toluene/CH_2Cl_2=7/3) due to a dramatic decrease in the surface area (ω phase), powdered $CsOH{\cdot}H_2O$ had higher reactivity than the liquid–liquid phase-transfer reaction conditions shown in Table 1. As expected, this liquid–solid phase-transfer system worked even at −70 °C with improved enantioselectivity (from 70 to 93% ee). Under the optimized conditions, we examined the scope and limitations of different electrophiles (Scheme 3). When 10 mol% of TaDiAS **3p** was used with cesium hydroxide, all phase-transfer alkylations of **1** with benzyl, allyl, and propargyl reagents proceeded at −70 °C in good to high enantiomeric excess. In addition, the reaction with 4-bromo- and 4-fluorobenzyl bromide, allyl bromide, propargyl bromide, and so on, afforded the corresponding protected synthetic α-amino acids, which can be a versatile intermediate of various synthetic α-amino acids.



Scheme 3. Catalytic asymmetric phase-transfer alkylation of various electrophiles under optimized conditions.

In a similar way, optically active α,α-disubstituted α-amino acids can be synthesized using aldimine **9** as a substrate instead of ketimine **1** (Scheme 4). Because of the low reactivity of aldimine **9**, the reaction can be performed under screening conditions (4 °C, shown in Table 1), but not in the optimized conditions (−70 °C, shown in Scheme 3). Therefore, even when using the best catalyst, TaDiAS **3p**, the obtained enantioselectivities were good to moderate (58–74% ee). Later, this low reactivity was improved by changing a counter anion of the catalyst (vide infra).



Scheme 4. Catalytic asymmetric phase-transfer alkylation using aldimine **9** to synthesize α,α-disubstituted α-amino ester **10** under screening conditions.

2.3. Catalytic asymmetric phase-transfer Michael addition[11]

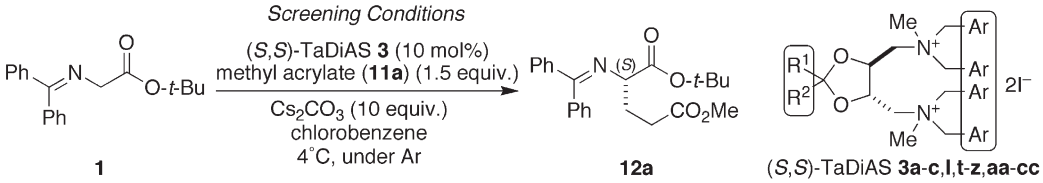
Next, catalytic asymmetric phase-transfer Michael addition of **1** to methyl acrylate (**11a**) was investigated. With a strong base such as KOH or CsOH, the Michael addition proceeded very rapidly, even in the absence of a phase-transfer catalyst. K_2CO_3 had very low reactivity, but Cs_2CO_3 was the best base to use in this reaction. Catalyst screening for phase-transfer Michael additions of **1** to **12a** were then performed under the screening conditions described in Table 2.[22] In contrast to the above-mentioned phase-transfer alkylation, C_2-symmetric catalysts gave better results (entries 1–13) than un-C_2-symmetric catalysts (entries 14 and 15) in Michael additions. In this reaction, 4-methylphenyl was the best aromatic substituent and **3t** (R^1=R^2=Pr), **3aa** (R^1=R^2=Bu), and **3bb** (R^1=R^2=*i*-Bu) gave the highest enantiomeric excess (64% ee). Surprisingly, using (*S*,*S*)-TaDiAS **3**, the obtained Michael product **12a** had an *S* configuration in all entries.[21]

The scope and limitations of the phase-transfer Michael addition were examined using the best catalyst **3t** under optimized conditions shown in Scheme 5. At lower temperature (−30 °C), the enantiomeric excess of the Michael adduct **12a** was improved from 64% ee (Table 2, entry 5) to 75% ee. Further improvement of the enantioselectivity was obtained using ethyl acrylate as an electrophile (**1→12b**, 82% ee). Using more reactive methyl vinyl ketone as an electrophile gave unsatisfactory selectivity, even at low temperature (33% ee, not optimized).

2.4. Counter anion effects[12a]

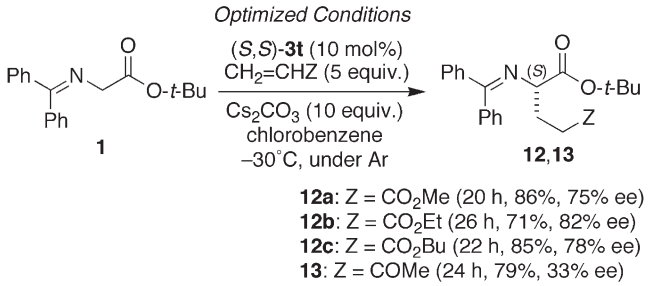
Although the phase-transfer Michael addition, in principle, requires only a catalytic amount of base, most reported phase-transfer Michael additions were performed in the presence of excess base.[3] In the case of our catalyst system for the Michael addition, a decrease in Cs_2CO_3 from 10 to 0.5 equiv. resulted in lower selectivity (57% ee, Table 3, entry 2); reactivity, however, was maintained. At this stage, we expected that the counter anion of the catalyst **3** would

Table 2. Catalytic asymmetric phase-transfer Michael addition: catalyst screening under screening conditions



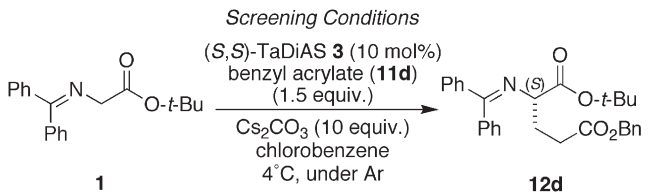
Entry	R^1	R^2	Ar	(*S*,*S*)-TaDiAS **3**	Time (h)	Yield (%)[a]	ee (%)[b]
1[c]	Me	Me	$-C_6H_5$	**3a**	20	70	37
2	Me	Me	$-C_6H_5$	**3a**	12	91	39
3	Et	Et	$-C_6H_5$	**3b**	19	78	49
4	Pr	Pr	$-C_6H_5$	**3c**	12	92	59
5	Pr	Pr	$-C_6H_4$-4-Me	**3t**	9	94	64
6	Pr	Pr	$-C_6H_4$-4-(*i*-Pr)	**3u**	11	87	59
7	Pr	Pr	$-C_6H_4$-4-(*t*-Bu)	**3v**	12	87	62
8	Pr	Pr	2-Naphthyl	**3w**	12	89	47
9	Pr	Pr	$-C_6H_4$-4-OMe	**3x**	9	93	54
10	Pr	Pr	$-C_6H_4$-4-OEt	**3y**	8	89	58
11	Pr	Pr	$-C_6H_4$-4-OPr	**3z**	12	93	57
12	Bu	Bu	$-C_6H_4$-4-Me	**3aa**	14	89	64
13	*i*-Bu	*i*-Bu	$-C_6H_4$-4-Me	**3bb**	12	88	64
14	*t*-Bu	H	$-C_6H_4$-4-Me	**3cc**	20	89	23
15	*t*-Bu	Me	$-C_6H_4$-4-Me	**3l**	20	67	40

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was performed under aerobic conditions.



Scheme 5. Catalytic asymmetric phase-transfer Michael addition of several electrophiles under optimized conditions.

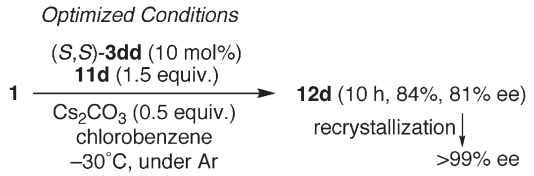
Table 3. Counter anion (X^-) effects in catalytic asymmetric phase-transfer Michael addition promoted by TaDiAS **3** under screening conditions[a]



Entry	X^-	Y (equiv.)	Time (h)	Yield (%)[b]	ee (%)[c]
1	I^-: **3t**	10	9	94	64
2	I^-: **3t**	0.5	10	84	57
3	BF_4^-: **3dd**	10	0.5	86	69
4	BF_4^-: **3dd**	0.5	0.5	85	69
5	BF_4^-: **3dd**	0.1	1.0	85	69
6[d]	BF_4^-: **3dd**	0.1	2.0	85	69
7	ClO_4^-: **3ee**	0.5	1.0	89	68
8	TfO^-: **3ff**	0.5	1.0	87	54
9	PF_6^-: **3gg**	0.5	1.0	85	52
10	SbF_6^-: **3hh**	0.5	35	43	43

[a] In all entries, R^1=R^2=Pr and Ar=C_6H_4-4-Me.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] One mole percent of catalyst was used.

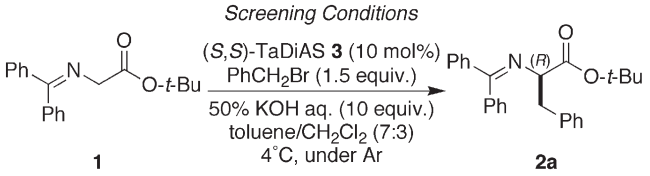
affect the reactivity in the catalytic base system. Thus, we examined counter anion effects of catalyst **3** in the present Michael addition system. A variety of new types of TaDiAS **3dd**–**hh** with hard counter anions such as tetrafluoroborate instead of iodide were synthesized by counter anion exchange using the corresponding silver salts. Those phase-transfer catalysts **3dd**–**hh** have lower polarity on silica-gel thin-layer chromatography and higher solubility in organic solvent than the iodide catalyst **3t**. As shown in Table 3, hard counter anions dramatically accelerated the phase-transfer Michael addition even in the case of a catalytic amount of Cs_2CO_3. Among the examined counter anions, tetrafluoroborate catalyst **3dd** had the highest reactivity with improved enantioselectivity (69% ee, entry 4). Moreover, only 1 mol% of the catalyst **3dd** gave the same result (entry 6) as that using 10 mol% of **3dd** (entry 3–5). The counter anion effects were also observed under optimized conditions (−30 °C)[23] to provide **12d** in 81% ee, the optical purity of which was further enriched to >99% ee by recrystallization (43% yield) (Scheme 6). To the best of our knowledge, this is the first example of such dramatic counter anion effects in PTC. These results clearly demonstrate that three-dimensional fine-tuning of the catalyst **3** can be realized by changing acetal moieties (R^1 and R^2), aromatic parts (Ar), and counter anions (X^-).



Scheme 6. Catalytic asymmetric phase-transfer Michael addition using the tetrafluoroborate catalyst **3dd** under optimized conditions.

Even in phase-transfer alkylation with excess hydroxide, there was a moderate counter anion effect (Table 4). The tetrafluoroborate catalyst **3ii**, which was directly synthesized from di-*tert*-amine intermediate **8** (R^1=*t*-Bu, R^2=Me, Ar=C_6H_4-4-OMe) using Meerwein reagent (Me_3OBF_4), had higher reactivity than the iodide catalyst **3p**.

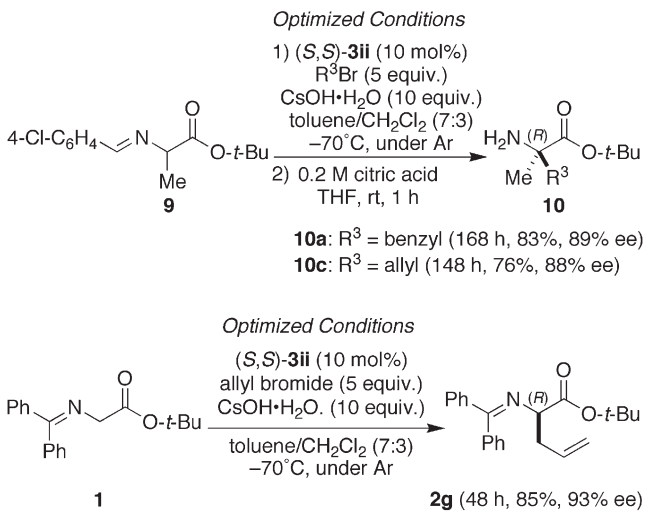
Table 4. Counter anion (X^-) effects in catalytic asymmetric phase-transfer alkylation promoted by TaDiAS **3** under screening conditions[a]



Entry	X^-	Time (h)	Yield (%)[b]	ee (%)[c]
1	I^-: **3p**	2	92	70
2	BF_4^-: **3ii**	1	91	70
3	ClO_4^-: **3jj**	1	87	63
4	TfO^-: **3kk**	1	88	55
5	PF_6^-: **3ll**	1	86	53

[a] In all entries, R^1=*t*-Bu, R^2=Me, and Ar=C_6H_4-4-OMe.
[b] Isolated yield.
[c] Determined by HPLC analysis.

Tetrafluoroborate catalyst **3ii** successfully promoted the alkylation of aldimine **9**, even at low temperature (−70 °C), to afford α,α-disubstituted α-amino ester **10a** (83 and 89% ee) and **10c** (76 and 88% ee) (Scheme 7, see also Scheme 4). The alkylation of **1** to **2g** also slightly improved (85% yield, 93% ee compared with 79% yield, 91% ee using the iodide



Scheme 7. Catalytic asymmetric phase-transfer alkylation using the tetrafluoroborate catalyst **3ii** under optimized conditions.

catalyst **3p** shown in Scheme 3). These results indicate that, even in the presence of excess hydroxide or enolate, one of the original counter anions remained unchanged in the catalyst.

2.5. Catalyst recovery and reuse[12a]

In contrast to commonly used *Cinchona* alkaloid-derived catalysts,[3–9] TaDiAS **3** is extremely stable under strongly basic conditions. In spite of the existence of β-hydrogens to the ammonium cation, catalyst decomposition, such as that due to Hoffman elimination, has not been observed under phase-transfer reaction conditions. As a result, TaDiAS **3** can be recovered from the reaction mixture in a high recovery yield. After quenching the reaction with water and diethyl ether, the catalyst appeared as a white solid between two layers. After stirring vigorously for 5–10 min, this white solid stuck to the glass wall. Thus, the solid was easily separated from the product by simple decantation (Fig. 4). The residual solid was dissolved with 30% MeOH in CH_2Cl_2 and filtered through a paper filter to remove inorganic salts, resulting in recovered catalyst after solvent evaporation.

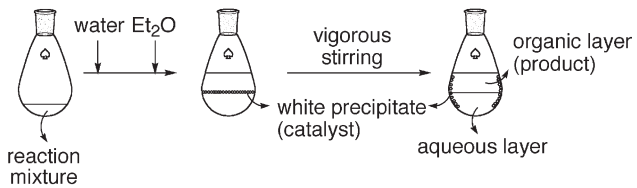
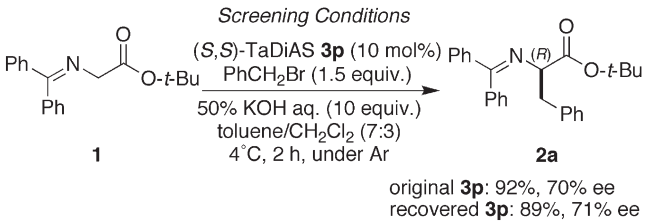


Figure 4. General procedure for recovery of the catalyst **3**.

We then investigated catalyst recovery with several combinations of counter anions and electrophiles after the standard phase-transfer alkylation of **1** to **2a**. As shown in Table 5, when the iodide catalyst **3p** was used, **3p** was recovered in approximately 90% yield as a white powder.[24] On the other hand, when the tetrafluoroborate catalyst **3ii** was used, complete (entry 3) or partial (entry 4) counter anion exchange proceeded with a lower recovery yield (approximately 80%). These findings suggest that the order of stability of counter anions in the catalyst should be $I^- > BF_4^- > Br^-$ and the reason for the counter anion effect in the alkylation shown in Scheme 7 might be due to the remaining BF_4^- in the catalyst complex during the reaction. The recovered catalyst **3p** (Table 5, entry 2) was reused in the same phase-transfer alkylation without further purification, and had the same catalyst efficiency (94% yield, 71% ee, Scheme 8). Thus, the catalyst can be recovered and reused using simple deposition and decantation techniques, as shown in Figure 4.

Table 5. Recovery of the catalyst **3** with several combinations of counter anions and electrophiles

Entry	X^-	Electrophile	X^- of the recovered catalyst
1	I^-: **3p**	$PhCH_2I$	I^-, I^-
2	I^-: **3p**	$PhCH_2Br$	I^-, I^-
3	BF_4^-: **3ii**	$PhCH_2I$	I^-, I^-
4	BF_4^-: **3ii**	$PhCH_2Br$	BF_4^-, BF_4^- or Br^-



Scheme 8. Reuse of the recovered catalyst **3p** under screening conditions.

2.6. Synthetic application[12]

With the practical asymmetric PTC using TaDiAS **3** with broad substrate generality in hand, we next examined the synthetic application of this asymmetric PTC to produce complex natural products. In addition, its easy accessibility to a variety of optically active natural and unnatural α-amino acids makes it possible to supply very valuable product libraries. First, we chose aeruginosin 298-A (Fig. 5, **14a**) as a target compound based on its unique serine protease inhibitor activity and the existence of nonstandard amino acids such as 2-carboxy-6-hydroxyoctahydroindole (Choi) in the molecule.[25a,26] To gain insight into the structure-activity relations, we developed a highly versatile synthetic method of aeruginosin 298-A as well as its analogues. We used the above-mentioned catalytic asymmetric phase-transfer alkylation for the synthesis of the D-Leu, L-Choi, and L-Algol portions and catalytic asymmetric epoxidation of α,β-unsaturated imidazolide, which was previously developed by our group,[27] for the synthesis of the (*R*)-3-(4-hydroxyphenyl)lactic acid (D-Hpla) portion. Because most of the aeruginosin families contain a D-Hpla portion, an L-Choi portion, and a guanidine unit,[25] we synthesized a variety of analogues by altering the second amino acid portion from the *N*-terminus (R^6) and arginine portion (R^7, R^8 as well as their enantiomers).

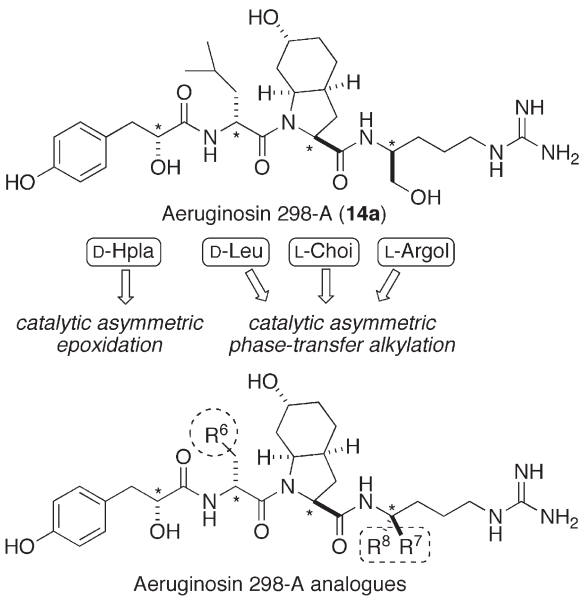
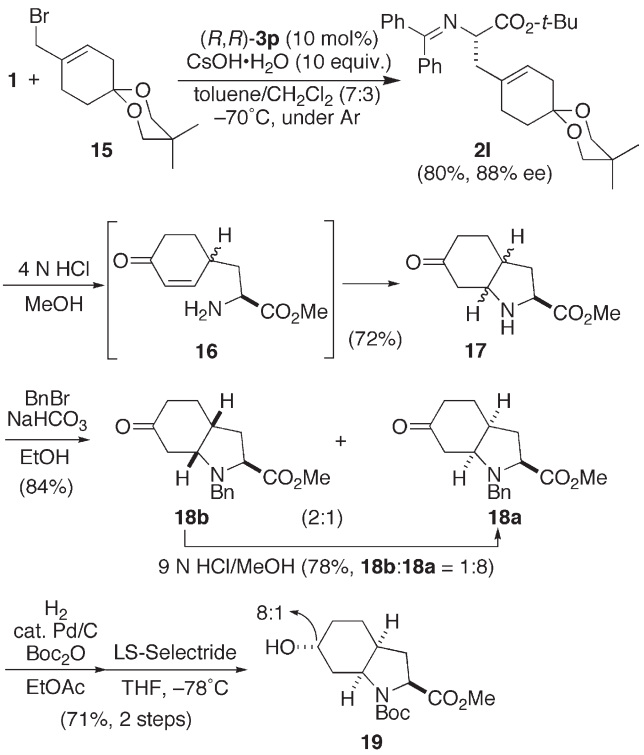


Figure 5. Structure of aeruginosin 298-A (**14a**) and its analogues.

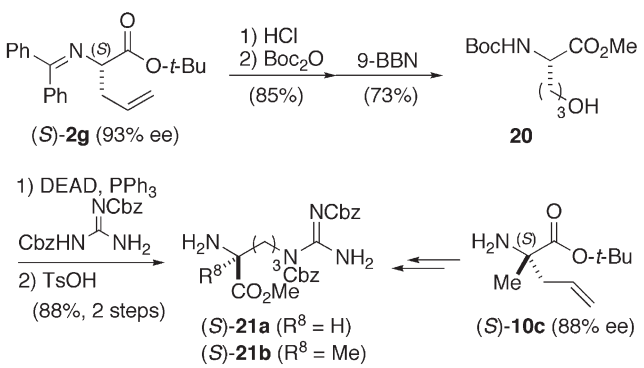
Synthesis of the unusual bicyclic amino acid L-Choi portion was achieved by catalytic asymmetric phase-transfer alkylation of **1** to (*S*)-**2l** with electrophile **15**[12a] using

10 mol% of (*R*,*R*)-TaDiAS **3p** and the following acid treatment, resulting in bicyclic amino ester **17** in high yield through five one-pot reactions (deprotection of the benzophenone imine and acetal, transesterification, migration of the C–C double bond to form enone, and 1,4-addition of the resulting amine to enone) (Scheme 9). After benzylation, the bicyclic amino ester **18** was obtained as a diastereomixture (84%, **18a**:**18b**=1:2). The undesired minor isomer **18b** was transformed to the desired **18a** under acidic conditions (78%, **18a**:**18b**=8:1) and **18a** was successfully converted to **19** (71% in 2 steps) following Bonjoch's procedure.[26a]



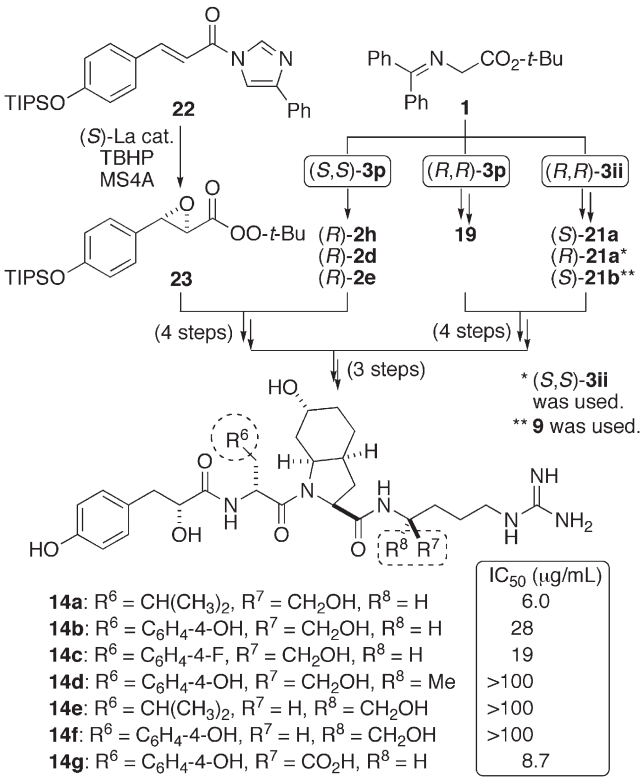
Scheme 9. Synthesis of the L-Choi portion **19**.

Synthesis of the L-Argol portion began from (*S*)-**2g**, which was prepared by the phase-transfer alkylation of the ketimine **1** using the tetrafluoroborate catalyst (*R*,*R*)-**3ii** shown in Scheme 7 (85 and 93% ee). Then, (*S*)-**2g** was converted to (*S*)-**21a** (R^8=H) through introduction of the guanidine moiety (Scheme 10). In a similar way, the enantiomer (*R*)-**21a** was prepared using (*S*,*S*)-**3ii** as a catalyst. Moreover, the α-methyl analogue (*S*)-**21b** (R^8=Me) was also synthesized from (*S*)-**10c** (Scheme 7, 76 and 88% ee).



Scheme 10. Synthesis of the L-Argol portion **21**.

The syntheses of aeruginosin 298-A and its analogues are summarized in Scheme 11. D-Leu and several derivatives, corresponding to the second amino acid portion from the *N*-terminus, were synthesized from (*R*)-**2h** (91% ee, for aeruginosin 298-A), **2d** (92% ee, for analogue), and **2e** (>99% ee after recrystallization, for analogue) (Scheme 3). The D-Hpla portion **23**, which was directly used for coupling with the above-mentioned second amino acid portions, was prepared in 95% yield and 94% ee based on catalytic asymmetric epoxidation of α,β-unsaturated imidazolide **22** using 10 mol% of La-(*S*)-BINOL-Ph_3P=O (1:1:3) complex. With all the component amino acids and their derivatives in hand, each peptide portion of aeruginosin 298-A and its six analogues was assembled. Using a peptide coupling of epoxy peroxy ester **23** and a subsequent regioselective one-pot epoxide-opening reaction (for D-Hpla-D-Leu) and normal peptide coupling protocols (for other couplings), enantioselective syntheses of aeruginosin 298-A (**14a**) and its six analogues were accomplished. Furthermore, inhibitory activity studies against the serine protease trypsin were examined. The biological activity studies of the newly synthesized aeruginosin analogues suggest that conformation of the Argol portion, especially the guanidine side-chain, is extremely important for the inhibitory activity. Access to additional derivatives and closer investigation are now possible through molecular design and chemical synthesis.

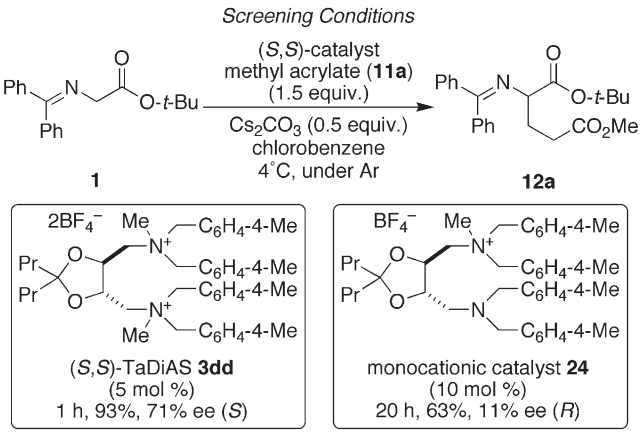


Scheme 11. Syntheses of aeruginosin 298-A (**14a**) and its analogues.

2.7. Preliminary mechanistic studies

As demonstrated above using molecular mechanics

simulations (Fig. 2), the existence of two cationic moieties in the catalyst is essential for obtaining high enantioselectivity. Monocationic catalyst **24** (10 mol%) had much lower reactivity and selectivity than dicationic catalyst **3dd** (5 mol %) in the phase-transfer Michael addition (Scheme 12). Although bis- and tris-*Cinchona* alkaloid ammonium salt catalysts were reported,[28] similar reactivity and selectivity were observed, compared with standard *Cinchona* alkaloid catalysts, even with the same catalyst loading. These results suggest that, as expected, substrate **1** is fixed in a chiral environment by two cationic moieties.



Scheme 12. Catalytic asymmetric phase-transfer Michael addition using dicationic catalyst **3dd** and monocationic catalyst **24** under screening conditions.

Based on molecular orbital calculations by Reetz et al. the positive charge of tetraalkylammonium cation (R_4N^+) was expected to be delocalized on the α-carbon and hydrogen atoms;[29a] that is, not delocalized on the nitrogen atom. Moreover, the presence of hydrogen bonds between the α-methylene units of the tetrabutylammonium cations and enolate oxygen atoms, making the anions and cations interact in a highly ordered manner, was revealed by several X-ray structural analyses.[29b,c] The magnitude of the stabilizing interaction of an aliphatic C–H bond attached to an ammonium nitrogen and a carbonyl oxygen (R_3N^+–C–H···O=C) was evaluated by Houk et al. using ab initio calculations.[29d] Because TaDiAS **3** has two-ammonium cation moieties in the molecule, we expect that it might form a tight complex with the *Z*-enolate of ketimine **1**.[30] To test our hypothesis, we performed more precise calculations of the ion pairs of the counter anion-free dicationic catalyst of (*S*,*S*)-TaDiAS and the *Z*-enolate of **1**. Starting from the structure shown in Figure 2, one of the acetal moiety substituents was changed to *t*-Bu from Me. After molecular mechanics optimization, the obtained structure was further optimized by ab initio calculation at the HF/3-21G level followed by B3LYP hybrid density functional methods using a 3-21G basis set with Gaussian 98. This calculation suggests that the *Z*-enolate of **1** is fixed with the catalyst **3** through several hydrogen bonds between the α-methylene or methyne unit of the ammonium cation units and the enolate oxygen atom and imine nitrogen atom of **1** (Fig. 6).

The precise reaction mechanism, especially the reason for opposite facial selectivity between alkylation and Michael addition, remains unclear. Further intensive studies aimed at determining the reaction mechanism are ongoing.

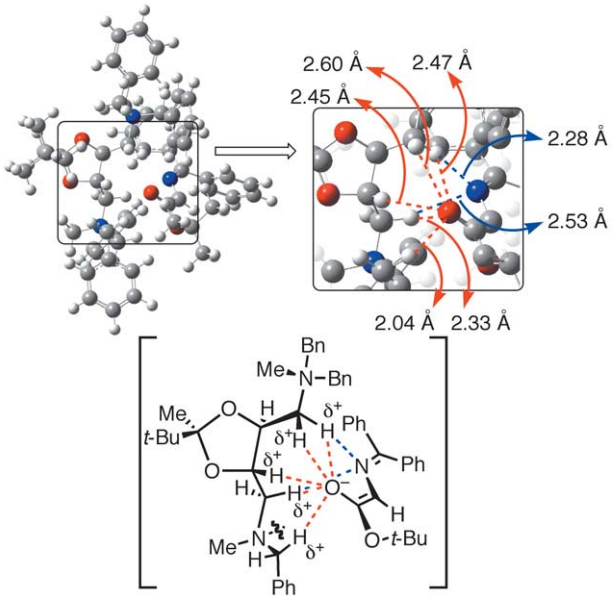


Figure 6. Results of optimization by molecular orbital calculations.

3. Conclusion

In conclusion, we designed a new versatile asymmetric two-center catalyst TaDiAS **3** and constructed a catalyst library. A variety of (*S*,*S*)- and (*R*,*R*)-TaDiAS **3** catalysts were easily synthesized from diethyl L- and D-tartrate, respectively, using only common and inexpensive reagents under operationally simple reaction conditions. They were applied in phase-transfer alkylations and Michael additions and,

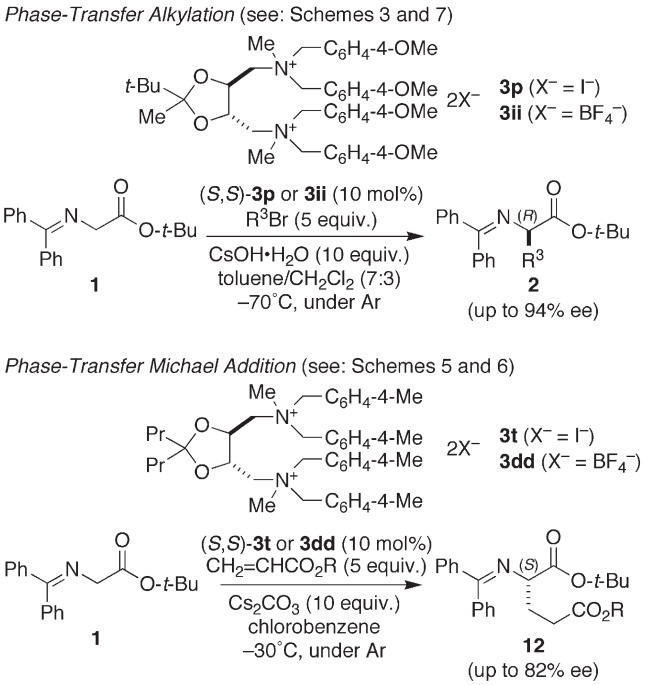


Figure 7. Summary of phase-transfer alkylation and Michael addition of **1** using TaDiAS **3**.

starting from the initial catalyst **3aa**, the enantiomeric excess of both alkylated products and Michael adducts was greatly improved (up to 94% ee and 82% ee, respectively) by screening the acetal moiety and the aromatic moiety in the catalyst **3**. Moreover, dramatic counter anion effects in PTC were observed for the first time, making it possible to further improve reactivity and selectivity. The results were summarized in Figure 7. These findings validate the usefulness of three-dimensional fine-tuning of the catalyst **3** (acetal, Ar, and counter anion) for optimization. Recovery using simple operations and reuse of the catalyst **3** were also performed. The present asymmetric PTC was successfully applied to the enantioselective syntheses of serine protease inhibitor aeruginosin 298-A and its analogues. Further studies on catalyst tuning, reaction mechanisms, application to other phase-transfer reactions, their industrial application, and the development of new types of bifunctional organocatalysts are in progress.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra (for LC-MS) were measured on a Waters micromass ZQ. EI mass spectra (for HR-MS) were measured on a JEOL JMS-MS/700V in positive ion mode. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric excess was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 or 280 nm; column, DAICEL CHIRALPAK AD, AS, AS-H, or OD; mobile phase, hexane-2-propanol or EtOH–2-propanol; flow rate, 0.4–1.0 mL/min. Reactions were performed in dry solvents under an argon atmosphere, unless otherwise stated.

4.2. General procedure for the synthesis of TaDiAS 3

4.2.1. Synthesis of (4*S*,5*S*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dicarboxamide (7p). A mixture of 3,3-dimethyl-2-butanone (12.5 mL, 0.10 mol), methyl orthoformate (16.4 mL, 0.15 mol), *p*-toluenesulfonic acid monohydrate (95 mg, 5 mmol), and methanol (50 mL) was gently heated while the methyl formate produced in the reaction was distilled off through a short Vigreux column. To the cooled reaction mixture, diethyl L-tartrate (13.7 mL, 0.08 mol) and toluene (30 mL) were added and brought to reflux for 24 h. The cooled reaction mixture was basified by the addition of potassium carbonate (5 g) and stirred at room temperature for 1 h. After evaporation of the reaction mixture, the residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford a mixture of methyl and ethyl ester, which was used for the next reaction without further purification. A solution of the esters (17.5 g) in methanol (100 mL) was cooled to 4 °C (ice-water bath) and then NH_3 gas was introduced by bubbling. Bubbling was continued for 2 h and then the solvent was evaporated to give crude **7p**, which was further purified by recrystallization from methanol (11.2 g, 0.049 mol, 61% from diethyl L-tartrate) as a white crystal. Mp 235–238 °C; $[\alpha]_D^{23}=+2.7$ (*c* 1.02, CH_3OH); FT-IR (KBr) ν_{max} 3460, 3295, 2979, 1665, 1087 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (br-s, 2H; $CONH_2$), 7.43 (br-s 2H; $CONH_2$), 4.46 (d, *J*=8.0 Hz, 1H; OCH), 4.18 (d, *J*=8.0 Hz, 1H; OCH), 1.28 (s, 3H; Me), 0.96 (s, 9H; *t*-Bu); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4 ($CONH_2$), 169.9 ($CONH_2$), 116.5 (*t*-Bu*C*Me), 78.2 (OCH), 77.1 (OCH), 38.4 ($C(CH_3)_3$), 25.0 ($C(CH_3)_3$), 19.5 (Me); MS [ESI(+)] *m*/*z* 253 (M+Na$^+$). Anal. calcd for $C_{10}H_{18}N_2O_4$: C 52.16, H 7.88, N 12.17. Found: C 52.12, H 7.78, N 12.14.

4.2.2. Synthesis of (4*S*,5*S*)-2-*tert*-butyl-*N*,*N*,*N*′,*N*′-tetrakis[(4-methoxyphenyl)methyl]-2-methyl-1,3-dioxolane-4,5-dimethanamine (8p). Diamide **7p** (3.45 g, 15 mmol) was placed in a Soxhlet thimble and extracted into a refluxing suspension of lithium aluminum hydride (2.0 g, 52.5 mmol) in anhydrous THF (200 mL). Refluxing was continued for 20 h and the suspension was cooled to room temperature. Water (2.0 mL) was added dropwise to the mixture, followed by 4 N aqueous NaOH (2.0 mL) and water (6.2 mL). The mixture was filtered, the resulting solid was washed with THF, and the combined filtrates were concentrated to afford the crude diamine (2.99 g, ca. 99%) as a pale brown oil. A solution of the diamine (2.62 g, 13 mmol) and *i*-Pr_2NEt (13.6 mL, 78 mmol) in CH_3CN (30 mL) was treated with 4-methoxybenzyl chloride (8.8 mL, 65 mmol) and TBAI (480 mg, 1.3 mmol) at 0 °C. After the starting material was completely consumed, the reaction was quenched by the addition of Et_3N (10 mL). After additional stirring for 1 h, water was added and the mixture was extracted with ether (10 mL×3), washed with brine (10 mL×3), and dried over Na_2SO_4. After evaporation, the crude mixture was purified by flash column chromatography (silica gel, 10–30% EtOAc in hexane) to give **8p** (7.27 g, 82%) as a colorless oil; R_f=0.41 (silica gel, EtOAc–hexane 1:3); $[\alpha]_D^{23}=-5.8$ (*c* 0.97, $CHCl_3$); FT-IR (neat) ν_{max} 2955, 2061, 1883, 1610, 1248, 1087, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J*=9.0 Hz, 4H; Ar-H), 7.20 (d, *J*=9.0 Hz, 4H; Ar-H), 6.82 (d, *J*=9.0 Hz, 8H; Ar-H), 3.84–3.73 (m, 1H; OCH), 3.76 (s, 12H; OCH_3), 3.61 (d, *J*=13.5 Hz, 2H; ArCH_2N), 3.60 (d, *J*=13.5 Hz, 2H; ArCH_2N), 3.58–3.54 (m, 1H; OCH), 3.47 (d, *J*=13.5 Hz, 2H; ArCH_2N), 3.43 (d, *J*=13.5 Hz, 2H; ArCH_2N), 2.56 (m, 2H; OCHCH_2N), 2.54 (dd, *J*=13.5, 3.5 Hz, 1H; OCHCH_2N), 2.48 (dd, *J*=13.5, 7.0 Hz, 1H; OCHCH_2N), 1.20 (s, 3H; Me), 0.92 (s, 9H; *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9 (Ar-O), 131.9 (Ar), 130.4 (Ar), 114.5(*t*-Bu*C*Me), 113.9 (Ar), 80.0 (OCH), 78.6 (OCH), 56.2 (OCH_3), 58.1 (ArCH_2N), 55.6 (ArCH_2N), 54.7 (OCH_3), 39.2($C(CH_3)_3$), 25.6 ($C(CH_3)_3$), 21.2 (Me); MS [ESI(+)] *m*/*z* 683 [M+H$^+$]; HR-MS [FAB(+)] calcd for $C_{42}H_{55}N_2O_6^+$ [M+H$^+$]: 683.4060. Found: 683.4074.

4.2.3. Synthesis of (4*S*,5*S*)-2-*tert*-Butyl-*N*,*N*,*N*′,*N*′-tetrakis[(4-methoxyphenyl)methyl]-*N*,*N*′−2-trimethyl-1,3-dioxolane-4,5-dimethanammonium diiodide ((*S*,*S*)-3p). Methyl iodide (11.2 mL, 180 mmol) was added to **8p** (5.92 g, 9.0 mmol) at room temperature. After stirring for 18 h, the mixture was evaporated and purified by flash

column chromatography (silica gel, EtOAc to 20% MeOH in EtOAc) to give (*S*,*S*)-**3p** (7.74 g, 8.0 mmol, 89%) as a yellow solid. Mp 132–135 °C; R_f=0.35 (silica gel, 10% MeOH in EtOAc); $[\alpha]_D^{23}$=−63 (*c* 1.05, $CDCl_3$); FT-IR (KBr) ν_{max} 3448, 2961, 1611, 1464, 1182, 1027, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.5 Hz, 2H; Ar-H), 7.60 (d, *J*=8.5 Hz, 2H; Ar-H), 7.54 (d, *J*=8.5 Hz, 2H; Ar-H), 7.47 (d, *J*=8.5 Hz, 2H; Ar-H), 6.93 (d, *J*=8.5 Hz, 6H; Ar-H), 6.89 (d, *J*=8.5 Hz, 2H; Ar-H), 5.94 (m, 1H; OCH), 5.49 (d, *J*=13.0 Hz, 1H; NC$H_a$$H_b$Ar), 5.40 (d, *J*=12.5 Hz, 1H; NC$H_c$$H_d$Ar), 5.18 (d, *J*=14.5 Hz, 1H; OCHC$H_a$$H_b$N), 5.06 (d, *J*=12.5 Hz, 1H; NC$H_e$$H_f$Ar), 4.78 (d, *J*=12.5 Hz, 1H; NC$H_g$$H_h$Ar), 4.76 (d, *J*=12.5 Hz, 1H; OCHC$H_c$$H_d$N), 4.71 (d, *J*=13.0 Hz, 1H; NCH$_a$$H_b$Ar), 4.67 (d, *J*=13.0 Hz, 1H; NCH$_e$$H_f$Ar) 4.64 (d, *J*=12.5 Hz, 1H; NCH$_g$$H_h$Ar), 4.56 (m, 1H; OCH), 4.31 (d, *J*=12.5 Hz, 1H; NCH$_c$$H_d$Ar), 4.10 (dd, *J*=12.5 Hz, 10.0 Hz, 1H; OCHCH$_c$-H_dN), 3.80 (s, 6H; OCH_3), 3.78 (s, 3H; OCH_3), 3.73 (s, 3H; OCH_3), 3.49 (dd, *J*=14.5, 6.0 Hz, 1H; OCHCH$_a$$H_b$N), 2.94 (s, 3H; NCH_3), 2.91 (s, 3H, NCH_3), 1.83 (s, 3H; Me), 0.96 (s, 9H; *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 161.6, 135.5, 135.4, 135.2, and 135.1 (Ar), 119.3 (*t*-Bu*C*Me), 118,7, 118.6, 118.4, 118.0, 115.6, 115.0, and 114.9 (Ar), 74.6 (OCH), 73.2 (OCH), 66.2, 65.8, 65.2, and 65.0 (4 C; ArCH_2N), 62.1 (OCHCH_2N^+), 60.6 (OCHCH_2N^+), 55.8 (OCH_3), 47.6 (N^+CH_3), 46.1 (N^+CH_3), 39.2 ($C(CH_3)_3$), 25.7 (C(CH_3)$_3$), 22.7 (Me); MS [ESI(+)] *m*/*z* 989 [M+Na^+], 839 [M−I^-], 591 [M−2I^--CH_2Ar]. Anal. calcd for $C_{44}H_{62}I_2N_2O_7$ (M+H_2O): C 53.66, H 6.35, N 2.84. Found: C 53.66, H 6.40, N 3.04.

4.2.4. (4*S*,5*S*)-*N*,*N*′-Dimethyl-*N*,*N*,*N*′,*N*′-tetrakis[(4-methylphenyl)methyl]-2,2-dipropyl-1,3-dioxolane-4,5-dimethanammonium diiodide ((*S*,*S*)-3t). A yellow pale solid. Mp 112–115 °C; R_f=0.41 (silica gel, EtOAc); $[\alpha]_D^{22}$=−56.3 (*c* 1.02, $CHCl_3$); FT-IR (KBr) ν_{max} 2958, 1614, 1464, 1105, 805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J*=7.5 Hz, 4H; Ar-H), 7.49 (d, *J*=7.5 Hz, 4H; Ar-H), 7.24–7.28 (m, 8H), 5.29 (m, 2H; OCH), 5.23 (d, *J*=12.5 Hz, 2H; ArCH_2N), 5.18 (d, *J*=12.5 Hz, 2H; ArCH_2N), 5.09 (d, *J*=14.0 Hz, 2H, OCHCH_2N), 4.73 (d, *J*=12.5 Hz, 2H; ArCH_2N), 4.40 (d, *J*=12.5 Hz, 2H; ArCH_2N), 3.85 (m, 2H; OCHCH_2N), 2.97 (s, 6H, NCH_3), 2.39 (s, 6H; Ar-CH_3), 2.35 (s, 6H; Ar-CH_3), 1.89 (m, 2H, Pr), 1.81 (m, 2H; Pr), 1.33 (m, 4H; Pr), 0.95 (t, *J*=7.0 Hz, 6H; Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2 and 141.1 (Ar), 133.4 and 133.2 (Ar), 130.1 and 130.0 (Ar), 123.3 and 123.1 (Ar), 116.7 (Pr*C*Pr), 73.0 (2 C; OCH), 66.0 (2 C; ArCH_2N), 65.1 (2 C; ArCH_2N), 61.4 (2 C; CHCH_2N), 46.4 (NCH_3), 39.7 (Pr), 21.2 (Ar-CH_3), 17.5 (Pr), 14.0 (Pr); MS [ESI(+)] *m*/*z* 789 [M−I^-], 557 [M−2I^--CH_2Ar]. Anal. calcd for $C_{45}H_{64}N_2O_3$ (M+H_2O): C 57.82, H 6.90, N 3.00. Found: C 57.77, H 6.86, N 3.04.

4.2.5. Synthesis of (4*S*,5*S*)-2-*tert*-butyl-*N*,*N*,*N*′,*N*′-tetrakis[(4-methoxyphenyl)methyl]-*N*,*N*′-2-trimethyl-1,3-dioxolane-4,5-dimethanammonium bistetrafluoroborate ((*S*,*S*)-3ii). Trimethyloxonium tetrafluoroborate (4.44 g, 30 mmol) was added to a solution of **8p** (6.32 g, 10 mmol) in CH_2Cl_2 (100 mL) at room temperature. The mixture was stirred for 6 h and concentrated. The residue was recrystallized from ethyl acetate and hexane to give **3ii** as a white solid (7.26 g, 8.7 mmol, 87%). Alternatively, **3ii** can be synthesized from **3p** using the following procedure. $AgBF_4$ (428 mg, 2.2 mmol) was added to a solution of **3p** (913 mg, 1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 2 h, and filtrated to remove the AgI. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 50–100% EtOAc in hexane) to give **3ii** (846 mg, 0.95 mmol, 95%). Mp 171–173.5 °C; R_f=0.72 (silica gel, EtOAc); $[\alpha]_D^{23}$=−33.2 (*c* 1.11, $CHCl_3$); FT-IR (KBr) ν_{max} 2972, 2841, 1613, 1518, 1468, 1029, 843, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.37 (m, 8H; Ar-H), 6.96 (d, *J*=9.0 Hz, 2H; Ar), 6.95 (d, *J*=9.0 Hz, 2H; Ar), 6.90 (d, *J*=8.5 Hz, 4H; Ar), 4.88 (m, 1H; OCH), 4.76 (d, *J*=14.0 Hz, 1H; NC$H_a$$H_b$Ar), 4.73 (d, *J*=14.0 Hz, 1H; NC$H_c$$H_d$Ar), 4.58 (d, *J*=13.0 Hz, 2H; NC$H_e$$H_fAr, NCH_g$$H_h$Ar), 4.41–4.32 (m, 4H; NCH$_a$$H_bAr, NCH_c$$H_dAr, NCH_e$$H_fAr, NCH_g$-$H_h$Ar), 4.30 (m, 1H; OCH), 3.82 (s, 6H; OMe), 3.80 (s, 3H; OMe), 3.78 (s, 3H; OMe), 3.76 (m, 2H; OCHCH_2N), 3.63 (m, 2H; OCHCH_2N), 2.81 (s, 6H; NMe), 1.49 (s, 3H; Me), 0.90 (s, 9H; *t*-Bu); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 161.6, 135.0, 134.9, 134.8, and 134.7 (Ar), 119.0 (*t*-Bu*C*Me), 118.4, 118.3, 118.2, 118.0, 115.1, 115.0, 114.94, and 114.91 (Ar), 74.0 (OCH), 72.6 (OCH), 67.6, 67.2, 66.6, and 66.2 (4 C; ArCH_2N), 62.3(CHCH_2N), 61.6 (CHCH_2N), 55.5 (OCH_3), 46.5 (NCH_3), 45.6 (NCH_3), 38.8 ($C(CH_3)_3$), 25.3 (C(CH_3)$_3$), 20.6 (Me); MS [ESI(+)] *m*/*z* 909 [M+Na^+], 799 [M−BF_4^-]; HR-MS [FAB (+)] calcd for $C_{44}H_{60}F_4N_2O_6B^+$ (M−BF_4^-): 799.4475. Found: 799.4469.

4.2.6. (4*S*,5*S*)-*N*,*N*′-Dimethyl-*N*,*N*,*N*′,*N*′-tetrakis[(4-methylphenyl)methyl]-2,2-dipropyl-1,3-dioxolane-4,5-dimethanammonium bistetrafuluoroborate ((*S*,*S*)-3dd). A white solid. Mp 201–204 °C; R_f=0.68 (silica gel, EtOAc); $[\alpha]_D^{22}$=−32.4 (*c* 0.98, $CHCl_3$); FT-IR (KBr) ν_{max} 2963, 1617, 1475, 1074, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J*=8.0 Hz, 4H; Ar-H), 7.36 (d, *J*=8.0 Hz, 4H; Ar-H), 7.28–7.23 (m, 8H; Ar-H), 4.80 (d, *J*=13.0 Hz, 2H; ArCH_2N), 4.77 (d, *J*=12.0 Hz, 2H; ArCH_2N), 4.70 (d, *J*=7.0 Hz, 2H; OCH), 4.40 (d, *J*=12.0 Hz, 2H; ArCH_2N), 4.30 (d, *J*=13.0 Hz, 2H; ArCH_2N), 3.96 (d, *J*=13.5 Hz, 2H; OCHCH_2N), 3.78 (dd, *J*=13.5, 8.0 Hz, 2H; OCHCH_2N), 2.40 (s, 6H; Ar-CH_3), 2.83 (s, 6H; NCH_3), 2.37 (s, 6H; Ar-CH_3), 1.70 (m, 4H, Pr), 1.27 (m, 4H; Pr), 0.91 (t, *J*=7.5 Hz, 6H; Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 130.3, 123.5, and 123.3 (Ar), 117.0 (Pr*C*Pr), 73.0 (OCH), 67.5 (2C; ArCH_2N), 66.6 (2C; ArCH_2N), 62.5 (OCHCH_2N), 46.1 (NCH_3), 14.2 (Pr), 39.5 (Pr), 21.4 (Ar-CH_3), 17.6 (Pr); MS [ESI(+)] *m*/*z* 749 [M−BF_4^-], 557 [M−2BF_4^--CH_2Ar]. Anal. calcd for $C_{45}H_{62}B_2F_8N_2O_2$: C 64.60, H 7.47, N 3.35. Found: C 64.49, H 7.37, N 3.31.

4.3. General procedure for the catalytic asymmetric phase-transfer alkylation using TaDiAS 3p under optimized conditions

A solution of 4-(triisopropylsilanyloxy)benzyl bromide (approximately 0.2 M in toluene, 7.0 mL, 3.5 mmol, 5.0 equiv.) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**1**) (207 mg, 0.70 mmol) and phase-transfer catalyst (*S*,*S*)-TaDiAS **3p** (67 mg, 0.070 mmol, 10 mol%) in CH_2Cl_2 (3.0 mL, total 0.07 M) at −70 °C. Finally, CsOH·H_2O (1.18 g, 7.0 mmol, 10 equiv.) was added directly to the reaction mixture at the

same temperature. After stirring for 72 h at the same temperature, the reaction was quenched by the addition of water followed by diethyl ether. After vigorous stirring at room temperature, both organic and aqueous layers were transferred to a separation funnel by simple decantation. The organic layer was separated and washed with brine. The combined aqueous layers were re-extracted with diethyl ether and the combined organic layers were dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (silica gel deactivated with Et_3N, hexane only to 5% EtOAc in hexane) to give (*R*)-**2d** (343.2 mg, 88%) as a colorless oil and the remaining excess electrophile was recovered (820 mg, 85%). The catalyst was also recovered (60 mg, 90%) using the procedure shown in Figure 4. Spectroscopic data of the alkylated products **2** were reported in Refs. 5, 6, 9, 12.

The ketimine (*R*)-**2d** was treated with 0.5 N aqueous citric acid solution (1.5 mL) in THF (6.2 mL) for 90 min at room temperature. The mixture was quenched with water and the aqueous phase was basified with solid $NaHCO_3$, extracted with CH_2Cl_2 (three times), and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (silica gel, 40–60% EtOAc in hexane) to give the corresponding α-amino ester (198 mg, 82%). Alternatively, transformation of (*R*)-**2d** to the α-amino ester was promoted by 5 mol % of Pd–C in MeOH under a hydrogen atmosphere (1 atm) (91% yield).

4.4. General procedure for the catalytic asymmetric phase-transfer Michael addition using TaDiAS 3dd under optimized conditions

Benzyl acrylate (**11d**, 20.3 μL, 0.23 mmol) was added to the solution of **1** (44.2 mg, 0.15 mmol) and phase-transfer catalyst (*S*,*S*)-TaDiAS **3dd** (12.5 mg, 0.015 mmol) in chlorobenzene (1.0 mL). The reaction mixture was stirred at −30 °C for 20 min, and then Cs_2CO_3 (24.4 mg, 0.075 mmol) was added. The mixture was stirred vigorously at the same temperature for 10 h. The reaction was quenched by the addition of water and extracted with Et_2O (10 mL×3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give (*S*)-**12d** (46.2 mg, 84%) as a colorless oil. Spectroscopic data of the alkylated products **2** were reported in Ref. 21.

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14. For example, (Sigma-Aldrich Co., St. Louis, MO), L-tartaric acid: 100 g, 4100 yen (ca. $ 33), diethyl L-tartrate: 100 g, 8600 yen (ca. $ 70), quinine: 100 g, 78000 yen (ca. $ 640), and (*R*)-BINOL: 100 g, 783000 yen (ca. $ 6420).
15. Computational simulation was performed with Cerius^2 (Accelrys Inc., San Diego, CA, and Cambridge, UK). The conformation depicted in Figure 2 was obtained using a random conformational search, the so-called Monte Carlo method, followed by a molecular mechanics minimization calculation (Universal Force Field v.1.02, see: Rappe, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W.A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024).
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17. Although TADDOL promotes asymmetric phase-transfer alkylation of aldimine, it is not effective for alkylation of ketimine. See Ref. 10a.
18. Both enantiomers of TaDiAS **3p** (R^1=*t*-Bu, R^2=Me, Ar=C_6H_4-4-OMe, X^-=I^-) and **3dd** (R^1=R^2=Pr, Ar=C_6H_4-4-Me, X^-=BF_4^-) are now commercially available from Wako Pure Chemical Industries, Ltd., Japan (fax: +81-120-052-806; e-mail: labchem-tec@wako-chem.co.jp) [Catalog No. 201-16141 for (*R*,*R*)-**3p**, 208-16151 for (*S*,*S*)-**3p**, 205-16161 for (*R*,*R*)-**3dd**, and 202-16171 for (*S*,*S*)-**3dd**].
19. For the purpose of catalyst screening, the described reaction conditions were selected based on reaction time. In preliminary studies, toluene gave the best selectivity and CH_2Cl_2 gave the best reactivity in phase-transfer alkylations. Finally, addition of CH_2Cl_2 to toluene (toluene/CH_2Cl_2 =7:3) enhanced reactivity efficiently without loss of selectivity.
20. When dimethyl acetal (R^1=R^2=Me) was used for catalyst synthesis, a mixture of diammonium salt and monoammonium salt was obtained due to low reactivity in the methylation step. Therefore, screening of the aromatic moiety was difficult with dimethyl acetal. Changing the acetal moiety solved this low reactivity problem.
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23. Because of the relatively high melting point of chlorobenzene (−45 °C), −30 °C should be the lowest temperature used in this system. Other solvents, such as toluene, had worse selectivity.
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Toward the modular synthesis of glycosaminoglycans: synthesis of hyaluronic acid disaccharide building blocks using a periodic acid oxidation

Emma R. Palmacci[†] and Peter H. Seeberger*,[‡]

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA

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Dedicated to Professor Dieter Seebach

Abstract—The synthesis of two differentially protected GluNAc-β(1→4)-GluA and GluA-β(1→3)-GluNAc disaccharide modules for the solid-phase assembly of hyaluronic acid are described. A periodic acid/chromium trioxide oxidation was the key transformation to facilitate access to the glucuronic acid moiety from glucose and should find wide application in the oxidation of primary alcohols.

1. Introduction

Glycosaminoglycans, the most acidic biopolymers, are part of the extracellular matrixproteoglycan and cell surface, and are found intracellularly in granules.[1] Ubiquitous in the human body, glycosaminoglycans play a key role in regulating the biological activity of several proteins in the coagulation cascade in addition to many other processes of biomedical importance including growth factor interactions, virus entry, and angiogenesis.[2,3]

The glycosaminoglycan structure-activity relationship is still poorly understood due to the complexity and heterogeneity of these polymers. It has become increasingly evident that defined lengths and sequences of glycosaminoglycans are responsible for binding to a particular protein and modulating its biological activity.[4–7] A more detailed understanding of the structure-function relationships of glycosaminoglycans provides an opportunity for the discovery of novel therapeutic interventions for a variety of disease states.

Heparin is the glycosaminoglycan studied in most detail, but hyaluronic acid (HA) has seen increased interest due to its involvement in wound healing,[8] tumor metastasis,[9] neurodegenerative diseases[10] and arthritis.[11,12] Clinically, modified hyaluronic acid is used as a postoperative anti-adhesive and as a biodegradable material for applications such as drug delivery and tissue engineering.[13] Hyaluronic acid, as is characteristic of glycosaminoglycan structures, is a large, linear repeating polymer of alternating hexosamine and uronic acid monosaccharides (Fig. 1).[3] Notably, HA is the only unsulfated glycosaminoglycan and is comprised of glucuronic acid β-(1→3) linked to *N*-acetyl glucosamine.

Access to defined oligosaccharides is crucial to understanding the role of hyaluronic acid in biological systems. Current methods for the isolation of hyaluronic acid rely on the degradation of polymers from animal sources or from enzymatic fermentation, resulting in a broad molecular weight distribution and sample contamination with other glycosaminoglycans.[4,14] Chemoenzymatic approaches have been applied to the acquisition of hyaluronic acid and chondroitin sulfate with promising results.[15] Still, the procurement of useful quantities of defined glycosaminoglycan structures relies mostly on synthetic methods.[16–19]

2. Synthetic strategy

We are currently pursuing an overall program aimed at the automated solid support synthesis of all naturally occurring

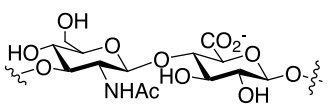

Figure 1. Hyaluronic acid.

Keywords: Hyaluronic acid; Oxidation; Glycosaminoglycans; Modular synthesis; Periodic acid.
* Corresponding author. Tel.: +41-1-633-2103; fax: +41-1-633-1235; e-mail address: seeberger@org.chem.ethz.ch
† Thios Pharmaceuticals, Emeryville, CA.
‡ Laboratory for Organic Chemistry, ETH-Zurich/HCI F 315, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland.

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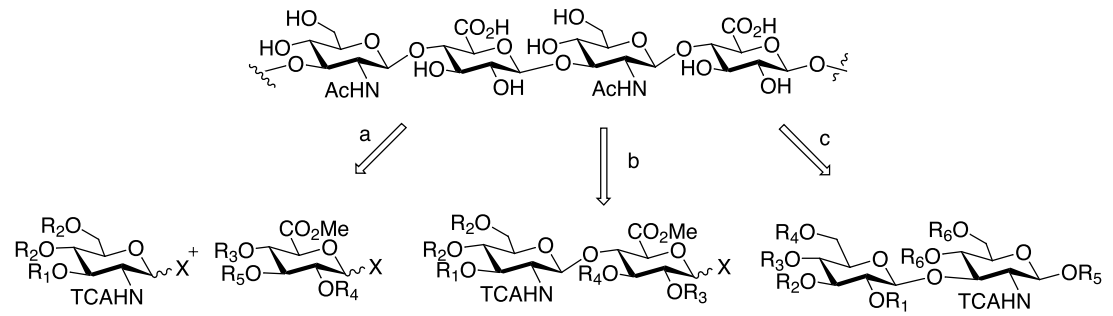


Scheme 1. Different synthetic strategies for the assembly of hyaluronic acid oligosaccharides. (a) Monosaccharide approach; (b) disaccharide approach using uronic acid reducing end; (c) disaccharide approach using glucosamine reducing end.

classes of glycoconjugates.[20] Particular interest has been focused on the modular assembly of glycosaminoglycans including heparin.[21] The automated synthesis of HA may be envisioned using either monosaccharides (Scheme 1(a)) or disaccharides (Scheme 1(b) or (c)). Two different disaccharide modules can be used that contain either a terminal uronic acid (Scheme 1(b)) or a terminal glucosamine (Scheme 1(c)).

Efficient glycosyl building blocks to be used in an automated assembly scheme, whether using the monosaccharide or disaccharide approach, must meet several criteria. The activation and deprotection conditions must be compatible with the linker and the solid support. Previous work with the automated synthesis of oligosaccharides demonstrated that trichloroacetimidates and glycosyl phosphates work well with the automated method, along with acetate, levulinate and silyl ethers temporary protecting groups.[20] The incompatibility of the glucuronic acid moiety in the glycosaminoglycan structures precludes the use of acetyl esters and silyl ethers, therefore the synthesis would be based on the levulinate temporary protecting group.[22] The amine protecting group chosen was the *N*-trichloroacetamide group, based on its successful use in previous synthesis requiring the glycosylation of the C3-hydroxyl of glucosamine and its direct transformation to the necessary *N*-acetamide.[23,24]

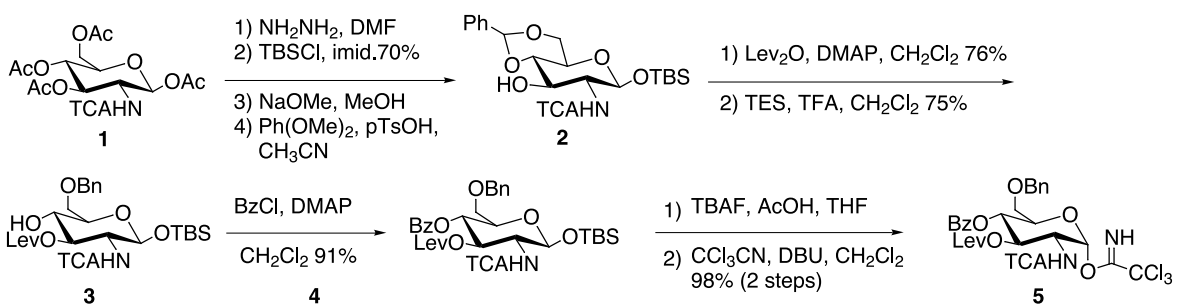
Following these principal strategic considerations the synthesis of the required building blocks to validate the feasibility of each approach was undertaken.

3. Synthesis of a differentially protected glucosamine building block

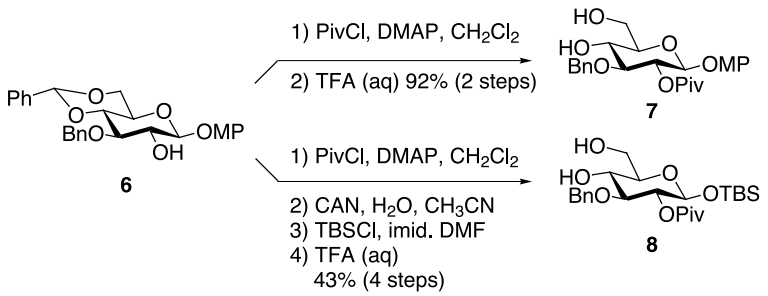
The three different strategies for the assembly of defined HA oligosaccharides will require the preparation of differentially protected glucosamine building blocks. In designing a monomer that would be not only useful for the synthesis of HA but that might also serve in the synthesis of chondroitin sulfate oligomers, a benzoate group was installed on the C4 hydroxyl group that could be removed at the oligosaccharide stage if desired. Synthesis of such a differentially protected monomer utilized known tetraacetyl *N*-trichloroacetamide glucosamine **1**[22] as starting material. The anomeric acetate of glucosamine **1** was exchanged for an anomeric silyl ether. Removal of the remaining acetates and installation of a 4,6-di-*O*-benzylidene afforded monosaccharide **2** (Scheme 2). Protection of the C3-hydroxyl as a levulinic ester and opening of the 4,6-benzylidene under reductive conditions (TES, TFA) afforded the C4-OH glucosamine **3**. Benzoylation of the liberated hydroxyl group afforded fully protected **4**. Conversion of **4** to glycosyl trichloroacetimidate **5** by cleavage of the anomeric silyl ether with TBAF and subsequent treatment of the lactol with trichloroacetonitrile and catalytic amounts of DBU was readily achieved.

4. Synthesis of a differentially protected glucuronic acid building block

In addition to the glucosamine monomer, straightforward access to a glucuronic acid monosaccharide is essential to synthesize hyaluronic acid. In previous syntheses, lengthy procedures were used to access differentially protected glucuronic acid modules.[16–19] For use in a disaccharide approach, a glucuronic acid acceptor would be equipped with a temporary protecting group at C1, an ester at C2 to confer stereochemistry in the glycosylation reaction and a C3-*O*-benzyl group to ensure high coupling yields.



Scheme 2. Synthesis of glucosamine building block **5**.



Scheme 3. Synthesis of diols for selective oxidation.

The synthesis of the glucuronic acid module was attempted initially through a selective glucose oxidation. TEMPO was reported to selectively oxidize primary hydroxyls, giving the corresponding uronic acid.[23,24] The direct conversion of a diol to the glucuronic acid hydroxyl acceptor would eliminate much of the protecting group manipulations that plagued previous syntheses of glucuronic acid.

Two differentially protected glucoses were studied for the oxidation to the corresponding C5-carboxylic acids (Scheme 3). Diols **7** and **8** were synthesized using known procedures and submitted to TEMPO oxidation conditions. The oxidations did not yield more than 20% of the desired compounds. Platinum[25,26] and palladium[27] on carbon in the presence of oxygen have been reported to selectively oxidize primary alcohols to acids. Refluxing diols **7** and **8** in dioxane/water in the presence of the metal catalyst and O_2 resulted in decomposed starting material.

Non-selective oxidation conditions with differentially protected glucose derivatives were examined next. Initial results with the silyl and methoxyphenyl anomeric protected monosaccharides revealed that these modes of protection were not stable under oxidizing conditions. The synthesis of allyl glycosides **10**–**13** was readily achieved by protecting group manipulations starting from 4,6-*p*-methoxybenzylidene protected glucose **9**. Installation of the C2-pivaloyl, followed by regioselective opening of the 4,6-benzylidene with $NaCNBH_3$ and TMS-Cl afforded C4-*p*-methoxybenzyl **11** (Scheme 4). Treatment of **11** with pyridinium dichromate (PDC)[28,29] or TEMPO in attempts to effect oxidation to the corresponding glucuronic acid resulted in decomposition of the PMB ether (Table 1). Further protecting group adjustments were needed to acquire a suitably protected glucose starting material. Treatment of **10** with $NaCNBH_3$ and trifluoroacetic acid afforded the corresponding C6-*p*-methoxylbenzyl ether. Masking of the C4-hydroxyl group as an acetyl ester and removal of the PMB ether resulted in differentially protected glucose **12**.

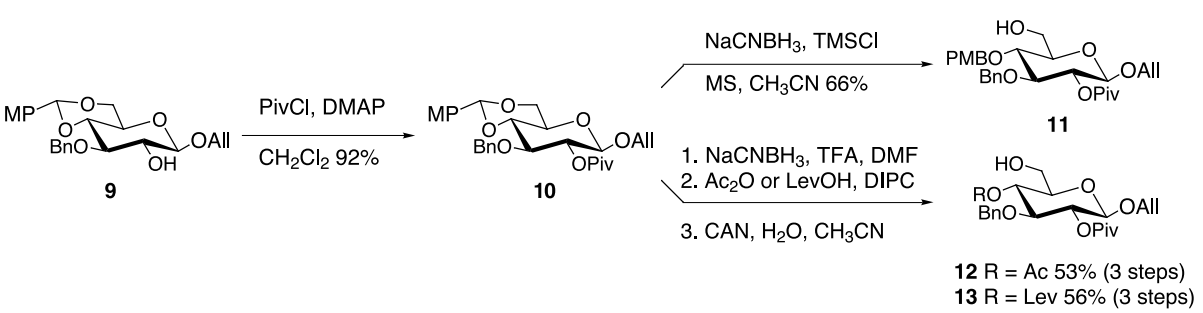
Table 1. Attempted oxidation of **7**, **8** and **11**

Starting material	Oxidation conditions	Yield (%)
7	TEMPO/NaOCl	20
	Pt/C or Pd/C, O_2	0
8	TEMPO/NaOCl	20
	Pt/C or Pd/C, O_2	0
11	TEMPO/NaOCl	0
	PDC/Ac_2O	0
	PDC/MS	0

Several methods for the oxidation of **12** were evaluated in the synthesis of the desired glucuronic acid (Table 2). Oxidation with PDC required six equivalents of the chromium oxidant and the difficult purification yielded only small amounts of the desired product. Use of resin-bound PDC was failed to remedy this problem as the support-bound reagent was too unreactive to facilitate the transformation.[30,31] TEMPO mediated oxidation with sodium hypochlorite was incompatible with allyl ether protected carbohydrates.[32] Attempts to oxidize the C6-hydroxyl group to the corresponding aldehyde via Swern oxidation[33] using either oxalyl chloride afforded the α,β-unsaturated aldehyde **14** as the major product due to elimination of the C4-*O*-acetate. The oxidation reagents TPAP,[34] $RuCl_2(PPh)_3$[35] and $NaNO_2/Ac_2O$[36] failed to react with the starting materials.

5. Successful oxidation and synthesis of the glucosamine–β(1→4)-glucuronic acid disaccharide

A chromium trioxide oxidation was reported to have

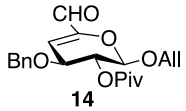


Scheme 4. Synthesis of allyl protected glucoses.

Table 2. Oxidation of **12**

Starting material	Oxidation conditions	Yield (%)
12	PDC/Ac_2O	20
	TPAP, O_2, ms	0
	TEMPO/NaOCl	0
		0
	Oxalyl-CI, DMSO, Et_3N	0[a]
	H_5IO_6, CrO_3	70[b]

[a] Oxidation yielded **14** but 0% of desired compound.
[b] Yield of **15** after methylation.



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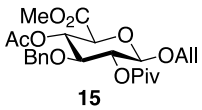

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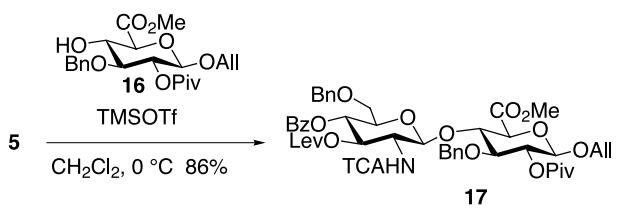
excellent functional group tolerance under conditions that would be suitable for a carbohydrate scaffold.[37–39] Oxidation of **12** with a solution of periodic acid and a catalytic amount of chromium trioxide[40] in wet acetonitrile cleanly afforded the corresponding glucuronic acid (Table 2). Formation of the methyl ester was accomplished with methyl iodide and $NaHCO_3$ in DMF to furnish **15** in 70% yield. Treatment of **15** with sodium methoxide in methanol yielded the desired glucuronic acid allyl glycoside **16** and the elimination product in approximately equal amounts. An improved pathway to **16** commenced with C4-levulinate protected **13**. Oxidation with H_5IO_6/CrO_3 and removal the levulinate protecting group cleanly afforded acceptor **16**. Glycosylation of **16** with glucosamine **5** afforded HA disaccharide **17** in 86% yield (Scheme 5). The disaccharide module **17** can serve either as reducing end disaccharide or as precursor for the preparation of a repeating disaccharide glycosylating agent that would merely require deprotection and installation of an anomeric leaving group.

6. Synthesis of glucuronic acid–β(1→3)-glucosamine disaccharide

In addition to disaccharide module **17** that may be used in the synthesis of HA oligosaccharides as outlined in Scheme 1, the reverse disaccharide module containing a glucosamine reducing end also was accessible utilizing the periodic acid oxidation. Allyl glycoside **18**[41] was employed for the synthesis of the glucosamine monosaccharide since this anomeric protecting group proved to be compatible with the periodic acid C6 oxidation. Protection of the C3-hydroxyl of **18**[42] with levulinic acid and opening of the 4,6-benzylidene yielded **19** (Scheme 6). Acetylation and treatment with hydrazine acetate afforded differentially protected glucosamine **20** ready for further elaboration.



Scheme 5. Construction of the disaccharide building block.

With the glucosamine portion of a putative disaccharide module in hand, we undertook the preparation of the glucose that at the disaccharide stage would become the glucuronic acid moiety by periodic acid oxidation. Thus, differentially protected glucose thioglycoside **22** was synthesized from known **21**[43] (Scheme 7) by selective opening of the 4,6-*p*-methoxybenzylidene ring and protection of the resulting hydroxyl. The anomeric thioether served to protect the anomeric position during the installation of the necessary protecting group and was utilized subsequently as glycosylating agent. Activation of **22** with MeOTf in the presence of **20** initiated the union to afford the corresponding disaccharide (Scheme 7). Treatment of the crude reaction mixture with ceric ammonium nitrate resulted in the removal of the PMB ether and provided disaccharide **23** in 50% yield. Oxidation of **23** with H_5IO_6/CrO_3 in acetonitrile and subsequent methylation afforded **24** (39%), still accompanied by unreacted disaccharide **23**. An increase in reaction time and equivalents of the oxidizing solution did not improve the conversion to the carboxylic acid. Nevertheless, access to the reducing end disaccharide module **24** that in addition can be readily converted into a repeating disaccharide module was achieved.

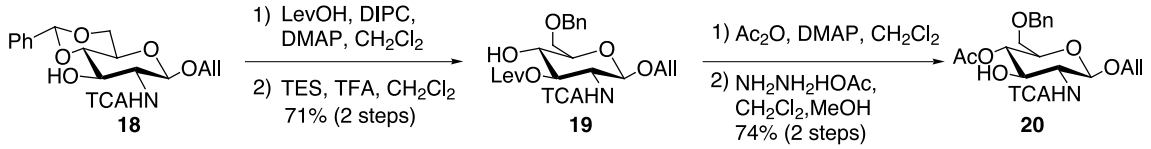
7. Summary

Described is the synthesis of several differentially protected glucosamine and glucuronic acid monosaccharides as well as two HA disaccharide modules that constitute key building blocks for the assembly of defined hyaluronic acid oligomers. A mild periodic acid oxidation protocol to operate on a glucose monosaccharide and a glucose–β(1→3)-glucosamine disaccharide to install the glucuronic acid moiety was developed. This transformation had been difficult or impossible with a long list of other oxidation procedures but was readily achieved applying a mild periodic acid oxidation. Future work will evaluate both disaccharides in the synthesis of hyaluronic acid oligomers in solution and on solid support. The periodic acid oxidation procedure should prove useful in the synthesis of other carboxylic acid containing carbohydrates.

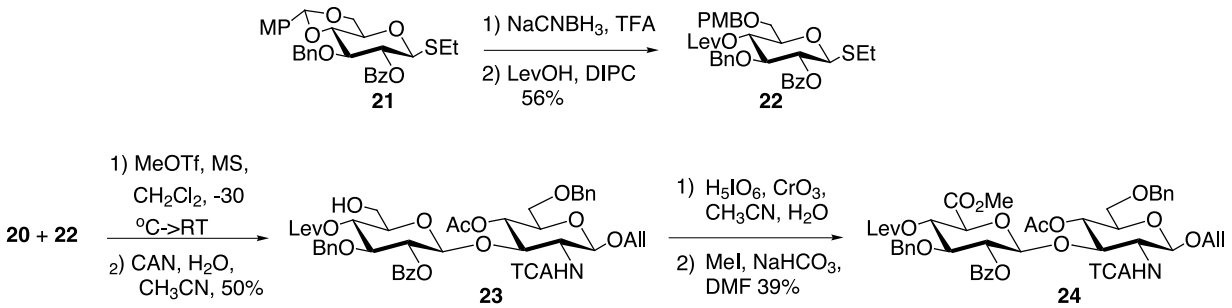
8. Experimental

8.1. General methods

All chemicals used were reagent grade and used as supplied except where noted. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) and toluene were purchased from JT Baker and purified by a Cycle-Tainer Solvent Delivery System. Pyridine was refluxed over calcium hydride and distilled prior to use. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was purchased from Acros Chemicals. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Liquid chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10–40 μm). ^1H NMR spectra were obtained on a Varian VXR-300



Scheme 6. Synthesis of allyl protected glucosamine **20**.



Scheme 7. Synthesis of thioglycoside **22** and disaccharide **24**.

(300 MHz), Varian VXR-500 (500 MHz) or a Bruker 400 (400 MHz) and are reported in parts per million (δ) relative to $CHCl_3$ (7.27 ppm). Coupling constants (J) are reported in Hertz. ^{13}C NMR spectra were obtained on a VXR-300 (75 MHz), a Bruker-400 (100 MHz) or a VXR-500 (125 MHz, CDCl3) and are reported in δ relative to $CDCl_3$ (77.23 ppm) as an internal reference. ^{31}P spectra were obtained on a VXR-300 (120 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference.

8.1.1. *tert*-Butyldimethylsilyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-glucopyranoside (1.18 g, 2.40 mmol) was dissolved in THF (20 mL). Benzyl amine (0.80 mL, 7.20 mmol) was added and the solution was stirred for 6 h. The mixture was diluted with EtOAc (100 mL) and washed with 5% HCl (100 mL). The aqueous layer was extracted with EtOAc (3×100 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and the solvents were removed in vacuo. The residue was dissolved in DMF (15 mL) and TBS chloride (0.470 g, 3.12 mmol) and imidazole (0.293 g, 4.80 mmol) were added. The solution was stirred for 12 h, diluted with Et_2O (100 mL) and washed with sat. $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvents were removed in vacuo. Chromatography (3:1 hexanes–EtOAc) afforded *tert*-butyldimethylsilyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside as a colorless oil (0.950 g, 70%). $[\alpha]_D^{24}=-4.2°$ (*c* 2.62, CH_2Cl_2); IR (thin film, NaCl) 2931, 2858, 1751, 1717, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, J=8.8 Hz, 1H), 5.31 (dd, J=9.2, 9.5 Hz, 1H), 5.09 (app t, J=9.5 Hz, 1H), 4.87 (d, J=7.9 Hz, 1H), 4.22 (dd, J=2.4, 12.2 Hz, 1H), 3.98–3.93 (m, 1H), 3.74 (ddd, J=2.4, 6.1, 9.8 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.8, 169.5, 162.0, 96.0, 92.5, 72.2, 71.8, 68.9, 62.6, 58.1, 25.7, 20.9, 20.8, 20.8, 18.0,-4.0, −5.1; ESI MS *m/z* $(M+NH_4)^+$: calcd 581.0 obsd 581.4.

8.1.2. *tert*-Butyldimethylsilyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside 2. *tert*-Butyldimethylsilyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside (2.70 g, 4.78 mmol) was dissolved in MeOH (30 mL) and cooled to 0 °C. Sodium methoxide (328 μL, 1.43 mmol, 25 wt% solution in MeOH) was added and the resulting solution was stirred for 2 h at 0 °C. Dowex acidic resin was added to adjust the pH to 7, the resin was filtered off and the solvents were removed in vacuo. The residue was dissolved in CH_3CN (40 mL) and benzaldehyde dimethylacetal (0.96 mL, 6.20 mmol) and *p*-toluenesulfonic acid (25 mg) were added. The reaction mixture was stirred for 1 h, diluted with EtOAc (100 mL) and washed with water (1×100 mL) and sat. $NaHCO_3$ (1×100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford *tert*-butyldimethylsilyl 4,6-*O*-benzylidene-2-deoxy-2-trichloroacetamido-β-D-glucopyranoside **2**; IR (thin film, NaCl) 3332, 2858, 1696, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.40–7.34 (m, 2H), 6.98 (d, J=7.0 Hz, 1H), 5.54 (s, 1H), 5.11 (d, J=7.9 Hz, 1H), 4.32–4.27 (m, 2H), 3.79 (app t, J=10.1 Hz, 1H), 3.59–3.48 (m, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 137.6, 130.9, 130.1, 129.2, 129.1, 127.0, 102.6, 95.9, 82.3, 70.3, 69.3, 66.9, 62.3, 26.3, 18.5, −3.4, −4.5; ESI MS *m/z* $(M)^+$: calcd 526.2 obsd 526.9. **2** was dissolved in CH_2Cl_2 (30 mL) and levulinic anhydride (2.05 g, 9.56 mmol) and DMAP (0.700 g, 5.74 mmol) were added. The reaction mixture was stirred for 30 min and diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with sat. $NaHCO_3$ (1×100 mL). The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Chromatography (5:1 hexanes–EtOAc) afforded *tert*-butyldimethylsilyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside as a colorless syrup (2.30 g, 76%). $[\alpha]_D^{24}=-23.9°$ (*c* 2.14, CH_2Cl_2); IR (thin film, NaCl) 2930, 2858, 1719, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.39–7.35 (m, 2H), 7.15 (d, J=9.1 Hz, 1H), 5.51 (s, 1H), 5.44 (app t, J=9.8 Hz, 1H), 4.86 (d, J=8.1 Hz, 1H), 4.11 (dd, J=5.2, 10.7 Hz, 1H), 4.01–3.96 (m, 1H), 3.76–3.70 (m, 2H), 3.47 (app td, J=5.2, 9.8 Hz, 1H), 2.71 (app td, J=3.4, 7.3 Hz, 2H), 2.60 (t, J=6.4 Hz, 2H), 2.14 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1,

173.2, 162.2, 137.2, 129.3, 128.4, 126.3, 101.5, 96.5, 92.7, 78.9, 77.5, 77.0, 71.5, 68.7, 66.6, 58.8, 38.2, 30.0, 28.3, 25.8, 18.0, −3.9, −4.9; ESI MS *m/z* $(M+NH_4)^+$: calcd 641.1 obsd 641.5.

8.1.3. *tert*-Butyldimethylsilyl 6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside 3. *tert*-Butyldimethylsilyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside (0.710 g, 1.14 mmol) was co-evaporated with toluene (3×10 mL), dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Triethylsilane (0.910 mL, 5.70 mmol) was added, followed by the slow addition of trifluoroacetic acid (0.440 mL, 5.70 mmol). After 3 h, the reaction mixture was diluted with EtOAc (50 mL). The organic layer was washed with water (50 mL) and sat. $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered and concentrated. Chromatography (3:2→1:2 hexanes–EtOAc) afforded **3** (0.526 g, 75%). $[\alpha]_D^{24}=-28.2°$ (*c* 1.57, CH_2Cl_2); IR (thin film, NaCl) 2956, 2858, 1742, 1717, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 4H), 7.05 (br s, 1H), 5.26–5.20 (m, 1H), 4.83 (d, *J*=7.9 Hz, 1H), 4.61 (d, *J*=12.1 Hz, 1H), 4.57 (d, *J*=12.1 Hz, 1H), 3.98–3.89 (m, 1H), 3.80–3.73 (m, 3H), 3.66–3.61 (m, 1H), 3.33 (br s, 1H), 2.78 (app t, *J*=6.4 Hz, 1H), 2.63–2.44 (m, 2H), 2.17 (s, 3H), 0.87 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 173.6, 162.1, 138.1, 128.6, 127.9, 127.8, 96.1, 92.7, 75.6, 74.5, 70.4, 70.0, 57.7, 38.5, 30.0, 28.5, 25.8, 18.0, −3.9, −5.0; ESI MS *m/z* $(M+NH_4)^+$: calcd 643.1 obsd 643.6.

8.1.4. *tert*-Butyldimethylsilyl 4-*O*-benzoyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside 4. *tert*-Butyldimethylsilyl 6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside **3** (1.02 g, 1.63 mmol) was dissolved in CH_2Cl_2 (15 mL) and benzoyl chloride (0.23 mL, 1.95 mmol) and DMAP (0.240 g, 1.95 mmol) were added. After 1 h, hexanes–EtOAc (3:1, 50 mL) was added and the white precipitate was removed by filtration through a silica plug. The solvents were removed in vacuo and chromatography (3:1→3:2 hexanes–EtOAc) afforded **4** as a colorless oil (1.09 g, 91%); IR (thin film, NaCl) 2956, 2930, 1724, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J*=8.4 Hz, 2H), 7.60–7.53 (m, 2H), 7.44 (t, *J*=7.9 Hz, 1H), 7.25–7.20 (m, 4H), 6.81 (d, *J*=8.9 Hz, 1H), 5.54 (dd, *J*=9.2, 10.7 Hz, 1H), 5.35 (app t, *J*=9.5 Hz, 1H), 5.07 (d, *J*=7.9 Hz, 1H), 4.52 (d, *J*=12.2 Hz, 1H), 4.49 (d, *J*=12.2 Hz, 1H), 3.91–3.84 (m, 2H), 3.63 (d, *J*=4.3 Hz, 2H), 2.58–2.56 (m, 2H), 2.47–2.39 (m, 2H), 2.02 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 172.7, 170.2, 165.5, 162.0, 137.8, 133.8, 133.7, 130.3, 130.0, 129.3, 128.7, 128.4, 127.8, 95.7, 92.5, 73.8, 73.7, 71.9, 69.9, 69.5, 58.7, 38.0, 29.7, 28.2, 25.8, 18.0, −3.9, −5.1; ESI MS *m/z* $(M+NH_4)^+$: calcd 747.2 obsd 747.4.

8.1.5. 4-*O*-Benzoyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-α-D-glucopyranosyl trichloroacetimidate 5. *tert*-Butyldimethylsilyl 4-*O*-benzoyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetamido-β-D-glucopyranoside **4** (0.200 g, 0.274 mmol) was dissolved in THF (3.0 mL) and the solution was cooled to 0 °C. TBAF (0.33 mL, 1 M solution in THF) and AcOH (18.7 μL, 0.328 mmol) were added simultaneously. After 1 h, EtOAc (20 mL) was added and the organic layer was washed with water (20 mL). The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (1×50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (2.0 mL) and the solution was cooled to 0 °C. Trichloroacetonitrile (1.0 mL) was added followed by the addition of DBU (25 μL). The reaction mixture was stirred for 1 h, filtered through a silica plug (3:1 hexanes–EtOAc) and the solvents were removed in vacuo to afford **5** as a yellow foam (0.254 g, 98%). $[\alpha]_D^{24}=+55.7°$ (*c* 4.35, CH_2Cl_2); IR (thin film, NaCl) 3064, 2960, 1728, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.97 (d, *J*=7.6 Hz, 2H), 7.59 (t, *J*=7.3 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 2H), 7.23–7.16 (m, 4H), 7.10 (d, *J*=8.2 Hz, 1H), 6.58 (d, *J*=3.4 Hz, 1H), 5.67 (app t, *J*=9.8 Hz, 1H), 5.60 (app t, *J*=9.8 Hz, 1H), 4.54–4.44 (m, 4H), 4.26 (dt, *J*=3.7, 9.8 Hz, 1H), 3.66 (dd, *J*=2.7, 11.3 Hz, 1H), 3.60 (dd, *J*=4.3, 11.3 Hz, 1H), 2.62–2.59 (m, 2H), 2.55–2.46 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 173.6, 165.1, 162.2, 160.2, 137.5, 133.8, 130.1, 129.1, 129.0, 128.7, 128.4, 128.0, 128.0, 127.8, 94.0, 91.9, 90.8, 73.8, 72.2, 70.7, 68.1, 68.0, 54.3, 37.8, 29.6, 28.2; ESI MS *m/z* $(M+NH_4)^+$: calcd 600.4 obsd 600.8.

8.1.6. *p*-Methoxyphenyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranoside 6. *p*-Methoxyphenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (1.16 g, 2.31 mmol) was dissolved in MeOH (25 mL) and NaOMe (25% wt in MeOH, 210 μL, 0.924 mmol) was added. After 3 h, the reaction mixture was neutralized with the addition of Dowex acid resin, filtered and the solvents were removed in vacuo. The residue was dissolved in CH_3CN (25 mL) and DMF (2.0 mL). Benzylidene dimethylacetal (430 μL, 2.77 mmol) and *p*-toluenesulfonic acid (50 mg) was added. After 15 h, the solid precipitate was collected on a fritted funnel to afford **6** (810 mg, 75%); IR (thin film, NaCl) 3479, 2869, 2361, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.27 (m, 5H), 7.03–6.82 (m, 5H), 5.61 (s, 1H), 5.01 (d, *J*=12.0 Hz, 1H), 4.91 (d, *J*=7.2 Hz, 1H), 4.83 (d, *J*=11.7 Hz, 1H), 4.38 (dd, *J*=4.8, 10.2 Hz, 1H), 3.88–3.81 (m, 5H), 3.72–3.50 (m, 2H), 2.37 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.3, 128.9, 128.7, 128.5, 128.3, 128.3, 128.3, 128.1, 126.2, 118.9, 118.3, 114.9, 114.8, 102.7, 101.5, 83.7, 81.4, 80.4, 75.6, 75.1, 74.9, 74.6, 74.2, 70.3, 68.9, 66.8, 62.8, 55.9; ESI MS *m/z* $(M)^+$: calcd 464.1 obsd 463.3.

8.1.7. *p*-Methoxyphenyl 3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside 7. *p*-Methoxyphenyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-β-D-glucopyranoside **6** (810 mg, 1.75 mmol) was dissolved in CH_2Cl_2 (20 mL) and pivaloyl chloride (257 μL, 2.10 mmol) and DMAP (427 mg, 3.50 mmol) were added. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with 5% HCl (150 mL), dried over Na_2SO_4, filtered and the solvents removed in vacuo. The crude mixture was dissolved in hexanes–EtOAc (3:1, 75 mL) and the solution was cooled to −25 °C. The white precipitate was collected and dried to afford *p*-methoxyphenyl 3-*O*-

benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside (798 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.24 (m, 5H), 6.95–6.78 (m, 4H), 5.59 (s, 1H), 5.30 (app t, J=8.3 Hz, 1H), 4.96 (d, J=8.0 Hz, 1H), 4.88 (d, J=11.6 Hz, 1H), 4.68 (d, J=11.8 Hz, 1H), 4.39 (dd, J=4.9, 10.7 Hz, 1H), 3.91–3.80 (m, 3H), 3.77 (s, 3H), 3.60–3.54 (m, 2H), 1.20 (s, 9H). *p*-Methoxyphenyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside (798 mg, 1.46 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. Trifluoroacetic acid (400 μL) and water (600 μL) were added and the solution was allowed to warm and stir over 4 h. CH_2Cl_2 (30 mL) was added and the organic layer was washed with sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL), the organic layers were dried over Na_2SO_4, filtered and the solvents were removed in vacuo. Column chromatography (3:2 hexanes–EtOAc) afforded **7** as a glassy solid (618 mg, 92%); IR (thin film, NaCl) 3402, 2967, 2931, 1738, 1508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 6.92–6.90 (m, 2H), 6.82–6.80 (m, 2H), 5.27 (dd, J=7.9, 9.5 Hz, 1H), 4.93 (d, J=7.9 Hz, 1H), 4.79 (d, J=11.3 Hz, 1H), 4.65 (d, J=11.6 Hz, 1H), 3.93 (dd, J=3.4, 12.2 Hz, 1H), 3.81 (dd, J=5.2, 12.2 Hz, 1H), 3.77 (s, 3H), 3.64 (app t, J=9.2 Hz, 1H), 3.55–3.49 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 155.5, 151.3, 138.1, 128.9, 128.3, 127.9, 118.0, 114.8, 100.6, 82.9, 75.6, 74.8, 72.8, 70.3, 62.6, 55.8, 39.1, 27.4.

8.1.8. *tert*-Butyldimethylsilyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside. *p*-Methoxyphenyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside (167 mg, 0.3 mmol) was dissolved in CH_3CN (4.0 mL) and water (1.0 mL). Ceric ammonium nitrate (822 mg, 1.50 mmol) was added and the reaction mixture was stirred for 30 min. The mixture was diluted with EtOAc (10 mL) and the organic layer was washed with sat. $NaHCO_3$ (10 mL). The aqueous layers were extracted with EtOAc (3×10 mL) and the combined organics were dried over $MgSO_4$, filtered and the solvents removed in vacuo. The residue was dissolved in DMF (3.0 mL) was *tert*-butyldimethylsilyl chloride (60 mg, 0.388 mmol) and imidazole (40 mg, 0.60 mmol) were added. After 15 h, the reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with sat. $NaHCO_3$ (10 mL). The aqueous layers were extracted with EtOAc (3×10 mL) and the combined organics were dried over $MgSO_4$, filtered and the solvents removed in vacuo. Column chromatography (5:1 hexanes–EtOAc) afforded *tert*-butyldimethylsilyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside (137 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.27 (m, 5H), 5.58 (s, 1H), 5.04 (dd, J=7.6, 8.8 Hz, 1H), 4.90 (d, J=11.6 Hz, 1H), 4.81 (d, J=7.5 Hz, 1H), 4.66 (d, J=11.6 Hz, 1H), 4.33 (dd, J=5.0, 10.5 Hz, 1H), 3.86–3.73 (m, 3H), 3.53–3.46 (m, 1H), 1.19 (s, 9H), 0.94 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 138.4, 137.4, 129.2, 128.5, 128.4, 127.6, 126.2, 101.4, 96.8, 81.8, 79.3, 74.8, 74.3, 68.9, 66.5, 38.9, 27.5, 25.9, 25.8, 18.0, −3.7, −3.8, −4.8.

8.1.9. *tert*-Butyldimethylsilyl 3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside 8. *tert*-Butyldimethylsilyl 3-*O*-benzyl-4,6-di-*O*-benzylidene-2-*O*-pivaloyl-β-D-glucopyranoside (136 mg, 0.245 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and water (40 μL). Trifluoroacetic acid (57.0 μL, 0.735 mmol) was added dropwise and the resulting solution was stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with sat. $NaHCO_3$ (10 mL). The aqueous layers were extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (5:1→3:2 hexanes–EtOAc) afforded **8** (60.5 mg, 52%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 5H), 4.99 (d, J=7.5, 7.6 Hz, 1H), 4.78 (d, J=11.6 Hz, 1H), 4.75 (d, J=7.6 Hz, 1H), 4.58 (d, J=11.6 Hz, 1H), 3.91–3.86 (m, 1H), 3.78–3.74 (m, 1H), 3.69 (app dt, J=3.1, 9.3 Hz, 1H), 3.55 (app t, J=9.2 Hz, 1H), 3.42–3.39 (m, 1H), 2.20 (d, J=2.8 Hz, 1H), 1.93 (t, J=6.6 Hz, 1H), 1.23 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 138.2, 128.9, 128.3, 127.8, 96.4,83.2, 75.3, 74.8, 74.4, 70.7, 63.0, 39.0, 27.5, 25.8, 18.0, −3.7, −4.6; ESI MS m/z $(M+NH_4)^+$: calcd 486.2 obsd 486.6.

8.1.10. Allyl 3-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzylidene-2-*O*-pivaloyl-β-D-glucopyranoside 10. Allyl 3-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzylidene-β-D-glucopyranoside **9** (1.00 g, 2.34 mmol) was dissolved in CH_2Cl_2 (20 mL) and pivaloyl chloride (340 μL, 2.80 mmol) and DMAP (630 mg, 5.85 mmol) were added. After 1 h, water (1 mL) was added and the solution was diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with sat. $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (10:1→3:1 hexanes–EtOAc) afforded **10** (1.10 g, 92%); IR (thin film, NaCl) 2971, 1736, 1518, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J=8.9 Hz, 2H), 7.30–7.26 (m, 5H), 6.91 (d, J=8.5 Hz, 2H), 5.86–5.76 (m, 1H), 5.54 (s, 1H), 5.29–5.17 (m, 1H), 5.10 (app t, J=8.1 Hz, 1H), 4.86 (d, J=11.8 Hz, 1H), 4.66 (d, J=11.8 Hz, 1H), 5.54 (d, J=7.9 Hz, 1H), 4.36–4.31 (m, 1H), 4.05 (dd, J=6.1, 12.7 Hz, 1H), 3.83–3.76 (m, 2H), 3.81 (s, 3H), 3.56–3.51 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 160.2, 138.3, 133.5, 129.9, 128.4, 127.8, 127.7, 127.5, 117.9, 113.8, 101.4, 100.9, 81.6, 79.1, 74.4, 72.8, 70.5, 68.9, 66.5, 55.5, 39.0, 27.3; ESI MS m/z $(M)^+$: calcd 512.2 obsd 513.6.

8.1.11. Allyl 3-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-pivaloyl-β-D-glucopyranoside. Allyl 3-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzylidene-2-*O*-pivaloyl-β-D-glucopyranoside **10** (609 mg, 1.19 mmol) was dissolved in DMF (8.0 mL) and 4 Å flame dried molecular sieves (250 mg) were added. The resulting mixture was stirred for 30 min, $NaCNBH_3$ (330 mg, 5.3 mmol) were added. After 30 min, the mixture was cooled to 0 °C and trifluoroacetic acid (810 μL in 6 mL DMF) was added dropwise. The resulting solution was allowed to warm and stir over 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) and passed through a pad of celite. The mixture was washed with sat. $NaHCO_3$ (20 mL) and the aqueous layers were extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded allyl 3-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-pivaloyl-β-D-glucopyranoside as a yellow oil (455 mg, 76%). $[\alpha]_D^{24}$=−37.8° (*c*

2.30, CH_2Cl_2); IR (thin film, NaCl) 3413, 2968, 2872, 1738, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 6.88 (d, J=7.8 Hz, 2H), 5.90–5.80 (m, 1H), 5.28–5.16 (m, 1H), 5.07 (app t, J=7.9 Hz, 1H), 4.74 (d, J=11.5 Hz, 1H), 4.70 (d, J=11.5 Hz, 1H), 4.55 (d, J=11.6 Hz, 1H), 4.51 (d, J=11.6 Hz, 1H), 4.45 (d, J=7.9 Hz, 1H), 4.35–4.31 (m, 1H), 4.05–4.01 (m, 1H), 3.81 (s, 3H), 3.75–3.73 (m, 2H), 3.56 (app t, J=9.5 Hz, 1H), 3.50–3.47 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 159.5, 138.4, 133.8, 130.0, 129.6, 128.7, 128.0, 127.8, 117.5, 114.0, 100.4, 82.8, 74.5, 74.2, 73.6, 72.7, 72.3, 70.2, 70.1, 55.5, 39.0, 27.3; ESI MS m/z $(M+NH_4)^+$: calcd 532.3 obsd 532.6.

8.1.12. Allyl 3-*O*-benzyl-4-*O*-*p*-methoxybenzyl-2-*O*-pivaloyl-β-D-glucopyranoside 11. Allyl 3-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzylidene-2-*O*-pivaloyl-β-D-glucopyranoside **10** (400 mg, 0.766 mmol) was co-evaporated with toluene (3×5 mL) and dissolved in CH_3CN (15 mL). The solution was cooled to 0 °C and 4 Å flame dried molecular sieves (200 mg) and $NaCNBH_3$ (290 mg, 4.60 mmol) were added. TMSCl (580 μL, 4.60 mmol, in 5 mL CH_3CN) was added and the solution was allowed to stir and warm to room temperature. After 2 h, TMS chloride (100 μL) was added and the solution was stirred at room temperature for 4 h. The solution was diluted with CH_2Cl_2 (20 mL) and passed through a plug of celite. The organic layer was washed with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded a 1:1 mixture of the 6-*O*-PMB ether and 4-*O*-PMB ether **11** (259 mg, 66%). Determination of the regiochemistry was accomplished by comparison of ^1H NMR in DMSO-d_6 before and after acetylation of the separate isomers. The acetylated hydroxyl results in a downfield shift of the ring proton that shows the expected apparent triplet for H_4 and complex splitting for the H_6 methylene; IR (thin film, NaCl) 3447, 2965, 2918, 1735, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 7.19 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.90–5.81 (m, 1H), 5.29–5.17 (m, 2H), 5.06 (dd, J=8.1, 8.2 Hz, 1H), 4.79 (d, J=11.1 Hz, 1H), 4.74 (d, J=10.6 Hz, 1H), 4.71 (d, J=11.1 Hz, 1H), 4.56 (d, J=10.6 Hz, 1H), 4.47 (d, J=8.0 Hz, 1H), 4.32 (ddt, J=1.3, 5.2, 13.0 Hz, 1H), 4.05 (ddt, J=1.3, 6.0, 13.0 Hz, 1H), 3.87 (dd, J=2.7, 12.0 Hz, 1H), 3.80 (s, 3H), 3.76–3.63 (m, 3H), 3.41–3.37 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 159.6, 138.3, 133.7, 130.1, 130.0, 128.6, 127.9, 127.6, 117.7, 114.1, 100.6, 83.2, 77.4, 77.4, 75.5, 75.2, 75.0, 70.5, 62.2, 55.5, 39.0, 27.3; ESI MS m/z $(M+NH_4)^+$: calcd 532.21 obsd 532.6.

8.1.13. Allyl 4-*O*-acetyl-4-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside 12. Allyl 4-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-pivaloyl-β-D-glucopyranoside (450 mg, 0.875 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and pyridine (1.0 mL). Acetic anhydride (125 μL, 1.10 mmol) and DMAP (0.100 g, 0.875 mmol) were added. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was dissolved in CH_3CN (9.0 mL) and water (1.0 mL). Ceric ammonium nitrate (660 mg, 1.2 mmol) was added, the mixture was stirred for 30 min and diluted with CH_2Cl_2 (20 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents removed in vacuo. Column chromatography (3:2 hexanes–EtOAc) afforded **12** (267 mg, 70%). $[\alpha]_D^{24}=-20.6°$ (c 0.36, CH_2Cl_2); IR (thin film, NaCl) 3471, 2968, 2921, 1739, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 5.90–5.80 (m, 1H), 5.30–5.25 (m, 2H), 5.29–5.00 (m, 3H), 4.67 (d, J=11.2 Hz, 1H), 4.56 (d, J=11.6 Hz, 1H), 4.51 (d, J=7.6 Hz, 1H), 4.37–4.32 (m, 1H), 4.10–4.05 (m, 1H), 3.80 (app t, J=9.2 Hz, 1H), 3.70 (dd, J=2.4, 12.4 Hz, 1H), 3.60 (dd, J=5.2, 12.4 Hz, 1H), 3.45–3.40 (m, 1H), 1.97 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 170.5, 138.0, 133.7, 128.6, 127.9, 127.7, 117.8, 100.4, 80.4, 74.6, 73.9, 72.5, 70.4, 70.2, 61.8, 39.0, 27.3, 21.0; ESI MS m/z $(M+NH_4)^+$: calcd 454.6 obsd 454.6.

8.1.14. Allyl 3-*O*-benzyl-4-*O*-levulinoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside. Allyl 4-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-pivaloyl-β-D-glucopyranoside (3.2 g, 6.44 mmol) was dissolved in CH_2Cl_2 (60 mL) and the solution was cooled to 0 °C. DMAP (780 mg, 6.39 mmol), Diisopropylcarbodiimide (DIPC) (1.6 mL, 10.2 mmol) and levulinic acid (1.0 mL, 9.6 mmol) were added, the mixture was shielded from light and was allowed to stir and warm for 3 h. Ethyl acetate (100 mL) was added and the mixture was passed through a plug of silica. The organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded allyl 3-*O*-benzyl-4-*O*-levulinoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (3.40 g, 87%). $[\alpha]_D^{24}=-16.1°$ (c 3.45, CH_2Cl_2); IR (thin film, NaCl) 2969, 2873, 1741, 1718, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 9H), 6.88–6.84 (m, 2H), 5.89–5.80 (m, 1H), 5.29–5.06 (m, 4H), 4.63 (d, J=11.3 Hz, 1H), 4.55 (d, J=11.3 Hz, 1H), 4.50–4.47 (m, 3H), 4.36 (ddt, J=1.5, 4.9, 13.0 Hz, 1H), 4.05 (ddt, J=1.3, 6.2, 13.0 Hz, 1H), 3.80 (s, 3H), 2.67–2.50 (m, 2H), 2.44–2.25 (m, 2H), 2.12 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 176.8, 171.7, 159.4, 138.2, 133.7, 130.3, 129.7, 128.5, 127.8, 127.7, 117.7, 113.9, 100.2, 80.5, 77.5, 73.8, 73.5, 73.4, 72.4, 70.9, 70.1, 69.4, 55.4, 38.9, 37.9, 29.9, 28.0, 27.3; ESI MS m/z $(M+NH_4)^+$: calcd 630.3 obsd 630.6.

8.1.15. Allyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-β-D-glucopyranoside 13. Allyl 4-*O*-benzyl-6-*O*-*p*-methoxybenzyl-2-*O*-pivaloyl-β-D-glucopyranoside (119 mg, 0.231 mmol) was dissolved in CH_2Cl_2 (3.0 mL), the solution was cooled to 0 °C and DIPC (54.0 μL, 0.350 mmol) and DMAP (28 mg, 0.231 mmol) were added. Levulinic acid (37.0 μL, 0.347 mmol) was added and the reaction mixture was shielded from light and allowed to stir for 15 h. The mixture was diluted with EtOAc (10 mL) and the solution was passed through a plug of silica and the solvents were removed in vacuo. The residue was dissolved in CH_3CN (900 μL) and water (100 μL) and ceric ammonium nitrate (240 mg, 0.444 mmol) was added. After 30 min, the mixture was

diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (1:1 hexanes–EtOAc) afforded **13** (89.0 mg, 85%). $[\alpha]_D^{24}=-35.5°$ (*c* 2.28, CH_2Cl_2); IR (thin film, NaCl) 3373, 2970, 2908, 1738, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 5.90–5.80 (m, 1H), 5.30–5.06 (m, 4H), 4.66 (d, *J*=11.4 Hz, 1H), 4.60 (d, *J*=11.4 Hz, 1H), 4.52 (d, *J*=8.1 Hz, 1H), 4.36–4.32 (m, 1H), 4.09–4.05 (m, 1H), 3.81 (app t, *J*=8.8 Hz, 1H), 3.75 (dd, *J*=2.6, 12.7 Hz, 1H), 3.67 (dd, *J*=4.6, 12.7 Hz, 1H), 3.46–3.42 (m, 1H), 2.82–2.77 (m, 1H), 2.61–2.50 (m, 2H), 2.31–2.25 (m, 1H), 2.18 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 176.8, 138.2, 133.7, 128.5, 127.8, 127.6, 117.8, 100.3, 80.4, 74.6, 73.9, 72.6, 70.7, 70.3, 61.6, 39.0, 38.0, 29.9, 27.9, 27.3, 23.5; ESI MS *m/z* $(M+NH_4)^+$: calcd 510.2 obsd 510.6.

8.1.16. Methyl (allyl 4-*O*-acetyl-3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosid)uronate 15. Allyl 4-*O*-acetyl-3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranoside **12** (125 mg, 0.285 mmol) was dissolved in CH_3CN (2.5 mL) and water (18 μL) and the solution was cooled to 0 °C. A solution of H_5IO_6/CrO_3 (1.5 mL, 2.5 equiv./1.1 mol% in 0.75% H_2O/CH_3CN) was added. After 90 min, the mixture was diluted with EtOAc (10 mL) and the organic layer was washed with sat. NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with water (25 mL). The organic layers were dried with $MgSO_4$, filter and the solvents were removed in vacuo. The residue was dissolved in DMF (4.0 mL) and $NaHCO_3$ (50 mg) and MeI (25 μL, 0.42 mmol) were added. After 15 h, the solution was diluted with EtOAc and the organic layer was washed with 5% aq. HCl (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the organic layer was dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded **15** (90.4 mg, 70%). $[\alpha]_D^{24}=-6.3°$ (*c* 0.30, CH_2Cl_2); IR (thin film, NaCl) 2971, 1740, 1764, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 5.90–5.79 (m, 1H), 5.30–5.20 (m, 4H), 4.67 (d, *J*=11.6 Hz, 1H), 4.57 (d, *J*=11.6 Hz, 1H), 4.54 (d, *J*=7.6 Hz, 1H), 4.40–4.35 (m, 1H), 4.08–4.03 (m, 1H), 3.95 (d, *J*=9.6 Hz, 1H), 3.81–3.76 (m, 1H), 3.75 (s, 3H), 1.95 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 169.6, 168.1, 137.9, 133.4, 128.6, 127.9, 127.7, 118.1, 100.1, 79.8, 77.6, 73.8, 73.2, 72.1, 70.8, 70.3, 53.1, 39.0, 27.3, 20.8; ESI MS *m/z* $(M+NH_4)^+$: calcd 482.6 obsd 464.2.

8.1.17. Methyl (allyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-β-D-glucopyranosid)uronate. Allyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-β-D-glucopyranoside **13** (2.20 g, 4.31 mmol) was dissolved in CH_3CN (40 mL) and water (300 μL) and the resulting solution was cooled to 0 °C. A solution of H_5IO_6/CrO_3 (25 mL, 2.5 equiv./1.1 mol%, 0.75% water/CH_3CN) was added dropwise. After 1.5 h, the mixture was diluted with EtOAc (60 mL) and the organic layers were washed with sat. NH_4Cl (75 mL). The aqueous layers were extracted with EtOAc (2×75 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo to give the acid as a yellow oil (2.0 g, 91%). A portion of the acid (557 mg, 1.32 mmol) was dissolved in DMF (15 mL) and $NaHCO_3$ (230 mg, 2.77 mmol) and MeI (90.0 μL, 1.45 mmol) were added. After 15 h, the mixture was diluted with EtOAc (40 mL) and the organic layer was washed with water (50 mL). The aqueous layers were extracted with EtOAc (2×75 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (5:1→3:2 hexanes–EtOAc) afforded methyl (allyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-β-D-glucopyranosid)uronate (406 mg, 59%). $[\alpha]_D^{24}=+1.2°$ (*c* 0.34, CH_2Cl_2); IR (thin film, NaCl) 2973, 1765, 1733, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 5.88–5.80 (m, 1H), 5.29–5.15 (m, 4H), 4.66 (d, *J*=11.4 Hz, 1H), 4.61 (d, *J*=11.4 Hz, 1H), 4.54 (d, *J*=7.6 Hz, 1H), 4.39–4.35 (m, 1H), 4.07–4.03 (m, 1H), 3.98 (d, *J*=9.8 Hz, 1H), 3.80 (app t, *J*=9.2 Hz, 1H), 3.75 (s, 3H), 2.72–2.35 (m, 4H), 2.15 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 176.7, 171.6, 168.0, 137.9, 133.4, 128.5, 127.9, 127.7, 118.1, 100.0, 79.8, 73.9, 73.1, 72.1, 71.2, 70.3, 53.1, 39.0, 37.8, 30.0, 27.8, 27.3; ESI MS *m/z* $(M+NH_4)^+$: calcd 538.2 obsd 538.6.

8.1.18. Methyl (allyl 3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosid)uronate 16. Methyl (allyl 3-*O*-benzyl-4-*O*-levulinoyl-2-*O*-pivaloyl-β-D-glucopyranosid)uronate (500 mg, 0.962 mmol) was dissolved in CH_2Cl_2 (10 mL) and MeOH (1.0 mL) and hydrazine acetate (88 mg, 0.962 mmol) was added. After 1 h, acetone (10 mL) was added and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded **16** as a colorless syrup (480 mg, 97%). $[\alpha]_D^{24}=-31.0°$ (*c* 0.12, CH_2Cl_2); IR (thin film, NaCl) 3351, 2921, 1738, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −7.35–7.26 (m, 5H), 5.85–5.73 (m, 1H), 5.27–5.14 (m, 1H), 5.05 (app t, *J*=7.7 Hz, 1H), 4.76 (d, *J*=11.6 Hz, 1H), 4.69 (d, *J*=11.6 Hz, 1H), 4.48 (d, *J*=7.6 Hz, 1H), 4.36–4.30 (m, 1H), 4.06–3.95 (m, 3H), 3.87–3.80 (m, 2H), 3.79 (s, 3H), 3.58 (app t, *J*=8.8 Hz, 1H), 2.95 (br s, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 169.9, 138.2, 133.4, 128.7, 127.9, 127.8, 118.0, 100.5, 81.2, 74.7, 74.4, 72.3, 71.9, 70.4, 53.1, 39.0, 27.3; ESI MS *m/z* $(M+NH_4)^+$: calcd 440.2 obsd 440.6.

8.1.19. Allyl (4-*O*-benzoyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranosyl)-(1→4)-(methyl 3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl) uronate 17. 4-*O*-Benzoyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-α-D-glucopyranosyl trichloroacetimidate **5** (70 mg, 0.093 mmol) and allyl (methyl 3-*O*-benzyl-2-*O*-pivaloyl-β-D-glucopyranosyl)uronate **16** (30 mg, 0.071 mmol) were combined and co-evaporated with toluene (3×5 mL) and dissolved in CH_2Cl_2 (1.5 mL). The resulting solution was cooled to 0 °C and TMSOTf (1.0 μL) was added. After 30 min, Et_3N (10 μL) was added and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded **17** (62.4 mg, 86%); IR (thin film, NaCl) 2957, 2872, 1726, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J*=8.4 Hz, 2H), 7.57 (t, *J*=6.8 Hz, 1H), 7.39 (t, *J*=8.0 Hz, 2H), 7.32–7.01 (M, 10H), 5.87–5.79 (m, 1H), 5.38–5.18 (M, 4H), 5.07–4.97 (m, 3H), 4.62 (d, *J*=11.6 Hz, 1H), 4.51 (d, *J*=6.8 Hz, 1H),

4.35–4.30 (m, 1H), 4.20–3.93 (m, 5H), 3.94 (d, J=9.2 Hz, 1H),.3.84 (s, 3H), 3.77–3.69 (m, 2H), 3.48–3.44 (m, 1H), 3.29–3.25 (m, 1H), 2.60–2.57 (m, 2H), 2.46–2.41 (m, 2H), 2.03 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 177.0, 172.7, 170.2, 165.5, 162.2, 138.8, 137.8, 133.6, 130.0, 129.3, 128.6, 128.4, 128.4, 127.8, 127.6, 127.5, 127.0, 118.1, 100.6, 100.5, 92.6, 80.7, 78.5, 77.5, 75.3, 74.2, 74.2, 73.7, 73.0, 70.5, 69.9, 69.5, 56.3, 53.3, 38.9, 38.0, 29.7, 28.2, 27.2; ESI MS m/z $(M+NH_4)^+$: calcd 1065.4 obsd 1065.6.

8.1.20. Allyl 4,6-di-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside. Allyl 4,6-di-*O*-benzylidene-2-deoxy-2-trichloroacetimido-β-D-glucopyranoside **18** (1.56 g, 3.45 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C. DIPC (860 μL, 5.52 mmol) and DMAP (420 mg, 3.45 mmol) were added followed by the addition of levulinic acid (545 μL, 5.18 mmol). The reaction mixture was shielded from light and was allowed to stir and warm for 13 h. Ethyl acetate (50 mL) was added and the organic layer was washed with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (5% MeOH/CH_2Cl_2) afforded allyl 4,6-di-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside (1.87 g, 98%). $[\alpha]_D^{24}=-5.0°$ (c 0.30, CH_2Cl_2); IR (thin film, NaCl) 2966, 2933, 1746, 1716, 1615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.27 (m, 5H), 5.85–5.77 (m, 1H), 5.54–5.50 (m, 2H), 5.25–5.14 (m, 2H), 4.58 (d, J=8.4 Hz, 1H), 4.20 (dd, J=5.0, 13.1 Hz, 1H), 4.15–4.09 (m, 2H), 3.91 (dd, J=5.9, 12.1 Hz, 1H), 3.74–3.69 (m, 2H), 3.59–3.54 (m, 1H), 2.76–2.73 (m, 2H), 2.66–2.56 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 173.4, 162.4, 137.2, 133.4, 129.1, 128.4, 126.1, 117.7, 101.1, 100.6, 78.9, 71.7, 70.7, 68.5, 66.1, 56.2, 38.1, 29.9, 28.3, 23.6; ESI MS m/z $(M+NH_4)^+$: calcd 567.0 obsd 567.4.

8.1.21. Allyl 6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside 19. Allyl 4,6-di-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside (1.10 g, 2.00 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C. Triethylsilane (1.27 mL, 7.97 mmol) and trifluoroacetic acid anhydride (30.0 μL, 0.211 mmol) was added followed by the dropwise addition of trifluoroacetic acid (616 μL, 7.97 mmol). After 10 h, sat. $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL), the organic layer was dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:1→3:2 hexanes–EtOAc) afforded **19** as a yellow syrup (800 mg, 72%); IR (thin film, NaCl) 3342, 2918, 1717, 1065 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 4H), 6.85–6.90 (d, J=9.0 Hz, 1H), 5.81–5.89 (m, 4H), 5.29–5.17 (m, 2H), 4.65–4.59 (m, 2H), 4.38–4.34 (m, 1H), 4.10–4.06 (m, 1H), 3.97 (dt, J=8.8, 10.8 Hz, 1H), 3.84–3.77 (m, 2H), 3.60 (q, J=4.7 Hz, 1H), 3.33 (d, J=3.1 Hz, 1H), 2.85–2.77 (m, 2H), 2.64–2.48 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 173.6, 162.2, 138.0, 133.6, 128.7, 128.0, 127.9, 117.9, 99.8, 92.6, 77.5, 75.3, 74.6, 73.9, 70.3, 70.2, 69.9, 55.7, 38.6, 30.0, 28.4; ESI MS m/z $(M+NH_4)^+$: calcd 569.1 obsd 569.4.

8.1.22. Allyl 4-*O*-acetyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside. Allyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside (2.03 g, 3.69 mmol) was dissolved in CH_2Cl_2 (35 mL) and the solution was cooled to 0 °C. Triethylsilane (2.3 mL, 14.76 mmol) and trifluoroacetic acid anhydride (50 μL, 0.352 mmol) was added. Trifluoroacetic acid (1.14 mL, 14.76 mmol) was added dropwise and the solution was stirred for 1 h at 0 °C and 3 h at ambient temperature. CH_2Cl_2 (50 mL) and water (50 mL) were added and the organic layer was washed with sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 and acetic anhydride (500 μL, 5.2 mmol) and DMAP (1.3 g, 10.7 mmol) were added. After 1 h, the mixture was diluted with hexanes–EtOAc (3:2, 30 mL) and the mixture was passed through a silica plug and the solvents were removed in vacuo. Column chromatography (3:2 hexanes–EtOAc) afforded allyl 4-*O*-acetyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside as a yellow syrup (1.82 g, 83%). $[\alpha]_D^{24}=-6.1°$ (c 7.42, CH_2Cl_2); IR (thin film, NaCl) 2916, 2873, 1750, 1718, 1226 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.99 (d, J=8.8 Hz, 1H), 5.86–5.81 (m, 1H), 5.37 (app t, J=9.6 Hz, 1H), 5.28–5.16 (m, 1H), 5.11 (app t, J=9.8 Hz, 1H), 4.72 (d, J=8.2 Hz, 1H), 4.57 (d, J=11.9 Hz, 1H), 4.51 (d, J=11.9 Hz, 1H), 4.09 (dd, J=6.1, 13.1 Hz, 1H), 3.99–3.93 (m, 1H), 3.73–3.70 (m, 1H), 3.59–3.54 (m, 2H), 2.72–2.67 (m, 2H), 2.55–2.40 (m, 2H), 2.13 (2, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 172.7, 170.0, 162.1, 137.8, 133.4, 128.6, 128.1, 128.0, 118.1, 99.5, 73.8, 73.7, 72.0, 70.4, 69.0, 69.0, 56.4, 37.9, 29.8, 28.2, 20.9; ESI MS m/z $(M+NH_4)^+$: calcd 611.1 obsd 611.4.

8.1.23. Thioethyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside 22. Thioethyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzylidene-β-D-glucopyranoside **21**[34] (175 mg, 0.326 mmol) was dissolved in DMF (3.0 mL) and 4 Å flame dried molecular sieves (100 mg) were added and the resulting solution was stirred for 2 h. $NaCNBH_3$ (103 mg, 1.63 mmol) was added and the mixture was cooled to 0 °C. Trifluoroacetic acid (250 μL, 3.26 mmol) was added dropwise and the reaction mixture was allowed to warm and stir for 14 h. Ethyl acetate (30 mL) was added and the mixture passed through a plug of celite. The organic layer was washed with sat. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3×30 mL), the organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (3 mL) and the solution was cooled to 0 °C. DIPC (81 μL, 0.522 mmol) and DMAP (40 mg, 0.326 mmol) were added followed by the addition of levulinic acid (49 μL, 0.489 mmol). The reaction mixture was shielded from light and was allowed to stir and warm for 13 h. Ethyl acetate (10 mL) was added and the organic layer was washed with sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:1 hexanes–EtOAc) afforded **22** as a white solid (115 mg, 56%). $[\alpha]_D^{24}=+32.9°$ (c 1.02, CH_2Cl_2);

IR (thin film, NaCl) 2930, 2870, 1720, 1514 cm^{-1}; ^1H NMR (125 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.61–7.58 (m, 1H), 7.48–7.44 (m, 2H), 7.27 (dt, J=2.1, 5.6 Hz, 2H), 7.16–7.11 (m, 5H), 6.88 (dt, J=2.1, 6.7 Hz, 2H), 5.33 (dd, J=9.3, 9.4 Hz, 1H), 5.14 (app t, J=9.7 Hz, 1H), 4.59 (s, 1H), 4.46 (d, J=11.3 Hz, 1H) 3.87 (t, J=9.2 Hz, 1H), 3.81 (s, 3H), 3.69–3.58 (m 3H), 2.75–2.60 (m, 4H), 2.44–2.32 (m 2H), 2.41 (s, 3H), 1.24 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 171.7, 165.2, 159.4, 137.9, 133.4, 130.3, 130.0, 129.9, 129.7, 128.6, 128.4, 128.0, 127.8, 113.9, 83.8, 81.5, 78.0, 74.3, 73.4, 72.2, 71.4, 69.6, 55.5, 37.9, 29.9, 28.0, 24.3, 15.1; ESI MS m/z $(M+NH_4)^+$: calcd 654.2 obsd 654.6.

8.1.24. Allyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-trichloroacetimido-β-D-glucopyranoside 23. Allyl 4-*O*-acetyl-6-*O*-benzyl-2-deoxy-3-*O*-levulinoyl-2-trichloroacetimido-β-D-glucopyranoside (100 mg, 0.168 mmol) was dissolved in MeOH (500 μL) and CH_2Cl_2 (1.0 mL) and hydrazine acetate (17 mg, 0.170 mmol) was added. After 1 h, acetone (5 mL) was added and the solvents were removed in vacuo. Column chromatography (3:1→3:2 hexanes–EtOAc) afforded allyl 4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-trichloroacetimido-β-D-glucopyranoside **20** (74 mg, 89%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H), 7.02 (d, J=6.8 Hz, 1H), 5.94–5.80 (m, 1H), 5.33–5.18 (m, 2H), 4.93 (app t, J=9.2 Hz, 1H), 4.87 (d, J=8.1 Hz, 1H), 4.61 (d, J=12.1 Hz, 1H), 4.50 (d, J=12.1 Hz, 1H), 4.40–4.34 (m, 1H), 4.22–4.07 (m, 2H), 3.68–3.48 (m, 4H), 3.2 (br s, 1H), 2.00 (s, 3H). Thioethyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside **22** (77.5 mg, 0.121 mmol) and **20** (40.5 mg, 0.60 mmol) were combined and dissolved in CH_2Cl_2 (1.0 mL) and 4 Å flame dried molecular sieves (150 mg) were added. After stirring for 1 h, the solution was cooled to −25 °C and MeOTf (50.0 μL, 0.400 mmol) was added. The reaction mixture was allowed to warm to ambient temperature over 14 h. Et_3N (100 μL) was added, the mixture filtered through celite and the solvents removed in vacuo. The residue was dissolved in CH_3CN (900 μL) and water (100 μL) and ceric ammonium nitrate (130 mg, 0.240 mmol) was added. After 30 min, dichloromethane (10 mL) was added and the organic layer was washed with water. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), dried over $MgSO_4$, filtered and the solvents were removed in vacuo. Column chromatography (3:2 hexanes–EtOAc) afforded **23** (38.1 mg, 50%). $[\alpha]_D^{24}$=+5.3° (c 0.30, CH_2Cl_2); IR (thin film, NaCl) 3392, 2918, 1733, 1716, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.46–7.43 (m, 2H), 7.35–7.08 (m, 10H), 6.99 (d, J=7.5 Hz, 1H), 5.76–5.69 (m, 1H), 5.27–5.11 (m, 3H), 5.04–4.93 (m, 2H), 4.85 (d, J=7.5 Hz, 1H), 4.73 (d, J=7.8 Hz, 1H), 4.62–4.47 (m, 5H), 4.22 (dd, J=5.2, 12.8 Hz, 1H), 4.00 (dd, J=6.4, 12.8 Hz, 1H), 3.80 (app t, J=9.2 Hz, 1H), 3.74–3.43 (m, 5H), 2.90 (br s, 1H), 2.95–2.35 (m, 4H), 2.04 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 172.7, 170.2, 164.9, 162.1, 137.9, 137.7, 133.6, 133.4, 130.2, 130.1, 129.6, 128.7, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 118.4, 99.5, 97.8, 92.5, 79.7, 75.0, 74.9, 74.2, 73.7, 73.7, 73.4, 73.3, 71.0, 70.3, 69.4, 69.2, 61.5, 57.9, 38.0, 29.9, 28.0, 20.9; ESI MS m/z $(M+NH_4)^+$: calcd 967.2 obsd 967.4.

8.1.25. Allyl (methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-trichloroacetimido-β-D-glucopyranoside 24. Allyl (2-*O*-benzoyl-3-*O*-benzyl-4-*O*-levulinoyl-β-D-glucopyranosyl)-(1→3)-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-trichloroacetimido-β-D-glucopyranoside **23** (30.7 mg, 0.0315 mmol) was dissolved in CH_3CN (1.0 mL) and water (7 μL) was added. The solution was cooled to 0 °C and a solution of H_5IO_6/CrO_3 (180 μL, 2.5 equiv/1.1 mol% in 0.75% H_2O/CH_3CN) was added portion-wise over 30 min. The resulting solution was stirred at 0 °C for 45 min and aqueous Na_2HPO_4 (1 mL) was added. CH_2Cl_2 (10 mL) was added and the organic layer was washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were washed with sat. $NaHSO_3$, dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The residue was dissolved in DMF (1.0 mL) and $NaHCO_3$ (5 mg) and iodomethane (4 μL) were added. After 16 h, EtOAc (5 mL) was added and the organic layer was washed with water (5 mL). The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvents removed in vacuo. Column chromatography (3:2 hexanes–EtOAc) afforded **24** (12.0 mg, 39%). $[\alpha]_D^{24}$=+40.0° (c 0.10, CH_2Cl_2); IR (thin film, NaCl) 2917, 1764, 1738, 1720 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.9 Hz, 2H), 7.34–7.08 (m, 10H), 5.82–5.75 (m, 1H), 5.28 (dd, J=7.7, 7.8 Hz, 1H), 5.23–5.14 (m, 1H), 5.08 (d, J=7.9 Hz, 1H), 5.02 (app t, J=9.3 Hz, 1H), 4.78 (d, J=7.6 Hz, 1H), 4.63 (d, J=9.9 Hz, 1H), 4.58 (d, J=13.4 Hz, 1H), 4.53 (d, J=11.9 Hz, 1H), 4.49 (d, J=12.1 Hz, 1H), 4.25 (dd, J=5.2, 12.7 Hz, 1H), 4.04 (dd, J=6.3, 12.8 Hz, 1H), 3.95 (d, J=9.9 Hz, 1H), 3.79 (app t, J=9.2 Hz, 1H), 3.72 (s, 3H), 3.64–3.61 (m, 1H), 3.54 (dd, J=2.9, 10.8 Hz, 1H), 3.48 (dd, J=5.3, 10.8 Hz, 1H), 3.26–3.23 (m, 1H), 2.73–2.39 (m, 4H), 2.17 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 171.6, 170.0, 167.6, 164.6, 162.2, 138.0, 137.5, 133.6, 133.6, 130.2, 129.6, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 98.8, 97.6, 79.3, 77.5, 74.2, 73.8, 73.6, 72.8, 72.4, 71.5, 70.7, 69.3, 59.4, 53.1, 37.8, 30.0, 27.9, 20.6; ESI MS m/z $(M+NH_4)^+$: calcd 995.2 obsd 995.4.

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Enantiomer separation of *rac*-2,2′-dihydroxy-1,1′-binaphthyl (BNO) by inclusion complexation with racemic or achiral ammonium salts and a novel transformation of a 1:1:1 racemic complex of BNO, $Me_4N^+ \cdot Cl^-$ and MeOH into a conglomerate complex in the solid state

Kazuhiro Yoshizawa, Shinji Toyota and Fumio Toda*

Department of Chemistry, Faculty of Science, Okayama University of Science, Ridai-cho 1-1, Okayama 700-0005, Japan

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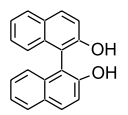
Abstract—The complete simultaneous and mutual enantiomer resolution of 2,2′-dihydroxy-1,1′-binaphthyl (BNO) and *N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride, $Me_3N^+CH_2CH(OH)CH_2Cl \cdot Cl^-$ into their enantiomers by inclusion complexation between their racemates in EtOH in the presence of a chiral seed crystal is reported. The enantiomer resolution of the *rac*-BNO was also accomplished easily by inclusion complexation with achiral ammonium salts, *N*-(2-hydroxyethyl)-*N*,*N*,*N*-trimethylammonium chloride, $Me_3N^+CH_2CH_2OH \cdot Cl^-$ and tetramethylammonium chloride, $Me_4N^+ \cdot Cl^-$. Inclusion complexation of the *rac*-BNO with $Me_3N^+CH_2CH_2OH \cdot Cl^-$ gave only a 1:1 conglomerate inclusion complex but not a racemic complex. Recrystallization of the *rac*-BNO and an equimolar amount of $Me_4N^+ \cdot Cl^-$ from MeOH (7 ml) and MeOH (15 ml) gave a 1:1:1 racemic complex, $BNO \cdot Me_4N^+ \cdot Cl^- \cdot MeOH$ and a 1:1 conglomerate complex, $BNO \cdot Me_4N^+ \cdot Cl^-$, respectively. Novel transformation of the former racemate into the latter conglomerate occurred by heating or by exposure to MeOH vapor in the solid state.

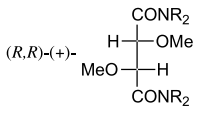
1. Introduction

Enantiomer separation of *rac*-2,2′-dihydroxy-1,1′-binaphthyl (*rac*-BNO, **1a**) is of considerable interest, since optically active BNO (**1b**, **1c**) is important as a chiral ligand for catalysis in asymmetric synthesis,[1] as a chiral host for enantiomer separation of *rac*-guests,[2] and as a chiral shift reagent for determination of optical purity of enantiomers using ^1H NMR spectral methods.[3] For example, enantiomer separation of **1a** by inclusion complexation with the chiral hosts, (*R*,*R*)-(+)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetraalkylsuccinamides (**2a**, **2b**),[4] (+)-*N*-benzylcinchonidinium chloride (**3**),[5] optically active *N*,*N*,*N*-trimethyl-*N*-(2-hydroxy-1-alkylethyl)ammonium bromide (**4a**-**d**),[6] and (*S*)-(−)-*N*-(3-chloro-2-hydroxypropyl)-*N*,*N*,*N*-trimethylammonium chloride (**5b**),[7] has been reported. A commercially available separation method of **1a** has also been reported.[8]



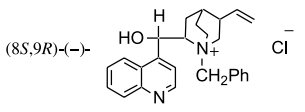
1

a: *rac*-form (racemates)
b: (*S*)-(−)-form
c: (*R*)-(+)-form



2

a: R=Me
b: R=C_6H_{11}



3

4

a: R=Me; (−)-form
b: R=^{i}Pr; (+)-form
c: R=^{t}Bu; (+)-form
d: R=^{s}Bu; (+)-form

We found, however, enantiomer separation of **1a** can easily be accomplished by that inclusion complexation with conglomeratic ammonium salt (**5a**) or achiral ammonium salts such as *N*,*N*,*N*-tetramethyl-*N*-(2-hydroxyethyl)ammonium chloride (**6**) and tetramethylammonium chloride (**9**).

Keywords: Enantiomer separation; Trimethylammonium chloride; Racemic complex.
* Corresponding author. Tel./fax: +81-86-256-9604;
e-mail address: toda@chem.ous.ac.jp

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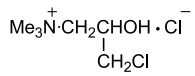
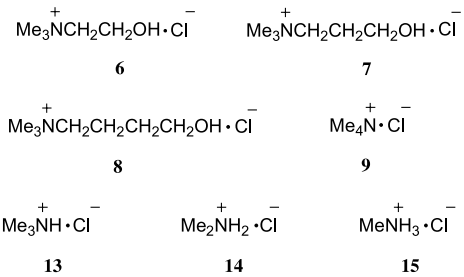


5

a: conglomerate
b: (*S*)-(−)-form
c: (*R*)-(+)-form



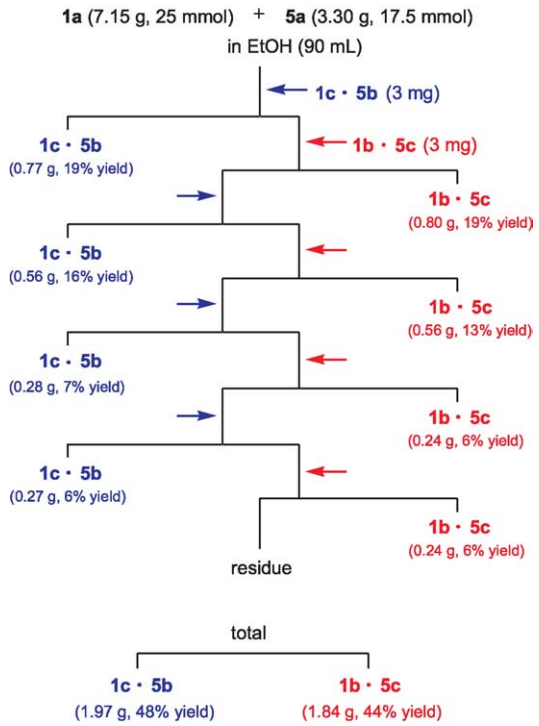
6 **7** **8** **9** **13** **14** **15**

In these enantiomer separations, no chiral source is necessary. Furthermore, through inclusion complexation between **1a** and **5a**, simultaneous and mutual resolution of both their components was accomplished easily. During the course of the studies on enantiomer separation of **1a** by complexation with **9**, the novel transformation of 1:1:1 racemic inclusion crystals of **1a**, **9** and MeOH into conglomerate crystals in the solid state was found.

2. Results and discussion

Previously, an efficient resolution of **1a** by complexation with **5b** in EtOH, which gives **1b** of 99.5% ee and **1c** of 99% ee in 69 and 63% yields, respectively, has been reported.[7] Recently, however, we found that the optically activity of the ammonium salt is not necessary for the efficient resolution of **1a**.

In other words, the enantiomer resolution of **1a** can be accomplished without using any optically active source. When a complexation of **1a** with the conglomeratic salt **5a** was carried out by seeding of 1:1 complexes of **1b** with **5b** and of **1c** with **5c**, efficient simultaneous and mutual optical resolutions of **1a** and **5a** were accomplished. According to the experimental sequences shown in Scheme 1, to a solution of **1a** (7.15 g, 25 mmol) and **5a** (3.30 g, 17.5 mmol) in EtOH (90 ml), was added powdered complex of **1c** and **5b** (3 mg) and the solution was kept at room temperature for 12 h to give a 1:1 complex of **1c** and **5b** (0.77 g, 19%). The complex was dissolved in a mixture of ether and water. From the ether phase, **1c** of 96% ee was obtained, and from aqueous phase, **5b** of 60% ee was obtained. To the EtOH solution left after separation of the complex of **1c** and **5b** by filtration, was added powdered complex of **1b** and **5c** (3 mg) and the solution was kept at room temperature for 14 h to give a 1:1 complex of **1b** and **5c** (0.80 g, 19%). The complex was dissolved in a mixture of ether and water. From ether solution, **1b** of 97.5% ee was obtained, and from aqueous solution, **5c** of 66% ee was obtained. By repeating the seeding experiments a total of eight times as shown in Scheme 1, **1c** of 96% ee (34% yield) and **5b** of 59% ee (48% yield), **1b** of 96.5% ee (31% yield), and **5c** of 62.5% ee (44% yield) were obtained in the yields indicated. In the mutual resolution between **1a** and **5a**, the efficiency for the



Scheme 1. Simultaneous and mutual resolution of **1a** and **5a** by preferential crystallization in the presence of chiral seed crystals.

resolution of **1a** was quite good, although that of **5a** was moderate. Nevertheless, the efficient resolution of **1a** by using only a small amount of the seed crystals of **1c·5b** and **1b·5c** complexes is valuable.

In order to learn the reason why chiral inclusion complex **1c·5b** or **1b·5c** crystallizes out preferentially (rather than the racemic one **1a·5a**) from a solution of **1a** and **5a** in MeOH, the difference in the stability of these complexes was estimated by comparison of their melting points. Although *rac*-BNO **1a** (mp 220 °C) melts at a higher temperature than does chiral BNO **1b** or **1c** (mp 211–212 °C), the 1:1 chiral complexes **1b·5b** or **1c·5c** melt at much higher temperature (mp 224–225 °C) than that of racemic complex **1a·5a** (mp 187 °C). These data suggest that the chiral complex is more stable than the racemic one. The fact that **5a** exists only as a conglomerate and not as a racemate also makes easier the formation of the chiral inclusion crystals **1b·5b** or **1b·5c**. Formation of the relatively unstable racemate complex **1a·5a** seems rather difficult.

Easy formation of the complex of the chiral BNO **1b** or **1c** with the ammonium salt **5** as a conglomerate rather than a racemate prompted us to develop further the efficient enantiomer separation method of **1a** by complexation with a much simpler ammonium salt. *N*-(2-Hydroxyethyl)-*N*,*N*,*N*-trimethylammonium chloride (**6**) was found to form a 1:1 inclusion complex with **1b** or **1c**. CD spectra of these chiral complexes in the solid state are shown in Figure 1. The racemic complex of **1a** and **6** was not formed. Recrystallization of **1a** and **6** from MeOH formed a 1:1 complex **1b·6** or **1c·6** as conglomerate crystals of about 2×7×4 mm in size and average 60 mg in weight for one piece of crystal. By using this easy formation of the conglomerate, enantiomer separation of **1a** was

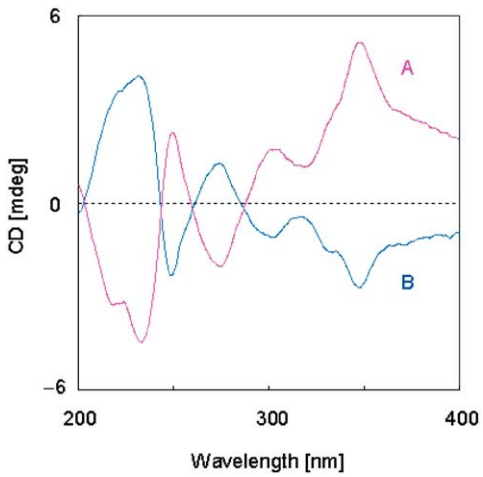
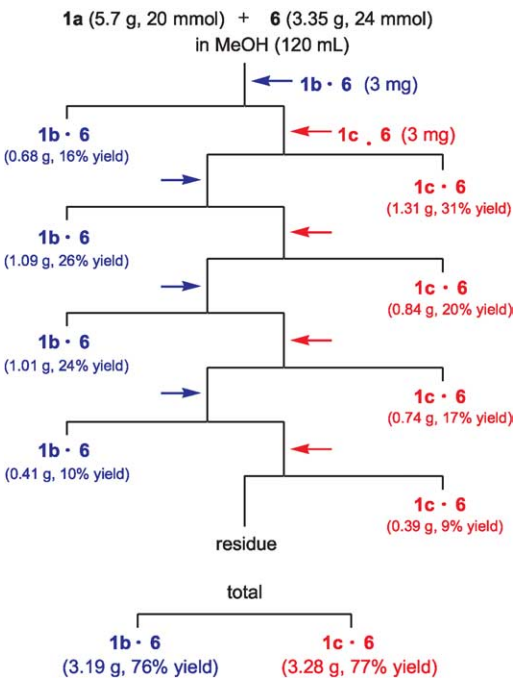


Figure 1. CD spectra of **1c·6** (A) and **1b·6** (B) as Nujol mulls.

accomplished by complexation with **6** in the presence of the chiral seed crystals.

To a solution of **1a** (5.72 g, 20 mmol) and **6** (2.79 g, 20 mmol) in MeOH (120 ml), was added powdered **1b·6** complex (3 mg) and the solution was kept at room temperature for 15 h to give **1b·6** complex (0.68 g, 16% yield). To the MeOH solution left after separation of the complex **1b·6** by filtration, was added powdered **1c·6** complex (3 mg) and the solution was kept at room temperature for 15 h to give **1c·6** complex (1.31 g, 31% yield). By repeating the same operations a further six times (as shown in Scheme 2) the **1b·6** complex (3.19 g, 76% yield) and **1c·6** complex (3.28 g, 77% yield) were obtained in the total yields indicated. The **1b·6** complex (3.19 g) was dissolved in a mixture of ether and water. From the ether solution, **1b** of 99% ee was obtained (1.87 g, 66%). The same treatment of the **1c·6** complex (3.28 g) gave **1c** of



Scheme 2. Resolution of **1a** by inclusion complexation with **6** in the presence of chiral seed crystals.

99.5% ee (1.85 g, 64% yield). From the aqueous solutions obtained from both experiments, and from the residue left after the resolution experiment, **6** (2.92 g, 87% yield) was recovered unchanged in the total yield indicated. Since **6** is very cheap, \$70/kg, the resolution of **1a** with **6** is economical. In order to clarify the mechanism of the efficient chiral recognition process between **6** and **1b** or **1c**, X-ray structure of the 1:1 complex of **6** and **1b** was analyzed (Table 1). As shown in Figure 2, the inclusion crystalline lattice is constructed by a hydrogen bond network between the OH groups of **1c** and the Cl^- of **6**. The intramolecular hydrogen bond between the OH group and Cl^- in **6** also plays an important role in construction of the inclusion crystalline lattice. These data suggest that similar ammonium chlorides substituted with trimethyl and hydroxyalkyl

Table 1. Crystallographic data for the inclusion complexes of **1c·6** and **1b·9**

	1c·6	**1b·9**
Formula	$C_{25}H_{28}ClNO_3$	$C_{24}H_{26}ClNO_2$
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)
a (Å)	9.1385(2)	9.0002(1)
b (Å)	13.9422(3)	14.1519(3)
c (Å)	16.9315(3)	16.6811(3)
Z	4	4
V (Å^3)	2157.26(7)	2124.67(6)
D_{calc}	1.311	1.238
R	0.0238	0.0434
Temperature (°C)	−150	−150

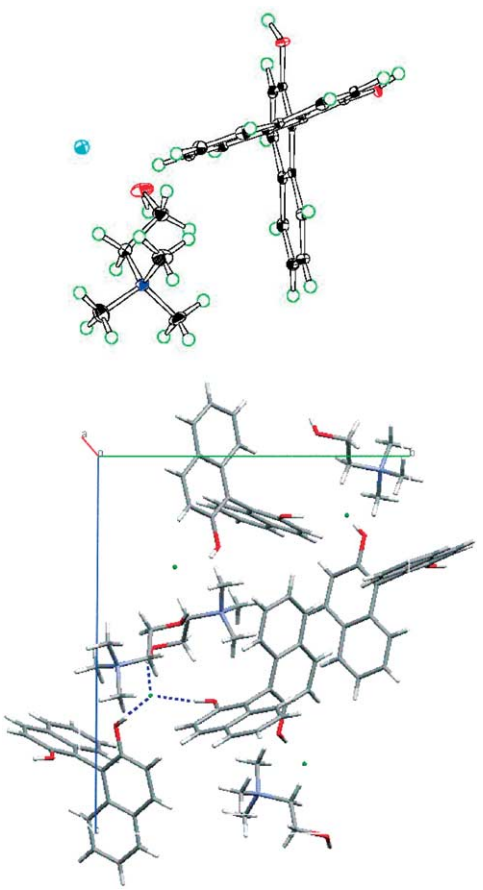


Figure 2. X-ray structure of **1c·6**.

groups such as *N*-(3-hydroxypropyl)-*N*,*N*,*N*-trimethylammoniuum chloride (**7**) and *N*-(4-hydroxybutyl)-*N*,*N*,*N*-trimethylammonium chloride (**8**) could also be used instead of **6** for the enantiomer separation of **1a**. Since **7** formed chiral crystals with **1b** or **1c**, **7** can probably be used for the enantiomer separation of **1a**. However, **8** formed only a racemic complex with **1a**, rather than a conglomerate complex. The alkyl chain length of the hydroxyalkyl group in **6**-**8** would be important for the construction of the inclusion complex with **1**. It has been reported that *N*-hexyl-*N*,*N*,*N*-trimethylammonium bromide forms only a racemic complex with **1a**.[9] This also supports that the idea that the alkyl chain length of the ammonium salt is important for the formation of conglomerate complexes.

During the course of the study of the enantiomer separation of **1a** by complexation with the simpler ammonium salt tetramethylammonium chloride (**9**), some interesting new results were found. In the inclusion complexation of **1a** with **6**, only the conglomerate complex **1b**·**6** and **1c**·**6** was formed, and the racemic complex **1a**·**6** was not formed. In the inclusion complexation of **1a** with **9**, however, both racemic (**1a**·**9**) and the conglomerate complex (**1b**·**9** and **1c**·**9**) was formed. When **1a** (1.43 g, 5 mmol) and **9** (0.55 g, 5 mmol) were recrystallized from MeOH (7 ml), a racemic 1:1:1 complex, **1a**·**9**·MeOH (**10**) crystallized out as colorless needles. However, when **1a** (1.43 g, 5 mmol) and **9** (0.55 g, 5 mmol) were recrystallized from MeOH (15 ml), a 1:1 mixture of the conglomerate complex **1b**·**9** and **1c**·**9** (**11**) crystallized out as colorless prisms. The racemic structure of **10** was elucidated by HPLC analysis and CD spectral measurement for one piece of single crystal. The IR spectrum (Fig. 6) and melting point of the conglomerate mixture **11** (mp 312 °C) are comparable to those of an authentic sample of the chiral **1b**·**9** or **1c**·**9** (mp 313–315 °C) which are prepared by complexation of **1b** or **1c** with **9** in MeOH. These two enantiomeric complexes gave the CD spectra in the solid state as nice mirror images (Fig. 3). The difference between the preferential formation of **10** and **11** in the complexation is very dependent on the concentration of the MeOH solution. However, conglomerate **11** is formed much more easily. For example, when recrystallization of **1a** and **9** from MeOH was carried out under the conditions which gave **10** in the former experiment, by occasional shaking of the flask or by seeding with conglomerate crystals, only **11** was produced. However, the reverse did not occur.

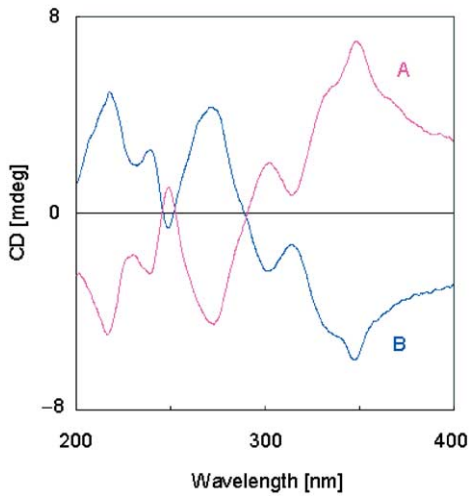
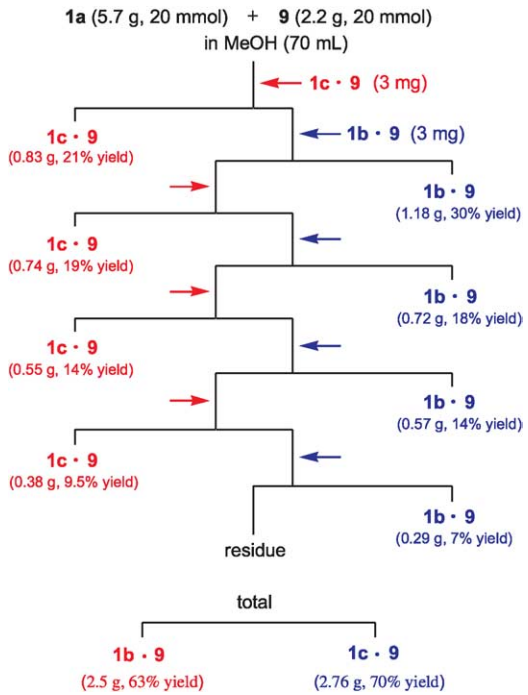


Figure 3. CD spectra of **1c**·**9** (A) and **1b**·**9** (B) as Nujol mulls.

Trimethylammonium chloride (**13**) also formed a conglomerate complex with **1**. However, dimethyl (**14**) and methylammonium chloride (**15**) did not form any complex with **1**. These results are contrasted with that of tetramethylammonium chloride (**9**) that forms both racemic and conglomerate complexes with **1**. The *N*-hexyl-*N*,*N*,*N*-trimethylammmonium bromide, which has a longer alkyl chain and does not form conglomerate complex, is also contrasted with **9**.[9]

By using this preferential crystallization of the conglomerates, an efficient enantiomer separation of **1a** was accomplished. For example, to a solution of **1a** (5.7 g, 20 mmol) and **9** (2.2 g, 20 mmol) in MeOH (70 ml), was added powdered **1c**·**9** (3 mg) as seed crystals and the solution was kept at room temperature for 16 h to give the chiral complex **1c**·**9** (0.83 g, 21% yield). To the filtrate left after separation of **1c**·**9** by filtration, was added powdered **1b**·**9** as seed crystals and the solution was kept at room temperature for 16 h to give the chiral complex **1b**·**9** (1.18 g, 30% yield). By repeating the preferential crystallization procedure a further six times as shown in Scheme 3, the two chiral complexes **1c**·**9** (2.5 g, 63.5% yield) and **1b**·**9** (2.76 g, 69% yield) were obtained in the total yields indicated. By treatment with an ether–water mixture by the same procedure applied for the resolution of **1a** with **5** or **6**, **1c** of 99% ee (1.5 g, 53% yield) and **1b** of 99% ee (1.44 g, 50% yield) were finally obtained in the total yields indicated. In order to clarify the precise chiral recognition mechanism between **1** and **9**, the X-ray crystal structure of the **1b**·**9** complex was studied (Fig. 4). As shown in Table 1, crystallographic data of the two



Scheme 3. Resolution of **1a** by inclusion complexation with **9** in the presence of chiral seed crystals.

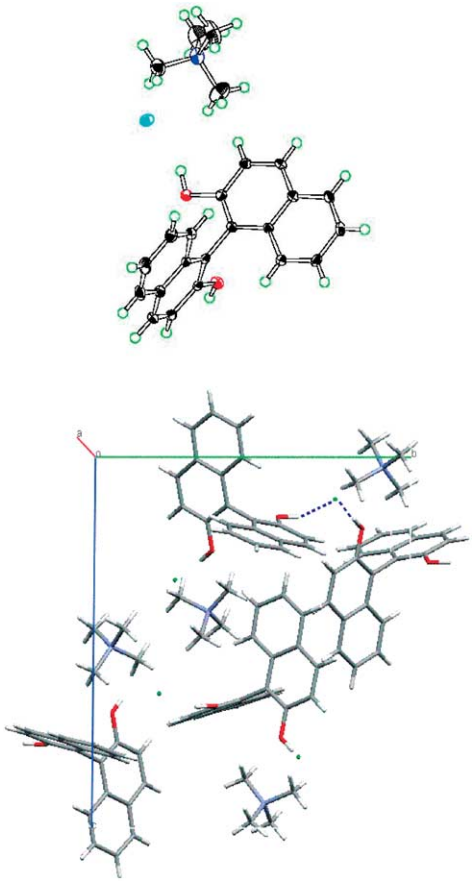


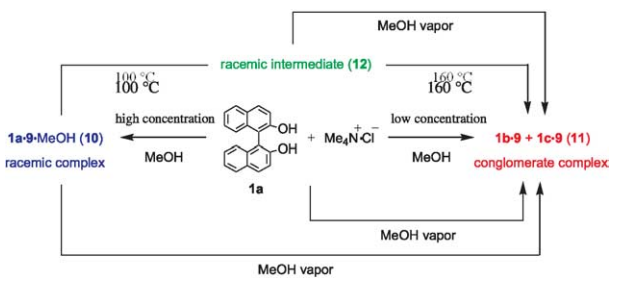
Figure 4. X-ray structure of **1b·9**.

inclusion complexes **1c·6** and **1b·9** are very comparable. The mechanism of chiral recognition in these complexes would also be very similar.

Similar enantiomer separations by the formation of conglomerate inclusion complexes of 2,7-dimethyltricyclo[4.3.1.1^{3,8}]undecane-*syn*-2,*syn*-7-diol with dimethylsulfoxide[10] and of 1,1′-binaphthyl-2,2′-dicarboxylic acid with pyrazoles[11] have been reported. The mechanism of these chiral recognitions using X-ray data analysis has also been well studied.

3. Transformation of racemic complex into a conglomerate complex

During the course of the study of the racemate **10** and conglomerate **11**, two interesting transformation courses of



Scheme 4. Formation of racemic complex **1a·9**·MeOH and conglomerate complexes **1b·9** and **1c·9**, and transformation of the former into the latter.

10 into **11** in the solid state were also found (Scheme 4). One is a thermal transformation. TG and DTA measurements of **10** showed the evaporation of MeOH at 120 °C and phase-transfer from racemate **10** to conglomerate **11** at 183 °C, and finally showed melting of **11** at 310 °C (Fig. 5).

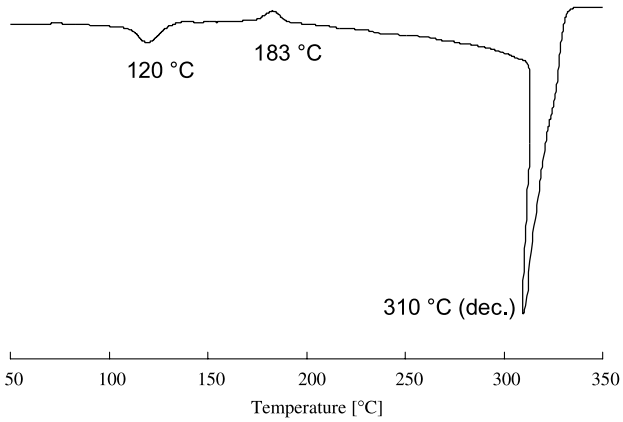


Figure 5. DTA measurement of racemic complex **1a·9**·MeOH (**10**).

The thermal transformation of **10** into **11** was monitored by continuous measurements of IR spectra in the solid state by using the ATR method (Fig. 6). By heating **10** up to 100 °C, the MeOH absorption of **10** at around 1000 cm^{-1} gradually decreased as MeOH evaporated from the complex and gave finally a MeOH-free racemic complex, **1a·9** (**12**). By further heating up to 160 °C, the racemic complex intermediate **12** turned into the conglomerate **1b·9** and **1c·9** (Scheme 4, Fig. 6). The spectrum of **11** (C in Fig. 6) is identical to that of an authentic sample of the pure chiral complex **1b·9** (D in Fig. 6). Finally, the thermal transformation from **10** into **11** was clarified to proceed via the meta-stable racemic complex intermediate **12**. What happens at the molecular level at the phase-transfer stage from the racemate **10** to the conglomerate **11**? Thermal reaction of one piece of single crystal of **10** at 160 °C was observed by microscope, but no special observation was noted, just final conversion into **11**. Heating of fine single needle crystals of **10** at 100 °C for 30 min gave **12** as needle crystals. Further heating of **12** at 160 °C for 5 min finally gave **11** as similar needle crystals (Fig. 7). However, neither **11** nor **12** seem to be single crystals. The crystalline shape of **11** is different from that of the pure chiral crystals **1c·9** (Fig. 7).

In order to certify that **11** is a conglomerate and not a racemate, the X-ray powder diffraction pattern of **11** was compared with that of an authentic sample of **1b·9**. As shown in Figure 8, the spectrum of **10** (A) is similar to that of **12** (B), since both are racemates. However, those of **10** and **12** are completely different from that of **11** (C). The spectrum of **11** is more similar to that of an authentic sample of the chiral crystal **1b·9** (D). Slight differences between the spectra of **11** and that of the authentic sample are probably due to a difference of molecular packing in the conglomerate crystals.

Very recently, a transformation of the racemic 2,3:6,7-dibenzo[3.3.1]-nona-2,6-diene-4,8-dione (**16**) into the conglomerate at 130 °C was found as the first example of the thermal transformation of a racemate to conglomerate in

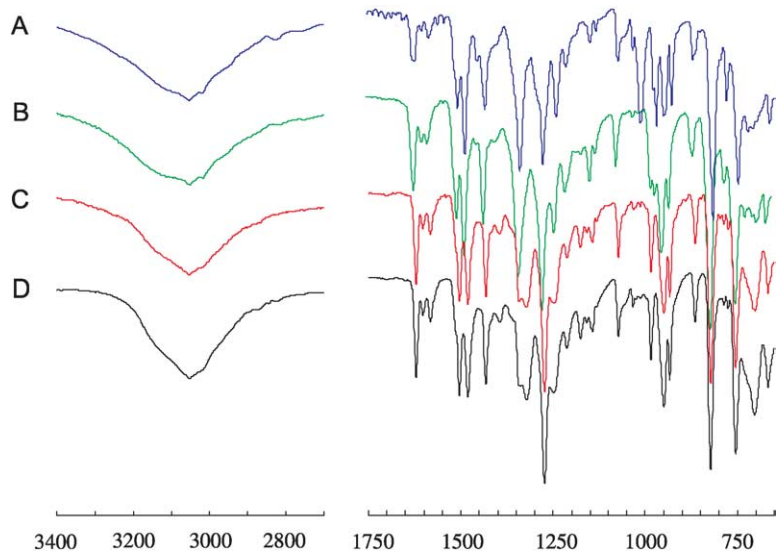


Figure 6. Monitoring by IR spectral measurements with using the ATR method of the thermal transformation of racemic complex **1a**·**9**·MeOH (**10**) into conglomerate complex (**11**) via racemic intermediate (**12**): (A) racemic complex (**10**), (B) racemic intermediate (**12**), (C) conglomerate complex (**11**), (D) authentic sample **1b**·**9**.

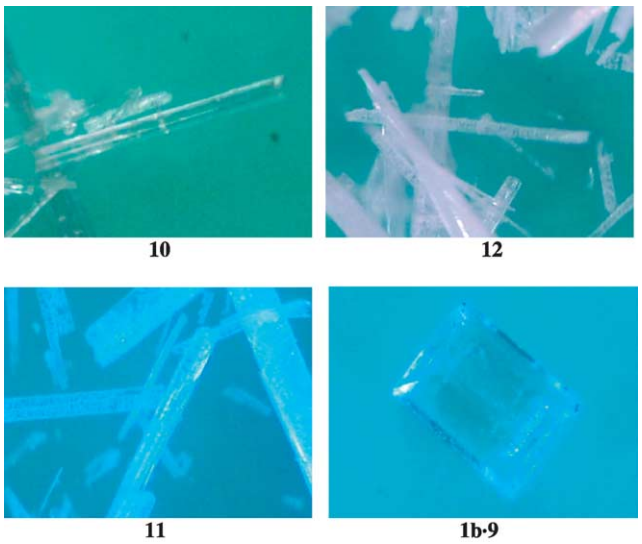
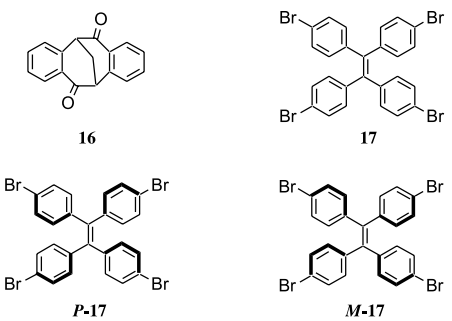


Figure 7. Observation of thermal transformation of racemic complex **1a**·**9**·MeOH (**10**) into conglomerate complex (**11**) via the racemic intermediate (**12**).

the solid state.[12] However, this transformation which occurs for the crystal of the compound **16** itself is slightly different from that occurs for the host–guest inclusion crystals of **1** and **9**

The transformation of **10** into **11** also occurred just by contact of **10** with MeOH vapor in the solid state (Scheme 4). For example, when powdered or crystalline **10** (30 mg) was kept in a flask filled with MeOH vapor for 30 min, **11** was obtained in a quantitative yield. The same treatment of **12** also gave **11**. Very interestingly, contact of a mixture of powdered **1a** and **9** with MeOH vapor for 30 min also gave **11** (Scheme 4), although simple mixing for 30 min of powdered **1a** with an equimolar amount of **9** using a mortar and pestle did not give any complex. However, contact of these compounds with $CHCl_3$, Et_2O, toluene, or hexane vapor did not cause any change.

Similar conglomerate complex formation by contact with MeOH vapor was observed for a combination of **1a** and **6**. When a 1:1 mixture of **1a** and **6** is exposed to MeOH vapor for 1 h, a 1:1 mixture of the chiral complexes **1b**·**6** and **1b**·**6** was obtained, although formation of this conglomerates by simple mixing of the components using a mortar and pestle took at least 7 days. The enantioselective movement and arrangement of BNO molecules in the solid state so as to form conglomerate complexes of **1** with **6** and **9** is very interesting. The reason for the interesting role of MeOH vapor in the formation of these conglomerate complexes in the solid state is not clear. However, it is known that solid state reactions can be accelerated in the presence of a small amount of a solvent molecule.[13] Similarly, the important role of guest compound vapor in the formation of conglomerate complexes has been reported. Generation of chirality in an inclusion complex of the achiral host, tetra-(*p*-bromophenyl)ethylene (**17**) and an achiral guest occurs by twisting of the *p*-bromophenyl groups from the molecular plane in a clockwise or counterclockwise direction. When crystalline **17** is exposed to THF and β-picoline vapor for 24 h, conglomerate complexes of **17** with THF (1:2) and β-picoline (1:1) were produced in the ratio indicated, although recrystallization of **17** from these neat guest gave the corresponding racemic complexes.[14]



In the case of BNO, however, MeOH vapor which plays an important role in the construction of the conglomerate crystalline lattice is not included in the complex formed.

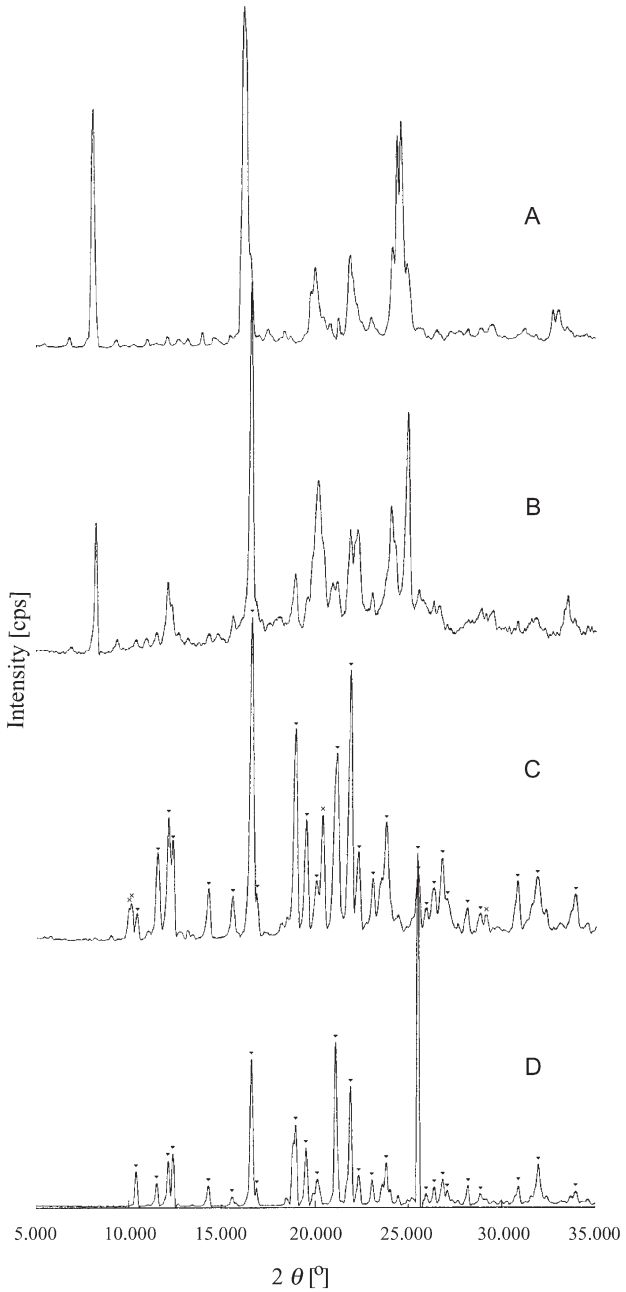


Figure 8. Monitoring of the thermal transformation of racemic complex **1a**·**9**·MeOH (**10**) into conglomerate complex (**11**) via racemic intermediate (**12**) by X-ray powder diffraction analyses: (A) racemic complex (**10**), (B) racemic intermediate (**12**), (C) conglomerate complex (**11**), (D) authentic sample **1b**·**9**.

Furthermore, the transformation of racemate into conglomerate occurs just by enantioselective molecular movement but not by change of molecular structure of BNO. Finally, this is the first example of the transformation of racemate into conglomerate which occurs by contact with molecular vapor in the solid state.

In the case of the transformation of **10** into **11** by exposure to MeOH vapor, a significant change in crystalline shape was observed. On exposure to MeOH vapor, a single crystal of racemic complex **1a**·**9**·MeOH (**10**) was changed into the polycrystalline conglomerate **1b**·**9** and **1c**·**9** (**11**) (Fig. 9). This transformation was also monitored by X-ray powder

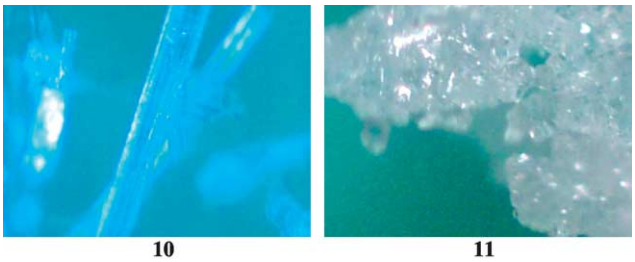


Figure 9. Observation of transformation of racemic complex **1a**·**9**·MeOH (**10**) into conglomerate complex (**11**) by exposure to MeOH vapor.

diffraction analysis. By exposure to MeOH vapor, the racemic complex crystal (A in Fig. 8) changed to the conglomerate complex **11** (A in Fig. 10). The spectrum of **11** (A in Fig. 10) is comparable to that of the authentic sample of the chiral complex **1b**·**9** (B in Fig. 10).

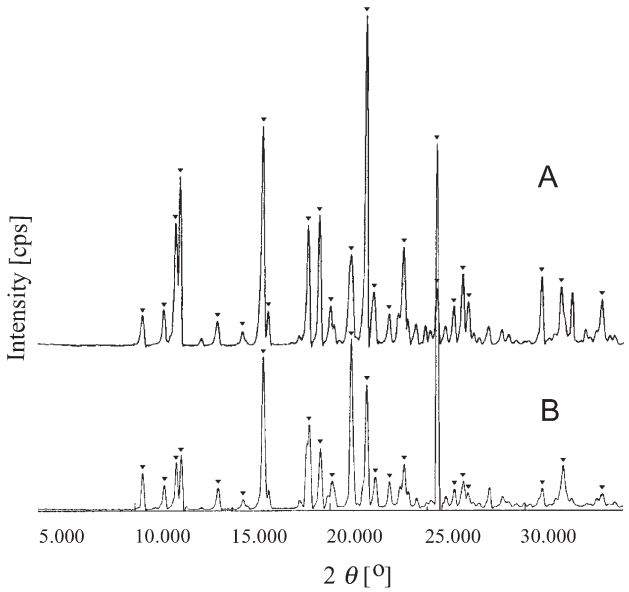


Figure 10. X-ray powder diffraction pattern of (A) conglomerate complex (**11**) formed by exposure of **10** to MeOH vapor and (B) authentic sample **1b**·**9** (**11**).

Unfortunately, however, each piece of the polycrystallite is too tiny in size to determine its conglomerate structure by spectral measurements just for one piece of single crystal.

4. Experimental

4.1. CD and IR spectra and X-ray analysis

CD spectra were measured as Nujol mulls according to the reported procedure.[15] IR spectra were measured by the ATR (Attenuated Total Reflection) method. X-ray analysis was carried out on a Rigaku RAXIS-IV apparatus.

4.1.1. Inclusion complexes 1b·6. Mp 281–283 °C, νOH, 3337 and 3139 cm^{-1}. Found: C, 70.49; H, 6.63; N, 3.29%. Calcd for $C_{25}H_{28}ClNO_3$: C, 70.35; H, 6.58; N, 3.10%. **1b**·**9**, mp 300–302 °C, νOH, 3052 cm^{-1}. Found: C, 72.81; H, 6.62; N, 3.54%. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.62; H, 6.59; N, 3.71%. **1a**·**9**·MeOH (**10**), mp was not determined, and did not give correct elemental analytical results, since MeOH

evaporates easily. The ratio was determined by TG and ^{1}H NMR measurements. Racemic structure was elucidated by HPLC analysis of one piece of single crystal. Conglomerate mixture of **1b**·**7** and **1c**·**7**, mp 243–245 °C, νOH, 3275 cm^{-1}. Found: C, 70.77; H, 6.71; N, 3.34%. Calcd for $C_{26}H_{30}ClNO_3$: C, 70.98; H, 6.87; N, %. **1a**·**8**, mp 188 °C, νOH, 3173 cm^{-1}. Found: C, 71.52; H, 7.39; N, 3.17%. Calcd for $C_{27}H_{32}ClNO_3$: C, 71.43; H, 7.10; N, %. Conglomerate mixture of **1b**·**13** and **1c**·**13**, mp 229–230 °C, νOH, 3178 cm^{-1}. Found: C, 72.54; H, 6.43; N, 3.76%. Calcd for $C_{23}H_{24}ClNO_2$: C, 72.34; H, 3.67; N, %.

4.1.2. Dissociation of inclusion complexes to the components by dissolving in a mixture of ether and water. For example, a 1:1 complex of **1b** and **6** (3.19 g) was dissolved in a 1:1 mixture of ether and water (200 ml). The ether layer was dried over $MgSO_4$ and kept at room temperature until **1b** crystallized out to give **1b** of 99% ee (1.87 g, 87% yield). Evaporation of aqueous solution gave **6** (0.98 g, 93% yield). When a 1:1 complex of **1c** and **9** (2.50 g) was dissolved in a 1:1 mixture of ether and water (200 ml), from the ether and aqueous solution, **1c** of 99% ee (1.52 g, 84% yield) and **9** (0.6 g, 86% yield) were obtained, respectively.

4.1.3. Determination of optical purity. Optical purity of **1b** and **1c** was determined by HPLC using the column containing Chiralpak AD (1:1 *i*-PrOH–hexane). Optical purity of **5b** and **5c** was determined by comparison of its $[\alpha]_D$ value with that of an authentic sample.

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Alpha- and beta-polypeptides show a different stability of helical secondary structure

Thereza Soares, Markus Christen, Kaifeng Hu and Wilfred F. van Gunsteren*

Laboratory of Physical Chemistry, Swiss Federal Institute of Technology Zurich ETH, Hönggerberg, CH-8093 Zürich, Switzerland

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Abstract—β-Polypeptides are known to adopt helical secondary structure in organic solvents, even for rather short chain lengths. It is investigated whether a short α-polypeptide with amino-acid side chains that enable β-peptides to adopt helical structures, can maintain or adopt stable helical structure in methanol or in water. The molecular dynamics simulations do not predict a particular fold, which indicates an essential role for the additional methylene moiety in the backbone of β-peptides regarding helix stability.

1. Introduction

In aqueous solution proteins, that is, long polypeptide chains of a particular composition of α-amino acid residues, generally adopt a specific tertiary structure or fold. Shorter α-polypeptides in the range of 10–30 residues may adopt secondary structure, such as α-helices or β-sheets, but their fold generally becomes less stable the shorter the polypeptide chain. In contrast, polypeptides made up of β-amino acids are known to adopt rather stable helical or β-sheet structures even for very short chain lengths of 4–7 residues, in particular when solvated in an organic solvent such as methanol.[1,2] Accordingly, short β-polypeptides are suitable molecules to investigate polypeptide stability and folding mechanism.[3–5] Yet, one may ask why short α-polypeptides do not adopt stable secondary structure. Is this due to their different backbone composition compared to β-peptides, or to the solvation effects of water compared to methanol, or to differences in side-chain sequences of the α- and β-polypeptides studied experimentally? Here, we address this question through molecular dynamics (MD) simulation of a 7-residue α-peptide (Val, Ala, Leu, Aib, Ile, Met, Phe) solvated both in methanol and in water. The α-amino acid composition has been proposed by our colleagues Jaun and Seebach in analogy to the β-amino acid sequence (Val, Ala, Leu, di-Ala, Val, Ala, Leu) of a 7 residue β-peptide that exhibits a rather stable 3_{14}-helical fold in methanol.[6] In this β-heptapeptide all side chains are at the β-carbon and the central residue is substituted with a methyl group at the α-carbon in addition. In order to facilitate the interpretation of NMR spectra to be measured all residues were chosen to be different. The central Aib residue should promote helix formation.[7] We investigate whether this α-heptapeptide that was designed to adopt a helical fold, will indeed maintain or adopt an α-helical conformation in methanol or in water.

The α-heptapeptide has been simulated for 26 ns in methanol and for 7.8 ns in water, both starting from an ideal α-helical initial structure and starting from a wholly extended backbone structure (Fig. 1). Because of the higher density of interacting atoms, the simulation in water is three

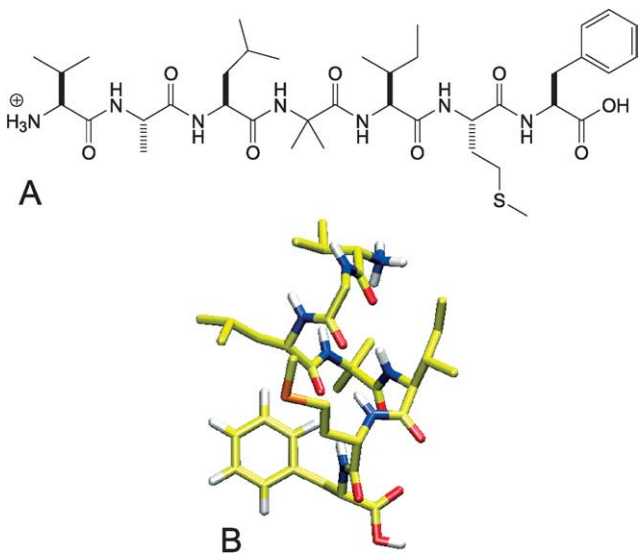

Figure 1. Panel A. Chemical formula of the α-heptapeptide studied. Panel B. α-Helical conformation of the peptide.

Keywords: Alpha-peptide; Beta-peptide; Molecular dynamics simulation; Peptide folding; Conformation analysis.
* Corresponding author. Tel.: +41-1-632-68-61; fax: +41-1-632-10-39; e-mail address: wfvgn@igc.phys.chem.ethz.ch

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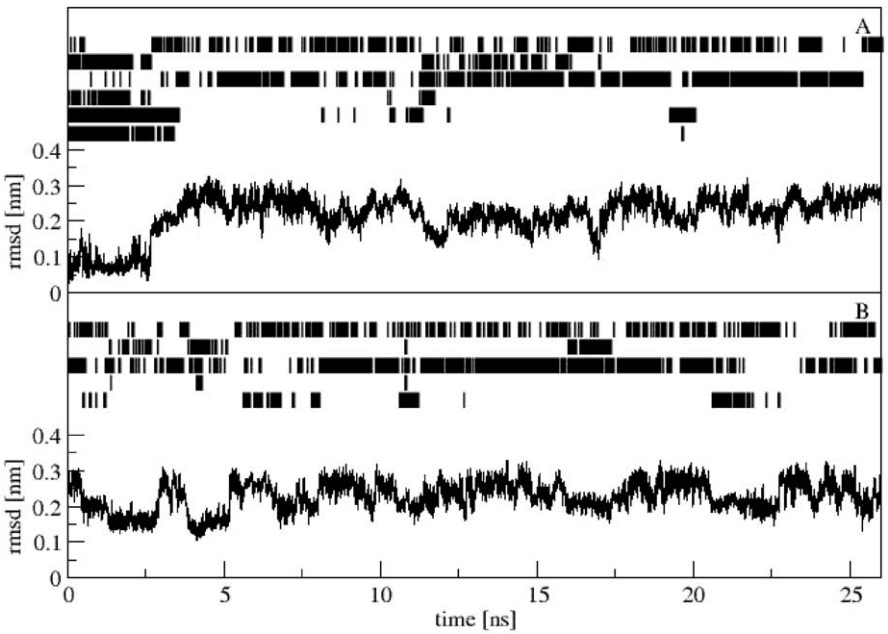

Figure 2. MD simulations of the α-heptapeptide in methanol starting from an α-helical initial conformation (Panel A) and from an extended initial conformation (Panel B). The evolution of all intramolecular hydrogen bonds with an occurrence larger than 5% is displayed together with the backbone (atoms N, C_α, C, O of residues 2–6) atom-positional root-mean-square deviation of the trajectory structures from an ideal α-helical structure. The hydrogen bonds are from top to bottom: NH(4)–O(2), NH(5)–O(2), NH(5)–O(3), NH(6)–O(2), NH(6)–O(3) and NH(7)–O(3).

to four times more expensive than that in methanol. This is why the water simulations are rather short compared to the methanol ones. The simulations were carried out using the GROMOS biomolecular simulation software[8,9] and the GROMOS biomolecular force field with parameter set 45A3.[8,10] This force field has been shown to accurately reproduce folding equilibria of a number of α- and β-polypeptides in agreement with experimental NMR data, as a function of amino-acid composition and solvent composition.[4,11–21] Therefore, one may expect this force field to be able to correctly predict the folding equilibrium of the α-heptapeptide, in methanol as well as in water.

2. Results

In Figure 2 the root-mean-square difference (rmsd) between the trajectory structures of the MD simulations of the α-heptapeptide in methanol and an ideal α-helical model structure is shown as a function of time together with the occurrence of intra-solute hydrogen bonds that occur for more than 5% in the simulations. Starting from an α-helical initial structure (Panel A), the helix is lost after 2.5 ns and is not formed again over the remaining 23.5 ns. Starting from an extended initial structure (Panel B), no α-helix is formed within 26 ns, although the molecule comes close after about 4 ns (rmsd 0.10 nm). As can be seen from Table 1, both simulations in methanol show the same dominant hydrogen bonds, which indicates a reasonable degree of convergence of the simulations. However, no NH(*i*)–O(*i*-4) hydrogen bonding (with residue number *i*=5, 6 or 7) characteristic for an α-helix is observed. This is also true for the corresponding simulations of the α-heptapeptide in water. Starting from an α-helical initial structure (Fig. 3A), the helix is only maintained for 1.5 ns and is not formed again in the remaining 6.3 ns. Starting from an extended initial structure (Fig. 3B), no helix is formed within 7.8 ns. We note that the hydrogen bond patterns observed in both water simulations are rather different, which indicates that 7.8 ns is not sufficient to sample the conformational ensemble of the solute in water at 300 K and 1 atm.

Table 1. Occurrence (%) intramolecular hydrogen bonds

Simulation initial structure	In methanol		In water	
	Helical	Extended	Helical	Extended
NH(4)–O(2)	8	4	3	1
NH(5)–O(2)	5	3	21	15
NH(5)–O(3)	30	26	12	38
NH(6)–O(2)	3	1	6	0
NH(6)–O(3)	12	7	17	0
NH(7)–O(1)	0	0	1	16
NH(7)–O(3)	6	0	5	0

Only hydrogen bonds occurring in more than 5% of the analysed conformations of a simulation have been considered. The residue sequence numbers of the atoms are indicated in parentheses. A hydrogen bond is considered to exist when the donor–hydrogen–acceptor angle is larger than 135° and the hydrogen–acceptor distance is smaller than 0.25 nm.

The conformational space that is sampled in a MD simulation and the degree of conformational overlap between two ensembles or simulation trajectories can be analysed using conformational cluster analysis. Such an analysis groups the structures of a trajectory or of combined trajectories into clusters of similar structures according to the atom-positional rmsd-value of the backbone (N, C_α, C, O) atoms (excluding the first and last residue) between pairs of structures from the trajectory or combined trajectories. In Figure 4 the results of the cluster analysis of the combined

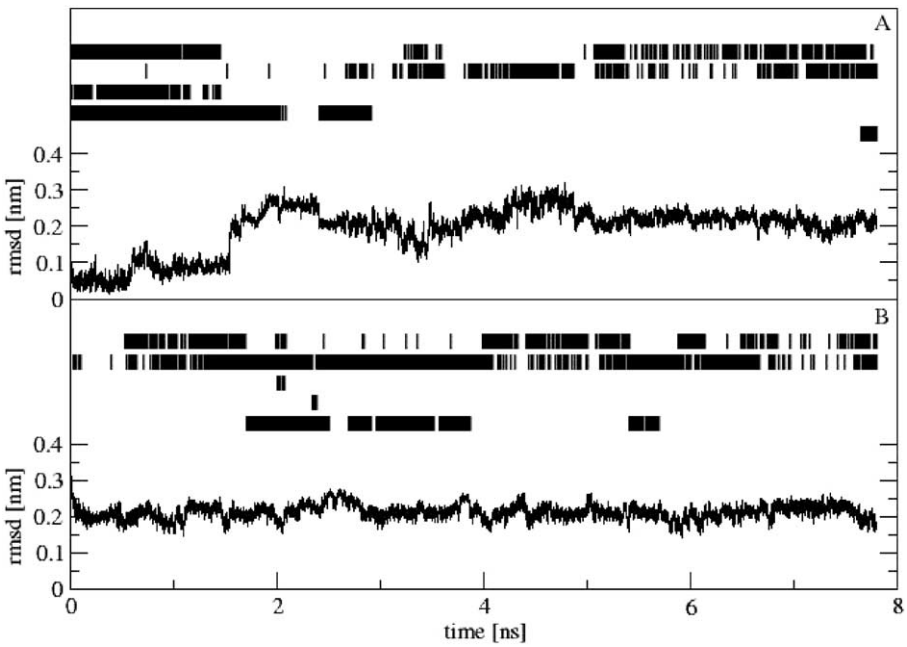

Figure 3. MD simulations of the α-heptapeptide in water starting from an α-helical initial conformation (Panel A) and from an extended initial conformation (Panel B). The evolution of all intramolecular hydrogen bonds with an occurrence larger than 5% is displayed together with the backbone (atoms N, C_α, C, O of residues 2–6) atom-positional root-mean-square deviation of the trajectory structures from an ideal α-helical structure. The hydrogen bonds are from top to bottom: NH(5)–O(2), NH(5)–O(3), NH(6)–O(2), NH(6)–O(3) and NH(7)–O(1).

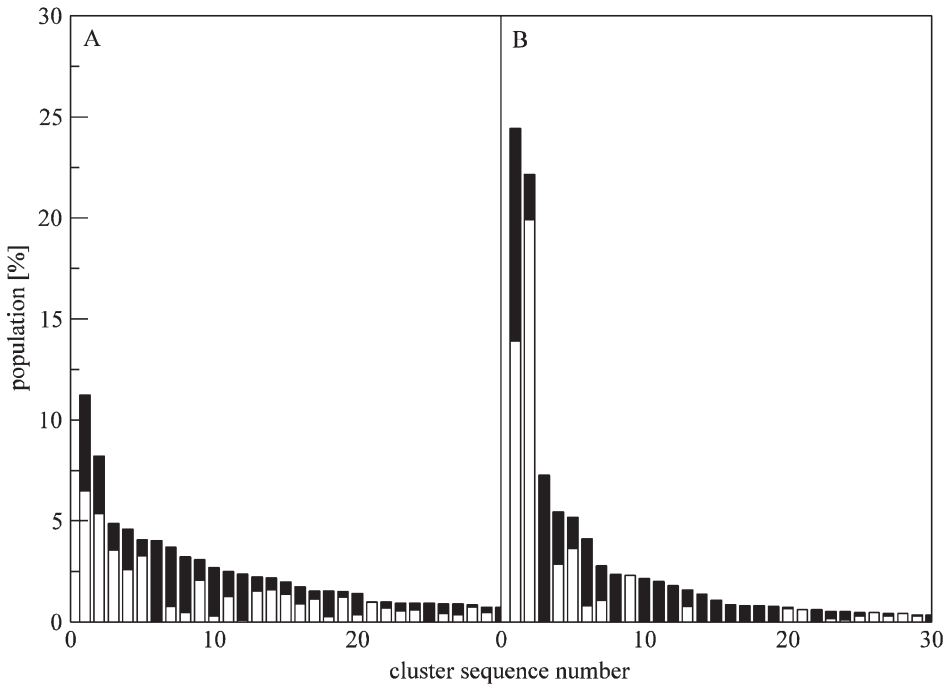

Figure 4. Conformational cluster analysis of pairs of MD trajectories of the α-heptapeptide. The plots show the population (in %) per cluster and the portion of structures per cluster that belongs to each of the two trajectories. Panel A. MD in methanol, starting from an ideal α-helix (black) or from an extended structure (white). Panel B. MD in water, starting from an ideal α-helix (black) or from an extended structure (white).

(starting from the helical and extended initial structures) trajectories of the α-heptapeptide in methanol (Panel A) and of the molecule in water (Panel B) are shown. A rmsd similarity criterion of 0.08 nm was used. In methanol both simulations sample the same set of conformers, of which none is very dominant (largest population 12%). The results for the simulations in water confirm that the sampling of the conformational space is not yet complete: both simulations sample partially different conformations. In Figure 5 the simulations in different solvents starting from identical initial structures are compared. Starting from an α-helical structure the α-heptapeptide seems to sample comparable parts of conformational space in methanol and in water. Starting from an extended structure (Panel B) more different

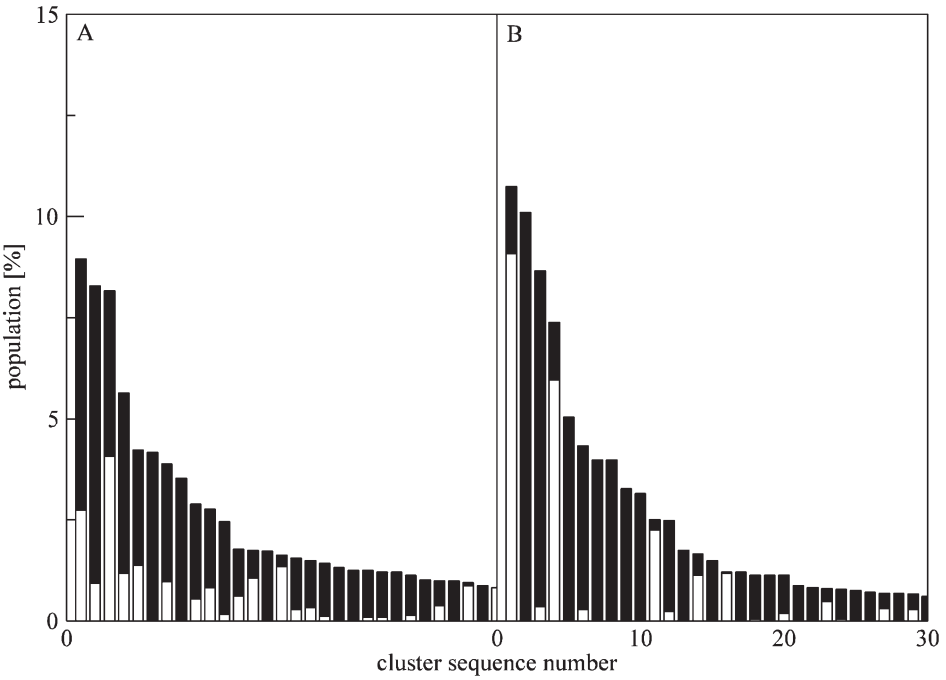

Figure 5. Conformational cluster analysis of pairs of MD trajectories of the α-heptapeptide. The plots show the population (in %) per cluster and the portion of structures per cluster that belongs to each of the two trajectories. Panel A. MD starting from an ideal α-helix in methanol (black) or in water (white). Panel B. MD starting from an extended structure in methanol (black) or in water (white).

conformations are visited in methanol compared to water. This is due to the lack of convergence of the water simulation.

In Figure 6 the central member structures of each of the three most populated clusters from each of the four simulations are shown together with their percentage population and dominant hydrogen bonds. The lowly populated structures are of irregular character, showing a variety of intramolecular hydrogen bonds. They have no helical character. However, many of the most populated conformers do show the NH(5)–O(3) hydrogen bond, particularly in methanol.

3. Conclusions

The four MD simulations of the α-heptapeptide shown in Figure 1, in methanol and in water, and starting from an α-helical and from an extended initial structure, predict that the α-heptapeptide will neither maintain nor adopt an α-helical conformation in methanol or in water. The conformational sampling over 26 ns in methanol seems to be rather complete, whereas in water 7.8 ns is not sufficient to obtain a converged ensemble of conformations. The conformers that dominate the conformational ensemble do not exhibit any particular secondary structure character. Although the α-heptapeptide was designed by Jaun and Seebach to maximize its tendency to adopt an α-helical conformation, simulations based on the GROMOS biomolecular force field do not predict any particular fold. This points at an essential role for the additional methylene moiety in the backbone of β-peptides regarding helix stability. We look forward to experimental (NMR) data that will confirm or contradict this prediction.

4. Methods

The MD simulations were carried out using the GROMOS software[8,9] and the GROMOS biomolecular force field,[8] parameter set 45A3.[10] Aliphatic CH_n groups were treated as united atoms, both in the peptide and in the solvent methanol.[22] For water the simple-point-charge (SPC) model[23] was used. Two initial α-heptapeptide structures were used: an α-helical one and an extended structure with $\varphi=\psi=180°$ for all residues. These peptide structures were placed in a truncated octahedron such that the minimum distance of a solute atom to one of the square walls was 1.5 nm. The remaining empty space in the truncated octahedron was filled with methanol or water molecules taken from an equilibrated configuration of these liquids. Four systems were generated: the peptide in the α-helical conformation with 633 methanol molecules and in the extended conformation with 1312 methanol molecules, and the peptide in corresponding conformations with 1396 and 2930 water molecules, respectively. Periodic boundary conditions were applied. After relaxation of the systems using steepest descent energy minimization the four MD simulations were started by taking the initial atomic velocities from a Maxwell distribution at low temperature followed by a gradual heating of the system till 300 K while position restraining the peptide atoms. Bond-lengths in the solute and all internal degrees of freedom of the solvent molecules were kept rigid using the SHAKE algorithm[24] with a geometric tolerance of 10^{-4}. Solute and solvent were separately coupled to a temperature bath at 300 K and with a relaxation time of 0.1 ps.[25] The pressure was calculated with a molecular virial and held constant at 1 atm using an isothermal compressibility of 4.575×10^{-4} $(\text{kJ mol}^{-1}\,\text{nm}^{-3})^{-1}$ and a relaxation time of 0.5 ps.[25] The equations of motion were integrated using the leap-frog algorithm and a time step of 2 fs. The non-bonded

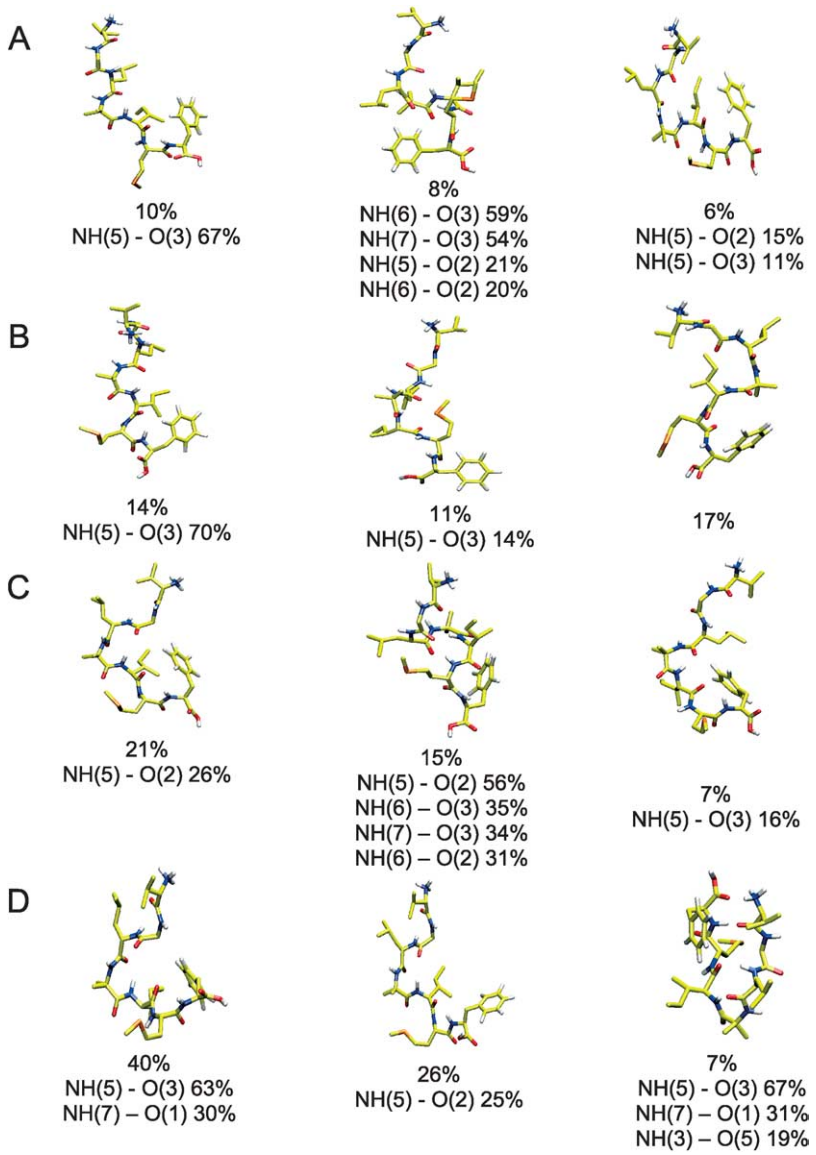

Figure 6. The three most populated conformers (central structures of the three most populated clusters using a backbone (N, C_α, C, O of residues 2–6) root-mean-square-difference (rmsd) criterion of 0.08 nm) observed in the four MD simulations. For each conformer, its corresponding population and occurrence of its most dominating hydrogen bonds is given. MD simulations in methanol (Panels A and B) and in water (Panels C and D) starting from an α-helical conformation (Panels A and C) or from an extended conformation (Panels B and D).

interaction between atoms grouped into so-called charge groups[8] was calculated according to a triple-range cut-off scheme: short-range van der Waals and electrostatic interactions were evaluated at every time step from a charge-group pair list that was generated with a short-range cut-off radius of 0.8 nm between the centres of geometry of the solute charge groups and the oxygen atoms of the methanol or water solvent molecules. Longer-range van der Waals and electrostatic interactions, between pairs at a distance longer than 0.8 nm and shorter than the long-range cut-off radius of 1.4 nm, were evaluated every tenth time step, at which point the pair list was also updated, and were kept unchanged between these updates. A Poisson–Boltzmann reaction-field[26] force was used to approximate electrostatic interactions due to the medium outside the long-range cut-off radius. The dielectric permittivity for the continuum outside the long-range cut-off radius was 66. Centre of mass translation and rotation of the whole system, peptide plus solvent, was eliminated every 10 time steps.

The two MD simulations in methanol were run for 26 ns, saving configurations every 0.4 ps for analysis. The two MD simulation in water were run for 7.8 ns, saving configurations every 0.2 ps. Least-squares translational and rotational superposition of trajectory structures for the calculation of atom-positional root-mean-square differences (rmsd) between pairs of structures was based on the backbone atoms (N, C_α, C, O) of residues 2–6. The conformational clustering analysis was performed as described by Daura et al.[27] on the sets of 3250 peptide structures from the methanol simulations and the sets of 975 peptide structures from the water simulations taken at 8 ps intervals. As similarity criterion the value of 0.08 nm for the mentioned backbone atom-positional rmsd was used, a value commonly used for β-hexapeptides.[12,17] Hydrogen

bonds were defined using a geometric criterion: a minimum donor–hydrogen–acceptor angle of 135° and a maximum hydrogen–acceptor distance of 0.25 nm.

Acknowledgements

We thank Prof. D. Seebach for challenging us to simulate the behaviour of the α-heptapeptide and thereby to predict its structure before the NMR measurement was to be carried out. We thank Alice Glättli for a critical reading of the manuscript. Financial support from the National Center of Competence in Research (NCCR) Structural Biology of the Swiss National Science Foundation is gratefully acknowledged.

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Xanthates derived from 1,3-dithiane and its monosulfoxide; one-carbon radical equivalents

Michiel de Greef and Samir Z. Zard*

Laboratoire de Synthèse Organique associé au C.N.R.S., Ecole Polytechnique, Route de Saclay, F-91128 Palaiseau, France

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Dedicated with respect and admiration to Professor Dieter Seebach, recipient of last year's Tetrahedron Prize

Abstract—The behaviour and synthetic scope of the C-2 centred radicals derived from 1,3-dithiane and 1,3-dithiane 1-oxide have been studied. Both radicals are available from the corresponding xanthates and have proved suitable substrates for the xanthate transfer reaction. However, the synthetic scope of the former is severely limited by the fact that it does not add to unactivated olefins. The latter on the other hand is a more promising radical precursor and undergoes smooth radical addition to a wide range of alkenes. Furthermore, subsequent transformations of some of the radical adducts confirm its utility as a synthetic equivalent of both the methyl and the formyl radical.

1. Introduction

Over the past few decades, dithioacetals have become common intermediates in organic synthesis. They are widely used as protecting groups for carbonyl compounds and provide a powerful method to make the normally electrophilic carbonyl carbon behave as a nucleophile.[1,2] The first reagent of this type that found general use was 1,3-dithiane, which on lithiation provides a powerful nucleophilic acyl equivalent that reacts with a wide range of alkyl halides, carbonyl compounds and other electrophilic reagents.[3] On the other hand, when halogenated, it provides an electrophilic acyl equivalent that is reactive towards a variety of carbon and heteroatom nucleophiles.[4,5]

Bearing these results in mind, it may be anticipated that the C-2 centred radical derived from 1,3-dithiane represents an interesting synthetic equivalent of the formyl radical and other one-carbon radicals, such as methyl and carboxyl. Despite its promising synthetic potential, however, the radical chemistry of 1,3-dithiane and derivatives has remained relatively unexplored and hence offers an interesting opportunity to further extend the synthetic scope of this heterocycle.[6–13]

Our approach is summarised in Scheme 1 and relies on a radical process that has been thoroughly developed over the past few years by our laboratory and is commonly referred to as the xanthate transfer reaction.[14–16] In contrast with other common radical processes, this method is characterised by the fact that the major competing pathway is degenerate. As a consequence, the intermediate radicals acquire an extended effective lifetime and are able to interact with a variety of relatively unreactive traps. Accordingly, the radical derived from xanthate **1** is expected to react with olefins **2** to give radical adducts **3**. The latter can then be further manipulated using established 1,3-dithiane chemistry, such as hydrolysis (path A), reduction (path B), or alkylation, followed by hydrolysis (path C) or reduction (path D). In this paper, we provide a full account of the progress that we have made while studying the subject.

2. Results and discussion

In order to access xanthate **1**, we relied on a procedure that was developed in the late 1970s by Kruse et al.[4,5] This procedure aims at transforming 1,3-dithiane into its 2-chlorinated derivative which is subsequently trapped by a suitable nucleophile. Thus, treatment of commercially available 1,3-dithiane **4** with sulfuryl chloride, followed directly by slow addition of the resulting 2-chloro-1,3-dithiane **5** to a solution of potassium *O*-ethyl xanthate in acetone gave **1** in quantitative yield (Scheme 2). This two-step-one-pot procedure turned out to be an effective and reliable method to prepare large quantities of **1**.

Subsequent attempts to use **1** in some intermolecular radical

Keywords: Radicals; Xanthates; Dithioacetals; 1,3-Dithiane; 1,3-Dithiane 1-oxide.
* Corresponding author. Tel.: +33-1-69-33-43-52; fax: +33-1-69-33-38-51; e-mail address: zard@poly.polytechnique.fr

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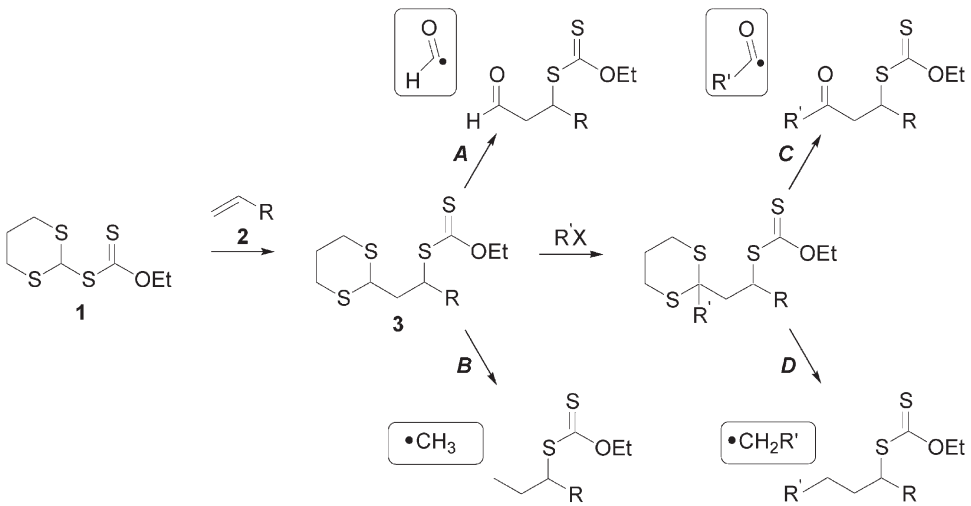
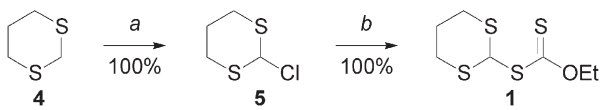


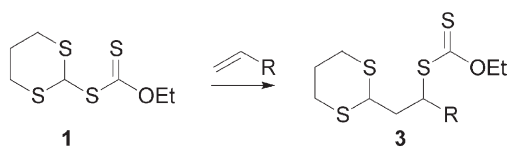
Scheme 1. Radical addition of xanthate **1** to olefins **2** and some of the conceivable transformations of the resulting radical adducts **3**.

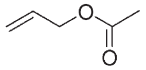
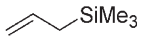
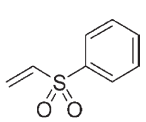
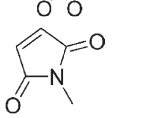


Scheme 2. Reagents and conditions: (a) SO_2Cl_2 (1.05 equiv.), dry $CHCl_3$, −40 °C→rt; (b) $EtOC(S)S^-$, K^+ (1.1 equiv.), acetone, −10 °C→rt.

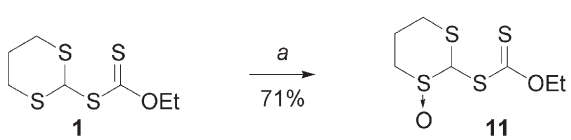
additions under standard reaction conditions gave disappointing results (Table 1, entries a–c). For example, when heating **1** with 2 equiv. of either allyl acetate **6**, or allyltrimethyl-silane **7** in refluxing 1,2-dichloroethane in the presence of lauroyl peroxide (DLP), no reaction was observed, despite the fact that 0.3 equiv. of initiator had been added. Similar results were obtained when phenylvinyl-sulfone **8** was used as olefin. Although in this case, some reaction took place, no radical adduct could be detected in the crude reaction product and a considerable amount of **1** was still present, despite the fact that 0.8 equiv. of DLP had been added. Slightly discouraged by these results, we were relieved to confirm that **1** is nonetheless a valid radical precursor, by trapping the corresponding radical with *N*-methyl maleimide **9** (Table 1, entry d). Thus, heating **1** with 2 equiv. of **9** in refluxing 1,2-dichloroethane afforded the expected radical adduct **10** in 52% yield after addition of 0.25 equiv. of initiator.

Table 1. Radical addition of xanthate **1**



Entry	Olefin		Radical adduct (%)
a		**6**	—
b		**7**	—
c		**8**	—
d		**9**	**10** (52)

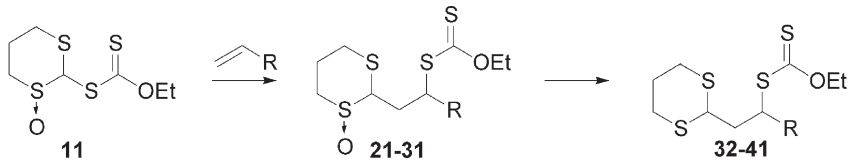
These results suggest that the radical derived from **1** is relatively electron-rich and needs highly activated traps in order to undergo efficient radical addition. It is interesting to note that Byers et al. made similar observations when they studied the photolytic addition of 2-phenylseleno-1,3-dithiane.[9] This reaction was successful only when electron-deficient alkenes were employed. In order to change the electronic properties of **1** and to achieve reversed reactivity, we decided to transform **1** into the corresponding monosulfoxide **11** (Scheme 3). As opposed to the radical derived from **1**, the radical derived from **11** is susceptible to take benefit from the captodative effect. Introduced in the late 1970s by Viehe et al. this concept states that the combined action of an electron-withdrawing and an electron-releasing substituent on a radical centre leads to enhanced stabilisation.[17] Selective oxidation was achieved by slow addition of 1 equiv. of *m*CPBA to a solution of **1** in dichloromethane. Under these conditions **11** was obtained in 71% yield as a solid 10:11 mixture of separable diastereomers. Although the isomers were isolated for identification purposes, the mixture was used as such in subsequent radical reactions, because of the fact that both diastereomers give rise to the same radical.

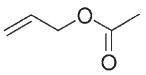
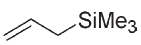
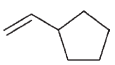
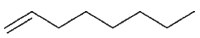
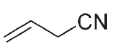
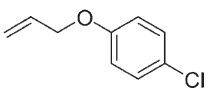
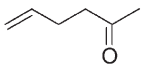
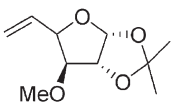
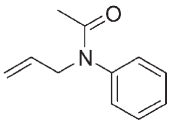
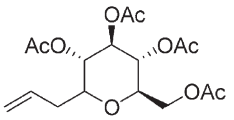
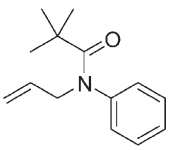


Scheme 3. Reagents and conditions: (a) *m*CPBA (1.06 equiv.), CH_2Cl_2, 0 °C→rt.

To our delight, **11** turned out to be a much more promising radical precursor than **1**, as is reflected by the fact that it underwent smooth radical addition to a wide range of alkenes (Table 2, entries a–k). The corresponding radical adducts **21**–**31** were normally obtained in reasonably good yields (60–75%), although some exceptions were observed

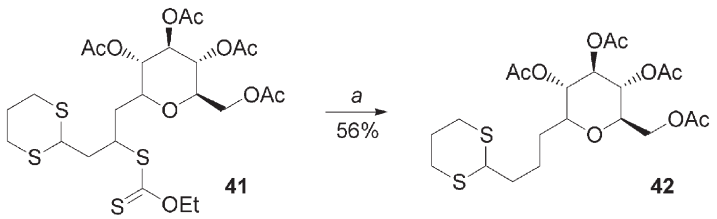
Table 2. Radical addition of xanthate **11**



Entry	Olefin		DLP (equiv.)	**21**–**31** (%)	**32**–**41** (%)
a		**6**	0.45	**21** (70)	**32** (63)
b		**7**	0.30	**22** (75)	**33** (88)
c		**12**	0.45	**23** (56 (63[a]))	**34** (67)
d		**13**	0.35	**24** (69)	**35** (69)
e		**14**	0.85	**25** (32)	**36** (89)
f		**15**	0.50	**26** (69)	**37** (77)
g		**16**	0.80	**27** (34)	**38** (66)
h		**17**	0.45	**28** (66 (72[a]))	**39** (67)
i		**18**	0.55	**29** (75)	**40** (77)
j		**19**	0.75	**30** (39)	**41** (60)
k		**20**	0.65	**31** (61)	[b]

[a] Yield based on recovered starting material.
[b] Radical adduct **31** was not reduced, but characterised after cyclisation and subsequent reduction.

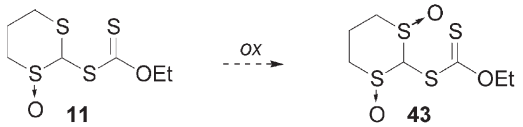
(Table 2, entries e, g, and j). The radical reaction proceeds under mild conditions and tolerates various functional groups commonly encountered in organic synthesis. It is worth noting that **11** displays a behaviour that is slightly different from that observed for most other xanthates.[14] Although it added correctly to most alkenes tested, its radical additions needed significantly more than catalytic quantities of peroxide to reach completion. In some cases (entries i and k), trace amounts of cylised reaction product were detected (TLC analysis), implying that some of the initiator had been used for rearomatisation purposes. For the other cases, the reason for this deviant behaviour is not fully understood. Another difficulty stems from the fact that **11** contains two non-fixed stereocenters and that a third stereocenter is created in a non-controlled way during the radical process. As a consequence, all reaction products **21**–**31** were obtained as complicated mixtures of diastereomers. Although several attempts have been made to characterise each isomer separately, it was judged much more convenient to subject the mixture to reductive conditions, which would considerably facilitate the task of characterisation since two stereocenters are removed in a single reaction step. Among several available methods for the transformation of sulfoxides into sulfides,[18–21] the use of trifluoroacetic anhydride and sodium iodide in dry acetone proved particularly suitable for our purpose.[18] This method allowed rapid reduction of sulfoxides **21**–**31** under mild conditions and gave the corresponding dithianes **32**–**41** in good yields (63–89%) after purification by flash chromatography on silica gel (Table 2, entries a–j). Dithiane **41** (Table 2, entry j) was obtained as an inseparable mixture of diastereomers and had to be further reduced in



Scheme 4. Reagents and conditions: (a) $(Me_3Si)_3SiH$ (2 equiv.), AIBN (cat.), heptane, reflux.

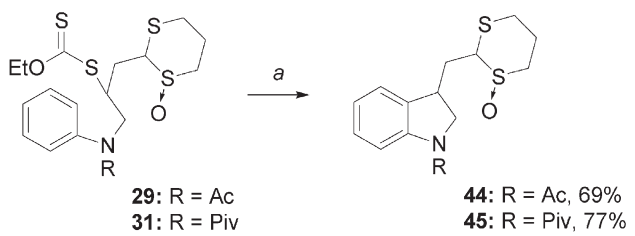
order to allow its full characterisation. Although other methods are available,[22] clean reduction was achieved by exposing **41** to 2 equiv. of tris(trimethylsilyl)silane and a small amount of AIBN in refluxing heptane, which afforded **42** in 56% yield (Scheme 4).

The difficulties related to moderate reactivity and stereochemical complexity may be overcome by transforming **11** into a symmetric and more electrophilic derivative. The most convenient way to do so seems to be the oxidation of **11** to the corresponding bis-sulfoxide **43** (Scheme 5). Initial attempts to carry out this transformation have revealed that the xanthate and the endocyclic sulfide show comparable reactivity toward most common oxidising agents and selective oxidation has become a challenge that we are still addressing.



Scheme 5. Transformation of **11** into the corresponding bis-sulfoxide **43**.

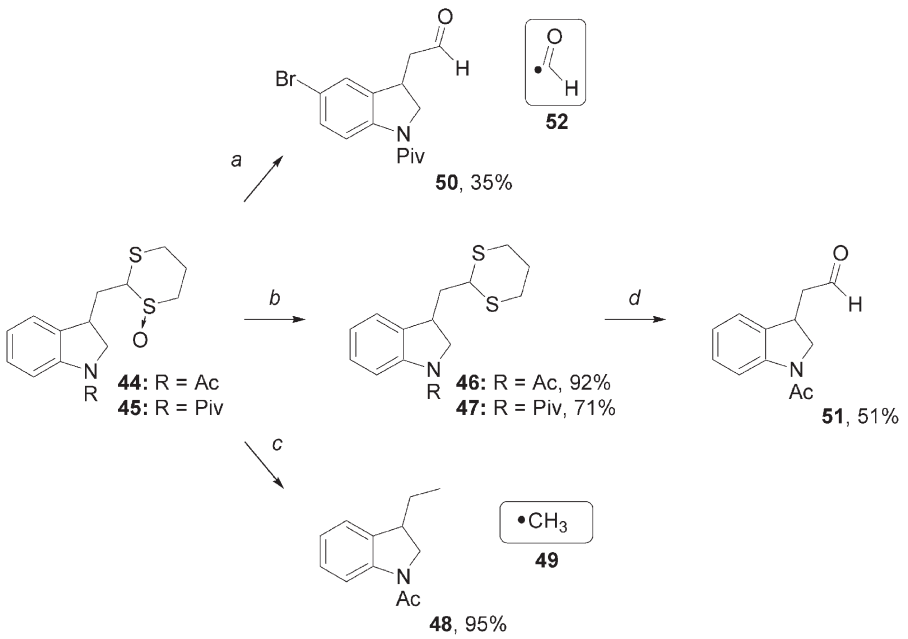
One of the major assets of the xanthate transfer reaction is that its reaction products still contain the xanthate. At this stage it may either serve to allow access to other functional groups or be used in a second radical transformation.[23–25] In order to exemplify the latter, we exposed adducts **29** and **31** to stoichiometric amounts of DLP in refluxing 1,2-dichloroethane (Scheme 6). In both cases, the reaction proceeded as expected and cyclisation onto the aromatic ring provided indolines **44** and **45** in 69 and 77% yield, respectively. As was the case for radical adducts **21**–**31**, both reaction products were obtained as complicated mixtures of diastereomers and had to be reduced as discussed previously in order to be fully characterised (Scheme 7).



Scheme 6. Reagents and conditions: (a) DLP (1.1–1.3 equiv.), 1,2-dichloroethane, reflux; (b) trifluoroacetic anhydride (2.4–2.6 equiv.), NaI (2.4 equiv.), dry acetone, 0 °C→rt.

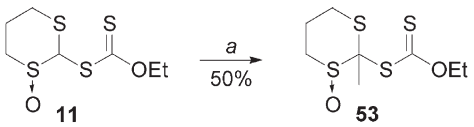
In order to validate our approach (Scheme 1), we next turned our attention to exploring some of the chemistry of the 1,3-dithiane 1-oxide moiety. For example, clean and efficient desulphurisation was achieved by treating **44** with excess Raney nickel in refluxing ethanol (Scheme 7). Inspection of the way **48** has been obtained reveals that the overall sequence is equivalent to the addition of a methyl radical **49** to **18**. Methyl radicals are reactive intermediates and it is worth noting that their generation and clean capture by unactivated olefins is not generally feasible. As is the case for 1,3-dithianes, 1,3-dithiane 1-oxides represent masked carbonyl compounds and are expected to undergo deprotection upon hydrolysis. Inspection of the literature reveals that 1,3-dithiane 1-oxides are most commonly hydrolysed by treatment with aqueous solutions of NBS.[26] Indeed, hydrolysis was achieved by treating **45** with excess NBS (8 equiv.) in aqueous acetone, but in modest yield and not without brominating the aromatic ring (Scheme 7). Attempts to achieve better selectivity by using less NBS and performing the reaction at lower temperature were only moderately successful. The best results were obtained by using 4 equiv. of NBS and carrying out the reaction at −20 °C. In this case, **50** was obtained in 15% yield along with an equimolar amount of its non-brominated derivative. When other reagents such as aqueous solutions of methyl iodide, Dess–Martin periodinane,[27] trifluoroacetic anhydride,[28] or bis(trifluoroacetoxy)iodobenzene[29] were used, no hydrolysis at all was observed. Clean hydrolysis was finally achieved by way of a two-step procedure. Thus, reduction of **44** followed by alkylative hydrolysis of the intermediate 1,3-dithiane **46**, gave the expected reaction product **51** in 47% overall yield (Scheme 7). These results led us to conclude that **11** is a valid synthetic equivalent of the formyl radical **52**.

In order to further extend the synthetic scope of **11**, we decided to attempt the alkylation of the 1,3-dithiane 1-oxide moiety present in indoline **45**. When followed by successful hydrolysis to give the corresponding ketone (similar to Scheme 1, path C), **11** provides a useful synthetic equivalent of acyl radicals. Furthermore, when followed by successful desulphurisation, **11** provides a synthetic equivalent of primary alkyl radicals (similar to Scheme 1, path D). Compared to the case of 1,3-dithianes, literature examples of successful alkylation of 1,3-dithiane 1-oxides are relatively scarce.[30–35] According to Carey et al. metalation of 2-substituted 1,3-dithiane 1-oxides is best carried out with lithium diisopropylamide (LDA).[32] However, when **45** was exposed to an equimolar amount of LDA, followed by excess methyl iodide, no alkylation was observed and most of the starting material was recovered unreacted. Inversion of the order of events, involving alkylation of **11** instead of **45**, seemed to be more promising. Thus, treatment of **11** with an equimolar amount of LDA and excess methyl iodide afforded the expected reaction product **53** as a 1:5 mixture



Scheme 7. Reagents and conditions: (a) NBS (8.3 equiv.), aqueous acetone, 0 °C; (b) trifluoroacetic anhydride (2.4–2.6 equiv.), NaI (2.4 equiv.), dry acetone, 0 °C→rt; (c) W2 Ra-Ni (excess), abs. EtOH, reflux; (d) MeI (50 equiv.), CH_2Cl_2, aqueous acetone, 45 °C.

of separable diastereomers in 50% yield (unoptimised) (Scheme 8). Unfortunately, **53** did not behave as expected when heated with 2 equiv. of **18** in refluxing 1,2-dichloroethane in the presence of DLP. Although some reaction took place, no radical adduct could be detected in the crude reaction product and a small amount of **53** was still present, despite the fact that 1.0 equiv. of DLP had been added at the end of the reaction. The reason for this failure is not clear, although it may be anticipated that the presence of the electron-releasing methyl group partially cancels the effect that the electron-withdrawing sulfoxide has on the reactivity of the corresponding radical.



Scheme 8. Reagents and conditions: (a) LDA (1.1 equiv.), MeI (2.4 equiv.), dry THF, −78 °C→rt.

3. Conclusion

In contrast with its anionic and cationic counterparts, the C-2 centred radical derived from 1,3-dithiane has revealed itself as being of rather limited synthetic scope. The corresponding monosulfoxide on the other hand has proved more useful. It is a suitable substrate for the xanthate transfer reaction and as such adds to a wide range of unactivated alkenes under mild, neutral conditions that are compatible with most functional groups encountered in modern organic synthesis. Furthermore, subsequent transformations of some of the radical adducts confirmed its utility as a synthetic equivalent of both the methyl and the formyl radical. Finally, we believe that the results presented in this paper justify the statement that our xanthate-based methodology allows considerable broadening of the synthetic scope of 1,3-dithiane chemistry and nicely complements the well-established ionic chemistry of this class of compounds.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources and used as supplied or purified using standard methods. Silica gel 60 Å C.C. 40-63 (SDS) was used for flash chromatography. TLC analysis was done on silica gel 60 F_{254} TLC plates (Merck). Petroleum ether refers to the fractions with bp 40–60 °C. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument. ^1H and ^{13}C chemical shifts are given with respect to the solvent as internal standard. IR spectra were measured on a Perkin–Elmer FT 1600 as solutions in CCl_4. Low resolution mass spectra were recorded at a HP 5989B mass spectrometer. Microanalyses were carried out by the microanalytical laboratory of the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

4.1.1. Dithiocarbonic acid *S*-[1,3]dithian-2-yl ester *O*-ethyl ester (1). A solution of 1,3-dithiane **4** (12.1 g, 100 mmol) in dry $CHCl_3$ (250 mL) was cooled to −40 °C under a nitrogen atmosphere, before dropwise addition of a solution of freshly distilled sulfuryl chloride (8.4 mL, 105 mmol) in dry $CHCl_3$ (50 mL). The yellow suspension thus obtained was allowed to warm to room temperature. The initially formed precipitate went into solution and the resulting orange solution was slowly transferred to a cooled (−10 °C) solution of dithiocarbonic acid *O*-ethyl ester potassium salt (17.6 g, 110 mmol) in acetone (250 mL). The yellow suspension thus obtained was stirred at −10 °C for another 60 min before being warmed to room temperature. The precipitate was removed by filtration and the resulting yellow solution was concentrated under reduced pressure

before addition of Et_2O (250 mL). The organic phase was extracted with water (2×150 mL), washed with brine (1×100 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded **1** (23.9 g, 100%) as a yellow oil which was sufficiently pure to be used directly in the next step. Analytical samples and samples appropriate for radical reactions were obtained by recrystallisation (petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 2.01–2.12 (m, 1H), 2.15–2.22 (m, 1H), 2.73–2.79 (m, 2H), 3.23 (ddd, J=2.8, 11.8, 14.2 Hz, 2H), 4.67 (q, J=7.2 Hz, 2H), 5.65 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.66 (CH_3), 25.01 (CH_2), 26.72 (2×CH_2), 49.84 (CH), 70.12 (CH_2), 211.07 (C=S) ppm. IR (CCl_4): 2985, 2955, 2939, 2904, 1442, 1432, 1424, 1414, 1388, 1363, 1292, 1280, 1229, 1148, 1111, 1045 cm^{-1}. MS (CI/NH_3): 119 (M−$C_3H_5OS_2$), 241 (MH^+), 258 (MNH_4^+). Anal. calcd C, 34.97; H, 5.03; found C, 35.48; H, 5.16.

4.1.2. Dithiocarbonic acid *S*-(4-[1,3]dithian-2-yl-1-methyl-2,5-dioxo-pyrrolidin-3-yl) ester *O*-ethyl ester (10). A solution of **1** (158 mg, 0.657 mmol) and **9** (148 mg, 1.33 mmol) in 1,2-dichloro-ethane (1.0 mL) was refluxed for 30 min DLP (0.05 equiv.) was then added and additional DLP (0.025 equiv.) was added every 90 min until complete consumption of **1**. After addition of 0.25 equiv. of DLP the mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (Et_2O–petroleum ether, 30:70 to 50:50 v/v) to afford **10** (104 mg, 52%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (t, J=7.2 Hz, 3H), 1.77–1.88 (m, 1H), 2.10–2.17 (m, 1H), 2.87–2.91 (m, 2H), 2.99 (ddd, J=2.4, 12.4, 14.4 Hz, 2H), 3.09 (s, 3H), 3.58 (dd, J=3.6, 5.6 Hz, 1H), 4.32 (d, J=5.6 Hz, 1H), 4.57 (q, J=7.2 Hz, 2H), 4.84 (d, J=3.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.48 (CH_3), 24.66 (CH_2), 25.57 (CH_3), 30.01 (CH_2), 30.95 (CH_2), 46.64 (CH), 47.04 (CH), 51.77 (CH), 172.37 (C=O), 173.52 (C=O), 209.12 (C=S) ppm. IR (CCl_4): 2940, 2903, 1790, 1719, 1432, 1379, 1288, 1240, 1222, 1198, 1176, 1118, 1113, 1054 cm^{-1}. MS (CI/NH_3): 352 (MH^+), 369 (MNH_4^+). Anal. calcd C, 41.00; H, 4.87; found C, 41.49; H, 5.01.

4.1.3. Dithiocarbonic acid *O*-ethyl ester *S*-(1-oxo-1λ^4-[1,3]dithian-2-yl) ester (11). A solution of **1** (23.9 g, 100 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C under a nitrogen atmosphere, before dropwise addition of a solution of *m*CPBA (24.9 g, 106 mmol) in CH_2Cl_2 (225 mL). The white suspension thus obtained was stirred at 0 °C for another 60 min before being warmed to room temperature. The mixture was then extracted with a saturated solution of $NaHCO_3$ (3×200 mL), washed with brine (1×150 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded crude **11** (24.8 g, 97%) as an orange oil. Purification was carried out in two steps. Flash chromatography on silica gel (Et_2O–petroleum ether, 25:75 v/v to Et_2O–EtOAc, 25:75 v/v) yielded nearly pure reaction product, which was further purified by recrystallisation (EtOAc–petroleum ether, 9:10 v/v) to afford **11** (18.4 g, 71%) as a solid 10:11 mixture (NMR analysis) of separable diastereomers. Analytical samples of both isomers were obtained by flash chromatography on silica gel (Et_2O–EtOAc, 60:40 v/v).

Less polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 2.24–2.35 (m, 1H), 2.38–2.45 (m, 1H), 2.51 (dt, J=3.6, 14.4 Hz, 1H), 2.74 (ddd, J=2.8, 12.0, 14.4 Hz, 1H), 2.84 (dt, J=3.2, 12.8 Hz, 1H), 3.08–3.13 (m, 1H), 4.70 (dq, J=1.2, 7.2 Hz, 2H), 6.13 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.76 (CH_3), 25.62 (CH_2), 27.99 (CH_2), 48.74 (CH_2), 66.22 (CH), 71.60 (CH_2), 208.78 (C=S) ppm. IR (CCl_4): 2985, 2957, 2939, 2911, 2866, 2844, 1462, 1436, 1425, 1415, 1388, 1365, 1292, 1243, 1181, 1150, 1111, 1089, 1073, 1043 cm^{-1}. MS (CI/NH_3): 257 (MH^+), 274 (MNH_4^+).

More polar isomer (*minor*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 1.79–1.86 (m, 1H), 2.52–2.57 (m, 1H), 2.60–2.71 (m, 1H), 2.88 (ddd, J=2.4, 11.6, 14.0 Hz, 1H), 2.90–2.95 (m, 1H), 3.04 (ddd, J=2.8, 12.0, 14.8 Hz, 1H), 4.68 (q, J=7.2 Hz, 2H), 5.54 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.75 (CH_3), 15.65 (CH_2), 25.98 (CH_2), 43.35 (CH_2), 63.04 (CH), 71.60, 207.62 (C=S) ppm. IR (CCl_4): 2985, 2958, 2940, 2910, 2870, 1471, 1460, 1442, 1425, 1406, 1388, 1365, 1293, 1241, 1150, 1110, 1077, 1040 cm^{-1}. MS (CI/NH_3): 257 (MH^+), 274 (MNH_4^+).

4.2. Radical addition of (11). General procedure

A solution of **11** (1.0 equiv.) and olefin (1.2–3.0 equiv.) in 1,2-dichloro–ethane (1.0 mL/mmol of **11**) was refluxed for 15 min DLP (0.1 equiv.) was then added and additional DLP (0.1 equiv.) was added every 90 min until complete consumption of **11**. The mixture was then cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the reaction products as complicated mixtures of diastereomers that were used as such in the next reaction step.

4.2.1. Acetic acid 2-ethoxythiocarbonylsulfanyl-3-(1-oxo-1λ^4-[1,3]dithian-2-yl)-propyl ester (21). The reaction was carried out with a solution of **11** (125 mg, 0.49 mmol) and **6** (0.16 mL, 1.5 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O, then MeOH–EtOAc, 5:95 v/v) afforded **21** (121 mg, 70%).

4.2.2. Dithiocarbonic acid *O*-ethyl ester *S*-[2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-1-trimethylsilanylmethyl-ethyl] ester (22). The reaction was carried out with a solution of **11** (262 mg, 1.0 mmol) and **7** (0.48 mL, 3.0 mmol) and needed 0.30 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 80:20 to 40:60 v/v) afforded **22** (282 mg, 75%).

4.2.3. Dithiocarbonic acid *S*-[1-cyclopentyl-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (23). The reaction was carried out with a solution of **11** (257 mg, 1.0 mmol) and **12** (288, 3.0 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then

Et_2O–EtOAc, 60:40 to 0:100 v/v, then MeOH–EtOAc, 5:95 v/v) afforded **23** (150 mg, 56%).

4.2.4. Dithiocarbonic acid *O*-ethyl ester *S*-[1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-heptyl] ester (24). The reaction was carried out with a solution of **11** (254 mg, 0.99 mmol) and **13** (0.47 mL, 3.0 mmol) and needed 0.35 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 80:20 to 40:60 v/v) afforded **24** (252 mg, 69%).

4.2.5. Dithiocarbonic acid *S*-[2-cyano-1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-ethyl] ester *O*-ethyl ester (25). The reaction was carried out with a solution of **11** (255 mg, 1.0 mmol) and **14** (0.24 mL, 3.0 mmol) and needed 0.85 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O, then MeOH–EtOAc, 0:100 to 10:90 v/v) afforded **25** (105 mg, 32%).

4.2.6. Dithiocarbonic acid *S*-[1-(4-chloro-phenoxymethyl)-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (26). The reaction was carried out with a solution of **11** (254 mg, 0.99 mmol) and **15** (338 mg, 2.0 mmol) and needed 0.50 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 85:15 to 20:80 v/v) afforded **26** (291 mg, 69%).

4.2.7. Dithiocarbonic acid *O*-ethyl ester *S*-[4-oxo-1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-pentyl] ester (27). The reaction was carried out with a solution of **11** (256 mg, 1.0 mmol) and **16** (0.35 mL, 3.0 mmol) and needed 0.80 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 3:97 to 10:90 v/v) afforded **27** (119 mg, 34%).

4.2.8. Dithiocarbonic acid *O*-ethyl ester *S*-[1-(6-methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester (28). The reaction was carried out with a solution of **11** (259 mg, 1.0 mmol) and **17** (398, 2.0 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 0:100 to 5:95 v/v) afforded **28** (300 mg, 66%).

4.2.9. Dithiocarbonic acid *S*-[1-[(acetyl-phenyl-amino)-methyl]-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (29). The reaction was carried out with a solution of **11** (437 mg, 1.71 mmol) and **18** (600 mg, 3.43 mmol) and needed 0.55 equiv. of DLP to go to completion. Flash chromatography on silica gel (MeOH–EtOAc, 0:100 to 10:90 v/v) afforded **29** (557 mg, 75%).

4.2.10. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-[2-ethoxythiocarbonylsulfanyl-3-(1-oxo-1λ^4-[1,3]dithian-2-yl)-propyl]-tetrahydro-pyran-4-yl ester (30). The reaction was carried out with a solution of **11** (59 mg, 0.23 mmol) and **19** (104, 0.28 mmol) and needed 0.75 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 4:96 v/v) afforded **30** (55 mg, 39%).

4.2.11. Dithiocarbonic acid *S*-[1-{[(2,2-dimethyl-propionyl)-phenyl-amino]-methyl}-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (31). The reaction was carried out with a solution of **11** (256 mg, 1.0 mmol) and **20** (439, 2.0 mmol) and needed 0.65 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 0:100 to 5:95 v/v) afforded **31** (288 mg, 61%).

4.3. Reduction of radical adducts (21)–(31). General procedure

A solution of sulfoxide (1.0 equiv.) and NaI (2.4 equiv.) in dry acetone (5.2 mL/mmol of sulfoxide) was cooled to 0 °C before dropwise addition of a solution of TFAA (2.4–2.6 equiv.) in dry acetone (2.0 mL/mmol TFAA). The red brown solution thus obtained was allowed to warm to room temperature and diluted with Et_2O. The mixture was extracted twice with a saturated solution of $Na_2S_2O_3$, washed once with water, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified as specified below.

4.3.1. Acetic acid 3-[1,3]dithian-2-yl-2-ethoxythiocarbonylsulfanyl-propyl ester (32). The reaction was carried out with **21** (99 mg, 0.28 mmol), TFAA (0.10 mL, 0.73 mmol), and NaI (102 mg, 0.67 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 15:185 to 10:90 v/v) afforded **32** (60 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (t, J=7.2 Hz, 3H), 1.85–1.95 (m, 1H), 2.05–2.25 (m, 3H), 2.09 (s, 3H), 2.85–2.90 (m, 4H), 4.17 (dd, J=6.0, 9.2 Hz, 1H), 4.22–4.28 (m, 2H), 4.34–4.39 (m, 1H), 4.66 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.67 (CH_3), 20.74 (CH_3), 25.66 (CH_2), 29.67 (CH_2), 29.91 (CH_2), 35.77 (CH_2), 43.92 (CH), 46.00 (CH), 65.07 (CH_2), 70.25 (CH_2), 170.56 (C=O), 211.98 (C=S) ppm. IR (CCl_4): 2984, 2939, 2902, 1749, 1462, 1441, 1423, 1380, 1362, 1227, 1112, 1051 cm^{-1}. MS (CI/NH_3): 341 (MH^+), 358 (MNH_4^+).

4.3.2. Dithiocarbonic acid *S*-(2-[1,3]dithian-2-yl-1-trimethylsilanylmethyl-ethyl) ester *O*-ethyl ester (33). The reaction was carried out with **22** (111 mg, 0.30 mmol), TFAA (0.11 mL, 0.78 mmol), and NaI (109 mg, 0.72 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 2:98 v/v) afforded **33** (93 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=0.10 (s, 9H), 1.07 (dd, J=8.4, 14.8 Hz, 1H), 1.18 (dd, J=6.8, 14.8 Hz, 1H), 1.44 (t, J=7.2 Hz, 3H), 1.84–1.94 (m, 1H), 2.03 (ddd, J=5.6, 8.4, 14.4 Hz, 1H), 2.09–2.16 (m, 2H), 2.81–2.92 (m, 4H), 4.04–4.11 (m, 1H), 4.15 (dd, J=5.6, 8.4 Hz, 1H), 4.61–4.69 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.69 (3×CH_3), 13.77 (CH_3), 23.29 (CH_2), 25.76 (CH_2), 29.94 (CH_2), 30.08 (CH_2), 41.99 (CH_2), 44.63 (CH), 45.42 (CH), 69.62 (CH_2), 213.51 (C=S) ppm. IR (CCl_4): 2956, 2900, 1423, 1276, 1250, 1216, 1111, 1051 cm^{-1}. MS (CI/NH_3): 233 ($MH^+-C_3H_6OS_2$), 355 (MH^+). Anal. calcd C, 44.02; H, 7.39; found C, 44.13; H, 7.35.

4.3.3. Dithiocarbonic acid *S*-(1-cyclopentyl-2-[1,3]dithian-2-yl-ethyl) ester *O*-ethyl ester (34). The

reaction was carried out with **23** (72 mg, 0.20 mmol), TFAA (74 μL, 0.52 mmol), and NaI (72 mg, 0.48 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 2:98 v/v) afforded **34** (45 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22–1.39 (m, 2H), 1.43 (t, J=7.2 Hz, 3H), 1.47–1.68 (m, 4H), 1.75–1.92 (m, 3H), 2.01–2.15 (m, 3H), 2.19–2.29 (m, 1H), 2.82–2.92 (m, 4H), 4.09–4.14 (m, 1H), 4.17 (dd, J=5.6, 8.8 Hz, 1H), 4.64 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73 (CH_3), 25.23 (CH_2), 25.48 (CH_2), 25.78 (CH_2), 29.57 (CH_2), 29.78 (CH_2), 30.05 (CH_2), 30.29 (CH_2), 39.18 (CH_2), 43.78 (CH), 44.43 (CH), 52.55(CH), 69.90 (CH_2), 213.99 (C=S) ppm. IR (CCl_4): 2955, 2903, 2869, 1433, 1424, 1387, 1362, 1292, 1276, 1216, 1145, 1112, 1051 cm^{-1}. MS (CI/NH_3): 337 (MH^+). Anal. calcd C, 49.96; H, 7.19; found C, 49.64; H, 7.16.

4.3.4. Dithiocarbonic acid *S*-(1-[1,3]dithian-2-ylmethyl-heptyl) ester *O*-ethyl ester (35). The reaction was carried out with **24** (89 mg, 0.24 mmol), TFAA (90 μL, 0.63 mmol), and NaI (87 mg, 0.58 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 3:197 v/v) afforded **35** (58 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.4 Hz, 3H), 1.22–1.51 (m, 8H), 1.44 (t, J=7.2 Hz, 3H), 1.65–1.76 (m, 2H), 1.85–1.95 (m, 1H), 2.04–2.16 (m, 3H), 2.82–2.92 (m, 4H), 3.95–4.02 (m, 1H), 4.16 (t, J=7.6 Hz, 1H), 4.66 (dq, J=2.0, 7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74 (CH_3), 14.00 (CH_3), 22.48 (CH_2), 25.77 (CH_2), 26.50 (CH_2), 28.93 (CH_2), 29.86 (CH_2), 29.99 (CH_2), 31.56 (CH_2), 34.07 (CH_2), 39.29 (CH_2), 44.42 (CH), 47.82 (CH), 69.76 (CH_2), 213.59 (C=S) ppm. IR (CCl_4): 2957, 2929, 2857, 2359, 1458, 1424, 1379, 1276, 1218, 1145, 1112, 1052 cm^{-1}. MS (CI/NH_3): 353 (MH^+), 370 (MNH_4^+). Anal. calcd C, 51.09; H, 8.00; found C, 50.92; H, 8.05.

4.3.5. Dithiocarbonic acid *S*-(2-cyano-1-[1,3]dithian-2-ylmethyl-ethyl) ester *O*-ethyl ester (36). The reaction was carried out with **25** (100 mg, 0.31 mmol), TFAA (0.11 mL, 0.81 mmol), and NaI (112 mg, 0.74 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 to 20:80 v/v) afforded **36** (85 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (t, J=7.2 Hz, 3H), 1.88–1.98 (m, 1H), 2.09–2.16 (m, 1H), 2.28 (ddd, J=2.8, 6.8, 8.8 Hz, 2H), 2.81–3.04 (m, 6H), 4.14 (dd, J=6.4, 8.4 Hz, 1H), 4.16–4.23 (m, 1H), 4.67 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.69 (CH_3), 23.63 (CH_2), 25.52 (CH_2), 29.28 (CH_2), 29.56 (CH_2), 37.18 (CH_2), 43.33 (CH), 43.44 (CH), 70.58 (CH_2), 116.76 (CN), 211.29 (C=S) ppm. IR (CCl_4): 2984, 2938, 2903, 2250, 1423, 1363, 1292, 1276, 1231, 1148, 1112, 1052 cm^{-1}. MS (CI/NH_3): 308 (MH^+), 325 (MNH_4^+). Anal. calcd C, 42.96; H, 5.57; found C, 42.82; H, 5.57.

4.3.6. Dithiocarbonic acid *S*-[1-(4-chloro-phenoxymethyl)-2-[1,3]dithian-2-yl-ethyl] ester *O*-ethyl ester (37). The reaction was carried out with **26** (128 mg, 0.30 mmol), TFAA (0.11 mL, 0.78 mmol), and NaI (110 mg, 0.73 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 2:98 v/v) afforded **37** (95 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (t, J=7.2 Hz, 3H), 1.87–1.96 (m, 1H), 2.10–2.15 (m, 1H), 2.20 (ddd, J=6.0, 9.2, 14.8 Hz, 1H), 2.44 (ddd, J=5.6, 9.2, 14.8 Hz, 1H), 2.81–2.89 (m, 4H), 4.09 (dd, J=6.4, 10.0 Hz, 1H), 4.18 (dd, J=5.6, 8.8 Hz, 1H), 4.27 (dd, J=3.6, 9.6 Hz, 1H), 4.36–4.43 (m, 1H), 4.66 (q, J=7.2 Hz), 6.86 (d, J=9.2 Hz, 2H), 7.24 (d, J=9.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73 (CH_3), 25.69 (CH_2), 29.52 (CH_2), 29.79 (CH_2), 35.68 (CH_2), 43.98 (CH), 46.70 (CH), 69.31 (CH_2), 70.27 (CH_2), 115.91 (CH), 126.02 (C), 129.26 (CH), 156.84 (C), 212.62 (C=S) ppm. IR (CCl_4): 2978, 2935, 2901, 2867, 1597, 1583, 1492, 1464, 1424, 1381, 1276, 1240, 1170, 1148, 1112, 1094, 1052 cm^{-1}. MS (CI/NH_3): 406 (M^+-H_2, $C_{16}H_{21}^{35}ClO_3S_4$), 408 ($M^+-H_2$, $C_{16}H_{21}^{37}ClO_3S_4$), 409 ($MH^+$, $C_{16}H_{21}^{35}ClO_3S_4$), 411 ($MH^+$, $C_{16}H_{21}^{37}ClO_3S_4$), 426 ($MNH_4^+$, $C_{16}H_{21}^{35}ClO_3S_4$), 428 ($MNH_4^+$, $C_{16}H_{21}^{37}ClO_3S_4$). Anal. calcd C, 46.98; H, 5.17; found C, 46.61; H, 5.21.

4.3.7. Dithiocarbonic acid *S*-(1-[1,3]dithian-2-ylmethyl-4-oxo-pentyl) ester *O*-ethyl ester (38). The reaction was carried out with **27** (119 mg, 0.34 mmol), TFAA (0.12 mL, 0.87 mmol), and NaI (121 mg, 0.81 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 15:85 v/v) afforded **38** (76 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 1.82–1.93 (m, 2H), 2.00–2.19 (m, 4H), 2.17 (s, 3H), 2.64 (t, J=8.0 Hz, 2H), 2.84–2.92 (m, 4H), 3.95–4.02 (m, 1H), 4.16 (t, J=7.6 Hz, 1H), 4.65 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.70 (CH_3), 25.68 (CH_2), 27.57 (CH_2), 29.81 (CH_2), 29.89 (CH_2), 30.00 (CH_3), 39.77 (CH_2), 40.57 (CH_2), 44.18 (CH), 47.36 (CH), 70.08 (CH_2), 208.34 (C=O), 212.96 (C=S) ppm. IR (CCl_4): 2984, 2937, 2902, 1721, 1442, 1423, 1367, 1276, 1217, 1162, 1112, 1050 cm^{-1}. MS (CI/NH_3): 339 (MH^+), 356 (MNH_4^+). Anal. calcd C, 46.12; H, 6.55; found C, 46.36; H, 6.55.

4.3.8. Dithiocarbonic acid *S*-[2-[1,3]dithian-2-yl-1-(6-methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*]-[1,3]dioxol-5-yl)-ethyl] ester *O*-ethyl ester (39). The reaction was carried out with **28** (135 mg, 0.30 mmol), TFAA (0.11 mL, 0.77 mmol), and NaI (113 mg, 0.75 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 13:87 to 20:80 v/v) afforded **39** (88 mg, 67%) as a 8:5 mixture (NMR analysis) of separable diastereoisomers.

Less polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 3H), 1.44 (t, J=7.2 Hz, 3H), 1.48 (s, 3H), 1.86–1.96 (m, 1H), 2.04–2.12 (m, 1H), 2.25 (ddd, J=4.8, 9.6, 14.8 Hz, 1H), 2.53 (ddd, J=4.0, 10.0, 14.4 Hz), 2.72–2.92 (m, 4H), 3.38 (s, 3H), 3.79 (d, J=3.2 Hz, 1H), 4.15–4.21 9M, 2H), 4.44 (dd, J=3.2, 8.8 Hz, 1H), 4.54 (d, J=3.6 Hz, 1H), 4.62–4.70 (m, 2H), 5.91 (d, J=3.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74 (CH_3), 25.76 (CH_2), 26.15 (CH_3), 26.74 (CH_3), 28.78 (CH_2), 29.20 (CH_2), 36.98 (CH_2), 43.80 (CH), 45.96 (CH), 57.75 (CH_3), 70.05 (CH_2), 81.02 (2×CH), 84.26 (CH), 105.15 (CH), 111.59 (C), 212.43 (C=S) ppm. IR (CCl_4): 2989, 2934, 2901, 2830,

1454, 1443, 1423, 1382, 1373, 1293, 1275, 1220, 1164, 1113, 1082, 1052, 1021 cm^{-1}. MS (CI/NH_3): 441 (MH^+).

More polar isomer (*minor*). ^1H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 3H), 1.43 (t, J=7.2 Hz, 3H), 1.48 (s, 3H), 1.84–1.93 (m, 1H), 2.05–2.13 (m, 2H), 2.30–2.37 (m, 1H), 2.75–2.92 (m, 4H), 3.41 (s, 3H), 3.79 (d, J=3.2 Hz), 4.18 (dd, J=4.0, 10.0 Hz, 1H), 4.40–4.51 (m, 2H), 4.57 (d, J=3.6 Hz, 1H), 4.66 (q, J=7.2 Hz, 2H), 5.92 (d, J=3.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.72 (CH_3), 25.77 (CH_2), 26.23 (CH_3), 26.80 (CH_3), 29.30 (CH_2), 29.89 (CH_2), 34.90 (CH_2), 44.24 (CH), 46.39 (CH), 57.56 (CH_3), 70.02 (CH_2), 79.81 (CH), 81.06 (CH), 84.69 (CH), 104.97 (CH), 111.61 (C), 212.77 (C=S) ppm. IR (CCl_4): 2990, 2933, 2830, 2359, 1454, 1423, 1382, 1373, 1294, 1276, 1220, 1165, 1110, 1081, 1053 cm^{-1}. MS (CI/NH_3): 441 (MH^+).

4.3.9. Dithiocarbonic acid *S*-{1-[(acetyl-phenyl-amino)-methyl]-2-[1,3]dithian-2-yl-ethyl} ester *O*-ethyl ester (40). The reaction was carried out with **29** (272 mg, 0.63 mmol), TFAA (0.21 mL, 1.5 mmol), and NaI (227 mg, 1.5 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 25:75 v/v) afforded **40** (203 mg, 77%).

^1H NMR (400 MHz, $CDCl_3$): δ=1.21 (t, J=7.2 Hz, 3H), 1.81–1.90 (m, 4H), 1.99–2.13 (m, 2H), 2.23 (ddd, J=4.0, 10.8, 14.8 Hz, 1H), 2.78–2.91 (m, 4H), 3.61 (dd, J=5.6, 13.6 Hz, 1H), 3.92–4.00 (m, 1H), 4.19 (dd, J=4.0, 10.8 Hz, 1H), 4.40–4.49 (m, 3H), 7.23–7.25 (m, 2H), 7.35–7.38 (m, 1H), 7.42–7.45 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.41 (CH_3), 22.64 (CH_3), 25.75 (CH_2), 29.92 (CH_2), 30.28 (CH_2), 35.94 (CH_2), 44.50 (CH), 45.47 (CH), 51.02 (CH_2), 69.84 (CH_2), 128. 17 (CH), 128.30 (CH), 129.69 (CH), 142.01 (C), 170.89 (C=O), 212.12 (C=S) ppm. IR (CCl_4): 3066, 3038, 2984, 2937, 2902, 1668, 1596, 1496, 1472, 1452, 1433, 1424, 1414, 1389, 1364, 1288, 1276, 1219, 1112, 1052 cm^{-1}. MS (CI/NH_3): 416 (MH^+), 433 (MNH_4^+).

4.3.10. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-(3-[1,3]dithian-2-yl-2-ethoxythiocarbonylsulfanyl-propyl)-tetrahydro-pyran-4-yl ester (41). The reaction was carried out with **30** (55 mg, 0.088 mmol), TFAA (33 μL, 0.23 mmol), and NaI (33 mg, 0.22 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 30:70 v/v) afforded **41** (32 mg, 60%) as a liquid 10:13 mixture (NMR analysis) of inseparable diastereoisomers.

IR (CCl_4): 2953, 2902, 1756, 1432, 1367, 1276, 1220, 1146, 1112, 1051 cm^{-1}. MS (CI/NH_3): 613 (MH^+), 630 (MNH_4^+).

4.3.11. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-(3-[1,3]dithian-2-yl-propyl)-tetrahydro-pyran-4-yl ester (42). A solution of **41** (31 mg, 0.051 mmol) and tris(trimethylsilyl) silane (31 μL, 0.10 mmol) in heptane (1 mL) was refluxed for 15 min before addition of a few crystals of AIBN. The solution was kept at reflux temperature and stirred for another 2 h before it was cooled to room temperature. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 27:73 v/v) to afford **42** (14 mg, 56%) as a slightly yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ=1.45–1.54 (m, 2H), 1.66–1.91 (m, 5H), 2.03 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.10–2.17 (m, 1H), 2.11 (s, 3H), 2.80–2.93 (m, 4H), 3.82 (ddd, J=2.4, 5.2, 9.2 Hz, 1H), 4.04–4.11 (m, 2H), 4.16 (ddd, J=3.6, 5.6, 11.2 Hz, 1H), 4.23 (d, J=5.2, 12.0 Hz, 1H), 4.97 (t, J=9.2 Hz, 1H), 5.07 (d, J=5.6, 9.2 Hz, 1H), 5.31 (t, J=9.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 20.76 (CH_3), 20.81 (CH_3), 20.84 (CH_3), 20.90 (CH_3), 22.19 (CH_2), 25.02 (CH_2), 26.00 (CH_2), 30.48 (2×CH_2), 35.00 (CH_2), 47.27 (CH), 62.37 (CH_2), 68.76 (CH), 68.86 (CH), 70.43 (CH), 70.48 (CH), 72.47 (CH), 169.65 (C=O), 169.76 (C=O), 170.30 (C=O), 170.86 (C=O) ppm. IR (CCl_4): 2952, 2902, 2831, 1757, 1455, 1424, 1367, 1226, 1099, 1065, 1031 cm^{-1}. MS (CI/NH_3): 494 (MH^+), 511 (MNH_4^+).

4.4. Radical cyclisation of adducts (29) and (31). General procedure

A solution of cyclisation precursor in 1,2-dichloro-ethane (10 mL/mmol of cyclisation precursor) was refluxed for 15 min DLP (0.1 equiv.) was then added and additional DLP (0.1 equiv.) was added every 90 min until complete consumption of starting material. The mixture was then cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the reaction products as complicated mixtures of diastereomers that were used as such in the next reaction step.

4.4.1. 1-[3-(1-Oxo-1λ^4-[1,3]dithian-2-ylmethyl)-2,3-dihydro-indol-1-yl]-ethanone (44). The reaction was carried out with a solution of **29** (638 mg, 1.48 mmol) and needed 1.1 equiv. of DLP to go to completion. Flash chromatography on silica gel (MeOH–EtOAc, 0:100 to 25:75 v/v) afforded **44** (310 mg, 69%).

4.4.2. 2,2-Dimethyl-1-[3-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-2,3-dihydro-indol-1-yl]-propan-1-one (45). The reaction was carried out with a solution of **31** (3.1 g, 6.4 mmol) and needed 1.3 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 5:95 to 10:90 v/v) afforded **45** (1.7 g, 77%).

4.5. Reduction of cyclisation products (44)–(45). General procedure

A solution of sulfoxide (1.0 equiv.) and NaI (2.4 equiv.) in dry acetone (5.2 mL/mmol of sulfoxide) was cooled to 0 °C before dropwise addition of a solution of TFAA (2.4–2.6 equiv.) in dry acetone (2.0 mL/mmol TFAA). The red brown solution thus obtained was allowed to warm to room temperature and diluted with Et_2O. The mixture was extracted twice with a saturated solution of $Na_2S_2O_3$, washed once with water, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified as specified below.

4.5.1. 1-(3-[1,3]Dithian-2-ylmethyl-2,3-dihydro-indol-1-yl)-ethanone (46). The reaction was carried out with **44** (464 mg, 1.5 mmol), TFAA (0.51 mL, 3.6 mmol), and NaI

(540 mg, 3.6 mmol). Recrystallisation of the crude reaction product from acetone afforded **46** (404 mg, 92%).

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.82–2.04 (m, 2H), 2.14–2.26 (m, 2H), 2.24 (s, 3H), 2.84–2.98 (m, 4H), 3.70–3.78 (m, 2H), 4.14 (t, *J*=6.8 Hz, 1H), 4.23 (t, *J*=8.8 Hz, 1H), 7.04 (t, *J*=7.2 Hz, 1H), 7.19–7.24 (m, 2H), 8.20 (d, *J*=8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.17 (CH_3), 25.66 (CH_2), 30.29 (2×CH_2), 37.36 (CH), 41.02 (CH_2), 45.16 (CH), 55.15 (CH_2), 116.96 (CH), 123.61 (CH), 123.75 (CH), 128.13 (CH), 133.69 (C), 142.50 (C), 168.53 (C=O) ppm. IR (CCl_4): 2939, 2904, 2252, 1653, 1598, 1482, 1461, 1406, 1358, 1338, 1290, 1277, 1244, 1177, 1132, 1032 cm^{-1}. MS (CI/NH_3): 294 (MH^+), 311 (MNH_4^+). Anal. calcd C, 61.39; H, 6.53; found C, 59.91; H, 6.43.

4.5.2. 1-(3-[1,3]Dithian-2-ylmethyl-2,3-dihydro-indol-1-yl)-2,2-dimethyl-propan-1-one (47). The reaction was carried out with **45** (177 mg, 0.50 mmol), TFAA (0.18 mL, 1.3 mmol), and NaI (184 mg, 1.2 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 v/v) afforded **47** (120 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 9H), 1.85–2.01 (m, 2H), 2.13–2.21 (m, 2H), 2.83–2.99 (m, 4H), 3.59–3.66 (m, 1H), 4.00 (dd, *J*=5.2, 10.4 Hz, 1H), 4.13 (t, *J*=7.6 Hz, 1H), 4.37 (dd, *J*=8.4, 10.4 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H), 7.21–7.25 (m, 2H), 8.22 (d, *J*=7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.76 (CH_2), 27.76 (3×CH_3), 30.32 (CH_2), 30.47 (CH_2), 38.51 (CH), 40.12 (CH_2), 40.17 ($C(CH_3)_3$), 45.42 (CH), 55.91 (CH_2), 118.53 (CH), 123.68 (CH), 123.76 (CH), 128.07 (CH), 133.52 (C), 144.30 (C), 176.50 (C=O) ppm. IR (CCl_4): 2933, 2903, 1652, 1598, 1477, 1460, 1432, 1423, 1414, 1400, 1372, 1360, 1334, 1288, 1276, 1242, 1186, 1107, 1090, 1026 cm^{-1}. MS (CI/NH_3): 336 (MH^+), 353 (MNH_4^+).

4.5.3. 1-(3-Ethyl-2,3-dihydro-indol-1-yl)-ethanone (48). To a suspension of freshly prepared W2 Raney Nickel (400 mg of residual material/0.1 mmol of **44**) in absolute EtOH (5 mL) was added **44** (178 mg, 0.57 mmol). The resulting mixture was refluxed for 4 h, then cooled to room temperature and filtered over Celite. Evaporation of the solvent gave analytically pure **48** (104 mg, 95%) as a white solid.

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.99 (t, *J*=7.2 Hz, 3H), 1.54–1.65 (m, 1H), 1.81–1.91 (m, 1H), 2.24 (s, 3H), 3.31–3.39 (m, 1H), 3.69 (dd, *J*=6.0, 10.4 Hz, 1H), 4.16 (t, *J*=10.0 Hz, 1H), 7.04 (t, *J*=7.6 Hz, 1H), 7.17–7.23 (m, 2H), 8.21 (d, *J*=8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.07 (CH_3), 24.16 (CH_3), 28.02 (CH_2), 41.38 (CH), 54.60 (CH_2), 116.79 (CH), 123.44 (CH), 123.70 (CH), 127.67 (CH), 134.84 (C), 142.62 (C), 168.55 (C=O) ppm. IR (CCl_4): 2963, 2931, 2876, 1670, 1599, 1482, 1461, 1400, 1353, 1332, 1286, 1274, 1173, 1131, 1096, 1030 cm^{-1}. MS (CI/NH_3): 190 (MH^+), 207 (MNH_4^+). Anal. calcd C, 76.16; H, 7.99; found C, 76.16; H, 8.09.

4.5.4. [5-Bromo-1-(2,2-dimethyl-propionyl)-2,3-dihydro-1*H*-indol-3-yl]-acetaldehyde (50). A solution of NBS (362 mg, 2.0 mmol) in a 97:3 mixture of acetone and water (10 mL) was cooled to 0 °C before dropwise addition of a solution of **45** (86 mg, 0.24 mmol) in a 97:3 mixture of acetone and water (0.5 mL). After another 10 min of stirring at 0 °C the reaction was quenched by addition of a saturated solution of Na_2SO_3 (20 mL). The aqueous mixture thus obtained was extracted with CH_2Cl_2 (3×20 mL) and the collected organic layers were extracted with water (1×30 mL), washed with brine (1×30 mL) and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 20:80 v/v) to afford **50** (27 mg, 35%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 9H), 2.75 (dd, *J*=9.2, 19.2 Hz, 1H), 3.02 (dd, *J*=4.0, 18.4 Hz, 1H), 3.75–3.86 (m, 2H), 4.50 (dd, *J*=8.4, 10.4 Hz, 1H), 7.25 (dd, *J*=0.8, 2.0 Hz, 1H), 7.33 (ddd, *J*=0.4, 6.0, 8.4 Hz, 1H), 8.11 (d, *J*=8.8 Hz, 1H), 9.87 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.48 (3×CH_3), 34.91 (CH), 40.12 ($C(CH_3)_3$), 48.52 (CH_2), 55.45 (CH_2), 100.54 (C), 116.06 (C), 119.86 (CH), 126.30 (CH), 130.94 (CH), 135.05 (C), 176.93 (C=O), 199.70 (C(O)H) ppm. IR (CCl_4): 2972, 2931, 2820, 2720, 1727, 1656, 1592, 1474, 1400, 1371, 1350, 1329, 1242, 1204, 1177, 1108, 1065 cm^{-1}. MS (CI/NH_3): 323 (MH^+, $C_{15}H_{18}^{79}BrNO_2$), 325 (MH^+, $C_{15}H_{18}^{81}BrNO_2$), 340 (MNH_4^+, $C_{15}H_{18}^{79}BrNO_2$), 342 (MNH_4^+, $C_{15}H_{18}^{81}BrNO_2$).

4.5.5. (1-Acetyl-2,3-dihydro-1*H*-indol-3-yl)-acetaldehyde (51). To a solution of **46** (143 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) were added methyl iodide (1.6 mL, 25 mmol), acetone (4 mL), and water (0.15 mL) and the mixture was stirred at 45 °C for 26 h. The resulting orange solution was concentrated under reduced pressure before addition of EtOAc (20 mL). The organic phase was extracted with water (1×20 mL), then with a saturated solution of NaS_2O_3 (1×20 mL), washed with brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 v/v) to afford **51** (51 mg, 51%) as a slightly yellow solid.

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.22 (s, 3H), 2.80 (dd, *J*=9.6, 18.8 Hz, 1H), 3.10 (dd, *J*=4.4, 18.8 Hz, 1H), 3.61 (dd, *J*=6.0, 18.8 Hz, 1H), 3.86–3.93 (m, 1H), 4.38 (dd, *J*=9.2, 10.8 Hz, 1H), 7.05 (dt, *J*=0.8, 7.4 Hz, 1H), 7.15 (d, *J*=7.2 Hz, 1H), 7.24–7.26 (m, 1H), 8.22 (d, *J*=8.0 Hz, 1H), 9.89 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.07 (CH_3), 33.93 (CH), 49.69 (CH_2), 55.00 (CH_2), 116.85 (CH), 123.34 (CH), 123.61 (CH), 128.17 (CH), 132.87 (C), 142.40 (C), 168.54 (C=O), 200.14 (C(O)H) ppm. IR (CCl_4): 2889, 2819, 2720, 1727, 1672, 1600, 1483, 1462, 1399, 1354, 1331, 1282, 1133, 1029 cm^{-1}. MS (CI/NH_3): 204 (MH^+), 221 (MNH_4^+).

4.5.6. Dithiocarbonic acid *O*-ethyl ester *S*-(2-methyl-1-oxo-1λ^4-[1,3]dithian-2-yl) ester (53). A solution of freshly distilled diisopropyl amine (0.21 mL, 1.5 mmol) in dry THF (7mL) was cooled to −78 °C under a nitrogen atmosphere, before dropwise addition of a 1.5 M solution of *n*BuLi in hexanes (0.73 mL, 1.1 mmol). To the colourless solution thus obtained was added a solution of **11** (256 mg,

1.0 mmol) in dry THF (5 mL). After 30 min of stirring at −78 °C methyl iodide (0.15 mL, 2.4 mmol) was added and the yellow solution thus obtained was allowed to warm to room temperature. After 90 min of additional stirring at room temperature, ice-cold water (20 mL) was added and the aqueous mixture extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were washed with brine (1×40 mL) and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (Et_2O–EtOAc, 60:40 v/v) to afford **53** (135 mg, 50%) as a liquid 1:5 mixture (NMR analysis) of separable diastereomers.

Less polar isomer (*minor*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (t, J=7.2 Hz, 3H), 2.27 (s, 3H), 2.29–2.47 (m, 3H), 3.04–3.15 (m, 2H), 3.32 (dt, J=3.2, 13.2 Hz, 1H), 4.66–4.74 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.51 (CH_3), 25.46 (CH_3), 27.03 (CH_2), 29.44 (CH_2), 48.23 (CH_2), 70.61 (CH_2), 73.82 (C), 208.20 (C=S) ppm. IR (CCl_4): 2983, 2923, 1436, 1424, 1410, 1365, 1292, 1258, 1242, 1113, 1077, 1067, 1033 cm^{-1}. MS (CI/NH_3): 271 (MH^+).

More polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.47 (t, J=7.2 Hz, 3H), 1.71–1.78 (m, 1H), 2.03 (s, 3H), 2.38–2.45 (m, 1H), 2.47–2.55 (m, 1H), 2.97–3.02 (m, 1H), 3.18 (ddd, J=2.0, 12.4, 14.0 Hz, 1H), 3.34 (ddd, J=2.8, 13.2, 14.8 Hz, 1H), 4.59–4.72 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.43 (CH_2), 13.61 (CH_3), 24.17 (CH_3), 25.68 (CH_2), 42.58 (CH_2), 69.36 (C), 70.76 (CH_2), 208.41 (C=S) ppm. IR (CCl_4): 2984, 2980, 2918, 1442, 1424, 1404, 1364, 1292, 1242, 1113, 1068, 1034 cm^{-1}. MS (CI/NH_3): 271 (MH^+).

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Fast diastereoselective Baylis–Hillman reaction by nitroalkanes: synthesis of di- and triene derivatives [Tetrahedron 60 (2004) 4995]

Roberto Ballini,* Luciano Barboni, Giovanna Bosica, Dennis Fiorini, Emanuela Mignini and Alessandro Palmieri

Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, I-62032 Camerino, Italy

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