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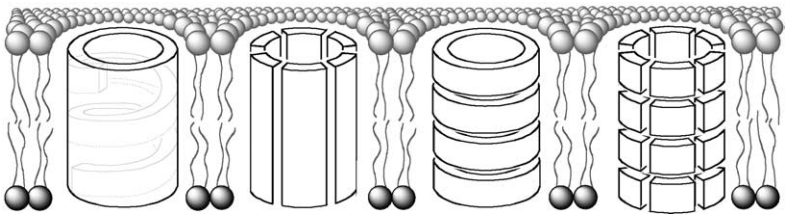
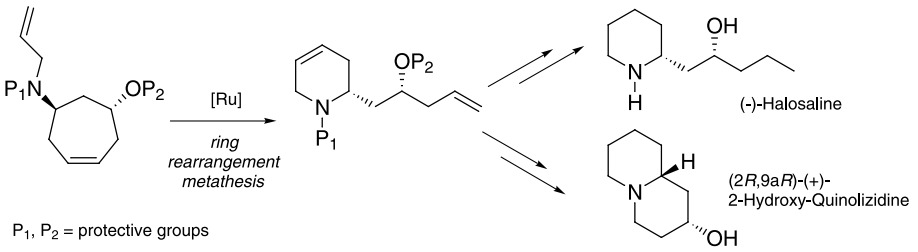
Contents

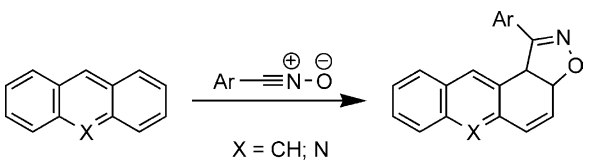
REPORT

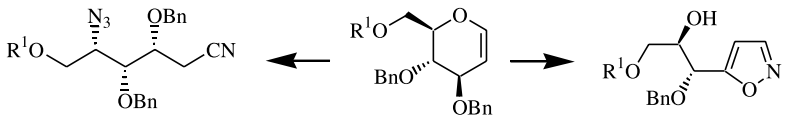


The development of the field of synthetic ion channels and pores from January 2000 to December 2003 is reviewed comprehensively. The report contains 220 references.

ARTICLES







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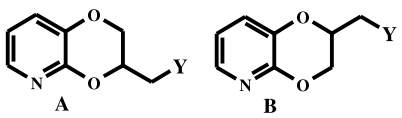

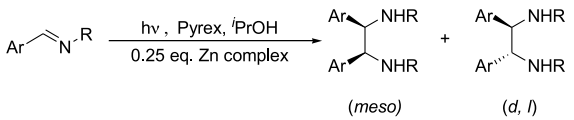

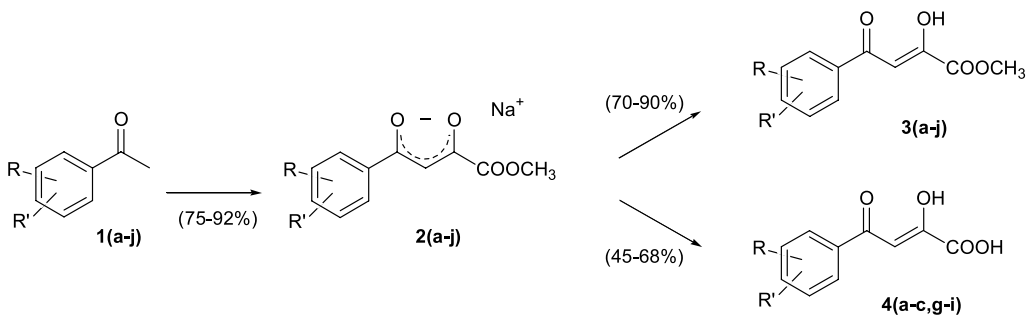

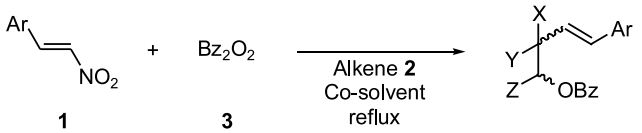

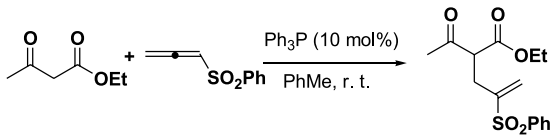

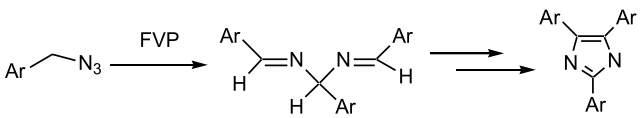

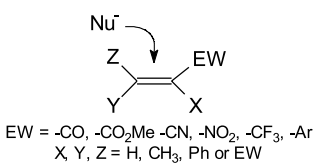

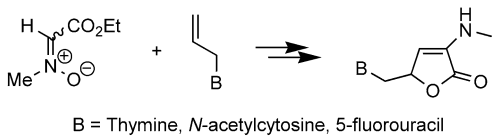

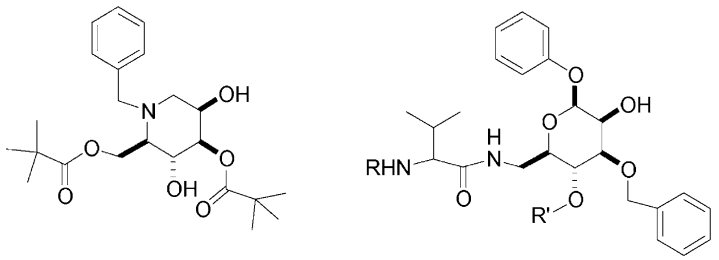

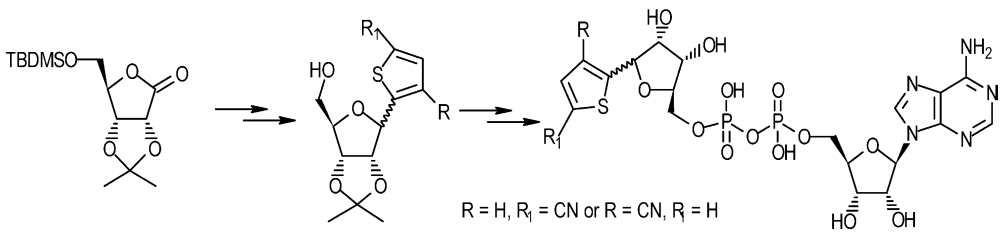

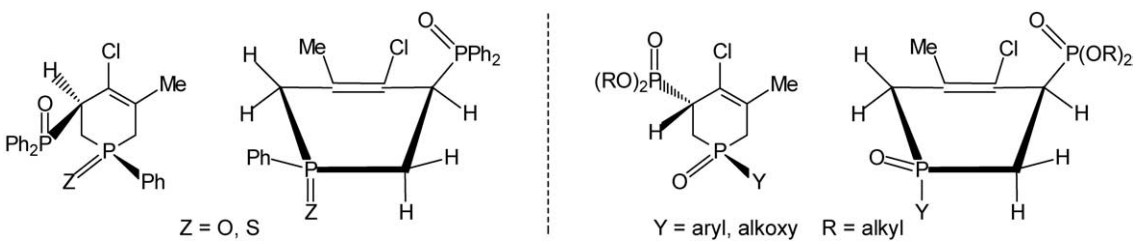

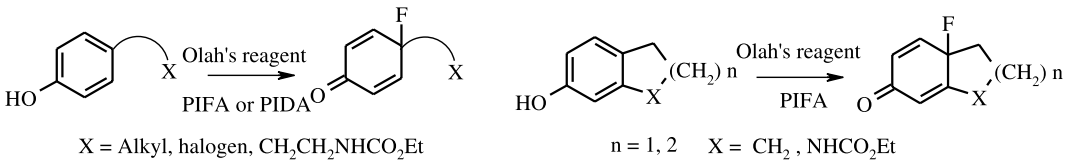

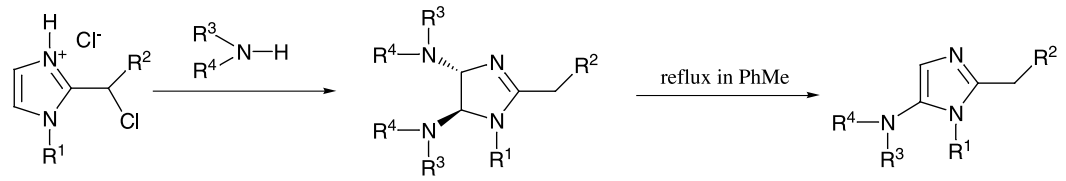

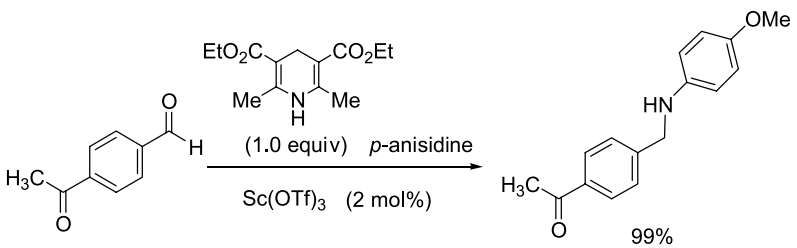

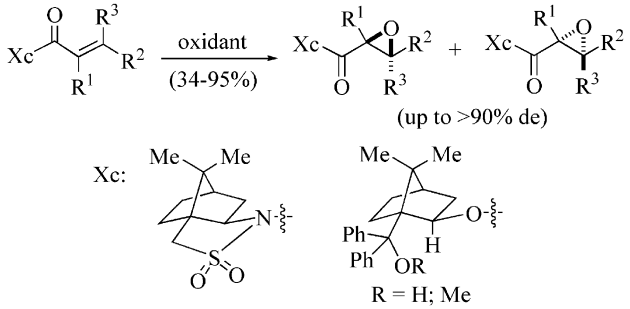

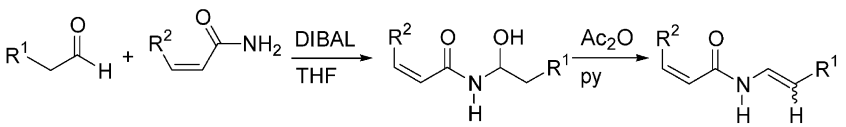

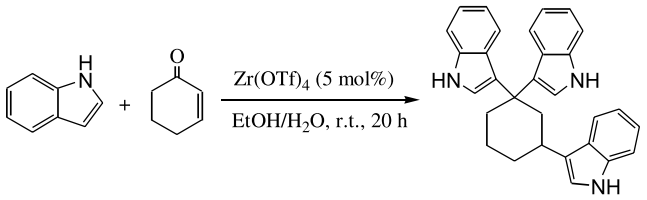

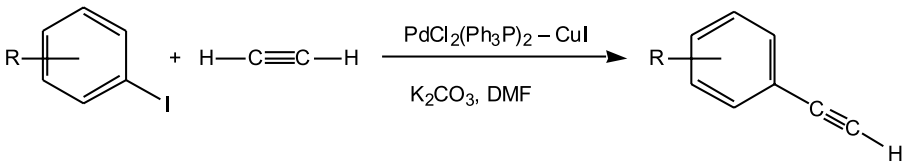

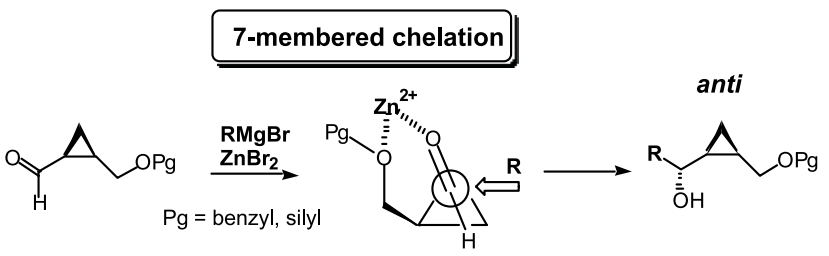

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Current design of synthetic ion channels and pores emphasizes, from left to right, unimolecular foldamers as well as supramolecular architecture covering barrel-stave, barrel-hoop, barrel-rosette and micellar motifs. A comprehensive collection of the compounds synthesized over the past four years along these lines can be found in *Tetrahedron* **2004**, *60*, 6405–6435.

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Recent synthetic ion channels and pores

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Contents

Keywords: Ion channels; Pores; Bilayer membranes; Molecular recognition; Supramolecules.

Abbreviations: PA, phosphatidic acid (1,2-diacyl-*sn*-glycero-3-phosphate); DOPA, dioleoyl phosphatidic acid; POPA, 1-palmitoyl-2-oleoyl phosphatidic acid; PC, phosphatidylcholine (1,2-diacyl-*sn*-glycero-3-phosphocholine); EYPC, egg yolk phosphatidylcholine; DMPC, dimyristoyl phosphatidylcholine (C14); DM_1PC, dimyristoleoyl phosphatidylcholine (C14:1); DPPC, dipalmitoyl phosphatidylcholine (C16); DP_1PC, dipalmitoleoyl phosphatidylcholine (C16:1); DPhPC, diphytanoyl phosphatidylcholine ($C16:Me_4$); DOPC, dioleoyl phosphatidylcholine (C18:1); POPC, 1-palmitoyl-2-oleoyl phosphatidylcholine; SOPC, 1-stearoyl-2-oleoyl phosphatidylcholine; DPC, dodecylphosphocholine; PE, phosphatidylethanolamine (1,2-diacyl-*sn*-glycero-3-phosphoethanolamine); DOPE, dioleoyl phosphatidylethanolamine; POPE, 1-palmitoyl-2-oleoyl phosphatidylethanolamine; PG, phosphatidylglycerol {1,2-diacyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)]}; POPG, 1-palmitoyl-2-oleoyl phosphatidylglycerol; PS, phosphatidylserine [1,2-diacyl-*sn*-glycero-(3-phospho-L-serine)]; SOPS, 1-stearoyl-2-oleoyl phosphatidylserine; CD, circular dichroism; CF, 5(6)-carboxyfluorescein; CPA, cationic peptide antibiotics; CSA, cationic steroid antibiotics; HPTS, 8-hydroxy-1,3,6-pyrenetrisulfonate; LUV, large unilamellar vesicle; PEG, poly(ethylene glycol); PHB, poly-*R*−3-hydroxybutyrate; SUV, small unilamellar vesicle; TM, transmembrane.

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1. Introduction

The first synthetic ion channel, a cyclodextrin derivative, has been reported in 1982 by the group of Tabushi in Tetrahedron Letters.[1] This occurred at a time when the rational design of peptide foldamers with ion channel activity[2] and the barrel-stave model for ion channels formed by macrolide antibiotics like amphotericin B[3,4] already attracted scientific attention. Since then, synthetic ion channels and pores have grown into an active field of research. A rich collection of reviews exists, focusing on developments until about 2000 or highlighting special topics.[5–20] This review aims to sum up progress from January 2000 to December 2003 comprehensively.

In this review, the term pore is used for transmembrane transport of organic molecules, whereas the term ion channel is used for inorganics. The term 'synthetic ion channels and pores' is restricted to compounds that have abiotic scaffolds (i.e. scaffolds that are not found in

biological ion channels and pores) and act in lipid bilayer membranes. This definition is made to draw a borderline as consistent as possible between the field of synthetic ion channels and pores and neighboring domains. It excludes the rich field of pore-forming de novo peptides that are made using synthetic organic chemistry but differ from biological ion channels and pores in the peptide sequence only. It also excludes an equally rich family of 'synthetic' ion channels and pores that are created by attachment of abiotic tails, spacers, bridges, crosslinks, sensors, tags, and so on to biological scaffolds.[21–27] Biological scaffolds beyond peptides and proteins like poly-/oligo-hydroxybutyrates[28] and ion-channel forming polyketides such as amphotericin B as well as their derivatives[29,30] are not covered in this definition either. Porous artificial membranes[31] and pores formed in materials other than bilayer membranes[32,33] are other attractive topics of current research that are not within the scope of this review.

The difference between synthetic ion channels/pores and synthetic carriers is that the former do not move substantially during action, whereas the latter—like ferries[34]—do. A carrier can be identified in a so-called 'U-tube experiment,' where phase transfer across bulk liquid membranes like chloroform from one aqueous phase to another is, in principle, possible with a mobile carrier but not with channels, pores and detergents. Because they act by destroying the bilayer structure itself, detergents can be identified by several methods reaching from bilayer conductance to light scattering experiments. Channels and pores can be differentiated from carriers and detergents by the occurrence of characteristic single-channel currents in planar bilayers (Fig. 1). Dependent on experimental conditions, single-channel conductances of some pS are typical for biological ion channels, whereas biological pores can have conductances well beyond 1 nS. Elimination of contributions from the electrolytes to these conductances with the Hille equation yields an approximative minimal inner diameter (to be interpreted with caution). The lifetimes of single ion channels and pores reveal their kinetic stability. Typical values are in the millisecond range, although lifetimes of seconds and even minutes can be observed with biological and sporadically also with synthetic ion channels and pores. The probability to detect open ion channels and pores and—with active supramolecules—the dependence on monomer concentration provide insights on thermodynamic stability.

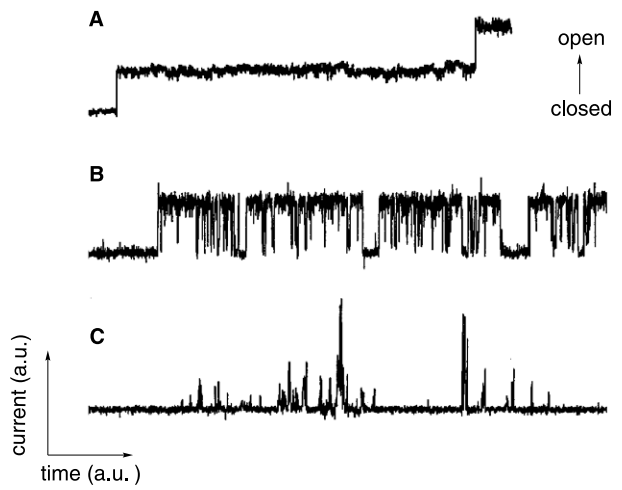


Figure 1. Synthetic ion channels and pores are characterized in planar bilayer conductance experiments by their lifetime—long (A), intermediate (B), short (C)—and conductance. The conductance is indicative for the inner diameter, lifetime for inertness/ lability of single channels/pores. a.u.: arbitrary units; see original publications [(A) reproduced from Ref.121 by permission of The Royal Society of Chemistry, (B) reproduced with permission from Ref.116, copyright 2001 Am. Chem. Soc., and (C) reprinted from Ref.123, Copyright (2004), with permission from Elsevier].

The characterization of ion channels is, however, not limited to planar bilayer conductance experiments, and it is erroneous to claim that this method is superior to others. Indeed, characterization of ion channels and pores in spherical bilayers (i.e. vesicles or liposomes) using spectroscopic methods provides complementary insights, particularly on the structural level. Results on function like voltage gating from vesicle flux experiments are fully comparable with results from planar bilayer conductance (Fig. 2). Key characteristics of synthetic ion channels and pores accessible in planar as well as spherical bilayers include inner diameter (from size-exclusion experiments), thermodynamic stability (from concentration dependence), ion selectivity (from salt gradients), voltage dependence (from membrane polarization), and ligand gating and blockage (from dose response curves).

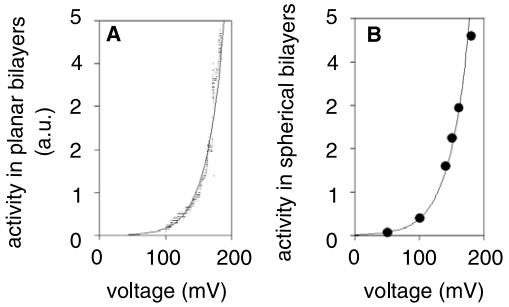


Figure 2. Fluorescence kinetics in spherical (B) and macroscopic conductance in planar bilayers (A) give compatible results. The example shows dependence of activity of a synthetic channel on membrane polarization (reproduced with permission from Ref.128, copyright 2003 Wiley-VCH).

The dependence of the activity of supramolecular ion channels and pores on the monomer concentration can provide qualitative insights on their thermodynamic stability with Hill coefficients $n \leq 1$ (i.e. linear dependence or saturation behavior) indicative for exergonic self-assembly and $n > 1$ (i.e. dependence on the n-th power of monomers present in the active supramolecule) for endergonic self-assembly.

The often pH-dependent anion/cation selectivity can provide insights on internal charge and counterions of synthetic ion channels and pores. Usual permeability ratios reach from 1 for no selectivity to 5 and more for high anion/cation selectivity. Common selectivity sequences include the Eisenman topologies for cations and the Hofmeister series for anions. Selectivity sequences are informative on internal diameters, ion dehydration during translocation as well as internal active sites of synthetic ion channels and pores.

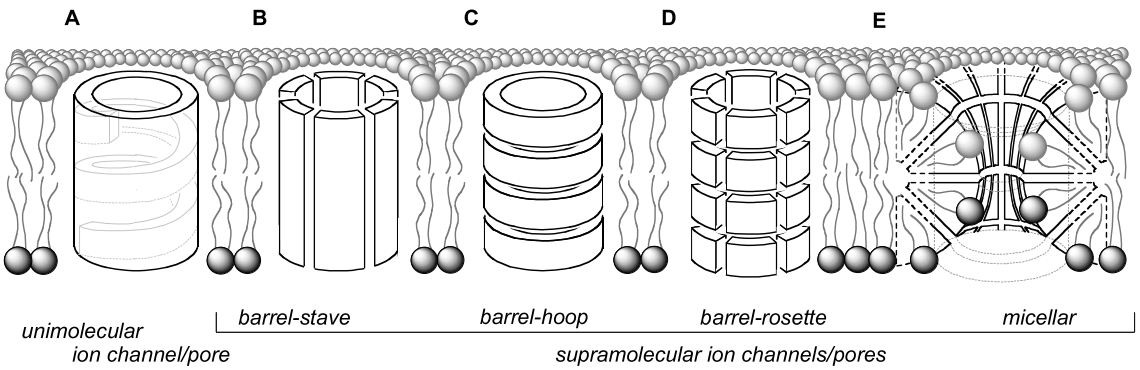


Figure 3. Design strategies in the field of synthetic ion channels and pores include (A) unimolecular approaches as well as self-assembly of (B) barrel-stave, (C) barrel-hoop, (D) barrel-rosette and (E) micellar supramolecules. Beyond helical foldamers (gray), unimolecular design deals with crosslinked barrel-stave and barrel-hoop supramolecules, whereas barrel-rosette supramolecules are fragmented barrel-stave or barrel-hoop motifs. The simplifying term 'micellar pore' is suggested to unify more complex, often transient motifs that also include membrane phase changes or fusion (e.g. 'toroidal pores' or 'interfacial carpets').

The terms 'ohmic' and 'non-ohmic' describe ion channels and pores with linear and exponential dependence of activity on membrane polarization, respectively (Fig. 2). Non-ohmic behavior is characterized by the gating charge z_g, reaching from 0.1 for weak to values of 1.0 and beyond for strong voltage dependence. On the single-channel level, non-ohmic behavior can result from non-ohmic open probability, lifetime or current (rectification). Ohmic behavior is observed with electrically symmetric compounds (including β-sheets), whereas asymmetric compounds with substantial macrodipoles (including α-helices) are needed to violate Ohm's law.

The regulation of synthetic ion channels and pores by ligands and blockers is usually reported in dose response curves with dissociation constant K_D and Hill coefficient n as characteristics (n can be indicative of the stoichiometry of the host–guest complex). The voltage dependence of the K_D provides information on the Woodhull distance l_A from channel entrance to the active site.

The 'functional' classification of membrane active compounds as carriers, channels, pores and detergents is not satisfactory. There is ample evidence that the involved criteria depend on experimental conditions. In general, transport mechanisms can shift from carrier to channel/pore and detergent with increasing concentration. More specifically, the archetype of an ion carrier, valinomycin, can act as ion channel under appropriate conditions.[35] Classical detergents like triton X-100, on the other hand, can exhibit characteristics like single-channel currents that are commonly used to define ion channels and pores.[36,37] Many ion channels and pores—particularly 'interesting ones' that recognize selected ions or molecules—exhibit activity in the bulk liquid membranes conventionally viewed as characteristic for carriers. Most carriers, ion channels and pores destroy bilayer membranes in a detergent-like manner at high-enough concentrations.

Experts on molecules, organic chemists, may prefer classifications that are based on structure rather than function, particularly if the latter is not free of ambiguity. With synthetic ion channels or pores, the 'organic-chemists' approach is, however, out of the question because active structures of synthetic ion channels and pores are unknown in most cases, at least at high resolution. Much evidence is available that structural studies of ion channels and pores by conventional spectroscopic methods at relevant (nanomolar or, at worst, low micromolar) concentrations are inapplicable in most cases because the dominant species in solution is an inactive monomer,[38] because active structures exist in bilayers only, or because active structures transform into inactive supramolecules at high concentration. Amusingly, it is the 'nanospace' within synthetic ion channels and pores—nearly invisible in conventional spectroscopy—that is most straightforward to characterize in bilayer membranes. Insights on internal 'nanospace' can then be used as an indirect source of information concerning the complementary structure of the surrounding ion channel or pore.

In reality, synthetic ion channels and pores are therefore often prepared based on 'designed structures' and then evaluated on the functional level without much knowledge of the elusive active structures. In this review, we explore the possibility to classify recent synthetic ion channels and pores based on 'design'. The simplest motif used in the design of synthetic ion channels and pores is a unimolecular macromolecule of 25–40 Å length (Fig. 3). Design strategies for supramolecular synthetic ion channels and pores have focused on the cylindrical self-assembly of linear, 'stave-like' monomers into barrel-stave pores[17] or the stacking of macrocyclic, 'hoop-like' monomers into 'barrel-hoop' pores. Even smaller modules are envisioned to self-assemble into stacked supramolecular rosettes. These complex suprastructures are conceivable either as stacked barrel-stave supramolecules with fragmented staves or barrel-hoop supramolecules with fragmented hoops. Here, these motifs are named 'barrel-rosette' pores.

The more complex and transient 'micellar pores' received renewed attention to explain characteristics of ion channels and pores formed by many toxic or antibiotic α-helical peptides.[39–41] Transient 'toroidal' pores are thought to form during diffusion- and/or field-driven translocation of these peptides from one membrane surface to the other. Micellar (toroidal) pores cause readily detectable lipid flip–flop similar to the pores formed by lipid bilayers in response to pressure and stress.[42] Vaguely reminiscent of a poorly organized, lipidic barrel-rosette motif, the key characteristic

of micellar pores is the partial, often transient destruction of the lipid bilayer. Detergents are classical examples for compounds that form micellar pores or cause more dramatic phase changes, transforming large areas of lipid bilayer membranes into mixed, reversed, disk or tubular micelles by complex mechanisms that may involve interfacial 'carpets'.[39–41,43]

The definitions and terms elaborated in this introduction are highly simplified. They are neither meant to be generally valid nor to question, invalidate or exclude other views of the topic. They are made for convenience with the only intention to assist reading of this review, particularly for chemists with less expertise.

2. New sources of inspiration

No painter would ever pretend to do better than Nature, but no painter would stop painting for this reason. Maybe he would point out that he is convinced that we only understand what we can create, maybe he would add that he considers his work as significant if it works out characteristics of, say, a landscape or a person that are decisive but otherwise difficult to identify and appreciate.

Along these lines, ion channels and pores formed by biological peptides and proteins have always been a constant and gratifying source of inspiration for the design of synthetic 'mimics'. Alamethicin, melittin, the magainins and M2 oligomers of many ion channels, pumps and receptors have influenced research on α-helical motifs as well as contributing to the development of concepts like the barrel-stave channel, the toroidal pore and detergent-like carpets. The porins[44] and α-hemolysin[32,45–48] have served very well as models of choice in studies on the larger β-barrel pores and their potential in biotechnological applications, whereas concepts like the barrel-hoop pore and the unimolecular pore originated from extensive work on the β-helical gramicidin.[24–26] Although of unclear structure, the amyloid pores[49,50] and those formed by many natural peptide antibiotics[39] attract much attention because of their medicinal importance.

Biological peptides and proteins continue to inspire. Among the many remarkable recent breakthroughs on ion selectivity, voltage sensitivity and osmotic stress, novel insights on the voltage gating of potassium channels may be particularly influential for the design of synthetic ion channels and pores (Fig. 4).[51–54] Namely, the 'voltage sensor' of potassium channels is an α-helix which is not part of the helix bundle that forms the channel. These peripheral voltage sensor helices lie perpendicular to the channel axis near the inner membrane/water interface with multiple arginine residues located in the hydrophobic core of the membrane. Upon changes in membrane polarization, these 'paddles' cross the bilayer, turn by about 90°, and align to the transmembrane helix bundle. This movement pulls at the side of the bundle where the paddles are attached to mechanically open the central channel.

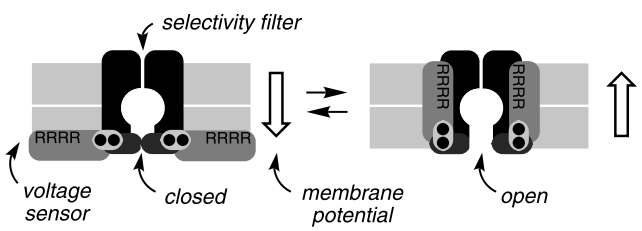


Figure 4. The controversial mechanical opening of biological potassium channels in response to membrane polarization by translocation of arginine-rich (R-rich) helices as a representative recent example for molecular biology as a central source of inspiration in the field of synthetic ion channels and pores.

One innovative (and controversial) aspect of this new mechanism is that voltage gating occurs by a movement of arginine-rich (R-rich) helices within and across the hydrophobic core of the bilayer. This partitioning of oligoguanidinium cations into and across a hydrophobic environment is reminiscent of the facile translocation of R-rich HIV-Tat-like transporters across bilayer membranes.[55] Recent model studies with poly-L-arginine suggest that both solubility and charge of oligo-/poly-arginines are adaptable to the environment by dynamic scavenging of amphiphilic and hydrophilic anions.[56] Experiments in U-tubes and anionic vesicles demonstrate that anion-polyarginine complexes can act as anion carriers in anionic membranes.

Another polypeptide, i.e. poly-L-glutamine, emerged recently as a less expected source of inspiration for the design of synthetic ion channels and pores.[57] In planar asolectin bilayers, poly-L-glutamines with more than 29 amino-acid residues form cation-selective ($H^+ > Cs^+ > K^+ > Na^+$), nearly ohmic ion channels of high stability (single-channel lifetime $\tau > 1$ min) and single-channel conductance indicative for a short inner diameter ($g = 17$ pS in 1 M CsCl). These characteristics are compatible with the short internal diameter of 1.5 Å of a unimolecular, hollow μ-helix (Fig. 5). A μ-helix is a 6.2-*P*-helix with all amide residues oriented towards the interior to form extended hydrogen-bonded chains. This internal location of amino-acid residues differs from external orientation in α-helices formed by all-L- and the hollow β-helices formed by D,L-peptides. Ion channel formation by μ-helices and its role in glutamine diseases are under discussion.[50a,c]

Among biological ion channels and pores formed by molecules other than peptides and proteins, polyketide macrolides like amphotericin B,[29,30] polyketide polyethers like monensin,[58] polyamines like squalamine (see Section 3.5) and polyesters like PHB–polyphosphate complexes[28] have served for as sources of inspiration in the field since quite some time. The putative active suprastructure of PHB–polyphosphate channels remains a rare example for a unimolecular barrel-stave-like (or barrel-hoop-like) PHB conformer with a (polyphosphate) rod in the middle.

However, non-peptide natural products continue to entertain with pleasant surprises. The most recent member of the polyketide macrolide family shown to form ion channels in planar soybean PC bilayers is elaiophylin, an antibiotic produced by *Streptomyces* strains (Fig. 6).[59] These ohmic ion channels exhibit high cation selectivity ($P_{K^+}/P_{Cl^-} > 24$, $Rb^+ > Cs^+ > K^+ > Na^+ > Li^+$), appreciable stability ($\tau \approx 5$ s

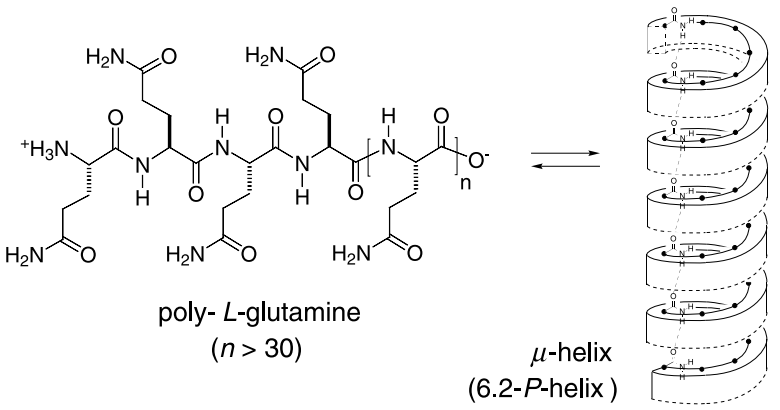
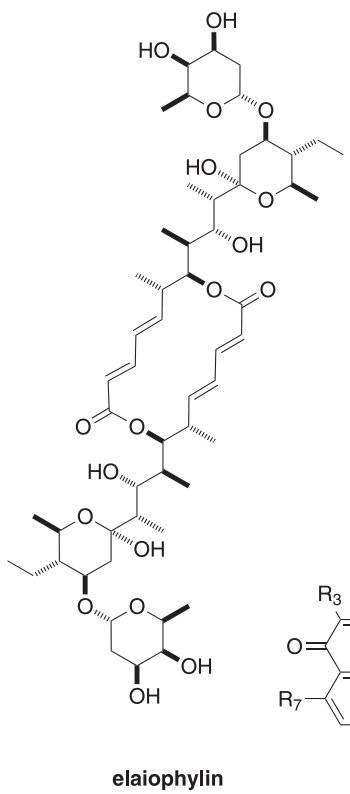


Figure 5. The recent μ-helix of polyglutamine channels as a representative example of perhaps less expected new sources of inspiration in the field of synthetic ion channels and pores.

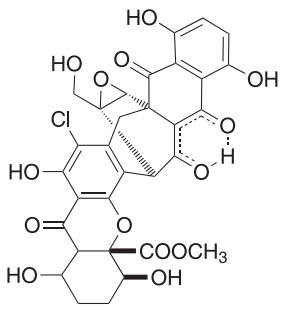
with subconductance bursts of $\tau \approx 100$ ms) and substantial single-channel conductance ($g=0.2$ nS in 200 mM KCl). According to the non-linear dependence of the multichannel conductance on elaiophylin concentration, more than five monomers form a barrel-stave active structure that may further dimerize into a minimalist barrel-rosette motif; contributions from bilayer deformation cannot be excluded.

Beticolin 3 is member of a family of non-host-specific toxins produced by the phytopathogenic fungus *Cercospora beticola* (Fig. 6).[60] Beticolin 3 forms Mg^{2+}-dependent, ohmic multilevel sodium channels in planar POPC/POPE bilayers (1:1) with substantial cation selectivity ($P_{Na^+}/P_{Cl^-}=5.6$, $Na^+ > Li^+ > K^+ > TEA^+$). The conductance levels are multiples of an elementary conductance, show identical selectivity and diameter but no transitions between the individual levels. These observations suggest that several ion channels form simultaneously as clusters. X-ray diffraction data indicate the formation of hollow dimeric Mg^{2+} complexes that may stack on top of each other to give formal 'barrel-rosette' channels which then further self-assemble into the active clusters.

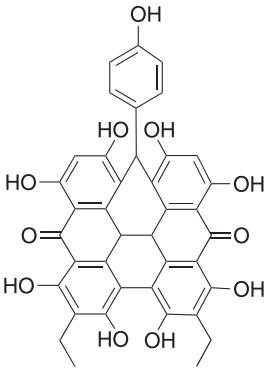
Blepharismin 1, a quinone pigment from granules of free-swimming protozoan *Blepharisma japonicum*, forms nearly ohmic ion channels in planar DPhPC bilayers (Fig. 6).[61] The single-channel conductances of these cation channels ($P_{K^+}/P_{Cl^-}=6.6$) are quite heterogenous, most frequently around the already remarkable 0.8 nS in 100 mM KCl, and sometimes reaching 2.8 nS under the same conditions.



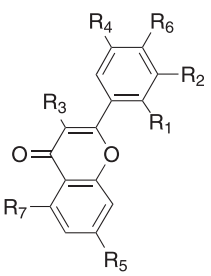
elaiophylin



beticolin 3

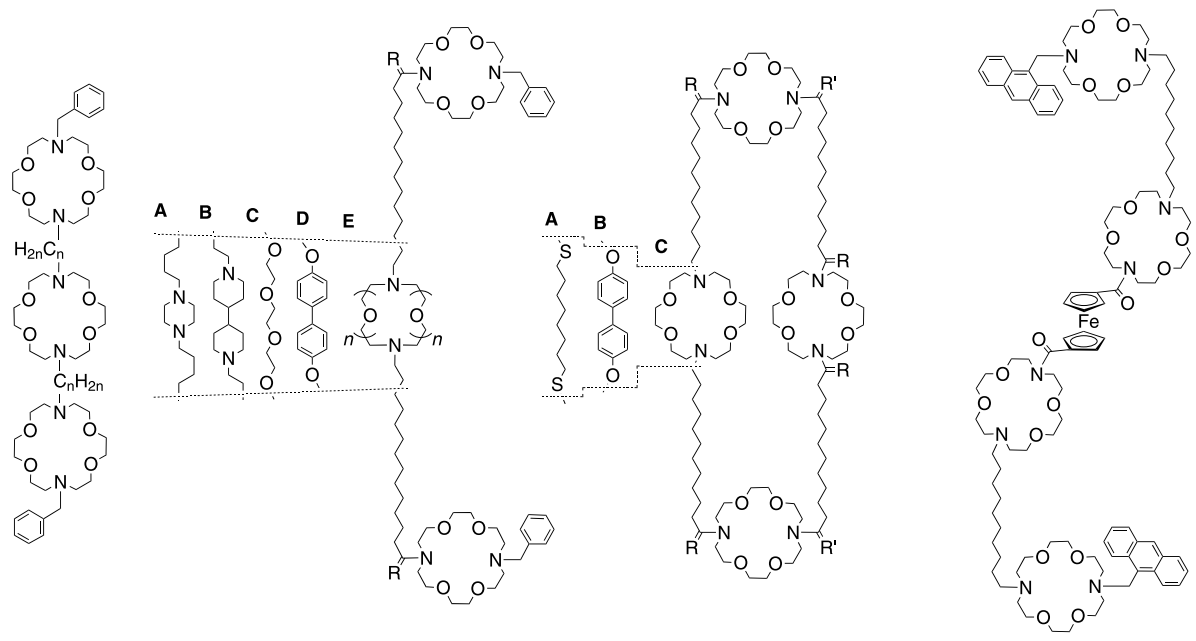


blepharismin 1



	R_1	R_2	R_3	R_4	R_5	R_6	R_7	*activity*
acacetin	H	H	H	H	OH	OMe	OH	+++
apigenin	H	H	H	H	OH	OH	OH	+++
luteolin	H	H	H	OH	OH	OH	OH	+
morin	OH	H	OH	H	OH	OH	OH	++
rhamnetin	H	H	OH	OH	OMe	OH	OH	+++
quercetin	H	H	OH	OH	OH	OH	OH	-
myricetin	H	OH	OH	OH	OH	OH	OH	-

Figure 6. Recent representative examples of ion channels and pores from natural product chemistry, a probably underappreciated source of inspiration in the field of synthetic ion channels and pores.



	n	activity
1	8	-
2	10	++
3	12	+++
4	14	+++
5	16	++

	n	relay	R	activity
6	1	**E**	H,H	+
7	2	**E**	H,H	++
8	3	**E**	H,H	+++
9	-	**A**	H,H	-
10	-	**B**	H,H	+
11	-	**C**	H,H	+
12	-	**D**	O	-

	relay	R	R'	activity
13	**C**	O	H,H	+++
14	**C**	H,H	H,H	++++
15	**A**	H,H	H,H	++
16	**B**	H,H	H,H	++

17

Figure 7. Unimolecular synthetic ion channels with oligocrown ionophores.

The dependence of calcein release from spherical EYPC membranes on the structure of flavonoid antioxidants is intriguing.[62] Whereas the classical quercetin is inactive under the employed conditions (pH 7.4), the structural isomer morin is active at 5 μg/ml. Increasing hydrophobicity in methylated rhamnetin, doubly-dehydroxylated apigenin and its methylated derivative acacetin results in increasing activity, whereas singly-dehydroxylated luteolin and, less surprisingly, singly hydroxylated myricetin are inactive. Quercetin itself alters the macroscopic conductance of planar DPPC membranes in a pH-dependent manner.[63] Maximal activity is observed at intermediate quercetin deprotonation around pH 5, whereas fully protonated quercetin is less active and fully deprotonated quercetin is inactive.

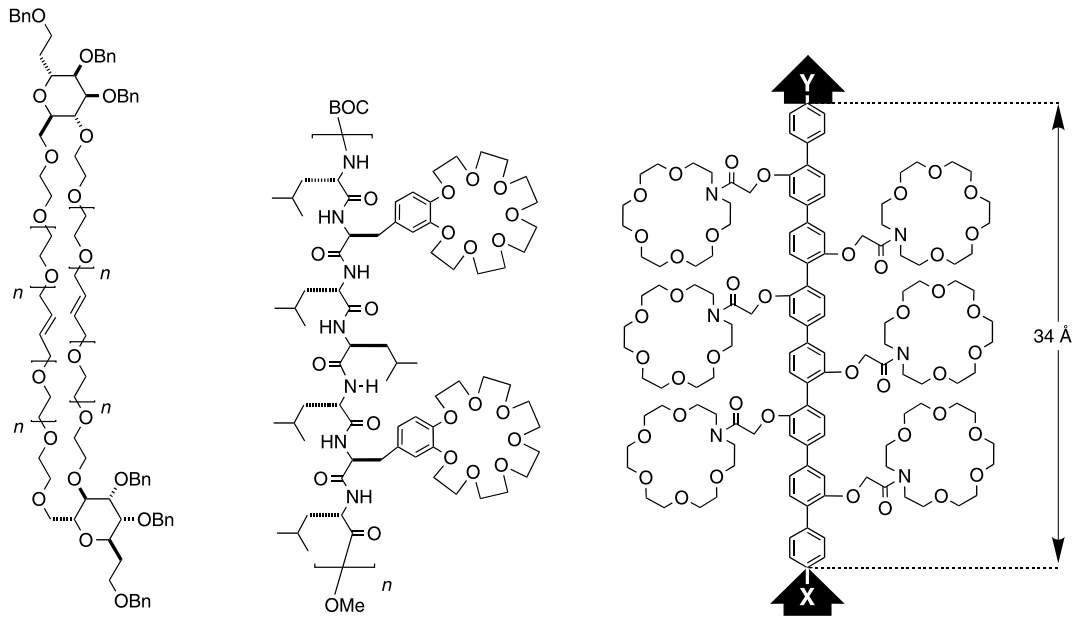
3. Design motifs

3.1. Unimolecular ion channels and pores

Many classical synthetic ion channels and pores were designed as unimolecular structures. Early design strategies include the crosslinking of barrel-stave supramolecules with central[64–66] or terminal hoops,[1,6–11] or the crosslinking of macrocyclic and helical hoops like crown ethers[6,7,15,16,67–69] and THF-peptides.[70] Many of these approaches were inspired by concepts in peptide engineering like the TASP-approach for terminal crosslinking of staves[71,72] and gramicidin conjugates for central crosslinking of helical hoops.[73] Several studies on unimolecular ion channels have been reported in this millennium.

Building on an extensively explored system,[6,7,15,16] oligocrowns **1**–**5** are designed to determine the dependence of the activity on the length of the alkyl spacers between the ionophores (Fig. 7).[74] Na NMR kinetics in spherical PC/PG membranes (4:1) indicate the best activity for oligomers **3** and **4** (range 5–20 μM) with a maximal length of 50–55 Å, respectively. Replacement of the terminal benzyl anchors by dansyls reduces the activity. The dependence of the activity on ionophore concentration is considered as supportive for the formation of unimolecular ion channels. Similar dependence on spacer length is reported for the bactericidal activity of oligocrowns **1**–**5**, maximal for **3** (IC_{50}=12 μM, *E. coli*) and 13-times lower for the least active shorter homolog **1**.[75]

Oligocrowns **6**–**12** are designed to determine the dependence of the activity on size and nature of the central relay of prototype **4** with optimized length. Decreasing activity with decreasing size of the central macrocycle in **6**–**8** is found by Na NMR kinetics in spherical PC/PG membranes (4:1).[76] Replacement of the central macrocycle by biphenyl and pyrazine spacers in **9** and **12** results in inactivity, whereas activity in the range of **6** is preserved with acyclic ethers in **11** and 4,4′-dipiperidyl relays in **10**. The addition of a second central relay in macrocycles **13**–**16** gives, always



	n	activity
18	0	-
19	1	+
20	2	++
21	3	+++
22	4	++
23	5	+

	n	activity
24	1	carrier
25	2	detergent
26	3	channel

	Y	X	recognition
27	-SMe	-SMe	-
28	$-SO_2Me$	-SMe	+
29	-SMe	$-SCH_2CH_2NH_3^+$	-
30	$-SO_2Me$	$-SCH_2CH_2NH_3^+$	-
31	$-SO_2CH_2CH_2NH_3^+$	-SMe	+

Figure 8. Unimolecular synthetic ion channels that expand the oligocrown motif to giant macrocycles, α-helical peptide scaffolds and rigid push–pull *p*-octiphenyl scaffolds for the recognition of polarized membranes.

according to Na NMR kinetics in PC/PG vesicles, the highest activity for tetracrown **14**.[77] Amides instead of amines in the crown regions reduce activity in **13**, and diamide crowns are inactive (R′=O, not shown). Replacement of one central crown relay by a biphenyl in **16** and a dithioether in **15** results in clearly reduced activity, and analogs without both central crowns C and D are inactive (not shown). ESI MS in choroform exhibits one sodium cation bound per macrocycle, i.e. four Na^+ with **14**, three Na^+ with **3**, and two Na^+ with a C_{12}-analog of **10**.[78]

Oligocrown **17** is equipped with a central ferrocene redox center and peripheral anthryl anchors.[79] According to photoelectron transfer and ^{13}C NMR experiments in organic solvents, 3–4 sodium cations are bound to tetracrown **17**. Such multiple cation binding is in support of ion channels that operate by a biomimetic 'billiard-ball' transport mechanism. In acetonitrile, sodium binding further causes a small anionic shift of Fe(II)/Fe(III) oxidation at 720 mV vs Ag/Ag(I). In planar PE bilayers (600 mM KCl, pH 7.2), nearly ohmic single channels **17** with a relatively small conductance (61 pS) and lifetimes between 50 ms and 20 s are observed. As expected for unimolecular ion channels, Na NMR kinetics in grade 1 lecithin vesicles (200 mM KCl, pH 6.5) show a linear dependence of cation exchange rates on oligocrown concentration. Oxidation of the ferrocene moiety of **17** before introduction into the membrane with Ce(IV) inhibits this transmembrane sodium transport activity.

The macrocyclic polyethers **18**–**23** with terminal arene arrays as potential interfacial anchors are designed to act as transmembrane monomeric cation channels (Fig. 8).[80] According to Na NMR kinetics in spherical lecithin membranes, the dependence of the cation exchange rate on monomer concentration (range 10–160 μM) is qualitatively compatible with a unimolecular active structure. Interpreted as support for transmembrane orientation, macrocycle **21** of a maximal length of 32 Å that roughly matches the thickness of the hydrophobic core of the membrane exhibits the highest activity.

Semi-rigid α-helical scaffolds are used in peptides **24**–**26** to align crown ethers one on top of the other to form a unimolecular ion channel. Structural studies of the longest helix **26** (31 Å) by total reflectance spectroscopy indicate an angle of about 55–58° between the plane of the membrane and the long axis of the helix, independent of the size and nature of the crown ether.[81] This angle can, however, be interpreted as the average of a random helix orientation or as a binary mixture of transmembrane channels and inactive populations lying at the interface. In spherical PC

membranes, helix **25** with intermediate length (21 Å) but neither shorter nor longer homologs mediates the release of organic dyes. Enhancement of this activity by the inverse-cone shaped lysoPC and inhibition by the cone-shaped POPE is interpreted as support for the formation of 'micellar pores' by the inverse-cone shaped peptide **25**.[82]

Ion channels **27**–**31** comprise ion-conducting azacrown modules placed along a rigid-rod *p*-octiphenyl scaffold with variable termini X and Y.[83] The sulfide π donors and sulfone π acceptors in rods **28**, **30** and **31** create an axial macrodipole. Control rods **27** and **29** contain π donors only. *p*-Octiphenyls **27** and **28** are neutral, and rods **29**–**31** are cationic. The terminal ammonium cation in **30** is near the positive end of the axial dipole, and that in **31** near the negative one.

According to the response of intravesicular, pH-sensitive fluorophores (HPTS), the ability of cationic ionophores **29**–**31** to mediate pH gradient collapse exceeds that of the neutral rods **27** and **28** in neutral and anionic spherical bilayers (EYPC and EYPG SUVs). These findings suggest that cationic rods have improved solubility in the media but do not recognize anionic membranes. Linear dependence of the activity on rod concentration and inability of all rods to mediate dye release from EYPC SUVs is as expected for unimolecular ion channels.

In doubly-labeled EYPC SUVs with inside negative membrane potentials, an internal pH-sensitive dye and an external potential-sensitive dye, push–pull rods **28** and **31** mediate membrane depolarization more efficiently than ionophores **27**, **28** and **30**. Increased activity of the neutral push–pull rod **28** compared to the dipole-free analog **27** in polarized membranes is as expected from earlier results on the importance of dipole-potential interactions for the recognition of polarized membranes.[84] Increased activity of the cationic push–pull rod **31** with an ammonium cation near the negative end of the axial rod dipole compared to structural isomer **30** suggests that unfavorable charge translocation across the bilayer suffices to prevent channel stabilization by dipole-potential interactions in weakly polarized SUVs. Structural studies by fluorescence depth quenching in polarized spherical bilayers are in support of this conclusion. Conductance experiments in planar EYPC bilayers indicate that single-channel rectification further contributes to the high activity of push–pull rod **31** at high polarization. The difference in activity of structural isomers **30** and **31** in polarized membranes is thought to contribute to the understanding of the mode of action of natural antibiotics like magainin compared to toxins like melittin.

Much truncation, terminal elongation and central cross-linking of the gramicidin channel as in the succinate-bridged and hydrophobically capped dimer **32** reported over the past decades has been accomplished without touching the functional biological scaffold.[24–27,85–87] This is not the case with synthetic ion channels **33**–**40**, where some of the original α-amino acids in the gramicidin are replaced by artificial δ-amino acids (Fig. 9). These new amino acids are designed to overcome the fundamental shortcoming of the gramicidin ion channel. Namely, the location of all amino-acid residues at the outer surface of the active β-helix is incompatible with internal design. The cyclohexyl ether (CHE) amino acids in peptides **33**–**35** are thought to add ether oxygens at the inner channel surface to possibly modulate its cation selectivity.[88] In planar soybean lecithin membranes, peptides **34** and **35** with four to six δ-amino acids can be observed only as occasional, short-lived proton channels (1 M HCl). Peptide **33** is detectable as ohmic cation channel with, compared to gramicidin, two rather than one strongly reduced conductance levels (g=0.7/1.1 pS versus 26.0 pS in 1 M KCl) and shortened lifetime (200–350 ms versus several seconds) as well as a more pronounced Eisenman I selectivity topology (P_{K^+}/P_{NH4^+}=0.14 versus 0.60, $H^+ > NH_4^+ > Cs^+ > K^+ > Na^+ > Li^+$).

Tetrahydrofuran (THF) in place of cyclohexyl ether (CHE) δ-amino acids gives ohmic ion channels with similar characteristics.[89] Peptide **36** with hydrophobic caps (and, more labile, also uncapped peptide **37**) exhibits two rather than one levels of, compared to gramicidin, reduced conductance (g=15.4/19.7 pS in 1 M KCl) and lifetime (up to 15 s). The Eisenman I selectivity (P_{K^+}/P_{NH4^+}=0.28, $NH_4^+ > Cs^+ > K^+ > Na^+$) is, as with CHE-peptide **33** and gramicidin, dominated by cation dehydration and not in support of significant cation binding by THF oxygens within the channels. In trabecular meshwork cells, THF-peptides **36** and **37** cause, similar to gramicidin, some depolarization and a shift of the reversal potential toward zero.[90]

In ion channel **38**, only amino acids 11 and 12 of the succinyl-bridged, hydrophobically capped gramicidin **32** are replaced by one artificial L-THF-δ-amino acid.[91] In ion channel **39**, a D-THF-δ-amino acid replaces amino acids 10 and 11. In ion channel **40**, one D-THF-peptide from **39** is coupled with an unchanged gramicidin scaffold. Synthetic ion channel **38** exhibits very little activity in planar DPhPC (1 M CsCl). Under the same conditions, single-channel currents are detected for THF-gramicidins **39** and **40**. Different to the Eisenman-I cesium selectivity of gramicidin derivatives **32**–**37**, channels **39** and **40** exhibit Eisenman-III rubidium selectivity (**39**: P_{K^+}/P_{NH4^+}=0.6, $NH_4^+ > Rb^+ > K^+ > Cs^+ > Na^+ \sim Li^+$). Together with reduced conductance compared to gramicidin (g=2.2/1.8 pS in 1 M KCl), this characteristic is compatible with cation binding to a THF oxygen pointing into the ion-conducting pathway within the unimolecular β-helix. The mono-THF-gramicidin controls, thought to dimerize into formal barrel-hoop supramolecules (Fig. 3(C)), show similar characteristics. The lifetime of the asymmetric single channel **40** depends on the applied voltage. This finding is indicative of voltage-gated blockage/destabilization of open channels rather than voltage-gated channel formation (expressed in voltage-dependent open probability) or rectification (expressed in voltage-dependent single-channel conductance).

3.2. Barrel-stave supramolecules

Early examples of this class are voltage-gated synthetic ion channels formed by macrocyclic bolaamphiphiles and rigid-rod *p*-octiphenyl polyols. However, the barrel-stave approach has attracted full attention only within the timeframe of this review.

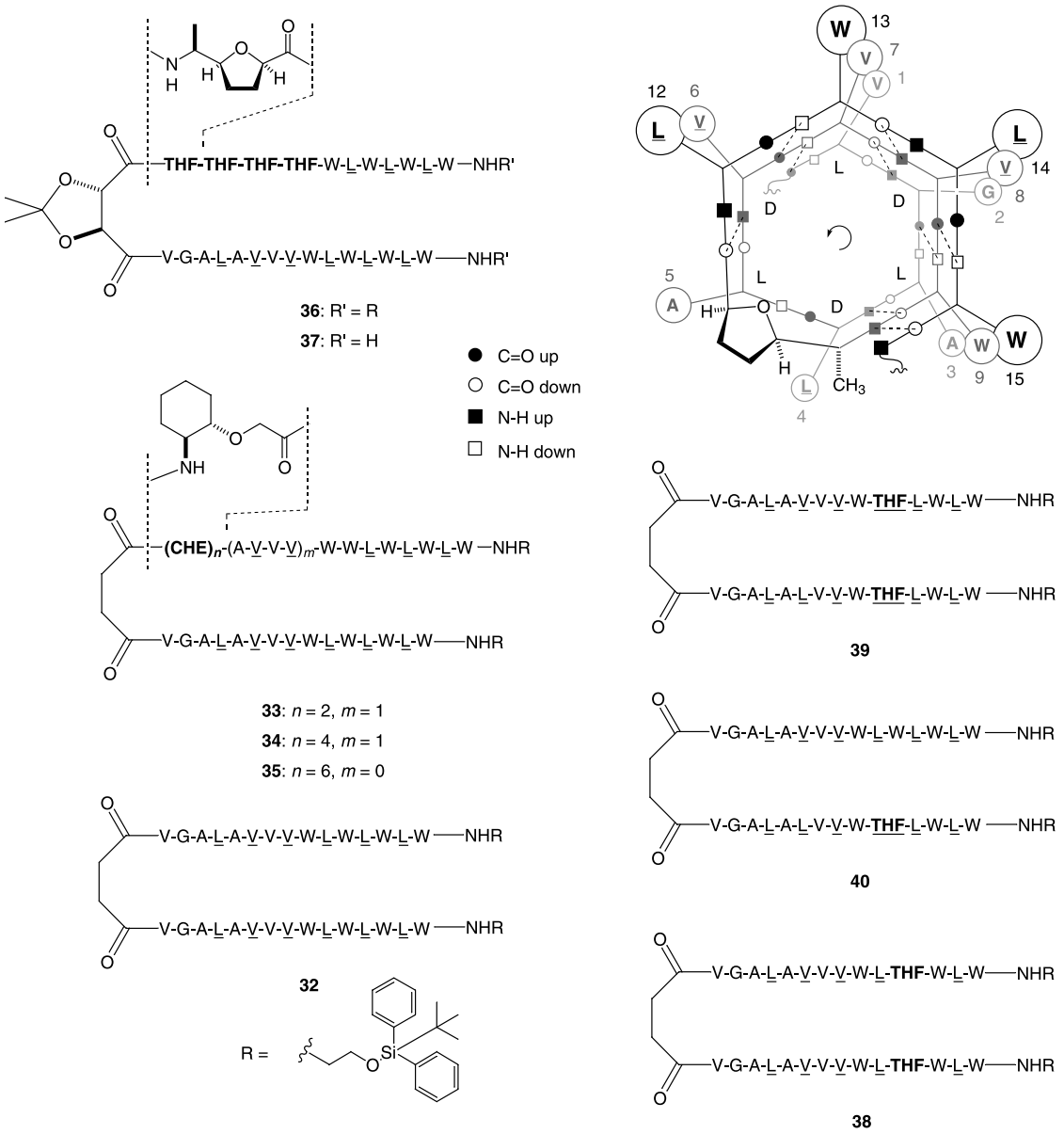


Figure 9. Unimolecular synthetic ion channels based on modification of the β-helical scaffold of gramicidin A. An axial view of ion channel **39** is added to illustrate the peptide backbone in β-helical conformation (solid lines) with indication of hydrogen bonds (dotted lines), residues per turn (6), axial chirality (*M*), orientation of backbone amides (dipole-free), and location of the THF-unit and the amino-acid residues (external only; single-letter abbreviations, D amino acids underlined).

3.2.1. Macrocyclic, branched and linear non-peptide bolaamphiphiles as staves. The design of acyclic bolaamphiphile **41** is the result of a systematic simplification of a family of originally unimolecular ion channels to first bismacrocyclic, then acyclic and branched and finally linear 'staves' (Fig. 10).[92] According to pH-stat experiments in spherical PC/PA/cholesterol bilayers (8:1:1), dianion **41** mediates transmembrane proton translocation with a concentration dependence (range 10–80 μM) indicative for dimeric active structures. Variation of cations (Cs^+, Rb^+, K^+, Na^+) does not influence proton gradient collapse, and carboxyfluorescein is released only above 200 μM of compound **41**. Compatible with these results, relatively small, quite uniform single channels with lifetimes of 1–3 s, a specific conductance of 13.7 pS, and a linear current-voltage profile are detected in planar DPhPC bilayers.

Compared to dicarboxylate **41**, arylamines **42**–**45** are insoluble in water. This property complicates delivery, incorporation, and intervesicular channel transfer.[93,94] Biphasic kinetics observed for proton gradient collapse mediated by cyclic, branched and linear amides **42**, **44** and **45** but not ester **43** in spherical PC/PA/cholesterol membranes (8:1:1) are as expected for water-insoluble channels. The rapid initial pH-gradient collapse with 20 μM amides **44** and **45** depends on the concentration of oligomeric active structures and requires low pH to protonate at least some terminal amines. Absence of initial bursts with ester **43** implies some role of the central amides for rapid self-assembly into, maybe, TM barrel-stave channels (Fig. 3(B)). The subsequent slow proton release observed for arylamines **42**–**45** is independent of channel concentration and the nature of the electrolyte. This

behavior is consistent with the general mechanism of water insoluble channels where the overall rate is limited by intervesicular channel transfer rather than channel formation. Release of large dyes like CF from spherical membranes is mediated at millimolar concentrations only.

Incorporation of insoluble bis(metacyclophane)bolaamphiphile **42** into planar PC/PA/cholesterol membranes (8:1:1) at pH 4.7 gives multichannel currents formed by single channels with a conductance of 13.7 pS and a linear current-voltage profile. Arylamines **43**–**45** in planar DPhPC membranes at pH 4–9 give ohmic cesium channels (P_{Cs^+}/P_{Cl^-}=5.6–4.7, $Cs^+ > Na^+ > Cl^-$). The main conductance levels are multiples of a specific conductance of about 39 pS in 1 M CsCl, and subconductance levels with reduced lifetime appear infrequently. The lifetime of the main conductance decreases from branched amide **44** (277 ms) to branched ester **43** (117 ms) and linear amide **45** (64 ms), suggesting that both branching and central amides contribute to the inertness of the active supramolecules.

3.2.2. Dimeric steroid staves. Polyhydroxylated norcholentriol dimer **46** can be conceived as a facially amphiphilic semi-rigid rod of a length sufficient to span a lipid bilayer membrane (Fig. 10).[95] According to Na NMR kinetics, dimeric steroid **46** mediates the influx of sodium cations into PC/PG vesicles (95:5). The concentration dependence of this activity is in agreement with endergonic formation of a trimeric barrel-stave supramolecule as the active structure.

The branched, facially amphiphilic bolaamphiphiles **47** and **48** contain two hydrophobic and rigid steroid walls and two partially hydrophilic polyether chains with polar heads radiating from an alditol core.[96] The ability of the sterol-polyether conjugates **47** and **48** to mediate the influx of

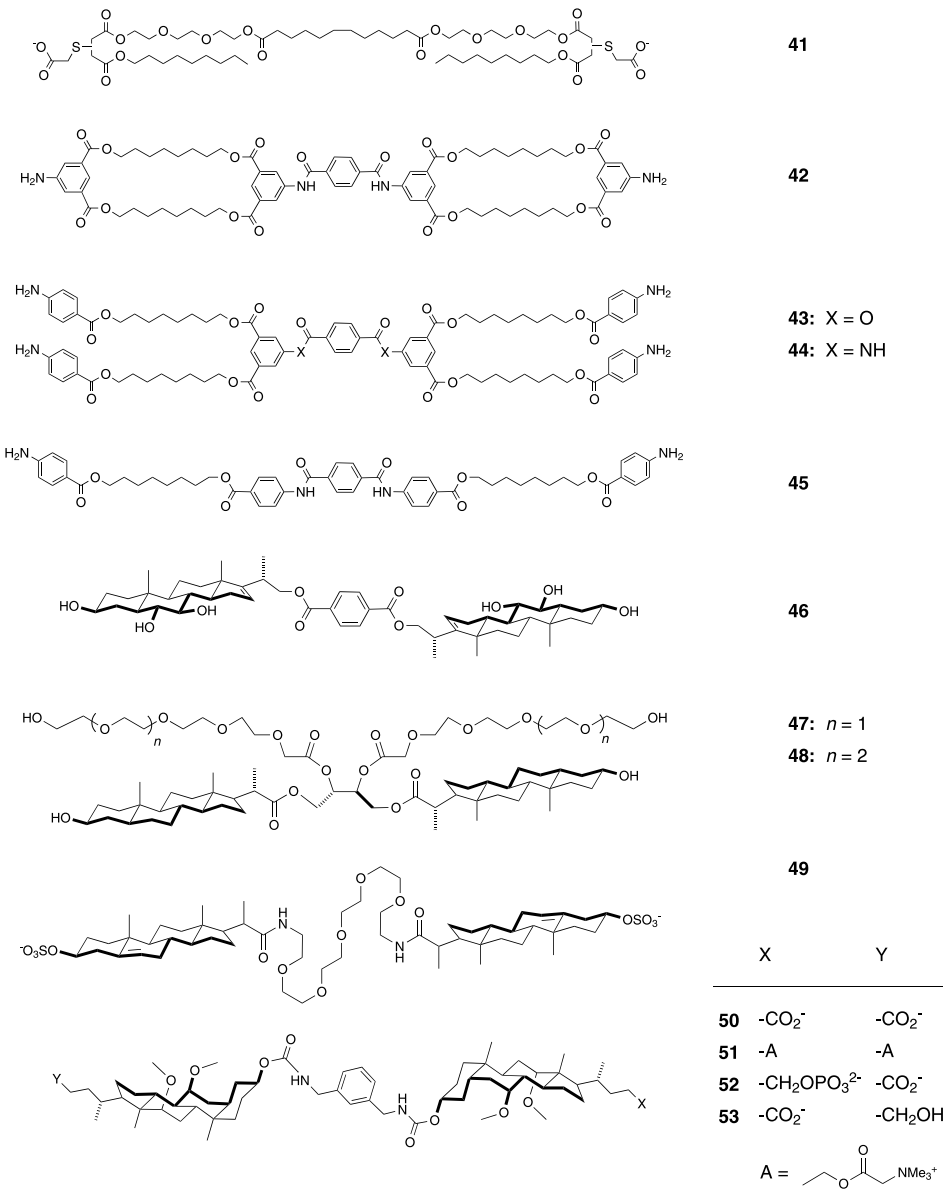


Figure 10. Synthetic ion channels formed by macrocyclic, branched and linear bolaamphiphiles and dimeric steroids. In most cases, these compounds are envisioned to serve as staves in barrel-stave supramolecules.

sodium cations into PC/PG vesicles (95:5) is about 70% of that of amphotericin B. The concentration dependence of this activity, indicative of relatively poor partitioning into the bilayer, is compatible with exergonic self-assembly and therefore not informative with regard to the stoichiometry of the active channel.

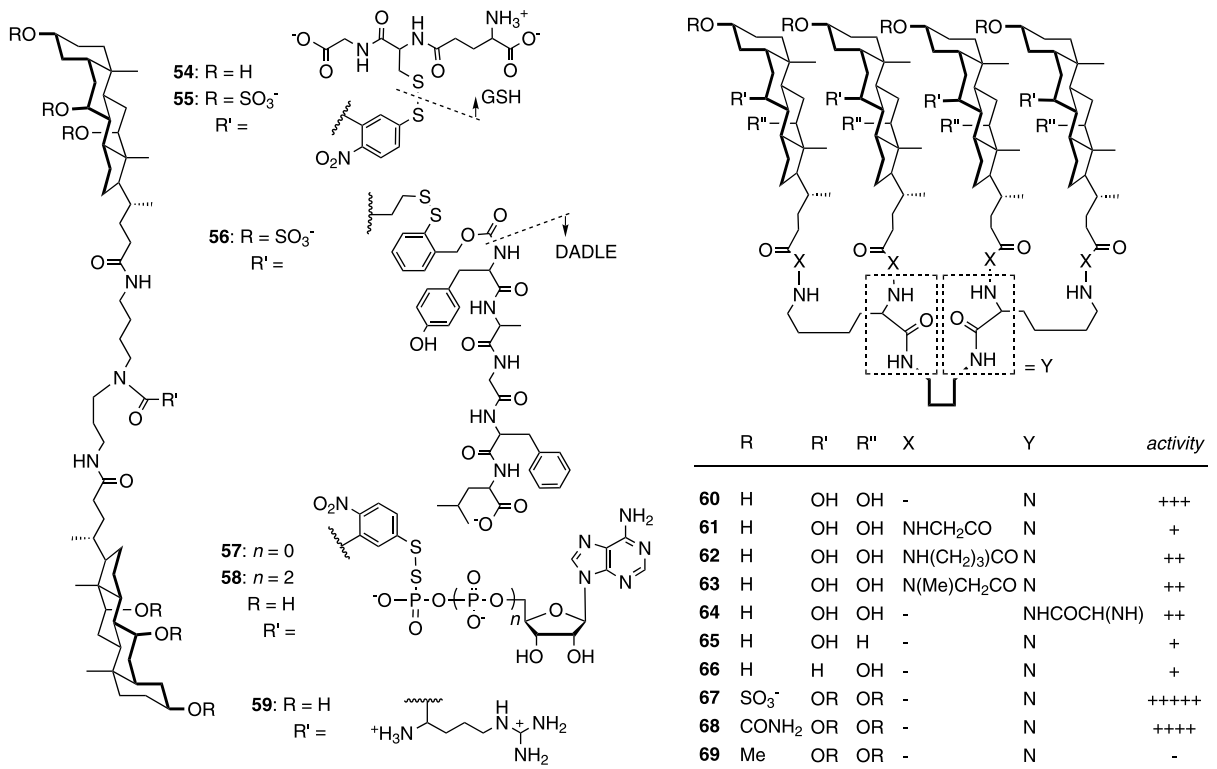
Two hydrophobic steroid scaffolds in **49** are linked with a long, flexible and ionophoric oligoethyleneglycol.[97] According to Na NMR kinetics, the activity of dimer **49** depends on the thickness of spherical bilayer membranes. Second-order kinetics in thin membranes (DP_1PC and shorter) is indicative of an active dimer, whereas the dependence of (reduced) activity on the fourth power of the monomer concentration in thick membranes (DOPC and longer) implies tetrameric active structures. Fourth-power dependence in membranes formed by a 1:1 mixture of short and long phospholipids (DM_1PC and DOPC) demonstrates, therefore, non-ideal mixing of mismatched lipids in bilayer membranes and preference of ionophores **49** to self-assemble into tetramers in thick membranes.

Different to the planar cholesterol scaffolds used in dimers **46**–**49**, dimers **50**–**53** contain cholate scaffolds.[98,99] Similar to dimer **46**, these scaffolds are linked together with a semi-rigid dicarbamate spacer, similar to dimers **47**–**49**, alkyl ethers are positioned on one side of the hydrophobic scaffold to possibly serve as ionophores. In neutral water, diacid **50** contains one negative charge at each end of the 'stave,' diamine **51** positive charges, whereas the asymmetric dimers **52** and **53** have an excess of one negative charge at one terminus. In planar soybean lecithin membranes, dianion **50** and, more surprisingly, dication **51** form cation channels (**50**: $P_{K^+}/P_{Cl^-}=17$, $K^+>Na^+$, **51**: $P_{K^+}/P_{Cl^-}=7.9$, $K^+>Na^+$) with relatively long lifetimes (10 ms to 10 s) and a relatively narrow range of low conductances (5–20 pS). When incorporated into polarized membranes in an oriented manner, the single-channel currents of asymmetric dimers **52** and **53** are different at a polarization of identical magnitude but opposite sign. Parallel self-assembly into barrel-stave supramolecules is proposed to explain this rectification.

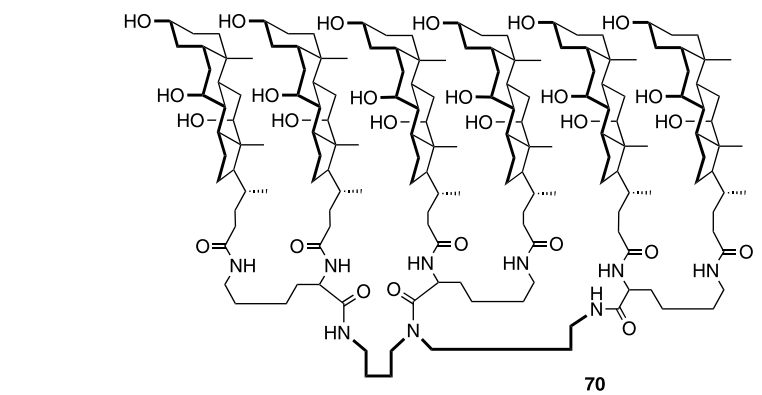
Cholate dimers **54**–**59** with hydroxy or sulfonate rather than methoxy groups for facial amphiphilicity are thought to act as carriers rather than as barrel-stave channels like **49**–**53** (Fig. 11).[100–105] A linear dependence of activity on the concentration of dimeric steroid **54** in spherical [1,2-di(1,3-*cis*-docosenoyl-2-oleyol-*sn*-glycero-3-PC]/POPG bilayers (95:5) is compatible with this view, particularly since the monomeric steroid control exhibits second-order kinetics. When entering a bilayer membrane, these dimeric steroids are thought to fold like umbrellas around the central substituents R′. The resulting compact conformers have a hydrophobic surface and hydrophilic interior containing R′. By this mechanism, hydrophilic compounds attached between the two cholate amphiphiles can translocate across bilayer membranes. Delivery of the hydrophilic glutathione (GSH) into POPC vesicles is possible using dimer **54**. Within the vesicles, the glutathione can be detached from the umbrella by disulfide exchange with an intravesicular thiol, and the resulting GSH-free umbrellas can be detected by the low-energy absorption of *p*-nitroaryl thiolates. The rate of intravesicular appearance of GSH-free umbrellas with dimer **54** is faster than with the persulfated analog **55**. Using the same strategy, the persulfated umbrella **56** is capable of delivering the opioid peptide DADLE within large unilamellar POPC/POPG/cholesterol vesicles (72:4:24). Similarly, disulfide-bridged nucleotide-umbrella conjugates **57** and **58** can move across bilayer membranes and release AMP and, less efficiently, ATP within POPC vesicles upon reaction with an intravesicular thiol.[104] In steroid dimer **59**, an arginine is incorporated between the cholate scaffolds for non-covalent delivery.[105] For instance, the guanidinium cation of the arginine residue in **59** should recognize the triphosphate anion of ATP. Indeed, dimer **59** mediates the release of ATP trapped within POPC/POPG vesicles (95:5) and the delivery of extravesicular ATP into the same vesicles with a turnover>2.4. In competition with ATP, phosphate-free guests (GSH) are not transported by umbrella **59**.

Only a few reports beyond dimeric steroids exist. According to Na NMR kinetics in spherical bilayers, transmembrane Na exchange mediated by tetrameric steroid **60** decreases rapidly with increasing membrane thickness ($DM_1PC>DP_1PC>$DOPC).[106] Supported by surface pressure experiments in planar DP_1PC monolayers, this finding can be explained by the folding of tetramer **60** into a 'unimolecular barrel-stave motif' that can span one leaflet of thin bilayers. Supported by the dependence of sodium exchange on the second power of the concentration of **60**, the stacking of two 'half-channels' on top of each other is thought to give the active supramolecule. Reminiscent of the self-assembly of gramicidin A into stacked dimers, dimeric 'barrel-stave' channels formed by **60** can also be classified as extreme cases of stacked 'incomplete' macrocycles or even as partially crosslinked stacked supramolecular rosettes (Fig. 3). Modification of the spacer and removal of hydroxyls in the cholate scaffold in dimers **61**–**66** reduce the rate of sodium exchange without changing the strong preference for thin membranes ($DM_1PC/DP_1PC=262$–2258, best for **64**) and kinetics indicative of active dimers.[107] Transformation of the hydroxyls in the cholate scaffold into sulfates and amides increases the activity of **67** and **68** in thin DM_1PC membranes by two and one orders of magnitude, respectively.[108] The selectivity for thin membranes is maximal with persulfated tetrameric steroid **67** ($DM_1PC/DOPC=2.1\times10^7$). Interesting in comparison with dimeric steroids **49**–**53** (Fig. 10), permethylated tetrameric steroid **69** is only weakly active in DM_1PC vesicles. The activity of persulfonated tetrameric steroid **67** further increases in hypotonic spherical DPPC, identifying an ionophore that recognizes osmotically stressed membranes.[109]

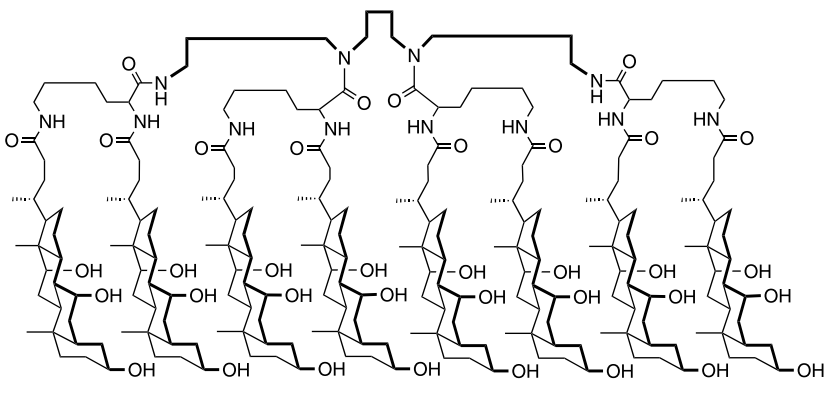
Hexameric and octameric steroids **70** and **71** are constructed based on the scaffold established in tetrameric steroid **64**.[110] In Na NMR kinetics, the rate of sodium/lithium exchange in spherical POPC membranes mediated by oligomeric steroids increases exponentially with the number of cholates per monomer. The dependence of activity on monomer concentration remains, however, constant and indicative for dimeric supramolecules. These findings support a universal active suprastructure composed of two covalent barrel-stave



	R	R'	R''	X	Y	*activity*
60	H	OH	OH	-	N	+++
61	H	OH	OH	$NHCH_2CO$	N	+
62	H	OH	OH	$NH(CH_2)_3CO$	N	++
63	H	OH	OH	$N(Me)CH_2CO$	N	++
64	H	OH	OH	-	NHCOCH(NH)	++
65	H	OH	H	-	N	+
66	H	H	OH	-	N	+
67	SO_3^-	OR	OR	-	N	+++++
68	$CONH_2$	OR	OR	-	N	++++
69	Me	OR	OR	-	N	-



70



71

Figure 11. Dimeric and oligomeric steroids that may act as carriers (**54**–**59**)—folding like umbrellas around hydrophilic guests—or as barrel-stave-like channels formed by two covalent dimers spanning one leaflet each (**60**–**71**).

foldamers stacked on top of each other (rather than membrane-spanning staves as in the case of dimers **46**–**53**).

3.2.3. *p*-Oligophenyls as staves in rigid-rod β-barrels. The cylindrical self-assembly of rigid-rod β-barrel pores **72**–**77** is preorganized by the non-planarity of *p*-octiphenyl

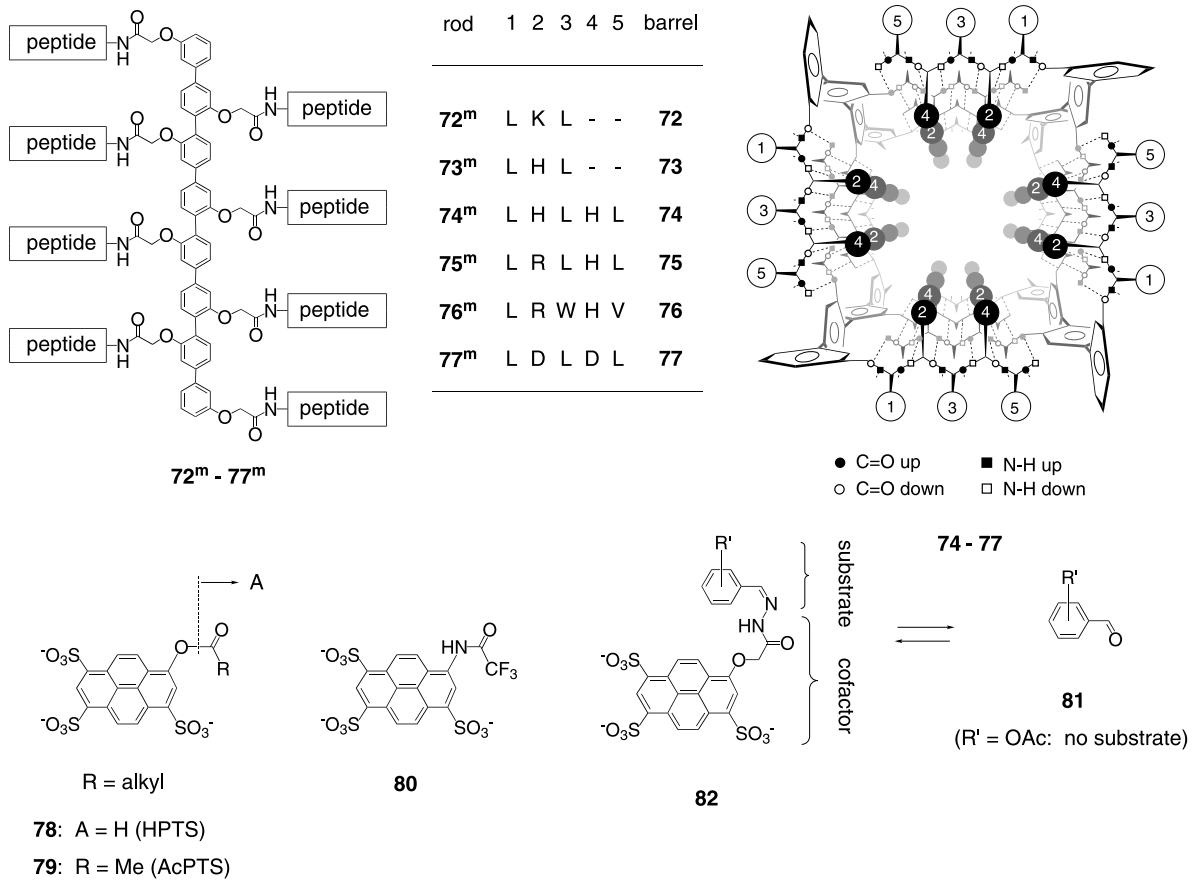


Figure 12. Synthetic multifunctional pores formed by self-assembly of *p*-octiphenyl staves **72**^{m}–**77**^{m} into rigid-rod β-barrels **72**–**77** with selected substrates **78**–**82** of catalysts **73**–**75** (see Ref.118 for possible R's in **81** and **82**). An axial view of rigid-rod β-barrels **74**–**77** is added to illustrate the peptide backbones in 8-stranded β-sheets (solid lines) with an indication of hydrogen bonds (dotted lines), staves per barrel (4), *p*-octiphenyl chirality (*M,P,M,P,M,P,M,P*), orientation of backbone amides (dipole-free), and location of the amino-acid residues (external black on white, internal white on black; single-letter abbreviations). Compare with side view of push–pull barrels in Figure 13.

staves in octapeptide-*p*-octiphenyl monomers **72**^{m}–**77**^{m} (Fig. 12). Rational, variable functionalization of the outer as well as the inner pore surface is possible using the β-sheet 'hoops'. Synthetic multifunctional pores formed by rigid-rod β-barrels have been reviewed recently and will not be covered in much detail.[111]

Rigid-rod β-barrel **72** is composed of hydrophobic leucines at the outer and cationic lysines at the inner surface. In planar EYPC bilayers, rigid-rod β_3-barrel **72** forms ohmic, large (conductance of 3.6 nS, corresponding to an inner 'Hille diameter' of $d_H \approx 25$ Å) and long-lived pores (lifetime beyond minutes)[112] that can be blocked with B-DNA [$d(AC)_7/d(GT)_7$: K_D=180 nM].[113] This model B-DNA also blocks CF efflux from spherical EYPC bilayers. Activity in these vesicles depends on monomer concentration in a manner indicative for active hexamers. The pH dependence of pore **72** is compatible with the ICR model (i.e. maximal activity at intermediate Internal Charge Repulsion, here partial amine protonation at pH≈7).[114] Structural studies by fluorescence depth quenching demonstrate transmembrane orientation of the *p*-octiphenyl fluorophores, absence of intervesicular transfer and formation of formal second-sphere inclusion complexes EYPC-SUVs⊃barrel **72**⊃B-DNA during pore blockage.

Replacement of the internal lysines by histidines gives rigid-rod β_3-barrel **73**.[115] The ohmic, long-lived pores **73** (lifetime several seconds) have a conductance compatible with a tetrameric active structure (0.7 nS, $d_H \sim 5.2$ Å). At high concentration, HPTS **78** weakly blocks pore **73** (K_D=1.5 mM) with a voltage dependence indicative of peripheral guest association on top of the contracted barrel (l_A=0.9 Å). In spherical EYPC bilayers, a pH profile in agreement with the ICR model, linear concentration dependence indicative of preassembly of 'prepores' in water, and weak esterolytic activity are observed.[114,115]

Barrel expansion by β-sheet elongation from rigid-rod β_3-barrel **73** to rigid-rod β_5-barrel **74** in planar EYPC bilayers gives ohmic pores with reduced lifetime (5 ms) and increased conductance (1.2 nS, $d_H \sim 7.0$ Å) (Fig. 1(B)). This inner diameter is large enough for HPTS **78** to enter pore **74** for >1000-times improved blockage compared to **73** (K_D=200 nM, l_A=2.7 Å).[115,116] Prepores of **74** in water and fibrils formed above 3 μM can be observed by AFM.[117] Pore **74** catalyzes the hydrolysis of esters[116,118] like AcPTS **79** (ground-state stabilization ΔG_{GS}=35 kJ/mol, transition-state stabilization ΔG_{TS}=56 kJ/mol),[119] activated amides like **80**,[118] carbamates[118] and RNA.[120] Because of their superb recognition by cationic residues at the inner barrel surface, pyrene-1,3,6-trisulfonates also serve well as cofactors to convert otherwise inaccessible substrates like **81** as hydrazide conjugates like **82**.[118]

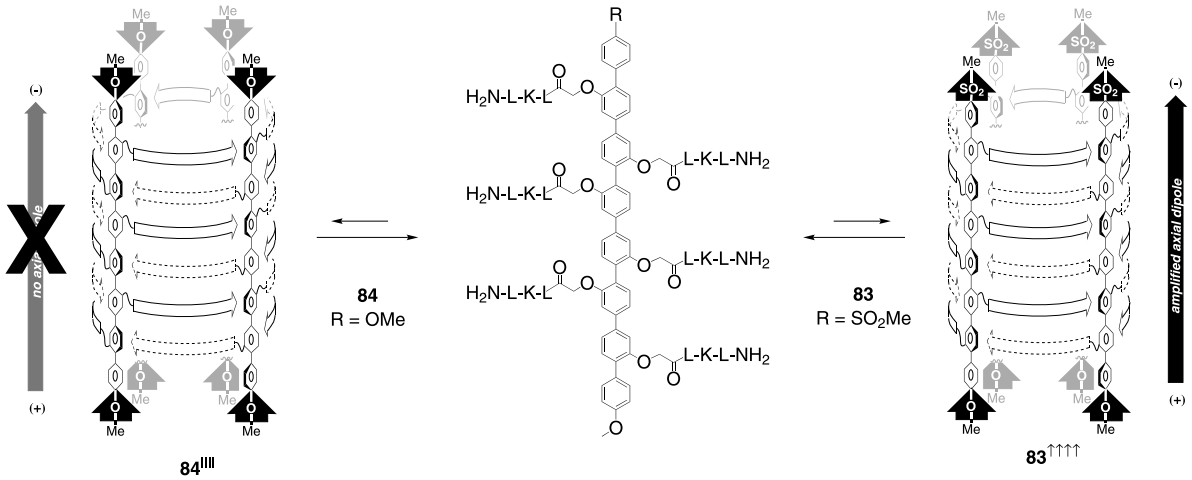


Figure 13. Synthetic multifunctional pores formed by self-assembly of *p*-octiphenyl staves (**83**, **84**) into rigid-rod push–pull (**83**$^{\uparrow\uparrow\uparrow\uparrow}$) and push-push (**84**$^{\text{IIII}}$) β-barrels (arrows between *p*-octiphenyl staves indicate 6-stranded β-sheets formed by tripeptides LKL; single-letter abbreviations). Compare with axial view of rigid-rod β-barrels in Figure 12.

In planar EYPC bilayers, rigid-rod β_5-barrel **75** with internal HR dyads forms ohmic pores with, in sharp contrast to HH-rich pores **74**, long lifetime (beyond minutes), comparably low conductance (0.3 nS, d_H~3.3 Å) and cation selectivity (P_{Cl^-}/P_{K^+}=0.5) that inverts into anion selectivity at pH≤5 (P_{Cl^-}/P_{K^+}=3.8) (Fig. 1(A)).[121] ESI-MS data support the view that the latter two less usual pore characteristics originate from permanent immobilization of phosphate counterions within the R-rich pore. These pores can be blocked in planar (HPTS **78**: K_D=3 μM) and spherical EYPC bilayers (poly-L-glutamic acid, K_D (0 mV)=150 nM, pH 4.5). The use of membrane polarization for α-helix recognition by pore **75** provides a rare example for molecular recognition by remote control, here long-range dipole-potential interactions, rather than the usual physical contact (poly-L-glutamate, K_D (−150 mV)=13 nM, pH 4.5).[122] Membrane polarization further accelerates the esterolysis of AcPTS within synthetic catalytic pore **75** (ΔG_{GS}=30 kJ/mol, ΔG_{TS}=52 kJ/mol, steering factor f_{off}=1.3).[119]

The introduction of external LWV triads in pore **76** with internal HR dyads gives short-lived, ohmic pores with, as with pore **75**, inversion of anion/cation selectivity at pH≤5 and blockage by HPTS **78** (K_D=3 μM) (Fig. 1(C)).[123] Fluorescence depth quenching reveals transmembrane *p*-octiphenyl orientation near physiological pH (with decreasing pH, the rigid-rod fluorophore accumulates in the middle of the membrane due to increasing external charge repulsion). Together with non-linear concentration dependence, these depth-quenching experiments suggest that even these 'dynamic' pores are barrel-stave tetramers and not micellar pores. In spherical EYPC bilayers, pore **76** can be blocked by nucleotide mono-, di- and triphosphates, single- and double-stranded polynucleotides [poly(dAT), polyU, polyA, polyC], anionic and neutral polypeptides (polyE, E, Q), polysaccharides like heparin or hyaluronan, and more.[124,125] This adaptable blockage is of use for noninvasive 'naked-eye' detection of the activity of the corresponding enzymes with pore sensor **76** (DNA polymerase, exonuclease, RNase, glycosyltransferase, heparinase, hyaluronidase, proteases, kinases, aldolase, apyrase).

In planar EYPC bilayers, rigid-rod β_5-barrel **77** with an anionic interior forms ohmic, cation-selective (P_{Cl^-}/P_{K^+}=0.2), short-lived (lifetime <1 ms) high-conductance pores (0.3 nS, d_H~10 Å).[121] Binding of Mg^{2+} by the internal aspartates (K_D=5.3 mM) results in pore stabilization (lifetime 12 ms) and deletion of anion selectivity (P_{Cl^-}/P_{K^+}=0.7). A bell-shaped pH profile maximal at pH 6, biphasic concentration dependence, and no flippase activity support a barrel-stave tetramer as the active structure.[126,127] Internal charge inversion by Mg^{2+}-binding is reflected in CF release from vesicles by the resulting metallopore **77**⊃Mg^{2+}. Blockage of this metallopore with nucleotides, thiamine and inositol phosphates, polyacetylenes, heparin, and so on, is relatively weak due to poor Mg^{2+} complexation but applicable to enzyme sensing (apyrase, aldolase).[124]

Because the amide dipoles are cancelled out in β-sheets, rigid-rod β-barrels **72**–**77** form ohmic pores. Non-ohmic behavior can be introduced with an axial dipole in push–pull staves **83** (Fig. 13).[128,129] Voltage-gated (gating charge≈0.9), parallel self-assembly into stable (lifetime beyond seconds), weakly lyotropic ($I^-\geq Cl^-\geq OAc^-\geq F^-$), anion-selective ($P_{Cl^-}/P_{K^+}$=3.7) and oriented (closing with sign inversion of applied voltage) β-barrel (ohmic without sign inversion) push–pull tetramer **83**$^{\uparrow\uparrow\uparrow\uparrow}$ occurs in planar as well as in spherical EYPC bilayers (Fig. 2). Fluorescence depth quenching and CD studies in polarized vesicles suggest voltage-dependent partitioning as the origin of voltage gating. Surface potentials inactivate push–pull pore **83**$^{\uparrow\uparrow\uparrow\uparrow}$. Replacement of the terminal methylsulfone π acceptor in **83** by a methoxy π donor gives dipole-free staves **84** that self-assemble into voltage-independent, stable pores **84**$^{\text{IIII}}$ (lifetime beyond seconds).

3.3. Synthetic polymers

The by now classical ion channels formed by biological polymers are the PHB channels.[28] However, several ion channels/pores formed by synthetic polymers have been reported before (polyalanine,[130] polyisocyanates,[68] polyacrylates,[131] and so on; see Figure 5 for polyglutamine channels) and within the timeframe covered in this review.

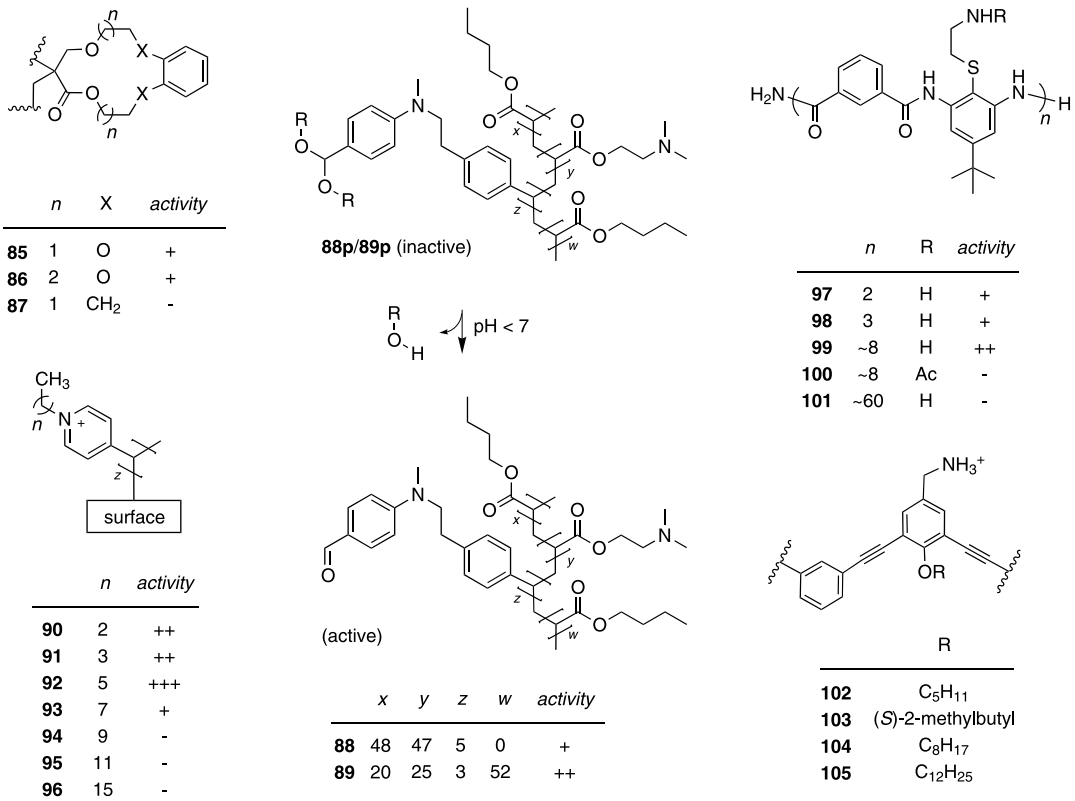


Figure 14. Synthetic ion channels and pores formed by ionophoric (**85**, **86**), 'smart' (**88**, **89**) and cationic (**90**–**105**) polymers of interest as antibiotics (**90**–**105**) and for drug delivery with triggered endosomal escape (**88**, **89**).

Although synthetic polymers seem predestined to act as monomers folded either into barrel-stave- or helical barrel-hoop-like conformers,[28] supramacromolecular active structures, particularly barrel-stave motifs, as well as more complex micellar motifs cannot be excluded (Fig. 3).

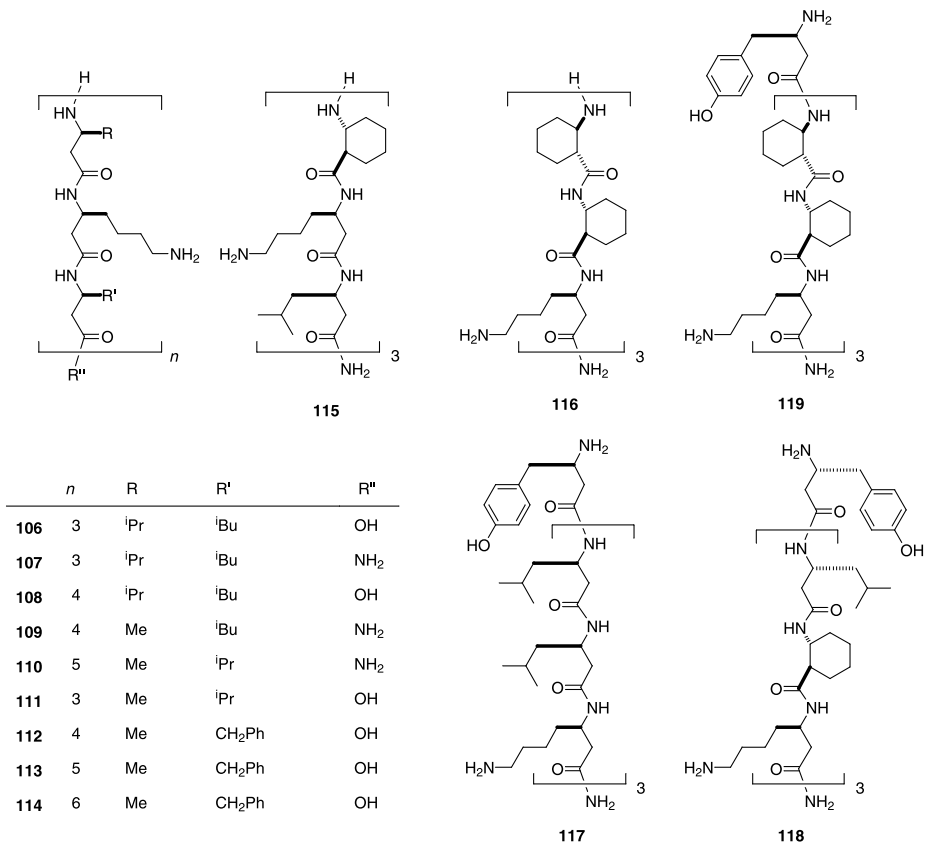
In dihexadecyl phosphate vesicles, polymeric crown ethers **85** and **86** accelerate the translocation of Co^{3+} (Fig. 14).[132,133] Removal of oxygens in macrocycle **87** results in inactivity. The extraction of picrate salts into bulk 1,2-dichloroethane membranes by polycrown **85** and the corresponding monomer is ion selective ($Li^+ > Na^+ \approx K^+ > Rb^+ > Cs^+$). Picrate extraction into bulk membranes by polymer **86** ($Na^+ > K^+ \approx Rb^+ > Cs^+ > Li^+$) is clearly more efficient than that by the corresponding monomer. A unimolecular channel structure is proposed.

'Smart' polymers **88** and **89**[134,135] are designed based on earlier experiences with membrane-disruptive activities of polymers like poly(propylacrylic acid).[131,136] In masked polymers **88p/89p**, the membrane-disruptive backbone is covered with inactive polymers via an acid-labile *p*-amino-benzaldehyde acetal. At pH<7, acetal hydrolysis is expected to release the membrane-disruptive polymers **88/89** together with ROH (R=fluorophores, peptides and carbohydrates). This pH gating is invented to specifically lyse endosomes and deliver hydrophilic ROH to the cytoplasm. Hemolytic activity of encrypted polymers at pH<5.4 (but not pH 7.0) increases with polymer hydrophobicity. Hemolysis is indicative of the presence of large, micellar pores or more dramatic membrane disruption.

Surface-attached poly(vinyl-*n*-alkylpyridinium) **90**–**96** can have, depending on the alkyl chain length, bactericidal activity that is attributed to membrane disruption.[137] Cationic *N*-alkylated polyethyleneimines exhibit similar activities, whereas neutral and zwitterionic polyethyleneimines obtained by acylation and carboxyalkylation are inactive.[138,139]

Cationic oligo/polymers **97**–**101** are designed to exhibit facial amphiphilicity like certain pore-forming α-helical peptides used by diverse organisms as antibiotics.[140] The best antimicrobial activities are reported for a 'polydisperse' octamer **99**, whereas removal of the positive charge in octamer **100** results in inactivity. Dimer **97** also accelerates calcein efflux from anionic SOPS/SOPC vesicles. Recent rapid progress on this topic, already beyond the time frame of this review, is noted.[140b,c]

Poly(*m*-phenylene ethylenes) **102**–**105** may exhibit a marvelous structural plasticity.[141,142] In extended conformation, they are facial amphiphiles with a semi rigid-rod scaffold that may assemble into supramolecular polymers looking, reminiscent of β-sheets, like pleated sheets. Supramolecular oligomerization into barrel-stave pores represents an attractive, so far not considered, alternative. Poly(*m*-phenylene ethylenes) are, however, not rigid-rod polymers. Rotation of every fourth single bond by 180° can, with sufficiently small alkyl groups R, produce a hollow 6.0-helix with a hydrophilic outer and hydrophobic inner surface. Such a rigidified foldamer resembles the β-helix formed by gramicidin A with the advantage that not only the outer, but also the inner, surface can, in principle, be



	n	R	R'	R''
106	3	^{i}Pr	^{i}Bu	OH
107	3	^{i}Pr	^{i}Bu	NH_2
108	4	^{i}Pr	^{i}Bu	OH
109	4	Me	^{i}Bu	NH_2
110	5	Me	^{i}Pr	NH_2
111	3	Me	^{i}Pr	OH
112	4	Me	CH_2Ph	OH
113	5	Me	CH_2Ph	OH
114	6	Me	CH_2Ph	OH

Figure 15. Cationic β-peptides with antibiotic activity, presumably acting as amphiphilic helices (compare Fig. 16) that form micellar pores in anionic bilayer membranes.

functionalized and expanded by insertion of linear, e.g. *p*-phenylene ethylene modules.

At air–water interfaces, polymers **102**–**105** form stable monolayers with a repeat of ~42 Å^2 that is compatible with an extended conformer (length=11 Å) and a π–π stacking distance of 4 Å. This result indicates interfacial assembly into stacked, linear, facially amphiphilic rods with ammonium cations in the water and hydrophobic alkyls in the air. Emission spectra of **102** in water are in support of self-assembly into such supramacromolecules. Polymers **102**–**105** mediate calcein efflux from anionic SOPS/SOPC vesicles (1:9) with a concentration dependence that may be indicative for oligomeric active structures.

3.4. Helical β-peptides

Facially amphiphilic α-helical peptide rods can be considered as ideal staves for the construction of barrel-stave pores. In practice, however, barrel-stave pores like those formed by alamethicin are rare. The weak helix–helix (or stave–stave) interactions fail to prevent the collapse of α-barrels into contracted α-helix bundles with an interior large enough for inorganics but not organics. Contracted α-helix bundles are indeed often found in biological ion channels, whereas the larger pores are usually formed by β-barrels. Additionally, because of weak helix–helix interactions, amphiphilic α-helices often partition to the interphase with the hydrophobic face towards the membrane and the hydrophilic face towards the water. Driven by diffusion, local electric fields, membrane potential or other effects, interfacial amphiphilic α-helices can then cause the formation of transient micellar pores or more catastrophic membrane damage by detergent-like 'carpets'.

Much ongoing research with amphiphilic α-helices is beyond the topic in this review. However, several membrane active helices formed by abiotic peptoid or peptide scaffolds containing β- rather than α-amino acids have been reported over the years.[143] β-Peptides **106**–**119** form 3.0-(*M*)-helices (Figs. 15 and 16). Hydrophobic–hydrophilic–hydrophobic triads will, therefore, produce an amphiphilic helix with a hydrophilic face covering roughly one-third (120°) of the surface. Building on previous results from a series of β-peptides with β^3-HVal-β^3-HLys-β^3-HLeu triads including **106** and **108**, β-peptides **109** and **110** are designed to decrease helix hydrophobicity.[144] C-capped β-peptides **109** and **110** have similar antimicrobial, but clearly reduced hemolytic, activity compared to the more hydrophobic, uncapped β-peptide **108** (B/M-selectivity 'bacteria/mammals'=110–180 versus 15). This suggests that the nonspecific formation of large pores or 'carpets' is reduced, but the activity to specifically disrupt bacterial membranes is maintained. This selectivity is explained by selective binding of helical β-peptides **109** and **110** to anionic [SOPS/SOPC 1:9, K_D=1.4 μM (**109**)/0.3 μM (**110**)] compared to neutral vesicles [SOPC, K_D=15 μM (**110**)]. Both peptides mediate calcein leakage from SOPS/SOPC vesicles (1:9), acting presumably via micellar pores with, however, clearly different active structures.

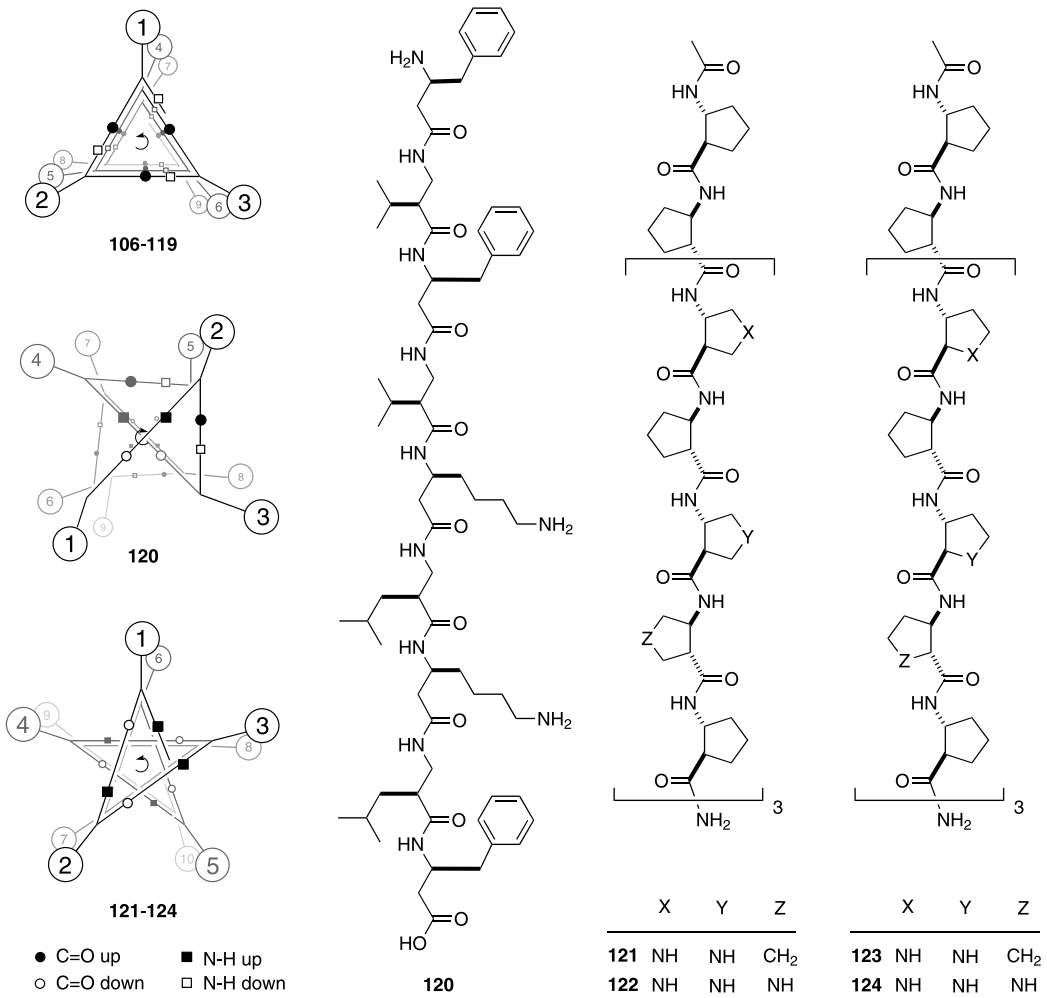
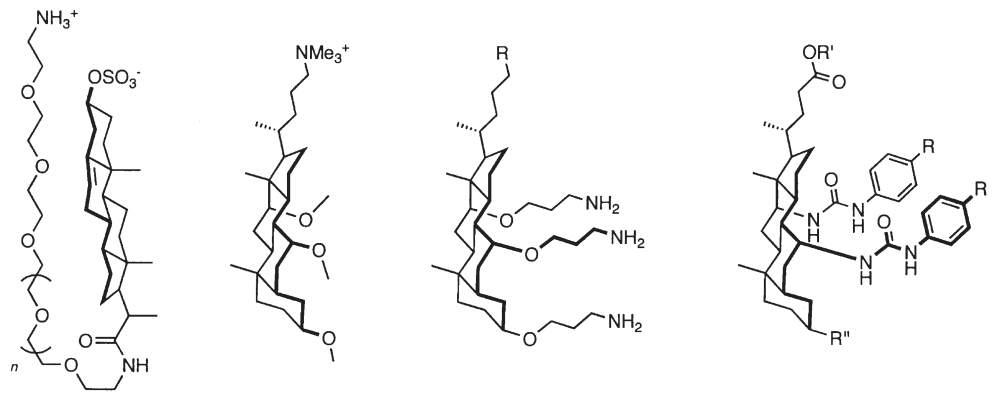


Figure 16. Cationic β-peptides with antibiotic activity that may act as amphiphilic helices, forming micellar pores in anionic bilayer membranes. Schematic axial views of **106**–**119** (top, left; compare Fig. 15), **120** (middle, left) and **121**–**124** (bottom, left) are added to illustrate the β-peptide backbone in helical conformation (solid lines) with the indication of residues per turn, axial chirality, orientation of backbone amides, and location of the amino-acid residues.

β-Peptides **111** and **112** with β^3-HAla-β^3-HLys-β^3-HPhe triads exhibit a concise spectrum of antimicrobial activity, whereas the longer analogs **113** and **114** are less active.[145]

The antimicrobial activity of β-peptide **106** with β^3-HVal-β^3-HLys-β^3-HLeu triads increases with C-capping in β-peptide **107**. The enantiomers of **106** and **107** show roughly unchanged activity.[146] Introduction of the cyclic β-amino acid 'ACHC' in β-nonapeptides **115** and **116** rigidifies the enantiomer of **107**. The same rigidification is probed with a series of β-decapeptides **117**–**119** that are known to self-assemble into tetra- to hexameric bundles.[147] In water, the content of facially amphiphilic 3.0-(*M*)-helices increases with cyclohexyl rigidification in both series. The flexible β-nonapeptide *ent*-**107** forms helices only in more hydrophobic solvents, and a rigidified but scrambled control forms helices but is neither antibiotic nor hemolytic. The antimicrobial activity of all peptides (*ent*-**107**, **115**–**119**) is quite similar, indicating independence of helical propensity. Uncapped analog **106** is less active. The weak hemolytic activity of β-nonapeptides *ent*-**107**, **115** and **116** increases slightly with helical propensity, whereas that of 'bundled' β-decapeptides **117**–**119** is clearly higher. Leakage of β-galactosidase from *B. subtilis* mediated by β-nonapeptides *ent*-**107**, **115** and **116** indicates the formation of large micellar pores or lysis.

β-Nonapeptide **120** with alternating β^2- and β^3-amino-acid residues forms $(P)_{12/10}$-helices in methanol and acidic water that unfold in neutral water (Fig. 16).[148] The two cationic residues are positioned to end up on the same side of this more complex foldamer to produce facial amphiphilicity. β-Nonapeptide **120** has antimicrobial activity (B/M-selectivity=2–35). The folding of rigidified β-peptides **121**–**124** into 2.5-(*M*)-helices implies that hydrophilic–hydrophobic–hydrophilic–hydrophobic–hydrophobic pentads will produce facial amphiphilicity.[149–151] β-Peptides **121** and **123** with a hydrophilic face that covers about 40% of the helix surface exhibit superb antimicrobial activity and high B/M-selectivity, whereas 2.5-(*M*)-helices **122** and **124** with a 60%-cationic face are nearly inactive. β-Peptides **121** and **123** mediate leakage of β-galactosidase from *B. subtilis*. Moreover, β-peptide **121** selectively binds to and lyses anionic vesicles of diverse lipid composition, presumably by promoting negative bilayer curvature and the formation of non-bilayer phases.[151]



	n	activity
125	1	+
126	3	-

127

	R	selectivity
128	OH	++
129	$NH(CH_2)_7Me$	+
130	$NH(CH_2)_3NH$-$(CH_2)_3NH_2$	+++

	R	R'	R"	activity
131	H	$C_{20}H_{41}$	$N(CH)_3^+$	n.d.
132	NO_2	Me	OAc	+++++
133	H	Me	OAc	+++
134	OMe	Me	OAc	++
135	Me	Me	OAc	+

Figure 17. Synthetic carriers, channels and pores formed by monomeric steroids. Synthetic cationic steroid antibiotics **128**–**130** may act by forming micellar pores in anionic membranes, neutral steroids as anion carriers (**132**–**135**) or supramolecular ion channels (**125**–**127**).

3.5. Monomeric steroids

As a first step towards 'complex minimalist systems,' monomeric steroid ionophores will be summarized next. Whereas dimeric steroids are often used as semi-rigid, facially amphiphilic staves in barrel-stave motifs (Figs. 3 and 10), the situation becomes ironically, more complex with simplification of the ionophore structure. Cutting a barrel-stave pore in the middle could evidently produce two stacked barrel-stave pores that, according to the classification proposed in the introduction, represent the simplest expression of a barrel-rosette pore (Fig. 3). However, micellar motifs including toroidal pores and lytic carpets on the one hand and carrier mechanisms on the other seem to become more dominant with structural simplification.

Steroid ionophore **125** illustrates this transition from minimalist barrel-stave to minimalist barrel-rosette motifs convincingly (Fig. 17).[152] According to Na NMR kinetics, ionophore **125** acts as dimer in DM_1PC vesicles with or without 30% ergosterol, whereas a less active tetramer operates in DM_1PC vesicles with 30% cholesterol. This difference can be explained by dimerization of facially amphiphilic hairpin **125** into a dimeric barrel-stave channel spanning the thin DM_1PC-ergosterol bilayers, whereas a stacked dimer (i.e. a minimal barrel-rosette channel) is needed to span a swollen DM_1PC-cholesterol bilayer. This interpretation is supported by exclusively tetrameric active suprastructures in the thicker DP_1PC membranes with or without cholesterol or ergosterol. Steroid ionophore **126** is more active in ergosterol-rich compared to cholesterol-rich membranes composed of unsaturated phospholipids. Recognition of ergosterol-rich membranes is of interest for the development of fungicides.

Analogous to the barrel-stave motif envisioned for the dimeric analogs **50**–**53** (Fig. 10), a minimalist barrel-rosette channel with ammonium cations at the interface and methoxy groups lining the ion-conducting pathway is proposed as the active structure of ohmic ion channel **127**. In planar bilayers, this channel has high open probability, a mean lifetime of 300 ms and conductances of 3–10 pS (500 mM NaCl, pH 7.2).[153]

Similar to most cationic α- and β-peptide antibiotics (CPAs, Figs. 15 and 16), cationic steroid antibiotics (CSAs) **128**–**130** are thought to act as lytic 'carpets' after binding specifically to lipid A in bacterial outer membranes.[154] Compared to squalamine mimics, these cationic cholates have reduced hemolytic activity, i.e. antibacterial activity with improved B/M-selectivity. This selectivity increases with hydrophilic (**130**) and decreases with hydrophobic side chains (**129**).

Steroid monomer **131** acts as anion carrier in bulk chloroform membranes.[155] A selectivity sequence different from the Hofmeister series is indicative of anion recognition (Cl^->Br^->NO_3^->I^->AcO^-). Plausible support of a carrier mechanism for monomeric steroids **132**–**135** by less than first-order kinetics and activity in DPPC vesicles only above phase transition does not necessarily exclude the formation of ion channels.[156] In POPC/cholesterol vesicles (7:3), ionophores **132**>**133**>**134**>**135** mediate anion antiport with Cl^->NO_3^->HCO_3^->SO_4^{2-} selectivity. This sequence corresponds to the anion affinity of the ionophores [(sub)micromolar K_Ds in chloroform]. Antiport inhibition by anions like SO_4^{2-} results in membrane polarization. Ionophore **132** also depolarizes epithelia cells in an anion-selective manner. CF efflux from POPC vesicles mediated by ionophores **132**–**135** indicates that a mechanism different from a carrier mechanism operates under these conditions. Neutral ionophores like **132**–**135** also translocate neutral PC headgroups from one interphase to the other, i.e. show flippase activity,[157] and ionophores like **131** mediate flip–flop of anionic PS headgroups.[158]

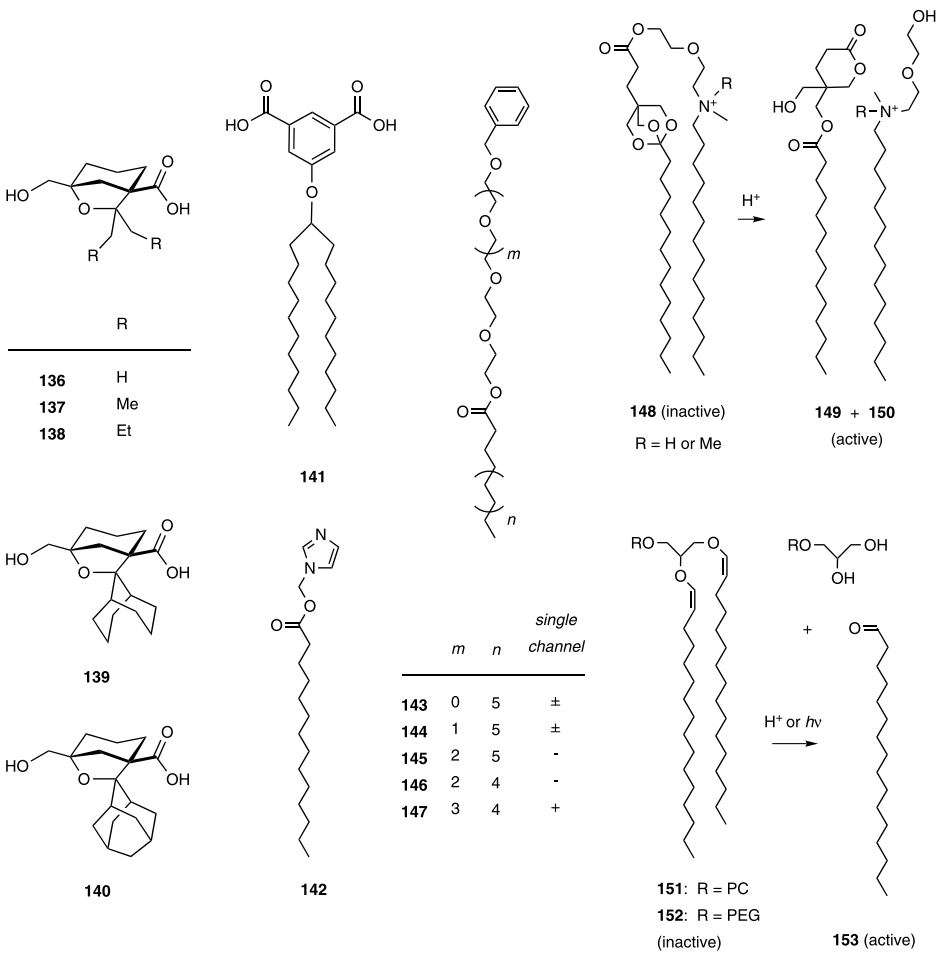


Figure 18. 'Minimalist' amphiphiles as synthetic ion channels and pores. Bicycles **136**–**140** may act as genuine barrel-rosette channels, and 'smart' single-chain amphiphiles (**142**, **149/150**, **153**) as 'micellar pores' in response to acid or light.

3.6. Complex minimalist systems

Although the creation of 'barrel-rosette' synthetic ion channels and pores assembled from genuine supramolecular rosettes seems only a matter of time, the activity of these classical motifs in bilayer membranes remains to be demonstrated.[159–162] However, membrane-active amphiphiles that could form such genuine barrel-rosette pores have attracted considerable attention over the past few years. Because suprastructural complexity seems to increase with structural simplicity, these approaches are referred to as complex minimalist systems.

In the solid state, bicyclic hydroxyacids **136** exist as porous tubes with a hydrophobic interior and hydrophobic exterior (Fig. 18).[163,164] These tubes are formed by stacked rosettes that are held together by hydrogen bonds in the plane of the rosette. According to Na NMR kinetics, bicyclic hydroxyacids **136**–**140** accelerate sodium exchange across spherical PC bilayers. As elaborated in the introduction, the linear concentration dependence of this activity does not necessarily exclude the existence of supramolecular 'barrel-rosette' ion channels.

The supramolecular rosette formed by isophthalic acids is a classical motif of exceptional beauty. Out of a set of 17 tested isophthalate analogs, however, only amphiphile **141** forms ion channels in planar PC/PS/cholesterol membranes (8:1:1).[165] Addition or removal of two methylenes in the alkyl chain already annihilates ion channel activity. The observed channels are ohmic, quite stable (lifetime of seconds), small (conductance of 15.4 pS in 1 M KCl) and cation selective ($Cs^+ > K^+ > Na^+$). The observed conductance is, however, incompatible (i.e. much too small) with the envisioned barrel-rosette motif.

Many minimalist amphiphiles similar to isophthalate **141** are known to permeabilize bilayer membranes. Among several tested single-chain amphiphiles, myristoyloxymethylimidazole **142** is most efficient in mediating pH-dependent hemolysis, being active in cationic form at pH 5.5 but inactive in neutral form at pH 7.0.[166] In spherical DPPC membranes, fatty acid-oligo(ethyleneglycol) esters **143**–**147** all mediate proton gradient collapse with similar, relatively weak activity (5–20 μM).[167] In planar soybean PC/cholesterol bilayers (9:1), only the most hydrophobic single-chain amphiphile **147** forms homogenous ohmic ion channels, with low conductance (26 pS), lifetimes of 0.2–2 s and an apparent Eisenman I selectivity dominated by cation dehydration rather than recognition ($Cs^+ > K^+ > Na^+$). The least hydrophobic single-chain amphiphiles **143** and **144** form heterogenous single channels, whereas the intermediate **145** and **146** are inactive or show carrier-like behavior in planar bilayers. A

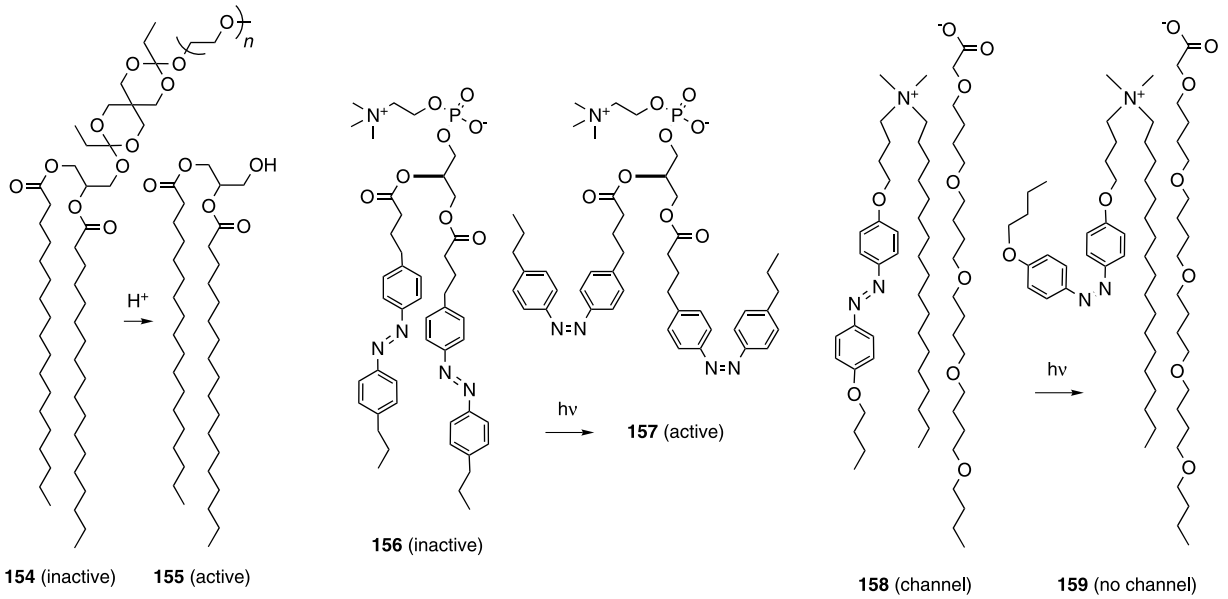


Figure 19. Membrane-active 'smart' double-chain amphiphiles, expected to form 'micellar pores' (**155** and **157**) or self-assemble into ion channels (**158**) in response to acid or light.

barrel-stave motif (Fig. 3(B)) as the common active structure is not supported by the reported concentration dependence of activity, the lack of a clear-cut dependence of activity on amphiphile length and the varied behavior in conductance experiments; contributions from more complex active structures are likely.

The in situ formation of single-chain amphiphiles is of interest for controlled drug release from vesicles. Research on triggered release of intravesicular drugs is well developed and continuously reviewed.[168,169] Acid-catalyzed release is of much interest because liposomal delivery occurs by receptor-mediated endocytosis to the mildly acidic endosomes. From there, either release into the cytoplasm or degradation in the lysosome is possible. One strategy to prevent the latter is the triggered release of amphiphiles from the vesicle carrier to transiently disrupt the endosomal membrane. Acid-catalyzed hydrolysis of 3,5,8-trioxabicyclo[2.2.2]octane followed by transesterification converts the inactive cation **148** into membrane-disruptive single-chain amphiphiles **149** and **150**.[170] Probably the best developed system for either acid- or light-triggered release of membrane-active single-chain amphiphiles is inspired by plasmalogen photooxidation.[169] Triggered cleavage of the vinyl ethers in double-chain amphiphiles **151** and **152** produces single-chain fatty aldehydes **153** (or acids) that form micellar pores (Fig. 3(E)) or induce more dramatic lamellar-hexagonal phase transitions and membrane fusion, particularly in the presence of (DO)PE in the vesicle. Poly(ethylene glycol) (PEG) headgroups as in amphiphile **152** are often added to stabilize drug-loaded vesicles during circulation before controlled release.

Triggered release of membrane-active double- rather than single-chain amphiphiles is also attracting considerable attention. Amphiphile **154** is composed of a vesicle-stabilizing PEG headgroup, an acid-labile *ortho*-ester and a distearoyl anchor (Fig. 19).[168,171,172] Hydrolysis of the 3,9-diethyl-2,4,8,10-tetraoxaspiro[5.5]undecane under endosomal conditions releases 1,2- (or, more likely, 1,3-)-distearoyl glycerol **155** that may form micellar pores or more complex hexagonal phases because of its conical structure. In fusogenic (DO)PE vesicles, hydrolysis of **154** naturally induces fusion with content release at pH 5.5 but not at pH 7.4.

Photoisomerization is used for triggered content release with bilayers containing lipid **156**.[173,174] The thermodynamically preferred, linear *trans*-azobenzene chromophore fits well into the packing of a lipid bilayer membrane. Photoisomerization produces the mismatched *cis*-isomer **157** that causes content leakage in crystalline but not in the more adaptable liquid-crystalline lipid bilayer membranes. The same photoisomerization is applied in ion pair **158**.[175] The anionic single-chain 3,8,13,18,23-pentaoxadocosate offers a hydrophilic, maybe ionophoric face, whereas the cationic double-chain amphiphile provides the hydrophobic face to produce the facially amphiphilic ion pair **158**. In planar soybean lecithin membranes, favorable (high open probability) formation of heterogenous, ohmic, small (2–12 pS in 500 mM KCl, pH 7.2) and quite inert (lifetimes from 50 ms to 2.3 s) cation channels ($P_{K^+}/P_{Cl^-}=6.1$, $P_{K^+}/P_{Na^+}=6.1$) with a selectivity dominated by dehydration rather than recognition ($Cs^+ \geq K^+ > Na^+$) is observed. Upon photoisomerization into *cis*-isomer **159**, these single-channel characteristics change into unordered current flickering typical for surfactants like 3-[3-chloroamidopropyl-dimethylammonio]-propanesulfonate (CHAPS). Occasionally, single-channel behavior indicative for thermal *cis–trans* isomerization reappears hours after irradiation.

Photopolymerization of vesicular dienone **160** enforces phase separation of the polymeric lipids **161** from unpolymerizable lipids in the bilayer host with defects at the phase boundaries that cause content release (Fig. 20).[176–178] Irradiation of vesicles containing dienone

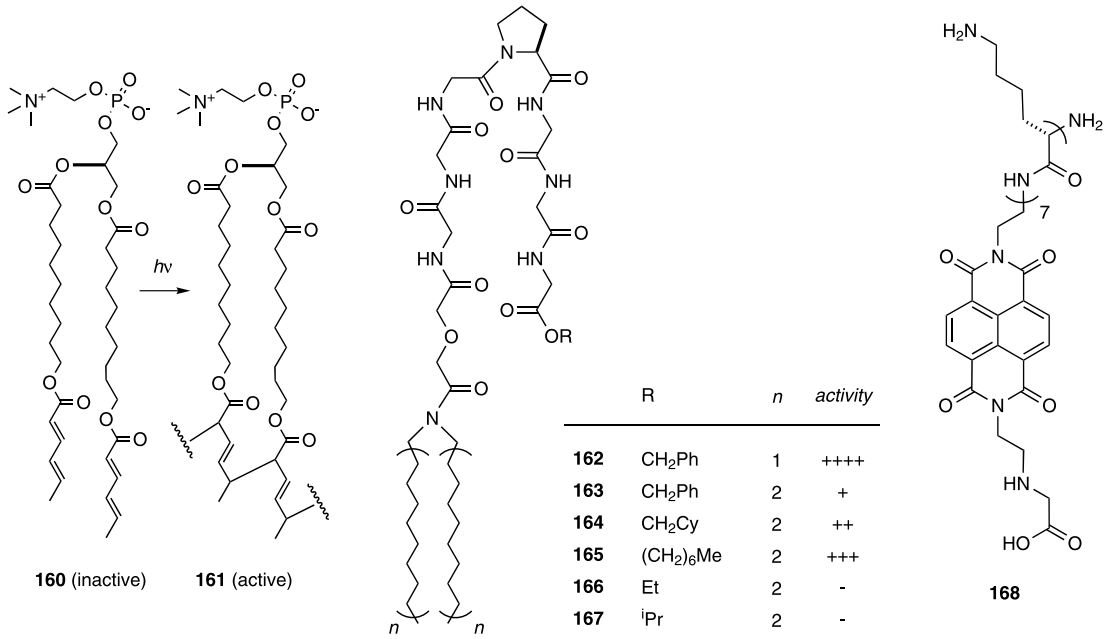


Figure 20. Double-chain amphiphiles that may form 'micellar pores' at the boundary between photopolymerized (**161**) and host bilayer domains and representative peptide conjugates that may self assemble into supramolecular pores (**162**–**165**) or exhibit antibiotic activity (**168**).

160, distearoyl indocarbocyanine as sensitizing lipid, PEG-DOPE as stabilizing lipid and cholesterol results in up to 60-times accelerated dye release.

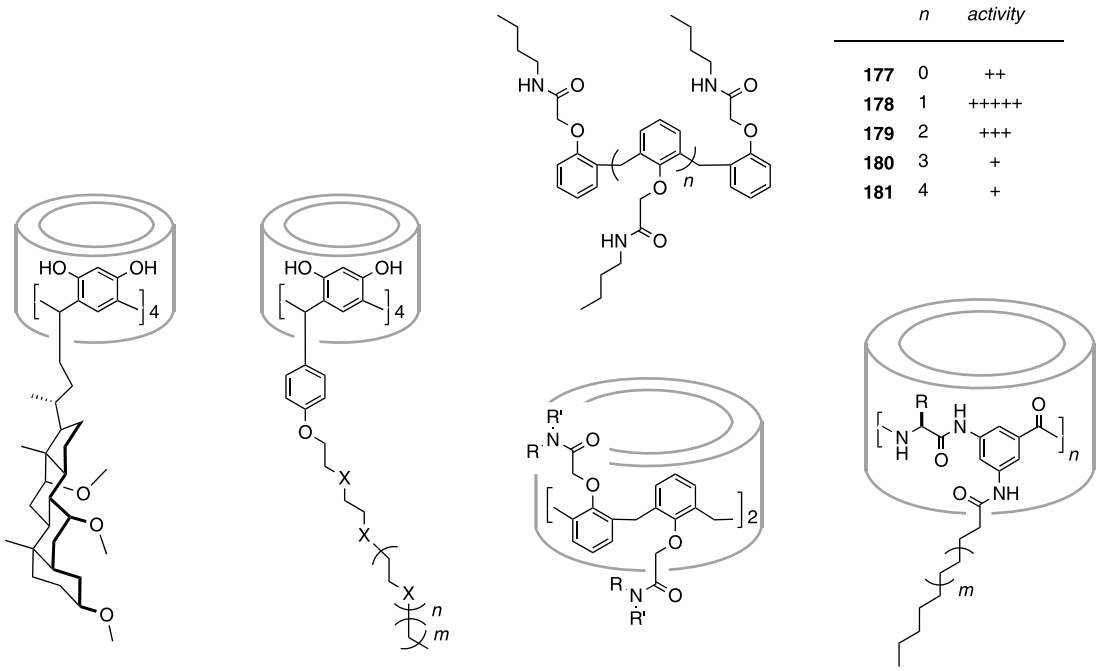
Conjugates **162**–**167** are composed of a hydrophobic double-chain tail, a peptide loop that includes the GxxGP motif of the selectivity filter of chloride channels and a second hydrophobic tail R.[179–183] In water, these conjugates assemble into large aggregates (350–500 nm) that form relatively large, slightly non-ohmic pores in planar bilayers [from 349 pS (**162**) to 0.6–1.3 nS (**163**)] at relatively high concentrations (24–90 μM) with lifetimes that depend strongly on the applied voltage. Size-selective dye release in spherical DOPC/POPA bilayers (3:1) suggests that these pores have a large inner diameter (~8 Å). Activity in vesicles is best with short alkyl tails in **162** (0.8–17 μM). Elongation of the double-chain tail reduces the activity by about 10-fold (**163**: 12–190 μM), whereas elongation of the single-chain tail at the other terminus restores some activity (**165**: 34–117 μM). Deletion of PGGG, P-L mutation and replacement of proline by pipecolic acid reduces activity. Conjugate **163** exhibits chloride selectivity in spherical ($Cl^- > NO_3^- > SO_4^{2-} > K^+$) and planar bilayers ($Cl^-/K^+ = 10$).

Another family of peptide conjugates has emerged from the screening of a combinatorial library for antibiotic activity.[184] 1,4,5,8-Naphthalenecarboxylicdiimide-oligolysine (NDI-K_7) conjugate **168**, for instance, exhibits bactericidal activity rivaling streptomycin and has no activity against mammalian cell lines. Replacement of lysines by arginines, addition of more lysines or NDIs, inversion of peptide stereochemistry and repositioning of the NDI within the peptide does not reduce this activity significantly. Inactivation, however, occurs with removal of the NDI, replacement of the electron-poor NDI by an electron-rich 1,8-dialkoxynaphthalene and reduction of positive charges. Little is known about the structural basis of the bactericidal activity of NDI-peptide **168**. Membrane-disrupting activity similar to that of antibiotic cationic peptides (Section 3.4) and monomeric steroids (Section 3.5) is suspected.

3.7. Non-peptide macrocycles as hoops

The rigid steroid scaffold, long enough to span nearly one leaflet of a lipid bilayer membrane, is an ideal module to illustrate the relation between barrel-stave, barrel-hoop and barrel-rosette motif (Fig. 3). Monomeric steroids can be designed to act either as carriers or detergents (Section 3.5). Self-assembly of monomeric steroids can produce formal barrel-rosette motifs (Section 3.5). Dimeric steroids can be found as rigidified staves in classical barrel-stave motifs (Section 3.2.2). However, dimeric and oligomeric steroids can also fold into crosslinked modules of a formal barrel-rosette motif (Section 3.2.2). Steroids attached to a macrocycle, finally, can assemble into formal barrel-hoop supramolecules. This possibility is illustrated by resorcin[4]arene **169** (Fig. 21).[185] Carrying four facially amphiphilic cholates on the side opposite to the hydrophilic hydroxy groups, this macrocycle is expected to form tail-to-tail barrel-hoop dimers in bilayer membranes. In planar soybean lecithin membranes, ohmic low-conductance (9.9 pS in 500 mM KCl) cation channels ($P_{K^+}/P_{Cl^-} = 8.2$, $P_{K^+}/P_{Na^+} = 2.8$, blockage by Rb^+) with high open probability and long lifetime are observed (2.5–4.5 s). Exceeding the lifetime of the biological gramicidin A channel, the latter characteristic is attributed to the stabilizing, rigid and amphiphilic cholates.

Resorcin[4]arenes **170**–**173** carry a second arene array below the macrocycle to increase cation selectivity, followed by alkyl tails of different length.[186] In planar type(II)-PC/cholesterol bilayers (9:1), resorcin[4]arene **170** with too short tails is inactive and resorcin[4]arene **173** with too hydrophilic tails shows detergent-like behavior.



	n	activity
177	0	++
178	1	+++++
179	2	+++
180	3	+
181	4	+

169

	X	m	n	activity
170	CH_2	0	0	-
171	CH_2	1	0	+
172	CH_2	0	1	+
173	O	1	1	(+)

	R	R'	activity
174	H	Me	-
175	H	Bu	anion
176	Bu	Bu	cation

	n	R	m
182	3	Me	1
183	4	Me	1
184	4	Me	4
185	5	Me	4
186	4	CH_2COOH	4
187	4	$(CH_2)_4NH_2$	5
188	4	CH_2OH	5

Figure 21. Synthetic ion channels formed by non-peptide macrocycles (**169**–**176**), acyclic analogs (**177**–**179**) and peptide macrocycles containing abiotic amino acids (**182**–**188**). In most cases, dimerization into active supramolecules is proposed.

Resorcin[4]arenes **171** and **172** form heterogenous, ohmic cation channels ($K^+/Na^+>50$) with long lifetime (several seconds) and conductances (13–140 pS in 500 mM KCl) that correspond to an inner diameter (0.5–1.7 Å) compatible with that of the macrocycle (5.3 Å C–C distance). The heterogenous single-channel conductances suggest that the expected barrel-hoop channels could further self assemble into barrel-rosette motifs.

Macrocycles **174**–**176** comprise a calix[4]arene 1,3-alt scaffold decorated with alkylamides.[187] Chloride-selective tetrabutylamide **175** mediates either Cl^-/H^+ symport or Cl^-/OH^- antiport in spherical bilayers loaded with pH-sensitive HPTS. The cation selectivity found for octabutylamide **176** under the same conditions is dominated by cation recognition rather than dehydration ($Na^+>K^+>Cs^+$). The difference in ion selectivity between **175** and **176** is attributed to the availability of N–H hydrogens for chloride binding with **175** but not **176**. In planar DPhPC bilayers, calixarene **175** forms long-lasting (several seconds), heterogenous, high-conductance ion channels (50 pS-2 nS in 1 M KCl, pH 7). In HEK-293 cell membranes, calixarene **175** forms voltage-dependent channels. Supported by the solid-state packing in X-ray structures of the inactive analog **174**, the macrocycles are thought to self-assemble into barrel-hoop 'staves' which at least dimerize into barrel-rosette channels with HCl (H_2O) bound between N–H receptors from adjacent 'staves'.

The observation that the suspected barrel-rosette channel does not require macrocyclic modules for activity is confirmed with acyclic homologs **177**–**181**.[188] In spherical EYPC membranes, chloride-selective trimer **178** shows the highest activity—one order of magnitude better than macrocycle **175**—to mediate proton gradient collapse by either Cl^-/H^+ symport or Cl^-/OH^- antiport. Chloride selectivity of **178** is supported by Cl NMR kinetics and polarizability of sulfate-loaded EYPC vesicles with extravesicular chloride.

3.8. Peptide macrocycles as hoops and staves

As long as they do not contain modules different from biological amino acids, it is difficult to consider peptide macrocycles covered in this final section as synthetic ion channels and pores. Cyclic peptides **182**–**188**, however, do contain abiotic 5-(*N*-alkanoylamido)-3-aminobenzoates as part of the scaffold.[189] In planar asolectin (IV) PC bilayers, all macrocycles form ohmic low-conductance (9–10 pS in 500 mM KCl) cation channels ($P_{Cl^-}/P_{Na^+}=0.14–0.19$, $P_{Na^+}/P_{K^+}=0.37–0.41$) with relatively short open times (1–200 ms), independent of variations of macrocycle diameter, charge, width and hydrophobicity. Symmetric

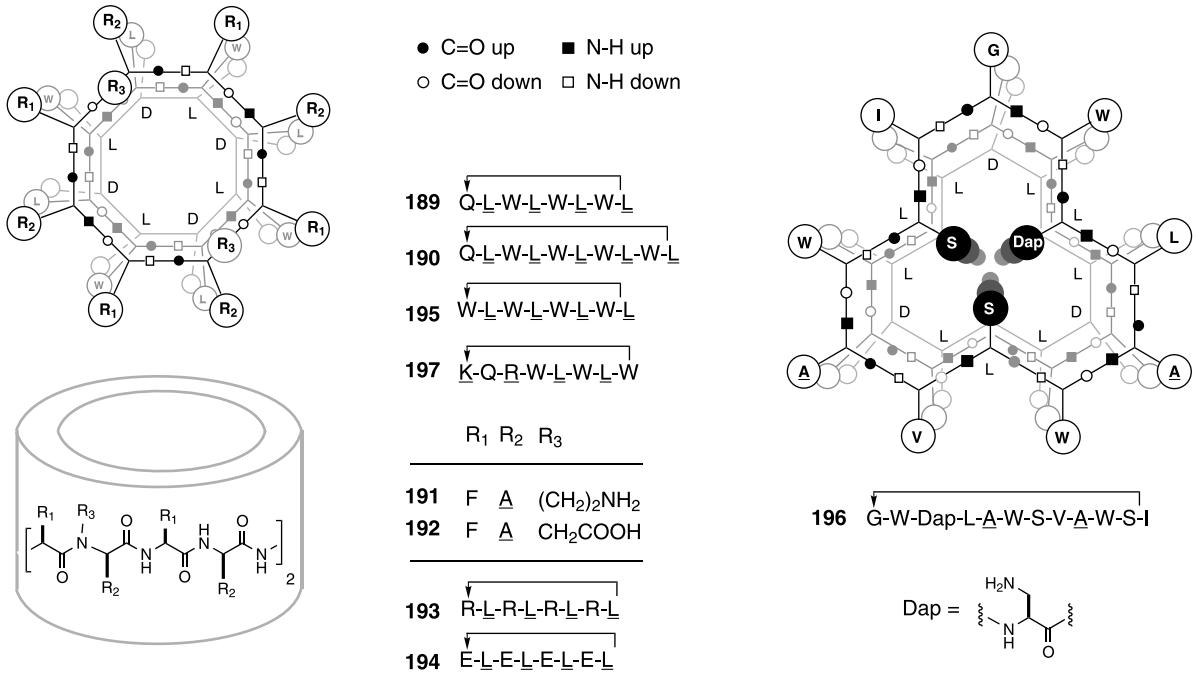


Figure 22. Synthetic ion channels formed by self assembly of macrocyclic peptides (**189**, **190**, **195**–**197**) into genuine barrel-hoop motifs that mimic the β-helix of gramicidin A with cyclic β-sheets (Fig. 9, arrows indicate N–C direction). General axial views illustrate the cyclic peptide backbones (solid lines) with an indication of amino acids per cycle, orientation of backbone amides (dipole-free), and location of the amino-acid residues (external black on white, internal white on black; single-letter abbreviations, D-amino acids underlined). Macrocycles **191**–**194** are designed to bind on top of channels **195**, and cationic antibiotics **197** (and several analogs) are proposed to form micellar pores in anionic membranes.

Ca^{2+} blockage (K_D=0.78–0.87 mM) may support a dimeric barrel-hoop channel structure. Weak voltage dependence indicates that the 'Woodhull distance' l_A from channel entrance to the Ca^{2+} binding site is very short (1.0–1.5 Å). The authors suggest that contributions from interdigitating alkyl tails explain the puzzling insensitivity of these peptide macrocycles towards structural modification—including, for example, a polycationic channel **187** that selects for cations.

Cyclic D,L-α-peptides **189** and **190** represent expanded and macrocyclic versions of the Trp-(D)-Leu-rich peripheral turn of the β-helix formed by gramicidin A (Fig. 22).[190,191] Six to eight of these macrocycles are thought to stack on top of each other to form a transmembrane barrel-hoop channel. This attractive suprastructure may be supported by—according to attenuated total reflection (ATR) FT-IR—a tilt angle of the β-sheet-like backbone amides relative to the surface normal of DMPC multilayers (28.5°) that is similar to that of the lipid tails (26°). As with peptide macrocycles **182**–**188**, the increase in inner diameter from cyclooctapeptide **189** (7 Å) to cyclodecapeptide **190** (10 Å) is poorly reflected by an increase in single-channel conductance from 11.5 to 13.0 pS. In planar DPhPC bilayers, the lifetime of these channels decreases with ring expansion (from 1.3 s to 168 ms). Channels formed by expanded macrocycle **190** are thought to be large enough for glutamate translocation despite opposing cation selectivity similar to that of gramicidin A. A very small shift of the reversal potential of 2–3 mV compared to gramicidin and contracted macrocycle **189** in the presence of a NaCl–NaGlu gradient is proposed to confirm this expectation (P_{Na^+}/P_{Glu^-}=6.4). A coupled three-component enzyme assay is used to demonstrate efficient glutamate release from spherical bilayers in the presence of expanded macrocycle **190**, whereas contracted macrocycle **189** and gramicidin A are inactive under the same conditions. Expanded macrocycle **190** is, however, still too small to mediate CF release.

Hydrophilic cycloocta-D,L-α-peptide caps **191**–**194** are designed to bind to and functionalize the termini of ion channel **195** formed by stacked cycloocta-D,L-α-peptides (nearly identical to **190**; open probability=0.76, open time=800 ms, conductance=21–44 pS).[192] Caps **191** and **192** are expected to introduce two cationic and anionic groups at the channel entrance, whereas caps **193** and **194** should introduce four cationic and anionic groups at the edge of the outer channel surface. Addition of cationic caps **191** and **193** from one side of planar lecithin membranes reduces the conductance of channel **195** with apparent K_D=45 μM and K_D=34 μM (100 mM KCl), respectively, and induces non-ohmic behavior. Weak dependence of these K_Ds on voltage supports peripheral binding. Surprisingly, cationic caps **191** and **193** reduce the cation selectivity of channel **195** only slightly. Similar trends seen with higher concentrations of Ca^{2+} in place of cationic caps **191** and **193** show that conductance experiments in planar bilayers need to be interpreted with caution. Anionic caps **192** and **194** change the conductance of channel **195** with apparent K_D=288 μM and K_D=222 μM (100 mM KCl).

The inner surface of channels formed by β-helical and stacked cyclo-D,L-α-peptides like gramicidin A, **189**, **190** and **195** cannot be functionalized. One approach to possibly overcome this limitation is to introduce abiotic δ-amino acids in the gramicidin A β-helix (Fig. 9). Another elegant

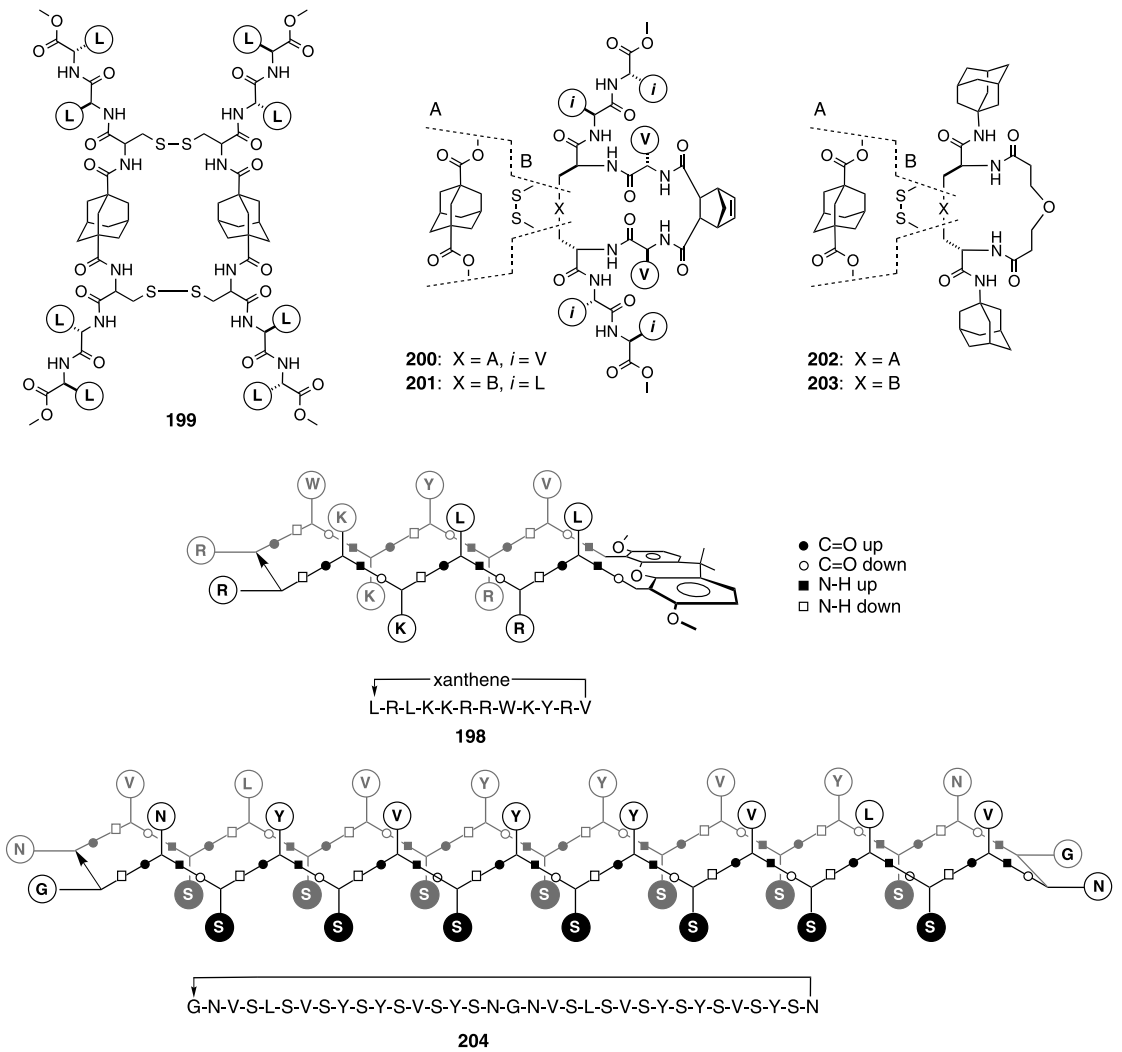


Figure 23. Synthetic carriers (**199**–**204**), antibiotics (**198** and analogs) and pores (**204** and analogs) formed by macrocyclic peptides with non-natural subunits (except **204**). Macrocycles **198** and **204** may act as β-sheets, possibly as staves of β-barrel-like pores (**204**). Schematic views illustrate the cyclic peptide backbones (solid lines) with indication of N–C direction (arrows), orientation of backbone amides (dipole-free), and, for **204** as stave, location of the aminoacid residues (external black on white, internal white on black; single-letter abbreviations).

strategy is to introduce stereochemical defects in the D,L-repeat. Building on pioneering work on β-helical peptide channels,[2] Roeske and co-workers designed cyclo-(L,L,L,D)$_3$-α-peptide **196** with hydrophilic serines and diaminopropionate (Dap) residues pointing towards the interior of the expected barrel-hoop channel.[193] In planar PS/PE membranes, low-conductance (8.6 pS in 500 mM KCl) cation channels ($NH_4^+ > Cs^+ > Rb^+ > Na^+ \geq K^+ > Li^+$) with very long lifetime (several seconds) are observed. Suggestive for some contribution from internal charge repulsion between protonated amines,[114] the conductance of channel **196** is maximal at pH 7.5. Circular dichroism and FT-IR spectra support the β-helix-like hydrogen-bonding pattern expected for a transmembrane barrel-hoop channel.

Cyclo-D,L-α-peptide **197** is a member of a family of amphiphilic macrocycles that exhibit antibiotic activity (B/M selectivity up to 20, compare Section 3.4).[194] Macrocyclic amphiphilicity is required for this activity, whereas ring size and nature of the cationic aminoacid residues are variable. Neutral and anionic macrocycles as well as non-amphiphilic cationic and linear controls are inactive. Cyclo-D,L-α-peptide **197** and active analogs depolarize bacterial membranes. Under different conditions, ATR-FTIR reveals an average tilt angle of β-sheet-like backbone amides relative to the surface normal of DMPC multilayers (70°). This angle is indicative of interfacial (rather than transmembrane) barrel-hoop supramolecules that induce the formation of micellar pores or more dramatic phase changes.

Cyclo-L-α-peptide **198** is a disulfide-bridge-free mimic of natural β-sheet antibiotics like protegrin, tachyplesin, polyphemusin or RTD-1 with a xanthene template to enforce β-hairpin formation (Fig. 23).[195] Macrocycle **198** exhibits antibiotic activity with substantial selectivity, and replacement of the xanthene turn by a P–P turn (D-Pro-L-Pro) increases activity in Gram-negative and decreases activity in Gram-positive bacteria. Replacement of the cationic residue (K) on the hydrophobic face of the β-sheet with a hydrophobic residue increases hemolytic activity. Active cyclo-L-α-peptides depolarize bacterial membranes. Binding to DPC micelles induces β-sheet formation. NMR experiments with 5-, 7-, and 12-doxylstearate-labeled DPC

micelles indicate that, different to many CPA and CPA mimics, the macrocycle is not located at the interface but orients parallel to the alkyl tails.

Peptide macrocycles **199**–**203** are the newest members of a large family that, depending on the chosen sequence, can transport ions across bilayer membranes and form polymeric barrel-hoop supramolecules in the solid state.[196] Bisadamantano peptide **199** depolarizes valinomycin polarized spherical POPC bilayers, possibly acting as an ion carrier of monovalent (Na^+, K^+) and divalent cations (Mg^{2+}, Ca^{2+}).[197] Introduction of a norbornene turn in **200** and **201** introduces specificity for monovalent cations. Cyclobisamides **202** and **203** with peripheral adamantanes exhibit similar activity but do not mediate the release of large anionic fluorescent probes.[198]

The giant 102-membered macrocycle **204** is designed not to form a barrel-hoop but a barrel-stave pore.[199] As in biological β-barrels, β-macrocycle **204** is expected to serve as a stave with the hydrophilic serines pointing to the interior of the pore and the hydrophobic face interacting with the bilayer. In spherical EYPC bilayers, submicromolar concentrations of **204** suffice to release entrapped carboxyfluorescein without—according to light scattering studies—destruction of the vesicle. Linear analogs are less active. CD spectra support β-sheet conformation in water, pH 7.4.

4. Perspectives

A colorful collection of synthetic ion channels and pores has appeared over the past four years. Although comparison of individual performances is not possible (and maybe also not necessary), it is safe to say that creation of synthetic ion channels and pores as such is not a challenge any more. Is this scientifically satisfactory situation the reason that the annual number of publications on synthetic ion channels and pores did not increase over the past four years and actually dropped dramatically in certain high-impact chemistry journals? Does this mean that all pertinent questions in the field are answered?

One key obstacle in the field concerns counterproductive fundamentalism in controversies on methodology, mechanisms and structure determination, amplified by some destructive interference from neighboring fields. To avoid confusion, errors, and ultimately decline of the field, it must, for example, be fully appreciated that activity can originate from a minor fraction of active conformers existing besides a major fraction of inactive conformers that obscures any structural studies by spectroscopic methods. The ongoing, breathtaking advances made in structure determination of biological ion channels and pores do not only provide inspiring insights on function, but they also reveal a complex structural polymorphism with the surrounding membrane host as key player. The structure of biological ion channels and pores in the presence and absence of matching bilayer membranes is not the same.[200–202] With the smaller synthetic ion channels and pores, this structural plasticity—dependent on the nature of the bilayer, concentration, pH, ionic strength, and so on—will be even more significant. Insights deduced from functional studies seem, for the time being, to be the most trustworthy source of structural information. High-level molecular modeling may turn out to be helpful in this situation. However, beyond these obstacles, the perspectives in the field are very exciting. A brief discussion of the most attractive ones, i.e. the shift of attention toward regulation mechanisms as well as medicinal and sensing applications, follows.

The preliminary results on the implementation of regulatory mechanisms in synthetic ion channels and pores promise much future excitement. Initial examples on voltage gating and new inspiration from biology will attract much desired attention on this mechanism. Efforts towards regulation of synthetic ion channels and pores by light, stress, pH, redox chemistry, blockage and enzymes are in progress.[203] Leading examples are discussed in this review. The challenging question of how to deliver synthetic ion channels and pores as water-soluble prepores to bilayer membranes, how to invert the solubility of such aqueous prepores for insertion into bilayer membranes, and how this molecular switching process can be improved remains to be addressed. This question is of particular urgency considering that many current synthetic ion channels and pores are made too hydrophobic to access bilayer membranes from the media for spontaneous incorporation. Membrane recognition in a more general context is a very attractive future topic of medicinal relevance because it combines organic biomembrane chemistry with the field of molecular recognition. The same factor accounts for ion selectivity and blockage, two interconnected topics with endless room for improvements as well as for ligand gating, an extremely promising topic that is practically unexplored. The pioneering examples on ligand gating from engineered biological motifs like a TREN-ligand conjugated to pore-forming peptaibols may serve as much appreciated sources of inspiration beyond insights from biological ligand gating.[23]

Three medicinal applications have stimulated and will continue to stimulate much innovative research in the field. Interest in drug delivery with triggerable vesicles has inspired research on the pH-gated formation of mainly micellar pores for endosomal escape and light-induced membrane disruption in the context of photodynamic therapies. Interest in the development of synthetic ion channels and pores with antimicrobial activity stems from the increasing resistance of many bacteria to classical antibiotics and is inspired by membrane-disruptive cationic peptide or steroid antibiotics found in nature. Future studies on membrane recognition focusing on parameters beyond surface potentials like lipid composition, polarization, stress, thickness, and so on, may allow for further progress in the development of synthetic pore-forming antimicrobials. Synthetic chloride channels or carriers are, finally, expected to provide strategies for the treatment of diseases based on chloride channel malfunction[204] beyond the currently emphasized peptides featuring active sequences of biological channels[205] and prodigiosin mimics.[206] Indeed, a synthetic steroid-polyamine is known to restore Cl^- efflux in cells from cystic fibrosis patients.[207]

Early examples of practical applications of synthetic ion

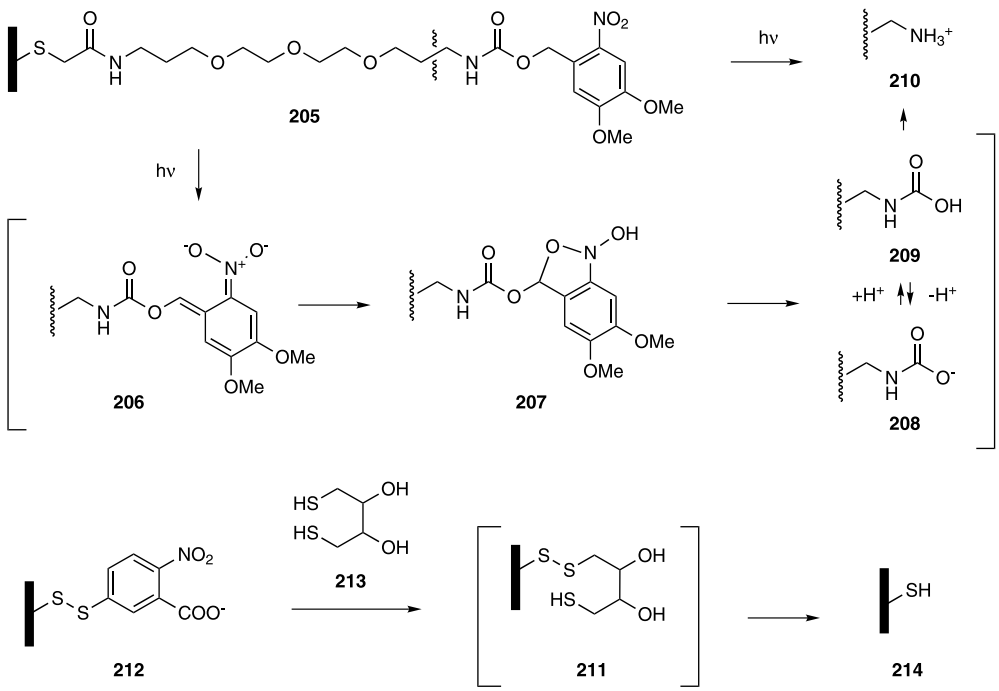


Figure 24. Bioengineered pores as sensors. Covalent capturing and fragmentations observed on the single-molecule level within engineered α-hemolysin pore **214** containing an internal reactive thiol.

channels and pores toward sensing and catalysis in spherical bilayers exist. Attractive perspectives of this approach include the possibility of remote and vectorial control of chemical processes that take place in synthetic pores as well as their detectability with the 'naked eye'. Insights from bioengineered ion channels and pores hint at the enormous scope of sensing and catalysis in supported and planar bilayers. For example, surface-attached melittin tetramers in supported bilayers have been conjugated to peptide antigens for electric detection of antibody binding.[22] The detectability of the conductance of single pores in planar bilayers suggests that chemical processes taking place within these pores can be detected on the single-molecule level as well. This attractive concept has been verified using mainly biological and bioengineered α-hemolysin β-barrel pores as stochastic sensors of analytes like cations, inositols, cyclodextrins and some of its guests, synthetic polymers, proteins, oligonucleotides, and so on.[32] Studies towards the sequencing of single genes with biological pores have been reported. A more recent report describes the covalent positioning of the photolabile 3,4-dimethoxy-6-nitrobenzylcarbamate **205** within a bioengineered α-hemolysin pore.[208] Upon irradiation, nitronate **206** transforms via nitrosoaldehyde **207** into carbamate **208**. The acid **209** then decarboxylates to release the primary amine **210** (Fig. 24). In planar bilayers, most reactive intermediates of this reaction could be detected and their lifetimes determined as a function of pH. This holds also for otherwise undetectable intermediates that decay faster than they form. Along the same lines, it was possible to detect and characterize the short-lived intermediate **211** of the reduction of disulfide **212** with dithiothreitol **213** within a bioengineered α-hemolysin pore **214**.[209]

These pioneering examples from biological and bioengineered pores on regulation, medicinal applications and sensing give an excellent flavor of the fact that the perspectives in the field of synthetic ion channels and pores are extremely attractive and without limits. We look forward to reviewing the next four-year period, January 2004 to December 2007, with the highest expectations.

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Biographical sketch

Stefan Matile received both his Diploma (1989) and his PhD (1994) from the University of Zurich, Switzerland. During this time, he contributed to the bioorganic chemistry of porphyrins studied in the group of Wolf Woggon, focusing on cytochrome *c* and P450 mimics. The topic of his postdoctoral research in the group of Koji Nakanishi, Columbia University, New York, USA, was circular dichroism spectroscopy of porphyrins (1994–1996). Because of their exceptional exciton coupling, he became interested in long, linear spacers like dimeric steroids or brevetoxins that would precisely position two porphyrin chromophores far apart in space. When he moved to Washington DC, USA, to join the faculty of Georgetown University as an Assistant Professor, he decided to focus on these spacers, i.e. rigid-rod molecules (1996). In 1999, he was appointed by the University of Geneva, where he currently is Professor of Organic Chemistry. He still wonders whether or not rigid-rod molecules could serve in the life sciences as well as they do in material sciences. Elaborating on this topic, he became interested in multistep organic synthesis reaching from refined rigid rods like *p*-oligophenyls to protein tertiary structures like artificial β-barrels. His recent contributions to bioorganic biomembrane chemistry are broadly centered around the concept of synthetic multifunctional pores with emphasis on molecular recognition, sensing and catalysis.

Abhigyan Som was born in 1975 in Calcutta, India. He received his BS from Presidency College, Calcutta and his MS from Indian Institute of Technology, Kanpur. In 2000, he moved to the University of Geneva, Switzerland, where he is currently carrying out his PhD under the supervision of Professor Matile. His research is focused on the design, synthesis and evaluation of artificial rigid-rod β-barrels with catalytic activity.

Nathalie Sordé was born in Annemasse, France in 1977. After two years of Preparatory Classes in Annecy, France, she entered the 'École Nationale Supérieure de Chimie de Montpellier,' where she completed undergraduate studies in 2000. She is currently carrying out her PhD under the guidance of Professor Matile at the University of Geneva, Switzerland. Her research concerns the use of synthetic multifunctional pores formed by rigid-rod β-barrels as noninvasive, 'universal' enzyme sensors.

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Concise asymmetric synthesis of (−)-halosaline and (2*R*,9a*R*)-(+)-2-hydroxy-quinolizidine by ruthenium-catalyzed ring-rearrangement metathesis

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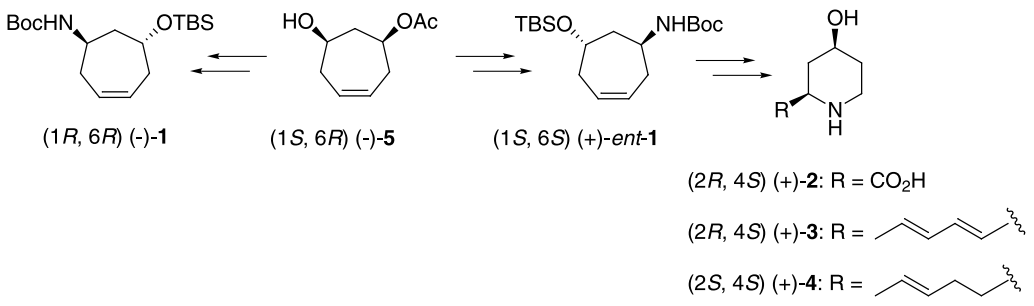
Abstract—A ruthenium-catalyzed ring opening–ring closing metathesis reaction serves as the key step in the stereoselective synthesis of a new enantiopure 2-substituted-4,5-dehydropiperidine skeleton, a valuable intermediate for the synthesis of piperidine alkaloids (such as (−)-halosaline) and of hydroxylated quinolizidines (such as (2*R*,9a*R*)-(+)-2-hydroxy-quinolizidine).

1. Introduction

The piperidine ring is a ubiquitous structural feature of many biologically active alkaloids and useful chemotherapeutic agents. For this reason, substituted piperidine ring systems have been the subject of considerable synthetic efforts, prompting an exceptional development of methodologies for the asymmetric approach to these kinds of compounds.[1]

As part of a program aimed at the design and preparation of polyfunctionalized chiral building blocks useful for the asymmetric synthesis of natural nitrogen-containing compounds, we recently reported[2] the application of optically pure, protected, *trans*-6-aminocyclohept-3-enols (**1** and *ent*-**1**) for the asymmetric synthesis of 2-substituted-4-hydroxy-piperidines. The utility of this new synthon is enhanced by its availability in both enantiomeric forms, which can be prepared in high yields from the enzymatically derived cyclohept-3-ene-1,6-diol monoacetate **5**. Particularly, starting from *ent*-**1**, we described a concise approach to *cis*-4-hydroxy-2-pipecolic acid **2** and to biologically relevant *cis*-2-alkyl-4-hydroxy-piperidines **3** and **4**. (Scheme 1). It was therefore interesting to further explore applications of these versatile intermediates for the asymmetric synthesis of piperidine alkaloids.

Recently, the Blechert[3] and Hoveyda[4] groups have made an important contribution to synthetic routes for heterocyclic compounds, by combining ring closing metathesis (RCM)



Scheme 1.

Keywords: Piperidine alkaloids; Quinolizidine; Ring rearrangement metathesis; Grubbs' catalyst.
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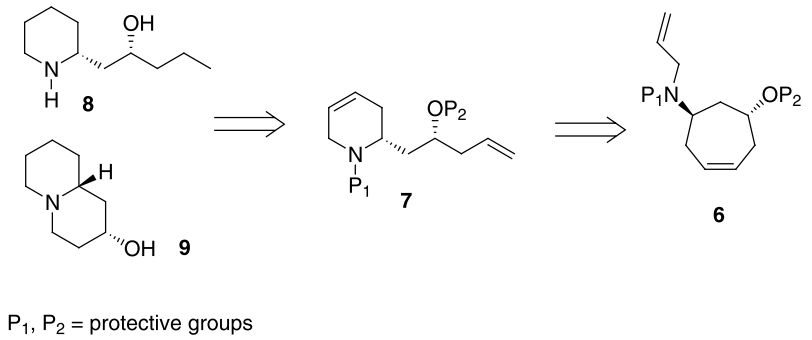


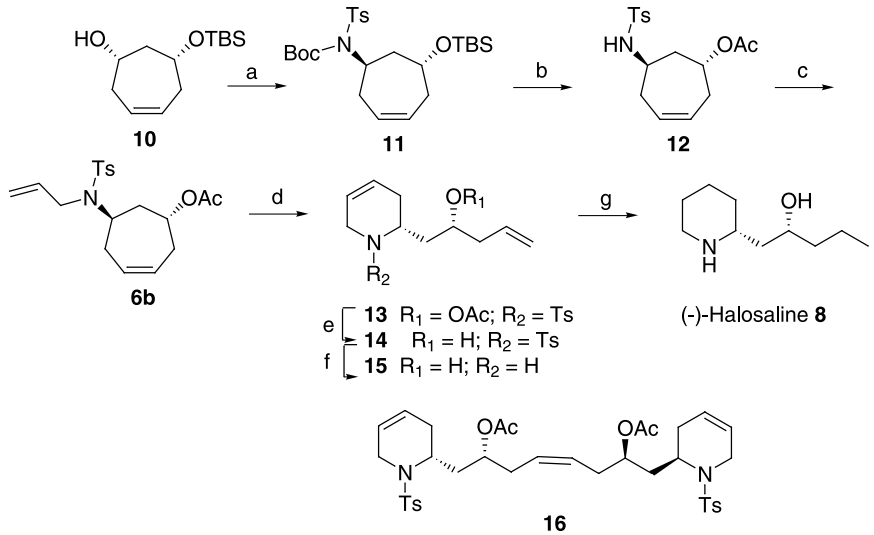
Scheme 2.

with ring opening metathesis (ROM) and cross metathesis (CM). By starting from easily accessible chiral cyclic olefin precursors, properly equipped with olefin substituents, intramolecular domino processes involving ring rearrangement metathesis (RRM) have been applied, to afford various N- and O-heterocycles, using ruthenium-based Grubbs' catalysts. This synthetic tool is highly modular, since both the ring size and the olefin-containing side chains in the final compounds can be easily varied, with complete transfer of chirality from carbocycles to newly formed heterocycles.

2. Results and discussion

We envisaged that the suitably substituted cycloheptene **6** (Scheme 2), easily derivable from **1**, could provide a properly functionalized substrate for a RRM reaction, to afford the new 2-substituted-4,5-dehydropiperidine skeleton **7**. This latter compound can be regarded as a valuable precursor of enantiopure piperidine alkaloids and non-natural N-heterocycles (Scheme 2).

The utility of **6**, as a polyfunctionalized chiral building block, is well illustrated by the concise, high-yielding enantioselective synthesis of natural (−)-halosaline **8**. Moreover, **7** could represent a useful intermediate in the synthesis of hydroxylated quinolizidines, which are interesting synthetic targets, due to their ability to inhibit glycohydrolases resulting in many potential pharmaceutical activities. As an example, here we also report the formation of the bicyclic skeleton of the 2-hydroxy-quinolizidine **9**, by means of appropriate elaborations of the 2-acetoxy-pent-4-enyl side chain of **7**. As the first step in our synthetic plan, we devised the preparation of the all-protected *trans*-N-allyl-aminoalcohol **6a** (P_1=Boc, P_2=TBS), by direct N-allylation of the corresponding N–H precursor **1**, under standard conditions. However, this reaction step afforded the desired product in low yields, probably because of the presence of the sterically-demanding Boc protecting group. The diolefinic substrate **6b** was then achieved by a four-step, high yield sequence, as described in Scheme 3. Enantiopure alcohol **10**[2] was treated under Mitsunobu conditions with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide,[5] to give cleanly the all-protected *trans*-aminoalcohol **11**. Double N- and O-deprotection by means of TFA, followed by O-acetylation, furnished **12** in quantitative yield, from which **6b** was derived (85% yield) by reaction with sodium hydride and allyl bromide. In the next stage, ring rearrangement metathesis on **6b** was preliminarily performed according to Blechert,[3a] with first generation Grubbs's ruthenium catalyst in variable amounts from 7 to 1 mol%. Although the reaction was performed in 0.05–0.10 M concentration of **6b** in CH_2Cl_2, the only isolable compound was in our case the homo-dimerization product

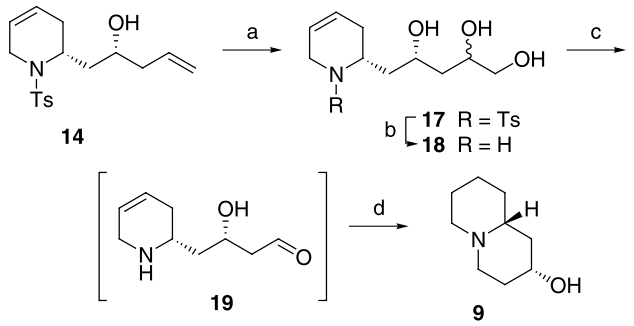


Scheme 3. Reagent and conditions: (a) BocNHTs, PPh_3, THF, DEAD, 50%; (b) TFA, CH_2Cl_2; then Ac_2O, Py, 98%; (c) NaH, DMF, allyl iodide, 85%; (d) Grubbs catalyst 2nd generation, CH_2Cl_2, 82%; (e) 0.5 M NaOH, MeOH, 98%; (f) Na/naph 1 M, THF, −78 °C, 79%; (g) PtO_2, H_2, MTBE, 94%.

16, which derives from the competitive reaction of the desired **13** with the intermediately formed ruthenium–carbene complex.

Together with **16** as the main product, a low yield (25%) of **13** was then achieved, running the reaction in even more diluted CH_2Cl_2 solution (0.01 M) and at long reaction time (24 h). We reasoned that a more active catalyst could speed up the reaction, promoting the desired ring rearrangement and thus depleting the dimerization process. So, the reaction was performed at the same 0.01 M dilution with 3 mol% of a more active catalyst, namely the second generation Grubbs ruthenium-based complex[6] equipped with the more basic saturated imidazole ligands. In these conditions, the dehydropiperidine **13** was achieved as the unique product, in satisfactory 92% yield. The compound **13** constitutes a highly functionalized intermediate and its versatility was preliminary demonstrated by straightforward conversion to the alkaloid (−)-halosaline **8**.[7] This natural product was isolated from *Haloxylon salicornicum* together with many other 2-(2-hydroxyalkyl)piperidines and it has been the target of a few asymmetric syntheses in the last few years.[8] According to Scheme 3, **13** was subjected to deprotection of the hydroxyl group (NaOH, MeOH, quantitative yield) to yield **14**, followed by efficient cleavage of the *N*-tosyl group with sodium naphthalenide. Catalytic hydrogenation of both double bonds of **15** using PtO_2 afforded **8** in quantitative yield, whose optical rotation ($[\alpha]_D^{20}=-18.1$ (*c* 1, EtOH)) was consistent with that reported for natural (−)-halosaline ($[\alpha]_D^{20}=-19.5$ (*c* 0.6, EtOH)). The ^1H NMR, ^{13}C NMR and MS spectra of synthetic **8** were also in good agreement with the reported values.

In order to explore the usefulness of this RRM methodology for the asymmetric synthesis of substituted quinolizidines, we addressed the regioselective dihydroxylation of the terminal double bond in **14** (Scheme 4). By employing a catalytic amount of OsO_4 and 1 equiv. of NMO, the triol **17** was isolated in 54% yield, as a 1:1 mixture of two diastereoisomers at the newly created stereogenic centre. Probably, the complete regioselectivity achieved in this step is due to the better accessibility of the terminal double bond with respect to the endocyclic bond. Lack of stereoselection at the side chain is not a problem at this stage, since the configuration of the new secondary hydroxyl group is not important in the synthesis. The triol **17** was successfully deprotected at the piperidine nitrogen to give **18**, and then cleaved with sodium periodate to afford the highly unstable aldehyde **19**. After work up, **19** was directly subjected to intramolecular reductive amination (10% Pd/C, H_2) affording the saturated bicycle **9** in 52% yield (over two steps).[9]



Scheme 4. Reagent and conditions: (a) OsO_4, NMO, acetone/water, 0 °C, 60%; (b) Na/naph 1 M, THF, −78 °C, 68%; (c) $NaIO_4$, dioxane/H_2O, then (d) 10% Pd/C, H_2, methanol, rt, 52%.

3. Conclusion

In conclusion, the highly functionalized chiral piperidine **13** was prepared from diolefinic heptacycle **6b**, by means of an efficient ruthenium-catalyzed RRM process, and then converted into the natural product (−)-halosaline **8**. In addition, piperidine **13** can be regarded as a valuable intermediate for the synthesis of various hydroxylated quinolizidines, as exemplified by the synthesis of (2*R*,9a*R*)-2-hydroxy-quinolizidine **9**.

4. Experimental

4.1. General

All solvents were distilled and properly dried, when necessary, prior to use. During usual workup, all organic extracts were dried (Na_2SO_4 or $MgSO_4$) and evaporated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography (FC) on Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 and AC 400 spectrometers in $CDCl_3$ solutions (if not otherwise stated) with TMS as internal standard. HR, EI (70 eV) and FAB mass spectra in the positive mode, were measured on VG 70-70 EQ-HF instrument equipped with its standard sources. Optical rotations were measured with Perkin–Elmer 241 polarimeter. Analytical liquid chromatography was carried out with a Kontron HPLC system equipped with a UV detector and a Chiracel OD HPLC column.

4.1.1. (1*R*,6*R*)-N-(*tert*-Butoxycarbonyl)-N-[(6-*tert*-butyldimethyl-silanyloxy)-cyclohept-3-enyl]-toluensulfonamide 11. To a stirred solution of **10** (1.28 g, 5.3 mmol) in anhydrous THF (30 mL), PPh_3 (2.07 g, 7.9 mmol) and N-*tert*-butoxycarbonyl-*p*-toluene-sulfonamide (2.2 g, 7.9 mmol) were added under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and after 5 min DEAD (1.26 mL, 7.9 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Then, the solvent was evaporated and the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane 1:5) to afford 1.2 g of pure **11**, as a pale yellow oil (50% yield): R_f (ethyl acetate/hexane 1:2) 0.56; $[\alpha]_D^{25}=-1.44$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (2H, d, *J*=8.5 Hz), 7.28 (2H, d, *J*=8.5 Hz), 5.86 (1H, m), 5.63 (1H, m), 4.80 (1H, tt, *J*=11.3, 2.9 Hz), 4.02 (1H, t, br, *J*=7.7 Hz), 3.12 (1H, t, br *J*=13.2 Hz), 2.70 (1H, ddd, *J*=13.8, 11.5, 3.4 Hz), 2.55 (1H, m), 2.44 (3H, s), 2.40–2.20 (3H, m), 1.38 (9H, s); 0.85 (9H, s), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ_C 150.6, 143.7, 138.1, 129.2, 127.5, 126.5, 84.3, 69.9, 52.7, 40.1, 34.9, 31.9, 27.8, 26.0, 21.3, 18.1, −4.0; HRMS calcd for $C_{25}H_{41}NO_5SSi$: 495.7592. Found: 495.7575. Anal. calcd for

$C_{25}H_{41}NO_5SSi$: C, 60.57; H, 8.34; N, 2.83; S, 6.47. Found: C, 60.71; H, 8.50; N, 2.71; S, 6.55.

4.1.2. (1*R*,6*R*)-Acetic acid 6-(N-*p*-toluene-sulfonyl-amino)-cyclohept-3-enyl ester 12. To a stirred solution of **11** (446 mg, 0.9 mmol) in CH_2Cl_2 (5 mL), TFA (5 mL) was added dropwise. After 30 min, the reaction mixture was cooled to 0 °C and a solution 2.5 M NaOH was slowly added until pH 9. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The crude *N*-Boc deprotected product was dissolved in anhydrous CH_2Cl_2, Ac_2O (1.1 equiv.) and TEA (1.1 equiv.) were added and the reaction was stirred for 12 h. Then, the mixture was poured into 5% aq. H_3PO_4 and extracted with ethyl ether. The organic layer was dried over Na_2SO_4 and concentrated to give, after flash chromatography (ethyl acetate/hexane 1:2), 290 mg of pure **12** (98% yield), as an oil: R_f (ethyl acetate/hexane 1:2) 0.32; $[\alpha]_D^{25}=-2.8$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (2H, d, *J*=8.3 Hz), 7.28 (2H, d, *J*=8.3 Hz), 5.75 (1H, dt, *J*=11.6, 6.2 Hz), 5.64 (1H, dt, *J*=11.6, 6.2 Hz), 4.80 (1H, m), 4.54 (1H, d, br, *J*=8.7 Hz), 3.66 (1H, m), 2.41 (3H, s), 2.40–2.10 (5H, m), 1.95 (3H, s), 1.88 (1H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.0, 143.4, 138.0, 129.6, 128.8, 128.4, 127.0, 67.6, 48.6, 42.8, 33.6, 33.5, 21.5, 21.1; HRMS calcd for $C_{16}H_{21}NO_4S$: 323.4141. Found: 323.4157. Anal. calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.91. Found: C, 59.59; H, 6.71; N, 4.25; S, 9.73.

4.1.3. (1*R*,6*R*)-Acetic acid 6-(N-allyl-N-*p*-toluene-sulfonylamino)-cyclohept-3-enyl ester 6b. To sodium hydride (174 mg, 6.0 mmol, 80% dispersion in mineral oil) in anhydrous DMF (10 mL) a solution of **12** (980 mg, 3.0 mmol) in DMF (10 mL) was added at 0 °C. After stirring 15 min, allyl iodide (563 l, 6.0 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. Then, the mixture was poured into 5% aq. H_3PO_4 and extracted with ethyl ether. The organic layer was dried over Na_2SO_4 and concentrated to give, after flash chromatography (ethyl acetate/hexane 1:5), 933 mg of pure **6b** (85% yield), as an oil: R_f (ethyl acetate/hexane 1:2) 0.44; $[\alpha]_D^{25}=+20.0$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (2H, d, *J*=8.3 Hz), 7.28 (2H, d, *J*=8.3 Hz), 5.85 (1H, ddt, *J*=16.3, 10.5, 6.1 Hz), 5.74 (1H, m), 5.56 (1H, m), 5.21 (1H, dq, *J*=17.1, 1.5 Hz), 5.13 (1H, dq, *J*=10.1, 1.5 Hz,), 5.05 (1H, m), 4.10 (1H, tdd, *J*=11.2, 4.0, 2.1 Hz), 3.85–3.80 (2H, m), 2.52–2.45 (2H, m), 2.42 (3H, s), 2.02 (3H, s), 2.25–1.98 (3H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.2, 143.1, 139.1, 136.0, 129.6, 128.9, 127.0, 126.9, 117.3, 69.4, 51.9, 47.6, 40.5, 34.7, 31.8, 21.5, 21.2; HRMS calcd for $C_{19}H_{25}NO_4S$: 363.4794. Found: 363.4782. Anal. calcd for $C_{19}H_{25}NO_4S$: C, 62.79; H, 6.93; N, 3.85; S, 8.82. Found: C, 62.85; H, 7.04; N, 3.95; S, 8.63.

4.1.4. (1*R*,2′*R*)-Acetic acid 1-[1′-(toluene-4-sulfonyl)-1′,2′,3′,6′-tetrahydro-pyridin-2′-ylmethyl]-but-3-enyl ester 13. To a solution of **6b** (305 mg, 0.8 mmol) in CH_2Cl_2 (80 mL) under nitrogen atmosphere, was added 2nd generation Grubbs catalyst (21 mg, 3 mol%) and the reaction mixture was stirred for 2 h. Then, DMSO (90 μl, 1.2 mmol) was added and this mixture was stirred overnight. The solvent was evaporated and the residue purified by flash chromatography (CH_2Cl_2/ethyl acetate 100:1) to afford 250 mg of pure **13** (82% yield), as an oil: R_f (CH_2Cl_2/ethyl acetate 100:5) 0.46; $[\alpha]_D^{25}=-6.5$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (2H, d, *J*=8.4 Hz), 7.24 (2H, d, *J*=8.4 Hz), 5.71 (1H, m), 5.62–5.52 (2H, m), 5.08 (1H, d, br, *J*=10.9 Hz), 5.06 (1H, d, br, *J*=17.5 Hz), 4.91 (1H, m), 4.24 (1H, m), 4.11 (1H, d, br, *J*=19.1 Hz), 3.55 (1H, d, br, *J*=19.1 Hz), 2.40 (3H, s), 2.36 (2H, t, br, *J*=7.3 Hz), 2.15 (1H, d, br, *J*=19.4 Hz), 2.05 (3H, s), 1.80 (1H, m), 1.76 (1H, d, *J*=19.4 Hz), 1.58 (1H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.5, 143.0, 137.7, 133.2, 129.6, 127.0, 123.5, 122.5, 118.1, 70.5, 47.0, 40.3, 38.7, 35.1, 27.9, 21.5, 21.2; HRMS calcd for $C_{19}H_{25}NO_4S$: 363.4794. Found: 363.4802. Anal. calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.38; S, 10.04. Found: C, 67.60; H, 8.02; N, 4.31; S, 9.86.

4.1.5. (2*R*,2′*R*)-1-[1′-(Toluene-4-sulfonyl)-1′,2′,3′,6′-tetra-hydro-pyridin-2′-yl]-pent-4-en-2-ol 14. To a solution of **13** (305 mg, 0.8 mmol) in MeOH (10 mL), 0.5 M NaOH (3 mL, 1.5 mmol) was added and the mixture was stirred at 45 °C for 10 h. The mixture was neutralized with HCl 1 N until pH 7 and MeOH was evaporated in vacuo. Then, water was added and the aqueous phase was extracted with ethyl acetate. The organic layer were dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield 264 mg (98%) of pure **14**, as an oil: R_f (CH_2Cl_2/ethyl acetate 100:5) 0.31; $[\alpha]_D^{25}=-4.8$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.66 (d, 2H, *J*=8.9 Hz), 7.24 (d, 2H, *J*=8.9 Hz), 5.97 (1H, dt, *J*=10.1, 2.2 Hz), 5.88 (1H, m), 5.78 (1H, dt, *J*=10.1, 3.4 Hz), 5.11 (1H, dd, *J*=16.1, 1.6 Hz), 4.89 (1H, dd, *J*=9.0, 1.6 Hz), 4.33 (1H, m), 4.07 (1H, m), 3.27 (1H, dd, *J*=17.7, 3.5 Hz), 3.20 (1H, dd, *J*=17.7, 3.5 Hz), 2.41–2.23 (4H, m), 2.33 (3H, s), 1.72–1.35 (2H, m), 0.77 (1H, br s); HRMS calcd for $C_{17}H_{23}NO_3S$: 321.4418. Found: 321.4415. Anal. calcd for $C_{17}H_{23}NO_3S$: C, 63,52; H, 7.21; N, 4.36; S, 9.98. Found: C, 63.71; H, 7.29; N, 4.21; S, 9.90.

4.1.6. (2*R*,2′*R*)-1-(1′,2′,3′,6′-Tetrahydro-pyridin-2′-yl)-pent-4-en-2-ol 15. A solution 1 M of sodium naphthalide in THF was prepared as follows: to a stirred solution of naphthalene (5 g, 39 mmol) in 39 mL of THF, sodium metal (1.1 g, 47 mmol) was added under nitrogen atmosphere, and the solution was stirred for 1 h.

A solution of **14** (263 mg, 0.8 mmol) in anhydrous THF (15 mL) was cooled to −78 °C under nitrogen atmosphere and 3.3 mL (3.3 mmol) of 1 M sodium naphthalenide in THF was added dropwise. The mixture was stirred for 40 min at this temperature and then 15 mL of saturated NH_4Cl aqueous solution was added. The solution was left to warm up to room temperature and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to give 264 mg (79% yield) of pure **15**, as an oil: R_f (ethyl acetate 5% NH_4OH) 0.18; $[\alpha]_D^{25}=-2.1$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 5.91 (1H, m), 5.77 (1H, dt, *J*=10.1, 3.6 Hz), 5.64 (1H, dt, *J*=10.1, 3.6 Hz), 5.11 (1H, dd, *J*=16.1, 1.7 Hz), 4.89 (1H, dd, *J*=8.9, 1.7 Hz), 4.04 (1H, m), 3.46 (1H, dd, *J*=17.8, 3.6 Hz), 3.21 (1H, dd, *J*=17.8, 3.6 Hz), 3.15 (1H, m), 2.38–2.26 (2H, m), 2.12–1.68 (2H, m), 1.61 (2H, m), 1.42–1.09 (2H, m); HRMS calcd for $C_{10}H_{17}NO$: 167.2531. Found:

167.2539. Anal. calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.97; H, 10.37; N, 8.41.

4.1.7. (−)-Halosaline 8. 20 mg of PtO_2 was added to a solution of **15** (210 mg, 1.3 mmol) in MTBE (20 mL) under H_2 atmosphere. The suspension was stirred for 8 h. The catalyst was filtered off and the solvent was removed under vacuum to give 204 mg (94% yield) of pure **8**, as an oil: R_f (ethyl acetate 5% NH_4OH) 0.10; $[\alpha]_D^{25}=-18.1$ (*c* 1, EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 3.90 (1H, m), 3.50–3.45 (2H, s, br), 3.10 (1H, dd, *J*=12.2, 3.3 Hz), 2.91 (1H, m), 2.60 (1H, ddt, *J*=14.1, 12.2, 3.3 Hz), 2.00–1.25 (12H, m), 0.90 (3H, t, *J*=6.5 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 68.4, 54.9, 46.5, 41.8, 31.5, 25.5, 24.7, 18.6; HRMS calcd for $C_{10}H_{21}NO$: 171.2850. Found: 171.2837. Anal. calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.92; H, 12.25; N, 8.24.

4.1.8. (2′*R*,4*S*)-5-[1′-(Toluene-4-sulfonyl)-1′,2′,3′,6′-tetrahydro-pyridin-2′-yl]-pentane-1,2,4-triol 17. To an ice-cooled solution of **14** (256 mg, 0.80 mmol) in acetone/water (2:1 v/v; 24 mL) were added 480 l of OsO_4, 0.039 M in water (0.019 mmol). After 5 min N-methylmorfoline-N-oxide (80 l, 0.80 mmol) was added to the solution in two portions. The mixture was allowed to warm up to room temperature and stirred overnight. Ethyl acetate and brine was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The resulting crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane 10:0.5) to give 170 mg (60% yield) of **17**, as a colorless oil: R_f (ethyl acetate/MeOH 10:1) 0.59; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (2H, d, *J*=8.9 Hz), 7.29 (2H, d, *J*=8.9 Hz), 5.65–5.55 (2H, m), 4.25 (1H, m), 4.12 (1H, dd, *J*=17.6, 1.6 Hz), 4.00 (1H, m), 3.75–3.60 (3H, m), 3.50 (1H, m), 2.39 (s, 3H), 1.95–1.50 (6H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.1, 136.6, 129.7 (2C), 127.0 (2C), 123.4, 122.5, 69.8, 67.1, 66.8, 46.9, 40.4, 39.2, 38.1, 27.8, 21.3; HRMS calcd for $C_{17}H_{25}NO_5S$: 355.4565. Found: 355.4554. Anal. calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94; S, 9.02. Found: C, 57.21; H, 7.00; N, 4.02; S, 9.22.

4.1.9. (2′*R*,4*S*)-5-(1′,2′,3′,6′-Tetrahydro-pyridin-2′-yl)-pentane-1,2,4-triol 18. A solution of **17** (150 mg, 0.42 mmol) in anhydrous THF (10 mL) was cooled to −78 °C under nitrogen atmosphere and 1.6 mL (1.6 mmol) of 1 M sodium naphthalenide in THF was added dropwise. The mixture was stirred for 30 min at this temperature and then 10 mL of saturated NH_4Cl aqueous solution was added. The solution was left to warm up to room temperature and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to give 67 mg (79% yield) of pure **18**, as an oil: R_f (ethyl acetate/MeOH 10:1, sat. NH_4OH) 0.15; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.55–5.50 (2H, m), 3.90 (1H, m), 3.73 (1H, m), 3.56 (2H, m), 3.45 (1H, dd, *J*=17.6, 2.5 Hz), 3.22 (1H, dd, *J*=17.6, 1.7 Hz), 3.15 (1H, m), 2.30 (4H, s, br), 2.05–1.10 (6H, m); HRMS calcd for $C_{10}H_{19}NO_3$: 201.2678. Found: 201.2695. Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.72; H, 9.68; N, 6.77.

4.1.10. (2*R*,9a*R*)-(+)-2-Hydroxy-quinolizidine 9. To a solution of **18** (60 mg, 0.30 mmol) in dioxane/H_2O 1:1 (5 mL), cooled to 0 °C, sodium periodate (105 mg, 0.50 mmol) was added. The mixture was stirred for 2 h, diluted with Et_2O, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue was dissolved in MeOH (5 mL), 10% Pd/C (6 mg) was added and the solution was stirred under hydrogen atmosphere for 12 h. After filtration of the catalyst and evaporation of the solvent, 24 mg (52% overall yield) of pure **9** were obtained: R_f (ethyl acetate/MeOH 10:1, sat. NH_4OH) 0.25; $[\alpha]_D^{25}=+20.1$ (*c* 1, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.80 (1H, tt, *J*=12.9, 2.8 Hz), 3.00 (1H, d, br, *J*=12.0 Hz), 2.90–2.78 (2H, m), 2.70 (1H, dt, *J*=12.0, 2.2 Hz), 2.55 (1H, s, br), 2.40 (1H, dt, *J*=11.0, 2.1 Hz), 1.90–1.75 (2H, m), 1.80–1.35 (8H, m); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 68.7, 60.7, 55.6, 54.5, 42.5, 35.0, 33.1, 25.7, 24.1; HRMS calcd for $C_9H_{17}NO$: 155.2419. Found: 155.2432. Anal. calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.70; H, 11.16; N, 8.90.

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A DFT rationalization for the observed regiochemistry in the nitrile oxide cycloaddition with anthracene and acridine☆

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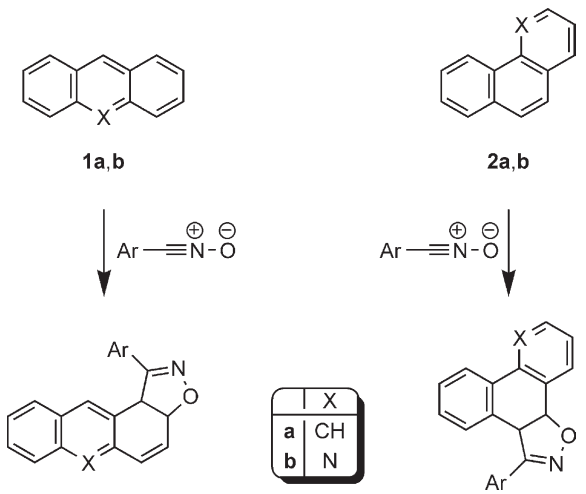
Abstract—A series of computational approaches, based on the global and local indexes defined in the context of the DFT, at the B3LYP/6-31G(d) computational level, were investigated to elucidate the regiochemistry and the energetics of the mesitonitrile oxide 1,3-dipolar cycloaddition with anthracene and the aza-analogue acridine. The results are in agreement with the observed regioselectivity and are in contrast with the ones predicted in terms of FMO theory.

1. Introduction

Nitrile oxides constitute a powerful class of 1,3-dipoles, able to react with the poorest dipolarophiles such as polycyclic and heterocyclic aromatics.[1] The synthetic utility of this kind of 1,3-dipolar cycloadditions (1,3-DCs), although limited by the low yields obtained, is noteworthy because 1,3-DCs open a new path to the selective functionalization of this type of dipolarophile.[2]

Recently, within our studies aimed at examining the dipolarophilic reactivity of polycyclic aromatic hydrocarbons (PAHs) and their aza-analogues (*N*-PAHs), we reported the reactions of some of them (anthracene, phenanthrene, pyrene, perylene, acridine, benzo[h]quinoline, 1,10-, 1,7-, 4,7-phenanthroline) with 2,4,6-trimethylphenyl- and 3,5-dichloro-2,4,6-trimethylphenylnitrile oxide, which gave mainly monocycloadducts.[3] As examples, the reactions of nitrile oxides with anthracene **1a** and acridine **1b** and those with phenanthrene **2a** and benzo[h]quinoline **2b** are illustrated in Scheme 1.

The dipolarophilic reactivity of PAHs towards nitrile oxides has been rationalized in terms of Frontier molecular orbital (FMO) theory using PM3 methods[4] by calculating the



Scheme 1.

HOMO and LUMO energies; the results are consistent with the dominant interaction HOMO (dipolarophile)—LUMO (dipole) and with energy gaps.[3a] Thus, with regard to the site-selectivity of the process, the formation of the unique isolated monocycloadduct for PHAs[3a] is controlled by the adjacent pair with higher orbital coefficients.[5]

The outcome of aza-analogues of anthracene and phenanthrene reactions is clearly influenced by the presence of the nitrogen atoms which lead to the initial formation of a labile 1,3-adduct at their nitrogen atom in equilibrium with reactants.[6] The normal pericyclic pathway is then changed into a pseudo pericyclic reaction[7] which involves the initial

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attack of nitrile oxide to nitrogen atom and then the subsequent electrocyclic closure.[6]

Because of the reversibility of the first addition step, in the case of *N*-PAHs, it was not possible to deduce such a fair rationalization of the relative reaction rates as for the nitrile oxide cycloaddition of pyridine[6] and diazines.[8] The different behaviour observed arises from the different positions of the nitrogen atoms in the molecule which affords 1,3-adducts with different thermodynamic stabilities.

In the case of the reaction of acridine in refluxing toluene, a monocycloadduct with the same structure of that deriving from anthracene was isolated, while at room temperature an addition product of the 1,3-dipole to the nitrogen atom was afforded which lead to the uncommon dioxadiazine dimer.[9]

The FMO arguments, however, do not provide a satisfactory explanation of the experimentally observed regioselectivity in the nitrile oxide cycloadditions to **1a**,**b**. In fact, the interaction of the atoms with the largest coefficients[10] should lead to the formation of cycloadducts with an inverse regiochemistry.

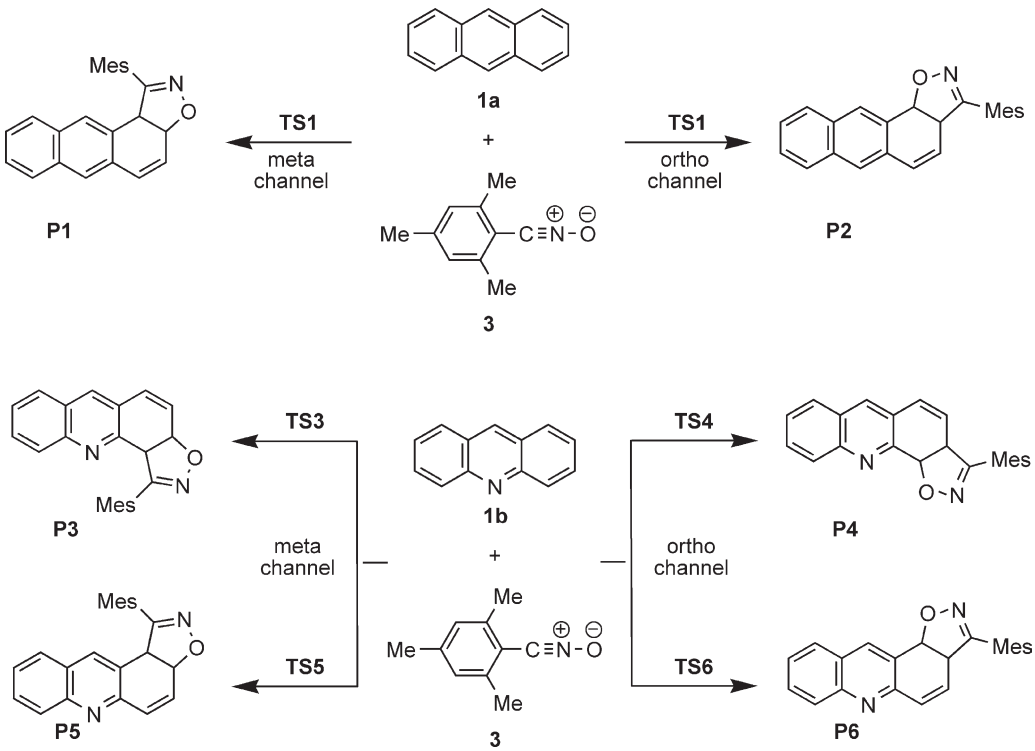
The failure of FMO approach in the regioselectivity prediction for the examined reactions can be rationalized on the basis of the subsequent considerations: (a) the FMO theory is based only on the properties of the Frontier molecular orbitals of the reactants and just for its simplicity it does not account for all other orbital interactions;[11] (b) moreover, FMO theory is normally applicable to exothermic reactions where, according to the Hammond postulate, an early transition state is involved. Conversely, in the case of endothermic reactions, the Hammond postulate claims a later TS, i.e. TS is product-like, and then the frontier orbital effects will be less noticeable.

Thus, although the FMO theory works well for a wide range of reactants, there are some exceptions[11e,12] which, on the contrary, are well rationalizable working with a more powerful level of theory, such as density functional theory (DFT).

For this reason, we have investigated a more powerful theoretical approach which is based on the formulation of the interaction energy of **1a**,**b** and mesitonitrile oxide **7** in terms of DFT,[13] which proved to be in agreement with the experimental results.

2. Computational methods

DFT calculations were carried out with the G98 system of programs.[14] Critical points (reactants, transition structures and products) were fully characterized as minima or first-order saddle points by diagonalizing the Hessian matrices of the optimized structures at the B3LYP/6-31G(d) level.[15] All the critical points were further characterized by analytic computation of harmonic frequencies at the B3LYP/6-31G(d) level. Transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-31G(d) optimized structures and used, unscaled, to compute both ZPVE and activation energies. The electronic structures of critical points were studied by the natural bond orbital (NBO) method.[16] Atomic electron populations were evaluated following the Merz-Kollman (MK) scheme[17]



Scheme 2.

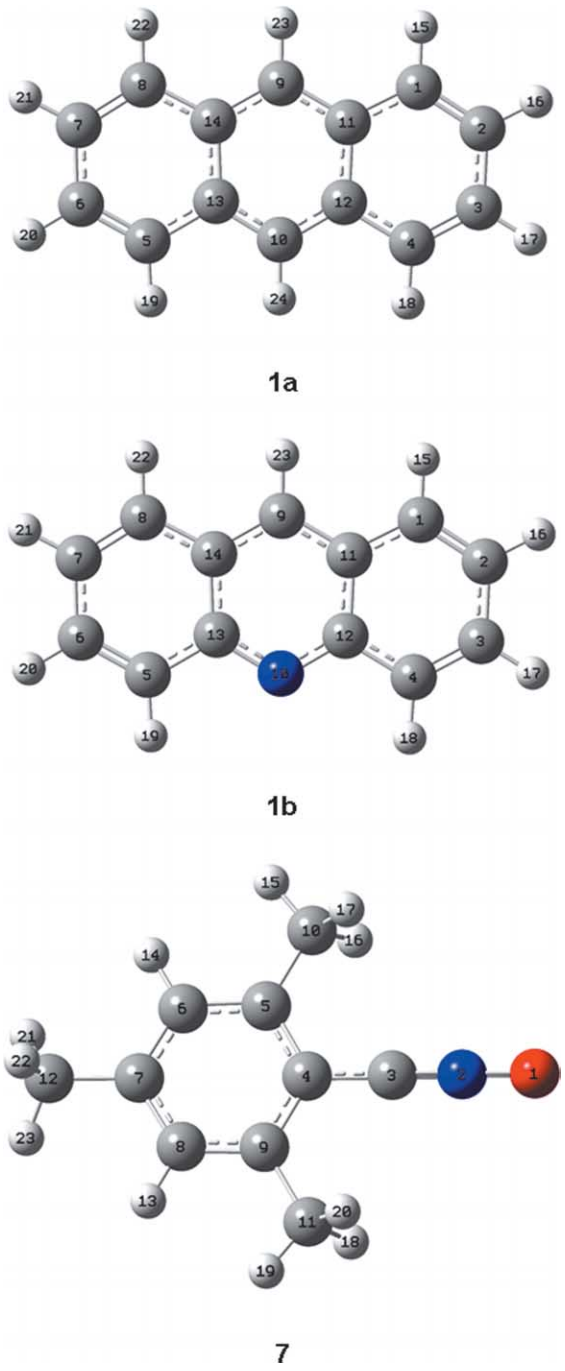


Figure 1. B3LYP/6-31G(d) optimized structures of the reactants.

that, other than already being proved to be reliable,[18] has been used in most DFT calculations of regiochemistry of 1,3-DCs.[19] The enthalpy and entropy changes were calculated from standard statistical thermodynamic formulas.[20] The intrinsic reaction coordinates[21] (IRC analysis) were also calculated to analyze the mechanism in detail for all the transition structures obtained.

We studied the regioselectivity of the 1,3-DC reaction of **1a**,**b** with **7**. We have considered two reaction channels, *meta* and *ortho*, corresponding to the formation of Δ^2-isoxazolines **P1**, **P3**, **P5** and **P2**, **P4**, **P6**, respectively. Consequently, the two transition states leading to the two cycloadducts have been located for the dipolarophile **1a**, whereas the four transition states leading to the four cycloadducts have been located for the dipolarophile **1b**. The nomenclature used for defining stationary points is given in Scheme 2.

3. Results and discussion

3.1. Reactants

The parameters of lowest energy structures for **1a**[22] and **1b**[23] corresponds to that reported in literature; to our best knowledge, no DFT calculations have been already reported for **3** (geometries and energies are reported as Supplementary data).

The optimized geometries, with the adopted numeration, of compounds **1a**,**b** and **3** are illustrated in Figure 1.

From the hardness values,[24] reported in Table 1, it emerges that **1b** is slightly more aromatic than **1a**, in agreement with experimental data.[25] Moreover, the global electrophilicity value of **3** is lower than that reported for benzonitrile oxide[26] and therefore **3** is a more moderate electrophile.

3.2. Prediction of regiochemistry

A simple way to predict the regiochemistry of 1,3-DC reactions and the trend of regioselectivity consists of using the charges obtained by the MK molecular electrostatic potential method,[17] which has been recently considered as an appropriate local descriptor of charge.[27] In the case at hand **1a** has a negative charge on both C_1 (−0.20) and C_2 (−0.12) atoms, so as **1b** on C_1 (−0.12), C_2 (−0.17), C_3 (−0.07) and C_4 (−0.30) atoms, whereas **3** has a negative charge on O_1 (−0.33) and a positive one on C_3 (+0.09). In the reaction of **1a** with **3**, the more nucleophilic oxygen of the dipole is prone to attach the C_2 atom of **1a**, because it is less negative than the C_1 one (Δq=0.08), leading to a prevalence of the **P1** regioisomer. In the reaction of **1b** with **3**, the difference of charge at the two possible sites of attachment C_1═C_2 and C_3═C_4, is 0.04 and 0.23, respectively, with the C_1 and C_3 atoms being less negative.

Table 1. Global properties (electronic chemical potential μ, chemical hardness η and chemical softness S values are in a.u.; electrophilicity power ω values are in eV) and local softness (s^+ for nucleophilic and s^- for electrophilic attack) of anthracene **1a**, acridine **1b** and mesitonitrile oxide **3**

	μ	η	s	ω	s^-				s^+				s^-		s^+	
					C_1	C_2	C_3	C_4	C_1	C_2	C_3	C_4	O_1	C_3	O_1	C_3
1a	−0.12601	0.13213	3.78	1.63	0.288	0.223			0.159	0.292						
1b	−0.14082	0.13606	3.67	1.98	0.355	0.264	0.147	0.369	0.124	0.351	0.198	0.252				
3	−0.13107	0.17910	2.79	1.31									0.646	0.278	0.510	0.574

So it is expected that the O_1 atom of **3** predominantly attacks the C_3 atom of **1b** leading to the **P3** arising from the 1,3-DC on C_3═C_4 double bond. The 1,3-DC on C_1═C_2 double bond is less favoured and, in any case, leads to a near equimolar mixture of **P5** and **P6** regioisomers.

Moreover, these 1,3-DC reactions have been analyzed using the global and local indexes, as defined in the context of DFT,[28] which are useful tools to understand the reactivity of molecules in their ground states. The electronic chemical potential μ, that is the negative of electronegativity χ, is usually associated with the charge transfer ability of the system in its ground state geometry and it can be approximated, using Koopmans' theorem, to the half value of the sum of the one-electron energies of the FMO HOMO and LUMO.[28a,29] The chemical hardness η is considered to be a measure of the stability of a system: the system having the maximum hardness being the most stable.[30] Essentially the hardness is approximated to be the difference between LUMO and HOMO energies. The chemical softness parameter S is strictly related to the chemical hardness and it is due to the inverse of 2η.[28]

Besides these indexes it is also possible to define the global electrophilicity power ω, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. The approximate expression for ω, in the ground-state parabola model, is[31]

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

and it may be classified within a unique relative scale in order to evaluate the polarity of transition state structures. Both Diels–Alder reactions[32] and 1,3-DCs[26] can be evaluated using such an absolute scale.

The values of μ, η, S and ω for compounds **1a**,**b** and **3**, calculated with the reported formulas, are listed in Table 1. The electronic chemical potential of **1a** is lower than that of **3**, thereby indicating that a net charge transfer will take place from **1a** to **3**. Instead, the chemical potential of **1b** is higher than that of **3**, thereby indicating that a net charge transfer will take place from **3** to **1b**. Indeed, the electrophilicity differences between **1a** and **3** ($\Delta\omega$=0.32 eV) indicates a lower polar character for this cycloaddition than that for the reaction between **1b** and **3** ($\Delta\omega$=0.67 eV). Both $\Delta\omega$ values are characteristic of non-polar (pericyclic) reactions[26,32] as is also indicated by the low charge transfer found in all cases. Whereas the global parameters help to understand the behaviour of a system, in a more local approach, the same parameters, also emerge as a useful tool for rationalizing, interpreting and predicting diverse aspects of chemical bonding and reaction mechanism. Recently, local softness s has been successfully applied for explaining the regiochemistry in more complex pericyclic reactions.[31] However, in order to explain the regiochemistry of four center reactions, like these cycloadditions, the HSAB principle, in a local sense, needs to also be considered apart from the local softness. Chandra and Nguyen have correlated the idea of the local HSAB concept and regioselectivity defining a quantity, said 'delta' (Δ), that suggests a measure of predominance of one reaction over the other on the base of local softness s.[33b,34] This quantity is so defined:

$$\Delta_{ij}^{kl} = (s_i - s_k)^2 + (s_j - s_l)^2 \tag{2}$$

where i and j are the atoms of a molecule **A** involved in the formation of a cycloadduct with atoms k and l of a molecule **B**, and s_i's are the appropriate type of atomic softnesses (if s_i and s_j are electrophilic then s_k and s_l are obviously nucleophilic).

The idea is based on the simultaneous fulfillment of the local HSAB concept at both termini. This is because, in the case of a multicenter addition reaction, it is not the similarities of softness at one center that are important. Δ can be considered a measure of how extensively the HSAB principle is satisfied. The reaction associated with a lower Δ value will be the preferred one.

The local softness s was calculated as a product fS, where f is the condensed form of Fukui functions calculated as reported elsewhere,[35] utilizing the MK derived charges.

The values obtained for s_i's and the corresponding Δs values, referred at both *meta* and *ortho* channels, for the cycloadditions of **3** with **1a** and **1b** are reported in Tables 1 and 2, respectively.

In the case of the 1,3-DC of **1a** with **3**, we should consider only the Δ values for a $HOMO_{1a}$–$LUMO_3$ approach, in agreement to global parameter analysis. The Δ values for both *meta* and *ortho* channels are similar with the *meta* channel slightly predominating and both regioisomers are expected to be formed. On the contrary, in the 1,3-DC between **1b** and **3**, we should consider only the Δ values for a $LUMO_{1b}$–$HOMO_3$ approach. In the case of the C_1═C_2 approach, the Δ value of the *meta* channel is lower than that of the *ortho* one, clearly indicating a net predominance of the **P5** regioisomer. On the contrary, in the case of the C_3═C_4 approach, the Δ value for the *ortho* channel slightly predominates and the **P4** regioisomer is favored. Nevertheless, the *meta* Δ value for the C_1═C_2 approach is the lowest one and then **P5** is the only product expected. Thus, the charge approach predicts the experimental results for the 1,3-DC reaction of **1a** well, whereas the local softness approach reproduces the experimentally observed results for the reaction of **1b**.

3.3. Cycloaddition with anthracene

3.3.1. Energies of the transition structures. The absolute and relative free and electronic energies with respect to reactants for the two transition structures located for the reaction between **1a** and **3** are collected in Table 3.

The predicted activation free energy for the *meta* channel is lower than that corresponding to the *ortho* channel. Accordingly, it can be predicted that the **P1** regioisomer will be formed preferentially, in agreement with experimental observations.

For **TS1** and **TS2**, which correspond to the transition structures for the approach in the *meta* and *ortho* channels,

Table 2. Δ values, for the 1,3-DC reactions of **1a** and **1b** with **3**, calculated as described in the text

1a+3						**1b+3**					
$C_1{=}C_2$[a]		$C_1{=}C_2$				$C_1{=}C_2$			$C_3{=}C_4$[a]		
$HOMO_{1a}-LUMO_3$	Δ_{ortho} 0.17	$LUMO_{1a}-HOMO_3$	Δ_{meta} 0.14	Δ_{ortho} 0.24	$HOMO_{1b}-LUMO_3$	Δ_{meta} 0.11	Δ_{ortho} 0.12	$LUMO_{1b}-HOMO_3$	Δ_{meta} 0.11	Δ_{ortho} 0.28	$HOMO_{1b}-LUMO_3$	Δ_{meta} 0.17	Δ_{ortho} 0.20	$LUMO_{1b}-HOMO_3$	Δ_{meta} 0.20	Δ_{ortho} 0.16
Δ_{meta} 0.16																

[a] Referred to the attach of **3** on the double bond of **1a,b**.

Table 3. B3LYP/6-31G(d) relative free energies (Δ*G*) (kcal/mol) and relative electronic energies (Δ*E*) (kcal/mol) for the reaction of **1a** with **3**

	Direct ΔE[a]	Inverse ΔE[b]	Direct ΔG[a]	Inverse ΔG[b]
TS1	23.81	30.65	36.99	29.95
TS2	24.50	32.03	37.67	30.46
P1	−6.84		7.04	
P2	−7.53		7.21	

[a] Referred to **1a**+**3**.
[b] Referred to the corresponding products.

respectively, Mulliken population analysis (MPA) provides some evidence for secondary orbital interactions (SOIs) between the two reactants.[36] In fact the **TS1** shows a positive overlap density of 0.003, 0.004, 0.003, 0.004 and 0.006 for C_6H_{28}, C_7H_{28}, $C_{10}C_{18}$, $C_{10}C_{19}$ and $H_{27}H_{29}$ respectively; similar interactions can be seen in **TS2** (C_8H_{30}=0.005, C_9H_{30}=0.006, $H_{27}H_{29}$=0.005 and $C_{18}H_{28}$=0.003), but these latter are, globally, less intense. Moreover, if we take into account that this 1,3-DC is mainly conducted in toluene at reflux temperature, i.e. at 110 °C, on the basis of the reverse barrier energies reported in Table 3, we can assume that the reactions at hand are reversible and then under thermodynamic control. Nevertheless, in this case the kinetic and thermodynamic products are coincident and then only the formation of **P1** is noticeable, in good agreement with the experimental.[3a]

3.3.2. Geometries of the transition structures. The optimized geometries of two transition structures corresponding to the reaction of **1a** with **3**, and leading to the two possible products **P1** and **P2**, are illustrated in Figure 2. Some relevant structural features of the transition structures are given in Table 4.

For both transition structures **TS1** and **TS2**, the lengths of the C−C forming bonds (2.08 and 2.09 Å) are markedly shorter than the lengths of the C−O ones (2.25 and 2.24 Å). Taking into consideration that C−O sigma bonds are shorter than C−C sigma bonds, the difference of the lengths of the two forming bonds are borderline for a concerted process with a significant asynchronicity. It is well-known that when a 1,3-DC cycloaddition presents asynchronous TSs, diradical structures could in principle be involved.[37] This as been ruled out repeating the TSs calculations using the keyword STABLE, present in Gaussian 98, at both RB3LYP/6-31G(d) and UB3LYP/6-31G(d) levels. In all cases the wavefunction was stable under the perturbations considered.

3.3.3. Bond order and charge analysis. The concept of bond order (BO) can be utilized to obtain a deeper analysis of the extent of bond formation or bond breaking along a reaction pathway. This theoretical tool has been used to study the molecular mechanism of chemical reactions. To follow the nature of the formation process for C_1-C_2 and C_3-O_4 bonds, the Wiberg bond indexes[38] have been computed by using the NBO population analysis as implemented in Gaussian 98. The results are included in Table 4.

The general analysis of the bond order values for the two TSs structures showed that the cycloaddition process is

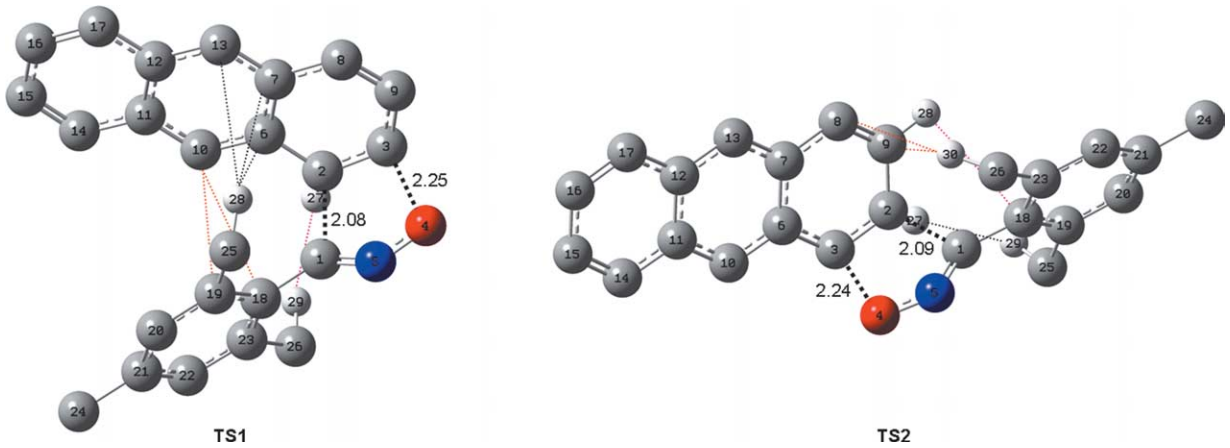


Figure 2. Optimized geometries at B3LYP/6-31G(d) level for transition structures leading to **P1** and **P2**. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms. SOI are represented by coloured dotted lines.

Table 4. Delocalization energies (ΔE in kcal/mol) from reactants to TSs, bond orders (Wiberg indexes) for the two forming bonds in the TSs and charge transfer (a.u.) in terms of the residual charge of the nitrile oxide fragment in the transition state

	ΔE^a	C_1-C_2	C_3-O_4	NPA q_{CT} (e)
TS1	319.12	0.394	0.247	−0.036
TS2	293.87	0.384	0.255	−0.040

[a] Calculated using a secondary-order perturbation theory (SOPT) analysis of the Fock matrix.

asynchronous with a greater value for the forming C_1-C_2 bonds in both cases, showing that the extent of asynchronicity is the same for the two channels.

The natural population analysis[39] allows the evaluation of the charge transferred between the two reactants at the TS geometry. The charge transfer in terms of the residual charge on the nitrile oxide, for all the optimized TSs, is shown in Table 4. The negative values are indicative of an electron flow from the HOMO of the **1a** to the LUMO of **3**, in agreement to their electronic chemical potential values, but their magnitudes reveal an almost neutral reaction.

From the results of the secondary-order perturbation theory (SOPT) analysis shown in Table 4, an important increment in the delocalization energy appears on passing from reactants to TSs. Even though there is not a strict correlation between the energies of the TSs and the total energies of delocalization, an examination of the contributions due to inter-reactant delocalizations, accounts for the SOI pointed out by the MPA. Thus, **TS1** is stabilized by a series of delocalizations that are: $\pi\rightarrow\sigma^*$ (0.13 kcal/mol) of the $C_6{=}C_{10}$ aromatic double bond of the anthracene moiety with the antibonding orbital of the $C_{25}-H_{28}$ bond of a methyl on nitrile oxide moiety and the analogous $\pi\rightarrow\sigma^*$ (0.19 kcal/mol), due to the $C_7{=}C_{13}$ with $C_{25}-H_{28}$. Moreover, two other stabilizations due to a $\pi\rightarrow\pi^*$ of the $C_6{=}C_{10}$ with $C_{18}{=}C_{23}$ and $C_{19}{=}C_{20}$ double bonds of the mesito ring (0.24 and 0.16 kcal/mol, respectively), are evident. Finally, the two mutually corresponding delocalizations $\sigma\rightarrow\sigma^*$ of C_2-H_{27} with $C_{26}-H_{29}$ and $C_{26}-H_{29}$ with C_2-H_{27} (0.22 and 0.43 kcal/mol, respectively) complete this framework. Although these singularly taken interactions are weak, their sum correspond to a delocalization energy of 1.37 kcal/mol. On the other hand, for the **TS2**, a $\pi\rightarrow\sigma^*$ (0.57 kcal/mol) stabilization, due to the $C_8{=}C_9$ double bond of **1a** with $C_{26}-H_{30}$ single bond of a methyl on **3**, and a $\sigma\rightarrow\sigma^*$ one (0.43 kcal/mol) due to the $C_{25}-H_{29}$ with C_2-H_{27}, for a total of 1.00 kcal/mol, are evident. This is completely in agreement with the greater stability of **TS1** vs. **TS2** due to the strongest SOI achieved in the approach.

3.4. Cycloaddition with acridine

3.4.1. Energies of the transition structures. The absolute and relative free energies for the four transition structures located for the reaction between **1b** and **3** are indicated in Table 5.

Table 5. B3LYP/6-31G(d) relative free energies (ΔG) (kcal/mol) and relative electronic energies (ΔE) (kcal/mol) for the reaction of **1b** with **3**

	Direct ΔE^a	Inverse ΔE^b	Direct ΔG^a	Inverse ΔG^b
TS3	22.62	31.28	36.65	28.62
TS4	25.02	31.82	37.94	30.03
TS5	23.70	30.44	36.83	29.51
TS6	24.12	31.60	37.36	30.09
P3	−8.65		8.03	
P4	−6.80		7.91	
P5	−6.74		7.32	
P6	−7.48		7.93	

[a] Referred to **1b**+**3**.
[b] Referred to the corresponding products.

As in the case of **1a**, the activation free energies for the *meta* channel are lower in energy than those corresponding to the *ortho* channel and they point to the prediction of a near equimolar mixture of **P3** and **P5** adducts. However, if we look to the inverse activation free energies, the 1,3-DC at hand is, once again, reversible and then under thermodynamic control and therefore the **P5** product is preferentially formed, in good agreement with experimental observations.[9]

Even in the case of **TS3** and **TS5**, MPA provides some evidence for their greater stability with respect to **TS4** and **TS6**, due to SOI effects. In particular, the **TS5** shows a series of positive overlap density of 0.002, 0.004, 0.004,

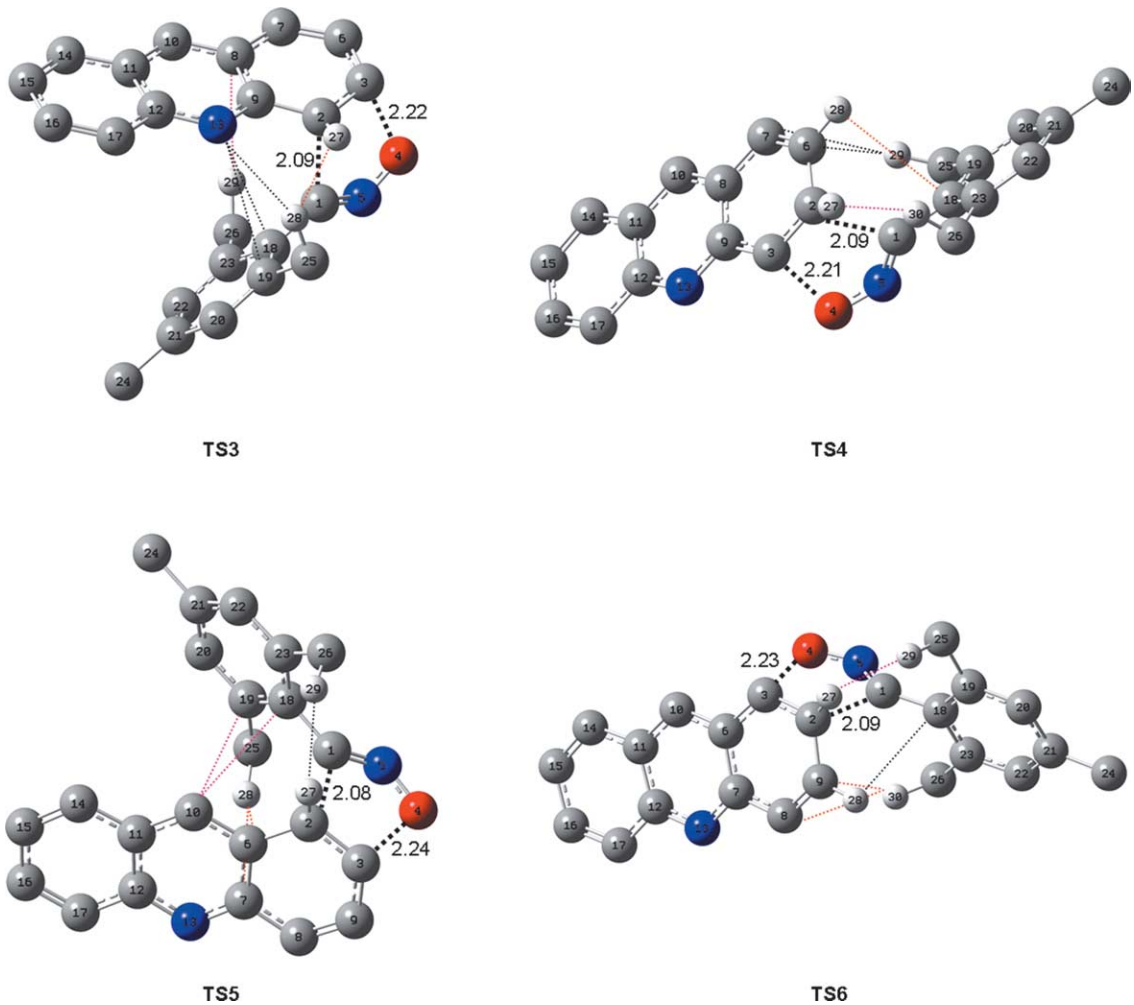


Figure 3. Optimized geometries at B3LYP/6-31G(d) level for transition structures leading to **P3**–**P6**. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms. SOI are represented by coloured dotted lines.

0.003 and 0.006 for C_6H_{28}, C_7H_{28}, $C_{10}C_{18}$, $C_{10}C_{19}$ and $H_{27}H_{29}$, respectively, that stabilizes it over the others.

3.4.2. Geometries of the transition structures. The optimized geometries of four transition structures corresponding to the reaction of **1b** with **3**, and leading to the four possible products **P3**, **P4**, **P5**, and **P6**, are illustrated in Figure 3.

For the cycloaddition of **1b** with **3**, the lengths of the forming bonds are closer than those for the reaction with **1a**. The lengths of the C–C forming bonds (2.08–2.09 Å) are shorter than the C–O forming bonds (2.21–2.24 Å) in both *meta* and *ortho* channels. Since C–O bonds are longer than C–C bonds, once again, this 1,3-DC is borderline of a concerted process with a significant asynchronicity.

3.4.3. Bond order and charge analysis. The general analysis of the bond order values for all the TSs structures showed that the cycloaddition process is particularly asynchronous with an interval, in the Wiberg bond indexes, of 0.381–0.394 for the forming C_1–C_2 bonds and 0.250–0.264 for the forming C_4–O_3 (Table 6). This analysis is also in agreement with the corresponding imaginary frequency values that are generally lower for the more asynchronous TSs.[40] What has been said, is also valid for the comparison of reactions of **3** with **1a** and **1b**: in the first case, the lower imaginary frequency value corresponds to the more asynchronous TS.

The charge transfer, evaluated by the natural population analysis, in terms of the residual charge on the nitrile oxide, for all the optimized TSs is shown in Table 6. The negative values are indicative of an electron flow from the HOMO of **1b** to the LUMO of **3**, in contrast to the lower value of the electronic chemical potential of **3** (μ=−0.13107) with respect to that of **1b** (μ=−0.14082), revealing an almost neutral reaction.

Table 6. Delocalization energies (ΔE in kcal/mol) from reactants to TSs, bond orders (Wiberg indexes) for the two forming bonds in the TSs and charge transfer (a.u.) in terms of the residual charge of the nitrile oxide fragment in the transition state

	ΔE^a	C_1–C_2	C_3–O_4	NPA q_{CT} (e)
TS3	476.21	0.387	0.256	−0.014
TS4	349.73	0.381	0.264	−0.013
TS5	378.98	0.394	0.250	−0.022
TS6	381.84	0.385	0.260	−0.029

[a] Calculated using a secondary-order perturbation theory (SOPT) analysis of the Fock matrix.

From the results of the SOPT analysis showed in Table 6 there is an important increment in the delocalization energy on passing from reactants to TSs. Even though there is not a strict correlation between the energies of the TSs and the total energies of delocalization, an examination of the contributions due to inter-reactant delocalizations, accounts for the SOI pointed out by the MPA. Thus, e.g. the **TS5** is stabilized by a series of delocalizations that are: the $\pi \rightarrow \sigma^*$ (0.11 kcal/mol) of the $C_6{=}C_{10}$ aromatic double bond of the acridine moiety with the antibonding orbital of the $C_{25}{-}H_{28}$ bond of a methyl on nitrile oxide moiety and the analogous $\pi \rightarrow \sigma^*$ (0.11 kcal/mol), due to the $C_7{=}N_{13}$ with $C_{25}{-}H_{28}$, and the two $\sigma \rightarrow \pi^*$ (0.03 and 0.05 kcal/mol) of $C_{25}{-}H_{28}$ with $C_6{=}C_{10}$ and $C_7{=}N_{13}$, respectively. Moreover, another two stabilizations due to a $\pi \rightarrow \pi^*$ of the $C_6{=}C_{10}$ with $C_{18}{=}C_{23}$ and $C_{19}{=}C_{20}$ double bonds of the mesito ring (0.25 and 0.15 kcal/mol, respectively), are found evident. Finally, the four mutually corresponding delocalizations $\sigma \rightarrow \sigma^*$ of $C_2{-}H_{27}$ with $C_{26}{-}H_{29}$ and $C_{26}{-}H_{29}$ with $C_2{-}H_{27}$ (0.21 and 0.43 kcal/mol, respectively) and $\pi \rightarrow \pi^*$ of the $C_{18}{=}C_{23}$ and $C_{19}{=}C_{20}$ with $C_6{=}C_{10}$ (0.09 and 0.06 kcal/mol, respectively) complete this framework. Although these singularly taken interactions are weak, their sum corresponds to a delocalization energy of 1.49 kcal/mol; thus, the **TS5** results, as a rough average, to be 0.27 kcal/mol more stabilized with respect to the other analogous TSs, by SOIs.

4. Conclusions

In conclusion, it may be generalized that in endothermic 1,3-DC reactions, such as the reactions at hands, the FMO theory does not provide a satisfactory explanation of the experimental results, while these are rationalized in terms of DFT calculations coupled to HSAB principle; this methodology has already demonstrated a more powerful level of reliability.[11d,e,12j]

In the 1,3-DCs of **1a**,**b** with **3**, the predicted preference for the *meta* channel transition structure is substantial, leading to a theoretical preference for **P1**, **P3** and **P5** regioisomers, respectively. The predominant production of **P1** and **P5** adducts is correctly predicted on further considerations of MPA and SOI interactions and thermodynamic control; moreover, their low yields are justifiable in consideration of the elevated cycloreversion process of the reactions, due to a partial loss of aromaticity. The results obtained agree with the experimental findings for both **1a**,**b**. Moreover, considerations based on the ground state lead to successful rationalization of the selectivity.

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Oxime-based methods for synthesis of stereodefined acyclic polyfunctionalized δ-azido-nitriles and 5-substituted isoxazoles from carbohydrate derivatives

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Abstract—Hydroxylamine-mediated syntheses of stereodefined acyclic polyfunctionalized δ-azido-nitriles and 5-substituted isoxazoles, bearing a differentially protected glycerol moiety, from 2-deoxysugars and glycals are described.

1. Introduction

Acyclic multifunctional compounds derived from sugars have played a key role in the field of synthetic organic chemistry for over 100 years, permitting useful transformations that are not possible with the parent sugars.[1] Significant reactions include treatment of sugars with nitrogen nucleophiles, such as hydroxylamine and phenylhydrazine.[2] Such reactions are generally irreversible and convert the parent sugars into the corresponding oximes and phenylhydrazones, which then can undergo further reactions.[3] It is well known that the construction of versatile building blocks has been a rewarding research topic, having provided us with powerful precursors for efficient synthesis of biologically active natural products.[4] Thus, the development of new methods in this field remains an important tool in modern synthetic chemistry.

In recent years, carbohydrate derivatives, such as glycals **1**, have shown an increasing synthetic versatility in many aspects of organic chemistry as valuable starting materials, allowing a range of preparatively useful applications.[5] To the best of our knowledge, few reports are available in the literature concerning the reactivity of glycals with nitrogen nucleophiles.[6]

Thus, a wide-ranging investigation of the use of glycals derived from both mono- and disaccharides in the reaction with nitrogen nucleophiles seemed to be of interest, as part of our continuing exploitation of the reactivity and the usefulness of carbohydrate derivatives in organic synthesis.[7] In the last few years, we have utilised cyclic enol ethers, easily available from disaccharides, such as lactose, cellobiose and melibiose, as attractive starting materials for the construction of unnatural glycosphingolipids.[8]

Here we describe some of our results in the development of carbohydrate-mediated applications, which have led us to prepare stereodefined polyfunctionalised hexanenitrile derivatives, that can be used as precursors in the synthesis of biologically active compounds, such as glycosylamines,[9] 1-β-amino-1-deoxynojirimycins[10] and D-glucoamidines[11] (Fig. 1).

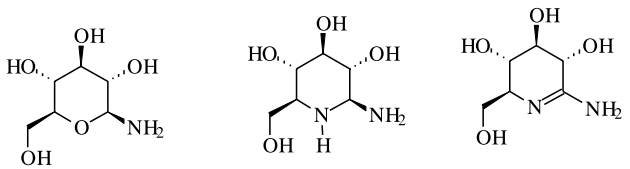

Figure 1. Structures of biologically active compounds.

It is worth noting that our particular aim was to find simplified synthetic strategies, and to be guided by readily available starting materials in conjunction with straightforward chemistry.

2. Results and discussion

2.1. Synthesis of stereodefined acyclic polyfunctional δ-azido-nitriles

We initially examined the reactivity of the glycals derived

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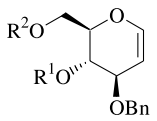
from disaccharides, such as perbenzylated melibial **1a**, lactal **1b**, cellobial **1c** and gentiobial **1d** with nitrogen nucleophiles. To our great surprise, the glycals **1a**, **b**, **c**, **d** were found to be completely unreactive upon treatment with hydroxylamine, even though the cyclic enol ethers should be regarded as a masked aldehydic group. However, the acid-catalysed reaction led to the formation of several decomposition products. Structures of compounds **1a**–**d** are as follows



1

a: melibial: R^1=Bn; R^2=2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl
b: lactal: R^1=2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl; R^2=Bn
c: cellobial: R^1=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl; R^2=Bn
d: gentiobial: R^1=Bn; R^2=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl

Recently, we described a short and valuable synthesis of 2-deoxysugars from glycals: protected glycals, derived from mono-, di- and trisaccharides were easily converted in excellent yields into the corresponding 2-deoxysugars, by treatment with aqueous mercuric(II) acetate/sodium borohydride in one reaction flask and on a large scale.[12] Stimulated by these results, we turned our attention to exploring the reactivity of 2-deoxysugars with nitrogen nucleophiles, particularly with the aim of finding strategies for the preparation of enantiomerically pure, multifunctional compounds.

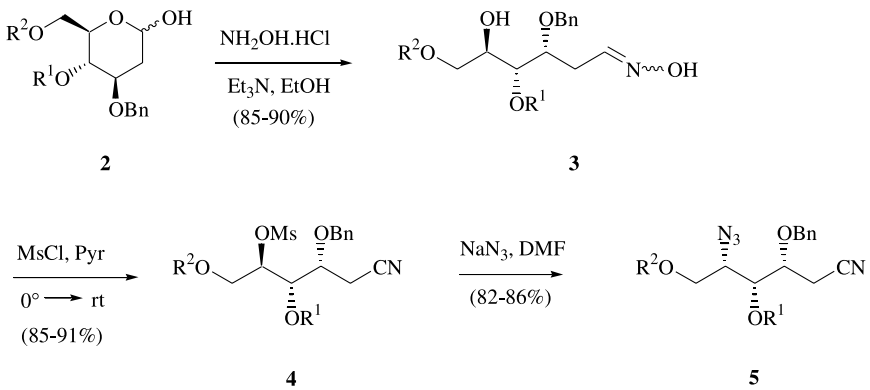
Reaction of 2-deoxysugars **2a**, **b**, **c**, **d** with two equivalents of hydroxylamine, prepared from hydroxylamine hydrochloride and triethylamine as an ethanolic solution, afforded the oxime derivatives **3a**, **b**, **c**, **d** as an inseparable *E*/*Z* mixture (70/30) in good yields (85–90%) (Scheme 1). The following dehydration was carried out in high yield by treatment with mesyl chloride in pyridine under described conditions, giving the corresponding δ-hydroxynitrile derivatives **4a**, **b**, **c**, **d** with the originally free hydroxyl group at C5 also protected as a mesylate (85–91%). This allows displacement of the mesylate and introduction of other functionality. For instance, the compounds **4** can easily undergo a nucleophilic substitution by reaction with sodium azide leading to the formation of the interesting *O*-glycosylated derivatives of (3*R*,4*R*,5*S*)-5-azido-3,4,6-trihydroxy-hexanenitrile, such as **5** (86%). It is worth noting that all the products **3**, **4**, **5** prepared according to the described protocol, are single stereoisomers, multifunctional compounds.

As described, conveniently protected multifunctional compounds, such as **4** and **5**, have been successfully utilised as key precursors in the asymmetric synthesis of glycosidase inhibitors,[13] sphingoid base scaffold,[14] several kinds of antibiotics,[15] unusually hydroxylated amino acids[16] and other biologically active compounds.[17] The results show the flexibility of the strategy, which allows variation of the stereochemistry of multifunctional compounds, by selecting the correct starting sugars, and allowing an easy access to a library of stereochemically pure chiral synthons.

2.2. Synthesis of 5-substituted isoxazoles

Stemming from the above results, we wanted to explore the reactivity of the cyclic enol ethers by introducing a keto group at C3 of the glycals to enhance its capability as a Michael acceptor. Recently, the conjugate additions of nucleophiles to cyclic enol ethers of glycals, such as 2-nitrogalactal, have received increasing interest, due to their high reactivity in this field of reaction, and permitting the synthesis of useful intermediates.[18]

The enones, such as **10**, were prepared following a modified procedure previously described by Kirschning.[19] Unfortunately, only the perbenzylated melibial **1a** and gentiobial **1d** could be oxidized to the corresponding enones (70% and 60% respectively) by treatment with bis-acetoxyiodobenzene (BAIB) and *para*-toluenesulfonic acid. The



2 **3** **4** **5**

a: R^1=Bn; R^2=2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl
b: R^1=2',3',4',6'-tetra-*O*-benzyl-β-D-galactopyranosyl; R^2=Bn
c: R^1=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl; R^2=Bn
d: R^1=Bn; R^2=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl

Scheme 1. Synthesis of **5a**–**c**.

perbenzylated lactal **1b** and cellobial **1c**, which possess a glycosyl moiety at C4, were completely recovered unchanged.

Indeed, the enones **10**, when treated with two equivalents of hydroxylamine were able to undergo conjugate addition at C1. However, the reaction directly afforded the isoxazolines **11** (80–83%) as an inseparable epimeric mixture, and containing a differentially functionalised glycerol moiety (Scheme 2). The results can be explained by initial attack of the nucleophile at C1, opening of the cyclic enol ether, formation of the oxime derived from the aldehydic group and its intramolecular ring closure on the keto group at C3. Then, the dehydration reaction, carried out by treatment with *para*-toluenesulfonic acid in dichloromethane at room temperature, gave isoxazole derivatives **12** (92–95%). The structure was completely in agreement with the ^{1}H NMR spectroscopy data: for instance, **12a** showed two doublets at 8.24 δ (J=2.0 Hz, 1H, 3-H) and at 6.36 δ (J=2.0 Hz, 1H, 4-H) respectively, typical of 5-substituted isoxazoles.[7a]

The transformation should be considered valuable, since isoxazole-containing natural and non-natural compounds show interesting biological properties,[20] such as nicotinic acetylcholine receptor ligands,[21] glutamic receptors agonists[22] or fungicides and herbicides.[23]

3. Conclusion

In conclusion, the exploration of the reactivity of carbohydrate derivatives, such as 2-deoxysugars and glycals, has led us to disclose a concise and efficient entry to a variety of stereodefined polyfunctionalised hexanenitrile derivatives, potentially valuable chiral molecules in the synthesis of biologically active compounds. Since the δ-azido-hexanenitriles were obtained in three simple steps from the corresponding reducing 2-deoxysugars, the methodology appears to be practical for large scale application. Various transformations of the multifunctional compounds are in progress and will be presented in due course.

4. Experimental

4.1. General

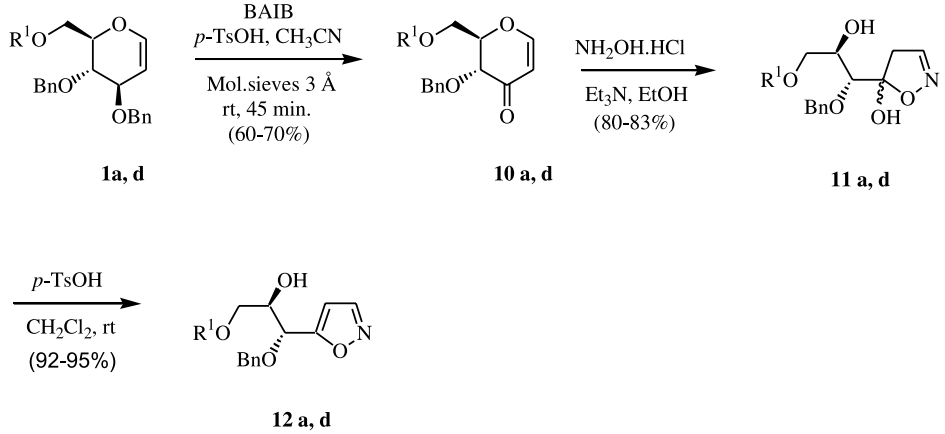
^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Varian Gemini 200 spectrometer with $CDCl_3$ as the solvent and as the internal standard. IR spectra were recorded on IR-470 infrared spectrophotometer Shimadzu. HRMS spectra were recorded with Micromass Q-TOF micro Mass Spectrometer (Waters). Optical rotations were measured using sodium D line on DIP 370 Jasco digital polarimeter. Yields are given for isolated products after column chromatography showing a single spot on TLC and no detectable impurities in ^{1}H NMR spectra. All reactions were performed under an inert atmosphere of N_2 in flame-dried glassware. All solvents and commercially available reagents were used without purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck F-254 silica glass plates visualized with UV/light and heat-gun treatment with 2 M H_2SO_4 solution. Column chromatography was performed with Merck silica gel 60 (230–400 mesh).

4.2. Starting materials

All glycosyl glycals **1a–d** were prepared from their corresponding disaccharides.[21] Since the compounds **1d** and **2d** were never described before, we report their analytical data in the Section 4.

4.3. General procedure for preparation of azide derivates

To a solution of **2** (1 mmol) in absolute ethanol (10 mL) was added triethylamine (3 mmol) and hydroxylamine hydrochloride (2 mmol) at 0 °C. The solution was stirred at room temperature for 12 h; thereafter the solution, concentrated in vacuo, was purified by silica gel chromatography (hexane/ethyl acetate 7:3) to give **3** as an inseparable *E*/*Z* mixture (70/30; yield 86–90%). Mesyl chloride (2.7 mmol) was



a: melibial: R^1=2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl

d: gentiobial: R^1=2',3',4',6'-tetra-*O*-benzyl-β-D-glucopyranosyl

Scheme 2. Synthesis of the isoxazoles **12a** and **12d**.

added to **3** (0.9 mmol) in dry pyridine (3.5 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was diluted with diethyl ether and, after treatment with ice-cold 6 M hydrochloric acid (9 mL) and saturated $NaHCO_3$, was washed with water, brine and, after dried over Na_2SO_4, the organic solution, concentrated in vacuo, was purified on silica gel chromatography (hexane/ethyl acetate 7.5:2.5) to give **4** (yield 86–91%). The mesyl derivative **4** (0.85 mmol) and NaN_3 (14 mmol) in dry DMF (12 mL) were stirred for 36 h at 100 °C. The reaction mixture was diluted with ethyl ether, washed with water, brine and, after dried over Na_2SO_4, was concentrated in vacuo and chromatographed on silica gel (hexane/ethyl acetate 4:1) to give **5** (yield 82–86%).

4.3.1. (3*R*,4*R*,5*S*)-3,4-Di-*O*-benzyl-5-azide-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl) hexanenitrile 5a. *Compound* **3a** (*E*/*Z* mixture), viscous colorless oil (0.90 mmol, 0.79 g, yield 90%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3570, 3350, 3090, 3080, 1500, 1460, 1095, 1070, 1030. ^1H NMR, δ ($CDCl_3$): 7.30–7.0 (30H, m); 6.83 (0.5H, t, J=4.5 Hz), 6.65 (0.5H, t, J=4.5 Hz); 4.82–4.22 (13H, m); 4.05–3.22 (10.5H, m); 2.89 (0.5H, q, J=8.5 Hz); 2.65 (1H, t, J=4.5 Hz); 2.43 (1H, t, J=4.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 149.3, 149.2 (C1); 139.4–138.0 ($C_{quat.}$, Ph); 129.4–125.9 (Ph); 99.2 (C1′); 80.5; 79.0; 77.4; 76.7; 74.9; 74.1; 74.0; 73.9; 73.9; 73.6; 72.9; 72.9; 70.8, 70.7, 70.4, 70.3 (CH_2Ph, C3, C4, C2′,C3′, C4′, C5′, C6, C6′); 69.9, 69.0 (C5); 42.9, 40.0 (C2). HRMS Calcd for $C_{54}H_{59}NO_{10}$ $[M+NH_4]^+$ 899.4139, found 899.4133.

Compound **4a**, viscous colorless oil (0.80 mmol, 0.75 g, yield 89%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3093, 3090, 3080, 2020, 1600, 1500, 1350, 1165, 1075. $[\alpha]_D$ +16.0 (*c* 1.2, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.60–7.25 (30H, m): 5.18–4.30 (15H, m); 4.22–3.89 (7H, m); 3.60 (2H, m); 2.86 (3H, s); 2.58 (2H, t, J=4.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.7, 138.6, 138.5, 138.1, 137.2, 137.1 ($C_{quat.}$, Ph); 128.8–128.7 (Ph); 117.8 (CN); 98.0 (C1′); 80.7; 79.3; 78.5; 76.4; 75.1; 74.0, 70.2 (C3, C4, C5, C2′,C3′, C4′, C5′); 74.8, 74.7, 73.8, 73.7, 73.4 (CH_2Ph); 69.2 (C6′); 65.9 (C6); 38.7 (CH_3SO_2); 19.9 (C2). HRMS Calcd for $C_{55}H_{59}NO_{11}S$ $[M+NH_4]^+$ 959.3809, found 959.3803.

Compound **5a**, viscous colorless oil (0.68 mmol, 0.61 g, yield 86%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 2990, 2985, 2099, 1510, 1460 1360, 1240, 1094, 1042. $[\alpha]_D$ +22.0 (*c* 1.6, $CHCl_3$). ^1H NMR, δ, ($CDCl_3$): 7.58–7.30 (30H, m); 5.09–4.45 (15H, m); 4.12–3.68 (8H, m); 3.60 (1H, m,); 2.65 (2H, t, J=4.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.8, 138.7, 138.1, 137.5, 137.3 ($C_{quat.}$, Ph); 128.7–127.7 (Ph); 118.1 (CN); 99.1 (C1′); 78.9; 78.6; 76.6; 75.2; 75.1 (C3, C4, C2′, C3′, C5′); 74.9, 74.7, 73.7, 73.6, 73.2, 73.2 (CH_2Ph); 70.2 (C4′); 69.3 (C6′); 63.3 (C6); 60.4 (C5); 19.6 (C2). HRMS Calcd for $C_{54}H_{56}N_4O_8$ $[M+NH_4]^+$ 906.4098, found 906.4091.

4.3.2. (3*R*,4*R*,5*S*)-3,6-Di-*O*-benzyl-5-azide-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl) hexanenitrile 5b. *Compound* **3b** (*E*/*Z* mixture), viscous colorless oil (0.90 mmol, 0.79 g, yield 90%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3575, 3350, 3090, 3080, 1600, 1460, 1095, 1075, 1040. ^1H NMR, δ ($CDCl_3$): 7.65–7.25 (30.5H, m); 6.90 (0.5H, t, J=4.5 Hz); 5.05–4.37 (13H, m); 4.25–3.40 (11H, m); 2.85 (1H, m); 2.65 (1H, m). ^{13}C NMR, δ ($CDCl_3$): 150.2 (C1); 138.8, 138.5, 138.3, 138.0 ($C_{quat.}$, Ph); 128.5–127.6 (Ph); 103.9 (C1′); 82.5; 79.4; 77.8; 77.4; 77.2; 76.9; 75.3; 74.7; 73.8; 73.6; 73.3; 73.0; 72.5, 72.3 (CH_2Ph, C3, C4, C2′,C3′, C4′, C5′); 70.8, 70.6 (C5); 68.8, 68.9 (C6, C6′); 30.4, 26.2 (C2). HRMS Calcd for $C_{54}H_{59}NO_{10}$ $[M+NH_4]^+$ 899.4139, found 899.4143.

Compound **4b**, viscous colorless oil (0.81 mmol, 0.77 g, yield 91%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3090, 3082, 3067, 2016, 1610, 1520, 1348, 1160, 1080. $[\alpha]_D$ +7.0 (*c* 1.0, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.50–7.20 (30H, m); 5.10–4.42 (15H, m); 4.28 (2H, s); 4.20–3.46 (7H, m); 2.93 (3H, s); 2.93 (1H, dd, A of ABX system, J_{AB}=12.0 Hz, J_{AX}=4.5 Hz); 2.72 (1H, dd, B of ABX system, J_{BA}=12.0 Hz, J_{BX}=7.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.8, 138.7, 138.4, 137.9, 137.6, 137.3 ($C_{quat.}$, Ph); 128.6–127.6 (Ph); 118.4 (CN); 103.3 (C1′); 82.6, 80.1, 79.2, 77.2, 74.5; 73.6, 73.5 (C3, C4, C5, C2′, C3′, C4′, C5′); 75.4, 74.8, 73.7, 73.6, 73.2, 73.0, 72.9, 68.2 (CH_2Ph, C6, C6′); 38.1 (CH_3SO_2); 19.6 (C2). HRMS Calcd for $C_{55}H_{59}NO_{11}S$ $[M+NH_4]^+$ 959.3809, found 959.3805.

Compound **5b**, viscous colorless oil (0.78 mmol, 0.69 g, yield 86%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 2920, 2898, 2099, 2122, 1500, 1460, 1368, 1190, 1015. $[\alpha]_D$ +5.8 (*c* 1.4, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.49–7.20 (30H, m); 5.01–4.35 (15H, m); 4.10 (1H, m, H-2) 3.95–3.45 (8H, m); 2.98 (1H, dd, A of ABX system, J_{AB}=12.2 Hz, J_{AX}=4.5 Hz); 2.80 (1H, dd, B of ABX system, J_{AB}=12.2 Hz, J_{BX}=7.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.7, 138.6, 138.4, 137.9, 137.7, 137.3 ($C_{quat.}$, Ph); 128.5–127.7 (Ph); 119.1 (CN); 105.0 (C1′); 82.5; 79.1, 75.5; 75.2; 74.7 73.0 (C3, C4, C2′, C3′, C4′, C5′); 73.7, 73.6, 73.2, 73.1 (CH_2Ph); 69.2; 68.9 (C6, C6′); 59.6 (C5); 19.7 (C2). HRMS Calcd for $C_{54}H_{56}N_4O_8$ $[M+NH_4]^+$ 906.4098, found 906.4094.

4.3.3. (3*R*,4*R*, 5*S*)-3,6-Di-*O*-benzyl-5-azide-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl) hexanenitrile (5c). *Compound* **3c** (*E*/*Z* mixture), viscous colorless oil (0.86 mmol, 0.76 g, yield 86%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3577, 3355, 3090, 3080, 1610, 1460, 1095, 1075, 1040. ^1H NMR, δ ($CDCl_3$): 7.62 (0.5H, t, J=4.5 Hz); 7.55–7.22 (30H, m); 7.0 (0.5H, t, J=4.5 Hz); 5.09–4.40 (13H, m); 4.30–3.40 (11H, m); 3.0–2.63 (2H, m). ^{13}C NMR, δ ($CDCl_3$): 150.2, 150.1 (C1); 138.8, 138.5, 138.3, 138.1 ($C_{quat.}$, Ph); 128.5–127.1 (Ph); 103.4 (C1′); 84.9, 82.3, 77.4, 75.7, 75.0, 74.8, 73.5, 73.4, 72.6, 72.4 (CH_2Ph, C3, C4, C2′,C3′, C4′, C5′); 72.5, 72.4 (C5); 69.6, 68.1 (C6, C6′); 30.5, 28.1 (C2). HRMS Calcd for $C_{54}H_{59}NO_{10}$ $[M+NH_4]^+$ 899.4139, found 899.4131.

Compound **4c**, viscous colorless oil (0.73 mmol, 0.69 g, yield 85%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3091, 3082, 3067, 2013, 1613, 1523, 1343, 1161, 1080. $[\alpha]_D$ +7.7 (*c* 1.2, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.52–7.20 (30H, m); 5.13–5.40 (13H, m); 4.34 (2H, s); 4.18 (1H, m, H-2); 3.85–3.36 (8H, m); 3.03 (1H, dd, A of ABX system, J_{AB}=11.8 Hz, J_{AX}=4.5 Hz); 3.92 (3H, s); 2.70 (1H, dd, B of ABX system, J_{BA}=11.8 Hz, J_{BX}=7.0 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.4, 138.2, 138.1, 137.2, ($C_{quat.}$, Ph); 128.4–127.6 (Ph); 118.1 (CN); 102.6 (C1′); 84.7, 81.8, 79.6, 75.5, 74.8 (C3, C4, C2′, C3′, C5′); 74.8, 74.7, 73.3 (CH_2Ph); 72.9, 72.8 (C5, C4′);

68.4, 67.8 (C6, C6′); 38.9 (CH_3SO_2); 19.4 (C2). HRMS Calcd for $C_{55}H_{59}NO_{11}S$ $[M+NH_4]^+$ 959.3809, found 959.3808.

Compound **5c**, viscous colorless oil (0.60 mmol, 0.53 g, yield 82%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3010, 2890, 2100, 1665, 1509, 1458, 1399, 1365, 1094. $[\alpha]_D$ +4.3 (*c* 1.5, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.46–7.18 (30H, m); 4.98–4.38 (13H, m); 4.36 (2H, s); 4.13 (1H, m, H-2); 3.78 (8H, m); 2.98 (1H, dd, A of ABX system, J_{AB}=11.8 Hz, J_{AX}=4.5 Hz); 2.80 (1H, dd, B of ABX system, J_{BA}=11.8 Hz, J_{BX}=7.0 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.4, 138.1, 137.3 ($C_{quat.}$, Ph); 128.5–127.6 (Ph); 118.9 (CN); 104.4 (C1′); 84.8, 81.9, 75.7, 75.3, 74.9 (C3, C4, C2′, C3′, C5′); 73.6, 73.26, 73.13, 72.92 (CH_2Ph, C4′); 69.2; 69.0 (C6, C6′); 59.9 (C5); 19.5 (C2). HRMS Calcd for $C_{54}H_{56}N_4O_8$ $[M+NH_4]^+$ 906.4098, found 906.4098.

4.3.4. 3,4-Di-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (gentiobial) 1d. The compound **1d** was prepared from the commercially available gentiobiose according to a described procedure.[24] Starting from gentiobiose (14.6 mmol, 5.0 g), **1d** was obtained as amorphous white solid (7.5 g, 8.9 mmol, yield 60%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3090, 3080, 1650, 1610, 1460, 1095, 1075, 1040. $[\alpha]_D$ +44.3 (*c* 1.1, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.52–7.20 (30H, m); 6.56 (1H, d, *J*=6,2 Hz); 5.20–4.7 [15H, m, C*H*$_2$Ph (12H), H-2, H-1′, H-3′]; 4.40–4.20 (4H, m, H-3, H-4, H-2′, H-4′); 4.10–3.57 (6H, m, H-5, H-5′, 2H-6, 2H-6′). ^{13}C NMR, δ ($CDCl_3$):145.02 (C1); 138.83, 138.78, 138.20, 137.47 ($C_{quat.}$, Ph); 128.77–127.63 (Ph); 104.27 (C1′); 99.86 (C2); 84.78, 82.13, 79.06, 75.77, 75.25, (C3, C4, C2′, C3′, C4′); 73.70, 73.61, 73.23, 73.17 (CH_2Ph); 73.15 (C5, C5′); 69.24; 68.94 (C6, C6′). HRMS Calcd for $C_{54}H_{56}O_9$ $[M+NH_4]^+$ 866.3924, found 866.3930.

4.3.5. 3,4-Di-*O*-benzyl-2-deoxy-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-D-glucopyranose 2d. *Compound* **2d** was prepared from the perbenzylated gentiobial **1d** following our previous method.[12] Starting from **1d** (1 mmol, 0.85 g), **2d** was obtained as viscous colorless oil (0.90 mmol, 0.78 g, yield 90%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3577, 3355, 3090, 3080, 1610, 1460, 1095, 1075, 1040. $[\alpha]_D$ +12.3 (*c* 1.3, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.52–7.20 (30H, m); 5.25 (1H, bs, H-1); 5.10–4.25, [14H, m, C*H*$_2$Ph (12H), H-1′, H-3′]; 4.40–4.20 (4H, m, H-3, H-4, H-2′, H-4′); 4.10–3.57 (6H, m, H-5, H-5′, 2H-6, 2H-6′); 2.27–1.92 (2H, m, 2H-2). ^{13}C NMR, δ ($CDCl_3$): 138.8–137.4 ($C_{quat.}$, Ph); 128.2–126.1 (Ph); 103.3, 102.6 (C1′); 93.0, 92.7 (C1); 82.3, 80.2, 79.1, 75.8, 73.8, 73.1, 72.3, 72.0, 71.8, 71.6, 70.2, 69.5, 67.1, (C3, C4, C5, C6, C2′, C3′, C4′, C5′, C6′, CH_2Ph); 36.6, 34.4 (C2). Anal. CALCD. for $C_{54}H_{58}O_{10}$: C, 74.80, H, 6.74. Found: C, 74.82, H, 6.59.

4.3.6. (3*R*,3*4*,5*S*)-3,4-Di-*O*-benzyl-5-azide-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-hexanenitrile 5d. *Compound* **3d**, (*E*/*Z* mixture), viscous colorless oil, (0.79 mmol, 0.70 g, yield 88%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3575, 3350, 3090, 3080, 1630, 1460, 1095, 1075, 1040. ^1H NMR, δ ($CDCl_3$): 7.65–7.25 (30.5H, m); 6.82 (0.5H, t, *J*=4.5 Hz); 5.13–4.28 (13H, m); 4.25–3.40 (11H, m); 2.85 (1H, m); 2.65 (1H, m). ^{13}C NMR, δ ($CDCl_3$):149.8, 149.6 (C1); 139.4–138.0 ($C_{quat.}$, Ph); 129.4–125.9 (Ph); 103.7 (C1′); 83.9, 82.3, 77.5, 75.7, 75.1, 74.8, 73.5, 73.4, 72.6, 72.4, 72.5, 72.4 (C3, C4, C5, C2′, C3′, C4′, C5′, CH_2Ph); 69.6, 68.1 (C6, C6′); 30.4, 28.2 (C2). HRMS Calcd for $C_{54}H_{59}NO_{10}$ $[M+NH_4]^+$ 899.4139, found 899.4141.

Compound **4d**, viscous colorless oil (0.72 mmol, 0.68 g, yield 91%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3091, 3067, 2990, 2013, 1613, 1523, 1343, 1161, 1080. $[\alpha]_D$ +18.7 (*c* 1.4, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.52–7.20 (30H, m); 5.13–5.40 (13H, m); 4.34 (2H, s); 4.18 (1H, m, H-2); 3.85–3.36 (8H, m); 3.92 (3H, s); 3.03 (1H, m, H_A-1); 2.70 (1H, m, H_B-1). ^{13}C NMR, δ ($CDCl_3$): 138.4, 138.2, 138.1, 137.2, ($C_{quat.}$, Ph); 128.4–127.6 (Ph); 117.3 (CN); 102.7 (C1′); 83.7, 81.7, 79.6, 75.6, 74.4 (C3, C4, C2′, C3′, C5′); 74.8, 74.7, 73.3 (CH_2Ph); 72.8, 72.8 (C5, C4′); 68.5, 67.6 (C6, C6′); 38.9 (CH_3SO_2); 19.3 (C2). HRMS Calcd for $C_{55}H_{59}NO_{11}S$ $[M+NH_4]^+$ 959.3809, found 959.3807.

Compound **5d**, viscous colorless oil (0.61 mmol, 0.54 g, yield 85%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 2950, 2890, 2100, 1680, 1500, 1450, 1360, 1099. $[\alpha]_D$ +31.0 (*c* 1.7, $CHCl_3$). ^1H NMR, δ, ($CDCl_3$): 7.58–7.30 (30H, m); 5.09–4.45 (15H, m); 4.12–3.68 (8H, m); 3.60 (1H, m,); 2.65 (2H, t, *J*=4.5 Hz). ^{13}C NMR, δ ($CDCl_3$): 138.83, 138.77, 138.15, 137.56, 137.27 ($C_{quat.}$, Ph); 128.71–127.71 (Ph); 118.11 (CN); 104.28 (C1′); 82.57; 79.06; 75.57; 75.25; 74.77 (C2, C3, C2′, C3′, C4′); 73.70, 73.61, 73.23, 73.17 (CH_2Ph); 73.10 (C5′); 69.24; 68.94 (C5, C6′); 59.62 (C4); 19.70 (C1). HRMS Calcd for $C_{54}H_{56}N_4O_8$ $[M+NH_4]^+$ 906.4098, found 906.4096.

4.4. General procedure for preparation of isoxazoles

To a solution of **1** (1.16 mmol) in dry CH_3CN (20 mL) and in the presence of molecular sieves, BAIB (450 mg, 1.15 mmol) was added and stirred for 10 min at room temperature. Then, *p*-TSOH (265 mg, 1.4 mmol) was added portionwise under stirring during 45 min, until no starting material was detectable and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (hexane/ethyl ether 7:3) to give pure compound **10** (yield 60–70%). To a solution of **10** (0.73 mmol) in absolute ethanol (5 ml) were added triethylamine (2.7 mmol) and hydroxylamine hydrochloride (1.8 mmol). The solution was stirred at room temperature for 4 h; thereafter the solution was evaporated, the crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate 7:3) to give **11** as inseparable epimeric mixture (yield 80–83%). A solution of **11** in dry CH_2Cl_2 (4 mL) was stirred with 5 mg of *para*-toluensulfonic acid for 6–8 h at room temperature; the reaction was diluted with diethyl ether and, after cold-ice treatment with saturated $NaHCO_3$, was washed with water, brine and, after dried over Na_2SO_4, the organic solution, concentrated in vacuo, was purified on silica gel chromatography (hexane/ethyl ether 6:4) to give **12** (yield 92–95%).

4.4.1. 5-[(1*R*,2*R*)-1-Benzyl-2-hydroxy-3-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)]isoxazole (12a). *Compound* **10a**, viscous colorless oil (0.81 mmol, 0.61 g, yield 70%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 2950, 2890, 1680 (C=O),

1500, 1450, 1360, 1099. $[\alpha]_D$ +7.0 (*c* 1.2, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.53–7.20 [26H, m, (5xPh, H-1)]; 5.37 (1H, d, *J*=3.5 Hz, H-1′); 5.08–4.40 [13H, m, (5×CH_2Ph, H-2, H-4, H-3′)]; 4.18–3.80 [5H, m, (H-5, H-2′, H-4′, 2H-6′)]; 3.65–3.40 [3H, m, (H-5′, 2H-6)]. ^{13}C NMR, δ ($CDCl_3$): 193.0 (C3); 161.8 (C1); 138.5–137.4 ($C_{quat.}$, Ph); 128.4–127.4 (Ph); 105.0 (C2); 98.1 (C1′); 81.1, 78.4, 76.9, 76.6, 74.9, 74.6 (C4, C5, C2′, C3′, C4′, C5′); 74.4, 74.2, 73.3, 73.1, 72.9 (CH_2Ph); 69.6, 68.3 (C6, C6′). HRMS Calcd for $C_{47}H_{48}O_9$ $[M+NH_4]^+$ 774.3298, found 774.3296.

Compound **11a**, viscous colorless oil (0.67 mmol, 0.53 g, yield 83%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3575, 3350, 3090, 3080, 2990, 1650, 1450, 1095, 1075, 1040. ^1H NMR, δ ($CDCl_3$): 7.52–7.25 [26H, m, (5xPh, H-1)]; 5.10–4.30 (16H, m); 4.20–3.40 (5H, m); 2.80 (2H, m). ^{13}C NMR, δ ($CDCl_3$): 147.2, 147.1 (C3); 138.4,137.7, 137.6, 137.5, 136.8 ($C_{quat.}$, Ph); 128.3–127.4 (Ph); 108.0, 106.8 (C5); 99.9, 99.6 (C1″); 80.0, 78.7, 76.3, 74.6, 74.4, 74.1, 73.4, 72.7, 72.2, 71.4, 70.7, 70.1, 69.0 (C1′, C2′, C3′ C2″, C3″, C4″, C5″, C6″ CH_2Ph); 43.2, 42.9 (C4). HRMS Calcd for $C_{47}H_{51}NO_{10}$ $[M+NH_4]^+$ 807.3513, found 807.3508.

Compound **12a**, viscous colorless oil (0.63 mmol, 0.49 g, yield 95%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3575, 3090, 2995, 1660, 1458, 1100, 1075, 1040. $[\alpha]_D$ +12.0 (*c* 1.2, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 8.24 (1H, d, *J*=2.0 Hz, H-3); 7.43–7.25 (25H, m, 5xPh); 6.36 (1H, d, *J*=2.0 Hz, H-4); 4.98–4.40 (15H, m); 4.18–3.40 (6H, m); 2.68 (1H, bs, OH). ^{13}C NMR, δ ($CDCl_3$): 170.08 (C5); 150.21 (C3); 138.08–137.17 ($C_{quat.}$, Ph); 128.56–127.57 (Ph); 102.56 (C4); 99.58 (C1″); 78.86, 77.98, 76.84, 76.50, 75.02, 74.86 (C1′, C2′, C2″, C3″, C4″, C5″); 73.86, 73.77, 73.50, 73.30, 73.15 (CH_2Ph); 70.82, 69.67 (C3′, C6″). HRMS Calcd for $C_{47}H_{49}NO_9$ $[M+NH_4]^+$ 789.3407, found 789.3997.

4.4.2. 5-[(1*R*,2*R*)-1-Benzyl-2-hydroxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)]isoxazole (12d). *Compound* **10d**, viscous colorless oil (0.69 mmol, 0.53 g, yield 60%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3010, 2985, 1670 (C═O), 1510, 1460 1360, 1240, 1094, 1042. $[\alpha]_D$ +97.0 (*c* 1.2, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 7.50–7.24 [26H, m, (5×Ph, H-1)]; 5.08–4.40 [14H, m, (5×CH_2Ph, H-2, H-4, H-1′, H-3′)]; 4.18–3.80 [5H, m, (H-5, H-2′, H-4′, 2H-6′)]; 3.65–3.40 [3H, m, (H-5′, 2H-6)]. ^{13}C NMR, δ ($CDCl_3$): 193.2 (C3); 162.1 (C1); 138.6–137.6 ($C_{quat.}$, Ph); 128.5–127.7 (Ph); 105.2 (C2); 104.1 (C1′); 84.8, 82.2, 81.0, 75.7, 75.0, 74.8 (C4, C5, C2′, C3′, C4′, C5′); 75.0, 74.8, 74.3, 73.6, 73.2 (CH_2Ph); 68.9, 67.9 (C6, C6′). HRMS Calcd for $C_{47}H_{48}O_9$ $[M+NH_4]^+$ 774.3298, found 774.3300.

Compound **11d**, viscous colorless oil (0.55 mmol, 0.44 g, yield 80%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3575, 3350, 3010, 1650, 1455, 1091, 1077, 1050. ^1H NMR, δ ($CDCl_3$): 7.58–7.25 [26H, m, (5xPh, H-1)]; 5.0–4.33 (16H, m); 4.20–3.45 (5H, m); 2.90 (2H, m). ^{13}C NMR, δ ($CDCl_3$): 147.3, 147.1 (C3); 138.3, 138.1, 137.9, 137.7, 137.5, 137.3 ($C_{quat.}$, Ph); 128.3–127.6 (Ph); 108.0, 106.9 (C5); 104.3, 104.1 (C1″); 84.4, 82.1, 79.5, 77.5, 75.6, 74.6, 74.4, 73.5, 70.8, 70.1, 68.7 (C1′, C2′, C3′ C2″, C3″, C4″, C5″, C6″ CH_2Ph); 44.2, 43.7 (C4). HRMS Calcd for $C_{47}H_{51}NO_{10}$ $[M+NH_4]^+$ 807.3513, found 807.3518.

Compound **12d**, viscous colorless oil (0.5 mmol, 0.39 g, yield 92%); IR ν_{max} ($CHCl_3$)/cm^{-1}: 3560, 3090, 3010, 2980, 1630, 1440, 1095, 1090, 1040. $[\alpha]_D$ +126.0 (*c* 1.5, $CHCl_3$). ^1H NMR, δ ($CDCl_3$): 8.22 (1H, d, *J*=2.0 Hz, H-4); 7.41–7.25 (25H, m, 5xPh); 6.31 (1H, d, *J*=2.0 Hz, H-4); 5.04–4.42 (13H, m); 4.25 (2H, m); 4.20–3.45 (6H, m); 2.55 (1H, bs, OH). ^{13}C NMR, δ ($CDCl_3$): 170.5 (C5); 150.1 (C3); 138.6–137.3 ($C_{quat.}$, Ph); 128.5–127.7 (Ph); 104.5 (C1″); 102.4 (C4); 84.6, 82.2, 77.8, 74.8, 73.8, 72.0 (C1′, C2′, C2″, C3″, C4″, C5″); 75.7, 75.0, 73.6, 72.6, 72.1 (CH_2Ph); 70.1, 68.8 (C3′, C6″). HRMS Calcd for $C_{47}H_{49}NO_9$ $[M+NH_4]^+$ 789.3407, found 789.3411.

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Efficient synthesis of 2- and 3-substituted-2,3-dihydro [1,4]dioxino[2,3-*b*]pyridine derivatives

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Abstract—A versatile new approach for the synthesis in three steps of 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **B** via a Smiles rearrangement using easily available reagents is described. A study illustrating the influence of experimental conditions on the progress of the reaction is reported.

1. Introduction

The 2,3-dihydro[1,4]benzodioxin ring constitutes an important skeletal fragment in medicinal chemistry and hence, a variety of reports have been presented for their synthesis and biological evaluation of compounds including this ring.[1] Some of them are antagonists of α-adrenergic receptors, with antihypertensive properties.[2–6] Other have affinities for serotonin receptors involved in nervous breakdown and schizophrenia[7–12] or represent an attractive therapeutic target for the treatment of glaucoma.[13] Moreover, they showed additional interesting properties used for the treatment and prevention of atherosclerosis and oxidative injuries.[14] Recently, 2,3-dihydro[1,4]benzodioxins have been developed as inhibitors of 5-lipoxygenase, an enzyme involved in the oxygenation of arachidonic acid to the leukotriens. They are also useful for the treatment of inflammatory diseases such as asthma and arthritis.[15] The occurrence of the 2,3-dihydro[1,4]-benzodioxin structure in various naturally abundant compounds has been already reported.[16,17]

In connection with the development of new potential 5-HT_{1A} ligands, we are interested in the study of the 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine skeleton. To the best of our knowledge, only this polyheterocyclic system has been prepared by treatment of 3-hydroxy-2-pyridone with base and 1,2-dibromoethane.[18] This method, unfortunately too restrictive, not only gives unsatisfactory yield but also makes the introduction of various substituents in the six-membered non aromatic moiety infeasible.

Previously, we have reported the synthesis of 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine derivatives functionalized at the oxygenated moiety in position 3 (**A** in Fig. 1).[19] Compounds **B** (Fig. 1) substituted in position 2 were mentioned only once and are obtained by a relatively long synthesis implementing starting materials such as the 2-chloro-3-pyridinol and the 1-acetoxy-3-benzyloxy-2-propanol.[20] In addition, E. Matesanz et al. have recently described a new strategy for the synthesis of 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine and 7-substituted-6,7-dihydro-[1,4]dioxino[2,3-*d*]pyrimidine developed as potential new therapeutic agents.[21]

Figure 1.

In continuation of our research program concerning the dioxinopyridines, we have reported a convenient effective synthetic pathway to 2-substituted-2,3-dihydro-[1,4]-dioxino[2,3-*b*]pyridines **B**[22] via a Smiles rearrangement.[23] A similar approach was developed by Y. J. Yoon et al. for the synthesis of pyrido[2,3-*b*][1,4]oxazin-2-ones by one-pot

Keywords: 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridine; Smiles rearrangement; Nucleophilic aromatic substitution.
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annulation of *N*-substituted-2-chloroacetamides with 2-halo-3-hydroxypyridines.[24] In addition, we recently described a practical and effective synthetic route to isomeric 2- and 3-substituted-2,3-dihydro-spiro[1,4]-dioxino[2,3-*b*]pyridine amino derivatives, developed as potential 5-HT_{1A} ligands.[25] The present paper is focused on the extension of this preliminary work and on the study of the influence of experimental conditions (e.g., base, solvent, nucleofuge and substrate structure) on the progress of the Smiles rearrangement.

2. Results and discussion

Our strategy consists, first, in the formation of the epoxide **2a**–**f** and then on its opening by appropriate nucleophiles to the corresponding alcohols **3a**–**f**, **4b**, **4e**, **5b**, **5e**, **6b**, **6e**, **7b** and **7e**. Alcohols are the key intermediates for the synthesis of the target molecules.

Epoxides **2a**–**f**, prepared by treatment of pyridinol **1a**–**f** with excess epichlorohydrin using NaH in DMF, were used after purification for subsequent reactions with nucleophiles (Scheme 1). Given the diversity of the possible means of opening for an oxirane, it is possible to prepare compounds bearing diversified substituents on the oxygenated moiety.

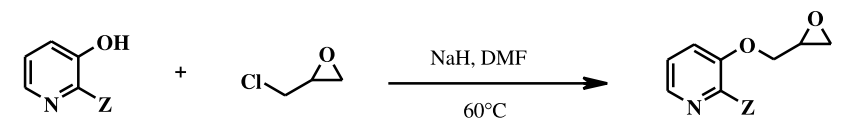
2.1. Preparation of the alcohols 3–6

Compounds containing an arylpiperazine moiety constitute a class of important agents with a variety of pharmacological activities.[26] Indeed, the ring opening of epoxide **2** with phenylpiperazine was promoted by use of THF at reflux, affording the corresponding amino alcohols **3a**–**f** in good yields (Scheme 2). The reaction was carried out with only 3 equiv. of amine.

A stirring slurry of activated commercially available Woelm 200 neutral chromatographic alumina (500 °C, 24 h) catalyzed the regioselective opening of epoxides **2b** and **2e** by benzyl alcohol under mild conditions (25 °C, THF)[27] to give the corresponding functionalized alcohols **4b** and **4e** in satisfactory yields (Scheme 3). The similar ring opening of epoxides **2b** and **2e** by *N*-methylbenzylamine or benzylamine at reflux of THF gave the corresponding amino alcohols **5b** and **5e** or **6b** and **6e** in good yields (Scheme 3). The synthesis of the azido alcohols **7b** and **7e** was achieved through the regioselectively opening of the epoxides **2b** and **2e** with sodium azide, in the presence of ammonium chloride[28] (Scheme 3).

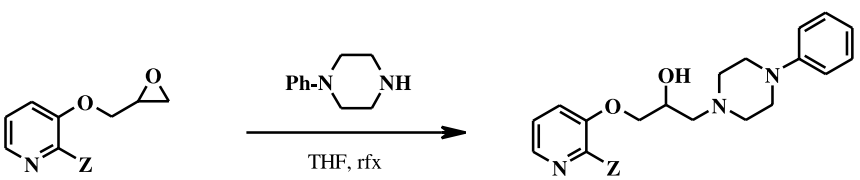
2.2. Cyclization reaction

The second part of the study concerned the cyclization of the alcohols **3**–**7** by intramolecular nucleophilic aromatic substitution (S_NAr) to afford the 3-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **A**[19d] (Scheme 4, pathway a). However, due to the selected experimental conditions (e.g., base, solvent, nucleofuge and substrate structure), 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]-pyridines **B** (Scheme 4, pathway b) have been isolated in fairly good yields. Formation of the isomers **B** could be explained by a Smiles rearrangement involving the attack of alkoxide on the 3-position of pyridine ring with displacement of the alkoxide, and the subsequent closure of the delivered alkoxide into the 2-position of pyridine ring.



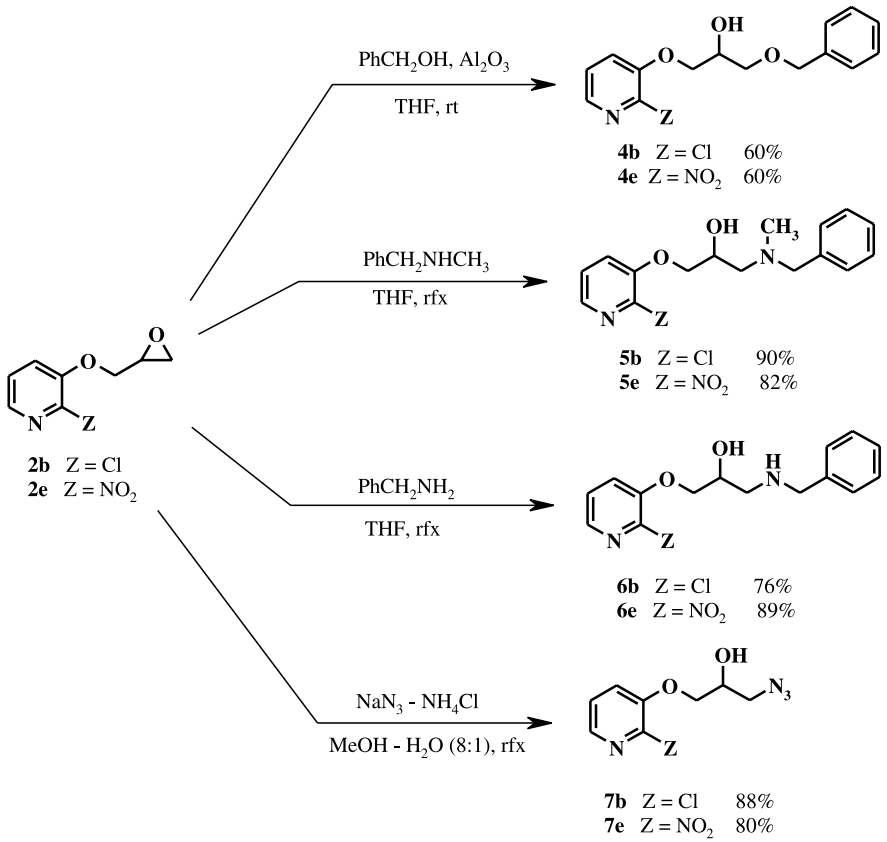
	1a	Z = F	**2a** Z = F 82%
	b	Z = Cl	**b** Z = Cl 85%
	c	Z = Br	**c** Z = Br 83%
a)	**d**	Z = I	**d** Z = I 75%
	e	$Z = NO_2$	**e** $Z = NO_2$ 81%
	f	Z = OMe	**f** Z = OMe 85%

Scheme 1. (a): (i) NaH, DMF, $PhCH_2Br$, rt; 91%. (ii) MeONa, DMF, 80 °C; 92%. (iii) H_2, Pd/C 10%, MeOH, rt; 85%.

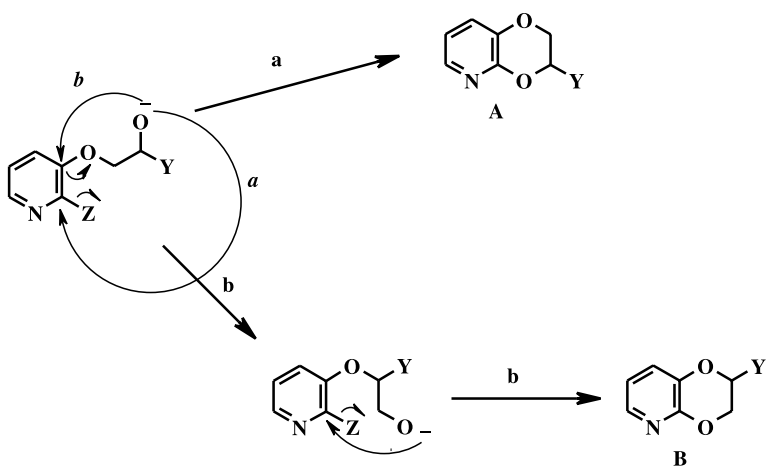


2a	Z = F	**3a**	Z = F 91%
b	Z = Cl	**b**	Z = Cl 95%
c	Z = Br	**c**	Z = Br 90%
d	Z = I	**d**	Z = I 85%
e	$Z = NO_2$	**e**	$Z = NO_2$ 88%
f	Z = OMe	**f**	Z = OMe 74%

Scheme 2.



Scheme 3.

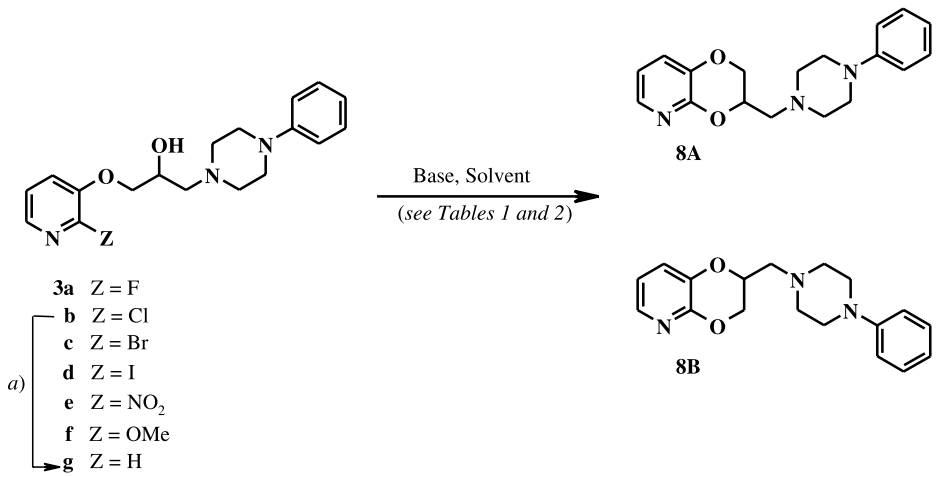


Scheme 4.

The two **A** and **B** isomers resulting from the cyclization of alcohols **3a**–**g** are presented in Scheme 5.

A study of conditions affecting this rearrangement was carried out by varying different parameters such as nucleofuge, base and solvent. The results obtained from the cyclization reaction of alcohols **3a**–**g** are summarized in Table 1.

The Smiles rearrangement is facilitated when the aromatic ring is activated by electron-withdrawing groups in the *ortho* position. In fact, after extensive optimization studies, we found that the use of the strong electron-withdrawing nitro group as leaving group increased the yield of rearranged product **B**. In the entry 5, whatever base and solvent conditions, it was found that the total yield of the intramolecular cyclization reaction is excellent, and consequently, the isomer **8B** was isolated as major product. These results are highly interesting because they afford an access to the isomer **B** in three steps starting from the pyridinols **1**. The isomers **8A** and **8B** were separated by flash chromatography and their structures were assigned mainly based on NMR (1D and 2D). Moreover, the structure of **8A**, as a racemic mixture, was confirmed by X-ray diffraction,



Scheme 5. (a): AcONa, Pd/C 10%, MeOH, rt, 12 h; 90%.

Table 1. Cyclization of compounds **3**

Entry	Z	Base/solvent	*T* (°C)	*t* (h)	Products **8** (yield %)[a]	
					A	**B**
1	F	NaH/DME	80	48	58	—
		t-BuOK/*t*-BuOH	80	48	50	7
2	Cl	NaH/DME	80	72	62	—
		t-BuOK/*t*-BuOH	80	72	45	15
3	Br	NaH/DME	80	48	67	—
		t-BuOK/*t*-BuOH	80	48	56	13
4	I	NaH/DME	80	48	65	8
		t-BuOK/*t*-BuOH	80	48	61	14
5	NO_2	NaH/DME	80	12	30	59
		t-BuOK/*t*-BuOH	80	12	44	52
6	OMe	NaH/DME	80	72	5[b]	—
7	H	NaH/DME	80	72	—[c]	—[c]

[a] Isolated yield of each isomer after separation by flash chromatography.
[b] The starting material was recovered in 78% yield.
[c] Only the starting material was recovered in 75% yield.

clearly identifying the substitution position on the dioxine ring (Fig. 2). In the solid state, the conformation of **8A** is quasi planar, with a dihedral angle O(15)–C(14)–C(13)–N(10)=−170.7(1)°. Bond lengths and angles do not show surprising features.

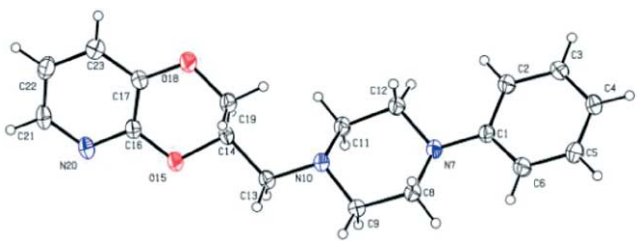


Figure 2. The ORTEP drawing of **8A** with thermal ellipsoids at 30% level.

After having shown the interest of the leaving group choice for the Smiles rearrangement pathway, we tested the feasibility of this rearrangement in absence of any leaving group. For this purpose, the corresponding **3g** alcohol was prepared from alcohol **3b** in the presence of AcONa, Pd/C in MeOH, in 90% yield. In this case, only the starting material without any trace of the rearranged compound was obtained by using the operating conditions described in Table 1, entry 7.

As can be seen from Table 1, the ratio of isomers **8A** and **B** varies also, with the nature of base and solvent. In entries 1–4, only one **A** isomer is obtained with the NaH/DME system, except with iodine ion, while similar low yields in rearranged product **B** are obtained with the *t*-BuOK/*t*-BuOH system (entries 2–4). Note also, when different counterions (Na^+, Li^+ and K^+) were tested, no particular influence was noticed concerning the formation of isomer **B** (Table 2).

Table 2. Effect of the counterion on the cyclization of the compound **3e**

Entry	Z	Base/solvent	*T* (°C)	*t* (h)	Products (yield %)	
					A	**B**
1	NO_2	NaH/DME	80	12	30	59
2	NO_2	LiH/DME	80	8	37	51
3	NO_2	KH/DME	80	4	34	50

In order to expand this study, on the basis of these results, we selected the alcohols **4**, **5**, **6** and **7** with chloro and nitro group as leaving groups to synthesize the corresponding **A** and **B** isomers. The desired products were obtained with satisfactory yields, by using the same conditions of cyclization reactions (Tables 3 and 4 and Scheme 6).

When NaH was used for deprotonation of chloro-alcohols **4b**, **6b** and **7b** (entries 1, 9 and 13, respectively), we obtained exclusively the **A** product from normal ring closure. However, a mixture of the **A** and **B** isomers was formed upon deprotonation by using *t*-BuOK in *t*-BuOH.

On the other hand, when *t*-BuOK/*t*-BuOH was used for deprotonation of **4b**, **5b** and **7b** (entries 2, 6 and 14, respectively) low yields of **B** were obtained, whereas only traces of **B** were observed from alcohol **6b** (entry 10).

Table 3. Cyclization of compounds **4**, **5** and **6**

Entry	Y	Z	Base/solvent	*T* (°C)/*t* (h)	Products (yield %)[a]	Ratio[b] (**A/B**)
1	OCH_2Ph	Cl	NaH/DME	80/72	65	100/0
2			*t*-BuOK/*t*-BuOH	80/72	60	70/30
3	OCH_2Ph	NO_2	NaH/DME	80/12	98	50/50
4			*t*-BuOK/*t*-BuOH	80/12	94	40/60
5	$N(CH_3)CH_2Ph$	Cl	NaH/DME	80/72	60	100/0
6			*t*-BuOK/*t*-BuOH	80/72	62	75/25
7	$N(CH_3)CH_2Ph$	NO_2	NaH/DME	80/12	88	70/30
8			*t*-BuOK/*t*-BuOH	80/12	89	30/70
9	$NHCH_2Ph$	Cl	NaH/DME	80/72	65	100/0
10			*t*-BuOK/*t*-BuOH	80/72	64	95/5
11	$NHCH_2Ph$	NO_2	NaH/DME	80/12	90	45/55
12			*t*-BuOK/*t*-BuOH	80/12	89	30/70

[a] Yields of cyclization reaction after flash chromatography.
[b] Ratio of each isomer determined by ^1H NMR.

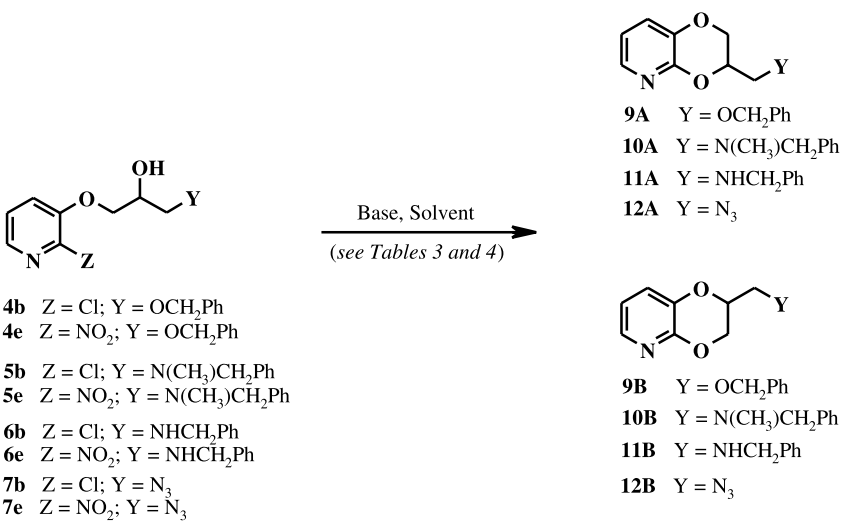
Table 4. Cyclization of compounds **7**

Entry	Y	Z	Base/solvent	*T* (°C)/*t* (h)	Products (yield %)[a]	
					A	**B**
13	N_3	Cl	NaH/DME	80/48	62	—
14			*t*-BuOK/*t*-BuOH	80/48	45	17
15	N_3	NO_2	NaH/DME	80/28	55	36
16			*t*-BuOK/*t*-BuOH	80/28	48	38

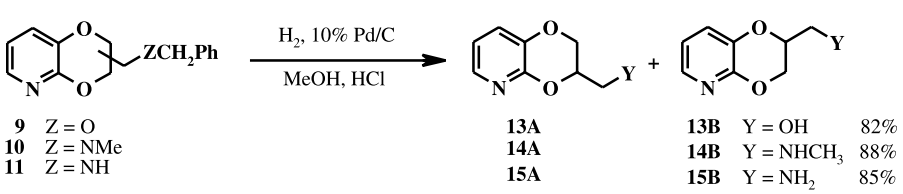
[a] Isolated yield after separation by flash chromatography.

Under similar cyclization reaction conditions the alcohols **4e**–**7e**, with a nitro leaving group, gave a mixture of the **A** and **B** isomers in various ratios (entries 3,7,11 and 15). Only isomers **12A** and **12B** were separated by column chromatography.

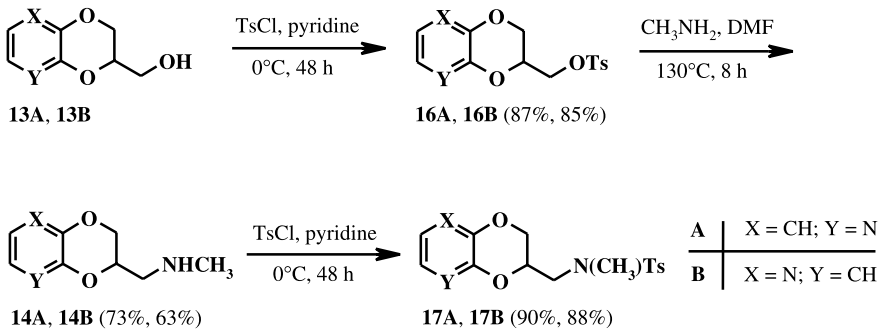
By analogy with results from a completed work in 2,3-dihydro[1,4]benzodioxin series,[12] it would be also necessary to have the aminomethyl or hydroxymethyl group in position 2 of the 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine. Thus, catalytic Pd/C hydrogenolysis of compounds **9**, **10** and **11** in methanol with a few drops of concentrated hydrochloric acid gave debenzylated products **13**, **14** and **15** in good yields (Scheme 7).



Scheme 6.



Scheme 7.



Scheme 8.

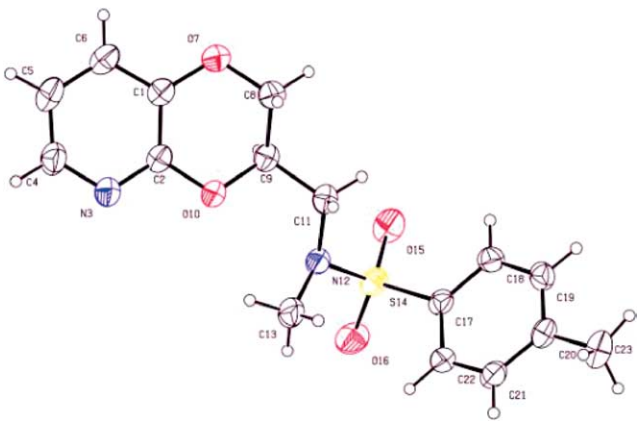


Figure 3. The ORTEP drawing of **17A** with thermal ellipsoids at 30% level.

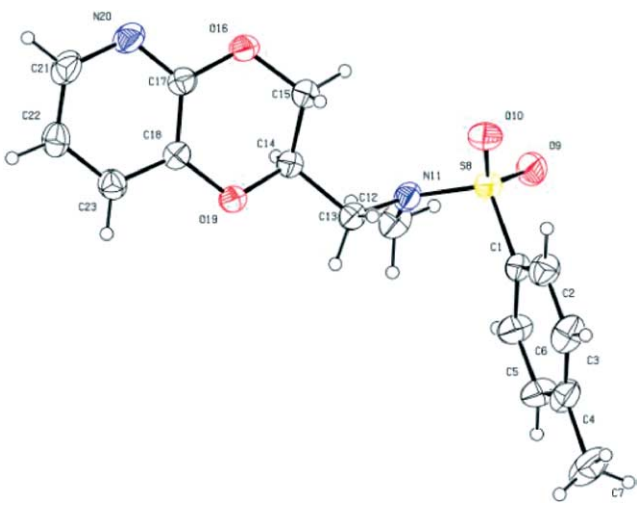


Figure 4. The ORTEP drawing of **17B** with thermal ellipsoids at 30% level.

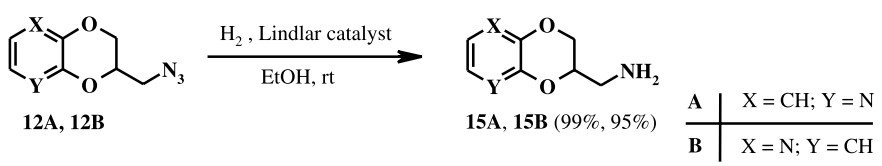
The isomeric mixtures (**13A**+**13B**), (**14A**+**14B**) and (**15A**+**15B**) were separated by column chromatography after debenzylation of compounds **9**, **10** and **11**, respectively.

By reaction with *p*-toluensulfonyl chloride in pyridine at 0 °C for 48 h the alcohols **13A** and **13B** afforded the expected derivatives **16A** and **16B** in excellent yields. Then, the nucleophilic replacement of the tosyl group with methylamine in DMF at 130 °C for 8 h produced the corresponding amines **14A** and **14B**.[29] Under similar sulfonation reaction conditions, the resulting amines **14A** and **14B** were converted into their sulfonated derivatives **17A** and **17B** in good yields (Scheme 8). The sulfonation reaction of the alcohols **13A** and **13B** and the *N*-methylamines **14A** and **14B** was realized to prove the structure of these isomers.

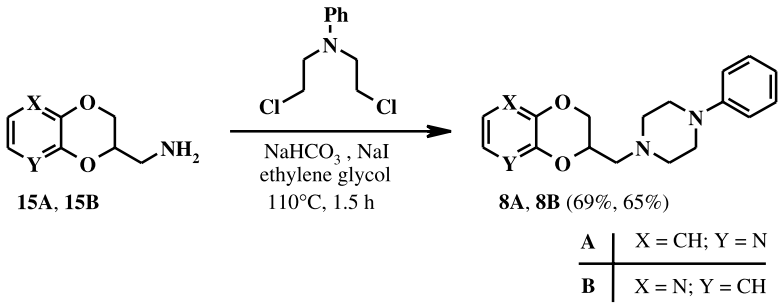
In order to formally establish the structure of these dioxinopyridine derivatives, an X-ray analysis was performed for **17A** and **17B**. ORTEP views of a single molecule of **17A** and **17B** are depicted in Figs. 3 and 4, respectively. In both cases, results confirmed the position of the lateral chain on the dioxine ring. In **17A** the C(9)–C(11) bond length is 1.524(5) Å, similar to the corresponding C(14)–C(13) bond length in **17B** [1.525(2) Å]. Fortuitously, the **17A** crystal used for the X-ray study is one enantiomer, as indicated by the spatial group ($P2_1$). The main conformational difference between **17A** and **17B** concerns the corresponding O(10)–C(9)–C(11)–N(12) and O(19)–C(14)–C(13)–N(11) dihedral angles, found at 59.9(2)° for **17A** and −164.7(2)° for **17B**, respectively. On the other hand, bond lengths and angles do not show surprising features. The X-ray data of **17A** and **17B** confirmed indirectly the structure of the alcohols **13A** and **13B** and the *N*-methylamines **14A** and **14B**.

As *N*-alkylated compounds are susceptible to present interesting biological proprieties, we decided to regenerate the free primary 2-(2,3-dihydro[1,4]-dioxino[2,3-*b*]pyridine)ylmethylamines **15A** and **15B**. Hence, the direct conversion of compounds **12** into the corresponding amines **15** was achieved by catalytic hydrogenation (Scheme 9).

These free amines **15A** and **15B** offer many possibilities for



Scheme 9.



Scheme 10.

further reactions. For example, the direct alkylation of these amines, with *N,N*-bis(2-chloroethyl)aniline in the presence of sodium hydrogen carbonate and sodium iodide in ethylene glycol afforded the expected dioxinopyridine derivatives **8A** and **8B** in 69%, 65% yields, respectively (Scheme 10). Moreover, this sequence allows to confirm the structures of **12A**, **12B**, and also of **15A**, **15B**.

3. Conclusion

In summary, using easily available reagents, we have developed a convenient strategy that gave access in satisfactory yields to the corresponding 2- and 3-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines (**A** and **B**). In comparison with classical synthesis of 3-substituted derivatives **A** by nucleophilic aromatic substitution (S_NAr), the access to 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **B** was realized in three steps via a Smiles rearrangement. By studying the influence of experimental conditions on the progress of the reaction we observed that the Smiles rearrangement is facilitated by activation of the aromatic ring by electron-withdrawing groups in the *ortho* position, for example, the use of the strong electron-withdrawing nitro group as leaving group increased the yield of rearranged product **B**. The functionalisation of these compounds in 2 or 3 position with aminomethyl or hydroxymethyl groups could be of potential utility for further developments in medicinal chemistry.

4. Experimental

Melting points were determined in capillary tubes with Büchi SMP-20 or on a Köfler apparatus and are uncorrected. IR spectra were obtained on Perkin–Elmer Paragon 1000 PC FT-IR. ^1H and ^{13}C NMR spectra were, respectively, recorded at 250 and 62.9 MHz on Bruker Avance DPX250. Chemical shifts (δ values) were reported in ppm and coupling constants (J values) in Hz. Me_4Si was the internal standard. Elemental analyses were performed by CNRS laboratory (Vernaison, France). Microanalyses for the elements indicated were within 0.3% of theoretical values. MS data were taken on a Perkin–Elmer SCIEX type API 300. TLC and flash chromatography separations were, respectively, performed on silica gel (Merck 60 F_{254}) plates and on silica gel (Merck 60, 230–400 mesh) columns. Commercial reagents were used as received without additional purification. All reactions involving moisture-sensitive reagents were performed under an argon atmosphere. All organic solvents were distilled immediately prior to use, and magnesium sulfate was used for drying solutions of organic solvents.

The crystal structures of **8A**, **17A** and **17B** have been determined by single-crystal X-ray diffraction techniques. Diffraction data were collected using a CAD4 Enraf–Nonius diffractometer with graphite monochromatized Cu Kα radiation. The cell parameters were determined by least-squares from the setting angles for 25 reflexions. An empirical absorption correction was applied. The data were also corrected for Lorentz and polarization effect. The positions of non-H atoms were determined by the program SHELXS 86[30] and the position of the H atoms were included for structure factor calculations but not refined.

For **8A**, the crystal is monoclinic, space group $P2_1/n$, with a=7.414(10) Å, b=7.005(4) Å, c=30.370(4) Å, β=90.94(1)°, and Z=4. A crystal 0.15×0.50×0.60 was chosen. For **17A**, the crystal is monoclinic, space group $P2_1$, with a=8.107(1) Å, b=6.179(1) Å, c=15.753(1) Å, β=92.74(1)°, and Z=2. A crystal 0.37×0.20×0.12 mm was chosen. For **17B**, the crystal is monoclinic, space group $P2_1/c$ with a=19.653(4) Å, b=5.828(1) Å, c=15.069(2) Å, β=112.33(2)°, and Z=4. A crystal 0.37×0.25×0.12 mm was chosen.

The X-ray results confirm the structure as anticipated on the basis of ^{13}C and ^1H NMR data. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Center (CCDC), UK, as Supplementary Materials.[31]

4.1. General procedure for the preparation of the epoxides 2a–f

To a stirred suspension of NaH (5.33 g of 60% oil dispersion, 158.60 mmol) in DMF (50 mL) was added dropwise a solution of appropriate pyridinol **1a–f** (132 mmol) in DMF (50 mL). After 45 min, a solution of epichlorohydrin (103.5 mL, 1.32 mol) in DMF (25 mL) was added and the mixture was stirred at 60 °C during 72 h. After cooling to room temperature, the DMF was evaporated to dryness. The residue was washed with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated and purified by column chromatography (eluent: AcOEt/petroleum ether, 1:1) to give the corresponding epoxides **2a–f**.

4.1.1. 2-Fluoro-3-oxiranylmethoxypyridine 2a. Oil; IR (film) ν 1289 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78

(dd, 1H, J=2.6, 4.8 Hz, Ar-O–CH_2–CH–CH_2), 2.93 (t, 1H, J=4.8 Hz, Ar-O–CH_2–CH–CH_2), 3.34–3.43 (m, 1H, CH_2–CH–CH_2), 4.00 (dd, 1H, J=6.1, 11.4 Hz, Ar-O–CH_2), 4.40 (dd, 1H, J=2.6, 11.4 Hz, Ar-O–CH_2), 7.14 (ddd, 1H, J=0.8, 4.9, 7.9 Hz, H_β), 7.33–7.45 (m, 1H, H_γ), 7.76 (dt, 1H, J=3.2, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.1, 50.1, 71.2, 118.0, 124.6, 142.2, 142.3, 153.9; MS (CI) m/z 170 (M+1); Anal. calcd for $C_8H_8FNO_2$: C, 56.80; H, 4.77; N, 8.28. Found: C, 56.91; H, 4.80; N, 8.39.

4.1.2. 2-Chloro-3-oxiranylmethoxypyridine 2b. Mp 35–36 °C; IR (KBr) ν 1280 and 1200 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.83 (dd, 1H, J=2.7, 4.9 Hz, Ar-O–CH_2–CH–CH_2), 2.94 (t, 1H, J=4.9 Hz, Ar-O–CH_2–CH–CH_2), 3.36–3.44 (m, 1H, CH_2–CH–CH_2), 4.04 (dd, 1H, J=5.4, 11.4 Hz, Ar-O–CH_2), 4.39 (dd, 1H, J=2.8, 11.3 Hz, Ar-O–CH_2), 7.20 (dd, 1H, J=4.7, 8.2 Hz, H_β), 7.30 (dd, 1H, 1.6, 8.2 Hz, H_γ), 8.01 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ NMR ($CDCl_3$) δ 44.1, 49.7, 69.5, 120.8, 123.2, 140.8, 141.0, 150.5; MS (CI) m/z 186 (M+1); Anal. calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.81; H, 4.42; N, 7.69.

4.1.3. 2-Bromo-3-oxiranylmethoxypyridine 2c. Mp 50–51 °C; IR (KBr) ν 1294 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (dd, 1H, J=2.7, 4.9 Hz, Ar-O–CH_2–CH–CH_2), 2.86 (t, 1H, J=4.9 Hz, Ar-O–CH_2–CH–CH_2), 3.28–3.37 (m, 1H, CH_2–CH–CH_2), 3.96 (dd, 1H, J=5.5, 11.4 Hz, Ar-O–CH_2), 4.33 (dd, 1H, J=2.7, 11.4 Hz, Ar-O–CH_2), 7.10–7.19 (m, 2H, H_β, H_γ), 7.92 (dd, 1H, J=2.7, 3.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.3, 49.8, 69.6, 120.4, 123.5, 132.9, 141.8, 151.9; MS (CI) m/z 230 (M+1 for ^{79}Br) and 232 (M+1 for ^{81}Br); Anal. calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.51; N, 6.09. Found: C, 41.91; H, 3.60; N, 6.15.

4.1.4. 2-Iodo-3-oxiranylmethoxypyridine 2d. Oil; IR (film) ν 1285 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.79–2.88 (m, 2H, Ar-O–CH_2–CH–CH_2), 3.27–3.37 (m, 1H, CH_2–CH–CH_2), 3.95 (dd, 1H, J=5.3, 11.4 Hz, Ar-O–CH_2), 4.32 (dd, 1H, J=2.4, 11.4 Hz, Ar-O–CH_2), 7.00 (dd, 1H, J=1.6, 8.2 Hz, H_γ), 7.11 (dd, 1H, J=4.6, 8.2 Hz, H_β), 7.91 (dd, 1H, J=1.6, 4.6 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.2, 49.6, 69.3, 111.7, 118.5, 123.5, 142.8, 153.9; MS (CI) m/z 278 (M+1); Anal. calcd for $C_8H_8INO_2$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.72; H, 3.03; N, 5.19.

4.1.5. 2-Nitro-3-oxiranylmethoxypyridine 2e. Mp 52–53 °C; IR (KBr) ν 1256 and 1170 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.79 (dd, 1H, J=2.8, 4.6 Hz, Ar-O–CH_2–CH–CH_2), 2.91 (t, 1H, J=4.6 Hz, Ar-O–CH_2–CH–CH_2), 3.31–3.41 (m, 1H, CH_2–CH–CH_2), 4.10 (dd, 1H, J=5.6, 11.6 Hz, Ar-O–CH_2), 4.49 (dd, 1H, J=2.5, 11.6 Hz, Ar-O–CH_2), 7.52 (dd, 1H, J=4.4, 8.5 Hz, H_β), 7.62 (dd, 1H, 1.3, 8.5 Hz, H_γ), 8.09 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.4, 49.8, 70.4, 124.6, 128.8, 140.0, 146.9; MS (CI) m/z 197 (M+1); Anal. calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.11; H, 4.23; N, 14.39.

4.1.6. 2-Methoxy-3-oxiranylmethoxypyridine 2f. Mp 31–32 °C; IR (KBr) ν 1283 and 1197 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, 1H, J=2.6, 4.8 Hz, Ar-O–CH_2–CH–CH_2), 2.84 (t, 1H, J=4.8 Hz, Ar-O–CH_2–CH–CH_2), 3.27–3.35 (m, 1H, CH_2–CH–CH_2), 3.88–3.98 (m, 4H, Ar-O–CH_2, CH_3), 4.22 (dd, 1H, J=3.1, 11.3 Hz, Ar-O–CH_2), 6.76 (dd, 1H, J=5.0, 7.8 Hz, H_β), 7.07 (dd, 1H, J=1.6, 7.8 Hz H_γ), 7.70 (dd, 1H, J=1.6, 5.0 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.7, 50.0, 53.5, 69.9, 116.7, 119.9, 138.1, 143.0, 154.8; MS (CI) m/z 182 (M+1); Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 6.30; N, 7.79.

4.2. General procedure for the preparation of the alcohols 3a–f

To a solution of appropriate epoxides **2a–f** (6.73 mmol) in THF (30 mL) was added 1-phenylpiperazine (20 mmol). The mixture was stirred at reflux for 24 h then diluted with H_2O, extracted with AcOEt, dried over $MgSO_4$ and the solvent removed in vacuo to give the crude product. This was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the corresponding alcohols **3a–f**.

4.2.1. 1-(2-Fluoropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3a. Oil; IR (film) ν 3500–3200 (OH), 1286 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49–2.68 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.84 (m, 2H, CH–CH_2–N), 3.10–3.24 (m, 4H, Ph-N(CH_2)$_2$), 3.98–4.20 (m, 4H, O–CH_2–CH–OH), 6.77–6.95 (m, 3H, H_γ, H_{Ar}), 7.07 (ddd, 1H, J=0.8, 4.9, 7.8 Hz, H_β), 7.17–7.38 (m, 3H, H_{ar}), 7.71 (dd, 1H, J=1.7, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.0, 53.2, 60.1, 65.5, 71.5, 115.9, 119.7, 122.4, 124.4, 129.1, 141.8, 142.2, 151.0, 154.0; MS (CI) m/z 332 (M+1); Anal. calcd for $C_{18}H_{22}FN_3O_2$: C, 65.24; H, 6.69; N, 12.68. Found: C, 65.33; H, 6.80; N, 12.76.

4.2.2. 1-(2-Chloropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3b. Mp 107–108 °C; IR (KBr) ν 3500–3200 (OH), 1284 and 1209 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58–2.73 (m, 4H, CH_2–N(CH_2)$_2$), 2.79–2.91 (m, 2H, CH–CH_2–N), 3.17–3.28 (m, 4H, Ph-N(CH_2)$_2$), 4.06–4.24 (m, 4H, O–CH_2–CH–OH), 6.81–6.96 (m, 3H, H_γ, H_{Ar}), 7.19 (dd, 1H, J=4.7, 8.1 Hz, H_β), 7.23–7.32 (m, 3H, H_{ar}), 8.00 (dd, 1H, J=1.5, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.4, 53.5, 60.4, 65.7, 71.5, 116.3, 120.1, 120.9, 123.3, 129.3, 141.1, 151.2, 151.3; MS (CI) m/z 348 (M+1); Anal. calcd for $C_{18}H_{22}ClN_3O_2$: C, 62.15; H, 6.38; N, 12.08. Found: C, 62.33; H, 6.45; N, 12.16.

4.2.3. 1-(2-Bromopyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3c. Mp 84–85 °C; IR (KBr) ν 3500–3200 (OH), 1291 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53–2.70 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.85 (m, 2H, CH–CH_2–N), 3.08–3.25 (m, 4H, Ph-N(CH_2)$_2$), 3.98–4.22 (m, 4H, O–CH_2–CH–OH), 6.78–6.95 (m, 3H, H_β, H_{Ar}), 7.11–7.30 (m, 4H, H_γ, H_{ar}), 7.94 (dd, 1H, J=1.4, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.1, 53.3, 60.3, 65.5, 71.4, 116.0, 119.7, 120.1, 123.4, 129.0, 132.9, 141.5, 151.0, 152.1; MS (CI) m/z 392 (M+1 for ^{79}Br) and 394 (M+1 for ^{81}Br); Anal. calcd for $C_{18}H_{22}BrN_3O_2$: C, 55.11; H, 5.65; N, 10.71. Found: C, 55.23; H, 5.80; N, 10.76.

4.2.4. 1-(2-Iodopyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3d. Mp 93–94 °C; IR (KBr) ν 3500–3200 (OH), 1284 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60–2.79 (m, 4H, CH_2–N(CH_2)$_2$), 2.81–2.94 (m, 2H, CH–CH_2–N), 3.16–3.35 (m, 4H, Ph-N(CH_2)$_2$), 4.05–4.26 (m,

4H, O–CH_2–CH–OH), 6.83–6.98 (m, 3H, H_β, H_{Ar}), 7.03–7.10 (m, 1H, H_γ), 7.16–7.32 (m, 3H, H_{ar}), 7.94 (dd, 1H, J=1.2, 5.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.3, 53.5, 60.5, 65.7, 71.5, 112.4, 116.2, 118.4, 120.0, 123.6, 129.2, 143.1, 151.2, 154.5; MS (CI) m/z 440 (M+1); Anal. calcd for $C_{18}H_{22}IN_3O_2$: C, 49.21; H, 5.05; N, 9.57. Found: C, 49.19; H, 5.11; N, 9.47.

4.2.5. 1-(2-Nitropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3e. Mp 102–103 °C; IR (KBr) ν 3500–3200 (OH), 1537 (NO_2), 1275 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49–2.70 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.85 (m, 2H, CH–CH_2–N), 3.10–3.25 (m, 4H, Ph-N(CH_2)$_2$), 4.08–4.30 (m, 4H, O–CH_2–CH–OH), 6.79–6.98 (m, 3H, H_{Ar}), 7.18–7.35 (m, 2H, H_{ar}), 7.50 (dd, 1H, J=4.4, 8.5 Hz, H_β), 7.60 (dd, 1H, J=1.3, 8.5 Hz, H_γ), 8.05 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 48.9, 53.1, 59.8, 65.4, 71.7, 115.9, 119.6, 124.3, 128.8, 128.9, 139.2, 147.2, 148.4, 150.9; MS (CI) m/z 359 (M+1); Anal. calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.23; H, 6.27; N, 15.56.

4.2.6. 1-(2-Methoxypyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3f. Oil; IR (film) ν 3500–3100 (OH), 1260 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50–2.68 (m, 4H, CH_2–N(CH_2)$_2$), 2.70–2.84 (m, 2H, CH–CH_2–N), 3.08–3.30 (m, 4H, Ph-N(CH_2)$_2$), 3.94–4.26 (m, 4H, O–CH_2–CH–OH), 6.75–6.98 (m, 4H, H_β, H_{Ar}), 7.05–7.15 (m, 1H, H_γ), 7.19–7.35 (m, 2H, H_{ar}), 7.75 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.0, 53.2, 53.3, 60.4, 71.5, 115.9, 116.6, 119.5, 119.6, 130.0, 137.6, 143.2, 151.0, 154.7; MS (CI) m/z 344 (M+1); Anal. calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.53; H, 7.40; N, 12.16.

4.3. Preparation of the alcohols 4

Epoxide **2b** or **2e** (5.38 mmol) was allowed to react in THF (50 mL) with 34 g of Woelm-200-neutral dehydrated alumina (500 °C, 24 h) doped with benzyl alcohol (5.6 mL, 53.80 mmol) for 1.5 h at room temperature. After the appropriate amount of time had elapsed, the slurry was filtered through a sintered glass funnel containing a Celite pad, and the collected alumina was washed with additional MeOH. The combined washings were concentrated, and the residue was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to leave the alcohol **4b** (60%) or **4e** (60%).

4.3.1. 1-Benzyloxy-3-(2-chloropyridin-3-yloxy)-propan-2-ol 4b. Oil; IR (film) ν 3500–3200 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (d, 2H, J=5.6 Hz, Ph-CH_2–O–CH_2), 4.08–4.33 (m, 4H, Ar-O–CH_2–CH–OH), 4.58 (s, 2H, Ph-CH_2), 7.15–7.38 (m, 7H, H_β, H_γ, H_{Ar}), 8.00 (dd, 1H, J=1.9, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 68.9, 70.2, 70.6, 73.7, 120.8, 123.3, 127.9, 128.0, 128.6, 137.7, 141.0, 141.1, 150.9; MS (CI) m/z 294 (M+1); Anal. calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.41; H, 5.40; N, 4.67.

4.3.2. 1-Benzyloxy-3-(2-nitropyridin-3-yloxy)-propan-2-ol 4e. Mp 74–75 °C; IR (KBr) ν 3500–3200 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (d, 2H, J=4.7 Hz, Ph-CH_2–O–CH_2), 4.06–4.26 (m, 4H, Ar-O–CH_2–CH–OH), 4.51 (s, 2H, Ph-CH_2), 7.20–7.35 (m, 5H, H_{ar}), 7.47 (dd, 1H, J=4.1, 8.4 Hz, H_β), 7.52 (dd, 1H, J=1.6, 8.4 Hz, H_γ), 8.03 (dd, 1H, J=1.6, 4.1 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 68.5, 70.3, 70.7, 73.5, 124.3, 127.8, 127.9, 128.4, 129.0, 137.6, 139.4, 147.2, 148.5; MS (CI) m/z 305 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.17; H, 5.42; N, 9.19.

4.4. Preparation of the amino alcohols 5 and 6

Following the procedure described for **3a**–**f** but substituting 1-phenylpiperazine by (20 mmol) of *N*-methylbenzylamine or benzylamine, the epoxide **2b** and **2e** gave the corresponding amino alcohol **5b** (90%), **5e** (82%), **6b** (76%) or **6e** (89%).

4.4.1. 1-(*N*-Benzyl-*N*-methylamino)-3-(2-chloropyridin-3-yloxy)-propan-2-ol 5b. Oil; IR (film) ν 3500–3200 (OH), 1291 and 1207 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 2.58 (dd, 1H, J=4.4, 12.2 Hz, CH–CH_2–N), 2.70 (dd, 1H, J=9.1, 12.2 Hz, CH–CH_2–N), 3.53 (d, 1H, J=12.9 Hz, O–CH_2–CH), 3.69 (d, 1H, J=12.9 Hz, O–CH_2–CH), 4.00–4.06 (m, 2H, CH_2-Ph), 4.08–4.20 (m, 2H, CH–OH), 7.11–7.40 (m, 7H, H_β, H_γ, H_{ar}), 7.98 (dt, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 42.5, 59.2, 62.6, 66.1, 71.4, 120.7, 123.2, 127.4, 128.4, 129.1, 138.2, 140.8, 141.2, 151.1; MS (CI) m/z 307 (M+1); Anal. calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.53; H, 6.30; N, 9.16.

4.4.2. 1-(*N*-Benzyl-*N*-methylamino)-3-(2-nitropyridin-3-yloxy)-propan-2-ol 5e. Oil; IR (film) ν 3500–3200 (OH), 1280 and 1190 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.52 (dd, 1H, J=4.7, 12.5 Hz, CH–CH_2–N), 2.63 (dd, 1H, J=8.0, 12.5 Hz, CH–CH_2–N), 3.50 (d, 1H, J=13.0 Hz, O–CH_2–CH), 3.61 (d, 1H, J=13.0 Hz, O–CH_2–CH), 4.01–4.20 (m, 4H, CH_2-Ph, CH–OH), 7.16–7.33 (m, 5H, H_{ar}), 7.48 (dd, 1H, J=4.4, 8.4 Hz, H_β), 7.57 (dd, 1H, 1.3, 8.4 Hz, H_γ), 8.02 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 42.2, 58.8, 62.3, 66.0, 71.8, 124.3, 127.1, 128.2, 128.8, 128.9, 138.0, 139.1, 147.2, 148.4; MS (CI) m/z 318 (M+1); Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.53; H, 6.00; N, 13.36.

4.4.3. 1-(*N*-Benzylamino)-3-(2-chloropyridin-3-yloxy)-propan-2-ol 6b. Mp 65–66 °C; IR (KBr) ν 3600–3200 (OH, NH), 1285 and 1205 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.83 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 2.92 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 3.35 (broad s, 2H, OH, NH), 3.77–3.92 (m, 2H, O–CH_2–CH), 4.00–4.06 (m, 2H, CH_2-Ph), 4.09–4.19 (m, 2H, CH–OH), 7.11–7.20 (m, 2H, H_β, H_γ), 7.21–7.39 (m, 5H, H_{ar}), 7.98 (dd, 1H, J=2.0, 4.2 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 51.0, 53.7, 67.8, 71.9, 120.7, 123.3, 127.4, 128.4, 128.6, 139.2, 140.9, 141.0, 151.0; MS (CI) m/z 293 (M+1); Anal. calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.62; H, 5.80; N, 9.76.

4.4.4. 1-(*N*-Benzylamino)-3-(2-nitropyridin-3-yloxy)-propan-2-ol 6e. Oil; IR (film) ν 3600–3200 (OH, NH), 1280 and 1210 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76–2.94 (m, 4H, OH, NH, CH–CH_2–N), 3.83 (dd, 2H, J=13.4,

16.5 Hz, CH_2–Ph), 4.01–4.11 (m, 2H, CH–OH), 4.13–4.22 (m, 2H, O–CH_2–CH), 7.21–7.38 (m, 5H, H_{ar}), 2.92 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 3.35 (broad s, 2H, OH, NH), 7.52 (dd, 1H, J=4.1, 8.5 Hz, H_β), 7.57 (dd, 1H, J=1.7, 8.5 Hz, H_γ), 8.10 (dd, 1H, J=1.7, 4.1 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 50.8, 53.9, 67.9, 72.5, 124.3, 127.3, 128.3, 128.6 128.9, 139.7, 139.8, 147.5; MS (CI) m/z 304 (M+1); Anal. calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.49; H, 5.80; N, 13.76.

4.5. Preparation of the azido alcohols 7

A solution of epoxide **2b** or **2e** (10.76 mmol) in MeOH (42 mL) and H_2O (6 mL) was treated with NaN_3 (2.10 g, 32.40 mmol) and NH_4Cl (1.40 g, 25.80 mmol). The mixture was heated at reflux for 24 h, cooled and the solvent removed in vacuo. The residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was further extracted with AcOEt. The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to give crude product. This was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the azido alcohol **7b** (88%) or **7e** (80%).

4.5.1. 1-Azido-3-(2-chloropyridin-3-yloxy)-propan-2-ol 7b. Oil; IR (film) ν 3400–3200 (OH), 2095 (N_3), 1280 and 1205 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51–3.68 (m, 2H, Ar-O–CH_2), 4.10 (d, 2H, J=5.4 Hz, CH_2–N_3), 4.20–4.32 (m, 2H, CH–OH), 7.18–7.30 (m, 2H, H_β, H_γ), 8.02 (dd, 1H, J=2.0, 4.3 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 53.3, 68.9, 70.3, 121.0, 123.4, 141.0, 141.3, 150.7; MS (CI) m/z 229 (M+1); Anal. calcd for $C_8H_9ClN_4O_2$: C, 42.03; H, 3.97; N, 24.50. Found: C, 42.19; H, 3.80; N, 24.36.

4.5.2. 1-Azido-3-(2-nitropyridin-3-yloxy)-propan-2-ol 7e. Mp 77–78 °C; IR (KBr) ν 3400–3200 (OH), 2098 (N_3), 1265 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25–3.44 (m, 2H, Ar-O–CH_2), 3.95–4.08 (m, 2H, CH–OH), 4.14–4.27 (m, 2H, CH_2–N_3), 7.75 (dd, 1H, J=4.5, 8.5 Hz, H_β), 7.99 (dd, 1H, J=1.3, 8.5 Hz, H_γ), 8.10 (dd, 1H, J=1.3, 4.5 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 53.3, 68.3, 71.2, 125.9, 130.3, 140.0, 146.8, 148.7; MS (CI) m/z 240 (M+1); Anal. calcd for $C_8H_9N_5O_4$: C, 40.17; H, 3.79; N, 29.28. Found: C, 40.33; H, 3.80; N, 29.36.

4.6. General procedure for the preparation of dioxinopyridines 8–12

To a solution or suspension of appropriate base (NaH, *t*-BuOK, LiH or KH, 3 mmol) in solvent (DME or *t*-BuOH, 5 mL) was added a solution of the appropriate alcohols **3**–**7** (1.5 mmol) in solvent (5 mL). The resulting mixture was heated (80 °C) for 4–72 h. After cooling to room temperature, the reaction was hydrolysed with H_2O and extracted with AcOEt. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by column chromatography (eluent: MeOH/CH_2Cl_2, gradient: 0.2:9.8 to 1:9) to afford dioxinopyridines **8**–**12** (see Tables 1–4). Using as starting materials the chloro-derivatives **4b**, **6b** and **7b** (Table 3, entry 1, 5 and 9) only the isomers **9A**, **10A** and **11A** are obtained. The structure and the ratio of **9B**, **10B** and **11B** were deduced from the spectral data of their isomeric mixture.

4.6.1. 3-(4-Phenylpiperazin-1-ylmethyl)-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 8A. Mp 119–120 °C; IR (KBr) ν 1270 and 1240 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64–2.87 (m, 6H, CH_2–N(CH_2)$_2$), 3.13–3.29 (m, 4H, Ph-N(CH_2)$_2$), 4.03 (dd, 1H, J=7.5, 11.5 Hz, O–CH_2–CH), 4.35 (dd, 1H, J=2.3, 11.5 Hz, O–CH_2–CH), 4.46–4.57 (m, 1H, O–CH$_2$–CH), 6.81–6.96 (m, 4H, H_β, H_{ar}), 7.18 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.21–7.31 (m, 2H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.3, 54.2, 58.4, 66.6, 72.7, 116.2, 118.5, 119.9, 124.7, 129.2, 139.1, 140.2, 150.9, 151.3; MS (CI) m/z 312 (M+1); Anal. calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.31; H, 6.75; N, 13.36.

4.6.2. 2-(4-Phenylpiperazin-1-ylmethyl)-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 8B. Oil; IR (film) ν 1277 and 1247 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60–2.82 (m, 6H, CH_2–N(CH_2)$_2$), 3.17–3.26 (m, 4H, Ph-N(CH_2)$_2$), 4.20 (dd, 1H, J=7.4, 11.4 Hz, O–CH_2–CH), 4.31–4.41 (m, 1H, O–CH$_2$–CH), 4.52 (dd, 1H, J=2.2, 11.4 Hz, O–CH_2–CH), 6.80–6.97 (m, 4H, H_β, H_{ar}), 7.20 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.25–7.31 (m, 2H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.2, 54.0, 58.3, 67.5, 71.2, 116.2, 118.6, 119.9, 125.0, 129.2, 138.8, 140.0, 151.0, 151.3; MS (CI) m/z 312 (M+1); Anal. calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.39; H, 6.77; N, 13.56.

4.6.3. 3-Benzyloxymethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 9A. Mp 84–85 °C; IR (KBr) ν 1281 and 1240 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (dd, 1H, J=6.4, 10.2 Hz, Ph-CH$_2$–O–CH_2), 3.83 (dd, 1H, J=4.5, 10.2 Hz, Ph-CH$_2$–O–CH_2), 4.09 (dd, 1H, J=7.5, 11.6 Hz, O–CH_2–CH), 4.33 (dd, 1H, J=2.3, 11.6 Hz, O–CH_2–CH), 4.45–4.55 (m, 1H, O–CH$_2$–CH), 4.59 (s, 2H, Ph-CH_2–O), 6.84 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.17 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.25–7.40 (m, 5H, H_{ar}), 7.81 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 65.4, 68.3, 73.0, 73.8, 118.5, 124.7, 127.8, 127.9, 128.5, 137.6, 139.0, 140.1, 150.8; MS (CI) m/z 258 (M+1); Anal. calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.17; H, 5.80; N, 5.56.

4.6.4. 2-Benzyloxymethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 9B. IR (film) ν 1281 and 1185 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (dd, 1H, J=5.3, 10.4 Hz, Ph-CH$_2$–O–CH_2), 3.75 (dd, 1H, J=4.8, 10.4 Hz, Ph-CH$_2$–O–CH_2), 4.27 (dd, 1H, J=7.2, 11.0 Hz, O–CH_2–CH), 4.31–4.43 (m, 1H, O–CH$_2$–CH), 4.48 (dd, 1H, J=1.9, 11.0 Hz, O–CH_2–CH), 4.90 (s, 2H, Ph-CH_2–O), 6.86 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.20 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.28–7.45 (m, 5H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 66.3, 68.3, 72.1, 73.9, 118.7, 125.0, 127.9, 128.1, 128.7, 137.3, 138.9, 140.0, 150.9; MS (CI) m/z 258 (M+1); Anal. calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.23; H, 5.90; N, 5.60.

4.6.5. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-methylamine 10A. Oil; IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3); 2.70–2.80 (m, 2H, Ph-CH_2–N); 3.47 (d, 1H, J=13.1 Hz, Ph-CH$_2$–NH–CH_2); 3.60 (d, 1H, J=13.1 Hz, Ph-CH$_2$–NH–CH_2); 3.84 (dd, 1H, J=7.7, 11.5 Hz, O–CH_2–CH);

4.27 (dd, 1H, *J*=2.4, 11.5 Hz, O–C*H*$_2$–CH); 4.39–4.50 (m, 1H, O–CH$_2$–C*H*); 6.77 (dd, 1H, *J*=4.8, 7.9 Hz, H$_\beta$,); 7.10 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$); 7.21–7.29 (m, 5H, H$_{ar}$); 7.77 (dd, 1H, *J*=1.6, 4.8 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 43.4; 56.8; 62.9; 66.5; 72.6; 118.2; 124.4; 127.1; 128.2; 128.8; 138.6; 139.0; 139.8; 150.8; MS (CI) *m*/*z* 271 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.21; H, 6.80; N, 10.28.

4.6.6. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-methylamine 10B. IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.34 (s, 3H, CH$_3$); 2.60–2.68 (m, 2H, Ph-C*H*$_2$–N); 3.49 (d, 1H, *J*=13.1 Hz, Ph-CH$_2$–NH–C*H*$_2$); 3.60 (d, 1H, *J*=13.1 Hz, Ph-CH$_2$–NH–C*H*$_2$); 4.04 (dd, 1H, *J*=7.7, 11.5 Hz, O–*CH*$_2$–CH); 4.27 (dd, 1H, *J*=2.4, 11.5 Hz, O–C*H*$_2$–CH); 4.37–4.50 (m, 1H, O–CH$_2$–C*H*); 6.76 (dd, 1H, *J*=4.8, 7.9 Hz, H$_\beta$,); 7.11 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$); 7.22–7.30 (m, 5H, H$_{ar}$); 7.79 (dd, 1H, *J*=1.6, 4.8 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 43.5; 56.9; 63.1; 67.6; 71.5; 118.5; 124.8; 127.4; 128.4; 129.0; 138.5; 138.9; 139.8; 151.1; MS (CI) *m*/*z* 271 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.34; H, 6.62; N, 10.30.

4.6.7. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-amine 11A. Oil; IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.83 (broad s, 1H, NH), 2.94 (d, 2H, *J*=4.5 Hz, Ph-CH$_2$–NH–C*H*$_2$), 3.83 (s, 2H, Ph-C*H*$_2$–N), 4.05 (dd, 1H, *J*=8.1, 11.5 Hz, O–C*H*$_2$–CH), 4.26 (dd, 1H, *J*=2.3, 11.5 Hz, O–C*H*$_2$–CH), 4.40–4.51 (m, 1H, O–CH$_2$–C*H*), 6.84 (dd, 1H, *J*=4.9, 7.9 Hz, H$_\beta$), 7.16 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.25–7.38 (m, 5H, H$_{ar}$), 7.80 (dd, 1H, *J*=1.7, 4.9 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 48.9, 54.0, 67.2, 72.7, 118.5, 124.9, 127.3, 128.2, 128.6, 138.9, 139.9, 140.0, 151.0; MS (CI) *m*/*z* 257 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.11; H, 6.30; N, 10.78.

4.6.8. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-amine 11B. IR (film) ν 1200 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.79 (broad s, 1H, NH), 2.97 (d, 2H, *J*=4.7 Hz, Ph-CH$_2$–NH–C*H*$_2$), 4.03 (s, 2H, Ph-C*H*$_2$–N), 4.13 (dd, 1H, *J*=7.9, 11.6 Hz, O–C*H*$_2$–CH), 4.41 (dd, 1H, *J*=2.3, 11.6 Hz, O–C*H*$_2$–CH), 4.45–4.56 (m, 1H, O–CH$_2$–C*H*), 6.87 (dd, 1H, *J*=4.8, 7.8 Hz, H$_\beta$), 7.20 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.29–7.42 (m, 5H, H$_{ar}$), 7.81 (dd, 1H, *J*=1.6, 4.9 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 49.8, 54.0, 66.3, 72.8, 118.7, 125.2, 127.4, 128.4, 128.9, 138.6, 139.8, 139.9, 151.1; MS (CI) *m*/*z* 257 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.15; H, 6.37; N, 10.83.

4.6.9. 3-Azidomethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 12A. Oil; IR (film) ν 2108 (N$_3$), 1277 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.59 (d, 2H, *J*=5.6 Hz, CH–C*H*$_2$–N$_3$), 4.02 (dd, 1H, *J*=7.3, 11.6 Hz, O–C*H*$_2$–CH), 4.23 (dd, 1H, *J*=2.5, 11.6 Hz, O–C*H*$_2$–CH), 4.39–4.48 (m, 1H, O–CH$_2$–C*H*), 6.84 (dd, 1H, *J*=4.7, 7.8 Hz, H$_\beta$), 7.15 (dd, 1H, *J*=1.7, 7.8 Hz, H$_\gamma$), 7.79 (dd, 1H, *J*=1.7, 4.7 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 50.5, 65.0, 72.6, 118.8, 124.9, 138.7, 140.3, 150.2; MS (CI) *m*/*z* 193 (M+1); Anal. calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.12; H, 4.35; N, 29.08.

4.6.10. 2-Azidomethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 12B. Oil; IR (film) ν 2108 (N$_3$), 1277 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.47 (d, 2H, *J*=5.3 Hz, CH–C*H*$_2$–N$_3$), 4.14 (dd, 1H, *J*=6.7, 11.1 Hz, O–C*H*$_2$–CH), 4.28–4.29 (m, 1H, O–CH$_2$–C*H*), 4.34 (dd, 1H, *J*=2.0, 11.1 Hz, O–C*H*$_2$–CH), 6.79 (dd, 1H, *J*=4.7, 7.8 Hz, H$_\beta$), 7.13 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$), 7.73 (dd, 1H, *J*=1.6, 4.7 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 50.2, 65.6, 71.6, 118.7, 124.9, 138.0, 140.0, 150.2; MS (CI) *m*/*z* 193 (M+1); Anal. calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.08; H, 4.17; N, 29.20.

4.7. General procedure for the preparation of the compounds 13–15

A solution of dioxinopyridines **9**, **10** or **11** (0.68 mmol) in MeOH (25 mL) with a few drops of HCl was shaken with Pd/C (10%, 20 mg) under hydrogen atmosphere. When the reaction was complete, the catalyst was removed by filtration and the combined filtrate was concentrated in vacuo to give **13**, **14** or **15** (82–88%).

(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-yl)-methanol (**13A**, **13B**), (2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-ylmethyl)-methylamine (**14A**, **14B**), (2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-yl)-methylamine (**15A**, **15B**). The analytical data of **13A**, **13B**, **14A**, **14B**, **15A** and **15B** were in accordance with the values described in the literature 22.

4.8. Preparation of the compounds 17 from 13

p-Toluenesulfonyl chloride (2.85 g, 15.00 mmol) was added to a solution of alcohol **13A** (or **13B**) (10.00 mmol) in pyridine (20 mL) at 0 °C. The reaction mixture was stirred for 48 h then the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography (eluent: CH_2Cl_2) to give **16A** (87%) (or **16B**, 85%).

4.8.1. 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl-4-methylbenzenesulfonate 16A. Oil; IR (film) ν 1350 and 1110 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.45 (s, 3H, CH$_3$), 4.07 (dd, 1H, *J*=6.7, 11.6 Hz, O–C*H*$_2$–CH), 4.17–4.40 (m, 3H, O–C*H*$_2$–CH, CH–C*H*$_2$–O–Ts), 4.51–4.65 (m, 1H, O–CH$_2$–C*H*), 6.87 (dd, 1H, *J*=5.0, 7.8 Hz, H$_\beta$), 7.18 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$), 7.31–7.45 (m, 2H, H$_{ar}$), 7.72–7.93 (m, 3H, H$_\alpha$, H$_{ar}$); ^{13}C NMR (CDCl$_3$) δ 21.7, 64.2, 66.7, 71.3, 118.9, 125.1, 128.1, 130.1, 132.1, 138.6, 140.4, 145.5, 150.0; MS (CI) *m*/*z* 322 (M+1); Anal. calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36. Found: C, 56.15; H, 4.85; N, 4.28.

4.8.2. 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl-4-methylbenzenesulfonate 16B. Oil; IR (film) ν 1345 and 1110 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.44 (s, 3H, CH$_3$), 4.14–4.29 (m, 3H, O–C*H*$_2$–C*H*), 4.37–4.47 (m, 2H, CH–C*H*$_2$–O–Ts), 6.86 (dd, 1H, *J*=4.9, 7.9 Hz, H$_\beta$), 7.10 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.36 (d, 2H, *J*=8.1 Hz, H$_{ar}$), 7.75–7.84 (m, 3H, H$_\alpha$, H$_{ar}$); ^{13}C NMR (CDCl$_3$) δ 21.6, 64.8, 66.9, 70.1, 118.8, 125.0, 127.9, 130.0, 132.1, 137.9, 140.1, 145.4, 150.1; MS (CI) *m*/*z* 322 (M+1); Anal. calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36. Found: C, 56.19; H, 4.55; N, 4.29.

The compound **16A** (or **16B**) (0.38 mmol) was heated at 130 °C for 8 h in a sealed tube with a mixture of methylamine (2 M, 5 mL) and DMF (5 mL). Addition of H_2O, extraction by CH_2Cl_2, drying over $MgSO_4$ and removal of the solvent afforded a crude product, which purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9), yielding 73% of the *N*-methylamine **14A** (or 63% of **14B**). The analytical data were identical with those reported above.

Under similar sulfonation reaction conditions described for **13**, the resulting amines **14A** and **14B** were converted into their sulfonated derivatives **17A** and **17B** in good yields 90 and 88%, respectively.

4.8.3. *N*-(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-4,*N*-dimethylbenzenesulfonamide 17A. Mp 135–136 °C; IR (KBr) ν 1463 (CH_3), 1335 (SO_2), 1278 and 1163 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 3.33 (dd, 1H, J=4.8, 14.6 Hz, O–CH_2–CH), 3.42 (dd, 1H, J=5.6, 14.6 Hz, O–CH_2–CH), 4.15 (dd, 1H, J=7.3, 11.7 Hz, CH–CH_2–N–CH_3), 4.45 (dd, 1H, J=7.3, 11.7 Hz, CH–CH_2–N–CH_3), 4.50–4.61 (m, 1H, O–CH_2–C*H*), 6.88 (dd, 1H, J=4.6, 7.8 Hz, H_β), 7.22 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.35 (d, 2H, J=8.2 Hz, H_{ar}), 7.69 (d, 2H, J=8.2 Hz, H_{ar}), 7.82 (dd, 1H, J=1.5, 4.6 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 21.7, 37.6, 50.5, 65.7, 73.3, 118.8, 125.0, 127.5, 130.0, 134.0, 139.0, 140.2, 144.0, 150.5; MS (CI) *m/z* 335 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.35; H, 5.39; N, 8.28.

4.8.4. *N*-(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-4,*N*-dimethylbenzenesulfonamide 17B. Mp 99–100 °C; IR (KBr) ν 1474 (CH_3), 1397 (SO_2), 1285 and 1153 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.26 (d, 2H, J=5.6 Hz, CH–CH_2–N–CH_3), 4.23 (dd, 1H, J=6.9, 11.6 Hz, O–CH_2–CH), 4.32–4.44 (m, 1H, O–CH_2–C*H*), 4.50 (dd, 1H, J=2.2, 11.6 Hz, O–CH_2–CH), 6.83 (dd, 1H, J=4.7, 7.9 Hz, H_β), 7.11 (dd, 1H, J=1.6, 7.9 Hz, H_γ), 7.25–7.35 (m, 2H, H_{ar}), 7.60–7.70 (m, 2H, H_{ar}), 7.78 (dd, 1H, J=1.6, 4.67 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 21.5, 37.4, 50.2, 66.4, 72.0, 118.7, 125.0, 127.4, 129.9, 134.0, 138.3, 140.1, 143.9, 150.6; MS (CI) *m/z* 335 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.38; H, 5.34; N, 8.47.

4.9. Preparation of the amines 15 from 12

Azide **12A** (or **12B**) (2.6 mmol) in EtOH (16 mL) was stirred with Lindlar palladium (0.08 mmol) in Parr apparatus under hydrogen pressure (30 psi). After 4 h, palladium was filtered and washed with EtOH. The solvent was evaporated and a column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) afforded the product **15A** as an oil in 99% yield (**15B** in 95% yield). The analytical data were identical with those reported above.

4.10. Preparation of the compounds 8 from 15

N,N-Bis(2-chloroethyl)aniline (1.0 g, 4.60 mmol), sodium hydrogen carbonate (1.16 g, 13.80 mmol), sodium iodide (1.38 g, 9.20 mmol) were added to a solution of the amine **15A** or **15B** (9.20 mmol) in ethylene glycol (40 mL). The reaction mixture was stirred at 110 °C for 1.5 h. The solution was cooled 25 °C and concentrated under reduced pressure. The residue was taken in CH_2Cl_2 and washed with H_2O. The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was subjected to flash silica gel chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the product **8A** in 69% yield (**8B** in 65% yield). The analytical data were identical with those reported above.

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Table 1. Conditions of cyclization reactions of alcohols **2**–**5**

Entry	Y	Base/solvent	*T* (°C)/*t* (h)	Yield %	Ratio **A/B**
5	CH_2NHCH_2Ph	NaH/DME	80/12	90	45/55
		t-BuOK/*t*-BuOH	80/12	89	30/70

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Zn-mediated catalytic photoreduction of aldimines. One-pot synthesis and separation of *meso* and *d,l* C_2 symmetrical diamines

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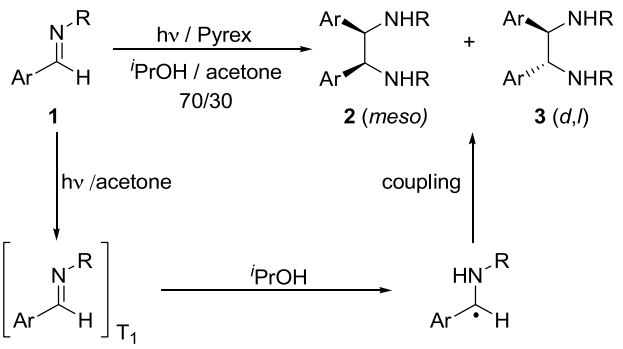
Abstract—A new one-pot method for the synthesis and selective separation of 1,2-diamines is reported. The methodology, which involves the photoreduction of imines using catalytic amounts of zinc as a photosensitizer, allows the direct preparation and separation of *meso* and *d,l* compounds on a multigram scale.

1. Introduction

The reductive coupling of imines is a useful method for the synthesis of vicinal 1,2-diamines,[1] which are important compounds in medicinal[2] and analytical chemistry,[1] as well as in the field of organic synthesis as chiral catalysts or as metal ligands in asymmetric reactions.[1,3]

In recent years, investigations have focused on the stereoselective synthesis of 1,2-diamines[4] but, unfortunately, the stereoselectivity of this process has not been sufficiently improved. Another area of great interest involves the metal-promoted coupling reaction of imines, which generally requires stoichiometric amounts or an excess of metal complexes.[1,4] Furthermore, in some cases, these processes involve a combination of different metal systems.[5]

Our experience in the photochemistry of azadienes[6] and imines[7] prompted us to study the photoreduction of heterocyclic aldimines. As a result, we have previously reported the acetone-sensitized photoreductive coupling of aldimines[8] (Scheme 1), where the reaction involves the formation of triplet species[9] which progress giving radical species by hydrogen abstraction of the isopropyl alcohol.[10] These radical species are coupled to give a mixture of *meso*/*d,l* symmetrical vicinal diamines in good to excellent yields. However, in most cases the isolation of each diastereomeric pair from the crude reaction mixture is particularly difficult. This fact motivated us to study the photoreductive coupling of aldimines in the presence of different metal complexes with the expectation that the reaction would take place with diastereoselectivity. Herein, we report our results from this investigation.



Scheme 1.

2. Results and discussion

Initially, a set of metal complexes of zinc, cadmium, copper and cobalt with different non-chiral and chiral ligands were synthesized[11] and tested in the photocoupling reaction of *N-tert*-butylbenzaldimine (**1a**) (Table 1). To test this methodology, an isopropyl alcohol/acetone solution of imine **1a** was irradiated, through Pyrex glass, in the presence of increasing amounts of complex derivatives until total consumption of the starting material had been achieved.

The preliminary results showed that only zinc derivatives gave the corresponding 1,2-diamines, whereas the rest of the

Keywords: 1,2-Diamines; Imines; Photoreductive coupling; Zinc-complexes.
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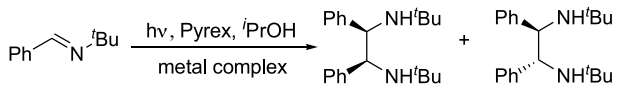
Table 1.



1a **2a** (*meso*) **3a** (*d*,*l*)

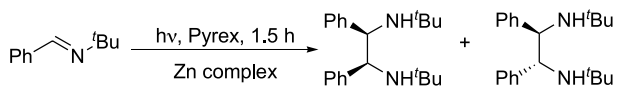
Entry	Metal complex[a]	Ratio **2a**/**3a**[b]
1	$Zn(CH_3)_2L$[c]	55/45
2	$Zn(Et_2CHCOO)_2L$[c]	85/15
3	$Zn(PhCOO)_2L$[c]	≥95/5
4	$Cd(CH_3COO)_2L$[c]	No reaction
5	$Cd(Et_2CHCOO)_2L$[d]	No reaction
6	$Co(Et_2CHCOO)_2L$[c]	No reaction
7	$Cu(Et_2CHCOO)_2L$[c]	No reaction

[a] 0.5 equiv. of metal complex for 1.8 mmol of imine **1a**.
[b] Free diamines determined by ^1H NMR analysis of the crude mixture.
[c] (*R*,*R*)-*N*,*N*′-ethylenebis(1-phenylmethylamine) was used as the chiral ligand L.
[d] Cinchonidine was used as the chiral ligand L.

complexes did not give any reaction (Table 1, entries 4–7). We therefore decided to focus our attention on the zinc complexes. Furthermore, the best selectivity in favour of the *meso* form was observed with zinc carboxylate derivatives (Table 1, entries 2 and 3). Diamine **2a** could be easily isolated from the crude reaction mixture by removing the solvent and then crystallising the residue from isopropyl alcohol at 0 °C.

The results obtained for different zinc complexes and reaction conditions are summarised in Table 2. A number of points warrant particular attention. As shown in entries 1 and 2, the addition of 0.25 equiv. of zinc complex bearing cinchonidine as a chiral ligand lead to a **2a**/**3a** ratio greater than 95/5. In an attempt to account for this ligand effect, we carried out the irradiation in the presence of *N*,*N*′-ethylenebis(benzylamine) or without ligand. It was found

Table 2.



1a **2a** (*meso*) **3a** (*d*,*l*)

Entry	Zn complex	Equiv.[a]	Ratio **2a**/**3a**[b]	Yield **2a** (%)[c]	Yield **3a** (%)[d]
1	$Zn(Et_2CHCOO)_2L$[e]	0.25	≥95/5	33	27
2	$Zn(PhCOO)_2L$[e]	0.25	≥95/5	30	24
3	$Zn(Et_2CHCOO)_2L$[f]	0.25	86/14	31	26
4	$Zn(PhCOO)_2L$[f]	0.25	≥95/5	35	28
5	$Zn(PhCOO)_2$	0.20	≥95/5	32	26
6	$Zn(Et_2CHCOO)_2$	0.20	≥95/5	36	29
7	$Zn(Et_2CHCOO)_2$	0.14	80/20	35	28
8	$Zn(Et_2CHCOO)_2$	0.05	60/40	38	31
9	$Zn(Et_2CHCOO)_2$[g]	0.20	≥95/5	40	35
10	$Zn(PhCOO)_2$[g]	0.20	≥95/5	38	30

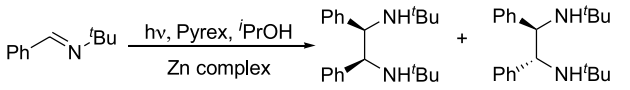
[a] Equiv. of Zn complex for 1.8 mmol of imine **1a**.
[b] Free diamines determined by ^1H NMR analysis of the crude mixture.
[c] Yield of isolated diamine **2a** after crystallisation.
[d] Yield of isolated diamine **3a** after treatment with sulfide salt and purification.
[e] Cinchonidine was used as the chiral ligand L.
[f] *N*,*N*′-ethylenebis(benzylamine) was used as a non-chiral ligand L.
[g] In the absence of acetone.

that a chiral environment was not a prerequisite to obtain excellent diastereoselectivity (entries 3–6) and, consequently, another factor must be involved in the reaction. Interestingly, the finding that the ratio of free diamines **3a**/**2a** (Table 2, entries 6–8) was reduced upon increasing the amount of metal indicates that *meso* and *d*,*l* diamines interact in a different way with the metal. Indeed, while the *d*,*l* diamines **3a** form a Zn–diamine complex, the *meso* compound **2a** remains free and can be easily isolated by crystallisation. Subsequent treatment of the Zn–diamine complex solution with a sulfide salt liberates the *d*,*l* diamines **3a**. It can also be seen from entries 5–10 that catalytic amounts of metal precursor were able to promote the photoreduction reaction of aldimines.

On the other hand, we observed that the combination of acetone and zinc clearly increases the reaction rate. In this sense, we studied the effect of the metal complex in the reaction by performing the irradiation of imine **1a** in isopropyl alcohol with catalytic amounts of Zn complex, but without acetone (Table 2, entries 9 and 10). Under these conditions 1,2-diamines could be obtained, which proves that acetone is not essential in the photocoupling reaction and the zinc complex is able to act as a photosensitizer.[12]

Moreover, the use of zinc as a photosensitizer in the photoreaction allowed us to carry out the reaction on a multigram scale, as can be seen in Table 3.

Table 3.

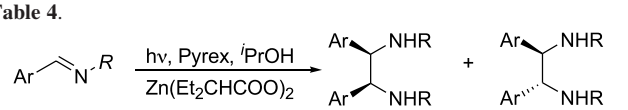


1a **2a** (*meso*) **3a** (*d*,*l*)

Entry	Photosensitizer	Time[a]	Yield (%)	
			2a	**3a**
1	Acetone	14	84[b]	
2	0.05 equiv. of Zn	8	75[b]	
3	0.25 equiv. of Zn	9	40[c]	35[d]

[a] Reaction carried out with 10 mmol of imine **1a**.
[b] Isolated yield of isomer mixture after column chromatography.
[c] Isolated yield after crystallisation.
[d] Isolated yield after treatment with sulfide salt and purification.

Table 4.



1 **2** (*meso*) **3** (*d*,*l*)

Imine	Ar	R	Time[a]	Yield (%)[b]	
				2a	**3a**
1a	Ph	^{t}Bu	9	40	35
1b	Ph	Cy	25	36	34
1c	*p*-Tol	^{t}Bu	29	34	31

[a] Reaction carried out with 10 mmol of imine **1**.
[b] Isolated yield of pure diamines after crystallisation (which gives the *meso* compound) followed by treatment with sulfide salt (which leads to the *d*,*l* derivatives).

Finally, we extended this methodology to other aryl-aldimines, which were synthesized by condensation of the corresponding aldehyde with different primary amines. As shown in Table 4, irradiation of benzaldimines **1a–c** under catalytic conditions, and without acetone as a photosensitizer, gave similar results to those reported above for **1a**.

3. Conclusions

In summary, we have developed a new one-pot method for the synthesis of 1,2-diamines. This methodology, which involves the photoreduction of imines using catalytic amounts of zinc as a photosensitizer, allows the easy synthesis and selective separation of *meso* and *d*,*l* compounds on a multigram scale.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$ with TMS as internal standard. Electrospray mass spectra were obtained on an HP 5989 B apparatus with an HP 59987 A interface, in positive-ion mode with methanol/water/acetic acid (60:35:5) as the mobile phase. IR spectra were obtained on a Perkin–Elmer 1000 spectrophotometer. Elemental analyses were obtained using a CE Instrument Model 1110. All solvents were purified by standard procedures and freshly distilled prior to use. Reagents were of commercial grade (Aldrich). Aldimines were prepared by condensation of the corresponding aldehyde with the amine according to a literature procedure.

4.2. Metal complex preparation

4.2.1. Ligand preparation. Chiral and non-chiral diamines were prepared according to the literature[11] from 1,2-dibromomethane and the corresponding amine. The chiral amino alcohol cinchonidine is commercially available.

4.2.2. Zinc complex preparation. The synthesis and spectroscopic data are identical to those reported in the literature.[11]

Zinc carboxylates were prepared by reaction of ZnO with the corresponding carboxylic acid in toluene at 120 °C with azeotropic distillation of water. To a solution of zinc carboxylates was added the appropriate ligand to give the different zinc complexes.

4.3. Typical procedure for the irradiation and selective separation of benzaldimines

A solution of benzaldimine **1a** (1.610 g, 10 mmol) and $Zn(Et_2CHCOO)_2$ (600 mg, 1 mmol) in isopropyl alcohol (50 mL) was bubbled with argon and irradiated through Pyrex, at room temperature under an Ar atmosphere, using a medium-pressure mercury lamp (400 W) until complete consumption of starting material was observed (monitored by ^{1}H NMR spectroscopy). The solvent was then removed under reduced pressure and a minimum amount of hot isopropyl alcohol was added to the crude reaction mixture. The resulting solution was cooled to 0 °C and the corresponding *meso* diamine **2a** crystallised as white crystals (650 mg, 2.01 mmol). The *meso* derivative was removed and the residue was treated with a 0.65 M solution of Na_2S until total precipitation of zinc metal as ZnS was observed. The solid was filtered off and the layers separated. The aqueous layer was extracted with a mixture of isopropyl alcohol/chloroform 1:3 (3×20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give a white solid, which was crystallised from isopropyl alcohol to give the *d*,*l* diamines **3a** (570 mg, 1.76 mmol). All diamines used in this work were obtained as described above and the physical data were identical to those reported in the literature.[13]

Acknowledgements

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9. The presence of triplet quenchers as oxygen inhibited the formation of diamine. In contrast, the presence of a triplet photosensitizer as acetone increased the reaction rate. See Ref. 8.

10. In the photoreduction process the solvent act as a source of hydrogen. Solvents without hydrogen donor capability, as *tert*-butyl alcohol or *n*-hexane, are ineffective in the photoreaction coupling. See Ref. 8.
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12. Photosensitization is a process in which an excited state with the appropriate energy (e.g., a triplet) of one molecular entity (photosensitizer) is deactivated to a lower-lying state by transferring energy to a second molecular entity, which is thereby raised to a higher energy state. See Braslavsky, S. E.; Houk, K. N. *Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC: Boca Raton, USA, 1989; Vol. 2, p 425, Chapter 23.
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Improved preparation and structural investigation of 4-aryl-4-oxo-2-hydroxy-2-butenoic acids and methyl esters

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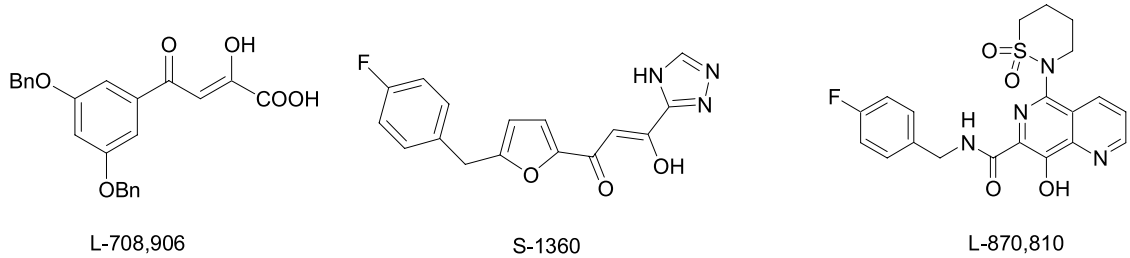
Abstract—A simple and efficient oxalylation of aryl methyl ketones was accomplished with dimethyl oxalate in the presence of sodium methoxide. The unpreviously reported sodium ketoenolate esters were isolated and gently hydrolyzed into the ketoenol esters in good yields. Alternatively the sodium ketoenolate esters hydrolysis could also be conducted to directly afford the ketoenol acids, which represent one of the most promising class of HIV-1 integrase inhibitors. Advantages over previously reported procedures were better yields and simplicity of the purification protocol.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the etiological agent of AIDS. The replicative cycle of this retrovirus has been intensively studied in order to identify targets and design specific inhibitors. To date, Food and Drug Administration approved drugs target reverse transcription (inhibition of reverse transcriptase), protein synthesis (inhibition of protease) and fusion (interaction with glycoprotein 41).[1] Persistence of latent HIV-1 in resting memory CD4+T cells, emergence of resistant HIV strains, drug toxicity and expensive medication have led to the development of novel drugs which interact with other viral replication processes. Integrase that catalyzes the insertion of the proviral DNA into the genome of the host cell, has emerged as an attractive target because it is necessary for stable infection and counterpart enzymes are lacking in the host.

Among numerous classes of molecules,[2] β-diketoacid containing inhibitors (their usual name is DKAs but their structures correspond to 4-aryl-(or 4-styryl-)[3] 4-oxo-2-hydroxy-2-butenoic acids, see Scheme 1) have emerged as the most promising drug candidates,[4] which are selective for integrase. S-1360[5] from Shionogi Company and L-708,906[6,7] from Merck Company are the best examples of this family, S-1360 being one of the only two currently available integrase inhibitors under clinical studies. Starting with this β-diketoacid structure, novel 8-hydroxynaphthyridine derivatives[8] have been designed and L-870,810 is under clinical evaluation.[9]

The synthesis of 4-aryl-4-oxo-2-hydroxy-2-butenoic acids **4** was achieved by the oxalylation of the corresponding aryl methyl ketones **1** in the presence of base followed by either alkaline or acidic hydrolysis (Scheme 2).[10–16] The



L-708,906 S-1360 L-870,810

Scheme 1.

Keywords: HIV integrase inhibitors; Tautomerism; Antiviral agents; Diketoacids.
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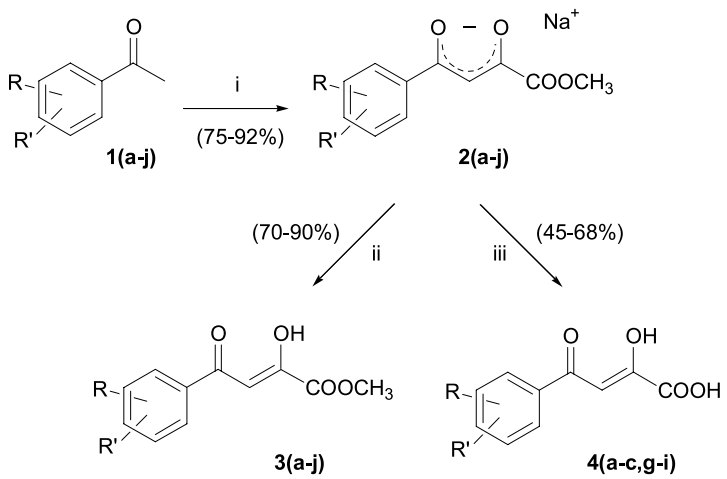


Scheme 2. Reagents and conditions: (i) dimethyl oxalate (1 equiv.) in Et_2O, then 2 M MeONa in MeOH, 1 h 30, rt; (ii) H_2O, then CH_3COOH to reach pH 3–4; (iii) 1,4-dioxane/1 M HCl, 4 h, reflux.

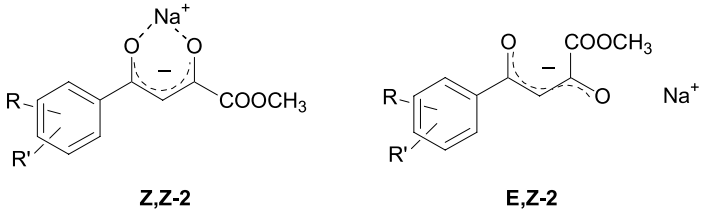
oxalylation of aryl methyl ketones afforded the ketoenol esters **3**, using diethyl or dimethyl oxalate in the presence of NaH (in benzene, toluene or DMF) or NaOEt or NaOMe (in the appropriate alcohol). The reported yields were moderate to good depending on the structure of the aryl methyl ketone and the reaction conditions (base, solvent, reaction temperature and time). Recently, in order to improve this key step, a new procedure using *tert*-butyl methyl oxalate was reported.[16] The reported procedures suffered from a lack of reproducibility, the use of commercially unavailable starting oxalate, long time reaction and high reaction temperature or sometimes tedious extractive work-up.

We herein report a rapid alternative method for the synthesis of ketoenol esters **3** from aryl methyl ketones **1** based on the isolation of sodium ketoenolate esters **2**. Ketoenol acids **4** may be obtained by hydrolysis of **3**[10–16] or more directly from **2** (this work).

2. Results and discussion

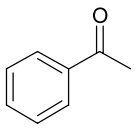
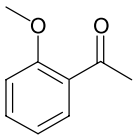
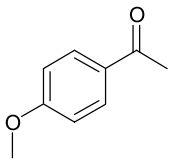
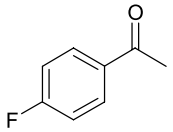
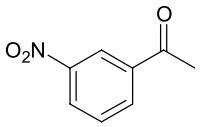
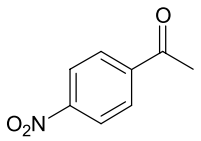
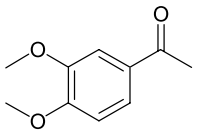
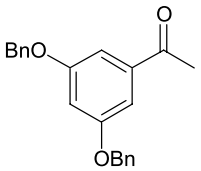
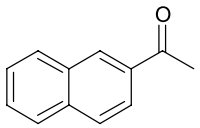
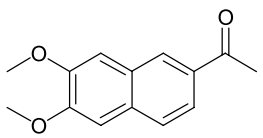
The causes for the absence of a general procedure, the differences in yield and the irreproducibility are mainly due to variable solubility of the starting materials. To overcome this problem, we decided to solubilize the aryl methyl ketone **1** and dimethyl oxalate in dry ether. To this ethereal solution, sodium methoxide in methanol was added. Depending on the aryl methyl ketone used, a precipitate appeared immediately or within half an hour. A reaction time standardized to one night gave satisfactory yields (75–92%) (Table 1). The sodium ketoenolate esters **2(a–j)** were obtained as white to yellowish powders and characterized by ^{1}H NMR spectroscopy (and ^{13}C NMR spectroscopy in the cases of **2a** and **2h**) (Table 2) as a mixture of two species, namely *Z*,*Z* and *E*,*Z* configurations according to Raban and Haritos[17] (Scheme 3). Depending on the ring substitution, the ^{1}H NMR spectra were more or less broadened probably due to a more or less rapid exchange between the two isomers. The sodium ketoenolate esters isomers could be differentiated by the methyl ester signal and the enolic proton signal. *Z*,*Z* Configurations gave a methyl ester signal at 3.63–3.70 ppm and an enolic proton signal at 6.05–6.56 ppm whereas for the *E*,*Z* forms the same signals were at 3.56–3.70 ppm and 5.05–5.57 ppm respectively. The *Z*,*Z*/*E*,*Z* ratio was estimated to be 4:1 except for **2e** (in this case, the characteristic signals of an *E*,*Z* isomer have not been observed on the ^{1}H and ^{13}C NMR spectra). In order to clearly establish the existence of ketoenolate anions and the respective structures of the two configurations, ^{13}C NMR spectra were recorded for **2a** and **2h**. The hydrogen attached to carbon 3 and the carbon 3 of the ketoenolate esters presented strong upfield shifts for the two configurations of **2** (for example: *Z*,*Z*-**2a**: 6.34 and 92.0 ppm, *E*,*Z*-**2a**: 5.31 and 91.9 ppm) versus the chemical shifts in **3** (**3a**: 7.12 and 98.1 ppm) whereas the quaternary carbon of the aromatic ring presented a strong downfield shift (142.2 and 142.4 ppm for *Z*,*Z*-**2a** and *E*,*Z*-**2a**, respectively versus 134.3 ppm for **3a**). These differences were in accordance with previous ^{1}H and ^{13}C NMR studies[18,19] on enolates.

2(a–j) were converted into the corresponding ketoenol esters **3(a–j)** by acidic hydrolysis in moderate to good yields (70–90%). **2(a–c;g–i)** were exhaustively hydrolyzed to give the corresponding ketoenol acids **4(a–c;g–i)** in 45–68% yields by stronger acidic conditions in refluxing dioxane/water mixture. Overall yields (**1→3**) ranged from 58 to 81%. These results suffer the comparison with



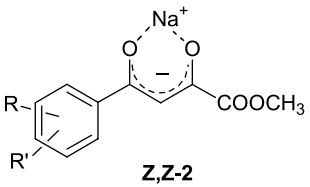
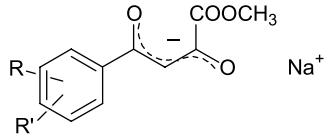
Scheme 3.

Table 1. Preparation of compounds **2**, **3** and **4**

	1	1→2[a] (%)	2→3[a] (%)	1→3	2→4[a] (%)	1→4
a		92	88	81% (lit. 38%[b], 59%[c])	68	63% (lit. 9%[20])
b		88	79	70%	58	51%
c		79	74	58%	50	40%
d		85	90	77% (lit. 100%[d],12%[e])		
e		86	73	63%		
f		80	70	56% (lit. 52%[d], 30%[e])		
g		79	87	69%	45	36%
h		75	82	62% (lit. 85%[f])	65	49% (lit. 64%[20])
i		82	74	61% (lit. 94%[g])	55	45% (lit. 38%[11])
j		86	76	65%		

[a] Yields in isolated pure mixtures of *Z,Z* and *E,Z* forms (**2**) or tautomers (**3** and **4**).
[b] $(CO_2Me)_2$, NaOMe, MeOH, rt, >12 h.[13]
[c] NaH, DMF, $(CO_2Me)_2$, 50 °C, 30 min.[12]
[d] *t*-BuOOCCOOMe, NaOMe, THF–DME (1:1), rt, <2 h.[16]
[e] $(CO_2Me)_2$, NaOMe, THF–DME (1:1), rt, >12 h.[16]
[f] NaH, Toluene, $(CO_2Et)_2$, reflux, 1 h.[20]
[g] NaH, MeOH, Benzene, then **1** and $(CO_2Me)_2$, 12 h.[11]

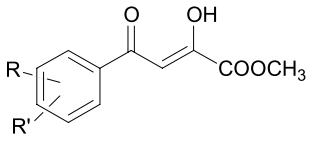
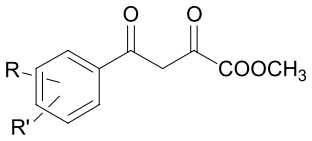
Table 2. Spectroscopic data of compounds **2(a–j)**

Product	 **Z,Z-2**		 **E,Z-2**
	^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)
2a	3.68 (s, 3H), 6.34 (s, 1H), 7.40 (m, 3H), 7.79 (br d, 2H)	51.5 (CH_3), 92.0 (CH), 126.5 (2CH), 128.0 (2CH), 129.8 (CH), 142.3 (C), 167.7 (C), 170.3 (C), 185.0 (C)	3.59 (s, 3H), 5.31 (s, 1H), 7.34 (m, 3H), 7.70 (br d, 2H)[a]
2b	3.63 (s, 3H), 3.74 (s, 3H), 6.05 (s, 1H), 6.91–7.00 (m, 2H), 7.28–7.34 (m, 2H)	51.5 (CH_3), 55.4 (CH_3), 97.6 (CH), 111.7 (CH), 120.0 (CH), 128.6 (CH), 129.7 (CH), 133.8 (C), 156.2 (C), 167.8 (C), 169.1 (C), 187.2 (C)	3.63 (s, 3H), 3.74 (s, 3H), 5.05 (br s, 1H), 6.91–7.00 (m, 2H), 7.28–7.34 (m, 2H)
2c	3.66 (s, 3H), 3.78 (s, 3H), 6.33 (s, 1H), 6.92 (d, 2H, ^3J=8.1), 7.77 (d, 2H, ^3J=8.1)	51.6 (CH_3), 55.2 (CH_3), 91.6 (CH), 113.3 (2CH), 128.4 (2CH), 134.5 (C), 160.9 (C), 167.9 (C), 169.5 (C), 184.8 (C)	3.56 (s, 3H), 3.78 (s, 3H), 5.28 (s, 1H), 6.88 (d, 2H, ^3J=7.6), 7.66 (d, 2H, ^3J=7.6)
2d	3.67 (s, 3H), 6.29 (s, 1H), 7.19 (br dd, 2H, $^3J_{HH}$=8.3, $^3J_{HF}$=9.0), 7.83 (dd, 2H, $^3J_{HH}$=8.3, $^4J_{HF}$=5.9)	51.7 (CH_3), 91.9 (CH), 114.8 (2CH, $^2J_{CF}$=22.0), 129.0 (2CH, $^3J_{CF}$=9.2), 138.5 (C, $^4J_{CF}$=3.0), 163.3 (C, $^1J_{CF}$=247.8), 167.6 (C), 170.2 (C), 184.2 (C)	3.58 (s, 3H), 5.28 (s, 1H), 7.14 (m, 2H), 7.77 (m, 2H)
2e	3.67 (s, 3H), 6.20 (br s, 1H), 7.68 (br t, 1H, ^3J=7.9), 8.19–8.26 (m, 2H), 8.53 (br s, 1H)	51.6 (CH_3), 92.1 (CH), 121.0 (CH), 124.5 (CH), 129.9 (CH), 132.8 (CH), 143.2 (C), 147.9 (C), 167.3 (C), 172.9 (C), 181.7 (C)	
2f	3.68 (s, 3H), 6.33 (s, 1H), 7.98 (d, 2H, ^3J=8.3), 8.23 (d, 2H, ^3J=8.3)	51.6 (CH_3), 92.5 (CH), 123.4 (2CH), 127.7 (2CH), 148.0 (C), 148.1 (C), 167.1 (C), 171.8 (C), 182.1 (C)	3.60 (s, 3H), 5.36 (s, 1H), 7.93 (d, 2H, ^3J=8.3), 8.17 (d, 2H, ^3J=8.3)
2g	3.66 (s, 3H), 3.77 (br s, 6H), 6.36 (br s, 1H), 6.94 (br d, 1H), 7.39 (m, 2H)	51.5 (CH_3), 55.3 (CH_3), 55.5 (CH_3), 91.6 (CH), 109.9 (CH), 110.7 (CH), 119.7 (CH), 134.7 (C), 148.2 (C), 150.6 (C), 167.8 (C), 169.8 (C), 184.6 (C)	3.66 (s, 3H), 3.77 (br s, 6H), 5.30 (br s, 1H), 6.94 (br d, 1H), 7.39 (m, 2H)
2h	3.66 (s, 3H), 5.10 (s, 4H), 6.22 (s, 1H), 6.73 (br s, 1H), 6.98 (br s, 2H), 7.32–7.43 (m, 10H)	51.4 (CH_3), 69.3 ($2CH_2$), 91.9 (CH), 103.4 (CH), 105.6 (2CH), 127.6 (4CH), 127.8 (2CH), 128.40 (4CH), 137.0 (2C), 144.8 (C), 159.2 (2C), 167.6 (C), 170.8 (C), 184.2 (C)	3.57 (s, 3H), 5.10 (s, 4H), 5.24 (s, 1H), 6.63 (br s, 1H), 6.95 (br s, 1H), 7.32–7.43 (m, 10H)[b]
2i	3.72 (s, 3H), 6.60 (s, 1H), 7.52 (br s, 2H), 7.91 (m, 4H), 8.39 (br s, 1H)	51.8 (CH_3), 92.6 (CH), 124.5 (CH), 126.4 (2CH), 127.0 (CH), 127.5 (CH), 127.6 (CH), 129.0 (CH), 132.6 (C), 133.9 (C), 139.6 (C), 167.8 (C), 170.4 (C), 185.4 (C)	3.72 (s, 3H), 5.57 (br s, 1H), 7.52 (br s, 2H), 7.91 (m, 4H), 8.39 (br s, 1H)
2j	3.69 (s, 3H), 3.88 (br s, 6H), 6.50 (br s, 1H), 7.29 (br s, 1H), 7.45 (br s, 1H), 7.73–7.80 (m, 2H), 8.23 (br s, 1H)	51.5 (CH_3), 55.4 (CH_3), 55.6 (CH_3), 92.1 (CH), 106.1 (CH), 107.5 (CH), 122.5 (CH), 124.9 (CH), 125.8 (CH), 128.2 (C), 129.9 (C), 137.7 (C), 149.4 (C), 150.1 (C), 167.9 (C), 170.2 (C), 185.3 (C)	3.60 (s, 3H), 3.88 (br s, 6H), 5.46 (br s, 1H), 7.29 (br s, 1H), 7.45 (br s, 1H), 7.73–7.80 (m, 2H), 8.12 (br s, 1H)

[a] ^{13}C NMR (50 MHz, DMSO-d_6): δ=50.3 (CH_3), 91.9 (CH), 126.4 (2CH), 127.6 (2CH), 129.0 (CH), 142.4 (C), 170.4 (C), 180.2 (C), 182.7 (C).

[b] ^{13}C NMR (50 MHz, DMSO-d_6): δ=50.3 (CH_3), 69.2 ($2CH_2$), 92.1 (CH), 103.2 (CH), 105.3 (2CH), 127.5 (4CH), 127.7 (2CH), 128.38 (4CH), 137.2 (2C), 145.1 (C), 158.9 (2C), 170.3 (C), 180.4 (C), 182.0 (C).

Table 3. Spectroscopic data of compounds **3(a–j)**

Product	Ketoenol/diketo ratio[a]	Ketoenol-form		Diketo-form
				
		^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{1}H NMR (200 MHz, DMSO-d_6) Detectable signals δ, ppm (J, Hz)
3a	90:10	3.86 (s, 3H), 7.12 (s, 1H), 7.57 (br t, 2H, ^3J=7.1), 7.70 (br t, 1H, ^3J=7.1), 8.06 (br d, 2H, ^3J=7.1)	53.0 (CH_3), 98.1 (CH), 127.9 (2CH), 129.1 (2CH), 134.1 (CH), 134.3 (C), 162.0 (C), 168.7 (C), 190.2 (C)	3.78 (s, 3H), 4.62 (s, 2H), 7.99 (br d, 2H)
3b	84:16	3.82 (s, 3H), 3.89 (s, 3H), 7.06 (br dd, 1H, ^3J=7.3, ^3J=6.7), 7.15 (s, 1H), 7.17 (br d, 1H, ^3J=8.8), 7.58 (1H, br dd, ^3J=8.8, ^3J=6.7), 7.77 (1H, br d, ^3J=7.3)	52.9 (CH_3), 55.9 (CH_3), 102.8 (CH), 112.7 (CH), 120.7 (CH), 123.6 (C), 130.0 (CH), 135.1 (CH), 158.9 (C), 162.3 (C), 168.4 (C), 189.4 (C)	4.38 (s, 2H), 7.73 (br d, 1H)
3c	96:4	3.84 (s, 3H), 3.85 (s, 3H), 7.05 (s, 1H), 7.07 (d, 2H, ^3J=8.9), 8.05 (d, 2H, ^3J=8.9)	52.9 (CH_3), 55.7 (CH_3), 97.7 (CH), 114.5 (2CH), 127.2 (C), 130.5 (2CH), 162.5 (C), 164.1 (C), 167.2 (C), 189.9 (C)	4.53 (s, 2H)
3d	91:9	3.85 (s, 3H), 7.10 (s, 1H), 7.38 (br dd, 2H, $^3J_{HH}$=8.6, $^3J_{HF}$=9.0), 8.15 (dd, 2H, $^3J_{HH}$=8.6, $^4J_{HF}$=5.6)	53.1 (CH_3), 98.2 (CH), 116.2 (2CH, $^2J_{CF}$=22.0), 131.1 (2CH, $^3J_{CF}$=9.8), 131.5 (C), 162.0 (C), 165.6 (C, $^1J_{CF}$=253.3), 167.8 (C), 189.4 (C)	3.77 (s, 3H), 4.60 (s, 2H), 7.38 (br dd, 2H, $^3J_{HH}$=8.6, $^3J_{HF}$=9.0), 8.05 (dd, 2H, $^3J_{HH}$=8.6, $^4J_{HF}$=5.6)
3e	90:10	3.86 (s, 3H), 7.14 (s, 1H), 7.82 (m, 1H), 8.44–8.47 (m, 2H), 8.64 (br s, 1H)	53.1 (CH_3), 98.6 (CH), 122.1 (CH), 127.9 (CH), 130.8 (CH), 134.0 (CH), 135.9 (C), 148.2 (C), 161.9 (C), 168.7 (C), 187.4 (C)	3.79 (s, 3H), 4.70 (s, 2H)
3f	93:7	3.86 (s, 3H), 7.12 (s, 1H), 8.27 (d, 2H, ^3J=9.0), 8.34 (d, 2H, ^3J=9.0)	53.2 (CH_3), 98.8 (CH), 124.0 (2CH), 129.2 (2CH), 139.5 (C), 150.2 (C), 161.9 (C), 170.2 (C), 186.5 (C)	3.78 (s, 3H), 4.68 (s, 2H), 8.20 (d, 2H, ^3J=9.0), 8.34 (d, 2H, ^3J=9.0)
3g	93:7	3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 7.10 (d, 1H, ^3J=8.6), 7.11 (s, 1H), 7.52 (d, 1H, ^4J=2.2), 7.77 (dd, 1H, ^3J=8.6, ^4J=2.2)	53.0 (CH_3), 55.6 (CH_3), 55.9 (CH_3), 98.1 (CH), 110.0 (CH), 111.3 (CH), 123.2 (CH), 127.1 (C), 148.9 (C), 154.2 (C), 162.3 (C), 166.7 (C), 190.5 (C)	3.77 (s, 3H), 3.81 (s, 3H), 4.56 (s, 2H), 7.08 (d, 1H, ^3J=8.7), 7.42 (br s, 1H), 7.63 (br d, 1H, ^3J=8.7)
3h	Diketo-form undetected	3.79 (s, 3H), 5.16 (br s, 4H), 6.93 (br s, 2H), 7.20 (br s, 2H), 7.37–7.44 (m, 10H)	52.5 (CH_3), 69.6 ($2CH_2$), 96.8 (CH), 106.4 (3CH), 127.7 (4CH), 127.9 (2CH), 128.5 (4CH), 136.7 (2C), 138.8 (C), 159.7 (2C), 163.7 (C), 169.5 (C), 188.3 (C)	
3i	97:3	3.86 (s, 3H), 7.24 (s, 1H), 7.60–7.66 (m, 2H), 7.95–8.00 (m, 3H), 8.13 (d, 1H, ^3J=7.6), 8.75 (br s, 1H)	53.0 (CH_3), 98.3 (CH), 123.0 (CH), 127.1 (CH), 127.7 (CH), 128.7 (CH), 129.1 (CH), 129.8 (CH), 130.1 (CH), 131.8 (C), 132.2 (C), 135.4 (C), 162.2 (C), 168.1 (C), 190.3 (C)	4.74 (s, 2H), 8.62 (br s, 1H)
3j	96:4	3.87 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 7.24 (s, 1H), 7.40 (s, 1H), 7.58 (s, 1H), 7.87 (m, 2H), 8.64 (br s, 1H)	53.0 (CH_3), 55.5 (CH_3), 55.7 (CH_3), 98.1 (CH), 106.4 (CH), 108.1 (CH), 121.5 (CH), 127.0 (CH), 128.1 (C), 128.5 (CH), 129.9 (C), 132.3 (C), 149.9 (C), 151.9 (C), 162.3 (C), 167.6 (C), 190.7 (C)	4.66 (s, 2H), 8.51 (br s, 1H)

[a] The ratios were calculated from the ethylenic proton signal of the ketoenol isomer and the methylenic protons signal of the diketo isomer in DMSO-d_6.

Table 4. Physical, analytical and mass spectroscopic data for compounds **3(b–c)**, **3(e–h)** and **3j**[a]

Product	State	Mp (°C)	Elemental analyses	MS (EI)
3b	Yellow powder	75–76	Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C, 61.01; H, 5.12. Found: C, 61.28; H, 5.22	*m/z* (%)=236 ([M^+], 1), 177 (56), 135 (100), 77 (19)
3c	Yellow powder	92–93	Anal. calcd for $C_{12}H_{12}O_5$ (236.22): C, 61.01; H, 5.12. Found: C, 61.35; H, 5.06	*m/z* (%)=236 ([M^+], 16), 178 (12), 177 (100), 135 (33), 109 (38), 94 (14), 77 (12), 69 (21)
3e	Beige powder	112–113	Anal. calcd for $C_{11}H_9NO_6$ (251.20): C, 52.60; H, 3.61; N, 5.58. Found: C, 52.31; H, 3.72; N, 5.35	*m/z* (%)=251 ([M^+], 2), 193 (10), 192 (100), 150 (18), 105 (11), 69 (11)
3f	White powder	161–162	Anal. calcd for $C_{11}H_9NO_6$ (251.20): C, 52.60; H, 3.61; N, 5.58. Found: C, 52.25; H, 3.68; N, 5.42	*m/z* (%)=251 ([M^+], 2), 193 (11), 192 (100), 150 (19), 146 (13), 105 (14), 69 (19)
3g	Yellow powder	150–151	Anal. calcd for $C_{13}H_{14}O_6$ (266.25): C, 58.64; H, 5.30. Found: C, 58.96; H, 5.22	*m/z* (%)=266 ([M^+], 56), 208 (12), 207 (100), 165 (24), 139 (87), 124 (69), 69 (14)
3h	Yellow powder	121–123	Anal. calcd for $C_{25}H_{22}O_6$ (418.45): C, 71.76; H, 5.30. Found: C, 71.95; H, 5.35	*m/z* (%)=418 ([M^+], 29), 359 (9), 327 (16), 227 (10), 181 (48), 180 (34), 91 (100)
3j	Yellow powder	170–172	Anal. calcd for $C_{17}H_{16}O_6$ (316.31): C, 64.55; H, 5.10. Found: C, 64.24; H, 5.15	*m/z* (%)=317 (11), 316 ([M^+], 64), 258 (19), 257 (98), 230 (12), 215 (46), 190 (14), 189 (100), 174 (78), 172 (11)

[a] Known products: **3a**, white powder, mp 57–58 °C (lit.[13] mp 56–57 °C); **3d**, white powder, mp 124–125 °C (lit.[13] mp 125 °C); **3i**, white powder, mp 104–105 °C (lit.[11] mp 104–106 °C).

previous articles except for the yield of **1d→3d** that was reported to reach 100% after column chromatography purification.[16] L-708,906, **4h** was obtained in 64% yield in a recent patent,[20] whereas its unsubstituted parent molecule **4a** was obtained in the same report in a poor 9% yield. No doubt the procedure for the synthesis of L-708,906 was optimized in comparison with that of **4a**. A 94% yield was also reported for the synthesis of **3i** but the yield of its conversion into **4i** dropped to 38%.[11] Since our overall yields in **4i** from **1i** are similar, we may have some doubt about the purity of **3i** in the cited paper. Physical data of ketoenol esters **3** are reported in Tables 3 and 4 and physical data of DKAs **4** in Table 5.

As a conclusion, we reported in this paper, a very simple and efficient procedure for the synthesis of ketoenol esters **3** and acids **4** that allows variable substitution on the aromatic ring. This new protocol involves the isolation of the unpreviously reported sodium keto enolate esters **2** as a key step that may be hydrolyzed under soft conditions into **3** or more hardly treated to give **4**. The yields in **2** are quite good and the conversions into **3** or **4** are acceptable. Due to its remarkable simplicity, this new procedure may be of great interest for the rapid synthesis of a wide range of new DKAs.

3. Experimental

All solvents were of commercial quality used from freshly opened containers and were dried and purified by conventional methods. Aryl methyl ketones **1** were purchased from Aldrich-Chimie (St Quentin-Fallavier, France) except for **1j**. 1-(6,7-dimethoxynaphthalen-2-yl)-ethanone **1j** was prepared in two steps from 2,3-dimethoxynaphthalene according to a known procedure.[23]

Mps were determined on a Reichert Thermopan apparatus, equipped with a microscope and are uncorrected. NMR spectra were obtained on a AC 200 Bruker spectrometer in DMSO-d_6 with TMS as internal reference. Mass spectra were recorded on a Thermo-Finnigan PolarisQ mass spectrometer (70 eV, Electronic Impact). Elemental analyses were performed by CNRS laboratories (Vernaison).

3.1. Synthesis of sodium ketoenolate ester 2. General procedure

Sodium (0.28 g, 12 mmol) was added slowly in methanol (6 mL) at −5 °C to give a 2 M solution of sodium methoxide. Arylmethyl ketone **1** (10 mmol) and dimethyl oxalate (1.18 g, 10 mmol) were dissolved in dried diethyl ether (10 mL) and the freshly prepared solution of sodium methoxide was slowly added. The mixture was stirred overnight, the solid was filtered off, washed with methanol, diethyl ether and dried. Sodium ketoenolate esters **2** were obtained in yields ranging from 75 to 92%.

3.2. Synthesis of ketoenol ester 3. General procedure

Sodium ketoenolate ester **2** (1 g) was dissolved in water (about 100 mL) at rt for 1 h. Then the solution was acidified by adding acetic acid to reach pH 3–4 and kept at 0 °C for 1 h. The precipitate was filtered off, washed with water and dried. Ketoenol esters **3** were obtained in yields ranging from 70 to 90%.

3.3. Synthesis of ketoenol acid 4. General procedure

Sodium ketoenolate ester **2** (1 g) was partially dissolved in 1,4-dioxane (20–30 mL) and 1 M HCl (100 mL) was added. The mixture was refluxed during 6 h. Removal of the solvent under reduced pressure gave a solid, which was washed with water, CH_2Cl_2 and dried. The product was recrystallized from diethyl ether (**4a**), toluene/ethyl acetate (**4b–c**) or ethyl acetate (**4g–i**). Ketoenol acids **4** were obtained as yellow solids in yields ranging from 45 to 68%.

Acknowledgements

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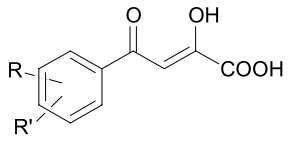
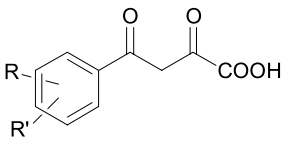
Table 5. Physical and spectroscopic data of compounds **4(a–c)** and **4(g–i)**

Product	Mp (°C)	Ketoenol/diketo ratio[a]			
			Ketoenol-form		Diketo-form
			^{1}H NMR (200 MHz, DMSO-d_6) δ, ppm (J, Hz)	^{13}C NMR (50 MHz, DMSO-d_6) δ, ppm	^{1}H NMR (200 MHz, DMSO-d_6), detectable signals δ, ppm (J, Hz)
4a	154–157 (lit.[15] 155–158)	91:9	7.09 (s, 1H), 7.55 (br dd, 2H, ^3J=7.3, ^3J=6.7), 7.68 (br t, 1H, ^3J=6.7), 8.04 (br d, 2H, ^3J=7.3)	97.8 (CH), 127.8 (2CH), 129.1 (2CH), 134.0 (CH), 134.6 (C), 163.1 (C), 170.1 (C), 190.4 (C)	4.56 (s, 2H), 7.96 (br d, 2H, ^3J=7.4)
4b	155–157[b]	83:17	3.89 (s, 3H), 7.07 (br dd, 1H, ^3J=7.3, ^3J=6.6), 7.17 (s, 1H), 7.19 (br d, 1H, ^3J=8.3), 7.59 (br dd, 1H, ^3J=8.3, ^3J=6.6), 7.78 (br d, 1H, ^3J=7.3)	56.1 (CH_3), 102.8 (CH), 112.8 (CH), 120.9 (CH), 124.0 (C), 130.1 (CH), 135.1 (CH), 158.9 (C), 163.4 (C), 169.8 (C), 189.9 (C)	3.81 (s, 3H), 4.34 (s, 2H), 7.72 (br d, 1H)
4c	157–158 (lit.[21] 160–162)	89:11	3.84 (s, 3H), 6.90 (s, 1H), 7.06 (d, 2H, ^3J=8.3), 8.01 (d, 2H, ^3J=8.3)	55.7 (CH_3), 97.4 (CH), 114.4 (2CH), 127.5 (C), 130.2 (2CH), 162.5 (C), 163.6 (C), 171.1 (C), 188.7 (C)	4.41 (s, 2H), 7.93 (d, 2H, ^3J=8.4)
4g	188–189 (lit.[22] 179–180 dec.)	90:10	3.84 (s, 3H), 3.86 (s, 3H), 7.08 (s, 1H), 7.10 (d, 1H, ^3J=8.6), 7.53 (d, 1H, ^4J=1.5), 7.76 (dd, 1H, ^3J=8.6, ^4J=1.5)	55.6 (CH_3), 55.9 (CH_3), 97.8 (CH), 109.9 (CH), 111.3 (CH), 123.0 (CH), 127.3 (C), 148.9 (C), 154.0 (C), 163.4 (C), 168.3 (C), 190.4 (C)	3.81 (s, 3H), 4.50 (s, 2H), 7.43 (br s, 1H), 7.63 (br d, 1H, ^3J=8.8)
4h	171–173 (lit.[15] 170–172)	90:10	5.18 (s, 4H), 6.99 (br s, 1H), 7.09 (s, 1H), 7.26 (br s, 2H), 7.31–7.47 (m, 10H)	69.7 ($2CH_2$), 98.2 (CH), 106.6 (2CH), 107.6 (CH), 127.8 (4CH), 128.0 (2CH), 128.5 (4CH), 136.6 (2C), 136.8 (C), 159.8 (2C), 163.2 (C), 170.2 (C), 190.0 (C)	4.54 (s, 2H), 7.20 (br s, 2H)
4i	174–175 (lit.[11] 173–175)	93:7	7.29 (s, 1H), 7.60–7.70 (m, 2H), 7.98–8.05 (m, 3H), 8.17 (d, 1H, ^3J=8.3), 8.81 (br s, 1H)	98.2 (CH), 123.1 (CH), 127.1 (CH), 127.7 (CH), 128.8 (CH), 129.1 (CH), 129.8 (CH), 130.1 (CH), 132.0 (C), 132.3 (C), 135.4 (C), 163.2 (C), 169.6 (C), 190.6 (C)	4.70 (s, 2H), 8.71 (br s, 1H)

[a] The ratios were calculated from the ethylenic proton signal of the ketoenol isomer and the methylenic protons signal of the diketo isomer in DMSO-d_6.
[b] Anal. calcd for $C_{11}H_{10}O_5$ (222.20): C, 59.46; H, 4.54. Found: C, 59.24; H, 4.63. MS (EI): m/z (%)=222 ([M^+], 2), 192 (11), 177 (70), 149 (10), 135 (100), 79 (12), 77 (27).

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Substrate-selective aqueous organometallic catalysis. How size and chemical modification of cyclodextrin influence the substrate selectivity

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Abstract—Randomly hydroxypropylated and methylated cyclodextrins with different cavity size have been used as inverse phase transfer catalysts in a palladium catalyzed Tsuji-Trost reaction with water-insoluble alkylallylcarbonates and alkylallylurethanes as substrate. It has been shown that the molecular recognition ability of both α-CD and β-CD derivatives towards these substrates was responsible for an increase in the reaction rates and remarkable substrate selectivities between a linear and a branched structure. By contrast, the too wide cavity of γ-CD derivatives did not allow these carriers to be efficient in terms of substrate selectivity. Thus, the performances of a cyclodextrin carrier in this cleavage reaction strongly depended on the size of the cavity in which the substrate had to fill in as close as possible the available space.

1. Introduction

Cyclodextrins (CDs) are α-(1-4)-linked cyclic oligosaccharides usually consisting of 6(α), 7(β) or 8(γ) glucopyranose units. They exhibit a torus-shaped structure with a hydrophobic cavity into which a guest molecule of appropriate size and shape can be incorporated.[1] The use of the host cavity as microreactor to perform chemical reactions has attracted the interest of numerous organic chemists since the 1960s. Indeed, the microenvironment around the reactant in the CD cavity is different from that in the reaction media and a change of the course of the reaction can be observed.[2] For example, there are numerous studies in which binding of the substrate into the host cavity alters the regio- or stereoselectivity of the attack by an external reagent.[3] These changes were attributed to a control of the substrate conformation or to the orientation of the substrate included in the cavity towards the reagent in solution.[4] The selective binding of the substrate by the CD cavity can also lead to substrate selective reaction. Indeed, when the cyclodextrin itself catalyzes the reaction, only the substrate that penetrates into the host cavity reacts.[5]

The combination of an aqueous organometallic catalyst and water soluble CD derivatives is also an original way to obtain substrate selective reactions. In fact, when the organic phase contains an isomers mixture, the CD preferentially transfers into the aqueous phase the isomer that interacts with the CD cavity. The substrate/CD complex can then reacts with the aqueous organometallic catalyst to give the product that is released into the organic phase, according to Figure 1.

The feasibility of this approach was clearly demonstrated with randomly methylated β-CD (Me-β-CD) in a palladium catalyzed Tsuji-Trost reaction with water-insoluble alkylallylcarbonates and alkylallylurethanes as substrates. Indeed, by using different pairs of structural isomers, it was found that the size-fit concept which postulates the highest reactivity for the best size-matched host–guest pair was a very useful tool for predicting the values of substrate selectivity.[6]

In this paper, experiments with different chemically modified CDs have been performed to systematically determine effect of the size cavity and the chemical modification on the substrate selectivity. Six CD derivatives have been evaluated in the palladium catalyzed cleavage of isomers of biphenylmethylallylcarbonate or *N*-alkyl-*O*-allylurethanes: the hydroxypropylated α-CD (HP-α-CD), the hydroxypropylated β-CD (HP-β-CD), the hydroxypropylated γ-CD (HP-γ-CD), the methylated α-CD (Me-α-CD), the methylated β-CD (Me-β-CD), and the methylated γ-CD (Me-γ-CD) (Fig. 2).

Keywords: Palladium; Water-soluble phosphines; Cyclodextrins; Molecular recognition; Carbonate and urethane cleavage.
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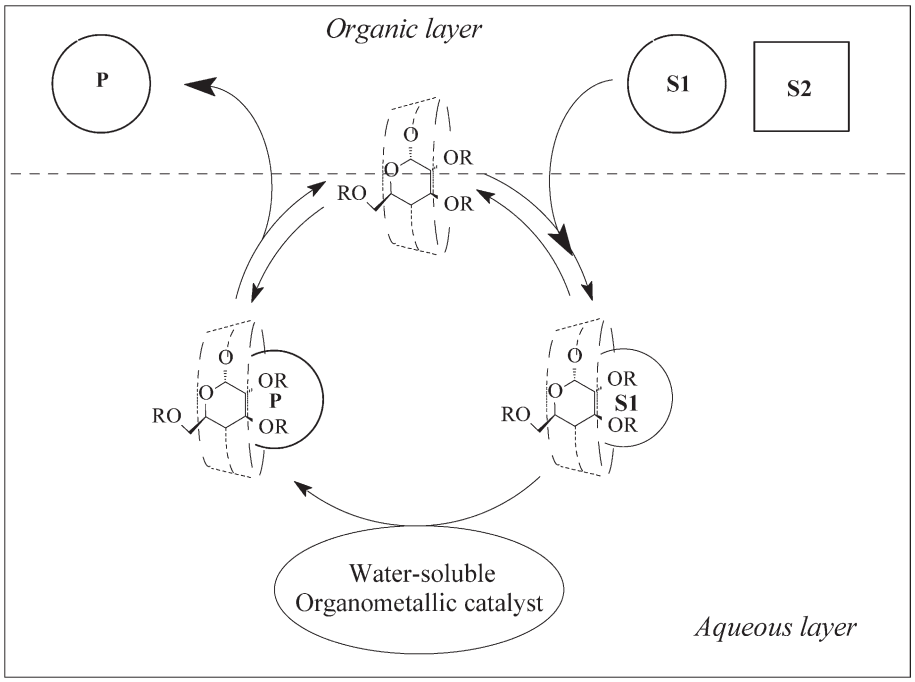
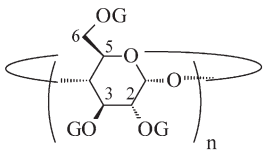


Figure 1. Concept of the substrate-selective aqueous organometallic catalysis mediated by cyclodextrin derivatives. Only the substrate **S1** fits properly in the host cavity of the cyclodextrin and, consequently reacts with the water soluble catalyst to give the product **P**.

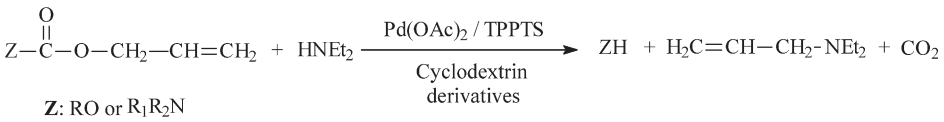
Structure of the chemically modified cyclodextrin



G: **H** or **R**

Abbreviations	n	**R**: group attached to the cyclodextrin	Carbon bearing the OR group	Average number of OH group substituted per glucopyranose unit
HP-α-CD	6	$-CH_2-CH(OH)-CH_3$	2	0.8
HP-β-CD	7	$-CH_2-CH(OH)-CH_3$	2	0.8
HP-γ-CD	8	$-CH_2-CH(OH)-CH_3$	2	0.8
Me-α-CD	6	$-CH_3$	2, 3, 6	1.8
Me-β-CD	7	$-CH_3$	2, 3, 6	1.8
Me-γ-CD	8	$-CH_3$	2, 3, 6	1.8

Figure 2. Chemically modified cyclodextrins used in this work.



Scheme 1.

The cleavage of these substrates was catalyzed by a palladium/trisulfonated triphenylphosphine combination in the presence of diethylamine as allyl scavenger (Scheme 1).[7]

This reaction can find numerous applications in the field of protection/deprotection chemistry by using the allyloxycarbonyl group (Alloc) as protecting group.[8]

2. Results and discussion

The first experiments that have been carried out in the following study were performed with two alkylallylcarbonate isomers: the linear *para*-biphenylmethylallylcarbonate and the bent *ortho*-biphenylmethylallylcarbonate. These two molecules strongly differed from their shape and consequently from the space they occupied in the CD cavity.

First of all, both isomers have been cleaved in a biphasic medium in which a classical co-solvent (acetonitrile) was used as mass-transfer promoter to reduce mass transfer limitation (see Section 4.3). This control experiment was carried out to make sure that substrate selectivity was not due to a different reactivity of the palladium species towards the substrate or nucleophile. Thus, the deprotection of a 50/50 mixture of *ortho*-biphenylmethylallylcarbonate and *para*-biphenylmethylallylcarbonate was carried out in the presence of 0.4 g of acetonitrile (20% by weight of acetonitrile in the aqueous phase). In these experimental conditions, the two isomers were cleaved at the same rate (initial activity of 1.2 h^{-1}) and, consequently, no substrate selectivity was observed. Thus, this experiment confirms that *ortho*-biphenylmethylallylcarbonate and *para*-biphenylmethylallylcarbonate form a relevant pair of isomers to evaluate the discriminating power of the CD derivatives.

The results obtained without addition of any CD (reference experiment) and in the presence of the six CD derivatives are gathered in Figure 3.

For both substrates, the relative reaction rate (ratio between the initial catalytic activity in the presence of CD and the initial catalytic activity without CD) has been measured and the ratio of that obtained with the linear isomer was divided by that of the bent isomer to give the substrate selectivity. As expected, the reaction rates without CD were very low (initial catalytic activity: 0.3 h^{-1}) and identical. This last result indicates clearly that the two isomers had the same water solubility and exhibited the same reactivity towards palladium species. When a modified CD was added to the system, the reaction rates increased whatever the CD and a discriminating process appeared with α- and β-CD derivatives.

More precisely, an analysis of the results obtained with HP-α-CD showed that the cleavage reaction of the linear *para*-biphenylmethylallylcarbonate occurred at a relative reaction rate of 53, whereas it was only 14 with the bent *ortho*-biphenylmethylallylcarbonate. The ratio between these two initial catalytic activities gave a substrate selectivity of 3.8, which means that the linear isomer was converted 3.8 times faster than the bent one. When using HP-β-CD as a carrier, relative reaction rates were higher than those obtained with HP-α-CD (88 and 37 for the *para*

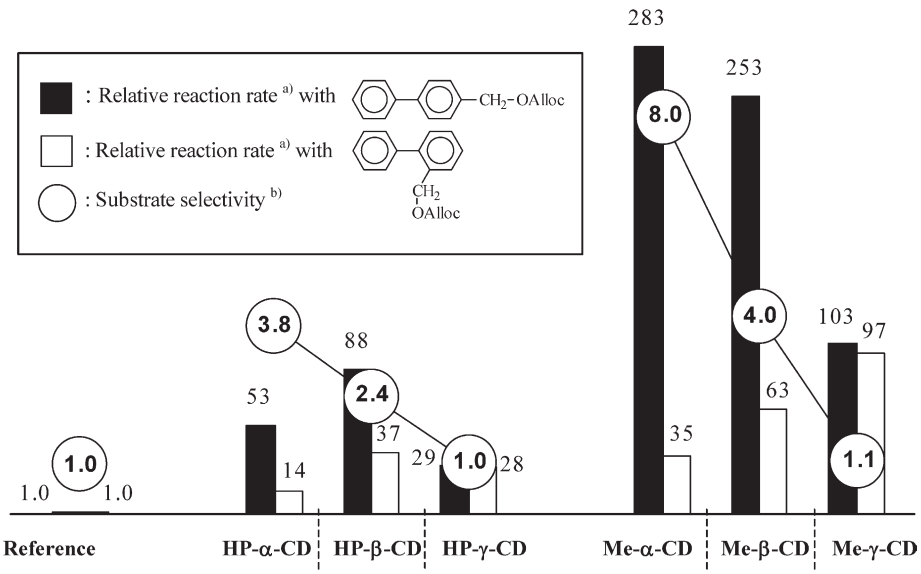


Figure 3. Reaction rate and substrate selectivity observed with *para*-biphenylmethylallyl carbonate and *ortho*-biphenylmethylallylcarbonate. (a) The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 0.3 h^{-1} for each isomer (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.

and *ortho* isomers respectively) but the substrate selectivity was lower (2.4). Although a rate enhancement was observed relative to the reference experiments, the relative reaction rates were lower with HP-γ-CD than with HP-β-CD (29 vs. 88 respectively for the *para* isomer and 28 vs. 37 respectively for the *ortho* isomer) and no substrate selectivity was observed with the HP-γ-CD.

These first results might be interpreted in terms of recognition ability of the supramolecular carrier towards the shape of the substrate. The HP-α-CD constitutes a better discriminant carrier than the HP-β-CD because of its smaller cavity. The *para*-biphenylmethyl group of the linear isomer is able to deeply penetrate inside the HP-α-CD cavity since no interaction hindered its recognition. By contrast, the bent isomer can only be slightly recognised by the cavity of HP-α-CD because the approach of both molecules is hindered by steric repulsions. Actually, if one considered that the biphenyl group comes into the cavity, the allylcarbonate moiety becomes very close to the edge of the CD and the inclusion is consequently not so deep than it is with the linear isomer. When the cavity size is increased, the penetration of both isomers in the cavity is easier. However, the benefit effect is more marked for the bent isomer that fits poorly in the HP-α-CD cavity than for the linear isomer that fits well in the cavity. This difference behaviour induces logically a decrease in the substrate selectivity (3.8 with HP-α-CD vs. 2.4 with HP-β-CD). In the case of HP-γ-CD, the cavity size is clearly too wide to efficiently recognise the linear isomer, resulting in a drastic decrease in the reaction rate. In fact, it appears that both isomers are transferred with the same rate in the aqueous phase leading to no substrate selectivity.

Experiments conducted with the methylated CDs instead of hydroxypropylated CDs gave a more clear view of processes leading to rate enhancement and substrate selectivity. What striked when looking at the values obtained with Me-α-CD, Me-β-CD and Me-γ-CD was their greater ability to improve the performances of the system whether in terms of reaction rate or substrate selectivity. The effect of methylation on the reaction rate was particularly visible with Me-α-CD for which a relative reaction rate of 283 was measured with the *para*-biphenylmethylallylcarbonate (it was only 53 with HP-α-CD). Similarly, the relative reaction rate observed with the *ortho* isomer was higher with Me-α-CD than with HP-α-CD (35 vs. 14 respectively). Me-β-CD and Me-γ-CD led to the same conclusions when compared respectively to HP-β-CD and HP-γ-CD but in a less extend. More interesting is the fact that the widening of the diameter of the Me-CDs led to a decrease in cleavage rate for the linear isomer in parallel to an increase in the cleavage rate for the bent isomer, inducing a drop of the substrate selectivity. Indeed, the substrate selectivity was 8.0, 4.0 and 1.1 with the Me-α-CD, Me-β-CD and Me-γ-CD, respectively. Interestingly, it is worth mentioning that the high substrate selectivities observed with the Me-α-CD and the Me-β-CD were also confirmed with competitive experiments. In these experiments, the deprotection of a 50/50 mixture of *ortho*- and *para*-biphenylmethylallyl carbonate was carried out with methylated CDs. The ratio of the products *p*-biphenylmethanol and *o*-biphenylmethanol, as determined by chromatography, was used as a measure for substrate selectivity. As already mentioned, no substrate selectivity was observed in a control experiment in which acetonitrile was used as a mass transfer promoter. By contrast, the use of Me-α-CD or Me-β-CD led to substantial substrate selectivity. Indeed, substrate selectivities of 7.2 and 3.6 were observed in the initial stages of the reaction with the Me-α-CD or Me-β-CD, respectively.

According to us, two factors can account for the higher efficiency of methylated CDs. The first is the surface-active behavior of these CDs.[9] Indeed, surface tension measurements indicated that all methylated CDs are much more surface active than hydroxypropylated CDs. So, by decreasing the interfacial tension between the aqueous and the organic layers, these CDs greatly contribute to increase the mass transfer between the two phases. The second factor, and the most important, is the presence of a well-defined extended hydrophobic host cavity. Indeed, attachment of 12.8 methyl groups to the β-CD extends its cavity. Thus, these methylated CDs have much more important cavity volumes approximately 10–20% larger than HP-CDs due to the increase in the height of the CD torus.[10,11] This gives rise to CDs that accommodate more easily highly hydrophobic substrates and, consequently transfer more efficiently the substrate into the aqueous phase.[11] Moreover, the benefit effect of an extended cavity is clearly much more important for a linear substrate than for a bent substrate. This last point is crucial to understand why the discrimination is higher with Me-CDs than with HP-CDs (substrate selectivity: 8 vs. 3.8 for α-CDs and 4.0 vs. 2.4 for β-CDs). Finally, it must be pointed out that the decrease in the substrate selectivity when the cavity was wider could be rationalized by assuming that a destabilization of the *para*-isomer/CD complex occurred because of a growing mobility of the guest in the host cavity and, by contrast, that the *ortho*-isomer/CD complex was more stabilized due to a deeper penetration of the substrate in the cavity.

In a second part of this study, we wanted to enlarge our conclusions to other substrates. Tsuji-Trost reactions have then been carried out in the same experimental conditions than those described above with two alkylallylurethane isomers: the linear *N*-dodecyl-*O*-allylurethane and the branched *N*,*N*-dihexyl-*O*-allylurethane. Due to the presence of alkyl chains, these substrates are expected to be more flexible than the biphenylmethylallylcarbonate isomers. As above mentioned for the carbonates, it was also carefully checked that these two isomers exhibited the same reactivity in a biphasic medium in which acetonitrile was used as a mass-transfer promoter (see Section 4.3). In these experiments, the deprotection of a 50/50 mixture of *N*,*N*-dihexyl-*O*-allylurethane and *N*-dodecyl-*O*-allylurethane was carried out in the presence of acetonitrile (2 g; 100% by weight of acetonitrile in the aqueous phase). The ratio of the products *N*-dodecylamine and *N*,*N*-dihexylamine was used as a measure for substrate selectivity. As expected, no substrate selectivity was observed in this control experiment. Indeed, the two substrates were converted at the same rate ($0.25\ h^{-1}$).

The results obtained without CD and in the presence of the CD derivatives are summarized in Figure 4.

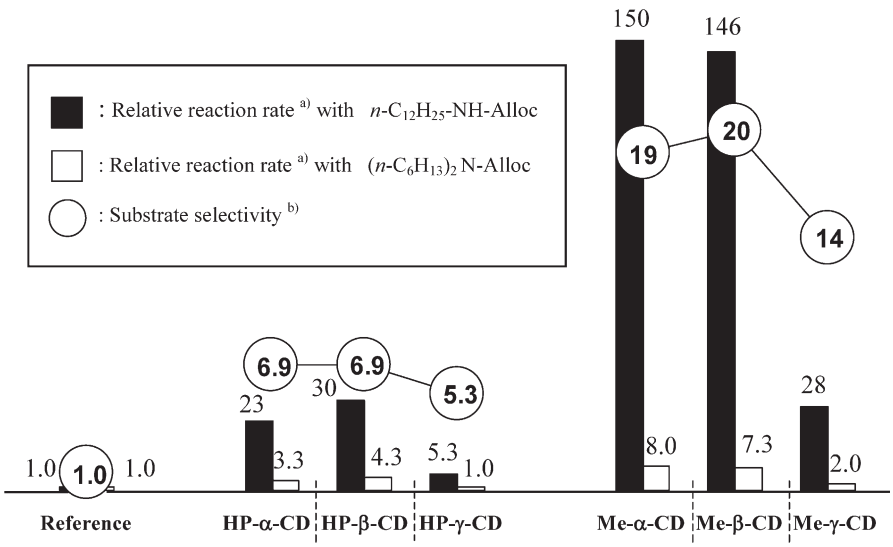


Figure 4. Reaction rate and substrate selectivity observed with *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allylurethane. (a) the relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 0.03 h^{-1} for each isomer (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.

As for alkylallylcarbonates, the solubility of both isomers appeared to be the same since they were cleaved at the same rate when no cyclodextrin was added to the catalytic system. Nevertheless, the intrinsic solubility of urethanes was lower than that of the carbonates since the latter were cleaved 10 times faster than the former (initial catalytic activity: 0.3 h^{-1} vs. 0.03 h^{-1} respectively).

When HP-CDs were used to transport the substrate from the organic phase to the aqueous phase, the relative reaction rates were all lower than those obtained with alkylallylcarbonates. Consequently, the CDs seemed to be more appropriate to recognise biphenylmethylallylcarbonates than *N*-alkyl-*O*-allylurethanes. In each case, the relative reaction rates were always higher for *N*-dodecyl-*O*-allylurethane than for *N*,*N*-dihexyl-*O*-allylurethane. As for the previous bent structure of the *ortho*-biphenylmethylcarbonate, the branched *N*,*N*-dihexyl-*O*-allylurethane could not penetrate as deeply in the cavity of the CDs than the linear *N*-dodecyl isomer. Both the length of the alkyl chains and the steric hindrance of the non-included moiety of the substrate were suspected to be responsible for this difference of cleavage rates. It can also be noticed that in that case, the discriminating power of HP-α-CD and HP-β-CD was the same (substrate selectivities=6.9) even if HP-β-CD led to better relative reaction rates than HP-α-CD (30 vs. 23 respectively for the *N*-dodecyl isomer and 4.3 vs. 3.3 respectively for the *N*,*N*-dihexyl isomer). This surprising result suggests that the flexible alkyl chains allow to urethanes to easily adjust to the size of the cavity. This assumption was partially confirmed by the result obtained with the HP-γ-CD. Indeed, the wider cavity of HP-γ-CD is always discriminant since a substrate selectivity of 5.3 was measured. In fact, the branched structure of the *N*,*N*-dihexyl-*O*-allylurethane was not recognised at all by the cavity of HP-γ-CD (relative reaction rate=1) whereas the long flexible *N*-dodecyl chain was always able to sufficiently interact with HP-γ-CD to allow the substrate to be carried to the aqueous phase. Whatever its potentialities in terms of substrate selectivity, HP-γ-CD remained a worse inverse phase transfer catalyst than HP-α-CD and HP-β-CD, as already observed for biphenylmethylallylcarbonates.

A last series of experiments concerned the randomly methylated cyclodextrins. The cleavage rates of *N*-dodecyl and *N*,*N*-dihexyl-*O*-allylurethanes were compared using Me-α-CD, Me-β-CD and Me-γ-CD successively (Fig. 4). Once again, the relative reaction rates were lower than those measured for biphenylmethylallylcarbonates in the same conditions, but the higher affinity of the cavity of Me-CDs for lipophilic substrates still appeared clearly through the comparison with the relative reaction rates obtained with HP-CDs (for example, 150 with Me-α-CD vs. 23 with HP-α-CD for the *N*-dodecyl isomer and 8 with Me-α-CD vs. 3.3 with HP-α-CD for the *N*,*N*-dihexyl isomer). Thus, the hypothesis according which the surface active properties and the presence of an extended hydrophobic cavity lead to better rate reaction appeared valid. In particular, an extended cavity allows to wrap more efficiently the linear isomer than the bent isomer, inducing a rate increase more

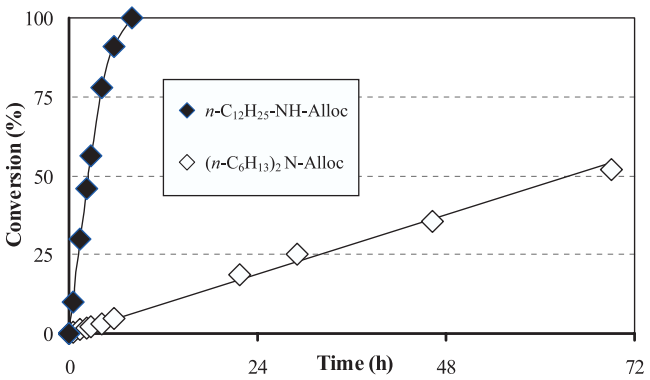


Figure 5. Conversion of *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allylurethane in function of time during a competition experiment in which both substrates are present. Experimental conditions: $Pd(OAc)_2$ (0.045 mmol), TPPTS (0.40 mmol), Me-β-CD (0.31 mmol), water (2 g), *N*-dodecyl-*O*-allylurethane (0.56 mmol), *N*,*N*-dihexyl-*O*-allylurethane (0.56 mmol), diethylamine (2.22 mmol, 160 mg) and toluene (2 g).

pronounced for the linear isomer than for the bent isomer and consequently explaining the higher discriminating power of the methylated CDs relative to the hydroxypropylated CDs. Finally, this high discrimination power of Me-β-CD was also confirmed by a competitive experiment. In this experiment, the deprotection of a 50/50 mixture of *N*,*N*-dihexyl-*O*-allylurethane and *N*-dodecyl-*O*-allylurethane was carried out in the presence of Me-β-CD (Fig. 5).

As displayed in Figure 5, the *N*-dodecyl-*O*-allylurethane was undoubtedly converted much faster than the *N*,*N*-dihexyl-*O*-allylurethane. In fact, a 96/4 product ratio was observed in the initial stages of the reaction, confirming the substrate selectivity obtained in the experiments where urethanes were tested alone (24 vs. 20). Interestingly, the curves profiles also indicated that no substrate or product inhibition occured.

3. Conclusion

This study has clearly demonstrated that the reaction rate and substrate selectivity strongly depended on the size and chemical modification of the CD. The methylated CDs are the most efficient CDs to perform substrate selective reactions due to their surface active behaviour and to the presence of a well defined hydrophobic cavity. Furthermore, it appears that cavity size is a crucial factor to control the substrate selectivity. For the tested substrates, the smaller the cavity, the higher the substrate selectivity. This conclusion is particularly true for rigid substrates. Thus, α-CDs were more discriminant than β-CDs and much more discriminant than γ-CDs for biphenylmethylallylcarbonate isomers. With urethanes containing flexible alkyl chains, the discriminating power of α-CDs and β-CDs was found equivalent and significantly higher than that of γ-CDs. Experiments are currently under way to examine the ability of these methylated CDs to perform enantioselective reactions.

4. Experimental

4.1. Materials

HP-α-CD and HP-β-CD were obtained from Aldrich Chemical Co. and was used as received without further purification. HP-γ-CD was a generous gift of Wacker Chemie Co. These HP-CDs were native CDs partially *O*-2-hydroxypropylated with statistically 0.8 OH groups modified per glucopyranose unit. Me-β-CD was purchased from Aldrich Chemical Co. The Me-α-CD and Me-γ-CD were prepared by adapting a procedure reported by Y. Kenichi et al.[12] These CDs were partially methylated; statistically 1.8 OH groups per glucopyranose unit were modified. Palladium acetate and organic compounds were purchased from Strem Chemicals, Aldrich Chemical Co. and Acros Organics in their highest purity and used without further purification. Trisodium tris(*m*-sulfonatophenyl)-phosphine (($P(C_6H_4SO_3Na)_3$; TPPTS)) was synthesized as reported by Gärtner et al.[13] The purity of the TPPTS was carefully controlled. In particular, $^{31}P\{^1H\}$ solution NMR indicated that the product was a mixture of TPPTS (ca. 98%) and its oxide (ca. 2%). Distilled deionized water was used in all experiments. All catalytic reactions were performed under nitrogen using standard Schlenk techniques. All solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze-pump-thaw cycles before use.

4.2. Catalytic experiments

In a typical experiment, $Pd(OAc)_2$ (0.045 mmol, 10 mg), TPPTS (0.40 mmol, 227 mg), cyclodextrin (0.31 mmol) and water (2 g) were introduced under nitrogen atmosphere into a Schlenk tube. After stirring with a magnetic bar for 1 h, the yellow solution was transferred into a mixture of the substrate (1.12 mmol), diethylamine (2.22 mmol, 160 mg), toluene (2 g) and dodecane as internal standard (0.10 g, 0.588 mmol). The medium was stirred at 1000 rpm at room temperature and the reaction was monitored by quantitative gas chromatographic analysis of the organic layer.

4.3. Competitive and control experiments

The competitive experiments with a 1:1 mixture of *ortho*-biphenylmethylallylcarbonate and *para*-biphenylmethylallylcarbonate in the presence of Me-α-CD or Me-β-CD were conducted as described in Section 4.2 except that a mixture of *ortho*-biphenylmethylallylcarbonate (0.56 mmol, 0.15 g) and *para*-biphenylmethylallylcarbonate (0.56 mmol, 0.15 g) was used. In the control experiment, 0.4 g of acetonitrile was added to the reaction medium in the place of Me-α-CD or Me-β-CD.

The competitive experiments with a 1:1 mixture of *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allylurethane was conducted as described in the in Section 4.2 except that a mixture of *N*-dodecyl *O*-allylurethane (0.56 mmol, 0.15 g) and *N*,*N*-dihexyl-*O*-allylurethane (0.56 mmol, 0.15 g) was used. In the control experiment, 2 g of acetonitrile was added to the reaction medium in the place of Me-β-CD.

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Intramolecular [4+2] cycloaddition reactions of indolylalkylpyridazines: synthesis of annulated carbazoles

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Dedicated with best wishes to Professor Peter Stanetty on the occasion of his 60th birthday

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Abstract—Mono- and bicyclic 1,2-diazines tethered to indole dienophiles by alkylene chains were found to undergo thermally induced intramolecular Diels–Alder reactions with inverse electron demand, affording tetra- and pentacyclic condensed carbazoles.

1. Introduction

The electron-rich C(2)–C(3) bond of indole has been known to participate as a dienophile in inverse-electron-demand Diels–Alder (IDA) reactions with electron-deficient azines as dienes, such as 1,2,4,5-tetrazines[1–9] and 1,2,4-triazines,[6,9–13] affording pyridazino[4,5-*b*]indoles or carbolines, respectively.[14] In the case of the 1,2,4-triazine ring system, various intramolecular IDA reactions with an indole as the dienophile component have been studied by Snyder,[6,9,11–13] and these reactions lead to bridged carbolines, e.g. 5,6-dihydro-4*H*-pyrido[1,2,3-*lm*]-β-carbolines featuring the skeleton of the canthine alkaloids.[11] Also for indole-tethered 1,2,4,5-tetrazines, some applications of such intramolecular [4+2] cycloaddition processes have been reported.[6,9]

So far, very few examples of pyridazines participating in IDA reactions with indole dienophiles have been described. The highly reactive tetramethyl pyridazine-3,4,5,6-tetracarboxylate was found to react with indole to afford a phenanthridone instead of the expected carbazole,[10] whereas 4,5-dicyanopyridazine on heating with indole or *N*-methylindole gives dicyanocarbazoles along with minor amounts of 3-(4-cyanopyridazin-5-yl)indole derivatives,[15] the latter resulting from nucleophilic substitution of one cyano group by the electron-rich indole C(3). Recently, the intramolecular IDA reaction of cyclophanes containing an indole and a pyridazine unit has been shown to yield pentacyclic compounds featuring a reduced carbazole skeleton very elegantly.[16,17]

In the course of our investigations on the synthesis and antitumour activity of polycyclic hetarenes, especially condensed carbazoles of the ellipticine/olivacine type (Fig. 1),[18–22] we became interested in the intramolecular IDA reaction of indoles with pyridazines as a promising tool for the construction of novel fused carbazoles with an alkylene bridge between the carbazole nitrogen in ring B and the adjacent carbon in ring C. Such compounds would combine some of the structural features of the *b*-fused carbazole antitumour agents like ellipticine as well as of the canthine alkaloids which are also known to possess cytotoxic activity.[23] Here, we report on the concise synthesis of suitable indol-1-ylalkyl-substituted pyridazines and fused pyridazines and on their intramolecular [4+2] cycloaddition reactions, affording annulated carbazoles.

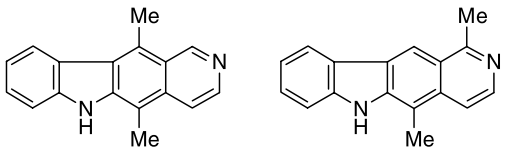

Figure 1.

2. Results and discussion

2.1. Synthesis of tethered cycloaddition educts

For the preparation of the requisite 3-(indol-1-yl)propyl-substituted pyridazines, two alternative pathways were developed. Starting from a *N*-propargylindole of type **1**, Sonogashira coupling with 3-iodopyridazine[24,25] (**2**) or

Keywords: Cycloaddition; Indoles; Pyridazines; Carbazoles.
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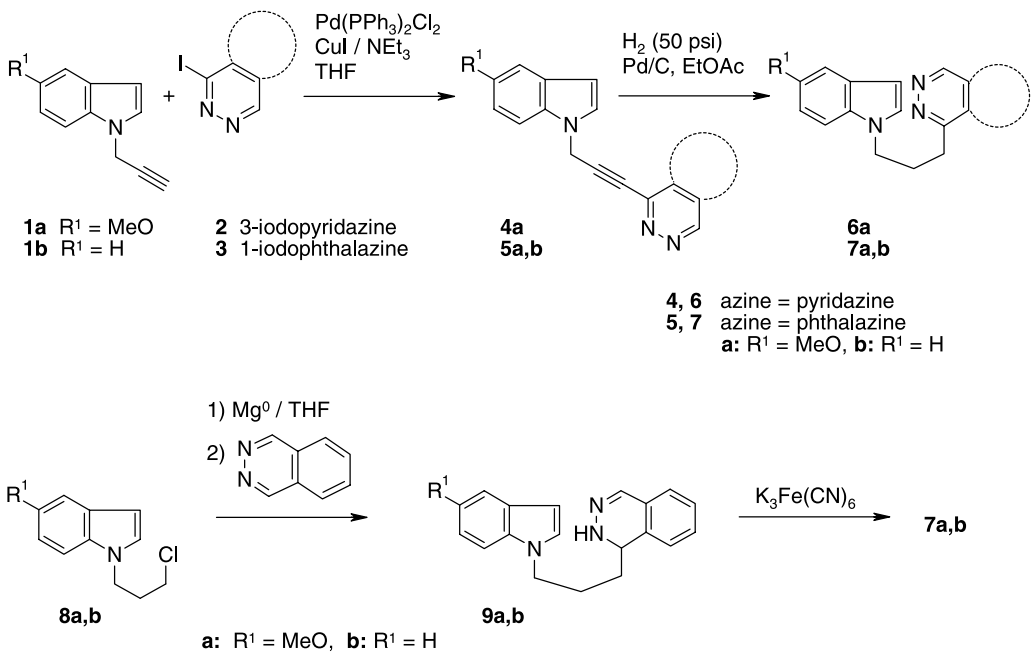
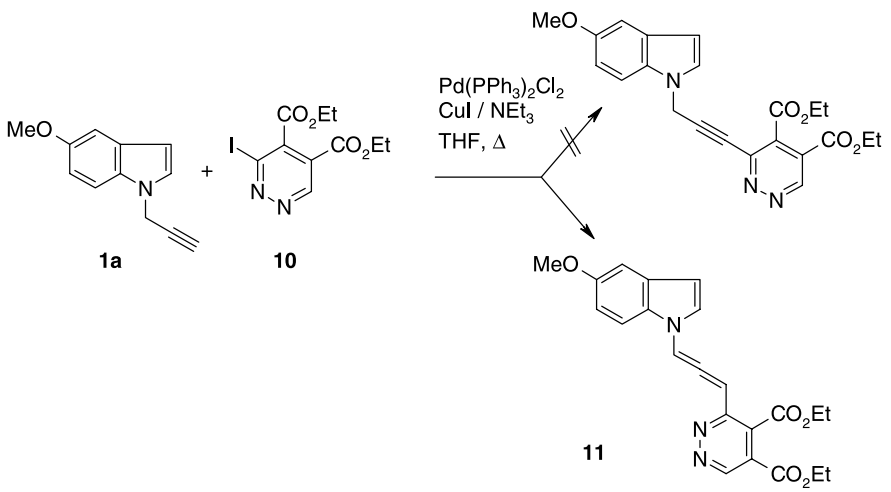


Scheme 1.

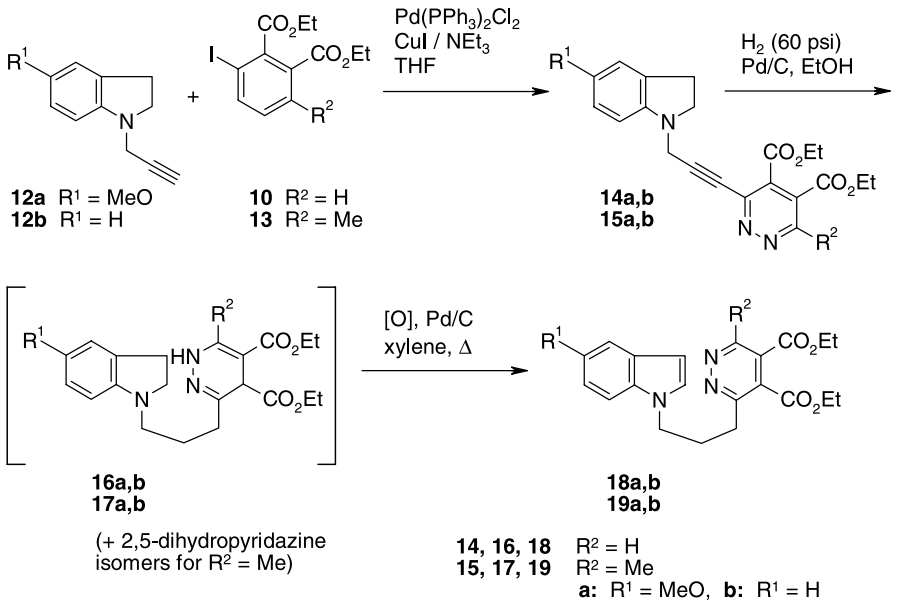
1-iodophthalazine[26] (**3**), respectively, gives the intermediate alkynes **4**, **5** which are hydrogenated to afford the desired compounds **6**, **7**. Alternatively, addition of a Grignard reagent generated from 1-(3-chloropropyl)indoles[27] (**8**) across the C(1)–N(2) bond of phthalazine, followed by dehydrogenation of the intermediate dihydrophthalazines **9** with $K_3Fe(CN)_6$ also leads to **7** in satisfactory yields.

In contrast to the smooth formation of compounds **4a** and **5a**,**b**, the palladium-catalyzed cross-coupling reaction of 5-methoxy-*N*-propargylindole (**1a**) with diethyl 3-iodopyridazine-4,5-dicarboxylate (**10**) (Scheme 2), which is easily accessible by free-radical ethoxycarbonylation of 3-iodopyridazine,[24] did not afford the desired indolylpropynylpyridazine derivative, but led to a red-colored compound which, according to its mass spectrum, is an isomer of the target propyne. Based on its spectral data (^{1}H NMR including DNOE, IR, MS, HRMS), the structure of the allene **11** was established for this compound. It proved to be very inert and all attempts failed to elaborate on the allenic structure by hydrogenation. Obviously, the alkyne/allene rearrangement is favored in this case by the increased CH acidity of the methylene group, as compared to the stable alkynes **4**, **5** which are lacking the electron-withdrawing ester functions at the diazine unit (Scheme 1).

In order to circumvent this problem, we sought to increase the electron density of the propyne synthon (thus decreasing the methylene CH acidity) by employing the corresponding indoline derivatives (**12a**, **12b**[28]) instead of the indoles (**1a**,**b**) as the cross-coupling partners with the iodopyridazine diester (**10**[24] or **13**,[24] respectively; Scheme 3). Indeed, here the Sonogashira reaction smoothly affords the desired alkyne-type coupling products **14**, **15** without any trace of an allenic rearrangement product. Catalytic hydrogenation of the triple bond in **14**, **15** was found to result in concomitant reduction of the highly electron-poor pyridazine ring, giving the corresponding dihydropyridazine



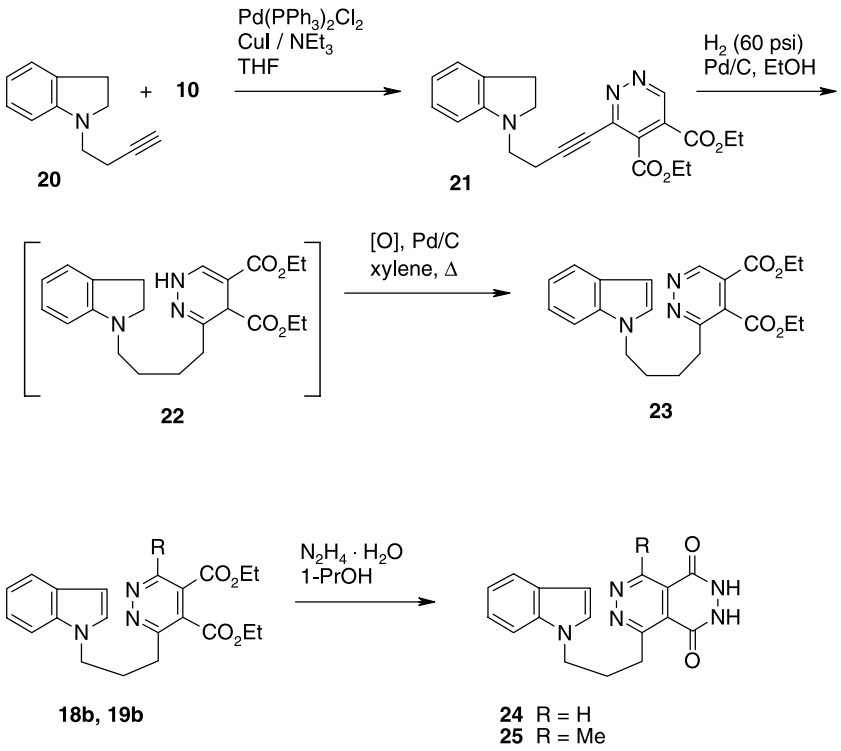
Scheme 2.



Scheme 3.

derivatives: in the case of the 3,4,5-trisubstituted pyridazines, the structure of the 1,4-dihydropyridazines **16** was established by their ^{1}H NMR spectra (coupling of the NH proton with pyridazine 6-H, J=4.2 Hz), whereas the tetrasubstituted pyridazines afforded unseparable mixtures of 1,4-dihydropyridazines (**17**) and their 2,5-dihydropyridazine isomers. Heating these compounds in xylene in the presence of air oxygen with palladium/carbon as the catalyst effects the required dehydrogenation/aromatization of the indole as well as of the pyridazine subunits to give compounds **18**, **19**. Thus, both the dienophile and the diene parts of the molecules can be generated conveniently from the precursors **16** or **17**, respectively, in a single step (Scheme 3).

In an analogous fashion, a cycloaddition candidate with a four-carbon tether chain (compound **23**, see Scheme 4) was prepared, starting from 1-(but-3-yn-1-yl)indole (**20**) and the iodopyridazine **10**. Catalytic hydrogenation, like in the transformation of **14** into **18** via **16**, results in the formation of a 1,4-dihydropyridazine intermediate (**22**) which is then dehydrogenated to give **23**. Moreover, refluxing of the



Scheme 4.

diesters **18b**, **19b** with hydrazine hydrate in 1-propanol smoothly affords the corresponding pyridazino[4,5-*d*]-pyridazinedione derivatives **24**, **25** (Scheme 4) as another type of candidates for the envisaged intramolecular cycloaddition step.

Application of the Grignard pathway (as described for the preparation of **7** from **8**, see above) to the pyrido[3,4-*d*]pyridazine ring system gave the desired compound only in low yield, together with other isomers. However, using the Sonogashira coupling route, starting from 1-chloro-pyrido[3,4-*d*]pyridazine[29] (**26**) and 1-prop-2-yn-1-ylindoline[28] (**12b**) provides a convenient access also to a cycloaddition educt with a pyrido[3,4-*d*]pyridazine system (compound **28**) as the diene unit (Scheme 5).

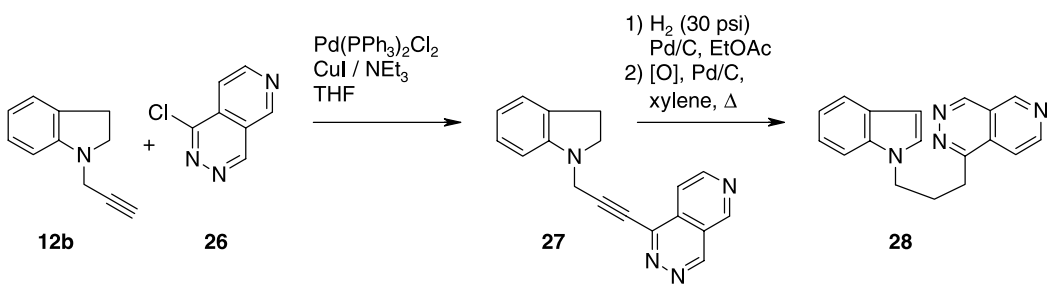
2.2. Intramolecular [4+2] cycloaddition reactions

Thermally induced intramolecular IDA reactions of the indolylalkylpyridazines could be anticipated to require drastic conditions, taking into account the lower degree of electron deficiency of these 1,2-diazine compounds as compared to structurally related 1,2,4-triazines.[11] Thus, 1,3,5-triisopropylbenzene (TIPB; bp=232 °C) was chosen as the solvent for all cycloaddition attempts to ensure sufficiently high reaction temperatures. All reactions were run under argon atmosphere in order to minimize formation of decomposition products.

Surprisingly, even the unactivated monocyclic pyridazine (compound **6a**; cf. Table 1, entry 1) was found to undergo an IDA reaction, albeit very slowly (2 weeks of refluxing) and giving a very low yield (8%) of the corresponding carbazole (**29**) besides substantial amounts of polymeric material. Obviously, compound **29** results from air oxidation/dehydrogenation of the initially formed dihydrocarbazole product (see Scheme 6) during work-up. With a phthalazine system as the diazadiene (compounds **7a**,**b**, entries 2 and 3), reactions are complete after 4 days at 232 °C, but the yields of the pentacyclic products **30a**,**b** are still rather low (mainly because of decomposition). Introduction of an additional nitrogen atom into the bicyclic diazadiene (i.e., replacement of the phthalazine by a pyrido[3,4-*d*]pyridazine structure, compound **28**) markedly increases the reaction rate (reaction time: 15 h; entry 4), however with no improvement of product yield (compound **31**). Substantially better yields are obtained with the very electron-poor pyridazinediesters **18a**,**b** and **19a**,**b**, respectively (products of type **32**, **33**; entries 5–8). Whereas the presence of an electron-donating methoxy group at the dienophilic indole subunit (**18a** and **19a**) does not significantly influence yields and reaction times as compared to the 5-unsubstituted indoles (**18b** and **19b**), the trisubstituted pyridazines **18** react considerably faster and give higher yields of carbazole products than the tetrasubstituted cyclization educts **19**, obviously as a consequence of the different degree of steric hindrance around the diazadiene structures. Expectedly, elongation of the tether chain by one methylene unit as in compound **23** leads to a marked decrease in reactivity, which is reflected by a longer reaction time and lower yield (product **34**; entry 9), as a result of the lower degree of 'entropic assistance'.

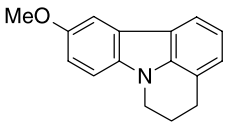
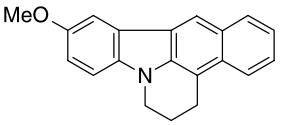
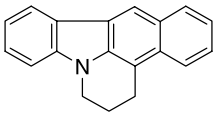
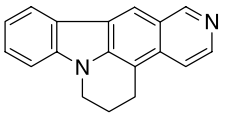
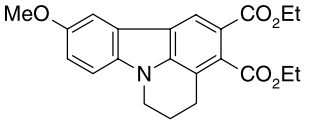
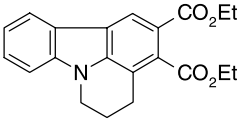
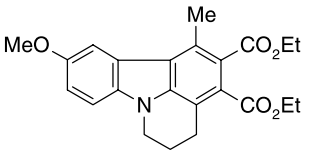
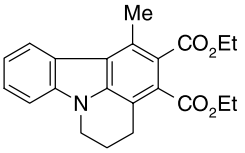
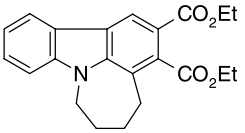
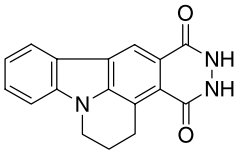
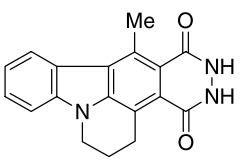
In all cases where pyridazinedicarboxylic acid diesters (compounds of type **18**, **19**, and **23**) were employed in the IDA reaction, we observed the formation of small amounts of side products in which one of the two ester groups is replaced by hydrogen, as exemplified by the isolation and characterization of ethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-3-carboxylate[30] from the cycloaddition of compound **18a**. As a possible explanation for this side reaction, one may assume partial hydrolysis of the diester by traces of water, followed by thermally induced decarboxylation.[31] Moreover, we investigated the possibility of performing the sequence starting from the indoline-tethered dihydropyridazines **16**, **17** via the aromatic pyridazines **18**, **19** into the carbazoles **32**, **33** as a one-pot reaction by refluxing the starting material in TIPB in the presence of air oxygen with palladium/carbon as a catalyst. Indeed, the expected domino reaction (double dehydrogenation–cycloaddition–cycloreversion–dehydrogenation) takes place under these conditions, as the formation of the corresponding carbazoles could be detected by GLC–MS and TLC. However, yields are very low and large amounts of decomposition products are formed, so that this one-pot variant is of no preparative use.

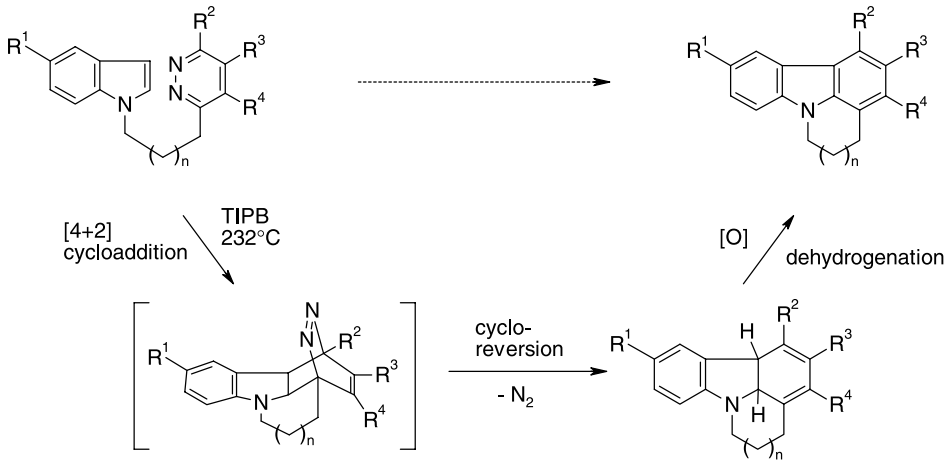
The highest yields of cycloaddition products (75 and 64% for compounds **35** and **36**, respectively) were obtained on employment of the pyridazine-fused pyridazinediones **24** and **25** as diazadienes (entries 10 and 11), and also the observed conversion rates were higher with these educts. Even with compound **25**, in which the diazadiene structure is sterically more crowded than in **24**, the transformation is complete within 24 h of refluxing, as compared to 50 h for the esters **19**. Inspection of the energy gaps between the involved frontier molecular orbitals (calculated with the PM3 method[32]) indicates a slight advantage for the bicyclic pyridazines **24** (ΔE: 6.89 eV) and **25** (ΔE: 6.93 eV) towards their monocyclic counterparts **18b** (ΔE: 7.11 eV) and **19b** (ΔE: 7.16 eV).[33] Moreover, a beneficial effect on reaction rates may be assumed to arise from the forced coplanarity of the CO groups with the pyridazine ring in **24** and **25**,



Scheme 5.

Table 1. Intramolecular [4+2] cycloaddition reactions of indolylalkylpyridazines

Entry	Educt	Product	Structure	Time	Yield (%)
1	**6a**	**29**		14 d	8
2	**7a**	**30a**		4 d	8
3	**7b**	**30b**		4 d	25
4	**28**	**31**		15 h	21
5	**18a**	**32a**		17 h	51
6	**18b**	**32b**		17 h	55
7	**19a**	**33a**		50 h	41
8	**19b**	**33b**		50 h	43
9	**23**	**34**		67 h	36
10	**24**	**35**		17 h	75
11	**25**	**36**		24 h	64



Scheme 6. General pathway of the cycloaddition reactions (for individual structures, see Table 1).

minimizing steric hindrance at this part of the diene structure, again in comparison to the esters **18**, **19**.

Cycloaddition products **29**–**34** were isolated by column chromatography whereas compounds **35** and **36** precipitated from the reaction mixtures. In all cases, the structures of the polycyclic products follow unambiguously from their elemental compositions and spectral data. In particular, the marked downfield shift of the carbazole proton which initially was 4-H in the indole precursor proved to be a convenient diagnostic tool in combination with significant NOE's which can be observed between this particular carbazole H at ring A and the neighbouring substituent R^2 (either H or CH_3) at ring C.

3. Conclusion

It can be stated that, despite its relatively high LUMO energy (as compared to 1,2,4-triazine and 1,2,4,5-tetrazine), the 1,2-diazine system is able to act as a diazadiene in intramolecular inverse-electron-demand Diels–Alder reactions with appropriately tethered indole dienophiles. Whereas unactivated pyridazines undergo these thermally induced [4+2] cycloaddition reactions only very sluggishly, the examples with more electron-deficient pyridazines, especially pyridazinediesters and pyridazino[4,5-*d*]pyridazinediones clearly demonstrate the synthetic usefulness of the intramolecular IDA strategy for the construction of polycyclic carbazoles. The target ring systems, which are of interest as core structures of new antitumour agents, are difficult to prepare via other routes[34] or (as in the case of compounds **30**, **35/36**) represent previously unknown ring systems.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. Silica gel plates (Merck, KGF_{254}) and silica gel 60 (Merck, 0.063–0.200 mm) were used for TLC and column chromatography. Medium-pressure liquid chromatography (MPLC) was carried out on Merck LiChroprep Si 60 (0.040–0.063 mm) with UV detection at 280 nm. Analytical grade solvents (Merck) were used, petroleum ether (PE) refers to the fraction of bp 50–70 °C. 1,3,5-Triisopropylbenzene (TIPB) was stored over Linde molecular sieves (0.4 nm). IR spectra were measured for KBr pellets on a Perkin–Elmer 1605 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity-Plus 300 spectrometer at 300 MHz. Mass spectra were obtained on a Hewlett–Packard 5890A/5970B GC-MSD or on a Shimadzu QP5050A DI 50 instrument. High-resolution mass spectra were measured on a Finnigan MAT 8230 at the Department of Organic Chemistry, University of Vienna. Microanalyses were performed at the Department of Physical Chemistry (Microanalytical Laboratory), University of Vienna. For semiempirical MO calculations, the MOPAC program as contained in the SYBYL 6.9 software package (Tripos Inc.) was used.

4.2. Preparation of cycloaddition educts

4.2.1. 5-Methoxy-1-prop-2-yn-1-yl-1*H*-indole (1a). To a solution of 5-methoxyindole (1.47 g, 10 mmol) and propargyl bromide (2.23 g of a 80% solution in toluene, 15 mmol) in toluene (30 mL) were added tetrabutylammonium bromide (0.161 g, 0.5 mmol) and 50% aqueous NaOH (6 mL). The two-phase mixture was vigorously stirred at rt for 1 h. Toluene (10 mL) was added and the layers were separated. The organic layer was washed with water, dried over Na_2SO_4, and the solvent was removed in vacuo to give an oil which slowly solidified. Recrystallization from ether/PE gave **1a** as yellow crystals (1.40 g, 74%): mp 65–69 °C. IR 3246, 2958, 2833, 2122, 1618, 1575, 1487, 1432, 1240, 1154, 1027, 840, 798, 725, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J_{6-7}=8.9 Hz, 1H, 7-H), 7.19 (d, J_{2-3}=3.2 Hz, 1H, 2-H), 7.13 (d, J_{4-6}=2.4 Hz, 1H, 4-H), 6.94 (dd, J_{6-7}=8.9 Hz, J_{4-6}=2.4 Hz, 1H, 6-H), 6.48 (d, J_{2-3}=3.2 Hz, 1H, 3-H), 4.85 (d, J=2.4 Hz, 2H, NCH_2-CCH), 3.88 (s, 3H, OCH_3), 2.41 (t, J=2.4 Hz, 1H, NCH_2CCH); MS (EI, 70 eV) *m*/*z* 185 (M^+, 100%), 170 (86), 146 (19), 142 (22), 115 (25), 103 (23), 89 (11), 76 (26), 63 (18), 51 (24). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.56; H, 6.16; N, 7.48.

4.2.2. 5-Methoxy-1-(3-pyridazin-3-ylprop-2-yn-1-yl)-1*H*-indole (4a). To a solution of **1a** (0.601 g, 3.25 mmol)

and 3-iodopyridazine[24,25] (**2**) (0.536 g, 2.6 mmol) in THF (6 mL) were added triethylamine (1.0 mL, 7.2 mmol), CuI (0.015 g, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (0.055 g, 0.08 mmol). The mixture was flushed with argon, then it was stirred under argon at rt for 5 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/PE, 4:1) to afford **4a** (0.320 g, 46%) as brownish crystals: mp 95–98 °C (from EtOAc). IR 3050, 2914, 2837, 2234, 1620, 1571, 1488, 1438, 1242, 1151, 1132, 1025, 803, 720, 596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.13 (dd, J_{5-6}=5.1 Hz, J_{4-6}=1.7 Hz, 1H, pyridazine 6-H), 7.50 (dd, J_{4-5}=8.4 Hz, J_{4-6}=1.7 Hz, 1H, pyridazine 4-H), 7.45–7.35 (m, 2H, pyridazine 5-H, indole 7-H), 7.23 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.12 (d, J_{4-6}=2.6 Hz, 1H, indole 4-H), 6.94 (dd, J_{6-7}=8.7 Hz, J_{4-6}=2.6 Hz, 1H, indole 6-H), 6.49 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 5.17 (s, 2H, NCH_2), 3.87 (s, 3H, OCH_3); MS (EI, 70 eV) *m/z* 263 (M^+, 100%), 248 (15), 220 (76), 192 (22), 166 (9), 140 (9), 110 (7), 89 (8), 76 (10), 63 (15), 51 (8); HRMS (EI, 70 eV) *m/z* 263.1070 (M^+ calcd for $C_{16}H_{13}N_3O$: 263.1059). Anal. Calcd for $C_{16}H_{13}N_3O$. $0.3H_2O$: C, 71.52; H, 5.10; N, 15.64. Found: C, 71.59; H, 5.08; N, 15.51.

4.2.3. 1-[3-(5-Methoxy-1*H*-indol-1-yl)prop-1-yn-1-yl]phthalazine (5a). This compound was prepared as described for **4a**, starting from 1-iodophthalazine[26] (**3**) (0.666 g, 2.6 mmol) instead of **2**. Chromatographic work-up (EtOAc) afforded **5a** (0.400 g, 49%) as brownish crystals: mp 143–145 °C (from EtOAc). IR 3091, 2954, 2831, 2242, 1621, 1485, 1396, 1239, 1150, 1028, 758, 593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.46 (s, 1H, phthalazine 4-H), 8.12–8.04 (m, 1H, phthalazine 8-H), 7.98–7.80 (m, 3H, phthalazine 5-H, 6-H, 7-H), 7.46 (d, J_{6-7}=8.8 Hz, 1H, indole 7-H), 7.30 (d, J_{2-3}=3.1 Hz, 1H, indole 2-H), 7.15 (d, J_{4-6}=2.4 Hz, 1H, indole 4-H), 6.96 (dd, J_{6-7}=8.8 Hz, J_{4-6}=2.4 Hz, 1H, indole 6-H), 6.52 (d, J_{2-3}=3.1 Hz, 1H, indole 3-H), 5.29 (s, 2H, NCH_2), 3.87 (s, 3H, OCH_3); MS (EI, 70 eV) *m/z* 313 (M^+, 4%), 170 (100), 156 (12), 115 (11), 102 (12), 76 (12), 69 (37), 63 (10), 51 (14). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.43; H, 5.05; N, 13.12.

4.2.4. 1-[3-(1*H*-Indol-1-yl)prop-1-yn-1-yl]phthalazine (5b). This compound was prepared as described for **4a**, starting from 1-iodophthalazine[26] (**3**) (0.666 g, 2.6 mmol) instead of **2** and 1-prop-2-yn-1-yl-1*H*-indole[35] (**1b**) (0.504 g, 3.25 mmol) instead of **1a**. Chromatographic work-up (EtOAc) afforded **5b** (0.400 g, 54%) as brownish crystals: mp 145–148 °C (from EtOAc). IR 3053, 2952, 2238, 1483, 1463, 1353, 1187, 749, 731, 594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.45 (s, 1H, phthalazine 4-H), 8.10–8.04 (m, 1H, phthalazine 8-H), 7.97–7.80 (m, 3H, phthalazine 5-H, 6-H, 7-H), 7.68 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.56 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.35–7.26 (m, 2H, indole 2-H, 6-H), 7.22–7.14 (m, 1H, indole 5-H), 6.60 (d, J_{2-3}=3.3 Hz, 1H, indole 3-H), 5.32 (s, 2H, NCH_2); MS (EI, 70 eV) *m/z* 283 (M^+, 88%), 282 (100), 266 (6), 255 (39), 228 (6), 154 (23), 139 (63), 128 (20), 116 (22), 113 (27), 101 (7), 89 (47), 75 (11), 63 (41), 50 (13), 43 (32). Anal. Calcd for $C_{19}H_{13}N_3$. $0.2H_2O$: C, 79.53; H, 4.71; N, 14.64. Found: C, 79.52; H, 4.77; N, 14.59.

4.2.5. 5-Methoxy-1-(3-pyridazin-3-ylpropyl)-1*H*-indole (6a). A solution of **4a** (0.200 g, 0.76 mmol) in EtOAc (100 mL), containing Pd/C catalyst (10%, 0.065 g), was hydrogenated in a Parr apparatus at a pressure of 50 psi until TLC (EtOAc) indicated the end of the reaction (65 h). The catalyst was filtered off and washed with EtOAc and EtOH. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by MPLC (EtOAc) to give **6a** (0.118 g, 58%) as a pale yellow oil. IR 2936, 2830, 1621, 1576, 1488, 1449, 1437, 1239, 1151, 1031, 801, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (dd, J_{5-6}=4.9 Hz, J_{4-6}=1.8 Hz, 1H, pyridazine 6-H), 7.35 (dd, J_{4-5}=8.4 Hz, J_{5-6}=4.9 Hz, 1H, pyridazine 5-H), 7.24–7.16 (m, 2H, pyridazine 4-H, indole 7-H), 7.12–7.06 (m, 2H, indole 2-H, 4-H), 6.87 (dd, J_{6-7}=9.0 Hz, J_{4-6}=2.4 Hz, 1H, indole 6-H), 6.40 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.24 (t, J=6.6 Hz, 2H, $NCH_2CH_2CH_2$), 3.86 (s, 3H, OCH_3), 2.98 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.48–2.35 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 267 (M^+, 25%), 173 (100), 158 (39), 130 (13), 121 (17), 117 (25), 103 (12), 94 (49), 77 (11); HRMS (EI, 70 eV) *m/z* 267.1383 (M^+ calcd for $C_{16}H_{17}N_3O$: 267.1372).

4.2.6. 1-(3-Chloropropyl)-5-methoxy-1*H*-indole (8a). A mixture of 5-methoxyindole (2.94 g, 20 mmol) and finely powdered KOH (85%; 1.72 g, 26 mmol) in DMSO (47 mL) was sonicated in an ultrasound cleaning bath for 10 min. It was cooled to 0 °C, and 1-bromo-3-chloropropane (9.42 g, 60 mmol) was added dropwise. The mixture was stirred at rt for 4 h, then it was poured into ice-water (100 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. The volatile components were removed in vacuo (first 10 mbar, then 10^{-2} mbar) and the residue was subjected to column chromatography (EtOAc/PE, 1:9) to afford **8a** (4.26 g, 96%) as a colorless oil. IR 2994, 2945, 2830, 1622, 1488, 1449, 1239, 1151, 1031, 802, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (d, J_{6-7}=9.0 Hz, 1H, 7-H), 7.15–7.09 (m, 2H, 2-H, 4-H), 6.90 (dd, J_{6-7}=9.0 Hz, J_{4-6}=2.4 Hz, 1H, 6-H), 6.44 (d, J_{2-3}=3.3 Hz, 1H, 3-H), 4.31 (t, J=6.3 Hz, 2H, $NCH_2CH_2CH_2$), 3.87 (s, 3H, OCH_3), 3.46 (t, J=6.1 Hz, 2H, $NCH_2CH_2CH_2$), 2.32–2.20 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 225 (M^+, 11%), 223 (M^+, 35), 208 (12), 160 (100), 145 (16), 130 (7), 117 (49), 103 (14), 89 (15), 76 (15), 63 (12), 51 (16); HRMS (EI, 70 eV) *m/z* 223.0768 (M^+ calcd for $C_{12}H_{14}ClNO$: 223.0764).

4.2.7. 1-[3-(5-Methoxy-1*H*-indol-1-yl)propyl]phthalazine (7a). *Method A*. A solution of **5a** (0.160 g, 0.51 mmol) in EtOAc (100 mL), containing Pd/C catalyst (10%, 0.040 g), was hydrogenated in a Parr apparatus at a pressure of 50 psi until TLC (EtOAc) indicated the end of the reaction (65 h). The catalyst was filtered off and washed with EtOAc and EtOH. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by MPLC (EtOAc) to give **7a** (0.065 g, 40%) as a pale yellow oil.

Method B. Magnesium turnings (0.60 g, 25 mmol) were suspended in dry THF (5 mL) and the reaction was initiated by addition of 1,2-dibromoethane (0.26 mL, 3 mmol). Then, a solution of **8a** (3.00 g, 13.5 mmol) in dry THF (10 mL) was added dropwise, and the mixture was refluxed for 0.5 h.

A solution of phthalazine (1.17 g, 9 mmol) in dry THF (10 mL) was added dropwise, and refluxing was continued for 5 h. After cooling, the mixture was poured into a solution of NH_4Cl (3.4 g) in ice-water (100 mL), and it was exhaustively extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to afford an oily residue (containing the dihydrophthalazine **9a**) which was immediately used for the following step without purification: the residue was dissolved in toluene (10 mL) and a solution of $K_3Fe(CN)_6$ (13.5 g, 41 mmol) in water (63 mL) as well as a solution of KOH (6.75 g, 120 mmol) in water (32 mL) were added. The mixture was vigorously stirred at rt for 2 h, then it was neutralized with AcOH and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was subjected to MPLC (EtOAc) to give **7a** (1.64 g, 57%) as a pale yellow oil. IR 2935, 2830, 1620, 1488, 1449, 1238, 1151, 1031, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.41 (s, 1H, phthalazine 4-H), 7.97–7.90 (m, 1H, phthalazine 5-H), 7.89–7.70 (m, 3H, phthalazine 6-H, 7-H, 8-H), 7.23 (d, J_{6-7}=8.8 Hz, 1H, indole 7-H), 7.14 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.11 (d, J_{4-6}=2.5 Hz, 1H, indole 4-H), 6.84 (dd, J_{6-7}=8.8 Hz, J_{4-6}=2.5 Hz, 1H, indole 6-H), 6.43 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.34 (t, J=6.7 Hz, 2H, $NCH_2CH_2CH_2$), 3.86 (s, 3H, OCH_3), 3.29 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.60–2.46 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 317 (M^+, 6%), 173 (34), 158 (15), 144 (100), 130 (6), 117 (12), 103 (5); HRMS (EI, 70 eV) *m/z* 317.1533 (M^+ calcd for $C_{20}H_{19}N_3O$: 317.1528).

4.2.8. 1-[3-(1*H*-Indol-1-yl)propyl]phthalazine (7b). *Method A*. Catalytic hydrogenation of **5b** (0.200 g, 0.71 mmol) as described for the preparation of **7a** from **5a** gave **7b** (0.110 g, 54%) as a pale yellow oil.

Method B. Grignard reaction and subsequent oxidation, as described for the preparation of **7a** from **8a**, starting from 1-(3-chloropropyl)-1*H*-indole[27] (**8b**) (2.60 g, 13.5 mmol) afforded **7b** (1.32 g, 51%) as a pale yellow oil. IR 3095, 2951, 2927, 1509, 1454, 1444, 1309, 1224, 756, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.44 (s, 1H, phthalazine 4-H), 7.99–7.92 (m, 1H, phthalazine 5-H), 7.91–7.73 (m, 3H, phthalazine 6-H, 7-H, 8-H), 7.67 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.37 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.26–7.17 (m, 2H, indole 2-H, 6-H), 7.17–7.08 (m, 1H, indole 5-H), 6.54 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.41 (t, J=6.6 Hz, 2H, $NCH_2CH_2CH_2$), 3.33 (t, J=7.3 Hz, 2H, $NCH_2CH_2CH_2$), 2.66–2.51 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 287 (M^+, 3%), 144 (100), 130 (6), 117 (7), 103 (6), 89 (8), 77 (10), 63 (5), 51 (4); HRMS (EI, 70 eV) *m/z* 287.1427 (M^+ calcd for $C_{19}H_{17}N_3$: 287.1422).

4.2.9. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propa-1,2-dien-1-yl]pyridazine-4,5-dicarboxylate (11). To a solution of diethyl 3-iodopyridazine-4,5-dicarboxylate[24] (**10**) (2.70 g, 7.71 mmol) and **1a** (1.78 g, 9.64 mmol) in THF (16 mL) were added triethylamine (3.0 mL, 21.6 mmol), CuI (0.044 g, 0.23 mmol) and $Pd(PPh_3)_2Cl_2$ (0.162 g, 0.23 mmol). The mixture was flushed with argon, then it was refluxed under argon for 3 h. Another portion of **1a** (0.71 g, 3.86 mmol) was added and refluxing was continued for 3 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was taken up in warm toluene (100 mL, 50 °C) and filtered again. Removal of the solvent in vacuo gave an oil which was subjected to column chromatography (toluene/EtOAc, 39:1) to afford the allene **11** (1.63 g, 52%) as a dark-red oil. IR 2981, 2934, 1739, 1715, 1548, 1473, 1263, 1187, 1032, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (s, 1H, pyridazine 6-H, shows positive NOE on irradiation of the quartet at 4.40 ppm), 7.45 (d, J_{2-3}=3.5 Hz, 1H, indole 2-H), 7.20–7.10 (m, 3H, NC*H*CCH, indole 4-H, 7-H), 6.94–6.86 (m, 2H, NCHCC*H*, indole 6-H, shows positive NOE on irradiation of the quartet at 4.59 ppm), 6.72 (d, J_{2-3}=3.5 Hz, 1H, indole 3-H), 4.59 (q, J=7.1 Hz, 2H, pyridazine 4-$CO_2CH_2CH_3$, 4.40 (q, J=7.1 Hz, 2H, pyridazine 5-$CO_2CH_2CH_3$, 3.88 (s, 3H, OCH_3), 1.49 (t, J=7.1 Hz, 3H, pyridazine 4-$CO_2CH_2CH_3$), 1.40 (t, J=7.1 Hz, 3H, pyridazine 5-$CO_2CH_2CH_3$, shows positive NOE on irradiation of the quartet at 4.40 ppm); MS (EI, 70 eV) *m/z* 407 (M^+, 100%), 379 (15), 351 (10), 307 (20), 292 (7), 264 (19), 246 (8), 218 (12), 192 (18), 164 (8), 132 (7), 103 (6), 88 (6); HRMS (EI, 70 eV) *m/z* 407.1488 (M^+ calcd for $C_{22}H_{21}N_3O_5$: 407.1481).

4.2.10. 5-Methoxy-1-prop-2-yn-1-ylindoline (12a). To a solution of 5-methoxyindoline[36] (1.50 g, 10.8 mmol) in toluene (20 mL) were added Na_2CO_3 (2.42 g, 22.8 mmol) and propargyl bromide (2.64 g of a 80% solution in toluene, 17.1 mmol), and the mixture was stirred under argon at rt for 20 h. The inorganic material was removed by filtration and the filtrate was evaporated in vacuo. Column chromatography (neutral Al_2O_3; EtOAc/PE, 1:19) of the residue gave **12a** (1.44 g, 68%) as a pale yellow oil which slowly solidified: mp 46–48 °C. IR 3262, 2930, 2844, 2105, 1593, 1490, 1433, 1288, 1238, 1137, 1026, 868, 801, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79–6.75 (m, 1H, 4-H), 6.71–6.64 (m, 1H, 6-H), 6.53 (d, J_{6-7}=8.4 Hz, 1H, 7-H), 3.89 (d, J=2.4 Hz, 2H, NCH_2CCH), 3.76 (s, 3H, OCH_3), 3.39 (t, J_{2-3}=8.0 Hz, 2H, 2-H), 2.95 (t, J_{2-3}=8.0 Hz, 2H, 3-H), 2.15 (t, J=2.4 Hz, 1H, NCH_2CCH); MS (EI, 70 eV) *m/z* 187 (M^+, 66%), 172 (69), 148 (100), 133 (71), 117 (36), 104 (39), 91 (23), 77 (28), 63 (17), 51 (18). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.94; H, 7.11; N, 7.47.

4.2.11. Diethyl 3-[3-(5-methoxy-2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyridazine-4,5-dicarboxylate (14a). To a solution of **12a** (0.608 g, 3.25 mmol) and diethyl 3-iodopyridazine-4,5-dicarboxylate[24] (**10**) (0.910 g, 2.6 mmol) in THF (6 mL) were added triethylamine (1.0 mL, 7.2 mmol), CuI (0.015 g, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (0.055 g, 0.08 mmol). The mixture was flushed with argon, then it was stirred under argon at rt for 7 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/PE, 2:3) to afford **14a** (0.734 g, 69%) as a brownish oil. IR 2982, 2937, 2832, 2235, 1735, 1491, 1337, 1291, 1237, 1026, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.53 (s, 1H, pyridazine 6-H), 6.79–6.40 (m, 1H, indoline 4-H), 6.67 (dd, J_{6-7}=8.4 Hz, J_{4-6}=2.7 Hz, 1H, indoline 6-H), 6.54 (d, J_{6-7}=8.4 Hz, 1H, indoline 7-H), 4.43 (q, J=7.2 Hz, 2H, CH_2CH_3), 4.21 (s, 2H, propargyl CH_2), 4.18 (q, J=7.2 Hz,

2H, CH_2CH$_3$), 3.75 (s, 3H, OCH$_3$), 3.46 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 2.98 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.27 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 409 (M$^+$, 8%), 262 (11), 233 (12), 148 (28), 133 (18), 77 (12), 58 (100); HRMS (EI, 70 eV) m/z 409.1656 (M$^+$ calcd for $C_{22}H_{23}N_3O_5$: 409.1638).

4.2.12. Diethyl 3-[3-(2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyridazine-4,5-dicarboxylate (14b). This compound was prepared as described for **14a**, starting from 1-prop-2-yn-1-ylindoline[28] (**12b**) (0.510 g, 3.25 mmol) instead of **12a**. Column chromatography (EtOAc/PE, 1:3) gave **14b** (0.757 g, 77%) as a brownish oil. IR 2981, 2849, 2236, 1734, 1487, 1286, 1024, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.53 (s, 1H, pyridazine 6-H), 7.16–7.07 (m, 2H, indoline 4-H, 6-H), 6.79–6.71 (m, 1H, indoline 5-H), 6.61 (d, J_{6-7}=7.8 Hz, 1H, indoline 7-H), 4.42 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.27 (s, 2H, propargyl CH$_2$), 4.14 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.51 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 3.02 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 1.39 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.25 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 379 (M$^+$, 11%), 304 (9), 262 (53), 233 (100), 205 (20), 188 (30), 160 (19), 118 (72), 91 (43), 65 (14); HRMS (EI, 70 eV) m/z 379.1517 (M$^+$ calcd for $C_{21}H_{21}N_3O_4$: 379.1532).

4.2.13. Diethyl 3-[3-(5-methoxy-2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]-6-methylpyridazine-4,5-dicarboxylate (15a). This compound was prepared as described for **14a**, starting from diethyl 3-iodo-6-methylpyridazine-4,5-dicarboxylate[24] (**13**) (0.946 g, 2.6 mmol) instead of **10**. Column chromatography (EtOAc/PE, 2:3) gave **15b** (0.970 g, 88%) as a brownish oil. IR 2982, 2936, 2832, 2236, 1739, 1491, 1242, 1037 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.78–6.73 (m, 1H, indoline 4-H), 6.66 (dd, J_{6-7}=8.5 Hz, J_{4-6}=2.5 Hz, 1H, indoline 6-H), 6.55 (d, J_{6-7}=8.5 Hz, 1H, indoline 7-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.20 (s, 2H, propargyl CH$_2$), 4.16 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.75 (s, 3H, OCH$_3$), 3.47 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 2.97 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 2.85 (s, 3H, CH$_3$), 1.37 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.27 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 423 (M$^+$, 7%), 276 (10), 247 (15), 203 (11), 148 (100), 133 (77), 117 (27), 101 (19), 77 (13); HRMS (EI, 70 eV) m/z 423.1810 (M$^+$ calcd for $C_{23}H_{25}N_3O_5$: 423.1794).

4.2.14. Diethyl 3-[3-(2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]-6-methylpyridazine-4,5-dicarboxylate (15b). This compound was prepared as described for **14a**, starting from 1-prop-2-yn-1-ylindoline[28] (**12b**) (0.510 g, 3.25 mmol) instead of **12a** and diethyl 3-iodo-6-methylpyridazine-4,5-dicarboxylate[24] (**13**) (0.946 g, 2.6 mmol) instead of **10**. Column chromatography (EtOAc/PE, 1:2) gave **15b** (0.980 g, 96%) as a brownish oil. IR 2981, 2936, 2846, 2235, 1739, 1488, 1386, 1244, 1036, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.16–7.06 (m, 2H, indoline 4-H, 6-H), 6.78–6.69 (m, 1H, indoline 5-H), 6.62 (d, J_{6-7}=7.8 Hz, 1H, indoline 7-H), 4.39 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.25 (s, 2H, propargyl CH$_2$), 4.12 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.51 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 3.00 (t, J_{2-3}=8.2 Hz, 2H, indoline 3-H), 2.85 (s, 3H, CH$_3$), 1.37 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.24 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 393 (M$^+$, 11%), 347 (7), 318 (14), 276 (70), 247 (100), 219 (21), 203 (50), 174 (17), 147 (14), 132 (27), 118 (50), 91 (52), 65 (16); HRMS (EI, 70 eV) m/z 393.1682 (M$^+$ calcd for $C_{22}H_{23}N_3O_4$: 393.1689).

4.2.15. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propyl]-pyridazine-4,5-dicarboxylate (18a). A solution of **14a** (0.630 g, 1.54 mmol) in EtOH (200 mL) containing Pd/C catalyst (10%, 0.130 g), was hydrogenated in a Parr apparatus at a pressure of 60 psi for 45 h. The catalyst was filtered off and washed with EtOH and EtOAc. The combined filtrate and washings were concentrated under reduced pressure to afford a brown oil (0.625 g) containing the dihydropyridazine **16a**.[37] This material was dissolved in xylene (61 mL), Pd/C catalyst (10%, 0.260 g) was added, and the mixture was refluxed with vigorous stirring for 62 h (reaction monitoring by GLC–MS). The catalyst was filtered off and washed with hot EtOH and hot EtOAc. The combined filtrate and washings were concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc/PE, 1:2) to afford **18a** (0.225 g, 35%) as a brownish oil. IR 2981, 2937, 1734, 1489, 1298, 1239, 1152, 1032, 802 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.54 (s, 1H, pyridazine 6-H), 7.24 (d, J_{6-7}=8.9 Hz, 1H, indole 7-H), 7.11 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.09 (d, J_{4-6}=2.6 Hz, 1H, indole 4-H), 6.88 (dd, J_{6-7}=8.9 Hz, J_{4-6}=2.6 Hz, 1H, indole 6-H), 6.42 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.43 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.32–4.19 (m, 4H, CH_2CH$_3$, NCH_2CH$_2$CH$_2$), 3.85 (s, 3H, OCH$_3$), 2.98 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.50–2.35 (m, 2H, NCH$_2$CH_2CH$_2$), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.24 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 411 (M$^+$, 8%), 238 (11), 209 (10), 173 (100), 165 (15), 158 (27), 130 (9), 117 (21), 65 (7); HRMS (EI, 70 eV) m/z 411.1811 (M$^+$ calcd for $C_{22}H_{25}N_3O_5$: 411.1794).

4.2.16. Diethyl 3-[3-(1*H*-indol-1-yl)propyl]pyridazine-4,5-dicarboxylate (18b). This compound was prepared as described for **18a**, starting from **14b** (0.710 g, 1.87 mmol). Column chromatography (EtOAc/PE, 1:3) gave **18b** (0.250 g, 35%) as a pale yellow oil. IR 2980, 2936, 1733, 1464, 1369, 1297, 1201, 1013, 742 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.54 (s, 1H, pyridazine 6-H), 7.63 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.35 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.26–7.17 (m, 1H, indole 6-H), 7.14 (d, J_{2-3}=3.2 Hz, 1H, indole 2-H), 7.13–7.06 (m, 1H, indole 5-H), 6.51 (d, J_{2-3}=3.2 Hz, 1H, indole 3-H), 4.42 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.30 (t, J=6.6 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.21 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 2.99 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.52–2.37 (m, 2H, NCH$_2$CH_2CH$_2$), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.22 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 381 (M$^+$, 16%), 335 (4), 290 (7), 264 (7), 238 (100), 209 (72), 164 (63), 143 (62), 130 (57), 94 (17), 77 (20), 63 (8); HRMS (EI, 70 eV) m/z 381.1679 (M$^+$ calcd for $C_{21}H_{23}N_3O_4$: 381.1689).

4.2.17. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propyl]-6-methylpyridazine-4,5-dicarboxylate (19a). This compound was prepared as described for **18a**, starting from **15a** (0.916 g, 2.17 mmol). Column chromatography (EtOAc/PE, 1:2) gave **19a** (0.300 g, 33%) as a brownish oil. IR 2982, 2937, 1737, 1489, 1238, 1031, 802, 718 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.23 (d, J_{6-7}=8.7 Hz, 1H, indole 7-H),

7.12 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.09 (d, J_{4-6}= 2.4 Hz, 1H, indole 4-H), 6.87 (dd, J_{6-7}=8.7 Hz, J_{4-6}= 2.4 Hz, 1H, indole 6-H), 6.41 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.24 (t, J=6.6 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.19 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.85 (s, 3H, OCH$_3$), 3.05 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.83 (s, 3H, CH$_3$), 2.45–2.30 (m, 2H, NCH$_2$CH_2CH$_2$), 1.38 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.22 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 425 (M^+, 42%), 334 (8), 278 (11), 252 (100), 223 (57), 179 (68), 173 (52), 158 (27), 117 (28), 108 (22), 77 (14), 51 (11); HRMS (EI, 70 eV) *m/z* 425.1966 (M^+ calcd for $C_{23}H_{27}N_3O_5$: 425.1951).

4.2.18. Diethyl 3-[3-(1*H*-indol-1-yl)propyl]-6-methylpyridazine-4,5-dicarboxylate (19b). This compound was prepared as described for **18a**, starting from **15b** (0.900 g, 2.29 mmol). Column chromatography (EtOAc/PE, 1:2) gave **19b** (0.384 g, 42%) as a brownish oil. IR 2981, 2936, 1734, 1464, 1394, 1257, 1217, 1030, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.35 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.24–7.16 (m, 1H, indole 6-H), 7.15 (d, J_{2-3}=3.3 Hz, 1H, indole 2-H), 7.13–7.06 (m, 1H, indole 5-H), 6.50 (d, J_{2-3}=3.3 Hz, 1H, indole 3-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.29 (t, J=6.7 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.16 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.06 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.83 (s, 3H, CH$_3$), 2.48–2.32 (m, 2H, NCH$_2$CH_2CH$_2$), 1.38 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.20 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 8%), 304 (6), 252 (100), 223 (70), 179 (81), 143 (26), 130 (45), 108 (29), 77 (20); HRMS (EI, 70 eV) *m/z* 395.1849 (M^+ calcd for $C_{22}H_{25}N_3O_4$: 395.1845).

4.2.19. 1-(But-3-yn-1-yl)indoline (20). A mixture of indoline (1.43 g, 12 mmol), Na_2CO_3 (2.54 g, 24 mmol) and but-3-yn-1-yl methanesulfonate[38] (2.66 g, 18 mmol) in toluene (20 mL) was refluxed under argon for 48 h. The inorganic material was filtered off and washed with EtOAc. The combined filtrate and washings were evaporated in vacuo and the residue was purified by column chromatography (EtOAc/PE, 1:29) to give **20** (1.83 g, 89%) as a colorless oil which slowly solidified: mp $<$ 30 °C. IR 3292, 2920, 2843, 2117, 1607, 1489, 1458, 1267, 1022, 747, 643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.06 (m, 2H, 4-H, 6-H), 6.74–6.65 (m, 1H, 5-H), 6.52 (d, J_{6-7}=8.1 Hz, 1H, 7-H), 3.46 (t, J_{2-3}=8.4 Hz, 2H, 2-H), 3.35 (t, ^3J=7.4 Hz, 2H, NCH_2CH$_2$-CCH), 3.02 (t, J_{2-3}=8.4 Hz, 2H, 3-H), 2.51 (dt, ^3J=7.4 Hz, ^4J=2.6 Hz, 2H, NCH$_2$CH_2CCH), 2.05 (t, ^4J=2.6 Hz, 1H, NCH$_2$CH$_2$CC*H*); MS (EI, 70 eV) *m/z* 171 (M^+, 14%), 133 (11), 132 (100), 130 (13), 117 (20), 115 (6), 103 (5), 77 (10), 51 (4); HRMS (EI, 70 eV) *m/z* 171.1047 (M^+ calcd for $C_{12}H_{13}N$: 171.1048).

4.2.20. Diethyl 3-[4-(2,3-dihydro-1*H*-indol-1-yl)but-1-yn-1-yl]pyridazine-4,5-dicarboxylate (21). This compound was prepared as described for **14a**, using the alkyne **20** (0.556 g, 3.25 mmol) instead of **12a**. Column chromatography (EtOAc/PE, 1:2) afforded **21** (0.873 g, 85%) as a brownish oil. IR 2981, 2844, 2236, 1735, 1607, 1490, 1276, 1209, 1029, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H, pyridazine 6-H), 7.15–7.06 (m, 2H, indoline 4-H, 6-H), 6.74–6.66 (m, 1H, indoline 5-H), 6.52 (d, J_{6-7}=8.1 Hz, 1H, indoline 7-H), 4.55–4.40 (m, 4H, CH_2CH$_3$), 3.55–3.40 (m, 4H, indoline 2-H, NCH_2CH$_2$CC), 3.03 (t, J_{2-3}=8.2 Hz, 2H, indoline 3-H), 2.83 (t, J=7.3 Hz, 2H, NCH$_2$CH_2CC), 1.50–1.35 (m, 6H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 393 (M^+, 2%), 347 (4), 318 (5), 132 (100), 130 (15), 117 (16), 77 (6); HRMS (EI, 70 eV) *m/z* 393.1674 (M^+ calcd for $C_{22}H_{23}N_3O_4$: 393.1689).

4.2.21. Diethyl 3-[4-(1*H*-indol-1-yl)butyl]pyridazine-4,5-dicarboxylate (23). This compound was prepared as described for **18a**, starting from **21** (0.815 g, 2.07 mmol); the hydrogenation time was 7 d. Column chromatography (EtOAc/PE, 1:2) gave **23** (0.410 g, 50%) as a brownish oil. IR 2936, 2870, 1733, 1464, 1297, 1193, 1019, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H, pyridazine 6-H), 7.65 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.36 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.29–7.18 (m, 1H, indole 6-H), 7.17–7.06 (m, 2H, indole 2-H, 5-H), 6.50 (d, J_{2-3}=3.1 Hz, 1H, indole 3-H), 4.46 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.20 (t, J=6.4 Hz, 2H, NCH_2CH$_2$CH$_2$CH$_2$), 3.10 (t, J=7.2 Hz, 2H, NCH$_2$CH$_2$CH$_2$CH_2), 2.05–1.83 (m, 4H, NCH$_2$CH_2CH_2CH$_2$), 1.43 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.34 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 13%), 322 (10), 278 (60), 233 (49), 205 (23), 156 (63), 130 (100), 117 (27), 103 (22), 77 (23); HRMS (EI, 70 eV) *m/z* 395.1857 (M^+ calcd for $C_{22}H_{25}N_3O_4$: 395.1845).

4.2.22. 5-[3-(1*H*-Indol-1-yl)propyl]-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,4-dione (24). A solution of **18b** (0.191 g, 0.5 mmol) and hydrazine hydrate (100%; 0.24 mL, 5 mmol) in 1-PrOH (5 mL) was refluxed under argon for 24 h. The volatile components were removed in vacuo and the yellow residue was taken up in water (5 mL) and acidified (pH 2) with 2 N HCl. The mixture was cooled and the precipitate was collected by filtration, washed with water and EtOH, and dried in vacuo to afford **24** (0.100 g, 61%) as pale yellow crystals: mp 259–262 °C. IR 3426, 3165, 3048, 2922, 2572, 1666, 1603, 1570, 1464, 1315, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, 2H, NH), 9.54 (s, 1H, pyridazinopyridazine 8-H), 7.61 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.45 (d, J_{6-7}=8.2 Hz, 1H, indole 7-H), 7.38 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.14–7.05 (m, 1H, indole 6-H), 7.02–6.93 (m, 1H, indole 5-H), 6.38 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.29 (t, J=7.0 Hz, 2H, NCH_2CH$_2$CH$_2$), 3.54 (t, J=7.5 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.34–2.20 (m, 2H, NCH$_2$CH_2CH$_2$); MS (EI, 70 eV) *m/z* 321 (M^+, 4%), 178 (15), 143 (100), 130 (33), 117 (16), 103 (12), 89 (13), 77 (14), 63 (10), 51 (8); HRMS (EI, 70 eV) *m/z* 321.1236 (M^+ calcd for $C_{17}H_{15}N_5O_2$: 321.1226). Anal. Calcd for $C_{17}H_{15}N_5O_2\cdot0.3H_2O$: C, 62.49; H, 4.81; N, 21.43. Found: C, 62.51; H, 4.73; N, 21.37.

4.2.23. 5-[3-(1*H*-Indol-1-yl)propyl]-8-methyl-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,4-dione (25). This compound was prepared as described for **24**, starting from the diester **19b** (0.200 g, 0.51 mmol). The product **25** (0.115 g, 67%) was obtained as pale yellow crystals: mp 259–263 °C. IR 3428, 3164, 3027, 2926, 2607, 1663, 1595, 1464, 1313, 741 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, 2H, NH), 7.53 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.46 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.38 (d, J_{2-3}=3.2 Hz, 1H, indole 2-H), 7.16–7.06 (m, 1H, indole 6-H), 7.04–6.96 (m, 1H, indole 5-H), 6.40 (d, J_{2-3}=3.2 Hz, 1H, indole 3-H), 4.29 (t, J=7.0 Hz, 2H, NCH_2CH$_2$CH$_2$), 3.50 (br t,

J=6.9 Hz, 2H, $NCH_2CH_2CH_2$), 2.99 (s, 3H, CH_3), 2.34–2.18 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) m/z 335 (M^+, 21%), 218 (8), 192 (100), 163 (16), 143 (66), 130 (40), 117 (12), 103 (15), 89 (12), 77 (22), 51 (12). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.21; H, 5.22; N, 20.64.

4.2.24. 1-[3-(2,3-Dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyrido[3,4-*d*]pyridazine (27). To a solution of **12b**[28] (1.02 g, 6.5 mmol) and 1-chloropyrido[3,4-*d*]pyridazine[29] (**26**) (0.860 g, 5.2 mmol) in THF (12 mL) were added triethylamine (2.0 mL, 14.4 mmol), CuI (0.030 g, 0.16 mmol) and $Pd(PPh_3)_2Cl_2$ (0.110 g, 0.16 mmol). The mixture was refluxed under argon for 3 h, then the solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/MeOH, 19:1) to afford **27** (1.04 g, 70%) as almost colorless crystals: mp 120–122 °C (from EtOAc/PE). IR 2920, 2835, 2224, 1606, 1484, 1359, 1242, 764, 668, 594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H, pyridopyridazine 4-H), 9.40 (s, 1H, pyridopyridazine 5-H), 8.86 (d, J_{7-8}=5.8 Hz, 1H, pyridopyridazine 7-H), 7.41 (d, J_{7-8}=5.8 Hz, 1H, pyridopyridazine 8-H), 7.24–7.15 (m, 2H, indoline 4-H, 6-H), 6.90–6.81 (m, 1H, indoline 5-H), 6.77 (d, J_{6-7}=7.7 Hz, 1H, indoline 7-H), 4.39 (s, 2H, propargyl CH_2), 3.57 (t, J_{2-3}=8.3 Hz, 2H, indoline 2-H), 3.05 (t, J_{2-3}=8.3 Hz, 2H, indoline 3-H); MS (EI, 70 eV) m/z 286 (M^+, 100%), 271 (12), 258 (7), 169 (43), 156 (12), 143 (25), 128 (17), 117 (27), 103 (14), 89 (16), 77 (35), 63 (15), 51 (19). Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.65; H, 5.00; N, 19.57.

4.2.25. 1-[3-(1*H*-Indol-1-yl)propyl]pyrido[3,4-*d*]pyridazine (28). A solution of **27** (0.500 g, 1.75 mmol) in EtOAc (200 mL) containing Pd/C catalyst (5%, 0.300 g), was hydrogenated in a Parr apparatus at a pressure of 30 psi for 5 h (TLC monitoring: EtOAc/MeOH, 19:1). The catalyst was filtered off and washed with EtOH and EtOAc. The combined filtrate and washings were concentrated under reduced pressure to afford a brown oil (0.500 g) containing the intermediate. This material was dissolved in xylene (90 mL), Pd/C catalyst (10%, 0.300 g) was added, and the mixture was refluxed with vigorous stirring for 120 h (reaction monitoring by GLC–MS). The catalyst was filtered off and washed with hot EtOH and hot EtOAc. The combined filtrate and washings were concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc/MeOH, 19:1) to afford **28** (0.107 g, 21%) as a brownish oil. IR 3048, 2918, 2849, 1610, 1463, 1315, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52 (s, 1H, pyridopyridazine 4-H), 9.40 (s, 1H, pyridopyridazine 5-H), 8.87 (d, J_{7-8}=5.7 Hz, 1H, pyridopyridazine 7-H), 7.63 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.41 (d, J_{7-8}=5.7 Hz, 1H, pyridopyridazine 8-H), 7.30 (d, J_{6-7}=7.9 Hz, 1H, indole 7-H), 7.22–7.05 (m, 3H, indole 2-H, 5-H, 6-H), 6.50 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.38 (t, J=6.4 Hz, 2H, $NCH_2CH_2CH_2$), 3.25 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.64–2.50 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) m/z 288 (M^+, 11%), 145 (100), 143 (80), 130 (15), 117 (9), 103 (11), 89 (14), 77 (19), 63 (12), 51 (7); HRMS (EI, 70 eV) m/z 288.1386 (M^+ calcd for $C_{18}H_{16}N_4$: 288.1375).

4.3. Intramolecular [4+2] cycloaddition reactions. General procedure

A solution (or suspension, in the case of **24**, **25**) of 0.5 mmol of the cycloaddition educt (0.11 mmol in the case of **6a**) in 1,3,5-triisopropylbenzene (7 mL) was heated to reflux under argon for the time given in Table 1. Except in those cases where the product precipitated from the mixture (compounds **35**, **36**), the solvent was removed by Kugelrohr distillation (10^{-1} mbar, 80 °C) and the residue was subjected to column chromatography.

4.3.1. 10-Methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole (29). Elution with EtOAc/PE (1:19) gave **29** (0.002 g, 8%) as a brownish oil. ^1H NMR ($CDCl_3$) δ 7.86 (d, J_{1-2}=7.8 Hz, 1H, 1-H), 7.60 (d, J_{9-11}=2.4 Hz, 1H, 11-H), 7.30 (d, J_{8-9}=9.0 Hz, 1H, 8-H), 7.19–7.06 (m, 3H, 2-H, 3-H, 9-H), 4.22 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.94 (s, 3H, OCH_3), 3.08 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.40–2.27 (m, 2H, 5-H); MS (EI, 70 eV) m/z 237 (M^+, 71%), 222 (100), 194 (24), 166 (13), 139 (7), 119 (8); HRMS (EI, 70 eV) m/z 237.1147 (M^+ calcd for $C_{16}H_{15}NO$: 237.1154).

4.3.2. 7-Methoxy-2,3-dihydro-1*H*-benzo[*b*]pyrido[1,2,3-*lm*]carbazole (30a). Elution with EtOAc/PE (1:9) gave an oil which was triturated with PE to afford **30a** (0.012 g, 8%) as yellow crystals: mp 131–132 °C (from toluene/PE). IR 2935, 2830, 1640, 1484, 1287, 1230, 1129, 1072, 835, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39 (s, 1H, 9-H), 8.09–7.99 (m, 2H, 10-H, 13-H), 7.74 (d, J_{6-8}=2.5 Hz, 1H, 8-H, shows positive NOE on irradiation at 8.39 ppm or at 3.97 ppm), 7.55–7.47 (m, 1H, 12-H), 7.42–7.33 (m, 1H, 11-H), 7.26 (d, J_{5-6}=8.7 Hz, 1H, 5-H), 7.17 (dd, J_{5-6}=8.7 Hz, J_{6-8}=2.5 Hz, 1H, 6-H), 4.20 (t, J_{2-3}=5.8 Hz, 2H, 3-H), 3.97 (s, 3H, OCH_3), 3.37 (t, J_{1-2}=6.1 Hz, 2H, 1-H), 2.52–2.40 (m, 2H, 2-H); MS (EI, 70 eV) m/z 287 (M^+, 100%), 272 (91), 244 (16), 216 (13), 144 (17), 121 (14), 109 (9). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.42; H, 6.13; N, 4.78.

4.3.3. 2,3-Dihydro-1*H*-benzo[*b*]pyrido[1,2,3-*lm*]carbazole (30b). Elution with EtOAc/PE (1:19) gave an oil which was triturated with PE to afford **30b** (0.032 g, 25%) as pale yellow crystals: mp 143 °C (from toluene/PE). IR 3052, 2936, 2854, 1637, 1607, 1475, 1364, 1240, 1131, 879, 736, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (s, 1H, 9-H, shows positive NOE on irradiation at 8.22 ppm), 8.22 (d, J_{7-8}=7.8 Hz, 1H, 8-H, shows positive NOE on irradiation at 8.43 ppm or at 7.28–7.20), 8.11–8.01 (m, 2H, 10-H, 13-H), 7.58–7.48 (m, 2H, 6-H, 12-H), 7.43–7.33 (m, 2H, 5-H, 11-H), 7.28–7.20 (m, 1H, 7-H), 4.24 (t, J_{2-3}=5.7 Hz, 2H, 3-H), 3.40 (t, J_{1-2}=6.0 Hz, 2H, 1-H), 2.53–2.41 (m, 2H, 2-H); MS (EI, 70 eV) m/z 257 (M^+, 100%), 254 (35), 241 (9), 229 (9), 202 (6), 129 (16), 127 (18), 121 (9), 100 (8). Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.40; H, 5.87; N, 5.33.

4.3.4. 2,3-Dihydro-1*H*-indolo[3,2,1-*gh*][3,7]phenanthroline (31). Elution with EtOAc gave **31** (0.028 g, 21%) as a yellow oil. IR 3049, 2929, 2859, 1604, 1460, 1361, 1309, 1243, 1132, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.36 (s, 1H, 10-H), 8.46 (d, J_{12-13}=6.5 Hz, 1H, 12-H), 8.43 (s, 1H, 9-H, shows positive NOE on irradiation at 8.20 ppm), 8.20 (d,

J_{7-8}=8.0 Hz, 1H, 8-H), 7.74 (d, J_{12-13}=6.5 Hz, 1H, 13-H), 7.62–7.52 (m, 1H, 6-H), 7.37 (d, J_{5-6}=8.3 Hz, 1H, 5-H), 7.33–7.25 (m, 1H, 7-H), 4.19 (t, J_{2-3}=6.0 Hz, 2H, 3-H), 3.28 (t, J_{1-2}=6.3 Hz, 2H, 1-H), 2.48–2.35 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 258 (M^+, 100%), 255 (25), 230 (16), 202 (7), 176 (5), 128 (24), 114 (16), 101 (8), 88 (9), 75 (7), 63 (4); HRMS (EI, 70 eV) *m/z* 258.1163 (M^+ calcd for $C_{18}H_{14}N_2$: 258.1157).

4.3.5. Diethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (32a). Elution with EtOAc/toluene (1:14) afforded **32a** (0.097 g, 51%) as a brownish oil.[30] IR 2979, 2937, 1725, 1707, 1485, 1300, 1265, 1209, 1120, 1048, 1031, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H, 1-H), 7.62 (d, J_{9-11}=2.4 Hz, 1H, 11-H), 7.34 (d, J_{8-9}=9.0 Hz, 1H, 8-H), 7.17 (dd, J_{8-9}=9.0 Hz, J_{9-11}=2.4 Hz, 1H, 9-H), 4.47 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.41 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.21 (t, J_{5-6}=5.8 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3), 3.08 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.40–2.27 (m, 2H, 5-H), 1.49–1.38 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 381 (M^+, 51%), 336 (10), 306 (100), 292 (17), 281 (7), 264 (7), 235 (21), 221 (22), 207 (20), 191 (14), 154 (15), 135 (6), 96 (5), 73 (10); HRMS (EI, 70 eV) *m/z* 381.1583 (M^+ calcd for $C_{22}H_{23}NO_5$: 381.1576).

4.3.6. Diethyl 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (32b). Elution with EtOAc/toluene (1:19) gave **32b** (0.097 g, 55%) as a brownish oil. IR 2978, 2935, 1727, 1709, 1476, 1329, 1264, 1224, 1144, 1078, 1048, 1023, 785, 747, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H, 1-H), 8.14 (d, J_{10-11}=8.1 Hz, 1H, 11-H), 7.58–7.48 (m, 1H, 9-H), 7.42 (d, J_{8-9}=8.1 Hz, 1H, 8-H), 7.36–7.24 (m, 1H, 10-H), 4.48 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.41 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.23 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.09 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.41–2.27 (m, 2H, 5-H), 1.51–1.47 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 351 (M^+, 29%), 305 (21), 276 (100), 204 (45), 177 (8), 151 (6); HRMS (EI, 70 eV) *m/z* 351.1467 (M^+ calcd for $C_{21}H_{21}NO_4$: 351.1471).

4.3.7. Diethyl 10-methoxy-1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (33a). Elution with EtOAc/toluene (1:14) afforded **33a** (0.081 g, 41%) as a brownish oil. IR 2955, 1721, 1489, 1299, 1175, 1038, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (d, J_{9-11}=2.5 Hz, 1H, 11-H), 7.36 (d, J_{8-9}=8.9 Hz, 1H, 8-H), 7.19 (dd, J_{8-9}=8.9 Hz, J_{9-11}=2.5 Hz, 1H, 9-H), 4.43 (q, *J*=7.2 Hz, 4H, CH_2CH_3), 4.20 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3), 3.21 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.91 (s, 3H, CH_3), 2.35–2.22 (m, 2H, 5-H), 1.46–1.35 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 44%), 350 (11), 320 (100), 306 (18), 277 (9), 249 (20), 234 (19), 207 (16), 178 (8), 161 (12), 102 (7); HRMS (EI, 70 eV) *m/z* 395.1721 (M^+ calcd for $C_{23}H_{25}NO_5$: 395.1733).

4.3.8. Diethyl 1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (33b). Elution with EtOAc/toluene (1:19) gave **33b** (0.079 g, 43%) as a brownish oil. IR 2979, 2938, 2902, 2869, 1722, 1484, 1375, 1316, 1260, 1203, 1162, 1055, 1029, 745, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (d, J_{10-11}=8.1 Hz, 1H, 11-H), 7.58–7.48 (m, 1H, 9-H), 7.44 (d, J_{8-9}=8.1 Hz, 1H, 8-H), 7.34–7.25 (m, 1H, 10-H), 4.47–4.33 (m, 4H, CH_2CH_3), 4.22 (t, J_{5-6}=5.8 Hz, 2H, 6-H), 3.22 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.92 (s, 3H, CH_3), 2.37–2.24 (m, 2H, 5-H), 1.41 (t, *J*=7.0 Hz, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 365 (M^+, 24%), 319 (12), 290 (100), 247 (12), 218 (30), 204 (13), 180 (7), 109 (7); HRMS (EI, 70 eV) *m/z* 365.1639 (M^+ calcd for $C_{22}H_{23}NO_4$: 365.1627).

4.3.9. Diethyl 4,5,6,7-tetrahydroazepino[3,2,1-*jk*]carbazole-2,3-dicarboxylate (34). Elution with EtOAc/toluene (1:19) gave **34** (0.066 g, 36%) as a brownish oil. IR 2977, 2932, 2865, 1728, 1711, 1592, 1474, 1367, 1336, 1261, 1144, 1040, 1022, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.66 (s, 1H, 1-H), 8.15 (d, J_{11-12}=7.8 Hz, 1H, 12-H, shows positive NOE on irradiation at 8.66 ppm), 7.59–7.50 (m, 1H, 10-H), 7.45 (d, J_{9-10}=8.4 Hz, 1H, 9-H), 7.37–7.27 (m, 1H, 11-H), 4.51 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.50–4.38 (m, 4H, 7-H, CH_2CH_3), 3.22 (t, J_{4-5}=5.8 Hz, 2H, 4-H), 2.34–2.13 (m, 4H, 5-H, 6-H), 1.52–1.40 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 365 (M^+, 15%), 319 (20), 290 (100), 246 (7), 218 (24), 204 (17), 191 (11); HRMS (EI, 70 eV) *m/z* 365.1634 (M^+ calcd for $C_{22}H_{23}NO_4$: 365.1627).

4.3.10. 2,3,11,12-Tetrahydro-1*H*-pyridazino[4,5-*b*]-pyrido[1,2,3-*lm*]carbazole-10,13-dione (35). The material which precipitated from the reaction mixture was collected by filtration and washed with EtOAc. It was then suspended in MeOH (10 mL) and refluxed for 0.5 h. After cooling, the solid was collected by filtration and dried to afford **35** (0.111 g, 75%) as almost colorless crystals: mp >330 °C (dec). IR 3404, 3154, 3018, 2937, 1645, 1625, 1474, 1328, 1246, 819, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.18 (s, 2H, NH), 8.73 (s, 1H, 9-H), 8.38 (d, J_{7-8}=7.8 Hz, 1H, 8-H), 7.65 (d, J_{5-6}=8.1 Hz, 1H, 5-H), 7.64–7.53 (m, 1H, 6-H), 7.36–7.25 (m, 1H, 7-H), 4.30 (t, J_{2-3}=5.5 Hz, 2H, 3-H), 3.76 (t, J_{1-2}=6.0 Hz, 2H, 1-H), 2.40–2.15 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 291 (M^+, 100%), 246 (9), 204 (24), 177 (8), 146 (9), 102 (20), 51 (9), 44 (13). Anal. Calcd for $C_{17}H_{13}N_3O_2 \cdot 0.25H_2O$: C, 69.03; H, 4.60; N, 14.20. Found: C, 68.95; H, 4.62; N, 14.08.

4.3.11. 9-Methyl-2,3,11,12-tetrahydro-1*H*-pyridazino-[4,5-*b*]pyrido[1,2,3-*lm*]carbazole-10,13-dione (36). The material which precipitated from the reaction mixture was collected by filtration and washed with EtOAc. It was then suspended in MeOH (10 mL) and refluxed for 0.5 h. After cooling, the solid was collected by filtration and dried to afford **36** (0.098 g, 64%) as beige crystals: mp >350 °C (dec). IR 3405, 3149, 3041, 2934, 1632, 1579, 1475, 1414, 1321, 1249, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.1 (br s, 2H, NH), 8.43 (d, J_{7-8}=7.8 Hz, 1H, 8-H), 7.70 (d, J_{5-6}=8.1 Hz, 1H, 5-H), 7.67–7.58 (m, 1H, 6-H), 7.40–7.30 (m, 1H, 7-H), 4.31 (t, J_{2-3}=5.7 Hz, 2H, 3-H), 3.73 (t, not resolved, 2H, 1-H), 3.44 (s, 3H, CH_3), 2.32–2.18 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 305 (M^+, 100%), 289 (17), 260 (20), 244 (9), 232 (12), 217 (21), 204 (14), 191 (11), 152 (14), 109 (12), 95 (11), 57 (10), 43 (20); HRMS (EI, 70 eV) *m/z* 305.1172 (M^+ calcd for $C_{18}H_{15}N_3O_2$: 305.1164).

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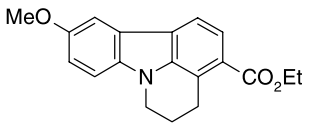
30. From the column fraction preceding the main product (**32a**), a side product was isolated. Purification of this material by MPLC (EtOAc/toluene, 1:14) gave ethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-3-carboxylate (0.016 g, 10%) as a yellow oil. IR 2927, 2855, 1704, 1490, 1243, 1213, 1138, 1076, 1040, 815, 749 cm^{-1}; ^1H NMR ($CDCl_3$) (7.88 (d, J_{1-2}=8.2 Hz, 1H, 1-H, shows positive NOE on irradiation at 6.60 ppm), 7.81 (d, J_{1-2}=8.2 Hz, 1H, 2-H), 6.60 (d, J_{9-11}= 2.5 Hz, 1H, 11-H), 7.33 (d, J_{8-9}=8.8 Hz, 1H, H-8), 7.18 (dd, J_{8-9}=8.8 Hz, J_{9-11}=2.5 Hz, 1H, 9-H), 4.42 (q, J=7.1 Hz, 2H, CH_2CH_3), 4.22 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3, shows positive NOE on irradiation at 6.60 ppm), 3.51 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.40-2.27 (m, 2H, 5-H), 1.45 (t, J=7.1 Hz, 3H, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 309 (M^*, 100%), 294 (38), 280 (22), 266 (33), 236 (15), 221 (19), 207 (12), 191 (21), 165 (9), 125 (11), 111 (10), 96 (12), 84 (10), 73 (6); HRMS (EI, 70 eV) *m*/*z* 309.1378 (M^* calcd for $C_{19}H_{19}NO_3$: 309.1365).



31. This assumption is supported by the observation that only one of the two possible monoesters is formed from pyridazines **18a**,**b** and **23**, in which one ester group is sterically more shielded than the other one, whereas from the tetrasubstituted pyridazines **19a**,**b** mixtures of both mono-decarboxylation products are formed. This is in agreement with the regioselective hydrolysis of 1-methylcarbazole-2,3-dicarboxylic acid dimethyl ester into 2-(methoxycarbonyl)-1-methyl-9*H*-carbazole-3-carboxylic acid, which was described recently[20].
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37. A sample of the intermediate **16a** was isolated by column chromatography (EtOAc/PE, 1:2) as a brownish oil. IR 3376, 2935, 2830, 1734, 1685, 1623, 1493, 1238, 1194, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (br d, J_{1-6}=4.2 Hz, 1H, NH), 7.52 (d, J_{1-6}=4.2 Hz, 1H, pyridazine 6-H), 6.76–6.71 (m, 1H, indoline 4-H), 6.62 (dd, J_{6-7}=8.5 Hz, J_{4-6}=2.5 Hz, 1H, indoline 6-H, shows positive NOE on irradiation at 6.40 ppm), 6.40 (d, J_{6-7}=8.5 Hz, 1H, indoline 7-H), 4.34 (s, 1H, pyridazine 4-H), 4.25–4.10 (m, 4H, CH_2CH_3), 3.74 (s, 3H, OCH_3), 3.28 (t, J_{2-3}=8.1 Hz, 2H, indoline 2-H), 3.03 (t, J=7.2 Hz, 2H, $NCH_2CH_2CH_2$), 2.92 (t, J_{2-3}=8.1 Hz, 2H, indoline 3-H), 2.70–2.40 (m, 2H, $NCH_2CH_2CH_2$), 2.06–1.80 (m, 2H, $NCH_2CH_2CH_2$), 1.32–1.20 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 415 (M^*, 13%), 193 (25), 175 (47), 162 (100), 148 (10), 130 (9), 57 (7); HRMS (EI, 70 eV) *m*/*z* 415.2118 (M^* calcd for $C_{22}H_{29}N_3O_5$: 415.2107).
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Enzyme catalyzed hydroxymethylation of aromatic aldehydes with formaldehyde. Synthesis of hydroxyacetophenones and (*S*)-benzoins

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Abstract—Benzaldehyde lyase from the *Pseudomonas Fluorescens* catalyzed reaction of aromatic aldehydes with formaldehyde providing 2-hydroxy-1-arylethan-1-one in high yields via an acyloin linkage. Kinetic resolution of *rac*-benzoins with formaldehyde providing (*S*)-benzoins and 2-hydroxy-1-arylethan-1-one via C–C bond cleavage and a bond formation reaction.

1. Introduction

Selective hydroxymethylation of aromatic aldehydes with formaldehyde leading to terminal hydroxymethyl functionality represents a potentially useful strategy for the one carbon extension of carbonyls in order to obtain hydroxy ketones. This method could have many advantages compared to other methods that lead to hydroxy ketones. Formaldehyde is a versatile reagent and is one of the most highly reactive C1 electrophiles in organic synthesis.[1] Dry gaseous formaldehyde that is required for many reactions has some disadvantages because it must be generated before use from solid polymer paraformaldehyde by way of thermal depolymerization, in which it easily self-polymerizes.[2] On the other hand, commercial formaldehyde solution, which is an aqueous solution containing 37% formaldehyde and 8–10% methanol is cheap, easy to handle, and stable even at room temperature. However, the use of this reagent is strongly restricted due to the existence of a large amount of water. For example, the titanium tetrachloride promoted hydroxymethylation reaction of silyl enol ethers was carried out using trioxane as a HCHO source under strict anhydrous conditions.[3] Aqueous formaldehyde solution could not be used because $TiCl_4$ and the silyl enol ether reacted with water rather than HCHO. Kobayashi et al. showed that Lanthanide triflates are able to function as Lewis acids in aqueous media and catalyze the aldol reaction of silyl enol ether with formaldehyde.[4]

Thiamine pyrophosphate (vitamin B_1) is a coenzyme which participates in a number of important biochemical reactions involving the formation and breaking of carbon–carbon bonds immediately adjacent to a carbonyl group (acyloins, α-diketones, α-keto acids).[5] Among the reactions catalyzed by thiazolium salts, the acyloin condensation, the intermolecular condensation of two molecules of aldehyde to produce an α-hydroxy ketone, is of much interest as a convenient method for carbon–carbon bond formation.[6] Inoue et al.[7] found that the condensation of formaldehyde (paraformaldehyde) with benzaldehyde and furfural catalyzed by 3-ethylbenzothiazolium bromide in the presence of triethylamine in dry ethanol or dioxane at 60 °C gave 2-hydroxy-1-phenyl ethanone and 2-hydroxy-1-(2-furyl)-ethanone in 17 and 6% yields, respectively.

2-Hydroxy-1-arylethan-1-ones are valuable synthetic intermediates for the preparation of a range of compounds of biological interest and pharmaceutical products such as the substituted 2-amino-1-arylethanols.[8] Benzaldehyde lyase (BAL, EC 4.1.2.38) from *Ps. fluorescens Biovar I* was first reported by Gonzáles and Vicuña.[9a,b] They showed that this strain can grow on benzoin as a sole carbon and energy source due to the ability of BAL to catalyze the cleavage of the acyloin linkage of benzoin yielding benzaldehyde. Furthermore, we have recently reported on benzaldehyde lyase (BAL), a novel thiamin diphosphate (ThDP) dependent enzyme from *Ps. Fluorescens Biovar I*, which is able to perform the enantioselective formation of (*R*)- and (*S*)-benzoins and (*R*)-2-hydroxypropiophenone ((*R*)-2-HPP) derivatives via C–C bond cleavage and C–C bond formation. (*R*)-2-HPP derivatives are formed in preparative scale by benzaldehyde lyase (BAL)-catalyzed C–C bond formation from aromatic aldehydes and acetaldehyde,

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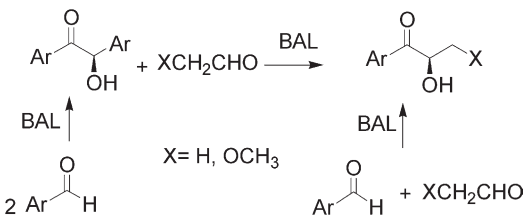


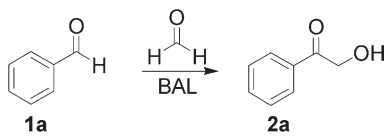
Scheme 1.

methoxy- and dimethoxyacetaldehyde in buffer/DMSO solution with remarkable ease in high chemical yields and high optical purity[9c–g] (Scheme 1).

We assumed that under the influence of a BAL catalyst, enzymatic coupling of aromatic aldehydes with formaldehyde would be a simple method for the synthesis of hydroxyacetophenones (HAP). We report herein, a new and efficient procedure for the direct hydroxymethylation of aromatic aldehydes with formaldehyde in one step, and kinetic resolution of *rac*-benzoins with formaldehyde to obtain (*S*)-benzoins and 2-hydroxy-1-arylethan-1-one via C–C bond cleavage and bond formation reaction in an aqueous medium. Carboligation with formaldehyde may be a new and efficient way to obtain important hydroxyacetophenone derivatives.

2. Results and discussion

As shown in Scheme 2, for the carboligation of aromatic aldehydes with formaldehyde, benzaldehyde (**1a**) was dissolved in a potassium phosphate buffer (pH 7.0, containing $MgSO_4$ and ThDP) containing 20% DMSO and formaldehyde solution. After the addition of BAL, the reaction was shaken and kept at 37 °C. The reaction was monitored by TLC and GC-MS using a commercially available authentic sample. After 3 days, no more change was observed and the purification of the crude product by column chromatography provided 2-hydroxy-1-phenylethan-1-one (**2a**) in a 94% yield (Table 1). We evaluated the influences of varying BAL and substrate concentrations, reaction time, and benzaldehyde substituents on the yield and range of products formed during reactions. Maximum yields were obtained with excess amounts of formaldehyde added at fixed time intervals. We observed that the benzaldehyde/formaldehyde ratio is very important for the product distribution, since excess formaldehyde resulted in high yield formation of **2a**, whereas a 1:1 ratio of benzaldehyde/formaldehyde gave mixture of (R)-benzoin and **2a**. Temperature had little influence on the reaction outcomes. A slight increase in yield was observed by passing nitrogen gas through the reaction solution at the onset of the reaction.



Scheme 2.

Table 1. Synthesis of 2-hydroxy-1-arylethan-1-one derivatives (Scheme 2)

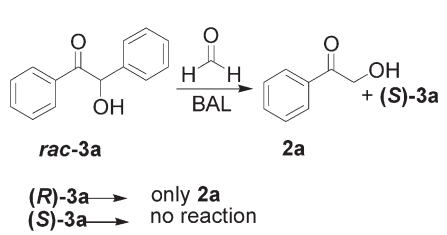
1	ArCHO	2	
		Yield (%)[a]	Mp (Lit. mp) °C
a	Ph	94	86–89[b]
b	4-MeC_6H_4	94	83–84 (83)[10]
c	4-MeOC_6H_4	91	105–106 (106–107)[10]
d	3-MeOC_6H_4	92	48–50 (50)[10]
e	2-MeOC_6H_4	68	81–83 (83)[10]
f	3-MeO-4-OHC_6H_3	51	177–179 (177–178)[11]
g	3-BrC_6H_4	83	104–106 (105–107)[c]
h	2-ClC_6H_4	77	Semisolid[8d]
i	4-ClC_6H_4	88	120–123 (122–123)[12]
j	4-OHC_6H_4	89	165–167 (165–167)[13]
k	2-furanyl	77	82–83 (84–86)[7]
l	4-pyridinyl	<5[d]	
m	3-pyridinyl	<5[d]	
n	2-FC_6H_4	<5[d]	
o	2,4-$F_2C_6H_3$	15	Semisolid (90–93)[14]
p	Indole-3-carbaldehyde	No reaction	

[a] Isolated yields (the yields are based on ArCHO). All compounds are known and all analytical data are in agreement with the previously reported data.
[b] Commercially available compound.
[c] Imperial chemical industries, US 4489074.
[d] Detected by GC-MS.

This carboligation reaction was carried out using the above described conditions with a wide range of aromatic aldehydes and heteroaromatic aldehydes, and the corresponding acyloin derivatives **2a**–**k** were obtained in high yields as summarized in Table 1. No acyloin formation was observed in the absence of the enzyme.

As shown in Table 1, BAL has the ability to bind a broad range of different aromatic and heteroaromatic aldehydes to C2-ThDP prior to ligation. The yield of the reaction depends on the structure of the aldehyde. Fluorine substitution on the 2- and 2,4-positions on the ring decreased the yield of the reaction. Pyridine carboxaldehyde also furnished a low yield. The steric and electronic demands of the substituent play a role in the yield of the reaction.

In our previous reports,[9c–g] we showed that BAL is also able to accept benzoin as a substrate to catalyze C–C bond cleavage followed by carboligation in the presence of acetaldehyde. Accordingly, (*R*)-benzoin was reacted with BAL in the presence of formaldehyde; the reaction was monitored by TLC and LC-MS (with the appropriate chiral column). Addition of formaldehyde provided 2-hydroxy-1-phenylethan-1-one (**2a**) in high yield (Scheme 3). As anticipated, the same reaction starting from (*S*)-benzoin failed. Repeating this reaction with *rac*-benzoin provided 2-hydroxy-1-phenylethan-1-one (**2a**) and (*S*)-benzoin ((*S*)-**3a**) (in an enantiomerically pure form) after the separation of the products by column chromatography. In order to obtain the full conversion of (*R*)-benzoin into HAP



Scheme 3.

Table 2. Synthesized (*S*)-benzoins and 2-HAP derivatives

rac. **3**		(*S*)-**3a–f**[9e]		**2** (Yield (%))
	Ar	Yield (%)[a]	ee (%)[b]	
a	Ph	41	>98[c]	**a** 40
b	4-ClC_6H_4	38	>98[d]	**i** 34
c	4-$MeOC_6H_4$	42	>98[e]	**c** 40
d	2-$MeOC_6H_4$	38	>98[f]	**e** 43
e	4-MeC_6H_4	39	96[g]	**b** 43
f	2-furanyl	37	93[h]	**k** 36

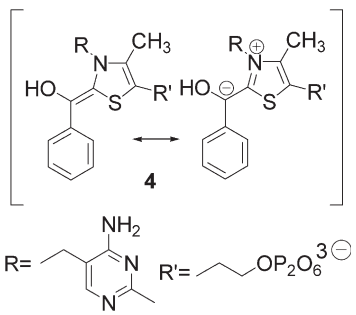
[a] Formaldehyde is used in excess amounts and yields are based on benzoin. All compounds are known and all analytical data are in agreement with the previously reported data.[9e]
[b] The ee value is measured immediately after work-up.
[c] $[\alpha]_D^{22}$=+112.1 (*c* 1.5, CH_3COCH_3), Chiralpak AD, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.8 mL/min. R_t(*R*)=27.8 min; R_t(*S*)=35.1 min.
[d] $[\alpha]_D^{20}$=+26.2 (*c* 0.1, CH_3OH), Chiralpak AD, UV detection at 254 nm, eluent: *n*-hexane/2-propanol=90:10, flow 0.8 mL/min. R_t(*R*)=26.3 min.; R_t(*S*)=31.1 min.
[e] $[\alpha]_D^{20}$=+88.6 (*c* 1.0, CH_3OH), Chiralpak AD, UV detection at 254 nm, 75:25 hexane/2-propanol, flow 0.95 mL/min. R_t(*R*)=25.7 min.; R_t(*S*)=31.2 min.
[f] $[\alpha]_D^{20}$=+123.0 (*c* 1.0, $CHCl_3$), Chiralpak AD, UV detection at 254 nm, 98:2 hexane/2-propanol, flow 0.90 mL/min. R_t(*R*)=31.8 min.; R_t(*S*)=42.7 min.
[g] $[\alpha]_D^{20}$=+148.2 (*c* 0.8, CH_3OH), Chiralpak AD, UV detection at 254 nm, eluent: *n*-hexane/2-propanol=90:10, flow 0.8 mL/min. R_t(*R*)=30.4 min; R_t(*S*)=35.8 min.
[h] $[\alpha]_D^{20}$=+26.4 (*c* 0.2, CH_3OH), Chiralpak AD, UV detection at 254 nm, 90:10 hexane/2-propanol, flow 0.8 mL/min. R_t(*S*)=22.4 min; R_t(*R*)=28.3 min.

derivatives, formaldehyde has to be used in excess and should be added to the reaction mixture at fixed time intervals. Some representative examples of (*S*)-benzoins **3a–f** and 2-HAP derivatives are shown in Table 2.

Since structural information about the enzyme is still missing, a structure-based discussion of the observed stereocontrol is not yet possible. From mechanistic considerations it is more likely that the enamine-carbanion intermediate **4** is the active species in the BAL-catalyzed carboligation (Scheme 4). No reaction was observed with BAL by using 2-hydroxy-1-phenylethan-1-one with and without formaldehyde.

3. Conclusion

The method described herein presents the enzyme-catalyzed hydroxymethylation of aromatic aldehydes with formaldehyde via acyloin linkage in high yield. In addition, starting from *rac*-benzoins and formaldehyde 2-hydroxy-1-arylethan-1-one and the corresponding (*S*)-benzoins (enzymatic kinetic resolution via C–C bond cleavage) are obtained in high enantiomeric excess via C–C bond cleavage and carboligation reactions. During the cleavage of the benzoin linkage, only (*R*)-benzoin is accepted as a substrate. The reaction functions in an organic-aqueous medium, and overcomes the solubility problem with organic substrates.



Scheme 4.

The products are obtained in high yields starting from simple, easily available aromatic aldehydes and benzoins.

4. Experimental

Enzymatic syntheses were performed in standard buffer consisting of potassium phosphate (50 mM, pH 7.0) containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM). NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ=254 nm). Enantiomeric excesses were determined by HPLC and LC-MS analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column, as described in the footnotes of the Tables. Optical rotations were measured with an Autopol IV automatic polarimeter.

Hexahistidine tagged BAL was obtained as described previously.[9c,d] One unit of activity is defined as the amount of enzyme which catalyses the cleavage of 1 μmol benzoin in 1 min at 30 °C.

4.1. General procedure for the synthesis of 2-hydroxy-1-arylethan-1-ones from aromatic aldehydes: representative example: 2-hydroxy-1-(4-hydroxyphenyl)-ethan-1-one 2j

4-Hydroxybenzaldehyde (122 mg, 1 mmol) was dissolved in a mixture of DMSO (10 mL) and potassium phosphate buffer (40 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)). To this solution was added formaldehyde solution (8 mmol, 0.64 mL 37% solution). After the addition of BAL (40 U), the reaction was allowed to stand at 37 °C. Every 24 h, 30–40 U of BAL and 8 mmol of formaldehyde solution were added. After 4 days (checked by TLC), the reaction mixture was filtered and extracted with dichloromethane (3×50 mL). After

drying the collected organic phase over $MgSO_4$, removal of the solvent under reduced pressure gave the crude product, which was then purified by flash column chromatography (EtOAc:hexane 1:3) to give 135 mg (89%) of the desired compound 2-hydroxy-1-(4-hydroxyphenyl)ethan-1-one. Mp 165–167 (Lit.[13] 165–167); ^{1}H NMR ($CDCl_3$): δ 4.03 (br s,OH, 1H), 4.67 (s, 2H), 6.79 (d, J=8.4 Hz, 2H), 7.72 (d, J=8.4 Hz, 2H).

4.2. General procedure for the synthesis of (*S*)-benzoins and 2-hydroxy-1-arylethan-1-one from *rac*. benzoins: representative example: (*S*)-2-hydroxy-1,2-bis(4-methylphenyl)ethan-1-one ((*S*)-3e) and 2-hydroxy-1-(4-methylphenyl)-1-one (2b)

Rac-**3e** (240 mg, 1 mmol) was dissolved in a mixture of DMSO (20 mL) and potassium phosphate buffer (80 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)). To this solution was added 4 mmol formaldehyde solution. After the addition of BAL (40 U), the reaction was allowed to stand at room temperature. After 24 h, 20–50 U of BAL and 4 mmol of formaldehyde solution were added. This was repeated every 24 h until no more (*R*)-benzoin was observed. After 6 days, only (*S*)-**3e** and **2b** were detected (HPLC). The mixture was extracted with dichloromethane (250 mL) and the organic layer washed with water (25 mL) and brine (25 mL) and dried over $MgSO_4$. Evaporation of the solvent and separation of the crude products by column chromatography afforded (*S*)-**3e** and **2b**.

4.2.1. Compound (*S*)-3e. Colorless solid; yield: 93 mg, 39%; mp 88 °C [Lit.[15], mp 89 °C]; $[\alpha]_D^{20}$=+148.2 (*c* 0.8, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83 (d, J=8.1 Hz, 2H), 7.18-7.22 (m, 4H), 7.16 (d, J=8.1 Hz, 2H), 5.88 (d, J=5.8 Hz, 1H), 4.52 (d, J=5.8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H).

4.2.2. Compound 2b. Yellow solid; yield: 129 mg, 43%; mp 84 °C [Lit.[10], mp 83 °C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83–7.81 (m, 2H), 7.32–7.28 (m, 2H), 4.86 (s, 2H), 3.52 (br s, 1H), 2.43 (s, 3H).

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Synthesis, experimental and theoretical NMR study of 2′-hydroxychalcones bearing a nitro substituent on their B ring

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Abstract—The synthesis of several 2′-hydroxynitrochalcones has been accomplished by an aldol reaction of equimolar amounts of the appropriate 2′-hydroxyacetophenones with nitrobenzaldehydes in alkaline medium. The reaction of 2′-hydroxyacetophenones bearing a 6′-methoxy with 2- or 4-nitrobenzaldehydes gave the expected 2′-hydroxynitrochalcones and also 4-methoxynitroaurones, being the latter ones the unique reaction products when using 2 molar equiv of nitrobenzaldehydes. The reaction mechanisms for the formation of both products are discussed. The ^{13}C NMR chemical shifts have been discussed first by means of an empirical additive model and then by comparison with GIAO/B3LYP calculated absolute shieldings.

1. Introduction

Chalcones (1,3-diaryl-2-propen-1-ones) are an import class of natural compounds belonging to the flavonoid family, which have demonstrated to possess an impressive array of pharmacological and agrochemical activities, namely, anti-protozoal, anti-inflammatory, immunomodulatory, nitric oxide and lipid peroxidation inhibition, antileishmanial, antimalarial, antiulcer, cytotoxic, anticancer, antitumour, antimicrobial and antiviral activities.[1–12] Certain natural and synthetic derivatives bearing a 2′-hydroxy group have also exhibited a wide spectrum of biological activities with potential applications as biocides and pharmaceutical drugs.[1,13–15] The presence of the enone function and the 2′-hydroxy group in these compounds are important structural features for their antibiotic activity.[1]

The importance of 2′-hydroxychalcones is due not only to their important biological activities, but also due to the fact that they are intermediates in the synthesis and biosynthesis of several flavonoids, such as flavanones, flavones, isoflavones and aurones.[1,16–21] As part of our interests in the area of flavonoids[22–24] and having in mind the potential applications of several nitro- and aminoflavonoid-type compounds,[2,10,25–33] we have expand our studies to the synthesis of several new 2′-hydroxynitrochalcone derivatives. Nitroflavones are selective and competitive ligands for central benzodiazepine receptors and possess anxiolytic properties. The presence of nitro groups is essential for these activities.[27,28,33] Flavones bearing amino groups on the A or B ring have been reported to be potential antineoplastic agents[26] and proved to be antimutagenic in the Ames test using different species of mutagens.[31] Some aminoflavones derivatives are also known as specific antitumour agents in breast cancer[29] and are reported by several authors as tyrosine kinases inhibitors[25] and as antimitotic agents.[32] On the other hand, a series of aminochalcones, synthesised as candidate of cytotoxic agents, displayed selective toxicity to certain malignant cell and were well tolerated in mice.[10]

The synthesis of 2′-hydroxychalcones have been extensively studied,[18,34–36] whereas to our knowledge only a few synthetic methods are available for the preparation of their nitro derivatives.[37–41] Taking these facts into consideration, we started a programme on the synthesis and transformation[41] of this type of compounds and on the study of their spectroscopic features which can give some insights about their biological activities. Recently, Lluch et al. studied the inverse dependence of the chemical shift of the hydroxyl proton of 4′-dimethylamino-2′-hydroxychalcone by theoretical calculations.[42] In this communication, we report the experimental and theoretical studies on the ^{1}H and ^{13}C NMR chemical shifts of twelve 2′-hydroxynitrochalcones **3b–m** and the comparison with those of the parent compound **3a**.

Keywords: 2′-Hydroxynitrochalcones; 4′-Methoxynitroaurones; Oxidation reactions; Aldol reaction; NMR; B3LYP; GIAO.
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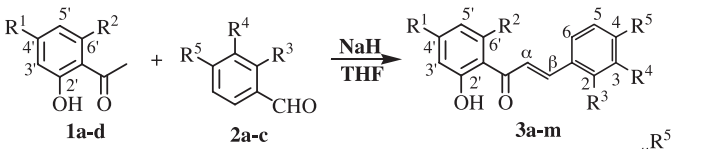
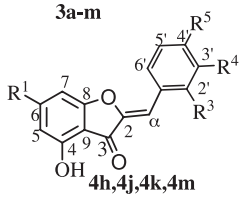


For compounds **1**:
a) $R^1 = R^2 = H$
b) $R^1 = OMe$, $R^2 = H$
c) $R^1 = H$, $R^2 = OMe$
d) $R^1 = R^2 = OMe$

For compounds **2**:
a) $R^3 = R^4 = R^5 = H$
b) $R^3 = NO_2$, $R^4 = R^5 = H$
c) $R^3 = R^5 = H$, $R^4 = NO_2$
d) $R^3 = R^4 = H$, $R^5 = NO_2$


4h,4j,4k,4m

For compounds **3a-m** and **4h**,**4j**,**4k** and **4m**:

	a	b	c	d	e	f	g	h	i	j	k	l	m
R^1	H	H	H	H	OMe	OMe	OMe	H	H	H	OMe	OMe	OMe
R^2	H	H	H	H	H	H	H	OMe	OMe	OMe	OMe	OMe	OMe
R^3	H	NO_2	H	H	NO_2	H	H	NO_2	H	H	NO_2	H	H
R^4	H	H	NO_2	H	H	NO_2	H	H	NO_2	H	H	NO_2	H
R^5	H	H	H	NO_2	H	H	NO_2	H	H	NO_2	H	H	NO_2

Scheme 1.

2. Results and discussion

Initial experiments considered the aldol reaction of 2′-hydroxyacetophenone (**1a**) with 1.1 molar equiv of 2-nitrobenzaldehyde (**2b**) in alkaline medium (2 molar equiv of sodium hydride have been used, since one is consumed by the hydroxyl group) (Scheme 1). After the disappearance of the starting materials, controlled by TLC, the expected 2′-hydroxy-2-nitrochalcone (**3b**) was obtained in 16% yield, after a tedious and hard purification process by preparative thin layer chromatography. In order to increase the yield of the reaction and to avoid some benzaldehyde oxidation, we have deoxygenated the reaction medium before the addition of 2-nitrobenzaldehyde (**2b**) and the expected chalcone (**3b**) was obtained in 24% yield. After this result we carried out the reactions of 2′-hydroxyacetophenones **1a**–**d** with 1.1 equiv of nitrobenzaldehydes (**2b**–**d**) in the same alkaline conditions and the expected 2′-hydroxynitrochalcones **3c**–**m** were obtained in moderate to good yields (Table 1). In the case of chalcones **3h**, **3j** and **3k** a new compound have been obtained in each case. These new compounds were identified as aurones **4h**, **4j** and **4k**. The reaction of 4-nitrobenzaldehyde (**2d**) and 2′-hydroxy-4′,6′-dimethoxyacetophenone (**1d**) does not gave the expected chalcone **3m** but a complex mixture of compounds where there was some starting acetophenone **1d**. Since some starting acetophenone **1d** was recovered in this case, we decided to increase the quantity of 4-nitrobenzaldeyde (**2d**) to 2 molar equiv 2′-Hydroxy-4′,6′-dimethoxy-4-nitrochalcone **3m** were obtained in 17% yield together with 4,6-dimethoxy-4′-nitroaurone (**4m**) (27% yield) after 2 h reaction time and only aurone **4m** (44% yield) after 10 h reaction time (Table 1). Since the yield of the expected chalcone **3m** was not increased after some changes in the experimental procedure, it was decided to perform all the other reactions in these conditions trying to get 2′-hydroxynitrochalcones **3b**–**m** in better yields. The aldol reactions of 2′-hydroxyacetophenones **1a**–**d** with 2 molar equiv of nitrobenzaldehydes **2b**–**d** gave the expected chalcones **3b**–**g**, **3i** and **3l** in better yields than when using 1.1 molar equiv of benzaldehydes **2b**–**d** (Table 1). However, in the cases where some aurones **4h**, **4j** and **4k** have been obtained using 1.1 equiv of benzaldehyde, with 2 equiv only these compounds have been obtained after 2 h reaction time (Table 1). These results indicate that the presence of a 6-methoxy group in the acetophenone moiety and a 2- and 4-nitro group in the benzaldehyde moiety (were there is an electronic conjugation between the nitro substituent and the formyl group) difficult the formation of chalcones, which after to be formed are oxidised (dehydrogenated) into the corresponding aurones **4h**, **4j**, **4k** and **4m**.[43]

In order to explain the formation of aurones **4h**, **4j**, **4k** and **4m**, we analysed by preparative tlc the reaction mixture of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**1d**) with 2 molar equiv of 4-nitrobenzaldehyde **2d** and 4-nitrobenzyl alcohol have been identified (vide experimental). This result indicates that one can envisage the dehydrogenation

Table 1. Yields obtained in the synthesis of 2′-hydroxynitrochalcones **3b**–**m**

Equiv. nitrobenzaldehydes	Yield of 2′-hydroxynitrochalcones **3b**–**m** (%)											
	3b	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**	**3m**
1.1	24	68	80	21	60	64	15[a]	64	19[b]	21[c]	60	—
2	44	75	89	40	72	74	—[d]	81	—[e]	—[f]	73	17[g]

[a] Plus 41% of **4h**.
[b] Plus 48% of **4j**.
[c] Plus 47% of **4k**.
[d] Only 89% of **4h**.
[e] Only 74% of **4j**.
[f] Only 78% of **4k**.
[g] Plus 27% of **4m**.

Table 2. ^{1}H and ^{13}C chemical shifts (δ, ppm, in DMSO-d_6) and matrix of substituents

Compound	H-α	H-β	OH	C-α	C-β	4′-OMe	6′-OMe	2-NO_2	3-NO_2	4-NO_2
3a	8.05	7.84	12.50	121.8	144.9	0	0	0	0	0
3b	7.98	8.06	12.11	126.6	138.8	0	0	1	0	0
3c	8.23	7.92	12.35	124.7	142.0	0	0	0	1	0
3d	8.15	7.85	12.15	126.2	141.3	0	0	0	0	1
3e	8.00	8.07	13.13	125.3	139.6	1	0	1	0	0
3f	8.22	7.91	13.31	124.1	141.6	1	0	0	1	0
3g	8.20	7.88	13.23	125.5	141.1	1	0	0	0	1
3h	7.15	7.64	10.41	132.3	138.2	0	1	1	0	0
3i	7.34	7.48	10.42	131.0	140.9	0	1	0	1	0
3j	7.35	7.45	10.41	132.0	140.3	0	1	0	0	1
3k	7.69	7.87	13.15	131.8	136.6	1	1	1	0	0
3l	7.85	7.71	13.22	130.4	139.3	1	1	0	1	0
3m	7.70	7.59	13.21	131.7	139.0	1	1	0	0	1

of 2′-hydroxychalcones **3h**, **3j**, **3k** and **3m** into the corresponding aurones **4h**, **4j**, **4k** and **4m** by hydrogen transfer to the corresponding benzaldehyde used in excess which is transformed into the obtained benzyl alcohol.

We report here the full characterisation of all synthesised 2′-hydroxynitrochalcones **3b**–**m** since a major part of them are new compounds and the references found for the others are old and do not report these data. The NMR data of 2′-hydroxychalcone **3a** are reported for the comparison study with the nitro derivatives (vide infra).

The main features of the NMR data of 2′-hydroxychalcones **3a**–**m** are the resonances of: (i) the hydroxyl groups at δ 10.41–13.23 ppm. The high frequency resonances of these protons are due to the intramolecular hydrogen bond formed with the carbonyl group; (ii) the vinylic protons appearing as doublets at $\delta_{H\alpha}$ 7.15–8.23 ppm and $\delta_{H\beta}$ 7.45–8.07 ppm. The coupling constants $^{3}J_{H\alpha-H\beta}$ ~15–16 Hz indicate the *trans* configuration of these vinylic system; (iii) the vinylic carbons which appear at $\delta_{C\alpha}$ 121.8–132.3 ppm and $\delta_{C\beta}$ 136.6–144.9 ppm. The resonances of C-β atoms appear at higher frequency values than those of C-α due to deshielding mesomeric effect of the carbonyl group; (iv) the carbonyl group appearing at δ 191.1–194.0 ppm, and (v) the aromatic carbons bonded to oxygen atoms, which appear at δ~157–166 ppm. The resonances of the hydroxyl proton and of the vinylic proton and carbon atoms are very sensitive to the substituents of both aryl rings of 2′-hydroxychalcones **3a**–**m** (vide infra).

The main NMR features of aurones **4h**, **4j**, **4k** and **4m** are the resonances of their vinylic proton, which appear at $\delta_{H\alpha}$ 6.75–7.00 ppm. These resonance frequency are consistent with a *Z* configuration of the olefinic bond of aurones, the thermodynamically more stable isomers of these compounds.[44] Another important resonances to support the structure of aurones are the carbon resonances of C-α (δ 103.4–107.4 ppm), C-2 (δ 147.7–149.2 ppm) and C=O (δ 180.1–180.5 ppm).

The comparison of the ^{1}H and ^{13}C chemical shifts of the parent compound 2′-hydroxychalcone **3a** with those of the twelve methoxy/nitro derivatives **3b**–**m**, shed some light in the effect of these substituents. The most sensitive signals are those belonging to H-α, H-β, OH, C-α and C-β. We have reported these values together with a presence/absence matrix in Table 2.

2.1. Empirical analysis of Table 2 chemical shifts

Using the presence/absence matrix the following correlations are obtained (n=13 points):

$$\delta\text{H-}\alpha = 8.05 + 0.24^{*}(4'\text{-OMe}) - 0.62^{*}(6'\text{-OMe}) - 0.16^{*}(2\text{-NO}_2) + 0.05^{*}(3\text{-NO}_2) - 0.01^{*}(4\text{-NO}_2),\ r^2 = 0.90 \quad (1)$$

$$\delta\text{H-}\beta = 7.84 + 0.10^{*}(4'\text{-OMe}) - 0.32^{*}(6'\text{-OMe}) + 0.18^{*}(2\text{-NO}_2) + 0.02^{*}(3\text{-NO}_2) - 0.04^{*}(4\text{-NO}_2),\ \pi^2 = 0.94 \quad (2)$$

$$\delta\text{OH} = 12.5 + 1.9^{*}(4'\text{-OMe}) - 0.91^{*}(6'\text{-OMe}) - 0.80^{*}(2\text{-NO}_2) - 0.67^{*}(3\text{-NO}_2) - 0.74^{*}(4\text{-NO}_2),\ r^2 = 0.94 \quad (3)$$

$$\delta\text{C-}\alpha = 121.8 - 0.7^{*}(4'\text{-OMe}) + 6.1^{*}(6'\text{-OMe}) + 4.5^{*}(2\text{-NO}_2) + 3.0^{*}(3\text{-NO}_2) + 4.3^{*}(4\text{-NO}_2),\ r^2 = 0.998 \quad (4)$$

$$\delta\text{C-}\beta = 144.9 - 0.7^{*}(4'\text{-OMe}) - 1.7^{*}(6'\text{-OMe}) - 5.4^{*}(2\text{-NO2}) - 2.8^{*}(3\text{-NO}_2) - 3.3^{*}(4\text{-NO}_2),\ r^2 = 0.95 \quad (5)$$

Since the goodness-of-fit, as represented by r^2, are not good, except in the case of δC-α, we suspect that the effect of the methoxy groups was not independent. We introduced a supplementary dummy when both are present simultaneously (compounds **3k**–**m**), (4′,6′-diOMe).

$$\begin{aligned}\delta\text{H-}\alpha &= 8.05 + 0.02^{*}(4'\text{-OMe}) - 0.84^{*}(6'\text{-MeO}) \\ &\quad - 0.05^{*}(2\text{-NO}_2) + 0.16^{*}(3\text{-NO}_2) \\ &\quad - 0.10^{*}(4\text{-NO}_2) + 0.45(4',6'\text{-diOMe}), \\ r^2 &= 0.991\end{aligned} \tag{6}$$

$$\begin{aligned}\delta\text{H-}\beta &= 7.84 + 0.01^{*}(4'\text{-OMe}) - 0.42^{*}(6'\text{-MeO}) \\ &\quad + 0.23^{*}(2\text{-NO}_2) + 0.07^{*}(3\text{-NO}_2) \\ &\quad + 0.01^{*}(4\text{-NO}_2) + 0.19(4',6'\text{-diOMe}), \\ r^2 &= 0.992\end{aligned} \tag{7}$$

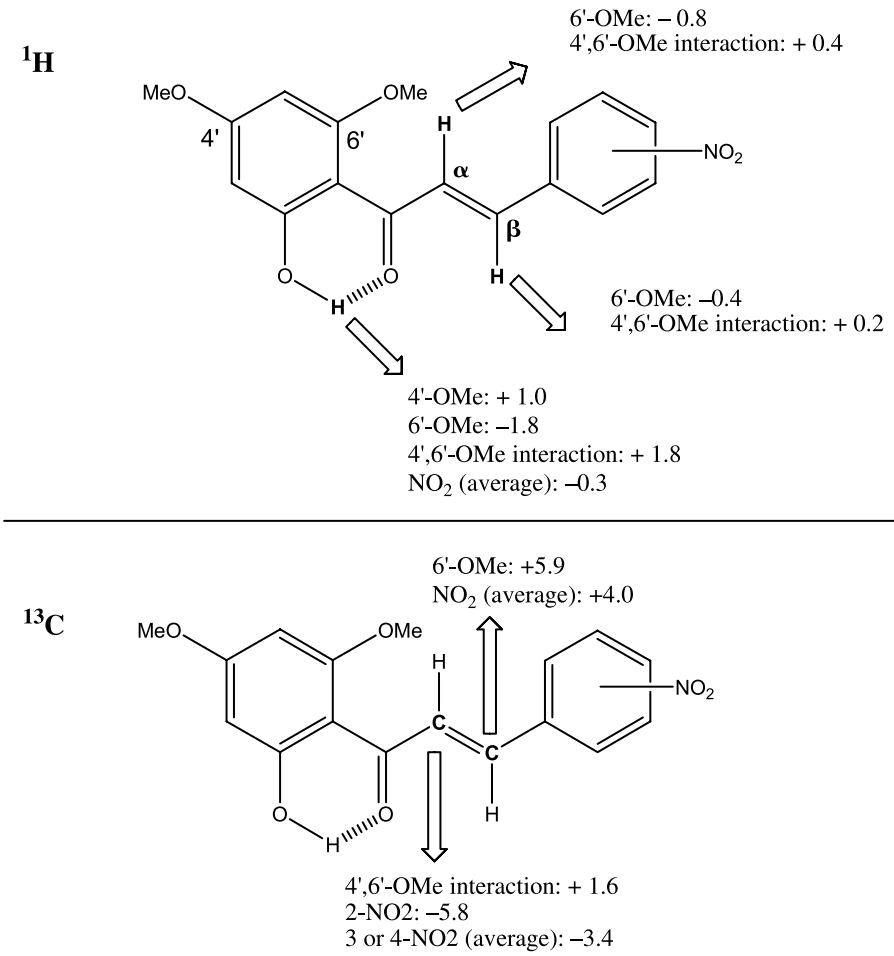
$$\begin{aligned}\delta\text{OH} &= 12.5 + 1.01^{*}(4'\text{-OMe}) - 1.79^{*}(6'\text{-MeO}) \\ &\quad - 0.33^{*}(2\text{-NO}_2) - 0.25^{*}(3\text{-NO}_2) \\ &\quad - 0.30^{*}(4\text{-NO}_2) + 1.77(4',6'\text{-diOMe}), \\ r^2 &= 0.999\end{aligned} \tag{8}$$

$$\begin{aligned}\delta\text{C-}\alpha &= 121.8 - 0.9^{*}(4'\text{-OMe}) + 5.9^{*}(6'\text{-MeO}) \\ &\quad + 4.6^{*}(2\text{-NO}_2) + 3.1^{*}(3\text{-NO}_2) \\ &\quad + 4.4^{*}(4\text{-NO}_2) + 0.4(4',6'\text{-diOMe}), \\ r^2 &= 0.999\end{aligned} \tag{9}$$

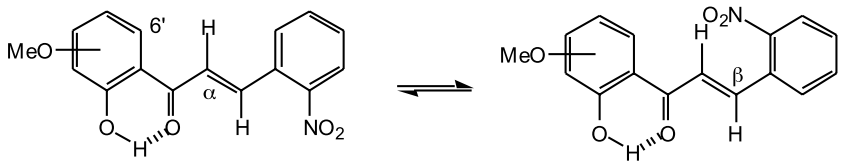
$$\begin{aligned}\delta\text{C-}\beta &= 144.9 - 0.1^{*}(4'\text{-OMe}) - 0.9^{*}(6'\text{-MeO}) \\ &\quad - 5.8^{*}(2\text{-NO}_2) - 3.1^{*}(3\text{-NO}_2) \\ &\quad - 3.7^{*}(4\text{-NO}_2) - 1.6(4',6'\text{-diOMe}), \\ r^2 &= 0.991\end{aligned} \tag{10}$$

Eqs. (6)–(10) can be summarised graphically as represented in Scheme 2.

Concerning the OH proton, the presence of a methoxy group at position 4′ produces a strengthening of the O–H···O hydrogen bond while a 6′-methoxy group weakens the HB. The first effect is electronic in origin, making the carbonyl group, in *para* position, a better HB acceptor. The *ortho* methoxy group should produce a similar effect but its steric effect counterbalanced it, the torsion about the CO-Cα bond weakens the HB. The presence of two methoxy groups has a strong positive effect on the HB, and somewhat



Scheme 2. Effects of the substituents (SCS, ppm) on ^{1}H and ^{13}C signals.



Scheme 3. Conformation of the *o*-nitrophenyl group.

counterbalances the steric effect of the 6′-methoxy group. The same effects, although attenuated, are observed on H-α and H-β, besides H-α is more sensitive to the closer by 6′-OMe while H-β is more sensitive to the *ortho* nitro group (this implies that the conformation of the nitrophenyl group has the NO_2 group close to H-β and not to H-α) (Scheme 3).

In ^{13}C NMR, the SCS of Scheme 2 show the sensibility to proximity effects (C-α to 6′-OMe group and C-β to all NO_2 groups but especially to the *ortho* one).

2.2. Theoretical analysis of Table 2 chemical shifts

It should be possible to verify the conclusions of the previous empirical discussion carrying GIAO/DFT calculations. We decided to calculate, as the most representative compounds, **3a**, **3b**, **3c**, **3d**, **3g**, **3j** and **3m**. Initially the structures have been optimised at the B3LYP/6-31G* level and its minimum nature has been confirmed by frequency calculations. A further optimisation has been carried out at the B3LYP/6-311++G** level and these structures have been used to obtain the theoretical absolute chemical shielding with the GIAO method. As this implies in a first step the optimisation (B3LYP/6-31G*), the first result is that of the two conformations of Scheme 3, that of the left side is the only one stable (compound **3b**). The geometrical characteristics of the O–H···O hydrogen bonds in the different compounds are gathered in Table 3.

Table 3. Distance (Å) and angle (°) of the structures optimised at the B3LYP/6-311++G** computational level

Compound	H···O	O–H···O
3a	1.638	148.0
3b	1.653	147.4
3c	1.652	147.4
3d	1.650	147.4
3g	1.646	148.1
3j	1.611	147.7
3m	1.598	149.1

The $\delta\,^{13}C$ are relatively well correlated with the calculated absolute shielding, σ. Although all nuclei of each molecule are calculated, we will limit ourselves to those corresponding to Table 1. For carbon atoms C-α and C-β, Eq. (11) is obtained.

$$\delta^{13}\mathrm{C(ppm)} = 162\ \mathrm{ppm} - 0.63\sigma^{13}\mathrm{C(ppm)}, n = 14, r^2 = 0.96 \quad (11)$$

The slope is far from 1 but the correlation coefficient is acceptable taking into account that the experimental (23 ppm) and calculated (33 ppm) ranges are quite narrow. An analysis of the calculated values similar to Eqs. (9) and (10) is possible but not interesting due to the proportionality between δ and σ (Eq. (11)). The theoretical calculated values do not need an empirical partition into contributing terms: they show that the experimental results are consistent with the optimised geometries and there are no large anomalies. Two points show the largest deviations both C-β carbons: **3b** (2-NO_2) fitted 143.0, experimental 138.8 ($\Delta\delta$=−4.2 ppm) and **3g** (4-NO_2) fitted 138.1, experimental 141.1 ($\Delta\delta$=+3.0 ppm). The NMR spectra have been recorded again and the experimental values do not change: we have no explanation for these differences that reflect some factor not well taken into account by the calculations, a rather unusual observation.

Concerning the ^1H chemical shifts, the CH and the OH cannot be treated together. This is an usual observation: protons linked to heteroatoms are different, not from the calculations, but from the experimental data. The calculations correspond to the isolated molecule and the experimental data are from DMSO-d_6 solutions. Obviously, the solvent plays an important role on the acidic proton.

3. Computational details

The structure of the molecules have been optimised with the hybrid B3LYP functional[45,46] and the 6-31G*[47] using the Gaussian-98 program.[48] At the same computational level, the minimum nature of the structures has been confirmed by frequency calculation. A further geometry optimisation has been carried out at the B3LYP/6-311++G**[49] computational level. The absolute chemical shieldings have been calculated using the GIAO method[50,51] at the B3LYP/6-311++G** level.

4. Experimental

Melting points were measured in a Büchi 535 apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX 300 spectrometer (300.13 for ^1H and 75.47 MHz for ^{13}C), with DMSO-d_6 as a solvent. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. The internal standard was TMS. Unequivocal ^{13}C assignments were made with the aid of 2D *g*HSQC and *g*HMBC (delays for one bond and long-range J C/H couplings were optimised for 147 and 7 Hz, respectively) experiments. Electron impact (EI, 70 eV) MS were recorded on VG Autospec Q spectrometer. Elemental Analyses were obtained on a Carlo Erba 1108 CHNS analyser. Preparative thin-layer chromatography was performed with Merck silica gel 60 DGF_{254}. Column chromatography was performed with Merck silica gel 60, 70–230 mesh. All other chemicals

and solvents used were obtained from commercial sources and used as received or dried using standard procedures.

4.1. Synthesis of 2′-hydroxychalcone (3a)

An aqueous solution of sodium hydroxide (60%, 160 mL) was added to a methanolic solution (160 mL) of 2′-hydroxyacetophenone (**1a**) (4 mL, 33 mmol). The obtained solution was cooled to room temperature, benzaldehyde (**2a**) (40 mmol) was added and the reaction mixture was stirred for 4 h. After this period, the reaction mixture was poured into a mixture of water (100 mL), ice and hydrochloric acid (pH adjusted to 2). The obtained solid was filtered, taken in chloroform (300 mL) and washed with a 5% aqueous solution of sodium hydrogen carbonate (2×200 mL). The organic layer was collected, dried and evaporated to dryness. The residue was crystallised from ethanol; giving 2′-hydroxychalcone **3a** (75%). Mp 81–83 °C (recrystallised from ethanol, lit.[40] 88 °C). ^{1}H NMR: δ 6.98–7.04 (m, 2H, H-3′ and H-5′), 7.57 (dt, 1H, H-4′, J=1.6, 7.8 Hz), 7.45–7.50 (m, 3H, H-3, H-4 and H-5), 7.84 (d, 1H, H-β, J=15.6 Hz), 7.91–7.93 (m, 1H, H-2,6), 8.05 (d, 1H, H-α, J=15.6 Hz), 8.25 (dd, 1H, H-6′, J=1.6, 8.3 Hz), 12.50 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 117.8 (C-3′), 119.2 (C-5′), 120.9 (C-1′), 121.8 (C-α), 129.0 (C-3,5), 130.9 (C-6′), 129.2 (C-2,6), 134.4 (C-1), 131.0 (C-4), 136.4 (C-4′), 144.9 (C-β), 161.9 (C-2′), 193.7 (C═O).

4.2. Synthesis of 2′-hydroxynitrochalcones 3b–m

Method A. Sodium hydride (0.88 g, 36.5 mmol) was slowly added to a solution of the appropriate 2′-hydroxyacetophenone **1a–d** (16.6 mmol) in dry tetrahydrofuran (10 mL) and the reaction mixture stirred at room temperature for 20 min. After this period the adequate nitrobenzaldehyde **2b–d** (18.3 mmol) dissolved in tetrahydrofuran (10 mL) was added. The solution was stirred, under nitrogen, at room temperature until the disappearance of the starting materials (~8 h). The solution was poured into ice and water, and the pH adjusted to 3 with hydrochloric acid. The obtained solid was removed by filtration, dissolved in chloroform (30 mL) and washed with water (2×20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness. In the case of 2′-hydroxynitrochalcones **3b–g**, **3i** and **3l**, the residue was crystallised from ethanol, ethyl acetate or ethanol:acetone. 2′-Hydroxynitrochalcones **3h**, **3j** and **3k** and the corresponding nitroaurones **4h**, **4j** and **4k** have been isolated from the reaction mixture by by column chromatography using different mixtures of chloroform:*n*-hexane as eluent. Finally all the synthesised compounds were recrystallised from ethanol, ethyl acetate or ethanol:acetone, and collected in the following yields: **3b**, 24%; **3c**, 68%; **3d**, 80%; **3e**, 21%; **3f**, 60%; **3g**, 64%; **3h**, 15% and **4h**, 41%; **3i**, 64%; **3j**, 19% and **4j**, 48%; **3k**, 21% and **4k**, 47%; **3l**, 60%.

Method B. This method is similar to method A, except the quantity of the adequate nitrobenzaldehyde **2b–d**, which was 33.2 mmol. The obtained yields were as follows: **3b**, 44%; **3c**, 75%; **3d**, 89%; **3e**, 40%; **3f**, 72%; **3g**, 74%; **4h**, 89%; **3i**, 81%; **4j**, 74%; **4k**, 78%; **3l**, 78%; **3m**, 17% and **4m**, 27%.

4.2.1. 2′-Hydroxy-2-nitrochalcone (3b). Mp 160.2–161.0 °C (recrystallised from ethanol). ^{1}H NMR: δ 7.00 (d, 2H, H-3′ and H-5′, J=7.9 Hz), 7.58 (dt, 1H, H-4′, J=1.7, 7.9 Hz), 7.71 (dt, 1H, H-4, J=1.4, 8.2 Hz), 7.84 (dt, 1H, H-5, J=1.2, 8.2 Hz), 7.98 (d, 1H, H-α, J=15.4 Hz), 8.06 (d, 1H, H-β, J=15.4 Hz), 8.11 (dd, 1H, H-3, J=1.2, 8.2 Hz), 8.16 (dd, 1H, H-6, J=1.4, 8.2 Hz), 8.19 (dd, 1H, H-6′, J=1.7, 7.9 Hz), 12.11 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 117.8 (C-3′), 119.4 (C-5′), 121.1 (C-1′), 126.6 (C-α), 124.8 (C-3), 131.1 (C-6′), 129.6 (C-1 and C-6), 131.3 (C-4), 133.9 (C-5), 136.5 (C-4′), 138.8 (C-β), 148.8 (C-2), 161.5 (C-2′), 193.0 (C═O). EI-MS: *m*/*z* (rel. intensity) 269 ($M^{+\cdot}$, 10), 252 (55), 222 (38), 165 (7), 132 (5), 121 (100), 102 (8), 93 (18), 77 (10), 65 (32). IR ν 1643, 1589, 1513, 1438, 1342, 1267, 1205, 1018 cm^{-1}. Anal. calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.09, N 5.20. Found: C 66.70, H 4.03, N 5.12.

4.2.2. 2′-Hydroxy-3-nitrochalcone (3c). Mp 163.5–163.9 °C (recrystallised from ethyl acetate, lit.[40] 163.0 °C). ^{1}H NMR: δ 7.02 (d, 2H, H-3′ and H-5′, J=8.0 Hz), 7.58 (dt, 1H, H-4′, J=1.4, 8.0 Hz), 7.75 (t, 1H, H-5, J=9.0 Hz), 7.92 (d, 1H, H-β, J=15.6 Hz), 8.23 (d, 1H, H-α, J=15.6 Hz), 8.27 (d, 1H, H-6, J=9.0 Hz), 8.31–8.35 (m, 2H, H-4 and H-6′), 8.78 (d, 1H, H-2, J=1.6 Hz), 12.35 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 117.7 (C-3′), 119.2 (C-5′), 120.7 (C-1′), 123.1 (C-2), 124.7 (C-α), 124.9 (C-6), 130.3 (C-5), 131.1 (C-6′), 135.2 (C-4), 136.3 (C-1), 136.5 (C-4′), 142.0 (C-β), 148.4 (C-3), 161.8 (C-2′), 193.3 (C═O). EI-MS: *m*/*z* (rel. intensity) 269 ($M^{+\cdot}$, 60), 268 (44), 252 (10), 222 (9), 194 (8), 176 (7), 152 (3), 147 (100), 121 (55), 102 (22), 93 (15), 76 (12), 65 (30). IR ν 1644, 1589, 1523, 1486, 1438, 1357, 1288, 1211, 1157 cm^{-1}. Anal. calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.09, N 5.20. Found: C 66.78, H 3.97, N 5.12.

4.2.3. 2′-Hydroxy-4-nitrochalcone (3d). Mp 141.8–142.1 °C (recrystallised from ethyl acetate, lit.[40] 206–207 °C, lit.[37] 153–154 °C). ^{1}H NMR: δ 6.99–7.04 (m, 2H, H-3′ and H-5′), 7.58 (dt, 1H, H-4′, J=1.5, 7.8 Hz), 7.86 (d, 1H, H-β, J=15.5 Hz), 8.14 (d, 2H, H-2,6, J=9.1 Hz), 8.15 (d, 1H, H-α, J=15.5 Hz), 8.20 (dd, 1H, H-6′, J=1.5, 8.3 Hz), 8.27 (d, 2H, H-3,5, J=9.1 Hz), 12.15 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 117.6 (C-3′), 119.1 (C-5′), 120.9 (C-1′), 123.8 (C-3,5), 126.2 (C-α), 129.8 (C-2,6), 130.9 (C-6′), 136.5 (C-4′), 140.8 (C-1), 141.3 (C-β), 148.1 (C-4), 161.5 (C-2′), 193.1 (C═O). EI-MS: *m*/*z* (rel. intensity) 269 ($M^{+\cdot}$, 82), 268 (60), 252 (16), 222 (15), 194 (6), 176 (10), 165 (13), 147 (100), 121 (62), 102 (19), 93 (15), 93 (17), 76 (9), 65 (27). IR ν 1644, 1590, 1515, 1490, 1440, 1340, 1270, 1209, 1157 cm^{-1}. Anal. calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.09, N 5.20. Found: C 66.64, H 3.97, N 5.17.

4.2.4. 2′-Hydroxy-4′-methoxy-2-nitrochalcone (3e). Mp 149.9–150.3 °C (recrystallised from ethanol). ^{1}H NMR: δ 3.87 (s, 3H, OC*H*$_3$), 6.55 (d, 1H, H-3′, J=2.5 Hz), 6.59 (dd, 1H, H-5′, J=2.5, 9.0 Hz), 7.72 (ddd, 1H, H-4, J=1.2, 7.6, 8.0 Hz), 7.85 (ddd, 1H, H-5, J=1.0, 7.6, 7.7 Hz), 8.00 (d, 1H, H-α, J=15.5 Hz), 8.07 (d, 1H, H-β, J=15.5 Hz), 8.11 (dd, 1H, H-3, J=1.0, 8.0 Hz), 8.22 (dd, 1H, H-6, J=1.2, 7.7 Hz), 8.27 (d, 1H, H-6′, J=9.0 Hz), 13.13 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.9 (O*C*H$_3$), 101.0 (C-3′), 107.7 (C-5′), 113.9 (C-1′), 124.8 (C-3), 125.8 (C-α), 129.6 (C-1), 129.7 (C-6), 131.2 (C-4), 133.0 (C-6′), 133.8 (C-5), 138.3 (C-β), 148.8 (C-2), 165.7 (C-2′), 166.4 (C-4′), 191.3 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 22), 282 (54), 252 (46), 226 (10),

177 (9), 164 (8), 151 (100), 120 (5), 108 (12), 102 (7), 95 (11), 77 (6), 65 (7). IR ν 1639, 1579, 1517, 1344, 1228, 1201, 1135 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 64.12, H 4.34, N 4.60.

4.2.5. 2′-Hydroxy-4′-methoxy-3-nitrochalcone (3f). Mp 177.6–178.3 °C (recrystallised from ethyl acetate, lit.[52] 172–173°C). ^{1}H NMR: δ 3.85 (s, 3H, OCH_3), 6.52 (d, 1H, H-3′, J=2.4 Hz), 6.58 (dd, 1H, H-5′, J=2.4, 9.0 Hz), 7.75 (t, 1H, H-5, J=8.0 Hz), 7.91 (d, 1H, H-β, J=15.7 Hz), 8.22 (d, 1H, H-α, J=15.7 Hz), 8.27 (dd, 1H, H-6′, J=2.4, 9.0 Hz), 8.31–8.35 (m, 2H, H-4 and H-6), 8.80 (br s, 1H, H-2), 13.31 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.9 (O*C*H$_3$), 100.9 (C-3′), 107.7 (C-5′), 113.9 (C-1′), 123.2 (C-2), 124.1 (C-α), 124.9 (C-6), 130.4 (C-5), 133.1 (C-6′), 135.4 (C-4), 136.3 (C-1), 141.6 (C-β), 148.5 (C-3), 165.9 (C-2′), 166.3 (C-4′), 191.7 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 100), 298 (38), 282 (8), 252 (6), 224 (10), 177 (97), 151 (53), 120 (9), 102 (9), 95 (7), 76 (5). IR ν 1641, 1581, 1527, 1438, 1353, 1284, 1230, 1132 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 63.88, H 4.33, N 4.61.

4.2.6. 2′-Hydroxy-4′-methoxy-4-nitrochalcone (3g). Mp 191.8–192.7°C (recrystallised from ethyl acetate, lit.[52] 194–195 °C). ^{1}H NMR: δ 3.86 (s, 3H, OCH_3), 6.54 (d, 1H, H-3′, J=2.4 Hz), 6.59 (dd, 1H, H-5′, J=2.4, 9.0 Hz), 7.88 (d, 1H, H-β, J=15.6 Hz), 8.18 (d, 2H, H-2,6, J=8.7 Hz), 8.20 (d, 1H, H-α, J=15.5 Hz), 8.29 (d, 2H, H-3,5, J=8.7 Hz), 8.30 (d, 1H, H-6′, J=9.0 Hz), 13.23 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.9 (O*C*H$_3$), 101.0 (C-3′), 107.7 (C-5′), 114.0 (C-1′), 124.0 (C-3,5), 125.5 (C-α), 130.1 (C-2,6), 133.0 (C-6′), 141.0 (C-1), 141.1 (C-β), 148.1 (C-4), 165.8 (C-2′), 166.4 (C-4′), 191.4 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 82), 298 (46), 282 (10), 271 (11), 252 (12), 224 (6), 210 (3), 177 (100), 165 (7), 151 (64), 130 (5), 102 (14), 95 (11), 76 (9). IR ν 1637, 1589, 1509, 1340, 1287, 1224, 1209, 1132 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 64.11, H 4.38, N 4.61.

4.2.7. 2′-Hydroxy-6′-methoxy-2-nitrochalcone (3h). Mp 180.2–181.4 °C (recrystallised from acetone:ethanol). ^{1}H NMR: δ 3.76 (s, 3H, OCH_3), 6.55 (d, 1H, H-3′, J=8.3 Hz), 6.58 (d, 1H, H-5′, J=8.3 Hz), 7.15 (d, 1H, H-α, J=15.9 Hz), 7.27 (t, 1H, H-4′, J=8.3 Hz), 7.64 (d, 1H, H-β, J=15.9 Hz), 7.67 (ddd, 1H, H-4, J=1.3, 7.6, 8.1 Hz), 7.78 (t, 1H, H-5, J=7.6 Hz), 7.97 (d, 1H, H-6, J=7.6 Hz), 8.06 (dd, 1H, H-3, J=1.0, 8.1 Hz), 10.41 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.8 (O*C*H$_3$), 102.3 (C-5′), 109.0 (C-3′), 115.2 (C-1′), 124.8 (C-3), 129.2 (C-6), 129.6 (C-1), 131.0 (C-4), 132.3 (C-4′ and C-α), 134.0 (C-5), 138.2 (C-β), 148.5 (C-2), 157.2 (C-2′), 158.3 (C-6′), 194.0 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 100), 282 (80), 252 (58), 177 (10), 164 (11), 136 (21), 108 (20), 77 (10), 65 (16). IR ν 1633, 1583, 1529, 1473, 1454, 1351, 1236, 1205, 1085 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 64.17, H 4.29, N 4.70.

4.2.8. 2′-Hydroxy-6′-methoxy-3-nitrochalcone (3i). Mp 137.0–138.6 °C (recrystallised from ethyl acetate). ^{1}H NMR: δ 3.74 (s, 3H, OCH_3), 6.55 (d, 1H, H-3′, J=8.3 Hz), 6.58 (d, 1H, H-5′, J=8.3 Hz), 7.27 (t, 1H, H-4′, J=8.3 Hz), 7.34 (d, 1H, H-α, J=16.1 Hz), 7.48 (d, 1H, H-β, J=16.1 Hz), 7.69 (t, 1H, H-5, J=8.0 Hz), 8.19 (d, 1H, H-6, J=8.0 Hz), 8.23 (dd, 1H, H-4, J=1.8, 8.0 Hz), 8.51 (t, 1H, H-2, J=1.8 Hz), 10.42 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.9 (O*C*H$_3$), 102.4 (C-5′), 109.1 (C-3′), 115.7 (C-1′), 123.3 (C-2), 124.7 (C-4), 130.5 (C-5), 131.0 (C-α), 132.2 (C-4′), 134.3 (C-6), 136.4 (C-1), 140.9 (C-β), 148.4 (C-3), 157.0 (C-2′), 158.3 (C-6′), 194.0 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 55), 298 (39), 282 (7), 252 (6), 224 (5), 210 (3), 177 (100), 162 (7), 151 (33), 136 (8), 107 (9), 102 (11). IR ν 1635, 1583, 1529, 1475, 1436, 1353, 1238, 1209, 1087 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 64.13, H 4.39, N 4.61.

4.2.9. 2′-Hydroxy-6′-methoxy-4-nitrochalcone (3j). Mp 160.3–161.0 °C (recrystallised from acetone:ethanol). ^{1}H NMR: δ 3.75 (s, 3H, OCH_3), 6.55 (d, 1H, H-3′, J=8.3 Hz), 6.59 (d, 1H, H-5′, J=8.3 Hz), 7.28 (t, 1H, H-4′, J=8.3 Hz), 7.35 (d, 1H, H-α, J=16.2 Hz), 7.45 (d, 1H, H-β, J=16.2 Hz), 8.00 (d, 2H, H-2,6, J=8.7 Hz), 8.23 (d, 2H, H-3,5, J=8.7 Hz), 10.41 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.8 (O*C*H$_3$), 102.4 (C-5′), 109.0 (C-3′), 115.5 (C-1′), 124.0 (C-3,5), 129.6 (C-2,6), 132.0 (C-α), 132.2 (C-4′), 140.3 (C-β), 141.0 (C-1), 148.0 (C-4), 157.1 (C-2′), 158.2 (C-6′), 194.0 (C═O). EI-MS: *m*/*z* (rel. intensity) 299 ($M^{+\cdot}$, 70), 298 (56), 282 (7), 252 (9), 177 (100), 162 (6) 151 (40), 136 (10), 130 (5), 122 (7), 107 (8), 102 (12). IR ν 1633, 1581, 1515, 1440, 1344, 1226, 1133 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO_5$: C 64.21, H 4.35, N 4.68. Found: C 64.22, H 4.33, N 4.77.

4.2.10. 2′-Hydroxy-4′,6′-dimethoxy-2-nitrochalcone (3k). Mp 173.0–173.9 °C (recrystallised from acetone:ethanol). ^{1}H NMR: δ 3.86 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.16 (d, 1H, H-3′, J=2.2 Hz), 6.18 (d, 1H, H-5′, J=2.2 Hz), 7.66–7.72 (m, 1H, H-4), 7.69 (d, 1H, H-α, J=15.6 Hz), 7.81 (d, 1H, H-5, J=7.5 Hz), 7.87 (d, 1H, H-β, J=15.6 Hz), 7.95 (d, 1H, H-6, J=7.5 Hz), 8.10 (dt, 1H, H-3, J=0.9, 8.1 Hz), 13.15 (s, 1H, 2′-O*H*). ^{13}C NMR: δ 55.9 (O*C*H$_3$), 56.4 (O*C*H$_3$), 91.3 (C-5′), 94.0 (C-3′), 106.3 (C-1′), 124.9 (C-3), 129.3 (C-6), 130.0 (C-1), 131.0 (C-4), 131.8 (C-α), 134.1 (C-5), 136.6 (C-β), 148.7 (C-2), 162.1 (C-6′), 165.5 (C-2′), 166.0 (C-4′), 191.9 (C═O). EI-MS: *m*/*z* (rel. intensity) 329 ($M^{+\cdot}$, 11), 312 (27), 282 (24), 253 (3), 207 (9), 194 (19), 181 (100), 166 (5), 138 (8), 102 (4), 95 (7), 69 (6). IR ν 1631, 1581, 1531, 1438, 1347, 1270, 1155 cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_6$: C 62.01, H 4.56, N 4.26. Found: C 62.32, H 4.56, N 4.19.

4.2.11. 2′-Hydroxy-4′,6′-dimethoxy-3-nitrochalcone (3l). Mp 169.1–170.0 °C (recrystallised from ethyl acetate). ^{1}H NMR: δ 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.14 (d, 1H, H-3′, J=2.1 Hz), 6.16 (d, 1H, H-5′, J=2.1 Hz), 7.71 (d, 1H, H-β, J=15.6 Hz), 7.73 (t, 1H, H-5, J=8.0 Hz), 7.85 (d, 1H, H-α, J=15.6 Hz), 8.20 (d, 1H, H-6, J=8.0 Hz), 8.25 (dd, 1H, H-4, J=1.5, 8.0 Hz), 8.51 (br s, 1H, H-2), 13.22 (s, 1H, 2-O*H*). ^{13}C NMR: δ 55.7 (O*C*H$_3$), 56.0 (O*C*H$_3$), 91.2 (C-5′), 94.0 (C-3′), 106.4 (C-1′), 123.1 (C-2), 124.5 (C-4), 130.4 (C-α), 130.6 (C-5), 134.0 (C-6), 136.8 (C-1), 139.3 (C-β), 148.4 (C-3), 162.0 (C-6′), 165.4 (C-2′), 165.9 (C-4′), 192.1 (C═O). EI-MS: *m*/*z* (rel. intensity) 329 ($M^{+\cdot}$, 61), 328 (39), 312 (13), 301 (15), 282 (5), 254 (9), 207 (100), 181 (46), 166 (7), 138 (8), 102 (10), 95 (6), 69 (7). IR ν 1635, 1581, 1531, 1438, 1347, 1270, 1218, 1159 cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_6$: C 62.01, H 4.56, N 4.26. Found: C 62.18, H 4.51, N 4.13.

4.2.12. 2′-Hydroxy-4′,6′-dimethoxy-4-nitrochalcone (3m). Mp 235.0–236.4 °C (recrystallised from acetone: ethanol). ^{1}H NMR: δ 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.17 (d, 1H, H-3′, J=1.9 Hz), 6.19 (d, 1H, H-5′, J=1.9 Hz), 7.59 (d, 1H, H-β, J=15.7 Hz), 7.70 (d, 1H, H-α, J=15.7 Hz), 8.02 (d, 2H, H-2,6, J=8.6 Hz), 8.29 (d, 2H, H-3,5, J=8.6 Hz), 13.21 (s, 1H, 2′-OH). ^{13}C NMR: δ 55.8 (OCH_3), 56.4 (OCH_3), 91.3 (C-5′), 93.9 (C-3′), 106.4 (C-1′), 124.1 (C-3,5), 129.5 (C-2,6), 131.7 (C-α), 139.0 (C-β), 141.4 (C-1), 148.0 (C-4), 162.0 (C-6′), 165.4 (C-2′), 166.0 (C-4′), 192.0 (C=O). EI-MS: m/z (rel. intensity) 329 ($M^{+\cdot}$, 69), 328 (32), 312 (8), 301 (20), 282 (5), 255 (3), 207 (100), 181 (53), 166 (9), 125 (10), 97 (21), 71 (25), 57 (35). IR ν 1639, 1583, 1519, 1438, 1342, 1216, 1160 cm^{-1}. Anal. calcd for $C_{17}H_{15}NO_6$: C 62.01, H 4.56, N 4.26. Found: C 62.23, H 4.49, N 4.31.

4.2.13. 4-Methoxy-2′-nitroaurone (4h). Mp 194.0–195.0 °C (recrystallised from ethanol). ^{1}H NMR: δ 3.95 (s, 3H, OCH_3), 6.87 (d, 1H, H-5, J=8.3 Hz), 6.97 (d, 1H, H-7, J=8.3 Hz), 7.00 (s, 1H, H-α), 7.67 (t, 1H, H-4′, J=7.9 Hz), 7.72 (t, 1H, H-6, J=8.3 Hz), 7.85 (t, 1H, H-5′, J=7.9 Hz), 8.10 (d, 1H, H-3′, J=7.9 Hz), 8.19 (d, 1H, H-6′, J=7.9 Hz). ^{13}C NMR: δ 56.2 (OCH_3), 104.0 (C-α), 104.4 (C-7), 106.7 (C-5), 109.4 (C-9), 124.8 (C-3′), 125.9 (C-1′), 130.1 (C-4′), 131.9 (C-6′), 133.3 (C-5′), 139.7 (C-6), 147.7 (C-2), 148.7 (C-2′), 158.2 (C-8), 166.3 (C-4), 180.4 (C=O). EI-MS: m/z (rel. intensity) 297 ($M^{+\cdot}$, 7), 280 (22), 267 (25), 251 (71), 236 (100), 221 (13), 208 (47), 180 (47), 165 (48). IR ν 1708, 1656, 1602, 1519, 1496, 1347, 1251, 1193, 1074, 794 cm^{-1}. Anal. calcd for $C_{16}H_{11}NO_5$: C 64.65, H 3.70, N 4.71. Found: C 64.45, H 3.67, N 4.62.

4.2.14. 4-Methoxy-4′-nitroaurone (4j). Mp 201.5–202.3 °C (recrystallised from ethanol). ^{1}H NMR: δ 3.95 (s, 3H, OCH_3), 6.89 (s, 1H, H-α), 7.04 (d, 1H, H-7, J=8.1 Hz), 7.74 (t, 1H, H-6, J=8.1 Hz), 7.88 (d, 1H, H-5, J=8.1 Hz), 8.16 (d, 2H, H-2′,6′, J=8.8 Hz), 8.28 (d, 2H, H-3′,5′, J=8.8 Hz). ^{13}C NMR: δ 56.1 (OCH_3), 104.4 (C-7), 106.7 (C-5), 107.4 (C-α), 109.3 (C-9), 123.6 (C-3′,5′), 131.5 (C-2′,6′), 138.5 (C-1′), 139.5 (C-6), 146.9 (C-4′), 147.8 (C-2), 158.1 (C-8), 166.2 (C-4), 180.5 (C=O). EI-MS: m/z (rel. intensity) 297 ($M^{+\cdot}$, 100), 298 (14), 280 (3), 268 (17), 236 (8), 221 (28), 165 (15), 139 (4), 107 (9), 89 (16), 76 (26), 63 (21). IR ν 1704, 1654, 1604, 1494, 1336, 1255, 1078, 796 cm^{-1}. Anal. calcd for $C_{16}H_{11}NO_5$: C 64.65, H 3.70, N 4.71. Found: C 64.46, H 3.66, N 4.71.

4.2.15. 4,6-Dimethoxy-2′-nitroaurone (4k). Mp 221.7–222.0 °C (recrystallised from ethanol). ^{1}H NMR: δ 3.93 (s, 6H, OCH_3), 6.40 (d, 1H, H-5, J=1.5 Hz), 6.68 (d, 1H, H-7, J=1.5 Hz), 6.95 (s, 1H, H-α), 7.68 (t, 1H, H-4′, J=7.8 Hz), 7.86 (t, 1H, H-5′, J=7.8 Hz), 8.13 (d, 1H, H-3′, J=7.8 Hz), 8.19 (d, 1H, H-6′, J=7.8 Hz). ^{13}C NMR: δ 56.4 (OCH_3), 56.6 (OCH_3), 90.2 (C-7), 94.7 (C-5), 103.4 (C-α), 103.8 (C-9), 124.4 (C-3′), 126.3 (C-1′), 130.1 (C-4′), 132.0 (C-6′), 133.6 (C-5′), 148.7 (C-2′), 148.9 (C-2), 159.7 (C-4), 169.1 (C-8), 169.6 (C-6), 180.1 (C=O). EI-MS: m/z (rel. intensity) 327 ($M^{+\cdot}$, 52), 310 (21), 297 (22), 281 (100), 266 (25), 237 (31), 223 (40), 208 (20), 195 (51). IR ν 1704, 1621, 1594, 1517, 1481, 1346, 1247, 1224, 1160, 1097, 825 cm^{-1}. Anal. calcd for $C_{17}H_{13}NO_6$: C 62.39, H 3.98, N 4.28. Found: C 62.47, H 3.99, N 4.38.

4.2.16. 4,6-Dimethoxy-4′-nitroaurone (4m). Mp 266.7–261.9 °C (recrystallised from ethanol). ^{1}H NMR: δ 3.95 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.17 (d, 1H, H-5, J=1.7 Hz), 6.43 (d, 1H, H-7, J=1.7 Hz), 6.75 (s, 1H, H-α), 7.99 (d, 2H, H-2′,6′, J=8.8 Hz), 8.26 (d, 2H, H-3′,5′, J=8.8 Hz). ^{13}C NMR: δ 56.3 (OCH_3), 56.4 (OCH_3), 89.6 (C-7), 94.4 (C-5), 104.7 (C-9), 107.3 (C-α), 123.9 (C-3′,5′), 131.4 (C-2′,6′), 139.1 (C-1′), 147.3 (C-4′), 149.6 (C-2), 159.7 (C-4), 169.1 (C-8), 169.6 (C-6), 180.1 (C=O). EI-MS: m/z (rel. intensity) 327 ($M^{+\cdot}$, 100), 326 (25), 310 (7), 298 (38), 251 (16), 180 (8), 137 (9), 106 (12), 85 (11), 69 (20), 57 (22). IR ν 1695, 1664, 1617, 1585, 1506, 1421, 1338, 1157, 1089, 827 cm^{-1}. Anal. calcd for $C_{17}H_{13}NO_6$: C 62.39, H 3.98, N 4.28. Found: C 62.39, H 4.00, N 4.46.

4.2.17. 4-Nitrobenzyl alcohol. ^{1}H NMR: δ 4.84 (s, 2H, CH_2), 7.54 (d, 2H, H-2,6, J=8.7 Hz), 8.22 (d, 2H, H-3,5, J=8.7 Hz). EI-MS: m/z (rel. intensity) 153 ($M^{+\cdot}$, 54), 137 (100), 120 (45), 92 69), 83 (11), 71 (27), 57 (37).

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Syntheses of ethyl 3-deoxy-3,3-difluoro-D-*arabino*-heptulosonate and analogues

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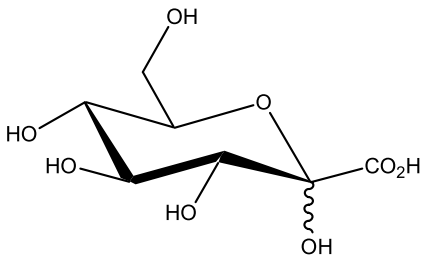
Abstract—The difluorinated analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) **12**, **24** and its enantiomer have been synthesised from D- and L-erythrose via a Reformatsky reaction which gave a mixture of diastereoiosmers in favour of the *anti* isomer.

The enzymatic conversion of carbohydrates to essential aromatics and aromatic amino acids utilised by micro-organisms, fungi and higher plants forms the shikimate pathway.[1] The recent discovery that this pathway is also operative in apicomplexan parasites including the most virulent malarial parasites (Plasmodium falciparum) has led to a resurgence of interest in the inhibitors of this biosynthetic pathway.[2] The shikimate pathway is absent in mammals and they have to obtain the three aromatic amino acids (L-phenylalanine, L-tyrosine, and L-tryptophan) through dietary means. It is therefore expected that inhibitors of the shikimate pathway will be devoid of toxicity and have low environmental impact. The most successful commercial enzyme inhibitor used in agriculture is glyphosate (*N*-phosphonomethylglycine), the active ingredient of the herbicide Roundup. It works by specifically inhibiting the 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, the sixth enzyme of the shikimate pathway.[3] Numerous analogues of shikimate pathway intermediates have been synthesised,[4,5] among which the fluorinated analogues have provided important insights into the mechanisms of several of the enzymes including dehydroquinate synthase,[5h] type I and II dehydroquinase,[5j,k] EPSP synthase[5d] and chorismate synthase.[5b]



DAH

To date extensive studies have yet to deliver a potent inhibitor of the 'upstream' enzymes of the shikimate pathway. Consideration of these results suggests the need for an alternative avenue for the search of pathway inhibitors, we therefore directed our attention to the study of inhibitors of the early intermediates in the shikimate pathway. Here we examined the synthesis of analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) as potential inhibitors for the enzymes of type II dehydroquinase and shikimate kinase,[6] and report on our synthesis of difluorinated analogues of DAH which are expected to have modified biological activities due to the replacement of hydrogen by fluorine atoms.

We have synthesised both enantiomers of the difluorinated DAH analogues. Treatment of D-ribose **1** in acetone with a small amount of concentrated hydrochloric acid gave the acetonide (90%) which was reduced with sodium borohydride and then oxidised with sodium periodate in one-pot to yield the L-erythrose derivative **2** in 80% yield (Scheme 1). Deprotection of compound **2** with aqueous acetic acid gave

Keywords: Reformatsky reaction; Shikimate pathway; Carbohydrate; Fluorinated ulosonates; Enzyme inhibitors.
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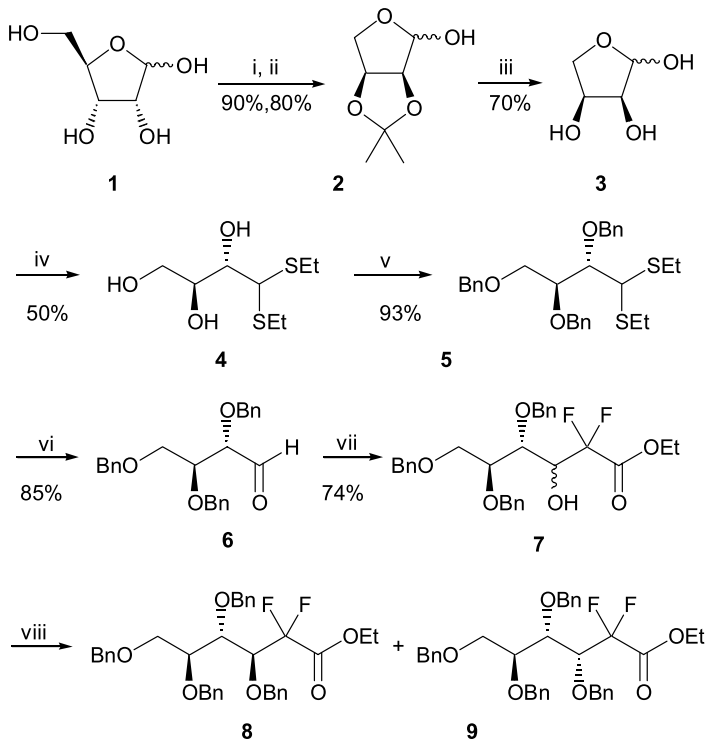
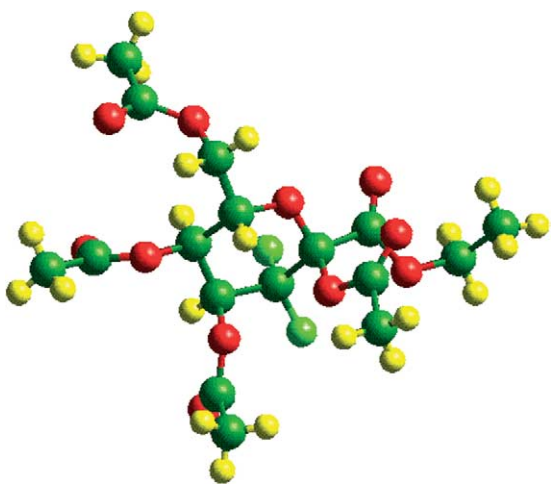


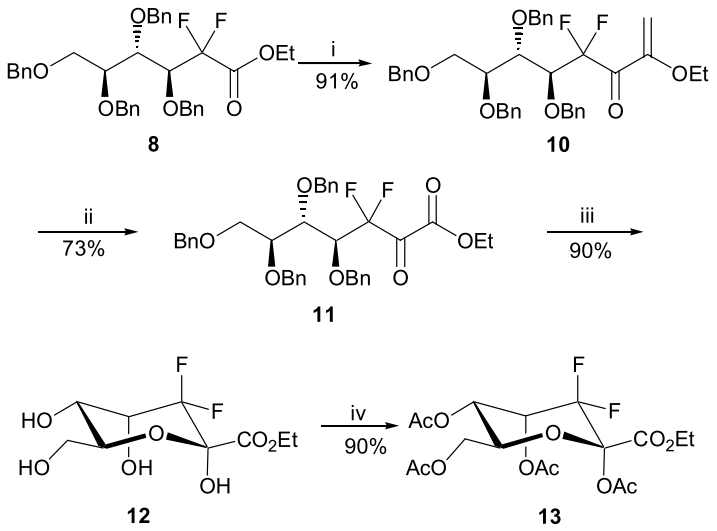
Scheme 1. Reagents and conditions: (i) acetone, conc. HCl (cat.), rt, 4 h; (ii) $NaBH_4$, MeOH–H_2O, 0 °C, 1 h, then $NaIO_4$, rt, 1 h; (iii) aq. HOAc, 4 h; (iv) conc. HCl, EtSH, rt, 2 h; (v) BnBr, NaH, DMF, rt, 8 h; (vi) $HgCl_2$, $CaCO_3$, MeCN–H_2O, rt, 3 h; (vii) Zn, $BrCF_2CO_2Et$, THF, reflux, 2 h; (viii) BnBr, NaH, DMF, rt, 8 h, 68% for **8** and 17% for **9**.

the free L-erythrose **3** (70%). Its diethyl dithioacetal **4** was prepared by treatment of L-erythrose with ethanethiol and concentrated hydrochloric acid. Benzylation of the hydroxyl groups in **4** with excess of benzyl bromide and sodium hydride gave the tri-*O*-benzyl derivative **5** (93%). Dethioacetalisation of compound **5** with mercury (II) chloride and calcium carbonate in aqueous acetonitrile provided the aldehyde **6** in 85% yield. With the aldehyde **6** available we examined its reaction under Reformatsky conditions with ethyl bromodifluoroacetate.[7] The reaction afforded alcohol **7** as a mixture of diastereoisomers in a yield of 74%. Our attempts to separate the diastereoisomers by flash chromatography were unsuccessful. However, further protection of alcohol **7** with benzyl bromide enabled the separation of the subsequent two diastereoisomers **8** and **9** in a ratio of ca. 3:1. At this juncture, we presumed that the major product **8** was the *syn* isomer. This assumption was based on literature precedence that gave support to a α-chelation transition state during the addition of the nucleophile to the carbonyl group, which often results in the *syn* isomer being formed as the major product.[7a,b,8] However, in our case this assumption was proved to be erroneous, as shown by our subsequent structural elaboration and data analysis (Scheme 2).

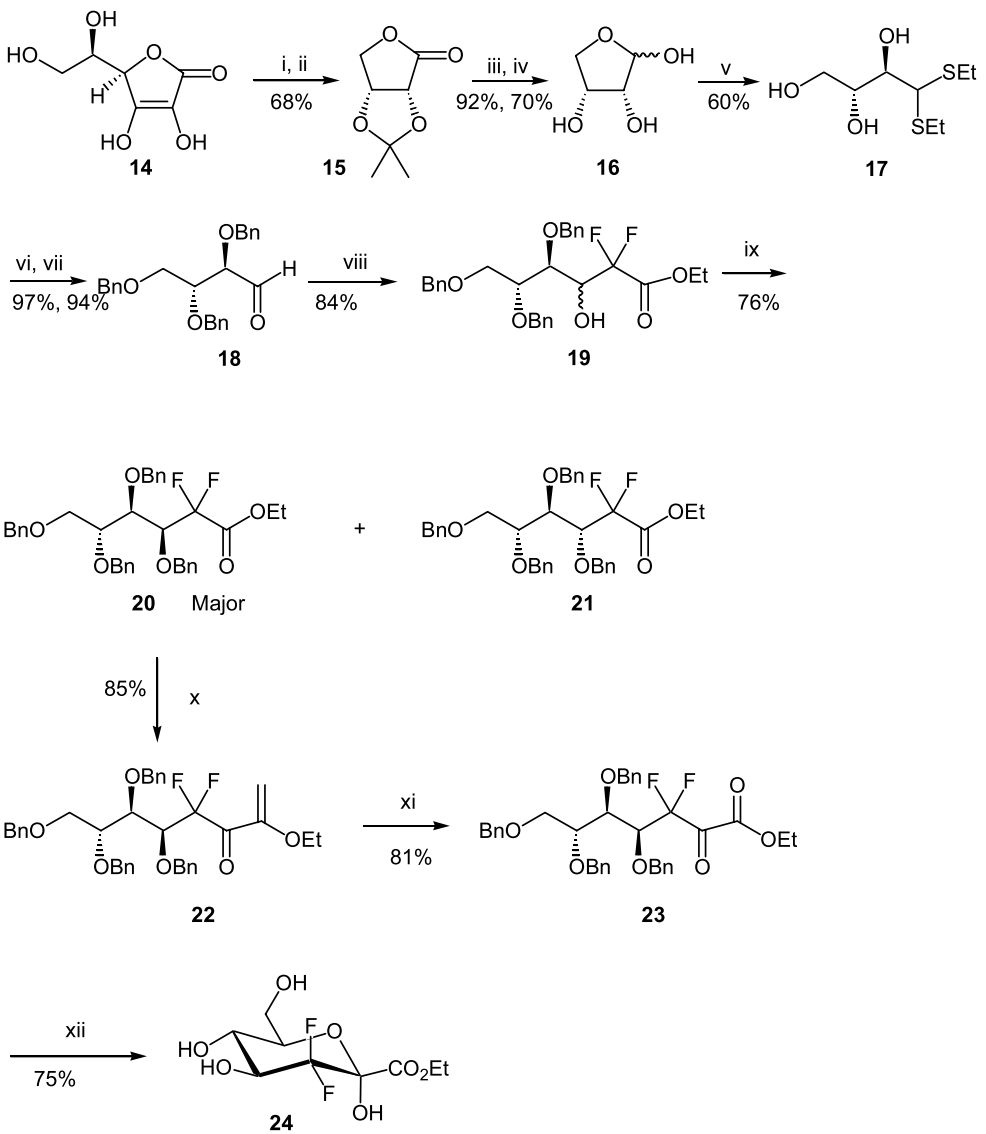


The major isomer **8** was treated with 1-ethoxyvinyllithium that was generated by treating ethyl vinyl ether with *tert*-butyllithium in tetrahydropyran to yield the intermediate ketone **10** in a yield of 91%.[9] Ozonolysis of the double bond in **10** gave the keto ester **11** (73%). Its debenzylation was effected using Pearlman's catalyst under transfer hydrogenation conditions to furnish the ethyl ulosonate **12** (90%) whose complex NMR spectrum made the stereochemical assignment on C-4 very difficult. We therefore converted **12** to tetraacetate **13** by acetylation. The compound **13** was crystalline and that enabled the single crystal X-ray diffraction data to be obtained to establish the stereochemistry at C-4.[10] The result showed that the major isomer **8** was in fact the *anti* isomer and the Reformatsky reaction probably proceeded by the Felkin-Anh transition state rather than an α-chelation one.

Following the above results, we then undertook the same chemistry using D-erythrose **16** as the starting material (Scheme 3). D-Erythrose was obtained from D-isoascorbic acid in four steps using published procedures,[11] and was



Scheme 2. Reagents and conditions: (i) 1-ethoxyvinyllithium, THF, −78 °C, 1 h; (ii) O_3, EtOH–CH_2Cl_2, −78 °C, 1 h, then Me_2S; (iii) $Pd(OH)_2$-C, cyclohexene, EtOH, reflux, 4 h; (iv) Ac_2O, DMAP, pyridine, rt, 2 h.



Scheme 3. Reagents and conditions: (i) Na_2CO_3, H_2O, then H_2O_2, 45 °C, Norit PN5, then aq. HCl; (ii) acetone, $Me_2C(OMe)_2$, *p*-TsOH, $MgSO_4$, rt, 3 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 1 h,; (iv) aq. HOAc, 4 h; (v) conc. HCl, EtSH, rt, 2 h; (vi) BnBr, NaH, DMF, rt, 8 h; (vii) $HgCl_2$, $CaCO_3$, MeCN–H_2O, rt, 3 h; (viii) Zn, $BrCF_2CO_2Et$, THF, reflux, 2 h; (ix) BnBr, NaH, DMF, rt, 8 h; (x) 1-ethoxyvinyllithium, THF, −78 °C, 1 h; (xi) O_3, EtOH–CH_2Cl_2, −78 °C, 1 h, then Me_2S; (xii) $Pd(OH)_2$-C, cyclohexene, EtOH, reflux, 4 h.

then converted to the alcohols **19** by a sequence of reactions similar to those described above. The desired tetra-*O*-benzyl isomer **20** was reacted with 1-ethoxyvinyllithium, followed by ozonolysis and debenzylation to give the difluorinated analogue of DAH **24**. In much the same way that its enantiomer was synthesised from compound **3**.

In summary, we have synthesised the difluorinated analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) from both L- and D-erythrose. These compounds are currently undergoing biological testing, and the results will be reported in due course.

1. Experimental

1.1. General

^{1}H NMR spectra were measured at 270 MHz with JEOL GSX 270 FT NMR spectrometer. Chemical shifts were measured relative to internal tetramethyl silane (δ 0). ^{13}C NMR spectra were recorded at 67.8 MHz on same instrument with internal $(CH_3)_4Si$ (δ 0, $CDCl_3$). IR spectra were recorded on a UNICAM series FT- instrument. Mass spectra were recorded on AEI MS 902 or VG ZAB-E instruments. Melting points were determined on Gallen-Kamp capillary melting point apparatus and are uncorrected. Optical rotations were measured in chloroform solution using Bellingham and Stanley ADP 220 polarimeter. Flash chromatography was performed using Fluka silica gel 60 (230–400 mesh) and the solvent petroleum ether (boiling range 40–60 °C) was distilled prior to use. Thin layer chromatography was carried out using pre-coated aluminium plates (Merck Kieselgel 60 F_{254}) which were visualised under UV light and then with either phosphomolybdic acid or basic aqueous potassium permanganate as appropriate. All anhydrous reactions were carried out under argon or nitrogen. Anhydrous transfers were done with standard syringe techniques, all glassware was pre-dried overnight. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves.

1.1.1. L-Erythro diethyl dithioacetal 4.[12a] L-Erythrose (4 g), was treated with conc. HCl (6 ml) and ethanethiol (6 ml) the resultant mixture was stirred for 3 h at rt. To this mixture water (60 ml) was added and the mixture neutralised by the addition of aq. sodium carbonate. The resultant mixture was extracted with CH_2Cl_2 (3×60 ml). The organic extracts were combined, dried and evaporated to yield L-erythrose diethyl dithioacetal as a syrup (4.6 g). Chromatography on silica gel eluting with light petroleum ether–diethyl ether (1:9) gave L-erythrose diethyl dithioacetal **4** (2.15 g, 31% for two steps) as colourless oil. $[\alpha]_D=-16.0$ (*c* 1.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3411. δ_H (270 MHz, $CDCl_3$) 1.19–1.25 (6H, t, *J*=7.4 Hz, 2×CH_2CH_3), 2.54–2.76 (4H, m, 2×CH_2CH_3), 3.77–3.85 (5H, m), 4.09 (1H, s, O*H*), 4.10 (1H, s, O*H*), 4.14 (1H, s, O*H*); δ_C (67.8 MHz, $CDCl_3$) 14.3, 14.5 (2C, 2×CH_3CH_2), 25.2, 25.3 (2C, 2×CH_2CH_3), 54.4 (*C*HSEtSEt), 63.3 (CH_2OH), 71.8 ($CH_2OHCHOHCHOH$), 73.6 ($CH_2OHCHOH$); *m/z* HRMS (CI, NH_3) found: 244.1039 $[M+NH_4]^+$ $C_8H_{22}NO_3S_2$ requires 244.1041.

1.1.2. 2,3,4-Tri-*O*-benzyl-L-erythro diethyl dithioacetal 5. A stirred, cooled (0 °C) solution, of **4** (2.15 g, 9.5 mmol) in 35 ml of dry DMF was treated with 2.27 g of sodium hydride (60% dispersion in mineral oil, 56.8 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (7.04 g, 41.2 mmol, 4.9 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (100 ml) and ethyl acetate (100 ml). The aqueous phase was extracted further with EtOAc (2×100 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford to afford **5** (4.65 g, 99%) as a colourless oil. $[\alpha]_D=-26.7$ (*c* 1.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3087, 1604, 1585, 1051, 1027, 912. δ_H (270 MHz, $CDCl_3$) 1.21–1.26 (3H, t, *J*=7.4 Hz, CH_2CH_3), 1.26–1.31 (3H, t, *J*=7.4 Hz, CH_2CH_3), 2.63–2.77 (4H, m, 2×CH_2CH_3), 3.68–3.73 (1H, dd, *J*=4.0, 10.6 Hz, C*H*HOBn), 3.81–3.85 (1H, dd, *J*=2.3, 10.6 Hz, CH*H*OBn), 3.99–4.04 (1H, ddd, *J*=2.3, 4.0, 7.9 Hz, C*H*OBnCH_2OBn), 4.06–4.10 (1H, dd, *J*=2.5, 7.9 Hz, C*H*OBnCHOBnCH_2OBn), 4.27–4.28 (1H, d, *J*=2.5 Hz, C*H*SEtSEt), 4.57–4.99 (6H, m, 3×CH_2Ph) and 7.25–7.38 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.4, 14.5 (2C, 2×CH_2CH_3), 24.9, 26.0 (2C, 2×CH_2CH_3), 53.7 (*C*HSEtSEt), 68.5 (CH_2OBn), 72.3, 73.3, 75.0 (3C, 3×CH_2Ph), 78.9 (CH_2OBnCHOBn*C*HOBn), 81.8 (CH_2OBn*C*HOBn), 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3 (15C, phenyl *C*H), 138.2, 138.3 and 138.4 (3C, phenyl *C*).

1.1.3. 2,3,4-Tri-*O*-benzyl-L-erythrose 6. A solution of 2,3,4-tri-*O*-benzyl-L-erythrose diethyl dithioacetal **5** (3.7 g, 7.45 mmol) in 80 ml of CH_3CN/H_2O (4:1) was treated with $HgCl_2$ (5.06 g, 18.63 mmol) and $CaCO_3$ (2.12 g, 21.16 mmol), and the mixture stirred for 2 h. The mixture was filtered and the filtrate concentrated. The residue was treated with 180 ml of CH_2Cl_2, washed with 150 ml KI (1% aqueous solution). The aqueous layer was further extracted with CH_2Cl_2 (2×100 ml). The organic layers were combined and washed again with 100 ml of KI (1% aqueous solution) and water (2×100 ml). The organic layer were dried, (Na_2SO_4), and evaporated to give a residue which was purified by column chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) to afford **6** (2.47 g, 85%) as a colourless oil. $[\alpha]_D=0$; ν_{max} (film)/cm^{-1} 3087, 1731, 1604, 910. δ_H (270 MHz, $CDCl_3$) 3.68–3.73 (1H, dd, *J*=5.3, 9.9 Hz, C*H*HOBn), 3.80–3.86 (1H, dd, *J*=6.6, 9.9 Hz, CH*H*OBn), 4.04–4.10 (1H, ddd, *J*=3.6, 6.6, 9.9 Hz, C*H*OBnCH_2OBn), 4.15–4.17 (1H, dd, *J*=1.5, 3.6 Hz, C*H*OBnCHOBnCH_2OBn), 4.49–4.85 (6H, m, 3×CH_2Ph), 7.26–7.42 (15H, m, *Ph*) and 9.77–9.78 (1H, d, *J*=0.7 Hz, C*H*O); δ_C (67.8 MHz, $CDCl_3$) 67.9 (CH_2OBn), 72.29, 72.9, 73.2 (3C, 3×CH_2Ph), 78.8 (CH_2OBn*C*HOBn), 82.6 (CH_2OBnCHOBn*C*HOBn), 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4 (15C, phenyl *C*H), 137.2, 137.6, 137.7 (3C, phenyl *C*) and 201.7 (C-1).

1.1.4. 4,5,6-Tri-*O*-benzyl-L-erythro 2-deoxy-2,2-difluoro ethyl acetates 7. To a refluxing suspension of activated zinc dust (0.505 g, 7.72 mmol) in dry THF (20 ml) was added ethyl bromodifluoroacetate (1.18 g, 0.74 ml, 5.79 mmol). After 1 min, a solution of 2,3,4-tri-*O*-benzyl-L-erythrose (1.51 g, 3.86 mmol) dissolved in 10 ml of THF was added dropwise, over 15 min. After complete addition the reaction was refluxed for a further 2 h. The mixture was cooled to rt and carefully poured into 20 ml 1 M HCl and 20 g of ice. Stirring of the resultant mixture was continued until all of the ice had melted. The mixture was extracted with EtOAc (3×100 ml). The organic layers were combined and washed with saturated $NaHCO_3$ (2×100 ml) and sat. aq. NaCl (2×100 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue. Chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) gave **7** (two diastereoisomers not separable) (1.48 g, 74%) as a colourless oil. $[\alpha]_D$=+10.1 (*c* 1.3 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3450, 3089, 1770, 1606, 1587, 1093, 1027, 912.

Major diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.11–1.16 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.47–3.49 (1H, d, *J*=5.1 Hz, O*H*), 3.67–3.73 (1H, dd, *J*=5.0, 10.1 Hz, CH*H*OBn), 3.82–3.88 (1H, dd, *J*=4.6, 10.1 Hz, C*H*HOBn), 3.92–4.08 (4H, m), 4.44–4.75 (7H, m, 3×CH_2Ph and C*H*OH) and 7.16–7.40 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.5 (CH_2CH_3), 68.9 (CH_2OB_n), 70.6–71.3 (1C, dd, $J_{(C,F)}$=22.8, 23.6 Hz, *C*HOH), 72.6, 73.4, 73.5 (3C, 3×*C*H_2Ph), 77.9, 78.6 (2C, 2×*C*HOBn), 110.7–118.2 (1C, dd, $J_{(C,F)}$=251.0, 257.1 Hz, CF_2CO_2), 127.6, 127.7, 127.8, 128.0, 128.2, 128.4 and 128. 5 (15C, phenyl *C*H), 137.5 (2C), 137.9 (3C, phenyl *C*) and 162.6–163.6 (1C, t, $J_{(C,F)}$=31.4 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.15 Hz), 123.5–124.61 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 532.2514 $[M+NH_4]^+$ $C_{29}H_{36}F_2NO_6$ requires 532.2511.

Minor diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.22–1.27 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.31–3.35 (1H, d, *J*=10.4 Hz, O*H*), 3.70–3.81 (2H, m, CH_2OBn), 3.92–4.09 (2H, m, 2×C*H*OBn), 4.23–4.29 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.46–4.76 (7H, m) and 7.26–7.35 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.8 (CH_2CH_3), 63.0 (CH_2CH_3), 67.6 (CH_2OBn), 69.5 (1C, t, $J_{(C,F)}$=23.6, *C*HOH), 72.5, 73.4, 73.9 (3C, 3×*C*H_2Ph), 77.9, 78.6 (2C, 2×*C*HOBn), 110.8–118.3 (1C, dd, $J_{(C,F)}$=261.4, 267.8, CF_2CO_2), 127.7–130.9 (15C, phenyl *C*H), 137.3, 137.8, 137.9 (3C, phenyl *C*) and 163.1–163.9 (1C, t, $J_{(C,F)}$=30.4 Hz, CF_2CO_2).

1.1.5. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro ethyl acetate 8,9. A stirred, cooled (0 °C) solution, of **7** (2.56 g, 5.0 mmol) in 60 ml of dry DMF was treated with 0.46 g of sodium hydride (60% dispersion in mineral oil, 10.15 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (1.30 g, 7.6 mmol, 0.9 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (150 ml) and ethyl acetate (150 ml). The aqueous phase was extracted further with EtOAc (2×150 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford two diastereoisomers: 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythrose ethyl acetate (2.54 g, 85%) (ratio, major/minor, 3.2:1) as colourless oils.

Less polar **8** (*anti product*). $[\alpha]_D$=−3.1 (*c* 0.98 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3089, 1772, 1606, 1587, 1095, 1027, 910. δ_H (270 MHz, $CDCl_3$) 1.01–1.06 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.62–3.81 (3H, m), 3.84–4.00 (3H, m), 4.35–4.83 (8H, m, 4×CH_2Ph), 4.48–4.53 (1H, dd, *J*=3.3, 9.1 Hz, C*H*OBnCF$_2$) and 7.18–7.34 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.3 (CH_2CH_3), 70.1 (CH_2OBn), 72.6, 73.3, 73.4, 75.4–75.4 (1C, d, $J_{(C,F)}$=4.2 Hz) (4C, 4×*C*H_2Ph), 77.2, 77.9, 78.3 (3C, 3×*C*HOBn), 111.8–119.3 (1C, dd, $J_{(C,F)}$=257.9, 259.6 Hz, CF_2CO_2), 127.6, 127.9, 128.2, 128.3, 128.7, 128.8, 128.9 and 129.6 (20C, phenyl *C*H), 137.3, 137.5, 138.1, 138.4 (4C, phenyl *C*) and 162.5–163.4 (1C, dd, $J_{(C,F)}$=32.5, 32.7 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 622.2973 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

More polar **9** (*syn product*). $[\alpha]_D$=0 (*c* 0.58 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3089, 1764, 1606, 1587, 1027, 910. δ_H (270 MHz, $CDCl_3$) 1.16–1.21 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.63–3.71 (1H, m), 3.78–3.87 (2H, m), 4.07–4.16 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.26–4.46 (2H, m), 4.48–4.75 (8H, m, 4×CH_2Ph) and 7.10–7.33 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.7 (CH_2CH_3), 62.8 (CH_2CH_3), 68.4 (CH_2OBn), 71.8, 73.3, 74.2, 74.9 (4C, 4×*C*H_2Ph), 76.5, 77.8, 78.1 (3C, 3×*C*HOBn), 111.2–118.7 (1C, dd, $J_{(C,F)}$=254.0, 260.0 Hz, CF_2CO_2), 127.4, 127.6, 127.7, 127.8, 127.8, 128.0, 128.1, 128.2, 128.3, 128.5 and 128.8 (20C, phenyl *C*H), 137.6, 138.1, 138.2, 138.2 (4C, phenyl *C*) and 162.9–163.8 (1C, t, $J_{(C,F)}$=31.0 Hz, CF_2CO_2); δ_F(67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 622.2990 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

1.1.6. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro vinyl ether 10. To a stirred, cooled (−78 °C) solution, of ethyl vinyl ether (0.62 g, 8.64 mmol, 0.8 ml) in tetrahydropyran (THP, 3 ml), *t*-BuLi (6.64 mmol, 1.7 M, 3.9 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to −3 to −5 °C, and stirred for a further 30 min. Following this the mixture was recooled to −78 °C, diluted with THF (6.0 ml) and treated with **21** (0.80 g, 0.95 mmol) in THF (1 ml). After stirring for 1 h at −78 °C, the reaction mixture was poured into water 20 ml) and evaporated under reduced pressure. The resultant residue was partitioned between water (150 ml) and EtOAc (150 ml). The aqueous phase was extracted with EtOAc (2×150 ml) and the combined organics dried (Na_2SO_4), and evaporated to give a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford 2-deoxy-2, 2-difluoro-3, 4, 5, 6-tetra-*O*-benzyl-L-erythro vinyl ether **10** (1.58 g, 90%) as colourless oil.

$[\alpha]_D$=+26.9 (*c* 1.25 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3031, 2927, 1729 (C=O), 1610 (C=C) and 1101. δ_H (270 MHz, $CDCl_3$) 1.20 (3H, t, *J*=6.9 Hz, CH_2CH_3), 3.56–3.72 (4H, m), 3.79 (1H, d, *J*=9.7 Hz), 4.00 (1H, t, *J*=5.7 Hz), 4.26 (1H, d, *J*=10.9 Hz, CHPh), 4.36–4.42 (3H, m, 3×CHPh), 4.53 (1H, d, *J*=11.1 Hz, CHPh), 4.62–4.68 (3H, m, 2×CHPh and C=CH), 4.79 (1H, ddd, *J*=3.1, 9.8, 21.4 Hz), 4.88 (1H, d, *J*=10.7 Hz, CHPh), 5.10 (1H, d, *J*=2.6 Hz, C=CH) and 7.10–7.29 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 63.9 (CH_2CH_3), 70.5 (CH_2OB_n), 72.2 (CH_2Ph), 72.8 (CH_2Ph), 73.2 (CH_2Ph), 75.2 (1C, d, $J_{(C,F)}$=4.4 Hz, CH_2Ph); 77.8 (CHOBn), 78.1 (CHOBn), 78.7 (CHOBn), 94.5 (C=CH_2), 118.1 (1C, dd, $J_{(C,F)}$=251.6, 257.5 Hz, CF_2CO_2), 127.5–128.3 (20C, phenyl CH), 137.2 (phenyl *C*), 137.4 (phenyl *C*), 138.2 (phenyl *C*), 138.6 (phenyl *C*), 155.0 (C=CH_2) and 181.9 (1C, t, $J_{(C,F)}$=26.5 Hz, CF_2CO_2); δ_F (282.4MHz, $CDCl_3$) 113.0 (1F, d, *J*=257.2 Hz), 124.1 (1F, dd, *J*=19.1, 263.5 Hz); *m*/*z* (CI, NH_3) $[M+NH_4]^+$ found: 648.3140 $C_{38}H_{44}F_2NO_6$ requires 648.3137.

1.1.7. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro-keto ethylacetate 11. The vinyl ether **10** (1.18 g, 1.87 mmol) was dissolved in 16 ml CH_2Cl_2–EtOH (1:1). The solution was ozonolysised at −78 °C. The production of the ozonide was determined by monitoring the presence of an excess of ozone using starch-KI paper. After 1 h of stirring, the reaction was quenched by the addition of 4 ml Me_2S at −78 °C. The reaction mixture was warmed to rt and evaporated under vacuum. The residue was partitioned between water (100 ml) and EtOAc (100 ml), and the aqueous layer extracted further with EtOAc (2×100 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was subjected to chromatography, silica gel, eluting with light petroleum ether–diethyl ether (2:1) to afford 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro-keto ethylacetate **11** (0.86 g, 73%) as a colourless oil. $[\alpha]_D$=+6.0 (*c* 1.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 1758, 1737, 1606, 1587, 975, 912. δ_H (270 MHz, $CDCl_3$) 1.01–1.07 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.60–3.63 (1H, d, *J*=5.8 Hz), 3.67–3.75 (1H, m), 3.76–3.80 (1H, d, *J*=10.1 Hz), 3.85–4.18 (3H, m), 4.42–4.98 (8H, m, 4×CH_2Ph), 4.92–5.05 (1H, ddd, *J*=3.9, 10.6, 21.6 Hz, CHOBnCF_2) and 7.09–7.31 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.4 (CH_2CH_3), 62.6 (CH_2CH_3), 69.8 (CH_2OBn), 72.3, 72.8, 73.3, 75.4 (1C, d, $J_{(C,F)}$=3.9 Hz) (4C, 4×CH_2Ph), 77.8, 78.1, 78.1 (3C, 3×CHOBn), 113.3–120.7 (1C, dd, $J_{(C,F)}$=250.7, 258.4 Hz, CF_2CO_2), 127.5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.0, 128.1, 128.3, 128.3, 128.5, 128.5 and 128.8 (20C, phenyl CH), 136.2, 137.2, 138.0, 138.2 (4C, phenyl *C*), 158.3 ($CF_2COCOOC_2H_5$) and 174.8–175.6 (1C, t, $J_{(C,F)}$=28.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz);); *m*/*z* (ES+) [M+Na] found: 655.2488.$C_{37}H_{38}F_2O_7Na$ requires 655.2483.

1.1.8. 3-Deoxy-3,3-difluoro-2,4,5,6-tetra-*O*-acetyl-L-*arabino*-hept-2-ethylulosonate 13. The ester **11** (0.37 g, 0.58 mmol) was dissolved in ethanol (8 ml). To the resultant solution $Pd(OH)_2$-C (30 mg) and cyclohexene (2 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude 3-deoxy-3,3-difluoro-L-*arabino*-hept-2-ethylulosonate which was utilised without further purification. The crude product was treated with pyridine (4 ml) and acetic anhydride (2 ml). The whole mixture was shaken into clear solution and maintained at a temperature range of 0–4 °C for 12 h. Water (2 ml) was added into the mixture to destroy the excess acetic anhydride. The mixture was partitioned between H_2SO_4 (2.5 M) (50 ml) and CH_2Cl_2 (50 ml). The aqueous phase was extracted with CH_2Cl_2 (2×50 ml). The organic layers was combined, washed with saturated $NaHCO_3$ (50 ml) and sat. aq. NaCl (50 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue which was purified by column chromatography, silica gel, eluting with diethyl ether to afford the title compound (0.21 g, 82%). $[\alpha]_D$=−69.1 (*c* 1.03, $CHCl_3$); ν_{max} (film)/cm^{-1} 2983, 1756 1083. δ_H (270 MHz, $CDCl_3$) 1.30 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.02 (3H, s, OCOCH_3), 2.08 (3H, s, OCOCH_3), 2.22 (6H, s, 2×OCOCH_3), 4.21–4.88 (5H, m), 5.19 (1H, d, *J*=8.7 Hz, CF_2CHOAcCHOAc) and 5.72 (1H, ddd, *J*=3.5, 5.8, 9.2 Hz, CF_2CHOAc); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 20.1 (OCOCH_3), 20.2 (OCOCH_3), 20.3 (OCOCH_3), 20.4 (OCOCH_3), 61.2 (CH_2CH_3), 64.1 (1C, d, *J*=3.9 Hz, CF_2CHOAcCHOAc), 67.0 (AcOCH_2CH), 67.3 (1C, dd, *J*=24.9, 34.5 Hz, CF_2CHOAc), 93.7 (1C, dd, *J*=27.5, 35.0 Hz, OCOAc$CO_2C_2H_5$), 112.2 (1C, dd, $J_{(C,F)}$=251.6, 270.0 Hz, CF_2), 161.7 (1C, d, $J_{(C,F)}$=1.6 Hz, $CO_2C_2H_5$), 167.0 (OCOCH$_3$), 168.6 (OCOCH$_3$), 168.8 (OCOCH$_3$) and 170.6 (OCOCH$_3$); δ_F (282.4 MHz, $CDCl_3$) 116.5 (1F, dd, *J*=2.0, 6.0 Hz), 116.8 (1F, d, *J*=6.0 Hz); *m*/*z* (CI, NH_3) $[M+NH_4]^+$ found: 458.1477 $C_{17}H_{26}F_2NO_{11}$ requires 458.1474.

1.1.9. D-Erythro-diethyl dithioacetal 17.[12a] D-Erythrose **16** (3.78 g), was treated with conc. HCl (6 ml) and ethanethiol (6 ml) were stirred for 3 h at rt. To this mixture water (60 ml) was added and the mixture neutralised by the addition of aq. sodium carbonate. The resultant mixture was extracted with CH_2Cl_2 (3×60 ml). The organic extracts were combined, dried and evaporated to yield D-erythro-diethyl dithioacetal as a syrup (4.6 g). Chromatography, silica, eluting with light petroleum ether–diethyl ether (1:9) gave D-erythro-diethyl dithioacetal **17** (2.63 g, 40% for two steps) as colourless oil. $[\alpha]_D$=+16.8 (*c* 0.97, $CHCl_3$); ν_{max} (film)/cm^{-1} 3411, 2965, 1644. δ_H (270 MHz, $CDCl_3$) 1.19–1.25 (6H, t, *J*=7.4 Hz, 2×CH_2CH_3), 2.54–2.76 (4H, m, 2×CH_2CH_3), 3.77–3.85 (5H, m), 4.09 (1H, s, OH), 4.10 (1H, s, OH), 4.14 (1H, s, OH); δ_C (67.8 MHz, $CDCl_3$) 14.3, 14.5 (2C, 2×CH_3CH_2), 25.2, 25.3 (2C, 2×CH_2CH_3), 54.4 (CHSEtSEt), 63.3 (CH_2OH), 71.8 ($CH_2OHCHOHCHOH$), 73.6 ($CH_2OHCHOH$).

1.1.10. 2,3,4-Tri-*O*-benzyl-D-erythrose 18.[12b] A stirred, cooled, (0 °C), solution, of **17** (2.63 g, 11.6 mmol) in 40 ml of dry DMF was treated with 2.77 g of sodium hydride (60% dispersion in mineral oil, 69.3 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (8.59 g, 50.2 mmol, 6.0 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in

order to destroy the excess of sodium hydride. Following this, the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (100 ml) and ethyl acetate (100 ml). The aqueous phase was extracted further with EtOAc (2×100 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified by chromatography, silica, eluting with light petroleum ether–diethyl ether (10:1) to afford the 2,3,4-tri-*O*-benzyl-D-erythro-diethyl dithioacetal (5.60 g, 97%) as colourless oil. $[\alpha]_D$=+27.1 (*c* 0.94, $CHCl_3$); ν_{max}(film)/cm^{-1} 3087, 3062, 1604. δ_H (270 MHz, $CDCl_3$) 1.16–1.21 (3H, t, *J*=7.4 Hz, CH_2CH_3), 1.21–1.26 (3H, t, *J*=7.4 Hz, CH_2CH_3), 2.58–2.71 (4H, m, 2×CH_2CH_3), 3.63–3.69(1H, dd, *J*=4.0, 10.6 Hz, C*H*HOBn), 3.76–3.81 (1H, dd, *J*=2.3, 10.6 Hz, CH*H*OBn), 3.94–4.05 (1H, ddd, *J*=2.3, 3.9, 7.9 Hz, C*H*OBnCH$_2$OBn), 4.01–4.05 (1H, dd, *J*=2.5, 7.9 Hz, C*H*OBnCHOBnCH$_2$OBn), 4.21–4.22 (1H, d, *J*=2.6 Hz, C*H*SEtSEt), 4.52–4.94 (6H, m, 3×CH_2Ph) and 7.12–7.33 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.4, 14.5 (2C, 2×CH_2CH_3), 24.9, 26.1 (2C, 2×CH_2CH_3), 53.7 (*C*HSEtSEt), 68.6 (CH_2OBn), 72.4, 73.3, 75.0 (3C, 3×CH_2Ph), 78.9 (CH$_2$OBnCHOBn*C*HOBn), 81.9 (CH$_2$OBn*C*HOBn), 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3, 128.4 (15C, phenyl *C*H) and 138.3, 138.3 and 138.4 (3C, phenyl *C*).

A solution of 2,3,4-tri-*O*-benzyl-D-erythrose diethyl dithioacetal (5.5 g, 11.1 mmol) in 125 ml of CH_3CN/H_2O (4:1) was treated with $HgCl_2$ (7.51 g, 27.7 mmol) and $CaCO_3$ (3.15 g, 31.5 mmol), and the mixture stirred for 2 h. The mixture was filtered and the filtrate concentrated. The residue was treated with 180 ml of CH_2Cl_2, washed with 150 ml KI (1% aqueous solution). The aqueous layer was further extracted with CH_2Cl_2 (2×100 ml). The organic layers were combined and washed again with 100 ml of KI (1% aqueous solution) and water (2×100 ml). The organic layers were dried, (Na_2SO_4), and evaporated to give a residue (4.3 g, 99.5%) which was directly used to next step.

1.1.11. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro ethyl acetate 20, 21. To a refluxing suspension of activated zinc dust (1.37 g, 21.0 mmol) in dry THF (35 ml) was added ethyl bromodifluoroacetate (3.20 g, 2.02 ml, 15.75 mmol). After 1 min, a solution of 2,3,4-tri-*O*-benzyl-D-erythrose (4.30 g, 11.0 mmol) dissolved in 15 ml of THF was added dropwise, over 15 min. After complete addition the reaction was refluxed for a further 2 h. The mixture was cooled to rt and carefully poured into 50 ml 1 M HCl and 50 g ice. Stirring of the resultant mixture was continued until all of the ice had melted. The mixture was extracted with EtOAc (3×100 ml). The organic layers were combined and washed with saturated $NaHCO_3$ (2×100 ml) and sat. aq. NaCl (2×100 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue. Chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) gave two diastereoisomers **19**, (not separable) (4.49 g, 79% for two steps) as colourless oils; ν_{max} (film)/cm^{-1} 3450, 3089, 3064, 3031, 2981, 2908, 2871, 1955, 1876, 1770, 1606, 1587, 1496, 1454, 1371, 1311, 1209, 1093, 1027, 912, 852, 746 and 698.

Major diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.11–1.16 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.47–3.49 (1H, d, *J*=5.1 Hz, O*H*), 3.67–3.73 (1H, dd, *J*=5.0, 10.1 Hz, CH*H*OBn), 3.82–3.88 (1H, dd, *J*=4.6, 10.1 Hz, C*H*HOBn), 3.92–4.08 (4H, m), 4.44–4.75 (7H, m, 3×CH_2Ph and C*H*OH) and 7.16–7.40 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.5 (CH_2CH_3), 68.9 (CH_2OB_n), 70.6–71.3 (1C, dd, $J_{(C,F)}$= 22.8, 23.6 Hz, *C*HOH), 72.6, 73.4, 73.5 (3C, 3×CH_2Ph), 77.9, 78.6 (2C, 2×*C*HOB$_n$), 110.7–118.2 (1C, dd, $J_{(C,F)}$= 251.0, 257.1 Hz, CF_2CO_2), 127.6, 127.7, 127.8, 128.08, 128.2, 128.4 and 128. 5 (15C, phenyl *C*H), 137.5 (2C), 137.9 (3C, phenyl *C*) and 162.6–163.6 (1C, t, $J_{(C,F)}$=31.4 Hz, CF_2CO_2).

Minor diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.22–1.27 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.31–3.35 (1H, d, *J*=10.4 Hz, O*H*), 3.70–3.81 (2H, m, CH_2OBn), 3.92–4.09 (2H, m, 2×C*H*OBn), 4.23–4.29 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.46–4.76 (7H, m) and 7.26–7.35 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.8 (CH_2CH_3), 63.0 (CH_2CH_3), 67.6 (CH_2OB_n), 69.5 (1C, t, $J_{(C,F)}$=23.6 Hz, *C*HOH), 72.5, 73.4, 73.9 (3C, 3×CH_2Ph), 77.9, 78.6 (2C, 2×*C*HOB$_n$), 110.8–118.3 (1C, dd, $J_{(C,F)}$=261.4, 267.8 Hz, CF_2CO_2), 127.7–130.9 (15C, phenyl *C*H), 137.3, 137.8, 137.9 (3C, phenyl *C*) and 163.1–163.9 (1C, t, $J_{(C,F)}$=30.4 Hz, CF_2CO_2).

A stirred, cooled (0 °C) solution, of the above mixture of daistereoisomers (3.0 g, 5.83 mmol), in 60 ml of dry DMF, was treated with 0.46 g of sodium hydride (60% dispersion in mineral oil, 10.15 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (1.50 g, 8.75 mmol, 1.0 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (150 ml) and ethyl acetate (150 ml). The aqueous phase was extracted further with EtOAc (2×150 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford two diastereoisomers: 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose ethyl acetate **20**, **21** (2.69 g, 76%) (major/minor, 3.6:1) as colourless oils.

Less polar (*anti product*). $[\alpha]_D$=0; ν_{max}(film)/cm^{-1} 3089, 3064, 1760, 1606, 1587, 910. δ_H (270 MHz, $CDCl_3$) 3.34 (3H, s, CH_3), 3.61–3.73 (2H, m, CH_2OBn), 3.87–3.90 (1H, d, *J*=9.2 Hz, CH$_2$OBnCHOBnC*H*OBn), 3.96–4.00 (1H, t, *J*=5.6 Hz, CH$_2$OBnC*H*OBn), 4.48–4.52 (1H, dd, *J*=3.2, 9.1 Hz, C*H*OBnCF$_2$), 4.38–4.83 (8H, m, 4×CH_2Ph) and 7.13–7.35 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 52.6 (CH_3), 70.0 (CH_2OB_n), 72.7, 73.3, 73.5, 75.4–75.5 (1C, d, $J_{(C,F)}$=4.4 Hz) (4C, 4×CH_2Ph), 77.1–77.7 (1c, t, $J_{(C,F)}$= 21.5 Hz), 78.0–78.1 (1C, d, $J_{(C,F)}$=2.9 Hz), 78.3 (3C, 3×*C*HOB$_n$), 111.9–119.3 (1C, dd, $J_{(C,F)}$=258.3, 264.3 Hz, CF_2CO_2), 127.6, 127.6, 127.7, 127. 9, 128.2, 128.2, 128.2, 128.3 and 128.4 (20C, phenyl *C*H), 137.3, 137.5, 138.2, 138.4 (4C, phenyl *C*) and 163.0–163.9 (1C, t, $J_{(C,F)}$= 31.9 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2

(1F, d, J=257.15 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z HRMS (CI, NH_3) found: 622.2992 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

More polar (*syn product*). $[\alpha]_D$=+3.4 (c 0.89 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 1764, 1606, 1587, 910. δ_H (270 MHz, $CDCl_3$) 3.64 (3H, s, CH_3), 3.67–3.71 (1H, m), 3.79–3.91 (2H, m), 4.05–4.09 (1H, t, J=5.4 Hz), 4.24–4.34 (1H, ddd, J=4.3, 9.6, 13.7 Hz, CHOBnCF_2), 4.42–4.72 (8H, m, 4×CH_2Ph) and 7.11–7.33 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 53.2 (CH_3), 68.5 (CH_2OB$_n$), 71.9, 73.3, 74.2, 75.0 (4C, 4×CH_2Ph), 76.5, 77.6–78.3 (1C, t, J=25.5 Hz), 78.0 (3C, 3×CHOB$_n$), 111.3–118.8 (1C, dd, $J_{(C,F)}$=254.5, 260.0 Hz, CF_2CO_2), 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3 and 128.4 (20C, phenyl *C*H), 137.5, 138.1, 138.2 (2C) (4C, phenyl *C*) and 163.8–164.7 (1C, t, $J_{(C,F)}$=33.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z HRMS (CI, NH_3) found: 622.2985 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

1.1.12. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro vinyl ether 22. To a stirred, cooled (−78 °C) solution, of ethyl vinyl ether (0.74 g, 10.3 mmol, 1.0 ml) in THP (3.5 ml), *t*-BuLi (7.92 mmol, 1.7 M, 4.7 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to −3 to −5 °C, and stirred for a further 30 min. Following this the mixture was recooled to −78 °C, diluted with THF (8.0 ml) and treated with **19** (1.95 g, 3.3 mmol) in THF (3.0 ml). After stirring for 1 h at −78 °C, the reaction mixture was poured into water, (20 ml), and evaporated under reduced pressure. The resultant residue was partitioned between water (150 ml) and EtOAc (150 ml). The aqueous phase was extracted with EtOAc (2×150 ml) and the combined organics dried (Na_2SO_4), and evaporated to give a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford 2-deoxy-2, 2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose vinyl ether **22** (1.48 g, 85%) as colourless oil. $[\alpha]_D$=−23.7 (c 0.9 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 3031, 2979, 2925, 2871, 1953, 1917, 1776, 1731, 1610, 1496, 1454, 1365, 1303, 1216, 1101, 1072, 1027, 973, 854, 738 and 698. δ_H (270 MHz, $CDCl_3$) 1.18–1.23 (3H, t, J=6.9 Hz, CH_2CH_3), 3.55–3.73 (4H, m), 3.77–3.81 (1H, d, J=9.9 Hz), 3.98–4.02 (1H, t, J=5.5 Hz), 4.24–4.28 (1H, d, J=10.9 Hz, CHHPh), 4.33–4.68 (7H, m), 4.72–4.85 (1H, ddd, J=3.3, 9.9, 21.3 Hz), 4.86–4.90 (1H, d, J=10.7 Hz, CHHPh), 5.11–5.12 (1H, d, J=2.6 Hz, C=CHH) and 7.12–7.29 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 63.9 (CH_2CH_3), 70.5 (CH_2OBn), 72.3, 72.9, 73.2, 75.2–75.3 (1C, d, $J_{(C,F)}$=4.2 Hz) (4C, 4×CH_2Ph); 77.8–78.5 (1C, t, $J_{(C,F)}$=20.9 Hz), 77.8–77.9 (1C, d, $J_{(C,F)}$=3.9 Hz), 78.7 (3C, 3×CHOBn), 94.5–94.6 (1C, d, $J_{(C,F)}$=2.3 Hz, C=CH_2), 114.3–121.8 (1C, dd, $J_{(C,F)}$=251.8, 257.6 Hz, CF_2CO_2), 127.5, 127.5, 127.5, 127.7, 127.9, 127.9, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 137.2, 137.4, 138.2, 138.6 (4C, phenyl *C*), 155.1 (C=CH_2) and 181.5–182.3 (1C, t, $J_{(C,F)}$=27.0 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z (CI, NH_3) $[M+NH_4]^+$ found: 648.3142 $C_{38}H_{44}F_2NO_6$ requires 648.3137.

1.1.13. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro-keto-ethylacetate 23. The vinyl ether **22** (1.45 g, 2.3 mmol) was dissolved in 18 ml CH_2Cl_2–EtOH (1:1). The solution was ozonolysized at −78 °C. The production of the ozonide was determined by monitoring the presence of an excess of ozone using starch-KI paper. After 1 h of stirring, the reaction was quenched by the addition of 4 ml Me_2S at −78 °C. The reaction mixture was warmed to rt and evaporated under vacuum. The residue was partitioned between water (100 ml) and EtOAc (100 ml), and the aqueous layer extracted further with EtOAc (2×100 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was subjected to chromatography, silica gel, eluting with light petroleum ether–diethyl ether (3:1) to afford 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose-keto-ethylacetate **23** (1.06 g, 81%) as a colourless oil. $[\alpha]_D$=−8.9 (c 0.8 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 3031, 2925, 2871, 1955, 1878, 1809, 1758, 1737, 1606, 1587, 1496, 1454, 1394, 1369, 1311, 1216, 1103, 1025, 975, 912, 740 and 698. δ_H (270 MHz, $CDCl_3$) 1.01–1.07 (3H, t, J=7.1 Hz, CH_2CH_3), 3.60–3.63 (1H, d, J=5.8 Hz), 3.67–3.75 (1H, m), 3.76–3.80 (1H, d, J=10.1 Hz), 3.85–4.18 (3H, m), 4.42–4.98 (8H, m, 4×CH_2Ph), 4.92–5.05 (1H, ddd, J=3.9, 10.6, 21.6 Hz, CHOBnCF_2) and 7.09–7.31 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.4 (CH_2CH_3), 62.6 (CH_2CH_3), 69.8 (CH_2OBn), 72.3, 72.8, 73.3, 75.4–75.4 (1C, d, $J_{(C,F)}$=3.9 Hz) (4C, 4×CH_2Ph), 77.8, 78.1, 78.1 (3C, 3×CHOBn), 113.3–120.7 (1C, dd, $J_{(C,F)}$=250.7, 258.4 Hz, CF_2CO_2), 127. 5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.0, 128.1, 128.3, 128.3, 128.5, 128.5, 128.8, 136.2, 137.2, 138.0, 138.2 (4C, phenyl *C*), 158.3 ($CF_2COCOOC_2H_5$) and 174.8–175.6 (1C, t, $J_{(C,F)}$=28.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz); m/z (ES+) [M+Na] found: 655.2485.$C_{37}H_{38}F_2O_7Na$ requires 655.2483.

1.1.14. Ethyl-3-deoxy-3,3-difluoro-D-*arabino* ulosonate 24. The keto ester **23** (0.98 g, 1.55 mmol) was dissolved in ethanol (15 ml). To the resultant solution $Pd(OH)_2$-C (100 mg) and cyclohexene (3 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude ethyl-3-deoxy-3,3-difluoro-D-*arabino* ulosonate. Chromatography, silica gel, eluting with ethyl acetate, yielded the title compound **20** (0.30 g, 72%). $[\alpha]_D$=+34.1 (c 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3451, 3359, 2987, 2942, 1745, 1643, 1448, 1396, 1374, 1301, 1284, 1224, 1178, 1095, 919 and 898. δ_H (270 MHz, CD_3OD) 1.29–1.34 (3H, t, J=7.1 Hz, CH_2CH_3), 3.60–3.91 (3H, m), 4.05–4.12 (2H, m), 4.21–4.35 (2H, m) and 4.88 (4H, s, 4×OH); δ_C (67.8 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 62.0 (CH_2CH_3), 63.7 (CH_2OH), 66.1 (CHOCH$_2$-OH), 71.2 (CHOHCHOCH$_2$OH), 72.0–72.8 (1C, t, $J_{(C,F)}$=26.1 Hz, CHOHCF_2), 95.2–96.1 (1C, t, $J_{(C,F)}$=29.7 Hz, COHCO$_2$C$_2$H$_5$), 112.3–119.8 (1C, dd, $J_{(C,F)}$=254.0, 260.2 Hz, CF_2CO$_2$C$_2$H$_5$) and 168.3 (CO_2C$_2$H$_5$); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz); m/z (CI, NH_3) $[M+NH_4]^+$ found: 290.1054 $C_9H_{18}F_2NO_7$ requires 290.1051.

1.1.15. Ethyl 3-deoxy-3,3-difluoro-D-*arabino*-ulosonate, [C-4 diastereomer 24], (*syn* diastereoisomer). The C-4

syn diastereoisomer of **23** (0.11 g, 0.18 mmol) was dissolved in ethanol (8 ml). To the resultant solution $Pd(OH)_2$-C (100 mg) and cyclohexene (2 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude ethyl 3-deoxy-3,3-difluoro-D-*arabino*-ulosonate. Chromatography, silica gel, eluting with ethyl acetate gave the title compound [Diastereomeric **24**] (37 mg, 75%). $[\alpha]_D$=+46.7 (*c* 0.9 in CH_3OH). δ_H (270 MHz, CD_3OD) 1.32 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.74–3.85 (3H, m), 3.98 (1H, ddd, *J*=5.4, 9.4, 21.6 Hz), 4.26–4.33 (3H, m) and 4.94 (4H, s, 4×O*H*); δ_C (67.8 MHz, CD_3OD) 14.3 (CH_2CH_3), 62.0 (CH_2CH_3), 63.7 (CH_2OH), 69.6 (1C, d, $J_{(C,F)}$=7.0 Hz, *C*HOHCHOCH$_2$OH), 72.7 (1C, t, $J_{(C,F)}$=19.2 Hz, *C*HOHCF$_2$), 75.3 (*C*HOCH$_2$OH), 95.3 (1C, t, $J_{(C,F)}$=35.1 Hz, *C*OHCO$_2$C$_2$H$_5$), 118.2 (1C, dd, $J_{(C,F)}$=247.4, 262.5 Hz, *C*F$_2$CO$_2$C$_2$H$_5$) and 168.3 (*C*O$_2$C$_2$H$_5$); δ_F (282.4 MHz, CD_3OD) 122.7 (1F, d, *J*=248.5 Hz), 130.3 (1F, d, *J*=248.5 Hz); *m/z* (CI, NH_3) $[M+NH_4]^+$ found: 290.1052 $C_9H_{18}F_2NO_7$ requires 290.1051.

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10. Crystal data: $C_{17}H_{22}F_2O_{11}$, *M*=440.35, monoclinic, space group C2, *a*=23.77(3) Å, *b*=7.807(12) Å, *c*=14.215(17) Å, β=125.49(1)°, *U*=2148 Å^3, d_{calc}=1.362 g cm^{-3}, *Z*=4. Cambridge crystallographic data reference no. CCDC194839.
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Iodine(III)-mediated aromatic amidation vs olefin amidohydroxylation. The amide *N*-substituent makes the difference☆

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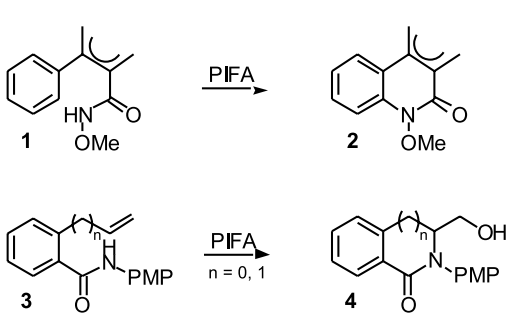
Abstract—A series of *N*-methoxy- and *N-para*-methoxyphenylacetamides simultaneously substituted at the α position by a benzyl and an allyl group have been treated with phenyliodine(III)bis(trifluoroacetate) to generate stabilized *N*-acylnitrenium intermediates. It has been observed that, when starting from *N*-methoxy substituted amides, such intermediates are intramolecularly trapped by nucleophilic arene rings to render the quinolinone skeleton. Alternatively, under the same reaction conditions, *N-para*-methoxyphenylamides afford pyrrolidinone derivatives through an olefin amidohydroxylation process.

1. Introduction

With the aim of developing the enormous potentiality that some hypervalent iodine reagents can provide in organic synthesis,[1] our group started a program directed to expand the applicability of phenyliodine(III)bis(trifluoroacetate) (PIFA) in heterocyclic chemistry.[2] Attracted by the clean transformations usually achieved, the mild conditions employed, and the low toxicity associated to it, we decided to expand the use of this iodine(III) reagent in new synthetic challenges. Thus, we have recently reported the synthesis of different heterocycle-fused quinolinones[3] of type **2** and 1,4-diazepin-2-ones[4] by an electrophilic aromatic amidation process, and the synthesis of the isoquinolinone and isoindolinone skeletons[5] of type **4** by a novel olefin amidohydroxylation reaction promoted by PIFA (see Scheme 1).[6] To explain the observed behavior, it is accepted[7] that when the mildly oxidant I(III) reagent reacts with properly substituted amides *N*-acylnitrenium intermediates are generated. Finally, in the presence of nucleophilic species, the so-obtained electrophilic intermediates are trapped intramolecularly to form new C–N linkages.

During the optimization of both protocols it was found that substitution on the amidic nitrogen played a determinant role in the success of the experiment. Thus, while the aromatic amidation protocol was best carried out on *N*-methoxy substituted amides, as **1** (see Scheme 1), the *N-para*-methoxyphenyl (PMP) substituted amides of type **3** were selected as the derivatives of choice to perform the amidohydroxylation process. Alerted by this intriguing observation, we were aware that a remarkable effect on the chemoselective outcome of the reaction would arise if the nitrenium intermediate were generated on a doubly-benzyl and allyl-substituted *N*-methoxy (or *N-para*-methoxyphenyl) acetamides of type **7** and **8**. According to our expectations, this intermediate would be eventually trapped univocally with only one of the internal nucleophiles. The results presented here will confirm this hypothesis.



Scheme 1. PIFA-mediated aromatic amidation and olefin amidohydroxylation reactions.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.007

Keywords: Hypervalent iodine; Quinolinones; Pyrrolidinones; *N*-acylnitrenium; PIFA.

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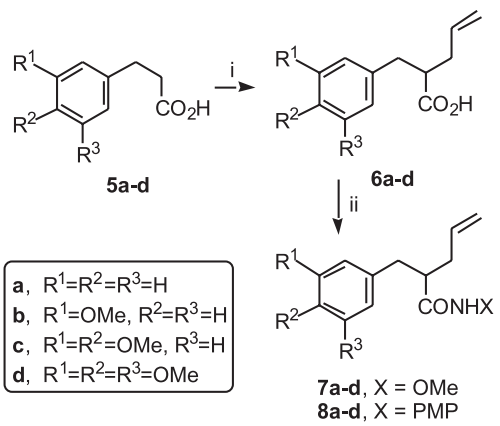
2. Results and discussion

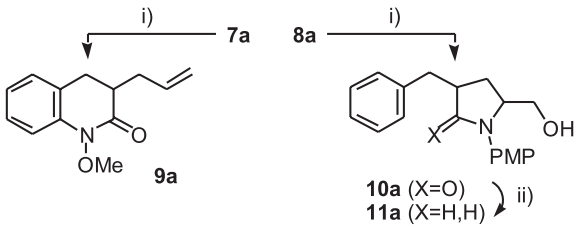
Amide precursors **7** and **8** were prepared (see Scheme 2) in a two-step sequence starting from commercially available hydrocinnamic acids **5a-d**, which were alkylated with allyl bromide under basic (LDA) conditions in good (69–98%) yields. With these substrates in hand, two series of amides were synthesized. Thus, by treatment of carboxylic acids **6a-d** with methoxylamine hydrochloride, amides **7a-d** were easily obtained when the reaction was assisted by the uronium-coupling reagent TBTU.[8] Alternatively, a combination of carbodiimide EDC and hydroxybenzotriazole HOBt was required to optimize the reaction of acids **6a-d** with *para*-anisidine to render amides **8a-d**.[9]



Scheme 2. Reagents and conditions: (i) LDA, AllylBr, THF, 0 °C to rt; (ii) for **7** series: $NH_2OMe{\cdot}HCl$, Et_3N, TBTU, MeCN; (ii) for **8** series: *p*-anisidine, EDC·HCl, Et_3N, HOBt, CH_2Cl_2, rt. Overall yields: 59% for **7a**, 70% for **7b**, 54% for **7c**, 63% for **7d**, 63% for **8a**, 78% for **8b**, 60% for **8c**, 54% for **8d**.

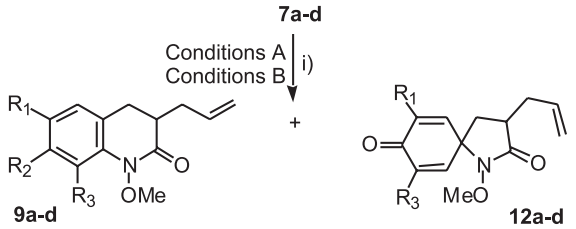
We first examined the behavior of amides **7a** and **8a** under the action of the I(III) reagent. Typically, a solution of 1.5 equiv. of PIFA in CF_3CH_2OH is added to a cold (−20 °C) solution of the amide in the same solvent (~5 mg/mL). When the starting material is consumed (~1 h), the reaction mixture is washed with Na_2CO_3 (10% aq.) and extracted with CH_2Cl_2. Finally, the residue is column chromatographed to afford the final products.

As originally planned, the optimized conditions employed for this transformation led to the construction of the quinolinone skeleton **9a** starting from amide **7a** (see Scheme 3). By altering the temperature and the solvent of the reaction (CH_2Cl_2), lowered yields were obtained but, in all cases, the allylic residue remained intact. Alternatively, amide **8a** was treated with PIFA under the same reaction conditions described above. In this case, the *N*-acyl-nitrenium ion generated was trapped by the olefin fragment with total chemoselectivity to afford pyrrolidinone **10a** in good yield without affecting the integrity of the benzyl group. Due to the instability of this pyrrolidinone compound, a full characterization was carried out on the corresponding reduced derivative **11a**, which was obtained by treatment of the crude **10a** with $BH_3{\cdot}SMe_2$.



Scheme 3. Reagents and conditions: (i) PIFA, CF_3CH_2OH, −20 °C (75% for **9a**); (ii) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt (72% for **11a** two steps).

A number of 3-allyl-quinolin-2-ones of type **9** can be found in Nature.[10] For that reason, and in order to test the potential effect that substitution can exert on the chemoselectivity of the process, we decided to prepare a series of methoxy-substituted quinolinones **9a-d** from **7a-d**. In addition, and trying to get more information about the behavior of these amide precursors under the action of the oxidative I(III) reagent, a further reaction condition was tested on methoxyamides **7a-d**. It has been previously shown that TFA, employed as an additive in CH_2Cl_2 as solvent, can activate the cyclization of such kind of substrates.[7c] In Scheme 4 a comparison of both methods is presented.

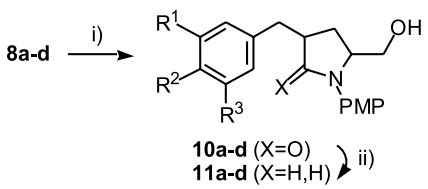


				Condt. A		Condt. B	
7	R^1	R^2	R^3	**9** (%)	**12** (%)	**9** (%)	**12** (%)
a	H	H	H	75	0	71	0
b	OMe	H	H	65	0	44	0
c	OMe	OMe	H	66	27*	28	43*
d	OMe	OMe	OMe	41	11	4	93

* Detected by GC-MS

Scheme 4. Reagents and conditions: (i) PIFA, CF_3CH_2OH, −20 °C (Condt. A); (i) PIFA, TFA, CH_2Cl_2, 0 °C (Condt. B).

Analogously, we next tried to expand the ability of PIFA to generate a series of pyrrolidinones **10** from the corresponding *N-para*-methoxyphenyl substituted amides **8** under the usual conditions depicted above (Scheme 5).



Scheme 5. Reagents and conditions: (i) PIFA, CF_3CH_2OH, 0 °C to rt; (ii) $BH_3{\cdot}SMe_2$, THF, rt. Overall yields: 72% for **11a**, 68% for **11b**, 67% for **11c**, 59% for **11d**.

As expected, in all cases under study, the action of PIFA on amides **8a-d** rendered chemoselectively pyrrolidinones **10a–d** as a series of unstable derivatives that were immediately reduced to the corresponding pyrrolidines **11a-d** in good overall yields.

The main observation that can be concluded from our experiments is that the cyclization process can take two

different pathways depending on the nature of the amide *N*-substituent to afford either quinoline or pyrrolidine skeletons. To sum up, when starting from *N*-methoxyamides **7a-d** quinolinones **9a-d** are obtained in all cases in moderate to good yields, along with the corresponding aza-spiro derivatives **12c** and **12d**, via intermedium **B**, when starting from **7c** and **7d**, respectively. In the latter cases, a methoxy group located in *para* position to the alkyl chain is responsible for the corresponding *ipso* attack of the internal electrophile.[11] When applying TFA as an activating agent, such process becomes dominant. Alternatively, intermedium **A** can be also trapped by the olefin fragment, when starting from amides **8a-d**, to form the heterocyclic core **C** stabilized as an aziridinium ion by the donating properties of the *para*-methoxyphenyl (PMP) group. This new intermediate is opened by a free trifluoroacetate group (delivered from PIFA), and the resulting non-isolated trifluoroacetylester is hydrolyzed during the work up (Na_2CO_3, H_2O) to render derivatives **10a-d**. A plausible mechanism for these transformations is shown in Figure 1.

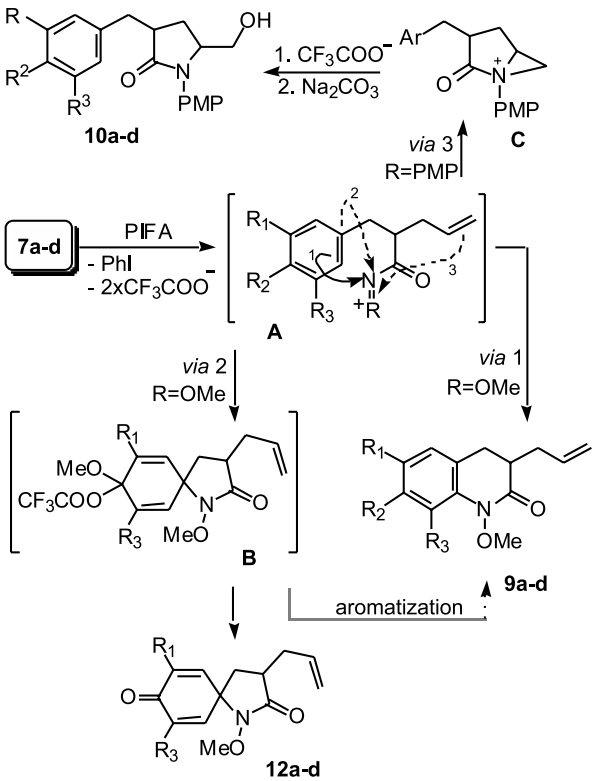


Figure 1. Proposed mechanisms for the transformation of amides **7** into quinolinones **9**, aza-spiro derivatives **12**, and pyrrolidines **10a-d**.

No simple explanation can be argued to justify these results. If we consider an electronic control in the reaction, no substantial differences can be estimated between the methoxy and the *para*-mehoxyphenyl groups. For that reason, we propose that steric effects may govern the course of the reaction since both groups have a significant difference in size volume. In fact, the notorious decrease in the yield for the transformation of amide **7d** into the 1,6,7,8-tetramethoxy substituted quinolinone **9d** as a result of a steric hindrance between methoxy groups in 1 and 8 positions, supports this suggestion.

3. Conclusions

In summary, the present work shows that the substituent required to stabilize the *N*-acylnitrenium intermediates generated by the action of PIFA on properly substituted amides can exert a selective control in the course of the cyclization reaction of 2-allyl-2-benzylacetamides to afford either 3-allyl-quinolin-2-ones or 3-benzyl-pyrrolidin-2-ones in good yields and complete selectivity.

4. Experimental

Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer R-1420 infrared spectrophotometer as KBr plates or as neat liquids and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 instrument (250 MHz for ^1H and 62.83 MHz for ^{13}C) at 20 °C. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.00 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT experiments were used to assist with the assignation of the signals. HRMS spectra were recorded at the University of Vigo on a VG Autospec M instrument.

4.1. General procedure for the α-alkylation of hydrocinnamic acids 5a-d

4.1.1. Synthesis of 2-allyl-3-phenylpropionic acid (6a). *n*-BuLi (26.2 mL, 1.6 M in *n*-hexane, 42 mmol) was added onto a cold (0 °C) solution of $^iPr_2NH$ (5.9 mL, 42 mmol) in 30 mL of THF, and the mixture was stirred for 30 min. Then, a solution of hydrocinnamic acid **5a** (3.0 g, 19.9 mmol) in 20 mL of THF was added dropwise over 20 min and stirring was continued for 30 min at the same temperature. The addition of allyl bromide (1.8 mL, 20.9 mmol) was followed by stirring until total consumption of the starting material (tlc, hexanes/EtOAc, 7/3, 6 h). For the work up, pH was adjusted to 2 by addition of HCl (3 M) and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. Then, pH of the aqueous layer was adjusted to 2 and extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 75/25) to afford carboxylic acid **6a** as a colorless oil (69%).[12]

4.1.2. 2-Allyl-3-(3-methoxyphenyl)propionic acid (6b). According to the general procedure carboxylic acid **6b** was obtained as a colorless oil from **5b** in 98% yield after purification by column chromatography (hexanes/EtOAc, 70/30). ^1H NMR: δ 2.26–2.47 (m, 2H, C*H*$_2$–CH=CH$_2$), 2.74–2.85 (m, 2H, CHCO, C*H*aAr), 2.99 (dd, *J*=15.8, 9.9 Hz, 1H, C*H*bAr), 3.80 (s, 3H, OCH_3), 5.08–5.16 (m, 2H, CH=C*H*$_2$), 5.72–5.88 (m, 1H, C*H*=CH$_2$), 6.77–6.81 (m, 3H, H_{arom}), 7.22 (t, *J*=7.9 Hz, 1H, H_{arom}), 11.1 (sa, 1H, COOH). ^{13}C NMR: δ 35.5, 37.2 (CH_2), 46.9 (CH), 55.0 (OCH_3), 117.5 (CH=*C*H$_2$), 111.8, 114.6, 121.2, 129.4, 134.6 (t-C_{arom}, *C*H=CH$_2$), 140.3, 159.5 (q-C_{arom}), 181.3 (CO). IR (film): 2900–3200 (OH), 1707 (CO). MS (EI) *m/z* (%): 220 (M^+, 24), 122 (100), 121 (58). HRMS calculated for $C_{13}H_{16}O_3$ 220.1099, found 220.1085.

4.1.3. 2-Allyl-3-(3,4-dimethoxyphenyl)propionic acid (6c). According to the general procedure carboxylic acid **6c** was obtained as a white solid from **5c** in 74% yield after purification by column chromatography (hexanes/EtOAc, 55/45) followed by crystallization from *n*-pentane. Mp: 64–65 °C (*n*-pentane). Lit.[13] 65–67 °C (benzene–hexane).

4.1.4. 2-Allyl-3-(3,4,5-trimethoxyphenyl)propionic acid (6d). According to the general procedure carboxylic acid **6d** was obtained as a white solid from **5d** in 68% yield after purification by column chromatography (hexanes/EtOAc, 40/60) followed by crystallization from hexanes. Mp: 85–87 °C (hexanes). Lit.[14] 87–89 °C. ^{1}H NMR: δ 2.24–2.44 (m, 2H, CH_2–CH=CH_2), 2.66–2.81 (m, 2H, CHCO, C*H*aAr), 2.91 (dd, *J*=10.3, 5.6 Hz, 1H, C*H*bAr), 3.80 (s, 9H, 3×OCH_3), 5.06–5.13 (m, 2H, CH=CH_2), 5.69–5.86 (m, 1H, C*H*=CH_2), 6.39 (s, 2H, H_{arom}). ^{13}C NMR: δ 35.6, 37.6 (CH_2), 46.9 (CH), 55.9, 60.7 (OCH_3), 117.5 (CH=*C*H_2), 105.7, 134.6 (t-C_{arom}, *C*H=CH_2), 134.4, 136.4, 153.0 (q-C_{arom}), 180.8 (CO). IR (KBr): 3000–3300 (OH), 1707 (CO). MS (El) *m*/*z* (%): 280 (M^+, 30), 182 (71), 181 (100). HRMS calculated for $C_{15}H_{20}O_5$ 280.1311, found 280.1302.

4.2. General procedure for the synthesis of *N*-methoxyamides 7a-d

4.2.1. Synthesis of 2-allyl-*N*-methoxy-3-phenylpropionamide (7a). Et_3N (0.3 mL, 2.1 mmol) was added dropwise onto a solution of carboxylic acid **6a** (200 mg, 1.05 mmol) and NH_2OMe·HCl (91 mg, 1.1 mmol) in MeCN (14 mL) as solvent. After stirring the mixture at room temperature for 30 min, TBTU (351 mg, 1.1 mmol) was added and the stirring was continued during 60 min. For the work-up, a saturated solution of NaCl (10 mL) was added and the solution was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with HC1 5% aq. (15 mL), water (15 mL), 5% aq. $NaHCO_3$ (15 mL) and water again (15 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 45/55) to afford amide **7a** as a colorless oil (86%). ^{1}H NMR: δ 2.20–2.30 (m, 1H, C*H*a–CH=CH_2), 2.37–2.47 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.75 (dd, *J*=13.5, 5.1 Hz, 1H, C*H*aPh), 2.92 (dd, *J*=13.5, 8.3 Hz, 1H, C*H*bPh), 3.48 (s, 3H, OCH_3), 5.00–5.12 (m, 2H, CH=CH_2), 5.68–5.84 (m, 1H, C*H*=CH_2), 7.15–7.27 (m, 5H, H_{arom}), 9.80 (s, 1H, NH). ^{13}C NMR: δ 36.2, 38.0 (CH_2), 45.1 (CH), 63.6 (OCH_3), 116.9 (CH=*C*H_2), 126.1, 128.1, 128.9, 135.0 (t-C_{arom}, *C*H=CH_2), 139.1 (q-C_{arom}), 171.7 (CO). IR (film): 3166 (NH), 1655 (CO). MS (El) *m*/*z* (%): 219 (M^+, 2), 178 (21), 91 (100). HRMS calculated for $C_{13}H_{17}NO_2$ 219.1259, found 219.1254.

4.2.2. 2-Allyl-*N*-methoxy-3-(3-methoxyphenyl)-propionamide (7b). According to the general procedure amide **7b** was obtained as a colorless oil from **6b** in 71% yield after purification by column chromatography (hexanes/EtOAc, 50/50). ^{1}H NMR: δ 2.21–2.30 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.39–2.51 (m, 1H, C*H*b–CH=CH_2), 2.73 (dd, *J*=13.3, 4.9 Hz, 1H, C*H*aAr), 2.89 (dd, *J*=13.3, 9.1 Hz, 1H, C*H*bAr), 3.54 (s, 3H, NHOCH_3), 3.76 (s, 3H, OCH_3), 5.02–5.13 (m, 2H, CH=CH_2,), 5.66–5.83 (m, 1H, C*H*=CH_2), 6.71–6.77 (m, 3H, H_{arom}), 7.17 (t, *J*=7.9 Hz, 1H, H_{arom}), 8.29 (s, 1H, NH). ^{13}C NMR: δ 36.3, 38.3 (CH_2), 46.2 (CH), 55.1, 64.2 (OCH_3), 117.4 (*C*H_2=CH), 111.7, 114.6. 121.3, 129.4, 134.9 (t-C_{arom}, *C*H=CH_2), 140.7, 159.6 (q-C_{arom}), 171.9 (CO). IR (film): 3177 (NH), 1648 (CO). MS (El) *m*/*z* (%): 249 (M^+, 3), 203 (12), 121 (100). HRMS calculated for $C_{14}H_{19}NO_3$ 249.1365, found 249.1375.

4.2.3. 2-Allyl-3-(3,4-dimethoxyphenyl)-*N*-methoxy-propionamide (7c). According to the general procedure amide **7c** was obtained as a colorless oil from **6c** in 73% yield after purification by column chromatography (hexanes/EtOAc, 45/55) followed by crystallization from *n*-pentane. Mp: 60–62 °C (*n*-pentane). ^{1}H NMR: δ 2.14–2.31 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.35–2.52 (m, 1H, C*H*b–CH=CH_2), 2.70 (dd, *J*=13.5, 5.1 Hz, 1H, C*H*aAr), 2.87 (dd, *J*=13.5, 9.9 Hz, 1H, C*H*bAr), 3.57 (s, 3H, NHOCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.04–5.14 (m, 2H, CH=CH_2,), 5.67–5.83 (m, 1H, C*H*=CH_2), 6.68–6.78 (m, 3H, H_{arom}), 7.92 (s, 1H, NH). ^{13}C NMR: δ 36.3, 37.8 (CH_2), 46.2 (CH), 55.7, 64.2 (OCH_3), 117.2 (*C*H_2=CH), 111.0, 112.1. 120.8, 134.9 (t-C_{arom}, *C*H=CH_2), 131.7, 147.4, 148.6 (q-C_{arom}), 172.0 (CO). IR (KBr): 3178 (NH), 1654 (CO). MS (El) *m*/*z* (%): 279 (M^+, 12), 151 (100). HRMS calculated for $C_{14}H_{19}NO_3$ 279.1471, found 279.1476.

4.2.4. 2-Allyl-*N*-methoxy-3-(3,4,5-trimethoxyphenyl)-propionamide (7d). According to the general procedure amide **7d** was obtained as a colorless oil from **6d** in 92% yield after purification by column chromatography (hexanes/EtOAc, 40/60). ^{1}H NMR: δ 2.16–2.26 (m, 2H, C*H*a–CH=CH_2, CHCO), 2.35–2.47 (m, 1H, C*H*b–CH=CH_2,), 2.64 (dd, *J*=13.6, 4.7 Hz, 1H, C*H*aAr), 2.84 (dd, *J*=13.6, 9.3 Hz, 1H, C*H*bAr), 3.53 (s, 3H, NHOCH_3), 3.74 (s, 3H, OCH_3), 3.76 (s, 6H, 2×OCH_3), 4.99–5.09 (m, 2H, CH=CH_2), 5.63–5.79 (m, 1H, C*H*=CH_2), 6.34 (s, 2H, H_{arom}), 8.77 (s, 1H, NH). ^{13}C NMR: δ 36.5, 38.5 (CH_2), 46.0 (CH), 55.9, 60.6, 64.0 (OCH_3), 117.3 (*C*H_2=CH), 105.7, 134.9 (t-C_{arom}, *C*H=CH_2), 135.0, 136.2, 152.9 (q-C_{arom}), 171.9 (CO). IR (film): 3176 (NH), 1654 (CO). MS (El) *m*/*z* (%): 309 (M^+, 15), 181 (100). HRMS calculated for $C_{16}H_{23}NO_5$ 309.1576, found 309.1575.

4.3. General procedure for the synthesis of *N*-*para*-methoxyphenylamides 8a-d

4.3.1. Synthesis of 2-allyl-*N*-(*para*-methoxyphenyl)-3-phenylpropionamide (8a). A solution of carboxylic acid **6a** (300 mg, 1.6 mmol) in CH_2Cl_2 (2 mL) and a solution of *p*-anisidine (291 mg, 2.4 mmol) in CH_2Cl_2 (2 mL) were added sequentially to a cold (0 °C) solution of EDC·HCl (454 mg, 2.4 mmol) and HOBt (299 mg, 2.2 mmol) in the same solvent (4 mL). Then, Et_3N, (0.3 mL, 2.4 mmol) was added dropwise and the mixture was stirred at the same temperature for 2 h and at rt until total consumption of the starting material (tlc, 14 h). For the work-up the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with HC1 5% aq. (2×15 mL) and with a saturated solution of $NaHCO_3$ (2×15 mL), dried over Na_2S0_4, filtered, and the solvent was evaporated under vacuum. The residue was

purified by crystallization from Et_2O to afford amide **8a** as a white solid (92%). Mp: 109–110 °C (Et_2O). ^1H NMR: δ 2.24–2.34 (m, 1H, C*H*a–CH=CH_2), 2.46–2.66 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.81 (dd, J=13.5, 5.1 Hz, 1H, C*H*aPh), 2.99 (dd, J=13.5, 8.7 Hz, 1H, C*H*bPh), 3.72 (s, 3H, OCH_3), 5.05–5.16 (m, 2H, CH=CH_2), 5.75–5.91 (m, 1H, C*H*=CH_2), 6.73 (d, J=8.7 Hz, 2H, H_{arom}), 7.17–7.28 (m, 7H, H_{arom}), 7.64 (s, 1H, NH). ^{13}C NMR: δ 36.6, 38.5 (CH_2), 49.8 (CH), 55.2 (OCH_3), 117.0 (*C*H_2=CH), 113.7, 122.3, 126.2, 128.3, 128.8, 135.3 (t-C_{arom}, *C*H=CH_2), 130.5, 139.4, 156.2, (q-C_{arom}), 172.7 (CO). IR (KBr): 3295 (NH), 1654 (CO). MS (El) m/z (%): 295 (M^+, 32), 254 (27), 123 (100), 108 (21). HRMS calculated for $C_{19}H_{21}NO_2$ 295.1572, found 295.1582.

4.3.2. 2-Allyl-3-(3-methoxyphenyl)-*N*-(*para*-methoxyphenyl)propionamide (8b). According to the general procedure amide **8b** was obtained as a white solid from **6b** in 80% yield after crystallization from Et_2O. Mp: 78–79 °C (Et_2O). ^1H NMR: δ 2.27–2.36 (m, 1H, C*H*a–CH=CH_2), 2.39–2.61 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.81 (dd, J=13.5, 5.1 Hz, 1H, C*H*aAr), 2.97 (dd, J=13.5. 8.7 Hz, 1H, C*H*bAr), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.06–5.18 (m, 2H, CH=CH_2), 5.76–5.92 (m, 1H, C*H*=CH_2), 6.73–6.81 (m, 5H, H_{arom}), 7.15–7.22 (m, 4H, H_{arom}, NH). ^{13}C NMR: δ 36.7, 38.6 (CH_2), 50.2 (CH), 54.9, 55.3 (OCH_3), 117.2 (*C*H_2=CH), 111.8, 113.8. 114.3, 121.2, 122.1, 129.4, 135.4 (t-C_{arom}, *C*H=CH_2), 130.5, 141.1, 156.3, 159.6 (q-C_{arom}), 172.5 (CO). IR (KBr): 3283 (NH), 1649 (CO). MS (El) m/z. (%): 325 (M^+, 21), 284 (24), 123 (100), 121 (52), 108 (21). HRMS calculated for $C_{20}H_{23}NO_3$ 325.1678, found 325.1694.

4.3.3. 2-Allyl-3-(3,4-dimethoxyphenyl)-*N*-(*para*-methoxyphenyl)propionamide (8c). According to the general procedure amide **8c** was obtained as a white solid from **6c** in 81% yield after crystallization from Et_2O. Mp: 123–124 °C (Et_2O). ^1H NMR: δ 2.25–2.33 (m, 1H, C*H*a–CH=CH_2), 2.39–2.58 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.74 (dd, J=13.5, 4.3 Hz, 1H, C*H*aAr), 2.93 (dd, J=13.5, 8.7 Hz, 1H, C*H*bAr), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.03–5.15 (m, 2H, CH=CH_2), 5.73–5.89 (m, 1H, C*H*=CH_2), 6.68–6.77 (m, 5H, H_{arom}), 7.11 (sa, 1H, NH), 7.22 (d, J=8.7 Hz, 2H, H_{arom}). ^{13}C NMR: δ 36.7, 38.1 (CH_2), 50.2 (CH), 55.1, 55.4, 55.6 (OCH_3), 116.9 (*C*H_2=CH), 111.0, 112.0, 113.7, 120.7, 121.9, 135.4 (t-C_{arom}, CH_2=*C*H), 130.6, 132.0, 147.2, 148.1, 156.1 (q-C_{arom}), 172.7 (CO). IR (KBr): 3319 (NH), 1654 (CO). MS (El) m/z (%): 355 (M^+, 44), 314 (63) 191 (68), 151 (100), 123 (89), 108 (26). HRMS calculated for $C_{21}H_{25}NO_4$ 355.1784, found 355.1770.

4.3.4. 2-Allyl-*N*-(*para*-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)propionamide (8d). According to the general procedure amide **8d** was obtained as a white solid from **6d** in 80% yield after crystallization from Et_2O. Mp: 120–121 °C (Et_2O). ^1H NMR: δ 2.24–2.33 (m, 1H, C*H*a–CH=CH_2), 2.38–2.59 (m, 2H, C*H*b–CH=CH_2, CHCO), 2.72 (dd, J=13.3, 4.4 Hz, 1H, C*H*aAr), 2.92 (dd, J=13.3, 9.3 Hz, 1H, C*H*bAr), 3.69 (s, 6H, 2×OCH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.03–5.16 (m, 2H, CH=CH_2), 5.73–5.89 (m, 1H, C*H*=CH_2), 6.37 (s, 2H, H_{arom}), 6.76 (d, J=8.9 Hz, 2H, H_{arom}) 7.07 (sa, 1H, NH), 7.22 (d, J=8.9 Hz, 2H, H_{arom}). ^{13}C NMR: δ 36.8, 39.1 (CH_2), 50.6 (CH), 55.3, 55.8, 60.7 (OCH_3), 117.2 (CH=*C*H_2), 105.7, 113.8, 121.8, 135.4 (t-C_{arom}, *C*H=CH_2), 130.6, 136.2, 153.03, 156.3 (q-C_{arom}), 172.5 (CO). IR (KBr): 3307 (NH), 1660 (CO). MS (El) m/z (%): 385 (M^+ 33), 344 (12), 221 (76), 204 (47), 181 (99), 123 (100), 108 (19). HRMS calculated for $C_{22}H_{27}NO_5$ 385.1889, found 385.1893.

4.4. General procedure for the cyclization of amides 7a–d with PIFA

4.4.1. Synthesis of 3-allyl-1-methoxyquinolin-2-one (9a). A solution of PIFA (147 mg, 0.34 mmol) in CF_3CH_2OH (10 mL) was added onto a cold (−20 °C) solution of amide **7a** (50 mg, 0.23 mmol) in 10 mL of the same solvent. The mixture was stirred at the same temperature until total consumption of the starting material (tlc, 60 min). The reaction was quenched with 10 mL of Na_2CO_3 (aq. 10%) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated solution of NaCl (15 mL), dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 75/25) to afford quinolinone **9a** as a colorless oil which was crystallized from *n*-pentane (75%). Mp: 63–65 °C (*n*-pentane). ^1H NMR: δ 2.15–2.27 (m, 1H, C*H*a–CH=CH_2), 2.62–2.77 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.94 (dd, J=19.8, 9.91 Hz, 1H, H-4b), 3.9 (s, 3H, OCH_3), 5.04–5.12 (m, 2H, CH=CH_2), 5.72–5.88 (m, 1H, C*H*=CH_2), 7.03 (t, J=7.1 Hz, 1H, H_{arom}), 7.14–7.31 (m, 3H, H_{arom}). ^{13}C NMR: δ 29.4, 33.9 (CH_3), 40.3 (CH), 62.4 (OCH_3), 117.7 (CH=*C*H_2), 112.0, 123.5, 127.6, 128.0, 134.9 (t-C_{arom}, CH=CH_2), 123.3, 137.4 (q-C_{arom}), 167.3 (CO). IR (KBr): 1684 (CO). MS (El) m/z (%): 217 (M^+, 100), 186 (52), 146 (67), 117 (76). HRMS calculated for $C_{13}H_{15}NO_2$ 217.1103, found 217.1092.

4.4.2. 3-Allyl-l,6-dimethoxyquinolin-2-one (9b). According to the general procedure quinolinone **9b** was obtained as a colorless oil from **7b** in 65% yield after purification by column chromatography (hexanes/EtOAc, 80/20) which was triturated with *n*-pentane. Mp: 40–41 °C (*n*-pentane). ^1H NMR: δ 2.13–2.26 (m, 1H, C*H*a–CH=CH_2), 2.58–2.73 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.91 (dd, J=19.8, 9.91 Hz, 1H, H-4b), 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.03–5.11 (m, 2H, CH=CH_2), 5.71–5.89 (m, 1H, C*H*=CH_2), 6.72 (d, J=2.8 Hz, 1H, H_{arom}), 6.80 (dd, J=8.9, 2.8 Hz, 1H, H_{arom}), 7.11 (d, J=8.9 Hz, 1H, H_{arom}). ^{13}C NMR: δ 29.7, 33.8 (CH_2), 40.3 (CH), 55.4, 62.3 (OCH_3), 117.7 (CH=*C*H_2), 112.1, 113.2, 114.2, 134.9 (t-C_{arom}, *C*H=CH_2), 124.8, 130.9, 155.9 (q-C_{arom}), 166.6 (CO). IR (KBr): 1678 (CO). MS (El) m/z (%): 247 (M^+, 96), 217 (55), 188 (25), 175 (88), 162 (100). HRMS calculated for $C_{14}H_{17}NO_3$ 247.1208, found 247.1204.

4.4.3. 3-Allyl-l,6,7-trimethoxyquinolin-2-one (9c). According to the general procedure quinolinone **9c** was obtained as a colorless oil from **7c** in 66% yield after purification by column chromatography (hexanes/EtOAc, 60/40). ^1H NMR: δ 2.11–2.24 (m, 1H, C*H*a–CH=CH_2), 2.56–2.67 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.86 (dd, J=20.1, 10.3 Hz, 1H, H-4b), 3.84 (s, 3H, OCH_3), 3.89 (s, 6H, 2×OCH_3), 5.02–5.09 (m, 2H, CH=CH_2), 5.70–5.89

(m, 1H, C*H*=CH_2), 6.67 (s, 1H, H_{arom}), 6.78 (s, 1H, H_{arom}). ^{13}C NMR: δ 29.1, 33.8 (CH_2), 40.6 (CH), 56.2, 56.3, 62.4 (OCH_3), 117.6 (CH=*C*H_2), 97.6, 111.8, 135.0 (t-Carom, *C*H=CH_2), 114.6, 130.9, 145.0, 148.4 (q-C_{arom}), 166.8 (CO). IR (film): 1678 (CO). MS (El) *m*/*z* (%): 277 (M^+, 39), 247 (100), 232 (40), 205 (81), 192 (39), 162 (20). HRMS calculated for $C_{15}H_{19}NO_4$ 277.1314, found 277.1310.

4.4.4. 3-Allyl-l,6,7,8-tetramethoxyquinolin-2-one (9d). According to the general procedure quinolinone **9d** was obtained as a white solid from **7d** in 41% yield after purification by column chromatography (hexanes/EtOAc, 50/50) and then by crystallization from *n*-pentane. Mp: 59–61 °C (*n*-pentane). ^{1}H NMR: δ 2.11–2.23 (m, 1H, C*H*a–CH=CH_2), 2.59–2.72 (m, 3H, C*H*b–CH=CH_2, H-3, H-4a), 2.82 (dd, *J*=20.2, 10.5 Hz, 1H, H-4b), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.04–5.10 (m, 2H, CH=CH_2), 5.74–5.90 (m, 1H, C*H*=CH_2), 6.45 (s, 1H, H_{arom}). ^{13}C NMR: δ 31.3, 33.3 (CH_2), 41.6 (CH), 56.1, 60.9, 61.4, 62.9 (OCH_3), 117.4 (CH=*C*H_2), 106.6, 135.3 (t-C_{arom}, *C*H=CH_2), 122.9, 126.0, 142.6, 144.4 150.3 (q-C_{arom}), 168.7 (CO). **IR** (KBr): 1684 (CO). MS (El) *m*/*z* (%): 307 (M^+, 75), 276 (100), 222 (93), 206 (56). HRMS calculated for $C_{16}H_{21}NO_5$ 307.1420, found 307.1412.

4.5. General procedure for the amidohydroxylation of amides 7a-d with PIFA

4.5.1. Synthesis of 4-benzyl-2-hydroxymethyl-1-(*para*-methoxyphenyl)pyrrolidine (11a). A solution of PIFA (219 mg, 0.51 mmol) in 7 mL of CF_3CH_2OH was added onto a cold (−20 °C) solution of amide **8a** (100 mg, 0.34 mmol) in 7 mL of the same solvent, and the mixture was stirred until total consumption of the starting material (tlc, 80 min). Then, 10 mL of Na_2CO_3 (aq. 10%) were added and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated solution of NaCl (15 mL), dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. Without any further purification, the resulting residue was dissolved in THF (4 mL), cooled to a 0 °C, and $BH_3{\cdot}SMe_2$ (1.7 mL, 2 M in THF, 3.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature until total consumption of the starting material (tlc, 10 h). Then, MeOH was added slowly and the stirring was continued for 15 min. The solvent was removed under vacuum, and treatment with MeOH was repeated twice more. The final residue was purified by column chromatography (hexanes/EtOAc, 30/70) to afford pyrrolidine **11a** as a colorless oil (72%). Mixture of diastereoisomers 1.8/1. ^{1}H NMR: δ 1.39–1.65 (m, 4H, 2×H-3a, 2×H-3b), 1.99–2.12 (m, 1H, H-4 min.), 2.17–2.27 (m, 1H, H-4 maj.), 2.58–2.76 (m, 4H, 2×CH_2Ph), 2.86 (sa, 2H, 2×OH, exchange with D_2O), 2.89–3.14 (m, 4H, 2×H-5a, 2×H-5b), 3.33–3.41 (m, 2H, 2×C*H*aOH), 3.50–3.57 (m, 2H, 2×C*H*bOH), 3.73 (s, 6H, 2×OCH_3), 3.82–3.91 (m, 2H, 2×H-2), 6.54 (d, *J*=9.1 Hz, 2H, H_{arom} maj.), 6.59 (d, *J*=9.1 Hz, 2H, H_{arom} min.), 6.73–6.76 (m, 4H, H_{arom}), 7.15–7.32 (m, 10H, H_{arom}). ^{13}C NMR: δ 36.0, 37.9 (CH_2), 36.5, 38.9 (C-4), 39.8, 40.6 (CH_2), 48.9, 50.6 (CH_2), 55.7 (OCH_3), 67.0, 67.2 (CH_2OH), 69.3, 70.9 (C-2), 114.7, 114.8 (t-C_{arom}), 115.1, 115.9 (t-C_{arom}), 126.21 (t-C_{arom}), 128.4, 129.1 (t-C_{arom}), 139.9, 140.0 (q-C_{arom}), 141.5, 142.0 (q-C_{arom}), 152.7–153.2 (q-C_{arom}). IR (film): 3000–3400 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 315 (M^++18, 20), 136 (100). HRMS calculated for $C_{19}H_{23}NO_2$ 297.1729, found 297.1727.

4.5.2. 2-Hydroxymethyl-l-(*para*-methoxyphenyl)-4-(3-methoxyphenyl)pyrrolidine (11b). According to the general procedure pyrrolidine **11b** was obtained as a colorless oil from **8b** in 68% yield after purification by column chromatography (hexanes/EtOAc, 20/80). Mixture of diastereoisomers 1.8/1. ^{1}H NMR: δ 1.40–1.66 (m, 4H, 2×H-3a, 2×H-3b), 2.04–2.14 (m, 1H, H-4 min.), 2.16–2.29 (m, 1H, H-4 maj.), 2.55–2.74 (m, 4H, 2×CH_2Ph), 2.89–3.15 (m, 4H. 2×H-5a, 2×H-5b), 3.21 (sa, 2H, 2×OH, exchange with D_2O), 3.35–3.42 (m, 2H, 2×C*H*aOH), 3.52–3.58 (m, 2H, 2×C*H*bOH), 3.73 (s, 6H, 2×OCH_3), 3.76–3.92 (m, 8H, 2×H-2, 2×OCH_3), 6.56 (d, *J*=9.1 Hz, 2H, H_{arom} maj.), 6.61 (d, *J*=9.1 Hz, 2H, H_{arom} min.), 6.72–6.77 (m, 10H, H_{arom}), 7.20 (m, 2H, H_{arom}). ^{13}C NMR: δ 35.9, 37.8 (CH_2), 36.3, 38.6 (C-4), 39.8, 40.4 (CH_2), 48.8, 50.4 (CH_2), 55.1, 55.7 (OCH_3), 67.0, 67.1 (CH_2OH), 69.3, 70.9 (C-2), 111.3, 111.4 (t-C_{arom}), 114.8, 114.9 (t-C_{arom}), 115.0, 115.1 (t-C_{arom}), 115.8 (t-C_{arom}), 121.5 (t-C_{arom}), 129.4 (t-C_{arom}), 141.6, 142.0 (q-C_{arom}), 152.6 (q-C_{arom}), 159.6 (q-C_{arom}). IR (film): 2900–3450 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 345 (M^++18, 21), 136 (100). HRMS calculated for $C_{20}H_{25}NO_3$ 327.1834, found 327.1837.

4.5.3. 4-(3,4-Dimethoxyphenyl)-2-hydroxymethyl-1-(*para*-methoxyphenyl)pyrrolidine (11c). According to the general procedure pyrrolidine **11c** was obtained as a colorless oil from **8c** in 67% yield after purification by column chromatography (EtOAc). Mixture of diastereoisomers 1.7/1. ^{1}H NMR: δ 1.36–1.61 (m, 4H, 2×H-3a, 2×H-3b), 2.00–2.09 (m, 1H, H-4 min.), 2.12–2.25 (m, 1H, H-4 maj.), 2.47–2.69 (m, 4H, 2×CH_2Ph), 2.84–3.09 (m, 4H, 2×H-5a, 2×H-5b), 3.14 (sa, 2H, 2×OH, exchange with D_2O), 3.32–3.39 (m, 2H, 2×C*H*aOH), 3.48–3.58 (m, 2H, 2×C*H*bOH), 3.65 (s, 6H, 2×OCH_3), 3.71–3.83 (m, 14H, 2×H-2. 4×OCH_3), 6.50–6.58 (m, 4H, H_{arom}), 6.66–6.78 (m, 10H, H_{arom}). ^{13}C NMR: δ 35.8, 37.5 (CH_2), 36.3, 38.3 (C-4), 39.3, 39.7 (CH_2), 48.5, 50.1 (CH_2), 55.6, 55.7, 55.8 (OCH_3), 67.0, 67.1 (CH_2OH), 69.4, 70.8 (C-2), 111.0, 112.3 (t-C_{arom}), 114.7, 114.9 (t-C_{arom}), 155.5, (t-C_{arom}), 120.9 (t-C_{arom}), 132.4, 132.5 (q-C_{arom}), 141.8, 142.1 (q-C_{arom}), 147.2 (q-C_{arom}), 148.7 (q-C_{arom}), 152.4, 152.8 (q-C_{arom}). IR (film): 3000–3400 (OH), 1508 (C=C). MS (El) *m*/*z* (%): 375 (M^++18, 16), 136 (100). HRMS calculated for $C_{21}H_{27}NO_4$ 357.1940, found 357.1939.

4.5.4. 2-Hydroxymethyl-1-(*para*-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)pyrrolidine (11d). According to the general procedure pyrrolidine **11d** was obtained as a colorless oil from **8d** in 67% yield after purification by column chromatography (EtOAc). Mixture of diastereoisomers 1.7/1. ^{1}H NMR: δ 1.39–1.68 (m, 4H, 2×H-3a, 2×H-3b), 2.02–2.14 (m, 1H, H-4 min.), 2.17–2.33 (m, 1H, H-4 maj.), 2.49–2.71 (m, 4H, 2×CH_2Ph), 2.89–3.14 (m, 4H, 2×H-5a, 2×H-5b), 2.71 (sa, 2H, 2×OH, exchange with D_2O), 3.33–3.44 (m, 2H, 2×C*H*aOH), 3.54–3.60 (m, 2H, 2×C*H*bOH), 3.72–3.82 (m, 30H, 2×H-2, 4×OCH_3), 6.37 (s, 4H, H_{arom}), 6.54 (d, *J*=8.9 Hz, 2H, H_{arom} maj.), 6.59 (d,

J=8.9 Hz, 2H, H_{arom} min.), 6.72–6.76 (m, 4H, H_{arom}). ^{13}C NMR: δ 36.1, 37.9 (CH_2), 36.3, 38.6 (C-4), 40.3, 40.8 (CH_2), 48.9, 50.6 (CH_2), 55.7, 56.0, 60.8 (OCH_3), 67.2, 67.2 (CH_2OH), 69.3, 70.9 (C-2), 105.8, 105.9 (t-C_{arom}), 114.8, 115.3 (t-C_{arom}), 116.2, (t-C_{arom}), 135.6, 135.7 (q-C_{arom}), 141.1, 141.6 (q-C_{arom}), 152.8 (q-C_{arom}), 153.1 (q-C_{arom}), 153.4 (q-C_{arom}). IR (film): 3100–3400 (OH), 1508 (C=C). MS (El) *m/z* (%): 405 (M^++18, 17), 136 (100). HRMS calculated for $C_{22}H_{29}NO_5$, 387.2046 found 387.2043.

4.5.5. Synthesis of 3-allyl-1-aza-1,7,9-trimethoxy-spiro[4.5]deca-6,9-dien-2,8-dione (12d). Typical procedure. TFA (0.03 mL, 0.45 mmol) was added onto a cold (0 °C) solution of amide **7d** (70 mg, 0.23 mmol) in CH_2C1_2 (2 mL) and then a solution of PIFA (146 mg, 0.34 mmol) in 3 mL of the same solvent was added slowly. The reaction mixture was stirred at the same temperature until total consumption of the starting material (tlc, 90 min). The reaction was quenched with 10 mL of a 10% aqueous solution of Na_2CO_3, and the aqueous layer was extracted with CH_2C1_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The residue was purified by column chromatography (CH_2C1_2/EtOAc, 20/80) to afford the spiro derivative **12d** as a yellowish oil which was crystallized from *n*-pentane (93%). Mp: 72–74 °C. ^1H NMR: δ 2.00 (dd, J=12.7, 9.5 Hz, 1H, H-4a), 2.21–2.38 (m, 2H, H-4b, C*H*aHbCH=CH_2), 2.65–2.77 (m, 2H, CHa*H*bCH=CH_2, H-3), 3.67 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.11–5.18 (m, 2H, CH=CH_2), 5.64 (s, 2H, H-6, H-10), 5.68–5.84 (m, 1H, C*H*=CH_2). ^{13}C NMR: δ 35.1, 35.8 (CH_2), 36.7 (CH), 55.4, 55.5, 65.4 (OCH_3), 118.1 (CH=*C*H_2), 113.6, 115.9, 133.8 (*C*H=C, *C*H=CH_2), 61.4, 151.3, 151.6 (q-C), 172.6, 175.8 (CO). IR (KBr): 1707 (CO), 1684 (CON), 1619 (C=C). MS (EI) *m/z* (%): 293 (M^+, 99), 262 (48), 252 (100), 192 (74). HRMS calculated for $C_{15}H_{19}NO_5$, 293.1263 found 293.1263.

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Diels–Alder cycloaddition of 2-azadienes to methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate in the synthesis of methyl 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylates

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Abstract—A number of fused 4-oxo-1,3-diazabicyclo[4.1.0]heptane-6-carboxylates, a new type of compound, have been obtained by Diels–Alder cycloaddition between nucleophilic 2-azadienes and an electrophilic 2*H*-azirine. The reactions are completely endo- and *regio*selective, the azirine being added by its less hindered face to the diene. There are two isomers **7** and **8** formed from dienes **1** due either to isomerization of the cycloadducts **7** and **8** or by isomerization of the C=N bond of the diene during the reaction. The isomer **10** is formed from diene **2e**, and a single diastereoisomer structure **4a–i** is formed from dienes **11**. Some pyrimidones **8a**, **7c/8c**, **7e**, **10**, **11d** have been hydrolyzed leading to functionalised aziridines **12**, **13** and **15**.

1. Introduction

Methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** has been reacted with dienes **1**, **2**[1] and **4**. It had been obtained before by pyrolysis of the methyl 3-(2,6-dichlorophenyl) α-azidopropenate[2] and used in [4+2] π cycloaddition with commercial dienes. Reactions occur at room temperature with excellent stereoselectivity, being *endo*[3] to carbodienes and *exo*[4] to furan and diphenylisobenzofuran. The 2-azadienes were obtained according to methodology developed by Ghosez[5] from acylimidates and *tert*-butyldimethylsilyl triflates for compounds **1** and **2**, and from LiHMDS, trimethylsilyl chloride and triethylamine in one pot reaction for compounds **4**.[5] Nucleophilic 2-azadienes of this type had been combined with a range of electron poor dienophiles, such as aldehydes,[6a,b] nitroso compounds,[7–9] olefinic compounds,[10] naphthoquinones,[11] quinones,[12] activated acetylenic dienophiles,[12,13] and activated nitriles,[12] in order to obtain the 6 membered ring compounds or their hydrolysis derivatives. A chiral nitroso compound was employed giving cycloadducts with high facial selectivity.[9] Also, activated olefinic dienophiles were used together with nucleophilic 2-azadienes in the presence of a chiral copper(II) complex to give enantiomerically pure piperidones.[14] The results we now report were obtained by Diels–Alder cycloaddition between electrophilic 2*H*-azirine **6** and the nucleophilic 2-azadiens **1**, **2** and **4**. The literature contains examples of the cycloaddition of electron poor 2-azadienes to simple imines and to an azirine[15] but this work represents the first examples of normal electron demanding cycloadditions between 2-azadienes and an azirine.

2. Results and discussion

2.1. Synthesis of 2-azadienes

2.1.1. From imidates. The 2-azadienes **1** and **2** were obtained in two steps according to the procedure devised by Ghosez et al. for this type of compound. Commercial imidates and acid chlorides were mixed together in dry DCM and over N_2, to form the acylimidates **3** as intermediates. The acylimidates were further silylated in ether in the presence of *tert*-butyldimethylsilyl chloride. Products were obtained in good yields (Scheme 1) contaminated with *N*-acylimidate, according to ^{1}H NMR spectra, and were used without purification in the synthesis of cycloadducts.

Compounds **1a** and **1b** have been prepared previously. Compound **1b** was shown to have the *Z* configuration for the C-3 to C-4 bond.[5] Compounds **1c** and **1d** are new compounds and the same configuration is assigned. In solution compounds **1b–d** were found to consist of mixture of stereomers in relation to C-1. The major isomers were deduced to have the *EZ* configuration, based on

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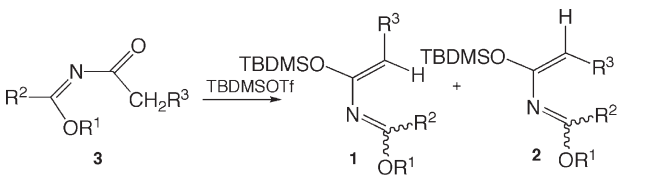


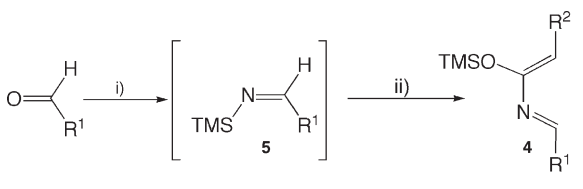
	R^1	R^2	R^3	Yield (%)	ratio 1: 2
a	Et	Me	H	65	100 : 0
b	Et	Me	Me	87	100 : 0
c	Et	Me	Ph	86	100 : 0
d	Me	Ph	Ph	88	100 : 0
e	Me	Ph	Me	82	20 : 80

Scheme 1. Preparation of 2-azadienes **1** and **2**.

spectroscopic evidence for cycloadducts obtained as discussed later. Stereomer **2** is formed in the series **e** together with stereomer **1**. Compounds **1e** and **2e** are formed in 1:4 ratio when neat TBDMSOTf is added to the acylimidate solution, and a 1:1 ratio of isomers when TBDMSOTf is added dropwise diluted in ether. This result led us to assume the diene **2e** to be the kinetic product of silylation of the acylimidate with TBDMSOTf. Stereomer **2e** was assigned as *EE* configuration on the basis of the spectroscopic data of cycloadduct **10** obtained along with the adduct **7e** in the reaction of **1e/2e** to azirine **6**.

2.1.2. From aldehydes. 2-Azadienes **4** were obtained in one pot reaction by combination of 4–5 fold excess of LiHMDS, freshly distilled aldehyde and trimethylsilyl chloride to produce the imine **5**, that was further acylated in the presence of an acid chloride and triethylamine, according to Scheme 2.

This is a modified method of one initially used by Ghosez to generate azadienes of type **4**.[5] Excellent yields were obtained in most cases. All 2-azadienes **4** referred to here are new compounds that were shown to be single isomers in solution, with the exception of **4i**, where a second isomer is observed (isomeric ratio 10:1). The *EZ* stereochemistry for the compounds is assigned in accordance with a range of



Compound	Yield
4a R^1 = Ph, R^2 =H	60
b R^1= 4-$NO_2C_6H_4$, R^2 =H	83
c R^1= 4-FC_6H_4, R^2 =H	65
d R^1= Ph, R^2 =Ph	100
e R^1= 4-$NO_2C_6H_4$, R^2 =Ph	99
f R^1= 4-FC_6H_4, R^2 =Ph	100
g R^1= 4-$MeOC_6H_4$, R^2 =Ph	71
h R^1= 3-furyl, R^2 =Ph	100
i R^1= 4-FC_6H_4, R^2 =Me	100[a)]

[a)] **4i** showed to be a mixture of isomers 10 (*EZ*) : 1 (*EE*) ratio

Method A: i) HMDS (1 eq.), BuLi (0.9 eq.), TMSCl (0.9 eq.); ii) Et_3N (1.1 eq.), R^2CH_2COCl (1.3 eq.);
Method B: i) LiHMDS (4 - 5 eq.), TMSCl (1.3 eq.); ii) Et_3N (1.1 eq.), R^2CH_2COCl (1.3 eq.);

Scheme 2. Preparation of 2-azadienes **4**.

analogous compounds obtained before.[5] Three examples are shown below (Fig. 1):

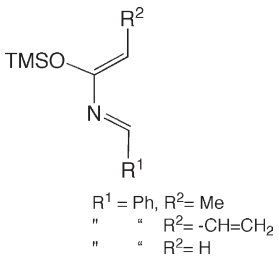
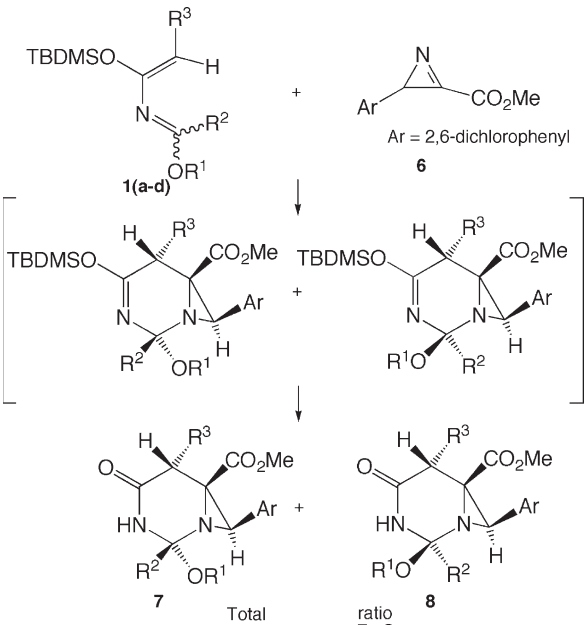


Figure 1. Some examples of *EZ* configuration of 2-azadienes reported in the literature.

The minor compound in series **i** is assumed to have the *EE* configuration according to other cases reported in literature for the same type of dienes.[5] Due to the instability of the 2-azadienes **4**, they were identified by ^1H NMR spectroscopy and were used without purification in the cycloadditions.

2.2. Cycloadditions of 2-azadienes 1 and 2 to 2*H*-azirine 6

2-Azadienes of type **1a**–**d** react at room temperature with the azirine **6** to give the cycloadducts **7** and **8** (Scheme 3). Usually, the desilylated compound precipitated out of the reaction mixture as a solid that was obtained by filtration. After repeating these reactions in several conditions, we find that the better yields correspond to reactions performed in very small amounts of diethyl ether. As an alternative procedure after the consumption of the azirine the reaction material was redissolved in DCM, stirred with SiO_2 followed by dry flash chromatography. Poorer yields of products **7/8** were obtained in all cases. Also treatment of



	Total yield %	ratio **7 : 8**
a R^1 =Et, R^2=Me, R^3=H	53	1:1
b R^1 =Et, R^2=Me, R^3=Me	51	isomer **7** only
c R^1 =Et, R^2=Me, R^3=Ph	58	4.5:1
d R^1 =Me, R^2=Ph, R^3=Ph	38	3:1

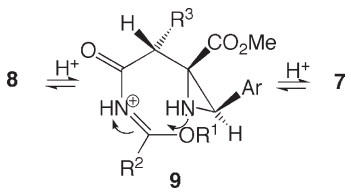
Scheme 3. Preparation of the pyrimidinones **7** and **8**.

the reaction mixture with tetramethylammonium fluoride gave compound **7b** in a poorer yield (41%). The primary silyloxy cycloadduct could never be isolated or even observed by ^{1}H NMR analysis.

The solid obtained from reaction of **1a** (one stereomer) with the azirine **6** was a mixture (1:1 ratio) of **7a/8a** in 53% yield. Redissolution of the solid in DCM and stirring the solution with SiO_2 for 24 h gave **7a** quantitatively. A single isomer **7b** was obtained from **1b** in 51% yield after filtration. The starting diene contained only traces of a minor isomer. Reaction of **1c** (4:1 mixture of stereomers) produced an oil that was treated with DCM and SiO_2 for 3 days. The crude showed two diastereomers **7c** and **8c** in a 1:1 ratio. After flash chromatography the isomer **7c** was partially separated (25%), together with a fraction containing the mixture of both isomers (33%), in total yield of 58%. Curiously the diastereomeric ratio after chromatography changed to 4.5 (**7c**): 1 (**8c**). Reaction of **1d** (2:1 ratio of stereomers) with the azirine **6** gave an oil which was treated with SiO_2 in DCM for 7 days. ^{1}H NMR spectrum of the reaction mixture showed a 3:1 mixture of diastereomers that were fully separated after flash chromatography as two solids, **7d** (27%) and **8d** (11%).

Unexpectedly no relationship is observed between the diastereomeric ratio of the adducts **7/8** and the stereomeric ratio of the precursor dienes. In cases where the products were obtained after treatment with SiO_2 a possible explanation is the isomerization of products **8** into **7**. It is also relevant that the diastereomeric ratio difference between a mixture of **7c** and **8c** that was enriched in **7c** after flash chromatography. In series **a** two isomers **7** and **8** (1:1 ratio) precipitated out of the reaction mixture before treatment with SiO_2, having started the cycloaddition from **1a** as a single isomer. In this case it is more plausible that the C=N bond rotation between the *EZ* and *ZZ* isomer forms can explain the isomeric ratio of adducts. Possibly a chemical equilibrium between the *EZ* and *ZZ* forms, that is not observable in $CDCl_3$ solution, occurs during the cycloaddition giving the respective adducts.

Another possibility is that a step-wise mechanism rather than a concerted Diels–Alder process could operate in this case. The same could not be said about the cycloaddition of 1b where a single diene isomer gave a single cycloadduct (Scheme 4).



Scheme 4. Possible isomerization mechanism between compounds **8** and **7**.

A crystal structure confirmed the structure of compound **7c**.[1] This shows that the reaction goes through an *endo* approach of the azirine **6** from its less hindered face to *EZ* configuration of the diene **1**. Also, NOESY spectra for **7c** show that the 5-H and 2-Me were on the same side of the molecule. On the other hand the minor isomer **8c** showed 7-H to be on the same side of 2-Me, which would be explained for the same *endo* approach of the less crowded face of the azirine to the minor diene isomer *ZZ* (Fig. 2). Further support for the difference between the diastereomers **7** and **8** in 2-C is obtained by hydrolysis of compounds **7c** and **8c** which gave the same product **12** as seen ahead (Scheme 6).

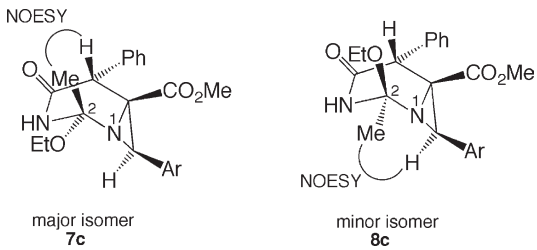


Figure 2. Compounds **7c** and **8c** showing the interaction through space (NOESY).

On reacting a mixture of dienes **1e** and **2e** (1:4 ratio) with the azirine **6** a white solid formed after stirring the reaction mixture for 7 days at room temperature. The solid was analysed by ^{1}H NMR showing it to be a mixture of diastereomers identified as **7e** and **10**, in 1.2 (**7e**): 1 (**10**) ratio. This is another case besides **a** and **b** where a solid is isolated, without previous contact with silica. As in case **a** the isomeric ratio of dienes does not match with the isomeric ratio of cycloadducts. So the observations made for the case **a** can now be used to explain to case **e**. Flash chromatography partially separated **7e** (30%) as a white solid together with a mixture of **7e** and **10** (21%) also as a solid, total yield 51%. The NOESY spectrum of **7e** showed the methoxy group at 2-C in the proximity of 7-H and the methyl group at 5-C close in space to 7-H. On the other hand the NOESY spectrum of the minor isomer **10** showed proximity between 5-H and 7-H, which would rule out structure **8** and strongly suggests structure **10** instead (Fig. 3).

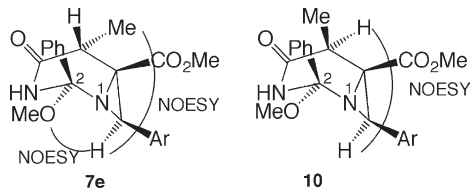


Figure 3. Compounds **7e** and **10** showing the interaction through space (NOESY).

Structure **10** should be formed from attack of the less hindered face of the azirine on the less stable diene configuration *EE*. The hydrolysis product of compound **10** confirms a different configuration of the stereocentre 5-C of this compound related to structures **7** and **8** as seen later. Cycloaddition preparations of series **e** showed that starting with a mixture of dienes **1e** and **2e** (ca. 1:1 ratio) and with a mixture of dienes **1e** and **2e** (ca. 1:4 ratio) isomers **7e** and **10** formed in the same isomeric ratio (1:1). This leads us to propose that an isomerization takes place about 3-C to 4-C in the diene during the course of the reaction.

^{1}H NMR spectra of compounds **7c** and **8c** showed the influence of the ethoxyl group through space on protons 5-H

and 7-H. When this proximity is observed the 5-H and 7-H protons suffer a shift to lower field in the spectra. In compound **7c** 7-H suffer a shift to lower field (+0.31 ppm) when compared to 7-H in compound **8c**. On the other hand, 5-H in compound **8c** shows up at lower field (+0.35 ppm) compared to 5-H in compound **7c**. Comparison of ^{1}H NMR chemical shifts of 5-H and 7-H obtained to the series **c** apply to the diastereomeric pair in series **d**, but not in series **a** (Table 1).

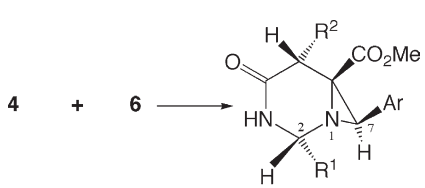
Table 1. Some data for pyrimidones **7**, **8** and **11**

Compound	Mp (°C)	^{1}H NMR[a], δ_H in ppm, J in Hz
7a	173.5–176.0	5-H 3.16 (d, J=18.3, 1H), 3.40 (d, J=18.3, 1H); 7-H 3.32 (s, 1H)
8a	176.0–177.5	5-H 3.08 (d, J=18.3, 1H), 3.34 (d, J=18.3, 1H); 7-H 3.58 (s, 1H)
7b	140.5–146.5	5-H 3.19 (q, J=7.2, 1H); 7-H 3.59 (s, 1H)
7c	181.2–183.2	5-H 4.40 (s, 1H,); 7-H 4.13 (s, 1H)
8c	134.5–137.5	5-H 4.75 (s, 1H); 7-H 3.82 (s, 1H)
7d	175.5–177.5	5-H 4.41 (s, 1H); 7-H 3.80 (s, 1H)
8d	189.1–190.1	5-H 5.09 (s, 1H); 7-H 3.66 (s, 1H)
7e	212.0–214.0	5-H 2.59 (q, J=6.9, 1H); 7-H 3.77 (s, 1H)
10	187.0–188.4	5-H 3.82 (q, J=7.2, 1H); 7-H 3.48 (s, 1H)
11a	166.6–169.7	5-H 3.40 (q, J=6.9, 1H); 7-H 3.74 (s, 1H)
11b	168.6–171.1	5-H 3.42 (q, J=6.9, 1H); 7-H 3.76 (s, 1H)
11c	189.6–191.2	5-H 3.57 (d, J=18.3, 1H), 3.16 (d, J=18.3, 1H); 7-H 3.75 (s, 1H)
11d	210.2–213.6	5-H 4.63 (s, 1H); 7-H 4.24 (s, 1H)
11e	195.1–196.8	5-H 4.63 (s, 1H); 7-H 4.26 (s, 1H)
11f	152.4–153.3	5-H 4.61 (s, 1H); 7-H 4.22 (s, 1H)
11g	208.1–210.3	5-H 4.61 (s, 1H); 7-H 4.22 (s, 1H)
11h	173.5–173.9	5-H 4.50 (s, 1H); 7-H 4.16 (s, 1H)
11i	213.4–215.0	5-H 3.39 (q, J=6.9, 1H); 7-H 3.72 (s, 1H)

[a] Selected peaks.

2.3. Cycloadditions of 2-azadienes 4 to 2*H*-azirine 6

2-Azadienes of type **4a**–**i** react at room temperature with the azirine **6** to give the cycloadducts **11** as single isomers. Products were generally obtained in good yields (Scheme 5). In most cases the desilylated compound precipitated out of the reaction as a solid practically pure (**b**, **d**, **e**, **f** and **g**) that was obtained by filtration. In other cases the product was obtained as an oil (**a**, **c**, **h**, **i**) that was subjected to dry flash chromatography (**a**, **h**, **i**) resulting in a drop in the yield of the reaction. In case **c** a polymer formed together with an oil. The oil crystallized after addition of diethyl ether. The primary silylated cycloadduct could never be observed by ^{1}H NMR analysis of the products. In accordance with results obtained for the cycloaddition of **7** and **8** the approach of reactants is proposed to take place from the less hindered face of the azirine.



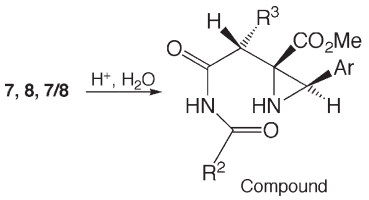
Compound / Yield (%)	
11a	28
b	71
c	16
d	75
e	61
f	70
g	60
h	28
i	33

Scheme 5. Preparation of pyrimidones **11**.

Major features of the ^{1}H NMR spectra for compounds **11** are the 5-H and 7-H chemical shifts, comparable to 5-H and 7-H chemical shifts of compounds **7**. Namely the 5-H in the 2,5-diphenyl disubstituted compounds **11d** and **7d** are, respectively, 4.63 and 4.41 ppm. Also the two 5-H of the monosubstituted **11c** and **7a** showed similar chemical shift values: 3.57/3.16 ppm (**11c**) and 3.40/3.16 ppm (**7a**). Compounds **8** showed chemical shifts somewhat further apart: 3.34/3.08 (**8a**) and 5.09 (**8d**). 2-H Chemical shifts in structures **11** are all around the same chemical shifts between 5.86 and 6.52 ppm, showing the influence of the nitrogen atoms and an aromatic ring attached to the 2-C.

2.4. Hydrolysis of the cycloadducts

Heating an ether solution of **7a** afforded the hydrolysis product in trace amounts. Compound **12a** could be obtained pure in 74% yield when a solution of **8a** in THF was treated with aq. HCl (1 equiv.) diluted in THF. Also, a mixture of **7c** and **8c** was treated the same way to give product **12c** in 87% yield (Scheme 6). As both diastereomers **7c** and **8c** gave the same hydrolysis product this confirms the stereochemistry of adducts discussed above.



Compound	Yield (%)
12a, R^2= Me, R^3= H	74
b, R^2= Me, R^3= Me	42
c, R^2= Me, R^3= Ph	87
d, R^2= Ph, R^3= Ph	68
e, R^2= Ph, R^3= Me	75

Scheme 6. Hydrolysis of compounds **7**, **8** or mixture of **7/8**.

The hydrolysis of the mixture of **7e/10** (1.2:1 ratio) produced a different result. In this case two products **12e** and **13** (Fig. 4) were obtained (1.2:1) that were characterized after separation by dry flash chromatography.

A possible mechanism for the hydrolysis can be envisaged

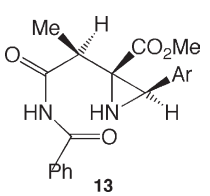


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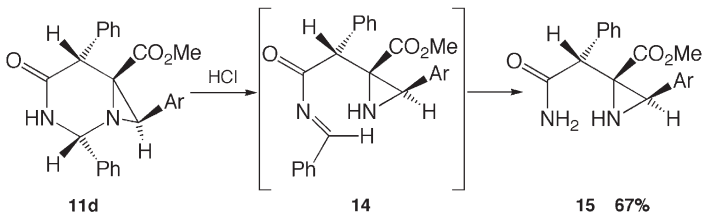
Figure 4. Structure of compound **13**.



Scheme 7. Hydrolysis of compound **11d**.

Table 2. Some data for aziridines **12**, **13** and **15**

Compound	Mp (°C)	Yield (%)	^{1}H NMR (CH and NH of the aziridine ring), δ_H in ppm, J in Hz
12a[a]	164.3–165.1	74	CH 3.21 (d, J=8.4, 1H); NH 2.87 (br d, J=8.4, 1H)
12b[b]	116.3–117.4	42	CH 3.37 (d, J=9, 1H); NH 2.85 (d, J=9, 1H)
12c[c]	191.1–191.6	87	CH 2.40 (d, J 9.9, 1H); NH 3.08 (d, J 9.9, 1H)
12d[d]	180.2–181.2	68	CH 2.51 (d, J=9.9, 1H); NH 3.02 (d, J=9.9, 1H)
12e[e]	189.3–190.0	29[f]	CH 3.39 (d, J=9.3, 1H); NH 2.83 (d, J=9.3, 1H)
13[e]	139.5–139.9	25[f]	CH 3.38 (d, J=9.0, 1H), NH 2.97 (d, J=9.0, 1H)
15	167.5–167.7	67	CH 2.42 (d, J=8.7, 1H), NH 3.04 (d, J=8.7, 1H)

[a] Obtained from hydrolysis of compound **8a**.
[b] Obtained from hydrolysis of compound **7b**.
[c] Obtained from hydrolysis of an isomeric mixture (1:1) of compounds **7c** and **8c**.
[d] Obtained from hydrolysis of compound **7d**.
[e] **12e** and **13** were obtained from hydrolysis of a mixture of compound **7e** and **10**.
[f] Partially separated after flash chromatography; total yield of **12e** and **13** is 75%.

from conversion of compounds **8a** into **7a**, through **9** as the intermediate (Scheme 4). On the other hand, compound **11d** would form the imine **14** in the presence of excess of HCl to generate the final product **15** (Scheme 7).

Major features for assignment of structures **12**, **13** and **15** are the two doublets due to the NH–CH moiety of the aziridine ring coupling J ca. 9 Hz at 2.5–3.5 ppm (Table 2). Addition of D_2O exchanged the mobile proton and the CH then shows up as a sharp singlet.

3. Conclusion

Fused systems containing 2-oxocarbonylaziridines have been obtained with excellent diastereoselectivity by Diels–Alder cycloaddition between an electrophilic 2*H*-azirine and nucleophilic 2-azadienes. The reaction occurs at room temperature in the absence of catalysis producing moderate to good yields of products. Since the purification of the intermediate compounds were avoided in all steps, the yields may be considered good even in compounds **7** and **8** and some **11** where the results are poorer. The pyrimidone compounds **7**, **8** and **11** are by themselves compounds with potential biological interest, but the same could be said about the hydrolysis products **12**, **13** and **15** which are also masked α-aminoesters with functionalised side chains. Specially structure **15**, where a β-amido group makes it a potential interesting compound after some minor manipulations. Introducing chirality both in the azirine and the diene in order to turn the reactions enantioselective are currently underway.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets(t), doublet of doublets (dd) quartets (q) doublet of quartets (dq) and multiplets (m). J values are in Hz. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin–Elmer 1600 FT-IR spectrometer. Solid samples were run as nujol mulls, and liquids as thin films. Mass spectra were recorded on a VG Autospec M. spectrometer as electron impact spectra (70 eV). Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Dry column flash chromatography was carried out using Kieselgel 60 and water pump vacumm. Thin layer chromatography (TLC) was carried out on 0.25 mm silica gel layer 60DC-Ferigplatter Durasil-25 UV_{254}. Diethyl ether and tetrahydrofuran were dried over sodium using benzophenone as indicator. Triethylamine and the acid chlorides were freshly distilled prior to use. The aldehydes were purified by crystallization if solids or by distillation if liquids. Dry flash chromatography was performed on silica gel 60<0.063 mm for columm chromatography. Petroleum ether 40–60 °C was distilled before use.

4.2. General procedure for the synthesis of the *N*-acylimidates

Triethylamine recently dried was added in one portion to a solution of the imidate hydrochloride in dry DCM, stirred at room temperature under nitrogen. The acid chloride was added dropwise to the reaction mixture. Stirring was continued for another 30 min, and dried petroleum ether 40–60 °C (40 mL) was added. The reaction mixture was filtered over celite and the filtrate concentrated to a residual oil that was redissolved in dry petroleum ether 40–60 °C (20 mL) and passed again over a pad of celite. The filtrate was concentrated to give a pale yellow oil that was identified as the respective acylimidate by ^{1}H NMR spectroscopy.

4.2.1. Ethyl *N*-acetylacetimidate 3a. Reaction mixture:

ethyl acetimidate hydrochloride (1.00 g, 8.10 mmol, 1 equiv.) in DCM (25 mL), triethylamine (2.46 mL, 17.8 mmol, 2.2 equiv.), acetyl chloride (0.58 mL, 8.10 mmol, 1 equiv.). Yield 0.82 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.93 (t, J=7.2 Hz, 3H), 1.68 (s, 3H), 1.89 (s, 3H), 3.82 (q, J=7.2 Hz, 2H) ppm.

4.2.2. Ethyl *N*-propionyl acetimidate 3b. Reaction mixture: ethyl acetimidate hydrochloride (2.00 g, 16.2 mmol, 1 equiv.) in DCM (25 mL), triethylamine (5.42 mL, 39.2 mmol, 2.2 equiv.), propionyl chloride (1.41 mL, 16.20 mmol, 1 equiv.). Yield 1.47 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.12 (t, J=7.2 Hz, 3H), 1.27 (t, J=7.5 Hz, 3H), 1.98 (s, 3H), 2.41 (q, J=7.5 Hz, 2H), 4.08 (q, J=7.2 Hz, 2H) ppm.

4.2.3. Ethyl *N*-phenylacetyl acetimidate 3c. Reaction mixture: ethyl acetimidate hydrochloride (0.58 g, 4.70 mmol, 1 equiv.) in DCM (25 mL), triethylamine (1.42 mL, 10.33 mmol, 2.2 equiv.), phenylacetyl chloride (0.62 mL, 4.70 mmol, 1 equiv.). Yield 0.95 g (98%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.25 (t, J=7.2 Hz, 3H), 1.77 (s, 3H), 3.72 (s, 2H), 4.07 (q, J=7.2 Hz, 2H), 7.30–7.40 (m, 5H, ArH) ppm.

4.2.4. Methyl *N*-phenylacetyl benzimidate 3d. Reaction mixture: methyl benzimidate hydrochloride (0.70 g, 4.08 mmol, 1 equiv.) in DCM (25 mL), triethylamine (1.24 mL, 8.98 mmol, 2.2 equiv.), phenylacetyl chloride (0.54 mL, 4.08 mmol, 1 equiv.). Yield 0.74 g (55%), contaminated with methyl benzimidate hydrochloride 23%. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.66 (s, 2H), 3.82 (s, 3H), 7.04–7.04 (m, 10H, ArH) ppm.

4.2.5. Methyl *N*-propionyl benzimidate 3e. Reaction mixture: methyl benzimidate hydrochloride (1.00 g, 5.83 mmol, 1 equiv.) in DCM (25 mL), triethylamine (1.77 mL, 12.80 mmol, 2.2 equiv.), propionyl chloride (0.51 mL, 5.83 mmol, 1 equiv.). Yield 0.82 g (74%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.06 (t, J=7.5 Hz, 3H), 2.34 (q, J=7.5 Hz, 2H), 3.87 (s, 3H), 7.24–7.62 (m, 5H, ArH) ppm.

4.3. General procedure for the synthesis of the 2-azadienes 1 and 2

Triethylamine recently dried was added in one portion to a solution of the acylimidate in dry ether stirred at room temperature and under N_2. *tert*-Butyldimethylsilyl triflate diluted in dry ether was added dropwise. After the addition was complete the reaction mixture was placed in the freezer for 10 min. The reaction mixture was allowed to reach room temperature and the ethereal phase was separated and the lower phase washed with dry ether (2×25 mL). The organic layers were combined, dried and the ether evaporated. A pale brown oil was obtained that was shown by ^{1}H NMR to be the respective 2-azadienes expected, contaminated with a variable amount of the starting acylimidate.

4.3.1. 4-Ethoxy-2-(*tert*-butyldimethylsilyloxy)-3-aza-1,3-pentadiene 1a. Reaction mixture: ethyl *N*-acetyl acetimidate **3a** (0.82 g, 6.82 mmol, 1 equiv.), dry diethyl ether (25 mL), triethylamine (1.05 mL, 7.59 mmol, 1.1 equiv.), *tert*-butyldimethylsilyl triflate (1.58 mL, 6.90 mmol, 1 equiv.), diluted in dry diethyl ether (10 mL). Yield 1.28 g (65%) contaminated with starting imidate (16%) in accordance with the ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.16 (s, 6H), 0.91 (s, 9H), 1.06 (t, J=7.2 Hz, 3H), 2.01 (s, 3H), 3.42 (s, 1H), 3.70 (s, 1H), 4.08 (q, J=6.9 Hz, 2H) ppm.

4.3.2. 2-Ethoxy-4-(*tert*-butyldimethylsilyloxy)-3-aza-2,4-hexadiene 1b. Reaction mixture: ethyl *N*-propionyl acetimidate **3b** (1.47 g, 10.30 mmol, 1 equiv.), dry diethyl ether (25 mL), triethylamine (1.57 mL, 11.30 mmol, 1.1 equiv.), *ter*t-butyldimethylsilyl triflate (2.36 mL, 10.30 mmol, 1 equiv.), diluted in dry diethyl ether (10 mL). Yield 2.90 g (87%), contaminated with starting acylimidate (20%) in accordance with the ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.12 (s, 6H), 0.90 (s, 9H), 1.26 (t, J=6.9 Hz, 3H), 1.57 (d, J=6.6 Hz, 3H), 1.98 (s, 3H), 3.78 (q, J=6.6 Hz, 1H), 4.10 (q, J=6.9 Hz, 2H) ppm.

4.3.3. 4-Ethoxy-1-phenyl-2-(*tert*-butyldimethylsilyloxy)-3-aza-1,3-pentadiene 1c. Reaction mixture: ethyl *N*-acetylphenyl acetimidate **3c** (0.95 g, 4.63 mmol, 1 equiv.), dry diethyl ether (25 mL), triethylamine (0.71 mL, 5.10 mmol, 1.1 equiv.), *tert*-butyldimethylsilyl triflate (1.10 mL, 4.63 mmol, 1 equiv.), diluted in dry diethyl ether (10 mL). Yield 1.46 g (86%), contaminated with starting imidate (13%) in accordance with the ^{1}H NMR data. Mixture of isomers (4:1). Major isomer ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.21 (s, 6H), 1.01 (s, 9H), 1.33 (t, J=7.2 Hz, 3H), 2.11 (s, 3H), 4.18 (q, J=7.2 Hz, 2H), 4.77 (s, 1H), 7.20–7.30 (m, 3H), 7.75 (d, J=7.2 Hz, 2H) ppm. Minor isomer (some peaks) 0.22 (s, 6H), 0.98 (s, 9H), 1.91 (s, 3H), 4.30 (q, J=7.5 Hz, 2H), 5.26 (s, 1H) ppm.

4.3.4. 1-Methoxy-1,4-diphenyl-3-(*tert*-butyldimethylsilyloxy)-2-aza-1,3-butadiene 1d. Reaction mixture: ethyl *N*-acetylphenyl benzimidate **3d** (0.74 g, 2.93 mmol, 1 equiv.), dry diethyl ether (25 mL), triethylamine (0.45 mL, 3.22 mmol, 1.1 equiv.), *tert*-butyldimethylsilyl triflate (0.67 mL, 2.93 mmol, 1 equiv.), diluted in dry diethyl ether (10 mL). Yield 1.05 g (88%), contaminated with starting acylimidate (10%) in accordance with the ^{1}H NMR data. Mixture of isomers (2:1). Major isomer (some peaks): ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.27 (s, 6H), 1.00 (s, 9H), 3.93 (s, 3H), 4.63 (s, 1H). Minor isomer (some peaks), 0.12 (s, 6H), 0.95 (s, 9H), 3.73 (s, 3H), 5.22 (s, 1H).

4.3.5. (1*E*, 3*Z*) 1-Methoxy-1-phenyl-3-(*t*-butyldimethylsilyloxy)-2-aza-1,3-pentadiene 1e and (1*E*, 3*E*) 1-methoxy-1-phenyl-3-(t-butyldimethylsilyloxy)-2-aza-1,3-pentadiene 2e. Reaction mixture: methyl *N*-propionyl benzimidate **3e** (0.82 g, 4.29 mmol, 1 equiv.), dry diethyl ether (25 mL), triethylamine (0.65 mL, 4.72 mmol, 1.1 equiv.), *tert*-butyldimethylsilyl triflate (0.99 mL, 4.29 mmol, 1 equiv.), diluted in dry diethyl ether (10 mL). Yield 1.14 g (82%), contaminated with starting acylimidate (18%) in accordance with the ^{1}H NMR data. Mixture of isomers (4:1). Major isomer (**2e**): ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.20 (s, 6H), 0.95 (s, 9H), 1.44 (d, J=6.6 Hz, 3H), 3.66 (q, J=6.6 Hz, 1H), 3.86 (s, 3H), 7.30–7.40 (m, 3H), 7.50–7.70 (m, 2H) ppm. Minor isomer (**1e**): 0.14 (s,

6H), 0.88 (s, 9H), 1.25 (d, J=6.6 Hz, 3H), 3.88 (s, 3H), 3.90 (q, J=6.6 Hz, 1H) ppm.

4.4. Synthesis of 2-azadienes 4

Method A. To 1,1,1,3,3,3-hexamethyldisilazane (1 equiv.) was added *n*-butyllithium (1.6 M in hexanes, 0.9 equiv.) over a 5 min period. The reaction solution was kept under magnetic stirring for 15 min at room temperature and then cooled in an ice/water bath. Dry THF (the amount needed for 0.6 M of LiHMDS) was added and the mixture stirred further for 20 min. A solution of the aldehyde (1 equiv.) freshly distilled in dry THF was added over a 7 min period and the resulting solution stirred for 30 min. Trimethylsilyl chloride (0.9 equiv.) was added in one portion and the stirring continued for 30 min. Triethylamine (1.1 equiv.) was added followed by the acid chloride (1.3 equiv.) in dry ether. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. The inorganic salts were filtrated off over celite and the ether was removed in the rotary evaporator to give the crude product, as a solid or an oil.

Method B. To lithium 1,1,1,3,3,3-hexamethyldisilazanate (4–5 equiv.) in dry ether, cooled at 0 °C and in N_2 atmosphere was added the aldehyde (1 equiv.) freshly distilled in dry ether over a 5 min period. The cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. Then the reaction mixture was cooled to 0 °C again and trimethylsilyl chloride (1.3 equiv.) added in one portion. After stirring the reaction mixture at 0 °C for 5 min, the bath was removed and the mixture stirred at room temperature for 1 h 15 min. After this time, triethylamine (1.1 equiv.) was added in one portion followed by dropwise addition of the acid chloride (1.3 equiv.) in dry ether. The reaction mixture was transferred to an water bath at 30 °C and the stirring was continued for another 2 h. The inorganic salts were filtrated off over celite and the ether was removed to give the crude product as a solid or an oil.

4.4.1. 1-Phenyl-3-trimethylsilyloxy-2-aza-1,3-pentadiene 4a. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.94 mL, 2.84 g, 16.97 mmol, 4.5 equiv.) in dry ether (20 mL), benzaldehyde (0.39 mL, 0.4 g, 3.77 mmol, 1 equiv.) dissolved in dry ether (1 mL), trimethylsilyl chloride (2.10 mL, 0.53 g, 16.97 mmol, 4.5 equiv.), triethylamine (0.57 mL, 0.42 g, 4.15 mmol, 1.1 equiv.), phenylacetyl chloride (0.33 mL, 0.35 g, 3.77 mmol, 1 equiv.) in dry ether (4 mL). Yield of a yellow solid 0.73 g (ca. 60%), contaminated with the starting aldehyde, in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.28 (s, 9H, $SiMe_3$), 1.77 (d, J=7.2 Hz, 3H), 5.25 (q, J=7.2 Hz, 1H), 7.25–7.35 (m, ArH, 1H), 7.38–7.50 (m, 2H, ArH), 7.78–7.82 (m, 2H, ArH), 8.35 (s, 1H, 1-H) ppm.

4.4.2. 1-(4-Nitrophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene 4b. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.08 mL, 2.22 g, 13.24 mmol, 5 equiv.) in dry ether (13 mL), 4-nitrobenzaldehyde (0.40 g, 2.65 mmol, 1 equiv.), trimethylsilyl chloride (0.39 mL, 0.35 g, 3.18 mmol, 1.2 equiv.), triethylamine (0.40 mL, 0.29 g, 2.91 mmol, 1.1 equiv.), propionyl chloride (0.30 mL, 0.32 g, 3.44 mmol, 1.3 equiv.) in dry ether (3 mL). Yield of a yellow solid 0.61 (ca. 83%) in accordance with ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.28 (s, 9H, $SiMe_3$), 1.81 (d, J=7.5 Hz, 3H), 5.43 (q, J=7.5 Hz, 1H, 4-H), 7.94 (d, J=9.0 Hz, 2H, ArH), 8.27 (d, J=9.0 Hz, 2H, ArH), 8.32 (s, 1H, 1-H) ppm.

4.4.3. 1-(4-Fluorophenyl)-3-trimethylsilyloxy-2-aza-1,3-butadiene 4c. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.75 mL, 2.70 g, 16.12 mmol, 5 equiv.) in dry ether (16 mL), 4-fluorobenzaldehyde (0.35 mL, 0.40 g, 3.22 mmol, 1 equiv.) in dry ether (3 mL), trimethylsilyl chloride (0.60 mL, 0.53 g, 4.84 mmol, 1.5 equiv.), triethylamine (0.49 mL, 0.36 g, 3.55 mmol, 1.1 equiv.), acetyl chloride (0.30 mL, 0.33 g, 4.19 mmol, 1.3 equiv.) in dry ether (4 mL). Yield of a yellow oil 0.64 g (65%), contaminated with the starting aldehyde (25%) in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$)[†], δ=4.31 (s, 1H, 4-H), 4.65 (s, 1H, 4-H), 8.25 (s, 1H, 1-H) ppm.

4.4.4. 1,4-Diphenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene 4d. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (4.38 mL, 3.15 g, 18.85 mmol, 5 equiv.) in dry ether (19 mL), benzaldehyde (0.38 mL, 0.40 g, 3.77 mmol, 1 equiv.) in dry ether (4 mL), trimethylsilyl chloride (0.56 mL, 0.49 g, 4.52 mmol, 1.2 equiv.), triethylamine (0.57 mL, 0.42 g, 4.15 mmol, 1.1 equiv.), phenylacetyl chloride (0.65 mL, 0.76 g, 4.90 mmol, 1.3 equiv.) in dry ether (5 mL). Yield of a orange oil 1.19 g (ca. 100%) in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.24 (s, 9H, $SiMe_3$), 5.90 (s, 1H, 4-H), 7.18 (t, J=7.5 Hz, 1H, ArH), 7.33 (t, J=7.5 Hz, 3H, ArH), 7.42–7.50 (m, 2H, ArH), 7.63 (d, J=7.5 Hz, 2H, ArH), 7.82–7.85 (m, 2H, ArH), 8.51 (s, 1H, 1-H) ppm.

4.4.5. 1-(4-Nitrophenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene 4e. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.08 mL, 2.22 g, 13.24 mmol, 5 equiv.) in dry ether (13 mL), 4-nitrobenzaldehyde (0.40 g, 2.65 mmol, 1 equiv.), trimethylsilyl chloride (0.39 mL, 0.35 g, 3.18 mmol, 1.2 equiv.), triethylamine (0.40 mL, 0.29 g, 2.91 mmol, 1.1 equiv.), phenylacetyl chloride (0.46 mL, 0.53 g, 3.44 mmol, 1.3 equiv.) in dry ether (3 mL). Yield of a red solid 0.90 g (ca. 99%) in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.29 (s, 9H, $SiMe_3$), 6.17 (s, 1H, 4-H), 7.35 (t, J=7.5 Hz, 2H, ArH), 7.63 (d, J=7.5 Hz, 2H, ArH), 8.01 (d, J=8.7 Hz, 2H, ArH), 8.31 (d, J=8.7 Hz, 2H, ArH), 8.52 (s, 1H, 1-H) ppm.

4.4.6. 1-(4-Fluorophenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene 4f. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.75 mL, 2.7 g, 16.12 mmol, 5 equiv.) in dry ether (16 mL), 4-fluorobenzaldehyde (0.35 mL, 0.40 g, 3.22 mmol, 1 equiv.) dissolved in dry ether (3 mL), trimethylsilyl chloride (0.6 mL, 0.53 g, 4.84 mmol, 1.5 eq), triethylamine (0.49 mL, 0.36 g, 3.55 mmol, 1.1 equiv.), phenylacetyl

[†] Only some peaks have been observed in the crude oil.

chloride (0.55mL, 0.65 g, 4.19 mmol, 1.3 equiv.) in dry ether (4 mL). Yield of a yellow solid 1.10 g (ca. 100%), in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.25 (s, 9H, $SiMe_3$), 5.92 (s, 1H, 4-H), 7.17 (m, 3H, ArH), 7.35 (t, J=7.8 Hz, 2H, ArH), 7.65 (d, J=7.8 Hz, 2H, ArH), 7.87 (dd, $J_{2',3'}$=8.7 Hz, $J_{F,3'}$=5.4 Hz, 2H), 8.48 (s, 1H, 1-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=0.7 ($SiMe_3$), 105.3 (4-C), 115.9 (d, $J_{F,3'}$=21.8 Hz, Ar), 126.0 (Ar), 128.1 (Ar), 128.5 (Ar), 130.8 (d, $J_{F,2'}$=8.3 Hz, Ar), 132.2 (d, $J_{F,1'}$=3.2 Hz, Ar), 136.3 (Ar), 153.3 (3-C), 154.2 (1-C), 164.6 (d, $J_{F,4'}$=252.2 Hz, Ar) ppm.

4.4.7. 1-(4-Methoxyphenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene 4g. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (2.73 mL, 1.97 g, 11.75 mmol, 4 equiv.) in dry ether (15 mL), 4-methoxybenzaldehyde (0.36 mL, 0.4 g, 2.94 mmol, 1 equiv.) dissolved in dry ether (4 mL), trimethylsilyl chloride (1.45 mL, 1.28 g, 11.75 mmol, 4 eq), triethylamine (0.45 mL, 0.33 g, 3.23 mmol, 1.1 equiv.), phenylacetyl chloride (0.56 mL, 0.68 g, 4.41 mmol, 1.5 equiv.) in dry ether (4 mL). Yield of an orange oil 0.94 g (71%) contaminated with 28% of the starting aldehyde in accordance with ^{1}H NMR data. ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.24 (s, 9H, $SiMe_3$), 3.88 (s, 3H), 5.78 (s, 1H, 4-H), 6.99 (d, J=9.0 Hz, 2H, ArH), 7.16 (t, J=7.5 Hz, 1H), 7.26–8.38 (m, 2H, ArH), 7.62 (d, J=7.5 Hz, 2H), 7.81 (d, J=9 Hz, 2H), 8.44 (s, 1H, 1-H) ppm.

4.4.8. 1-(3-Furyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene 4h. Reaction mixture: hexamethyldisilazane (0.98 mL, 0.75 g, 4.63 mmol, 1 equiv.), in dry THF (8 mL), *n*-butyllithium (1.6 M in hexanes, 2.6 mL, 4.16 mmol, 0.9 equiv.) in dry tetrahydrofuran (8 mL), 3-furaldehyde (0.35 mL, 0.4 g, 4.16 mmol, 0.9 equiv.) dissolved in dry tetrahydrofuran (1 mL), trimethylsilyl chloride (0.51 mL, 0.45 g, 4.16 mmol, 1.9 equiv.), triethylamine (0.66 mL, 0.46 g, 4.68 mmol, 1.1 equiv.), phenylacetyl chloride (0.71 mL, 0.84 g, 5.41 mmol, 1.3 equiv.) in dry ether (6 mL). Yield of a yellow solid 1.36 g (ca. 100%) in accordance with ^{1}H NMR data.

^{1}H NMR (300 MHz, $CDCl_3$), δ=0.20 (s, 9H, $SiMe_3$), 5.83 (s, 1H, 4-H), 6.89 (br s, 1H, furyl), 7.16 (t, J=7.5 Hz, 1H), 7.31 (t, J=7.5 Hz, 2H), 7.48 (s, 1H, furyl), 7.59 (d, J=7.2 Hz, 1H), 7.85 (s, 1H, furyl), 8.44 (s, 1H, 1-H) ppm.

4.4.9. 1-(4-Fluorophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene 4i. Reaction mixture: lithium 1,1,1,3,3,3-hexamethyldisilazanate (3.75 mL, 2.70 g, 16.12 mmol, 5 equiv.) in dry ether (16 mL), 4-fluorobenzaldehyde (0.35 mL, 0.40 g, 3.22 mmol, 1 equiv.) dissolved in dry ether (3 mL), trimethylsilyl chloride (0.48 mL, 0.42 g, 3.87 mmol, 1.2 equiv.), triethylamine (0.49 mL, 0.36 g, 3.55 mmol, 1.1 equiv.), propionyl chloride (0.36 mL, 0.39 g, 4.19 mmol, 1.3 equiv.) in dry ether (4 mL). Yield of a yellow solid 0.75 g (93%) in accordance with ^{1}H NMR data. The solid is a mixture of isomers in a ratio 10:1 according to ^{1}H NMR data. Major isomer, ^{1}H NMR (300 MHz, $CDCl_3$), δ=0.27 (s, 9H, $SiMe_3$), 1.76 (d, J=7.2 Hz, 3H), 5.23 (q, J=7.2 Hz, 1H, 4-H), 7.10 (t, J=9.0 Hz, 2H, ArH), 7.78 (dd, $J_{2',3'}$=9.0 Hz, $J_{F,3'}$=5.7 Hz, 2H,), 8.27 (s, 1H, 1-H) ppm. The ^{1}H NMR of the minor isomer is coincident with the spectrum of the major isomer except for a peak at δ=1.98 (d, J=7.2 Hz, 3H) ppm.

4.5. General procedure for the cycloaddition products 7 and 8

To a solution of the 2-azadiene dissolved in dry ether, methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate was added in one portion. The reaction mixture was stirred at room temperature under N_2 for 3 to 7 days, after which the reaction was complete according to TLC (DCM). In some cases a white solid precipitated out of the reaction mixture and was characterized as the cycloadduct **7** or the cycloadduct **8** or a mixture of **7** and **8**. In other cases no precipitate was formed. The solvent was removed, the residual oil dissolved in DCM and SiO_2 was added. The mixture was stirred for several days at room temperature, SiO_2 was filtered off, the solvent was removed leaving an oil that was subject to dry flash chromatography (SiO_2, diethyl ether/petroleum ether 40–60 °C, polarity gradient) to give the respective cycloadducts **7** and **8**, as a white solids.

4.5.1. Methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-2β-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 7a. 4-Ethoxy-2-(*tert*-butyldimethylsilyloxy)-3-aza-1,3-pentadiene **1a** (0.67 g, 2.76 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.61 g, 2.48 mmol, 0.9 equiv.), dry diethyl ether (5 mL), 7 days. Yield 0.50 g (53%). White solid, mixture of two isomers (1:1): methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-2α-methyl-4-oxo-1,3-diaza-bicyclo(4.1.0(heptane-6β-carboxylate **7a** and methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-2β-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **8a**. Treatment of the solid with DCM (20 mL), SiO_2 (1 g), 5 days, formed exclusively methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-2α-methyl-4-oxo-1,3-diaza-bicyclo(4.1.0(heptan-6β-carboxylate **7a** 0.50 g (53%). White solid, mp 173.5–176.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.18 (t, J=6.9 Hz, 3H), 1.85 (s, 2H), 3.16 (d, J=18.3 Hz, 1H), 3.32 (s, 1H, 7-H), 3.40 (d, J=18.3 Hz, 1-H), 3.46 (s, 3H, OMe), 3.65 (dq, J=9.0, 7.2 Hz, 1H), 3.84 (dq, J=9.0, 7.2 Hz, 1H), 6.42 (br s, 1H, N H, disappears after D_2O exchange), 7.14 (m, 1H), 7.28 (dd, J=6.9, 0.9 Hz, 2H) ppm.^{13}C NMR (75.7 MHz, $CDCl_3$), δ=15.3 (Me), 23.5 (Me), 30.3 (CH_2), 44.2 (CH), 52.4 (OMe)[‡], 58.7 (OCH_2), 97.2 (2-C), 128.4 (Ar), 128.7 (Ar), 130.1 (Ar), 135.3 (Ar), 168.9 (CO), 169.8 (CO). IR (nujol), ν=1725, 1750, 3101, 3206 cm^{-1}. $C_{16}H_{18}Cl_2N_2O_4$ (373.2): calcd C 51.45, H 4.82, N 7.51; found C 51.12, H 4.87, N 7.59.

4.5.2. Methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-2α-methyl-4-oxo-1,3-diaza-bicyclo(4.1.0(heptane-6β-carboxylate 8a. 4-Ethoxy-2-(*tert*-butyldimethylsilyloxy)-3-aza-1,3-pentadiene **1a** (0.63 g, 2.59 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.57 g, 2.33 mmol, 0.9 equiv.), dry diethyl ether (15 mL). Yield 0.22 g (25%). White solid, mp 176.0–177.5 °C. ^{1}H NMR, (300 MHz, $CDCl_3$), δ=1.24 (t, J=7.2 Hz, 3H), 1.78 (s, 3H), 3.08 (d, J=18.3 Hz, 1H, 1-H), 3.34 (d, J=18.3 Hz, 1H, 1-H), 3.49 (s, 3H, OMe), 3.58 (s, 1H, 7-H), 3.82 (dq, J=7.2, 9.0 Hz, 1H), 3.96 (dq, J=9.0, 7.2 Hz, 1H), 5.84 (br s, 1H, N

[‡] 6-C May coincide with OMe at δ 52.4 ppm.

H, disappears after D_2O exchange), 7.14 (m, 1H), 7.28 (dd, J=9.0, 6.9 Hz, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=15.4 (Me), 23.9 (Me), 30.5 (CH_2), 44.3 (CH), 52.5 (OMe)[§], 58.9 (OCH_2), 97.2 (2-C), 128.9 (Ar), 129.5 (Ar), 130.1 (Ar), 135.4 (Ar), 168.7 (CO), 168.9 (CO). IR (nujol), ν=1737, 3182, 3269, 3301 cm^{-1}. $C_{16}H_{18}Cl_2N_2O_4$ (373.2): calcd C 51.44, H 4.82, N 7.51; found C 51.27, H 4.66, N 7.33.

4.5.3. Methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-2β,5α-dimethyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 7b. *Method A*. 2-Ethoxy-4-(*tert*-butyldimethylsilyloxy)-3-aza-2,4-hexadiene **1b** (0.65 g, 2.52 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.55 g, 2.23 mmol, 0.9 equiv.), dry diethyl ether (15 mL), 5 days. Yield 0.44 g (51%). White solid, mp 140.5–146.5 °C.[¶] ^1H NMR (300 MHz, $CDCl_3$), δ=1.18 (t, J=7.2 Hz, 3H), 1.56 (d, J=7.2 Hz, 3H), 1.77 (s, 3H), 3.19 (q, J=7.2 Hz, 1H, 5-H), 3.56 (s, 3H, OMe), 3.59 (s, 1H, 7-H), 3.76 (dq, J=8.4, 7.2 Hz, 1H), 3.91 (dq, J=7.2, 8.4 Hz, 1H), 5.88 (br s, 1H, N H, disappears after D_2O exchange), 7.12 (m, 1H), 7.30 (d, J=6.9 Hz, 2H) ppm.^{13}C NMR (75.7 MHz, $CDCl_3$), δ=13.0 (Me), 15.1 (Me), 27.9 (Me), 34.4 (CH), 41.1 (CH), 47.6 (6-C), 52.5 (OMe), 59.2 (OCH_2), 95.8 (2-C), 128.4 (Ar), 129.0 (Ar), 129.9 (Ar), 135.4 (Ar), 169.0 (CO), 169.6 (CO) ppm. IR (nujol), ν=1667, 1723, 3164 cm^{-1}. $C_{17}H_{20}Cl_2N_2O_4$ (387.3): calcd C 52.73, H 5.21, N 7.23; found C 52.59, H 5.19, N 7.26.

Method B. To a solution of the 2-ethoxy-4-(*tert*-butyldimethylsilyloxy)-3-aza-2,4-hexadiene **1b** (0.68 g, 2.64 mmol, 1 equiv.) dissolved in dry ether (15 mL) methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.58 g, 2.37 mmol, 0.9 equiv.) was added in one portion. The reaction mixture was stirred at room temperature under N_2 for 5 days, until complete according to TLC (DCM). The reaction mixture was evaporated and the residual oil was dissolved in DCM (10 mL). Tetrabutylammonium fluoride (1.37 mL, 4.74 mmol, 1.8 equiv.) was added. The mixture was stirred for 45 min at room temperature and then washed with water (2×15 mL). The organic layer was dried over $MgSO_4$ and the solvent removed giving an oil that was kept in the freezer for 48 h. A white solid was formed and washed with diethyl ether (0.38 g, 42%), that proved to be the title compound as shown by a comparison (NMR, TLC) with the specimen obtained previously.

4.5.4. Methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-5α-phenyl-2β-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 7c and methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-5α-phenyl-2α-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 8c. 4-Ethoxy-1-phenyl-2-(*tert*-butyldimethylsilyloxy)-3-aza-1,3-pentadiene **1c**, (1.94 g, 6.05 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (1.18 g, 4.84 mmol, 0.8 equiv.), dry diethyl ether (15 mL), 6 days. Oil was formed which is a mixture of two diastereomers 1 (**7c**): 1 (**8c**) ratio. Flash chromatography (SiO_2, diethyl ether/petroleum ether 40–60 °C, polarity gradient) gave two fractions: (i) mixture of a major and a minor isomers 2 (**7c**): 1 (**8c**), 0.72 g (33%), further separated by recrystallization DCM/petroleum ether giving a major isomer 0.45 g (21%) and a minor isomer 0.24 g (11%); (ii) **7c**, major isomer 0.55 g (25%). Total yield of isomer **4c** 1.0 g (46%), white solid, mp 181.2–183.2 °C. ^1H NMR (300 MHz; $CDCl_3$), δ=1.13 (t, J=7.2 Hz, 3H), 1.91 (s, 3H), 3.40 (s, 3H), 3.75 (dq, J=9.0, 7.2 Hz, 1H), 3.94 (dq, J=9.0, 7.2 Hz, 1H), 4.13 (s, 1H, H-7), 4.40 (s, 1H, H-5), 6.03 (br s, 1H, N H, disappears after D_2O exchange), 7.06–7.13 (m, 1H), 7.23–7.28 (m, 2H), 7.28–7.37 (m, 3H), 7.41–7.46 (m, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=15.3 (Me), 27.5 (Me), 40.7 (CH), 46.9 (CH), 49.7 (6-C), 52.4 (OMe), 59.2 (OCH_2), 96.0 (2-C), 127.9 (Ar), 128.2 (Ar), 128.5 (Ar), 129.4 (Ar), 129.5 (Ar), 130.3 (Ar), 133.3 (Ar), 135.7 (Ar), 167.4 (CO), 168.7 (CO) ppm. IR (nujol), ν=1750, 3062, 3167 cm^{-1}. $C_{22}H_{22}Cl_2N_2O_4$ (449.3): calcd C 58.76, H 4.89, N 6.23; found C 58.84, H 4.96, N 6.24. Minor isomer **8c** 0.24 g (11%), white solid, mp 134.5–137.5 °C. ^1H NMR, (400 MHz, $CDCl_3$), δ=1.29 (t, J=7.2 Hz, 3H), 1.80 (s, 3H), 3.39 (s, 3H), 3.73 (dq, J=9.0, 7.2 Hz, 1H), 3.82 (s, 1H, 7-H), 4.03 (dq, J=7.2, 9.0 Hz, 1H), 4.75 (s, 1H, 5-H), 6.29 (br s, N H, disappears after D_2O exchange, 1H), 7.07–7.11 (m, 1H), 7.29–7.32 (m, 3H), 7.46 (d, J=6.9 Hz, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=15.3 (Me), 23.8 (Me), 42.9 (CH), 46.8 (CH), 49.3 (6-C), 52.0 (OMe), 59.1 (OCH_2), 97.7 (2-C), 127.7 (Ar), 127.8 (Ar), 128.6 (Ar), 129.0 (Ar), 130.1 (Ar), 131.2 (Ar), 133.9 (Ar), 135.5 (Ar), 168.4 (CO), 169.5 (CO) ppm. IR (nujol), ν=1742, 1757, 3094, 3203 cm^{-1}. $C_{22}H_{22}Cl_2N_2O_4$ (449.3): calcd C 58.76, H 4.89, N 6.23; found C 58.69, H 5.22, N 6.14.

4.5.5. Methyl 7-(2,6-dichlorophenyl)-2β,5α-diphenyl-2α-methoxy-4-oxo-1,3-diazabicyclo (4.1.0(heptane-6β-carboxylate 7d and methyl 7-(2,6-dichlorophenyl)-2α,5β-diphenyl-2β-methoxy-4-oxo-1,3-diazabicyclo-(4.1.0(heptane-6β-carboxylate 8d. 1-Methoxy-1,4-diphenyl-3-(*tert*-butyldimethylsilyloxy)-2-aza-1,3-butadiene **1d** (1.75 g, 4.76 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (1.04 g, 4.28 mmol, 0.9 equiv.), dry diethyl ether (15 mL), 6 days. Total yield 0.81 g (38%). White solid, mixture of the two isomers 3 (**7d**): 1 (**8d**). The major isomer **7d**, white solid, mp 175.5–177.5 °C. ^1H NMR (300 MHz, $CDCl_3$), δ=3.22 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.80 (s, 1H, 7-H), 4.41 (s, 1H, 5-H), 6.59 (br s, 1H, N H, disappears after D_2O exchange), 7.10–7.18 (m, 1H), 7.24–7.38 (m, 7H), 7.48–7.56 (m, 3H), 7.88–7.93 (m, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=39.7 (CH), 47.9 (CH), 50.1 (6-C), 52.0 (OMe), 52.2 (OMe), 98.2 (2-C), 127.6 (Ar), 128.0 (Ar), 128.2 (Ar), 128.5 (Ar), 128.6 (Ar), 129.57 (Ar), 129.6 (Ar), 130.4 (Ar), 132.6 135.8 (Ar), 138.8 (Ar), 167.0 (CO), 168.0 (CO) ppm. IR (nujol), ν=1673, 1735, 3064, 3187, 3278 cm^{-1}. HR MS (EI): calcd for $C_{26}H_{22}Cl_2N_2O_4$ 496.0956 [M^+]; found 496.0960. The minor isomer **8d**, white solid, mp 189.1–190.1 °C. ^1H NMR (300 MHz, $CDCl_3$), δ=3.13 (s, 3H, OMe), 3.15 (s, 3H, OMe), 3.66 (s, 1H, 7-H), 5.09 (s, 1H, 5-H), 6.37 (br s, NH, disappears after D_2O exchange, 1H), 7.03 (m, 1H), 7.13 (m, 2H), 7.24–7.38 (m, 3H), 7.44–7.51 (m, 3H), 7.68–7.74 (m, 2H), 7.78–7.84 (m, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=43.6 (CH), 47.2 (CH), 50.7 (Me), 51.2 (6-C), 52.0 (OMe), 99.2 (2-C), 127.3 (Ar), 127.4 (Ar), 128.3 (Ar), 128.5 (Ar), 128.8 (Ar), 128.91(Ar), 128.94

[§] 6-C May coincide with OMe at δ 52.5 ppm.
[¶] Traces of a second isomer evidence for which are signals at δ 1.80 ppm (s, 3H) and 6.04 (br s, 1H, N H).

(Ar), 130.0 (Ar), 135.5 (Ar), 135.8 (Ar), 136.8 (Ar), 167.0 (CO), 169.2 (CO) ppm. IR (nujol), ν=1674, 1750, 3069, 3177 cm^{-1}. HR MS (EI): *m/z* (%)=(43) [M^+-CH_3O]: calcd for $C_{25}H_{19}Cl_2N_2O_4$ 465.0772 [M^+]; found 465.0767.

4.5.6. Methyl 7-(2,6-dichlorophenyl)-2β-phenyl-5α-methyl-2α-methoxy-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 7e and methyl 7-(2,6-dichlorophenyl)-2α-phenyl-5α-methyl-2β-methoxy-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate 10. 1-Methoxy-1-phenyl-3-(*tert*-butyldimethylsilyloxy)-2-aza-1,3-pentadiene 4 (**1e**): 1 (**2e**) ratio (0.59 g, 1.93 mmol, 1 equiv.), methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.42 g, 1.74 mmol, 0.9 equiv.), dry diethyl ether (15 mL), 7 days. Total yield 0.39 g (51%) as a mixture of the two diastereomers 1.2 (**7e**): 1 (**10**). Flash chromatography gave the major product **7e** 0.23 g (30%), and a mixture of **7e** and **10** (21%) also as a solid. Compound **7e** is a white solid, mp 212.0–214.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.48 (d, *J*=6.9 Hz, 3H), 2.59 (q, *J*=6.9 Hz, 1H, 5-H), 3.22 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.77 (s, 1H, 7-H), 6.62 (br s, 1H, N H, disappears after D_2O exchange), 7.18 (t, *J*=7.8 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 2H), 7.38–7.44 (m, 3H), 7.72–7.75 (m, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=12.5 (Me), 35.5 (CH), 40.7 (CH), 47.8 (6-C), 52.3 (OMe), 52.8 (OMe), 98.1 (2-C), 127.3 (Ar), 128.4 (Ar), 128.6 (Ar), 129.0 (Ar), 129.6 (Ar), 130.2 (Ar), 135.5 (Ar), 139.1 (Ar), 168.8 (CO), 169.5 (CO) ppm. IR (nujol), ν=1673, 1731, 1746, 3067, 3176, 3276 cm^{-1}. $C_{21}H_{20}Cl_2N_2O_4$ (435.3): calcd C 57.89, H 4.59, N 6.43; found C 57.70, H 4.70, N 6.50. The sample containing the mixture of two isomers was subjected again to flash chromatography (SiO_2, diethyl ether/petroleum ether, polarity gradient) giving a small amount of the minor isomer **10** as a white solid, mp 187.0–188.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.65 (d, *J*=7.2 Hz, 3H), 3.32 (s, 3H, OMe), 3.36 (s, 3H, OMe), 3.48 (s, 1H, 7-H), 3.82 (q, *J*=7.2 Hz, 1H, 5-H), 6.37 (br s, 1H, N H, disappears after D_2O exchange), 7.00–7.06 (m, 1H), 7.13 (d, *J*=7.5 Hz, 2H), 7.42–7.50 (m, 3H), 7.60–7.68 (m, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=16.1 (Me), 36.1 (CH), 44.1 (CH), 51.0 (OMe), 51.3 (6-C), 52.0 (OMe), 99.0 (2-C), 127.0 (Ar), 128.5 (Ar), 128.7 (Ar), 128.8 (Ar), 129.9 (Ar), 135.6 (Ar), 136.6 (Ar), 167.5 (CO), 172.7 (CO) ppm. IR (nujol), ν=1680, 1751, 3063, 3179 cm^{-1}. $C_{21}H_{20}Cl_2N_2O_4$ (435.3): calcd C 57.89, H 4.59, N 6.43; found C 57.63, H 4.55, N 6.51.

4.6. General procedure for the cycloaddition products 11

To the crude 2-azadiene in ether was added the methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.9 equiv.) at room temperature. The progress of the reaction was followed by TLC until disappearance of the starting azirine. In most cases products precipitated pure (**11b**, **11c**, **11d**, **11e**, **11f**, **11g**) and were washed with cold ether. In cases **11a**, **11h** and **11i**, the reaction mixture gave an oil or a mixture of an oil and a solid that were combined and subjected to dry flash chromatography.

4.6.1. Methyl 7-(2,6-dichlorophenyl)-2α-phenyl-5α-methyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11a. 1-Phenyl-3-trimethylsilyloxy-2-aza-1,3-pentadiene **4a** (0.37 g, 1.57 mmol, 1 equiv.) in ether (10 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.35 g, 1.41 mmol, 0.9 equiv.); reaction was complete in 6 days. Yield 0.13 g (28%) after flash chromatography (SiO_2, diethyl ether/petroleum ether, gradient polarity). White solid, mp 166.6–169.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.70 (d, *J*=7.2 Hz, 3H), 3.40 (q, *J*=6.9 Hz, 1H, 5-H), 3.51 (s, 3H, OMe), 3.74 (s, 1H, 7-H), 5.86 (s, 1H, 2-H), 5.96 (br s, 1H, NH), 7.02–7.20 (m, 3H, ArH), 7.38–7.52 (m, 5H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), 13.0 (Me), 35.8 (CH), 37.4 (CH), 48.3 (6-C), 52.4 (OMe), 70.1 (CH), 127.4 (Ar), 128.3 (Ar), 128.5 (Ar), 128.8 (Ar), 129.6 (Ar), 130.4 (Ar), 135.2 (Ar), 136.7 (Ar), 169.1 (CO), 171.5 (CO). IR (nujol), ν=1724, 1738, 3083, 3216 cm^{-1}. $C_{20}H_{18}Cl_2N_2O_3$ (405.3): calcd C 59.26, H 4.49, N 6.91; found C 59.12, H 4.64, N 6.93.

4.6.2. Methyl 7-(2,6-dichlorophenyl)-2α-[4-(nitrophenyl)]-5α-methyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11b. 1-(4-Nitrophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **4b** (0.17 g, 0.61 mmol, 1 equiv.) in ether (10 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.14 g, 0.55 mmol, 0.9 equiv.). The reaction was complete in 1 day. Yield 0.39 g (71%), white solid mp 168.6–171.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.58 (d, *J*=6.9 Hz, 3H), 3.42 (q, *J*=6.9 Hz, 1H, 5-H), 3.53 (s, 3H, OMe), 3.76 (s, 1H, 7-H), 5.98 (s, 2H, 2-H+N H), 7.09 (dd, *J*=6.9, 9 Hz, 1H, ArH), 7.17 (d, *J*=6.9 Hz, 2H, ArH), 7.70 (d, *J*=9 Hz, 2H, ArH), 8.31 (d, *J*=9 Hz, 2H, ArH,) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=13.0 (Me), 35.9 (CH), 37.4 (CH), 48.4 (6-C), 52.6 (OMe), 69.3 (CH), 124.0 (Ar), 128.7 (Ar), 128.8 (Ar), 129.8 (Ar), 135.0 (Ar), 143.1 (Ar), 148.5 (Ar), 168.7 (CO), 171.8 (CO) ppm. IR (nujol), ν=1674, 1749, 3223 cm^{-1}. $C_{20}H_{17}Cl_2N_3O_5$ (450.3): calcd C 53.34, H 3.80, N 9.33; found C 53.36, H 4.13, N 9.19.

4.6.3. Methyl 7-(2,6-dichlorophenyl)-2α-4-fluorophenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11c. 1-(4-Fluorophenyl)-3-trimethylsilyloxy-2-aza-1,3-butadiene **4c** (0.50 g, 2.09 mmol, 1 equiv.) in ether (15 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.41 g, 1.67 mmol, 0.8 equiv.). The reaction was complete in 6 days. Yield 0.11 g (16%), white solid after washings with ether, mp 189.6–191.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.16 (d, *J*=18.3 Hz, 1H, 5-H), 3.48 (s, 3H, OMe), 3.57 (d, *J*=18.3 Hz, 1H, 5-H), 3.75 (s, 1H, 7-H), 5.87 (br s, 1H, N H), 5.89 (s, 1H, 2-H), 7.04–7.19 (m, 5H, ArH), 7.48–7.54 (m, 2H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=30.8 (CH_2), 39.4 (CH), 45.1 (6-C), 52.7 (OMe), 70.3 (CH), 115.9 (d, $J_{F,3'}$=22.0 Hz, Ar), 128.4 (Ar), 128.8 (Ar), 129.5 (d, $J_{F,2'}$=8.4 Hz, Ar), 129.7 (Ar), 132.5 (d, $J_{F,1'}$=3.2 Hz, Ar), 135.4 (Ar), 163.4 (d, $J_{F,4'}$=249.3 Hz, Ar), 168.8 (CO), 168.9 (CO) ppm. IR (nujol), ν=1686, 1748, 3098, 3257 cm^{-1}. $C_{19}H_{15}Cl_2F\,N_2O_3$ (409.3): calcd C 55.76, H 3.70, N 6.85; found C 55.73, H 4.12, N 6.77.

4.6.4. Methyl 7-(2,6-dichlorophenyl)-2α,5α-diphenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11d. 1,4-Diphenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **4d** (0.62 g, 2.11 mmol, 1 equiv.) in ether (15 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.41 g, 1.69 mmol, 0.8 equiv.). The reaction was complete in 4 days. Yield 0.59 g (75%), white solid, mp 210.2–213.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$), δ=3.38 (s, 3H, OMe), 4.24 (s, 1H, 7-H), 4.63 (s, 1H, 5-H), 6.04 (s, 1H, 2-H), 6.06 (br s, 1H, N H), 7.05 (dd, J=6.9, 9 Hz, 1H, ArH), 7.15 (d, J=6.9 Hz, 2H, ArH), 7.32–7.38 (m, 3H, ArH) 7.42–7.44 (m, 3H, ArH), 7.46–7.60 (m, 4H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=37.4 (CH), 48.2 (CH), 49.2 (6-C), 52.3 (OMe), 70.2 (CH), 127.0 (Ar), 127.90 (Ar), 127.94 (Ar), 128.5 (Ar), 128.9 (Ar), 129.0 (Ar), 129.6 (Ar), 129.8 (Ar), 131.1 (Ar), 133.1 (Ar), 135.7 (Ar), 136.6 (Ar), 168.4 (CO), 169.4 (CO) ppm. IR (nujol), ν=1680, 1735, 3147, 3235 cm^{-1}. $C_{25}H_{20}Cl_2N_2O_3$ (467.4): calcd C 64.24, H 4.74, N 5.99; found C 64.22, H 4.62, N 6.07.

4.6.5. Methyl 7-(2,6-dichlorophenyl)-2α-4-(nitrophenyl)-5α-phenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11e. 1-(4-Nitrophenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **4e** (0.20 g, 0.59 mmol, 1 equiv.) in ether (10 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.13 g, 0.53 mmol, 0.9 equiv.). The reaction was complete in 2 days. Yield 0.17 g (61%). White solid, mp 195.1–196.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.86 (s, 3H, OMe), 4.26 (s, 1H, 7-H), 4.63 (s, 1H, 5-H), 6.15 (s, 1H, 2-H), 6.25 (br s, 1H, N H), 7.04–7.10 (m, 1H, ArH), 7.14–7.20 (m, 2H, ArH), 7.32–7.42 (m, 3H, ArH) 7.50–7.58 (m, 2H, ArH), 7.74 (d, J=9 Hz, 2H, ArH), 8.30 (d, J=9 Hz, 2H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=37.8 (CH), 48.8 (CH), 49.6 (6-C), 52.8 (OMe), 69.9 (CH), 124.5 (Ar), 128.0 (Ar), 128.4 (Ar), 128.7 (Ar), 129.2 (Ar), 129.4 (Ar), 129.6 (Ar), 131.3 (Ar), 133.1 (Ar), 136.0 (Ar), 143.4 (Ar),148.8 (Ar), 168.5 (CO), 170.5 (CO) ppm. IR (nujol), ν=1681, 1748, 3092, 3194 cm^{-1}. $C_{25}H_{19}Cl_2N_3O_5$ (512.4): calcd C 58.60, H 3.75, N 8.20; found C 58.61, H 4.01, N 8.24.

4.6.6. Methyl 7-(2,6-dichlorophenyl)-2α-4-fluorophenyl-5α-phenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11f. 1-(4-Fluorophenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **4f** (0.59 g, 1.97 mmol, 1 equiv.) in ether (15 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.43 g, 1.78 mmol, 0.9 equiv.). The reaction was complete in 2 days. Yield 0.60 g (70%). White solid, mp 152.4–153.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.38 (s, 3H, OMe), 4.22 (s, 1H, 7-H), 4.61 (s, 1H, 5-H), 6.03 (s, 1H, 2-H), 6.09 (br s, 1H, NH), 7.02–7.19 (m, 5H, ArH), 7.32–7.40 (m, 3H, ArH), 7.44–7.48 (m, 4H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=37.8 (CH), 48.6 (CH), 49.6 (6-C), 52.7 (OMe), 116.3 (d, $J_{F,3'}$=22.0 Hz), 128.28 (Ar), 128.30 (Ar), 129.0 (Ar), 129.4 (Ar), 129.5 (d, $J_{F,2'}$=6.8 Hz), 130.2 (Ar), 131.5 (Ar), 132.0 (d, $J_{F,1'}$= 3.0 Hz), 133.5 (Ar), 136.1 (Ar), 163.5 (d, $J_{F,4'}$=249.0 Hz), 168.8 (CO), 170.3 (CO). IR (nujol), ν=1688, 1743, 3187 cm^{-1}. $C_{25}H_{19}FCl_2N_2O_3$ (485.4): calcd C 61.86, H 3.95, N 5.77; found C 61.53, H 4.67, N 5.54.

4.6.7. Methyl 7-(2,6-dichlorophenyl)-2α-4-(methoxyphenyl)-5α-phenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11g. 1-(4-Methoxyphenyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **4g** (0.68 g, 2.07 mmol, 1 equiv.) in ether (10 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.40 g, 1.66 mmol, 0.8 equiv.). The reaction was complete in 2.5 days. Yield 0.49 g (60%). White solid, mp 208.1–210.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.37 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.22 (s, 1H, 7-H), 4.61 (s, 1H, 5-H), 5.99 (s, 1H, 2-H), 6.02 (br s, 1H, N H), 6.94 (d, J=8.7 Hz, 2H, ArH), 7.04 (dd, J=9, 6.9 Hz, 1H, ArH), 7.14 (d, J=6.9 Hz, 2H, ArH), 7.30–7.37 (m, 3H, ArH), 7.43 (d, J=8.7 Hz, 2H, ArH), 8.30 (dd, J=8.1, 6.3 Hz, 2H, ArH,) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=37.4 (CH), 48.1 (CH), 49.2 (6-C), 52.3 (OMe), 55.3 (OMe), 69.8 (CH), 114.2 (Ar), 127.85 (Ar), 127.88 (Ar), 128.3 (Ar), 128.5 (Ar), 128.86 (Ar), 128.88 (Ar), 129.9 (Ar), 131.1 (Ar), 133.2 (Ar), 135.7 (Ar), 160.3 (Ar), 168.5 (CO), 169.5 (CO). IR (nujol), ν=1675, 1727, 3168 cm^{-1}. $C_{26}H_{22}Cl_2N_2O_4$ (497.4): calcd C 62.78, H 4.47, N 5.63; found C 62.54, H 4.77, N 5.47.

4.6.8. Methyl 7-(2,6-dichlorophenyl)-2α-3-furyl-5α-phenyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11h. 1-(3-Furyl)-4-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **4h** (0.65 g, 2.27 mmol, 1 equiv.) in ether (15 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.44 g, 0.82 mmol, 0.8 equiv.). The reaction was complete in 7 days. Yield 0.23 g (28%) after flash chromatography (SiO_2, diethyl ether/petroleum ether, polarity gradient). White solid, mp 173.5–173.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=3.36 (s, 3H, OMe), 4.16 (s, 1H, 7-H), 4.50 (s, 1H, 5-H), 6.01 (br s, 1H, N H), 6.52 (s, 1H, 2-H), 7.06 (dd, J=6.9, 9.0 Hz, 1H, ArH), 7.21 (d, J=6.9 Hz, 2H, ArH), 7.31–7.39 (m, 4H, ArH) 7.43–7.44 (m, 1H, ArH), 7.47–7.50 (m, 2H, ArH), 7.63 (s, 1H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=37.6 (CH), 48.8 (CH), 49.9 (6-C), 52.7 (OMe), 64.5 (CH), 109.3 (furyl), 123.0 (Ar), 128.5 (Ar), 129.0 (Ar), 129.6 (Ar), 130.0 (Ar), 131.2 (Ar), 133.3 (Ar), 136.2 (Ar), 141.1 (Ar), 144.3 (furyl), 168.7 (CO), 169.8 (CO) ppm. IR (nujol), ν=1736, 1753, 3213 cm^{-1}. $C_{23}H_{18}Cl_2N_2O_4$ (457.3): calcd C 60.40, H 3.98, N 6.13; found C 60.42, H 4.22, N 6.06.

4.6.9. Methyl 7-(2,6-dichlorophenyl)-2α-4-(fluorophenyl)-5α-methyl-4-oxo-1,3-diazabicyclo[4.1.0]heptane-6β-carboxylate 11i. 1-(4-Fluorophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **4i** (0.29 g, 1.16 mmol, 1 equiv.) in ether (10 mL) and 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **6** (0.26 g, 1.05 mmol, 0.9 equiv.). The reaction was complete in 1 day. Yield 0.15 g (96%), brownish oil (very impure). After dry flash chromatography (diethyl ether/petroleum ether, polarity gradient) gave a white solid (33%), mp 213.4–215.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.70 (d, J=6.9 Hz, 3H), 3.39 (q, J=6.9 Hz, 1H, 5-H), 3.51 (s, 3H), 3.72 (s, 1H, 7-H), 5.86 (s, 2H, 2-H+N H), 7.04–7.19 (m, 5H, ArH), 7.44–7.50 (m, 2H, ArH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=13.5 (Me), 36.3 (CH), 37.9 (CH), 48.8 (6-C), 52.9 (OMe), 69.9 (CH), 116.3 (d, $J_{F,3'}$=22.0 Hz), 128.9 (Ar), 129.1 (Ar), 129.8 (d, $J_{F,2'}$=8.3 Hz), 130.7 (Ar), 133.2 (d, $J_{F,1'}$=3.0 Hz), 135.7 (Ar), 163.7 (d, $J_{F,4'}$=249.0 Hz), 169.4 (CO), 171.9 (CO) ppm. IR (nujol), ν=1674, 1751, 3088, 3193 cm^{-1}. $C_{20}H_{17}Cl_2FN_2O_3$ (423.3): calcd C 56.74, H 4.06, N 6.62; found C 56.60, H 4.16, N 6.63.

4.7. General procedure for the hydrolysis products 12, 13 and 15

To a solution of the pyrimidone or of the mixture of diastereomeric pyrimidones in THF was added dropwise HCl diluted in THF, in an ice/water bath. After the addition

was complete the mixture was stirred at room temperature for 1 h. THF was partially removed to a 1/3 of the original volume and aq. $NaHCO_3$ (20 mL) was added. The mixture was vigorously stirred for 15 min. The organic phase was separated and the aq. phase was washed with DCM (3×25 mL). The organic phases were combined, washed with water (25 mL), and dried over $MgSO_4$. The solvent was removed giving a pale yellow oil that crystallized in the fridge. The solid was recrystallized from DCM/petroleum ether 40–60 °C giving the product as a white solid. In one case (**e**) the hydrolysis compounds **12** and **13** were shown to be a mixture of two isomers that were separated by flash chromatography (SiO_2, diethyl ether/petroleum ether, gradient polarity).

4.7.1. Methyl 2-((2-acetylamino)-2-oxoethyl(-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 12a. Methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-2α-methyl-4-oxo-1,3-diaza-bicyclo(4.1.0(heptan-6β-carboxylate **8a** (0.21 g, 0.56 mmol), THF (10 mL) and conc. HCl (46 μL) in THF (5 mL). Yield 0.14 g (74%). White solid, mp 164.3–165.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=2.35 (s, 3H, Me), 2.67 (d, J=17.1 Hz, 1H), 2.87 (br d, J=8.4 Hz, 1H, N H aziridine, disappears after D_2O exchange), 3.21 (d, J=8.4 Hz, 1H, 3-H), 3.57 (s, 3H, OMe), 3.83 (d, J=17.1 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.27 (d, J=7.5 Hz, 2H), 8.82 (br s, 1H, N H) ppm. ^{13}C NMR, (75.7 MHz, $CDCl_3$) δ=25.0 (Me), 41.0 (CH_2), 42.6 (2-C), 45.5 (CH), 53.0 (OMe), 127.8 (Ar) 128.9 (Ar), 129.5 (Ar), 130.9 (Ar), 135.7 (Ar), 170.5 (CO), 171.0 (CO), 171.3 (CO) ppm. IR (nujol), ν=1725, 1745, 3205, 3255 cm^{-1}. $C_{14}H_{14}Cl_2N_2O_4$ (345.0): calcd C 48.71, H 4.06, N 8.12; found C 48.26, H 4.16, N 8.07. HR MS (EI): m/z (%)=(0.1) [M $^+$]: calcd for $C_{14}H_{14}O_4N_2Cl_2$ 344.0331; found 344.0325.

4.7.2. Methyl 2-((2-acetylamino)-2-oxoethyl(-1-methyl-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 12b. Methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-2β,5α-dimethyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **7b** (0.60 g, 2.46 mmol), THF (15 mL) and conc. HCl (200 μL) in THF (10 mL). Yield 0.37 g (42%). White solid, mp 116.3–117.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.30 (d, J=7.2 Hz, 3H), 2.43 (s, 3H, Me), 2.85 (br d, J=9.0 Hz, 1H, N H aziridine, disappears after D_2O exchange), 3.37 (d, J=9.0 Hz, 1H, 3-H), 3.56 (s, 3H, OMe), 3.75 (q, J=7.2 Hz, 1H), 7.18 (t, J=8.4 Hz, 1H), 7.28 (d, J=8.4 Hz, 2H), 8.71 (br s, 1H, N H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=12.9 (Me), 25.5 (Me), 41.2 (CH), 41.8 (CH), 45.8 (2-C), 53.2 (OMe), 127.9 (Ar) 129.1 (Ar), 129.4 (Ar), 130.9 (Ar), 135.5 (Ar), 170.4 (CO), 172.1 (CO), 173.1 (CO) ppm. IR (nujol), ν=1724, 1741, 3067, 3157, 3211 cm^{-1}. $C_{15}H_{16}O_4N_2Cl_2$ (359.2): calcd C 50.15, H 4.45, N 7.80; found C 50.24, H 4.68, N 7.80.

4.7.3. Methyl 2-((2-acetylamino)-2-oxoethyl(-1-phenyl-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 12c. Methyl 7-(2,6-dichlorophenyl)-2α-ethoxy-5α-phenyl-2β-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **7c** and methyl 7-(2,6-dichlorophenyl)-2β-ethoxy-5α-phenyl-2α-methyl-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **8c** (0.21 g, 0.46 mmol), THF (10 mL) and conc. HCl (38 μL) in THF (5 mL). Yield 0.17 g (87%). White solid, mp 191.1–191.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=2.40 (d, J=9.9 Hz, 1H, 3-H), 2.43 (s, 3H, Me), 3.08 (br d, J=9.9 Hz, 1H, N H aziridine, disappears after D_2O exchange), 3.56 (s, 3H, OMe), 5.02 (s, 1H, 1-H), 7.12 (t, J=7.5 Hz, 1H), 7.28 (d, J=7.5 Hz, 2H), 7.36–7.45 (m, 5H), 7.88 (br s, 1H, N H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=25.3(Me), 41.5 (CH), 45.5 (2-C), 53.0 (CH), 53.3 (OMe), 127.7 (Ar) 128.9 (Ar), 129.0 (Ar), 129.9 (Ar), 130.5 (Ar), 131.1 (Ar), 131.7 (Ar), 135.5 (Ar), 170.7 (CO), 171.0 (CO), 171.9 (CO) ppm. IR (nujol), ν=1735, 3168, 3242 cm^{-1}. $C_{20}H_{18}Cl_2N_2O_4$. 1/2H_2O (430.3): calcd C 55.82, H 4.23, N 6.51; found C 55.87, H 4.43, N 6.47.

4.7.4. Methyl 2-((2-benzoylamino)-2-oxoethyl(-1-phenyl-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 12d. Methyl 7-(2,6-dichlorophenyl)-2β,5α-diphenyl-2α-methoxy-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **7d** (0.22 g, 0.44 mmol), THF (10 mL) and conc. HCl (37 μL) in THF (5 mL). Yield 0.15 g (68%). White solid, mp 180.2–181.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=2.51 (d, J=9.9 Hz, 1H, 3-H), 3.02 (br d, J=9.9 Hz, 1H, N H aziridine, disappears after D_2O exchange), 3.55 (s, 3H, OMe), 5.93 (s, 1H, 1-H), 7.09–7.15 (m, 1H), 7.22–7.62 (m, 10H), 7.75 (d, J=7.2 Hz, 2H), 8.66 (br s, 1H, N H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=40.8 (CH), 46.0 (2-C), 52.5 (CH), 53.0 (OMe), 127.7 (Ar) 128.3 (Ar), 128.9 (Ar), 129.0 (Ar), 131.1 (Ar), 131.5 (Ar), 131.7 (Ar), 131.8 (Ar), 132.6 (Ar), 133.2 (Ar), 135.7 (Ar), 164.6 (CO), 171.1 (CO), 173.6 (CO) ppm. IR (nujol), ν=1714, 1731, 3168, 3263 cm^{-1}. HR MS (FAB): calcd 483.0878 [M+1]; found 483.0876.

4.7.5. Methyl 2-((2-benzoylamino)-2-oxoethyl(-1-methyl-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 12e and 13. Methyl 7-(2,6-dichlorophenyl)-2β-phenyl-5α-methyl-2α-methoxy-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **7e** and methyl 7-(2,6-dichlorophenyl)-2α-phenyl-5α-methyl-2β-methoxy-4-oxo-1,3-diazabicyclo(4.1.0(heptane-6β-carboxylate **10**, mixture 1.2 (**7e**): 1 (**10**), (0.37 g, 0.85 mmol), THF (10 mL), conc. HCl (71 μL) in THF (5 mL). Total yield 0.27 g (75%): two isomers 1.2 (**12e**): 1 (**13**). The isomers were partially isolated after flash chromatography (SiO_2, diethyl ether/petroleum ether 40–60 °C, polarity gradient). Compound **12e** (0.1 g, 29%), white solid, mp 189.3–190.0 °C. ^{1}H NMR, (300 MHz, $CDCl_3$), δ=1.41 (d, J=7.2 Hz, 3H), 2.38 (d, J=9.3 Hz, 1H), 3.39 (d, J=9.3 Hz, 1H, 3-H), 3.58 (s, 3H, OMe), 4.44 (q, J=7.2 Hz, 1H, 1-H), 7.18 (t, J=8.1 Hz, 1H), 7.30 (br d, J=7.5 Hz, 2H), 7.54 (m, 2H), 7.63 (m, 1H), 7.92 (dd, J=8.4, 1.2 Hz, 2H), 9.25 (br s, 1H, N H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=12.8 (Me), 41.0 (CH), 46.1 (2-C), 51.1 (OMe), 127.7 (Ar) 128.9 (Ar), 129.3 (Ar), 131.3 (Ar), 132.8 (Ar), 133.2 (Ar), 135.6 (Ar), 165.1 (CO), 171.0 (CO), 175.3 (CO) ppm. IR (nujol), ν=1712, 1735, 3071, 3279 cm^{-1}. $C_{20}H_{18}Cl_2N_2O_4$. 1/2H_2O (421.3): calcd C 55.82, H 4.23, N 6.51; found C 55.99, H 4.31, N 6.54.

Compound **13**, white solid, mp 139.5–139.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.58 (d, J=7.5 Hz, 3H), 2.97 (d, J=9.0 Hz, 1H, NH aziridine), 3.38 (d, J=9 Hz, 1H, 3-H), 3.42 (q, J=7.5 Hz, 1H, 1-H), 3.64 (s, 3H, OMe), 7.20 (t, J=7.8 Hz, 1H), 7.31 (d, J=7.8 Hz, 1H), 7.40–7.55 (m, 2H), 7.55–7.70 (m, 1H), 7.98 (dd, J=6.9, 1.5 Hz, 2H), 10.4 (br s, 1H, N H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=14.6 (Me), 44.4 (CH), 44.7 (CH), 46.6 (2-C), 53.3 (OMe), 127.0

(Ar) 127.8 (Ar), 128.5 (Ar), 128.9 (Ar), 129.9 (Ar), 130.4 (Ar), 133.0 (Ar), 135.5 (Ar), 164.9 (CO), 169.9 (CO), 170.8 (CO) ppm. IR (nujol), ν=1725, 1735, 3070, 3295 cm^{-1}. HR MS (FAB): calcd 421.0722 [M+1]; found 421.0703.

4.7.6. Methyl 2-[carbamoyl(phenyl)methyl]-3-(2,6-dichlorophenyl)aziridine-2-carboxylate 15. Methyl-7-(2,6-dichlorophenyl)-2α,5α-diphenyl-4-oxo-1,3-diaza-bicyclo[4.1.0]heptane-6β-carboxylate **11d** (0.32 g, 0.68 mmol, 1 equiv.), THF (15 mL), containing conc. HCl (2.44 mL). Yellow solid 0.17 g (67%), mp 167.5–167.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ=2.42 (d, J=8.7 Hz, 1H, 3-H), 3.04 (d, J=8.7 Hz, 1H, NH aziridine), 3.58 (s, 3H, OMe), 4.88 (s, 1H, 1′ H), 5.77 (s, 2H, NH_2), 7.10 (t, J=7.2 Hz, 1H), 7.22 (d, J=7.5 Hz, 2H), 7.33–7.40 (m, 3H), 7.48 (d, J=7.8 Hz, 2H) ppm. ^{13}C NMR (75.7 MHz, $CDCl_3$), δ=42.0 (CH), 46.1 (2-C), 51.9 (CH), 53.0 (OMe), 127.6 (Ar) 128.3 (Ar), 128.7 (Ar), 129.0 (Ar), 130.2 (Ar), 131.2 (Ar), 133.7 (Ar), 135.5 (Ar), 171.0 (CO), 173.7 (CO). IR (nujol), ν=1685, 1740, 3171, 3290 cm^{-1}. $C_{18}H_{16}Cl_2N_2O_3$ (379.3): calcd C 57.00, H 4.26, N 7.39; found C 56.99, H 4.48, N 7.20.

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In-water reactivity of nucleosides and nucleotides: one-step preparation and biological evaluation of novel ferrocenyl-derivatives

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Abstract—The reactivity in water of a series of nucleosides and nucleotides towards ferrocenemethanol was investigated. Several adducts incorporating the ferrocenemethyl moiety into the heterocyclic base were isolated and their activity was tested against HIV-1, HBV, YFV, BVDV and several bacteria. However, none of the new compounds showed significant antiviral activity nor cytotoxicity. The reaction with ferrocenemethanol of the model dinucleotide $^{5'}$dCpdG$^{3'}$, for a direct comparison of the behaviour of purine versus pyrimidine bases, is also discussed.

1. Introduction

Metallocenes are known to exhibit a wide range of biological activity.[1] Among them, ferrocene has attracted special attention since it is a neutral, chemically stable and non-toxic molecule, which is able to cross cell membranes.[2] Ferrocene can be easily derivatized and functionalized or also oxidized to ferricenium salts. Many iron-containing sandwich compounds have displayed interesting cytotoxic,[3–5] antitumour,[6,7] antimalarial,[8,9] antifungal[10] and DNA-cleaving activity.[5]

Metalloceno-nucleosides, that is structurally modified nucleosides bearing ferrocene residues attached to the bases, have been first designed by Meunier and co-workers.[3] They envisaged a new class of analogues in which the biological activity due to the nucleoside moieties could be coupled to the specific properties imparted by the ferrocene residue (e.g., enhanced cell uptake, ability to form non-covalent, stable interactions with cellular targets, for instance, nucleic acids) in order to obtain new lead compounds to be tested as antivirals and/or antitumorals. By exploiting palladium-catalyzed reactions, they synthesized nucleosides and nucleobases linking the ferrocene group at the 5-position of pyrimidines or at the 8-position of adenine; however, these derivatives turned out to be only slightly cytotoxic.

In addition to their potential in therapeutics, ferrocene units have also been recognized as useful tools for diagnostic applications by virtue of their reversible and highly tunable redox properties.[11] Synthetic oligonucleotides (ODNs) labelled with a ferrocene residue proved to be extremely sensitive electrochemically active probes for the specific detection, even on a femtomole scale, of single-stranded nucleic acids or duplex DNA carrying the complementary sequence. Various ferrocene-containing building blocks have, therefore, been synthesized and either linked at the 5′-end,[12–14] or, once converted into the appropriate phosphoramidite derivative, inserted at specific internal positions of ODN chains by automated solid phase oligonucleotide synthesis.[15–18] Another approach has involved the preparation of two ferrocene-labelled analogues of thymidine-5′-triphosphate, incorporated into DNA chains by polymerase-mediated enzymatic synthesis.[19] In addition, as a novel nucleoside bearing the ferrocene electrophore for electron transfer studies, 5′-ferrocene-amido-5′-deoxy-adenosine has been synthesized by mixing ferrocenoyl hydroxybenzotriazole ester and

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5′-amino-5′-deoxy-adenosine in THF–borate buffer at pH=9.0.[20]

In our studies on modified nucleosides and oligonucleotides, we recently reported the synthesis of a new ferrocenyl-thymidine analogue, obtained in high yields by Mitsunobu condensation of ferrocenemethanol and an appropriately ribose-protected thymidine derivative.[21] This reaction, carried out in benzene in the presence of an excess of tri-*n*-butylphosphine and azodicarboxylic dipiperidide (ADDP), led to the incorporation of the ferrocene unit exclusively at the 3-N position of the nucleobase.

In order to explore the reactivity of nucleosides and nucleotides in a non-protected form and more friendly reaction systems, it occurred to us that ferrocenemethanol could be a suitable reaction substrate, because of the well-recognized electrophilicity of the methylene unit attached to the ferrocene residue.[22,23] In particular, our aim was to investigate the viability of pseudo-biomimetic conditions, specifically the use of water as the solvent of choice, for the synthesis of new nucleoside analogues. We report here the direct formation of nucleoside adducts in a synthetic approach involving neither temporary protection procedures nor the use of additives as condensing agents. A similar approach has been also followed in previous experiments, in which ribo- and 2′-deoxyribonucleosides, mixed in water as such with sugars, were found to form adducts, even if in extremely low amounts, which for instance could account for DNA alterations in patients affected with diabetes mellitus.[24–26] This study can also furnish useful models to gain a deeper insight into nucleic acids–metallocenes interactions and open perspectives for post-synthetic labelling of ODNs with a non-isotopic, redox tag.

2. Results and discussion

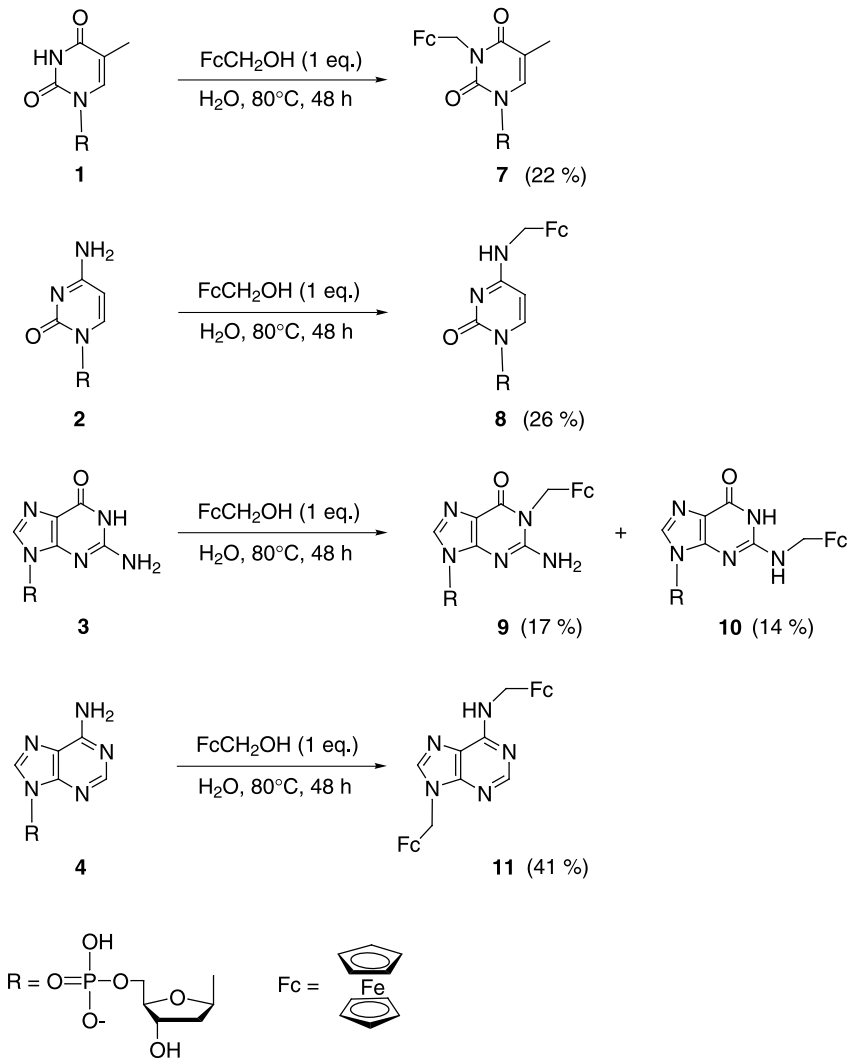
2.1. Chemistry

In a typical experiment, 0.2 mmol of the starting nucleoside or nucleotide (**1**–**6**) were incubated with an equimolar amount of ferrocenemethanol in water (10 mL) at 80 °C. After 2 days, the reaction mixtures, monitored by TLC, showed the partial consumption of the starting material and the concomitant formation of new products incorporating the ferrocene moiety, as revealed by the blue spots appearing on the TLC after acidic spraying. For the reactions with compounds **1**–**3**, extraction with $CHCl_3$ allowed the recovery of pure unreacted ferrocenemethanol, with the reaction products and the other starting materials collected in the aqueous phase. The resulting ferrocenyl-nucleotides **7**–**10** (Scheme 1) were easily purified from the starting nucleoside-5′-monophosphates by filtration on SEP-PAK RP18 cartridges. In the case of adduct **11**, the reaction product was recovered in the organic phase and separated from unreacted ferrocenemethanol by silica gel chromatography. The crude reaction mixtures obtained from uridine (**5**) and 3′-deoxy-3′-α-azidothymidine (**6**) were purified on silica gel columns, respectively furnishing adducts **12**, **13** and **14**, with the latter two compounds obtained as a mixture, then separated by HPLC on a RP18 column (Scheme 2). Average yields of purified ferrocenyl compounds were always ca. 20%, except in the case of **11**, which was obtained in 41% yield.

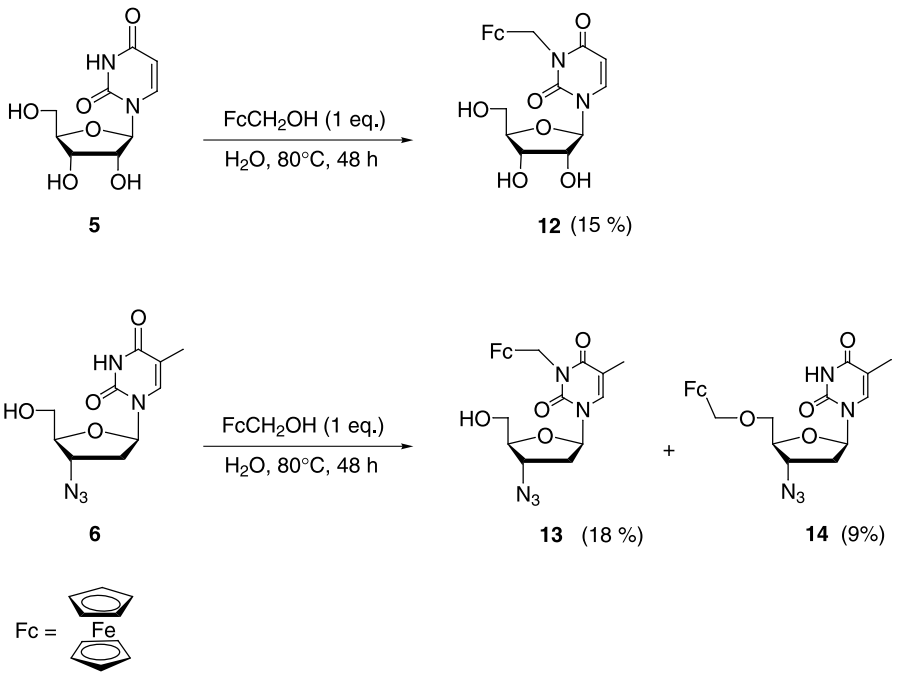
The identity and purity of all the isolated compounds were ascertained by ^{1}H, ^{31}P, ^{13}C NMR spectroscopy and MS data. Notably, all adducts (except **14**, which in fact was identified as the 5′-O-ferrocenylated derivative) showed a characteristic upfield shift, both in the ^{1}H and ^{13}C NMR spectra, of the signal attributed to the CH_2 attached to the ferrocene residue, indicative of the insertion of the ferrocenemethyl group into one of the nitrogen atoms of the heterocyclic base. In all cases, this can be interpreted as the result of the nucleophilic attack of the nitrogen atoms of the nucleobases on this methylene group, affording mono-ferrocenylated derivatives **7**–**10** and **12**–**13**. Only in the case of **6**, was a minor, but detectable, amount (9%) of the adduct bearing the ferrocenemethyl group on the 5′-OH position (**14**) found. The formation of **11** from 2′-deoxyadenosine-5′-monophosphate in the same reaction system could be explained assuming, as the first event, the insertion of one ferrocenemethyl group at the 6-N position of the nucleobase; as a result of the base alkylation, a strong destabilization of the N-glycosidic bond is induced,[27] which, once cleaved, renders the 5-membered ring of adenine susceptible to a second alkylation by ferrocenemethanol.

This hypothesis has been confirmed by reacting the sole adenine base with ferrocenemethanol in the same reaction conditions. The reaction mixture gave **11** as the major product, together with the mono-ferrocenylated adduct, bearing the ferrocenemethyl residue attached to the N-6 position. The structure of **11** has been assigned on the basis of ^{1}H and ^{13}C NMR spectra. Particularly the presence of NOE effects between the sharp singlet integrating for two protons at 5.11 ppm, and, therefore, attributed to the CH_2 linked to the ferrocene residue which is not attached to the N-6 position, and both the H-2 and H-8 protons of the adenine residue, respectively at 8.47 and 7.67 ppm, allowed the exclusion of the other possible regioisomer, with the second ferrocenemethyl group attached to N-7. In addition, NH at C6 gave NOE only with the H-2 and H-8 protons of the adenine residue, while no NOE was found between the $NH-CH_2$ system at C6 and the CH_2 at 5.11 ppm, which should be expected if in the presence of N^6,7-N-bis-ferrocenemethyl-adenine.

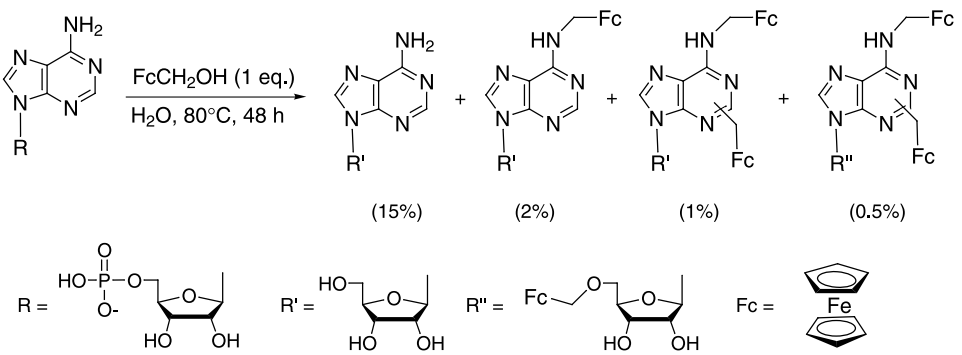
In order to further investigate the reactivity of adenine nucleotides towards ferrocenemethanol, this treatment was extended to adenosine-5′-monophosphate, intrinsically having a more resistant N-glycosidic bond than its 2′-deoxy congener. Interestingly, when the purine ribonucleotide was left in contact with equimolar amounts of ferrocenemethanol for 2 days at 80 °C, in a more concentrated reaction system (ca. 0.06 M), no putative ferrocenyl nucleotide adduct could be found and the starting material was recovered mostly unmodified. A detectable amount (ca. 15%) of adenosine was observed, which in turn generated, even if in traces, the corresponding mono-, bis- and even tri-ferrocenylated derivative (ca. 2, 1 and 0.5% yields, respectively, Scheme 3), thus demonstrating that, after the phosphate loss, the resulting adenosine behaved not differently from the other ribonucleoside examined, that is, uridine. These adducts, after extraction into the organic



Scheme 1.



Scheme 2.

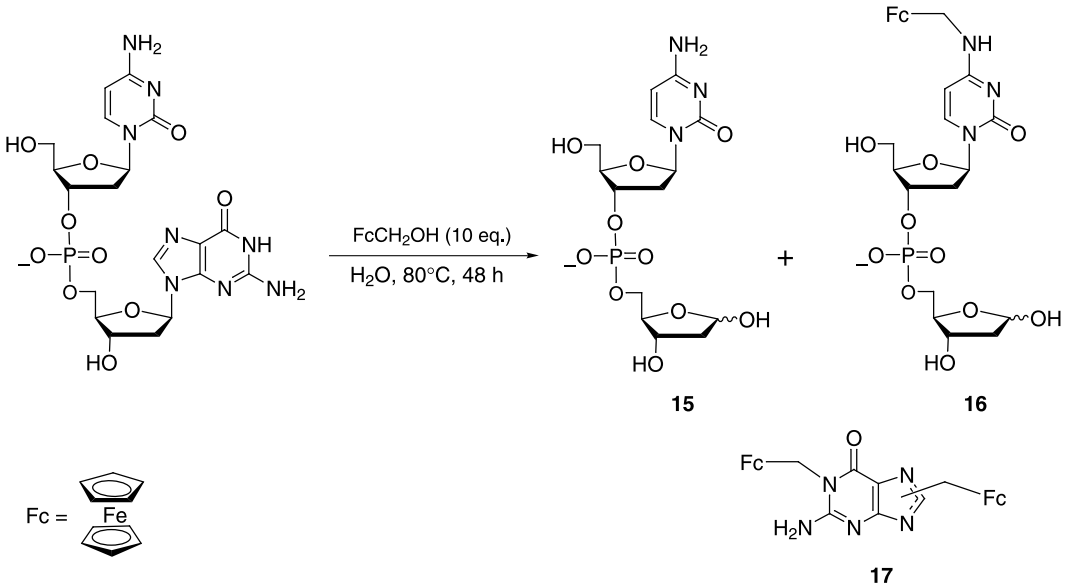


Scheme 3.

phase, could be isolated by silica gel chromatography and were identified on the basis of their ESI-MS and NMR data (significantly, no signal was detected in their ^{31}P NMR spectra). Most probably, the dephosphorylation process of the ribonucleotide was simply thermally induced, since almost the same percentage of free adenosine could be recovered when adenosine-5′-monophosphate was incubated in water at 80 °C for 48 h in the absence of ferrocenemethanol as a control.

The not negligible reactivity of the nucleobases in water towards ferrocenemethanol can be forced to completion by using an excess of ferrocenemethanol versus the starting nucleoside/nucleotide. This has been confirmed using a model dinucleotide as the substrate. $^{5'}$dCpdG$^{3'}$ (Scheme 4), treated with a 10-fold excess of ferrocenemethanol, was completely converted into a mixture (ca. 1:1) of two compounds, which, after washings with $CHCl_3$ to remove the unreacted ferrocenemethanol, were easily separated by RP-HPLC. These two derivatives have been identified, on the basis of ^1H, ^{31}P NMR and ESI-MS, as **15** and **16**, respectively, that is the dimers having an abasic site at the guanine level, with the one eluting at higher retention time incorporating one ferrocenemethyl residue on the exocyclic amino group of the cytosine base. Interestingly, in the presence of an excess of ferrocenemethanol, the 2′-deoxyguanosine moiety in the dimer showed the same behaviour as 2′-deoxyadenosine-5′-monophosphate.

In order to confirm this, we investigated the $CHCl_3$ extract of the reaction mixture, which, as the sole new compound, contained a bis-ferrocenylated adduct of guanine in ca. 1:1 molar ratio with respect to the starting dinucleotide. This adduct, in analogy with adenine derivative **11**, was identified as **17** and found to be identical to the compound obtained independently, for comparison, by reacting guanine with an excess of ferrocenemethanol in the same reaction conditions. In addition, a reinvestigation of the reaction of **3**, carried out with equimolar amount of ferrocenemethanol, led to the isolation also in this reaction of crude **17**, present in traces. In this case, it was not possible to identify the obtained compound as the N-7 or the N-9 ferrocenylated adduct. The ^1H NMR data allowed us to exclude alkylation on N-2 (a broad singlet integrating for two protons was found at 7.05 ppm, exchangeable with D_2O and, therefore, assigned to the exocyclic NH_2 moiety attached to C-2) and both ^1H and ^{13}C NMR data indicated that no O^6-alkylation has occurred. Since no NH protons were found, two regioisomers were proposed: 1-N, N^7- and 1-N, N^9-bis-ferrocenemethylguanine. Probably as a consequence of strong base-stacking interactions, unfortunately NOESY spectra failed to give unambiguous information on



Scheme 4.

the position of the ferrocenemethyl groups. Whatever the fate of guanine, in all cases a general reactivity for purine 2′-deoxyribonucleotides towards ferrocenemethanol can be hypothesized: the first event is a base alkylation, which in appropriate conditions can be followed by depurination, with the 2′-deoxyadenosine-5′-monophosphate more labile in its N-glycosidic bond compared to the 2′-deoxyguanosine derivative. The latter in fact gives nucleobase excision only in the presence of an excess of alkylating reagent.

From these preliminary experiments, it seems plausible that, by appropriately modulating the amount of ferrocenemethanol, this reagent could be exploited to induce an abasic site in an oligodeoxyribonucleotide chain selectively at the sole adenine level, or at all the purine nucleosides present. In all cases, it was demonstrated that ferrocenemethanol does not affect the phosphodiester linkages in oligonucleotides, reacting only with purines and pyrimidines. By virtue of the ease of purification of the reaction system, the described method, after optimization, can be exploited for post-synthetic labelling of oligodeoxyribonucleotides, where the specific insertion of the redox-active ferrocene probe on the bases can be desirable. Further studies on longer model oligonucleotides are in progress to evaluate the synthetic potential of the here described method for ODNs labelling experiments and/or for producing nucleobase excision selectively at the purine sites under very mild conditions.

Novel ferrocenyl-nucleosides **7**–**14** have been tested for their cytotoxicity and antiviral, antifungal and antimicrobial activities.

3. Biological results

The ferrocenemethyl-derivatives **7**–**14** were evaluated for anti-HIV-1 activity in MT-4 cells. The evaluation of cytotoxicity (see Table 1) was carried out in parallel to determine whether the compounds were endowed with selective antiviral or antimicrobial activity. As far as the cytotoxicity is concerned, only compounds bearing thymine (**7**, **13**, **14**) showed significant cytotoxicity against MT-4 cells (Table 1). The ferrocenyl-derivatives of 3′-deoxy-3′-α-azidothymidine **13** and **14** were the sole compounds active against HIV-1. However, they proved to be 10 to 300-fold less potent than AZT, used as the reference drug.

Table 1. Cytotoxicity and anti-HIV-1 activity of ferrocenyl-derivatives **7**–**14**

Compound	CC_{50}[a] (MT-4)	EC_{50}[b] (HIV-1)	SI[c] (CC_{50}/EC_{50})
7	49	>49	
8	>100	>100	
9	≥100	>100	
10	>100	>100	
11	>100	>100	
12	>100	>100	
13	29	3.2	9
14	53	0.1	530
AZT[d]	150	0.01	15,000

[a] Compound concentration (μM) required to reduce the viability of mock-infected MT-4 cells by 50%, as determined by the MTT method.
[b] Compound concentration (μM) required to achieve 50% protection of MT-4 cells from the HIV-1 induced cytopathogeneticy, as determined by the MTT method.
[c] Ratio CC_{50}/EC_{50}. Data represent mean values for three independent determinations. Variation among duplicate samples was less than 15%.
[d] 3′-α-Azidothymidine (AZT) was used as reference drug.

When tested for broader antiviral activity, the above compounds were inactive against representatives of different classes of viruses, such as a Hepadnavirus (HBV), Yellow Fever Virus (YFV) and Bovine Viral Diarrhoea Virus (BVDV).

Furthermore, when tested against representative bacteria (*Staphylococcus aureus* and *Salmonella* spp.), mycobacteria (*Mycobacterium smegmatis* and *Mycobacterium fortuitum*) and fungi (*Candida albicans* and *Aspergillus fumigatus*), none of the derivatives showed significant activity (data not shown).

4. Conclusions

Unprotected nucleosides and nucleotides **1**–**6**, dissolved in water with equimolar amounts of ferrocenemethanol, were shown to form, in the absence of condensing agents, new compounds **7**–**14**, incorporating the ferrocene moiety into the heterocyclic base. This procedure, far from being efficient in terms of yields, presents several advantages: (1) it is based on a one-pot reaction; (2) a friendly reaction system is adopted; (3) no expensive condensing agents are required; (4) tedious procedures to introduce and, once the final adducts have been obtained, to remove protecting groups are avoided; (5) very simple final mixtures are obtained, from which the desired ferrocenylated derivatives can be easily purified; in most cases, in fact, the target compounds could be isolated in a very pure form by a rapid filtration on C-18 SEP-PAK cartridges; (6) the starting materials are in all cases easily recovered unmodified and can be recycled. The new ferrocenylated nucleosides and nucleotides were tested for their biological activities, which in all the studied cases were found to be quite modest. The treatment with ferrocenemethanol was also carried out on a ribonucleotide (adenosine-5′-monophosphate), which proved to be unreactive as such, but, once dephosphorylated, was able to generate ferrocenemethyl adducts in analogy with the other ribonucleoside studied, that is, uridine. In addition, the dinucleotide $^{5'}$dCpdG$^{3'}$ was taken as a model in a preliminary experiment aimed at the extension of this study to ODNs. In the presence of an excess of ferrocenemethanol, an abasic site was quantitatively produced at the guanine level, and the cytosine residue was alkylated on the base with almost 40% efficiency. In our opinion, this synthetic study is of interest for a better comprehension of metallocene–nucleic acids interactions in a pseudo-biomimetic system, as well as allowing a simple protocol for a post-synthetic labelling of oligonucleotides with redox-active tagging and/or for purine base excision in mild conditions.

5. Experimental

Ferrocenemethanol was purchased from Aldrich. Column chromatography was performed on silica gel (Merck,

Kieselgel 40, 0.063–0.200 mm). TLC analysis was carried out on Merck Kieselgel 60 F254 0.25 mm plates, visualized with UV light. UV measurements were performed on a Jasco V 530 spectrophotometer. NMR spectra were recorded on Bruker WM-400 and Varian INOVA 500 spectrometers. All chemical shifts are expressed in ppm with respect to the residual solvent signal. ^{31}P NMR spectra were recorded on a Bruker WM-400 spectrometer at 161.98 MHz using 85% H_3PO_4 as external standard. The oligonucleotide $^{5'}$dCpdG$^{3'}$ was assembled on a Millipore Cyclone Plus DNA synthesizer, using standard commercially available 5′-*O*-(4,4′-dimethoxytrityl)-3′-*O*-[(2-cyanoethyl)-*N*,*N*-diisopropyl]-2′-deoxyribonucleoside phosphoramidites as the building blocks. HPLC analyses and purifications were performed on a Beckman System Gold instrument equipped with a UV detector module 166 and a Shimadzu Chromatopac C-R6A integrator, using a Nucleosil 100-5 C_{18} column (Macherey-Nagel, 4.6×250 mm, 5 μm). ESI mass spectrometric analyses were performed on a Waters Micromass ZQ mass spectrometer, equipped with an Electrospray source used in the negative and/or positive mode.

The abbreviation Cp has been introduced for the cyclopentadienyl rings of the ferrocene unit; Cp_a is for the ring linking the methylene group, Cp_b for the unfunctionalized one.

Compounds. Test compounds were dissolved in DMSO at 100 mM and then diluted into the culture medium.

Cells. MT-4 cells were grown at 37 °C in a 5% CO_2 atmosphere in RPMI 1640 medium, supplemented with 10% foetal calf serum (FCS), 100 UI/mL penicillin G and 100 μg/mL streptomycin. Cell cultures were checked periodically for the absence of mycoplasma contamination with the MycoTect Kit (Gibco).

Virus. Human immunodeficiency virus type 1 (HIV-1) was obtained from supernatants of persistently infected H9/III$_B$ cells. The HIV-1 stock solution had a titre of 1.0×10^7 cell culture infectious dose 50 ($CCID_{50}$)/mL.

Antiviral assays. Activity of compounds against HIV-1 was based on inhibition of virus-induced cytopathogenicity in MT-4 cells acutely infected at a multiplicity of infection of 0.01. Cytotoxicity of test compounds was evaluated in parallel with their antiviral activity and was based on the viability of mock-infected cells, as monitored by the MTT method.[28]

Antibacterial and antimycotic assays. *S. aureus*, *Salmonella* spp. and *A. fumigatus* are clinical isolates, *C. albicans* 10231 is an ATCC strain. Assays were carried out in Triptosio agar for *S. aureus* and *Salmonella* spp., and in Sabouraud dextrose broth for *C. albicans* and *A. fumigatus*, with an inoculum of 10^3 bacteria/mL and 5×10^3 yeast/mL. *A. fumigatus* inocula were obtained from cultures grown at 37 °C for 1 day and then diluting to 0.05 OD_{50}/mL. Minimum inhibitory concentrations (MIC) were determined after incubations at 37 °C for 18 h in the presence of serial dilutions of test compounds.

Anti-mycobacterial assays. *Mycobacterium tuberculosis* 27294 and *M. smegmatis* 19420 are ATCC strains, *M. fortuitum* is a clinical isolate. MICs were assessed in microtiter plates by adding 20 μL aliquots of a culture suspension to 80 μL of Middlebrook 7H9 medium containing serial dilutions of test compounds. At the end of incubation, the number of viable mycobacteria was determined by the MTT method.[28]

5.1. Synthesis

5.1.1. 3-*N*-Ferrocenemethyl-thymidine-5′-monophosphate (7). Thymidine-5′-monophosphate, sodium salt (75 mg, 0.23 mmol), was dissolved in water (10 mL) and left in contact with ferrocenemethanol (50 mg, 0.23 mmol) at 80 °C for 2 days. Then $CHCl_3$ (10 mL) was added to the reaction mixture and the two phases separated. The organic phase gave the unreacted, pure ferrocenemethanol (37 mg, 74%); the concentrated aqueous phase was purified using SEP-PAK C18 cartridges, eluted first with H_2O, then with H_2O/CH_3OH (1:1, v/v). The fractions eluted with H_2O/CH_3OH (1:1, v/v), collected and taken to dryness, afforded 26 mg (0.05 mmol, 22% yield) of **7** as a yellow, amorphous solid: R_f 0.30 [*tert*-butanol–acetic acid–H_2O 60:25:15 (v/v/v)]; ^{1}H NMR (200 MHz, CD_3OD): δ 7.85 (1H, s, H-6 T); 6.36 (1H, dd, *J*=6.5, 6.5 Hz, H-1′); 4.74 (2H, s, H-3 and H-4 of Cp_a); 4.51–4.47 (3H, overlapped signals, H-2 and H-5 Cp_a, H-3′); 4.34–4.23 (7H, overlapped signals, 5H of Cp_b and CH_2-Cp_a); 4.05–4.00 (3H, overlapped signals, H-4′ and H_2-5′); 2.24–2.19 (2H, m, H_2-2′); 1.94 (3H, s, CH_3 T). ^{13}C NMR (50 MHz, DMSO-d_6): δ 162.42 (C-4 T); 150.34 (C-2 T); 135.09 (C-6 T); 109.02 (C-5 T); 86.38 (C-1′); 84.71 (C-4′); 83.03 (quaternary C of Cp_a); 70.77 (C-3′); 69.78 (C-3 and C-4 of Cp_a); 68.36 (5C of Cp_b); 67.53 (C-2 and C-5 of Cp_a); 64.11 (C-5′); 39.54 and 39.17 (C-2′ and CH_2-Cp_a); 12.75 (CH_3 T). ^{31}P NMR (161.98 MHz, DMSO-d_6): δ 1.96. ESI-MS (negative ions): found *m*/*z*: 518.37 $(M-H)^-$. HRMS (FAB, negative mode): Calcd for $C_{21}H_{24}N_2O_8PFe$ $(M-H)^-$: 518.05415; found: 518.05781.

5.1.2. N^4-Ferrocenemethyl-2′-deoxycytidine-5′-monophosphate (8). 2′-Deoxycytidine-5′-monophosphate, sodium salt (71 mg, 0.23 mmol), was dissolved in water (10 mL) and left in contact with ferrocenemethanol (50 mg, 0.23 mmol) at 80 °C for 2 days. Then $CHCl_3$ (10 mL) was added to the reaction mixture and the two phases separated. The organic phase gave the unreacted, pure ferrocenemethanol (35 mg, 70%); the concentrated aqueous phase was purified using SEP-PAK C18 cartridges, eluted first with H_2O, then with H_2O/CH_3OH (1:1, v/v). The fractions eluted with H_2O/CH_3OH (1:1, v/v), collected and taken to dryness, afforded 30 mg (0.06 mmol, 26% yield) of pure compound **8** as a yellow, amorphous solid: R_f 0.45 [*tert*-butanol–acetic acid–H_2O 60:25:15 (v/v/v)]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (1H, d, *J*=7.6 Hz, H-6 C); 6.37 (1H, dd, *J*=6.5, 6.5 Hz, H-1′); 5.90 (1H, d, *J*=7.6 Hz, H-5 C); 4.81 (H-3 and H-4 of Cp_a buried under HDO signal); 4.49 (1H, m, H-3′); 4.33 (2H, s, H-2 and H-5 of Cp_a); 4.27 (2H, s, CH_2-Cp_a); 4.17 (5H, s, 5H of Cp_b); 4.12 (1H, m, H-4′); 4.04 (2H, m, H_2-5′); 2.35–2.16 (2H, m, H_2-2′). ^{1}H NMR (400 MHz, DMSO-d_6) significant signals at δ 7.50 (1H, t, N*H*–C). ^{13}C NMR (100 MHz, CD_3OD): δ 165.18 (C-2); 159.10 (C-4); 141.99 (C-6); 112.78 (C-5);

97.79 (C-1′); 88.20 (quaternary C of Cp_a); 87.69 (C-4′); 73.01 (C-3′); 70.24 (C-3 and C-4 of Cp_a); 70.08 (5C of Cp_b); 69.51 (C-2 and C-5 of Cp_a); 66.28 (C-5′); 42.36 and 41.44 (C-2′ and *C*H_2-Cp_a). ^{31}P NMR (161.98 MHz, CD_3OD): δ 1.06. ESI-MS (negative ions): found *m*/*z*: 504.34 $(M-H)^-$. HRMS (FAB, negative mode): Calcd for $C_{20}H_{23}N_3O_7PFe$ $(M-H)^-$: 504.06230; found: 504.06128.

5.1.3. 1-*N*-Ferrocenemethyl-2′-deoxyguanosine-5′-monophosphate (9) and N^2-ferrocenemethyl-2′-deoxyguanosine-5′-monophosphate (10). 2′-Deoxyguanosine-5′-monophosphate, sodium salt (80 mg, 0.23 mmol), was dissolved in water (10 mL) and left in contact with ferrocenemethanol (50 mg, 0.23 mmol) at 80 °C for 2 days. Then $CHCl_3$ (10 mL) was added to the reaction mixture and the two phases were separated. The organic phase gave the unreacted, pure ferrocenemethanol (32 mg, 64%); the concentrated aqueous phase was purified using SEP-PAK C18 cartridges, eluted first with H_2O, then with H_2O containing increasing amounts of CH_3OH. The fractions were eluted with H_2O/CH_3OH (7:3, v/v), collected and taken to dryness, to afford a mixture of two compounds. This mixture was then purified by HPLC on a RP18 analytical column using a linear gradient from 0 to 100% of eluent B in A in 30 min (eluent A: 0.1 M TEAB, pH=7.0; eluent B=CH_3CN, flow 1.0 mL/min, λ=260 nm), generating pure **9** (retention time: 18.3 min, 21 mg, 0.038 mmol, 17% yields) and **10** (retention time: 20.5 min, 18 mg, 0.033 mmol, 14% yields).

Compound **9**, yellow, amorphous solid: R_f 0.50 [*tert*-butanol–acetic acid–H_2O 60:25:15 (v/v/v)]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.09 (1H, s, H-8 G); 6.40 (1H, dd, *J*=6.0, 6.0 Hz, H-1′); 4.81 (H-3 and H-4 of Cp_a buried under HDO signal); 4.66 (1H, m, H-3′); 4.30 (2H, s, H-2 and H-5 of Cp_a); 4.27 (1H, m, H-4′); 4.20 (5H, s, 5H of Cp_b); 4.14 (2H, s, CH_2-Cp_a); 4.09–3.98 (2H, m, H_2-5′); 2.77–2.70 (1H, m, H-2′$_a$); 2.43–2.36 (1H, m, H-2′$_b$). ^{1}H NMR (400 MHz, DMSO-d_6) significant signals at δ 6.71 (2H, bs, NH_2). ^{13}C NMR (100 MHz, CD_3OD): δ 160.04 (C-6 G); 154.33 (C-2 G); 153.20 (C-4 G); 138.42 (C-8 G); 115.80 (C-5 G); 88.41 (C-4′); 86.84 (C-1′); 85.57 (quaternary C of Cp_a); 73.89 (C-3′); 70–06 (C-2, C-3, C-4, C-5 of Cp_a); 69.59 (5C of Cp_b); 66.61 (C-5′); 41.93 and 41.71 (C-2′ and *C*H_2-Cp_a). ^{31}P NMR (161.98 MHz, CD_3OD): δ 1.52. ESI-MS (negative ions): found *m*/*z*: 544.37 $(M-H)^-$. HRMS (FAB, negative mode): Calcd for $C_{21}H_{23}N_5O_7PFe$ $(M-H)^-$: 544.06845; found: 544.06996.

Compound **10**, yellow, amorphous solid; R_f 0.50 [*tert*-butanol–acetic acid–H_2O 60:25:15 (v/v/v)]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (1H, s, H-8); 6.24 (1H, dd, *J*=6.0, 6.0 Hz, H-1′); 5.03 (2H, s, H-3 and H-4 of Cp_a); 4.64 (1H, m, H-3′); 4.41 (2H, s, H-2 and H-5 of Cp_a); 4.20 (5H, s, 5H of Cp_b); 4.12 (2H, s, CH_2-Cp_a); 4.09 (2H, apparent singlet, overlapped signals, H-4′ and H-5′$_a$); 4.02–3.96 (1H, m, H-5′$_b$); 2.89–2.84 (1H, m, H-2′$_a$); 2.30–2.25 (1H, m, H-2′$_b$). ^{1}H NMR (400 MHz, DMSO-d_6): significant signals at δ 7.24 (1H, broad triplet, N*H*-G). ^{13}C NMR (75 MHz, CD_3OD) upfield signals: δ 88.18 (C-4′); 86.02 (C-1′); 84.24 (quaternary C of Cp_a); 73.70 (C-3′); 70.79 (C-2 and C-5 of Cp_a); 70.13 (5C of Cp_b); 69.41 (C-3 and C-4 of Cp_a); 67.25 (C-5′); 41.68 and 40.38 (C-2′ and *C*H_2-Cp_a). ^{31}P NMR (161.98 MHz, CD_3OD): δ 1.44. ESI-MS (negative ions): found *m*/*z*: 544.40 $(M-H)^-$. HRMS (FAB, negative mode): Calcd for $C_{21}H_{23}N_5O_7PFe$ $(M-H)^-$: 544.06845; found: 544.07002.

5.1.4. N^6,9-*N*-bis-Ferrocenemethyl-adenine (11). 2′-Deoxyadenosine-5′-monophosphate, sodium salt (77 mg, 0.23 mmol), was dissolved in water (10 mL) and left in contact with ferrocenemethanol (50 mg, 0.23 mmol) at 80 °C for 2 days. A yellowish powder precipitated, which was found to be soluble in organic solvents, and the reaction mixture was extracted with $CHCl_3$ (10 mL); the organic phase was then purified by silica gel chromatography using $CHCl_3/CH_3OH$ 99:1 (v/v) as the eluent, affording 50 mg of a pure compound, as a yellow, amorphous solid, identified as **11** (41% yields); R_f 0.40 [CH_2Cl_2/CH_3OH 95:5 (v/v)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (1H, s, H-2); 7.67 (1H, s, H-8); 5.90 (1H, broad triplet, N*H*-A); 5.11 (2H, s, CH_2-Cp_a of the ferrocene unit linked to N-9); 4.50 (2H, d, *J*=4.5 Hz, CH_2-Cp_a of the ferrocene unit linked to N-6); 4.32–4.13 (18H, m, protons of Cp of the two ferrocene unit). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.97 (C-6); 139.10 (C-2); 130.77 (C-4); 128.69 (C-8); 119.38 (C-5); 81.80 (2 quaternary C of Cp_a); 68.93, 68.75, 68.49, 68.24, 68.05 (10C of Cp_b; C-2, C-3, C-4 and C-5 of Cp_a for the two ferrocene units); 43.01 and 38.61 (2 *C*H_2-Cp_a). ESI-MS (positive ions): found *m*/*z*: 532.38 $(M+H)^+$. HRMS (FAB, positive mode): Calcd for $C_{27}H_{25}N_5Fe_2Na$ $(M+Na)^+$: 554.07064; found: 554.07006.

5.1.5. 3-*N*-Ferrocenemethyl-uridine (12). Uridine (113 mg, 0.46 mmol) was dissolved in water (10 mL) and left in contact with ferrocenemethanol (100 mg, 0.46 mmol) at 80 °C for 2 days. The reaction mixture was extracted with $CHCl_3$ (10 mL); the organic phase was then purified by silica gel chromatography using $CHCl_3/CH_3OH$ 9:1 (v/v) as the eluent, affording 30 mg of a pure compound, as a yellow, amorphous solid, identified as **12** (15% yields): R_f 0.50 [CH_2Cl_2/CH_3OH 85:15 (v/v)]; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96 (1H, d, *J*=7.5 Hz, H-5 U); 5.86 (1H, d, *J*=5.0 Hz, H-1′); 5.81 (1H, d, *J*=7.5 Hz, H-6 U); 5.43 (1H, d, *J*=5.5 Hz, OH-2′); 5.14 (1H, d, *J*=5.0 Hz, OH-3′); 4.77 (1H, m, OH-5′); 4.31 (2H, s, H-3 and H-4 of Cp_a); 4.24 (5H, s, 5H of Cp_b); 4.13 (2H, s, H-2 and H-5 of Cp_a); 4.06 (1H, m, H-2′); 3.99 (1H, m, H-3′); 3.89 (1H, m, H-4′); 3.68–3.54 (2H, m, H_2-5′); 3.38 (2H, s, CH_2-Cp_a). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.13 (C-4 U); 151.24 (C-2 U); 139.88 (C-6 U); 101.69 (C-5 U); 89.43 (C-1′); 85.54 (C-4′); 83.53 (quaternary C of Cp_a); 74.30 (C-2′); 70.50 (C-3 and C-4 of Cp_a); 70.47 (C-3′); 69.14 (5C of Cp_b); 68.34 (C-2 and C-5 of Cp_a); 61.44 (C-5′); *C*H_2-Cp_a is buried under the residual solvent signal. ESI-MS (positive ions): found *m*/*z*: 442.97 $(M+H)^+$. HRMS (FAB, positive mode): Calcd for $C_{20}H_{22}N_2O_6FeNa$ $(M+Na)^+$: 463.05684; found: 463.05910.

5.1.6. 3-*N*-Ferrocenemethyl-3′-deoxy-3′-α-azidothymidine (13) and 5′-*O*-ferrocenemethyl-3′-deoxy-3′-α-azidothymidine (14). 3′-Deoxy-3′-α-azidothymidine (50 mg, 0.19 mmol) was dissolved in water (10 mL) and left in contact with ferrocenemethanol (41 mg, 0.19 mmol) at 80 °C for 2 days. The reaction mixture was extracted with $CHCl_3$ (10 mL); the organic phase was then taken to dryness, redissolved in H_2O/CH_3CN 9:1 (v/v) and purified

by HPLC on a RP18 analytical column using a linear gradient from 0 to 100% of eluent B in A in 30 min (eluent A: 0.1 M TEAB, pH=7.0; eluent B=CH_3CN, flow 1.0 mL/min, λ=260 nm), allowing pure **13** (retention time: 20.4 min, 16 mg, 0.034 mmol, 18% yields) and **14** (retention time: 20.8 min, 8 mg, 0.017 mmol, 9% yields).

Compound **13**: R_f 0.75 [CH_2Cl_2/CH_3OH 95:5 (v/v)]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.78 (1H, s, H-6 T); 6.19 (1H, dd, J=6.0, 6.4 Hz, H-1′); 4.84 (2H, s, H-3 and H-4 of Cp_a); 4.36–4.30 (3H, overlapped signals, H-2 and H-5 of Cp_a and H-3′); 4.17 (5H, s, 5H of Cp_b); 4.08 (2H, s, CH_2-Cp_a); 3.91 (1H, m, H-4′); 3.84–3.70 (2H, m, H_2-5′); 2.38 (2H, dd, J=6.0, 6.4 Hz, H_2-2′); 1.89 (3H, s, CH_3 T). ^{13}C NMR (100 MHz, CD_3OD): δ 165.54 (C-4 T); 152.58 (C-2 T); 136.82 (C-6 T); 111.38 (C-5 T); 87.39 (C-1′); 86.66 (C-4′); 84.63 (quaternary C of Cp_a); 71.78 (C-3 and C-4 of Cp_a); 70.06 (5C of Cp_b); 69.48 (C-2 and C-5 of Cp_a); 62.82 (C-3′); 62.02 (C-5′); 41.67 (CH_2-Cp_a); 38.91 (C-2′); 13.68 (CH_3 T). ESI-MS (positive ions): found m/z 466.40 $(M+H)^+$. HRMS (FAB, positive mode): Calcd for $C_{21}H_{23}N_5O_4FeNa$ $(M+Na)^+$: 488.09971; found: 488.10228.

Compound **14**, R_f 0.70 [CH_2Cl_2/CH_3OH 95:5 (v/v)]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.66 (1H, s, H-6 T); 6.15 (1H, dd, J=6.0, 6.4 Hz, H-1′); 4.89 (H-3 and H-4 of Cp_a buried under the HDO signal); 4.43 (2H, s, H-2 and H-5 of Cp_a); 4.35–4.16 (8H, overlapped signals, H-3′, 5H of Cp_b and CH_2-Cp_a); 4.00 (1H, m, H-4′); 3.82–3.60 (2H, m, H_2-5′); 2.34 (2H, dd, J=6.0, 6.4 Hz, H_2-2′); 1.76 (3H, s, CH_3 T). ^{13}C NMR (100 MHz, CD_3OD): δ 166.87 (C-4 T); 152.97 (C-2 T); 138.29 (C-6 T); 112.01 (C-5 T); 86.62, 85.40 (C-1′ and C-4′); 84.46 (quaternary C of Cp_a); 71.57 (CH_2-Cp_a); 71.22 (C-3 and C-4 of Cp_a); 70.86 (C-5′); 70.22 (5C of Cp_b); 70.04 (C-2 and C-5 of Cp_a); 62.88 (C-3′); 38.92 (C-2′); 13.21 (CH_3 T). ESI-MS (positive ions): found m/z 466.03 $(M+H)^+$. HRMS (FAB, positive mode): Calcd for $C_{21}H_{23}N_5O_4FeNa$ $(M+Na)^+$: 488.09971; found: 488.09863.

5.2. Reaction of ferrocenemethanol with adenosine-5′-monophosphate

Adenosine-5′-monophosphate, sodium salt (200 mg, 0.56 mmol), was dissolved in 10 mL of water and left in contact with ferrocenemethanol (120 mg, 0.56 mmol) at 80 °C for 2 days. The reaction mixture was extracted with $CHCl_3$ (10 mL); the aqueous phase was concentrated and purified on SEP-PAK cartridges, which afforded pure adenosine (ca. 15% yields) as well as the starting material. The organic phase was then purified by preparative TLC eluted with $CHCl_3$/CH_3OH 95:5 (v/v), affording three new bands, respectively at R_f 0.25, 0.35 and 0.70—in the same eluent system—which were isolated in very low yields (ca. 2, 1 and 0.5%, respectively). These new compounds, which significantly gave no signal in their ^{31}P NMR spectra, were identified on the basis of their ESI-MS (m/z signals, in the positive mode, at 465.20, 663.22, 861.26, respectively) and NMR spectra (data not shown) as the mono-, bis- and tri-ferrocenylated derivatives of adenosine.

5.2.1. Reaction of ferrocenemethanol with the dinucleotide $^{5'}$dCpdG$^{3'}$. Dinucleotide $^{5'}$dCpdG$^{3'}$ (8.0 mg, 0.013 mmol) was dissolved in water (2 mL) and left in contact with ferrocenemethanol (28 mg, 0.13 mmol) at 80 °C for 2 days. The reaction mixture was extracted with $CHCl_3$ (2 mL); the aqueous phase was then taken to dryness, redissolved in H_2O/CH_3CN 9:1 (v/v) and purified by HPLC on a RP18 analytical column using a linear gradient from 0 to 25% of eluent B in A in 60 min (eluent A: 0.1 M TEAB, pH=7.0; eluent B=CH_3CN, flow 1.0 mL/min, λ=260 nm), allowing pure **15** (retention time: 14.2 min, 2.2 mg, 0.0052 mmol, 40% yields) and **16** (retention time: 27.6 min, 2.9 mg, 0.0047 mmol, 36% yields). The organic extract was then chromatographed by preparative TLC, eluting with $CHCl_3$/CH_3OH 95:5 (v/v). Several bands, UV–visible and blue after acidic spraying and, therefore, attributed to ferrocene derivatives, could be separated. After scratching off the bands from the plate and eluting with $CHCl_3$/CH_3OH 8:2 (v/v), the isolated compounds were analysed by ^{1}H NMR. Only the compound isolated from the band at R_f=0.40 in $CHCl_3$/CH_3OH 95:5 (v/v) exhibited signals diagnostic of guanine and was further investigated, being identified as **17** (6 mg, 0.010 mmol, 80% yields).

Compound **15**, as a 1:1 mixture of the dimers incorporating both the β- and the α-2′deoxyribofuranose unit at the 3′-end: ^{1}H NMR (400 MHz, D_2O): δ 7.96 (2H, d, J=7.5 Hz, H-6 C); 6.31 (2H, dd, J=6.5, 6.5 Hz, H-1′ C); 6.15 (2H, d, J=7.5 Hz, H-5 C); 5.63 (1H, dd, J=6.4, 6.4 Hz, H-1 β-anomer 2′-deoxyribose abasic site); 5.60 (1H, dd, J=3.6, 9.5 Hz, H-1 α-anomer 2′-deoxyribose abasic site); 4.69 (H-3′ phosphate buried under the HDO signal); 4.47 (1H, m, H-3′ OH β-anomer 2′-deoxyribose abasic site); 4.36 (1H, m, H-3′ OH α-anomer 2′-deoxyribose abasic site); 4.30–4.26 (4H, overlapped signals, H-4′ C and 2′-deoxyribose abasic site); 4.05–3.92 (4H, m, H_2-5′ phosphate); 3.89–3.76 (4H, m, H_2-5′ OH); 2.68–2.60 (2H, m, H-2′$_a$ C); 2.44–2.35 (4H, overlapped signals, H-2′$_b$ C and H_2-2′ α-anomer 2′-deoxyribose abasic site); 2.22–2.16 (1H, m, H-2′$_a$ β-anomer 2′-deoxyribose abasic site); 1.94–1.90 (1H, m, H-2′$_b$ β-anomer 2′-deoxyribose abasic site). ^{31}P NMR (161.98 MHz, D_2O): δ 2.55. ESI-MS (negative ions): found m/z: 422.25 (M−guanine+H_2O−H)$^-$.

Compound **16**, as a 1:1 mixture of the dimers incorporating both the β- and the α-2′deoxyribofuranose unit at the 3′-end: ^{1}H NMR (400 MHz, D_2O): δ 7.87 (2H, d, J=7.5 Hz, H-6 C); 6.30 (2H, dd, J=6.5, 6.5 Hz, H-1′ C); 6.18 (2H, d, J=7.5 Hz, H-5 C); 5.64 (1H, dd, J=6.4, 6.4 Hz, H-1 β-anomer 2′-deoxyribose abasic site); 5.61 (1H, dd, J=3.6, 9.5 Hz, H-1 α-anomer 2′-deoxyribose abasic site); 4.70 (H-3′ phosphate buried under the residual HDO signal); 4.51 (1H, m, H-3′ OH β-anomer 2′-deoxyribose abasic site); 4.40 (1H, m, H-4′ β-anomer 2′-deoxyribose abasic site); 4.36 (1H, m, H-3′ OH α-anomer 2′-deoxyribose abasic site); 4.30 (1H, m, H-4′ α-anomer 2′-deoxyribose abasic site); 4.26 (2H, m, H-4′ C); 4.24–4.12 (18H, unresolved signals, ferrocene protons); 4.10 (4H, s, NH–CH_2-Fc); 4.05–3.94 (4H, m, H_2-5′ phosphate); 3.87–3.70 (4H, m, H_2-5′ OH); 2.62–2.58 (4H, m, H_2-2′ C); 2.48–2.35 (2H, m, H_2-2′ α-anomer 2′-deoxyribose abasic site); 2.20 (1H, m, H-2′$_a$ β-anomer 2′-deoxyribose abasic site); 1.94 (1H, m, H-2′$_b$ β-anomer 2′-deoxyribose abasic site). ^{1}H NMR (400 MHz, DMSO-d_6): significant signal at δ 7.95 (2H, broad triplet, exchangeable protons upon addition of D_2O, NH-6 C), from H–H COSY spectra coupled with the signal at 4.24; 4.65 (2H, m,

H-3′ phosphate); 4.28 (4H, s, H-3 and H-4 of Cp_a); 4.24 (4H, s, NH–CH_2-Cp_a); 4.23 (10H, s, protons of Cp_b); 4.16 (4H, s, H-2 and H-5 of Cp_a). ^{31}P NMR (161.98 MHz, D_2O): δ 2.56. ESI-MS (negative ions): found *m/z*: 620.18 [M−guanine+H_2O+(Fc-CH_2)−H]$^-$.

Compound **17**, yellow powder; R_f 0.40 [$CHCl_3$/CH_3OH 95:5 (v/v)]; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.75 (1H, s, H-8); 7.05 (2H, broad singlet, exchangeable protons upon addition of D_2O, NH_2); 4.97 (2H, s, CH_2-Cp_a of ferrocene unit A); 4.87 (2H, s, CH_2-Cp_a of ferrocene unit B); 4.44 (2H, s, H-3 and H-4 Cp_a of ferrocene unit A); 4.35 (2H, s, H-3 and H-4 Cp_a of ferrocene unit B); 4.23 (5H, s, protons Cp_b of ferrocene unit A); 4.21 (5H, s, protons Cp_b of ferrocene unit B); 4.16 (2H, s, H-2 and H-5 Cp_a of ferrocene unit B); 4.11 (2H, s, H-2 and H-5 Cp_a of ferrocene unit A). ^{13}C NMR (100 MHz, $CDCl_3$): upfield signals at δ 83.17 (2 quaternary C of Cp_a); 79.98, 79.32, 78.66 (C-2, C-3, C-4 and C-5 of Cp_a for the two ferrocene units); 69.38 (10C of Cp_b for the two ferrocene units); 40.61 and 37.53 (2 *C*H_2-Cp_a). ESI-MS (positive ions): found *m/z*: 548.22 $(M+H)^+$; 570.12 $(M+Na)^+$; 586.18 $(M+K)^+$.

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A highly diastereoselective Tandem radical reaction. Facile three-component routes to protected (*E*)-polysubstituted homoallylic alcohols

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Abstract—A facile synthesis of geometrically pure (*E*)-1,2,4-trisubstituted and (*E*)-1,2,4-tetrasubstituted homoallylic benzoates was developed. Various Lewis acids were subsequently evaluated in the diastereoselective radical substitution of (*E*)-β-nitrostyrene, and Titanium (IV) 2-ethylhexoxide emerged as the best Lewis acid in terms of yield and diastereoselectivity (up to 98% de). These reactions occurred with high regio-, diastereo- and stereoselectivity, and a possible mechanism to explain this transformation was proposed.

1. Introduction

Over the last two decades, interest in free radical reactions in organic synthesis has greatly increased, with many radical reaction types now providing useful synthetic strategies. Of various radical based reactions, the addition of carbonyloxyl radicals to olefins represents a well-known subset. While the spectroscopic and kinetic studies of carbonyloxyl radical additions to alkenes have also been made, little advanced work has been reported in the area of tandem radical reactions with trappers for synthetic application. As part of ongoing efforts to enlarge the diversity of functional groups belonged to the radical donors in the radical chemistry of (*E*)-β-nitrostyrenes **1**,[1] herein we report the tandem radical reactions of carbonyloxyl radical and (*E*)-β-nitrostyrenes, including the generation of synthetically important protected and free polysubstituted homoallylic alcohols.

Being important building blocks and versatile synthons, homoallylic alcohols are highly featured in the organic synthesis of many biological active molecules such as macrolides, polyhydroxylated natural products, and polyether antibiotics.[2] Among the existing means to construct these synthetically and biologically important molecules, metal-mediated allylation is one of the most common.[3] Furthermore, with the intensive and further development of catalytic diastereo- and stereoselective synthesis of homoallylic alcohols,[4] one or two stereo-issues can be assembled in a single step. This is highly efficient in terms of atom economics, as all of the carbons form the scaffold of the desired molecules. Although reagents of boron, silicon and tin have emerged as the most popular allyl transfer agents for carbonyl compounds,[5] these methods[6] suffer from one or many drawbacks such as air or moisture sensitivity, the need for a multistep preparation of reagents, strictly reaction conditions, or incompatibility with substrates. Despite extensive investigations, there is yet no general method using polysubstituted allylation reagents for the diastereo- and stereocontrolled formation of a wide variety of polysubstituted homoallylic alcohol products. This is probably because the conditions achieving the polysubstituted allylation of ketones would be too severe to control the selective addition owing to the much lower reactivity of ketones than that of aldehydes and the more complicated regioselectivity leading to the α- or γ-adducts of polysubstituted allylation reagents than that of simple allylation or crotylation reagents. In fact, as far as we know, even the stereoselective addition of a cinnamyl nucleophile to ketones has not so far been reported with determination of the stereochemistry of the products that are tertiary homoallylic alcohols. Thus, the search continues for an efficient, practical solution to the problem of diastereoselective synthesis of polysubstituted homoallylic alcohols in general.

The chemistry of carbonyloxyl radicals has a long history that can be traced back to the early part of the last century.[7] Nevertheless, the application of carbonyloxyl radicals in current organic synthesis, such as the topic concerning the tandem radical three-component combination reactions of

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carbonyloxyl radicals, olefins and trappers, has lagged behind the Kharasch allylic oxidation of olefins or the initiator purpose in radical polymerizations until relatively recently.[8] Since the allylic ester can easily be converted into allylic alcohol by saponification or reduction method, the Kharasch reaction eventually becomes an allylic alcohol synthesis. This result, in turn, prompted us to investigate a possibility of the synthesis of homoallylic alcohols through carbonyloxyl radical chemistry.

Although the reactions of diaroyl peroxide have been studied in great detail by various workers during the past several decades,[9] the chemistry of benzoyloxy radical additions, except for several kinetic studies,[10] has received little attention. Homolysis of diaroyl peroxides, such as dibenzoyl peroxide, yields the corresponding aroyloxyl radicals, which may decarboxylate to give aryl radicals, abstract a hydrogen atom from substrates, or add to olefins and aromatic rings. In view of the competitive decarboxylation or hydrogen abstraction reaction of the carbonyloxyl radical and of the difficulties in isolating well-defined products from its reaction mixtures this fact is not surprising. While there are a few scruples in the fine organic application of benzoyloxy radicals, the benefits in elongating the carbon-chain length of a molecule and increasing an oxygen functionality via the benzoyloxy radical addition to olefin are too significant of building the desired structure to be ignored. Furthermore, in connection with our previous work,[1] the radical NO_2-substitution chemistry of (*E*)-β-nitrostyrenes **1** would be a good choice to introduce the carbon–carbon double bond for forming the homoallylic alcohol backbone. Accordingly, we recognized the opportunities for installing a fresh tandem oxygen–carbon then carbon–carbon bond sequence via intermolecular three-component combination of carbonyloxyl radicals, olefins and trappers. This process would provide an unambiguous route to (*E*)-geometrically defined styryl polysubstituted alkenes necessarily bearing a homoallylic oxygen functionality. On the basis of these proposals, we conceived that this tandem radical coupling of olefins and (*E*)-β-nitrostyrenes **1** with dibenzoyl peroxide would provide a useful entry to stereodefined homoallylic alcohols that is fully complementary to the methods cited above.

2. Results and discussion

2.1. Structure and strategy

In the light of the proposal above, we first constructed the retrosynthesis of this strategy for the preparation of stereodefined, polysubstituted homoallylic alcohols. From the antithetic analysis (Fig. 1), it was envisioned that the intermediate **B** and substrate **C**, where the styryl double bond would define the new (*E*)-geometry in target **A**, would conveniently furnish the homoallylic alcohol **A** as mentioned above. Intermediate **B** could be derived by radical mediated addition of olefin and benzoyloxy radical, which in turn could be visualised from 'dibenzoyl peroxide'.

Before testing the feasibility of the overall transformation, our work began with the evaluation of four different methods for generating the intermediate **B**, and the reaction we chose to investigate was the addition of the benzoyloxy radical to cyclohexene using (*E*)-β-nitrostyrene as the radical trapper, and therefore, the results from these experiments are recorded in Scheme 1. As expected, the homoallylic alcoholic skeleton of products was readily formed no matter which initiation method we used. However, dramatically different results were observed and several limitations or drawbacks remained unresolved and then restricted application of some methods.

First, when the reaction was carried out using Barton's approach[11] (Method A) as the protocol to introduce benzoyloxy radicals, although the predicted product was formed in medium diastereoselectivity (58% de), the preparation and usage of *N*-hydroxy-2-thiopyridone ester were expensive and inconvenient due to its photosensitivity and photo-instability, and furthermore the yield was too low to be applied in current organic synthesis. On the other hand, it is noteworthy that only one diastereoisomer was produced while in situ Ag^{2+} oxidation system (Method B) was adopted, but this procedure always did not proceeded to completion and the yield was also disappointingly low along with a large degree of polymerization and hydrolysis of the starting (*E*)-β-nitrostyrene. Moreover, low yield and especially low de suggest that in-depth study of the method

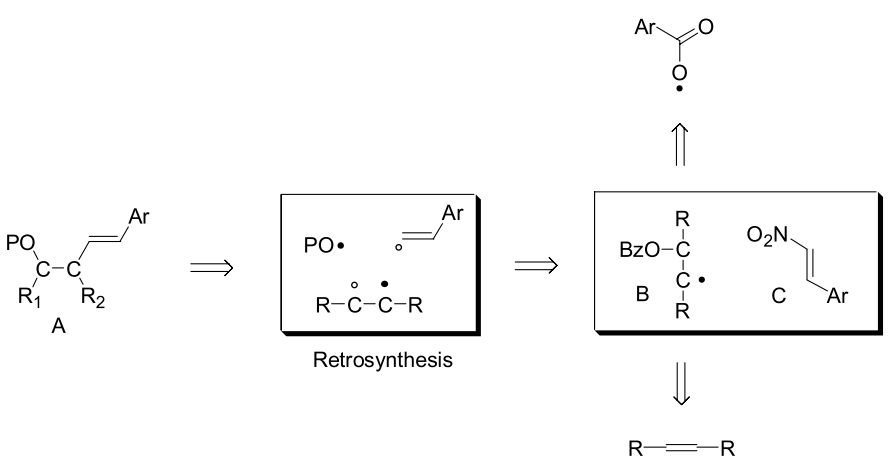
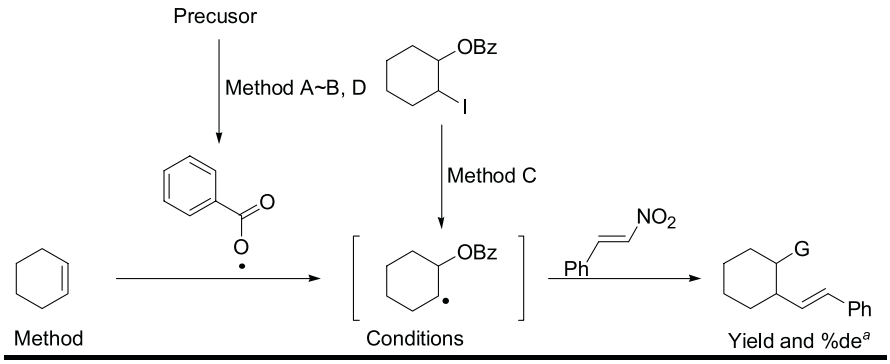


Figure 1. Forming homoallylic C═C and C–O bonds by Tandem radical reactions.



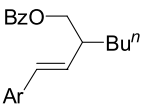
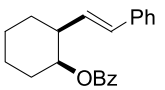
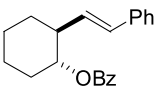
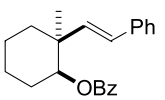
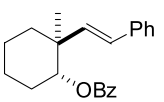
Method	Conditions	Yield and %de[a]
A	8 mmol N-hydroxy-2-thiopyridone benzoate, 8 mL cyclohexene,1 mmol *(E)*-β-Nitrostyrene, irradiated in a quartz tube using a Rayonet reactor (352 nm) at room temperature (23°C) for 4h.	G=OBz 39% yield 58% de (*syn*)
B	10 mmol benzoic acid, 10 mmol $Na_2S_2O_8$, catalytic amount $AgNO_3$, 10 mL pure water, 10 mL cyclohexene, 1 mmol *(E)*-β-Nitrostyrene , room temperature (23°C), 3h.	G=OH 35% yield *syn*-only
C	16 mmol 2-iodo-cyclohexyl benzoate, 10 mL DMSO, 1 mmol *(E)*-β-Nitrostyrene, 4 mmol Et_3B, Air, room temperature (23°C), 2h.	G=OBz 28% yield 24% de (*syn*)
D	2.5 mmol dibenzoyl peroxide, 1 mmol *(E)*-β-Nitrostyrene, 8 mL cyclohexene, reflux 4h.	G=OBz 95% yield 68% de (*syn*)

Scheme 1. Screening results with several usual initiation methods on the reaction yields and de (%) in the diastereoselective synthesis of homoallylic alcohols. [a]Isolated yields and 400 MHZ-NMR rations form crude spectra. *syn*-Isomer is the major product.

C is not warranted. When confronting some of the limitations listed above it is desirable to develop a different radical precursor in connection with different methods for the generation of carbonyloxy radicals.

Dibenzoyl peroxide is a well-known precursor of aroyloxy radicals in the initiator pool and has been used for a number of chemical transformations. Consequently, we chose the dibenzoyl peroxide as the benzoyloxy radical precursor and

Table 1. Three-components combination reactions between (*E*)-β-nitrostyrenes **1**, alkyl alkene **2**, and benzoyl peroxide **3**

Entry	**1**	**3** (equiv.)	Alkene **2** (mL)	Co-solvent mL)[a]	Reflux (h)	Product yield (%)[b]	
1	**1a**	2.5	1-Hexene **2a** (2 mL)	Toluene (6 mL)	4		
						4a (43)	
2	**1b**	2.25	**2a** (2 mL)	Toluene (6 mL)	4	**4a** (46)	
3	**1c**	2.75	**2a** (mL)	Toluene (6 mL)	5	**4c** (30)	
4	**1a**	2.5	Cyclohexene **2b** (8 mL)	—	4		
						syn-**5a** (80)	*anti*-**5a** (15)
5	**1b**	2.25	**2b** (8 mL)	—	4	*syn*-**5a** (81)	*anti*-**5b** (16)
6	**1c**	2.5	**2b** (8 mL)	—	4	*syn*-**5a** (70)	*anti*-**5c** (15)
7	**1a**	2.5	1-Methyl-cyclohexene **2c** (2 mL)	Benzene 6 mL	4		
						syn-**6a** (15)	*anti*-**6a** (82)
8	**1b**	2.25	**2c** (2 mL)	Benzene 6 mL	4	*syn*-**6a** (17)	*anti*-**6b** (82)
9	**1b**	2.25	**2c** (2 mL)	Benzene 6 mL	5	*syn*-**6a** (16)	*anti*-**6a** (64)

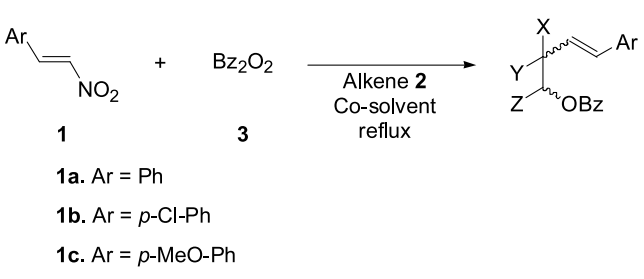
[a] In entries 1–3 and 7–9, reactions are conducted in the specified radion of alkyl alkene **2** and arene solutions, but in the cyclohexene **2b** only in entries 4–6.
[b] Isolated yield and 400 MHZ-NMR rations from crude spectra.

examined the process of the method D. Under these conditions, the addition of benzoyloxy radicals, when they were produced by homolysis of dibenzoyl peroxide via thermolysis path gave (*E*)-geometrically pure products with a striking high yield (95% yield), albeit in medium diastereoselectivity (68% de). This yield was higher than when obtained through other three methods, with no need for preparing the commercially available radical precursor showing that the convenience of the benzoyloxy radical generation allow for optimal exploitation for high diastereoselectivity. From these results, it is realized that the tandem three-component combination reaction of the benzoyloxy radical, alkene and (*E*)-β-nitrostyrene using conditions of the method D is a hopeful beginning to synthesize stereodefined homoallylic alcohols.

2.2. Scope and limitations studies

With these results of model experiments in hand, we turned our attention to survey this reaction with various olefins and (*E*)-β-nitrostyrenes. First, we began our studies with the dibenzoyl peroxide mediated reactions outlined in Eq. 1 and Table 1. When (*E*)-β-nitrostyrene **1a** was treated with 2.5 equiv. of dibenzoyl peroxide in a 1-hexene **2a** and toluene co-solvent–solution under reflux condition for 4 h, (*E*)-2-styryl-hexyl benzoate **4a** was obtained as the sole product in 43% yield (Table 1, entry 1), and none of the (*Z*)-isomer was detected in the crude product. The operative mechanism of this reaction is presumably similar to our previous studies in the radical addition–elimination reactions of (*E*)-β-nitrostyrenes **1** and various radicals.[1] Initiation occurs with the regioselective addition of the benzoyloxy radical generated from dibenzoyl peroxide to the terminal position of the double bond in 1-hexene **2a**. The only resulting secondary radical species undergo intermolecular addition to the (*E*)-β-nitrostyrene **1a** followed by elimination of NO_2· to yield (*E*)-alkene because the product stability of (*E*)-alkene is much more stable than (*Z*)-alkene in energy.

The strategy of using toluene as co-solvent instead of alkene itself as solvent only described in method D above was in order to elevate the temperature inside the reaction system when reflux due to the low boiling point of 1-hexene **2a**. Benzene was ever one of our choices for increasing the temperature enough to initiate the cleavage of dibenzoyl peroxide, but always some starting material ((*E*)-β-nitrostyrene **1a**) was recovered under such reaction conditions. Finally, a solution with the specified ratio of toluene and 1-hexene **2a** satisfied our demand and was adopted for further investigation.



(1)

Therefore, in order to ascertain the scope of this (*E*)-homoallylic benzoate construction, we went on examining the substitution reaction of analogous substrates. In addition to (*E*)-**1a**, a series of (*E*)-nitroalkenes with various aromatic parts owning different electron-demand were examined, and the results revealed the tendency towards the higher electrophilic ability of the functional group in nitroalkenes the higher reactivity of it. For example, the reaction of **2a** with (*E*)-β-nitrostyrene containing an electron-withdrawing group **1b** gave the corresponding (*E*)-**4b** in higher yield than that of (*E*)-**1c** due to the strong electron-donating ability of the methoxy group (Table 1, entries 2 and 3). Furthermore, this phenomenon led us to realize that our substrates ((*E*)-β-nitrostyrenes 1) were good radical acceptors and had great capacity for trapping electron-rich alkyl radicals. Although the yields were not very high in these three entries, the excellent selectivities, which no other regio- or stereoisomers were found, could not be ignored, and the ease of polymerization in 1-hexene **2a** might be responsible for the decreased yields in these cases. This obvious difference between 1-hexene **2a** and cyclohexene **2b** strongly suggests that the more substituents in alkenes preventing from polymerization the higher yields in reactions.

In view of the above results and supposition, we decided to examine generality and the steric effect of this radical NO_2-substitution procedure, by replacing **2a** with other alkenes **2**, since the *n*-butyl moiety can be introduced first, increasing the likelihood that the chemistry of the new introduced alkyl moieties in **2** can be analyzed. It is well known that the degree of the carbon radical center always plays important roles in different radical reactions. To study this steric effect for more precisely, the reactive radical centers with equal degree ('secondary' radicals) must be employed. Toward this purpose, we determined to investigate in more detail the reactions with the alkene **2b** in similar conditions (Table 1, entries 4–6). As shown, products *syn*-(*E*)-**5** were obtained as major products together with the minor products *anti*-(*E*)-**5** in good to quantitative total yields, and the assignment of the relative stereochemistry of these compounds was deduced from the 2D NOESY NMR (500 MHz) spectral analysis (Fig. 2). Not beyond our expectations, no matter what kind electron demand of substituents in the benzene ring yields in the cyclohexene **2b** system always much more than that in the 1-hexene **2a** system. On the other hand, 1-methyl-cyclohexene **2c** was chosen as a readily available model for evaluating the influence of radical degree. To our surprised, not only similar products were obtained without loss of configurational integrity at the double bond, but the NO_2-substitutions with **2c** were also found to proceed almost identically efficiently to that with **2b** as indicated by their yields. At this stage, we believe the behavior of alkenes

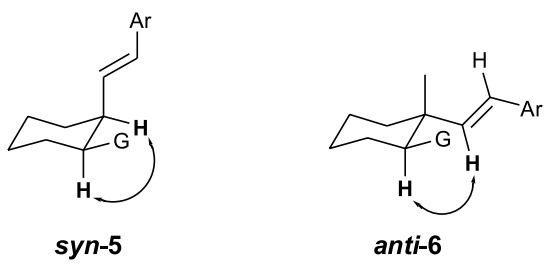
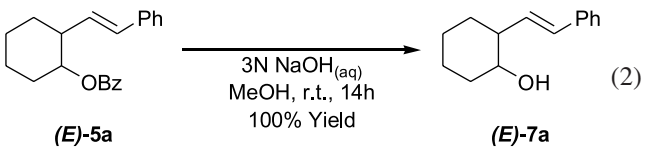


Figure 2. 2D NOESY spatial correlations in *syn*-**5** and *anti*-**6** (G=OBz).

2 are mainly influenced by alkyl substituents at the double bond not by radical degree, that is to say, applying this method to build polysubstituted homoallylic alcohol structures is more efficiently in internal alkenes than terminal ones. Accordingly, product (*E*)-**5a** was converted to the corresponding alcohol (*E*)-**7a** by treatment with 3N NaOH as the final transformation in our proposal (100% yield, Eq. 2).



(2)

2.3. Diastereoselectivities and mechanism studies

The results in Table 1 deserve a further comment: as shown, the yields mainly lied in the 30–99% range. By a synthetic point of view they can be considered acceptable values since they corresponded to the overall yield of a three-component tandem sequence. The recourse to three-component sequential transformations is generally highly desirable in organic synthesis because of the economic and environmental benefits associated to the reduction of the overall number of synthetic steps, such as reduction of cost, time, and waste production. However, there was still no significant evidence allowed us to construct the mechanistic pictures for explaining the relative stereochemistry of products. A more detailed look into our results revealed, that the diastereoselectivity varied with the same tendency in both **2b** and **2c** series even though the choice of the solvent system was completely different in them. Therefore, it occurred to us that solvent effects might be a key to solve the stereochemical problem. First, we undertook to clarify the stereochemistry of this radical substitution in various solvents and described the results as studied from the viewpoints of mechanism and solvent effects. An examination of the solvent nature with respect to the reaction outcome revealed a strong influence, as shown in Scheme 2 for the diastereoselective synthesis of products **5a** and **6a**. The highest diastereoselectivity was observed in methanol and the lowest in benzene, while other solvents were worse than methanol. The results showed, that with methanol and benzene on both ends of the diastereoselectivity range and THF in the middle, obviously polar effects can be held responsible for these findings. It can rather be assumed, that the solvation of intermediates play an important role:

entry	Product	Benzene	THF	CH_3CN	MeOH
1	**5a**	(55, 60)	(76, 23)	(80, 37)	(86, 7)
2	**6a**	(36, 30)	(81, 8)	(84, 27)	(99, 4)

[a] Volume ratio of Co-solvent : Alkene = 1:1.
All reactions are conducted in the conditions described in **Table 1** except for the co-solvent system.
All data in this scheme are recorded in the format : (%*de*, yield).

Scheme 2. Influence of the solvent on the de (%) and yields in the diastereoselective synthesis of **5a** and **6a**[a].

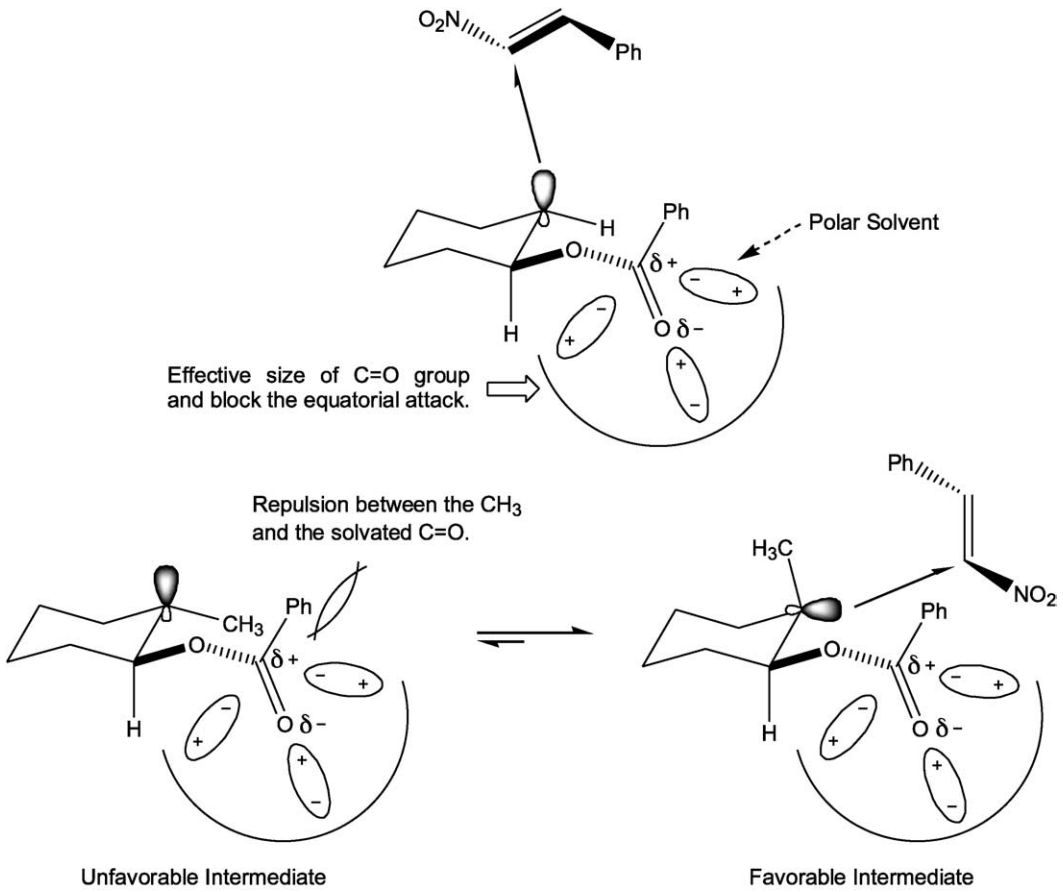
methanol is an excellent solvating solvent for polar substituents, while acetonitrile is less solvating. Tetrahydrofuran possesses rather weak solvating properties and benzene none. The conclusion must be, that solvents with strong solvating ability for polar intermediates lead to an increase in diastereoselectivity by probably increasing the effective size of a polar substituent in the intermediates.

The effective size of a polar substituent can be influenced by increasing the polarity of the solvent, and by complexing with Lewis acids. In Scheme 3, a likely transition state arrangement for radical attack from six-membered cyclic radicals to (*E*)-β-nitrostyrenes is depicted: the level of the axial attack of the α-benzoyl-cyclohexyl radical to (*E*)-β-nitrostyrene increases because of blocking of the equatorial attack by the increasing effective size of the C═O substituent if the polarity of the solvent is raised. In accordance with the experimental results (Table 1, entry 4), the situation depicted above would preferentially yield *syn*-configured product **5a**. In contrast, the repulsion between the methyl group and the solvated C═O substituent drives the methyl group to lie in the axial position, raises the level of the equatorial attack, and preferentially yields *anti*-configured product **6a** in agreement with the experimental results (Table 1, entry 7). Although the diastereoselectivity goes up quite substantially by raising the solvent polarity, it generally accompanies the slash in yields at the same time and then cannot be directly applied to benefit these reactions. As discussed earlier, not only solvating with solvents but also complexing with Lewis acids can modify the effective size of a polar substituent. Consequently, using Lewis acids to mediate these reactions may be a good alternative to mildly elevate the diastereoselectivity without large decrease in yields, and details of this additive effect are more fully discussed below.

2.4. Lewis acid studies

Lewis acids are known for their ability to form complexes with carbonyl groups. Therefore, a coordinating interaction of Lewis acids with the ester function of intermediates can be assumed to take place in our case. As Lewis acids play such an important role for diastereoselectivity in complex-controlled radical reactions, we decided to test the influence of some of these additives on the outcome of our reactions. Several Lewis acids were initially screened in the diastereoselective synthesis of (*E*)-**5a** (Table 2−1), but most of these Lewis acids did not lead to considerable increase in both yields and % de>. Reactions with $BF_3{\cdot}Et_2O$, B(O-*n*-Bu)$_3$, and $TiCl_4$ (entries 2, 3 and 5) led to poor % de, and in-depth analysis of them was not warranted. In contrast, high levels of % de were observed with $AlBr_3$ and especially with Ti(O-*n*-Bu)$_4$ as a Lewis acid in entries 4 and 6, and therefore, further investigation on them was carried out for elevating the yields immediately.

After a more complete evaluation of the Lewis acid complex-controlled effect, notable is the fact that solubility is an important factor concerning how much extent Lewis acids affect reactions. Unfortunately, most Lewis acids of the types AlX_3 and $Al(OR)_3$ except for $AlBr_3$ are insoluble in the alkene or benzene solutions in our preliminary test, and the results using them are almost identical to that



Scheme 3. A diagrammatic explanation of the diastereoselectivities in the synthesis of **5a** and **6a**.

without Lewis acids. In contrast to aluminum Lewis acids, most commercially available $Ti(OR)_4$ reagents are liquids and easily soluble in the reaction mixture. On the other hand, keeping in mind that fine tuning of the strength of the Lewis acidity of $Ti(OR)_4$ from strong to mild is readily achieved by changing the counterions. Alteration of the reactivity of titanium species in this way sometimes dramatically improves the product yields and/or the product composition, although $Ti(OR)_4$ have limited use as a Lewis acid. As a consequence, titanium compounds, which take advantage of their affinity for oxygen functional groups, are considered as a possible candidate as the Lewis acid and will be examined further.

To evaluate the ligand-diastereoselectivity profile, six experiments with various titanium species as the Lewis acids were conducted (Table 3). As expected, every ligand induces different steric hindrance and modifies the effective size of the ester function of intermediates to various extents. This ligand-effect screening reveals two features: (1) in general, larger ligands effect milder Lewis acids and higher yields. Thus, the yields increase with the trend: $Ti(OEt)_4$<$Ti(O\text{-}n\text{-}Pr)_4$<$Ti(O\text{-}i\text{-}Pr)_4$<$Ti(O\text{-}n\text{-}Bu)_4$<$Ti(O\text{-}t\text{-}Bu)_4$<$Ti[O(2\text{-}Et\text{-}hexyl)]_4$; and (2) diastereoselectivities (% de) decrease with the tendency: *n*-alkoxide>*i*-alkoxide>*t*-alkoxide. As a result, $Ti[O(2\text{-}Et\text{-}hexyl)]_4$ stands out above the rest to be the most suitable choice in this transformation, and a practical and highly diastereoselective methodology has been developed for the synthesis of (*E*)-polysubstituted homoallylic benzoates from nitroalkenes **1** in relative ease.

With a reproducible procedure in hand, we next explored the scope of the reaction with regard to the nature and position

Table 2. Initial screening results with some Lewis acids on the reaction yields and de (%) in the diastereoselective synthesis of **5a**

Entry	**3** (equiv.)	Lewis acid (equiv.)	Reflux (h)	**5a** Yield (%)	% de[a]
1[b]	2.5	—	4	95	68
2	2.5	$BF_3{\cdot}Et_2O$ (0.5)	2	55	76
3	2.5	$B(O\text{-}n\text{-}Bu)_3$ (0.5)	2	72	52
4	2.5	$AlBr_3$ (0.5)	2	35	90
5	2.5	TiC_4 (0.5)	2	43	58
6	2.5	$Ti(O\text{-}n\text{-}Bu)_4$ (0.5)	2	45	92

[a] *syn*-Isomer is the major product.
[b] This result is adopted from the entry 4 in Table 1.

Table 3. Ligand effects on the reaction yields and de (%) in the titanium mediated diastereoselective synthesis of **5a**

Entry	Lewis acid[a]	**5a** Yield (%)	% de[b]
1	$Ti(OEt)_4$	31	76
2	$Ti(O\text{-}n\text{-}Pr)_4$	37	87
3	$Ti(O\text{-}i\text{-}Pr)_4$	40	73
4	$Ti(O\text{-}n\text{-}Bu)_4$	45	92
5	$Ti(O\text{-}t\text{-}Bu)_4$	47	74
6	$Ti[O(2\text{-}Et\text{-}hexyl)]_4$	55	98

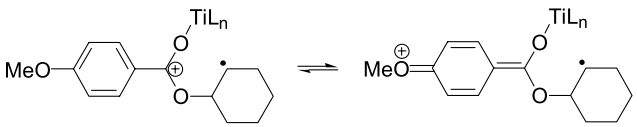
[a] All reactions are conducted in the conditions described in Table 2, entry 6.
[b] *syn*-Isomer is the major product.

of substituents on the benzene ring, and therefore, a series of nitroalkenes (**1a**–**c**) and olefins (**2b**–**c**) were subjected to the Lewis acid mediated conditions to give the corresponding homoallylic benzoates **5** and **6**. In all cases, the three-component tandem radical reactions proceeded with high diastereoselectivity (up to 98% de) and moderate yield (Table 4). Noteworthy is the fact that the reactions showed higher diastereoselectivities when **1c** was used as the substrate than **1b**, but the corresponding products **5c** or **6c** were produced in lower yields. To rationalize this finding, we propose the following resonance structures based on previous criteria (Scheme 4). The crucial one is the so powerful electron-donating ability of the methoxy group of the substrate **1c** that the resonance structures are successfully stabilized and enhance the coordination between titanium species and the ester function of intermediates. On the contrary, the strong electron-withdrawing ability of the chlorine group of **1b** is so unfavorable to stabilize the complex that the % de only increases slightly in comparison with the results without Lewis acids assistance. As regards the yields, the results show the same behavior with those in Table 1: the higher electrophilic ability of the functional group in nitroalkenes the higher reactivity of it. To a certain extent, the higher reactivity of **1b** resulting from the chlorine group not only increases the probability of attacks from favorable directions but also that from unfavorable ones. For that matter, the strong electron-withdrawing ability of the chlorine group only benefits the yields and might be partially responsible for the decreased % de in these cases.

Table 4. Optioned results with Lewis acid–Ti[O(2-Et-hexyl)]$_4$ on the reaction yields and de (%) in the diastereoselective synthesis of **5** and **6**

Entry	**3** (equiv.)	Ti[O(2-Et-hexyl)]$_4$ (equiv.)	Reflux (h)	Product yield (%)	% de
1	2.5	0.5	2	**5a**-55(95)[a]	98(68)[b]
2	2.2	0.5	1	**5b**-55(97)	77(67)
3	2.5	0.75	2	**5c**-38(85)	98(65)
4	2.5	1	2	**6a**-52(97)	96(69)
5	2.2	0.75	2	**6b**-58(99)	72(66)
6	2.5	0.5	2.5	**6c**-4080)	97(60)

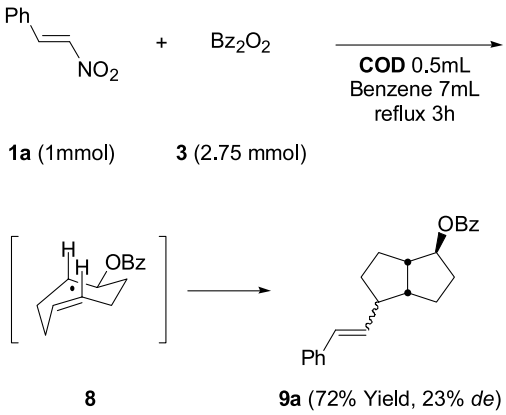
[a] The yields without Lewis and are recorded in the parentheses.
[b] The % de without Lewis acid are recorded in the parentheses.



Scheme 4. Resonance structures for an explanation of the specially high % de when **1c** is used as the substrate in the Lewis acid mediated reactions.

2.5. Tandem radical cyclizations

In order to demonstrate the utility and generality of this method, we subsequently tried the radical cyclization strategy to yield the bicyclo- and fused-ring system, which are often present in the natural products as substructures. Formations of carbon–carbon bonds by intramolecular additions of carbon radicals onto alkenes are important reactions in organic synthesis. Of various intramolecular based reactions, tandem radical reactions rank among the most powerful methods to construct polycyclic ring systems in one step from unsaturated precursors, and the characteristic advantages such as high extent of reactivity, regioselectivity and stereoselectivity would be promising for natural product synthesis. Many examples in the literature[12] have illustrated that *cis*, *cis*-1,5-cyclooctadiene (COD) is a good radical cyclization template for in situ generating a secondary cyclopentyl radical and the bicyclo[3, 3, 0] skeleton via intramolecular cyclizations. Moreover, this also suggests that intermolecular addition of exogenous heteroatom radicals to an alkene or alkyne can initiate a cyclization event when a second radical acceptor moiety is appropriately situated. Accordingly, COD was subjected to the radical reaction conditions in benzene under reflux to give the corresponding products **9a**, in which three contiguous stereocenters were produced in a single synthetic operation from achiral precursors in 72% total yield (Eq. 3). The cyclization of **8** set the relative configurations of three of the four stereocenters in the product **9a**, and it probably occurred through the depicted chair-equatorial transition state. Conformational alternatives to transition state **8** are higher in energy either because the connecting chain between the radical and the alkene is too short to form a *trans*-fused arrangement of radical and alkene substituents or because the benzoyl group resides in a crowded configuration. As expected, the cyclization yields bicyclo[3, 3, 0] products which have significant potential as building blocks for the synthesis of a variety of natural products. In summary, we demonstrate that our method is not only practical for the synthesis of (*E*)-polysubstituted homoallylic alcohols but also effective for the radical cyclization in polyenes to afford elongating styryl alcohols and related derivatives.



(3)

3. Conclusion

The present, expeditious approach to the homoallylic benzoate skeleton underscores the synthetic potential of the free alcohols. The use of more functionalized alkenes should allow access to the more complex members of this family of homoallylic derivatives. In conclusion, these studies have uncovered a new role for dibenzoyl peroxide in fine organic synthesis besides radical initiation or polymerization. This methodology should be complementary to the preparation of polysubstituted homoallylic alcohols by organometallic-based carbonyl addition methods and is currently being extended to the synthesis of other related systems.

4. Experimental

4.1. General remarks

All reactions were performed in flame or oven-dried glassware under a positive pressure of nitrogen. THF, CH_3CN, toluene and benzene were used directly without purification. Analytical thin layer chromatography was performed with E. Merck silica gel 60F glass plates and flash chromatography used E. Merck silica gel 60 (230–400 mesh). MS or HRMS were measured by JEOL JMS-D300 or FINNIGAN MAT-95XL spectrometer. ^{1}H NMR, ^{13}C NMR and 2D NOESY NMR spectra were recorded with Bruker AV 400 FT NMR or Bruker AV 500 FT NMR. All NMR data were obtained in $CDCl_3$ solution and chemical shifts (δ) were given in ppm relative to TMS.

4.2. Materials

All Lewis acids in Tables 2 and 3 were purchased from Strem Chemicals, Inc., and other commercially available reagents were purchased from Aldrich Chemical Co. and used directly without further purification.

4.3. General experimental procedures for the synthesis of (*E*)-2-styryl-alkyl benzoate from the reaction of alkenes with (*E*)-β-nitrostyrenes—preparation of (*E*)-4a

(*E*)-β-Nitrostyrene **1a** (149.2 mg, 1.0 mmol) and dibenzoyl peroxide (605.6 mg, 2.5 mmol) were placed in a 1-hexene **2a** (2 mL) and toluene (6 mL) co-solvent solution. The mixture was stirred for 4 h under reflux and then concentrated in vacuo. After evaporating the solvent, the residue was purified by silica gel chromatography to yield the desired product (*E*)-**4a** as a colorless oil.

Similar procedures were used when other alkenes **2b–c** were used to prepare products **5–6** in different solvents. All the experimental data concerning these reactions, the solvents used, and the yields of products **4–6** can be found in Table 1.

4.4. General experimental procedures for the diastereoselective synthesis of (*E*)-2-styryl-alkyl benzoate from the reaction of alkenes with (*E*)-β-nitrostyrenes under Lewis acid catalysis—preparation of (*E*)-5a

(*E*)-β-Nitrostyrene **1a** (149.2 mg, 1.0 mmol), dibenzoyl peroxide (605.6 mg, 2.5 mmol) and Titanium (IV) 2-ethylhexoxide (282.4 mg, 0.5 mmol) were placed in a cyclohexene **2b** (8 mL) solution. The mixture was stirred for 2 h under reflux and then concentrated in vacuo. After evaporating the solvent, the residue was diluted with CH_2Cl_2, washed with cold dil. 5% HCl and water, dried ($MgSO_4$) and evaporated. The residue obtained was purified by silica gel chromatography to yield the desired product (*E*)-**5a** as a colorless oil.

Similar procedures were used when other alkenes **2b–c** were used to diastereoselectively prepare products **5–6** in different Lewis acids catalysis. All the experimental data concerning these reactions, the Lewis acids used, the diastereoselectivity, and the yields of products **5–6** can be found in Tables 2–4.

4.4.1. (*E*)-2-styryl-hexyl benzoate (4a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.55–7.21 (m, 8H), 6.49 (d, J=16 Hz, 1H), 6.09 (dd, J=16, 8.8 Hz, 1H), 4.37–4.28 (m, 2H), 2.68–2.67 (m, 1H), 1.57–1.33 (m, 6H), 0.92–0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.59, 137.42, 132.84, 131.64, 131.01, 130.43, 129.55, 128.50, 128.34, 127.20, 126.15, 67.93, 42.66, 31.33, 29.22, 22.74, 13.99. FAB-MS m/z (relative intensity) 308 (M^+, 8), 144 (92), 129 (91), 117 (100), 105 (100), 91 (100). HR-FAB-MS Calcd for $C_{21}H_{25}O_2$ (M^++1) 309.1855, found 309.1854.

4.4.2. (*E*)-2-[2-(4-chloro-phenyl)-vinyl]-hexyl benzoate (4b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–8.00 (m, 2H), 7.56–7.42 (m, 3H), 7.29–7.24 (m, 4H), 6.43 (d, J=16 Hz, 1H), 6.06 (dd, J=16, 8.8 Hz, 1H), 4.36–4.27 (m, 2H), 2.69–2.64 (m, 1H), 1.63–1.31 (m, 6H), 0.90–0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.54, 135.88, 132.88, 132.80, 131.78, 130.43, 130.37, 129.52, 128.63, 128.35, 127.34, 67.74, 42.68, 31.24, 29.22, 22.71, 13.96. MS m/z (relative intensity) 342 (M^+, 0.07), 220 (29), 178 (39), 163 (26), 105 (100), 77 (29). HRMS Calcd for $C_{21}H_{23}ClO_2$ (M^+) 342.1386, found 342.1378.

4.4.3. (*E*)-2-[2-(4-methoxy-phenyl)-vinyl]-hexyl benzoate (4c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.01 (m, 2H), 7.54–7.40 (m, 3H), 7.30–7.26 (m, 2H), 6.85–6.83 (m, 2H), 6.42 (d, J=16 Hz, 1H), 5.93 (dd, J=16, 8.7 Hz, 1H), 4.32–4.29 (m, 2H), 3.8 (s, 3H), 2.65–2.63 (m, 1H), 1.57–1.31 (m, 6H), 0.91–0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.60, 158.96, 132.80, 130.98, 130.48, 130.28, 129.55, 128.79, 128.33, 127.25, 113.95, 68.07, 55.30, 42.62, 31.42, 29.23, 22.74, 13.99. MS m/z (relative intensity) 338 (M^+, 0.59), 159 (57), 121 (66), 115 (100), 105 (92), 69 (58). HRMS Calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1889.

4.4.4. (*E*)-2-styryl-cyclohexyl benzoate (5a). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the major isomer are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.48–7.13 (m, 8H), 6.43 (d, J=16 Hz, 1H), 6.10 (dd, J=16, 8.4 Hz, 1H), 4.95–4.90 (m, 1H), 2.49–2.44 (m, 1H), 2.17–2.15 (m, 1H), 1.91–1.36 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.09, 137.54, 132.57, 131.93, 130.82, 130.59, 129.44, 128.34, 128.18, 126.93, 126.05, 76.22, 46.82, 31.55, 31.52, 24.83, 24.41. MS m/z (relative intensity) 306 (M^+, 0.4), 185 (15), 184 (100), 141 (18), 105 (88), 77 (28). HRMS Calcd for $C_{21}H_{22}O_2$ (M^+) 306.1420, found 306.1614.

4.4.5. (*E*)-2-[2-(4-chloro-phenyl)-vinyl]-cyclohexyl benzoate (5b). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the major isomer are ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.97 (m, 2H), 7.52–7.37 (m, 3H), 7.19–7.14 (m, 4H), 6.37 (d, J=16 Hz, 1H), 6.07 (dd, J=16, 8.4 Hz, 1H), 4.94–4.91 (m, 1H), 2.19–2.15 (m, 1H), 1.94–1.86 (m, 1H), 1.78–0.86 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.10, 135.98, 132.67, 132.51, 130.72, 129.42, 129.39, 128.47, 128.23, 127.25, 76.10, 46.99, 31.53, 31.47, 24.82, 24.42. FAB-MS m/z (relative intensity) 340 (M^+, 3), 219 (85), 151 (60), 105 (100), 81 (96), 55 (87). HR-FAB-MS Calcd for $C_{21}H_{22}ClO_2$ (M^++1) 341.1309, found 341.1314.

4.4.6. (*E*)-2-[2-(4-methoxy-phenyl)-vinyl]-cyclohexyl benzoate (5c). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the major isomer are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.50–7.36 (m, 3H), 7.19–7.17 (m, 2H), 6.78–6.76 (m, 2H), 6.37 (d, J=16 Hz, 1H), 5.95 (dd, J=16, 8.4 Hz, 1H), 4.92–4.88 (m, 1H), 3.76 (s, 3H), 2.47–2.45 (m, 1H), 2.17–2.15 (m, 1H), 1.91–1.38 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.16, 158.76, 132.57, 130.90, 130.43, 129.94, 129.83, 129.47, 128.20, 127.16, 113.81, 76.37, 55.25, 46.81, 31.66, 31.55, 24.89, 24.45. MS *m*/*z* (relative intensity) 336 (M^+, 0.4), 214 (33), 147 (44), 105 (100), 81 (33), 77 (39). HRMS Calcd for $C_{22}H_{24}O_3$ (M^++1) 336.1725, found 336.1721.

4.4.7. (*E*)-2-methyl-2-styryl-cyclohexyl benzoate (6a). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The ^{1}H NMR spectral data of the mixture of these two isomers are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H, major and minor), 7.54–7.17 (m, 8H, major and minor), 6.58 (d, J=16.4 Hz, 1H, minor), 6.50 (d, J=16.4 Hz, 1H, minor), 6.42 (d, J=16.4 Hz, 1H, major), 6.23 (d, J=16.4 Hz, 1H, major), 5.13–5.10 (m, 1H, major), 4.99–4.96 (m, 1H, minor), 2.04–1.57 (m, 8H, major and minor), 1.26 (s, 3H, major), 1.19 (s, 3H, minor). The ^{13}C NMR spectral data of the major isomer are ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94, 137.97, 137.73, 132.71, 130.87, 129.52, 128.35, 128.31, 127.73, 127.02, 126.09, 77.48, 40.40, 36.02, 27.18, 23.02, 21.24, 20.35. MS *m*/*z* (relative intensity) 320 (M^+, 17), 215 (22), 105 (100), 95 (58), 91 (19), 77 (27). HRMS Calcd for $C_{22}H_{24}O_2$ (M^+) 320.1776, found 320.1771.

4.4.8. (*E*)-2-[2-(4-chloro-phenyl)-vinyl]-2-methyl-cyclohexyl benzoate (6b). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the major isomer are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.02 (m, 2H), 7.56–7.20 (m, 7H), 6.36 (d, J=16 Hz, 1H), 6.20 (d, J=16 Hz, 1H), 5.11–5.08 (m, 1H), 1.89–1.57 (m, 8H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.94, 138.80, 136.22, 132.78, 132.59, 130.78, 129.50, 128.56, 128.34, 127.30, 126.55, 77.37, 40.55, 36.10, 27.17, 23.15, 21.17, 19.90. MS *m*/*z* (relative intensity) 354 (M^+, 27), 249 (25), 218 (11), 125 (9), 105 (100), 77 (12). HRMS Calcd for $C_{22}H_{23}ClO_2$ (M^+) 354.1387, found 354.1386.

4.4.9. (*E*)-2-[2-(4-methoxy-phenyl)-vinyl]-2-methyl-cyclohexyl benzoate (6c). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the major isomer are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.03 (m, 2H), 7.54–7.52 (m, 1H), 7.45–7.41 (m, 2H), 7.26–7.23 (m, 2H), 6.82–6.79 (m, 2H), 6.36 (d, J=16.4 Hz, 1H), 6.09 (d, J=16.4 Hz, 1H), 5.11–5.08 (m, 1H), 3.77 (s, 3H), 1.91–1.44 (m, 8H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.97, 158.83, 135.86, 132.69, 130.92, 130.56, 129.52, 128.30, 127.17, 127.05, 113.90, 77.61, 55.28, 40.26, 36.07, 27.18, 23.01, 21.27, 14.09. MS *m*/*z* (relative intensity) 350 (M^+, 48), 245 (100), 161 (12), 121 (31), 105 (69), 77 (19). HRMS Calcd for $C_{23}H_{26}O_3$ (M^+) 350.1882, found 350.1889.

4.4.10. (*E*)-2-styryl-cyclohexanol (7a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 6.53 (d, J=16 Hz, 1H), 6.08 (dd, J=16, 8.8 Hz, 1H), 3.37–3.33 (m, 1H), 2.08–2.05 (m, 2H), 1.83–1.26 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.08, 132.15, 131.98, 128.55, 127.36, 126.17, 73.25, 50.59, 33.90, 31.44, 25.21, 24.81. MS *m*/*z* (relative intensity) 202 (M^+, 20), 98 (68), 81 (100), 67 (53), 57 (72), 55 (35). HRMS Calcd for $C_{14}H_{18}O$ (M^+) 202.1357, found 202.1361.

4.4.11. (*E*)-6-styryl-*exo*-2-benzoyl-*cis*-bicyclo[3.3.0]-octane (9a). Two isomers were observed after the reaction and inseparable even after separation by HPLC. The spectral data of the mixture of these two isomers are ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2H, major and minor), 7.55–7.20 (m, 8H, major and minor), 6.41 (d, J=16 Hz, 1H, minor), 6.40 (d, J=16 Hz, 1H, major), 6.20 (dd, J=16, 7.5 Hz, 1H, minor), 6.19 (dd, J=16, 7.9 Hz, 1H, major), 5.27–5.25 (m, 1H, minor), 5.19–5.14 (m, 1H, major), 2.95–2.87 (m, 1H, minor), 2.71–2.64 (m, 1H, major), 2.32–1.21 (m, 10H, major and minor). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.28, 137.68, 134.20, 134.08, 132.79, 132.71, 130.90, 130.67, 129.51, 129.48, 128.74, 128.69, 128.50, 128.35, 128.27, 126.90, 125.97, 82.86, 77.76, 52.40, 51.25, 50.38, 49.09, 49.02, 45.73, 35.03, 34.74, 30.96, 30.66, 30.53, 28.65, 27.01, 26.28. MS *m*/*z* (relative intensity) 332 (M^+, 6), 210 (55), 130 (18), 106 (17), 105 (100), 77 (22). HRMS calcd for $C_{23}H_{24}O_2$ (M^+) 332.1776, found 332.1782.

Acknowledgements

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Unexpected results in the reaction of active methylene compounds with phenylsulfonyl-1,2-propadiene triggered by triphenylphosphine

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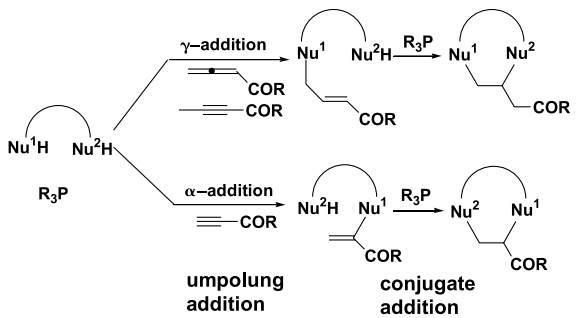
Abstract—Some unexpected phenomena were observed in the reaction of active methylene compounds with phenylsulfonyl-1,2-propadiene in the presence of Ph_3P. The reaction gave three types of products: Michael adducts, rearranged adducts or a three-component adduct. It could be explained as an interesting phosphine-triggered, sulfinate anion-catalyzed reaction.

1. Introduction

A number of reports on organocatalytic transformations have appeared covering a wide range of reactions. Among them, some important reactions were discovered in the phosphine-catalyzed reaction of 2,3-butadienoates or 2-butynoates,[1] such as isomerization,[2] α-addition,[3] γ-addition,[4] and [3+2]-cycloaddition.[5] Recently, we reported the phosphine-catalyzed tandem reactions of electron-deficient allenes (allenoates, allenones) or alkynes (alkynoates, alkynones) with various types of bifunctional nucleophiles, which offer an efficient route to construct heterocycles under mild conditions with high efficiency (Scheme 1).[6]

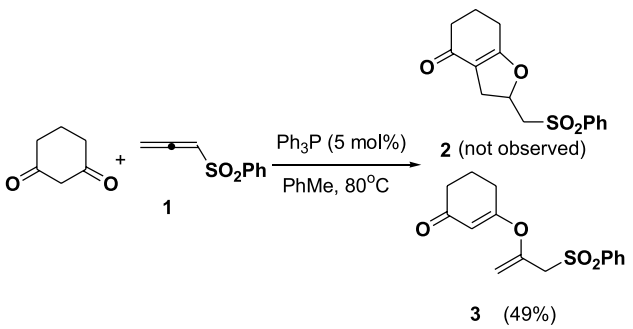
Based on the phosphine-catalyzed tandem reactions, more efforts were made to investigate the reactions of other electron-deficient allenes. However, some unexpected results were obtained when phenylsulfonyl-1,2-propadiene were used. Herein we wish to report the unexpected results obtained from the reactions of active methylene compounds with phenylsulfonyl-1,2-propadiene.



Scheme 1.

2. Results and discussions

Heating a mixture of 1,3-cyclohexanedione and phenylsulfonyl-1,2-propadiene in toluene in the presence of a catalytic amount of Ph_3P gave 49% yield of the adduct **3**, not the expected cyclized product **2** formed from tandem nucleophilic additions (Scheme 2).[6]



Scheme 2.

Reaction of acetylacetone with phenylsulfonyl-1,2-propadiene was similar to that of the 1,3-cyclohexanedione (Scheme 3).

Keywords: Phosphine; Active methylene compounds; Allenic sulfone; Sulfinate.
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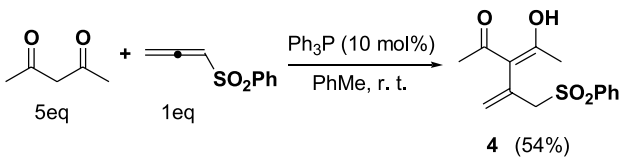
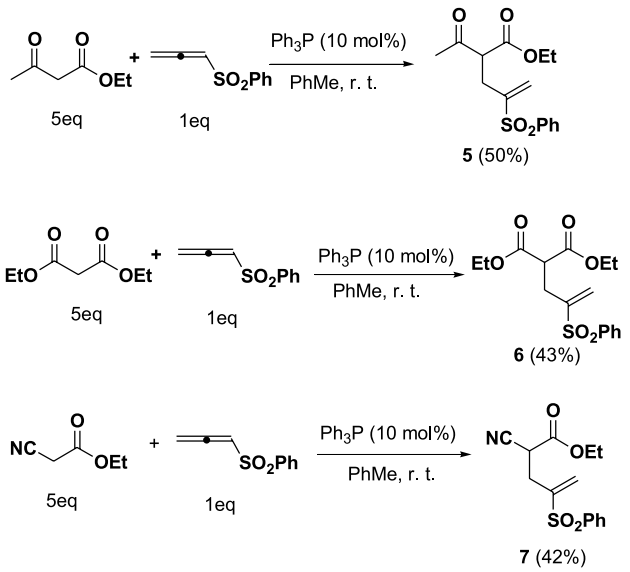


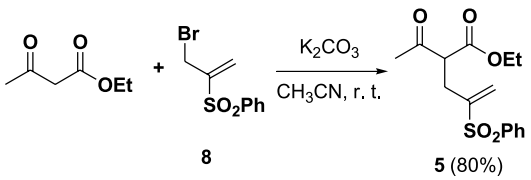
Scheme 3.

The unexpected results urged us to make further investigation on the reactions. To our surprise, another type of product was obtained when other active methylene compounds were used instead of cyclohexane-1,3-dione or acetylacetone (Scheme 4).



Scheme 4.

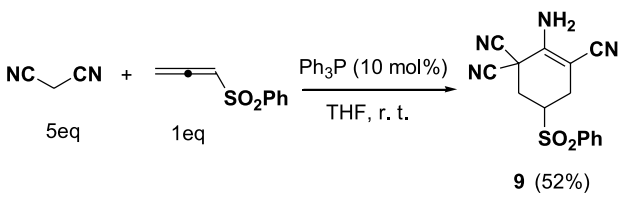
Reaction of ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate with phenylsulfonyl-1,2-propadiene gave rearranged adducts in which the sulfonyl group migrated from the terminal carbon atom of the allenic sulfone to the central carbon atom. An independent synthesis of **5** from the reaction of 3-bromo-2-phenylsulfonylpropene (**8**) with ethyl acetoacetate in the presence of a base comfirmed the sulfonyl-migrated structure (Scheme 5).



Scheme 5.

Reaction of malononitrile with phenylsulfonyl-1,2-propadiene afforded an enamine derivative (**9**), a three-component adduct (Scheme 6).[7] The sulfonyl group in the product also migrated. It is quite difficult to explain these phenomena provided that Ph_3P is the catalyst, because umpolung adduct should be formed according to our experience in the related work.[1a,3,4]

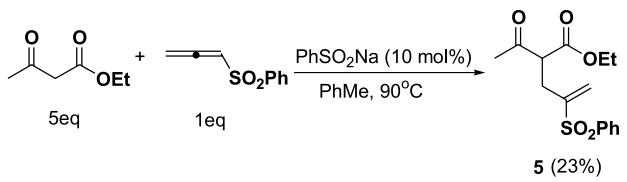
Then, we turned our attention to the chemistry of allenic sulfones. Padwa's work on the sulfinate anion-mediated



Scheme 6.

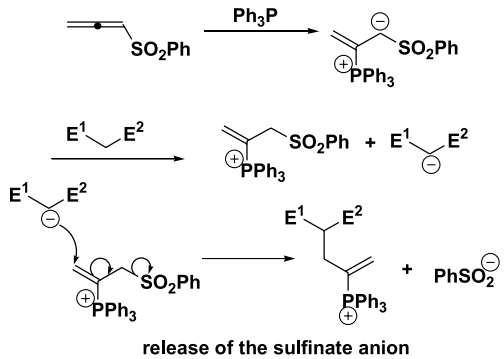
reaction of allenic sulfones[8] inspired us to understand more about the abnormal phenomena we observed. We wonder that the reaction of active methylene compounds with phenylsulfonyl-1,2-propadiene is possibly triggered by PPh_3 and mediated by sulfinate anion.

To test the possibility of the sulfinate anion mediated formation of the abnormal product, a mixture of ethyl acetoacetate, phenylsulfonyl-1,2-propadiene and $PhSO_2Na$ was heated in toluene, and indeed the rearranged product **5** was obtained in 23% yield (Scheme 7). No reaction occurred in the absence of $PhSO_2Na$.



Scheme 7.

Since no sulfinates were added in the reaction discussed before, we were puzzled by the origin of the sulfinate anion. Although the detailed mechanism is still unclear, we proposed that it was generated in situ as illustrated in Scheme 8.

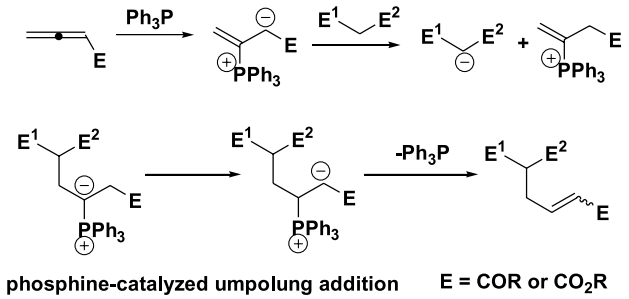


Scheme 8.

Nucleophilic addition of triphenylphosphine to phenylsulfonyl-1,2-propadiene forms a zwitterionic intermediate, the carbanion center of which would deprotonate the acidic proton of the active methylene compound to effect further conjugate addition of the carbonucleophile to the vinyl phosphonium salt[9] and simultaneous release of the sulfinate anion.

It is reasonable that the above process is favored by the presence of a good releasing group (sulfonyl group). If the sulfonyl group was replaced by an ester or acyl group that are not good releasing groups, this process was not likely to

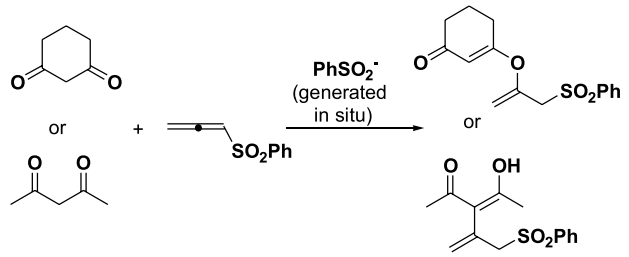
happen. In this case, an alternative pathway would be possible, from which the umpolung product can be formed (Scheme 9). This could partly explain why allenic sulfones show a completely different reaction behavior from the corresponding allenoates or allenones towards active methylene compounds in the presence of tertiary phosphines.



Scheme 9.

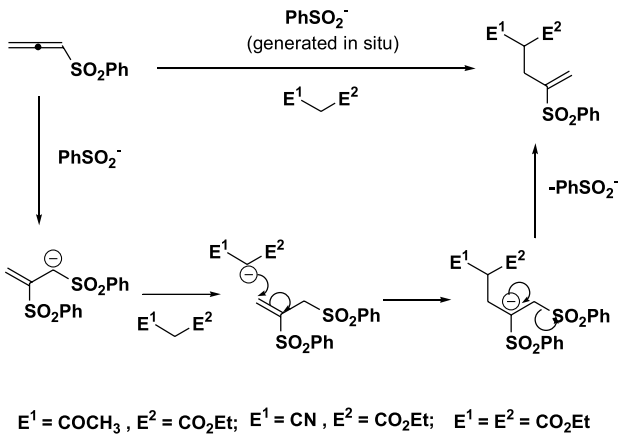
The sulfinate anion generated as described above can further catalyze the reactions of active methylene compounds with phenylsulfonyl-1,2-propadiene and the results can be classified into three types:

(1) For the reaction of those active methylene compounds with relatively higher kinetic acidity (1,3-cyclohexanedione or acetylacetone), the sulfinate anion simply served as a base to promote the normal Michael addition reaction (Scheme 10).
(2) For the reaction of those active methylene compounds with relatively low kinetic acidity, the competition between the sulfinate anion and the carbanion of the active methylene compounds will occur. In this case, the sulfinate ion served as a nucleophilic catalyst to promote the formation of the rearranged product (Scheme 11). The sulfinate anion attacks the central carbon of the allene to initiate the reaction and the catalytic cycle is completed by the release of another sulfinate anion from the terminal carbon to give the sulfonyl group-migrated product.
(3) For the reaction of malononitrile with phenylsulfonyl-1,2-propadiene, the sulfinate anion also served as a nucleophilic catalyst. The reaction intermediate was further captured by a second molecule of malononitrile and effected intramolecular cyclization reaction to form a six-member enamine derivative (Scheme 12).

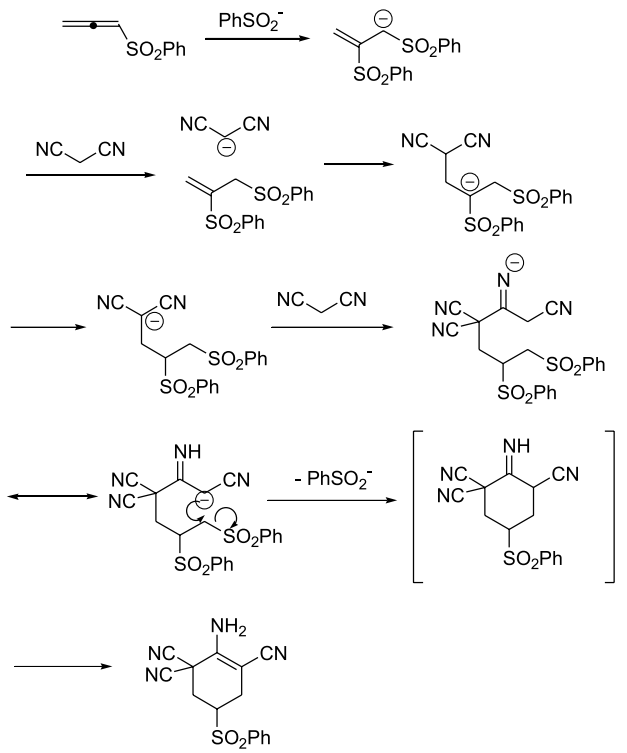


Scheme 10.

In summary, we have found that the reaction of active methylene compounds with phenylsulfonyl-1,2-propadiene could be interestingly triggered by triphenylphosphine and



Scheme 11.



Scheme 12.

catalyzed by the in situ generated sulfinate anion to give three types of adducts: Michael adducts, rearranged adducts or a three-component adduct.

3. Experimental

3.1. General

Phenylsulfonyl-1,2-propadiene (**1**)[10] and 3-bromo-2-phenylsulfonylpropene (**8**)[11] were prepared by the methods described in the literature.

3.1.1. Reaction of 1,3-cyclohexanedione with phenylsulfonyl-1,2-propadiene (1) in the presence of Ph_3P. To a stirred solution of 1,3-cyclohexanedione (56 mg, 0.5 mmol) and Ph_3P (6.5 mg, 0.025 mol) in toluene (1.5 mL) at 80 °C

under nitrogen was added a solution of phenylsulfonyl-1,2-propadiene (**1**, 90 mg, 0.5 mmol) in toluene (1 mL). The solution was stirred for another 9 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give **3** as an oil (72 mg, 49%). Oil. IR (KBr): ν 2951, 1656, 1612, 1323, 1311, 1172, 1136 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J=8.5 Hz, 2H), 7.70–7.67 (m, 1H), 7.61–7.56 (m, 2H), 5,35 (s, 1H), 5.00 (d, J=1.5 Hz, 1H), 4.96 (d, J=1.5 Hz, 1H), 3.95 (s, 2H), 2.32 (t, J=6.7 Hz, 2H), 2.24 (t, J=6.5 Hz, 2H), 1.98–1.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 199.2, 174.7, 145.5, 138.2, 134.1, 129.2, 128.5, 109.9, 106.5, 59.3, 27.7, 20.8. MS (*m*/*z*): 292 (M^+), 217, 151, 84, 77, 49 (100), 43. HRMS-EI calcd for $C_{15}H_{16}O_4S$: (M^+) 292.0769. Found: 292.0780.

3.1.2. Reaction of acetylacetone with phenylsulfonyl-1,2-propadiene (1) in the presence of Ph_3P. To a stirred solution of acetylacetone (250 mg, 2.5 mmol) and Ph_3P (13.1 mg, 0.05 mol) in toluene (1.5 mL) at room temperature under nitrogen was added a solution of **1** (90 mg, 0.5 mmol) in toluene (1 mL) by a syringe over 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give **4** as a solid (75 mg, 54%). Mp 102–104 °C. IR (neat): ν 2750, 1600, 1447, 1170, 954 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 16.75 (s, 1H), 7.94 (d, J=7.3 Hz, 2H), 7.94 (d, J=7.3 Hz, 2H), 7.68 (d, J=7.3 Hz, 1H), 7.60 (t, J=7.3 Hz, 2H), 6.43 (s, 1H), 5.62 (s, 1H), 3.18 (s, 2H), 1.85 (s, 6H). (^1H NMR shows trace amount of the corresponding diketone tautomer). ^{13}C NMR (75 MHz, $CDCl_3$): 191.9, 149.1, 138.1, 133.8, 129.3, 128.2, 128.1, 123.3, 104.3, 29.8, 27.7, 22.4. MS (*m*/*z*): 280 (M^+), 139 (100), 138, 123, 96, 95, 43. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.92; H, 5.74.

3.1.3. General procedure for the reaction of active methylene compounds (ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate) with 1 in the presence of Ph_3P. To a stirred solution of active methylene compound (2.5 mmol) and Ph_3P (13.1 mg, 0.05 mol) in toluene (1.5 mL) at room temperature under nitrogen was added a solution of **1** (90 mg, 0.5 mmol) in toluene (1 mL) by a syringe over 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give the rearranged product as oil.

3.1.4. Ethyl 2-acetyl-4-phenylsulfonyl-pent-4-enoate (5). Yield (50%). Oil. IR (neat): ν 2986, 1742, 1718, 1307, 1148, 1127, 750, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J=8.2 Hz, 2H), 7.65 (t, J=7.7 Hz, 1H), 7.56 (dd, J=7.7, 8.2 Hz, 2H), 6.38 (s, 1H), 5.83 (s, 1H), 4.17 (q, J=7.1 Hz, 2H), 4.03 (t, J=7.1 Hz, 1H), 2.76 (dq, J=7.1 Hz, 15.5 Hz, 2H), 2.36 (s, 3H), 1.25 (t, J=7.1 Hz, 3H). (^1H NMR shows the presence of the corresponding enol tautomer: 12.87 (s, 1H), 7.87 (d, J=8.2 Hz, 2H), 7.65 (t, J=7.7 Hz, 1H), 7.56 (dd, J=7.7, 8.2 Hz, 2H), 5.60 (s, 1H), 3.96 (q, J=7.1 Hz, 2H), 3.15 (s, 2H), 1.02 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 201.3, 168.1, 146.7, 138.1, 133.7, 129.3, 129.0, 128.1, 128.0, 127.0, 61.7, 57.4, 29.8, 27.9, 13.9. MS (*m*/*z*): 310 (M^+), 265, 169, 126, 125, 97, 77, 43 (100). Anal. Calcd for $C_{15}H_{18}O_5S$: C, 58.05; H, 5.85. Found: C, 58.19; H, 5.81.

3.1.5. Diethyl 2-(2′phenylsulfonylallyl)malonate (6). Yield (43%). Oil. IR (neat): ν 2895, 1733, 1718, 1448, 1307, 1138, 1136, 751, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J=7.6 Hz, 2H), 7.64 (t, J=7.6 Hz, 1H), 7.56 (t, J=7.6 Hz, 2H), 6.42 (s, 1H), 5.85 (s, 1H), 4.16 (q, J=7.1 Hz, 4H), 3.76 (t, J=7.5 Hz, 1H), 2.85 (d, J=7.5 Hz, 2H), 1.13 (t, J=7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.0, 146.7, 138.2, 133.7, 129.3, 128.2, 126.4, 61.7, 50.3, 28.8, 13.9. MS (*m*/*z*) 295 (M^+-OEt), 249, 199, 171, 143, 125 (100), 97. Anal. Calcd for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92. Found: C, 56.69; H, 6.17.

3.1.6. Ethyl 4-phenylsulfonyl-2-cyanopent-4-enoate (7). Yield (42%). Oil. IR (neat): ν 2987, 2254, 1747, 1718, 1448, 1138, 749, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J=7.6 Hz, 2H), 7.68 (t, J=7.6 Hz, 1H), 7.60 (t, J=7.6 Hz, 2H), 6.52 (d, J=1.2 Hz, 1H), 6.05 (d, J=1.2 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 4.02 (dd, J=5.7, 9.5 Hz, 1H), 2.97 (dd, J=5.7 Hz, 15.6 Hz, 1H), 2.73 (dd, J=9.5 Hz, 15.6 Hz, 1H), 1.31 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 164.6, 144.5, 137.6, 134.1, 129.5, 128.8, 128.3, 115.3, 63.3, 36.6, 30.1, 13.9. MS (*m*/*z*): 248 (M^+-OEt), 152, 124 (100), 97, 78, 77, 51, 43. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.00; H, 5.40; N, 4.87.

3.1.7. Synthesis of 5 from the reaction of 3-bromo-2-phenylpropene with ethyl acetoacetate. To a stirred solution of 3-bromo-2-phenylpropene (2 mmol) in acetonitrile (2 mL) at room temperature was added ethyl acetoacetate (2 mmol) and potassium carbonate (2 mmol), and the suspension was stirred for 48 h. The solid was filtered and the filtrate was subject to reduced pressure to remove the solvent. The residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give **5** as an oil. The ^1H NMR of the product was identical to that obtained from the reaction of ethyl acetoacetate with phenylsulfonyl-1,2-propadiene in the presence of Ph_3P.

3.1.8. Reaction of malononitrile with 1 in the presence of Ph_3P. To a stirred solution of malononitrile (2.5 mmol) and Ph_3P (13.1 mg, 0.05 mol) in toluene (1.5 mL) at room temperature under nitrogen was added a solution of **1** (90 mg, 0.5 mmol) in toluene (1 mL) by a syringe over 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give the rearranged product **9** as a solid. Yield (52%). Mp 177–178 °C. IR (neat): ν 3437, 3340, 3228, 2213, 1658, 1448, 1324, 1152 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 8.04 (d, J=7.5 Hz, 2H), 7.87 (t, J=7.5 Hz, 1H), 7.58 (t, J=7.5 Hz, 2H), 7.37 (weak singlet), 3.75–3.68 (m, 1H), 3.26 (dt, J=13.2, 2.0 Hz, 1H), 2.69 (t, J=13.2 Hz, 1H), 2.63 (d, J=15.3 Hz, 1H), 2.53 (ddd, J=15.3, 5.7, 2.0 Hz, 2H). MS (*m*/*z*): 312 (M^+), 170 (100), 143, 124, 117, 105, 77, 51. HRMS-EI calcd for $C_{15}H_{12}N_4O_2S$: (M^+) 312.0681. Found 312.0657. The structure of **9** was further confirmed by X-ray crystallography.[7]

3.1.9. Reaction of ethyl acetoacetate with 1 in the presence of sodium benzenesulfinate. In a reaction tube was charged with sodium benzenesulfinate dihydrate (10 mg, 0.05 mmol). The reaction tube was heated under vacuum to remove the water. A solution of ethyl acetoacetate (325 mg, 2.5 mmol) in toluene (1 mL) was added under nitrogen. The mixture was heated to 90 °C. A solution of **1** (90 mg, 0.5 mmol) in toluene (1 mL) was added by a syringe over 5 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (eluents: ethyl acetate/petroleum ether) to give **5** as an oil. The ^{1}H NMR of product was identical to that obtained from the reaction of ethyl acetoacetate with **1** in the presence of Ph_3P.

Acknowledgements

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Synthesis of *N*,*N*-di(arylmethylidene)arylmethanediamines by flash vacuum pyrolysis of arylmethylazides

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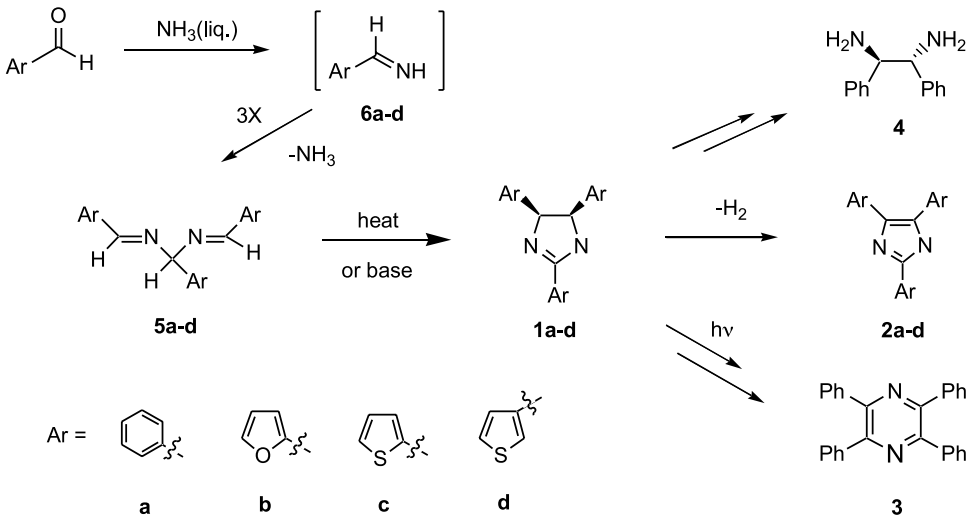
Abstract—Flash vacuum pyrolysis of arylmethylazides **7a-d** gave 2,4-diazapentadienes **5a-d** in high yield (76–92%). The thermal cyclization of **5a-d** gave *cis*-imidazolines **1a-d**, further heating or Swern oxidation of **1a-d** gave dehydrogenated products, imidazoles **2a-d**.

1. Introduction

Amarine **1a** is a very useful precursor for organic synthesis, which was found to give the corresponding imidazole **2a** by dehydrogenation.[1] **1a** can rearrange to 2,3,5,6-tetra-phenylpyrazine (**3**) by irradiation,[2] and converts to ligand **4**,[3] which has been employed for enantioselective synthesis.[4] Amarine **1a** can be prepared by cyclization of the *N*,*N*-di(arylmethylidene)arylmethanediamine **5a** with a strong base or under thermal condition. Compound **5a** was formed previously by condensation of imine **6a**, which was generated in liquid ammonia with benzaldehyde[5] (Scheme 1). Synthesis of **5** and **1** from arylaldehydes has also been accomplished by microwave irradiation or heating with hexamethyldisilazane.[6] Recently, we have synthesized **5a-d** by the flash vacuum pyrolysis of their corresponding arylmethylazides **7a-d**. We report here the results of this work.

2. Results and discussion

Arylmethylazides **7a-d** were prepared from the reported method.[7] FVP of **7a-d** at 450–550 °C and ca. 1×10^{-2} Torr, gave presumably gaseous nitrenes **8a-d** as the primary pyrolysis products. 1,2-Hydrogen shift of **8a-d** would give imines **9a-d**, which then underwent a condensed



Scheme 1.

Keywords: Arylmethylazides; Pyrolysis; *N*,*N*-Di(arylmethylidene)arylmethanediamines.
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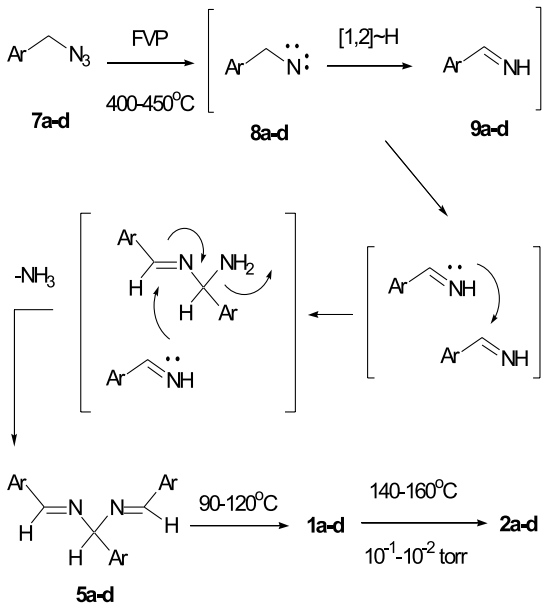
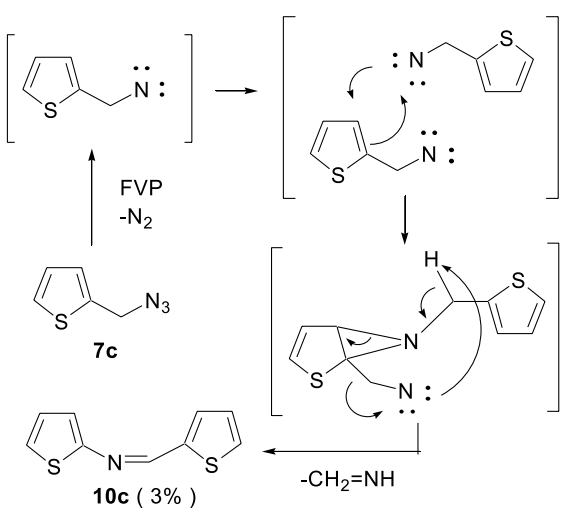


Scheme 2.

trimerization reaction to give **5a**-**d** in high yield (76–92%). Thermal isomerization of compounds **5a**-**d** under 90–120 °C for 4–6 h gave *cis*-imidazolines **1a**-**d**. Further heating of **1a**-**d** at 140–160 °C under low pressure condition (ca. 1×10^{-1} Torr) gave dehydrogenated products, imidazoles **2a**-**d**. The route to the pyrolysis products and thermally isomerized products from **8a**-**d** are summarized in Scheme 2 and the yields of each product are listed in Table 1. Since further heating of **1b** gave only decomposed products and **5d** cyclized directly to give **2d**, we did not isolate **2b** and **1d**.

Table 1. Products and yields from FVP of **7a**-**d**, and from thermolysis of the resulting compounds

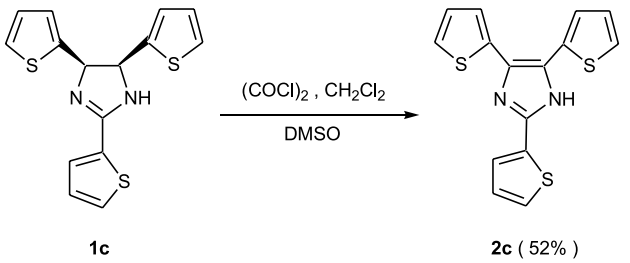
Entry	Starting materials	Products (yields, %)		
		5a-d	**1a-d**	**2a-d**
1	**7a**	92	84	55
2	**7b**	78	79	—
3	**7c**	86	63	31
4	**7d**	76	—	33



Scheme 3.

We also found that FVP of **7c**,**d** gave not only the condensed trimers **5c**,**d** as the major products, but also a small amount of dimers **10c**,**d**. We propose the mechanism for the formation of **10c** as shown in Scheme 3. The formation of **10d** follows the same type of mechanism.

It is noteworthy that the yields of imidazoles **2** from *cis*-imidazolines **1** can be improved by performing Swern oxidation. For instance, the yield of **2c** can be increased to 52% by Swern oxidation of **1c** (Scheme 4) as compared to 31% from simple heating of **1c** (Table 1).[8]



Scheme 4.

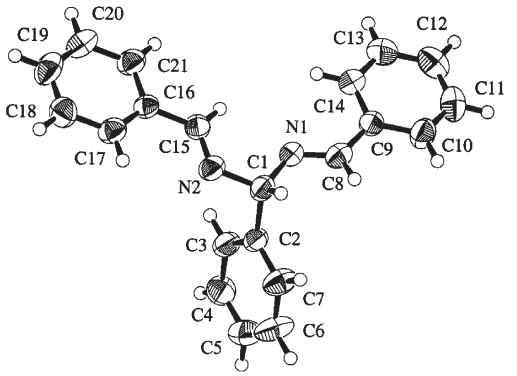


Figure 1. Crystal structure of **5a**.

Pure **5a** can be recrystallized from CH_2Cl_2. The structure of **5a** was analyzed by X-ray crystallography and shown as Figure 1.[9a] Pure **2c** was recrystallized from ethyl acetate and *n*-hexane. The structure of **2c** was analyzed by X-ray crystallography and shown as Figure 2.[9b]

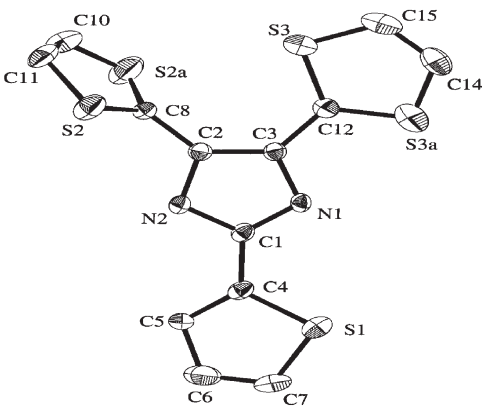


Figure 2. Crystal structure of **2c**. S2/S2a and S3/S3a are the disordered sites for S/CH disorder within the thiophene rings.

3. Conclusion

In conclusion, the flash vacuum pyrolysis of arylmethylazides **7a-d** is a new and efficient method to generate 2,4-diazapentadienes **5a-d**, further heating of **5a-d** can induce ring cyclization to give *cis*-imidazolines **1a-d**. We also found the yield of dehydrogenated products, imidazoles **2a-d** from **1a-d**, can be improved by performing Swern oxidation.

4. Experimental

4.1. General

Infrared spectra were recorded with a FTS-175/185 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were carried out in $CDCl_3$ or acetone-d_6 in a Varian VXR-300 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Mass spectra were recorded with a VG QUATTRO 5022 spectrometer. The X-ray structures were analyzed by a RIGAKU AFC7S diffractoneter.

4.2. General pyrolysis procedure[10]

The furnace was maintained at temperatures in the range 400–450 °C. A sample for pyrolysis was placed into the sample chamber and the system was evacuated to ca. 10^{-2} Torr. During the pyrolysis $CDCl_3$ was deposited into the cold trap through a side arm. After the pyrolysis was completed, nitrogen was introduced into the system, the liquid-nitrogen-cooled trap was warmed to room temperature and all the FVP products were collected. At the exit of the horizontal fused quartz tube, the pure products **5a-d** were obtained without purification. These products were analyzed by ^{1}H, ^{13}C NMR, IR and Mass. The percent yields were determined from ^{1}H NMR.

4.3. Heating of 2,4-diazapentadienes 5a-d and *cis*-imidazolines 1a-d

A sample of FVP products **5a-d** was placed into the sample chamber of the bulb-to-bulb distillation, and the whole system was maintained at a pressure of 10^{-2} Torr. The sample chamber was heated to 120 °C for 5 h to give **1a-d**. Further heating of **1a-d** at 140–160 °C gave dehydrogenated products, imidazoles **2a-d**. These crude products were purified using preparative TLC or column chromatography on silica gel.

4.4. Swern oxidation of imidazoline 1c

A stirred solution of oxalyl chloride (0.79 mL, 1.6 equiv.) in CH_2Cl_2 (20 mL) at −78 °C was treated with DMSO (1.37 mL, 3.2 equiv.) in CH_2Cl_2 (10 mL), dropwise over 5 min. After 10 min, imidazoline **1c** (1.75g, 5.53 mmol) in CH_2Cl_2 (10 mL) was added over 10 min, followed by triethylamine (3.9 mL, 5 equiv.), dropwise over 10 min. The mixture was stirred with gradual warming overnight, and then the reaction was quenched with water. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concertrated to give the crude product. The crude product was purified by flash chromatography on silica gel using 2:1 *n*-hexane/ethyl acetate to give 0.90 g (52%) imidazole **2c**.

4.5. Spectral data of products

4.5.1. *N*,*N*-Di(phenylmethylidene)phenylmethane diamine (5a). IR ($CDCl_3$, cm^{-1}) 3085, 2844, 1639, 1579. Mp 105–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 2H), 7.83–7.86 (m, 4H), 7.18–7.53 (m, 11H), 5.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 141.6, 135.9, 130.9, 128.6, 128.5, 128.4, 127.7, 127.1, 92.6. MS (FAB) *m*/*z* (%) 299 [(M+1)$^+$, 5.0]. (Lit. [5a] Mp 101–102 °C).

4.5.2. *N*,*N*-Di[(2-furanyl)methylidene](2-furanyl)methanediamine (5b). IR ($CDCl_3$, cm^{-1}) 1635. Mp 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, J=0.6 Hz, 2H), 7.56 (d, J=1.2 Hz, 2H), 7.39 (d, J=0.6 Hz, 1H), 6.88 (d, J=3.3 Hz, 2H), 6.51 (q, J=1.8 Hz, 2H), 6.39 (d, J=3.3 Hz, 1H), 6.35 (q, J=1.8 Hz, 1H), 6.13 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 151.5, 150.5, 145.3, 142.5, 115.8, 111.8, 110.4, 107.8, 84.1. MS (LR, 70 eV) *m*/*z* (%) 268 (M$^+$, 11.34). (Lit. [5a] Mp 116–117 °C).

4.5.3. *N*,*N*-Di[(2-thienyl)methylidene](2-thienyl)methanediamine (5c). IR (neat, cm^{-1}) 3166, 2252, 1691, 1626. ^{1}H NMR (300 MHz, acetone-d_6): δ 8.75 (s, 2H), 7.65 (d, J=8.5 Hz, 2H), 7.46 (dd, J=6.5, 1.5 Hz, 2H), 7.39 (dd, J=8.5, 1.5 Hz, 1H), 7.14 (dd, J=8.5, 6.0 Hz, 2H), 7.08 (d, J=5.5 Hz, 1H), 6.99–7.01 (m, 1H), 6.23 (s, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ 155.5, 146.9, 143.4, 133.2, 131.0, 128.6, 127.5, 126.3, 125.2, 87.3. HRMS Calcd for $C_{15}H_{12}N_2S_3$: 316.0163, found: 316.0165.

4.5.4. *N*,*N*-Di[(3-thienyl)methylidene](3-thienyl)methane diamine (5d). IR (neat, cm^{-1}) 2927, 2254, 1692, 1635. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 2H), 7.70 (t, J=1.5 Hz, 2H), 7.65 (d, J=5.0 Hz, 2H), 7.30–7.33 (m, 4H), 7.13–7.14 (m, 1H), 5.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 142.9, 140.3, 129.6, 126.5, 126.4, 126.1, 126.0, 122.1, 89.0. HRMS Calcd for $C_{15}H_{12}N_2S_3$: 316.0163, found: 316.0161.

4.5.5. *cis*-2,4,5-Triphenylimidazoline (1a). IR ($CDCl_3$, cm^{-1}) 2834, 2347, 1636. Mp 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J=8.4 Hz, 2H), 7.53–7.46 (m, 4H), 7.03–6.90 (m, 10H), 5.41 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 138.6, 131.2, 129.5, 128.6, 127.6, 127.4, 127.3, 126.8, 70.6. MS (LR, 70 eV) *m*/*z* (%) 298 (M$^+$, 8.3). (Lit.[5a] Mp 127–128 °C).

4.5.6. *cis*-2,4,5-Tri(2-furanyl)imidazoline (1b). IR ($CDCl_3$, cm^{-1}) 3124, 2936, 2873, 1633. Mp 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J=0.9 Hz, 1H), 7.19 (t, J=0.6 Hz, 2H), 7.14 (d, J=3.3 Hz, 1H), 6.52 (q, J=1.8 Hz, 1H), 6.17 (q, J=2.1 Hz, 2H), 6.04 (d, J=3.0 Hz, 2H), 5.38 (s, 2H), 5.00 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 151.9, 144.7, 144.2, 141.8, 112.9, 111.9, 110.1, 107.2, 63.3. MS (LR, 70 eV) *m*/*z* (%) 268 (M$^+$, 38.2). (Lit.[5a] Mp 115–116 °C).

4.5.7. *cis*-2,4,5-Tri(2-thienyl)imidazoline (1c). IR (neat, cm^{-1}) 1716, 1699, 1627. Mp 127–128 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.75 (d, J=4.0 Hz, 1H), 7.67 (d,

J=5.0 Hz, 1H), 7.17–7.19 (m, 1H), 7.11–7.12 (m, 2H), 6.76–6.78 (m, 4H), 5.65 (s, 2H), 3.20 (br, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ 160.3, 144.2, 134.9, 130.5, 129.4, 128.4, 126.9, 126.0, 125.3. HRMS Calcd for $C_{15}H_{12}N_2S_3$: 316.0163, found: 316.0165. (Lit.[6a] Mp 125–126 °C).

4.5.8. 2,4,5-Triphenylimidazole (2a). IR (KBr, cm^{-1}) 3028, 2926, 1786, 1647. Mp 274–275 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 11.73 (br, 1H), 8.13–8.15 (m, 2H), 7.15–7.68 (m, 13H). ^{13}C NMR (75 MHz, acetone-d_6): δ 148.8, 138.6, 136.2, 131.2, 130.4, 130.1, 129.7, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.9, 128.2, 127.0. HRMS: Calcd for $C_{21}H_{16}N_2$: 296.1313, found: 296.1317. (Lit.[11] Mp 270–273 °C).

4.5.9. 2,4,5-Tri(2-thienyl)imidazole (2c). IR (neat, cm^{-1}) 3304, 2927, 1736, 1716, 1687. Mp 248–249 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.64–7.65 (m, 1H), 7.59 (br, 2H), 7.51–7.52 (m, 1H), 7.35 (br, 2H), 7.11–7.24 (m, 3H), 6.97 (br, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ 143.1, 138.5, 135.1, 134.6, 127.9, 129.7, 128.6, 127.4, 125.3. HRMS Calcd for $C_{15}H_{10}N_2S_3$: 314.0006, found: 314.0009.

4.5.10. 2,4,5-Tri(3-thienyl)imidazole (2d). IR (neat, cm^{-1}) 2985, 2252, 1731, 1693. Mp 244–246 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.96 (t, J=1.5 Hz, 1H), 7.73 (d, J=1.5 Hz, 1H), 7.55–7.57 (m, 3H), 7.48 (dd, J=5.0, 3.0 Hz, 2H), 7.30 (dd, J=5.0, 1.0 Hz, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 143.4, 135.0, 133.7, 128.4, 127.3, 126.9, 126.5, 122.7, 122.3. HRMS Calcd for $C_{15}H_{10}N_2S_3$: 314.0006, found: 314.0003.

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Reactivity of the carbon–carbon double bond towards nucleophilic additions. A DFT analysis

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Abstract—The global and local electrophilicity indexes have been used to characterize the reactivity pattern of the C=C double bond towards nucleophilic addition reactions. A wide family of molecules including ketones, esters, anhydrides, nitriles and nitrocompounds containing appropriate substitution on the C=C double bond have been classified within an unique scale of reactivity. The predictive capability of the theoretical model is tested against a series of benzylidenemalononitriles and substituted α-nitrostilbenes.

1. Introduction

The soft π electron density present on the C=C double bond constitutes a reactive site on the hydrocarbon skeleton. In the case of unsubstituted alkenes, the two carbon atoms participating in the double bond present a negative charge because of the larger electronegativity of the carbon atom relative to the hydrogen atom (C=C–H). The more electronegative character of the sp^2 hybrid respect to the sp^3 one is an additional source for the better stabilization of a negative charge in the former case. Therefore, the expected reactivity pattern of the C=C functionality is the attack by electrophiles, E^+. However, this behavior can be drastically modified by suitable substitutions. For instance, the presence of an electron-withdrawing substituent at the C=C double bond modifies the reactivity pattern of an adjacent carbonyl group, thereby leading to the well known result that the α,β-unsaturated carbonyl compounds usually undergo conjugate nucleophilic additions, named Michael additions. The nucleophilic activation of the α,β-unsaturated carbonyl compounds is a challenging problem involving intramolecular selectivity in polyfunctional systems, that may be conveniently treated in terms of local (regional) reactivity indexes within a simple model we shall discuss here.

The study of polar processes involving the interaction of electrophiles and nucleophiles may be significantly facilitated if reliable scales of electrophilicity and nucleophilicity are available. The utility of such global reactivity scales is of great importance to answer some fundamental questions in chemistry such as reaction feasibility (whether or not a given reaction will take place) or intermolecular selectivity. An excellent source that illustrates this concept well is the review work recently published by Mayr et al.[1] The development of theoretical scales of nucleophilicity and electrophilicity on the other hand is also desirable, as a validated theoretical scale may be further used to project the global reactivity onto particular regions in the molecule, thereby allowing the intramolecular selectivity to be also assessed.

There are different ways to model the electrophilicity concept using the electronic structure of molecules. A suitable one is that based on Parr et al.'s definition of global electrophilicity[2] which will shortly be described in the next Section. This scale has been largely validated against the experimental scale proposed by Mayr's group[3] and other scales.[4] The validation has been done for a large number of organic molecules, including Diels–Alder (DA) reagents,[5] molecules participating in 1,3 dipolar cycloadditions,[6] carbenes,[7] as well as benzhydryl cations[8] and diazonium ions.[9] The electrophilicity index has been further shown to be almost insensitive to solvent effects.[10] The global electrophilicity index is also a useful tool to elucidate the reaction mechanism (concerted vs stepwise) in some

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cycloaddition reactions.[5,6] For a long time we have been interested in the study of the molecular mechanism of the polar DA reactions. These cycloadditions and the Michael reactions are mechanistically related, as the first step of these stepwise cycloadditions may be viewed as a Michael process in several cases.[11] In this line, Mayr et al. has proposed that for the stepwise [2+2] cycloaddition between morpholinoisobutene and benzylidenemalononitrile (**9** see Chart 1) the first step may be viewed as Michael addition of morpholinoisobutene to **9**.[12] Adequate substitution on the diene/dienophile pair favors the cycloaddition through a polar process. For instance, α,β-unsaturated carbonyl compounds are commonly used as activated dienophiles. Coordination of a Lewis acid to the carbonyl oxygen atom increases the reactivity of these dienophiles through an enhancement of the global electrophilicity. These polar cycloadditions, which take place along highly asynchronous transitions states, can be described as a consecutive Michael type addition/cyclization processes to afford the final cycloadduct.

Previous effort to explain the nucleophilic activation of Michael acceptors has been recently presented.[13] In this work the authors performed a charge analysis at the ground state of the α,β-unsaturated carbonyl compounds and they showed that the two carbon atoms of the C=C double bond displayed negative charges, thereby preventing reactions towards nucleophiles. They further showed that local reactivity indexes like local softness and the electrophilic Fukui function (i.e. the Fukui function for nucleophilic attack) performed better in describing the nucleophilic activation for a series of six Michael acceptors. However, local softness and the Fukui function contain essentially the same information as the Fukui function corresponds to a normalized softness. Recently, Mayr and Lemek[12] presented a kinetic study on the reactivity of a series of benzylidenemalononitriles towards a wide variety of nucleophiles. These authors used an experimental scale of electrophilicity to predict the reactivity of these systems. Extensive kinetic work on the nucleophilic additions to activated olefins have been reported by Bernasconi et al.[14–17] They include the thiolate ion addition to substituted α-nitrostilbenes[14] and morpholine and piperidine additions to substituted benzylidenemalononitriles.[15] Both, Mayr's and Bernasconi's groups have provided experimental rate coefficients that will be used in this work to test the predictive capability of the theoretical electrophilicity scale based on Parr et al. definition of global electrophilicity.[2]

Our working hypothesis establishes that the electrophilicity indexes (both global and local) are better descriptors of reactivity that the global softness and the Fukui function, in the sense that other effects coming from the

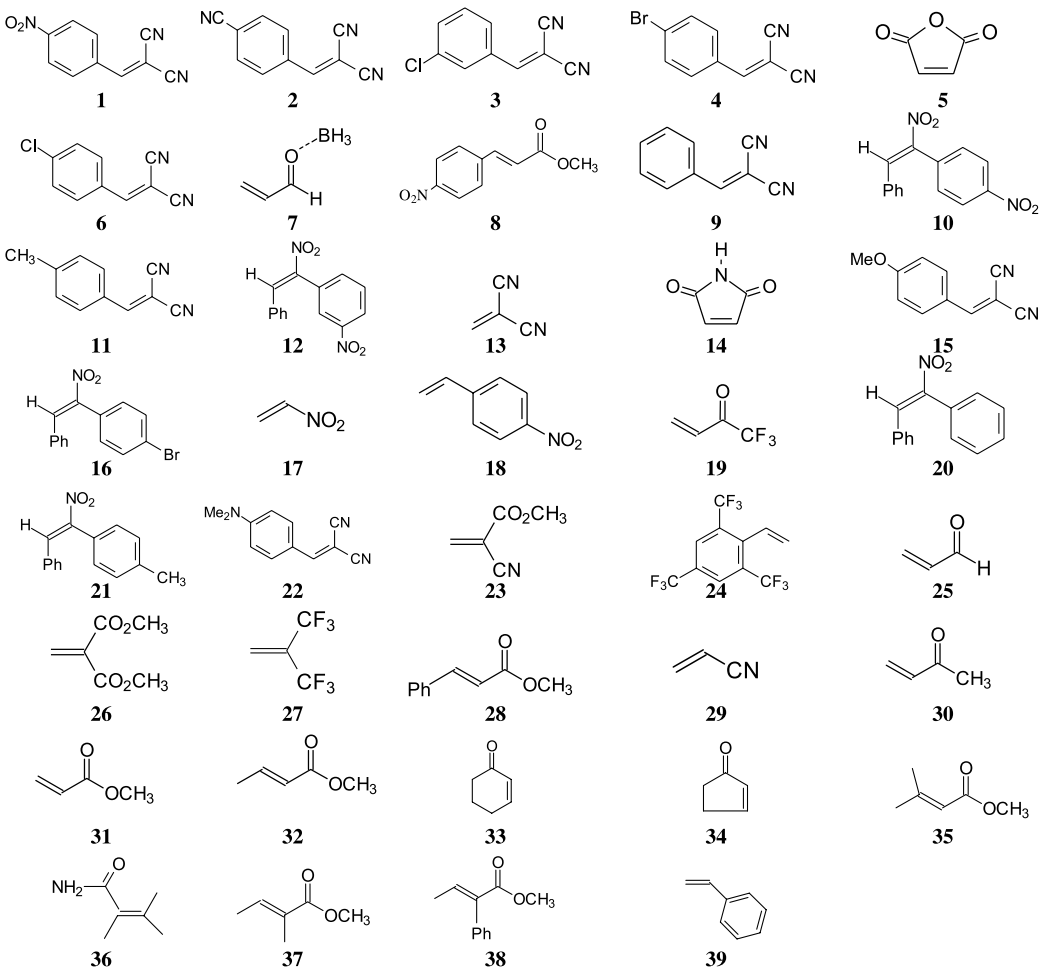

Chart 1. Series of molecules included in the present study.

electronegativity of the electron acceptors are incorporated in a single index encompassing the effect of the global softness.

In this work we present a systematic study on the global and local electrophilicity indexes for a wide family of substituted alkenes including α,β-unsaturated aldehydes, ketones, esters, anhydrides, nitriles and nitro derivatives as well as fluoroderivatives. We illustrate the usefulness of the global and local electrophilicity scales to explain the feasibility of the C=C double bond to react towards nucleophiles. Even though most of the members of the series included in the present study are Michael acceptors, some other cases are also considered.

2. The model

The concept of electrophilicity viewed as a reactivity index was introduced rather recently by Parr et al.[2] It is based on a second order expansion of the electronic energy with respect to the charge transfer ΔN at fixed geometry. Since electrophiles are species that stabilize upon receiving an additional amount of electronic charge from the environment, there exists a minimum of energy for a particular ΔN^* value. Using this simple idea Parr et al. performed a variational calculation that led to the definition of the global electrophilicity index as $\omega=-\Delta E(\Delta N^*)$, which may be recast into the more familiar form:[2]

$$\omega = \frac{\mu^2}{2\eta}; \tag{1}$$

in terms of the electronic chemical potential μ and the chemical hardness η. The ω index establishes an absolute scale of electrophilicity in the sense that the hierarchy of electrophilicity is built up from the electronic structure of molecules, independent of the nucleophilic partner, which is replaced by an unspecified environment viewed as sea of electrons.[2]

Beside the global electrophilicity index, it is possible to define its local (or regional) counterpart condensed to atoms. The local electrophilicity index ω_k condensed to atom k is easily obtained by projecting the global quantity onto any atomic center k in the molecule by using the electrophilic Fukui function (i.e. the Fukui function for nucleophilic attack, f_k^+). There result:[18]

$$\omega_k = f_k^+ \omega. \tag{2}$$

The regional or condensed to atom electrophilicity index has been shown to correctly assess the regioselectivity in a number of cases.[7–9,18,19] In summary, while the global electrophilicity index categorizes within a unique scale the electron acceptor ability of molecules, its local or regional counterpart plays a key role in the elucidation of the intramolecular selectivity of the same systems. Note that site electrophilic activation may also be assessed as the variation in local electrophilicity induced for instance by chemical substitution or any source of external perturbation to the molecular system. Some applications that illustrate this concept have been already reported in the literature.[7–9,18,19]

3. Computational details

All the structures included in this study were optimized at the B3LYP/6-31G(d) level of theory using the Gaussian98 package of programs.[20] The calculation of the electronic chemical potential and the chemical hardness were obtained from the expressions $\mu\approx(\varepsilon_H+\varepsilon_L)/2$ and $\eta\approx\varepsilon_L-\varepsilon_H$, in terms of the one electron energies of the HOMO and LUMO frontier molecular orbitals, ε_H and ε_L, respectively.[21] With these quantities at hand, the global electrophilicity was obtained using Eq. 1. The local electrophilicity values are obtained from the global electrophilicity index and the electrophilic Fukui function using Eq. 2. The electrophilic Fukui function is evaluated from a single point calculation in terms of the molecular orbital coefficients and the overlap matrix using a procedure described elsewhere.[22,23]

4. Results and discussion

The systems considered in the present study are depicted in Chart 1, while the global electrophilicity valves are given in Table 1. Included in this series are the most common functionalities associated with the chemistry of the nucleophilic addition to the C=C double bond, namely aldehydes, ketones, esters, anhydrides, nitriles including a short series of benzylidenemalononitriles recently evaluated by Mayr et al.[12] as well as trifluoromethyl derivatives of ethylene, styrene and substituted α-nitrostilbenes.[14] Using the same criteria taken to classify the electrophilic power of dienes, dienophiles,[5] dipoles and dipolarophiles,[6] we may recognize a first subgroup of strong electrophiles with global electrophilicity values $\omega>1.50$ eV (compounds **1**–**31** in Chart 1) and a second group of moderate electrophiles with $\omega<1.50$ eV (compounds **32**–**39**, in Chart 1). It is interesting to note that the electrophilicity hierarchy may be systematically rationalized in terms of the substituent effects induced by electron-withdrawing groups that result, as expected, in electrophilic activation, and the effect of electron-releasing groups leading to electrophilic deactivation. Consider for instance the series of carbonyl compounds. Starting from acrolein (**25**) we have on one hand a strong electrophilic activation induced by a Lewis acid (LA) catalyst modeled by BH_3 (**7**). Substitution of the aldehyde hydrogen atom in **25** by an electron-releasing methyl group to give methyl vinyl ketone (**30**) causes a moderate electrophilic deactivation. Substitution of this hydrogen atom by a methoxy group in methyl acrylate (**31**) produces an electrophilic deactivation. The π electron-releasing character of the $-OCH_3$ group overcome the σ electron-withdrawing one, and as a result, methyl acrylate (**31**) experiments a larger deactivation relative to acrolein **25**. Note that substitution of the aldehyde hydrogen atom in **25** by the strong electron withdrawing CF_3 group to give compound **19** causes the opposite effect leading to a significant electrophilic activation.

For the carboxylic derivative series we take compound **31** as reference. Increasing substitution by methyl groups at the conjugated double bond to the carbonyl group consistently results in electrophilic deactivation (see compounds **32**, **35**, **37**). Note however that while substitution of a hydrogen atom by a phenyl group in **32** to give **38** results in a moderate electrophilic deactivation, the substitution by a

Table 1. Global properties[a] and local electrophilicities of the series of electrophilically activated ethylenes **1-39**

Molecules	μ	η	ω	ω_k (Cβ)	ω_k (Cα)
1	−0.2112	0.1451	4.18	0.74	0.58
2	−0.2030	0.1454	3.85	0.90	0.61
3	−0.1907	0.1503	3.27	0.93	0.54
4	−0.1860	0.1447	3.25	0.92	0.52
5	−0.2083	0.1821	3.24	0.77	0.77
6	−0.1874	0.1472	3.24	0.92	0.52
7	−0.1837	0.1516	3.20	1.14	0.25
8	−0.1836	0.1533	2.99	0.34	0.20
9	−0.1832	0.1529	2.99	0.88	0.48
10	−0.1815	0.1501	2.99	0.67	0.25
11	−0.1774	0.1490	2.87	0.85	0.45
12	−0.1788	0.1536	2.83	0.63	0.24
13	−0.2074	0.2075	2.82	1.41	0.59
14	−0.1870	0.1740	2.73	0.61	0.61
15	−0.1672	0.1419	2.68	0.81	0.41
16	−0.1681	0.1463	2.63	0.59	0.22
17	−0.1958	0.2001	2.61	0.73	0.20
18	−0.1724	0.1577	2.56	0.26	0.05
19	−0.1865	0.1930	2.45	0.83	0.23
20	−0.1647	0.1504	2.45	0.53	0.22
21	−0.1614	0.1474	2.41	0.52	0.21
22	−0.1489	0.1279	2.36	0.70	0.33
23	−0.1907	0.2119	2.33	1.10	0.45
24	−0.1698	0.1985	1.97	0.26	0.08
25	−0.1610	0.1922	1.84	0.68	0.25
26	−0.1683	0.2135	1.80	0.82	0.33
27	−0.1872	0.2671	1.78	0.93	0.60
28	−0.1495	0.1706	1.78	0.39	0.33
29	−0.1726	0.2329	1.74	0.82	0.46
30	−0.1509	0.1929	1.60	0.60	0.23
31	−0.1586	0.2268	1.51	0.62	0.30
32	−0.1522	0.2144	1.47	0.59	0.24
33	−0.1423	0.1882	1.46	0.51	0.19
34	−0.1410	0.1933	1.40	0.54	0.20
35	−0.1474	0.2175	1.36	0.53	0.21
36	−0.1430	0.2125	1.31	0.52	0.32
37	−0.1418	0.2180	1.25	0.47	0.20
38	−0.1305	0.1923	1.20	0.39	0.17
39	−0.1261	0.1912	1.13	0.31	0.15

[a] Electronic chemical potential, μ, and chemical hardness, η, in atomic units; global, ω, and local, ω_k, electrophilicities, in eV. See the text for definitions.

phenyl group in **31** at the β position to give compound **28** results in an electrophilic activation. Substitution at the *para*-position by a nitro group of the phenyl moiety in **28**, to give compound **8**, results in an even higher electrophilic activation.

The presence of two electron-withdrawing substituents on the ethylene markedly increases the electrophilicity of the corresponding ethylene derivative. Thus, while cyano-ethylene (**29**) and methyl acrylate (**31**) are located on the bottom of the strong electrophiles subgroup, 1,1-dicyano-ethylene (**13**), methyl α-cyanoacrylate (**23**) and dimethyl fumarate (**26**) are classified as strong electrophiles. In this series the substitution by a −CN group produce a larger electrophilic activation than the $-CO_2Me$ group. Note that acyl substitution results in an even higher electrophilic activation to give the maleic anhydride (**5**), located at the top of the scale, and malonoimide (compound **14**) within the series. However, the resulting symmetry in these compounds produces a significant lost of effectiveness as Michael acceptor, similar to the loss of reactivity already reported for the series of cyano-ethylenes.[19]

1,1-Ditrifluoromethylethylene **27** presents a larger electrophilic activation than ketones and esters which are usually used as Michael acceptors. In this case, the strong σ electron-withdrawing character of the CF_3 group is responsible for the larger electrophilic activation of ethylene. Furthermore, while styrene **39** is classified as a moderate electrophile, the substitution on the benzene moiety by three trifluoromethyl groups produces a strong electrophilic activation of the ethylene derivative **24**, which is classified as a strong electrophile within the present theoretical scale.

On the other hand, α-nitrostilbenes substituted at the α-phenyl ring present electrophilic activation when the hydrogen atom at the *para*-position of the aromatic ring in compound **20** is replaced by the strong electron-withdrawing group $-NO_2$ to give compound **10**. Note that the presence of an −Me group at the same position in compound **21** results in electrophilic deactivation.

The nitrile derivatives subseries is particularly interesting, since it contains a short series of benzylidenemalononitriles compounds (**9**, **15**, **22**), which have been kinetically evaluated by Mayr. For these compounds, there exist data for both the rate coefficients and the electrophilicity numbers (E).[12] This subseries will give us the opportunity to test the predictive value of our model. Consider for instance compounds **9**, **15** and **22**. The experimental order of electrophilicity (E) is **22**<**15**<**9**. Note that our predicted electrophilicity is in good qualitative agreement with this order. Unfortunately, the quantitative comparison is difficult since the experimental rate coefficients and electrophilicity values in comparable conditions (20 °C, H_2O/DMSO 1/1 v/v, piperidine as reference nucleophile) is only available for these three benzylidenemalononitriles (compounds **1a**–**c** in Ref. 12. Despite this limitation we compare in Figure 1 our predicted electrophilicity values with the experimental reaction rate coefficients reported by Mayr et al. It may be seen that the agreement is reasonably good. From the regression Eq. 3

$$\mathrm{Ln}\,(k) = 5.55\omega - 4.09 \qquad (3)$$

we predict that the expected reaction rate coefficient for the reaction of compound **1** with piperidine would be about one

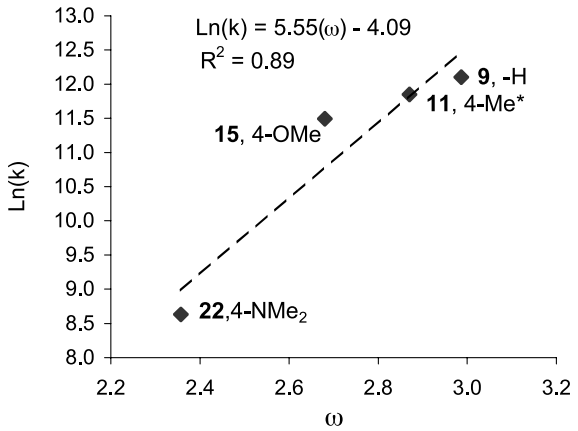

Figure 1. Plot of Ln(k) versus the electrophilicity index ω for the reaction of benzylidenemalononitriles series with piperidine. (*) Predicted value. Rate coefficients k from Ref. 12.

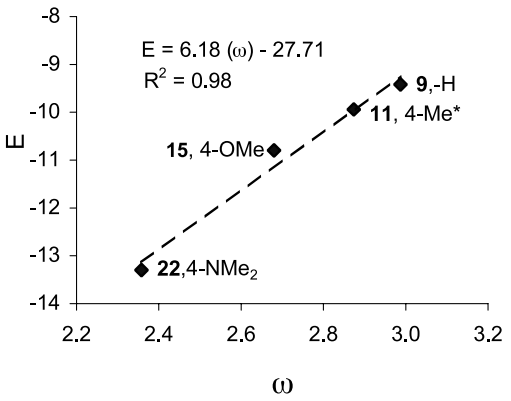

Figure 2. Plot of experimental electrophilic parameter E versus the electrophilicity index ω for the benzylidenemalononitriles series. (*) Predicted value. Rate coefficients k from Ref. 12.

thousand times faster than the reaction of piperidine with compound **9** (compound **1a** in Ref. 12). However, due to symmetry considerations that we will discuss below, such an enhancement should be significantly less than this figure. The predicted electrophilicity value for compound **1**, not evaluated in Mayr et al.'s database is $E=-1.88$ using the regression equation in Figure 2. However, this extrapolation is weak in view of the small number of experimental points available. A more reliable quantitative comparison may be obtained by an interpolation procedure for a compound that is expected to be bound, both in the experimental E scale and in the reaction rate coefficients. This is the case of compound **11**, whose predicted electrophilicity in the theoretical scale is $\omega=2.87$ eV. Using the regression Eq in Figure 2, this theoretical electrophilicity leads to the prediction that in the experimental scale compound **11** should show an E number around -9.94. Furthermore, the predicted rate coefficient for the reaction of this compound with piperidine in the same conditions should be bound by the rate coefficients of compounds **15** and **9** ($k\approx1.4\times10^5$ M^{-1} s^{-1}, obtained from the regression Eq. 3). Following a suggestion by a reviewer, regarding the incorporation of the experimental rate coefficients evaluated for compound **11** by Bernasconi's group in comparable experimental conditions,[15] the experimental value for the reaction of compound **11** with piperidine in a solvent mixture 50% Me_2SO-50% H_2O is $k=2.14\times10^5$ M^{-1} s^{-1}, thereby showing the predictive capability of the global electrophilicity index.

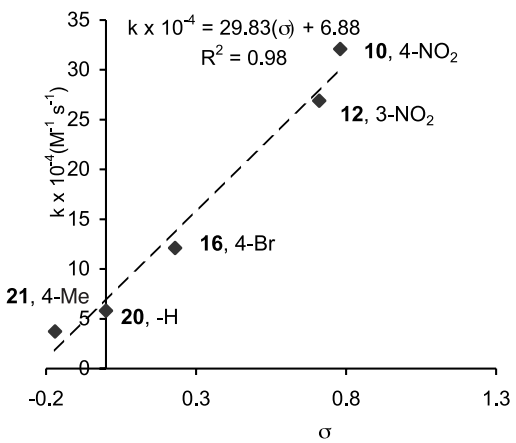

Figure 3. Plot of rate coefficients k versus Hammett substituent constant σ for the reaction of the addition of $HOCH_2CH_2S^-$ to substituted α-nitrostilbenes. Rate coefficients k from Ref. 14.

Figure 3 shows the comparison between the rate coefficient and the Hammett substituent constant (σ) for the addition of $HOCH_2CH_2S^-$ to substituted α-nitrostilbenes reported by Bernasconi et al.[14] In a previous work, we have reported on a quantitative relationship between Hammett substituent constant (σ) for substituted ethylene and the global electrophilicity index.[24] Therefore it is not surprising to find a good correlation between Ln k and the global electrophilicity index ω, as shown in Figure 4.

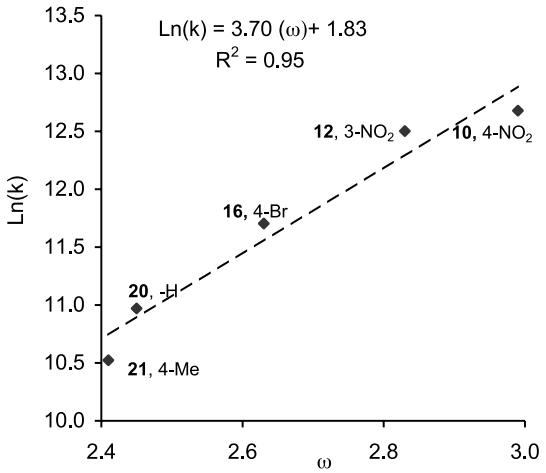

Figure 4. Plot of Ln(k) versus the electrophilicity index ω for the reaction of the addition of $HOCH_2CH_2S^-$ to substituted α-nitrostilbenes. Rate coefficients k from Ref. 14.

Following a remark addressed by a reviewer, we have incorporated 5 new substituted benzylidenemalononitriles[15] to the Mayr et al.'s series. The result of the comparison between Ln k and the global electrophilicity index ω is displayed in Figure 5. Note that this time the quantitative comparison between both quantities is not as good as the previously discussed correlation ($R^2=0.75$). The main factor that may account for this deviation may be traced

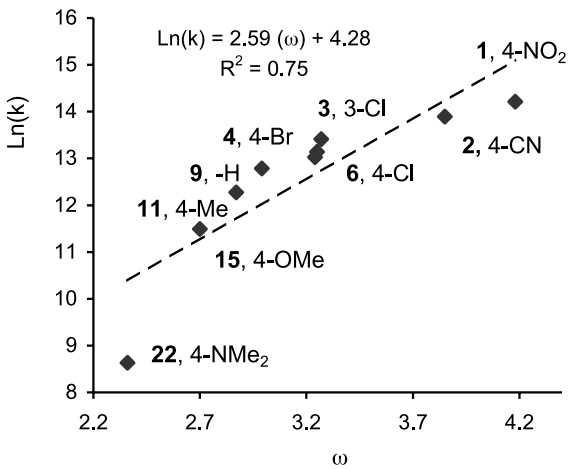

Figure 5. Plot of Ln(k) versus the electrophilicity index ω for the reaction of substituted benzylidenemalononitriles series with piperidine. Rate coefficients k from Ref. 15.

to solvent effects (not incorporated in the evaluation of the global electrophilicity index), preferentially affecting the highly polar electron releasing $-NMe_2$ group (compound **22**) and the highly polar electron withdrawing $-NO_2$ and –CN groups (compounds **1** and **2**).[24] Thus, if we exclude the compound **22** of this series, the correlation improves considerably (R^2=0.90).

A final remark concerning the local reactivity picture is worth making. The local electrophilicity values ω_k, for the two carbon atom belonging to the C=C double bond, named as Cα and Cβ, of the series of 39 substituted ethylenes are given in Table 1. A joint analysis of the global electrophilicity of these molecules, and the projected local electrophilicity at the sites Cα and Cβ, allows to obtain some additional conclusions: (i) in most of the cases the local electrophilicity value at the Cβ position is larger than that at the Cα position. In general, the ω_k value at the Cβ is ca. 2.4 times the one localized at the Cα position; (ii) the inclusion of a phenyl group at the Cβ position decreases this relation to ca. 1.9 (see Mayr's subseries including compounds **9**, **15** and **22**). Note that for compound **1**, whose global electrophilicity is predicted to be drastically enhanced with respect to the parent compounds **9**, **15** and **22** by the presence of the $-NO_2$ group at the *para* position of the phenyl substituent, the $\omega_{C\beta}/\omega_{C\alpha}$ ratio decreases to 1.3. This result may suggest a loss of effectiveness of this molecule as a potential strong Michael acceptor in the sense that despite its high global electrophilicity it becomes at the same time less regioselective. This result is reminiscent of that obtained in the analysis of the cyanoethylene subseries.[19] Therein, the tetracyano derivative was shown to display the highest global electrophilicity, yet its reaction mechanism with cyclopentadiene was consistently predicted to proceed via a polar concerted synchronous pathway, not a stepwise one with a first step corresponding to a Michael addition.[19] Note that the same effect seems to be present in the symmetrically substituted compounds **5** and **14**, for which the $\omega_{C\beta}/\omega_{C\alpha}$ ratio approaches unity; (iii) the distribution of the local electrophilicity at the carbon atoms belonging to the C=C double bond represents in most of the cases ca. 50% of the global electrophilicity of the molecule. Only in three out of the 39 cases considered here (compounds **8**, **18** and **24**), this distribution represents less than 30% of the global electrophilicity. This fact together with the large activation of the Cβ position respect the Cα one allows to conclude that the Cβ site is the most electrophilically activated center of these electron-deficient substituted ethylenes, in complete agreement with experimentally observed regioselectivity shown by these molecules in the Michael addition reactions. Note that for the carbonyl and carboxyl derivatives given in this series the $\omega_{C\beta}/\omega_{C(carbonyl)}$ ratio is within the range of 1.4–2.4, the Cβ position being more electrophilically activated than the C(carbonyl) one.

5. Concluding remarks

The global electrophilicity index provides a quantitative classification of the absolute electrophilicity of α,β-unsaturated ketones, esters, anhydrides, nitriles, nitrocompounds and substituted styrenes and α-nitrostilbenes. If we add to this database, the previously reported scale of global electrophilicity, including dienes, dienophiles, dipoles and dipolarophiles as well as the charged electrophiles including benzhydryl and diazonium cations, there results a useful theoretical scale. This scale may be used to explain, on a quantitative basis, the known reactivity of a significant body of organic compounds. The predictive power of the present scale of electrophilicity has been illustrated here for a short series of benzylidenemalononitriles and α-nitrostilbenes.

A validated theoretical reactivity scale on the other hand, is also a useful tool in the sense that this global property may be conveniently distributed in the molecule using the electrophilic Fukui function. The projected electrophilicity in turn, appears as a promising selectivity index. This has been illustrated in this work, by explaining the known regioselectivity displayed in the Michael's addition reaction.

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Synthesis of pyrimidine-containing 3-aminobutenolides

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Abstract—An efficient synthesis of pyrimidine-containing butenolides is reported, starting from *C*-alkoxycarbonyl isoxazolidines. Two competitive reaction routes are operating: the pathway leading to homo-*N*,*O*-nucleosides, based on the reduction of an ester group at C_3, and the reaction channel leading to butenolides promoted by the removal of the hydrogen atom at C_3. The two reaction pathways can be easily controlled according to the adopted experimental conditions

1. Introduction

Recently, there has been a great deal of interest in the synthesis of 2-(5*H*)furanones;[1] this ring system constitutes the central skeleton of a series of natural compounds such as fimbrolides,[2] dihydroxerulin,[3] and protoanemonin.[4] The biological importance of these unsaturated lactones is well-known: butenolides have been used to prepare peptide analogues or HIV-1 protease inhibitors;[5] protoanemonin, its analogues and its derivatives possess antiviral, antibiotic and anticancer activity,[6] as well as 4-(1-alkynyl)-substituted 2-(5*H*)-furanones.[7] On the basis of these considerations, unsaturated analogues of nucleosides appear a focus of much attention as potential antiviral and antitumor agents.[8]

We have recently reported a versatile entry to functionalized 2-(5*H*)furanones through a new rearrangement pattern of the isoxazolidine nucleus, easily accessible by 1,3-dipolar cycloaddition of nitrones with suitable alkenes.[9] The reaction consists of a basic treatment of isoxazolidines, suitably activated at position 3 of the nucleus with NaH at room temperature.

The same reaction sequence has been exploited as a synthetic route towards a new series of modified nucleosides, potential candidates of a new class of antiviral agents. Herein, we report the synthesis of pyrimidine derivatives of unsaturated lactones **1**: the synthetic route appears versatile and extendable to the preparation of all purine and pyrimidine derivatives (Fig. 1).

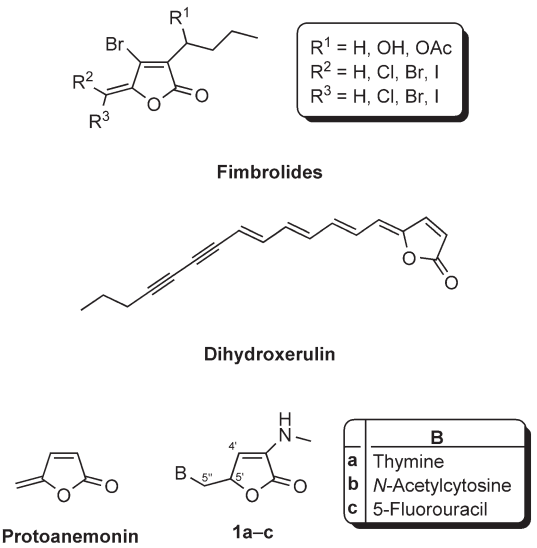

Figure 1.

2. Results and discussion

The cycloaddition reaction between *N*-methyl-*C*-ethoxycarbonyl nitrone **2**[10] (*E*/*Z* ratio 4:1) and allyl nucleobases **3** proceeded smoothly in anhydrous toluene at 80 °C for 14 h to give isoxazolidines **4** and **5** in ca. 2:1 ratio and 93–96% yields.[11] As reported,[11] the successive reduction of the estereal group by treatment with $LiAlH_4$ afforded the

Keywords: 1,3-Dipolar cycloaddition; Butenolides; Homo-nucleoside analogues.
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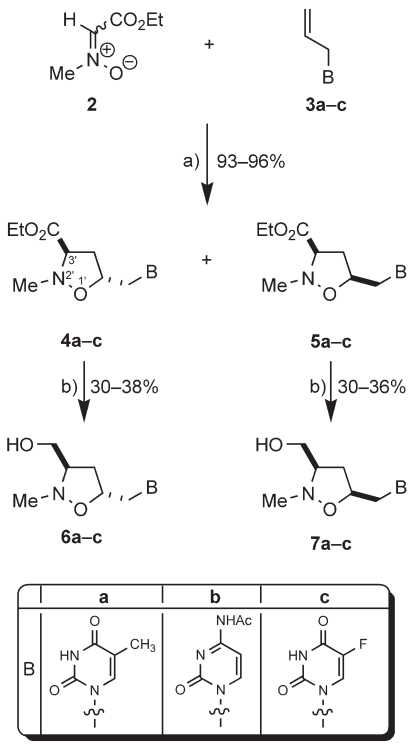
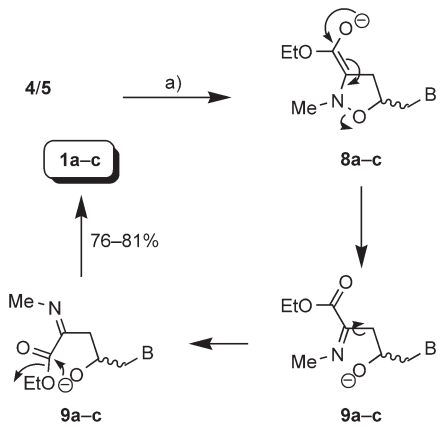


Scheme 1. (a) Toluene, sealed tube, 80 °C, 1 h; (b) $LiAlH_4$, THF, 0 °C, 1 h.



Scheme 2. (a) NaH, THF, rt, 4 h.

expected homo-*N*,*O*-nucleosides **6** and **7** in moderate yields (Scheme 1).

However, the presence of the ethoxycarbonyl group at position 3 in isoxazolidines **4** and **5** increases the acidity of the hydrogen atom at the same position, thus suggesting the possibility of an alternative reaction course following the treatment of isoxazolidines **4** and **5** with basic reagents. Thus, its deprotonation by NaH leads to the formation of enolate **8** which evolves, via ring-opening, towards the anion **9**; the subsequent intramolecular nucleophilic acyl substitution affords lactones **1a**–**c**, in high yields (76–81%) (Scheme 2).

Structural assignments have been performed on the basis of spectroscopic data. The molecular formula of furanones follows from an exact mass determination; the IR absorptions of the carbonyl group at 1720 cm^{-1} are in accord with the γ-lactones.

The ^1H NMR spectra of compounds **1a** show the $H_{4'}$ protons as doublets at δ 5.61, while $H_{5'}$ protons resonate as ddd at 5.17. Moreover, the methylene substituents at $C_{5'}$ give rise two dd centered at δ 3.67 and 4.07 and the *N*-methyl groups resonate as doublets (J=4.8 Hz) at δ 2.49.

With reference to the previously reported synthesis of homo-*N*,*O*-nucleosides,[11] the results obtained can be rationalized by assuming that, starting from isoxazolidines **4** and **5**, two different competing reaction routes are operating. The use of a nucleophilic reagent such as $LiAlH_4$ induces a nucleophilic attack of the hydride ion to the estereal functionality, so promoting the reduction process towards the already reported homo-nucleosides **6** and **7**.

Alternatively, the driving force for the transformation of **4** and **5** into **1** is represented by the low critical energy required to induce an ionic center at position 3′ of isoxazolidines **4** and **5**, which promotes the ring opening of the heterocyclic system and the subsequent intramolecular lactonization. With NaH, the acid–base process is the only one operating, with the exclusive formation of lactone **1**.

Table 1. Reactions of isoxazolidines **4** and **5** with different reagents

Entry	Compounds	Conditions[a]	Product yields (%)[b]
1	**4a/5a**	NaH, THF, 4 h	**1a** (81)
2	**4b/5b**	NaH, THF, 4 h	**1b** (76)
3	**4c/5c**	NaH, THF, 4 h	d.p.[c]
4	**4a/5a**	EtONa, THF, 4 h	**1a** (80)
5	**4b/5b**	EtONa, THF, 4 h	**1b** (70)
6	**4c/5c**	EtONa, THF, 4 h	**1c** (74)
7	**4a/5a**	MeOH, $NaBH_4$, 1 h, 0 °C	**1a** (40)
8	**4b/5b**	MeOH, $NaBH_4$, 1 h, 0 °C	**1b** (37)
9	**4c/5c**	MeOH, $NaBH_4$, 1 h,0 °C	**1c** (30)
10	**4a/5a**	TBAF, THF, 1 h	**1a** (99)
11	**4b/5b**	TBAF, THF, 1 h	**1b** (98)
12	**4c/5c**	TBAF, THF, 1 h	**1c** (95)
13	**4a–c**	MeOH/H_2O 95/5 or dioxane/H_2O 1/1, $NaBH_4$, 1 h	**6a–c** (99)
14	**5a–c**	MeOH/H_2O 95/5 or dioxane/H_2O 1/1, $NaBH_4$, 1 h	**7a–c** (99)

[a] Reaction performed at room temperature.
[b] Isolated yield.
[c] Decomposition products.

As a confirmation, also the use of different bases, with a decreasing basicity, such as sodium ethoxide and TBAF, promotes the same reaction path, leading to the formation of lactones in better yields and with an easier work-up (Table 1).

Noteworthy, when isoxazolidines **4** and **5** have been reacted with $NaBH_4$, the formation of both homo-nucleosides or lactones has been observed, according to the experimental conditions adopted. With anhydrous MeOH, the exclusive formation of lactones has been detected (40% yield) together with decomposition products; while with MeOH/water (95:5) or dioxane/water (1:1) as a solvent, the homo-nucleosides were obtained in a nearly quantitative yield.

The results obtained can be rationalized on the basis of the following considerations. With respect to $LiAlH_4$, sodium borohydride is less nucleophilic;[12] thus, in MeOH anhydrous as solvent, the reaction route is driven by the basic attack of $NaBH_4$ at $H_{3'}$, which leads to lactone **1**. However, when water is present in the reaction medium, the formation of the enolate ion **8** is suppressed and thus the route towards lactone **1** is blocked. The equilibrium turns back to the original isoxazolidines and, then, through the attack of hydride ion on the ester group, to the corresponding homo-nucleoside.

In conclusion, an efficient synthesis of pyrimidine containing butenolides is reported. Starting from isoxazolidines, obtained by 1,3-dipolar cycloaddition of *C*-alkoxycarbonyl nitrones with allyl nucleobases, two competitive reaction routes are operating: the pathway leading to homo-*N*,*O*-nucleosides, based on the reduction of ester group at $C_{3'}$, and the reaction channel leading to butenolides promoted by the removal of the hydrogen atom at $C_{3'}$. The two reaction pathways can be easily controlled according to the adopted experimental conditions.

Biological evaluation as potential antiviral agents of the new series of pyrimidine butenolides is in progress.

3. Experimental

3.1. General

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra were recorded on a Perkin–Elmer Paragon 500 FT-IR Spectrometer using potassium bromide discs. ^{1}H- and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 in deuterated DMSO. Chemical shifts are expressed in ppm from DMSO (2.50 ppm for ^{1}H and 29.5 ppm for ^{13}C). Thin-layer chromatographic separations were performed on Merck silica gel 60-F_{254} precoated aluminium plates. Preparative separations were made by flash column chromatography using Merck silica gel (0.035–0.070 mm) eluant $CHCl_3$/MeOH 95:5.

Compounds **4** and **5** have been previously reported.[11]

3.2. General procedure for the preparation of pyrimidine butenolides 1a–c

Method A. (Entry 1–3). To a solution of isoxazolidines **4a–c/5a–c** (2 mmol) in dry THF (20 mL) was added NaH (48.0 mg, 2 mmol), and the mixture was stirred for 4 h at room temperature, until the TLC showed the disappearance of the starting material. The reaction mixture was then quenched with water (0.5 mL) and evaporated under reduced pressure. The residue was then purified by column flash chromatography.

Method B. (Entry 4–6). To a solution of isoxazolidines **4a–c/5a–c** (2 mmol) in dry THF (10 mL) was added a solution of sodium ethoxide (0.73 mL, 21 wt% solution in denaturated ethyl alcohol, 2 mmol), the mixture was stirred for 4 h at room temperature, until the TLC showed the disappearance of the starting material. The reaction mixture was then quenched with water (0.5 mL) and evaporated under reduced pressure. The residue was then purified by flash column chromatography.

Method C. (Entry 7–9). $NaBH_4$ (20.0 mg, 5 mmol) was added at 0 °C to a stirred solution of isoxazolidines **4a–c/5a–c** (1 mmol) in dry MeOH (30 mL), and the mixture was stirred for 1 h at the same temperature. The reaction mixture was evaporated under reduced pressure. The residue was then purified by flash column chromatography.

Method D. (Entry 10–12). To a solution of isoxazolidines **4a–c/5a–c** (1 mmol) in dry THF (20 mL), TBAF (1.05 mL, 1.1 mmol, 1 M solution in THF) was added, and the mixture was stirred at room temperature for 1 h. At the end of this time, the solvent was removed and the residue was subjected to silica gel flash column chromatography.

3.2.1. 5-Methyl-1-{[4-(methylamino)-5-oxo-2,5-dihydrofuran-2-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (1a). Yield 99%; white solid: mp 180–184 °C. IR (KBr) ν 3270, 2850, 1752, 1710, 1660, 1618, 1559, 1450, 1370, 1320, 1260, 1165, 1150, 983, 775 cm^{-1}. ^{1}H NMR ($DMSO_{d6}$, 300 MHz): δ 1.72 (d, 3H, J=0.8 Hz), 2.49 (d, 3H, *N*–CH_3, J=4.8 Hz), 3.67 (dd, 1H, $H_{5''a}$, J=6.9, 14.2 Hz,), 4.07 (dd, 1H, $H_{5''b}$, J=3.0, 14.2 Hz,), 5.17 (ddd, 1H, $H_{5'}$, J=2.0, 3.0, 6.9 Hz), 5.61 (d, 1H, $H_{4'}$, J=2.0 Hz), 5.67 (d, 1H, *N*–H, J=4.8 Hz), 7.41 (q, 1H, H_6, J=0.8 Hz), 11.31 (bs, 1H, NH). ^{13}C NMR ($DMSO_{d6}$, 75 MHz): δ 11.9, 30.7, 50.1, 78.6, 105.4, 108.1, 137.1, 141.7, 150.9, 164.2, 179.5. Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.73%. Found: C, 52.79; H, 5.20; N, 16.76%. Exact mass calculated for $C_{11}H_{13}N_3O_4$: 251.0906. Found: 251.0907.

3.2.2. *N*-(5-Methyl-1-{[4-(methylamino)-5-oxo-2,5-dihydrofuran-2-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide 1b. Yield 98%; white solid: mp 153–155 °C. IR (KBr) ν 3300, 2928, 1762, 1714, 1666, 1628, 1567, 1500, 1374, 1313, 1259, 1232, 1170, 1141, 1037, 785 cm^{-1}. ^{1}H NMR ($DMSO_{d6}$, 300 MHz): δ 2.08 (s, 3H), 2.56 (d, 3H, *N*–CH_3, J=4.9 Hz), 3.84 (dd, 1H, $H_{5''a}$, J=7.1, 14.0 Hz), 4.22 (dd, 1H, $H_{5''b}$, J=3.0, 14.0 Hz), 5.24 (ddd, 1H, $H_{5'}$, J=0.5, 3.0, 7.1 Hz), 5.64 (d, 1H, $H_{4'}$, J=0.5 Hz), 5.67 (d, 1H, NH, J=4.9 Hz), 7.12 (d, 1H, J=7.2 Hz), 7.96 (d, 1H, J=7.2 Hz), 10.08 (bs, 1H, NH). ^{13}C NMR ($DMSO_{d6}$, 75 MHz): δ 24.2, 30.6, 52.3, 78.0, 94.9, 105.4, 137.1, 149.6, 150.7, 162.6, 169.0, 170.9. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13%. Found: C, 51.55; H, 4.95; N,

19.95%. Exact mass calculated for $C_{12}H_{14}N_4O_4$: 278.1015. Found: 278.1010.

3.2.3. 5-Fluoro-1-{[4-(methylamino)-5-oxo-2,5-dihydrofuran-2-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione 1c. Yield 95%; white solid: mp 175–178 °C. IR (KBr) ν 3285, 2890, 1770, 1698, 1675, 1630, 1570, 1490, 1382, 1318, 1265, 1220, 1165, 1100, 1027, 795 cm^{-1}. ^1H NMR ($DMSO_{d6}$, 300 MHz): δ 2.50 (d, 3H, *N*–CH_3, *J*=4.7 Hz), 3.60 (dd, 1H, $H_{5''a}$, *J*=6.9, 14.3 Hz), 3.99 (dd, 1H, $H_{5''b}$, *J*=3.3, 14.3 Hz), 5.11 (ddd, 1H, $H_{5'}$, *J*=0.6, 3.3, 6.9 Hz), 5.55 (d, 1H, $H_{4'}$, *J*=0.6 Hz), 5.62 (d, 1H, NH, *J*=4.7 Hz), 7.92 (d, 1H, H_6, *J*=6.7 Hz), 11.78 (bs, 1H, NH). ^{13}C NMR ($DMSO_{d6}$, 75 MHz): δ 30.7, 50.5, 78.3, 105.3, 130.5, 137.2, 141.5, 149.6, 158.2, 169.1. Anal. Calcd for $C_{10}H_{10}FN_3O_4$: C, 47.06; H, 3.95; N, 16.47%. Found: C, 46.88; H, 3.94; N, 16.50%. Exact mass calculated for $C_{10}H_{10}FN_3O_4$: 255.0655. Found: 255.0653.

3.3. General procedure for the preparation of homo-*N*,*O*-nucleosides 6 and 7 (entry 13 and 14)

Sodium borohydride (40.0 mg, 10 mmol) was added to a solution of isoxazolidines **4a**–**c** or **5a**–**c** (1 mmol) in a 1:1 dioxane/water mixture (15 mL) or 95:5 methanol/water mixture (15 mL), and the reaction was vigorously stirred for 1 h, at 0 °C. After this period, the solvent was removed and the residue was then purified by flash column chromatography.

Acknowledgements

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Synthesis of peptidomimetics based on iminosugar and β-D-glucopyranoside scaffolds and inhibiton of HIV-protease

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Abstract—Synthetic routes to peptidomimetic compounds derived from saccharide scaffolds are described. The regioselective introduction of pivaloyl groups was achieved from *N*-benzyloxycarbonyl protected 1-deoxymannojirimycin or via D-fructopyranosides. The results from biological evaluation of the saccharide derivatives as HIV-protease inhibitors are included.

1. Introduction

Several aspartic acid proteases[1] are of interest as therapeutic targets. Examples include renin, HIV-1 protease and memapsin 2 (β-secretase) which are respectively involved in hypertension,[2] viral infection and Alzheimer's disease.[3] Only in the case of the HIV-1 protease have inhibitors of this class of enzymes attained clinical importance.[4] This is due mostly to the lack of bioavailability of the potent inhibitors, which is caused in many cases by the high peptide character of these compounds. Also, despite the successes of using protease inhibitors for treatment of HIV, there remain a number of problems with current therapies. Consequently much work is being carried out to develop new anti-HIV agents. Previously the design and synthesis of β-D-glucopyranoside and β-D-mannopyranoside as peptidomimetic based inhibitors has been reported from our group. Peptidomimetic research is concerned with developing bioactive agents which have improved pharmacokinetic properties over peptides.[5] The general principle is that pharmacophoric groups are grafted onto a non-peptide scaffold, which orient them in the direction of their binding subsites. Researchers at the University of Pennsylvania were first to validate β-D-glucopyranose (e.g., **2**), its enantiomer and a diastereomer (β-D-mannopyranose) as scaffolds suitable for providing bioactive compounds that bind to peptide receptors.[6] This has led to other groups utilising sugar scaffolds in peptidomimetic and other research.[7,8] Herein we describe the synthesis of conjugates of β-D-glucopyranosides and 1-deoxymannojirimycin and the results of their evaluation as HIV protease inhibitors.

2. Results and discussion

2.1. Design of second generation carbohydrate based peptidomimetics

The glucoside **1** and mannoside **3** (Fig. 1) are examples of carbohydrate conjugates[9] that have demonstrated a modest inhibition of HIV-1 protease; their design and synthesis has been described previously.[10] It was hypothesized by us that **1** and **3** may be binding competitively in the active site of the enzyme, that the hydrophobic groups attached to the sugar scaffold were thus oriented into enzyme subsites and that the 2-OH group of the mannopyranose or glycopyranose was hydrogen bonding with the catalytic aspartate residues in the active site.[11] Compounds **2** and **4** were selected for synthesis in order to obtain support for this assumption and to try to develop more potent saccharide derivatives.

Thus it was expected that **2** would bind with higher affinity than the β-D-glucopyranoside **1** because the iminosugar would be a charged hydrogen bond donor, contrasting with **1** where the pyranose oxygen atom has hydrogen bond acceptor potential (Fig. 1). Molecular modelling indicated that the protonated nitrogen of **3** would hydrogen bond with a carbonyl group of the HIV protease amide backbone if the molecule bound as predicted. β-D-Glucopyranosides of the type **4** would be expected to show improved activity when compared to **2** (and other mannosides and glucosides that have been evaluated previously); molecular

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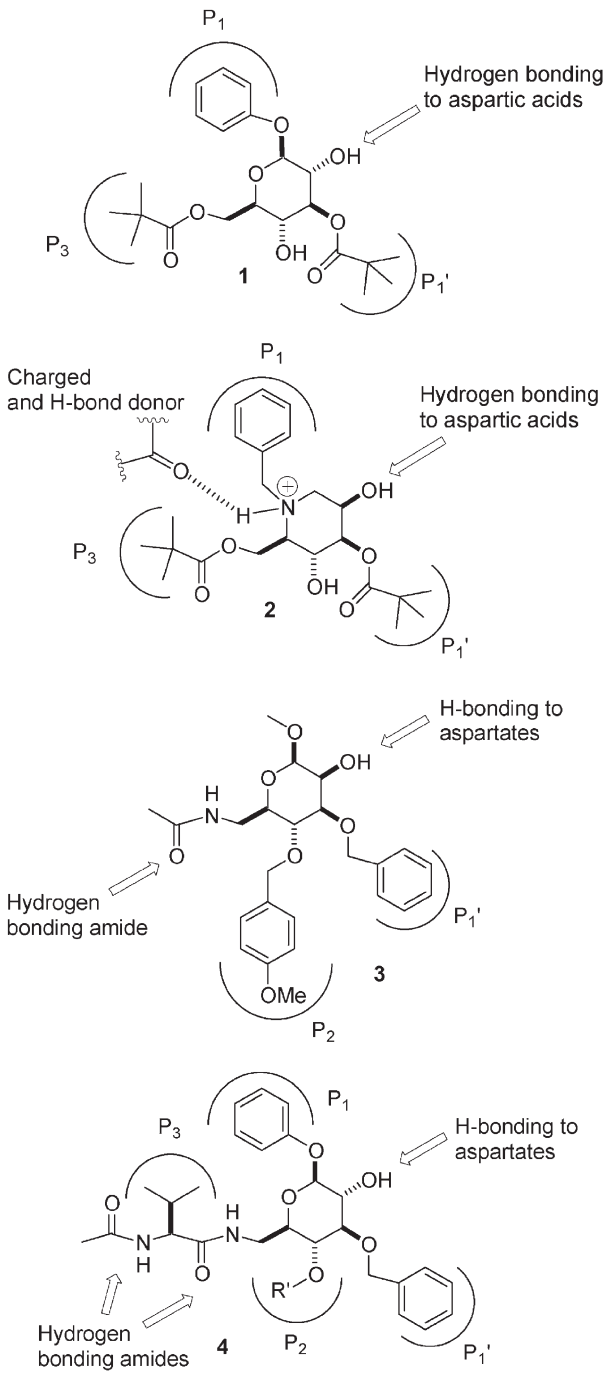
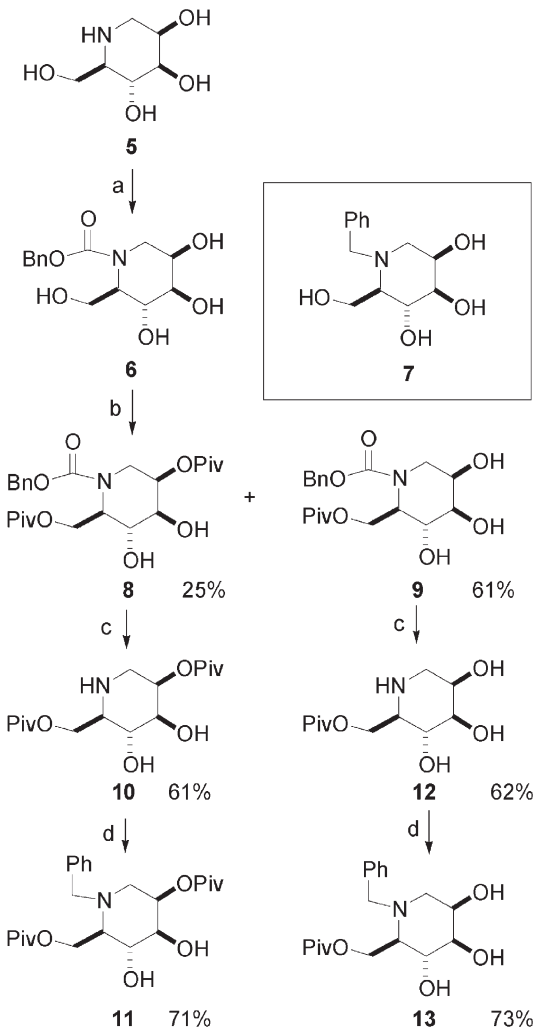


Figure 1. Design of iminosugar **2** and glucopyranoside peptidomimetics **4**.

modeling indicated that the valine residue attached to the glucopyranose C-6, would have additional binding interactions with the enzyme.

2.2. Synthesis from 1-deoxymannojirimycin

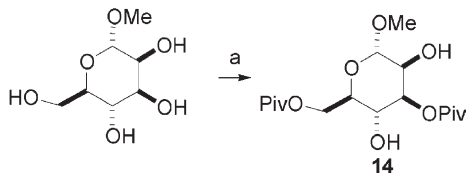
The first approach taken towards **2** involved investigation of 1-deoxymannojirimycin (DMJ) as a starting compound. Syntheses of **5** were thus first carried out as described previously.[12,13] The nitrogen atom of **5** was then protected with Cbz according to literature procedure[14] giving **6**.[15] A 61:25 mixture of the diester **8** and monoester **9** was obtained when **6** was reacted with trimethylacetyl chloride in pyridine at 0 °C,[16] regioselective di-*O*-pivaloylation occurring selectively at O-2 and O-6. The chemical behaviour of the DMJ derivative **6** was not comparable with methyl α-D-mannopyranoside which gave **14** as a result of pivaloylation at O-3 and O-6 (Scheme 2). Attempts to alter the regioselectivity of the pivaloylation by using $(Bu_3Sn)_2O$/PivCl led only to intractable product mixtures or the recovery of **6**. Attempts to obtain pivaloylated products from **7**[17] were not successful. However, it was possible to convert **8** into 2,6-di-*O*-pivaloylated DMJ derivative **10** and subsequent N-benzylation gave **11**; in a similar way **9** was converted into monopivaloylated derivative **13** via **12** (Scheme 1). In general the reactions of DMJ derivatives were low yielding, especially if crude rather than purified DMJ was used. The products from **5** were also prone to decomposition. These difficulties led us to investigate alternative routes to **2**.



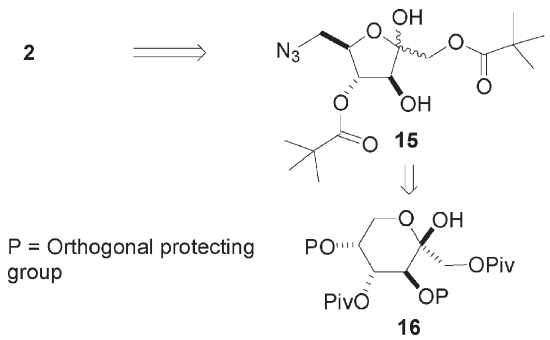
Scheme 1. Reagents and conditions: (a) CbzCl, $NaHCO_3$, dioxane, H_2O, 74%; (b) PivCl, Py. 2 h; (c) 10% Pd–C, H_2, MeOH; (d) K_2CO_3, BnBr, DMF.

2.3. Synthesis of iminosugar conjugates from D-fructose

One of the shortest syntheses of DMJ has been achieved by Stütz and co-workers from D-fructose.[18] Based on this route we proposed (Scheme 2) that the azidofructofuranoside **15** would be a viable intermediate for synthesis of **2** and that it could be prepared from **16** (Scheme 3).

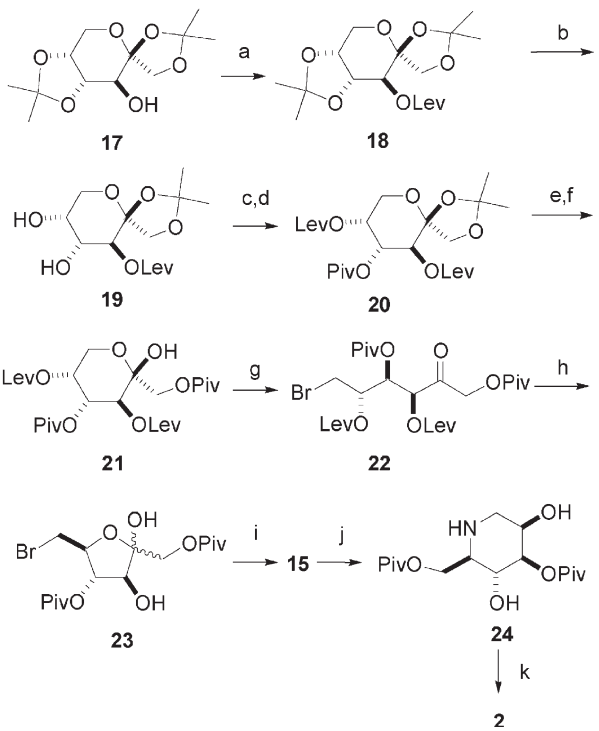


Scheme 2. Reagents and conditions: (a) PivCl (2 equiv.), Py. 2 h.



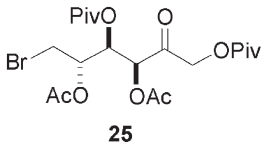
Scheme 3. Retrosynthetic analysis.

The use of the levulinate protecting group was ultimately successful (Scheme 4). Thus **18** was first prepared by the DCC-DMAP promoted coupling of levulinic acid[19] with **17**, which is obtained from D-fructose.[20] Selective deprotection of the 4,5-di-*O*-isopropylidene group using 80% aqueous acetic acid at 45 °C gave **19**. Regioselective pivaloylation of the 4-OH of **19** and introduction of a second levulinate group at O-5 and gave **20**. The 1,2-di-*O*-isopropylidene was next removed using aqueous TFA and another regioselective pivaloylation at O-1 gave **21**. Reaction of **21** with triphenylphosphine-bromine as described by Stütz gave the 6-deoxy-6-bromofructose derivative **22** (93%). The levulinate groups were then removed using hydrazine hydrate to give furanose **23** and its subsequent reaction with sodium azide in DMF gave the desired intermediate **15**. The catalytic hydrogenation of **15** gave the 3,6-di-*O*-pivaloylated DMJ **24** (22%), which was then converted to the *N*-benzyl derivative **2** using potassium carbonate and benzyl bromide in DMF (60%).



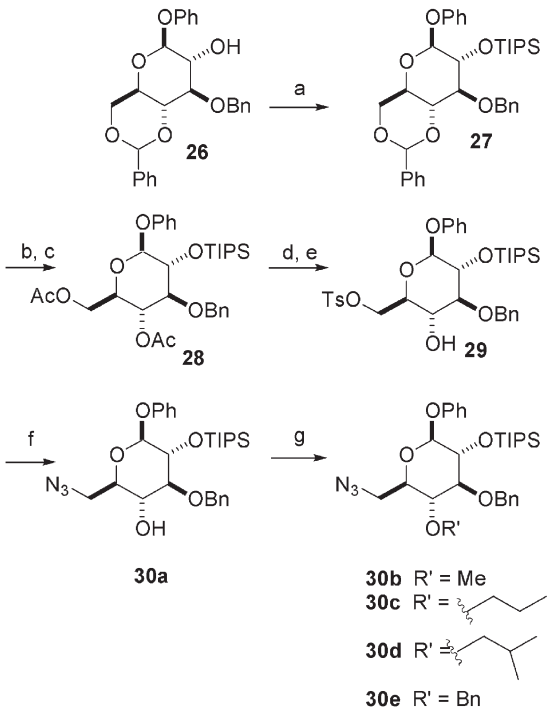
Scheme 4. Reagents and conditions: (a) Levulinic acid, DCC (2 equiv.), DMAP (cat.), THF, 91%; (b) 80% AcOH, 45 °C, 4 h; (c) PivCl (1.1 equiv., Py. −78 °C to RT overnight, 98%; (d) Levulinic acid (1.8 equiv.), DCC (2 equiv.), DMAP (cat.), THF, 77%; (e) TFA/H_2O (4:1), 2 h, 85%; (f) PivCl (1.2 equiv.), Py. 15 h, 90%; (g) PPh_3Br_2, Py. CH_2Cl_2, 3 h, heat at reflux, 93%; (h) $NH_2NH_2{\cdot}H_2O$, AcOH, H_2O, 0 °C, 66%, (i) NaN_3, DMF, rt, 48 h, 53%; (j) 10% Pd–C, H_2, MeOH, 22%; (k) K_2CO_3 (0.6 equiv.), BnBr (1.15 equiv.), DMF, 60%.

Other potential intermediates such as **25** were prepared but the selective removal of the acetates could not be achieved in our hands. Also the reaction of **25** with sodium azide led to decomposition and resulted in an intractable product mixture.

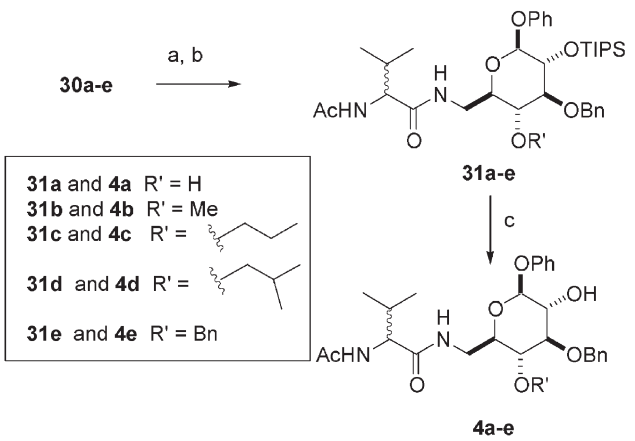


2.4. Synthesis of β-D-glucopyranosides

Phenyl β-D-glucopyranoside was used as the starting compound for the synthesis of **4a**–**e** (Schemes 5 and 6). The 3-*O*-benzyl derivative **26** was prepared as described previously.[9] The 2-OH group was then reacted with TIPSOTf in dichloromethane in presence of 2,6-lutidine to



Scheme 5. Reagents and Conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (b) TFA, CH_2Cl_2, r.t.; (c) Ac_2O, Py, r.t., 66% for two steps; (d) NaOMe, MeOH, r.t.; (e) TsCl, Py, 0 °C, 85% for two steps; (f) NaN_3, DMF, 80 °C, 72% (g) NaH, R'I or R'Br, DMF, 0 °C to r.t., 30–94%.

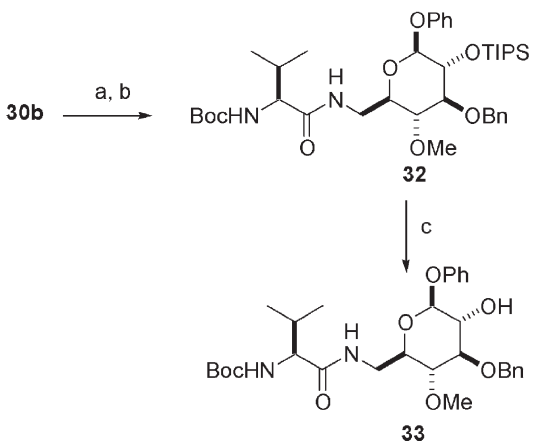


Scheme 6. Reagents and Conditions: (a) Lindlar catalyst, H_2, EtOH:EtOAc; (b) AcVal–OH (L-isomer), BOP-Cl, DIPEA, CH_2Cl_2, 33–79%, two steps (c) TBAF, THF, 0 °C, 44–88%.

give **27**. Removal of the benzylidene group followed by acetylation[21] gave **28**. This was followed by deacetylation and regioselective tosylation to give **29**. Reaction of this tosyl derivative with sodium azide in DMF gives 6-deoxy-6-azido derivative **30a**, which when treated with NaH in DMF in the presence of the appropriate alkyl iodide or bromide gave **30b–e**.

Azides **30a–e** were reacted with Lindlar catalyst in the presence of H_2 and the resulting amine coupled to AcVal–OH (L-isomer) using BOP–Cl in dichloromethane in the presence of DIPEA (28–66% over two steps) giving **31a–e** and subsequent removal of the TIPS protecting group was accomplished using TBAF in THF to give **4a–e** (65–96%). The ^{13}C NMR spectra of **31a–e** and **4a–e** contained two signal sets indicating that each sample was a mixture of diasteroisomers (~2:1), resulting from epimerization of the chiral centre of the valine residue (Scheme 6).

In addition the Boc protected derivative **32** was prepared by coupling of **30b** with BocVal–OH using HBTU, HOBt in presence of DIPEA. Subsequent removal of the silyl protecting group gave **33** (Scheme 7).



Scheme 7. Reagents and Conditions: (a) Lindlar catalyst, H_2, EtOH:EtOAc; (b) BocVal–OH (L-isomer), HOBt, HBTU, DIPEA, CH_2Cl_2, 18% two steps; (c) TBAF, THF, 0 °C, 66%.

2.5. Evaluation of iminosugars and glucopyranosides as HIV protease inhibitors

The HIV-1 protease inhibition data[22] data for sugar derivatives prepared during the course of this study are provided in Table 1. The IC_{50} value for pepstatin, a known inhibitor of HIV-protease, was 4.3–7.4 μM in this assay. The glucoside **1**, prepared and evaluated previously, showed modest inhibition (24% at 1.0×10^{-4} M) and was the most potent of the series of saccharides evaluated,[23] all new compounds being less potent at 1.0×10^{-4} M. It would seem that the modest inhibition observed for these carbohydrates and for those described previously may be due to them having a different mode of action than that hypothesized; structural modifications that were expected to increase binding at the active site did not lead to any improvement in inhibitory activity.

Table 1. % Inhibition of HIV-1 protease by sugar derivatives at 1×10^{-4} M[a]

Compound	% Inhibition[b]
1	24
2	8
4a	14
4b	19
4c	20
4d	16
4e	Not active
33	11

[a] IC_{50} value for pepstatin in this assay was 4.3–7.4 μM.
[b] Values are mean of two experiments.

3. Summary

In summary, a series of β-D-glucopyranosides have been prepared and a synthetic approach with potential to be further developed towards diversely functionalized 1-deoxymannojirimycin derivatives has been described. The saccharides show modest inhibitory activity for the HIV-1 protease indicating the design of potent carbohydrate peptidomimetics, related to those described herein, as inhibitors of aspartic proteases will not be trivial.

4. Experimental

4.1. General

Optical rotations were determined at the sodium D line at 23 °C. Chemical shifts in ^1H NMR spectra are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or HOD for D_2O (δ 4.84) or CD_2HOD (δ 3.36) for ^1H and $CDCl_3$ (δ 77.0) or CD_3OD (δ 47.7) for ^{13}C. ^1H NMR signals were assigned with the aid of COSY. ^{13}C NMR signals were assigned with the aid of DEPT. Coupling constants are reported in Hertz. The IR spectra were recorded using either a thin film between NaCl plates or KBr discs, as specified. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel 60 (HF_{254}, E. Merck) and spots visualized by UV and charring with H_2SO_4–EtOH (1:20). Flash column chromatography was carried out with silica gel 60 (0.040–0.630 mm, E. Merck) and using a stepwise solvent polarity gradient (EtOAc–petroleum ether unless otherwise stated) correlated with TLC mobility.

Chromatography solvents used were EtOAc and MeOH (Riedel–deHaen) and petroleum ether (bp 40–60 °C, BDH laboratory supplies). Toluene (Aldrich) and CH_2Cl_2 (Riedel–deHaen) benzene (Aldrich) and CH_2Cl_2 reaction solvents were freshly distilled from calcium hydride and anhydrous DMF was used as purchased from Sigma-Aldrich. Phenyl β-D-glucopyranoside was purchased from Sigma-Aldrich. MS is Electrospray MS unless otherwise stated.

4.1.1. *N*-Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol 6. 1-Deoxymannojirimycin (115 mg, 0.7 mmol) was dissolved in a mixture of dioxane/water (1:1, 12 mL), then $NaHCO_3$ was added (1.75 equiv.) and benzylchloroformate (1.54 equiv.).[18] The mixture was stirred for 18 h at room temperature. The dioxane was then evaporated and the aqueous layer was extracted with dichloromethane to remove excess reagent. The aqueous phase was evaporated and the residue purified by chromatography (EtOAc/MeOH/water, 90:8:2 then 85:10:5) to give **6** (155 mg, 74%, clear syrup); $[\alpha]_D$=+1 (*c* 0.7, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 7.30–7.42 (m, 5H, Ph), 5.14 (AB d, 2H, J=−13.5 Hz, CH_2), 4.31 (t, 1H, J=6.6 Hz, H-5), 4.03 (dd, 1H, J_{2-1a}=4.5 Hz, J_{1a-1b}=−13.2, H-1a), 3.96–3.88 (m, 4H, H-2-4, H-6a), 3.75 (dd, 1H, J_{5-6b}=5.1 Hz, J_{6a-6b}=−11.1 Hz, H-6b), 3.14 (dd, 1H, J=11.7, −13.2 Hz, H-1b); ^{13}C NMR (75 MHz, CD_3OD) δ 158.3 (s, CO) 138.2 (s, aromatic C), 129.5, 128.9, 128.7 (each d, aromatic CH), 71.9, 71.0, 65.6, (each d, C-2-4), 68.4 (t, Cbz CH_2), 61.2 (t, C-6), 60.5 (d, C-5), 41.5 (t, C-1); LRMS: 296.0 $[M-H]^-$. Acetylation of **6** (52 mg) with pyridine (0.5 mL), Ac_2O (0.5 mL) and DMAP (2 mg) followed by removal of volatile reagents by distillation and purification of the residue by chromatography gave an analytical sample of 2,3,4,6-tetra-*O*-acetyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol; $[\alpha]_D$=−41 (*c* 1.7, $CHCl_3$). Anal. Calcd for $C_{24}H_{27}NO_{10}$: C, 56.77; H, 5.85; N, 3.01. Found: C, 56.37; H, 5.66; N, 3.04.

4.1.2. 2,6-Di-*O*-pivaloyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol 8 and 6-*O*-pivaloyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-mannitol 9. To a stirred solution of **6** (149 mg, 0.5 mmol) in pyridine (3 mL) at 0 °C was slowly added PivCl (2 equiv.). After 1 h further PivCl was added (2 equiv.) and after 3 h the reaction mixture was diluted with ethyl acetate and methanol. The solvent was removed under reduced pressure and the residue purified by chromatography (petroleum ether/EtOAc 1:1, then 0:1) to give in order of elution **8** (25%) and **9** (61%) both as colourless gums. Analytical data for **8**: $[\alpha]_D$=−4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.28 (m, 5H, Ph), 5.07 (AB d, 2H, J=−13.5 Hz, CH_2), 4.98–5.05 (m, 1H, H-2), 4.61 (t, J=11.1 Hz, H-5), 4.51 (d, 1H, J_{6a-6b}=−9.9 Hz, H-6a, 4.06–4.13 (m, 2H, H-1a, H-6b), 3.94–4.02 (m, 2H, H-3, H-4),), 3.19 (t, 1H, J_{1b-2}=12.9 Hz, J_{1a-1b}=−12.9 Hz, H-1b), 1.13, 1.03, (2s, each 9H each Piv); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 177.5 (each s, Piv C═O), 156.4 (s, Cbz C═O), 136.3 (s, aromatic C), 128.5, 128.1, 127.9 (each d, aromatic CH), 69.3, 69.1, 67.6 (each d, C-2-4), 67.7 (t, C-6), 60.8 (t, C-1), 56.2 (d, C-5), 39.0, 38.7 (each s, each Me_3C), 37.3 (t, CH_2), 27.2, 27.1 (each q, Piv CH_3); LRMS: 488.1 $[M+Na]^+$. Analytical data for **9**: $[\alpha]_D$=−4 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.31 (m, 5H, Ph), 5.08 (AB d, 2H, J=−12.3 Hz, CH_2), 4.61 (t, 1H, J=10.5 Hz, H-5), 4.51 (broad d, 1H, J_{6a-6b}=−9.6 Hz, H-6a), 3.94–4.10 (m, 5H, H-1b, H-2-4, H-6b), 3.08 (t, 1H, J=−11.7 Hz, H-1b), 1.06 (s, 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1 (s, Piv C═O), 156.8 (s, Cbz C═O), 136.2 (s, aromatic C), 128.5, 128.2, 127.8 (each d, aromatic CH), 70.5, 69.4, 64.5, (each d, C-2-4), 67.7 (t, C-6), 60.9 (t, C-1), 55.9 (d, C-5), 39.8 (t, CH_2), 38.7 (s, Me_3C), 27.0 (q, Piv CH_3); IR: 3700–3100 (broad), 2970, 2909, 1728, 1682, 1538, 1479, 1431, 1281, 1164, 1058, 854, 765 cm^{-1}. LRMS: 404.1 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.58; H, 7.14; N, 3.49.

4.1.3. 2,6-Di-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol 10. Pivalic acid ester **8** (150 mg, 0.32 mmol) was dissolved in MeOH (5 mL), then 10% Pd–C was added (30 mg). The mixture was stirred at room temperature overnight under H_2. The solvent was evaporated and the residue purified by chromatography (EtOAc then EtOAc/MeOH/H_2O 90:8:2, 85:10:5) to give title compound **10** (66 mg, 61%, colourless gum); ^{1}H NMR (300MHz, CD_3OD): δ 5.16 (broad s, 1H, H-2, 4.47 (dd, 1H, J_{5-6a}= 3.6 Hz, J_{6a-6b}=−11.4 Hz, H-6a), 4.21 (dd, 1H, J_{5-6b}= 2.4 Hz, J_{6a-6b}=−11.4 Hz, H-6b), 3.65–3.74 (m, 2H, H-3, H-4), 3.09 (dd, 1H, J_{1a-2}=2.7 Hz, J_{1a-1b}=−14.7 Hz, H-1a), 2.92 (dd, 1H, J_{1b-2}=2.7 Hz, J_{1a-1b}=−14.7 Hz, H-1b), 2.72 (dt, 1H, J=9.3, 3.0 Hz, H-5), 1.31, 1.30 (each s, each 9H, Piv); ^{13}C NMR (75MHz, CD_3OD) δ 178.0, 178.4 (each s, C═O), 73.6, 72.4, 68.7, 58.9 (each d, C-2-5), 63.5, 46.8, (each t, C-1, C-6), 38.8, 38.7 (each s, Me_3C), 26.4, 26.3 (each q, CH_3); HRMS: Found 332.2067, required 332.2073. $[M+H]^+$.

4.1.4. *N*-Benzyl-2,6-di-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol 11. Iminosugar **10** (55 mg, 0.167 mmol) was dissolved in DMF (1 mL), then K_2CO_3 (0.6 equiv.) was added followed by benzyl bromide (1.15 equiv.) and the mixture stirred for 4 h at 60 °C. The solvent was then evaporated and the residue purified by chromatography (petroleum ether/EtOAc 7:3 then 1:1) to give the title compound (50 mg, 71%, colourless gum); $[\alpha]_D$=−93 (*c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.38 (m, 5H, Ph), 5.12 (broad s, 1H, H-2), 4.73 (dd, 1H, J_{5-6a}<0.5 Hz, J_{6a-6b}=−12.6 Hz, H-6a), 4.56 (d, 1H, J_{6a-6b}=−12.6 Hz, H-6b), 4.30 (d, 1H, J=−17.4 Hz, C(H)*H*), 3.67–3.79 (m, 2H, H-3, H-4), 3.09 (d, 1H, J=−17.4 Hz, C(*H*)H), 2.99 (dd, 1H, J_{1a-2}=3.6 Hz, J_{1a-1b}=−13.2 Hz, H-1a), 2.44 (d, 1H, J=8.4 Hz, H-5), 2.26 (dd, 1H, J_{1b-2}=2.8 Hz, J_{1a-1b}=−13.2 Hz, H-1b), 1.26, 1.30 (2s, each 9H each, Piv); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 179.5 (each s, C═O), 138.7 (s, aromatic C), 128.4, 128.3, 127.4, 127.2 (each d, aromatic CH), 74.0, 69.4, 69.2, 65.8 (each d, C-2-5), 60.5, 56.6, 52.9 (each t, CH_2, C-1, C-6), 39.0 (Me_3C), 27.3, 27.2, (each q, CH_3); IR: 3441 (broad), 2971, 2930, 2873, 2799, 1726, 1480, 1286, 1155, 1087, 1031, 910 cm^{-1}; HRMS: Found 422.2547, required 422.2543 $[M+H]^+$.

4.1.5. 6-*O*-Pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol 12. Pivalic acid ester **9** (150 mg, 0.39 mmol) was dissolved was dissolved in MeOH (5 mL), then 10% Pd/C was added (30 mg). The mixture was stirred at room temperature

overnight under H_2. The residue obtained from evaporation of solvent purified by chromatography (EtOAc then EtOAc/MeOH/H_2O 90:8:2 then 85:10:5) to give **12** (60 mg, 62%, colourless gum); ^{1}H NMR (300 MHz, CD_3OD): δ 4.41 (dd, 1H, J_{5-6a}=3.9 Hz, J_{6a-6b}=−11.4 Hz, H-6a), 4.28 (d, 1H, J_{5-6b}<0.5 Hz, J_{6a-6b}=−11.4 Hz, H-6b), 3.97 (broad s, 1H, H-2), 3.70 (t, 1H, J=9.6 Hz, H-4), 3.50 (d, 1H, J_{2-3}=2.1 Hz, H-3), 3.09 (d, 1H, J_{1a-1b}=−12.3 Hz, H-1a), 2.87 (d, 1H, J_{1a-1b}=−12.3 Hz, H-1b), 2.74 (broad d, 1H, J=9.6 Hz, H-5), 1.29 (s, 9H, Piv); ^{13}C NMR (75 MHz, CD_3OD) δ 178.5 (C=O), 74.9, 68.8, 68.2 (C-2-4), 63.2 (C-1, C-6), 59.1 (C-5), 49.0, 38.7 (Me_3C), 26.2 (CH_3); IR: 3600–3000 (broad), 2970, 2874, 1725, 1286, 1161, 1068 cm^{-1}. HRMS: Found 248.1486, required 248.1489. [M+H]$^+$.

4.1.6. *N*-Benzyl-6-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol 13. Pivalic acid ester **12** (50 mg, 0.2 mmol) was dissolved in DMF (1 mL), then K_2CO_3 (0.6 equiv.) and benzyl bromide (1.15 equiv.) were added. The mixture was stirred for 4 h at 60 °C. Then solvent was evaporated and the residue purified by chromatography (petroleum ether/AcOEt 7:3, 1:1) to give **13** (50 mg, 73%, colourless gum); $[\alpha]_D$=−81 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.34 (m, 5H, Bn), 4.60 (d, 1H, J_{6a-6b}=−12.3 Hz, H-6a), 4.51 (dd, 1H, J_{5-6b}=3.0 Hz, J_{6a-6b}=−12.3 Hz, H-6b), 4.18 (d, 1H, J=−13.2 Hz, CH_2), 3.79 (broad s, 1H, H-2), 3.63 (t, 1H, J=9.0 Hz, H-4), 3.41 (dd, 1H, J=2.4, 9.0 Hz, H-3), 3.24 (d, 1H, J=−13.2 Hz, CH_2), 2.90 (dd, 1H, J_{1a-2}=−3.6 Hz, H-1a), 2.41 (broad d, 1H, J_{4-5}=9.0 Hz, H-5), 2.20 (d, 1H, J_{1a-1b}=−13.2 Hz, H-1b), 1.23 (s, 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9 (s, C=O), 138.1 (s, aromatic C), 128.8, 128.6, 127.4, (each d, aromatic CH), 75.6, 69.5, 67.7, 65.7 (each d, C-2-5), 61.3, 57.0, 54.7 (each t, CH_2, C-1, C-6), 38.9 (s, Me_3C), 27.3 (q, Piv); IR: 3407 (broad), 2972, 2924, 2803, 1725, 1480, 1453, 1397, 1286, 1160, 1097 cm^{-1}; HRMS: Found 338.1968, required 338.1967 [M+H]$^+$.

4.1.7. 3-*O*-Levulinoyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose 18. Fructose derivative **17**[20] (1.0 g, 3.8 mmol) was dissolved in THF (30 mL) then DCC (2 equiv.), levulinic acid (1.8 equiv.) and DMAP (10%) were added, the reaction was stirred overnight at room temperature. The mixture was then filtered and the solvent removed and the residue purified by chromatography (toluene/EtOAc 9:1 then 85:15) to give title compound **18** (1.25 g, 91%, colourless oil); $[\alpha]_D$=−143 (*c* 5.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.04 (d, 1H, J_{3-4}=7.8 Hz, H-3), 4.21 (dd, 1H, J_{4-5}=5.4 Hz, J_{3-4}=7.8 Hz, H-4), 4.15 (dd, 1H, J_{5-6a}=1.8 Hz, J_{4-5}=5.4 Hz, H-5), 4.07 (dd, 1H, J_{5-6a}=1.8 Hz, J_{6a-6b}=−13.2 Hz, H-6a), 3.99 (d, 1H, J_{6a-6b}=−13.2 Hz, H-6b), 3.86 (d, 1H, J_{1a-1b}=−9.3 Hz, H-1a), 3.80 (d, 1H, J_{1a-1b}=−9.3 Hz, H-1b), 2.47–2.87 (m, 4H, CH_2CH_2), 2.11 (s, 3H, Lev CH_3), 1.46, 1.42, 1.36, 1.28 (each s, 12H, isopropylidene CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2 (s, C=O, ketone), 172.4 (s, C=O ester), 109.6, 112.1 (each s, isopropylidene C), 103.6 (s, C-2), 74.8, 73.7, 70.9 (each d, C-3-5), 71.5, 60.3 (each t, C-1, C-6), 37.9, 28.0 (each t, CH_2CH_2), 29.7 (q, Lev CH_3), 27.8, 26.6, 26.4, 25.9 (each q, isopropylidene CH_3); MS: 381.2 [M+Na]$^+$. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.92; H, 7.15.

4.1.8. 3-*O*-Levulinoyl-1,2-*O*-isopropylidene-β-D-fructopyranose. Ester **18** (1.8 g, 5 mmol) was dissolved in 80% AcOH and the mixture was heated at 45 °C for 4 h. The solvent was evaporated and toluene then added and evaporated to remove residual water and AcOH. The residue was purified by chromatography (petroleum ether/AcOEt 1:1) to give the title compound **19** (1.04 g, 65%, white solid); $[\alpha]_D$=−70 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.21 (d, 1H, J_{3-4}=9.6 Hz, H-3), 3.97–4.03 (m, 6H, H-1a, H-3, H-4, H-6a), 3.89 (d, 1H, J_{1a-1b}=−9.3 Hz, H-1b), 3.84 (dd, 1H, J_{5-6b}=1.2 Hz, J_{6a-6b}=−12.6 Hz, H-6b), 2.82–2.87 (m, 2H, CH_2), 2.54–2.70 (m, 2H, CH_2), 2.20 (s, 3H, Lev CH_3), 1.48, 1.43 (each s, 6H, isopropylidene CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8 (s, C=O, ketone), 173.4 (s, C=O, ester), 111.9 (s, isopropylidene C), 104.3 (s, C-2), 71.9, 69.8, 69.4, (each d, C-3-5), 71.9, 63.9 (each t, C-1, C-6), 38.4, 28.2, (each t, CH_2CH_2), 29.8 (q, Lev CH_3), 26.1, 26.5 (each q, isopropylidene CH_3); LRMS 341.2 [M+Na]$^+$. Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 53.08; H, 6.88.

4.1.9. 3,5-Di-*O*-levulinoyl-4-*O*-pivaloyl-1,2-*O*-isopropylidene-β-D-fructopyranose 20. Fructose derivative **19** (800 mg, 2.5 mmol) was dissolved in pyridine and CH_2Cl_2, (20 mL, 1:1) and the mixture was stirred at −78 °C; PivCl (1.1 equiv.) was then added slowly. The temperature was allowed to slowly increase to room temperature overnight. The mixture was diluted with chloroform (5 mL) and washed with cold 5% HCl, then with 5% $NaHCO_3$. After drying over $MgSO_4$, the solution was evaporated and the residue purified by chromatography (petroleum ether/EtOAc 6:4 then 1:1) to give 3-*O*-levulinoyl-4-*O*-pivaloyl-1,2-*O*-isopropylidene-β-D-fructopyranose (0.991 g, 98%, white gum); $[\alpha]_D$=−116 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.47 (d, 1H, J_{3-4}=10.5 Hz, H-3), 5.17 (dd, 1H, J=3.0, 10.5 Hz, H-4), 4.13 (m, 1H, H-5), 4.07 (dd, 1H, J_{5-6a}=1.2 Hz, J_{6a-6b}=−12.6 Hz, H-6a), 3.99 (d, 1H, J_{1a-1b}=−9.3 Hz, H-1a), 3.91 (d, 1H, J_{1a-1b}=−9.3 Hz, H-1b), 3.80 (dd, 1H, J_{5-6b}=1.8 Hz, J_{6a-6b}=−12.6 Hz, H-6b), 2.45–2.83 (m, 4H, CH_2CH_2), 2.18 (s, 3H, Lev CH_3), 1.49, 1.45 (2s, 6H, each isopropylidene), 1.20 (s, 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0 (s, C=O, ketone), 177.5, 172.2, (each s, each C=O, ester), 112.2 (s, isopropylidene C), 104.5 (C-2), 71.7, 63.9, (each t, C-1, C-6), 71.6, 67.9, 66.7, (each d, C-3-5), 38.9 (s, Me_3C), 37.8, 27.9, (each t, CH_2CH_2), 29.7 (q, Lev CH_3), 27.1 (q, Piv CH_3), 26.5, 26.1 (each q, isopropylidene CH_3); LRMS: 425.15 [M+Na]$^+$. This intermediate (933 mg, 2.3 mmol) was dissolved in THF (30 mL) and DCC (2 equiv.), levulinic acid (1.8 equiv.) and DMAP (10%) were added and the mixture was stirred overnight at rt. The reaction mixture was then filtered, the solvent removed and the residue purified by chromatography (toluene/EtOAc 9:1 then 8:2) to give **20** (893 mg, 77%, colourless oil); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46 (d, 1H, J_{3-4}=10.5 Hz, H-3), 5.41 (d, 1H, J_{4-5}=3.0 Hz, H-5), 5.31 (dd, 1H, J_{4-5}=3.0 Hz, J_{3-4}=10.5 Hz, H-4), 4.64 (d, 1H, J_{6a-6b}=−13.2 Hz, H-6a), 4.03 (d, 1H, J_{1a-1b}=−9.0 Hz, H-1a), 3.98 (d, 1H, J_{1a-1b}=−9.0 Hz, H-1b), 2.57–2.82 (m, 8H, CH_2CH_2), 3.80 (d, 1H, J_{6a-6b}=−13.2 Hz, H-6b), 2.23 (s, 6H, Lev CH_3), 1.53, 1.51 (2s, 6H, isopropylidene CH_3), 1.18 (s, 9H, Piv); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 206.1, 205.9 (each s, C=O, Lev ketone), 177.3 (s, C=O, Piv), 172.2, 171.9 (each s, C=O, Lev ester), 112.3 (s, isopropylidene *C*), 71.7, 62.3 (each t, C-1, C-6), 69.3, 68.9, 66.8 (each C-3-5), 104.5 (s, C-2), 38.8 (s, Me_3C), 37.8, 28.0, 27.9 (each t, CH_2CH_2), 29.8, 29.7 (each q, Lev CH_3), 26.9 (q, Piv CH_3), 26.5, 26.0 (each q, isopropylidene CH_3); $[\alpha]_D=-93$ (*c*, 2.3, $CHCl_3$); LRMS: 518.2 $[M+H_2O]^+$ 523.1 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{36}O_{11}$: C, 57.59; H, 7.25. Found: C, 57.95; H, 7.30.

4.1.10. 3,5-Di-*O*-levulinoyl-1,4-di-*O*-pivaloyl-β-D-fructopyranose 21. Fructose derivative **20** (700 mg) was dissolved in TFA/H_2O 4:1 (10 mL) and the mixture stirred at room temperature for 2 h. The reaction mixture was then evaporated and coevaporated with toluene. The residue was purified by chromatography (petroleum ether/AcOEt 1:1 then 0:1) and gave 3,5-di-*O*-levulinoyl-4-*O*-pivaloyl-β-D-fructopyranose (85%, white solid) and 1,5-di-*O*-levulinoyl-4-*O*-pivaloyl-β-D-fructopyranose (11%, heavy syrup, resulting from migration of levulinate from O-3). Analytical data for the 3,5-di-*O*-levulinate: ^1H NMR (300 MHz, $CDCl_3$): δ 5.27–5.40 (m, 3H, H-3-5), 4.16 (d, 1H, $J_{6a-6b}=-13.2$ Hz, H-6a), 3.84 (d, 1H, $J_{6a-6b}=-13.2$ Hz, H-6b), 3.64 (d, 1H, $J=-11.7$ Hz, H-1a), 3.56 (d, 1H, $J_{1a-1b}=-11.7$ Hz, H-1b), 2.47–2.80 (m, 8H, CH_2CH_2), 2.20, 2.19 (2s, 6H, Lev CH_3), 1.12 (s, 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 206.9 (each s, C=O, Lev ketone), 177.3 (s, C=O, Piv ester), 172.2, 171.9 (each s, C=O Lev ester), 97.3 (s, C-2), 69.5, 68.2, 68.1 (each d, C-5), 65.3, 61.5 (each t, C-1, C-6), 38.8 (s, Me_3C), 29.9, 29.8 (each q, Lev CH_3), 37.9, 37.8, 27.9 (each t, CH_2CH_2), 26.9 (q, CH_3, Piv); $[\alpha]_D=-74$ (*c* 1.6, $CHCl_3$); LRMS: 483.15 $[M+Na]^+$. Anal. Calcd for $C_{21}H_{32}O_{11}$: C, 54.78; H, 7.00. Found: C, 54.79; H, 7.10. Analytical data for the 1,5-di-*O*-levulinate: $[\alpha]_D=-56$ (*c* 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.28 (dd, 1H, $J=3.6$, 1.8 Hz, H-5), 5.21 (dd, 1H, $J_{4-5}=3.6$ Hz, H-4), 4.45 (d, 1H, $J_{1a-1b}=-11.4$ Hz, H-1a), 4.21 (d, 1H, $J_{1a-1b}=-11.4$ Hz, H-1b), 4.14 (dd, 1H, $J_{5-6a}=0.9$ Hz, $J_{6a-6b}=-12.9$ Hz, H-6a), 3.88 (d, 1H, $J_{3-4}=10.2$ Hz, H-3), 3.75 (dd, 1H, $J_{5-6b}=1.8$ Hz, H-6b), 2.62–2.85 (m, 8H, CH_2CH_2=Lev), 2.19, 2.21 (each s, 6H, Lev CH_3), 1.19 (s, 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 207.7 (each s, C=O, Lev ketone), 178.3 (s, C=O, Piv ester), 173.0, 171.9 (s, C=O Lev ester), 97.2 (s, C-2), 70.4, 69.6, 68.1 (each d, C-3, C-4, C-5), 66.4, 61.7 (each t, C-1, C-6), 38.9 (s, Me_3C), 38.2, 37.8, 27.9 (each t, CH_2CH_2), 29.8 (q, Lev CH_3), 27.0 (q, CH_3, Piv); LRMS: 483.15 $[M+Na]^+$. The 3,5-di-*O*-levulinate (579 mg, 1.25 mmol) was dissolved in pyridine (5 mL), and PivCl (1.2 equiv.) added and the mixture was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 and consecutively washed with 5% HCl and 5% $NaHCO_3$. After drying over magnesium sulfate, the solution was concentrated under reduced pressure and the residue chromatographed (petroleum ether/EtOAc, 1:1) to give **21** (616 mg, 90%, white solid; $[\alpha]_D=-38$ (*c* 2.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.43 (d, 1H, $J_{3-4}=10.2$ Hz, H-3), 5.24–5.28 (m, 2H, H-4, H-5), 4.11 (d, 1H, $J_{6a-6b}=-13.2$ Hz, H-6a), 4.04 (s, 2H, H-1a, H-1b), 3.69 (d, 1H, $J_{6a-6b}=-13.2$ Hz, H-6b), 2.66–2.48 (m, 8H, CH_2CH_2), 2.11 (each s, 6H, Lev), 1.05, 1.17 (each s, 18H, Piv); ^{13}C NMR (75MHz, $CDCl_3$) δ 206.3, 206.5 (s, C=O, Lev ketone), 177.5, 178.4 (s, C=O, piv ester), 171.9, 171.1 (s, C=O Lev ester), 96.7 (s, C-2), 69.4, 68.4, 67.5 (each d, C-3-5), 65.1, 61.6 (each t, C-1, C-6), 38.9, 38.8 (each s, Me_3C), 37.7, 27.8 (each t, CH_2CH_2), 29.8, 29.7 (each q, Lev CH_3), 26.9, 27.1 (each q, Piv CH_3); LRMS: 562.3 $[M+H_2O]^+$, 567.21 $[M+Na]^+$, 583.19 $[M+K]^+$. Anal. Calcd for $C_{26}H_{40}O_{12}$: C, 57.34; H, 7.40. Found: C, 57.04; H, 7.35.

4.1.11. 6-Bromo-6-deoxy-3,5-di-*O*-levulinoyl-1,4-di-*O*-pivaloyl-D-fructose 22. Fructose derivative **21** (2.5 g, 4.59 mmol) was dissolved in dry CH_2Cl_2=(50 mL) then pyridine (0.5 mL) and triphenylphosphane dibromide (1.3 equiv.) were added, and the mixture was stirred whilst heating at reflux for 3 h. Satd. aq. $NaHCO_3$=was then added slowly to the cooled solution and the organic layer consecutively washed with 5% HCl and 5% $NaHCO_3$. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue purified by chromatography (petroleum ether/ EtOAc 7:3 then 6:4) to give **22** (2.59 g, 93%, colourless gum); $[\alpha]_D=+17$ (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.68 (dd, 1H, $J_{4-5}=9.3$ Hz, $J_{3,4}=2.1$ Hz, H-4, 5.49 (d, 1H, $J_{3-4}=2.1$ Hz, H-3), 4.78 (d, 1H, $J_{1a-1b}=-17.4$ Hz, H-1b), 5.28 (ddd, 1H, $J=4.5$, 9.3, 3.3 Hz, H-5), 4.84 (d, 1H, $J_{1a-1b}=-17.4$ Hz, H-1a), 3.64 (dd, 1H, $J_{5-6a}=3.3$ Hz, $J_{6a-6b}=-11.7$ Hz, H-6a), 3.45 (dd, 1H, $J_{6a-6b}=-11.7$ Hz, $J_{5-6b}=4.5$ Hz, H-6b), 2.56–2.82 (m, 8H, CH_2CH_2), 2.18 (each s, 6H, Lev CH_3), 1.19, 1.28 (each s, 18H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.2, 206.1 (s, C=O Lev ketone), 197.8 (s, C-2), 177.2, 176.8 (s, C=O, Piv), 171.8, 171.4, (s, C=O Lev ester), 73.9, 69.2, 68.8 (each d, C-3-5), 67.1 (t, C-1), 38.9, 38.8 (q, Me_3C), 31.4 (t, C-6), 37.9, 37.8, 27.9, 27.6 (each t, CH_2CH_2), 29.7 (q, Lev CH_3), 27.2, 26.8 (each q, Piv CH_3); LRMS: 625.2 $[M+H_2O]^+$, 630.2 $[M+Na]^+$, 646.2, $[M+K]^+$. Anal. Calcd for $C_{26}H_{39}BrO_{11}$: C, 51.41; H, 6.47; Br, 13.15. Found: C, 51.11; H, 6.19; Br, 13.06.

4.1.12. 6-Bromo-6-deoxy-1,4-di-*O*-pivaloyl-β-D-fructofuranose 23. Fructose derivative **22** (1.331 g, 2.19 mmol) was dissolved in pyridine (10 mL) and acetic acid (5 mL), cooled to 0 °C then hydrazine hydrate (3 equiv.) was added and the mixture stirred until reaction was judged complete by TLC analysis. The mixture was then diluted with dichloromethane (25 mL) and washed with a cold 5% aqueous HCl, then with 5% aqueous $NaHCO_3$. After drying over $MgSO_4$, the solvent was evaporated and the residue purified by chromatography (petroleum ether/AcOEt 7:3) to give the title compound **23** (593 mg, 66%, colourless powder); ^1H NMR (300 MHz, $CDCl_3$): δ 4.96 (t, 1H, $J=4.8$ Hz, H-4), 4.19–4.28 (m, 2H, H-1a, H-1b), 4.09–4.16 (m, 2H, H-3, H-5), 3.85 (broad d, 1H, OH), 3.57–3.69 (m, 2H, H-6a, H-6b), 1.24, 1.22 (each s, 18H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 178.3 (each s, C=O), 102.3 (s, C-2), 83.3, 79.9, 77.6 (each d, C-3-5), 64.9 (t, C-1), 38.7, 38.9 (Me_3C), 33.2 (t, C-6), 27.0, 27.1 (each q, CH_3); HRMS: Found 409.0855, required 409.0862 $[M-H]^-$.

4.1.13. 6-Azido-6-deoxy-1,4-di-*O*-pivaloyl-β-D-fructofuranose 15. Bromide **23** (50 mg, 0.115 mmol) was dissolved in DMF (1 mL) and then NaN_3 (20 equiv.) was added. The mixture was stirred for 2 days at room temperature. Then solvent was then evaporated and the residue chromatographed (petroleum ether/EtOAc, 7:3) to

give the title compound **15** (23 mg, 53%, colourless gum); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (t, 1H, J=4.8 Hz, H-4), 4.21–4.31 (m, 2H, H-1a, H-1b), 4.14 (d, 1H, J_{3-4}=5.4 Hz, H-3), 4.02–4.07 (m, 1H, H-5), 3.61 (dd, 1H, J_{5-6a}=5.7 Hz, J_{6a-6b}=−12.9 Hz, H-6a), 3.53 (dd, 1H, J_{5-6b}=4.2 Hz, J_{6a-6b}=−12.9 Hz, H-6b), 1.22, 1.24 (each s, each 9H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4, 178.4 (each s, C=O), 102.1 (s, C-2), 81.3, 80.7, 76.7 (each d, C-3-5), 65.1 (t, C-1), 53.4 (t, C-6), 38.9, 38.8 (each s, Me_3C), 27.1, 27.0 (each q, CH_3),; IR: 3450 (broad), 2973, 2936, 2875, 2103, 1730, 1482, 1461, 1399, 1367, 1285, 1150, 1039, 942, 770, 635 cm^{-1}; HRMS: Found 327.1779, required 327.1771 [M+H]$^+$.

4.1.14. *N*-Benzyl-3,6-di-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol 2. The azide **15** (100 mg, 0.27 mmol) was dissolved in MeOH (5 mL), then 10% Pd–C (30 mg) was added and the mixture stirred at room temperature overnight under H_2. The mixture was filtered and solvent evaporated and the residue purified by chromatography (EtOAc then EtOAc/MeOH/H_2O 90:8:2 then 85:10:5) to give **24** (19.5 mg, 22%, colourless gum); ^{1}H NMR (300 MHz, CD_3OD): δ 4.75 (dd, 1H, J_{2-3}=3.0 Hz, H-3), 4.41 (dd, 1H, J_{5-6a}=4.2 Hz, J_{6a-6b}=−11.4 Hz, H-6a), 4.28 (dd, 1H, J_{5-6b}=2.4 Hz, J_{6a-6b}=−11.4 Hz, H-6b), 4.07 (broad s, 1H, H-2), 3.93 (t, 1H, J_{3-4}=J_{4-5}=9.9 Hz, H-4), 3.06 (dd, 1H, J_{1a-2}=3.0 Hz, J_{1a-1b}=−13.8 Hz, H-1a),2.96 (d, 1H, J_{1a-1b}=−13.8 Hz, H-1b), 2.79 (dt, 1H, J_{4-5}=9.3 Hz, J=3.2 Hz, H-5), 1.30, 1.31 (each s, each 9H, Piv); ^{13}C NMR (75 MHz, CD_3OD): δ 178.5, 178.3 (each s, C=O), 76.8, 65.9, 65.3, 59.4 (each C-2-5), 62.7, 49.0 (each t, C-1, C-6), 38.7 (s, Me_3C), 26.2, 26.1 (each q, CH_3); LRMS: 332.2 [M+H]$^+$, 354.2 [M+Na]$^+$. This intermediate (25 mg, 0.076 mmol) was dissolved in DMF (1 mL) and then K_2CO_3 (0.6 equiv.) and benzyl bromide (1.15 equiv.) were added and the mixture stirred for 4 h at 60 °C. The solvent was then evaporated and the residue purified by chromatography (petroleum ether/EtOAc, 7:3, 1:1) to give the title compound (19 mg, 60%, colourless gum); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.38 (m, 5H, Ph), 4.68 (dd, 1H, J_{2-3}=3.0 Hz, J_{3-4}=9.0 Hz, H-3), 4.61 (dd, 1H, J_{5-6a}=3.3 Hz, J_{6a-6b}=−12.6 Hz, H-6a), 4.54 (dd, 1H, J_{5-6b}=3.0 Hz, J_{6a-6b}=−12.6 Hz, H-6b), 4.15 (d, 1H, J=−13.2 Hz, CH_2), 3.86–3.91 (m, 2H, H-2, H-4), 3.35 (d, 1H, J=−13.2 Hz, CH_2), 2.87 (dd, 1H, J_{1a-2}=4.5 Hz, J_{1a-1b}=−12.0 Hz, H-1a), 2.55 (dt, 1H, J=3.0, 9.5 Hz, H-5), 2.33 (broad d, 1H, J_{1a-1b}=−12.0 Hz, H-1b), 1.25 (s, 18H, Piv); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 177.8 (each s, Piv C=O), 136.8 (each s, aromatic C), 127.9, 127.7, 127.6, 126.5 (each d, aromatic CH), 77.2, 67.4, 65.9, 65.8, (each d, C-2-5), 59.3, 55.8, 52.9 (each t, CH_2, C-1, C-6), 38.1, 37.9 (each s, Me_3C), 26.2, 26.1 (each q, CH_3); HRMS: Found 422.5345, required 422.5351 [M+H]$^+$.

4.1.15. Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-triisopropylsilyl-β-D-glucopyranoside 27. To a stirred solution of **26** (11.5 g, 26.5 mmol) and 2,6-lutidine (18.5 mL, 159 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added triisopropylsilyl triflate (28.5 mL, 160 mmol). The solution was allowed to warm to room temperature and the reaction was allowed to stir overnight. The solution was then diluted with CH_2Cl_2 (50 mL) and washed with a satd. soln of NH_4Cl (2×100 mL) and then washed with water (2×100 mL). It was then concentrated and purified by chromatography to give **27** (quant. yield, white solid); mp 120–121 °C; $[\alpha]_D$=−51.8 (c 0.09, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.01 (m, 15H, aromatic H), 5.59 (s, 1H, CHC$_6$H$_4$), 5.17 (d, 1H, $J_{1,2}$=7.2 Hz, H-1), 4.85 (AB d, 2H, J=−11.3 Hz, OCH_2Ph), 4.37 (dd, 1H, $J_{5,6a}$=4.8 Hz, $J_{6a,6b}$=−10.4 Hz, H-6a), 4.05 (t, 1H, J=7.4 Hz, H-2), 3.78 (m, 3H), 3.63 (dd, 1H, J=4.5, 9.2 Hz), 1.11–1.02 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 156.7, 139.0, 137.5 (each s, each aromatic C) 129.7, 129.2, 128.5, 128.4, 127.9, 127.6, 126.2, 122.5, 116.1 (each d, aromatic CH), 101.5, 100.9, 82.7, 82.2 (each d), 75.3 (d), 74.9 (t), 69.1 (t), 66.1 (d), 18.4, 18.3, 13.1; IR (KBr): 2944, 2867, 1598, 1493, 1389, 1223, 1093, 1027 cm^{-1}. HRMS-CI: Found 591.3142, required 591.3141 [M+H]$^+$.

4.1.16. Phenyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 28. Glucoside **27** (12.0 g, 20.3 mmol) was dissolved in wet 30% TFA/CH_2Cl_2 solution (240 mL) and the mixture was stirred for 6 h until judged complete by TLC analysis. Pyridine (200 mL) was added, followed by acetic anhydride (200 mL). After 16 h the solution was concentrated and chromatography gave **28** (7.86 g, 66% for two steps, white solid); $[\alpha]_D$=−64.2 (c 0.26, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.15 (m, 10H, aromatic H), 5.03 (t, 1H, J=9.4 Hz, H-4), 4.92 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 4.68 (AB d, 2H, J=−11.7 Hz, OCH_2Ph), 4.13 (dd, 1H, $J_{5,6a}$=6.3 Hz, $J_{6a,6b}$=−12.2 Hz, H-6a), 4.01 (m, 2H, H-6b, H-2), 3.68 (ddd, 1H, J=2.6, 6.3, 12.2 Hz, H-5), 3.59 (t, 1H, J=8.8 Hz, H-3), 1.94 and 1.77 (each s, CH_3), 1.02–0.92 (m, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 170.9, 169.9 (each s, C=O), 156.6, 138.6 (each s, aromatic C) 129.6, 128.5, 127.7, 127.5, 122.5, 116.4 (each d, aromatic CH), 100.2 (d, C-1), 84.1 (d), 75.4 (t, CH_2Ph), 75.3, 72.2, 70.7 (each d), 62.9 (t, C-6), 20.9, 20.9 (each d), 18.4, 18.3, 13.3; IR (NaCl): 2946, 2887, 1745, 1599, 1498, 1366, 1228, 1057, 884, 783 cm^{-1}. HRMS-CI: Found 604.3301, required 604.3306 [M+NH_4]$^+$.

4.1.17. Phenyl 3-*O*-benzyl-6-*O*-tosyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 29. Diacetate **28** (1.82 g, 3.1 mmol) was dissolved in methanol (100 mL) and sodium (0.1 g) was added. The solution was stirred for 5 min and then amberlite IR-120 (plus) ion exchange resin was added, which after 5 min was filtered and the solvent removed. The residue was dissolved in pyridine (20 mL) and cooled to 0 °C. Tosyl chloride (4.0 g, 20.6 mmol) was added and the mixture stirred for 3 h and then diluted with EtOAc (60 mL). The excess tosyl chloride was removed by several aqueous washes (100 mL each). After drying and filtration the EtOAc was removed and residue purified by chromatography to give **29** (1.73 g, 85%, clear syrup); $[\alpha]_D$=−65.8 (c 0.44, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–6.92 (m, 14H, aromatic H), 4.85 (AB d, 2H, J=−12.0 Hz, OCH_2Ph), 4.98 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.77 (dd, 1H, $J_{5,6a}$=2.05 Hz, $J_{6a,6b}$=−11.7 Hz, H-6a), 4.35 (dd, 1H, $J_{5,6b}$=6.1 Hz, $J_{6a,6b}$=−11.7 Hz, H-6b), 3.97 (t, 1H, J=8.0 Hz, H-2), 3.64 (ddd, 1H, J=2.1, 9.9, 6.1 Hz, H-5), 3.59 (dd, 1H, $J_{4,3}$=8.7 Hz, $J_{4,5}$=9.9 Hz, H-4), 3.45 (t, 1H, J=8.7 Hz, H-3), 2.38 (s, 3H, CH_3), 2.25 (br s, 1H, OH), 1.14–1.04 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 156.5, 144.9, 138.8, 132.7 (each s, each aromatic C) 129.9, 129.6, 128.9, 128.2, 128.1, 127.9, 122.4, 116.6 (each d, aromatic CH),

99.7 (d, C-1), 85.9 (d), 75.4 (t), 74.9, 73.5, 69.6 (each d), 68.9 (t), 21.8, 18.4, 18.3, 13.4; IR (film on NaCl): 3471, 2945, 2856, 1588, 1495, 1359, 1232, 1174, 1070, 883, 748, 668 cm^{-1}. HRMS: Found 679.2740, required 679.2737. $[M+Na]^+$.

4.1.18. Phenyl 6-azido-6-deoxy-3-*O*-benzyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 30a. Tosylate **29** (1.7 g, 2.6 mmol) was dissolved in DMF (52 mL) and sodium azide (1.36 g, 21 mmol) was added. The suspension was stirred and heated at 90 °C for 16 h, after which the reaction was complete. The solution was diluted with EtOAc (50 mL) and the excess sodium azide removed with several aqueous washes (50 mL). Filtration through silica gave **30a** (0.98 g, 72%, clear syrup); $[\alpha]_D=-147.6$ (*c* 0.49, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–7.03 (m, 10H, aromatic H), 5.08 (d, 1H, $J_{1,2}$=7.2 Hz, H-1), 4.90 (AB d, 2H, $J=-11.8$ Hz, OCH_2Ph), 4.11 (t, 1H, J=8.0 Hz, H-2), 3.57–3.39 (m, 5H, H-3, 4, 5, 6a, 6b), 2.42 (broad s, 1H, OH), 1.21–1.10 (m, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 156.5, 138.9 (each s, aromatic C) 129.7, 128.9, 128.2, 127.9, 122.5, 116.0 (each d, aromatic CH), 100.0 (d, C-1), 86.3 (d), 75.5 (t), 75.3, 75.0, 70.9 (each d), 51.9 (t), 18.4, 18.3, 13.5; IR (KBr): 2943, 2885, 2101, 1598, 1495, 1236, 1072, 883, 753, 695 cm^{-1}. HRMS-CI: Found 545.3159, required 545.3159 $[M+NH_4]^+$.

4.1.19. Phenyl 6-azido-6-deoxy-3-*O*-benzyl-4-*O*-methyl-*O*-triisopropylsilyl-β-D-glucopyranoside 30b. Azide **30a** (0.1 g, 0.19 mmol) was dissolved in anhyd. DMF (5 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 0.19 g) was added and the suspension was stirred for 20 min. Methyl iodide (0.2 mL, 1.4 mmol) was then added and the mixture warmed to room temperature. After 3 h the reaction was quenched by careful addition of methanol. The solution was then diluted with ethyl acetate (30 mL) and washed with water (2×30 mL). Chromatography gave recovered **30a** (14 mg, 12%) and **30b** (90 mg, 88%, clear syrup); $[\alpha]_D=-114$ (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–6.96 (m, 10H, aromatic H), 4.98 (d, 1H, $J_{1,2}$=7.4 Hz, H-1), 4.88 (s, 2H, OCH_2Ph), 3.98 (t, 1H, J=8.0 Hz, H-2), 3.57–3.37 (m, 7H, H-3, 5, 6a, 6b, OMe), 3.25 (t, 1H, $J_{4,5}$=9.0 Hz, H-4), 1.09–0.99 (m, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 156.6, 138.9 (each s, aromatic C) 129.6, 128.5, 127.6, 127.4, 122.5, 116.5 (each d, aromatic CH), 100.2 (d, C-1), 86.1, 81.3 (each d), 75.5 (t, *C*H_2Ph), 75.3, 74.7, 61.6 (each d), 51.7 (t), 18.4, 18.3, 13.4; IR (KBr): 2942, 2866, 2100, 1599, 1495, 1360, 1283, 1231, 1160, 1092, 1066 cm^{-1}; HRMS-CI: Found 559.3314, required 559.3316 $[M+NH_4]^+$.

4.1.20. Phenyl 6-azido-6-deoxy-3-*O*-benzyl-4-*O*-propyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 30c. Reaction of azide **30a** (0.21 g, 0.4 mmol) with 1-bromopropane as described for preparation of **30b** gave **30c** (0.18 g, 79%, clear syrup); $[\alpha]_D=-53.3$ (*c* 0.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–6.96 (m, 10H, aromatic H), 4.99 (d, 1H, $J_{1,2}$=7.4 Hz, H-1), 4.89 (s, 2H, OCH_2Ph), 3.99 (t, 1H, J=7.0 Hz), 3.76 (dd, 1H, J=6.7, 8.7 Hz), 3.67–3.37 (m, 6H), 1.56 (m, 2H, CH_2CH$_3$), 1.16–1.06 (m, 21H, TIPS), 0.89 (t, 3H, J=7.2 Hz, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$): δ 156.6, 138.0 (each s, aromatic C) 129.6, 128.4, 127.5, 127.2, 116.1 (each d, aromatic *C*H), 100.2 (d, C-1), 86.2, 79.4 (each d), 75.5 (t), 75.3 (d), 75.1 (t), 74.9 (d), 51.7, 23.7 (each t), 18.4 (2s), 13.4, 10.7; IR (KBr): 2941, 2866, 2101, 1599, 1495, 1232, 1163, 1097 cm^{-1}. HRMS-CI: Found 587.3631, required 587.3629 $[M+NH_4]^+$.

4.1.21. Phenyl 6-azido-6-deoxy-3-*O*-benzyl-4-*O*-isobutyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 30d. Reaction of azide **30a** (0.28 g, 0.53 mmol) with 1-bromo-2-methylpropane as described for preparation of **30b** gave unreacted **30a** (0.165 g, 54%) and **30d** (90 mg, 30%, clear syrup); $[\alpha]_D=-56.8$ (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.00 (m, 10H, aromatic H), 5.03 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.92 (s, 2H, OCH_2Ph), 4.03 (t, 1H, J=8.5 Hz), 3.65–3.54 (m, 4H), 3.44 (dd, 1H, $J_{6a,5}$=6.6 Hz, $J_{6a,6b}=-12.8$ Hz, H-6a), 3.36 (t, 1H, J=9.4 Hz), 3.22 (t, 1H, J=7.3 Hz), 1.76 (m, 1H, isobutyl C*H*), 1.29–1.02 (m, 21H, TIPS), 0.89, 0.83 (each d, 6H, J=6.6 Hz, isobutyl CH$_3$); ^{13}C NMR ($CDCl_3$): δ 156.5, 139.0 (each s, aromatic C) 129.6, 128.4, 127.5, 127.2, 122.4, 116.1 (each d, aromatic CH), 100.1 (d, C-1), 86.2 (d), 80.1 (t), 79.4 (d), 75.4 (t), 75.3, 74.0 (each d), 51.7 (t, C-6), 19.6, 19.4, 18.4, 18.3, 13.4. HRMS-CI: Found 601.3789, required 601.3785 $[M+NH_4]^+$.

4.1.22. Phenyl 6-azido-6-deoxy-3,4-di-*O*-benzyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 30e. Reaction of azide **30a** (0.1 g, 0.19 mmol) with 1-bromo-2-methylpropane as described for preparation of **30b** gave **30e** (97 mg, 81%, clear syrup); $[\alpha]_D=-45$ (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–6.96 (m, 15H, aromatic H), 5.07 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 5.00 (AB d, 2H, $J=-11.0$ Hz, OCH_2Ph), 4.75 (AB d, 2H, $J=-11.1$ Hz, OCH_2Ph), 4.13 (t, 1H, J=6.9 Hz), 3.67 (m, 3H), 3.53 (dd, 1H, $J=-13.0$, 2.0 Hz), 3.37 (dd, 1H, J=6.2, −13.0 Hz), 1.10–1.00 (m, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 156.5, 138.9, 137.9 (each s, aromatic C) 129.7, 128.7, 128.5, 128.2, 128.2, 127.6, 127.3, 122.5, 116.1 (each d, aromatic CH), 100.2 (d, C-1), 86.4, 78.9 (each d), 75.6 (d), 75.6, 75.3 (each t), 74.6 (d), 51.6 (t), 18.5, 18.4, 13.5; IR (KBr): 3414, 2925, 2867, 2100, 1599, 1495, 1454, 1231, 1163, 1071, 751, 694 cm^{-1}. HRMS-CI: Found 635.3626, required 635.3629 $[M+NH_4]^+$.

4.1.23. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-β-D-glucopyranoside 4a. Azide **30a** (0.23 g, 0.43 mmol) was dissolved in EtOH:EtOAc (5:3, 15 mL) and Lindlar catalyst (0.4 g) was added. The suspension was stirred under H_2 (1 atm) for 2.5 h, then filtered and the solvent removed. The residue was dissolved in dichloromethane and added to a solution of Ac-Val-OH (0.13 g, 0.6 mmol), BOP–Cl (0.16 g, 0.63 mmol) and DIPEA (0.28 mL) which had been stirred for 5 min in dichloromethane (10 mL) at rt. The reaction was complete after 5 h as judged by TLC analysis and purification by chromatography gave **31a** (50 mg, 79%, clear syrup); $[\alpha]_D=-43$ (*c* 0.075, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–6.90 (m, 10H, aromatic H), 6.10–6.38 (overlapping signals, 2H, N*H*), 4.90 (AB d, 2H, $J=-11.4$ Hz, OCH_2Ph), 4.90 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 4.20 (dd, 1H, J=6.9, 8.8 Hz, NHC*H*CH(Me)$_2$), 3.29–3.85 (m, 3H), 3.67–3.36 (m, 3H), 3.28 (dd, 1H, J=2.9, −14.0 Hz), 2.01 (m, 1H, (Me)$_2$C*H*), 1.92 (s, 3H, Ac), 0.99–0.91 (m, 21H, TIPS), 0.80 and 0.83 (2×d, 6H, J=7.0 Hz, (CH_3)$_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$): 173.1, 170.5 (each s, C=O), 156.4, 139.1 (each s,

aromatic C), 129.5, 128.1, 127.4, 127.3, 122.1, 115.5, (each d, aromatic C), 99.8 (d, C-1), 84.7, 74.7 (each d), 74.3 (t, CH_2Ph), 71.5 (d), 58.4 (t, C-6), 40.2, 30.9, 29.7, 22.9, 19.2, 18.1, 18.0, 12.9; LRMS: 665.4 $[M+Na]^+$. This intermediate (50 mg, 0.078 mmol) was dissolved in anhyd. THF (2.5 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (38 mg, 0.15 mmol) was added and the solution was stirred for 30 min. The solvent was removed and the residue purified by chromatography to give **4a** (25 mg, 65%, white solid); $[\alpha]_D=-35.2$ (*c* 0.38, MeOH); ^1H NMR (300 MHz, CD_3OD): δ 7.45–6.98 (m, 10H, aromatic H), 4.93 (d, 1H, $J_{1,2}=7.6$ Hz, H-1), 4.90 (AB d, 2H, $J=11.1$ Hz, OCH_2Ph), 4.14 (d, 1H, $J=7.0$ Hz), 3.44–3.64 (m, 4H), 3.37 (t, 1H, $J=9.0$ Hz), 2.03 (s, 3H, Ac), 2.00 (m, 1H, $(CH_3)_2CH$), 0.90–0.88 (m, 6H, $(CH_3)_2CH$); ^{13}C NMR (CD_3OD): δ 174.4, 173.4 (each s, C=O), 159.1, 140.5 (each s, aromatic C) 130.6, 129.2, 129.1, 128.5, 123.5, 117.8 (each d, aromatic CH), 102.1 (d, C-1), 85.7, 75.9, 75.1, 72.8 (each d, C-2-5), 76.1 (t), 60.6 (d), 41.6 (t, C-6), 31.8, (d), 22.5, 19.8, 18.6; HRMS-CI: Found 487.2443, required 487.2444; $[M+H]^+$.

4.1.24. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-methyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 31b. Azide **30b** (0.17 g, 0.3 mmol) was treated as described for **30a** and gave the title compound **31b** (0.117 g, 66%, clear syrup) as a mixture of diasteroisomers; $[\alpha]_D=-8.7$ (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–6.90 (m, 10H, aromatic H), 6.10–6.23 (overlapping signals, 2H, NH), 5.00 and 5.02 (each d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.88 (s, 2H, OCH_2Ph), 4.13–4.21 (2 overlapping t, 1H, $J=8.5$ Hz), 3.99 and 3.98 (each t, 1H, $J=8.0$ Hz), 3.82 (ddd, 1H, $J=3.7$, 6.3, 13.7 Hz, H-6a), 3.56 (t, 1H, $J=9.5$ Hz), 3.48 (s, 3H, OCH_3), 3.41–3.56 (m, 3H), 3.14 (t, 1H, $J=9.0$ Hz, H-4), 2.05 (m, 1H, $CH(Me)_2$), 1.97 (s, 3H, Ac), 1.08–0.90 (m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): 171.2, 170.1 (each s, C=O), 156.0 (s, aromatic C), 129.6, 128.1, 127.4, 127.3, 122.3, 115.4, (each d, aromatic C), 99.2 (d, C-1), 85.7, 81.7 (each d), 75.3 (t, CH_2Ph), 74.9, 73.4, 60.8, 58.6 (each d), 40.1 (t, C-6), 31.5, 31.1 29.7, 23.2, 19.1, 18.1, 13.1; ^{13}C NMR (75 MHz, $CDCl_3$, selected signals for minor isomer); δ 171.1, 170.0 (each s, C=O), 156.2 (s, aromatic C), 129.5, 128.1, 127.3, 127.2, 122.4, 115.6, (each d, aromatic CH), 99.6 (d, C-1), 85.6, 81.4 (each d), 75.2 (t, CH_2Ph), 74.8, 73.8, 60.8, 58.3 (each d), 40.0 (t, C-6), 31.9, 29.7, 23.2, 19.1, 18.2, 13.1; IR (NaCl plates): 3288, 2930, 1634, 1557, 1373, 1231, 1103 cm^{-1}; HRMS-FAB: Found 679.3755, required 679.3755, $[M+Na]^+$.

4.1.25. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-methyl-β-D-glucopyranoside 4b. Glucoside **31b** (0.11 g, 0.17 mmol) was treated as described for **31a** to give **4b** (75 mg, 88%, white solid); $[\alpha]_D=-0.2$ (*c* 0.05, MeOH); ^1H NMR (500 MHz, CD_3OD): δ 7.44–7.02 (m, 10H, aromatic H), 4.88 (d, 1H, $J_{1,2}=7.6$ Hz, H-1), 4.85 (AB d, 2H, $J=-11.1$ Hz, OCH_2Ph), 4.10 (d, 1H, $J=6.8$ Hz, $CHCH(Me)_2$), 3.59–3.49 (m, 4H), 3.36 (s, 3H), 3.07 (t, 1H, $J=8.4$ Hz), 2.08 (s, 3H, Ac), 1.97 (m, 1H, $(CH_3)_2CH$), 0.90–0.86 (m, 6H, $(CH_3)_2CH$); ^1H NMR (500 MHz, CD_3CN, selected data) δ 6.68 (br s, 1H, NH) and 6.55 (d, 1H, $J=6.3$ Hz, NH): ^{13}C NMR (75 MHz, $CDCl_3$, major diastereoisomer): δ 174.0, 173.4 (each s, C=O), 159.1, 140.3 (each s, aromatic C) 130.6, 129.3, 129.1, 128.6, 123.5, 117.7 (each d, aromatic CH), 101.9 (d, C-1), 86.0, 82.0, 75.5, 74.8 (each d, C-2-5), 76.2 (t, CH_2Ph), 61.2 (d), 60.7 (q), 41.2 (t, C-6), 31.8 (d, $(CH_3)_2CH$), 22.5, (q, Ac), 19.8, 18.5 (each q, $(CH_3)_2CH$); δ ^{13}C NMR ($CDCl_3$, selected data for minor diastereoisomer): δ 173.8, 173.9 (each s, C=O), 159.1, (s, aromatic C) 130.5, 129.1, 123.6, 118.0 (each d, aromatic CH), 102.3 (d, C-1), 85.9, 81.8, 75.1 (each d), 76.2 (t), 61.1 (d), 60.3 (q), 41.1 (t); IR (KBr): 3330, 2924, 2859, 1655, 1565, 1497, 1233, 1104, 1077, 766, 567 cm^{-1}. HRMS-CI: Found 501.2600, required 501.2601; $[M+H]^+$.

4.1.26. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-propyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 31c. Azide **30c** (0.178 g, 0.31 mmol) was treated as described for **30a** and gave the title compound **31c** (50 mg, 23%, clear syrup); $[\alpha]_D=-7.2$ (*c* 0.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–6.96 (m, 10H, aromatic H), 6.37 (d, 1H, $J=8.8$ Hz, N*H*, minor diastereoisomer), 6.22 (d, 1H, $J=8.6$ Hz, N*H*, major diastereoisomer), 6.20 (t, 1H, $J=5.5$ Hz, NH), 5.05 and 5.01 (2d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.91 (s, 2H, OCH_2Ph), 4.20 (t, 1H, $J=6.5$ Hz, $CHCH(Me)_2$), 3.97 (t, 1H, $J=8.7$ Hz), 3.84 (ddd, 1H, $J=2.9$, 5.8, −13.6 Hz, H-6a), 3.29–3.72 (m, 3H), 3.24 (t, $J=9.0$ Hz, 1H), 2.06 (m, 1H), 1.98 (s, 3H), 1.55 (m, 2H), 0.87–1.15 (m, 30H); ^{13}C NMR ($CDCl_3$): 171.2, 170.1 (each s, C=O), 156.1, 138.7 (each s, aromatic C), 129.6, 128.1, 127.3, 127.0, 122.3, 115.3 (each d, aromatic CH), 99.2 (d, C-1), 85.8, 79.9 (each d), 75.2 (t), 74.9 (d), 74.8 (t), 74.0, 73.6 (d), 58.6 (t, C-6), 40.2 (t), 31.1, 23.5, 23.1, 19.1, 18.1, 18.0, 13.1, 10.4; IR (film on NaCl); 3286, 2962, 1642, 1547, 1370, 1231, 1092 cm^{-1}; HRMS-FAB: Found 707.4062, required 707.4068 $[M+Na]^+$.

4.1.27. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-propyl-β-D-glucopyranoside 4c. Glucoside **31c** (0.11g, 0.16 mmol) was treated as described for **31a** to give the title compound **4c** (37 mg, 44%, white solid); $[\alpha]_D=-22.5$ (*c* 0.18, MeOH); ^1H NMR (500 MHz, CD_3OD): δ 7.41–6.98 (m, 10H, aromatic H), 4.90 (AB d, 2H, $J=-11.0$ Hz, OCH_2Ph), 4.92 (d, 1H, $J_{1,2}=7.2$ Hz, H-1), 4.15 (d, 1H, $J=6.8$ Hz), 3.51–3.80 (m, 5H), 3.16 (t, 1H, $J=8.6$ Hz), 2.15 (m, 1H), 1.98 (s, 3H), 1.54 (m, 2H), 0.92–0.87 (m, 6H); ^{13}C NMR (CD_3OD, major diastereoisomer): δ 173.9, 173.4 (each s, C=O), 159.2, 140.3 (each s, aromatic C) 130.6, 129.3, 128.9, 128.6, 123.5, 117.7 (each d, aromatic CH), 101.95 (d, C-1), 76.3 (t), 76.25 (t), 86.1, 80.4, 75.8, 75.5, 74.9, 60.6 (each d), 41.2 (t), 31.8, 24.6, 22.4, 19.8, 10.9; ^{13}C NMR (CD_3OD, selected data for minor diastereoisomer): δ 173.8, 173.3 (each s, C=O), 159.2, 140.3 (each s, each aromatic C) 130.5, 129.3, 128.9, 128.5, 123.6, 118.0 (each d, each aromatic CH), 102.3 (d, C-1), 86.0, 80.2, 75.8, 75.5, 75.2, 60.3 (each d), 41.1 (t, C-6), 30.8, 24.6, 19.8, 11.0; HRMS-CI: Found 529.2917, required 529.2914; $[M+H]^+$.

4.1.28. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-isobutyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 31d. Azide **30d** (0.137 g, 0.23 mmol) was treated as described for **30a** and gave the title compound **31d** (60 mg, 38%, white solid); $[\alpha]_D=-15$ (*c* 0.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–6.90 (m, 10H, aromatic H), 6.37 (d, 1H, $J=8.7$ Hz, NH, minor

diastereoisomer), 6.25 (d, 1H, J=8.7 Hz, NH, major diastereoisomer), 5.50 (t, 1H, J=5.5 Hz, NH), 5.00 and 5.03 (each d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.88 (s, 2H, OCH_2Ph), 4.16 (2d, 1H, J=6.4 Hz), 3.94 (t, 1H, J=7.8 Hz), 3.86 (ddd, 1H, J=2.8, 6.1, −13.5 Hz, H-6a), 3.17–3.59 (m, 5H), 1.96 (s, 3H), 1.78 (m, 1H), 0.86–1.08 (m, 33H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.5, 170.1 (each s, *C*=*O*), 156.2, 138.8 (each s, aromatic C), 129.7, 128.2, 127.3, 127.1, 127.0, 122.3 (each d, aromatic CH), 115.7, 115.4 (each d), 99.6 (d, C-1), 85.8 (d), 80.0 (t), 79.9 (d), 75.1 (t), 73.7, 58.6 (each d), 40.2 (t), 31.2, 29.1, 23.2, 19.4, 19.2, 19.1, 18.2, 18.1, 13.2; HRMS-FAB: Found 721.4224, required 721.4224; $[M+Na]^+$.

4.1.29. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-isobutyl-β-D-glucopyranoside 4d. Glucoside **31e** (60 mg, 0.086 mmol) was treated as described for **31a** to give the title compound **4e** (39 mg, 83%, white solid); mp: 209–210 °C; $[\alpha]_D$=−17.1 (*c* 0.24, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 7.41–7.0 (m, 10H, aromatic H), 4.89 (AB d, 2H, J=−10.9 Hz, OCH_2Ph), 4.93 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.14 and 4.16 (each d, 1H, J=6.8 Hz), 3.48–3.70 (m, 8H), 1.82 (m, 1H), 1.99 (s, 3H), 0.90–0.89 (m, 6H); ^{13}C NMR (CD_3OD, major diastereoisomer): δ 172.5, 170.0 (each s, C=O), 155.9, 138.4 (each s, aromatic C) 129.2, 129.1, 127.9, 127.5, 122.0, 116.3 (each d, aromatic C), 100.5 (d, C-1), 84.8, 78.9, 74.1, 73.5 (each d, C-2-5), 79.4 (t), 74.8 (t), 59.2 (d), 39.8 (t), 30.4, 28.9, 21.1, 18.4, 18.3, 17.1; ^{13}C NMR (CD_3OD, selected data for minor diastereoisomer): δ 116.6 (d, aromatic C), 101.0 (d, C-1); IR (film on NaCl); 3300, 2957, 2430, 1637, 1544, 1495, 1370, 1235, 1066, 751, 698 cm^{-1}; HRMS-Cl: Found 543.3075, required 543.3072; $[M+H]^+$

4.1.30. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3,4-di-*O*-benzyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 31e. Glucoside **30e** (0.21 g, 0.33 mmol) was treated as described for **30a** to give the title compound **31e** (78 mg, 31%, clear syrup); $[\alpha]_D$=−4.0 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–6.93 (m, 15H, aromatic H), 6.37 (d, J=8.7 Hz, NH, minor diastereoisomer), 6.28 (d, 1H, J=8.7 Hz, NH, major diastereoisomer), 6.22 (t, 1H, J=5.5 Hz), 5.04 (d, 1H, $J_{1,2}$=7.4 Hz, H-1), 4.92 (AB d, 2H, J=−11.5 Hz, OCH_2Ph), 4.66 (AB d, 2H, J=−10.6 Hz, OCH_2Ph), 4.10–4.20 (m, 2H); 4.04 and 4.05 (each t, 1H, J=7.5 Hz), 3.32–3.80 (m, 3H), 3.46 (t, 1H, J=9.1 Hz), 2.03 (m, 1H), 1.95 (s, 3H), 0.85–1.09 (m, 27H); ^{13}C NMR ($CDCl_3$): 171.3, 170.1 (each s, C=O), 156.0, 138.5, 137.6 (each s, aromatic C), 129.6, 128.4, 128.0, 127.9, 127.3, 126.99, 126.9 122.3, 115.3 (each d, aromatic C), 99.2 (d, C-1), 85.9, 79.3 (each d), 75.3 (t), 75.1 (d), 74.9 (t), 73.3, 58.6 (each d), 40.0 (t, C-6), 31.1, 23.1, 19.2, 18.3, 18.0, 13.1; HRMS-FAB: Found 755.4065, required 755.4068; $[M+Na]^+$.

4.1.31. Phenyl 6-(*N*-acetylvalinyl)amino-6-deoxy-3, 4-*O*-benzyl-β-D-glucopyranoside 4e. Valine derivative **31e** (66 mg, 0.1 mmol) was treated as described for **31a** to give **4e** (40 mg, 77%, white solid); $[\alpha]_D$=−2.7 (*c* 0.15, CH_3CN); ^{1}H NMR (500 MHz, CD_3OD): δ 7.40–6.98 (m, 15H, aromatic H), 4.88 (AB d, 2H, J=−11.0 Hz, OCH_2Ph), 4.80 (d, 1H, $J_{1,2}$=7.6 Hz, H-1, overlapping with HOD), 4.16 (d, 1H, J=6.88 Hz), 3.32–3.72 (m, 8H), 2.02 (m, 1H), 1.96 (s, 1H), 0.93 (m, 6H); ^{13}C NMR (CD_3OD, major diastereoisomer): δ 174.0, 173.5 (each s, C=O), 159.2, 140.2, 139. 8 (each s, aromatic C) 130.6, 129.4, 129.3 (2s), 129.2, 129.1, 128.8, 123.5, 117.7 (each d, aromatic CH), 102.0 (d, C-1), 86.3 (d), 79.9, 76.3 (t) 74.8 76.0, 75.7, 74.8, 60.7 (each d), 41.1 (t), 31.8, 22.5, 19.9, 18.6; ^{13}C NMR (CD_3OD, selected data for minor diastereoisomer): δ 173.9, 173.3 (each s, C=O), 159.1, 140.3, 139.7 (each s, aromatic C) 130.7, 130.6, 129.4, 129.22, 129.2, 129.1, 128.7, 123.7, 118.0 (each d, aromatic CH), 102.4 (d, C-1), 86.2 (d), 79.6, 76.3 (each t), 75.9, 75.7, 75.1, 60.4 (each d), 41.1 (t, C-6), 22.5, 19.8; IR (film on NaCl); 3304, 2945, 1641, 1545, 1496, 1384, 1232, 1059.4 cm^{-1}; HRMS-Cl: Found 577.2916, required 577.2914; $[M+H]^+$.

4.1.32. Phenyl 6-(*N*-tert-butoxycarbonylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-methyl-2-*O*-triisopropylsilyl-β-D-glucopyranoside 32. Azide **30b** (0.13 g, 0.24 mmol) was dissolved in EtOH:EtOAc (5:3, 9 mL) and Lindlar catalyst (0.22 g) was added and the suspension was stirred under hydrogen (1 atm) for 6 h, then filtered and solvent removed. The residue was dissolved in dichloromethane and added to a mixture of BocVal–OH (14 mg, 0.063 mmol), HOBT (9 mg, 0.07 mmol), HBTU (26 mg, 0.07 mmol) and DIPEA (16 mg, 0.12 mmol) which had been stirred for 5 min in dichloromethane (12 mL) at rt. The reaction was judged complete by TLC analysis after 0.5 h and the title compound (31 mg, 18%, white solid) as obtained after chromatography of the residue; $[\alpha]_D$=−25.2 (*c* 0.29, $CHCl_3$); mp: 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–6.9 (m, 10H, aromatic H), 6.17 (broad s, 1H, NH), 5.00 (d, 1H, $J_{1,2}$=7.3 Hz, H-1), 4.95–5.0 (broad s, 1H, NH); 4.83 (d, 2H, J=−11.3 Hz, OCH_2Ph), 3.93 (t, 1H, J=8.3 Hz), 3.74–3.88 (m, 2H) 3.42–3.56 (m), 3.48 (s, 3H), 3.13 (t, 1H, J=9.1 Hz), 2.07 (m, 1H), 1.43 (s, 9H), 1.15–0.98 (m, 21H, TIPS), 0.84 and 0.89 (2 d, J=6.8 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 171.5 (s, C=O), 156.3, 138.8 (each s, aromatic C), 129.7, 128.2, 127.4, 127.2, 122.4, 115.6, (each d, aromatic CH), 99.6 (d, C-1), 85.8, 81.6 (each d), 77.5 (t, *C*H$_2$Ph), 77.1, 76.7, 75.3, 75.0, 73.7, 60.9 (each d), 40.0 (t, C-6), 30.9, 29.7, 28.4, 19.3, 17.6, 18.2, 18.1, 13.6; IR (film on NaCl); 3420, 2941, 1655, 1495, 1355, 1233, 1067, 884 cm^{-1}; HRMS-FAB: Found 737.4169, required 737.4173; $[M+Na]^+$. Anal. Calcd for $C_{39}H_{62}N_2O_8Si$: C, 65.51; H, 8.74; N, 3.92; Found: C, 65.28; H, 8.81; N, 3.63.

4.1.33. Phenyl 6-(*N*-tert-butoxycarbonylvalinyl)amino-6-deoxy-3-*O*-benzyl-4-*O*-methyl-2-β-D-glucopyranoside 33. TIPS protected **32** (25 mg, 0.035 mmol) was dissolved in anhyd. THF (2 mL) and cooled to 0 °C. Tetrabutylammonium fluoride (18 mg, 0.07 mmol) was added and the solution was stirred for 30 min. The solvent was then removed and purified by chromatography to give the title compound **33** (13 mg, 66%, white solid): $[\alpha]_D$=−40 (*c* 0.085, CD_3OD); ^{1}H NMR (500 MHz, CD_3OD): δ 7.80 (1H, broad s), 7.43–6.97 (m, 10H, aromatic H), 6.51 (d, 1H, J=7.7 Hz), 4.88 (AB d, 2H, J=−11.0 Hz, OCH_2Ph), 5.00 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 3.86 (t, 1H, J=7.8 Hz), 3.54 (s, 3H, OMe), 3.45–3.60 (m, 4H), 3.09 (t, 1H, J=8.8 Hz), 2.06 (m, 1H), 1.45 (s, 9H), 0.9–0.85 (2d, 6H, J=6.8 Hz, CH(Me)$_2$); ^{13}C NMR (CD_3OD): δ 178.0, 173.4 (each s, C=O), 157.6, 138.9 (each s, aromatic C) 129.2, 127.9, 127.6, 127.2, 122.0, 116.3 (each d, aromatic CH), 100.5 (d,

C-1), 84.7, 80.4 (each d), 74.8 (t), 74.1, 73.3, 59.8, 48.5 (d), 46.8 (q), 39.5 (t), 29.4, 27.4, 18.5, 16.9, 19.8, 18.5; IR (film between NaCl plates); 3335, 2927, 2480, 1681, 1650, 1496, 1420, 1238, 1172, 1087, 762, 622 cm^{-1}; HRMS−Cl: Found 559.3024, required 559.3020; $[M+H]^+$.

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Novel nicotinamide adenine dinucleotide analogues as selective inhibitors of NAD+-dependent enzymes

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Abstract—Three novel dinucleotide analogues of nicotinamide adenine dinucleotide (NAD^+) have been synthesised from D-ribonolactone. These compounds incorporate a thiophene moiety in place of nicotinamide and are hydrolytically stable. They have been evaluated as inhibitors of adenosine diphosphate ribosyl cyclase, glutamate dehydrogenase and Sir2 acyltransferase activities. Enzyme specificity and a high level of inhibition was observed for the dehydrogenase.

1. Introduction

C-nucleoside analogues of ribosyl nicotinamide (Fig. 1) have been widely studied and some are currently in clinical trials.[1] They are endowed with several biological effects ranging from anti-tumour activities to inhibition of G-protein mediated cellular mechanisms.[2–4] Some of these effects have been directly related to the capacity of their adenine dinucleotide derivatives at inhibiting inosine monophosphate dehydrogenase.[2,5,6] Yet, C-nucleosides, such as ribosyl benzamide and tiazofurin (Fig. 1) can be inhibitors of other nicotinamide adenine dinucleotide (NAD^+) dependent enzymes, such as oxidoreductases, glycohydrolases and transferases, after their conversion to dinucleotide cofactor analogues. For instance, BAD, the NAD^+ analogue incorporating benzamide is a potent inhibitor of adenosine diphosphate (ADP) ribosyl cyclase, an important regulatory enzyme involved in the production of a modulator of Ca^{2+} concentration in cells.[7] Consequently, whilst most of these compounds act as potent anti-tumour agents by shutting down the guanosine monophosphate synthesis, they are also highly toxic to healthy cells.

Thiophenfurin, the thiophene homologue of ribosyl nicotinamide, was shown to possess good selectivity towards tumour cells in vitro and high-level of conversion to its dinucleotide form. Yet, in vivo, this derivative was found to be toxic.[8] Unspecific enzyme inhibition and metabolic modifications of thiophenfurin might be responsible for such an outcome.

Consequently, in order to optimise enzyme and cell selectivity and maintain high levels of inhibition, novel C-nucleosides that possess particular structural features for specific recognition are required. Many dinucleotide-binding enzymes bind NAD^+ via a fold consisting of two mononucleotide-binding motifs.[9] When one considers the

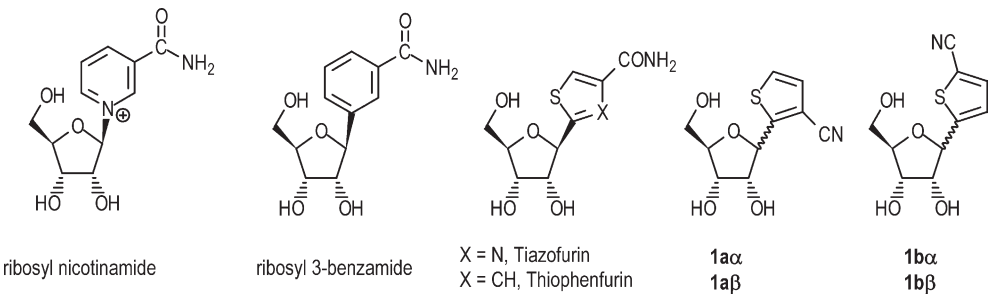

Figure 1. Ribosyl nicotinamide and analogues.

Keywords: C-nucleosides; Dinucleotides; NAD^+ analogues.
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structural features of all the ribosyl nicotinamide analogues synthesised thus far, one notices that the amide moiety is a conserved functionality. Indeed, based on the available crystallographic data of enzymes co-crystallised with C-NAD^+ analogues, the amide moiety is involved in important hydrogen bonding interactions, acting as a hydrogen bond donor.[10–13] Consequently, a slight modification of this important structural feature might result in an abolition of binding when such interaction accounts for much of the recognition and stabilisation of the inhibitor–enzyme complexes. Meanwhile, such modification might provide the means to improve selectivity. We aim to establish whether selective enzymatic recognition can be observed amongst different classes of NAD^+-dependent enzymes by exchanging the amide moiety for an isoelectronic group capable of hydrogen bond interactions. As such, a nitrile group can be viewed as an isosteric group to an amide, capable of engaging in hydrogen bond interactions with an enzyme-binding pocket as a hydrogen-bond acceptor. To the best of our knowledge, there are no nitrile containing C-nucleosides, analogues of ribosyl nicotinamide thus far reported in the literature. Considering the good selectivity for tumour cells showed by thiophenfurin and the possibility of improving upon enzyme specificity by modifying the amide moiety, we have synthesised four novel C-nucleoside analogues (**1aα/β** and **1bα/β**) that incorporate a thiophene residue substituted by a nitrile group (Fig. 1). Three of these C-nucleosides have been converted to their dinucleotide parents and evaluated against three NAD^+-dependent enzymes that catalyse different types of reaction.

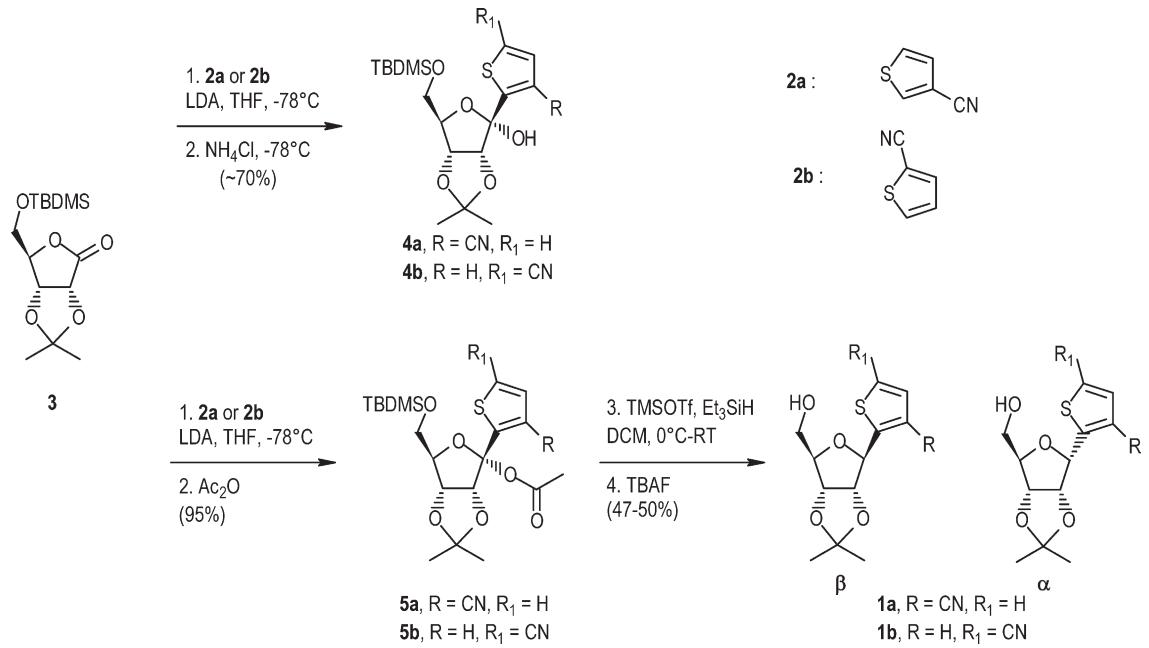
2. Results and discussion

2.1. Chemistry

Franchetti et al. have reported the synthesis of 2-(α/β)-D-ribofuranosylthiophene-3-carboxamide and 5-(α/β)-D-ribofuranosylthiophene-3-carboxamide using classical Friedel–Crafts' conditions starting with the tetraacetate ribofuranose and the appropriate ethyl thiophene carboxylates.[8] When applied to carbonitrile thiophenes, this method failed to yield any C-glycosylation product. Attempts to introduce any other types of thiophenes, including the ethyl thiophene carboxylate employed by Franchetti and thiophene itself, either led to no product formation or polymerised unidentifiable material.

Consequently, the addition of the lithiated derivatives of thiophenes **2a** and **2b** to the easily accessible 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-D-ribono-1,4-lactone **3**,[14] followed by removal of the hydroxyl group in position 1′ of lactol **4** was employed.[15,16] (Scheme 1) The thiophene-3 (and -2)-carbonitrile **2a** (and **2b**), treated with LDA in THF, were reacted with lactone **3** for 30 min at −78 °C to form the lactol. Quenching of the reaction at −78 °C by addition of a solution of saturated NH_4Cl allowed the isolation of the hemiketals **4a** and **4b** as single isomers. Allowing the reaction to warm up or increasing the reaction time led to the opening of the sugar rings to form the ketones. The ketones were easily identified by ^1H NMR; for instance, δH-4′ shifted from 4.46 ppm of **4b** to 3.70 ppm in the ketone. A shift of the thiophene protons was also observed; δH-3 and δH-4 were 7.47 and 7.10 ppm for **4b**, respectively and 7.94 and 7.57 ppm for the corresponding ketone. This observation is in agreement with the strong deshielding effect a carbonyl has on aromatic protons. While combinations of silane and Lewis acids are known to reduce hemiketals, attempts to carry out direct dehydroxylation of **4a** and **4b** were unsuccessful. The chemical instability of similar carbohydrates towards such reaction conditions had been previously observed.[16,17]

Townsend had reported a procedure involving an acetylated hemiketal intermediate prepared in situ by trapping of the



Scheme 1. Synthesis of carbonitrile thiophene C-nucleoside analogues.

alkoxide, addition product of the lithiated aryl onto the lactone, with acetic anhydride at −70 °C.[18] This two-step reaction yielded the acetylated hemiketals **5a** and **5b**, quantitatively. It should be noticed that unlike previously reported, only one single 'anomer' was formed. Attempts to identify the stereochemistry at C-1′ either by ^{1}H NMR and proton-proton nuclear Overhauser effect (NOE) difference experiments or by crystallographic analyses were unsuccessful. Therefore, the assignments of the anomeric configurations were based on the ^{1}H NMR-$\Delta\delta$ values of the isopropylidene methyl groups.[19] $\Delta\delta$ values superior to 0.20 ppm indicate that the acetate group is *cis* to the isopropylidene moiety.

The formation and isolation of a single isomer whether the arylation reaction is quenched with NH_4Cl or Ac_2O at low temperature is at odds with the results reported by Townsend[18] and by Dondoni.[16] Yet, Benhinda recognised that the condensation step was very sensitive to steric factors imposed by the incoming nucleophile,[17] which could explain the results described by Townsend. However, the nucleophile employed in the study by Dondoni, a thiazolyl anion, is isosteric to the thiophene-3 (and -2) -carbonitrile **2a** (and **2b**) used in the present study. When the tribenzylated ribonolactone was used instead of **3**, no addition product could be detected. Consequently, activation of the lactone and α-configuration of the product could be attributed to a complexation of the lactone oxygen atoms at position 1 and 2 by the lithium cation, thus puckering the ribonolactone ring such that only an axial nucleophilic attack can be favoured. In addition, it is expected that steric effects due to the isopropylidene substituent would direct the attack of the nucleophile to the less hindered face of the lactone. When 5-*O*-TBDPS-2,3-*O*,*O*-isopropylidene ribonolactone was used instead of **3**, the two anomers α and β were identified by ^{1}H NMR (2:1 ratio). Yet no ring-open form could be detected when the reaction was quenched with Ac_2O at low temperature, indicating that the two stereoisomers were addition but not rearrangement products. Such explanation should tally with Dondoni's results when thiazole was used as nucleophile, yet it did not, as Dondoni observed the formation of opened compounds. The electronic effect of the nucleophile must therefore be considered.

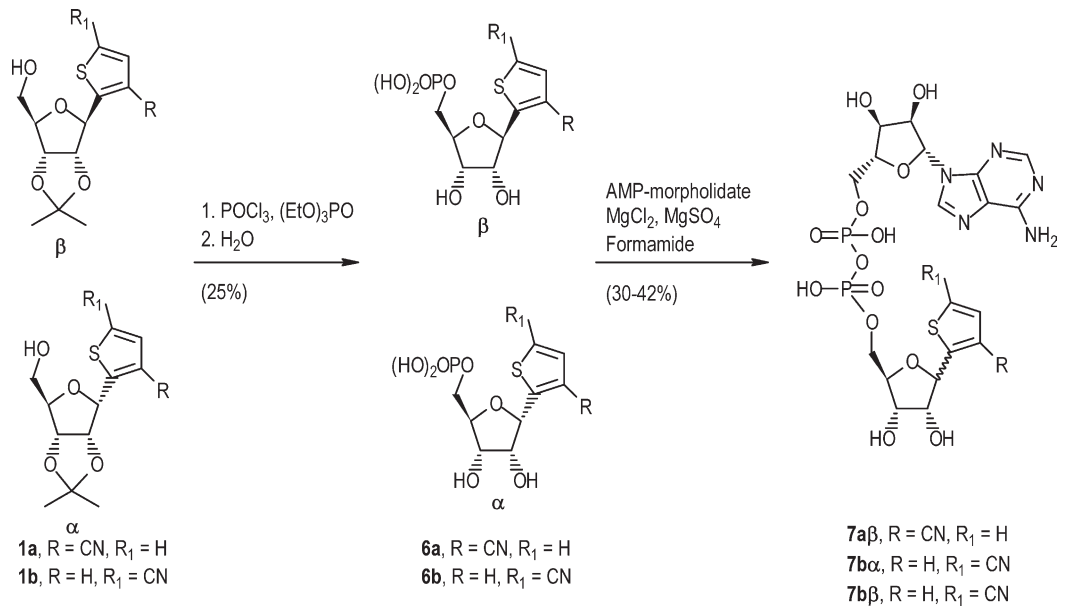
Since the thiophene-3 (and -2)-carbonitrile **2a** (and **2b**), both yield a single anomeric adduct product when reacted with **3**, it is highly probable that both reagents yield the kinetic addition products, which are also the most thermodynamically stable compounds under the reaction conditions. Compared with carbonitrile thiophenene, thiazole is a more electron-deficient aromatic. The formation of the thermodynamic product enol–ether intermediate in the α/β-rearrangement of the glycosylation product, obtained by addition of the lithiothiazole on **3**, might result from such a chemical characteristic. Such an enol is stabilised through conjugation between the thiazolyl substituent and the enol double bond.[16] Carbonitrile thiophenyl substituents, on the other hand, are sufficiently stable to not require extra conjugation that entails ring opening and electron delocalisation between the ketone and the thiophene ring. Indeed, no enol acetate was ever detected during this investigation. Consequently, in order to correlate the present results observed during the nucleophilic addition on lactone **3** to the literature precedents, one must consider the combination of effects due to the steric bulk of the nucleophile, the steric bulk of the 5′-substituent on the lactone, the activation of the lactone through complexation and finally the electronic nature of the nucleophile.

The subsequent removal of the acetoxy residue under Lewis acid conditions was optimised when TMSOTf and Et_3SiH in DCM were used in excess and the reaction was carried out over 30 min. Partial desilylation was detected and, consequently, after addition of triethylamine, TBAF was added to yield the desilylated C-nucleosides **1aα/β** and **1bα/β**. The C-nucleosides **1** were recovered in moderate yields (47–50%) after purification as the α and β isomers. The α/β ratio was always found to be in favour of the α isomer at 1.4/1 when TBDMS was used as protecting group at C-5′. The yields for this reaction were also slightly low when compared with those reported in the literature for similar C-glycosides.[15,17] The α and β anomers were identified by ^{1}H NMR NOE experiments as the anomeric protons were distinctively deshielded (δ=5.65 ppm for **1aα** versus δ=5.20 ppm for **1aβ**). When selectively irradiated, the signal of the α anomer **1aα** H-1′ gives an intensity enhancement of the H-2′ and H-3′ signals. The glycosylation position was determined by ^{1}H NMR. The NMR pattern for the aromatic protons of **1a**, a doublet, confirms the position of glycosylation of the thiophene at C-2. When the H-1′ signal of **1b** was irradiated, an NOE effect was observed at H-3.

Various conditions have been tried in order to increase yields and selectivity. Alternative Lewis acids, solvent and reducing reagents were considered, yet TMSOTf/Et_3SiH remained the only suitable combination. Competitive desilylation and removal of the isopropylidene group were thought to take place when $BF_3{\cdot}Et_2O$ was used as Lewis acid. Unidentifiable material was formed when DIBAH was used in combination with $AlCl_3$, while no reaction occurred with $Y(OTf)_3$. Finally, $SnCl_4$ yielded only the α-anomer products in poor yields. Optimised conditions were found to be 5 equiv. of Et_3SiH, 2.5 equiv. of TMSOTf in DCM starting the reaction at 0 °C and warming up to room temperature (Scheme 2).

The phosphorylation reaction of the C-nucleosides **1aα/β** and **1bα/β** was carried out following the Yoshikawa procedure,[7] this employing triethyl phosphate as solvent and activator. Addition of $POCl_3$ was done at room temperature and the reaction was monitored by HPLC (SAX column, $K_2HPO_4{\cdot}$50 mM, 5% MeOH, pH 3.5). Once the reaction complete, the excess of $POCl_3$ is quenched by addition of water. This resulted in the simultaneous removal of the isopropylidene group. Purifications of the C-nucleotides were achieved on AG-MP1 anion exchange resin using a gradient of TFA with an average recovery of 25%. The purification was not optimised.

The diphosphate linkage formation between **6aβ** and **6bα/β** and adenosine monophosphate employed the commercially available adenosine 5′-monophosphomorpholidate (4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt).[20] The reaction was carried out in 4 days in a 0.2 M solution of $MnCl_2$ in formamide in presence $MgSO_4$ and was



Scheme 2. Dinucleotide analogues synthesis.

monitored by HPLC (SAX column, K_2HPO_4 50 mM, 5% MeOH, pH 3.5). Purifications of the three dinucleotides **7aβ** and **7bα** and **7bβ** were carried out on DEAE sepharose columns with a triethylammonium formate gradient. The isolated yields ranged from 30 to 42% after purification as calculated by phosphorus titration using Ames' assay.[21]

2.2. Enzyme inhibition

Franchetti has carried out extensive crystallography and computational studies on furafurin and thiophenfurin.[8] In his study, he observed that the S-atom remained *cis* to the furanose-oxygen and ab initio calculations suggested that this conformation was stabilised by an electrostatic interaction between a positively charged thiophene sulfur and a negatively charged furanose oxygen. Therefore, based on these observations, we could assume similar restricted rotation around the C-glycosidic bond of **7aβ** and **7bβ**. With such assumption, none of the C-dinucleotides are expected to bind like NAD^+ since the carbonitrile substituent will not be in an appropriate position to share hydrogen-bonding interactions with the amino acid residues that are involved in bonding interactions with the amide moiety of nicotinamide in NAD^+. Yet, the following results describe the effect of each of these C-NAD^+ analogues on three enzymes, each of which catalyses a distinct chemical reaction and each known to bind NAD^+ via a slightly different pattern.

2.2.1. Adenosine diphosphate ribosyl cyclase. Based on crystallographic data, this enzyme was thought to bind NAD^+ via the two nucleoside moieties (i.e., adenosine and ribosyl nicotinamide) with little binding stabilisation involving the pyrophosphate linkage.[22,23] Indeed this assumption was further supported by the fact that the cyclase catalyses the cyclisation of an NAD^+ derivative for which the pyrophosphate group was partially protected with *o*-nitro-phenol moieties.[24] Furthermore, nicotinamide mononucleotide (NMN) is a known potent inhibitor of the cyclase, while adenosine monophosphate is not.[12] This observation indicated that the initial recognition and binding of NAD^+ must occur at the northern ribose (NMN-end of NAD^+). Co-crystallisation of the cyclase with nicotinamide indicated strong hydrogen-bonding interaction between the amide moiety of nicotinamide and polar residues present in the binding pocket. As could be anticipated, when the three carbonitrile thiophene adenine dinucleotides **7aβ**, **7bα** and **7bβ** were evaluated against *Aplysia* ADP ribosyl cyclase in the presence of NAD^+ (data not shown), none of them was found to be an inhibitor. When high concentrations of C-dinucleotides were used (c.a. 500 μM, K_{mNAD}~ 120 μM), activation of the cyclase was clearly detected (data not shown). While such activation has never been reported for the *Aplysia Californica* cyclase, the human homologue, CD38, has been shown to be modulated by nucleotides such as GTP and ATP.[25,26] It is possible that at high concentration of C-dinucleotides, *Aplysia* cyclase is itself allosterically modulated.

2.2.2. Glutamate dehydrogenase. In the case of glutamate dehydrogenase (GDH) from *C. symbiosum*, NAD^+ is the co-factor which allows the oxidative deamination of L-glutamate to obtain the corresponding 2-oxo-glutarate. Baker et al.[27] showed that 'the dinucleotide is bound in an extended conformation with the nicotinamide moiety deep in the cleft between the two domains' of GDH. In this case, the NH_2 group of the nicotinamide in the *syn* conformation is involved in a hydrogen bond with the oxygen of the asparagine in position 240, while the hydroxyl group of threonine 209 interacts with the CO of the same nicotinamide moiety. On the other side, the enzyme provides a pocket for the adenine ring and several amino acids are involved in the stabilization of the ribose and the phosphate groups. These characteristics appear to be conserved in all the hexameric GDH sequences.

An initial screening of compounds **7aβ**, **7bα** and **7bβ** was performed in presence of a standard concentration of NAD^+ (1 mM) and L-glutamate (40 mM)[28] and showed the strongest inhibition effect for **7bβ** as reported in Figure 2.

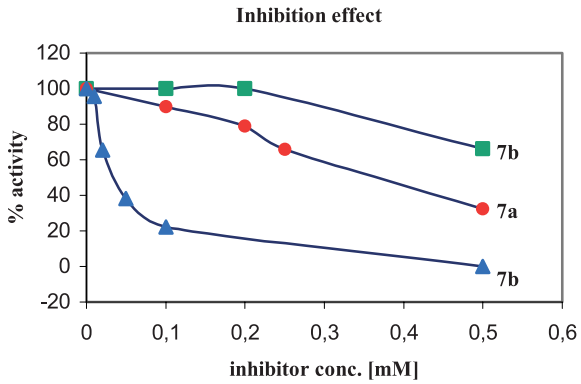


Figure 2. Effect of **7aβ**, **7bβ**, **7bα** on the specific activity (reported as 100% without inhibitor) of GDH.

Despite the fact that the concentration of 1 mM NAD^+ is ~10 fold the K_m, 0.5 mM of **7bβ** inhibited the activity of the enzyme almost completely. In marked contrast, **7bα** had very little effect.

A more detailed experiment was carried out with compound **7bβ** to define its K_i. In this case, the concentration of NAD^+ in solution was varied from 100 to 500 μM and for each concentration of NAD^+ a set of five concentrations of the inhibitor (0.1–5 μM) was tested. The reactions were performed at 25 °C in phosphate buffer 0.1 M at pH 7.0, and the activity was measured by following the formation of NADH at 340 nm (UV Spec, Cary 50). The results are shown in Figure 3.

From each experiment, a K_m value was calculated and plotted versus the concentration of the inhibitor in Figure 3 to obtain the inhibition constant K_i measured as the negative abscissa intercept (Fig. 4).

This elaboration yielded a K_i=1.09 μM for **7bβ**, confirming the strong inhibition effect produced by this NAD^+ analogue. From the observation of the V_{max} in Figure 2, we can also conclude that **7bβ** is a predominantly competitive inhibitor.

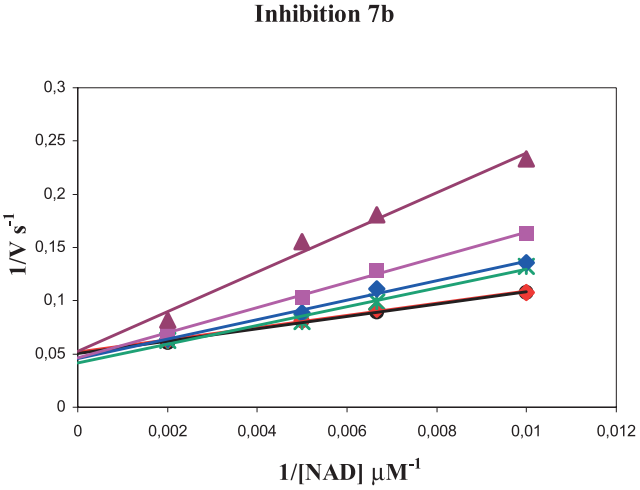


Figure 3. Lineweaver–Burk plot of the inhibition effect of **7bβ** on the GDH reaction. The inhibitor concentrations were 5 μM (▲), 1 μM (■), 0.5 μM (◆), 0.25 μM (✳), 0.1 μM (◆), and 0 μM (●).

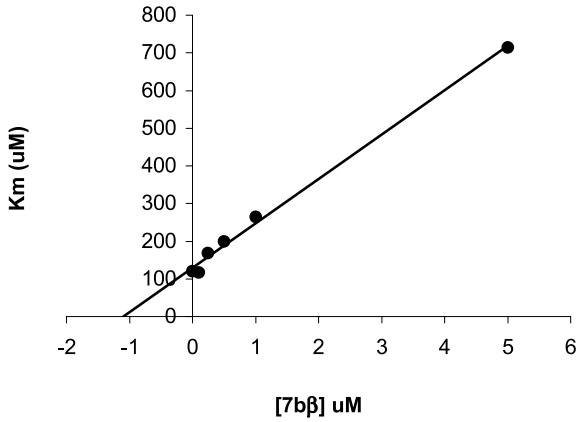


Figure 4. K_ms of **7bβ** obtained for different concentrations of the substrate.

2.2.3. Histone deacetylase, Sir2. Sir2 histone deacetylase has recently come under scrutiny when it was discovered that unlike most histone deactylase, it was an NAD^+ dependent enzyme.[29] The nature of the product of the reaction (1′-*O*-Ac- vs 2′-*O*-Ac-ADP) and the mechanism by which the products are formed are still controversial and under investigation. The assay methods currently available are also limited and while chromatographic analyses developed for the kinetic evaluations of *Aplysia* cyclase were initially deemed appropriate, the results obtained were inconsistent and no conclusive results could be drawn with regards to the effect of these dinucleotides on this deacetylase. We are currently optimising methods to assay for deacetylase activity more reliably.

3. Conclusion

Both β-NAD^+ analogues were selective inhibitors of the dehydrogenase, yet potency was dependent of the substitution pattern on the thiophene ring. Potent inhibition was obtained when the thiophene carbonitrile group could act as a hydrogen bond acceptor. To position the nitrile group and achieve appropriate binding, the electrostatic interactions between the positively charged thiophene sulfur and the negatively charged furanose oxygen must have been compensated for. One can therefore anticipate that a carbonitrile-benzene derivative will achieve similar interaction with the dehydrogenase-binding pocket and display better inhibition due to the improved overall stabilisation. We are currently synthesising such carbonitrile-containing NAD^+ analogues to establish whether improved selectivity compared to that of the benzamide derivatives and potency compared to that of the thiophene series described here could be observed.

4. Experimental

4.1. Generalities

Chemicals were purchased from Sigma-Aldrich Chemical Company, Lancaster or ACROS. Solvents for extractions and chromatography were technical grade. Solvents used in reactions were freshly distilled from appropriated drying agents before use. All other reagents were recrystallised or

distilled as necessary. All reactions requiring anhydrous or inert conditions were carried out in oven-dried glassware under a positive atmosphere of argon. Solutions or liquids were introduced using oven dried syringes or cannula through rubber septa. All reactions were stirred magnetically using Teflon-coated stirs bars. In the cases requiring −78 °C cooling, the reactions were chilled with a dry ice/acetone bath. Removal of solvents was accomplished using a rotary evaporator at water aspirator pressure or under high vacuum (0.5 mm Hg). Analytical TLC was performed with Merck Silica gel 60 F_{254} plates. Visualisation was accomplished by UV-light (λ=254 nm) and/or staining with an anisaldehyde solution, followed by heating. Column chromatography were carried out using Fluorochem Silica gel 40−63 μm, 60 Å. HPLC monitoring was accomplished using a Supelcosil SAX1 (120 Å, 5 μm, 25 cm×4.6 mm) using a buffer KH_2PO_4 50 mM/MeOH 95/5, pH=3.5 at a flow rate of 1 mL/min. Purification of phosphate compounds were carried out as specified on BioRad AG®MP-1M resin (100–200 mesh, chloride form) or Amersham Biosciences DEAE Sepharose™ Fast Flow resin. ^{1}H, ^{13}C and 2D (H-COSY, HMQC) NMR spectra were all recorded on Brüker avance DPX 300 and Brüker avance DPX 500. Infrared spectra were recorded on a Perkin Elmer Spectrum RX 1 FT-IR System, using KBr discs. UV spectra were recorded using a Perkin Elmer Lambda 800 UV/Vis spectrometer. For known compounds, NMR data are compared to the one given in the literature. The names given between parenthesis use casual nomenclature.

4.2. Synthetic Procedures

5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-γ-ribonolactone 3.[14] *Method A*. γ-Ribonolactone (500 mg, 3.37 mmol) was suspended in 10 mL of acetone and 2,2-dimethoxypropane (0.83 mL, 13.49 mmol, 2 equiv.) and HCR-W2 H^+-Dowex resin (100 mg) were added. After stirring at room temperature for 4 h, the mixture was filtered and the resin rinsed with acetone. The filtrate was concentrated to give in a quantitative yield the intermediate as a white powder, which was used without further purification. δ ^{1}H ppm ($CDCl_3$, 500 MHz): 1.39 and 1.48 (s×2, 6H, $C(CH_3)_2$), 2.81 (br, 1H, 5-OH), 3.81 (bd, 1H, *J*=12.3 Hz, H-5a), 4.00 (bd, 1H, *J*=12.3 Hz, H-5b), 4.64 (t, 1H, *J*=1.9 Hz, H-4), 4.77 (d, 1H, *J*=5.6 Hz, H-3), 4.84 (d, 1H, *J*=5.7 Hz, H-2). δ ^{13}C ppm ($CDCl_3$, 75 MHz): 25.8 and 27.1 ($C(CH_3)_2$), 62.3 (C-5), 76.1, 78.7 (C-2,C-3), 83.2 (C-4), 113.5 ($C(CH_3)_2$), 175.5 (C=O-1). IR cm^{-1}(KBr): 3463 (OH), 2991, 2934 (CH), 1752 (C=O).

To a dry DCM solution (5 mL) of the partially protected lactone was added DMAP (41 mg, 0.34 mmol, 0.1 equiv.) and triethylamine (0.48 mL, 3.71 mmol, 1.1 equiv.). After cooling the solution to 0 °C, *tert*-butyldimethylsilyl chloride (560 mg, 3.71 mmol, 1.1 equiv.) was added. The mixture was stirred overnight under argon atmosphere. DCM (20 mL) was added to the solution and washed with a saturated solution of NH_4Cl then water. The resulting organic layer was dried over $MgSO_4$ and concentrated. The crude mixture is purified by silica gel column chromatography (PE/acetone 99/1) to give **3** as white crystals (688 mg, 68% over the two steps). **3**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 0.01 and 0.02 (s×2, 6H, $(CH_3)_2Si$), 0.84 (s, 9H, $(CH_3)_3CSi$), 1.35 and 1.42 (s×2, 6H, $C(CH_3)_2$), 3.74 (dd, 1H, *J*=11.3, 1.4 Hz, H-5a), 3.83 (dd, 1H, *J*=11.3, 2.1 Hz, H-5b), 4.55 (m, 1H, H-4), 4.65 and 4.67 (2×d, 2H, *J*=5.6, 5.6 Hz, H-2, H-3). δ ^{13}C ppm ($CDCl_3$, 75 MHz): −5.4 and −5.2 (($CH_3)_2Si$), 18.6 ($SiC(CH_3)_3$), 26.0, 26.1, 27.8 ($C(CH_3)_2$, $SiC(CH_3)_3$), 63.3 (C-5), 76.2, 78.8 (C-2, C-3), 82.6 (C-4), 113.4 ($C(CH_3)_2$), 174.5 (C=O-1). IR cm^{-1}(KBr): 2989, 2954, 2859 (CH), 1775 (C=O).

Method B. D-Ribose (5.0 g, 33.30 mmol) was suspended in acetone and 2,2-dimethoxypropane (8.2 mL, 66.60 mmol, 2 equiv.) followed by HCR-W2 H^+-Dowex resin, was added to the mixture. When the solution had become clear, the resin was filtered off and rinsed with acetone. After concentration, the crude yellow oil was dissolved in dry dichloromethane (15 mL) and DMAP (0.41 g, 3.33 mmol, 0.1 equiv.) and triethylamine (4.75 mL, 36.60 mmol, 1.1 equiv.) were added to the solution. After cooling the solution to 0 °C, *tert*butyldimethylsilyl chloride was added (5.52 g, 36.60 mmol, 1.1 equiv.) and the solution was stirred under argon atmosphere for 6 h. The mixture was then filtered over celite and washed with saturated aqueous NH_4Cl. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated and used without purification. The crude mixture was dissolved in 300 mL of acetone and 10.53 g (66.60 mmol, 2 equiv.) of potassium permanganate are added. The solution was stirred at 50 °C for 6 h. The mixture was filtered over celite and concentrated. The same purification as described previously yielded **3** (4.00 g, 40% over the three steps).

2,2-Dimethyl-4-(3-cyano-thiophen-2-yl)-6-hydroxymethyl-tetrahydro-furo[3,4-*a*][1,3]dioxole 1a. (2-(2′,3′-*O*,*O*-isopropylidene-1′-deoxyribofuranosyl)thiophene-3-carbonitrile).

Intermediate 4a. 6-(*tert*-Butyl-dimethyl-silanoxymethyl)-2,2-dimethyl-4-(3-cyano-thiophen-2-yl)-tetrahydro-furo[3,4-*a*][1,3]dioxol-4-ol. (5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-1-(2-thiophene-3-carbonitrile)-α-D-ribofuranose).

n-Butyl lithium (2 M solution in pentane) (1.25 mL, 2.42 mmol, 1.5 equiv.) was added to a freshly distilled THF (20 mL) solution of diisopropylamine (0.35 mL, 2.42 mmol, 1.5 equiv.) at −78 °C under argon atmosphere. The solution was stirred at −78 °C for 5 min. Then thiophene-3-carbonitrile **2a** (0.226 mL, 2.42 mmol, 1.5 equiv.) was added and the solution was stirred at −78 °C for 20 min. To this mixture was added by cannula a solution of **3** (500 mg, 1.66 mmol, 1 equiv.) in dry THF (20 mL). The solution was stirred at −78 °C for 30 min then the reaction was quenched at −60 °C by addition of ether (30 mL) and a saturated solution of NH_4Cl (30 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ then water. The resulting organic layers were gathered, dried on $MgSO_4$ and concentrated. For analysis purposes, it was purified by silica gel chromatography column (hexane/EtOAc 95/5 to 1/1) to obtain **4a** (468 mg, 69%) as a light yellow oil. However, this compound is readily decomposed upon storage. **4a**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 0.17, 0.18 (s×2, 3H×2, $(CH_3)_2Si$), 0.96 (s, 9H, $(CH_3)_3CSi$), 1.25, 1.48 (s×2, 3H×2, $C(CH_3)_2$), 3.84 (dd, 1H,

J=2.1, 11.2 Hz, H-5a), 3.90 (dd, 1H, J=2.2, 11.2 Hz, H-5b), 4.56 (m, 1H, H-4), 4.71 (d, 1H, J=5.7 Hz, H-2), 4.90 (dd, 1H, J=1.2, 5.7 Hz, H-3), 7.22 (d, 1H, J=5.2 Hz, H_{Th}-4), 7.36 (d, 1H, J=5.2 Hz, H_{Th}-5). δ ^{13}C ppm ($CDCl_3$, 75 MHz): −5.2 (($CH_3)_2$Si), 18.7 (($CH_3)_3C$Si), 25.0, 26.2, 26.4 (C($CH_3)_2$, ($CH_3)_3$CSi), 64.9 (C-5), 82.0 (C-3), 87.1 (C-4), 89.0 (C-2), 106.1 (C-1), 109.5, 113.7, 115.6 (C_{Th}-3, CN, $C(CH_3)_2$), 126.3 (C_{Th}-4), 130.3 (C_{Th}-5), 152.2 (C_{Th}-2).

Intermediate 5a. Acetic acid 6-(*tert*-butyl-dimethyl-silanoxymethyl)-2,2-dimethyl-4-(3-cyano-thiophen-2-yl)-tetrahydro-furo[3,4-*a*][1,3]dioxol-4-yl ester. (1-*O*-acetyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-1-(2-thiophene-3-carbonitrile)-α-D-ribofuranose).

n-Butyl lithium (2 M solution in pentane) (1.25 mL, 2.42 mmol, 1.5 equiv.) was added to a freshly distilled THF (20 mL) solution of diisopropylamine (0.35 mL, 2.42 mmol, 1.5 equiv.) at −78 °C under argon atmosphere. The solution was stirred at −78 °C for 5 min. Then thiophene-3-carbonitrile **2a** (0.226 mL, 2.42 mmol, 1.5 equiv.) was added and the solution was stirred at −78 °C for 20 min. To this mixture was added by cannula a solution of **3** (500 mg, 1.66 mmol, 1 equiv.) in dry THF (20 mL). The solution was stirred at −78 °C for 30 min then warmed to −70 °C/−60 °C and acetic anhydride (0.78 mL, 8.28 mmol, 5 equiv.) was added. After stirring another 30 min at −60 °C, the reaction was quenched at −60 °C by addition of ether (30 mL) and a saturated solution of NH_4Cl (30 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ then water. The combined aqueous layers were washed with ether and the resulting organic layers were gathered, dried on $MgSO_4$ and concentrated. This crude mixture was nearly pure and used without purification for the next step. For analysis purposes, it was purified by silica gel chromatography column (PE/Acetone 9/1) to obtain **5a** (713 mg, 95%) as a light yellow oil However this compound is readily decomposed upon storage. **5a**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 0.06 and 0.07 (s×2, 6H, ($CH_3)_2$Si)), 0.86 (s, 9H, ($CH_3)_3$CSi), 1.39, 1.73 (s×2, 3H×2, C($CH_3)_2$), 2.25 (s, 3H, OAc), 3.83 (dd, 1H, J=11.3, 2.6 Hz, H-5a), 3.91 (dd, 1H, J=11.3, 3.2 Hz, H-5b), 4.49 (m, 1H, H-4), 4.61 (d, 1H, J=6.4 Hz, H-2), 4.83 (dd, 1H, J=6.4, 2.1 Hz, H-3), 7.14 (d, 1H, J=5.3 Hz, H_{Th}-4), 7.33 (d, 1H, J=5.3 Hz, H_{Th}-5). δ ^{13}C ppm ($CDCl_3$, 75 MHz): −5.2 and −4.9 (($CH_3)_2$Si), 18.6 (($CH_3)_3C$Si), 21.8 (CH_3 Ac), 26.1 (), 26.2 (($CH_3)_3$CSi), 63.0 (C-5), 81.1 (C-2), 84.9 (C-4), 88.7 (C-3), 103.7 (C-1), 106.8, 114.5, 116.3 (C_{Th}-3, CN, $C(CH_3)_2$), 125.8 (C_{Th}-5), 130.4 (C_{Th}-4), 153.8 (C_{Th}-2), 168.8 (OAc). IR (KBr) cm^{-1}: 2932, 2858 (CH), 2232 (CN), 1763 (C=O). MS (LSIMS) M-OAc: 394.

The crude mixture of **5a** (1.19 mmol) was dissolved in dry dichloromethane (10 mL) with molecular sieves, under argon atmosphere. Triethylsilane (0.95 mL, 5.97 mmol, 5 equiv.) and freshly distilled trimethylsilyl trifluoromethanesulfonate (0.54 mL, 2.98 mmol, 2.5 equiv.) were added to the solution at 0 °C. The reaction was then warmed up to room temperature and stirred for 30 min. No remaining starting material was detected on TLC, triethylamine (2 mL) were added to the solution and then tetrabutylammonium fluoride (1 M solution in THF) (2.4 mL, 2.38 mmol, 2 equiv.). After 4 h, the mixture was quenched by a saturated solution of NH_4Cl and extracted with dichloromethane. The organic layer was washed with water, dried on $MgSO_4$ and concentrated. After purification on silica gel chromatography column, **1aα** (74 mg, 29%) and **1aβ** (54 mg, 21%) were isolated. **1aβ**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 1.37, 1.64 (s×2, 3H×2, C($CH_3)_2$), 2.23 (m, 1H, OH-5′), 3.85 (ddd, 1H, J=12.4, 3.6, 8.5 Hz, H-5′a), 4.00 (ddd, 1H, J=12.4, 2.8, 4.45 Hz, H-5′b), 4.25 (m, 1H, H-4′), 4.63 (m, 1H, H-2′), 4.87 (dd, 1H, J=3.6, 6.6 Hz, H-3′), 5.20 (d, 1H, J=5.7 Hz, H-1′), 7.23 (d, 1H, J=5.3 Hz, H_{Th}-4), 7.33 (d, 1H, J=5.3 Hz, H_{Th}-5). δ ^{13}C ppm ($CDCl_3$, 75 MHz): 25.7, 27.9 (C($CH_3)_2$), 62.9 (C-5′), 81.8, 81.8 (C-1′, C-3′), 85.5 (C-4′), 87.4 (C-2′), 108.1, 115.4, 115.8 (C_{Th}-3, CN, $C(CH_3)_2$), 126.2 (C_{Th}-5), 129.8 (C_{Th}-4), 153.1 (C_{Th}-2). IR (KBr) cm^{-1}: 3447 (OH), 2926 (CH), 2229 (CN). MS (LSIMS) M+H calculated: 282.0800; measured: 282.0795. **1aα**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 1.34, 1.49 (s×2, 3H×2, C($CH_3)_2$), 1.91 (m, 1H, OH-5′), 3.85 (m, 2H, H-5′a and H-5′b), 4.34 (m, 1H, H-4′), 4.88 (dd, 1H, J=0.9, 5.9 Hz, H-3′), 4.97 (dd, 1H, J=4.0, 5.9 Hz, H-2′), 5.65 (d, 1H, J=4.0 Hz, H-1′), 7.19 (d, 1H, J=5.3 Hz, H_{Th}-4), 7.38 (d, 1H, J=5.3 Hz, H_{Th}-5). δ ^{13}C ppm ($CDCl_3$, 75 MHz): 25.1, 26.5 (C($CH_3)_2$), 63.2 (C-5′), 79.3 (C-1′), 82.1 (C-2′), 83.3 (C-3′), 85.1 (C-4′), 108.1, 113.7, 115.1 (C_{Th}-3, CN, $C(CH_3)_2$), 127.6 (C_{Th}-5), 128.0 (C_{Th}-4), 151.5 (C_{Th}-2). IR (KBr) cm^{-1}: 3436 (OH), 2924 (CH), 2230 (CN). MS (LSIMS) M+H calculated: 282.0800; measured: 282.0806.

2,2-Dimethyl-4-(2-cyano-thiophen-5-yl)-6-hydroxy-methyl-tetradro-furo[3,4-*a*][1,3]dioxole 1b. (5-(2′, 3′-*O*,*O*-isopropylidene-1′-deoxyribofuranosyl)thiophene-2-carbonitrile).

Intermediate 4b. 6-(*tert*-Butyl-dimethyl-silanoxymethyl)-2,2-dimethyl-4-(2-cyanothiophen-5-yl)-tetrahydro-furo[3,4-*a*][1,3]dioxol-4-ol. (5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-1-(5-thiophene-2-carbonitrile)-α-D-ribofuranose).

The same procedure as the one used to prepare **4a** was used to prepare **4b** for analysis purposes. However, the compound is readily decomposed upon storage. **4b** δ ^{1}H ppm ($CDCl_3$, 300 MHz): 0.18, 0.19 (s×2, 3H×2, ($CH_3)_2$Si), 0.96 (s, 9H, ($CH_3)_3$CSi), 1.30, 1.56 (s×2, 3H×2, C($CH_3)_2$), 3.83 (dd, 1H, J=2.1, 11.3 Hz, H-5a), 3.87 (dd, 1H, J=2.0, 11.3 Hz, H-5b), 4.46 (m, 1H, H-4), 4.59 (d, 1H, J=5.7 Hz, H-2), 4.90 (dd, 1H, J=4.6, 5.7 Hz, H-3), 7.24 (d, 1H, J=4.1 Hz, H_{Th}-4), 7.67 (d, 1H, J=4.1 Hz, H_{Th}-3). δ ^{13}C ppm ($CDCl_3$, 75 MHz): −5.3(($CH_3)_2$Si), 18.7 (($CH_3)_3C$Si), 25.2, 26.2, 26.8 (C($CH_3)_2$, ($CH_3)_3$CSi), 64.9 (C-5), 82.2 (C-2), 86.8 (C-4), 88.9 (C-3), 105.8, 110.2, 113.6, 115.0 (C-1, C_{Th}-2, CN, $C(CH_3)_2$), 126,9 (C_{Th}-4), 137.3 (C_{Th}-3), 150.5 (C_{Th}-5). IR (KBr) cm^{-1}: 3328 (OH), 2933, 2859 (CH), 2221.1 (CN).

Intermediate 5b. Acetic acid 6-(*tert*-butyl-dimethyl-silanoxymethyl)-2,2-dimethyl-4-(3-cyano-thiophen-5-yl)-tetrahydro-furo[3,4-*a*][1,3]dioxol-4-yl ester. (1-*O*-acetyl-5-*O*-*tert*-butyldimethylsilyl-2,3-*O*,*O*-isopropylidene-1-(5-thiophene-2-carbonitrile)-α-D-ribofuranose).

The same procedure as the one used to prepare **5a** was used to prepare **5b**. Purification for analysis purposes on silica gel

column (PE/Acetone 95/5) afforded pure **5b** as a powder (95%). However the compound is readily decomposed upon storage. **5b**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 0.05 and 0.06 (s×2, 3H×2, $(CH_3)_2Si$), 0.85 (s, 9H, $(CH_3)_3CSi$),1.39, 1.69 (s×2, 3H×2, $C(CH_3)_2$), 2.18 (s, 3H, OAc), 3.81 (dd, 1H, J=2.5, 11.3 Hz, H-5a), 3.90 (dd, 1H, J=2.8, 11.3 Hz, H-5b), 4.48 (m, 1H, H-4), 4.61 (d, 1H, J=6.4 Hz, H-2), 4.83 (dd, 1H, H-3, J=2.1, 6.4 Hz, H-2), 7.10 (d, 1H, J=3.9 Hz, H_{Th}-4), 7.47 (d, 1H, J=3.9 Hz, H_{Th}-3). δ ^{13}C ppm ($CDCl_3$, 75 MHz): −5.2, −5.0 ($(CH_3)_2Si$), 18.6 ($(CH_3)_3CSi$), 23.0 (OAc), 25.9, 26.2 ($C(CH_3)_2$, $(CH_3)_3CSi$), 63.1 (C-5), 81.0 (C-2), 85.0 (C-4), 88.3 (C-3), 124.9 (C_{Th}-4), 137.6 (C_{Th}-3).

The same procedure as the described for **1a** was used for the synthesis of **1b** and afford 27% of α isomer and 20% of β isomer. **1bβ**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 1.37, 1.60 (s×2, 3H×2, $C(CH_3)_2$), 3.77 (dd, 1H, J=4.1, 12.1 Hz, H-5′a), 3.89 (dd, 1H, J=3.3, 12.1 Hz, H-5′b), 4.22 (m, 1H, H-4′), 4.59 (dd, 1H, J=5.3, 6.6 Hz, H-2′), 4.79 (dd, 1H, J=3.7, 6.6 Hz, H-3′), 5.10 (d, 1H, J=5.2 Hz, H-1′), 7.07 (d, 1H, J=3.8 Hz, H_{Th}-4), 7.54 (d, 1H, J=3.8 Hz, H_{Th}-3). δ ^{13}C ppm ($CDCl_3$, 75 MHz): 25.8, 27.8 ($C(CH_3)_2$), 63.0 (C-5′), 82.1, 82.9 (C-1′, C-3′), 85.5 (C-4′), 87.2 (C-2′), 109.3, 114.5, 115.7 (C_{Th}-2, CN, $C(CH_3)_2$), 124.6 (C_{Th}-4), 138.1 (C_{Th}-3), 151.7 (C_{Th}-5). IR (KBr) cm^{-1}: 3445 (OH), 2925 (CH), 2228 (CN). MS (LSIMS) M+H calculated: 282.0800; measured: 282.0807. **1bα**: δ ^{1}H ppm ($CDCl_3$, 300 MHz): 1.34, 1.53 (s×2, 3H×2, $C(CH_3)_2$), 1.86 (bs, 1H, OH-5′), 3.82 (m, 2H, H-5′a and H-5′b), 4.30 (m, 1H, H-4′), 4.83 (dd, 1H, J=3.9, 5.9 Hz, H-2′), 4.88 (dd, 1H, J=1.0, 5.9 Hz, H-3′), 5.43 (d, 1H, J=3.9 Hz, H-1′), 7.07 (d, 1H, J=3.8 Hz, H_{Th}-4), 7.52 (d, 1H, J=3.8 Hz, H_{Th}-3). δ ^{13}C ppm ($CDCl_3$, 75 MHz): 25.2, 26.5 ($C(CH_3)_2$), 63.5 (C-5′), 80.1 (C-1′), 82.5 (C-2′), 83.3 (C-3′), 84.9 (C-4′), 110.7, 113.8 (C_{Th}-2, CN, $C(CH_3)_2$), 126.2 (C_{Th}-4), 136.8 (C_{Th}-3), 147.8 (C_{Th}-5). IR (KBr) cm^{-1}: 3467 (OH), 2925 (CH), 2226 (CN). MS (LSIMS) M+H calculated: 282.0800; measured: 282.0785.

β-2(3-cyanothiophene) adenine dinucleotide 7aβ

Intermediate 6aβ. Phosphoric acid mono-[5(*R*)-(3-cyano-thiophen-2-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl methyl] ester. (2-β-D-[1′-(5′-phosphateribofuranosyl)] thiophene-3-carbonitrile).

Compound **1aβ** (32 mg, 0.114 mmol) was solubilised in triethyl phosphate (1.2 mL) and heated at 50 °C. Then after cooling down at 0 °C, phosphorus oxychloride (32 μL, 0.342 mmol, 3 equiv.) was added. The mixture was stirred for 2 days at room temperature and monitored by anion exchange HPLC (Supelcosil SAX1, buffer KH_2PO_4 50 mM/MeOH 95/5). Another 32 μL of $POCl_3$ were added if needed to complete the reaction. The reaction was quenched at 0 °C by addition of ice-cold water and stirred for 1 h. The mixture was extracted with diethyl ether (20 mL×3) and the aqueous layer was freeze-dried. The crude mixture was purified on AG MP1 resin with a gradient of 0–150 mM TFA to give **6aβ** (10 mg, 25%). **6aβ**: δ ^{1}H ppm (D_2O, 500 MHz): 3.95 (m, 2H, H-5′a, H-5′b), 4.10–4.17 (m, 3H, H-2′, H-3′, H-4′), 5.17 (d, 1H, J=7.1 Hz, H-1′), 7.18 (d, 1H, J=5.0 Hz, H-4), 7.43 (d, 1H, J=5.0 Hz, H-5). δ ^{13}C ppm (D_2O, 125 MHz): 65.9 (C-5′), 72.1, 78.4 (C-2′, C-3′), 79.4 (C-1′), 84.4 (d, $J_{C-C-O-P}$=8.5 Hz, C-4′), 108.1, 115.7 (C-3, CN), 128.1 (C-5), 129.5 (C-4), 154.6 (C-2). δ ^{31}P ppm (D_2O, 121 MHz): 1.3 (s). MS (ESI-) M−H: 320.

Compound **6aβ** (11 mg, 34.3 μmol) was dissolved in a 0.2 M solution of manganese chloride in formamide left on molecular sieves during several days (0.5 mL). $MgSO_4$ (8 mg, 68.5 μmol, 2 equiv.) and adenosine 5′-monophosphomorpholidate·4-morpholine-*N*,*N*′-dicyclohexylcarboxamidine salt (48.6 mg, 68.5 μmol, 2 equiv.) were added to this solution. The mixture was sonicated and left to react for 4 days after which no evolution was observed by HPLC SAX monitoring. 20 μL of water were added to quench the reaction. The mixture was then purified on a DEAE sepharose resin column eluted with a gradient of triethylammonium formate 20 to 250 mM to give **7aβ** with 39% yield. **7aβ**: δ ^{1}H ppm (D_2O, 500 MHz): 3.60–4.45 (m, protons of the sugars), 4.73 (d, 1H, J=6.04 Hz, H_{Th}-1′), 5.67 (d, 1H, J=4.0 Hz, H_{Ad}-1′), 6.68 (d, 1H, J=4.9 Hz, H_{Th}-4), 6.90 (d, 1H, J=4.7 Hz, H_{Th}-5), 7.70 (Ad). δ ^{31}P ppm (D_2O, 121 MHz): −9.53 (m). λ_{max} (H_2O)=253 nm. MS (ES-) M−H calculated: 649.0525, measured: 649.0528.

β-5(2-cyanothiophene) adenine dinucleotide 7bβ

Intermediate 6bβ: phosphoric acid mono-[5(*R*)-(2-cyano-thiophen-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl methyl] ester. (5-β-D-[1′-(5′-phosphateribofuranosyl)] thiophene-2-carbonitrile).

The same procedure as described for **6aβ** was used for the synthesis of **6bβ** (25%). **6bβ**: δ ^{1}H ppm (D_2O, 500 MHz): 4.20 (m, 2H, H-5′a, H-5′b), 4.29–4.44 (m, 3H, H-2′, H-3′, H-4′), 5.25 (d, 1H, J=7.1 Hz, H-1′), 7.36 (d, 1H, J=3.7 Hz, H_{Th}-4), 7.85 (d, 1H, J=3.8 Hz, H_{Th}-3). δ ^{13}C ppm (D_2O, 75 MHz): 67.3 (d, J_{C-O-P}=5.0 Hz, C-5′), 73.5, 79.5 (C-3′, C-2′) 81.3 (C-1′), 85.6 (d, $J_{C-C-O-P}$=8.7 Hz, C-4′), 109.8, 117.0 (C_{Th}-2, CN), 127.8 (C_{Th}-4), 141.2 (C_{Th}-3), 153.4 (C_{Th}-5). δ ^{31}P ppm (D_2O, 121 MHz): 1.3 (s). MS (ESI-) M−H: 320. The same procedure as described for **7aβ** was used for the synthesis of **7bβ** (42%). **7bβ**: δ ^{1}H ppm (D_2O, 500 MHz): 3.7–3.9 (m, H-5′ ×4), 4.0–4.4 (m, protons of the sugars), 5.75 (d, J=3.6 Hz, H_{Ad}-1′), 6.74 (H_{Th}-4), 7.22 (H_{Th}-3). δ ^{13}C ppm (D_2O, 75 MHz): 67.9, 68.5, 69.4, 72.9, 74.1, 77.1, 80.3, 82.4, 86.0, 86.5, 90.3, 109.9, 117.7, 128.1, 141.9, 152.4, 155.0. δ ^{31}P ppm (D_2O, 121 MHz): −10.0 (m). λ_{max} (H_2O)=260 nm. MS (ES-) M−H calculated: 649.0525, measured: 649.0530.

α-5(2-cyanothiophene) adenine dinucleotide 7bα

Intermediate 6bα: phosphoric acid mono-[5(*S*)-(2-cyano-thiophen-5-yl)-3,4-dihydroxy-tetrahydro-furan-2-yl methyl] ester. (5-α-D-[1′-(5′-phosphateribofuranosyl)] thiophene-2-carbonitrile).

The same procedure as described for **6aβ** was used for the synthesis of **6bα** (15%). **6bα**: δ ^{1}H ppm (D_2O, 300 MHz): 3.70–4.39 (m, 5H, H-2′, H-3′, H-4′, H-5′a, H-5′b), 5.36 (broad s, 1H, H-1′), 7.02 (d, 1H, J=3.6 Hz, H_{Th}-4), 7.59 (d, 1H, J=3.6 Hz, H_{Th}-3). δ ^{13}C ppm (D_2O, 75 MHz): 65.4 (d, J_{C-O-P}=4.83 Hz, C-5′), 72.4, 73.7(C-2′, C-3′), 79.5 (C-1′), 80.9 (d, $J_{C-C-O-P}$=7.9 Hz, C-4′), 108.7, 115.7 (C_{Th}-2,

CN), 126.8 (C_{Th}-4), 139.1 (C_{Th}-3), 149.0 (C_{Th}-5). δ ^{31}P ppm (D_2O, 121.45 MHz): 1.7 (s). MS (ESI-) M−H: 320.

The same procedure as described for **7aβ** was used for the synthesis of **7bα** (30%). **7bα**: δ ^{1}H ppm (D_2O, 500 MHz): 3.7–4.5 (m, protons of the sugars), 5.05 (s, 1H, H_{Th}-1′), 5.90 (d, 1H, J=5.05 Hz, H_{Ad}-1′), 6.71 (d, 1H, H_{Th}-4), 7.32 (d, 1H, J=3.0 Hz, H_{Th}-3), 8.05 (s, H_{Ad}-2), 8.34 (s, H_{Ad}-8). δ ^{31}P ppm (D_2O, 121 MHz): −9.79 (m). λ_{max} (H_2O)=261 nm. MS (ES-) M−H calculated: 649.0525, measured: 649.0527.

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Weak intramolecular interactions as controlling factors in the diastereoselective formation of 3-phosphinoxido- and 3-phosphono-1,2,3,6-tetrahydrophosphinine 1-oxides☆

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Abstract—A series of 3-phosphinoxido-and 3-phosphono-1,2,3,6-tetrahydrophosphinine oxides was synthesized by the diastereoselective addition of diphenylphosphine oxide and dialkyl phosphites to the α,β-double-bond of 1,2-dihydrophosphinine oxides. Further refunctionalizations led to a 3-P(O)$(OH)_2$ derivative and to a disulfide. The conformation of the products was evaluated using the B3LYP/6-31+G*//B3LYP/3-21G* method, validated by calculation for a simple tetrahydrophosphinine oxide with a known stereostructure. The preferred conformers of the 3-P(X)Z_2-tetrahydrophosphinine derivatives were among the twist-boat forms containing the exocyclic P-function in the axial position due to three kinds of favorable intramolecular interactions. Only the 3-P(O)$(OH)_2$ derivative was found to adopt a half-chair conformation as a consequence of intramolecular H-bonding.

1. Introduction

Within the class of six-membered P-heterocycles, the partially saturated 1,2-dihydro- and 1,2,3,6-tetrahydrophosphinine oxides form a representative group.[2,3] Perhaps the most convenient method for the preparation of dihydro- and tetrahydrophosphinine oxides involves ring enlargement of easily available 2,5-dihydro-1*H*-phosphole oxides by the dichlorocarbene addition method.[4,5] Thermolysis of the 3-phosphabicyclo[3.1.0]hexane 3-oxide furnished dihydrophosphinine oxides[6,7] giving tetrahydrophosphinine derivatives by selective reduction.[8] Solvolysis of the phosphabicyclohexanes in protic solvents led to 3-alkoxy and 3-hydroxy-1,2,3,6-tetrahydrophosphinine oxides.[9] For the time being, not much is known on the conformation of tetrahydrophosphinine oxides that are 'phosphacyclohexenes'.[8,9]

We aimed at the synthesis of 1,2,3,6-tetrahydrophosphinine oxides with an exocyclic P-function in position 3, to make available interesting model compounds and to study their conformational equilibria.

2. Results and discussion

2.1. Synthesis and characterisation of the model compounds, 3-phosphinoxido- and 3-phosphono-1,2,3,6-tetrahydrophosphinine oxides

We wished to synthesize 1,2,3,6-tetrahydrophosphinine 1-oxides (**2**–**5**) with an exocyclic P═O function in position 3 by the Michael type addition of diphenylphosphine oxide or dialkyl phosphites onto the electron-poor α,β-double-bond of the 1,2-dihydrophosphinine oxides (**1**).[10–12] The >P(O)H compounds were first activated by reaction with trimethylaluminium at 0 °C in chloroform as in earlier examples.[13] The $>P(O)^-$ anion so formed reacted efficiently with the α,β-double-bond of the dihydrophosphinine oxides (**1a**–**c**) at 0 °C. The use of diphenylphosphine oxide, dimethyl phosphite, diethyl phosphite and dibenzyl phosphite led to 3-substituted tetrahydrophosphinine oxides **2a**, **3a**,**c**, **4a**–**c** and **5c**, respectively (Scheme 1). Except 3-phosphinoxido derivative **2a**, the other products were 3-phosphono species. It is noteworthy that the Michael

☆ See Ref. 1.

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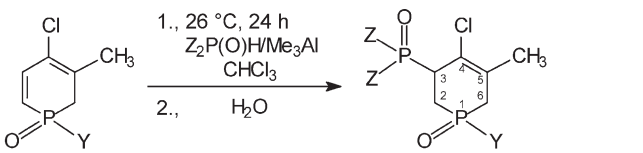


	Y
1a	Ph
1b	pMeC$_6$H$_4$
1c	EtO

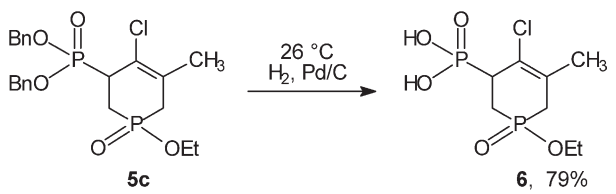
	Y	Z	Yield (%)
2a	Ph	Ph	72
3a	Ph	MeO	40
4a	Ph	EtO	46
4b	pMeC$_6$H$_4$	EtO	25
3c	EtO	MeO	54
4c	EtO	EtO	48
5c	EtO	PhCH$_2$O	37

Scheme 1.

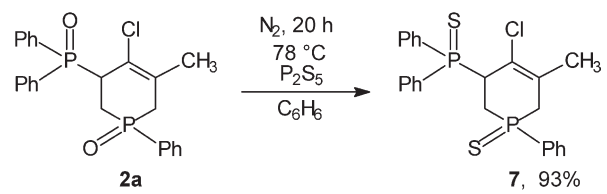
addition took place selectively; only one of the two possible diastereomers of products **2**–**5** was formed in each case. (For the assignment, see Section 2.2)

The 3-P(O)Z_2 tetrahydrophosphinine oxides (**2**–**5**) obtained mostly in about 50% yield after purification by column chromatography were characterized by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy, as well as mass spectrometry. The ^{31}P NMR spectra of the products (**2**–**5**) revealed two doublets with J_{PP} 13.8–22.1 Hz. In the ^{13}C NMR spectra, the C_3 and the C_5 carbon atoms were, in each case, coupled to both phosphorus atoms.

The dibenzylphosphono-tetrahydrophosphinine oxide (**5c**) was easily debenzylated by catalytically activated hydrogen to afford phosphonic derivative **6** (Scheme 2). The reaction of diphenylphosphinoxido-tetrahydrophosphinine-oxide **2a** with phosphorus pentasulfide yielded a newer representative of the 3-substituted six-membered ring products, disulfide **7** (Scheme 3). Products **6** and **7** were characterized by NMR spectroscopy and mass spectrometry.



Scheme 2.

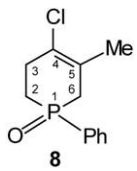


Scheme 3.

The new tetrahydrophosphinine oxides, especially **2a**, after deoxygenation, may serve as novel bidentate ligands in transition metal complexes. On the other hand, products of the bis(phosphine oxide), phosphine oxide–phosphonate and phosphinate–phosphonate type may show some biological activity.

2.2. Conformational analysis of 3-substituted 1,2,3,6-tetrahydrophosphinine oxides

2.2.1. Validation of the B3LYP/6-31+G*//B3LYP/3-21G(*) method of calculation for the tetrahydrophosphinine oxides. Our first model compound to be studied by quantum chemical calculations[14,15] was 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine oxide (**8**).[8]



8

The calculations were carried out at different levels of the theory to investigate the effect of different basis sets and also electron correlation effects (Table 1). All the calculations suggested that from among the four possible conformations (half-chair$_1$, half-chair$_2$, twist-boat$_1$ and twist-boat$_2$, where index$_1$ means an axial-, while index$_2$ an equatorial O-atom), half-chair$_1$ is the most favorable form (Fig. 1), although the computed energy differences are small. Single crystal X-ray analysis also suggested the half-chair$_1$ conformation for compound **8**.[8] Moreover, the

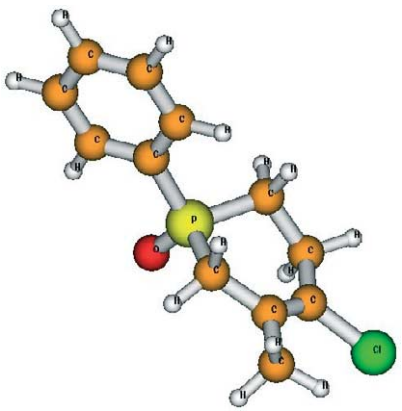
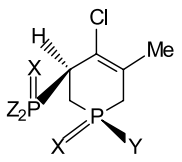


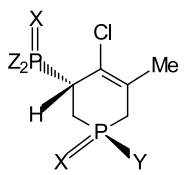
Figure 1. Perspective view of the half-chair$_1$ conformer of **8** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21g* level of theory; the data obtained by X-ray are shown in parentheses. P(1)–C(2) 1.818 [1.798], C(2)–C(3) 1.551 [1.536], C(3)–C(4) 1.518 [1.488], C(4)–C(5) 1.338 [1.323], C(5)–C(6) 1.533 [1.513], C(6)–P(1) 1.830 [1.801], O–P(1)–C(2) 115.9 [114.8], O–P(1)–C(6) 116.6 [114.1], C(2)–P(1)–C(6) 99.2 [100.1], O–P(1)–C(1′;) 112.5 [112.5].

Table 1. Relative energies of **8** calculated at different levels of the theory (in kcal/mol)

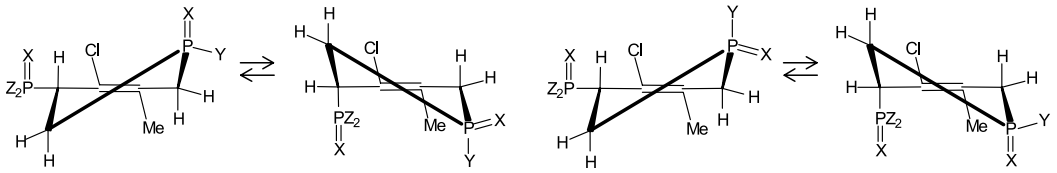
	half-chair$_1$	half-chair$_2$	twist-boat$_1$	twist-boat$_2$
B3LYP/6-31+G*//3-21G*	0.0	0.9	2.2	1.5
B3LYP/6-31+G*	0.0	1.0	2.2	1.4
B3LYP/6-311+G**	0.1	1.1	2.1	1.4
MP2/6-31+G*	0.0	0.7	2.0	1.1

Table 2. Relative energies for the conformers of the *trans* and *cis* diastereomers of tetrahydrophosphinine oxides (**2**-**7**) calculated by the B3LYP/6-31+G*//B3LYP/3-21G* method (in kcal/mol)





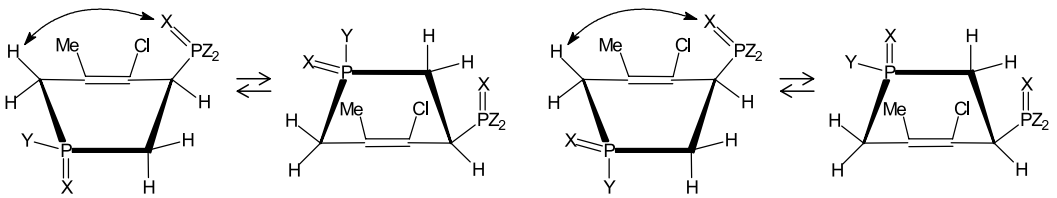
half-chair conformers



Compound

X	Y	Z		$trans_1$	$trans_2$	cis_1	cis_2
O	Ph	Ph	(**2a**)	10.8	9.1	—	7.6
O	Ph	MeO	(**3a**)	6.8	4.0	1.9	4.5
O	Ph	EtO	(**4a**)	7.8	3.6	7.9	4.3
O	pMePh	EtO	(**4b**)	7.2	3.1	7.4	3.6
O	EtO	MeO	(**3c**)	4.7	3.7	3.1	3.8
O	EtO	EtO	(**4c**)	8.3	7.9	7.9	3.7
O	EtO	BnO	(**5c**)	5.6	7.0	3.9	2.8
O	EtO	HO	(**6**)	4.9	12.3	0.0	8.2
S	Ph	Ph	(**7**)	7.7	5.8	—	5.7

twist-boat conformers



Compound

X	Y	Z		$trans_1$	$trans_2$	cis_1	cis_2
O	Ph	Ph	(**2a**)	0.0	8.9	3.3	9.0
O	Ph	MeO	(**3a**)	0.5	5.1	0.0	3.7
O	Ph	EtO	(**4a**)	0.9	5.2	0.0	7.3
O	pMePh	EtO	(**4b**)	0.5	4.6	0.0	6.7
O	EtO	MeO	(**3c**)	2.7	3.7	0.0	8.6
O	EtO	EtO	(**4c**)	3.2	7.0	0.0	5.0
O	EtO	BnO	(**5c**)	3.9	6.0	0.0	7.2
O	EtO	HO	(**6**)	5.7	11.5	—	8.5
S	Ph	Ph	(**7**)	0.0	5.6	3.3	6.9

geometrical parameters obtained by quantum chemical calculations and those established from the X-ray structure were in good agreement (Fig. 1).

Although the X-ray structures affected by crystal forces are not directly comparable with the computed (gas phase) structures, on the basis of the above evidence we can assume that the B3LYP/6-31+G*//B3LYP/3-21G(*) method[14,15] provides a reasonably good description for the relative stabilities and for the geometry of the tetrahydrophosphinine oxides. Due to the relatively small energy differences between the conformers, it can be expected that the conformational preference for the title compounds will be governed by possible intramolecular interactions.

2.2.2. The conformation of 3-phosphinoxido/sulfido- and 3-phosphono-1,2,3,6-tetrahydrophosphinine oxides. Each diastereomer of the 3-substituted 1,2,3,6-tetrahydrophosphinine oxides (**2**-**6**) may exist as a pair of half-chair conformers, or as a pair of twist-boat conformers. The two

half-chair forms and the two twist-boat conformers form two equilibria. Quantum chemical calculations were carried out to find the minima on the potential energy hypersurface, that is, to evaluate which conformers of the *trans* and *cis* diastereomers are preferred. The B3LYP/6-31+G*// B3LYP/3-21G(*) relative energies for the four possible conformers of each tetrahydrophosphinine oxide (**2**-**6**/*trans* and **2**-**6**/*cis*) are listed in Table 2. Despite our efforts, three structures (**2a** half-chair/cis_1, **7** half-chair/cis_1 and **6** twist-boat/cis_1) could not be located as minima, as upon geometry optimization they rearranged to one of the more stable forms.

It can be seen that with one exception (**6**), all 3-P(O)Z_2 substituted tetrahydrophosphinine oxides (**2**–**5**) prefer adopting one of the twist-boat conformations. Moreover, two typical cases could be observed. For the 3-phosphinoxido-tetrahydrophosphinine oxide (**2a**), the twist-boat/$trans_1$ conformer, while for all of the 3-phosphono model compounds (**3**–**5**), the twist-boat/cis_1 conformer seemed to be the most preferred one. While for some of the compounds (**2a**, **3c**, **4c** and **5c**), the energy difference between the twist-boat/$trans_1$ and the twist-boat/cis_1 forms is around 3 kcal/mol, this value for **3a**, **4a** and **4b** is less than 1 kcal/mol. The rest of the structures are by 3–12 kcal/mol higher in energy than the most stable form. Hence, the remaining twist-boat conformers ($trans_2$, cis_1 and cis_2 for **2a** and cis_2, $trans_1$ and $trans_2$ for **3**-**5**) and the four half-chair conformers are relatively unfavorable for **2a** and **3**–**5**.

As representative examples, the stereostructures of the favorable twist-boat conformers of tetrahydrophosphinine oxides **2a** and **3a**, together with the geometrical parameters selected are shown in Figures 2 and 3, respectively. The optimized structure for tetrahydrophosphinine oxides **4a** and **4b** was found to be analogous with that substantiated for **3a**. Practically, the stereostructure of **5c** is also similar. The P(O)Z_2 moiety (Z=Ph or alkoxy) is in the axial position

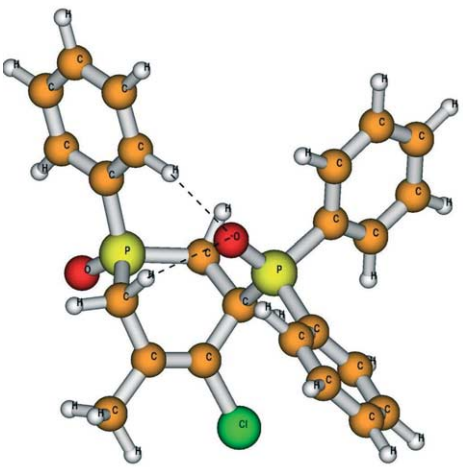


Figure 2. Perspectie view of the twist-boat/$trans_1$ conformer of **2a** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21G* level of theory. P(1)–C(2) 1.849, C(2)–C(3) 1.575, C(3)–C(4) 1.523, C(4)–C(5) 1.340, C(5)–C(6) 1.527, C(6)–P(1) 1.829, O–P(1)–C(2) 114.2, O–P(1)–C(6) 116.2, O–P–C(1′) 111.7, C(2)–P(1)–C(6) 100.8, P(1)–C(2)–C(3)–P −93.9, P(1)–C(2)–C(3)–C(4) 32.1, P(1)–C(6)–C(5)–CH(3) −121.23, P(1)–C(6)–C(5)–C(4) 55.5, C(6)–C(5)–C(4)–C(3) −1.7, C(6)–P(1)–C(2)–C(3) 13.6.

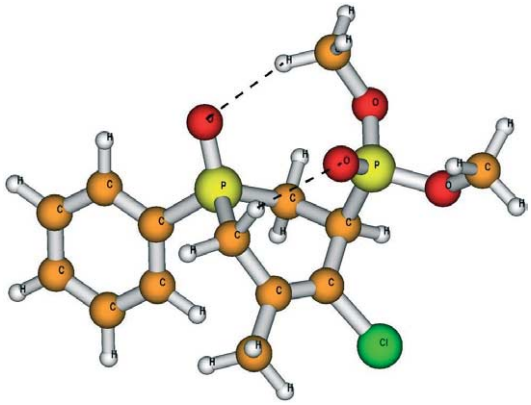


Figure 3. Perspective view of the twist-boat/cis_1 conformer of **3a** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21G* level of theory. P(1)–C(2) 1.834, C(2)–C(3) 1.559, C(3)–C(4) 1.520, C(4)–C(5) 1.340, C(5)–C(6) 1.528, C(6)–P(1) 1.834, P(1)–C′ 1.810, C(3)–P′ 1.832, P(1)–C(2)–C(3) 113.1, C(2)–C(3)–C(4) 109.5, C(3)–C(4)–C(5) 123.9, C(4)–C(5)–C(6) 119.0, C(5)–C(6)–P(1) 114.8, C(6)–P(1)–C(2) 102.6, C(2)–C(3)–P′ 112.2, C(4)–C(3)–P′ 112.1, C(2)–P(1)–C′ 105.2, C(6)–P(1)–C′ 105.9, P1–C(2)–C(3)–C(4) 58.3, P(1)–C(6)–C(5)–C(4) 46.0, P(1)–C(2)–C(3)–P′ −66.9, C(5)–C(4)–C(3)–C(2) −40.9, C(5)–C(6)–P(1)–C′ 87.7.

in the above cases (**2a**, **3a**, **4a**, **4b** and **5c**); at the same time, for **2a** the $P_1{=}O$ is in the axial position, while for the remaining cases (**3a**, **4a**, **4b** and **5c**) the $P_1{=}O$ is in the equatorial position. (Accordingly, the 1-phenyl or the 1-alkoxy substituent is in the equatorial and in the axial disposition, respectively.)

The optimized geometry for alkoxy substituted tetrahydrophosphinine oxides **4c** can be seen in Figure 4.

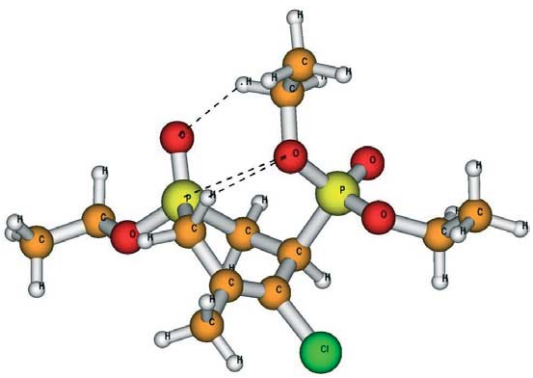


Figure 4. Perspective view of the twist-boat/cis_1 conformer of **4c** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21G* level of theory. P(1)–C(2) 1.829, C(2)–C(3) 1.560, C(3)–C(4) 1.515, C(4)–C(5) 1.338, C(5)–C(6) 1.527, C(6)–P(1) 1.818, P(1)–O′ 1.628, C(3)–P′ 1.828, P(1)–C(2)–C(3) 113.8, C(2)–C(3)–C(4) 111.8, C(3)–C(4)–C(5) 126.5, C(4)–C(5)–C(6) 121.0, C(5)–C(6)–P(1) 116.4, C(6)–P(1)–C(2) 105.3, C(2)–C(3)–P′ 110.3, C(4)–C(3)–P′ 114.1, C(2)–P(1)–O′ 103.7, C(6)–P(1)–O′ 98.4, P1–C(2)–C(3)–C(4) 51.4, P(1)–C(6)–C(5)–C(4) 34.8, P(1)–C(2)–C(3)–P′ −76.6, C(5)–C(4)–C(3)–C(2) −40.1, C(5)–C(6)–P(1)–O′ 90.1.

For the 3-P(O)$(OH)_2$-tetrahydrophosphinine oxide (**6**), a significantly different conformational situation was obtained. According to this, for compound **6** the half-chair/cis_1 form is the preferred conformer (Table 1). It can be seen in Figure 5 that, in this case, an intramolecular H-bonding between the hydroxy group of the P(O)$(OH)_2$

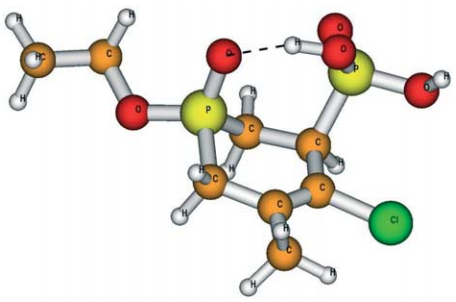


Figure 5. Perspective view of the half-chair/cis_1 conformer of **6c** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21G* level of theory. P(1)–C(2) 1.802, C(2)–C(3) 1.566, C(3)–C(4) 1.517, C(4)–C(5) 1.342, C(5)–C(6) 1.537, C(6)–P(1) 1.800, P(1)–O′ 1.604, C(3)–P′ 1.853, P(1)–C(2)–C(3) 109.1, C(2)–C(3)–C(4) 112.8, C(3)–C(4)–C(5) 128.9, C(4)–C(5)–C(6) 123.3, C(5)–C(6)–P(1) 113.2, C(6)–P(1)–C(2) 101.1, C(2)–C(3)–P′ 107.8, C(4)–C(3)–P′ 115.5, C(2)–P(1)–O′ 108.7, C(6)–P(1)–O′ 102.6, P1–C(2)–C(3)–C(4) 50.1, P(1)–C(6)–C(5)–C(4) −17.1, P(1)–C(2)–C(3)–P′ −78.6, C(5)–C(4)–C(3)–C(2) −18.1, C(5)–C(6)–P(1)–O′ 156.6.

unit and the oxygen of the P═O function stabilizes the conformer, where the OH···O═P distance is 1.55 Å. The presence of the hydrogen bond has also been substantiated by performing a Bader analysis[16,17] showing indeed one bond critical point on the OH···O═P path. The electron density at the critical point was 0.06. For comparison, the MP2/6-311++G** electron density at the bond critical point of the proton bridge in the dimers of water and formic acid was 0.02 and 0.04, respectively.[18]

The suspiciously short distances found between the not directly bonded atoms of the lowest energy form of the remaining tetrahydrophosphinine oxides (**2a**, **3a**, **4a**, **4b** and **5c**) were studied by the Bader analysis. These calculations revealed several bond critical points with low electron densities (between 0.01 and 0.015) indicating weak interactions. Such bond critical points were found between the oxygen atom of the P═O units and the hydrogens of methyl or methylene groups (i), between the oxygen atom of alkoxy groups and the hydrogens of methyl or methylene groups (ii) suggesting special H-bondings. A further interaction between the phosphorus atom of P_1═O and the oxygen atom of the exocyclic POR moiety (iii) can also be concluded from the Bader analysis of **4c** and **3c**. The distance between the hydrogen and the oxygen atoms in cases (i) and (ii) was between 2.0 and 2.5 Å, while in case of the phosphorus–oxygen interaction (iii) it was 3.0–3.5 Å.

In the case of **2a**, **3a**, **4a**, **4b** and **5c**, the preference for the twist-boat conformer with axial P(O)Z_2 substituent is the consequence of an intramolecular interaction of type (i) between the double-bonded oxygen atom of the Z_2P═O moiety and the corresponding hydrogen atom of the P_1CH_2 unit that may stabilise the molecule. No similar interaction can take place in the other conformers. The distance between the oxygen atom of the Z_2P═O moiety and the hydrogen atom of the P_1CH_2 unit is of 2.0–2.2 Å that can be regarded as a weak H-bonding.

It is of interest that the twist-boat conformation of compounds **3a**, **4a** and **4b** is also stabilized by another kind of intramolecular interaction of type (i) that is between the oxygen atom of the P_1═O group and a suitable hydrogen atom of the C(3)–P(O)CH_2 moiety. The average distance between the corresponding H and the O atom is 2.15 Å, suggesting again a H-bonding.

The P–OH···O═P intramolecular H-bonding in the half-chair/cis_1 conformation of **6** is more favorable than the intramolecular interactions in the twist-boat/cis_1 conformation of product **5c**. The comparison of the non-bonded O–H distances (1.55 Å vs 2.15 Å) and the densities at the bond critical point (0.06 vs 0.015) are in accord with the above conclusion. It follows that on debenzylation, the twist-boat conformer of **5c** is converted into the more stable half-chair/cis_1 form of **6**.

The P_1═O···H_2COP(O) type of interaction (i) was found to be one of the stabilizing factors in the most stable twist-boat/cis_1 conformation of **4c** and **3c**, (Fig. 4). Another favorable intramolecular interaction of type (ii) is also present in **4c** and **3c** between the oxygen atom of the alkoxy group of the exocyclic P-function and the suitable hydrogen of one of the PCH_2 moieties. The distance of 2.37 Å between the oxygen atom and the proton corresponds to a H-bonding. It is interesting that the oxygen atom of the alkoxy group in the exocyclic P-function is as suitable in forming a H-bonding, as that of a P═O unit.

According to the small differences (less than 1 kcal/mol) between the relative energies for the twist-boat/cis_1 conformations of type **4c** and **3a** differing only in the rotation position of the exocyclic P-moiety, the stability of the two conformers is comparable.

It is noteworthy that the optimized structure of **2a** suggested an additional interaction between a P═O function and a suitable proton of the P_1-phenyl ring (see Fig. 2).

The interaction of type (iii) can be seen in (**4c**) Figure 4, exhibiting the proximity (3.0 Å) of the endocyclic phosphorus atom and the oxygen of the exocyclic POR moiety. The same oxygen atom is also involved in an O···H interaction of type (ii)—see above.

The energy difference of at least 3 kcal/mol between the conformers within the pairs seems to support that, the equilibria are shifted towards the more stable form that is twist-boat/$trans_1$ for **2a**, and twist-boat/cis_1 for **3**–**5**.

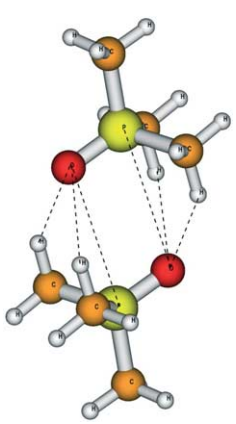


Figure 6. Perspective view of the dimeric associate of Me_3P═O obtained at the B3LYP/6-31+G* level of theory.

According to the Boltzmann-distribution, the ratio of the comformers is about 150:1.

In order to estimate how large energy results from the intramolecular interactions, the dimeric associate of $Me_3P{=}O$ has been calculated (Fig. 6). The stability of the associate is 7.9 kcal/mol at the B3LYP/6-31+G* level, 7.4 kcal/mol at the B3LYP/aug-cc-PVTZ level, while 13.3 kcal/mol at the MP2/6-31+G* level of theory. The Bader analysis reveals four (C)H···O (2.47 Å) and two P···O (3.57 Å) interactions. Thus, the stabilization energy in one interaction can be roughly estimated to be 1–1.5 kcal/mol.

It is noted that hydrogen bonding interactions with the involvement of C–H bond are known.[19–22] The $CH_4{\cdots}H_2O$ associate had a 0.004 (HF/6-31++G**//HF/6-311G**) electron density at the bond critical point.[21] In case of the $CH_3CH_2CH_2O^-$ anion, the (B3LYP/6-311++G**) density at the bond critical point on the path connecting the methyl hydrogen to the oxygen within the same anion was 0.016.[22] All these data compare favorably to our results.

The diastereoselective addition of the $>P(O)^-$ anion onto the α,β-double-bond in tetrahydrophosphinine oxide **1** (only one diastereomer was formed in each case) is the consequence of the preference for the twist-boat conformer with axial $P(O)Y_2$ substituent making possible some types of intramolecular stabilization shown above. Using the Hammond's principle[23] and assuming product-like transition states, it is the stability of the tetrahydrophosphinine oxides (**2**–**5**) that controls the outcome and hence the diastereoselectivity of the Michael addition. The stability of the tetrahydrophosphinine oxides (**2**–**5**) is in turn influenced by the intramolecular interactions shown above.

Likewise **2a**, the disulfide derivative (**7**) also prefers the twist-boat/*trans*$_1$ form (Table 2), being apparently stabilized by the $Ph_2P{=}S{\cdots}H_2C{-}P$ interaction (Fig. 7). The H···S distance is 2.69 Å, suggesting a weaker interaction as compared with that observed in the corresponding P-oxide (**2a**). It is notworthy that there is also an interaction between the P=S moiety and an aromatic proton. The situation is fully analogous with that observed for the P-oxide (**2a**). From the above examples one can see how a variety of favorable intramolecular interactions may influence the conformational situation and hence the diastereoselectivity.

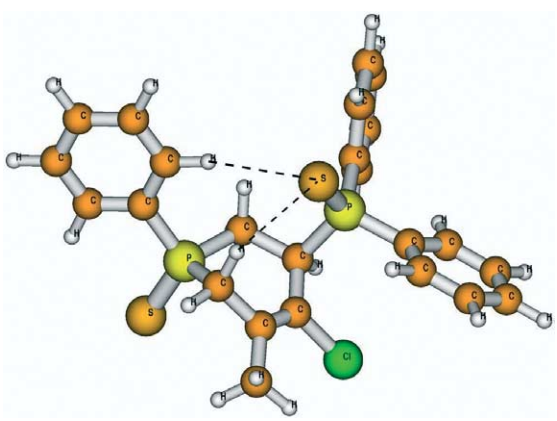


Figure 7. Perspective view of the twist-boat/*trans*$_1$ conformer of **7** with bond lengths (Å), bond angles (°) and torsion angles (°) obtained at the B3LYP/6-31+G*//3-21G* level of theory. P(1)–C(2) 1.849, C(2)–C(3) 1.578, C(3)–C(4) 1.521, C(4)–C(5) 1.339, C(5)–C(6) 1.526, C(6)–P(1) 1.840, P(1)–C′ 1.824, C(3)–P′ 1.881, P(1)–C(2)–C(3) 115.1, C(2)–C(3)–C(4) 116.0, C(3)–C(4)–C(5) 126.5, C(4)–C(5)–C(6) 119.2, C(5)–C(6)–P(1) 107.4, C(6)–P(1)–C(2) 99.5, C(2)–C(3)–P′ 109.0, C(4)–C(3)–P′ 111.6, C(2)–P(1)–C′ 104.8, C(6)–P(1)–C′ 105.5, P1–C(2)–C(3)–C(4) 8.3, P(1)–C(6)–C(5)–C(4) 51.1, P(1)–C(2)–C(3)–P′ −118.6, C(5)–C(4)–C(3)–C(2) −32.9, C(5)–C(6)–P(1)–C′ −169.8.

3. Summary

In summary, a diastereoselective synthesis of a series of 1,2,3,6-tetrahydrophosphinine oxides with an exocyclic P-function in position 3 was developed by the Michael addition of $>P(O)^-$ to the α,β-double-bond of 1,2-dihydrophosphinine oxides.

The conformational situation of the new tetrahydrophosphinine oxides was evaluated by high level quantum chemical calculations that proved to be reliable on the basis of a comparison with a reference structure. It was found that the conformation of the 1,2,3,6-tetrahydrophosphinine oxides is highly sensitive towards the substituent effects.

The tetrahydrophosphinine oxide lacking any substituent in position 3 exists in a half-chair conformation. At the same time, the 3-phosphinoxido- and 3-phosphono-tetrahydrophosphinine derivatives adopt a twist-boat conformation containing the exocyclic P-function in the axial position that may make at least three kinds of weak intramolecular interactions possible. A half-chair conformer is preferred, however, in the case of the 3-$P(O)(OH)_2$ substituent due to an intramolecular H-bonding.

4. Experimental

4.1. General

The ^{31}P-, ^{13}C and ^1H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hertz. FAB mass spectrometry was performed on a ZAB-2SEQ instrument at 70 eV.

4.2. General procedure

To 2.47 mmol of the dialkyl phosphite or diphenylphosphine oxide in 15 mL of dry chloroform was added 1.24 mL (2.47 mmol) of 2 M trimethylaluminum in hexane at 0 °C. After a period of 20 min stirring, 2.47 mmol of the corresponding dihydrophosphinine oxide (**1a**–**c**)[10–12] in 5 mL of chloroform was added dropwise. After complete addition, the cooling bath was removed and the contents of the flask were stirred for 20 h. Then, the mixture was hydrolyzed by the addition of 2.4 mL of conc. hydrochloric acid in 22 mL of water. After filtration, the organic phase was separated and dried (Na_2SO_4). The crude product obtained after filtration and evaporation was purified by column chromatography (silica gel, 3% methanol in chloroform) to afford compound **2a** [from **1a** and

$Ph_2P(O)H$], products **3a**,**c**, **4a**–**c** and **5c** [from **1a**–**c** and $(MeO)_2P(O)H$, $(EtO)_2P(O)H$ or $(BnO)_2P(O)H$, respectively]. The following products were thus synthesized:

4.2.1. 4-Chloro-3-diphenylphosphinoxido-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine-1-oxide (2a). Yield: 0.78 g (72%) as a crystalline compound; mp: 170–172 °C; δ_{P_2} 34.0 (d, $^3J_{PP}$=13.8 Hz), δ_{P_1} 34.8 (d, $^3J_{PP}$=13.8 Hz); δ_C 23.6 (dd, ^1J=6.0 Hz, ^2J=1.71 Hz, C_5–CH_3), 25.3 (d, ^1J=71.8 Hz, C_2), 34.8 (d, ^1J=61.0 Hz, C_6), 45.0 (dd, ^1J=5.2 Hz, ^2J=65.5 Hz, C_3), 122.7 (dd, ^1J=8.0 Hz, ^2J=16.7 Hz, C_5), 128.2 (d, ^2J=12.0 Hz, $C_{3''}$),[a] 128.5 (d, ^2J=11.8 Hz, $C_{3''}$),[a] 128.9 (d, ^1J=11.3 Hz, $C_{3'}$),[a] 129.7 (d, ^1J=8.9 Hz, $C_{2'}$),[a] 130.1 (d, ^1J=3.6 Hz, C_4), 131.1 (d, ^2J=63.2 Hz, $C_{1''}$), 131.1 (d, ^2J=8.8 Hz, $C_{2''}$),[a] 131.4 (d, ^2J=9.4 Hz, $C_{2''}$),[a] 131.7 (d, ^1J=2.0 Hz, $C_{4'}$),[b] 132.0 ($C_{4''}$),[b] 132.1 (d, ^2J=2.0 Hz, $C_{4''}$),[b] 133.7 (d, ^1J=99.2 Hz, $C_{1'}$), [a,b]tentative assigment; δ_H 1.77 (J=4.4 Hz, 3H, C_5–CH_3), 2.51–2.71 (m, 3H, C(3)H and P–CH_2), 3.83–3.93 (m, 2H, P–CH_2), 7.42–7.94 (m, 15H, Ar); IR (KBr disc) 1182, 1120, 725 cm^{-1}; $(M+H)^+$ found 441.0911, $C_{24}H_{24}ClO_2P_2$ requires 441.0940 for the ^{35}Cl isotope.

4.2.2. 4-Chloro-3-dimethylphosphono-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine-1-oxide (3a). Yield: 0.34 g (40%) as a thick oil; δ_{P_2} 27.9 (d, $^3J_{PP}$=18.4 Hz), δ_{P_1} 32.2 (d, $^3J_{PP}$=18.4 Hz); δ_C 23.8 (dd, ^1J=7.2 Hz, ^2J=3.2 Hz, C_5–CH_3), 26.7 (dd, ^1J=71.5 Hz, ^2J=3.5 Hz, C_2), 34.8 (dd, ^1J=63.7 Hz, ^2J=1.9 Hz, C_6), 41.8 (dd, ^1J=5.7 Hz, ^2J=144.5 Hz, C_3), 53.4 (d, ^2J=7.1 Hz, CH_3O), 53.8 (d, ^2J=7.1 Hz, CH_3O), 122.8 (dd, ^1J=10.3 Hz, ^2J=15.1 Hz, C_5), 128.8 (d, ^1J=10.7 Hz, $C_{3'}$), 129.7 (d, ^1J=8.7 Hz, $C_{2'}$), 130.3 (dd, ^1J=10.0 Hz, ^2J=7.1 Hz, C_4), 132.0 (d, ^1J=2.1 Hz, $C_{4'}$), 133.8 (d, ^1J=99.5 Hz, $C_{1'}$); δ_H 1.84 (J=5.0 Hz, 3H, C_5–CH_3), 2.48–2.67 (m, 3H, C(3)H and P–CH_2), 3.23–3.39 (m, 2H, P–CH_2), 3.80 (^1J=7.1 Hz, 3H, CH_3O), 3.82 (^1J=7.2 Hz, 3H, CH_3O), 7.35–7.67 (m, 5H, Ar); IR ν_{max} (film) 1243, 1189, 1051 cm^{-1}; $(M+H)^+$ found 349.0510, $C_{14}H_{20}ClO_4P_2$ requires 349.0525 for the ^{35}Cl isotope.

4.2.3. 4-Chloro-3-diethylphosphono-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine-1-oxide (4a). Yield: 0.43 g (46%) as a thick oil; δ_{P_2} 25.5 (d, $^3J_{PP}$=17.9 Hz), δ_{P_1} 32.7 (d, $^3J_{PP}$=17.9 Hz); δ_C 16.5 (d, ^2J=4.8 Hz, CH_3CH_2), 16.5 (d, ^2J=5.2 Hz, CH_3CH_2), 23.8 (dd, ^1J=6.9 Hz, ^2J=2.8 Hz, C_5–CH_3), 26.7 (dd, ^1J=71.8 Hz, ^2J=3.3 Hz, C_2), 34.8 (d, ^1J=62.5 Hz, C_6), 42.4 (dd, ^1J=5.8 Hz, ^2J=144.2 Hz, C_3), 63.1 (d, ^2J=7.1 Hz, CH_2O), 63.5 (d, ^2J=7.1 Hz, CH_2O), 123.2 (dd, ^1J=10.2 Hz, ^2J=15.3 Hz, C_5), 128.9 (d, ^1J=11.3 Hz, $C_{3'}$)*, 129.8 (d, ^1J=9.1 Hz, $C_{2'}$)*, 130.1 (dd, ^1J=10.2 Hz, ^2J=7.1 Hz, C_4), 132.1 (d, ^1J=2.2 Hz, $C_{4'}$), 134.0 (d, ^1J=99.9 Hz, $C_{1'}$), *may be reversed; δ_H 1.32 (t, J=7.0 Hz, 3H, CH_2CH_3), 1.32 (t, J=7.0 Hz, 6H, CH_2CH_3), 1.83 (d, J=5.7 Hz, 3H, C_5–CH_3), 2.48–2.66 (m, 3H, C(3)H and P–CH_2), 3.22–3.44 (m, 2H, P–CH_2), 4.13–4.22 (m, 4H, CH_2O), 7.37–7.62 (m, 5H, Ar); IR ν_{max} (film) 1243, 1194, 1023 cm^{-1}; $(M+H)^+$ found 377.0821, $C_{16}H_{24}ClO_4P_2$ requires 377.0838 for the ^{35}Cl isotope.

4.2.4. 4-Chloro-3-diethylphosphono-5-methyl-1-(4-methyl)phenyl-1,2,3,6-tetrahydrophosphinine-1-oxide (4b). Yield: 0.24 g (25%) as a thick oil; δ_{P_2} 25.5 (d, $^3J_{PP}$=18.4 Hz), δ_{P_1} 32.3 (d, $^3J_{PP}$=18.4 Hz); δ_C 16.6 (d, ^2J=5.4 Hz, CH_3CH_2), 21.7 (ArCH_3), 24.0 (dd, ^1J=7.2 Hz, ^2J=2.6 Hz, C_5–CH_3), 26.8 (dd, ^1J=71.7 Hz, ^2J=4.0 Hz, C_2), 35.0 (d, ^1J=61.5 Hz, C_6), 42.6 (dd, ^1J=5.7 Hz, ^2J=144.4 Hz, C_3), 63.1 (d, ^2J=7.0 Hz, CH_2O), 63.5 (d, ^2J=7.0 Hz, CH_2O), 123.2 (dd, ^1J=10.2 Hz, ^2J=15.4 Hz, C_5), 129.7 (d, ^1J=12.0 Hz, $C_{3'}$), 129.9 (d, ^1J=9.3 Hz, $C_{2'}$), 130.2 (dd, ^1J=^2J~9.0 Hz, C_4), 130.8 (d, ^1J=102.0 Hz, $C_{1'}$), 142.6 (d, ^1J=2.3 Hz, $C_{4'}$); δ_H 1.36 (t, J=7.1 Hz, 6H, CH_2CH_3), 1.86 (d, J=5.8 Hz, 3H, C_5–CH_3), 2.38 (s, 3H, ArCH_3), 2.53–2.63 (m, 3H, C(3)H and P–CH_2), 3.25–3.43 (m, 2H, P–CH_2), 4.13–4.25 (m, 4H, CH_2O); $(M+H)^+$ found 391.0973, $C_{17}H_{27}ClO_4P_2$ requires 391.0995 for the ^{35}Cl isotope.

4.2.5. 4-Chloro-3-dimethylphosphono-5-methyl-1-etoxy-1,2,3,6-tetrahydrophosphinine-1-oxide (3c). Yield: 0.42 g (54%) as a thick oil; δ_{P_2} 28.0 (d, $^3J_{PP}$=20.1 Hz), δ_{P_1} 50.1 (d, $^3J_{PP}$=20.1 Hz); δ_C 16.3 (d, ^1J=5.9 Hz, CH_2CH_3), 23.5 (d, ^1J=9.5 Hz, C_5–CH_3), 24.0 (dd, ^1J=97.5 Hz, ^2J=4.5 Hz, C_2), 31.6 (d, ^1J=85.6 Hz, C_6), 41.1 (dd, ^1J=4.8 Hz, ^2J=144.3 Hz, C_3), 53.0 (d, ^2J=6.8 Hz, CH_3O), 53.4 (d, ^2J=6.9 Hz, CH_3O), 60.3 (d, ^1J=6.1 Hz, CH_2O), 120.9 (dd, ^1J=10.3 Hz, ^2J=16.5 Hz, C_5), 130.0 (dd, ^1J=10.5 Hz, ^2J=7.5 Hz, C_4); δ_H 1.26 (t, J=7.0 Hz, 3H, CH_2CH_3), 1.91 (d, J=5.5 Hz, 3H, C_5–CH_3), 2.13–2.39 (m, 3H, C(3)H and P–CH_2), 2.98 (dt, J_1=16.1 Hz, J_2=7.0 Hz, 1H, P–CH), 3.17–3.30 (m, 1H, P–CH), 3.75 (d, J=7.7 Hz, 3H, CH_3O), 3.78 (d, J=8.0 Hz, 3H, CH_3O), 3.98–4.05 (m, 2H, CH_2O); IR ν_{max} (film) 1214, 1184, 1031 cm^{-1}; $(M+H)^+$ found 317.0465, $C_{10}H_{20}ClO_5P_2$ requires 317.0475 for the ^{35}Cl isotope.

4.2.6. 4-Chloro-3-diethylphosphono-5-methyl-1-etoxy-1,2,3,6-tetrahydrophosphinine-1-oxide (4c). Yield: 0.41 g (48%) as a thick oil; δ_{P_2} 25.4 (d, $^3J_{PP}$=19.2 Hz), δ_{P_1} 50.8 (d, $^3J_{PP}$=19.2 Hz); δ_C 15.8 (d, J=5.4 Hz, CH_3CH_2), 15.9 (CH_3CH_2), 16.1 (d, J=5.9 Hz, CH_3CH_2), 23.2 (d, ^1J=2.4 Hz, C_5–CH_3), 23.7 (dd, ^1J=103.8 Hz, ^2J=5.1 Hz, C_2), 31.4 (d, ^1J=85.1 Hz, C_6), 41.3 (dd, ^1J=4.9 Hz, ^2J=144.0 Hz, C_3), 60.1 (d, J=6.2 Hz, CH_2O), 62.3 (d, J=7.1 Hz, CH_2O), 62.8 (d, J=7.1 Hz, CH_2O), 121.0 (dd, ^1J=10.1 Hz, ^2J=17.0 Hz, C_5), 129.6 (dd, ^1J=10.2 Hz, ^2J=8.0 Hz, C_4); δ_H 0.95–1.02 (m, 9H, CH_2CH_3), 1.62 (d, J=5.4 Hz, 3H, C_5–CH_3), 1.92–2.01 (m, 2H, P–CH_2), 2.03–2.14 (m, 1H, C(3)H), 2.76 (dt, J_1=15.0 Hz, J_2=7.2 Hz, 1H, P–CH), 2.88–3.02 (m, 1H, P–CH), 3.68–3.79 (m, 2H, CH_2O), 3.79–3.91 (m, 4H, CH_2O); IR ν_{max} (film) 1244, 1181, 1030 cm^{-1}; $(M+H)^+$ found 345.0765, $C_{12}H_{24}ClO_5P_2$ requires 345.0788 for the ^{35}Cl isotope.

4.2.7. 4-Chloro-3-dibezylphosphono-5-methyl-1-etoxy-1,2,3,6-tetrahydrophosphinine-1-oxide (5c). Yield: 0.43 g (37%) as a thick oil; δ_{P_2} 26.3 (d, $^3J_{PP}$=22.1 Hz), δ_{P_1} 49.2 (d, $^3J_{PP}$=22.1 Hz); δ_C 16.6 (d, ^2J=5.6 Hz, CH_3CH_2), 23.9 (d, ^1J=8.0 Hz, C_5–CH_3), 24.3 (d, ^1J=99.2 Hz, C_2), 31.4 (d, ^1J=85.4 Hz, C_6), 42.2 (d, ^2J=111.3 Hz, C_3), 60.4 (d, ^2J=6.1 Hz, CH_3CH_2), 68.0 (d, J=7.1 Hz, PhCH_2), 68.5 (d, J=7.0 Hz, PhCH_2), 121.0 (dd, ^1J=10.5 Hz, ^2J=16.7 Hz, C_5), 127.9 (C_β), 128.0 (C_β), 128.3 (C_γ, C_δ), 129.9 (dd, ^1J=10.5 Hz, ^2J=7.9 Hz, C_4), 135.5 (d, ^2J=5.4 Hz, C_α), 135.6 (d, ^2J=5.4 Hz, C_α); δ_H 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.92 (d, J=5.6 Hz, 3H, CH_3),

2.19–2.39 (m, 3H, C(3)H and P–CH_2), 2.95 (dt, J_1=16.2 Hz, J_2=7.2 Hz, 1H, P–CH), 3.24–3.40 (m, 1H, P–CH), 3.95–4.12 (m, 2H, OCH_2), 5.04–5.14 (m, 4H, PhCH_2); IR ν_{max} (film) 1247, 1208, 1024 cm^{-1}; $(M+H)^+$ found 469.1521, $C_{22}H_{28}ClO_5P_2$ requires 469.1547 for the ^{35}Cl isotope.

4.2.8. 4-Chloro-3-phosphono-5-methyl-1-ethoxy-1,2,3,6-tetrahydrophosphinine-1-oxide (6). To the mixture of 0.60 g (1.28 mmol) of the 3-dibenzylphosphono-tetrahydrophosphinine oxide (**5c**) in 40 mL of methanol was added 0.60 g of SQ-6 palladium on carbon. The suspension was hydrogenated at 1 bar at room temperature until 55 cm^3 of hydrogen was absorbed (6 min). The mixture was filtered, the solvent evaporated and the residue was purified by column chromatography (silica gel, 3% methanol in chloroform) to give 0.30 g (79%) of **6** as a crystalline compound; mp: 164–166 °C. δ_{P_2} 24.3 (d, $^3J_{PP}$=16.6 Hz), δ_{P_1} 55.9 (d, $^3J_{PP}$=16.6 Hz); δ_C 16.6 (d, ^2J=5.8 Hz, CH_3CH_2), 23.8 (d, ^1J=8.4 Hz, C_5–CH_3), 24.5 (d, ^1J=97.3 Hz, C_2), 31.6 (d, ^1J=85.8 Hz, C_6), 42.8 (d, ^2J=141.1 Hz, C_3), 61.3 (d, ^2J=6.5 Hz, CH_3CH_2), 123.0 (dd, ^1J=9.7 Hz, ^2J=16.6 Hz, C_5), 128.1 (dd, ^1J=9.8 Hz, ^2J=7.9 Hz, C_4); δ_H 1.34 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.96 (d, J=5.4 Hz, 3H, C_5–CH_3), 3.99–4.14 (m, 2H, CH_2O); IR (KBr disc) 3450, 1244, 1134, 1029 cm^{-1}; $(M+H)^+$ found 289.0151, $C_8H_{16}ClO_5P_2$ requires 289.0162 for the ^{35}Cl isotope.

4.2.9. 4-Chloro-3-diphenylphosphinsulfido-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine-1-sulfide (7). To 0.10 g (0.23 mmol) of the 3-diphenylphosphinoxido-tetrahydrophosphinine oxide (**2a**) in 15 mL of dry benzene was added 0.06 g (0.26 mmol) of phosphorus pentasulfide. The mixture was refluxed and stirred for 20 h under nitrogen. After filtration and evaporating of the solvent the residue was purified by column chromatography (silica gel, 3% MeOH in $CHCl_3$) to give 0.10 g (93%) of product **7** as a thick oil. δ_{P_2} 31.6 (d, $^3J_{PP}$=27.1 Hz), δ_{P_1} 55.7 (d, $^3J_{PP}$=27.1 Hz); δ_C 25.5 (d, ^1J=7.6 Hz, C_5–CH_3), 31.6 (d, ^1J=53.2 Hz, C_2), 37.6 (dd, ^1J=2.1 Hz, ^2J=50.8 Hz, C_6), 44.0 (dd, ^1J=5.0 Hz, ^2J=53.1 Hz, C_3), 122.7 (dd, ^1J=8.4 Hz, ^2J=18.3 Hz, C_5), 128.4 (d, ^2J=12.2 Hz, $C_{3''}$),[a] 128.9 (d, ^2J=12.1 Hz, $C_{3''}$),[a] 129.1 (d, ^1J=11.9 Hz, $C_{3'}$),[a] 130.8 (d, ^2J=79.4 Hz, $C_{1''}$),[b] 130.9 (d, ^1J=77.5 Hz, $C_{1'}$),[b] 131.6 (d, ^2J=8.7 Hz, $C_{2''}$),[a] 131.6 (d, ^2J=10.4 Hz, $C_{2''}$),[a] 131.8 ($C_{4'}$),[c] 132.0 (d, ^2J=4.3 Hz, $C_{4''}$),[c] 132.0 (d, ^1J=10.2 Hz, $C_{2'}$),[b] 132.3 (d, ^2J=3.2 Hz, $C_{4''}$),[c] 132.5 (C_4), [a–c]tentative assignment; δ_H 2.04 (J=4.6 Hz, 3H, C_5–CH_3), 2.09–2.20 (m, 1H, P–CH), 2.50 (dt, J_1=15.0 Hz, J_2=3.1 Hz, 1H, C(3)H), 3.00–3.10 (m, 1H, P–CH), 3.75–3.84 (m, 1H, P–CH), 4.55–4.64 (m, 1H, P–CH), 7.42–8.08 (m, 15H, Ar); $(M+H)^+$ found 472.0382, $C_{24}H_{23}ClS_2P_2$ requires 472.0405 for the ^{35}Cl isotope.

Acknowledgements

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Efficient oxidative *ipso*-fluorination of *para*-substituted phenols using pyridinium polyhydrogen fluoride in combination with hypervalent iodine(III) reagents

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Abstract—Diacetoxyiodobenzene (PIDA) and bis(trifluoroacetoxy)iodobenzene (PIFA) in the presence of pyridinium polyhydrogen fluoride (PPHF) are effective for the fluorination of *para*-substituted phenols to give a variety of 4-fluorocyclohexa-2,5-dienones in a good yield. (*R*,*S*)-1,1′-Bi-5,6,7,8-tetrahydro-2-naphthol (and its monoacetate) yields atropoisomeric fluorocyclohexadienones. The 4-substituted carbamate open-chain phenols were readily converted to fluorohydroindolenone and fluorohydroquinolenone derivatives by intramolecular conjugate addition.

1. Introduction

The importance of fluorinated compounds, in particular to the agrochemical and pharmaceutical industries, has stimulated considerable interest in the development of general and convenient fluorinating agents.[1]

Using electrophilic fluorinating reagents (fluorine,[2] trifluoromethylhypofluorite CF_3OF,[3] perchloryl fluoride ClO_3F,[4] N-fluoroperfluoroalkylsulfonylimides,[5] Selectfluor™ F-TEDA BF_4[6]) as the source of fluorine, was previously reported for more or less efficient synthesis of 4-fluorocyclohexa-2,5-dienones. These reagents are also strong oxidants, and require special equipment due to their unstability and toxicity.[7]

Olah's regent (pyridinium polyhydrogen fluoride) was found to be convenient and effective nucleophilic fluorinating agent.[8] The oxidative fluorination of phenols using HF-base in combination with Pb(IV), was reported to give *ipso*-fluorination, but the application of this method was limited to few phenols derivatives and yields of dienones are low or unspecified.[9] Moreover, heavy metal oxidants are highly toxic and must be handled very carefully.

Hypervalent iodine(III) reagents have been used for the synthesis of many 4,4-disubstitued cyclohexa-2,5-dienones from phenols derivatives.[10–16] In particular phenyliodine bis(trifluoroacetate) (PIFA) or phenyliodine diacetate (PIDA) have received a great deal of attention due to low toxicity, ready availability, easy handling, and reactivities similar to that of heavy metal reagents or anodic oxidation.

The nucleophilic *ipso*-fluorination of 4-alkylphenols, using pyridinium polyhydrogen fluoride (PPHF), and phenyliodine bis(trifluoroacetate) PIFA, or phenyliodine-(diacetate) PIDA is much easier to handle and extremely simplifies work-up. Having reported on its applicability in preliminary communications,[17–19] we now report in full the use of remarkable combination of Olah's reagent and hypervalent iodine(III) reagent as a convenient general purpose for *ipso*-fluorination of various *para*-alkylphenols.

The postulated mechanism implies reaction of the reagent PIFA on the phenolic group and trapping of the resulting intermediate by a nucleophilic fluorine (Scheme 1). The structure of *para*-fluoroalkyldienones was supported by spectral data and elemental analysis. The ^{1}H NMR spectrum showed signals for vinylic hydrogen at $6.2<\delta<6.4$ (d, $J_{H-H}=10$ Hz, H-2) and $6.9<\delta<7.2$ (dd, $J_{H-H}=10$ Hz, $J_{H-F}=6$ Hz, H-3) characteristic of an α,β-unsaturated fluorodienone. This was supported by the presence in the ^{13}C NMR spectra of the coupling constants between fluorine

Keywords: Ipsofluorination; Pyridinium polyhydrogen fluoride; Hypervalent iodine; Fluorodienone.
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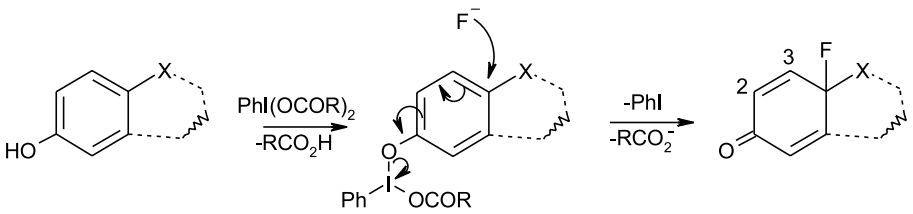


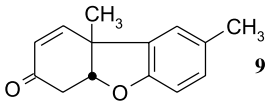
Scheme 1.

and carbons, $160<J_1<170$, $22<J_2<30$, $7<J_3<10$ and $4<J_4<7$.

2. Results and discussion

2.1. *Ipso*-fluorination of monocyclic *para*-substituted phenols

The fluorination reaction of *para*-alkylphenols **1**–**3** was examined by treatment with PIFA-PPHF in dichloromethane at 25 °C. The reaction proceeded smoothly to give the 4-fluoro-4-alkylcyclohexa-2,5-dienones **8**–**11**. Formation of the known Pummerer ketone **9** (8%) as a by-product was observed when starting from *para*-cresol **1**. This oxidative dimerization can be accounted for by similar process.

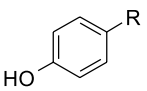
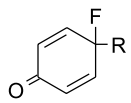


9

Pummerer ketone

Similarly, 4-halophenols **4** and **5** were converted by treatment with PIDA-PPHF to the corresponding fluorocyclohexadienones **12** and **13** in fair yields (Table 1). Reaction of phenols **4** and **5** with PIFA is very rapid giving a complex mixture of products. In the presence of the more acidic trifluoroacetic acid generated in the reaction, the corresponding dienones **12** and **13** yield *para*-benzoquinone and phenols resulting from dienone-phenol rearrangement.

Table 1.

Phenols		Products (%)
		
1 R=CH_3	PIFA-PPHF	**8** (68)
2 R=CH_3CH_2		**10** (61)
3 R=CH_2CH_2Br		**11** (48)
4 R=F	PIDA-PPHF	**12** (67)
5 R=Cl		**13** (40)
6 R=NO_2		—[a]
7 R=CN		—[a]

[a] No reaction.

Use of anodic oxidation on Pt[20] or oxidant Pb((IV)[9] was reported to yield dienones **12** (26%) and **13** (15%). The reaction between electrophilic fluorinating agents and 4-halophenols derivatives was reported to introduce fluorine in *ortho* position of an aromatic ring[21] or to give only traces of 4-halo-4-fluorodienones in the crude reaction mixture.[6]

No reaction proceeded when using compounds **6** or **7** bearing a strong inductive electron-attracting NO_2 or CN substituents.

2.2. *Ipso*-fluorination of bicyclic phenols

In order to extend this method, the bicyclic rings were selected as branched phenols. Thus phenols **14** and **15** were readily transformed by treatment with PIFA-PPHF into the corresponding 4-fluorocyclohexa-2,5-dienone derivatives **17** and **18** in 42–66% yield (Table 2).

The reactivity of bicyclic compounds led to study the reaction of 4-chloronaphtalen-1-ol **16**, by treatment with PIDA-PPHF. The reaction resulted in the formation of 4-chloro-4-fluorodienone **19** (30%) and naphtoquinone **20** as a by-product.

The use of 1.2 mmol of phenyliodine bis(trifluoroacetate) PIFA or phenyliodine diacetate PIDA and 0.1 mL of pyridinium polyhydrogen fluoride (70:30; v:v) per one mmol of phenol has been found to be effective.

Several variables were examined in effort to enhance the formation of fluorodienones. Changing the ratio of HF and pyridine or employing other amine poly-(hydrogen fluoride), complexes did not improve the yield of dienones.

2.3. Synthesis of atropoisomeric fluorocyclohexadienones

The synthesis of atropoisomeric fluorocyclohexadienones, starting from (*R*,*S*)-1,1′-bi-5,6,7,8-tetrahydro-2-naphthol **21a** (and its monoacetate **21b**) prepared by hydrogenation of the commercially available (*R*,*S*)-1,1′-bi-2-naphthol was similarly achieved.

The reaction was carried out as previously described, pyridinium polyhydrogen fluoride, then $C_6H_5I(OCOCF_3)_2$ being added to a solution of the phenol in dichloromethane.

Table 3 shows that with 1.2 equiv. of PIFA fluorination of phenol **26a** yields a complex mixture of mono and difluoro derivatives and of the starting material. Phenols acetates being unreactive, reaction of monoester **21b** gives only racemic cyclohexadienones **22b** and **23b**.

In these compounds the configuration *R* or *S* of the newly created asymmetric center 4a, coupled with the atropoisomeric system (indicated as *Ra* or *Sa*), accounts for the formation of these products. Structure of dienone **22b** has been determined by X-ray analysis (Fig. 1), implying for dienone **23b** the proposed structure.

Table 2.

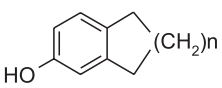
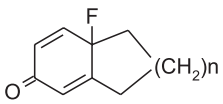
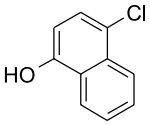
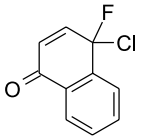
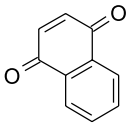
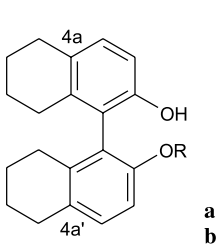
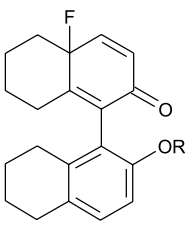
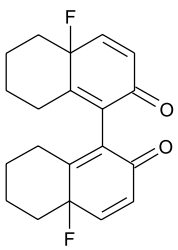
Phenols	Conditions	Products (%)	
			
14 n=1 **15** n=2	PIFA-PPHF	**17** (42) **18** (66)	
			
16	PIDA-PPHF	**19** (30)	**20** (20)

Table 3.



a R=H
b R= $COCH_3$





(*R*,*S*)-21

22 (*RSa*,*SRa*)
23 (*RRa*,*SSa*)

24 (R^*, R^*, Ra^*)
25 (R^*, S^*, Ra^*)
26 (R^*, R^*, Sa^*)

Entry	Substrate	PIFA (equiv.)	Products (%)
1	**21a**	1.2	**21a**+**22a**+**23a**+**24**+**25**+**26**
2	**21b**	1.2	**22b**+**23b** (65)(molar ratio 40/60)
3	**22a**	1.2	**25**+**26** (42) (molar ratio 28/72)
4	**23a**	1.2	**25**+**24** (48) (molar ratio 83/17)
5	**21a**	2.4	**24**+**25**+**26** (45) (molar ratio 17/65/18)

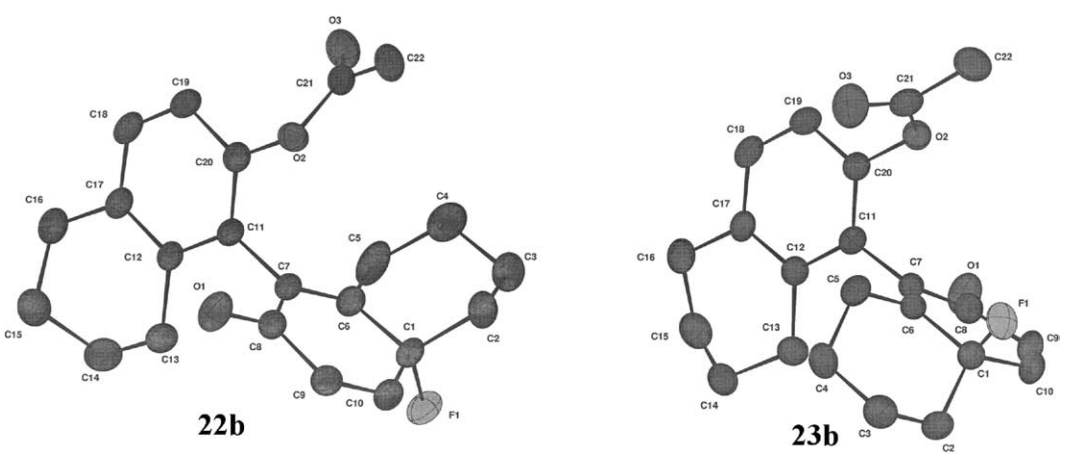


Figure 1. X-ray diagram of compounds **22b** and **23b**.

Mild hydrolysis ($NaHCO_3/H_2O$) of esters **22b** and **23b** yields the corresponding phenols **22a** and **23a**. Entries 3 and 4 show that fluorination of these phenols leads to racemic ketones **25** and **26**, and **24** and **25**, respectively, confirming that the configuration of atropoisomers has been maintained during alkaline hydrolysis of esters **22b** and **23b**. Ketones **24**, **25** and **26** are obtained directly when the reaction is carried out on phenol **21a** (entry 5). The second fluorination

creates a second asymmetric center at C-4′a, identical with the first one. Six isomers could be formed and are effectively obtained, corresponding to racemic ketones **24**, **25** and **26**.

Formation of a common difluorodienone **25** starting either from phenol **22a** or from phenol **23a** was expected and its structure has been confirmed by X-ray analysis[22] (Fig. 2). Structures of isomers **24** and **26** follow from those of their respective precursors **23a** and **22a**.

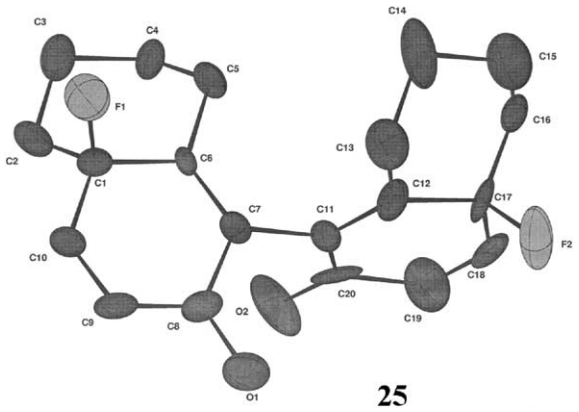
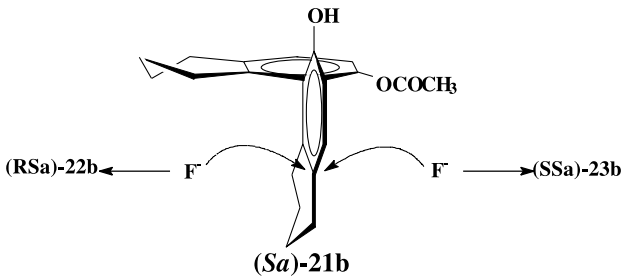


Figure 2. X-ray diagram of compound **25**.

It should be noticed that whereas ketones **24** and **26** exhibit only ten different carbon signals in ^{13}C NMR, twenty signals are observed for ketone **25**, in concordance with different configurations for the asymmetric carbons. These results deserve several comments.

Fluorination of monoester **21b** appears to be poorly stereoselective (**22b/23b** molar ratio 40/60). This reflects, according to the conformation of the substrate, a slight preference for nucleophilic fluorination on the face occupied by the acetoxy group (Scheme 2).



Scheme 2.

On the other hand, from the results of entries 3–5 we can infer that fluorination of **21a** is much more selective, with a pronounced preference for the face occupied by the hydroxyl group (**22a/23a** calculated molar ratio 23/78).

This selectivity might be due to an anchimeric assistance through an hydrogen bond between the hydroxyl group and the solvated fluoride $F(HF)_n^-$. A similar effect was observed previously in the addition of hydrogen fluoride on unsaturated alcohols in the steroid series.[23]

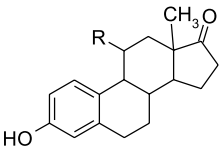
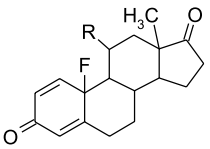
A complete reversal of selectivity is observed in the second fluorination (entries 3 and 4). The reaction occurs preferentially on the face of the phenol opposite to the carbonyl group (selectivity 28/72 with **22a**, and 17/83 with **23a**) and this is probably due to a repulsive interaction between the solvated fluoride and the oxygen atom of the carbonyl group.

2.4. Application to estrogen steroids

For preparation of angular fluorinated compounds, we applied the reaction to estrogen steroids and found that the best yield was obtained with estrone **27** to give 10β-fluoroestra-1,4-dien-3,17-dione **29**.

A similar reaction can be carried out with the 11β-hydroxy analog **28**, to yield dienone **30** (58%). Presence of a hydroxyl substituent at C-11 is known to be associated with corticosteroid activities (Table 4).[24]

Table 4.

Phenols	Products (%)
	
27 R=H **28** R=OH	**29** (77) **30** (58)

2.5. Synthesis of hydrindolenones and hydroquinolenones

Syntheses of indole derivatives have been described by oxidation of tyramine or tyrosine derivatives by treatment with phenyliodine bis(trifluoroacetate) (PIFA) or phenyliodine diacetate (PIDA), respectively.[25,26] Formation of the hexahydroindol-6-ones can be rationalized by intramolecular Michael-type reaction of the nitrogen group to the double bond of the intermediate dienone.

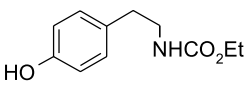
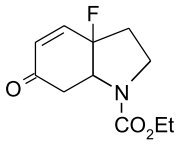
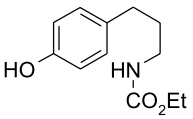
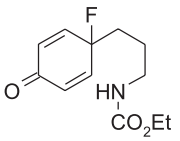
We report the synthesis of fluoro hydroindol-6-ones and of hydroquinolin-7-ones under the action of PIFA-pyridinium polyhydrogen fluoride (PPHF) on monocyclic phenols, followed by cyclization of the resulting open-chain dienones.[17,18]

Fluorination of phenols was carried out using methodology previously reported, pyridinium polyhydrogen fluoride then $C_6H_5I(OCOCF_3)_2$ being added to a solution of the phenol in dichloromethane.

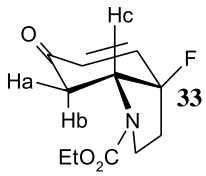
Reaction of phenol **31** with PIFA-PPHF leads directly to enone **33**, the intermediate dienone isomerizing spontaneously in the reaction conditions (Table 5). Cyclization of dienone **34** into the corresponding enones **35a** was performed by treatment with HCl in tetrahydrofuran.

In enones **33** and **35a** the ring junction was expected to be *cis* for steric reasons.[25,26] This was confirmed by NMR experiments complicated by the presence of two carbamate bond rotamers in approximately 1:1 ratio.

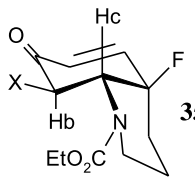
Table 5.

Phenols	Products (%)
	
31	**33** (35)
	
32	**34** (43)

Moreover, the observed $^{3}J_{HC-F}$ coupling constant (J=20 Hz) is in agreement with a *cis* ring junction, higher values being expected for a *trans* one.[27]



33



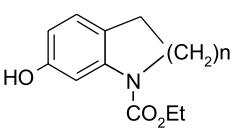
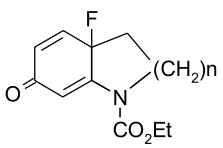
35 a X=H
b X=Br

In ^{1}H NMR experiments, coupling constants could not be measured with ketone **35a**, even at high temperature, on account of the carbamate rotamers. This problem could be circumvented by synthesizing the bromo analog **35b** (X=Br) by reaction of pyridinium perbromide on ketone **35a** in THF.[28] In the resulting ketone **35b** (X=Br, 40% yield) coupling constants J_{HBHC}=12 Hz, J_{HC-F}=12 Hz confirm the *cis* ring junction.

2.6. *Ipso*-fluorination of nitrogen-substituted polycyclic phenols

We have shown that the *ipso*-fluorination of polycyclic phenols with PIFA-PPHF yields 4-fluorocyclohexadienones. We have discovered that an analogous fluorination, can be performed on the nitrogen analogs **36** and **37** to give the corresponding dienones (Table 6). The presence of the carbamate moiety, *meta* to the hydroxyl group, does not modify the reactivity of the aromatic ring. This novel oxidative dearomatization of nitrogen-substituted polycyclic phenols should find applications in natural product chemistry.

Table 6.

Phenols	Products (%)
	
36 n=1 **37** n=2	**38** n=1 (39) **39** n=2 (29)

In summary, this study demonstrates the synthetic interest of hypervalent iodine reagents in heterocyclization chemistry, especially to prepare angular substituted fluorocyclohexenones.

3. Conclusion

A facile and efficient preparation of 4-fluorocyclohexa-2,5-dienones compounds has been developed by using Pyridinium Polyhydrogen Fluoride (PPHF) in combination with the hypervalent iodine, diacetoxyiodobenzene (PIDA) and bis(trifluoroacetoxy)iodobenzene (PIFA). Our investigations provide preparative approaches to new and complex fluorodienones. Hence, hypervalent iodine reagents show promise in replacing highly toxic heavy metal oxidants and should provide a useful tool for the syntheses of various biologically active natural products containing phenolic systems.

4. Experimental

4.1. General methods

Melting points were obtained on a BÜCHI apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz spectrometer use $CDCl_3$ as solvent with TMS as internal standard. Chemical shifts values are reported in δ ppm downfield and J values are given in Hertz. Low resolution MS was recorded on a device FINIGAN INCOS 500 in electronic impact. All reactions were run under an inert atmosphere. CH_2Cl_2 was distilled from P_2O_5. Organic extract mixtures were dried over anhydrous $MgSO_4$ and filtered and the solvent was then removed under reduced pressure. All separations were done under recrystallization or flash chromatography (MPLC) conditions on silica gel (25–40 mμ) completed, if necessary, by preparative thin-layer chromatography (TLC) performed on silica gel plates (60 GF254).

Crystal data for **22b**, **23b** and **25** were recorded at room temperature with a Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator and an X-ray tube with a Mo anticathode (l=0.71069 Å). The structure was solved using direct methods[29] and refined using least square calculation.[30]

4.2. Typical procedure for reaction PIFA or PIDA-PPHF

To a stirred solution of the phenol (1 mmol) in methylene chloride (20 ml), at first pyridinium polyhydrogen fluoride (70:30; v:v) (0.1 mL) and then phenyliodine bis(trifluoroacetate) PIFA or phenyliodine diacetate PIDA (1.2 mmol) was added. The mixture was stirred at room temperature for 30 min (PIFA), or 15 min (PIDA). Excess of solid K_2CO_3 was added and the resulting mixture was stirred under the same conditions for 5 min. After filtration, the organic filtrate was evaporated and the residue was flash chromatographed over SiO_2 to yield the dienone.

4.2.1. Preparation of 4-fluoro-4-methyl-cyclohexa-2,5-dienone (8).[2] Obtained from *para*-cresol **1** (200 mg;

1.85 mmol); PIFA (950 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.2 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (5:95; v:v) gave the following compounds.

Dienone **8** (158 mg-68%). ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 3H, J_{HF}=21.4 Hz, CH_3); 6.21 (d, 2H, J=10.2 Hz, Hα); 6.90 (dd, 2H, J=9.6 Hz, J_{HF}=6 Hz, Hβ). ^{13}C NMR ($CDCl_3$)δ 26 (d, J_2=27 Hz, –CH_3); 86.5 (d, J=161 Hz, C–F); 128.6 (d, J_3=7.5 Hz, C-2+C-6); 146.5 (d, J_2=18 Hz, C-3+C-5); 184 (C=O). EI MS (C_7H_7FO) *m/z* 126 (28) [M]+, 111 (28); 97 (100). HR MS (C_7H_7FO): calcd: 126.04809, found: 126.0480.

Pummerer ketone **9** (16 mg-8%). ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H, CH_3); 2.32 (s, 3H, CH_3Ar); 2.80 (dd, J_{gem}=17.5, 3 Hz, 1H); 3.05 (dd, J_{gem}=17.5, 3 Hz, 1H); 4.7 (m, 1H, –CH–O); 5.9 (d, 1H, J=10.2 Hz, CH=); 6.47 (d, 1H, J=10.2 Hz, CH=); 6.7 (d, 1H, J=8 Hz, H ar); 6.99 (d, 1H, J=8 Hz, H ar); 7.01 (s, 1H, H ar). EI MS *m/z*: 214 (100); 199 (89); 185 (13); 171 (71).

4.2.2. Preparation of 4-fluoro-4-ethyl-cyclohexa-2,5-dienone (10). Obtained from 4-ethylphenol **2** (1 g; 7.3 mmol); PIFA (3.8 g, 1.2 mmol); HF–pyridine (70:30; v:v) (0.8 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (5:95; v:v) gave **10** (625 mg-61%). ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, CH_3); 1.91 (m, 2H, CH_2); 6.25 (d, 2H, J=10 Hz); 6.85 (dd, 2H, J=10 Hz). ^{13}C NMR ($CDCl_3$) δ 7.4 (d, J=7 Hz, CH_3); 31.8 (d, J=24 Hz, CH_2); 89. 5 (d, J=163 Hz, C–F); 129.5 (d, J=8 Hz, C-2+C-6); 145 (d, J=22 Hz, C-3+C-5); 185 (C=O). EI-MS *m/z* (C_8H_9FO): 140; 121; 95 (100). HR MS (C_8H_9FO): calcd: 140.06374, found: 140.06370.

4.2.3. Preparation of 4-fluoro-4-(2′-bromoethyl)-cyclohexa-2,5-dienone (11). Obtained from 4-(2′-bromoethyl)-phenol **3** (150 mg, 0.83 mmol); PIFA (430 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.08 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (5:95; v:v) gave **11** (87 mg-48%). ^{1}H NMR ($CDCl_3$) δ 2.50 (m, 2H, CH_2); 3.38 (t, 2H, CH_2Br); 6.30 (d, 2H, J=10 Hz); 6.93 (dd, 2H, J=10 Hz). ^{13}C NMR ($CDCl_3$) δ 29 (CH_3); 42 (d, J=14 Hz, CH_2); 89. 5 (d, J=163 Hz, C–F); 129.5 (d, J=8 Hz, C-2+C-6); 145 (d, J=22 Hz, C-3+C-5); 185 (C=O). EI MS *m/z* (C_8H_8BrFO): 220 (10), 218 (10), 111 (47), 109 (100), 107 (100). HR MS (C_8H_8BrFO): calcd: 217.97425, found: 217.97420.

4.2.4. Preparation of 4,4-difluorocyclohexa-2,5-dienone (12). Obtained from 4-fluorophenol **4** (343 mg; 3.06 mmol); PIDA (1.2 g, 1.2 mmol); HF–pyridine (70:30; v:v) (0.3 mL) as described in typical experimental procedure. Chromatography from methylene chloride–pentane (10:90; v:v) gave **12** (266 mg-67%). ^{1}H NMR ($CDCl_3$) δ 6.34 (d, 2H, J=10 Hz, Hα); 6.84 (2H, Hβ). ^{13}C NMR ($CDCl_3$) δ 110.3 (t, J=225 Hz, CF_2); 131.7 (t, J_3=9 Hz, C-2+C-6); 137.8 (t, J_2=29 Hz, C-3+C-5); 184.1 (t, J_4=5 Hz, C=O). MS (CI isobutane) MH+: 131.

4.2.5. Preparation of 4-chloro-4-fluorocyclohexa-2,5-dienone (13). Obtained from 4-chlorophenol **5** (373 mg; 2.90 mmol); PIDA (1.1 g, 1.2 mmol); HF–pyridine (70:30; v:v) (0.3 mL) as described in typical experimental procedure. Chromatography from methylene chloride–pentane (10:90; v:v) gave **13** (176 mg-41%). ^{1}H NMR ($CDCl_3$) δ 6.23 (d, 2H, J=10 Hz, Hα); 7.04 (dd, 2H, J=10 Hz, J_{HF}=6 Hz, Hβ). ^{13}C NMR ($CDCl_3$) δ 99.3 (d, J=233 Hz, C–F); 127.8 (d, J_3=7.6 Hz, C-2+C-6); 141.3 (d, J_2=25 Hz, C-3+C-5); 182.9 (d, J_4=5 Hz, C=O). MS (CI isobutane) MH+: 147 (100), 149 (36).

4.2.6. Preparation of 7a-fluoro-1, 2, 3, 7a-tetrahydro-inden-5-one (17). Obtained from 5-indanol **14** (250 mg, 1.86 mmol); PIFA (1 g, 1.2 mmol); HF–pyridine (70:30; v:v) (0.5 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (12:88; v:v) gave **17** (120 mg-41%). ^{1}H NMR ($CDCl_3$) δ 0.8–3 (m, 6H), 6.10 (s, 1H, Hα); 6.22 (dd, 1H, J=10, 2 Hz, Hβ); 6.98 (dd, 1H, J=10, 5 Hz, Hβ). ^{13}C NMR ($CDCl_3$) δ 92.5 (d, J=161 Hz, C-7a); 123.8 (d, J=4 Hz, C-4); 131 (d, J=7 Hz, C-6); 140.5 (d, J=19 Hz); 162.5 (d, J=13 Hz, Ca); 185.7 (C=O). EI MS *m/z*: 152 (78); 133 (47); 134 (28); 109 (76); 96 (100). HR MS (C_9H_9FO): calcd: 152.06374, found: 152.0637

4.2.7. Preparation of 4a-fluoro-5,6,7,8-tetrahydro-*4aH*-naphtalen-2-one (18). Obtained from 5,6,7,8-tetrahydro-napht-2-ol **15** (300 mg, 2 mmol); PIFA (1 g, 1.2 mmol); HF–pyridine (70:30; v:v) (0.6 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (12:88; v:v) gave **18** (220 mg-66%). ^{1}H NMR ($CDCl_3$) δ 0.8–3 (m, 8H), 6.06 (s, 1H, Hα); 6.19 (dd, 1H, J_1=9.6 Hz, J_2=2.5 Hz, Hβ); 6.90 (dd, 1H, J=9.6, 6 Hz, Hβ). ^{13}C NMR ($CDCl_3$) δ 20.53 (s, C-6); 27.4 (s, C-7); 32.0 (s, C-8); 38.3 (d, J=25 Hz, C-5); 87.5 (d, J=163 Hz, C-4a); 123.9 (d, J=5 Hz, C-1); 129.35 (d, J=7.6 Hz, C-3); 145.8 (d, J=22.7 Hz, C-4), 158.7 (d, J=19.4 Hz, C-8a), 185.5 (C=O). EI MS *m/z*:166 (72); 151 (16); 138 (50); 109 (92); 96 (100). HR MS ($C_{10}H_{11}FO$): calcd: 166.07939, found: 166.0790.

4.2.8. Preparation of 4-chloro-4-fluoro-4*H*-naphtalen-1-one (19). Obtained from 4-chloronapht-1-ol **16** (175 mg; 0.98 mmol) PIDA (383 mg); HF–pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (5:95; v:v) gave the following compounds.

Dienone **19** (56 mg-29%). ^{1}H NMR ($CDCl_3$) δ 6.40 (d, 1H, J=10 Hz, C-2); 7.17 (dd, 1H, J=10 Hz, J_{HF}=6 Hz, C-3); 7.59 (t, 1H, C-7); 7.74 (t, 1H, C-6); 7.91 (d, 1H, C-5); 8.07 (d, 1H, C-8). ^{13}C NMR ($CDCl_3$) δ 101.1 (d, J=237.5 Hz, C–F); 126.5 (s, C-7); 127.0 (s, C-6+C-8); 128.2 (d, J_3=7.5 Hz, C-2); 130.7 (s, C-5); 133.9 (s, C-8a); 138.7 (d, J_2=24 Hz, C-4a); 141.8 (d, J_2=25 Hz, C-3); 182.3 (d, J_4=3.5 Hz, C=O). EI MS *m/z* ($C_{10}H_6ClFO$): 197 (11); 196 (33); 161 (100); 151 (20); 133 (98). HR MS ($C_{10}H_6ClFO$): calcd: 196.0091, found: 196.0090.

1,4-Naphtoquinone **20** (31 mg-20%). ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 2H, H-2+H-3); 7.76 (m, 2H, H-6+H-7); 8.07 (d, 2H, H-5+H-8). ^{13}C NMR ($CDCl_3$) δ 126.2 (C-5+C-8); 131.9 (C-4a+C-8a); 133.8 (C-6+C-7); 138.6 (C-2+C-3); 184.8 (C-1).

4.2.9. Preparation of (*R*,*S*)-1,1′-bi-5,6,7,8-tetrahydro-napht-2-ol (21a). To a suspension of Ru (5%)/C (0.75 g) in ethyl acetate/ethanol (1/1) (100 ml) was added racemic (*R*,*S*) 1,1′-binapht-2-ol (5 g, 17.46 mmol). The mixture was stirred at 165 °C under pressure of hydrogen (110 bars) for 4 h. After filtration, the organic filtrate was evaporated and the residue was flash chromatographed from ethyl acetate/hexane (10/90) over SiO_2 to yield **21a** (3.9 g, 75.8%). ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 2.20 (m, 4H, 2 CH_2); 2.72 (m, 4H); 4.67 (2H, OH); 6.80 (d. 4H, H-3+H-3′); 7.02 (d, 4H, H-4+H-4′). ^{13}C NMR ($CDCl_3$) δ 23.0 and 23.9 (4 CH_2, C-6+C-7+C-6′+C-7′); 27.1 and 29.2 (4 CH_2, C-5+C-8+C-5′+C-8′); 113.0 (2 CH, C-3+C-3′); 118.9 (C-1+C-1′); 130.1 and 137.1 (C-4a+C-8a+C-4a′+C-8a′); 131.0 (CH, C-4+C-4′); 151.4 (2 C–OH, C-2+C-2′). MS *m*/*z* (%): 294 (100); 248 (15). HR-MS: ($C_{20}H_{22}O_2$) calcd: 294.16198, found: 294.16370.

4.2.10. Preparation of 2′-acetoxy-1,1′-bi-5,6,7,8-tetrahydro-napht-2-ol (21b). To a solution of **21a** (495 mg, 1.68 mmol) in dichloromethane (5 mL), acetic anhydride (0.16 ml, 1.68 mmol) and pyridine (0.3 mL) were added. The mixture was stirred for 12 h at room temperature. The resulting mixture was poured into water (50 mL) and extracted with dichloroethane. The combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give **21b** (536 mg, 94.9%). ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 1.91 (s, 3H, CH_3); 1.90–2.45 (m, 4H, 2 CH_2); 2.78 (m, 4H); 4.75 (s, 1H, OH); 6.77 (d, 2H, H-3); 6.89 and 6.98 (2d, H-4+H-3′); 7.17 (d, 1H, H-4′). ^{13}C NMR ($CDCl_3$) δ 20.3 (CH3); 22.6, 22.8, 23.1 and 23.14 (4 CH_2, C-6+C-7+C-6′+C-7′); 27.0, 27.3, 29.5 and 29.7 (4 CH_2, C-5+C-8+C-5′+C-8′); 129.8 and 113.0 (2 CH, C-3+C-3′); 122.1 and 122.2 (C-1+C-1′); 129.8 and 130.3 (CH, C-4+C-4′); 129.3, 135.8, 136.1 and 138.4 (C-4a+C-8a+C-4a′+C-8a′); 147.0 (C-OR, C-2′); 150.5 (2 C-OH, C-2); 170.8 (C=O). MS *m*/*z* (%): 336 (56); 295 (100); 251 (37). HR MS: ($C_{22}H_{24}O_3$) calcd: 336.17254, found: 336.17460.

Fluorination of 2′-acetoxy-1,1′-bi-5,6,7,8-tetrahydro-napht-2-ol **21b**. To a stirred solution **21b** (467 mg, 1.39 mmol) in methylene chloride (20 ml), at first pyridinium polyhydrogen fluoride (70:30; v:v) (0.3 mL) and then phenyliodine bis(trifluoroacetate) (740 mg) was added. The mixture was stirred at room temperature for 20 min. Excess of solid K_2CO_3 was added and the resulting mixture was stirred under the same conditions for 5 min. Chromatography from ethyl acetate–hexane (10:90; v:v) gave **22b** and **23b** (molar ratio 40/60) (322 mg, 65%).

Relative yields have been determined by HPLC: chromatographic conditions: column: spherisorb 5 μm Silica, 4.6–250 mm, HPLC Technology LTD; eluent: AcOEt–hexane=2:8 (v:v), flow rate: 1 mL/min, detection λ=280 nm; HPLC. System: WATERS.

The products have been separated using preparative TLC (Plates Kieselgel 60 F_{254} MERCK).

(RRa,SSa)-1-[5′,6′,7′,8′-tetrahydro-2′-acetoxy-naphtalen-(4aH)]-4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4aH)-one (**23b**) (*less polar*) (106 mg). Compound **23b** was recrystallized in ethyl acetate/hexane (10/90, v/v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{22}H_{23}O_3F$, molecular weight *M*=354.42, crystal system: orthorhombique, *a*=8.182(2) Å, *b*=11.151(7) Å, *c*=19.990(4) Å, volume of unit cell *V*=1824(1) Å^3, space group $P2_12_12_1$, *Z*=4, D_c=1.29 g cm^{-3}, *F*(000)=752.24, μ(MoKα)=0.86 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 2.09 (s, 3H, CH_3); 2.28 (m, 6H, 3 CH_2); 2.81 (m, 2 H); 6.34 (d, *J*=10 Hz, 1H, H-3); 6.88 (m, 2H, H-4+H-3′); 7.11 (d, *J*=4.5 Hz, 1H, H-4′). ^{13}C NMR ($CDCl_3$) δ 20.9 (d, *J*=2.0 Hz), 21.0, 23.1 (d, J_3=5.4 Hz), 27.1 (d, *J*=1 Hz), 27.8, 29.6, 29.8, 38.9 (d, J_2=28.8 Hz), 87.8 (d, J_1=162.7 Hz), 119.8, 126.3, 126.8, 129.7 (d, J_3=8.0 Hz), 130.4, 130.8 (d, J_3=5.7 Hz), 135.4, 137.7, 145.9 (d, J_2=21.5 Hz), 146.5, 156.0 (d, J_2=18.8 Hz), 169.9, 183.8. MS *m*/*z* (%): 354 (13); 312 (48); 292 (100); 275 (30); 264 (47). HR MS: calcd for $C_{22}H_{23}FO_3$: 354.1631, found: 354.16100. Anal. calcd $C_{22}H_{23}FO_3$: C, 74.56; H, 6.54; F, 5.36, found: C, 74.40; H, 6.51; F, 5.57.

(RSa,SRa)-1-[5′,6′,7′,8′-tetrahydro-2′-acetoxy-naphtalen-(4aH)]-4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4aH)-one (**22b**) (*more polar*) (58 mg). Compound **22b** was recrystallized in ethyl acetate/hexane (10/90, v/v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{22}H_{23}O_3F$, molecular weight *M*=354.42, crystal system: triclinique, *a*=9.3763(9) Å, *b*=7.7472(5) Å, *c*=11.0316(9) Å, α=78.584(6)°, β=86.462(7)°, γ=68.758(7)° volume of unit cell *V*=921(1)Å^3, space group *P*-1, *Z*=2, D_c=1.29 g cm^{-3}, *F*(000)=376.12, μ(MoKα)=0.86 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 2.10 (s, 3H, CH_3); 2.23 (m, 6H, 3 CH_2); 2.77 (m, 2H); 6.35 (d, *J*=10 Hz, 1H, H-3); 6.90 (m, 2H, H-4+H-3′); 7.12 (d, *J*=4.5 Hz, 1H, H-4′). ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8 (d, *J*=2.1 Hz), 21.3, 23.1 (d, J_3=8.5 Hz), 26.8, 27.4, 29.2, 29.9, 39.5 (d, J_2=26.0 Hz), 87.9 (d, J_1=163.5 Hz), 119.7, 126.3 (d, *J*=3.6 Hz), 129.8 (d, J_3=8.0 Hz), 130.4, 130.9 (d, J_3=5.0 Hz), 135.5, 137.5, 145.9 (d, J_2=21.5 Hz), 146.8, 155.8 (d, J_2=18.8 Hz), 169.6, 183.8. MS *m*/*z* (%): 354 (8); 312 (100); 292 (23); 264 (16). HR MS: calcd for $C_{22}H_{23}FO_3$: 354.16312, found: 354.16130. Anal. calcd for $C_{22}H_{23}FO_3$: C, 74.56; H, 6.54; F, 5.36, found: C, 74.14; H, 6.59; F, 6.04.

4.2.11. Preparation of (*RSa,SRa*)-1-[5′,6′,7′,8′-tetrahydro-naphtalen(4a*H*)]-4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4a*H*)-one (22a). To a solution of **22b** (150 mg, 0.42 mmol) in methanol (15 ml) $KHCO_3$ (500 mg) was added. After 5 h, the mixture was filtered, and the organic filtrate was evaporated to give **22a** (125 mg, 95%). RMN ^{1}H ($CDCl_3$) δ 1.30–1.90 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 2.10–2.40 (m, 6H); 2.60–2.80 (m, 2H); 6.29 (d, *J*=10 Hz, 1H, H-3); 6.69 (d, *J*=4.5 Hz, 1H, H-3′); 6.86 (m, 2H, H-4+H-4′).

4.2.12. Preparation of (*RRa,SSa*)-1-[5′,6′,7′,8′-tetrahydro-naphtalen(4a*H*)]-4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4a*H*)-one (23a). To a solution of **23b** (102 mg, 0.30 mmol) in methanol (10 ml) $KHCO_3$

(400 mg) was added. After 5 h, the mixture was filtered, and the organic filtrate was evaporated to give **23a** (86 mg, 95.7%). RMN ^{1}H ($CDCl_3$) δ 1.30–1.90 (m, 8H, 4 CH_2, H-6+H-7+H-6′+H-7′); 2.10–2.40 (m, 6H); 2.60–2.80 (m, 2H); 6.29 (d, J=10 Hz, 1H, H-3); 6.69 (d, J=4.5 Hz, 1H, H-3′); 6.86 (m, 2H, H-4+H-4′).

Fluorination of (R,S)-1,1′-bi-5,6,7,8-tetrahydronapht-2-ol (**21a**). To a stirred solution **21a** (575 mg, 1.95 mmol) in methylene chloride (25 ml), at first pyridinium polyhydrogen fluoride (70:30; v:v) (0.4 mL) and then phenyliodine bis(trifluoroacetate) (2.017 g, 4.8 mmol) was added. The mixture was stirred at room temperature for 20 min. Excess of solid K_2CO_3 was added and the resulting mixture was stirred under the same conditions for 5 min. Chromatography from ethyl acetate–hexane (10:90; v:v) gave **24**, **25** and **26** (molar ratio 18/65/17) (289 mg, 45%).

Relative yields have been determined by HPLC: chromatographic conditions: column: Spherisorb 5 μm Silica, 4.6–250 mm, HPLC Technology LTD; eluent: AcOEt–hexane=2:8 (v/v); flow rate: 1 mL/min; detection λ=280 nm; HPLC. System: WATERS.

The products have been separated using preparative TLC (Plates Kieselgel 60 F_{254} MERCK).

(R,R*,Sa*)-Bi-(4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4aH)-one)* (**26**) (30 mg). ^{1}H NMR ($CDCl_3$) δ 1.05–2.40 (m, 16H); 6.26 (d, J=9.9 Hz, 2H, H-3+H-3′); 6.85 (m, 2H, H-4+H-4′). ^{13}C NMR ($CDCl_3$) δ 128.4 (d, J_3=6 Hz), 183.3 (d, J_4=5.3 Hz), 129.1 (d, J_3=8.0 Hz), 145.8 (d, J_2=23.1 Hz), 88.1 (d, J_{C-F}=163.8 Hz), 38.7 (d, J_2=25.5 Hz), 26.4, 20.5, 29.1, 156.1 (d, J_2=19.2 Hz). MS *m/z* (%): 330 (8); 310 (13); 289 (55); 262 (72); 55 (100). HR MS: ($C_{20}H_{20}O_2F_2$) calcd: 330.14314, found: 330.14190.

(R,R*,Ra*)-Bi-(4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4aH)-one)* (**24**) (13 mg). ^{1}H NMR ($CDCl_3$) δ 1.05–2.40 (m, 16H); 6.26 (d, J=9.9 Hz, 2H, H-3+H-3′); 6.85 (m, 2H, H-4+H-4′). ^{13}C NMR ($CDCl_3$) δ 128.0 (d, J_3=5.4 Hz), 182.7 (d, J_4=5.1 Hz), 129.1 (d, J_3=8.0 Hz), 145.4 (d, J_2=21.7 Hz), 87.1 (d, J_{C-F}=164.8 Hz), 39.0 (d, J_2=25.7 Hz), 27.0, 20.4, 29.2, 156.2 (d, J_2=19.4 Hz). MS *m/z* (%): 330 (7); 310 (18); 289 (73); 262 (100). HR MS ($C_{20}H_{20}O_2F_2$) calcd: 330.14314, found: 330.14190.

(R,S*,Ra*)-Bi-(4a-fluoro-5,6,7,8-tetrahydro-naphtalen-2-(4aH)-one)* (**25**) (55 mg). Compound **25** was recrystallized in ethyl acetate–hexane (10:90, v:v) and the single crystal was selected for X-ray experiment.

Crystal color: colorless prisms, chemical formula $C_{22}H_{23}O_3F$, molecular weight M=354.42, crystal system: triclinique, a=9.3763(9) Å, b=7.7472(5) Å, c=11.0316(9) Å, α=78.584(6)°, β=86.462(7)°, γ=68.758(7)° volume of unit cell V=921(1)Å^3, space group P-1, Z=2, D_c=1.29 g cm^{-3}, F(000)=376.12, μ(MoKα)=0.86 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.05–2.40 (m, 16H); 6.26 (d, J=9.9 Hz, 2H, H-3+H-3′); 6.85 (m, 2H, H-4+H-4′). ^{13}C NMR ($CDCl_3$) δ 128.0 (d, J_3=5.2 Hz), 128.4 (d, J_3=5.6 Hz), 182.8 (d, J_4=5.3 Hz), 183.3 (d, J_4=4.9 Hz), 129.0 (d, J_3=7.9 Hz), 129.1 (d, J_3=8.0 Hz), 145.6 (d, J_2=22.2 Hz), 145.8 (d, J_2=25.6 Hz), 87.7 (d, J_{C-F}=165.7 Hz), 88.0 (d, J_{C-F}=163.3 Hz), 38.5 (d, J_2=25.3 Hz), 39.1 (d, J_2=23.4 Hz), 26.6, 26.7, 20.4, 29.0, 29.7, 156.0 (d, J_2=19.1 Hz), 156.5 (d, J_2=19.2 Hz). MS *m/z* (%): 330 (12); 310 (30); 289 (71); 262 (100). HR MS calcd for $C_{20}H_{20}O_2F_2$: 330.14314, found: 330.14190. Anal. calcd for $C_{20}H_{20}O_2F_2$: C, 72.71; H, 6.10; F, 11.50, found: C, 72.60; H, 6.07; F, 12.17.

4.2.13. Fluorination of compound 22a. To a stirred solution **22a** (180 mg, 0.67 mmol) in methylene chloride (25 ml), at first pyridinium polyhydrogen fluoride (70:30; v:v) (0.1 mL) and then phenyliodine bis(trifluoroacetate) PIFA (414 mg, 0.80 mmol) was added. The mixture was stirred at room temperature for 20 min. Excess of solid K_2CO_3 was added and the resulting mixture was stirred under the same conditions for 5 min. After filtration, the organic filtrate was evaporated and the residue was flash chromatographed from ethyl acetate–hexane (20:80; v:v) over SiO_2 to give **25** and **26** (molar ratio 28/72) (80 mg-48%).

4.2.14. Fluorination of compound 23a. To a stirred solution **23a** (86 mg, 0.27 mmol) in methylene chloride (7 ml), at first pyridinium polyhydrogen fluoride (70:30; v:v) (0.03 mL) and then phenyliodine bis(trifluoroacetate) PIFA (414 mg, 0.80 mmol) was added. The mixture was stirred at room temperature for 20 min. Excess of solid K_2CO_3 was added and the resulting mixture was stirred under the same conditions for 5 min. After filtration, the organic filtrate was evaporated and the residue was flash chromatographed from ethyl acetate–hexane (20:80; v:v) over SiO_2 to give **25** and **24** (molar ratio 83/17) (95 mg-48%).

4.2.15. Preparation of 10β-fluoroestra-1,4-dien-3,17-dione (29).[4] Obtained from estrone **27** (200 mg, 0.74 mmol); PIFA (516 mg, 1.5 mmol); HF–pyridine (70:30; v:v) (0.2 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (25:75; v:v) gave **29** (165 mg-77%), mp: 143–144 °C. ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H, $-CH_3$); 6.09 (d, 1H, J=1.5 Hz, H-4); 6.19 (dd, 1H, J_1=9.6 Hz, J_2=1.5 Hz, H-2); 7.13 (dd, 1H, J=9.6, 7.5 Hz, H-1). ^{13}C NMR ($CDCl_3$) δ 13.6 (s, C-18); 54.1 (d, J=24.5 Hz, C-9); 89 (d, J=168 Hz, C-10); 123.7 (d, J=4.5 Hz, C-4); 129.4 (d, J=8.5 Hz, C-2); 144.7 (d, J=23.8 Hz, C-1); 159.7 (d, J=19.3 Hz, C-5); 184.6 (C-3); 219.2 (C-17). EI MS *m/z*: 288 (11); 270 (6); 247 (10); 231 (12); 126 (100). IR (CH_2Cl_2): 2950, 1730, 1660, 1600 cm^{-1}.

Estrone **27** (10 mg, 5%) identical with the starting material.

4.2.16. Preparation of 10β-fluoro-11-hydroxyestra-1,4-dien-3,17-dione (30). Obtained from 11β-hydroxy-estrone **28** (130 mg, 0.45 mmol); PIFA (360 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (40:60, v:v) gave **30** (80 mg-58%), mp: 160–161 °C. ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H, $-CH_3$); 3.00 (d, J=24 Hz, H-9); 4.51 (m, 1H, H-11);. 6.06 (d, 1H, J=1.5 Hz, H-4); 6.30 (dd, 1H, J_1=10 Hz, J_2=1.5 Hz, H-2); 7.30 (dd, 1H, J=10, 6.6 Hz, H-1). ^{13}C NMR ($CDCl_3$) δ 15.8

(s, CH_3−18); 57.5 (d, *J*=22 Hz, C-9); 69.2 (s, C-11); 90.5 (d, *J*=164 Hz, C-10); 123.5 (d, *J*=4 Hz, C-4); 130.6 (d, *J*=7 Hz, C-2); 143.2 (d, *J*=22 Hz, C-1); 158.5 (d, *J*=18 Hz, C-5); 184.5 (C-3); 217.8 (C-17). EI MS *m/z*: 304 (6); 286 (8); 240 (30); 84 (100). HR MS ($C_{18}H_{21}FO_3$): calcd: 304.14740, found: 304.14740.

4.2.17. Preparation of 3a-fluoro-6-oxo-2,3,3a,6,7,7a-hexahydro-indole-1-carboxylic acid ethyl ester (33). Obtained from (2-(4-hydroxyphenyl)-ethyl)-carbamic acid ethyl ester **31** (208 mg, 1 mmol), PIFA (516 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **33** (80 mg-35%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, CH_3); 2.36 (m, 3H); 3.19 (m, 1H); 3.73 (m, 2H); 4.13 (q, 2H, CH_2); 4.48 (m, 1H); 6.09 (d, 1H, *J*=10 Hz); 6.90 (dd, 1H, J_1=10 Hz, J_2=8 Hz). ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3); 34.4; 42.5; 45; 61.5 (CH_2); 91 (d, *J*=170 Hz, C–F); 130 (d, *J*=8.5 Hz); 143 (d, *J*=27 Hz); 154.6 (N-CO); 195.13 (C=O). MS *m/z*: 227 (11), 207 (30), 170 (18), 128 (28), 56 (100). HR MS ($C_{11}H_{14}FNO_3$): calcd: 227.09577, found: 227.09600.

4.2.18. Preparation of 4-fluoro-4-(3′-(N-ethoxy-carbonyl)-propyl)-cyclohexadienone (34). Obtained from (2-(4-hydroxyphenyl)-propyl)-carbamic acid ethyl ester **32** (100 mg, 0.45 mmol), PIFA (215 mg, 1.2 mmol); HF-pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **34** (50 mg-43%). ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3); 1.60 (m, 4H, 2 CH_2); 3.18 (q, 2H, CH_2NH); 4.09 (q, 2H, CH_2); 6.25 (d, 2H, *J*=10.2 Hz); 6.87 (dd, 2H, *J*=10.2, 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3); 24.5; 35.7; 40.75 (3 CH_2); 60.9 (CH_2); 88 (d, *J*=170 Hz, C–F); 129 (d, *J*=7.6 Hz); 145 (d, *J*=22 Hz); 155 (N–CO); 184 (C=O). MS *m/z*: 221 (4); 192 (8); 112 (32); 102 (100). HR MS ($C_{12}H_{16}FNO_3$): calcd: 241.1114, found: 241.1100.

4.2.19. Preparation of 4a-fluoro-7-oxo-3,4,4a,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid ethyl ester (35a). To a stirred suspension of dienone **34** (50 mg, 0.2 mmol) in THF (2 mL) hydrogen hydrochloride 1N (0.4 mL) was added. The mixture was refluxed for 24 h. The reaction mixture was filtered, and the organic phase was extracted three times with methylene chloride, dried over $MgSO_4$, and evaporated to dryness. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **35a** (30 mg, 58%). (Mixture of rotamers): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, CH_3); 1.5–2.36 (m, 7H); 2.65 (m, 2H, H-8), 2.9 (m, 1H, 1 H-5); 4.13 (q, 2H, CH); 4.15 (m, 1H); 4.85 (m, 1H), 5.97 (d, 1H, *J*=10.3 Hz), 6.86 (dd, 1H, *J*=10.3, 10.3 Hz). ^{13}C NMR ($CDCl_3$) δ 29.6 (d, *J*=25 Hz), 37.8, 37.9, 61.8, 90.2 (d, *J*=173 Hz, C–F), 129.0 (d, *J*=8.5 Hz), 150.2 (d, *J*=28 Hz), 155 (N-CO), 196.5 (C-7). EI MS *m/z* (%): 241 (22), 221 (90), 56 (100); HR-MS: calcd: 241.1114, found: 241.1100.

4.2.20. Preparation of 8-bromo-4a-fluoro-7-oxo-3,4,4a,7,8,8a-hexahydro-2H-quinoline-1-carboxylic acid ethyl ester (35b). To a stirred suspension of enone of **35a** (80 mg, 0.33 mmol) in THF (10 mL), pyridinium per-bromide (127 mg, 0.39 mmol) was added. The mixture was stirred for 2 h. The reaction mixture was filtered and the organic phase was extracted three times with methylene chloride, dried over $MgSO_4$ and evaporated to dryness. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **35b** (42 mg, 40%). (Mixture of rotamers): ^{1}H NMR ($CDCl_3$) δ 4.87 and 4.98 (t, 1H, *J*=12, 12 Hz), 5.48 and 5.53 (d, 1H, *J*=12 Hz), 6.23 (d, 1H, *J*=10.3 Hz), 7.15 and 7.17 (dd, 1H, *J*=10.3, 10.5 Hz). ^{13}C NMR ($CDCl_3$) δ 52.7 and 52.9 (2d, *J*=10 Hz), 59.4 and 60.2 (2d, *J*=23 Hz), 90.2 and 90.3 (2d, *J*=179 Hz, C–F), 127.5 and 127.6 (2d, *J*=9 Hz), 149.9 and 150.0 (2d, *J*=26 Hz), 155.4 and 155.7 (N-CO), 189.2 (C-7). EI MS *m/z* (%): 321 (10), 319 (10), 301 (5), 299 (5), 240 (60), 220 (75), 192 (90), 56 (100).

4.2.21. Preparation of 4a-fluoro-7-oxo-3,4,4a,7-tetra-hydro-2H-quinoline-1-carboxylic acid ethyl ester (39). Obtained from 7-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester **37** (221 mg, 1 mmol), PIFA (516 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **39** (65 mg-29%). ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H, CH_3OCO), 6.25 (m, 1H), 6.37 (m, 1H), 6.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 33.8 (d, *J*=25.5 Hz), 53.6 (CH_3OCO), 85.1 (d, *J*=166.5 Hz), 119.8 (d, *J*=4 Hz), 128.9 (d, *J*=7 Hz), 142.4 (d, *J*=20 Hz), 150.6 (d, *J*=18 Hz), 154.7 (N-CO), 186.1. EI MS *m/z* (%): 225 (96), 197 (40), 59 (100); HR-MS: calcd: 225.0796, found: 225.0801.

4.2.22. Preparation of 3a-fluoro-6-oxo-2,3,3a,6-tetra-hydro-indole-1-carboxylic acid ethyl ester (38). Obtained from 6-hydroxy-2,3-dihydroindole-1-carboxylic acid ethyl ester **36** (193 mg, 1 mmol), PIFA (516 mg, 1.2 mmol); HF–pyridine (70:30; v:v) (0.1 mL) as described in typical experimental procedure. Chromatography from ethyl acetate–hexane (30:70, v:v) gave **38** (82 mg-39%). ^{1}H NMR ($CDCl_3$) δ 2–2.23 (m, 1H, 1H), 2.50 (td, 1H, 1H), 3.88 (s, 3H, CH_3OCO), 3.96 (m, 2H, 1H), 6.28 (m, 1H), 6.48 (s, 1H), 6.82 (dd, *J*=9.9, 3.0 Hz). ^{13}C NMR ($CDCl_3$) δ 32.2 (d, *J*=27.3 Hz), 47.8, 53.6 (CH_3OCO), 91.1 (d, *J*=163.3 Hz), 107.7 (d, *J*=2.8 Hz), 132.8 (d, *J*=7.6 Hz), 134.7 (d, *J*=16.5 Hz), 186.6. EI MS *m/z* (%): 211 (97), 183 (40), 166 (32), 59 (100). HR-MS: calcd: 211.0649, found: 211.0645.

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Double nucleophilic reaction of amines to the imidazole nucleus and selective synthesis of 5-aminoimidazoles

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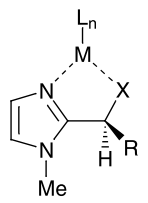
Abstract—Reaction of 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole with an excess of *N*,*N*-dimethylamine at room temperature gave an abnormal adduct, *trans*-4,5-bis(dimethylamino)-1-methyl-2,2-dimethylpropyl-2-imidazoline, which was derived from a serial, double nucleophilic addition into the imidazole nucleus in 74% yield together with a normal S_N product, 1-methyl-2-(1-dimethylamino-2,2-dimethylpropyl)-1*H*-imidazole in 15% yield. The former was easily converted to 1-methyl-5-(dimethylamino)-2-(2,2-dimethylpropyl)-1*H*-imidazole by only reflux in toluene in 90% yield. The scope, mechanism and limitation of these reactions are discussed.

1. Introduction

Electrophilic substitutions of an imidazole nucleus[1] and nucleophilic substitutions via lithioimidazoles[2] have been well known for the preparation of imidazole compounds, and we have applied the reactions of lithioimidazoles[3] and imidazolium salts[4] to the synthesis of several pharmaceutically interesting compounds and natural products.[5] While, nucleophilic reactions to the imidazole ring have been performed mainly through the activation by quaternization of the ring[6] or introduction of an appropriate electron-withdrawing group such as halogen atom(s) into the nucleus,[7] other examples have been quite rare.[8,9] On the other hand, although the structure of 1,2-disubstituted 5-amino-1*H*-imidazole is found in some interesting bioactive compounds such as gonadotropin-releasing hormone receptor antagonists,[10] preparation methods for these aminoimidazole derivatives have been almost unknown in the literature.[11] In this paper, we would like to present a novel, serial double nucleophilic addition of amines into the imidazole nucleus to give 1,2-disubstituted 4,5-bis(amino)-2-imidazolines[9] and the highly regioselective elimination of 2-imidazoline compounds to provide 1,2-disubstituted 5-amino-1*H*-imidazoles.

2. Results and discussion

In the course of our investigations on the synthesis of chiral imidazole bidentate ligands for transition metals as shown in Figure 1, we planned the preparation of 1-methyl-2-(1-aminoalkyl)-1*H*-imidazole, which would be easily derived by a simple S_N2 reaction of an amine with 1-methyl-2-(1-chloroalkyl)-1*H*-imidazole as reported by Miocque.[12] Thus, 1-methyl-2-(1-hydroxy-2,2-dimethylpropyl)-1*H*-imidazole **1a**[13] was chlorinated with thionyl chloride in $CHCl_3$ to give 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole hydrochloride **2a** as colorless crystals in 86% yield. The chloride **2a** was treated with an excess of *N*,*N*-dimethylamine; however, the expected normal S_N product **3a** was obtained in only 15% yield, and the unexpected addition product **4a** was obtained in 74% yield as the major component (Scheme 1, Entry 1 in Table 1). All spectral data of the latter supported the structure of **4a**, and finally it was confirmed by X-ray crystallographic analysis after being derived to the corresponding dipicrate.[9] To our best



X = N, O, P, S....
M = Transition Metal

Figure 1.

Keywords: Imidazoles; Nucleophilic reaction; Stereoselective addition.
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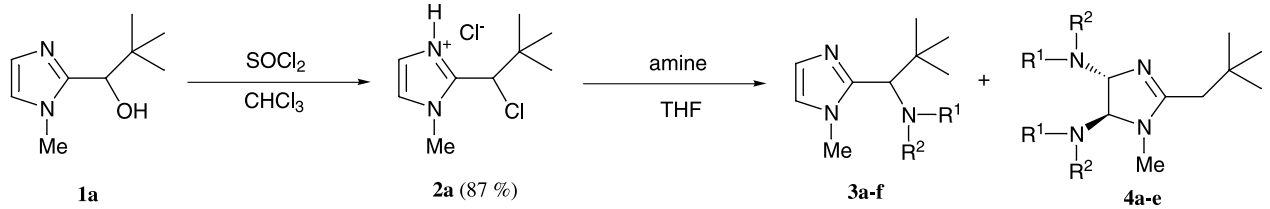


Scheme 1.

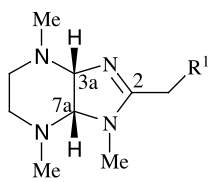
Table 1. Reaction of **2a** with various amines

Entry	Amine	R^1	R^2	Yield (%) (Product)	
				3	**4**
1	Me_2NH	Me	Me	15 (**3a**)	74 (**4a**)
2	Pyrroridine	$-(CH_2)_4-$		6 (**3b**)	68 (**4b**)
3	Piperidine	$-(CH_2)_5-$		13 (**3c**)	61 (**4c**)
4	$BnNH_2$	Bn	H	67 (**3d**)	—[a]
5	$MeNH(CH_2)_2NHMe$	Me	$-(CH)_2NHMe$	—[a]	78 (**4e**)[b]
6	1,2-Diaminobenzene	$2\text{-}NH_2\text{-}C_6H_4$	H	78 (**3f**)	—[a]

[a] Not detected in the reaction mixture.
[b] Obtained product **4e** was the *cis*-isomer shown in Figure 2.

knowledge, this was the first example of direct nucleophilic addition under dearomatizing to the imidazole ring without any electron-withdrawing substituent on the nucleus or through quarternary imidazolium salts.

The reaction of **2a** with various amines was also examined, and the results are shown in Table 1. Reaction of **2a** with secondary amines gave the serial double nucleophilic addition products **4a**–**c** as major products in 61–74% yields (Entries 1–3), whereas the reaction with primary amines gave only S_N products **3d** and **3f** in 67, 78% yields, respectively (Entries 4 and 6). Interestingly, treatment of *N*,*N*′-dimethylethylenediamine provided a bicyclic compound as the sole product, 1*H*-imidazo[4,5-*b*]piperazine **4e** in good yield (78%) (Entry 5, Fig. 2), and its *cis*-fused ring system was confirmed by observation of NOE between H3a and H7a protons and comparison with the ^1H NMR coupling constant of H3a–H7a in the ring (J=8.6 Hz) as these values of H4–H5 in *trans*-4,5-disubstituted 2-imidazolines **4a**–**c** (J=3.8–4.0 Hz).

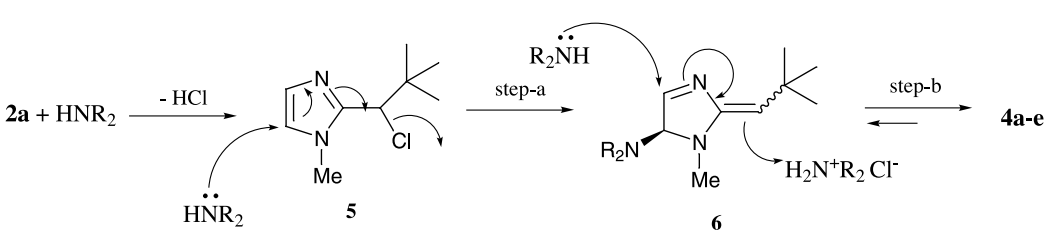


4e R^1 = *t*-Bu
4k R^1 = *i*-Pr

Figure 2.

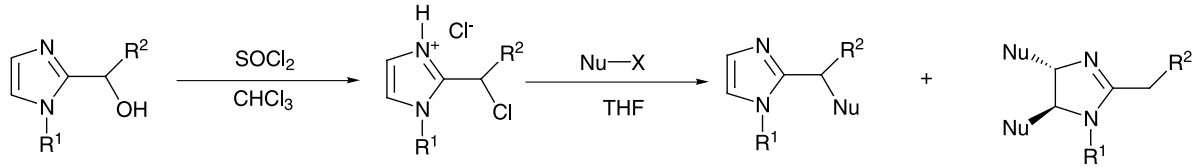
A plausible reaction mechanism for producing the di-adducts **4a**–**e** is given in Scheme 2. The free imidazole **5** reacted with secondary amines at the 5-position of the imidazole ring by a nucleophilic *tele*-substitution reaction mechanism[14] to give the intermediate **6**, and the second molecule of R_2NH might readily add to the unstable ketenediiminal intermediate **6** under assist by protonation with $H_2N^+R_2$ to produce **4**. Main reason for producing the adduct **4** may be difficulty in approach of the amine molecule to the sterically hindered –CHCl– portion where a bulky alkyl group attaches.

Then, the reaction of **2b**–**e** with various nucleophiles was examined, and the results are summarized in Table 2. When compound **2b** (R^2=*i*-Pr) was treated with secondary amines, di-adducts (**4g**–**i**) were obtained in 50–64% overall yield from **1b** (Entries 1–3) together with some S_N products (**3g**–**i**) in 17–19% yield. The treatment with a primary amine gave only S_N product (**3j**) in 36% yield (Entry 4), and *N*,*N*′-dimethylethylenediamine gave bicyclic 1*H*-imidazo[4,5-*b*]piperazine (**4k**) having *cis* stereochemistry in 29% yield (Entry 5, Fig. 2). The reaction showed almost the same tendency as the reaction of **2a** (R^2=*t*-Bu) with amines



Scheme 2.

Table 2. Reaction of **2b**–**e** with various nucleophiles



1b R^1 = Me, R^2 = *i*-Pr
1c R^1 = Me, R^2 = *n*-C_6H_{13}
1d R^1 = Bn, R^2 = *t*-Bu
1e R^1 = H, R^2 = *t*-Bu

2b R^1 = Me, R^2 = *i*-Pr (crude)
2c R^1 = Me, R^2 = *n*-C_6H_{13} (63 %)
2d R^1 = Bn, R^2 = *t*-Bu (73 %)
2e R^1 = H, R^2 = *t*-Bu (crude)

3g-t

4g-q

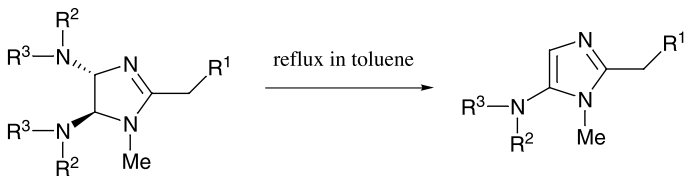
Entry	R^1	R^2	Nu-X	Nu	Yield (%) (Product)	
					3	**4**
1	Me	*i*-Pr	Me_2NH	$-NMe_2$	17 (**3g**)[a]	64 (**4g**)[a]
2	Me	*i*-Pr	Pyrroridine	$-N(CH_2)_4$	19 (**3h**)[a]	50 (**4h**)[a]
3	Me	*i*-Pr	Piperidine	$-N(CH_2)_5$	17 (**3i**)[a]	61 (**4i**)[a]
4	Me	*i*-Pr	$BnNH_2$	–NHBn	36 (**3j**)[a]	—[b]
5	Me	*i*-Pr	$MeNH(CH_2)_2NHMe$	$-NMe(CH_2)_2NMe$	—[b]	29 (**4k**)[a,c]
6	Me	*i*-Pr	PhC(O)SNa	PhC(O)S–	49 (**3l**)[a]	—[b]
7	Me	*n*-C_6H_{13}	Me_2NH	$-NMe_2$	31 (**3m**)	46 (**4m**)
8	Me	*n*-C_6H_{13}	Pyrroridine	$-N(CH_2)_4$	43 (**3n**)	41 (**4n**)
9	Bn	*t*-Bu	Me_2NH	$-NMe_2$	12 (**3p**)	80 (**4p**)
10	Bn	*t*-Bu	Pyrroridine	$-N(CH_2)_4$	18 (**3q**)	72 (**4q**)
11[d]	Bn	*t*-Bu	Me_2CHOH	Me_2CHO-	34 (**3r**)	—[b]
12[d]	Bn	*t*-Bu	PhOH	PhO–	51 (**3s**)	—[b]
13	H	*t*-Bu	Me_2NH	$-NMe_2$	83 (**3t**)[e]	—[b]

[a] Yield from **1b**.
[b] Not detected in the reaction mixture.
[c] Obtained product **4k** was the *cis*-isomer shown in Figure 2.
[d] The reaction was carried out in presence of Et_3N.
[e] Yield from **1e**.

but the ratio of S_N products in Entries 1–3 was slightly increased.

When 2-(1-chloroheptyl)-1-methyl-1*H*-imidazole hydrochloride (**2c**) derived from **1c**[15] bearing a primary alkyl group neighboring the –CHCl– moiety was used as a substrate, double nucleophilic addition products **4m** and **4n** were given in 41–46% yield by the reaction with secondary amines, but the ratio of normal S_N products **3m** and **3n** considerably increased to 31–43% (Entries 7 and 8). The reaction of **2d** (R_1=Bn, R_2=*t*-Bu) with secondary amines gave desired di-adducts **4p** and **4q** in good yields (80, 72%, respectively) as we expected (Entries 9 and 10); however, the reaction of 1-unsubstituted imidazole **2e** afforded only S_N product **3t** in 83% yield (Entry 13). These results might support the steric hindrance around the –CHCl– moiety was one of the important factors for the attack of nucleophiles into the imidazole nucleus as described above. The reaction of **2b** and **2d** with other nucleophiles such as thioate, alcohol and phenol under the same conditions gave only S_N products **3l**, **3r** and **3s** in moderate yields (34–51%) (Entries 6, 11 and 12); these results also

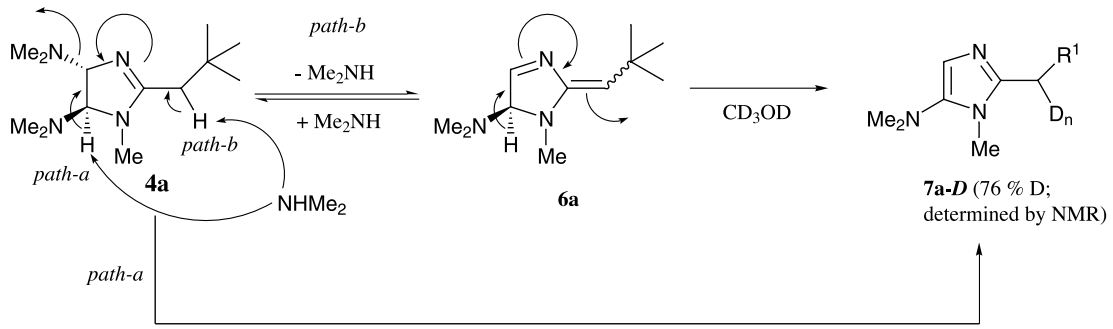
Table 3. Reaction of **4** in reflux toluene



4 **7**

Entry	R^1	**4**	R^2	R^3	Yield (%) (Product)
1	*t*-Bu	**4a**	Me	Me	90 (**7a**)
2	*t*-Bu	**4b**	$-(CH_2)_4-$		83 (**7b**)
3	*t*-Bu	**4e**	[a]		—[b]
4	*i*-Pr	**4g**	Me	Me	66 (**7c**)
5	*i*-Pr	**4h**	$-(CH_2)_4-$		80 (**7d**)

[a] Starting compound was *cis*-isomer **4e** shown in Figure 2.
[b] Not detected in the reaction mixture.



Scheme 3.

showed that one important factor to afford 2-imidazolines **4** was the steric hindrance of nucleophiles as well as their nucleophilicity.

Reaction of double nucleophilic addition products **4a** was examined (Table 3). Regioselective elimination of one of the two *N*,*N*-dimethylamino groups smoothly proceeded in boiling toluene to give 1-methyl-5-dimethylamino-2-(2,2-dimethylpropyl)-1*H*-imidazole **7a** as the sole product in 90% yield (Entry 1). The structure of **7a** was confirmed by the observation of HMBC correlations. Although Stradi reported a conversion of 4,5-diamino-1,2-diaryl-2-imidazolines to 5-amino-1,2-diaryl-1*H*-imidazoles in the presence of triethylamine hydrochloride at 125 °C,[11a] the transformation from **4a** to **7a** could be achieved by only reflux in toluene without any catalyst.

To confirm the reaction mechanism of the selective elimination of **4a**, the reaction was performed in the presence of CD_3OD at 120 °C, and it was found that 76% of deuterium was incorporated into the methylene group of the side chain in the product **7a**–***D***. From this result, we considered that the main reaction course was *path-b* through a *tele*-elimination mechanism[16] as shown in Scheme 3.

This selective elimination reaction was examined toward several 4,5-diaminoimidazoles **4b**, **4e**, **4g** and **4h** and the results are listed in Table 3. The reaction of **4b**, **4g** and **4h** provided the corresponding 1,2-disubstituted 5-amino-1*H*-imidazoles **7b**–**d** in 66–83% yields (Entries 2, 4 and 5). However, the reaction of **4e** mainly recovered the starting compound and gave no desired eliminating product (Entry 3), this result might be explained by the faster intramolecular cyclization of **6e** to **4e** than the approach of the –NHMe portion of **6e** to the sterically hindered H5 for producing **7e** (Scheme 4).

3. Conclusion

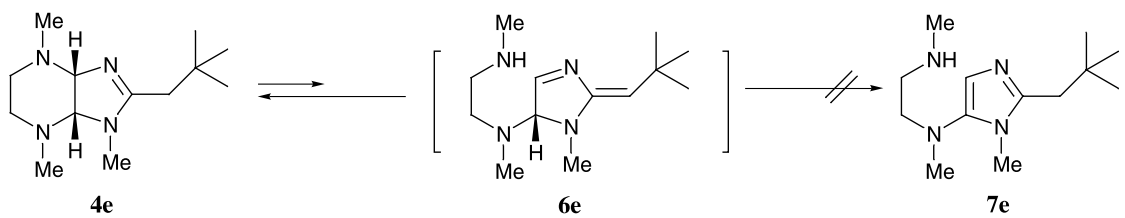
In summary, we have demonstrated a novel dearomatizing reaction of the imidazole ring by the double nucleophilic reaction of amines to give 1,2-dialkyl-4,5-diamino-2-imidazolines and their conversion to 1,2-disubstituted 5-amino-1*H*-imidazoles.

4. Experimental

4.1. General

All melting points were measured with a Yanaco MP micro-melting-point apparatus and are uncorrected. IR spectra were taken with Shimadzu IR-435 spectrophotometer. NMR (^1H and ^{13}C) spectra were measured on Varian UNITY INOVA 400NB (^1H: 400 MHz), JEOL EX-300 (^1H: 300 MHz, ^{13}C: 75 MHz) or JEOL EX-270 (^1H: 270 MHz, ^{13}C: 68 MHz) spectrometer and the chemical shifts were expressed in parts per million downfield from tetramethylsilane as the internal standard. Mass spectra (MS) were measured on JEOL JMS-SX 102A QQ (FAB) or JEOL JMS BU-20 (EI and CI) spectrometer, respectively. Silica gel (Merck Art. 7737) or Al_2O_3 (Nakalai Tesque, Alumina activated 300) was used for column chromatography.

4.1.1. Synthesis of 2-(1-hydroxy-2-methylpropyl)-1-methyl-1*H*-imidazole 1b—general procedure for the synthesis of the alcohols 1. *n*-BuLi (1.6 M in *n*-hexane; 32.8 mL, 52.5 mmol) was added to a stirred solution of 1-methylimidazole (4.4 mL, 55 mmol) in THF (50 mL) under N_2 at −78 °C. After stirring for 30 min at the same temperature, isobutylaldehyde (4.54 mL, 50 mmol) was added and the whole was stirred for 2 h at ambient temperature. The mixture was acidified with HCl aq. (10%, 50 mL) and washed with diethyl ether (30 mL×2).



Scheme 4.

The aqueous layer was basified with K_2CO_3 powder and extracted with AcOEt (30 mL×3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was recrystallized from AcOEt-*n*-hexane to give **1b** as colorless prisms (3.58 g, 46%). Mp 77–79 °C.

δ_H (300 MHz, $CDCl_3$): 0.81 (3H, d, *J*=6.8 Hz, $CH(CH_3)_2$), 1.06 (3H, d, *J*=6.6 Hz, $CH(CH_3)_2$), 2.06–2.22 (1H, m, $CH(CH_3)_2$), 3.67 (3H, s, NCH_3), 4.25 (1H, br, OH), 4.34 (1H, d, *J*=7.9 Hz, C*H*(OH)), 6.77 (1H, d, *J*=1.1 Hz, Im-H), 6.91 (1H, d, *J*=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 18.6, 19.0, 32.9, 33.9, 72.3, 121.0, 126.6, 149.7. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1489, 2942, 3099. EI MS (*m*/*z*, %): 83 (24), 111 (100), 137 (4), 154 (M^+, 7). HRMS (EI): found M^+ 154.1103, $C_8H_{14}N_2O$ requires M^+ 154.1106. Anal. calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17; found: C, 62.12; H, 9.26; N, 17.95.

The alcohols **1a**[13] and **1c**[15] are known compounds in literature.

4.1.2. 1-Benzyl-2-(1-hydroxy-2,2-dimethylpropyl)-1*H*-imidazole 1d.[17] Obtained, after silica gel column chromatography (AcOEt/*n*-hexane=2:1) and recrystallization from EtOH–Et_2O, as colorless needles (1.98 g, 41%) from 1-benzylimidazole (20 mmol). Mp 113–115 °C.

δ_H (300 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 3.08 (1H, br, OH), 4.41 (1H, s, C*H*(OH)), 5.16 (2H, s, NCH_2), 6.76 (1H, d, *J*=1.3 Hz, Im-H), 7.02 (1H, d, *J*=1.3 Hz, Im-H), 7.08–7.11 (2H, m, Ar-H), 7.27–7.37 (3H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 25.8, 37.0, 50.0, 73.8, 119.9, 126.9, 127.5, 128.1, 128.9, 136.3, 149.0. ν_{max} ($CHCl_3$, cm^{-1}): 1449, 1475, 1491, 1622, 2936, 3000–3500. EI MS (*m*/*z*, %): 91 (84), 97 (16), 187 (100), 211 (8), 244 (M^+, 10). HRMS (EI): found M^+ 244.1575, $C_{15}H_{20}N_2O$ requires M^+ 244.1576. Anal. calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47; found: C, 73.49; H, 8.37; N, 11.75.

4.1.3. 2-(1-Hydroxy-2,2-dimethylpropyl)-1*H*-imidazole 1e. Following the reported procedure by Curtis and Brown[18] starting from 1-diethoxymethyl-1*H*-imidazole and trimethylacetaldehyde, the title compound was obtained in 35% yield as colorless prisms, mp 179–181 °C (recrystallized from EtOH–Et_2O).

δ_H (300 MHz, DMSO-d_6): 0.84 (9H, s, $C(CH_3)_3$), 4.24 (1H, d, *J*=4.4 Hz, C*H*(OH)), 5.42 (1H, d, *J*=4.8 Hz, OH), 6.76 (1H, br, Im-H), 6.93 (1H, br, Im-H). δ_C (75 MHz, DMSO-d_6): 26.0, 35.4, 75.1, 115.1, 126.5, 149.4. ν_{max} (KBr, cm^{-1}): 1448, 1639, 2619, 2942, 3163, 3000–3500. EI MS (*m*/*z*, %): 69 (16), 98 (100), 121 (20), 154 (M^+, 8). HRMS (EI): found M^+ 154.1093, $C_8H_{14}N_2O$ requires M^+ 154.1106. Anal. calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17; found: C, 61.92; H, 9.09; N, 17.98.

4.1.4. Synthesis of 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole hydrochloride 2a—general procedure for the synthesis of the chlorides 2. $SOCl_2$ (0.73 mL, 10 mmol) was added to a stirred solution of 2-(1-hydroxy-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole[13] (840 mg, 5 mmol) in $CHCl_3$ (5 mL) under N_2 at 0 °C. After stirring for 2 h at room temperature, solvents were evaporated to give a crystalline residue, which was recrystallized from EtOH–AcOEt. The compound was obtained as a colorless powder, 961 mg (86%). Mp 168–170 °C.

δ_H (300 MHz, CD_3OD): 1.15 (9H, s, $C(CH_3)_3$), 4.00 (3H, s, NCH_3), 5.54 (1H, s, C*H*Cl), 7.62 (1H, d, *J*=2.2 Hz, Im-H), 7.66 (1H, d, *J*=1.8 Hz, Im-H). δ_C (75 MHz, CD_3OD): 26.4, 36.3, 39.7, 59.7, 121.0, 125.4, 145.3. ν_{max} (KBr, cm^{-1}): 1463, 1514, 1591, 2913, 3396. EI MS (*m*/*z*, %): 57 (6), 81 (11), 95 (36), 121 (13), 130 (100), 132 (32), 151 (15), 171 (5), 186 (M^+, 4), 188 (1). HRMS (EI): found M^+ 186.0933, $C_9H_{15}ClN_2$ requires M^+ 186.0924. Anal. calcd for $C_9H_{16}Cl_2N_2$: C, 48.44; H, 7.23; N, 12.55; found: C, 48.51; H, 7.34; N, 12.24.

4.1.5. 2-(1-Chloro-2-methylpropyl)-1-methyl-1*H*-imidazole hydrochloride 2b. Obtained, after evaporation of the solvents from **1b**, as a pale yellow crystalline residue, which was used in the next reaction without further purification.

δ_H (270 MHz, $CDCl_3$): 0.96 (3H, d, *J*=6.6 Hz, $CH(CH_3)_2$), 1.29 (3H, d, *J*=6.4 Hz, $CH(CH_3)_2$), 2.63–2.77 (1H, m, $CH(CH_3)_2$), 4.10 (3H, s, NCH_3), 5.34 (1H, d, *J*=10.2 Hz, C*H*Cl), 7.36 (1H, d, *J*=1.8 Hz, Im-H), 7.63 (1H, d, *J*=1.8 Hz, Im-H). δ_C (68 MHz, $CDCl_3$): 19.8, 20.1, 34.1, 35.8, 55.4, 118.7, 124.2, 143.5. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1594, 2950, 3138, 3360. EI MS (*m*/*z*, %): 81 (27), 96 (48), 121 (90), 130 (75), 132 (25), 137 (100), 172 (M^+, 10), 174 (3). HRMS (EI): found M^+ 172.0773, $C_8H_{13}ClN_2$ requires M^+ 172.0767.

4.1.6. 2-(1-Chloroheptyl)-1-methyl-1*H*-imidazole hydrochloride 2c. Obtained, after recrystallization from AcOEt–Et_2O, as a colorless powder (478 mg, 63%) from **1c** (3 mmol). Mp 107–111 °C.

δ_H (300 MHz, $CDCl_3$): 0.87 (3H, t, *J*=6.8 Hz, CH_2CH_3), 1.26–1.69 (8H, m, $CH_2(CH_2)_4CH_3$), 2.30–2.51 (2H, m, $CH_2C_5H_{11}$), 4.06 (3H, s, NCH_3), 5.55 (1H, dd, *J*=6.8, 8.8 Hz, C*H*Cl), 7.35 (1H, d, *J*=1.8 Hz, Im-H), 7.47 (1H, d, *J*=1.6 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 26.5, 28.2, 31.4, 35.3, 35.5, 49.0, 119.1, 124.0, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1458, 1518, 1593, 1842, 2422, 2936. EI MS (*m*/*z*, %): 109 (45), 130 (100), 135 (32), 179 (53), 185 (14), 214 (M^+, 5), 216 (2). HRMS (EI): found M^+ 214.1251, $C_{11}H_{19}ClN_2$ requires M^+ 214.1237. Anal. calcd for $C_{11}H_{20}Cl_2N_2$: C, 52.60; H, 8.03; N, 11.15; found: C, 52.28; H, 8.02; N, 11.11.

4.1.7. 1-Benzyl-2-(1-chloro-2,2-dimethylpropyl)-1*H*-imidazole hydrochloride 2d. Obtained, after recrystallization from EtOH–Et_2O as a colorless powder (218 mg, 73%) from **1d** (1 mmol). Mp 151–152 °C.

δ_H (300 MHz, DMSO-d_6): 1.07 (9H, s, $C(CH_3)_3$), 5.53 and 5.725 (1H each, each d, *J*=15.4 Hz, NCH_2), 5.733 (1H, s, C*H*Cl), 7.29–7.80 (7H, m, Ar-H and Im-H). δ_C (75 MHz, DMSO-d_6): 25.9, 37.7, 50.4, 58.4, 121.9, 122.9, 127.6, 128.5, 129.0, 134.9, 142.9. ν_{max} (KBr, cm^{-1}): 1462, 1502, 1598, 1626, 2638, 3394. EI MS (*m*/*z*, %): 91 (100), 115 (30), 171 (90), 206 (50), 262 (M^+, 18), 264 (6). HRMS (EI): found M^+ 262.1223, $C_{15}H_{19}ClN_2$ requires M^+ 262.1237.

Anal. calcd for $C_{15}H_{20}Cl_2N_2$: C, 60.21; H, 6.74; N, 9.36; found: C, 60.35; H, 7.05; N, 8.99.

4.1.8. 2-(1-Chloro-2,2-dimethylpropyl)-1*H*-imidazole hydrochloride 2e. Obtained, after evaporation of the solvents from **1e**, as a pale yellow crystalline residue, which was used in the next reaction without further purification.

4.1.9. Synthesis of 1-methyl-2-(2,2-dimethyl-1-dimethylaminopropyl)-1*H*-imidazole 3a and (4*R,5*R**)-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-2-(2,2-dimethylpropyl)-1*H*-imidazole 4a—general procedure for the synthesis of 3 and 4 (Entry 1 in Table 1 as an example).** *N*,*N*-Dimethylamine aqueous solution (3 mL, 33 mmol) was added to a suspension of **2a** (669 mg, 3 mmol) in THF (3 mL) under N_2 and ice cooling, and the mixture was stirred for 4 h at 0 °C. 10% K_2CO_3 aqueous solution (5 mL) was added to the reaction mixture and the products were extracted with AcOEt (10 mL×3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was separated by Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt only) to give **3a** (first fraction, 88 mg, 15%) and **4a** (second fraction, 534 mg, 74%) as a yellow viscous oil, respectively.

3a: δ_H (400 MHz, $CDCl_3$): 1.06 (9H, s, $C(CH_3)_3$), 2.34 (6H, s, $N(CH_3)_2$), 3.38 (1H, s, $CHC(CH_3)_3$), 3.64 (3H, s, NCH_3), 6.81 (1H, d, J=1.3 Hz, Im-H), 7.05 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 27.9, 33.4, 36.9, 44.7, 67.3, 120.0, 126.8, 145.4. ν_{max} ($CHCl_3$, cm^{-1}): 1477, 2956. EI MS (*m*/*z*, %): 110 (57), 138 (100), 195 (M^+, 6). HRMS (EI): found M^+ 195.1732, $C_{11}H_{21}N_3$ requires M^+ 195.1735.

4a: δ_H (400 MHz, $CDCl_3$): 1.08 (9H, s, $C(CH_3)_3$), 2.24 (6H, s, $N(CH_3)_2$), 2.30 (6H, s, $N(CH_3)_2$), 2.21 (1H, d, J=13.6 Hz, $CH_2C(CH_3)_3$), 2.26 (1H, d, J=13.7 Hz, $CH_2C(CH_3)_3$, 2.90 (3H, s, NCH_3), 3.96 (1H, d, J=3.8 Hz, Im-H), 4.25 (1H, d, J=3.8 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 29.9, 31.4, 31.9, 38.4, 40.0, 40.1, 82.8, 85.5, 164.7. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1586, 2920. EI MS (*m*/*z*, %): 138 (100), 195 (31), 240 (M^+, 1.7). HRMS (EI): found M^+ 240.2309, $C_{13}H_{28}N_4$ requires M^+ 240.2314.

4.1.10. 2-[2,2-Dimethyl-1-(1-pyrrolidinyl)propyl]-1-methyl-1*H*-imidazole 3b and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2,2-dimethylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4b.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5 to AcOEt only), as a yellow viscous oil [(**3b**; 14 mg, 6%), (**4b**; 199 mg, 68%)] from pyrrolidine (5 mmol) and **2a** (1 mmol).

3b: δ_H (400 MHz, $CDCl_3$): 1.05 (9H, s, $C(CH_3)_3$), 1.61–1.68 (4H, m, $NCH_2(CH_2)_2$), 2.56–2.58 (2H, m, NCH_2CH_2), 2.82 (2H, br, NCH_2CH_2), 3.62 (1H, s, $CHC(CH_3)_3$), 3.64 (3H, s, NCH_3), 6.78 (1H, d, J=1.1 Hz, Im-H,), 7.03 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 23.6, 28.2, 33.3, 36.8, 52.0, 65.1, 119.7, 126.8, 147.1. ν_{max} ($CHCl_3$, cm^{-1}): 1477, 2934. HRMS (FAB+): found MH^+ 222.1977, $C_{13}H_{23}N_3$+H requires MH^+ 222.1970.

4b: δ_H (300 MHz, $CDCl_3$): 1.07 (9H, s, $C(CH_3)_3$), 1.71–1.81 (8H, m, NCH_2CH_2), 2.22 (2H, s, $CH_2C(CH_3)_3$), 2.59–2.78 (8H, m, NCH_2CH_2), 2.90 (3H, s, NCH_3), 4.29 (1H, d, J=3.8 Hz, Im-H), 4.36 (1H, d, J=3.8 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 23.4, 23.7, 30.0, 31.5, 33.0, 40.3, 46.7, 48.2, 82.3, 82.7, 164.9. ν_{max} ($CHCl_3$, cm^{-1}): 1585, 2912. EI MS (*m*/*z*, %): 83 (100), 111 (27), 164 (86), 221 (23), 292 (M^+, 9). HRMS (EI): found M^+ 292.2621, $C_{17}H_{32}N_4$ requires M^+ 292.2627.

4.1.11. 2-[2,2-Dimethyl-1-(1-piperidinyl)propyl]-1-methyl-1*H*-imidazole 3c and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2,2-dimethylpropyl)-4,5-bis(1-piperidinyl)-1*H*-imidazole 4c.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only), as a yellow viscous oil [(**3c**; 63 mg, 13%), (**4c**; 389 mg, 61%)] from piperidine (10 mmol) and **2a** (2 mmol).

3c: δ_H (300 MHz, $CDCl_3$): 1.04 (9H, s, $C(CH_3)_3$), 1.24–1.35 (2H, m, $NCH_2CH_2CH_2$), 1.46–1.53 (4H, m, NCH_2CH_2), 2.11–2.41 (2H, m, NCH_2CH_2), 2.67–2.96 (2H, m, NCH_2CH_2), 3.28 (1H, s, $CHC(CH_3)_3$), 3.63 (3H, s, NCH_3), 6.79 (1H, d, J=1.1 Hz, Im-H), 7.02 (1H, d, J=1.3 Hz, Im-H,). δ_C (75 MHz, $CDCl_3$): 24.4, 26.8, 27.5, 33.4, 37.2, 54.4, 68.1, 119.8, 126.5, 146.4. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1655, 2917. HRMS (FAB+): found MH^+ 236.2123, $C_{14}H_{25}N_3$+H requires MH^+ 236.2127.

4c: δ_H (300 MHz, $CDCl_3$): 1.06 (9H, s, $C(CH_3)_3$), 1.42–1.60 (12H, m, $NCH_2(CH_2)_3$), 2.18 and 2.24 (1H each, each d, J=13.6 Hz, $CH_2C(CH_3)_3$), 2.45–2.60 (8H, m, NCH_2CH_2), 2.87 (3H, s, NCH_3), 3.95 (1H, d, J=4.0 Hz, Im-H), 4.24 (1H, d, J=3.9 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 24.7, 24.8, 26.16, 26.22, 30.1, 31.6, 32.7, 40.3, 48.4, 49.3, 85.0, 86.0, 164.7. ν_{max} ($CHCl_3$, cm^{-1}): 1590, 2843. HRMS (FAB+): found MH^+ 321.3026, $C_{19}H_{36}N_4$+H requires MH^+ 321.3018.

4.1.12. 2-(1-Benzylamino-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole 3d. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=2:1 to AcOEt only), as a yellow viscous oil (347 mg, 67%) from benzylamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 0.96 (9H, s, $C(CH_3)_3$), 2.37 (1H, br, NH), 3.27–3.31 (2H, overlap, $CHC(CH_3)_3$ and NCH_2), 3.35 (3H, s, NCH_3), 3.76 (1H, d, J=13.6 Hz, NCH_2), 6.74 (1H, d, J=1.1 Hz, Im-H), 7.04 (1H, d, J=1.1 Hz, Im-H), 7.18–7.30 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 26.6, 32.6, 36.0, 51.9, 60.7, 119.8, 126.6, 127.1, 128.0, 128.1, 140.2, 149.5. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1598, 2936, 3156. EI MS (*m*/*z*, %): 65 (17), 91 (38), 152 (11), 200 (100), 257 (M^+, 1). HRMS (EI): found M^+ 257.1887, $C_{16}H_{23}N_3$ requires M^+ 257.1892.

4.1.13. (3*aR,7*aS**)-3a,4,5,6,7,7a-Hexahydro-1,4,7-trimethyl-2-(2,2-dimethylpropyl)-1*H*-imidazo[4,5-*b*]pyrazine 4e.** Obtained, after Al_2O_3 column chromatography (AcOEt only to AcOEt/MeOH=10:1), as a yellow viscous oil (372 mg, 78%) from *N*,*N*′-dimethylethylenediamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 1.08 (9H, s, $C(CH_3)_3$), 2.15 and 2.23 (1H each, each d, J=13.4 Hz, $CH_2C(CH_3)_3$), 2.49 (3H, s, CH_2NCH_3), 2.57 (3H, s, CH_2NCH_3), 2.52–2.80 (4H, m,

CH_2CH_2), 2.87 (3H, s, NCH_3), 4.17 (1H, d, J=8.6 Hz, Im-H), 4.55 (1H, d, J=8.6 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 29.9, 31.4, 34.1, 40.5, 42.1, 42.9, 44.7, 45.5, 79.5, 81.1, 166.5. ν_{max} ($CHCl_3$, cm^{-1}): 1461, 1590, 2899. EI MS (*m*/*z*, %): 96 (47), 99 (27), 112 (55), 126 (34), 153 (100), 182 (15), 238 (M^+, 20). HRMS (EI): found M^+ 238.2153, $C_{13}H_{26}N_4$ requires M^+ 238.2157.

4.1.14. 2-[1-(2-Aminophenylamino)-2,2-dimethylpropyl]-1-methyl-1*H*-imidazole 3f. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3), as a solid (403 mg, 78%) from *o*-phenylenediamine (10 mmol) and **2a** (2 mmol).

δ_H (300 MHz, $CDCl_3$): 1.12 (9H, s, $C(CH_3)_3$), 3.44 (3H, s, NCH_3), 3.58–3.77 (2H, br, NH_2), 3.99 (1H, d, J=10.3 Hz, NH), 4.09 (1H, d, J=9.5 Hz,, C*H*C$(CH_3)_3$), 6.49–6.71 (5H, m, Ar-H and Im-H), 6.97 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 26.7, 32.9, 36.7, 60.2, 116.4, 118.0, 119.7, 120.0, 121.2, 127.0, 136.4, 137.7, 149.5. ν_{max} ($CHCl_3$, cm^{-1}): 1497, 1608, 2936, 3186, 3381. EI MS (*m*/*z*, %): 83 (100), 119 (34), 201 (13), 258 (M^+, 10). HRMS (EI): found M^+ 258.1848, $C_{15}H_{22}N_4$ requires M^+ 258.1844.

4.1.15. 1-Methyl-2-(2-methyl-1-dimethylaminopropyl)-1*H*-imidazole 3g and (4*R,5*R**)-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-2-(2-methylpropyl)-1*H*-imidazole 4g.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt/MeOH=10:1), as a yellow viscous oil [(**3g**; 155 mg, 17%), (**4g**; 723 mg, 64%)] from crude **2b** (starting from 5 mmol of **1b**).

3g: δ_H (300 MHz, $CDCl_3$): 0.68 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.08 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 2.24 (6H, s, $N(CH_3)_2$), 2.32–2.46 (1H, m, –C*H*$(CH_3)_2$), 3.24 (1H, d, J=9.9 Hz, C*H*$CH(CH_3)_2$), 3.65 (3H, s, NCH_3), 6.79 (1H, d, J=1.1 Hz, Im-H,), 7.02 (1H, d, J=1.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 19.7, 20.1, 29.8, 32.6, 41.1, 65.7, 119.8, 126.8, 146.2. ν_{max} ($CHCl_3$, cm^{-1}): 1479, 2924. EI MS (*m*/*z*, %): 97 (14), 123 (24), 138 (100), 181 (M^+, 1). HRMS (EI): found M^+ 181.1591, $C_{10}H_{19}N_3$ requires M^+ 181.1579.

4g: δ_H (300 MHz, $CDCl_3$): 0.94 (3H, d, J=5.7 Hz, $CH(CH_3)_2$), 0.95 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.93–2.25 (3H, m, $CH_2CH(CH_3)_2$), 2.15 (6H, s, $N(CH_3)_2$), 2.21 (6H, s, $N(CH_3)_2$), 2.82 (3H, s, NCH_3), 3.89 (1H, d, J=3.7 Hz, Im-H), 4.14 (1H, d, J=3.7 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.2, 22.8, 26.3, 30.9, 36.5, 38.2, 39.8, 82.7, 85.4, 165.5. ν_{max} ($CHCl_3$, cm^{-1}): 1594, 2933. EI MS (*m*/*z*, %): 91 (62), 138 (58), 181 (37), 205 (100), 226 (M^+, 12). HRMS (EI): found M^+ 226.2153, $C_{12}H_{26}N_4$ requires M^+ 226.2157.

4.1.16. 1-Methyl-2-[2-methyl-1-(1-pyrrolidinyl)propyl]-1*H*-imidazole 3h and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2-methylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4h.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5 to AcOEt/MeOH=10:1), as a yellow viscous oil [(**3h**; 118 mg, 19%), (**4h**; 418 mg, 50%)] from pyrrolidine (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

3h: δ_H (300 MHz, $CDCl_3$): 0.79 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.02 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.60–1.78 (4H, m, NCH_2CH_2), 2.26–2.41 (3H, m, NCH_2CH_2 and $CH(CH_3)_2$), 2.70–2.77 (2H, m, NCH_2CH_2), 3.48 (1H, d, J=8.4 Hz, C*H*C$H(CH_3)_2$), 3.68 (3H, s, NCH_3), 6.78 (1H, d, J=1.1 Hz, Im-H), 7.00 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 19.1, 20.5, 23.0, 31.3, 32.9, 49.6, 64.1, 120.1, 127.0, 146.9. ν_{max} ($CHCl_3$, cm^{-1}): 1478, 1657, 2924. EI MS (*m*/*z*, %): 123 (93), 138 (100), 164 (99), 207 (M^+, 1). HRMS (EI): found M^+ 207.1737, $C_{12}H_{21}N_3$ requires M^+ 207.1735.

4h: δ_H (300 MHz, $CDCl_3$): 0.91 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 0.92 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.62–1.72 (8H, m, NCH_2CH_2), 1.86–2.15 (3H, m, CH_2-C*H*C$(CH_3)_2$), 2.49–2.69 (8H, m, NCH_2CH_2), 2.82 (3H, s, NCH_3), 4.22 (1H, d, J=3.3 Hz, Im-H), 4.25 (1H, d, J=3.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.3, 22.9, 23.2, 23.7, 26.4, 31.7, 36.6, 46.5, 48.4, 82.2, 82.4, 165.8. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1592, 2934. EI MS (*m*/*z*, %): 164 (100), 179 (7), 207 (28), 263 (5), 278 (M^+, 5). HRMS (EI): found M^+ 278.2478, $C_{16}H_{30}N_4$ requires M^+ 278.2470.

4.1.17. 1-Methyl-2-[2-methyl-1-(1-piperidinyl)propyl]-1*H*-imidazole (3i) and (4*R,5*R**)-4,5-dihydro-1-methyl-2-(2-methylpropyl)-4,5-bis(1-piperidinyl)-1*H*-imidazole (4i).** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5), as a yellow viscous oil [(**3i**; 115 mg, 17%), (**4i**; 562 mg, 61%) from piperidine (15 mmol)] and crude **2b** (starting from 3 mmol of **1b**).

3i: δ_H (300 MHz, $CDCl_3$): 0.66 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.07 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.26–1.63 (6H, m, $NCH_2(CH_2)_3$), 2.37–2.49 (5H, m, NCH_2CH_2 and $CH(CH_3)_2$), 3.21 (1H, d, J=10.1 Hz, C*H*C$H(CH_3)_2$), 3.64 (3H, s, NCH_3), 6.77 (1H, d, J=1.1 Hz, Im-H), 7.01 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 20.1, 20.3, 24.6, 26.4, 29.4, 32.8, 50.5, 66.9, 119.8, 126.8, 147.2. ν_{max} ($CHCl_3$, cm^{-1}): 1452, 1478, 1580, 2915. EI MS (*m*/*z*, %): 123 (98), 138 (87), 178 (100), 221 (M^+, 3). HRMS (EI): found M^+ 221.1891, $C_{13}H_{23}N_3$ requires M^+ 221.1892.

4i: δ_H (300 MHz, $CDCl_3$): 1.007 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 1.010 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.42–1.59 (12H, m, $NCH_2(CH_2)_3$), 2.01–2.26 (3H, m, CH_2-C*H*$(CH_3)_2$), 2.40–2.62 (8H, m, NCH_2CH_2), 2.89 (3H, s, NCH_3), 4.00 (1H, d, J=3.7 Hz, Im-H), 4.23 (1H, d, J=3.5 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.4, 23.0, 24.5, 24.7, 26.0, 26.1, 26.6, 31.5, 36.5, 48.1, 49.1, 84.2, 85.8, 165.7. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1592, 2914. EI MS (*m*/*z*, %): 84 (91), 97 (100), 178 (90), 221 (25), 291 (20), 306 (M^+, 18). HRMS (EI): found M^+ 306.2779, $C_{18}H_{34}N_4$ requires M^+ 306.2783.

4.1.18. 2-(1-Benzylamino-2-methylpropyl)-1-methyl-1*H*-imidazole 3j. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:5), as a yellow viscous oil (176 mg, 36%) from benzylamine (10 mmol) and crude **2b** (starting from 2 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 0.77 (3H, d, J=6.8 Hz, $CH(CH_3)_2$), 1.05 (3H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.95–2.11 (1H, m, C*H*$(CH_3)_2$), 2.22 (1H, br, N*H*CH_2), 3.41 (1H, d, J=7.9 Hz,

C*H*CH(CH_3)$_2$), 3.43 (1H, d, J=13.6 Hz, NCH_2), 3.48 (3H, s, NCH_3), 3.73 (1H, d, J=13.4 Hz, NCH_2), 6.76 (1H, d, J=1.1 Hz, Im-H), 7.01 (1H, d, J=0.9 Hz, Im-H), 7.18–7.32 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 19.5, 19.6, 32.5, 33.6, 51.5, 59.9, 120.3, 126.7, 127.2, 128.0, 128.2, 140.3, 149.7. ν_{max} ($CHCl_3$, cm^{-1}): 1460, 1485, 1599, 1657, 2950, 3300–3500. CI MS (*m*/*z*, %): 83 (12), 91 (62), 123 (22), 138 (50), 200 (100), 244 (M^++H, 52). HRMS (CI+): found MH^+ 244.1820, $C_{15}H_{21}N_3$+H requires MH^+ 244.1814.

4.1.19. (3*aR* *,7*aS* *)-3a,4,5,6,7,7a-Hexahydro-1,4,7-trimethyl-2-(2-methylpropyl)-1*H*-imidazo[4,5-*b*]pyrazine 4k. Obtained, after Al_2O_3 column chromatography (AcOEt/MeOH=10:1), as a yellow viscous oil (193 mg, 29%) from *N*,*N*′-dimethylethylenediamine (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 1.015 (3H, d, J=6.4 Hz, CH(C*H*$_3$)$_2$), 1.019 (3H, d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 1.98–2.10 (1H, m, C*H*(CH_3)$_2$), 2.20–2.30 (2H, m, C*H*$_2$CH(CH_3)$_2$), 2.53–2.84 (4H, m, (C*H*$_2$)$_2$), 2.50 (3H, s, NC*H*$_3$), 2.62 (3H, s, NC*H*$_3$), 2.89 (3H, s, NC*H*$_3$), 4.24 (1H, d, J=8.4 Hz, Im-H), 4.53 (1H, d, J=8.4 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 22.6, 26.6, 32.2, 36.4, 42.0, 43.0, 44.6, 45.2, 77.4, 80.8, 168.1. ν_{max} ($CHCl_3$, cm^{-1}): 1450, 1598, 2919. EI MS (*m*/*z*, %): 85 (58), 114 (100), 142 (63), 185 (57), 198 (39), 224 (M^+, 2). HRMS (EI): found M^+ 224.1992, $C_{12}H_{24}N_4$ requires M^+ 224.2001.

4.1.20. *S*−2-Methyl-1-(1-methyl-1*H*-imidazol-2-yl)-propyl thiobenzoate 3l. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2), as a yellow viscous oil (400 mg, 49%) from sodium benzenethioate (15 mmol), NaH (15 mmol) and crude **2b** (starting from 3 mmol of **1b**).

δ_H (300 MHz, $CDCl_3$): 1.00 (3H, d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 1.16 (3H, d, J=7.0 Hz, CH(C*H*$_3$)$_2$), 2.42–2.58 (1H, m, C*H*(CH_3)$_2$), 3.71 (3H, s, NCH_3), 4.80 (1H, d, J=8.4 Hz, C*H*CH(CH_3)$_2$), 6.76 (1H, d, J=1.5 Hz, Im-H), 7.00 (1H, d, J=1.1 Hz, Im-H), 7.40–7.59 (3H, m, Ar-H), 7.95–7.99 (2H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 20.3, 20.8, 32.8, 33.1, 45.2, 120.3, 127.3, 127.9, 128.6, 133.5, 136.5, 147.5, 191.3. ν_{max} ($CHCl_3$, cm^{-1}): 1485, 1652, 1698, 2946. EI MS (*m*/*z*, %): 105 (55), 137 (100), 169 (99), 274 (M^+, 10). HRMS (EI): found M^+ 274.1152, $C_{15}H_{18}N_2OS$ requires M^+ 274.1140.

4.1.21. 1-Methyl-2-(1-dimethylaminoheptyl)-1*H*-imidazole 3m and (4*R* *,5*R* *)-2-heptyl-4,5-dihydro-1-methyl-4,5-bis(dimethylamino)-1*H*-imidazole 4m. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:1 to AcOEt only), as a yellow viscous oil [(**3m**; 69 mg, 31%), (**4m**; 124 mg, 46%)] from **2c** (1 mmol).

3m: δ_H (300 MHz, $CDCl_3$): 0.85 (3H, t, J=6.8 Hz, CH_2CH_3), 1.11–1.34 (8H, m, $CH_2(CH_2)_4CH_3$), 1.78–2.07 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.23 (6H, s, $N(CH_3)_2$), 3.56 (1H, dd, J=4.6, 10.1 Hz, C*H*C$_6$H$_{13}$), 3.67 (3H, s, NCH_3), 6.80 (1H, d, J=1.1 Hz, Im-H), 6.96 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 14.0, 22.5, 27.0, 28.1, 29.3, 31.7, 32.7, 41.6, 61.5, 120.8, 126.7, 147.5. ν_{max} ($CHCl_3$, cm^{-1}): 1455, 1480, 2763, 2909. EI MS (*m*/*z*, %): 96 (32), 109 (100), 138 (43), 180 (68), 223 (M^+, 1). HRMS (EI): found M^+ 223.2034, $C_{13}H_{25}N_3$ requires M^+ 223.2048.

4m: δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, J=6.8 Hz, CH_2CH_3), 1.28–1.41 (8H, m, $CH_2(CH_2)_4CH_3$), 1.59–1.69 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.21 (6H, s, $N(CH_3)_2$), 2.19–2.30 (2H, m, C*H*$_2$C$_6$H$_{13}$), 2.27 (6H, s, $N(CH_3)_2$), 2.90 (3H, s, NCH_3), 3.96 (1H, d, J=3.5 Hz, Im-H), 4.20 (1H, d, J=3.3 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 26.9, 27.9, 28.9, 29.5, 30.8, 31.6, 38.3, 39.9, 82.6, 85.4, 166.6. ν_{max} ($CHCl_3$, cm^{-1}): 1449, 1594, 2773, 2907. EI MS (*m*/*z*, %): 124 (33), 139 (100), 152 (44), 223 (45), 268 (M^+, 7). HRMS (EI): found M^+ 268.2620, $C_{15}H_{32}N_4$ requires M^+ 268.2627.

4.1.22. 1-Methyl-2-[1-(1-pyrrolidinyl)heptyl]-1*H*-imidazole 3n and (4*R* *,5*R* *)-2-heptyl-4,5-dihydro-1-methyl-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4n. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only), as a yellow viscous oil [(**3n**; 106 mg, 43%), (**4n**; 130 mg, 41%)] from pyrrolidine (5 mmol) and **2c** (1 mmol).

3n: δ_H (300 MHz, $CDCl_3$): 0.84 (3H, t, J=6.8 Hz, CH_2CH_3), 0.98–1.30 (8H, m, $CH_2(CH_2)_4CH_3$), 1.65–1.77 (4H, m, $NCH_2(CH_2)_2$), 1.84–2.00 (2H, m, C*H*$_2$C$_5$H$_{11}$), 2.25–2.38 (2H, m, NC*H*$_2$CH$_2$), 2.60–2.68 (2H, m, NC*H*$_2$CH$_2$), 3.62 (1H, dd, J=5.7, 9.4 Hz, C*H*C$_6$H$_{13}$), 3.72 (3H, s, NCH_3), 6.77 (1H, d, J=1.1 Hz, Im-H), 6.93 (1H, d, J=1.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 23.1, 26.4, 29.2, 31.6, 32.5, 32.8, 51.0, 61.5, 120.7, 126.7, 148.2. ν_{max} ($CHCl_3$, cm^{-1}): 1457, 1493, 2780, 2909. EI MS (*m*/*z*, %): 96 (24), 109 (100), 180 (65), 249 (M^+, 1). HRMS (EI): found M^+ 249.2207, $C_{15}H_{27}N_3$ requires M^+ 249.2205.

4n: δ_H (300 MHz, $CDCl_3$): 0.88 (3H, t, J=6.8 Hz, CH_2CH_3), 1.23–1.40 (8H, m, $CH_2(CH_2)_4CH_3$), 1.56–1.82 (10H, m, C*H*$_2$C$_5$H$_{11}$, and NCH_2CH_2), 2.26 (2H, t, J=7.9 Hz, C*H*$_2$C$_6$H$_{13}$), 2.60–2.77 (8H, m, NC*H*$_2$CH$_2$), 2.91 (3H, s, NCH_3), 4.26 (1H, d, J=3.1 Hz, Im-H), 4.32 (1H, d, J=3.1 Hz, Im-H). δ_C (75 MHz, $CDCl_3$): 13.9, 22.4, 23.2, 23.7, 26.8, 28.0, 28.9, 29.5, 31.4, 31.6, 46.4, 48.5, 82.2, 82.6, 166.6. ν_{max} ($CHCl_3$, cm^{-1}): 1476, 1593, 1666, 2906. EI MS (*m*/*z*, %): 71 (54), 165 (96), 178 (37), 249 (100), 320 (M^+, 13). HRMS (EI): found M^+ 320.2924, $C_{19}H_{36}N_4$ requires M^+ 320.2940.

4.1.23. 1-Benzyl-2-(1-dimethylamino-2,2-dimethylpropyl)-1*H*-imidazole 3p and (4*R* *,5*R* *)-1-benzyl-4,5-dihydro-4,5-bis(dimethylamino)-2-(2,2,-dimethylpropyl)-1*H*-imidazole 4p. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3 to AcOEt only), as a yellow viscous oil (**3p**; 32 mg, 12%) and a solid (**4p**; 253 mg, 80%) from **2d** (1 mmol).

3p: δ_H (300 MHz, $CDCl_3$): 0.97 (9H, s, C(CH_3)$_3$), 2.30 (6H, s, $N(CH_3)_2$), 3.37 (1H, s, C*H*C(CH_3)$_3$), 5.12 and 5.18 (1H each, each d, J=15.8 Hz, NCH_2), 6.85 (1H, d, J=1.3 Hz, Im-H), 7.11 (1H, d, J=1.1 Hz, Im-H), 7.12–7.37 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 27.8, 37.2, 45.0, 50.0, 67.2, 119.5, 127.0, 127.2, 128.0, 128.8, 136.7, 146.0. ν_{max} ($CHCl_3$, cm^{-1}): 1450, 1471, 2928. EI MS (*m*/*z*, %): 91 (12), 123 (3), 173 (2), 214 (100), 257 (3), 271 (M^+, 1).

HRMS (EI): found M^+ 271.2041, $C_{17}H_{25}N_3$ requires M^+ 271.2048.

4p: δ_H (300 MHz, $CDCl_3$): 1.11 (9H, s, $C(CH_3)_3$), 2.18 (6H, s, $N(CH_3)_2$), 2.21 (6H, s, $N(CH_3)_2$), 2.37 (2H, s, $CH_2C(CH_3)_3$), 3.91 (1H, d, J=4.0 Hz, Im-H), 4.27 (1H, d, J=15.8 Hz, NCH_2), 4.33 (1H, d, J=4.4 Hz, Im-H), 4.57 (1H, d, J=15.4 Hz, NCH_2), 7.21–7.35 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 30.2, 31.7, 38.4, 40.3, 40.4, 47.3, 81.1, 82.2, 127.4, 127.8, 128.5, 137.3, 164.1. ν_{max} ($CHCl_3$, cm^{-1}): 1587, 2923, 3132. EI MS (*m*/*z*, %): 91 (17), 124 (53), 214 (100), 225 (69), 271 (96), 316 (M^+, 2). HRMS (EI): found M^+ 316.2613, $C_{19}H_{32}N_4$ requires M^+ 316.2627.

4.1.24. 1-Benzyl-2-[2,2-dimethyl-1-(1-pyrrolidinyl)-propyl]-1*H*-imidazole 3q and (4*R,5*R**)-1-benzyl-4,5-dihydro-2-(2,2-dimethylpropyl)-4,5-bis(1-pyrrolidinyl)-1*H*-imidazole 4q.** Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3 to AcOEt only), as a yellow viscous oil (**3q**; 27 mg, 18%) and a solid (**4q**; 132 mg, 72%) from pyrrolidine (2.5 mmol) and **2d** (0.5 mmol).

3q: δ_H (300 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 1.54–1.67 (4H, m, $NCH_2(CH_2)_2$), 2.30–2.85 (4H, m, NCH_2CH_2), 3.65 (1H, s, $CHC(CH_3)_3$), 5.14 (2H, s, NCH_2), 6.82 (1H, d, J=1.3 Hz, Im-H), 7.09 (1H, d, J=1.3 Hz, Im-H), 7.11–7.37 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 23.6, 28.1, 37.0, 50.0, 52.1, 64.8, 119.3, 127.2, 127.3, 128.0, 128.8, 136.5, 146.7. ν_{max} ($CHCl_3$, cm^{-1}): 1451, 1473, 2937. EI MS (*m*/*z*, %): 91 (13), 213 (12), 240 (100), 297 (M^+, 0.2). HRMS (EI): found M^+ 297.2224, $C_{19}H_{27}N_3$ requires M^+ 297.2205.

4q: δ_H (300 MHz, $CDCl_3$): 1.09 (9H, s, $C(CH_3)_3$), 1.67–1.76 (8H, m, $NCH_2(CH_2)_2$), 2.34 (2H, s, $CH_2(CH_3)_3$), 2.57–2.67 (8H, m, NCH_2CH_2), 4.28 (1H, d, J=4.0 Hz, Im-H), 4.29 (1H, d, J=15.8 Hz, NCH_2), 4.53–4.59 (2H, m, Im-H and NCH_2), 7.22–7.34 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 23.5, 24.0, 30.2, 31.7, 40.4, 46.5, 47.7, 47.8, 77.9, 80.9, 127.2, 127.6, 128.4, 137.8, 164.0. ν_{max} ($CHCl_3$, cm^{-1}): 1457, 1586, 2933. EI MS (*m*/*z*, %): 70 (51), 91 (93), 150 (42), 240 (100), 277 (86), 297 (36), 368 (M^+, 1). HRMS (EI): found M^+ 368.2952, $C_{23}H_{36}N_4$ requires M^+ 368.2940.

4.1.25. 1-Benzyl-2-[1-(1-methylethoxy)-2,2-dimethyl-propyl]-1H-imidazole 3r. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2), as colorless needles (48 mg, 34%) from 2-propanol (5 mmol), Et_3N (3 mmol) and **2d** (0.5 mmol). Mp 47–50 °C.

δ_H (300 MHz, $CDCl_3$): 0.92 (3H, d, J=5.9 Hz, $CH(CH_3)_2$), 0.97 (9H, s, $C(CH_3)_3$), 1.02 (3H, d, J=6.2 Hz, $CH(CH_3)_2$), 3.42 (1H, hept., J=6.1 Hz, $CH(CH_3)_2$), 4.39 (1H, s, $CHC(CH_3)_3$), 5.21 and 5.50 (1H each, each d, J=15.8 Hz, NCH_2), 6.72 (1H, d, J=1.5 Hz, Im-H), 7.01 (1H, d, J=1.1 Hz, Im-H), 7.09–7.12 (2H, m, Ar-H), 7.27–7.36 (3H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.0, 22.8, 26.7, 36.7, 50.4, 70.7, 82.0, 120.5, 127.0, 127.5, 127.7, 128.7, 137.3, 147.2. ν_{max} ($CHCl_3$, cm^{-1}): 1475, 2931. EI MS (*m*/*z*, %): 91 (43), 187 (100), 229 (79), 286 (M^+, 4). HRMS (EI): found M^+ 286.2037, $C_{18}H_{26}N_2O$ requires M^+ 286.2045.

4.1.26. 1-Benzyl-2-(2,2-dimethyl-1-phenoxypropyl)-1*H*-imidazole 3s. Obtained, after Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:3), as a colorless powder (82 mg, 51%) from phenol (3 mmol), Et_3N (2.5 mmol) and **2d** (0.5 mmol). Mp 84–87 °C.

δ_H (300 MHz, $CDCl_3$): 1.14 (9H, s, $C(CH_3)_3$), 5.06 and 5.37 (1H each, each d, J=15.4 Hz, NCH_2), 5.19 (1H, s, $CHC(CH_3)_3$), 6.58 (1H, d, J=1.1 Hz, Im-H), 6.74–6.91 (5H, m, Ar-H), 7.02 (1H, d, J=1.5 Hz, Im-H), 7.11–7.18 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 26.7, 37.1, 50.6, 83.7, 115.5, 120.6, 121.1, 127.5, 127.6, 127.9, 128.5, 129.4, 136.4, 144.9, 158.2. ν_{max} ($CHCl_3$, cm^{-1}): 1489, 1584, 1595, 2936. EI MS (*m*/*z*, %): 91 (15), 169 (4), 227 (100), 263 (12), 320 (M^+, 1). HRMS (EI): found M^+ 320.1886, $C_{21}H_{24}N_2O$ requires M^+ 320.1889.

4.1.27. 2-(2,2-Dimethyl-1-dimethylaminopropyl)-1*H*-imidazole 3t. Obtained, after recrystallization of the crude extracts from AcOEt, as colorless prisms (150 mg, 83%) from **2e** (starting from 1 mmol of **1e**). Mp 134–136 °C.

δ_H (300 MHz, DMSO-d_6): 0.97 (9H, s, $C(CH_3)_3$), 2.15 (6H, s, $N(CH_3)_2$), 3.24 (1H, s, $CHC(CH_3)_3$), 6.87 (1H, br, Im-H), 6.99 (1H, br, Im-H). δ_C (75 MHz, DMSO-d_6): 27.6, 35.9, 44.8, 70.2, 114.5, 127.2, 144.7. ν_{max} (KBr, cm^{-1}): 1441, 2807, 2931, 3097. EI MS (*m*/*z*, %): 83 (21), 95 (8), 108 (6), 124 (100), 181 (M^+, 3). HRMS (EI): found M^+ 181.1589, $C_{10}H_{19}N_3$ requires M^+ 181.1579. Anal. calcd for $C_{10}H_{19}N_3$: C, 66.26; H, 10.56; N, 23.18; found: C, 66.09; H, 10.57; N, 23.14.

4.2. Synthesis of 5-amino-1-methylimidazoles 7

A toluene (1 mL) solution of **4** (0.5 mmol) was heated at 120 °C with stirring under N_2 until no starting material (**4**) remained on TLC (5–12 h). The solution was cooled to rt, and the solvent was evaporated to give an oily residue, which was purified by Al_2O_3 column chromatography (AcOEt/*n*-hexane=1:2 to AcOEt only) to obtain pure **7** as a yellow viscous oil.

4.2.1. 1-Methyl-5-dimethylamino-2-(2,2-dimethyl-propyl)-1*H*-imidazole 7a. Yield, 88 mg (90%). δ_H (300 MHz, $CDCl_3$): 1.00 (9H, s, $C(CH_3)_3$), 2.51 (2H, s, $CH_2C(CH_3)_3$), 2.64 (6H, s, $N(CH_3)_2$), 3.40 (3H, s, NCH_3), 6.50 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 29.5, 29.6, 32.7, 40.4, 44.8, 112.8, 143.0, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1465, 1491, 1567, 2926. EI MS (*m*/*z*, %): 70 (9), 138 (100), 180 (4), 195 (M^+, 14). HRMS (EI): found M^+ 195.1720, $C_{11}H_{21}N_3$ requires M^+ 195.1735.

4.2.2. 1-Methyl-2-(2,2-dimethylpropyl)-5-(1-pyrrolidinyl)-1*H*-imidazole 7b. Yield, 92 mg (83%). δ_H (300 MHz, $CDCl_3$): 0.99 (9H, s, $C(CH_3)_3$), 1.90–1.95 (4H, m, $NCH_2(CH_2)_2$), 2.52 (2H, s, $CH_2C(CH_3)_3$), 3.00–3.05 (4H, m, NCH_2CH_2), 3.41 (3H, s, NCH_3), 6.46 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 24.5, 29.6, 30.3, 32.8, 40.4, 52.8, 111.6, 141.8, 142.9. ν_{max} ($CHCl_3$, cm^{-1}): 1464, 1490, 1566, 2934. EI MS (*m*/*z*, %): 96 (3), 122 (6), 164 (100), 206 (4), 221 (M^+, 14). HRMS (EI): found M^+ 221.1898, $C_{13}H_{23}N_3$ requires M^+ 221.1892.

4.2.3. 1-Methyl-5-dimethylamino-2-(2-methylpropyl)-1*H*-imidazole 7c. Yield, 60 mg (66%). δ_H (300 MHz,

$CDCl_3$): 0.97 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 2.01–2.17 (1H, m, $CH(CH_3)_2$), 2.48 (2H, d, J=7.3 Hz, $CH_2CH(CH_3)_2$), 2.64 (6H, s, $N(CH_3)_2$), 3.38 (3H, s, NCH_3), 6.47 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 27.7, 28.9, 36.5, 44.9, 112.7, 143.8, 144.1. ν_{max} ($CHCl_3$, cm^{-1}): 1461, 1497, 1568, 2933. EI MS (*m*/*z*, %): 70 (12), 124 (5), 138 (100), 166 (6), 181 (M^+, 26). HRMS (EI): found M^+ 181.1585, $C_{10}H_{19}N_3$ requires M^+ 181.1579.

4.2.4. 1-Methyl-2-(2-methylpropyl)-5-(1-pyrrolidinyl)-1*H*-imidazole 7d. Yield, 83 mg (80%). δ_H (300 MHz, $CDCl_3$): 0.97 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.87–1.96 (4H, m, $NCH_2(CH_2)_2$), 2.00–2.18 (1H, m, $CH(CH_3)_2$), 2.48 (2H, d, J=7.2 Hz, $CH_2CH(CH_3)_2$), 3.00–3.04 (4H, m, NCH_2CH_2), 3.40 (3H, s, NCH_3), 6.42 (1H, s, Im-H). δ_C (75 MHz, $CDCl_3$): 22.5, 24.4, 27.8, 29.4, 36.5, 52.8, 111.6, 141.7, 143.8. ν_{max} ($CHCl_3$, cm^{-1}): 1459, 1496, 1567, 2938. EI MS (*m*/*z*, %): 96 (4), 122 (8), 164 (100), 207 (M^+, 19). HRMS (EI): found M^+ 207.1750, $C_{12}H_{21}N_3$ requires M^+ 207.1735.

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A selective reductive amination of aldehydes by the use of Hantzsch dihydropyridines as reductant

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Abstract—Direct reductive amination of an aldehyde was carried out using a Hantzsch dihydropyridine as the reductant in the presence of a catalytic amount of scandium triflate. The reaction was highly selective towards aldehydes over ketones, and other reducible functional groups did not affect the reaction.

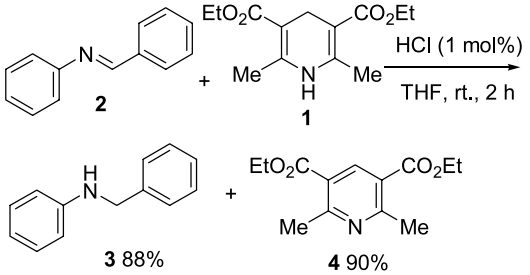
1. Introduction

Reductive amination of aldehydes or ketones, in which a mixture of an aldehyde (or ketone) and an amine is treated with a reductant in one-pot fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds;[1] thus, there are many approaches to carry out this direct process. Sodium cyanoborohydride $NaBH_3CN$ is a representative reducing agent,[2] and various modified borohydride derivatives have been used which involve $NaBH(OAc)_3$,[3] pyridine–BH_3,[4] $ZnCl_2$–$NaBH_4$,[5] silica gel–$Zn(BH_4)_2$,[6] $Ti(O\textit{i}\text{-}Pr)_4$–$NaBH_4$,[7] and $NiCl_2$–$NaBH_4$.[8] It is necessary, however, to use excess amount of amines in these reactions to obtain good yields of the products, since aldehydes or ketones are also reduced by the reductants. Although alternative metal hydride reagents have recently been developed such as Bu_3SnH,[9] Bu_2SnClH,[10] Bu_2SnIH,[10] Et_3SiH–trifluoroacetic acid,[11] $Ti(O\textit{i}Pr)_4$–polymethylhydrosiloxane,[12] and $PhSiH_3$–Bu_2SnCl_2,[13] to overcome the above defect, toxic metal ions were used in most of these reactions.

In the course of our study on the reactivity of Hantzsch dihydropyridine,[14] we have found that the compound can be used as a reducing agent for imines in the presence of a catalytic amount of Lewis acid.[15] It was revealed that the reduction was completely selective for aldehyde-derived imines over ketone-derived ones. This paper describes these results in detail.

2. Results and discussion

Hantzsch dihydropyridines (e.g., **1**) are classic aza compounds which are readily prepared from the reaction of an aldehyde, acetoacetate ester, and ammonia in a multi-gram scale.[16] Some derivatives of them have cardiovascular activities and have been used as drugs for the treatment of hypertension.[17] In spite of the 1,4-dihydro structure which is analogous to that of NADH, their role as a reductant has scarcely been reported compared to other NADH analogues.[18] In addition, the application of dihydropyridines to organic synthesis has been limited to the reduction of cyanoethylidene malonate and their derivatives.[19] In the present study, it has been found that Hantzsch pyridine **1**[20] reduces benzilydeneaniline (**2**) to the corresponding amine **3** in the presence of a catalytic amount of HCl (Eq. 1).[21]



(1)

Since the reaction hardly proceeded without the addition of HCl (Table 1, entry 1), the acid was supposed to function as

Keywords: Aldehyde; Ketone; Direct reductive amination; Imine; Hantzsch dihydropyridine; Scandium (III) triflate; Lewis acid.
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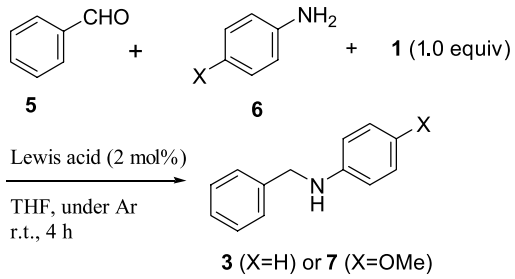
Table 1. Catalytic activity of Lewis acid in the reduction of benzylideneaniline (**2**) using Hantzsch pyridine **1**

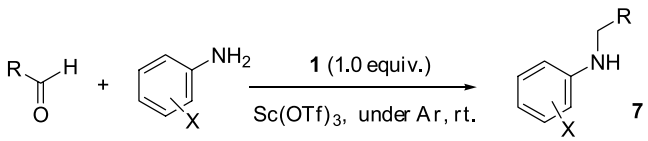
Entry	Lewis acid (1 mol%)	Yield of **3** (%)	Yield of **4** (%)
1	—	Trace	Trace
2	$Sc(OTf)_3$	94	96
3	$Yb(OTf)_3$	79	79
4	$Cu(OTf)_2$	76	78
5	$Sn(OTf)_2$	99	99
6	$Ti(OEt)_4$	58	58
7	BF_3–OEt	86	89
8	HCl	88	90

Table 2. Reaction of benzaldehyde with an amine in the presence of **1**



Entry	X	Lewis acid	Yield of **3** or **7** (%)
1	H	$Sc(OTf)_3$	99
2	H	$Sn(OTf)_2$	99
3	OMe	$Sc(OTf)_3$	98
4	OMe	$Sn(OTf)_2$	92
5	OMe	HCl	62

Table 3. Direct reductive amination using various aldehydes and amines



Entry	R	X	$Sc(OTf)_3$ (mol%)	Solvent	Time (h)	Yield of **7** (%)
1	Ph	*p*-MeO	2	THF	4	98 (**7a**)
2	*p*-$NO_2C_6H_4$	*p*-MeO	1	THF	34	93 (**7b**)
3	*p*-CNC_6H_4	*p*-MeO	1	THF	22	89 (**7c**)
4	Cyclohexyl	*p*-MeO	2	CH_2Cl_2	6	98 (**7d**)
5	Ph	*o*-OH	1	THF	24	94 (**7e**)
6	Ph	*o*-CO_2H	2	CH_2Cl_2	26	84 (**7f**)
7	*o*-OHC_6H_4	*o*-OH	2	CH_2Cl_2	4	78 (**7g**)

a catalyst. Thus, the catalytic effect of several Lewis acids on the reaction was investigated, and the results are summarized in Table 1. Various Lewis acids accelerated the reaction, and $Sc(OTf)_3$ and $Sn(OTf)_2$ gave superior results among them (entries 2 and 5).

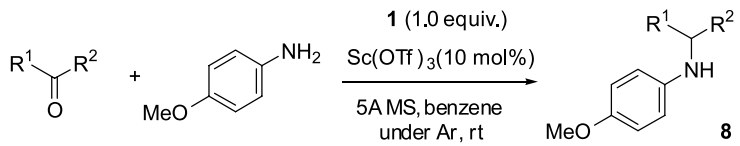
Furthermore, it was revealed that benzaldehyde itself was not reduced under these conditions. The result prompted us to carry out the direct reductive amination using benzaldehyde and an amine (Table 2). It was shown that equimolar amounts of compounds **1**, **5**, and **6** were sufficient for obtaining quantitative yields of the corresponding amines. Sc(III) and Sn(II) showed comparable reactivity, and HCl afforded a lower yield of the product. Since Sc(III) is more environmentally benign than Sn(II), scandium (III) triflate was selected as a catalyst for further study.

Next, the reaction was applied to various aldehydes and the results are summarized in Table 3. The reaction of aldehydes proceeded smoothly in THF and CH_2Cl_2 without reduction of any other functional group such as a nitro or cyano group (Table 3, entries 2 and 3). In addition, acidic functional groups (phenolic OH and carboxyl group) did not affect the product yields (entries 5 to 7).

Although reductive amination of ketones was much slower than that of aldehydes, the amination reaction proceeded in the presence of 5 Å molecular sieves[22] using 10 mol% catalyst[23] to give the corresponding products in moderate to good yields (Table 4).[24] In the absence of the dehydrating agent, the product was hardly obtained. For example, when the reaction was carried out using the same substrate as in entry 1 in the absence of molecular sieves, the product **8a** was formed only in 4% yield.

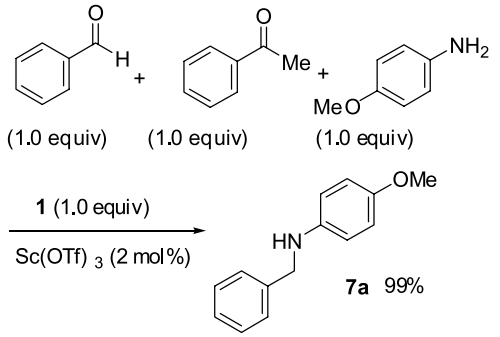
The above results indicate that the present reduction system might be selective for the imines derived from aldehyde in the presence of ketone. Thus, the reaction was carried out in the presence of both benzaldehyde and acetophenone (Eq. 2), and it was found that the product **7a** was obtained in a quantitative yield with complete recovery of acetophenone. This complete selectivity was applied to the reaction of compounds **9** and **10**, both of which have an aldehyde and a ketone in a molecule. The products **11** and **12**, which were derived from the reaction of the aldehyde group, were formed in excellent yields in both cases (Eqs. 3 and 4). Therefore, the reaction was

Table 4. Direct reductive amination of ketones in the presence of molecular sieves

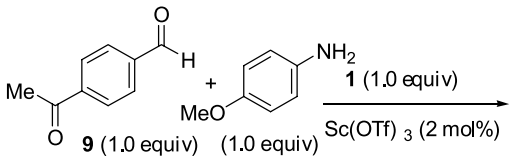


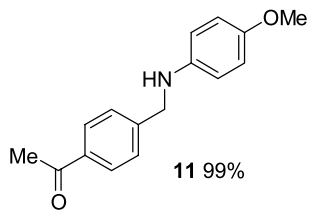
Entry	R^1	R^2	Time (h)	Yield of **8** (%)
1	Ph	Me	24	75 (**8a**)
2	CH_2=$CHCH_2CH_2$	Me	24	67 (**8b**)
3	$PhCH_2CH_2$	Me	24	82 (**8c**)
4	Ph	Et	72	62 (**8d**)
5	2-Naphthyl	Me	24	68 (**8e**)
6	2-Pyridyl	Me	24	82 (**8f**)
7	*p*-$NO_2C_6H_4$	Me	96	69 (**8g**)

proved to proceed in an absolutely selective manner toward the aldehyde group.

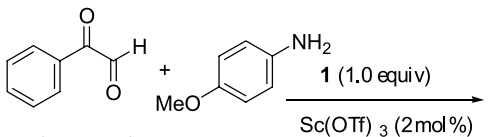


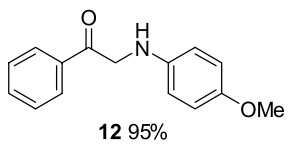
(2)





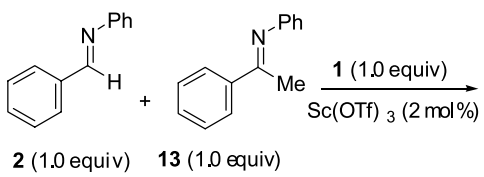
(3)



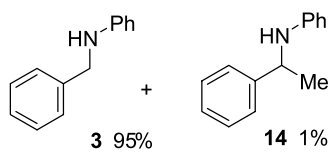


(4)

In order to clarify the step that is crucial for the rate determining, isolated imines **2** and **13** derived from benzaldehyde and acetophenone, respectively, were allowed to react with the reductant **1** (Eq. 5). The reaction proceeded smoothly to give the amine **3** in a high yield, and the amine derived from **13** was obtained in a very low yield. Thus, it was found that the reduction of imines by **1** with $Sc(OTf)_3$ was considerably affected by the steric hindrance of the substrate.



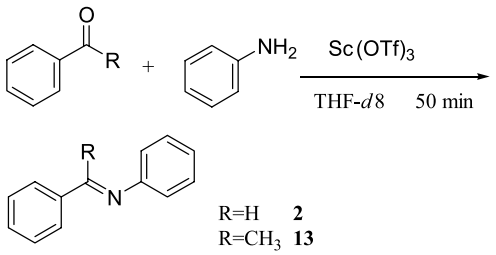
(5)



As a control experiment, we studied whether the steric effect of the substrate imine appeared in the reaction using sodium cyanoborohydride $NaBH_3CN$, which is a representative reductant for conventional reductive amination. In this case, however, the imines **2** and **13** were both reduced to give amine **3** and **14** in 45 and 16% yields, respectively (amine **3**/amine **14**=2.8:1).[25] Thus, the selectivity shown in Eq. 5 is a novel feature of the present reaction.

Next, the step of the imine formation in situ was investigated using ^1H NMR. In the absence of $Sc(OTf)_3$, the corresponding imine **2** or **13** was seldom or never obtained (Table 5, entries 1 and 2). Although the addition of the Lewis acid accelerated the imine formation from the aldehyde (entry 3), the ketone-derived imine **13** was not obtained under the conditions (entry 4).

Table 5. Formation of the imine intermediate **2** or **13**



Entry	R	Amount of $Sc(OTf)_3$ (mol%)	Yield of **2** or **13** (%)
1	H	0	16
2	CH_3	0	0
3	H	2	81
4	CH_3	2	0

Therefore, it was revealed that the complete selectivity of the present reaction was originated from both steps of the reaction, and $Sc(OTf)_3$ catalyzed these two steps effectively.[26]

The interaction between the substrates and $Sc(OTf)_3$ was studied by an electrochemical method. The reduction potential of benzaldehyde (**5**) and benzylideneaniline (**2**)

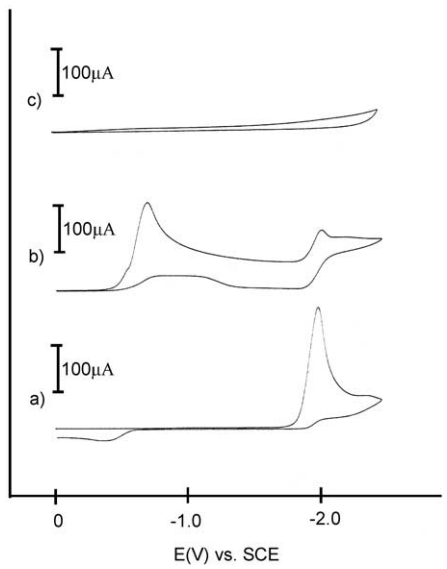


Figure 1. Cyclic voltammograms of (a) benzylideneaniline (10 mM), (b) benzylideneaniline (10 mM)+$Sc(OTf)_3$ (5 mM) and (c) $Sc(OTf)_3$ (5 mM) at glassy carbon electrode in MeCN+0.1 M Et_4NClO_4. Sweep rate 0.1 V s^{-1}.

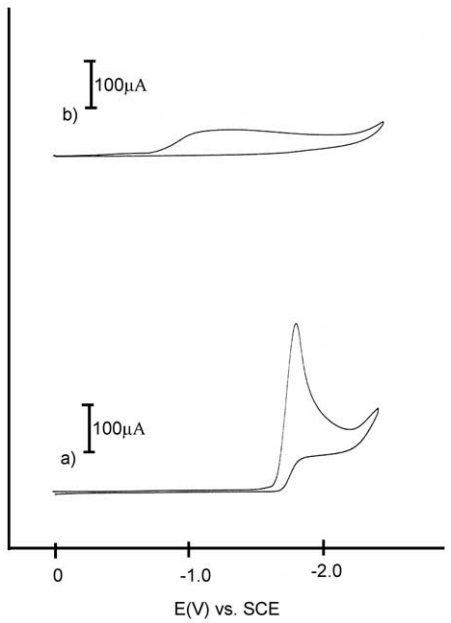


Figure 2. Cyclic voltammograms of (a) benzaldehyde (10 mM) and (b) benzaldehyde (10 mM)+$Sc(OTf)_3$ (5 mM) at glassy carbon electrode in MeCN+0.1 M Et_4NClO_4. Sweep rate 0.1 V s^{-1}.

was measured in the presence or absence of the Lewis acid using cyclic voltammetry, and the results are shown in Figures 1 and 2. In the cyclic voltammograms of the imine **2** (Fig. 1a) and aldehyde **5** (Fig. 2a) the reduction waves appeared at −1.93 and −1.78 V vs. SCE, respectively. Thus, the imine **2** was found to be less reducible than **5** under the conditions. The addition of $Sc(OTf)_3$ altered the reduction waves to more positive values, that is, −0.60 V (**2**+$Sc(OTf)_3$) and −0.95 V (**5**+$Sc(OTf)_3$) vs. SCE, respectively (Figs. 1b and 2b). These results suggested that the complex formed from the imine and $Sc(OTf)_3$ is more reducible than that formed from aldehyde and $Sc(OTf)_3$ although the parent aldehyde is more reducible than the corresponding imine. Therefore, Hantzsch dihydropyridine **1** might have a weak, selective reducing potential to react with only the most reducible imine–$Sc(OTf)_3$ complex in the reaction, although it remains unclear whether the reaction was initiated by an electron transfer or a hydride transfer.

The high selectivity of the reaction enabled us to examine dialkylation of diamines because an excess amount of aldehyde can be used for to the reaction. Thus, the reaction of phenylenediamines with benzaldehyde was carried out as shown in Scheme 1.

In the presence of 3 equiv. of benzaldehyde, *N*,*N*′-dibenzyl derivatives were obtained in good yields in the cases of *p* and *m*-phenylenediamine.[27] *o*-Phenylenediamine gave a moderate yield because of the formation of cyclic byproducts.[28] Thus, the present reaction system was proved to be useful for the reductive amination using polyamino compounds.

In this paper, we disclosed that Hantzsch dihydropyridine **1** is a versatile reducing agent for the direct reductive amination in the presence of a catalytic amount of $Sc(OTf)_3$. In particular, the selective reaction of the aldehyde-derived imine was carried out with the coexistence of other reducible functional groups including a ketone. Studies aimed at broadening the scope of the present reaction system, and the application of the products to organic synthesis of other compounds are now in progress.

3. Experimental

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively, using tetramethylsilane as a standard. All melting points are uncorrected.

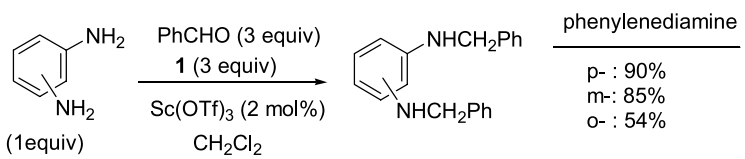
3.1. Reaction of benzylideneaniline and a Hantzsch dihydropyridine 1 in the presence of a Lewis acid (Table 1)

To the THF solution (1 ml) of benzylideneaniline (36 mg, 0.2 mmol) were added Hantzsch dihydropyridine **1** (51 mg, 0.2 mmol) and a Lewis acid (1 mol%), and the mixture was allowed to react for 2 h under Ar at room temperature. After AcOEt (12 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. Then the solvent was evaporated off, and the product was analyzed by ^1H NMR using mesitylene as an internal standard.

The reaction procedure concerning Table 2. To the THF solution (1 ml) of aniline (18 μl, 0.2 mmol) or *p*-anisidine (25 mg, 0.2 mmol) were added compound **1** (51 mg, 0.2 mmol) and a Lewis acid (2 mol%), and the mixture was allowed to react for 4 h at room temperature. The work-up and the analysis processes were the same as the above.

3.2. Reaction of various aldehydes with an amine in the presence of 1 catalyzed by $Sc(OTf)_3$

Typical procedure. To the CH_2Cl_2 solution (1 ml) of cyclohexanecarbaldehyde (24 μl, 0.2 mmol) and *p*-anisidine (25 mg, 0.2 mmol) were added compound **1** (51 mg, 0.2 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol), and the mixture was allowed to react for 6 h. After AcOEt (12 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was



Scheme 1.

chromatographed on silica gel (CH_2Cl_2/AcOEt=20) to give **7d** (43 mg, yield 98%).

3.2.1. *N*-Benzyl-*p*-anisidine (7a). Yield 98%; colorless granules; mp 48.6–48.9 °C; ^{1}H NMR ($CDCl_3$) δ: 3.73 (3H, s), 4.26 (2H, s), 6.58 (2H, dt, J=9.0, 3.0 Hz), 6.76 (2H, dt, J=9.0, 2.9 Hz), 7.25 (1H, tt, J=6.9, 2.1 Hz), 7.30–7.37 (4H, m); ^{13}C NMR ($CDCl_3$) δ: 49.2, 55.8, 114.0, 114.8, 127.0, 127.4, 128.4, 139.5, 142.2, 152.0. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.87; H, 7.21; N, 6.58.

3.2.2. *N*-(*p*-Nitrobenzyl)-*p*-anisidine (7b). Yield 93%; yellow granules; mp 97.7–97.9 °C; ^{1}H NMR ($CDCl_3$) δ: 3.73 (3H, s), 4.42 (2H, s), 6.55 (2H, dt, J=9.0, 2.3 Hz), 6.75 (2H, dt, J=9.0, 2.3 Hz), 7.53 (2H, d, J=8.8 Hz), 8.18 (2H, dt, J=8.8, 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 48.4, 55.6, 114.0, 114.7, 123.6, 127.5, 140.9, 146.8, 147.3, 152.3. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.88; H, 5.48; N, 10.63.

3.2.3. *N*-(*p*-Cyanobenzyl)-*p*-anisidine (7c). Yield 89%; yellow powder; mp 76.1–76.3 °C; ^{1}H NMR ($CDCl_3$) δ: 3.73 (3H, s), 4.73 (2H, s), 6.54 (2H, dt, J=9.0, 2.9 Hz), 6.76 (2H, dt, J=9.0, 2.9 Hz), 7.47 (2H, d, J=8.2 Hz), 7.61 (2H, d, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 48.6, 55.6, 110.6, 114.0, 114.7, 118.6, 127.5, 132.1, 141.1, 145.2, 152.2. Anal. Calcd for $C_{15}H_{14}N_2O_3 \cdot 1/4H_2O$: C, 74.28; H, 5.92; N, 11.55. Found: C, 74.58; H, 5.99; N, 11.21.

3.2.4. *N*-Cyclohexylmethyl-*p*-anisidine (7d). Yield 98%; reddish oil; ^{1}H NMR ($CDCl_3$) δ: 0.92–1.02 (2H, m), 1.12–1.30 (3H, m), 1.56 (1H, m), 1.66–1.82 (5H, m), 2.90 (2H, d, J=6.6 Hz), 3.40 (1H, brs), 3.74 (3H, s), 6.56 (2H, d, J=9.0 Hz), 6.77 (2H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 26.0, 26.6, 31.3, 37.6, 51.7, 55.9, 113.9, 114.9, 143.0, 151.8. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.70; H, 9.65; N, 6.39. Found: C, 76.52; H, 10.22; N, 6.23.

3.2.5. *o*-(Benzylamino)phenol (7e). Yield 94%; colorless needles; mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ: 4.32 (2H, s), 4.68 (1H, brs), 6.59–6.68 (3H, m), 6.82 (1H, t, J=7.4 Hz), 7.22–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 48.57, 112.54, 114.37, 117.84, 121.71, 127.19, 127.56, 128.59, 136.95, 139.38, 143.45. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.12; H, 6.60; N, 6.95.

3.2.6. 2-Benzylaminobenzoic acid (7f). Yield 84%; colorless needles; mp 172–173 °C; ^{1}H NMR (CD_3CN) δ: 4.47 (2H, s), 6.58 (1H, td, J=7.0, 0.9 Hz), 6.67 (1H, d, J=8.5 Hz), 7.24–7.37 (6H, m), 7.87 (1H, dd, J=7.8, 1.8 Hz); ^{13}C NMR (CD_3CN) δ: 47.2, 110.5, 112.8, 115.7, 128.1, 128.1, 129.6, 133.0, 135.8, 140.5, 152.3, 170.6. Anal. Calcd for: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.91; H, 5.72; N, 6.11.

3.2.7. 2-[(2-Hydroxyphenyl)methyl]aminophenol (7g). Yield 78%; reddish powder; mp 99–101 °C (lit.[29] 98–100 °C); ^{1}H NMR ($CDCl_3$) δ: 4.42 (2H, s), 6.73–6.79 (2H, m), 6.83–6.90 (4H, m), 7.16 (1H, d, J=7.2 Hz), 7.22 (1H, td, J=8.1, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 48.8, 114.6, 115.2, 116.5, 119.9, 120.6, 121.5, 123.0, 128.5, 128.9, 135.7, 144.6, 156.6. FAB-MS: 216 $(M+H)^+$.

3.3. Reaction of various ketones with an amine in the presence of 1 catalyzed by $Sc(OTf)_3$

Typical procedure. To the benzene solution (1 ml) of acetophenone (27 mg, 0.2 mmol) and *p*-anisidine (25 mg, 0.2 mmol) were added compound **1** (51 mg, 0.2 mmol), $Sc(OTf)_3$ (2 mg, 0.004 mmol) and MS 5 Å (400 mg), and the mixture was allowed to react for 24 h at room temperature under Ar. After AcOEt (12 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (EtOAc/hexane=2) to give **8a** (34 mg, yield 75%).

3.3.1. *N*-(1-Phenylethyl)-*p*-anisidine (8a). Yield 75%; white powder; mp 56.3–56.7 °C; ^{1}H NMR ($CDCl_3$) δ: 1.49 (3H, d, J=6.6 Hz), 3.69 (3H, s), 4.40 (1H, q, J=6.8 Hz), 5.40 (1H, brs), 6.47 (2H, d, J=8.8 Hz), 6.69 (2H, d, J=8.8 Hz), 7.21 (1H, tt, J=7.1, 1.7 Hz), 7.29–7.37 (4H, m); ^{13}C NMR ($CDCl_3$) δ: 25.1, 54.2, 55.7, 114.5, 114.7, 125.9, 126.8, 128.6, 141.5, 145.5, 151.9. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.01; H, 7.78; N, 6.12.

3.3.2. *N*-(5-Hexen-2-yl)-*p*-anisidine (8b). Yield 67%; yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.2 Hz), 1.51 (1H, qui, J=7.6 Hz), 1.65 (1H, dq, J=7.2, 6.0 Hz), 2.15 (2H, q, J=7.4 Hz), 3.40 (1H, sxt, J=6.3 Hz), 3.74 (3H, s), 4.96 (1H, d, J=11.0 Hz), 5.03 (1H, dd, J=17.1, 1.8 Hz), 5.77–5.87 (1H, m), 6.56 (2H, d, J=9.0 Hz), 6.77 (2H, d, J=9.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.8, 30.5, 36.3, 49.2, 55.8, 114.6, 114.7, 114.8, 138.2, 141.5, 151.8. Anal. Calcd for $C_{16}H_{17}NO \cdot 1/5H_2O$: C, 74.74; H, 9.36; N, 6.70. Found: C, 75.01; H, 9.66; N, 6.64.

3.3.3. *N*-(1-Methyl-3-phenylpropyl)-*p*-anisidine (8c). Yield 82%; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H, d, J=6.4 Hz), 1.73 (1H, m), 1.84 (1H, m), 2.71 (2H, t, J=7.9 Hz), 3.39 (1H, sxt, J=6.3 Hz), 3.73 (3H, s), 6.50 (2H, dt, J=9.0, 2.9 Hz), 6.75 (2H, dt, J=9.0, 2.9 Hz), 7.18 (3H, t, J=7.6 Hz), 7.27 (2H, t, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.8, 32.5, 38.8, 48.9, 55.8, 114.7, 114.9, 125.8, 128.4, 141.7. Anal. Calcd for $C_{17}H_{21}NO \cdot 1/8H_2O$: C, 79.32; H, 8.51; N, 5.18. Found: C, 79.26; H, 8.31; N, 5.43.

3.3.4. *N*-(1-Phenylpropyl)-*p*-anisidine (8d). Yield 62%; yellow viscous oil; ^{1}H NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.5 Hz), 1.74–1.87 (2H, m), 3.67 (3H, s), 4.14 (1H, t, J=6.9 Hz), 6.46 (2H, dt, J=9.0, 2.9 Hz), 6.67 (2H, dt, J=9.2, 3.0 Hz), 7.20 (1H, tt, J=6.6, 2.0 Hz), 7.27–7.34 (4H, m); ^{13}C NMR ($CDCl_3$) δ: 10.9, 31.8, 60.3, 60.9, 114.5 (114.7), 126.4, 126.7, 128.3, 141.6, 143.9, 151.6. Anal. Calcd for $C_{16}H_{17}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 8.03; N, 5.83.

3.3.5. *N*-(1-Naphthalen-2-ylethyl)-*p*-anisidine (8e). Yield 68%; yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6.4 Hz), 2.71 (3H, s), 3.51 (1H, qui, J=6.2 Hz), 6.55 (2H, dt, J=9.0, 3.5 Hz), 6.76 (2H, dt, J=9.0, 3.5 Hz), 7.52–7.61 (2H, m), 7.87 (2H, t, J=8.6 Hz), 7.94 (1H, d, J=8.6 Hz), 8.02 (1H, dd, J=8.6, 1.8 Hz), 8.45 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 25.1, 26.7, 45.4, 114.7, 123.7, 126.6, 127.6, 128.2, 128.3, 129.3, 130.0, 132.3, 134.2, 135.3, 151.7,

197.7. FAB-MS: 278 $(M+H)^+$; HRMS (FAB): calcd for $C_{19}H_{20}NO$ $(M+H)^+$: 278.1545. Found: 278.1593.

3.3.6. *N*-(1-Pyridin-2-ylethyl)-*p*-anisidine (8f). Yield 82%; pale yellow oil; ^1H NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6.8 Hz), 3.69 (3H, s), 4.54 (1H, q, J=6.8 Hz), 6.52 (2H, dt, J=9.0, 2.9 Hz), 6.70 (2H, dt, J=9.0, 2.9 Hz), 7.13 (1H, ddd, J=7.5, 4.7, 1.1 Hz), 7.33 (1H, d, J=7.9 Hz), 7.60 (1H, td, J=7.7, 1.8 Hz), 8.56 (1H, d, J=5.9 Hz); ^{13}C NMR ($CDCl_3$) δ: 23.2, 55.5, 55.6, 114.5, 116.1, 120.1, 121.7, 136.5, 141.0, 148.9, 151.7, 163.8. FAB-MS: 229 $(M+H)^+$. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.65; H, 7.24; N, 12.19.

3.3.7. *N*-[1-(4-Nitrophenyl)ethyl]-*p*-anisidine (8g). Yield 69%; brown powder; mp 70.6–71.2 °C; ^1H NMR ($CDCl_3$) δ: 1.52 (3H, d, J=6.8 Hz), 3.69 (3H, s), 4.49 (1H, q, J=6.8 Hz), 6.40 (2H, dt, J=8.8, 2.9 Hz), 6.68 (2H, dt, J=9.0, 2.9 Hz), 7.54 (2H, d, J=8.6 Hz), 8.18 (2H, dt, J=8.8, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 25.1, 54.0, 55.7, 114.5, 114.8, 123.9, 124.0, 126.8, 129.3, 140.7, 147.0, 152.3, 153.5. Anal. Calcd for $C_{16}H_{17}NO$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.04; H, 5.85; N, 10.12.

3.3.8. *N*-(*p*-Acetylbenzyl)-*p*-anisidine (11). To the THF solution (2 ml) of 4-acetylbenzaldehyde 61 mg (0.41 mmol) and *p*-anisidine (52 mg, 0.42 mmol) were added compound **1** (108 mg, 0.43 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol), and the mixture was allowed to react for 15 h under Ar. After AcOEt (20 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (CH_2Cl_2/AcOEt=10) to give **11** (93 mg, y.89%). ^1H NMR analysis of the residue before chromatography using mesitylene as an internal standard showed the yield to be quantitative. Pale yellow solid; mp 92.8–94.5 °C; ^1H NMR ($CDCl_3$) δ: 2.59 (3H, s), 3.73 (3H, s), 4.36 (2H, s), 6.56 (2H, dt, J=9.0, 2.9 Hz), 6.76 (2H, dt, J=9.0, 2.9 Hz), 7.45 (2H, d, J=8.2 Hz), 7.92 (2H, d, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 26.6, 26.8, 48.9, 114.1, 127.1, 128.5, 128.6, 136.0, 141.7, 145.3, 152.2, 197.5. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.71; N, 5.49. Found: C, 74.96; H, 6.86; N, 5.50.

3.3.9. 2-(4-Methoxyphenylamino)-1-phenylethanone (12). To the THF solution (5 ml) of phenylglyoxal monohydrate (152 mg, 1.0 mmol) and *p*-anisidine (123 mg, 1.0 mmol) were added compound **1** (253 mg, 1.0 mmol) and $Sc(OTf)_3$ (5 mg, 0.01 mmol), and the mixture was allowed to react for 24 h at room temperature under Ar. After AcOEt (60 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (CH_2Cl_2/AcOEt=50) to give **12** (217 mg, yield 90%). ^1H NMR analysis of the residue before chromatography using mesitylene as an internal standard showed the yield to be 99%. Pale yellow needles (hexane); mp 91–92 °C; ^1H NMR ($CDCl_3$) δ: 3.09 (3H, s), 4.54 (2H, s), 6.65 (2H, d, J=9.0 Hz), 6.80 (2H, d, J=9.0 Hz), 7.48 (2H, t, J=7.3 Hz), 7.59 (1H, t, J=7.3 Hz), 7.98 (2H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 51.3, 55.7, 114.2, 115.0, 127.7, 128.8, 133.8, 135.0, 141.5, 195.5. FAB-MS: 242 $(M+H)^+$. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.72; N, 5.81. Found: C, 74.75; H, 6.28; N, 5.65.

3.4. Cyclic voltammogram

The substrate (0.1 mmol) was dissolved in 10 ml of 0.1 M Et_4NClO_4 solution of MeCN. After bubbling N_2 through the solution for 10 min, the reduction potentials were measured by cyclic voltammetry with a Yanaco P-1100 polarographic analyzer. The working electrode was a glassy carbon electrode and the counter electrode was a platinum wire. A saturated calomel electrode (SCE) was used as a reference. When the cyclic voltammetry was carried out in the presence of $Sc(OTf)_3$, 0.05 mmol of $Sc(OTf)_3$ was added after N_2 was bubbled for 10 min.

3.5. Reaction of phenylenediamines with benzaldehyde in the presence of 1 catalyzed by $Sc(OTf)_3$

Typical procedure. To the CH_2Cl_2 solution (9 ml) of *p*-phenylenediamine (11 mg, 0.1 mmol) and compound **1** (76 mg, 0.3 mmol) was added $Sc(OTf)_3$ (1 mg, 0.002 mmol), and the mixture was allowed to react for 4 h under Ar. After AcOEt (15 ml) was added, the mixture was washed with 5% aqueous Na_2CO_3 solution and brine, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (CH_2Cl_2/AcOEt=20) to give *N*,*N*′-dibenzyl-*p*-phenylenediamine (25 mg, yield 90%).

3.5.1. *N*,*N*′-Dibenzyl-*p*-phenylenediamine. Colorless needles; mp 105.6–106.4 °C; ^1H NMR ($CDCl_3$) δ: 4.26 (4H, s), 6.57 (4H, s), 7.24–7.27 (2H, m), 7.31–7.38 (8H, m); ^{13}C NMR ($CDCl_3$) δ: 49.6, 114.6, 127.0, 127.5, 128.5, 139.9, 140.7. FAB-MS: 289 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.17; H, 7.04; N, 9.74.

3.5.2. *N*,*N*′-Dibenzyl-*m*-phenylenediamine. Mp 73–74 °C (lit.[30] 71.5–72.5 °C); ^1H NMR ($CDCl_3$) δ: 4.27 (4H, s), 5.92 (1H, t, J=2.2 Hz), 6.06 (2H, dd, J=8.1, 2.2 Hz), 7.00 (1H, t, J=8.0 Hz), 7.24–7.28 (2H, m), 7.30–7.35 (8H, m); ^{13}C NMR ($CDCl_3$) δ: 48.4, 97.3, 103.1, 127.1, 127.4, 128.5, 129.9, 139.5, 149.2.

3.5.3. *N*,*N*′-Dibenzyl-*o*-phenylenediamine. ^1H NMR ($CDCl_3$) δ: 4.30 (4H, m), 6.70–6.73 (2H, m), 6.77–6.80 (2H, m), 7.25–7.28 (2H, m), 7.31–7.39 (8H, m); ^{13}C NMR ($CDCl_3$) δ: 48.8, 111.9, 119.3, 127.1, 127.7, 128.5, 137.0, 139.3. HRMS (FAB): Calcd for $C_{20}H_{21}N_2$ $(M+H)^+$: 289.171. Found: 289.170.

References and notes

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20. Several Hantzsch dihydropyridine derivatives were synthesized and applied to the reaction. Other 4,4-dihydro derivatives afforded the reduction products, but the yields were slightly lower than that of **1a**. 4-Substituted (alkyl or aryl) Hantzsch dihydropyridines did not react under the conditions.
21. For a reference of the reduction by organic dihydro derivatives, see:Kellog, R. M. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 79.
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23. When $Sn(OTf)_2$ or HCl was used instead of $Sc(OTf)_3$ in the reaction of entry 1, the yield were 34 and 5%, respectively.
24. In the reaction of ketones, $Sn(OTf)_2$ and HCl afforded lower yields than that of $Sc(OTf)_3$.
25. The reaction was run using 0.4 equiv. of $NaBH_3CN$ in order to clarify whether $NaBH_3CN$ shows the selectivity between two substrates.
26. In the one-pot reductive amination using benzaldehyde and aniline, the product was not obtained in the absence of $Sc(OTf)_3$. Instead, the imine **2** was produced in 46% yield by the 4 h reaction in THF-d_8. The results suggested that the participation of Lewis acid is crucial for the reaction progress, and that the iminium ion, which would be obtained via formation of the imine, did not play an important role in the reaction.
27. When the mixture of *p*-phenylenediamine (0.2 mmol) and benzaldehyde (0.6 mmol) was treated with $NaBH_3CN$ (0.4 mmol) in methanol, only 0.078 mmol (39%) of *N*,*N*′-dibenzyl derivative was obtained along with 0.16 mmol of benzyl alcohol.
28. The by-products included 2-phenyl- and 1-benzyl-2-phenylbenzimidazoles. In the presence of molecular oxygen, the yields of these compounds increased, and the results were applied to the synthesis of 2-arylbenzimidazole derivatives; see: Nagata, K.; Itoh, T.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2003**, *61*, 93.
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On the scope of diastereoselective epoxidation of various chiral auxiliaries derived enones: the conformational analysis of camphor derived *N*- and *O*-enones

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Dedicated to Professor A. B. Smith (University of Pennsylvania) on the occasion of his 60th birthday

Abstract—Various camphor derived *N*- and *O*-enones were treated with selected oxidants to provide the corresponding epoxides in a wide range of diastereoselectivity. For camphorsultam derived activated alkenes, high to excellent stereoselectivities were obtained when the *s-trans* enones were treated with methyl(trifluoromethyl)dioxirane. On the other hand, for *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**) derived alkenes, the use of *s-cis* enones gave the desired epoxide with excellent diastereoselectivity under the same reaction conditions. The stereoselectivity was highly dependent on the geometry of the auxiliaries derived enones and the stereochemical induction is discussed.

1. Introduction

The development of efficient methods for the synthesis of nonracemic chiral epoxides is of considerable interest, since they are important building blocks in organic synthesis.[1] The asymmetric epoxidation of allylic alcohols,[2] the metal-catalyzed epoxidation of unfunctionalized olefins,[3] and the nucleophilic epoxidation of α,β-enones[4] have been well documented. In spite of the fact that much progress have been achieved, an efficient system for the diastereoselective epoxidation of a compound bearing a chiral auxiliary is still in demand particularly for electron-deficient olefins. Oppolzer camphorsultam (**1**) is among the most promising chiral auxiliaries presently available for asymmetric reactions and, we were surprised to find a near absence of studies of the asymmetric epoxidation of camphorsultam derived *N*-enones.[5] Three novel camphor-derived auxiliaries [camphorpyrazolidinone (**2**), *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**)] were developed in this laboratory and have proved to be synthetically useful for asymmetric syntheses leading to a high degree of stereoselectivity (Fig. 1).[6] We recently reported on the diastereoselective epoxidation of camphorpyrazolidinone derived *N*-enones using a urea hydrogen peroxide complex (UHP) in the presence of trifluoroacetic anhydride (TFAA).[7] A wide range of selectivities were obtained for various chiral alkene substituents. In addition, both epoxide diastereomers were produced in high optical purity when *N*-methacryloyl camphorpyrazolidinone and *N*-tigloyl camphorpyrazolidinone were treated with UHP/TFAA and methyl(trifluoromethyl)dioxirane, respectively.[8] The synthesis of both enantiomerically enriched stereoisomers without resorting to the use of an enantiomeric chiral resource is attractive in asymmetric syntheses.[9,8,6b] We wish to report here on the scope of the epoxidation with respect to substituent tolerance on chiral auxiliaries. In general, for electron deficient alkenes high material yields were obtained when methyl(trifluoromethyl)dioxirane was used. Stereoselectivity is highly dependent on the geometry of the auxiliaries derived enones. Stereochemical bias will be discussed.

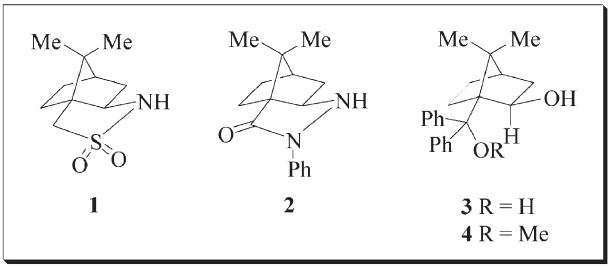

Figure 1.

Keywords: Asymmetric epoxidation.
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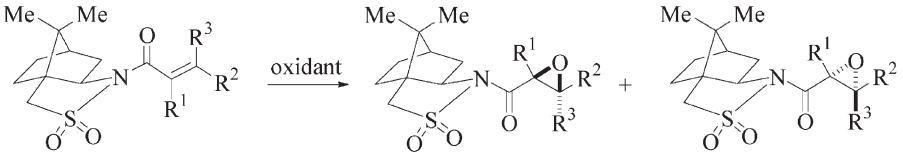
2. Results and discussion

Various chiral enones **5**–**7** can be readily prepared from the corresponding auxiliaries (**1**, **3**, and **4**) using standard acylation conditions. Three commonly used oxidants were investigated. Treatment of camphorsultam derived acrylate (**5a**, R^1=R^2=R^3=H) with in situ generated dioxirane gave the desired epoxide in low stereoselectivity (Table 1, entry 1). The use of β-substituent substrates provide the desired products with low to moderate selectivities (entries 2–4). The use of monoethyl fumaroyl camphorsultam failed to give the desired product (entry 5). This is due to the relatively poor electron density of the olefin. The selectivity was significantly improved when α-substituent substrates were used. Thus, excellent diastereoselectivity was obtained when *N*-methacryloylsultam (**5f**) was used (entry 6). The diastereoselectivity was determined to be greater than 90% de based on an ^{1}H NMR analysis of the relevant peaks. The opposite sense of diastereoselectivity was observed when the epoxidation was carried out with UHP/TFAA (entry 7). This is analogous to our previous studies in which camphorpyrazolidinone was used as a chiral auxiliary.[8] The absolute stereochemistry of the newly generated stereogenic center of both diastereomers was determined by single crystal X-ray analysis. The use of *N*-tigloylsultam (**5g**) also provide the desired epoxide in excellent stereoselectivity (entry 9). A similar phenomena was observed when the α-methy β-ethyl substituted substrate (**5h**) was treated with these two different oxidants (entries 11 and 12). Surprisingly, the use of the β,β-dimethyl substituted alkene provide the desired product in excellent stereoselectivity with the *R* configuration predominating (entry 13). The stereoselectivity dropped significantly when the reaction was carried out with the UHP/TFAA system (entry 14). In most cases, both of the diastereomeric epoxides were crystalline and could be easily recrystallized for a single crystal X-ray analysis.

An appropriate disposition of the α,β-enone functionality is extremely critical in determining the transition state structure in epoxidation reactions that affect stereodifferentiation. The conformational preference of amide linked enones is different from those of ester linked unsaturated alkenes. The reaction conditions (reagents, H-bonding, solvent polarity and etc), of course, also contribute to determining the product stereoselectivity. We then further examined the epoxidation of the *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**) derived *O*-enones. Treatment of auxiliary **3** derived acrylate with methyl(trifluoromethyl)dioxirane provided the desired product in low material yield (Table 2, entry 1). The use of crotonoyl *O*-enone **6b** under the same reaction conditions afforded the desired epoxide in 82% material yield in good stereoselectivity (entry 2). The absolute stereochemistry of the newly generated stereogenic center was determined to be the (*R*, *S*) configuration based on a single crystal X-ray analysis. Similar results were obtained with β-substituted substrates (entries 3 and 4). Excellent stereoselectivity was obtained when the β,β-disubstituted substrate (**6e**) was used (entry 5). The use of UHP/TFAA as an oxidant failed to give the desired epoxide (entry 6). In contrast to the camphorsultam and camphorpyrazolidinone derived α-substituted substrates which afford the desired products in high to excellent stereoselectivity (Table 1, entries 6, 9 and 11) similar substituent substrates derived from auxiliary **3**

Table 1. Asymmetric epoxidation of chiral camphorsultam derived *N*-enones **5a**–**i** under different epoxidation conditions[a]

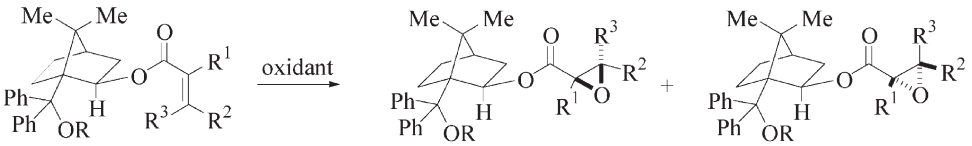


5a-i **8a-i** **9a-i**

Entry	R^1, R^2, R^3	Oxidant[b]	*t*/h	Yield (%)[c]	**8**:**9**[d]
1	**5a** R^1=R^2=R^3=H	A	10	60	31:69
2	**5b** R^1=H, R^2=Me, R^3=H	A	10	86	40:60
3	**5c** R^1=H, R^2=Pr, R^3=H	A	9	88	40[e]:60
4	**5d** R^1=H, R^2=Ph, R^3=H	A	8	91	19:81[e]
5	**5e** R^1=H, R^2=COOEt, R^3=H	A	3	0	—
6	**5f** R^1=Me, R^2=R^3=H	A	3	90	>95[e]:05
7	**5f** R^1=Me R^2=R^3=H	B	6	42	31:69[e]
8	**5f** R^1=Me R^2=R^3=H	C	4 d	88	67:33
9	**5g** R^1=R^2=Me R^3=H	A	2	95	>95[e]:05
10	**5g** R^1=R^2=Me, R^3=H	B	2	90	12:88[e]
11	**5h** R^1=Me, R^2=Et, R^3=H	A	2	99	>95[e]:05
12	**5h** R^1=Me, R^2=Et, R^3=H	B	1	99	17:83[e]
13	**5i** R^1=H, R^2=R^3=Me	A	2	97	<05:95[e]
14	**5i** R^1=H, R^2=R^3=Me	B	$\frac{1}{4}$	96	31[e]:69

[a] Unless specifically noted, all reactions were carried out with substrate **5** (0.17 mmol) at 0 °C.
[b] Method A: in situ generated dioxirane [1,1,1-trifluoroacetone (33.0 equiv.), Oxone (4.0 equiv.), Na_2EDTA (aq.), $NaHCO_3$] was used in aq. CH_3CN.; method B: UHP/TFAA (20.0/5.0 equiv.) in CH_2Cl_2; method C: *m*CPBA (6.0 equiv.) in CH_2Cl_2.
[c] Isolated yield.
[d] Determined by ^{1}H NMR analysis of relevant peaks.
[e] Absolute stereochemistry was determined by single crystal X-ray analysis.

Table 2. Asymmetric epoxidation of chiral camphor derived *O*-enones **6** and **7** under different epoxidation conditions[a]



6a-h R = H
7a-b R = Me

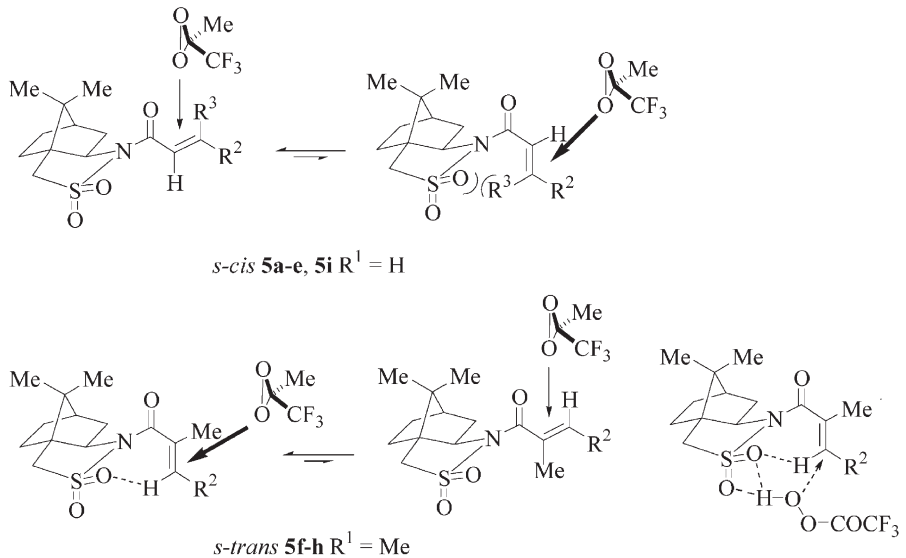
10a-h **11a-h**

Entry	R^1, R^2, R^3	Oxidant[b]	*t*/*h*	Yield (%)[c]	**10**:**11**[d]
1	**6a** R^1=R^2 =R^3=H	A	6	34	nd[e]
2	**6b** R^1=H, R^2=Me, R^3=H	A	4	82	88[f]:12
3	**6c** R^1=H, R^2=Pr, R^3=H	A	4	66	85[f]:15
4	**6d** R^1=H, R^2=Ph, R^3=H	A	2	94	93:07[f]
5	**6e** R^1=H, R^2=R^3=Me	A	2	96	>95[f]:05
6	**6e** R^1=H, R^2=R^3=Me	B	2	0	—
7	**6e** R^1=H, R^2=R^3=Me	C	3 d	85	77:23
8	**6f** R^1=Me R^2=R^3=H	A	2	95	61:39
9	**6g** R^1=R^2=Me, R^3=H	A	4	96	57:43
10	**6h** R^1=Me R^2=Et, R^3=H	A	6	80	64:36
11	**7a** R^1=H, R^2=R^3=Me	A	3	74	96:04
12	**7b** R^1=H, R^2=Ph, R^3=H	A	3	68	69:31

[a] Unless specifically noted, all reactions were carried out with substrate **6** or **7** (0.12 mmol) at 0 °C.
[b] Method A: in situ generated dioxirane [1,1,1-trifluoroacetone (47.0 equiv.), oxone (2.0 equiv.), Na_2EDTA (aq.), $NaHCO_3$] is used in aq. CH_3CN.; method B: UHP/TFAA (20.0/6.0 equiv.) in CH_2Cl_2; method C: *m*CPBA (6.0 equiv.) in CH_2Cl_2.
[c] Isolated yield.
[d] Determined by ^{1}H NMR analysis of relevant peaks.
[e] Not determined.
[f] Absolute stereochemistry was determined by single crystal X-ray analysis.

afforded the desired product in only moderate stereoselectivity (entries 8–10). The auxiliary **4** derived β,β-disubstituted enone (**7a**) provide the desired epoxide in 92% de (entry 11).

The geometry of camphorsultam conjugated enones have been studied by both Oppolzer[10] and Curren.[11] For α-unsubstituted *N*-enones, the planar *s-cis* arrangement predominates (*s-cis* **5a–e** and **5i**) while the nonplanar *s-trans*-like conformation is energetically favoured for α-substituted and α,β-disubstituted auxiliaries in the solid state conformation (*s-trans* **5f–h**; Fig. 2). The carbonyl group is oriented away from the sulfonyl moiety to minimize the unfavored dipole repulsions. It is interesting to note that, similar to camphorpyrazolidinone derived *N*-enones,[7a,8] *s-trans N*-enones **5f–h** give the epoxides in high to excellent diastereoselectivity (Table 1, entries 6, 9 and 11). The structural similarity of the α,β-enone moiety may account for the observed stereoinduction. For *s-cis* **5a–e** and **5i** an attack of methyl(trifluoromethyl)dioxirane from the top Cα *re* face gives the desired major epoxides. It is believed that this avoids electronic repulsion between the dioxirane and the α-sulfonyl oxygen atom. The low to moderate selectivity obtained with *s-cis N*-enones **5** may be due to the relative rapid equilibrium between the *s-cis N*-enones with their *s-trans* counter conformers. The fact



s-cis **5a-e**, **5i** R^1 = H

s-trans **5f-h** R^1 = Me

Figure 2. Proposed mechanism for the asymmetric epoxidation of various camphorsultam derived *N*-enones **5**.

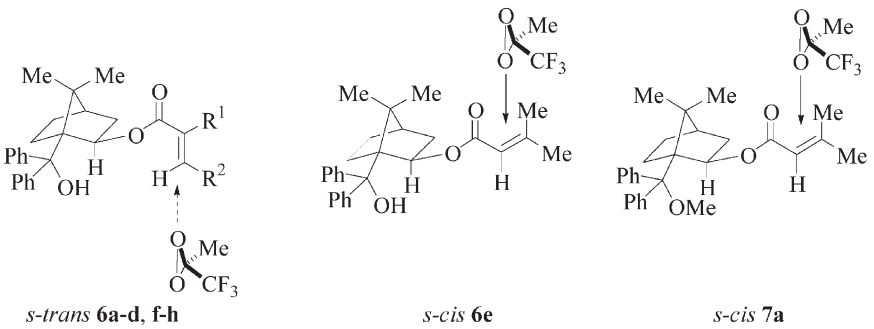


Figure 3. Proposed mechanism for the asymmetric epoxidation of the *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**) derived *O*-enones **6** and **7**.

that the β,β-dimethyl substituent **5i** afforded the desired epoxide in excellent diastereoselectivity can be explained by steric interactions between the sulfonyl group with one of the β-methyl groups (Table 1, entry 13 and Fig. 2). The *s-cis* conformation in **5i** is energetically favored for the dioxirane to attack from the Cα *re* face. On the other hand, the dioxirane attacks the *s-trans* enone from the top Cα *si* face. In general, high to excellent stereoselectivity was achieved (Table 1, entries 6, 9 and 11). The intramolecular stabilization of the *s-trans* conformation between the sulfonyl group and Cβ hydrogen may contribute to the high stereoselectivity. Further, the opposite sense of diastereoselectivity was observed when *s-trans* substrates were epoxidized with UHP/TFAA. This may be due to H-bonding between the UHP/TFAA oxidant and the sulfonyl group that directs the transfer of oxygen atom from the Cα *re* face.

In contrast to the *N*-enone functionality, *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**) derived *O*-enones moiety favor the *s-trans* disposition (Fig. 3). The X-ray diffraction analyses of **6b**–**c**,**f**–**g** confirmed the conformation in the solid state. On the other hand, for the β,β-dimethyl substituted **6e**, the *s-cis* conformation is energetically favored as indicated by single crystal X-ray analysis. The in situ generated methyl(trifluoromethyl)dioxirane approaches the double bond from the less hindered bottom Cα *re* face for the *s-trans* enones **6a**–**d**,**f**–**h** and from the top Cα *re* face for **6e**. The high stereoselectivity obtained for the β,β-dimethyl substituted **6e** may be due to a significant conformational change, analogous to the camphorsultam derived β,β-dimethyl substituted **5i**. A similar explanation can be applied to the β,β-dimethyl substrate **7a** derived from *exo*-10,10-diphenyl-10-methoxy-2-camphanol.

3. Conclusion

In summary, the epoxidation of various camphor derived *N*- and *O*-enones have been studied, to achieve a wide range of stereoselectivity (up to 90% de). High to excellent selectivity was obtained for α-substituted and α,β-disubstituted substrates derived from camphorsultam when methyl(trifluoromethyl)dioxirane was used. The opposite diastereoselectivity was observed when these substrates were treated with UHP/TFAA. On the other hand, a high stereoselectivity was obtained in the case of β,β-dimethyl substituted *O*-enones derived from *exo*-10,10-diphenyl-2,10-camphanediol (**3**) and *exo*-10,10-diphenyl-10-methoxy-2-camphanol (**4**) when methyl(trifluoromethyl)-dioxirane was used.

4. Experimental

4.1. General methods

All reactions were carried out in flame or oven-dried glassware under a positive pressure of nitrogen. Air- and moisture-sensitive compounds were introduced by the use of a cannula through a rubber septum. Most reagents were commercially available and were of synthetic grade. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Dichloromethane and toluene were dried over CaH_2 and distilled before use. Analytical thin layer chromatography was performed using silica gel 60F glass plates and flash column chromatography was performed using silica gel 60 (230–400 mesh). HRMS values were measured either by chemical ionization (MS-CI) or electronic impact (MS-EI). Elemental analyses were performed by Taipei Instrumentation Center, College of Science (National Taiwan University). ^1H and ^{13}C NMR spectra were recorded routinely in $CDCl_3$ on a 200 or 400 MHz instrument.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated the deposit numbers CCDC 239702–239714.[12]

4.2. General procedure for the epoxidation of various camphor derived *N*- and *O*-enones

Method A. To a solution of the *N*-tigloylsultam **5g** (50 mg, 0.17 mmol) in CH_3CN (1.5 mL), aq. Na_2EDTA (1.0 mL, 4×10^{-4} M), was added 1,1,1-trifluoroacetone (0.5 mL, 5.59 mmol) at 0 °C. This was followed by the addition of Oxone (210 mg, 0.34 mmol) and $NaHCO_3$ (85 mg, 1.01 mmol) in one portion. The reaction was monitored by TLC (hexanes/EtOAc=4/1) and additional portions of Oxone/$NaHCO_3$ (1/3) were added at 1 h intervals until the reaction was complete (a total of 4 equiv. of Oxone was used). The resulting solution was extracted with EtOAc (30 mL) and the layers separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel

chromatography using hexanes/EtOAc as the eluent (4/1) to give a total of 50.0 mg (95%) of epoxides (>90% de by ^{1}H NMR analysis of crude mixtures) as a white solid.

Method B. To a solution of the *N*-tigloylsultam **5g** (50 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added urea-hydrogen peroxide complex (316 mg, 3.36 mmol) at 0 °C. TFAA (0.12 mL, 0.84 mmol) was added to this mixture over 2 h and the reaction was then quenched with aq. $NaHCO_3$ (10 mL). The resulting solution was extracted with CH_2Cl_2 (50 mL) and the layers separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography using hexanes/EtOAc as the eluent (4/1) to give a total of 47.4 mg (90%) of epoxides (76% de by ^{1}H NMR analysis of crude mixtures) as a white solid.

4.2.1. Compound 8g. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, 1H, J=7.5, 5.4 Hz), 3.49 (q, 1H, J=5.4 Hz), 3.47 (d, 1H, J=13.9 Hz), 3.45 (d, 1H, J=13.8 Hz), 2.14–2.03 (m, 2H), 1.96–1.86 (m, 3H), 1.56 (s, 3H), 1.45–1.40 (m, 1H), 1.35 (d, 3H, J=5.4 Hz), 1.40–1.31 (m, 1H), 1.10 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 65.3, 60.7, 59.0, 53.1, 48.8, 47.8, 44.5, 38.2, 32.8, 26.3, 20.7, 19.8, 14.3, 12.8; HRMS *m/z* 313.1388 (calcd for $C_{15}H_{23}NO_4S$: 313.1348) Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; N, 4.47; S, 10.23. Found: C, 57.50; H, 7.24; N, 4.35; S, 10.08. Crystal data for **8g** at 25 °C: $C_{15}H_{23}NO_4S$, M 313.41, monoclinic, $P2_1$, a=8.6983 (21) Å, b=7.8284 (21) Å, c=11.860 (3) Å, V=786.1 (4) Å^3, Z=2, λ=0.70930 Å, D_c=1.324 Mg/m^3, μ=0.22 mm^{-1}, 1566 reflections, 190 parameters, R=0.048, R_w=0.052 for all data.

4.2.2. Compound 9g. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (dd, 1H, J=7.6, 4.9 Hz), 3.45 (d, 1H, J=13.7 Hz), 3.41 (d, 1H, J=13.7 Hz), 3.33 (q, 1H, J=5.4 Hz), 2.08 (dd, 1H, J=13.8, 7.8 Hz), 2.03–1.98 (m, 1H), 1.93–1.89 (m, 3H), 1.57 (s, 3H), 1.46–1.32 (m, 2H), 1.39 (d, 3H, J=5.3 Hz), 1.16 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 65.0, 60.7, 58.2, 53.1, 48.7, 47.8, 44.6, 38.0, 32.7, 26.4, 20.7, 19.8, 14.8, 12.9; HRMS *m/z* 313.1337 (calcd for $C_{15}H_{23}NO_4S$: 313.1348). Crystal data for **9g** at 25 °C: $C_{15}H_{23}NO_4S$, M 313.416, triclinic, $P1$, a=8.1182 (3) Å, b=9.1785 (3) Å, c=11.3661 (4) Å, V=791.17 (5) Å^3, Z=2, λ=0.71073 Å, D_c=1.316 Mg/m^3, μ=0.22 mm^{-1}, 3248 reflections, 380 parameters, R=0.040, R_w=0.095 for all data.

4.2.3. Compounds 8a and 9a. Inseperable diastereomeric mixture: HRMS *m/z* 285.1025 (calcd for $C_{13}H_{19}NO_4S$: 285.1035).

4.2.4. Compounds 8b and 9b. Inseperable diastereomeric mixture: HRMS *m/z* 299.1193 (calcd for $C_{14}H_{21}NO_4S$: 299.1191).

4.2.5. Compound 8c. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (dd, 1H, J=7.3, 5.4 Hz), 3.86 (d, 1H, J=1.8 Hz), 3.53 (d, 1H, J=13.8 Hz), 3.51 (d, 1H, J=13.9 Hz), 3.18 (ddd, 1H, J=6.5, 4.3, 1.9 Hz), 2.16–2.06 (m, 2H), 1.98–1.88 (m 3H), 1.71–1.56 (m. 2H), 1.55–1.30 (m, 4H), 1.14 (s, 3H), 0.98 (s, 3H), 0.96 (t, 3H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 65.2, 59.2, 53.1, 52.8, 49.1, 47.7, 44.6, 38.0, 33.2, 32.7, 26.3, 20.7, 19.8, 18.8, 13.6; HRMS *m/z* 327.1498 (calcd for $C_{16}H_{25}NO_4S$: 327.1504). Crystal data for **8c** at 25 °C: $C_{16}H_{25}NO_4S$, M 327.443, orthorhombic, $P2_12_12_1$, a=7.8466 (6) Å, b=12.9765 (10) Å, c=16.603 (2) Å, V=1690.5 (3) Å^3, Z=4, λ=0.71073 Å, D_c=1.287 Mg/m^3, μ=0.21 mm^{-1}, 1215 reflections, 200 parameters, R=0.055, R_w=0.095 for all data.

4.2.6. Compound 9c. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, 1H, J=7.7, 5.0 Hz), 3.81 (d, 1H, J=1.9 Hz), 3.52 (d, 1H, J=13.8 Hz), 3.46 (d, 1H, J=13.8 Hz), 3.12 (ddd, 1H, J=6.2, 4.6, 1.9 Hz), 2.18–2.12 (m, 1H), 2.09 (dd, 1H, J=13.9, 7.8 Hz), 1.94–1.87 (m, 3H), 1.75–1.69 (m, 1H), 1.62–1.48 (m, 3H), 1.45–1.32 (m, 2H), 1.19 (s, 3H), 0.98 (s, 3H), 0.96 (t, 3H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 65.0, 59.8, 53.3, 52.8, 49.2, 47.8, 44.6, 38.0, 33.4, 32.7, 26.3, 20.7, 19.8, 18.6, 13.7; HRMS *m/z* 327.1500 (calcd for $C_{16}H_{25}NO_4S$: 327.1504).

4.2.7. Compound 9d. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.32 (m, 5H), 4.09 (d, 1H, J=1.8 Hz), 4.07 (d, 1H, J=1.8 Hz), 3.95 (dd, 1H, J=7.8, 5.0 Hz), 3.49 (d, 1H, J=13.8 Hz), 3.44 (d, 1H, J=13.8 Hz), 2.22–2.16 (m, 1H), 2.12 (dd, 1H, J=13.9, 7.8 Hz), 1.97–1.86 (m, 3H), 1.46–1.33 (m, 2H), 1.19 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 134.7, 128.8, 128.5, 126.0, 65.1, 59.3, 56.6, 52.9, 49.3, 47.9, 44.7, 38.1, 32.8, 26.4, 20.8, 19.8; HRMS *m/z* 361.1342 (calcd for $C_{19}H_{23}NO_4S$: 361.1348) Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88; S, 8.87. Found: C, 63.14; H, 6.37; N, 3.76; S, 8.72. Crystal data for **9d** at 25 °C: $C_{19}H_{23}NO_4S$, M 361.45, monoclinic, $P2_1$, a=7.793 (10) Å, b=13.251 (6) Å, c=18.037 (4) Å, V=1827 (3) Å^3, Z=4, λ=0.70930 Å, D_c=1.314 Mg/m^3, μ=0.20 mm^{-1}, 3472 reflections, 451 parameters, R=0.049, R_w=0.055 for all data.

4.2.8. Compound 8f. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (dd, 1H, J=6.9, 6.9 Hz), 3.49 (d, 1H, J=13.7 Hz), 3.46 (d, 1H, J=13.7 Hz), 3.31 (d, 1H, J=4.2 Hz), 2.88 (d, 1H, J=4.2 Hz), 2.11–2.03 (m, 2H), 1.97–1.87 (m, 3H), 1.64 (s, 3H), 1.46–1.31 (m, 2H), 1.11 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 65.4, 57.2, 53.6, 53.1, 48.8, 47.8, 44.6, 38.2, 32.9, 26.3, 20.7, 19.8, 18.8; HRMS *m/z* 299.1200 (calcd for $C_{14}H_{21}NO_4S$: 299.1191). Crystal data for **8f** at 25 °C: $C_{14}H_{21}NO_4S$, M 299.389, monoclinic, $P2_1$, a=16.3325 (5) Å, b=11.3516 (3) Å, c=16.9962 (6) Å, V=3094.2 (2) Å^3, Z=8, λ=0.71073 Å, D_c=1.285 Mg/m^3, μ=0.22 mm^{-1}, 3869 reflections, 716 parameters, R=0.063, R_w=0.104 for all data.

4.2.9. Compound 9f. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (dd, 1H, J=7.6, 4.8 Hz), 3.48 (d, 1H, J=13.6 Hz), 3.43 (d, 1H, J=13.6 Hz), 3.14 (d, 1H, J=5.2 Hz), 2.90 (d, 1H, J=5.2 Hz), 2.08 (dd, 1H, J=13.8, 7.8 Hz), 2.04–1.86 (m, 4H), 1.66 (s, 3H), 1.46–1.33 (m, 2H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 65.2, 57.3, 53.2, 53.1, 48.7, 47.8, 44.6, 38.1, 32.8, 26.4, 20.7, 19.8, 19.2; HRMS *m/z* 299.1192 (calcd for $C_{14}H_{21}NO_4S$: 299.1191). Crystal data for **9f** at 25 °C: $C_{14}H_{21}NO_4S$, M 299.389, orthorhombic, $P2_12_12_1$, a=12.2654 (2) Å, b=15.2353 (2) Å, c=24.3218 (4) Å, V=4544.94 (12) Å^3, Z=12, λ=0.71073 Å, D_c=1.313 Mg/m^3, μ=0.23 mm^{-1}, 3256 reflections, 542 parameters, R=0.051, R_w=0.081 for all data.

4.2.10. Compound 8h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, 1H, J=7.6, 2.4 Hz), 3.47 (d, 1H, J=14.0 Hz), 3.45 (d, 1H, J=14.0 Hz), 3.34 (dd, 1H, J=7.6, 4.8 Hz), 2.14–2.03 (m, 2H), 1.96–1.86 (m, 3H), 1.79–1.68 (m, 1H), 1.56 (s, 3H), 1.54–1.46 (m, 1H), 1.45–1.25 (m, 2H), 1.12 (s, 3H), 1.08 (t, 3H, J=7.6 Hz), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 65.4, 63.9, 61.3, 53.1, 48.8, 47.7, 44.5, 38.2, 32.9, 26.3, 21.0, 20.8, 19.8, 14.5, 10.3; HRMS m/z 327.1484 (calcd for $C_{16}H_{25}NO_4S$: 327.1504) Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28; S, 9.79. Found: C, 58.92; H, 7.48; N, 4.30; S, 9.88. Crystal data for **8h** at 25 °C: $C_{16}H_{25}NO_4S$, M 327.43, orthorhombic, $P2_12_12_1$, a=6.918 (4) Å, b=11.0011 (21) Å, c=22.216 (4) Å, V=1690.8 (11) Å^3, Z=4, λ=0.70930 Å, D_c=1.286 Mg/m^3, μ=0.21 mm^{-1}, 1733 reflections, 200 parameters, R=0.045, R_w=0.044 for all data.

4.2.11. Compound 9h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (dd, 1H, J=7.7, 4.9 Hz), 3.46 (d, 1H, J=13.7 Hz), 3.42 (d, 1H, J=13.7 Hz), 3.15 (dd, 1H, J=6.9, 5.3 Hz), 2.07 (dd, 1H, J=13.8, 7.8 Hz), 2.03–1.96 (m, 1H), 1.94–1.85 (m, 3H), 1.74–1.67 (m, 1H), 1.62–1.53 (m, 1H), 1.58 (s, 3H), 1.46–1.32 (m, 2H), 1.16 (s, 3H), 1.09 (t, 3H, J=7.6 Hz), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 65.0, 63.3, 61.1, 53.0, 48.6, 47.7, 44.5, 38.0, 32.7, 26.3, 21.0, 20.6, 19.7, 14.9, 10.1; HRMS m/z 327.1497 (calcd for $C_{16}H_{25}NO_4S$: 327.1504). Crystal data for **9h** at 25 °C: $C_{16}H_{25}NO_4S$, M 327.443, monoclinic, $P2_1$, a=12.7086 (4) Å, b=7.0864 (2) Å, c=19.3559 (7) Å, V=1716.41 (10) Å^3, Z=4, λ=0.71073 Å, D_c=1.267 Mg/m^3, μ=0.20 mm^{-1}, 2242 reflections, 398 parameters, R=0.042, R_w=0.086 for all data.

4.2.12. Compound 8i. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (dd, 1H, J=7.5, 5.4 Hz), 3.89 (s, 1H), 3.50 (d, 1H, J=13.9 Hz), 3.49 (d, 1H, J=13.9 Hz), 2.21–2.10 (m, 2H), 1.97–1.87 (m, 3H), 1.46–1.32 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H), 1.12 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 65.0, 61.0, 60.6, 52.7, 49.4, 47.8, 44.5, 38.2, 32.7, 26.3, 23.5, 20.6, 19.8, 18.5; HRMS m/z 313.1345 (calcd for $C_{15}H_{23}NO_4S$: 313.1348). Crystal data for **8i** at 25 °C: $C_{15}H_{23}NO_4S$, M 313.41, orthorhombic, $P2_12_12_1$, a=7.897 (4) Å, b=13.0751 (25) Å, c=15.743 (3) Å, V=1625.6 (8) Å^3, Z=4, λ=0.70930 Å, D_c=1.281 Mg/m^3, μ=0.21 mm^{-1}, 1658 reflections, 191 parameters, R=0.068, R_w=0.102 for all data.

4.2.13. Compound 9i. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09 (dd, 1H, J=7.6, 5.1 Hz), 3.84 (s, 1H), 3.50 (d, 1H, J=13.8 Hz), 3.45 (d, 1H, J=13.8 Hz), 2.21–2.14 (m, 1H), 2.11 (dd, 1H, J=13.9, 7.8 Hz), 1.97–1.86 (m, 3H), 1.46 (s, 3H), 1.44–1.32 (m, 2H), 1.30 (s, 3H), 1.19 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 64.8, 62.2, 60.2, 52.8, 49.2, 47.8, 44.5, 38.0, 32.7, 26.4, 23.8, 20.6, 19.8, 18.1; HRMS m/z 313.1347 (calcd for $C_{15}H_{23}NO_4S$: 313.1348). Crystal data for **9i** at 25 °C: $C_{15}H_{23}NO_4S$, M 313.416, orthorhombic, $P2_12_12_1$, a=10.9353 (2) Å, b=13.8847 (3) Å, c=20.9791 (4) Å, V=3185.33 (11) Å^3, Z=8, λ=0.71073 Å, D_c=1.307 Mg/m^3, μ=0.22 mm^{-1}, 3034 reflections, 380 parameters, R=0.047, R_w=0.089 for all data.

4.2.14. Compound 10a. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, 2H, J=7.4, 1.1 Hz), 7.62 (dd, 2H, J=7.4, 1.2 Hz), 7.28 (t, 2H, J=7.4 Hz), 7.22 (t, 2H, J=7.2 Hz), 7.18–7.10 (m, 2H), 5.29 (dd, 1H, J=8.0, 3.6 Hz), 3.79 (br, 1H), 3.06 (dd, 1H, J=4.3, 2.3 Hz), 2.83 (dd, 1H, J=6.1, 4.4 Hz), 2.63 (dd, 1H, J=6.1, 2.2 Hz) 2.30 (td, 1H, J=12.5, 4.2 Hz), 1.99–1.91 (m, 1H), 1.89 (dd, 1H, J=13.7, 8.2 Hz), 1.77–1.72 (m, 1H), 1.67–1.63 (m, 1H), 1.51–1.49 (m, 1H), 1.47 (s, 3H), 1.17–1.11 (m, 1H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 148.7, 143.2, 128.4, 127.9, 126.8, 126.5, 126.1, 82.1, 81.1, 59.3, 51.4, 47.7, 47.0, 46.2, 38.0, 31.0, 26.9, 24.4, 22.5; HRMS m/z 392.1953 (calcd for $C_{25}H_{28}O_4$: 392.1988).

4.2.15. Compound 11a. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (dd, 2H, J=7.5, 1.1 Hz), 7.51 (dd, 2H, J=7.3, 1.2 Hz), 7.28–7.19 (m, 4H), 7.16–7.10 (m, 2H), 5.29 (dd, 1H, J=8.0, 3.7 Hz), 3.78 (br, 1H), 3.20 (q, 1H, J=2.3 Hz), 2.64 (dd, 1H, J=5.9, 4.6 Hz), 2.32–2.25 (m, 1H), 2.08 (dd, 1H, J=6.0, 2.3 Hz), 2.04 (dd, 1H, J=13.0, 8.0 Hz), 1.99–1.93 (m, 1H), 1.90–1.84 (m, 1H), 1.69–1.63 (m, 1H), 1.49 (s, 3H), 1.21–1.10 (m, 2H), 0.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 149.8, 143.8, 128.5, 128.0, 126.7, 126.6, 126.3, 126.1, 83.1, 81.3, 58.7, 51.5, 47.6, 47.3, 45.4, 38.6, 31.0, 26.9, 24.6, 22.6.

4.2.16. Compound 10b. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (dd, 2H, J=7.4, 1.0 Hz), 7.62 (dd, 2H, J=7.4, 1.2 Hz), 7.28 (t, 2H, J=7.4 Hz), 7.21 (t, 2H, J=7.2 Hz), 7.17–7.10 (m, 2H), 5.27 (dd, 1H, J=11.6, 3.6 Hz), 3.86 (br, 1H), 2.90 (qd, 1H, J=5.1, 1.8 Hz), 2.81 (d, 1H, J=1.8 Hz), 2.30 (td, 1H, J=12.4, 4.1 Hz), 1.99–1.92 (m, 1H), 1.88 (dd, 1H, J=13.7, 8.3 Hz), 1.77–1.72 (m, 1H), 1.66–1.62 (m, 1H), 1.51–1.48 (m, 1H), 1.47 (s, 3H), 1.33 (d, 3H, J=5.1 Hz), 1.17–1.11 (m, 1H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 148.8, 143.2, 128.4, 127.9, 126.7, 126.5, 126.1, 81.8, 81.1, 59.2, 54.6, 53.6, 51.3, 47.6, 38.0, 30.9, 26.9, 24.5, 22.4, 17.0; HRMS m/z 406.2144 (calcd for $C_{26}H_{30}O_4$: 406.2144). Crystal data for **10b** at 25 °C: $C_{26}H_{30}O_4$, M 406.522, monoclinic, $C2$, a=16.2748 (6) Å, b=6.9261 (3) Å, c=20.7081 (9) Å, V=2206.3 (2) Å^3, Z=4, λ=0.71073 Å, D_c=1.224 Mg/m^3, μ=0.08 mm^{-1}, 1426 reflections, 272 parameters, R=0.059, R_w=0.151 for all data.

4.2.17. Compound 11b. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 2H, J=7.5, 1.1 Hz), 7.51 (dd, 2H, J=7.4, 1.2 Hz), 7.27–7.19 (m, 4H), 7.15–7.12 (m, 2H), 5.27 (dd, 1H, J=13.2, 4.8 Hz), 3.83 (br, 1H), 2.93 (d, 1H, J=4.8 Hz), 2.31–2.24 (m, 2H), 2.02 (dd, 1H, J=13.7, 8.0 Hz), 1.98–1.92 (m, 1H), 1.88–1.83 (m, 1H), 1.67–1.62 (m, 1H), 1.48 (s, 3H), 1.20 (d, 3H, J=5.1 Hz), 1.22–1.14 (m, 2H), 0.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 149.8, 143.8, 128.5, 127.9, 126.7, 126.5, 126.4, 126.1, 82.9, 81.3, 58.7, 53.8, 53.6, 51.5, 47.6, 38.6, 31.0, 26.9, 24.6, 22.6, 17.0.

4.2.18. Compound 10c. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (dd, 2H, J=7.4, 1.1 Hz), 7.62 (dd, 2H, J=7.4, 1.2 Hz), 7.28 (t, 2H, J=7.4 Hz), 7.21 (t, 2H, J=7.2 Hz), 7.17–7.10 (m, 2H), 5.28 (dd, 1H, J=8.3, 3.6 Hz), 3.89 (br, 1H), 2.84–2.81 (m, 2H), 2.30 (td, 1H, J=12.5, 4.2 Hz), 1.98–1.95 (m, 1H), 1.89 (dd, 1H, J=13.6, 8.2 Hz), 1.77–1.72 (m, 1H), 1.65–1.57 (m, 1H), 1.56–1.51 (m, 2H), 1.48 (s, 3H), 1.50–1.41 (m, 3H), 1.17–1.13 (m, 1H), 0.95 (t, 3H, J=7.1 Hz), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 148.7, 143.3,

128.4, 127.9, 126.7, 126.5, 126.2, 126.1, 81.8, 81.1, 59.2, 58.3, 52.6, 51.3, 47.7, 38.0, 33.3, 30.9, 26.9, 24.5, 22.5, 18.9, 13.7; HRMS *m/z* 434.2441 (calcd for $C_{28}H_{34}O_4$: 434.2457). Crystal data for **10c** at 25 °C: $C_{28}H_{34}O_4$, *M* 434.57, monoclinic, *P212121*, *a*=9.2875 (20) Å, *b*=10.012 (3) Å, *c*=26.376 (6) Å, *V*=2452.6 (10) Å^3, *Z*=4, λ=0.70930 Å, D_c=1.177 Mg/m^3, μ=0.08 mm^{-1}, 2463 reflections, 290 parameters, *R*=0.048, R_w=0.045 for all data.

4.2.19. Compound 10d. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, 2H, *J*=7.4, 1.2 Hz), 7.62 (dd, 2H, *J*=7.4, 1.2 Hz), 7.38–7.33 (m, 2H), 7.29–7.16 (m, 7H), 7.13–7.10 (m, 2H), 5.34 (dd, 1H, *J*=8.1, 3.6 Hz), 3.81 (br, 1H), 3.74 (d, 1H, *J*=1.6 Hz), 3.15 (d, 1H, *J*=1.7 Hz), 2.32 (td, 1H, *J*=12.4, 4.2 Hz), 2.01–1.90 (m, 2H), 1.86–1.80 (m, 1H), 1.70–1.63 (m, 1H), 1.52 (s, 3H), 1.55–1.53 (m, 1H), 1.19–1.13 (m, 1H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 148.8, 143.2, 134.4, 129.0, 128.6, 128.4, 128.0, 126.8, 126.5, 126.1, 125.8, 82.2, 81.1, 59.3, 57.9, 56.2, 51.4, 47.7, 38.1, 31.0, 26.9, 24.5, 22.5; HRMS *m/z* 468.2283 (calcd for $C_{31}H_{32}O_4$: 468.2301).

4.2.20. Compound 11d. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (dd, 2H, *J*=7.4, 1.2 Hz), 7.62 (dd, 2H, *J*=7.3, 1.1 Hz), 7.35–7.30 (m, 5H), 7.27–7.19 (m, 3H), 7.14–7.06 (m, 3H), 5.36 (dd, 1H, *J*=8.0, 3.8 Hz), 3.89 (br 1H), 3.24 (d, 1H, *J*=1.8 Hz), 3.07 (d, 1H, *J*=1.7 Hz), 2.30 (td, 1H, *J*=12.6, 4.3 Hz), 2.08 (dd, 1H, *J*=13.8, 8.0 Hz), 2.02–1.88 (m, 2H), 1.71–1.64 (m, 1H), 1.51 (s, 3H), 1.51–1.50 (m, 1H), 1.23–1.66 (m, 1H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 150.2, 143.9, 134.7, 128.9, 128.6, 128.5, 128.2, 126.7, 126.6, 126.6, 126.1, 125.5, 83.2, 81.4, 58.7, 56.8, 56.6, 51.5, 47.6, 38.7, 31.0, 27.0, 24.6, 22.6; HRMS *m/z* 468.2295 (calcd for $C_{31}H_{32}O_4$: 468.2301). Crystal data for **11d** at 25 °C: $C_{31}H_{32}O_4$, *M* 468.593, monoclinic, $P2_12_12_1$, *a*=7.34060 (10) Å, *b*=16.1417 (3) Å, *c*=21.6388 (4) Å, *V*=2563.98 (8) Å^3, *Z*=4, λ=0.71073 Å, D_c=1.214 Mg/m^3, μ=0.079 mm^{-1}, 4517 reflections, 316 parameters, *R*=0.0587, R_w=0.1431 for all data.

4.2.21. Compound 10e. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 2H, *J*=7.8 Hz), 7.60 (d, 2H, *J*=7.7 Hz), 7.26 (t, 2H, *J*=7.5 Hz), 7.21 (t, 2H, *J*=7.4 Hz), 7.15–7.09 (m, 2H), 5.24 (dd, 1H, *J*=8.2, 3.6 Hz), 3.89 (br 1H), 2.89 (s, 1H), 2.31 (td, 1H, *J*=12.5, 4.2 Hz), 2.02–1.93 (m, 2H), 1.82–1.76 (m, 1H), 1.68–1.61 (m, 1H), 1.50 (s, 3H), 1.49–1.48 (m, 1H), 1.29 (s, 3H), 1.18–1.11 (m, 1H), 1.07 (s, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 149.2, 143.3, 128.4, 127.9, 126.7, 126.4, 126.1, 126.0, 82.6, 81.1, 60.6, 59.0, 58.9, 51.3, 47.6, 38.4, 31.0, 26.9, 24.5, 24.2, 22.4, 17.9; HRMS *m/z* 420.2266 (calcd for $C_{27}H_{32}O_4$: 420.2301). Crystal data for **10e** at 25 °C: $C_{27}H_{32}O_4$, *M* 420.54, monoclinic, *C2*, *a*=16.6348 (23) Å, *b*=7.0448 (17) Å, *c*=21.913 (10) Å, *V*=2309.7 Å^3, *Z*=4, λ=0.70930 Å, D_c=1.209 Mg/m^3, μ=0.08 mm^{-1}, 2263 reflections, 280 parameters, *R*=0.042, R_w=0.041 for all data.

4.2.22. Compound 10f. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, 2H, *J*=7.7 Hz), 7.62 (d, 2H, *J*=7.6 Hz), 7.29 (t, 2H, *J*=7.5 Hz), 7.21 (t, 2H, *J*=7.4 Hz), 7.16–7.09 (m, 2H), 5.25 (dd, 1H, *J*=8.1, 3.3 Hz), 4.01 (br 1H), 2.85 (d, 1H, *J*=5.7 Hz), 2.69 (d, 1H, *J*=5.7 Hz), 2.29 (td, 1H, *J*=12.5, 4.2 Hz), 1.99–1.92 (m, 1H), 1.83 (dd, 1H, *J*=13.5, 8.2 Hz), 1.73–1.60 (m, 2H), 1.49–1.47 (m, 1H), 1.45 (s, 3H), 1.25 (s, 3H), 1.16–1.10 (m, 1H), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 148.7, 143.4, 128.5, 127.9, 126.7, 126.4, 126.3, 126.0, 81.5, 81.0, 59.3, 53.3, 52.7, 51.3, 47.6, 37.9, 30.9, 27.0, 24.4, 22.5, 16.7; HRMS *m/z* 406.2126 (calcd for $C_{26}H_{30}O_4$: 406.2144).

4.2.23. Compound 11f. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, 2H, *J*=7.4, 1.0 Hz), 7.49 (dd, 2H, *J*=7.4, 0.9 Hz), 7.26–7.18 (m, 4H), 7.14–7.09 (m, 2H), 5.26 (dd, 1H, *J*=8.0, 3.6 Hz), 3.91 (br 1H), 2.42 (d, 1H, *J*=5.5 Hz), 2.26 (td, 1H, *J*=12.5, 4.2 Hz), 2.07 (d, 1H, *J*=5.3 Hz), 2.04 (dd, 1H, *J*=10.2, 8.0 Hz), 1.99–1.92 (m, 1H), 1.87–1.81 (m, 1H), 1.69–1.61 (m, 1H), 1.53–1.47 (m, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.20–1.14 (m, 1H), 0.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 149.9, 144.0, 128.6, 127.9, 126.6, 126.5, 126.0, 83.0, 81.3, 58.5, 53.6, 51.9, 51.4, 47.6, 38.8, 30.9, 27.0, 24.5, 22.6, 17.4; HRMS *m/z* 406.2127 (calcd for $C_{26}H_{30}O_4$: 406.2144).

4.2.24. Compound 10g. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, 2H, *J*=7.4, 1.2 Hz), 7.62 (dd, 2H, *J*=7.3, 1.3 Hz), 7.28 (t, 2H, *J*=7.4 Hz), 7.21 (t, 2H, *J*=7.3 Hz), 7.17–7.09 (m, 2H), 5.24 (dd, 1H, *J*=8.1, 3.4 Hz), 4.11 (br, 1H), 3.04 (q, 1H, *J*=5.4 Hz), 2.28 (td, 1H, *J*=12.5, 4.2 Hz), 1.99–1.92 (m, 1H), 1.85 (dd, 1H, *J*=13.5, 8.2 Hz), 1.73–1.60 (m, 2H), 1.49–1.48 (m, 1H), 1.46 (s, 3H), 1.29 (d, 3H, *J*=5.4 Hz), 1.17 (s, 3H), 1.15–1.10 (m, 1H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 148.8, 143.4, 128.4, 127.9, 126.7, 126.3, 126.3, 126.0, 81.4, 80.9, 59.2, 57.9, 57.0, 51.3, 47.6, 37.8, 30.9, 26.9, 24.5, 22.5, 13.3, 12.6; HRMS *m/z* 420.2292 (calcd for $C_{27}H_{32}O_4$: 420.2301).

4.2.25. Compound 11g. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, 2H, *J*=7.4, 1.1 Hz), 7.48 (d, 2H, *J*=7.4 Hz), 7.25–7.18 (m, 4H), 7.14–7.09 (m, 2H), 5.23 (dd, 1H, *J*=8.0, 3.7 Hz), 4.01 (br 1H), 2.28 (td, 1H, *J*=12.4, 4.0 Hz), 2.10 (q, 1H, *J*=5.4 Hz), 2.04 (dd, 1H, *J*=13.8, 8.1 Hz), 1.99–1.92 (m, 1H), 1.87–1.82 (m, 1H,), 1.68–1.60 (m, 1H), 1.51–1.46 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.21–1.14 (m, 1H), 1.10 (d, 3H, *J*=5.4 Hz), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 150.1, 144.1, 128.6, 127.8, 126.6, 126.4, 126.0, 82.8, 81.3, 58.5, 57.3, 56.8, 51.5, 47.6, 38.8, 30.8, 27.0, 24.6, 22.6, 13.1, 13.0; HRMS *m/z* 420.2286 (calcd for $C_{27}H_{32}O_4$: 420.2301).

4.2.26. Compound 10h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 2H, *J*=7.8 Hz), 7.62 (d, 2H, *J*=7.6 Hz), 7.28 (t, 2H, *J*=7.6 Hz), 7.21 (t, 2H, *J*=7.4 Hz), 7.17–7.09 (m, 2H), 5.25 (dd, 1H, *J*=8.4, 3.6 Hz), 4.12 (br 1H), 2.86 (t, 1H, *J*=6.2 Hz), 2.28 (td, 1H, *J*=12.5, 4.1 Hz), 1.99–1.93 (m, 2H), 1.84 (dd, 1H, *J*=13.5, 8.2 Hz), 1.73–1.67 (m, 1H), 1.66–1.57 (m, 1H), 1.52–1.45 (m, 2H), 1.47 (s, 3H), 1.17 (s, 3H), 1.16–1.107 (m, 1H), 1.02 (t, 3H, *J*=7.5 Hz), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 148.8, 143.4, 128.4, 127.9, 126.7, 126.3, 126.3, 126.0, 81.4, 81.0, 63.2, 59.2, 57.1, 51.3, 47.6, 37.9, 30.9, 26.9, 24.5, 22.5, 21.3, 12.7, 10.2; HRMS *m/z* 434.2443 (calcd for $C_{28}H_{34}O_4$: 434.2457).

4.2.27. Compound 11h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 2H, *J*=7.4, 1.2 Hz), 7.48 (dd, 2H, *J*=7.4 Hz), 7.25–7.18 (m, 4H), 7.15–7.11 (m, 2H), 5.24 (dd, 1H, *J*=8.0,

3.6 Hz), 4.04 (br 1H), 2.27 (td, 1H, J=12.4, 4.3 Hz), 2.04 (dd, 1H, J=13.7, 8.0 Hz), 1.99–1.93 (m, 2H), 1.86–1.82 (m, 1H), 1.67–1.55 (m, 1H), 1.48 (s, 3H), 1.47–1.45 (m, 1H), 1.44–1.29 (m, 2H), 1.36 (s, 3H), 1.21–1.15 (m, 1H), 0.88 (t, 3H, J=7.5 Hz), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 150.2, 144.2, 128.6, 128.0, 126.7, 126.6, 126.4, 126.0, 82.8, 81.4, 62.0, 58.5, 57.4, 51.5, 47.6, 38.8, 30.8, 27.0, 24.6, 22.7, 21.1, 13.1, 10.0; HRMS m/z 434.2448 (calcd for $C_{28}H_{34}O_4$: 434.2457).

4.2.28. Compound 11b. (R=Me): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, 2H, J=7.6 Hz), 7.60 (d, 2H, J=7.6 Hz), 7.38–7.26 (m, 9H), 7.25–7.18 (m, 2H), 5.00 (dd, 1H, J=8.0, 3.6 Hz), 3.58 (d, 1H, J=1.6 Hz), 3.08 (d, 1H, J=1.8 Hz), 2.87 (td, 1H, J=13.1, 4.2 Hz), 2.78 (s, 3H), 1.91 (dd, 1H, J=13.4, 8.0 Hz), 1.69–1.59 (m, 2H), 1.46 (t, 1H, J=4.4 Hz), 1.23–1.17 (m, 1H), 1.08 (s, 3H), 1.05–0.97 (m, 1H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 140.5, 138.8, 135.2, 131.6, 129.8, 128.8, 128.6, 127.5, 127.2, 126.9, 126.8, 125.8, 87.5, 82.5, 61.3, 57.0, 56.8, 52.5, 49.8, 49.2, 39.4, 31.7, 25.6, 23.4, 22.4; HRMS m/z 482.2447 (calcd for $C_{32}H_{34}O_4$: 482.2457).

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Synthesis of enamides from aldehydes and amides

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Abstract—A range of double unsaturated amides (**15**, **19**, and **21**), obtained by cross-coupling reactions was reacted with aldehydes to hemiaminals. Heating the hemiaminals in the presence of Ac_2O and pyridine affected clean conversion to the corresponding enamides, such as **42**, **45**, and **47**. Alternatively, N,S-acetals were prepared which were oxidized to the sulfones. Treatment with base also gave the enamides, favoring the *cis*-isomer. However, this method is less general. Application of these methods led to the natural products lansiumamide-A (**30**_*cis*), lansiumamide-I (**31**) and lansiumamide-B (**32**).

1. Introduction

A number of natural products are known that contain an acylated enamine (=enamide) as a key structural feature (Fig. 1). These enamides may be further distinguished whether the carboxylic acid part is saturated or unsaturated. Protonation of the enamide would lead to a highly electrophilic acyliminium ion[1] which could be involved in the mode of action of such compounds. Depicted is the proteasome inhibitor TMC-95A (**1**),[2] the cytotoxic alkaloid

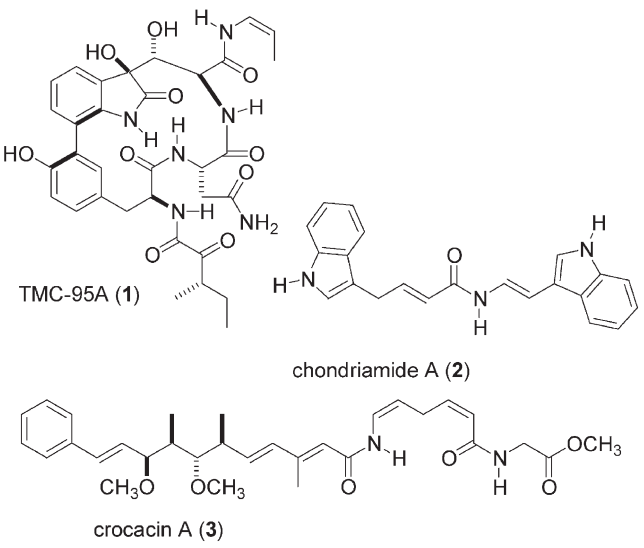

Figure 1. Some natural products that contain an enamide subunit.

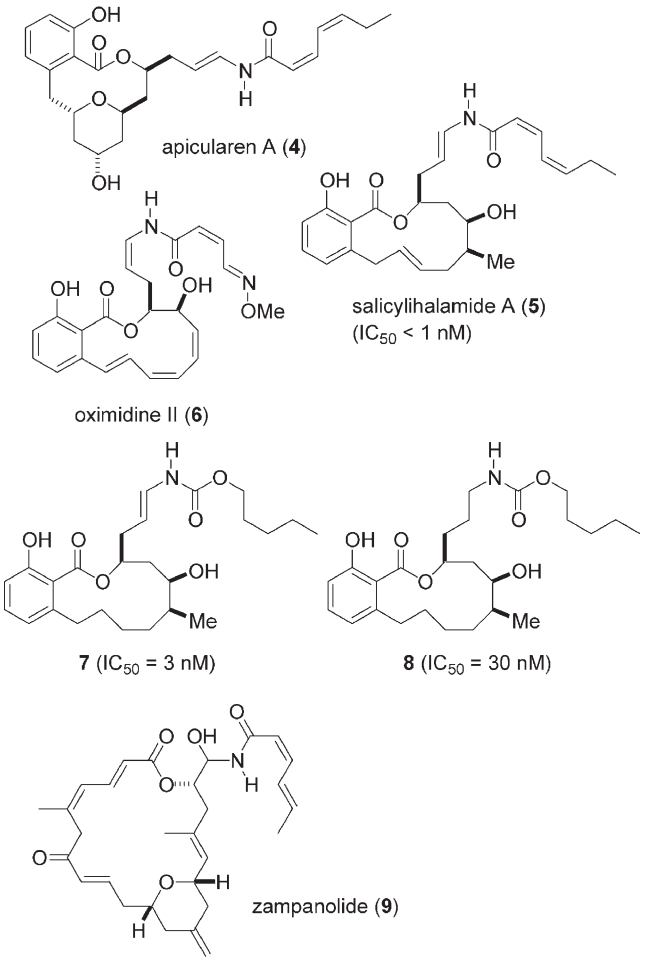

Figure 2. Representative benzolactone enamides and analogs **7** and **8**.

Keywords: Enamides; Cross-coupling; N,S-Acetals; Benzolactones.
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chondriamide A (**2**),[3] and the antifungal and cytotoxic compound crocacin A (**3**).[4]

Probably, the most interesting compounds of this class are the recently discovered benzolactone enamides.[5] Some important benzolactone enamides are apicularen A,[6] salicylihalamide A[7] and oximidine II (Fig. 2).[8] These compounds have been found to be potent inhibitors of human cancer cells. It seems that the mode of action is due to the selective inhibition of mammalian vacuolar V-ATPases.[9] The comparison of the three compounds **5**, **7** and **8** clearly demonstrates that the enamide is related to the biological activity.[10] Besides the enamides, there are also existing hydrated enamides. One example is the macrolide (−)-zampanolide (**9**) which contains such a rather uncommon *N*-acyl hemiaminal side chain.[11] Usually, aminals and hemiaminals are unstable, however, acylation confers some hydrolytic stability, possibly due to the presence of a hydrogen bond.[12]

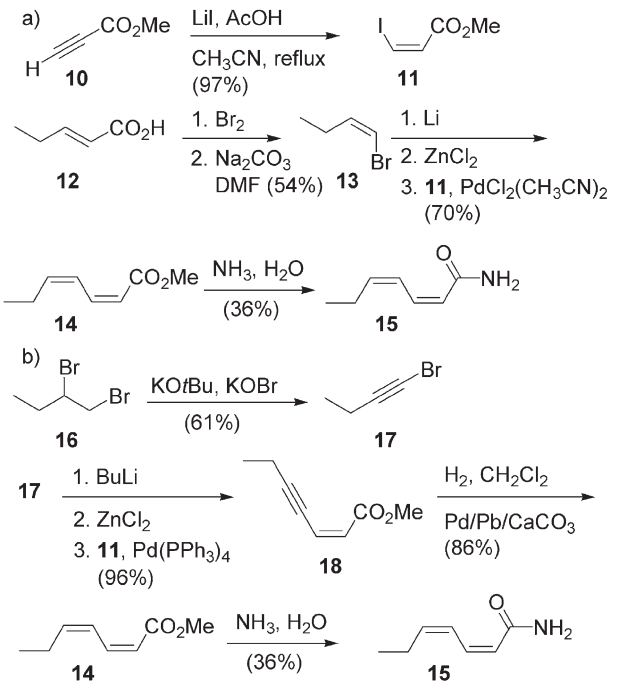
While the synthesis of the macrocyclic core of the more complex enamides represents a challenge for itself, the establishment of the enamide functionality can be a bottleneck in a synthesis endeavor. So far, five different strategies have been described in the context of enamide natural products: (a) trapping of isocyanates that were generated by Curtius rearrangement with vinyl metal species.[13] (b) Cross-coupling of a vinyl iodide with an (unsaturated) amide in the presence of a copper carboxylate.[14] (c) Base-induced elimination of an amide from a bisacylated aminal.[15] (d) Peterson-type elimination of an acylated amino alcohol with the trialkylsilyl group next to the nitrogen.[16] (e) Rearrangement–hydrolysis of α-silyl-allyl amides.[17]

The *N*-acyl hemiaminal can be synthesized by oxidative decarboxylation from a suitable *N*-acyl-α-amino acid,[12a] by acylation of a protected hemiaminal[18] or in a direct fashion by reaction of an aldehyde with an amide anion.[19] In this paper we present our own studies towards the synthesis of unsaturated enamides. In the course of this work, we discovered a practical method for the conversion of N-acylated hemiaminals to enamides.

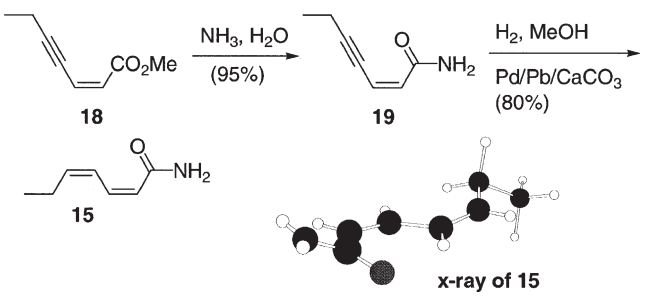
2. Results

2.1. Syntheses of unsaturated amides

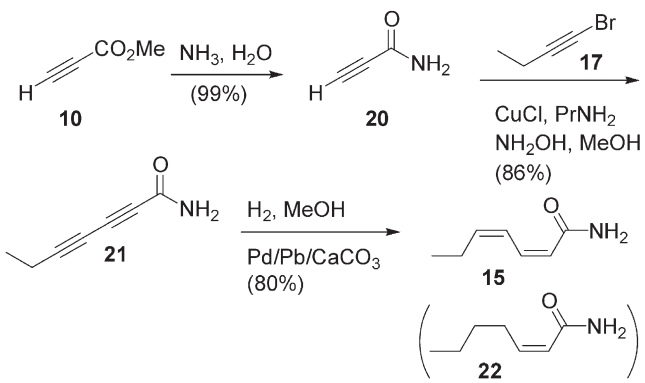
Several of the carboxylic acids present in the natural enamides are highly unsaturated. The presence of *cis* double bonds complicates the synthesis and makes these carboxylic acid derivatives prone to isomerization. In order to prepare the (*Z*,*Z*)-di-unsaturated amide **15** or its ester **14**, we compared the direct diene synthesis, the reduction of the enyne **18**, and the reduction of the diyne **21** (Schemes 1–3). First, the *Z*-iodoacrylate **11** was prepared by addition of hydrogen iodide to the triple bond.[20] The direct synthesis began with pentenoic acid **12** that was converted in two steps to the *Z*-bromide **13**.[21] Metallation to the vinyllithium intermediate, transmetalation with $ZnCl_2$, followed by cross-coupling reaction with *Z*-3-iodoacrylic ester (**11**) provided the (*Z*,*Z*)-configurated ester **14** in good yield.



Scheme 1. Synthesis of the (*Z*,*Z*)-heptadienamide **15**.



Scheme 2. Synthesis of the (*Z*,*Z*)-heptadienamide **15** from the heptenynamide **19**.



Scheme 3. Synthesis of the (*Z*,*Z*)-heptadienamide **15** from the heptadiynamide **21**.

However, under these conditions, isomerization of the double bond next to the carboxyl group occurred (2*Z*,4*Z*/2*E*,4*Z*=64:36). Moreover, the subsequent aminolysis of the ester to the amide **15** proceeded in low yield (36%).

A variation of the Fürstner strategy[22] started with the cross-coupling reaction of butynylzinc [prepared from

1-bromo-1-butyne (**17**)[23]] with the 3-iodoacrylic ester **11**. While the Lindlar reduction of the enyne **18** provided the *Z*,*Z*-dienoate **14** in high yield, the aminolysis gave the amide **15** only in moderate yield.

Changing the order of events improved the overall yield (Scheme 2). Thus, aminolysis of the ester **18** gave the heptenynamide **19** in excellent yield. A selective hydrogenation under Lindlar conditions then furnished the *Z*,*Z*-configurated amide **15**. In order to prevent over-reduction the consumption of hydrogen has to be carefully monitored. The X-ray structure analysis revealed that the amide group of **15** is rotated slightly out of plane of the diene system.[24]

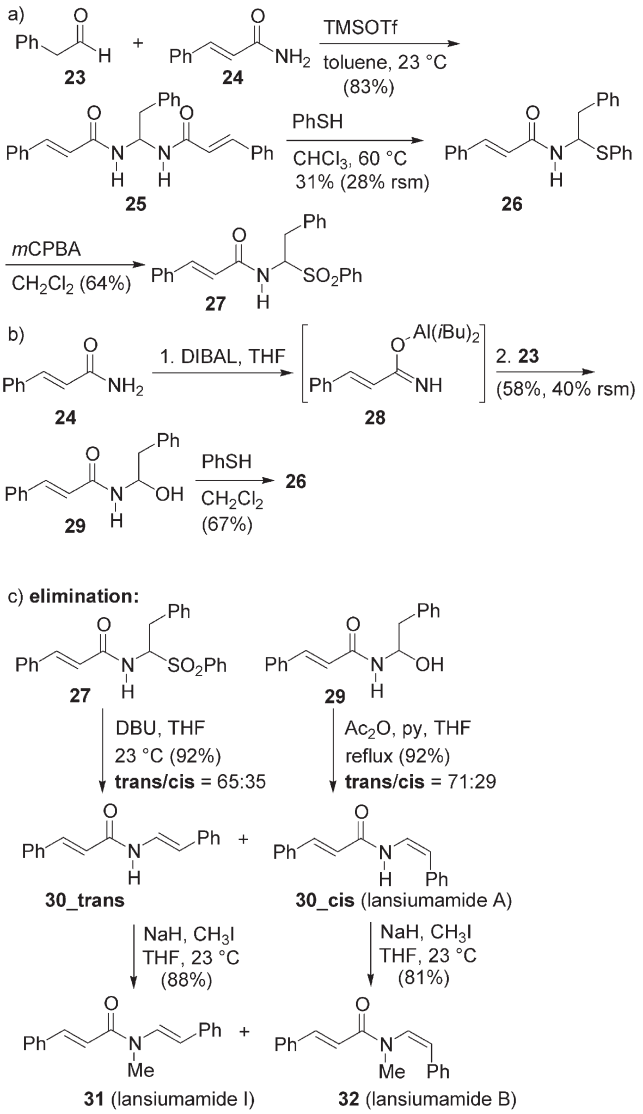
A third route to the amide **15** also started with the alkynyl bromide **17** available by base induced elimination of HBr from 1,2-dibromobutane (Scheme 3). A diethyl ether solution of the volatile bromide **17** was coupled in the presence of CuCl with the alkyne[25] **20** (Cadiot–Chodkiewicz–Coupling) providing the diyne **21** in good yield. A Lindlar hydrogenation also led to the (*Z*,*Z*)-amide **15**. Like with the other Lindlar reduction, over-reduction can occur, resulting in formation of *Z*-configurated 1,2-unsaturated amide **22**.

2.2. Formation of enamides from aldehydes and amides

A simple strategy towards enamides would involve the elimination of water from a *N*-acylhemiaminal. Initially, we thought a better leaving group might facilitate the elimination and prevent the hydrolysis. Using the cinnamamide **24** and 2-phenylacetaldehyde (**23**) as model compounds, various conditions for affecting the desired transformation were screened (Scheme 4). For example, treatment of the amide **24** with aldehyde **23** in the presence of trimethylsilyl triflate gave the bisacylated aminal **25** with no trace of the hemiaminal **29**. Stirring of the aminal derivative **25** with thiophenol in $CHCl_3$ at 60 °C provided the thioaminal **26**. The chloroform solvent dissolves the starting material and provides the trace of acid that is necessary to replace one of the amides from the bisacylated aminal. Heating, treatment with acid or base did not give any of the enamide **30** from the hemithioaminal **26**. Therefore, the sulfide **26** was oxidized to the corresponding sulfone **27** with *m*CPBA.

An alternative route to the sulfide **26** utilized addition of the aluminum carboximidoate **28**, generated from the amide **24** and diisobutylaluminium hydride,[19] to the aldehyde **23** providing the hemiaminal **29** in reasonable yield. Treatment of this compound with thiophenol in dichloromethane provided the sulfide **26** as well.

Elimination studies were carried out on the sulfone **27** and the hemiaminal **29**. Thus, stirring a solution of the sulfone **27** in THF in the presence of DBU affected clean elimination affording the (*E*)-and (*Z*)-enamide **30**_*trans* and **30**_*cis* in good yield (*E*/*Z*=65:35). Alternatively, formation of the enamide could be affected by refluxing the hemiaminal **29** in a solution of THF containing acetic anhydride (15 equiv.) and pyridine (30 equiv.). In this case however, the *E*/*Z* changed slightly to 71:29. Each of the two

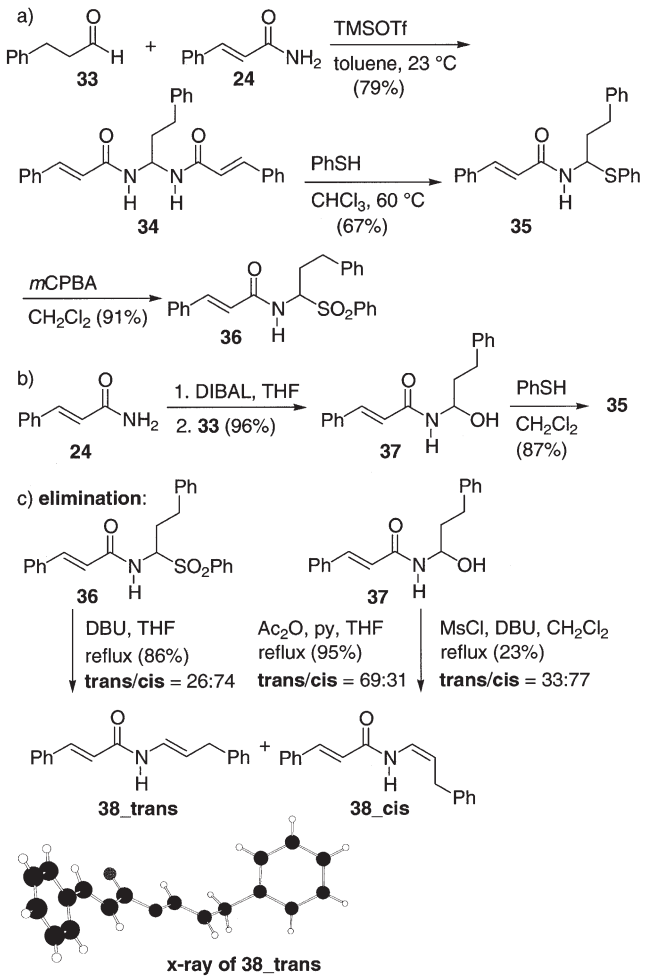


Scheme 4. Synthesis of the enamides **30**–**32** from the sulfone **27** and the hemiaminal **29**.

enamides **30**_*trans* and **30**_*cis* could be converted to the corresponding *N*-methyl derivative by deprotonation with NaH and alkylation with methyl iodide. Compound **31** corresponds to the natural product lansiumamide-I, whereas the *Z*-isomer **32** is called lansiumamide B.[26] The enamide **30**_*cis* is the natural product lansiumamide A.

A similar sequence of reactions was utilized to produce the enamides **38**_*trans* and **38**_*cis* (Scheme 5). In this case, the cinnamamide **24** ((2*E*)-3-phenylacrylamide) was reacted with 3-phenylpropanal (**33**). Thus, **24** and **33** in presence of TMSOTf yielded the bisacylated aminal **34** in 79% yield. Replacement of one amide group with thiophenol led to the N,S-acetal **35** which served as precursor to the sulfone **36**. Elimination of phenylsulfinic acid under the action of DBU led to the predominant formation of the *cis*-isomer **38**_*cis* (*trans*/*cis* ratio=26:74). The difference can be attributed to the formation of a conjugated system (influence of the phenyl group) in the case of **30**_*trans* and **30**_*cis*.

The combination of the amide **24** and the aldehyde **33** was also done with the aza-aldol reaction, resulting in the



Scheme 5. Synthesis of the enamides **38** from the sulfone **36** and the hemiaminal **37**.

hemiaminal **37**. Again, the method using acetic anhydride in the presence of pyridine gave an excellent yield for the enamides **38**_*trans* and **38**_*cis*. Remarkably, the isomer ratio changed under these conditions leading predominantly to the *trans* isomer **38**_*trans*. The X-ray structure of this isomer is shown in Scheme 5.[24]

With substrate **37** another set of conditions was tried for the elimination. Thus, treatment of the hemiaminal **37** with mesyl chloride, DBU in CH_2Cl_2 did indeed give the enamides **38**_*trans* and **38**_*cis*, but only in low yield. The dominant formation of the *cis* isomer (*trans*/*cis* ratio=33:77) points to a similar mechanism for the elimination step.

Regarding the mechanism of elimination we propose that the enamide formation via the sulfone and the mesylate proceeds through an acylimine intermediate, which subsequently undergoes tautomerization (Fig. 3). The different ratios with the Ac_2O/pyridine method and the fact that the elimination needs heating supports a concerted Tschugaew mechanism.

Having established two methods for the formation of the enamide from an aldehyde and an amide, we next employed the double unsaturated amides that were prepared with a

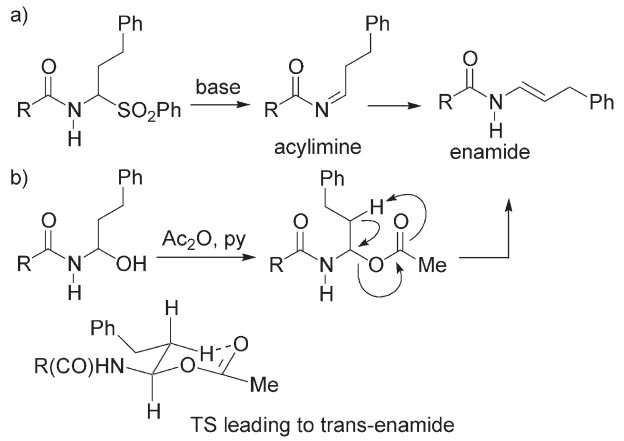
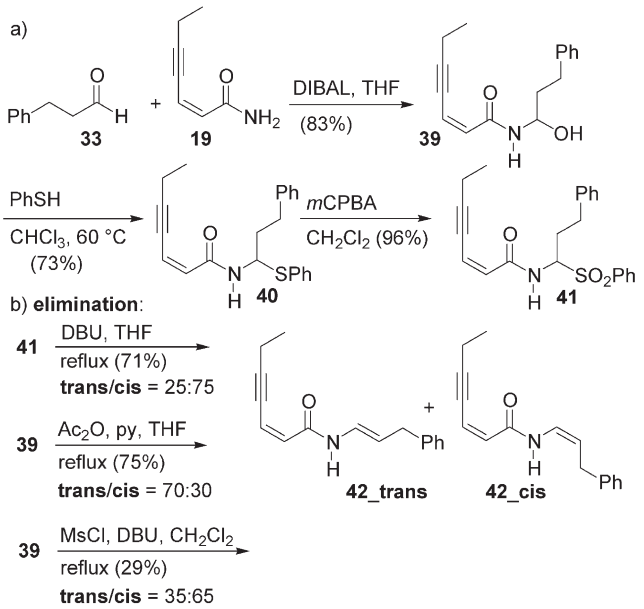


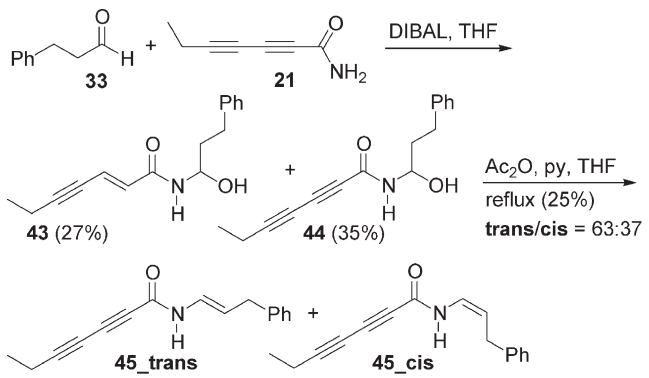
Figure 3. Possible mechanism for the formation of the enamides.



Scheme 6. Synthesis of the enamides **42** from the sulfone **41** and the hemiaminal **39**.

view to incorporate them into some benzolactone enamides (Scheme 6). Thus, the enynamide **19** was converted to the corresponding aluminiumiminoate and then added to phenylpropanal **33** resulting in the hemiaminal **39** in good yield. Treatment with thiophenol in chloroform provided the N,S-acetal **40**. This transacetalization was accompanied by some isomerization of the double bond. Oxidation of the sulfide **40** led to the sulfone **41**. Elimination of the sulfinic acid under basic conditions furnished the enamides **42** as a *cis*/*trans* mixture (*trans*/*cis*=25:75). In this case, the route via the bisaminal and the sulfone was not successful. While the diaminal from amide **19** and the aldehyde **33** could be prepared (19% yield) replacement of one amide with a thiophenol led to a mixture of compounds.

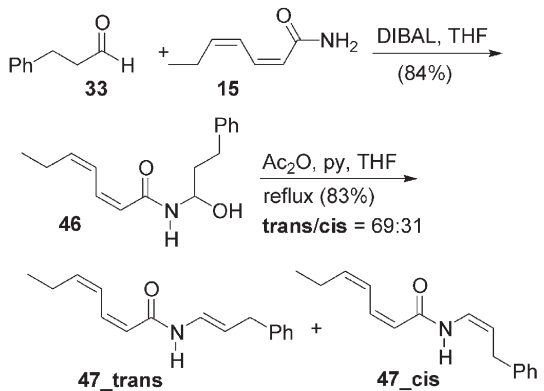
If the aza-aldol reaction was applied to the diynamide **21**, the corresponding hemiaminal **44** was obtained in lower yield (Scheme 7). In this case, as a substantial amount of the *trans* amide **43** was formed due to reduction of the first triple bond by DIBAL. After chromatographic separation of the two compounds, water elimination from **44** provided the



Scheme 7. Synthesis of the enamides **45**_*trans* and **45**_*cis* containing a diynamide.

enamides **45**, with the *trans* isomer being the major diastereomer (*trans*/*cis*=63:37). With the diynamide **21** and aldehyde **33** the bisacylated aminal could be obtained (76%), but the subsequent reaction with thiophenol did not give the desired N,S-acetal.

Finally, this direct synthesis of an enamide was performed with the *Z*,*Z*-dienamide **15** and the aldehyde **33**. As it turned out, both steps proceeded with good efficiency. Thus, reaction of the aluminum anion of the amide **15** with aldehyde **33** gave the hemiaminal **46** in 84% yield. The subsequent dehydration under the action of acetic anhydride and pyridine furnished the enamides **47**_*trans* and **47**_*cis* in high yield. Again, the *trans* isomer **47**_*trans* was slightly favored over the corresponding *cis* isomer (*trans*/*cis*= 69:31) (Scheme 8).



Scheme 8. Synthesis of the enamides **47**_*trans* and **47**_*cis* containing a *Z*,*Z*-dienamide.

Table 1. Comparison of isolated yields and *trans*/*cis*-ratios

Entry	Enamide	DBU, THF, reflux		MsCl, DBU, CH_2Cl_2, reflux		Ac_2O, py, THF, reflux	
		Yield (%)	*trans*/*cis*	Yield (%)	*trans*/*cis*	Yield (%)	*trans*/*cis*
1	**30**	92	65:35	—	—	92	71:29
2	**38**	86	26:74	23	33:77	95	69:31
3	**42**	71	25:75	29	35:65	75	70:30
4	**45**	—	—	—	—	25	63:37
5	**47**	—	—	—	—	83	69:31

Table 1 summarizes the results of the enamide forming reactions. With exception of the lansiumamide cases (Scheme 4, enamide **30**) it can be outlined that the base-induced elimination of the sulfones and the mesylates leads preferentially to the *cis* isomers whereas the thermal elimination (Ac_2O, pyridine, reflux) produces the *trans* enamides as major products.

3. Summary

In summary, we described efficient routes to several double unsaturated amides using cross-coupling methods. Via the corresponding aluminium anions, the amides were reacted with aldehydes such as 3-phenylpropanal. Conversion of the resulting hemiaminals to the enamides was affected by simply heating the hemiaminal in the presence of acetic anhydride and pyridine. Due to some reduction of the triple bond by DIBAL, the hemiaminal formation was less efficient in the case of the diynamide **21**. In some cases, the enamide was formed from the bisacylated aminals which were obtained from the unsaturated amide and an aldehyde. Replacement of one amide group by thiophenol, oxidation to the sulfone and base-induced elimination also can provide the enamide structure. However, we found this method to be less general and it also involves more steps. Both of the methods provide the enamides as *cis*/trans mixtures. While, the dehydration of the hemiaminals usually gives the *trans*-isomer as the major product, the elimination of the sulfinic acid favors the *cis*-isomer. With these methods the natural products lansiumamide were synthesized. The dehydration procedure has great potential for application toward the synthesis of natural benzolactone enamides, such as apicularen A. Studies along these lines are currently underway in our laboratory.

4. Experimental

4.1. General

^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K either in $CDCl_3$, C_6D_6, DMSO-d_6, THF-d_8, acetone-d_6 or DMF-d_7; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm), C_6D_6 (δH 7.16, δC 128.0 ppm), DMSO-d_6 (δH 2.49, δC 39.5 ppm), THF-d_8 (δH 1.73, 3.58, δC 25.3, 67.4 ppm), acetone-d_6 (δH 2.04, δC 29.8, 206.7 ppm), or DMF-d_7 (δH 2.74, 2.91, 8.01, δC 30.1, 35.2, 162.7 ppm). Melting points: Büchi Melting Point B-540, uncorrected. IR: Jasco FT/IR-430. EI-MS: Finnigan Triple-Stage-Quadrupol (TSQ-70). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under an argon atmosphere. Compounds **16** (1,2-dibromobutane) and **24** (cinnamamide) were obtained from commercial sources. The preparation of **14** from **18**, and **15** from **14** was performed according to the literature.[22] Compounds **11**,[20] **13**,[21] and **20**[25] were prepared according to the literature.

General procedure 1 for aza-aldol-reaction. To a well stirred solution of the amide (1 equiv.) in dry THF (4 mL/mmol) was added DIBAL (1.0 M in hexane, 1.15 equiv.) dropwise at 0 °C. After the mixture was stirred for 30 min at 0 °C, the aldehyde (1.5 equiv.) was added. The resulting solution was stirred overnight at 0 °C, before it was diluted with ethyl acetate (10 mL/mmol) and quenched with water (10 mL/mmol) at 0 °C. After separation of the layers, the aqueous layer was extracted with ethyl acetate (2× 10 mL/mmol). The combined organic layers were washed with brine (2 mL/mmol), dried over $MgSO_4$, filtered, and concentrated in vacuo.

General procedure 2 for elimination-reaction by intermediate acetylation. To a stirred solution of the hydroxyamide (1 equiv.) in dry THF (15 mL/mmol) was added dry pyridine (30 equiv.) and dry acetic anhydride (15 equiv.). After refluxing the mixture for 3 days, it was cooled to room temperature, and diluted with ethyl acetate (200 mL/mmol) and water (100 mL/mmol). The layers were separated, and the organic layer was washed with saturated NH_4Cl solution (3×75 mL/mmol), water (75 mL/mmol) and brine (25 mL/mmol), dried over $MgSO_4$, filtered, and concentrated in vacuo.

General procedure 3 for elimination-reaction by intermediate mesylation. To a well stirred solution of the hydroxyamide (1 equiv.) in dry CH_2Cl_2 (10 mL/mmol) was added dry 1,8-diazabicyclo-[5.4.0]-undec-7-en (DBU) (1.2 equiv.) at 0 °C. After the mixture was stirred for 10 min at 0 °C, mesylchloride (1.1 equiv.) was added. The solution was stirred for another 15 min at 0 °C, before additionally dry DBU (1.2 equiv.) was added at 0 °C. The mixture was allowed to reach room temperature, and stirred overnight. After quenching the reaction by addition of water (10 mL/mmol), the layers were separated, and the aqueous layer was extracted with dichloromethane (2× 10 mL/mmol). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

General procedure 4 for methylation of enamides. To a well stirred solution of the enamide (1 equiv.) in dry THF (12.5 mL/mmol) was slowly added sodium hydride (1.05 equiv.) at 0 °C. After the mixture was stirred for 1 h at 0 °C, methyl iodide (1.1 equiv.) was added. The mixture was allowed to reach room temperature, and stirred overnight. After quenching the reaction by addition of water (60 mL/mmol), the layers were separated, and the aqueous layer was extracted with diethyl ether (2× 60 mL/mmol). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

General procedure 5 for substitution of hydroxyamide with thiophenol. To a well stirred solution of the hydroxyamide (1 equiv.) in dry CH_2Cl_2 (10 mL/mmol) and dry THF (2 mL/mmol) was added thiophenol (1.2 equiv.). After stirring overnight at room temperature, silica gel was added to the reaction mixture, followed by concentration in vacuo.

General procedure 6 for oxidation of phenylthioamide with mCPBA. To a well stirred solution of phenylthioamide (1 equiv.) in dry CH_2Cl_2 (15 mL/mmol) was added in small portions at −10 °C *m*-chloroperbenzoicacid (*m*CPBA) (2.2 equiv.), which was purified by washing three times with pH 7 buffer and drying in vacuo prior to use. The mixture was allowed to warm to 0 °C within 30 min. The resulting suspension was diluted with CH_2Cl_2, filtered, washed with CH_2Cl_2, and concentrated in vacuo.

General procedure 7 for coupling of an amide with an aldehyde to give a diacylated aminal. To a well stirred suspension of cinnamamide (2 equiv.) in dry CH_2Cl_2 (1 mL/mmol) was added the aldehyde (1.1 equiv.) and trimethylsilyltrifluoromethane sulfonate (0.025 equiv.). The mixture was vigorously stirred overnight at room temperature, diluted with toluene (1 mL/mmol), and filtered. The precipitate was washed several times with toluene (0.05 mL/mmol) and dried under reduced pressure to yield the pure product.

General procedure 8 for substitution of an amide from a diamide with thiophenol. To a well stirred suspension of the diamide (1 equiv.) in $CHCl_3$ (25 mL/mmol) was added thiophenol (1 equiv.). The mixture was heated under reflux overnight, and concentrated in vacuo.

General procedure 9 for aminolysis. To a stirred solution of the methyl ester (1 equiv.) in methanol (0.65 mL/mmol) was added a 25% solution of ammonia in water (17 mL/mmol). After vigorously stirring at room temperature for four days, the mixture was extracted with ethyl acetate (5×17 mL/mmol). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo.

4.1.1. (2*Z*,4*Z*)-Hepta-2,4-dienoic methyl ester (14). To a stirred suspension of lithium (0.017 g, 2.5 mmol, 5.0 equiv.) in dry diethyl ether (2 mL) was slowly added a solution of (1*Z*)-1-bromobut-1-ene[21] (**13**) (0.17 g, 1.3 mmol, 2.5 equiv.) in dry diethyl ether (1 mL) within 1 h at 0 °C. The resulting reaction mixture was stirred for additional 30 min at room temperature, before the remaining unreacted lithium was removed. The mixture was again cooled to 0 °C, and a solution of zinc chloride (0.19 g, 1.4 mmol, 2.8 equiv.) in dry THF (2 mL) was added. After stirring for 20 min at 0 °C, a solution of *Z*-3-iodoacrylic methylester (**11**) (0.11 g, 0.50 mmol, 1 equiv.) and bis(acetonitrile) palladium(II) chloride (0.013 g, 0.050 mmol, 0.10 equiv.) in dry THF (3 mL) was added at 0 °C. The reaction mixture was allowed to reach room temperature, and stirred overnight. After quenching the reaction by addition of water (25 mL), the layers were separated, and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether/diethyl ether, 25:1) gave 0.049 g (70%) of **14** as a colorless oil (2*Z*,4*Z*/2*E*,4*Z*=64:36). Data for the major product: TLC (petroleum ether/diethyl ether, 25:1): R_f=0.39; ^{1}H NMR ($CDCl_3$): δ 1.02 (t, J=7.6 Hz, 3H, CH_3), 2.27 (dtd, J=15.2, 7.6, 1.3 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 5.67 (d, J=11.6 Hz, 1H, CH), 5.86–5.94 (m, 1H, CH), 6.93 (dd, J=11.9, 11.6 Hz, 1H, CH), 7.18–7.23 (m, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.9 (C-7), 20.8 (C-6), 51.1 (OCH_3), 116.9 (C-2), 123.7 (C-4), 139.0 (C-5), 143.3 (C-3), 167.0 (CO); IR (film): 2967, 2938, 2875, 1720, 1631, 1592,

1444, 1365, 1289, 1231, 1195, 1175, 1132 cm^{-1}; MS (EI), *m/z* (%): 140 (24) $[M]^+$, 111 (100), 109 (16), 81 (32), 79 (34), 55 (8), 53 (11), 41 (9), 39 (8); HRMS (EI): $[M]^+$ calcd for $C_8H_{12}O_2$ 140.083721, found 140.086261.

4.1.2. (2*Z*,4*Z*)-Hepta-2,4-dienamide (15). (a) *From diynamide* **21**. To a stirred suspension of commercially available Lindlar catalyst (0.005 g, 0.30 mol%) and quinoline (0.024 mL, 0.12 mmol, 12 mol%) in methanol (5 mL), was added diynamide **21** (0.061 g, 0.50 mmol, 1 equiv.) and the resulting suspension was vigorously stirred under an atmosphere of H_2 (approximately 1 atm). The consumption of H_2 was carefully monitored and the reaction stopped after 175 min, when a decrease in the consumption of H_2 was noticed. The mixture was filtered through a pad of Celite, washed with methanol (3×5 mL), and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave 0.050 g (80%) of **15** as colorless crystals.

(b) *From (2Z)-hept-2-en-4-ynamide* (**19**). To a stirred suspension of commercially available Lindlar catalyst (0.010 g, 1.2 mol%) and quinoline (0.015 mL, 0.075 mmol, 15 mol%) in methanol (5 mL), was added (2*Z*)-hept-2-en-4-ynamide (**19**) (0.062 g, 0.50 mmol, 1 equiv.) and the resulting suspension was vigorously stirred under an atmosphere of H_2 (approximately 1 atm). The consumption of H_2 was carefully monitored and the reaction stopped, when a decrease in the consumption of H_2 was noticed. The mixture was filtered through a pad of Celite, washed with methanol (3 × 5 mL), and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:3) gave 0.050 g (80%) of **15** as colorless crystals.

(c) *From (Z,Z)-configurated ester* **14**. (2*Z*,4*Z*)-Hepta-2,4-dienoic methyl ester (**14**) (0.18 g, 1.3 mmol) was converted to **15** according to general procedure 9. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave 0.058 g (36%) of **15** as colorless crystals.

Data for amide **15**. Mp 82 °C; TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.41; ^{1}H NMR ($CDCl_3$): δ 1.02 (t, *J*=7.6 Hz, 3H, CH_3), 2.25 (dtd, *J*=15.2, 7.6, 1.5 Hz, 2H, CH_2), 5.39–5.74 (s, br, 2H, NH_2), 5.64 (d, *J*=11.5 Hz, 1H, CH), 5.81–5.87 (m, 1H, CH), 6.81 (dd, *J*=11.9, 11.5 Hz, 1H, CH), 7.17–7.23 (m, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 14.0 (C-7), 20.7 (C-6), 119.1 (C-2), 123.6 (C-4), 136.4 (C-3), 142.1 (C-5), 168.5 (CO); IR (film): 3396, 3196, 3009, 2967, 2934, 1651, 1606, 1455, 1369, 1326, 1299, 1263, 851 cm^{-1}; MS (EI), *m/z* (%): 125 (6) $[M]^+$, 109 (5), 96 (100), 81 (22), 79 (28), 67 (14), 53 (12), 41 (12), 39 (14); HRMS (EI): $[M]^+$ calcd for $C_7H_{11}NO$ 125.084064, found 125.085354.

Data for amide **22**. Mp 70 °C; TLC (petroleum ether/ethyl acetate, 1:3): R_f=0.48; ^{1}H NMR ($CDCl_3$): δ 0.88 (t, *J*=7.1 Hz, 3H, CH_3), 1.28–1.43 (m, 4H, CH_2), 2.59–2.65 (m, 2H, CH_2), 5.49 (s, br, 1H, NH_2), 5.72 (dt, *J*=11.6, 1.5 Hz, 1H, CH), 5.76 (s, br, 1H, NH_2), 5.99–6.06 (m, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 13.9 (C-7), 22.3 (C-6), 28.4 (C-5), 31.4 (C-4), 121.2 (C-2), 147.1 (C-3), 168.6 (CO); IR (KBr): 3381, 3195, 2951, 2924, 2860, 1670, 1617, 1438, 1332, 1230, 1134 cm^{-1}; MS (EI), *m/z* (%): 127 (40) $[M]^+$, 112 (37), 98 (100), 81 (80), 69 (40), 59 (58), 55 (76), 44 (67), 41 (72); HRMS (EI): $[M]^+$ calcd for $C_7H_{13}NO$ 127.099705, found 127.100488.

4.1.3. 1-Bromobut-1-yne (17). In a round-bottomed flask connected with a cold trap, which was cooled to −60 °C, a well stirred suspension of potassium *tert*-butanolate (11.2 g, 0.10 mol, 2.0 equiv.) and [18]-crown-6 (0.026 g, 0.10 mmol, 0.0020 equiv.) in dry diethyl ether (50 mL) was slowly treated with 1,2-dibromobutane (**16**) (6.1 mL, 50 mmol, 1.0 equiv.). After the reflux from the exothermic reaction ceases, the mixture was heated at 40 °C under reflux of the cold trap for 2 h. While the mixture was cooling down to room temperature, in a second flask, bromine (3.86 mL, 75 mmol, 1.5 equiv.) was slowly added to a solution of potassium hydroxide (11.2 g, 0.20 mol, 4 equiv.) in water (50 mL) at −5 °C. This solution was added to the reaction mixture of but-1-yne, and the resulting mixture was vigorously stirred at 25 °C for 7 h. After separation of the phases, the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo (up to 700 mbar at 40 °C) to yield 4.34 g (61%) of a colorless, 75 M solution of 1-bromobut-1-yne (**17**) in diethyl ether (concentration was estimated from the NMR integration). ^{1}H NMR ($CDCl_3$): δ 1.13 (t, *J*=7.6 Hz, 3H, CH_3), 2.20 (q, *J*=7.6 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 13.4 (C-4), 13.4 (C-3), 37.1 (C-1), 81.6 (C-2); IR (film): 3272, 3062, 3034, 2925, 1722, 1683, 1628, 1532, 1448, 1344, 1308, 1209, 1146, 1081 cm^{-1}; MS (EI), *m/z* (%): 134 (95) [M, ^{81}Br]$^+$, 132 (100) [M, ^{79}Br]$^+$, 119 (48) [M−CH_3, ^{81}Br]$^+$, 117 (53) [M−CH_3, ^{79}Br]$^+$, 53 (29); HRMS (EI): $[M]^+$ calcd for C_4H_5Br 131.95746, found 131.95807.

4.1.4. (2*Z*)-Hept-2-en-4-ynamide (19). (2*Z*)-Hept-2-en-4-ynoic methyl ester (**18**) (0.207 g, 1.50 mmol) was converted to amide **19** according to general procedure 9. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:3) gave 0.175 g (95%) of **19** as a colorless solid, mp 48 °C. TLC (petroleum ether/ethyl acetate, 1:3): R_f=0.33; ^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J*=7.6 Hz, 3H, CH_3), 2.44 (qd, *J*=7.6, 2.0 Hz, 2H, CH_2), 6.02 (d, *J*=12.1 Hz, 1H, CH), 6.07 (td, *J*=12.1, 2.0 Hz, 1H, CH), 6.20 (s, br, 1H, NH_2), 7.17 (s, br, 1H, NH_2); ^{13}C NMR ($CDCl_3$): δ 13.3 (C-7), 13.5 (C-6), 76.4 (C-4), 105.3 (C-5), 117.7 (C-3), 132.4 (C-2), 167.2 (CO); IR (film): 3355, 3194, 2981, 2942, 2881, 2279, 2210, 1665, 1606, 1435, 1324, 1238, 1061 cm^{-1}; MS (EI), *m/z* (%): 123 (25) $[M]^+$, 122 (100) $[M-H]^+$, 108 (18), 95 (30), 82 (68), 77 (36), 54 (29), 39 (26); HRMS (EI): $[M-H]^+$ calcd for C_7H_8NO 122.06059, found 122.05986.

4.1.5. Hepta-2,4-diynamide (21). To a well stirred suspension of hydroxylamine hydrochloride (0.34 g, 5.0 mmol, 0.73 equiv.), copper(I) chloride (0.062 g, 0.63 mol, 0.093 equiv.) and propylamine (0.96 mL, 12 mmol, 1.7 equiv.) in dry methanol (25 mL) was added propiolamide (**20**) (0.47 g, 6.8 mmol, 1 equiv.) at 30 °C. After the further addition of dry methanol (10 mL), a 75 M solution of 1-bromobut-1-yne (**17**) in diethyl ether diluted with dry methanol (15 mL) was added dropwise at 30 °C. After the mixture was stirred overnight at 30 °C, methanol was partly

evaporated. The resulting suspension was diluted with water (100 mL) and extracted with a 1:1 mixture of diethyl ether and ethyl acetate (4×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave 0.70 g (86%) of **21** as colorless leaflets, mp 149 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.49; ^{1}H NMR (acetone-d_6): δ 1.15 (t, J=7.6 Hz, 3H, CH_3), 2.39 (q, J=7.6 Hz, 2H, CH_2), 6.99 (s, br, 1H, NH_2), 7.44 (s, br, 1H, NH_2); ^{13}C NMR (acetone-d_6): δ 13.1 (C-6), 13.2 (C-7), 63.5 (C-4), 69.3 (C-3), 69.6 (C-2), 88.0 (C-5), 153.7 (CO); IR (KBr): 3316, 3274, 3205, 2988, 2942, 2769, 2406, 2248, 2158, 1652, 1608, 1457, 1389, 1312, 1200, 1130, 1063 cm^{-1}; MS (EI), m/z (%): 121 (93) $[M]^+$, 105 (100), 93 (40), 77 (64), 51 (47); HRMS (EI): $[M]^+$ calcd for C_7H_7NO 121.05276, found 121.05473.

4.1.6. 1,1-Dicinnamido-2-phenylethane (25). Conversion of phenylacetaldehyde (**23**) (5.05 mL, 55.0 mmol) according to general procedure 7 gave 16.4 g (83%) of diamide **25** as a colorless solid, mp 181 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.53; ^{1}H NMR (DMF-d_7): δ 3.13–3.15 (m, 2H, CH_2Ph), 5.92–5.99 (m, 1H, CH), 6.74 (d, J=15.7 Hz, 2H, CH), 7.10–7.56 (m, 15H, CH_{ar}), 7.49 (d, J=15.7 Hz, 2H, CH), 8.54 (d, br, J=7.6 Hz, 2H, NH); ^{13}C NMR (DMF-d_7): δ 41.1 (C-2), 58.9 (C-1), 122.7 (C-2′), 127.0 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.9 (CH_{ar}), 128.9 (CH_{ar}), 129.6 (CH_{ar}), 129.6 (CH_{ar}), 130.0 (CH_{ar}), 130.0 (CH_{ar}), 130.2 (CH_{ar}), 135.9 (C_{ar}), 138.6 (C_{ar}), 140.1 (C-3′), 165.3 (CO); IR (KBr): 3376, 3283, 3175, 3029, 1662, 1630, 1562, 1512, 1449, 1399, 1350, 1234, 1206, 975 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{24}N_2NaO_2$ 419.17300, found 419.17275.

4.1.7. (2*E*)-3-Phenyl-*N*-[2-phenyl-1-(phenylthio)ethyl]-acrylamide (26). (a) *From diamide* **25**. Diamide **25** (3.97 g, 10.0 mmol) was converted to phenylthioamide **26** according to general procedure 8. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 1.12 g (28%) of unreacted starting material **25** and 1.13 g (31%) of **26** as a colorless solid.

(b) *From hydroxyamide* **29**. Hydroxyamide **29** (0.067 g, 0.25 mmol) was converted to phenylthioamide **26** according to general procedure 5. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.060 g (67%) of **26** as a colorless solid, mp 98 °C. TLC (petroleum ether/ethyl acetate, 3:1): R_f=0.45; ^{1}H NMR (THF-d_8): δ 3.06–3.18 (m, 2H, CH_2Ph), 5.84–5.89 (m, 1H, CHSPh), 6.42 (d, J=15.7 Hz, 1H, CH), 7.13–7.50 (m, 15H, CH_{ar}), 7.44 (d, J=15.7 Hz, 1H, CH), 7.72 (d, br, J=9.1 Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 42.9 (C-2′), 58.2 (C-1′), 121.9 (C-2), 127.3 (CH_{ar}), 127.5 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.9 (CH_{ar}), 128.9 (CH_{ar}), 129.5 (CH_{ar}), 129.5 (CH_{ar}), 129.5 (CH_{ar}), 129.5 (CH_{ar}), 130.0 (CH_{ar}), 130.2 (CH_{ar}), 130.2 (CH_{ar}), 132.2 (CH_{ar}), 132.2 (CH_{ar}), 135.5 (C_{ar}), 136.4 (C_{ar}), 138.4 (C_{ar}), 141.0 (C-3), 165.0 (CO); IR (KBr): 3242, 3059, 3026, 2920, 2750, 1949, 1880, 1652, 1620, 1548, 1495, 1483, 1449, 1439, 1348, 1284, 1215 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{21}NNaOS$ 382.12361, found 382.12370.

4.1.8. (2*E*)-3-Phenyl-*N*-[2-phenyl-1-(phenylsulfonyl)-ethyl]acrylamide (27). Phenylthioamide **26** (1.43 g, 3.97 mmol) was converted to phenylsulfonylamide **27** according to general procedure 6. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.991 g (64%) of **27** as colorless oil. TLC (petroleum ether/ethyl acetate, 3:1): R_f=0.30; ^{1}H NMR ($CDCl_3$): δ 3.20 (dd, J=14.6, 10.9 Hz, 1H, CH_2Ph), 3.70 (dd, J=14.6, 3.8 Hz, 1H, CH_2Ph), 5.73 (ddd, J=10.9, 10.4, 3.8 Hz, 1H, $CHSO_2$Ph), 6.22 (d, J=15.7 Hz, 1H, CH), 6.48 (d, br, J=10.4 Hz, 1H, NH), 7.18–7.64 (m, 13H, CH_{ar}), 7.29 (d, J=15.7 Hz, 1H, CH), 7.95–8.01 (m, 2H, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ 32.7 (C-2′), 69.6 (C-1′), 118.5 (C-2), 127.3 (CH_{ar}), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 130.2 (CH_{ar}), 134.1 (C_{ar}), 134.3 (CH_{ar}), 134.5 (C_{ar}), 136.5 (C_{ar}), 142.8 (C-3), 164.8 (CO); IR (film): 3272, 3062, 3034, 2925, 1722, 1683, 1628, 1532, 1448, 1344, 1308, 1209, 1146, 1081 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{23}H_{21}NNaO_3S$ 414.11344, found 414.11377.

4.1.9. (2*E*)-*N*-(1-Hydroxy-2-phenylethyl)-3-phenylacrylamide (29). Cinnamamide (**24**) (0.294 g, 2.00 mmol) was converted to hydroxyamide **29** according to general procedure 1 by treatment with phenylacetaldehyde (**23**). Purification of the crude reaction mixture by flash chromatography (dichloromethane/acetone, 5:1) gave 0.117 g (40%) of unreacted amide and 0.307 g (58%) of **29** as a colorless solid, mp 111 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.45; ^{1}H NMR (THF-d_8): δ 2.84–2.94 (m, 2H, CH_2Ph), 5.16 (d, J=4.0 Hz, 1H, OH), 5.62–5.68 (m, 1H, C*H*OH), 6.50 (d, J=15.7 Hz, 1H, CH), 7.11–7.51 (m, 10H, CH_{ar}), 7.54 (d, J=15.7 Hz, 1H, CH), 7.63 (d, br, J=7.8 Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 43.5 (C-2′), 75.3 (C-1′), 122.7 (C-2), 126.8 (CH_{ar}), 128.4 (CH_{ar}), 128.7 (CH_{ar}), 129.5 (CH_{ar}), 130.0 (CH_{ar}), 130.5 (CH_{ar}), 136.5 (C_{ar}), 138.9 (C-3), 140.6 (C_{ar}), 165.3 (CO); IR (KBr): 3347, 3279, 3060, 3029, 2934, 2914, 1652, 1597, 1539, 1451, 1227, 1079, 1055 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{17}H_{17}NNaO_2$ 290.11515, found 290.11525.

4.1.10. (2*E*)-3-Phenyl-*N*-[(*E*/*Z*)-2-phenylvinyl]acrylamide (30). (a) *From sulfone* **27**. A solution of phenylsulfonylamide **27** (0.059 g, 0.15 mmol, 1 equiv.) and dry DBU (0.024 mL, 0.16 mmol, 1.05 equiv.) in dry THF (5.0 mL) was stirred at room temperature overnight. The mixture was diluted with water (15 mL), and extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.034 g (92%) of **30** as yellow crystals (*E*/*Z*=65:35).

(b) *From hydroxyamide* **29**. Hydroxyamide **29** (0.027 g, 0.10 mmol) was converted to enamide **30** according to general procedure 2. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.023 g (92%) of **30** as yellow crystals (*E*/*Z*=71:29).

Compound **30**_*trans*. Mp 210 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.54; ^{1}H NMR (DMSO-d_6): δ 6.24

(d, J=14.7 Hz, 1H, CH), 6.71 (d, J=15.9 Hz, 1H, CH), 7.13–7.58 (m, 10H, CH_{ar}), 7.60 (m, 1H, CH), 7.61 (m, 1H, CH), 10.48 (d, br, J=10.1 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 112.2 (C-2′), 120.9 (C-2), 123.7 (C-1′), 125.2 (CH_{ar}), 125.2 (CH_{ar}), 126.2 (CH_{ar}), 127.8 (CH_{ar}), 127.8 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.9 (CH_{ar}), 134.6 (C_{ar}), 136.5 (C_{ar}), 140.6 (C-3), 162.6 (CO); IR (KBr): 3220, 3027, 1951, 1883, 1805, 1745, 1637, 1608, 1518, 1486, 1450, 1345, 1243, 1195 cm^{-1}.

Compound **30**_*cis*. Mp 124 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.70; ^{1}H NMR ($CDCl_3$): δ 5.83 (d, J=9.8 Hz, 1H, CH), 6.37 (d, J=15.4 Hz, 1H, CH), 7.13 (dd, J=11.1, 9.8 Hz, 1H, CH), 7.25–7.52 (m, 10H, CH_{ar}), 7.73 (d, J=15.4 Hz, 1H, CH), 7.74 (d, br, J=11.1 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 110.6 (C-2′), 119.4 (C-2), 122.3 (C-1′), 127.0 (CH_{ar}), 128.0 (CH_{ar}), 128.0 (CH_{ar}), 128.0 (CH_{ar}), 128.0 (CH_{ar}), 128.9 (CH_{ar}), 128.9 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 130.2 (CH_{ar}), 134.5 (C_{ar}), 135.8 (C_{ar}), 143.1 (C-3), 163.1 (CO); IR (KBr): 3241, 3052, 3023, 1952, 1899, 1661, 1644, 1625, 1512, 1488, 1451, 1337, 1256, 1205, 1190 cm^{-1}; MS (EI), *m*/*z* (%): 249 (28) [M]$^+$, 207 (14), 149 (28), 131 (100), 119 (84), 103 (84), 77 (49); HRMS (EI): [M]$^+$ calcd for $C_{17}H_{15}NO$ 249.11536, found 249.11360.

4.1.11. (2*E*)-*N*-Methyl-3-phenyl-*N*-[(*E*)-2-phenylvinyl]-acrylamide (31). Enamide **30**_*trans* (0.040 g, 0.16 mmol) was converted to *N*-methyl-enamide **31** according to general procedure 4. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.037 g (88%) of **31** as yellow crystals, mp 118 °C. TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.38; ^{1}H NMR (250 MHz, 356 K, DMSO-d_6): δ 3.03 (s, 3H, CH_3), 6.18 (d, J=14.7 Hz, 1H, CH), 7.14–7.47 (m, 8H, CH_{ar}), 7.37 (d, J=15.3 Hz, 1H, CH), 7.62 (d, J=15.3 Hz, 1H, CH), 7.72–7.76 (m, 2H, CH_{ar}), 7.93 (d, J=14.7 Hz, 1H, CH); ^{13}C NMR (62.9 MHz, 356 K, DMSO-d_6): δ 30.9 (CH_3), 111.1 (C-2′), 117.9 (C-2), 125.2 (CH_{ar}), 125.2 (CH_{ar}), 125.7 (CH_{ar}), 127.7 (CH_{ar}), 127.7 (CH_{ar}), 128.1 (CH_{ar}), 128.1 (CH_{ar}), 128.1 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 129.3 (C-1′), 134.6 (C_{ar}), 136.5 (C_{ar}), 142.6 (C-3), 164.6 (CO); IR (KBr): 3080, 3028, 1653, 1636, 1608, 1448, 1386, 1344, 1295, 1226, 1116, 978, 965 cm^{-1}; MS (EI), *m*/*z* (%): 263 (19) [M]$^+$, 172 (7), 160 (18), 131 (100), 103 (60), 77 (37); HRMS (EI): [M]$^+$ calcd for $C_{18}H_{17}NO$ 263.131005, found 263.136118.

4.1.12. (2*E*)-*N*-Methyl-3-phenyl-*N*-[(*Z*)-2-phenylvinyl]-acrylamide (32). Hydroxyamide **30**_*cis* (0.040 g, 0.16 mmol) was converted to *N*-methyl-enamide **32** according to general procedure 4. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.034 g (81%) of **32** as yellow crystals, mp 74 °C. TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.36; ^{1}H NMR ($CDCl_3$): δ 3.02 (s, 3H, CH_3), 6.17 (d, J=8.6 Hz, 1H, CH), 6.43 (d, J=8.6 Hz, 1H, CH), 6.86 (d, J=15.4 Hz, 1H, CH), 7.14–7.39 (m, 10H, CH_{ar}), 7.56 (d, J=15.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 34.6 (CH_3), 118.3 (C-2), 125.0 (C-2′), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.6 (C-1′), 128.6 (CH_{ar}), 128.6 (CH_{ar}), 128.6 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 128.8 (CH_{ar}), 129.7 (CH_{ar}), 134.4 (C_{ar}), 135.2 (C_{ar}), 142.7 (C-3), 166.4 (CO); IR (KBr): 3060, 3025, 1658, 1637, 1614, 1495, 1449, 1362, 1176, 1111, 1085 cm^{-1}; MS (EI), *m*/*z* (%): 263 (5) [M]$^+$, 207 (5), 172 (5), 131 (26), 103 (27), 84 (100); HRMS (EI): [M]$^+$ calcd for $C_{18}H_{17}NO$ 263.13101, found 263.13218.

4.1.13. 1,1-Dicinnamido-3-phenylpropane (34). Conversion of phenylpropanal (**33**) (7.83 mL, 59.2 mmol) according to general procedure 7 gave 17.5 g (79%) of diamide **34** as a colorless solid, mp 176 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.35; ^{1}H NMR (DMSO-d_6): δ 2.01–2.07 (m, 2H, CH_2), 2.63 (dd, J=8.1, 7.6 Hz, 2H, CH_2Ph), 5.53–5.61 (m, 1H, CH), 6.70 (d, J=15.9 Hz, 2H, CH), 6.95–7.57 (m, 15H, CH_{ar}), 7.46 (d, J=15.9 Hz, 2H, CH), 8.51 (d, J=7.6 Hz, 2H, NH); ^{13}C NMR (DMSO-d_6): δ 31.1 (C-3), 35.7 (C-2), 55.9 (C-1), 122.0 (C-2′), 125.8 (CH_{ar}), 127.5 (CH_{ar}), 127.5 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.5 (CH_{ar}), 134.9 (C_{ar}), 139.2 (C-3′), 141.2 (C_{ar}), 164.3 (CO); IR (KBr): 3282, 3115, 3024, 2952, 2918, 2858, 1659, 1628, 1562, 1519, 1448, 1349, 1209, 1090, 971 cm^{-1}; HRMS (ESI): [M+Na]$^+$ calcd for $C_{27}H_{26}N_2NaO_2$ 433.18865, found 433.18870.

4.1.14. (2*E*)-3-Phenyl-*N*-[3-phenyl-1-(phenylthio)propyl]-acrylamide (35). (a) *From diamide* **34**. Diamide **34** (0.31 g, 0.75 mmol) was converted to phenylthioamide **35** according to general procedure 8. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.19 g (67%) of **35** as a colorless solid.

(b) *From hydroxyamide* **37**. Hydroxyamide **37** (0.070 g, 0.25 mmol) was converted to phenylthioamide **35** according to general procedure 5. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.081 g (87%) of **35** as a colorless solid, mp 108 °C. TLC (petroleum ether/ethyl acetate, 3:1): R_f=0.47; ^{1}H NMR ($CDCl_3$): δ 2.07–2.22 (m, 2H, CH_2), 2.76–2.96 (m, 2H, CH_2Ph), 5.59–5.65 (m, 1H, CHSPh), 5.82 (d, br, J=9.6 Hz, 1H, NH), 6.24 (d, J=15.4 Hz, 1H, CH), 7.18–7.50 (m, 15H, CH_{ar}), 7.54 (d, J=15.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 32.6 (C-3′), 37.7 (C-2′), 56.5 (C-1′), 119.8 (C-2), 126.1 (CH_{ar}), 127.7 (CH_{ar}), 127.8 (CH_{ar}), 127.8 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.5 (CH_{ar}), 128.5 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.9 (CH_{ar}), 132.5 (CH_{ar}), 132.5 (CH_{ar}), 132.5 (C_{ar}), 134.5 (C_{ar}), 140.7 (C_{ar}), 141.9 (C-3), 164.8 (CO); IR (KBr): 3284, 3026, 2918, 2855, 1650, 1615, 1525, 1449, 1348, 1220, 1026, 975 cm^{-1}; HRMS (ESI): [M+Na]$^+$ calcd for $C_{24}H_{23}NNaOS$ 396.13926, found 396.13914.

4.1.15. (2*E*)-3-Phenyl-*N*-[3-phenyl-1-(phenylsulfonyl)-propyl]acrylamide (36). Phenylthioamide **35** (1.51 g, 4.03 mmol) was converted to phenylsulfonylamide **36** according to general procedure 6. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave 1.48 g (91%) of **36** as a colorless solid, mp 62 °C. TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.34; ^{1}H NMR ($CDCl_3$): δ 2.13–2.24 (m, 1H, CH_2), 2.60–2.69 (m, 1H, CH_2), 2.73–2.86 (m, 2H, CH_2Ph), 5.59–5.65 (m, 1H, $CHSO_2$Ph), 6.26 (d, J=15.7 Hz, 1H, CH), 6.32 (d, br, J=10.4 Hz, 1H, NH), 7.15–7.62 (m, 11H, CH_{ar}), 7.48 (d, J=15.7 Hz, 1H, CH), 7.86–8.08 (m, 4H, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ 28.5 (C-2′),

31.5 (C-3′), 69.0 (C-1′), 118.7 (C-2), 126.4 (CH_{ar}), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.6 (CH_{ar}), 128.6 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.1 (CH_{ar}), 129.1 (CH_{ar}), 130.1 (CH_{ar}), 134.2 (CH_{ar}), 134.2 (C_{ar}), 136.4 (C_{ar}), 139.8 (C_{ar}), 142.8 (C-3), 165.3 (CO); IR (KBr): 3285, 3060, 3029, 2932, 2858, 1726, 1661, 1631, 1531, 1447, 1344, 1307, 1207, 1145, 1082, 975 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{23}NNaO_3S$ 428.12909, found 428.12923.

4.1.16. (2*E*)-*N*-(1-Hydroxy-3-phenylpropyl)-3-phenylacrylamide (37). Cinnamamide **24** (1.47 g, 10.0 mmol) was converted to hydroxyamide **37** according to general procedure 1 by treatment with 3-phenylpropanal. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave 2.70 g (96%) of **37** as a colorless solid, mp 114 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.52; ^{1}H NMR (DMSO-d_6): δ 1.74–1.89 (m, 2H, CH_2), 2.56–2.68 (m, 2H, CH_2Ph), 5.24–5.31 (m, 1H, C*H*OH), 5.75 (d, *J*=4.8 Hz, 1H, OH), 6.66 (d, *J*=15.9 Hz, 1H, CH), 7.15–7.56 (m, 10H, CH_{ar}), 7.41 (d, *J*=15.9 Hz, 1H, CH), 8.47 (d, *J*=8.6 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 30.9 (C-3′), 38.0 (C-2′), 72.0 (C-1′), 122.4 (C-2), 125.7 (CH_{ar}), 127.5 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.9 (CH_{ar}), 129.5 (CH_{ar}), 134.9 (C_{ar}), 139.1 (C-3), 141.7 (C_{ar}), 164.2 (CO); IR (KBr): 3283, 3063, 3025, 2959, 2921, 2856, 1656, 1626, 1537, 1455, 1360, 1328, 1221, 1042 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{19}NNaO_2$ 304.13080, found 304.13083.

4.1.17. (2*E*)-3-Phenyl-*N*-[(1*E*/*Z*)-3-phenylprop-1-enyl]-acrylamide (38). (a) *From sulfone* **36**. A solution of phenylsulfonylamide **36** (0.125 g, 0.308 mmol, 1 equiv.) and dry DBU (0.0487 mL, 0.323 mmol, 1.05 equiv.) in dry THF (7.5 mL) was heated under reflux for 4 h. The mixture was allowed to reach room temperature, diluted with water (25 mL), and extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.070 g (86%) of **38** as colorless crystals (*E*/*Z*=26:74).

(b) *From hydroxyamide* **37**. Hydroxamide **37** (0.056 g, 0.20 mmol) was converted to enamide **38** according to general procedure 2. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.050 g (95%) of **38** as colorless crystals (*E*/*Z*=69:31). Conversion of hydroxyamide **37** (0.051 g, 0.18 mmol) to enamide **38** was also performed according to general procedure 3. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.011 g (23%) of **38** as colorless crystals (*E*/*Z*=33:67).

Compound **38**_*trans*. Mp 132 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.58; ^{1}H NMR ($CDCl_3$): δ 3.44 (d, *J*=7.3 Hz, 2H, CH_2Ph), 5.41 (dt, *J*=13.9, 7.3 Hz, 1H, CH), 6.43 (d, *J*=15.4 Hz, 1H, CH), 7.08 (dd, *J*=13.9, 10.9 Hz, 1H, CH), 7.23–7.55 (m, 10H, CH_{ar}), 7.25 (d, br, *J*=10.9 Hz, 1H, NH), 7.75 (d, *J*=15.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 36.2 (C-3′), 112.7 (C-2′), 119.8 (C-2), 123.7 (C-1′), 126.2 (CH_{ar}), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 129.9 (CH_{ar}), 134.5 (C_{ar}), 140.4 (C_{ar}), 142.4 (C-3), 163.0 (CO); IR (KBr): 3263, 3188, 3064, 3027, 2904, 1650, 1625, 1527, 1346, 1223, 950 cm^{-1}.

Compound **38**_*cis*. Mp 118 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.65; ^{1}H NMR ($CDCl_3$): δ 3.46 (d, *J*=7.3 Hz, 2H, CH_2Ph), 5.05 (dt, *J*=8.3, 7.3 Hz, 1H, CH), 6.31 (d, *J*=15.4 Hz, 1H, CH), 7.01 (dd, *J*=8.3, 10.6 Hz, 1H, CH), 7.15 (d, br, *J*=10.6 Hz, 1H, NH), 7.25–7.48 (m, 10H, CH_{ar}), 7.62 (d, *J*=15.4 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$): δ 32.2 (C-3′), 109.6 (C-2′), 119.7 (C-2), 122.4 (C-1′), 126.5 (CH_{ar}), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 130.0 (CH_{ar}), 134.5 (C_{ar}), 139.5 (C_{ar}), 142.5 (C-3), 163.0 (CO); IR (KBr): 3272, 3192, 3058, 3026, 2897, 1650, 1618, 1516, 1340, 1255, 1210, 980 cm^{-1}; MS (EI), *m*/*z* (%): 263 (52) $[M]^+$, 172 (80), 131 (100), 103 (75), 77 (61); HRMS (EI): $[M]^+$ calcd for $C_{18}H_{17}NO$ 263.131005, found 263.132184.

4.1.18. (2*Z*)-*N*-(1-Hydroxy-3-phenylpropyl)hept-2-en-4-ynamide (39). Amide **19** (0.123 g, 1.00 mmol) was converted to hydroxyamide **39** according to general procedure 1 by treatment with 3-phenylpropanal (**33**). Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 1:1) gave 0.213 g (83%) of **39** as a colorless solid, mp 80 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.37; ^{1}H NMR (C_6D_6): δ 0.77 (t, *J*=7.3 Hz, 3H, CH_3), 1.77–2.02 (m, 2H, CH_2), 1.87 (qd, *J*=7.3, 2.2 Hz, 2H, CH_2), 2.64–2.80 (m, 2H, CH_2Ph), 4.60 (s, br, 1H, OH), 5.55 (dt, *J*=12.1, 2.2 Hz, 1H, CH), 5.62 (m, 1H, C*H*OH), 5.93 (d, *J*=12.1 Hz, 1H, CH), 7.02–7.13 (m, 5H, CH_{ar}), 7.66 (d, br, *J*=6.8 Hz, 1H, NH); ^{13}C NMR (C_6D_6): δ 13.1 (C-7), 13.3 (C-6), 31.4 (C-3′), 37.7 (C-2′), 74.3 (C-1′), 77.0 (C-4), 104.7 (C-5), 116.8 (C-3), 126.2 (CH_{ar}), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 133.3 (C-2), 141.7 (C_{ar}), 165.3 (CO); IR (KBr): 3262, 3178, 3060, 2972, 2213, 1656, 1608, 1543, 1318, 1278, 1226, 1174 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{19}NNaO_2$ 280.13080, found 280.13070.

4.1.19. (2*E*/*Z*)-*N*-[3-Phenyl-1-(phenylthio)propyl]hept-2-en-4-ynamide (40). Hydroxyamide **39** (0.028 g, 0.11 mmol) was converted to phenylthioamide **40** according to general procedure 5. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 0.035 g (91%) of **40** as a colorless solid (*E*/*Z*=20:80).

Compound **40**_*trans*. Mp 111 °C; TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.52; ^{1}H NMR (THF-d_8): δ 1.13 (t, *J*=7.6 Hz, 3H, CH_3), 1.93–2.12 (m, 2H, CH_2), 2.34 (td, *J*=7.6, 2.3 Hz, 2H, CH_2), 2.73 (dd, *J*=8.1, 7.8 Hz, 2H, CH_2Ph), 5.52–5.58 (m, 1H, CHSPh), 6.13 (d, *J*=15.4 Hz, 1H, CH), 6.58 (dt, *J*=15.4, 2.3 Hz, 1H, CH), 7.10–7.25 (m, 8H, CH_{ar}), 7.38–7.40 (m, 2H, CH_{ar}), 7.78 (d, br, *J*=9.4 Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 13.8 (C-7), 14.0 (C-6), 33.5 (C-3(′), 38.9 (C-2′), 56.9 (C-1′), 78.5 (C-4), 99.5 (C-5), 122.2 (C-3), 126.7 (CH_{ar}), 127.7 (CH_{ar}), 129.1 (CH_{ar}), 129.1 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.5 (CH_{ar}), 129.5 (CH_{ar}), 132.7 (CH_{ar}), 132.7 (CH_{ar}), 132.9 (C-2), 134.9 (C_{ar}), 142.2 (C_{ar}), 164.3 (CO); IR (KBr): 3292, 3056, 2920, 2845, 2215, 1644, 1615, 1530, 1483, 1455, 1317, 1274, 1216,

1197, 1166, 1079, 1025 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{23}NNaOS$ 372.13926, found 372.13937.

Compound **40**_*cis*. Mp 74 °C; TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.43; ^1H NMR (THF-d_8): δ 1.12 (t, J=7.6 Hz, 3H, CH_3), 1.98–2.15 (m, 2H, CH_2), 2.34 (td, J=7.6, 0.8 Hz, 2H, CH_2), 2.34 (dd, J=8.1, 7.8 Hz, 2H, CH_2Ph), 5.51–5.57 (m, 1H, CHSPh), 5.95 (m, 2H, 2×CH), 7.10–7.27 (m, 8H, CH_{ar}), 7.41–7.43 (m, 2H, CH_{ar}), 7.69 (d, br, J=9.4Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 13.6 (C-7), 13.8 (C-6), 33.2 (C-3′), 38.8 (C-2′), 56.7 (C-1′), 77.5 (C-4), 103.3 (C-5), 117.4 (C-3), 126.5 (CH_{ar}), 127.6 (CH_{ar}), 128.9 (CH_{ar}), 128.9 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.4 (CH_{ar}), 129.4 (CH_{ar}), 132.7 (CH_{ar}), 132.7 (CH_{ar}), 132.9 (C-2), 134.6 (C_{ar}), 141.9 (C_{ar}), 163.7 (CO); IR (KBr): 3227, 3056, 3028, 2979, 2207, 1652, 1606, 1537, 1455, 1317, 1286, 1263, 1227, 1152, 1087, 1040 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{23}NNaOS$ 372.13926, found 372.13904.

4.1.20. (2*Z*)-*N*-[3-Phenyl-1-(phenylsulfonyl)propyl]hept-2-en-4-ynamide (41). Phenylthioamide **40** (0.017 g, 0.049 mmol) was converted to phenylsulfonylamide **41** according to general procedure 6, with additional stirring of the reaction mixture at 0 °C for 2 h before workup. Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave 0.018 g (96%) of **41** as colorless crystals, mp 52 °C. TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.35; ^1H NMR (THF-d_8): δ 1.20 (t, J=7.6 Hz, 3H, CH_3), 2.00–2.11 (m, 1H, CH_2), 2.46 (td, J=7.6, 2.2 Hz, 2H, CH_2), 2.49–2.56 (m, 1H, CH_2), 2.64–2.72 (m, 1H, CH_2Ph), 2.76–2.83 (m, 1H, CH_2Ph), 5.28–5.34 (m, 1H, $CHSO_2Ph$), 5.84 (d, J=11.6, 1H, CH), 5.99 (dt, J=11.6, 2.2, 1H, CH), 7.12–7.25 (m, 5H, CH_{ar}), 7.47–7.62 (m, 3H, CH_{ar}), 7.85–7.86 (m, 2H, CH_{ar}), 7.98 (d, br, J=10.4 Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 13.7 (C-7), 14.1 (C-6), 29.8 (C-2′), 32.3 (C-3′), 69.1 (C-1′), 77.5 (C-4), 104.9 (C-5), 118.7 (C-3), 126.9 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.2 (CH_{ar}), 129.6 (CH_{ar}), 129.6 (CH_{ar}), 130.1 (CH_{ar}), 130.1 (CH_{ar}), 132.0 (C-2), 134.4 (CH_{ar}), 138.8 (C_{ar}), 141.6 (C_{ar}), 163.8 (CO); IR (KBr): 3295, 3063, 3025, 2977, 2935, 2207, 1660, 1608, 1525, 1449, 1322, 1305, 1214, 1149, 1084 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{23}NNaO_3S$ 404.12909, found 404.12926.

4.1.21. (2*Z*)-*N*-[(1*E*/*Z*)-3-Phenylprop-1-enyl]hept-2-en-4-ynamide (42). (a) *From sulfone* **41**. A solution of phenylsulfonylamide **41** (9.2 mg, 0.024 mmol, 1 equiv.) and dry DBU (3.8 μL, 0.025 mmol, 1.05 equiv.) in dry THF (2.0 mL) was heated under reflux overnight. The mixture was cooled to room temperature, and diluted with water (2 mL) and ethyl acetate (10 mL). The organic layer was washed with saturated NH_4Cl solution (3 mL), water (3 mL) and brine (2 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave 4.1 mg (71%) of **42** as colorless crystals (*E*/*Z*=25:75).

(b) *From hydroxyamide* **39**. Hydroxyamide **39** (0.026 g, 0.10 mmol) was converted to enamide **42** according to general procedure 2. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 0.018 g (75%) of **42** as colorless crystals (*E*/*Z*=70:30). Conversion of hydroxyamide **39** (0.025 g, 0.097 mmol) to enamide **42** was also performed according to general procedure 3. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 5.0 mg (42%) of amide **19** and 6.7 mg (29%) of **42** as colorless crystals (*E*/*Z*=35:65).

Compound **42**_*trans*. Mp 89 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.55; ^1H NMR (C_6D_6): δ 0.71 (t, J=7.3 Hz, 3H, CH_3), 1.79 (qd, J=7.3 Hz, 2.0 Hz, 2H, CH_2), 3.12 (d, J=7.3 Hz, 2H, CH_2Ph), 5.08 (dt, J=14.2, 7.3 Hz, 1H, CH), 5.50 (dt, J=12.1, 2.0 Hz, 1H, CH), 5.93 (d, J=12.1 Hz, 1H, CH), 7.02–7.14 (m, 5H, CH_{ar}), 7.29 (dd, J=14.2, 10.6 Hz, 1H, CH), 8.51 (d, br, J=10.6 Hz, 1H, NH); ^{13}C NMR (C_6D_6): δ 13.2 (C-7), 13.2 (C-6), 36.5 (C-3′), 77.0 (C-4), 104.6 (C-5), 111.5 (C-2′), 116.4 (C-3), 124.2 (C-1′), 126.3 (CH_{ar}), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.3 (CH_{ar}), 128.7 (CH_{ar}), 133.2 (C-2), 141.0 (C_{ar}), 161.3 (CO); IR (KBr): 3234, 3032, 2976, 2205, 1645, 1603, 1526, 1300, 1275, 1226, 1081 cm^{-1}.

Compound **42**_*cis*. Mp 73 °C; TLC (petroleum ether/ethyl acetate, 2:1): R_f=0.63; ^1H NMR (C_6D_6): δ 0.66 (t, J=7.3 Hz, 3H, CH_3), 1.74 (dq, J=7.3, 2.0 Hz, 2H, CH_2), 3.16 (d, J=7.6 Hz, 2H, CH_2Ph), 4.75 (dt, J=8.7, 7.6 Hz, 1H, CH), 5.52 (dt, J=12.1, 2.0 Hz, 1H, CH), 5.99 (d, J=12.1 Hz, 1H, CH), 6.96–7.12 (m, 5H, CH_{ar}), 7.36 (dd, J=8.7, 7.9 Hz, 1H, CH), 9.01 (d, br, J=7.9 Hz, 1H, NH); ^{13}C NMR (C_6D_6): δ 13.1 (C-7), 13.4 (C-6), 32.7 (C-3′), 77.1 (C-4), 105.1 (C-5), 109.0 (C-2′), 116.1 (C-3), 122.8 (C-1′), 126.5 (CH_{ar}), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.3 (CH_{ar}), 128.8 (CH_{ar}), 133.4 (C-2), 139.8 (C_{ar}), 161.5 (CO); IR (KBr): 3265, 3027, 2205, 1651, 1607, 1523, 1265, 1218, 1113 cm^{-1}; MS (EI), *m*/*z* (%): 239 (13) $[M]^+$, 224 (17) $[M-CH_3]^+$, 210 (15) $[M-Et]^+$, 148 (46), 132 (53), 122 (100), 107 (56), 91 (98), 77 (64); HRMS (EI): $[M]^+$ calcd for $C_{16}H_{17}NO$ 239.131005, found 239.133176.

4.1.22. *N*-(1-Hydroxy-3-phenylpropyl)hepta-2,4-diynamide (44). Amide **21** (0.12 g, 1.0 mmol) was converted to hydroxyamide **44** according to general procedure 1 by treatment with 3-phenylpropanal (**33**). Purification of the reaction mixture by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave 0.069 g (27%) of **43** as a yellow oil and 0.089 g (35%) of **44** as a colorless oil.

Data for **43**. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.59; ^1H NMR ($CDCl_3$): δ 1.17 (t, J=7.6 Hz, 3H, CH_3), 1.86–2.07 (m, 2H, CH_2), 2.37 (qd, J=7.6, 2.1 Hz, 2H, CH_2), 2.68–2.86 (m, 2H, CH_2Ph), 3.75 (s, br, 1H, OH), 5.36–5.41 (m, 1H, C*H*OH), 5.94 (d, br, J=5.8 Hz, 1H, NH), 6.01 (d, J=15.4 Hz, 1H, CH), 6.68 (dt, J=15.4, 2.1 Hz, 1H, CH), 7.16–7.31 (m, 5H, CH_{ar}); ^{13}C NMR ($CDCl_3$): δ 13.4 (C-7), 13.4 (C-6), 30.9 (C-3′), 36.3 (C-2′), 74.4 (C-1′), 77.2 (C-4), 101.2 (C-5), 123.9 (C-3), 126.2 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.6 (CH_{ar}), 128.6 (CH_{ar}), 130.5 (C-2), 140.8 (C_{ar}), 165.9 (CO); IR (film): 3227, 2977, 2958, 2885, 2243, 2214, 1655, 1614, 1534, 1456, 1367, 1314, 1192, 1121, 1068, 1037 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{19}NNaO_2$ 280.13080, found 280.13083.

Data for **44**. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.66; ^1H NMR (THF-d_8): δ 1.15 (t, J=7.6 Hz, 3H, CH_3),

1.75–1.90 (m, 2H, CH_2), 2.35 (q, J=7.6 Hz, 2H, CH_2), 2.60–2.74 (m, 2H, CH_2Ph), 5.22 (d, br, J=4.1 Hz, 1H, OH), 5.27–5.33 (m, 1H, C*H*OH), 7.09–7.23 (m, 5H, CH_{ar}), 8.27 (d, br, J=7.8 Hz, 1H, NH); ^{13}C NMR (THF-d_8): δ 13.3 (C-7), 13.4 (C-6), 32.2 (C-2′), 38.7 (C-3′), 63.9 (C-4), 68.8 (C-2), 70.1 (C-3), 73.7 (C-1′), 87.3 (C-5), 126.5 (CH_{ar}), 129.0 (CH_{ar}), 129.0 (CH_{ar}), 129.1 (CH_{ar}), 129.1 (CH_{ar}), 142.8 (C_{ar}), 151.9 (CO); IR (film): 3272, 3028, 2984, 2940, 2243, 2152, 1635, 1532, 1497, 1455, 1281, 1192, 1094, 1042 cm^{-1}; HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{17}NNaO_2$ 278.11515, found 278.11512.

4.1.23. *N*-[(1*E*/*Z*)-3-Phenylprop-1-enyl]hepta-2,4-diynamide (45). Hydroxyamide **44** (0.026 g, 0.10 mmol) was converted to the enamides **45** according to general procedure 2. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave 6.0 mg (25%) of **45** as a colorless solid (*E*/*Z*=63:37).

Compound **45**_*trans*. Mp 115 °C; TLC (petroleum ether/ethyl acetate, 3:1): R_f=0.53; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J=7.6 Hz, 3H, CH_3), 2.34 (d, J=7.6 Hz, 2H, CH_2), 3.35 (d, J=7.3 Hz, 2H, CH_2Ph), 5.35 (dt, J=14.1, 7.3 Hz, 1H, CH), 6.83 (ddt, J=14.1, 10.9, 1.4 Hz, 1H, CH), 7.15–7.30 (m, 5H, CH_{ar}), 7.16 (d, br, J=10.9 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.8 (C-7), 13.2 (C-6), 36.1 (C-3′), 63.0 (C-4), 67.5 (C-2), 77.2 (C-3), 88.6 (C-5), 113.8 (C-2′), 122.5 (C-1′), 126.4 (CH_{ar}), 128.4 (CH_{ar}), 128.4 (CH_{ar}), 128.5 (CH_{ar}), 128.5 (CH_{ar}), 139.8 (C_{ar}), 148.9 (CO); IR (KBr): 3233, 3183, 2925, 2854, 2241, 2152, 1624, 1458, 1375, 1291, 1246 cm^{-1}.

Compound **45**_*cis*. Mp 82 °C; TLC (petroleum ether/ethyl acetate, 3:1) R_f=0.59; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J=7.6 Hz, 3H, CH_3), 2.35 (d, J=7.6 Hz, 2H, CH_2), 3.38 (d, J=7.3 Hz, 2H, CH_2Ph), 5.04 (dt, J=8.6, 7.3 Hz, 1H, CH), 6.84 (ddt, J=10.9, 8.6, 1.5 Hz, 1H, CH), 7.15–7.34 (m, 5H, CH_{ar}), 7.19 (d, br, J=10.9 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.8 (C-7), 13.2 (C-6), 32.0 (C-3′), 63.0 (C-4), 67.5 (C-2), 77.2 (C-3), 88.8 (C-5), 111.0 (C-2′), 121.0 (C-1′), 126.6 (CH_{ar}), 128.2 (CH_{ar}), 128.2 (CH_{ar}), 128.8 (CH_{ar}), 128.8 (CH_{ar}), 138.9 (C_{ar}), 149.1 (CO); IR (KBr): 3259, 3170, 2922, 2851, 2242, 2153, 1621, 1520, 1454, 1378, 1282, 1246, 1187 cm^{-1}; MS (EI), *m*/*z* (%): 237 (24) $[M]^+$, 236 (100) $[M-H]^+$, 222 (56) $[M-CH_3]^+$, 208 (34) $[M-Et]^+$, 146 (52), 130 (20), 105 (100), 91 (30), 77 (69), 51 (22); HRMS (EI): $[M-H]^+$ calcd for $C_{16}H_{14}NO$ 236.107530, found 236.112115.

4.1.24. (2*Z*,4*Z*)-*N*-(1-Hydroxy-3-phenylpropyl)hepta-2,4-dienamide (46). Amide **15** (0.063 g, 0.50 mmol) was converted to hydroxyamide **46** according to general procedure 1 by treatment with 3-phenylpropanal (**33**). Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave 0.11 g (84%) of **46** as colorless crystals, mp 97 °C. TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.51; ^{1}H NMR (DMSO-d_6): δ 0.95 (t, J=7.3 Hz, 3H, CH_3), 1.67–1.83 (m, 2H, CH_2), 2.18–2.25 (m, 2H, CH_2), 2.54–2.62 (m, 2H, CH_2Ph), 5.14–5.20 (m, 1H, C*H*OH), 5.64 (d, J=4.8 Hz, 1H, OH), 5.72 (m, 1H, CH), 5.74 (d, J=11.4 Hz, 1H, CH), 6.75 (dd, J=11.6, 11.4 Hz, 1H, CH), 7.14–7.19 (m, 3H, CH_{ar}), 7.25–7.28 (m, 2H, CH_{ar}), 7.35 (dd, J=11.6, 11.1 Hz, 1H, CH), 8.37 (d, br, J=8.3 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.0 (C-7), 19.9 (C-6), 30.9 (C-3′), 37.9 (C-2′), 71.5 (C-1′), 121.5 (C-2), 124.2 (C-4), 125.7 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 134.5 (C-3), 139.9 (C-5), 141.7 (C_{ar}), 165.1 (CO); IR (KBr): 3299, 2928, 2871, 1660, 1532, 1455, 1255, 1217, 1097, 1067 cm^{-1}; HRMS (ESI): $[2M+Na]^+$ calcd for $C_{32}H_{42}N_2NaO_4$ 541.30368, found 541.30358.

4.1.25. (2*Z*,4*Z*)-*N*-[(1*E*/*Z*)-3-Phenylprop-1-enyl]hepta-2,4-dienamide (47). Hydroxyamide **46** (0.026 g, 0.10 mmol) was converted to enamide **47** according to general procedure 2. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 5:1) gave 0.020 g (83%) of **47** as a colorless solid (*E*/*Z*=69:31).

Compound **47**_*trans*. Mp 104 °C; TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.60; ^{1}H NMR (C_6D_6): δ 0.79 (t, J=7.6 Hz, 3H, CH_3), 1.99 (dq, J=7.6, 7.8 Hz, 2H, CH_2), 3.08 (d, J=7.3 Hz, 2H, CH_2Ph), 4.82 (dt, J=14.2, 7.3 Hz, 1H, CH), 5.03 (d, J=11.4 Hz, 1H, CH), 5.63 (dt, J=11.1, 7.8 Hz, 1H, CH), 6.19 (d, br, J=8.6 Hz, 1H, NH), 6.63 (dd, J=11.9, 11.4 Hz, 1H, CH), 7.03–7.16 (m, 5H, CH_{ar}), 7.18 (m, 1H, CH), 8.00 (dd, J=11.9, 11.1 Hz, 1H, CH); ^{13}C NMR (C_6D_6): δ 14.0 (C-7), 20.8 (C-6), 36.5 (C-3′), 111.3 (C-2′), 119.8 (C-2), 124.2 (C-1′), 124.9 (C-4), 126.3 (CH_{ar}), 127.9 (CH_{ar}), 128.1 (CH_{ar}), 128.7 (CH_{ar}), 128.7 (CH_{ar}), 136.7 (C-3), 141.2 (C_{ar}), 141.6 (C-5), 162.7 (CO); IR (KBr): 3247, 3183, 3028, 2665, 2871, 1639, 1542, 1455, 1367, 1296, 1243, 1221, 951 cm^{-1}.

Compound **47**_*cis*. Mp 104 °C; TLC (petroleum ether/ethyl acetate, 4:1): R_f=0.70; ^{1}H NMR (C_6D_6): δ 0.77 (t, J=7.6 Hz, 3H, CH_3), 1.97 (dq, J=7.6, 7.8 Hz, 2H, CH_2), 2.94 (d, J=7.3 Hz, 2H, CH_2Ph), 4.69 (dt, J=8.6, 7.3 Hz, 1H, CH), 4.98 (d, J=11.4 Hz, 1H, CH), 5.62 (dt, J=11.1, 7.8 Hz, 1H, CH), 6.52 (d, br, J=8.6 Hz, 1H, NH), 6.58 (dd, J=11.9, 11.4 Hz, 1H, CH), 6.96–7.13 (m, 5H, CH_{ar}), 7.23 (m, 1H, CH), 7.94 (dd, J=11.9, 11.1 Hz, 1H, CH); ^{13}C NMR (C_6D_6): δ 14.0 (C-7), 20.8 (C-6), 32.1 (C-3′), 108.2 (C-2′), 119.6 (C-2), 122.9 (C-1′), 124.8 (C-4), 126.5 (CH_{ar}), 128.3 (CH_{ar}), 128.3 (CH_{ar}), 128.5 (CH_{ar}), 128.9 (CH_{ar}), 137.0 (C-3), 141.1 (C_{ar}), 141.8 (C-5), 162.7 (CO); IR (KBr): 3340, 3065, 3027, 2966, 2929, 1647, 1590, 1500, 1454, 1370, 1262, 1208 cm^{-1}; MS (EI), *m*/*z* (%): 241 (13) $[M]^+$, 212 (25) $[M-Et]^+$, 150 (20), 132 (37), 124 (42), 96 (41), 91 (100), 81 (32); HRMS (EI): $[M]^+$ calcd for $C_{16}H_{19}NO$ 241.146655, found 241.148525.

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Zirconium triflate-catalyzed reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone

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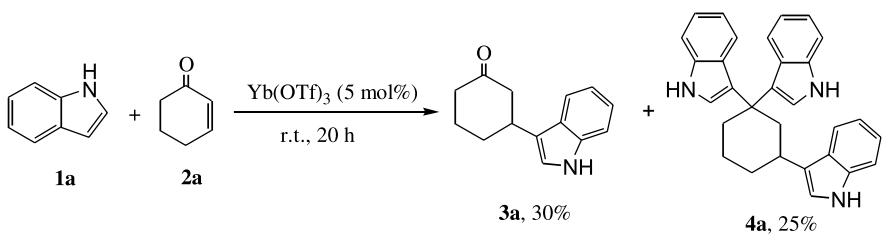
Abstract—The $Zr(OTf)_4$-catalyzed reaction of indole, 1-methylindole or pyrrole with α,β-unsaturated ketone generated the corresponding trisindolyl-, tris(1-methylindolyl-), and trispyrrolylalkanes in moderate to high yields in the mixed solvent $EtOH/H_2O$.

1. Introduction

The Michael addition reaction is one of the most important C–C bond forming reactions in organic chemistry.[1] Recently, many high-yielding, environmentally-benign, oxygen and moisture tolerant Lewis acids such as $Ln(OTf)_3$ (Ln=Yb, Sc, Y, La, etc.) or bismuth nitrate [$Bi(NO_3)_3$] have been applied to this transformation.[2] Among them the addition of indole to electron-deficient olefins is a widely investigated process because this reaction is involved in the total synthesis of a class of bioactive indole alkaloids known as the hapalindoles.[2,3] However, in our ongoing investigations of this interesting reaction, we found that this typical Michael addition reaction become complicated in the presence of excess amounts of indoles. For example, in the reaction of indole **1a** (1.5 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.), this reaction produces product **4a** in which three indole moieties have been incorporated, in 25% yield via a 1,4-addition, 1,2-addition and a dehydration process, along with the normal 1,4-addition (Michael addition) product **3a** in 30% yield in the presence of $Yb(OTf)_3$ (5 mol%) under solvent free conditions (Scheme 1).[4] So far the formation of a triindolylalkane has been reported only in the reaction of 1-methylindole with 3-methyl-2-cyclohexene-1-one to give triindolylcyclohexane in low yield as a byproduct under vigorous conditions.[5] Herein, we wish to report this interesting three indole-addition reaction in the presence of various metal triflate Lewis acids under mild conditions.

2. Results and discussion

The promoters for the reaction of indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.) were systematically examined at first in neat 2-cyclohexen-1-one in the absence of organic solvent. The results are summarized in Table 1. We found that in the reaction of indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.), the major reaction product was compound **4a** in the presence of various



Scheme 1.

Keywords: Indole; Pyrrole; α,β-Unsaturated ketone; $Zr(OTf)_4$; Lewis acid; Michael addition; Trisindolylalkane.
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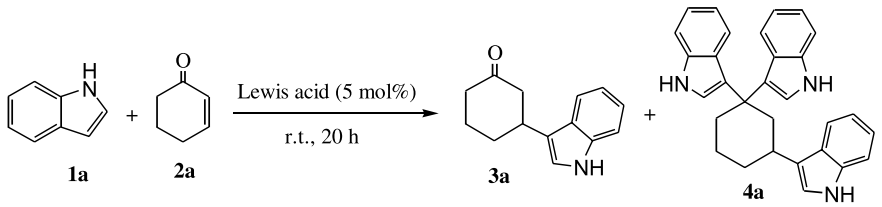
Table 1. The reaction indole **1a** (3.0 equiv.) with 2-cyclohexen-1-one **2a** (1.0 equiv.) in the presence of Lewis acid

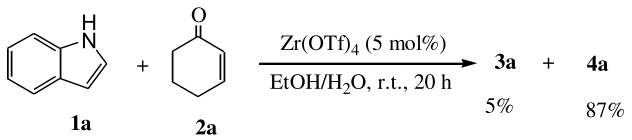


Entry[a]	Lewis acid	Yield [%][b]	
		3a	**4a**
1	$Yb(OTf)_3$	30	43
2	$Sc(OTf)_3$	23	53
3	$Eu(OTf)_3$	26	38
4	$Zr(OTf)_4$	20	60
5	$Hf(OTf)_4$	27	45
6	$Cu(OTf)_2$	27	36
7	$Sn(OTf)_2$	32	36
8	$Ti(OPr^i)_4$	NR	

[a] The reaction was carried out in neat 2-cyclohexene-1one without organic solvent.
[b] Isolated yields.

metal triflate Lewis acids (Table 1, entries 1–7). The Lewis acid $Ti(O^iPr)_4$ showed no catalytic activity for this reaction (Table 1, entry 8). $Zr(OTf)_4$ gave the best result under identical conditions. The three indole-incorporated product **4a** can be isolated in 60% yield under mild conditions using $Zr(OTf)_4$ as a Lewis acid promoter (Table 1, entry 4).

In order to improve the isolated yield of **4a**, solvent effects were examined in various organic solvents in the presence of $Zr(OTf)_4$ (5 mol%). We found that in the mixed polar solvent $EtOH/H_2O$ (2/1), the isolated yield of **4a** can reach 87% in the presence of $Zr(OTf)_4$ (5 mol%) along with 5% of **3a** under mild conditions (Scheme 2).



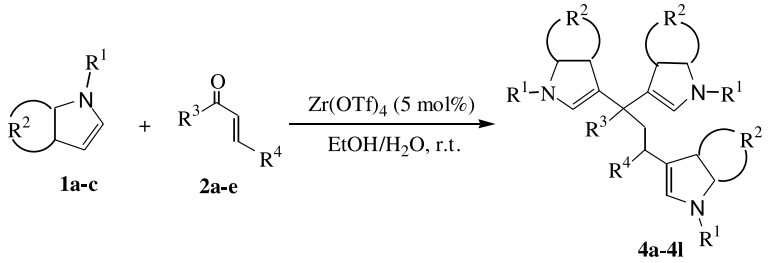
Scheme 2.

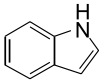
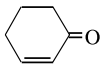
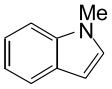
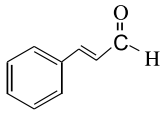
Under these optimized reaction conditions, we next examined the reactions of indole **1a** (5.0 equiv.), 1-methylindole **1b** (5.0 equiv.), pyrrole **1c** (5.0 equiv.) with various α,β-unsaturated ketone (1.0 equiv.) in the presence of $Zr(OTf)_4$ (5 mol%). The results are summarized in Table 2. As can be seen from Table 2, the yields of triindolylalkanes are very sensitive to the substrates employed (Table 2, entries 1–11). Using acrolein **2c**, crotonaldehyde **2d**, *trans*-cinnamaldehyde **2e** as substrates, the corresponding triindolylalkanes **4d**, **4f** and **4h** were produced in moderate to good yields (Table 2, entries 4, 6, and 8). Their yields could be slightly improved by prolonging the reaction time (3 days). For the reaction of indole **1a** with 2-cyclohexene-1-one **2a**, the triindolylalkane **4a** was obtained in 99% yield after 3 days under the same conditions (Table 2, entry 1). For 2-cyclopenten-1-one **2b**, the corresponding triindolylalkane **4b** was obtained in low yield under the same conditions even after a prolonged reaction time (Table 2, entry 2). This may be due to the rigid five-membered ring, which disfavors the 1,4- or 1,2-addition of sterically-demanding indoles in the presence of Lewis acid. On the other hand, using 1-methylindole **1b** to react with 2-cyclohexene-1-one **2a** or crotonaldehyde **2d** under the same conditions, similar results were obtained (Table 2, entries 3 and 7), although in the reaction of **1b** with acrolein **2c** and *trans*-cinnamaldehyde **2e**, the corresponding triindolylalkanes **4e** and **4i** were obtained in lower yields (Table 2, entries 5 and 9). It should be emphasized here that in the case of the reaction of **1b** with **2e**, product **4j** in which two 1-methylindole moieties were incorporated was isolated as a major product in 28% yield (Scheme 3). Using pyrrole **1c** instead of indole, the corresponding tripyrrolylcyclohexane **4k** was formed in 40% under the same conditions (Table 2, entry 10). In addition, the reaction of indole (5.0 equiv.) with methyl vinyl ketone (1.0 equiv.) produced the corresponding triindolylalkane **4l** under the same conditions, although the isolated yield was 8% (Table 2, entry 11).

The mechanism for this three indole or pyrrole incorporating reaction is shown in Scheme 3. The 1,4- and 1,2-additions of indole to α,β-unsaturated ketone take place sequentially to give intermediate **A** in the presence of Lewis acid $Zr(OTf)_4$ (Scheme 3). The dehydration of **A** gives another intermediate **B** which is further activated by Lewis acid $Zr(OTf)_4$ and serves as an electrophile to react with a third molecule of indole, affording intermediate **C**. The corresponding three indole-incorporated product is subsequently formed from intermediate **C** (Scheme 4). We confirmed that product **3a** can be completely transformed to **4a** in the presence of $Zr(OTf)_4$ and indole under the same conditions (Scheme 4). Thus, this result supports the proposed reaction mechanism.

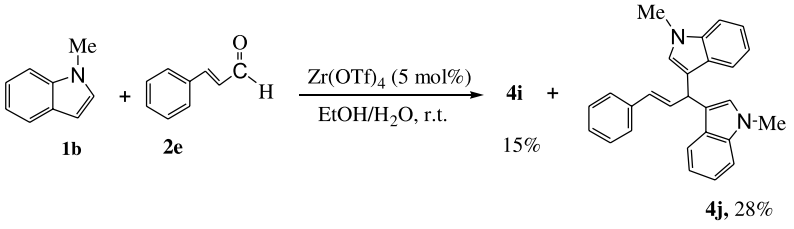
In conclusion, we found that in the reaction of excess amounts of indole, 1-methylindole or pyrrole with

Table 2. Reactions of indole, l-methylindole or pyrrole with α,β-unsaturated ketones in the presence of $Zr(OTf)_4$



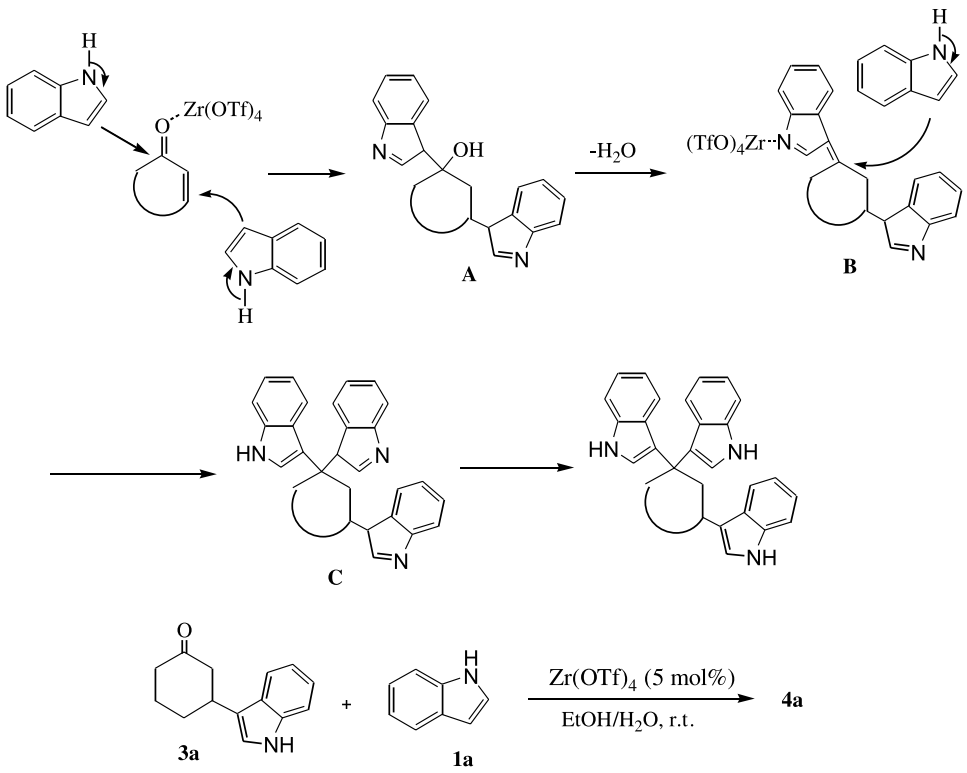
Entry[a]					Time/[days]	Yield [%][b], **4a**–**4l**
1		**1a**		**2a**	3	**4a**, 99
2	**1a**			**2b**	3	**4b**, 4
3		**1b**	**2a**		3	**4c**, 80
4	**1a**			**2c**	1 (3)	**4d**, 50 (53)
5	**1b**		**2c**		3	**4e**, 20
6	**1a**			**2d**	1 (3)	**4f**, 60 (61)
7	**1b**		**2d**		3	**4g**, 63
8	**1a**			**2e**	1 (3)	**4h**, 70 (80)
9	**1b**		**2e**		3	**4i**, 15[c]
10		**1c**	**2a**		3	**4k**, 40
11	**1a**			**2f**	3	**4l**, 8

[a] $Zr(OTf)_4$ (5.0 mol%), **1a**–**c** (5.0 equiv.) and α,β-unsaturated ketones (1.0 equiv.) were dissolved in 1.0 mL of $EtOH/H_20$(2/1) solvent.
[b] Isolated yields.
[c] Anothere product **4j** was isolated in 28% yield.



Scheme 3.

α,β-unsaturated ketone the trisindolyl- or trispyrrolylalkanes can be produced in the presence of Lewis acid $Zr(OTf)_4$ under mild conditions. Although the isolated yields are highly dependent on the employed substrates, this reaction pathway is interesting and the products obtained are novel. Efforts are underway to elucidate the mechanistic details of this catalytic system and to extend the scope of this interesting reaction.



Scheme 4.

3. Experimental

3.1. General methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI methods, and HRMS were measured on a Finnigan MA$^+$ mass spectrometer. Organic solvents used were dried by standard methods when necessary. The solid compounds reported in this paper gave satisfactory CHN microanalyses. Commercially available reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

A typical reaction procedure for the reaction of indole with 2-cyclohexen-1-one in the presence of Zr(OTf)$_4$. Lewis acid $Zr(OTf)_4$ (5.0 mol%) and indole (292.3 mg, 2.5 mmol) were dissolved in 1.0 mL of EtOH/H_2O (2/1) mixed solvent. 2-Cyclohexene-1-one (34.5 mg, 0.5 mmol) was added dropwise into the reaction system by a syringe and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give 1,1,3-tris(3-indolyl)cyclohexane **4a** as a white solid.

3.1.1. 1,1,3-Tris(3-indolyl)cyclohexane 4a. This compound was isolated by flash chromatography to give **4a** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 212 mg, yield: 99%.

Mp: 217–219 °C; IR (KBr) ν 3470, 3401, 3054, 1456, 1418, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.63–1.74 (1H, m, CH_2), 1.81–2.02 (2H, m, CH_2), 2.15–2.47 (3H, m, CH_2), 2.98–3.08 (1H, m, CH), 3.28–3.35 (2H, m, CH_2), 6.88–6.92 (3H, m, ArH), 6.96–7.18 (5H, m, ArH), 7.24–7.28 (1H, m, ArH), 7.34 (2H, t, J=8.0 Hz, ArH), 7.46 (2H, m, ArH), 7.54 (1H, d, J=7.9 Hz, ArH), 7.67 (1H, d, J=8.1 Hz, ArH), 7.81 (1H, s, NH), 7.89 (1H, s, NH), 8.11 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.3, 31.0, 34.0, 36.6, 40.3, 43.9, 111.1, 111.1, 111.2, 118.5, 118.6, 118.9, 119.4, 119.6, 119.6, 120.4, 120.8, 121.1, 121.2, 121.4, 121.8, 121.9, 122.7, 123.2, 125.8, 126.3, 126.7, 136.3, 137.0, 137.0; MS (EI) m/z 429 (M$^+$, 44.19), 312 (M$^+$−117, 90.34), 143 (M$^+$−286, 100). Anal. calcd for $C_{30}H_{33}N_3$: requires C, 83.88; H, 6.34; N, 9.78. Found: C, 83.74; H, 6.21; N, 9.65%.

3.1.2. 1,1,3-Tris(3-indolyl)cyclopropane 4b. This compound was isolated by flash chromatography to give **4b** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 8.3 mg, yield: 4%.

IR (KBr) ν 3053, 2926, 2854, 1465, 1265 cm^{-1}; ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS): δ 2.09–2.19 (1H, m, CH_2), 2.39–2.78 (3H, m, CH_2), 2.91–3.20 (1H, m, CH_2), 3.15–3.24 (1H, m, CH_2), 3.60–3.74 (1H, m, CH), 6.73–6.80 (2H, m, ArH), 6.90–6.99 (3H, m, ArH), 7.02–7.09 (1H, m, ArH), 7.15–7.17 (1H, m, ArH), 7.29–7.39 (3H, m, ArH), 7.47–7.60 (5H, m, ArH), 9.91 (2H, s, NH), 10.04 (1H, s, NH); MS (EI) m/z 415 (M$^+$, 24.23), 298 (M$^+$−117, 87.24), 129 (M$^+$−286, 100); HRMS (EI) calcd for $C_{28}H_{25}N_3$ 415.2049. Found: 415.2034.

3.1.3. 1,1,3-Tris(3-*N*-methylindolyl)cyclohexane 4c. This compound was isolated by flash chromatography to give **4c**

as white crystals (eluent: petroleum ether/ethyl acetate=4/1). 187 mg, yield: 79%.

Mp: 215–216 °C; IR (KBr): 3054, 2987, 2306, 1712, 1422, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.54–1.69 (1H, m, CH_2), 1.78–1.99 (m, 2H, CH_2), 2.14–2.50 (3H, m, CH_2), 2.92–3.01 (1H, m, CH), 3.20–3.34 (2H, m, CH_2), 3.63 (3H, s, NCH_3), 3.72 (3H, s, NCH_3), 3.86 (3H, s, NCH_3), 6.67 (1H, s, ArH), 6.84 (1H, s, ArH), 6.88–7.32 (m, 10H, ArH), 7.46 (1H, d, J=8.0 Hz, ArH), 7.57 (1H, d, J=8.0 Hz, ArH), 7.71 (1H, d, J=8.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.4, 31.0, 32.5, 32.5, 32.9, 34.3, 36.9, 40.4, 44.3, 109.0, 109.1, 109.2, 117.9, 118.1, 118.3, 118.9, 119.6, 120.7, 120.8, 121.2, 121.3, 121.3, 122.0, 124.4, 125.2, 125.7, 126.1, 127.1, 127.1, 128.0, 137.0, 137.7, 137.7; MS (EI) m/z 471 (M^+, 20.08), 340 (M^+-131, 100), 144 (M^+-327, 34.04), 131 (M^+-340, 75.54). Anal calcd for $C_{33}H_{33}N_3$ requires C, 84.04; H, 7.05; N, 8.91. Found: C, 83.60; H, 7.20; N, 8.77%.

3.1.4. 1,1,3-Tris(3-indolyl)propane 4d. This compound was isolated by flash chromatography to give **4d** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 103 mg, yield: 53%.

IR (KBr) ν 3050, 2920, 2861, 1461, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.61 (2H, q, J=7.3 Hz, CH_2), 2.85 (2H, t, J=7.3 Hz, CH_2), 4.56 (1H, t, J=7.3 Hz, CH), 6.80–7.33 (12H, m, ArH), 7.49–7.55 (3H, m, ArH), 7.76 (3H, s, NH); MS (EI) m/z 389 (M^+, 24.59), 258 (M^+-131, 48.24), 245 (M^+-144, 100); HRMS (EI) calcd for $C_{27}H_{23}N_3$ requires 389.1892. Found: 389.1852.

3.1.5. 1,1,3-Tris(3-*N*-methylindolyl)propane 4e. This compound was isolated by flash chromatography to give **4e** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 42 mg, yield: 20%.

Mp: 111–113 °C; IR ($CHCl_3$) ν 3042, 2914, 1604, 1483, 1352, 1328, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.57–2.67 (2H, m, CH_2), 2.80–2.89 (2H, m, CH_2), 3.71 (3H, s, NCH_3), 3.72 (6H, s, NCH_3), 4.57 (1H, t, J=7.4 Hz, CH), 6.78 (1H, s, ArH), 6.88 (2H, s, ArH), 6.98–7.07 (3H, m, ArH), 7.14–7.30 (6H, m, ArH), 7.50 (1H, d, J=7.8 Hz, ArH), 7.57 (2H, d, J=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.8, 32.5, 32.6, 33.6, 36.6, 109.0, 109.0, 115.3, 118.3, 118.4, 118.9, 119.2, 119.8, 121.2, 121.3, 126.0, 126.3, 127.5, 127.9, 137.0, 137.2; MS (EI) m/z 431 (M^+, 6.11), 300 (M^+-131, 4.91), 273 (M^+-158, 62.20), 144 (M^+-287, 100), 131 (M^+-300, 56.68); HRMS (MALDI) calcd for $C_{30}H_{29}N_3$+Na 454.2259. Found: 454.2254.

3.1.6. 1,1,3-Tris(3-indolyl)butane 4f. This compound was isolated by flash chromatography to give **4f** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 123 mg, yield: 61%.

Mp: 108–110 °C; IR (KBr) ν 3056, 2925, 2851, 1460, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.34 (3H, d, J=6.9 Hz, CH_3), 2.31–2.43 (1H, m, CH_2), 2.54–2.67 (1H, m, CH_2), 2.91–3.30 (1H, m, CH), 4.46 (1H, t, J=7.7 Hz, CH), 6.54 (1H, s, NH), 6.59 (1H, s, NH), 6.65 (1H, s, NH), 6.88–7.55 (15H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 28.8, 31.7, 43.6, 111.1, 111.2, 111.2, 118.8, 118.9, 119.5, 119.6, 119.62, 119.9, 120.0, 120.2, 121.5, 121.56, 121.60, 121.63, 121.68, 121.7, 122.2, 126.85, 126.87, 126.89, 136.31, 136.34, 136.4; MS (EI) m/z 403 (M^+, 4.14), 245 (M^+-158, 30.78), 84 (M^+-319, 100); HRMS (EI) calcd for $C_{28}H_{25}N_3$ 403.2048. Found: 403.2071 (M^+).

3.1.7. 1,1,3-Tris(3-*N*-methylindolyl)butane 4g. This compound was isolated by flash chromatography to give **4g** as a white solid (eluent: petroleum ether/ethyl acetate=4/1). 140 mg, yield: 63%.

Mp: 115–117 °C; IR (KBr) ν 3050, 2927, 1613, 1483, 1372, 1326, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 1.41 (3H, d, J=7.1 Hz, CH_3), 2.47 (1H, dt, J=7.4 Hz, 13.3 Hz, CH_2), 2.71 (1H, dt, J=7.4, 13.3 Hz, CH_2), 3.01–3.15 (1H, m, CH), 3.70 (6H, s, NCH_3), 3.72 (3H, s, NCH_3), 4.55 (1H, t, J=7.4 Hz, CH), 6.77 (1H, s, ArH), 6.78 (1H, s, ArH), 6.88 (1H, s, ArH), 6.92–7.04 (3H, m, ArH), 7.12–7.30 (6H, m, ArH), 7.43 (2H, d, J=7.8 Hz, ArH), 7.57 (1H, d, J=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.3, 29.1, 31.9, 32.6, 32.6, 44.5, 109.1, 109.2, 109.3, 118.3, 118.41, 118.42, 119.1, 119.18, 119.18, 119.86, 119.88, 119.95, 121.2, 121.28, 121.32, 121.33, 121.33, 125.2, 126.3, 126.5, 127.3, 127.6, 137.27, 137.34, 137.38; MS (EI) m/z 445 (M^+, 15.67), 314 (M^+-131, 10.31), 273 (M^+-172, 100), 159 (M^+-286, 37.89); HRMS (MALDI) calcd for $C_{31}H_{31}N_3$+Na 468.2416. Found: 468.2410.

3.1.8. 1,1,3-Tris(3-indolyl)-3-phenylpropane 4h. This compound was isolated by flash chromatography to give **4h** as a white powder (eluent: petroleum ether/ethyl acetate=4/1). 186 mg, yield: 80%.

Mp: 208–210 °C; IR (KBr) ν 3044, 2920, 2844, 1469, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.80–2.96 (1H, m, CH_2), 2.99–3.11 (1H, m, CH_2), 4.24 (1H, dd, J=10.0, 6.9 Hz, CH), 4.43 (1H, dd, J=10.0, 6.9 Hz, CH), 6.81 (1H, d, J=2.6 Hz, ArH), 6.88–7.35 (18H, m, ArH), 7.41 (1H, d, J=8.4 Hz, ArH), 7.70 (1H, s, NH), 7.88 (1H, s, NH), 7.90 (1H, s, NH); MS (EI) m/z 465 (M^+, 2.41), 245 (M^+-220, 100), 207 (M^+-248, 60.18). Anal. calcd for $C_{33}H_{27}N_3$ requires C, 85.13; H, 5.85; N, 9.03. Found: C, 84.86; H, 5.85; N, 8.92%.

3.1.9. 1,1,3-Tris(3-*N*-methylindolyl)-3-phenylpropane 4i. This compound was isolated by flash chromatography to give **4i** as white crystals (eluent: petroleum ether/ethyl acetate=4/1). 39 mg, yield: 15%.

Mp: 222–224 °C; IR (KBr): ν 3052, 2931, 1614, 1484, 1471, 1155, 1013, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.84–2.95 (1H, m, CH_2), 2.98–3.09 (1H, m, CH_2), 3.65 (3H, s, NCH_3), 3.73 (3H, s, NCH_3), 3.76 (3H, s, NCH_3), 4.25 (1H, dd, J=9.4, 6.1 Hz, CH), 4.41 (1H, dd, J=9.4, 6.1 Hz, CH), 6.72 (1H, s, ArH), 6.88–7.01 (5H, m, ArH), 7.11–7.34 (13H, m, ArH), 7.43 (1H, dd, J=8.0, 0.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.3, 32.6, 32.63, 32.7, 40.6, 42.7, 108.9, 109.00, 109.01, 118.0, 118.3, 118.35, 118.43, 118.43, 119.0, 119.43, 119.56, 119.56, 119.8, 120.0, 120.0, 121.19, 121.27, 121.37, 125.88, 125.93,

126.28, 126.41, 127.2, 128.21, 128.23, 137.14, 137.31, 145.4; MS (EI) *m/z* 507 (M^+, 15.46), 376 (M^+-131, 49.35), 273 (M^+-234, 100), 245 (M^+-262, 4.29), 221 (M^+-286, 35.92), 144 (M^+-363, 10.75). Anal calcd for $C_{36}H_{33}N_3$ requires C, 85.17; H, 6.55; N, 8.28. Found: C, 84.88; H, 6.51; N, 8.21%.

3.1.10. [3,3-Bis(3-*N*-methylindolyl)propenyl]benzene 4j. This compound was isolated by flash chromatography to give **4j** as colorless crystals (eluent: petroleum ether/ethyl acetate=10/1). 52 mg, yield: 28%.

Mp: 167–169 °C; IR (KBr) ν 3054, 2929, 2306, 1613, 1469, 1422, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 3.67 (1H, s, CH), 3.71 (6H, s, NCH_3), 5.39 (1H, d, J=7.1 Hz, CH), 6.49–6.56 (1H, m, CH), 6.74–6.82 (2H, m, ArH), 7.00–7.07 (2H, m, ArH), 7.14–7.38 (9H, m, ArH), 7.60 (2H, d, J=6.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 32.7, 37.3, 109.1, 116.9, 118.7, 120.1, 121.4, 126.3, 126.9, 127.3, 127.34, 128.4, 129.6, 132.8, 137.4, 137.8; MS (EI) *m/z* 376 (M^+, 100), 299 (M^+-77, 13.05), 273 (M^+-103, 46.55), 144 (M^+-232, 25.47), 77 (M^+-299, 9.24). Anal calcd for $C_{36}H_{33}N_3$ requires C, 86.13; H, 6.43; N, 7.44. Found: C, 86.33; H, 6.41; N, 7.43%.

3.1.11. 1,1,3-Tris(2-pyrolyl)cyclohexane 4k. This compound was isolated by flash chromatography to give **4k** as a yellowish oil (eluent: petroleum ether/ethyl acetate=4/1). 56 mg, yield: 40%.

Mp: 189–191 °C; IR (KBr) ν 3043, 2921, 2866, 1478, 1258 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz, TMS): δ 1.55–1.77 (2H, m, CH_2), 1.78–2.01 (4H, m, CH_2), 2.58 (1H, d, J=13.7 Hz, CH), 2.74–2.91 (2H, m, CH_2), 5.69–6.17 (6H, m, ArH), 6.49–6.72 (3H, m, ArH), 9.32 (1H, s, NH), 9.83 (1H, s, NH), 9.94 (1H, s, NH); MS (EI) *m/z* 279 (M^+, 100), 212 (M^+-67, 58.54), 145 (M^+-134, 36.61); HRMS (EI) calcd for $C_{18}H_{21}N_3$ requires 279.1735. Found: 279.1741.

3.1.12. 2,2,4-Tris(3-indolyl)butane 4l. This compound was isolated by flash chromatography to give **4l** as s white solid (eluent: petroleum ether/ethyl acetate=4/1). 16 mg, yield: 8%.

Mp: 155–157 °C; IR (KBr) ν 3053, 2926, 2854, 1465, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.00 (3H, s, CH_3), 2.60 (2H, t, J=8.6 Hz, CH_2), 2.80 (2H, t, J=8.6 Hz, CH_2), 6.81–7.18 (9H, m, ArH), 7.31 (4H, t, J=7.3 Hz, ArH), 7.41 (2H, d, J=8.4 Hz, ArH), 7.84 (1H, s, NH), 7.97 (2H, s, NH); MS (EI) *m/z* 403 (M^+, 15.08), 259 (M^+-144, 100). Anal. calcd for $C_{28}H_{25}N_3$ requires C, 83.34; H, 6.29; N, 10.41. Found: C, 83.31; H, 6.19; N, 10.27%.

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One-pot synthesis of monosubstituted aryl(hetaryl)acetylenes by direct introduction of the C≡CH residue into arenes and hetarenes

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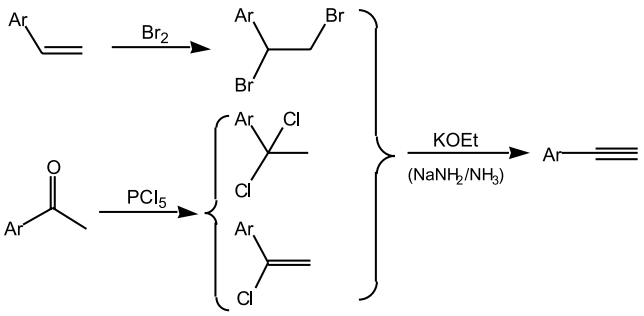
Abstract—A convenient one-pot synthesis of aryl(hetaryl)acetylenes by cross-coupling of aryl(hetaryl)iodides with acetylene in presence of $PdCl_2(Ph_3)_2$, CuI and K_2CO_3 in DMF has been developed.

1. Introduction

The diverse and high reactivity of the C≡C bond and the unusually high CH-acidity of monosubstituted acetylenes has determined an unabated interest on 1-alkynes for many years.[1–4] The C≡CH moiety is susceptible of nucleophilic, electrophilic, radical and cycloaddition reactions, and can be used both for functionalizing and building up C–C bonds. In fact, terminal acetylenes are very important key-compounds in the widely applied Mannich,[5] Hay,[6] Cadiot-Chodkiewicz,[7] and Sonogashira-Heck[8] reactions for preparing the corresponding propargyl-amines, symmetrical and unsymmetrical 1,3-diynes and disubstituted acetylenes.

Ethynyl derivatives occupy a special place, because monosubstituted acetylenes have not only a reactive triple bond but also an active hydrogen which allows to carry out various transformations of the molecule with preservation of the multiple bond. The properties of such compounds as C–H acids are used for functionalization and construction of C–C bonds.

Usually classical methods for preparing aryl(hetaryl)alk-1-ynes involve the sequence halogenation–dehalogenation of vinyl aromatic compounds[9] or halogenation–dehydrohalogenation of dihaloderivatives from vinylarenes(hetarenes) or methylaryl(hetaryl)-ketones (Scheme 1).[10]



Scheme 1.

However, a review of the publications dealing with the study of the transformations of vinylic or ketonic groups into acetylenes under the action of bases indicates the sensitivity of these reactions to experimental conditions, the structure of the starting substrate and the nature of the base.[10,11] Thus, the yields of all possible isomers of ethynylpyridine and ethynylquinoline obtained by the dehydrohalogenation varied from 0.1 to 33%.[10] An attempt to dehydrobrominate a pyrrolo-dibromoderivative under the action of sodium ethoxide failed.[10] The present authors[12] found that pyrazolylvinylchlorides, which are not substituted at the nitrogen of the ring, under the effect of sodium amide lead to complex mixtures.

In the last three decades, beginning from the discovery of Japanese chemists who found new effective catalysts for the cross-coupling reaction of arylhalides with monosubstituted acetylenes,[10] this method has become the main one for producing not only disubstituted, but also monosubstituted arylacetylenes. This approach involves protecting one end

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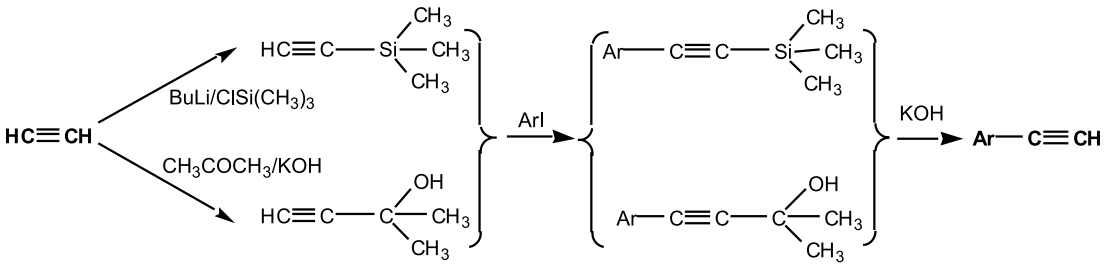


Scheme 2.

of acetylene, introduction of 1-alkyne via coupling at the free end of acetylene, followed by deprotection of the acetylenic moiety of aryl- or hetarylacetylenes (Scheme 2).

A usual way for ethynylarene synthesis involves the cleavage of the tertiary acetylenic alcohols or trimethylsilylacetylene derivatives by treatment with a catalytic amount of alkali. However, the starting reagent, trimethylsilylacetylene, is rather expensive and gives only trimethylsilyl derivatives. On the other hand, the second method—base-induced cleavage of α-acetylenic alcohols into carbonyl and ethynyl compounds (the reverse Favorsky reaction) requires hard reaction conditions (strong alkali, high temperature) and cannot be applied for obtaining labile acetylenic compounds.

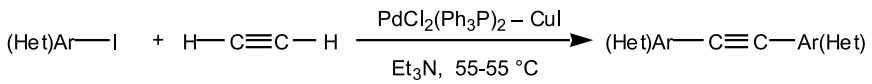
In 1980 Japanese chemists tried to carry out cross-coupling of aryliodides with acetylene itself using the typical catalytic system $PdCl_2(PPh_3)_2$–CuI–R_3N for preparing of ethynylarenes (Scheme 3). But their attempts were unsuccessful; the main products being tolanes as a result of the reaction of the arylalk-1-yne formed with the starting iodo component.[1,13]

We supposed that this negative result was related with using volatile amines, having high vapor pressure, which decrease partial pressure of acetylene and therefore its concentration. Nevertheless, we undertook a first attempt to carry out the cross-coupling of acetylene with iodoarenes and -hetarenes for preparing the desired monosubstituted acetylenes.[14] For achieving our aim we changed the traditional conditions of a reaction of cross-coupling. In this paper we describe full experimental conditions and new additional examples.

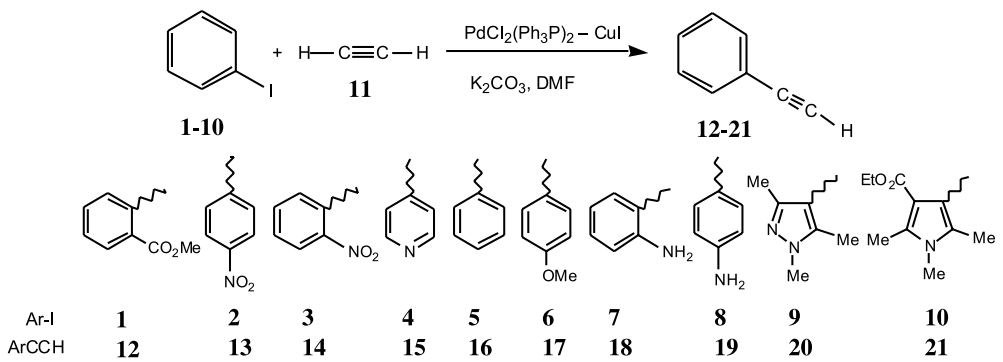
We have proposed that it is necessary to have a large excess of acetylenes in the reaction mixture for diminishing the competition reaction of the iodoarene with the initially generated ethynylarene. Thus, we decided to use a solvent with high boiling point and which dissolves large amounts of acetylene. Dimethylformamide is a solvent, which has just such properties. Below is given the solubility of HC≡CH at 20 °C and 760 mm Hg in different solvents: volumes of HC≡CH per 1 volume of solvent: ether 5.5, THF 18.5, DMF 33–37.[15] To increase additionally the high concentration of HC≡CH we used a relatively large amount of DMF (the weight ratio iodide/DMF=1:200).

It is also known that the application of stronger bases in cross-coupling substantially increases the reaction rate, thus we used potassium carbonate instead of the usual di- and trialkylamines. Taking into account the facts mentioned above, we carried out cross-coupling of a series of iodoarenes and -hetarenes in an acetylene current in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$, CuI and excess of K_2CO_3 in DMF at 50–55 °C (Scheme 4).

Iodoarenes and hetarenes with low reactivity like *p*-iodoaniline, 4-iodo-1,3,5-trimethylpyrazole, 4-iodo-3-ethoxycarbonyl-1,2,5-trimethylpyrrole, due to the strong +M-effect of the nitrogen atom underwent ethynylation in low yields



Scheme 3.



Scheme 4.

Table 1. Ethynylarenes and -hetarenes

Compound	Time, h	Yield, % (%, from copper salt)	Boiling points (melting points), °C	Literature
o-Ethynylcarbomethoxybenzene (**12**)	12	73.2 (56.4)	80–85/1 Torr n_d^{22}=1.5550	14
p-Ethynylnitrobenzene (**13**)	12.5	76.4	146.5–147.5	19
o-Ethynylnitrobenzene (**14**)	8	64.4	79.5–81	19
4-Ethynylpyridine (**15**)	17	60.2	96–97	21
Phenylacetylene (**16**)	17	60.0 (56.4)	44/23 Torr n_d^{17}=1.5507	19
p-Ethynylanisole (**17**)	17	64.2 (50.0)	27–28 96–98/14 Torr	19
p-Ethynylaniline (**18**)		(10.0)	99–100	19
o-Ethynylaniline (**19**)		(47.4)	99–101/13 Torr	19
4-Ethynyl-1,3,5-trimethyl-1*H*-pyrazole (**20**)	36	24.0 (20.3)	45.5–56.5	11
4-Ethynyl-1,2,5-trimethyl-3-carbomethoxy-1*H*-pyrrole (**21**)		35.4 (20.0)	87.5–88.5	22

(15–35%). Iodobenzene and even *p*-methoxyiodobenzene gave monoarylated products in moderate yields (50–55%). Iodoarenes (hetarenes) with electron withdrawing substituents gave the desired ethynyl derivatives in high yields (65–75%).

The different behavior of *p*- and *o*-iodoaniline is noteworthy. The yield in the case of the deactivated *o*-iodoaniline was rather high (50%). We explain this fact by the proximity of the amino group in *ortho*-position to the halogeno atom, which assist the formation of the complex of palladium salt followed by the introduction of palladium between carbon and iodine atoms—the first step of the cross-coupling. We had already observed the same trends for other analogous cases.[16]

Our studies on the one-pot synthesis of aryl(hetaryl)alk-1-ynes from iodoarenes(hetarenes) show that target compounds can be prepared in moderate yields (60–75%) for activated iodides and in low yields (15–35%) from halo derivatives with low reactivity. Unusual results were obtained for *o*- and *p*-iodoanilines. For the experimental details of the synthesis as well as physical constants and yields of ethynyl derivatives see Section 2 and Table 1.

2. Experimental

2.1. General procedures

Melting points were determined with a hot-stage microscope. Column chromatography was performed on silica gel (Merck 60, 70–230 mesh). The R_f values were measured on aluminium backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. ^{1}H NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz) spectrometer. Chemical shifts (δ in ppm) are given from internal $CHCl_3$ (7.24 ppm). Coupling constants (J in Hz) are accurate to $\pm$0.2 Hz. Mass spectra (HRMS) were measured at 70 eV using the electron impact mode. Commercially available iodoarenes **2**–**8** ('Aldrich') were used without additional purification. Iodides **1**,[17] **9**,[18] **10**[19] were prepared by previously reported methods. Copper(I) acetylides were prepared from liquid acetylenes (**12**, **17**–**21**) according to the published procedure.[20]

2.2. General procedures of ethynylation

The flask was fitted with a gas inlet tube, thermometer and dropping funnel. After a rubber stopper fitted with a glass tube was tightly placed on the flask, the air was replaced by acetylene (purified from acetone passing through water and then sulfuric acid). The flask was charged with 260 mL of DMF, powdered potassium carbonate (2 g, 15 mmol), $PdCl_2(Ph_3P)_2$ (50 mg) and CuI (25 mg). After the mixture was additionally saturated with acetylene with vigorous stirring, the temperature was raised up to 50 °C and a solution of iodides **1**–**10** (10 mmol) in 30–40 mL of DMF (also previously saturated with acetylene) was slowly added during 5–6 h. Reaction was carried out at 50–55 °C and under a permanent stream of acetylene up to completion of the reaction (TLC control).

After cooling the reaction mixture to room temperature, 700 mL of ether (or 700 mL of chloroform) and then 800–900 mL of water was added. The aqueous layer was extracted twice with ether [or $CHCl_3$ (2×100 mL)]. The combined organic solutions were washed three times with 200 mL of water in order to remove as much as possible of the DMF and were dried over $MgSO_4$. After filtering the solution through a thick layer of neutral Al_2O_3 (3×2 cm) on a sintered-glass funnel, the solvent was removed to dryness under reduced pressure. The desired acetylenes were purified by distillation or by recrystallization. Time of reaction, yields and melting point of compounds are reported in Table 1.

Acknowledgements

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The unusual 1,4-chelation-controlled nucleophilic addition to aldehydes with high stereoselectivity. A systematic study of stereoselectivity in the addition reaction of carbon nucleophiles to *cis*-substituted cyclopropanecarbaldehydes

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Abstract—The addition reaction of carbon nucleophiles to *cis*-substituted cyclopropanecarbaldehydes was systematically investigated. Ab initio calculations of model cyclopropanecarbaldehydes suggested that the bisected *s-cis* and *s-trans* conformers are the only two minimum energy conformers, which are stabilized due to the π-donating stereoelectronic effect of the cyclopropane ring. The experimental results of a series of substrates, that is, cyclopropanecarbaldehydes **1**–**5** bearing a *cis*-(*tert*-butyldiphenylsilyloxy)methyl group, a *cis*-benzyloxymethyl group, a *cis*-(*p*-methoxybenzyloxy)methyl group, *cis*-*N,N*-diethylcarbamoyl and *trans*-phenyl groups, and *cis*-(*tert*-butyldiphenylsilyloxy)-methyl and *trans*-phenyl groups, respectively, showed that highly *anti*-selective Grignard additions could be realized. It turned out that it occurred via an unusual 7-membered 1,4-chelation-controlled pathway. Highly stereoselective Grignard addition via the chelation-controlled pathway occurred even in the reaction of the usually non-chelating silyl ether-type substrate **5**. The results have great importance because the 1,4-chelation-controlled stereoselective addition reactions can indeed be realized. Under non-chelation conditions, the *syn*-products were produced with moderate stereoselectivity, which are likely to be formed via the bisected *s-cis* conformation-like transition state stabilized by the characteristic orbital interaction. These reactions, especially the chelation-controlled reaction, should be useful because of their t stereoselectivity and stereochemical predictability.

1. Introduction

Much attention has been focused on the stereoselective synthesis of cyclopropane derivatives, because cyclopropanes are important as key fragments in many natural products and as synthetic intermediates due to the ease of their ring-opening.[1–4] A cyclopropane ring is also useful for restricting the conformation of biologically active compounds in medicinal chemical studies.[3]

Cyclopropyl ketones and cyclopropanecarbaldehydes, which are useful as synthetic intermediate for various biologically active compounds having a cyclopropane backbone, prefer the bisected *s-trans* and *s-cis* conformations, as shown in Figure 1, due to the characteristic stereoelectronic effects of the cyclopropane ring.[1a,b,5] Highly stereoselective nucleophilic hydride reduction of cyclopropyl ketones[6–8] and addition to cyclopropanecarbaldehydes by carbon nucleophiles[8–10] have been reported,[11] and these stereoselectivities are thought to be related to the characteristic stereoelectronic effect of the cyclopropane ring. We most recently showed that stereoselective hydride reduction of cyclopropyl ketones is explained effectively by the bisected *s-cis*-transition-state reaction model.[7]

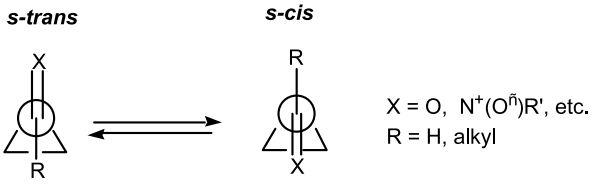

Figure 1. Bisected *s-cis* and *s-trans* conformations of α,β-unsaturated cyclopropanes.

In the course of our studies using a cyclopropane ring for conformational restriction of biologically active compounds,[3,4] we have found that nucleophilic attack of Grignard reagents on the cyclopropanecarbaldehydes **I** occurs highly stereoselectively to give the *anti*-product **III**

Keywords: Aldehydes; Conformational analysis; Cyclopropanes; Diastereoselectivity; Grignard reactions.
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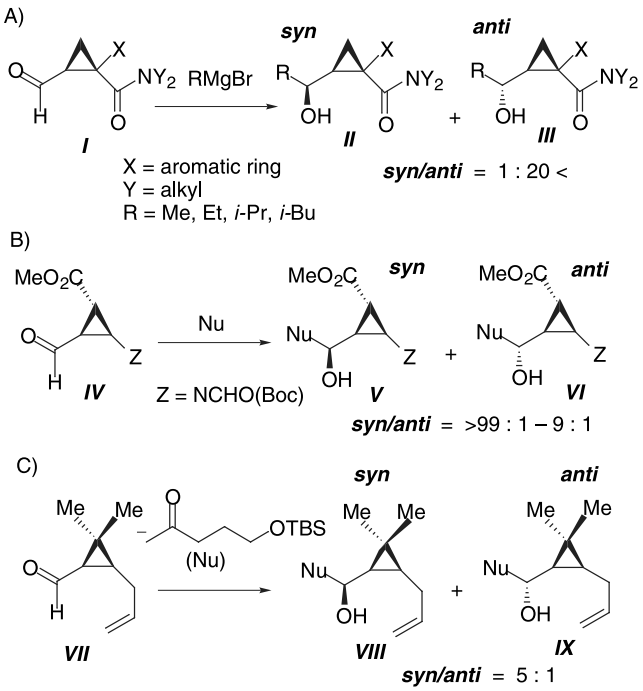
in high yield, as shown in Scheme 1A.[4a–c,8] We initially attributed these highly selective stereochemical results to the bisected-conformational transition state stabilized by the characteristic electron-donating effect of the cyclopropane ring.[8] However, further studies were needed to confirm the reaction mechanism. Thus, in order to clarify the mode of addition of carbon nucleophiles to *cis*-substituted cyclopropanecarbaldehydes in a general way and to develop a versatile method for the highly stereoselective reactions, we performed a systematic study of the addition reaction using a series of cyclopropanecarbaldehyde substrates **1**–**5**, the structures of which are shown in Figure 2. Conformational analysis of the substrates and their model compounds was also performed to clarify the mode of nucleophilic addition reaction to the cyclopropanecarbaldehydes. These studies showed that the highly *anti*-selective Grignard addition to *cis*-substituted cyclopropanecarbaldehydes occurs via an unusual 7-membered 1,4-chelation-controlled pathway.



Scheme 1. Nucleophilic additions to *cis*-cyclopropanecarbaldehydes reported previously.

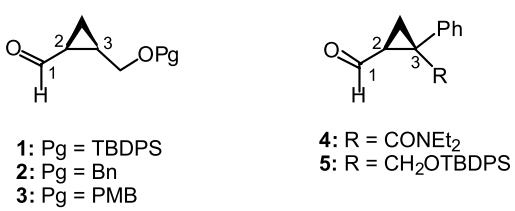


Figure 2. Structurally simplified cyclopropanecarbaldehydes as reaction substrates.

2. Results and discussion

2.1. The previous studies

Only limited examples of nucleophilic additions to cyclopropanecarbaldehydes are known.[8–10,12] As described above, the addition of Grignard reagents to the cyclopropanecarbaldehydes **I** having a phenyl and a carbamoyl group at the *trans* and *cis* positions, respectively, to the formyl group on the cyclopropane ring, occurs highly stereoselectively to produce the corresponding *anti*-alcohol **III** as the major product (Scheme 1A).[8] The stereochemical results in the reaction were explained by the nucleophilic attack occurring from the less hindered face of the substrates in the bisected *s-trans* conformation, as shown in Figure 3A.[8] The previous studies showed that cyclopropanecarbaldehydes preferentially exist in the bisected *s-trans* and the *s-cis* conformation,[5] and the X-ray crystallographic analysis of the aldehyde **I** (X=Ph, Y=Et) actually

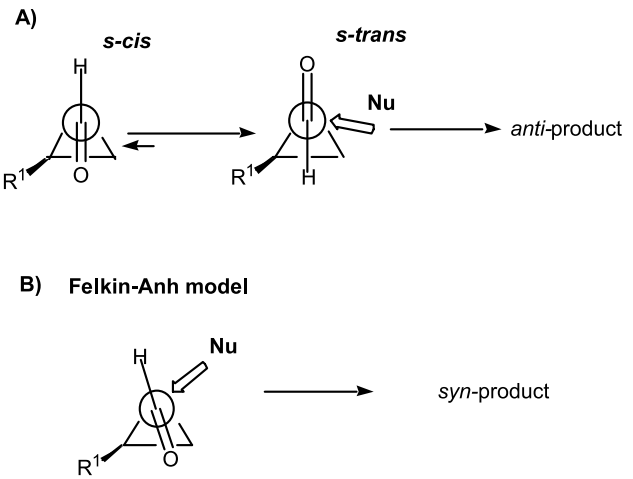


Figure 3. Conceivable reaction pathways of the nucleophilic attack on cyclopropanecarbaldehydes.

showed that it assumes the bisected *s-trans* conformation in the solid state.[8b]

After publication of our results, Reiser and co-workers reported very efficient reactions that nucleophilic addition reaction to the 2,3-disubstituted cyclopropanecarbaldehyde **IV** occurred highly stereoselectively (Scheme 1B).[10] Because the substrate was unstable under basic conditions, they investigated Lewis acid-promoted addition reactions with organo-silicon nucleophiles and also nitroaldol reactions, as summarized in Table 1. Surprisingly, the stereochemical outcome was opposite to that in our above described case. For example, when **IV** was subjected to the reaction with $CH_2{=}CHCH_2TMS/BF_3{\cdot}OEt_2$, the corresponding *syn*-alcohol was produced almost exclusively. They concluded that the stereoselectivity could be explained by the Felkin–Anh model, as shown in Figure 3B. They summarized the Felkin–Anh-type reactions in an excellent review and suggested that the *anti*-selective stereocontrol in our studies (Scheme 1A) would occur via a chelation-controlled pathway.[10b] However, we initially thought this unlikely since highly stereoselective addition to carbonyls via such a 7-membered chelation-controlled pathway was unknown.[10b,13–15]

On the other hand, Dauben and co-workers reported that the aldol reaction with a cyclopropanecarbaldehyde **VII** was moderately stereoselective to give a *syn*/*anti*-mixture in a 5:1 ratio (Scheme 1C).[9]

Table 1. Nucleophilic additions to the 2,3-di-substituted cyclopropanecarbaldehydes **IV** reported by Reiser and co-workers[10]

Substrate	Nucleophile	Promoter	Solvent	Temp (°C)	Yield (%)	*Syn*/*anti*
IV	$TMSCH_2CH_2{=}CH$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	92	99:1
IV	$CH_2{=}CH(Ph)OTMS$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	71	99:1
IV	TMSCN	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	94	9:1
IV	TMSCN	none	CH_2Cl_2	25	100[a]	10:1
IV	*i*-$PrNO_2$ (solvent)	Et_3N	—	0	91[b]	99:1

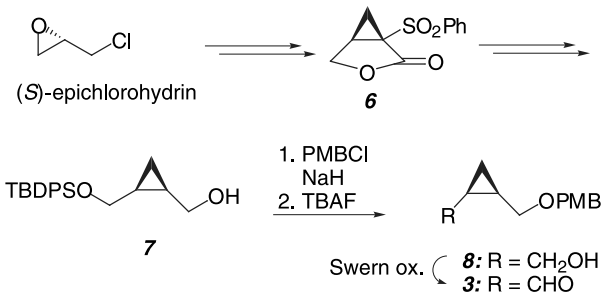
[a] The corresponding *O*-TMS ether products were obtained.
[b] The *N*-formyl group migrated to the hydroxyl.

As stated above, the stereochemical outcome of the nucleophilic additions to the *cis*-substituted cyclopropanecarbaldehydes is significantly different depending on the structure of substrates and the reaction conditions used, and therefore the reaction mechanisms have not been clearly understood.

2.2. Design and synthesis of the structurally simplified substrates

The substrates used in the previous studies possessed different functional groups, which could affect the stereochemical results, at least to some extent. Furthermore, the nucleophiles and the reaction conditions employed in these studies were quite different. We planned to perform a systematic study of the reactions using structurally simplified substrates to clarify the mode of nucleophilic addition to the cyclopropanecarbaldehydes.

Thus, we designed the structurally simplified substrates, the cyclopropanecarbaldehyde bearing a *cis*-(*tert*-butyldiphenylsilyl (TBDPS) oxy)methyl group (**1**) and its *O*-benzyl- and *O*-*p*-methoxybenzyl (PMB)-protected congeners **2** and **3**, for investigating the reactions under various conditions. We used these substrates in an optically active form, since the stereochemistries of the resulting secondary alcoholic products should be easily determined by the modified Mosher's method.[16] The substrates **1** and **2** were synthesized from chiral epichlorohydrins according to the method recently developed in our laboratory.[3,7] The *O*-PMB-protected substrate **3** was synthesized from (*S*)-epichlorohydrin via the key intermediate **6**, as shown in Scheme 2.



Scheme 2. Preparation of the *O*-PMB-protected substrate **3**.

2.3. Conformational analysis of the substrates

The X-ray crystallographic structure of the *O*-TBDPS-protected substrate **1**[17] shows that **1** exists in the bisected

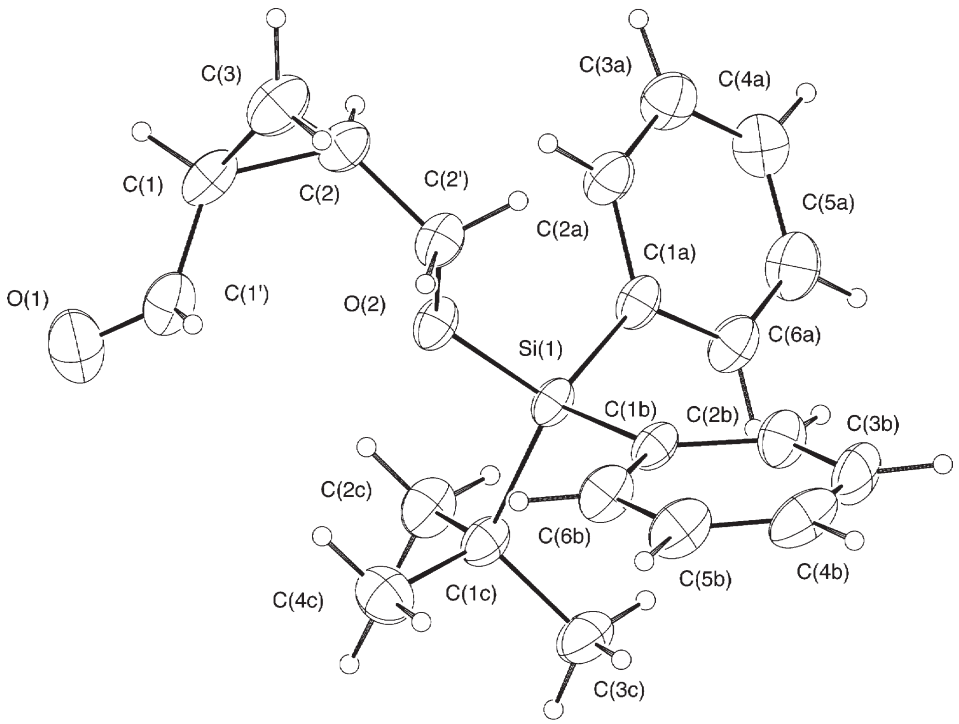


Figure 4. X-ray crystallographic structure of **1**.

s-trans conformation in the solid state (Fig. 4). The conformation of **1** in solution was also investigated by NOE experiments in CD_2Cl_2 at −78 °C. When the formyl proton was irradiated, NOEs were observed at H-4 (2.7%), attached to the position *cis* to the formyl moiety on the cyclopropane ring, and at the silyloxymethylene proton (2.2%) oriented on the concave side, as shown in Figure 5A. An NOE (5.4%) was also observed at the formyl proton by the irradiation of the concave proton in the silyloxymethylene group (Fig. 5B). Thus, there is no discrepancy between the NOE data and the results of the X-ray analysis which would indicate that the cyclopropanecarboxaldehyde **1** prefers the bisected *s-trans* conformation.

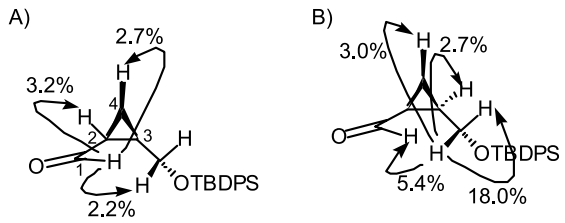


Figure 5. NOE experimental data of **1** (500 MHz, CD_2Cl_2, −78 °C).

Moreover, the conformation of the cyclopropanecarbaldehydes was studied using model compounds, that is, cyclopropanecarbaldehyde (**i**) and *cis*−3-methylcyclopropanecarbaldehyde (**ii**) (Fig. 6), by ab initio calculations based on the density functional theory (DFT) using the GAUSSIAN98 program.[18] We calculated the rotational barrier around the O_1–C_1–C_2–H_2 dihedral angle in the model compounds. The dihedral angle was rotated from 0 to 360° at 20° intervals, and the conformations were optimized at RHF/3-21G(d). The single point energies of each optimized conformer were calculated at RB3LYP/6-231G(d). The results are shown in Figure 7. The minimum energy values were observed around 0° (360°) and 180° for **i**, and around 0° (360°) and 190° for **ii**, where they assume the bisected *s-trans* and *s-cis* (or *s-cis*-like) conformations, respectively. The maximum values are observed around the angles at 90 and 270° for both, where they are in perpendicular conformations. The bisected conformers at 0 or 180° (or 190°) are 6–7 kcal/mol more stable than the perpendicular conformers at 90 or 270° in the model compounds.

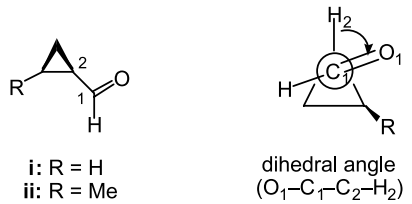


Figure 6. Cyclopropanecarbaldehydes as the model compounds for the calculation studies.

Next, the bisected *s-cis* and *trans* conformers of **i** and **ii** were fully optimized at a higher level of theory using RB3LYP/6-31G(d), and the obtained stable conformations and their relative energies calculated by RB3LYP/6-31G(d) are shown in Figure 8. The calculations showed that while the *s-cis* conformer is more stable than the corresponding *s-trans* conformer in cyclopropanecarbaldehyde (**i**), while the energy difference is insignificant (Δ 0.42 kcal/mol). When a methyl group is introduced into the position *cis* to the formyl group of **i**, that is, **ii**, the *s-cis*-conformation becomes somewhat more stable (*Δ* 1.25 kcal/mol). However, the energy difference between the two bisected *s-cis* and *s-trans* conformers is small in both **i** and **ii**, which is in accord with the previous experimental and theoretical calculation results of the cyclopropanecarbaldehydes.[5h]

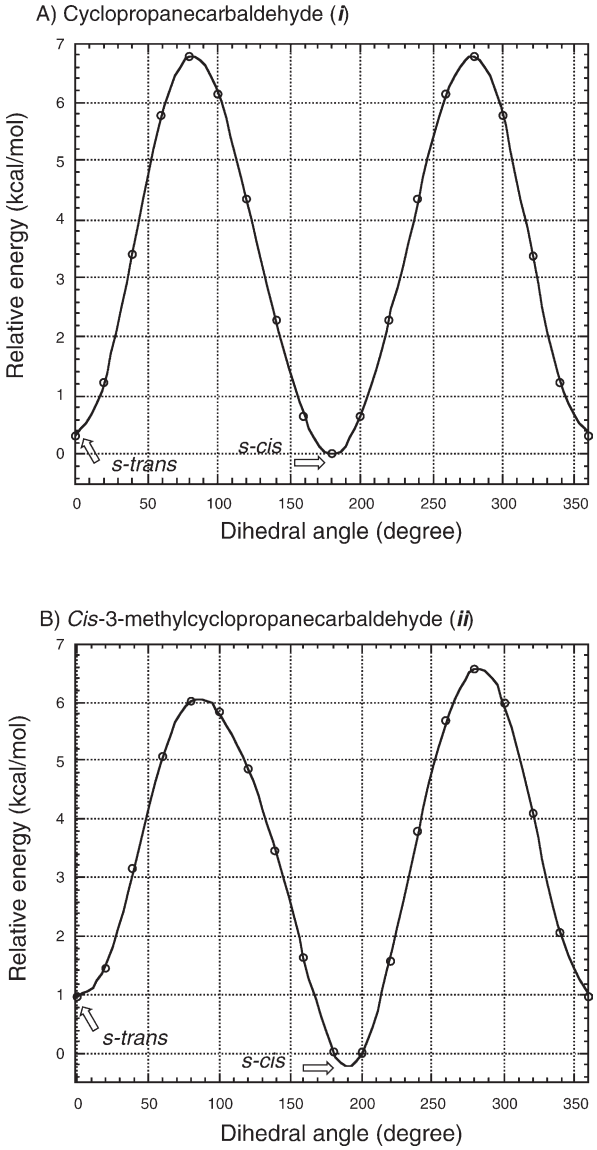


Figure 7. Rotational barrier energies around the O_1–C_1–C_2–H_2 dihedral angle of the model compounds **i** and **ii**.

2.4. Grignard reactions of the structurally simplified substrates[19]

Using the *O*-TBDPS-protected substrate **1**, the Grignard reactions were examined with Me–, Et–, *i*-Bu–, or CH_2═$CHCH_2MgBr$ in CH_2Cl_2 or THF at −78 °C (Scheme 3), and the results are summarized in Table 2. These reactions gave a mixture of the addition products **9a–d** and **10a–d**[20,21] with small to moderate stereoselectivities. These data were clearly different from both

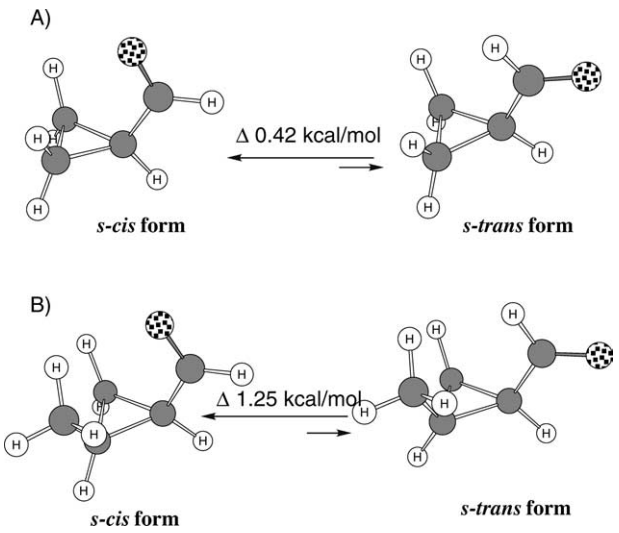
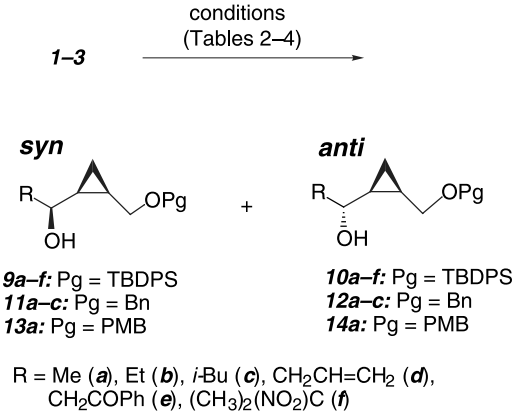


Figure 8. Structures of the minimum energy *s-cis*- and *s-trans*-conformers and their relative energies obtained by the ab initio calculations of the model compound **i** (A) and **ii** (B).



Scheme 3. Nucleophilic additions to the *cis*-cyclopropanecarbaldehydes **1**–**3**.

of the highly *anti*-selective additions in our previous results[8] and the highly *syn*-selective ones of Reiser.[10] It may be important that the stereoselectivity changed depending on the reaction solvent; slightly *anti*-selective in CH_2Cl_2 (entries 1–4, *syn*/*anti*=1:1.3–1:2.0), but moderately *syn*-selective in THF (entries 5–8, *syn*/*anti*=2.3:1–4.2:1).

The effect of additives on the Grignard reaction was next investigated in CH_2Cl_2 (Table 3). The Grignard reactions of the *O*-TBDPS-protected substrate **1** with MeMgBr were first carried out in the presence of a variety of additives (entries 1–5). The reactions with $BF_3{\cdot}OEt_2$, $AlCl_3$, or HMPA as the additive were almost non-stereoselective (entries 1, 2, and 5), similar to the above mentioned reaction without an additive (Table 2, entry 1). However, addition of $ZnBr_2$ or $TiCl_4$, which is known to form a chelate effectively with oxygen atoms,[13] to the Grignard reaction system produced the *anti*-alcohol **10a** as the major product with moderate selectivity (entries 3 and 4, *syn*/*anti*=1:3.1 and 1:2.8). When the *O*-benzyl-protected substrate **2** was used, the reaction selectively gave the *anti*-alcohol **12a**[20] without any additives (entry 6, *syn*/*anti*=1:4.3). By employing the *O*-benzyl substrate **2** the effect of $ZnBr_2$ as the additive was further enhanced to improve the stereoselectivity (entry 7, *syn*/*anti*=1:7.2). The *anti*-alcohol **12a** seemed to be produced via the chelation-controlled pathway, since the *anti*-selectivity disappeared in the presence of HMPA (entry 8, *syn*/*anti*=1.3:1). The chelation-controlled pathway was supported by the results with the *O*-PMB-protected substrate **3**, where the *anti*-selectivity was further improved (entry 9, without additive, *syn*/*anti*=1:5.7; entry 10, with $ZnBr_2$, *syn*/*anti*=1:9.3)[22] compared with those of the *O*-benzyl-substrate **2** (entries 6 and 7), probably due to the effective chelate formation for the electron-donating *p*-methoxy group. The reactions with EtMgBr or *i*-BuMgBr instead of MeMgBr under the conditions using $ZnBr_2$ as the additive also stereoselectively produced the corresponding *anti*-alcohols as the major product (entries 11–14); the *O*-Bn-protected substrate **2** showed high stereoselectivity (entries 12 and 14, *syn*/*anti*=1:10 and 1:20),[22] while the selectivity in the *O*-TBDPS-protected substrate **1** was moderate (entries 11 and 13, *syn*/*anti*=1:3.0 and 1:5.9).

2.5. Lewis acid-promoted addition and nitroaldol reaction of the structurally simplified substrates

The Lewis acid-promoted addition and nitroaldol reaction, which were employed in the previous studies by Reiser and co-workers,[10] were next examined. The reactions were carried out using the *O*-TBDPS-protected substrate **1**, and the results are shown in Table 4. Treatment of substrate **1** with $CH_2{=}CHCH_2TMS$ in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C gave a mixture of the corresponding *syn* and *anti*-products **9d** and **10d** in a 7.3:1 ratio (entry 1). Similar treatment of **1** with $CH_2{=}C(Ph)OTMS$ as the nucleophile was non-stereoselective (entry 2).[21] These results were in contrast to the highly *syn*-selective results

Table 2. Addition reactions of Grignard reagents to the cyclopropanecarbaldehyde **1**: effect of solvent[a]

Entry	Substrate	Pg	Nucleophile	Solvent	Time (h)	Products	Yield (%)	*Syn*/*anti*[b]
1	**1**	TBDPS	MeMgBr	CH_2Cl_2	5	**9a**, **10a**	95	1:1.3
2	**1**	TBDPS	EtMgBr	CH_2Cl_2	5	**9b**, **10b**	77 (23)[c]	1:1.5
3	**1**	TBDPS	*i*-BuMgBr	CH_2Cl_2	8	**9c**, **10c**	54 (42)[c]	1:2.0
4	**1**	TBDPS	$CH_2{=}CHCHMgBr$	CH_2Cl_2	8	**9d**, **10d**	81	1:1.7
5	**1**	TBDPS	MeMgBr	THF	3	**9a**, **10a**	94	2.3:1
6	**1**	TBDPS	EtMgBr	THF	3	**9b**, **10b**	84	2.8:1
7	**1**	TBDPS	*i*-BuMgBr	THF	8	**9c**, **10c**	99	4.2:1
8	**1**	TBDPS	$CH_2{=}CHCHMgBr$	THF	8	**9d**, **10d**	87	2.5:1

[a] Reaction was performed with 2 equiv. of Grignard reagent at −78 °C. A trace of other solvent, toluene/THF in entry 1, Et_2O in entries 2, 4, 6 and 8, and THF in entries 3 and 8, was included in the reaction system: see Section 3.
[b] Determined by ^1H NMR.
[c] Yield of the substrate recovered is given in parenthesis.

Table 3. Addition reactions of Grignard reagents to the cyclopropanecarbaldehydes **1**–**3**: effect of additives[a]

Entry	Substrate	Pg	Nucleophile	Additive	Time (h)	Products	Yield (%)	*Syn*/*anti*[b]
1	**1**	TBDPS	MeMgBr	$BF_3{\cdot}OEt_2$	3	**9a**, **10a**	85 (15)[c]	1.4:1
2	**1**	TBDPS	MeMgBr	$AlCl_3$	5	**9a**, **10a**	53 (37)[c]	1:1.5
3	**1**	TBDPS	MeMgBr	$ZnBr_2$	8	**9a**, **10a**	99	1:3.1
4	**1**	TBDPS	MeMgBr	$TiCl_4$	3	**9a**, **10a**	98	1:2.8
5	**1**	TBDPS	MeMgBr	HMPA	8	**9a**, **10a**	82 (18)[c]	1:1.1
6	**2**	Bn	MeMgBr	none	5	**11a**, **12a**	71 (23)[c]	1:4.3
7	**2**	Bn	MeMgBr	$ZnBr_2$	8	**11a**, **12a**	92	1:7.2
8	**2**	Bn	MeMgBr	HMPA	8	**11a**, **12a**	58 (42)[c]	1.3:1
9	**3**	PMB	MeMgBr	none	5	**13a**, **14a**	75 (19)[c]	1:5.7
10	**3**	PMB	MeMgBr	$ZnBr_2$	5	**13a**, **14a**	95	1:9.3
11	**1**	TBDPS	EtMgBr	$ZnBr_2$	5	**9b**, **10b**	80 (19)[c]	1:3.0
12	**2**	Bn	EtMgBr	$ZnBr_2$	8	**11b**, **12b**	64 (30)[c]	1:10
13	**1**	TBDPS	*i*-BuMgBr	$ZnBr_2$	8	**9c**, **10c**	86	1:5.9
14	**2**	Bn	*i*-BuMgBr	$ZnBr_2$	8	**11c**, **12c**	91	1:20

[a] Reaction was performed with 2 equiv. of Grignard reagent and 2 equiv. of additive in CH_2Cl_2 at −78 °C. A trace of other solvent, toluene/THF in entries 1–10, Et_2O in entries 11 and 12, and THF in entries 13 and 14, was included in the reaction system: see Section 3.
[b] Determined by ^1H NMR.
[c] Yield of the substrate recovered is given in parenthesis.

Table 4. Lewis acid-promoted and nitroaldol-type nucleophilic addition reactions to the cyclopropanecarbaldehyde **1**[a]

Entry	Substrate	Pg	Nucleophile	Promoter	Solvent	Temp (°C)	Time (h)	Products	Yield (%)	*Syn*/*anti*[b]
1	**1**	TBDPS	$CH_2{=}CHCH_2TMS$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	48	**9d**, **10d**	93	7.3:1
2	**1**	TBDPS	$CH_2{=}C(Ph)OTMS$	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	2	**9e**, **10e**	84 (4)[c]	1:1.1
3	**1**	TBDPS	*i*-$PrNO_2$ (solvent)	Et_3N	—	rt	340	**9f**, **10f**	80 (10)[c]	1:1.0

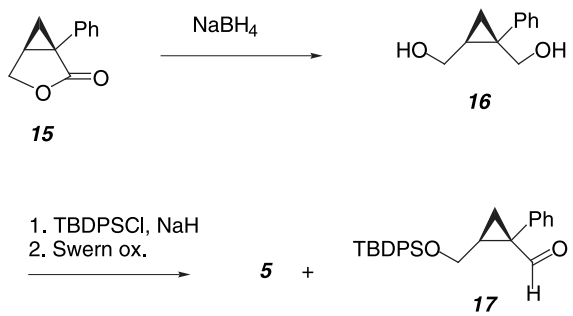
[a] Reaction was performed with 8 equiv. of nucleophile and 3 equiv. of promoter (entry 1), 1 equiv. of nucleophile and 1 equiv. of promoter (entry 2), or 1 equiv. of promoter (entry 3).
[b] Determined by ^1H NMR.
[c] Yield of the substrate recovered is given in parenthesis.

by Reiser and co-workers (Table 1, entries 1 and 2, *syn*/*anti*=99:1). On the other hand, in the nitroaldol reaction of **1** with an *i*-$PrNO_2/Et_3N$ the *syn*/*anti* ratio was changed depending on the reaction time, and it gave a 1:1 *syn*/*anti*-mixture of the addition product after 14 days. This is because the stereochemical outcome in the nitroaldol reaction is not kinetically controlled under the reaction conditions.[23]

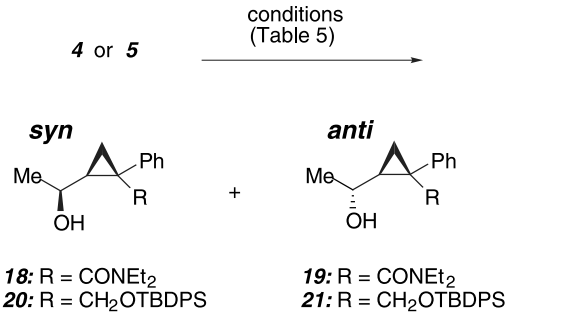
2.6. Reaction of the *trans*-phenyl-substituted substrates

We previously speculated that the highly *anti*-selective additions of Grignard reagents to the cyclopropanecarbaldehydes **I** would occur via the bisected *s-trans*-pathway.[8] However, the above-mentioned stereochemical results with the structurally simplified cyclopropanecarbaldehydes **1**–**3** in the present study suggest that the *anti*-products would not be formed via the bisected *s-trans* but rather via the chelation-controlled pathway, as suggested by Reiser.[10b] To confirm the reaction mechanism, we planned to examine the reactions further with the *trans*-phenyl-substituted substrate **4** used in the previous studies[8] and its related substrate **5**, in which the carbamoyl group of **4** was replaced with a TBDPS–O–CH_2-group. Substrate **5** was prepared from the known lactone **15**, as shown in Scheme 4.

The reactions were performed with MeMgBr or Me_3Al as the nucleophile and the effect of HMPA and $ZnBr_2$ on the reaction was investigated (Scheme 5). The results are summarized in Table 5. The effect of HMPA on the stereoselectivity of the reaction was first investigated. In the Grignard reaction of the carbamoyl-type substrate **4** with MeMgBr in the presence of excess (10 equiv.) of HMPA in THF, the *anti*-selectivity was somewhat lower (entry 3, *syn*/*anti*=1:15) compared with reactions without HMPA



Scheme 4. Preparation of the *O*-TBDPS-protected substrate **5**.



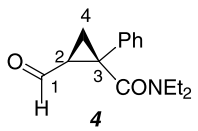
Scheme 5. Nucleophilic additions to the *cis*-cyclopropanecarbaldehydes **4** and **5**.

Table 5. Addition reactions of MeMgBr or Me_3Al to the cyclopropanecarbaldehydes **4** and **5**[a]

Entry	Substrate	R	Nucleophile	Additive	Solvent	Temp (°C)	Time (h)	Products	Yield (%)	*Syn*/*anti*[b]
1[c]	**4**	$CONEt_2$	MeMgBr	None	THF	−20	2	**18**, **19**	95	1:23
2	**4**	$CONEt_2$	MeMgBr	None	CH_2Cl_2	−20	2	**18**, **19**	67 (29)[d]	1:24
3	**4**	$CONEt_2$	MeMgBr	HMPA	THF	−20	2	**18**, **19**	81 (10)[b]	1:15
4	**4**	$CONEt_2$	MeMgBr	HMPA		−20	2	**18**, **19**	77	1:3.9
5	**4**	$CONEt_2$	MeMgBr	None	THF	66	2	**18**, **19**	78 (19)[b]	1:24
6	**4**	$CONEt_2$	Me_3Al	None	THF	66	12	**18**, **19**	62 (6)[b]	1:2.8
7	**4**	$CONEt_2$	MeMgBr	$ZnBr_2$	CH_2Cl_2	−20	2	**19**	48 (49)[b]	*Anti* only
8	**5**	$CH_2OTBDPS$	MeMgBr	None	THF	−78	8	**20**, **21**	85 (12)[b]	2.8:1
9	**5**	$CH_2OTBDPS$	MeMgBr	None	CH_2Cl_2	−78	8	**20**, **21**	77 (14)[b]	1.3:1
10	**5**	$CH_2OTBDPS$	MeMgBr	$ZnBr_2$	CH_2Cl_2	−78	8	**21**	93	*Anti* only

[a] Reaction was performed with 2 equiv. of a nucleophile and 10 equiv. (entry 3) or 2 equiv (entries 7 and 10) of additive. A trace of other solvent, toluene/THF in entries 2, 7, 9 and 10, and hexane in entry 6, was included in the reaction system: see Section 3.
[b] Determined by ^1H NMR.
[c] The data were taken from Ref. 8b.
[d] Yield of the substrate recovered is given in parenthesis.

Table 6. ^{13}C NMR chemical shifts (δ) of the substrate **4** in the absence or the presence of $ZnBr_2$ (1 equiv.)[a]



4

	C1	C2	C3	C4	CON	NCH_2	CH_3	Ph
4	198.3	37.4	40.7	20.0	167.7	40.0, 42.0	12.5, 13.1	126.3, 127.8, 129.3, 138.6
4+$ZnBr_2$	—[b]	37.4	41.4	24.1	171.9[c]	43.9, 44.9	12.4, 12.7	127.7, 129.3, 129.9, 135.0
$\Delta\delta$[d]	—	0	−0.7	−4.1	−4.2	−3.9, −2.8	+0.1,+0.4	

[a] Measured at 100 MHz in CD_2Cl_2 at room temperature.
[b] Not detected.
[c] Observed as a broad peak.
[d] δ (**4**)−δ (**4**+$ZnBr_2$).

(entries 1 and 2, *syn*/*anti*=1:23 and 1:24). When HMPA was used as the reaction solvent, the *anti*-selectivity clearly decreased to give a *syn*/*anti*-mixture of **18** and **19** in a 1:3.9 ratio (entry 4). Reactions with Me_3Al, a relatively ineffective chelate-forming agent compared with Grignard reagents, was next carried out. Although the reaction did not proceed at room temperature, the addition products were obtained with low *anti*-selectivity (entry 6, *syn*/*anti*=1:2.8) by heating **4** with Me_3Al in THF under reflux. On the other hand, similar heating of **4** with MeMgBr as the nucleophile again gave the *anti*-product highly selectively (entry 5, *syn*/*anti*=1:24). When $ZnBr_2$ was used as the additive in the Grignard reaction, as in the above cases, the stereoselectivity effectively increased to give the *anti*-alcohol **19** as the sole product (entry 7).

The reactions of the silyloxymethyl-type substrate **5** were next investigated. In contrast to the high-*anti*-selectivity in the case of **4** (entries 1 and 2), the Grignard reaction of **5** without an additive was almost non-stereoselective (entries 8 and 9, *syn*/*anti*=2.8:1 and 1.3:1). However, when $ZnBr_2$ was present with MeMgBr in the reaction system, the stereoselectivity was dramatically improved to furnish the *anti*-product **21** exclusively in high yield (entry 10).[21]

We measured the ^{13}C NMR spectrum of the carbamoyl-type substrate **4** in the presence of 1 equiv. of $ZnBr_2$ and compared the data with those of **4** without the additive. As shown in Table 6, in the presence of $ZnBr_2$, clear down-field shifts of the CO and the NCH_2 signals of the carbamoyl moiety of **4** were observed, which suggests that coordination of Zn^{2+} to the carbamoyl CO occurs during the course of the reaction.

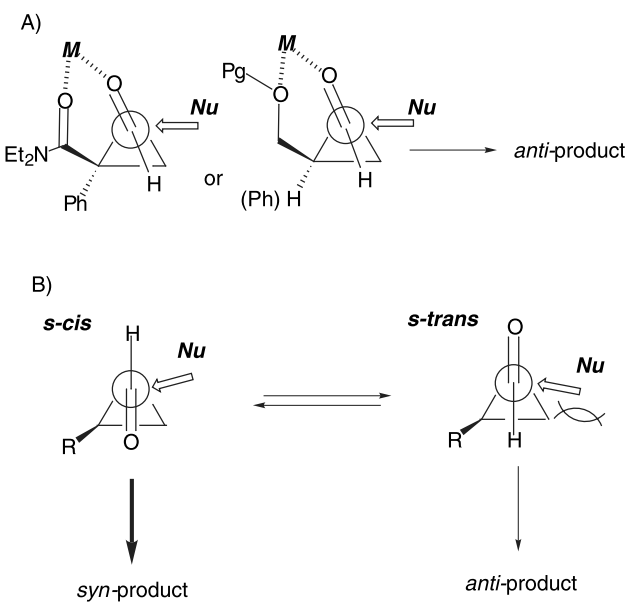


Figure 9. Reaction mechanisms proposed for nucleophilic addition to cyclopropanecarbaldehydes via the chelation-controlled pathway (A) and the bisected conformation-controlled pathway (B).

The above described results clearly show that in the case of the carbamoyl-type substrates **I** (in Scheme 1A) the *anti*-products are not formed via the bisected pathway but rather via the unusual 7-membered 1,4-chelation-controlled pathway, as shown in Figure 9A.

2.7. Discussion

In this study, the stereoselectivity in nucleophilic addition reactions to the *cis*-substituted cyclopropanecarbaldehydes was investigated experimentally in a systematic manner, where a series of structurally simplified substrates was used to make the results easy to be interpreted. The conformations of the substrates, which are very important for considering the mode of the reactions, were also analyzed. Therefore, the results obtained from this study would contribute to the understanding of the reaction pathways.

The conformation of the transition state and the intermediate can be strongly influenced by conformational effects, which stabilize the ground state conformation.[24] In nucleophilic additions to cyclopropanecarbaldehydes, the conformations of the transition state and the ground state may be similar for the following characteristic stereoelectronic reason. Cyclopropanecarbaldehydes prefer the bisected *s-cis* and/or *s-trans* conformations. With the Walsh model,[25] which is effective for understanding the conjugating ability of the cyclopropane ring, this conformational stability is explained by effective interaction between the p-orbitals on the cyclopropyl carbon and the adjacent π^* (C=O) orbital because of their planar arrangement.[1a,b,5h] We calculated the rotational barrier around the $H_2-C_2-C_1-O_1$ dihedral angle on the model cyclopropanecarbaldehydes. The calculations showed that the bisected *s-cis* (or *s-cis* like) and *s-trans* conformers are the only two minimum energy conformers, in which the orbital interaction effectively lowers the energy of the compounds. Such orbital interaction should also stabilize the transition state of the nucleophilic attack, as shown in Figure 10. In the course of the attack, the p-orbital on the cyclopropyl carbon, which can be characterized as a strong π-donor,[1a,b,5h] interacts with the antibonding orbital ($\sigma^{*\neq}$) of the electron-deficient incipient bond between the nucleophile and the carbonyl carbon. The p-$\sigma^{*\neq}$ orbital interaction is maximized in the bisected conformation, in which the orbitals of the newly

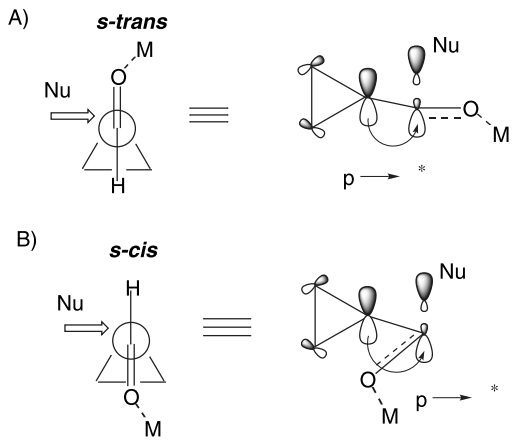


Figure 10. The transition state model for the nucleophilic attack on the cyclopropanecarbaldehydes: *s-trans* (A) and *s-cis* (B).

forming bond and the cyclopropane C–C bond are in an almost planar arrangement. This kind of transition state stabilization in nucleophilic attack on carbonyl carbons by the antibonding orbital interaction is well known as the Cieplak theory.[26] Accordingly, we initially speculated that it was possible for the nucleophilic addition to cyclopropanecarbaldehydes to occur via the attack on the less hindered side of the bisected *s-cis* and/or *s-trans*-conformation.

The stereoselectivity in the Grignard reaction of the *O*-TBDPS-protected substrate **1** without an additive was low, as summarized in Table 2. Ab initio calculations showed that the bisected *s-cis*- (or *s-cis* like) and *s-trans* conformers are quite stable compared with the other conformations. Although the X-ray and NOE analyses of the substrate **1** suggested that it might prefer the *s-trans* conformation, ab initio calculations with the model compounds in this study and the previous experimental and theoretical calculation studies[5] indicated that the energy difference between the two conformers was rather small. This may account for the low stereoselectivity in the nucleophilic addition to cyclopropanecarbaldehydes under non-chelation conditions. Nucleophilic attacks on carbonyl carbons are known to occur at an angle of about 109°,[27] and the trajectory of the nucleophile to the *s-trans* conformer could be interfering with the cyclopropane ring, as shown in Figure 9B.[10b] Therefore, the reaction via the *s-cis* intermediate might be preferred to give selectively the *syn*-product **9a** in the reactions using THF as the reaction solvent (Table 2, entries 5–8), although the selectivity was not high. In the reactions with non-Lewis basic CH_2Cl_2 as the solvent, the *anti*-product via the chelation-controlled pathway might have increased at least to some extent, compared with the reactions in Lewis basic THF, to result in the somewhat *anti*-selective outcome (Table 2, entries 1–4). The Lewis acid-promoted allylation with $CH_2{=}CHCH_2$-TMS of **1** occurred with considerable *syn*-selectivity (*syn*/*anti*=7.3:1, Table 4, entry 1), compared to the allylation using the Grignard reagent (*syn*/*anti*=1:1.7 and 2.5:1, Table 2, entries 4 and 8). Although both $CH_2{=}CHCH_2TMS$ and $CH_2{=}CHCH_2MgBr$ are known to react with aldehydes at the γ-position, the reaction transition state with the former reagent would be more electron deficient.[28] Therefore, the bisected *s-cis* and *s-trans* transition states in the Lewis acid-promoted allylation could be effectively stabilized by the p-$\sigma^{*\neq}$ hyperconjugation due to the strong electron-donating feature of the cyclopropane ring, where the nucleophilic attack to the *s-cis* would be preferred because of the above described steric reason, as shown in Figure 9B, to result in the *syn*-selective outcome.

In contrast to these results, nucleophilic hydride reduction of cyclopropyl ketones with a *cis*-substituent occurs highly stereoselectively, which can be explained by the bisected *s-cis* transition state reaction model.[7] The different stereoselectivities would be dependent on the relative stability of the bisected *s-cis* and *s-trans* conformations: the *s-cis* and the *s-trans* have similar stability in the aldehydes, whereas the *s-cis* is significantly more stable than the *s-trans* in the ketones.[7]

The reactions using a variety of additives demonstrated that

use of effective chelation forming Lewis acids, such as $TiCl_4$ or $ZnBr_2$, increased the amount of the *anti*-products, as summarized in Table 3. The oxygen of the *O*-Bn group is known to form a chelate more efficiently than the oxygen of *O*-silyl groups.[13] Thus, the effect of $ZnBr_2$ was significantly increased when the *O*-Bn or *O*-PMB protected substrates **2** and **3** were used. These results suggest that the *anti*-products can be selectively obtained in the nucleophilic additions to cyclopropanecarbaldehydes via the 7-membered 1,4-chelation-controlled pathway.

The chelating additive $ZnBr_2$ was again effective in the reactions with the phenyl-substituted substrates **4** and **5** (Table 5). Under non-chelation conditions, typically seen when HMPA was used as the solvent (entry 4), the stereoselectivity of the nucleophilic addition to the carbamoyl-type substrate **4** was low. However, the substrate **4** seems to chelate quite effectively with the Grignard reagent to give the *anti*-product highly selectively. The Grignard reaction of **4** gave the chelation-controlled *anti*-product selectively even in the presence of 10 equiv. of HMPA (entry 3). When the carbamoyl group was replaced with a CH_2O-TBDPS group, the chelating ability of the substrate was diminished dramatically (entries 8 and 9, *syn*/*anti*=2.8:1 and 1.3:1, respectively), whereas addition of $ZnBr_2$ to the Grignard reaction system of the *O*-TBDPS substrate **5** resulted in complete *anti*-selectivity via the chelation-controlled pathway. The stereoselectivity-improving effect of the *trans*-phenyl substituent on the cyclopropane ring in **4** or **5** is significant because the corresponding des-phenyl substrate **1**, in contrast, showed only low *anti*-selectivity (Table 3, entry 3, *syn*/*anti*=1:3.1) under the same $MeMgBr/ZnBr_2/CH_2Cl_2$ conditions. The phenyl group, probably due to steric demand, may restrict the three-dimensional location of the CH_2O-TBDPS or $CONEt_2$ group attached to the same carbon in the cyclopropane ring to facilitate chelate formation. These results suggest that not only the substituent at the position *cis* but also the substituent at the position *trans* to the formyl group can significantly affect the stereoselectivity in nucleophilic additions to cyclopropanecarboxaldehydes. A number of studies on 1,2- and 1,3-chelations have demonstrated the non-chelating nature of the silyl ether oxygen.[13] However, surprisingly, the highly stereoselective chelation-controlled Grignard addition occurred in the *O*-TBDPS-protected substrate **5** via the unusual 7-membered 1,4-chelation pathway.

The present study showed that, in the nucleophilic additions to the *cis*-substituted cyclopropanecarbaldehydes, the high *anti*-selectivity can be realized via the 7-membered chelation-controlled pathway. Although a number of highly stereoselective additions to carbonyl compounds via 5- and 6-membered chelation-controlled pathways are known, there is no precedent for such a highly stereoselective addition reaction via a 7-membered 1,4-chelation-controlled pathway.[10b,13–15] The *cis*-substituted cyclopropane structure seems to facilitate formation of the unusual 7-membered chelate.

On the other hand, under non-chelation conditions, the *syn*-products were produced in moderate selectivity, which is in accord with the previous moderate *syn*-selective results by Dauben (Scheme 1C).[9] However, these are in contrast to the highly *syn*-selective results obtained by Reiser using the substrate **IV** (Scheme 1B and Table 1).[10] We initially speculated that the different stereoselectivity might be due to the different reaction conditions used in the two studies, for example, the Grignard reactions and the Lewis acid-promoted reactions with silicon nucleophiles. Therefore, the reactions of our simplified substrate **1** under conditions similar to those used by Reiser[10c] were next examined. However, the Lewis acid-promoted nucleophilic additions to **1** were moderate or almost non-stereoselective, as summarized in Table 4. The X-ray crystallographic analysis of **IV** showed that it assumes the bisected *s-cis* conformation in the solid state, where the adjacent *C*-formyl carbonyl and the *N*-formyl carbonyl groups are in the antiparallel arrangement due probably to stereoelectronic reasons.[10c] The substrate **IV** also has unusually high reactivity as an electrophile; it smoothly reacted with TMSCN without any promoter to give the corresponding addition products in high yields, and its nitroaldol product was obtained as the *N*-formyl-migrated *O*-formate.[10c] These results suggest that the substrate **IV** may be a unique cyclopropanecarboxaldehyde, which is very stable and which is also particularly reactive to nucleophiles in the *s-cis* conformation. This may explain why the reaction of **IV** proceeds with exceptionally high stereoselectivity, while stereoselectivity in non-chelation-controlled additions to carbonyl compounds are usually not so high.[13]

We consider that reactions under non-chelation-controlled conditions likely proceed mainly via the bisected conformation-like transition state stabilized by the characteristic orbital interaction described above. However, the *syn*-selective stereochemical results of the nucleophilic additions are also in accord with those predicted by the Felkin–Anh model, as described by Reiser and co-workers.[10] Therefore, it is very important, from a synthetic organic chemistry standpoint, that both the bisected and the Felkin–Anh models predict the same stereochemical outcome.

2.8. Conclusion

This study showed that the *anti*-selective Grignard additions to *cis*-substituted cyclopropanecarboxaldehydes occurred via the unusual 7-membered 1,4-chelation-controlled pathway. The results have great importance because they suggest that 1,4-chelation-controlled stereoselective addition reactions can indeed be realized. Under non-chelation conditions, the *syn*-products, which are likely to be formed via the bisected *s-cis* conformation-like transition state effectively stabilized by the characteristic orbital interaction, were produced with moderate stereoselectivity. The predictability of stereochemical outcome based on the chelation or the bisected *s-cis* reaction model make these reactions highly useful.

3. Experimental

3.1. General experimental methods

Melting points are uncorrected. NMR spectra were recorded

at 400 or 500 MHz (^{1}H) and at 100 or 125 MHz (^{13}C), and are reported in ppm downfield from Me_4Si. The ^{1}H NMR assignments indicated were in agreement with COSY spectra. Mass spectra were obtained by electron ionization (EI) or the fast atom bombardment (FAB) method. Thin-layer chromatography was performed on Merck coated plate $60F_{254}$. Silica gel chromatography was performed with Merck silica gel 5715 or 9385 (neutral). Reactions were carried out under an argon atmosphere.

3.1.1. (1*S*,2*R*)-1-Hydroxymethyl-2-(4-methoxybenzyloxymethyl)cyclopropane (8). After stirring a mixture of **7** (102 mg, 0.30 mmol) and NaH (60% in paraffin liquid, 18 mg, 0.45 mmol) in THF (5 mL) at 0 °C for 1 h, PMBnCl (163 μL, 1.20 mmol) was added, and the resulting mixture was stirred at the same temperature for 10 min and at room temperature for further 1 h. After addition of MeOH, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and TBAF (1.0 M in THF, 0.60 mL, 0.60 mmol) in THF (10 mL) was stirred at room temperature for 12 h, and then the resulting mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane 1:4 then 1:2) to give **8** (51 mg, 77%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.20 (1H, m), 0.80 (1H, m), 1.25–1.38 (2H, m), 3.09–3.18 (3H, m), 3.81 (3H, s), 3.89 (1H, dd, J=5.5, 10.7 Hz), 3.93 (1H, m), 4.44 (1H, d, J=10.7 Hz), 4.52 (1H, d, J=11.4 Hz), 6.90 (2H, d, J=8.6 Hz), 7.30 (2H, d, J=8.6 Hz); LR-MS (EI): m/z (%): 222 (6) [M^+]; elemental analysis calcd (%) for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.16, H 8.10.

3.1.2. (1*S*,2*R*)-1-Formyl-2-(4-methoxybenzyloxymethyl)-cyclopropane (3). To a solution of oxalyl chloride (35 μL, 0.40 mmol) in CH_2Cl_2 (8 mL) was added a solution of DMSO (57 μL, 0.80 mmol) in CH_2Cl_2 (1 mL) at −78 °C slowly over 30 min, and then a solution of **8** (45 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The resulting mixture was stirred at the same temperature for 1 h, and then Et_3N (225 μL, 16.0 mmol) was added. After stirring the resulting mixture at the same temperature for further 30 min, aqueous saturated NH_4Cl and then CH_2Cl_2 were added. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane 1:15) to give **3** as a colorless oil (28 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.24 (1H, m), 1.32 (1H, m), 1.83 (1H, m), 2.03 (1H, m), 3.39 (1H, dd, J=8.6, 10.3 Hz), 3.46 (1H, dd, J=5.8, 10.3 Hz), 3.80 (3H, s), 4.38 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.5 Hz), 6.87 (2H, d, J=8.6 Hz), 7.23 (2H, d, J=8.6 Hz), 9.44 (1H, d, J=4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.36, 23.62, 26.82, 55.23, 67.55, 72.56, 113.81, 129.36, 130.02, 159.27, 200.42; LR-MS (EI): m/z (%): 220 (7) [M^+]; elemental analysis calcd (%) for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.67, H 7.53.

3.2. General procedure for the Grignard addition to aldehydes 1–5 (Tables 2, 3, and 5)

After stirring a mixture of an aldehyde **1**–**5** (0.10 mmol) and an additive (2 equiv., if required) in a solvent (2 mL) at room temperature for 30 min, the mixture was cooled to the temperature indicated in the Table, and then a solution of Grignard reagent [2 equiv, (MeMgBr, 3 M in THF or 1.4 M in toluene/THF (3:1); EtMgBr 3.0 M in Et_2O; CH_2=$CHCH_2MgBr$, 1.0 M in Et_2O; *i*PrMgCl, 2.0 M in THF; *i*BuMgBr, 2.0 M in THF; Me_3Al, 1.0 M in hexane] was added slowly. The mixture was stirred at the same temperature for 0.5–8 h, and then MeOH was added. After additional stirring for 10 min at ambient temperature, the resulting mixture was evaporated. The residue was partitioned between AcOEt and H_2O, and then the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:9) to give a *syn*/*anti*-mixture of the corresponding Grignard addition products, the *syn*/*anti* ratio of which was determined by the ^{1}H NMR spectrum. The ^{1}H NMR data of the products **9a**–**c**, **10a**–**c**, **11a**, **12a**, **18** and **19** were in accord with those of the authentic samples previously synthesized by another method.[7] The stereochemistries of other Grignard addition products were determined as described below.[19,20]

3.2.1. (1*S*,2*R*)-2-*t*-Butyldiphenylsilyloxymethyl-1-[(*S*)-1-hydroxy-3-butenyl]cyclopropane (9d) and (1*S*,2*R*)-2-*t*-butyldiphenylsilyloxymethyl-1-[(*R*)-1-hydroxy-3-butenyl]cyclopropane (10d). The mixture of **9d** and **10d** (163 mg) was separated by column chromatography (silica gel; AcOEt/hexane 1:19) to give **9d** (79 mg) and **10d** (70 mg) in a pure form.

Compound **9d**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.27 (1H, m), 0.72 (1H, m), 1.05 (9H, s), 1.07 (1H, m), 1.23 (1H, m), 1.76 (1H, br s), 2.38 (1H, m), 2.66 (1H, m), 3.41 (1H, m), 3.52 (1H, dd, J=8.8, 11.2 Hz), 3.87 (1H, dd, J=5.8, 11.2 Hz), 5.14 (2H, m), 5.90 (1H, m), 7.37–7.45 (6H, m), 7.65–7.69 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=7.45, 18.4, 19.1, 22.5, 26.82, 42.3, 64.2, 71.0, 117.7, 127.6, 127.7, 129.6, 133.7, 135.0, 135.5, 135.6; LR-MS (FAB): m/z (%): 381 (13) [$(M+H)^+$]; elemental analysis calcd (%) for $C_{24}H_{32}O_2Si$: C 75.74, H 8.47; found: C 75.42, H 8.32.

Compound **10d**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.13 (1H, m), 0.72 (1H, m), 1.04 (1H, m), 1.06 (9H, s), 1.20 (1H, m), 2.49 (2H, m), 3.25–3.42 (2H, m), 3.89 (1H, br s), 4.09 (1H, dd, J=5.8, 11.6 Hz), 5.06–5.17 (2H, m), 5.98 (1H, m), 7.34–7.46 (6H, m), 7.64–7.73 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.6, 17.0, 19.0, 23.0, 26.8, 41.1, 65.4, 72.5, 116.5, 127.8, 127.8, 129.8, 129.9, 132.9, 133.0, 135.4, 135.5, 135.6; LR-MS (FAB): m/z (%): 381 (13) [$(M+H)^+$]; elemental analysis calcd (%) for $C_{24}H_{32}O_2Si$: C 75.74, H, 8.47; found: C 75.52, H 8.40.

3.2.2. The mixture of (1*S*,2*R*)-2-benzyloxymethyl-1-[(*S*)-1-hydroxypropyl]cyclopropane (11b) and (1*S*,2*R*)-2-benzyloxymethyl-1-[(*R*)-1-hydroxypropyl]cyclopropane (12b). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.22 (0.9H, m), 0.34 (0.1H, m), 0.81 (1H, m), 0.97 (0.3H, t, J=7.4 Hz), 0.99 (2.7H, t, J=7.4 Hz), 1.10 (1H, m), 1.25 (1H, m), 1.55–1.69 (2H, m), 3.10 (0.9H, m), 3.17 (0.9H, dd, J=10.3, 10.8 Hz), 3.20 (0.1H, m), 3.41 (0.1H, dd), 3.79 (0.1H, dd), 3.95 (0.9H, dd, J=5.5, 10.3 Hz), 4.47 (1H, m), 4.54 (1H, m), 7.26–7.36 (5H, m); HR-MS (EI) calcd $C_{14}H_{20}O_2$ 220.1463, found 220.1453 (M^+).

3.2.3. The mixture of (1*S*,2*R*)-2-benzyloxymethyl-1-[(*S*)-1-hydroxy-3-methylbutyl]cyclopropane (11c) and (1*S*,2*R*)-2-benzyloxymethyl-1-[(*R*)-1-hydroxy-3-methylbutyl]cyclopropane (12c). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.19 (0.95H, m), 0.35 (0.05H, m), 0.80 (1H, m), 0.88–0.94 (6H, m), 1.06 (1H, m), 1.33 (1H, m), 1.38 (1H, m), 1.60 (1H, m), 1.87 (1H, m), 3.17 (1H, dd, *J*=10.5, 10.8 Hz), 3.23 (1H, m), 3.61 (0.05H, dd), 3.64 (0.95H, br s), 3.82 (0.05H, dd), 3.94 (0.95H, dd, *J*=5.5, 10.5 Hz), 4.51–4.60 (2H, m,), 7.27–7.36 (5H, m); HR-MS (EI) calcd $C_{16}H_{24}O_2$ 248.1776, found 248.1769 (M^+).

3.2.4. (1*S*,2*R*)-1-[(*S*)-1-Hydroxyethyl]-2-(4-methoxybenzyloxymethyl)cyclopropane (13a) and (1*S*,2*R*)-1-[(*R*)-1-hydroxyethyl]-2-(4-methoxybenzyloxymethyl)-cyclopropane (14a). The mixture of **13a** and **14a** (65 mg) was separated by column chromatography (silica gel; AcOEt/hexane 1:19) to give **13a** (10 mg) and **14a** (50 mg) in a pure form.

Compound **13a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.31 (1H, m), 0.80 (1H, m), 3.32 (1H, dd, *J*=8.5, 10.1 Hz), 3.44 (1H, m), 3.59 (1H, dd, *J*=6.5, 10.1 Hz), 3.81 (3H, s), 4.40 (1H, d, *J*=11.6 Hz), 4.48 (1H, d, *J*=11.6 Hz), 6.86–6.89 (2H, m), 7.24–7.27 (2H, m); HR-MS (EI) calcd $C_{14}H_{20}O_3$ 236.1412. found 236.1422 (M^+).

Compound **14a**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.17 (1H, m), 0.78 (1H, m), 1.08 (1H, m), 1.25 (1H, m), 1.30 (3H, d, *J*=6.1 Hz), 3.13 (1H, dd, *J*=9.6, 10.5 Hz), 3.33 (1H, m), 3.80 (3H, s), 3.93 (1H, dd, *J*=5.5, 10.5 Hz), 4.44 (1H, d, *J*=11.2 Hz), 4.51 (1H, d, *J*=11.2 Hz), 6.88 (2H, d, *J*=8.5 Hz), 7.27 (2H, d, *J*=8.5 Hz); HR-MS (EI) calcd $C_{14}H_{20}O_3$ 236.1412, found 236.1432 (M^+).

3.3. Conversion of the mixture of 13a/14a into the mixture of 9a/10a

A mixture of **13a** and **14a** (22 mg, 95 μmol) and 10% Pd-charcoal (5 mg) in MeOH (1 mL) was stirred under atmospheric pressure of hydrogen gas at room temperature for 1 h, and then the catalyst was filtered off. The filtrate was evaporated, and a mixture of the residue, TBDPSCl (26 μL, 95 μmol) and imidazole (6.4 mg, 95 μmol) in DMF (1 mL) was stirred at room temperature for 5 h. After addition of MeOH, the resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:9) to give a mixture of **9a** and **10a** (30 mg, 90%) as an oil.

3.4. Conversion of the mixture of 11b/12b into the mixture of 9b/10b

The mixture of **11b/12b** (14 mg, 64 μmol) was converted into the mixture of **9b/10b** (22 mg, 95%) as described above for the mixture of **13a/14a**.

3.5. Conversion of the mixture of 11c/12c into the mixture of 9c/10c

The mixture of **11c/12c** (23 mg, 91 μmol) was converted into the mixture of **9c/10c** (32 mg, 89%) as described above for the mixture of **13a/14a**.

3.5.1. (1*S*,2*R*)-2-*t*-Butyldiphenylsilyloxymethyl-1-[(*S*)-1-hydroxy-3-oxo-3-phenylpropyl]cyclopropane (9e) and (1*S*,2*R*)-2-*t*-butyldiphenylsilyloxymethyl-1-[(*R*)-1-hydroxy-3-oxo-3-phenylpropyl]cyclopropane (10e). To a solution of **1** (34 mg, 0.10 mmol) and CH_2=CH(Ph)OTMS (21 μL, 0.10 mmol) in CH_2Cl_2 (2 mL) was added BF_3·Et_2O (13 μL, 0.10 mmol) at −78 °C, and the mixture was stirred at the same temperature for 2 h. After addition of aqueous saturated $NaHCO_3$, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:9) to give **9e** (18 mg) and **10e** (20 mg) as a colorless oil, respectively.

Compound **9e**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.35 (1H, m), 0.81 (1H, m), 0.96 (9H, s), 1.20 (1H, m), 1.28 (1H, m), 3.34 (1H, dd, *J*=9.2, 17.9 Hz), 3.39 (1H, br s), 3.40 (1H, dd, *J*=5.3, 11.5 Hz), 3.76 (1H, dd, *J*=2.1, 17.9 Hz), 3.92 (1H, ddd, *J*=2.1, 2.3, 9.2 Hz), 4.02 (1H, dd, *J*=5.0, 11.5 Hz), 7.31–7.34 (4H, m), 7.37–7.45 (4H, m), 7.53–7.59 (3H, m), 7.62–7.64 (2H, m), 7.92–7.96 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=7.9, 18.1, 19.1, 21.9, 26.8, 46.0, 64.5, 68.5, 127.7, 127.7, 128.2, 128.5, 129.6, 129.7, 133.4, 133.5, 133.5, 135.4, 135.5, 137.7, 201.0; LR-MS (FAB): *m/z* (%): 459 (25 [(M+H)$^+$]; elemental analysis calcd (%) for $C_{29}H_{34}O_3Si$·H_2O: C 73.07, H 7.11; found: C 72.80, H 7.11.

Compound **10e**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.24 (1H, m), 0.66 (1H, m), 1.05 (9H, s), 1.20–1.29 (2H, m), 3.25 (1H, dd, *J*=5.5, 15.8 Hz), 3.47 (1H, dd, *J*=7.1, 15.8 Hz), 3.48 (1H, dd, *J*=8.6, 10.6 Hz), 3.97 (1H, br s), 4.06 (1H, m), 4.10 (1H, dd, *J*=5.3, 10.6 Hz), 7.38–7.48 (8H, m), 7.56 (1H, m), 7.67–7.73 (4H, m), 8.01 (2H, d, *J*=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=8.7, 17.6, 19.1, 23.3, 26.8, 45.5, 65.2, 69.4, 127.8, 127.8, 128.3, 128.5, 129.8, 129.9, 132.9, 133.0, 135.5, 135.6, 137.4, 198.7; LR-MS (FAB): *m/z* (%): 459 (28) [(M+H)$^+$]; elemental analysis calcd (%) for $C_{29}H_{34}O_3Si$·0.8H_2O: C 73.63, H 7.58; found: C 73.68, H 7.54.

Reaction of **1** *and* CH_2=$CHCH_2TMS/BF_3$·Et_2O. To a solution of **1** (135 mg, 0.40 mmol) and CH_2=$CHCH_2$TMS (509 μL, 3.2 mmol) in CH_2Cl_2 (5 mL) was added BF_3·Et_2O (152 μL, 1.2 mmol) at −78 °C, and the mixture was stirred at the same temperature for 48 h. After addition of saturated $NaHCO_3$, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:19) to give **9d** (124 mg, 81%) and **10d** (17 mg, 11%) as a colorless oil, respectively.

3.5.2. (1*S*,2*R*)-2-*t*-Butyldiphenylsilyloxymethyl-1-[(*S*)-1-hydroxy-3-methyl-3-nitropropyl]cyclopropane (9f) and (1*S*,2*R*)-2-*t*-butyldiphenylsilyloxymethyl-1-[(*R*)-1-hydroxy-3-methyl-3-nitropropyl]cyclopropane (10f). A mixture of **1** (169 mg, 0.50 mmol) and Et_3N (70.3 mL, 0.50 mmol) in 2-nitropropane (2 mL) was stirred at room temperature for 1 week. After addition of aqueous saturated

NH_4Cl, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:19 then 1:9) to give stereoisomers **9f** (48 mg, 22%) and **10f** (48 mg, 22%) as a colorless oil, respectively, the 1′-configurations of which were not determined. Isomer eluted early; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.35 (1H, m), 0.81 (1H, m), 0.96 (9H, s), 1.20 (1H, m), 1.28 (1H, m), 3.34 (1H, dd, J=9.2, 17.9 Hz), 3.39 (1H, br s), 3.40 (1H, dd, J=5.3, 11.5 Hz), 3.76 (1H, dd, J=2.1, 17.9 Hz), 3.92 (1H, ddd, J=2.1, 2.3, 9.2 Hz), 4.02 (1H, dd, J=5.0, 11.5 Hz), 7.31–7.34 (4H, m), 7.37–7.45 (4H, m), 7.53–7.59 (3H, m), 7.62–7.64 (2H, m), 7.92–7.96 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=5.8, 18.3, 19.0, 19.2, 20.2, 24.3, 26.8, 63.3, 73.5, 92.4, 127.7, 127.8, 129.8, 133.4, 133.4, 135.6, 135.6; HR-MS (FAB) calcd $C_{24}H_{34}NO_4Si$ 428.2257, found 428.2283 ($(M+H)^+$). Isomer eluted late; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.24 (1H, m), 0.66 (1H, m), 1.05 (9H, s), 1.20–1.29 (2H, m), 3.25 (1H, dd, J=5.5, 15.8 Hz), 3.47 (1H, dd, J=7.1, 15.8 Hz), 3.48 (1H, dd, J=8.6, 10.6 Hz), 3.97 (1H, br s), 4.06 (1H, m), 4.10 (1H, dd, J=5.3, 10.6 Hz), 7.38–7.48 (8H, m), 7.56 (1H, m), 7.67–7.73 (4H, m), 8.01 (2H, d, J=7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=9.6, 16.1, 18.5, 19.0, 20.6, 23.1, 26.8, 65.0, 76.56, 91.4, 127.8, 127.9, 130.0, 132.5, 132.6, 135.5, 135.6; HR-MS (FAB) calcd $C_{24}H_{34}NO_4Si$ 428.2257, found 428.2251 ($(M+H)^+$).

3.5.3. (1*R*,2*S*)-1,2-Dihydroxymethyl-1-phenylcyclopropane (16). A mixture of **15**[8] (3.48 g, 20.0 mmol) and $NaBH_4$ (1.51 g, 40.0 mmol) in MeOH/THF (1:2, 150 mL) was stirred at room temperature for 3 h, and then AcOH was added. The resulting mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane 1:4, then 1:2) to give **16** (3.56 g, 100%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.75 (1H, dd, J=5.0, 5.4 Hz), 1.06 (1H, dd, J=5.0, 8.6 Hz), 1.66 (1H, m), 2.96 (1H, br s), 2.38 (2H, m), 3.52 (1H, d, J=11.9 Hz), 4.09–4.14 (2H, m), 7.23 (1H, n), 7.31 (2H, m), 7.39 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.8, 25.8, 32.3, 63.5, 67.5, 126.6, 128.4, 129.2, 143.9; LR-MS (EI): m/z (%): 160 (19) [$(M-H_2O)^+$]; elemental analysis calcd (%) for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 74.03, H 7.93.

3.5.4. (1*R*,2*S*)-1-*t*-Butyldiphenylsilyloxymethyl-2-formyl-1-phenylcyclopropane (5). After stirring a mixture of **16** (3.56 g, 20.0 mmol) and NaH (60% in paraffin liquid, 880 mg, 22.0 mmol) in THF (50 mL) at −20 °C for 1 h, TBDPSCl (5.20 mL, 20.0 mmol) was added, and the resulting mixture was stirred at the same temperature for 1 h. After addition of MeOH, the mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated and purified by column chromatography (silica gel; AcOEt/hexane 1:19) to give a mixture of the mono-silylated products (8.12 g, 97%) as a colorless oil. To a solution of oxalyl chloride (3.32 mL, 36.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of DMSO (5.39 mL, 76.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C slowly over 30 min, and then a solution of the mono-silylated products (7.92 g, 19.0 mmol) in CH_2Cl_2 (10 mL) was added slowly. The resulting mixture was stirred at the same temperature for 2 h, and then Et_3N (21.4 mL, 152 mmol) was added. After stirring the resulting mixture at the same temperature for a further 30 min, aqueous saturated NH_4Cl and then CH_2Cl_2 was added. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane 1:99) to give **5** as white crystals (1.95 g, 25%). M.p. (hexane/iPr$_2$O) 64–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.96 (9H, s), 1.48 (1H, dd, J=4.9, 8.1 Hz), 1.78 (1H, dd, J=4.9, 5.4 Hz), 2.29 (1H, ddd, J=5.2, 5.4, 8.1 Hz), 3.77 (1H, d, J=11.1 Hz), 4.05 (1H, d, J=11.1 Hz), 7.19–7.22 (2H, m), 7.25–7.28 (2H, m), 7.30–7.35 (6H, m), 7.37–7.41 (3H, m), 7.50–7.51 (2H, m), 9.63 (1H, d, J=5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.6, 19.1, 26.67, 34.3, 41.1, 66.5, 127.4, 127.5, 127.7, 128.3, 129.5, 129.7, 129.7, 132.8, 133.0, 135.4, 135.5, 142.0, 200.0; LR-MS (EI): m/z (%): 414 (2) [M^+]; elemental analysis calcd (%) for $C_{27}H_{30}O_2Si$: C 78.22, H 7.29; found: C 78.12, H 7.45.

3.5.5. (1*R*,2*S*)-2-*t*-Butyldiphenylsilyloxymethyl-2-[(*S*)-hydroxyethyl]-1-phenylcyclopropane (20) and (1*R*,2*S*)-2-*t*-butyldiphenylsilyloxymethyl-2-[(*R*)-hydroxyethyl]-1-phenylcyclopropane (21). The mixture of **20** and **21** (160 mg) was separated by column chromatography (silica gel; AcOEt/hexane 1:19) to give **20** (96 mg) and **21** (58 mg) in a pure form, respectively.

Compound **20**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.78 (1H, dd, J=4.9, 5.8 Hz), 0.95 (9H, s), 0.99 (1H, dd, J=4.8, 8.5 Hz), 1.40 (1H, ddd, J=5.4, 8.5, 8.8 Hz), 1.61 (3H, d, J=6.2 Hz), 3.60 (1H, d, J=9.0 Hz), 3.75 (1H, dq, J=6.1, 9.8 Hz), 3.94 (1H, d, J=9.0 Hz), 7.17–7.21 (4H, m), 7.25–7.41 (9H, m), 7.50–7.52 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.9, 19.1, 24.1, 26.7, 32.4, 33.5, 68.4, 68.6, 126.6 127.5, 127.6, 128.0, 129.4, 129.6 130.1, 132.8, 133.4, 135.5, 135.5, 144.3; LR-MS (EI): m/z (%): 412 (13) [$(M-H_2O)^+$]; Anal. Calcd for $C_{28}H_{34}O_2Si$: C, 78.09; H, 7.96; found: C, 77.89; H, 8.03.

Compound **21**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.65 (1H, dd, J=4.9, 5.8 Hz), 0.93 (1H, dd, J=4.9, 9.1 Hz), 0.96 (9H, s), 1.42 (3H, d, J=6.1 Hz), 1.56 (1H, ddd, J=5.8, 9.1, 9.8 Hz), 3.58 (1H, d, J=11.2 Hz), 3.67 (1H, dq, J=6.1, 9.8 Hz), 4.08 (1H, d, J=11.2 Hz), 4.14 (1H, br s), 7.04 (2H, d, J=7.0 Hz), 7.11 (2H, t, J=7.6 Hz), 7.23–7.46 (9H, m), 7.58 (2H, d, J=7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.1, 21.7, 26.7, 32.2, 32.7, 69.4, 69.7, 126.8, 127.5, 127.8, 128.2, 129.5, 129.8. 130.5, 131.2, 131.7, 135.4, 135.5, 143.98; LR-MS (EI): m/z (%): 412 (3) [$(M-H_2O)^+$]; elemental analysis calcd (%) for $C_{28}H_{34}O_2Si$: C 78.09, H 7.96; found: C 77.87, H 8.07.

3.6. General procedure for preparing the MTPA esters

A mixture of an alcohol (0.10 mmol), (*S*)- or (*R*)-MTPA (28 mg, 0.12 mmol), EDC·HCl (23 mg, 0.12 mmol) and DMAP (3.7 mg, 30 μmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 12 h, and then MeOH was added. The mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by

column chromatography (silica gel; AcOEt/hexane 1:49) to give the corresponding MTPA ester as a colorless oil.

3.6.1. (*S*)-MTPA ester of 20. Yield 99% (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.924628 (1H, dd, H-3a, $J_{3a,3b}$=4.9 Hz, $J_{3a,2}$=6.0 Hz), 0.96584 (9H, s, –C(CH_3)$_3$), 1.02113 (1H, dd, H-3b, $J_{3b,3a}$=4.9 Hz, $J_{3b,2}$=8.4 Hz), 1.56472 (1H, ddd, H-2, $J_{2,3a}$=6.0 Hz, $J_{2,3b}$=8.4 Hz, $J_{2,1''}$=10.0 Hz), 1.71023 (3H, d, H-2″, $J_{2'',1''}$=6.3 Hz), 3.58820 (3H, s, –OMe), 3.69080 (1H, d, H-1′a, $J_{1'a,1'b}$=11.1 Hz), 4.02150 (1H, d, H-1′b, $J_{1'b,1'a}$=11.1 Hz), 5.21330 (1H, dq, H-1″, $J_{1'',2''}$=6.3 Hz, $J_{1'',2}$=10.0 Hz), 7.17580–7.21600 (4H, m, aromatic), 7.24580–7.42600 (12H, m, aromatic), 7.52860–7.57840 (4H, m, aromatic); HR-MS (FAB) calcd $C_{38}H_{41}F_3NaO_4Si$ 669.2624, found 669.2621 ((M+Na)$^+$).

3.6.2. (*R*)-MTPA ester of 20. Yield 97% (63 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90778 (1H, dd, H-3a, $J_{3a,3b}$=5.2 Hz, $J_{3a,2}$=6.2 Hz), 0.93488 (1H, dd, H-3b, $J_{3b,3a}$=5.2 Hz, $J_{3b,2}$=8.4 Hz), 0.96786 (9H, s, –C(CH_3)$_3$), 1.46095 (1H, ddd, H-2, $J_{2,3a}$=6.2 Hz, $J_{2,3b}$=8.4 Hz, $J_{2,1''}$=10.0 Hz), 1.78783 (3H, d, H-2″, $J_{2'',1''}$=6.3 Hz), 3.58200 (3H, s, –OMe), 3.66570 (1H, d, H-1′a, $J_{1'a,1'b}$=11.1 Hz), 4.01160 (1H, d, H-1′b, $J_{1'b,1'a}$=11.1 Hz), 5.21920 (1H, dq, H-1″, $J_{1'',2''}$=6.3 Hz, $J_{1'',2}$=10.0 Hz), 7.17260–7.20000 (4H, m, aromatic), 7.23840–7.42600 (12H, m, aromatic), 7.53340–7.55540 (4H, m, aromatic); HR-MS (FAB) calcd $C_{38}H_{41}F_3NaO_4Si$ 669.2624, found 669.2628 ((M+Na)$^+$).

3.6.3. (*S*)-MTPA ester of 9d. Yield 95% (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.42900 (1H, m, H-3a), 0.72092 (1H, m, H-3b), 1.06144 (9H, s, –C(CH_3)$_3$), 1.25006 (1H, m, H-2), 1.29378 (1H, m, H-1), 2.58350 (1H, m, H-2′a), 2.77450 (1H, m, H-2′b), 3.57770 (1H, dd, H-1″a, $J_{1''a,1''b}$=11.6 Hz), 3.59040 (3H, s, –OMe), 3.96970 (1H, dd, H-1″b, $J_{1''b,1''a}$=11.6 Hz), 4.98260 (2H, m, H-4′), 5.03270 (1H, m, H-1′), 5.67000 (1H, m, H-3′), 7.35520-7.45580 (9H, m, aromatic), 7.57560–7.59120 (2H, m, aromatic), 7.66320–7.70360 (4H, m, aromatic); HR-MS (FAB) calcd $C_{34}H_{39}F_3O_4Si$ 597.2648, found 597.2663 ((M+H)$^+$).

3.6.4. (*R*)-MTPA ester of 9d. Yield 100% (68 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40896 (1H, m, H-3a), 0.62952 (1H, m, H-3b), 1.06042 (9H, s, –C(CH_3)$_3$), 1.13647 (1H, m, H-2), 1.24478 (1H, m, H-1), 2.64880 (1H, m, H-2′a), 2.85370 (1H, m, H-2′b), 3.53680 (1H, dd, H-1″a, $J_{1''a,2}$=8.6 Hz, $J_{1''a,1''b}$=11.4 Hz), 3.55900 (3H, s, –OMe), 3.96080 (1H, dd, H-1″b, $J_{1''b,2}$=5.2 Hz, $J_{1''b,1''a}$=11.4 Hz), 5.05600 (1H, m, H-1′), 5.10380 (2H, m, H-4′), 5.82830 (1H, m, H-3′), 7.35260–7.45420 (9H, m, aromatic), 7.53420–7.57000 (2H, m, aromatic), 7.66420–7.69700 (4H, m, aromatic); HR-MS (FAB) calcd $C_{34}H_{39}F_3O_4Si$ 597.2648, found 597.2621 ((M+H)$^+$).

3.6.5. (*R*)-MTPA ester of 9e. Yield 95% (64 mg); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.61320 (1H, m, H-3a), 0.78480 (1H, m, H-3b), 0.85940 (9H, s, –C(CH_3)$_3$), 1.27920 (1H, m, H-2), 1.34960 (1H, m, H-1), 3.48350 (3H, s, –OMe), 3.56180 (1H, dd, H-1″a, $J_{1''a,2}$=9.7 Hz, $J_{1''a,1''b}$=11.1 Hz), 3.69960 (1H, dd, H-2′a, $J_{2'a,1'}$=1.3 Hz, $J_{2'a,2'b}$=18.4 Hz), 3.98900 (1H, dd, H-1″b, $J_{1''b,2}$=4.8 Hz, $J_{1''b,1''a}$=11.1 Hz), 4.01190 (1H, dd, H-2′b, $J_{2'b,1'}$=10.6 Hz, $J_{2'b,2'a}$=18.4 Hz), 5.63820 (1H, m, H-1′), 7.34640–7.68560 (18H, m, aromatic), 7.97540–8.01100 (2H, m, aromatic); HR-MS (FAB) calcd $C_{39}H_{41}F_3NaO_5Si$ 697.2573, found 697.2559 ((M+Na)$^+$).

3.6.6. (*S*)-MTPA ester of 9e. Yield 100% (68 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55832 (1H, m, H-3a), 0.85980 (1H, m, H-3b), 0.87000 (9H, s, –C(CH_3)$_3$), 1.40686 (1H, m, H-2), 1.48887 (1H, m, H-1), 3.50240 (3H, s, –OMe), 3.57450 (1H, dd, H-1″a, $J_{1''a,2}$=10.2 Hz, $J_{1''a,1''b}$=11.4 Hz), 3.64490 (1H, dd, H-2′a, $J_{2'a,1'}$=1.2 Hz, $J_{2'a,2'b}$=18.3 Hz), 3.93480 (1H, dd, H-2′b, $J_{2'b,1'}$=10.3 Hz, $J_{2'b,2'a}$=18.3 Hz), 4.01630 (1H, dd, H-1″b, $J_{1''b,2}$=4.9 Hz, $J_{1''b,1''a}$=11.4 Hz), 5.67300 (1H, m, H-1′), 7.35080–7.67320 (18H, m, aromatic), 7.91920–7.93620 (2H, m, aromatic); HR-MS (FAB) calcd $C_{39}H_{41}F_3NaO_5Si$ 697.2573, found 697.2565 ((M+Na)$^+$).

3.7. X-ray crystallographic data of 1[17]

$C_{21}H_{26}O_2Si$, M=338.52, Monoclinic, $P2_1$, a=10.652 (3) Å, b=9.022 (3) Å, c=10.632 (3) Å, β=104.66 (2)°, V=1033.4 (4) Å^3, Z=2, D_{calc}=1.137 Mg cm^{-3}. Cell parameters were determined and refined from 26 reflections in the range 26.5°<θ<30.0°. A colorless crystal (0.60×0.40×0.30 mm^3) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu K_α radiation (λ=1.54178 Å). Data collection using the $\omega/2\theta$ scan technique gave 1662 reflections at room temperature, 1522 unique, of which 1522 with I>3.00 $\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz, polarization, and the extinction effect, but not for the absorption. The structure was solved by the direct method and refined by full-matrix least squares technique using maXus (ver. 4.3) as the computer program. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. The R value was 0.059.

3.8. Calculations

All ab initio and density functional theory (DFT) calculations were performed using the GAUSSIAN98 program[17] on an SGI O2 workstation. The O_1–C_1–C_2–H_2 dihedral angle of **i** or **ii** was rotated from 0 to 360° at the intervals of 20°, and the conformations were optimized at RHF/3-21G(d). Finally, single point energies were calculated at RB3LYP/6-31G(d). The bisected *s-cis* and *trans* conformers of **i** and **ii** were fully optimized at RB3LYP/6-31G(d) and their single point energies also were calculated by RB3LYP/6-31G(d).

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