Tetrahedron

Tetrahedron Vol. 60, No. 32, 2004

Contents

REPORT

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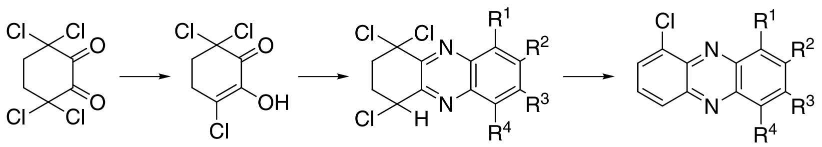
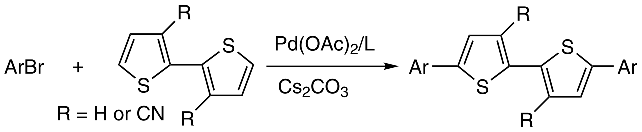
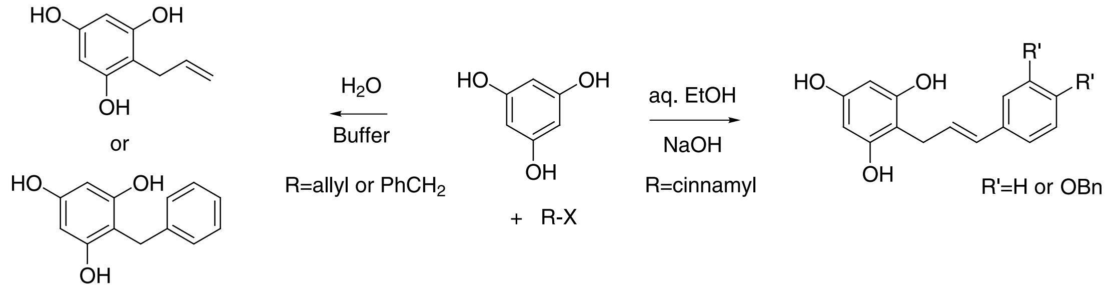
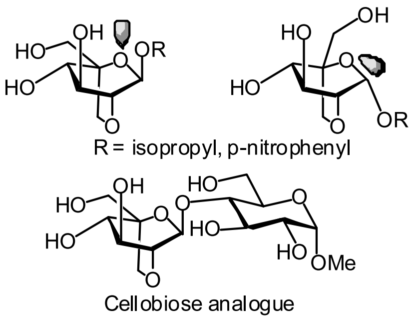
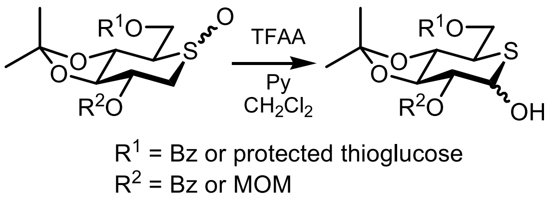


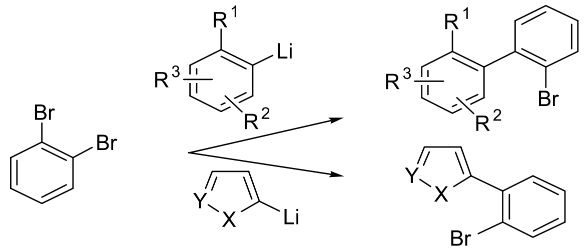


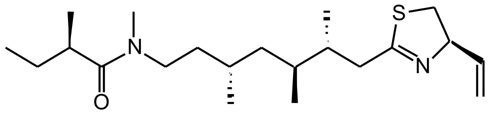


Isopropyl and *p*-nitrophenyl α- and β-D-glucopyranosides, restrained in a conformation close to $B_{2,5}$ via an oxymethylene bridge have been synthesized and found to be hydrolyzed at similar rates, close to those observed for the parent unconstrained glucosides. In such derivatives, either α or β, the exocyclic cleaved bond is synperiplanar to an endocyclic oxygen lone pair. This conformationally locked glucopyranosyl moiety was also incorporated into a cellobiose analogue.



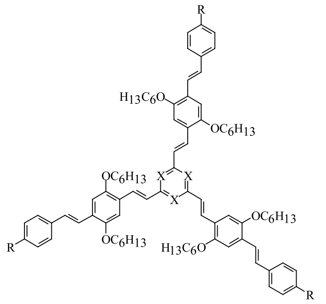






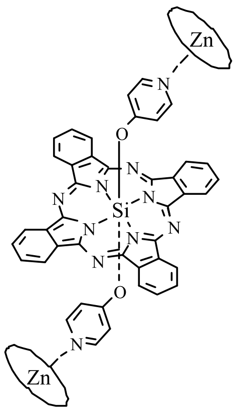
(3*R*,7*R*,8*S*,10*S*,2′*R*)-Kalkitoxin (**7**)

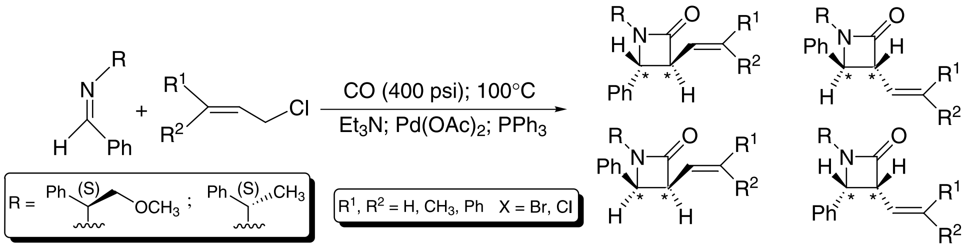
Kalkitoxin, a potent neurotoxin isolated from a marine cyanobacteria, and its congeners were efficiently synthesized, which determined the absolute stereostructure of natural kalkitoxin to be **7**.

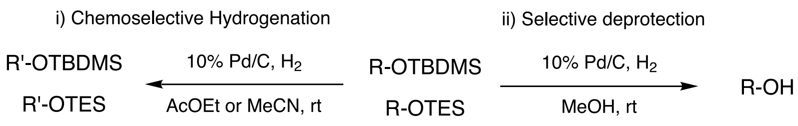


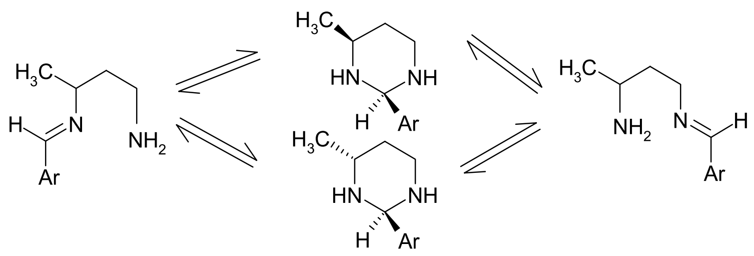
X = CH, N
R = H, CN

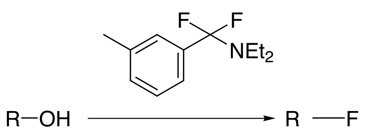
Bis(4-pyridinolato) silicon(IV) phthalocyanine complexes with a series of zinc(II) tetrapyrrole derivatives using the two pyridyl ligands, forming the corresponding 1:2 or 1:1 molecular assemblies. The molecular structure of the first axially linked trinuclear phthalocyanine–porphyrin complex has also been determined.

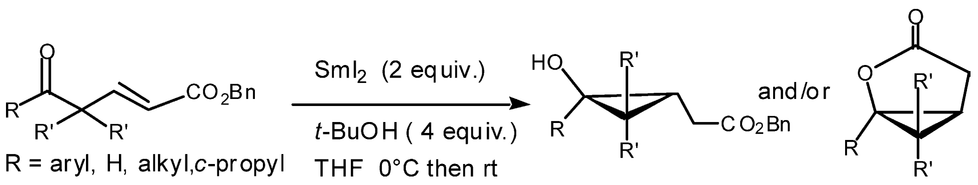


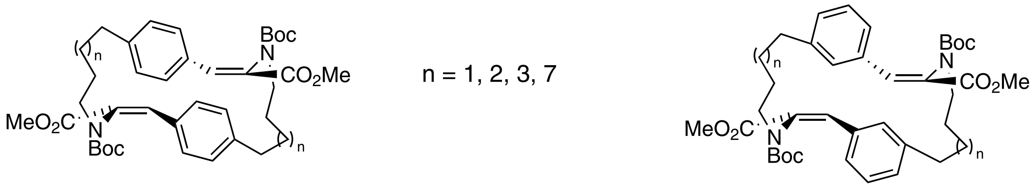



i) Chemoselective Hydrogenation
ii) Selective deprotection
R'-OTBDMS
R'-OTES
10% Pd/C, H2
AcOEt or MeCN, rt
R-OTBDMS
R-OTES
10% Pd/C, H2
MeOH, rt
R-OH


H3C
N
H
Ar
NH2
HN
NH
H
Ar


F
F
NEt2
R—OH
R —F


O
R
R'
R'
CO2Bn
R = aryl, H, alkyl,c-propyl
SmI2 (2 equiv.)
t-BuOH (4 equiv.)
THF 0°C then rt
HO
R
R'
R'
CO2Bn
and/or
O
O
R'
R
R'



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

meta- and *para*cyclophanes containing two unsaturated amino acid residues have been synthesized via a modular approach that relies on a Heck macrocyclisation reaction. In addition an X-ray crystallographic and molecular modelling study of the cyclophanes is presented. *Tetrahedron* **2004**, *60*, 6945–6958.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

ISSN 0040-4020

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Tetrahedron

Tetrahedron 60 (2004) 6711–6745

Tetrahedron report number 686

Synthesis of fluorinated amino acids

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Received 14 May 2004

Available online 15 June 2004

Contents

1. Introduction

Fluorine is one of the most abundant elements on earth, yet it occurs extremely rarely in biological compounds. Due to the specific properties of fluorine atom(s), including their small steric size, high electronegativity and carbon–fluorine bond strength and the sensitivity of ^{19}F NMR spectroscopy along with large $^{19}F-^{1}H$ coupling constants etc, the introduction of fluorine atom(s) into many biologically active molecules can bring about remarkable and profound changes in their physical, chemical and biological properties.[1] Among them, fluorine-containing amino acids and

Keywords: Amino acids; Fluorinated organic compounds.

Abbreviations: AIB, α-aminoisobutyric acid; AIBN, 2,2′-azobis(2-methylpropionnitrile); α-Tfm, AAs, α-trifluoromethylmethyl α-amino acids; Boc_2O, di-*tert*-butyl dicarbonate; BtH, benzotriazole; Bz_2O_2, dibenzoyl peroxide; CAN, cerium ammonium nitrate; CbzOSuc, *N*-(benzyloxycarbonyloxy)succinimide; *m*-CPBA, *m*-chloroperoxybenzoic acid; DABCO, 1,4-diazabicyclo[2.2.2]octane; DAST, diethylaminosulfur trifluoride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DFT, density functional theory; DIBAL-H, diisobutylaluminum hydride; DMAP, 4-*N*,*N*′-dimethylaminopyridine; DMBCl, bis(4-methoxyphenyl)chloromethane; DMI, 1,3-dimethyl-2-imidazolidinone; DMP, 2,2-dimethoxypropane; DMPU, *N*,*N*′-dimethylpropylene urea; EDC·HCl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; F-αAAs, fluorinated α-amino acids; F-βAAs, fluorinated β-amino acids; F-C-AAs, fluorinated cyclic amino acids; HMPT, hexamethylphosphorous triamide; i-NOS, induced nitric oxide synthase; KHMDS, potassium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; L-NIL, iminoethyl-L-lysine; MBH, Morita–Baylis–Hillman; MO, molecular orbital; Morpho-DAST, morpholinotrifluorosulphurate; NBS, *N*-bromosuccinimide; NFSi, *N*-fluorobezenesulphonimide; PDC, pyridinium dichromate; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); PET, positron emisson tomography; PhthNH, phthalimide; (*R*)-BINAP, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; RCY, radiochemical yield; TBAF, tetrabutylammonium fluoride; TBAI, tetrabutylammonium iodide; TBDMSCl, *tert*-butyldimethylsilyl chloride; TBHP, *tert*-butyl hydroperoxide; TEMPO, 2,2,6,6-tetramethyl-1-piperidinooxy; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; Tf_2O, trifluoromethanesulphonic anhydride; TMSCl, trimethylsilyl chloride; TMSCN, trimethylsilyl cyanide; TMSI, trimethylsilyl iodide; TMSOTf, trimethylsilyl trifluoromethanesulfonate.

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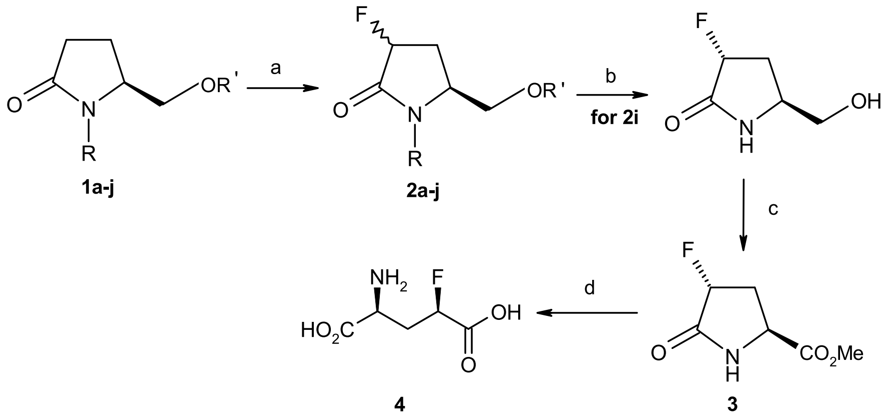
0040–4020/$ - see front matter
doi:10.1016/j.tet.2004.05.051



Scheme 1. Reagents and conditions: (a) (i) LDA (1.3 equiv.), THF, −78 °C; (ii) NFSi (1.4 equiv.), THF, −78 °C; (b) TFA/Et_3SiH, CH_2Cl_2, 0 °C, 2 h or HCl/MeOH, 48 h; (c) (i) oxidation; (ii) CH_2N_2, Et_2O; (d) (i) 6 N HCl; (ii) propylene oxide, EtOH.

large molecules containing them have enjoyed widespread bioorganic applications such as biological tracers, mechanistic probes, enzyme inhibitors and medical applications including control of blood pressure, allergies, and tumor growth.[2] Moreover, fluorinated amino acids have recently emerged as valuable building blocks for the design of hyperstable protein folds as well as directing highly specific protein–protein interactions.[3,4] At the same time, protein (peptide) design and engineering of fluorinated amino acids have also achieved remarkable progress.[5,6] For all of these reasons, fluorinated amino acids have been the subjects of intensive synthetic research activities and some related reviews[7] and a book[8] in this area have been published recently.

The present review is intended to focus on the recent developments in the synthesis of fluorinated amino acids from 1999 to the end of 2003 (in 2000, Sutherland's review[7d] covered the literature from 1990 to the end of 1998). The fluorinated amino acids in this review are grouped into three main types: fluorinated α-amino acids (F-αAAs), fluorinated β-amino acids (F-βAAs) and fluorinated cyclic amino acids (F-CAAs).

2. Fluorinated α-amino acids

Fluorinated α-amino acids (F-αAAs) have recently received extensive attention and have played more and more important roles in biological and peptide chemistry. F-αAAs have been shown to be irreversible inhibitors of pyridoxal phosphate-dependent enzymes.[1b] For example, β-fluoroalanine[9] and (*S*)-α-fluoromethylhistidine[10] are good irreversible inhibitors for the corresponding bacterial alanine racemases and histidine decarboxylase. On the other hand, F-αAAs have also been shown to be of importance in the development of drugs, such as antitumour agents.[11]

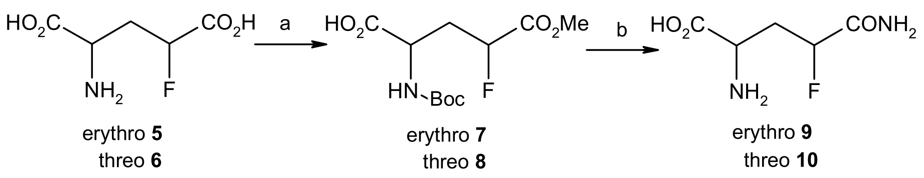
2.1. Monofluorinated α-amino acids

In living cells, both glutamic acid and glutamine are the main storage forms of nitrogen for the synthesis of macromolecules, and fluorinated analogues of glutamine might interfere with the normal nitrogen transfer processes,[7e] which provides the basis for possible therapeutic agents. Introduction of fluorine atom(s) into the C-4 position of glutamic acid has also been realised in the screening of modulators for folate poly-γ-glutamate biosynthesis and to study the role of analogous derivatives of antifolates such as methotrexate in the cytotoxic action of these drugs.[7e] These have resulted in intensive synthetic demands for fluorinated glutamic acids and glutamines. There are a large number of reports on the racemic and asymmetric preparation of 4-fluoroglutamic acids via a Michael reaction,[12] an inverse Michael reaction,[13] and electrophilic fluorination,[14] along with resolution techniques.[15] Recently, Coward and Konas[16] have investigated the electrophilic fluorination of enantiomerically pure 2-pyrrolidinones **1a–i** for the synthesis of single stereoisomers of 4-fluorinated glutamic acid derivatives **2**. Reaction of the lactam enolates derived from **1a–i** with *N*-fluorobenzenesulphonimide (NFSi) resulted in a completely diastereoselective monofluorination reaction to yield the monocyclic *trans*-substituted α-fluoro lactams **2a–i** as the major products in moderate yields (Scheme 1 and Table 1). Deprotection of **2i** with TFA/Et_3SiH or HCl/MeOH followed by oxidation and esterification gave the pyroglutamate **3**. Compound **3** was further treated with 6 N HCl to yield the optically active 4-fluoroglutamic acid **4**.

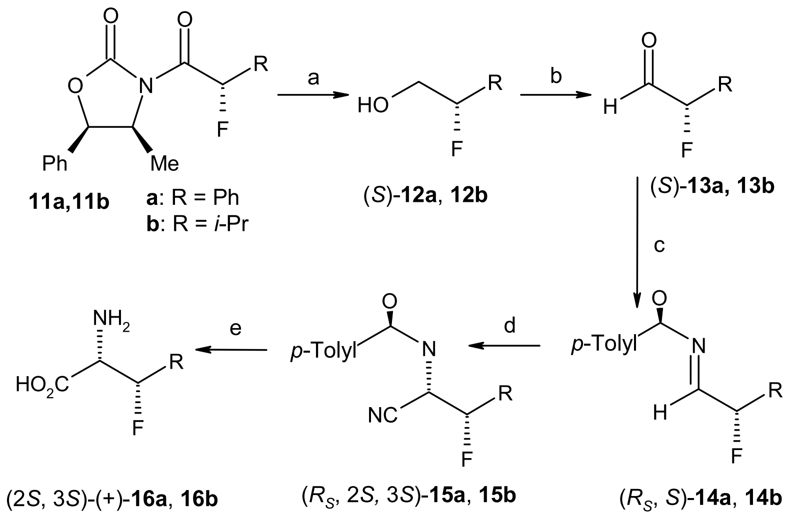
Table 1. Summary of monofluorinations of lactams **1a–i** with NFSi[16]

Compound	R	R′	% Yield (**2**)	Isomer ratio
1a	Bn	TBDMS	68	5.7:1.0
1b	Bn	TBDPS	66	3.3:1.0
1c	Bn	TIPS	>50	4.9:1.0
1d	Bn	Me	70	5.7:1.0
1e	Bn	CPh_3	0	N/A
1f	4-(MeO)-Bn	TBDMS	64	4.9:1.0
1g	Boc	TBDMS	40	1.6:1.0
1h	Boc	Me	<38	1.7:1.0
1i	Boc	CPh_3	20	Single isomer

Tolman and Sedmera[17] prepared the diastereomeric 4-fluoroglutamines **9** and **10** from the corresponding *erythro*- and *threo*-4-fluoroglutamic acids (Scheme 2). The racemic *erythro*- and *threo*-4-fluoroglutamic acids **5** and **6** were individually converted into their 5-methyl ester hydrochloride salts with $SOCl_2$ and MeOH. Temporary



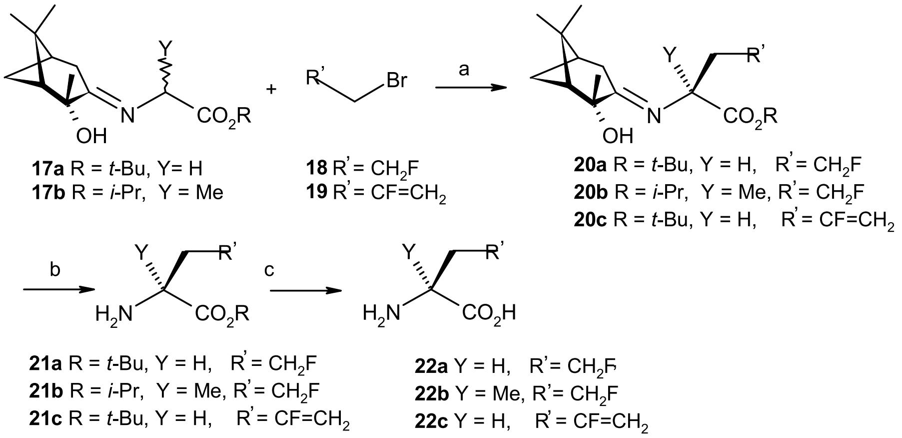
Scheme 2. Reagents and conditions: (a) (i) MeOH/$SOCl_2$; (ii) Et_3N, Boc_2O, MeOH, 50 °C, 40 min; (b) (i) 28% aqueous NH_3, $KHSO_4$; (ii) CF_3CO_2H, 20 °C, 1 h.



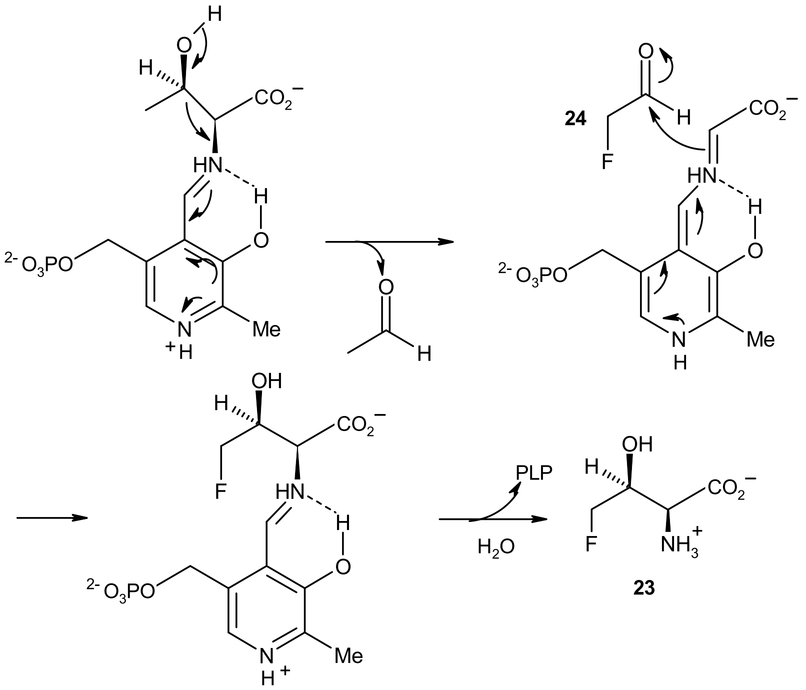
Scheme 3. Reagents and conditions: (a) $LiBH_4$, THF, 0 °C, 2–3 h; (b) Dess–Martin reagent (1.6 equiv.), CH_2Cl_2, 5–7 min; (c) (*R*)-(−)-*p*-toluenesulphinamide, CH_2Cl_2, 4 Å sieves; (d) Et_2AlCN/*i*-PrOH, THF, −78 °C to rt; (e) (i) 6 N HCl, reflux; (ii) propylene oxide, *i*-PrOH.

protection of the amino groups as the *tert*-butyloxycarbonyl derivatives **7** and **8** followed by aminolysis with 28% aqueous ammonia gave the N-protected 4-fluoroglutamines. Finally, release of the Boc protecting groups with TFA gave the *erythro*-4-fluoroglutamine **9** and *threo*-4-fluoroglutamine **10** in 35 and 39% overall yields, respectively, based on the corresponding diastereomeric 4-fluoroglutamic acids.

Davis[18] has described an asymmetric synthesis of β-fluoro α-amino acids (2*S*,3*S*)-(+)-**16a**, **16b** via an asymmetric Strecker type of reaction involving an α-fluoro sulphinimide intermediate (Scheme 3). Reductive removal of the auxiliaries of **11a** and **11b**, prepared by electrophilic fluorination of the corresponding oxazolidone sodium enolates with *N*-fluorobenzenesulphonimide(NFSi),[19] with $LiBH_4$ in THF afforded the 2-fluorohydrins (*S*)-**12a**, **12b** in 79–84% yields and >97% ee. Oxidation of (*S*)-**12a**, **12b** with 1.6 equiv. of the Dess–Martin reagent at rt provided the aldehydes (*S*)-**13a**, **13b** in 90 and 98% crude yields with 80 and 95% ee, respectively. Without purification, due to their decomposition on silica gel, (*S*)-**13a**, **13b** were directly treated with (*R*)-(−)-*p*-toluenesulphinamide in CH_2Cl_2 to give the desired sulphinimides **14a**, **14b** in 62 and 70% yield, respectively. The sulphinimides were further treated with Et_2AlCN/*i*-PrOH in THF to afford the β-fluoro-α-amino nitriles **15a**, **15b** in 78 and 63% yield with 78 and



Scheme 4. Reagents and conditions: (a) LDA, THF, −78 °C to rt; (b) 15% citric acid; (c) (i) 6 N HCl, reflux (for **21a**,**21b**) or TFA, H_2O, CH_2Cl_2 (for **21c**); (ii) propylene oxide, EtOH.



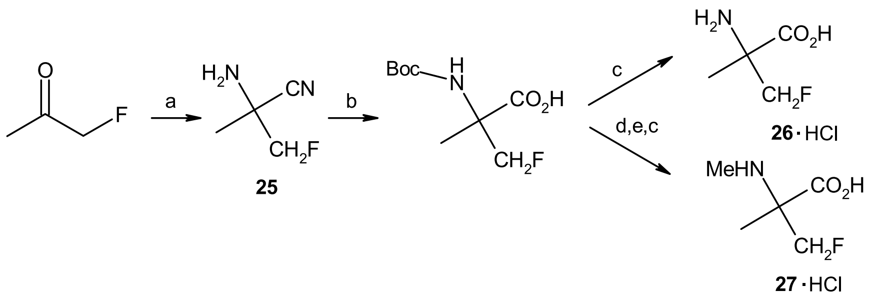
Scheme 5. Proposed mechanism for the formation of 4-fluorothreonine by threonine transaldolase.

>96% de, respectively. Finally, the amino nitriles **15a**, **15b** were hydrolysed to give (2*S*,3*S*)-(+)-3-fluorophenylalanine **16a** and (2*S*,3*S*)-(+)-3-fluoroleucine **16b** in 69 and 58% yield, respectively. In addition, starting from the opposite enantiomeric fluoro aldehyde or sulphinamide and by using the same methodology, (2*S*,3*R*)-(−)-3-fluorophenylalanine was also conveniently synthesised.

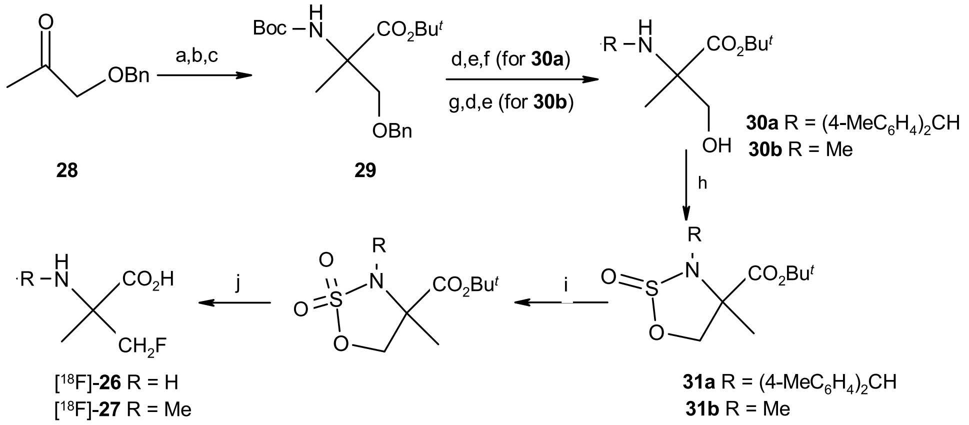
The stereoselective synthesis of γ-monofluorinated α-amino acids was conducted in Haufe's group[20] by using chiral 2-hydroxy-3-pinanone as an auxiliary via a diastereoselective alkylation of the esters **17a** and **17b** (Scheme 4). Alkylation of the Schiff base **17a** with 1-bromo-2-fluoroethane **18** afforded the imine ester **20a** in 37% yield with >98% ds. Alkylation of **17b** with **18**, however, proceeded with poor diastereoselectivity (68:32). The addition of *N*,*N*′-dimethylpropylene urea (DMPU) to the reaction system improved both the yield of **20b** and the diastereoselectivity (89%). Similarly, alkylation of **17a** with 3-bromo-2-fluoropropene **19** in the presence of DMPU afforded the desired imine ester **20c** in 73% chemical yield with high diastereoselectivity (>97%). Removal of the auxiliaries of **20a**, **20b** and **20c** was achieved by treatment with 15% citric acid to give the corresponding esters **21a**, **21b** and **21c**. Finally, these esters were further hydrolysed in 6 N HCl or TFA followed by treatment with propylene oxide in EtOH to yield the enantioenriched γ-monofluorinated α-amino acids **22a** (>96% ee), **22b** (>85% ee) and **22c** (81% ee).

O'Hagan and co-workers[21] reported that L-threonine condensed with fluoroacetaldehyde **24** in *S. cattleya* to generate 4-fluorothreonine **23** in a transaldolase-mediated reaction. The proposed mechanism is shown in Scheme 5. By the same mechanism, 4-chloroacetaldehyde could also be converted into the corresponding 4-chlorothreonine. This suggested the mode of biosynthesis of this metabolite in other organisms. The enzyme is important in the biosynthesis of 4-fluorothreonine in *S. cattleya* and it is of interest to further investigate if the reversible interconversion has any metabolic significance with regard to the organism's amino acid biochemistry.

Novel radiopharmaceuticals, including fluorinated amino acids, have shown promising results in preclinical and clinical studies. Goodman and co-workers[22] developed fluorinated analogues of α-aminoisobutyric acid (AIB) suitable for labelling with ^{19}F and use in positron emission



Scheme 6. Reagents and conditions: (a) KCN, NH_4Cl, H_2O; (b) HCl and then $(Boc)_2O$, MeOH, Et_3N; (c) aqueous HCl; (d) $Cl_3CC(=NH)OtBu$, CH_2Cl_2; (e) NaH, DMF, MeI, rt.



28 **29**

[18F]-**26** R = H
[18F]-**27** R = Me

31a R = (4-MeC$_6$H$_4$)$_2$CH
31b R = Me

Scheme 7. Reagents and conditions: (a) $(NH_4)_2CO_3$, KCN, NH_4Cl, EtOH, H_2O; (b) 5 N NaOH, 180 °C and then $(Boc)_2O$, MeOH, Et_3N; (c) $Cl_3CC(=NH)O^tBu$, CH_2Cl_2; (d) 10% Pd/C, H_2, MeOH; (e) *p*-TsOH·H_2O, EtOH, 40 °C; (f) DMBCl, Et_3N, CH_2Cl_2; (g) NaH, DMF, MeI; (h) $SOCl_2$, Et_3N, toluene or CH_2Cl_2; (i) $NaIO_4$, catalytic RuO_2, H_2O, CH_3CN; (j) [^{18}F]-HF, $K_{2,2,2}$, K_2CO_3, MeCN, 85 °C and then 6 N HCl, 85 °C.

tomography (PET) imaging. 2-Amino-3-fluoro-2-methylpropanoic acid (FMAP, **26**) and 3-fluoro-2-methyl-2-(methylamino)propanoic acid (*N*-MeFMAP, **27**) were therefore synthesised, radiolabelled and biologically evaluated. The compounds **26** and **27** could be prepared in a straightforward fashion starting from the aminonitrile intermediate **25** derived from fluoroacetone by a Strecker-type reaction (Scheme 6).

This strategy was not, however, amenable to the radiosynthesis of [^{18}F]-**26** and [^{18}F]-**27**. Cyclic sulphamidates were suitable synthetic precursors of [^{18}F]-**26** and [^{18}F]-**27** according to the literature.[23] The α-methyl serine derivative **29**, prepared from 3-benzyloxypropanone **28**, served as a common intermediate in the synthesis of [^{18}F]-**26** and [^{18}F]-**27**. It was converted into the aminoalcohols **30a** and **30b** by two different routes (Scheme 7) and **30a** and **30b** were then treated with $SOCl_2$ in the presence of Et_3N to form the cyclic sulphamidites **31a** and **31b**. Oxidation of **31a** and **31b** using $NaIO_4$ in the presence of catalytic ruthenium(IV) oxide followed by radiolabelling with [^{18}F]-HF and hydrolysis in 6 N HCl provided [^{18}F]-**26** and [^{18}F]-**27** successfully.

Fokina et al.[24] wished to synthesise four types of optically pure fluorinated amino acids from (*R*)-2,3-*O*-isopropylideneglyceraldehyde **32** involving the Mitsunobu reaction for the introduction of the amino function and the incorporation of fluorine atom(s) by the fluorination reagent: morpholinotrifluorosulphurane (Morpho-DAST) (Fig. 1). As representative mono- and difluoro-amino acids from **32**, 2-amino-3-fluoroundecanoic acid (type A, R=C_8H_{17}) and 3-amino-2,2-difluoroundecanoic acid (type B, R=C_8H_{17}) were synthesised. [Type C and D not mentioned in the text.]

Addition of *n*-octylmagnesium bromide to (2*R*)-**32** afforded a mixture of the diastereomeric alcohols **33a**,**b** in a 2.5:1 (2*R*,3*S*)/(2*R*,3*R*) ratio in 80% yield (Scheme 8). Direct fluorination of the alcohols **33a**,**b** afforded the fluorinated compounds **35a**,**b** in low yields (10–20%). On the other hand, fluorination of **33a**,**b** was conducted via the trimethylsilated intermediates **34a**,**b** with Morpho-DAST and **35a**,**b** were obtained in 50% yield with a 5.7:1 (2*R*,3*R*)/(2*R*,3*S*) ratio. Hydrolysis of **35a**,**b** with 4 N HCl followed by protection of the hydroxy group at the C^1 position with a *tert*-butyldimethylsilyl group provided **36a** and **36b**, and the two isomers could be separated by flash chromatography. A Mitsunobu reaction was performed with the major diastereomer (2*R*,3*R*)-**36a** utilising Ph_3P, DEAD and phthalimide (PhthNH) and the compound (2*S*,3*R*)-**37** was obtained in 80% yield. Finally, removal of the TBDMS protecting group in a dioxane/HCl system followed by oxidation of the

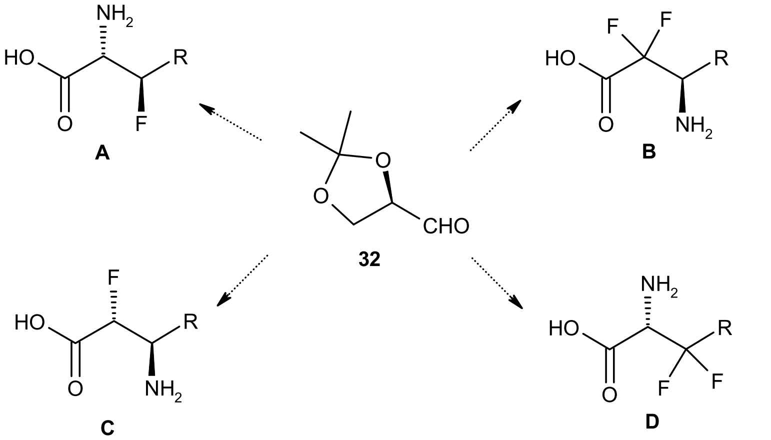
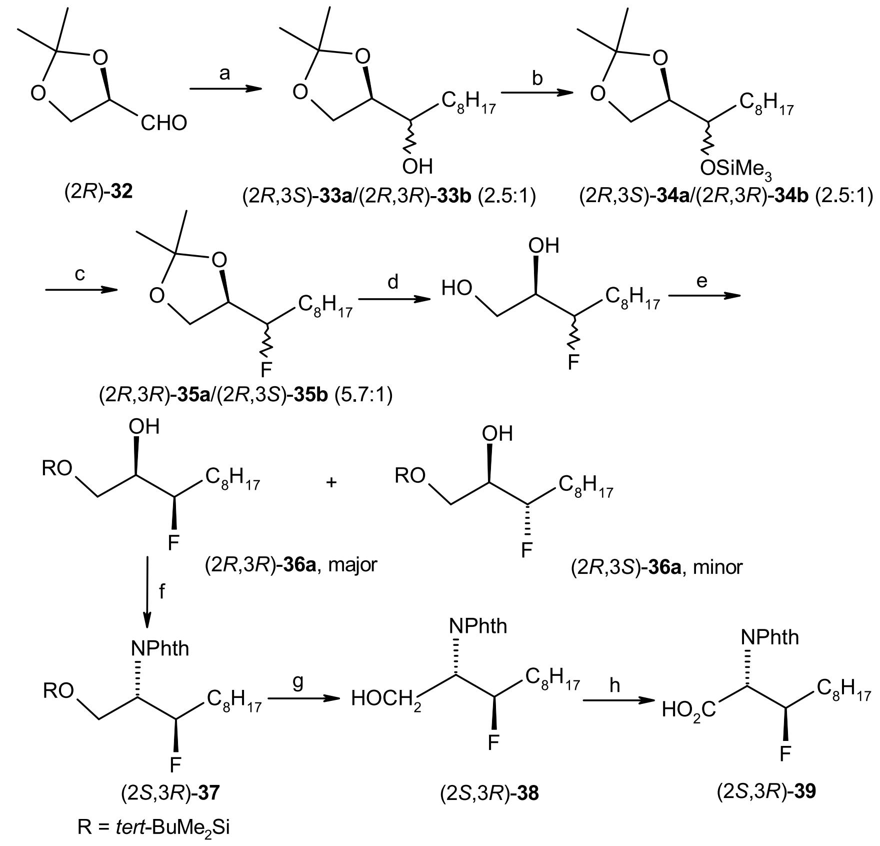
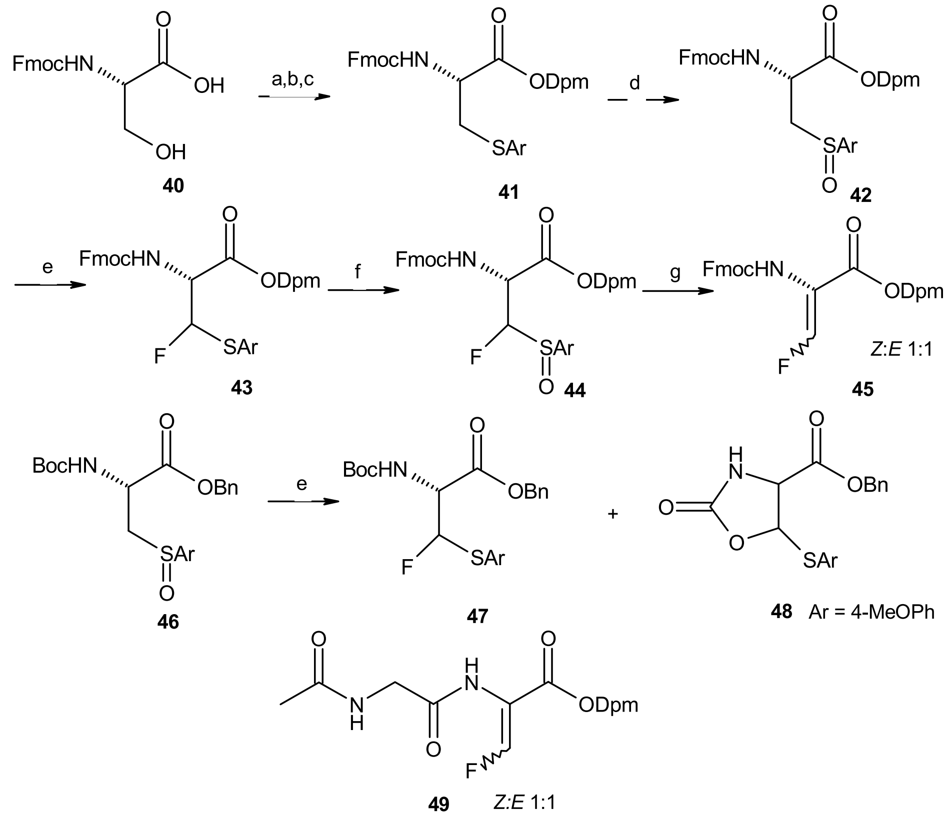


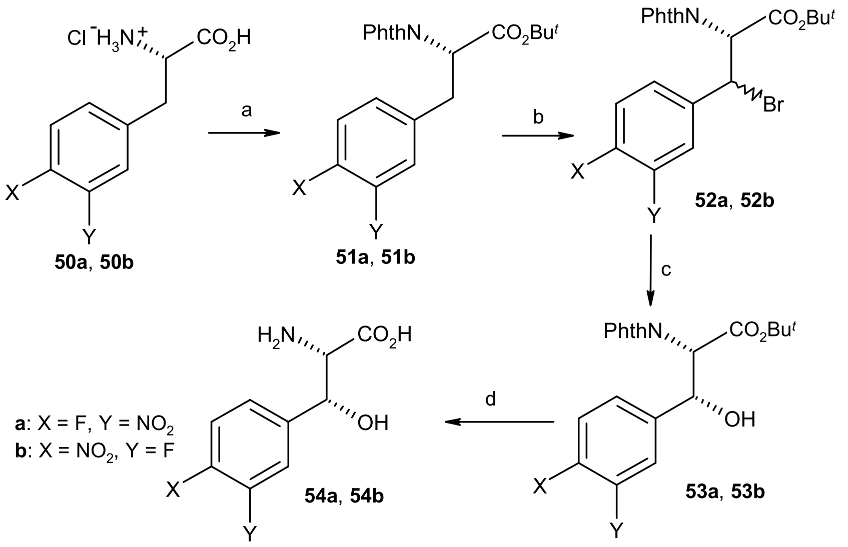
Figure 1. Four possible fluorinated amino acids obtainable from **32**.



Scheme 8. Reagents and conditions: (a) n-$C_8H_{17}MgBr$, THF, −30 °C to rt, 1 h; (b) Me_3SiCl, DMAP, CH_2Cl_2, −15 °C to rt, 1 h; (c) Morpho-DAST, CH_2Cl_2, −25 °C, 2 h; (d) 4 N HCl, THF, rt, 24 h; (e) t-$BuMe_2SiCl$, DMAP, CH_2Cl_2, rt, 16 h; (f) PhthNH, DEAD, Ph_3P, toluene, 0 °C then rt, 24 h; (g) dioxane/HCl/H_2O (93:5:2), rt, 20 h; (h) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CCl_4–MeCN–H_2O, rt, 3.5 h.



Scheme 9. Reagents and conditions: (a) $Ph_2C{=}NNH_2$, I_2, $PhI(OAc)_2$; (b) MsCl, Et_3N; (c) 4-MeOPhSH, Et_3N, THF; (d) m-CPBA, −40 °C; (e) DAST, cat. $SbCl_3$; (f) m-CPBA, −20 to −5 °C; (g) heat.



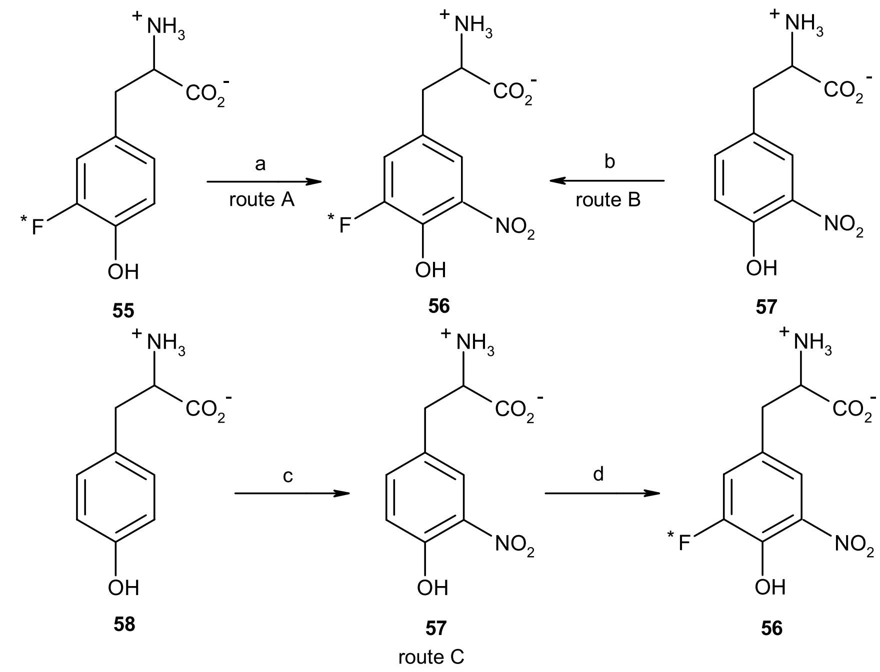
Scheme 10. Reagents and conditions: (a) (i) *N*-carbethoxyphthalimide, Na_2CO_3; (ii) EtOCOCl, Et_3N; (iii) *t*-$BuNH_2$; (b) NBS, CCl_4, hν; (c) Ag_2SO_4, acetone, H_2O; (d) aqueous HCl, AcOH.

resulting alcohol **38** with $NaIO_4/RuCl_3$ successfully gave the N-protected fluorinated amino acid (2*S*,3*R*)-**39** with a high diastereomeric purity (de >99%).

Michael acceptors such as dehydroalanines have been the popular functionalities for the design of enzyme inhibitors and active site affinity labels.[25] Introduction of a halogen on the terminal vinyl carbon could alleviate the potential drawback of the reversibility of conjugate additions, which, in certain cases, precluded the identification of the nucleophile. The (*E*)- and (*Z*)-3-fluorodehydroalanine derivatives **45** have therefore been prepared from serine via a fluoro-Pummerer rearrangement by Zhou et al. (Scheme 9).[26] The Fmoc-serine derivative **41** was prepared from **40** in 52% yield over three steps. Oxidation of **41** to **42** with *m*-CPBA followed by treatment under the fluoro-Pummerer rearrangement conditions[27] successfully gave the fluorinated cysteine derivative **43** as a 1:1 mixture of diastereomers. The compound **43** was oxidised with *m*-CPBA to yield four diastereomers of the fluorinated sulphoxide **44**, and this was subjected to subsequent thermolytic elimination in benzene to afford the two 3-fluorodehydroalanine isomers **45** (*Z*/*E*=1:1) in 47% yield over two steps. When a Boc group was used instead of an Fmoc group, the fluoro-Pummerer rearrangement of **46** gave the desired compound **47**, along with the byproduct **48**. The byproduct was formed by cyclisation of the carbamate carbonyl oxygen onto the thiocarbenium intermediate. The amount of **48** could be reduced in some cases by increasing the overall concentration of the reaction mixture. This methodology was also successfully applied to the synthesis of the dipeptide **49**.

In 1999, Hutton[28] provided a rapid, high-yield and stereospecific route to both 3-fluoro-4-nitro- and 4-fluoro-3-nitro-(2*S*,3*R*)-β-hydroxyphenylalanines **54a**, **54b** starting from (*S*)-4-fluoro-3-nitrophenylalanine **50a** and (*S*)-3-fluoro-4-nitrophenylalanine **50b** using bromination–hydrolysis methodology,[29] although several syntheses of 4-fluoro-3-nitro-β-hydroxyphenylalanine derivatives have been reported.[30] The amino acids **50a**, **50b** were first protected with *N*-phthaloyl and *tert*-butylamino groups to give the N^a-phthaloyl-*N*-*tert*-butylamide derivatives **51a**, **51b** in 78 and 74% yield, respectively (Scheme 10). Bromination of **51a**, **51b** with NBS afforded the corresponding bromides **52a**, **52b** as a 1:1 mixture of diastereomers in 99 and 98% yields, respectively. Subsequent treatment of **52a**, **52b** with silver sulphate in aqueous acetone yielded the desired alcohols **53a**, **53b** in 67–85% yields. Finally, deprotection of the β-hydroxyarylalanine derivatives **53a**, **53b** upon treatment with 5 N HCl/acetic acid (2:1) gave the free amino acids **54a**, **54b** smoothly in 82 and 78% yield, respectively. When the *tert*-butyl protecting group in **52a** was replaced by a methyl group, however, treatment of the corresponding methyl ester also with Ag_2SO_4 in aqueous acetone afforded the desired product only in 35% yield along with the (*Z*)-dehydroarylalanine derivative byproduct in 50% yield.

The detection of 3-nitro-L-tyrosine has been used as a biomarker of reactive nitrogen species in biological matrices. A number of analytical procedures including UV, HPLC, MS etc. have been used for the separation, detection and quantification of 3-nitro-L-tyrosine.[31] Recently, labelled compounds have also been considered for the detection and quantification of 3-nitro-L-tyrosine. Chirakal and co-workers[32] synthesised ^{18}F labelled 5-fluoro-3-nitro-L-tyrosine [^{18}F]-FNT **56** via three synthetic routes (Scheme 11). The direct nitration of [^{18}F]-3-fluoro-L-tyrosine **55** (route A) using $NaNO_3$ in TFA at 4 °C produced [^{18}F]-FNT with a radiochemical yield (RCY) of 96±2% with respect to [^{18}F]-3-fluoro-L-tyrosine **55**. Direct fluorination of 3-nitro-L-tyrosine **57**, however, using [^{18}F]-F_2 resulted in RCYs of 13 and 15% in TFA and HF, respectively, for [^{18}F]-FNT (route B). One-pot nitration of L-tyrosine **58** using TFA and HF as solvents, followed by fluorination using [^{18}F]-F_2, was also carried out and provided the [^{18}F]-FNT with RCYs of 14 and 12%, respectively (route C). The low RCYs of [^{18}F]-FNT which resulted from the direct fluorination of 3-nitro-L-tyrosine (route B and C) were due to the electron-withdrawing nitro



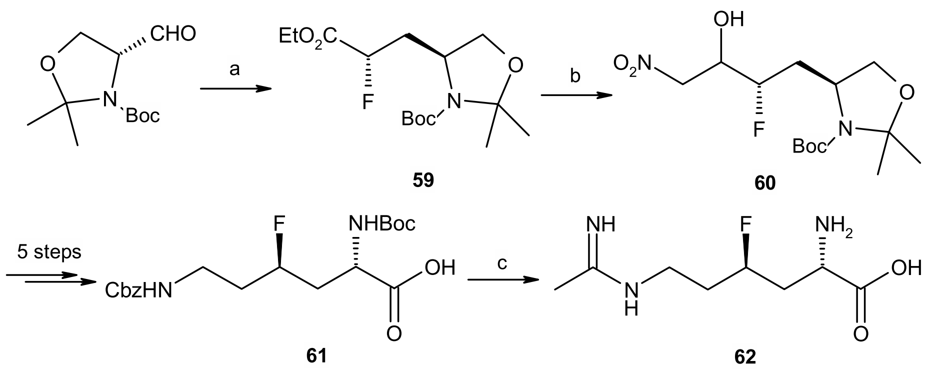
Scheme 11. Reagents and conditions: (a) $NaNO_3$, TFA, 4 °C, 5 min; (b) $[^{18}F]$-F_2, TFA or HF; (c) $NaNO_3$, TFA or HF; (d) $[^{18}F]$-F_2.

group, which renders the aromatic ring less susceptible to electrophilic aromatic substitution.

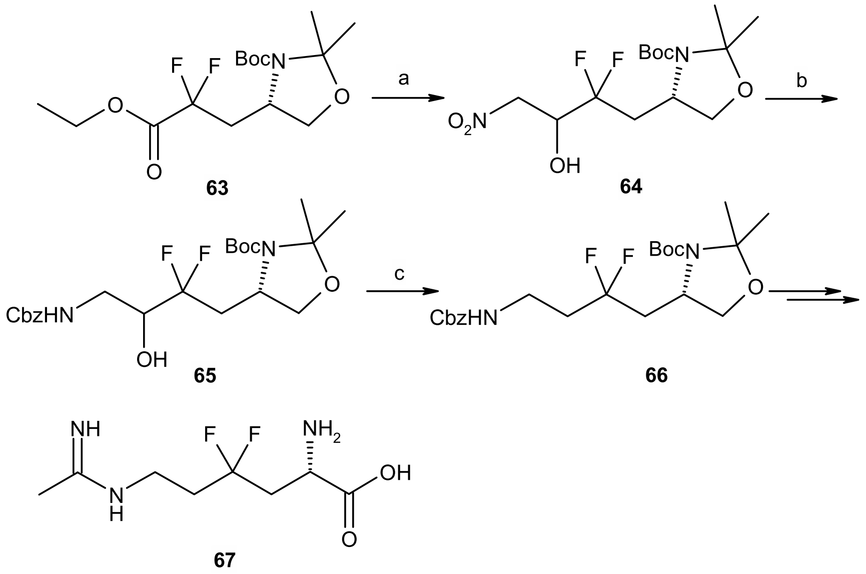
During the course of the research on selective inhibitors of inducible nitric oxide synthase (iNOS), iminoethyl-L-lysine (L-NIL) was identified as a potent selective inhibitor of iNOS.[33] Hallinan et al.[34] recently introduced fluorine atom(s) into the C-4 position of L-NIL for probing the stereochemical and electronic requirements of the arginine binding site of iNOS and synthesised (4*R*)-fluoro-L-NIL **62** and 4,4-difluoro-L-NIL **67**. Treatment of Garner's aldehyde under Wadsworth–Emmons conditions (triethyl 2-fluoro-2-phosphonoacetate, NaH, THF) followed by hydrogenation of the resulting double bond yielded the fluoro ester **59**. Reduction of **59** with $NaBH_4$ followed by treatment with Henry reaction conditions ($MeNO_2$, Na_2CO_3, THF) gave the compound **60** (Scheme 12). The key intermediate **61** was successfully obtained in a straightforward fashion from **60** over five steps, involving the removal of the hydroxyl group, reduction of the nitro ester, protection of the resulting amine with a Cbz group, hydrolysis of the hemiaminal moiety and oxidation of the hydroxymethyl moiety into the acid. The compound **61** was deprotected by catalytic hydrogenation, amidinated with ethyl acetimidate hydrochloride, and finally hydrolysed in 4 M HCl/AcOH to give the target molecule, (4*R*)-fluoro-L-NIL **62** smoothly.

The oxazolidine **63** was the pivotal intermediate for 4,4-difluoro-L-NIL **67** (for convenience, the synthesis of difluorinated α-amino acids **67** is summarised here). Reduction of the ester moiety of **63** with $NaBH_4$ or DIBAL-H followed by treatment of the resulting hemiacetal with $MeNO_2$ gave the desired hydroxynitro adduct **64** (Scheme 13). Reduction of the nitro group of **64** and subsequent protection of the resulting amine with the benzyloxycarbonyl group smoothly afforded the compound **65**. Finally, deoxygenation of **65** yielded the oxazolidine **66**.The compound **66** could be successfully converted into the desired 4,4-difluoro- L-NIL **67** using the same conditions just described for the synthesis of (4*R*)-fluoro-L-NIL **62**.

The natural amino acid L-proline is a very good chiral

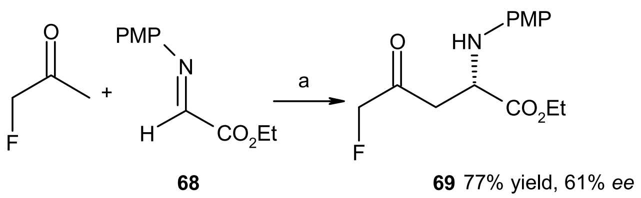


Scheme 12. Reagents and conditions: (a) (i) triethyl 2-fluoro-2-phosphonoacetate, NaH, THF, −40 °C to rt; (ii) H_2, 60 psi, Pd/C, EtOH; (b) (i) $NaBH_4$, MeOH, −50 to 0 °C; (ii) $MeNO_2$, Na_2CO_3, THF, rt, 2 days; (c) (i) Pd/C, MeOH, H_2, 5 psi, rt; (ii) ethyl acetimidate hydrochloride, NaOH, EtOH, rt; (iii) 4 M HCl–dioxane, AcOH.



Scheme 13. Reagents and conditions: (a) (i) 1 M DIBAL-H in toluene, toluene, 1.5 h, −78 °C; (ii) $MeNO_2$, K_2CO_3, 20 h, rt; (b) (i) 20% $Pd(OH)_2$/C, AcOH, 3 h, rt; (ii) CbzOSuc, $NaHCO_3$, acetone–H_2O (1:1), 18 h, 0 °C to rt; (c) (i) thiocarbonyldiimidazole, DMAP, CH_2Cl_2, 1 h, rt; (ii) benzoyl peroxide, Et_3SiH, toluene, 3 h, reflux.

catalyst in Aldol condensations and Mannich-type reactions. A proline-catalysed Mannich-type reaction of N-PMP-protected α-imino ethyl glyoxylate **68** with a variety of unmodified ketones provided the functionalised α-amino acids in high yields with excellent regio-, diastereo- and enantioselectivities.[35] The fluorinated α-amino acid derivative **69** was synthesised in 77% yield with 61% ee using the proline-catalysed Mannich-type reaction (Scheme 14).

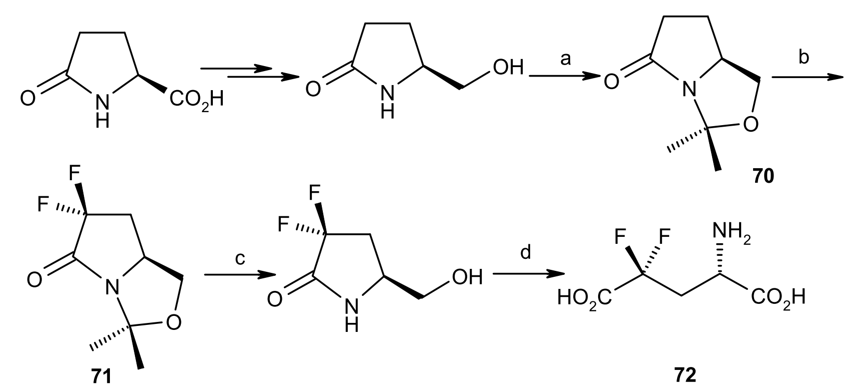


Scheme 14. Reagents and conditions: (a) (L)-proline (20 mol%), DMSO, 2–24 h, rt.

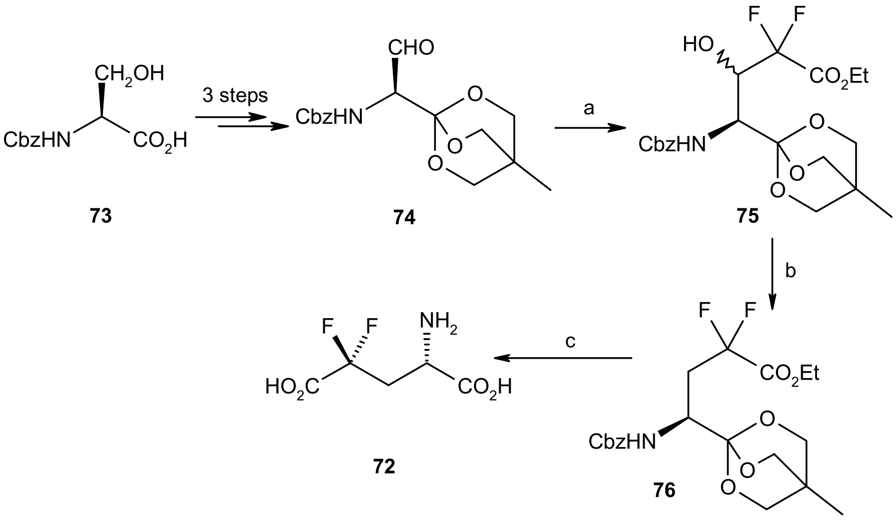
2.2. *gem*-Difluoromethylated α-amino acids

4,4-Difluoroglutamic acid **72** is an attractive unnatural amino acid target because it can be easily converted to 4,4-difluoroglutamine and 4,4-difluoroornithine. A stereoselective synthesis of L-4,4-difluoroglutamate has been reported in 1990, but this requires a commercially unavailable starting material.[36] A new synthetic method for **72** starting from readily available starting materials was presented by Coward and Konas in 1999 (Scheme 15).[37] Enantiomerically pure **70**, derived from pyroglutamic acid, was difluorinated by NFSi to give the bicyclic lactam **71** in 42% yield. Deprotection of **71** with acetic acid followed by Jones oxidation of the resulting hydroxymethyl moiety and hydrolysis with 6 N HCl afforded the optically pure L-4,4-difluoroglutamic acid **72** in 14% overall yield based on **70**.

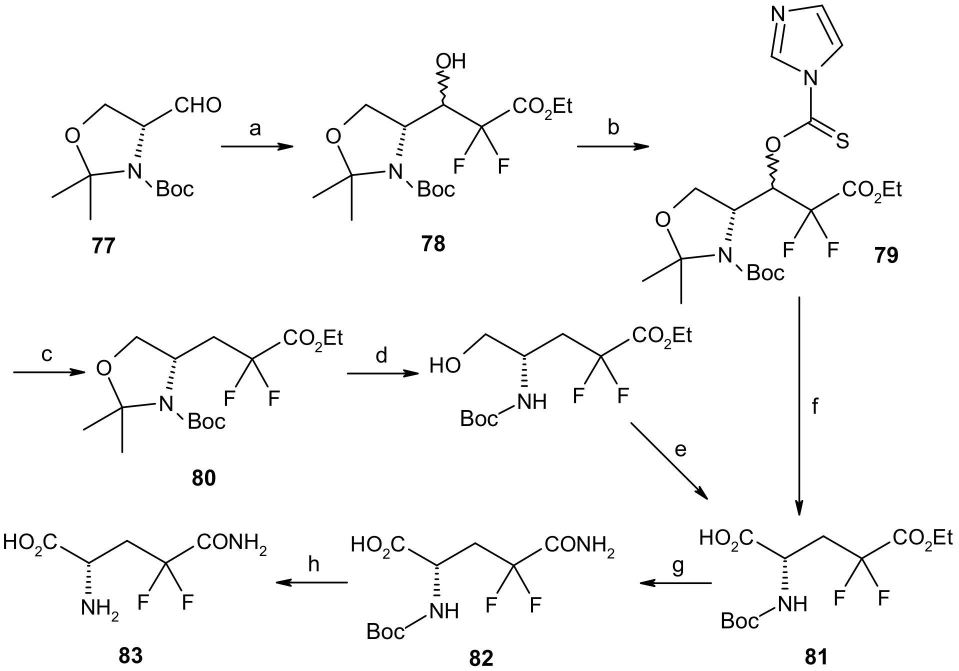
Two years later, Richards and co-workers[38] provided another route to the optically active L-4,4-difluoroglutamic acid **72** via nucleophilic addition to a chiral aldehyde. Their synthesis used the configurationally stable L-serine



Scheme 15. Reagents and conditions: (a) DMP, TsOH, toluene, 80–90 °C; (b) (i) LDA, NFSi, THF, −78 °C; (ii) LDA, NFSi, THF, −78 °C; (c) AcOH/MeCN/H_2O, 90 °C; (d) (i) H_2CrO_4, acetone; (ii) 6 N HCl, reflux.

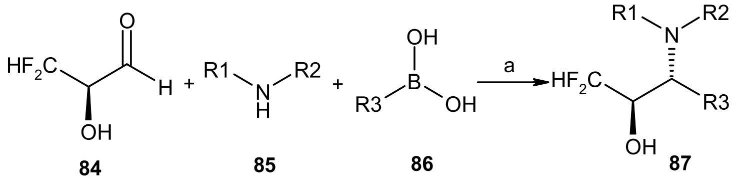


Scheme 16. Reagents and conditions: (a) $BrZnCF_2CO_2Et$, THF, rt; (b) (i) $(C_3H_3N_2)$=S, dry THF, rt; (ii) Et_3SiH, $(PhCO_2)_2$, benzene, reflux; (c) 6 N HCl, reflux, then anion-exchange chromatography.

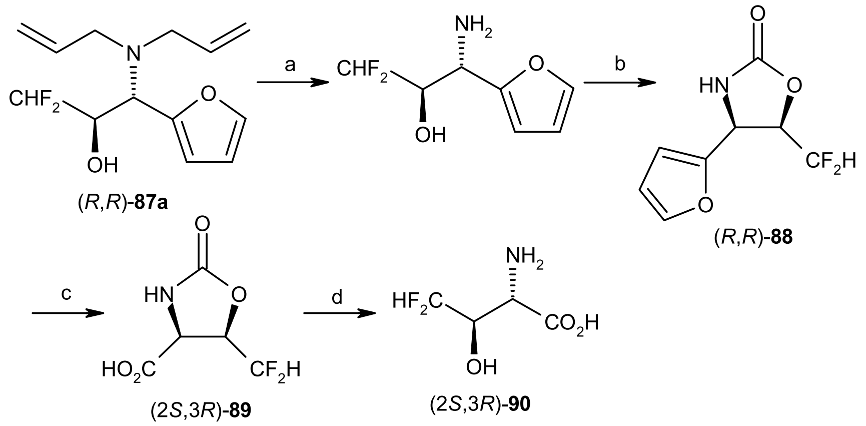


Scheme 17. Reagents and conditions: (a) $BrCF_2CO_2Et$, Zn, ultrasound, THF, rt, 8 h; (b) thiocarbonyldiimidazole, 1,2-dichloroethane, rt, 20 h; (c) Et_3SiH, Bz_2O_2, reflux, 1.5 h; (d) TFA/MeOH, rt, 3 h or Dowex H^+/MeOH, rt, 4 days; (e) CrO_3, H_2SO_4, H_2O/acetone, 0 °C to rt, 3 h or PDC/DMF, rt, 21 h; (f) (i) Et_3SiH, Bz_2O_2, reflux, 1.5 h; (ii) cat. CrO_3, H_5IO_6, MeCN, 0 °C to rt, 15 min; (g) 28% aq. NH_3, rt, 18 h then 1 N aq. $KHSO_4$; (h) TFA, rt, 1 h.

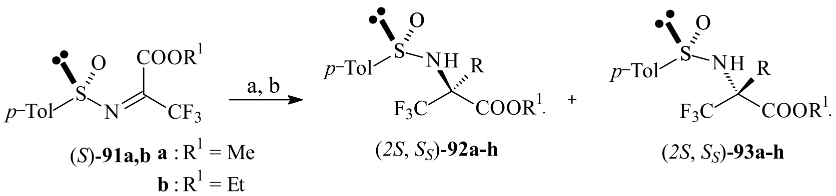
aldehyde **74** as the chiral building block (Scheme 16), which was prepared from N-protected L-serine **73** in three steps. Reformatsky reaction of ethyl bromodifluoroacetate with the aldehyde **74** gave a mixture of the *anti*/*syn* (7:1) alcohol derivative **75** in 70% yield. The diastereomeric mixture was thiocarbonylated and then subjected to radical-promoted deoxygenation to afford the compound **76**. Acidic hydrolysis of **76** followed by anion-exchange chromatography smoothly gave the optically pure L-4,4-difluoroglutamic acid **72** in 37% yield.



Scheme 18. Reagents and conditions: (a) EtOH, rt, 24–48 h.



Scheme 19. Reagents and conditions: (a) $Pd(PPh_3)_4$, CH_2Cl_2, *N*,*N*′-dimethylbarbituric acid; (b) (i) Boc_2O, dioxane, rt; (ii) NaH, DMF, rt; (c) $MeOH/O_3$, −78 °C; (d) 6 N HCl, reflux, 8 h.



Scheme 20. Reagents and conditions: (a) RMgX, THF, −70 °C; (b) NH_4Cl, H_2O.

Meffre and co-workers[39] first synthesised the optically pure L-4,4-difluoroglutamine **83** from (*R*)-Garner's aldehyde **77** using a Reformatsky reaction as the key step (Scheme 17), although racemic 4,4-difluoroglutamine has been prepared from D,L-4,4-difluoroglutamic acid.[40] Treatment of **77** with $BrCF_2CO_2Et/Zn$ in THF under ultrasonic conditions afforded the diastereoisomeric mixture of alcohols **78** (81% yield), which was further converted to the imidazolyl-thiocarbonates **79** in 80% yield. Barton–McCombie radical deoxygenation of **79** with Et_3SiH/Bz_2O_2 under reflux condition gave the crude product **80** in quantitative yield. Oxazolidine ring opening of **80**, however, and subsequent oxidation of the resulting alcohol using the Jones reagent or PDC/DMF provided the desired compound **81** in low yield (15–18%). Alternatively, the compound **81** could also be prepared in 46% yield by deoxygenation of **79** followed by direct oxidation using a stoichiometric amount of H_5IO_6 in the presence of a catalytic amount of CrO_3. Finally, aminolysis of the ester **81** with 28% aqueous NH_3 at rt smoothly provided Boc-protected L-4,4-difluoroglutamine **82**, which was further treated with TFA at rt to yield the desired L-4,4-difluoroglutamine **83** in 80% yield with high ee (>99%).

In 2002, Prakash and co-workers[41] developed a facile and efficient methodology for the stereoselective synthesis of *anti*-α-(difluoromethyl)-β-amino alcohols **87** by a boronic acid-based three-component condensation involving a difluoromethylated carbonyl compound **84**, an amine **85** and an organoboronic acid **86** (Scheme 18). A series of *anti*-α-(difluoromethyl)-β-amino alcohols **87** could be provided via this methodology in good yields (30–90%) with high ee (>86%). The further conversion of the fluorinated amino alcohols could lead to some biologically important compounds, such as fluorinated amino acids. In one example, compound **87a** was conveniently converted into (2*S*,3*R*)-difluorothreonine **90** (Scheme 19), which was the first asymmetric synthesis of *anti*-difluorothreonine. Compound **87a** was first deallylated with $Pd(PPh_3)_4$/*N*,*N*′-dimethyl-barbituric acid in CH_2Cl_2 and subsequently converted into the oxazolidinone **88** using Boc_2O in 90% yield. Next, ozonolytic oxidation of the furyl moiety of **88** with O_3 in MeOH at −78 °C gave the acid **89** in 75% yield and finally, the acid **89** was further hydrolysed to provide *anti*-difluorothreonine (2*S*,3*R*)-**90**.

2.3. Trifluoromethylated and polyfluorinated α-amino acids

α-Trifluoromethylated α-amino acids (α-Tfm AAs) form a special class of man-made quaternary α,α-disubstituted α-amino acids of considerable interest in modern peptide chemistry due to the unique properties of the trifluoromethyl group. Previous methodologies for the synthesis of α-Tfm AAs have suffered from some drawbacks, such as poor stereocontrol in the formation of the stereogenic quaternary centre.[42] Crucianelli and co-workers[43] provided a novel and efficient route for non-racemic α-trifluoromethyl α-amino acids starting from the chiral sulphinimines **91a** and **91b** of trifluoropyruvate. The key step is the treatment of different Grignard reagents (RMgX, X=Cl or Br) with the sulphinimines (*S*)-**91a** and (*S*)-**91b** (Scheme 20). The corresponding diastereomeric sulphinamides (2*S*,S_S)-**92a–h** and (2*R*,S_S)-**93a–h** were obtained with variable stereoselectivities, depending mainly on the nature of the Grignard reagents (Table 2). The compounds (2*S*,S_S)-**92a–h** and (2*R*,S_S)-**93a–h** were provided in diastereomerically and chemically pure forms by flash chromatography. Finally,

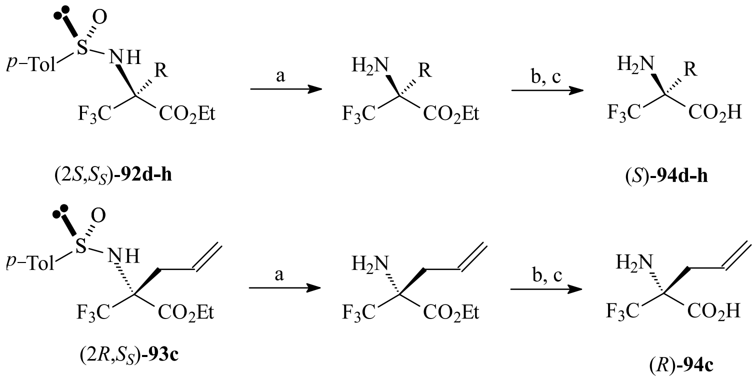
Table 2. Summary of reactions of (*S*)-**91a**,**b** with different Grignard reagents RMgX[43]

Entry	Product	R	R^1	X	ee (%)	Yield (%)	**92/93**
1	**92**,**93a**	Benzyl	Me	Cl	92.5	68	30:70
2	**92**,**93b**	Benzyl	Et	Cl	92.5	68	30:70
3	**92**,**93c**	Allyl	Et	Cl	85	55	34:66
4	**92**,**93d**	Isobutyl	Et	Br	88	65	88:12
5	**92**,**93e**	Isopropyl	Et	Cl	90.5	72	84:16
6	**92**,**93f**	*n*-Butyl	Et	Cl	n.m.	55	74:26
7	**92**,**93g**	Ethyl	Et	Br	>96	70	73:27
8	**92**,**93g**	Ethyl	Et	Cl	92	55	72:28
9	**92**,**93h**	Methyl	Et	Cl	>96	52	55:45

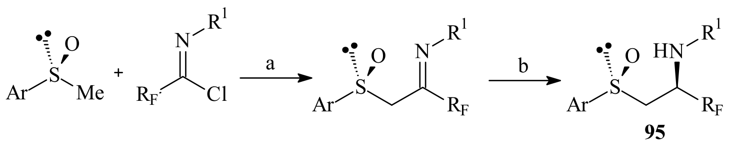
cleavage of the *N*-sulphinyl groups from the sulphinamides **92d–h** and **93c** with TFA in MeOH followed by hydrolysis of the resulting products using 0.5 N KOH in MeOH/H_2O provided a series of α-trifluoromethyl α-amino acids **94c–h**, along with the recovery of menthyl sulphinate (Scheme 21).

In the same year, Fustero's group[44] synthesised cyclic and acyclic fluorinated α-amino acids and their derivatives in high diastereoselectivity also using chiral arylsulphinyl compounds as auxiliaries. The key step is hydride reduction of C=N bonds stereocontrolled by intramolecular π-stacking interactions of the arylsulphinyl and *N*-aryl groups. Generally, the hydride reduction with Bu_4NBH_4 in pure methanol or THF/methanol (-70 °C) provided the best diastereocontrol (*syn*/*anti*=66:34 to 99:1) and the fluorinated β-sulphinylamines **95** were formed in good yields (33–>98%) (Scheme 22). Both ab initio molecular orbital (MO) and density functional theory (DFT) calculations strongly suggested the presence of an attractive π–π interaction. This interaction had a decisive influence on the stereochemical outcome of C=N bond reduction, because the *si* face for R_F=CF_3 or CHF_2 and the *re* face for R_F=$CClF_2$ were exposed to the hydride attack, whereas the other diastereofaces were efficiently shielded.

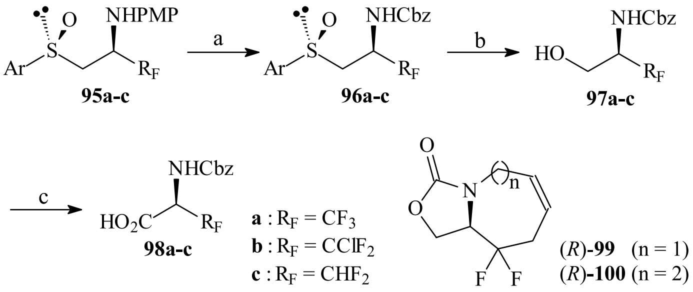
Removal of the PMP groups in *syn*-**95a–c** with cerium ammonium nitrate (CAN) followed by reprotection of the resulting amino groups with Cbz groups afforded *syn*-**96a–c** in 68–89% yield (two steps) (Scheme 23). The replacement of the 1-naphthylsulphinyl auxiliary by the hydroxy group with the non-oxidative Pummerer reaction[45] provided (*R*)-**97a–c** in good to excellent yields (70–90%). Finally, oxidation of the hydroxy group with $RuO_2{\cdot}xH_2O/NaIO_4$ provided the fluorinated alanines **98a–c** in 65–70% yield. An application of this methodology conveniently resulted in the first synthesis of enantiomerically pure fluorinated cyclic β-amino alcohol derivatives **99** and **100** featuring seven- and eight-membered rings.



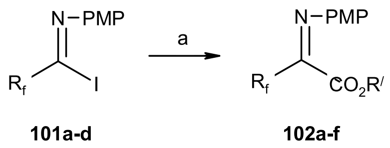
Scheme 21. Reagents and conditions: (a) TFA, MeOH; (b) 0.5 N KOH, MeOH/H_2O (7:3); (c) DOWEX-50W.



Scheme 22. Reagents and conditions: (a) LDA (2.0 equiv.), THF, −78 °C; (b) Bu_4NBH_4, MeOH, −70 °C.



Scheme 23. Reagents and conditions: (a) (i) CAN, MeCN/H_2O, rt; (ii) $ClCO_2Bn$, dioxane, 50% aqueous K_2CO_3; (b) (i) TFAA, MeCN, *sym*-collidine, 0 °C; (ii) 10% K_2CO_3; (iii) $NaBH_4$, H_2O; (c) $RuO_2{\cdot}xH_2O/NaIO_4$, acetone/H_2O, rt.



Scheme 24. Reagents and conditions: (a) $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd: 0.10 equiv.), CO (1 atm), R′OH, K_2CO_3, DMF or DMI, rt.

The transition metal-catalysed carbonylation of organic halides is one of the most versatile and convenient processes for the introduction of carbonyl groups into molecules[46] and the resulting products could be conveniently converted into many kinds of compounds, including amino acids. Uneyama et al.[47] synthesised a series of fluorinated iminoesters **102a–f** in moderate yields via the palladium-catalysed

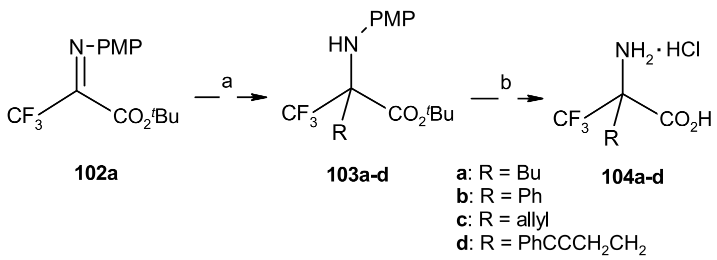
Table 3. Summary of Pd-catalysed carbonylation with alcohols[47]

Entry	R_F	R′	Solvent/additive	Time (days)	**102** (% yield)
1	CF_3 (**101a**)	*t*-Bu	*t*-BuOH	2	**102a** (25)
2	CF_3 (**101a**)	*t*-Bu	*t*-BuOH/DMF	4	**102a** (52)
3	CF_3 (**101a**)	*t*-Bu	*t*-BuOH/DMI	3	**102a** (62)
4	C_3F_7 (**101b**)	*t*-Bu	*t*-BuOH/DMI	4	**102b** (71)
5	C_7F_{15} (**101c**)	*t*-Bu	*t*-BuOH/DMI	4	**102c** (74)
6	CF_2Cl (**101d**)	*t*-Bu	*t*-BuOH/DMI	5	**102d** (41)
7	CF_3 (**101a**)	*i*-Pr	Toluene	1	**102e** (49)
8	CF_3 (**101a**)	*i*-Pr	Toluene/DMF	1	**102e** (72)
9	CF_3 (**101a**)	(*l*)-Menthyl	Toluene	2	**102f** (12)
10	CF_3 (**101a**)	(*l*)-Menthyl	Toluene/DMI	2	**102f** (51)

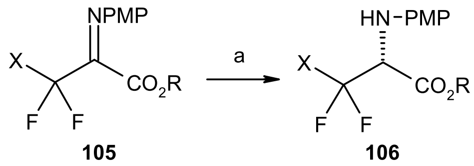
($Pd_2(dba)_3{\cdot}CHCl_3$) carbonylation of fluorinated imidoyl iodides **101a–d** with DMF or DMI as an additive (Scheme 24). The addition of DMF or DMI was essential for improving the yields of the *tert*-butyl or *iso*-propyl iminoesters **102a–e** (Table 3). The fluorinated iminoester **102a**, possessing both an easily removable N-protecting group (PMP) and *O*-protecting group (*t*-Bu), could be conveniently alkylated to form the *tert*-butyl *N*-(*p*-methoxyphenyl)amino-3,3,3-trifluoropropanoates **103a–d** in high yield (>95%) (Scheme 25). Oxidative removal of the PMP groups of **103a–d** by treatment with cerium ammonium nitrate (CAN) followed by deprotection of the *t*-Bu groups under acidic conditions (HCl gas) smoothly provided the corresponding α-amino-3,3,3-trifluoropropanoic acid derivatives **104a–d** in good yield (68–95%, two steps).

The asymmetric hydrogenation of α-fluorinated iminoesters **105** was also carried out by Uneyama and Amii (Scheme 26).[48] The solvents and catalysts in the hydrogenation of the iminoesters **105** had profound effects on the yields and ees of the fluoro α-amino acid derivatives **106**. The best result was obtained when the reactions were catalysed by a palladium(II) trifluoroacetate and (*R*)-BINAP complex in 2,2,2-trifluoroethanol and the corresponding fluorinated α-amino acid derivatives **106** were obtained in good yield (69–99%) with moderate to high ee (Table 4).

Erlenmeyer azalactone synthesis is a well known and important approach for the preparation of DL-α-amino acids



Scheme 25. Reagents and conditions: (a) BuLi, THF, −78 °C (for **103a**); PhLi, THF, −78 °C (for **103b**); $CH_2{=}CHCH_2MgCl$, THF, 0 °C (for **103c**); $PhC{\equiv}CCH_2CH_2I$, *t*-BuLi, THF, −100 °C (for **103d**); (b) (i) CAN, $MeCN/H_2O$, rt; (ii) aq. HCl, MeOH, rt.



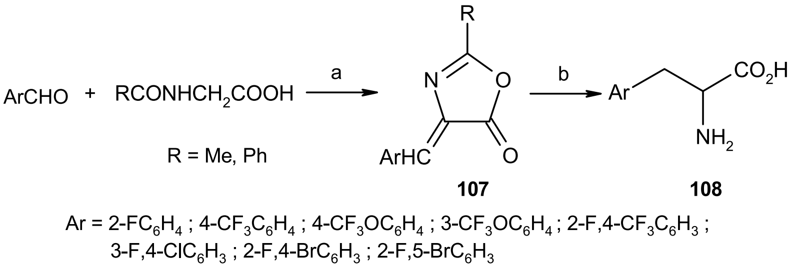
Scheme 26. Reagents and conditions: (a) $Pd(OCOCF_3)_2$, (*R*)-BINAP, H_2 (100 atm), CF_3CH_2OH, rt, 24 h.

Table 4. Summary of the asymmetric hydrogenation of α-fluorinated iminoesters **105**[48]

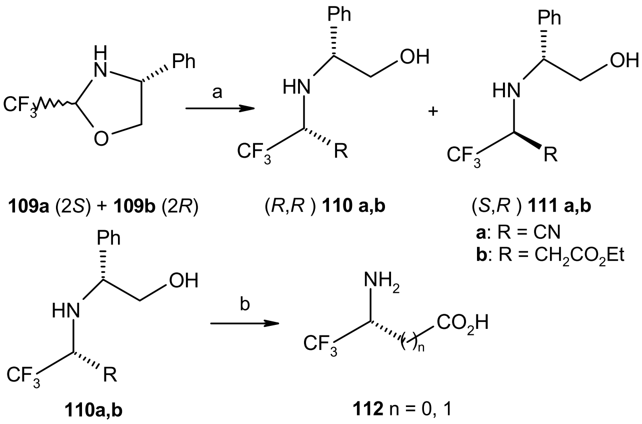
X	R	Yield (%)	ee (%)
F	Et	99	88 (*R*)
F	*t*-Bu	92	85 (*R*)
F	Bn	95	84 (*R*)
Cl	*t*-Bu	69	81 (*R*)
H	Bn	75	30 (*R*)
C_6F_{13}	Bn	98	61 (*R*)

including optically active amino acids from carbonyl compounds.[49] Samet and co-workers[50] synthesised a series of fluorinated DL-phenylalanines **108** in moderate yield (23–62%) from the corresponding aromatic aldehydes by an improved one-pot procedure involving an Erlenmeyer reaction and subsequent reduction of the resulting oxazolones **107** (without prior isolation) using P/HI (Scheme 27). Both *N*-acetyl- and *N*-benzoylglycine could be successfully used in the reactions. The yields with hippuric acid are, however, markedly lower, probably due to the higher stability of phenyl-substituted azalactones towards acidic hydrolysis compared to their methyl-substituted analogues. It is noteworthy that the yields for known compounds using this procedure are comparable or higher than those achieved by known multistep procedures involving the Erlenmeyer reaction.

Chiral 2-trifluoromethyl-1,3-oxazolidines **109a**,**b**, readily prepared from (*R*)-(−)-phenylglycinol, are important building blocks towards the synthesis of enantiopure



Scheme 27. Reagents and conditions: (a) Ac_2O, 110–115 °C, 30 min; (b) P, HI, Ac_2O, reflux, 3.5 h.



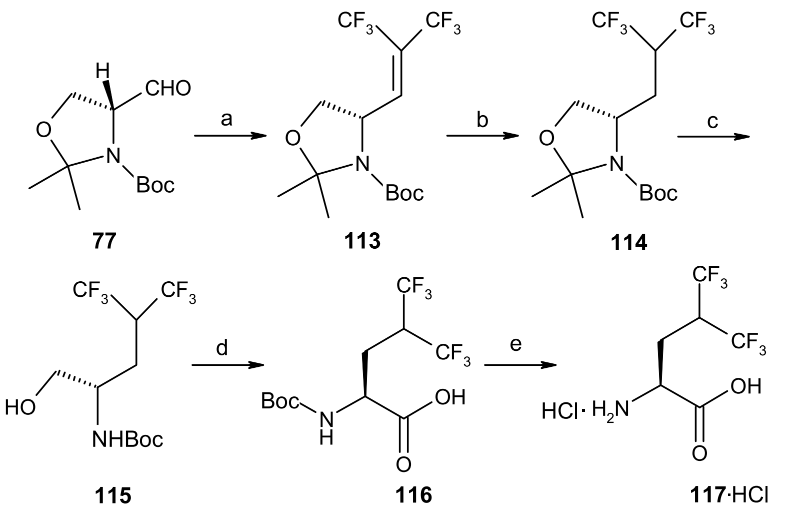
Scheme 28. Reagents and conditions: (a) TMSCN or $H_2C{=}C(OTMS)OEt$, Lewis acid; (b) $Pb(OAc)_4$, CH_2Cl_2/MeOH (2:1), then conc. HCl, reflux, 4 h. H^+ resin.

trifluoromethylamino compounds. Brigaud and co-workers[51] investigated the Strecker reaction of **109a**,**b** with various silylated nucleophiles under Lewis acid activation (Scheme 28). The aminonitriles **110a**, **111a** and aminoesters **110b**, **111b** were obtained as a diastereomeric mixture in high yield (73–91%) with $BF_3{\cdot}Et_2O$ (1.5 equiv.) or a catalytic amount of TMSOTf as the Lewis acid (Table 5). The major diastereomers **110a**,**b** were separated by flash chromatography. The moderate stereoselectivities resulted from the nucleophilic attack of the silylated nucleophiles on the less-hindered *re* face of the iminium intermediates. The resulting functionalised α-trifluoromethylamines **110a**,**b** could be readily converted into (+)-3,3,3-trifluoroalanine **112** (n=0) and (+)-4,4,4-trifluoro-3-aminobutanoic acid **112** (n=1) in a one-step procedure.

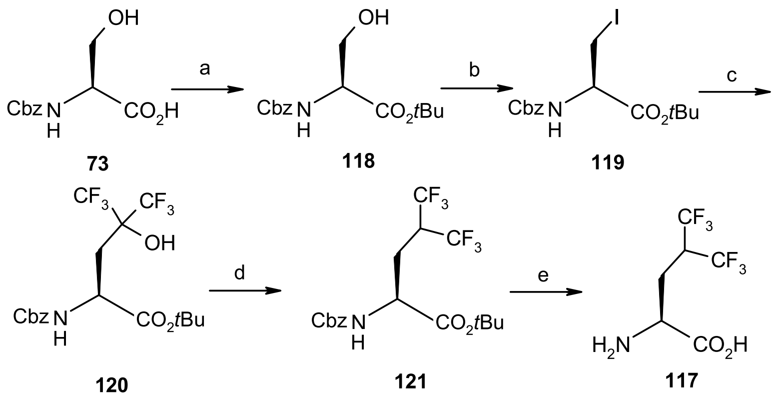
Leucine plays an important role in the folding of many proteins. Many important results were shown in recent reports describing the properties of peptides designed to form dimeric coiled-coil structures, based either on the leucine zipper domain of the transcription factor GCN4 or

Table 5. Summary of the reaction of **109a**,**b** with different silylated nucleophiles[51]

Entry	**109a**:**109b**	Silylated nucleophile	Lewis acid (equiv.)	Yield (%)	(*R*,*R*):(*S*,*R*)
1	62:38	TMSCN	$BF_3{\cdot}OEt_2$ (1.5)	91	**110a**:**111a**=83:17
2	87:13	TMSCN	TMSOTf (0.1)	87	**110a**:**111a**=81:19
3	20:80	TMSCN	TMSOTf (0.1)	84	**110a**:**111a**=83:17
4	—	$H_2C{=}C(OTMS)OEt$	$BF_3{\cdot}OEt_2$	73	**110b**:**111b**=86:14



Scheme 29. Reagents and conditions: (a) PPh_3, $[(CF_3)_2C]_2S_2$, Et_2O, −78 °C to rt, 3 days; (b) H_2, 10% Pd/C, THF; (c) TsOH, MeOH, rt; 1 day; (d) PDC, DMF, 18 h; (e) 40% CF_3CO_2H/CH_2Cl_2 then HCl, 10 min, rt.

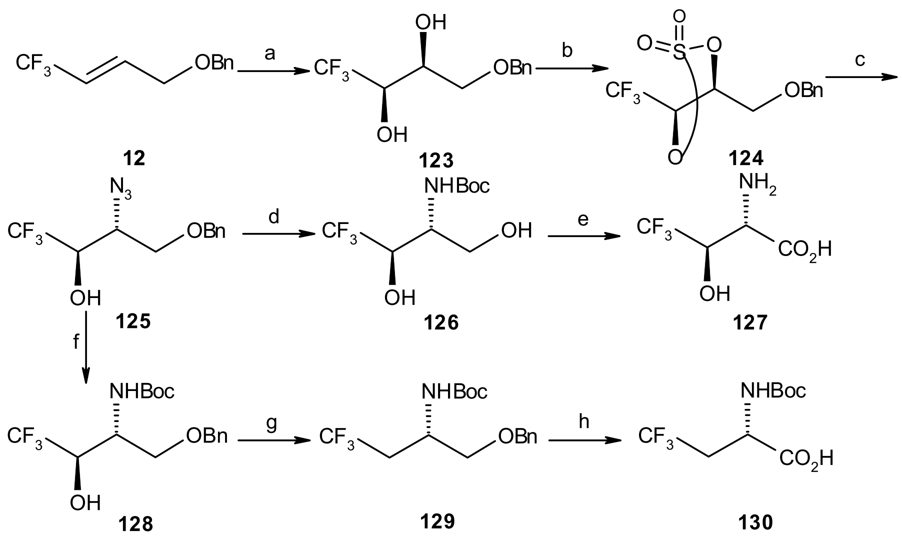


Scheme 30. Reagents and conditions: (a) K_2CO_3, $BnNEt_3Cl$, *t*BuBr, MeCN, 45–50 °C; (b) $(PhO)_3PMeI$, DMF; (c) (i) Zn (dust), 1,2-dibromoethane, TMSCl, $CuBr·SMe_2$, DMF; (ii) hexafluoroacetone (g), −25 to −30 °C; (d) (i) $ClCOCO_2Ph$, pyridine, toluene; (ii) Bu_3SnH, AIBN, toluene, 100 °C; (iii) KF-Celite, Et_2O; (e) (i) TFA/CH_2Cl_2, 0 °C to rt; (ii) H_2, 10% Pd/C, MeOH.

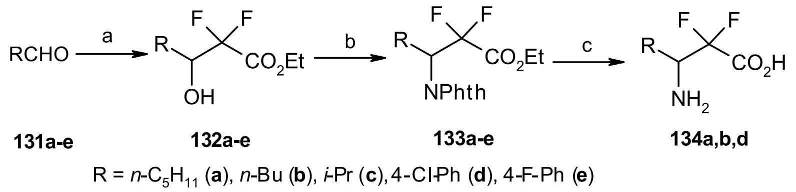
de novo designed sequences that incorporate (4*R*,4*S*)-L-trifluoroleucine,[52] (3*R*,3*S*)-L-trifluorovaline,[6a] L-hexafluoroleucine[6e,f] and trifluoroisoleucine.[6d] Although there are some reports[53] on the synthesis of racemic and non-racemic (81% ee) 5,5,5,5′,5′,5′-hexafluoroleucine, Kumar and co-workers[54] have provided an efficient route to (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine in >99% ee for direct use in solid-phase peptide synthesis. Garner's aldehyde **77** was converted to the bis-trifluoromethyl olefin **113** by a Wittig reaction in 92% yield (Scheme 29). Catalytic hydrogenation of **113** using Pd/C as a catalyst in THF afforded the oxazolidine **114**. The oxazolidine **114** was subjected to subsequent acid-catalysed ring cleavage to give the amino alcohol **115** in 78% yield over two steps. Oxidation of the hydroxymethyl moiety of **115** with pyridinium dichromate yielded the carboxylic acid **116** in 75% yield. Finally, removal of the Boc protecting group by TFA yielded the hydrochloride salt of 5,5,5,5′,5′,5′-hexafluoroleucine **117**, and the enantiomeric excess was verified to be >99% ee.

One year later, Marsh et al.[55] provided another short and efficient route to L-5,5,5,5′,5′,5′-hexafluoroleucine **117** starting from *N*-Cbz-L-serine **73** in 50% overall yield with 99% ee on a multigram scale (Scheme 30). The protected iodoalanine compound **119**, derived from **73** via the *tert*-butyl ester intermediate **118** in two steps, was converted into the corresponding organozincate and reacted directly with hexafluoroacetone to yield the compound **120** in 94% yield over two steps. Subsequent deoxygenation of **120** using the radical deoxygenation methodology gave the protected hexafluoroleucine **121** in 84% yield. Finally, removal of the *tert*-butyl and Cbz protecting groups afforded the optically pure L-5,5,5,5′,5′,5′-hexafluoroleucine **117**.

4,4,4-Trifluorothreonines are widely studied because of their potential pharmaceutical utility and their versatility as chiral building blocks with three distinguishable functionalities. All of the previously reported methodologies for the synthesis of enantiomerically pure 4,4,4-trifluorothreonines, however, required either resolution of racemates or a preformed chiral centre's stereoinduction. Recently, Qing and Jiang[56] reported the asymmetric synthesis of both enantiomers of *anti*-4,4,4-trifluorothreonine and 2-amino-4,4,4-trifluorobutanoic acid starting from the trifluoromethylated *trans*-disubstituted alkene **122** involving the Sharpless AD reaction as the key step (Scheme 31).



Scheme 31. Reagents and conditions: (a) AD-mix-β, $MeSO_2NH_2$, H_2O, *t*-BuOH, rt, 4 days; (b) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (ii) $NaIO_4$, $RuCl_3$, MeCN, CCl_4, rt; (c) (i) NaN_3, DMF, 80 °C, 4 h; (ii) H_3O^+; (d) $Pd(OH)_2$, Boc_2O, H_2, THF, rt; (e) (i) Jones reagent; (ii) CF_3CO_2H, CH_2Cl_2, 0 °C; (f) Pd/C, Boc_2O, H_2, THF, rt; (g) (i) PhOCSCl, DMAP, toluene; (ii) Bu_3SnH, AIBN, toluene; (h) (i) $Pd(OH)_2$, H_2, THF; (ii) Jones reagent.



Scheme 32. Reagents and conditions: (a) Zn, THF, $BrCF_2CO_2Et$; (b) DEAD, Ph_3P, PhthNH, solvent; (c) HOAc, HBr, reflux, then propylene oxide.

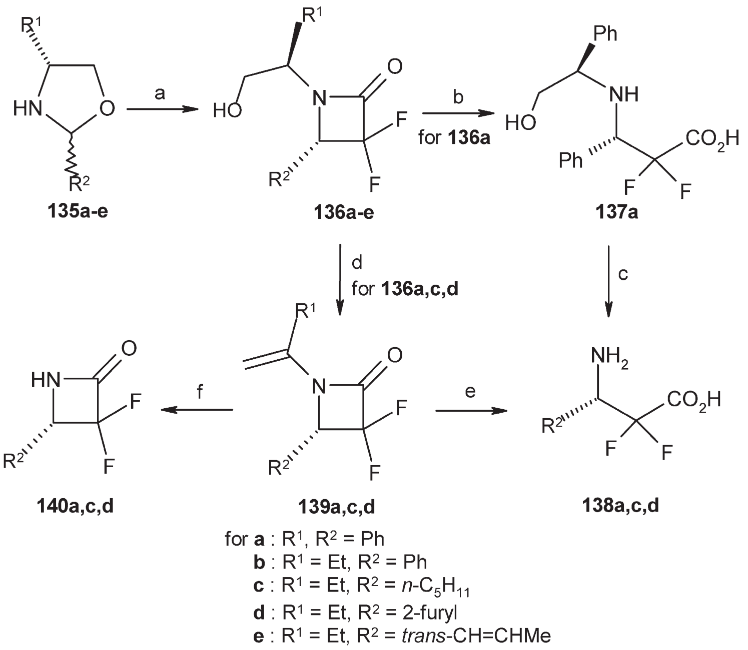
Sharpless AD reaction of the compound **122** with AD-mix-β provided (2*S*,3*R*)-1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **123** in 95% yield with 93% ee. Conversion of the vicinal diol **123** into the 2,3-cyclic sulphite with $SOCl_2$ followed by further oxidation with $NaIO_4/RuCl_3$ gave the cyclic sulphate **124** in 91% yield over two steps. Ring opening of **124** with NaN_3 in DMF followed by acidic hydrolysis provided the alcohol **125** in 96% yield. Hydrogenation of **125** in the presence of Boc_2O with $Pd(OH)_2$ as a catalyst yielded the diol **126**. The diol was then converted into optically pure (2*S*,3*R*)-4,4,4-trifluorothreonine **127** via oxidation of the hydroxymethyl moiety with the Jones reagent followed by removal of the Boc protecting group with TFA. On the other hand, hydrogenation of **125** in the presence of Boc_2O with Pd/C as a catalyst provided the alcohol **128** in 92% yield. Treatment of **128** with PhOCSCl followed by the radical-mediated dehydroxylation of the resulting compound gave **129**. Finally, **129** was converted into the desired (*S*)-2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid **130** via hydrogenation with $Pd(OH)_2$ as a catalyst followed by oxidation of the resulting hydroxymethyl moiety with the Jones reagent. Using a similar route and conditions, the other two enantiomers of **127** and **130** were also synthesised.

3. Fluorinated β-amino acids

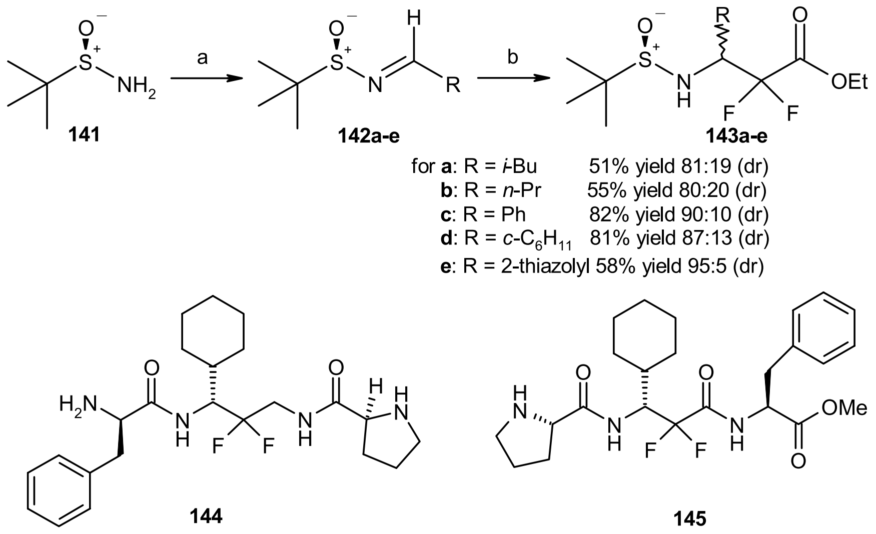
The synthesis of β-amino acids has gained considerable attention due to their biologically important properties, their occurrence in natural products, and as their potential as precursors for β-lactams.[57] In view of the special physical and biological properties of fluorinated compounds, fluorinated β-amino acids (F-βAAs) have recently become of great interest in both medicinal and bioorganic chemistry and some good results have been achieved.[58] As an example, the CH_2 to CF_2 transposition in the β-amino acid fragment of the naturally occurring antifungal tetrapeptide, rhodopeptin,[58c] results in an improved toxicity profile for this class of compounds. Additionally, F-βAAs are now recognised as potentially exciting building blocks for the synthesis of β-peptides, antibiotics and enzyme inhibitors,[59] although fluorinated β-peptides have not been reported to date.

3.1. *gem*-Difluoromethylated β-amino acids

Ethyl bromodifluoroacetate is a very important building block for the synthesis of *gem*-difluoromethylated compounds, including *gem*-difluoromethylated amino acids. Fokina and co-workers[60] have synthesised biologically



Scheme 33. Reagents and conditions: (a) $BrCF_2CO_2Et$ (3.5 equiv.), Zn, THF; (b) 6 N HCl; (c) H_2, Pd/C, MeOH; (d) (i) Tf_2O, pyridine; (ii) DBU or *t*-BuOK; (e) 6 N HCl; (f) 30 N H_2SO_4, Et_2O.

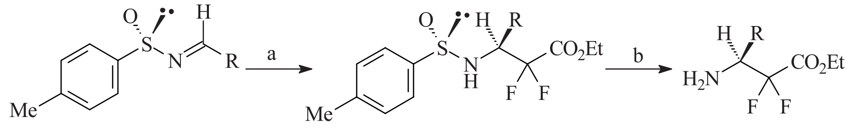


Scheme 34. Reagents and conditions: (a) RCHO, $CuSO_4$, CH_2Cl_2, MS (4A°), rt, 18 h; (b) $BrZnCF_2CO_2Et$ (3.5 equiv.), THF, rt, 18 h.

important α,α-difluoro-β-amino acids in three steps from the aldehydes **131a–e** and ethyl bromodifluoroacetate. The α,α-difluoro-β-hydroxy acid derivatives **132a–e** were prepared in 81–92% yield via a Reformatsky reaction of ethyl bromodifluoroacetate with the aliphatic and aromatic aldehydes **131a–e** (Scheme 32). A Mitsunobu reaction of the esters **132a–e** gave the nitrogen-containing derivatives **133a–e** in moderate to good yield along with some byproducts, the 2,2-difluoro-3-(ethoxycarbonylazo)-propanoic acid ethyl esters. Different solvents (toluene being the best), orders of addition and ratios of reactants for the Mitsunobu reaction have been investigated to optimise the reaction conditions. ^{31}P- and ^{19}F NMR spectroscopy were used to study the differences in the Mitsunobu reaction proceeding for alkyl- and aryl-substituted α, α-difluoro-β-hydroxy acid esters. Finally, removal of the phthalimido moiety together with the ethyl protecting group with HBr/HOAc under reflux condition followed by treatment with propylene oxide gave the desired α, α-difluoro-β-amino acids **134a**,**b**,**d** in 53–57% yield.

Similarly, Quirion's group[61] reported the synthesis of α, α-difluoro-β-amino acids **138a**,**c**,**d** and 3,3-difluoro-azetidin-2-ones **140a**,**c**,**d** via the Reformatsky reaction of **135a–e** (Scheme 33). The chiral 1,3-oxazolidines **135a–e** were treated with ethyl bromodifluoroacetate (3.5 equiv.) in the presence of activated Zn dust to furnish the 3,3-difluoroazetidin-2-ones **136a–e** as the major products. Although the yields (32–69%) were moderate, high diastereomeric excesses (85–>99% de) were observed. Conversions of **136a**,**c**,**d** into the corresponding fluorinated amino acids **138a**,**c**,**d** were achieved by removal of the chiral auxiliaries and ring-opening of the β-lactams via two different routes, one of which is the acidic treatment of **136a** to form **137a** followed by cleavage of the phenylglycinol moiety via catalytic hydrogenolysis to afford the 3-amino-2,2-difluoro-3-phenyl-propanoic acid **138a** in 64% yield over two steps. The other route is transformation of the alcohol functionalities of **136a**,**c**,**d** to triflates followed by treatment with strong base (DBU or *t*-BuOK) to provide the enamides **139a**,**c**,**d**. Further treatment with 6 N HCl under reflux conditions gave the corresponding α,α-difluoro-β-amino acids **138a**,**c**,**d** in 64–75% yield over two steps. Additionally, treatment of **139a**,**c**,**d** with acid conveniently furnished the optically pure azetidinones **140a**,**c**,**d** in 53–61% yield.

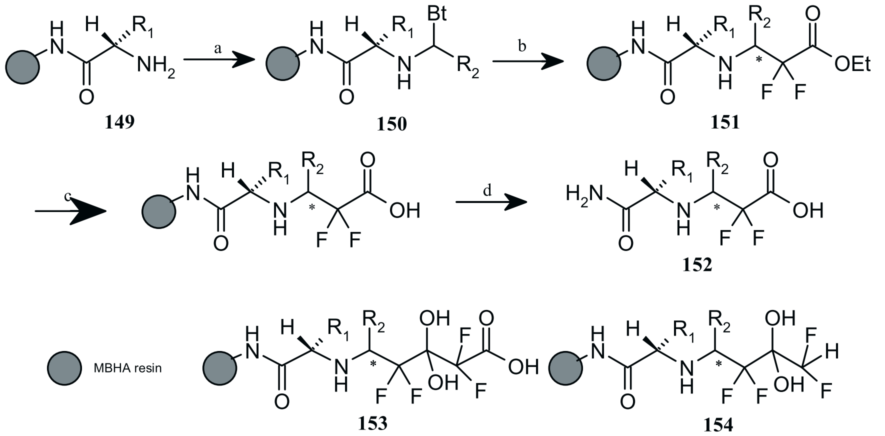
Later, Staas and co-workers[62] reported another efficient route to α,α-difluoro-β-amino acids using Ellman's *N-tert*-butyl sulphinimine **141** as the chiral auxiliary (Scheme 34). Here, the *N-tert*-butyl sulphinyl group played the dual roles of chiral auxiliary and protecting group for subsequent transformations. This route can be applied for solid-phase peptide synthesis. The sulphinimines **142a–e**, derived from the condensation of commercially available aldehydes and **141**, were treated with the Reformatsky reagent ($BrZnCF_2$-CO_2Et, 3.5 equiv.) at rt for 18 h to afford the α,α-difluoro-β-amino acid derivatives **143a–e** in 51–82% yield and in good diastereomeric ratios ranging from 81:19 to 95:5. As two examples of the application of this methodology to efficient convenient fluorinated peptide synthesis, the pseudotripeptide **144** and the tripeptide **145** were prepared.



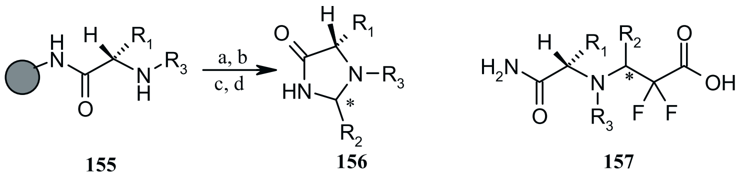
(*S*)-**146a-i** (*S*$_S$, 3*S*)-**147a-i** + (*S*$_S$, 3*R*) isomers (*S*)-**148a-e, g-i**

R = C_6H_5 (**a**), 4-MeO-C_6H_4 (**b**), 4-F-C_6H_4 (**c**), 4-Cl-C_6H_4 (**d**), 4-CF_3-C_6H_4 (**e**), 2-furyl (**f**), *n*-C_5H_{11} (**g**), *i*-Pr (**h**), *t*-Bu (**i**)

Scheme 35. Reagents and conditions: (a) $BrCF_2CO_2Et$, THF, reflux, 15 min; (b) (i) 6 N HCl, reflux, 4 h; (ii) propylene oxide, *i*-PrOH, rt, 5 h.



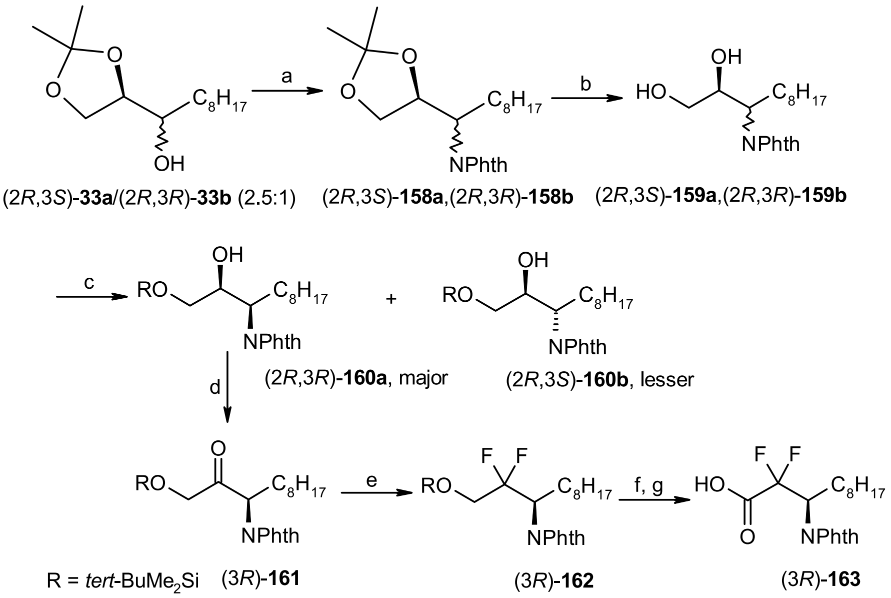
Scheme 36. Reagents and conditions: (a) BtH, R_2CHO, benzene, reflux; (b) Zn, TMSCl, $BrCF_2CO_2Et$, THF, reflux; (c) LiOH, H_2O, THF, rt; (d) HF/anisole.



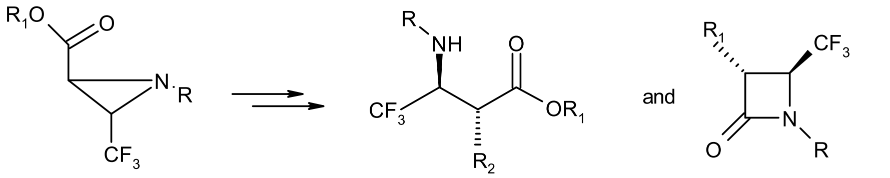
Scheme 37. Reagents and conditions: (a) BtH, R_2CHO, benzene, reflux; (b) Zn, TMSCl, $BrCF_2CO_2Et$, THF, reflux; (c) LiOH, H_2O, THF, rt; (d) HF/anisole.

Interestingly, Soloshonok and co-workers[63,64] recently applied an enantiopure *p*-toluenesulphinyl group as a chiral auxiliary for the preparation of β-substituted α,α-difluoro-β-amino acids. Treatment of *p*-toluenesulphinimines **146a–i** with ethyl bromodifluoroacetate in the presence of activated Zn dust in boiling THF afforded the corresponding *p*-toluenesulphinamides **147a–i** in 60–85% yield and 72–>98% de (Scheme 35). Further studies found that the fluorine atoms in ethyl bromodifluoroacetate had no effect on the stereochemical outcome of the reactions. Finally, removal of all of the protecting groups in 6 N HCl gave the desired β-substituted α,α-difluoro-β-amino acids **148a–e**,**g–i** in 56–96% yield. Apparently, the important advantages of *p*-toluenesulphinimine over other imine auxiliaries (such as its cheapness and ready availability and its ready removal under mild acidic condition without any extensive epimerisation) together with the high chemical and stereochemical yields render this method synthetically superior over the previously reported approaches.

Solid-phase synthetic technology provides an efficient and rapid synthesis of large libraries of low-molecular-weight compounds. In 2001, Houghten's group[65] reported the first



Scheme 38. Reagents and conditions: (a) PhthNH, DEAD, Ph_3P, toluene, 0 °C, 1 h, then rt, 24 h; (b) 4 N HCl, THF, rt, 12 h; (c) *t*-$BuMe_2SiCl$, DMAP, CH_2Cl_2, rt, 16 h; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 1 h; (e) Morpho-DAST, CH_2Cl_2, 30 °C, 45 h; (f) dioxane–HCl–H_2O (93:5:2), 35–40 °C, 25 h; (g) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CCl_4–MeCN–H_2O, rt, 24 h.



164a-d
a)R = Bn,R_1 = Et
b)R = Bn,R_1 = H
c)R = Bn,R_1 = Me
d)R = H; R_1 = Et

165a-h
a)R = Bn,R_1 = Et,R_2 = Cl
b)R = Bn,R_1 = Et,R_2 = Br
c)R = Bn,R_1 = Et,R_2 = H
d)R = Bn,R_1 = Et,R_2 = OH
e)R = H,R_1 = Et,R_2 = OH
f)R = Bn,R_1 = Me,R_2 = OH
g)R = H,R_1 = Me,R_2 = OH
h)R = $COCF_3$,R_1 = Et,R_2 = OH

166a-b
a)R_1 = Cl,R = Bn
b) R_1 = OTBDMS,R = H

Scheme 39.

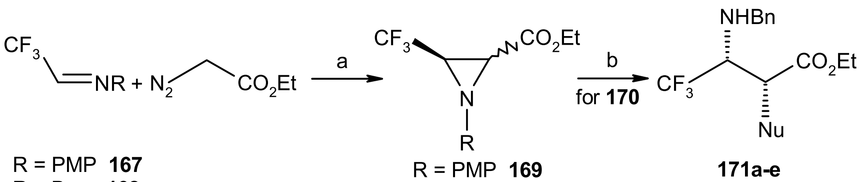
solid-phase parallel synthesis of α,α-difluoro-β-amino acid derivatives **152** via the Reformatsky reaction of $BrCF_2CO_2$-Et (Scheme 36). The *N*-(α-aminoalkyl)benzotriazoles **150** were prepared from the resin-bound amino acids **149** using Katritzky's approach.[66] Compounds **150** were used as iminium salt precursors to provide the α,α-difluoro-β-amino acid esters **151** via a Reformatsky reaction with $BrCF_2CO_2Et$/zinc/TMSCl. The diastereoselectivities of the esters **151** were moderate and strongly dependent on the nature of the aldehydes. During the course of the reaction, two tetrafluorinated byproducts **153** and **154** were obtained when the Reformatsky reagent was used in a large excess (14 equiv.) When 10 equiv. of the Reformatsky reagent were used, the reaction progressed well, without any tetrafluorinated byproducts being observed. Saponification of **151** in a lithium hydroxide solution followed by cleavage from the resin with HF gave the corresponding α,α-difluoro-β-amino acids **152** as a mixture of diastereoisomers. When the resin-bound secondary amino acids **155** were treated in the same manner, however, no expected Reformatsky-type products **157** were formed and only the N-alkylated imidazolidinones **156** were obtained in high yields (Scheme 37).

The synthesis of a 3-amino-2,2-difluoroundecanoic acid derivative **163** starting from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde was also realised via Mitsunobu amination followed by difluorination with Morpho-DAST (Scheme 38),[24] the Mitsunobu amination of **33a**,**b** affording **158a**,**b** in 87% yield. Hydrolysis of **158a**,**b** to **159a**,**b** followed by subsequent protection with a *tert*-butyl-dimethylsilyl group gave alcohols **160a**,**b** as a mixture of two diastereomers. The major diastereomer **160a** was separated by column chromatography followed by Swern oxidation to furnish the corresponding ketone **161** in 76% yield. Difluorination of **161** with Morpho-DAST, however, afforded the desired product **162** in low yield (13–34%) due to the steric hindrance. Removal of the *tert*-butyldimethyl-silyl group with the dioxane/HCl system followed by oxidation with $NaIO_4/RuCl_3$ yielded the N-protected difluorinated β-amino acid (3*R*)-**163** in 44% yield over two steps.

3.2. Trifluoromethylated and polyfluorinated β-amino acids

Aziridine-2-carboxylates are known to be versatile key intermediates for the synthesis of α- and β-amino acids.[67] Prati and co-workers[68] stereoselectively synthesised fluorinated β-amino acid derivatives **165** from the *trans*-*N*-benzyl-3-trifluoromethylaziridine-2-carboxylates **164**, which are easily obtained in enantiopure forms by *Candida antarctica* lipase-catalysed enzymatic resolution (Scheme 39). The ring-opening reactions were performed on the racemic or optically pure aziridines **164** by treatment with BrØnsted acids, such as HCl, MgBr in H_2SO_4 and trifluoroacetic acid, and resulted in the synthesis of fluorinated *anti*-α-functionalised β-amino acids, including β-trifluoromethyl-β-alanine derivatives **165a**–**c** and *anti*-3-(trifluoromethyl)isoserinates **165d**–**h**, with high regio- and stereoselectivities. The regiospecific C-2 attack of nucleophiles might be attributed to the strong electron-withdrawing effect of the trifluoromethyl group as well as to the electrostatic repulsion between the trifluoromethyl group and nucleophiles, which prevent C-3 attack.[69] Additionally, Grignard-mediated intramolecular cyclisation of **165a**,**e** conveniently resulted in the synthesis of *trans*-3-halo- and 3-hydroxy-β-lactams **166a**,**b** in good yield (68–96%).

Two year later, Crousse and co-workers[70] provided another new route to trifluoromethyl α-functionalised β-amino acids from 3-trifluoromethyl-2-carboxyl-aziridines **170** (Scheme 40). First, treatment of the imines **167** and **168** with 1.5 equiv. of ethyl diazoacetate using 10 mol% of a Lewis acid afforded the corresponding aziridines **169** and **170**. The solvents, Lewis acids and reaction temperatures

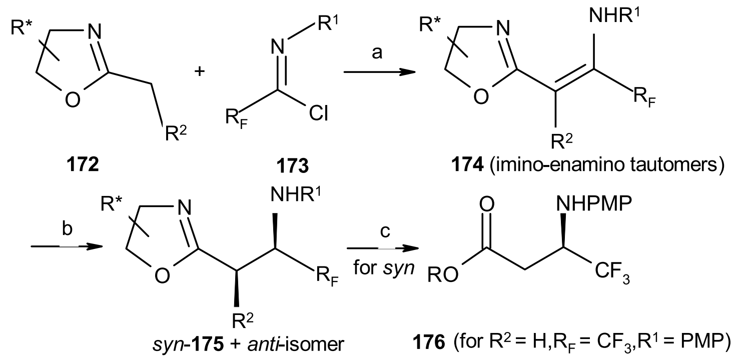


R = PMP **167**
R = Bn **168**

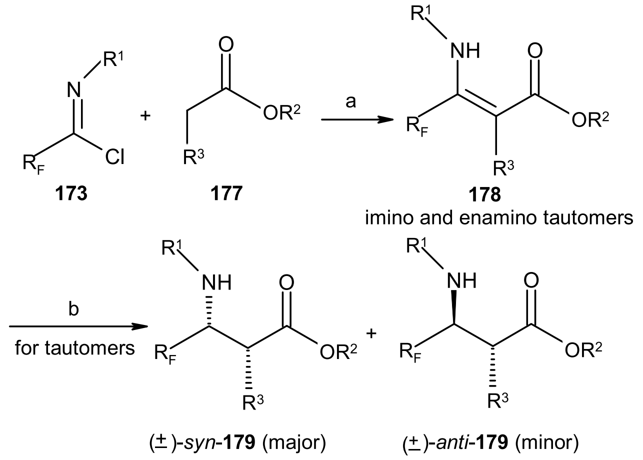
R = PMP **169**
R = Bn **170**

171a-e
Nu = Cl(**a**), OH(**b**), SPh(**c**)
SBn(**d**), SEt(**e**)

Scheme 40. Reagents and conditions: (a) $BF_3 \cdot Et_2O$, ether, −78 °C, 2 h; (b) HCl, 25 °C, 4 h (for **a**); TFA, 80 °C, 8 h (for **b**); $PhSH/CF_3SO_3H$, 22 h, 25 °C (for **c**); $BnSH/CF_3SO_3H$, 16 h, 25 °C (for **d**); $EtSH/CF_3SO_3H$, 6 h, 25 °C (for **e**).



Scheme 41. Reagents and conditions: (a) LDA (2.0 equiv.), THF, −78 °C, 2–8 h; (b) $NaBH_4$, ZnI_2, CH_2Cl_2, rt or H_2, Pd/C, MeOH, rt; (c) (i)1 N HCl, heat; (ii) ROH/HCl.

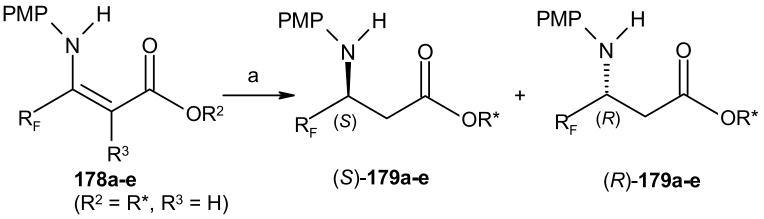


Scheme 42. Reagents and conditions: (a) (i) LDA (2.0 equiv.), THF, −78 °C; (ii) sat. NH_4Cl; (b) $NaBH_4$ (5.0 equiv.), ZnI_2 (3.0 equiv.), CH_2Cl_2, rt.

have significant effects on the yields and diastereoselectivities of the products **169** and **170**. The best results were achieved when the reactions were performed with Et_2O as the solvent in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ at −78 °C and the products **169** and **170** were obtained in high yields (86–93%) and high diastereoselectivities (*cis*/*anti*=95:5). The compound **170** was treated with different nucleophiles to give the β-trifluoromethyl-β-amino acid esters **171a–e** in moderate to high yields (59–95%).

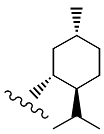
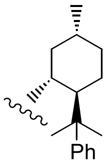
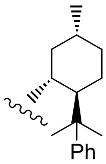
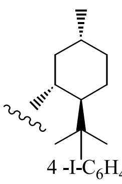
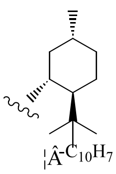
Recently, Fustero and co-workers[71] used chiral non-racemic Δ^2-oxazolines as effective masked carboxylic acid moieties and chiral auxiliary groups for the chemo- and diastereoselective synthesis of fluorinated β-amino acid derivatives (Scheme 41). Treatment of chiral Δ^2-oxazolines **172** (1.0 equiv.) with 2.0 equiv. of LDA followed by the addition of fluorinated imidoyl chlorides **173** provided the corresponding C-oxazoline-protected compounds **174** in good yields (62–92%). In general, the compounds **174** were isolated as a mixture of imino–enamino tautomers. Reduction of the chiral tautomers **174** with $NaBH_4/ZnI_2$ in CH_2Cl_2 afforded the fluorinated β-amino acid derivatives **175** in good yields and moderate to good diastereoselectivities. Catalytic hydrogenation of **174** with Pd/C in MeOH, however, only resulted in low yields and low diastereoselectivities. Hydrolysis of enantiopure **175** with 1 N HCl followed by esterification of the resulting compounds gave the N-protected fluorinated β-amino acid esters **176** in moderate yields (60–65%) over two steps.

In 2002, Fustero and co-workers[72] further investigated this methodology without using a chiral Δ^2-oxazoline as an auxiliary group. The fluorinated esters **178** were prepared in good to high yields (64–99%) by treatment of the fluorinated imidoyl chlorides **173** (1.0 equiv.) with the lithium enolates of alkyl esters **177** (Scheme 42). Similarly, the products **178** were generally isolated as a mixture of imino and enamino tautomers and the ratio (imino/enamino) was affected by the length of the perfluoroalkyl chain.[73] It was observed that the longer the perfluoroalkyl chain, the higher the ratio of the imino tautomer. Different reducing agents, solvents, and temperatures were investigated for chemo- and stereoselective reduction of **178** (tautomers). The best results were achieved when the reactions were performed using an excess of anhydrous ZnI_2 (3.0 equiv.) and $NaBH_4$ (5.0 equiv.) in anhydrous CH_2Cl_2 at rt, and the α-alkyl-β-fluoroalkyl-β-amino esters (±)-*syn*-**179** and (±)-*anti*-**179** were obtained in high yields and moderate to good diastereoselectivities. The good stereochemical outcome of the reduction reaction of the esters **178** to the major diastereoisomer (±)-*syn*-**179** could be elucidated through a cyclic model in which the hydride attacks the imino double



Scheme 43. Reagents and conditions: (a) ZnI_2 (3.0 equiv.), $NaBH_4$ (5.0 equiv.), dry CH_2Cl_2, rt.

Table 6. Synthesis of chiral γ-fluorinated β-amino esters **179a–e**[72a]

Entry	**178**	R_F	R^2	*t* (h)	Product	Ratio (*S*/*R*)	Yield (%)
1	**178a**	CF_3		19	**179a**	55/45	93
2	**178b**	CF_3		48	**179b**	80/20	85
3	**178c**	CF_2Cl		28	**179c**	74/26	80
4	**178d**	CF_3		36	**179d**	72/28	75
5	**178e**	CF_3		20	**179e**	77/23	80

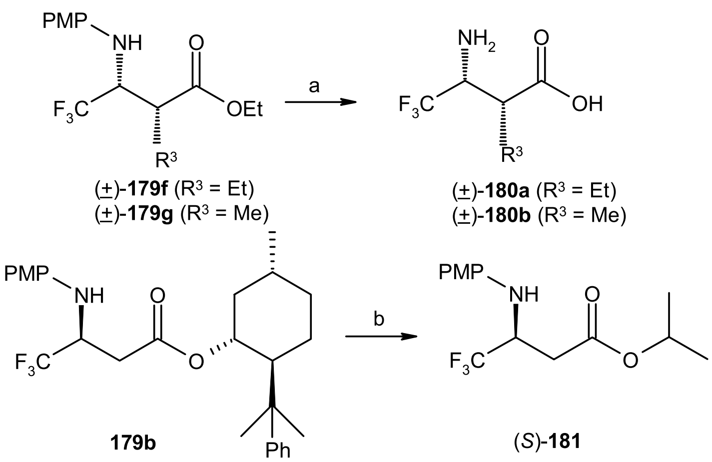
bond from the opposite side (*si* face) to the α-alkyl group (*ul*-1,2-addition).

Fustero et al. also found that using (−)-8-phenylmenthol, (−)-8-(2-naphthyl)menthol, (−)-8-(4-iodo)phenylmenthol and (−)-menthol as chiral auxiliaries in the ester moiety of **178a–e** allowed the preparation of enantiopure α-non-substituted β-fluoroalkyl β-amino esters **179a–e** in a short and highly efficient manner (Scheme 43). Reduction of **178a–e** using the aforementioned optimised conditions (3.0 equiv. ZnI_2, 5.0 equiv. $NaBH_4$, CH_2Cl_2, rt) provided the chiral β-amino esters **179a–e** in good yields (75–93%) and moderate diastereoselectivities (Table 6).

Finally, removal of the *p*-methoxyphenyl protecting groups in (±)-*syn*-**179f** and (±)-*syn*-**179g** with cerium ammonium nitrate (CAN) in MeCN–H_2O (2:1) at rt followed by acidic hydrolysis with 6 N HCl at 50 °C for 2 h gave the fluorinated amino acids **180a**,**b** in 50–60% yields (Scheme 44). Removal of the chiral auxiliary of (*S*)-**179b** was carried out with Ti(*i*-PrO)$_4$ in refluxing *i*-propanol and the optically pure fluorinated amino acid derivative (*S*)-**181** was provided in >95% yield, along with recovery of the chiral auxiliary (−)-8-phenylmenthol in 91% yield.

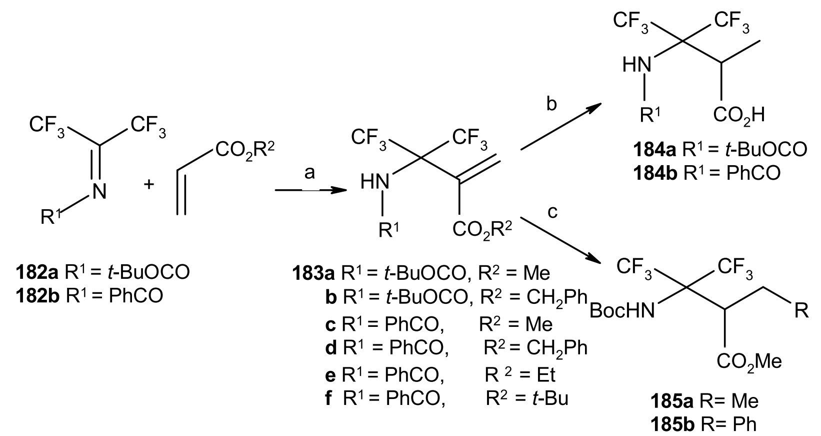
The Morita–Baylis–Hillman (MBH) reaction is an important carbon–carbon bond formation process.[74] Burger and co-workers[75] recently synthesised partially fluorinated β-amino acids via an MBH reaction of hexafluoroacetone imines with acrylic esters (Scheme 45). Treatment of the hexafluoroacetone imines **182a**,**b** with acrylic esters using classic MBH reaction conditions (10 mol% DABCO, THF) gave the corresponding products only in low yields. Further studies found that the addition of CaH_2 to the mixture of imines **182a**,**b**, acrylic esters and a stoichiometric amount of DABCO at rt gave the desired products **183a–f** in increased yields (27–65%). Finally, hydrogenation of **183a–d** and saponification of the ester moieties by KOH in MeOH successfully gave the N-protected β-amino acids **184a**,**b**. In addition, cuprate addition to the double bond of **183a** with R_2CuLi (2.5–3.5 equiv.) in Et_2O could introduce various substituents into the α-position of β-bis(trifluoromethyl) β-amino acids and the α-substituted β,β-bis(trifluoromethyl)-β-amino acid derivatives **185a**,**b** were obtained in 65–73% yields.

Later, Burger et al.[76] synthesised fluorinated dehydro-β-amino acid derivatives **188a–e** similarly via an improved MBH reaction (Scheme 46). Using the Ramachandran protocol[77] for the reactions of **186a–c**, the desired products were obtained only in poor yields, probably due to the reduction of the imines by excess DIBAL-H. The improved

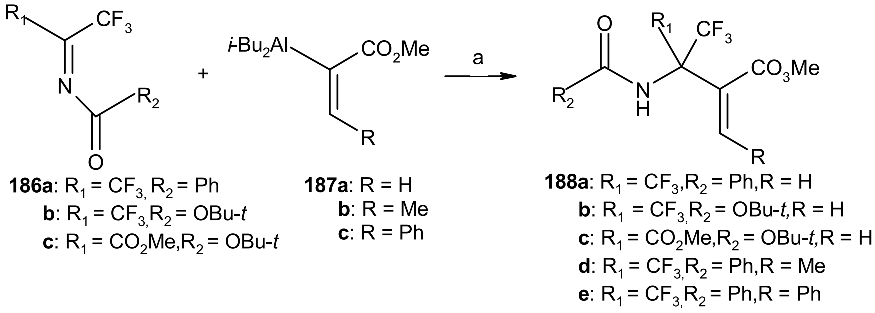


(±)-**179f** (R³ = Et)
(±)-**179g** (R³ = Me)
(±)-**180a** (R³ = Et)
(±)-**180b** (R³ = Me)
179b
(*S*)-**181**

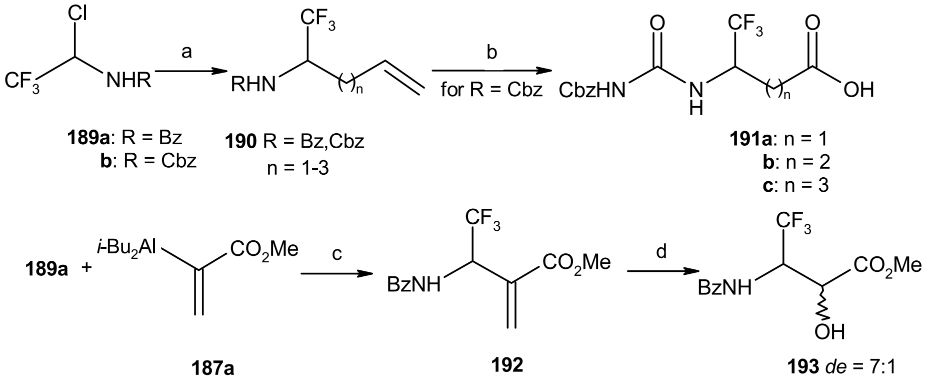
Scheme 44. Reagents and conditions: (a) (i) $Ce(NH_4)_2(NO_3)_6$, CH_3CN–H_2O (2:1), rt; (ii) 6 N HCl, 50 °C; (iii) Dowex-H^+; (b) Ti(*i*-PrO)$_4$, *i*-PrOH, △, 14 days.



Scheme 45. Reagents and conditions: (a) DABCO, CaH_2, THF; (b) Pd/C, H_2, MeOH then KOH, MeOH (for **183a**,**c**) or Pd/C, H_2, MeOH (for **183b**,**d**); (c) R_2CuLi (R=Me, Ph), Et_2O (for **183a**).



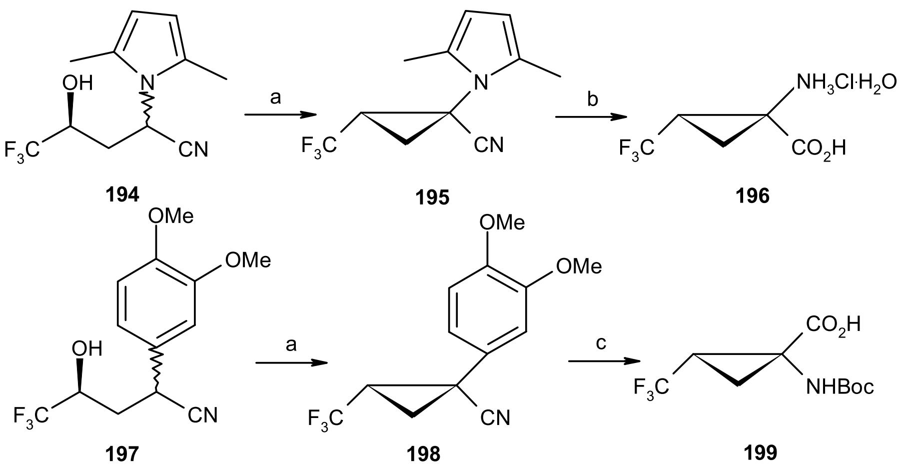
Scheme 46. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, THF, −78 °C to rt, overnight.



Scheme 47. Reagents and conditions: (a) $CH_2{=}CH(CH_2)_nMgBr$ (2.0 equiv.), THF, −78 °C; (b) $NaIO_4$, $KMnO_4$, H_2O; (c) $BF_3{\cdot}Et_2O$, THF, −78 °C. (d) (i) O_3, CH_2Cl_2; (ii) $NaBH_4$, MeOH, 0 °C, 1.5 h.

procedure was that the [α-(methoxycarbonyl)vinyl]diisobutylaluminium reagents **187** were prepared by mixing stoichiometric amounts of propiolate and DIBAL-H in THF in the presence of 2.0 equiv. HMPT. Treatment of the resulting [α-(methoxycarbonyl)vinyl]diisobutylaluminium reagent **187a** (1.3 equiv.) with *N*-acylimines **186a–c** (1.0 equiv.) in the presence of $BF_3{\cdot}Et_2O$ smoothly provided the corresponding trifluoromethyl-substituted dehydro-β-amino acid derivatives **188a–c** in 56–76% yields. Additionally, β-branched aluminium reagents **187b**,**c** were also suited for this reaction and the corresponding fluorinated β-amino acid derivatives **188d**,**e** were obtained in 32 and 58% yield, respectively.

A series of ω-trifluoromethyl-substituted amino acids were also prepared by Burger's group[78] starting from the *N*-acyl-1-chloro-2,2,2-trifluoroethylamines **189a**,**b** (Scheme 47). The construction of the amino acid backbones was accomplished by treatment of **189a**,**b** with Grignard reagents of type $CH_2{=}CH(CH_2)_nMgBr$ (n=1–3) and the compounds **190** were afforded in 64–89% yields. Further oxidation of the double bond in **190** with $NaIO_4/KMnO_4/$



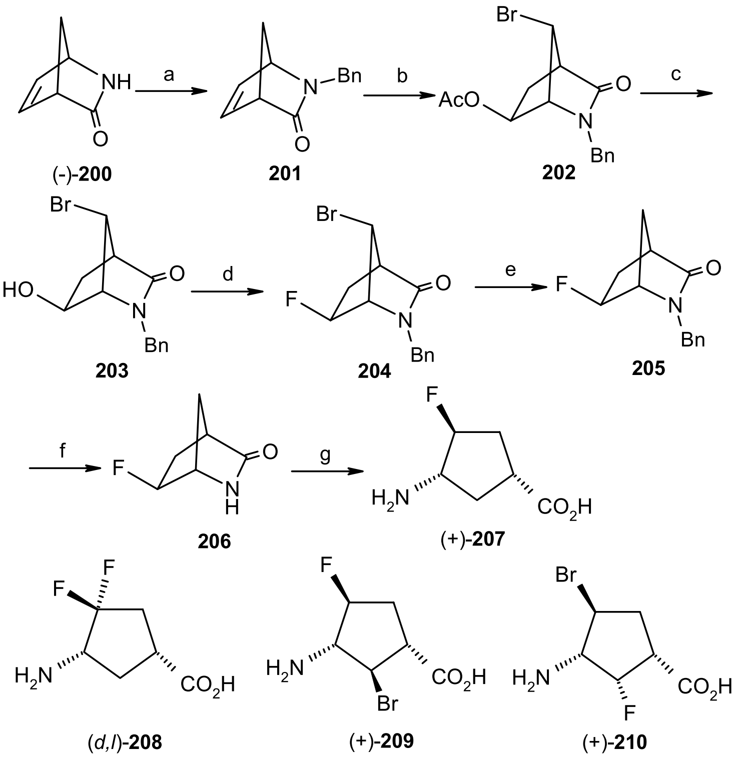
Scheme 48. Reagents and conditions: (a) *p*-TsCl, NaH, THF, rt; (b) (i) $RuCl_3$ (cat.), $NaIO_4$, MeCN, CCl_4, H_2O; (ii) aq. HCl; (c) (i) NaOH, H_2O_2, reflux; (ii) $Pb(OAc)_4$, *t*-BuOH, reflux; (iii) $RuCl_3$ (cat.), $NaIO_4$, MeCN, CCl_4, H_2O.

H_2O successfully gave the N-protected ω-trifluoromethyl-substituted amino acids **191a–c** in 61–70% yields. In addition, treatment of **189a** with the aluminium reagent **187a** (2.0 equiv.) in the presence of $BF_3{\cdot}Et_2O$ smoothly gave the unsaturated ester **192** in 65% yield. Ozonolysis of the compound **192** followed by reduction of the resultant keto group with $NaBH_4$ provided the N-protected 4,4,4-trifluoroisothreonine **193** with a moderate diastereoselectivity (de=7:1).

4. Fluorinated cyclic amino acids

Cyclic amino acids are extremely useful intermediates in the synthesis of natural products, peptides and peptidomimetics.[79] The introduction of cyclic amino acids into peptide chains constitutes the most prominent pathway to conformationally constrained peptidomimetics. These conformationally constrained peptidomimetics play a significant role in the development of superior pharmaceutical agents and in establishing structure–bioactivity relationships.[80] Fluorinated cyclic amino acids (F-C-AAs) have recently received increasing attention because the introduction of fluorine atom(s) into cyclic amino acids could improve the biological properties of peptides.[6c,81]

Norcoronamic acid (2-methyl-1-aminocyclopropane-1-carboxylic acid), a naturally occurring cyclopropyl amino acid,

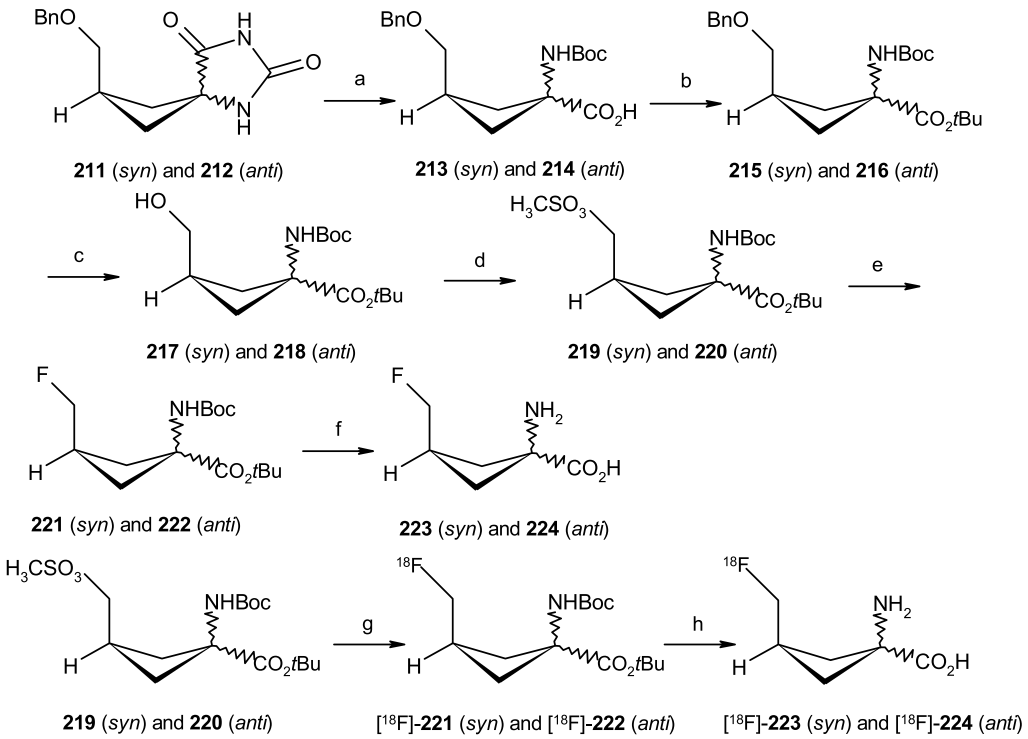


Scheme 49. Reagents and conditions: (a) BnBr, KOH, DMSO, TBAI; (b) 1,3-dibromo-5,5-dimethylhydantoin, AcOH; (c) K_2CO_3, MeOH/H_2O; (d) DAST, 0 °C then rt; (e) Bu_3SnH, AIBN, benzene, reflux; (f) $Na/NH_3/t$-BuOH; (g) 2 M HCl, 65 °C.

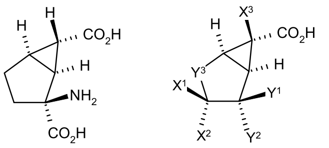
is isolated after hydrolysis of the bacterial toxin, norcoronatine, from *Pseudomonas syringae*.[82] In 2000, Uneyama's group[83] synthesised the optically active trifluorinated analogues of norcoronamic acid, the 2-trifluoromethyl-1-aminocyclopropane-1-carboxylic acids **196** and **199** (Scheme 48). Uneyama's synthesis is based on a highly stereospecific and diastereoselective S_N2 cyclisation of γ-cyanohydrins **194** and **197** prepared from optically active 2,3-epoxy-1,1,1-trifluoropropane using their reported procedure.[84] Treatment of the 4-hydroxy-5,5,5-trifluoronorvaline cyanide derivative **194** with *p*-TsCl/NaH gave the cyclopropyl cyanide **195** (82% yield, >99% de, 75% ee) and, after recrystallisation, optically pure **195** was obtained (>99% de, >99% ee). Oxidative cleavage of the pyrrole ring of **195** with $RuCl_3$ (cat.)/$NaIO_4$ followed by hydrolysis of the cyano group with aqueous HCl produced the optically active trifluoronorcoronamic acid **196** (>99% de, >99% ee) in 48% yield over two steps. Similarly, cyclisation of the cyanohydrins **197** using the same conditions as described for the preparation of **195** gave the cyclopropyl cyanide **198** (90% de, 75% ee), which was also recrystallised to give the optically pure form (>99% de, >99% ee). Hydrolysis of the cyano group in **198** followed by Hoffmann rearrangement and further oxidative cleavage of the 3,4-dimethoxyphenyl group gave the desired Boc-protected trifluoro-*allo*-norcoronamic acid 1**99** in 24% yield over three steps.

Silverman and co-workers[85]prepared mono- and di-fluoro-substituted conformationally rigid analogues of 4-amino-5-halopentanoic acids to determine if the conversion of acyclic into cyclic inactivators generally interferes with the mechanism-based inactivation of γ-aminobutyric acid aminotransferase. Treatment of (−)-**200** with benzyl bromide in the presence of powdered potassium hydroxide gave the lactam **201**. The compound **201** was further treated with a solution of 1,3-dibromo-5,5-dimethylhydantoin in AcOH at rt to afford **202** (Scheme 49).[86] Basic hydrolysis of **202** with K_2CO_3 followed by fluorination of the resultant compound **203** with DAST gave the desired product **204** in 87% yield over two steps. Debromination of **204** with Bu_3SnH furnished the lactam **205** in 94% yield. Finally, Birch reduction of **205** followed by direct acidic hydrolysis of the resultant lactam **206** gave (1*R*,3*S*,4*S*)-3-amino-4-fluorocyclopentane-1-carboxylic acid (+)-**207** in 86% yield over two steps. Similarly, the other three conformationally rigid cyclic fluorinated amino acids (D,L)-**208**, (+)-**209** and (+)-**210** were successfully synthesised starting from the same starting material (−)-**200**, and all the fluorine atom(s) were incorporated via the key fluorination reagent, DAST.

In order to evaluate the contributions of C-3 substitution and configuration on the uptake of radiolabelled *anti*-1-amino-3-[^{18}F]-fluorocyclobutyl-1-carboxylic acid (FACBC) in a rodent model of brain tumours, two analogues of FACBC, *syn*- and *anti*-1-amino-3-[^{18}F]-fluoromethyl-cyclobutane-1-carboxylic acids (FMACBC) were synthesised by Goodman and co-workers (Scheme 50).[87] Hydrolysis of the hydantoins **211** and **212**, prepared from allyl benzyl ether in three steps, followed by treatment of the resultant crude products with Boc_2O yielded the *N*-Boc amino acids **213** and **214** in 70 and 60% yields, respectively. Protection of the carboxylic acid moiety with a *t*-butyl group gave the desired products **215** and **216** in good yields. Hydrogenolysis of the benzyl ethers **215** and **216** with 10% Pd/C in MeOH yielded the corresponding alcohols **217** and **218** in quantitative yields. Mesylation of the hydroxy groups in **217** and **218**



Scheme 50. Reagents and conditions: (a) (i) 3 N NaOH; 120 °C, 12 h; (ii) Boc_2O, MeOH, Et_3N, rt, 12 h; (b) $Cl_3CC(=NH)O^tBu$, CH_2Cl_2, rt, 15 h; (c) H_2, 10% Pd/C, MeOH, 3 h; (d) $MeSO_2Cl$, 2,6-lutidine, CH_2Cl_2, rt, 2 h; (e) TBAF, THF, rt; (f) 3 N HCl, MeOH, 60 °C; (g) [^{18}F]-KF, $K_{2,2,2}$, MeCN; (h) 6 N HCl, 85 °C, 10 min.



225 **226-232**

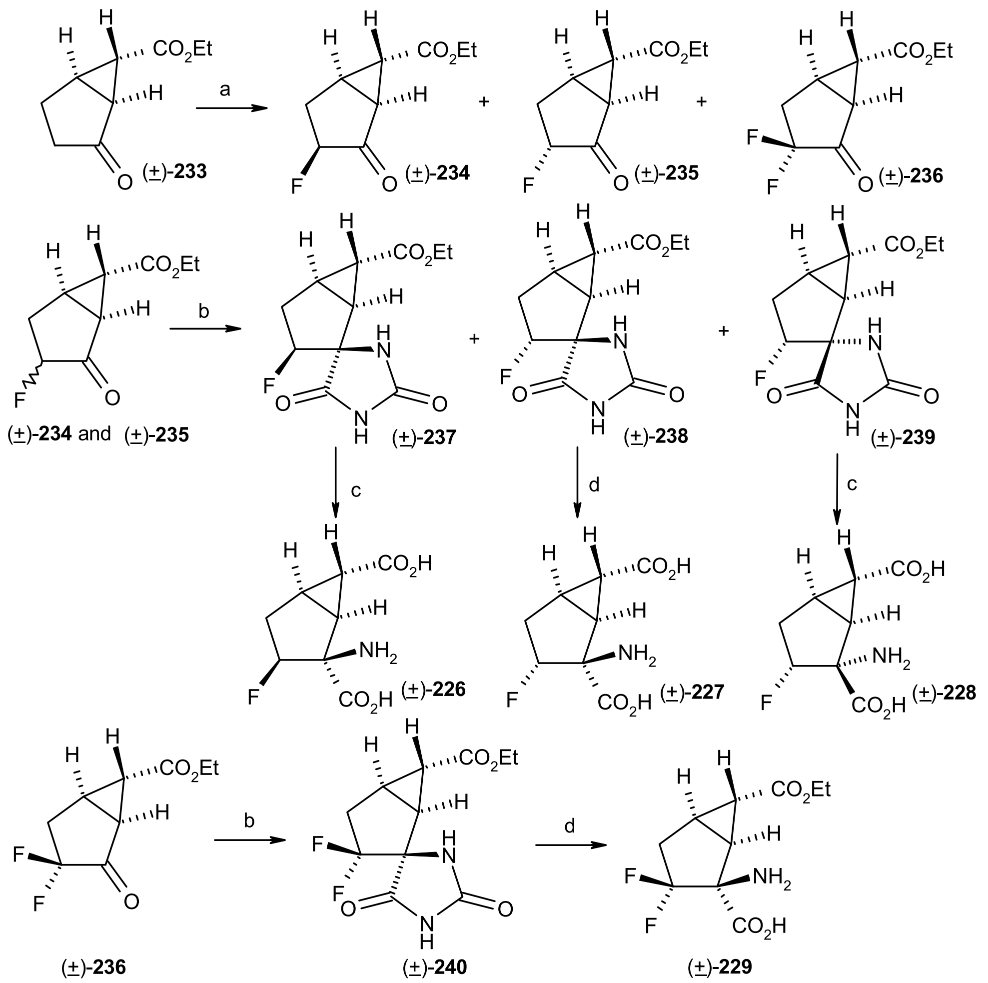
Compound	X^1	X^2	X^3	Y^1	Y^2	Y^3
226	F	H	H	NH_2	CO_2H	CH_2
227	H	F	H	NH_2	CO_2H	CH_2
228	H	F	H	CO_2H	NH_2	CH_2
229	F	F	H	NH_2	CO_2H	CH_2
230	H	H	F	NH_2	CO_2H	CH_2
231	H	H	F	NH_2	CO_2H	CHOH
232	H	H	F	NH_2	CO_2H	CO

Figure 2. Fluorinated (+)-2-aminocyclo[3.1.0]hexane-2,6-dicarboxylic acid analogues **226**–**232**.

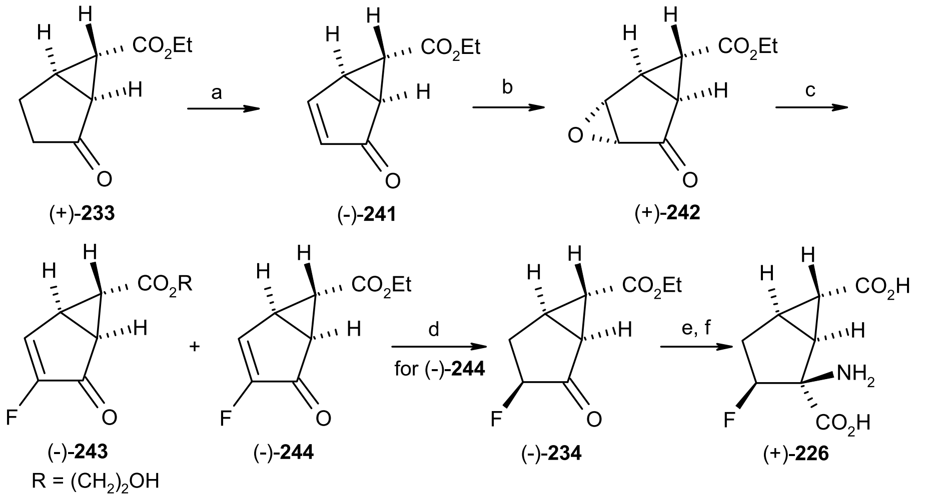
followed by treatment of the resulting mesylates **219** and **220** with TBAF in THF afforded the protected fluorinated amino acids **221** and **222** in 50 and 35% yield, respectively. Removal of the protecting groups of **221** and **222** with 3 N HCl at 60 °C afforded the *syn*-FMACBC **223** and *anti*-FMACBC **224**, respectively. Similarly, *syn*- and *anti*-[^{18}F]-FMACBC **223** and **224** were prepared from the intermediates **219** and **220** by no-carrier-added nucleophilic substitution with dried [^{18}F]-KF, potassium carbonate and Kryptofix in acetonitrile. Removal of the protecting groups was achieved by acid hydrolysis to provide the desired *syn*- and *anti*-[^{18}F]-FMACBC **223** and **224**.

L-Glutamate is a neurotransmitter at the vast majority of excitatory synapses in the brain. The glutamate receptors are broadly classified into two types:[88] the ionotropic glutamate receptors (iGluRs), having an ion channel structure, and the metabotropic glutamate receptors (mGluRs), which are coupled to cellular effectors via GTP-binding proteins. Recently, a highly selective mGluR agonist, (+)-2-aminocyclo[3.1.0]hexane-2,6-dicarboxylic acid **225** (Fig. 2), has been found to have oral activities in mice and to have potent antipsychotic effects in an animal model designed specifically to mimic the glutamatergic dysfunction observed in schizophrenia and drug addiction.[89]The introduction of fluorine atom(s) into **225** has attracted the attention of several groups. In 2000, Nakazato and co-workers[90] synthesised a series of fluorinated (+)-2-aminocyclo[3.1.0]hexane-2,6-dicarboxylic acid analogues **226**–**232** and achieved good results in terms of EC_{50} values and oral activities for laboratory animal tests.

The racemic ethyl 2-oxobicyclo[3.1.0]hexane-6-carboxylate (±)-**233**, prepared according to the reported



Scheme 51. Reagents and conditions: (a) (i) LHMDS, TMSCl, THF; (ii) *N*-fluoro-benzenesulphonamide, CH_2Cl_2, rt, 16.5 h; (b) $(NH_4)_2CO_3$, KCN, EtOH–H_2O, 35 °C; (c) 60% aq. H_2SO_4; (d) 2.5 or 3.0 M aq. NaOH.

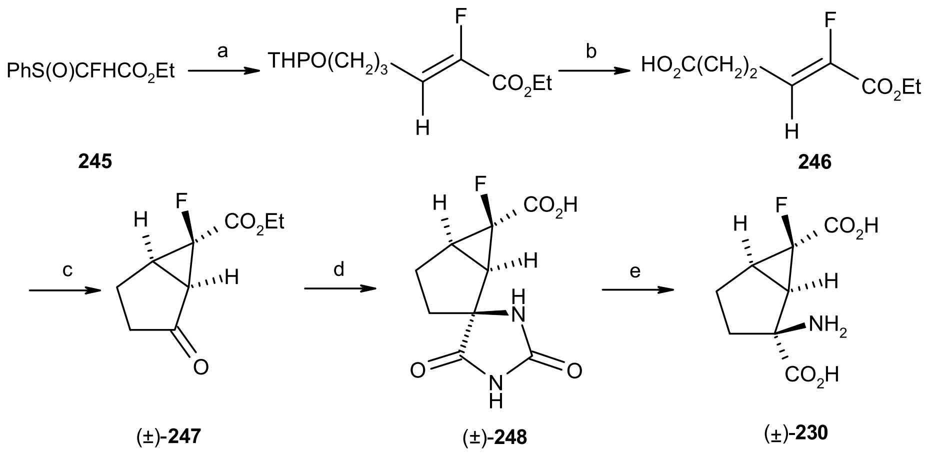


Scheme 52. Reagents and conditions: (a) (i) LHMDS, TMSCl, THF, rt, 1 h; (ii) $Pd(OAc)_2$, MeCN, rt, 16 h; (b) TBHP, Triton B, toluene, rt, 30 min; (c) KF·HF, ethylene glycol, 130 °C, 2 h; (d) H_2, Pd/C, EtOH; (e) $(NH_4)_2CO_3$, KCN, EtOH–H_2O, 35 °C, 1.5 days; (f) 60% aq. H_2SO_4, 140 °C, 2 days.

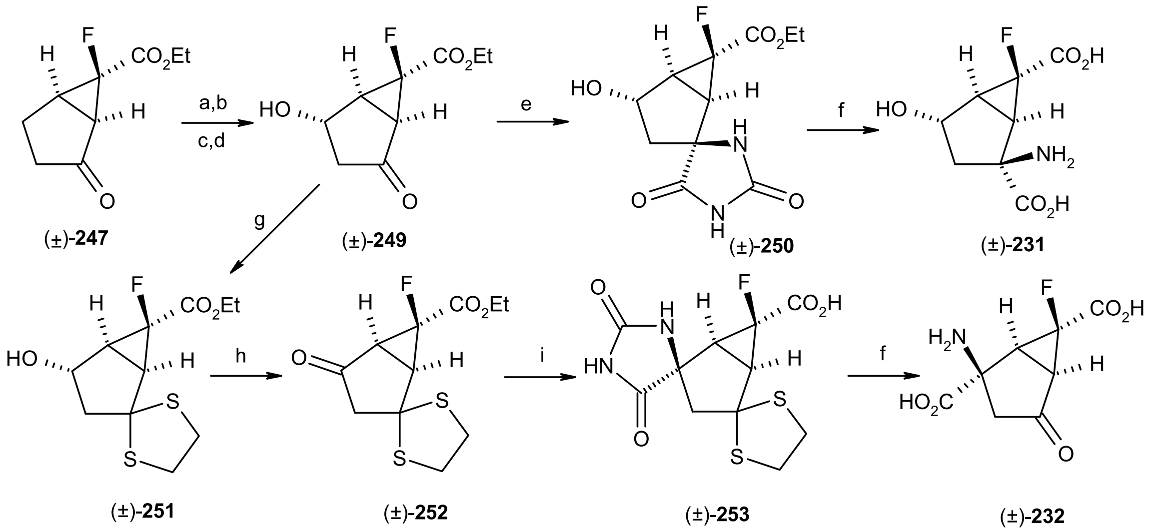
procedure,[89a] was treated with TMSCl in the presence of LHMDS in THF followed by fluorination with *N*-fluorobenzenesulphonamide (NFSi) to give a mixture of monofluoro compounds (±)-**234**, (±)-**235** and difluoro compound (±)-**236** after flash chromatography (Scheme 51). The mixture of (±)-**234** and (±)-**235** was treated under Bucherer–Bergs conditions ($(NH_4)_2CO_3$/KCN/EtOH/H_2O) to provide three hydantoins (±)-**237**, (±)-**238**, (±)-**239** after flash chromatography and recrystallisation. The hydantoin (±)-**240** was prepared from the corresponding difluorinated compound (±)-**236** under the same conditions. Hydrolysis of the four hydantoins (±)-**237**, (±)-**238**, (±)-**239** and (±)-**240** under either acidic (60% aq. H_2SO_4) or basic (2.5 or 3. M aq. NaOH) conditions gave the desired compounds (±)-**226**, (±)-**227**, (±)-**228** and (±)-**229**, respectively.

Moreover, the optically pure compound (+)-**226** was synthesised starting from the optically pure ester (+)-**233** (Scheme 52) obtained by chiral HPLC resolution of racemic (±)-**233**. Treatment of optically pure (+)-**233** with TMSCl in the presence of LHMDS followed by palladium acetate afforded the enone compound (−)-**241**. The enone (−)-**241** was further stereoselectively epoxidised by *tert*-butyl hydroperoxide (TBHP) in the presence of Triton B to yield the epoxide (+)-**242** in 63% yield based on (+)-**233**. Subsequent fluorination of the epoxide (+)-**242** with KF·HF in ethylene glycol yielded the key intermediate (−)-**244** (18% yield), along with the ester-exchange product (−)-**243**. Hydrogenation of (−)-**244** with Pd/C in EtOH stereoselectively afforded the ester (−)-**234** as the only product. The ester (−)-**234** was smoothly converted to optically pure (+)-**226** using the same conditions as described for the preparation of (±)-**226** from (±)-**234**.

The racemic fluorinated amino acid (±)-**230** was synthesised starting from ethyl (*Z*)-2-fluoro-5-carboxy-2-pentenate **246** prepared from ethyl phenylsulphinylfluoroacetate **245** by coupling with 1-bromo-4-tetrahydropyranyloxybutane in the presence of NaH followed by oxidation with the Jones reagent (Scheme 53). The compound **246** was treated with oxalyl chloride in refluxing hexane and then diazomethane/Et_2O followed by intramolecular cyclisation with $Cu(TBS)_2$ in refluxing benzene to give 6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylate (±)-**247** as the key intermediate. Hydrolysis of the ethyl ester moiety of



Scheme 53. Reagents and conditions: (a) THPO-$(CH_2)_4$Br, NaH, DMF; (b) Jones reagent; (c) (i) $(COCl)_2$, hexane, reflux, 3 h; (ii) CH_2N_2, Et_2O, rt, 1 h; (iii) $Cu(TBS)_2$, benzene, reflux, 30 min; (d) (i) 1 N aq. NaOH, EtOH, 10 min; (ii) $(NH_4)_2CO_3$, KCN, EtOH–H_2O, 55 °C, 8.5 h; (e) 60% H_2SO_4, 140–150 °C, 6 days.

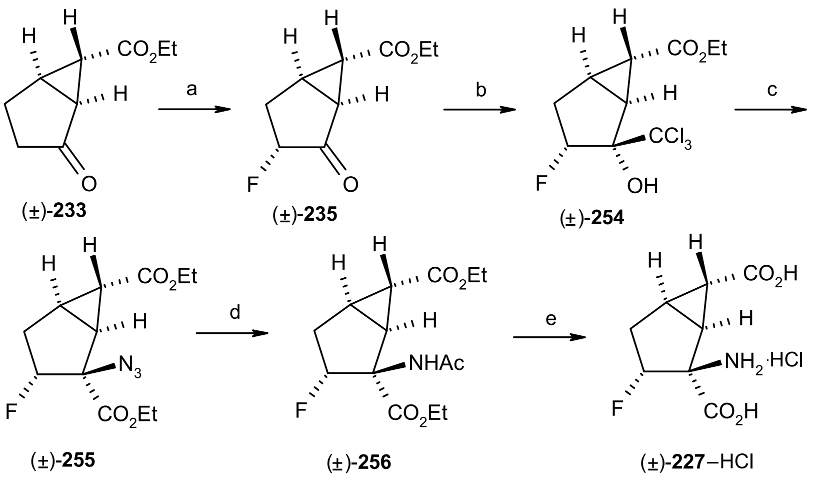


Scheme 54. Reagents and conditions: (a) LHMDS, TMSCl, THF, rt, 1.5 h; (b) $Pd(OAc)_2$, MeCN, rt, 16 h; (c) TBHP, Triton B, toluene, rt. 4 h; (d) $(PhSe)_2$, $NaBH_4$, AcOH, EtOH; (e) (i) 1 N aq. NaOH, EtOH; (ii) $(NH_4)_2CO_3$, KCN, EtOH–H_2O, 35 °C, 3 days; (iii) EtOH, EDC·HCl, DMAP, DMF, rt, 16 h; (f) 60% H_2SO_4, 140–150 °C; (g) (i) TBDMSCl, imidazole, DMF, 16 h; (ii) $HS(CH_2)_2SH$, $BF_3 \cdot Et_2O$, $CHCl_3$, 16 h; (h) DMSO, DCC, Py–TFA, rt, 16 h; (i) (i)1 N aq. NaOH; (ii) $(NH_4)_2CO_3$, KCN, EtOH–H_2O.

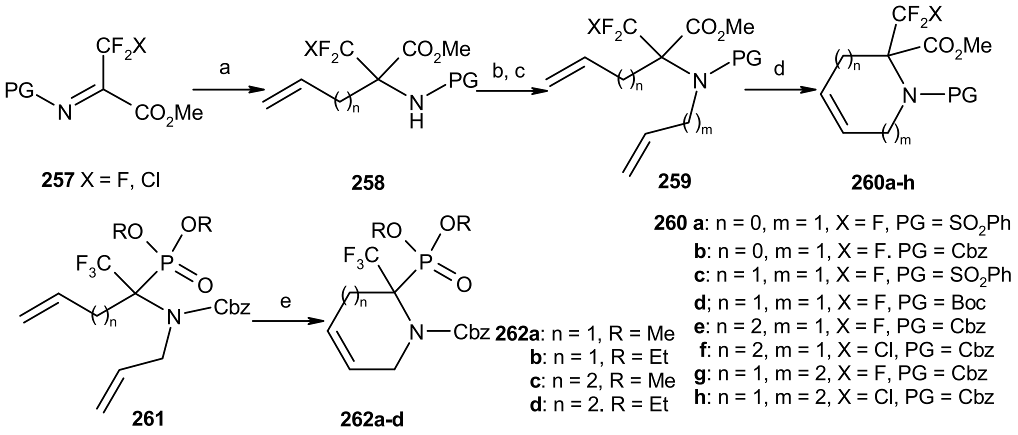
(±)-**247** followed by treatment under Bucherer–Bergs conditions afforded the hydantoin (±)-**248** as a single product, which was hydrolysed under acidic conditions to give the fluorinated amino acid (±)-**230**.

Both compounds (±)-**231** and (±)-**232** were synthesised from another key intermediate (±)-**249** (Scheme 54) prepared from the ester (±)-**247** in four steps, including treatment with TMSCl under basic conditions using LHMDS followed by $Pd(OAc)_2$ in MeCN, stereoselective epoxidation by TBHP in the presence of Triton B and regiospecific reduction of the resulting epoxide using benzeneselenol generated *in situ* by the reduction of $(PhSe)_2$ with $NaBH_4$ in the presence of AcOH. Hydrolysis of the ester (±)-**249** with 1 N aqueous NaOH followed by treatment under Bucherer–Bergs conditions and further esterification of the resulting product gave the compound (±)-**250**. The compound (±)-**250** was hydrolysed under acidic conditions to yield (±)-**231**. Protection of the hydroxyl group in (±)-**249** with a TBS group followed by thioketalysation of the carbonyl group gave the compound (±)-**251**. Oxidation of (±)-**251** with DMSO/DCC in the presence of pyridine/TFA gave the compound (±)-**252**. Basic hydrolysis of (±)-**252** followed by treatment under Bucherer–Bergs conditions afforded the compound (±)-**253**, which was further hydrolysed with 60% H_2SO_4 to yield the desired compound (±)-**232**. In addition, the optically pure isomers (+)-**247** and (−)-**247** could be obtained by chiral HPLC resolution and optically pure (+)-**253** and (−)-**253** by coupling with (*R*)-(+)-1-phenylethylamine followed by flash chromatography. The optically pure isomers (+)-**231** and (−)-**231** or (+)-**232** and (−)-**232** could be prepared from the corresponding isomers (+)-**247** and (−)-**247** in a similar manner.

In 2002, Pedregal and Prowse[91] provided another more efficient route to 2-amino-3-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (±)-**227** (Scheme 55). Conversion of



Scheme 55. Reagents and conditions: (a) (i) TMSI, Et_3N, CH_2Cl_2, rt, overnight; (ii) $(PhSO_2)_2NF/CH_2Cl_2$, rt, 48 h; (b) CCl_3H/LHMDS; (c) NaN_3/DBU/EtOH, overnight; (d) Pd/C, H_2, EtOH/Ac_2O, overnight; (e) 6 N HCl, reflux.

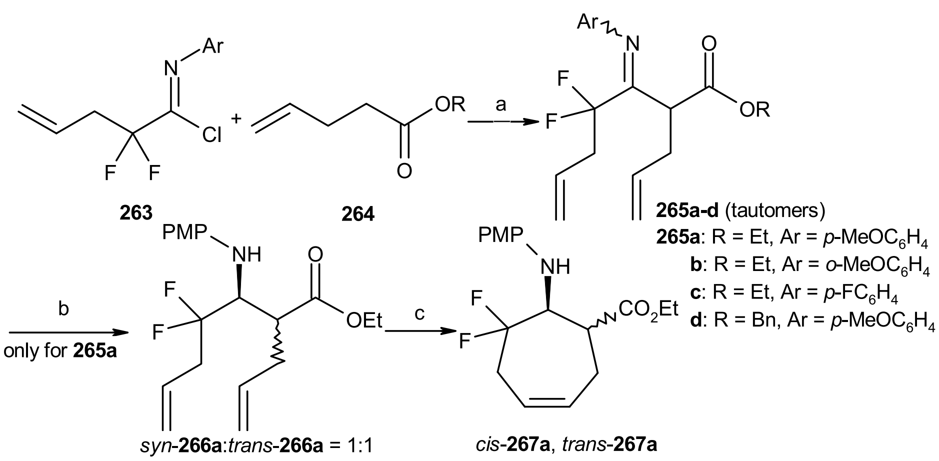


Scheme 56. Reagents and conditions: (a) $CH_2{=}CH(CH_2)_nMgBr$, THF, −78 °C to rt; (b) NaH, DMF, −5 °C to rt; (c) $CH_2{=}CHCH_2Br$ or $CH_2{=}CHCH_2CH_2Br$, rt; (d) $Ru({=}CHPh)Cl_2(PCy_3)$, CH_2Cl_2, rt; (e) $[Ru({=}C{=}C{=}CPh_2)Cl(p\text{-cymene})(PCy_3)]OTf$, toluene, 80 °C.

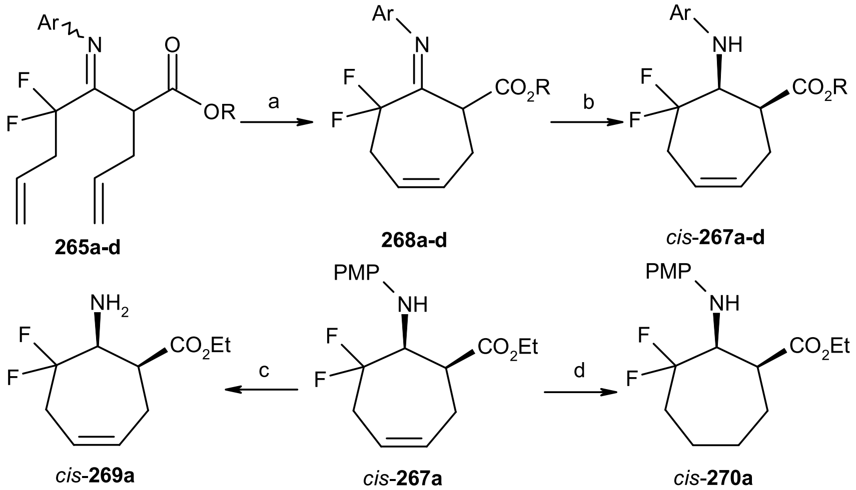
the carbonyl moiety to the corresponding amino acid moiety was realised without using the Bucherer–Bergs reaction, a key step in Nakazato's synthesis. Treatment of (±)-**233** with TMSI/Et_3N in CH_2Cl_2 followed by fluorination of the resultant silyl enol ether with NFSi proceeded with a high degree of stereocontrol and exclusively yielded the isomer (±)-**235** in 53% yield. The compound (±)-**235** was treated with LHMDS/$CHCl_3$ in THF at −78 °C to give the trichlorocarbinol (±)-**254** in 96% yield. The compound (±)-**254** was further converted into the azidoester (±)-**255** in 89% yield using modified Corey–Link reaction conditions (NaN_3/DBU/EtOH). Catalytic hydrogenation of (±)-**255** in EtOH/Ac_2O gave the acetamide (±)-**256** in 74% yield, which was further hydrolysed using 6 N HCl to afford the desired bicyclic fluorinated amino acid hydrochloride (±)-**227**.

Ring-closing olefin metathesis (RCM) now constitutes a powerful method for the production of carbo-, hetero- and macrocycles.[92]Osipov and co-workers[93] reported a synthesis of cyclic α-amino α-(fluoromethyl) acid esters and their α-aminophosphonate analogues by RCM (Scheme 56). The addition of vinyl-, allyl- and homoallylmagnesium bromides to highly electrophilic imines **257** gave the corresponding unsaturated α-amino acid esters **258** in moderate yields (54–79%). Deprotonation of the esters **258** with NaH and subsequent alkylation with allyl- and homoallyl bromides afforded the dienes **259** in 55–81% yields. The RCM of the dienes **259** catalysed by 5–10 mol% $Ru({=}CHPh)Cl_2(PCy_3)$ gave the corresponding cyclic fluorinated α-amino acid esters **260a–h** in moderate to good yields (45–96%). In a similar manner, the fluorinated cyclic α-aminophosphonate derivatives **262a–d** were prepared in 61–70% yields via RCM of the α-aminophosphonates **261** catalysed by 10 mol% $[Ru({=}C{=}C{=}CPh_2)Cl(p\text{-cymene})(PCy_3)]OTf$.

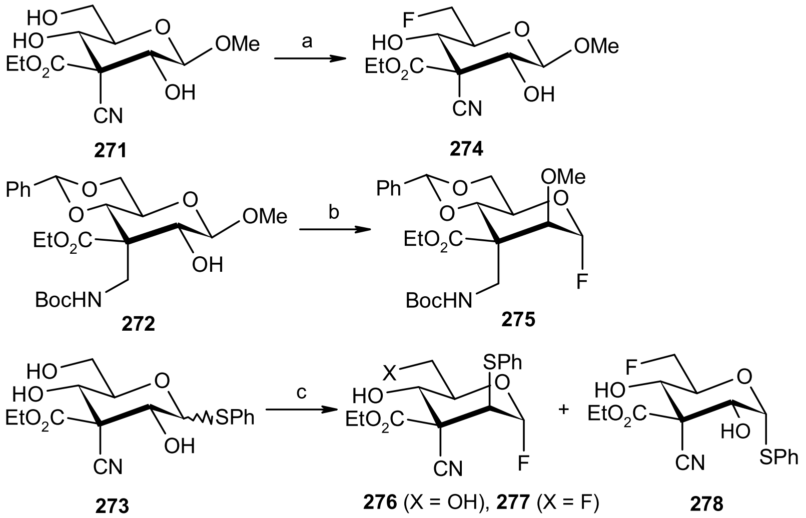
Recently, Fustereo et al.[94] have reported the synthesis of *cis* and *trans* seven-membered γ,γ-*gem*-difluoromethylated β-amino acid derivatives via RCM (Schemes 57 and 58). Coupling of the fluorinated imidoyl chlorides **263**, prepared by the reported procedures,[95] with the 4-pentenoic acid esters **264** yielded the corresponding fluorinated esters **265a–d** (76–85% yield) as a mixture of the imino and enamino forms. Two different strategies were investigated to make the target molecules, one of which is to reduce the C=N bond followed by RCM reaction and the other is to carry out an RCM reaction followed by reduction of the imine. The imine **265a** was reduced with $NaBH_3CN$ in THF/TFA at 0 °C to give two diastereoisomers *syn*-**266a** and *anti*-**266a**, which were separated by flash chromatography (Scheme 57). RCM reactions of *syn*-**266a** and



Scheme 57. Reagents and conditions: (a) (i) LDA (2.0 equiv.), THF, −78 °C; (ii) aq. NH_4Cl; (b) (i) $NaCNBH_3$ (3.0 equiv.), THF, TFA, 0 °C; (ii) sat. aq. NH_4Cl; (c) $(IHMes)(PCy_3)Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C.



Scheme 58. Reagents and conditions: (a) $(PCy_3)_2Cl_2Ru{=}CHPh$ or $(IHMes)(PCy_3)Cl_2Ru{=}CHPh$, CH_2Cl_2, 25–40 °C; (b) $NaCNBH_3$ (3.0 equiv.), THF, TFA, 0 °C; (c) $Ce(NH_4)_2(NO_3)_6$/MeCN, H_2O, 0 °C, 2 h; (d) H_2 (1 atm), Pd/C (10%), MeOH, 2 h.

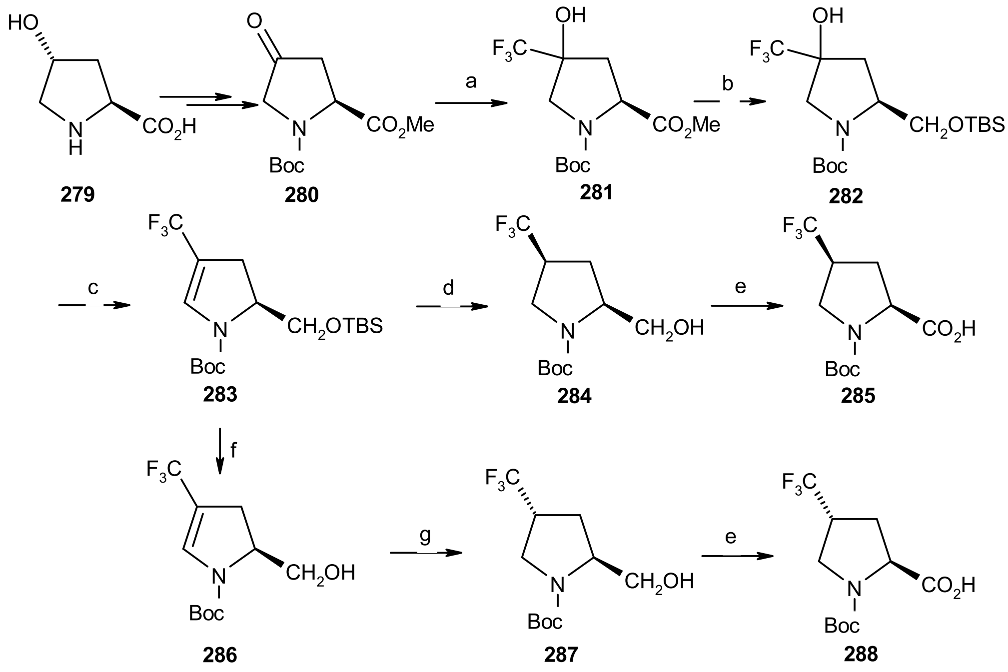


Scheme 59. Reagents and conditions: (a) DAST, CH_2Cl_2, rt, 5 h.; (b) DAST, CH_2Cl_2, reflux, 5 h; (c) DAST, CH_2Cl_2, −40 °C to rt.

anti-**266a** using $(IHMes)(PCy_3)Cl_2Ru{=}CHPh$ as a catalyst, however, gave the desired compounds *cis*-**267a** and *trans*-**267a** in low yields (27% in both cases) and the RCM reactions of **265a–d** yielded the desired cyclic products **268a–d** in 65–90% yield (Scheme 58). The reduction of **268a–d** with $NaBH_3CN$ in THF/TFA at 0 °C successfully provided *cis*-**267a–d** as the only diastereoisomer. Removal of the *p*-$MeOC_6H_4$ protecting group of *cis*-**267a** with ceric ammonium nitrate in aqueous MeCN yielded the cyclic fluorinated amino acid ester *cis*-**269a** in 95% yield. In addition, the catalytic hydrogenation of *cis*-**267a** provided the fluorinated cyclic amino acid ester *cis*-**270a** in 99% yield.

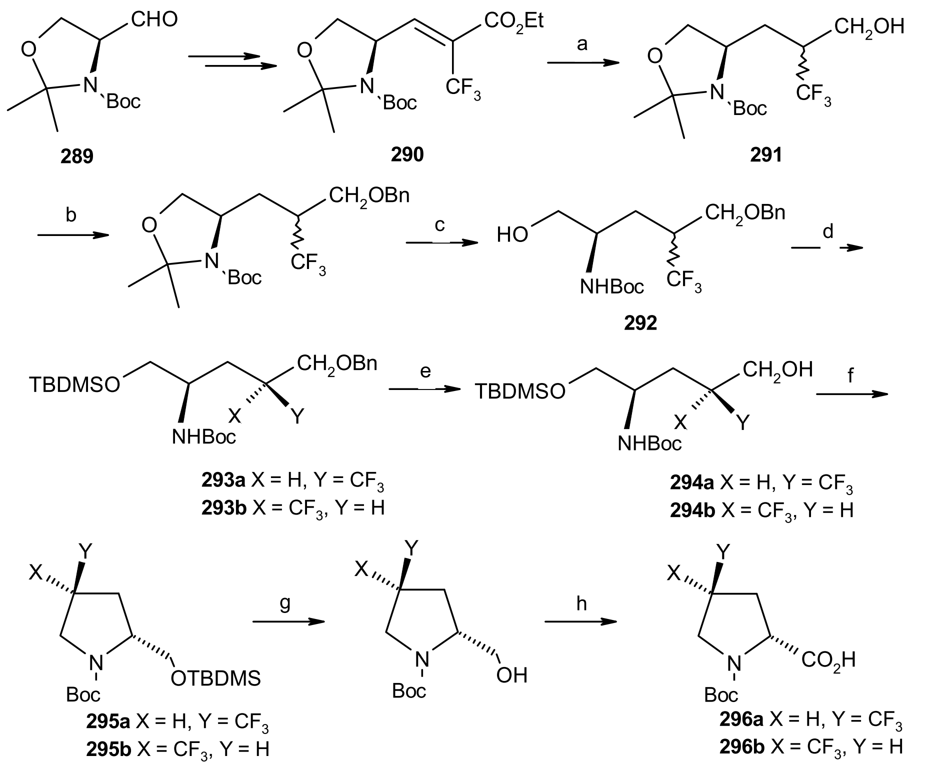
Cabrera–Escribano and co-workers[96] also synthesised several cyclic, conformationally constrained, fluorine-containing β-amino acid derivatives **274–278** from D-glucose in moderate yields, involving the fluorination of methyl 3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside **271**, methyl 4,6-*O*-(*R*)-benzylidene-3-*C*-[(*tert*-butoxycarbonylamino)methyl]-3-deoxy-3-ethoxycarbonyl-β-D-glucopyranoside **272** and phenyl-3-*C*-cyano-3-deoxy-3-ethoxycarbonyl-1-thio-α/β-D-glucopyranoside **273** with DAST in CH_2Cl_2 (Scheme 59). The course of the fluorination strongly depended upon the reaction temperature and the substitution pattern of the substrates. The expected rearrangement reactions for the compounds **272** and **273** were involved. It is noteworthy that this methodology provides a simple route to enantiopure conformationally constrained cyclic fluorinated β-amino acids having the α carbon atom shared with a pyranose ring.

Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen-mimetic triple helices, with *trans*-4-fluoroproline yielding the most striking results.[81c,d,97] In connection with the unique properties of trifluoromethyl and difluoromethyl groups, two research groups have stereoselectively synthesised



Scheme 60. Reagents and conditions: (a) 2 equiv. CF_3TMS, 2.1 equiv. TBAF, 0 °C to rt, 24 h; (b) (i) $NaBH_4$, LiCl, EtOH–THF (2:1), rt, 18 h; (ii) TBDMSCl, DMAP, CH_2Cl_2, rt, 18 h; (c) (i) TosCl, NaH, 0 °C to rt, 2 h; (ii) 2 equiv. *t*-BuOK, THF, −40 °C, 2 h; (d) H_2 (1 atm), Pd/C, EtOAc, rt; (e) NaClO, $NaClO_2$, TEMPO, MeCN, pH 6.7 NaH_2PO_4 buffer (0.67 M), 45 °C, 24 h; (f) TBAF, THF, rt, 30 min; (g) H_2 (1 atm), 2 mol% [Ir(cod)(py)PCy_3], CH_2Cl_2, rt, 4 h.

4-trifluoromethyl- and 4-difluoromethyl- prolines via different strategies. Goodman and Del Valle[98] stereoselectively synthesised Boc-protected *cis*- and *trans*-4-trifluoromethyl-prolines by asymmetric hydrogenation reactions starting from the commercially available and inexpensive *trans*-4-hydroxyproline **279** (Scheme 60). Treatment of the ketone **280** with trimethyl(trifluoromethyl)silane (CF_3TMS) in the presence of a catalytic amount of TBAF gave the tertiary alcohol **281** in 56% yield. Reduction of the ester group with $LiBH_4$ followed by selective protection of the resulting primary alcohol afforded **282** in 84% yield over two steps. Tosylation of



Scheme 61. Reagents and conditions: (a) (i) H_2, Raney Ni, MeOH, rt, overnight; (ii) $LiAlH_4$, Et_2O, 0 °C; (b) BnBr, NaH, TBAF, THF, rt, 5 h; (c) 80% AcOH, 50 °C, overnight; (d) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 h; (e) 10% Pd/C, H_2, EtOH, rt, overnight; (f) (i) MsCl, Et_3N, CH_2Cl_2, rt, overnight; (ii) KHMDS, THF, 0 °C, 24 h; (g) TBAF, THF, rt, 2 h; (h) Jones reagent.

the tertiary alkoxide of **282** followed by direct treatment with *t*-BuOK furnished the key pyrroline intermediate **283** in good yield (76%, two steps). The heterogenous hydrogenation of **283** with Pd/C as a catalyst resulted in almost complete removal of the TBDMS protecting group. The best facial selectivity (15:1, *cis*/*trans*) was observed by using 5% Pd/C as a catalyst in EtOAc. Oxidation of **284** gave the desired Boc-protected *cis*-4-trifluoromethyl-L-proline **285** in 94% yield. On the other hand, removal of the TBDMS protecting group in compound **283** with TBAF followed by hydroxy-directed asymmetric hydrogenation gave the fluorinated alcohol **286**. The best diastereoselectivity (158:1, *trans*/*cis*) was obtained with 2 mol% [Ir(cod)(py)PCy_3] as a catalyst. Oxidation of **287** gave the Boc-protected *anti*-4-trifluoromethyl-L-proline **288** in 96% yield.

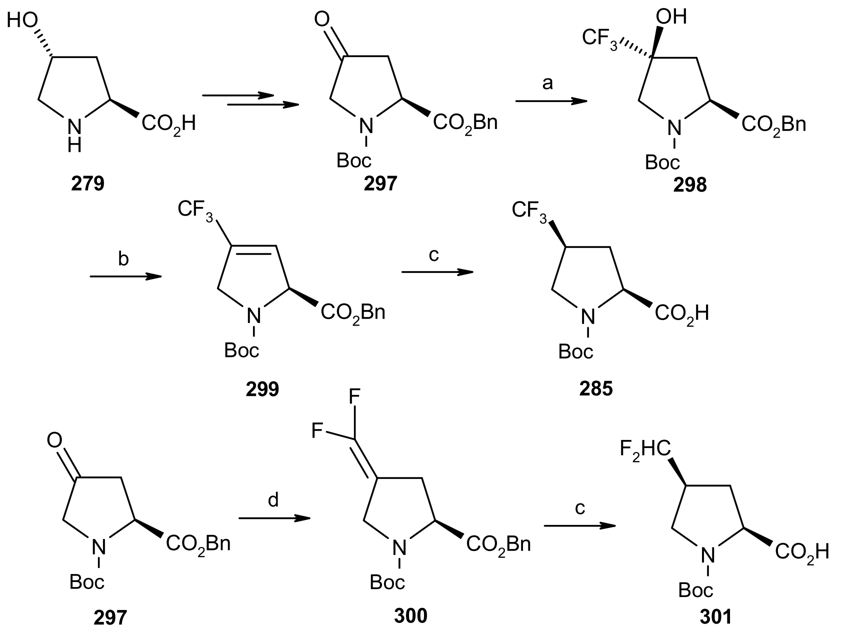
Qing and Qiu[99] prepared Boc-protected *cis*- and *trans*-4-trifluoromethyl-D-prolines starting from Garner's aldehyde **289** (Scheme 61). The key pyrroline skeleton was constructed via the cyclisation reaction. The compound **290** was prepared from **289** in two steps according to the reported procedures.[100]Initial hydrogenation of the double bond in **290** with Raney Ni in MeOH followed by reduction of the ester group with $LiAlH_4$ afforded the alcohol **291** in 94% yield. Benzylation of **291** followed by hydrolysis of the hemiaminal moiety with 80% AcOH at 50 °C afforded **292** in 75% yield over two steps. Protection of **292** with a TBDMS group gave **293** and the two diastereoisomers could be separated by flash chromatography. The catalytic hydrogenations of **293a** and **293b** yielded **294a** and **294b** in 99 and 91% yield, respectively. Mesylation of **294a** and **294b** followed by treatment with KHMDS in THF furnished the desired cyclisation products **295a** and **295b** in 83 and 80% yield, respectively. Removal of the TBDMS protecting groups with TBAF followed by oxidation with the Jones reagent gave the desired Boc-protected *trans*- and *cis*-4-trifluoromethyl-D-prolines **296a** and **296b**.

Qing and Qiu[101] also synthesised Boc-protected *cis*-4-trifluoromethyl- and *cis*-4-difluoromethyl-L-prolines via a key intermediate **297** prepared from **279** in three steps. Trifluoromethylation of the carbonyl group of **297** with CF_3TMS gave an alcohol **298** (Scheme 62). The alcohol **298** was treated with $SOCl_2$/pyridine under reflux conditions to give the olefin **299**. Hydrogenation and deprotection of **299** with Pd/C as a catalyst in EtOH yielded a single diastereoisomer, *N*-Boc-*cis*-4-trifluoromethyl-L-proline **285**. In addition, treatment of **297** with CF_2Br_2/Zn/HMPT in THF gave the olefin **300** in 48% yield. Hydrogenation of **300** stereoselectively afforded the fluorinated amino acid, *N*-Boc-*cis*-4-difluoromethyl-L-proline **301**.

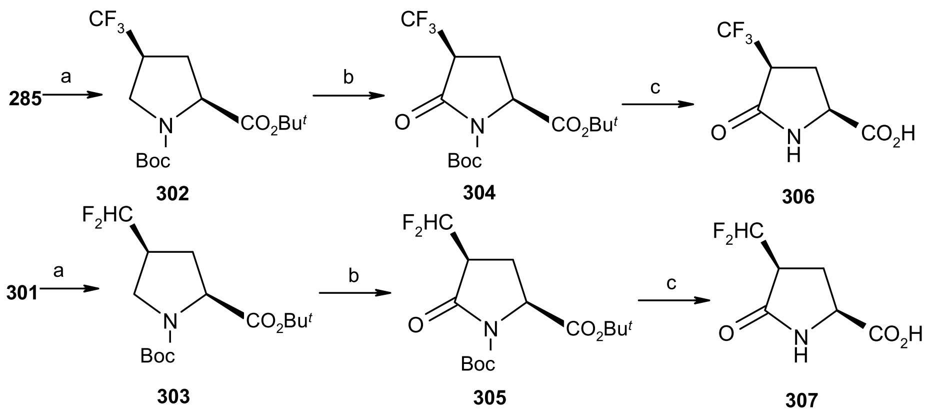
In addition, the *cis*-4-trifluoromethyl- and *cis*-4-difluoromethyl-L-pyroglutamic acids **306** and **307** were also synthesised from **285** and **301** (Scheme 63).[102] Protection of the carboxylic groups of **285** and **301** with a *tert*-butyl group provided the corresponding esters **302** and **303** in 89 and 94% yield, respectively. Oxidation of **302** and **303** with $RuO_2 \cdot xH_2O/NaIO_4$ in an $EtOAc/H_2O$ biphasic solvent afforded the desired pyroglutamates **304** and **305** in 58 and 78% yield, respectively. One-step removal of the protecting groups with trifluoroacetic acid in CH_2Cl_2 successfully gave the target compounds, *cis*-4-trifluoromethyl-L-pyroglutamic acid **306** and *cis*-4-difluoromethyl-L-pyroglutamic acid **307**.

5. Conclusions

This review has summarised the recent achievements in the synthesis of fluorinated amino acids. It is evident that tremendous progress has been made in the past five years.



Scheme 62. Reagents and conditions: (a) (i) CF_3SiMe_3, TBAF (cat.), rt, overnight; (ii) sat. aq. NH_4Cl, rt, 15 min, then TBAF, rt, 1 h; (b) $SOCl_2$, pyridine, reflux, 20 min; (c) Pd/C, H_2, EtOH; (d) CF_2Br_2, Zn, HMPT, THF, reflux, 3.5 h.



Scheme 63. Reagents and conditions: (a) Boc_2O, Et_3N, DMAP, rt, overnight; (b) $RuO_2 \cdot xH_2O$, $NaIO_4$, EtOAc, H_2O; (c) CF_3CO_2H, CH_2Cl_2, rt.

The development of efficient processes suitable for the stereoselective and asymmetric synthesis of fluorinated amino acids, better in large scale, along with the site-specific incorporation of these compounds into peptides, proteins and enzymes remains a continuous and significant challenge. No doubt the increasing interest in fluorinated amino acids and bioactive compounds containing them will stimulate new and improved methods for their synthesis in the near future.

Acknowledgements

We thank the National Natural Science Foundation of China and and the Ministry of Education of China for financial support.

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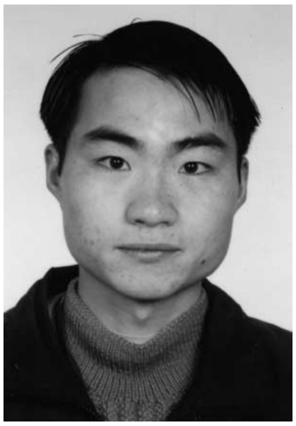
Biographical sketch



Xiao-Long Qiu was born in 1977 in Zizhong county, Sichuan province of China. He received his BS degree from Southwest China Normal University in 2000. After that, he conducted his PhD degree at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Professor Feng-Ling Qing and would receive his PhD degree in 2005. His current research interest lies on the amino acids, peptides, nucleosides and the total synthesis of biologically important natural products.

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Tetrahedron
Tetrahedron 60 (2004) 6747–6755

An efficient method for the synthesis of 1-chlorophenazines based on the selective cathodic reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione☆

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Received 6 April 2004; revised 7 June 2004; accepted 16 June 2004

Available online 2 July 2004

Dedicated to Professor José Vicente on the occasion of his 60th birthday

Abstract—An efficient method for the synthesis of 1-chlorophenazines has been established. It is based on the use of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** as a synthetic equivalent of 3-chloro-1,2-benzoquinone **3**. The intermediate **4** was prepared in near quantitative yield by electroreductive monodechlorination of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**, which is an inexpensive and easily available starting material. Efficient reactions of **4** with primary 1,2-phenylenediamines provided the corresponding 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6**, which were directly aromatized by treatment with 2,6-lutidine to give the title compounds in high yields. X-ray crystallographic structures for 1,1,4-trichloro-1,2,3,4-tetrahydro-6-methylphenazine **6f**, 8-benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine **6ea**, and 1,7-dichlorophenazine **10db** have been determined.

1. Introduction

Phenazines show properties with a wide range of significant applications.[1] One special interest lies in the biological activity of certain naturally occurring phenazines or analogues. Some of these compounds have been demonstrated to have important therapeutic utility, mainly as antibiotic and anticancer agents.[2] This has renewed the interest in the progress of the synthesis of phenazines. Because of the remarkable reluctance of phenazines to undergo electrophilic substitution reactions, the displacement of the halogen atoms of chlorophenazines by a variety of nucleophiles can play an important role in the production of a wide variety of phenazine derivatives. However, the difficulty in preparing the appropriate chlorinated starting materials frequently results in a lack of applicability of the procedure. Chlorophenazines have, in fact, provided good entries to a number of functionalized phenazine derivatives via nucleophilic substitution.[3] The development of improved methods for the synthesis of chlorophenazines is, therefore, of substantial interest. However, 1-chlorophenazines still remain almost inaccessible.[4–10]

The main general methods[1] for the synthesis of phenazines include cyclization of 2-nitro- and 2-aminodiphenylamines, coupling between anilines and nitrobenzenes, treatment of benzofuroxans with dienophiles, and double condensation of 1,2-benzoquinones with phenylene diamines. Some other preparative methods of less extensive use have also been reported. However, when these approaches are applied in preparing chlorophenazines they frequently fail in both versatility and yield. It is apparent that the procedures reported for synthesizing 1-chlorophenazines are remarkably deficient mainly because of the inherent low activity of the aromatic intermediates implied in nucleophilic substitution processes. The drastic experimental conditions that are normally required to promote these reactions cause the removal of the majority of the functional groups present in the starting materials as well as a remarkable loss of yields. On the other hand, direct chlorination of phenazine by treatment with chlorine under different conditions[4] has been found to be remarkably unselective, leading to very complex mixtures of monochloro and polychlorophenazines. Results for chlorination reactions applied to functionalized phenazines have not been reported to date.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.089

Keywords: Phenazines; 1,2-Phenylenediamines; α,α′-Polychloro-1,2-cyclohexanodiones; Electrosynthesis; Reduction; Dehydrochlorination; Aromatization.

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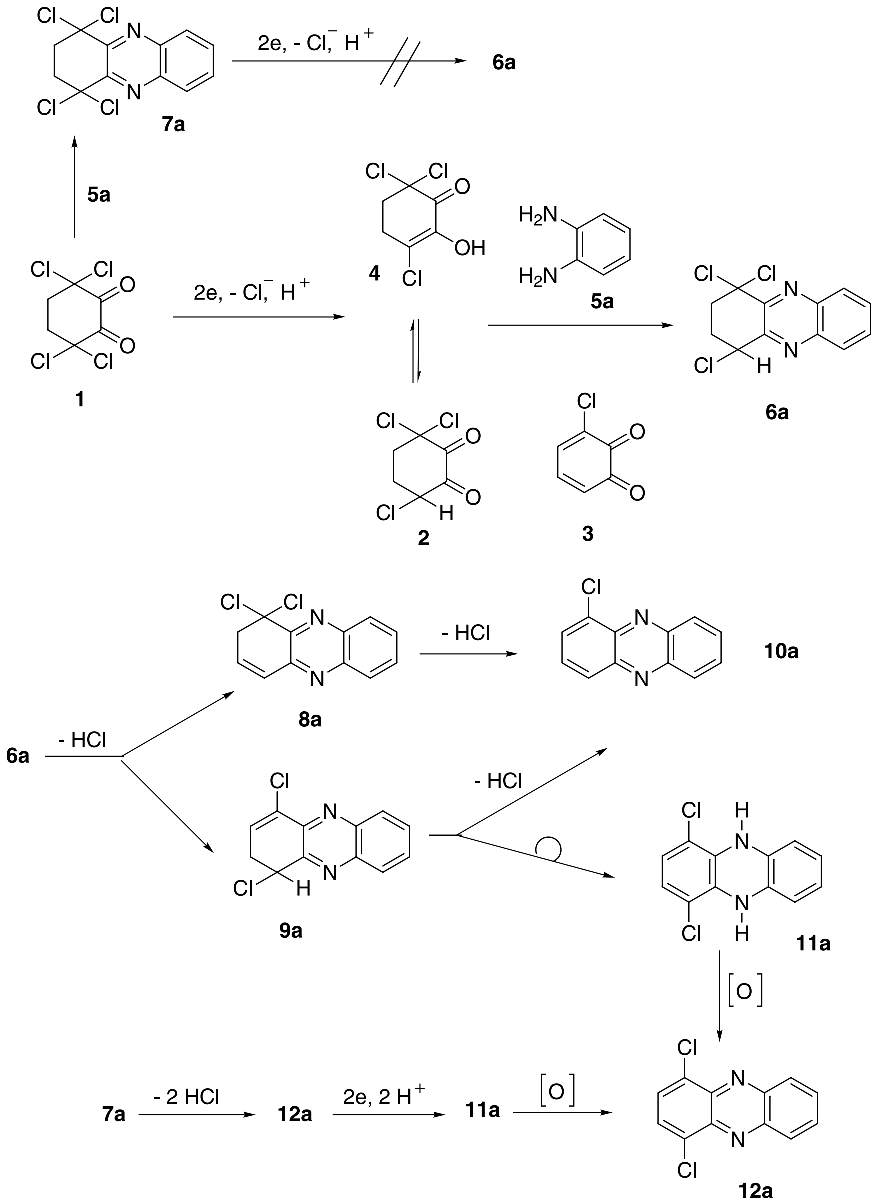
doi:10.1016/j.tet.2004.06.089

Regarding the above, it is clear that a good and versatile method for preparing 1-chlorophenazines does not seem likely to be available on this basis. Thus, the synthesis of the parent compound 1-chlorophenazine **10a** has been achieved by different procedures, involving thermal cyclation of 2′-chloro-2-nitrodiphenylamine in the presence of ferrous oxalate[5] (4.4%), a Wohl-Aue reaction[6] (18%), treatment of phenazine-N-oxide with thionyl chloride[7] (23%), chlorination of catechol followed by oxidation with silver oxide and treatment with 1,2-phenylenediamine[8] (16% overall yield) or direct chlorination of phenazine[4a] (negligible yield). Some low yield preparations of polychlorinated phenazines bearing one of the chlorine substituents at C-1 have also been reported.[9,10] These procedures seem to be incompatible with the synthesis of functionalized 1-chlorophenazines.

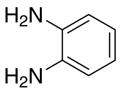
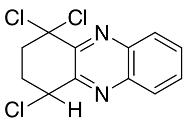
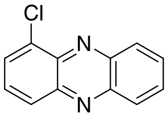
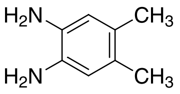
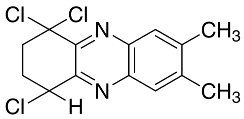
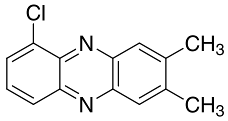
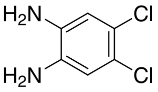
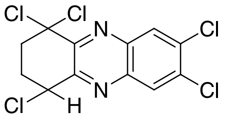
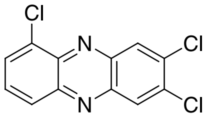
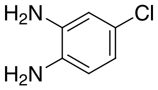
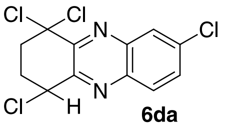
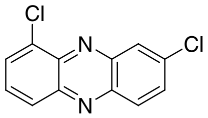
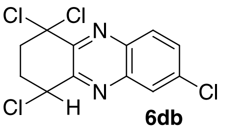
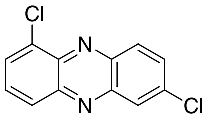
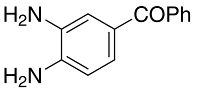
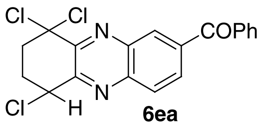
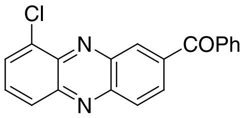
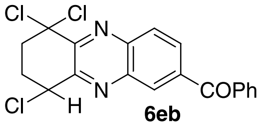
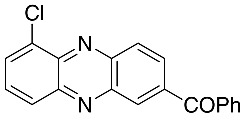
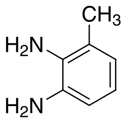
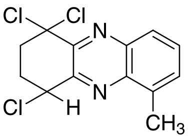
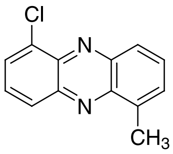
Given the precariousness of the reported syntheses of some classes of chlorophenazines, we focused on the research of improved synthetic methods for these compounds on the basis of the search for good synthetic equivalents of chlorinated *o*-quinones. It should be noted that condensation of *o*-quinones with aromatic 1,2-diamines leads directly to phenazines. However, this process appears to be unsatisfactory since the reaction of *o*-phenylenediamine with *o*-benzoquinone gives phenazine[11] in remarkable low yield (35%). Moreover, in most of cases the difficulty in preparing the appropriate *o*-quinone is an extreme synthetic problem.

Working in this project, we first reported[12] a new, efficient and versatile method for the synthesis of 1,4-dichlorophenazines by starting from 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. It is a cheap, readily available compound. Its peculiar reactivity was found to be usable as an excellent synthetic equivalent of 3,6-dichloro-1,2-benzoquinone, which is a practically unavailable compound, whereas this synthetic equivalent can be easily obtained in quantitative yield by direct treatment of commercial *trans*-cyclohexanediol with chlorine.[12,13]



Scheme 1.

Table 1. Preparation of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6a-f** and 1-chlorophenazines **10a-f**

Entry	Diamines **5**	Intermediates **6**	Yield (%)	Products **10**	Yield (%)
a			85		96
b			90		93
c			83		89
d		 **6da**	46	 **10da**	96
		 **6db**	35	 **10db**	96
e		 **6ea**	45	 **10ea**	91
		 **6eb**	41	 **10eb**	93
f			92		91

As was reported in a preliminary communication,[13] we successfully extended the above novel synthetic methodology to the synthesis of 1-chlorophenazines. In this paper we describe full details of the previous report on this subject as well as new outcomes of this preparative procedure which is illustrated in Scheme 1 and Table 1. The aim of this approach is to circumvent the use of 3-chloro-1,2-benzoquinone **3** which is a rare and practically inaccessible compound.[8,14–16] Moreover, the advantage of a highly efficient reaction between vicinal dicarbonyl groups with aromatic 1,2-diamines instead of *o*-quinonoid ones is another attractive feature of this procedure.

2. Results and discussion

The preparation of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** was attempted by reaction of cyclohexanone with copper dichloride[17] (ratio 1:20) in dioxane–water. Because of the low yield and the requirement of a difficult chromatographic isolation of the product, this reaction was found to be of little synthetic use. However, this obstacle could be satisfactorily overcome by an efficient and highly selective electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. Thus, electrolysis of **1** under a constant cathodic potential in a protic medium gave a single product quantitatively, which was isolated and identified as the compound **4** which corresponds to the enol form of the intended key intermediate **2**.

In order to achieve the synthesis of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6** to be used as precursors of the targeted 1-chlorophenazines, reactions of **4** with 1,2-phenylenediamines **5** were carried out. The reactivity of **4** was observed to be similar to that predictable for the dione **2**. High yields in the expected products **6** were obtained by performing the reaction in benzene with continuous azeotropic removal of water. These products were easily obtained in a crystalline state and were stable enough to permit prolonged storage without receiving any special care. There are no precedents for this family of compounds. It should be noted that reactions with symmetrical diamines such as **5a**-**c** gave the corresponding single products **6a**-**c**. However, the reactions with nonsymmetrical diamines **5d**,**e** gave two pairs of the possible isomeric products (**6d**-**a**,**b** and **6e**-**a**,**b**), which were formed in a comparable ratio. All these isomers could be definitively differentiated by X-ray crystallographic analysis of either a member of each product pair or a phenazine derivative, thus single crystals of compound **6ea** and **10db** were analyzed by X-ray crystallography. The molecular structures are illustrated in Figures 1 and 2, respectively. Selected bond lengths are given in Tables 2 and 3, respectively.

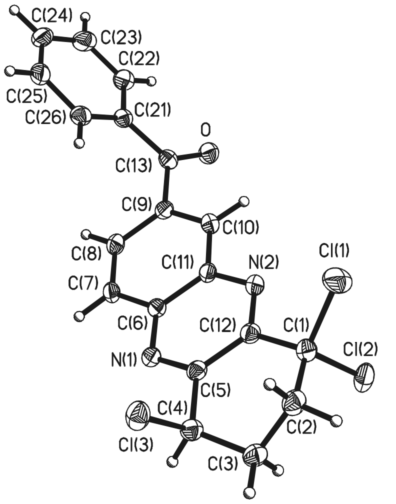


Figure 1. Molecular structure of **6ea**, showing the crystallographic numbering system used.

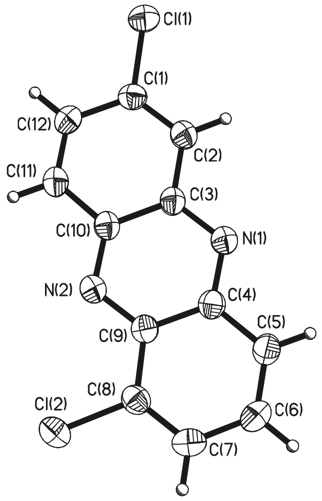


Figure 2. Molecular structure of **10db**, showing the crystallographic numbering system used.

The reaction with 3-methyl-1,2-phenylenediamine **5f** was found to be fully selective towards the formation of 1,1,4-trichloro-1,2,3,4-tetrahydro-6-methylphenazine **6f**. The molecular structure of this product was corroborated by single crystal X-ray diffraction analysis. It seems reasonable to presume that steric factors are implied in the exclusive formation of this product

Table 2. Selected bond lengths in crystal structure of **6ea**

Cl(1)–C(1)	1.788(2)	C(1)–C(2)	1.521(3)
Cl(2)–C(1)	1.804(2)	C(3)–C(4)	1.513(3)
Cl(3)–C(4)	1.824(2)	C(4)–C(5)	1.502(3)
O–C(13)	1.222(2)	C(9)–C(13)	1.503(3)
C(1)–C(12)	1.521(3)	C(13)–C(21)	1.488(3)

Table 3. Selected bond lengths in crystal structure of **10db**

Cl(1)–C(1)	1.740(2)	N(2)–C(9)	1.340(2)
Cl(2)–C(8)	1.736(2)	N(2)–C(10)	1.343(2)
N(1)–C(4)	1.341(2)	C(3)–C(10)	1.436(2)
N(1)–C(3)	1.343(2)	C(4)–C(9)	1.439(2)

In the search for an alternative approach to 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines **6**, the electrochemical reduction of 1,1,4,4-tetrachloro-1,2,3,4-tetrahydrophenazine **7a** at constant potential in a protic medium was carried out. However, this electrolysis was found to be remarkably unselective and it led to a complex mixture of products with a different dechlorination degree.

The first experiments, focused on establishing effective experimental conditions to achieve the conversion of intermediates **6** to the corresponding 1-chlorophenazines **10**, gave surprising and somewhat disappointing results. Thus, the treatment of **6a** with pyridine yielded the expected 1-chlorophenazine **10a** in moderate yield (62%) but accompanied by a considerable amount of 1,4-dichlorophenazine **12a** (26%). The reaction with sodium methoxide gave a similar result. Some other experiments were carried out, showing the generation of 1-chlorophenazines along with the undesired 1,4-dichlorophenazines as a general synthetic limitation of these reactions.

It was considered that the formation of the targeted 1-chlorophenazines implies an aromatization process associated with a double elimination of hydrogen chloride from intermediates **6**. However, aromatization leading to 1,4-dichlorophenazines obviously involve a monodehydrohalogenation process of the same intermediates. Therefore, the collaboration of an oxidation process must be necessarily postulated to clarify the formation of the lateral products **12**. This hypothesis leads us to conclude that a crucial influence of the site where the intermediates **6** undergo a first deprotonation provides the most plausible explanation that may be offered for these facts. Thus, deprotonation at C-3 would promote the formation of intermediates **8**, which would give the targeted products **10** exclusively. However, deprotonation at C-2 would generate the intermediates **9**, which could reasonably undergo dehydrochlorination to give products **10**, but also rearrangement to 1,4-dichloro-5,10-dihydrophenazines **11**, whose oxidation explains the formation of products **12**.

This reaction route is well supported by the following facts: (1) the great proclivity of 5,10-dihydrophenazines towards undergoing oxidation yielding phenazines is well known;[14] (2) a sample of 1,4-dichloro-5,10-dihydrophenazine **11a** was prepared by electrochemical reduction of **12a** in a protic medium. When compound **11a** was exposed to a similar experimental conditions as those operating in the conversion of **6a** to **10a**, an almost instantaneous quantitative formation of 1,4-dichlorophenazine **12a** was observed even when working under nitrogen atmosphere; (3) the generation of product **12a** was fully prevented by treatment of **6a** with 2,6-lutidine instead of pyridine. In this case the exclusive formation of 1-chlorophenazine **10a** (96%) occurred. This result is in excellent agreement with the expected effect of a bulky base determining regioselectivity towards the less hindered reactive site. It seems reasonable, therefore, in this case to assume a process with the exclusive generation of **10a** without participation of the intermediates **9a** and **11a**.

In conclusion, a simple and effective method for the synthesis of 1-chlorophenazines **10** is reported whose selectivity is helped by steric effects developed by the base promoting aromatization. Nearly quantitative yields, easy availability of starting materials are valuable, noteworthy advantages of the method which allows the access to previously unattainable compounds. It is also to be noted that this work has revealed 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **4** as an excellent synthetic equivalent of 3-chloro-1,2-benzoquinone **3**. Since the usefulness of quinones in organic synthesis is well known the compound **4** seems likely to be a promising intermediate in allowing the selective synthesis of a wide variety of specifically chlorinated compounds.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AC-200 or Varian Unity 300 Unity instruments with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on Hewlett–Packard 5995 and Autospect 5000 VG spectrometers under an ionizing voltage of 70 eV. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 spectrophotometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Kofler hot-plate melting point apparatus, and are uncorrected. Electrochemical experiments were performed with an Amel 557 potentiostat coupled to an Amel 558 integrator. 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1** was prepared as previously described.[12]

X-ray crystallographic data were collected using Mo K_α radiation (λ=0.71073 Å). For compounds **6f** and **6ea** a Siemens P4 diffractometer was used (ω-scans, $2\theta_{max}$ 50°); for the structure of **10db**, a Bruker SMART CCD (ω and ø-scans, $2\theta_{max}$ 56°, absorption correction using multiple scans). Structures were refined anisotropically on F^2 using the program SHELXL-93 (G. M. Sheldrick, University of Göttingen). Hydrogen atoms were included using rigid methyl groups or a riding model. Full structural information has been deposited with the Cambridge Crystallographic Data Centre.[18]

3.1.1. Preparation of 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one (4). A reductive electrolysis[19] of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1** was carried out under a constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm; Luggin-capillary situated to the side of the pool) was used as the cathode and a platinum plate as the anode. The current intensity was 240 mA at the beginning, and 10 mA at the end. The cell voltage remained below 6 V. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in MeCN (40 mL)—AcOH (10 mL)—$LiClO_4$ (3 g); 35 mL and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (0.2 g) was placed in the anode compartment. A solution of **1** (5 mmol) was electrolyzed under a cathodic potential of −0.05 V versus SCE. The electricity consumption was 2 F/mol. Isolation of product **4** was carried out by removing the solvent in vacuo,[20] adding water (150 mL) and extracting the mixture with chloroform (3×40 mL). The combined organic layers were washed with cold water and dried on anhydrous sodium sulphate. After evaporation of chloroform under reduced pressure the solid residue was crystallized from petroleum ether, yield 95%, white needles; mp 120–121 °C (lit.[17] 119–120 °C) (Found: C, 33.30; H, 2.40; $C_6H_5Cl_3O_2$ requires: C, 33.45; H, 2.34); ^1H NMR δ ($CDCl_3$, 300 MHz): 2.84–2.95 (m, 4H), 6.20 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 30.47, 42.46, 82.70, 129.2, 140.70, 180.52; MS *m/z* (%) 218 [M^++4] (5), 216 [M^++2] (15), 214 [M^+] (18), 179 (15), 161 (7), 153 (55), 151 (100), 118 (66), 90 (43), 54 (90); IR (Nujol) 3389, 1698, 1638, 1355, 1273, 1152, 1132, 1056, 970, 910, 876, 808, 702 cm^{-1}.

This synthesis was found to be reproducible when using graphite instead of mercury as cathodic material. The preparation of **4** was achieved in 83% yield by a procedure as described above but with an operating potential of −0.30 V versus SCE. The current intensity was 310 mA at the beginning, and 10 mA at the end. The cell voltage remained below 8 V. The electricity consumption was 2 F/mol.

3.1.2. Preparation of 1,1,4-trichloro-1,2,3,4-tetrahydrophenazines (6). A benzene solution (75 mL) of **4** (5.56 mmol) and the appropriate diamine **5** (5.48 mmol) was refluxed with a Dean–Stark water separator for 24 h. The solvent was evaporated under reduced pressure and the residue was shaken with ether (75 mL). The small amount of a white solid remaining in suspension was removed by filtration. After evaporation of ether, highly pure products **6** were isolated and crystallized in the appropriate solvent. Products **6d-a**,**b** and **6e-a**,**b** were isolated by column chromatography.

3.1.3. 1,1,4-Trichloro-1,2,3,4-tetrahydrophenazine (6a). (85%); Crystallization from petroleum ether gave white prisms; mp 135–137 °C. (Found: C, 49.33; H, 3.23; N, 9.86; $C_{12}H_9Cl_3N_2$ requires: C, 50.12; H, 3.15; N, 9.74); ^1H NMR δ ($CDCl_3$, 300 MHz): 2.49–2.59 (m, 1H), 2.81–2.94 (m, 1H), 3.05–3.14 (m, 1H), 3.41–3.53 (m, 1H), 5.53–5.56 (m, 1H), 7.80–7.87 (m, 2H), 8.09–8.15 (m, 1H) 8.19–8.26 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 29.73, 40.77, 57.18, 85.59, 129.05, 129.59, 131.48, 131.86, 142.39, 142.69, 146.97, 149.65; MS, *m/z* (%): 290 [M^++4] (3), 288 [M^++2] (9), 286 [M^+] (9), 251 (21), 215 (100), 217 (31), 181 (23), 108 (21), 102 (33), 76 (67). IR (Nujol) 1556, 1356, 1235, 948, 921, 900, 832, 787, 769, 689 cm^{-1}.

3.1.4. 1,1,4-Trichloro-1,2,3,4-tetrahydro-7,8-dimethylphenazine (6b). (90%); Crystallization from petroleum ether gave white prisms; mp 197–198 °C. (Found: C, 52.97; H, 4.09; N, 8.96; $C_{14}H_{13}Cl_3N_2$ requires: C, 53.28; H, 4.15; N, 8.88);^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.41–2.58 (m, 1H), 2.50 (s, 6H), 2.77–2.95 (m, 1H), 3.00–3.13 (m, 1H), 3.37–3.53 (m, 1H), 5.49–5.53 (m, 1H), 7.85 (s, 1H), 7.98 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 20.49, 20.58, 29.78, 40.78, 57.45, 85.91, 127.83, 128.36, 141.49, 141.82, 142.67, 143.13, 145.81, 148.63; MS *m/z* (%) 318 [M^++4] (1), 316 [M^++2] (3), 314 [M^+] (3), 279 (15), 243 (76), 245 (25), 209 (22), 193 (13), 103 (79), 89 (25), 77 (99), 51 (100); IR (Nujol) 1357, 1205, 1009, 942, 922, 871, 806, 782, 760, 655 cm^{-1}.

3.1.5. 1,1,4,7,8-Pentachloro-1,2,3,4-tetrahydrophenazine (6c). (83%); Crystallization from petroleum ether gave white prisms; mp 152–153 °C. (Found: C, 40.60; H, 2.04; N, 7.99; $C_{12}H_7Cl_5N_2$ requires: C, 40.43; H, 1.98; N, 7.86); ^{1}H NMR δ ($CDCl_3$, 200 MHz): 2.47–2.61 (m, 1H), 2.78–2.96 (m, 1H), 3.02–3.14 (m, 1H), 3.36–3.53 (m, 1H), 5.47–5.52 (m, 1H), 8.25 (s, 1H), 8.37 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 29.53, 40.53, 56.73, 85.02, 129.54, 130.04, 136.64, 136.99, 140.99, 141.30, 148.25, 150.74; MS *m/z* (%) 354 [M^+] (2), 321 (8), 285 (30); 283 (30), 249 (12), 213 (14), 134 (19), 124 (27), 109 (52), 100 (32), 75 (76), 61 (46), 51 (100); IR (Nujol) 1380, 1229, 1111, 985, 942, 922, 891, 847, 802, 753 cm^{-1}.

3.1.6. 1,1,4,8-Tetrachloro-1,2,3,4-tetrahydrophenazine (6da). (46%); Chromatography (AcOEt/petroleum ether, 15:85) gave white powder; mp 150–151 °C. (Found: C, 44.61; H, 2.41; N, 8.77; $C_{12}H_8Cl_4N_2$ requires: C, 44.76; H, 2.50; N, 8.70; ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.47–2.61 (m, 1H), 2.79–2.97 (m, 1H), 3.03–3.15 (m, 1H), 3.38–3.54 (m, 1H), 5.49–5.54 (m, 1H), 7.79 (dd, *J*=9.1, 2.3 Hz, 1H), 8.12 (d, *J*=2.3 Hz, 1H), 8.18 (d, *J*=9.1 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 29.57, 40.59, 56.86, 85.29, 127.87, 130.76, 132.74, 138.09, 140.88, 142.84, 148.01, 149.81; MS *m/z* (%) 324 [M^++4] (3), 322 [M^++2] (6), 320 [M^+] (4), 287 (21), 285 (21), 251 (62), 249 (100), 215 (38), 179 (28), 163 (20), 100 (35), 75 (99). IR (Nujol) 1607, 1354, 1188, 1064, 951, 928, 844, 836, 817, 723, 653 cm^{-1}.

3.1.7. 1,1,4,7-Tetrachloro-1,2,3,4-tetrahydrophenazine (6db). (35%); Chromatography (AcOEt/ petroleum ether, 15:85) gave white powder; mp 194–195 °C. (Found: C, 44.53; H, 2.58; N, 8.61; $C_{12}H_8Cl_4N_2$ requires: C, 44.76; H, 2.50; N, 8.70.); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.48–2.61 (m, 1H), 2.79–2.97 (m, 1H), 3.02–3.16 (m, 1H), 3.38–3.54 (m, 1H), 5.49–5.54 (m, 1H), 7.79 (dd, *J*=9.0, 2.3 Hz, 1H), 8.07 (d, *J*=9.0 Hz, 1H), 8.25 (d, *J*=2.3 Hz, 1H). ^{13}C NMR δ ($CDCl_3$, 50.3 MHz) 29.64, 40.61, 57.00, 85.24, 128.43, 130.29, 133.16, 137.80, 141.27, 142.65, 147.25, 150.63. MS *m/z* (%) 324 [M^++4] (2), 322 [M^++2] (4), 320 [M^+] (4), 287 (9), 285 (9), 251 (41), 249 (63), 215 (21), 179 (17), 163 (15), 100 (31), 75 (92), 51 (100). IR (Nujol) 1601, 1351, 1233, 1128, 1096, 955, 930, 841, 799, 753, 721, 640 cm^{-1}.

Crystallographic details. Yellow needle-like single crystals were grown from a solution in chloroform. A crystal of approximate dimensions 0.40×0.05×0.03 mm^3 was selected and mounted on a glass fiber. A total of 6632 reflections ($-5\leq h\leq 5$, $-16\leq k\leq 10$, $-28\leq l\leq 27$) were collected at T=173(2) K in the θ range from 1.88 to 28.31° of which 2509 were unique (R_{int}=0.0277; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.306 and −0.200 e/Å^3. The absorption coefficient was 0.601 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0628 (all data), wR_2=0.0934, and GOF=1.065 [$I>2\sigma(I)$]. $C_{12}H_6Cl_2N_2$, monoclinic, space group $P2_1/c$, a=3.9055(10) Å, b=12.130(4) Å, c=21.623(8) Å, α=90°, β=92.00(3)°, γ=90°, V=1023.7(6) Å^3, Z=4, ρ_{calc}=1.616 g/cm^3, $F(0,0,0)$=504, $R(F)$=0.0385, $wR(F_2)$=0.0835.

3.1.8. 8-Benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine (6ea). (45%); Chromatography (CH_2Cl_2/AcOEt/hexane, 80:10:10) gave white powder; mp 161–162 °C. (Found: C, 57.32; H, 3.21; N, 7.22; $C_{19}H_{13}Cl_3N_2O$ requires: C, 58.26; H, 3.35; N, 7.15; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.52–2.62 (m, 1H), 2.84–2.97 (m, 1H), 3.06–3.15 (m, 1H), 3.41–3.52 (m, 1H), 5.55–5.58 (m, 1H), 7.54 (tt, *J*=7.5, 1.5 Hz, 2H), 7.66 (tt, *J*=7.5, 1.5 Hz, 1H), 7.88 (dt, *J*=7.5, 1.5 Hz, 2H), 8.25 (dd, *J*=8.6, 0.6 Hz, 1H), 8.33 (dd, *J*=8.6, 1.8 Hz, 1H), 8.57 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 29.42, 40.46, 57.79, 85.10, 128.59, 129.53, 129.99, 131.55, 132.28, 133.04, 136.59, 139.64, 141.40, 144.06, 148.76, 150.74, 195.11; MS *m/z* (%) 394 [M^++4] (2), 392 [M^++2], (6), 390 [M^+] (6), 357 (9), 355 (13), 319 (97), 321 (32), 179 (20), 105 (91), 77 (100). IR (Nujol) 1666, 1355, 1267, 946, 894, 846, 827, 790, 711, 676 cm^{-1}.

Crystallographic details. Colourless block-like crystals were obtained by slow diffusion of *n*-hexane into a solution of **6ea** in chloroform. A crystal of approximate dimensions 0.60×0.40×0.20 mm^3 was selected and mounted on a glass fiber. A total of 3304 reflections ($-9\leq h\leq 9$, $-10\leq k\leq 1$, $-15\leq l\leq 15$) were collected at T=173(2) K in the θ range from 3.16 to 24.99° of which 2989 were unique (R_{int}=0.0248; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.239 and −0.227 e/Å^3. The absorption coefficient was 0.545 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0358 (all data), wR_2=0.0863, and GOF=1.087 [$I>2\sigma(I)$]. $C_{19}H_{13}Cl_3N_2O$, triclinic, space group P-1, a=7.6607(7) Å, b=8.8706(6) Å, c=13.1580(12) Å, α=75.939(7)°, β=82.475(7)°, γ=83.248(6) °, V=856.5(2) Å^3, Z=2, ρ_{calc}=1.519 g/cm^3, $F(0,0,0)$=400, $R(F)$=0.0301, $wR(F^2)$=0.0824.

3.1.9. 7-Benzoyl-1,1,4-trichloro-1,2,3,4-tetrahydrophenazine (6eb). (41%); Chromatography (CH_2Cl_2/AcOEt/hexane, 80:10:10) gave white powder; mp 138–140 °C. (Found: C, 58.59; H, 3.44; N, 7.03; $C_{19}H_{13}Cl_3N_2O$ requires: C, 58.26; H, 3.35; N, 7.15); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.52–2.61 (m, 1H), 2.83–2.96 (m, 1H), 3.07–3.16 (m, 1H), 3.43–3.54 (m, 1H), 5.52–5.55 (m, 1H), 7.54 (tt, *J*=7.4, 1.6 Hz, 2H), 7.66 (tt, *J*=7.4, 1.6 Hz, 1H), 7.88 (dt, *J*=7.4, 1.6 Hz, 2H), 8.31 (dd, *J*=9.0, 1.8 Hz, 1H), 8.36 (dd, *J*=9.0, 0.6 Hz, 1H), 8.47 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C

NMR δ ($CDCl_3$, 75.4 MHz) 29.63, 40.63, 56.93, 85.23, 128.70, 130.13, 130.16, 131.31, 131.81, 133.22, 136.71, 140.11, 141.88, 143.95, 148.31, 151.35, 195.24; MS *m/z* (%) 394 [M^++4] (12), 392 [M^++2], (36), 390 [M^+] (40), 357 (33), 355 (49), 319 (65), 290 (43), 179 (92), 105 (78), 77 (100); IR (Nujol) 1666, 1378, 1265, 949, 847, 830, 792, 730, 715 cm^{-1}.

3.1.10. 1,1,4-Trichloro-1,2,3,4-tetrahydro-6-methylphenazine (6f). (92%); Crystallization from acetonitrile gave white microcystals; mp 140–142 °C. (Found: C, 51.74; H, 3.74; N, 9.37; $C_{13}H_{11}Cl_3N_2$ requires: C, 51.77; H, 3.68; N, 9.29); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 2.48–2.58 (m, 1H), 2.78 (s, 3H), 2.80–2.93 (m, 1H), 3.04–3.12 (m, 1H), 3.42–3.54 (m, 1H), 5.53–5.57 (m, 1H), 7.63 (br d, *J*=6.9 Hz, 1H), 7.67–7.74 (m, 1H), 8.05 (dd, *J*=8.4, 0.6 Hz, 1H). ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 17.20, 29.82, 40.87, 57.54, 85.80, 127.33, 131.35, 131.50, 137.77, 142.04, 142.59, 145.62, 149.11. MS *m/z* (%) 304 [M^++4] (3), 302 [M^++2] (7), 300 [M^+] (8), 265 (16), 231 (29), 229 (100), 193 (48), 97 (40), 89 (43), 75 (25), 63 (47); IR (Nujol) 1378, 1238, 947, 919, 817, 788, 767, 760, 679 cm^{-1}.

Crystallographic details. Colourless block-like single crystals were obtained by slow diffusion of petroleum ether into a solution of **6f** in chloroform. A crystal of approximate dimensions 0.42×0.35×0.32 mm^3 was selected and mounted on a glass fiber. A total of 2836 reflections ($-8\leq h\leq 8$, $-23\leq k\leq 4$, $-10\leq l\leq 0$) were collected at T=173(2) K in the θ range from 3.12 to 24.99° of which 2235 were unique (R_{int}=0.0387; Mo K_α radiation (λ=0.71073 Å). The residual peak and hole electron density were 0.428 and −0.411 e/Å^3. The absorption coefficient was 0.699 mm^{-1}. The least-squares refinement converged normally with residuals of R_1=0.0619 (all data), wR_2=0.1227, and GOF=1.100 [$I>2\sigma(I)$]. $C_{13}H_{11}Cl_3N_2$, monoclinic, space group $P2_1/n$, a=7.4190(10) Å, b=19.689(2) Å, c=8.7640(10) Å, α=90°, β=94.420(10)°, γ=90°, V=1276.4(3) Å^3, Z=4, ρ_{calc}=1.569 g/cm^3, F(0,0,0)=616, $R(F)$=0.0447, $wR(F^2)$=0.1138.

3.2. Preparation of 1-chlorophenazines (10)

A dimethylformamide solution (30 mL) of the appropriate intermediate **6** (3.5 mmol) and 2,6-lutidine (2 mL) was refluxed for 2 h. After cooling the reaction products were isolated by dropping the solution onto cold brine (400 mL) and filtration. The directly collected solid crude products were washed with cold water, dried and crystallized from the appropriate solvent.

3.2.1. 1-Chlorophenazine (10a). (96%); Crystallization from hexane gave yellow needles; mp 123–124 °C (lit.[6] 122 °C). ^{1}H NMR δ ($CDCl_3$, 200 MHz): 7.62–7.71 (m, 1H), 7.76–7.91 (m, 3H), 8.05–8.19 (m, 2H), 8.26–8.35 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 128.77, 129.28, 129.58, 129.69, 129.93, 130.94, 131.16, 132.97, 139.87, 143.13, 143.46, 143.67; MS *m/z* (%) 216 [M^++2] (32), 214 [M^+] (93), 179 (49), 152 (23), 129 (10), 125 (11), 107 (18), 100 (20), 89 (11), 75 (100), 63 (32), 50 (92). IR (Nujol) 1510, 1380, 958, 821, 762, 742, 676 cm^{-1}.

3.2.2. 1-Chloro-7,8-dimethylphenazine (10b). (93%); Crystallization from petroleum ether/Cl_3CH gave yellow needles; mp 224–225 °C. (Found: C, 69.19; H, 4.62; N, 11.60. $C_{14}H_{11}ClN_2$ requires: C, 69.28; H, 4.57; N, 11.54); ^{1}H NMR δ ($CDCl_3$, 200 MHz): 2.56 (s, 6H), 7.64–7.73 (m, 1H), 7.90 (dd, *J*=7.3, 1.0 Hz, 1H), 7.95 (s, 1H), 8.11–8.16 (m, 2H). ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 20.75, 20.83, 127.69, 128.41, 128.83, 129.05, 129.24, 132.97, 139.74, 142.73, 142.87, 142.96, 143.19, 143.57; MS *m/z* (%) 244 [M^++2] (31), 242 [M^+] (100), 229 (8), 227 (28), 205 (16), 179 (15), 136 (10), 121 (18), 103 (37), 89 (30), 75 (81), 63 (60), 51 (85). IR (Nujol) 1505, 1380, 1353, 956, 860, 823, 779, 743, 727 cm^{-1}.

3.2.3. 1,7,8-Trichlorophenazine (10c). (89%); Crystallization from petroleum ether gave yellow needles; mp 237–238 °C. (Found: C, 50.98; H, 1.83; N, 9.11; $C_{12}H_5Cl_3N_2$ requires: C, 50.83; H, 1.78; N, 9.88); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.73–7.79 (m, 1H), 7.96 (dd, *J*=7.5, 1.2 Hz, 1H), 8.14 (dd, *J*=8.7, 1.2 Hz, 1H), 8.32 (s, 1H), 8.52 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 129.10, 129.82, 130.43, 130.65, 130.72, 133.68, 136.42, 136.62, 140.75, 141.93, 142.37, 144.56; MS *m/z* (%) 286 [M^++4] (7), 284 [M^++2] (23), 282 [M^+] (24), 249 (7), 247 (11), 141 (10), 136 (15), 134 (11), 124 (15), 109 (31), 100 (47), 75 (100), 50 (57); IR (Nujol) 1613, 1378, 1103, 994, 958, 884, 871, 825, 775, 753, 738 cm^{-1}.

3.2.4. 1,8-Dichlorophenazine (10da). (96%); Crystallization from Cl_3CH gave yellow needles; mp 226–227 °C (lit.[6] 219–220 °C). ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.67–7.77 (m, 2H), 7.91 (dd, *J*=7.2, 1.2 Hz, 1H), 8.10 (dd, *J*=9.1, 1.2 Hz, 1H), 8.19 (dd, *J*=1.2, 0.6 Hz, 1H), 8.26 (dd, *J*=9.1, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 127.92, 128.91, 130.02, 130.30, 131.41, 132.43, 133.55, 137.48, 140.20, 141.84, 143.69, 144.39; MS *m/z* (%) 252 [M^++4] (24), 250 [M^++2] (87), 248 [M^+] (100), 215 (17), 213 (50), 178 (8), 124 (15), 75 (19); IR (Nujol) 1508, 1411, 1344, 1067, 957, 935, 888, 885, 811, 739, 713 cm^{-1}.

3.2.5. 1,7-Dichlorophenazine (10db). (96%); Crystallization from Cl_3CH gave yellow needles; mp 259–260 °C. (Found: C, 58.02; H, 2.48; N, 11.20; $C_{12}H_6Cl_2N_2$ requires: C, 57.86; H, 2.43; N, 11.25); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.70–7.81 (m, 2H), 7.95 (br d, *J*=7.2 Hz, 1H), 8.13–8.19 (m, 2H), 8.37 (dd, *J*=1.8, 0.6 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 128.66, 129.14, 130.02, 130.52, 130.89, 132.78, 133.52, 137.41, 140.69, 142.36, 143.41, 144.11; MS *m/z* (%) 252 [M^++4] (12), 250 [M^++2] (70), 248 [M^+] (100), 215 (10), 213 (29), 124 (8), 100 (5), 75 (11); IR (Nujol) 1619, 1593, 1419, 1061, 956, 946, 856, 835, 766, 738, 715 cm^{-1}.

3.2.6. 8-Benzoyl-1-chlorophenazine (10ea). (91%); Crystallization from Cl_3CH gave yellow needles; mp 184–186 °C. (Found: C, 71.72; H, 3.54; N, 8.87; $C_{19}H_{11}ClN_2O$ requires: C, 71.59; H, 3.48; N, 8.79); ^{1}H NMR δ ($CDCl_3$, 300 MHz): 7.55 (tt, *J*=7.5, 1.2 Hz, 2H), 7.66 (tt, *J*=7.5, 1.7 Hz, 1H), 7.76–7.83 (m, 1H), 7.91–7.99 (m, 3H), 8.19 (dd, *J*=9, 1.2 Hz, 1H), 8.31–8.39 (m, 2H), 8.68–8.70 (m, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 128.74, 129.11, 130.17, 130.43, 130.70, 130.95, 133.09, 133.53, 133.63, 137.05, 139.20, 140.91, 142.39, 144.83, 144.88, 195.59; MS *m/z* (%) 320 [M^++2] (68), 318 [M^+] (98), 289 (88), 243 (29), 241 (78), 215 (29), 213 (69), 178 (15), 105 (100), 77

(90); IR (Nujol) 1658, 1380, 1321, 1244, 953, 901, 856, 825, 728, 675 cm^{-1}.

3.2.7. 7-Benzoyl-1-chlorophenazine (10eb). (93%); Crystallization from Cl_3CH gave yellow needles; mp 277–279 °C. (Found: C, 71.44; H, 3.51; N, 8.63; $C_{19}H_{11}ClN_2O$ requires: C, 71.59; H, 3.48; N, 8.79); ^1H NMR δ ($CDCl_3$, 200 MHz): 7.55 (tt, J=7.3, 1.5 Hz, 2H), 7.68 (tt, J=7.3, 1.2 Hz, 1H), 7.91–8.04 (m, 3H), 8.17 (dd, J=8.8, 1.3 Hz, 1H), 8.35 (dd, J=9.0, 1.7 Hz, 1H), 8.49 (d, J=9.0 Hz, 1H), 8.60 (d, J=1.7 Hz, 1H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 128.69, 129.12, 130.20, 130.41, 130.45, 130.72, 130.97, 133.06, 133.13, 133.41, 136.85, 139.26, 140.99, 142.72, 144.38, 144.61, 195.47; MS m/z (%) 320 [M^++2] (34), 318 [M^+] (100), 290 (77), 289 (58), 241 (52), 213 (42), 178 (10), 105 (84), 77 (57); IR (Nujol) 1661, 1380, 1322, 1302, 1245, 1112, 955, 899, 855, 725, 698, 673 cm^{-1}.

3.2.8. 1-Chloro-6-methylphenazine (10f). (91%); Crystallization from petroleum ether /Cl_3CH gave yellow needles; mp 316–317 °C. (Found: C, 68.41; H, 3.88; N, 12.31; $C_{13}H_9ClN_2$ requires: C, 68.28; H, 3.97; N, 12.25); ^1H NMR δ ($CDCl_3$, 300 MHz): 2.92 (s, 3H), 7.64–7.78 (m, 3H), 7.92 (dd, J=7.4, 1.4 Hz, 1H), 8.18–8.23 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz): 17.60, 128.18, 129.23, 129.49, 129.69, 130.37, 131.07, 133.22, 138.04, 140.02, 143.39, 143.62, 143.82; MS m/z (%) 230 [M^+ +2] (30), 228 [M^+] (100), 193 (16), 192 (30), 165 (21), 140 (10), 114 (26), 100 (19), 89 (31), 75 (58), 63 (61). IR (Nujol) 1618, 1558, 1378, 1346, 1119, 1075, 1057, 952, 849, 805, 747, 721, 670 cm^{-1}.

3.3. Preparation of 1,4-dichloro-5,10-dihydrophenazine (11a)

A cathodic reduction of 1,4-dichlorophenazine **12a** was carried out under a constant cathodic potential in a cell and an electrolysis medium like that described for the electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in MeCN (40 mL)—AcOH (10 mL)—$LiClO_4$ (3 g); 35 and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (0.2 g) was placed in the anode compartment. A solution of **12a** (5 mmol) was electrolyzed under a cathodic potential of −0.70 V versus SCE. The electricity consumption was 2 F/mol. It was observed that the initial intensive yellow colour of the catholyte solution became progressively violet according to the progress of the electricity pass. Isolation of product **11a** was carried out by removing the solvent in vacuo,[20] adding water (150 mL) and collecting the blue solid precipitate by vacuum filtration. Crystallization from acetonitrile gave blue needles; mp 75 °C dec, yield 95%; (Found: C, 57.31; H, 3.18; N, 11.14; $C_{12}H_8Cl_2N_2$ requires: C, 57.40; H, 3.21; N, 11.16); ^1H NMR δ ($CDCl_3$, 200 MHz): 5.26 (br s, 2H), 6.16–6.21 (m, 2H), 6.38 (s, 2H), 6.46–6.53 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 50.3 MHz): 113.07, 114.62, 121.01, 122.37, 130.75, 131.21; MS m/z (%) 254 [M^++4] (9), 252 [M^++2] (55), 250 [M^+] (100), 214 (26), 179 (68), 152 (25), 125 (48), 102 (35), 89 (38), 76 (48); IR (Nujol) 3423, 1615, 1516, 1287, 1169, 1110, 946, 908, 769, 738 cm^{-1}.

4. Supporting Information Available

Complex X-ray crystallographic data for **6f**, **6ea** and **10db**.

Acknowledgements

Author J.I.-L thanks the Fundación Séneca (Comunidad Autónoma de Murcia) for a postgraduate grant.

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18. Supplementary publication number CCDC-231412 (**6ea**), -231411 (**6f**), -231413 (**10db**) can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB12 1E2, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. For a review about electrochemistry of halogenated organic compounds see Peters, D. G. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, 2001; Chapter 8.
20. Caution must be exercised when handling perchlorates in order to exclude explosion risk. Evaporation of organic solutions containing perchlorates requires to be carried out in vacuo and at moderate temperature. The contact with strong acids must be avoided.

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Tetrahedron 60 (2004) 6757–6763

Synthesis of 5,5′-diarylated 2,2′-bithiophenes via palladium-catalyzed arylation reactions

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Received 3 June 2004; revised 15 June 2004; accepted 15 June 2004

Abstract—2,2′-Bithiophene and 3,3′-dicyano-2,2′-bithiophenes are diarylated directly with aryl bromides at the 5- and 5′-positions accompanied by C–H bond cleavage in the presence of $Pd(OAc)_2$ and a bulky phosphine ligand using Cs_2CO_3 as base. In the reaction using (2,2′-bithiophen-5-yl)diphenylmethanol as the substrate, monoarylation at the 5-position via C–C bond cleavage occurs selectively to give 5-aryl-2,2′-bithiophenes and the subsequent arylation with a different aryl bromide affords the corresponding unsymmetrically 5,5′-diarylated products.

1. Introduction

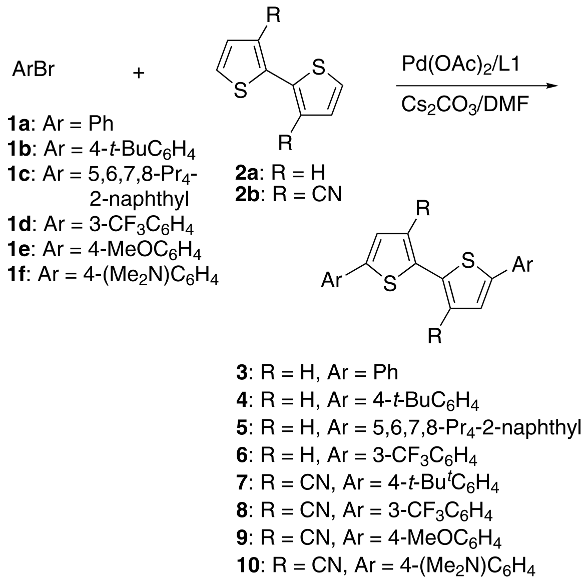
Poly- and oligoaryl compounds involving a thiophene unit have attracted much attention as the organic components of electronic devices.[1] Among the most useful methods to prepare such arylheterocycles is the palladium-catalyzed cross-coupling of either heteroaryl halides with arylmetals or aryl halides with heteroarylmetals. Thus, the reaction has been extensively studied.[2]

Meanwhile, it is known that aryl halides can couple directly with a number of five-membered heteroaromatics[3] including thiophenes[3,4] at their 2- and/or 5-position(s) in the presence of a palladium catalyst. The method has a significant advantage, not requiring stoichiometric metalation of the heterocycles. We recently reported that thiophenes[5a] as well as thiazoles[5b] are effectively arylated with aryl bromides in the presence of $Pd(OAc)_2$ and a bulky phosphine ligand using Cs_2CO_3 as base.

5,5′-Diaryl-2,2′-bithiophenes have been shown to be useful compounds as organic semiconductors[1c,d] and fluorescent materials.[1e,f] Consequently, we have examined the direct arylation of 2,2′-bithiophene as well as its 3,3′-dicyano derivative by means of palladium catalysis. It has also been undertaken to prepare unsymmetrically 5,5′-diarylated 2,2′-bithiophenes using diphenyl(2,2′-bithiophen-5-yl)diphenylmethanol as the strating substrate; the first step is based on our method recently developed for preparing unsymmetrical biaryls by the palladium-catalyzed arylation of *tert*-benzylalcohols via C–C bond cleavage.[6] The results are reported herein.

2. Results and discussion

The arylation of 2,2′-bithiophene (**2a**) (1 mmol) was first carried out with bromobenzene (**1a**) (4 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol) and P(biphenyl-2-yl)-(t-Bu)$_2$ (L1)[7] (0.2 mmol) using Cs_2CO_3 as base in DMF at 150 °C for 48 h. As expected, 5,5′-diphenyl-2,2′-bithiophene (**3**) was obtained in 60% yield (Scheme 1 and entry 1 in Table 1).



Scheme 1.

Keywords: Arylation; Aryl halides; Palladium and compounds; Thiophenes.
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doi:10.1016/j.tet.2004.06.075

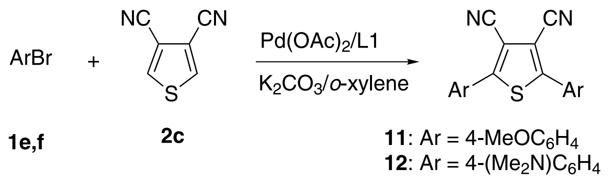
Table 1. Diarylation of 2,2′-bithiophene (**2a**), 3,3′-dicyano-2,2′-bithiophene (**2b**), and 3,4-dicyanothiophene (**2c**) with aryl bromides **1a–f**[a]

Entry	Bromide	Thiophene	Conditions[b]	Time (h)	Product, yield[c] (%)
1	**1a**	**2a**	A[d]	48	**3**, 60
2	**1b**	**2a**	A	8	**4**, 60
3	**1c**	**2a**	B	48	**5**, 87
4	**1d**	**2a**	A	8	**6**, 91
5	**1b**	**2b**	B	4	**7**, 66
6	**1d**	**2b**	B	4	**8**, 93
7	**1e**	**2b**	B	1	**9**, 96
8	**1e**	**2b**	B[e]	4	**9**, 87
9	**1f**	**2b**	B	4	**10**, 94
10	**1e**	**2c**	B[e,f]	8	**11**, 76
11	**1f**	**2c**	B[e,f]	18	**12**, 62

[a] The reaction was carried out in DMF under N_2 unless otherwise noted.
[b] A: [**1**]:[**2**]:[$Pd(OAc)_2$]:[L1]:[Cs_2CO_3]=2.4:1:0.1:0.2:2.4 (in mmol). B: [**1**]:[**2**]:[$Pd(OAc)_2$]:[L1]:[Cs_2CO_3]=1.2:0.5:0.05:0.1:1.2 (in mmol). L1=P(biphenyl-2-yl)(t-Bu)$_2$.
[c] Isolated yield.
[d] [**1**]:[**2**]:[Cs_2CO_3]=4:1:4.
[e] Reaction in o-xylene.
[f] K_2CO_3 was used in place of Cs_2CO_3.

Using less volatile 1-bromo-4-*tert*-butylbenzene (**1b**) (2.4 mmol), the same yield of the corresponding product **4** was attained after 8 h (entry 2). The symmetrically diarylated compounds **3** and **4** are relatively less soluble, and therefore, they were isolated by filtration through a silica gel pad and extraction with hot toluene. Use of 2-bromo-5,6,7,8-tetrapropylnaphthalene (**1c**)[8] as arylating reagent afforded 5,5′-bis(5,6,7,8-tetrapropylnaphthalen-2-yl)-2,2′-bithiophene (**5**), which was readily soluble in ether and isolated in a higher yield (entry 3). The reaction with 1-bromo-3-(trifluoromethyl)benzene (**1d**) also gave a relatively soluble compound **6** (entry 4). While the reaction with 4-bromoanisole (**1e**) proceeded, isolation of the product in pure state was not successful due to its insolubility.

It has been reported that 3,3′-dicyano-2,2′-bithiophene (**2b**) exhibits a high fluorescence quantum yield (Φ=0.995), while its molar extinction coefficient is relatively low (log ε=3.86).[9] On the other hand, 3-cyanothiophene was found to be readily arylated by the direct method.[3c,4,5a] Thus, we next examined the diarylation of **2b**. Treatment of **2b** with **1b**,**d**,**e** and 4-bromo-*N*,*N*-dimethylaniline (**1f**) gave 5,5′-diaryl-3,3′-dicyano-2,2′-bithiophenes **7–10** in good yields (Scheme 1 and entries 5–9 in Table 1). For the comparison of their properties, 2,5-di(4-methoxyphenyl)-(**11**) and 2,5-bis[4-(dimethylamino)phenyl]-3,4-dicyanothiophenes (**12**) were also prepared by the reaction of 3,4-dicyanothiophene (**2c**) with **1e** and **1f** (Scheme 2 and entries 10 and 11, the optical properties are described later). For the reaction of **2c**, K_2CO_3 and o-xylene were used as base and solvent, respectively. The products appeared to be unstable

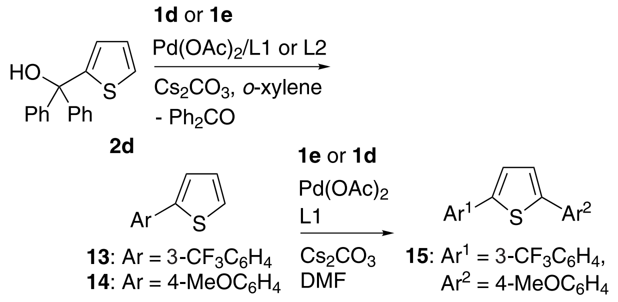


Scheme 2.

in the presence of Cs_2CO_3 in DMF, although the reaction of **2b** proceeded more efficiently in DMF than in o-xylene (entries 7 vs 8).

While the above direct method is useful for the symmetrical diarylation, it is not successful for the monoarylation, since a mixture of mono- and diarylated products is formed even with a limited amount of an aryl bromide. Thus, another strategy is required to furnish the unsymmetrical 5,5′-diarylation, especially for the initial step. We have recently reported that the palladium-catalyzed arylation of *tert*-benzylalcohols with aryl halides efficiently occurs accompanied by C–C bond cleavage to give unsymmetrical biaryls along with the corresponding ketones.[6] In order to see applicability of this new cross-coupling method to a bithiophene system, we have undertaken the reaction of (2,2′-bithiophen-5-yl)diphenylmethanol (**2e**).

Before beginning the examination with **2e**, the reaction of diphenyl(thiophen-2-yl)methanol (**2d**) was carried out in order to obtain appropriate conditions (Scheme 3 and Table 2).



Scheme 3.

Table 2. Arylation of diphenyl(thiophen-2-yl)methanol (**2d**) and 2-arylthiophenes **13** and **14** with aryl bromides **1d** and **1e**[a]

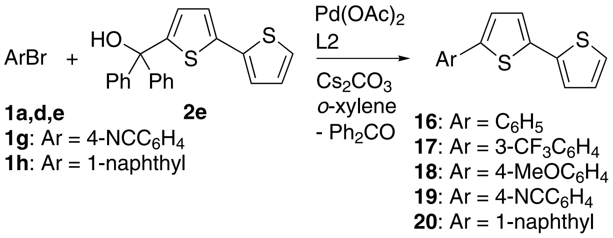
Entry	Bromide	Thiophene	Ligand[b]	Solvent	Time (h)	Product, yield[c] (%)
1[d]	**1d**	**2d**	L1	o-xylene	2	**13**, 62
2[e]	**1d**	**2d**	L2	o-xylene	1	**13**, 91 (71)
3[f]	**1e**	**2d**	L1	o-xylene	1.5	**14**, 88
4[d]	**1e**	**2d**	L1	DMF	2	**14**, 59
5[e]	**1e**	**2d**	L2	o-xylene	1	**14**, 88 (82)
6[g]	**1e**	**13**	L1	DMF	8	**15**, 85 (64)
7[g]	**1d**	**14**	L1	DMF	24	**15**, 72

[a] The reaction was carried out at 150 °C under N_2.
[b] L1=P(biphenyl-2-yl)(t-Bu)$_2$, L2=P(cyclohexyl)$_3$.
[c] Determined by GLC abalysis. Value in parenthesis is isolated yield.
[d] [**1**]:[**2**]:[$Pd(OAc)_2$]:[L]:[Cs_2CO_3]=1:1:0.025:0.05:1 (in mmol).
[e] [**1**]:[**2**]:[$Pd(OAc)_2$]:[L]:[Cs_2CO_3]=1.5:1.5:0.025:0.05:1 (in mmol).
[f] [**1**]:[**2**]:[$Pd(OAc)_2$]:[L]:[Cs_2CO_3]=1.8:1.5:0.025:0.05:1 (in mmol).
[g] [**1**]:[**13 or 14**]:[$Pd(OAc)_2$]:[L]:[Cs_2CO_3]=0.6:0.5:0.05:0.1:0.6 (in mmol).

The reactions of **2d** with **1d** in o-xylene using L1 and P(cyclohexyl)$_3$ (L2) indicated that L2 is superior than L1, as was observed in the reaction of triphenylmethanol (entry 2 vs 1).[6] In the reaction with **1e**, however, the ligand effect was not important (entries 3 and 5). The origin of this discrepancy between **1d** and **1e** is not definitive at the present stage. DMF as solvent was not effective for the reaction (entry 4 vs 3). This may be attributed to the fact that coordination of the oxygen of the alcohol to metal center is the key for the coupling.[6]

The obtained 2-arylthiophenes **13** and **14** were then treated with **1e** and **1b** in DMF as for the reaction of **2a**. Both the reactions gave 2-(4-methoxyphenyl)-5-(3-trifluoromethylphenyl)thiophene (**15**), while **13** reacted more efficiently (entries 6 and 7 in Table 2). The electron-withdrawing group in **13** seems to promote the deprotonation in the catalytic cycle.[4a] An attempt to use 2-(2-thienyl)-2-propanol in place of **2d** was unsuccessful.

Based on the above results, alcohol **2e** was reacted with **1a**,**d**,**e**, 1-bromo-4-cyanobenzene (**1g**) and 1-bromonaphthalene (**1h**) using L2 in *o*-xylene (Scheme 4). As shown in Table 3, 5-aryl-2,2′-bithiophenes **16**–**20** were obtained in good yields.



Scheme 4.

Table 3. Arylation of (2,2′-bithiophen-5-yl)diphenylmethanol (**2e**) with aryl bromides **1a**,**d**,**e**,**g**,**h**[a]

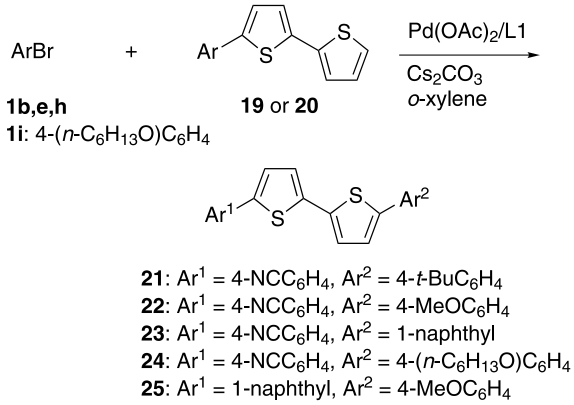
Entry	Bromide	Conditions[b]	Time (h)	Product, yield[c] (%)
1	**1a**	A	1	**16**, 96 (94)
2	**1d**	A	1	**17**, 75 (60)
3	**1e**	A	2	**18**, 71
4	**1e**	B	24	**18**, 71 (55)
5	**1g**	B	1	**19**, 99 (91)
6	**1h**	B	1	**20**, 76 (74)

[a] The reaction was carried out in *o*-xylene at 150 °C under N_2.
[b] A; [**1**]:[**2e**]:[$Pd(OAc)_2$]:[L2]:[Cs_2CO_3]=0.525:0.5:0.025:0.05:0.525 (in mmol). B; [**1**]:[**2e**]:[$Pd(OAc)_2$]:[L2]:[Cs_2CO_3]=1.575:1.5:0.025:0.05:1.575 (in mmol). L2=P(cyclohexyl)$_3$.
[c] Determined by GLC abalysis. Value in parenthesis is isolated yield.

Then, the arylation reactions of **19** with **1b**,**e**,**h** and 1-bromo-4-hexyloxybenzene (**1i**) and of **20** with **1e** were conducted as for that of **13** (Scheme 5 and Table 4). The unsymmetrically disubstituted bithiophenes **21**–**25** could be extracted with ethyl acetate or chloroform and were relatively tractable.

Shown in Table 5 are the optical properties of diarylated bithiophenes and thiophenes measured for the corresponding chloroform solutions under ambient conditions.

The optical band gap E_{00} was estimated from the interception of the absorption and emission spectra; the influence of Stokes shifts was neglected.[9] It can be seen that fine-tuning of the gap of 5,5′-diaryl-2,2′-bithiophene (compounds **3**–**10** and **21**–**25**) is possible by substituent effects; it is perturbed in a range of 2.33–3.22 eV. The emission spectra of compounds **3**–**6**, **21** and **23** showed two



Scheme 5.

Table 4. Arylation of 5-aryl-2,2′-bithiophenes **19** and **20** with aryl bromides **1b**,**e**,**h**,**i**[a]

Entry	Bromide	Thiophene	Time (h)	Product, yield[b] (%)
1	**1b**	**19**	8	**21**, 57
2	**1e**	**19**	4	**22**, 51
3	**1h**	**19**	4	**23**, 63
4	**1i**	**19**	4	**24**, 91
5	**1e**	**20**	8	**25**, 53

[a] The reaction was carried out in DMF at 150 °C under N_2. [**1**]:[**19** or **20**]:[$Pd(OAc)_2$]:[L1]:[Cs_2CO_3]=0.75:0.5:0.05:0.1:0.75 (in mmol). L1=P(biphenyl-2-yl)(t-Bu)$_2$.
[b] Isolated yield.

maxima; such a behavior has been reported to be often characteristic for 5,5′-diaryl-2,2′-bithiophene. It is worth noting that the introduction of two cyano groups to the 3,3′-positions of 5,5′-di(4-*tert*-butylphenyl)-2,2′-bithiophene (**4**) increased the quantum yield as expected (compound **7** versus **4**). 3,3′-Dicyano-5,5′-di(4-methoxyphenyl)-2,2′-bithiophene (**9**) also showed a relatively high quantum yield. In the case of the bis[3-(trifluoromethyl)phenyl] derivative **8**, however, it was significantly low (compound **8** versus **6**). The introduction of strongly electron-donating 4-*N*,*N*-dimethylamino group allowed a remarkable red-shift

Table 5. Optical absorption and emission maxima, extinction coefficient, fluorescent quantum yield, and optical band gap of diarylated bithiophenes **3**–**10**, **21** and **23**–**25** and those of diarylated thiophenes **11**, **12**, and **15**[a]

Compound	λ_{abs} (nm)	λ_{em} (nm)	log ε	Φ[b]	E_{00} (eV)
3	373	431, 455	4.54	0.17	2.98
4	377	436, 462	4.51	0.16	2.94
5	399	462, 491	4.72	0.29	2.78
6	374	431, 455	4.57	0.17	2.98
7	394	478	4.35	0.33	2.73
8	309	429	4.12	0.01	3.22
9	407	497	4.39	0.42	2.64
10	460	565	4.44	0.12	2.33
21	396	467, 476	4.63	0.12	2.80
23	384	469, 478	4.59	0.21	2.84
24	400	491	4.63	0.12	2.80
25	369	461	4.53	0.18	2.92
11	348	436	4.38	0.08	3.13
12	412	488	4.59	0.04	2.70
15	338	414	4.49	0.32	3.25

[a] Absorption and emission spectra were measured as a chloroform solution (5×10^{-5} M and 0.1 to 2.5×10^{-6} M, respectively).
[b] Determined by comparison of quinine sulfate (Φ=0.546).

(compound **10**). The fluorescent efficiencies of 2,5-diaryl-3,4-dicyanothiophenes **11** and **12** were low. While the relation of structures of the dicyanothiophenes with the emission properties can not be rationalized, it is remarkable that compounds **7** and **9** having a larger torsion angle around the C2–C2′bond show relatively high emission efficiencies.

In summary, we have described that 2,2′-bithiophene and 3,3′-dicyano-2,2′-bithiophene can be directly and effectively diarylated at the 5- and 5′-positions by means of palladium catalysis. The diarylated 3,3′-dicyano-2,2′-bithiophenes with aryl bromides having an electron-donating substituent shows relatively high fluorescent efficiency. Using (2,2′-bithiophen-5-yl)diphenylmethanol as the substrate, 5-aryl-2,2′-bithiophenes can be obtained selectively and the successive direct arylation affords unsymmetrically 5,5′-diarylated products. Thus, the arylation method accompanying C–C bond cleavage as well as that via C–H bond cleavage we reported previously can be applied effectively to bithiophene systems.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. MS analysis was made by EI. GC analysis was carried out using a Silicone OV-17 glass column (i.d. 2.6 mm×1.5 m).

3.2. Preparation of thiophenes 2

Bithiophene **2a** was commercially available. Thiophenes **2b**,[10] **2c**[11] and **2d**[6b] were prepared according to the methods reported previously.

3.2.1. (2,2′-Bithiophen-5-yl)diphenylmethanol (2e). In a 200 cm^3 three-necked flask were added 2,2′-bithiophene (3.34 g, 20 mmol) and THF (50 cm^3). Then, BuLi in hexane (1.57 M, 13 ml) and TMEDA (3 cm^3, 20 mmol) was added with srirring at −78 °C under N_2 (balloon) and allowed to warm to room temperature. After stirring 30 min, the mixture was cooled to −10 °C and benzophenone (3.09 g, 17 mmol) in THF (10 cm^3) was added. Then, the mixture was stirred at room temperature for 15 h, after which it was poured into aq. NH_4Cl, extracted with ethyl acetate and dried over Na_2SO_4. Evaporation of the solvents and column chromatography on silica gel using hexane–toluene (8:2, v/v) as eluent gave compound **2e** (5.74 g, 97%): Viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (s, 1H), 6.62 (d, J=3.7 Hz, 1H), 6.98 (dd, J=3.7, 5.1 Hz, 1H), 7.00 (d, J=3.7 Hz, 1H), 7.11 (dd, J=1.1, 3.7 Hz, 1H), 7.18 (dd, J=1.1, 5.1 Hz, 1H), 7.28–7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.12, 122.94, 123.69, 124.41, 127.24, 127.48, 127.72, 127.76, 128.05, 137.27, 137.67, 146.16, 151.03; HR-MS m/z (M$^+$). Calcd for $C_{21}H_{16}OS_2$ 348.0643. Found 348.0648.

3.3. Synthesis of 5,5′-diaryl-2,2′-bithiophenes

The following experimental procedures may be regarded as typical in methodology and scale.

3.3.1. 5,5′-Di(4-*tert*-butylphenyl)-2,2′-bithiophene (4). In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (2.4 mmol, 782 mg), which was then dried at 150 °C in vacuo for 2 h. Then, $Pd(OAc)_2$ (0.1 mmol, 22.4 mg), P(biphenyl-2-yl)(t-Bu)$_2$ (L1) (0.2 mmol, 40.5 mg), 1-bromo-4-*tert*-butylbenzene (**1b**) (2.4 mmol, 511 mg), 2,2′-bithiophene (**2a**) (1 mmol, 166 mg), 1-methylnaphthalene (ca. 100 mg) as internal standard and DMF (5 cm^3) were added. The resulting mixture was stirred under N_2 (balloon) at 150 °C for 8 h. The reaction mixture was filtered through a silica gel pad (ca. 20 g) with hot toluene. After evaporation of the solvents, the residue was washed with hexane and recrystallized with toluene to give compound **4** (256 mg, 60%).

3.3.2. 5,5′-Di(4-*tert*-butylphenyl)-3,3′-dicyano-2,2′-bithiophene (7). In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (1.2 mmol, 391 mg) and dried as above. Then, $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), P(biphenyl-2-yl)(t-Bu)$_2$ (L1) (0.1 mmol, 20.3 mg), 1-bromo-4-*tert*-butylbenzene (**1b**) (1.2 mmol, 256 mg), 3,3′-dicyano-2,2′-bithiophene (**2b**) (0.5 mmol, 108 mg) and DMF (5 cm^3) were added. The resulting mixture was stirred under N_2 (balloon) at 150 °C for 4 h. After cooling, the reaction mixture was extracted with ethyl acetate. Column chromatography on silica gel using hexane–ethyl acetate (98.5:1.5, v/v) gave compound **7** (159 mg, 66%).

3.3.3. 5-(4-*tert*-Butylphenyl)-5′-(4-cyanophenly)-2,2′-bithiophene (21). In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (1.575 mmol, 513 mg) and dried as above. Then, $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), P(cyclohexyl)$_3$ (L2) (0.05 mmol, 14 mg), 1-bromo-4-cyanobenzene (**1g**) (1.575 mmol, 286 mg), diphenyl(2,2′-bithiophen-5-yl)methanol (**2e**) (1.5 mmol, 522 mg), 1-methylnaphthalene (ca. 100 mg) as internal standard and *o*-xylene (5 cm^3) were added. The resulting mixture was stirred under N_2 (balloon) at 150 °C for 1 h. After cooling, the reaction mixture was extracted with ethyl acetate. After evaporation of the solvents, the residue was washed with hexane to give compound **19** (364 mg, 91%). Then, **19** (130 mg, 0.5 mmol) was treated with 1-bromo-4-*tert*-butylbenzene (**1b**) (136 mg, 0.75 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), P(biphenyl-2-yl)(t-Bu)$_2$ (L1) (0.1 mmol, 20.3 mg) and Cs_2CO_3 (0.75 mmol, 244 mg) in DMF (5 cm^3) under N_2 at 150 °C for 8 h. Compound **21** (114 mg, 57%) was obtained by extraction with chloroform, washing with hexane and recrystallization with toluene.

3.4. Characterization data of products

3.4.1. 5,5′-Diphenyl-2,2′-bithiophene (3).[12] Mp 239.5–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J=4.0 Hz, 2H), 7.25 (d, J=4.0 Hz, 2H), 7.29 (t, J=7.3 Hz, 2H), 7.39 (t, J=7.7 Hz, 4H), 7.61 (d, J=7.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.80, 124.48, 125.62, 127.61, 128.96, 134.04, 136.72, 143.16; MS m/z 318 (M$^+$).

3.4.2. 5,5′-Di(4-*tert*-butylphenyl)-2,2′-bithiophene (4). Mp 282–283 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 18H), 7.15 (d, J=3.8 Hz, 2H), 7.20 (d, J=3.8 Hz, 2H), 7.41 (d, J=8.6 Hz, 4H), 7.54 (d, J=8.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.26, 34.63, 123.35, 124.30, 125.35, 125.86, 131.31, 136.37, 143.10, 150.76; HR-MS *m/z* (M^+). Calcd for $C_{28}H_{30}S_2$ 430.1780. Found 430.1789.

3.4.3. 5,5′-Bis(5,6,7,8-tetrapropylnaphtalen-2-yl)-2,2′-bithiophene (5). Mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.20 (m, 24H), 1.57–1.78 (m, 16H), 2.72–2.77 (m, 8H), 2.99–3.08 (m, 8H), 7.24 (d, *J*=3.6 Hz, 2H), 7.33 (d, *J*=3.6 Hz, 2H), 7.66 (d, *J*=8.7 Hz, 2H), 8.00 (d, *J*=8.7 Hz, 2H), 8.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 15.1, 15.1, 24.6, 24.7, 24.9, 24.9, 31.2, 31.2, 32.6, 32.7, 121.1, 122.5, 123.7, 124.6, 125.3, 129.9, 130.6, 131.3, 134.3, 134.4, 136.6, 137.4, 137.8, 144.2; MS *m/z* 754 (M^+). Anal. Calcd for $C_{52}H_{66}S_2$: C, 82.70; H, 8.81; S, 8.49. Found C, 82.44; H, 8.69; S, 8.60.

3.4.4. 5,5′-Di(3-trifluoromethylphenyl)-2,2′-bithiophene (6). Mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J*=4.0 Hz, 2H), 7.31 (d, *J*=4.0 Hz, 2H), 7.49–7.55 (m, 4H), 7.55–7.77 (m, 2H), 7.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.24 (q, *J*=3.7 Hz), 124.31 (q, *J*=3.7 Hz), 124.91, 124.93, 126.65 (q, *J*=273 Hz), 128.70, 129.50, 131.49 (q, *J*=32.2 Hz), 134.72, 137.37, 141.59; HR-MS *m/z* (M^+). Calcd for $C_{22}H_{12}F_6S_2$ 454.0285. Found 454.0293.

3.4.5. 5,5′-Di(4-*tert*-butylphenyl)-3,3′-dicyano-2,2′-bithiophene (7). Mp 275–276.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 18H), 7.44 (s, 2H), 7.47 (d, *J*=8.6 Hz, 4H), 7.55 (d, *J*=8.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.17, 34.85, 109.78, 114.86, 124.92, 126.01, 126.31, 128.71, 139.40, 147.01, 153.04; HR-MS *m/z* (M^+). Calcd for $C_{30}H_{28}N_2S_2$ 480.1694. Found 480.1697.

3.4.6. 5,5′-Di(3-trifluoromethylphenyl)-3,3′-dicyano-2,2′-bithiophene (8). Mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 2H), 7.62 (t, *J*=7.7 Hz, 2H), 7.69 (d, *J*=7.7 Hz, 2H), 7.81 (d, *J*=7.7 Hz, 2H), 7.86 (s, 2H); ^{13}C NMR (100 MHz, DMF-d_7) δ 116.55, 119.99, 128.43 (q, *J*=4.6 Hz), 129.85 (q, *J*=272 Hz), 131.76 (q, *J*=3.7 Hz), 134.13, 135.82, 136.46, 136.55 (q, *J*=32.2 Hz), 138.22, 145.41, 150.78; HR-MS *m/z* (M^+). Calcd for $C_{24}H_{10}F_6N_2S_2$ 504.0190. Found 504.0192.

3.4.7. 5,5′-Di(4-methoxyphenyl)-3,3′-dicyano-2,2′-bithiophene (9). Mp 266–267.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 6H), 7.06 (d, *J*=8.8 Hz, 4H), 7.71 (d, *J*=8.8 Hz, 4H), 7.99 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.57, 109.91, 114.75, 115.05, 123.76, 125.45, 127.65, 137.86, 146.52, 160.51; HR-MS *m/z* (M^+). Calcd for $C_{24}H_{16}N_2O_2S_2$ 428.0653. Found 428.0650.

3.4.8. 5,5′-Bis[4-(*N*,*N*-dimethylamino)phenyl]-3,3′-dicyano-2,2′-bithiophene (10). Mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 12H), 6.72 (d, *J*=8.9 Hz, 4H), 7.26 (s, 2H), 7.47 (d, *J*=8.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.23, 109.09, 112.24, 115.33, 119.42, 122.64, 127.18, 137.98, 147.49, 151.00; HR-MS *m/z* (M^+). Calcd for $C_{26}H_{22}N_4S_2$ 454.1286. Found 454.1284.

3.4.9. 2,5-Di(4-methoxyphenyl)-3,4-dicyanothiophene (11). Mp 225.5–227.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 6H), 7.02 (d, *J*=8.8 Hz, 4H), 7.67 (d, *J*=8.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.53, 106.87, 113.43, 114.96, 122.31, 129.11, 152.40, 161.65; HR-MS *m/z* (M^+). Calcd for $C_{20}H_{14}N_2O_2S$ 346.0776. Found 346.0774.

3.4.10. 2,5-Bis[4-(*N*,*N*-dimethylamino)phenyl]-3,4-dicyanothiophene (12). Mp 228.5–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.01 (s, 12H), 6.85 (d, *J*=8.8 Hz, 4H), 7.65 (d, *J*=8.8 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.82, 103.31, 112.26, 114.45, 116.51, 128.35, 151.79, 152.09; HR-MS *m/z* (M^+). Calcd for $C_{22}H_{20}N_4S$ 372.1409. Found 372.1415.

3.4.11. 2-(3-Trifluoromethylphenyl)thiophene (13). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J*=3.5, 5.1 Hz 1H), 7.33 (dd, *J*=1.1, 5.1 Hz, 1H), 7.35 (dd, *J*=1.1, 3.5 Hz, 1H), 7.45–7.53 (m, 2H), 7.76 (d, *J*=8.0 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.55 (d, *J*=3.7 Hz), 123.94 (q, *J*=3.7 Hz), 124.11, 125.82, 127.30 (q, *J*=297 Hz), 128.23, 129.07, 129.37, 131.34 (q, *J*=32.2 Hz), 135.20, 142.64; HR-MS *m/z* (M^+). Calcd for $C_{11}H_7F_3S$ 228.0221. Found 228.0235.

3.4.12. 2-(4-Methoxyphenyl)thiophene (14).[13] Mp 106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.90–6.93 (m, 2H), 7.05 (dd, *J*=3.6, 5.1 Hz, 1H), 7.19 (dd, *J*=1.5, 3.6 Hz, 1H), 7.21 (dd, *J*=1.5, 5.1 Hz, 1H), 7.51–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.34, 114.27, 122.07, 123.81, 127.22, 127.31, 127.89, 144.33, 159.18; MS *m/z* 190 (M^+).

3.4.13. 2-(4-Methoxyphenyl)-5-(3-trifluoromethylphenyl)thiophene (15). Mp 103.5–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.94 (d, *J*=8.7 Hz, 2H), 7.20 (d, *J*=3.8 Hz, 1H), 7.33 (d, *J*=3.8 Hz, 1H), 7.47–7.55 (m, 2H), 7.57 (d, *J*=8.7 Hz, 2H), 7.76–7.78 (m, 1H), 7.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.39, 114.39, 122.09 (q, *J*=3.8 Hz), 123.09, 123.71 (q, *J*=3.8 Hz), 124.02 (q, *J*=272 Hz), 124.97, 126.82, 127.03, 128.56, 129.38, 131.43 (q, *J*=32.7 Hz), 135.22, 140.62, 144.80, 159.51; MS *m/z* 334 (M^+). Anal. Calcd for $C_{18}H_{13}F_3OS$: C, 64.66; H, 3.92; F, 17.05; S, 9.59. Found C, 64.36; H, 3.70; F, 17.34; S, 9.70.

3.4.14. 5-Phenyl-2,2′-bithiophene (16).[14] Mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, *J*=3.6, 5.1 Hz, 1H), 7.15 (d, *J*=3.8 Hz, 1H), 7.20 (dd, *J*=1.1, 3.6 Hz, 1H), 7.22 (dd, *J*=1.1, 5.1 Hz, 1H), 7.22 (d, *J*=3.8 Hz, 1H), 7.27–7.31 (m, 1H), 7.36–7.41 (m, 2H), 7.58–7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.62, 123.70, 124.37, 124.59, 125.61, 127.57, 127.85, 128.93, 134.06, 136.71, 137.43, 143.12; MS *m/z* 242 (M^+).

3.4.15. 5-(3-Trifluoromethylphenyl)-2,2′-bithiophene (17). Mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J*=3.7, 5.1 Hz 1H), 7.17 (d, *J*=4.0 Hz, 1H), 7.23 (dd, *J*=1.1, 3.7 Hz, 1H), 7.25 (dd, *J*=1.1, 5.1 Hz, 1H), 7.29 (d, *J*=4.0 Hz, 1H), 7.47–7.54 (m, 2H), 7.74–7.77 (m, 1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.19 (q, *J*=4.6 Hz), 123.96 (q, *J*=272 Hz), 124.00 (q, *J*=4.6 Hz), 124.02, 124.69, 124.77, 124.81, 127.94, 128.66, 129.45, 131.43 (q, *J*=32.2 Hz), 134.86, 136.99, 137.87, 141.12; HR-MS *m/z* (M^+). Calcd for $C_{15}H_9F_3S_2$ 310.0098. Found 310.0095.

3.4.16. 5-(4-Methoxyphenyl)-2,2′-bithiophene (18). Mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.92 (d, *J*=8.8 Hz, 2H), 7.02 (dd, *J*=3.5, 5.0 Hz, 1H), 7.10 (d, *J*=4.0 Hz, 1H), 7.12 (d, *J*=4.0 Hz, 1H), 7.17 (dd, *J*=1.1, 3.5 Hz, 1H), 7.20 (dd, *J*=1.1, 5.0 Hz, 1H), 7.52 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.36, 114.34, 122.64, 123.36, 124.10, 124.56, 126.91, 127.79, 128.05, 135.69, 137.59, 143.15, 159.30; HR-MS *m/z* (M^+). Calcd for $C_{15}H_{12}OS_2$ 272.0329. Found 272.0323.

3.4.17. 5-(4-Cyanophenyl)-2,2′-bithiophene (19). Mp 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J*=3.6, 5.1 Hz, 1H), 7.18 (d, *J*=3.8 Hz, 1H), 7.24 (dd, *J*=1.1, 3.6 Hz, 1H), 7.27 (dd, *J*=1.1, 5.1 Hz, 1H), 7.34 (d, *J*=3.8 Hz, 1H), 7.64–7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.49, 118.81, 124.33, 124.85, 125.20, 125.67, 125.84, 128.02, 132.76, 136.69, 138.29, 139.13, 140.38; HR-MS *m/z* (M^+). Calcd for $C_{15}H_9NS_2$ 267.0176. Found 267.0171.

3.4.18. 5-(Naphthalen-1-yl)-2,2′-bithiophene (20).[15] Mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J*=3.7, 5.1 Hz, 1H), 7.16 (d, *J*=3.7 Hz, 1H), 7.23 (dd, *J*=1.1, 3.8 Hz, 1H), 7.25–7.26 (m, 2H), 7.48–7.54 (m, 3H), 7.58–7.61 (m, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 7.89–7.91 (m, 1H), 8.29–8.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.71, 123.98, 124.40, 125.27, 125.66, 126.08, 126.54, 127.86, 128.02, 128.07, 128.39, 128.54, 131.69, 132.03, 133.91, 137.34, 137.63, 140.80; MS *m/z* 292 (M^+).

3.4.19. 5-(4-*tert*-Butylphenyl)-5′-(4-cyanophenyl)-2,2′-bithiophene (21). Mp 285.5–286 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 1.34 (s, 9H), 7.41–7.42 (m, 2H), 7.47 (d, *J*=3.7 Hz, 1H), 7.50 (d, *J*=8.4 Hz, 2H), 7.65 (d, *J*=8.4 Hz, 2H), 7.71 (d, *J*=4.0 Hz, 1H), 7.85 (d, *J*=8.8 Hz, 2H), 7.91 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.41, 31.29, 110.93, 119.14, 124.83, 125.89, 125.89, 126.39, 126.47, 126.59, 127.70, 131.52, 133.61, 135.81, 138.70, 139.27, 140.96, 144.45, 151.81; HR-MS *m/z* (M^+). Calcd for $C_{25}H_{21}NS_2$ 399.1115. Found 399.1111.

3.4.20. 5-(4-Cyanophenyl)-5′-(4-methoxyphenyl)-2,2′-bithiophene (22). Mp 187–188 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 3.87 (s, 3H), 7.06 (d, *J*=8.7 Hz, 2H), 7.43–7.46 (m, 3H), 7.67 (d, *J*=8.7 Hz, 2H), 7.79 (d, *J*=8.7 Hz, 1H), 7.91 (d, *J*=8.7 Hz, 2H), 7.95 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMF-d_7) δ 55.76, 110.77, 115.30, 124.25, 125.84, 126.42, 126.56, 126.92, 127.51, 127.97, 133.80, 135.10, 138.70, 139.35, 140.66, 144.42, 160.45, 162.88; HR-MS *m/z* (M^+). Calcd for $C_{22}H_{15}NOS_2$ 373.0595. Found 373.0599.

3.4.21. 5-(4-Cyanophenyl)-5′-(naphthalen-1-yl)-2,2′-bithiophene (23). Mp 197.5–198 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 7.41 (d, *J*=3.7 Hz, 1H), 7.55 (d, *J*=4.0 Hz, 1H), 7.61–7.66 (m, 4H), 7.71 (dd, *J*=1.1, 7.0 Hz, 1H), 7.83 (d, *J*=4.0 Hz, 1H), 7.93 (d, *J*=8.8 Hz, 2H), 7.98 (d, *J*=8.8 Hz, 2H), 8.02–8.09 (m, 2H), 8.31–8.33 (m, 1H); ^{13}C NMR (100 MHz, DMF-d_7) δ 115.89, 124.41, 130.73, 130.98, 131.24, 131.32, 131.50, 132.07, 132.70, 133.04, 133.82, 134.34, 134.65, 134.70, 136.89, 137.01, 138.84, 139.78, 142.38, 143.66, 143.98, 146.10, 146.83; HR-MS *m/z* (M^+). Calcd for $C_{25}H_{15}NS_2$ 393.0646. Found 393.0651.

3.4.22. 5-(4-Cyanophenyl)-5′-(4-hexyloxyphenyl)-2,2′-bithiophene (24). Mp 209.5–210.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J*=6.6 Hz, 3H), 1.34–1.36 (m, 4H), 1.43–1.51 (m, 2H), 1.76–1.83 (m, 2H), 3.98 (t, *J*=7.0 Hz, 2H), 6.91 (d, *J*=7.0 Hz, 2H), 7.12–7.17 (m, 3H), 7.34 (d, *J*=2.9 Hz, 1H), 7.51 (d, *J*=7.3 Hz, 2H), 7.65 (d, *J*=2.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.02, 22.59, 25.70, 29.20, 31.57, 68.18, 110.37, 114.97, 118.82, 122.74, 124.39, 125.21, 125.61, 125.92, 126.40, 126.95, 132.75, 134.75, 138.33, 139.41, 139.99, 144.29, 159.14; HR-MS *m/z* (M^+). Calcd for $C_{27}H_{25}NOS_2$ 443.1378. Found 443.1375.

3.4.23. 5-(4-Methoxyphenyl)-5′-(naphthalen-1-yl)-2,2′-bithiophene (25). Mp 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.93 (d, *J*=8.8 Hz, 2H), 7.14 (d, *J*=3.7 Hz, 1H), 7.17 (m, 2H), 7.25 (m, 1H), 7.48–7.56 (m, 5H), 7.60 (dd, *J*=1.1, 7.0 Hz, 1H), 7.86 (d, *J*=8.1 Hz, 1H), 7.89–7.92 (m, 1H), 8.31–8.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.38, 114.38, 122.75, 123.61, 124.53, 125.29, 125.68, 126.08, 126.55, 126.94, 126.94, 128.01, 128.13, 128.40, 128.53, 131.68, 132.06, 133.93, 135.60, 137.83, 140.55, 143.22, 159.34; MS *m/z* 398 (M^+). Anal. Calcd for $C_{25}H_{18}OS_2$: C, 75.34; H, 4.55; S, 16.09. Found C, 75.08; H, 4.64; S, 15.83.

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Tetrahedron 60 (2004) 6765–6775

Liquid crystals in the series of 2,4,6-tristyryl-1,3,5-triazines

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Received 2 April 2004; revised 8 June 2004; accepted 8 June 2004

Abstract—Alkaline condensation reactions of 2,4,6-trimethyl-1,3,5-triazine (**1**) and substituted benzaldehydes (**2a–n**) yield 2,4,6-tristyryl-1,3,5-triazines (**3a–n**). A sufficient number and length of the alkoxy chains at the benzene rings provide liquid crystalline phases Col_{hd}. A special structure was found for compound **3i** with 9 hexyloxy chains; it exists in the solid state in a helical columnar arrangement, which is transformed by heating to a hexagonal columnar mesophase. Irradiation of the mesophases of **3i–3m** leads to partial cyclodimerization reactions, which cause different textures and lower the clearing points. The border line between the irradiated and the unirradiated zones is preserved in the solid and the liquid crystalline temperature range but also over a surprisingly long period in the molten state. A detailed study of this imaging technique was performed for the LC phase of **3i**.

1. Introduction

Star-shaped stilbenoid compounds with a 1,3,5-triazine core and peripheral alkoxy groups represent octupolar structures with interesting non-linear optical properties (NLO); moreover, they can form liquid crystalline columnar phases provided that they contain a large enough fraction of long flexible side chains. The hyperpolarizabilities β of 2,4,6-triphenyl-1,3,5-triazines have been reported recently.[1–3] The β_0 values, extrapolated to infinite wavelength and related to 4-nitroaniline as standard gave a value β_{rel}

$$\beta_{rel} = \frac{\beta_0(2,4,6\text{-triphenyl-}1,3,5\text{-triazine}) \times \text{molecular mass}(4\text{-nitroaniline})}{\beta_0(4\text{-nitroaniline}) \times \text{molecular mass}(2,4,6\text{-triphenyl-}1,3,5\text{-triazine})}$$

which at most was slightly better than the standard value 1.0 for 4-nitroaniline.[1–3] An extension of the conjugation by 2,4,6-tris(4-diethylaminophenylethynyl) substituents improved considerably the results.[1,2]

We tried now to combine the extension of the conjugated arms with the capability of forming liquid crystalline phases and attached alkoxy substituted styryl groups in 2,4,6-position to the 1,3,5-triazine ring. Mesophases of star-shaped triazine systems were found in the past for some triphenyl derivatives,[4] some dendritic compounds whose arms consist of tolane units,[5,6] a tris(phenylethynyl) compound,[7] and systems with oligo(1,4-phenylenevinylene) [OPV] arms.[8]

2. Results and discussion

2.1. Preparation of alkoxy substituted 2,4,6-tristyryl-1,3,5-triazines

The methyl groups in 2,4,6-trimethyl-1,3,5-triazine (**1**) undergo in an alkaline medium [CH_3OH/KOH or THF/$KOC(CH_3)_3$] threefold condensation reactions with substituted benzaldehydes (**2a–n**). The aldehydes **2j** and **2n** are not described in the literature; they were prepared from 3,4,5-trihydroxybenzoic acid ethyl ester by threefold *O*-alkylation, reduction to the corresponding benzyl alcohol and oxidation with DDQ.

The highly stereoselective condensation reaction affords (*E*,*E*,*E*)-2,4,6-tristyryl-1,3,5-triazines (**3a–n**) in good yields (Scheme 1). The ^{1}H and ^{13}C NMR spectra of the purified products do not contain any hints for *Z* configurations; the detection limit is about 3%. A thermal isomerization in the neat state or in solution can be excluded for temperatures below 150 °C.

Keywords: Columnar arrangement; Condensation; Cyclodimerization; Helical arrangement; Imaging technique; Liquid crystals.
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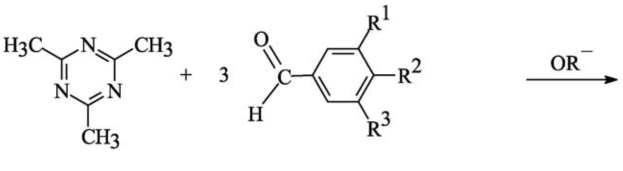
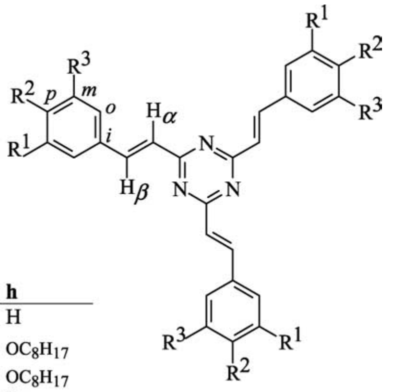
doi:10.1016/j.tet.2004.06.031



1 2a - n



3a - n

3	a	b	c	d	e	f	g	h
R^1	H	H	H	H	H	H	H	H
R^2	OCH_3	OC_3H_7	OC_5H_{11}	OC_6H_{13}	OC_7H_{15}	OC_8H_{17}	$OC_{12}H_{25}$	OC_8H_{17}
R^3	H	H	H	H	H	H	H	OC_8H_{17}
Yield [%]	94	86	80	55	64	61	86	82

	i	j	k	l	m	n
R^1	OC_6H_{13}	OC_8H_{17}	$OC_{10}H_{21}$	$OC_{12}H_{25}$	$OC_{16}H_{33}$	$O\text{-}(CH_2)_2\text{-}CH(CH_3)\text{-}(CH_2)_3\text{-}CH(CH_3)_2$
R^2	OC_6H_{13}	OC_8H_{17}	$OC_{10}H_{21}$	$OC_{12}H_{25}$	$OC_{16}H_{33}$	$O\text{-}(CH_2)_2\text{-}CH(CH_3)\text{-}(CH_2)_3\text{-}CH(CH_3)_2$
R^3	OC_6H_{13}	OC_8H_{17}	$OC_{10}H_{21}$	$OC_{12}H_{25}$	$OC_{16}H_{33}$	$O\text{-}(CH_2)_2\text{-}CH(CH_3)\text{-}(CH_2)_3\text{-}CH(CH_3)_2$
Yield [%]	79	87	69	82	89	85

Scheme 1. Preparation of (*E*,*E*,*E*)-2,4,6-tristyryl-1,3,5-triazines.

2.2. Formation of LC phases

2,4,6-Tristyryl-1,3,5-triazines can be regarded as disc-like molecules, which can exhibit a regular aggregation by π stacking and by the interaction of additionally present side chains. The compounds **3a–g** bear three alkoxy chains; irrespective of the chain length, this number of side chains proved to be not sufficient for the formation of thermotropic liquid crystals. Accordingly, the yellow crystals of **3a–g** exhibit sharp melting points at 228, 99, 109, 96, 85, 76 and 63 °C, respectively. A slight exception was only found for **3d** which showed in the heating curve of the differential scanning calorimetry (DSC) an endothermic peak at 96 °C with a shoulder at 94 °C. Obviously, a further (crystalline) phase exists in this 2 degrees broad temperature interval. This behavior, observed in the first heating curve (rate: 10 °C/min), can be repeated in the second heating curve after a delay of about 5 days at room temperature.

Three further side chains, introduced in **3h**, lead already to a mesophase between 75 and 82 °C (second heating curve). The texture obtained by polarizing microscopy reveals a liquid crystalline phase. This result encouraged us to study the compounds **3i–n** which contain 9 side chains, each. Table 1 summarizes the DSC measurements.

Figure 1 shows, as an example, the thermo-mechanical characteristics of the **3l** sample. The DSC diagrams indicate two transitions and the temperature dependences of components of the complex shear modulus reveal related changes of mechanical properties. The solid state ($G' > 10^8$ Pa) at low temperatures is transformed at the low temperature transition to a considerable softer phase ($G' \approx 10^5$ Pa) and the material melts at the other transition becoming liquid-like with viscosity dependent on the side chain length and temperature (in this example $\eta \approx 5$ Pa s just above the transition). The two transitions have been

Table 1. DSC measurements of the phase transitions K⇄LC⇄I (crystal⇄liquid crystal⇄melt) of the compounds **3i–n**: H second heating curve, C first cooling curve, rate: 10 °C per min

Compound	Process	Phase transitions					
3	H/C	K⇄LC			LC⇄I		
		Temperature [°C]		ΔH	Temperature [°C]		ΔH
		Onset	Maximum	kJ mol^{-1}	Onset	Maximum	kJ mol^{-1}
3i	H	63.4	68.4	8.6	109.5	112.0	7.8
	C	49.5	47.6	−5.3	110.8	108.8	−7.6
3j[a]	H	32.2	42.6	2.3	86.3	101.8	8.8
	C				101.3	96.4	−6.6
3k	H	−56.6	−23.2	21.7	79.0	90.1	8.5
	C	−10.4	−33.7	−18.6	88.4	84.2	−7.4
3l	H	2.6	8.7	37.4	88.1	90.1	12.0
	C	5.2	1.7	−42.5	87.8	86.9	−9.9
3m[b]	H	40.0/48.8	44.9/50.3	127.5	76.8	80.3	14.3
	C	33.0/43.4	29.6/42.3	−69.7	79.1	77.9	−12.8
3n[c]	H				36.5	45.3	8.0

[a] The phase transition LC→K is extremely slow. The second heating curve was measured after 1 week.

[b] The processes K→LC and LC→K are characterized by double peaks; the phase in between is highly viscous and seems to have a plastic crystalline status. The enthalpy for the formation of the LC phase, which has a low viscosity is very high.

[c] The phase transition I→LC in **3n**, which has branched sidechains, is extremely slow; a crystallization could not be observed in the DSC.

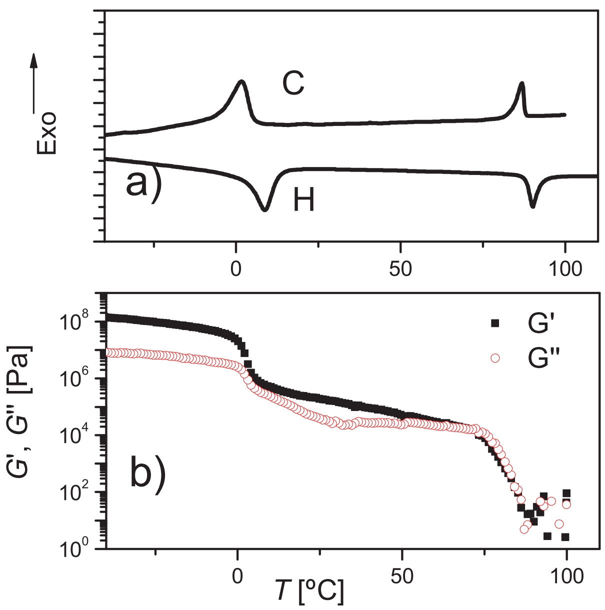


Figure 1. An example of the thermo-mechanical characteristics for the **3l** sample: (a) the DSC traces recorded during cooling (C) and second heating (H) with the rate of 10 °C/min and (b) the temperature dependencies of the real (G') and imaginary (G'') components of the complex shear modulus recorded in the dynamic mechanical test with the frequency of 10 rad/s under cooling with the rate of 2 °C/min.

observed for all samples with the 9 side chains. Polarizing optical microscopy observations revealed textures suggesting liquid crystalline states below the transitions at higher temperatures. Figure 2 shows the DSC thermograms recorded for samples with various side chain lengths indicating a behavior very sensitive to this structural parameter. Increasing length of the alkoxy side chains leads to a steady decrease of the temperatures for the phase transiton LC⟶I, whereas the temperatures for K⟶LC

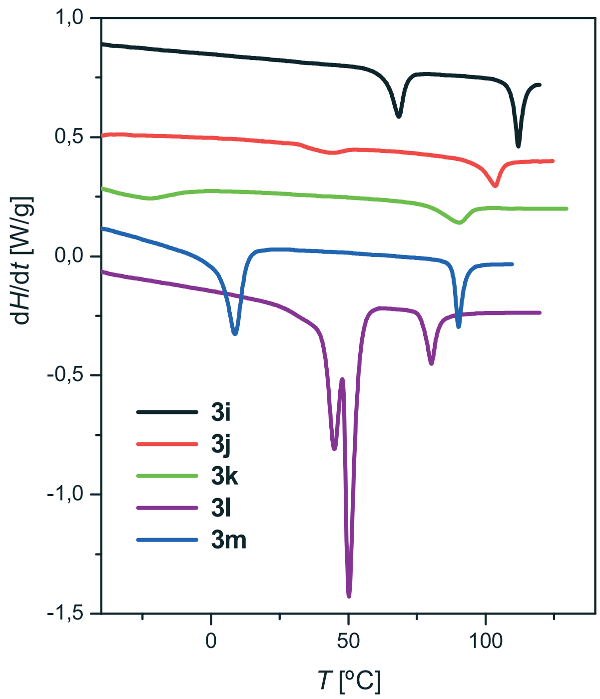


Figure 2. DSC thermograms for the series of samples **3i**–**m** recorded during the second heating run with the rate of 10 °C/min.

exhibit a minimum for the decyloxy substituted compound **3k**. Figure 3 shows the temperature intervals in which the mesophases of **3i**–**m** exist. Extension of the length of the OC_nH_{2n+1} chains (n=6, 8, 10, 12, 16) permits the regulation of the width of the LC phase. The maximum width is reached with $\Delta T \approx 113$ °C for **3k** (n=10).

X-ray scattering studies of **3i**–**m** revealed some structural details of the phases separated by the above transitions. Examples of the X-ray intensity distributions recorded at various states of the **3j** sample are shown in Figure 4. The intensity profiles differ remarkably not only when recorded at different temperatures but they are also very sensitive to thermal history. Especially, the states at low temperatures considered as crystalline (Fig. 4(a) and (d)) were dependent on the annealing and cooling conditions. The intermediate state (Fig. 4(b))—the mesophase—was in all samples recognized as a hexagonal columnar phase Col_{hd}. A special technique was used to measure the columns in a macroscopic orientation.[9] The oriented samples were obtained by extrusion at temperatures of the mesophase. An example of the 2D X-ray scattering pattern of such a structure is shown in Figure 5(a). The pattern exhibits small angle equatorial reflections indicating well oriented hexagonally ordered columns and a diffuse meridional halo superimposed on the less intense isotropic amorphous halo. Figure 5(b) shows the equatorial intensity distributions for various samples. For the **3i** sample, an assignment of reflections is given in Table 2, as an example. Variation of relative reflection intensities in various samples results from the variation of the columnar core/shell volume fractions with the length of the side chains.[10]

The reflections in the small angle area prove the hexagonal columnar arrangement, since the values of a, b, and c in the diffractogram correspond to the expected ratio:

$$s(\mathrm{a}) : s(\mathrm{b}) : s(\mathrm{c}) = 0.43 : 0.74 : 0.85 \approx 1 : \sqrt{3} : 2 \tag{1}$$

The calculated values (Eq. (2)) and the observed values for s^{-1} (Fig. 5) agree very well. The length a of the elementary cell amounts to 2.72 nm.

$$s^2 = \frac{4}{3a^2}(h^2 + k^2 + hk) \tag{2}$$

Table 3 contains the parameters d of **3i**–**m**. They represent the distance of the columns in the hexagonal arrangement and are compared to the hypothetic diameters D of the discs, which are valid for all-*anti* conformations of the alkoxy chains. The increasing difference $\Delta = D - d$ with increasing numbers n can be rationalized by an increasing interdigitation of the chains of neighboring columns and/or by an increasing deviation of the chains from the all-*anti* conformation.

In the optically isotropic state at high temperatures, a small angle halo (Fig. 4(c)) indicates an ordering over distances comparable to the molecular sizes. This can be attributed to the molecular excluded volume effect, which is detectable due to the electron density contrast between the aromatic center and the aliphatic periphery of the molecules. In this state, the molecules can be regarded as multiarm stars for which this kind of ordering has been detected even for much

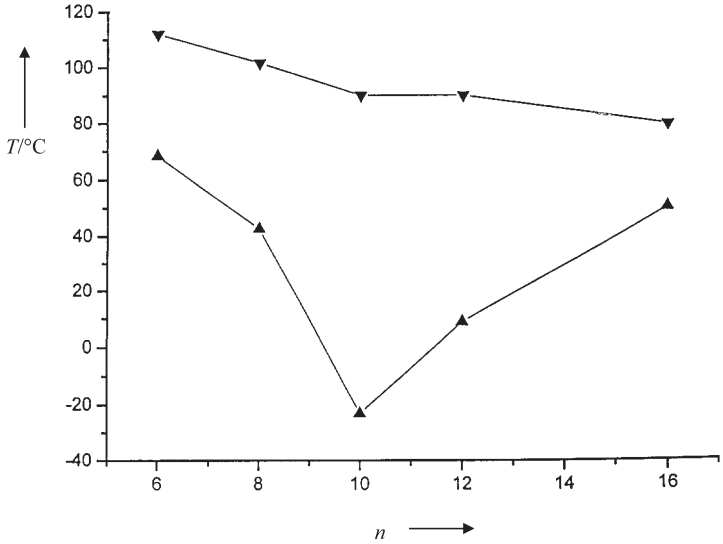


Figure 3. Temperature intervals in which the LC phases of **3i**–**3m** (n=6, 8, 10, 12, 16) exist; the phase transition temperatures (▼ and ▲) represent the peak maxima in the DSC (second heating run with a rate of 10 °C min^{-1}).

longer side chains.[11] The position of the maximum of this small angle halo is dependent on the side chain length and reflects the correlation distance between the molecular centers. In the case of a three dimensional disorder (no preaggregation of the molecules into short columnar stacks), this correlation distance should scale with the molecular mass of the molecules as $M^{1/3}$.[11] In contrast to that, for the two-dimensionally packed columns the intercolumnar distances should scale as $M^{1/2}$, if the intermolecular distance along the columns remains constant. In Figure 6, the correlation distances for the isotropic phase and for the mesophase are compared with the respective dependencies (dashed lines). These scalings are nearly fulfilled which further confirms the validity of the assignments made.

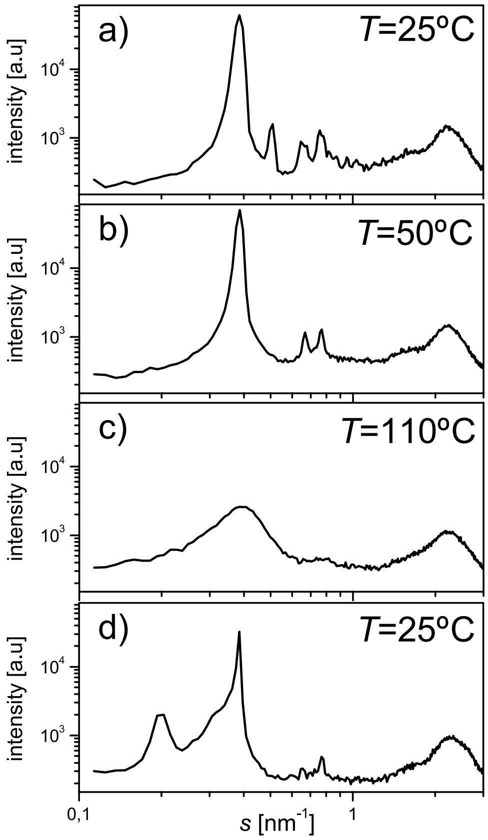


Figure 4. An example of the diffracted X-ray intensity distributions recorded at various states of the **3j** sample: (a) as drawn filament at room temperature (crystalline state), (b) at T=50 °C—mesophase, (c) isotropic melt at 110 °C and (d) an ordered state at room temperature after slow cooling through the mesophase.

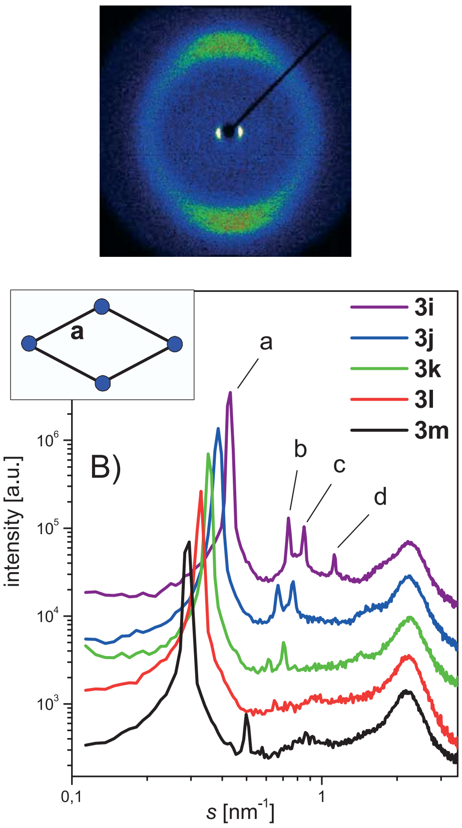


Figure 5. A characteristic scattering 2D pattern for an oriented filament in the mesophase (A) and corresponding equatorial X-ray intensity distributions for the series of samples **3i**–**m** (B). The insert in B illustrates the unit cell of a hexagonal lattice assumed for the lateral packing of columns.

Table 2. X-ray diffraction pattern shown in Figure 5 for **3i**; measurement at 77 °C

Reflection	Miller index			s^{-1} [nm]	
	h	*k*	*l*	Calcd	Found
a	1	0	0	2.36	2.33
b	1	1	0	1.36	1.35
c	2	0	0	1.18	1.18
d	2	1	0	0.89	0.89

Table 3. Diameter *D* of the disc-like molecules **3i**–**3m** (sidechains in all-*anti* conformation) and distance *d* of the columns in the LC phases

Compound	*n*	Temperature [°C]	*D* [Å]	*d* [Å]	*D*−*d* [Å]
3i	6	77	33.0	27.2	5.8
3j	8	77	38.1	30.2	7.9
3k	10	27	43.2	32.2	10.9
3l	12	27	48.3	34.6	13.7
3m	16	57	58.5	39.8	18.7

It has been observed that annealing or slow cooling through the mesophase of the macroscopically oriented samples resulted in longer range correlations in the structures formed at low temperatures, considered as the crystalline state (Fig. 4(d)). These correlations were manifested in small angle reflections appearing at these temperatures in some cases only in addition to the hexagonal columnar order as in the example in Figure 4(d). Moreover, these correlation distances were observed to be side chain length dependent as seen in Figure 6.

Special arrangements of the discotic molecules were found in the solid states of **3i** and **3m** samples. Figure 7 shows the 2D patterns of X-ray diffraction recorded at the room temperature for these systems. In both cases, a helical arrangement is conjectured, however, a detailed modeling is necessary to make such conclusions. Especially, in the case of **3i**, the scattering pattern exhibits several characteristic features of diffraction on helical structures: the layered distribution of intensities, the reflections aligned in an

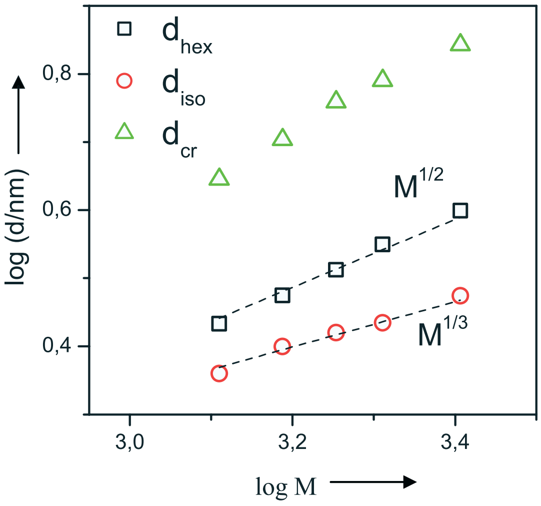


Figure 6. Molecular mass dependencies of the correlation distances detected for various states. The dashed lines represent suggested scaling dependencies.

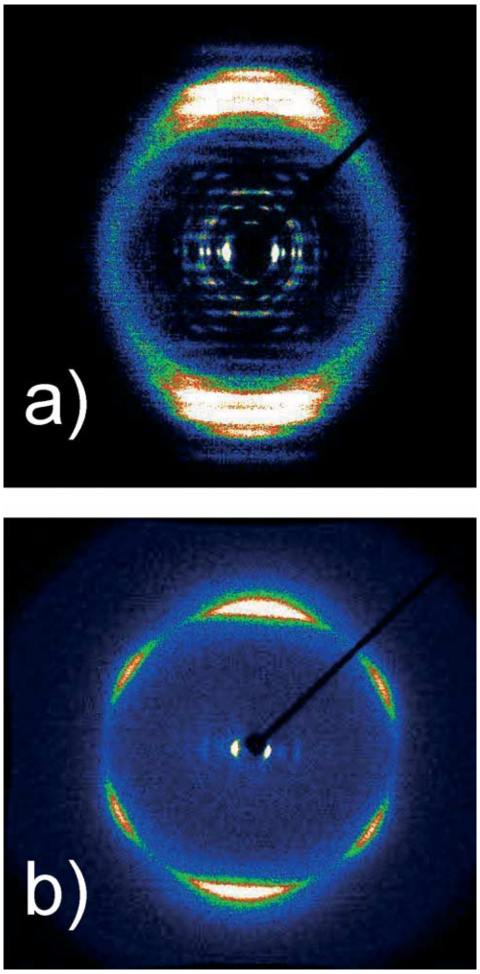


Figure 7. Examples of scattering patterns recorded for highly ordered crystalline states of the samples (a) **3i** and (b) **3m**.

X-pattern and lack of meridional reflections up to the 11th layer. This allows extraction of some parameters of the structure. The layer spacing gives the helical pitch P=3.97 nm and the meridional reflection of the 11th layer line indicates 11 molecules per pitch with the intermolecular separation d=0.36 nm. The X-like distribution of reflections seems to indicate pairs of columns forming a helix. The structure of **3m** is much less complicated. The columns remain here hexagonally ordered and each second molecule seems to be in identical position. The intermolecular distance along the columns is considerably larger (d=0.42 nm).

All experience with the studied compounds indicates a very high sensitivity of intermolecular organization to the details of molecular architecture. In addition to the results already reported, two effects are shown in Figure 8. The DSC traces indicate drastic changes of transition temperatures and enthalpies as a result of variation of some intramolecular details. In Figure 8(a) the effect of the number of side chains and in Figure 8(b) the effect of the side chain architecture is documented.

In the second case, both the total molecular mass and the molecular mass of the side chains are kept constant; nevertheless, the slightly different skeleton of bonds causes

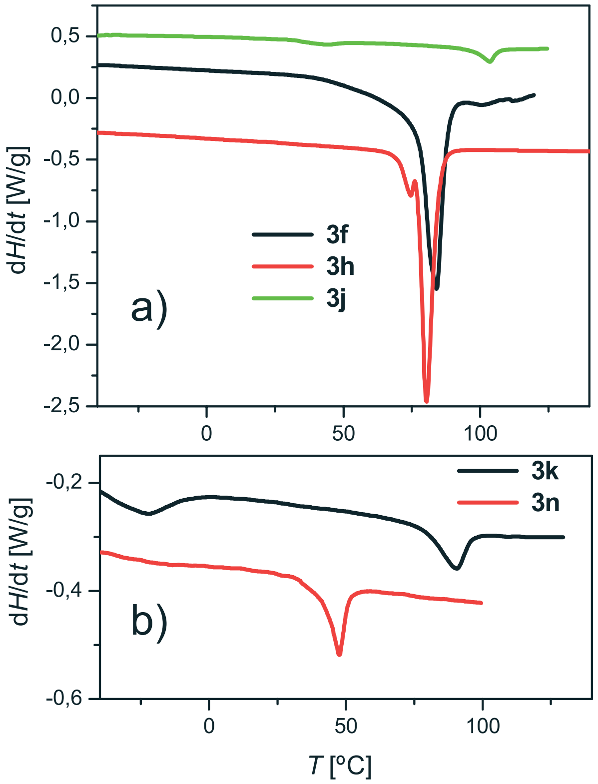


Figure 8. Effects of molecular architecture on the thermodynamic behavior detected by means of the DSC: (a) effect of the number of side chains and (b) effect of the side chain architecture.

a variation of the temperature of isotropization by nearly 40 °C.

2.3. Light absorption and photochemistry

Tristyryltriazine **3i** shows a long-wavelength absorption in CH_2Cl_2 with a maximum at 366.5±1 nm. The intense band (log ε=4.90) corresponds to an intramolecular charge transfer from one of the three donor moieties to the central 1,3,5-triazine ring as acceptor. Apart from a positive solvatochromic effect, the UV/vis spectrum is affected by a protonating medium. Continuous addition of trifluoroacetic acid to a solution of **3i** in $CHCl_3$ provokes a bathochromic shift till the maximum reaches the λ_{max} value of 449 nm. Protonation of the 1,3,5-triazine ring enhances the push–pull effect. 2,4,6-Tris{(*E*)-2-[(4-dimethylamino)-phenyl]ethenyl}-1,3,5-triazine[8] shows first a similar effect; the yellow solution in $CHCl_3$ (λ_{max}=427 nm) turns violet on protonation (λ_{max}=549 nm) but then a subsequent protonation of the amino groups causes a hypsochromic effect to yield a colorless solution (λ_{max}=365 nm). The weak basicity of the alkoxy groups in **3i** is obviously not capable of reverting the red-shift.

On monochromatic irradiation with λ=366 nm, **3i** proved to be photostable in the solid state. However, as soon as an enhanced mobility of the molecules was achieved in the LC phase, a photoreaction started. Figure 9 shows the changes in the LC phase. The irradiation at 95 °C in the left upper part led to the disappearance of the texture (a→b→c). On cooling from 95 to 70 °C a texture reappeared (c→d); however, it was different from the original texture. In the right lower part, which was covered and did not absorb light, the original LC phase was preserved. Figure 9(e) demonstrates the new texture (left upper part) and the unirradiated crystals (right lower part) at 25 °C (birefringence). Warming to 95 °C led to the picture (9f). The original LC phase is again formed (T_{cl}=112 °C), whereas the new texture has disappeared. The border line between the two textures persists during many heating and cooling processes. The breakdown of the LC phase can be already provoked by the photochemical transformation of a few percent *trans* isomer to the *cis* configuration. In the case of **3i**, however, we found predominantly the formation of a cyclodimer with one four-membered ring and four *trans* configured styryl units.[12] We assume that the diffusion of such a dimer in the LC phase or even in the molten state is so slow that the border line between the irradiated and the unirradiated zone is kept intact for many days.

The analogous irradiation experiments, performed with **3j–m**, gave the corresponding results. However, one has to realize that **3k** and **3l** form light-sensitive mesophases already at room temperature. Therefore from a technical point of view, it seems to be more appropriate to warm and 'write' with a laser beam in the Col_{hd} phase of **3i** and to 'read' it at ambient temperatures, where the daylight including its UV portion is inactive.

3. Conclusions

Alkaline condensation reactions of 2,4,6-trimethyl-1,3,5-triazine (**1**) and substituted benzaldehydes (**2a–n**) yield 2,4,6-tristyryl-1,3,5-triazines (**3a–n**). At least two, but better three long flexible alkoxy chains, attached to each of the terminal benzene rings, are necessary to provide liquid crystalline properties. The Col_{hd} mesophases of **3i–m** were characterized by DSC, polarized mircoscopy and X-ray diffraction. A special structure was found for compound **3i** with 9 hexyloxy chains; it exists in the solid state in a helical columnar arrangement, which is transformed to disordered hexagonal columns in the mesophase. Irradiation (λ=366 nm) of the mesophases of **3i–m** provokes partial cyclodimerization reactions, which cause lower clearing points and different textures. Diffusion processes of the dimer are so ineffective that the border line between the original LC phase and the photoconverted LC phase is preserved—even in the molten state. Thus, the compounds **3i–m** seem to be suitable for an optical data storage in LC materials. A report on the NLO properties of **3a–n** shall be given later.

4. Experimental

4.1. General remarks

Melting points of **3a–3g** were measured on a Büchi melting point apparatus and are uncorrected. The DSC measurements of **3d** and **3h–3n** were obtained by means of a DSC 7 Perkin–Elmer apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX400 or Avance-600. The mass spectra were obtained on a Finnigan MAT95 with the field desorption technique (FD). The UV/vis spectra were

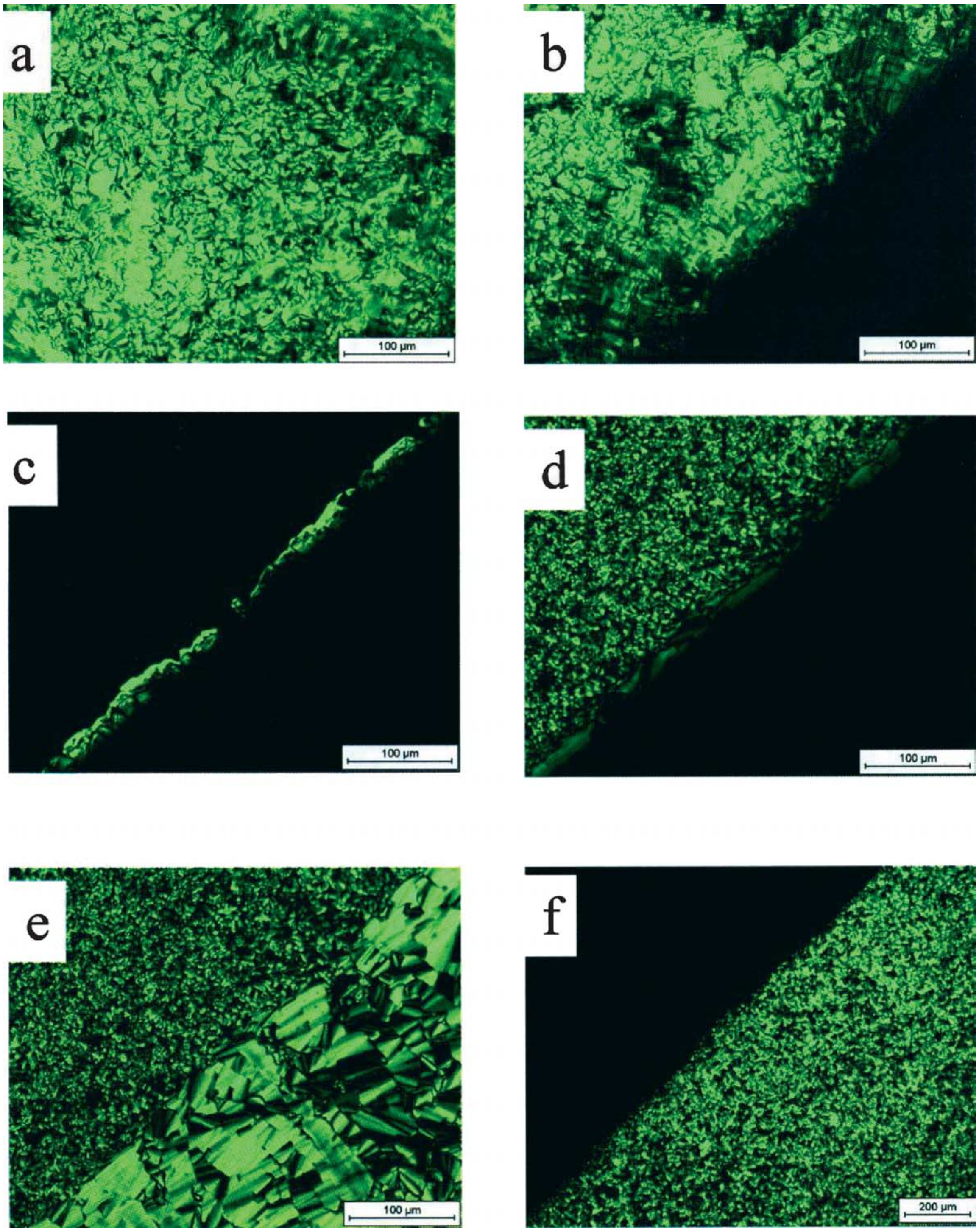


Figure 9. Irradiation (λ=366 nm) of a thin film of the Col_{hd} phase of **3i** under the polarizing microscope: (a) texture of the unirradiated mesophase measured at 95 °C (left upper part); (b) beginning change of the mesophase by irradiation at 95 °C (left upper part), covered (right lower part); (c) isothermal transformation of the mesophase to the isotropic melt by irradiation at 95 °C (left upper part), covered (right lower part); (d) texture obtained by cooling to 70 °C (left upper part), covered (right lower part); (e) texture of the new mesophase at 25 °C (left upper part), unirradiated crystals at 25 °C, birefringence (right lower part); (f) transformation of the new mesophase to the isotropic melt at 95 °C (left upper part), original mesophase, which still exists at 95 °C (right lower part). The green color is due to the used interference filter (λ=546 nm), which excludes unwanted light, which can be absorbed by the LC film; the black color represents in the left upper parts of c and f non-birefringent molten states and in the right lower parts of b, c and d covered regions, which are protected from light.

recorded with a Zeiss MCS 320/340. A set-up of Jenapol Zeiss, a Linkam TMS 93 and a Soft Imaging System CC-12 served for the polarizing microscopy. Rheometric Scientific ARES systems was used to determine the dynamic mechanical behavior. The X-ray studies were performed using two instruments: a $\theta-\theta$ diffractometer (Siemens) and a set-up with pinhole collimation of the X-ray beam and a two-dimensional detector (Bruker) with 1024×1024 pixels. In order to obtain macroscopically oriented samples, the materials studied have been extruded using a simple mini-extruder.[9] All samples have been deformed at temperatures within the mesophase to the draw ration λ=8 which gave the filaments of the diameter of about 0.7 mm. The 2D patterns have been recorded with vertical orientations of filaments. The results of intensity distributions are presented as functions of the scattering vector (s=2 sin θ/λ, where θ is the scattering angle).

4.2. General procedure for the preparation of the 2,4,6-tristyryl-1,3,5-triazines 3a–n

Variant A. To 2,4,6-trimethyl-1,3,5-triazine (**1**)[13] [123.2 mg, 1.00 mmol] in 20 mL 10% methanolic KOH, the corresponding aldehyde **2** (3.00–4.00 mmol) dissolved in 20 mL methanol was added. After a few minutes of stirring at room temperature, the reaction mixture was refluxed, till the TLC control (SiO_2, diethyl ether) showed, that the reaction has come to the end. The precipitate formed at 5 °C was filtered off and washed with cold methanol. Column chromatography (SiO_2, petroleum/ethyl acetate) and/or recrystallization yielded the analytically pure product. The variant A was used for the preparations of **3a–3f**.

Variant B. Instead of KOH/methanol, $KOC(CH_3)_3$/THF was used. The ratio of **1** and **2** was the same as for variant A. In the majority of cases, the product formation was already complete at room temperature. The work-up was performed as described above. The variant B was applied for the preparations of **3g–3n**.

Aldehyde **2a** is commercially available, the aldehydes **2b**,[14] **2c**,[15] **2d**,[16] **2e**,[16] **2f**,[16] **2g**,[14] **2h**,[17] **2i**,[18] **2k**,[18] **2l**[19] and **2m**[20] were prepared according to the literature.

4.2.1. 3,4,5-Trioctyloxybenzaldehyde (2j). Ethyl 3,4,5-trihydroxybenzoate (5.0 g, 25.3 mmol) was treated with 1-bromooctane (16.2 g, 83.8 mmol) in 100 mL acetone in the presence of K_2CO_3 (13.8 g, 100.0 mmol) and KI (33 mg, 0.20 mmol). After 5 days refluxing and stirring, the mixture was filtered and the solvent evaporated. Column chromatography (12×8 cm SiO_2, toluene) yielded 11.9 g (88%) of ethyl 3,4,5-trioctyloxybenzoate, a colorless oil which was spectroscopically characterized and then directly used for the next step. [^{1}H NMR ($CDCl_3$): δ=0.87 (t, 9H, CH_3), 1.27 (m, 24H, CH_2), 1.36 (t, 3H, CH_3, ethoxy), 1.46 (m, 6H, CH_2), 1.73 (m, 2H, CH_2), 1.80 (m, 4H, CH_2), 4.00 (m, 6H, OCH_2), 4.33 (q, 2H, OCH_2, ethoxy), 6.88 (s, 2H, 2-H, 6-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 14.4 (CH_3, ethoxy), 22.6, 26.1, 29.2, 29.3, 29.4, 30.3, 31.8, 31.9 (CH_2, partly superimposed), 69.2 (OCH_2), 73.4 (OCH_2), 108.0 (C-2, C-6), 125.0 (C-1), 142.3 (C-4), 152.8 (C-3, C-5), 166.4 (CO); FD MS: m/z (%)=535 (100, M+H$^+$)]. The ester (11.8 g, 22.09 mmol) was reduced with $LiAlH_4$ (0.460 g, 12.1 mmol) in 50 mL dry diethyl ether. After 1 h refluxing and destruction of the excess $LiAlH_4$ with water/10% H_2SO_4, 3,4,5-trioctyloxybenzyl alcohol (8.50 g, 78%) was isolated as a colorless wax (mp 50 °C). After the spectroscopic characterization, it was used for the following step without further purification. [^{1}H NMR ($CDCl_3$): δ=0.87 (t, 9H, CH_3), 1.26 (m, 24H, CH_2), 1.45 (m, 6H, CH_2), 1.76 (m, 6H, CH_2), 3.91 (t, 2H, OCH_2), 3.95 (t, 4H, OCH_2), 4.56 (s, 2H, CH_2OH), 6.53 (s, 2H, 2-H, 6-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.6, 26.1, 29.3, 29.4, 29.5, 30.3, 31.8 (CH_2, partly superimposed), 65.6 (CH_2OH), 69.1 (OCH_2), 73.4 (OCH_2), 105.3 (C-2, C-6), 137.6 (C-1), 139.0 (C-4), 153.2 (C-3, C-5); FD MS: m/z (%)=493 (100, M+H$^+$)]. The oxidation of the benzyl alcohol (8.34 g, 16.95 mmol) was performed with DDQ (4.54 g, 20.0 mmol) in 80 mL dry 1,4-dioxane. After having stirred over night at room temperature, the reaction mixture was filtered and the solvent evaporated. The distillation yielded 6.12 g (74%) of the colorless compound **2j** (bp 220 °C at 0.02 torr). ^{1}H NMR ($CDCl_3$): δ=0.86 (t, 9H, CH_3), 1.26 (m, 24H, CH_2), 1.46 (m, 6H, CH_2), 1.73 (m, 2H, CH_2), 1.80 (m, 4H, CH_2), 4.01 (t, 4H, OCH_2), 4.03 (t, 2H, OCH_2), 7.06 (s, 2H, 2-H, 6-H), 9.80 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3) 22.6, 26.0, 29.2, 29.3, 29.4, 30.3, 31.8, 31.9 (CH_2), 69.2 (OCH_2), 73.6 (OCH_2), 107.8 (C-2, C-6), 131.4 (C-1), 143.8 (C-4), 153.5 (C-3, C-5), 191.3 (CHO); FD MS: m/z (%)=490 (100) [M$^+$]. Anal. calcd for $C_{31}H_{54}O_4$ (490.8): C, 75.87; H, 11.09. Found: C, 75.71; H, 11.17.

4.2.2. 3,4,5-Tris(3,7-dimethyloctyloxy)benzaldehyde (2n). Ethyl 3,4,5-trihydroxybenzoate (4.0 g, 20.2 mmol) was treated with racemic 1-bromo-3,7-dimethyloctane (15.0 g, 67.8 mmol) in 100 mL acetone in the presence of K_2CO_3 (13.8 g, 100 mmol), KI (33 mg, 0.20 mmol) and a drop of Aliquat 366. After 5 days refluxing and vigorous stirring, the mixture was filtered and the solvent evaporated. The raw material of ethyl 3,4,5-tris(3,7-dimethyloctyloxy)benzoate (11.2 g, 90%) was filtered over SiO_2 (as described above), spectroscopically characterized and used for the next step without further purification. [^{1}H NMR ($CDCl_3$): δ=0.84 (d, 18H, terminal CH_3), 0.89 (d, 3H, CH_3), 0.92 (d, 6H, CH_3), 1.10–1.95 (m, 30H, CH_2 and CH), 1.36 (t, 3H, CH_3, ethoxy), 4.02 (m, 6H, OCH_2), 4.33 (q, 2H, OCH_2, ethoxy), 7.24 (s, 2H, 2-H, 6-H); ^{13}C NMR ($CDCl_3$): δ=14.4 (CH_3, ethoxy), 19.6 (CH_3), 22.6, 22.7 (terminal CH_3), 24.7 (CH_2), 28.0, 28.0, 29.6, 29.8 (CH), 36.3, 37.3, 37.5, 39.2, 39.3 (CH_2, partly superimposed), 61.0 (OCH_2, ethoxy), 67.4, 71.7 (OCH_2), 107.8 (C-2, C-6), 125.0 (C-1), 142.2 (C-4), 152.8 (C-3, C-5), 166.5 (CO); FD MS: m/z (%)=619 (100, M$^+$)]. The reduction of 10.50 g (16.96 mmol) ester with 342 mg (9.0 mmol) $LiAlH_4$ in dry ether, as described above, yielded 9.50 g (97%) of 3,4,5-tris(3,7-dimethyloctyloxy)benzyl alcohol. The colorless oil was spectroscopically characterized and then used for the following step. [^{1}H NMR ($CDCl_3$): δ=0.84 (d, 18H, terminal CH_3), 0.89 (d, 3H, CH_3), 0.91 (d, 6H, CH_3), 1.10–1.90 (m, 30H, CH_2 and CH), 3.98 (m, 6H, OCH_2), 4.57 (s, 2H, CH_2OH), 6.54 (s, 2H, 2-H), 6-H); ^{13}C NMR ($CDCl_3$): δ=19.6 (CH_3), 22.6, 22.7 (terminal CH_3), 24.7 (CH_2), 28.0, 28.0, 29.7, 29.8 (CH), 36.4, 37.3, 37.5, 39.3, 39.4 (CH_2, partly superimposed), 65.7 (CH_2OH), 67.4, 71.6 (OCH_2), 105.2 (C-2, C-6), 136.0 (C-1), 137.5 (C-4), 153.3 (C-3, C-5); FD MS: m/z (%)=577 (100, M$^+$)]. The oxidation was performed as described above for **2j**; 9.00 g (15.6 mmol) of the alcohol and 3.90 g (17.2 mmol) DDQ in 80 mL dry 1,4-dioxane yielded 7.80 g (87%) of the colorless oil **2n**. (Further purification is possible by a filtration over SiO_2 (12×8 cm) using CH_2Cl_2 as solvent). ^{1}H NMR ($CDCl_3$): δ=0.84 (d, 6H, terminal CH_3), 0.85 (d, 12H, terminal CH_3), 0.90 (d, 3H, CH_3), 0.93 (d, 6H, CH_3), 1.10–1.90 (m, 30H, CH_2 and CH), 4.04 (m, 6H, OCH_2), 7.07 (s, 2H, 2-H, 6-H), 9.82 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ=19.6 (CH_3), 22.6, 22.7 (terminal CH_3), 24.7 (CH_2), 28.0, 28.0, 29.6, 29.8 (CH), 36.2, 37.3, 37.4, 39.2, 39.3 (CH_2, partly superimposed), 67.1, 71.8 (OCH_2), 107.8 (C-2, C-6), 131.4 (C-1), 143.7 (C-4), 153.5 (C-3, C-5), 191.3 (CHO); FD MS: *m/z* (%)=575 (100) [M^+]. Anal. calcd for $C_{37}H_{66}O_4$ (574.9): C, 77.30; H 11.57. Found: C, 77.15; H, 11.71.

4.2.3. 2,4,6-Tris[(*E*)-2-(4-methoxyphenyl)ethenyl]-1,3,5-triazine (3a). Yield 94%, yellow needles, mp 228 °C. UV (CH_2Cl_2): λ_{max}=356 nm, log ε=5.04. ^{1}H NMR ($CDCl_3$): δ=3.85 (s, 9H, OCH_3), 6.94 (AA′, 6H, *m*-H), 7.01 (d, ^3J= 15.8 Hz, 3H, α-H), 7.62 (MM′, 6H, *o*-H), 8.21 (d, ^3J= 15.8 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=55.4 (OCH_3), 114.4 (*m*-CH), 124.3 (α-CH), 128.5 (*i*-C_q), 129.7 (*o*-CH), 141.0 (β-CH), 161.1 (*p*-C_qO), 171.4 (C-2); FD MS: *m/z* (%)=477 (100) [M^+]. Anal. calcd for $C_{30}H_{27}N_3O_3$ (477.6): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.31; H, 5.88; N, 8.72.

4.2.4. 2,4,6-Tris[(*E*)-2-(4-propoxyphenyl)ethenyl]-1,3,5-triazine (3b). Yield 86%, yellow powder, mp 99 °C. UV (CH_2Cl_2): λ_{max}=360 nm, log ε=5.04. ^{1}H NMR ($CDCl_3$): δ=1.04 (t, 9H, CH_3), 1.82 (m, 6H, CH_2), 3.96 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=16.0 Hz, 3H, α-H), 7.61 (MM′, 6H, *o*-H), 8.21 (d, ^3J=16.0 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=10.5 (CH_3), 22.6 (CH_2), 69.7 (OCH_2), 115.0 (*m*-CH), 124.1 (α-CH), 128.3 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.4 (C-2); FD MS: *m/z* (%)=562 (100) [M^+]. Anal. calcd for $C_{36}H_{39}N_3O_3$ (561.7): C, 76.98; H, 7.00; N, 7.48. Found: C, 76.83; H, 7.18; N, 7.62.

4.2.5. 2,4,6-Tris[(*E*)-2-(4-pentyloxyphenyl)ethenyl]-1,3,5-triazine (3c). Yield 80%, yellow needles, mp 109 °C. UV (CH_2Cl_2): λ_{max}=360 nm, log ε=5.03. ^{1}H NMR ($CDCl_3$): δ=0.93 (t, 9H, CH_3), 1.41 (m, 12H, CH_2), 1.80 (m, 6H, CH_2), 3.99 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=15.8 Hz, 3H, α-H), 7.60 (MM′, 6H, *o*-H), 8.20 (d, ^3J=15.8 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.0 (CH_3), 22.4, 28.2, 28.9 (CH_2), 68.1 (OCH_2), 114.8 (*m*-CH), 123.9 (α-CH), 128.1 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.3 (C-2); FD MS: *m/z* (%)=646 (98) [M^+], 647 (100) [$M+H^+$]. Anal. calcd for $C_{42}H_{51}N_3O_3$ (645.9): C, 78.10; H, 7.96; N, 6.51. Found: C, 77.78; H, 8.24; N, 6.52.

4.2.6. 2,4,6-Tris[(*E*)-2-(4-hexyloxyphenyl)ethenyl]-1,3,5-triazine (3d). Yield 55%, yellow powder, mp 96 °C. UV (CH_2Cl_2): λ_{max}=361 nm, log ε=5.02. ^{1}H NMR ($CDCl_3$): δ=0.90 (t, 9H, CH_3), 1.34 (m, 12H, CH_2), 1.46 (m, 6H, CH_2), 1.79 (m, 6H, CH_2), 3.99 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=15.7 Hz, 3H, α-H), 7.61 (MM′, 6H, *o*-H), 8.20 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.0 (CH_3), 22.6, 25.7, 29.2, 31.6 (CH_2), 68.2 (OCH_2), 114.9 (*m*-CH), 124.1 (α-CH), 128.3 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.4 (C-2); FD MS: *m/z* (%)=688 (100) [M^+]. Anal. calcd for $C_{45}H_{57}N_3O_3$ (687.9): C, 78.56, H, 8.35, N, 6.11. Found: C, 78.33; H, 8.61; N, 5.88.

4.2.7. 2,4,6-Tris[(*E*)-2-(4-heptyloxyphenyl)ethenyl]-1,3,5-triazine (3e). Yield 64%, yellow powder, mp 85 °C. UV (CH_2Cl_2): λ_{max}=360 nm, log ε=5.01. ^{1}H NMR ($CDCl_3$): δ=0.88 (t, 9H, CH_3), 1.30 (m, 18H, CH_2), 1.45 (m, 6H, CH_2), 1.79 (m, 6H, CH_2), 3.99 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=16.0 Hz, 3H, α-H), 7.61 (MM′, 6H, *o*-H), 8.20 (d, ^3J=16.0 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.6, 26.0, 29.1, 29.2, 31.8 (CH_2), 68.1 (OCH_2), 114.8 (*m*-CH), 123.9 (α-CH), 128.1 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.3 (C-2); FD MS: *m/z* (%)=730 (100) [M^+]. Anal. cacd for $C_{48}H_{63}N_3O_3$ (730.0): C, 78.97; H, 8.70; N, 5.76. Found: C, 78.67; H, 8.84; N, 5.68.

4.2.8. 2,4,6-Tris[(*E*)-2-(4-octyloxyphenyl)ethenyl]-1,3,5-triazine (3f). Yield 61%, yellow powder, mp 76 °C. UV (CH_2Cl_2): λ_{max}=362 nm, log ε=5.03. ^{1}H NMR ($CDCl_3$): δ=0.87 (t, 9H, CH_3), 1.28 (m, 24H, CH_2), 1.45 (m, 6H, CH_2), 1.79 (m, 6H, CH_2), 3.99 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=16.1 Hz, 3H, β-H), 7.61 (MM′, 6H, *o*-H), 8.20 (d, ^3J=16.1 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.6, 26.0, 29.2, 29.2, 29.3, 31.8 (CH_2), 68.1 (OCH_2), 114.8 (*m*-CH), 123.9 (α-CH), 128.1 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.3 (C-2); FD MS: *m/z* (%)=772 (100) [M^+]. Anal. calcd for $C_{51}H_{69}N_3O_3$ (772.1): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.22; H, 9.17; N, 5.57.

4.2.9. 2,4,6-Tris[(*E*)-2-(4-dodecyloxyphenyl)ethenyl]-1,3,5-triazine (3g). Yield 86%, yellow solid, mp 63 °C. UV (CH_2Cl_2): λ_{max}=362 nm, log ε=5.03. ^{1}H NMR ($CDCl_3$): δ=0.86 (t, 9H, CH_3), 1.25 (m, 54H, CH_2), 1.45 (m, 6H, CH_2), 1.79 (m, 6H, CH_2), 3.99 (t, 6H, OCH_2), 6.92 (AA′, 6H, *m*-H), 7.00 (d, ^3J=16.0 Hz, 3H, α-H), 7.61 (MM′, 6H, *o*-H), 8.21 (d, ^3J=16.0 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.6–31.9 (CH_2, partly superimposed), 69.2 (OCH_2), 114.9 (*m*-CH), 123.9 (α-CH), 128.1 (*i*-C_q), 129.7 (*o*-CH), 141.1 (β-CH), 160.7 (*p*-C_qO), 171.3 (C-2); FD MS: *m/z* (%)=940 (100) [M^+], 1882 (69) [M_2+H^+]. Anal. calcd for $C_{63}H_{93}N_3O_3$ (940.4): C, 80.46; H, 9.97; N, 4.47. Found: C, 80.19; H, 10.26; N, 4.51.

4.2.10. 2,4,6-Tris[(*E*)-2-(3,4-dioctyloxyphenyl)ethenyl]-1,3,5-triazine (3h). Yield 82%, green-yellow powder, T_{cl} 82 °C. UV (CH_2Cl_2): λ_{max}=376 nm, log ε=4.99. ^{1}H NMR (DCl_3): δ=0.87 (m, 18H, CH_3), 1.29 (m, 48H, CH_2), 1.47 (m, 12H, CH_2), 1.83 (m, 12H, CH_2), 4.03 (2t, 12H, OCH_2), 6.88 (d, ^3J=8.2 Hz, phenyl-H), 6.98 (d, ^3J=16.0 Hz, 3H, α-H), 7.19 (dd, ^3J=8.2 Hz, ^4J=2.0 Hz, 3H, phenyl-H), 7.23 (d, ^4J=2.0 Hz, 3H, phenyl-H), 8.18 (d, ^3J=16.0 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.6, 26.0, 29.2, 29.3, 29.4, 31.8 (CH_2, partly superimposed), 69.1 (OCH_2), 69.1 (OCH_2), 112.0 (*m*-CH), 113.0 (*o*-CH), 122.6 (*o*′-CH), 124.0 (α-CH), 128.4 (*i*-C_q), 141.4 (β-CH), 149.2 (*m*′-C_qO), 151.0 (*p*-C_qO), 171.2 (C-2); FD MS: *m/z* (%)=1156 (100) [M^+]. Anal. calcd for $C_{75}H_{117}N_3O_6$ (1156.8): C, 77.87; H, 10.19; N, 3.63. Found: C, 77.72; H, 1031; N, 3.55.

4.2.11. 2,4,6-Tris[(*E*)-2-(3,4,5-trihexyloxyphenyl)ethenyl]-1,3,5-triazine (3i). Yield 79%, yellow wax, T_{cl}=112 °C. The analytical and spectroscopic data were published earlier.[8]

4.2.12. 2,4,6-Tris[(*E*)-2-(3,4,5-trioctyloxyphenyl)ethenyl]-1,3,5-triazine (3j). Yield 87%, yellow wax, T_{cl}=102 °C. UV (CH_2Cl_2): λ_{max}=365 nm, log ε=4.90. ^{1}H NMR ($CDCl_3$): δ=0.87 (m, 27H, CH_3), 1.28 (m, 82H, CH_2), 1.48 (m, 18H, CH_2), 1.74 (m, 2H, CH_2), 1.82 (m, 4H, CH_2), 3.99 (t, 6H, OCH_2), 4.01 (t, 12H, OCH_2), 6.88 (s, 6H, *o*-H), 7.00 (d, ^3J=15.7 Hz, 3H, α-H); 8.15 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 29.3, 29.4, 29.5, 30.3, 31.8, 31.9 (CH_2, partly superimposed), 69.1 (OCH_2), 73.6 (OCH_2), 106.6 (*o*-CH), 125.1 (α-CH), 130.5 (*i*-C_q), 140.1 (*p*-C_qO), 141.8 (β-CH), 153.3 (*m*-C_qO), 171.2 (C-2); FD MS: *m*/*z* (%)=1541 (100) [M^+]. Anal. calcd for $C_{99}H_{165}N_3O_9$ (1541.4): C, 77.14; H, 10.79; N, 2.73. Found: C, 77.01; H, 10.95; N, 2.62.

4.2.13. 2,4,6-Tris[(*E*)-2-(3,4,5-tridecyloxyphenyl)-ethenyl]-1,3,5-triazine (3k). Yield 69%, yellow wax, T_{cl}=90 °C. UV (CH_2Cl_2): λ_{max}=365 nm, log ε=4.89. ^1H NMR ($CDCl_3$): δ=0.86 (m, 27H, CH_3), 1.26 (m, 108H, CH_2), 1.48 (m, 18H, CH_2), 1.74 (m, 2H, CH_2), 1.81 (m, 4H, CH_2), 3.99 (t, 6H, OCH_2), 4.01 (t, 12H, OCH_2), 6.88 (s, 6H, *o*-H); 7.00 (d, ^3J=15.7 Hz, 3H, α-H), 8.14 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 29.4, 29.6, 29.7, 30.3, 31.9 (CH_2, partly superimposed), 69.1 (OCH_2), 73.6 (OCH_2), 106.6 (*o*-CH), 125.1 (α-CH), 130.5 (*i*-C_q), 140.1 (*p*-C_qO), 141.8 (β-CH), 153.3 (*m*-C_qO), 171.2 (C-2); FD MS: *m*/*z* (%)=1795 (100) [M+H^+]. Anal. calcd for $C_{117}H_{201}N_3O_9$ (1793.9): C, 78.34; H, 12.29; N, 2.34. Found: C, 78.11; H, 12.56; N, 2.12.

4.2.14. 2,4,6-Tris[(*E*)-2-(3,4,5-tridodecyloxyphenyl)-ethenyl]-1,3,5-triazine (3l). Yield 82%, yellow wax, T_{cl}=90 °C. UV (CH_2Cl_2): λ_{max}=366 nm, log ε=4.90. ^1H NMR ($CDCl_3$): δ=0.86 (m, 27H, CH_3), 1.25 (m, 144H, CH_2), 1.48 (m, 18H, CH_2), 1.74 (m, 6H, CH_2), 1.82 (m, 12H, CH_2), 3.99 (t, 6H, OCH_2), 4.01 (t, 12H, OCH_2), 6.88 (s, 6H, *o*-H), 7.00 (d, ^3J=15.7 Hz, 3H, α-H), 8.15 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 29.4, 29.6, 29.7, 30.4, 31.9 (CH_2, partly superimposed), 69.2 (OCH_2), 73.6 (OCH_2), 106.6 (*o*-CH), 125.1 (α-CH), 130.5 (*i*-C_q), 140.1 (*p*-C_qO), 141.8 (β-CH), 153.3 (*m*-C_qO), 171.1 (C-2); FD MS: *m*/*z* (%)=2047 (100) [M^+]. Anal. calcd for $C_{135}H_{237}N_3O_9$ (2046.4): C, 79.24; H, 11.67; N, 2.05. Found: C, 79.23; H, 11.55; N, 2.08.

4.2.15. 2,4,6-Tris[(*E*)-2-(3,4,5,-trihexadecyloxyphenyl)-ethenyl]-1,3,5-triazine (3m). Yield 89%, yellow wax, T_{cl}=80 °C. UV (CH_2Cl_2): λ_{max}=367 nm, log ε=4.90. ^1H NMR ($CDCl_3$): δ=0.85 (m, 27H, CH_3), 1.24 (m, 216H, CH_2), 1.48 (m, 18H, CH_2), 1.75 (m, 6H, CH_2), 1.82 (m, 12H, CH_2), 3.99 (t, 6H, OCH_2), 4.01 (t, 12H, OCH_2), 6.88 (s, 6H, *o*-H), 7.01 (d, ^3J=15.7 Hz, 3H, α-H), 8.15 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=14.1 (CH_3), 22.7, 26.1, 29.4, 29.6, 29.7, 30.3, 31.9 (CH_2, partly superimposed), 69.1 (OCH_2), 73.6 (OCH_2), 106.6 (*o*-CH), 125.1 (α-CH), 130.5 (*i*-C_q), 140.1 (*p*-C_qO), 141.8 (β-CH), 153.3 (*m*-C_qO), 171.2 (C-2); FD MS: *m*/*z* (%)=2552 (100) [M^+]. Anal. calcd for $C_{171}H_{309}N_3O_9$ (2551.3): C, 80.50; H, 12.21; N, 1.65. Found: C, 80.27; H, 12.48; N, 1.38.

4.2.16. 2,4,6-Tris{(*E*)-2[3,4,5-tris(3,7-dimethyloctyl)-phenyl]ethenyl}-1,3,5-triazine (3n). Yield 85%, yellow wax, T_{cl}=45 °C. UV (CH_2Cl_2): λ_{max}=366 nm, log ε=4.77. ^1H NMR ($CDCl_3$): δ=0.85 (m, 54H, CH_3), 0.94 (m, 27H, CH_3), 1.10–1.95 (m, 90H, CH_2 and CH), 4.04 (m, 18H, OCH_2), 6.90 (s, 6H, *o*-H), 7.03 (d, ^3J=15.7 Hz, 3H, α-H), 8.17 (d, ^3J=15.7 Hz, 3H, β-H); ^{13}C NMR ($CDCl_3$): δ=19.6, 22.6, 22.7 (CH_3), 24.7 (CH_2), 28.0, 29.6, 29.8 (CH, partly superimposed), 36.4, 37.3, 37.5, 39.2, 39.3 (CH_2, partly superimposed), 67.4 (OCH_2), 71.8 (OCH_2), 106.5 (*o*-CH), 125.1 (α-CH), 130.5 (*i*-C_q), 140.1 (*p*-C_qO), 141.8 (β-CH), 153.3 (*m*-C_qO), 171.2 (C-2); FD MS: *m*/*z* (%)=1794 (100) [M^+]. Anal. calcd for $C_{117}H_{201}N_3O_9$ (1793.9): C, 78.34; H, 12.29; N, 2.34. Found: C, 77.91; H, 11.95; N, 2.26.

4.3. Irradiation of the LC phases

The Col_{hd} phase of **3i** was irradiated (λ=366 nm) on a glass plate at 95 °C and observed with polarizing microscopy. The change of the texture was accompanied by a continuous lowering of the temperature for the isotropization. The ^1H NMR spectra of the irradiated probe, dissolved in $CDCl_3$, revealed the formation of a small amount of (*E*,*E*,*Z*) configuration and the formation of a dimer which contains one four-membered ring (AA′MM′ spin pattern at δ=4.87 and 5.27 which is assigned to a head-to-tail *anti* photocyclodimerization).[21] The irradiation of the Col_{hd} phases of **3j–3m** gives similar results, however, one has to take into account that the normal or undercooled LC phases of these compounds can exist at room temperature, so that they are sensitive toward daylight.[22]

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie for financial support.

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22. In the absence of a topochemically controlled reaction in the crystalline state, the enhanced molecular mobility in the LC phases is a precondition for the photodimerization.

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Tetrahedron

Tetrahedron 60 (2004) 6777–6783

Novel Knöevenagel-type reaction via titanium enolate derived from $Ti(O\text{-}i\text{-}Pr)_4$ and diketene☆

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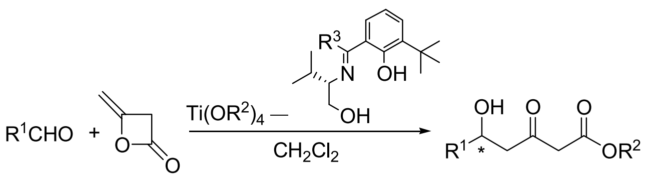
Received 14 May 2004; revised 5 June 2004; accepted 7 June 2004

Abstract—Knöevenagel-type reaction between diketene and aldehydes proceeded in the presence of $Ti(O\text{-}i\text{-}Pr)_4$. This reaction proceeded via titanium enolate derived from $Ti(O\text{-}i\text{-}Pr)_4$ and diketene. As for the stereoselectivity of the products, *E*-isomers were produced predominantly in the case of aromatic aldehydes.

1. Introduction

The Knöevenagel reaction is a classical and well-known reaction as a condensation between carbonyl compounds and activated methylene compounds catalyzed by amines.[1] As activated methylene compounds, alkyl acetoacetates and dialkyl malonates have been often used.

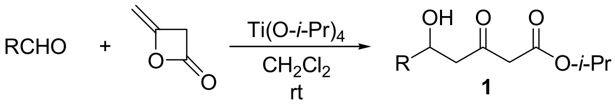
In 1994, we reported that the reaction of diketene with aldehydes was promoted by $Ti(O\text{-}i\text{-}Pr)_4$ and demonstrated the first example of an asymmetric version of this reaction. That is, chiral Schiff base-titanium alkoxide complexes promoted the enantioselective reaction of diketene to aldehydes which leads to the asymmetric synthesis of optically active 5-hydroxy-3-ketoesters (Eq. (1)).[2] This reaction was applied to asymmetric synthesis of potential inhibitors of HMG coenzyme reductase.[3]



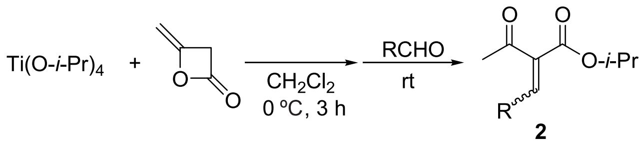
(1)

2. Results and discussion

During the course of our study of the reaction mechanism of $Ti(O\text{-}i\text{-}Pr)_4$-promoted reaction of diketene with aldehydes, we found that a change of the order of addition of the reagents afforded different products (Eqs. (2) and (3)). That is, 5-hydroxy-3-ketoesters **1** were obtained when diketene was added to the mixture of aldehydes and $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2. On the other hand, when diketene and $Ti(O\text{-}i\text{-}Pr)_4$ were mixed in advance and the mixture was stirred for 3 h, subsequent addition of aldehydes to the reaction mixture gave Knöevenagel reaction products **2**.



(2)



(3)

Since a mixture of **1** and **2** was obtained when aldehydes were added instantly after diketene and $Ti(O\text{-}i\text{-}Pr)_4$ were mixed, the stirring time of 3 h is important for the reaction of Eq. (3). The titanium enolate species were considered to be generated from $Ti(O\text{-}i\text{-}Pr)_4$ and diketene as intermediate. The reaction of titanium enolates prepared from titanium reagents/amine system with electrophiles such as alkyl halides and aldehydes has been well studied,[4] but to our knowledge, few examples of this type of Knöevenagel reaction using diketene were reported so far.[5,6] In this paper, we would like to report the details of a new type of Knöevenagel reaction via titanium enolate derived from $Ti(O\text{-}i\text{-}Pr)_4$ and diketene.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.018.

Keywords: Knöevenagel reaction; Titanium enolate; Diketene.

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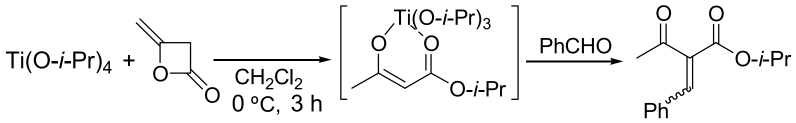
doi:10.1016/j.tet.2004.06.018

Table 1. Effect of the ratio of Ti(O-*i*-Pr)$_4$ and diketene on the chemical yield of the product[a]



Entry	Ti(O-*i*-Pr)$_4$/equiv	Diketene/equiv	Conditions		Product
			Temp/°C	Time/h	% Yield (*E*/*Z*)[b]
1	1	1	20	48	34 (88/12)
2	2	1	25	43	68 (89/11)
3	1	2	24	44	0 (–)

[a] 1.0 equiv. of PhCHO was used.
[b] *E*/*Z* ratio was determined by ^{1}H NMR analysis.

At first, we examined the effect of the ratio of Ti(O-*i*-Pr)$_4$ and diketene on the chemical yield of the product (Table 1). As shown in Table 1, the ratio of Ti(O-*i*-Pr)$_4$, diketene and benzaldehyde in 2:1:1 afforded the product in highest yield (68%). However, when 2.0 equiv of diketene was used, no product was obtained. To understand these results and to confirm the generation of titanium enolate, we measured the ^{1}H NMR spectra of mixtures of Ti(O-*i*-Pr)$_4$ and diketene in a variety of ratios (Figs. 1–3).

Figure 1 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 1:1 in $CDCl_3$ after 3.5 h. The generated species were assumed as titanium enolate **3b** with a double bond at the internal site of the isopropyl acetoacetate moiety. The peaks which appeared in 4.9 ppm of ^{1}H NMR and in 92 ppm of the ^{13}C NMR spectra should indicate the presence of double bond of internal titanium enolate. It should be noted that the peaks of Ti(O-*i*-Pr)$_4$ remained, although diketene disappeared completely in the reaction mixture. This result thus indicates that the diketene does not only react with Ti(O-*i*-Pr)$_4$ in a ratio of 1:1, but also reacts in the 1:2 ratio. We presumed that each peak of 1:1 and 1:2 enolates would be the same chemical shift value. When Ti(O-*i*-Pr)$_4$ was mixed with diketene in a ratio of 1:1, the product distribution was found to be 22% of 1:1 enolate, 31% of 1:2 enolate and 47% of Ti(O-*i*-Pr)$_4$. The ratio of 1:1 enolate, 1:2 enolate and Ti(O-*i*-Pr)$_4$ was calculated by integration of five methine proton peaks in isopropoxide moiety which appeared in the region of 4.9–4.5 ppm in Figure 1. The geometry of titanium enolate was determined by NOE experiment (see supplementary information).

Figure 2 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 1:2 in $CDCl_3$ after 6 h. The peaks of Ti(O-*i*-Pr)$_4$ were completely diminished. The product distribution was found to be 26% of 1:1 enolate, 74% of 1:2 enolate and 26% of diketene. Ti(O-*i*-Pr)$_4$ did not remain.

Furthermore, Figure 3 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 2:1 after 2.5 h which afforded the products in 5% of 1:1 enolate, 19% of 1:2 enolate and 76% of Ti(O-*i*-Pr)$_4$.

A possible mechanism of the Knöevenagel-type reaction via titanium enolate is illustrated in Scheme 1. The titanium enolate **3a** which has a double bond at the terminal site of the isopropyl acetoacetate moiety should be first generated from Ti(O-*i*-Pr)$_4$ and diketene. However, it will immediately isomerize to the internal titanium enolate **3b**. Therefore, the

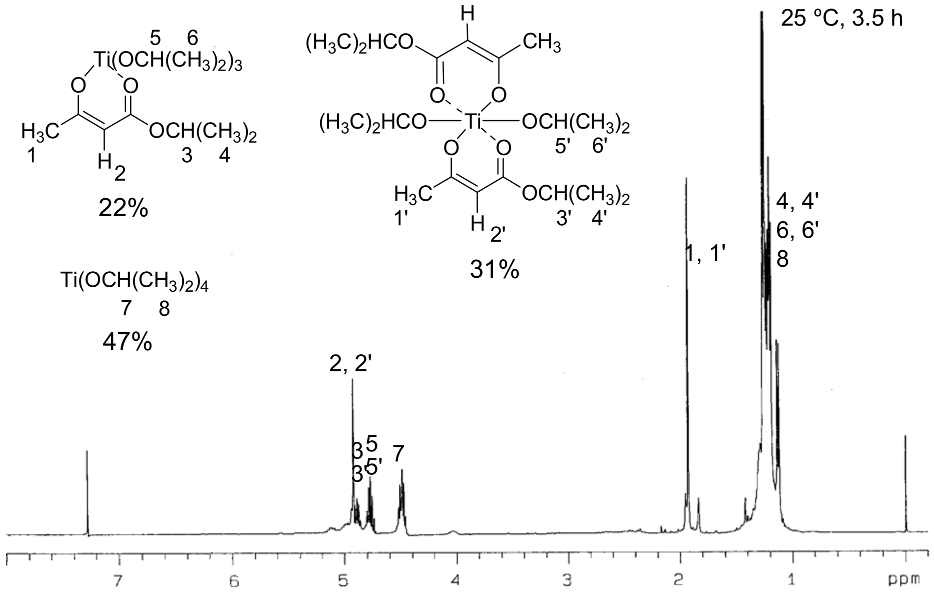


Figure 1. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 1:1.

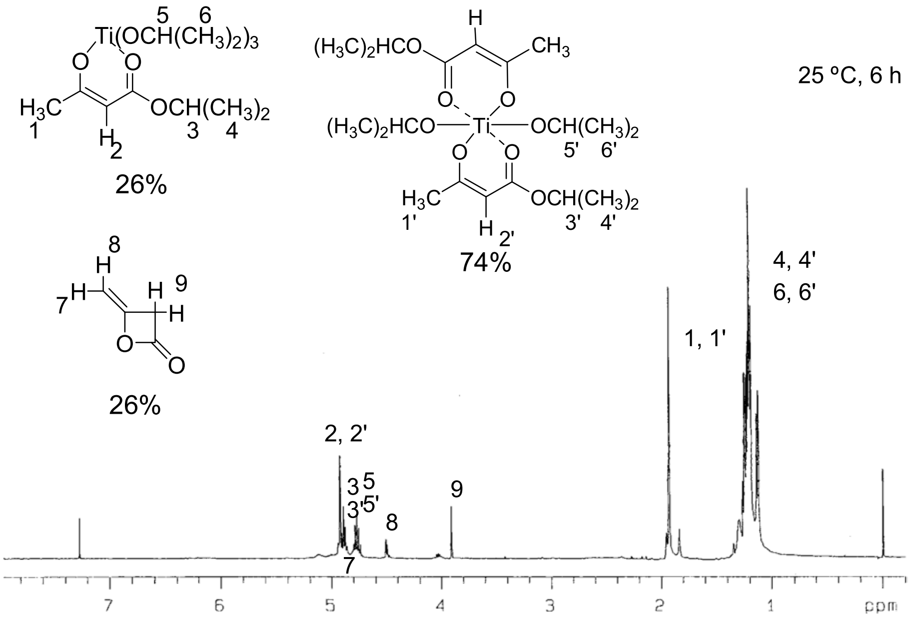


Figure 2. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 1:2.

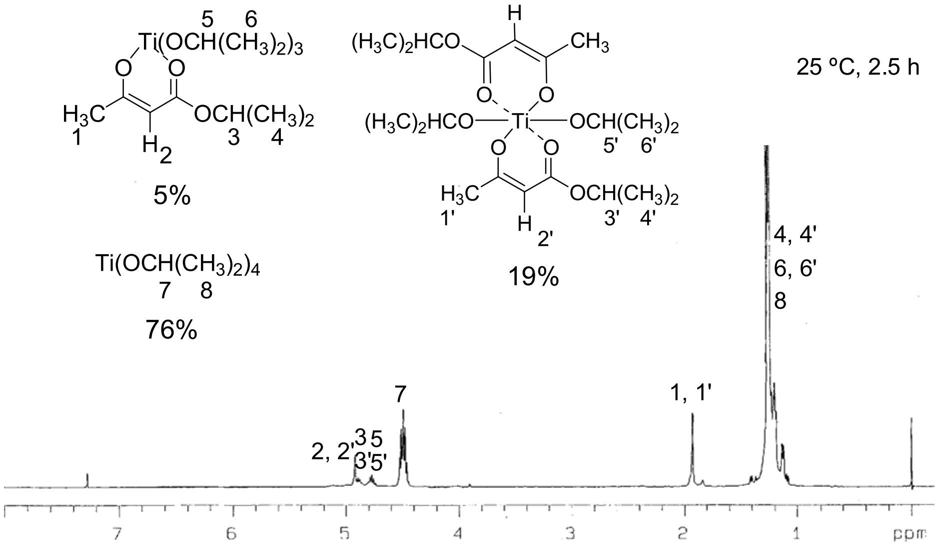
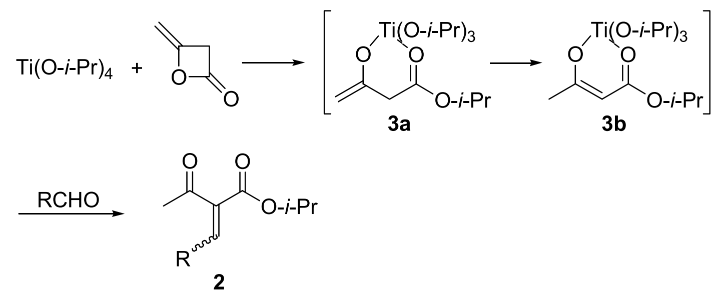


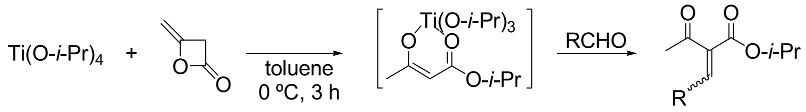
Figure 3. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 2:1.

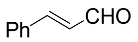
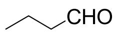
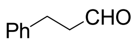


Scheme 1.

terminal titanium enolate **3a** was not observed by ^{1}H NMR. Subsequent reaction of internal titanium enolate **3b** with aldehydes produces Knöevenagel reaction products. When free Ti(O-*i*-Pr)$_4$ did not exist in the mixture (Fig. 2), the reaction did not proceed at all (entry 3 in Table 1). The fact that the presence of free Ti(O-*i*-Pr)$_4$ is necessary should indicate that titanium enolate **3b** itself has not enough reactivity to react with aldehydes. The activation of aldehyde by Ti(O-*i*-Pr)$_4$ will be required. We consider that the 1:1 enolate would be more reactive than 1:2 enolate.

Table 2. Reaction of titanium enolate with a variety of aldehydes[a]



Entry	Aldehyde	Conditions		Product	Conventional Knoevenagel condition[b]
		Temp/°C	Time/h	% Yield (*E*/*Z*)[c]	% Yield (*E*/*Z*)[c]
1	C_6H_5CHO	28	48	**2a** 79 (91/9)	48 (31/69)
2	*p*-ClC_6H_4CHO	21	46	**2b** 77 (96/4)	70 (40/60)
3	*p*-MeC_6H_4CHO	21	48	**2c** 70 (94/6)	62 (36/64)
4	*p*-$MeOC_6H_4CHO$	21	48	**2d** 62 (91/9)	54 (37/63)
5		21	6	**2e** 76 (60/40)	73 (35/65)
6	$C_6H_{11}CHO$	22	17	**2f** 80 (60/40)	80 (35/65)
7		21	5	**2g** 90 (31/69)	36 (35/65)
8		22	22	**2h** 70 (33/67)	46 (48/52)

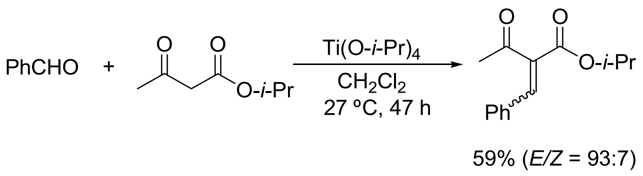
[a] The ratio of diketene: Ti(O-*i*-Pr)$_4$:aldehyde was 1:2:1.
[b] The ratio of isopropyl acetoacetate:aldehyde:piperidine was 1:1:0.1.
[c] *E*/*Z* ratio was determined by the integration of vinylic proton in the compounds **2a**–**2h** by ^{1}H NMR analysis.

Aiming at improvement of chemical yield and stereoselectivity, we examined solvents suitable for this reaction. As a result, it was found that toluene was a suitable solvent for this reaction.

A variety of aldehydes were employed in the reaction with titanium enolate (Table 2). Generally, aliphatic aldehydes exhibited higher reactivity than aromatic aldehydes. As for the geometry of the products, the reaction of aromatic aldehydes (entries 1–4) afforded *E*-geometrical isomers predominantly, which was in sharp contrast with the conventional Knöevenagel reaction.[7] The configurations of *E* and *Z* were identified by NOE experiment (see supplementary information). That is, when benzaldehyde was treated with isopropyl acetoacetate in the presence of piperidine, mixtures of *E*- and *Z*-isomers (31/69) were obtained.

On the other hand, in the cases of aliphatic aldehydes, the mixtures of *E*- and *Z*-isomers were obtained in different ratio in each aldehyde. The reaction of cinnamaldehyde and cyclohexanecarboxaldehyde furnished the *E*-isomer preferentially (60/40), but that of *n*-butanal and 3-phenyl propionaldehyde produced the *Z*-isomer preferentially (31/69 and 33/67, respectively). When we traced the reaction by ^{1}H NMR, the ratio of *E*/*Z* isomers was not changed during the reaction. Furthermore, we confirmed that it took 6–18 h to reach equilibrium (thermodynamic) ratio even at high temperature (90 °C) in the case of a cyclohexane derivative.[8] Although the detailed mechanism of this reaction including stereoselectivity is unclear, we consider that the reactivity of aldehydes affects the selectivity.

Finally, we found that when isopropyl acetoacetate was used as substrate instead of diketene, titanium enolate species were also generated from Ti(O-*i*-Pr)$_4$ and isopropyl acetoacetate. The reaction of isopropyl acetoacetate and benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$ in the ratio of 1:1:2 gave Knöevenagel product **2** (59%) in the *E*/*Z* ratio of 97.3 (Eq. (4)).



(4)

In conclusion, the present Knöevenagel reaction has the following characteristic features. (1) Alkyl acetoacetate is not used, but diketene was used as the C-4 unit source. (2) The reaction takes place not under basic conditions like the conventional Knöevenagel reaction, but proceeds under mild acidic conditions. (3) The stereoselectivity of the double bond of the products was in contrast to the conventional Knöevenagel reaction. Especially, in the case of aromatic aldehydes, *E*-isomers were produced exclusively.

3. Experimental

3.1. General methods

All melting points were measured on a Yanaco MP-500D and uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-GX 400 by use of $CDCl_3$ containing TMS as the internal standard. IR spectra were measured on a HITACHI I-2000. Elemental analyses were performed on a Yanaco CHN Corder MT-5. Mass spectra were taken on a Shimadzu GCMS-QP 2000A. Thin-layer chromatography (TLC) was carried out on foil plates, Silica Gel 60 F254 (E. Merck; layer thickness 0.2 mm). Preparative column chromatography was carried out on Fuji Silysia BW-820MH.

3.2. Typical procedure for the Knöevenagel type reaction via titanium enolate

A mixture of Ti(O-*i*-Pr)$_4$ 2.95 mL (10 mmol) and toluene 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, diketene 0.39 mL (5 mmol) was added and stirred at 0 °C for 3 h. Then, benzaldehyde 0.51 mL (5 mmol) was added and the mixture was stirred at room temperature for 48 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and the extract was washed with sodium bicarbonate and brine solution. The organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the *E*/*Z* ratio was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 926.9 mg (79%) was obtained in the *E*/*Z* ratio of 91/9.

3.3. Typical procedure for the conventional Knöevenagel reaction catalyzed by piperidine

A mixture of isopropyl acetoacetate 0.77 mL (5 mmol), benzaldehyde 0.51 mL (5 mmol), and toluene 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, piperidine 0.05 mL (0.5 mmol) was added and stirred at room temperature for 48 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and extract was washed with sodium bicarbonate and brine solution. Organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the ratio of *E*- and *Z*-isomers was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 556.8 mg (48%) was obtained in the *E*/*Z* ratio of 35/65.

3.4. Reaction of benzaldehyde with isopropyl acetoacetate promoted by Ti(O-*i*-Pr)$_4$ (Eq. (4))

A mixture of isopropyl acetoacetate 0.77 mL (5 mmol), benzaldehyde 0.51 mL (5 mmol), and dichloromethane 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, Ti(O-*i*-Pr)$_4$ 2.95 mL (10 mmol) was added and stirred at room temperature for 47 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and the extract was washed with sodium bicarbonate and brine solution. The organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the *E*/*Z* ratio was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 685.2 mg (59%) was obtained in the *E*/*Z* ratio of 93/7.

3.4.1. (*E*)-Isopropyl 2-acetyl-3-phenyl-2-propenoate ((*E*)-2a). R_f=0.51 (5:1 hexane–ethyl acetate); mp 42.6–43.6 °C; IR (KBr, ν_{max} (cm^{-1})): 1704, 1620; ^{1}H NMR: δ 7.64 (s, 1H), 7.4–7.3 (m, 5H), 5.2–5.1 (m, 1H), 2.35 (s, 3H), 1.32 (d, *J*=6.0 Hz, 6H); ^{13}C NMR: δ 203.8, 163.9, 140.0, 134.2, 133.0, 130.4, 129.8, 128.9, 69.0, 31.6, 21.8; MS *m*/*z* (relative intensity): 232 (42%), 189 (62%), 173 (22%), 131 (47%), 103 (31%), 77 (22%), 43 (100%); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.43; H, 7.06.

3.4.2. (*Z*)-Isopropyl 2-acetyl-3-phenyl-2-propenoate ((*Z*)-2a). R_f=0.32 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1666, 1620; ^{1}H NMR: δ 7.56 (s, 1H), 7.5–7.4 (m, 5H), 5.3–5.2 (m, 1H), 2.42 (s, 3H), 1.27 (d, *J*=6.0 Hz, 6H); ^{13}C NMR: δ 194.5, 167.3, 140.8, 135.0, 133.1, 130.6, 129.6, 128.7, 69.5, 26.6, 21.5; MS *m*/*z* (relative intensity): 232 (26%), 189 (36%), 173 (17%), 131 (28%), 103 (18%), 77 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 7.02.

3.4.3. (*E*)-Isopropyl 2-acetyl-3-(*p*-chlorophenyl)-2-propenoate ((*E*)-2b). R_f=0.51 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1627, 1589; ^{1}H NMR: δ 7.57 (s, 1H), 7.34 (s, 4H), 5.2–5.1 (m, 1H), 2.35 (s, 3H), 1.31 (d, *J*=6 Hz, 6H); ^{13}C NMR: δ 202.9, 163.6, 138.6, 136.3, 135.0, 131.3, 130.8, 129.0, 69.3, 31.0, 21.6; MS *m*/*z* (relative intensity): 266 (10%), 231 (4%), 223 (6%), 209 (25%), 165 (18%), 43 (100%); Anal. Calcd for $C_{14}H_{15}O_3Cl$: C, 63.04; H, 5.67. Found: C, 63.07; H, 5.74.

3.4.4. (*Z*)-Isopropyl 2-acetyl-3-(*p*-chlorophenyl)-2-propenoate ((*Z*)-2b). R_f=0.32 (5:1 hexane–ethyl acetate); mp 49.0–51.0 °C; IR (KBr, ν_{max} (cm^{-1})): 1736, 1666, 1620, 1589, ^{1}H NMR: δ 7.49 (s, 1H), 7.41 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 5.3–5.2 (m, 1H), 2.41 (s, 3H), 1.28 (d, *J*=6.4 Hz, 6H), ^{13}C NMR: δ 194.0, 167.5, 139.0, 136.7, 135.3, 131.5, 130.8, 129.0, 69.9, 26.0, 21.4; MS *m*/*z* (relative intensity): 266 (5%), 231 (3%), 209 (13%), 189 (14%), 165 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{15}O_3Cl$: C, 63.04; H, 5.67. Found: C, 63.04; H, 5.67.

3.4.5. (*E*)-Isopropyl 2-acetyl-3-(*p*-methylphenyl)-2-propenoate ((*E*)-2c). R_f=0.50 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1620, ^{1}H NMR: δ 7.61 (s, 1H), 7.29 (d, *J*=8.4 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 5.2–5.1 (m, 1H), 2.36 (s, 6H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 203.7, 164.1, 140.9, 140.3, 133.5, 130.2, 129.8, 129.6, 69.1, 31.2, 21.8, 21.4; MS *m*/*z* (relative intensity): 246 (7%), 189 (47%), 145 (24%), 115 (25%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.51.

3.4.6. (*Z*)-Isopropyl 2-acetyl-3-(*p*-methylphenyl)-2-propenoate ((*Z*)-2c). R_f=0.34 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1666, 1604; ^{1}H NMR: δ 7.51 (s, 1H), 7.38 (d, *J*=8 Hz, 2H), 7.18 (d, *J*=8 Hz, 2H), 5.3–5.2 (m, 1H), 2.39 (s, 6H), 1.29 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 194.6, 167.6, 141.3, 140.8, 134.0, 130.1, 129.8, 129.5, 69.4, 26.5, 21.5; MS *m*/*z* (relative intensity): 189 (88%), 145 (37%), 115 (35%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.43; H, 7.51.

3.4.7. (*E*)-Isopropyl 2-acetyl-3-(*p*-methoxylphenyl)-2-propenoate ((*E*)-2d). R_f=0.34 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1605; ^{1}H NMR: δ 7.58 (s, 1H), 7.36 (d, *J*=8.4 Hz, 2H), 6.88 (d, *J*=8.4 Hz, 2H), 5.3–5.2 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 203.9, 164.3, 161.4, 140.0, 131.8, 131.7, 125.6, 114.4, 69.0, 55.4, 31.2, 21.8; MS *m*/*z* (relative intensity): 262 (9%), 231 (15%), 189 (36%), 145 (12%), 43

(100%); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.52; H, 6.97.

3.4.8. (*Z*)-Isopropyl 2-acetyl-3-(*p*-methoxylphenyl)-2-propenoate ((Z)-2d). R_f=0.17 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1720, 1658, 1597; ^{1}H NMR: δ 7.49 (s, 1H), 7.45 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.3–5.2 (m, 1H), 3.84 (s, 3H), 2.39 (s, 3H), 1.31 (d, J=6.4 Hz, 6H); ^{13}C NMR: δ 194.6, 167.9, 161.7, 140.7, 132.6, 131.8, 125.3, 114.3, 69.2, 55.4, 26.5, 21.6; MS *m/z* (relative intensity): 262 (5%), 231 (16%), 189 (37%), 145 (14%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.48; H, 6.99.

3.4.9. (*E*,*E*)-Isopropyl 2-acetyl-5-phenyl-2, 4-pentadienoate ((*E*)-2e). R_f=0.53 (5:1 hexane–ethyl acetate); mp: 67.0–67.4 °C; IR (KBr, ν_{max} (cm^{-1})): 1689, 1604, 1574; ^{1}H NMR: δ 7.50 (d, J=7.6 Hz, 2H), 7.44 (d, J= 11.6 Hz, 1H), 7.4–7.3 (m, 3H), 7.30 (d, J=15.2 Hz, 1H), 7.06 (d, J=15.2 Hz, 1H), 5.2–5.1 (m, 1H), 2.45 (s, 3H), 1.33 (d, J=6.4 Hz, 6H); ^{13}C NMR: δ 200.5, 164.9, 145.4, 144.8, 135.7, 132.4, 129.8, 128.9, 127.8, 123.5, 68.8, 31.2, 21.8; MS *m/z* (relative intensity): 258 (8%), 215 (29%), 171 (22%), 128 (31%), 43 (100%); Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.31; H, 6.98.

3.4.10. (*Z*,*E*)-Isopropyl 2-acetyl-5-phenyl-2,4-pentadienoate ((Z)-2e). R_f=0.32 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1712, 1612, 1581; ^{1}H NMR: δ 7.49 (d, J=7.6 Hz, 2H), 7.42 (d, J=11.6 Hz, 1H), 7.4–7.3 (m, 3H), 7.30 (d, J=11.6 Hz, 1H), 7.09 (d, J=14.8 Hz, 1H), 5.3–5.2 (m, 1H), 2.40 (s, 3H), 1.39 (d, J=6.4 Hz, 6H); ^{13}C NMR: δ 195.5, 165.9, 145.5, 144.2, 135.7, 132.8, 129.9, 128.9, 127.7, 123.6, 69.0, 38.0, 21.9; MS *m/z* (relative intensity): 258 (6%), 215 (17%), 171 (15%), 128 (20%), 43 (100%); Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.31; H, 6.98.

3.4.11. (*E*)-Isopropyl 2-acetyl-3-cyclohexyl-2-propenoate ((*E*)-2f). R_f=0.64 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1635; ^{1}H NMR: δ 6.69 (d, J=10.8 Hz, 1H), 5.2–5.1 (m, 1H), 2.36 (s, 3H), 2.4–2.3 (m, 1H), 1.7–1.6 (m, 4H), 1.28 (d, J=6.4 Hz, 6H), 1.3–1.2 (m, 6H); ^{13}C NMR: δ 201.4, 164.2, 152.5, 134.4, 68.7, 38.2, 31.9, 31.3, 25.6, 25.1, 21.7; MS *m/z* (relative intensity): 238 (3%), 195 (7%), 178 (26%), 135 (25%), 83 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.49.

3.4.12. (*Z*)-Isopropyl 2-acetyl-3-cyclohexyl-2-propenoate ((Z)-2f). R_f=0.50 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1674, 1628; ^{1}H NMR: δ 6.62 (d, J=10.0 Hz, 1H), 5.3–5.2 (m, 1H), 2.4–2.3 (m, 1H), 2.30 (s, 3H), 1.8–1.7 (m, 4H), 1.32 (d, J=6.4 Hz, 6H), 1.3–1.2 (m, 6H); ^{13}C NMR: δ 195.4, 166.3, 152.0, 135.6, 68.8, 39.2, 31.8, 26.9, 25.6, 25.2, 21.8; MS *m/z* (relative intensity): 238 (1%), 195 (3%), 178 (26%), 135 (22%), 83 (9%), 43 (100%); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.40; H, 9.39.

3.4.13. (*E*)-Isopropyl 2-acetyl-2-hexenoate ((*E*)-2g). R_f=0.61 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1635; ^{1}H NMR: δ 6.89 (t, J=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.36 (s, 3H), 2.22 (q, J=7.6, 7.6 Hz, 2H), 1.6–1.5 (m, 2H), 1.29 (d, J=6.0 Hz, 6H), 0.90 (t, J=7.6 Hz, 3H); ^{13}C NMR: δ 201.2, 164.1, 148.4, 135.0, 68.8, 31.3, 31.1, 21.9, 21.8, 13.8; MS *m/z* (relative intensity): 198 (1%), 156 (13%), 137 (26%), 96 (44%), 43 (100%); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 65.26; H, 9.15.

3.4.14. (*Z*)-Isopropyl 2-acetyl-2-hexenoate ((*Z*)-2g). R_f=0.44 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1674, 1635; ^{1}H NMR: δ 6.83 (t, J=7.6 Hz, 1H), 5.3–5.2 (m, 1H), 2.31 (s, 3H), 2.29 (q, J=7.6, 7.6 Hz, 2H), 1.5–1.4 (m, 2H), 1.32 (d, J=6.0 Hz, 6H), 0.96 (t, J=7.6 Hz, 3H); ^{13}C NMR: δ 195.0, 166.1, 147.7, 137.5, 68.9, 31.7, 26.9, 21.7, 21.6, 13.8; MS *m/z* (relative intensity): 156 (4%), 137 (2%), 96 (11%), 43 (100%); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 65.81; H, 9.21.

3.4.15. (*E*)-Isopropyl 2-acetyl-5-phenyl-2-pentenoate ((*E*)-2h). R_f=0.53 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1704, 1635, 1604; ^{1}H NMR: δ 7.3–7.2 (m, 5H), 6.92 (t, J=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.78 (t, J=7.6 Hz, 2H), 2.58 (q, J=7.6, 7.6 Hz, 2H), 2.18 (s, 3H), 1.27 (d, J=6.0 Hz, 6H); ^{13}C NMR: δ 208.0, 163.9, 147.2, 140.5, 136.3, 128.6, 128.4, 126.3, 68.8, 34.7, 31.1, 30.8, 21.7; MS *m/z* (relative intensity): 218 (8%), 200 (19%), 104 (7%), 91 (100%); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.83.

3.4.16. (*Z*)-Isopropyl 2-acetyl-5-phenyl-2-pentenoate ((Z)-2h). R_f=0.38 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1720, 1628; ^{1}H NMR: δ 7.3–7.2 (m, 5H), 6.83 (t, J=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.81 (t, J=7.6 Hz, 2H), 2.65 (q, J=7.6, 7.6 Hz, 2H), 2.29 (s, 3H), 1.31 (d, J=6.4 Hz, 6H); ^{13}C NMR: δ 195.0, 165.8, 146.6, 140.3, 137.6, 128.5, 128.2, 126.3, 67.0, 34.4, 31.4, 27.0, 21.7; MS *m/z* (relative intensity): 260 (1%), 200 (15%), 104 (6%), 91 (81%), 43 (100%); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.83.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Dr. Hideki Amii for valuable discussions.

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8. From the *E*-isomer (100%) it took 6 h at 90 °C to reach thermodynamic ratio (E/Z=33/67) (at room temperature it took more than 2 weeks). On the other hand, from the *Z*-isomer it took 18 h to reach thermodynamic ratio (E/Z=33/67) at the same temperature.

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Tetrahedron 60 (2004) 6785–6789
Tetrahedron

Total synthesis of the naphthyridine alkaloid jasminine

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Received 14 April 2004; revised 28 May 2004; accepted 7 June 2004

Abstract—The synthesis of (±)-jasminine (**1**), a member of a small group of naphthyridine alkaloids, has been achieved. The synthetic route takes advantage of the reactivity of dihydropyridine intermediates for the preparation of trisubstituted pyridine **4**, which gives access to the alkaloid by a reductive amination-lactamization tandem reaction.

1. Introduction

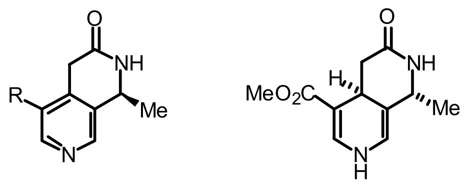
Jasminine (**1**, Fig. 1) is a monoterpene alkaloid isolated in 1968 from *Jasminum gracile* and other *Oleaceae* species,[1] which is characterized by a pyridine ring fused to a six-membered lactam moiety. This singular 2,7-naphthyridin-3-one skeleton is also present in jasminidine (**2**)[2] and dihydrojasminine (**3**),[3] which co-occur with **1** in *Syringa vulgaris* and *Osmanthus austrocaledonica*, respectively.[4] These alkaloids have attracted little synthetic attention: to our knowledge, only a biomimetic hemisynthesis of jasminine (**1**) from related secoiridoids[5] has been reported to date.

As a part of our continuing interest in the chemistry of dihydropyridines,[6] which are useful intermediates for natural product synthesis,[7] we present here a concise, total synthesis of (±)-jasminine (**1**). In planning our approach, we found it logical to close the lactam ring in the last synthetic step by a reductive amination–lactamization process from pyridine **4** (Scheme 1), which, in turn, would be prepared from commercially available 3-acetylpyridine by the sequential introduction of substituents at the 4- and 5-positions of the ring. To this end, we could take advantage of our previously reported procedure for the synthesis of substituted dihydropyridines, based on the addition of carbon nucleophiles to *N*-alkylpyridinium substrates, followed by acylation of the resultant dihydropyridine adducts.[8] This nucleophilic addition–acylation sequence would have to be combined with a final oxidative step, with concomitant or subsequent *N*-dealkylation.

2. Results and discussion

The synthesis of the pivotal intermediate **4** through dihydropyridines **6** and **7** is depicted in Scheme 2. The benzhydryl group was selected as the nitrogen substituent for the starting pyridinium salt **5** as it is easily installed in a 3-acylpyridine and can be removed in relatively mild conditions.[8d,9] Based on our own experience, we decided to use the enolate of methyl α-(methylsulfanyl)acetate[10] as the nucleophilic partner for the introduction of the acetate chain at the 4-position of the pyridine ring.[11] Satisfactorily, the reaction of this enolate with **5**, followed by acylation with trichloroacetic anhydride gave dihydropyridine **6** (70% yield, mixture of epimers) along with minor amounts of regioisomeric 1,2-dihydropyridines (not isolated). 1,4-Dihydropyridine **6** was subjected to haloform reaction with sodium methoxide and radical desulfurization with Ph_3SnH–AIBN to give **7** in 75% yield.

With 1,4-dihydropyridine **7** in hand, attention was turned to the oxidative step. We initially tested the oxidative reagent system (TFA–phenol–Pd/C, 50 °C) we had successfully used for the tandem *N*-dealkylation–oxidation of 4-unsubstituted *N*-(benzhydryl)dihydropyridines.[9,12] However, under these conditions the desired pyridine **4** was isolated in poor yields (15% yield) and pyridine **8**,[13] lacking the acetic ester, was the major product (50% yield). As



1 R = CO_2Me Jasminine
2 R = H Jasminidine
3 Dihydrojasminine

Figure 1. Jasminine and related alkaloids.

Keywords: Dihydropyridines; Pyridines; Acylation; Alkaloids.
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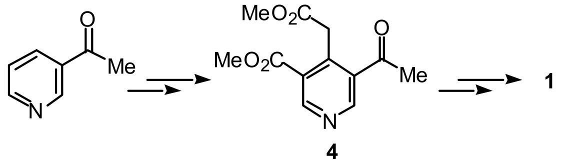
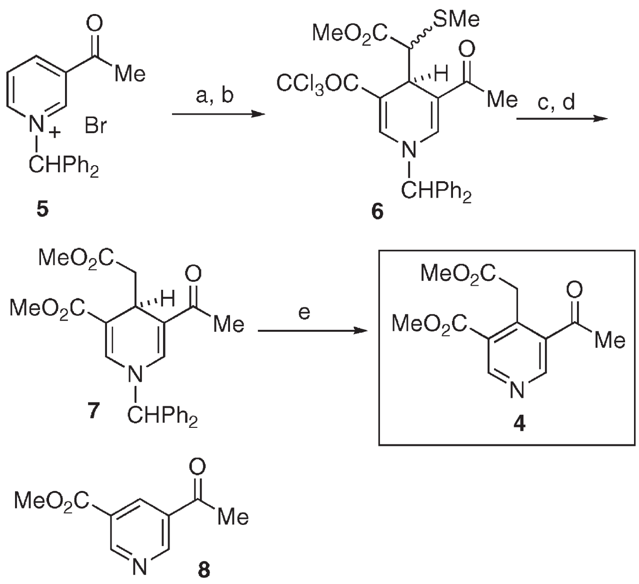
doi:10.1016/j.tet.2004.06.027



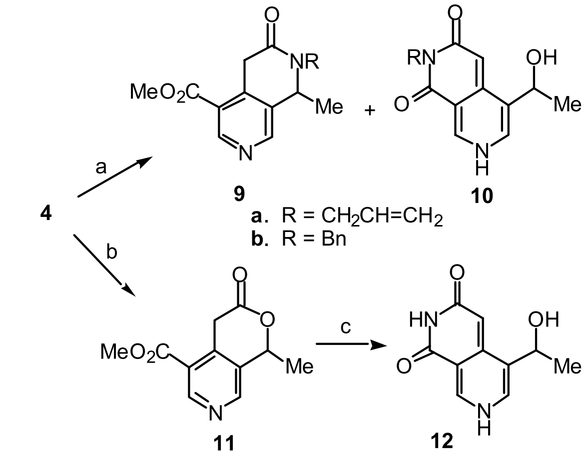
Scheme 1. Synthetic approach.

formation of **8** is presumably the result of a retroaddition reaction that occurs from the initially formed *N*-unsubstituted dihydropyridine, we reasoned that in order to minimize this undesired process oxidation should take place prior to *N*-dealkylation. We were proved right since when **7** was treated with $Mn(OAc)_3$ in TFA–acetic acid[14] and then with phenol the yield of pyridine **4** increased to 80%, with little or no formation of **8**.

Having established a functional protocol for the preparation of pyridine **4**, we then proceeded to construct the naphthyridine ring system of jasminine (**1**) using a reductive amination–lactamization tandem reaction sequence.[15] We examined first the behavior in this process of ammonia equivalents such as allylamine or benzylamine. After recovering the starting material under standard reaction conditions using $Na(CN)BH_3$[16] or $Na(AcO)_3BH$[15,17] as reducing agents, the desired jasminine lactams **9a** and **9b** were obtained, although in low yield (20%), when the reductive amination was effected in the presence of decaborane acting as both the catalyst for the imine formation and the reducing agent (Scheme 3).[18,19] Significantly, bicyclic imides **10a** and **10b** were also isolated from the reaction mixtures in 40% and 10% yields, respectively. These compounds have the 2,7-naphthyridin-1,3-dione skeleton characteristic of the alkaloid sebasnine,[20] which was shown by NMR to be in the highly conjugated 4-alkylidene-1,4-dihydropyridine tautomeric form depicted in **10**. We suspected that formation of **10** involved the initial reduction of the acetyl carbonyl group of **4**, followed by aminolysis of a lactone intermediate, with subsequent cyclization to the aromatic ester group. This hypothesis could be confirmed since reduction of **4** with $NaBH_4$ in methanol gave lactone **11** (80% yield), which upon a short exposure to a methanolic solution of ammonia afforded imide **12**, the *N*-unsubstituted derivative of **10**, in 78% yield.

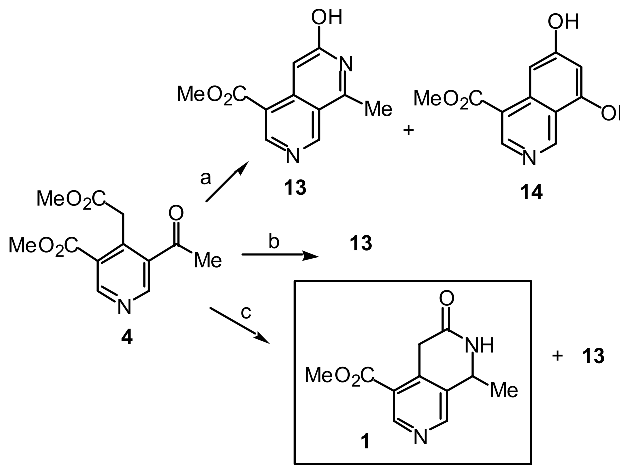


Scheme 2. Synthesis of pyridine **4**. Reagents and conditions: (a) $MeSCH_2CO_2Me$, LDA, THF, −78 °C, 30 min, then −40 °C, 2 h; (b) $(Cl_3CCO)_2O$, triethylamine, rt, 12 h, 70%; (c) MeONa, MeOH, rt, 1 min; (d) Ph_3SnH, AIBN, benzene, reflux, 2 h, 75%; (e) $Mn(OAc)_3{\cdot}2H_2O$, 1:1 TFA–AcOH, 45 °C, 1h, then phenol, 45 °C, 2 h, 80%.



Scheme 3. Reagents and conditions: (a) Allylamine or benzylamine, $B_{10}H_{14}$, MeOH, rt, 48 h, **9a**: 20%, **10a**: 40%, **9b**: 20%, **10b**: 10%; (b) $NaBH_4$, MeOH, 0 °C, 10 min, 80%; (c) NH_3, MeOH, rt, 1 h, 78%.

The low yield of lactams **9** and the need for an additional *N*-deprotection step to complete the synthesis[21] motivated us to address the synthesis of jasminine (**1**) using a reductive amination with ammonia. Again this seemingly simple task was complicated by the low reactivity of the acetyl carbonyl group and the intensive functionalization of our substrate. Thus, the use of standard protocols such as $AcONH_4$–$Na(CN)BH_3$ or $AcONH_4$–$Na(AcO)_3BH$ resulted, as above, in the recovery of **4**. On the other hand, several noteworthy results were obtained when the amination reaction was carried out with more nucleophilic reagents or under more energetic conditions. Exposure of **4** to $MeAl(Cl)NH_2$[22,23] at room temperature in benzene resulted in the formation of a nearly equimolecular mixture of two fully aromatic bicycles, **13** and **14**, in 60% yield (Scheme 4). Whereas



Scheme 4. Synthesis of (±)-jasminine (**1**). Reagents and conditions: (a) $MeAl(Cl)NH_2$, C_6H_6, rt, 5 h, **13**: 30%, **14**: 30%; (b) Ammonium formate, 150 °C, 10 min, 75%; (c) NH_4Cl, Et_3N, $Ti(i\text{-}PrO)_4$, rt, overnight, then $NaBH_4$, rt, 2 h, **1**: 25%; **13**: 40%.

dihydroxyisoquinoline **14** is the result of a Claisen condensation promoted by the basic character of the reagent, formation of naphthyridinol **13**, a didehydro derivative of the natural product, is striking as it involves an intramolecular acylation at the imine stage. This premature lactamization precludes the subsequent reduction to jasminine as treatment of **4** with ammonium formate (both an ammonia source and a reducing agent)[24] at 150 °C for a short time (10 min) resulted in the exclusive formation of **13** in 75% yield. This serious drawback could be partially countered by the sequential treatment of **4** with ammonia, generated in situ from NH_4Cl and Et_3N at room temperature in the presence of Ti(*i*-PrO)$_4$, and then with $NaBH_4$.[25] Under these conditions, **13** was still the major product (40% yield), but the desired lactam **1**, (±)-jasminine, was isolated in a consistent, reproducible 25% yield. Our synthetic product displayed ^{1}H NMR data identical to those reported for the natural product,[2,3] and its ^{13}C NMR and analytical data were in full agreement with the proposed structure.

3. Conclusions

In conclusion, the present work provides the first total synthesis of the naphthyridine alkaloid jasminine, not an easy target in spite of its apparent structural simplicity. The strategy employed hinges on the straightforward preparation of a 3,4,5-trisubstituted pyridine from a 3-substituted pyridine, emphasizing the well-known utility of 1,4-dihydropyridines as intermediates for alkaloid synthesis.

4. Experimental

4.1. General

All nonaqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points are uncorrected. Chemical shifts of NMR spectra are reported in ppm downfield (δ) from Me_4Si.

4.1.1. 3-Acetyl-1-benzhydrylpyridinium bromide (5). A solution of 3-acetylpyridine (7 mL, 63.8 mmol) and bromodiphenylmethane (18.9 g, 76.6 mmol) in dry acetone (60 mL) was stirred at rt for a week. The white solid which appeared was collected by filtration and washed with Et_2O to give pyridinium salt **5** (12.8 g, 55%): mp 145–6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (s, 3H), 7.31 (m, 4H), 7.49 (m, 6H), 7.84 (s, 1H), 8.30 (dd, J=6, 8.1 Hz, 1H), 9.10 (d, J=8.1 Hz, 1H), 9.18 (d, J=6 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (75.4 MHz) δ 27.7, 76.0, 129.0, 129.2, 129.5, 129.7, 135.8, 136.0, 145.1, 145.4, 146.6, 194.1.

4.1.2. Methyl 3-acetyl-1-benzhydryl-α-(methylsulfanyl)-5-(trichloroacetyl)-1,4-dihydropyridine-4-acetate (6). LDA (1.5 M in cyclohexane, 4.40 mL, 6.60 mmol) was slowly added to a cooled (−78 °C) solution of methyl (methylsulfanyl)acetate (0.72 mL, 6.60 mmol) in dry THF (110 mL), and the resulting solution was stirred at −78 °C for 30 min. Pyridinium salt **5** (2 g, 5.50 mmol) was added in portions at −78 °C, and the mixture was allowed to rise to −40 °C. After 2 h at this temperature, the mixture was treated with Et_3N (4.60 mL, 33 mmol) and TCAA (6 mL, 33 mmol) and stirred at rt overnight. The reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. The solvent was removed and the crude product was chromatographed (75:25 hexanes–AcOEt) to give **6** (2.12 g, 70%, mixture of epimers): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.04 and 2.05 (2s, 3H), 2.20 and 2.27 (2s, 3H), 3.42 and 3.43 (2d, J=4.8, 5.1 Hz, 1H), 3.62 and 3.69 (2s, 3H), 4.88 and 4.93 (2d, J=5.1, 4.8 Hz, 1H), 6.10 (s, 1H), 7.20–7.45 (m, 11H), 7.86 and 7.90 (2s, 1H). Anal. Calcd for $C_{26}H_{24}Cl_3NO_4S$: C, 56.48; H, 4.38; N, 2.53. Found: C, 56.12; H, 4.36; N, 2.47.

4.1.3. Methyl 3-acetyl-1-benzhydryl-5-(methoxycarbonyl)-1,4-dihydropyridine-4-acetate (7). A solution of (trichloroacetyl)-1,4-dihydropyridine **6** (2 g, 3.6 mmol) in THF (65 mL) was added to a solution of MeONa (10.5 mmol) in MeOH (35 mL), and the mixture was stirred at rt for 1 min. The solvent was removed and the resulting residue was partitioned between Et_2O and H_2O, and extracted with Et_2O. After concentration of the organic extracts, the resulting residue was dissolved in C_6H_6 (100 mL) and treated with triphenyltin hydride (0.89 mL, 3.5 mmol) and AIBN (58 mg. 0.35 mmol). After stirring at reflux temperature for 1 h, triphenyltin hydride (0.89 mL, 3.5 mmol) and AIBN (58 mg. 0.35 mmol) were again added and heating was continued for 2 h. The solvent was removed and the resulting residue was partitioned between Et_2O and H_2O, and extracted with Et_2O. The organic extracts were concentrated and the residue was chromatographed (75:25 hexanes–AcOEt) to give **7** (1.13 g; 75%): ^{1}H NMR (300 MHz) δ 2.07 (s, 3H), 2.45 and 2.53 (2dd, J=5.1, 13.8 Hz, 2H), 3.55 (s, 3H), 3.67 (s, 3H), 4.36 (t, J=5.1 Hz, 1H), 5.91 (s, 1H), 7.05 (d, J=1.2 Hz, 1H), 7.23 (m, 5H), 7.39 (m, 6H); ^{13}C NMR (75.4 MHz) δ 24.6, 29.0, 39.9, 51.1, 51.3, 70.7, 107.3, 116.3, 128.2, 128.3, 128.4, 128.5, 128.9, 137.7, 137.8, 138.6, 139.6, 166.8, 172.0, 194.8. Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.28; H, 6.16; N, 3.23.

4.1.4. Methyl 3-acetyl-5-(methoxycarbonyl)pyridine-4-acetate (4). $Mn(AcO)_3\cdot 2H_2O$ (0.54 g, 2 mmol) was added to a solution of 1,4-dihydropyridine **7** (0.42 g, 1 mmol) in AcOH–TFA (1:1, 20 mL). After stirring at 45 °C for 1.5 h, phenol (1.32 g, 14 mmol) was added in 7 portions over 2 h at 45 °C. The reaction mixture was cooled (ice bath), basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. The solvent was removed and the residue was chromatographed (58:42 hexanes–AcOEt) to give pyridine **4** (0.2 g, 80% yield) as a yellow solid: mp 20–22 °C; ^{1}H NMR (400 MHz) δ 2.67 (s, 3H), 3.72 (s, 3H), 3.95 (s, 3H), 4.39 (s, 2H), 9.05 (s, 1H), 9.20 (s, 1H); ^{13}C NMR (100.6 MHz) δ 30.2, 34.8, 52.5, 53.0, 127.8, 135.0, 144.3, 152.4, 153.9, 166.1, 170.7, 200.1. For the hydrochloride: mp 60–61 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 3H), 3.59 (s, 3H), 3.85 (s, 3H), 4.17 (s, 2H), 9.08 (s, 1H), 9.22 (s, 1H). Anal. Calcd for $C_{12}H_{13}NO_5\cdot HCl$: C, 50.10; H, 4.90; N, 4.87. Found: C, 50.52; H, 4.96; N, 4.91.

4.2. Tandem reductive amination–lactamization from pyridine 4 and primary amines

A mixture of pyridine **4** (0.25 g, 1 mmol), the appropriate amine (10 mmol) and $B_{10}H_{14}$ (37 mg, 0.30 mmol) in MeOH (15 mL) was stirred at rt for 48 h. The solvent was removed and the resulting residue was chromatographed to give naphthyridines **9** and **10**.

4.2.1. Methyl 2-allyl-1,4-dihydro-1-methyl-3-oxo-2*H*−2,7-naphthyridine-5-carboxylate (9a). Elution with 99:1 CH_2Cl_2–MeOH; yield 20%; ^{1}H NMR (300 MHz) δ 1.46 (d, J=6.6 Hz, 3H), 3.68 (dd, J=6.9, 16.2 Hz, 1H), 3.79 and 4.46 (2d, J=21 Hz, 2H), 3.96 (s, 3H), 4.65 (q, J=6.6 Hz, 1H), 4.73 (dddd, J=1.8, 1.8, 4.8, 16.2 Hz, 1H), 5.20 (m, 2H), 5.78 (dddd, J=4.8, 6.9, 10.2, 17.1 Hz, 1H), 8.54 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (75.4 MHz) δ 22.2, 34.7, 47.2, 52.5, 53.7, 118.0, 123.9, 132.4, 133.5, 142.3, 149.0, 150.4, 165.5, 166.7; HRMS calcd for $C_{14}H_{16}N_2O_3$ 260.1157, found 260.1151.

4.2.2. 2-Allyl-5-(1-hydroxyethyl)-2,7-naphthyridin-1,3-dione (10a). Elution with 96:4 CH_2Cl_2–MeOH; yield 40%; yellow solid; mp 205–6 °C; ^{1}H NMR (200 MHz, DMSO-d_6, HSQC and HMBC) δ 1.30 (d, J=6.5 Hz, 3H, CH_3), 4.46 (d, J=5 Hz, 2H, CH_2–CH=CH_2), 4.67 (m, 1H, CH_3CH), 4.97 and 5.01 (2m, 2H, CH_2=), 5.23 (s, 1H, 4-H), 5.33 (d, J=4.5 Hz, 1H, OH), 5.80 (m, 1H, CH=), 7.47 (s, 1H, 6-H), 8.30 (s, 1H, 8-H); ^{13}C NMR (75.4 MHz, DMSO-d_6, HSQC and HMBC) δ 22.7 (CH_3), 40.8 (CH_2–CH=CH_2), 63.2 (CH_3CH), 88.6 (C-4), 109.6 (C-8a), 115.7 (CH_2=), 128.6 (C-6), 130.7 (C-5), 133.8 (CH=), 139.1 (C-8), 141.8 (C-4a), 162.9 (C-1), 163.4 (C-3); CI-MS m/z 247 (MH^+), 229. Anal. Calcd for $C_{13}H_{14}N_2O_3$.1/3H_2O: C, 61.91; H, 5.86; N, 11.11. Found: C, 61.72; H, 5.82; N, 10.97.

4.2.3. Methyl 2-benzyl-1,4-dihydro-1-methyl-3-oxo-2*H*-2,7-naphthyridine-5-carboxylate (9b). Elution with 99:1 CH_2Cl_2–MeOH; yield 20%; ^{1}H NMR (200 MHz) δ 1.42 (d, J=7 Hz, 3H), 3.84 and 4.55 (2d, J=20.8 Hz, 2H), 3.97 (s, 3H), 4.17 and 5.44 (2d, J=15 Hz, 2H), 4.55 (q, J=7 Hz, 1H), 7.20–7.40 (m, 5H), 8.40 (s, 1H), 9.05 (s, 1H); HRMS calcd for $C_{18}H_{18}N_2O_3$ 310.1313, found 310.1324.

4.2.4. 2-Benzyl-5-(1-hydroxyethyl)-2,7-naphthyridin-1,3-dione (10b). Elution with 96:4 CH_2Cl_2–MeOH; yield 10%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.30 (d, J=6.2 Hz, 3H), 4.69 (q, J=6.2 Hz, 1H), 5.06 (s, 2H), 5.22 (s, 1H), 7.25–7.35 (m, 5H), 7.53 (s, 1H), 8.33 (s, 1H).

4.2.5. 5-(1-Hydroxyethyl)-2,7-naphthyridin-1,3-dione (12). $NaBH_4$ (15 mg, 0.40 mmol) was added to a solution of pyridine **4** (0.1 g, 0.40 mmol) in MeOH (4 mL) cooled at 0 °C, and the mixture was stirred at 0 °C for 10 min. The solvent was removed and the residue was partitioned between H_2O_2 and CH_2Cl_2, and extracted with CH_2Cl_2. The organic extracts were concentrated and the residue was chromatographed (CH_2Cl_2) to give lactone **11** (70 mg, 80% yield): ^{1}H NMR (300 MHz) δ 1.82 (d, J=6.9 Hz, 3H), 3.98 (s, 3H), 4.08 and 4.47 (2d, J=20.1 Hz, 2H), 5.59 (q, J=6.9 Hz, 1H), 8.65 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.8, 33.1, 52.6, 73.9, 123.3, 131.8, 141.6, 147.7, 151.5, 165.1, 168.3.

Lactone **11** (0.11 g, 0.50 mmol) in a saturated methanolic solution of NH_3 (4 mL) was stirred at rt for 1 h. The solvent was removed and the residue was triturated with Et_2O to give **12** (80 mg, 78% yield) as a yellow solid: mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, J=6.3 Hz, 3H), 4.63 (q, J=6 Hz, 1H), 5.07 (s, 1H), 5.20–5.40 (br s, 1H), 7.43 (s, 1H), 8.23 (s, 1H), 10.55 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 22.5, 63.1, 88.9, 110.2, 128.5, 130.6, 138.3, 143.3, 163.8, 164.9; CI-MS m/z 207 (MH^+), 189. Anal. Calcd for $C_{10}H_{10}N_2O_3$.1/2H_2O: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.73; H, 5.06; N, 12.70.

4.2.6. Methyl 3-hydroxy-1-methyl-2,7-naphthyridine-5-carboxylate (13). A mixture of pyridine **4** (0.1 g, 0.40 mmol) and ammonium formate (0.1 g, 1.59 mmol) was heated at 150 °C for 10 min. The solid residue was triturated with CH_2Cl_2 to give **13** (65 mg, 75% yield) as a yellow solid: mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6, major tautomer) δ 2.90 (s, 3H), 3.90 (s, 3H), 7.44 (s, 1H), 8.93 (s, 1H), 9.50 (s, 1H), 12.0 (br s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6, major tautomer) δ 20.3, 52.4, 97.3, 117.2, 140.4, 150.0, 156.6, 161.2, 163.0, 165.9; CI-MS m/z 219 (MH^+). Anal. Calcd for $C_{11}H_{10}N_2O_3 \cdot H_2O$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.81; H, 5.26; N, 11.72.

4.2.7. Reaction of pyridine 4 with $CH_3AlClNH_2$. A solution of $CH_3AlClNH_2$[22] in C_6H_6 (0.67 M, 66 µl, 0.044 mmol) was added to a solution of pyridine **4** (10 mg, 0.040 mmol) in C_6H_6 (0.5 mL) and the mixture was stirred at rt for 5 h. The solvent was removed and the resulting residue was partitioned between saturated aqueous $NaHCO_3$ and AcOEt, and extracted with AcOEt. The organic extracts were concentrated and the residue was chromatographed (95:5 CH_2Cl_2–MeOH). First elution gave methyl 6,7-dihydroxyisoquinoline-4-carboxylate **14**: 2.6 mg (30%); ^{1}H NMR (300 MHz, CD_3OD) δ 3.96 (s, 3H), 6.56 (d, J=2.4 Hz, 1H), 7.70 (d, J=2.4 Hz, 1H), 8.85 (s, 1H), 9.36 (s, 1H); CI-MS m/z 220 (MH^+), 194; HRMS calcd for $C_{11}H_9NO_4$ 219.0529, found 219.0522. Further elution gave **13**: 2.6 mg (30%).

4.2.8. (±)-Jasminine (1). A mixture of pyridine **4** (0.1 g, 0.40 mmol), Ti(i-PrO)$_4$ (0.24 mL, 0.80 mmol), NH_4Cl (43 mg, 0.80 mmol) and Et_3N (0.11 mL, 0.80 mmol) in dry MeOH (1 mL) was stirred in a sealed tube at rt overnight. $NaBH_4$ (23 mg, 0.60 mmol) was then added and the resulting mixture was stirred at rt for 7 h. The reaction mixture was poured into a 2 M aqueous solution of NH_3 (3 mL), and the precipitate was filtered and washed successively with CH_2Cl_2 and 1:1 CH_2Cl_2–MeOH. Solvents were removed and the resulting residue was chromatographed. Elution with 97:3 CH_2Cl_2–MeOH gave **1** (22 mg, 25%) as a pale yellow solid; mp 163–4 °C (CH_2Cl_2); ^{1}H NMR (400 MHz) δ 1.59 (d, J=6.4 Hz, 3H), 3.96 (s, 3H), 3.99 and 4.15 (2d, J=21.6 Hz, 2H), 4.80 (br q, J=5.6 Hz, 1H), 6.77 (br s, 1H), 8.60 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (100.6 MHz) δ 25.0, 34.2, 49.7, 52.8, 124.3, 132.6, 142.1, 149.9, 150.9, 165.9, 169.4. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.50; H, 5.71; N, 12.61. Elution with 95:5 CH_2Cl_2–MeOH gave **13**: 35 mg (40%).

Acknowledgements

Financial support from the 'Ministerio de Ciencia y Tecnología' (MCYT), Spain (project BQU2000-0785) and MCYT-FEDER (project BQU2003-04967-C02-02) is gratefully acknowledged. We also thank the DURSI (Generalitat de Catalunya) for Grant 2001SGR00084 and for a fellowship to M.M.

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Tetrahedron 60 (2004) 6791–6805

On the tautomerism of pyrazolones: the geminal ^2J[pyrazole C-4,H-3(5)] spin coupling constant as a diagnostic tool☆

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Received 5 April 2004; revised 28 May 2004; accepted 7 June 2004

Abstract—The tautomerism of pyrazolones unsubstituted at position 3(5) has been investigated by ^{13}C- and ^{1}H NMR spectroscopic methods. Apart from chemical shift considerations and NOE effects the magnitude of the geminal ^2J[pyrazole C-4,H3(5)] spin coupling constant permits the unambiguous differentiation between 1*H*-pyrazol-5-ol (OH) and 1,2-dihydro-3*H*-pyrazol-3-one (NH) forms. Whereas 1*H*-pyrazol-5-ols and 2,4-dihydro-3*H*-pyrazol-3-ones (CH-form) exhibit ^2J values of approximately 9–11 Hz, in 1,2-dihydro-3*H*-pyrazol-3-ones this coupling constant is considerably reduced to 4–5 Hz. This can be mainly attributed to the removal of the lone-pair at pyrazole *N*−1 in the latter due to protonation or alkylation. According to the data obtained, 2-substituted 4-acyl-1,2-dihydro-3*H*-pyrazol-3-ones exist predominantly as pyrazol-5-ols in $CDCl_3$ or benzene-d_6 solution, whereas in DMSO-d_6 also minor amounts of NH tautomer may contribute to the tautomeric composition. 2,4-Dihydro-2-phenyl-3*H*-pyrazol-3-one (1-phenyl-2-pyrazolin-5-one) exists in benzene-d_6 solely in the CH-form, in $CDCl_3$ as a mixture of CH and OH-form, whereas in DMSO-d_6 a fast equilibrium between OH and NH isomer (with the former far predominating) is probable. For 11 compounds, including neutral and protonated molecules, we have calculated at the B3LYP/6-311++G** level, the $^2J(^1H,^{13}C)$ coupling constants which are in good agreement with those measured experimentally.

1. Introduction

The tautomerism of pyrazolones is an old problem of pyrazole chemistry and thus it has been the subject of a considerable number of studies.[2–13] In principle, for compounds unsubstituted at pyrazole C-4, OH- (**A**), CH- (**B**) and NH-isomers (**C**) are possible (Fig. 1, upper line), assigned as 1*H*-pyrazol-5-ols, 2,4-dihydro-3*H*-pyrazol-3-ones and 1,2-dihydro-3*H*-pyrazol-3-ones according to *Chemical Abstracts* nomenclature. In the case of 4-acyl congeners, which are popular chelating and extracting ligands for metal ions[14] as well as starting materials for biologically active compounds,[15] additional species (**D**, **E**, middle line) have to be considered since in this case the 4-substituent can participate in tautomerism and also stabilization by intramolecular hydrogen bonds may occur (**A′**, **D′**, Fig. 1, lower line). Whereas in the solid state unambiguous results were obtained on the basis of X-ray crystallographic data,[8–12] the situation in solution is much more complicated and the determination of the tautomeric composition can be difficult. The simultaneous presence of several tautomeric forms can either result in distinct signal sets in the NMR spectra due to the individual isomers (slow interconversion rate on the NMR timescale) or in the observation of one averaged signal set in case of rapid chemical exchange. Fast exchange frequently occurs between OH- and NH-tautomers, whereas those equilibria which involve a proton moving from a carbon atom (CH-tautomers) are normally slow.[16]

Nearly all investigations regarding pyrazolone tautomerism were carried out with 3(5)-methyl substituted model compounds (R^3=Me) due to the easy availability of the latter upon reaction of alkyl acetoacetates with substituted hydrazines. In a recent study, we concluded that 4-acyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones (Fig. 1: R^1=Ph, R^3=Me, R^4=Me, Ph, 2-thienyl, styryl) are present in the chelated 5-hydroxypyrazole form (**A′**) in apolar solvents such as $CDCl_3$ or benzene-d_6, whereas in

☆ See Ref. 1.

Keywords: Pyrazolones; Tautomerism; Methylation; Spin coupling constants; NOE-difference spectroscopy; DFT-calculations.

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doi:10.1016/j.tet.2004.06.039

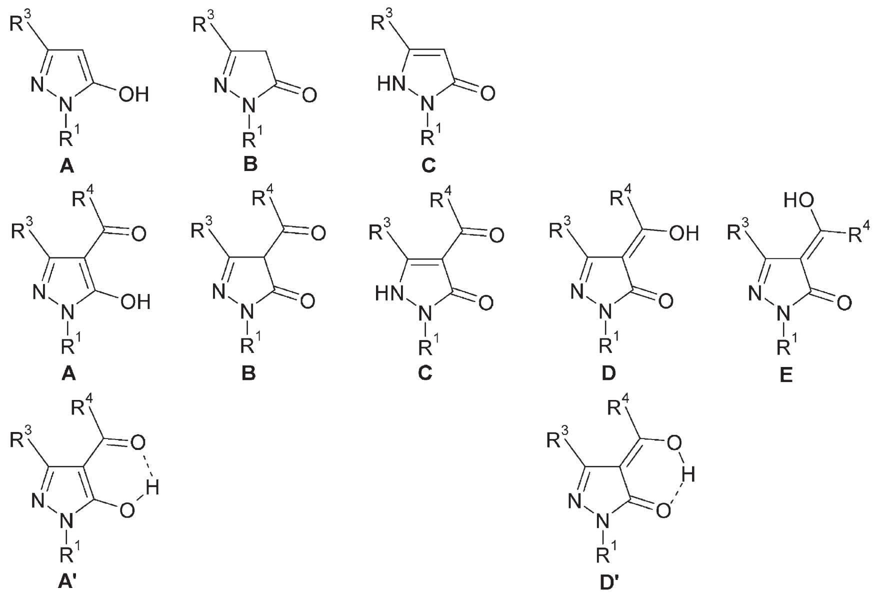


Figure 1. Tautomeric forms of (4-acyl)pyrazolones.

DMSO-d_6 solution additionally, some NH-tautomer (**C**) seems to contribute to the tautomeric composition.[12] Continuing with our previous studies[12,15,17–23] on pyrazolones (hydroxypyrazoles) we here present detailed NMR spectroscopic investigations with representatives **2** unsubstituted at C-3(5), as well as with corresponding 'fixed' tautomers—such as *O*-methyl (**3**) and *N*-methyl derivatives (**4**) (Fig. 2) or suitable condensed systems—in order to obtain insight into the tautomeric behavior of the title compounds **2**. In compounds **2-4**, the hydrogen atom at pyrazole H-3(5) on one hand can act as an irradiation target or as a probe in NOE experiments, on the other hand this proton is involved in different $^{13}C,^{1}H$ spin couplings. The value of the corresponding coupling constants and their changes upon structural alterations may help to answer the questions raised.

2. Results and discussion

2.1. Chemistry

Compound **1** was prepared in two steps from diethyl ethoxymethylenemalonate and phenylhydrazine according to literature,[24,25] 4-acylpyrazolones **2b-e** were obtained from **1** and the corresponding carboxylic acid chlorides via the method described by Jensen (RCOCl, $Ca(OH)_2$, dioxane).[26] Treatment of **1** with methyl 4-toluenesulfonate in DMF in the presence of potassium carbonate afforded 5-methoxy-1-phenyl-1*H*-pyrazole (**3a**); in contrast, the use of xylene as solvent and performing the reaction without addition of a base led to the corresponding *N*-methyl derivative **4a**. Products **3b-e** and **4b-e** were obtained by methylation of compounds **2b-e**: whereas heating of the starting materials with dimethyl sulfate in alkaline medium mainly afforded *N*-methyl derivatives **4**, upon treatment with trimethylsilyl-diazomethane/HBF_4 in dichloromethane isomeric mixtures were obtained, with the *O*-methyl derivatives **3** far predominating.[19] The 4-cinnamoyl-5-methoxypyrazole **3e** was synthesized from **2e** via Mitsunobu reaction (diethyl azodicarboxylate, triphenylphosphine, methanol).[20] All syntheses were devoted to obtain material for the NMR-spectroscopic investigations, thus no efforts were undertaken to optimize yields.

2.2. NMR spectroscopic investigations

The NMR data of the compounds investigated are presented in Tables 1–7. It should be mentioned that for all proton and carbon resonances complete and unambiguous assignments were achieved by combined application of standard NMR techniques (^{1}H-coupled ^{13}C NMR, APT,[27] NOE-difference,[28] 1D-TOCSY,[29] 1D-HETCOR,[30] HMQC,[31] and long-range INEPT experiments with selective excitation in a 1D[32] and a 2D-version[33]) without relying on empirical rules.

2.2.1. Chemical shift considerations. The *O*-methyl (**3**) and *N*-methylpyrazoles (**4**) can be seen as fixed OH or NH-tautomers and thus can provide valuable data for the

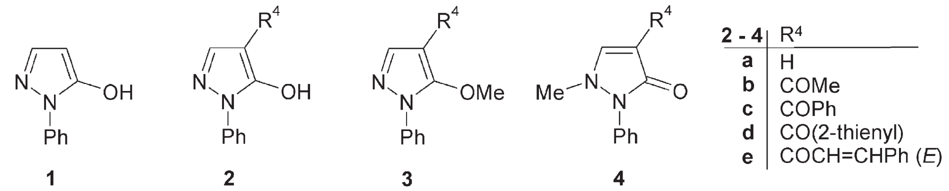


Figure 2. Investigated pyrazolone (**1**≡**2a**) and 4-acylpyrazol-5-ones (**2b-e**)≡(4-acyl)-5-hydroxypyrazoles and their fixed *O*-Me (**3**) and *N*-Me (**4**) derivatives.

Table 1. ^{1}H NMR chemical shifts (δ, ppm) of compounds **1** and **2** (numbering of atoms for the hydroxypyrazole form)

No.	Solvent	H-3	*N*-phenyl			OH	H of 4-substituent R
			H-2,6	H-3,5	H-4		
1[a]	$CDCl_3$	7.46	7.85	7.41	7.22	—	3.47 (d, ^3J=1.1 Hz, 2H, H-4)
1[b]	$CDCl_3$	7.24	7.58	7.35	7.24	9.78	5.38 (d, ^3J=2.2 Hz, 1H, H-4)
1[a]	C_6D_6	6.30	8.26	7.22	6.95	—	2.19 (d, ^3J=1.3 Hz, 2H, H-4)
1[b]	DMSO-d_6	7.40	7.75	7.44	7.24	11.57	5.54 (d, ^3J=1.9 Hz, 1H, H-4)
2b	$CDCl_3$	7.79	7.83	7.46	7.32	10.18	2.43 (Me)
2b	DMSO-d_6	8.06	7.71	7.49	7.33	10.32	2.38 (Me)
2c	$CDCl_3$	7.97	7.90	7.49	7.34	11.80	7.96 (Ph-2,6), 7.55 (Ph-3,5), 7.64 (Ph-4)
2c	C_6D_6	7.67	8.07	7.15	6.96	10.68	7.73 (Ph-2,6), 7.03 (Ph-3,5), 7.12 (Ph-4)
2c	DMSO-d_6	7.97	7.77	7.52	7.37	9.12	7.88 (Ph-2,6), 7.56 (Ph-3,5), 7.65 (Ph-4)
2d	$CDCl_3$	8.12	7.88	7.48	7.33	11.10	7.98 (Th-3), 7.23 (Th-4), 7.73 (Th-5)[c]
2d	C_6D_6	7.84	8.02	7.13	6.96	11.68	7.46 (Th-3), 6.54 (Th-4), 6.89 (Th-5)[c]
2d	DMSO-d_6	8.29	7.76	7.52	7.37	10.63	8.13 (Th-3), 7.29 (Th-4), 8.02 (Th-5)[c]
2e	$CDCl_3$	7.93	7.93	7.46	7.29	12.05	7.05 (COCH)[d], 7.88 (C*H*Ph)[d], 7.64 (Ph-2,6), 7.44 (Ph-3,5), 7.44 (Ph-4)
2e	C_6D_6	7.50	8.23	7.18	6.96	10.75	6.57 (COCH)[d], 7.81 (C*H*Ph)[d], 7.13 (Ph-2,6), 7.04 (Ph-3,5), 7.04 (Ph-4)
2e	DMSO-d_6	8.42	7.81	7.49	7.31	11.79	7.75 (COCH)[d], 7.73 (C*H*Ph)[d], 7.82 (Ph-2,6), 7.46 (Ph-3,5), 7.46 (Ph-4)

[a] CH-isomer.
[b] OH-isomer.
[c] Thiophene ring: $^3J(3,4)$=3.8 Hz, $^3J(4,5)$=5.0 Hz, $^4J(3,5)$=1.1 Hz.
[d] ^3J=15.9 Hz.

Table 2. ^{1}H NMR chemical shifts (δ, ppm) of 5-methoxy-1-phenyl-1*H*-pyrazoles **3**

No.	Solvent	H-3	*N*-phenyl			OMe	H of 4-substituent R
			H-2,6	H-3,5	H-4		
3a	$CDCl_3$	7.50	7.72	7.42	7.27	3.93	5.66 (d, ^3J=2.0 Hz, H-4)
3a	DMSO-d_6	7.50	7.66	7.46	7.29	3.92	5.87 (d, ^3J=2.0 Hz, H-4)
3b	$CDCl_3$	7.92	7.63	7.46	7.35	4.05	2.46 (Me)
3c	$CDCl_3$	7.78	7.70	7.48	7.37	4.10	7.89 (Ph-2,6), 7.50 (Ph-3,5), 7.59 (Ph-4)
3c	DMSO-d_6	7.85	7.68	7.55	7.43	4.01	7.84 (Ph-2,6), 7.56 (Ph-3,5), 7.65 (Ph-4)
3d	$CDCl_3$	8.00	7.69	7.48	7.37	4.10	7.81 (Th-3), 7.19 (Th-4), 7.69 (Th-5)[a]
3d	C_6D_6	7.91	7.71	7.10	6.97	3.68	7.48 (Th-3), 6.62 (Th-4), 6.96 (Th-5)[a]
3d	DMSO-d_6	8.17	7.67	7.55	7.44	4.02	7.93 (Th-3), 7.28 (Th-4), 8.05 (Th-5)[a]
3e	$CDCl_3$	8.08	7.70	7.48	7.37	4.11	7.34 (COCH)[b], 7.80 (C*H*Ph)[b], 7.64 (Ph-2,6), 7.41 (Ph-3,5), 7.41 (Ph-4)
3e	DMSO-d_6	8.52	7.66	7.55	7.45	4.11	7.68 (COCH)[b], 7.68 (C*H*Ph)[b], 7.85 (Ph-2,6), 7.45 (Ph-3,5), 7.45 (Ph-4)

[a] Thiophene ring: $^3J(3,4)$=3.8 Hz, $^3J(4,5)$=5.0 Hz, $^4J(3,5)$=1.1 Hz.
[b] ^3J=15.8 Hz.

Table 3. ^{1}H NMR chemical shifts (δ, ppm) of 1-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones **4**

No.	Solvent	H-5	*N*-phenyl			NMe	H of 4-substituent R
			H-2,6	H-3,5	H-4		
4a	$CDCl_3$	7.36	7.36	7.45	7.30	3.11	5.56 (d, ^3J=3.5 Hz, H-4)
4a	DMSO-d_6	7.91	7.33	7.48	7.31	3.11	5.42 (d, ^3J=3.5 Hz, H-4)
4b	$CDCl_3$	8.01	7.32	7.53	7.45	3.42	2.55 (Me)
4c	$CDCl_3$	8.09	7.31	7.48	7.40	3.41	7.98 (Ph-2,6), 7.40 (Ph-3,5), 7.49 (Ph-4)
4c	DMSO-d_6	8.52	7.41	7.55	7.46	3.45	7.83 (Ph-2,6), 7.46 (Ph-3,5), 7.56 (Ph-4)
4d	$CDCl_3$	8.23	7.36	7.53	7.45	3.46	8.95 (Th-3), 7.12 (Th-4), 7.60 (Th-5)[a]
4d	DMSO-d_6	8.66	7.44	7.57	7.49	3.47	8.69 (Th-3), 7.20 (Th-4), 7.91 (Th-5)[a]
4e	$CDCl_3$	8.17	7.34	7.53	7.45	3.45	8.21 (COCH)[b], 7.79 (C*H*Ph)[b], 7.65 (Ph-2,6), 7.33 (Ph-3,4,5)
4e	DMSO-d_6	8.64	7.43	7.54	7.52	3.46	8.05 (COCH)[c], 7.63 (C*H*Ph)[c], 7.64 (Ph-2,6), 7.41 (Ph-3,5), 7.40 (Ph-4)

[a] Thiophene ring: $^3J(3,4)$=3.8 Hz, $^3J(4,5)$=5.0 Hz, $^4J(3,5)$=1.1 Hz.
[b] ^3J=15.9 Hz.
[c] ^3J=16.0 Hz.

assignment of the tautomeric composition in the pyrazolones **1** or **2**. As a representative set of compounds, the thenoyl substituted pyrazoles **2d**, **3d**, and **4d** may serve for the following discussion. A comparison of the ^{13}C chemicals shifts (in $CDCl_3$) between these compounds shows, that the data of the tautomeric pyrazolone **2d**—in comparable parts such as the 1-phenyl moiety—resemble somewhat more those of the *O*-methyl **3d** than those of the

Table 4. ^{13}C NMR chemical shifts (δ, ppm) of compounds **1-3**

No.	Solvent	Pyrazole–C			OMe	C of *N*-phenyl				C=O	C of 4-substituent R
		C-3	C-4	C-5		C-1	C-2,6	C-3,5	C-4		
1[a]	$CDCl_3$	147.0	40.9	170.0	—	137.8	118.9	128.8	125.4	—	—
1[b]	$CDCl_3$	138.6	90.3	156.8	—	137.2	122.3	128.8	126.6	—	—
1[a]	C_6D_6	146.3	40.1	169.4	—	139.2	118.4	129.1	125.0	—	—
1[b]	DMSO-d_6	139.6	87.9	153.1	—	138.9	121.0	128.8	125.5	—	—
2b	$CDCl_3$	138.7	105.0	158.2	—	137.3	120.9	129.1	127.0	195.1	25.8 (Me)
2b	DMSO-d_6	140.4	106.1	155.7	—	137.4	121.6	129.0	126.6	191.1	26.6 (Me)
2c	$CDCl_3$	139.6	103.2	160.8	—	137.3	120.9	129.1	127.0	189.4	136.7 (Ph-1), 128.5 (Ph-2,6), 128.9 (Ph-3,5), 133.0 (Ph-4)
2c	C_6D_6	139.4	103.6	161.7	—	138.2	120.8	129.2	126.7	188.7	136.9 (Ph-1), 128.77 (Ph-2,6), 128.8 (Ph-3,5), 132.7 (Ph-4)
2c	DMSO-d_6	141.0	104.0	156.9	—	137.3	121.8	129.1	127.0	187.7	137.8 (Ph-1), 128.4 (Ph-2,6), 128.6 (Ph-3,5), 132.3 (Ph-4)
2d	$CDCl_3$	138.4	102.3	160.2	—	137.3	121.0	129.1	127.0	180.5	141.2 (Th-2), 132.3 (Th-3), 128.4 (Th-4), 133.7 (Th-5)
2d	C_6D_6	138.4	102.6	161.0	—	138.2	120.9	129.2	126.8	180.5	141.6 (Th-2), 132.3 (Th-3), 128.2 (Th-4), 133.6 (Th-5)
2d	DMSO-d_6	140.0	103.3	156.7	—	137.2	121.8	129.1	127.0	179.0	143.2 (Th-2), 132.7 (Th-3), 128.8 (Th-4), 134.2 (Th-5)
2e	$CDCl_3$	137.9	105.2	162.3	—	137.6	120.2	129.0	126.4	180.4	119.6 (COCH), 144.0 (*C*HPh), 134.2 (Ph-1), 128.6 (Ph-2,6), 129.0 (Ph-3,5), 131.0 (Ph-4)
2e	C_6D_6	137.9	105.7	163.5	—	138.7	120.1	129.2	126.3	179.7	119.9 (COCH), 143.6 (*C*HPh), 134.7 (Ph-1), 128.8 (Ph-2,6), 129.0 (Ph-3,5), 130.8 (Ph-4)
2e	DMSO-d_6	140.1	106.1	159.4	—	137.5	120.6	128.9	126.2	178.9	121.8 (COCH), 142.1 (*C*HPh), 134.5 (Ph-1), 128.7 (Ph-2,6), 129.0 (Ph-3,5), 130.6 (Ph-4)
3a	$CDCl_3$	139.6	85.7	155.5	58.8	138.6	122.0	128.7	126.2	—	—
3a	DMSO-d_6	139.6	86.4	155.3	59.2	138.3	121.5	128.9	126.1	—	—
3b	$CDCl_3$	141.6	109.7	154.7	62.6	137.5	123.2	129.1	127.8	191.1	28.4 (Me)
3c	$CDCl_3$	142.8	107.4	156.1	62.4	137.6	123.2	129.0	127.7	188.4	139.1 (Ph-1), 129.1 (Ph-2,6), 128.4 (Ph-3,5), 132.3 (Ph-4)
3c	DMSO-d_6	142.3	107.1	155.6	62.3	137.1	123.2	129.2	127.8	187.4	138.6 (Ph-1), 128.8 (Ph-2,6), 128.5 (Ph-3,5), 132.4 (Ph-4)
3d	$CDCl_3$	141.7	107.1	155.8	62.3	137.6	123.2	129.0	127.7	179.5	145.0 (Th-2), 132.7 (Th-3), 127.9 (Th-4), 133.3 (Th-5)
3d	C_6D_6	141.8	107.6	156.1	61.9	138.5	123.3	129.0	127.4	179.0	145.9 (Th-2), 132.5 (Th-3), 127.8 (Th-4), 132.9 (Th-5)
3d	DMSO-d_6	141.4	106.6	155.3	62.2	137.1	123.2	129.2	127.9	178.6	144.2 (Th-2), 133.4 (Th-3), 128.6 (Th-4), 134.5 (Th-5)
3e	$CDCl_3$	141.2	110.0	155.4	62.7	137.6	123.1	129.0	127.8	182.9	123.7 (COCH), 143.0 (*C*HPh), 134.8 (Ph-1), 128.3 (Ph-2,6), 128.9 (Ph-3,5), 130.3 (Ph-4)
3e	DMSO-d_6	141.9	109.7	155.1	62.6	137.1	123.2	129.2	127.9	181.9	124.1 (COCH), 142.0 (*C*HPh), 134.6 (Ph-1), 128.6 (Ph-2,6), 128.8 (Ph-3,5), 130.3 (Ph-4)

[a] CH-isomer.
[b] OH-isomer.

Table 5. ^{13}C NMR chemical shifts (δ, ppm) of compounds **4**

No.	Solvent	Pyrazole–C			NMe	C of N-phenyl				C=O	C of 4-substituent R
		C-5	C-4	C-3		C-1	C-2,6	C-3,5	C-4		
4a	$CDCl_3$	145.8	98.8	166.3	37.7	134.2	124.6	129.2	127.0	—	—
4a	DMSO-d_6	147.7	96.5	165.5	37.3	134.4	124.1	128.9	126.4	—	—
4b	$CDCl_3$	142.5	109.4	163.1	37.4	132.9	127.0	129.7	129.1	193.1	28.4 (Me)
4c	$CDCl_3$	145.1	108.3	161.8	37.4	132.9	127.0	129.5	128.9	188.1	137.9 (Ph-1), 129.3 (Ph-2,6), 127.8 (Ph-3,5), 132.1 (Ph-4)
4c	DMSO-d_6	145.2	105.5	161.2	36.9	133.0	127.4	129.3	128.7	186.8	138.6 (Ph-1), 128.7 (Ph-2,6), 127.9 (Ph-3,5), 131.6 (Ph-4)
4d	$CDCl_3$	145.3	108.6	161.4	37.5	133.0	127.2	129.7	129.2	178.8	144.7 (Th-2), 135.0 (Th-3), 128.2 (Th-4), 133.4 (Th-5)
4d	DMSO-d_6	144.7	105.5	160.5	37.0	132.8	127.7	129.3	128.8	177.6	144.9 (Th-2), 133.4 (Th-3), 128.2 (Th-4), 133.6 (Th-5)
4e	$CDCl_3$	143.3	109.4	163.0	37.4	132.8	127.1	129.7	129.2	183.5	124.2 (COCH), 142.0 (CHPh), 135.3 (Ph-1), 128.6 (Ph-2,6), 128.64 (Ph-3,5), 130.0 (Ph-4)
4e	DMSO-d_6	143.0	106.9	161.9	37.0	132.7	127.7	129.3	128.9	181.5	124.4 (COCH), 140.2 (CHPh), 135.0 (Ph-1), 128.0 (Ph-2,6), 128.9 (Ph-3,5), 130.0 (Ph-4)

N-methyl derivative **4d** (Fig. 3). This is also the case considering the data in DMSO-d_6 (Tables 4 and 5). However, based on these data an unambiguous assignment of **2d** to one of the tautomeric forms seems questionable. Moreover, occasional line broadening in the spectra of **2**, particularly in DMSO-d_6 solution, points to a dynamic behavior.

Also, the comparison of ^{1}H NMR chemical shifts in **2d**, **3d**, and **4d** shows some remarkable features. Whereas the data of **3d** and **2d** do not differ substantially, with **4d** a drastic downfield shift is observed for the signal due to thiophene H-3 (Fig. 4). Thus, for instance, in benzene-d_6 the difference for thiophene H-3 proton shift between **2d** and **4d** is found to be 2.3 ppm (Fig. 4). This can be explained by a substantial contribution of conformational isomers having the pyrazolone C=O group close to the thiophene H-3 proton (similar to conformer Y), which would be markedly deshielded due to the anisotropy of the bond magnetic susceptibility of the C=O bond. The contribution of conformer X is less probable due to the absence of an NOE between pyrazole H-5 and thiophene H-3 in the NOE difference spectrum of **4d** (Fig. 4). In contrast, such a through-space interaction can be clearly observed in similar experiments with compounds **2d** and **3d** indicating also that those conformers displayed in Figure 4 contribute to the overall situation.

Amongst the tautomeric pyrazolones investigated, compound **1** occupies an exceptional position due to the lack of a substituent at the 4-position of the heterocyclic ring. Whereas in benzene-d_6 solution the compound solely exists as the CH-isomer [CH_2-substructure with $\delta(^1H)$ 2.19 ppm and δ (^{13}C) 40.1 ppm], in $CDCl_3$ solution ($c\sim0.2$ mol/l) a mixture of CH and—mainly—OH form ($\sim1.7:1$) was found at 28 °C, confirming a sufficiently slow interconversion of the CH-isomer compared to the NMR timescale. In contrast, in polar aprotic DMSO-d_6 only one signal set emerged, which can be attributed to the OH form—possibly being in fast exchange with the NH isomer. However, on the basis of chemical shift considerations[7] (δ pyrazole C-5 153.1 ppm), NOEs (only very weak NOE between acidic proton and Ph H-2,6), and considering ^{1}H,^{1}H as well as ^{13}C,^{1}H spin coupling constants (see below) dominance of the OH-form can be concluded. These results are in accordance with those reported for related 3-methyl-1-phenyl-2-pyrazolin-5-one.[34,35]

2.2.2. NOE-difference experiments. NOE-difference experiments show some differences between recordings in apolar solvents such as $CDCl_3$ or benzene-d_6 compared to those in polar ones such as DMSO-d_6. In the latter solvent, for **2d** through-space connectivities can be observed between the XH-proton and pyrazole H-3(5) as well as to H-2/6 of *N*-phenyl (Fig. 5). A possible explanation of this phenomenon is some contribution of the NH-isomer to the tautomeric composition or the presence of intermolecular effects. In contrast, in $CDCl_3$ and benzene-d_6 a spatial closeness of XH and pyrazole H-3 is not detectable (Fig. 6) indicating the absence of NH-tautomer. We believe compounds **2** in these non-polar solvents to be present in a chelated hydroxypyrazole form (isomer **A′** in Fig. 1). NOE-difference experiments with pyrazolone **1** in $CDCl_3$ are characterized by strong saturation transfer effects (e.g.,

Table 6. $^{13}C,^{1}H$ spin coupling constants (Hz) of compounds **1-3**

No.	Solvent	^{1}J(C3,H3)	^{2}J(C4,H3)	^{3}J(C5,H3)	^{1}J(OMe)	Other couplings
1[a]	$CDCl_3$	196.2	11.1	[b]	—	^{1}J(C4,H4)=134.6 Hz; ^{2}J(C3,H4)=5.4 Hz
1[c]	$CDCl_3$	185.4	8.1	[b]	—	^{1}J(C4,H4)=180.2 Hz; ^{2}J(C3,H4)=6.0 Hz
1[a]	C_6D_6	195.5	11.1	[b]	—	^{1}J(C4,H4)=134.4 Hz; ^{2}J(C3,H4)=5.5 Hz
1[c]	DMSO-d_6	184.1	[d]	[b]	—	^{1}J(C4,H4)=177.2 Hz; ^{2}J(C3,H4)=4.9 Hz
2b	$CDCl_3$	188.6	10.7	4.8	—	^{1}J(Me)=127.9 Hz
2b	DMSO-d_6	189.3	9.5	[b]	—	^{1}J(Me)=127.3 Hz; ^{3}J(C4,Me)=1.5 Hz
2c	$CDCl_3$	190.7	11.0	4.8	—	^{3}J(CO,Ph-2,6)=4.0 Hz
2c	C_6D_6	190.4	11.0	4.7	—	
2c	DMSO-d_6	190.1	10.6	4.8	—	
2d	$CDCl_3$	189.6	11.1	4.9	—	Th: ^{2}J(C2,H3)=6.5 Hz; ^{3}J(C2,H4)=9.2 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=168.6 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=170.5 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.4 Hz; ^{1}J(C5,H5)=186.1 Hz; ^{2}J(C5,H4)=7.2 Hz; ^{3}J(C5,H3)=10.9 Hz
2d	C_6D_6	189.4	11.2	4.9	—	Th: ^{2}J(C2,H3)=6.6 Hz; ^{3}J(C2,H4)=9.2 Hz; ^{3}J(C2,H5)=5.7 Hz; ^{1}J(C3,H3)=168.6 Hz; ^{2}J(C3,H4)=5.6 Hz; ^{3}J(C3,H5)=9.3 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.5 Hz; ^{1}J(C5,H5)=185.5 Hz; ^{2}J(C5,H4)=7.6 Hz; ^{3}J(C5,H3)=10.8 Hz
2d	DMSO-d_6	190.0	10.6	5.0	—	Th: ^{2}J(C2,H3)=7.3 Hz; ^{3}J(C2,H4)=9.0 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=169.4 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{3}J(C3,H5)=9.3 Hz; ^{1}J(C4,H4)=170.4 Hz, ^{2}J(C4,H3)=^{3}J(C4,H5)=4.4 Hz; ^{1}J(C5,H5)=188.0 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.6 Hz
2e	$CDCl_3$	189.8	10.4	4.6	—	^{1}J(CO*C*H)=157.9 Hz; ^{2}J=2.3 Hz; ^{1}J(*C*HPh)=156.5 Hz
2e	C_6D_6	189.7	10.7	4.3	—	^{1}J(CO*C*H)=158.0 Hz; ^{2}J=2.4 Hz; ^{1}J(*C*HPh)=156.0 Hz
2e	DMSO-d_6	191.6	9.8	4.5	—	^{1}J(CO*C*H)=161.9 Hz; ^{2}J=4.3 Hz; ^{1}J(*C*HPh)=157.6 Hz
3a	$CDCl_3$	185.9	10.7	[b]	146.0	^{1}J(C4,H4)=177.7 Hz; ^{2}J(C3,H4)=4.1 Hz
3a	DMSO-d_6	186.0	10.7	[b]	146.8	^{1}J(C4,H4)=179.2 Hz; ^{2}J(C3,H4)=4.2 Hz
3b	$CDCl_3$	188.1	9.6	4.4	147.8	^{1}J(CO*Me*)=127.5 Hz; ^{2}J(CO,COMe)=5.9 Hz; ^{3}J(C4,COMe) 1.3 Hz; ^{3}J(C5,OMe)=4.4 Hz
3c	$CDCl_3$	189.8	9.8	4.9	147.9	^{3}J(C5,OMe)=4.4 Hz
3c	DMSO-d_6	190.5	9.9	4.4	148.2	^{3}J(C5,OMe)=4.4 Hz
3d	$CDCl_3$	190.0	9.9	5.1	147.9	Th: ^{2}J(C2,H3)=6.6 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.6 Hz; ^{1}J(C3,H3)=168.5 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.1 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=4.9 Hz; ^{3}J(C4,H5)=4.0 Hz; ^{1}J(C5,H5)=185.4 Hz; ^{2}J(C5,H4)=7.2 Hz; ^{3}J(C5,H3)=10.9 Hz; ^{3}J(C5,OMe)=4.2 Hz
3d	C_6D_6	189.2	10.1	4.4	147.8	Th: ^{2}J(C2,H3)=6.8 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.5 Hz; ^{1}J(C3,H3)=168.2 Hz; ^{2}J(C3,H4)=5.6 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=169.2 Hz, ^{2}J(C4,H3)=4.6 Hz; ^{3}J(C4,H5)=4.6 Hz; ^{1}J(C5,H5)=184.8 Hz; ^{2}J(C5,H4)=7.5 Hz; ^{3}J(C5,H3)=11.0 Hz; ^{3}J(C5,OMe)=4.4 Hz
3d	DMSO-d_6	190.8	10.1	4.5	148.2	Th: ^{2}J(C2,H3)=7.0 Hz; ^{3}J(C2,H4)=8.7 Hz; ^{3}J(C2,H5)=5.6 Hz; ^{1}J(C3,H3)=169.6 Hz; ^{2}J(C3,H4)=5.7 Hz; ^{3}J(C3,H5)=9.2 Hz; ^{1}J(C4,H4)=170.7 Hz, ^{2}J(C4,H3)=4.5 Hz; ^{3}J(C4,H5)=4.5 Hz; ^{1}J(C5,H5)=188.0 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.6 Hz; ^{3}J(C5,OMe)=4.5 Hz
3e	$CDCl_3$	188.5	9.6	4.3	147.8	^{1}J(CO*C*H)=155.9 Hz; ^{2}J=1.9 Hz; ^{1}J(*C*HPh)=154.9 Hz; ^{3}J(C5,OMe)=4.3 Hz
3e	DMSO-d_6	190.3	9.7	4.4	148.1	^{1}J(CO*C*H)=160.1 Hz; ^{2}J=4.5 Hz; ^{1}J(*C*HPh)=156.9 Hz; ^{3}J(C5,OMe)=4.3 Hz

[a] CH-isomer.
[b] Not unequivocally determined.
[c] OH-isomer.
[d] Small couplings not resolved due to marked line broadening.

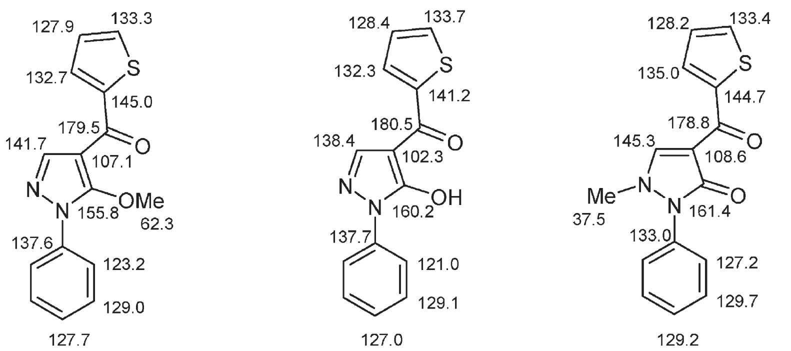
of pyrazole H-4 between forms **A** and **B**) confirming interconversion between the tautomeric forms. In DMSO-d_6, where only one (averaged) signal set appeared, the observed saturation transfer between pyrazole H-4 and the acidic proton provides a possible hint for the involvement of the CH-isomer into the proton transfer reactions. Due to an NOE observed for the signal of NPh H-2,6 upon irradiation of the transition of the acidic proton (11.57 ppm) also the presence of a certain percentage of NH-tautomer cannot be excluded.

2.2.3. The geminal ^{2}J[pyrazole C4,H3(5)] spin coupling constant as a structural probe. Comparing a variety of $^{13}C,^{1}H$ spin coupling constants of compounds **3** and **4** it is noticeable that ^{2}J[pyrazole C-4,H3(5)] suffers the most remarkable change when switching from *O*-methyl compounds **3** to the corresponding *N*-methyl derivatives **4**. Comparing compounds within the thenoyl series **d** reveals the magnitude of this coupling to be reduced from ~10 Hz in **3d** to 4–5 Hz in **4d**, very similar results were obtained for 4-acetyl (**b**), 4-benzoyl (**c**) and 4-cinnamoyl (**e**) congeners (Tables 6 and 7). The tautomeric pyrazolones **2b-d** showed values in the range of 9.5 Hz (**2b** in DMSO-d_6) to 11.2 Hz (**2d** in benzene-d_6), again giving a strong hint for the preferential presence of compounds **2** in the hydroxy form.

A possible explanation for the remarkable changes in the magnitude of ^{2}J[C4,H3(5)] between structures **3** and **4** as

Table 7. $^{13}C,^{1}H$ spin coupling constants (Hz) of compounds **4**

No.	Solvent	^{1}J(C5,H5)	^{2}J(C4,H5)	^{3}J(C3,H5)	^{1}J(NMe)	Other couplings
4a	$CDCl_3$	186.3	6.3	8.6	140.6	^{1}J(C4,H4)=182.4 Hz; ^{2}J(C3,H4)=5.3 Hz; ^{2}J(C5,H4)=7.1 Hz; ^{3}J(C5,NMe)=3.5 Hz; ^{3}J(NMe,H5)=1.6 Hz
4a	DMSO-d_6	189.0	6.7	8.6	140.8	^{1}J(C4,H4)=181.3 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{2}J(C5,H4)=7.0 Hz; ^{3}J(C5,NMe)=3.5 Hz; ^{3}J(NMe,H5)=1.6 Hz
4b	$CDCl_3$	190.1	4.2	7.0	142.4	^{1}J(Me)=128.0 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4c	$CDCl_3$	190.7	4.6	6.8	142.6	^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4c	DMSO-d_6	192.9	5.3	6.9	143.0	^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4d	$CDCl_3$	191.3	4.0	6.6	142.5	Th: ^{2}J(C2,H3)=6.3 Hz; ^{3}J(C2,H4)=8.9 Hz; ^{3}J(C2,H5)=6.3 Hz; ^{1}J(C3,H3)=172.0 Hz; ^{2}J(C3,H4)=5.8 Hz; ^{3}J(C3,H5)=8.8 Hz; ^{1}J(C4,H4)=169.2 Hz, ^{2}J(C4,H3)=5.0 Hz; ^{3}J(C4,H5)=4.0 Hz; ^{1}J(C5,H5)=183.8 Hz; ^{2}J(C5,H4)=7.1 Hz; ^{3}J(C5,H3)=11.1 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4d	DMSO-d_6	193.7	5.0	6.7	143.3	Th: ^{2}J(C2,H3)=6.5 Hz; ^{3}J(C2,H4)=8.8 Hz; ^{3}J(C2,H5)=5.8 Hz; ^{1}J(C3,H3)=171.1 Hz; ^{2}J(C3,H4)=6.0 Hz; ^{3}J(C3,H5)=9.0 Hz; ^{1}J(C4,H4)=169.6 Hz, ^{2}J(C4,H3)=5.2 Hz; ^{3}J(C4,H5)=4.3 Hz; ^{1}J(C5,H5)=186.8 Hz; ^{2}J(C5,H4)=7.3 Hz; ^{3}J(C5,H3)=10.8 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H5)=2.0 Hz
4e	$CDCl_3$	190.6	4.4	6.9	142.3	^{1}J(COCH)=159.9 Hz; ^{2}J(COCH=CH)=2.1 Hz; ^{1}J(CHPh)=154.4 Hz; ^{3}J(=CHPh,Ph-2,6)=4.7 Hz; ^{3}J(C5,NMe)=3.3 Hz; ^{3}J(NMe,H-5)=2.0 Hz
4e	DMSO-d_6	193.2	5.1	6.9	143.2	^{1}J(COCH)=158.3 Hz; ^{2}J(COCH=CH)=2.0 Hz; ^{1}J(CHPh)=154.4 Hz; ^{3}J(=CHPh,Ph-2,6)=4.6 Hz; ^{3}J(C5,NMe)=3.4 Hz; ^{3}J(NMe,H-5)=2.0 Hz



3d **2d** **4d**

Figure 3. ^{13}C NMR chemical shifts of **2d**, **3d**, and **4d** ($CDCl_3$).

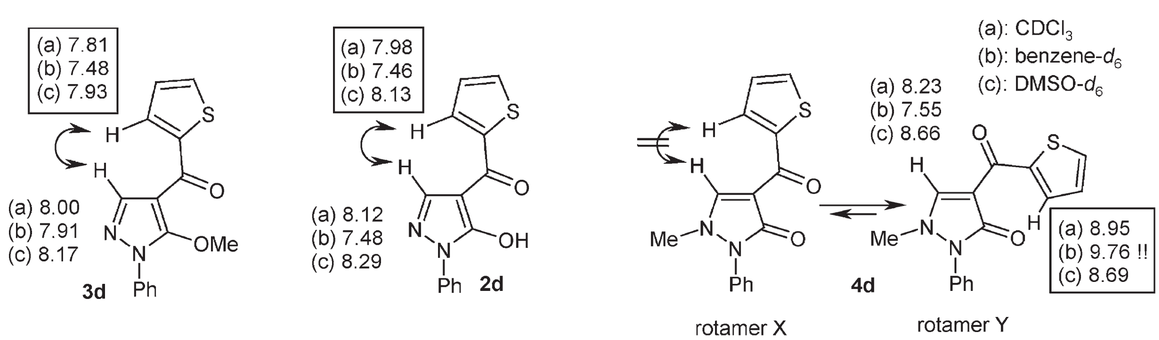


Figure 4. ^{1}H NMR chemical shifts (δ, ppm) for pyrazole H-3(5) and thiophene H-3 (framed) and observed NOEs (arrows) with compounds **2d**, **3d**, and **4d**.

well as between OH (CH) isomers (**A**, **B** in Fig. 1) on the one hand, and NH-forms (**C** in Fig. 1) on the other hand can be given on the basis of lone-pair effect considerations. It is well known from the literature that lone-pair effects can drastically influence a large variety of different spin coupling constants.[36] In the case of pyrazole ^{2}J[C4,H3(5)] the H-C–C axis is coplanar with the sp^2-hybridized lone-pair in α-position at pyrazole N2(1), what according to theory should lead to a positive effect and, inversely, to a decrease in magnitude upon removal of such a lone-pair by alkylation, protonation, oxidation or complexation.[36] A related, well known example is the reduction of ^{2}J(C3,H2) in pyridine (+8.5 Hz) to 5.1 Hz on protonation and to 4.2 Hz on *N*-oxide formation (Fig. 7, upper trace).[37,38] The

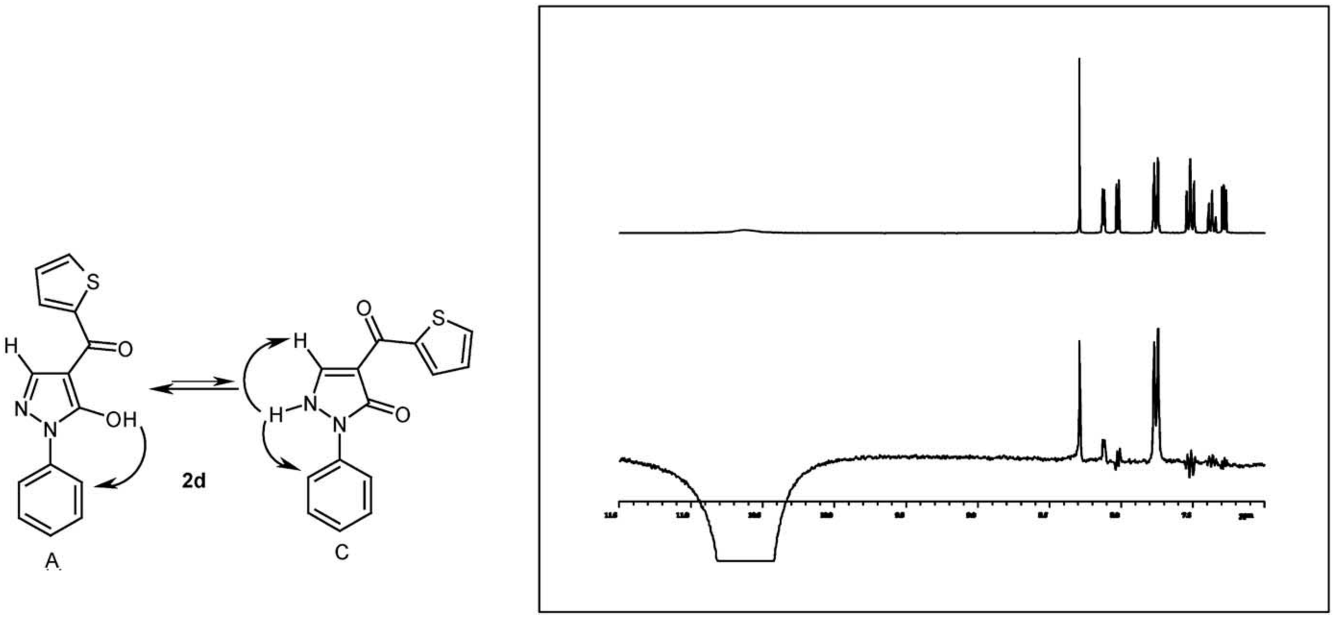


Figure 5. NOE-difference spectrum of **2d** obtained upon irradiation of the XH-resonance (7.0–11.5 ppm, in DMSO-d_6).

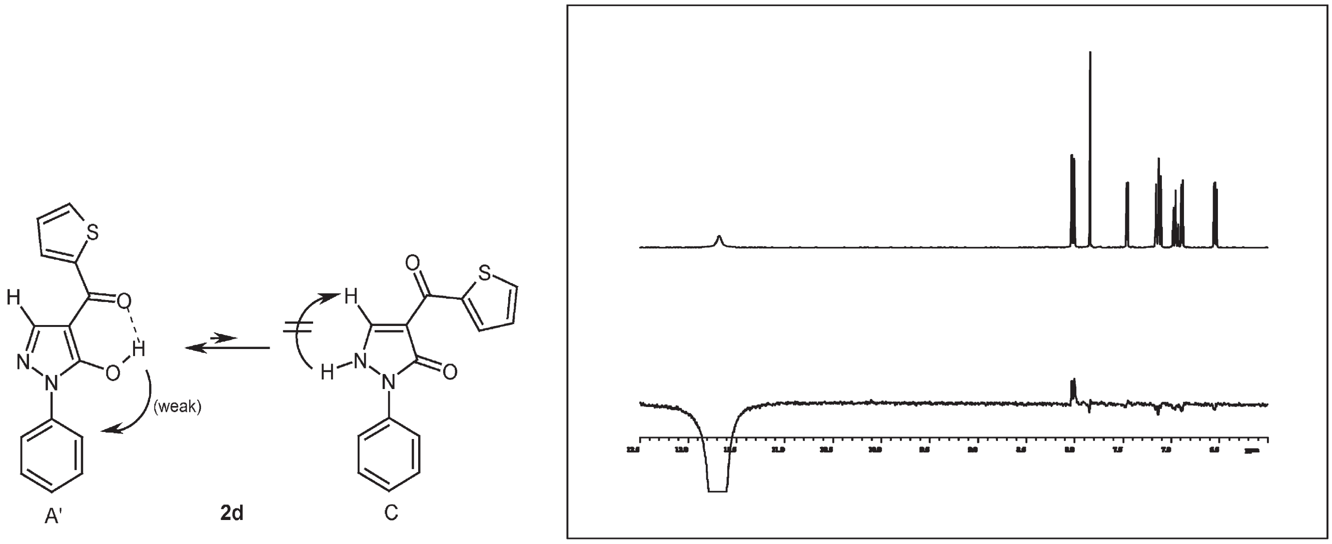


Figure 6. NOE-difference spectrum of **2d** obtained upon irradiation of the XH-resonance (6.0–12.5 ppm, in benzene-d_6).

value of this coupling indicates that 2-aminopyridines are present in the NH_2-form (^2J=7 Hz), but 2-hydroxypyridines exist as pyridones (^2J=3 Hz), whereas in the fixed 2-methoxypyridine the 'intact' coplanar lone-pair increases ^2J(C5,H6) again to 8 Hz (Fig. 7, middle trace).[39] Similarly, all pyrazole derivatives investigated in the present study characterized by an intact lone-pair at pyrazole N–2(1) (a 'pyridine'-type nitrogen atom) exhibit a large value for ^2J[(C4,H3(5)], whereas *N*-methyl compounds of type **4** show markedly lower ones (Fig. 7, lower trace). Similar sp^2-hybridized nitrogen atoms are not only present in 5-alkoxy or 5-hydroxypyrazoles, but also in 2,4-dihydro-3*H*-pyrazol-3-ones (e.g., the CH-isomer of **1**), the latter exhibiting even slightly larger values. Thus, in **1B**—the CH-isomer of **1**—this ^2J coupling constant was found to be 11.1 Hz in $CDCl_3$ or benzene-d_6 solution (Fig. 7, lower trace).

It should be noted that the magnitude of the considered geminal ^{13}C,^1H spin coupling constant is also dependent from additional factors such as bond lengths, bond angles and substituents.[37] However, within the different types of pyrazoles investigated the changes within these parameters are not anticipated to lead to such drastic changes. Thus, we believe the described lone-pair effects to play the dominant role here.

In Figure 8, the pyrazole ^2J[C4,H3(5)] spin coupling constants for a variety of pyrazole derivatives are displayed.[40–49] In the two lowest rows, the effects of protonation, alkylation, *N*-oxidation and complexation are presented for pyrazole (**16**), 1-methyl (**18**), and 1-phenylpyrazole (**22**), respectively. Thus, pyrazole (**16**) in $CDCl_3$ or acetone-d_6 exhibits ^2J(C4,H3)=9.9 Hz,[40,41] being identical

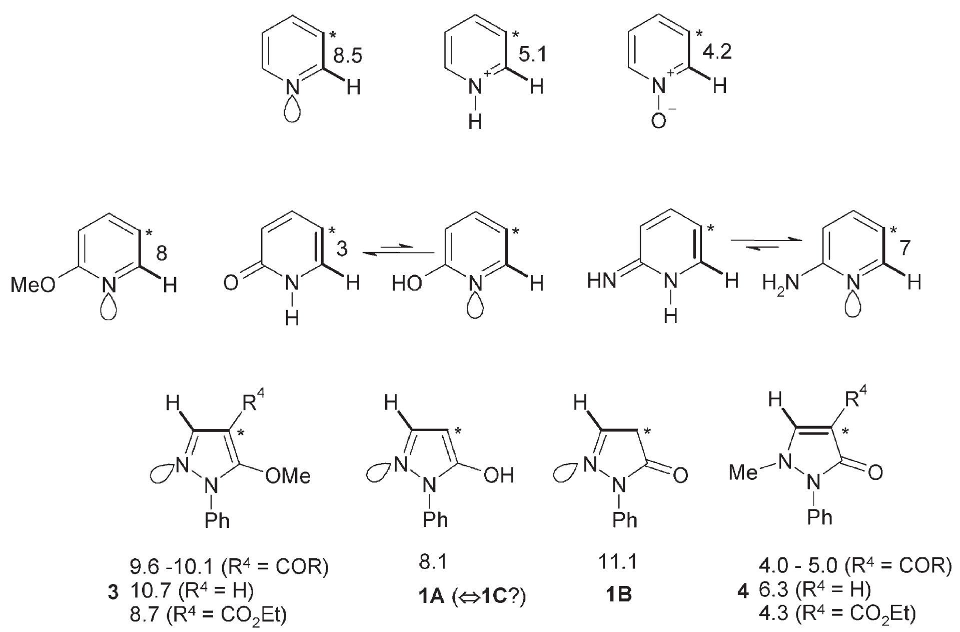


Figure 7. Geminal spin coupling constants in pyridine and pyrazole derivatives (in Hz).

with ^2J(C4,H5) due to fast prototropic exchange at room temperature. According to this situation, the observed 9.9 Hz represent a mean value between the larger ^2J(C4,H3) coupling and the smaller ^2J(C4,H5) one. In fixed 1-methylpyrazole (**18**) the different magnitudes of these geminal couplings clearly emerge [^2J(C4,H3)=10.5 Hz; ^2J(C4,H5)=8.7 Hz].[42] However, switching from pyrazole (**16**) to its cation **17** (in H_2SO_4) reduces ^2J(C4,H3) [and also ^2J(C4,H5)] from 9.9 to 6.7 Hz.[43] The same or a similar value of ^2J was found in *N*-methylpyrazolium salt **19** (6.7 Hz in H_2SO_4,[44] 7.2 Hz in CF_3CO_2H[45]) and in 1,2-dimethyl-pyrazolium cation **20** (7.1 Hz in DMSO-d_6, 6.8 Hz in TFA).[45] The effect caused by involvement of the lone-pair in the complexation is obviously somewhat smaller than that of protonation, as ^2J(C4,H3) in the ruthenium complexes **21** was found to be 7.6 and 9.1 Hz, respectively.[46] Comparison of ^2J(C4,H3) in 1-phenylpyrazole (**22**) (10.5 Hz),[45] and in the corresponding cations **23** (6.7 Hz in conc. H_2SO_4),[43] and **24** (7.0 Hz in CF_3CO_2D) support the above considerations, as well as the value found for *N*-oxide **25**.[47]

2.2.4. The vicinal ^3J[pyrazole H3(5),H4] spin coupling constant in compounds 1, 3a and 4a. The 4-unsubstituted compounds **1**, **3a** and **4a** exhibit interesting differences regarding the magnitude of the vicinal pyrazole H3(5),H4 coupling constant.[6] Whereas this coupling constant in *N*-methyl derivative **4a** was found to be 3.5 Hz (in $CDCl_3$ as well as in DMSO-d_6), for the corresponding *O*-methyl isomer **3a** a considerably reduced value of 2.0 Hz was determined (Fig. 9). Thus, the observed values for pyrazolone **1** (2.2 Hz in $CDCl_3$, 1.9 Hz in DMSO-d_6) suggest the predominance of the OH-form **1A**, what is in full accordance with the findings based on other criteria. In the CH-isomer **1B** the corresponding coupling is further reduced to 1.1 Hz ($CDCl_3$) and 1.3 Hz (benzene-d_6), respectively (Fig. 9).

2.3. DFT-calculations

Having thus collected a large number of $^{13}C,^1H$ coupling constants we decided to complete them with some literature data and carry out DFT calculations to determine the generality of our assumptions. In Table 8 are collected the experimental values and their origin.

For all these situations we carried out DFT calculations of the four terms (see Table 9) that are involved in coupling constants: diamagnetic spin orbit (DSO), Fermi contact (FC), paramagnetic spin orbit (PSO) and spin dipole (SD) terms. As it is well known for atoms of the first rows excluding ^{19}F, the FC largely dominates.[52]

We should note that according to the calculations, $^2J(^{13}C,^1H)$ is always positive and that the calculated sign is in general correct[52] (this is known experimentally for benzene).[37]

The line corresponds to Experimental $J=(0.90\pm0.03)$, Calculated J, $n=11$, $r^2=0.988$. The effect of the lone pair on the adjacent $^{13}C,^1H$ coupling constant is clearly observed in the upper corner of Figure 10.

3. Conclusion

Considering the—easily obtainable—magnitude of the geminal pyrazole C-4,H-3(5) spin coupling constant, the observed NOEs as well as the chemical shifts it can be concluded that *N*-phenyl-4-acylpyrazolones **2** are present as 5-hydroxypyrazoles in $CDCl_3$ or benzene-d_6 solution. In polar DMSO-d_6, a minor contribution of the NH-forms seems to be probable. In contrast, the NMR recordings unambiguously assign compound **1** to be present solely as the CH-isomer in benzene-d_6 solution. In $CDCl_3$ solution, a mixture of CH-isomer and—probably—OH-form [^2J(C4,H3)=8.1 Hz] was found, whereas **1** occurs mainly as hydroxypyrazole in DMSO-d_6. Theoretical calculations of the ^2J(C4,H3) coupling constants for a wide variety of compounds assess that they always have a positive sign and

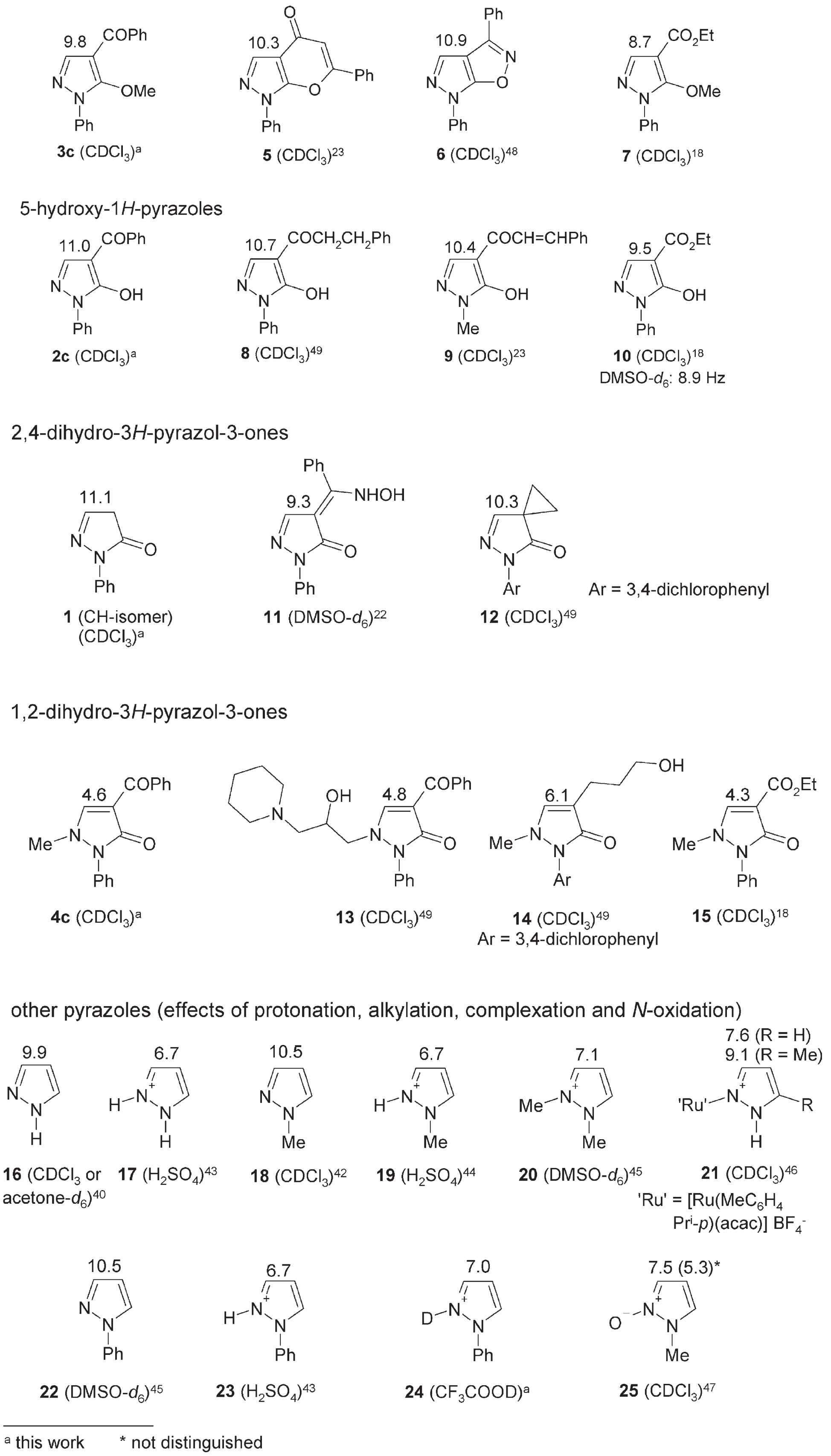
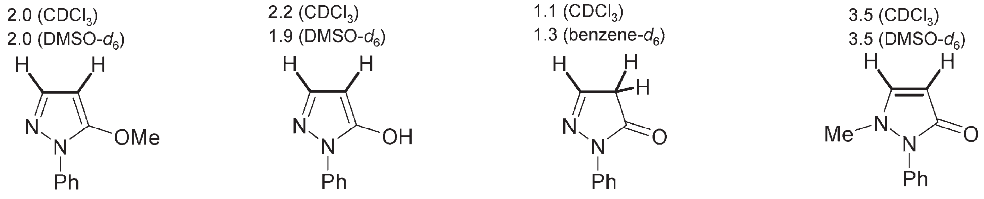


Figure 8. Pyrazole ^{2}J[C4,H3(5)] spin coupling constants (Hz) in different pyrazole derivatives.



3a **1A** **1B** **4a**

Figure 9. The vicinal ^3J[pyrazole H3(5),H4] spin coupling constant in compounds **1**, **3a** and **4a**.

Table 8. Experimental values

Molecule	Point	$^2J(^{13}C,^1H)$	Source
C_6H_6	**1**	1.15	Ref. 50
Pyridine (C3–H2)	**2**	8.47	Ref. 51
Pyridine (C2–H3)	**3**	3.12	Ref. 51
Pyridinium$^+$ (C3–H2)	**4**	4.09	Ref. 51
Pyridinium$^+$ (C2–H3)	**5**	4.62	Ref. 51
Pyridinium N–O	**6**	4.2	This work
Pyrazole	**7**	10.5	Ref. 42
Pyrazolium (H^+)	**8**	6.7	Refs. 42,44
5-OH Pyrazole	**9**	10	This work
4*H*-Δ^2-Pyrazolinone	**10**	10	This work
2*H*-Δ^3-Pyrazolinone	**11**	4.5	This work

Table 9. Calculations of the four terms that contribute to the total $^2J(^{13}C,^1H)$

Molecule (Point)	DSO	FC	PSO	SD
C_6H_6 (**1**)	−0.35	3.12	−0.90	0.00
Pyridine (C3–H2) (**2**)	−0.34	10.13	−0.75	0.03
Pyridine (C2–H3) (**3**)	−0.31	5.04	−0.97	−0.02
Pyridinium$^+$ (C3–H2) (**4**)	−0.41	5.08	−0.74	−0.02
Pyridinium$^+$ (C2–H3) (**5**)	−0.32	6.91	−0.95	−0.05
Pyridinium *N*-oxide (**6**)	−0.38	5.87	−0.68	0.00
Pyrazole (**7**)	−0.44	12.21	−0.42	0.03
Pyrazolium (H^+) (**8**)	−0.50	7.58	−0.43	−0.02
5-OH Pyrazole (**9**)	−0.39	12.20	−0.41	0.02
4*H*-Δ^2-Pyrazolinone (**10**)	−0.35	11.62	0.11	0.06
2*H*-Δ^3-Pyrazolinone (**11**)	−0.49	6.24	−0.62	−0.03
	Total *J*	Experimental *J* (Table 1)	Fitted	
C_6H_6 (**1**)	1.87	1.15	1.69	
Pyridine (C3–H2) (**2**)	9.07	8.47	8.18	
Pyridine (C2–H3) (**3**)	3.74	3.12	3.37	
Pyridinium$^+$ (C3–H2) (**4**)	3.91	4.09	3.52	
Pyridinium$^+$ (C2–H3) (**5**)	5.59	4.62	4.34	
Pyridinium N–O (**6**)	4.81	4.2	5.04	
Pyrazole (**7**)	11.38	10.5	10.26	
Pyrazolium (H^+) (**8**)	6.63	6.7	5.98	
5-OH Pyrazole (**9**)	11.42	10	10.29	
4*H*-Δ^2-Pyrazolinone (**10**)	11.44	10	10.31	
2*H*-Δ^3-Pyrazolinone (**11**)	5.10	4.5	4.61	

that the adjacent lone pair makes an important contribution to their value.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded on an ATI Mattson Genesis Series FTIR™ spectrophotometer. Mass spectra were obtained on a Shimadzu DI-QP1000 instrument (EI, 70 eV). The NMR spectra were recorded on a Varian Unity Plus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28 °C. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H, $CDCl_3$), δ 2.49 ppm (^{1}H, DMSO-d_6), δ 7.16 ppm (^{1}H, benzene-d_6), δ 77.0 ppm (^{13}C, $CDCl_3$), δ 39.5 ppm (^{13}C, DMSO-d_6), δ 128.0 ppm (^{13}C, benzene-d_6). The digital resolutions in the gated-decoupled ^{13}C NMR spectra were 0.33 Hz/data point. Preparative layer chromatography was performed on Merck 60F_{254} 20×20 cm glass plates (2 mm thickness). Column chromatographic separations were performed on Merck Kieselgel 60 (70–230 mesh). As not otherwise indicated all reagents are commercially available, the yields given below are not optimized and refer to analytically pure compounds.

4.2. 4-Acylpyrazolones 2; general procedure

To a mixture of pyrazolone **1** (3.204 g, 20 mmol) and $Ca(OH)_2$ (2.932 g, 40 mmol) in dioxane (35 mL, stored over 4 Å molsieve) was added the appropriate carboxylic acid chloride (20 mmol) in dioxane (10 mL) within 5 min. The resulting mixture was heated to reflux for 2 h and then

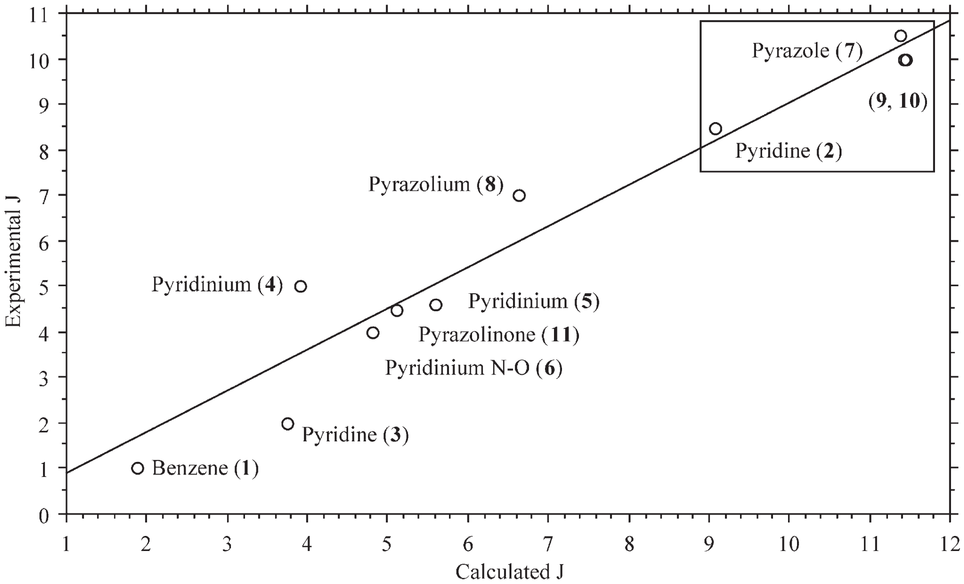


Figure 10. Plot of experimental versus calculated $^2J(^{13}C,^1H)$ coupling constants (Hz).

allowed to cool to room temperature. After addition of 2 N HCl (50 mL) the mixture was stirred for 1 h, then poured onto H_2O (150 mL). The precipitated product was filtered off, washed several times with H_2O and recrystallized from the solvent given below.

4.2.1. 1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (2b).[53] Yield 2.18 g (54%) of colorless crystals, mp 124 °C (EtOH). IR: 1664 cm^{-1} (C=O). MS (Th, %): 203 (M^++1, 17), 202 (M^+, 100), 187 (77), 77 (40), 51 (34), 43 (48). Anal. calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.37; H, 5.26; N, 13.95.

4.2.2. 1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone (2c). Yield 4.02 g (76%) of yellowish leaflets, mp 159–161 °C (EtOH) (lit.[54] mp 160–161 °C). MS (Th, %): 265 (M^++1, 13), 264 (M^+, 68), 186 (39), 105 (100), 91 (89), 77 (98), 69 (32), 55 (25), 53 (68), 51 (62), 43 (27). Anal. calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.42; H, 4.65; N, 10.50.

4.2.3. (5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)(2-thienyl)-methanone (2d). Yield 3.53 g (65%) of yellowish crystals, mp 161 °C (EtOH). MS (Th, %): 270 (M^+, 48), 186 (100), 118 (35), 111 (86), 91 (38), 81 (24), 77 (34), 69 (51), 57 (20), 55 (27), 53 (92), 51 (39), 43 (24), 41 (39). Anal. calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.37; N, 10.36. Found: C, 62.07; H, 3.95; N, 10.40.

4.2.4. (*E*)-1-(5-Hydroxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (2e).[23] Yield 3.52 g (61%) of orange needles, mp 182–183 °C (EtOH).[23]

4.3. Preparation of *O*-methyl (3) and *N*-methyl derivatives (4)

4.3.1. 5-Methoxy-1-phenyl-1*H*-pyrazole (3a).[55] To a stirred mixture of pyrazolone **1** (250 mg, 1.561 mmol), K_2CO_3 (432 mg, 3.126 mmol) and dry DMF (3 mL) was added dropwise methyl 4-toluenesulfonate (291 mg, 1.563 mmol). After stirring for 15 h at room temperature the mixture was poured onto 2 N HCl (20 mL) and washed with light petroleum (3 times). The aqueous phase was made alkaline with solid Na_2CO_3 and extracted with Et_2O (3 times). The combined etheral phases were washed with H_2O and brine, dried (Na_2SO_4) and evaporated under reduced pressure to afford a nearly colorless oil. Yield: 152 mg (56%).

4.3.2. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (3b) and 4-acetyl-1,2-dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4b). Under vigorous stirring, to a solution of **2b** (1.011 g, 5 mmol) in CH_2Cl_2 (20 mL) was added a 40% aqueous solution of HBF_4 (1.100 g, 5 mmol) at 0 °C. Then a 2 M solution of trimethylsilyldiazomethane in *n*-hexane (2.5 mL, 5 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. After a second portion of reagent (2.5 mL, 5 mmol) had been added and stirring was continued for another 1 h, the mixture was poured onto H_2O (45 mL). After extraction with CH_2Cl_2 (3×50 mL) the combined organic phases were washed with 2 N NaOH (2×75 mL) and H_2O (2×75 mL), dried (Na_2SO_4) and evaporated. The residual tan oil (531 mg), which crystallized on standing, was subjected to preparative layer chromatography (silica gel, CH_2Cl_2/EtOAc 7:3) giving **3b** as the less retarded and **4b** as the more polar fraction. The compounds were removed from the stationary phase by repeated extraction with warm EtOAc.

Compound **3b**. Yield: 299 mg (28%) of tan crystals, mp 63 °C. IR: 1656 cm^{-1} (C=O). MS (Th, %): 216 (M^+, 7), 201 (20), 91 (22), 77 (33), 51 (26), 43 (100), 41 (20). Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.94; H, 5.55; N, 12.77.

Compound **4b**. Yield: 50 mg (5%) of colorless crystals after recrystallization from diisopropyl ether, mp 220–222 °C (lit.[56] mp 216–217 °C). HRMS: Th (M^+); calcd for $C_{12}H_{12}N_2O_2$: 216.0900. Found: 216.0903±0.0011.

4.3.3. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone (3c). Compound **3c** was obtained from **2c** (1.321 g, 5 mmol) and Me_3SiCHN_2/HBF_4 similarly as described for the synthesis of **3b** from **2b**. Preparative layer chromatography (CH_2Cl_2/EtOAc 7:3) afforded **3c** as the less retarded component accompanied by small amounts (5%) of isomer **4c**.

Compound **3c**. Yield: 473 mg (34%) of a reddish oil. IR: 1656 cm^{-1} (C═O). MS (Th, %): 278 (M^+, 5), 105 (41), 91 (36), 77 (100), 51 (29). Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.02; H, 5.00; N, 9.82.

4.3.4. (5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)(2-thienyl)-methanone (3d). Compound **3d** was obtained from **2d** (1.352 g, 5 mmol) and Me_3SiCHN_2/HBF_4 similarly as described for the synthesis of **3b** from **2b**. Preparative layer chromatography (CH_2Cl_2/EtOAc 3:2) afforded **3d** as the less retarded component accompanied by traces of isomer **4d**. The product was crystallized from diisopropyl ether with addition of charcoal. Yield: 341 mg (24%) of yellowish crystals, mp 105 °C. IR: 1622 cm^{-1} (C═O). MS (Th, %): 285 (M^++1, 11), 284 (M^+, 55), 144 (23), 111 (100), 91 (53), 77 (74), 53 (34), 51 (64). Anal. calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.06; H, 4.33; N, 9.82.

4.3.5. (*E*)-1-(5-Methoxy-1-phenyl-1*H*-pyrazol-4-yl)-3-phenyl-2-propen-1-one (3e). To a mixture of **2e** (871 mg, 3 mmol), PPh_3 (1.179 g, 4.5 mmol) and MeOH (120 mg, 3.75 mmol) in CH_2Cl_2 (60 mL) was added dropwise diethyl azodicarboxylate (783 mg, 4.5 mmol). After stirring for 20 h at room temperature, MeOH (3 mL) was added and the mixture was poured onto H_2O (60 mL). After exhaustive extraction with CH_2Cl_2, the combined organic phases were washed several times with 2 N NaOH and then with H_2O. After drying (Na_2SO_4), the solvent was evaporated and the residue was subjected to preparative layer chromatography (CH_2Cl_2/EtOAc 3:2). The less retarded zone was removed and extracted several times with warm EtOAc. The residue obtained after filtration and evaporation of the solvent was recrystallized from diisopropyl ether. Yield: 307 mg (34%) of colorless crystals, mp 165 °C. IR: 1654 cm^{-1} (C═O). MS (Th, %): 304 (M^+, 24), 213 (19), 187 (28), 186 (21), 131 (16), 103 (32), 91 (33), 77 (100), 51 (42). Anal. calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.80; H, 5.33; N, 9.12.

4.3.6. 1,2-Dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4a). A mixture of pyrazolone **1** (250 mg, 1.561 mmol), methyl 4-toluenesulfonate (291 mg, 1.561 mmol) and dry xylene (5 mL) was heated to reflux for 24 h under anhydrous conditions. After cooling, to the mixture was added light petroleum (3 mL), the organic phase was cautiously removed, the remaining oil was taken up in 2 N NaOH (3 mL) and exhaustively extracted with $CHCl_3$ (6 times). The combined $CHCl_3$ phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from EtOAc to afford cream crystals. Yield: 183 mg (67%); mp 115–117 °C (lit.[57] mp 117–118 °C).

4.3.7. 4-Benzoyl-1,2-dihydro-1-methyl-2-phenyl-3*H*-pyrazol-3-one (4c). A mixture of **2c** (300 mg, 1.135 mmol) and dimethyl sulfate (430 mg, 3.41 mmol) was heated to reflux on an oil bath (T=190–200 °C) for 15 min. Then, the mixture was poured onto hot H_2O (5 mL), stirred for 20 min, made alkaline with solid Na_2CO_3 and 2 N NaOH and extracted exhaustively with CH_2Cl_2. The combined organic phases were washed twice with H_2O and then brine, dried (Na_2SO_4) and evaporated. The residue was recrystallized from toluene (ca. 30 mL) to afford a colorless solid; yield: 148 mg (47%); mp 157–159 °C. MS (Th, %): 279 (M^++1, 10), 278 (M^+, 52), 201 (15), 158 (47), 121 (74), 105 (100), 91 (12), 77 (85), 51 (23). HRMS: Th (M^+); calcd for $C_{17}H_{14}N_2O_2$: 278.1055. Found: 278.1049±0.0014. Anal. calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.11; H, 5.33; N, 10.02.

4.3.8. 1,2-Dihydro-1-methyl-2-phenyl-4-(2-thienylcarbonyl)-3*H*-pyrazol-3-one (4d). A mixture of **2d** (811 mg, 3 mmol), 1 N aq. NaOH (9 mL), H_2O (6 mL), and dimethyl sulfate (756 mg, 6 mmol) was heated to reflux for 4 h before it was stirred at rt for additional 16 h. The combined organic phases obtained after extraction with CH_2Cl_2 (3×10 mL) were washed with H_2O, dried (Na_2SO_4) and evaporated. The residue (610 mg) was subjected to preparative layer chromatography (CH_2Cl_2/EtOAc 1:9). From the central area the product was desorbed by repeated extraction with EtOAc. Yield: 40 mg (5%) of colorless crystals; mp 209 °C. MS (Th, %): 285 (M^++1, 10), 284 (M^+, 51), 111 (100), 97 (29), 77 (33), 53 (14). Anal. calcd for $C_{15}H_{12}N_2O_2S\cdot 0.5H_2O$: C, 61.42; H, 4.47; N, 9.55. Found: C, 61.31; H, 4.32; N, 9.36.

4.3.9. (*E*)-1,2-Dihydro-1-methyl-2-phenyl-4-(3-phenylacryloyl)-3*H*-pyrazol-3-one (4e). A mixture of **2e** (450 mg, 1.55 mmol) and dimethyl sulfate (1.95 g, 15.45 mmol) was heated to 100 °C for 24 h with stirring. Then the excess reagent was removed by bulb-to-bulb distillation (75 °C). The residue was stirred with sat. aqueous Na_2CO_3 (2 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined CH_2Cl_2-phases were dried (Na_2SO_4) and evaporated to dryness. The oily residue crystallized upon treatment with water, and was washed with cold ethanol and then recrystallization from EtOH. Yield: 179 mg (38%) of nearly colorless crystals; mp 201 °C [lit.[58] mp 234 °C, Beilstein (Reg. Nr. 30915) mp 198–199 °C, lit.[59] mp 190–192 °C]. MS (Th, %): 305 (M^++1, 21), 304 (M^+, 100), 303 (30), 275 (31), 193 (19), 184 (63), 174 (22), 131 (32), 121 (65), 103 (45), 77 (38). HRMS: Th (M^+); calcd for $C_{19}H_{16}N_2O_2$: 304.1212. Found: 304.1208±0.0015.

Computational part. The optimization was carried out at the B3LYP/6-311++G** level[60,61] and the calculation of the four components of the coupling constant at the same level using the facilities provided by the Gaussian 03 package.[62,63]

Acknowledgements

We thank Dr. L. Jirovetz for recording the mass spectra. Financial support was provided by the Spanish DGI/MCYT (Projects no. BQU2003-00976 and BQU2003-01251).

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Buffer-induced, selective mono-*C*-alkylation of phloroglucinol: application to the synthesis of an advanced intermediate of catechin

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Received 16 January 2004; revised 17 May 2004; accepted 7 June 2004

Abstract—A straightforward mono-selective and *C*-specific alkylation of phloroglucinol with activated alkyl halides is presented. The use of water as solvent limits the amount of over-alkylated by-products. Provided some minor changes in the experimental conditions, hydrophobic cinnamyl halides can also be reacted, thus giving a direct access to advanced intermediates of natural flavonoids.

1. Introduction

The flavonoids are a family of polyphenolic compounds found in the plant kingdom. They feature interesting anti-oxidative properties responsible for the health-benefits associated with a diet rich in vegetables and are found in large quantities in red wines and green teas.[1] However, due to the lack of reliable chemical methods for their synthesis, only natural extracts with ill-defined chemical compositions are usually evaluated for their biological activity. Undoubtedly, the poor overall stability of flavonoids is responsible for the lack of general methods for their chemical synthesis. Consequently, *protecting-group free* syntheses of polyphenols are scarce. The target molecules cannot often withstand the conditions required for removal of most of the conventional protecting groups. To the best of our knowledge, only benzyl derivatives have been used successfully as protecting groups in the total synthesis of natural flavonoids.[2] The phloroglucinol motif (1,3,5-benzenetriol) is ubiquitous in all natural flavonoids structures. As such, it constitutes the ultimate starting material en route to the synthesis of elaborated (un)natural polyphenols. Unfortunately, the benzylation of phloroglucinol is not selective and gives a mixture of both *O*- and *C*-benzylated products.[3] Hence, many efforts have been aimed at methods to achieve the specific mono-, di-, or tri-*O*-benzylation of phloroglucinol.[4] These methods are multi-step and require careful control of the reaction conditions. Most interestingly, the selective *C*-alkylation of phloroglucinol has never been reported, the only examples found in the literature concerning reactions with protected versions of phloroglucinol.[5] Though apparently simple, this transformation offers several synthetic challenges. As phloroglucinol contains six nucleophilic sites, an ideal reaction will be mono- and *C*-specific. Undoubtedly, such a reaction would constitute an easy and straightforward approach toward the synthesis of natural unprotected flavonoids like catechin whose retrosynthesis is depicted in the following scheme.

Our approach to catechin is very concise and involves the intramolecular ring closing between a phenol of the phloroglucinol core and the epoxide as the last step. This epoxide intermediate is ideally synthesized in two steps starting from the selective alkylation of phloroglucinol followed by the epoxidation of the double bond. In this communication, we show that phloroglucinol can be *C*-specifically and mono-selectively alkylated with various activated alkyl halides in buffered aqueous solutions. The use of buffered aqueous solutions as the reaction media proved crucial to control the regio-selectivity of the reaction.

2. Results and discussion

The reaction of phloroglucinol with allyl bromide was investigated first (Table 1, entries 1–6). Interestingly,

Keywords: Flavonoids; Polyphenol compounds; Phloroglucinol; Alkylation; Synthetic methodology.
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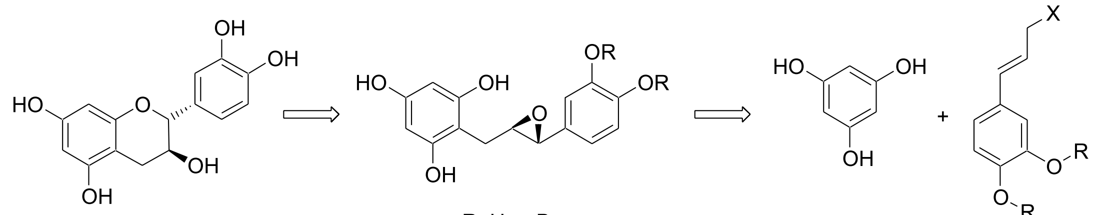
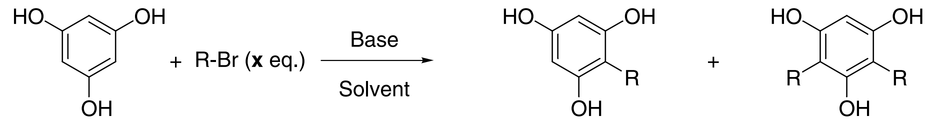
doi:10.1016/j.tet.2004.06.026



(+)-catechin R=H or Bn

Scheme 1. Retrosynthetic scheme of catechin.

Table 1. Conditions tested for the alkylation of phloroglucinol in water



phloroglucinol **1a** (R=allyl) **1b** (R=CH_2Ph) **2a** **2b**

Entry	Base (equiv.)	*x*	R	Solvent	*T* (°C)	Time (h)	Yields (%)[a]	
							1	**2**
1	None	5	Allyl	$EtOH_{40\%}$	20	72	36	30
2	None	5	Allyl	H_2O	20	72	68	23
3	NaOH (1)	1.1	Allyl	H_2O	20	12	45	17
4	NaOH (2)	1.1	Allyl	H_2O	20	5	n.d.[b]	
5	Buffer[c]	4	Allyl	H_2O	20	4	62	24
6	Buffer[c]	4	Allyl	H_2O	10	10	35	12
7	Buffer[c]	2	Benzyl	H_2O	20	4	54	21
8	NaOH (2)	2	Benzyl	EtOH	20	4	40	26
9	TEA (3)	2	Benzyl	THF	20	5	42	23

[a] Isolated yields.
[b] Not determined, see text.
[c] Phosphate buffer 0.2 M, pH 7.8.

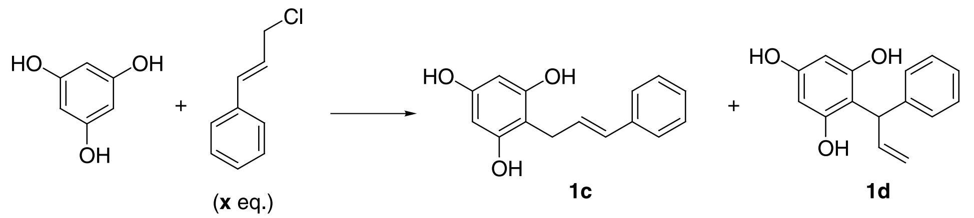
phloroglucinol is nucleophilic enough to undergo alkylation in aqueous ethanol in the absence of base, with allyl phloroglucinol **1a** being obtained in 36% yield (entry 1). No products resulting from the *O*-alkylation of phloroglucinol are detected in the crude reaction mixture. However, the reaction is not mono-selective and gives substantial amounts of the di-alkylated product **2a**. The extent of mono-alkylation as well as the yield of the desired compound **1a** is greatly improved in pure water (entry 2). The lower solubility of **2a** in water in comparison to the starting phloroglucinol may account for this better selectivity.

Although **1a** is obtained in good yield (68%, entry 2) in water, the pH of the reaction medium becomes increasingly acidic as the allyl phloroglucinol is formed. Since most of the polyphenols are pH-sensitive, milder conditions are required for the synthesis of more elaborate adducts. Using stoichiometric amounts of sodium hydroxide, the phenolate of phloroglucinol is formed and the reaction is faster (entry 3). Yet, the mono-alkylation selectivity is low. This can be ascribed to the better solubility of the phenolate of **1a** in water in comparison to its neutral form. Consequently, **1a** is more likely to over-react in basic solutions and lesser mono-selectivity is observed (entry 3). A complex mixture of products is obtained with excess quantities of base (entry 4). Partial migration of the double bond of **1a** and **2a** in (conjugate) benzylic position takes place under these conditions. Alternatively, use of a buffered, ca. neutral, aqueous solution proved very successful. Since the pH is maintained throughout the course of the reaction, the reaction time is short and the yield of **1a** remains quite good (entry 5). Reducing the reaction temperature to 10 °C not only slows product formation but also results in lower selectivity and overall yield (entry 6).

Under the same conditions (0.2 M phosphate buffer, pH 7.8, 25 °C), the reaction of phloroglucinol with benzyl bromide gave **1b** and **2b** in 54 and 21% yield, respectively. As for allyl bromide (results not shown), no *O*-benzylated phloroglucinol was obtained in ethanol or THF (entry 8 and 9),[6] and the reaction must be carried out in DMF to observe the formation of benzyl ethers (results not shown).[7] Hence, water does not influence the *C*-selectivity of the reaction. Indeed, both the phloroglucinol and activated alkyl halides are known to favor *C*-alkylation.[8,9] This is in sharp contrast to the reaction of non-activated alkyl bromides with phloroglucinol where water has a marked influence both on the *C*- and on the mono-selectivity.[10]

The reaction of phloroglucinol with cinnamyl halides (Table 2) readily gives access to the skeleton of natural flavonoids (Scheme 1). Yet, these adducts are quite acid-sensitive. This may in turn explain why the synthesis of simple intermediates like **1c** have only been reported in a low 30% yield,[9,11] or not achieved at all.[12] The reaction of

Table 2. Cinnamylation of phloroglucinol in aqueous solutions



Entry	Conditions	*x*	Yields (%)	
			1c	**1d**
1	Phosphate buffer 0.2 M, pH 7.8	2	35	35
2	NaOH (1.25 equiv.), H_2O/EtOH 15/85 (v/v)	1.25	69	Traces

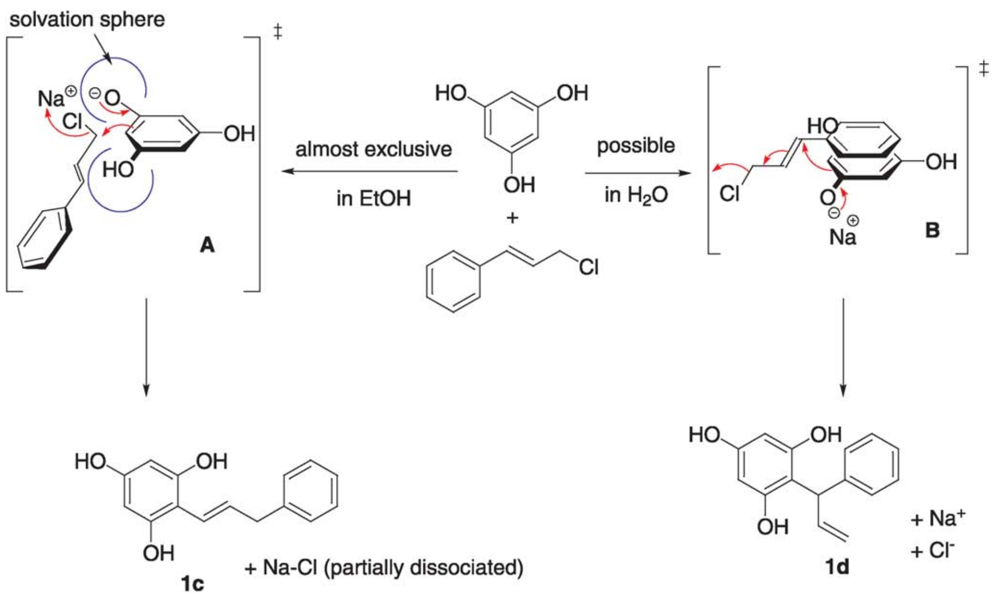
cinnamyl halides is actually even more challenging. In addition to the classical mono- and *C*-/*O*-alkylation issues encountered so far with allyl and benzyl halides, cinnamyl halides can give two additional regioisomers upon reaction with a nucleophile. Indeed, both regioisomers **1c** and **1d** are formed in equal amounts under our buffered reaction conditions (Table 2, entry 1).

We found the desired isomer **1c** is cleanly obtained in a mixture of ethanol and aqueous sodium hydroxide. Several factors may account for this selectivity. First, the dielectric constant of the solution decreases with increasing amounts of ethanol. Hence, the dissociation of ion pairs is less likely in solutions containing higher concentration of ethanol. The sodium counter-ion of the phenolate and the chlorine of cinnamyl chloride may be in close vicinity throughout the reaction pathway in ethanol-rich aqueous solutions as in transition state **A**, which leads to **1c** (Scheme 2). However, the strong hydrophobic effect and high cohesive energy density expected in water alone as a solvent should favor transition state **B** and thus produce **1d**.[13] Yet, the phenols are also thoroughly solvated in water. This should favor the attack on the less crowded terminal position of the alkyl halide leading to **1c**. These two opposing effects, hydrophobicity and solvation of the phenols, may account for the absence of selectivity in water.

With this result in hand, we then synthesized the advanced intermediate of catechin **1e** starting from the highly hydrophobic functionalized cinnamyl chloride **3** (Table 3). This compound is efficiently synthesized in four steps starting from the commercially available 3,4-dihydroxybenzaldehyde (Scheme 3).

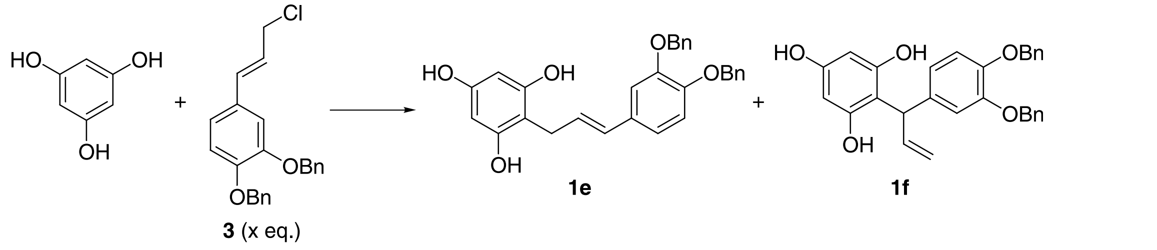
The cinnamyl chloride **3** was then reacted with the phloroglucinol under a variety of aqueous ethanolic conditions (Table 3).

In contrast to allyl bromide and cinnamyl chloride, the substituted cinnamyl chloride **3** is not soluble in ethanol or water. Consequently, no adduct is formed under the conditions optimized with cinnamyl chloride (entry 1). Under ultrasonic irradiation, the desired product **1e** is formed, yet not selectively (entry 2), the other regioisomer **1f** being obtained in substantial amounts.[14] When a solution of **3** in a minimum of THF is added slowly to the



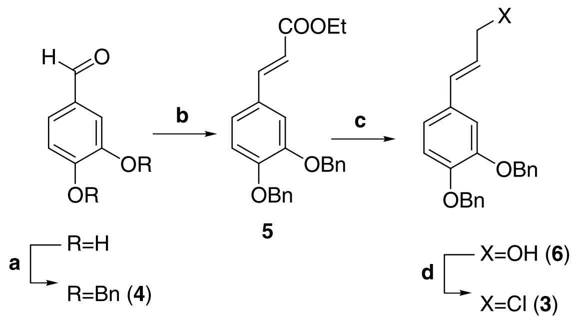
Scheme 2. Solvent-dependant transition states in the cinnamylation of phloroglucinol.

Table 3. Synthesis of an advanced intermediate of catechin



	Conditions	x	Yields (%)	
			1e	**1f**
1	NaOH (1.3 equiv.), $EtOH_{90\%}$ (vol.), 2 h	1.25	0	0
2	NaOH (1.3 equiv.), $EtOH_{90\%}$ (vol.), 0.1 h	1.25	45	12
3	NaOH (2 equiv.), EtOH/H_2O/THF 72/14/14, 20–50 °C, 9 h	0.33[a]	53	Traces

[a] **3** in a minimum of THF was added slowly to the reaction over a 4 h period.



Scheme 3. Synthesis of the cinnamyl chloride **3**. Reagents: (a) NaH, BnBr, DMF; (b) NaH, triethylphosphonoacetate, THF; (c) LAH, Et_2O, −15 °C; (d) $SOCl_2$, Net_3, CH_2Cl_2, 0 °C.

phloroglucinol in aqueous ethanol under gentle heating, only trace amounts of the undesired **1f** are observed and **1e** is obtained pure in a satisfactory 53% yield after flash chromatography (entry 3). This product has already been synthesized in low yield (17%) from phloroglucinol and the corresponding palladium π-acetate.[8] This advanced intermediate of natural flavonoids is obtained in our case in 53% yield under very simple and straightforward conditions.

In conclusion, a mild, high-yielding *C*-specific and mono-selective alkylation of phloroglucinol with activated alkyl halides has been developed. The *C*-specificity of this reaction comes from the fact that both phloroglucinol and activated alkyl halides favor *C*-alkylation. On the other hand, the solubility of mono-*C*-adducts are limited in water, thereby, preventing overalkylation reactions and giving good mono-alkylation selectivity. With minor changes in the experimental conditions, these aqueous conditions have been utilized with highly hydrophobic substrates to afford an advanced intermediate of catechin. The subsequent epoxidation of the double bond of **1e** has not been successful so far due to the high reactivity of the phloroglucinol toward oxidants. Yet, preliminary results indicate that iodination of the double bond is feasible. We are now concentrating our efforts on trying to make this reaction more selective and then achieve a straightforward, protection-free, total synthesis of catechin.

3. Experimental

3.1. General

3.1.1. 2-Allylphloroglucinol (1a). To a solution of phloroglucinol·$2H_2O$ (0.1 g, 0.61 mmol) in 10.98 mL 0.2 M Na_2HPO_4 and 1.02 mL of 0.2 M NaH_2PO_4 is added the allyl bromide (0.21 mL, 2.44 mmol). The reaction is stirred for 3 h and the aqueous phase is extracted twice with ether. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The residue was purified by flash chromatography on silica gel (25–35% AcOEt/hexane). $C_9H_{10}O_3$ (166.06); R_f 0.45 (40% AcOEt/hexane); ^1H (200 MHz, ε CD_3OD/$CDCl_3$): δ=3.34 (d, ^3J=5.2 Hz, 2H, H_5), 5.00–5.14 (m, 2H, H_7), 5.85–6.07 (m, 1H, H_6), 5.91 (s, 2H, H_2). ^{13}C (75 MHz, ε CD_3OD/$CDCl_3$): δ=27.6, 96.2, 104.6, 116.0, 136.5, 153.5, 154.4. IR (neat): ν_{max}=3454 (br, OH), 2924 (Ar.), 1621 (Ar-O), 1452, 1212 (br), 1112 cm^{-1}. MS (NH_4^+): *m/z*: 167 [M+H]$^+$.

3.1.2. 2,4-Diallylphloroglucinol (2a). $C_{12}H_{14}O_3$ (206.24); R_f 0.7 (60% AcOEt/hexane); ^1H (200 MHz, $CDCl_3$): δ=3.42 (m, 4H), 5.13–5.25 (m, 4H), 5.94–6.07 (m, 2H), 6.01 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ=27.1, 95.8, 104.2, 115.5, 136.6, 155.5, 155.9; IR: ν_{max}=3492 (br, OH), 2924 (Ar.), 1623 (Ar-O), 1464, 1150 cm^{-1}; MS (NH_4^+): *m/z*: 207 [M+H]$^+$.

3.1.3. 2-Benzylphloroglucinol (1b). Same procedure as for **1a** (benzyl bromide as the electrophile). $C_{13}H_{12}O_3$ (216.23); R_f 0.4 (60% AcOEt/hexane); ^1H (200 MHz, ε CD_3OD/$CDCl_3$): δ=3.96 (s, 2H), 5.95 (s, 2H), 7.12–7.26 (m, 5H); ^{13}C (50 MHz, ε CD_3OD/$CDCl_3$): δ=28.4, 96.0, 106.5, 126.2, 128.2, 128.6, 140.3, 155.4, 155.8; IR (neat): ν_{max}=3359 (br, OH), 2927 (Ar.), 1615 (br, Ar-O), 1456, 1144 cm−1; MS (NH_4^+): *m/z*: 217 (100) [M+H]$^+$, 234 (49.8) [M+NH_4]$^+$, 251 (10.8) [M+NH_3+NH_4]$^+$.

3.1.4. 2,4-Dibenzylphloroglucinol (2b). $C_{20}H_{18}O_3$ (306.36); R_f 0.7 (60% AcOEt/hexane); ^1H (200 MHz, $CDCl_3$): δ=3.99 (s, 4H), 4.81 (s, 3H, OH), 5.99 (s, 1H), 7.12–7.30 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ=28.9, 96.2, 106.7, 126.4, 128.2, 128.7, 139.8, 153.4, 154.1; IR (neat): ν_{max}=3526 (br, OH), 3028, 2924 (Ar.), 1619 (br, Ar-O), 1447, 1186, 1039 cm^{-1}; MS (NH_4^+): *m/z*: 307 (100) $[M+H]^+$, 323 (54.6) $[M+NH_4]^+$.

3.1.5. 2-Cinnamylphloroglucinol (1c). The cinnamyl chloride (7.62 mL, 54.00 mmol) is added to the phloroglucinol·$2H_2O$ (7 g, 43.17 mmol) in solution in 200 mL of ethanol and 25 mL of 2 M NaOH. After 3 h, the ethanol is partially evaporated under reduced pressure. The resulting aqueous solution is first washed with 200 mL of hexane and extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The residue was purified by flash chromatography on silica gel (25–40% AcOEt/hexane). $C_{15}H_{14}O_3$ (242.27); R_f 0.45 (60% AcOEt/hexane); ^{1}H (200 MHz, ε $CD_3OD/CDCl_3$): δ=3.57 (d, ^3J=5.4 Hz, 2H), 6.01 (s, 2H), 6.36 (dt, $^3J_1$=15.9 Hz, $^3J_2$=5.6 Hz, 1H), 6.53 (d, ^3J=15.9 Hz, 1H), 7.22–7.39 (m, 5H); ^{13}C (75 MHz, ε $CD_3OD/CDCl_3$): δ 26.2, 96.0, 104.7, 126.2, 127.2, 128.0, 128.5, 130.7, 137.4, 155.4, 155.8; IR (neat): ν_{max}=3381 (br, OH), 2986, 2870 (Ar.), 1612 (Ar-O), 1142 cm^{-}1; MS (NH_4^+): *m/z*: 243 (56.9) $[M+H]^+$, 260 (100) $[M+NH_4]^+$, 277 (20.3) $[M+NH_3+NH_4]^+$.

3.1.6. 2-(1-Phenyl-allyl)-phloroglucinol (1d). $C_{15}H_{14}O_3$ (242.27); R_f 0.5 (60% AcOEt/hexane); ^{1}H (300 MHz, ε $CD_3OD/CDCl_3$): δ=5.07–5.39 (m, 2H), 5.21 (br s, 2H, OH), 5.31 (d, ^3J=5.9 Hz, 1H), 5.96 (s, 2H), 7.24–7.34 (m, 5H); IR (neat): ν_{max}=3446 (br, OH), 2983 (Ar.), 1615 (Ar-O), 1217 cm^{-1}; MS (NH_4^+): *m/z*: 243 $[M+H]^+$, 260 $[M+NH_4]^+$.

3.1.7. 2-[3-(3,4-Bisbenzyloxy-phenyl)-allyl]-phloroglucinol (1e). The cinnamyl chloride **3** (0.3 g, 0.82 mmol) in 1.5 mL of THF is slowly added (0.35 mL/h) to the phloroglucinol·$2H_2O$ (0.4 g, 2.47 mmol) in 8 mL of ethanol and 1.5 mL of water and NaOH (0.2 g, 5 mmol). The reaction is stirred at 50 °C for 4 h and the ethanol is partially evaporated under reduced pressure. The resulting aqueous solution is first washed with 200 mL of hexane and extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The residue was purified by flash chromatography on silica gel (30–40% AcOEt/hexane). $C_{29}H_{26}O_5$ (454.51); R_f 0.45 (60% AcOEt/hexane); ^{1}H (300 MHz, ε $CD_3OD/CDCl_3$): δ=3.39 (d, ^3J=5.0 Hz, 2H), 5.02, 5.03 (s, 4H), 5.89 (s, 2H), 6.11 (dt, $^3J_1$=15.9 Hz, $^3J_2$=5.9 Hz, 1H), 6.28 (d, ^3J=15.9 Hz, 1H), 6.78 (dd, $^3J_1$=8.4 Hz, $^4J_2$=1.9 Hz, 1H), 6.84 (d, ^3J=8.4 Hz, 1H), 6.97 (d, ^4J=1.9 Hz, 1H), 7.23–7.41 (m, 10H); ^{13}C (75 MHz, ε $CD_3OD/CDCl_3$): δ=26.8, 72.3, 72.4, 95.4, 106.1, 113.5, 116.3, 120.5, 128.4, 128.5, 128.6, 129.1, 129.2, 133.7, 138.3, 148.7, 149.9, 156.9, 157.4; IR (neat): ν_{max}=3388 (br, OH), 3032, 2925 (Ar.), 1606 (Ar-O), 1509, 1262, 1133 cm^{-1}; MS (NH_4^+): *m/z*: 472 $[M+NH_4]^+$.

3.1.8. 2-[3-(3,4-Bisbenzyloxy-phenyl)-allyl]-phloroglucinol (1f). $C_{29}H_{26}O_5$ (454.51); R_f 0.55 (60% AcOEt/hexane); ^{1}H (300 MHz, $CDCl_3$): δ=5.01–5.28 (m, 2H), 5.07, 5.10 (s, 4H), 5.19 (d, ^3J=6.2 Hz, 1H), 5.92 (s, 2H), 6.30–6.41 (m, 1H), 6.77–6.90 (m, 3H), 7.26–7.43 (m, 10H); MS (NH_4^+): *m/z*: 472 $[M+NH_4]^+$.

3.1.9. 3,4-Dibenzyloxybenzaldehyde (4). A first portion of sodium hydride (60%, 7 g) is added to the 3,4-dihydroxybenzaldehyde (18.65 g, 135 mmol) in 300 mL of dry DMF. After the evolution of gas had ceased, the benzyl bromide (32.92 mL) is added dropwise on the solution. After 1 h, the rest of the NaH is added (5.88 g, 297 mmol total). The reaction is stirred for four additional hours and 600 g of ice is added to the reaction mixture. The aqueous solution is extracted three times with ether. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The brown solid thus obtained is triturated with methanol to afford 36.4 g (85%) of **4**. $C_{21}H_{18}O_3$ (318.37); R_f 0.55 (30% AcOEt/hexane); ^{1}H (200 MHz, $CDCl_3$): δ=5.22 (s, 2H), 5.26 (s, 2H), 7.03 (d, ^3J=8.0 Hz, 1H), 7.26–7.51 (m, 11H), 9.82 (s, 1H); ^{13}C (50 MHz, $CDCl_3$): δ=70.8, 71.0, 112.5, 113.1, 126.6, 127.0, 127.3, 128.0, 128.1, 128.5, 128.6, 130.3, 136.2, 136.5, 149.2, 154.3, 190.8; IR (neat): ν_{max}=3034, 2825, 2729, 1683, 1262, 1130 cm^{-1}; MS (NH_4^+): *m/z*: 319 $[M+H]^+$.

3.1.10. 3-(3,4-Bis-benzyloxy-phenyl)-acrylic acid ethyl ester (5). NaH (5.26 g, 130 mmol) is added to a solution of triethylphosphonoacetate (24.05 mL, 120 mmol) in 300 mL of THF. After the evolution of gas had ceased, the 3,4-dibenzyloxybenzaldehyde (36.4 g, 114 mmol) is added and the reaction is stirred for 10 min. 400 g of ice is added to the reaction mixture and the aqueous solution is extracted three times with ethyl acetate. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The residue was rapidly filtered (AcOEt) on a short pad of silica to afford 44.2 g (100%) of the acrylate. $C_{25}H_{24}O_4$ (388.46); R_f 0.45 (20% AcOEt/hexane); ^{1}H (200 MHz, $CDCl_3$): δ=1.33 (t, ^3J=7.2 Hz, 3H), 4.25 (q, ^3J=7.2 Hz, 2H), 5.19 (s, 2H), 5.20 (s, 2H), 6.25 (d, ^3J=15.9 Hz, 1H), 6.92 (d, ^3J=8.4 Hz, 1H), 7.07 (dd, $^3J_1$=8.4 Hz, $^4J_2$=2.2 Hz, 1H), 7.13 (d, ^4J=2.2 Hz, 1H), 7.32–7.48 (m, 10H), 7.80 (d, ^3J=15.9 Hz, 1H); ^{13}C (50 MHz, $CDCl_3$): δ=14.4, 60.4, 71.0, 71.3, 113.7, 114.3, 116.2, 122.8, 127.2, 127.3, 128.0, 128.6, 136.8, 144.4, 148.9, 151.0, 167.2. IR (neat): ν_{max}=2972, 2926, 2866, 1739, 1716, 1511, 1230 cm^{-1}. MS (NH_4^+): *m/z*: 389 $[M+H]^+$.

3.1.11. 3′,4′-Dibenzyloxycinnamyl alcohol (6). $LiAlH_4$ (0.195 g, 5.15 mmol) is added over 5 min to a solution of the acrylate (2.00 g, 5.15 mmol) in 60 mL anhydrous ether at −15 °C (RM: to avoid the precipitation of the acrylate, the addition must start right after the flask is cooled). The reaction is stirred for 2 h and a few drops of conc. $Na_2S_2O_5$ and 5 g of Na_2SO_4 are added. The residue is rapidly filtered (AcOEt) on a short pad of silica to afford 1.34 g (75%) of pure **6**. $C_{23}H_{22}O_3$ (346.42); R_f 0.25 (40% AcOEt/hexane); ^{1}H (200 MHz, $CDCl_3$): δ=4.27 (dd, $^3J_1$=5.9 Hz, $^4J_2$=1.5 Hz, 2H), 5.18, 5.17 (s, 4H), 6.18 (dt, $^3J_1$=15.9 Hz, $^3J_2$=5.9 Hz, 1H), 6.50 (dt, $^3J_1$=15.9 Hz, $^4J_2$=1.5 Hz, 1H), 6.90–7.04 (m, 3H), 7.28–7.51 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ=61.9, 69.4, 69.5, 111.1, 113.1, 118.5, 125.0, 125.4, 125.5, 126.0, 126.1, 126.7, 126.8, 128.6, 129.0, 135.4, 147.0, 147.2; IR (neat): ν_{max}=3065 (br, OH), 3035, 2920, 1512, 1259 cm^{-1}; MS (NH_4^+): *m/z*: 364 $[M+NH_4]^+$.

3.1.12. 3-(3,4-Bis-benzyloxy-phenyl)-1-chloro-prop-2-ene (3). Thionyl chloride (0.93 mL, 12.71 mmol) is added dropwise to the cinnamyl alcohol (4 g, 11.56 mmol) and triethylamine (1.85 mL, 13.29 mmol) in 100 mL of dichloromethane at 0 °C. After 1 h, 100 mL of water is added and the resulting aqueous solution is extracted three times with methylene chloride. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated under vaccum. The residue was purified by a rapid flash chromatography on silica gel (50% AcOEt/hexane) to give 3.72 g (88%) of the cinnamyl chloride **3**. $C_{23}H_{21}Cl_1O_2$ (364.86). ^1H (200 MHz, $CDCl_3$): δ=4.22 (dd, $^3J_1$=7.3 Hz, $^3J_2$=1.3 Hz, 2H), 5.18, (s, 4H), 6.14 (dt, $^3J_1$=15.7 Hz, $^3J_2$=7.3 Hz, 1H), 6.55 (d, ^3J=15.7 Hz, 1H), 6.88–7.03 (m, 3H), 7.31–7.50 (m, 10H); ^{13}C (50 MHz, $CDCl_3$): δ=46.1, 71.6, 71.9, 113.6, 115.3, 121.1, 123.6, 127.7, 127.8, 128.3, 128.9, 130.0, 134.3, 137.5, 149.5, 149.8; IR (neat): ν_{max}=3032, 2936, 1511, 1263, 1135 cm^{-1}; MS (NH_4^+): *m/z*: 382 $[M+NH_4]^+$.

Acknowledgements

We thank Shannon Biros for reviewing this manuscript and the *Ministère de la recherche et de l'enseignement supérieur* for financial support through a MRE grant to Arnaud Gissot.

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7. *O*/*C*-benzylation=8/2 according to the NMR analysis of the crude mixture.
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Tetrahedron 60 (2004) 6813–6828

Synthesis and acid catalyzed hydrolysis of $B_{2,5}$ type conformationally constrained glucopyranosides: incorporation into a cellobiose analogue

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Accepted 3 June 2004

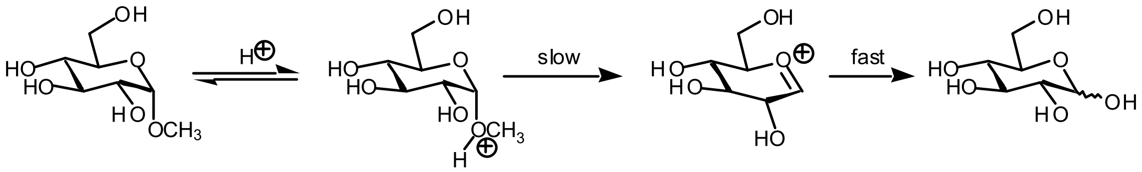
Abstract—Isopropyl and *p*-nitrophenyl α- and β-D-glucopyranosides, restrained in a conformation close to $B_{2,5}$ via an oxymethylene bridge have been synthesized. These four glucopyranosides were found to be hydrolyzed at similar rates, close to those observed for the parent unconstrained glucosides. In such derivatives, either α or β, the exocyclic cleaved bond is synperiplanar to an endocyclic oxygen lone pair. This conformationally locked glucopyranosyl moiety was also incorporated into a disaccharide, affording a conformationally restrained cellobiose analogue which was assayed against various glycosidases.

1. Introduction

Oligo- and polysaccharides, the most abundant biomolecules on earth, are made of monosaccharide monomers connected together through a glycosidic linkage. This bond, which is formed or cleaved during bioprocesses is thus inherently critical for the emergence of the numerous biological properties of this class of compounds. As a consequence, an in-depth understanding of the mechanism of glycosidic bond cleavage is essential.

An increasing number of articles dissecting the enzymatic cleavage of the glycosidic bond by glycosidases have appeared recently, taking advantage of kinetic studies and protein crystallography,[1] but few recent papers are indeed dealing with the non-enzymatic hydrolysis of glycosides:[2] the same set of pioneering articles is usually cited. The chemical hydrolysis of glycopyranosides is indeed a much-studied reaction with a well-established mechanism involving a specific acid catalysis, the rate determining step being the formation of a cyclic alkoxycarbenium ion intermediate (Scheme 1).[3]

Nevertheless, some features of this reaction have yet to be fully explored to quantify the effects, which control reactivity in glycosyl transfer. Bols and co-workers have demonstrated that steric effects are not the cause of the rate difference observed during hydrolysis of stereoisomeric glycopyranosides[4] ruling out long-standing Edward's proposal.[5] They rather suggested that the rate difference can be attributed to the different electron-withdrawing effects of axially and equatorially oriented hydroxyl groups involved in the destabilization of the transient cyclic alkoxycarbenium ion. These findings are in agreement with Withers results invoking a Kirkwood–Westheimer model of field effects to explain the opposite effect on the



Scheme 1. A mechanism for the chemical hydrolysis of alkyl glycopyranosides, involving the protonation of the exocyclic oxygen atom.

Keywords: Carbohydrates; Cellobiose; Conformation; Glycosidase; Hydrolysis.
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doi:10.1016/j.tet.2004.06.009

hydrolysis rates of glycopyranosides of the deoxygenation of hydroxyl groups and their replacement by fluorine.[6] Furthermore, the contribution of torsional effects on reactivity in glycosyl transfer has a significant albeit not large effect on the rate of hydrolysis of glycopyranosides.[7]

The conformational aspects of the chemical hydrolysis of glycopyranosides have been less explored due to the short lifetime of the transient cyclic alkoxycarbenium and the difficulty of probing the conformation of this intermediate.[8] Bennet and Sinnott, using kinetic isotopic effects, have studied the acid-catalyzed hydrolysis of methyl D-glucopyranosides,[9] and concluded that methyl α-D-glucopyranoside was hydrolyzed via a skew or boat conformation whereas the β-anomer reacted through a chair-like conformation. Similar conclusions were drawn with xylopyranosides.[10] We disclose here another approach to generating the conformation adopted by the cyclic alkoxycarbenium and/or the glucopyranoside at the point of hydrolysis: locking the structure of the glycopyranoside in a defined conformation and a subsequent analysis of its behavior towards acid-catalyzed hydrolysis should tell us if this conformation can be operative during oxycarbenium formation.[11] A careful study is necessary because conformational restraints have been shown to have significant effects on the reactivity of tetrahydropyranyl acetals.[12]

Whatever the exact mechanism of glycoside hydrolysis, nucleophilic substitution at the glycosidic bond involves the sugar becoming either an oxycarbenium ion intermediate or passing through a transition state that is highly oxycarbenium ion-like.

Considering the complete map of pyranoid ring interconversions (Fig. 1), including the boat/skew-boat pseudorotational itinerary of the pyranoid ring,[13] and as suggested previously,[14] not only $^4H_3$ and $^3H_4$, but also $B_{2,5}$ and $^{2,5}B$

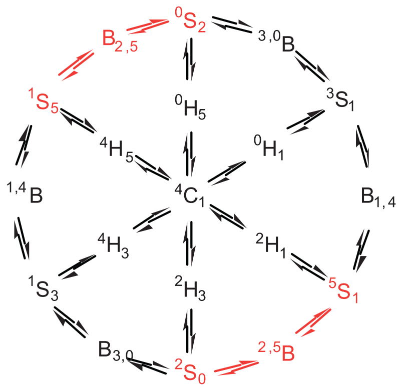


Figure 1. Partial map of pyranoside ring interconversions (adapted from Stoddart).[13]

conformations (Fig. 2) are possible candidates for the conformation of the glycopyranosyl oxycarbenium ion, wherein the four atoms C-5, O-5, C-1 and C-2 become coplanar as the anomeric center is rehybridized from sp^3 to sp^2. An increasing number of these boat type conformations have recently been convincingly observed in nature for some glycosidases that distort the substrate away from the ground state $^4C_1$ conformation before enzymatic hydrolysis.[15]

If the conformation adopted by the sugar prior to oxygen–carbon bond cleavage is indeed $B_{2,5}$ (or $^{2,5}B$), this implies that the antiperiplanar lone pair effect (ALPE)[16] is not operating in the hydrolytic process. Such a cleavage would rather be compatible with synperiplanar assistance, known to be effective in the hydrolysis of constrained tetrahydropyranyl acetals,[17] and consistent with the relevant least nuclear motion effect.[18]

2. Results

In this context, we report the synthesis of *p*-nitrophenyl and isopropyl α- and β-D-glucopyranosides locked in a $B_{2,5}$ conformation and on their rates of hydrolysis under acidic conditions. The selected constrained targets are **1**–**4**, carbon atoms 2 and 5 linked via an oxymethylene bridge.[19] We also envisioned an oxycarbonyl linkage to lock the conformation as in compound **5** (Fig. 3). The choice of both isopropyl and *p*-nitrophenyl glycosides is designed to detect the possibility of endocyclic cleavage, which is always a potential complication, particularly in the acid-catalysed hydrolysis of conformationally restricted glycosides. Comparison of kinetics for these compounds will enable us to tell whether this mechanism is operative because the endocyclic pathway for the hydrolysis of nitrophenyl glycosides would be orders of magnitude slower than for isopropyl derivatives.

Compounds **1**–**5** are confined for stringent geometrical reasons to the following conformational domain of the boat/skew boat itinerary close to $B_{2,5}$:

$$(^1S_5 \rightleftharpoons B_{2,5} \rightleftharpoons {}^0S_2)$$

3. Results and discussion

3.1. Chemical synthesis

The strategy used to synthesize compounds **1**–**5** starts from the known vinyl derivative **6**.[20] It was first converted

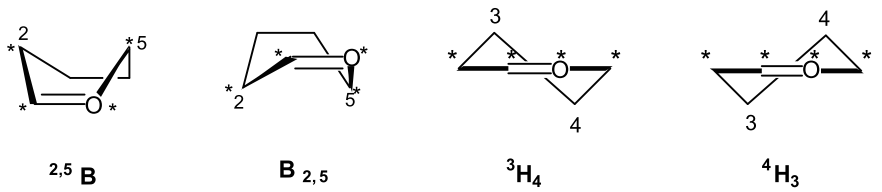


Figure 2. Possible conformations for a glycopyranosyl oxycarbenium ion. Hydroxyl groups have been omitted for the sake of clarity. Coplanar atoms are indicated with asterisks (adapted from Berti and Tanaka).[14]

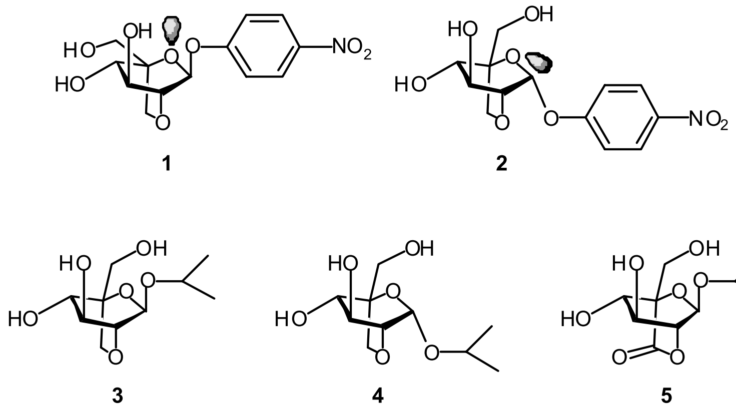
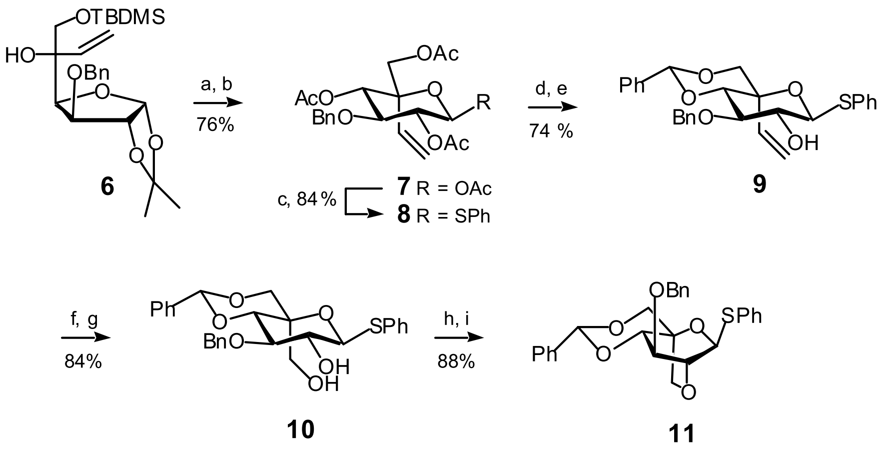


Figure 3. Structure of the conformationally constrained α- and β-D-glucopyranosides **1**–**5**, showing the *syn*-periplanarity of one pyranoside orbital of the intracyclic oxygen and of the glycosidic bond.



Scheme 2. Synthesis of the glycosyl donor **11**. Reagents and conditions: (a) IR-120 H^+ resin, dioxan, H_2O, 90 °C; (b) Ac_2O, DMAP, pyridine, rt; (c) PhSH, $BF_3{\cdot}OEt_2$, anhydrous CH_2Cl_2, rt; (d) CH_3ONa, CH_3OH, rt; (e) $PhCH(OMe)_2$, CSA, DMF, rt; (f) O_3, CH_2Cl_2, −78 °C; (g) $NaBH_4$, EtOH, rt; (h) TsCl, DMAP, pyridine, rt; (i) NaH, DMF, rt.

into the conformationally restrained glycosyl donor **11** (Scheme 2).

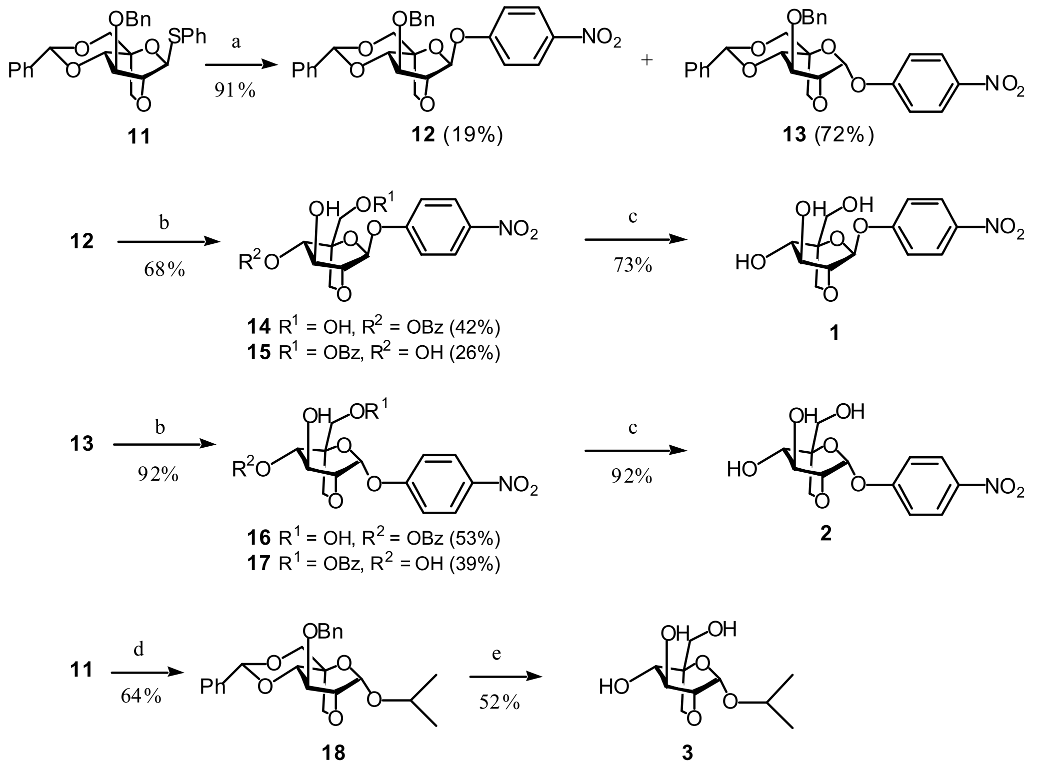
Treatment of compound **6** under acidic conditions afforded the corresponding glucopyranose derivative, which was isolated in 76% yield as the peracetylated derivative **7**. Reaction of **7** with PhSH and $BF_3{\cdot}OEt_2$ in dry dichloromethane gave the thiophenyl derivative **8** in 84% yield. Deacetylation of **8** was followed by the easy formation of alcohol **9**. Careful ozonolysis of compound **9**, in order to avoid sulfur oxidation, led to the corresponding aldehyde which was not isolated and directly reduced to the alcohol using sodium borohydride in ethanol to give diol **10** in 62% yield from the thiophenyl glycoside **8**. Subsequent tosylation of the 'neopentylic' alcohol of diol **10**, followed by treatment with NaH in DMF led to cyclisation, affording the glycopyranosyl donor **11** in 88% yield. Compound **11** constitutes a novel conformationally locked glucopyranosyl donor, which was now used to obtain the conformationally locked glycosides **1**, **2** and **3** (Scheme 3).

When compound **11** was treated with *para*-nitrophenol in the presence of *N*-iodosuccinimide (NIS) and triflic acid in dichloromethane, the *para*-nitrophenyl β-D-glucopyranoside **12** and α-D-glucopyranoside **13** were obtained in high yield (91%) and in a 1:4 ratio. Treatment of glucoside **12** with sodium bromate and sodium dithionite in ethyl acetate/water[21] simultaneously performed the opening of the benzylidene acetal and the cleavage of the benzyl ether to afford a mixture of the 4-*O*-benzoyl derivative **14** and the 6-*O*-benzoyl derivative **15** in 68% yield. Deprotection of the benzoate **14** and **15** with sodium methoxide in methanol afforded the *p*-nitrophenyl β-D-glucoside **1** in 73% yield.

The same sequence was uneventfully applied to compound **13** to afford the *p*-nitrophenyl α-D-glucoside **2** in 84% overall yield.

Compound **3** was also obtained from glycosyl donor **11**. Its treatment with dry isopropanol in the presence of *N*-chlorosuccinimide (NCS) gave the protected isopropyl α-D-glucoside **18** along with traces of the corresponding protected β-D-glucoside. Surprisingly, hydrogenolysis of **18** under various conditions only led to decomposition products. Fortunately, reduction with Na-liq. NH_3 afforded the pure α-D-glucoside **3** after careful column chromatography.

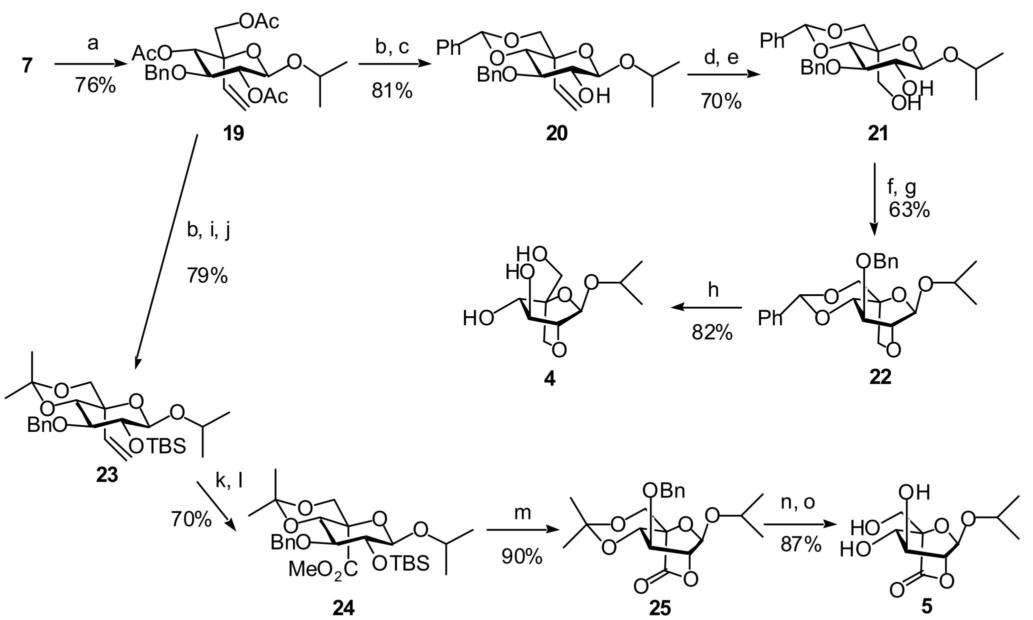
Compounds **4** and **5** were now synthesized from the isopropyl β-D-glucopyranoside **19**, obtained by glycosylation



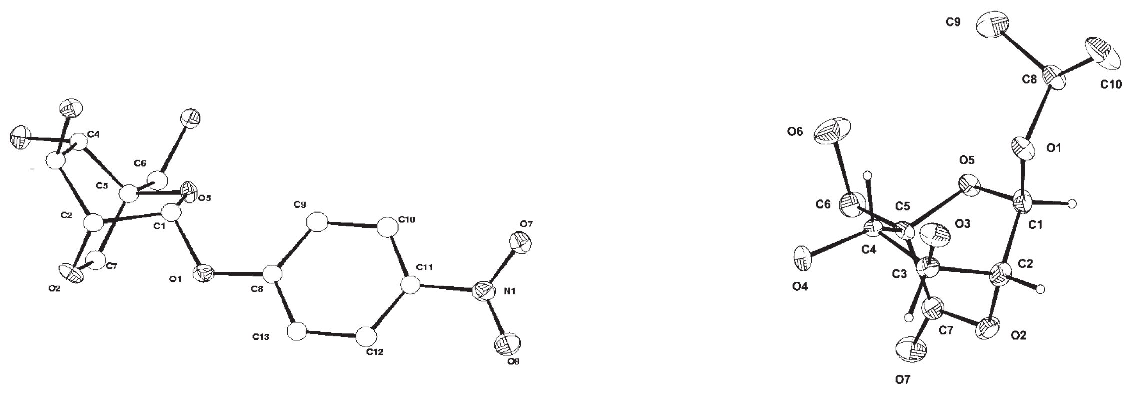
Scheme 3. Synthesis of compounds **1**, **2** and **3**. Reagents and conditions: (a) *para*-nitrophenol, NIS, TfOH, CH_2Cl_2, −30 °C; (b) $NaBrO_3$, $Na_2S_2O_4$, EtOAc, H_2O, rt; (c) CH_3ONa, CH_3OH, rt; (d) NCS, dry isopropanol, rt; (e) Na, liq. NH_3.

in 76% yield from the acetate **7** using anhydrous isopropanol and TMSOTf (Scheme 4). An unevent series of reactions similar to that previously described led to the target **4**.

The lactone **5** was obtained in eight steps from isopropyl β-D-glucopyranoside **19** which was first deacetylated and then fully protected using isopropylidene acetal and *tert*-butyldimethylsilyl protecting groups to give compound **23**. Prolonged ozonolysis of the C═C bond yielded the corresponding carboxylic acid which was not isolated and directly converted to its methyl ester **24** using iodomethane and $KHCO_3$ in DMF. Selective removal of the silyl protection group with TBAF gave the corresponding



Scheme 4. Synthesis of compounds **4** and **5**. Reagents and conditions: (a) TMSOTf, dry isopropanol, rt; (b) CH_3ONa, CH_3OH, rt; (c) $PhCH(OMe)_2$, CSA, DMF, rt; (d) O_3, CH_2Cl_2, −78 °C; (e) $NaBH_4$, EtOH, rt; (f) TsCl, DMAP, pyridine, rt; (g) NaH, DMF, rt; (h) H_2, Pd/C, CH_3OH, rt; (i) $Me_2CH(OMe)_2$, CSA, DMF, rt; (j) TBDMSCl, imidazole, DMF, 60 °C; (k) O_3, CH_2Cl_2, −78 °C; (l) MeI, $KHCO_3$, DMF, rt; (m) TBAF, THF, rt; (n) 60% aq. AcOH, 60 °C; (e) H_2, Pd/C, CH_3OH, rt.



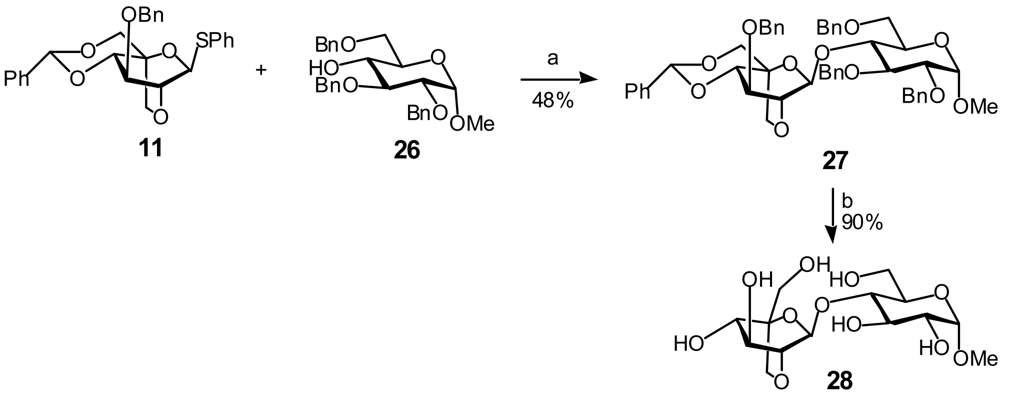
Compound **2** Compound **5**

Figure 4. Crystallographic structure of compounds **2** and **5**.

alcoholate with spontaneously lactonized, affording the fully protected δ-lactone **25**. Final deprotection using aq. AcOH followed by hydrogenolysis furnished compound **5** as a crystalline compound. Compound **5** is interesting regarding human α-L-iduronidase, a family 39 glycosidase supposed to distort its substrate in a ^{2,5}B conformation with a possible neighboring group participation of the carboxylate.[22] Lactone **5** could thus mimick the conformationally locked intermediate suggested by Withers.

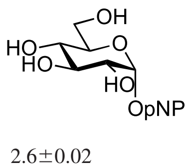
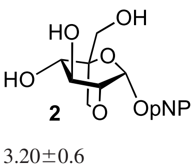
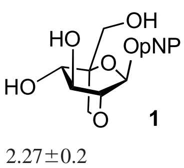
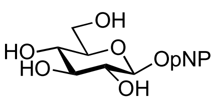
^{1}H NMR of compounds **1**–**5** indicated that they adopted in solution a conformation close to $B_{2,5}$.[23] This boat conformation was also observed in the solid state for compounds **2** and **5**, which were crystalline, and for which X-ray structures have been solved (Fig. 4).[11,24]

Finally, the conformationally restrained glycosyl donor **11** was used to obtain a cellobiose analogue containing a monosaccharide unit locked in $B_{2,5}$ conformation. Reaction of thiophenyl glucoside **11** with the known methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[25] **26** in the presence of NIS, triflic acid and 4 Å molecular sieves in dry dichloromethane afforded exclusively the β linked fully protected disaccharide **27**. This selectivity can be explained by the steric hindrance created by the oxymethylene bridge vis à vis the bulky glycosyl acceptor. Hydrogenolysis of the



Scheme 5. Synthesis of disaccharide **28**. Reagents and conditions: (a) NIS, 4 Å molecular sieves, dry dichloromethane, −40 °C; (b) H_2, Pd/C, CH_3OH, rt.

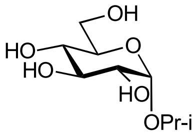
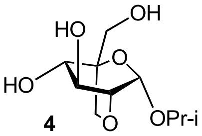
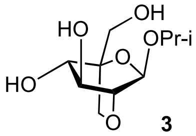
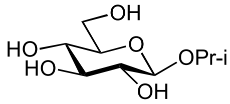
Table 1. Hydrolysis of *p*-nitrophenyl compounds[a]

		 **2**	 **1**	
$10^4 k_{obs}/s^{-1}$	2.6±0.02	3.20±0.6	2.27±0.2	0.35±0.01[b]
k_{rel} (70 °C)	1.0	1.23	0.87	0.13[5]
$\Delta H^{\ddagger}$/kJ mol^{-1}	116±8	108±3	96.2±1.4	110±12
$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}	24±23	2.4±10	−35±42	−8±34

[a] Notes. Data collected at three temperatures in the ranges 60–70 °C, in 1 M aqueous HCl. Rate constants quoted are for 70 °C (full data appear in Table 3 below). Rates and thermodynamic parameters for the parent glucosides are consistent with previous measurements.

[b] Data collected at three temperatures in the ranges 70–80 °C, in 1 M aqueous HCl.

Table 2. Hydrolysis of isopropyl compounds[a]

		 **4**	 **3**	
$10^4 k_{obs}/s^{-1}$	6.9±0.4	4.2±1.1	2.3±0.5	1.6±0.1
k_{rel} (80 °C)	1.0	0.61	0.33	0.23
No. signals followed[b]	3 (1)	4 (2)	5 (2)	2 (1)

[a] Notes. Reactions followed by ^{1}H NMR at 80 °C, in 1 M aqueous DCl/D_2O. For solubility reasons the solvent D_2O contained 10% of dioxan-d_8 for the reactions of the constrained compounds (**3** and **4**). Rate constants for the parent glucosides are consistent with previous measurements.

[b] Number of readily discernable peaks followed to stable end point (see the text).

benzyl groups yielded the cellobiose analogue **28** (Scheme 5).

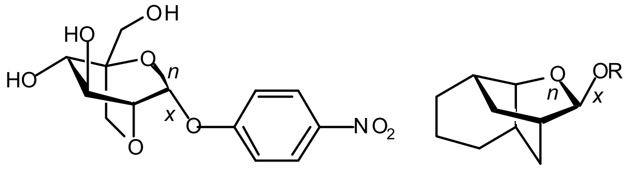
3.2. Reactivity of the constrained glycosides

We report rates of acid-catalyzed hydrolysis for the four conformationally constrained compounds **1**–**4** under standard conditions (1 M HCl, ionic strength 1.0 M). For comparison we have measured also the rates of hydrolysis of the corresponding unconstrained glucosides, *p*-nitrophenyl and isopropyl α- and β-glucopyranosides,[26] under the same conditions. Results appear in Tables 1 and 2.[27] The reactions of the *p*-nitrophenyl derivatives were studied over a range of temperatures and HCl concentrations, providing second order rate constants for acid catalysis and thermodynamic parameters for the hydrolysis reactions (see Section 5, Table 3). Table 1 compares first order rate constants in 1 M HCl (identical to the second order rate constants) at 70 °C for the *p*-nitrophenyl compounds. The hydrolyses of the isopropyl compounds were followed by ^{1}H NMR, in 10% dioxan-d_8—D_2O in 1 M DCl at 80 °C. Thus internal comparisons, for the *p*-nitrophenyl compounds (Table 1) and the isopropyl derivatives (Table 2) are for identical conditions, but comparisons between the tables are not. However, the differences are expected to be small: the solvent deuterium isotope effect, of the order of 2 for the acid catalyzed hydrolysis of alkyl glycosides, slows the reactions of the isopropyl compounds by this factor, partly compensating for the higher temperature (a factor of the order of 3 for 10 °C, according to the thermodynamic parameters of Table 1). The solvent effect of 10% dioxan is considered negligible.

Table 3. Second order rate constants for the acid-catalysed hydrolysis of *p*-nitrophenyl glycosides, in 0.8–1.0 M HCl and ionic strength 1.0

Compound	$k_{H+}\times10^5$/dm^3 mol^{-1} s^{-1} at temperature (in °C) given below				
	60	65	70	75	80
α-pNP-Glu	6.7±0.4	13.7±1.0	26.0±2.0		
2 α-constr	10.0±0.9	18.6±1.5	32.0±3.6		
1 β-constr	8.0±0.5	11.9±3.2	22.7±2.9		
β-pNP-Glu			3.5±0.2	5.6±0.4	10.9±0.7

The clear conclusion from the results summarized in Tables 1 and 2 is that compounds **1**–**4** are hydrolyzed at rates similar to those of the corresponding unconstrained α-glucosides. The severe conformational constraint imposed by the [2,2,2] bicyclic system, which excludes a significant antiperiplanar n_O-σ^*_{C-OR} interaction in the reactant, reduces reactivity scarcely at all for either *p*-nitrophenyl system **1** or **2**: and by factors of only 2 and 3 for the isopropyl derivatives **3** and **4**. In each case the differences are smaller than the well-known differences in reactivity between the anomers of the parent unconstrained glucosides. Apparently the synperiplanar lone pairs of these constrained compounds stabilize the developing oxocarbenium ion character in the transition state for acid catalyzed cleavage about as effectively as the antiperiplanar lone pairs of the unconstrained α-glucosides. In the case of the tetrahydropyranyl system **29** (R=Ar) (Fig. 5) it was concluded, on the basis of a crystal structure correlation (see below), that the synperiplanar n_O-σ^*_{C-OR} interaction is somewhat weaker in the reactant ground state, and that at least part of its observed reactivity must derive from the higher ground state energy of the boat conformation.



2 **29**

Figure 5. Structure of compounds **2** and **29**.

Though both α- and β-constrained compounds possess similar synperiplanar lone pair/leaving group n_O-σ^*_{C-OR} interactions in their ground states the rates of hydrolysis of the α-constrained compounds are higher than those of the β-constrained compounds, by 41 and 83%, respectively, for the *p*-nitrophenyl and isopropyl compounds. It is unlikely that these small effects have a simple, single explanation. Possible contributions from the different patterns of functionalities surrounding the glycosidic center are the enhanced β-effect of the C(2)–O of the C(6)–O bridge, which is antiperiplanar to the bond to the leaving group in the β-anomers, and internal hydrogen-bonding between the C(3)–OH and the incoming water nucleophile (similar to that suggested by Sinnott and Jencks to explain differences in reactivity to solvolysis of α- and β-glucopyranosyl fluorides).[28]

3.3. Ground state effects

Bond length (x)—leaving group (pK_a of ROH) correlations for the series of tetrahydropyranyl acetals **29** (R=Ar), constrained in the symmetrical boat conformation by the 3-carbon bridge, are consistent with a substantial ground state n_O-σ^*_{C-OR} interaction, though one which is weaker in the synperiplanar than in the antiperiplanar geometry[17] (observed bond-length changes are considered a 'more or less uncomplicated measure of stereoelectronic effects' in this system). However, the rates of (spontaneous) hydrolysis are significantly more sensitive to the leaving group for the constrained system. The rate of acid catalyzed hydrolysis of the methyl acetal (**29**, R=Me) is similar to that of 2-methoxytetrahydropyran (corresponding conformationally to an α-glucoside), as observed for the isopropyl derivative **4** described in this paper.

Of the present series of compounds we have a crystal structure only for the constrained α-*p*-nitrophenyl derivative **2** (Fig. 4). The data are not of high accuracy, and conclusions based on a single structure must be very tentative. However, the pattern of bond lengths at the anomeric center is consistent with the operation of substantial (and comparable) n_O-σ^*_{C-OR} interactions in **2** and in the corresponding α-D-glucopyranoside, but little or none in the case of the β-D-glucopyranoside. Thus the length of the exocyclic C–O bond *x* at the acetal center is 1.413(8) Å in **2**, the same as observed for *p*-nitrophenyl α-D-glucopyranoside (1.415(3) Å[29] and significantly greater than the value of 1.404 Å (based on the good bond length-leaving group correlation established for a series of β-D-glucopyranosides)[29] expected for the corresponding bond in *p*-nitrophenyl β-D-glucopyranoside.

3.4. Glycosidase inhibition

Cellobiose analogue **28** was first assayed against a variety of commercially available glycosidases. Compound **28** did not show inhibition at a concentration of 0.2 mmol mL^{-1} on yeast α-glucosidase, almond β-glucosidase, Jack bean α-mannosidase, green coffee bean α-galactosidase, bovine liver α-galactosidase, bovine kidney β-*N*-acetylglucosaminidase, *Penicillium decumbens* naringinase, *Aspergillus niger* amyloglucosidase and human placenta α-L-fucosidase. We then investigated the inhibition of compound **28** on barley β-D-glucan glucohydrolase, a family GH3 glycoside hydrolase that catalyses hydrolytic removal of non-reducing glucosyl residues from β-D-glucans.[30] We expected compound **28** to fit in the two −1 and +1 subsite-binding sites of this glycosidase recently proved to perform substrate distortion.[31] Disaccharide **28** was found to be a weak competitive inhibitor (K_i 16.1 mM) of this enzyme, probably because this glycosidase does not perform a substrate distorsion toward a $B_{2,5}$ conformation but rather a $^4H_3$ conformation as suggested by the very tight binding of a glucophenylimidazole adopting a $^4H_3$ conformation.[31] Finally, compound **28** was tested against Cel6A, Cel7A and Cel7B cellobiohydrolases from *Trichoderma Reesei*,[32] which degrade crystalline cellulose very efficiently, releasing cellobiose from one or the other chain end. Vasella et al. showed that glycosidase inhibitors based on a lactone motif and adopting a half-chair conformation happened to be weak inhibitors of these enzymes, their shape being probably not complementary to the −1 subsite of these cellulases.[33] This is in keeping with the distorsion of the glucosyl unit in the −1 subsite towards a skew-boat conformation observed in the crystal structure of one of the members of the family-7 glycosidases, EGI of *Fusarium oxysporum*, in complex with a thioglucoside.[34] Disaccharide **28**, displaying a distorted $B_{2,5}$ glucose unit, was only found to inhibit weakly Cel7B (K_i 3.4 mM) and did not inhibit nor was cleaved by Cel6A and Cel7A. The limited size of disaccharide **28** makes it unable to span in the important −2, −1, +1 and +2 subsites of the active site and is probably responsible for its lack of inhibition.[35] These results could also be rationalized by a possible steric clash between the nucleophile in the active site and the bridge present in the disaccharide.

4. Conclusion

We have synthesized five monosaccharides **1**–**5** locked in a $B_{2,5}$ conformation. Compounds **1**–**4** were hydrolyzed in acid at similar rates, close to those reported for the corresponding unlocked glucosides. This confirms that $B_{2,5}$ transient conformations of glycosides can indeed be acceptable candidates for direct acid hydrolysis, despite the fact that ALPE is not operating. Incorporation of this glucosyl unit into a disaccharide **28** yielded a cellobiose analogue which displayed only weak inhibition of cellobiohydrolases and barley β-D-glucan glucohydrolase. Nevertheless, these new glucosyl scaffolds adopting a boat conformation are interesting candidates to probe glycosidases that distort their substrate towards a $B_{2,5}$ conformation during or prior to hydrolysis. This is in keeping with the design of an increasing number of inhibitors adopting a boat conformation.[36] Furthermore, inhibitory results for several inhibitors have now been rationalized by invoking such a boat conformation.[37]

5. Experimental

5.1. Kinetics of hydrolysis

The hydrolyses of the *p*-nitrophenyl glucosides and the constrained compounds **1** and **2** were followed spectrophotometrically 348.6 nm, the wavelength of maximum change in absorbance for the hydrolysis of *p*-nitrophenyl glucosides to *p*-nitrophenol occurs. Stock solutions (containing approximately 6 mg mL^{-1}) were prepared in water (*p*-nitrophenyl glucosides) and 20% v/v 1,4-dioxane/water (for constrained compounds **1** and **2**, which are insoluble in pure water). 'Constant pH' solutions 1.0, 0.9 and 0.8 M in hydrochloric acid were made from Convol® stock solutions and their ionic strength adjusted to a value of 1.0 M (where necessary) by the addition of an appropriate volume of 2.0 M potassium chloride solution. For kinetic runs aliquots (20 or 60 μL) were injected into 2.4 mL volumes of the constant pH solutions, to give final 1,4-dioxane concentrations <0.5% v/v in the case of the constrained compounds. Reactions were followed over a range of temperatures for each glycoside and pseudo-first-order rate constants (k_{obs}, Table 3) obtained by non-linear least squares fitting of $A_{348.6}$ vs. time data to a standard first order equation. Derived second order rate constants are given in Table 3.

The isopropyl glucosides and the constrained compounds **3** and **4** do not contain strong chromophores, and their acid catalyzed hydrolysis reactions cannot be followed by UV spectroscopy. The hydrolysis of alkyl glycosides is most often followed by polarimetry, observing a change in optical rotation of with time. Choice of a suitable wavelength, at which a large change in specific rotation occurs over the course of a reaction, allows relatively low (mg mL^{-1}) concentrations of glycosides to be used. Compounds **3** and **4** were available in only small quantities, but a variable wavelength polarimeter was not available. So the rates of acid catalyzed hydrolysis of the isopropyl glycosides and their hydrolyses were followed by ^{1}H NMR. This method also required relatively large amounts of material (ca. 30 mg per kinetic run), so a maximum of two runs could be carried out for each compound. Reactions were followed in 1 M DCl in D_2O (containing 10% 1,4-dioxane-d_8 for the constrained compounds), so the rates of reaction obtained are not exactly comparable with those of the *p*-nitrophenylglucosides (obtained in protic media): though the opposite effects of the solvent deuterium isotope effect and the 10 °C difference in temperature partly cancel out.

The ^{1}H NMR spectra obtained for these hydrolysis experiments were less than ideal for the purpose. Peaks that could be readily assigned to starting material or product were often not well resolved, and in such cases it was not possible to derive kinetic data from changes in integrated peak areas. However, the reactions of the isopropylglucosides could be followed by observing the variation in chemical shift for a number of protons in the spectra. The data obtained in this way are shown in Table 4.

Table 4. Rate constants for the hydrolysis of isopropyl glycosides, in 1 M HCl at 80 °C and ionic strength 1.0[a]

Compound	k_{D+}×10^5/M^{-1} s^{-1} at 80 °C	No. of peaks followed (no. of runs carried out)
α-*i*-Pr-Glu	69±4	3 (1)
4 α-constr	46±17	4 (2)
3 β-constr	23±5	5 (2)
β-*i*-Pr-Glu	16±1	2 (1)

[a] Notes. Rates followed by ^{1}H NMR (see the text).

5.2. General methods

Melting points were determined with a Büchi model 535 mp apparatus and are uncorrected. Optical rotations were measured at 20±2 °C with a Perkin Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Chemical Ionisation Mass Spectra (CI-MS ammonia) and Fast Atom Bombardment Mass Spectra (FAB-MS) were obtained with a JMS-700 spectrometer. Elemental analyses were performed by Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 250 or a Bruker DRX 400. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck).

5.2.1. 1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-5-*C*-vinyl-β-D-glucopyranoside 7. Vinyl derivative **6** (14.66 g, 0.032 mol) was dissolved in a 1:1 mixture of 1,4-dioxane/water (200 mL). Ion exchange resin IR-120 (20 g) was added and the solution was stirred for 18 h at 90 °C. The reaction mixture was cooled to rt and the resin was filtered, washed with water (100 mL). The solvent was evaporated and the residue was dried on a vacuum pump to afford the crude tetrol, which was directly used for the next step. Crude tetrol was dissolved in dry pyridine (100 mL) under argon and the solution cooled to 0 °C. Acetic anhydride (30 mL) and DMAP (50 mg) were added and the reaction mixture was stirred for 15 h at rt. The solvent was removed under reduced pressure and the residue co-evaporated with toluene (2×50 mL). Purification by column chromatography (EtOAc/cyclohexane 1:4→1:3) afforded compound **7** (11.5 g, 0.025 mol, 76%) as a crystalline solid.

$[\alpha]_D^{22}=-73$ (c=1 in $CHCl_3$); mp 111 °C (ethyl acetate/*n*-pentane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.37–7.25 (m, 5H, Ph), 5.98–5.89 (m, 3H, H-1, H-7, H-8), 5.67 (dd, *J*=3.0, 9.2 Hz, 1H, H-8′), 5.46 (d, *J*=10.1 Hz, 1H, H-4), 5.26 (dd, *J*=8.4, 9.6 Hz, 1H, H-2), 4.63 (s, 2H, CH_2Ph), 4.18 (d, *J*=12.5 Hz, 1H, H-6), 3.76 (t, *J*=9.8 Hz, 1H, H-3), 3.72 (d, *J*=12.5 Hz, 1H, H-6′), 2.21 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.14 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.61, 169.44, 168.97, 168.90, (4×C=O), 137.56 (C*ipso*), 129.66 (CH-7), 128.41, 127.82, 127.56 (Ph), 121.98 (CH_2-8), 88.67 (CH-1), 78.36 (C-5), 77.83 (CH-3), 74.54 (CH_2Ph), 72.44 (CH-2), 69.28 (CH-4), 64.99 (CH_2-6), 20.85, 20.78, 20.69, 20.62 (4×OAc); MS (CI, NH_3): *m*/*z* (%): 482 (100) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{23}H_{28}O_{10}$ (464.47): C 59.47, H 6.07; found C 59.59, H 6.17.

5.2.2. Phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-5-*C*-vinyl-1-thio-β-D-glucopyranoside 8. Tetraacetate **7** (11.5 g, 0.025 mol) was dissolved in dry CH_2Cl_2 (150 mL) and the solution cooled to 0 °C. Thiophenol (3.1 mL) was added dropwise followed by $BF_3·OEt_2$ (9.35 mL) and the reaction mixture was stirred at rt. After 10 h, the reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with saturated aq. $NaHCO_3$ (150 mL) and water (150 mL). Organic extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography (EtOAc/cyclohexane 1:4) afforded the thiophenyl derivative **8** (10.83 g, 0.021 mol, 84% yield) as an oil.

$[\alpha]_D^{20}=-64$ (c=1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.63–7.23 (m, 10H, 2×Ph), 5.91 (dd, *J*=11.2, 17.8 Hz, 1H, H-7), 5.49 (d, *J*=11.2 Hz, 1H, H-8), 5.36 (d, *J*=10.2 Hz, 1H, H-1), 5.26 (dd, *J*=0.9, 17.8 Hz, 1H, H-8′), 5.07 (dd, *J*=9.3, 10.1 Hz, 1H, H-3), 4.85 (d, *J*=10.1 Hz, 1H, H-4), 4.62 (d, *J*=11.6 Hz, 1H, CH_2Ph), 4.56 (d, *J*=11.6 Hz, 1H, CH_2Ph), 4.09 (d, *J*=12.2 Hz, 1H, H-6), 3.84 (d, *J*=12.2 Hz, 1H, H-6′), 3.72 (dd, *J*=9.4, 10.1 Hz, 1H, H-2), 2.12, 2.06, 1.99 (3×s, 9H, 3×OAc); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.70, 169.02, 168.91 (3×C=O), 137.70, 130.86 (2×C*ipso*), 134.82, 128.65, 128.40, 127.77, 127.58 (Ph), 130.62 (CH-7), 121.62 (CH_2-8), 80.88 (CH-4), 79.42 (C-5), 79.17 (CH-2), 74.54 (CH_2Ph), 72.13 (CH-3), 69.56 (CH-1), 65.45 (CH_2-6), 20.92, 20.84, 20.73 (3×OAc); MS (CI, NH_3): *m*/*z* (%): 532 (100) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{27}H_{30}O_8S$ (514.60): C 63.02, H 5.88; found C 63.05, H 6.06.

5.2.3. Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-5-*C*-vinyl-1-thio-β-D-glucopyranoside 9. Compound **8** (10.83 g, 0.021 mol) was dissolved in CH_3OH (200 mL) and sodium (500 mg) was added. The solution was stirred for 1 h at rt, ion exchange resin IR-120 (20 g) was added and the reaction mixture stirred for 1 h. The resin was filtered and washed with CH_3OH (100 mL). The solvent was evaporated and the resulting oil was dried on a vacuum pump. The crude diol was dissolved in dry DMF (100 mL) under argon. Benzaldehyde dimethyl acetal (11.5 mL, 0.084 mol) and camphorsulphonic acid (100 mg) were added under argon and the soluton stirred at rt for 14 h. The reaction was quenched by addition of triethylamine (2 mL). The solvent was removed under vacuum and co-evaporated with toluene (2×50 mL). Purification by column chromatography (EtOAc/cyclohexane 1:6) afforded the alcohol **9** (8.28 g, 0.016 mol, 74% yield) as an oil.

$[\alpha]_D^{20}=-8$ (c=1 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.19–7.48 (m, 15H, 3×Ph), 6.28 (dd, J=11.4, 17.9 Hz, 1H, H-7), 5.69 (s, 1H, CHPh), 5.51 (d, J=11.3 Hz, 1H, H-8), 5.39 (d, J=17.9 Hz, 1H, H-8′), 5.03 (d, J=9.8 Hz, 1H, H-1), 4.98 (d, J=11.5 Hz, 1H, CH_2Ph), 4.82 (d, J=11.5 Hz, 1H, CH_2Ph), 4.13 (d, J=9.7 Hz, 1H, H-6), 3.96 (d, J=9.7 Hz, 1H, H-6′), 3.81 (m, 2H, H-3, H-4), 3.60 (m, 1H, H-2), 2.77 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.03, 137.08, 130.93 (3×C*ipso*), 134.85 (CH-7), 128.98, 128.85, 128.43, 128.33, 128.17, 127.98, 127.75, 126.02 (Ph), 119.16 (CH_2-8), 102.30 (CHPh), 83.64 (CH-1), 83.00 (CH-4), 78.27 (CH-3), 77.25 (CH_2-6), 74.62 (CH_2Ph), 73.23 (CH-2), 72.51 (C-5); MS (CI, NH_3): m/z (%): 494 (100) $[M+NH_4^+]$; elemental analysis: calcd (%) for $C_{28}H_{28}O_5S$ (476.17): C 70.57, H 5.92; found C 70.56, H 5.97.

5.2.4. Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-5-*C*-hydroxymethyl-1-thio-β-D-glucopyranoside 10. Compound **9** (1.1 g, 2.12 mmol) was dissolved in CH_2Cl_2 (50 mL). The solution was cooled to −78 °C. Ozone was bubbled through the solution until appearance of a pale blue colour (2 min). The reaction was then quenched by addition of dimethylsulfide (0.2 mL). The solution was allowed to warm to rt for 1 h, the solvent was evaporated to afford the crude aldehyde which was used directly for the next step. The crude aldehyde was dissolved in EtOH (50 mL) at 0 °C, sodium borohydride (92 mg, 2.54 mmol) was added slowly to the solution and the reaction mixture was stirred at rt for 18 h. The reaction was quenched with methanol (20 mL) and the solvent was removed under reduced pressure and co-evaporated with methanol (2×20 mL). The residue was preadsorbed on silica. Purification by column chromatography (EtOAc/cyclohexane 1:3) afforded the diol **10** (858 mg, 1.79 mmol, 84% yield) as an oil.

$[\alpha]_D^{20}=-34$ (c=0.7 in $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz): δ=7.53–7.07 (m, 15H, 3×Ph), 5.54 (s, 1H, CHPh), 4.85 (d, J=9.9 Hz, 1H, H-1), 4.77 (d, J=11.5 Hz, 1H, CH_2Ph), 4.63 (d, J=11.5 Hz, 1H, CH_2Ph), 4.33 (d, J=10.2 Hz, 1H, H-6), 4.04 (m, 1H, H-7), 3.94 (m, 1H, H-7′), 3.78–3.66 (m, 2H, H-3, H-4), 3.48 (d, J=10.2 Hz, 1H, H-6′), 3.43 (ddd, 1H, H-2), 2.73 (s, 1H, OH), 1.77 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=139.08, 138.03, 132.02 (3×C*ipso*), 130.65, 129.97, 128.95, 128.54, 128.28, 128.22, 128.12, 128.07, 127.90, 125.94 (3×Ph), 102.69 (CHPh), 83.65 (CH-1), 82.92 (CH-4), 77.72 (CH-3), 74.74 (CH_2Ph), 73.13 (CH-2), 72.90 (C-5), 70.62 (CH_2-6), 57.1 (CH_2-7); (CI, NH_3): m/z (%): 498 (100) $[M+NH_4^+]$; elemental analysis: calcd (%) for $C_{27}H_{28}O_6S$ (480.58): C 67.48, H 5.87; found C 67.13, H 6.08.

5.2.5. Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-1-thio-β-D-glucopyranoside 11. Diol **10** (0.76 g, 1.58 mmol) was dissolved in anhydrous pyridine (10 mL) under argon. The solution was cooled to 0 °C. Tosyl chloride (0.6 g, 3.16 mmol) and DMAP (20 mg) were added under argon and the solution stirred at rt for 15 h. Tosyl chloride (300 mg) was further added to complete the reaction. After 7 h, the solvent was removed under reduced pressure and co-evaporated with toluene (2×10 mL). The crude tosylate was dried under vacuum for 1 h and was then dissolved in anhydrous DMF (15 mL) under argon. Sodium hydride (380 mg, 15.8 mmol) was added slowly and the suspension was stirred at rt for 18 h. The reaction was quenched with methanol (30 mL) and the solvent was removed under vacuum and co-evaporated with toluene (2×20 mL). The residue was dissolved in ethyl acetate (80 mL) and washed with water (80 mL). Organic extracts were dried over $MgSO_4$ and the solution concentrated. Purification by column chromatography (EtOAc/cyclohexane 1:4) afforded the bicycle **11** (0.65 g, 1.40 mmol, 88% yield) as an oil.

5.2.6. Spectroscopic data for phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-5-*C*-(2-tosyloxymethyl)-1-thio-β-D-glucopyranoside. $[\alpha]_D^{20}=-7$ (c=1 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.81–7.30 (m, 19H, 4×Ph), 5.60 (s, 1H, CHPh), 4.89 (d, J=10.0 Hz, 1H, H-1), 4.84 (d, J=11.4 Hz, 1H, CH_2Ph), 4.74 (d, J=11.4 Hz, 1H, CH_2Ph), 4.62 (d, J=11.2 Hz, 1H, H-7), 4.54 (d, J=11.2 Hz, 1H, H-7′), 4.34 (d, J=10.8 Hz, 1H, H-6), 3.80 (d, J=10.5 Hz, 1H, H-4), 3.72 (m, 1H, H-3), 3.65 (d, J=10.8 Hz, 1H, H-6′), 3.55 (dd, 1H, H-2), 2.48 (s, 3H, $PhCH_3$ tosyl), 2.09 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=[145.13, 137.87, 136.55, 131.97, 131.53 (5×C*ipso*)], [132.15, 130.00, 129.97, 129.19, 129.12, 128.98, 128.62, 128.43, 128.18, 128.13, 128.07, 128.00, 127.96, 127.94, 127.89, 125.95 (4×Ph)], 102.69 (CHPh), 83.90 (CH-1), 82.46 (CH-4), 77.64 (CH-3), 74.86 (CH_2Ph), 73.17 (CH-2), 71.47 (C-5), 70.48 (CH_2-6), 63.35 (CH_2-7); (CI, NH_3): m/z (%): 652 (100) $[M+NH_4^+]$.

5.2.7. Data for bicycle 11. $[\alpha]_D^{20}=-218$ (c=1 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.58–7.30 (m, 15H, 3×Ph), 5.81 (dd, J=2.3, 1.5 Hz, 1H, H-1), 5.64 (s, 1H, CHPh), 4.32 (t, J=2.7 Hz, 1H, H-2), 4.08 (ddd, J=1.5, 2.7, 4.3 Hz, 1H, H-3), 4.04 (d, J=11.3 Hz, 1H, H-6), 5.98 (d, J=11.3 Hz, 1H, H-6′), 3.91 (dd, J=1.9, 9.4 Hz, 1H, H-7), 4.85 (d, J=11.8 Hz, 1H, CH_2Ph), 4.78 (d, J=11.8 Hz, 1H, CH_2Ph), 4.51 (dd, J=1.7, 4.1 Hz, 1H, H-4), 4.51 (d, J=9.4 Hz, 1H, H-7′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 137.44, 136.95, 136.59 (3×C*ipso*), 130.61, 129.25, 129.03, 128.97, 128.36, 127.81, 127.76, 127.16, 126.15, 126.12 (3×Ph), 101.35 (CHPh), 86.54 (CH-1), 81.23 (CH-4), 78.31 (CH-3), 71.54 (CH_2Ph), 69.97 (CH_2-6), 67.99 (CH-2), 66.45 (CH_2-7), 66.01 (C-5); (CI, NH_3): m/z (%): 480 (100) $[M+NH_4^+]$; elemental analysis: calcd (%) for $C_{27}H_{26}O_5S$ (462.57): C 70.10, H 5.67; found C 70.07, H 5.79.

5.2.8. *para*-Nitrophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-β-D-glucopyranoside 12, *para*-nitrophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-α-D-glucopyranoside 13. Bicycle **11** (652 mg, 1.41 mmol), *para*-nitrophenol (235 mg, 1.69 mmol), 4 Å molecular sieves (1.3 g) were suspended in dry CH_2Cl_2 (20 mL) under argon and the suspension was stirred for 30 min and then cooled to −40 °C. *N*-Iodosuccinimide (381 mg, 1.69 mmol) and triflic acid (19 μL, 0.211 mmol) were added and the solution was stirred at −40 °C to afford a red coloured solution. After 1 h, the reaction mixture was quenched with aq. sat. $NaHCO_3$ (30 mL) and diluted with Et_2O (50 mL). The organic layer was separated, washed with sat. $Na_2S_2O_3$ (50 mL). The aqueous layer was extracted with Et_2O (80 mL). Organic extracts were combined, dried over $MgSO_4$ and the solution concentrated. Purification by column chromatography (EtOAc/cyclohexane 1:10) afforded the α-*para*-nitrophenyl derivative **13** (500 mg, 1.18 mmol, 72% yield) as an oil.

$[\alpha]_D^{22}$=+44 (*c*=0.34 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=8.25 (d, *J*=9.2 Hz, 2H, $PhNO_2$), 7.40–7.55 (m, 10H, 2×Ph), 7.18 (d, *J*=9.2 Hz, 2H, $PhNO_2$), 5.95 (d, *J*=1.1 Hz, 1H, H-1), 5.65 (s, 1H, CHPh), 4.81 (d, *J*=11.6 Hz, 1H, CH_2Ph), 4.69 (d, *J*=11.6 Hz, 1H, CH_2Ph), 4.57 (d, *J*=9.7 Hz, 1H, H-7), 4.22 (dd, *J*=1.1, 3.6 Hz, 1H, H-2), 4.12 (m, 3H, H-3, H-4, H-7′), 4.03 (d, *J*=11.2 Hz, 1H, H-6), 3.91 (d, *J*=11.2 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=161.59, 142.43, 136.97, 136.61, (4×C*ipso*), 129.38, 128.52, 128.35, 128.14, 127.86, 126.12, 125.74, 116.29 (3×Ph), 101.90 (CHPh), 95.97 (CH-1), 81.92, 77.00 (CH-3, CH-4), 71.86 (CH_2Ph), 69.48 (CH_2-6), 68.19 (CH-2), 67.35 (C-5), 66.16 (CH_2-7); MS (CI, NH_3): *m/z* (%): 509 (100) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{27}H_{25}O_8N$ (491.50): C 65.98, H 5.13, N 2.85; found C 65.81, H 5.32, N 2.75.

Further elution afforded the β-*para*-nitrophenyl derivative **12** (130 mg, 0.26 mmol, 19% yield) as an oil.

$[\alpha]_D^{22}$=−265 (*c*=0.21 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=8.26 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 7.38–7.51 (m, 10H, 2×Ph), 7.13 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 5.96 (dd, *J*=1.3, 2.9 Hz, 1H, H-1), 5.59 (s, 1H, CHPh), 4.82 (d, *J*=11.7 Hz, 1H, CH_2Ph), 4.76 (d, *J*=11.7 Hz, 1H, CH_2Ph), 4.50 (d, *J*=9.4 Hz, 1H, H-7), 4.41 (dd, *J*=1.8, 5.0 Hz, H-4), 4.23 (t, *J*=2.7 Hz, 1H, H-2), 4.13 (ddd, *J*=1.3, 2.7 Hz, *J*=5.0 Hz, 1H, H-3), 4.10 (d, *J*=11.5 Hz, 1H, H-6), 3.93 (d, *J*=11.5 Hz, 1H, H-6′), 3.81 (dd, *J*=1.9, 9.4 Hz, H-7′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=161.15, 142.51, 137.78, 136.73 (4×C*ipso*), 129.32, 128.41, 128.34, 127.83, 127.59, 126.07, 125.81, 116.23 (3×Ph), 101.26 (CHPh), 96.82 (CH-1), 81.12 (CH-4), 78.20 (CH-3), 71.74 (CH_2Ph), 69.66 (CH_2-6), 66.09 (C-5), 75.72 (CH_2-7), 75.56 (CH-2); MS (CI, NH_3): *m/z* (%): 509 (100) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{27}H_{25}O_8N$ (491.50): C 65.98, H 5.13, N 2.85; found C 65.80, H 5.25, N 2.72.

5.2.9. *para*-Nitrophenyl 4-*O*-benzoyl-2-*O*,5-*C*-methylene-β-D-glucopyranoside 14 and *para*-nitrophenyl 6-*O*-benzoyl-2-*O*,5-*C*-methylene-β-D-glucopyranoside 15. The β-*para*-nitrophenyl derivative **12** (78 mg, 0.158 mmol) was dissolved in EtOAc (2 mL). A solution of $NaBrO_3$ (144 mg, 0.953 mmol) in water (1.5 mL) was then added at rt followed by dropwise addition over 10 min under vigorous stirring of an aqueous solution (3 mL) of $Na_2S_2O_4$ (150 mg). After 24 h, the reaction mixture was diluted with EtOAc (20 mL). The organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL). Organic extracts were dried over $MgSO_4$ and concentrated. The residue was preadsorbed on silica gel. Purification by column chromatography (EtOAc/cyclohexane 1:2→1:1→EtOAc) afforded the diol **14** (28 mg, 0.067 mmol, 42% yield) as an oil.

$[\alpha]_D^{22}$=−120 (*c*=0.4 in CH_3OH); ^1H NMR (CD_3OD, 400 MHz): δ=8.42 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 8.26 (m, 2H, Ph), 7.83 (m, 1H, Ph), 7.68 (m, 2H, Ph), 7.53 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 6.23 (dd, *J*=1.1, 2.7 Hz, 1H, H-1), 5.63 (dd, *J*=1.8, 4.8 Hz, 1H, H-4), 4.48 (m, 1H, H-3), 4.28 (m, 2H, H-2, H-7), 4.11 (dd, *J*=1.8, 9.7 Hz, 1H, H-7′), 3.85 (d, *J*=12.3 Hz, 1H, H-6), 3.74 (d, *J*=12.3 Hz, 1H, H-6′); ^{13}C NMR (CD_3OD, 100 MHz): δ=167.30, 144.20, 131.10, (3×C*ipso*), 163.32 (C=O), 134.98, 131.06, 130.04 (Ph), 126.89, 118.22 (2×$PhNO_2$), 98.80 (CH-1), 77.40 (CH-4), 77.14 (C-5), 74.92 (CH-3), 69.96 (CH-2), 64.65 (CH_2-7), 62.31 (CH_2-6); MS (CI, NH_3): *m/z* (%): 435 (100) [M+NH_4^+]; HRMS (positive-ion CI, NH_3): calcd for $C_{20}H_{23}O_9N_2$ (M+NH_4^+) 435.1404, found 435.1394.

Further elution afforded the diol **15** (17 mg, 0.040 mmol, 26% yield) as an oil.

$[\alpha]_D^{22}$=−122 (*c*=0.6 in CH_3OH); ^1H NMR (CD_3OD, 400 MHz): δ=8.29 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 8.10 (m, 2H, Ph), 7.72 (m, 1H, Ph), 7.72 (m, 2H, Ph), 7.56 (m, 2H, Ph), 7.38 (d, *J*=9.3 Hz, 2H, $PhNO_2$), 6.16 (d, *J*=1.3, 2.8 Hz, 1H, H-1), 4.72 (d, *J*=11.9 Hz, 1H, H-6), 4.57 (d, *J*=11.9 Hz, 1H, H-6′), 4.32 (dd, *J*=1.8, 5.3 Hz, 1H, H-4), 4.23 (m, 1H, H-3), 4.21 (d, *J*=9.3 Hz, 1H, H-7), 4.18 (t, *J*=2.8 Hz, 1H, H-2), 3.93 (dd, *J*=1.8, 9.3 Hz, 1H, H-7′); ^{13}C NMR (CD_3OD, 100 MHz): δ=167.81, 144.01, 131.35, (3×C*ipso*), 162.89 (C=O), 134.60, 130.84, 129.77 (Ph), 126.77, 118.23 (2×$PhNO_2$), 98.41 (CH-1), 77.10 (C-5), 76.88 (CH-3), 75.13 (CH-4), 69.98 (CH-2), 63.82 (CH_2-6), 63.72 (CH_2-7); MS (CI, NH_3): *m/z* (%): 435 (100) [M+NH_4^+]; HRMS (positive-ion CI, NH_3): calcd for $C_{20}H_{23}O_9N_2$ (M+NH_4^+) 435.1404, found 435.1397.

5.2.10. *para*-Nitrophenyl 2-*O*,5-*C*-methylene-β-D-glucopyranoside 1. *Compound* **1** *from diol* **14**. Diol **14** (20 mg, 0.048 mmol) was dissolved in CH_3OH (10 mL) and CH_3ONa (200 μL of a 1 M methanolic solution) was added. After 30 min, the reaction was complete and was quenched by stirring with resin IR-120 (1 g) for 1 h. The resin was filtered and washed with CH_3OH (20 mL). The solvent was removed under reduced pressure and purification by column chromatography (EtOAc) afforded the triol **1** (11 mg, 0.035 mmol, 73% yield) as a foam.

Compound **1** *from diol* **15**. The same procedure as the one used above afforded triol **1** (12 mg, 0.038 mmol, 70% yield).

$[\alpha]_D^{22}$=−128 (*c*=0.55 in CH_3OH); ^1H NMR (400 MHz, D_2O): δ=8.21 (d, *J*=9.0 Hz, 2H, $PhNO_2$), 7.21 (d,

J=9.0 Hz, 2H, $PhNO_2$), 6.01 (dd, J=1.0, 2.6 Hz, 1H, H-1), 4.12 (t, J=2.7 Hz, 1H, H-2), 4.06 (m, 1H, H-3), 4.02 (dd, J=1.6, 5.1 Hz, 1H, H-4), 3.91 (d, J=9.8 Hz, 1H, H-7), 3.76 (dd, J=1.6, 9.8 Hz, 1H, H-7′), 3.68 (d, J=12.8 Hz, 1H, H-6), 3.64 (d, J=12.8 Hz, 1H, H-6′); ^{13}C NMR (100 MHz, D_2O): δ=161.51, 142.67 (2×C*ipso*), 126.37 (Ph), 116.97 (Ph), 97.09 (CH-1), 76.76 (C-5), 74.62, 73.59, 67.99 (CH-2, CH-3, CH-4), 62.46, 60.48 (CH_2-6, CH_2-7); MS (CI, NH_3): *m/z* (%): 331 (100) [$M+NH_4^+$]; HRMS (positive-ion CI, NH_3): calcd for $C_{13}H_{19}O_8N_2$ ($M+NH_4^+$) 331.1141, found 331.1140.

5.2.11. *para*-Nitrophenyl 4-*O*-benzoyl-2-*O*,5-*C*-methylene-α-D-glucopyranoside 16 and *para*-nitrophenyl 6-*O*-benzoyl-2-*O*,5-*C*-methylene-α-D-glucopyranoside 17. The same procedure as the one used to obtain compounds **14** and **15** was applied to the α-*para*-nitrophenyl derivative **13** (304 mg, 0.619 mmol) to afford the diol **16** (137 mg, 0.328 mmol, 53% yield) as an oil.

$[\alpha]_D^{22}$=+100 (c=0.25 in CH_3OH); ^1H NMR (CD_3OD, 400 MHz): δ=8.44 (d, J=9.3 Hz, 2H, $PhNO_2$), 8.25 (m, 2H, Ph), 7.83 (m, 1H, Ph), 7.72 (m, 2H, Ph), 7.48 (d, J=9.3 Hz, 2H, $PhNO_2$), 6.20 (d, J=1.4 Hz, 1H, H-1), 5.31 (m, 2H, H-1, H-4), 4.34–4.30 (m, 4H, H-2, H-3, H-7, H-7′), 3.81 (d, J=12.5 Hz, 1H, H-6), 3.73 (d, J=12.5 Hz, 1H, H-6′); ^{13}C NMR (CD_3OD, 100 MHz): δ=167.32, 144.08, 131.20 (3×C*ipso*), 163.79 (C=O), 135.00, 131.01, 130.08 (Ph), 127.02, 118.10 (2×$PhNO_2$), 97.16 (CH-1), 78.21 (C-5), 76.17 (CH-4), 73.21, 71.45 (CH-2, CH-3), 65.84 (CH_2-7), 62.80 (CH_2-6); MS (CI, NH_3): *m/z* (%): 435 (100) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{20}H_{19}O_9N$ (417.37): C 57.55, H 4.59, N 3.35; found C 57.64, H 4.77, N 3.22.

Further elution afforded the diol **17** (102 mg, 0.244 mmol, 39% yield) as an oil.

$[\alpha]_D^{22}$=+111 (c=0.3 in CH_3OH); ^1H NMR (CD_3OD, 400 MHz): δ=8.27 (d, J=9.3 Hz, 2H, $PhNO_2$), 7.97 (m, 2H, Ph), 7.68 (m, 1H, Ph), 7.50 (m, 2H, Ph), 7.31 (d, J=9.3 Hz, 2H, $PhNO_2$), 6.12 (d, J=1.4 Hz, 1H, H-1), 4.74 (d, J=12.1 Hz, 1H, H-6), 4.50 (d, J=12.1 Hz, 1H, H-6′), 4.29 (m, 2H, H-4, H-7), 4.24 (m, 2H, H-2, H-7′), 4.02 (m, 1H, H-3); ^{13}C NMR (CD_3OD, 100 MHz): δ=167.65, 143.79, 131.20, (3×C*ipso*), 163.28 (C=O), 134.54, 130.73, 129.70 (Ph), 126.87, 117.97 (2×$PhNO_2$), 96.43 (CH-1), 78.16 (C-5), 75.40, 75.31, 71.96 (CH-2, CH-3, CH-4), 65.35 (CH_2-6), 64.79 (CH_2-7); MS (CI, NH_3): *m/z* (%): 435 (100) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{20}H_{19}O_9N$ (417.37): C 57.55, H 4.59, N 3.35; found C 57.70, H 4.89, N 3.13.

5.2.12. *para*-Nitrophenyl 2-*O*,5-*C*-methylene-α-D-glucopyranoside 2. The same procedure as the one used to obtain compound **1** was applied to diol **17** (102 mg, 0.244 mmol) to afford the triol **2** (70 mg, 0.223 mmol, 92% yield), which was recrystallized from EtOAc.

$[\alpha]_D^{22}$=+106 (c=0.94 in CH_3OH); mp 229–230 °C (EtOAc); ^1H NMR (400 MHz, CD_3OD): δ=8.38 (d, J=9.2 Hz, 2H, $PhNO_2$), 7.44 (d, J=9.2 Hz, 2H, $PhNO_2$), 6.07 (d, J=1.4 Hz, 1H, H-1), 4.18 (dd, J=1.6, 4.5 Hz, 1H, H-3), 4.16 (dd, J=1.4, 4.5 Hz, 1H, H-2), 4.16 (d, J=9.4 Hz, 1H, H-7), 4.12 (dd, J=1.0, 9.4 Hz, 1H, H-7′), 3.97 (m, 1H, H-4), 3.79 (d, J=12.3 Hz, 1H, H-6), 3.75 (d, J=12.3 Hz, 1H, H-6′); ^{13}C NMR (100 MHz, CD_3OD): δ=[164.01, 143.91, (2×C*ipso*)], 126.97 (Ph), 118.02 (Ph), 97.16 (CH-1), 79.34 (C-5), 75.36, 74.38, 71.92 (CH-2, CH-3, CH-4), 65.07, 63.18 (CH_2-6, CH_2-7); MS (CI, NH_3): *m/z* (%): 331 (52) [$M+NH_4^+$]; elemental analysis: calcd (%) for $C_{13}H_{15}O_8N$ (313.26): C 49.84, H 4.83, N 4.47; found C 49.87, H 4.87, N 4.30.

5.2.13. Isopropyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-α-D-glucopyranoside 18. Thiophenyl derivative **11** (500 mg, 1.08 mmol) was dissolved in dry isopropanol (50 mL) and NBS (98 mg, 5.5 mmol) was added under argon. The slurry solution was stirred for 48 h at rt, filtered and concentrated. The crude product was purified by column chromatography (EtOAc/cyclohexane 1:10) to afford compound **18** (290 mg, 0.070 mmol, 64% yield) as a colourless oil.

$[\alpha]_D^{20}$=−38 (c=0.6 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.53–7.30 (m, 10H, 2×Ph), 5.58 (s, 1H, CHPh), 5.30 (s, 1H, H-1), 4.77 (d, J=11.7 Hz, 1H, CHPh), 4.64 (d, J=11.7 Hz, 1H, CHPh), 4.45 (d, J=9.3 Hz, 1H, H-7), 4.05 (dd, J=0.7, 9.3 Hz, 1H, H-7′), 4.01 (t, J=6.2 Hz, 1H, H-8), 3.99 (m, 2H, H-3, H-4), 3.98 (d, J=11.1 Hz, 1H, H-6), 3.91 (m, 1H, H-2), 3.83 (d, J=11.1 Hz, 1H, H-6′), 1.33 (d, J=6.2 Hz, 3H, CH_3-*i*Pr),1.22 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ=138.3, 137.7 (2×C*ipso*), 129.2–126.2 (2×Ph), 101.8 (CHPh), 95.8 (CH-1), 82.3 (CH-3 or CH-4), 77.6 (CH-3 or CH-4), 71.6 (CH_2Ph), 70.5 (CH-8), 70.0 (CH_2-6), 69.0 (CH-2), 66.2 (CH_2-7), 64.9 (C-5), 23.8, 21.9 (2×CH_3-*i*Pr); (CI, NH_3): *m/z* (%): 413 (100) [$M+H^+$]; HRMS (positive-ion CI, NH_3): calcd for $C_{24}H_{29}O_6$ ($M+H^+$) 413.1964, found 413.1963.

5.2.14. Isopropyl 2-*O*,5-*C*-methylene-α-D-glucopyranoside 3. A round-bottom flask, fitted with an ammonia condenser, was charged with **18** (200 mg, 0.49 mmol), dry THF (50 mL) and ammonia (~10 mL) and was cooled to −78 °C. A small amount of lithium was added and the reaction was stirred for 2 min and quenched with NH_4Cl. The reaction mixture was allowed to warm to rt and concentrated. The crude product was purified by column chromatography (EtOAc/cyclohexane 3:1) to afford compound **3** (60 mg, 0.26 mmol, 52% yield) as a colourless oil.

$[\alpha]_D^{22}$=−58 (c=1.65 in CH_3OH); ^1H NMR (CD_3OD, 400 MHz): δ=5.47 (dd, J=1.5, 2.7 Hz, 1H, H-1), 4.24 (m, J=6.2 Hz, 1H, H-8), 4.05 (dd, J=1.8, 4.3 Hz, 1H, H-4), 3.99 (d, J=9.2 Hz, 1H, H-7), 3.92 (m, 1H, H-3), 3.87 (t, J=2.7 Hz, 1H, H-2), 3.78 (s, 2H, H-6, H-6′), 3.77 (dd, J=1.8, 9.2 Hz, 1H, H-7′), 1.43 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.34 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR (D_2O, 100 MHz): δ=99.20 (CH-1), 77.71 (CH-3), 76.79 (C-5), 76.77 (CH-4), 72.15 (CH-8), 69.64 (CH-2), 63.62 (CH_2-7), 62.96 (CH_2-6), 24.33 (CH_3-*i*Pr), 22.24 (CH_3-*i*Pr); MS (CI, NH_3): *m/z* (%): 252 (100) [$M+NH_4^+$]; HRMS (positive-ion CI, NH_3): calcd for $C_{10}H_{22}O_6N$ ($M+NH_4^+$) 252.1447, found 252.1450.

5.2.15. Isopropyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-5-*C*-vinyl-β-D-glucopyranoside 19. Tetraacetate **7** (20 g, 43.1 mmol) was dissolved in dry CH_2Cl_2 (230 mL) and extra dry isopropanol (4.83 mL) and powdered 4 Å molecular sieves (32 g) were added. The solution was stirred for 2 h, cooled to −78 °C and TMSOTf (11.7 mL, 64.6 mmol) was added slowly. The reaction mixture was allowed to warm up to room temperature under stirring and was stirred for another 5 h. The reaction mixture was then quenched with Et_3N, filtered through celite and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (EtOAc/cyclohexane 1:3) afforded the isopropyl derivative **19** (15.3 g, 33 mmol, 76% yield) as a colourless syrup.

$[\alpha]_D^{20}=-79$ (c=0.86 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.26–7.35 (m, 5H, Ph), 6.02 (dd, J=11.1, 17.8 Hz, 1H, H-7), 5.62 (dd, J=1.2, 17.8 Hz, 1H, H-8), 5.59 (dd, J=0.9, 11.1 Hz, 1H, H-8′), 5.44 (d, J=10.1 Hz, 1H, H-4), 5.08 (dd, J=8.0, 9.5 Hz, 1H, H-2), 4.75 (d, J=8.0 Hz, 1H, H-1), 5.07 (dd, J=9.3, 10.1 Hz, 1H, H-3), 4.63 (d, J=11.7 Hz, 1H, CHPh), 4.59 (d, J=11.7 Hz, 1H, CHPh), 4.08 (d, J=12.2 Hz, 1H, H-6), 3.88 (m, J=6.2 Hz, 1H, H-9), 3.83 (d, J=12.2 Hz, 1H, H-6′), 2.12, 2.01 (2×s, 9H, 3×OAc), 1.43 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.34 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.88, 169.03, 168.99 (3×C=O), 137.87 (C*ipso*), 132.19 (CH-7), 128.36, 127.71, 127.62 (Ph), 120.49 (CH_2-8), 95.49 (CH-1), 77.84 (CH-3), 76.63 (C-5), 73.89 (CH_2Ph), 73.70 (CH-2), 72.25 (CH-9), 69.77 (CH-4), 65.68 (CH_2-6), 23.34 (CH_3-*i*Pr), 22.06 (CH_3-*i*Pr), 20.88, 20.78 (3×OAc); MS (CI, NH_3): m/z (%): 582 (100) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{24}H_{32}O_9$ (564.20): C 62.06, H 6.94; found C 62.08, H 6.93.

5.2.16. Isopropyl 3-*O*-benzyl-4,6-*O*-benzylidene-5-*C*-vinyl-β-D-glucopyranoside 20. Compound **19** (2.3 g, 4.96 mmol) was dissolved in dry CH_3OH (70 mL) under argon and sodium (50 mg) was added. The solution was stirred for 16 h, ion exchange resin IR-120 (5 g) was added and the reaction mixture stirred for 1 h. The resin was filtered and washed with CH_3OH (30 mL). The solvent was evaporated and the resulting oil was dissolved in ethyl acetate (50 mL) and washed with water (30 mL). The organic layer was dried over $MgSO_4$ and evaporated. To a solution of crude triol in dry CH_2Cl_2 (75 mL) was added benzaldehyde dimethyl acetal (1.1 mL, 7.2 mmol) and camphorsulphonic acid (50 mg) under argon and the solution was stirred at rt for 12 h. The reaction mixture was quenched with $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (EtOAc/cyclohexane 1:6) afforded alcohol **20** (1.7 g, 3.99 mmol, 81%) as a white needles.

$[\alpha]_D^{20}=-35$ (c=0.62 in $CHCl_3$); mp 99 °C (*n*-pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.93–7.56 (m, 10H, 2×Ph), 6.37 (dd, J=11.2, 18.0 Hz, 1H, H-7), 5.70 (s, 1H, CHPh), 5.65 (dd, J=1.2, 18.0 Hz, 1H, H-8), 5.57 (dd, J=1.2, 11.2 Hz, 1H, H-8′), 4.97 (d, J=11.7 Hz, 1H, CH_2Ph), 4.84 (d, J=7.7 Hz, 1H, H-1), 4.83 (d, J=11.7 Hz, 1H, CH_2Ph), 4.07 (d, J=9.7 Hz, 1H, H-6), 4.03 (m, J=6.2 Hz 1H, H-9), 3.95 (d, J=9.7 Hz, 1H, H-6′), 3.88 (d, J=10.1 Hz, 1H, H-4), 3.75 (dd, J=8.8, 10.1 Hz, 1H, H-3), 3.61 (dt, J=2.4, 7.9 Hz, 1H, H-2), 2.48 (d, J=2.1 Hz, 1H, OH),1.34 (d, J=6.2 Hz, 3H, CH_3-*i*Pr),1.25 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.33, 137.24 (2×C*ipso*), 136.23 (CH-7), 128.98, 128.33, 128.20, 127.91, 127.67, 126.10 (Ph), 118.25 (CH_2-8), 102.38 (CHPh), 97.47 (CH-1), 83.24 (CH-4), 77.46 (CH_2-6), 77.28 (CH-3), 75.36 (CH-2), 74.41 (CH_2Ph), 71.97 (CH-9), 69.75 (C-5), 23.40, 22.00 (2×CH_3-*i*Pr); MS (CI, NH_3): m/z (%): 444 (100) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{25}H_{30}O_6$ (426.5): C 70.40, H 7.09; found C 70.50, H 7.22.

5.2.17. Isopropyl 3-*O*-benzyl-4,6-*O*-benzylidene-5-*C*-hydroxymethyl-β-D-glucopyranoside 21. Ozone was passed through a stirred solution of olefin **20** (1.0 g, 2.3 mmol) in anhydrous CH_2Cl_2 (50 mL) cooled to −78 °C until the appearance of a pale blue colour. The reaction mixture was quenched with $(CH_3)_2S$ (0.2 mL) and allowed to warm to room temperature. The solvent was evaporated. The residue was dissolved in methanol (20 mL) and the solution was cooled to 0 °C, $NaBH_4$ (250 mg, 6.9 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 1 h, cooled to 0 °C and quenched with NH_4Cl. The reaction mixture was evaporated, the residue dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (EtOAc/cyclohexane 1:3) to afford the diol **21** (0.7 g, 70%) as a solid.

$[\alpha]_D^{20}=-46$ (c=0.86 in $CHCl_3$); mp 141 °C (*n*-pentane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.52–7.30 (m, 10H, 2×Ph), 5.68 (s, 1H, CHPh), 4.92 (d, J=11.7 Hz, 1H, CH_2Ph), 4.88 (d, J=7.7 Hz, 1H, H-1), 4.81 (d, J=11.7 Hz, 1H, CH_2Ph), 4.36 (d, J=10.4 Hz, 1H, H-6), 4.22 (dd, J=7.1, 12.0 Hz, 1H, H-7), 4.09 (dd, J=2.7, 12.0 Hz, 1H, H-7′), 4.03 (m, J=6.2 Hz, 1H, H-8), 3.97 (d, J=10.2 Hz, 1H, H-4), 3.88 (dd, J=8.2, 10.2 Hz, 1H, H-3), 3.66 (dd, J=1.2, 10.4 Hz, 1H, H-6′), 3.62 (dd, J=2.7, 7.9 Hz, 1H, H-2), 2.62 (d, J=7.9 Hz, 1H, OH-2), 1.82 (dd, J=3.8, 7.1 Hz, 1H, OH-7), 1.32 (d, J=6.2 Hz, 3H, CH_3-*i*Pr),1.27 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.31, 137.13 (2×C*ipso*), 129.07–126.00 (2×Ph), 102.59 (CHPh), 97.79 (CH-1), 83.08 (CH-4), 77.02 (CH-3), 75.40 (CH-2), 74.35 (CH_2Ph), 72.43 (CH-8), 70.90 (CH_2-6), 70.35 (C-5), 58.30 (CH_2-7), 23.39, 21.97 (2×CH_3-*i*Pr); (CI, NH_3): m/z (%): 448 (35) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{24}H_{30}O_7$ (430,49): C 66.96, H 7.02; found C 66.69, H 7.21.

5.2.18. Isopropyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-β-D-glucopyranoside 22. To a stirred solution of diol **21** (700 mg, 1.6 mmol) in anhydrous pyridine (10 mL) was added TsCl (370 mg, 1.95 mmol), followed by DMAP (50 mg). The reaction mixture was stirred for 12 h at 60 °C, cooled to room temperature and quenched with water. Ethyl acetate was added and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (EtOAc/cyclohexane 1:5) yielding the corresponding tosylate as a colourless oil (700 mg, 1.2 mmol, 74% yield).

5.2.19. Spectroscopic data for tosylate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.86 (d, 2H, aromatic H), 7.84–7.30 (m, 12H, aromatic H), 5.59 (s, 1H, CHPh), 4.87 (d, J=11.7 Hz, 1H, CHPh), 4.86 (d, J=7.9 Hz, 1H, H-1), 4.78 (d, J=11.7 Hz, 1H, CHPh), 4.54 (s, 2H, H-7, H-7′), 4.26 (d, J=10.7 Hz, 1H, H-6), 4.06 (m, J=6.2 Hz, 1H, H-8), 3.89 (d, J=10.3 Hz, 1H, H-4), 3.72 (dd, J=8.7, 10.3 Hz, 1H, H-3), 3.65 (d, J=10.7 Hz, 1H, H-6′), 3.60 (dt, J=2.2, 8.2 Hz, 1H, H-2), 2.47 (s, 3H, CH_3-Ts), 2.44 (d, J=2.5 Hz, 1H, OH-2), 1.31 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.26 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=145.13, 136.70 (2×C*ipso* tosyl), 138.18, 132.29 (2×C*ipso*), 129.98–125.94 (2×Ph), 102.67 (CHPh), 97.62 (CH-1), 82.83 (CH-4), 77.01 (CH-3), 75.33 (CH-2), 74.60 (CH_2Ph), 72.82 (CH-8), 70.68 (CH_2-6), 68.89 (C-5), 64.29 (CH_2-7), 23.31, 21.99 (2×CH_3-*i*Pr), 21.67 (CH_3 tosyl); (CI, NH_3): *m*/*z* (%): 602 (100) [M+NH_4^+]; HRMS (positive-ion CI, NH_3): calcd for $C_{31}H_{40}O_9NS$ (M+NH_4^+) 602.2424, found 602.2430.

The tosylate (500 mg, 0.86 mmol) was dissolved in dry DMF (5 mL) under argon. The solution was cooled to 0 °C and sodium hydride (100 mg, 60% in oil, 2.5 mmol) was added and the reaction mixture was stirred for 1 h at room temperature and quenched with NH_4Cl. Ethyl acetate was added and the organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (EtOAc/cyclohexane 1:8) yielding compound **22** (340 mg, 95%) as a colourless oil.

$[\alpha]_D^{20}$=−42 (c=0.8 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.49–7.30 (m, 10H, aromatic H), 5.57 (s, 1H, CHPh), 5.34 (dd, J=1.2, 2.5 Hz, 1H, H-1), 4.72 (s, 2H, CH_2Ph), 4.40 (d, J=9.2 Hz, 1H, H-7), 4.35 (dd, J=1.8, 4.8 Hz, 1H, H-3 or H-4), 4.03 (d, J=11.2 Hz, 1H, H-6), 4.01 (t, J=6.1 Hz, 1H, H-3 or H-4), 3.99 (m, J=6.2 Hz, 1H, H-8), 3.97 (t, J=2.5 Hz, 1H, H-2), 3.89 (d, J=11.2 Hz, 1H, H-6′), 3.69 (dd, J=1.9, 9.2 Hz, 1H, H-7′), 1.34 (d, J=6.2 Hz, 3H, CH_3-*i*Pr),1.24 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.31, 137.18 (2×C*ipso*), 129.14–126.12 (2×Ph), 101.14 (CHPh), 97.91 (CH-1), 81.46 (CH-3 or CH-4), 78.57 (CH-3 or CH-4), 71.22 (CH_2Ph), 70.43 (CH-8), 70.24 (CH_2-6), 66.56 (CH-2), 65.91 (CH_2-7), 64.89 (C-5), 23.65, 21.77 (2×CH_3-*i*Pr); (CI, NH_3): *m*/*z* (%): 430 (100) [M+NH_4^+]; elemental analysis: calcd (%) for $C_{24}H_{28}O_6$ (412.48): C 69.88, H 6.84; found C 70.08, H 7.10.

5.2.20. Isopropyl 2-*O*,5-*C*-methylene-β-D-glucopyranoside 4. Compound **22** (300 mg, 0.728 mmol) was dissolved in dry methanol (10 mL) and 10% Pd/C (30 mg) was added. The solution was purged with hydrogen and stirred at rt overnight. After completion of the reaction, the reaction mixture was filtered through celite and washed with methanol. The solvent was concentrated and the crude product was purified by column chromatography (EtOAc/cyclohexane 2:1) to afford compound **4** (140 mg, 0.598 mmol, 82% yield) as colourless oil.

$[\alpha]_D^{22}$=+20 (c=0.44 in CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ=5.36 (d, J=1.6 Hz, 1H, H-1), 4.27 (m, J=6.2 Hz, 1H, H-8), 4.13 (dd, J=1.3, 9.0 Hz, 1H, H-7), 4.07 (dd, J=1.6, 4.5 Hz, 1H, H-3), 4.03 (dd, J=0.9, 9.0 Hz, 1H, H-7′), 3.85 (dd, J=1.6, 4.5 Hz, 1H, H-2), 3.83 (m, 1H, H-4), 3.73 (s, 2H, H-6, H-6′), 1.47 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.35 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR (100 MHz, CD_3OD): δ=95.86 (CH-1), 77.83 (C-5), 75.72 (CH-3), 74.88 (CH-4), 72.69 (CH-2), 71.12 (CH-8), 65.00 (CH_2-7), 63.77 (CH_2-6), 24.56 (CH_3-*i*Pr), 22.41 (CH_3-*i*Pr); MS (CI, NH_3): *m*/*z* (%): 252 (100) [M+NH_4^+]; HRMS (positive-ion CI, NH_3): calcd for $C_{10}H_{22}O_6N$ (M+NH_4^+) 252.1447, found 252.1448.

5.2.21. Isopropyl 3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-4,6-*O*-isopropylidene-5-*C*-vinyl-β-D-glucopyranoside 23. Sodium (600 mg, 26.1 mmol) was added at 0 °C to a solution of compound **19** (15.1 g, 32.3 mmol) in methanol (300 mL). After 8 h of stirring at rt, the reaction mixture was neutralized with ion exchange resin IR-120 H^+ stirring for 1 h. The mixture was filtered, eluted with methanol and the solvent removed under vacuum to afford the corresponding triol (10.43 g, 30.86 mmol, 95%), which was used directly for the next reaction.

Triol (8.89 g, 26.3 mmol) was dissolved in dry acetone (39 mL), and 2,2′-dimethoxypropane (39 mL) followed by camphorsulphonic acid (610 mg, 2.63 mmol) were added. The reaction was stirred at rt overnight under argon, then quenched by addition of a saturated aqueous solution of $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by column chromatography (cyclohexane/EtOAc 6:1) to afford the corresponding 4,6-*O*-isopropylidene derivative (8.6 g, 22.75 mmol, 86%) as a white powder.

This alcohol (8.23 g, 21.77 mmol) was dissolved in dry DMF (55 mL) and TBDMSCl (4.27 g, 28.3 mmol) followed by imidazole (1.92 g, 28.3 mmol) were added under argon. The reaction mixture was stirred at 60 °C for 3.5 h, then cooled to rt, and finally poured in a water–ice mixture and extracted with ether. The organic layer was dried over $MgSO_4$, concentrated and the residue was purified by column chromatography (cyclohexane/EtOAc 4:1) to afford compound **23** (10.45 g, 21.2 mmol, 97%) as a crystalline solid.

$[\alpha]_D^{20}$=−44 (c=0.92 in $CHCl_3$); mp 113 °C (*n*-pentane/EtOAc); ^1H NMR ($CDCl_3$, 400 MHz): δ=7.50–7.30 (m, 5H, Ph), 6.33 (dd, J=11.3, 17.9 Hz, 1H, H-7), 5.60 (dd, J=1.5, 17.9 Hz, 1H, H-8′), 5.53 (dd, J=1.3, 11.3 Hz, 1H, H-8), 4.85 (d, J=11.1 Hz, 1H, CHPh), 4.71 (d, J=7.2 Hz, 1H, H-1), 4.69 (d, J=11.1 Hz, 1H, CHPh), 4.02 (m, J=6.2 Hz, 1H, H-9), 3.93 (d, J=10.1 Hz, 1H, H-6′), 3.85 (d, J=9.5 Hz, 1H, H-4), 3.64 (d, J=10.1 Hz, 1H, H-6), 3.50 (m, 2H, H-2, H-3), 1.47 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.29 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.20 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 0.93 (s, 9H, tBu), 0.12 (s, 3H, CH_3), 0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.87 (Cipso), 136.58 (CH-7), 128.12, 128.06, 127.34 (Ph), 117.70 (CH_2-8), 99.96 ($C(CH_3)_2$), 97.45 (CH-1), 78.91 (CH-2), 73.33 (CH-4), 75.96 (CH-3), 74.61 (CH_2Ph), 71.51 (CH_2-6), 70.58 (CH-9), 72.43 (CH-8), 69.90 (C-5), 29.18, 18.92 (2×CH_3), 25.92 (tBu), 23.48, 21.56 (2×CH_3-*i*Pr), −4.08, −4.31 (2×CH_3-Si); (CI, NH_3): *m*/*z* (%): 510 (10) [M+NH_4^+], 493 (20) [M+H^+], 392 (100); HRMS (positive-ion CI, NH_3): calcd for $C_{27}H_{45}O_6Si$ (M+H^+) 493.2985, found 493.2982.

5.2.22. Isopropyl 3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-4,6-*O*-isopropylidene-5-*C*-methanoate-β-D-glucopyranoside 24. Ozone was passed through a stirred solution of olefin **23** (1.0 g, 2.03 mmol) in CH_2Cl_2 (50 mL) cooled to −78 °C for 4 h. The reaction mixture was quenched with $(CH_3)_2S$ (0.2 mL) and allowed to warm to room temperature. The solvent was evaporated. The crude carboxylic acid was dissolved in dry DMF (20 mL). Iodomethane (8 mL) and $KHCO_3$ (570 mg) were added and the reaction mixture was stirred under argon for 16 h. The solvent was removed under reduced pressure and the residue dissolved in EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (cyclohexane/EtOAc 10:1) afforded the methyl ester derivative **24** (744 mg, 1.42 mmol, 70% yield) as an oil.

$[\alpha]_D^{20}=-18$ (c=1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.38–7.30 (m, 5H, Ph), 4.93 (d, J=10.8 Hz, 1H, CHPh), 4.72 (d, J=10.8 Hz, 1H, CHPh), 4.36 (d, J=7.8 Hz, 1H, H-1), 4.18 (d, J=9.9 Hz, 1H, H-6), 4.13 (dd, J=9.8, 8.1 Hz, 1H, H-3), 4.00 (m, J=6.2 Hz, 1H, H-8), 3.89 (d, J=10.1 Hz, 1H, H-4), 3.88 (s, 3H, CO_2CH_3), 3.86 (d, J=9.9 Hz, 1H, H-6′), 3.49 (t, J=7.9 Hz, 1H, H-2), 1.48 (s, 1H, CH_3-isopropylidene), 1.44 (s, 1H, CH_3-isopropylidene), 1.25 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.18 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 0.91 (s, 9H, tBu), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=169.88 (C=O), 138.96 (C*ipso*), 129.68, 128.11, 128.06, 127.31 (Ph), 100.20 ($C(CH_3)_2$), 99.54 (CH-1), 78.98 (CH-3), 76.02 (CH-4), 75.18 (CH-2), 74.66 (CH_2Ph), 71.71 (C-5), 71.34 (CH-8), 67.02 (CH_2-6), 52.17 (CO_2CH_3), 29.10, 18.51 (2×CH_3-isopropylidene), 25.87 (tBu), 23.16, 21.29 (2×CH_3-*i*Pr), −4.18, −4.40 (2×$SiCH_3$); (CI, NH_3): m/z (%): 542 (100) $[M+NH_4^+]$; HRMS (positive-ion CI, NH_3): calcd for $C_{27}H_{48}O_8NSi$ $(M+NH_4^+)$ 542.3149, found 542.3143.

5.2.23. Isopropyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-carbonyl-β-D-glucopyranoside 25. Tetrabutylammonium fluoride (190 mg, 0.6 mmol) was added to a solution of methyl ester derivative **24** (104 mg, 0.2 mmol) in dry THF (10 mL) under argon and the solution was stirred for 3 h at rt. The reaction mixture was then poured in ice–water, extracted with EtOAc, the organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (cyclohexane/EtOAc 9:1) afforded the lactonized compound **25** (68 mg, 0.18 mmol, 90% yield) as a crystalline compound.

$[\alpha]_D^{20}=-74$ (c=2.31 in $CHCl_3$); mp 91–92 °C (n-pentane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.43–7.30 (m, 5H, Ph), 5.28 (dd, J=1.3, 2.8 Hz, 1H, H-1), 4.73 (d, J=12.1 Hz, 1H, CHPh), 4.69 (d, J=12.1 Hz, 1H, CHPh), 4.58 (t, J=2.8 Hz, 1H, H-2), 4.44 (d, J=5.0 Hz, 1H, H-4), 4.27 (d, J=11.8 Hz, 1H, H-6), 4.01 (m, J=6.2 Hz, 1H, H-7), 3.85 (d, J=11.8 Hz, 1H, H-6′), 3.83 (ddd, J=1.3, 5.0, 2.8 Hz, 1H, H-3), 1.48 (s, 3H, CH_3-isopropylidene), 1.42 (s, 3H, CH_3-isopropylidene), 1.34 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.24 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=168.42 (C=O), 137.65 (C*ipso*), 128.30, 127.78, 127.56 (Ph), 99.65 ($C(CH_3)_2$), 96.40 (CH-1), 78.90 (CH-3), 72.91 (CH-2), 72.31 (CH-4), 72.17 (CH-7), 72.14 (CH_2Ph), 67.05 (C-5), 60.73 (CH_2-6), 27.94, 19.15 (2×CH_3-isopropylidene), 23.42, 21.69 (2×CH_3-*i*Pr); (CI, NH_3): m/z (%): 396 (100) $[M+NH_4^+]$; HRMS (positive-ion CI, NH_3): calcd for $C_{20}H_{27}O_7$ $(M+H^+)$ 379.1757, found 379.1759.

5.2.24. Isopropyl 2-*O*,5-*C*-carbonyl-β-D-glucopyranoside 5. Compound **25** (53 mg, 0.14 mmol) was dissolved in $AcOH/H_2O$ (3:2, 2 mL) and stirred at 60 °C for 3.5 h. The solvent was removed under reduced pressure and the residue co-evaporated with toluene (2×5 mL) to afford the crude diol, which was used directly in the next step. The diol (47 mg, 0.139 mmol) was dissolved in EtOAc (10 mL) and Pd/C (10 mg) was added. The suspension was stirred under H_2 for 1 h at rt, filtered through celite (eluted with EtOAc) and the solvent was removed under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 1:1) afforded compound **5** (29 mg, 0.121 mmol, 87% yield) as crystalline compound.

$[\alpha]_D^{20}=-110$ (c=0.3 in $CHCl_3$); mp 118 °C (n-pentane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=5.39 (dd, J=1.5, 2.8 Hz, 1H, H-1), 4.62 (t, J=2.8 Hz, 1H, H-2), 4.33 (d, J=3.9 Hz, 1H, H-4), 4.17 (d, J=12.6 Hz, 1H, H-6), 4.10 (m, J=6.2 Hz, 1H, H-7), 3.98 (d, J=12.6 Hz, 1H, H-6′), 3.94 (m, 1H, H-3), 3.64 (d, J=11.9 Hz, 1H, OH), 3.30 (s, 1H, OH), 1.64 (s, 1H, OH), 1.33 (d, J=6.2 Hz, 3H, CH_3-*i*Pr), 1.26 (d, J=6.2 Hz, 3H, CH_3-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=169.0 (C=O), 95.90 (CH-1), 75.91 (CH-4), 75.15 (CH-3), 73.46 (CH-2), 73.06 (CH-7), 61.94 (CH_2-6), 23.53, 21.57 (2×CH_3-*i*Pr); (CI, NH_3): m/z (%): 266 (100) $[M+NH_4^+]$; HRMS (positive-ion CI, NH_3): calcd for $C_{10}H_{17}O_7$ $(M+H^+)$ 249.0974, found 249.0979.

5.2.25. Methyl (3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*,5-*C*-methylene-β-D-glucopyranosyl)-(1,4)-*O*-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside 27. Thiophenyl derivative **11** (110 mg, 0.24 mmol), alcohol **26** (133 mg, 0.29 mmol) and powdered 4 Å molecular sieves (350 mg) were suspended in dry CH_2Cl_2 (13 mL) under argon and the suspension was stirred for 30 min at rt. The reaction mixture was then cooled to −30 °C, NIS (108 mg, 0.48 mmol) followed by triflic acid (4 μL, 0.036 mmol) were added to give a red solution. After 15 min of stirring at −30 °C, the reaction mixture was neutralized with sat. aq. $NaHCO_3$, diluted with Et_2O (50 mL), washed with sat. aq. $Na_2S_2O_3$, brine, and dried over $MgSO_4$. Purification by column chromatography (cyclohexane/EtOAc 5:1) afforded the protected disaccharide **27** (93 mg, 0.114 mmol, 48% yield) as an oil.

$[\alpha]_D^{20}=-37$ (c=1 in $CHCl_3$); ^{1}H RMN ($CDCl_3$, 400 MHz): δ=7.48–7,30 (m, 5H, Ph), 5.37 (dd, J=2.5, 1.1 Hz, 1H, H-1′), 5.07 (s, 2H, CH_2Ph), 4.97 (s, 1H, CHPh), 4.82 (d, J=12.3 Hz, 1H, CHPh), 4.71 (d, J=12.3 Hz, 1H, CHPh), 4.67 (d, J=12.0 Hz, 1H, CHPh), 4.66 (d, J=3.4 Hz, 1H, H-1), 4.64 (d, J=11.3 Hz, 1H, CHPh), 4.56 (d, J=12.0 Hz, 1H, CHPh), 4.45 (d, J=11.3 Hz, 1H, CHPh), 4.29 (d, J=9.5 Hz, 1H, H-7), 4.12 (dd, J=4.8, 1.6 Hz, 1H, H-4′), 3.97 (t, J=9.1 Hz, 1H, H-3), 3.90 (t, J=9.2 Hz, 1H, H-4), 3.87 (m, 1H, H-3′), 3.76 (d, J=11.2 Hz, 1H, H-6a′), 3.74 (m, J=9.4 Hz, 1H, H-5), 3.69 (t, J=2.6 Hz, 1H, H-2′), 3.68 (dd, J=3.0, 10.4 Hz, 1H, H-6a), 3.62 (dd, J=3.4, 9.1 Hz, 1H, H-2), 3.56 (d, J=1.9 Hz, 1H, H-6b), 3.55 (dd, J=1.7, 9.5 Hz, 1H, H-7b′), 3.46 (d, J=11.2 Hz, 1H, H-6b′), 3.43 (s, 3H, OCH_3); ^{13}C RMN ($CDCl_3$, 400 MHz): δ=139.64, 138.05, 137.98, 137.62, 137.14 (5×C*ipso*), 129.05–126.03 (5×Ph), 100.6 (CHPh), 100.08 (C-1′), 98.27 (C-1), 81.02 (C-4′), 80.16 (C-3), 79.21 (C-2), 78.36 (C-3′), 76.42 (C-4), 74.76 (CH_2Ph), 73.51 (CH_2Ph), 73.35 (CH_2Ph), 71.35 (CH_2Ph), 69.65 (C-5), 69.61 (C-6′), 68.16 (C-6), 66.45 (C-2′), 65.66 (C-7′), 65.02 (C-5′), 55.22 (OCH_3); (CI, NH_3): *m/z* (%): 834 (100) [M+NH_4^+]; $C_{49}H_{52}O_{11}$ (816.95): calcd C 72.04, H 6.42; found C 71.81, H 6.65.

5.2.26. Methyl (2-*O*,5-*C*-methylene-β-D-glucopyranosyl)-(1,4)-α-D-glucopyranoside 28. Disaccharide **27** (25 mg, 0.030 mmol) was dissolved in methanol (5 mL) and 10% Pd/C (10 mg) was added. The suspension was stirred under H_2 for 1 h at rt, filtered through celite eluted with methanol and concentrated. Purification by column chromatography (10% CH_3OH in EtOAc) afforded the disaccharide **28** (10 mg, 0.027 mmol, 90% yield) as a foam.

$[\alpha]_D^{20}$=+61 (c=1.05 in H_2O); ^{1}H RMN (D_2O, 500 MHz): δ=5.33 (dd, J=2.7, 1.3 Hz, 1H, H-1′), 4.81 (d, J=3.8 Hz, 1H, H-1), 4.07 (dd, J=5.2, 1.7 Hz, 1H, H-4′), 3.98 (t, J=2.7 Hz, 1H, H-2′), 3.95 (dd, J=2.7, 5.2 Hz, 1H, H-3′), 3.84 (d, J=12.0 Hz, 1H, H-6a), 3.83 (dd, J=9.2, 9.8 Hz, 1H, H-3), 3.85 (d, J=9.8 Hz, 1H, H-7′a), 3.77 (dd, J=4.5, 12.0 Hz, 1H, H-6b), 3.76 (ddd, J=4.5, 9.8, 12.0 Hz, 1H, H-5), 3.73 (d, J=12.7 Hz, 1H, H-6a′), 3.65 (dd, J=1.7, 9.8 Hz, 1H, H-7b′), 3.62 (dd, J=3.8, 9.8 Hz, 1H, H-2), 3.59 (dd, J=9.2, 9.8 Hz, 1H, H-4), 3.64 (d, J=12.7 Hz, 1H, H-6b′), 3.39 (s, 3H, OCH_3); ^{13}C RMN (D_2O, 100 MHz): δ=100.06 (CH-1′), 99.42 (CH-1), 78.92 (CH-4), 73.33 (C-5′), 74.72 (CH-3′), 73.53 (CH-4′), 71.81 (CH-3), 71.78 (CH-2), 70.50 (CH-5), 68.31 (CH-2′), 62.22 (CH_2-7′), 60.38 (CH_2-6, CH_2-6′), 55.39 (OCH_3); (CI, NH_3): *m/z* (%): 386 (100) [M+NH_4^+]; HRMS (positive-ion CI, NH_3): calcd for $C_{14}H_{28}O_{11}N$ (M+NH_4^+) 386.1662, found 386.1654.

Acknowledgements

The authors would like to thank Dr. C. Guyard-Duhayon (Centre des Résolutions de Structures, Université Pierre and Marie Curie) for solving the crystal structures, Dr R. Nash (MolecularNature Ltd, IGER, Aberystwyth, Wales) for performing inhibition tests on commercially available glycosidases, Dr M. Hrmova (University of Adelaide, Australia) for the study on barley β-D-glucan glucohydrolase, and Dr K. Piens (University of Gent, Belgium) for the study on cellobiohydrolases from *T. Reesei*. A.J.H. acknowledges the financial support provided through the European Community's Human Potential Programme under contract HPRN-CT-2002-00173.

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Tetrahedron 60 (2004) 6829–6851

Tetrahedron

Synthesis of thiosaccharides employing the Pummerer rearrangement of tetrahydrothiopyran oxides☆

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Received 9 April 2004; revised 2 June 2004; accepted 3 June 2004

Available online 4 July 2004

Abstract—The Pummerer rearrangement of 1-deoxy-5-thioglucopyranose derivatives carrying acetonides at the C3,4-positions proceeded regioselectively at the C1 position by treating with TFAA in the presence of pyridine. Studies employing deuterium-labelled derivatives revealed that the reaction was induced by E2 1,2-elimination of trifluoroacetic acid of the trifluoroacetoxy sulfonium intermediate. This methodology was applied to the synthesis of an isomaltotriose derivative consisting of 5-thioglucopyranoside units.

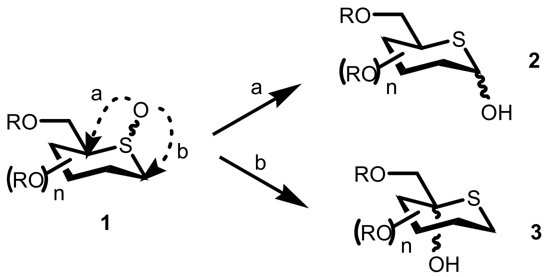
1. Introduction

Carbomimetics, analogues which structurally mimic carbohydrates, are candidates not only as potent probes in the mechanistic investigation of glycosidases but also as novel drugs for some digestive or infective diseases.[1–7] We have made efforts towards the synthesis of oligosaccharide derivatives consisting of 5-thiopyranoses based on the concept that replacement of the oxygens in the pyranose rings of oligosaccharides with sulfur atoms may realize tolerance against glycosidases with minimum structural alterations.[8,9] As part of these studies, we have discovered that the Pummerer rearrangement of thiopyranose oxides having O-3 and O-4 protected as an O-isopropylidene derivative proceeded and reported this finding as a communication.[10] Further investigation employing deuterium-labelled derivatives enabled us to discuss details of the reaction. Now, we would like to report the details of these studies and an application of this strategy to a synthesis of sulfur-substituted isomaltotrioside.

2. Results and discussions

2.1. Basic methodology

Since the Pummerer rearrangement provides a synthetic equivalent of carbonyl compounds from sulfoxides, an equivalent for alcohols, under non-oxidative conditions, it has been utilized in total syntheses of natural products as an alternative protocol for oxidation of the alcohols.[11,12] This rearrangement will be desirable for introduction of the C1 hemithioacetal function of thiosugars if we can perform the rearrangement of 1-deoxy-5-thiopyranose oxides at the C1 position regioselectively as shown in Scheme 1.[13] In spite of extensive studies by Oae[14,15] and Crucianelli[16] on the Pummerer rearrangements, the regioselectivity for highly functionalized asymmetric sulfoxides has not been fully discussed. Recently, Naka et al.[17,18] and Zhang et al.[19] independently investigated regio- and stereoselective formation of thionucleosides via Pummerer-type



Scheme 1. Basic strategy.

☆ Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2004.06.006

Keywords: Thiosaccharids; Pummerer rearrangements; Reaction mechanism; Isomaltotriose analogue.

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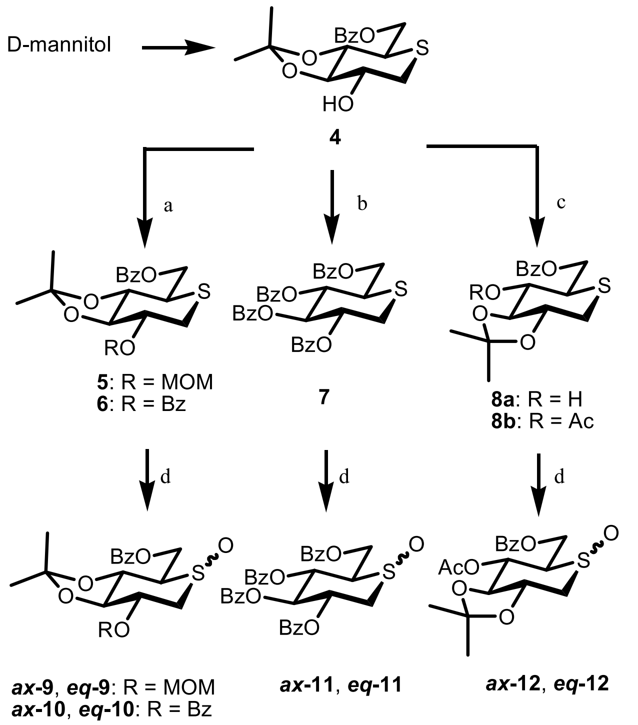
doi:10.1016/j.tet.2004.06.006

glycosidation. However, the factors determining regioselectivity have not been fully elucidated. Thus, we had to study the reaction courses caused by the differences in the stereochemistry of the sulfoxides and in the protective groups at the C2–C6 positions in the rearrangement.

2.2. Preparation of 1-deoxy-5-thio-D-glucopyranose oxides

We first synthesized axial and equatorial oxides of 1-deoxy-5-thioglucopyranoses carrying a series of protective groups **9**-**12** (Scheme 2). Thiane **4** was readily prepared from D-mannitol following the protocol reported by Merrer et al.[20] The hydroxy group of **4** was protected in the form of methoxymethyl (MOM) ether under usual conditions to give **5** in 86% yield. The sulfide function of **5** was oxidized to the sulfoxide with *m*-chloroperbenzoic acid (*m*CPBA) in CH_2Cl_2 at −20 °C for 30 min. This oxidation proceeded without stereoselectivity, giving a separable mixture (50:50) of the axial- and equatorial-sulfoxides, *ax*-**9** and *eq*-**9**, in 87% yield. In a similar manner, **4** was converted into the benzoates *ax*-**10** and *eq*-**10** in good overall yield. Benzoylation after removal of the acetonide of **4** gave **7** in 85% yield in two steps. The acetonide group of **4** migrated to the C2–C3 positions (carbohydrate numbering) by treatment of **4** with *p*-toluenesulfonic acid in acetone to afford **8a** (60%) along with recovery of **4** (32%). The hydroxy function of **8a** was protected as the acetate, giving **8b** in quantitative yield. In a similar manner described for **9** and **10**, sulfides **7** and **8b** were converted into both isomeric mixtures of sulfoxides **11** and **12**, respectively. Those isomers could also be readily separated by silica gel column chromatography.



Scheme 2. Reagents and conditions: (a) for **5**; MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C (86%), for **6**; BzCl, pyridine, rt (95%); (b) (i) cat. HCl, MeOH, rt (85%), (ii) BzCl, pyridine, rt (100%); (c) (i) cat. *p*-TsOH, rt, acetone, then separation, (ii) Ac_2O, pyridine, rt (100%); (d) *m*CPBA, CH_2Cl_2, −20 °C (**9**, 87%, **10**, 91%, **11**, 96%, **12**, 92%, isomeric ratios (*eq*/*ax*) **9**: (50:50), **10**: (60:40), **11**: (50:50), **12**: (60:40).

2.3. Stereochemistry of the sulfoxides

Stereochemistries of the sulfoxide moieties of **9**-**12** were next studied. Since there were few precedents regarding the effect of stereochemistry of sulfoxides on the regioselectivity in the Pummerer rearrangements, assignment of those stereochemistries was required. In the ^{1}H NMR spectra of both isomers of **9**-**12**, large coupling constants for $J_{C1Hax,C2H}$, $J_{C2H,C3H}$, $J_{C3H,C4H}$, and $J_{C4H,C5H}$ (carbohydrate numbering) of the tetrahydrothiopyran ring moieties

Table 1. The characteristic ^{1}H- and ^{13}C NMR chemical shifts of sulfoxides **9**-**12** and their differences Δδ (=δ(*eq*)−δ(*ax*), italic) and the coupling constants for $J_{C1Heq-C1Hax}$ and $J_{C5H-C6H}$

Signals	9[a]			10[a]			11[b]			12[a]		
	eq	*ax*	Δδ	*eq*	*ax*	Δδ	*eq*	*ax*	Δδ	*eq*	*ax*	Δδ
C1H*ax*	2.75	1.69	*+1.06*	2.66	1.58	*+1.08*	3.22	2.72	*+0.50*	2.55	1.63	*+0.92*
C1H*eq*	3.32	3.20	*+0.12*	3.24	3.33	*−0.09*	4.02	3.85	*+0.17*	3.28	3.03	*+0.25*
C2H	3.63	4.62	*−0.99*	5.32	6.13	*−0.81*	5.45	6.10	*−0.65*	3.05	4.61	*−1.56*
C5H	2.69	2.53	*+0.16*	2.82	2.65	*+0.17*	3.49	3.38	*+0.11*	2.73	2.52	*+0.21*
C1	55.4	50.6	*+4.8*	53.4	49.2	*+4.2*	52.6	47.4	*+5.2*	52.2	48.1	*+4.1*
C2	69.2	71.1	*−1.9*	67.8	69.3	*−1.5*	65.3	67.3	*−2.0*	69.1	71.6	*−2.5*
C4	71.0	72.7	*−1.7*	71.4	72.9	*−1.5*	64.8	67.9	*−3.1*	65.0	68.9	*−3.9*
C5	64.2	58.8	*+5.4*	64.8	59.2	*+5.6*	65.7	59.0	*+6.7*	67.0	60.6	*+6.4*
$J_{C1Heq-C1Hax}$	*12.2*	*14.6*		*12.7*	*14.1*		*11.8*	*14.2*		*10.7*	*13.2*	
$J_{C5H-C6H}$	*3.0* *4.4*	*4.4* *11.7*		*3.4* *5.4*	*4.4* *11.2*		*2.5* *2.5*	*4.9* *9.3*		*3.0* *4.8*	*3.9* *9.8*	

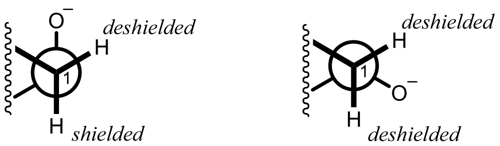
[a] Observed in C_6D_6.
[b] Observed in $CDCl_3$.

suggested that those protons are in axial orientations. Thus, the tetrahydrothiopyran rings of isomers **9-12** adopt $^4C_1$ conformations. The characteristic signals in their ^{1}H- and ^{13}C NMR spectra are shown in Table 1. Signs of the $\Delta\delta$ value [$=\delta$(*eq*-isomer)$-\delta$(*ax*-isomer)] are consistent with the literature[21] without exception about the C2H, C4H, and C5H signals in the ^{1}H NMR spectra as well as resonances due to C1, C2, C4, and C5 in the ^{13}C NMR spectra. The coupling constants, $J_{\mathrm{C1H}eq-\mathrm{C1H}ax}$ (geminal coupling), for axial sulfoxides *ax*-**9-12** were larger than those of the corresponding equatorial isomers *eq*-**9-12**, which also supported those stereochemistries according to Eliel's report.[22–24]

The stereochemistries of these sulfoxides were studied further. In the axial sulfoxide (*ax*-isomer), the electron-donating oxide moiety should shield the *anti*-periplanar-orientated axial proton (C1H*ax*) of the C1 position as shown in Figure 1[22,25,26] In contrast, the lone pair electrons of the equatorial sulfoxide (*eq*-isomer) did not induce the above effect for the C1H*ax*. This suggested that the signs of the $\Delta\delta$ values for C1H*ax* should be positive. On the other hand, the $\Delta\delta$ values for the C1H*eq* are expected to be small, since the sulfoxide moiety equally affected those protons because of the *gauche* relationships between the oxygen of the sulfoxides and the C1 equatorial protons for both axial and equatorial sulfoxides. The observed $\Delta\delta$ values for the C1H*eq* accorded with the discussion. These $\Delta\delta$ values were also supported by theoretical calculations for tetrahydrothiopyran oxides employed as the model molecules. The estimated chemical shifts for the C1 methylene protons (carbohydrate numbering) of the axial thiane oxide *ax*-**14** and the corresponding equatorial isomer *eq*-**14** are shown in Figure 2. These chemical shifts were calculated using Spartan 04.[27] Optimization of these structures was performed prior to the calculations of their chemical shifts. In order to take the contribution of the *d*-orbitals of the sulfur atoms into account, the 6-31G* basis set[28] was employed for these computations. The chemical shifts of the C1H*ax* (carbohydrate numbering) in the axial isomer *ax*-**14** was predicted to appear at higher field than those of the corresponding equatorial isomer *eq*-**14** and sulfide **13**.

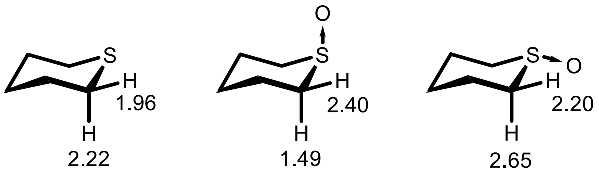
2.4. The Pummerer rearrangement of sulfoxides 9-12

With the sulfoxides **9-12** in hand, Pummerer rearrangements were attempted. The rearrangement did not proceed at room temperature when acetic anhydride (Ac_2O) was employed.[29] The heating conditions with Ac_2O resulted in the formation of complex mixtures in the cases that both *ax*- and *eq*-**11** were employed. Preparative TLC after refluxing *ax*-**9** and Ac_2O in pyridine gave only trace amounts of **15** and thiane **5**.



***ax*-sulfoxide** ***eq*-sulfoxide**

Figure 1. Shielding and deshielding of the C1 protons by the sulfoxide oxygen.

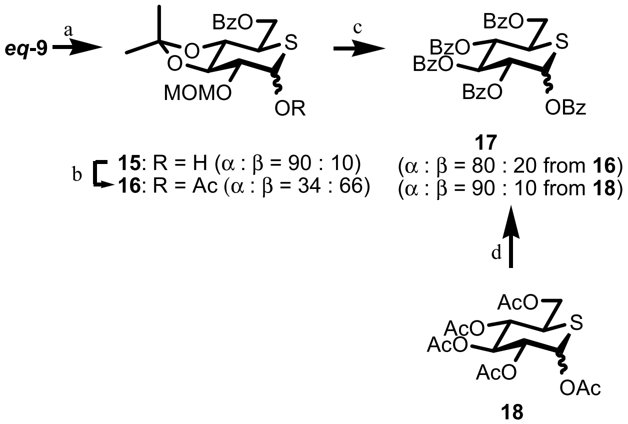


13 ***ax*-14** ***eq*-14**

Figure 2. Estimated chemical shifts (ppm) of the α-methylene protons of thiane and its oxides.[25]

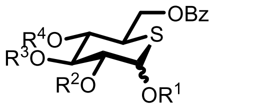
The conditions using trifluoroacetic anhydride (TFAA) in place of Ac_2O, the modified protocol developed by one of present authors,[12] was found to promote the rearrangement smoothly at room temperature. Thus, the treatment of *eq*-**9** with TFAA (5.0 equiv.) in the presence of pyridine (10 equiv.) in CH_2Cl_2 at room temperature for 3 h realized the rearrangement in highly stereoselective manner, providing 5-thioglucopyranose derivative **15** as shown in Scheme 3. The trifluoroacetyl group introduced was hydrolyzed during the work-up. The existence of the OH group in **15** was confirmed by observing strong absorption at 3440 cm^{-1} (broad) in the IR spectrum. The ^{1}H NMR spectrum indicated that **15** exists as a 90:10 anomeric mixture. Since **15** appeared as a broad spot on the TLC due to the equilibrium between the anomers, the accurate yield of **15** after silica gel column chromatography in this reaction could not be obtained. It was estimated to be 66% after acetylation, giving an anomeric mixture (α/β=34:66) of **16**. Those isomers could be separated by preparative silica gel TLC. The structure of **16** was confirmed after converting it into pentabenzoate **17**. Treatment of the α-isomer of **16** with aqueous trifluoroacetic acid promoted hydrolysis of the acetonide and the C1 acetyl group. The following benzoylation under usual conditions gave **17** as an inseparable mixture (α/β=80:20) in 63% yield in two steps. The ^{1}H NMR spectrum of this sample was identical, except for the isomeric ratio, with that of **17** prepared from 5-thioglucopyranosyl peracetate **18**[30] by saponification and the subsequent benzoylation. The isomeric ratio of **17** prepared from **18** was α/β=90:10.

The rearrangements for other congeners *eq*-**10**-**12** were also

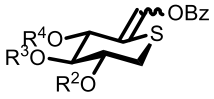


Scheme 3. The Pummerer rearrangement of *eq*-**9**. Reagents and conditions: (a) TFAA, Py, CH_2Cl_2, rt; (b) Ac_2O, Py, rt, then separation (66% two steps); (c) (i) *aq*. TFA, rt, (ii) BzCl, Py, rt (63% two steps); (d) (i) NaOMe, MeOH, rt, (ii) BzCl, Py, rt (67% two steps).

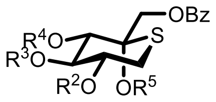
Table 2. Products obtained by Pummerer rearrangement of sulfoxides **9**-**12**



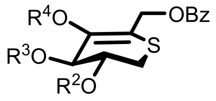
20: R^1 = H, R^2 = Bz, R^3, R^4 = acetonide
24: R^1 = H, R^2, R^3, R^4 = Bz
29: R^1 = H, R^2, R^3 = acetonide, R^4 = Ac



19: R^2 = MOM, R^3, R^4 = acetonide
21: R^2 = Bz, R^3, R^4 = acetonide
25: R^2, R^3, R^4 = Bz
30: R^2, R^3 = acetonide, R^4 = Ac



22: R^2 = Bz, R^3, R^4 = acetonide, R^5 = H
23: R^2 = Bz, R^3, R^4 = acetonide, R^5 = TFA
26: R^2, R^3, R^4 = Bz, R^5 = H
27: R^2, R^3, R^4 = Bz, R^5 = TFA
31: R^2, R^3 = acetonide, R^4 = Ac, R^5 = H
32: R^2, R^3 = acetonide, R^4 = Ac, R^5 = TFA



28: R^2, R^3, R^4 = Bz

Run	Sulfoxides	5-Thioglucose derivatives (α/β, yields)	Other products
1	*eq*-**9**	**15** (34:66, 66%)[a]	Not detected
2	*ax*-**9**	**15** (34:66, 84%)[a]	**19**[b] (trace)
3	*eq*-**10**	**20** (91:9, 55%)	**21**, **22**, **23** (trace each)[b]
4	*ax*-**10**	**20** (90:10, 61%)	**21**, **22**, **23** (trace each)[b]
5	*eq*-**10**	**20** (90:10, 66%)[c]	Not detected
6	*ax*-**10**	**20** (90:10, 65%)[c]	Not detected
7	*eq*-**11**	**24** (90:10, 5.7%)	**25** (4.0%), **26** (50%), **27** (8.9%)[d], **28** (9.5%)
8	*ax*-**11**	**24** (90:10, 2.7%)	**25** (0.3%), **26** (41%), **27** (5.6%)[d], **28** (8.9%)
9	*eq*-**12**	**29** (not detected)	**30** (14%), **31** (40%), **32** (1.7%)[d]
10	*ax*-**12**	**29** (not detected)	**30** (9.4%), **31** (45%), **32** (1.2%)[d]

[a] The isomeric ratio and yield were determined after acetylation (→**16**).
[b] Structures of minor **19**, **21**, **22**, and **23** were assigned by comparing those ^{1}H NMR spectra with those of the corresponding compounds **25**-**32**.
[c] Pyridine was employed as the solvent.
[d] Structures of **27** and **32** were estimated based on the product obtained by treating with Et_3N in methanol.

investigated. The results are summarized in Table 2. In the reaction of *eq*-**10**, carrying benzoate in place of the MOM group of **9**, the rearrangement occurred in similar selectivity to that of **9**, giving 5-thioglucopyranose derivative **20** in 55% yield along with trace amounts of other products **21**-**23** (run 3). Products **21**-**23** were obtained via the rearrangement to the C5 position. The structures of **21**-**23** could not be fully determined because of their trace amounts; however, those were tentatively assigned by comparing their ^{1}H NMR spectra with those of **25**-**32** (vide infra). An attempt employing pyridine as the solvent slightly improved the yield of desired **20** (run 5).

In contrast, the rearrangement for perbenzoate *eq*-**11** proceeded at the C5 position predominantly to give undesired 5-hydroxy derivative **26** (50%), the corresponding trifluoroacetate **27** (8.9%), *exo*-olefin **25** (4.0%), and *endo*-olefin **28** (9.5%) (run 7). 5-Thioglucose derivative **24** was obtained as a minor product (5.7%) by this experiment. Interestingly, anomers α-**24** and β-**24** could be separated by silica gel column chromatography, whereas the corresponding anomers of **15** were inseparable due to equilibration. Trifluoroacetate **27** was not stable enough to obtain its spectral data; however, two-dimensional silica gel TLC analysis of **27** disclosed that **27** was easily transformed into the corresponding alcohol **26**. This observation suggested that **27** was a trifluoroacetate ester of **26**. Alcohol **26** was produced as a single isomer at C5; the stereochemistry of **26** and **27**, however, could not be assigned by NOE studies. The stereochemistry of **26** was tentatively assigned as 5*R* (carbohydrate numbering) taking the anomeric effect into account. *exo*-Olefin **25** was obtained as a single isomer, but assignment of the stereochemistry for the C5–C6 double bond has remained unclear.

Notably, when 2,3-*O*-acetonide *eq*-**12** was subjected to the Pummerer reaction, the rearrangement proceeded with higher regioselectivity at the C5 position (carbohydrate numbering) to give a mixture of **30**-**32** (run 9). Thioglucopyranose **29**, obtainable through the rearrangement at the C1 position, was not observed under these conditions.

Axial sulfoxides *ax*-**9**-**12** were also subjected to the Pummerer reaction under similar conditions (run 2, 4, 6, 8, and 10). The same products as those provided from the corresponding equatorial sulfoxides were afforded in similar yields. Noteworthily, *ax*-**9** gave **16** in 84% yield after acetylation. It seems that the stereochemistry of the sulfoxide moiety is not important for the regioselectivity in the rearrangement based on these observations. This is inconsistent with Naka's report,[17] disclosing the stereochemistry of sulfoxides contributes significantly to the regioselectivity, although TMSOTf was used as the activator.

The regioselectivities are next discussed. Acetonides **9** and **10** carry an electron-withdrawing benzoate ester and an electron-donating MOM ether, respectively, at their C2 positions (carbohydrate numbering). These protective groups were expected to affect the stability of the cationic intermediates produced during the Pummerer rearrangement. However, **9** and **10** provided similar results. Accordingly, an electrostatic factor might contribute less to the regioselectivity. On the other hand, the position of the acetonide group dramatically influenced the selectivity as mentioned above. Thus, the relationship between the selectivity and the conformation of the ring moieties of **9-12** was investigated using molecular modeling calculations.[31] Model compounds **X**, **Y**, and **Z** were selected in order to save the time required for the calculations. Since these model compounds involve sulfoxide functions, an ab initio method based on the 6-31G* basis set was employed. The results are summarized in Table 3.

In the cases of bicyclic **Y** and **Z**, the annular bond angles of the carbons, where the rearrangement occurs mainly in the experiments (∠S–C5–C4 for **Y**, ∠S–C1–C2 for **Z**), were suggested to be around 115°. This angle approximates that of sp^2 carbons. Thus, these carbons can be easily transformed to the planar sp^2 thiocarbenium intermediate. On the other hand, the angles for the other sites (∠S–C1–C2 for **Y**, ∠S–C5–C4 for **Z**) were estimated to be around 105°, which is rather small comparing to that of the standard sp^3 carbon. So, these carbons might remain intact during the reactions. While there was no remarkable difference between the angles ∠S–C1–C2 and ∠S–C5–C4 for monocyclic **X** according to similar calculations, the Pummerer rearrangement of **11** proceeded selectively at C5. This can be explained by considering the Saytzeff rule.

The rearrangement must provide the C1–OTFA esters as the intermediate. However, the TFA ester moieties of them were converted into C1–alcohols during the work up. This might proceed by hydrolysis of the ester moiety (retention) and/or substitution with hydroxyl group at C1 position (inversion). Further, many of the C1–OH derivatives of 5-thiosugars are under equilibrium between anomers. Thus, the stereochemistry of the addition of the trifluoroacetate ion remains unclear. The *O*-benzoyl group at C2 position of thiosugars may not induce β-stereoselectivity, so called the neighboring effect, in this steps based on our experiences,[9] although *O*-acyl function at C2 contributes for the β-addition in regular carbohydrate chemistry.

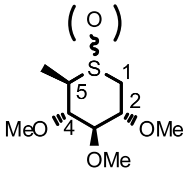
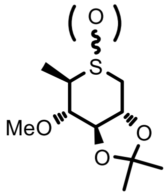
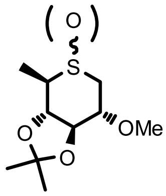
2.5. Mechanistic studies on the Pummerer reaction

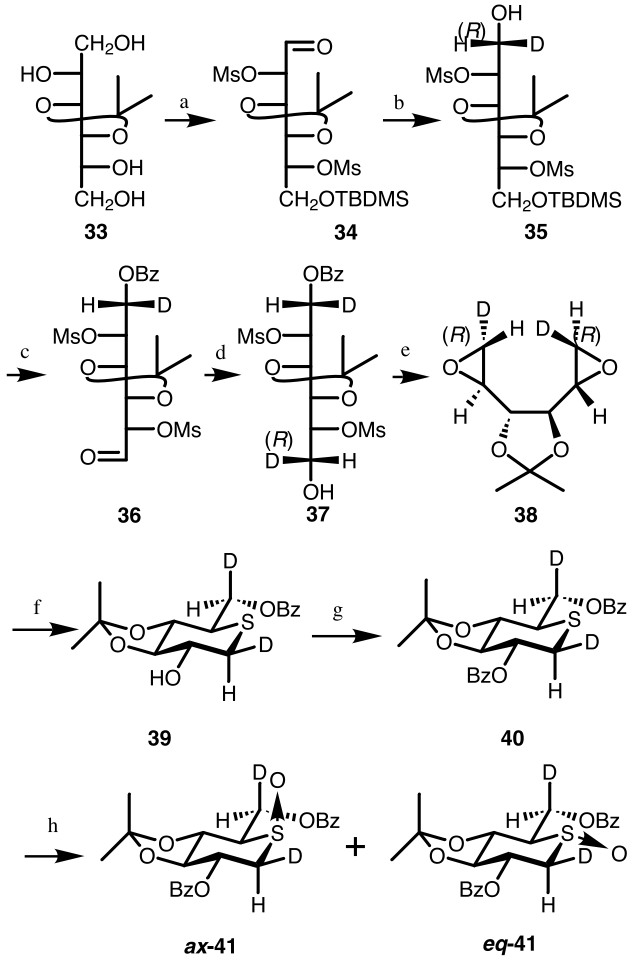
2.5.1. Preparation of deuterium-labelled sulfoxides *ax*-41 and *eq*-41. Exposing the sulfoxide *eq*-**10** to the Pummerer conditions (TFAA, Py-CH_2Cl_2), at a lower temperature (0 °C) for a shorter period (20 min) afforded the *ax*-**10** in 60% yield along with the rearranged product **20** (27%). This observation suggests the occurrence of epimerization of the sulfoxide moiety under the conditions we employed. Oae et al. reported mechanistic details about the Pummerer rearrangement of thianes;[14] however, epimerization of the sulfoxide moiety during the Pummerer reaction was not mentioned. Thus, there might be some difference in the reaction pathways from that which they reported. In order to examine the reaction details, the Pummerer rearrangement employing both isomers of deuterium-labelled derivatives *ax*- and *eq*-**41** was next attempted.

Preparation of isomeric pair of **41** were achieved by modifying Merrer's protocol.[20] Deuterium atoms were required to be introduced stereoselectively at the C1 position of 1-deoxy-5-thioglucopyranose derivatives for our purpose (Scheme 4). We designed stereoselective reduction of the aldehyde **34** for the introduction of the deuterium atom. The aldehyde **34** was prepared from **33** by a sequence of the reactions: (i) protection of both terminal alcohols of 3,4-*O*-isopropylidene mannitol in forms of the *tert*-butyldimethylsilyl (TBDMS) ethers, (ii) mesylation (iii) partial deprotection of the silyl ether by treatment with 1 equiv. of tetrabutylammonium fluoride (TBAF) in the presence of acetic acid, and (iv) oxidation with Dess-Martin reagent.[32]

It was found that reduction of **34** with sodium borodeuteride in the presence of cerium (III) chloride in methanol[33] took place stereoselectively, giving alcohol **35** in 91% yield with (1*R*)-configuration. The stereoselectivity was estimated to be 90:10 judging from its ^{1}H NMR spectrum. The stereochemistry of the newly introduced deuterium was established at a later stage of the synthesis. The reduction

Table 3. Bond angles ∠S–C1–C2 and ∠S–C5–C4 of the model sulfoxides suggested by molecular modeling calculations (6-31G*)

Model	 **X**	 **Y**	 **Z**
∠S–C1–C2			
Sulfide	112.2	107.3	115.3
eq-Oxide	112.1	106.5	116.3
ax-Oxide	112.6	107.7	116.2
∠S–C5–C4			
Sulfide	110.9	113.9	106.3
eq-Oxide	110.6	114.6	105.4
ax-Oxide	111.1	114.3	106.5



Scheme 4. Reagents and conditions: (a) (i) TBDMSCl, Et_3N, DMF, rt (100%), (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C (99%), (iii) TBAF, AcOH, THF, 0 °C (67%), (iv) Dess-Martin reagent, CH_2Cl_2, rt (100%); (b) $NaBD_4$, $CeCl_3$, MeOH, rt (91%); (c) (i) BzCl, Py, CH_2Cl_2, rt (90%), (ii) TBAF, AcOH, THF, rt (98%), (iii) Dess-Martin reagent, CH_2Cl_2, rt; (d) $NaBD_4$, $CeCl_3$, MeOH, rt (85% two steps); (e) K_2CO_3, MeOH, CH_2Cl_2, 0 °C (67%); (f) (i) Na_2S, DMF, rt (77%), (ii) DEAD, PPh_3, benzoic acid, THF, rt (94%); (g) BzCl, Py, CH_2Cl_2, rt (72%); (h) *m*CPBA, CH_2Cl_2, 0 °C (74%, *ax*-**41**/*eq*-**41**=60:40).

with sodium borodeuteride or zinc borodueteride[34,35] in various solvents was found to be ineffective for the stereoselectivity. Since our synthetic route adopted *C*2 symmetrical **38** as a key intermediate, deuterium atom had to be introduced also at another terminal carbon with the same configuration in order to obtain the labelled substrate with the deuterium atom at the C1 position (carbohydrate numbering) in high concentration. Thus, after the TBDMS group of **35** was removed, the regenerated alcohol moiety was oxidized again under the same conditions as above to give aldehyde **36**. As expected, the reduction with cerium (III) chloride–sodium borodeuteride in methanol introduced deuterium in the same stereoselectivity (90:10), giving alcohol **37** in high yield. Then, **37** was converted into Merrer's bisepoxide **38** in 67% yield by treatment with potassium carbonate in methanol at 0 °C. Bisepoxide **38** thus prepared was converted into 1-deoxy-5-thioglucose derivative **39** according to their report. Treatment of **38** with sodium sulfide in methanol gave the corresponding thiepane, which was followed by ring contraction reaction under the Mitsunobu conditions[36] to provide **39** in 72% yield in two steps. In the same manner as that for **4**, the alcohol function of **39** was converted into benzoate giving **40** in 72% yield. Oxidation of the sulfide group proceeded smoothly to provide *ax*-**41** and *eq*-**41** in good yields.

The stereochemistries of deuterium-labelled carbons of **41** were next determined. The ^{1}H NMR spectrum of **40** was quite similar to that of **6** except for the disappearance of two signals for the C1H (δ 2.78 ppm) and one of the C6 methylene protons (δ 4.27 ppm) owing to incorporation of the deuterium atoms[37] as shown in Figure 3. The coupling constant between the remained C1H (2.35 ppm) and C2H was 9.8 Hz, which suggests that the equatorial proton was substituted with deuterium. Accordingly, the configuration at the C1 position was estimated to be (*S*).

The signal for the remained C6H appeared as a doublet (J=3.9 Hz) at 4.82 ppm. Comparing the coupling constant with that between C5H and C6H in **6** (7.8 Hz) and taking also the *gauche* effect[38] into account, the stereochemistry at the C5 position should be (*R*). This indicates that the stereochemistries of the primary alcohol moieties of **35** and **37** were both (*R*)-configuration. Thus, the reduction of both **34** and **36** was presumed to have proceeded through the six-membered chelation intermediate.[39]

The ^{1}H NMR spectra of the labelled sulfoxides *ax*-**41** and *eq*-**41** displayed good accordance with those of the non-labelled *ax*-**10** and *eq*-**10**, respectively. These comparisons of the ^{1}H NMR spectra as well as the R_f values on silica gel TLC made their stereochemistry incontestable as depicted in Scheme 4.

2.5.2. Discussion about the mechanism of the Pummerer rearrangement based on the results employing *ax*-41 and *eq*-41. The Pummerer rearrangements were examined employing the labelled substrates *ax*-**41** and *eq*-**41** thus in hand. As expected, the rearrangement of both *ax*-**41** and *eq*-**41** took place smoothly by treating with TFAA in the

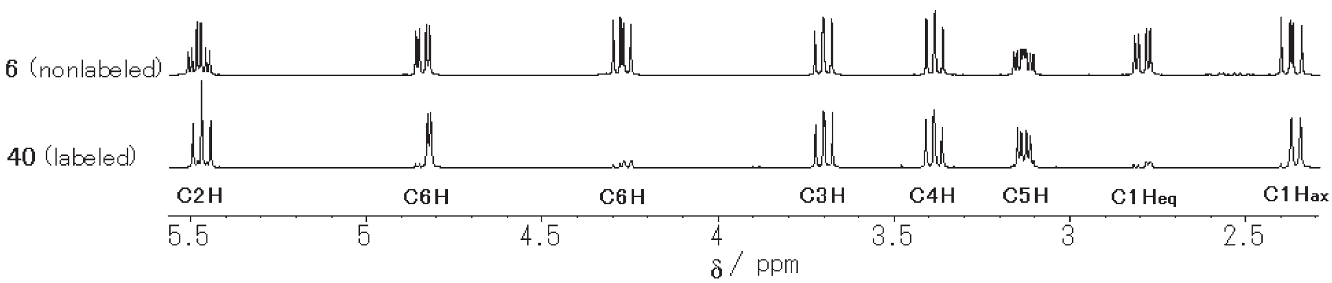
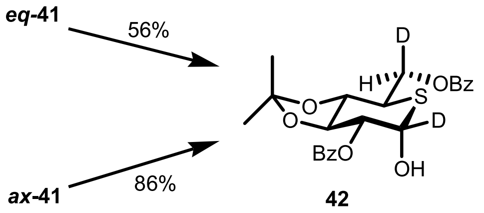


Figure 3. Part of ^{1}H NMR spectra (2.3–5.6 ppm) of **6** (non-labelled, upper) and **40** (labelled, lower) in C_6D_6.

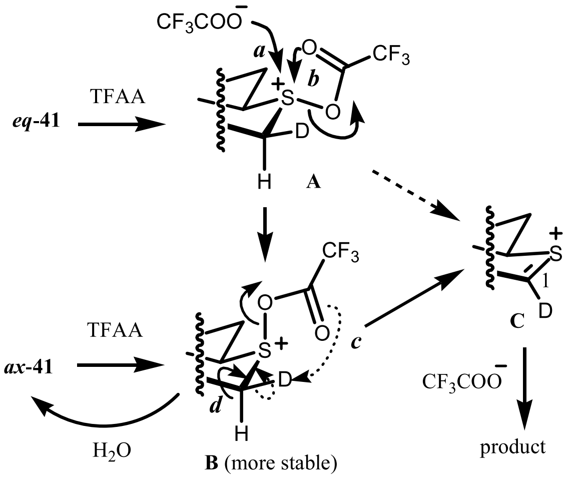
presence of pyridine in CH_2Cl_2 at room temperature, giving **42** in 56 and 86%, respectively (Scheme 5). The structure of **42** was confirmed by comparing the ^1H NMR spectrum to that of **20**. The ^1H NMR spectrum suggested that the deuterium atom was completely retained through the reaction. Interestingly, the ^1H NMR spectrum suggested that **42** existed as a single isomer, while **20** was observed as a anomeric mixtures (α/β=91:9). Since anomers **20** were under equilibrium on the basis of two-dimensional silica gel TLC, this might be caused due to isotope effect after conversion of the corresponding trifluoroacetate into **20**. The signal corresponding to C1H was not detected in the ^1H NMR spectrum of **42**. Due to the absence of the C1H signal, the stereochemistry of the anomeric position could not be established from the coupling constant. However, the stereochemistry for the C1 position could be assigned to be (*S*)-configuration by taking into account the spectral profile of other signals in the ^1H NMR spectrum as well as its behavior on silica gel TLC.

Since there was only small difference in the yields between the reaction of the labelled and non-labelled substrates, it is unlikely that the deuterium atom at the C1 position affected the reaction process.



Scheme 5. The Pummerer rearrangement of deuterium labelled *eq*-**41** and *ax*-**41** by TFAA.

As mentioned in Section 2.5.1, we observed a complete epimerization at the sulfoxide moieties of non-labelled *eq*-**10** into *ax*-**10** by quenching at the early stage of the Pummerer reaction. Similar isomerization took place under the same conditions also in the case of labelled *eq*-**41**. Thus, this isomerization might occur generally under these conditions. The isomerization of sulfonium ion **A** to **B** may proceed through intermolecular path a or intramolecular path b as shown in Scheme 6, although we cannot figure out at this stage which pathway predominantly contributes to the isomerization process. Probably, thiocarbenium ion **C** might be formed from sulfonium **B**, because not even trace amounts of the axial sulfoxides were detected on the silica gel TLC in the reactions of the equatorial sulfoxides. The sulfonium ion **B** seemed to be hydrolyzed to sulfoxides on the silica gel TLC and also during the work-up, giving the axial sulfoxides. Inversion of **A** by a hydroxy anion can be ruled out because of the existence of excess TFAA that consumes H_2O quickly. In the process **B** to **C**, the possibility of intramolecular pericyclic deprotonation (path c)[40,41] can be eliminated, because only the C1H*ax* was lost exclusively (path d) during the reaction in our experiments. Indeed, the ^1H NMR spectrum of **42** did not display the anomeric proton. These are consistent with Oae's report disclosing that the Pummerer rearrangement of cyclic sulfoxides proceeds through E2 1,2-elimination.[14] As mentioned above, the stereochemistry of the addition step of the trifluoroacetate



Scheme 6.

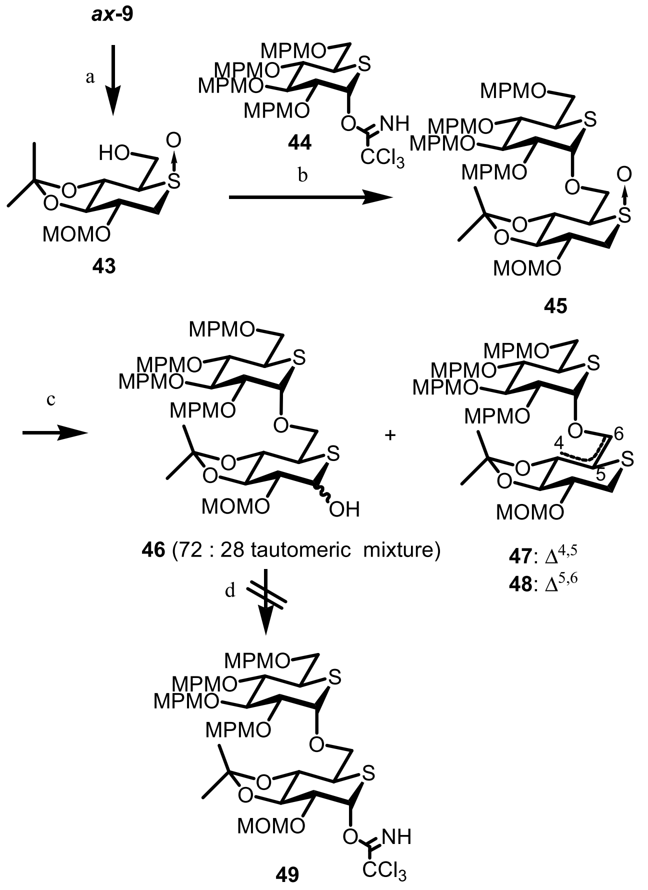
ion was unclear because of epimerization during and/or after work up, giving **42**.

However, as regards the reaction mechanism for the equatorial isomer, our results were different from that reported by Oae et al. In our experiments, the deuterium atom at the C1 position was also retained after the Pummerer reaction of *eq*-**41**, which indicates that the bond between C1 and the axial proton bond was cleaved under the conditions. In contrast, Oae disclosed that the C2 equatorial proton of octahydro-2*H*-thiocromene was removed by E2 1,2-elimination after flipping the thiane ring to the twisted boat conformation in the case of equatorial sulfoxide. It is hard to explain the detail of this difference at this stage, because a complex mixture was obtained when we attempted the rearrangement of *eq*-**41** under their conditions (heating with dicyclohexylcarbodiimide, Ac_2O). In our case, the potent leaving ability of the trifluoroacetoxy group might accelerate the elimination step giving thiocarbenium ion **C** at lower temperature and this might give rise to the difference in the reaction mechanisms (Scheme 6).

2.6. Synthesis of sulfur substituted isomaltotriose 58 as an application

Since the sulfur atom, a member of carcogen, is expected to exhibit similar chemical and physical properties to the oxygen atom, sulfur-substituted analogues of oligosaccharides may be useful inhibitors against the glycosidases.[8,42] We applied this rearrangement to a synthesis of sulfur-substituted isomaltotriose **58** in order to examine its scope and limitation.

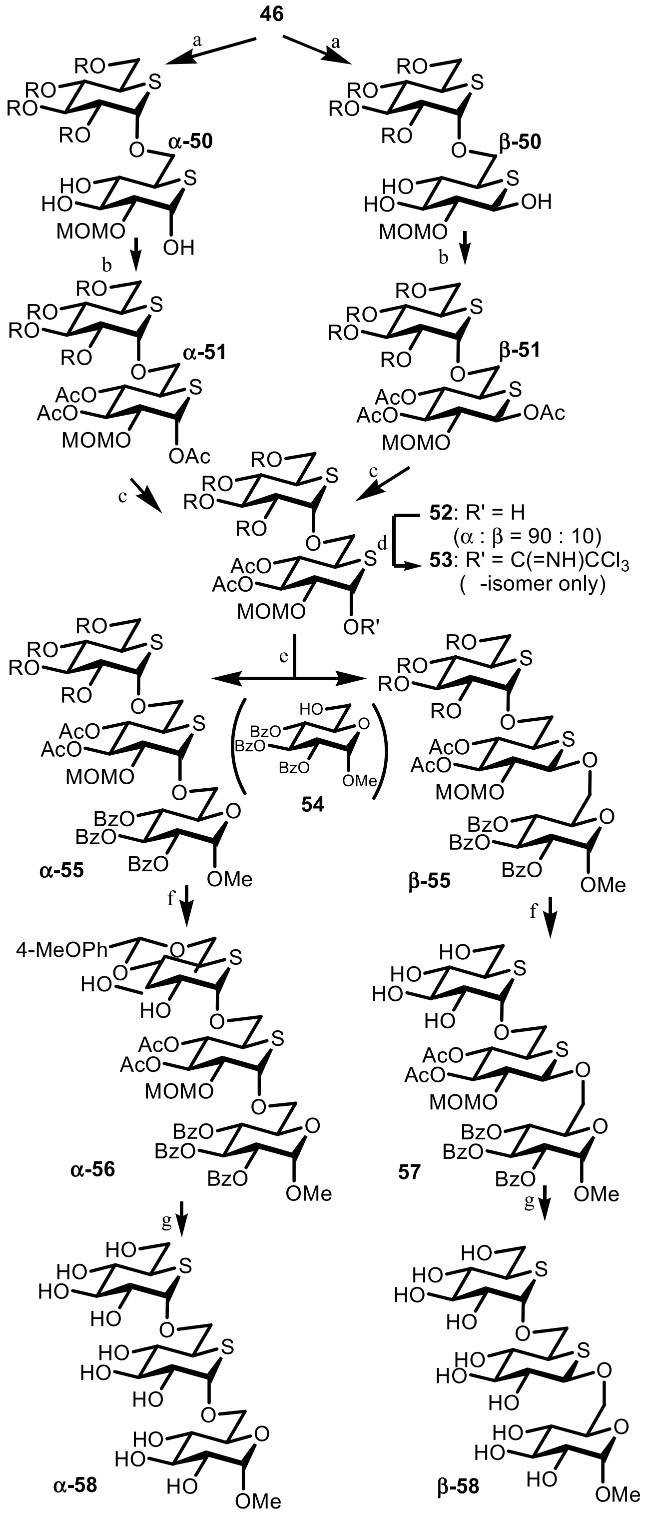
The benzoyl group of *ax*-**9** was removed by sodium methoxide in methanol. The resulting alcohol **43** was coupled with thioglucopyranosyl trichloroacetimidate **44**[8] in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[43] in CH_2Cl_2, giving the α-glycoside **45** stereoselectively[8] in 93% yield (Scheme 7). Production of the isomer of **45** with β-glycoside linkage was not detected in this reaction. Stereochemistry of the newly introduced α-glycoside of **45** was confirmed by observing a small coupling constant between C1′H and C2′H (J=2.5 Hz).



Scheme 7. Reagents and conditions: (a) NaOMe, MeOH, rt (100%); (b) **44**, TMSOTf, MS4A, CH_2Cl_2, −78 °C (93%); (c) TFAA, Py, CH_2Cl_2, 0 °C→rt (**46**: 51%, **47**: 26%, **48**: 13%); (d) CCl_3CN.

On treatment of **45** with TFAA in CH_2Cl_2 in the presence of pyridine, the Pummerer rearrangement proceeded to give alcohol **46** in 51% yield after aqueous work-up. Product **46** was observed as a 72:28 inseparable anomeric mixture. Stereochemistry of the anomeric position could not be assigned due to spectral crowding in the ^1H NMR spectrum. Contrary to our expectation, the regioselectivity of the rearrangement for **45** was a little lower than that in previous experiments. *endo*-Olefin **47** and *exo*-olefin **48** produced through the rearrangement to the C5 position were isolated in 26 and 13% yields, respectively. Probably, the bulky thioglucose moiety attached to the C6 position might affect the reaction courses of the rearrangement (Scheme 8).

We failed in all attempts to convert the alcohol **46** into trichloroacetimidate **49** which is required for extension of the sugar chain. As mentioned in Section 2.4, the acetonide group of **46** was expected to strain the angle ∠S–C1–C2 to be around 115°. This distortion might accelerate the detachment of the imidate group which might result in the decomposition of **49** on silica gel. The acetonide group of **46** was removed in order to overcome this problem. Treatment of the tautomeric mixture of **46** with catalytic hydrochloric acid in methanol gave an anomeric mixture of triols α-**50** and β-**50**. The ^1H NMR spectrum of this mixture indicated that α-**50** was the predominant isomer α-**50**/β-**50**=67:33). Interestingly, these anomers could be separated by silica gel column chromatography, although isomers of anomeric

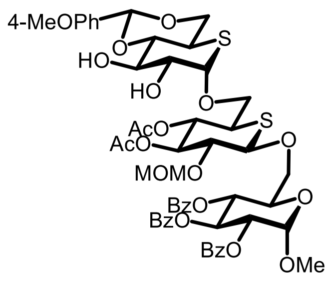


R = MPM

Scheme 8. Reagents and conditions: (a) cat. HCl, MeOH, rt (α-**50**:61%, β-**50**:30%); (b) Ac_2O, Py, rt (α-**51**: 83%, β-**51**: 89%); (c) H_2NNH_2–AcOH, DMF, rt [(α-**52**: 79%, β-**52**: 7.8%) from α-**51**, (α-**52**: 69%, β-**52**: 7.0%) from β-**51**]; (d) cat. DBU, CCl_3CN, CH_2Cl_2, 0 °C→rt (77%); (e) **54**, TMSOTf, MS4A, CH_2Cl_2, −78 °C, then separation (α-**55**: 57%, β-**55**: 19%); (f) DDQ, CH_2Cl_2, H_2O, rt (α-**56**: 70%, β-**56**: 44%, **57**: 26%); (g) (i) NaOMe, MeOH, rt (α-isomer: 79%, β-isomer: 100%), (ii) cat. HCl, MeOH, rt (α-**58**: 78%, β-**58**: 40%).

alcohols were usually inseparable because of tautomerization. Both isomers could be converted to the triacetate without remarkable isomerization, giving α-**51** and β-**51** both as almost pure forms in 83 and 89% yields, respectively. However, on cleavage of the C1 acetyl group by hydrazine acetate the isomerization resumed. Thus, both α-**51** and β-**51** gave a separable mixture of alcohols α-**52** and β-**52** (91:9 ratio). As expected, α-**52** could successfully be converted into trichloroacetimidate **53** in 77% yield as a single isomer by treating with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[43] The stereochemistry of **53** was confirmed to be α-configuration by observing the characteristic coupling constant (J=3.4 Hz) for the C1 proton (6.42 ppm).

Glycosidation of alcohol **54** with the imidate **53** took place smoothly by treating with catalytic TMSOTf in the presence of molecular sieves 4 Å, giving adducts α-**55** and β-**55** (75:25 ratio) in 76% yield. These isomers could be separated by medium-pressure silica gel column chromatography. MOM group at the C2 position may partially contribute to the β-glycosidation. Finally, all protective groups of **55** were removed. Treatment of α-**55** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) smoothly oxidized MPM ethers.[44] These conditions constructed 4-methoxybenzylidene acetal at the C4″ and C6″ positions to give α-**56** in 70% yield without oxidizing the sulfide moieties.[8] The same oxidation converted β-**55** into the benzylidene acetal β-**56** in 44% yield along with tetraol **57** (26%). It was found that the benzylidene moiety of β-**56** was gradually cleaved in $CDCl_3$, affording **57** in quantitative yield. Then, the benzoyl and acetyl protective groups of both α-**56** and **57** were removed under basic conditions, providing the corresponding nonanols in 79 and 100%, respectively. In the last step, treatment with catalytic hydrochloric acid in methanol cleaved the MOM ether and 4-methoxybenzylidene to provide α-**58** in 78%. The same treatment removed the MOM ether to afford β-**58** in 40% yield. The final products



β-56

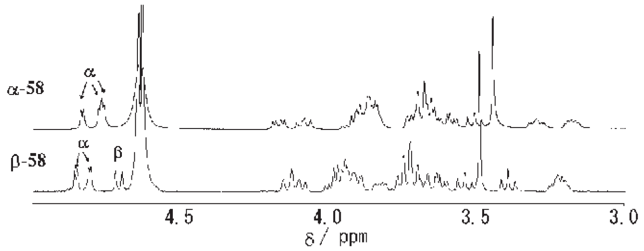


Figure 4. [1]H NMR spectra (homo decoupling) of isomaltotriose α-**58** and its epimer β-**58** in D_2O.

α-**58** and β-**58** were purified by medium-pressure ODS column chromatography.

The ^{1}H NMR spectra of α-**58** and its epimer β-**58** are shown in Figure 4. The signal patterns of the anomeric protons of α-**58** revealed that all of the glucosyl bonds of α-**58** are linked by α-configuration, while one of the signals corresponding to the anomeric protons of β-**58** indicates the existence of β-glycoside linkage. The HSQC and mass spectra also supported those structures.

3. Conclusion

We have succeeded in developing stereoselective Pummerer rearrangement reaction of 1-deoxy-5-thio-D-glucopyranose derivatives carrying an acetonide group at the C3 and C4 positions. Experiments employing deuterium-labelled derivatives revealed the details of the rearrangement. Further, this reaction was applied to the preparation of sulfur-substituted isomaltotriose α-**58** and its epimer β-**58**. Those carbomimetics are expected to be an effective antagonist for glycosidases. Enzymatic experiments employing them are under investigation in our laboratories.

4. Experimental

4.1. General

Melting points were determined with a Yanako MP-J3 micro melting point apparatus and were uncorrected. Optical rotations were measured on a HORIBA SEPA300 high-sensitivity polarimeter. For some compounds, consisted of a mixture of diastereomers, the optical rotations were not measured. ^{1}H NMR spectra were measured on a JEOL ALPHA 400 spectrometer (400 MHz). The chemical shifts are expressed in ppm downfield from the signal of trimethylsilane used as an internal standard in the case of $CDCl_3$. When another solvent was employed, the remained proton signals in deuterosolvents C_6HD_5 (7.15 ppm), CHD_2OD (3.30 ppm), or HDO (4.63 ppm) were used as the internal standards. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). ^{13}C NMR spectra were recorded also on a JEOL ALPHA 400 spectrometer (100 MHz). The isotope ^{13}C in the solvents were used as the internal standard ($^{13}CDCl_3$; 77.0 ppm, $^{13}C_6D_6$; 128.0 ppm, or $^{13}CD_3OD$; 49.5 ppm). For ^{13}C NMR spectra measured in D_2O, default offset was employed and did not perform correction. Assignments of the signals are according to the numbering based on IUPAC nomenclature if not mentioned. For carbohydrate derivatives numbering based on carbohydrate nomenclature is employed. IR spectra were obtained with a HORIBA FT-720 Fourier transform infrared spectrometer on a KBr cell. Measurements of electron impact, field desorption, fast atom bombardment, and electrospray ionization mass spectra (EI-MS, FD-MS, FAB-MS, and ESI-MS, respectively) were performed on a JEOL JMS AX500 or JEOL JMS AX102A spectrometers in Hokkaido University. When MS spectra were measured by negative mode, 'negative mode' is mentioned. MS analysis for unstable compounds such as glycosyl imidates was not performed.

Analytical and preparative thin-layer chromatographies were carried out using precoated silica gel plates, Merck silica gel $60F_{254}$ (Art. 1.05715). Silica gel used for column chromatography was Merck silica gel 60 (Art. 1.07734). Medium-pressure column chromatographies were performed employing Yamazene ULTRA PACK SI-40B or Merck Lobar® LiChroprep® RP-18 Type A) equipped with FMI LAB PUMP RP-SY. All reactions were carried out under N_2 or Ar atmosphere using dried solvents except for aqueous conditions. Dichloromethane and tetrahydropyran were freshly distilled from diphosphorus pentoxide and benzophenone-ketyl, respectively. Molecular sieves 4 Å were finely powdered and activated (200 °C in vacuo for 1 h) before use.

4.1.1. 6-*O*-Benzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-2-*O*-methoxymethyl-5-thio-D-glucopyranose (5). A mixture of 6-*O*-benzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (**4**) (317 mg, 978 μmol), prepared according to Merrer et al.,[20] MOMCl (150 mg, 2.45 mmol), and ${}^{i}Pr_2NEt$ (420 μL, 4.39 mmol) in CH_2Cl_2 (500 μL) was stirred at room temperature for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/EtOAc=85:15) gave **5** (311 mg, 86%) as an oil. $[\alpha]_D^{24}=-13.3$ (*c* 1.60, $CHCl_3$), IR (film) δ 2985, 2935, 2890, 1725, 1270, 1150, 1105, 1040, 715 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.41 (6H, s, C(CH_3)$_2$), 2.68 (1H, dd, *J*=10.3, 13.2 Hz, C1*H*H), 2.92 (1H, dd, *J*=4.4, 13.2 Hz, C1*H*H), 3.34 (1H, t, *J*=10.3 Hz, C3*H*), 3.38 (3H, s, C*H*$_3$O), 3.40 (1H, dt, *J*=3.9, 8.8 Hz, C5*H*), 3.66 (1H, dd, *J*=8.8, 10.3 Hz, C4*H*), 3.93 (1H, dt, *J*=4.4, 10.3 Hz, C2*H*), 4.31 (1H, dd, *J*=8.8, 11.7 Hz, C6*H*), 4.73 (1H, d, *J*=6.9 Hz, OCH*H*O), 4.75 (1H, dd, *J*=3.9, 11.7 Hz, C6*H*), 4.85 (1H, d, *J*=6.9 Hz, OCH*H*O), 7.43–8.03 (5H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 26.7, 26.9 (C(*C*H$_3$)$_2$), 31.9 (*C*1), 44.6 (*C*5), 55.5 (*C*H$_3$O), 63.9 (*C*6), 77.0 (*C*2), 77.9 (*C*4), 82.0 (*C*3), 96.2 (O*C*H$_2$O), 109.4 (*C*(CH$_3$)$_2$), 128.4, 129.7, 129.8, 133.1 (aromatic carbons), 166.0 (Ph*C*O), EI-MS (rel. int., %) *m/z*=353 (7.0, $[M-CH_3]^+$), 306 (7.0, M−$[MOMOH]^+$), 105 (100, $PhCO^+$), FD-MS (rel. int., %) *m/z*=368 (100, M^+), 353 (41, $[M-CH_3]^+$), EI-HRMS; found: *m/z* 353.1046. Calcd for $C_{17}H_{21}O_5S$: $[M-CH_3]^+$, 353.1059.

4.1.2. 2,6-*O*-Dibenzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (6). A mixture of **4** (69.4 mg, 214 μmol), BzCl (49.7 μL, 427 μmol), and pyridine (43.2 μL, 534 μmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 20 h. The mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine dried over $MgSO_4$, and then concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/EtOAc=88:12) gave **6** (86.9 mg, 95%) as an oil. $[\alpha]_D^{23}=+81.3$ (*c* 1.18, $CHCl_3$), IR (film) 2985, 1725, 1270, 1110, 1070, 1025, 710 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.44, 1.45 (each 3H, s, C(C*H*$_3$)$_2$), 2.76 (1H, dd, *J*=10.3, 13.7 Hz, C1*H*H), 3.10 (1H, dd, *J*=4.9, 13.7 Hz, C1*H*H), 3.49 (1H, ddd, *J*=3.5, 7.8, 8.8 Hz, C5*H*), 3.61 (1H, t, *J*=10.3 Hz, C3*H*), 3.84 (1H, dd, *J*=8.8, 10.3 Hz, C4*H*), 4.38 (1H, dd, *J*=7.8, 11.8 Hz, C6*H*), 4.81 (1H, dd, *J*=3.5, 11.8 Hz, C6*H*), 5.34 (1H, dt, *J*=4.9, 10.3 Hz, C2*H*), 7.45–8.06 (10H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 26.7, 26.8 (C(*C*H$_3$)$_2$), 30.7 (*C*1), 44.8 (*C*5), 63.8 (*C*6), 73.4 (*C*2), 78.1 (*C*4), 80.3 (*C*3), 109.9 (*C*(CH$_3$)$_2$), 128.35, 128.41, 129.68, 129.72, 129.72, 129.9, 133.2, 133.3 (aromatic carbons), 165.6, 166.1 (Ph*C*O×2), EI-MS (rel. int., %) *m/z*=413 (6.0, $[M-CH_3]^+$), 306 (2.4, M−$[PhCOOH]^+$), 248 (10, $[M-PhCOOH-acetone]^+$), 105 (100, $PhCO^+$), FD-MS (rel. int., %) *m/z*=428 (63, M^+), 413 (100, $[M-CH_3]^+$), EI-HRMS; found: *m/z* 413.1024. Calcd for $C_{22}H_{21}O_6S$: $[M-CH_3]^+$, 413.1059.

4.2. 2,3,4,6-*O*-Tetrabenzoyl-1,5-dideoxy-5-thio-D-glucopyranose (7)

4.2.1. Removal of the acetonide. A solution of **4** (224 mg, 690 μmol) in methanol (10 mL) was stirred with concentrated aqueous HCl (10 μL) at room temperature for 3 h. After the mixture was neutralized with Et_3N, the mixture was concentrated in vacuo. Silica gel column chromatography of the residue (CH_2Cl_2/acetone=70:30) gave the corresponding triol (166 mg, 85%) as a solid. Analytical sample was obtained by recrystallization from hexane/EtOAc (50:50) to give colorless needles. mp=143–144 °C, $[\alpha]_D^{24}=+46.5$ (*c* 0.95, MeOH), IR (KBr) 3400, 2920, 1712, 1275, 1065, 710 cm^{-1}, ^1H NMR (CD_3OD), δ 2.58–2.68 (2H, C1*H*$_2$), 3.09 (1H, ddd, *J*=3.4, 6.4, 10.2 Hz, C5*H*), 3.14 (1H, t, *J*=8.8 Hz, C3*H*), 3.54 (1H, dd, *J*=8.8, 10.2 Hz, C4*H*), 3.61 (1H, dt, *J*=5.3, 8.8 Hz, C2*H*), 4.48 (1H, dd, *J*=6.4, 11.7 Hz, C6*H*), 4.70 (1H, dd, *J*=3.4, 11.7 Hz, C6*H*), 7.47–8.02 (5H, aromatic protons), ^{13}C NMR (CD_3OD), 33.4 (*C*1), 47.3 (*C*5), 65.1 (*C*6), 74.8 (*C*2), 75.4 (*C*4), 80.7 (*C*3), 129.6, 130.6, 131.2, 134.3 (aromatic carbons), 167.8 (Ph*C*O), EI-MS (rel. int., %) *m/z*=284 (0.2, M^+), 266 (4.4, $[M-H_2O]^+$), 248 (3.8, $[M-2H_2O]^+$), 162 (68, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 284.0765. Calcd for $C_{13}H_{16}O_5S$: M^+, 284.0718.

4.2.2. Benzoylation giving 7. A mixture of the product (166 mg, 584 μmol) and BzCl (340 μL, 2.92 mmol) was stirred in pyridine (7.0 mL) at room temperature for 24 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=85: 15) gave **7** (347 mg, 100%) as a colorless oil. $[\alpha]_D^{24}=+31.1$ (*c* 0.88, $CHCl_3$), IR (film) 1730, 1450, 1270, 1105, 710 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.86 (1H, dd, *J*=10.8, 13.2 Hz, C1*H*H), 3.09 (1H, dd, *J*=4.4, 13.2 Hz, C1*H*H), 3.53 (1H, ddd, *J*=3.9, 5.8, 9.7 Hz, C5*H*), 4.36 (1H, dd, *J*=5.8, 11.7 Hz, C6*H*), 4.54 (1H, dd, *J*=3.9, 11.7 Hz, C6*H*), 5.42 (1H, ddd, *J*=4.4, 9.7, 10.8 Hz, C2*H*), 5.64 (1H, t, *J*=9.7 Hz, C3*H*), 5.76 (1H, t, *J*=9.7 Hz, C4*H*), 7.10–7.92 (20H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 30.1 (*C*1), 44.7 (*C*5), 62.6 (*C*6), 73.0 (*C*4), 73.4 (*C*2), 74.6 (*C*3), 128.1, 128.25, 128.33, 128.33, 128.8, 128.9, 129.1, 129.4, 129.5, 129.65, 129.65, 129.72, 133.0, 133.1, 133.2, 133.3 (aromatic carbons), 165.3, 165.4, 165.8, 165.9 (Ph*C*O×4), FD-MS (rel. int., %) *m/z*=596 (7.0, M^+), 595 (13, $[M-H]^+$), 122 (100, $PCOOH^+$), FD-HRMS; found: *m/z* 596.1485. Calcd for $C_{34}H_{28}O_8S$: M^+, 596.1505.

4.2.3. 6-*O*-Benzoyl-1,5-dideoxy-2,3-*O*-isopropylidene-5-thio-D-glucopyranose (8a). A solution of **4** (326 mg, 1.00 mmol) in acetone (5.0 mL) was stirred with p-TsOH·H_2O (10 mg, 52.6 μmol) at room temperature for 2.5 h. After the mixture was neutralized by the addition of Et_3N, the mixture was concentrated in vacuo. Medium pressured silica gel column chromatography of the residue (hexane/EtOAc=90:10) gave **8a** (196 mg, 60%) and recovered **4** (105 mg, 32%) both as oils. The ^{1}H NMR spectrum of recovered **4** was identical with the authentic sample.

4.2.4. Physical data for 8a. $[\alpha]_D^{21}$=+55.8 (*c* 0.90, $CHCl_3$), IR (film) 2985, 2920, 1720, 1270, 1115, 715 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.32, 1.33 (each 3H, s, C(CH_3)$_2$), 2.43 (2H, C1H_2), 2.88 (1H, dt, *J*=4.4, 9.2 Hz, C5*H*), 3.05 (1H, t, *J*=9.2 Hz, C4*H*), 3.66 (1H, dt, *J*=6.8, 9.2 Hz, C2*H*), 3.75 (1H, t, *J*=9.2 Hz, C3*H*), 4.65 (2H, d, *J*=4.4 Hz, C6H_2), 7.02–8.16 (5H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.9, 27.0 (C(CH$_3$)$_2$), 30.6 (*C*1), 47.0 (*C*5), 63.1 (*C*6), 72.6 (*C*4), 77.1 (*C*2), 84.2 (*C*3), 109.6 (*C*(CH$_3$)$_2$), 128.5, 128.6, 130.1, 130.4, 133.1 (aromatic carbons), 166.4 (Ph*C*O), EI-MS (rel. int., %), 309(3.5, [M−CH$_3$]$^+$), 267 (1.4, [M−isobutene]$^+$), 105 (51, PhCO$^+$), EI-HRMS; found: *m/z* 309.0788. Calcd for $C_{15}H_{17}O_5S$: [M−CH$_3$]$^+$, 309.0797.

4.2.5. 4-Acetoxy-6-*O*-benzoyl-1,5-dideoxy-2,3-*O*-isopropylidene-5-thio-D-glucopyranose (8b). A solution of **8a** (340 mg, 1.05 mmol) in a mixture of Ac_2O (3.0 mL) and pyridine (6.0 mL) was stirred at room temperature for 1.5 h. After concentration, silica gel column chromatography of the residue (hexane/EtOAc=80:20) gave **8b** (384 mg, 100%) as a colorless oil. $[\alpha]_D^{21}$=+51.8 (*c* 6.2, $CHCl_3$), IR (film) 2985, 1725, 1375, 1240, 1115, 1025, 715 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.26, 1.29 (each 3H, s, C(CH_3)$_2$), 1.64 (3H, s, CH_3CO), 2.37 (2H, C1H_2), 2.98 (1H, ddd, *J*=3.4, 6.3, 9.7 Hz, C5*H*), 3.17 (1H, dd, *J*=8.8, 9.7 Hz, C3*H*), 3.75 (1H, dt, *J*=7.3, 8.8 Hz, C2*H*), 4.30 (1H, dd, *J*=6.3, 12.2 Hz, C6*H*H), 4.58 (1H, dd, *J*=3.4, 12.2 Hz, C6*H*H), 5.55 (1H, t, *J*=9.7 Hz, C4*H*), 7.05–8.23 (5H, aromatic protons), ^{13}C NMR (C_6D_6) 20.3 (*C*H$_3$CO), 26.87, 26.88 (C(*C*H$_3$)$_2$), 30.5 (*C*1), 45.2 (*C*5), 62.4 (*C*6), 72.6 (*C*4), 77.5 (*C*2), 81.9 (*C*3), 109.9 (*C*(CH$_3$)$_2$), 128.5, 128.6, 130.1, 130.4, 133.1 (aromatic carbons), 165.9, 169.2 (Ph*C*O×2), EI-MS (rel. int., %) *m/z*=351 (3.7, [M−CH$_3$]$^+$), 306 (0.7, [M−AcOH]$^+$), 184 (34, [M−AcOH−PhCOOH]$^+$), 126 (57, [M−AcOH−PhCOOH−acetone]$^+$), 105 (100, PhCO$^+$), EI-HRMS; found: *m/z* 351.0902. Calcd for $C_{17}H_{19}O_6S$: [M−CH$_3$]$^+$, 351.0902.

4.3. 6-*O*-Benzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-2-*O*-methoxymethyl-5-thio-D-glucopyranose (*R*)-*S*-oxide (*eq*-9) and its (*S*)-isomer (*ax*-9)

4.3.1. Preparation. A mixture of **5** (658 mg, 1.79 mmol) and *m*CPBA (70% purity, 439 mg, 1.79 mmol) was stirred in CH_2Cl_2 (5.0 mL) at −20 °C for 30 min. The mixture was poured into 5% aqueous sodium thiosulfate solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (benzene/EtOAc=70:30) gave *eq*-**9** (302 mg, 44%) and *ax*-**9** (298 mg, 43%) both as colorless oils.

4.3.2. Physical data for *eq*-9. $[\alpha]_D^{23}$=−45.3 (*c* 1.35, $CHCl_3$), (film) 2980, 2925, 1725, 1270, 1150, 1105, 1050, 1035, 710 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.14, 1.21 (each 3H, s, C(CH_3)$_2$), 2.69 (1H, ddd, *J*=3.0, 4.4, 11.7 Hz, C5*H*), 2.75 (1H, dd, *J*=9.3, 12.2 Hz, C1*H*H), 3.08 (3H, s, CH_3O), 3.19 (1H, dd, *J*=9.3, 11.7 Hz, C4*H*), 3.32 (1H, dd, *J*=4.4, 12.2 Hz, C1*H*H), 3.58 (1H, t, *J*=9.3 Hz, C3*H*), 3.63 (1H, dt, *J*=4.4, 9.3 Hz, C2*H*), 4.36, 4.64 (each 1H, d, *J*=6.8 Hz, OCH_2O), 4.72 (1H, dd, *J*=4.4, 12.2 Hz, C6*H*H), 4.93 (1H, dd, *J*=3.0, 12,2 Hz, C6*H*H), 7.03–7.12 (3H, aromatic protons), 8.17–8.19 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.71, 26.74 (C(*C*H$_3$)$_2$), 55.2 (*C*H3O), 55.4 (*C*1), 59.6 (*C*6), 64.2 (*C*5), 69.2 (*C*2), 71.0 (*C*4), 82.4 (*C*3), 95.6 (O*C*H$_2$O), 111.7 (*C*(CH$_3$)$_2$), 128.6, 130.0, 130.5, 133.1 (aromatic carbons), 165.7 (Ph*C*O), EI-MS (rel. int., %) *m/z*=385 (trace, M+H$^+$), 369 (5.7, [M−CH$_3$]$^+$), 322 (1.0 [M−MOMOH]$^+$), 105 (100, PhCO$^+$), FD-MS (rel. int., %) *m/z*=385 (18, [M+H]$^+$), 369 (100, [M−CH$_3$]$^+$), EI-HRMS; found: *m/z* 369.0986. Calcd for $C_{17}H_{21}O_7S$: [M−CH$_3$]$^+$, 369.1008.

4.3.3. Physical data for *ax*-9. $[\alpha]_D^{23}$=+15.1 (*c* 0.98, $CHCl_3$), IR (film) 2985, 2935, 2895, 1725, 1270, 1235, 1150, 1105, 1060, 1035, 715 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.21, 1.30 (each 3H, s, C(CH_3)$_2$), 1.69 (1H, dd, *J*=11.2, 14.6 Hz, C1*H*H), 2.53 (1H, dt, *J*=4.4, 11.7 Hz, C5*H*), 3.10 (3H, s, CH_3O), 3.20 (1H, dd, *J*=4.4, 14.6 Hz, C1*H*H), 3.29 (1H, t, *J*=9.3 Hz, C3*H*), 4.25 (1H, dd, *J*=9.3, 11.7 Hz, C4*H*), 4.45 (1H, d, *J*=6.4 Hz, OCH*H*O), 4.62 (1H, ddd, *J*=4.4, 9.3, 11.2 Hz, C2*H*), 4.68 (1H, dd, *J*=10.8, 11.7 Hz, C6*H*H), 4.74 (1H, d, *J*=6.4 Hz, OCH*H*O), 5.14 (1H, dd, *J*=4.4, 10.8 Hz, C6*H*H), 7.03–7.13 (3H, aromatic protons), 8.15–8.17 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.6, 26.9 (C(*C*H$_3$)$_2$), 50.6 (*C*1), 55.2 (*C*H3O), 58.8 (*C*5), 59.9 (*C*6), 71.1 (*C*2), 72.7 (*C*4), 82.3 (*C*3), 96.1 (O*C*H$_2$O), 109.9 (*C*(CH$_3$)$_2$), 128.5, 128.6, 130.1, 130.3, 133.2 (aromatic carbons), 165.8 (Ph*C*O), EI-MS (rel. int., %) *m/z*=369 (4.0, [M−CH$_3$]$^+$), 262 (13, [M−PhCOOH]$^+$), 105 (100, PhCO$^+$), FD-MS (rel. int., %) *m/z*=384 (31, M$^+$), 369 (100, [M−CH$_3$]$^+$), EI-HRMS; found: *m/z* 369.1024. Calcd for $C_{17}H_{21}O_7S$: [M−CH$_3$]$^+$, 369.1008.

4.4. 2,6-*O*-Dibenzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (*R*)-*S*-oxide (*eq*-10) and its (*S*)-isomer (*ax*-10)

Treatment of **6** (25.0 mg, 58.3 μmol) in a similar manner as described in Section 4.3.1 gave *eq*-**10** (14.1 mg, 55%) *ax*-**10** (9.5 mg, 36.7%) after silica gel column chromatography (benzene/EtOAc=95:5).

4.4.1. Physical data for *eq*-10. $[\alpha]_D^{24}$=+41.9 (*c* 0.80, $CHCl_3$), IR (film) 3445, 2985, 1725, 1270, 1265, 1105, 1045, 705 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.13, 1.22 (each 3H, s, C(CH_3)$_2$), 2.66 (1H, dd, *J*=9.3, 12.7 Hz, C1*H*H), 2.82 (1H, ddd, *J*=3.4, 5.4, 11.2 Hz, C5*H*), 3.24 (1H, dd, *J*=4.9, 12.7 Hz, C1*H*H), 3.25 (1H, dd, *J*=9.3, 11.2 Hz, C4*H*), 3.99 (1H, t, *J*=9.3 Hz, C3*H*), 4.62 (1H, dd, *J*=5.4, 12.2 Hz, C6*H*H), 4.82 (1H, dd, *J*=3.4, 12.2 Hz, C6*H*H), 5.32 (1H, dt, *J*=4.9, 9.3 Hz, C2*H*), 6.98–8.16 (10H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.6, 26.8 (C(*C*H$_3$)$_2$), 53.4 (*C*1), 60.0 (*C*6), 64.8 (*C*5), 67.8 (*C*2), 71.4 (*C*4), 79.8 (*C*3), 112.1 (*C*(CH$_3$)$_2$), 128.55, 128.60, 129.9, 130.0, 130.1, 130.3, 133.2, 133.4 (aromatic carbons), 165.2, 166.7 (Ph*C*O×2), EI-MS (rel. int., %) *m/z*=445 (0.3, [M+H]$^+$), 429 (0.8,

$[M-CH_3]^+$), 264 (0.6, $[M-PhCOOH-acetone]^+$), 105 (100, $PhCO^+$), EI-HRMS; found *m/z* 445.1291. Calcd for $C_{23}H_{25}O_7S$: $[M+H]^+$, 445.1321.

4.4.2. Physical data for *ax*-10. $[\alpha]_D^{24}=+46.1$ (*c* 0.92, $CHCl_3$), IR (film) 3735, 2920, 2850, 1720, 1270, 1105, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.15, 1.30 (each 3H, s, $C(CH_3)_2$), 1.58 (1H, dd, *J*=10.7, 14.1 Hz, C1*H*H), 2.65 (1H, dt, *J*=4.4, 11.2 Hz, C5*H*), 3.33 (1H, dd, *J*=3.9, 14.1 Hz, C1*H*H), 3.48 (1H, dd, *J*=9.8, 10.7 Hz, C3*H*), 4.39 (1H, dd, *J*=9.8, 11.2 Hz, C4*H*), 4.68 (1H, d, *J*=11.2, 12.7 Hz, C6*H*H), 5.16 (1H, dd, *J*=4.4, 12.7 Hz, C6*H*H), 6.13 (1H, dt, *J*=3.9, 10.7 Hz, C2*H*), 6.99–8.16 (10H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.4, 27.0 ($C(CH_3)_2$), 49.2 (*C*1), 59.2 (*C*5), 59.9 (*C*6), 69.3 (*C*2), 72.9 (*C*4), 80.3 (*C*3), 110.5 ($C(CH_3)_2$), 128.5, 128.7, 130.0, 130.0, 130.1, 130.2, 133.2, 133.3 (aromatic carbons), 165.0, 165.8 (Ph*C*O×2), EI-MS (rel. int., %) *m/z*=444 (0.7, M+), 429 (1.0, $[M-CH_3]^+$), 322 (1.8, $[M-PhCOOH]^+$), 264 (5.5, $[M-PhCOOH-acetone]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 444.1214. Calcd for $C_{23}H_{24}O_7S$: M^+, 444.1243.

4.5. 2,3,4,6-*O*-Tetrabenzoyl-1,5-dideoxy-5-thio-D-glucopyranose (*R*)-*S*-oxide (*eq*-11) and its (*S*)-isomer (*ax*-11)

Treatment of **7** (347 mg, 581 μmol) in a similar manner as described in Section 4.3.1 gave *eq*-**11** (170 mg, 48%) and *ax*-**11** (172 mg, 48%) after silica gel column chromatography (benzene/EtOAc=90: 10).

4.5.1. Physical data for *eq*-11. $[\alpha]_D^{24}=+45.2$ (*c* 0.80, $CHCl_3$), IR (film) 1730, 1265, 1105, 710 cm^{-1}, ^1H NMR ($CDCl_3$) δ 3.22 (1H, t, *J*=11.8 Hz, C1*H*H), 3.49 (1H, dt, *J*=2.5, 11.7 Hz, C5*H*), 4.02 (1H, dd, *J*=3.9, 11.8 Hz, C1*H*H), 4.68 (1H, dd, *J*=2.5, 12.7 Hz, C6*H*H), 4.86 (1H, dd, *J*=2.5, 12.7 Hz, C6*H*H), 5.45 (1H, ddd, *J*=3.9, 9.8, 11.8 Hz, C2*H*), 5.79 (1H, dd, *J*=9.8, 11.7 Hz, C4*H*), 5.90 (1H, t, *J*=9.8 Hz, C3*H*), 7.10–7.5 (20H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 52.6 (*C*1), 56.6 (*C*6), 64.8 (*C*4), 65.3 (*C*2), 65.7 (*C*5), 74.0 (*C*3), 128.1, 128.2, 128.27, 128.32, 128.36, 128.39, 128.44, 128.5, 129.6, 129.7, 129.8, 129.8, 133.3, 133.4, 133.6, 133.7 (aromatic carbons), 164.7, 165.1, 165.5, 165.6 (Ph*C*O×4), EI-MS (rel. int., %) *m/z*=612 (0.6, M^+), 490 (3.3, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 612.1484. Calcd for $C_{34}H_{28}O_9S$: M^+, 612.1454.

4.5.2. Physical data for *ax*-11. $[\alpha]_D^{23}=+12.8$ (*c* 1.0, $CHCl_3$), IR (film) 1730, 1270, 1105, 710 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.72 (1H, dd, *J*=11.7, 14.2 Hz, C1*H*H), 3.38 (1H, ddd, *J*=4.9, 9.3, 11.2 Hz, C5*H*), 3.85 (1H, dd, *J*=3.9, 14.2 Hz, C1*H*H), 4.64 (1H, dd, *J*=9.3, 12.2 Hz, C6*H*H), 4.78 (1H, dd, *J*=4.9, 12.2 Hz, C6*H*H), 5.90 (1H, t, *J*=9.8 Hz, C3*H*), 6.10 (1H, ddd, *J*=3.9, 9.8, 11.7 Hz, C2*H*), 6.23 (1H, dd, *J*=9.8, 11.2 Hz, C4*H*), 7.11–7.88 (20H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 47.4 (*C*1), 59.0 (*C*5), 60.0 (*C*6), 67.3 (*C*2), 67.9 (*C*4), 73.8 (*C*3), 128.2, 128.3, 128.38, 128.38, 128.42, 128.5, 128.8, 129.0, 129.6, 129.7, 129.76, 129.80, 133.3, 133.41, 133.43, 133.5 (aromatic carbons), 164.9, 165.2, 165.8, 165.9 (Ph*C*O×4), EI-MS (rel. int., %) *m/z*=612 (3.1, M^+), 490 (1.4, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 612.1484. Calcd for $C_{34}H_{28}O_9S$: M^+, 612.1454.

4.6. 4-Acetoxy-6-*O*-benzoyl-1,5-dideoxy-2,3-*O*-isopropylidene-5-thio-D-glucopyranose (*R*)-*S*-oxide (*eq*-12) and its (*S*)-isomer (*ax*-12)

Treatment of **8b** (74.4 mg, 203 μmol) in a similar manner as described in Section 4.3.1 gave *eq*-**12** (42.6 mg, 55%) and *ax*-**12** (28.7 mg, 37%) after silica gel column chromatography (benzene/EtOAc=80:20). Analytical sample for *ax*-**12** was obtained by recrystallization from hexane/EtOAc (50:50) giving plates.

4.6.1. Physical data for *eq*-12. $[\alpha]_D^{21}=-16.2$ (*c* 0.39, $CHCl_3$), IR (film) 2985, 1730, 1375, 1240, 1100, 1025, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.12, 1.21 (each 3H, s, $C(CH_3)_2$), 1.51 (3H, s, CH_3CO), 2.55 (1H, dd, *J*=10.7, 13.2 Hz, C1*H*H), 2.73 (1H, ddd, *J*=3.0, 4.8, 11.2 Hz, C5*H*), 3.05 (1H, ddd, *J*=2.4, 9.3, 13.2 Hz, C2*H*), 3.28 (1H, dd, *J*=2.4, 10.7 Hz, C1*H*H), 3.44 (1H, t, *J*=9.3 Hz, C3*H*), 4.68 (1H, dd, *J*=3.0, 12.7 Hz, C6*H*H), 4.93 (1H, dd, *J*=4.8, 12.7 Hz, C6*H*H), 5.50 (1H, dd, *J*=9.3, 11.2 Hz, C4*H*), 7.03–8.21 (5H, aromatic protons), ^{13}C NMR (C_6D_6) δ 20.1 (CH_3CO), 26.5, 26.7 ($C(CH_3)_2$), 52.2 (*C*1), 56.5 (*C*6), 65.0 (*C*4), 67.0 (*C*5), 69.1 (*C*2), 81.6 (*C*5), 111.8 ($C(CH_3)_2$), 127.9, 128.6, 130.1, 133.2 (aromatic carbons), 165.8, 168.6 (CH_3CO and Ph*C*O), EI-MS (rel. int., %) *m/z*=383 (0.4, $[M+H]^+$), 367 (1.5, $[M-CH_3]^+$), 322 (1.2, $[M-AcOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 383.1168. Calcd for $C_{18}H_{23}O_7S$: M^+, 383.1164.

4.6.2. Physical data for *ax*-12. Mp=181–182 °C, $[\alpha]_D^{21}=+142$ (*c* 1.78, $CHCl_3$), IR (KBr) 2985, 1730, 1375, 1240, 1100, 1050, 715 cm^{-1}, ^1H NMR (C_6D_6) δ 1.18, 1.29 (each 3H, s, $C(CH_3)_2$), 1.63 (1H, dd, *J*=12.2, 13.2 Hz, C1*H*H), 1.65 (3H, s, CH_3CO), 2.52 (1H, dt, *J*=3.9, 9.8 Hz, C5*H*), 3.03 (1H, dd, *J*=3.4, 13.2 Hz, C1*H*H), 3.30 (1H, t, *J*=9.8 Hz, C3*H*), 4.61 (1H, ddd, *J*=3.4, 9.8, 12.2 Hz, C2*H*), 4.68 (1H, dd, *J*=9.8, 11.7 Hz, C6*H*H), 4.86 (1H, dd, *J*=3.9, 11.7 Hz, C6*H*H), 6.00 (1H, t, *J*=9.8 Hz, C4*H*), 7.04–8.16 (5H, aromatic protons), ^{13}C NMR (C_6D_6) δ 20.2 (CH_3CO), 26.5, 27.0 ($C(CH_3)_2$), 48.1 (*C*1), 59.8 (*C*6), 60.6 (*C*5), 68.9 (*C*4), 71.6 (*C*2), 81.1 (*C*3), 110.6 ($C(CH_3)_2$), 128.7, 130.05, 130.11, 133.4 (aromatic carbons), 165.9, 169.2 (CH_3CO and Ph*C*O), EI-MS (rel. int., %) *m/z*=383 (2.1, $[M+H]^+$), 367 (0.7, $[M-CH_3]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m/z* 383.1208. Calcd for $C_{18}H_{23}O_7S$: $[M+H]^+$, 383.1164.

4.7. Pummerer rearrangement of 1,5-dideoxy-5-thio-D-glucopyranose derivatives

4.7.1. Typical conditions. To a mixture of sulfoxide and pyridine (10 equiv.) in CH_2Cl_2, TFAA (5 equiv.) was added at 0 °C. After 5 min, the cooling bath was removed and the mixture was stirred at room temperature until TLC indicated that the starting sulfoxide was disappeared. After addition of MeOH to decompose excess TFAA, the mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue gave products.

4.7.2. Reaction of *eq*-9 (run 1). Treatment of *eq*-**9** (15.0 mg, 39.3 μmol) in a similar manner as described in Section 4.7.1 gave **15** (14 mg) as an oil after silica gel column chromatography (benzene/EtOAc=90: 10). Since **15** was observed as broad spot on silica gel TLC, accurate yield of **15** could not be obtained. Analytical sample was prepared from a part of the fractions. The yield of this reaction was estimated to be 66% after acetylation of the alcohol moiety as described in Section 4.12. Physical data for **15** are follows; $[\alpha]_D^{23}=+32.9$ (*c* 1.56, $CHCl_3$), IR (film) 3440, 2930, 1725, 1275, 1235, 1155, 1106, 1070, 1030, 715 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from the C1 anomeric position (α-anomer/β-anomer=90:10). Assignments of the signals for the main isomer and some for the minor isomer are described. ^1H NMR (C_6D_6, *a*=0.9, *b*=0.1) δ 1.27, 1.29 (each 3H×*a*, s, C(C*H*$_3$)$_2$ (α-isomer)), 3.11 (3H×*a*, s, C*H*$_3$O (α-isomer)), 3.16 (3H×*b*, s, C*H*$_3$O (β-isomer)), 3.46 (1H×*b*, t, *J*=9.3 Hz, C4*H* (β-isomer)), 3.65 (1H×*a*, ddd, *J*=2.9, 6.8, 10.8 Hz, C5*H* (α-isomer)), 3.71 (1H×*a*, dd, *J*=8.3, 10.8 Hz, C4*H* (α-isomer)), 3.92 (1H×*a*, dd, *J*=3.0, 10.3 Hz, C2*H* (α-isomer)), 4.07 (1H×*a*, dd, *J*=8.3, 10.3 Hz, C3*H* (α-isomer)), 4.35 (1H×*b*, dd, *J*=7.3, 11.2 Hz, C6*H*H (β-isomer)), 4.41 (1H×*a*, dd, *J*=7.3, 11.7 Hz, C6*H*H (α-isomer)), 4.47 (1H×*a*, d, *J*=6.8 Hz, OC*H*HO (α-isomer)), 4.63 (1H×*b*, d, *J*=6.4 Hz, OC*H*HO (β-isomer)), 4.70 (1H×*a*, d, *J*=6.8 Hz, OC*H*HO (α-isomer)), 4.74 (1H×*b*, d, *J*=6.4 Hz, OC*H*HO (β-isomer)), 4.78 (1H×*a*, dd, *J*=2.9, 11.7 Hz, C6*H*H (α-isomer)), 4.80 (1H×*a*, d, *J*=3.0 Hz, C1*H* (α-isomer)), 7.00–7.05 (3H, aromatic protons), 8.17 (2H, aromatic protons), ^{13}C NMR (C_6D_6, signals for only major isomer are described.) δ 26.7, 27.1 (C(*C*H$_3$)$_2$), 42.2 (*C*5), 55.3 (*C*H$_3$O), 63.7 (*C*6), 75.0 (*C*1), 77.5 (*C*3), 78.9 (*C*4), 79.5 (*C*2), 95.9 (O*C*H$_2$O), 109.4 (*C*(CH$_3$)$_2$), 128.5, 130.1, 130.5, 133.0 (aromatic carbons), 165.9 (Ph*C*O), FD-MS (rel. int., %) *m*/*z*=384 (75, M^+), 369 (100, $[M-CH_3]^+$), FD-HRMS; found: *m*/*z* 384.1261. Calcd for $C_{18}H_{24}O_7S$: M^+, 384.1243.

4.7.3. Reaction of *ax*-9 (run 2). Treatment of *ax*-**9** (46.6 mg, 121 μmol) in a similar manner as described in Section 4.7.1 gave **15** (60 mg), and trace amount of **19**. The yield of **15** was estimated to be 84% after acetylation. The ^1H NMR spectrum of **15** was identical with that prepared from *eq*-**9**.

4.7.4. Reaction of *eq*-10 in CH_2Cl_2 (run 3). Treatment of *eq*-**10** (30.1 mg, 67.7 μmol) in a similar manner as described in Section 4.7.1 gave **20** (22.3 mg, 55%) and trace amount of **21**, **22**, and **23** after column chromatography (hexane/EtOAc=80:20).

4.7.5. Physical data for 20. $[\alpha]_D^{24}=+99.9$ (*c* 3.02, $CHCl_3$), IR (film) 3440, 2985, 2980, 1720, 1270, 1110, 1070, 710 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from the C1 anomeric position (α-anomer/β-anomer=91:9). Assignments of the signals for the main isomer and some for the minor isomer are described. ^1H NMR (C_6D_6, *a*=0.9, *b*=0.1) δ 1.28, 1.30 (each 3H×*a*, s, C(C*H*$_3$)$_2$ (α-isomer)), 1.24, 1.25 (each 3H×*b*, s, C(C*H*$_3$)$_2$ (β-isomer)), 3.66 (1H×*a*, ddd, *J*=3.9, 7.8, 11.2 Hz, C5*H* (α-isomer)), 3.82 (1H×*a*, dd, *J*=8.8, 10.8 Hz, C4*H* (α-isomer)), 4.08 (1H×*b*, t, *J*=8.0 Hz, C4*H* (β-isomer)), 4.38 (1H×*a*, dd, *J*=7.3, 11.7 Hz, C6*H*H (α-isomer)), 4.40 (1H×*a*, dd, *J*=8.8, 10.8 Hz, C3*H* (α-isomer)), 4.78 (1H×*a*, dd, *J*=3.9, 11.7 Hz, C6*H*H (α-isomer)), 5.11 (1H×*a*, br, C1*H* (α-isomer)), 5.54 (1H×*a*, dd, *J*=2.9, 10.7 Hz, C2*H* (α-isomer)), 5.65 (1H×*b*, dd, *J*=8.0, 10.3 Hz, C2*H* (β-isomer)), 6.96–7.15 (6H, aromatic protons), 8.16–8.20 (4H, aromatic protons), ^{13}C NMR (C_6D_6, signals for only major isomer are described.) δ 26.7, 27.0 (C(*C*H$_3$)$_2$), 42.2 (*C*5), 63.6 (*C*6), 74.1 (*C*1), 75.8 (*C*3), 76.5 (*C*2), 79.2 (*C*4), 109.9 (*C*(CH$_3$)$_2$), 128.46, 128.54, 130.1, 130.2, 130.3, 130.4, 133.1, 133.2 (aromatic carbons), 165.91, 169.94 (Ph*C*O×2), EI-MS (rel. int., %) *m*/*z*=445 (0.8, MH^+), 429 (1.8, $[M-CH_3]^+$), 369 (1.2, $[M-acetone-OH]^+$), 322 (4.5, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), FD-MS *m*/*z*=445 (76, MH^+), 429 (100, $[M-CH_3]^+$), EI-HRMS; found: *m*/*z* 429.1012. Calcd for $C_{22}H_{21}O_7S$: $[M-CH_3]^+$, 429.1008.

4.8. Reaction of *ax*-10 in CH_2Cl_2 (run 4)

Treatment of *ax*-**10** (45.0 mg, 101 μmol) in a similar manner as described in Section 4.7.1 gave **20** (22.3 mg, 55%) and trace amount of **21**, **22**, and **23** after column chromatography. The ^1H NMR spectrum of **20** was identical with that prepared from *eq*-**10**.

4.9. Reaction of *eq*-10 in pyridine (run 5)

Treatment of *eq*-**10** (40.5 mg, 91.2 μmol) with TFAA (30 μL, 212 μmol) in pyridine (1.5 mL) in a similar manner as described in Section 4.7.1 gave **20** (26.5 mg, 66%) after column chromatography. The ^1H NMR spectrum of **20** was identical with that reported in Section 4.7.4.

4.10. Reaction of *ax*-10 in pyridine (run 6)

Treatment of *ax*-**10** (60.1 mg, 135 μmol) in a similar manner as described in Section 4.7.1 gave **20** (39.7 mg, 65%) after column chromatography. The ^1H NMR spectrum of **20** was identical with that reported in Section 4.7.5.

4.11. Reaction of *eq*-11 (run 7)

Treatment of *eq*-**11** (74 mg, 121 μmol) in a similar manner as described in Section 4.7.1 gave **24** (4.2 mg, 5.7%), **25** (4.8 mg, 4.0%), **26** (37.0 mg, 50%), **27** (5.6 mg, 8.9%), and **28** (11.5 mg, 8.9%) after column chromatography. The structure of **27** was estimated from the results that treatment of **27** with Et_3N in MeOH at room temperature produced **26**.

4.11.1. Physical data for α-24. $[\alpha]_D^{22}=+90.3$ (*c* 0.56, $CHCl_3$), IR (film) 3450, 1730, 1270, 1105, 710 cm^{-1}, ^1H NMR ($CDCl_3$), δ 2.51 (1H, d, *J*=2.0 Hz, O*H*), 4.00 (1H, ddd, *J*=3.9, 4.8, 10.7 Hz, C5*H*), 4.42 (1H, dd, *J*=4.8, 11.7 Hz, C6*H*H), 4.50 (1H, dd, *J*=3.9, 11.7 Hz, C6*H*H), 5.35 (1H, dd, *J*=2.0, 2.9 Hz, C1*H*), 5.49 (1H, dd, *J*=2.9, 10.3 Hz, C2*H*), 5.82 (1H, t, *J*=10.7 Hz, C4*H*), 6.13 (1H, dd, *J*=10.3, 10.7 Hz, C3*H*), 7.08–7.45 (12H, aromatic protons), 7.66–7.92 (8H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 39.5 (*C*5), 62.2 (*C*6), 70.8 (*C*3), 71.9 (*C*1), 73.1(*C*4), 75.9 (*C*2), 128.18, 128.23, 128.3, 128.40, 128.42, 128.9, 129.0, 129.4, 129.5, 129.8, 129.81, 129.84, 133.0, 133.2, 133.3, 133.4 (aromatic carbons), 165.4, 165.7, 165.8, 166.0 (Ph*C*O×4), FD-MS (rel. int., %) *m*/*z*=612 (19, M^+), 611

(34, $[M-H]^+$), 491 (36, $[MH-PhCOOH]^+$), 122 (99, $PhCOOH^+$), 105 (100, $PhCO^+$), FD-HRMS; found: *m*/*z* 612.1470. Calcd for $C_{34}H_{28}O_9S$: M^+, 612.1454.

4.11.2. Physical data for β-24. $[\alpha]_D^{22}$=+36.4 (*c* 0.44, $CHCl_3$), IR (film) 3440, 1730, 1270, 1105, 710 cm^{-1}, ^1H NMR ($CDCl_3$), δ 3.20 (1H, d, *J*=8.3 Hz, O*H*), 3.67 (1H, ddd, *J*=4.4, 5.9, 10.7 Hz, C5*H*), 4.49 (1H, dd, *J*=5.9, 11.7 Hz, C6*H*H), 4.63 (1H, dd, *J*=4.4, 11.7 Hz, C6*H*H), 5.18 (1H, t, *J*=8.3 Hz, C1*H*), 5.64 (1H, t, *J*=8.3 Hz, C2*H*), 5.77 (1H, dd, *J*=8.3, 10.7 Hz, C3*H*), 5.87 (1H, t, *J*=10.7 Hz, C4*H*), 7.15–7.55 (12H, aromatic protons), 7.75–8.05 (8H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 41.9 (*C*5), 62.5 (*C*6), 72.62 (*C*3), 72.67 (*C*4), 74.9 (*C*1), 77.5 (*C*2), 128.2, 128.35, 128.41, 128.43, 128.65, 128.69, 128.7, 129.3, 129.6, 129.75, 129.81, 129.9, 133.24, 133.24, 133.4, 133.7 (aromatic carbons), 165.3, 165.7, 166.0, 167.3 (PhCO×4), FD-MS (rel. int., %) *m*/*z*=612 (20, M^+), 611 (31, $[M-H]^+$), 491 (25, $[MH-PhCOOH]^+$), 122 (56, $PhCOOH^+$), 105 (100, $PhCO^+$), FD-HRMS; found: *m*/*z* 612.1429. Calcd for $C_{34}H_{28}O_9S$: M^+, 612.1454.

4.11.3. Physical data for 25. $[\alpha]_D^{22}$=−66.3 (*c* 0.41, $CHCl_3$), IR (film) 1730, 1260, 1095, 710 cm^{-1}, ^1H NMR ($CDCl_3$), δ 2.98 (1H, dd, *J*=9.8, 12.7 Hz, C1*H*H), 3.14 (1H, dd, *J*=4.4, 12.7 Hz, C1*H*H), 5.50 (1H, ddd, *J*=4.4, 7.8, 9.8 Hz, C2*H*), 5.63 (1H, t, *J*=7.8 Hz, C3*H*), 6.03 (1H, dd, *J*=1.5, 7.8 Hz, C4*H*), 7.20–7.53 (12H, aromatic protons), 7.76 (1H, d, *J*=1.5 Hz, C6*H*), 7.77–8.04 (8H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 29.9 (*C*1), 71.6 (*C*4), 72.2 (*C*2), 73.7 (*C*3), 112.9 (*C*5), 128.33, 128.35, 128.4, 128.5, 128.7, 128.8, 129.0, 129.2, 129.7, 129.8, 129.9, 130.3, 133.3, 133.4, 133.5, 134.0 (aromatic carbons), 135.9 (*C*6), 162.6, 165.0, 165.47, 165.49 (Ph*C*O×4), FD-MS (rel. int., %) *m*/*z*=594 (100, M^+), 105 (36, $PhCO^+$), FD-HRMS; found: *m*/*z* 594.1381. Calcd for $C_{34}H_{26}O_8S$: M^+, 594.1348.

4.11.4. Physical data for 26. $[\alpha]_D^{23}$=−19.6 (*c* 6.08, $CHCl_3$), IR (film), 1730, 1270, 1110, 710 cm^{-1}, ^1H NMR ($CDCl_3$), 2.98 (1H, dd, *J*=4.4, 13.2 Hz, C1*H*H), 3.24 (1H, dd, *J*=11.2, 13.2 Hz, C1*H*H), 3.91 (1H, s, O*H*), 4.46, 4.56 (each 1H, d, *J*=11.7 Hz, C6*H*H), 5.45 (1H, ddd, *J*=4.4, 9.7, 11.2 Hz, C2*H*), 5.86 (1H, d, *J*=9.7 Hz, C4*H*), 6.15 (1H, t, *J*=9.7 Hz, C3*H*), 7.08–7.45 (12H, aromatic protons), 7.65–7.90 (8H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 26.3 (*C*1), 68.3 (*C*6), 71.6 (*C*3), 73.9 (*C*2), 75.4 (*C*4), 82.7 (*C*5), 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.2, 129.5, 129.8, 129.86, 129.93, 133.0, 133.3, 133.4, 133.6 (aromatic carbons), 165.6, 165.7, 165.8, 166.9 (Ph*C*O×4), EI-MS (rel. int., %) *m*/*z*=594 (0.1, M^+), 472 (0.3, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 594.1322. Calcd for $C_{34}H_{26}O_8S$: M^+, 594.1348.

4.11.5. Physical data for 28. $[\alpha]_D^{23}$=+153.1 (*c* 1.96, $CHCl_3$), IR (film), 1725, 1260, 1095, 705 cm^{-1}, ^1H NMR (C_6D_6), 2.94 (1H, dd, *J*=5.4, 13.7 Hz, C1*H*H), 2.99 (1H, dd, *J*=3.0, 13.7 Hz, C1*H*H), 5.03, 5.08 (each 1H, d, *J*=13.1 Hz, C6*H*H), 5.58 (1H, ddd, *J*=3.0, 4.4, 5.4 Hz, C2*H*), 6.43 (1H, d, *J*=4.4 Hz, C3*H*), 6.85–7.10 (12H, aromatic protons), 7.94–8.28 (8H, aromatic protons), ^{13}C NMR (C_6D_6, Signals for C4 and C5 could not be detected probably due to those relaxation time) δ 27.0 (*C*1), 61.0 (*C*6), 68.1 (*C*3), 68.6 (*C*2), 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.2, 129.5, 129.8, 129.9, 129.93, 132.96, 133.3, 133.4, 133.6 (aromatic carbons), 165.61, 165.65, 165.8, 166.9 (Ph*C*O×4), FD-MS (rel. int., %) *m*/*z*=612 (100, M^+), 595 (19, $[M-OH]^+$), FD-HRMS; found: *m*/*z* 612.1478. Calcd for $C_{34}H_{28}O_9S$: M^+, 612.1454.

4.11.6. Reaction of *ax*-11 (run 8). Treatment of *eq*-**11** (106 mg, 173 μmol) in a similar manner as described in Section 4.7.1 gave **24** (2.8 mg, 2.7%), **25** (0.3 mg, 0.3%), **26** (43.5 mg, 41%), **27** (5.6 mg, 5.6%), and **28** (9.1 mg, 8.1%) after column chromatography.

4.11.7. Reaction of *eq*-12 (run 9). Treatment of *eq*-**12** (52.2 mg, 136 μmol) in a similar manner as described in Section 4.7.1 gave **30** (6.9 mg, 14%), **31** (20.9 mg, 40%) and **32** (1.1 mg, 1.7%), after column chromatography. The structure of **32** was estimated by production of **30** and **31** by treating **32** with Et_3N in MeOH at room temperature.

4.11.8. Physical data for 30. $[\alpha]_D^{22}$=−159.2 (*c* 0.68, $CHCl_3$), IR (film) 3450, 2985, 2935, 1740, 1225, 1135, 1080, 1045, 705 cm^{-1}, ^1H NMR (C_6D_6) δ 1.27, 1.29 (each 3H, s, C(C*H*$_3$)$_2$), 1.64 (3H, s, C*H*$_3$CO), 2.45 (2H, C1*H*$_2$), 3.40 (1H, dd, *J*=8.8, 10.2 Hz, C3*H*), 3.78 (1H, dt, *J*=5.8, 8.8 Hz, C2*H*), 6.05 (1H, dd, *J*=2.0, 10.2 Hz, C4*H*), 6.99–8.19 (5H, aromatic protons), 7.93 (1H, d, *J*=2.0 Hz, C6*H*), ^{13}C NMR (C_6D_6) δ 20.1 (*C*H$_3$CO), 26.8, 26.9 (C(*C*H$_3$)$_2$), 31.7 (*C*1), 72.8 (*C*4), 76.6 (*C*2), 81.1 (*C*3), 109.9 (*C*(CH$_3$)$_2$), 114.8 (*C*5), 128.7, 130.5, 133.8, 134.9 (aromatic carbons), 162.7, 169.0 (CH$_3$*C*O and Ph*C*O), EI-MS (rel. int., %) *m*/*z*=364 (0.5, M^+), 349 (0.5, $[M-CH_3]^+$), 289 (1.3, $[M-acetone-OH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 364.0972. Calcd for $C_{18}H_{20}O_6S$: M^+, 364.0981.

4.11.9. Physical data for 31. Mp=145–146 °C (needles, from hexane/EtOAc (50:50)), $[\alpha]_D^{23}$=−17.7 (*c* 0.73, $CHCl_3$), IR (KBr) 3430, 1640, 1295, 1225, 715 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.41, 1.43 (each 3H, s, C(C*H*$_3$)$_2$), 2.14 (3H, s, C*H*$_3$CO), 2.82 (1H, dd, *J*=3.4, 11.7 Hz, C1*H*H), 3.04 (1H, dd, *J*=10.7, 11.7 Hz, C1*H*H), 3.34 (1H, s, O*H*), 3.91 (1H, dt, *J*=3,4, 10.7 Hz, C2*H*), 3.98 (1H, t, *J*=10.7 Hz, C3*H*), 4.36, 4.52 (each 1H, d, *J*=11.7 Hz, C6*H*H), 5.43 (1H, d, *J*=10.7 Hz, C4*H*), 7.44–8.04 (5H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 20.9, (*C*H$_3$CO), 26.6, 27.0 (C(*C*H$_3$)$_2$), 28.1 (*C*1), 67.9 (*C*6), 74.5 (*C*4), 76.9 (*C*3), 77.7 (*C*2), 84.2 (*C*5), 110.2 (*C*(CH$_3$)$_2$), 128.6, 129.0, 130.0, 133.6 (aromatic carbons), 166.6, 170.0 (CH$_3$*C*O and Ph*C*O), EI-MS (rel. int., %) *m*/*z*=367 (0.8, $[M-CH_3]^+$), 307 (1.6, $[M-acetone-OH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 367.0831. Calcd for $C_{17}H_{19}O_7S$: $[M-CH_3]^+$, 367.0852.

4.12. Acetylation of 15 giving 1-acetoxy-6-*O*-benzoyl-1,5-dideoxy-3,4-*O*-isopropylidene-2-*O*-methoxymetyl-5-thio-α-D-glucopyranose (α-16) and its β-isomer (β-16)

A mixture of the Pummerer product obtained in Section 4.7.2 and Ac_2O (0.2 mL, excess) was stirred in pyridine (1.0 mL) at room temperature for 30 min. After concentration in vacuo, silica gel column chromatography (benzene/EtOAc=90:10) gave a diastereomeric mixture of

16 (11 mg, 66%). Analytical sample was further purified by preparative silica gel column chromatography (benzene/EtOAc=80:20).

4.12.1. Physical data for α-16. $[\alpha]_D^{23}$=+91.5 (*c* 0.94, $CHCl_3$), IR (film) 2985, 2895, 1750, 1725, 1270, 1215, 1110, 1045, 1020, 710 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.28, 1.29 (each 3H, s, C(C*H*$_3$)$_2$), 1.64 (3H, s, C*H*$_3$CO), 3.20 (3H, s, C*H*$_3$O), 3.63 (2H, C4*H*, C5*H*), 4.01 (1H, dd, *J*=7.8, 10.2 Hz, C3*H*), 4.10 (1H, dd, *J*=3.4, 10.2 Hz, C2*H*), 4.32 (1H, dd, *J*=7.3, 11.7 Hz, C6*H*H), 4.56, 4.71 (each 1H, d, *J*=6.8 Hz, OC*H*HO), 4.80 (1H, dd, *J*=3.4, 11.7 Hz, C6*H*H), 6.40 (1H, d, *J*=3.4 Hz, C1*H*), 6.97–7.08 (3H, aromatic protons), 8.12 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 20.5 (*C*H$_3$CO), 26.7, 27.0 (C(*C*H$_3$)$_2$), 43.1 (*C*5), 55.4 (*C*H$_3$O), 63.9 (*C*6), 73.5 (*C*1), 77.5 (*C*2), 78.0 (*C*3), 78.6 (*C*4), 95.8 (O*C*H$_2$O), 109.6 (*C*(CH$_3$)$_2$), 128.5, 130.0, 130.3, 133.1 (aromatic carbons), 165.8, 168.8 (CH$_3$*C*O and Ph*C*O), EI-MS (rel. int., %) *m/z*=411 (10, $[M-CH_3]^+$), 304 (18, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), FD-MS (rel. int., %) *m/z*=426 (16, M^+), 411 (100, $[M-CH_3]^+$), EI-HRMS; found *m/z* 411.1121. Calcd for $C_{19}H_{23}O_8S$: $[M-CH_3]^+$, 411.1114.

4.12.2. Physical data for β-16. $[\alpha]_D^{23}$=−43.4 (*c* 1.45, $CHCl_3$), IR (film) 2930, 2895, 1755, 1725, 1270, 1215, 1105, 1030, 710 cm^{-1}, ^{1}H NMR (C_6D_6) δ 1.25, 1.27 (each 3H, s, C(C*H*$_3$)$_2$), 1.52 (3H, s, C*H*$_3$CO), 3.15 (1H, ddd, *J*=5.8, 7.3, 9.2 Hz, C5*H*), 3.21 (3H, s, C*H*$_3$O), 3.59 (1H, t, *J*=9.2 Hz, C3*H*), 3.88 (1H, t, *J*=9.2 Hz, C4*H*), 4.23 (1H, dd, *J*=4.8, 9.2 Hz, C2*H*), 4.30 (1H, dd, *J*=7.8, 11.2 Hz, C6*H*H), 4.66 (1H, d, *J*=6.9 Hz, OC*H*HO), 4.69 (1H, dd, *J*=5.4, 11.2 Hz, C6*H*H), 4.82 (1H, d, *J*=6.9 Hz, OC*H*HO), 6.91 (1H, d, *J*=4.8 Hz, C1*H*), 7.01–7.10 (3H, aromatic protons), 8.16 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 20.2 (*C*H$_3$CO), 26.9, 27.1 (C(*C*H$_3$)$_2$), 43.9 (C5), 55.4(*C*H$_3$O), 65.4 (*C*6), 76.1 (*C*4), 76.3 (*C*1), 79.5(*C*2), 81.7(*C*3), 95.9 (O*C*H$_2$O), 110.9(*C*(CH$_3$)$_2$), 128.5, 130.0, 130.5, 133.0 (aromatic carbons), 165.9, 168.2 (CH$_3$*C*O and Ph*C*O), EI-MS (rel. int., %) *m/z*=411 (7.0, $[M-CH_3]^+$), 364 (6.3, $[M-MOMOH]^+$), 304 (39, $[M-PhCOOH]^+$), 105 (100, $PhCO^+$), FD-MS (rel. int., %) *m/z*=426 (29, M^+), 411 (100, $[M-CH_3]^+$), EI-HRMS; found: *m/z* 411.1137. Calcd for $C_{19}H_{23}O_8S$: $[M-CH_3]^+$, 411.1114.

4.13. 1,2,3,4,6-*O*-Pentabenzoyl-5-deoxy-5-thio-D-glucopyranose (17)

4.13.1. Preparation from 16. A solution of **16** (22.0 mg, 51.5 μmol) in 50% aqueous TFA was stirred at room temperature for 3 h. After concentration in vacuo, the residue was stirred with BzCl (59.9 μL, 258 μmol) in pyridine (300 μL) at room temperature for 15 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were washed with 2 M aqueous HCl and brine successively, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=85:15) gave **17** (25.0 mg, 63% two steps) as an anomeric mixture (α/β=80:20). $[\alpha]_D^{19}$=+161 (*c* 3.40, $CHCl_3$), IR (film) 1730, 1265, 1105, 1070, 705 cm^{-1}, The ^{1}H NMR spectrum of this sample showed that it consists of the two isomers arising from the C1 anomeric position (α/β=80:20). Assignments of the signals for the main isomer and some for the minor isomer are described. ^{1}H NMR ($CDCl_3$, *a*=0.8, *b*=0.2) δ 3.76 (1H×*b*, dt, *J*=9.3, 5.4 Hz, C5*H* (minor)), 3.96 (1H×*a*, dt, *J*=3.9, 10.3 Hz, C5*H* (major)), 4.45, 4.50 (each 1H×*a*, dd, *J*=3.9, 12.2 Hz, C6*H*H (major)), 4.63 (1H×*b*, dd, *J*=4.9, 11.7 Hz, C6*H*H (minor)), 5.75 (1H×*a*, dd, *J*=3.0, 10.3 Hz, C2*H* (major)), 5.95 (1H×*a*, t, *J*=10.3 Hz, C4*H* (major)), 6.19 (1H×*a*, t, *J*=10.3 Hz, C3*H* (major)), 6.36 (1H×*b*, d, *J*=7.8 Hz, C1*H* (minor)), 6.54 (1H×*a*, d, *J*=3.0 Hz, C1*H* (major)), 7.08–7.56 (15H, aromatic protons), 7.67–8.06 (10H, aromatic protons), EI-MS (rel. int. %) *m/z*=595 (0.1, $[M-PhCOO]^+$), 472 (1.9, $[M-2\times PhCOOH]^+$), 350 (21, $[M-3\times PhCOOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; Found *m/z* 595.1426. Calcd for $C_{34}H_{27}O_8S$: $[M-PhCOO]^+$, 595.1427.

4.13.2. Preparation from 18. A mixture of 1,2,3,4,6-*O*-pentaacetyl-5-deoxy-5-thio-D-glucopyranose **18** (72.0 mg, 177 μmol), prepared according to Driguez et al.,[30] and NaOMe (57.4 mg, 1.06 mmol) in MeOH (1.0 mL) was stirred at room temperature for 12 h. After concentration in vacuo, the residue was diluted with H_2O (2.0 mL), then was passed through ion exchange resin (DOWEX 50W-X4, H^+ form). The eluate was concentrated in vacuo. The residue was stirred with BzCl (0.2 mL, 1.72 mmol) in pyridine (0.5 mL) at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with 2 M aqueous HCl and brine successively, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=85:15) gave **17** (85.0 mg, 67% in two steps) as an anomeric mixture (α/β=90:10). The ^{1}H NMR spectrum of this sample was identical except for the isomeric ratio with that of described in Section 4.13.1.

4.14. 6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-2,5-*O*-bis(methanesulfonyl)-D-mannose (34)

4.14.1. Protection of terminal alcohols as the bis-TBDMS ether. A mixture of 3,4-*O*-isopropylidene-D-mannitol (**33**) (102.6 mg, 462 μmol), TBDMSCl (139.2 mg, 923 μmol), and Et_3N (0.19 mL, 1.39 mmol) in DMF (3 mL) was stirred at room temperature for 30 min. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous NH_4Cl and brine successively, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=92:8) gave the corresponding 1,6-bisTBDMS ether (208 mg, 100%) as an oil. $[\alpha]_D^{23}$=+15.3 (*c* 1.14, $CHCl_3$), IR (film) 3400, 2925, 2855, 1465, 1375, 1255, 1215, 1070 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 0.04 (12H, s, Si(C*H*$_3$)$_2$×2), 0.85 (18H, s, SiC(C*H*$_3$)$_3$×2), 1.30 (6H, s, C(C*H*$_3$)$_2$), 3.37 (2H, br, O*H*×2), 3.58 (2H, C2*H*, C5*H*), 3.65 (2H, dd, *J*=5.8, 10.2 Hz, C1H*H*, C6H*H*), 3.83 (4H, C1H*H*, C3*H*, C4*H*, C6H*H*), ^{13}C NMR ($CDCl_3$) δ −5.4 (Si(*C*H$_3$)$_2$×2), 18.3 (Si*C*(CH$_3$)$_3$×2), 25.8 (SiC(*C*H$_3$)$_3$×2), 26.9 (C(*C*H$_3$)$_2$), 64.4 (*C*1, *C*6) 73.0 (*C*2, *C*5), 79.3 (*C*3, *C*4), 109.1 (*C*(CH$_3$)$_2$), EI-MS (rel. int., %) *m/z*=451 (0.8, $[M+H]^+$), 449 (0.1, $[M-H]^+$), 435 (7.0, $[M-CH_3]^+$), 393 (9.7, $[M-{}^tBu]^+$), 335 (19, $[M-{}^tBu-acetone]^+$), 117 (100), EI-HRMS; found: *m/z* 435.2627. Calcd for $C_{20}H_{43}O_6Si_2$: $[M-CH_3]^+$, 435.2598.

4.14.2. Mesylation of the 2,5-hydroxy groups. A mixture of the product (1.76 g, 3.90 mmol), MsCl (604 μL, 7.81 mmol), and Et_3N (1.63 mL, 11.7 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 30 min. The mixture was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=95:5) gave the corresponding 2,5-bismesylate ether (2.35 mg, 99%) as an oil. $[\alpha]_D^{17}$=+17.3 (*c* 1.58, $CHCl_3$), IR (film) 2925, 2850, 1700, 1105, 1025 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.00 (12H, s, Si(C*H*$_3$)$_2$×2), 0.81 (18H, s, SiC(C*H*$_3$)$_3$×2), 1.32 (6H, s, C(C*H*$_3$)$_2$), 3.01 (6H, s, SO$_2$C*H*$_3$×2), 3.75 (2H, dd, *J*=6.3, 11.7 Hz, C1H*H*, C6H*H*), 3.92 (2H, dd, *J*=3.4, 11.7 Hz, C1H*H*, C6H*H*), 4.26 (2H, C3*H*, C4*H*), 4.62 (2H, C2*H*, C5*H*), ^{13}C NMR ($CDCl_3$) δ −5.6 (Si(*C*H$_3$)$_2$×2), 18.2 (Si*C*(CH$_3$)$_3$×2), 25.7 (SiC(*C*H$_3$)$_3$×2), 26.9 (C(*C*H$_3$)$_2$), 38.6 (SO$_2$*C*H$_3$×2), 62.4 (*C*1, *C*6) 76.1 (*C*2, *C*5), 82.3 (*C*3, *C*4), 110.9 (*C*(CH$_3$)$_2$), EI-MS (rel. int., %) *m*/*z*=591 (20, $[M-CH_3]^+$), 549 (8.2, $[M-{}^tBu]^+$), 153 (100), EI-HRMS; found: *m*/*z* 591.2138. Calcd for $C_{22}H_{47}O_{10}Si_2S_2$: $[M-CH_3]^+$, 591.2149.

4.14.3. Desilylation giving the corresponding monoalcohol. A mixture of the product obtained in Section 4.14.2 (1.84 g, 3.04 mmol), 1 M TBAF in THF (3.0 mL, 3.0 mmol), and AcOH (364 mg, 2.80 mmol) in THF (20 mL) was stirred at 0 °C for 3 h. The mixture was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=75:25) gave the corresponding monoalcohol (1.01 mg, 67%), recovered bis-TBDMS ether (368 mg, 20%), and the diol (115 mg, 10%) as an oil. The ^1H NMR spectra of the recovered bis-TBDMS ether and diol were identical with those of the authentic samples.

4.14.4. Physical data for the mono-TBDMS ether. $[\alpha]_D^{17}$=+22.0 (*c* 0.48, $CHCl_3$), IR (film) 3510, 2935, 2855, 1340, 1175 cm^{-1}, ^1H NMR ($CDCl_3$) δ −0.01, 0.00 (each 3H, s, Si(C*H*$_3$)$_2$), 0.82 (9H, s, SiC(C*H*$_3$)$_3$), 1.31, 1.32 (each 3H, s, C(C*H*$_3$)$_2$), 3.02, 3.04 (each 3H, s, SO$_2$C*H*$_3$), 3.74 (1H, dd, *J*=4.4, 11.7 Hz, C6H*H*), 3.76 (1H, dd, *J*=3.0, 11.7 Hz, C1*H*H), 3.87 (1H, dd, *J*=3.4, 11.7 Hz, C1*H*H), 3.92 (1H, dd, *J*=3.4, 11.7 Hz, C6H*H*), 4.16 (1H, t, *J*=6.8 Hz, C3*H*), 4.31 (1H, t, *J*=6.8 Hz, C4*H*), 4.60 (1H, ddd, *J*=3.0, 3.4, 6.8 Hz, C2*H*), 4.66 (1H, ddd, *J*=3.4, 4.4, 6.8 Hz, C5*H*), ^{13}C NMR ($CDCl_3$) δ −5.2 (Si(*C*H$_3$)$_2$), 18.6 (Si*C*(CH$_3$)$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 27.2, 27.3, (C(*C*H$_3$)$_2$), 38.8, 39.1 (SO$_2$*C*H$_3$×2), 61.9, 62.9 (*C*1, *C*6) 76.4,77.0 (*C*2, *C*5), 82.0, 83.2 (*C*3, *C*4), 111.5 (*C*(CH$_3$)$_2$), EI-MS (rel. int., %) *m*/*z*=477 (14, $[M-CH_3]^+$), 435 (3.1, $[M-{}^tBu]^+$), 153 (100), EI-HRMS; found: *m*/*z* 477.1295. Calcd for $C_{16}H_{33}O_{10}SiS_2$: $[M-CH_3]^+$, 477.1284.

4.14.5. Oxidation giving 34. A mixture of the mono-TBDMS ether obtained in Section 4.14.3 (59.2 mg, 120 μmol) and Dess-Martin reagent (76.4 mg, 180 μmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 3 h. The mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and 10% $Na_2S_2O_3$ (10 mL) and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=85:15) gave **34** (59.1 mg, 100%). ^1H NMR ($CDCl_3$) δ 0.09 (6H, s, Si(C*H*$_3$)$_2$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 1.40, 1.43 (each 3H, s, C(C*H*$_3$)$_2$), 3.13, 3.19 (each 3H, s, SO$_2$C*H*$_3$), 3.83 (1H, dd, *J*=6.8, 12.2 Hz, C6H*H*), 3.97 (1H, dd, *J*=2.9, 12.2 Hz, C6*H*H), 4.30 (1H, t, *J*=7.8 Hz, C4*H*), 4.56 (1H, dd, *J*=2.9, 7.8 Hz, C3*H*), 4.67 (1H, ddd, *J*=2.9, 6.8, 7.8 Hz, C5*H*), 4.98 (1H, d, *J*=2.9 Hz, C2*H*), 9.66 (1H, s, C1*H*). This sample was subjected to the next step without further purification.

4.14.6. (1*R*)-6-*O*-*tert*-Butyldimethylsilyl-1-deuterio-3,4-*O*-isopropylidene-2,5-*O*-bis(methanesulfonyl)-D-mannitol (35). To a mixture of **34** (689 mg, 1.40 mmol) and Ce (III) chloride (1.04 g, 2.81 mmol) in MeOH (10 mL), $NaBD_4$ (117 mg, 2.80 mmol) was added at room temperature. After stirring for 1 h, the mixture was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=80:20) gave **35** (626 mg, 91%) as an oil. $[\alpha]_D^{17}$=+16.6 (*c* 1.60, $CHCl_3$), IR (film) 3510, 2935, 2855, 1340, 1175 cm^{-1}, The ^1H NMR spectrum indicated that the sample consists of 90:10 diastereomeric isomers, ^1H NMR (C_6D_6) δ 0.01, 0.02 (each 3H, s, Si(C*H*$_3$)$_2$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 1.20, 1.22 (each 3H, s, C(C*H*$_3$)$_2$), 2.52, 2.56 (each 3H, s, SO$_2$C*H*$_3$), 3.65 (1H×0.1, br, C1H*H*), 3.79 (1H, dd, *J*=6.4, 11.7 Hz, C6H*H*), 3.82 (1H×0.9, br, C1*H*H), 4.06 (1H, dd, *J*=3.0, 11.7 Hz, C6H*H*), 4.16 (1H, t, *J*=6.8 Hz, C4*H*), 4.31 (1H, t, *J*=6.8 Hz, C3*H*), 4.60 (1H, dd, *J*=3.9, 6.8 Hz, C2*H*), 4.66 (1H, ddd, *J*=3.0, 3.4, 6.8 Hz, C5*H*), ^{13}C NMR (C_6D_6) δ −5.48 (Si(*C*H$_3$)$_2$), 18.5 (Si*C*(CH$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 27.0 (C(*C*H$_3$)$_2$), 38.2, 38.4 (SO$_2$*C*H$_3$×2), 61.7 (C1, observed as triplet due to deuterium), 63.5 (*C*6) 76.5 (C4), 77.2 (*C*3), 82.1 (*C*2), 82.5 (C5), 111.5 (*C*(CH$_3$)$_2$), EI-MS (rel. int., %) *m*/*z*=478 (14, $[M-CH_3]^+$), 436 (2.6, $[M-{}^tBu]^+$), 153 (100), EI-HRMS; found: *m*/*z* 478.1332. Calcd for $C_{16}H_{32}DO_{10}S_2Si$: $[M-CH_3]^+$, 478.1346.

4.15. (6*R*)-6-*O*-Benzoyl-6-deuterio-3,4-*O*-isopropylidene-2,5-*O*-bis(methanesulfonyl)-D-mannose (36)

4.15.1. Benzoylation of 35. A mixture of **35** (615 mg, 1.24 mmol), BzCl (210 μL, 1.86 mmol), and pyridine (200 μL, 2.59 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=85:15) gave the corresponding benzoate (674 mg, 90%) as an oil. $[\alpha]_D^{17}$=+28.8 (*c* 0.67, $CHCl_3$), IR (film) 3445, 2930, 2855, 1730, 1360, 1175 cm^{-1}. The ^1H NMR spectrum indicated that the sample consists of 90:10 diastereomeric isomers, ^1H NMR (C_6D_6) δ 0.03, 0.04 (each 3H, s, Si(C*H*$_3$)$_2$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 1.21 (6H, s, C(C*H*$_3$)$_2$), 2.46, 2.59 (each 3H, s, SO$_2$C*H*$_3$), 3.81 (1H, dd, *J*=5.4, 11.7 Hz, C6H*H*), 4.08 (1H, dd, *J*=2.9, 11.7 Hz, C6*H*H), 4.55 (1H, dd, *J*=6.4, 7.3 Hz, C4*H*), 4.69 (1H, t, *J*=6.4 Hz, C3*H*), 4.83 (2H, C1*H*, C5*H*), 5.16 (1H, dd, *J*=2.4, 6.4 Hz, C2*H*), 7.08 (3H, aromatic protons), 8.25 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ −5.47, −5.43

(Si(CH_3)$_2$), 18.5 (SiC(CH_3)$_3$), 26.0 ((SiC(CH_3)$_3$), 26.95, 27.02 (C(CH_3)$_2$), 38.3, 38.4 (SO_2CH_3×2), 63.1, (*C*6), 63.2 (*C*1, observed as triplet due to deuterium), 76.1 (*C*4) 77.7 (*C*3), 78.5 (*C*2), 81.7 (*C*5), 111.5 (C(CH_3)$_2$), 128.6, 130.17, 130.20, 133.2 (aromatic carbons), 166.2 (Ph*C*O), EI-MS (rel. int., %) *m*/*z*=582 (17, $(M-CH_3)^+$), 540 (24, $[M-{}^tBu]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 582.1606. Calcd for $C_{23}H_{36}DO_{11}S_2Si$: $[M-CH_3]^+$, 582.1608.

4.15.2. Desilylation. A mixture of the benzoate obtained in Section 4.15.1 (670 mg, 1.12 mmol), 1.0 M TBAF in THF (1.68 mL, 1.68 mmol), and AcOH (130 μL, 2.24 mmol) in THF (8.0 mL) was stirred at room temperature for 30 min. The mixture was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=75:25) gave the corresponding alcohol (533 mg, 98%) as an oil. $[\alpha]_D^{17}=+25.8$ (*c* 1.56, $CHCl_3$), IR (film) 3535, 2940, 1725, 1345, 1175, 915 cm^{-1}. The ^1H NMR spectrum indicated that the sample consists of 90:10 diastereomeric isomers, thus, the signals for the major isomer are described. ^1H NMR (C_6D_6) δ 1.14, 1.18 (each 3H, s, C(CH_3)$_2$), 2.40, 2.51 (each 3H, s, SO_2CH_3), 3.67 (1H, dd, *J*=5.4, 12.2 Hz, C1H*H*), 3.85 (1H, dd, *J*=3.4, 12.2 Hz, C1*H*H), 4.38 (1H, dd, *J*=6.4, 6.8 Hz, C3*H*), 4.54 (1H, dd, *J*=5.4, 6.4 Hz, C4*H*), 4.73 (2H, C2*H*, C6*H*), 5.13 (1H, dd, *J*=2.4, 5.4 Hz, C5*H*), 7.06 (3H, aromatic protons), 8.23 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.8, 26.9 (C(CH_3)$_2$), 38.1, 38.4 (SO_2CH_3), 62.1, (*C*1), 63.4 (*C*6, observed as triplet due to deuterium), 76.5 (*C*3) 77.7 (*C*4), 78.6 (*C*5), 81.8 (*C*2), 111.5 (C(CH_3)$_2$), 127.8, 128.7, 130.2 133.3 (aromatic carbons), 166.3 (Ph*C*O), EI-MS (rel. int., %) *m*/*z*=468 (17, $[M-CH_3]^+$), 372 (19, $[M-CH_3-MsOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 468.0704. Calcd for $C_{17}H_{22}DO_{11}S_2$: $[M-CH_3]^+$, 468.0744.

4.15.3. Oxidation giving 36. A mixture of the alcohol obtained in Section 4.15.2 (780 g, 1.61 mmol) and Dess-Martin reagent (684 mg, 1.61 mmol) in CH_2Cl_2 (7.0 mL) was stirred at room temperature for 2 h. The mixture was poured into a mixture of saturated aqueous $NaHCO_3$ (50 mL) and 10% $Na_2S_2O_3$ (10 mL) and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, then concentrated in vacuo to give the crude aldehyde **36** (803 mg), ^1H NMR ($CDCl_3$) δ 1.32, 1.35 (each 3H, s, C(CH_3)$_2$), 2.90, 3.10 (each 3H, s, OSO_2CH_3), 4.37 (2H, C3*H*, C4*H*), 4.48 (1H, dd, *J*=3.4, 7.3 Hz, C2*H*), 4.70 (1H, d, *J*=2.4 Hz, C6*H*), 4.91 (1H, dd, *J*=2.4, 6.8 Hz, C5*H*), 7.36 (2H, aromatic protons), 7.48 (1H, m, aromatic proton), 7.95 (2H, aromatic protons), 9.68 (1H, s, C1*H*), This sample was subjected to the next step without purification.

4.15.4. (1*R*,6*R*)-6-*O*-Benzoyl-1,6-dideuterio-3,4-*O*-isopropylidene-2,5-*O*-bis(methanesulfonyl)-D-mannitol (37). To a mixture of the crude aldehyde **36** (803 mg) and Ce (III) chloride (1.36 g, 3.65 mmol) in MeOH (10 mL), $NaBD_4$ (153 mg, 3.66 mmol) was added at room temperature. After stirring for 1 h, the mixture was poured into H_2O, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=70:30) gave **37** (660 mg, 85% in two steps) as an oil. $[\alpha]_D^{17}=+38.0$ (*c* 0.50, $CHCl_3$), IR (film) 3540, 2940, 1725, 1355, 1175, 915 cm^{-1}. The ^1H NMR spectrum indicated that the sample consists of 90:10 diastereomeric isomers, thus, the signals for the major product are reported. ^1H NMR (C_6D_6) δ 1.16, 1.19 (each 3H, s, C(CH_3)$_2$), 2.45, 2.56 (each 3H, s, OSO_2CH_3), 3.86 (1H, br, C1*H*), 4.41 (1H, dd, *J*=6.4, 6.8 Hz, C3*H*), 4.55 (1H. dd, *J*=5.4, 6.4 Hz, C4*H*), 4.76 (2H, C2*H*, C6*H*), 5.15 (1H, dd, *J*=2.4, 5.4 Hz, C5*H*), 7.08 (3H, aromatic protons), 8.23 (2H, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.8, 26.9 (C(CH_3)$_2$), 38.1, 38.4 (OSO_2CH_3), 62.0, 63.4 (*C*1, *C*6 each signals were observed as triplet because of deuterium attached.), 76.5 (*C*3), 77.7 (*C*4), 78.6 (*C*5), 81.7 (*C*2), 111.5 (C(CH_3)$_2$), 130.1, 130.2, 133.3 (aromatic carbons), 166.3 (Ph*C*O), EI-MS (rel. int., %) *m*/*z*=469 (12, $[M-CH_3]^+$), 372 (19, $[M-CH_3-MsOH]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 469.0849. Calcd for $C_{17}H_{21}D_2O_{11}S_2$: $[M-CH_3]^+$, 469.0805.

4.15.5. (1*R*,2*S*,3*R*,4*R*,5*S*,6*R*)-1,6-Dideuterio-1,2-5,6-bis-epoxy-3,4-*O*-isopropylidene-3,4-hexandiol (38). A mixture of **37** (146 mg, 302 μmol) and K_2CO_3 (208 mg, 1.51 mmol) in a mixture of MeOH (2.0 mL) and CH_2Cl_2 (2.0 mL) was stirred at 0 °C. The mixture was allowed to warm to room temperature. After 4 h, ether (20 mL) was added and the mixture was stirred for 30 min at room temperature. After filtration under suction, the mixture was poured into H_2O, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=70: 30) gave **38** (37.8 mg, 67%) as an oil. $[\alpha]_D^{17}=-15.4$ (*c* 0.50, $CHCl_3$), IR (film) 1990, 1245, 1215, 1050, 860 cm^{-1}. The ^1H NMR spectrum indicated that the sample consists of 90:10 diastereomeric isomers, thus, the signals for the major product are reported. ^1H NMR (C_6D_6) δ 1.33, (6H, s, C(CH_3)$_2$), 2.30 (2H, d, *J*=2.9 Hz, C1*H*, C6*H*), 2.54 (2H, dd, *J*=2.9, 3.4 Hz, C2*H*, C5*H*), 3.62 (2H, dd, *J*=2.0, 3.4 Hz, C3*H*, C4*H*), ^{13}C NMR (C_6D_6) δ 26.8 (C(CH_3)$_2$), 42.7 (*C*1 and *C*6, the signal was observed as triplet because of deuterium attached.), 50.8 (*C*2, *C*5) 78.3 (*C*3, *C*4), EI-MS (rel. int., %) *m*/*z*=173 (56, $[M-CH_3]^+$), 43 (100), EI-HRMS; found: *m*/*z* 173.0799. Calcd for $C_8H_9D_2O_4$: $[M-CH_3]^+$, 173.0781.

4.16. (1*R*,6*R*)-6-*O*-Benzoyl-1,5-dideoxy-1,6-dideuterio-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (39)

4.16.1. Thiepane formation from 38. According to the established procedure by Merrer et al., a mixture of **38** (120 mg, 638 μmol) and $Na_2S{\cdot}9H_2O$ (199 mg, 829 mmol) in DMF (5.0 mL) was stirred at room temperature for 11 h. After concentration in vacuo at 50 °C, the residue was purified by silica gel column chromatography (benzene/EtOAc=60:40) to afford the corresponding thiepane (110 mg, 77%) as an oil. $[\alpha]_D^{17}=+80.1$ (*c* 0.90, MeOH), IR (film) 3480, 1240, 1220 cm^{-1}, ^1H NMR (CD_3OD) δ 1.39 (6H, s, C(CH_3)$_2$), 2.62 (2H, d, *J*=5.9 Hz, C2*H*, C7*H*), 3.83 (2H, dt, *J*=2.4, 5.9 Hz, C3*H*, C6*H*), 3.94 (2H, C4*H*, C5*H*), EI-MS (rel. int., %) *m*/*z*=207 (37, $[M-CH_3]^+$), 204 (91, $[M-H_2O]^+$), 156 (100), EI-HRMS; found: *m*/*z* 207.0674. Calcd for $C_8H_{11}D_2O_4S$: $[M-CH_3]^+$, 207.0658.

4.16.2. Ring contraction by Mitsunobu reaction giving 39. To a mixture of the product obtained in Section 4.16.1 (135 mg, 608 μmol), benzoic acid (96.5 mg, 790 μmol), and PPh_3 (207 mg, 790 μmol) in THF (5.0 mL), diethyl azodicarboxylate (40% toluene solution, 310 μL, 790 μmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (hexane/EtOAc=75:25) gave **39** (187 mg, 94%) as an oil, $[\alpha]_D^{23}$=+80.1 (*c* 1.42 $CHCl_3$), IR (film) 3450, 2985, 1720, 1270, 1230, 1065, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.31, 1.32 (each 3H, s, C(C*H*$_3$)$_2$), 2.57 (1H, d, *J*=10.3 Hz, C1*H*), 3.17 (1H, t, *J*=8.8 Hz, C3*H*), 3.30 (1H, dd, *J*=4.0, 10.3 Hz, C5*H*), 3.55 (1H, dd, *J*=8.8, 10.3 Hz, C4*H*), 3.92 (1H, dd, *J*=8.8, 10.3 Hz, C2*H*), 4.63 (1 h, d, *J*=4.0 Hz, C6*H*), 7.32 (2H, aromatic protons), 7.45 (1H, m, aromatic proton), 7.94 (2H, aromatic protons), EI-MS (rel. int., %) *m*/*z*=311 (4.0, $[M-CH_3]^+$), 250 (6.0, $[M-H_2O-\text{acetone}]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 311.0951. Calcd for $C_{15}H_{15}D_2O_5S$: $[M-CH_3]^+$, 311.0920.

4.16.3. (1*R*,6*R*)-2,6-*O*-Dibenzoyl-1,5-dideoxy-1,6-dideuterio-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (*R*)-*S*-oxide (*eq*-41) and its (*S*)-isomer (*ax*-41). Benzoylation of **39** (180 mg, 552 μmol) in a similar manner as described in Section 4.22 gave the corresponding benzoate (170 mg, 72%) as an oil after silica gel column chromatography. $[\alpha]_D^{19}$=+86.3 (*c* 1.05 $CHCl_3$), IR (film) 1720, 1270, 1110, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.24, 1.29 (each 3H, s, C(C*H*$_3$)$_2$), 2.35 (1H, d, *J*=9.8 Hz, C1*H*), 3.13 (1H, dd, *J*=3.9, 10.3 Hz, C5*H*), 3.38 (1H, dd, *J*=8.8, 10.3 Hz, C3*H*), 3.70 (1H, dd, *J*=8.8, 10.3 Hz, C4*H*), 4.82 (1H, d, *J*=3.9 Hz, C6*H*), 5.47 (1H, dd, *J*=9.8, 10.3 Hz, C2*H*), 6.97–7.10 (6H, aromatic protons), 8.08–8.19 (4H, aromatic protons), EI-MS (rel. int., %) *m*/*z*=415 (5.0, $[M-CH_3]^+$), 250 (8.5, $[M-PhCOOH-\text{acetone}]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 415.1145. Calcd for $C_{22}H_{19}D_2O_6S$: $[M-CH_3]^+$, 415.1182.

Oxidation of the product (170 mg, 395 μmol) in the same manner as described in Section 4.3.1 gave *eq*-**41** (75.3 mg, 43%) and *ax*-**41** (54.5 mg, 31%) both as oils after silica gel column chromatography.

4.16.4. Physical data for *eq*-41. $[\alpha]_D^{19}$=+37.8 (*c* 0.65 $CHCl_3$), IR (film) 1725, 1270, 1110, 1040, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.16, 1.24 (each 3H, s, C(C*H*$_3$)$_2$), 2.77 (1H, d, *J*=9.3 Hz, C1*H*), 2.96 (1H, dd, *J*=3.4, 11.2 Hz, C5*H*), 3.34 (1H, dd, *J*=9.3, 11.2 Hz, C4*H*), 4.07 (1H, t, *J*=9.3 Hz, C3*H*), 4.86 (1H, d, *J*=3.4 Hz, C6*H*), 5.37 (1H, t, *J*=9.3 Hz, C2*H*), 6.96–7.18 (6H, aromatic protons), 8.04–8.17 (4H, aromatic protons), EI-MS (rel. int., %) *m*/*z*=447 (0.6, $[M+H]^+$), 431 (1.4, $[M-CH_3]^+$), 266 (1.1, $[M-PhCOOH-\text{acetone}]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 431.1115. Calcd for $C_{22}H_{19}D_2O_7S$: $[M-CH_3]^+$, 431.1132.

4.16.5. Physical data for *ax*-41. $[\alpha]_D^{19}$=+49.6 (*c* 0.52 $CHCl_3$), IR (film) 1720, 1270, 1110, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.17, 1.31 (each 3H, s, C(C*H*$_3$)$_2$), 1.64 (1H, d, *J*=10.3 Hz, C1*H*), 2.70 (1H, dd, *J*=4.4, 9.3 Hz, C5*H*), 3.52 (1H, t, *J*=9.3 Hz, C4*H*), 4.41 (1H, dd, *J*=9.3, 10.3 Hz, C3*H*), 5.15 (1H, d, *J*=4.4 Hz, C6*H*), 6.13 (1H, t, *J*=10.3 Hz, C2*H*), 6.97–7.18 (6H, aromatic protons), 8.05–8.17 (4H, aromatic protons), EI-MS (rel. int., %) *m*/*z*=446 (0.9, M^+), 431 (0.9, $[M-CH_3]^+$), 324 (1.0, $[M-PhCOOH]^+$), 266 (5.0, $[M-PhCOOH-\text{acetone}]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 446.1342. Calcd for $C_{23}H_{22}D_2O_7S$: $[M-CH_3]^+$, 446.1366.

4.17. The Pummerer rearrangement of deuterium labelled 41 giving (1*R*,6*R*)-2,6-*O*-dibenzoyl-5-deoxy-1,6-dideutreio-3,4-*O*-isopropylidene-5-thio-D-glucopyranose (42)

4.17.1. Reaction of *eq*-41. Treatment of *eq*-**41** (9.3 mg, 20.8 μmol) in a similar manner as described in Section 4.7.1 gave **42** (5.2 mg, 56%) as an oil after silica gel column chromatography. $[\alpha]_D^{19}$=+74.9 (*c* 0.39 $CHCl_3$), IR (film) 3445, 1720, 1270, 1115, 710 cm^{-1}, ^1H NMR (C_6D_6) δ 1.26, 1.29 (each 3H, s, C(C*H*$_3$)$_2$), 3.63 (1H, dd, *J*=3.9, 10.7 Hz, C5*H*), 3.80 (1H, dd, *J*=8.8, 10.7 Hz, C4*H*), 4.37 (1H, dd, *J*=8.8, 10.8 Hz, C3*H*), 4.77 (1H, d, *J*=3.9 Hz, C6*H*), 5.52 (1H, d, *J*=10.8 Hz, C2*H*), 6.94–7.17 (6H, aromatic protons), 8.17–8.20 (4H, aromatic protons), EI-MS (rel. int., %) *m*/*z*=446 (0.3, M^+), 431 (0.8, $[M-CH_3]^+$), 324 (3.0, $[M-PhCOOH]^+$), 266 (1.8, $[M-PhCOOH-\text{acetone}]^+$), 105 (100, $PhCO^+$), EI-HRMS; found: *m*/*z* 446.1380. Calcd for $C_{23}H_{22}D_2O_7S$: $[M-CH_3]^+$, 446.1366.

4.18. Reaction of *ax*-41

Treatment of *ax*-**41** (8.1 mg, 18.1 μmol) in a similar manner as described in Section 4.7.1 gave **42** (7.0 mg, 86%) as an oil after silica gel column chromatography. The ^1H NMR spectrum of the product was identical with that of the authentic sample prepared in Section 4.17.1.

4.18.1. 1,5-Dideoxy-3,4-*O*-isopropylidene-2-*O*-methoxymethyl-5-thio-D-glucopyranose (*S*)-*S*-oxide (43). A mixture of *ax*-**9** (171 mg, 445 μmol) and NaOMe (48.0 mg, 890 μmol) was stirred in MeOH (5.0 mL) at room temperature for 20 h. After addition of ion exchange resin (DOWEX 50W-X4, H^+ form, ca. 100 mg), the mixture was filtered, then concentrated in vacuo. Silica gel column chromatography of the residue (CH_2Cl_2/acetone=75:25) gave **43** (142 mg, 100%) as a solid. Analytical sample was obtained by recrystallization (hexane/EtOAc=50:50) giving needles. Mp=135–136 °C, $[\alpha]_D^{23}$=+11.9 (*c* 2.10, MeOH), IR (KB) 3400, 2985, 2930, 2895, 1155, 1055, 1020 cm^{-1}, ^1H NMR (CD_3OD) δ 1.40, 1.42 (each 3H, s, C(C*H*$_3$)$_2$), 2.69 (1H, dd, *J*=11.3, 14.7 Hz, C1*H*H), 3.04 (1H, dt, *J*=4.4, 11.3 Hz, C5*H*), 3.38 (3H, s, C*H*$_3$O), 3.62 (1H, dd, *J*=4.4, 14.7 Hz C1H*H*), 3.65 (1H, t, *J*=9.3 Hz, C3*H*), 3.88 (1H, t, *J*=10.7 Hz, C4*H*), 3.89 (1H, dd, *J*=8.8, 11.7 Hz, C6*H*H), 4.05 (1H, ddd, *J*=0.9, 4.4, 11.7 Hz, C6*H*H), 4.38 (1H, ddd, *J*=3.9, 9.7, 10.7 Hz, C2*H*), 4.69, 4.83 (each 1H, d, *J*=6.9 Hz, OC*H*HO), ^{13}C NMR (CD_3OD) δ 26.9, 27.0 (C(*C*H$_3$)$_2$), 50.2 (*C*1), 55.9 (*C*H$_3$O), 57.8 (*C*6), 62.9 (*C*5), 72.3 (*C*2), 73.7 (*C*4), 82.7 (*C*3), 97.0 (O*C*H$_2$O), 111.0 (*C*(CH$_3$)$_2$), FD-MS (rel. int., %) *m*/*z*=280 (47, M^+), 265 (97, $[M-Me]^+$), 262 (100, $[M-H_2O]^+$), FD-HRMS; found: *m*/*z* 280.0985. Calcd for $C_{11}H_{20}O_6S$: M^+, 280.0981.

4.18.2. 1,5-Dideoxy-3,4-*O*-isopropylidene-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-D-glucopyranose (*S*)-*S*-oxide (45). To a mixture of **43** (30.0 mg, 107 μmol), 2,3,4,6-*O*-tetrakis(4-methoxyphenylmethyl)-5-deoxy-5-thio-α-D-glucopyranosyl trichloroacetimidate (**44**) (80.0 mg, 97.4 μmol), and MS4A (200 mg) in CH_2Cl_2 (5.0 mL), TMSOTf (0.9 μL, 4.9 μmol) in CH_2Cl_2 (100 μL) was added at −78 °C. The mixture was allowed to warm to room temperature for 2 h. After addition of Et_3N (50 μL, 361 mmol), the mixture was filtered through Celite® pad and the filtrate was concentrated in vacuo. Silica gel column chromatography of the residue (benzene/EtOAc=85:15) gave **45** (85.0 mg, 93%) as an oil. $[\alpha]_D^{23}$=+68.7 (*c* 3.8, $CHCl_3$), IR (film) 2995, 2915, 2835, 1510, 1250, 1100, 1035 cm^{-1}, ^1H NMR (C_6D_6) δ 1.21, 1.31 (each 3H, s, $C(CH_3)_2$), 1.64 (1H, dd, *J*=11.2, 14.7 Hz, C1*H*H), 2.54 (1H, dt, *J*=3.9, 11.7 Hz, C5*H*), 3.08 (3H, s, CH_3O), 3.13 (1H, dd, *J*=3.9, 14.7 Hz, C1*H*H), 3.26 (1H, t, *J*=9.3 Hz, C3*H*), 3.275, 3.278, 3.296, 3.302 (each 3H, s, CH_3O×4), 3.75–3.85 (3H, C′5*H*, C6′*H*H, C6*H*H), 3.99 (1H, dd, *J*=2.5, 9.3 Hz, C2′*H*), 4.18–4.24 (3H, C4*H*, C4′*H*, C6′*H*H), 4.28 (1H, d, *J*=11.7 Hz, ArC*H*HO), 4.34 (1H, t, *J*=9.3 Hz, C3′*H*), 4.42–4.47 (3H, ArCH_2O, OC*H*HO), 4.50 (1H, d, *J*=2.5 Hz, C1′*H*), 4.58 (1H, d, *J*=11.2 Hz, ArC*H*HO), 4.58 (1H, m, C2*H*), 4.65 (1H, t, *J*=10.7 Hz, C6*H*), 4.73–4.74 (2H, OC*H*HO, ArC*H*HO), 5.07 (1H, d, *J*=10.3 Hz, ArC*H*HO), 5.09 (1H, d, *J*=10.8 Hz, ArC*H*HO), 5.21 (1H, d, *J*=10.8 Hz, ArC*H*HO), 6.72–7.41 (16*H*, aromatic protons), ^{13}C NMR (C_6D_6) δ 26.7, 27.0 ($C(CH_3)_2$), 42.3 (*C*′5), 50.2 (*C*1), 54.66, 54.70, 54.70, 54.72 (CH_3O×4), 55.2 (CH_3O), 59.2 (*C*5), 63.3 (*C*6), 68.0 (*C*′6), 71.4 (*C*2), 72.8, 72.9, 75.5, 76.0 (ArCH_2O×4), 80.7 (*C*′1), 82.5 (*C*3), 84.1 (*C*′4), 85.3 (*C*′3), 96.1 (*C*′2), 109.7 (OCH_2O), 113.93, 113.97, 114.0, 114.1, 129.3, 129.6, 129.68, 129.76, 130.8, 131.2, 131.7, 132.2, 159.52, 159.57, 159.67, 159.76 (aromatic carbons), FD-MS (rel. int., %) *m*/*z*=940 (57, $[MH+1]^+$), 939 (100, $[M+H]^+$), 938 (99. M^+), FD-HRMS; found: *m*/*z* 938.3583. Calcd for $C_{49}H_{62}O_{14}S_2$: M^+, 938.3581.

4.19. The Pummerer rearrangement of 45 giving 5-deoxy-3,4-*O*-isopropylidene-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-D-glucopyranose (46) and its isomers 47, 48

Treatment of **45** (133 mg, 141 μmol) in a similar manner as described in Section 4.7.1 gave **46** (68.0 mg, 51%), **47** (4,5-olefin, 34.1 mg, 26%), and **48** (5,6-olefin 17.0 mg, 13%) as oils after silica gel column chromatography.

4.19.1. Physical data for 46. IR (film) 3395, 2930, 1510, 1250, 1035 cm^{-1}. The ^1H NMR spectrum of this sample showed that it consists of the two tautomers arising from the C1 anomeric position (isomeric ratio=72:28). Assignments of the signals for the main isomer and some for the minor isomer are described. ^1H NMR (C_6D_6, *a*=0.72, *b*=0.28) δ 1.28 (3H×*b*, s, CH_3 (minor)), 1.31 (3H×*a*, s, CH_3 (major)), 1.33 (3H×*b*, s, CH_3 (minor)), 1.36 (3H×*a*, s, CH_3 (major)), 2.95 (1H, m, C5*H* or C5′*H*), 3.15 (3H×*a*, s, CH_3O (major)), 3.20 (3H×*b*, s, CH_3O (minor)), 3.28 (3H×*b*, s, CH_3O (minor)), 3.294 (3H×*b*, s, CH_3O (major)), 3.296 (3H×*b*, s, CH_3O (minor)), 3.301 (3H×*b*, s, OCH_3 (minor)), 3.306 (3H×*b*, s, CH_3O (major)), 3.310 (3H×*b*, s, CH_3O (major)), 3.318 (3H×*b*, s, CH_3O (major)), 3.321 (3H×*b*, s, CH_3O (minor)), 3.43 (1H×*b*, ddd, *J*=2.4, 3.9, 10.2 Hz, C5*H* (minor) or C5′*H* (minor)), 3.47 (1H×*a*, dt, *J*=3.9, 12.0 Hz, C5*H* (major) or C5′*H* (major)), 3.66–4.76 (21H), 4.88–4.94 (2H, m), 4.94 (1H×*b*, br, C1*H* (minor) or C1′*H* (minor)), 4.99 (1H×*b*, d, *J*=10.2 Hz, OCH*H*O (minor) or ArCH*H*O (minor)), 5.02 (1H, × a, d, *J*=10.7 Hz, OCH*H*O (major) or ArCH*H*O (major)), 5.03 (1H, d, *J*=10.7 Hz, OCH*H*O or ArCH*H*O), 6.79 (8H, aromatic protons), 7.15–7.35 (8H, aromatic protons). This sample was used for the next step without further measurement of physical data because of a mixture of anomers.

4.19.2. Physical data for 47 (4,5-olefin). $[\alpha]_D^{22}$=+37.4 (*c* 0.98, $CHCl_3$), IR (film) 2930, 2835, 1510, 1250, 1035 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.33, 1.37 (each 3H, s, $C(CH_3)_2$), 2.69 (1H, dd, *J*=8.8, 12.7 Hz, C1*H*H), 2.88 (1H, dd, *J*=5.3, 12.7 Hz, C1*H*H), 3.12 (1H, dt, *J*=3.4, 6.3 Hz, C5′*H*), 3.28 (3H, s, CH_3O), 3.40 (1H, dd, *J*=3.4, 10.2 Hz, C6′*H*H), 3.59–3.80 (16H, CH_3O×4, C2′*H*, C4′*H*, C3′*H*, C6′*H*), 3.88 (1H, ddd, *J*=5.3, 8.8, 9.3 Hz, C2*H*), 4.11 (1H, d, *J*=11.7 Hz, C6*H*H), 4.41–4.52 (6H, ArC*H*HO×4, C3*H*, C6*H*H), 4.58 (1H, d, *J*=2.9 Hz, C1′*H*), 4.68–4.80 (7H, ArC*H*HO×5, OCH_2O), 6.67–7.20 (16H, aromatic protons), ^{13}C NMR ($CDCl_3$) δ 24.9, 26.7 ($C(CH_3)_2$), 29.1 (*C*1), 41.2 (*C*5′), 55.19, 55.23, 55.25, 55.25 (CH_3O×4), 55.6 (CH_3O), 64.3 (*C*6), 67.5 (C6′), 72.4 (ArCH_2O), 72.8 (ArCH_2O), 75.1 (ArCH_2O), 75.7 (ArCH_2O), 76.8 (*C*2), 77.5 (*C*3), 78.9 (*C*1′), 81.5 (*C*4′), 83.0 (*C*3′), 83.9 (*C*2′), 95.9 (OCH_2O), 97.7 ($C(CH_3)_2$), 112.2 (*C*5), 113.66, 113.70, 113.70, 113.75, 129.39, 129.41, 129.5, 129.7, 130.0, 130.7, 130.8, 131.4 (aromatic carbons), 142.9 (*C*4), 158.97, 159.0, 159.15, 159.20, (aromatic carbons), FD-MS (rel. int., %) *m*/*z*=921 (65, $[MH]^+$), 920 (100, M^+), FD-HRMS; found: *m*/*z* 920.3483. Calcd for $C_{49}H_{60}O_{13}S_2$: M^+, 920.3475.

4.19.3. Physical data for 48 (5,6-olefin). $[\alpha]_D^{22}$=−21.8 (*c* 0.85, $CHCl_3$), IR (film) 2930, 2835, 1610, 1510, 1250, 1035, 515 cm^{-1}, ^1H NMR (C_6D_6) δ 1.34, 1.38 (each 3H, s, $C(CH_3)_2$), 2.58 (2H, C1H_2), 3.08 (3H, s, CH_3O), 3.27 (6H, s, CH_3O×2), 3.29, 3.31 (each 3H, s, CH_3O), 3.46 (1H, t, *J*=8.8 Hz, C3*H*), 3.46 (1H, m, C6′*H*H), 3.63 (1H, dt, *J*=3.9, 6.4 Hz, C5′*H*), 3.90 (1H, dd, *J*=2.5, 9.3 Hz, C2′*H*), 3.99 (2H, C6′*H*H, C2*H*), 4.10 (1H, t, *J*=9.3 Hz, C4′*H*), 4.18 (1H, dd, *J*=1.5, 8.8 Hz, C4*H*), 4.20 (1H, d, *J*=11.2 Hz, ArCH*H*O), 4.30 (1H, d, *J*=11.2 Hz, ArCH*H*O), 4.37 (1H, t, *J*=9.3 Hz, C3′*H*), 4.43 (3H, ArC*H*HO×2, OC*H*HO), 4.64 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4.68 (1H, d, *J*=2.5 Hz, C1′*H*), 4.71 (1H, d, *J*=6.8 Hz, OC*H*HO), 4.89 (1H, d, *J*=10.7 Hz, ArC*H*HO), 5.03 (2H, d, *J*=10.7 Hz, ArC*H*HO×2), 6.72–6.85 (8H, aromatic protons), 6.90 (1H, d, *J*=1.5 Hz, C6*H*), 7.15–7.31 (8H, aromatic protons), ^{13}C NMR (C_6D_6, assignment of signals was not performed.) δ 26.9, 27.3, 33.1, 42.6, 54.7, 55.1, 67.6, 72.6, 72.9, 75.5, 75.9, 76.4, 77.4, 82.1, 82.2, 83.7, 83.9, 84.6, 95.7, 109.8, 109.9, 113.9, 114.1, 129.6, 130.5, 131.0 131.6, 132.7, 140.2, 149.4, 158.2, 158.3, 159.7, 159.8, FD-MS (rel. int., %) *m*/*z*=921 (65, $[MH]^+$), 920 (100, M^+), FD-HRMS; found: *m*/*z* 920.3458. Calcd for $C_{49}H_{60}O_{13}S_2$: M^+, 920.3475.

4.20. 5-Deoxy-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-α-D-glucopyranose (α-50) and the β-anomer (β-50)

A solution of **46** (61.5 mg, 66.6 μmol) in MeOH (3.0 mL) was stirred with conc. HCl (5.0 μL) at room temperature for 1 h. After neutralization by addition of Et_3N (100 μL), the mixture was concentrated in vacuo. Silica gel column chromatography of the residue (CH_2Cl_2/acetone=90:10) gave α-**50** (36.5 mg, 61%) and β-**50** (18.3 mg, 30%) both as oils.

4.20.1. Physical data for α-50. $[\alpha]_D^{23}$=+123 (*c* 1.20, MeOH), IR (film) 3430, 2930, 1510, 1250, 1100, 1035 cm^{-1}, ^1H NMR (C_6D_6+D_2O) δ 3.24 (3H, s, CH_3O), 3.30, 3.32, 3.33, 3.34 (each 3H, CH_3O), 3.57 (1H, ddd, *J*=9.3, 2.9, 3.9 Hz, C5′*H*), 3.66 (1H, dd, *J*=2.0, 9.3 Hz, C6′*H*H), 3.74 (1H, dd, *J*=3.9, 9.3 Hz, C6*H*H), 3.79–3.84 (2H, C2*H*, C5*H*), 3.87–3.93 (2H, C2′*H*, C3*H*), 4.03–4.09 (2H, C4′*H*, C6′*H*), 4.16–4.24 (2H, C3′*H*, C4*H*), 4.28–4.32 (2H, C6*H*H, ArC*H*HO,), 4.40 (1H, d, *J*=11.7 Hz, ArCH*H*O), 4.45 (1H, d, *J*=2.5 Hz, C1′*H*), 4.53, 4.57 (each 1H, d, *J*=11.7 Hz, ArCH_2O), 4.63–4.66 (2H, OC*H*HO and ArC*H*HO), 4.72 (1H, d, *J*=6.8 Hz, OC*H*HO), 4.87 (1H, d, *J*=2.9 Hz, C1*H*), 4.98 (1H, d, *J*=9.7 Hz, ArC*H*HO), 4.99 (1H, d, *J*=9.8 Hz, ArC*H*HO), 5.13 (1H, d, *J*=10.7 Hz, ArC*H*HO), 6.77–6.85 (8H, aromatic protons), 7.16–7.42 (8H, aromatic protons), FAB-MS (negative mode, rel. int., %) *m/z*=897 (1.6, $[M-H]^-$), 537 (4.9, $C_{30}H_{33}O_7S^-$), 148 (100), FAB-HRMS (negative mode); found: *m/z* 897.3163. Calcd for $C_{46}H_{57}O_{14}S_2$: $[M-H]^-$, 897.3190.

4.20.2. Physical data for β-50. $[\alpha]_D^{23}$=+93.9 (*c* 1.40, MeOH), IR (film) 3450, 2910, 1610, 1510, 1250, 1100, 1035 cm^{-1}, ^1H NMR (C_6D_6) δ 2.97 (1H, m, C5*H*), 3.00 (3H, s, CH_3O), 3.29 (6H, s, CH_3O×2), 3.30, 3.31 (each 3H, s, CH_3O), 3.31 (1H, m, C6*H*H), 3.48 (1H, t, *J*=8.3 Hz, C3*H*), 3.53 (1H, ddd, *J*=2.9, 4.9, 10.7 Hz, C5′*H*), 3.60 (1H, dd, *J*=2.4, 9.7 Hz, C6′*H*H), 3.69 (1H, dd, *J*=6.8, 7.8 Hz, C2*H*), 3.88 (1H, dd, *J*=6.9, 9.3 Hz, C2′*H*), 3.93–4.00 (2H, C4H, C6′*H*H), 4.03 (1H, dd, *J*=9.3, 10.7 Hz, C4′*H*), 4.19 (1H, t, *J*=9.3 Hz, C3′*H*), 4.25–4.29 (2H, ArC*H*HO, C6*H*H), 4.34 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4.35 (1H, d, *J*=3.4 Hz, C1′*H*), 4.45–4.55 (3H, OCH_2O, ArC*H*HO), 4.64 (1H, d, *J*=10.7, ArC*H*HO), 4.67 (1H, d, *J*=6.9 Hz, C1*H*), 4.93 (1H, d, *J*=10.8 Hz, ArC*H*HO), 5.02 (1H, d, *J*=10.8 Hz, ArC*H*HO), 5.06 (1H, d, *J*=10.8 Hz, ArC*H*HO), 6.75–6.83 (8H, aromatic protons), 7.18, 7.21, 7.29, 7.35 (each br d, *J*=8.8 Hz, aromatic protons), FAB-MS (negative mode, rel. int., %) *m/z*=897 (2.1, $[M-H]^-$), 537 (8.7, $C_{30}H_{33}O_7S^-$), 148 (100), FAB-HRMS (negative mode); found: *m/z* 897.3218. Calcd for $C_{46}H_{57}O_{14}S_2$: $[M-H]^-$, 897.3190.

4.20.3. 1,3,4-*O*-Triacetoxy-5-deoxy-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-α-D-glucopyranose (α-51). A mixture of α-**50** (30.0 mg, 33.4 μmol), Ac_2O (100 μL, 1.06 mmol), and pyridine (200 μL, 2.48 mmol) in CH_2Cl_2 (500 μL) was stirred at room temperature for 33 h. After concentration in vacuo, silica gel column chromatography of the residue (benzene/EtOAc=85:15) gave α-**51** (28 mg, 83%) in an almost pure form as an oil. $[\alpha]_D^{23}$=+170 (*c* 0.15, $CHCl_3$), IR (film) 2955, 2840, 1750, 1510, 1245, 1215, 1100, 1035 cm^{-1}. The ^1H NMR spectrum of this sample showed that it contains small amount of β-**51** (α-**51**/β-**51**=97:3). Assignments of the signals for the main isomer and some for the minor isomer are described. ^1H NMR (C_6D_6, *a*=0.97, *b*=0.03) δ 1.50 (3H×*a*, s, CH_3CO (major)), 1.54 (3H×*b*, s, CH_3CO (minor)), 1.73, (3H, s, CH_3CO), 1.80 (3H×*b*, s, CH_3CO (minor)), 1.86 (3H×*a*, s, CH_3CO (minor)), 3.06 (3H×*a*, s, CH_3O (major)), 3.07 (3H×*b*, s, CH_3O (major)), 3.22 (1H×*b*, C6*H*H (minor)), 3.27 (1H, m, C6*H*H), 3.28, 3.29, 3.30, 3.30 (each 3H, s, CH_3O), 3.54 (1H, ddd, *J*=2.9, 4.4,, 10.8 Hz, C5′*H*), 3.60 (1H, dt, *J*=10.7, 3.9 Hz, C5*H*), 3.66 (1H, dd, *J*=2.4, 9.7 Hz, C6′*H*H), 3.87 (2H, C2*H*, C2′*H*), 4.07 (3H, C4′*H*, C6H*H*, C6′H*H*), 4.21 (1H, t, *J*=9.3 Hz, C3′*H*), 4.26 (1H, d, *J*=2.9 Hz, C1′*H*), 4.32 (3H, OCH_2O, ArC*H*HO), 4.39 (1H, d, *J*=6.9 Hz, ArC*H*HO), 4.46, 4.53 (each 1H, d, *J*=11.3 Hz, OC*H*HO), 4.68 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4.87 (1H, d, *J*=10.3 Hz, ArC*H*HO), 5.02 (1H, d, *J*=10.7 Hz, ArC*H*HO), 5.06 (1H, d, *J*=10.3 Hz, ArC*H*HO), 5.23 (1H × b, dd, *J*=8.3, 10.3 Hz, C3*H* (minor)), 5.61 (1H, t, *J*=9.8 Hz, C4*H*), 5.72 (1H×*a*, t, *J*=9.8 Hz, C3*H* (major)), 6.05 (1H×*b*, d, *J*=8.3 Hz, C1*H* (minor)), 6.23 (1H×*a*, d, *J*=2.9 Hz, C1*H* (major)), 6.74–6.84 (8H, aromatic protons), 7.21 (4H, aromatic protons), 7.32 (4H, aromatic protons), FD-MS (rel. int., %) *m/z*=1025 (17, $[M+H]^+$), 1024 (7.6, M^+), 1023 (11, $[M-H]^+$), 903 (100, $[M-(CH_3OPhCH_2)+H]^+$), FD-HRMS; found: *m/z* 1024.3593. Calcd for $C_{52}H_{64}O_{17}S_2$: M^+, 1024.3585.

4.20.4. 1,3,4-*O*-Triacetoxy-5-deoxy-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-β-D-glucopyranose (β-51). Treatment of β-**50** (9.0 mg, 10 μmol) in a similar manner as described in Section 4.20.3 gave β-**51** (9.0 mg, 89%) as an oil after silica gel column chromatography. $[\alpha]_D^{23}$=+65.3 (*c* 0.10, $CHCl_3$), IR (film) 2925, 2860, 1750, 1510, 1245, 1215, 1100, 1035 cm^{-1}. The ^1H NMR spectrum of this sample showed that it contains small amount of α-**51** (α-**51**/β-**51**=9:91). Assignments of the signals for the main isomer and some for the minor isomer are described. ^1H NMR (C_6D_6, *a*=0.09, *b*=0.91) δ 1.50 (3H×*b*, s, CH_3CO (minor)), 1.54 (3H×*a*, s, CH_3CO (major)), 1.73 (3H×*b*, s, CH_3CO (minor)), 1.74 (3H×*a*, s, CH_3CO (major)), 1.80 (3H×*a*, s, CH_3CO (major)), 1.86 (3H×*b*, s, CH_3CO (minor)), 2.72 (1H, dt, *J*=3.9 Hz, C5′*H*), 3.07 (3H, s, CH_3O), 3.22 (1H, dd, *J*=3.9, 9.8 Hz, C6*H*H), 3.28, 3.29, 3.30, 3.30 (each 3H, s, CH_3O), 3.55 (1H, ddd, *J*=2.4, 3.9, 10.7 Hz, C5′*H*), 3.66 (1H, dd, *J*=2.4, 9.7 Hz, C6′*H*H), 3.88 (1H, dd, *J*=3.0, 8.8 Hz, C2′*H*), 3.89 (1H, t, *J*=8.3 Hz, C2*H*), 3.94 (1H, dd, *J*=3.9, 9.8 Hz, C6*H*H), 4.08 (2H, C4*H*, C6′*H*H), 4.21 (1H, t, *J*=8.8 Hz, C3′*H*), 4.25 (1H, d, *J*=3.0 Hz, C1′*H*), 4.30 (1H, d, *J*=11.7 Hz, ArC*H*HO), 4.35 (1H, d, *J*=11.7 Hz, ArC*H*HO), 4.46 (2H, s, OCH_2O), 4.47 (1H, d, *J*=11.2 Hz, ArC*H*HO), 4.56 (1H, d, *J*=11.2 Hz, ArC*H*HO), 4.69 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4.90 (1H, d, *J*=10.3 Hz, ArC*H*HO), 5.04 (1H, d, *J*=10.3 Hz, ArC*H*HO), 5.05 (1H, d, *J*=10.7 Hz, ArC*H*HO), 5.23 (1H×*a*, dd, *J*=8.3, 10.3 Hz, C3*H* (major)), 5.56 (1H×*a*, dd, 8.3, 10.3 Hz, C4*H* (major)), 5.61 (1H×*b*, t, *J*=9.8 Hz, C4*H* (minor)), 5.72 (1H×*b*, t, *J*=9.8 Hz, C3*H* (minor)), 6.05 (1H, d, *J*=8.3 Hz, C1*H*), 6.23 (1H×*b*, d, *J*=2.9 Hz, C1*H* (minor)), 6.74–6.83 (8H, aromatic protons), 7.20 (4H, aromatic protons), 7.32 (4H, m, aromatic protons), FD-MS (rel. int., %) *m/z*=1024 (24, M^+), 1023 (24, $[M-H]^+$), 903 (100, $[M-(CH_3OPhCH_2)+H]^+$), FD-HRMS; found: *m/z* 1024.3566. Calcd for $C_{52}H_{64}O_{17}S_2$: M^+, 1024.3585.

4.21. 3,4-*O*-Diacetoxy-5-deoxy-6-*O*-[5′-deoxy-2′,3′,4′,6′-*O*-tetrakis(4-methoxyphenylmethyl)-5′-thio-α-D-glucopyranosyl]-2-*O*-methoxymethyl-5-thio-α-D-glucopyranose (α-52) and the β-anomer (β-52)

A mixture of α-**51** (25.1 mg, 24.9 μmol) and hydrazine acetate (2.8 mg, 29.0 μmol) in DMF (1.0 mL) was stirred at room temperature for 12 h. The mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (benzene/EtOAc=80:20) gave α-**52** (19.4 mg, 79%) and β-**52** (1.9 mg, 7.8%) both as oils.

4.21.1. Physical data for α-52. The ^{1}H NMR spectrum suggested that the deuterium atom was completely retained through the reaction.

4.21.2. Physical data for β-52. The ^{1}H NMR spectrum suggested that the deuterium atom was completely retained through the reaction.

4.21.3. Physical data for α-55. $[\alpha]_D^{23}$=+113 (*c* 1.35, $CHCl_3$), IR (film) 2930, 1730, 1510, 1245, 1100, 1030 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.84, 1.89 (each 3H, s, CH_3CO), 3.04 (1H, ddd, *J*=2.5, 3.9, 10.7 Hz, C5″*H*), 3.16 (3H, s, CH_3O), 3.20 (1H, dd, *J*=2.9, 10.2 Hz, C6′*H*H), 3.35 (1H, dd, *J*=2.5, 9.8 Hz, C6″*H*H), 3.41 (3H, s, CH_3O), 3.44 (2H, C5′*H*, C6HH), 3.60–3.74 (3H, C2″*H*, C3″*H*, C4″*H*), 3.63, 3.66, 3.67, 3.69 (each 3H, s, CH_3O), 3.80 (1H, dd, *J*=3.9, 9.8 Hz, C6″*H*H), 3.86 (1H, dd, *J*=2.4, 9.7 Hz, C2′*H*), 3.89 (1H, dd, *J*=4.4, 10.2 Hz, C6′*H*H), 4.05 (1H, dd, *J*=7.3, 10.2 Hz, C6*H*H), 4.25–4.35 (4H, C1″*H*, C5*H*, ArCH_2O), 4.36 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4.47, 4.51 (each 1H, d, *J*=11.7 Hz, ArC*H*HO), 4.52 (2H, s, OCH_2O), 4,60 (1H, d, *J*=10.2 Hz, ArC*H*HO), 4.61 (1H, d, *J*=2.4 Hz, C1′*H*), 4,68 (1H, d, *J*=10.7 Hz, ArC*H*HO), 4,73 (1H, d, *J*=10.2 Hz, ArC*H*HO), 5.11–5.20 (3H, C1*H*, C2*H*, C4′*H*), 5.34 (1H, t, *J*=9.7 Hz, C3′*H*), 5.39 (1H, t, *J*=10.2 Hz, C4*H*), 6.05 (1H, t, *J*=10.2 Hz, C3*H*), 6.68–6.78 (8H, aromatic protons), 6.98–7.40 (17H, aromatic protons), 7.74–7.87 (6H, aromatic protons), FD-MS (rel. int., %) *m/z*=1470 (12, M^+), 1469 (18, $[M-H]^+$), 1350 (92, $[M-(CH_3OPhCH_2+H)]^+$), 1349 (100, $[M-PhCOO]^+$), FD-HRMS; found: *m/z* 1470.4965. Calcd for $C_{78}H_{86}O_{24}S_2$: M^+, 1470.4951.

4.21.4. Physical data for β-55. $[\alpha]_D^{27}$=+75.1 (*c* 0.77, $CHCl_3$), IR (film) 2930, 1730, 1510, 1245, 1095, 1030 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.86, 1.94 (each 3H, s, CH_3CO), 3.02 (2H, C5′*H*, C5″*H*), 3.21 (3H, s, CH_3O), 3.27 (1H, dd, *J*=3.9, 9.8 Hz, C6′*H*H), 3.31 (3H, s, CH_3O), 3.33 (1H, dd, *J*=2.0, 9.8 Hz, C6″*H*H), 3.57–3.73 (5H, C2″*H*, C3″*H*, C4″*H*, C6*H*, C6′*H*), 3.64, 3.65, 3.67, 3.68 (each 3H, s, CH_3O), 3.79 (2H, C2′*H*, C6″*H*H), 3.88 (1H, dd, *J*=2.4, 11.2 Hz, C6*H*H), 4.08 (1H, ddd, *J*=2.4, 5.8, 9.8 Hz, C5*H*), 4.14 (1H, d, *J*=2.9 Hz, C1″*H*), 4.27, 4.31 (each 1H, d, *J*=12.2 Hz, ArC*H*HO), 4.32 (1H, d, *J*=10.3 Hz, ArC*H*HO), 4.41 (1H, d, *J*=11.8 Hz, ArC*H*HO), 4.47 (1H, d, *J*=7.8 Hz, C1′*H*), 4.53 (1H, d, *J*=11.8 Hz, ArC*H*HO), 4,57 (1H, d, *J*=10.3 Hz, ArC*H*HO), 4.61 (1H, d, *J*=6.9 Hz, OC*H*HO), 4.66 (1H, d, *J*=10.3 Hz, ArC*H*HO), 4,69 (1H, d, *J*=10.3 Hz, ArC*H*HO), 4.74 (1H, d, *J*=6.9 Hz, OC*H*HO), 4.88 (1H, dd, *J*=8.3, 9.3 Hz, C3′*H*), 5.10 (3H, C1*H*, C2*H*, C4′*H*), 5.36 (1H, t, *J*=9.8 Hz, C4*H*), 6.00 (1H, t, *J*=9.8 Hz, C3*H*), 6.67–6.73 (9H, aromatic protons), 6.94–7.40 (14H, aromatic protons), 7.71–7.86 (6H, aromatic protons), FD-MS (rel. int., %) *m/z*=1471 (26, $[M+H]^+$), 1470 (19, M^+), 1469 (24, $[M-H]^+$), 1350 (100, $[M-(CH_3OPhCH_2)+H]^+$), FD-HRMS; found: *m/z* 1470.4956. Calcd for $C_{78}H_{86}O_{24}S_2$: $[M]^+$, 1470.4951.

4.22. Methyl 6-*O*-[5′-deoxy-6′-*O*-(5″-deoxy-5″-thio-α-D-glucopyranosyl)-5′-thio-α-D-glucopyranosyl]-α-D-glucopyranoside (α-58)

4.22.1. Removal of the MPM ethers giving methyl 6-*O*-[3′,4′-*O*-diacetyl-5′-deoxy-6′-*O*-[5″-deoxy-4″,6″-*O*-(4-methoxyphenylmethylidene)-5″-thio-α-D-glucopyranosyl]-2′-*O*-methoxymethyl-5′-thio-α-D-glucopyranosyl]-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (α-56). A mixture of α-**55** (65.1 mg, 44.2 μmol) and DDQ (50 mg, 220 μmol) in a mixture of CH_2Cl_2 (1.0 mL) and H_2O (100 μL) was stirred at room temperature for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (benzene/EtOAc=70:30) gave α-**56** (34.0 mg, 70%) as an oil. $[\alpha]_D^{23}$=+176 (*c* 3.54, $CHCl_3$), IR (film) 1455, 2930, 1730, 1280, 1250, 1105, 1070, 1025 cm^{-1}, ^{1}H NMR (C_6D_6+D_2O) δ 1.80, 1.81 (each 3H, s, CH_3CO), 3.09, 3.29, 3.35 (each 3H, s, CH_3O), 3.45 (1H, dd, *J*=2.4, 10.2 Hz, C6′*H*H), 3.54 (2H, C6*H*H, C6″*H*H), 3.65 (1H, dt, *J*=3.9, 9.7 Hz, C″5*H*), 3.75 (1H, ddd, *J*=3.5, 4.9, 11.3 Hz, C5′*H*), 3.83 (1H, t, *J*=9.7 Hz, C4″*H*), 3.93 (1H, dd, *J*=2.4, 9.8 Hz, C2′*H*), 4.02 (2H, C6′*H*H, C2″*H*), 4.23 (3H, C6*H*H, C3″*H*, C6″*H*H), 4.43 (1H, d, *J*=2.9 Hz, C1″*H*), 4.43 (1H, m, C5*H*), 4.46 (2H, s, OCH_2O), 4.51 (1H, d, *J*=2.5 Hz, C1′*H*), 5.36 (1H, d, *J*=3.5 Hz, C1*H*), 5.49 (1H, s, ArC*H*(OR)$_2$), 5.58 (2H, C2H, C4′*H*), 5.86 (2H, C3′*H*, C4*H*), 6.65 (1H, t, *J*=9.8 Hz, C3*H*), 6.81–7.04 (11H, aromatic protons), 7.61–8.14 (8H, aromatic protons), FD-MS (rel. int., %) *m/z*=1109, (69, $[M+H]^+$), 1008 (100, M^+), FD-HRMS; found: *m/z* 1108.3058. Calcd for $C_{54}H_{66}O_{21}S_2$: M^+, 1108.3069.

4.22.2. Removal of the acetyl and benzoyl groups giving methyl 6-*O*-[5′-deoxy-6′-*O*-[5″-deoxy-4″,6″-*O*-(4-methoxyphenylmethylidene)-5″-thio-α-D-glucopyranosyl]-2′-*O*-methoxymethyl-5′-thio-α-D-glucopyranosyl]-α-D-glucopyranoside. A mixture of the benzoate obtained in Section 4.23.1. (33.0 mg, 29.8 μmol) and NaOMe (9.6 mg, 178 μmol) in MeOH (1.0 mL) was stirred at room temperature for 2.5 h. To the mixture DOWEX 50W-X4 (H^+ form, 10 mg) was added. After stirring for another 5 min, the mixture was filtrated and concentrated in vacuo. Silica gel column chromatography of the residue (EtOAc/MeOH=80:20) gave the corresponding alcohol (16.7 mg, 79%) as an oil. $[\alpha]_D^{25}$=+258 (*c* 1.5, MeOH), ^{1}H NMR (CD_3OD) δ 3.34 (3H, s, CH_3O), 3.35–3.45 (4H), 3.39, 3.42 (each 3H, s, CH_3O), 3.55–3.87 (13H), 4.01 (1H, dd, J=7.8, 10.3 Hz, C6′HH or C6″HH), 4.11 (1H, dd, J=5.9, 10.7 Hz, C6HH), 4.14 (1H, dd, J=4.4, 10.7 Hz, C6′HH or C6″HH), 4.67 (1H, d, J=3.9 Hz, C1″H), 4.71 (1H, d, J=2.9 Hz, C1′H), 4.78 (2H, s, OCH_2O), 4.81 (1H, br, C1H), 5.60 (1H, s, ArCH(OR)$_2$), 6.90, 7.42 (each 2H, br, J=8.3 Hz, aromatic protons), FAB-MS (negative mode, rel. int., %) m/z=747 (23, [M+Cl]$^-$), 711 (30, [M−H]$^-$), 255 (100), 148 (99), FAB-HRMS (negative mode); found: m/z 711.1994. Calcd for $C_{29}H_{43}O_{16}S_2$: [M−H]$^-$, 711.1993.

4.22.3. Removal of the MOM and methoxybenzylidene groups under acidic conditions giving α-58. A solution of the MOM ether obtained in Section 4.22.2 (15.0 mg, 21.0 mmol) in MeOH (500 μL) was stirred with conc. HCl (5.0 μL) at room temperature for 1 day. To the mixture DIAION DA30 (free base form, 10 mg) was added. After stirring for another 5 min, the mixture was filtered and concentrated in vacuo. The residue was passed through SepPack (ODS, MeOH/H_2O=10:90) and the eluates were concentrated. Medium pressured column chromatography (ODS, MeOH/H_2O=10:90) of the residue gave α-**58** (9.0 mg, 78%) as an oil. $[\alpha]_D^{23}$=+292 (c 0.73, H_2O), IR spectrum was not measured because this sample was soluble only in H_2O. ^{1}H NMR (D_2O) δ 3.08 (1H, ddd, J=2.9, 5.4, 9.3 Hz, C5′H or C5″H), 3.19 (1H, ddd, J=3.0, 7.9, 10.3 Hz, C5′H or C5″H), 3.34 (3H, s, CH_3O), 3.41 (1H, t, J=9.2 Hz, C4H), 3.48 (1H, dd, J=3.9, 9.8 Hz, C2H), 3.51–3.62 (6H, m), 3.73–3.86 (6H, m), 3.98 (1H, dd, J=7.9, 10.3 Hz, C6′HH or C6″HH), 4.09 (1H, dd, J=4.4, 11.2 Hz, C6HH), 4.65 (1H, d, J=3.4 Hz, C1′H or C1″H), 4.66 (1H, d, J=3.9 Hz, C1′H or C1″H), 4.73 (1H, d, J=3.9 Hz, C1H), FAB-MS (negative mode, rel. int., %) m/z=549 (13, [M−H]$^-$), 195 (27, [$C_6H_{11}O_5S$]$^-$), 148 (100), FAB-HRMS (negative mode); found: m/z 549.1306. Calcd for $C_{19}H_{33}O_{14}S_2$: [M−H]$^-$, 549.1312.

4.23. Methyl 6-*O*-[5′-deoxy-6′-*O*-(5″-deoxy-5″-thio-α-D-glucopyranosyl)-5′-thio-β-D-glucopyranosyl]-α-D-glucopyranoside (β-58)

4.23.1. Removal of the MPM ethers giving methyl 6-*O*-[3′,4′-*O*-diacetyl-5′-deoxy-6′-*O*-[5″-deoxy-5″-thio-α-D-glucopyranosyl]-2′-*O*-methoxymethyl-5′-thio-β-D-glucopyranosyl]-2,3,4-*O*-tribenzoyl-α-D-glucopyranoside (57) and its 4″,6″-*O*-(4-methoxybenzylidene)acetal (β-56). Treatment of β-**55** (40.3 mg, 27.4 μmol) with DDQ (31 mg, 137 μmol) in a similar manner as described in Section 4.22.1 gave benzylidene acetal β-**56** (13.3 mg, 44%) and **57** (7.0 mg, 26%) as oils after silica gel column chromatography. The methoxybenzylidene group at C4″, C6″ position was cleaved during measurement of its ^{1}H NMR spectrum in $CDCl_3$ (a signal appeared at 9.77 ppm corresponding to the decomposed anisaldehyde and the intensity of this signal gradually increased). Thus, the sample (13.3 mg) was purified again by silica gel column chromatography to give **57** (12.1 mg, 45% two steps). Thus, the total yield of the tetraol **57** was 71%. $[\alpha]_D^{23}$=+114 (c 1.41, $CHCl_3$), IR (film) 3450, 1730, 1280, 1250, 1095, 1025 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.95, 1.96 (each 3H, s, CH_3CO), 3.03 (2H, C5′H, C5″H), 3.22 (3H, s, CH_3O), 3.36 (1H, m, C6′HH), 3.37 (3H, s, CH_3O), 3.53–3.70 (5H, m), 3.77 (1H, dd, J=5.7, 11.7 Hz, C6″HH), 3.84 (2H, C2′H, C6HH), 3.95 (1H, dd, J=4.8, 10.2 Hz, C6′HH), 4.12 (1H, ddd, J=2.4, 5.9, 9.7 Hz, C5H), 4.44 (1H, d, J=2.5 Hz, C1″H), 4.56 (1H, d, J=7.3 Hz, C1′H), 4.61, 4.75 (each 1H, d, J=6.9 Hz, OCHHO), 4.91 (1H, dd, J=8.3, 9.3 Hz, C3′H), 5.12 (2H, C1H, C2H), 5.22 (1H, t, J=9.8 Hz, C4′H), 5.39 (1H, t. J=9.7 Hz, C4H), 6.02 (1H, t, J=9.7 Hz, C3H), 7.16–7.43 (9H, aromatic protons), 7.71–7.86 (6H, aromatic protons).

4.23.2. Removal of the acetyl and the benzoyl groups. Treatment of the tetraol **57** (16.8 mg, 16.9 μmol) in a similar manner as described in Section 4.22.2 gave the corresponding nonanol (10.1 mg, 100%) as an oil. $[\alpha]_D^{25}$=+29.8 (c 0.75, MeOH), ^{1}H NMR (CD_3OD) δ 3.00 (1H, ddd, J=3.9, 7.8, 11.7 Hz, C5′H or C5″H), 3.12 (1H, ddd, J=3.0, 7.9, 12.7 Hz, C5′H or C5″H), 3.23–3.41 (3H), 3.34, 3.40 (each 3H, s, CH_3O), 3.49–3.73 (8H), 3.79–3.85 (3H), 4.00 (1H, dd, J=7.8, 9.8 Hz, C6′HH or C6″HH), 4.05 (1H, dd, J=1.5, 10.7 Hz, C6HH), 4.58 (1H, d, J=3.0 Hz, C1″H), 4.61 (1H, d, J=8.3 Hz, C1′H), 4.63 (1H, d, J=4.4 Hz, C1H), 4.81, 4.94 (each 1H, d, J=6.3 Hz, OCHHO), FD-MS (rel. int., %) m/z=617 (100, [M+Na]$^+$), FD-HRMS; found: m/z 617.1536. Calcd for $C_{21}H_{38}O_{15}S_2Na$: [M+Na]$^+$, 617.1550.

4.23.3. Removal of the MOM group under acidic conditions giving β-58. Treatment of the nonanol obtained in Section 4.23.2. (7.0 mg, 11.8 μmol) in a similar manner as described in Section 4.22.3 followed by also a similar purification gave the β-**58** (2.6 mg, 40%) as an oil. $[\alpha]_D^{23}$=−75.0 (c 0.20, H_2O), IR spectrum was not measured because this sample was soluble only in H_2O. ^{1}H NMR (D_2O) δ 3.19–3.25 (2H, m, C5′H, C5″H), 3.39 (1H, t, J=9.3 Hz, C3′H or C3″H), 3.49 (3H, s, CH_3O), 3.54 (1H, t, J=9.8 Hz, C4H), 3.61 (1H, dd, J=3.4, 9.8 Hz, C2H), 3.64–3.76 (6H, m), 3.82 (1H, m, C5H), 3.89–4.01 (4H, m), 4.07–4.15 (2H, [C6HH, C6′HH] or [C6HH, C6″HH]), 4.70 (1H, d, J=9.3 Hz, C1′H), 4.80 (1H, d, J=2.4 Hz, C1″H), 4.84 (1H, d, J=3.4 Hz, C1H), FAB-MS (negative mode, rel. int., %) m/z=549 (11, [M−H]$^-$), 195 (50, [$C_6H_{11}O_5S$]$^-$), 148 (100), FAB-HRMS (negative mode); found: m/z 549.1318. Calcd for $C_{19}H_{33}O_{14}S_2$: [M−H]$^-$, 549.1312.

5. Supporting information

^{1}H NMR spectra are given for new compounds.

Acknowledgements

Part of this work was supported by Grant-in-Aid for Scientific Research (No. 12780434) from the Ministry of Education, Science, Sports, and Culture of Japan. The authors would like to thank Professor Jun Kawabata and Dr. Eri Fukushi of Hokkaido University for measurements of mass spectra. The authors are grateful to Professor Kazuo Miyairi of Hirosaki University for fruitful discussions.

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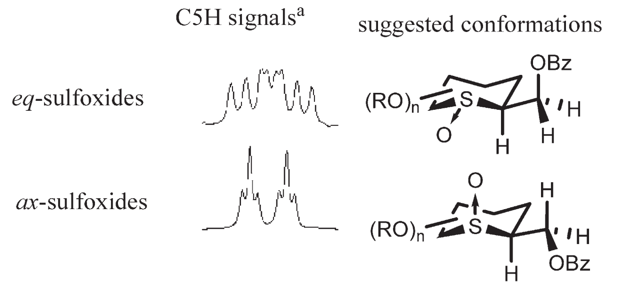
24. Interestingly, the configuration of the sulfoxide influences the conformation around its C5–C6 bonds. The signal patterns of the C5H in ^{1}H NMR spectrum clearly divided into two groups, the *ax*- and *eq*-sulfoxide groups. The coupling constants between C5H and both of the C6 methylene protons in the equatorial sulfoxides *eq*-**9**–**12** were 2.5–5.4 Hz, which suggests that the relationship between H5 and H6 and H6′ of the equatorial isomers were both *gauche*, that is the conformation about the C5–C6 bond is *gg*. In contrast, the sizes of the coupling constants between H5 and one of the two H6s for the corresponding axial sulfoxides of **9**–**12** were large (9.3–11.7 Hz), indicating that these protons had an *anti* relationship. It appears that the potential 1,3-diaxial relationship with the equatorial oxygen atom O-4 causes the *tg* conformation be of high energy and similarly the potential 1,3-diaxial relationship with the axial sulfoxide oxygen atom causes the *gg* conformation be of high energy. Thus, the axial sulfoxides of **9**–**12** adopt the *tg* conformations about the C5–C6 bond almost exclusively, as shown.



(a) The figure shows the C5H proton signals observed in ***eq-11*** *and* ***ax-11****.*

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37. Very small differences were observed in the chemical shifts for the C1H*ax* (Δδ 0.012 ppm), the remained C6H (Δδ 0.018 ppm), and C2H (Δδ 0.009 ppm) due to the isotope effect as shown in Figure 3 of the text.
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Tetrahedron 60 (2004) 6853–6857
Tetrahedron

A straightforward anionic coupling for the synthesis of *ortho*-bromobiaryls

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Received 22 April 2004; revised 26 May 2004; accepted 3 June 2004

Available online 4 July 2004

Abstract—Non-catalyzed anionic coupling of aryllithiums with 1,2-dibromobenzene gives straightforward access to valuable *ortho*-bromobiaryls.

1. Introduction

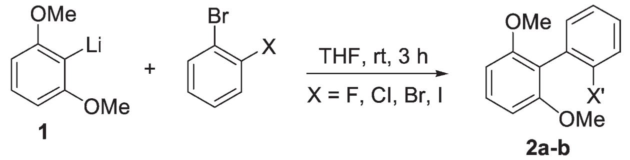
In recent years, *ortho*-functionalized biaryls have been found as central motifs of active molecules in various therapeutic areas[1,2] and molecular recognition devices.[3] Such biaryl structures are usually prepared through Pd-catalyzed Stille or Suzuki cross-coupling reactions[4] of *ortho*-functionalized precursors.[5] However, these methods have some drawbacks. For instance, the Stille coupling requires the use of toxic tin reagents and both cross-couplings precursors are often tedious to prepare and require expensive reactants. The alternative route, by functionalization of an *ortho*-bromobiaryl through metal–halogen exchange and subsequent reaction with various electrophiles, offers another synthetic strategy. However, here again, the synthesis of the *ortho*-halobiaryl intermediate is not often straightforward since it is achieved through a Pd-catalyzed cross-coupling reaction.[5] In a previous paper[6] we have shown that, contrary to the common belief,[7] aryllithiums react with 2-chloroanisole to afford regiospecifically 2-methoxybiaryls. These results, together with previous reports of Gilman[8] and Schlosser,[9] prompted us to investigate whether other classes of substrates, and particularly 1,2-dihalobenzenes, could undergo a similar regiospecific reaction and thus provide easy access to synthetically valuable *ortho*-halobiaryls.

In 1957, Gilman and Gaj observed that 2 equiv. of 1,2-dibromobenzene react with 1 equiv. of *n*-BuLi in THF at −78 °C to give 2,2′-dibromo-biphenyl in 74% yield.[8] More recently, taking advantage of this homocoupling reaction, Schlosser reported the synthesis of halogenated biaryls featuring uncommon substitution patterns.[9] Building on these reports and on our previous work, we show herein that non-catalyzed anionic coupling of aryllithiums with 1,2-dibromobenzene provides efficient access to valuable *ortho*-bromobiaryls.

2. Results and discussion

Addition of 1 equiv. of 1,2-dibromobenzene to a solution containing 1.2 equiv. of 2-lithio-1,3-dimethoxybenzene (2-lithio-1,3-DMB) **1** in THF at rt for 3 h gives regiospecifically the expected *ortho*-bromobiaryl structure in 95% yield (Table 1, entry 1). While the condensation is rapid at rt, it proceeds at −78 °C in 6 h. The aryllithium **1** reacts with various 1-bromo-2-halobenzenes. 1-Bromo-2-chlorobenzene (entry 2) and 1-bromo-2-fluorobenzene (entry 3) afford regiospecifically the expected *ortho*-bromobiaryl **2a** in 70 and 63% yields, respectively. Interestingly, this *ortho* isomer is regiospecifically obtained

Table 1. Reaction of 2-lithio-1,3-DMB and 1,2-dihalobenzenes



Entry	X	X′	Product	Yield (%)[a]
1	Br	Br	**2a**	95
2	Cl	Br	**2a**	70
3	F	Br	**2a**	63
4	I	I	**2b**	77

[a] Isolated yields.

Keywords: C–C Coupling; Biaryls; Metallation; Synthetic methods.
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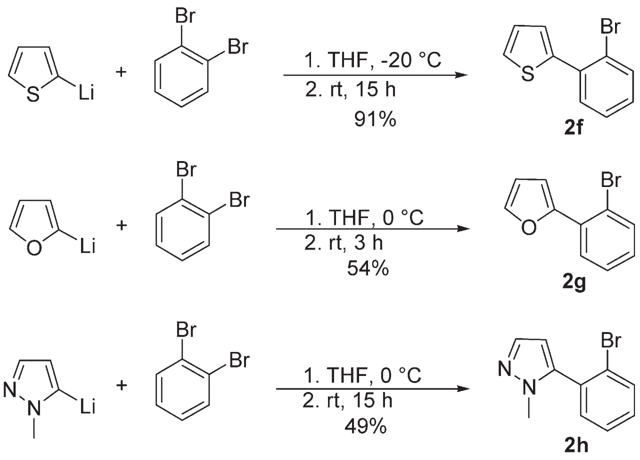
doi:10.1016/j.tet.2004.06.010

and the yield decreases from 1,2-dibromobenzene to 1-bromo-2-fluorobenzene. Finally, 1-bromo-2-iodobenzene (entry 4) gives the *ortho*-iodobiaryl **2b** regiospecifically in 77% yield.

The reaction could proceed as might be expected, via a transient aryne intermediate generated either by abstraction of the proton *ortho* to the halogen[7c] or via an X′/Li exchange reaction.[9] In the first case, supposing that the 1,2-dihalobenzenes undergo coupling reaction under the same mechanism, 1-bromo-2-fluorobenzene would be the most reactive substrate.[6,7c] Moreover, an ambivalent aryne intermediate would be likely to afford a mixture of isomers. Also, in that case, 2 equiv. of the aryllithium would be necessary to obtain a high coupling yield. In the second case, bromoarene by-products resulting from a Br/Li exchange reaction are expected (entries 1–3). However, such brominated by-products were never observed by GC/MS analysis of the crude reaction mixtures. In addition, no transient aryne intermediate could be trapped through formation of a Diels–Alder cycloadduct when the reaction was performed in the presence of 10 equiv. of furan. For all these reasons, the aryne mechanism might be disqualified. Alternatively, the reaction could proceed through an $S_{RN}1$ pathway due to the high propensity of electron rich aryllithiums to act as electron donors.[10] In order to examine the validity of an $S_{RN}1$ mechanism, we performed the coupling reaction of **1** with 1,2-dibromobenzene in the absence of light.[10] Again **2a** was generated in an excellent 94% yield. Similarly, in the presence of a radical scavenger like TEMPO,[10] **2a** was obtained in 80% yield. These experimental evidences disqualify the 'aryne' and the 'electron transfer' pathways. We next considered the validity of a SN_{Ar} mechanism. As shown in Table 1, the reactivity of the 1-bromo-2-halobenzenes is increased with the decrease of the alpha-acidifying (F>Cl>Br) and the increase of the leaving group ability of the halogen (F>Cl>Br).[7c] As in our previous paper, experimental results—reactivity, stoichiometry, regio-specificity, presence of a radical scavenger—support a direct nucleophilic substitution pathway. Further mechanistic investigations are currently in progress in order to further demonstrate the validity of the SN_{Ar} mechanism.

We have extended the scope of this reaction by coupling various aryllithium species, generated under classical *ortho*-metallation conditions, with 1,2-dibromobenzene (Table 2).

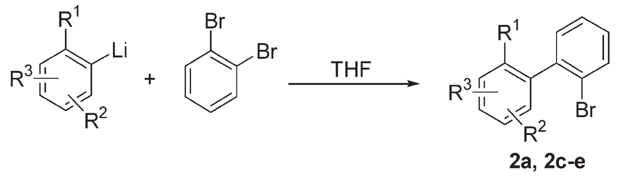
2-Lithio-1,3-DMB (entry 1) and 2-lithio-1,3,5-trimethoxybenzene (entry 2) both afford the desired *ortho*-bromobiaryl structure in an excellent 95% yield. 2-Lithio-4-methylanisole (entry 3) gives the expected biaryl in 67% yield. Noteworthy, the temperature sensitive 2-lithio-1,3-difluorobenzene[11] (entry 4) also gives the expected *ortho*-bromobiaryl at −78 °C in 81% yield, showing that this reaction can be used successfully for sensitive substrates. Surprisingly, no reaction occurs with the aryllithiums derived from phenyloxazoline[12] and *N*-*tert*-butylbenzamide.[13] In the later case, only 2-bromo-*N*-*tert*-butylbenzamide that results from a halogen–metal exchange reaction is isolated. Finally, the reaction of α-metallated heterocycles like 2-lithio-thiophene,[14] 2-lithio-furan,[15] or 2-lithio-methylpyrazole,[16] with 1,2-dibromobenzene, gives the desired *ortho*-bromobiaryls in 91, 54 and 49% isolated yields, respectively (Scheme 1).



Scheme 1. Reaction of α-metallated heterocycles with 1,2-dibromobenzene.

In the next part of our work, 2-lithio-1,3-DMB was reacted with 1,2-, 1,3- and 1,4-dibromobenzene (Table 3). While 2-lithio-1,3-DMB reacts with 1,2-dibromobenzene (entry 1) and gives the *ortho*-bromobiaryl in 95% yield, 1,3-dibromobenzene (entry 2) leads to a statistical mixture of *meta* and

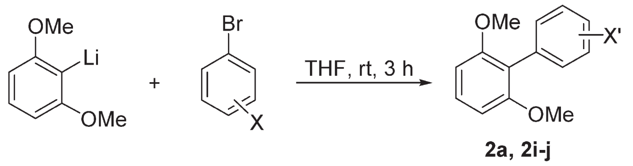
Table 2. Reaction of aryllithiums and 1,2-dibromobenzene



Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1[b]	1-OMe	3-OMe	H	**2a**	95
2	1-OMe	3-OMe	5-OMe	**2c**	95
3	1-OMe	4-Me	H	**2d**	67
4[c]	1-F	3-F	H	**2e**	81

[a] Isolated yields.
[b] See Section 3.
[c] Reaction performed at −78 °C.

Table 3. Reaction of 2-lithio-1,3-DMB with 1,2-; 1,3- and 1,4-dibromobenzene



Entry	X	X′	Product	Yield (%)[a]
1	2-Br	2-Br	**2a**	95
2	3-Br	3-+4-Br[b]	**2i**	57
3	4-Br	4-Br	**2j**	34[c]

[a] Isolated yields.
[b] Traces of *meta* and *para* terphenyls are observed.
[c] Starting material is recovered.

para biaryls arising from addition of 2-lithio-1,3-DMB to the transient aryne intermediate in 57% yield together with traces of terphenyls. 1,4-Dibromobenzene (entry 3) affords the *para*-bromobiaryl in 34% yield in accordance with an early observation of Gilman.[8]

Finally, we studied the *ortho*-functionalization of the *ortho*-bromobiaryls by reacting **2a** with *n*-butyllithium in THF at 0 °C during 2 h, followed by quenching the resulting aryllithium with benzaldehyde. The expected alcohol is quantitatively isolated, asserting the synthetic potential of *ortho*-bromobiaryls.

In conclusion, we have developed a simple and inexpensive method for the synthesis of *ortho*-bromobiaryls building blocks that are valuable intermediates toward complex *ortho*-substituted biaryl structures. Our coupling procedure was efficiently carried out on a 1 mol scale without any noticeable difficulty or loss in efficiency. The reported results, together with our previous report, open new prospects into non-catalyzed anionic coupling. Other classes of substrates are currently under reinvestigation to expand the scope of this synthetically useful non-catalyzed reaction.

3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra are recorded using whether a 200 or 300 MHz instrument in $CDCl_3$ with the solvent residual peak ($CDCl_3$: ^{1}H=7.27 ppm, ^{13}C=77.0 ppm). Chemical shifts are reported in parts per million (∂) downfield from TMS. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet) and m (multiplet). IR absorbances are reported in reciprocal centimeters (cm^{-1}). The mass spectra are recorded on a Finnigan-Mat 4600 mass spectrometer by the ionization technique using ammonia gas. Tetrahydrofuran (THF) is distilled from sodium/benzophenone. All biaryls syntheses using our methodology are performed in flame dry glassware under argon atmosphere.

3.2. Typical procedure for the synthesis of 2a–d

n-Butyllithium (1.6 M solution in hexane, 1.56 mL, 2.5 mmol, 1.2 equiv.) is added dropwise at rt under an atmosphere of argon to a solution of 1,3-dimethoxybenzene (0.33 mL, 2.5 mmol, 1.2 equiv.) in anhydrous THF (8 mL). The reaction mixture is stirred for 1 h at rt. Then, 1-bromo-2-halobenzene (2.1 mmol, 1 equiv.) is added dropwise at rt. After stirring for another 3 h at rt, the reaction mixture is quenched by addition of H_2O (10 mL). The aqueous layer is extracted twice with Et_2O (total 30 mL) and the combined organic layers are dried over $MgSO_4$, filtered under vacuum and concentrated under reduced pressure. The residue is purified by flash silica gel chromatography to yield the corresponding *ortho*-bromobiaryls.

3.2.1. 2′-Bromo-2,6-dimethoxybiphenyl (2a). Colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 6H), 6.69 (d, *J*=8.7 Hz, 2H), 7.21–7.41 (m, 4H), 7.69 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.9, 103.9, 118.9, 125.1, 126.8, 128.5, 129.4, 132.2, 135.9, 157.5. IR (CH_2Cl_2): 3003, 2941, 1599, 1587, 1473, 1432, 1248, 1111, 905, 732. MS: $[M+NH_4]^+$=311. Elemental analysis calcd (%) for $C_{14}H_{13}BrO_2$ (293.16): C 57.36, H 4.47, Br 27.26, O 10.92; found C 57.24, H 4.46, O 11.02.

3.2.2. 2′-Iodo-2,6-dimethoxybiphenyl (2b). Colorless solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.74 (s, 6H), 6.67 (d, *J*=8.3 Hz, 2H), 6.99–7.47 (m, 4H), 7.96 (dd, *J*=7.8, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.9, 101.9, 104.0, 122.1, 127.7, 128.5, 129.4, 131.1, 138.6, 140.5, 157.4. IR (CH_2Cl_2): 3054, 2935, 1597, 1589, 1470, 1248, 1111, 907, 732. MS: $[M+H]^+$=341. Elemental analysis calcd (%) for $C_{14}H_{13}IO_2$ (340.16): C 49.43, H 3.85, I 37.31, O 9.41; found C 49.21, H 3.88, O 9.37.

3.2.3. 2′-Bromo-2,4,6-trimethoxybiphenyl (2c). Colorless solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.77 (s, 6H), 3.92 (s, 3H), 6.27 (s, 2H), 7.16–7.41 (m, 3H), 7.69 (dd, *J*=8.1, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.3, 55.9, 90.7, 111.9, 125.9, 126.8, 128.4, 132.2, 132.8, 136.0, 158.3, 161.2. IR (CH_2Cl_2): 3054, 2982, 1610, 1582, 1465, 1264, 1130, 745. MS: $[M+H]^+$=324. Elemental analysis calcd (%) for $C_{15}H_{15}BrO_3$ (323.18): C 55.75, H 4.68, Br 24.72, O 14.85; found C 55.91, H 4.61, O 14.79.

3.2.4. 2′-Bromo-2-methoxy-5-methylbiphenyl (2d). Colorless solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.37 (s, 3H), 3.77 (s, 3H), 6.91 (d, *J*=8.3 Hz, 2H), 7.01 (d, *J*=2.2 Hz, 1H), 7.15–7.42 (m, 4H), 7.68 (dd, *J*=7.8, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4, 55.7, 111.2, 124.2, 127.0, 128.5, 129.4, 129.6, 130.0, 131.4, 131.5, 132.4, 140.0, 154.5. IR (CH_2Cl_2): 3049, 2946, 1610, 1589, 1558, 1504, 1465, 1277, 1248, 1181, 1145, 1034, 807, 750. MS: $[M+NH_4]^+$=295. Elemental analysis calcd (%) for $C_{14}H_{13}BrO$ (277.16): C 60.67, H 4.73, Br 28.83, O 5.77; found C 60.79, H 4.76, O 5.89.

3.2.5. 2′-Bromo-2,6-difluorobiphenyl (2e). A solution of 1,3-difluorobenzene (0.49 mL, 5.0 mmol, 1.2 equiv.) in anhydrous THF (1.5 mL) is added dropwise at −78 °C under an atmosphere of argon to a solution of *n*-butyllithium (1.6 M solution in hexane, 3.13 mL, 5.0 mmol, 1.2 equiv.). The reaction mixture is stirred at −78 °C for 1 h. Then, 1,2-dibromobenzene (0.50 mL, 4.17 mmol, 1 equiv.) is added dropwise at −78 °C. The reaction mixture is warmed to rt during 12 h, then quenched by addition of H_2O (10 mL). The aqueous layer is extracted twice with Et_2O (total 30 mL) and the combined organic layers are dried over $MgSO_4$, filtered under vacuum and concentrated under reduced pressure. The residue is purified by flash silica gel chromatography (hexane) to yield **2e** as a colorless solid in 81% yield (910 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.94–7.06 (m, 2H), 7.12–7.51 (m, 4H), 7.72 (d, *J*=8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 111.1 (d, *J*=1.8 Hz), 117.9 (t, *J*=21.0 Hz), 124.4, 127.1, 129.9 (t, *J*=10.1 Hz), 130.8, 131.9, 132.7, 158.2 (d, *J*=6.4 Hz), 161.9 (d, *J*=6.4 Hz). IR (CH_2Cl_2): 3054, 2987, 1628, 1579, 1465, 1264, 1233, 1006, 742, 706. MS: $[M+NH_4]^+$=287. Elemental analysis calcd (%) for $C_{12}H_7BrF_2$ (269.08): C 53.56, H 2.62, Br 29.69, O 14.12; found C 53.76, H 2.59, O 14.26.

3.2.6. 2-(2-Bromophenyl)thiophene (2f). *n*-Butyllithium (1.6 M solution in hexane, 5.62 mL, 9.0 mmol, 3 equiv.) is added dropwise at −40 °C under an atmosphere of argon to a solution of thiophene (0.72 mL, 9.0 mmol, 3 equiv.) in anhydrous THF (7 mL). The reaction mixture is stirred for 1 h at −20 °C. Then, 1,2-dibromobenzene (0.36 mL, 3.0 mmol, 1 equiv.) is added dropwise at −20 °C. The reaction mixture is warmed to rt during 15 h, then quenched by addition of H_2O (10 mL). The aqueous layer is extracted twice with Et_2O (total 30 mL) and the combined organic layers are dried over $MgSO_4$, filtered under vacuum and concentrated under reduced pressure. The residue is purified by flash silica gel chromatography (hexane) to yield **2f** as a colorless oil in 91% yield (653 mg). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09–7.59 (m, 6H), 7.72 (dd, J=8.1, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 122.7, 125.9, 126.8, 127.3, 127.6, 128.8, 131.8, 133.5, 135.1, 141.5. IR (CH_2Cl_2): 3054, 1558, 1468, 1432, 1261, 1029, 851, 755, 703. MS: $[M+H]^+$=240. Elemental analysis calcd (%) for $C_{10}H_7BrS$ (239.13): C 50.23, H 2.95, Br 33.41, S 13.41; found C 50.37, H 2.93, S 13.24.

3.2.7. 2-(2-Bromophenyl)furan (2g). *n*-Butyllithium (1.6 M solution in hexane, 5.19 mL, 8.3 mmol, 2.8 equiv.) is added dropwise at −10 °C under an atmosphere of argon to a solution of furan (0.65 mL, 9.0 mmol, 3 equiv.) in anhydrous THF (9 mL). The reaction mixture is stirred for 3 h at −10 °C. Then, 1,2-dibromobenzene (0.36 mL, 3.0 mmol, 1 equiv.) is added dropwise at 0 °C. The reaction mixture is warmed to rt during 3 h, then quenched by addition of H_2O (10 mL). The aqueous layer is extracted twice with Et_2O (total 30 mL) and the combined organic layers are dried over $MgSO_4$, filtered under vacuum and concentrated under reduced pressure. The residue is purified by flash silica gel chromatography (hexane) to yield **2g** as a colorless oil in 54% yield (361 mg). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.57 (dd, J=3.4, 1.9 Hz, 1H), 7.05–7.75 (m, 5H), 7.82 (dd, J=7.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 110.5, 111.4, 119.6, 127.3, 128.3, 128.7, 131.2, 134.0, 142.1, 151.2. IR (CH_2Cl_2): 3059, 2920, 1757, 1706, 1589, 1468, 1429, 1261, 1026, 758. $[M+H]^+$=224. Elemental analysis calcd (%) for $C_{10}H_7BrO$ (223.07): C 53.84, H 3.16, Br 35.82, O 7.17; found C 53.99, H 3.18, O 7.14.

3.2.8. 5-(2-Bromophenyl)-1-1*H*-methyl-pyrazole (2h). *n*-Butyllithium (1.6 M solution in hexane, 1.88 mL, 3.0 mmol, 1 equiv.) is added dropwise at 0 °C under an atmosphere of argon to a solution of *N*-methyl-pyrazole (0.25 mL, 3.0 mmol, 1 equiv.) in anhydrous THF (5 mL). The reaction mixture is stirred for 2 h at 0 °C. Then, 1,2-dibromobenzene (1.09 mL, 9.0 mmol, 3 equiv.) is added dropwise at 0 °C. The reaction mixture is warmed to rt during 15 h, then quenched by addition of H_2O (10 mL). The aqueous layer is extracted twice with Et_2O (total 30 mL) and the combined organic layers are dried over $MgSO_4$, filtered under vacuum and concentrated under reduced pressure. The residue is purified by flash silica gel chromatography (hexane) to yield **2h** as a colorless solid in 49% yield (348 mg). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.73 (s, 3H), 6.28 (d, J=1.3 Hz, 1H), 7.24–7.43 (m, 3H), 7.55 (d, J=1.3 Hz, 1H), 7.70 (d, J=6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.9, 106.8, 124.4, 127.3, 130.5, 131.2, 132.2, 132.9, 138.2, 141.8. IR (CH_2Cl_2): 3054, 2941, 1600, 1561, 1470, 1421, 1390, 1282, 1225, 1176, 1026, 980, 931, 758. $[M+H]^+$=238. Elemental analysis calcd (%) for $C_{10}H_9BrN_2$ (237.10): C 50.66, H 3.83, Br 33.70, N 11.82; found C 50.79, H 3.85, N 11.71.

Acknowledgements

This work was supported by the Ministère de l'Education Nationale, de la Recherche et de la Technologie through a MENRT grant to J. -M. Becht.

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An expeditious total synthesis of kalkitoxins: determination of the absolute stereostructure of natural kalkitoxin☆

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Received 22 February 2004; revised 14 May 2004; accepted 3 June 2004

Abstract—Kalkitoxin, a potent neurotoxin isolated from the marine cyanobacteria *Lyngbya majuscula*, and its congeners (**1**–**7**) were efficiently synthesized utilizing Hruby's diastereoselective 1,4-addition and the Wipf's oxazoline-thiazoline conversion as key steps. These synthetic efforts in combination with spectral studies of natural kalkitoxin clearly determined the absolute stereostructure of kalkitoxin to be **7**.

1. Introduction

This paper describes an expeditious total synthesis of kalkitoxin, a novel potent neurotoxin, and its congeners via a highly convergent and versatile synthetic strategy, which clearly determined the absolute stereostructure of natural kalkitoxin. Kalkitoxin was isolated from the marine cyanobacterium *Lyngbya majuscula* aided by bioassay-guided fractionation using the brine shrimp and gold fish toxicity assays.[1,2] Kalkitoxin was revealed to be strongly ichthyotoxic to the common goldfish (*Carassius auratus*, LC_{50} 700 nM), potently brine shrimp toxic (*Artemia salina*, LC_{50} 170 nM), and potently inhibited cell division in a fertilized sea urchin embryo assay (IC_{50}~25 nM), while in a primary cell culture of rat neurons kalkitoxin displayed an exceptional level of neurotoxicity (LC_{50} 3.86 nM) and its effects were inhibitable with NMDA receptor antagonists.[3] In addition, kalkitoxin was highly active in an inflammatory disease model which measured IL-1β-induced $sPLA_2$ secretion from HepG2 cells (IC_{50} 27 nM). Furthermore, preliminary evidence suggests that kalkitoxin is a potent blocker of the voltage sensitive Na^+ channel in mouse neuro-2a cells (EC_{50} 1 nM).

Kalkitoxin is a lipoamide containing four methyl groups on the carbon chain and possessing five stereogenic centers, an *N*-methylamide, and a thiazoline ring. Free rotation around the chain precluded the NOE assignment of the structure, and the *N*-methylamide function causes restricted rotation resulting in a complex pattern in its NMR spectra. These structural characteristics precluded the determination of absolute stereostructure. In continuation of our interests on the total synthesis of biologically active aquatic natural products,[4,5] kalkitoxin's potent biological activity and limited natural availability prompted us to synthesize this unique molecule and its congeners and to determine its absolute configuration. Our synthetic efforts supplied kalkitoxin and its congeners (**1**–**7**), culminating in the determination of the absolute stereostructure of kalkitoxin to be **7** (Fig. 1).[1,6]

2. Synthetic strategy

When we initiated the synthetic studies of kalkitoxin, the stereochemical structure was still undetermined, which led us to adopt a highly flexible synthetic route to kalkitoxins having any possible stereostructure. As shown in Scheme 1, the whole molecule of kalkitoxin was divided into three building blocks **8**–**10**, of which the left fragment **8** is commercially available and the right fragment **10** would be

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.014

Keywords: Kalkitoxin; Marine cyanobacteria; Total synthesis; Absolute configuration; Stereoselective 1,4-addition.
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doi:10.1016/j.tet.2004.06.014

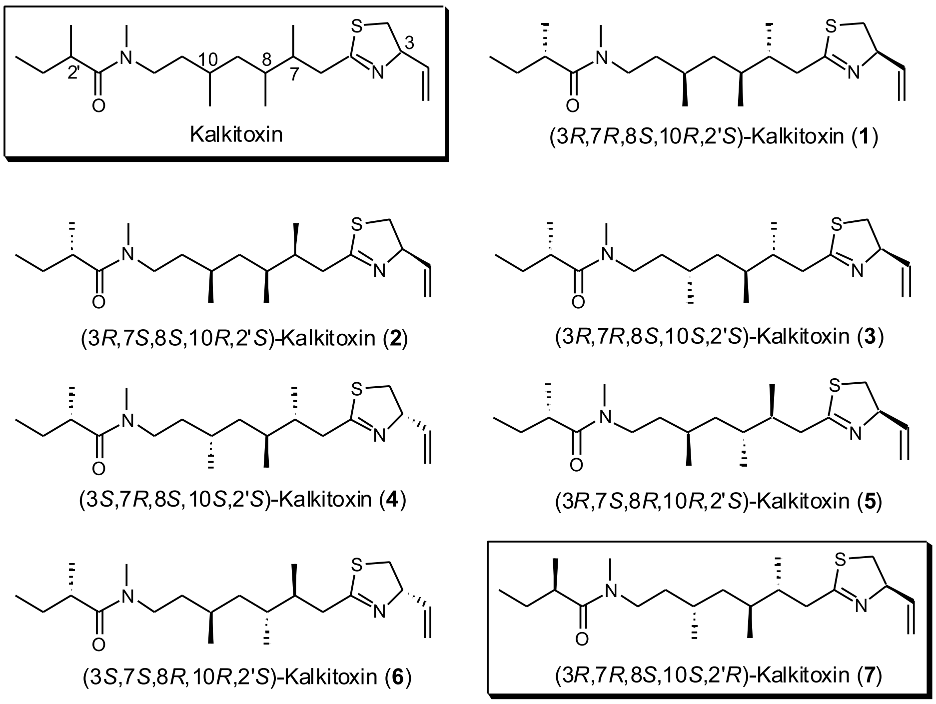
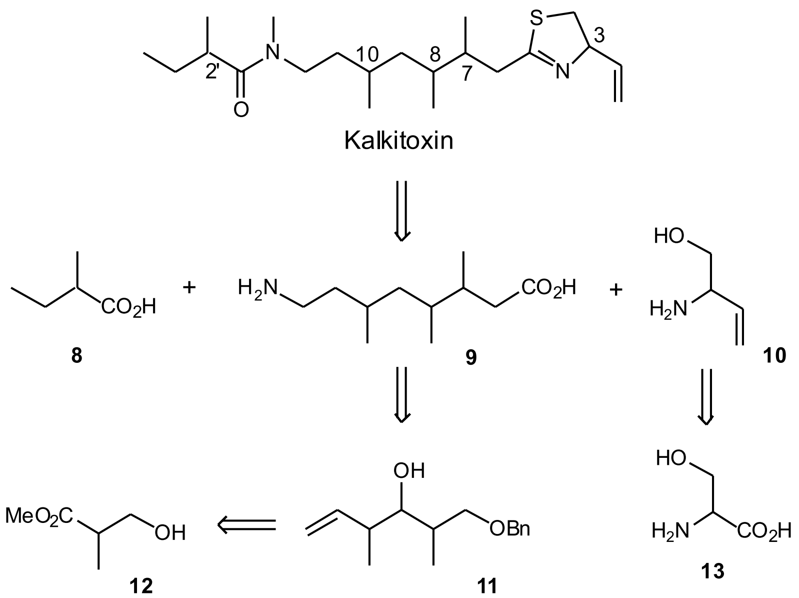


Figure 1.

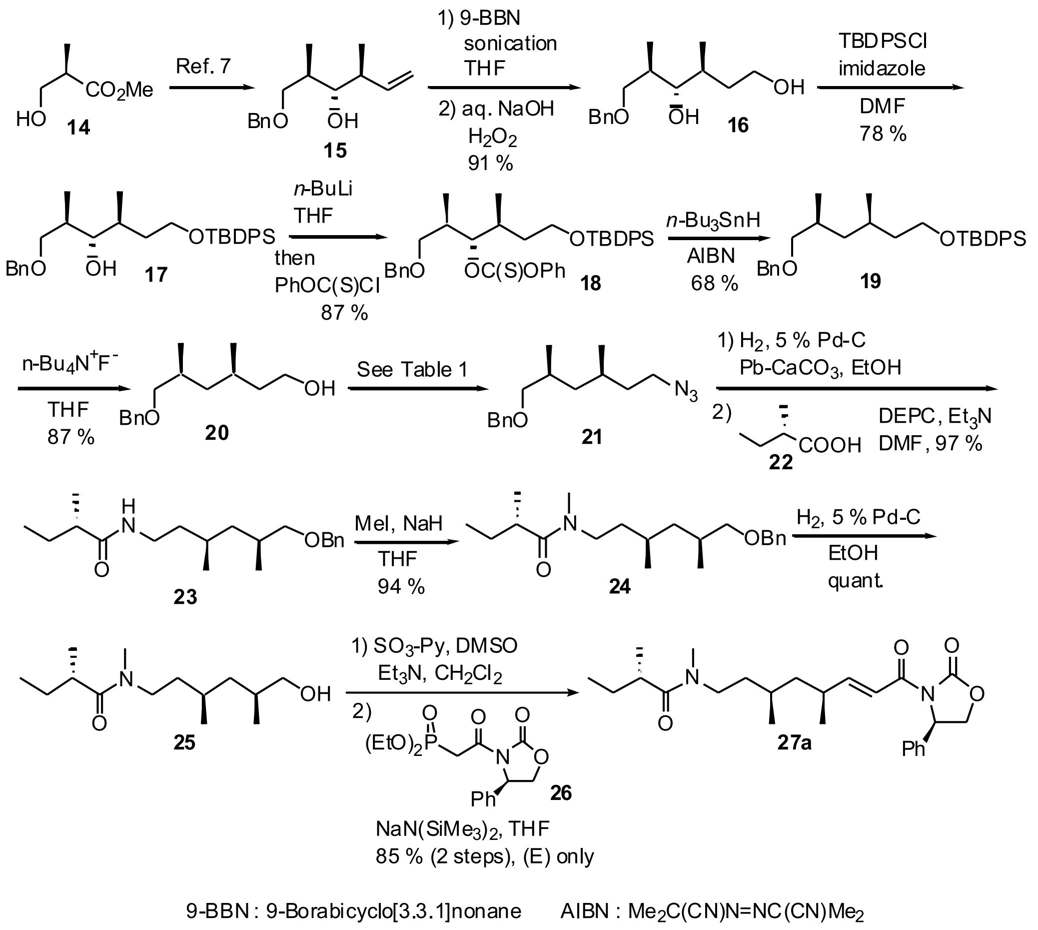


Scheme 1.

synthesized from serine (**13**). The central fragment **9** would be synthesized from methyl 3-hydroxy-2-methylpropionate (**12**) by asymmetric crotylation followed by deoxygenation of the resulting alcohol **11**. The stereogenic center at C7 would be introduced by 1,4-addition of the chiral oxazolidinone after coupling with the left fragment **8**. Since the thiazoline ring was thought to be fragile during synthesis, its construction should be carried out at the final stage of the synthesis. In addition, it was thought to be preferable that the starting materials adopted should be available in a stereochemically clear form and the reactions chosen should proceed in a highly stereoselective manner. According to this strategy, we launched the total synthesis of the kalkitoxins.

3. Results and discussion

We first started the synthesis of (3*R*,7*R*,8*S*,10*R*,2′*S*)-kalkitoxin (**1**) to establish the facile synthetic route toward kalkitoxins. The known[7] hexenol **15**, prepared from methyl (*R*)-3-hydroxy-2-methylpropionate (**14**) in 4 steps, was converted to the diol **16** by hydroboration with 9-BBN under sonication conditions[8] followed by oxidation, shown



Scheme 2.

in Scheme 2. After protection of the primary hydroxyl function with TBDPSCl (^{t}Bu(C_6H_5)$_2$SiCl), the secondary hydroxyl group of **17** was deoxygenated via the thiocarbonate **18** according to the Barton–McCombie procedure[9] by thiocarbonylation and then radical reduction. The deoxygenated product **19** was treated with TBAF ($Bu_4N^+F^-$) to give the alcohol **20**, which was converted to the azide **21** under various conditions, shown in Table 1. The ordinary two-step process of the mesylation and then azidation afforded the desired azide **21** in 88% yield. The one step procedure utilizing DPPA ((C_6H_5O)$_2$P(O)N_3) and DBU (1,8-diazabicyclo[5.4.0]unde-7-ene)[10] sluggishly proceeded at room temperature and required heating for a longer time. The use of *p*-NO_2-DPPA (*p*-NO_2–(C_6H_4O)$_2$P(O)N_3)[11] in place of DPPA accelerated the reaction and shortened the reaction time to give the azide **21** in good yield.

Table 1. One-pot azidation of using DPPA (C_6H_5O)$_2$P(O)N_3 or *p*-NO_2-DPPA (*p*-$NO_2C_6H_4O$)$_2$P(O)N_3

Entry	Reagent (equiv.)	Base (equiv.)	Reaction conditions	Yield (%)
1	DPPA (1.5)	DBU (1.5)	0 °C, 1.5 h; rt, 21 h	23[a]
2	DPPA (1.5)	DBU (1.5)	0 °C, 1.5 h; 65 °C, 21 h	97
3	*p*-NO_2-DPPA (1.5)	DBU (1.5)	0 °C, 1 h; rt, 7 h	79
4	*p*-NO_2-DPPA (1.5)	DBU (1.5)	0 °C, 1 h; 65 °C, 5 h	81

[a] Diphenyl phosphate was obtained in 63% yield.

The azide **21** thus obtained underwent catalytic hydrogenation over Lindlar catalyst[12] to give the corresponding amine, which was coupled with (*S*)-2-methylbutyric acid (**22**), the left fragment of kalkitoxins, by use of DEPC ((EtO)$_2$P(O)CN)[13] in the presence of triethylamine to produce the amide **23** in excellent yield. After the *N*-methylation, catalytic removal of the benzyl group from **24** afforded the alcohol **25**. The conversion of **25** to the (*E*)-enimide **27a** was smoothly accomplished by the Parikh–Doering oxidation[14] followed by the Horner–Wadsworth–Emmons reaction with the oxazolidinone **26** derived from (*R*)-phenylglycine.[15]

The next problem to overcome was the stereoselective introduction of the methyl group at the C7 position[16] by 1,4-addition. Hruby and co-workers[17] already revealed that the 1,4-addition of a methyl group into the optically active α,β-unsaturated acyl-4-phenyloxazolidinone by use of a combination of methyl magnesium bromide and cuprous bromide·dimethyl sulfide proceeded with high diastereoselectivity, and Romo and co-workers[15] utilized this method for the total synthesis of (−)-pateamine A. High stereoselectivity is explained by the fixed conformation due to the chelation of magnesium by the two carbonyl groups of the oxazolidinone and enimide, and by the attack of the methyl group from the opposite side of the phenyl group in the oxazolidinone, as shown in Figure 2.

Since both enantiomers of the 5-phenyloxazolidinone are

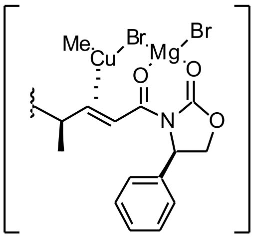
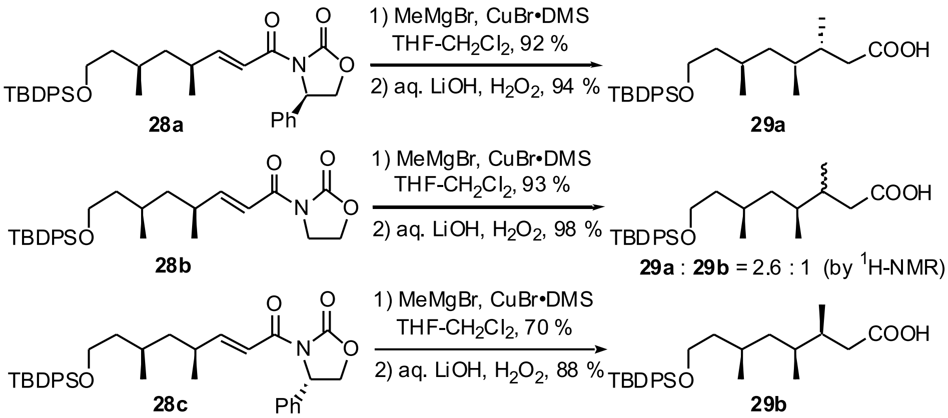


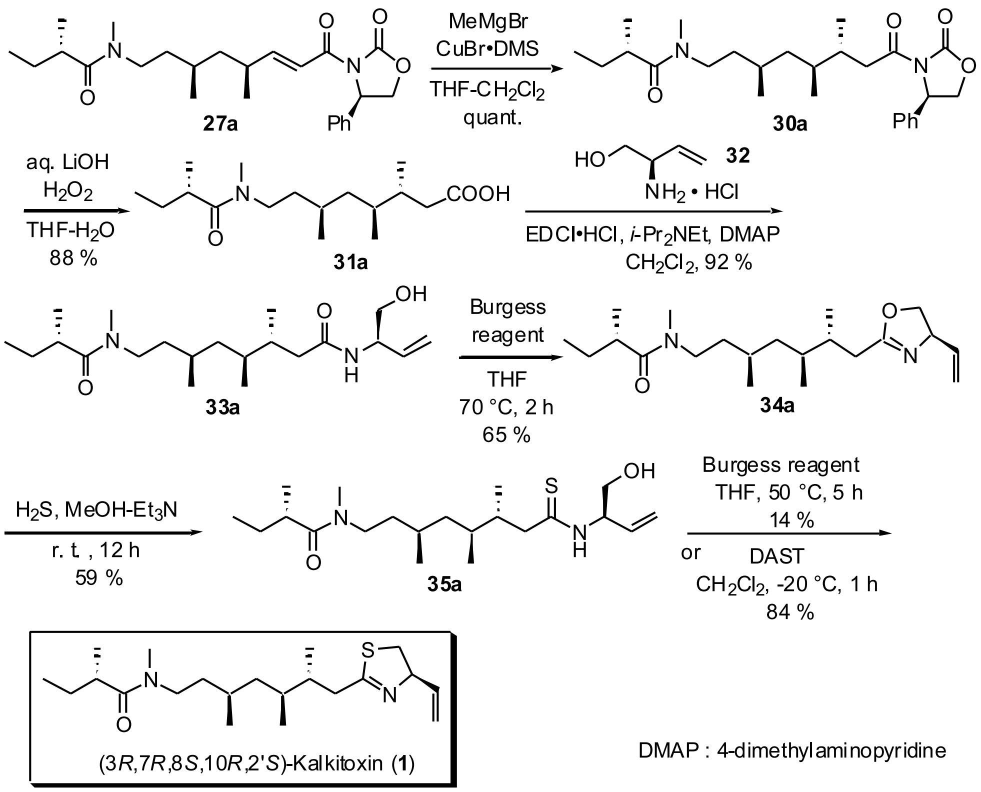
Figure 2.

easily available, their proper use will produce both enantiomers different at the C7 methyl function. This flexibility led us to adopt the Hruby's diastereoselective 1,4-addition method (Scheme 3).[18,19] Thus, the 1,4-addition reaction to the oxazolidinone **27a** was carried out under analogous conditions using methyl magnesium bromide and cuprous bromide·dimethyl sulfide, giving the (7*R*)-oxazolidinone **30a** quantitatively with complete stereoselectivity. Removal of the oxazolidinone moiety with alkaline hydrogen peroxide afforded the carboxylic acid **31a**.[20]

Coupling of the acid **31a** with (*R*)-2-amino-3-butenol hydrochloride (**32**)[21] smoothly proceeded by use of EDCI·HCl ($Me_2N(CH_2)_3$–N=C=N–Et) to give the amide **33a**, which was converted to the oxazoline **34a** with the Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$),[22] as shown in Scheme 4. Transformation of the oxazoline ring in **34a** to the thiazoline ring in kalkitoxin (**1**) was accomplished according to the method of Wipf.[23] Thus, treatment of the oxazoline **34a** with hydrogen sulfide led to ring-opening to give the thioamide **35a**, which underwent the recyclization with the Burgess reagent to give kalkitoxin



Scheme 3.



Scheme 4.

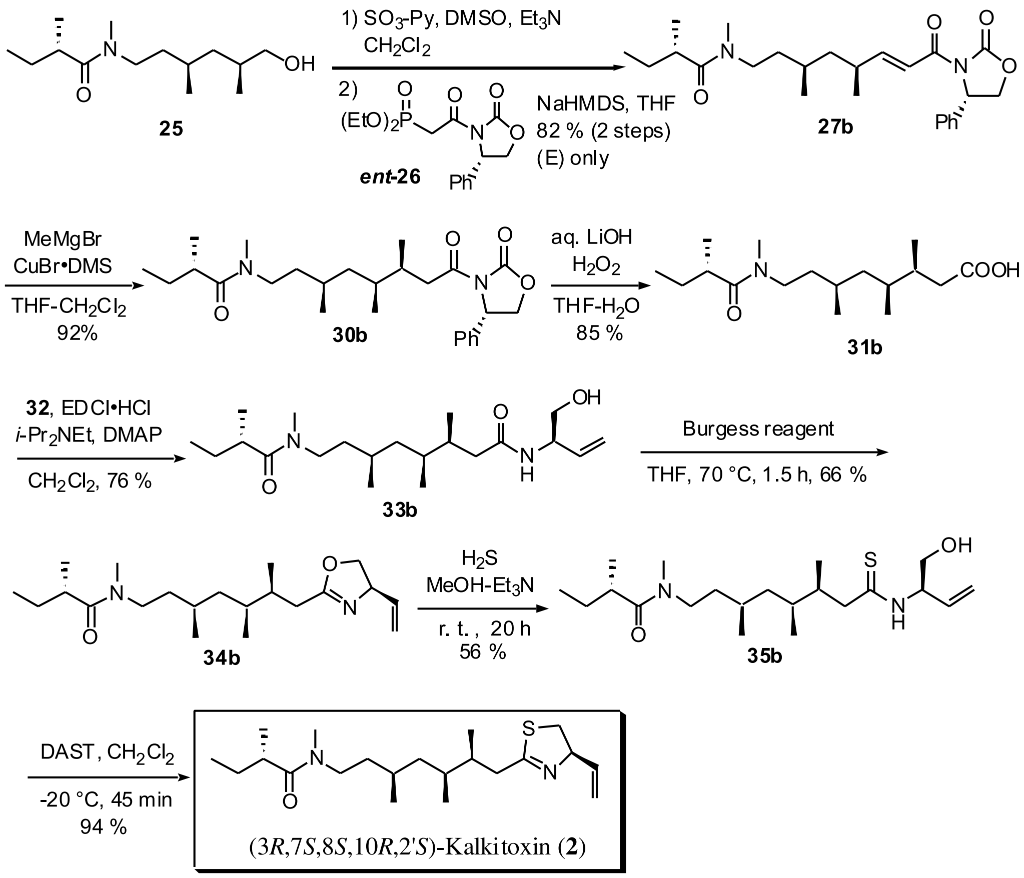
1 having (3*R*,7*R*,8*S*,10*R*,2′*S*)-configuration in 14% yield. Replacement of the Burgess reagent with DAST (Et_2NSF_3)[24] increased the yield to 84%.

Analogously, the enimide **27b** was synthesized by the oxidation of the alcohol **25** and then the Horner–Wadsworth–Emmons reaction with the (*S*)-phosphonate *ent*-**26**. The diastereoselective 1,4-addition of the methyl group to **27b**, followed by alkaline removal of the chiral auxiliary afforded the (7*S*)-carboxylic acid **31b**, which was coupled with **32** to give the amide **33b**. Analogous transformation of the amide **33b** as above produced kalkitoxin **2** with (3*R*,7*S*,8*S*,10R,2′S)-configuration, as shown in Scheme 5.

Although the kalkitoxin **1** exhibited a similar specific rotation, $[\alpha]_D=+15.5$, to that of natural kalkitoxin, $[\alpha]_D=+16$, the ^{13}C NMR spectra were slightly different from each other and, especially, the difference of 0.12–0.19 ppm was observed at the C10, C11, and *N*-methyl carbon signals. The ^1H NMR spectrum of **1** was also different at the chemical shift of the C10, C11, and C12 positions. The specific rotation of the kalkitoxin **2** was +49.6, and its ^{13}C NMR spectrum differed from that of the natural one at the signals of the C6 (δ 3.45 ppm) and C9 (δ 2.63 ppm) positions. In addition, the ^1H NMR spectrum was also not identical. These spectral features clearly showed that the synthesized kalkitoxins **1** and **2** have different stereochemistries from those of the natural product.

During the investigation of the above synthetic works, the Oregon group led by Gerwick determined the absolute configuration of the C3 position to be *R* [1,25] by obtaining cysteinic acid through ozonolysis and then acid hydrolysis of natural kalkitoxin and by identification of L-configuration through Marfey's analysis.[26] The relative stereochemistry of the three chiral centers within the aliphatic chain of kalkitoxin was also suggested to be 7*R**, 8*S**, and 10*S** by *J*-based configuration analysis[27] using the E.COSY NMR pulse sequence, HSQMBC,[28] and a cryoprobe NMR technology (see Supplementary data). Although the limited amount of natural kalkitoxin precluded determination of the C′2 stereochemistry, the above stereostructure studies reduced the total number of stereochemical possibilities to four: (3*R*,7*R*,8*S*,10*S*,2′*S*), (3*R*,7*R*,8*S*,10*S*,2′*R*), (3*R*,7*S*,8*R*,10*R*,2′*S*), or (3*R*,7*S*,8*R*,10*R*,2′*R*).

To determine the absolute configuration of natural kalkitoxin, the four kalkitoxins having possible configurations were synthesized. Since the 2-methylbutyric acid part is introduced at an early stage of our synthetic strategy (Scheme 2), efforts were required to synthesize kalkitoxins isomeric at the C2′ position. Thus the C2′ configuration of the intermediates was fixed to be *S*. Instead, both (3*R*)- and (3*S*)-isomers were synthesized because the thiazoline ring was introduced at the final stage of the synthesis. This strategy would furnish kalkitoxin having natural configuration or its antipode. Thus the (3*R*,7*R*,8*S*,10*S*,2′*S*), (3*S*,7*R*,8*S*,10*S*,2′*S*) (corresponding to the antipode of the

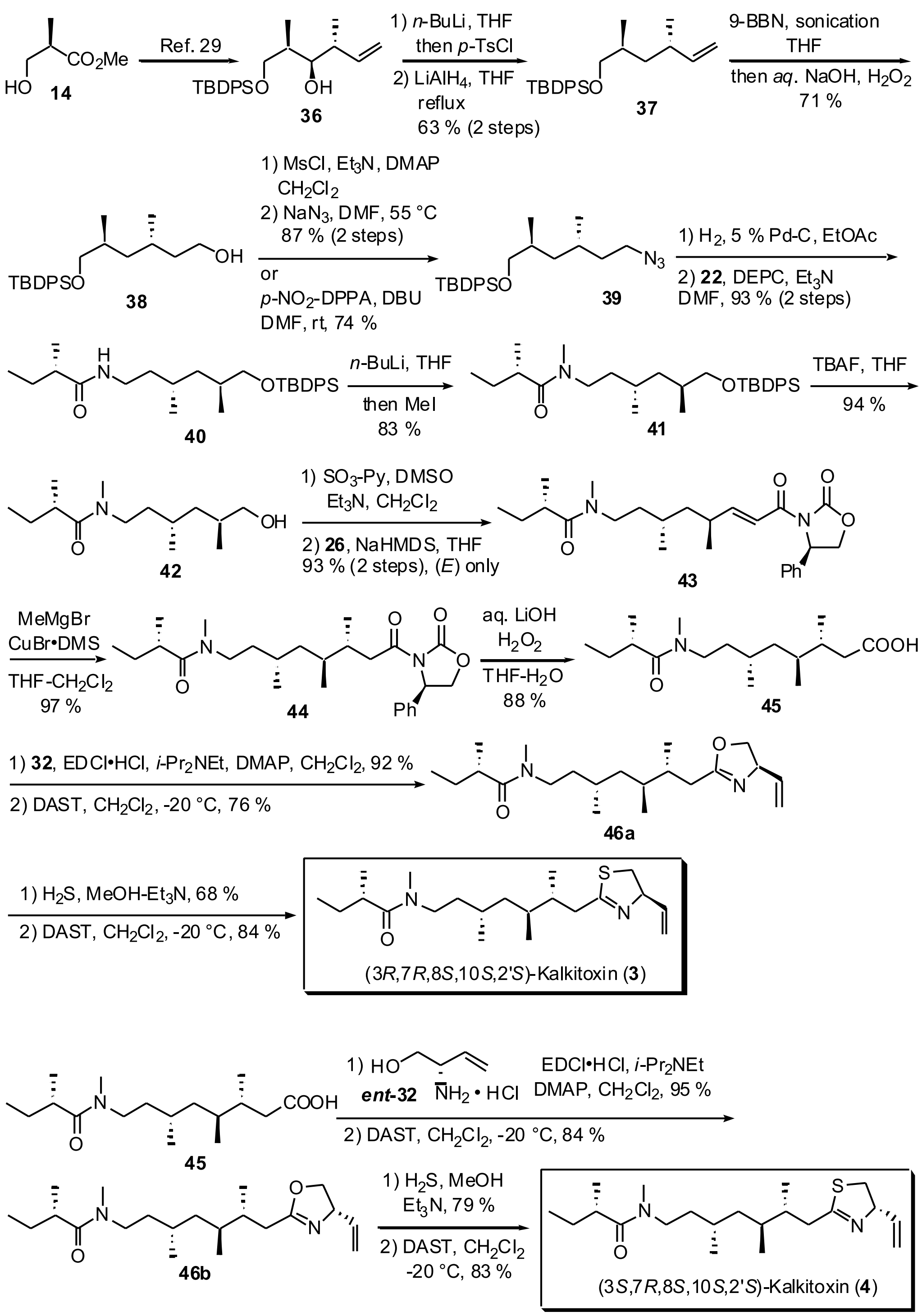


Scheme 5.

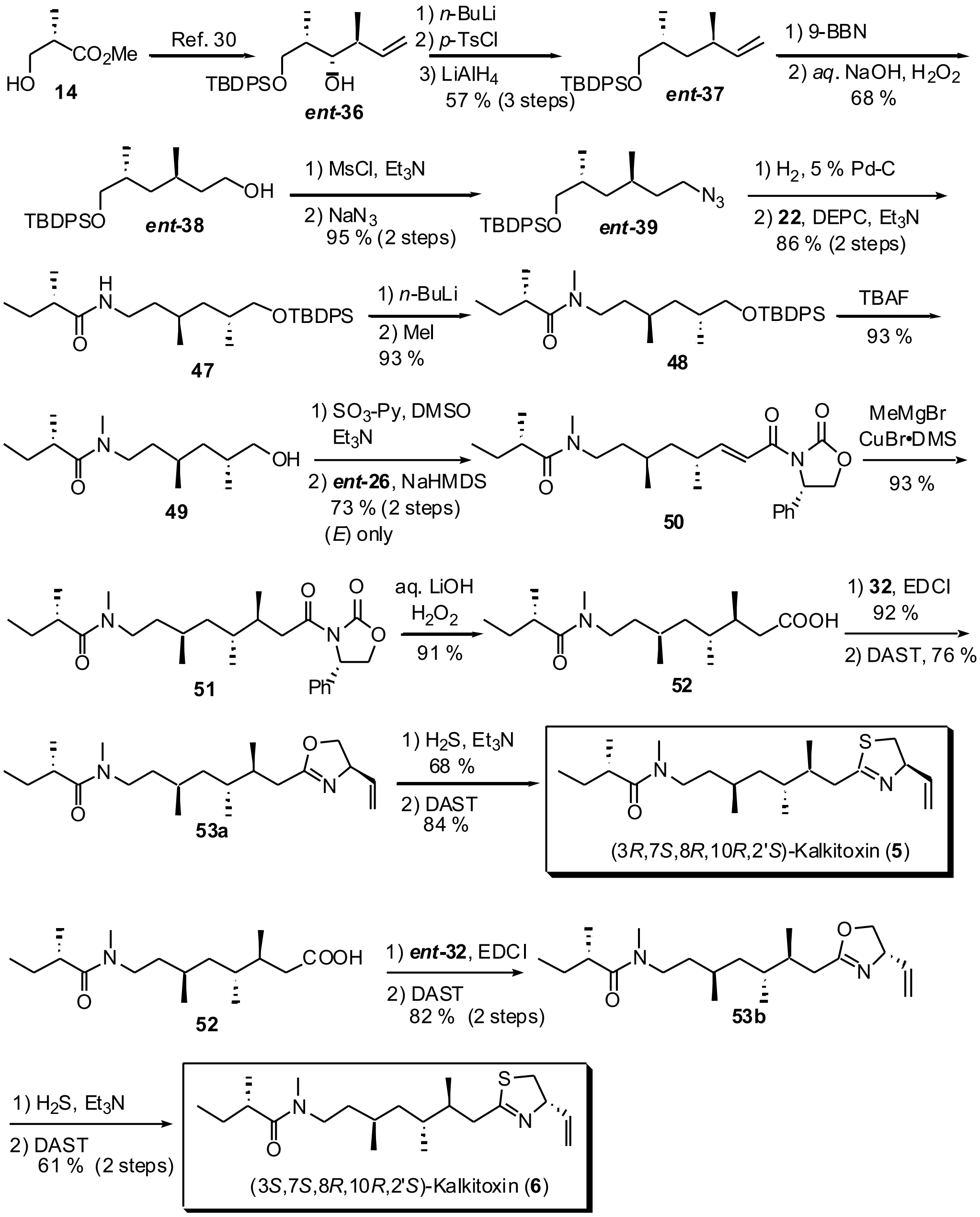
(3*R*,7*S*,8*R*,10*R*,2′*R*)-isomer), (3*R*,7*S*,8*R*,10*R*,2′*S*), and (3*S*,7*S*,8*R*,10*R*,2′*S*)-isomers (corresponding to the antipode of the (3*R*, 7*R*, 8*S*,10*S*,2′*R*)-isomer) were synthesized by use of analogous method, as shown in Schemes 6–8.

Starting from (*R*)-3-hydroxy-2-methylpropionic acid (**14**), the alcohol **36** with the TBDPS function was prepared according to the literature.[29] Removal of the hydroxyl group of **36** was carried out by tosylation followed by hydride reduction to give the deoxygenated compound **37**, as shown in Scheme 6. Sequence of the reactions analogous to the synthesis of **1** and **2** smoothly and stereoselectively afforded the carboxylic acid **45** utilizing (*S*)-2-methylbutyric acid (**22**) and the phosphonate **26**. Coupling of the acid **45** with (*R*)- and (*S*)-2-amino-3-buten-1-ol hydrochlorides (**32** and *ent*-**32**), followed by treatment with DAST, respectively, produced **46a** and **46b**, from which the thiazoline ring was constructed to give (3*R*,7*R*,8*S*,10*S*,2′*S*)-kalkitoxin (**3**) and its (3*S*)-isomer (**4**), respectively.

Analogously, the alcohol *ent*-**36** was prepared from the ester **14**.[30] Analogous reaction sequences as above afforded



Scheme 6.



Scheme 7.

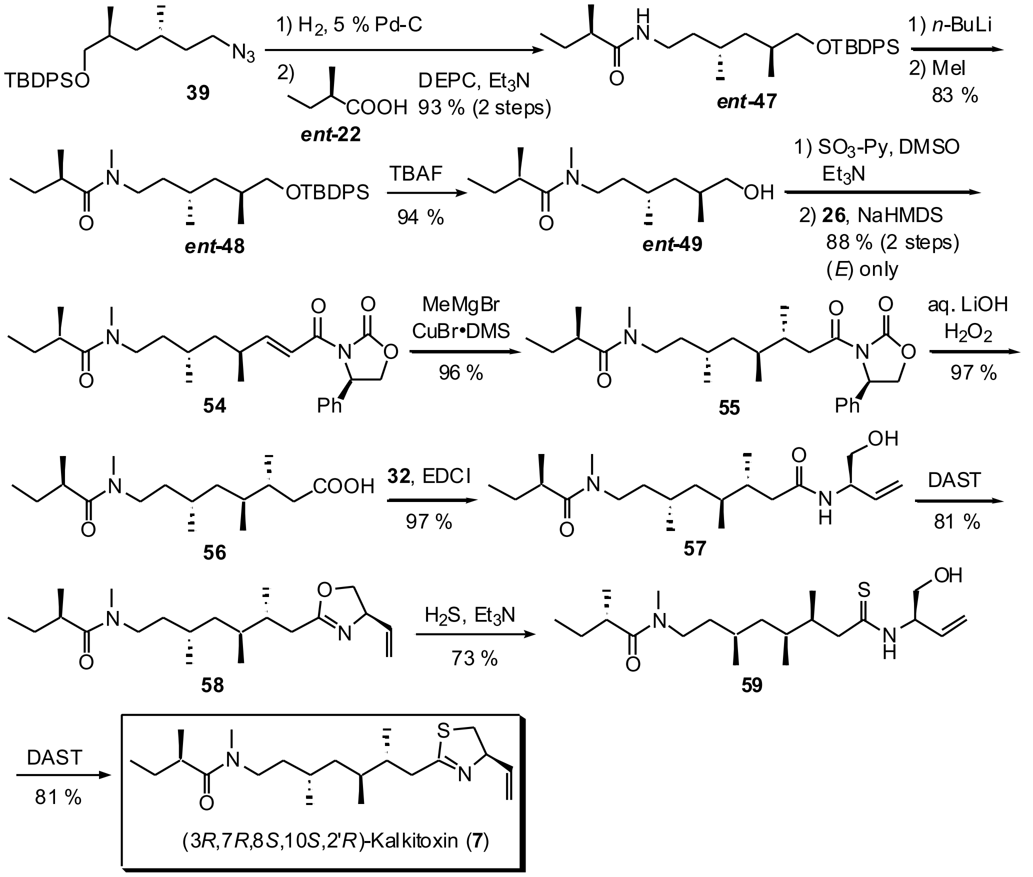
(3*R*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**5**) and its (3*S*)-isomer (**6**), as shown in Scheme 7.

A comparison of the ^{13}C NMR spectra of these synthesized four kalkitoxins **3**–**6** with that of natural kalkitoxin is shown in Figure 3. Close similarity was observed in the (3*S*,7*S*,8*R*,10*R*,2′*S*)-isomer **6**: the mean difference was 0.006 ppm and the maximal difference was 0.014 ppm. But its specific rotation showed −7.5 (*c* 0.8, $CHCl_3$) while that of natural kalkitoxin was +16 (*c* 0.07, $CHCl_3$). The CD spectra of both compounds exhibited the reverse Cotton effect (see Supplementary data). The ^{1}H NMR spectra of **6** and natural one were almost identical each other. These results indicated that **6** was the antipode of natural kalkitoxin.

Utilizing (*R*)-2-methylbutyric acid (*ent*-**22**), (3*R*,7*R*,8*S*,10*S*,2′*R*)-(+)-kalkitoxin (**7**) was synthesized through the same strategy, as shown in Scheme 8. This kalkitoxin was essentially identical to natural compound. Thus, the absolute stereochemistry of natural kalkitoxin was fully determined by this total synthesis in addition to spectral studies.

4. Biological activity

With seven kalkitoxins in hand, toxicity against brine shrimp (*Artemia salina*) was measured. Synthetic kalkitoxin **7** showed strong toxicity (LC_{50} 170 nM) which was the same as the natural material. Interestingly, the synthesized enantiomer **6** of kalkitoxin was 50 times less potent, LC_{50} 9300 nM. The isomer **3** with unnatural 2′*S* configuration, the isomer **1** with unnatural 2′*S* and 10*R* configurations, and the



Scheme 8.

isomer **4** with unnatural 2′*S* and 3*S* configurations were 3–10 times less potent: LC_{50} 550 nM for **3**, 1100 nM for **1**, and 1700 nM for 4. The configurations at the C7, C8, and C10 also affected the toxicity, which decreased as increasing the number of the reversed configurations. The isomers **2** and **5** were almost inactive.

In conclusion, we have succeeded in the total synthesis of

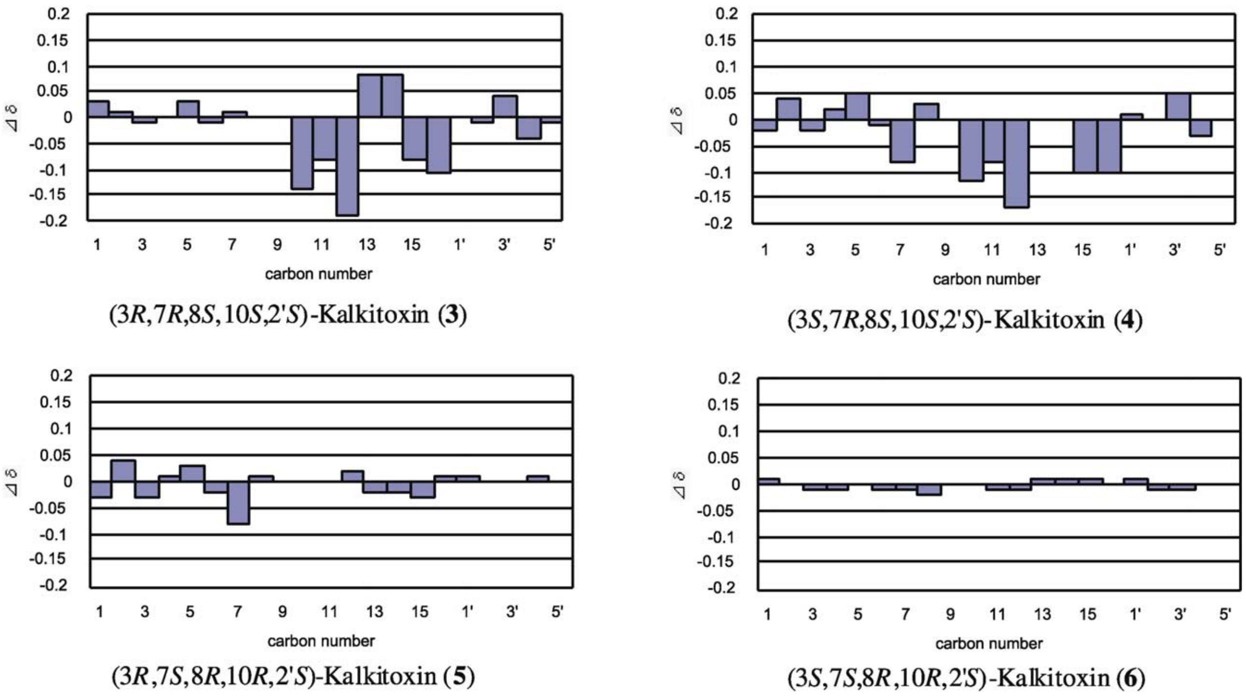


Figure 3. Comparison of ^{13}C NMR spectral difference (in DMSO-d_6 at 25 °C) of natural and synthetic kalkitoxins.

kalkitoxin and its congeners, which clearly elucidated the absolute configuration of this new marine neurotoxin. Our synthesis is straightforward, efficient, and suitable for large scale production, which will be useful for the detailed investigation of the biological properties of kalkitoxin.

5. Experimental

5.1. General

Melting points were measured on a YANACO melting point apparatus (hot plate) and are uncorrected. Infrared (IR) spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a DIP-1000 digital polarimeter with a sodium lamp (λ=589 nm, D line) and are reported as follows: $[\alpha]_D^T$ (*c* g/100 ml, solvent). ^{1}H NMR spectra were recorded on a JEOL EX-270 (270 MHz) spectrometer, unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, bd=broad, m=multiplet), coupling constants (Hz), and assignment. Kalkitoxin numbering is used for assignments on all intermediates. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane, deuterochloroform (δ_C 77.0 ppm) or d^6-dimethylsulfoxide (δ_C 39.5 ppm) with solvents as the internal standard. Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel $60F_{254}$/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Preparative thin layer chromatography was performed on Merck Art. 5744, Kiselgel $60F_{254}$/0.5 mm thickness plates. Elementary analysis (Anal) and high resolution mass spectra (HRMS) were done at the Analytical Facility at Nagoya City University.

Solvents for extraction and chromatography were reagent grade. Liquid chromatography was performed with forced flow (flash chromatography of the indicated solvent mixture on silica gel BW-820MH or BW-200 (Fuji Silysia Co.)). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), methanol (MeOH), and acetonitrile (CH_3CN) were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. Triethylamine was dried over potassium hydroxide. All other commercially obtained reagents were used as received.

General procedures A–M were described for (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (**7**)

5.1.1. General procedure A for the synthesis of (2*S*,4*R*)-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)-5-hexene (37) and its stereoisomers. To a solution of the alcohol **36**[29] (2.16 g, 5.65 mmol) in THF (15 mL) under argon at −78 °C was added *n*-BuLi (4.1 mL, 6.21 mmol, 1.5 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 30 min, then a solution of *p*-toluenesulfonyl chloride (1.3 g, 6.78 mmol) in THF (3 mL plus 1 mL–2 rinse) was added via cannula. After 10 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Cold (0 °C) water was then added. After the mixture was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with ether (×3). The organic extracts were combined and washed successively with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated to give the crude tosylate as a pale yellow oil (3.10 g). This intermediate was used in the next reaction without further purification.

To a solution of the above tosylate in THF (25 mL) under argon at room temperature was added $LiAlH_4$ (650 mg, 17.1 mmol). The resulting mixture was heated to reflux for 1.5 h. After the mixture was cooled to 0 °C, the reaction was quenched with cold brine (added dropwise). After the mixture was stirred for 10 min, the layers were separated, and the aqueous layer was extracted with ether (×2). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/ether=50:1–20:1) to afford the desired product **37** as a colorless oil (1.30 g, 63%): $[\alpha]_D^{26}$=+1.6 (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2959, 1472, 1428, 1113, 1086; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.92 (3H, d, *J*=1.5 Hz, C_8–C*H*$_3$), 0.94 (3H, d, *J*=1.5 Hz, C_{10}–C*H*$_3$), 1.07 (s, 9H, (C*H*$_3$)$_3$C), 1.28–1.41 (2H, m, C_9–C*H*$_2$), 1.67–1.78 (1H, m, C_8–C*H*), 2.09–2.19 (1H, m, C_{10}–C*H*), 3.39–3.56 (2H, m, C*H*$_2$O), 4.83–4.89 (2H, m, C_{12}–C*H*$_2$), 5.60–5.73 (1H, m, C_{11}–C*H*), 7.37–7.41 (6H, m, Ar*H*), 7.65–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 17.5, 17.9, 20.3, 27.0, 27.6, 33.3, 35.3, 40.3, 68.7, 112.1, 127.5, 127.7, 129.3, 129.4, 133.9, 134.0, 135.5, 135.6, 145.1. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{25}OSi$: 309.1675 (M^+−*t*-Bu). Found: 309.1688.

5.1.2. General procedure B for the synthesis of (3*S*,5*S*)-3,5-dimethyl-6-(*tert*-butyldiphenylsilyloxy)hexanol (38) and its stereoisomers. To a solution of the silyloxyhexene **37** (1.28 g, 3.49 mmol) in THF (17 mL) was added 9-borabicyclononane dimer (1.70 g, 6.97 mmol). The resulting solution was stirred for 10 min, and then placed in a water bath and sonicated for 40 min. Aqueous NaOH solution (4 M, 3.5 mL) and 30% aqueous H_2O_2 (3.5 mL) were added sequentially at −5 °C. The resulting mixture was diluted with water and extracted with $CHCl_3$ (×3). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=5:1) to afford the desired product **38** as a colorless oil (955 mg, 71%): $[\alpha]_D^{24}$=−10.6 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 2959, 1472, 1428, 1389, 1113, 1092, 1071; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, *J*=6.3 Hz, C_8–C*H*$_3$), 0.89 (3H, d, *J*=6.6 Hz, C_{10}–C*H*$_3$), 1.05 (s, 9H, (C*H*$_3$)$_3$C), 1.18–1.28 (1H, m, C_{11}–C*H*), 1.33–1.46 (1H, m, C_8–C*H*), 1.48–1.62 (3H, m, C_9–C*H*$_2$, C_{11}–C*H*), 1.68–1.79 (1H, m, C_{11}–C*H*), 3.39–3.51 (2H, m, C*H*$_2$O), 3.57–3.71 (2H, m, C*H*$_2$OH), 7.34–7.44 (6H, m, Ar*H*), 7.65–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.7, 19.4, 19.5, 26.8, 27.0, 33.2, 40.8, 40.9, 61.1, 69.5, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{27}O_2Si$: 327.1780 (M^+−*t*-Bu). Found: 327.1782.

5.1.3. General procedure C for the synthesis of (2*S*,4*S*)-6-azido-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)hexane (39) and its stereoisomers. *(a) MsCl–NaN$_3$ method*. To a solution of the alcohol **38** (873 mg, 2.27 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (0.47 mL, 3.39 mmol), methanesulfonyl chloride (0.23 mL, 2.97 mmol), DMAP (10 mg, 0.082 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with ether, and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the crude mesylate as a colorless oil (1.102 g). This intermediate was used in the next reaction without further purification.

To a solution of the above mesylate in DMF (7 mL) at room temperature was added sodium azide (738 mg, 11.4 mmol). The resulting mixture was diluted with ether, and washed with water (×2) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820 MH, hexane/ether=30:1) to afford the desired product **39** as a colorless oil (807 mg, 87%).

(b) p-NO$_2$-DPPA method. To a solution of the alcohol **38** (42.7 mg, 0.111 mmol) in DMF (0.4 mL) was added bis(*p*-nitrophenyl)phosphorazidate (*p*-NO$_2$-DPPA) (61 mg, 0.166 mmol) and DBU (25 μL, 0.166 mmol) at 0 °C. After 1.5 h, the cooling bath was removed and the reaction mixture was stirred at room temperature for 20 h. The mixture was diluted with EtOAc, and washed with water (×2), 1 M aqueous $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/ether=20:1) to afford the desired product **39** as a colorless oil (33.8 mg, 74%): $[\alpha]_D^{25}=-8.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2980, 2095, 1472, 1428, 1389, 1262, 1113, 1092; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86 (3H, d, *J*=6.3 Hz, C_8–CH_3), 0.89 (3H, d, *J*=6.6 Hz, C_{10}–CH_3), 1.07 (9H, s, (CH_3)$_3$C), 1.19–1.31 (1H, m, C_{10}–C*H*), 1.33–1.49 (1H, m, C8–CH), 1.50–1.58 (3H, m, C9–CH_2, C11–CH), 1.67–1.78 (1H, m, C11–CH), 3.18–3.34 (2H, m, C12–CH2)88, $_3$.4$_1$–3.52 (2H, m, C7–CH2), 7.35–7.45 (6H, m, ArH), 7.65–7.68 (4H, m, ArH); ^{13}C NMR (67.8 MHz, CHCl3/CDCl3) δ 16.6, 19.2, 19.4, 26.9, 27.7, 33.2, 36.6, 40.5, 49.5, 69.4, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m*/*z* Calcd for $C_{20}H_{26}N_3OSi$: 352.1845 (M$^+$−*t*-Bu). Found: 352.1843.

5.1.4. General procedure D for the synthesis of (2*R*)-*N*-[(3*S*,5*S*)-3,5-dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (*ent*-47) and its stereoisomers. To a solution of the azide **39** (774 mg, 1.89 mmol) in EtOAc (7 mL) was added 5% Pd on carbon (100 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1.5 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated to give the crude amine as a pale brown oil (799 mg). This intermediate was used in the next reaction without further purification.

To a solution of the above amine and (*R*)-2-methylbutyric acid (*ent*-**22**) (0.24 mL, 2.10 mmol) in DMF (6 mL) at 0 °C was successively added diethyl phosphorocyanidate (0.32 mL, 2.11 mmol) and triethylamine (0.52 mL, 3.75 mmol). After 1 h, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=4:1) to afford the desired product *ent*-**47** as a pale yellow oil (826 mg, 93%): $[\alpha]_D^{26}=-15.1$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3295 (bd), 2963, 1644, 1553, 1462, 1428, 1387, 1237, 1113, 1092; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.84–0.91 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, (CH_3)$_3$C), 1.10 (3H, d, *J*=6.8 Hz, $C_{2'}$–CH_3), 1.19–1.80 (8H, m, $C_{3'}$–CH_2, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.96–2.09 (1H, m, $C_{2'}$–C*H*), 3.12–3.36 (2H, m, C_{12}–CH_2), 3.38–3.50 (2H, m, CH_2O), 5.30 (1H, bd-s, N*H*), 7.33–7.45 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.6, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 134.0, 135.5, 176.1. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}NO_2Si$ (M$^+$−*t*-Bu): 410.2516. Found: 410.2556.

5.1.5. General procedure E for the synthesis of (2*R*)-*N*-methyl-*N*-[(3*S*,5*S*)-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hex-1-yl]-2-methylbutyramide (*ent*-48) and its stereoisomers. To a solution of the amide *ent*-**47** (565 mg, 1.21 mmol) in THF (7 mL) under argon at −78 °C was added *n*-BuLi (0.94 mL, 1.41 mmol, 1.5 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 20 min, then MeI (0.3 mL, 4.82 mmol) was added. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl was then added. After dilution with EtOAc and water, the organic layer was separated, and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=6:1) to afford the desired product *ent*-**48** as a pale brown oil (480 mg, 83%): $[\alpha]_D^{24}=-18.8$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1646, 1472, 1464, 1428, 1113, 1090; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.82–0.92 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, 1 rotamer, (CH_3)$_3$C), 1.06 (9H, s, 1 rotamer, (CH_3)$_3$C), 1.05–1.11 (3H, m, $C_{2'}$–CH_3), 1.16–1.57 (4H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*), 1.58–1.80 (4H, m, C_9–CH_2, C_{11}–CH_2), 2.44–2.61 (1H, m, $C_{2'}$–C*H*), 2.90 (3H, s, 1 rotamer, N–CH_3), 2.98 (3H, s, 1 rotamer, N–CH_3), 3.19–3.50 (4H, m, C_{12}–CH_2, CH_2O), 7.32–7.44 (6H, m, Ar*H*), 7.63–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.1, 33.2, 33.7, 35.2, 37.0, 37.2, 37.4, 40.6, 40.7, 46.2, 48.0, 69.4, 69.5, 127.4, 129.3, 129.4, 133.9, 134.0, 135.5, 175.9, 176.2. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{38}NO_2Si$ (M$^+$−*t*-Bu): 424.2672. Found: 424.2703.

5.1.6. General procedure F for the synthesis of (2*R*)-*N*-methyl-*N*-((3*S*,5*S*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (*ent*-49) and its stereoisomers. To a solution of the *N*-methylamide *ent*-**48** (446 mg, 0.926 mmol) in THF (5 mL) was added TBAF (610 mg, 2.33 mmol) at 0 °C. After 30 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc, and washed with water (×2) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=6:1) to afford the desired product *ent*-**49** as a pale yellow oil (211 mg, 94%): $[\alpha]_D^{24}=-38.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432(bd), 2963, 1626, 1464, 1415, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.94 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.08 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.11 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.15–1.28 (2H, m, C_9–CH_2), 1.29–1.50 (4H, m, $C_{3'}$–CH_2, C_{11}–CH_2), 1.51–1.94 (3H, m, C_8–*CH*, C_{10}–*CH*, O*H*), 2.49–2.66 (1H, m, $C_{2'}$–C*H*), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.24–3.52 (4H, m, C_{12}–CH_2, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.3, 16.4, 17.1, 17.8, 19.2, 19.4, 27.0, 27.4, 27.9, 28.0, 33.1, 33.7, 35.0, 35.3, 37.0, 37.1, 37.4, 40.4, 40.6, 46.1, 48.0, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m/z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2207.

5.1.7. (4*R*)-3-[(Diethylphosphoro)-acetyl]-4-phenyl-2-oxazolidinone (26). This compound was prepared according to the published procedure (see Ref. 15).

To a flask equipped with a reflux condenser and charged with (*R*)-3-(bromoacetyl)-4-phenyl-2-oxazolidinone (2.02 g, 7.11 mmol) was added triethyl phosphite (2.6 mL, 14.2 mmol), and the mixture was heated to 100 °C. After 3 h, the reaction mixture was cooled to room temperature and then purified by silica gel column chromatography (BW-820MH, $CHCl_3$/MeOH=50:1) to afford the desired (*R*)-phosphonate **26** as a pale orange oil (1.72g, 71%): $[\alpha]_D^{25}=-61.6$ (*c* 2.5, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2986, 1779, 1705, 1392, 1330, 1260, 1208, 1163; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 1.28 (6H, app q, *J*=7.0 Hz, CH_3CH_2), 3.68–3.89 (2H, m, CH_2), 4.06–4.17 (4H, m, CH_3CH_2), 4.28 (1H, dd, *J*=3.9, 8.8 Hz, CH_2O), 4.71 (1H, t, *J*=8.8 Hz, Ar–C*H*), 5.46 (1H, dd, *J*=3.9, 8.8 Hz, CH_2O), 7.29–7.41 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.3 (*J*p=2.5 Hz), 34.5 (*J*p=13.2 Hz), 57.9, 62.7 (*J*p=3.4 Hz), 69.8, 125.9, 128.6, 129.0, 153.4, 164.2 (*J*p=6.7 Hz). HRMS (EI) *m/z* Calcd for $C_{15}H_{20}NO_6P$: 341.1028. Found: 341.1020.

5.1.8. General procedure G for the synthesis of (4*R*)-phenyl-3-[(4*R*,6*S*)-4,6-dimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (54) and its stereoisomers. To a solution of the alcohol *ent*-**49** (126 mg, 0.517 mmol) in CH_2Cl_2 (3 mL) was added DMSO (1 mL), triethylamine (0.36 mL), sulfur trioxide-pyridine complex (420 mg, 2.59 mmol) at 0 °C. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 50 min. After addition of ice water, the mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude aldehyde as a colorless oil (191 mg). This intermediate was used in the next reaction without further purification.

To a solution of the (*R*)-phosphonate **26** (265 mg, 0.776 mmol) in THF (2 mL) under argon was added sodium bis(trimethysilyl)amide solution (0.62 mL, 0.621 mmol, 1.0 M in THF) at 0 °C. After 5 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature. After 45 min, a solution of crude aldehyde in THF (0.8 mL plus 0.3 mL ×2 rinse) was added via cannula at 0 °C. After 2 h, pH 7 buffer was added and the mixture was diluted with EtOAc, washed successively with 1 M aqueous $KHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=2:1–1:1) to afford the desired product **54** as a colorless oil (195 mg, 88%): $[\alpha]_D^{25}=-51.9$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1779, 1688, 1634, 1456, 1383, 1362, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.89 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.97 (3H, d, *J*=6.2 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.99 (3H, d, *J*=6.2 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.12–1.38 (5H, m, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.39–1.61 (2H, m, $C_{3'}$–CH_2), 2.40–2.66 (2H, m, $C_{2'}$–C*H*, C_8–*H*), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.19–3.42 (2H, m, C_{12}–CH_2), 4.18 (1H, dd, *J*=3.6, 8.6 Hz, CH_2O), 4.75 (1H, t, *J*=8.6 Hz, Ar–C*H*), 5.50 (1H, dd, *J*=3.6, 8.6 Hz, CH_2O), 6.82 (1H, dd, *J*=7.7, 15.4 Hz, C_6–C*H*), 7.16 (1H, d, *J*=15.4 Hz, C_7–C*H*), 7.27–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 17.2, 19.1, 19.6, 26.6, 27.5, 33.4, 33.8, 34.5, 36.2, 39.4, 42.7, 57.0, 70.1, 118.5, 125.7, 127.8, 128.6, 139.7, 153.5, 155.5, 163.6, 174.6. HRMS (EI) *m/z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2676.

5.1.9. General procedure H for the synthesis of (4*R*)-4-phenyl-3-[(3*R*,4*S*,6*S*)-3,4,6-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (55) and its stereoisomers. To a slurry of copper (I) bromide-dimethylsulfide complex (290 mg, 1.39 mmol) in THF (2.4 mL) was added dimethylsulfide (1.6 mL) under argon, and cooled to −78 °C. Methyl magnesium bromide (2.0 mL, 1.87 mmol, 0.93 M in THF) was slowly added. After 20 min, the mixture was warmed to 0 °C for 20 min and then recooled to −78 °C before being transferred via cannula to a cooled (−78 °C) solution of the enimide **54** (239 mg, 0.559 mmol) in THF (1.4 mL) and CH_2Cl_2 (0.7 mL). After 30 min, the mixture was warmed to −30 °C over 1 h and stirred at this temperature for 1 h. Phosphate buffer (pH 7) was added to the mixture, which was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$ (×2), water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/Acetone=3:1) to afford the desired product **55** as a colorless oil (238 mg, 96%): $[\alpha]_D^{26}=-58.6$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2965, 1781, 1705, 1634, 1456, 1385, 1325, 1198, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3),1.00–1.11 (2H, m, C_9–CH_2), 1.13–1.59 (6H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*, C_{11}–CH_2), 1.82–1.96 (1H, m, C_7–C*H*), 2.54–2.83 (3H, m, $C_{2'}$–C*H*, C_6–CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.21–3.38 (2H, m, C_{12}–CH_2), 4.14 (1H, dd, J=3.6, 8.7 Hz, CH_2O), 4.72 (1H, t, J=8.7 Hz, Ar–CH), 5.46 (1H, dd, J=3.6, 8.7 Hz, CH_2O), 7.26–7.40 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.1, 17.1, 18.9, 26.6, 27.4, 33.5, 34.1, 34.7, 36.2, 36.7, 38.2, 39.4, 44.9, 69.9, 125.7, 127.9, 128.7, 140.0, 153.7, 171.9, 174.8. HRMS (EI) m/z Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2997.

5.1.10. General procedure I for the synthesis of (3*R*,4*S*,6*S*)-3,4,6-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)-octanoic acid (56) and its stereoisomers. To a solution of the imide **55** (203 mg, 0.457 mmol) in THF–water (4:1, 1.9 mL) was added 30% aqueous H_2O_2 (0.26 mL), followed by the addition of 0.5 M aqueous LiOH (2.7 mL) at 0 °C. After 30 min, the mixture was stirred at room temperature for 10 h. After dilution with water, the aqueous layer was acidified by the addition of 1 N aqueous HCl and extracted with EtOAc (×3). The combined organic extracts were washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the desired product **56** as a colorless oil (132 mg, 97%): $[\alpha]_D^{26}$=−40.9 (c 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3154 (bd), 2964, 1713, 1615, 1462, 1406, 1383, 1250, 1194; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.84 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.01–1.15 (2H, m, C_9–CH_2), 1.16–1.61 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.74–2.00 (2H, m, C_6–CH, C_7–CH), 2.16–2.27 (1H, m, C_6–CH), 2.54–2.68 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.21–3.35 (2H, m, C_{12}–CH_2), 12.0 (1H, bd-s, COOH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.4, 17.1, 19.1, 26.7, 27.5, 33.6, 34.6, 34.7, 36.2, 36.7, 37.8, 39.4, 44.9, 174.4, 174.8. HRMS (EI) m/z Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2440.

5.1.11. General procedure J for the synthesis of *N*-((2*R*)-3-butenol-2-yl)-[(3*R*,4*S*,6*S*)-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)]octanamide (57) and its stereoisomers. (2*R*)-*N*-Boc-amino-3-butenol **32**[21] (68.0 mg, 0.361 mmol) was dissolved in 4 N HCl–EtOAc at 0 °C. After 15 min, the mixture was warmed to room temperature. The solution was concentrated after 1 h, and the residue was azeotropically concentrated with toluene (×4). The resulting residue and the carboxylic acid (2′*R*)-**56** (72.1 mg, 0.241 mmol) were dissolved in CH_2Cl_2 (1.2 mL), and *i*-Pr_2NEt (0.10 mL, 0.60 mmol) and then DMAP (15 mg, 0.120 mmol) were added. EDCI·HCl (138 mg, 0.722 mmol) was added after 10 min and the reaction mixture was stirred for 13 h. After dilution with water, the aqueous layer was acidified by the addition of 1 N aqueous HCl and extracted with EtOAc (×4). The combined organic extracts were washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, $CHCl_3$/MeOH=20:1) to afford the desired product **57** as a colorless oil (85.8 mg, 97%): $[\alpha]_D^{26}$=−10.8 (c 0.84, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3304, 2964, 1717, 1651, 1539, 1464, 1381, 1252, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.14 (2H, m, C_9–CH_2), 1.15–1.61 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.68–2.01 (2H, m, C_6–CH,C_7–CH), 2.02–2.15 (1H, m, C_6–CH), 2.54–2.71 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.27–3.45 (4H, m, C_4–CH_2, C_{12}–CH_2), 4.26–4.39 (1H, m, C_4–OH), 4.66–4.75 (1H, m, C_3–CH), 5.05 (1H, d, J=11.7 Hz, C_1–CH), 5.10 (1H, d, J=17.0 Hz, C_1–CH), 5.83 (1H, ddd, J=6.4, 11.7, 17.0 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.1, 17.1, 19.1, 26.7, 27.5, 33.1, 33.7, 34.7, 35.0, 36.2, 36.8, 39.4, 44.9, 52.7, 63.4, 114.7, 137.2, 171.5, 174.8. HRMS (EI) m/z Calcd for $C_{21}H_{40}N_2O_3$: 368.3039. Found: 368.3035.

5.1.12. General procedure K for the synthesis of (4*R*)-4-ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*R*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (58) and its stereoisomers. To a solution of the amide **57** (75.3 mg, 0.204 mmol) in CH_2Cl_2 (2 mL) was added DAST (30 μL, 0.224 mmol) at −20 °C under argon. After 30 min, 4 M aqueous NH_3 was added and then the mixture was diluted with water. The aqueous layer was extracted with EtOAc (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired product **58** as a colorless oil (57.8 mg, 81%): $[\alpha]_D^{26}$=+18.6 (c 0.76, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1666, 1646, 1456, 1381, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.14 (2H, m, C_9–CH_2), 1.15–1.61 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.74–1.89 (1H, bd-m, C_7–CH), 1.90–2.03 (1H, m, C_6–CH), 2.17–2.28 (1H, m, C_6–CH), 2.54–2.68 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.25–3.35 (2H, m, C_{12}–CH_2), 3.84 (1H, app t, J=8.0 Hz, C_4–CH), 4.31 (1H, app t, J=9.1 Hz, C_4–CH), 4.48–4.59 (1H, m, C_3–CH), 5.07 (1H, d, J=10.5 Hz, C_1–CH), 5.18(1H, d, J=17.2 Hz, C_1–CH), 5.80 (1H, ddd, J=6.8, 10.5, 17.2 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.1, 19.1, 26.6, 27.4, 31.1, 33.5, 34.7, 35.3, 36.7, 39.4, 44.9, 67.4, 71.1, 115.3, 139.1, 166.6, 174.8. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2922.

5.1.13. General procedure L for the synthesis of *N*-((2*R*)-3-butenol-2-yl)-[(3*R*,4*S*,6*S*)-trimethyl-8-((2*R*)-*N*-methyl-2-methylbutyramido)]octanethioamide (59) and its stereoisomers. The oxazoline (2′*R*)-**58** (44.2 mg, 0.126 mmol) was dissolved in MeOH–triethylamine (1:1, 2 mL, saturated with H_2S), and stirred at room temperature for 12 h. The mixture was concentrated and the residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=6:1) to afford the desired product **59** as a pale yellow oil (35.6 mg, 73%): $[\alpha]_D^{25}$=+9.6 (c 0.44, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3340 (bd), 2964, 1622, 1464, 1415, 1381, 1217, 1080; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ

0.73–0.87 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.04–1.16 (2H, m, C_9–CH_2), 1.17–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 2.05–2.28 (1H, bd-m, C_7–CH), 2.38–2.51 (2H, m, C_6–CH_2), 2.54–2.73 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.98 (3H, s, 1 rotamer, N–CH_3), 3.23–3.35 (2H, m, C_{12}–CH_2), 3.44–3.58 (2H, m, C_4–CH_2), 4.88 (1H, t, J=5.6 Hz, C_3–CH), 5.05–5.21 (3H, m, C_1–CH_2, C_4–OH), 5.85 (1H, ddd, J=6.4, 11.4, 16.5 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.1, 16.2, 17.1, 19.1, 26.7, 27.4, 33.1, 33.7, 34.7, 36.2, 36.6, 38.0, 39.4, 44.9, 59.0, 67.4, 115.9, 135.1, 174.8, 203.8. HRMS (EI) m/z Calcd for $C_{21}H_{40}N_2O_2S$: 384.2810. Found: 384.2825.

5.1.14. General procedure M for the synthesis of (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (7) and its stereoisomers. To a solution of thioamide 59 (27.9 mg, 0.0725 mmol) in CH_2Cl_2 (0.7 mL) was added DAST (11 μL, 0.0797 mmol) at −20 °C under argon. After 30 min, 4 M aqueous NH_3 was added and then the mixture was diluted with water. The aqueous layer was extracted with EtOAc (×3) and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the synthetic (3*R*,7*R*,8*S*,10*S*,2′*R*)-kalkitoxin (7) as a pale yellow oil (21.6 mg, 81%): $[\alpha]_D^{26}$=+7.0 (c 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1464, 1412, 1381, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=7.1 Hz, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, $C_{2'}$–CH_3), 1.01–1.16 (2H, m, C_9–CH_2), 1.17–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.73–1.89 (1H, bd–m, C_7–CH), 2.17–2.30 (1H, m, C_6–CH_2), 2.40–2.47 (1H, m, C_6–CH_2), 2.54–2.69 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.02 (1H, dd, J=8.4, 11.0 Hz, C_4–CH), 3.25–3.39 (2H, m, C_{12}–CH_2), 3.48 (1H, dd, J=8.4, 11.0 Hz, C_4–CH), 4.84–4.97 (1H, m, C_3–CH), 5.10 (1H, d, J=10.4 Hz, C_1–CH), 5.23 (1H, d, J=17.1 Hz, C_1–CH), 5.90 (1H, ddd, J=6.4, 10.4, 17.1 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.70, 16.02(CH_3×2), 17.14, 19.08, 26.64, 27.47, 33.39, 34.70, 34.92, 36.20, 36.68, 37.49, 37.85, 39.40, 44.88, 77.90, 115.27, 137.97, 169.20, 174.80. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2722.

5.1.15. Natural kalkitoxin. Pure natural kalkitoxin showed the following physicochemical data: $[\alpha]_D^{25}$=+16 (c 0.07, $CHCl_3$); CD c 0.022, EtOH λ_{ext} 226 nm ($\Delta\varepsilon$+4.75), 207.8 (0.0) and see Figure 6 in Supplementary data; IR ($CHCl_3$) 2961, 2928, 2880, 1643, 1464, 1086, 1410, 1380 cm^{-1}; UV (MeOH) λ_{max} 250 nm (ε=2600); ^{1}H NMR (benzene-d_6, 500 MHz) δ 0.76 (3H, d, J=6.8 Hz), 0.85 (3H, d, J=6.1 Hz), 0.88 (3H, d, J=7.5 Hz), 0.95 (d, 3H, J=6.8 Hz), 1.02 (1H, m), 1.10 (1H, m), 1.10 (3H, d, J=6.7 Hz), 1.24 (1H, m), 1.34 (1H, m), 1.38 (1H, m), 1.39 (1H, m), 1.54 (1H, m), 1.87 (1H, m), 2.05 (1H, m), 2.28 (1H, m), 2.31 (1H, m), 2.43 (3H, s), 2.55 (1H, m), 2.72 (1H, dd, J=10.7, 8.4 Hz), 2.94 (1H, dd, J=10.5, 8.8 Hz), 3.35 (2H, m), 4.75 (1H, dd, J=7.8, 7.5 Hz), 5.01 (1H, d, J=10.3 Hz), 5.24 (1H, ddd, J=17.2, 1.6, 1.6 Hz), 5.85 (1H, ddd, J=17.2, 10.3, 6.1 Hz); ^{13}C NMR (DMSO-d$_6$, 100 MHz) δ 11.69 (C-4′), 16.0 (C-13), 16.0 (C-14), 17.13 (C-5′), 19.07 (C-15), 26.64 (C-3′), 27.47 (C-10), 33.40 (C-8), 34.70 (C-16), 34.92 (C-11), 36.20 (C-2′), 36.68 (C-7), 37.49 (C-6), 37.85 (C-4), 39.4 (C-9), 44.88 (C-12), 77.91 (C-3), 115.24 (C-1), 137.96 (C-2), 169.18 (C-5), 174.79 (C-1′); ^{13}C NMR (benzene-d_6, 125 MHz, from HSQC and HSQMBC data sets) δ 12.4 (C-4′), 16.4 (C-13), 16.4 (C-14), 17.8 (C-5′), 19.5 (C-15), 27.8 (C-3′), 28.3 (C-10), 34.4 (C-8), 34.5 (C-16), 36.0 (C-11), 37.5 (C-7), 37.6 (C-2′), 38.6 (C-6), 38.9 (C-4), 40.3 (C-9), 46.0 (C-12), 79.2 (C-3), 115.3 (C-1), 138.3 (C-2), 170.2 (C-5), 175.5 (C-1′).

Description of tertiary amide isomers in the NMR spectra of kalkitoxin. Complication in the NMR-based strategy for structure elucidation of kalkitoxin resulted from a 3:2 ratio of tertiary amide isomers in its room temperature ^{1}H NMR (DMSO-d_6, 298 K). This required that structure elucidation of kalkitoxin **7** be based on a combination of data sets for experiments run at both 298 and 340 K. The origin of the ‘twinning’of signals was confirmed by observing alterations in the signal ratios as a function of different NMR solvents (ratio between *E* and *Z* olefin isomers ranged from a low of 0.5:1.0 in benzene-d_6 to a high of 1.58:1.0 in acetone-d_6) and temperature. At relatively high temperature (340 K) these ‘twinned’ signals coalesced to singlets; however, the value of this elevated temperature experiment was compromised because, for reasons that we do not understand, several ^{13}C NMR signals and ^{1}H–^{13}C NMR correlations that should have been present were lost.

HRMS (EI) m/z obs. $[M]^+$ 366.2696 (15.9, 0.9 mmu dev. for $C_{21}H_{38}N_2OS$); HR-EIMS cleavages between C6–C7 in kalkitoxin obs. m/s 240.2329 for $[C_{15}H_{30}NO]^+$ (25%, 0.2 mmu dev.) and m/z 127.0459 for $[C_6H_9NS]^+$ (26%, 0.3 mmu dev.); cleavage C7–C8 obs. m/z 154.0683 for $[C_8H_{12}NS]^+$ (100%, 0.8 mmu dev.).

5.1.16. (2*S*)-*N*-[(3*S*,5*S*)-3,5-Dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (40). According to general procedure D (using (*S*)-2-methylbutyric acid **22**), the azide **39** (774 mg, 1.89 mmol) provided the amide **40** as a pale yellow oil (826 mg, 93%): $[\alpha]_D^{25}$=−3.7 (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3295, 2930, 1644, 1553, 1462, 1428, 1387, 1237, 1113, 1094; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.82–0.91 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, $(CH_3)_3C$), 1.11 (3H, d, J=6.9 Hz, $C_{2'}$–CH_3), 1.18–1.79 (8H, m, $C_{3'}$–CH_2, C_9–CH_2, C_{10}–CH, C_{11}–CH_2), 1.95–2.09 (1H, m, $C_{2'}$–CH), 3.16–3.31 (2H, m, C_{12}–CH_2), 3.37–3.51 (2H, m, CH_2O), 5.27 (1H, bd-s, NH), 7.35–7.42 (6H, m, ArH), 7.63–7.67 (4H, m, ArH); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.7, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 134.0, 135.5, 176.0. HRMS (EI) m/z Calcd for $C_{25}H_{36}NO_2Si$: 410.2515 (M^+−t-Bu). Found: 410.2491.

5.1.17. (2*S*)-*N*-Methyl-*N*-[(3*S*,5*S*)-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hex-1-yl]-2-methylbutyramide (41). According to general procedure E, the amide **40** (565 mg, 1.21 mmol) provided the *N*-methylamide **41** as a pale brown oil (480 mg, 83%): $[\alpha]_D^{24}$=+3.0 (c 1.0, $CHCl_3$); IR ν_{max}^{neat}

cm^{-1} 2961, 1646, 1472, 1464, 1428, 1113, 1090; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.82–0.93 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.06 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.07–1.12 (3H, m, $C_{2'}$–CH_3), 1.19–1.56 (4H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH), 1.57–1.80 (4H, m, C_9–CH_2, C_{11}–CH_2), 2.45–2.61 (1H, m, $C_{2'}$–CH), 2.90 (3H, s, 1 rotamer, N–CH3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.20–3.34 (2H, m, C_{12}–CH_2), 3.35–3.52 (2H, m, CH_2O), 7.36–7.45 (6H, m, Ar*H*), 7.62–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.0, 28.1, 33.2, 33.3, 33.7, 35.2, 37.0, 37.2, 37.4, 40.6, 40.7, 46.0, 48.0, 69.4, 69.5, 127.4, 129.3, 129.4, 133.8, 133.9, 134.0, 135.5, 175.9, 176.2. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{38}NO_2Si$: 424.2672 (M^+−*t*-Bu). Found: 424.2654.

5.1.18. (2*S*)-*N*-Methyl-*N*-((3*S*,5*S*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (42). According to general procedure F, the *N*-methylamide **41** (446 mg, 0.926 mmol) provided the alcohol **42** as a pale yellow oil (211 mg, 94%): $[\alpha]_D^{24}$=+6.0 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 2928, 1626, 1464, 1414, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.93 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.07–1.14 (3H, m, $C_{2'}$–CH_3), 1.15–1.27 (2H, m, C_9–CH_2), 1.28–1.62 (4H, m, $C_{3'}$–CH_2, C_{11}–CH_2), 1.63–1.80 (2H, m, C_8–CH, C_{10}–CH), 2.46–2.64 (1H, m, $C_{2'}$–CH), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.01 (3H, s, 1 rotamer, N–CH_3), 3.20–3.56 (4H, m, C_{12}–CH_2, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.2, 16.3, 17.1, 17.8, 19.2, 19.4, 27.1, 27.4, 27.8, 28.0, 33.1, 33.7, 35.0, 35.2, 37.0, 37.1, 37.3, 40.4, 40.6, 46.0, 48.1, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m*/*z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2203.

5.1.19. (4*R*)-Phenyl-3-[(4*R*,6*S*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (43). According to general procedure G, the alcohol **42** (204 mg, 0.838 mmol) provided the enimide **43** as a colorless oil (333 mg, 93%): $[\alpha]_D^{24}$=−27.5 (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2980, 1779, 1688, 1634, 1456, 1383, 1362, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.67–0.88 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.92–1.00 (3H, m, $C_{2'}$–CH_3), 1.09–1.37 (5H, m, C_9–CH_2, C_{10}–CH, C_{11}–CH_2), 1.39–1.68 (2H, m, $C_{3'}$–CH_2), 2.42–2.63 (2H, m, $C_{2'}$–CH, C_8–CH), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.90 (3H, s, 1 rotamer, N–CH_3), 3.06–3.51 (2H, m, C_{12}–CH_2), 4.18 (1H, dd, *J*=8.5, 3.3 Hz, CH_2O), 4.75 (1H, t, *J*=8.5 Hz, Ar–CH), 5.50 (1H, dd, *J*=8.5, 3.3 Hz, CH_2O), 6.82 (1H, dd, *J*=15.4, 7.8 Hz, C_6–CH), 7.16 (1H, d, *J*=15.4 Hz, C_7–CH), 7.28–7.38 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 17.1, 19.1, 19.5, 26.7, 27.3, 33.2, 33.8, 34.4, 36.2, 39.4, 42.8, 57.1, 70.1, 118.9, 125.9, 128.0, 128.8, 139.7, 153.8, 155.7, 163.8, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2673.

5.1.20. (4R)-4-Phenyl-3-[(3R,4S,6S)-3,4,6-trimethyl-8-((2S)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (44). According to general procedure H, the enimide 43 (86 mg, 0.201 mmol) provided the imide **44** as a colorless oil (87 mg, 97%): [α]D^{25} −32.8 (*c* 1.5, CHCl3); IR ν maxneat cm−1 2930, 1782, 1705, 1636, 1458, 1385, 1325, 1198, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.6 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=6.6 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.08 (2H, m, C_9–CH_2), 1.15–1.58 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.82–1.96 (1H, m, C_7–CH), 2.50–2.76 (3H, m, $C_{2'}$–CH, C_6–CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.15–3.42 (2H, m, C_{12}–CH_2), 4.14 (1H, dd, *J*=8.7, 3.5 Hz, CH_2O), 4.72 (1H, t, *J*=8.7 Hz, Ar–CH), 5.46 (1H, dd, *J*=8.7, 3.5 Hz, CH_2O), 7.26–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 16.1, 17.1, 18.8, 26.7, 27.3, 33.5, 34.1, 34.6, 36.2, 36.8, 38.2, 39.4, 44.7, 57.0, 69.9, 125.7, 127.9, 128.7, 140.0, 153.7, 171.8, 174.8. HRMS (EI) *m*/*z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2990.

5.1.21. (3*R*,4*S*,6*S*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (45). According to general procedure I, the imide **44** (212 mg, 0.476 mmol) provided the carboxylic acid **45** as a colorless oil (126 mg, 88%): $[\alpha]_D^{25}$=−2.9 (*c* 1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3346 (bd), 2964, 1732, 1634, 1404, 1383, 1252, 1190; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.84 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.01–1.14 (2H, m, C_9–CH_2), 1.16–1.60 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.74–1.99 (2H, m, C_6–CH, C_7–CH), 2.15–2.27 (1H, m, C_6–CH), 2.52–2.70 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.25 (2H, m, C_{12}–CH_2), 10.20 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.5, 17.2, 19.0, 26.7, 27.4, 33.7, 34.6, 34.9, 36.2, 36.8, 37.8, 39.4, 44.7, 174.1, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2458.

5.1.22. (4*R*)-4-Ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (46a). According to general procedures J and K, the carboxylic acid **45** (79.3 mg, 0.265 mmol) provided the oxazoline **46a** as a colorless oil (45.1 mg, 70%, 2 steps): $[\alpha]_D^{25}$=+53.0 (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1660, 1646, 1464, 1381, 1196; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.14 (2H, m, C_9–CH_2), 1.15–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.71–1.89 (1H, m, C_7–CH), 1.90–2.08 (1H, m, C_6–CH), 2.15–2.30 (1H, m, C_6–CH), 2.55–2.69 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.37 (2H, m, C_{12}–CH_2), 3.84 (1H, app t, *J*=7.9 Hz, C_4–CH), 4.31 (1H, app t, *J*=8.9 Hz, C_4–CH), 4.45–4.61 (1H, m, C_3–CH), 5.07 (1H, d, *J*=10.2 Hz, C_1–CH), 5.17 (1H, d, *J*=16.8 Hz, C_1–CH), 5.80 (1H, ddd, *J*=17.1, 10.4, 6.6 Hz, C_2–CH); 13C NMR (67.8 MHz, DMSO/DMSO-d6), the major rotamer, δ 11.7, 16.3, 17.2, 19.0, 26.7, 27.3, 31.1, 33.5, 34.8, 35.3, 36.2, 36.7, 39.4, 44.7, 67.4, 71.1, 115.1, 138.9, 166.4, 174.5. HRMS (EI) *m*/*z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2944.

5.1.23. (3*R*,7*R*,8*S*,10*S*,2′*S*)-Kalkitoxin (3). According to general procedures L and M, the oxazoline **46a** (42.9 mg, 0.122 mmol) provided the synthetic (3R,7R,8S,10S,2′S)-kalkitoxin (**3**) as a pale yellow oil (24.2 mg, 57%, 2 steps): $[\alpha]_D^{25}=+39.7$ (*c* 0.88, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1412, 1381, 1082; ^{1}H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.95 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.01–1.17 (2H, m, C_9-CH_2), 1.19–1.64 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.90 (1H, bd-m, C_7-CH), 2.16–2.30 (1H, m, C_6-CH_2), 2.39–2.46 (1H, m, C_6-CH_2), 2.54–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.02 (1H, dd, *J*=8.4, 10.9 Hz, C_4-CH), 3.12–3.30 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=8.4, 10.9 Hz, C_4-CH), 4.83–4.97 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.2 Hz, C_1-CH), 5.23 (1H, d, *J*=17.1 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.3, 10.2, 17.1 Hz, C_2-CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.65, 16.08 ($CH_3\times2$), 17.12, 18.99, 26.68, 27.33, 33.40, 34.59, 34.84, 36.19, 36.69, 37.48, 37.85, 39.40, 44.69, 77.90, 115.27, 137.97, 169.21, 174.79. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2722.

5.1.24. (4*S*)-4-Ethenyl-2-[(2*R*,3*S*,5*S*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (46b). According to general procedure J (using (2*S*)-*N*-Boc-amino-3-butenol *ent*-**32**) and procedure K, the carboxylic acid **45** (69.9 mg, 0.233 mmol) provided the oxazoline **46b** as a colorless oil (64.4 mg, 80%, 2 steps): $[\alpha]_D^{26}=-62.7$ (*c* 0.19, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2968, 1666, 1646, 1464, 1381, 1196; ^{1}H NMR (270 MHz, DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.85 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}-CH_3$), 1.00–1.15 (2H, m, C_9-CH_2), 1.16–1.62 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.70–1.88 (1H, bd-m, C_7-CH), 1.90–2.03 (1H, m, C_6-CH), 2.16–2.29 (1H, m, C_6-CH), 2.54–2.71 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.95 (3H, s, 1 rotamer, $N-CH_3$), 3.10–3.24 (2H, m, $C_{12}-CH_2$), 3.84 (1H, app t, *J*=7.8 Hz, C_4-CH), 4.31 (1H, app t, *J*=8.6 Hz, C_4-CH), 4.46–4.61 (1H, m, C_3-CH), 5.07 (1H, d, *J*=10.2 Hz, C_1-CH), 5.17 (1H, d, *J*=17.2 Hz, C_1-CH), 5.79 (1H, ddd, *J*=6.4, 10.2, 17.2 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO-d_6), the major rotamer, δ 11.6, 15.9, 16.2, 17.1, 18.9, 26.7, 27.3, 31.0, 33.5, 34.6, 35.2, 36.2, 36.7, 39.4, 44.7, 67.4, 71.1, 115.2, 139.1, 166.6, 174.8. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2943.

5.1.25. (3*S*,7*R*,8*S*,10*S*,2′*S*)-Kalkitoxin (4). According to general procedures L and M, the oxazoline **46b** (60.7 mg, 0.173 mmol) provided the synthetic (3*S*,7*R*,8*S*,10*S*,2′*S*)-kalkitoxin (**4**) as a pale yellow oil (40.4 mg, 66%, 2 steps): $[\alpha]_D^{25}=-46.1$ (*c* 0.81, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2874, 1646, 1464, 1412, 1381, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}-CH_3$, C_8-CH_3, $C_{10}-CH_3$), 0.94 (3H, d, *J*=6.7 Hz, $C_{2'}-CH_3$), 0.97 (3H, d, *J*=6.7 Hz, $C_{2'}-CH_3$), 1.01–1.17 (2H, m, C_9-CH_2), 1.18–1.65 (6H, m, $C_{3'}-CH_2$, C_8-CH, $C_{10}-CH$, $C_{11}-CH_2$), 1.71–1.90 (1H, bd–m, C_7-CH), 2.18–2.32 (1H, m, C_6-CH), 2.39–2.46 (1H, m, C_6-CH), 2.55–2.72 (1H, m, $C_{2'}-CH$), 2.79 (3H, s, 1 rotamer, $N-CH_3$), 2.96 (3H, s, 1 rotamer, $N-CH_3$), 3.03 (1H, dd, *J*=7.9, 10.4 Hz, C_4-CH), 3.12–3.29 (2H, m, $C_{12}-CH_2$), 3.48 (1H, dd, *J*=7.9, 10.4 Hz, C_4-CH), 4.86–5.00 (1H, m, C_3-CH), 5.10 (1H, d, *J*=10.2 Hz, C_1-CH), 5.22 (1H, d, *J*=17.2 Hz, C_1-CH), 5.90 (1H, ddd, *J*=6.6, 10.2, 17.2 Hz, C_2-CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.66, 16.00 ($CH_3\times2$), 17.13, 18.97, 26.69, 27.35, 33.43, 34.60, 34.84, 36.20, 36.60, 37.48, 37.87, 39.4, 44.71, 77.89, 115.22, 138.00, 169.23, 174.80. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2694.

5.1.26. (2*R*,4*S*)-2,4-Dimethyl-1-(*tert*-butyldiphenylsilyloxy)-5-hexene (*ent*-37). According to general procedure A, the alcohol *ent*-**36**[30] (5.37 g, 14.04 mmol) provided the silyloxyhexene *ent*-**37** as a pale yellow oil (2.95 g, 57%): $[\alpha]_D^{25}=-1.1$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2957, 1428, 1113, 804; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.92 (3H, d, *J*=1.6 Hz, C_8-CH_3), 0.94 (3H, d, *J*=1.6 Hz, $C_{10}-CH_3$), 1.07 (9H, s, $(CH_3)_3C$), 1.27–1.43 (2H, m, C_9-CH_2), 1.66–1.78 (1H, m, C_8-CH), 2.09–2.19 (1H, m, $C_{10}-CH$), 3.39–3.56 (2H, m, CH_2O), 4.83–4.89 (2H, m, $C_{12}-CH_2$), 5.60–5.73 (1H, m, $C_{11}-CH$), 7.35–7.41 (6H, m, Ar*H*), 7.65–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 17.5, 17.9, 20.3, 27.0, 27.6, 33.3, 35.3, 40.3, 68.7, 112.1, 127.5, 127.7, 129.3, 129.4, 133.9, 134.0, 135.5, 135.6, 145.1. HRMS (EI) *m/z* Calcd for $C_{20}H_{25}OSi$: 309.1675 (M^+-t-Bu). Found: 309.1688.

5.1.27. (3*R*,5*R*)-3,5-Dimethyl-6-(*tert*-butyldiphenylsilyloxy)hexanol (*ent*-38). According to general procedure B, the silyloxyhexene *ent*-**37** (2.95 g, 8.05 mmol) provided the alcohol *ent*-**38** as a colorless oil (2.10 g, 68%): $[\alpha]_D^{24}=+11.2$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3346, 2859, 1472, 1428, 1389, 1113, 1091, 1071; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, *J*=6.4 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.6 Hz, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.18–1.28 (1H, m, $C_{11}-CH$), 1.33–1.46 (1H, m, C_8-CH), 1.49–1.62 (3H, m, C_9-CH_2, $C_{11}-CH$), 1.68–1.78 (1H, m, $C_{11}-CH$), 3.39–3.51 (2H, m, CH_2O), 3.58–3.70 (2H, m, CH_2OH), 7.35–7.44 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.7, 19.4, 19.5, 26.8, 26.9, 33.2, 40.7, 40.8, 60.9, 69.4, 127.4, 129.4, 133.9, 135.5. HRMS (EI) *m/z* Calcd for $C_{20}H_{27}O_2Si$: 327.1781 (M^+-t-Bu). Found: 327.1782.

5.1.28. (2*R*,4*R*)-6-Azido-2,4-dimethyl-1-(*tert*-butyldiphenylsilyloxy)hexane (*ent*-39). According to general procedure C, the alcohol *ent*-**38** (1.90 g, 4.95 mmol) provided the azide *ent*-**39** as a colorless oil (1.93 g, 95%): $[\alpha]_D^{24}=+8.5$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2959, 2095, 1472, 1428, 1389, 1262, 1113, 1092; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.85 (3H, d, *J*=6.4 Hz, C_8-CH_3), 0.89 (3H, d, *J*=6.8 Hz, $C_{10}-CH_3$), 1.05 (9H, s, $(CH_3)_3C$), 1.19–1.30 (1H, m, $C_{10}-CH$), 1.33–1.49 (1H, m, C_8-CH), 1.50–1.58 (3H, m, C_9-CH_2, $C_{11}-CH$), 1.67–1.77 (1H, m, $C_{11}-CH$), 3.17–3.33 (2H, m, $C_{12}-CH_2$), 3.40–3.50 (2H, m, C_7-CH_2), 7.35–7.45 (6H, m, Ar*H*), 7.64–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.6, 19.2, 19.4, 26.9, 27.7, 33.2, 36.5, 40.5, 49.5, 69.4, 127.5, 129.4, 133.9, 135.5. HRMS (EI) *m/z* Calcd for $C_{20}H_{26}N_3OSi$: 352.1845 (M^+-t-Bu). Found: 352.1835.

5.1.29. (2*S*)-*N*-[(3*R*,5*R*)-3,5-Dimethyl-6-(*tert*-butylsilyloxy)-hex-1-yl]-2-methylbutyramide (47). According to general procedure D (using (*S*)-2-methylbutyric acid **22**), the azide *ent*-**39** (1.87 g, 4.57 mmol) provided the amide **47** as a pale yellow oil (1.84 g, 86%): $[\alpha]_D^{24}=+13.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3325, 2963, 1644, 1553, 1462, 1427, 1389, 1237, 1113, 1094; ^1H NMR (270 MHz, TMS/$CDCl_3$) δ 0.84–0.91 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, $(CH_3)_3C$), 1.10 (3H, d, *J*=6.9 Hz, $C_{2'}$–CH_3), 1.18–1.76 (8H, m, $C_{3'}$–CH_2, C_9–CH_2, C_{10}–*CH*, C_{11}–CH_2), 1.98–2.09 (1H, m, $C_{2'}$–*CH*), 3.16–3.33 (2H, m, C_{12}–CH_2), 3.38–3.52 (2H, m, CH_2O), 5.27 (1H, bd-s, N*H*), 7.35–7.45 (6H, m, Ar*H*), 7.63–7.67 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.0, 16.7, 17.6, 19.3, 19.4, 26.9, 27.4, 27.9, 33.2, 37.4, 37.7, 40.7, 43.3, 69.4, 127.4, 129.4, 133.9, 135.5, 176.0. HRMS (EI) *m/z* Calcd for $C_{25}H_{36}NO_2Si$: 410.2515 (M^+-t-Bu). Found: 410.2537.

5.1.30. (2*S*)-*N*-Methyl-*N*-[(3*R*,5*R*)-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hex-1-yl]-2-methylbutyramide (48). According to general procedure E, the amide **47** (1.83 g, 3.91 mmol) provided the *N*-methylamide **48** as a pale brown oil (1.76 g, 93%): $[\alpha]_D^{25}=+17.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1646, 1472, 1464, 1428, 1113, 1090; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.83–0.90 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.05 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.06 (9H, s, 1 rotamer, $(CH_3)_3C$), 1.07 (3H, d, *J*=6.7 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.10 (3H, d, *J*=6.7 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.19–1.55 (4H, m, $C_{3'}$–CH_2, C_8–*CH*, C_{10}–*CH*), 1.58–1.75 (4H, m, C_9–CH_2, C_{11}–CH_2), 2.49–2.61 (1H, m, $C_{2'}$–*CH*), 2.90 (3H, s, 1 rotamer, N–CH_3), 2.98 (3H, s, 1 rotamer, N–CH_3), 3.22–3.51 (4H, m, C_{12}–CH_2, CH_2O), 7.35–7.44 (6H, m, Ar*H*), 7.64–7.66 (4H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.1, 12.2, 16.6, 17.2, 17.9, 19.3, 19.4, 26.9, 27.1, 27.5, 28.1, 33.1, 33.2, 33.7, 35.2, 36.9, 37.2, 37.4, 40.6, 40.7, 46.1, 48.0, 69.3, 69.5, 127.4, 129.3, 129.4, 133.8, 133.9, 135.4, 175.9, 176.2. HRMS (EI) *m/z* Calcd for $C_{26}H_{38}NO_2Si$: 424.2672 (M^+-t-Bu). Found: 424.2675.

5.1.31. (2*S*)-*N*-Methyl-*N*-((3*R*,5*R*)-3,5-dimethyl-6-hydroxy-hex-1-yl)-2-methylbutyramide (49). According to general procedure F, the *N*-methylamide **48** (1.72 g, 3.57 mmol) provided the alcohol **49** as a pale yellow oil (804 mg, 93%): $[\alpha]_D^{24}=+35.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3432, 2928, 1626, 1464, 1414, 1379, 1048; ^1H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.85–0.93 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 1.08 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.11 (3H, d, *J*=6.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.14–1.29 (2H, m, C_9–CH_2), 1.30–1.60 (4H, m, $C_{3'}$–CH_2, C_{11}–CH_2), 1.61–1.80 (2H, m, C_8–*CH*, C_{10}–*CH*), 2.51–2.63 (1H, m, $C_{2'}$–*CH*), 2.93 (3H, s, 1 rotamer, N–CH_3), 3.01 (3H, s, 1 rotamer, N–CH_3), 3.18–3.45 (4H, m, C_{12}–CH_2, CH_2O); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 12.0, 12.2, 16.3, 16.4, 17.1, 17.8, 19.2, 19.4, 27.1, 27.4, 27.9, 28.0, 33.1, 33.7, 35.0, 35.3, 37.0, 37.2, 37.4, 40.4, 40.6, 46.1, 48.0, 68.6, 68.7, 176.0, 176.3. HRMS (EI) *m/z* Calcd for $C_{14}H_{29}NO_2$: 243.2199. Found: 243.2204.

5.1.32. (4*S*)-Phenyl-3-[(4*S*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (50). According to general procedure G (using (*S*)-phosphonate *ent*-**26**), the alcohol **49** (115 mg, 0.472 mmol) provided the enimide **50** as a colorless oil (147 mg, 73%): $[\alpha]_D^{25}=+52.8$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2966, 1779, 1688, 1634, 1458, 1383, 1329, 1200, 1103, 1082; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.76–0.88 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95–0.98 (3H, m, $C_{2'}$–CH_3), 1.15–1.39 (5H, m, C_9–CH_2, C_{10}–*CH*, C_{11}–CH_2), 1.40–1.53 (2H, m, $C_{3'}$–CH_2), 2.39–2.61 (2H, m, $C_{2'}$–*CH*, C_8–*CH*), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.92 (3H, s, 1 rotamer, N–CH_3), 3.20–3.42 (2H, m, C_{12}–CH_2), 4.17 (1H, dd, *J*=3.4, 8.6 Hz, CH_2O), 4.75 (1H, t, *J*=8.6 Hz, Ar–*CH*), 5.50 (1H, dd, *J*=3.4, 8.6 Hz, CH_2O), 6.83 (1H, dd, *J*=15.4, 7.5 Hz, C_6–*CH*), 7.16 (1H, d, *J*=15.4 Hz, C_7–*CH*), 7.31–7.38 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.8, 17.2, 19.2, 19.6, 26.6, 27.5, 33.4, 33.8, 34.5, 36.2, 39.4, 42.7, 57.1, 70.1, 118.5, 125.7, 127.8, 128.6, 139.7, 153.6, 155.5, 163.6, 174.7. HRMS (EI) *m/z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2673.

5.1.33. (4*S*)-4-Phenyl-3-[(3*S*,4*R*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (51). According to general procedure H, the enimide **50** (172 mg, 0.402 mmol) provided the imide **51** as a colorless oil (167 mg, 93%): $[\alpha]_D^{24}=+55.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2930, 1782, 1705, 1634, 1458, 1385, 1327, 1198, 1136; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.74–0.81 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.96 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.03–1.11 (2H, m, C_9–CH_2), 1.15–1.53 (6H, m, $C_{3'}$–CH_2, C_8–*CH*, C_{10}–*CH*, C_{11}–CH_2), 1.84–1.95 (1H, m, C_7–*CH*), 2.50–2.74 (3H, m, $C_{2'}$–*CH*, C_6–CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.22–3.38 (2H, m, C_{12}–CH_2), 4.14 (1H, dd, *J*=8.7, 3.4 Hz, CH_2O), 4.72 (1H, t, *J*=8.7 Hz, Ar–*CH*), 5.46 (1H, dd, *J*=8.7, 3.4 Hz, CH_2O), 7.26–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.1, 17.1, 18.8, 18.9, 26.6, 27.5, 33.5, 34.1, 34.9, 36.2, 36.7, 38.2, 39.4, 44.9, 56.9, 69.8, 125.5, 127.7, 128.5, 139.7, 153.5, 171.6, 174.5. HRMS (EI) *m/z* Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2983.

5.1.34. (3*S*,4*R*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (52). According to general procedure I, the imide **51** (167 mg, 0.375 mmol) provided the carboxylic acid **52** as a colorless oil (102 mg, 91%): $[\alpha]_D^{25}=+38.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3218, 2964, 1728, 1634, 1456, 1404, 1381, 1246, 1192, 1084; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.77–0.82 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.04–1.09 (2H, m, C_9–CH_2), 1.15–1.60 (6H, m, $C_{3'}$–CH_2, C_8–*CH*, C_{10}–*CH*, C_{11}–CH_2), 1.76–1.95 (2H, m, C_6–*CH*, C_7–*CH*), 2.17–2.26 (1H, m, C_6–*CH*), 2.54–2.69 (1H, m, $C_{2'}$–*CH*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.23–3.33 (2H, m, C_{12}–CH_2), 12.0 (1H, bd-s, COO*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 16.0, 16.4, 17.2, 19.1, 26.7, 27.5, 33.7, 34.6, 34.7, 36.2, 36.7, 37.8, 39.4, 44.9, 174.1, 174.5. HRMS (EI) *m/z* Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2450.

5.1.35. (4*S*)-4-Ethenyl-2-[(2*S*,3*R*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (53b). According to general procedure J (using (2*S*)-*N*-Boc-amino-3-butenol *ent*-**32**) and procedure K, the carboxylic acid **52** (61.2 mg, 0.204 mmol) provided the oxazoline **53b** as a colorless oil (56.0 mg, 82%, 2 steps): $[\alpha]_D^{26}=-13.7$ (*c* 0.11, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2961, 1667, 1647, 1464, 1379, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=7.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=7.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.14 (2H, m, C_9–CH_2), 1.15–1.61 (6H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*, C_{11}–CH_2), 1.73–1.89 (1H, bd-m, C_7–C*H*), 1.90–2.05 (1H, m, C_6–C*H*), 2.16–2.29 (1H, m, C_6–C*H*), 2.54–2.69 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.24–3.32 (2H, m, C_{12}–CH_2), 3.84 (1H, app t, *J*=8.1 Hz, C_4–C*H*), 4.31 (1H, app t, *J*=8.4 Hz, C_4–C*H*), 4.47–4.60 (1H, m, C_3–C*H*), 5.07 (1H, d, *J*=10.2 Hz, C_1–C*H*), 5.18 (1H, d, *J*=17.1 Hz, C_1–C*H*), 5.80 (1H, ddd, *J*=6.6, 10.2, 17.1 Hz, C_2–C*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.1, 19.1, 26.6, 27.4, 31.1, 33.5, 34.7, 35.3, 36.2, 36.7, 39.4, 44.9, 67.4, 71.1, 115.3, 139.1, 166.6, 174.8. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2940.

5.1.36. (3*S*,7*S*,8*R*,10*R*,2′*S*)-Kalkitoxin (6). According to general procedures L and M, the oxazoline **53b** (54.1 mg, 0.154 mmol) provided the synthetic (3*S*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**6**) as a pale yellow oil (33.7 mg, 61%, 2 steps): $[\alpha]_D^{26}=-7.5$ (*c* 0.80, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2928, 2874, 1646, 1464, 1412, 1381, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, *J*=7.1 Hz, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=7.1 Hz, $C_{2'}$–CH_3), 1.01–1.16 (2H, m, C_9–CH_2), 1.17–1.62 (6H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*, C_{11}–CH_2), 1.73–1.89 (1H, bd-m, C_7–C*H*), 2.17–2.30 (1H, m, C_6–C*H*), 2.40–2.47 (1H, m, C_6–C*H*), 2.55–2.68 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.02 (1H, dd, *J*=8.0, 10.9 Hz, C_4–C*H*), 3.25–3.39 (2H, m, C_{12}–CH_2), 3.48 (1H, dd, *J*=8.0, 10.9 Hz, C_4–C*H*), 4.85–4.97 (1H, m, C_3–C*H*), 5.10 (1H, d, *J*=10.4 Hz, C_1–C*H*), 5.23 (1H, d, *J*=17.1 Hz, C_1–C*H*), 5.90 (1H, ddd, *J*=6.4, 10.4, 17.1 Hz, C_2–C*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.69, 16.01($CH_3\times2$), 17.13, 19.08, 26.63, 27.47, 33.38, 34.70, 34.91, 36.19, 36.67, 37.48, 37.84, 39.40, 44.87, 77.90, 115.25, 137.96, 169.18, 174.80. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2693.

5.1.37. (4*R*)-4-Ethenyl-2-[(2*S*,3*R*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido-heptyl)]oxazoline (53a). According to general procedures J and K, the carboxylic acid **52** (57.8 mg, 0.193 mmol) provided the oxazoline **53a** as a colorless oil (52.0 mg, 82%): $[\alpha]_D^{25}=+95.4$ (*c* 0.89, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1660, 1645, 1464, 1381, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=7.0 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.15 (2H, m, C_9–CH_2), 1.16–1.61 (6H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*, C_{11}–CH_2), 1.71–1.89 (1H, m, C_7–C*H*), 1.90–2.05 (1H, m, C_6–C*H*), 2.16–2.28 (1H, m, C_6–C*H*), 2.54–2.69 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.24–3.34 (2H, m, C_{12}–CH_2), 3.84 (1H, app t, *J*=8.1 Hz, C_4–C*H*), 4.31 (1H, app t, *J*=8.4 Hz, C_4–C*H*), 4.46–4.60 (1H, m, C_3–C*H*), 5.07 (1H, d, *J*=10.4 Hz, C_1–C*H*), 5.17 (1H, d, *J*=17.1 Hz, C_1–C*H*), 5.80 (1H, ddd, *J*=17.1, 10.6, 6.6 Hz, C1–C*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.7, 15.9, 16.2, 17.2, 19.1, 26.7, 27.5, 31.1, 33.5, 34.9, 35.2, 36.2, 36.7, 44.9, 67.4, 71.1, 115.1, 138.9, 166.3, 174.5. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2934.

5.1.38. (3*R*,7*S*,8*R*,10*R*,2′*S*)-Kalkitoxin (5). According to general procedures L and M, the oxazoline **53a** (48.4 mg, 0.138 mmol) provided the synthetic (3*R*,7*S*,8*R*,10*R*,2′*S*)-kalkitoxin (**5**) as a pale yellow oil (33.6 mg, 70%, 2 steps): $[\alpha]_D^{26}=+77.2$ (*c* 0.83, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2930, 2876, 1640, 1464, 1412, 1381, 1082; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.88 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, *J*=7.1 Hz, $C_{2'}$–CH_3), 0.97 (3H, d, *J*=7.1 Hz, $C_{2'}$–CH_3), 1.01–1.17 (2H, m, C_9–CH_2), 1.18–1.63 (6H, m, $C_{3'}$–CH_2, C_8–C*H*, C_{10}–C*H*, C_{11}–CH_2), 1.72–1.90 (1H, bd-m, C_7–C*H*), 2.18–2.31 (1H, m, C_6–C*H*), 2.38–2.46 (1H, m, C_6–C*H*), 2.54–2.70 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.97 (3H, s, 1 rotamer, N–CH_3), 3.03 (1H, dd, *J*=8.3, 10.9 Hz, C_4–C*H*), 3.25–3.36 (2H, m, C_{12}–CH_2), 3.48 (1H, dd, *J*=8.3, 10.9 Hz, C_4–C*H*), 4.85–4.98 (1H, m, C_3–C*H*), 5.10 (1H, d, *J*=10.4 Hz, C_1–C*H*), 5.23 (1H, d, *J*=17.1 Hz, C_1–C*H*), 5.90 (1H, ddd, *J*=6.6, 10.4, 17.1 Hz, C_2–C*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.70, 15.98 ($CH_3\times2$), 17.13, 19.04, 26.64, 27.47, 33.41, 34.71, 34.92, 36.20, 36.66, 37.47, 37.86, 39.40, 44.90, 77.88, 115.21, 138.00, 169.21, 174.80. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2710.

5.1.39. (2*R*,3*R*,4*S*)-1-Benzyloxy-2,4-dimethyl-3,6-hexanediol (16). To a solution of the benzyloxyhexene **15**[7] (101 mg, 0.431 mmol) in THF (2 mL) was added 9-borabicyclononane dimer (322 mg, 1.29 mmol). The resulting solution was stirred for 10 min, and then placed in a water bath and sonicated for 40 min. Aqueous NaOH solution (4 N, 1 mL) and 30% aqueous H_2O_2 (1 mL) were added sequentially at −5 °C. The resulting mixture was diluted with water and extracted with EtOAc (×2). The combined organic extracts were washed with 1 M aqueous $KHSO_4$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:1) to afford the desired product **16** as a colorless oil (99 mg, 91%): $[\alpha]_D^{24}=+7.9$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3367 (bd), 2875, 1454, 1363, 1089; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86 (3H, d, *J*=6.7 Hz, C_8–CH_3), 0.98 (3H, d, *J*=6.7 Hz, C_{10}–CH_3), 1.54–1.96 (4H, m, C_7–CH_2, C_8–C*H*, C_{10}–C*H*), 3.49–3.64 (4H, m, CH_2O, CH_2OH), 3.71–3.79 (1H, m, C_9–C*H*), 4.49 (1H, d, *J*=11.9 Hz, Ar–CH_2), 4.54 (1H, d, *J*=11.9 Hz, Ar–CH_2), 7.28–7.38 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 9.5, 17.5, 34.7, 34.9, 37.9, 61.2, 73.5, 76.5, 78.5, 127.5, 127.7, 128.4, 137.8. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.14; H, 9.66.

5.1.40. (2*R*,3*R*,4*S*)-1-Benzyloxy-2,4-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-3-hexanol (17). To a solution of the diol **16** (1.08 g, 4.29 mmol) in DMF (20 mL) was added *tert*-butyldiphenylsilyl chloride (1.3 mL, 4.72 mmol), imidazole (585 mg, 8.58 mmol) at 0 °C. After 5 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ether, and washed with water (×5), 1 M aqueous $KHSO_4$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=9:1–4:1–2:1) to afford the desired product **17** as a colorless oil (1.65 g, 78%): $[\alpha]_D^{25}=+3.9$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3453 (bd), 2858, 1496, 1427, 1111, 1089; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.81 (3H, d, *J*=6.9 Hz, C_8–CH_3), 0.95 (3H, d, *J*=6.9 Hz, C_{10}–CH_3), 1.05 (s, 9H, $(CH_3)_3C$), 1.45–2.04 (4H, m, C_7–CH_2, C_8–C*H*, C_{10}–C*H*), 3.46–3.82 (5H, m, CH_2O ×2, C_9–C*H*), 4.51 (2H, s, Ar–CH_2), 7.27–7.73 (15H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 9.8, 16.5, 19.1, 26.8, 33.7, 35.3, 35.8, 62.3, 73.3, 75.0, 76.8, 127.5, 127.6, 127.7, 128.3, 128.4, 129.6, 133.6, 134.8, 135.6, 138.4. Anal. Calcd for $C_{31}H_{42}O_3Si$: C, 75.87; H, 8.63. Found: C, 75.70; H, 8.66.

5.1.41. (2*R*,3*R*,4*S*)-*O*-Phenyl-3-[1-benzyloxy-2,4-dimethyl-6-(*tert*-butyldiphenylsilyloxy)-hexyl]thiocarbonate (18). To a solution of the alcohol **17** (297 mg, 0.606 mmol) in THF (19 mL) under argon at −78 °C was added *n*-BuLi (0.46 mL, 0.727 mmol, 1.6 M in hexane) dropwise via syringe. The solution was stirred at −78 °C for 5 min, then phenyl chlorothionoformate (0.10 mL, 0.727 mmol) was added dropwise. After 15 min, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 1 h. Cold (0 °C) water was then added. The mixture was diluted with ether and washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=12:1) to afford the desired product **18** as a yellow oil (330 mg, 87%): $[\alpha]_D^{25}=-9.6$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2858, 1740, 1489, 1282, 1197, 1111; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.90 (3H, d, *J*=6.7 Hz, C_8–CH_3), 1.01 (3H, d, *J*=6.7 Hz, C_{10}–CH_3), 1.06 (s, 9H, $(CH_3)_3C$), 1.25–1.45 (1H, m, C_8–C*H*), 1.82–1.98 (1H, m, C_{10}–C*H*), 2.12–2.30 (2H, m, C_7–CH_2), 3.34–3.47 (2H, m, CH_2O), 3.63–3.77 (2H, m, CH_2O), 4.43 (1H, d, *J*=11.6 Hz, Ar–CH_2), 4.51 (1H, d, *J*=11.6 Hz, Ar–CH_2), 5.52 (1H, dd, *J*=4.3, 6.9 Hz, C_9–C*H*), 7.00–7.68 (20H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 11.7, 15.9, 19.2, 26.9, 31.8, 34.5, 35.6, 61.7, 72.6, 73.3, 90.1, 121.9, 126.3, 127.5, 127.6, 127.7, 128.3, 129.4, 129.6, 133.8, 133.9, 135.5, 138.3, 153.4, 195.6. Anal. Calcd for $C_{38}H_{46}O_4SSi$: C, 72.80; H, 7.40. Found: C, 72.62; H, 7.32.

5.1.42. (2*S*,4*R*)-1-Benzyloxy-6-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexane (19). Under argon, the thiocarbonate **18** (247 mg, 0.394 mmol) was dissolved in *n*-Bu_3SnH (1 mL) and AIBN (3 mg) was added. The mixture was heated to 100 °C. After 20 min, the reaction mixture was cooled to room temperature and then purified by silica gel column chromatography (BW-200, hexane–hexane/Et_2O=20:1) to afford the desired product **19** as a colorless oil (128 mg, 68%): $[\alpha]_D^{26}=-3.3$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2857, 1495, 1427, 1361, 1207, 1111; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.80 (3H, d, *J*=6.6 Hz, C_8–CH_3), 0.89 (3H, d, *J*=6.6 Hz, C_{10}–CH_3), 1.04 (s, 9H, $(CH_3)_3C$), 1.10–1.62 (4H, m, C_7–CH_2,C_9–CH_2), 1.65–1.95 (2H, m, C_8–C*H*, C_{10}–C*H*), 3.17–3.32 (2H, m, CH_2O), 3.62–3.74 (2H, m, CH_2O), 4.46 (1H, d, *J*=12.2 Hz, Ar–CH_2), 4.51 (1H, d, *J*=12.2 Hz, Ar–CH_2), 7.27–7.69 (15H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 17.2, 19.6, 19.7, 26.8, 27.2, 31.2, 40.9, 41.4, 62.4, 73.3, 76.9, 127.7, 127.8, 127.9, 128.6, 129.8, 134.5, 135.9, 139.2. Anal. Calcd for $C_{31}H_{42}O_2Si$: C, 78.43; H, 8.92. Found: C, 78.37; H, 8.90.

5.1.43. (3*R*,5*S*)-6-Benzyloxy-3,5-dimethylhexanol (20). To a solution of the deoxyganated product **19** (90 mg, 0.189 mmol) in THF (1 mL) was added TBAF (100 mg, 0.380 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 35 min. The reaction mixture was diluted with EtOAc, and washed with water (×2) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=4:1) to afford the desired product **20** as a colorless oil (39 mg, 87%): $[\alpha]_D^{26}=-11.0$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3368 (bd), 2928, 1454, 1377, 1096, 1074; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.88 (3H, d, *J*=6.7 Hz, C_8–CH_3), 0.91 (3H, d, *J*=6.6 Hz, C_{10}–CH_3), 1.05–1.36 (2H, m, C_9–CH_2), 1.36–1.65 (3H, m, C_7–CH_2, O*H*), 1.82–1.95 (1H, m, C_{10}–C*H*), 3.24 (1H, dd, *J*=6.6, 8.9 Hz, CH_2O), 3.30 (1H, dd, *J*=6.6, 8.9 Hz, CH_2O), 3.62–3.69 (2H, m, CH_2OH), 4.50 (2H, s, Ar–CH_2), 7.27–7.35 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.9, 19.3, 26.6, 30.8, 40.6, 41.2, 60.9, 72.9, 76.5, 127.4, 127.5, 128.3, 138.7. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.94; H, 10.43.

5.1.44. (2*S*,4*R*)-5-Azido-1-benzyloxy-2,4-dimethylhexane (21). To a solution of the alcohol **20** (1.04 g, 4.40 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (1.2 mL, 8.8 mmol), methanesulfonyl chloride (0.51 mL, 6.6 mmol), DMAP (16 mg, 0.132 mmol) at 0 °C. After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 11 h. The mixture was diluted with EtOAc, and washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the crude mesylate as a pale yellow oil (1.38 g). This intermediate was used in the next reaction without further purification.

To a solution of the above mesylate in DMF (15 mL) at room temperature was added sodium azide (855 mg, 13.2 mmol), and then the mixture was heated to 50 °C. After 2 h, the resulting mixture was diluted with ether, and washed with water (×5) and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=12:1) to afford the desired product **21** as a colorless oil (1.01 mg, 88%): $[\alpha]_D^{26}=-8.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2925, 2096, 1728, 1454, 1265, 1099; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.88 (3H, d, *J*=7.3 Hz, C_8–CH_3), 0.91 (3H, d, *J*=6.9 Hz, C_{10}–CH_3), 1.03–1.31 (2H, m, C_9–CH_2), 1.35–1.72 (3H, m, C_7–CH_2, C_8–C*H*), 1.79–1.95 (1H, m, C_{10}–C*H*), 3.20–3.34 (4H, m, CH_2O, CH_2N_3), 4.50 (2H, s, Ar–CH_2), 7.33 (5H, s, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 16.8, 18.9, 27.5, 30.8, 36.5, 40.8, 49.4, 72.9, 76.5, 127.4, 127.5, 128.3, 138.7. Anal. Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 69.01; H, 8.83; N, 15.77.

5.1.45. (2*S*)-*N*-((3*R*,5*S*)-3,5-Dimethyl-6-benzyloxy-hexyl)-2-methylbutyramide (23). To a solution of the azide **21** (248 mg, 0.950 mmol) in EtOH (10 mL) was added Lindlar catalyst (5% Pd on carbon/Pb–$CaCO_3$) (100 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated to give the crude amine as a yellow oil (228 mg). This intermediate was used in the next reaction without further purification.

To a solution of the above amine and (*S*)-2-methylbutyric acid (**22**) (0.11 mL, 0.97 mmol) in DMF (2 mL) at 0 °C was successively added diethyl phosphorocyanidate (0.18 mL, 1.07 mmol) and triethylamine (0.27 mL, 1.94 mmol). After 15 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with EtOAc, and washed with water (×5) and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=2:1) to afford the desired product **23** as a pale yellow oil (298 mg, 97%): $[\alpha]_D^{25}=-1.1$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3296, 2874, 1645, 1556, 1454, 1377, 1236, 1101; ^{1}H NMR (270 MHz, TMS/$CDCl_3$) δ 0.86–0.91 (9H, m, C_8–CH_3, C_{10}–CH_3, $C_{3'}$–CH_3), 1.11(3H, d, *J*=6.6 Hz, $C_{2'}$–CH_3), 1.19–1.70 (7H, m, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.82–1.91(1H, m, C_8–C*H*), 1.99–2.07 (1H, m, $C_{2'}$–C*H*), 3.23–3.32 (4H, m, CH_2O, C_{12}–CH_2), 4.50 (2H, s, Ar–CH_2), 5.50 (1H, bd-s, N*H*), 7.27–7.35 (5H, s, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$) δ 12.2, 17.2, 17.9, 19.5, 27.6, 28.1, 31.1, 37.6, 37.9, 41.3, 43.6, 73.3, 76.9, 127.7, 127.8, 128.6, 139.0, 176.6. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.11; H, 10.28; N, 4.37.

5.1.46. (2*S*)-*N*-Methyl-*N*-((3*R*,5*S*)-3,5-dimethyl-6-benzyl-oxy-hexyl)-2-methylbutyramide (24). To a solution of the amide **23** (108 mg, 0.333 mmol) in THF (1.5 mL) under argon at 0 °C was added NaH (133 mg, 3.33 mmol). The solution was stirred at −78 °C for 20 min, then CH_3I (0.3 mL, 4.82 mmol) was added. After 10 min, the cooling bath was removed, and the reaction mixture was stirred at room temperature. After 20 h, water was added to the mixture, which was diluted with EtOAc, and washed with water, 1 M aqueous $KHSO_4$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography (BW-820MH, hexane/EtOAc=2:1) to afford the desired product **24** as a pale yellow oil (106 mg, 94%): $[\alpha]_D^{28}=+9.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2874, 1643, 1454, 1410, 1375, 1099; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.75–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.93–0.98 (3H, m, $C_{2'}$–CH_3), 1.06–1.57 (7H, m, $C_{3'}$–CH_2, C_9–CH_2, C_8–C*H*, C_{11}–CH_2), 1.71–1.85 (1H, m, C_{10}–C*H*), 2.51–2.67 (1H, m, $C_{2'}$–C*H*), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.93 (3H, s, 1 rotamer, N–CH_3), 3.12–3.47 (4H, m, C_{12}–CH_2, CH_2O), 4.44 (2H, s, Ar–C*H*2), 7.22–7.37 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 11.6, 11.8, 16.7, 17.1, 17.8, 19.1, 26.7, 27.0, 27.1, 27.3, 30.3, 33.1, 34.4, 34.5, 36.1, 36.2, 36.4, 40.6, 41.1, 44.7, 47.1, 71.9, 75.6, 75.7, 127.3, 128.2, 128.6, 138.7, 174.8, 175.0. Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.45; H, 10.65; N, 4.23.

5.1.47. (2*S*)-*N*-Methyl-*N*-((3*R*,5*S*)-3,5-dimethyl)-6-hexa-nol (25). To a solution of the amide **24** (91 mg, 0.269 mmol) in EtOH (1.5 mL) was added 5% Pd on carbon (40 mg) at room temperature. The black slurry was stirred under 1 atm H_2 for 1 h. The reaction mixture was filtered through a pad of celite (EtOAc rinse) and the filtrate was concentrated. The residue was purified by silica gel column chromatography (BW-8280 MH, hexane/EtOAc=1:1–EtOAc) to afford the desired product **25** as a colorless oil (67 mg, quant.): $[\alpha]_D^{29}=+8.2$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3410 (bd), 2874, 1628, 1464, 1416, 1379, 1045; ^{1}H NMR (270 MHz, TMS/$CDCl_3$), both rotamers unless stated otherwise, δ 0.76–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.93–0.99 (3H, m, $C_{2'}$–CH_3), 1.07–1.62 (8H, m, C_9–CH_2, $C_{3'}$–CH_2, C_{11}–CH_2, C_8–C*H*, C_{10}–C*H*), 2.51–2.67 (1H, m, $C_{2'}$–C*H*), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.12–3.49 (4H, m, C_{12}–CH_2, CH_2O), 4.33–4.41 (1H, bd-m, O*H*); ^{13}C NMR (67.8 MHz, $CHCl_3$/$CDCl_3$), both rotamers, δ 11.6, 11.8, 16.4, 16.5, 17.1, 17.8, 19.2, 26.7, 27.0, 27.2, 27.4, 32.8, 33.1, 34.6, 34.7, 36.1, 36.2, 36.6, 40.4, 40.8, 44.8, 47.2, 66.8, 66.9, 174.8, 175.0. Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 68.81; H, 12.07; N, 5.66.

5.1.48. (4*R*)-Phenyl-3-[(4*R*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxa-zolidinone (27a). According to general procedure G, the alcohol **25** (67 mg, 0.275 mmol) provided the enimide **27a** as a colorless oil (104 mg, 85%): $[\alpha]_D^{25}=-30.7$ (*c* 1.1, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2964, 1770, 1687, 1633, 1456, 1383, 1197; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.65–0.87 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.91–0.99 (3H, m, $C_{2'}$–CH_3), 1.13–1.38 (5H, m, C_9–CH_2, C_{10}–C*H*, C_{11}–CH_2), 1.39–1.58 (2H, m, $C_{3'}$–CH_2), 2.39–2.60 (2H, m, $C_{2'}$–C*H*, C_8–*H*), 2.77 (3H, s, 1 rotamer, N–CH_3), 2.89 (3H, s, 1 rotamer, N–CH_3), 3.05–3.16 (2H, m, 1 rotamer, C_{12}–CH_2), 3.18–3.35 (2H, m, 1 rotamer, C_{12}–CH_2), 4.16 (1H, dd, *J*=3.6, 8.7 Hz, CH_2O), 4.75 (1H, t, *J*=8.7 Hz, Ar–C*H*), 5.49 (1H, dd, *J*=3.6, 8.7 Hz, CH_2O), 6.81 (1H, ddd, *J*=2.3, 7.9, 15.3 Hz, C_6–C*H*), 7.15 (1H, d, *J*=15.3 Hz, C_7–C*H*), 7.27–7.40 (5H, m, Ar*H*); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.5, 17.1, 19.1, 19.5, 26.7, 27.4, 33.2, 33.8, 34.4, 36.2, 39.4, 42.8, 57.1, 70.1, 118.7, 125.9, 128.0, 128.8, 139.9, 153.7, 155.6, 163.8, 174.8. Anal. Calcd For $C_{25}H_{36}N_2O_4$: C, 70.06; H, 8.47; N, 6.54. Found: C, 69.92; H, 8.74; N, 6.34.

5.1.49. (4*R*)-4-Phenyl-3-[(3*R*,4*S*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxa-zolidinone (30a). According to general procedure H, the enimide **27a** (37 mg, 0.0864 mmol) provided the imide **30a** as a colorless oil (41 mg, quant.): $[\alpha]_D^{25}=-35.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2963, 1782, 1705, 1639, 1456, 1385, 1323, 1197; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.71–0.82 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=6.6 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.96 (3H, d, J=6.6 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.02–1.12 (2H, m, C_9–CH_2), 1.16–1.59 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.82–1.98 (1H, m, C_7–CH), 2.50–2.76 (3H, m, $C_{2'}$–CH, C_6–CH_2), 2.78 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.11–3.42 (2H, m, C_{12}–CH_2), 4.13 (1H, dd, J=8.6, 3.6 Hz, CH_2O), 4.72 (1H, t, J=8.6 Hz, Ar–CH), 5.46 (1H, dd, J=8.6, 3.6 Hz, CH_2O), 7.26–7.41 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.9, 16.4, 17.4, 18.0, 19.1, 27.0, 27.6, 33.8, 34.4, 34.9, 36.4, 36.5, 37.1, 39.4, 45.0, 57.3, 70.2, 126.0, 128.2, 129.0, 140.3, 154.0, 172.1, 175.1. Anal. Calcd For $C_{26}H_{40}N_2O_4$· or 1/5H_2O: C, 69.67; H, 9.09; N, 6.25. Found: C, 69.81; H, 9.14; N, 6.24.

5.1.50. (3*R*,4*S*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (31a). According to general procedure I, the imide **30a** (84 mg, 0.189 mmol) provided the carboxylic acid **31a** as a colorless oil (50 mg, 88%): $[\alpha]_D^{25}$=−3.9 (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3278 (bd), 2964, 1728, 1634, 1456, 1379, 1247, 1184, 1102; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.02–1.12 (2H, m, C_9–CH_2), 1.17–1.59 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.72–1.98 (2H, m, C_6–CH, C_7–CH), 2.16–2.27 (1H, m, C_6–CH), 2.52–2.71 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.24–3.42 (2H, m, C_{12}–CH_2), 12.0 (1H, bd-s, COOH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 15.9, 16.4, 17.1, 19.0, 26.7, 27.4, 33.7, 34.6, 34.8, 36.2, 36.8, 37.8, 39.4, 44.7, 174.4, 174.8. Anal. Calcd For $C_{17}H_{33}NO_3$· or 1/4H_2O: C, 67.18; H, 11.11; N, 4.61. Found: C, 67.16; H, 11.20; N, 4.63.

5.1.51. (4*R*)-4-Ethenyl-2-[(2*R*,3*S*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (34a). According to general procedure J, the carboxylic acid **31a** (60.1 mg, 0.201 mmol) provided the amide **33a** as a colorless oil (68.4 mg, 92%), which was directly used for the next step. To a solution of amide (61.0 mg, 0.166 mmol) in THF (1 mL) was added Burgess reagent (83 mg, 0.662 mmol) under argon. The mixture was heated to 70 °C. After 2 h, the reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired oxazoline **34a** as a colorless oil (37.8 mg, 65%): $[\alpha]_D^{28}$=+41.6 (*c* 0.68, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2968, 1667, 1644, 1464, 1379, 1196; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.75–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.00–1.15 (2H, m, C_9–CH_2), 1.16–1.62 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.71–1.88 (1H, m, C_7–CH), 1.89–2.03 (1H, m, C_6–CH), 2.15–2.27 (1H, m, C_6–CH), 2.56–2.72 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.15–3.25 (2H, m, C_{12}–CH_2), 3.84 (1H, app t, J=7.9 Hz, C_4–CH), 4.31 (1H, app t, J=8.3 Hz, C_4–CH), 4.47–4.60 (1H, m, C_3–CH), 5.07 (1H, d, J=10.2 Hz, C_1–CH), 5.17 (1H, d, J=16.8 Hz, C_1–CH), 5.80 (1H, ddd, J=17.2, 10.6, 6.9 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 16.0, 16.3, 17.1, 19.0, 26.7, 27.3, 31.1, 33.5, 34.8, 35.3, 36.2, 36.8, 39.4, 44.7, 67.4, 115.3, 139.1, 166.6, 174.8. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2935.

5.1.52. (3*R*,7*R*,8*S*,10*R*,2′*S*)-Kalkitoxin (1). According to general procedures L and M, the oxazoline **34a** (37.0 mg, 0.105 mmol) provided the synthetic (3*R*,7*R*,8*S*,10*R*,2′*S*)-kalkitoxin (**1**) as a pale yellow oil (18.9 mg, 50%, 2 steps): $[\alpha]_D^{27}$=+15.5 (*c* 0.75, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2928, 2874, 1646, 1464, 1412, 1379, 1084; ^{1}H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.76–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.01–1.15 (2H, m, C_9–CH_2), 1.17–1.63 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.71–1.90 (1H, bd–m, C_7–CH), 2.17–2.29 (1H, m, C_6–CH_2), 2.39–2.46 (1H, m, C_6–CH_2), 2.53–2.71 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.02 (1H, dd, J=8.3, 11.2 Hz, C_4–CH), 3.11–3.31 (2H, m, C_{12}–CH_2), 3.45 (1H, dd, J=8.3, 11.2 Hz, C_4–CH), 4.84–4.96 (1H, m, C_3–CH), 5.10 (1H, d, J=10.9 Hz, C_1–CH), 5.23 (1H, d, J=16.8 Hz, C_1–CH), 5.90 (1H, ddd, J=6.6, 10.9, 16.8 Hz, C_2–CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.65, 16.07 (CH_3×2), 17.11, 19.00, 26.69, 27.35, 33.43, 34.59, 34.85, 36.19, 36.70, 37.49, 37.87, 39.39, 44.69, 77.90, 115.26, 137.95, 169.24, 174.81. HRMS (EI) *m/z* Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2715.

5.1.53. (4*S*)-Phenyl-3-[(4*R*,6*R*)-4,6-dimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-(*E*)-2-octenoyl]-2-oxazolidinone (27b). According to general procedure G (using (*S*)-phosphonate *ent*-**26**), the alcohol **25** (131 mg, 0.538 mmol) provided the enimide **27b** as a colorless oil (188 mg, 82%): $[\alpha]_D^{24}$=+93.9 (*c* 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2960, 1779, 1688, 1634, 1458, 1383, 1200; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.72–0.91 (9H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.92–1.01 (3H, m, $C_{2'}$–CH_3), 1.15–1.38 (5H, m, C_9–CH_2, C_{10}–CH, C_{11}–CH_2), 1.39–1.61 (2H, m, $C_{3'}$–CH_2), 2.40–2.66 (2H, m, $C_{2'}$–CH, C_8–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.95 (3H, s, 1 rotamer, N–CH_3), 3.15–3.42 (2H, m, C_{12}–CH_2), 4.18 (1H, dd, J=3.4, 8.7 Hz, CH_2O), 4.76 (1H, t, J=8.7 Hz, Ar–CH), 5.51 (1H, dd, J=3.4, 8.7 Hz, CH_2O), 6.83 (1H, dd, J=15.5, 7.9 Hz, C_6–CH), 7.15 (1H, d, J=15.5 Hz, C_7–CH), 7.27–7.41 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 17.1, 18.9, 19.5, 26.7, 27.5, 33.1, 33.8, 34.5, 36.2, 42.7, 57.1, 70.1, 118.5, 125.9, 128.0, 128.8, 139.8, 153.8, 155.8, 163.9, 175.0. HRMS (EI) *m/z* Calcd for $C_{25}H_{36}N_2O_4$: 428.2675. Found: 428.2670.

5.1.54. (4*S*)-4-Phenyl-3-[(3*S*,4*S*,6*R*)-3,4,6-trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)-octanoyl]-2-oxazolidinone (30b). According to general procedure H, the enimide **27b** (259 mg, 0.604 mmol) provided the imide **30b** as a colorless oil (246 mg, 92%): $[\alpha]_D^{27}$=+39.2 (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2964, 1782, 1705, 1639, 1385, 1242, 1198; ^{1}H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.68–0.86 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=6.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.96 (3H, d, J=6.1 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.02–1.13 (2H, m, C_9–CH_2), 1.14–1.61 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.84–2.00 (1H, m, C_7–CH), 2.50–2.70 (1H, m, $C_{2'}$–CH), 2.72–2.90 (2H, m, C_6–CH_2), 2.77 (3H, s, 1 rotamer, N–CH_3), 2.93 (3H, s, 1 rotamer, N–CH_3), 3.10–3.49 (2H, m, C_{12}–CH_2), 4.13 (1H, dd, J=8.7, 3.6 Hz, CH_2O), 4.72 (1H, t, J=8.7 Hz, Ar–CH), 5.46 (1H, dd, J=8.7, 3.6 Hz, CH_2O), 7.26–7.39 (5H, m, ArH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.1, 17.1, 17.8, 19.2, 26.7, 27.3, 32.8, 33.1, 33.3, 34.5, 36.1, 36.2, 39.4, 44.6, 57.0, 70.0, 125.7, 127.9, 128.8, 140.0, 153.7, 171.7, 174.8. HRMS (EI) m/z Calcd for $C_{26}H_{40}N_2O_4$: 444.2988. Found: 444.2996.

5.1.55. (3*S*,4*S*,6*R*)-3,4,6-Trimethyl-8-((2*S*)-*N*-methyl-2-methylbutyramido)octanoic acid (31b). According to general procedure I, the imide **30b** (217 mg, 0.489 mmol) provided the carboxylic acid **31b** as a colorless oil (124 mg, 85%): $[\alpha]_D^{25}$=+8.6 (c 1.0, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3250 (bd), 2964, 1724, 1614, 1464, 1383; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.70–0.89 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.95 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=6.8 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.03–1.15 (2H, m, C_9–CH_2), 1.16–1.61 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.77–1.91 (1H, m, C_7–CH), 1.93–2.09 (1H, m, C_6–CH), 2.13–2.27 (1H, m, C_6–CH), 2.54–2.60 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.10–3.52 (2H, m, C_{12}–CH_2), 12.0 (1H, bd-s, COOH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.3, 14.5, 17.1, 19.2, 26.7, 27.2, 33.0, 33.7, 33.8, 34.3, 34.5, 36.2, 39.4, 44.6, 174.2, 174.8. HRMS (EI) m/z Calcd for $C_{17}H_{33}NO_3$: 299.2460. Found: 299.2462.

5.1.56. (4*R*)-4-Ethenyl-2-[(2*S*,3*S*,5*R*)-2,3,5-trimethyl-7-((2*S*)-*N*-methyl-2-methylbutyramido)-heptyl]oxazoline (34b). According to general procedure J, the carboxylic acid **31b** (78.0 mg, 0.260 mmol) provided the amide **33b** as a colorless oil (72.5 mg, 76%), which was directly used for the next step. To a solution of the amide **33b** (70.4 mg, 0.191 mmol) in THF (1.5 mL) was added Burgess reagent (97 mg, 0.764 mmol) under argon. The mixture was heated to 70 °C. After 1.5 h, the reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography (BW-200, hexane/EtOAc=1:3) to afford the desired oxazoline **34b** as a colorless oil (44.1 mg, 66%): $[\alpha]_D^{25}$=+63.5 (c 0.98, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 1663, 1646, 1458, 1379, 1196; ^1H NMR (270 MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.73–0.89 (12H, m, C_3–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=7.3 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=7.3 Hz, 1 rotamer, C_2–CH_3), 1.01–1.16 (2H, m, C_9–CH_2), 1.17–1.63 (6H, m, C_3–CH_2,C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.73–1.90 (1H, m, C_7–CH), 1.95–2.12 (1H, m, C_6–CH), 2.15–2.27 (1H, m, C_6–CH), 2.55–2.72 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.11–3.36 (2H, m, C_{12}–CH_2), 3.85 (1H, app t, J=7.9 Hz, C_4–CH), 4.26–4.36 (1H, m, C_4–CH), 4.47–4.62 (1H, m, C_3–CH), 5.07 (1H, d, J=10.6 Hz, C_1–CH), 5.17 (1H, d, J=16.8 Hz, C_1–CH), 5.80 (1H, ddd, J=16.8, 10.6, 6.6 Hz, C_2–CH); ^{13}C NMR (67.8 MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.6, 14.2, 17.1, 19.2 (CH_3×2), 26.7, 26.7, 27.2, 32.6, 33.1, 34.2, 34.5, 36.1, 36.2, 39.4, 44.5, 67.5, 71.1, 115.3, 139.1, 166.5, 174.8. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2O_2$: 350.2933. Found: 350.2930.

5.1.57. (3*R*,7*S*,8*S*,10*R*,2′*S*)-Kalkitoxin (2). According to general procedures L and M, the oxazoline **34b** (43.5 mg, 0.124 mmol) provided the synthetic (3*R*,7*S*,8*S*,10*R*,2′*S*)-kalkitoxin (**2**) as a pale yellow oil (22.9 mg, 53%, 2 steps): $[\alpha]_D^{26}$=+49.6 (c 0.64, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2963, 2929, 2874, 1646, 1464, 1412, 1381, 1082; ^1H NMR (270MHz, DMSO/DMSO-d_6), both rotamers unless stated otherwise, δ 0.71–0.87 (12H, m, $C_{3'}$–CH_3, C_8–CH_3, C_{10}–CH_3), 0.94 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 0.97 (3H, d, J=6.9 Hz, 1 rotamer, $C_{2'}$–CH_3), 1.01–1.18 (2H, m, C_9–CH_2), 1.19–1.67 (6H, m, $C_{3'}$–CH_2, C_8–CH, C_{10}–CH, C_{11}–CH_2), 1.72–1.90 (1H, bd–m, C_7–CH), 2.22–2.37 (1H, m, C_6–CH_2), 2.38–2.49 (1H, m, C_6–CH_2), 2.55–2.71 (1H, m, $C_{2'}$–CH), 2.79 (3H, s, 1 rotamer, N–CH_3), 2.96 (3H, s, 1 rotamer, N–CH_3), 3.03 (1H, dd, J=8.3, 10.2 Hz, C_4–CH), 3.09–3.25 (2H, m, C_{12}–CH_2), 3.48 (1H, dd, J=8.3, 10.2 Hz, C_4–CH), 4.86–4.99 (1H, m, C_3–CH), 5.10 (1H, d, J=10.3 Hz, C_1–CH), 5.23 (1H, d, J=17.0 Hz, C_1–CH), 5.90 (1H, ddd, J=6.3, 10.3, 17.0 Hz, C_2–CH); ^{13}C NMR (67.8MHz, DMSO/DMSO-d_6), the major rotamer, δ 11.99, 14.40 (CH_3×2), 17.47, 19.63, 27.01, 27.53, 32.89, 34.52, 34.89, 36.52 (CH ×2), 38.90, 40.94, 42.03, 44.89, 78.22, 115.60, 138.28, 169.42, 175.11. HRMS (EI) m/z Calcd for $C_{21}H_{38}N_2OS$: 366.2705. Found: 366.2706.

Acknowledgements

Work in Nagoya was partially supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to F. Y. and T. S.) and Nagoya City University (to F. Y.). Work in Oregon was supported by NIH GM 86354 and the MFBS Center at OSU (ES03850), and a JSPS fellowship to T. O.

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16. The numbering of each intermediate is adopted that of kalkitoxin.
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18. There are two possible influential factors in the methylation of the oxazolidinone **27**: the stereogenic methyl group at the γ-position to the imidocarbonyl group[19] and the phenyl group in the oxazolidinone nucleus. Since the presence of the rotational isomers caused by the *N*-methylamide function gives rise to a complex pattern in ^{1}H NMR spectra, the model compounds **28a**–**c** without the *N*-methylamide group were chosen as reaction substrates to investigate the stereoselectivity of the 1,4-addition, and the stereoselectivity was determined as the carboxylic acid **29** by ^{1}H NMR spectra after removal of the oxazolidinone group. As shown in, the 1,4-addition of methyl magnesium bromide to the achiral oxazolidinone **28b** in the presence of cuprous bromide(dimethyl sulfide followed by alkaline hydroxide afforded a diastereoisomeric mixture of the carboxylic acid **29** in a ratio of 2.6:1 in preference of the (*R*)-isomer **29a**. This will be due to the influence of the stereogenic γ-methyl function.[19] The α,β-unsaturated carbonyl compound **28a** having the Hruby's (*R*)-4-phenyloxazolidinone auxiliary, in which the γ-methyl group would not be influential, diastereoselectively and solely afforded the (3*R*)-carboxylic acid **29a**. On the other hand, the 1,4-addition of the compound **28c** having the (*S*)-4-phenyloxazolidinone moiety also diastereoselectively proceeded through the influence of the (*S*)-phenyl substituent to give the (3*S*)-carboxylic acid **29b** as a sole product. These experiments proved that the influence of the γ-stereogenic center to the 1,4-addition reaction would be little if any (Scheme 3).
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Tetrahedron 60 (2004) 6881–6888
Tetrahedron

Star-shaped conjugated compounds forming nematic discotic systems

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Received 2 April 2004; accepted 3 June 2004

Available online 4 July 2004

Abstract—Star-shaped compounds, having a benzene (**9a**,**b**) or a 1,3,5-triazine (**11a**,**b**) core and stilbenoid arms were prepared. Hexyloxy chains, attached in the middle of the arms, provide nematic discotic phases N_D, which are unusual for such systems. The position of the sidechains prevents the micro-segregation, which is valid for star-shaped discs of columnar phases. The stilbenoid character of **9a**,**b** and **11a**,**b** guarantees a high light sensitivity. Apart from the statistical CC bond formation by irradiation in solution or in the LC phases, a topochemically controlled chemo-, regio- and stereoselective photocyclodimerization **11a→12** was found in the crystalline state. The structure determination of **12** is based on different two-dimensional NMR techniques (COSY, NOESY, HMQC, HMBC).

1. Introduction

Molecules with an arene or hetarene core and three or more conjugated arms, which consist of oligo(1,4-phenylenevinylene) arms (OPV) or oligo(1,4-phenylene-ethynylene) arms (OPE), form (in the time average) planar discs and represent, therefore, suitable mesogens for discotic liquid crystals (LC). Most common are benzene cores[1–17] and 1,3,5-triazine or pyrazine cores[18–23] and long, flexible alkyl or alkoxy chains at the periphery. Such a molecular design provokes the formation of hexagonal or rectangular columnar LC phases having a micro-segregation between the region of the π electron systems and the region of the saturated chains. However, the attachment of alkoxy chains in the middle of the arms should prevent such an arrangement, so that nematic mesophases, formed by single discs or two or more weakly aggregated discs, can be expected. Moreover, we attached CN groups at the periphery of the arms in order to generate a donor–acceptor or an acceptor–donor–acceptor character of the arms. The multipolarity should increase the interaction between the discs. Thus, the molecular concept was based on benzene or 1,3,5-triazine cores with three corresponding stilbenoid arms—as shown for the compounds **9a**,**b** and **11a**,**b** in Scheme 1.

2. Results and discussion

2.1. Synthesis of star-shaped compounds

1,4-Dihexyloxybenzene (**1**) represents an electron-rich arene which enters a twofold electrophilic substitution by an uncatalyzed reaction with bromine.[24–26] The obtained 1,4-dibromo-2,5-dihexyloxybenzene (**2**) can be transformed by a Bouveault reaction to the monoaldehyde **3**. Acetal formation with trimethoxymethane in the presence of Dowex furnishes high yields of the corresponding dimethyl acetal **4**, which gives in a second Bouveault process the mono-protected terephthalaldehyde **5**. The Wittig–Horner reaction of **5** and phosphonate **6a**[27] or **6b**[28] leads to the (*E*)-stilbenes **7a** and **7b**, respectively. The protected aldehyde function is deprotected by acidic work-up (Scheme 1). After the purification of **7a**,**b** by column chromatopraphy, the amount of (*Z*)-isomer is below the limit of detection (3%) in the ^{1}H and ^{13}C NMR spectroscopy. The subsequent Wittig–Horner reaction of the triphosphonate **8**[13,29] with **7a**,**b** yields the target compounds **9a**,**b**. In contrast to mesitylene, 2,4,6-trimethyl-1,3,5-triazine (**10**) shows with the aldehydes **7a**,**b** a smooth threefold condensation reaction, which yields the target compounds **11a**,**b**. Particularly **7b**, which contains an electron-withdrawing CN group, gives high yields of the star-shaped compound **11b**.

2.2. Spectroscopic characterization

The compounds **9a** and **9b** generate yellow solutions in CH_2Cl_2 with λ_{max}=405 nm (ε_{max}=1.24×10^5 L mol^{-1} cm^{-1}) and λ_{max}=418 nm (ε_{max}=1.39×10^5 L mol^{-1} cm^{-1}),

Keywords: Condensation; Liquid crystals; Photoreactivity.
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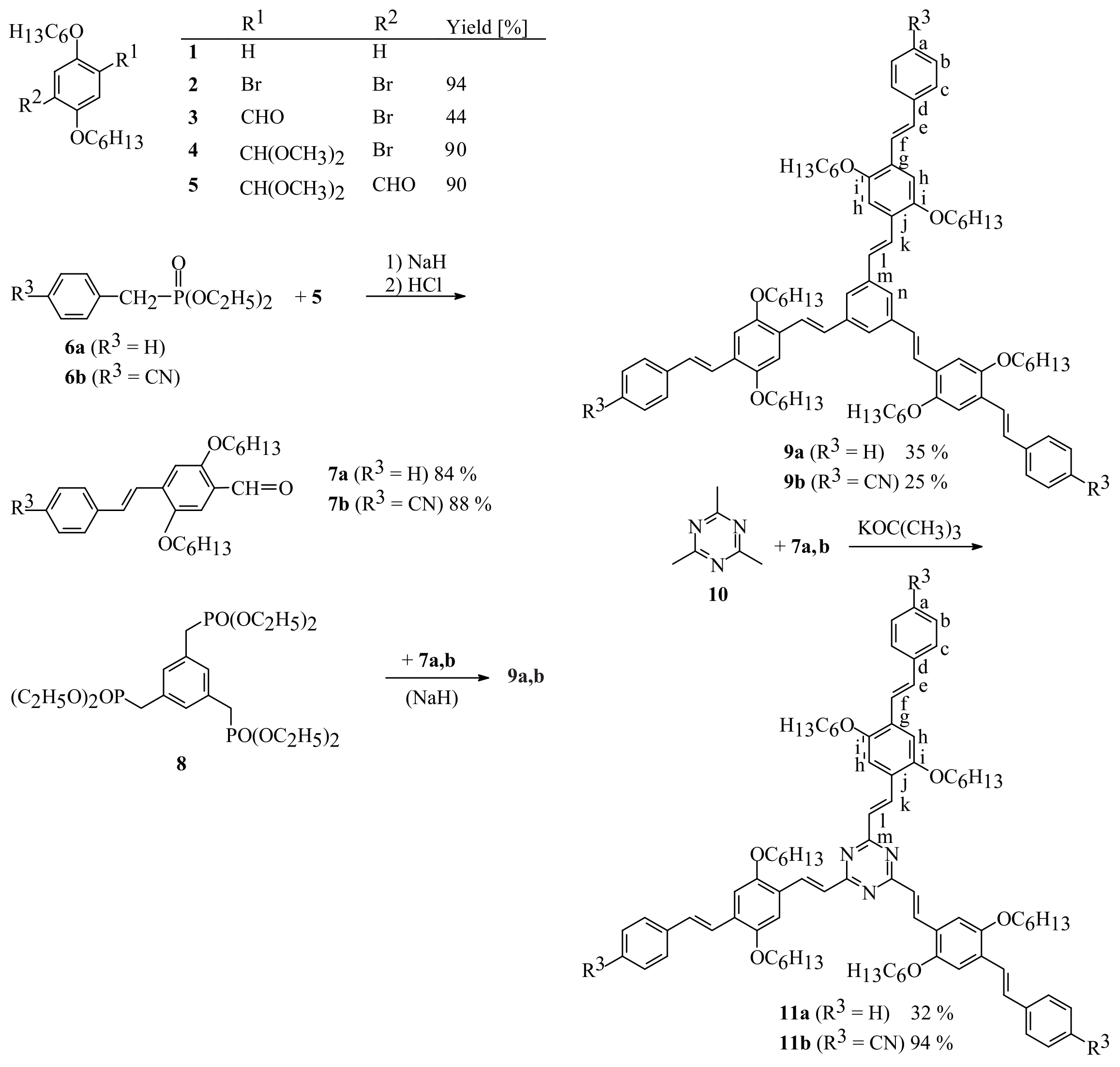
doi:10.1016/j.tet.2004.06.012



Scheme 1. Preparation of the star-shaped compounds **9a**,**b** and **11a**,**b**.

respectively. Due to the 1,3,5-trisubstitution at the central benzene ring, these values correspond to absorptions of 1,4-distyrylbenzenes;[30] the effect of the cross-conjugation can be neglected. The 1,3,5-triazine systems **11a** and **11b** exhibit bathochromically shifted absorption maxima at 431 and 435 nm, respectively [$\varepsilon_{max}=(1.23\pm0.1)\times10^5$ L mol^{-1} cm^{-1}]. Each arm of **11a** can be regarded as an acceptor–donor (A–D) system and of **11b** as an A–D–A system.

The ^{1}H and ^{13}C NMR data of **2**–**5** and **9a**, **9b**, **11a**, **11b** are summarized in the Tables 1 and 2, respectively. The assignment of the signals to certain ^{1}H and ^{13}C nuclei is based on two-dimensional measurements (HMQC and HMBC).[31] The (*E*)-configurations of the CC double bonds are certified by coupling constants ^3J (H,H)=16.2±0.2 Hz for the olefinic AB spin systems. The IR and MS data of **2**–**5**, **9a**,**b** and **11a**,**b** as well as IR, NMR and MS data of the stilbenes **7a** and **7b** are listed in Section 4.

Table 1. ^{1}H and ^{13}C NMR data of **2-5** (solvent: $CDCl_3$, TMS as internal standard)

Compound	C-1	C-2	HC-3	C-4	C-5	HC-6	α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	ε-CH_2	CH_3	R^1, R^2
2			7.06			7.06	3.92	1.78	1.41	1.31	1.31	0.89	
	111.2	150.1	118.5	111.2	150.1	118.5	70.4	29.1	25.6	31.5	22.5	14.0	
3			7.19			7.27	3.98	1.78	1.41	1.31	1.31	0.88	10.38/188.9 (CHO)
	124.3	155.6	118.5	121.0	149.9	110.7	69.5	29.0	25.6	31.5	22.6	14.0	
							69.9						
4			7.07			7.05	3.93	1.76	1.45	1.31	1.31	0.88	3.36/54.2 (OCH_3)
	126.8	151.0	117.4	112.6	149.6	112.6	69.4	29.2	25.7	31.5	22.6	14.0	5.54/99.3 (CH)
							70.1						
5			7.28			7.17	3.96	1.78	1.43	1.31	1.31	0.88	10.44/189.6 (CHO)
							4.04						3.40/54.6 (OCH_3)
	124.7	156.1	109.8	134.7	150.5	112.1	68.9	29.2	25.7	31.5	22.6	14.0	5.58/99.3 (CH)
							69.2						

Table 2. ^{1}H and ^{13}C NMR data of the star-shaped compounds **9a**, **9b**, **11a** and **11b** ($CDCl_3$, TMS an internal standard)

Compound	Positions (shown in Scheme 1)										
	a	b	c	d	e	f	g	h,h′	i,i′	j	k
9a	7.26	7.37	7.54	—	7.15	7.51	—	7.15/7.16	—	—	7.55
	127.2	128.6	126.6	138.1	129.0	123.7	127.1	111.0/111.2	151.3/151.3	127.1	124.3
9b	—	7.62	7.59	—	7.13	7.60	—	7.12/7.15	—	—	7.53
	119.1	132.4	126.9	142.6	127.4	126.9	125.9	111.0/111.2	151.2/151.6	128.2	124.2
11a	7.27	7.36	7.55	—	7.18	7.49	—	7.16/7.23	—	—	8.60
	127.6	128.6	126.5	137.7	129.9	123.3	129.2	110.0/111.3	150.9/152.3	125.1	136.3
11b	—	7.63	7.56	—	7.17	7.58	—	7.13/7.23	—	—	8.59
	119.1	132.5	126.8	142.2	127.8	127.3	127.9	110.9/111.8	151.2/152.2	126.1	136.2
	l	m	n	α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	ε-CH_2	CH_3	CN	
9a	7.21	—	7.59	4.06/4.10	1.90	1.56	1.40	1.40	0.88/0.93	—	
	128.9	138.7	124.0	69.7/69.8	29.5/29.6	25.9/26.0	31.6/31.7	22.6	14.0	—	
9b	7.22	—	7.56	4.07/4.08	1.89	1.55	1.38	1.38	0.87/0.92	—	
	129.5	138.6	124.2	69.6/69.8	29.5	26.0	31.6	22.6	14.0	119.1	
11a	7.21	—	—	4.04/4.11	1.90	1.55	1.38	1.38	0.85/0.92	—	
	126.7	171.5	—	69.4/69.6	29.3/29.4	25.8/25.9	31.6	22.6	14.0	—	
11b	7.22	—	—	4.05/4.10	1.90	1.54	1.37	1.37	9.84/0.91	—	
	127.0	171.5		69.3/69.6	29.3	25.8/25.9	31.6	22.6	14.0	119.1	

2.3. Formation of liquid crystalline phases

Star-shaped compounds, which consist of stilbenoid building blocks and long flexible chains in peripheral positions, can generate thermotropic mesophases. In contrast to earlier studied systems,[23,32] the compounds **9a**, **9b**, **11a** and **11b** bear hexyloxy chains in the middle of the three arms—and not at the periphery. Thus, the usual micro-segregation between the π-electron regions and the aliphatic regions cannot be realized. Consequently, nematic discotic phases can be expected instead of columnar phases. The differential scanning calorimetry (DSC) of **9a** reveals in the second heating curve (rate 10° per min) a glass transition (T_g=8 °C) to a first nematic discotic phase N_D. A second mesophase N'_D is formed at 114 °C. The small endothermic peak for the latter transition corresponds to a low transition enthalpy of 0.2 kJ mol^{-1}. Finally, the isotropic molten phase is reached at 126 °C (ΔH=0.4 kJ mol^{-1}). The first (and second) cooling curve exhibits only one nematic discotic phase, which is formed at 126 °C (ΔH=0.4 kJ mol^{-1}) and disappears at T_g=2 °C. The structural difference between the two nematic phases is not known. The polarized optical microscopy shows typical nematic 'Schlieren' textures[33,34] for both phases, which have a low viscosity. Moreover, at 114 °C a homeotropic reorganization becomes visible in the microscope. Possibly, the N_D phase consists of molecular pairs (or higher aggregates), whereas the N'_D phase consists of single discs.

The introduction of cyano groups causes a push–pull character of the arms; the phase transition temperatures and the corresponding ΔH values of **9b** are much higher. The second heating curve (heating rate 10° per min) reveals a transformation of the crystalline phase to a nematic discotic phase at 209 °C (ΔH=40 kJ mol^{-1}) and the formation of the isotropic phase at 232 °C (ΔH=1 kJ mol^{-1}). The cooling curve confirms this phase behavior; at 232 °C (ΔH=−1 kJ mol^{-1}) the nematic phase is found and at 201 °C (ΔH=−37 kJ mol^{-1}) the crystalline phase. Figure 1 shows the typical nematic textures of **9b** and **11a**. The 1,3,5-triazine **11a** exhibits in the second heating curve an N_D phase (T_g=95 °C) before the isotropic melt is reached at 107 °C (ΔH=35 kJ mol^{-1}). The acceptor–donor–acceptor (A–D–A) character of **11b** leads to a strong increase of the phase transition temperatures. A nematic phase is obtained at T_g=210 °C and disappears at 236 °C (ΔH=49.8 kJ mol^{-1}). The cooling curve of **11b** shows the formation of the nematic phase at 213 °C; the undercooling effect for **11a** is so high and the rate of the phase transitions so low, that the DSC of **11a** does not exhibit an endothermic peak in the cooling curve. These observations and the high ΔH

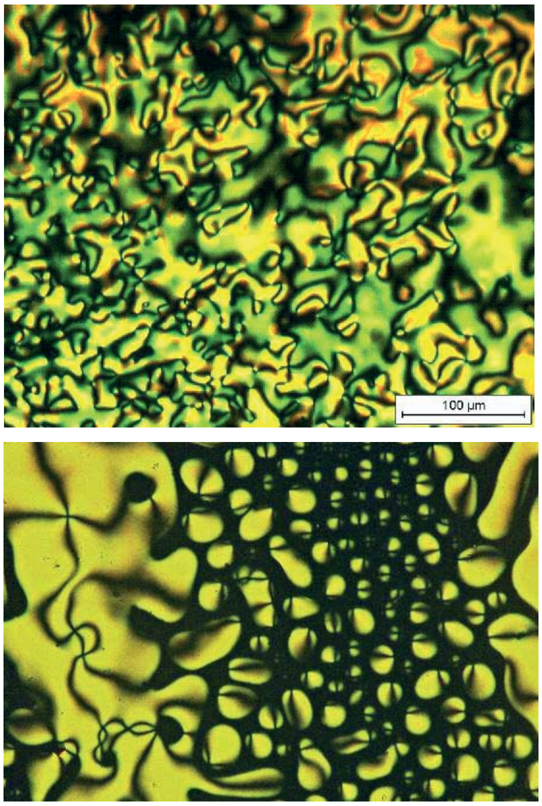
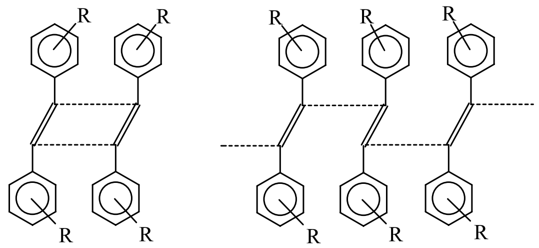


Figure 1. Nematic 'Schlieren' textures obtained by polarization microscopy. Upper part: measurement of **11a** at 99 °C; lower part: measurement of **9b** at 224 °C.

values for the isotropization of **11a** and **11b** are an indication for N_{col} phases.[35]

2.4. Photochemistry

Stilbenoid compounds like **9a**,**b** and **11a**,**b** are light-sensitive.[36] The major irreversible process in solution as well as in the LC phases consists of CC bond formations between the original olefinic centers (Scheme 2). Monochromatic irradiation with λ=366 nm or even an extended absorption of daylight is sufficient for the break-down of the LC phases of **9a**,**b** and **11a**,**b**. Finally crosslinked oligomers and polymers are generated, in which four-membered rings and CC bonds in different directions are generated. The process can be used as imaging technique with liquid crystals.

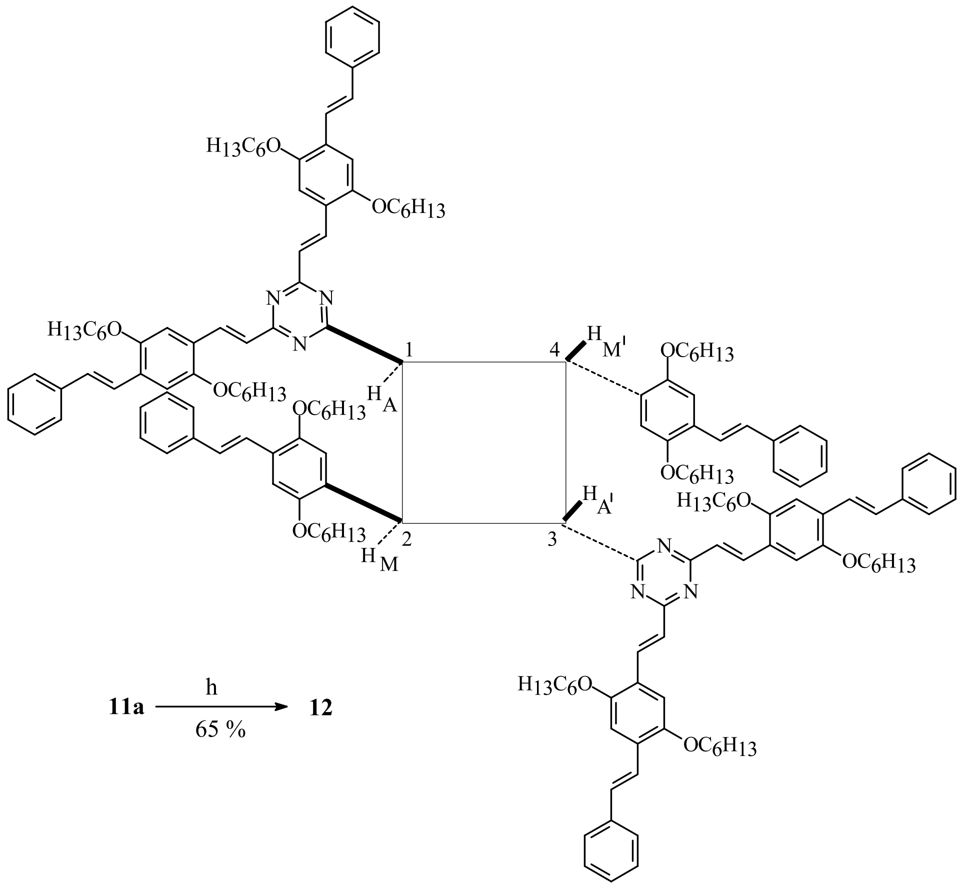


Scheme 2. Photochemical CC bond formation between olefinic centers of stilbenoid compounds.

In contrast to the statistical CC bond formation, **11a** shows in the crystalline state a selective photodimerization. Daylight or monochromatic irradiation with λ=366 nm provokes a chemoselective [2π+2π] cycloaddition of the inner, more polar olefinic double bonds. The NMR studies reveal a regioselective head-to-tail dimerization with a stereoselective *syn* arrangement of head and tail and a preservation of the *trans* configuration, which is originally present at the olefinic CC bonds (Scheme 3). The chemo-, regio- and stereoselectivity can be explained by a topochemical control. Amorphous **11a** does not exhibit this photocyclodimerization.

The structure elucidation of **12** is based on one- and two-dimensional NMR techniques (COSY, NOESY, HMQC and HMBC).[31] The integration of the ^1H NMR signals proves that only one four-membered ring is formed. The symmetry of the dimer is manifested in the number of ^1H and ^{13}C NMR signals. The chemoselective reaction of the inner CC double bonds in **11b** becomes obvious (HMBC) by the couplings of 1-H (δ=4.87) and 2-H (δ=5.27) with the quaternary carbon atom OC_q (δ=151.2) of the adjacent benzene ring and the carbon atom NC_q (δ=178.2) of the 1,3,5-triazine ring. The *syn* head-to-tail cycloaddition is revealed by the through-space interactions (NOESY) of the substituents on C-1 and C-4 of **12**.

The protons on the four-membered ring constitute an AA′MM′ spin system. Figure 2 shows the measured and



Scheme 3. Topochemically controlled photodimerization of **11a**.

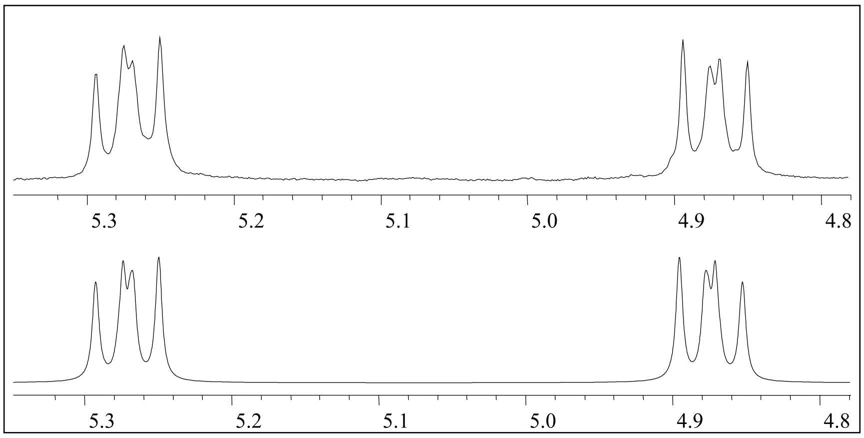


Figure 2. ^{1}H NMR signals of the protons at the four-membered ring of **12**, representing an AA′MM′ spin pattern. Upper part: measured signals in $CDCl_3$; lower part: calculated spectrum[38] ($^3J_{AM}$=$^3J_{A'M'}$=10.7 Hz, $^3J_{AM'}$=$^3J_{A'M}$=7.2 Hz, $|^4J_{AA'}|$=0.5 Hz, $|^4J_{MM'}|$=0.8 Hz).

the calculated signal pattern. A head-to-tail addition with *anti* orientation would lead to an A_2M_2 spin system with a completely different pattern.[37]

3. Conclusion

The star-shaped compounds **9a**,**b** having a benzene core and **11a**,**b** having a 1,3,5-triazine core could be obtained by Wittig–Horner reactions and alkaline condensation reactions, respectively. Due to the attachment of hexyloxy chains in the middle of the arms, nematic LC phases are formed-and no columnar phases, which require extended micro-segregations. The stilbenoid character of the arms provokes a high photoreactivity. The LC phases are transformed isothermally by irradiation to isotropic melts by statistical photochemical CC bond formations. This irreversible process provides an imaging technique with liquid crystals. A chemo-, regio- and stereoselective photocyclodimerization was found for **11a** in the crystalline state. The topochemically controlled reaction works already in the daylight; amorphous particles of **11a** do not show this process.

4. Experimental

4.1. General remarks

Melting points were measured on a Büchi melting point apparatus and are uncorrected. The phase transitions of **9a**,**b** and **11a**,**b** were studied with a Perkin Elmer DSC 7. The polarization microscopy was performed with a Zeiss Jenapol equipped with a Linkam TMS 93 and a digital camera CC12, Soft Imaging System. The ^{1}H and ^{13}C NMR spectra were recorded with the Bruker spectrometers AMX 400, ARX 400 and Avance 600. The UV/Vis spectra were obtained with a Zeiss MCS 320/340. A Perkin Elmer GX was used for the measurement of the IR spectra in transmission, whereas a Nicolet 5 SXB with a LOT-Oriel Golden-Gate ATR unit served for the measurements in reflection. The mass spectra were obtained on a Finnigan MAT 95 spectrometer with the field desorption (FD) technique. The elemental analyses were determined in the Microanalytical Laboratory of the Chemistry Department of the University of Mainz.

4.1.1. 1,4-Dibromo-2,5-dihexyloxybenzene (2). Preparation according to the literature.[24–26]

4.1.2. 4-Bromo-2,5-dihexyloxybenzaldehyde (3). To 80.0 g (0.18 mol) **2**, dissolved in 300 mL dry diethylether, 71.9 mL (0.20 mol) of a 2.7 M solution of *n*-BuLi in *n*-heptane were slowly added under argon at −20 °C. After 1 h stirring at this temperature, the reaction mixture was brought to room temperature and treated tropwise with dry DMF till the reaction came to the end. After stirring for another hour, 30 mL 6 M HCl was added. The organic layer was separated, washed two times with the equivalent amount of water, dried with Na_2SO_4 and evaporated. The residue was purified by column filtration (10×15 cm SiO_2, CCl_4); 31.1 g (44%) aldehyde **3** could be obtained as a colorless solid, which melted at 58 °C. (Apart from the main fraction 3.0 g (5%) of 2,5-dihexyloxyterephthaldialdehyde could be isolated). **3**: IR (KBr): $\tilde{\nu}$ (cm^{-1})=2970, 2850, 1670, 1590, 1490, 1470, 1380, 1260, 1200, 1020, 990, 970, 880, 750; FD MS: *m*/*z* (%)=385 (100) [M+H$^+$], Br isotope pattern. Anal. Calcd for $C_{19}H_{29}O_3Br$ (385.3): C, 59.22; H, 7.59; Br 20.74. Found: C, 59.51; H, 7.41; Br, 20.35.

4.1.3. 4-Bromo-2,5-dihexyloxybenzaldehyde dimethyl acetal (4). Aldehyde **3** (24.0 g, 62.3 mmol), trimethoxymethane (19.83 g, 190 mmol) and 3.0 g Dowex 50 W-X8 were refluxed for 10 h. After stirring for 10 min with 2.5 g (23.6 mmol) Na_2CO_3 at room temperature, the reaction mixture was filtered and evaporated. The residue was boiled with 50 mL dry *n*-hexane for 10 min and immediately filtered. After removal of the volatile parts, 24.13 g (90%) of an oil was obtained. IR (film): $\tilde{\nu}$ (cm^{-1})=2930, 2850, 1490, 1460, 1370, 1200, 1090, 1050, 980, 880, 750; FD MS: *m*/*z* (%)=430 (100) [M$^+$]. Anal. Calcd for $C_{21}H_{35}O_4Br$ (431.4): C, 58.47; H, 8.18; Br, 18.52. Found: C, 58.80; H, 7.95; Br, 18.02.

4.1.4. 2,5-Dihexyloxy-4-dimethoxymethylbenzaldehyde (5). To 23.13 g (53.36 mmol) **4** in 300 mL dry diethylether, 23.80 mL (64.40 mmol) of a 2.7 M solution of *n*-BuLi were dropped at −25 °C. After 2 h dry DMF was dropwise added at room temperature till the reaction stopped. Water (50 mL) was added, the organic layer was separated and the water phase several times extracted with diethylether. The combined organic phases were dried with Na_2SO_4 and evaporated. Column filtration (15×10 cm SiO_2, CH_2Cl_2–triethylamine 99:1) yielded 18.40 g (90%) of a yellow oil. IR (film): $\tilde{\nu}$ (cm^{-1})=2950, 2840, 1670, 1600, 1480, 1460, 1410, 1380, 1200, 1150, 1070, 980, 950, 880; FD MS: *m/z* (%)=380 (100) [M$^+$]. Anal. Calcd for $C_{22}H_{36}O_5$ (380.5): C, 69.44; H, 9.54. Found: C, 69.10; H, 9.84.

4.1.5. (*E*)-2,5-Dihexyloxy-4-(2-phenylethenyl)benzaldehyde (7a). Diethyl benzylphosphonate (**6a**)[27] (1.23 g, 5.4 mmol) and **5** (2.00 g, 5.3 mmol) were dissolved in 20 mL dry THF and dropped under Ar at 0 °C to 0.30 g (12.5 mmol) NaH in 40 mL dry THF. After 24 h 0.20 g (8.33 mmol) NaH in 30 mL dry THF was added and the stirring continued at room temperature for further 24 h. The mixture was cooled to 0 °C before 50 mL H_2O were slowly added. The product was extracted with 100 mL $CHCl_3$ and the solution vigorously stirred with 20 mL 2 M HCl for 2 h. The organic layer was separated, washed with 50 mL saturated $NaHCO_3$ and 50 mL H_2O. The organic phase was dried with $MgSO_4$ and evaporated. Column chromatography [20×10 cm SiO_2, petroleum (bp 40–70 °C)/ethyl–acetate 25:1] yielded 1.80 g (84%) of a yellow oil. IR (film): $\tilde{\nu}$ (cm^{-1})=3050, 3020, 2940, 2920, 2860, 1655, 1595, 1205, 970, 750, 690; ^{1}H NMR ($CDCl_3$): δ=0.90 (m, 6 H, CH_3), 1.24–1.56 (m, 12H, CH_2), 1.83 (m, 4H, CH_2), 4.01 (t, 2H, OCH_2), 4.10 (t, 2H, OCH_2), 7.16 (s, 1H, 3-H), 7.31 (s, 1H, 6-H), 7.22/7.46 (AB, ^3J=16.6 Hz, 2H, olefin. H), 7.29 (m, 1H, *p*-H, phenyl), 7.36 (m, 2H, *m*-H, phenyl), 7.53 (m, 2H, *o*-H, phenyl), 10.43 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$); δ=13.9 (CH_3), 22.5–31.5 (CH_2, partly superimposed), 69.2, 69.4 (OCH_2), 110.3, 110.8, 123.7, 126.9, 128.2, 128.7, 132.3 (aromat. and olefin. CH), 124.5, 134.4, 137.3 (aromat. C_q), 150.9, 156.3 (C_qO), 189.0 (CHO); FD MS: *m/z* (%)=408 (100) [M$^+$]. Anal. Calcd for $C_{27}H_{36}O_3$ (408.6): C, 79,37;H, 8.88. Found: C, 79.40;H, 8.74.

4.1.6. (*E*)-4-[2-(4-Formyl-2,5-dihexyloxyphenyl)-ethenyl]benzonitrile (7b). 137 g (5.4 mmol) diethyl 4-cyanobenzylphosphonate (**6b**),[28] 2.00 g (5.3 mmol) **5** and 0.60 g (25.0 mmol) NaH in 40 mL dry THF were reacted as described for **7a**. The corresponding work-up and the column chromatography [petroleum (bp 40–70 °C)/ ethyl–acetate 15:1] yielded 2.00 g (88%) of a yellow oil which was used without further purification for the following reaction step. Spectroscopic characterization. IR (film): $\tilde{\nu}$ (cm^{-1})=3040, 2940, 2920, 2840, 1665, 1600, 1415, 1205, 970, 865; ^{1}H NMR ($CDCl_3$): δ=0.88 (m, 6H, CH_3), 1.23–1.51 (m, 12H, CH_2), 1.83 (m, 4H, CH_2), 4.01 (t, 2H, OCH_2), 4.08 (t, 2H, OCH_2), 7.14 (s, 1H, aromat. H), 7.31 (s, 1H, aromat. H), 7.20/7.55 (AB, ^3J=16.6 Hz, 2H, olefin. H), 7.58/7.63 (AA′BB′, 4H, aromat. H), 10.43 (CHO); ^{13}C NMR ($CDCl_3$): δ=14.0 (CH_3), 22.5-31.5 (CH_2, partly superimposed), 69.1, 69.3 (OCH_2), 110.3/ 111.1 (aromat. CH and C-1), 127.1, 126.7, 130.1, 132.5 (aromat. and olefin. CH), 118.9 (CN), 125.0, 132.8, 141.7 (aromat. C_q), 151.0, 156.0 (aromat. C_qO), 189.0 (CHO); FD MS: *m/z* (%)=433 (100) [M$^+$].

4.1.7. *all*-(*E*)-1,3,5-Tris{2-[2,5-dihexyloxy-4-(2-phenylethenyl)phenyl]ethenyl}benzene (9a). Tri-phosphonate **8**[13] (0.42 g, 0.79 mmol) and aldehyde **7a** (1.00 g, 2.45 mmol) were dissolved in 10 mL dry THF and dropped at 0 °C under Ar to 0.25 g (6.3 mmol) NaH (60% in paraffin) suspended in 40 mL dry THF. The reaction mixture was warmed to room temperature and stirred for 2H, before it was poured on 50 g crushed ice; 50 mL 2 M HCl was added. The precipitate was filtered off, dried and dissolved in CH_2Cl_2 (10 mL). Portionwise addition of ethanol yielded 0.36 g (35%) of a yellow solid with the clearing point T_{cl}=126 °C. IR (KBr): $\tilde{\nu}$ (cm^{-1})=3030, 2950, 2920, 2860, 1590, 1570, 1200, 970, 755, 695; UV/Vis (CH_2Cl_2): λ_{max}=405 nm, ε=1.24×10^5 L mol^{-1} cm^{-1}; FD MS: *m/z* (%)=1293 (100) [M+H$^+$]. Anal. Calcd for $C_{90}H_{114}O_6$ (1291.9): C, 83.68;H, 8.89. Found: C, 83.47;H, 8.82.

4.1.8. *all*-(*E*)-1,3,5-Tris(2-{4-[2-(4-cyanophenyl)ethenyl]-2,5-dihexloxyphenyl}ethenyl)benzene (9b) or *all*-(*E*)-4-[2-(4-{2-[3,5-bis(2-{4-[2-(4-cyanophenyl)ethenyl]-2,5-dihexyloxyphenyl}ethenyl)phenyl]ethenyl}-2,5-dihexyl-oxyphenyl)ethenyl]benzonitrile (9b). According to the preparation of **9a**, 0.26 g (25%) of pure **9b** was obtained from 1.00 g (2.3 mmol) **7b**, 0.40 g (0.8 mmol) **8** and 0.25 g (6.3 mmol) NaH. The raw product (about 1.0 g) was first purified on a column [10×15 cm SiO_2, toluene–ethyl acetate 2:1] before it was recrystallized from CH_2Cl_2/ C_2H_5OH as described for **9a**. The yellow solid **9b** has a clearing point T_{cl}=232 °C. IR (KBr): $\tilde{\nu}$ (cm^{-1})=3020, 2940, 2910, 2850, 2220, 1615, 1580, 1200, 960, 855, 815; UV/Vis (CH_2Cl_2): λ_{max}=418 nm, ε=1.39×10^5 L mol^{-1} cm^{-1}; FD MS: *m/z* (%)=1368 (100) [M+H$^+$]. Anal. Calcd for $C_{93}H_{111}N_3O_6$ (1366.9): C, 81.72;H, 8.18; N, 3.07. Found: C, 81.34;H, 7.90; N, 2.91.

4.1.9. *all*-(*E*)-2,4,6-Tris{2-[2,5-dihexyloxy-4-(2-phenylethenyl)phenyl]ethenyl}-1,3,5-triazine (11a). Aldehyde **7a** (0.5 g, 1.22 mmol), dissolved in 7 mL dry THF, was added to 45.2 mg (0.37 mmol) **10** and 180 mg (1.60 mmol) $KOC(CH_3)_3$ in 7 mL dry THF. After stirring for 5 d at ambient temperature, the raw product was precipitated by the addition of methanol. Column chromatography (4×40 cm SiO_2, toluene) yielded 153 mg (32%) of a yellow solid; T_{cl}=107.5 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1})=3081, 3057, 3025, 2953, 2928, 2869, 2857, 1623, 1601, 1504, 1467, 1422, 1376, 1288, 1251, 1207, 1030, 986, 964, 873, 852, 753, 692; UV/Vis (CH_2Cl_2): λ_{max}=431 nm, log ε=5.0; FD MS: *m/z* (%)=1296 (100) [M+H$^+$]. Anal. Calcd for $C_{87}H_{111}N_3O_6$ (1294.9): C, 80.70;H, 8.64; N, 3.25. Found: C, 80.48;H, 8.84; N, 3.21.

4.1.10. *all*-(*E*)-2,4,6-Tris(2-{4-[2-(4-cyanophenyl)-ethenyl]-2,5-dihexyloxyphenyl}ethenyl)-1,3,5-triazine (11b) or *all*-(*E*)-4[2-(4-{2-[4,6-bis(2-{4-[2-(4-cyano-phenyl)ethenyl]-2,5-dihexyloxyphenyl}ethenyl)-1,3,5-triazin-2-yl]ethenyl}-2,5-dihexyloxyphenyl)ethenyl]-benzonitrile (11b). According to the preparation of **11a**, 257 mg (94%) of **11b** was obtained from 286 mg (0.66 mmol) **7b**, 24.5 mg (0.20 mmol) **10** and 67.5 mg (0.60 mmol) $KOC(CH_3)_3$ in 15 mL dry THF. After refluxing for 2 d, the purification was performed by column chromatography [4×40 cm SiO_2, petroleum (bp 40–70 °C/ ethyl–acetate 7:1] and crystallization from CH_2Cl_2/

CH_3OH. The orange solid has a clearing point at T_{cl}=235.8 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1})=3060, 2926, 2856, 2222, 1679, 1623, 1601, 1483, 1467, 1423, 1374, 1337, 1320, 1285, 1253, 1204, 1173, 1029, 987, 968, 855, 817, 726, 666; UV/Vis (CH_2Cl_2): λ_{max}=435, log ε=5.09; FD MS: *m*/*z* (%)=1371 (100) [M+H^+]. Anal. Calcd for $C_{90}H_{108}N_6O_6$ (1369.9): C, 78.91;H, 7.95; N, 6.13. Found: C, 78.74;H, 8.13; N, 6.09.

4.1.11. *all*-(*E*)-1r,3t-Bis(4,6-bis{2-[2,5-dihexyloxy-4-(2-phenylethenyl)phenyl]ethenyl}-1,3,5-triazin-2-yl)-2c,4t-bis[2,5-dihexyloxy-4-(2-phenylethenyl)phenyl]cyclobutan (12). A saturated solution of 129 mg (0.1 mmol) **11a** in $CHCl_3$ was spread on a glass surface; the solvent was slowly vaporized and crystallization of **11a** started. Irradiation of the ready thin crystalline layer with monochromatic light (λ=366 nm) or with day light led to the dimerization, which was followed by TLC control (SiO_2, toluene).Column chromatography (20×3 cm SiO_2, toluene) yielded up to 84 mg (65%) of **12**, which melted at 160 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1})=2954, 2932, 2870, 2858, 1624, 1600, 1518, 1467, 1424, 1378, 1288, 1251, 1207, 1030, 991, 962, 753, 691; ^{1}H NMR ($CDCl_3$): δ=0.77 (t, 6H, CH_3), 0.79 (t, 6H, CH_3), 0.80 (t, 12H, CH_3), 0.90 (t, 12H, CH_3), 1.14–1.58 (m, 72H, CH_2), 1.84 (m, 24H, CH_2), 3.70 (m, 2H, OCH_2), 3.78 (m, 2H, OCH_2), 3.88 (m, 4H, OCH_2), 4.01 (t, 8H, OCH_2), 4.05 (t, 8H, OCH_2), 4.87 (AA′ of AA′MM′, 2H, 1-H, 3-H), 5.27 (MM′, 2H, 2-H, 4-H), 6.86 (s, 2H, aromat. H), 6.91/7.31 (AM, ^3J=16.4 Hz, 4H, olefin. H), 7.03 (s, 2H, aromat. H), 7.08/8.47 (AX, ^3J=16.2 Hz, 8H, olefin. H), 7.11 (s, 4H, aromat. H), 7.16/7.48 (AM, ^3J=16.2 Hz, 8H, olefin. H), 7.16 (s, 4H, aromat. H), 7.25 (m, 6H, aromat. H), 7.37 (m, 12H, aromat. H), 7.53 (m, 12H, aromat. H); ^{13}C NMR ($CDCl_3$): δ=14.0 (12 CH_3), 22.6 (12 CH_2), 25.7–25.9 (12 CH_2), 29.2–29.4 (12 CH_2), 31.5–31.9 (12 CH_2), 40.5 (C-1, C-3), 49.5 (C-2, C-4), 69.4 (4 OCH_2), 69.5 (4 OCH_2), 70.1 (2 OCH_2), 109.0 (2 aromat. CH), 110.5 (4 aromat. CH), 111.8 (4 aromat. CH), 114.4 (2 aromat. CH), 123.4 (4 olefin. CH), 123.9 (2 olefin. CH), 124.9 (2 aromat. C_q,) 125.0 (4 aromat. C_q), 126.3 (4 aromat. CH), 126.5 (4 olefin. CH), 126.6 (8 aromat. CH), 126.9 (2 aromat. CH), 127.6 (2 olefin. CH), 127.6 (4 aromat. CH), 128.5 (4 aromat. CH), 128.7 (8 aromat. CH), 129.1 (4 aromat. C_q), 129.7 (4 olefin. CH), 130.6 (2 aromat. C_q), 136.1 (4 olefin. CH), 137.8 (4 aromat. C_q), 138.2 (2 aromat. C_q), 150.6 (2 aromat. C_qO), 150.9 (4 aromat. C_qO), 151.2 (2 aromat. C_qO), 152.3 (4 aromat. C_qO), 170.9 (4 C_qN), 178.2 (2 C_qN); FD MS: *m*/*z* (%)=1295 (100) [M^{2+}], 2590 (88) [M^+]. Anal. Calcd for $C_{174}H_{222}N_6O_{12}$ (2589.7): C, 80.70;H, 8.64; N, 3.25. Found: C, 80.57;H, 8.91; N, 3.32.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

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38. Software MestRe—C 2.3.a.

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Tetrahedron 60 (2004) 6889–6894
Tetrahedron

Assembling tetrapyrrole derivatives through axial coordination☆

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Received 6 February 2004; revised 14 May 2004; accepted 28 May 2004

Available online 2 July 2004

Abstract—Bis(4-pyridinolato) silicon(IV) phthalocyanine (**1**) binds with a series of zinc(II) tetrapyrrole derivatives with the two pyridyl ligands forming the corresponding 1:2 or 1:1 molecular assemblies. The molecular structure of the first axially linked trinuclear phthalocyanine–porphyrin array has also been determined.

1. Introduction

Tetrapyrrole derivatives such as phthalocyanines and porphyrins are very common yet important functional dyes. Multi-tetrapyrrole systems, in particular of porphyrins, have received much current attention because of their potential use as molecular devices for light harvesting, information storage, and other photonic and optoelectronic applications.[1] Since phthalocyanines and porphyrins exhibit complementary absorptions mainly in the orange-red (600–700 nm) and in the violet (400–450 nm) region respectively, a mixed system of these chromophores should absorb strongly over a large part of the solar spectrum. This property is highly beneficial in artificial photosynthetic systems and molecular photonic devices. The macrocycles, which exhibit distinct electronic and optical properties, may also couple with each other in the hybrids resulting in characteristic features which cannot be found in the individual components.[2] To our knowledge, mixed phthalocyanine–porphyrin assemblies are confined to sandwich-type metal complexes[2] and the few examples of covalently linked systems,[3] oxo- and nitrido-bridged binuclear and trinuclear complexes,[4] and face-to-face aggregates held by electrostatic interactions.[5] We have recently reported the first edge-to-face arrays of pyridyl porphyrins and a zinc(II) phthalocyanine assembled through axial coordination.[6,7] In contrast to the numerous self-assembled porphyrin systems held by axial coordination,[8] phthalocyanine analogues linked in this manner are extremely rare.[9] The coordination chemistry of zinc(II) phthalocyanines has also been little studied.[6,9] We describe herein an extension of our previous work using bis(4-pyridinolato) silicon(IV) phthalocyanine (**1**) as the core to complex with a series of zinc(II) tetrapyrrole derivatives (Scheme 1), forming the corresponding 1:2 or 1:1 arrays. The molecular structure of a rare axially linked phthalocyanine–porphyrin conjugate, namely the 1:2 complex of **1** and zinc(II) *meso*-tetraphenylporphyrin (**2**), is also reported.

2. Results and discussion

Compound **1** was prepared in 75% yield by ligand substitution of the commercially available silicon(IV) phthalocyanine dichloride with 4-hydroxypyridine in the presence of pyridine. Complexation was first performed with zinc(II) porphyrin **2**. Figure 1 shows the ^{1}H NMR spectra of **1**, **2**, and mixtures of these two macrocycles in different ratios. It can be seen that the signals for all the phthalocyanine and porphyrin ring protons are shifted upfield upon addition of the other component, in particular for the α-protons of **1** (AA′BB′ multiplet at δ 9.64–9.67) and the β″-protons of **2** (singlet at δ 8.94), which are close to the ring centers. The two doublets at δ 6.76 and 2.44 for the α′ and β′ pyridyl protons of **1** become broadened (in particular the former) and eventually vanish upon addition of **2**. Replacement of **2** with the metal-free analogue did not cause any shifts of the ^{1}H NMR signals. All these observations clearly indicate an axial coordination of **2** with the pyridyl groups of **1**. The upfield shifts are due to the ring current generated by the coordinated partner and the broadening of pyridyl protons' signals suggests that the complexation is rather weak and there is an extensive exchange between the coordinated and the free pyridyl groups. The corresponding Job's plot[10] (Fig. 2) shows a minimum when the mole fraction of **2** is about 0.65. The 1:2 stoichiometry for compounds **1** and **2** suggests the formation of a trinuclear tetrapyrrole array $\mathbf{1}\cdot(\mathbf{2})_2$.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.05.114

Keywords: Phthalocyanines; Porphyrins; Axial coordination.
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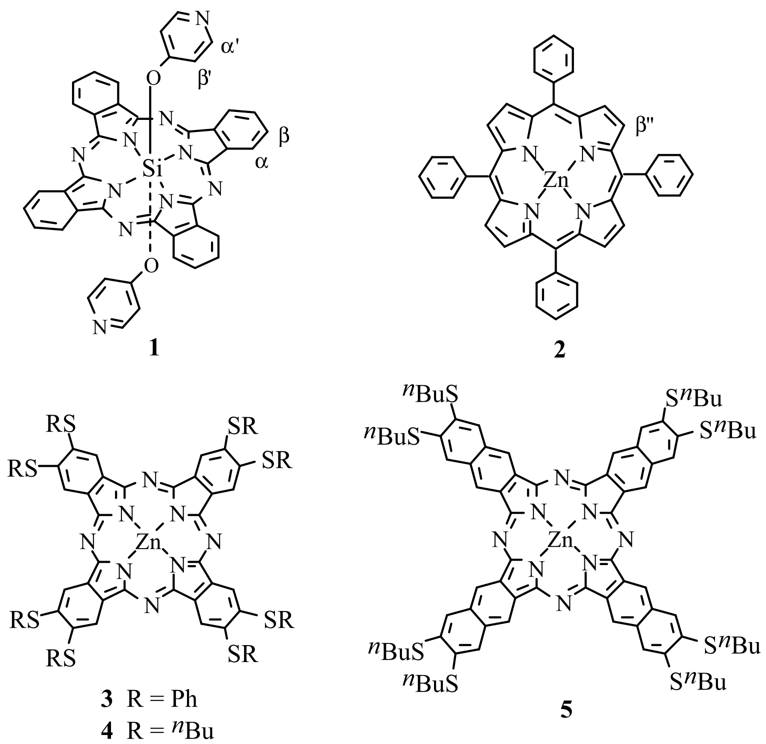
doi:10.1016/j.tet.2004.05.114



Scheme 1. Structures of tetrapyrrole derivatives **1**–**5**.

The structure of this supramolecular assembly was unambiguously confirmed by X-ray diffraction analysis. As shown in Figure 3, each of the two pyridyl groups of **1** binds to the zinc center of **2** with a Zn–N distance of 2.177 Å, which is comparable with the average of the other four Zn–N distances (2.067 Å). The zinc center adopts a typical square pyramidal geometry with a displacement of 0.324 Å above the porphyrin N_4 plane. The phthalocyanine ring of **1** is essentially planar forming a tilted face-to-face trinuclear system with the two porphyrin rings with a dihedral angle of 54.1° between the phthalocyanine N(isoindole)$_4$ plane and the porphyrin N_4 plane. This kind of structure is rare for multi-tetrapyrrole systems and the assembly represents the first mixed phthalocyanine and porphyrin system other than sandwich-type[2] and μ-nitrido[4a,b] complexes which has been structurally characterized.

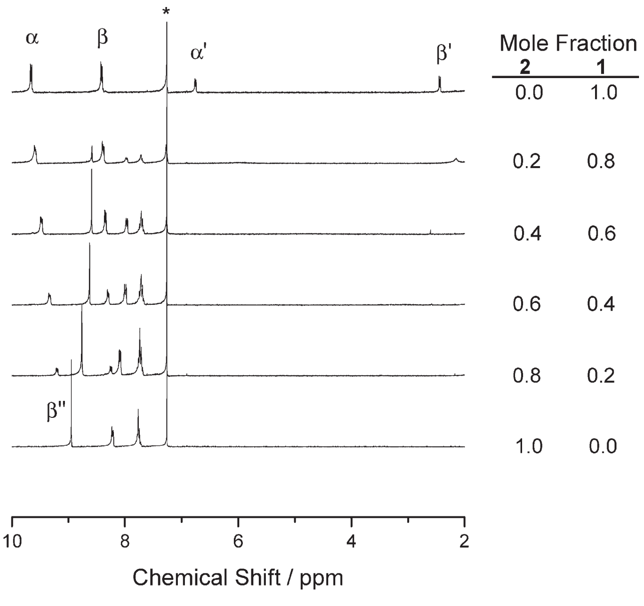


Figure 1. ^{1}H NMR spectra of **1** (top), **2** (bottom), and mixtures of these two compounds in $CDCl_3$. The total concentration of **1** and **2** was fixed at 2 mM; * denotes residual $CHCl_3$.

Upon titration with **1** (up to 100 equiv.) in $CHCl_3$, the Soret band of **2** remained essentially unshifted and no isosbestic points were observed (see Fig. S1 in the Supporting Information). The spectra were essentially the sum of the spectra of **1** and **2**, showing that the two π-systems do not exhibit a substantial ground state interaction. Compound **1**,

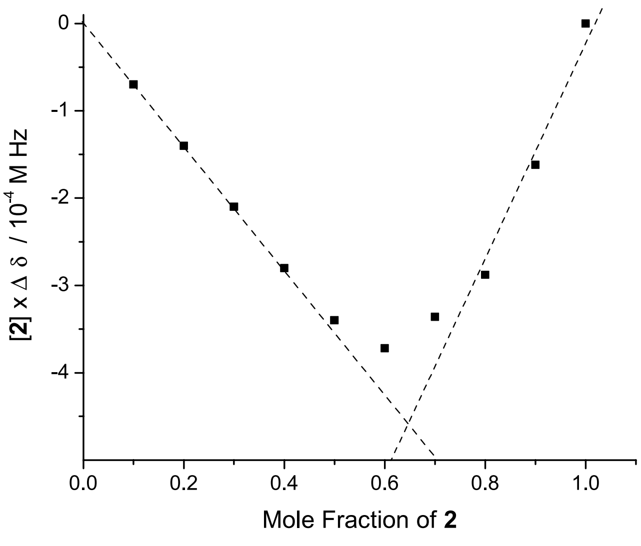


Figure 2. Modified Job's plot for the complexation of **1** and **2** in $CDCl_3$ by monitoring the ^{1}H NMR signal of the β''-protons of **2**.

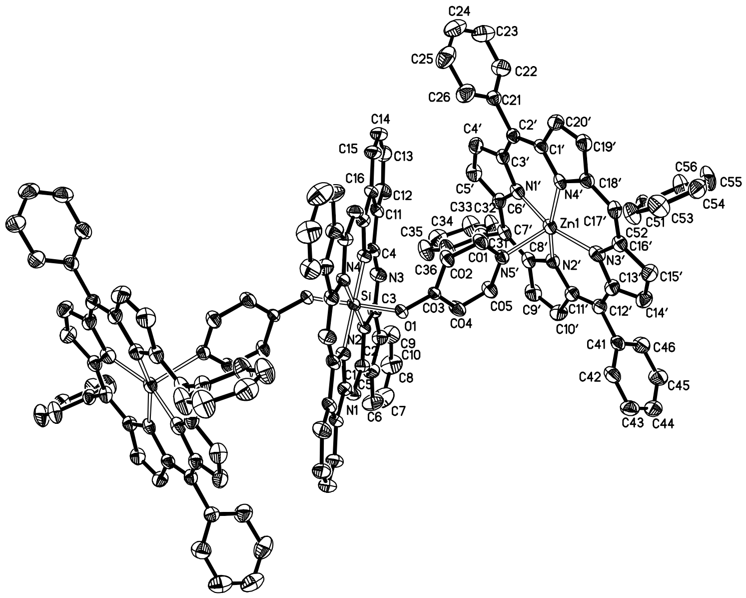


Figure 3. Molecular structure of $\mathbf{1}\cdot(\mathbf{2})_2$ showing the 30% probability thermal ellipsoids for all non-hydrogen atoms.

however, was a fluorescence quencher for **2**. As shown in Figure 4, the fluorescence intensity of **2** decreases upon addition of **1** in $CHCl_3$. The emission at ca. 690 nm is due to direct excitation of **1** at 423 nm, which was confirmed by excitation spectroscopy. Photo-induced energy transfer from the excited porphyrins to the phthalocyanine core was not observed. It is likely that the fluorescence quenching is mainly due to an electron-transfer pathway in which **1** serves as an electron acceptor. To provide further insight, the free energy change ($\Delta G°$) for this process was estimated by the Rehm–Weller equation:[11] $\Delta G° \approx e[E_{1/2}(D^{\cdot+}/D) - E_{1/2}(A/A^{\cdot-})] - \Delta E(0,0)$, where e is the charge on the electron, $E_{1/2}$ is the half-wave reduction potential for either the donor ($D^{\cdot+}/D$) or acceptor ($A/A^{\cdot-}$) couples in volts, $\Delta E(0,0)$ is the relevant singlet state energy. The half-wave potentials ($E_{1/2}$) for the donor **2** ($D^{\cdot+}/D$, 0.79 V) and the acceptor **1** ($A/A^{\cdot-}$, −0.59 V) were measured by cyclic voltammetry in CH_2Cl_2 using $[Bu_4N][PF_6]$ as electrolyte and were relative to saturated calomel electrode (SCE). On the basis of these data and the value of $\Delta E(0,0)$ for **2** (2.05 eV),[12] $\Delta G°$ was estimated to be −0.67 eV showing that this process is thermodynamically favorable.

Apart from zinc porphyrin **2**, we also examined the complexation of **1** with zinc phthalocyanines **3** and **4**. These known compounds were prepared by base-promoted cyclization of the corresponding phthalonitriles in the presence of $Zn(OAc)_2\cdot 2H_2O$.[13] While no ^{1}H NMR signals for **3** were observed in $CDCl_3$ due to the aggregation effect,[13,14] a singlet at ca. δ 8.9 and two multiplets around δ 7.5 emerged upon addition of **1**, which can be assigned to the phthalocyanine and phenyl ring protons respectively (Fig. 5). This is in accord with our previous observation that addition of pyridine can relieve the aggregation of zinc(II)

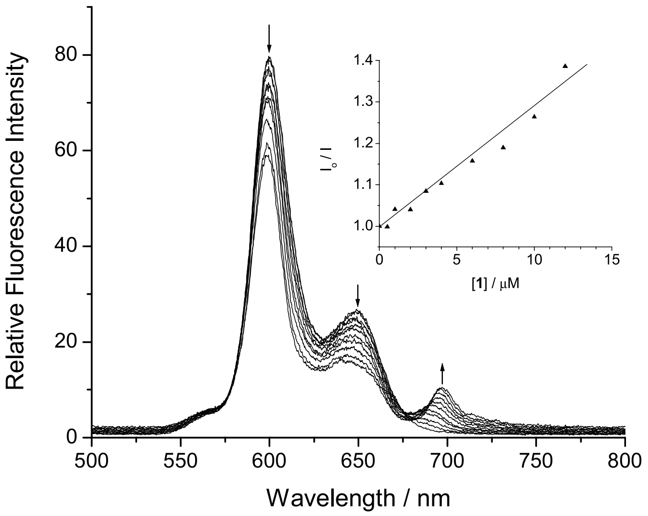


Figure 4. Change of fluorescence spectrum of **2** (1 μM, excited at 423 nm) upon addition of **1** (from 0.5 to 12 μM) in $CHCl_3$. The inset shows the corresponding Stern-Volmer plot.

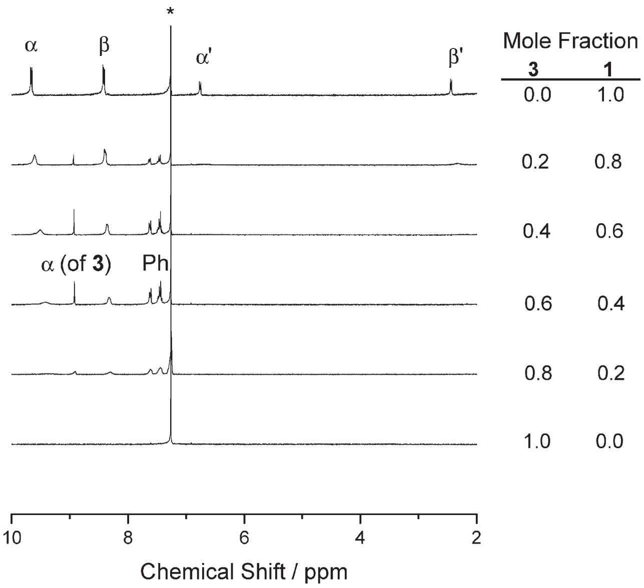


Figure 5. ^{1}H NMR spectra of **1** (top), **3** (bottom), and mixtures of these two compounds in $CDCl_3$. The total concentration of **1** and **3** was fixed at 2 mM; * denotes residual $CHCl_3$.

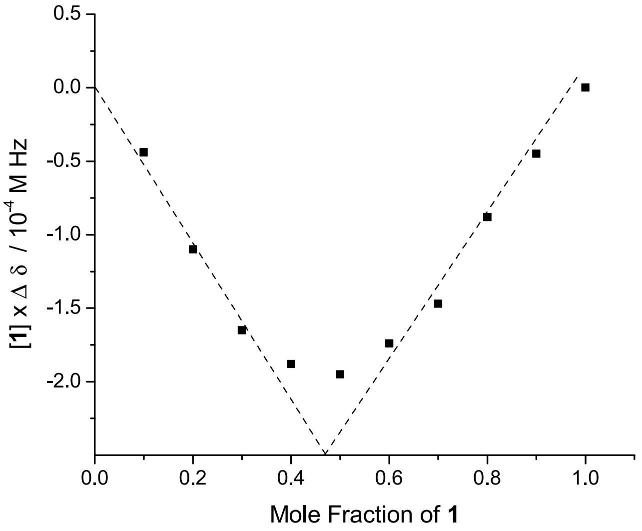


Figure 6. Modified Job's plot for the complexation of **1** and **3** in $CDCl_3$ by monitoring the ^{1}H NMR signals of the α-protons of **1** (center of the AA′BB′ multiplet).

phthalocyanines and facilitate the acquisition of NMR spectra.[13,14] The AA′BB′ signals for the α and β protons of **1** were also shifted upfield upon addition of **3** as in the case of complexation of **1** and **2** (Fig. 1). However, the Job's plot (Fig. 6) clearly revealed a 1:1 instead of 1:2 stoichiometry. The binding constant was determined from the plot of $1/\Delta\delta$ against 1/[**3**] (see Fig. S2 in the Supporting Information) according to the standard equation for 1:1 binding isotherm: $1/\Delta\delta = 1/\{\Delta\delta_{11} K_{11}[L]\} + 1/\Delta\delta_{11}$,[15] where $\Delta\delta = \delta - \delta_S$, $\Delta\delta_{11} = \delta_{SL} - \delta_S$, and K_{11}=stability constant for the formation of the 1:1 complex SL, in which S is the interactant (i.e., **1** in this case) whose properties are experimentally observed and L is the interactant (i.e., **3**) whose concentration is the independent variable. The value (270 M^{-1}) is about one order of magnitude smaller than the typical values for axial coordination of zinc(II) porphyrins with pyridine.[16] Complexation of **1** with the thiobutyl analogue **4** behaved similarly giving a 1:1 binding stoichiometry and a binding constant of 390 M^{-1}. We tentatively propose that alternating coordination polymers are formed between the silicon (IV) and zinc(II) phthalocyanines in 1:1 ratio, in which each of the zinc centers binds to two pyridyl groups from two molecules of **1**. Although square-pyramidal zinc(II) tetrapyrrole complexes are well-documented, hexa-coordinated analogues are not unprecedented.[17] Attempts to characterize the arrays of **1** and **3** (as well as **1** and **2**) by electrospray ionization mass spectrometry and gel permeation chromatography, however, were not successful. As shown by UV–Vis spectroscopy, the phthalocyanine rings do not interact substantially in the ground state. Analysis of the fluorescence quenching results was found to be difficult because of the extensive overlap in the absorption spectra of these phthalocyanines.

Complexation of **1** with 2,3-naphthalocyanine **5**[13] was also monitored by ^{1}H NMR spectroscopy. When a small amount of **5** was added, all the signals of **1** were slightly broadened with their positions remained essentially unchanged, while additional broad signals were also observed for the ring (δ 8.8 and 7.8) and thiobutyl (δ 3.2, 2.0, 1.8, and 1.2) protons of **5**. When about 1 equiv. of **5** was added, all the downfield signals coalesced to become a very broad band, showing the presence of an extensive exchange process. Since most of the signals were not shifted, the stoichiometry could not be determined by the continuous variation method and it appeared that the complexation between these two tetrapyrroles is very weak compared with the binding of **1** with porphyrin and phthalocyanine counterparts.

In summary, we have prepared a dipyridyl phthalocyanine **1**, which can axially bind to zinc(II) porphyrin, phthalocyanine, and 2,3-naphthalocyanine derivatives in different manners. The molecular structure of a non-covalent phthalocyanine–porphyrin conjugate has also been determined. Since axial coordination of zinc(II) phthalocyanines and 2,3-naphthalocyanines has been little studied, the rationale accounting for the different complexation behavior of these tetrapyrrole derivatives remains elusive at this stage. This requires further investigation.

3. Experimental

3.1. General

Toluene was distilled from sodium. Dichloromethane for voltammetric studies was freshly distilled from CaH_2 under nitrogen. All other solvents and reagents were used as received. Silicon(IV) phthalocyanine dichloride[18] and the macrocycles **3**,[19] **4**,[13] and **5**[13] were prepared according to literature procedure. ^{1}H NMR spectra were recorded on a Bruker DPX 300 spectrometer (^{1}H, 300 MHz) in $CDCl_3$ solutions. Chemical shifts are relative to internal $SiMe_4$ (δ=0 ppm). UV–Vis spectra were taken on a Cary 5G spectrophotometer. Elemental analysis was performed by Medac Ltd., Brunel Science Centre, UK. Electrochemical measurements were carried out with a BAS CV-50W voltammetric analyzer. The cell comprised inlets for a platinum-sphere working electrode, a silver-wire counter electrode, and an $Ag/AgNO_3$ (0.1 M in CH_3CN) reference electrode, which was connected to the solution by a Luggin capillary whose tip was placed close to the working electrode. Typically, a 0.1 M solution of $[Bu_4N][PF_6]$ in CH_2Cl_2 containing the sample was purged with nitrogen for 15 min, then the voltammograms were recorded at ambient temperature. Results were corrected for junction potentials by being referenced internally to the ferrocenium/ferrocene couple ($E_{1/2}$=+0.45 V vs SCE).

3.2. Preparation of bis(4-pyridinolato) silicon(IV) phthalocyanine (1)

A mixture of silicon(IV) phthalocyanine dichloride (1.0 g, 1.64 mmol), 4-hydroxypyridine (0.32 g, 3.36 mmol), and pyridine (2 mL) in toluene (50 mL) was heated at reflux overnight. The volatiles were then removed under reduced pressure and the residue was chromatographed on a silica gel column (Macherey–Nagel, 70–230 mesh) using $CHCl_3/CH_3OH$ (9:1) as eluent to give the product as a blue solid (0.89 g, 75%). ^{1}H NMR: δ=9.64–9.67 (m, 8H, Pc-H_α), 8.40–8.43 (m, 8H, Pc-H_β), 6.76 (d, J=6.6 Hz, 4H, Py-$H_{\alpha'}$), 2.44 (d, J=6.6 Hz, 4H, Py-$H_{\beta'}$). UV–Vis ($CHCl_3$) [λ_{max}/nm (log ε)]: 357 (4.86), 614 (4.55), 654 (4.48), 684 (5.32). Anal. Calcd for $C_{43}H_{28}N_{10}O_3Si$ (1·CH_3OH): C, 67.88; H, 3.71; N, 18.41. Found: C, 68.05; H, 3.32; N, 18.47%.

3.3. X-ray crystallographic analysis of $1{\cdot}(2)_2{\cdot}2CH_3OH$

Single crystals of the trinuclear array were grown by layering CH_3OH onto a $CHCl_3$ solution of **1** and **2** in 1:2 molar ratio. Crystal data and details of data collection and structure refinement are given in Table 1. Data collection was performed on a Bruker SMART CCD diffractometer with Mo K_α radiation (λ=0.71073 Å) in a sealed tube at 293 K, using an ω-scan mode with an increment of 0.3°. Preliminary unit cell parameters were obtained from 45 frames. Final unit cell parameters were derived by global refinements of reflections obtained from integration of all the frame data. The collected frames were integrated by using the preliminary cell-orientation matrix. The following software was employed: SMART to collect frames of data, index reflections, and determine the lattice constants; SAINT-PLUS to integrate the intensity of reflections and for scaling;[20] SADABS for absorption correction;[21] and SHELXL for space group and structure determination, refinements, graphics, and structure reporting.[22] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-217222. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 1. Crystallographic data for $1{\cdot}(2)_2{\cdot}2CH_3OH$

	$1{\cdot}(2)_2{\cdot}2CH_3OH$
Formula	$C_{132}H_{88}N_{18}O_4SiZn_2$
M_r	2149.03
Crystal size (mm^3)	0.27×0.22×0.07
Crystal system	Triclinic
Space group	$P_{\bar{1}}$
a (Å)	10.2656 (13)
b (Å)	11.7273 (14)
c (Å)	23.785 (3)
α (°)	98.775 (3)
β (°)	101.013 (3)
γ (°)	105.116 (3)
V (Å)	2650.9 (6)
Z	1
F (000)	1112
ρ_{calcd} (Mg m^{-3})	1.346
μ (mm^{-1})	0.531
θ range (°)	0.89–28.05
Reflections collected	18439
Independent reflections	12642 (R_{int}=0.1145)
Parameters	699
$R1$ ($I>2\sigma(I)$)	0.0737
$wR2$ ($I>2\sigma(I)$)	0.1708
Goodness of fit	0.853

Acknowledgements

We thank Prof. Jinzhi Wang and Hoi-Shan Chan for solving the structure of $1{\cdot}(2)_2$. This work was supported by The Chinese University of Hong Kong.

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Tetrahedron 60 (2004) 6895–6900

[2+2] Carbonylative cycloaddition catalyzed by palladium: stereoselective synthesis of β-lactams

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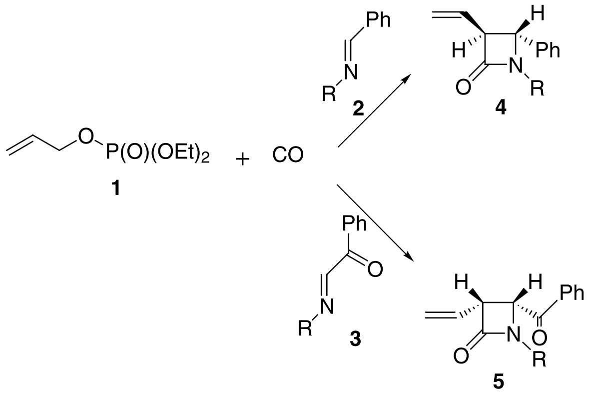
Received 25 February 2004; revised 5 May 2004; accepted 27 May 2004

Available online 4 July 2004

Abstract—[2+2] Carbonylative cycloaddition of chiral imines to various allyl halides, under CO pressure, in the presence of Et_3N, a catalytic amount of $Pd(OAc)_2$ and PPh_3 as ligand, are carried out. Separable diastereomeric mixtures of chiral alkenyl-β-lactams are isolated with good yields and high *trans* diastereoselections. Absolute configurations are assigned by X-ray measurements and ^1H NMR spectroscopy.

1. Introduction

The palladium catalyzed carbonylation of allyl-phosphate **1** in the presence of imines under CO pressure, leads stereoselectively to the formation of *trans*-**4** or *cis*-**5** β-lactam according to the imine used for the coupling: unconjugated with a carbonyl group **2** or conjugated **3**, respectively (Scheme 1).[1,2]



Scheme 1.

No reaction products or just traces of β-lactams were reported using allyl bromide,[1–5] allyl-acetate,[6,7] allyl-phenyl ether,[8] allyl-carbonate[9,10] and allyl-sulphide[11] under similar reaction conditions.

In contrast with these observations, we found[12] that a variety of simple allyl halides react with imines in tetrahydrofuran (THF) using Et_3N as base and $Pd(OAc)_2$ (2% of substrate) complexed with PPh_3 (8% of substrate) as catalyst, to give in good yields β-lactams of *trans* configuration, prevalently.

To further investigate the applications of our methodology we considered the possibility of inducing stereoselectivity on the two new stereocenters (C3 and C4), formed on the β-lactamic ring, through a cyclocarbonylation on chiral optically pure imines.

2. Results and discussion

The enantiopure (*S*)-(−)-benzilidene(2-methoxy-1-phenyl-ethyl)amine **A** was reacted with allyl bromide in THF at 100 °C, under pressure of CO (400 psi) for 18 h, with a catalytic amount of palladium (II) complexed by PPh_3. We presume that the catalytic complex is $(PPh_3)_4Pd(0)$, indeed, using the commercial tetrakis(triphenylphophine)-palladium(0) the reaction showed high yields. Optically pure *trans* β-lactams (−)-**1a** and (+)-**1b** (in a diasteromeric ratio of 53/43) together with a small amount of *cis* β-lactam (−)-**1c** were isolated with an overall yield of 98%. The three diastereomers were obtained in pure form after column chromatography (silica gel, petroleum ether/Et_2O, 7:3) and the optical rotation values were measured.

The *trans* and *cis* configurations, in this and in the following cases, have been assigned from the ^1H NMR spectra through the coupling constant J_{H-H} of the two protons on C3 and C4 ($J_{cis}>J_{trans}$), as reported previously for smaller

Keywords: Chiral β-lactams; Enantiopure imines; Carbonylative cycloaddition; Stereoselectivity.

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doi:10.1016/j.tet.2004.05.079

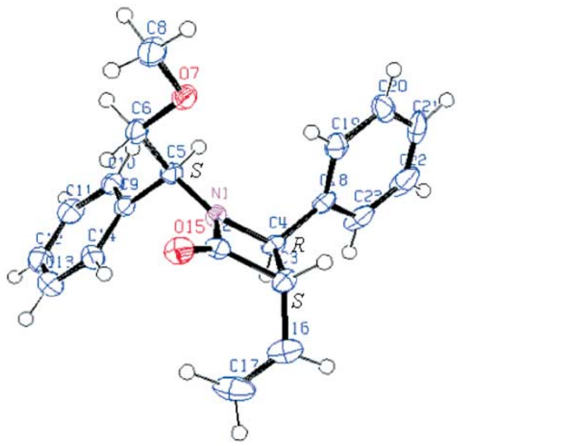


Figure 1. ORTEP view of compound (−)-**1a**.

heterocycles.[13,14] X-ray crystal structure analysis of (−)-**1a** confirms the ^{1}H NMR assignment and shows that the absolute configuration of the new two centers is 3*S* and 4*R*.[15]

In the other *trans* structure (+)-**1b** the new two centers, C3 and C4, are obviously of opposite configuration, 3*R* and 4*S*. As shown by Figure 1, the nitrogen configuration is almost planar; this is due to the strong interaction between the nitrogen lone pair and the π electrons of the C=O double bond. A further confirmation is given by the C2–N distance of 1.355 Å, shorter than the typical value in β-lactams (1.385 Å). The result is not surprising if we consider that the four-membered ring rich in substituents has not much tendency to bend along its diagonal. The configuration of structure (−)-**1c** was assigned in comparison with the previous two structures: in this case a stronger J_{H-H} coupling constant between the two protons in the β-lactamic ring is consistent with a *cis* structure (3*R**, 4*R**). It is possible to make a resonable assumption on the absolute configuration of the new chiral centers for (−)-**1c** according to the following observations. The ^{1}H NMR spectra of the diastereomeric couple (−)-**1a** and (+)-**1b** show similar coupling constants J_{H-H} between the protons of the β-lactamic cycle. On the contrary, the spectra show different chemical shifts for the protons of the group bonded to the nitrogen because of a different diamagnetic interaction between them and the phenyl group on C4 (in (−)-**1a** the configuration is 4*R*, in (+)-**1b** is 4*S*). Since the spectrum of (−)-**1c** shows, for the protons of the group bonded to the nitrogen, chemical shifts similar to those of the (+)-**1b** isomer (with configuration 4*S*), we can argue that also (−)-**1c** has a *S* configuration on the C4 atom. Since the structure is *cis*, the C3 center must also be of *S* configuration.

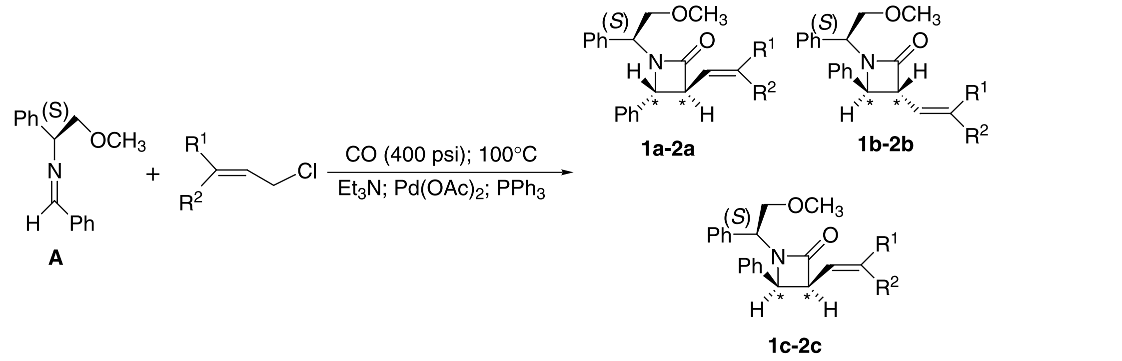
Moreover, when the imine **A** was used in the optically pure form (*R*)-(+), a similar procedure led to the enantiomers (+)-**1a**, (−)-**1b**, and (+)-**1c**. These three new compounds showed, in fact, identical ^{1}H NMR and ^{13}C NMR spectra but optical rotation of opposite sign and equal absolute value.

Table 1 shows the results of the reaction of imine **A**, in both enantiomeric forms, with the allyl bromide and 1-chloro-3-methyl-2-butene. This latter gave, in lower yields, approximately the same amount of *trans* diastereomers (−)- and (+)-**2a**, (+)- and (−)-**2b** and traces of the **2c** isomer.

The absolute configurations of (−)-**2a** and (+)-**2b**, have been assigned as (3*S*,4*R*) and (3*R*,4*S*), from the comparison of the chemical shifts with (−)-**1a** and (+)-**1b**, respectively. Also the relative yields of **2a** and **2b** followed a similar trend to **1a** and **1b**.

The HPLC analysis of the crude mixture, obtained by the reaction of the racemic imine **A** with 1-chloro-3-methyl-2-butene showed two pair of peaks of nearly equal intensity, corresponding to the diastereoisomers (±)-**2a** and (±)-**2b**,

Table 1. Synthesis of chiral β-lactams from allyl halides and the enantiopure imine **A**



Entry	Absol. config. of imine **A**	R^1, R^2	X	Yield (%)[a]	dr[b] $[\alpha]_D^{22c}$		
1	(*S*)	R^1=R^2=H	Br	98	(−)-**1a** (53) [−44.7]	(+)-**1b** (43) [+57.2]	(−)-**1c** (4) [−37.2]
2	(*R*)[d]	R^1=R^2=H	Br	95	(+)-**1a** (53) [+43.4]	(−)-**1b** (43) [−55.4]	(+)-**1c** (4) [+35.0]
3	(*S*)	R^1=R^2=CH_3	Cl	54	(−)-**2a** (53) [−40.0]	(+)-**2b** (47) [+24.0]	**2c** (traces)[e]
4	(*R*)[d]	R^1=R^2=CH_3	Cl	40	(+)-**2a** (53) [+40.8]	(−)-**2b** (47) [−21.5]	**2c** (traces)[e]

[a] Isolated yields.
[b] Diasteromeric ratios determined by GC gas-chromatography of the crude product.
[c] *c* 0.01–0.03, $CHCl_3$ (see Section 4 for details).
[d] Using the enantiopure (*R*)-imine **A**, the products **1a**–**2a**, **1b**–**2b** and **1c** are the enantiomers of those obtained with the enantiopure (*S*)-imine **A**.
[e] Traces determined by ^{1}H NMR spectroscopy and GC–MS.

respectively. When the same reaction was carried out with the enantiopure *S* imine **A** (Table 1, entry **3**), the HPLC analysis showed only two peaks. One peak corresponded to the first peak of the first pair, and the other to the second peak of the second pair: they were related to the isomers (−)-**2a** and (+)-**2b**, respectively. The remaining two peaks, one for each pair, were observed on the HPLC analysis of the reaction carried out with the enantiopure *R* imine **A** (Table 1, entry **4**). These latter two peaks were ascribed to the isomers (+)-**2a** and (−)-**2b**, respectively.

Analogous results were obtained performing a similar reaction with a second imine, benzylidene(1-phenyl-ethyl)-amine **B**, used in both the enantiomerically pure forms (*S*)-(+) and (*R*)-(−). The cyclocarbonylation of **B** with different allyl halides led, in similar reaction conditions, each time, to two optically active *trans* diastereomers with only traces of the *cis* form. The results of these cyclocarbonylations are collected in Table 2.

An attempt was made to assign the absolute configurations of the newly induced chiral centers, comparing the chemical shifts and the coupling constants J_{H-H} of the C3 and C4 protons of these latter structures with those of Table 1. We assigned the configurations (3*S*,4*R*) and (3*R*,4*S*) to the structures **3a**–**5a**, depending whether the starting imine had configuration of *S* or *R*, respectively. Vice versa we assigned the configurations (3*R*,4*S*) and (3*S*,4*R*) to the structures **3b**–**5b**, depending whether the starting imine had configuration *S* or *R*, respectively. *Cis* type diastereomers, as an inseparable mixture (dr=7/3, yield 6%), have been also isolated in the carbonylation with cinnamyl chloride (entries **3** and **4**).

The configuration of the vinylic moiety of the compounds **4a**–**4c**, **5a**, **5b** (J_{H-H}=16.0 Hz for vinylic protons) was found to be always *trans*.

Finally, when 3-chloro-1-butene was used in the carbonylation of **B** (in the enatiomerically pure (*R*)-(−) configuration) the isomers (−)-**5a** and (+)-**5b** were isolated with the same relative yield of entry **6**. As we reported in a previous paper[12] for similar reactions performed with non-chiral imines, an isomerization occurs during the catalytic cycle with the insertion of CO on the C1 of the alkene.

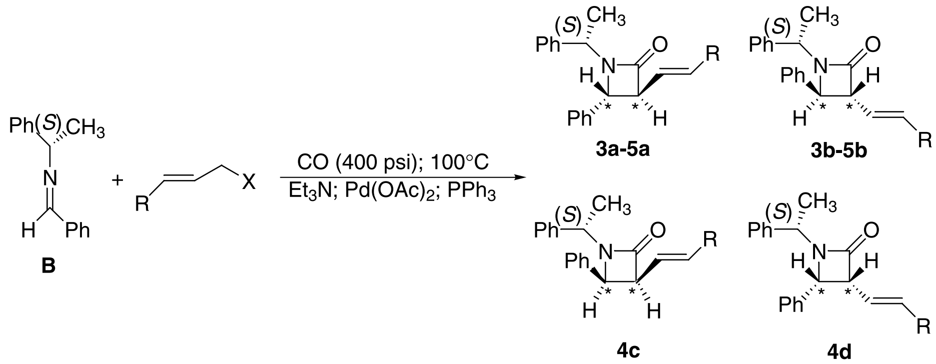
3. Conclusion

To the best of our knowledge, notwithstanding the interest in the synthesis of β-lactams through cyclocarbonylation, stereoselective syntheses leading to optically pure enantiomers have not been reported in the literature. In this paper we have described an efficient stereoselective synthesis of several β-lactams that exploits the asymmetric induction due to a chiral center preexisting on one of the reagents. A simple chromatographic separation allowed the isolation of enantiomerically pure β-lactams with three chiral centers whose absolute configurations were assigned through ^{1}H NMR spectroscopy and X-ray crystallography.

4. Experimental

THF, allyl bromide, crotyl chloride, 1-chloro-3-methyl-2-butene, cinnamyl chloride, 3-chloro-1-butene, (*R*)-(−)-2-amino-2-phenylethanol, (*S*)-(+)-2-amino-2-phenylethanol, (*R*)-(+)-1-phenylethylamine, (*S*)-(−)-1-phenylethylamine, triethylamine, palladium (II) acetate, triphenylphosphine were of commercial grade (Aldrich), and were used without

Table 2. Synthesis of chiral β-lactams from allyl halides and the enantiopure (*S*)-imine **B**



Entry	Absol. config. of imine **B**	R	X	Yield (%)[a]	dr[b] $[\alpha]_D^{22c}$		
1	(*S*)	H	Br	93	(+)-**3a** (66) [+34.0]	(−)-**3b** (34) [−35.0]	—
2	(*R*)[d]	H	Br	92	(−)-**3a** (66) [−39.6]	(+)-**3b** (34) [+34.1]	—
3	(*S*)	Ph	Cl	63	(+)-**4a** (74) [+199.7]	(−)-**4b** (20) [−194.3]	**4c**+**4d** (6)[e]
4	(*R*)[d]	Ph	Cl	90	(−)-**4a** (74) [−226.7]	(+)-**4b** (20) [+210.3]	**4c**+**4d** (6)[e]
5	(*S*)	CH_3	Cl	85	(+)-**5a** (60) [+62.9]	(−)-**5b** (40) [−41.0]	—
6	(*R*)[d]	CH_3	Cl	78	(−)-**5a** (60) [−65.5]	(+)-**5b** (40) [+40.1]	—

[a] Isolated yields.
[b] Diasteromeric ratios determined by GC gas-chromatography of the crude product.
[c] *c* 0.01–0.05, $CHCl_3$ (see Section 4 for details).
[d] Using the enantiopure (*R*)-imine **B**, the products **3a**–**5a**, **3b**–**5b**, **4c** and **4d** are the enantiomers of those obtained with the enantiopure (*S*)-imine **B**.
[e] Inseparable mixture of diasteromers, dr=7/3, determined by ^{1}H NMR spectroscopy and GC–MS.

further purification. Benzaldehyde of commercial grade (Aldrich), was purified by distillation prior to use. Imines were prepared starting from the corresponding carbonyl compounds and amines, following known synthetic protocols.[16] Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard (δ=7.24 for ^{1}H spectra; δ=77.0 for ^{13}C spectra). The IR spectra were recorded on a Perkin Elmer spectrometer Model 283. GC–MS analyses were performed with Hewlett-Packard HP-5890 series II gas chromatograph (5% diphenyl/95% dimethylpolysiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an HP 5971 mass-selective detector operating at 70 eV (EI). HPLC analyses were performed with a Perkin–Elmer series 10 Liquid Chromatograph equipped with an UV–Vis (254 nm) detector and chiral column (Chiral cell OB-H, 25 cm, 0.46 cm i.d.). Eluent mixtures used for HPLC were *n*-hexane/ethanol=95:5. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. Melting points were determined using an electrothermal melting point apparatus and are uncorrected. Polarimetric measurements were performed by a Jasco P-1020 polarimeter. TLC were performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 μm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques.

4.1. General procedure for the preparation of alkenyl-β-lactams

A mixture of 1.0 mmol of **A** or **B**, 1.5 mmol of allyl halides, 0.08 mmol of PPh_3, 0.02 mmol of $Pd(AcO)_2$, and 2 mmol of Et_3N were dissolved in 10 mL of solvent (THF) and placed in a 45 mL autoclave. The autoclave was purged, pressurized (400 psi CO), and then heated to 100 °C for 18 h. The reaction was then cooled to room temperature, and worked up by the addition of water (15 mL) and extraction with Et_2O (3×5 mL). The combined organic layer were dried (Na_2SO_4) and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O=7:3) to afford the pure β-lactams; yields: 40–98%.

4.1.1. 1-(2-Methoxy-1-phenylethyl)-4-phenyl-3-vinylazetidin-2-one (−)-1a. Yield: 159.6 mg, (52%), white solid, mp 83–85 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 3.40 (s, 3H), 3.61 (dd, *J*=7.9, 2.0 Hz, 1H), 3.69 (dd, *J*=6.9, 2.4 Hz, 1H), 4.22 (d, *J*=2.0 Hz, 1H), 4.28–4.33 (m, 2H), 5.25 (dd, *J*=19.0, 10.4 Hz, 2H), 5.90–5.98 (m, 1H), 7.19–7.36 (m, 10 H). ^{13}C NMR (100.62 MHz): δ 58.7, 59.0, 60.4, 63.4, 73.0, 119.0, 126.6, 127.4, 127.8, 128.3, 128.6, 128.7, 131.0, 137.5, 137.6, 168.1. GC–MS (70 eV) *m*/*z* (rel. int.): 307 (<1%, M^+), 262 (9), 240 (1), 194 (25), 130 (100), 129 (85), 115 (50), 91 (27). IR ($CHCl_3$): 3060, 3030, 2920, 2850, 1735, 1600, 1520, 1490, 1430, 1340, 1310, 1110, 960, 760, 730, 690 cm^{-1}. $[\alpha]_D^{22}$=−44.7 (*c* 0.01, $CHCl_3$). Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.55. Found: C, 78.10; H, 7.02; N, 4.50. (+)-**1b**. Yield: 129.3 mg, (42%), white solid, mp 55–57 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 3.25 (s, 3H), 3.43 (dd, *J*=9.3, 5.4 Hz, 1H), 3.60 (dd, *J*=8.0, 2.0 Hz, 1H), 3.75 (t, *J*=9.3 Hz, 1H), 4.24 (d, *J*=2.0 Hz, 1H), 4.81 (dd, *J*=9.3, 5.4 Hz, 1H), 5.18–5.23 (m, 2H), 5.83–5.97 (m, 1H), 7.22–7.34 (m, 10H). ^{13}C NMR (100.62 MHz): δ 57.8, 58.5, 62.3, 63.2, 72.0, 119.0, 126.6, 126.8, 127.8, 127.9, 128.3, 128.6, 130.9, 136.7, 138.6, 168.7. GC–MS (70 eV) *m*/*z* (rel. int.): 307 (<1%, M^+), 262 (12), 240 (1), 194 (27), 130 (100), 129 (82), 115 (46), 91 (26). IR (film): 3060, 3030, 2920, 2850, 1600, 1520, 1490, 1430, 1340, 1310, 1110, 960, 760, 730, 690 cm^{-1}. $[\alpha]_D^{22}$=+57.2 (*c* 0.01, $CHCl_3$). Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.14; H. 6.89; N, 4.55. Found: C, 78.50; H, 7.10; N, 4.45. (−)-**1c**. Yield: 12.0 mg, (3.9%), oil. ^{1}H NMR (400.13 MHz): δ 3.31 (s, 3H), 3.48 (dd, *J*=9.6, 5.3 Hz, 1H), 3.91 (t, *J*=9.6 Hz, 1H), 4.07 (t, *J*=5.7 Hz, 1H), 4.73–4.78 (m, 2H), 5.02–5.05 (m, 1H), 5.22–5.30 (m, 2H), 7.17–7.39 (m, 10H). ^{13}C NMR (100.62 MHz): δ 29.6, 58.2, 58.6, 60.5, 72.6, 120.0, 127.7, 128.0, 128.2, 128.4, 128.5, 128.7, 133.9, 134.1, 136.8, 168.7. GC–MS (70 eV) *m*/*z* (rel. int.): 307 (<1%, M^+), 262 (10), 240 (21), 194 (27), 130 (100), 129 (81), 115 (50), 91 (28). IR (film): 3060, 3030, 2920, 2850, 1600, 1520, 1490, 1430, 1340, 1310, 1110, 960, 760, 730, 690 cm^{-1}. $[\alpha]_D^{22}$=−37.2 (*c* 0.01, $CHCl_3$).

4.1.2. 1-(2-Methoxy-1-phenylethyl)-4-phenyl-3-vinylazetidin-2-one (+)-1a. Yield: 154.5 mg, (50%), white solid. Mp, spectroscopic data and GC–MS are the same of those reported for the enantiomer (−)-**1a**. $[\alpha]_D^{22}$=+43.4 (*c* 0.01, $CHCl_3$). (−)-**1b**. Yield: 125.4 mg, (42%), white solid. Mp, spectroscopic data and GC–MS data are the same of those reported for the enantiomer (+)-**1b**. $[\alpha]_D^{22}$=−55.4 (*c* 0.01, $CHCl_3$). (+)-**1c**. Yield: 11.6 mg (3.8%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (−)-**1c**. $[\alpha]_D^{22}$=+35.0 (*c* 0.01, $CHCl_3$).

4.1.3. 1-(2-Methoxy-1-phenylethyl)-3-(2-methylpropenyl)-4-phenylazetidin-2-one (−)-2a. Yield: 97.1 mg (29%), white solid, mp 58–59 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.53 (s, 3H), 1.74 (s, 3H), 3.40 (s, 3H), 3.69 (dd, *J*=9.2, 4.9 Hz, 1H), 3.79 (dd, *J*=9.1, 2.1 Hz, 1H), 4.10 (d, *J*=2.1 Hz, 1H), 4.25–4.34 (m, 2H), 5.30 (d, *J*=9.1 Hz, 1H), 7.21–7.36 (m, 10H). ^{13}C NMR (100.62 MHz): δ 18.6, 25.6, 58.8, 59.1, 59.8, 61.5, 73.1, 117.6, 126.7, 127.5, 127.8, 128.2, 128.6, 128.7, 137.9, 138.0, 138.1, 169.8. GC–MS (70 eV) *m*/*z* (rel. int.): 335 (<1%, M^+), 194 (14), 158 (97), 143 (100), 128 (19), 115 (10), 91 (19), 77 (15). IR (film): 3060, 3020, 2900, 1735, 1600, 1485, 1450, 1340, 1100, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=−40.0 (*c* 0.03, $CHCl_3$). Anal. calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.01; H, 7.39; N, 4.29. (+)-**2b**. Yield: 85.0 mg (25%), white solid, mp 38–39 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.49 (s, 3H), 1.71 (s, 3H), 3.26 (s, 3H), 3.43 (dd, *J*=9.4, 5.5 Hz, 1H), 3.72 (t, *J*=9.4 Hz, 1H), 3.79 (dd, *J*=9.2, 2.1 Hz, 1H), 4.12 (d, *J*=2.0 Hz, 1H), 4.83 (dd, *J*=9.4, 5.5 Hz, 1H), 5.24 (d, *J*=9.2 Hz, 1H), 7.16–7.34 (m, 10H). ^{13}C NMR (100.62 MHz): δ 18.6, 25.6, 57.7, 58.5, 59.5, 63.2, 72.1, 117.4, 126.6, 127.7, 127.9, 128.0, 128.6, 128.7, 136.7, 138.1, 139.1, 170.3. GC–MS (70 eV) *m*/*z* (rel. int.): 335 (<1%, M^+), 194 (7), 158 (98), 143 (100), 128 (20), 115 (10), 91 (17), 77 (16). IR (film): 3060, 3020, 2900, 1735, 1600, 1485, 1450, 1340, 1100, 750, 690 cm^{-1}.

$[\alpha]_D^{22}$=+24.0 (*c* 0.03, $CHCl_3$). Anal. calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 79.10; H, 7.40; N, 4.30.

4.1.4. 1-(2-Methoxy-1-phenylethyl)-3-(2-methylpropenyl)-4-phenylazetidin-2-one (+)-2a. Yield: 71.0 mg (21%), white solid. Mp, spectroscopic data and GC–MS data are the same of those reported for the enantiomer (−)-**2a**. $[\alpha]_D^{22}$=+40.8 (*c* 0.02, $CHCl_3$). (−)-**2b**. Yield: 63.6 mg (19%), white solid. Mp, spectroscopic data and GC–MS data are the same of those reported for the enantiomer (+)-**2b**. $[\alpha]_D^{22}$=−21.5 (*c* 0.02, $CHCl_3$).

4.1.5. 4-Phenyl-1-(1-phenylethyl)-3-vinylazetidin-2-one (+)-3a. Yield: 170.0 mg (61%), oil. ^{1}H NMR (400.13 MHz): δ 1.80 (d, *J*=7.1 Hz, 3H), 3.59 (dd, *J*=7.7, 1.9 Hz, 1H), 4.13 (d, *J*=1.9 Hz, 1H), 4.28 (q, *J*=7.1 Hz, 1H), 5.24 (dd, *J*=17.7, 10.3 Hz, 2H), 5.87–5.96 (m, 1H), 7.16–7.32 (m, 10H). ^{13}C NMR (100.62 MHz): δ 20.1, 54.6, 60.5, 63.1, 118.9, 126.5, 126.7, 127.4, 128.3, 128.5, 128.8, 131.0, 137.6, 141.3, 168.0. GC–MS (70 eV) *m*/*z* (rel. int.): 277 (<1%, M^+), 130 (100), 129 (47), 115 (20), 105 (24), 77 (16). IR (film): 3060, 2980, 1735, 1450 cm^{-1}. $[\alpha]_D^{22}$=+34.0 (*c* 0.11, $CHCl_3$). (−)-**3b**. Yield: 87.6 mg (32%), oil. ^{1}H NMR (400.13 MHz): δ 1.31 (d, *J*=7.2 Hz, 3H), 3.62 (dd, *J*=7.6, 2.2 Hz, 1H), 4.05 (d, *J*=2.2 Hz, 1H), 5.06 (q, *J*=7.2 Hz, 1H,), 5.15–5.26 (m, 2H), 5.77–5.86 (m, 1H), 7.20–7.33 (m, 10H). ^{13}C NMR (100.62 MHz): δ 18.6, 52.0, 60.7, 63.2, 119.0, 126.7, 127.2, 127.7, 128.5, 128.6, 128.7, 130.7, 138.9, 139.8, 168.2. GC–MS (70 eV) *m*/*z* (rel. int.): 277 (<1%, M^+), 130 (100), 129 (49), 115 (17), 105 (23), 77 (19). IR (film): 3060, 2980, 1735, 1450 cm^{-1}. $[\alpha]_D^{22}$=−35.0 (*c* 0.03, $CHCl_3$).

4.1.6. 4-Phenyl-1-(1-phenylethyl)-3-vinylazetidin-2-one (−)-3a. Yield: 168.2 mg (61%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (+)-**3a**. $[\alpha]_D^{22}$=−39.6 (*c* 0.05, $CHCl_3$). (+)-**3b**. Yield: 86.6 mg (31%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (−)-**3b**. $[\alpha]_D^{22}$=+34.1 (*c* 0.03, $CHCl_3$).

4.1.7. 4-Phenyl-1-(1-phenylethyl)-3-styrylazetidin-2-one (+)-4a. Yield: 166.0 mg (47%), oil. ^{1}H NMR (400.13 MHz): δ 1.82 (d, *J*=7.2 Hz, 3H), 3.75 (dd, *J*=8.0, 2.0 Hz, 1H), 4.20 (d, *J*=2.0 Hz, 1H), 4.31 (q, *J*=7.2 Hz, 1H), 6.25 (dd, *J*=15.8, 8.0 Hz, 1H), 6.56 (d, *J*=15.8 Hz, 1H), 7.20–7.35 (m, 15H). ^{13}C NMR (100.62 MHz): δ 20.1, 54.6, 61.1, 62.8, 122.3, 126.3, 126.5, 126.7, 127.5, 127.7, 128.4, 128.5, 128.6, 128.8, 133.9, 136.4, 137.5, 141.3, 168.1. GC–MS (70 eV) *m*/*z* (rel. int.): 353 (<1%, M^+), 209 (39), 208 (27), 194 (32), 144 (69), 115 (62), 105 (100). IR (film): 3025, 2060, 1735, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=+199.7. (*c* 0.01, $CHCl_3$). (−)-**4b**. Yield: 44.4 mg (13%), oil. ^{1}H NMR (400.13 MHz): δ 1.35 (d, *J*=7.2 Hz, 3H), 3.78 (dd, *J*=8.1, 2.0 Hz, 1H), 4.11 (d, *J*=2.0 Hz, 1H), 5.10 (q, *J*=7.2 Hz, 1H), 6.15 (dd, *J*=15.8, 8.1 Hz, 1H), 6.51 (d, *J*=15.8 Hz, 1H), 7.19–7.37 (m, 15H). ^{13}C NMR (100.62 MHz): δ 18.8, 52.2, 61.4, 62.9, 122.0, 126.3, 126.8, 127.3, 127.7, 127.8, 128.4, 128.5, 128.7, 128.8, 134.0, 136.4, 138.8, 139.8, 168.4. GC–MS (70 eV) *m*/*z* (rel. int.): 353 (<1%, M^+), 209 (45), 208 (32), 194 (30), 144 (63), 115 (65), 105 (100). IR (film): 3025, 2060, 1735, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=−194.3 (*c* 0.01, $CHCl_3$). **4c**+**4d**. Yield: 14.1 mg (4%), oil. Inseparable mixture of two *cis*-configurated diasteromeric β-lactams (dr=7/3 by ^{1}H NMR and GC–MS). **4c**: ^{1}H NMR (400.13 MHz): δ 1.44 (d, *J*=7.2 Hz, 3H), 4.15 (dd, *J*=7.5, 5.7 Hz, 1H), 4.60 (d, *J*=5.7 Hz, 1H), 5.08 (q, *J*=7.2 Hz, 1H), 5.64 (dd, *J*=16.0, 7.5 Hz, 1H), 6.60 (d, *J*=16.0 Hz, 1H), 7.08–7.50 (m, 15H). GC–MS (70 eV) *m*/*z* (rel. int.): 353 (<1%, M^+), 209 (43), 208 (35), 194 (28), 144 (62), 115 (69), 105 (100). **4d**: ^{1}H NMR (400.13 MHz): δ 1.88 (d, *J*=7.2 Hz, 3H), 4.19 (dd, *J*=7.5, 5.7 Hz, 1H), 4.66 (d, *J*=5.7 Hz, 1H), 5.08 (q, *J*=7.2 Hz, 1H,), 5.64 (dd, *J*=16.0, 7.5 Hz, 1H), 6.60 (d, *J*=16.0 Hz, 1H), 7.08–7.50 (m, 15H). GC–MS (70 eV) *m*/*z* (rel. int.) 353 (<1%, M^+), 209 (46), 208 (31), 194 (32), 144 (63), 115 (62), 105 (100). ^{13}C NMR and IR data were measured on the mixture. ^{13}C NMR (100.62 MHz): δ 19.4, 20.0, 52.6, 54.8, 57.6, 57.7, 58.7, 59.0, 121.1, 122.0, 125.7, 126.3, 126.8, 126.9, 127.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.2, 128.3, 128.5, 128.7, 130.1, 134.3, 135.5, 136.6, 136.8, 139.9, 140.0, 141.4, 168.3, 168.5. IR (film): 3025, 2060, 1735, 750, 690 cm^{-1}.

4.1.8. 4-Phenyl-1-(1-phenylethyl)-3-styrylazetidin-2-one (−)-4a. Yield: 235.0 mg (67%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (+)-**4a**. $[\alpha]_D^{22}$=−226.7 (*c* 0.02, $CHCl_3$). (+)-**4b**. Yield: 63.5 mg (18%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (−)-**4b**. $[\alpha]_D^{22}$=+210.3 (*c* 0.02, $CHCl_3$). **4c**+**4d**. Yield: 19.1 mg (5%), oil. Inseparable mixture of two *cis*-configurated diasteromeric β-lactams (dr=7/3 by ^{1}H NMR and GC–MS). Spectroscopic data and GC–MS data are the same of those reported for the enantiomers obtained with the imine (*S*)-(+).

4.1.9. 4-Phenyl-1-(1-phenyl-ethyl)-3-propenyl-azetidin-2-one (+)-5a. Yield: 148.4 mg (51%), oil. ^{1}H NMR (400.13 MHz): δ 1.69 (d, *J*=6.2 Hz, 3H), 1.79 (d, *J*=7.1 Hz, 3H) 3.52 (dd, *J*=8.0, 1.9 Hz, 1H), 4.08 (d, *J*=1.9 Hz, 1H), 4.28 (q, *J*=7.1 Hz, 1H), 5.50–5.58 (m, 1H), 5.63–5.74 (m, 1H), 7.20–7.35 (m, 10H). ^{13}C NMR (100.62 MHz): δ 17.9, 20.1, 54.5, 61.1, 62.6, 123.9, 126.5, 126.7, 127.4, 128.2, 128.5, 128.7, 129.7, 130.4, 141.5, 168.8. GC–MS (70 eV) *m*/*z* (rel. int.): 291 (<1%, M^+), 144 (92), 129 (100), 115 (10), 105 (40), 77 (27). IR (film): 3025, 2060, 1735, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=+62.9. (*c* 0.02, $CHCl_3$). (−)-**5b**. Yield: 99.0 mg (34%), oil. ^{1}H NMR (400.13 MHz): δ 1.30 (d, *J*=7.2 Hz, 3H), 1.65 (d, *J*=5.4 Hz, 3H), 3.55 (dd, *J*=8.1, 2.0 Hz, 1H), 4.0 (d, *J*=2.0 Hz, 1H), 5.05 (q, *J*=7.2 Hz, 1H), 5.39–5.50 (m, 1H), 5.57–5.70 (m, 1H), 7.10–7.50 (m, 10H). ^{13}C NMR (100.62 MHz): δ 17.9, 18.7, 52.0, 61.3, 62.7, 123.6, 126.7, 127.2, 127.3, 127.6, 127.9, 128.1, 128.3, 139.1, 141.0, 169.2. GC–MS (70 eV) *m*/*z* (rel. int.): 291 (<1%, M^+), 144 (90), 129 (100), 115 (10), 105 (40), 77 (27). IR (film): 3025, 2060, 1735, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=−41.0 (*c* 0.02, $CHCl_3$).

4.1.10. 4-Phenyl-1-(1-phenylethyl)-3-propenylazetidin-2-one (−)-5a. Yield: 136.1 mg (47%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (+)-**5a**. $[\alpha]_D^{22}$=−65.5 (*c* 0.02, $CHCl_3$). ((+)-**5b**. Yield: 90.1 mg (31%), oil. Spectroscopic data and GC–MS data are the same of those reported for the enantiomer (−)-**5b**. $[\alpha]_D^{22}$=+40.1 (*c* 0.02, $CHCl_3$).

Acknowledgements

This work was carried out within the framework of the National Project 'Stereoselezione in Sintesi Organica: Metodologie ed Applicazioni' supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome) and the University Lecce.

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Tetrahedron 60 (2004) 6901–6911
Tetrahedron

Solvent-modulated Pd/C-catalyzed deprotection of silyl ethers and chemoselective hydrogenation

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Received 30 April 2004; accepted 27 May 2004

Available online 4 July 2004

Abstract—Recently we have reported undesirable and frequent deprotection of the TBDMS protective group of a variety of hydroxyl functions occurred under neutral and mild hydrogenation conditions using 10% Pd/C in MeOH. The deprotection of silyl ethers is susceptible to significant solvent effect. TBDMS and TES protecting groups were selectively cleaved in the presence of acid-sensitive functional groups such as TIPS ether, TBDPS ether and dimethyl acetal under hydrogenation condition using 10% Pd/C in MeOH. In contrast, chemoselective hydrogenation of reducible functional groups such as acetylene, olefin and benzyl ether, proceeds in the presence of TBDMS or TES ethers in AcOEt or MeCN.

1. Introduction

Hydroxyl groups are partial structures of a number of organic compounds. During oxidation, acylation, halogenation or dehydration reaction of these compounds, the hydroxyl groups must be protected. Silyl ethers are among the most frequently used protective groups for alcohols in organic synthesis,[1] because they can be easily installed in high yield and can withstand a variety of reaction conditions. Although silyl ethers can be easily deprotected by treatment with a fluoride anion,[2] the strongly basic conditions make it inappropriate to apply to base-sensitive substrates.[2] Many alternative and mild methods have been reported for the deprotection of silyl ethers under mild conditions.[1] However, most of these methods suffer from the use of acidic and basic conditions, strong oxidising and reducing reagents and complicated workup.[3] In this context, it is very important to develop a novel, neutral and mild deprotection method of silyl ethers.

On the other hand, Pd/C is one of the most useful heterogeneous hydrogenation catalysts in organic synthesis,[4] because it can be safely handled and removed from the reaction mixture by simple filtration. Although it has been well known that the TBDMS (*tert*-butyldimethylsilyl) ether is inert toward Pd/C-catalyzed hydrogenation conditions,[5] we have recently reported that the TBDMS ethers are easily and frequently cleaved under hydrogenation conditions using Pd/C as a catalyst in MeOH.[6] In a related reaction, we found that the reductive deprotection of the silyl ether under hydrogenation conditions using 10% Pd/C was strongly affected by the solvent. Herein, we report a selective cleavage method of TES and TBDMS ethers under mild and neutral hydrogenation conditions using 10% Pd/C in MeOH, and a selective hydrogenation method of some reducible functionalities in the presence of TES and TBDMS ethers using 10% Pd/C in MeCN or AcOEt.[7]

2. Results and discussion

Our initial studies focused on the solvent effect toward the deprotection of TBDMS ethers under hydrogenation conditions using 10% Pd/C. 1-*tert*-Butyldimethylsilyloxy-3-phenyl-2-propene (**1a**) was hydrogenated with 10% Pd/C (10% of the weight of the substrate (**1a**); 2.3 mol% as Pd metal) for 24 h at room temperature in various solvents (Table 1). While smooth hydrogenation of the olefin function and complete deprotection of the TBDMS protective group of **1a** simultaneously proceeded in MeOH (entry 1), TBDMS cleavage reaction was slightly depressed in EtOH and strongly inhibited in ^{t}BuOH (entries 2 and 3). In spite of the poor water solubility of **1a**, considerable cleavage (77%) of the TBDMS ether was observed (entry 4). As compared with protic solvents, use of aprotic solvents is inconvenient for the deprotection of TBDMS ether (**1a**) under hydrogenation conditions using Pd/C (entries 5–11). Especially in toluene, AcOEt and MeCN, the TBDMS ether was stable and selective hydrogenation of the olefin was achieved (entries 9–11). While no deprotection of the TBDMS group was observed in the absence of hydrogen or 10% Pd/C in MeOH, both

Keywords: Silyl ether; Hydrogenation; Palladium on carbon; Solvent effect; Deprotection.
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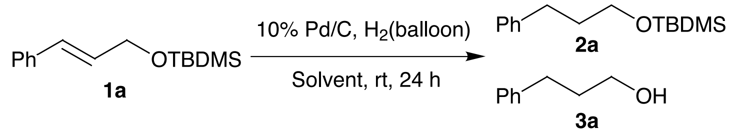
doi:10.1016/j.tet.2004.05.098

Table 1. Solvent effect toward the deprotection of the TBDMS ether (**1a**) using 10% Pd/C[a]



Entry	Solvent	Relative yield (%)[b]	
		2a	**3a**
1	MeOH[c]	0	100
2	EtOH	34	66
3	^{t}BuOH	92	8
4	H_2O	23	77
5	Hexane	86	14
6	Cyclohexane	89	11
7	DMF	87	13
8	THF	98	2
9	Toluene	100	0
10	EtOAc	100	0
11	MeCN	100	0

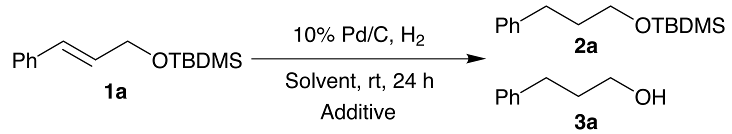
[a] 10% Pd/C was purchased from Aldrich (Aldrich product number 20,569-9).
[b] Determined by ^{1}H NMR.
[c] No reaction was observed under Ar.

hydrogen and Pd/C were essential for the deprotection of the TBDMS group.[8]

The effect of the addition of a small amount of MeOH or H_2O (0.1 mL of MeOH or H_2O/1 mL of EtOAc or MeCN) into the reaction mixture of TBDMS ether (**1a**) under 10% Pd/C-catalyzed hydrogenation conditions in AcOEt or MeCN is summarized in Table 2. The addition of MeOH or H_2O into the reaction mixture did not affect cleavage of the TBDMS ether at all and the olefin of **1a** was reduced selectively to form TBDMS ether (**2a**) in high yield (entries 1, 3 and 4). These data imply that AcOEt or MeCN strongly coordinates with the Pd metal to compete with the reacting substance and decreases the catalyst activity toward the deprotection of the TBDMS ether.[10] When a small amount of H_2O was added into the reaction mixture in AcOEt as a solvent, partial TBDMS deprotection was exceptionally observed for the following reason (entry 2). The reaction mixture of entry 2 separated into two layers (H_2O and AcOEt), and the deprotection of TBDMS progressed in the aqueous layer as well as in Table 1, entry 4. On the other hand, the reaction mixture in MeCN in the presence of a small amount of H_2O consisted of a homogeneous layer (single layer) and, no cleavage of the TBDMS ether was observed (entry 4).

To further explore the solvent effect toward the deprotection of various kinds of silyl ethers, we carried out the Pd/C-catalyzed hydrogenation reaction of TBDMS, TES (triethylsilyl), TPS (triphenylsilyl), TBDPS (*tert*-butyldiphenylsilyl) and TIPS (triisopropylsilyl) ethers in several solvents (Table 3). While TIPS (**1d**) and TBDPS ethers (**1e**) were stable under hydrogenation conditions using Pd/C even in MeOH (entries 4 and 5), TES (**1b**) and TPS ethers (**1c**) were completely deprotected in MeOH as well as the TBDMS ether (**1a**) (entries 1–3). The cleavage of silyl ethers was apparently depressed in aprotic solvents such as THF and EtOAc (entries 6–8 and 11–13) and silyl ethers were nearly stable in MeCN (entries 16–18). Although a small amount of TBDMS deprotection was observed in THF, it was entirely stable in AcOEt and MeCN (compare entries 6 with 11 and 16). In THF and AcOEt, the TES ether (**1b**) was partially cleaved, but it was completely suppressed by the use of MeCN as a solvent (entry 17). On the other

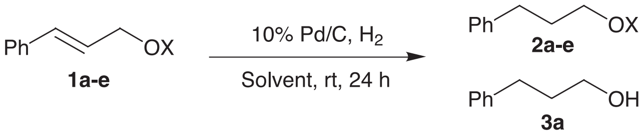
Table 2. Effect of the addition of a small amount of MeOH or H_2O into the reaction mixture of TBDMS ether (**1a**) in AcOEt or MeCN using 10% Pd/C[a] as a catalyst



Entry	Solvent	Additive[b]	Product	Yield (%)[c]
1	EtOAc	MeOH	**2a**	86
2	EtOAc	H_2O	**2a** (26),[d] **3a** (74)[d]	—
3	MeCN	MeOH	**2a**	100
4	MeCN	H_2O	**2a**	75

[a] 10% Pd/C was purchased from Aldrich (Aldrich product number 20,569-9).
[b] 0.1 mL of an additive/1 mL of EtOAc or MeCN.
[c] Isolated yield.
[d] The ratio was determined by ^{1}H NMR.

Table 3. Solvent effect toward the deprotection of various kinds of silyl ethers using 10% Pd/C[a]



Entry	Substrate	X	Solvent	Relative yield (%)[b]	
				2a–e	**3a**
1	**1a**	TBDMS	MeOH	0	100
2	**1b**	TES	MeOH	0	100
3	**1c**	TPS	MeOH	0	100
4	**1d**	TIPS	MeOH	100	0
5	**1e**	TBDPS	MeOH	100	0
6	**1a**	TBDMS	THF	98	2
7	**1b**	TES	THF	63	37
8	**1c**	TPS	THF	62	38
9	**1d**	TIPS	THF	100	0
10	**1e**	TBDPS	THF	100	0
11	**1a**	TBDMS	EtOAc	100	0
12	**1b**	TES	EtOAc	67	33
13	**1c**	TPS	EtOAc	100	0
14	**1d**	TIPS	EtOAc	100	0
15	**1e**	TBDPS	EtOAc	100	0
16	**1a**	TBDMS	MeCN	100	0
17	**1b**	TES	MeCN	100	0
18	**1c**	TPS	MeCN	97	3
19	**1d**	TIPS	MeCN	100	0
20	**1e**	TBDPS	MeCN	100	0

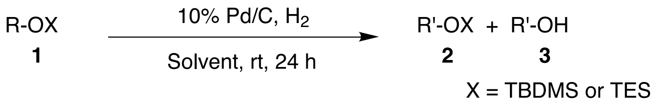
[a] 10% Pd/C was purchased from Aldrich (Aldrich product number 20,569-9).
[b] Determined by ^{1}H NMR.

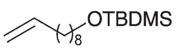
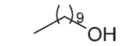
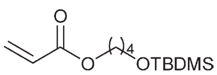
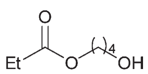
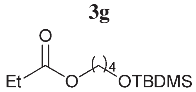
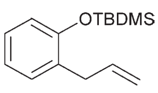
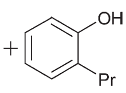
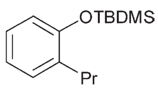
hand, partial TPS deprotection was observed in THF and MeCN while no cleavage of the TPS ether (**1c**) in AcOEt was achieved. Needless to say, TBDPS and TIPS ethers were quite stable under Pd/C-catalyzed hydrogenation condition in aprotic solvents (entries 9, 10, 14, 15, 19 and 20).

Next, we applied the present solvent effect to the chemoselective hydrogenation of some reducible functionalities in the presence of silyl ethers in AcOEt or MeCN and to the mild deprotection method of silyl ethers in MeOH. TBDMS or TES ethers (**1f–m**) possessing olefin or acetylene within a molecule were hydrogenated in MeOH, AcOEt or MeCN (Table 4). The reduction of olefin and the deprotection of the alkyl-*O*-TBDMS ether of **1f** or **1g** simultaneously proceeded to afford the corresponding saturated alcohols (**3f** or **3g**) (entries 1 and 3). However, the cleavage of the TBDMS group of **1h** and **1n–q** was incomplete under the hydrogenation conditions because of steric hindrance or an electronic factor (entry 5 and Fig. 1). In AcOEt olefin and benzyl ether functionalities of **1f–h** were hydrogenated chemoselectively to form the corresponding TBDMS ethers (**2f–h**) (entries 2, 4 and 6).

On the other hand, the TES ethers of primary (**1i** or **j**), secondary (**1k**), tertiary (**1l**) and phenolic (**1m**) alcohols possessing an olefin or acetylene functionality within the molecule were reduced and cleaved smoothly under the hydrogenation conditions in MeOH (entries 7, 9, 11, 13 and 15). On the contrary, during the hydrogenation of an olefin or acetylene functionality, the deprotection of the TES ether of aliphatic alcohols was not observed in MeCN (entries 8, 10, 12 and 14). While the TBDMS protective group of

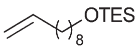
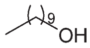
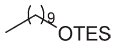
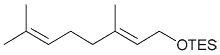
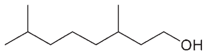
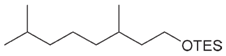
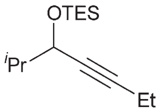
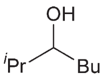
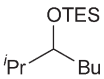
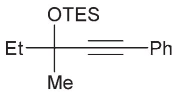
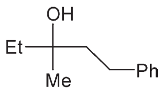
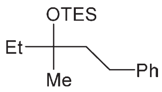
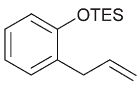
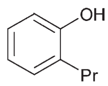
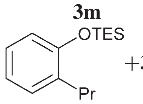
Table 4. Cleavage of the TBDMS or TES ethers and chemoselective hydrogenation using 10% Pd/C[a]



Entry	Substrate	Solvent	**2**:**3**[b]	Product	Yield (%)[c]
1	 **1f**	MeOH	0:100	 **3f**	80
2		AcOEt	100:0	 **2f**	98
3	 **1g**	MeOH	0:100	 **3g**	71
4		AcOEt	100:0	 **2g**	98
5	 **1h**	MeOH	92:8	**2h** +  **3h**	—
6		AcOEt	100:0	 **2h**	100

(*continued on next page*)

Table 4 (*continued*)

Entry	Substrate	Solvent	**2**:**3**[b]	Product	Yield (%)[c]
7	 **1i**	MeOH	0:100	 **3f**	94[d] (67)[e]
8		MeCN	100:0	 **2i**	99
9	 **1j**	MeOH	0:100	 **3j**	92[d] (45)[e]
10		MeCN	100:0	 **2j**	88
11	 **1k**	MeOH	0:100	 **3k**	90[d] (21)[e]
12		MeCN	100:0	 **2k**	93
13	 **1l**	MeOH	0:100	 **3l**	96
14		MeCN	100:0	 **2l**	98
15	 **1m**	MeOH	0:100	 **3m**	83
16		MeCN	3:97	 +**3m** **2m**	-

[a] 10% Pd/C was purchased from Aldrich (Aldrich product number 20,569-9).
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] Product contaminated with a small amount of TES-OH.
[e] The yield of isolated and analytically pure product is indicated in parentheses. The low isolated yield is due to the volatile nature of the product and difficulty using silica gel column chromatography.

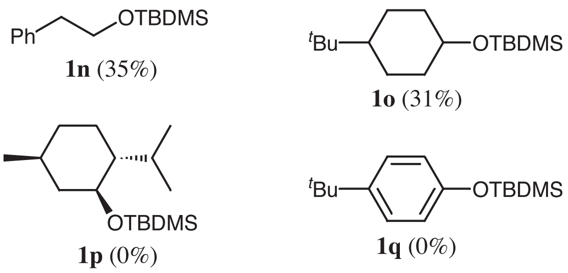
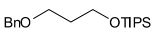
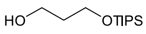
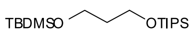
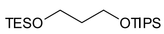
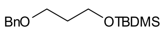
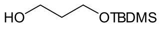
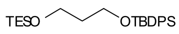
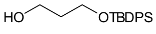
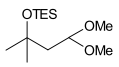
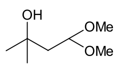


Figure 1. Cleavage of TBDMS ether in MeOH using 10% Pd/C (the ratio of desilylated mother alcohol was indicated in parentheses).

phenolic alcohols (**1h** and **1q**) was quite stable even in MeOH (entry 5 and Fig. 1), the TES protective group of the phenolic alcohol (**1m**) was deprotected easily not only in MeOH but also even in MeCN (entries 15 and 16).

Manipulation of functional groups is a fundamental process in synthetic organic chemistry and, hence, the development of new selective transformations remains of great interest.[11] Since hydroxyl groups are quite general functionalities of organic compounds, the development of a new, selective removal method of a specific protective group of hydroxyl groups among various protective groups is extremely important.[1,12] To examine the scope of our deprotection

Table 5. Selective deprotection under hydrogenation conditions in MeOH using 10% Pd/C[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1r**	30	 **3r**	86
2	 **1s**	26	**3r**	61
3	 **1t**	10	**3r**	100
4[c]	 **1u**	36	 **3u**	95
5	 **1v**	41	 **3v**	91
6	 **1w**	24	 **3w**	47[d]

[a] 10% Pd/C was purchased from Aldrich (Aldrich product number 20,569-9).
[b] Isolated yield.
[c] This reaction was performed in EtOAc.
[d] The low isolated yield is due to the volatile nature of the product and difficulty using silica gel column chromatography.

method using hydrogenation conditions, we have carried out a selective deprotection of Bn, TBDMS and TES protective groups of alcohols in the presence of other protective groups. The stability of the TIPS and TBDPS groups under the hydrogenation conditions (Table 3, entries 4 and 5) has been exploited for the selective deprotection of benzyl (**1r** and **1u**), TBDMS (**1s**) and TES ethers (**1t** and **1v**) in the presence of TIPS or TBDPS ether within the molecule. The results shown in Table 5 demonstrate that the selective deprotection of benzyl, TBDMS and TES ethers can be successfully carried out in the presence of TIPS or TBDPS ether using 10% Pd/C in MeOH or AcOEt as a solvent (entries 1–5).[12] The present procedure can be also applied to the chemoselective cleavage of a TES ether as distinguished from an acetal-type protective group (**1w**) (entry 6). Accordingly, this method may serve as a useful component to the existing methodologies and find applications in the synthesis of complicated molecules.

3. Conclusion

In summary, the cleavage of TBDMS, TES and TPS ethers under hydrogenation conditions using 10% Pd/C indicates significant solvent effect. While TIPS and TBDPS ethers were quite stable under the hydrogenation conditions in MeOH, THF, AcOEt and MeCN, TBDMS and TES protective groups were readily cleaved in MeOH. Consequently, Pd/C-catalyzed hydrogenation in MeOH can be applied to the convenient and neutral[8] deprotection method of TBDMS and TES protective groups in the presence of other protective groups. In contrast, the TBDMS ether was not deprotected under the hydrogenation conditions in AcOEt and MeCN at all, and the TES ether was stable in MeCN. Thus, chemoselective hydrogenation of reducible functionalities such as olefin, acetylene and benzyl ethers, as distinguished from TBDMS and TES ethers can be achieved using 10% Pd/C-catalyzed hydrogenation conditions in AcOEt or MeCN as a solvent. Since catalytic hydrogenation using Pd/C as a catalyst has found numerous applications in organic synthesis, the present solvent effect is extremely important information for synthetic organic chemists. The present mild and neutral deprotection method of TBDMS and TES protective groups will serve as a useful complement to the existing methodologies.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer, JEOL AL-400 spectrometer (^1H: 400 MHz, ^{13}C: 100 MHz), or a GL-270 spectrometer (^1H: 270 MHz) with tetramethylsilane or residual protiated solvent used as a reference. EI and FAB Mass spectra were taken on a JEOL JMS-SX102A instrument. Elemental analyses were performed by YANACO CHN CORDER MT-5 instrument. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). HPLC grade MeOH and H_2O and anhydrous EtOH were purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. Anhydrous hexane, cyclohexane, DMF, toluene, AcOEt and MeCN were purchased from Kanto Kagaku Co., Ltd. and used without further purification. THF was distilled from sodium benzophenone ketyl immediately prior to use. ^{t}BuOH and CH_2Cl_2 were distilled on CaH_2. 10% Pd/C was purchased from Aldrich (product number: 20,569-9). All other reagents were purchased from commercial sources and used without further purification.

4.2. General procedure for the synthesis of silyl ethers

Method A. To a solution of an alcohol, DMAP (0.01 equiv.), and Et_3N (1.2 equiv.) in CH_2Cl_2 (20 mL) was added silyl chloride (1.1 equiv.). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic layer were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

Method B. To a solution of an alcohol and imidazole (1.2 equiv.) in CH_2Cl_2 (20 mL) was added silyl chloride (1.2 equiv.). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ether (50 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

4.2.1. 1-*tert*-Butyldimethylsilyloxy-3-phenyl-2-propene (1a).[13] With Method A, cinnamyl alcohol (1.34 g, 10.0 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (1.21 g, 12.0 mmol), and *tert*-butyldimethylsilyl chloride (904 mg, 12.0 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1a**) as a colorless oil (2.20 g, 90%).

^{1}H NMR ($CDCl_3$): δ 7.38–7.20 (m, 5H), 6.59 (d, *J*=15.9 Hz, 1H), 6.28 (dt, *J*=4.9, 15.9 Hz, 1H), 4.35 (d, *J*=4.9 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 137.1, 129.5, 129.1, 128.4, 127.3, 126.4, 63.9, 26.0, 18.4, −5.2.

4.2.2. 1-Triethylsilyloxy-3-phenyl-2-propene (1b).[14] With Method B, cinnamyl alcohol (671 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triethylsilyl chloride (904 mg, 1.20 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1b**) as a colorless oil (717 mg, 93%).

^{1}H NMR ($CDCl_3$): δ 7.37 (d, *J*=7.5 Hz, 2H), 7.30 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.5 Hz, 1H), 6.60 (d, *J*=16.1 Hz, 1H), 6.29 (dt, *J*=5.1, 16.1 Hz, 1H), 4.35 (d, *J*=5.1 Hz, 2H), 0.99 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.9 Hz, 6H).

4.2.3. 1-Triphenylsilyloxy-3-phenyl-2-propene (1c). With Method B, cinnamyl alcohol (671 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triphenylsilyl chloride (1.77 g, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1c**) as a colorless needles (1.14 g, 58%).

^{1}H NMR ($CDCl_3$): δ 7.67 (dd, *J*=1.47, 7.82 Hz, 6H), 7.48–7.19 (m, 14H), 6.59 (d, *J*=15.9 Hz, 1H), 6.29 (dt, *J*=5.1, 15.9 Hz, 1H), 4.51 (dd, *J*=1.47, 4.63 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 136.9, 135.4, 134.0, 130.1, 130.1, 128.4, 128.2, 127.9, 127.3, 126.4, 64.5. MS (EI) *m/z* 392 (M^+, 24%), 314 (22), 260 (22), 259 (100), 236 (23), 199 (45), 181 (22), 117 (16), 115 (15). Anal. Calcd for $C_{27}H_{24}OSi$: C, 82.61; H, 6.16. Found C, 82.49; H, 6.19.

4.2.4. 1-Triisopropylsilyloxy-3-phenyl-2-propene (1d). With Method B, cinnamyl alcohol (671 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triisopropylsilyl chloride (1.16 g, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1d**) as a colorless oil (1.22 g, 85%).

^{1}H NMR ($CDCl_3$): δ 7.42–7.24 (m, 5H), 6.67 (d, *J*=15.6 Hz, 1H), 6.34 (dt, *J*=15.6, 4.9 Hz, 1H), 4.46 (dd, *J*=4.9, 1.5 Hz, 2H), 1.21–1.12 (m, 3H and 18H). ^{13}C NMR ($CDCl_3$): δ 137.3, 129.4, 129.0, 128.5, 127.2, 126.4, 63.9, 18.0, 12.1. MS (EI) *m/z* 290.5 (M^+, 20%), 248 (21), 247 (100), 117 (47), 115 (15). HRMS (EI) calcd for $C_{18}H_{30}OSi$ (M^+) 290.2066. Found 290.2057.

4.2.5. 1-*tert*-Butyldiphenylsilyloxy-3-phenyl-2-propene (1e).[15] With Method B, cinnamyl alcohol (335 mg, 2.50 mmol), imidazole (204 mg, 3.00 mmol), and *tert*-butyldiphenylsilyl chloride (825 mg, 3.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1e**) as a colorless oil (799 mg, 86%).

^{1}H NMR ($CDCl_3$): δ 7.71 (dd, *J*=1.5, 7.8 Hz, 4H), 7.45–7.20 (m, 11H), 6.64 (d, *J*=15.6 Hz, 1H), 6.28 (dt, *J*=4.9, 15.6 Hz, 1H), 4.38 (d, *J*=4.9 Hz, 2H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 137.2, 135.6, 133.6, 129.7, 129.4, 128.7, 128.5, 127.7, 127.3, 126.4, 64.5, 26.8, 19.3.

4.2.6. 1-*tert*-Butyldimethylsilyloxy-9-decene (1f).[16] With Method A, 9-decen-1-ol (1.56 g, 10.0 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (1.20 g, 12.0 mmol), and *tert*-butyldimethylsilyl chloride (1.66 g, 11.0 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1f**) as a colorless oil (1.81 g, 67%).

^{1}H NMR ($CDCl_3$): δ 5.89–5.73 (m, 1H), 5.30–4.90 (m, 2H), 3.59 (t, *J*=5.6 Hz, 2H), 2.07–2.00 (m, 2H), 1.53–1.29 (m, 12H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 139.1, 114.1, 63.3, 33.8, 32.9, 29.5, 29.4, 29.1, 29.0, 26.0, 25.8, 18.4, −5.3.

4.2.7. 4-*tert*-Butyldimethylsilyloxy-1-butyl acrylate (1g). With Method A, 4-hydroxybutyl acrylate (2.88 g, 20.0 mmol), DMAP (98 mg, 0.80 mmol), Et_3N (2.23 g, 22.0 mmol), and *tert*-butyldimethylsilyl chloride (3.17g, 21.0 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1g**) as a colorless oil (5.04 g, 98%).

^{1}H NMR ($CDCl_3$): δ 6.40 (dd, *J*=1.3, 17.5 Hz, 1H), 6.12 (dd, *J*=1.05, 17.5 Hz, 1H), 4.18 (t, *J*=6.5 Hz, 2H), 3.65 (t, *J*=6.5 Hz, 2H), 1.78–1.71 (m, 2H), 1.64–1.57 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.0, 130.2, 128.6, 64.3, 62.4, 29.1, 25.8, 25.2, 18.2, −5.5. MS (EI) *m/z* 201 ($M^+-C_4H_9$, 10%), 129 (100), 75 (15), 55 (35). HRMS (EI) calcd for $C_9H_{17}O_3Si$ ($M^+-C_4H_9$) 201.0947. Found 201.0939.

4.2.8. 1-*tert*-Butyldimethylsilyloxy-2-(2-propenyl)benzene (1h).[17] With Method B, 2-allylphenol (1.34 g, 10.0 mmol), imidazole (1.36 g, 20.0 mmol), and *tert*-butyldimethylsilyl chloride (1.80 g, 12.0 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1h**) as a colorless oil (1.89 g, 76%).

^{1}H NMR ($CDCl_3$): δ 7.13 (d, *J*=7.6 Hz, 1H), 7.08 (t, *J*=7.6 Hz, 1H), 6.89 (t, *J*=7.6 Hz, 1H), 6.78 (d, *J*=7.6 Hz, 1H), 6.02–5.92 (m, 1H), 5.05 (s, 1H), 5.02 (d, *J*=3.9 Hz, 1H), 3.37 (d, *J*=6.8 Hz, 2H), 1.01 (s, 9H), 0.23 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 153.4, 137.0, 130.7, 130.2, 127.0, 121.1, 118.4, 115.4, 34.4, 25.8, 18.3, −4.1.

4.2.9. 1-Triethylsilyloxy-9-decene (1i). With Method A, 9-decene-1-ol (753 mg, 4.80 mmol), DMAP (110 mg, 0.90 mmol), triethylsilyl chloride (1.00 g, 7.23 mmol) in pyridine (10 mL) used as a solvent instead of CH_2Cl_2. The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1i**) as a colorless oil (1.11 g, 85%).

^{1}H NMR ($CDCl_3$): δ 5.86–5.76 (m, 1H), 4.99 (dd, *J*=2.0, 17.1 Hz, 1H), 4.92 (dd, *J*=2.0, 10.3 Hz, 1H), 3.59 (t, *J*=6.8 Hz, 2H), 2.03 (q, *J*=7.0 Hz, 2H), 1.55–1.51 (m, 2H), 1.37–1.29 (m, 10H), 0.95 (t, *J*=8.0 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 139.2, 114.1, 63.0, 33.8, 32.9, 29.5, 29.4, 29.1, 28.9, 25.8, 6.8, 4.5. MS (EI) *m/z* 271

($M^+-C_2H_5$), 213 (15%), 103 (100), 75 (33), 57 (15), 55 (14). HRMS (EI) calcd for $C_{16}H_{34}OSi$ ($M^+-C_2H_5$) 241.1975. Found 241.1988.

4.2.10. Geranyl triethylsilyl ether (1j).[18] With Method B, geraniol (771 mg, 5.00 mmol), imidazole (409 mg, 6.00 mmol), and triethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1j**) as a colorless oil (1.07 g, 86%).

^1H NMR ($CDCl_3$): δ 5.33 (t, J=6.0 Hz, 1H), 5.10 (t, J=7.3 Hz, 1H), 4.18 (d, J=6.0 Hz, 2H), 2.10 (q, J=7.3 Hz, 2H), 2.01 (t, J=7.3 Hz, 2H), 1.67 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 0.97 (t, J=8.0 Hz, 9H), 0.61 (q, J=8.0 Hz, 6H). HRMS (EI) calcd for $C_{16}H_{32}OSi$ (M^+): 268.2222. Found: 268.2230.

4.2.11. 7-Methyl-5-triethylsilyloxy-3-octyne (1k). With Method B, 2-methyl-5-octyne-4-ol (701 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1k**) as a colorless oil (1.09 g, 86%).

^1H NMR ($CDCl_3$): δ 4.38 (t, J=7.1 Hz, 1H), 2.20 and 2.19 (each q, J=7.4 Hz, 1H), 1.84–1.78 (m, 1H), 1.61–1.43 (m, 2H), 1.12 (t, J=7.4 Hz, 3H), 0.98 (t, J=7.8 Hz, 9H), 0.91 and 0.90 (each d, J=6.6 Hz, 3H), 0.72–0.62 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 85.6, 81.4, 61.4, 48.2, 24.6, 22.7, 22.5, 13.8, 12.4, 6.8, 4.9. MS (EI) m/z 225 ($M^+-C_2H_5$, 100%), 197 (35), 171 (18), 141 (20), 111 (36), 103 (21), 75 (19), 44 (24). HRMS (EI) calcd for $C_{15}H_{30}OSi$ ($M^+-C_2H_5$) 225.1634. Found 225.1675.

4.2.12. 1-Phenyl-3-methyl-3-triethylsilyloxy-1-pentyne (1l). With Method B, 1-phenyl-3-methyl-1-pentyne-3-ol (871 mg, 5.00 mmol), imidazole (613 mg, 9.00 mmol), and triethylsilyl chloride (1.36 g, 9.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1l**) as a colorless oil (1.31 g, 91%).

^1H NMR ($CDCl_3$): δ 7.41–7.38 (m, 2H), 7.31–7.29 (m, 3H), 1.79–1.68 (m, 2H), 1.55 (s, 3H), 1.04 (t, J=7.3 Hz, 3H), 0.98 (t, J=7.7 Hz, 9H), 0.71 (q, J=7.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 131.4, 128.3, 128.0, 123.3, 93.8, 83.5, 70.0, 38.2, 30.5, 9.1, 7.1, 6.1. MS (EI) m/z 259 ($M^+-C_2H_5$, 100%), 187 (10), 149 (13), 61 (9), 44 (53). HRMS (EI) calcd for $C_{16}H_{23}OSi$ ($M^+-C_2H_5$) 259.1518. Found 259.1523.

4.2.13. 1-Triethylsilyloxy-2-(2-propenyl)benzene (1m). With Method B, 2-allylphenol (671 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1m**) as a colorless oil (1.27 g, 85%).

^1H NMR ($CDCl_3$): δ 7.12 (d, J=7.6 Hz, 1H), 7.07 (t, J=7.6 Hz, 1H), 6.88 (t, J=7.6 Hz, 1H), 6.78 (d, J=7.6 Hz, 1H), 6.02–5.92 (m, 1H), 5.07–5.02 (m, 2H), 3.37 (d, J=6.4 Hz, 2H), 1.00 (t, J=7.7 Hz, 6H), 0.77 (q, J=7.7 Hz, 9H). ^{13}C NMR ($CDCl_3$): δ 153.5, 137.1, 130.6, 130.0, 127.0, 121.0, 118.2, 115.3, 34.5, 6.7, 5.3. MS (FAB, NBA) m/z 249 (M^++H, 10%), 248 (15), 219 (11). HRMS (EI) calcd for $C_{15}H_{24}OSi$ (M^+) 248.1597. Found 248.1623.

4.2.14. 1-*tert*-Butyldimethylsilyloxy-2-phenylethane (1n).[19] With Method B, 2-phenylethan-1-ol (335 mg, 2.50 mmol), imidazole (204 mg, 3.00 mmol), and *tert*-butyldimethyl chloride (825 mg, 3.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1n**) as a colorless oil (799 mg, 86%).

^1H NMR ($CDCl_3$): δ 7.67 (dd, J=1.5, 7.8 Hz, 4H), 7.44–7.15 (m, 16H), 3.69 (t, J=6.4 Hz, 2H), 2.72 (t, J=7.8 Hz, 2H), 1.91–1.84 (m, 2H), 1.07 (s, 9H).

4.2.15. 1-*tert*-Butyldimethylsilyloxy-4-*tert*-butylcyclohexane (1o).[15] With Method A, 4-*tert*-butylcyclohexanol (781 mg, 5.00 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (607 mg, 6.00 mmol), and *tert*-butyldimethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1o**) as a colorless oil (718 mg, 53%).

^1H NMR ($CDCl_3$): δ 3.51–3.43 (m, 1H), 1.89–1.86 (m, 2H), 1.75–1.72 (m, 2H), 1.29–1.21 (m, 2H), 1.04–0.91 (m, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.05 (s, 6H).

4.2.16. (−)-Menthyl *tert*-butyldimethylsilyl ether (1p).[20] With Method A, (−)-menthol (781 mg, 5.00 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (607 mg, 6.00 mmol), and *tert*-butyldimethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1p**) as a colorless oil (639 mg, 47%).

^1H NMR ($CDCl_3$): δ 3.37 (dt, J=4.2, 10.3 Hz, 1H), 3.40–3.34 (m, 1H), 2.60–2.18 (m, 1H), 1.86–1.83 (m, 1H), 1.64–1.57 (m, 1H), 1.38–1.32 (m, 1H), 1.58–1.09 (m, 1H), 1.04–0.77 (m, 4H), 0.90 (s, 6H), 0.88 (s, 9H), 0.72 (d, J=6.8 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

4.2.17. 1-*tert*-Butyldimethylsilyloxy-4-*tert*-butylbenzene (1q).[21] With Method A, 4-*tert*-butylphenol (751 mg, 5.00 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (607 mg, 6.00 mmol), and *tert*-butyldimethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1q**) as a colorless oil (743 mg, 56%).

^1H NMR ($CDCl_3$): δ 7.22 and 6.75 (each d, J=8.3 Hz, 4H), 1.28 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H).

4.2.18. 1-Benzyloxy-3-triisopropylsilyloxypropane (1r). With Method B, 3-benzyloxy-1-propanol (831 mg, 5.00 mmol), imidazole (408 mg, 6.00 mmol), and triisopropylsilyl chloride (1.16 g, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane/ether 10:1) to give the title compound (**1r**) as a colorless oil (1.46 g, 91%).

^{1}H NMR ($CDCl_3$): δ 7.34–7.26 (m, 5H), 4.51 (s, 2H), 3.80 (t, *J*=6.2 Hz, 2H), 3.60 (t, *J*=6.2 Hz, 2H), 1.88–1.82 (m, 2H), 1.11–1.00 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 138.7, 128.3, 127.6, 127.4, 73.0, 67.2, 60.2, 33.2, 18.0, 12.0. MS (FAB, NBA) *m/z* 323 (M^++H, 12%), 91 (100). HRMS (FAB, NBA) calcd for $C_{19}H_{35}O_2Si$ (M^++H) 323.2406. Found 323.24103.

4.2.19. 1-*tert*-Butyldimethylsiyloxy-3-triisopropylsilyloxypropane (1s).[22] After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of 1-benzyloxy-3-triisopropylsilyloxypropane (**1r**) (1.40 g, 5.00 mmol), 10% Pd/C (70.1 mg, 5 wt% of the substrate) in solvent (10 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered using a membrane filter (Millex®-LG, 0.20 μm) and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ether 5:1) to afford 3-triisopropylsilyloxypropan-1-ol (**3r**) as a colorless oil (1.70 g, 73%). ^{1}H NMR ($CDCl_3$): δ 3.94 (t, *J*=5.4 Hz, 2H), 3.84 (q, *J*=5.4 Hz, 2H), 2.76 (t, *J*=5.4 Hz, OH), 1.83–1.78 (m, 2H), 1.17–1.03 (m, 21H). ^{13}C NMR ($CDCl_3$): δ 63.6, 62.7, 34.2, 17.9, 11.8. MS (FAB, NBA) *m/z* 233 (M^++H, 60%), 189 (36). HRMS (FAB, NBA) calcd for $C_{12}H_{28}O_2Si$ (M^++H) 233.1937. Found 233.1930. With Method A, **3r** (403 mg, 1.70 mmol), DMAP (37 mg, 0.30 mmol), Et_3N (202 mg, 2.00 mmol), and *tert*-butyldimethylsilyl chloride (301 mg, 3.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1s**) as a colorless oil (449 mg, 67%).

^{1}H NMR ($CDCl_3$): δ 3.76 (t, *J*=6.1 Hz, 2H), 3.73 (t, *J*=6.1 Hz, 2H), 1.77–1.71 (m, 2H), 1.13–1.01 (m, 21H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 60.0, 59.8, 36.1, 25.9, 18.3, 12.0, −5.4. MS (FAB, NBA) *m/z* 347 (M^++H, 21%), 303 (40), 157 (25), 115 (28), 73 (100). HRMS (FAB, NBA) calcd for $C_{18}H_{43}O_2Si_2$ (M^+) 347.2817. Found 347.2802.

4.2.20. 1-Triethylsilyloxy-3-triisopropylsilyloxypropane (1t). With Method A, 3-triisopropylsilyloxypropan-1-ol (**3r**) (465 mg, 2.00 mmol), DMAP (49 mg, 0.40 mmol), Et_3N (243 mg, 2.40 mmol), and triethylsilyl chloride (362 mg, 2.40 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane/ether 10:1) to give the title compound (**1t**) as a colorless oil (603 mg, 87%).

^{1}H NMR ($CDCl_3$): δ 3.77 (t, *J*=6.2 Hz, 2H), 3.73 (t, *J*=6.2 Hz, 2H), 1.79–1.73 (m, 2H), 1.11–1.00 (m, 21H), 0.96 (t, *J*=8.0 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 60.1, 59.7, 36.2, 18.0, 12.0, 6.8, 4.4. MS (FAB, NBA) *m/z* 347 (M^++H, 40%), 303 (62), 245 (28), 157 (40), 115 (99), 87 (82), 59 (40). HRMS (FAB, NBA) calcd for $C_{18}H_{43}O_2Si_2$ (M^++H) 347.2802. Found 347.2806.

4.2.21. 3-*tert*-Butyldimethylsilyloxy-1-propyl benzyl ether (1u). With Method A, 3-benzyloxy-1-propanol (831 mg, 5.00 mmol), DMAP (48 mg, 0.40 mmol), Et_3N (607 g, 6.00 mmol), and *tert*-butyldimethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane) to give the title compound (**1u**) as a colorless oil (1.26 g, 90%).

^{1}H NMR ($CDCl_3$): δ 7.34–7.26 (m, 5H), 4.50 (s, 2H), 3.72 (t, *J*=6.4 Hz, 2H), 3.57 (t, *J*=6.4 Hz, 2H), 1.82 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 138.6, 128.3, 127.6, 127.4, 72.9, 67.0, 59.9, 33.0, 25.9, 18.3, −5.4. MS (FAB, NBA) *m/z* 281 (M^++H, 28%), 91 (100), 73 (19). HRMS (FAB, NBA) calcd for $C_{16}H_{29}O_2Si$ (M^++H) 281.1937. Found 281.1933.

4.2.22. 1-*tert*-Butyldiphenylsiyloxy-3-triethylsilyloxypropane (1v). To a solution of 1,3-propandiol (761 mg, 10.0 mmol), diisopropylethylamine (1.29 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added *tert*-butyldiphenylsilyl chloride (2.75 mg, 10.0 mmol). The reaction mixture was stirred at room temperature for 19 h. The reaction mixture was diluted with ether (50 mL) and washed with saturated NH_4Cl solution (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ether 2:1) to afford 3-*tert*-butyldiphenylsilyloxypropan-1-ol (**3v**)[23] as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.68 (dd, *J*=1.5, 7.8 Hz, 4H), 7.46–7.38 (m, 6H), 3.87–3.83 (m, 4H), 2.36 (t, *J*=5.6 Hz, OH), 1.84–1.78 (m, 2H), 1.06 (s, 9H). With Method A, **3v** (944 mg, 3.00 mmol), DMAP (37 mg, 0.3 mmol), imidazole (245 mg, 3.60 mmol) instead of Et_3N, and triethylsilyl chloride (453 mg, 3.60 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane/ether 20:1) to give the title compound (**1v**) as a colorless oil (1.23 g, 96%).

^{1}H NMR ($CDCl_3$): δ 7.67 (dt, *J*=1.5, 7.8 Hz, 4H), 7.44–7.35 (m, 6H), 3.77–3.73 (m, 4H), 1.81–1.74 (m, 2H), 0.94 (t, *J*=8.0 Hz, 9H), 0.59 (q, *J*=8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 135.6, 134.0, 129.5, 127.5, 60.6, 59.6, 35.8, 26.8, 19.2, 6.8, 4.4. MS (FAB, NBA) *m/z* 429 (M^++H, 10%), 371 (29), 197 (12), 87 (35). Anal. Calcd for $C_{25}H_{40}O_2Si_2$: C, 70.03; H, 9.40. Found C, 70.19; H, 9.77.

4.2.23. 4,4-Dimethoxy-2-methyl-2-triethylsilyloxybutane (1w). With Method A, 4,4-dimethoxy-2-methyl-2-butanol (**3w**) (741 mg, 5.00 mmol), DMAP (61 mg, 0.50 mmol), imidazole (408 mg, 6.00 mmol), and triethylsilyl chloride (904 mg, 6.00 mmol). The crude product was purified by column chromatography on silica gel (eluting with hexane/ether 10:1) to give the title compound (**1w**) as a colorless oil (1.36 g, 91%).

^{1}H NMR ($CDCl_3$): δ 4.60 (t, *J*=4.9 Hz, 1H), 3.31 (s, 6H), 1.75 (d, *J*=4.9 Hz, 2H), 1.25 (s, 6H), 0.95 (t, *J*=7.8 Hz, 9H), 0.58 (q, *J*=7.8 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 102.6, 72.0, 52.5, 47.3, 30.4, 7.1, 6.7. MS (EI) 175 (85), 117 (100), 89 (23), 75 (40). Anal. Calcd for $C_{13}H_{30}O_3Si$ 1/3H_2O: C, 58.16; H, 11.50. Found C, 82.49; H, 6.19.

4.3. General procedure for solvent effect toward the deprotection of the TBDMS ether (1a) using 10% Pd/C (Table 1)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of 1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (**1a**) (62.0 mg, 0.25 mmol), 10% Pd/C (6.2 mg, 10 wt% of the substrate) in solvent (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered using a membrane filter (Millex®-LG, 0.20 μm) and the filtrate was concentrated under reduced pressure to afford a colorless oil. (When using H_2O as a solvent, ether was added to the reaction mixture and filtrated using a membrane filter (Millex®-LG, 0.20 μm). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the colorless oil. The ratio of the 1-*tert*-butyldimethylsilyloxy-3-phenylpropane (**2a**) (86%, entry 10) and 3-phenyl-1-propanol (**3a**) (88%, entry 1) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.3.1. 1-*tert*-Butyldimethylsilyloxy-3-phenylpropane (2a).[24] 86% yield as a colorless oil (entry 10). ^{1}H NMR ($CDCl_3$): δ 7.67 (dd, *J*=1.5, 7.8, 4H), 7.44–7.15 (m, 16H), 3.69 (t, *J*=6.4 Hz, 2H), 2.72 (t, *J*=7.8 Hz, 2H), 1.91–1.84 (m, 2H), 1.07 (s, 9H).

4.4. General procedure for effect of the addition of a small amount of MeOH or H_2O into the reaction mixture of TBDMS ether (1a) in AcOEt or MeCN using 10% Pd/C as a catalyst (Table 2)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of 1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (**1a**) (62.0 mg, 0.25 mmol), 10% Pd/C (6.2 mg, 10 wt% of the substrate) and MeOH or H_2O (0.1 mL) in EtOAc or MeCN (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered using a membrane filter (Millex®-LG, 0.20 μm,) and the filtrate was concentrated under reduced pressure to afford the colorless oil. The ratio of the 1-*tert*-butyldimethylsilyloxy-3-phenylpropane (**2a**) and 3-phenyl-1-propanol (**3a**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.5. General procedure for solvent effect toward the deprotection of the silyl ethers using 10% Pd/C (Table 3)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of a silyl ether (**1a**–**e**) (0.25 mmol), 10% Pd/C (10 wt% of the substrate) in solvent (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered using a membrane filter (Millex®-LG, 0.20 μm) and the filtrate was concentrated under reduced pressure to afford the colorless oil. The ratio of the corresponding silyl ether (**2a**–**e**) and 3-phenyl-1-propanol (**3a**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.5.1. 1-Triethylsilyloxy-3-phenylpropane (2b).[14] 91% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.29–7.15 (m, 5H), 3.64 (t, *J*=6.4 Hz, 2H), 2.68 (t, *J*=7.8 Hz, 2H), 1.89–1.82 (m, 2H), 0.96 (t, *J*=8.0 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H).

4.5.2. 1-Triphenylsilyloxy-3-phenylpropane (2c). 100% yield as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, *J*=1.6, 8.1 Hz, 6H), 7.46–7.36 (m, 10H), 7.26–7.11 (m, 4H), 3.83 (t, *J*=6.9 Hz, 2H), 2.71 (t, *J*=6.9 Hz, 2H), 1.92–1.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 142.1, 135.4, 135.2, 134.4, 130.0, 128.5, 128.3, 127.9, 125.7, 63.1, 34.1, 32.1. MS (FAB, NBA) *m/z* 395 (M^++H, 40%), 317 (25), 259 (40), 199 (30), 118 (30), 91 (35). Anal. Calcd for $C_{27}H_{26}OSi$ 1/10H_2O: C, 81.81; H, 6.66. Found C, 81.87; 6.58.

4.5.3. 1-Triisopropylsilyloxy-3-phenylpropane (2d). 93% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.29–7.17 (m, 5H), 3.71 (t, *J*=6.1 Hz, 2H), 2.71 (t, *J*=7.8 Hz, 2H), 1.89–1.82 (m, 2H), 1.12–1.04 (m, 3H and 18H). ^{13}C NMR ($CDCl_3$): δ 142.4, 128.5, 128.2, 125.6, 62.6, 34.7, 32.1, 18.0, 12.0, 11.8. MS (EI) *m/z* 249 ($M^+-C_3H_7$, 100%). HRMS (EI) calcd for $C_{15}H_{25}OSi$ ($M^+-C_3H_7$) 249.1675. Found 249.1667.

4.5.4. 1-*tert*-Butyldiphenylsilyloxy-3-phenylpropane (2e).[25] 99% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.67 (dd, *J*=1.5, 7.8 Hz, 4H), 7.44–7.15 (m, 16H), 3.69 (t, *J*=6.4 Hz, 2H), 2.72 (t, *J*=7.8 Hz, 2H), 1.91–1.84 (m, 2H), 1.07 (s, 9H).

4.6. General procedure for cleavage of the TBDMS or TES ethers and chemoselective hydrogenation using 10% Pd/C (Table 4)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of a silyl ether (**1f**–**n**) (0.25 mmol), 10% Pd/C (10 wt% of the substrate) in MeOH or AcOEt or MeCN (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C). The reaction mixture was filtered using a membrane filter (Millex®-LG, 0.20 μm) and the filtrate was concentrated under reduced pressure to afford a colorless oil. The ratio of the corresponding silyl ether (**2f**–**m**) and corresponding alcohol (**3f-3m**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ether 20:1 for **3f**, hexane/ether 10:1 for **3g**, hexane/ether 10:1 for **3k**, hexane/ether 10:1 for **3l**, hexane/ether 20:1 for **3n**) to give **3f** (80%, entry 1), **3f** (67%, entry 7), **3g** (71%), **3k** (21%), **3l** (96%), **3m** (83%) as a colorless oil. ^{1}H NMR were comparable with each authentic sample.

4.6.1. 1-*tert*-Butyldimethylsilyloxydecane (2f).[26] 98% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.59 (t, *J*=6.6 Hz, 2H), 1.55–1.51 (m, 2H), 1.35–1.26 (m, 14H), 0.89 (s, 9H), 0.88 (t, *J*=7.3 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 63.3, 32.9, 31.9, 29.7, 29.6, 29.5, 29.4, 26.0, 25.8, 22.7, 18.4, 14.1, −5.3.

4.6.2. 4-*tert*-Butyldimethylsilyloxybutyl propionate (2g). 98% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.09 (t, *J*=6.3 Hz, 2H), 3.63 (t, *J*=6.3 Hz, 2H), 2.32 (q, *J*=7.7 Hz, 2H), 1.61–1.56 (m, 2H), 1.16–1.12 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 174.5, 64.2, 62.6, 29.2, 27.6, 25.9, 25.2, 18.3, 9.2, −5.3. MS (FAB, NBA) *m/z* 261 (M^++H, 50%), 203 (37), 187 (62), 131 (139), 73 (45), 57 (38). HRMS (FAB, NBA) calcd for $C_{13}H_{29}O_3Si$ (M^++H) 261.1886. Found 261.1886.

4.6.3. 1-*tert*-Butyldimethylsilyloxy-2-propylbenzene (2h). 100% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ

7.12 (d, J=7.6 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 6.87 (t, J=7.6 Hz, 1H), 6.77 (d, J=7.6 Hz, 1H), 2.55 (t, J=7.5 Hz, 2H), 1.58 (hex, J=7.5 Hz, 2H), 1.02 (s, 9H), 0.94 (t, J=7.5 Hz, 3H), 0.23 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 153.5, 133.3, 130.2, 126.5, 120.9, 118.3, 32.7, 25.8, 23.3, 18.2, 14.1, −4.2. Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 71.68; H, 10.60.

4.6.4. 1-Triethylsilyloxydecane (2i). 99% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.59 (t, J=6.6 Hz, 2H), 1.54–1.51 (m, 2H), 1.36–1.22 (m, 14H), 0.96 (t, J=7.9 Hz, 9H), 0.89 (t, J=6.8 Hz, 3H), 0.55 (q, J=7.9 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 63.0, 32.9, 31.9, 29.6, 29.6, 29.5, 29.3, 25.8, 22.7, 14.1, 6.8, 4.4. MS (FAB: NBA) *m/z* 273 (M^++H, 10%), 271 (8), 243 (25), 214 (42), 115 (22), 103 (20). HRMS (FAB: NBA) calcd for $C_{16}H_{36}OSi$ (M^++H) 273.2614. Found 273.2610.

4.6.5. 3,7-Dimethyl-1-triethylsilyloxyoctane (2j). 88% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.67–3.58 (m, 2H), 1.61–1.48 (m, 4H), 1.37–1.31 (m, 4H), 1.28–1.10 (m, 2H), 0.96 (t, J=7.8 Hz, 9H), 0.88–0.86 (m, 9H), 0.60 (q, J=7.8 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 61.2, 40.1, 39.3, 37.4, 29.6, 28.0, 24.7, 22.7, 22.6, 19.8, 6.8, 4.5. MS (EI) 243 ($M^+-C_2H_5$, 100), 205 (46), 83 (83), 57 (53). HRMS (EI) calcd for $C_{14}H_{31}OSi$ ($M^+-C_2H_5$) 243.2154. Found 243.2144.

4.6.6. 2-Methyl-4-triethylsilyloxyoctane (2k). 93% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.73–3.67 (m, 1H), 1.72–1.63 (m, 1H), 1.44–1.22 (m, 8H), 0.69 (t, J=7.9 Hz, 9H), 0.89–0.87 (m, 9H), 0.60 (q, J=7.9 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 70.6, 46.7, 37.5, 27.4, 24.5, 23.2, 22.9, 22.8, 14.1, 7.0, 5.2. MS (EI) 229 ($M^+-C_2H_4$, 99%), 201 (55), 173 (22), 115 (26), 103 (100), 87, (21), 75 (37), 44 (20). MS (EI) *m/z* 229 ($M^+-C_2H_5$, 99%), 201 (55), 173 (22), 115 (26), 103, (100), 75 (37). HRMS (EI) calcd for $C_{13}H_{29}OSi$ ($M^+-C_2H_5$) 229.1988. Found 229.1981.

4.6.7. 3-Methyl-1-phenyl-3-(triethylsilyl)oxypentane (2l). 98% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.30–7.27 (m, 2H), 7.26–7.14 (m, 3H), 2.66–2.60 (m, 2H), 1.75–1.68 (m, 2H), 1.55 (q, J=7.4 Hz, 2H), 1.23 (s, 3H), 0.97 (t, J=7.9 Hz, 9H), 0.88 (t, J=7.4 Hz, 3H), 0.60 (q, J=7.9 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 143.3, 128.3, 125.5, 75.5, 43.7, 34.8, 30.6, 27.2, 8.8, 7.2, 7.0. MS (EI) *m/z* 263 ($M^+-C_2H_5$, 93%), 187 (33), 160 (13), 131 (10), 115, (20), 103 (100), 91 (23), 75 (26), 44 (14). HRMS (EI) calcd for $C_{16}H_{27}OSi$ ($M^+-C_2H_5$) 263.1831. Found 263.1824.

4.6.8. 1-Triethylsilyloxy-2-propylbenzene (2m).[27] The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford **2n** as a colorless oil (3% yield). ^{1}H NMR ($CDCl_3$): δ 7.11 (d, J=7.6 Hz, 1H), 7.04 (t, J=7.6 Hz, 1H), 6.86 (t, J=7.6 Hz, 1H), 6.76 (d, J=7.6 Hz, 1H), 2.56 (t, J=7.6 Hz, 1H), 1.65–1.54 (m, 2H), 1.00 (t, J=7.7 Hz, 9H), 0.94 (t, J=7.6 Hz, 3H), 0.77 (q, J=7.7 Hz, 6H).

4.7. General procedure for selective deprotection under the hydrogenation condition in MeOH using 10% Pd/C (Table 5)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of silyl ether (**1r–w**) (0.25 mmol), 10% Pd/C (10 wt% of the substrate) in MeOH was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C). The reaction mixture was filtered using a membrane filter (Millex®-LG or LH, 0.20 μm, 0.45 μm) and the filtrate was concentrated under reduced pressure to afford a colorless oil. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ether 5:1 for **3r**, hexane/ether 95:5 for **3v**, hexane/ether 10:1 for **3w**) to give **3r** (86%, entry 1), (61%, entry 2), (100%, entry 3), **3u** (95%), **3v** (91%) and **3w** (47%) as colorless oils. These samples were identified with commercial samples.

4.7.1. 3-*tert*-Butyldimethylsilyloxy-1-propanol (3u).[28] 95% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.84 (t, J=5.6 Hz, 2H), 3.84–3.80 (m, 2H), 2.61 (brs, 1H), 1.81–1.76 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 63.0, 62.5, 34.1, 25.9, 18.2, −5.5.

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Tetrahedron 60 (2004) 6913–6921
Tetrahedron

Chain-ring-chain tautomerism in 2-aryl-substituted hexahydropyrimidines and 1*H*-2,3-dihydroperimidines. Does it appear?

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Received 26 March 2004; revised 19 May 2004; accepted 27 May 2004

Available online 2 July 2004

Abstract—A series of 2-aryl substituted hexahydropyrimidines and perimidines were synthesized from aromatic aldehydes and substituted 1,3-propanediamines or 1,8-naphthalenediamine. The ^{1}H and ^{13}C NMR spectra showed that 2-arylperimidines and 2-aryl-4,4,6-trimethylhexahydropyrimidines exist exclusively in ring forms even in DMSO solutions, whereas 2-aryl-4-methylhexahydropyrimidines undergo chain-ring-chain tautomerism with a good linear correlation between the ring-chain equilibrium constants (log K, where K=[ring]/[chain]) and the Hammett–Brown σ^+ parameters of the aromatic substituents. 4,4,6-Trimethylhexahydropyrimidines underwent complete and irreversible ring opening in CF_3COOH solutions giving two different chain forms.

1. Introduction

The ring-chain tautomerism of 1,3-N,N-heterocycles,[1,2] unlike that of their 1,3-O,N- and 1,3-S,N-analogues has received little attention until very recently.[3] During the last decade, ring-chain equilibria were observed in N-unsubstituted imidazolidines and hexahydropyrimidines derived from simple diamines (ethylenediamine and 1,3-propylenediamine) and carbonyl compounds[4,5] and they were followed by systematic quantitative studies on N-substituted 2-aryl-1,3-N,N-heterocycles including 1-aryl(alkyl)imidazolidines,[6,7] hexahydropyrimidines,[8] tetrahydroquinazolines,[8,9] and decahydroquinazolines.[10] Based on these data, the relative tendency for ring-chain tautomerism in a series of 1,3-X,N-heterocycles (X=O, NR, NAr, S) was estimated.[3] In fact, tautomeric equilibria similar to those in such 1,3-X,N heterocycles were experimentally observed for the condensation products of propylenediamine with aldoses[11] and of 2-aminomethylaniline with 5-hydroxyisoxazolidines.[12]

It should be noted that N-unsubstituted 1,3-N,N-heterocycles substantially differ from their N-substituted 1,3-N,N-analogues and from 1,3-O,N- and 1,3-S,N-heterocycles because tautomeric equilibria in N-unsubstituted 1,3-N,N-heterocycles derived from asymmetric diamines may involve two distinct chain forms. Such chain-ring-chain tautomerism has not been observed so far in 1,3-N,N-heterocycles.

Previously, chain-ring-chain transitions were observed in the case of *cis*/*trans* isomerism of hydrazones bearing an additional nucleophilic fragment (OH, NH_2, or SH), such as thiosemicarbazones.[13] In this case the tautomerism involves only one C=N double bond, and the two chain forms are *Z*,*E*-isomers of the same compound. But similar tautomeric processes in 1,3-N,N-heterocycles derived from asymmetric diamines would involve two differently substituted C=N bonds and, therefore, two distinct chain forms. Analogous transformations are also expected to occur in other classes of organic compounds, e.g. during *trans*-amination of diamino acids.

Theoretical calculations[14] suggest that the reaction enthalpies for the formation of Schiff bases involving benzylic amines and aromatic amines (anilines) are close to each other. Accordingly, we attempted to discover chain-ring-chain equilibria in the condensation products of 2-aminomethylaniline with carbonyl compounds.[9,15] However, only one type of chain forms were observed in solutions, which corresponded to imines derived from the benzylic amino group.[9]

Keywords: Diamines; Tautomerism; Pyrimidines; Perimidines.
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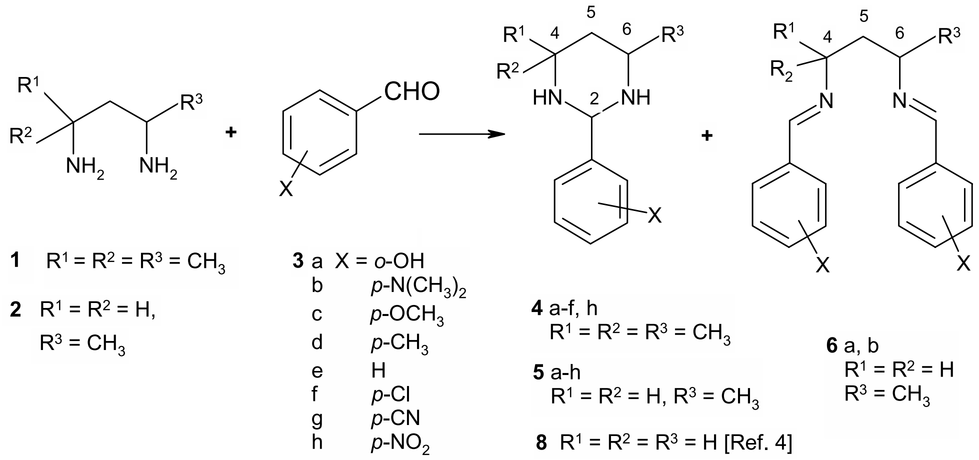
doi:10.1016/j.tet.2004.05.092



Scheme 1.

Next, we hypothesized that both chain forms could be observed in such 1,3-N,N-heterocycles where the two nitrogen atoms resemble each other by their chemical environments, although still are inequivalent. To test this possibility, we synthesized 2-aryl-4-methyl- and 2-aryl-4,4,6-trimethylhexahydropyrimidines starting from aromatic aldehydes and aliphatic diamines (Scheme 1). One of the starting diamines (1,3-butanediamine) has the amino groups attached to secondary and tertiary carbons, whereas the other (4-methyl-2,4-pentanediamine) has the amino groups attached to tertiary and quaternary carbons. A few condensation products of the latter diamine with carbonyl compounds have been reported in the literature,[16] but their structure in solutions was not investigated.

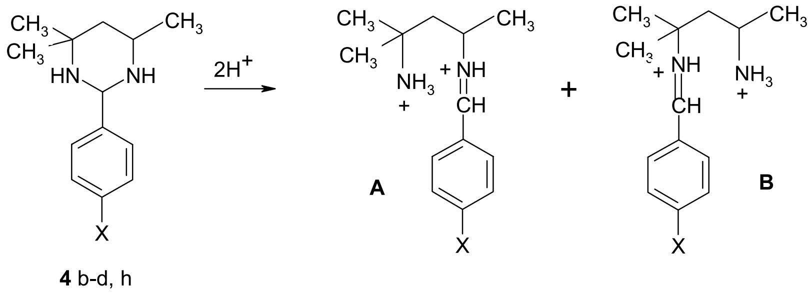
2. Results and discussion

4-Methyl- (**4**) and 4,4,6-trimethylhexahydropyrimidines (**5**) were obtained in good yields, as shown in Scheme 1. However, considerable amounts of the bis-adducts **6** were formed as side products in the reactions of 2-methylpentane-2,4-diamine with aromatic aldehydes bearing electron-acceptor substituents.

2.1. Structure of compounds 4

The spectral data indicated that 2-aryl-4,4,6-trimethylhexahydropyrimidines **4** exist solely in the ring form since no sign of the CH=N carbon or proton signals were found in the NMR spectra and the results observed were completely in agreement with a single ring form (see Section 4) even in such a highly polar solvent as DMSO, which is known[9] to stabilize chain tautomers. Neither steric factors (e.g. in **4a**) nor electronic effects of the substituent (e.g. in **4b**, the most negative σ value) were sufficient to produce identifiable amounts of the chain form. The preferred conformation of the hexahydropyrimidine ring was determined from the NOE data measured for compound **4h**. According to our measurements, the H-2 and H-6 protons are spatially close to each other. It follows that they are both axial, and the aryl and methyl substituents in positions 2 and 6 are therefore equatorial to avoid the strong 1,3-diaxial interactions with the axial 4-Me group. Signals from the two methyl groups in position 6 were also assigned based on NOE data.

Previously, ring-chain tautomerism was observed in the related heterocycles, imidazolidines,[17] when dissolved in acetic acid. Therefore, we recorded NMR spectra of hexahydropyrimidines **4b–f** and **4h** in CH_3COOH+25% $CDCl_3$ and for **4b**,**h** also in CD_3COOD. In all cases, the heterocycles opened completely to produce two chain forms, the A form (Scheme 2) always being the major one. Ring opening was confirmed by the disappearance of C-2 and H-2 signals. Instead, two well-resolved singlets at 8.5–9.2 ppm were found in the ^{1}H NMR spectra corresponding to the C*H*=N protons of the A and B forms, and two well-resolved carbon signals at 167–172 ppm corresponding to the *C*=N carbons. Signals of both chain forms were assigned using a variety of NMR experiments including primary DQF–COSY, DEPT, HMQC, and



Scheme 2.

HMBC. The NOE spectra (interpreted as chemical exchange spectra) proved, e.g. for compound **4h**, that the two chain forms do not interconvert, i.e. that both nitrogen atoms are protonated under these conditions (Scheme 2). This differs from what has been postulated for the imidazolidine case.[17]

2.2. EI mass spectrometry of compounds 4 and 5

The base peaks in the 70 eV EI mass spectra of compounds **4** nearly always (except **4a**, see Section 4) correspond to $[M-H]^+$ ions. The stability of the $M^{+\cdot}$ ions is rather low and does not exceed 3–5% of the relative abundance (RA) after correction for the isotopic contributions from $[M-H]^+$ ions for compounds **4c–h**. Only for compounds **4a**,**b** bearing strongly electron-donating substituents, the corrected $M^{+\cdot}$ abundancies are between 30 and 50% RA. This suggests that the cyclic hexahydropyrimidine form, which dominates in solutions of compounds **4**, is also preserved in the gas phase under mass-spectrometric conditions. The loss of a hydrogen atom from C-2 of a cyclic $M^{+\cdot}$ structure would produce a stable $[M-H]^+$ ion. The increased RA of the $M^{+\cdot}$ in **4a**,**b** suggests that at least a fraction of these $M^{+\cdot}$ ions exist in an open-chain form (cf. Scheme 3 for compounds **5**) in accordance with the electron-donating nature of their aromatic substituents. Another fact speaking for the possible appearance of the chain tautomers in the gas phase for compounds **4** is the abundance of the ions $[M-(CH_3)_2CNH_2]^+$ and $[M-CH_2C(CH_3)_2NH_2]^+$ corresponding to the loss of 58 and 72 amu, respectively, which can in principle happen through either of the possible open-chain forms. The appearance of the chain tautomers has often been proved in comparable studies[18] of, e.g. oxazolidines and perhydro-1,3-oxazines.[18a–c]

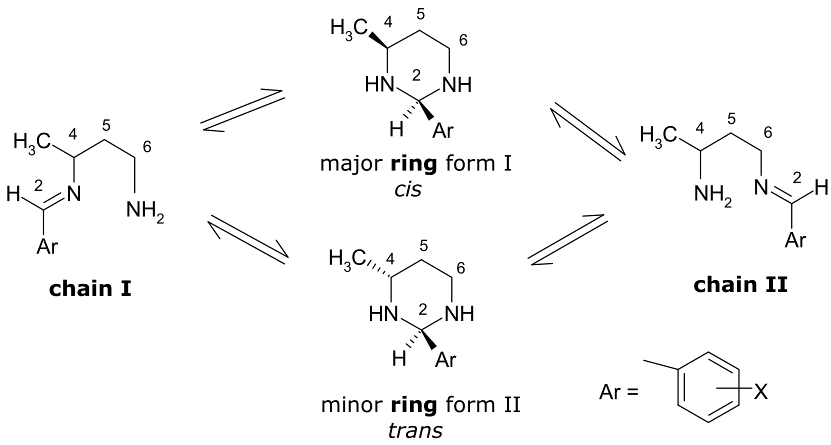
The aryl substituent effect is clearly seen in the EI mass spectra of compounds **5** (although **5a** could not be purified from the accompanying bis-adduct). A comparison between the mass spectra of **5b** and **5h** (see Section 4) reveals a drastic difference in the relative stability of their $M^{+\cdot}$ and $[M-H]^+$ ions. The RA of $M^{+\cdot}$ in the case of nitro substitution (electron-withdrawing effect) is estimated at ca. 3% RA after correction for the isotopic contribution from $[M-H]^+$. Accordingly, the $[M-H]^+$ ions are nearly 30 times less stable (relative to $M^{+\cdot}$) in **5h** than in **5b**. However, no straightforward substituent effect correlation with σ^+ values prevails. At any rate, most probably the ring and chain forms of $M^{+\cdot}$ ions might co-exist in the gas phase (cf. Scheme 3), and one can postulate that the chain forms lead to the fragments $[M-C_2H_4NH_2]^+$ (mostly the base peaks), $[M-CH_2CH(CH_3)NH_2]^+$, and $[M-CH_2NH_2]^+$ corresponding to the loss of 44 (from Chain II or Chain I, Scheme 3), 58 (from Chain II, Scheme 3) and 30 mass units (from Chain I, Scheme 3). However, there is no fragment ions which could be exclusively assigned to the linear forms of $M^{+\cdot}$. In the absence of direct evidence, no firm conclusion can be made about the actual structure of $M^{+\cdot}$ ions.

The more abundant characteristic fragment ions originate from the loss of C_2H_5N, which may occur by at least two distinct ring cleavage processes. The metastable ions corresponding to this fragment loss confirm that it occurs from both $M^{+\cdot}$ and $[M-H]^+$ ions, and also from $[M-HNO_2]^{+\cdot}$ (*m/z* 174) in the case of **5h**. Note that the complementary $C_2H_6N^+$ ions (*m/z* 44) are also very abundant in all compounds **5** and especially in **5b** (100%), **5g** (100%), and **5h** (73%). Ions $[M-Ar]^+$ (*m/z* 99 and 127, respectively) and $ArCNH^+$ ($Ar{=}XC_6H_4$) are also formed both from **4** and **5**.

2.3. Structure of compounds 5

2-Aryl-4-methylhexahydropyrimidines **5** were synthesized as shown in Scheme 1. In some cases (**5a**, **5b**) the reaction afforded considerable amounts of the bis-adduct **6**, which was difficult to separate from the targeted 1:1 condensation product. Pure compounds **6a** and **6b** were prepared by a different synthetic protocol (see Section 4), so that the NMR signals of bis-adducts **6** could be assigned in the spectra of the mixtures. To simplify the discussion, the numbering of atoms in the hexahydropyrimidine ring was preserved in the chain forms (Scheme 3).

The NMR spectra of compounds **5** in $CDCl_3$ solutions indicated four different tautomeric forms (Scheme 3). Thus, for the salicylaldehyde derivative, 2-(2′-hydroxyphenyl)-4-methylhexahydro-pyrimidine **5a**, the presence of two chain forms was confirmed by the well-resolved ^{13}C signals at 164.8 and 163.0 ppm and by the partly overlapping ^1H signals at 8.33 and 8.35 ppm corresponding to the CH=N



Scheme 3.

moieties. The signal at 8.35 ppm is an unresolved triplet and therefore can be assigned to the methine H atom of the Chain II form (coupling with H-6 protons, Scheme 3). The HMQC spectra show that this proton is connected to the carbon resonating at 164.77 ppm. Accordingly, the other pair of signals at 8.33 ppm (^{1}H) and 163.0 ppm (^{13}C) corresponds to the CH=N group of the Chain I form (Table 1). The rest of the *CH*=N carbon and proton signals were also assigned (Tables 1 and 2) as well as the aliphatic carbon signals for the chain forms of **5a–c** (Table 1) using a combination of 1D and 2D NMR experiments.

Table 1. The signals of the CH=N protons and the non-aromatic carbon atoms for the chain forms (I and II) of compounds **5a–c** in $CDCl_3$ (total amount of chain forms >10%)

	Chain form	*CH*=N	CH_3	*C*-5	*C*-6	*C*-4	CH=N
5a	I	8.34	22.71	41.41	39.01	62.53	162.90
	II	8.35	24.34	40.74	56.66	44.68	164.77
5b	I	8.13	22.83	41.59	39.38	64.17	159.13
	II	8.14	24.02	41.14	58.80	45.06	160.65
5c	I	8.17	22.77	41.68	39.43	64.20	158.20
	II	8.18	24.27	41.18	45.26	58.92	160.09

Table 2. The CH=N proton and carbon signals for the chain forms of compounds **5d–g** in $CDCl_3$ (total amount of chain forms <6.5%)

Chain form	*CH*=N	*C*H=N
5d I	8.23	157.92
5d II	8.25	159.80
5e I	8.27	159.27
5e II	8.29	160.88
5f I	8.22	158.09
5f II	8.24	159.67
5g I	8.31	158.71
5g II	8.33	156.84
5h I	8.29	156.77
5h II	8.31	158.64

The relative amounts of chain forms I and II, however, could not be determined accurately from the ^{1}H NMR spectra, because the azomethine proton signals overlapped somewhat. Together with the relative intensities of the respective carbon signals it can, however, be suggested that Chain II is always the major linear form (ca. ≥70%) for all compounds **5**.

On the other hand, the signals of methine H-2 protons of the cyclic forms are well resolved. For the compound **5a** these signals appear at 4.69 (major) and 5.17 ppm (minor cyclic form) with a ratio of 10:1. The corresponding C-2 signals appear at 73.1 and 67.3 ppm. (Table 3). The NOE data obtained for compound **5h** demonstrated that the H-2 and H-4 in the main cyclic form (*cis* isomer) are spatially close to each other. As the cyclic forms are in the chair conformation, it is obvious that these protons are axial, and the substituents (methyl and phenyl) equatorial.

In the case of compound **5a**, the relatively higher stability of the chain form is probably due to a steric rather than electronic factors (intramolecular hydrogen bond). For the rest of 2-aryl-4-methylpiperimidines **5b–h**, the electronic properties of substituents are decisive: the more electron-accepting the substituent, the smaller is the amount of the chain forms (Table 4). This behavior is in accordance with theoretical predictions and gives a good linear correlation between the ring-chain equilibrium constants (log *K*, where *K*=[ring]/[chain]) and the Hammett–Brown σ^+ parameters of the aromatic substituents for both the major (*cis*) and minor (*trans*) ring forms (Eqs. (1) and (2)).

cis-**5**

$$\log K = 0.56(2)\sigma^+ + 1.38(2); \quad R = 0.997 \quad (1)$$

trans-**5**

$$\log K = 0.69(6)\sigma^+ - 0.20(5); \quad R = 0.983 \quad (2)$$

Compounds **8**[4]

$$\log K = 0.84(1)\sigma^+ + 0.93(1); \quad R = 0.99 \quad (3)$$

Comparing the slope (ρ) values for the prevously studied[4,8] 2-aryl hexahydropyrimidines **8** (Scheme 1, Eq. (3)) with those for the ring-substituted compounds **5** it is seen that for the six-membered 1,3-*N*,*N*-heterocycles[8–10] in contrast with the 1,3-*O*,*N*-heterocycles[2,8,9] the ρ value is not characteristic

Table 3. The resonance positions of the H-2 and C-2 signals for the minor cyclic forms of compounds **5**

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**
X	*o*-OH	$N(CH_3)_2$	OCH_3	CH_3	H	Cl	CN	NO_2
H-2	5.16	4.86	4.85	4.92	4.95	4.92	5.00	4.95
C-2	67.27	n.d.	67.05	66.52	67.49	67.19	67.26	67.19

n.d.=not detected.

Table 4. The chain-ring-chain equilibria of compounds **5** as a function of the Hammett σ^+ parameters

Compound		σ^+	Major cyclic form (%)	Minor cyclic form (%)	Chain (the total of two forms) (%)
5a	*o*-OH		31.2	3.4	65.4
5b	*p*-$N(CH_3)_2$	−1.70	72.7	1.4	25.9
5c	*p*-OCH_3	−0.78	88.5	1.8	9.7
5d	*p*-CH_3	−0.31	91.7	1.9	6.4
5e	H	0.00	93.5	1.9 (5)	4.5 (5)
5f	*p*-Cl	0.11	94.4	2.3	3.3
5g	*p*-CN	0.66	94.8	3.6	1.6
5h	*p*-NO_2	0.79	94.9 (3)	3.7 (2)	1.3 (5)

of the ring system but depends strongly both on the N-substituent[8] and on the ring substitution, as does the intercept. By comparing the intercept values for the ring forms of compounds **5** and **8** it can be concluded that the equatorial C-4 methyl substitution (diequatorial *cis* isomer) somewhat increases the stability of the ring form whereas in the equatorial, axial *trans* isomer the stability substantially decreases as could be expected.

It has been proposed[8,19] that in the case of ring-chain tautomeric systems showing the $\log K$ correlations, the effects of structural variations on the relative stability of the ring form can be expressed by a value c, which is the difference in intercept between a given series and the corresponding reference series of heterocycles. A positive c value means a relatively more stable ring form. For instance, 1,3-*N*,*N*-heterocycles **8** (intercept, +0.93)[4,8] compared to analogous 1,3-*O*,*N*-heterocycles[19] (intercept, −0.15) show that the stability of the ring form increases (O<NH) with replacing one of the heteroatoms (c=1.08). Similarly, a comparison of the correlation equations for **5** and **8** (Eqs. (1)–(3)) shows that methyl substitution in the 1,3-*N*,*N* system further stabilizes the ring form if the incoming substituent is *cis* relative to the aryl group (c=0.45), but greatly destabilizes it (c=−1.13) if they are in *trans* configuration (Scheme 3).

2.4. Compounds 7

The cyclic tautomer should be especially stable in 2,3-dihydro-1*H*-perimidines **7**, which are polycyclic analogues of hexahydropyrimidines **4** and **5**. We assumed that even protonation by CF_3COOH would be insufficient for total ring opening in this case, and synthesized a number of known perimidines **7a–f**,**h** (Scheme 4)[20] to verify this assumption. Some of them were characterized but poorly in the early paper;[20] therefore a full NMR characterization is now given in Section 4.

As expected, only ring forms were observed in neutral DMSO solutions of **7**. When dissolved in TFA, compounds **7b–f**,**h** seem to undergo dehydrogenation leading to aromatic 1H-perimidines. No signals corresponding to either ring or chain forms of **7** were detected when the NMR spectra were recorded in TFA. Facile oxidation/aromatization of compounds **7** has been previously mentioned in the literature.[21]

Thus, chain-ring(-chain) tautomerism could not be observed in compounds **4** and **7**, although irreversible ring opening of hexahydropyrimidine free bases into bis-protonated linear azomethines was achieved experimentally. A chain-ring-chain equilibrium involving two linear forms was, however, observed in compounds **5**.

3. Conclusion

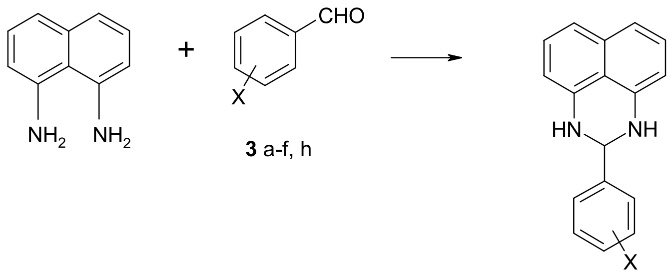
We have demonstrated the presence of an unusual multi-component chain-ring-chain tautomeric equilibrium involving two regioisomeric chain forms and two ring forms in 2-aryl-4-methylhexahydropyrimidines **5**. Either increased substitution of the hexahydropyrimidine ring (2-aryl-4,4,6-trimethylhexahydropyrimidines **4**) or annelation of the hexahydropyrimidine ring with an aromatic system (perimidines **7**) shifts the equilibrium practically totally towards the ring forms. These observations are in a good agreement with the available literature data[1] discussing the general structural factors that influence ring-chain equilibria in heterocyclic systems.

4. Experimental

4.1. NMR-measurements

NMR-spectra were acquired using a JEOL JNM-A-500 spectrometer operating at 500.16 MHz for ^{1}H and 125.78 MHz for ^{13}C, a JEOL JNM-L-400 spectrometer operating at 399.78 MHz for ^{1}H and 100.54 MHz for ^{13}C or a Bruker 200 Aspect 3000 spectrometer operating at 200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C. Spectra were recorded at 30 °C in DMSO-d_6 and at 25 °C in $CDCl_3$. Proton and carbon spectra were referenced internally to the solvent signals using values 2.49 ppm for ^{1}H and 39.50 ppm for ^{13}C in DMSO-d_6 and values 7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C in $CDCl_3$.

1D proton spectra were acquired with normal single-pulse excitation, 45° flip-angle consisting of 32k data points. 1D carbon spectra were acquired with normal single-pulse excitation, broad-band proton decoupling, 45° flip-angle and with spectral widths of 30 kHz consisting of 65k data points and with 0.3–0.5 Hz exponential weighting applied prior to Fourier transformation. DEPT spectra were acquired as carbon spectra. NOE difference experiments were acquired using saturation times of 6–8 s and enhancements are expressed as a percentage, integrated with respect to the irradiated spin (set to −100%). Prior to NOE measurements, samples were deoxygenated by nitrogen bubbling. 2D heteronuclear one bond correlation experiments were acquired using either carbon detected CH-shift correlation



3 a-f, h

7 a-f, h

Scheme 4.

with partial homonuclear decoupling in the f1 dimension or proton detected HMQC with gradient selection. Long-range heteronuclear correlation experiments included either carbon detected COLOC or proton detected HMBC with gradient selection. One-bond coupling constant was 145 Hz and the long-range coupling constants were 5–12 Hz in proton-carbon correlation spectra. 2D homonuclear H,H-correlation experiments were acquired using phase-sensitive double quantum filtered COSY. The spectral widths of 2D spectra were optimised from 1D spectra. All spectra were made using standard pulse sequences.

4.2. Mass spectra

The 70 eV low-resolution EI spectra were recorded using a VG Analytical (Manchester, UK) VG ZABSpec instrument, equipped with OPUS data system. Samples were introduced using a direct insertion probe at ambient temperatures. Accurate mass measurements were performed on the same instrument at a resolving power of 8000–10,000 (10% valley definition) using peak matching technique and perfluorokerosene (PFK) as a reference compound. All the HRMS measurements listed in Section 4 are at least within 5 ppm from the calculated values.

4.3. General synthetic procedures

Procedure A (*compounds* **4b–f**, **4h**, **7a–f**, **7h**). A solution of aldehyde (2 mmol) in 2 mL of dry benzene was added dropwise to a stirred solution of diamine (2 mmol) in 3 mL of dry benzene at room temperature. When the reaction was completed (control by TLC on Silufol UV-254 plates, eluent ether:benzene 2:1), the mixture was concentrated in vacuo. Solid residues were recrystallised (for details, see below).

Procedure B (*compounds* **4a**, **5a–h**). A solution of aldehyde (2 mmol) in 2 mL of dry chloroform was slowly added dropwise to a cooled (ice-salt bath) well-stirred solution of diamine (6 mmol) in 3 mL of dry chloroform. After addition was completed (approx. 2 h) the reaction mixture was allowed to warm to room temperature and dried with sodium sulfate overnight. Mixture was concentrated in vacuo, the excess diamine was evacuated using oil pump and the residue was washed with hexane at −65 °C.

Procedure C (*compounds* **6a**,**b**). A solution of diamine (1 mmol) in 2 mL of dry benzene was added dropwise to a stirred solution of aldehyde (2 mmol) in 3 mL of dry benzene. Mixture was dried over sodium sulfate overnight, concentrated in vacuo and recrystallised.

4.3.1. 4,4,6-Trimethyl-2-(2-hydroxyphenyl)hexahydropyrimidine (4a). Yield 52%, white crystals, mp 48 °C (hexane). HRMS: $C_{13}H_{20}N_2O$ $M^{+\cdot}$ calcd 220.1576; obsd 220.1565. MS (EI, 70 eV): 220 ($M^{+\cdot}$, 53), 219 (48), 163 (61.5), 162 (37), 148 (59), 146 (22), 127 (28), 122 (17), 121 (54), 120 (18), 107 (7), 84 (33), 58 (100), 44 (37), 42 (17). δ_H (DMSO-d_6): 0.94 (1H, dd, J_{5ax5eq}=12 Hz, J_{5ax6ax}=12 Hz, H-5ax), 1.03 (3H, d, J=6.0 Hz, 6-CH$_3$), 1.08 (3H, s, 4-CH$_3$-eq), 1.17 (3H, s, 4-CH$_3$-ax), 1.47 (1H, d, J_{5ax5eq}=12 Hz, H-5eq), 2.99 (1H, m, H-6ax), 4.74 (1H, s, H-2ax), 6.67 (1H, d, J=7.9 Hz, H-3′), 6.73 (1H, t, J=7.2 Hz, H-5′), 7.10 (1H, t, J=7.0 Hz, H-4′), 7.25 (1H, d, J=7.3 Hz, H-6′). δ_C (DMSO-d_6): 22.6 (6-CH$_3$), 23.6 (4-CH$_3$-ax), 32.6 (4-CH$_3$-eq), 45.3 (C-5), 46.3 (C-6), 49.5 (C-4), 66.8 (C-2), 115.9 (C-3′), 118.0 (C-5′), 126.6 (C-1′), 127.0 (C-6′), 128.5 (C-4′), 157.2 (C-2′).

4.3.2. 4,4,6-Trimethyl-2-(4-dimethylaminophenyl)hexahydropyrimidine (4b). Yield 78%, colorless crystals, mp 49 °C (ether–hexane). HRMS: $C_{15}H_{25}N_3$ $M^{+\cdot}$ calcd 247.2048; obsd 247.2036. MS (EI, 70 eV): 247 ($M^{+\cdot}$, 45), 246 (100), 190 (64), 189 (86), 175 (41), 149 (17), 148 (84), 147 (41.5), 134 (17), 127 (19), 84 (13), 58 (21), 44 (12), 42 (12). δ_H (DMSO-d_6): 0.85 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 0.98 (3H, d, J=6.2 Hz, 6-CH$_3$), 1.03 (3H, s, 4-CH$_3$-eq), 1.12 (3H, s, 4-CH$_3$-ax), 1.27 (2H, broad s, NH), 1.40 (1H, dd, J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.4 Hz, H-5eq), 2.84 (6H, s, N(CH$_3$)$_2$), 2.92 (1H, m, H-6ax), 4.49 (1H, s, H-2ax), 6.64 (2H, d, J=8.6 Hz, H-3′, H-5′), 7.26 (2H, d, J=8.6 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 22.8 (6-CH$_3$), 24.0 (4-CH$_3$-ax), 33.0 (4-CH$_3$-eq), 40.3 ((CH$_3$)$_2$N), 45.9 (C-5), 46.9 (C-6), 49.5 (C-4), 67.8 (C-2), 111.8 (C-3′, C-5′), 127.1 (C-2′, C-6′), 131.8 (C-1′), 149.7 (C-4′).

4.3.3. 4,4,6-Trimethyl-2-(4-methoxyphenyl)hexahydropyrimidine (4c). Yield 92%, colorless oil. HRMS: $C_{14}H_{21}N_2O$ $(M-H)^+$ calcd 233.1654; obsd 233.1646. MS (EI, 70 eV): 234 ($M^{+\cdot}$, 18), 233 (100), 177 (27), 176 (22.5), 162 (24), 136 (11), 135 (41), 134 (27), 127 (15), 121 (7), 84 (15), 58 (24), 44 (14), 42 (9). δ_H (DMSO-d_6): 0.87 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 1.00 (3H, d, J=6.2 Hz, 6-CH$_3$), 1.05 (3H, s, 4-CH$_3$-eq), 1.13 (3H, s, 4-CH$_3$-ax), 1.42 (1H, dd, J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.6 Hz, H-5eq), 2.94 (1H, m, H-6ax), 3.73 (3H, s, OCH$_3$), 4.55 (1H, s, H-2ax), 6.85 (2H, d, J=8.7 Hz, H-3′, H-5′), 7.40 (2H, d, J=8.7 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 22.8 (6-CH$_3$), 24.0 (4-CH$_3$-ax), 32.9 (4-CH$_3$-eq), 45.8 (C-5), 47.0 (C-6), 49.6 (C-4), 55.0 (OCH$_3$), 67.8 (C-2), 113.1 (C-3′, C-5′), 127.7 (C-2′, C-6′), 136.0 (C-1′), 158.3 (C-4′).

4.3.4. 4,4,6-Trimethyl-2-(4-methylphenyl)hexahydropyrimidine (4d). Yield 80%, colorless oil. HRMS: $C_{14}H_{21}N_2$ $(M-H)^+$ calcd 217.1705; obsd 217.1702. MS (EI, 70 eV): 218 ($M^{+\cdot}$, 18), 217 (100), 161 (18), 160 (19), 146 (29), 127 (26), 120 (11), 119 (21), 118 (25), 84 (12), 58 (36.5), 44 (25.5), 42 (9). δ_H (DMSO-d_6): 0.88 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 1.01 (3H, d, J=6.2 Hz, 6-CH$_3$), 1.05 (3H, s, 4-CH$_3$-e), 1.14 (3H, s, 4-CH$_3$-ax), 1.43 (1H, dd, J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.6 Hz, H-5eq), 2.28 (3H, s, CH$_3$-Ph), 2.94 (1H, m, H-6ax), 4.56 (1H, s, H-2ax), 7.10 (2H, d, J=8.1 Hz, H-3′, H-5′), 7.37 (2H, d, J=8.1 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 20.6 (CH$_3$-Ph), 22.7 (6-CH$_3$), 24.0 (4-CH$_3$-ax), 32.9 (4-CH$_3$-eq), 45.8 (C-5), 46.9 (C-6), 49.6 (C-4), 68.0 (C-2), 126.4, 128.2 (C-2′, C-6′; C-3′, C-5′), 135.9, 140.7 (C-4′, C-1′).

4.3.5. 4,4,6-Trimethyl-2-phenyl-hexahydropyrimidine (4e). Yield 88%, colorless oil. HRMS: $C_{13}H_{19}N_2$ $(M-H)^+$ calcd 203.1548; obsd 203.1559. MS (EI, 70 eV): 204 ($M^{+\cdot}$, 15), 203 (100), 147 (17), 146 (25), 132 (25), 127 (40), 106 (14), 105 (14), 104 (25), 84 (13), 58 (23), 44 (14), 42 (11). δ_H (DMSO-d_6): 0.90 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 1.02 (3H, d, J=6.3 Hz, 6-CH$_3$), 1.07 (3H, s, 4-CH$_3$-eq), 1.16 (3H, s, 4-CH$_3$-ax), 1.43 (1H, dd,

J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.6 Hz, H-5eq), 2.96 (1H, m, H-6ax), 4.60 (1H, s, H-2ax), 7.30 (3H, m, H-3′, H-4′, H-5′), 7.49 (2H, dd, *J*=8.8, 1.8 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 22.7 (6-CH_3), 24.0 (4-CH_3-ax), 32.9 (4-CH_3-eq), 45.8 (C-5), 47.0 (C-6), 49.6 (C-4), 68.2 (C-2), 126.6 (C-2′, C-6′), 126.9 (C-4′), 128.2 (C-3′, C-5′), 143.6 (C-1′).

4.3.6. 4,4,6-Trimethyl-2-(4-chlorophenyl)hexahydropyrimidine (4f). Yield 52%, colorless oil. HRMS: $C_{13}H_{18}ClN_2$ $(M-H)^+$: calcd (^{35}Cl) 237.1159; obsd 237.1152. MS (EI, 70 eV): 238 ($M^{+\cdot}$, 16), 237 (100), 181 (18.5), 180 (21), 166 (26), 140 (20), 139 (18.5), 138 (28), 127 (40), 84 (26), 58 (48), 44 (27), 42 (15). δ_H (DMSO-d_6): 0.87 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 0.99 (3H, d, *J*=5.8 Hz, 6-CH_3), 1.04 (3H, s, 4-CH_3-eq), 1.12 (3H, s, 4-CH_3-ax), 1.40 (1H, dd, J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.5 Hz, H-5eq), 2.94 (1H, m, H-6ax), 4.58 (1H, s, H-2ax), 7.34 (2H, d, *J*=8.9 Hz, H-3′, H-5′), 7.50 (2H, d, *J*=8.9 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 22.7 (6-CH_3), 23.9 (4-CH_3-ax), 32.8 (4-CH_3-eq), 45.6 (C-5), 47.0 (C-6), 49.8 (C-4), 67.6 (C-2), 127.7 (C-3′, C-5′), 128.6 (C-2′, C-6′), 131.5 (C-4′), 142.6 (C-1′).

4.3.7. 4,4,6-Trimethyl-2-(4-nitrophenyl)hexahydropyrimidine (4h). Yield 68%, light yellow crystals, mp 66 °C (ether). HRMS: $C_{13}H_{18}N_3O_2$ $(M-H)^+$ calcd 248.1399; obsd 248.1405. MS (EI, 70 eV): 249 ($M^{+\cdot}$, 16), 248 (100), 202 (8), 192 (16), 191 (14), 177 (24), 151 (12), 149 (5), 127 (40), 84 (19.5), 58 (50), 44 (26), 42 (12). δ_H (DMSO-d_6): 0.90 (1H, t, J_{5ax5eq}=12.0 Hz, J_{5ax6ax}=12.0 Hz, H-5ax), 1.02 (3H, d, *J*=6.1 Hz, 6-CH_3), 1.07 (3H, s, 4-CH_3-eq), 1.16 (3H, s, 4-CH_3-ax), 1.44 (1H, dd, J_{5ax5eq}=12.0 Hz, J_{5eq6ax}=2.6 Hz, H-5eq), 1.69 (2H, broad s, NH), 2.98 (1H, m, H-6ax), 4.72 (1H, s, H-2ax), 7.78 (2H, d, *J*=8.8 Hz, H-2′, H-6′), 8.18 (2H, d, *J*=8.8 Hz, H-3′, H-5′). δ_C (DMSO-d_6): 22.7 (6-CH_3), 23.9 (4-CH_3-ax), 32.7 (4-CH_3-eq), 45.6 (C-5), 47.0 (C-6), 49.8 (C-4), 67.6 (C-2), 122.9 (C-3′, C-5′), 128.1 (C-2′, C-6′), 146.5 (C-4′), 151.1 (C-1′).

4.3.8. 4-Methyl-2-(2′-hydroxyphenyl)hexahydropyrimidine (5a). Yield 61%, colorless oil. HRMS: $C_{11}H_{16}N_2O$ $M^{+\cdot}$ calcd 192.1263; obsd 192.1272. MS (EI, 70 eV): 192 ($M^{+\cdot}$, 17), 191 (6), 162 (86), 149 (95), 148 (100), 135 (61), 134 (46), 121 (23), 120 (25), 99 (10), 44 (28.5),42 (15). δ_H ($CDCl_3$): 1.13 (3H, d, *J*=6.2 Hz, CH_3), 1.25 (1H, m, H-5ax), 1.72 (1H, m, H-5eq), 3.0 (2H, m, H-4ax, H-6ax), 3.26 (1H, ddd, J_{6eq6ax}=13.0 Hz, J_{6eq5ax}=4.2 Hz, J_{6eq5eq}=1.9 Hz, H-6eq), 4.68 (1H, s, H-2), 6.80–6.96 (2H, m, H-3′, H-5′), 7.16–7.32 (2H, m, H-4′, H-6′). δ_C ($CDCl_3$): 22.7 (CH_3), 34.5 (C-5), 45.0 (C-6), 51.0 (C-4), 73.1 (C-2), 116.9 (C-3′), 119.1 (C-5′), 125.4 (C-1′), 126.8 (C-6′), 129.4 (C-4′), 157.1 (C-2′).

4.3.9. 4-Methyl-2-(4-dimethylaminophenyl)hexahydropyrimidine (5b). Yield 67%, colorless oil. HRMS: $C_{13}H_{21}N_3$ $M^{+\cdot}$ calcd 219.1735; obsd 219.1743. MS (EI, 70 eV): 219 ($M^{+\cdot}$, 41), 218 (35), 176 (38), 175 (79), 162 (30), 161 (48), 148 (38), 147 (22), 99 (8.5), 71 (48), 56 (24), 44 (100), 42 (21.5). δ_H ($CDCl_3$): 1.10 (3H, d, *J*=6.4 Hz, CH_3), 1.22 (1H, m, H-5ax), 1.56 (1H, m, J_{5eq5ax}=13.0 Hz, H-5eq), 2.90 (6H, s, $(CH_3)_2N$), 2.92 (2H, m, H-4ax, H-6ax), 3.23 (1H, ddd, J_{6eq6ax}=12.8 Hz, J_{6eq5ax}=4.5 Hz, J_{6eq5eq}=1.9 Hz, H-6eq), 4.67 (1H, s, H-2), 6.67 (2H, m, H-3′, H-5′), 7.32 (2H, m, H-2′, H-6′). δ_C ($CDCl_3$): 22.8 (CH_3), 34.7 (C-5), 40.5 ($(CH_3)_2N$), 46.0 (C-6), 51.7 (C-4), 74.2 (C-2), 112.2 (C-3′, C-5′), 126.9 (C-2′, C-6′), 130.7 (C-1′), 150.1 (C-4′).

4.3.10. 4-Methyl-2-(4-methoxyphenyl)hexahydropyrimidine (5c). Yield 79%, colorless oil. HRMS: $C_{12}H_{17}N_2O$ $(M-H)^+$ calcd 205.1341; obsd 205.1338. MS (EI, 70 eV): 206 ($M^{+\cdot}$, 29), 205 (88), 176 (21), 163 (56), 162 (100), 149 (35), 148 (66), 135 (70), 134 (64), 121 (29), 99 (22), 71 (12), 44 (63), 42 (16). δ_H ($CDCl_3$): 1.10 (3H, d, *J*=6.2 Hz, CH_3), 1.18 (1H, m, H-5ax), 1.37 (1H, broad s, NH), 1.55 (1H, m, J_{5eq5ax}=12.8 Hz, H-5eq), 2.90 (2H, m, H-4ax, H-6ax), 3.21 (1H, ddd, J_{6eq6ax}=12.8 Hz, J_{6eq5ax}=4.3 Hz, J_{6eq5eq}=1.9 Hz, H-6eq), 3.73 (3H, s, OCH_3), 4.67 (1H, s, H-2), 6.83 (2H, d, *J*=8.8, H-3′, H-5′), 7.37 (2H, d, *J*=8.8 Hz, H-2′, H-6′).δ_C ($CDCl_3$): 23.0 (CH_3), 34.9 (C-5), 46.2 (C-6), 51.8 (C-4), 55.1 (OCH_3), 74.2 (C-2), 113.6 (C-3′, C-5′), 127.5 (C-2′, C-6′), 135.2 (C-1′), 159.2 (C-4′).

4.3.11. 4-Methyl-2-(4-methylphenyl)hexahydropyrimidine (5d). Yield 94%, colorless oil. HRMS: $C_{12}H_{17}N_2$ $(M-H)^+$ calcd 189.1392; obsd 189.1389. MS (EI, 70 eV): 190 ($M^{+\cdot}$, 16), 189 (85), 175 (21), 160 (47), 147 (59), 146 (100), 133 (47), 132 (79), 119 (60), 118 (90), 105 (38), 99 (37), 73 (17), 44 (26), 42 (25). δ_H ($CDCl_3$): 1.13 (3H, d, *J*=6.3 Hz, CH_3), 1.25 (1H, m, H-5ax), 1.60 (1H, m, J_{5eq5ax}=12.9 Hz, H-5eq), 2.32 (3H, s, CH_3Ph), 2.96 (2H, m, H-4ax, H-6ax), 3.27 (1H, ddd, J_{6eq6ax}=12.9 Hz, J_{6eq5ax}=4.5 Hz, J_{6eq5eq}=2.0 Hz, H-6eq), 4.53 (1H, s, H-2), 7.13 (2H, d, *J*=7.9 Hz, H-3′, H-5′), 7.36 (2H, d, *J*=7.9 Hz, H-2′, H-6′). δ_C ($CDCl_3$): 21.2 (*CH_3*Ph), 23.2 (CH_3), 35.2 (C-5), 46.4 (C-6), 52.1 (C-4), 74.7 (C-2), 126.4 (C-2′, C-6′), 129.2 (C-3′, C-5′), 137.7 (C-4′), 139.9 (C-1′).

4.3.12. 4-Methyl-2-phenylhexahydropyrimidine (5e). Yield 96%, colorless oil. HRMS: $C_{11}H_{15}N_2$ $(M-H)^+$ calcd 175.1235; obsd 175.1236. MS (EI, 70 eV): 176 ($M^{+\cdot}$, 2.4), 175 (17), 161 (26), 146 (58), 133 (47), 132 (100), 119 (62), 118 (67), 105 (35.5), 104 (27), 91 (46), 99 (10), 44 (89), 42 (14). δ_H ($CDCl_3$): 1.13 (3H, d, *J*=6.4 Hz, CH_3), 1.23 (1H, m, H-5ax), 1.46 (1H, broad s, NH), 1.60 (1H, m, J_{5eq5ax}=12.9 Hz, H-5eq), 2.95 (2H, m, H-4ax, H-6ax), 3.26 (1H, ddd, J_{6eq6ax}=13.0 Hz, J_{6eq5ax}=4.5 Hz, J_{6eq5eq}=1.9 Hz, H-6eq), 4.55 (1H, s, H-2), 7.31 (3H, m, H-3′, H-4′, H-5′), 7.46 (2H, d, *J*=7.8 Hz, H-2′, H-6′). δ_C ($CDCl_3$): 22.9 (CH_3), 34.9 (C-5), 46.1 (C-6), 51.8 (C-4), 74.6 (C-2), 126.3 (C-2′, C-6′), 127.8 (C-4′), 128.3 (C-3′, C-5′), 142.5 (C-1′).

4.3.13. 4-Methyl-2-(4-chlorophenyl)hexahydropyrimidine (5f). Yield 75%, colorless oil. HRMS: $C_{11}H_{14}ClN_2$ $(M-H)^+$ (^{35}Cl) calcd 209.0846; obsd 209.0843. MS (EI, 70 eV): 210 ($M^{+\cdot}$, 8), 209 (48), 195 (22), 180 (59) 167 (70), 166 (100), 153 (65), 152 (64), 139 (96), 138 (51), 125 (51), 118 (16), 99 (71), 73 (21), 44 (47), 42 (29). δ_H ($CDCl_3$): 1.12 (3H, d, *J*=6.3 Hz, CH_3), 1.23 (1H, m, H-5ax), 1.60 (1H, ddd, J_{5eq5ax}=13.0 Hz, J_{5eq4ax}=5.0 Hz, J_{5eq6eq}=2.4 Hz, H-5eq), 1.80 (1H, broad s, NH), 2.93 (2H, m, H-4ax, H-6ax), 3.25 (1H, ddd, J_{6eq6ax}=13.0 Hz, J_{6eq5ax}=4.6 Hz, J_{5eq6eq}=2.4 Hz, H-6eq), 4.52 (1H, s, H-2), 7.29 (2H, d, *J*=8.5 Hz, H-3′, H-5′), 7.42 (2H, d, *J*=8.5 Hz, H-2′, H-6′). δ_C ($CDCl_3$): 22.9 (CH_3), 34.8 (C-5), 46.0 (C-6), 51.8 (C-4), 73.9 (C-2), 127.8 (C-3′, C-5′), 129.4 (C-2′, C-6′), 132.8 (C-4′), 140.8 (C-1′).

4.3.14. 4-Methyl-2-(4-cyanophenyl)hexahydropyrimidine (5g). Yield 73%, colorless oil. HRMS: $C_{12}H_{14}N_3$ $(M-H)^+$ calcd 200.1188; obsd 200.1189. MS (EI, 70 eV): 201 ($M^{+\cdot}$, 14), 200 (45), 171 (9), 158 (26.5), 157 (45), 144 (8), 143 (26), 130 (16), 129 (35), 116 (15), 99 (28), 73 (8), 71 (18), 44 (100), 42 (16). δ_H ($CDCl_3$): 1.15 (3H, d, J=6.3 Hz, CH_3), 1.24 (1H, m, H-5ax), 1.64 (1H, m, J_{5eq5ax}=13.0 Hz, H-5eq), 2.97 (2H, m, H-4ax, H-6ax), 3.30 (1H, ddd, J_{6eq6ax}=13.3 Hz, J_{6eq5ax}=4.5 Hz, J_{6eq5eq}=2.0 Hz, H-6eq), 4.62 (1H, s, H-2), 7.62 (4H, s, H-2′, H-6′, H-3′, H-5′). δ_C ($CDCl_3$): 22.9 (CH_3), 34.8 (C-5), 46.0 (C-6), 51.8 (C-4), 73.9 (C-2), 111.7 (C-4′), 118.7 (CN), 127.3 and 132.2 (C-3′, C-5′ and C-2′, C-6′), 147.5 (C-1′).

4.3.15. 4-Methyl-2-(4-nitrophenyl)hexahydropyrimidine (5h). Yield 77%, yellow crystals, mp 48 °C (hexane). HRMS: $C_{11}H_{14}N_3O_2$ $(M-H)^+$ calcd 220.1086; obsd 220.1087. MS (EI, 70 eV): 221 ($M^{+\cdot}$, 17), 220 (100), 191 (11), 178 (60), 177 (29), 174 (23), 164 (12), 163 (18.5), 161 (20), 149 (25), 131 (26), 117 (18), 104 (17), 103 (15), 99 (52), 44 (73), 42 (14). δ_H ($CDCl_3$): 1.07 (3H, d, J=6.2 Hz, CH_3), 1.15 (1H, m, H-5ax), 1.27 (1H, broad s, NH), 1.56 (1H, m, J_{5eq5ax}=13.0 Hz, H-5eq), 2.93 (2H, m, H-4ax, H-6ax), 3.22 (1H, ddd, J_{6eq6ax}=13.0 Hz, J_{6eq5ax}=4.3 Hz, J_{6eq5eq}=1.9 Hz, H-6eq), 4.58 (1H, s, H-2), 7.61 (2H, d, J=8.8 Hz, H-2′, H-6′), 8.08 (2H, d, J=8.8 Hz, H-3′, H-5′). δ_C ($CDCl_3$): 22.8 (CH_3), 34.8 (C-5), 46.0 (C-6), 51.7 (C-4), 73.6 (C-2), 123.4 (C-3′, C-5′), 127.4 (C-2′, C-6′), 147.4 (C-4′), 149.5 (C-1′).

4.3.16. 1,3-Bis(*o*-hydroxybenzylidenamino)butane (6a). Yield 72%, light yellow crystals, mp 87 °C (benzene–hexane). HRMS: $C_{18}H_{20}N_2O_2$ $M^{+\cdot}$ calcd 296.1525; obsd 296.1537. δ_H ($CDCl_3$): 1.32 (3H, d, J=6.3 Hz, CH_3), 1.99 (2H, q, J=6.7 Hz, 2H-5), 3.56 (3H, m, 2H-6, H-4), 6.89 (4H, m, 2H-3′, 2H-5′), 7.25 (4H, m, 2H-4′, 2H-6′), 8.28 (1H, s, CH=N), 8.34 (1H, s, CH=N). δ_C ($CDCl_3$): 22.7 (CH_3), 38.5 (C-5), 56.3 (C-6), 62.4 (C-4), 116.9 (2 C-3′), 118.6 (2 C-1′, 2 C-5′), 131.2 and 131.3 (2 C-6′), 132.2 (2 C-4′), 161.1 (2 C-2′), 163.6 (CH=N), 165.2 (CH=N).

4.3.17. 1,3-Bis(*p*-dimethylaminobenzylidenamino)-butane (6b). Yield 80%, yellow oil. HRMS: $C_{22}H_{30}N_4$ $M^{+\cdot}$ calcd 350.2470; obsd 350.2478. δ_H ($CDCl_3$): 1.27 (3H, d, J=6.4 Hz, CH_3), 1.98 (2H, q, J=6.6 Hz, 2H-5), 2.97 (12H, s, $2(CH_3)_2N$), 3.48 (3H, m, 2H-6, H-4), 6.67 (4H, d, J=7.3 Hz, 2H-3′, 2H-5′), 7.58 (4H, m, 2H-2′, 2H-6′), 8.07 (1H, s, CH=N), 8.12 (1H, s, CH=N). δ_C ($CDCl_3$): 22.8 (CH_3), 38.9 (C-5), 40.1 ($(CH_3)_2N$), 58.7 (C-6), 64.0 (C-4), 111.6 (2C-3′, 2C-5′), 124.6 (2C-1′), 129.2 and 129.3 (2C-2′ and 2C-6′), 151.8 (2C-4′), 159.1 (CH=N), 160.8 (CH=N).

4.3.18. 2-(2-Hydroxyphenyl)-2,3-dihydro-1*H*-perimidine (7a). Yield 54%, off-pink crystals, mp 195 °C (acetonitrile). δ_H (DMSO-d_6): 5.67 (1H, s, H-2), 6.53 (2H, d, J_{45}=J_{89}=7.3 Hz, H-4, H-9,), 6.54 (2H, broad s, 2NH), 6.83 (1H, t, $J_{4'5'}$=$J_{5'6'}$=7.5 Hz, H-5′), 6.90 (1H, d, $J_{3'4'}$=8.1 Hz, H-3′), 6.98 (2H, d, J_{56}=J_{78}=7.9 Hz, H-6, H-7), 7.16 (3H, m, H-5, H-8, H-4′), 7.46 (1H, dd, $J_{5'6'}$=7.6 Hz, $J_{4'6'}$=1.5 Hz, H-6′), 9.66 (1H, s, OH). δ_C (DMSO-d_6): 60.9 (C-2), 104.6 (C-4, C-9), 112.5 (C-9b), 115.4 (C-6, C-7), 115.4 (C-3′), 118.9 (C-5′), 126.8 (C-5, C-8), 127.1 (C-1′), 128.4 (C-4′or C-6′), 129.1 (C-4′or C-6′), 134.4 (C-6a), 143.2 (C-3a, C-9a), 155.4 (C-2′).

4.3.19. 2-(4-Dimethylaminophenyl)-2,3-dihydro-1*H*-perimidine (7b). Yield 83%, white crystals, mp 168 °C (acetonitrile). δ_H (DMSO-d_6): 2.89 (6H, s, $2CH_3$), 5.23 (1H, s, H-2), 6.47 (2H, d, J_{45}=J_{89}=7.6 Hz, H-4, H-9), 6.55 (2H, broad s, 2NH), 6.75 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.1 Hz, H-3′, H-5′), 6.95 (2H, d, J_{56}=J_{78}=8.1 Hz, H-6, H-7), 7.12 (2H, t, J_{56}=J_{78}=8.1 Hz, J_{45}=J_{89}=7.6 Hz, H-5, H-8), 7.39 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.1 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 40.2 ($2CH_3$), 66.2 (C-2), 104.1 (C-4, C-9), 111.9 (C-3′, C-5′), 112.4 (C-9b), 114.9 (C-6, C-7), 126.7 (C-5, C-8), 128.4 (C-2′, C-6′), 129.0 (C-1′), 134.3 (C-6a), 143.4 (C-3a, C-9a), 150.8 (C-4′).

4.3.20. 2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-perimidine (7c). Yield 80%, white crystals, mp 152 °C (acetonitrile). δ_H (DMSO-d_6): 3.78 (3H, s, CH_3), 5.34 (1H, s, H-2), 6.53 (2H, d, J_{45}=J_{89}=7.3 Hz, H-4, H-9), 6.68 (2H, broad s, 2NH), 7.02 (4H, m, H-3′, H-5′, H-6, H-7,), 7.18 (2H, dd, J_{56}=J_{78}=J_{45}=J_{89}=7.3 Hz, H-5, H-8), 7.56 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.2 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 55.2 (CH_3), 66.0 (C-2), 104.3 (C-4, C-9), 112.5 (C-9b), 113.5 (C-3′, C-5′), 115.2 (C-6, C-7), 126.8 (C-5, C-8), 129.1 (C-2′, C-6′), 133.8 (C-1′), 134.4 (C-6a), 143.2 (C-3a, C-9a), 159.5 (C-4′).

4.3.21. 2-(4-Methylphenyl)-2,3-dihydro-1*H*-perimidine (7d). Yield 78%, light beige crystals, mp 164 °C (acetonitrile). δ_H (DMSO-d_6): 2.35 (3H, s, CH_3), 5.36 (1H, s, H-2), 6.54 (2H, d, J_{45}=J_{89}=7.2 Hz, H-4, H-9), 6.72 (2H, broad s, 2NH), 7.01 (2H, d, J_{56}=J_{78}=7.9 Hz, H-6, H-7), 7.20 (4H, m, H-5, H-8, H-3′, H-5′), 7.52 (2H, d, $J_{2'3'}$=$J_{5'6'}$=7.8 Hz, H-2′, H-6′). δ_C (DMSO-d_6): 20.8 (CH_3), 66.2 (C-2), 104.3 (C-4, C-9), 112.5 (C-9b), 115.2 (C-6, C-7), 126.8 (C-5, C-8), 127.8 (C-3′, C-5′ or C-2′, C-6′), 128.7 (C-3′, C-5′ or C-2′, C-6′), 134.4 (C-6a), 137.7 (C-4′), 138.8 (C-1′), 143.1 (C-3a, C-9a).

4.3.22. 2-Phenyl-2,3-dihydro-1*H*-perimidine (7e). Yield 96%, white crystals, mp 104 °C (acetonitrile). δ_H (DMSO-d_6): 5.40 (1H, s, H-2), 6.54 (2H, d, J_{45}=J_{89}=7.8 Hz, H-4, H-9), 7.02 (2H, d, J_{56}=J_{78}=8.0 Hz, H-6, H-7), 7.19 (2H, t, J_{56}=J_{78}=7.6 Hz, J_{45}=J_{89}=7.8 Hz, H-5, H-8), 7.43 (3H, m, H-3′, H-4′, H-5′), 7.64 (2H, m, H-2′, H-6′). δ_C (DMSO-d$_6$): 66.4 (C-2), 104.4 (C-4, C-9), 112.5 (C-6a), 115.3 (C-6, C-7), 126.8 (C-5, C-8), 127.9 (C-3′, C-5′ or C-2′, C-6′), 128.2 (C-3′, C-5′ or C-2′, C-6′), 128.5 (C-4′), 134.4 (C-9b), 141.8 (C-1′), 143.0 (C-3a, C-9a).

4.3.23. 2-(4-Chlorophenyl)-2,3-dihydro-1*H*-perimidine (7f). Yield 82%, white crystals, mp 173 °C (acetonitrile). δ_H (DMSO-d_6): 5.40 (1H, s, H-2), 6.53 (2H, d, J_{45}=J_{89}=7.3 Hz, H-4, H-9), 6.80 (2H, broad s, 2NH), 7.02 (2H, d, J_{56}=J_{78}=7.7 Hz, H-6, H-7), 7.18 (2H, t, J_{56}=J_{78}=7.7 Hz, J_{45}=J_{89}=7.3 Hz, H-5, H-8), 7.48 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.2 Hz, H-3′, H-5′), 7.66 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.2 Hz, H-2′, H-6′). δ_C (DMSO-d$_6$): 65.5 (C-2), 104.4 (C-4, C-9), 112.4 (C-9b), 115.4 (C-6, C-7), 126.8 (C-5, C-8), 128.1 (C-3′, C-5′), 129.7 (C-2′, C-6′), 132.9 (C-4′), 134.3 (C-6a), 140.9 (C-3a, C-9a), 142.7 (C-1′).

4.3.24. 2-(4-Nitrophenyl)-2,3-dihydro-1*H*-perimidine (7h). Yield 56%, orange crystals, mp>200 °C (benzene), decomp. δ_H (DMSO-d_6): 5.54 (1H, s, H-2), 6.51 (2H, d, J_{45}=J_{89}=7.6 Hz, H-4, H-9), 6.95 (2H, s, 2NH), 6.99 (2H, d, J_{56}=J_{78}=7.7 Hz, H-6, H-7), 7.16 (2H, t, J_{56}=J_{78}=7.7 Hz, J_{45}=J_{89}=7.7 Hz, H-5, H-8), 7.83 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.6 Hz, H-2′, H-6′), 8.26 (2H, d, $J_{2'3'}$=$J_{5'6'}$=8.6 Hz, H-3′, H-5′). δ_C (DMSO-d_6): 64.8 (C-2), 104.5 (C-4, C-9), 112.3 (C-9b), 115.5 (C-6, C-7), 123.3 (C-3′, C-5′), 126.8 (C-5, C-8), 128.9 (C-2′, C-6′), 134.2 (C-6a), 141.9 (C-3a, C-9a), 147.3 (C-4′), 149.8 (C-1′).

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Tetrahedron 60 (2004) 6923–6930
Tetrahedron

Deoxyfluorination of alcohols using *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine

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Received 1 April 2004; accepted 24 May 2004

Abstract—Deoxyfluorination of alcohols was carried out using *N*,*N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine (DFMBA). Primary alcohols were effectively converted to fluorides under microwave irradiation or conventional heating. Deoxyfluorination of an anomeric hydroxy group in sugars by DFMBA proceeded at below room temperature and glycosyl fluorides could be obtained in good yields. The deoxyfluorination reaction chemoselectively proceeded and various protecting groups on the sugar can survive under the reaction conditions.

1. Introduction

Deoxyfluorination reaction of alcohols is useful for the synthesis of organo fluorine compounds, and diethylaminosulfur trifluoride (DAST) has been the most frequently used.[1] Recently, α-fluoroamines, such as 2,2-difluoro-1,3-dimethylimidazolidine (DFI),[2] have been reevaluated as thermally stable deoxyfluorination reagents. *N*,*N*-Dimethyl-α,α-difluorobenzylamine was also used for the deoxyfluorination reaction of simple alcohols.[3] However, due to the mild reactivity of the reagent, relatively high reaction temperature was required to convert butanol to butyl fluoride. In order to apply the reagent for the deoxyfluorination of more complex alcohols, higher reaction temperature would be required and its thermal stability was problematic.[4] Quite recently, a similar fluoroamine, *N*,*N*-diethyl-α,α-difluoro(*m*-methylbenzyl)amine (DFMBA, **1**), was reported to have high thermal stability (ARC 180 °C)[6] and we successfully used DFMBA for the deoxyfluorination reaction of sugars.[7] We wish to report here details of the deoxyfluorination reaction of various alcohols using DFMBA.

2. Result and discussion

2.1. Fluorination of alcohols using DFMBA

DFMBA is a colorless liquid and can be conveniently prepared from the corresponding amide in two steps through a chloroiminium salt.[6] It slowly reacted with 1-dodecanol (**2a**) at room temperature to give 1-dodecyl fluoride (**3a**) in 12% yield after 17 h and most of **2a** remained as an ester (**4a**) (Eq. 1). Under reflux in heptane, the fluorination reaction was completed in 1 h to give **3a** in good yield. Recently, microwave irradiation is reported to be effective to complete the thermal reaction in short time, and we applied the microwave irradiation to the reaction.[8] The reaction was carried out using a modified household microwave oven. In an acetonitrile or without a solvent, the reaction mixture was refluxed vigorously under the irradiation of microwave and the reaction was completed in 10 min to give **3a** in good yields. However, a dark tarry material was also formed. Both DFMBA and acetonitrile can absorb microwave energy very well and the reaction mixture could reach a high temperature. As it is difficult to control the reaction temperature in the household oven, we used a hydrocarbon solvent which does not absorb microwave energy well.[8] Though the reaction mixture was refluxed vigorously even in heptane under microwave irradiation, the formation of the tarry material was not observed and **3a** was obtained in good yield in 10 min (Table 1).

Table 1. Reaction of 1-dodecanol **2a** with DFMBA **1**[a]

React. temp.	React. Time	Solvent	Yield of **3a** (%)[b]	Yield of **4a** (%)[c]
25 °C	17 h	Heptane	12	76
98 °C	10 min	Heptane	67	7
98 °C	1 h	Heptane	86	Trace
MW	10 min	CH_3CN	83	Trace
MW	10 min	—	85	Trace
MW	10 min	Heptane	88	Trace

[a] The reaction was carried out using 1.2 equiv. of **1** to **2a**.
[b] Isolated yield based on **2a**.
[c] GC yield.

Keywords: Deoxyfluorination; DFMBA; Fluoro sugars; Microwave.
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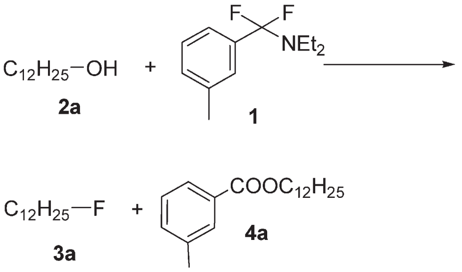
doi:10.1016/j.tet.2004.05.089

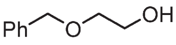
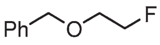
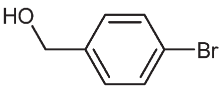
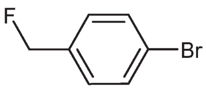


(1)

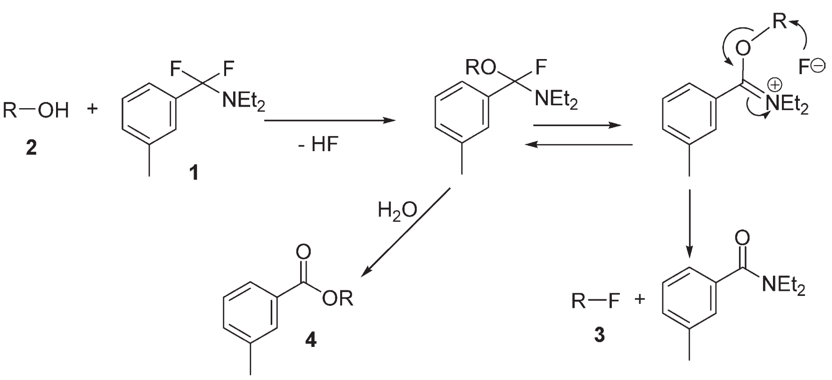
The deoxyfluorination reaction of various alcohols was carried out using **1** as shown in Table 2. Under the microwave irradiation, primary alcohols **2b**, **c**, **d**, **h**, **i** could be converted to the corresponding fluorides **3b**, **c**, **d**, **h**, **i** in good yields without the formation of olefinic by-products or the esters **4**, and the functional groups, such as the double bond **2b**, ether **2c** and ester group **2i**, remained unchanged. On the other hand, secondary alcohols **2e**, **f**, **g** were converted to the corresponding fluorides in moderate yields and olefinic by-products were also formed (8– 40%). A benzylic alcohol **2j** is more reactive than the others, and it could be converted to the fluoride **3j** in high yield without the microwave irradiation.

The proposed reaction mechanism is as follows. The alcohol **2** reacts with DFMBA **1** to give an adduct. This step is fast even at room temperature and hydrolysis at this stage gives ester **4**. A fluoride attacks the alkyl group of the alcohol to

Table 2. Deoxyfluorination of alcohols using DFMBA[a]

Substrate	Condition	Solvent	Product	Yield, %[b]
$CH_2{=}CH(CH_2)_9{-}OH$ **2b**	MW 10 min	Heptane	$CH_2{=}CH(CH_2)_9{-}F$ **3b**	86
 **2c**	MW 10 min	Heptane	 **3c**	72
$C_{10}H_{21}{-}CHFCH_2{-}OH$ **2d**	MW 30 min	Dodecane	$C_{10}H_{21}{-}CHFCH_2{-}F$ **3d**	87[c]
$C_{10}H_{21}{-}CH(OH)CH_2CH_2F$ **2e**	MW 30 min	Dodecane	$C_{10}H_{21}{-}CHFCH_2CH_2F$ **3d**	63[c,d]
$C_{10}H_{21}{-}CH(OH)CH_3$ **2f**	MW 30 min	Dodecane	$C_{10}H_{21}{-}CHFCH_3$ **3f**	72[c,e]
Hex−CH(OH)−Hex **2g**	MW 30 min	Dodecane	Hex−CHF−Hex **3g**	50[c,f]
$HO{-}(CH_2)_{12}{-}OH$ **2h**	MW 10 min	Heptane	$F{-}(CH_2)_{12}{-}F$ **3h**	91
$HO{-}(CH_2)_4{-}COOBu$ **2i**	MW 10 min	Heptane	$F{-}(CH_2)_4{-}COOBu$ **3i**	80
 **2j**	50 °C 2 h	Heptane	 **3j**	95[c]

[a] If otherwise not mentioned, the reaction was carried out using 1.2 equiv. of **1** to **2**.
[b] Isolated yield based on **2** used.
[c] 1.5 equiv. of **1** to **2** was used.
[d] Olefinic by-products were also formed (8%).
[e] Olefinic by-products were also formed (20%).
[f] Olefinic by products were also formed (40%).

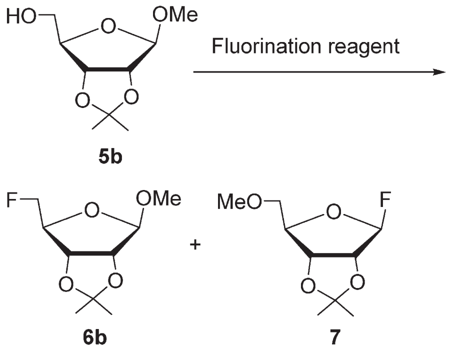


Scheme 1.

give alkyl fluoride **3** and an amide. This step is slow, and heating or the microwave irradiation is required to complete the reaction (Scheme 1).

2.2. Deoxyfluorination of sugars using DFMBA

Fluorinated carbohydrates have recently received much attention because of their important role in the study of enzyme–carbohydrate interactions as well as their interesting biological activities,[9] and we applied **1** to the fluorinated carbohydrate synthesis. The reaction of methyl 2,3-*O*-isopropylidene-β-D-ribofuranose (**5b**) with DAST was previously reported to cause migration of a methoxy group from 1- to 5-position, and an unexpected 5-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl fluoride (**7**) was obtained instead of the desired 5-deoxy-5-fluoro derivative (**6b**).[10] In the reaction of **5b** with **1** under the microwave irradiation, the desired **6b** could be obtained in 51% yield but **7** was also formed in 20% yield. Under the microwave irradiation conditions, it was difficult to control the reaction temperature and selectivity, and we examined the reaction under conventional thermal heating conditions. The fluorination reaction was slow under the thermal conditions, and **6a** was obtained only in 28% yield at 98 °C in 3 h. Moreover, migration of the methoxy group also took place under the thermal conditions. In order to accelerate the fluorination at the 5-position of **5b**, we added spray dry KF as a fluoride source and used a polar solvent, dioxane, to dissolve the KF. By carrying out the reaction at 100 °C for 16 h, migration of the methoxy group could be prevented and **6b** could be selectively obtained in 67% yield (Eq. 2).

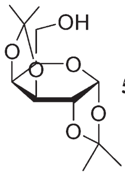
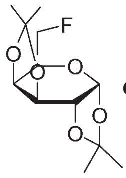
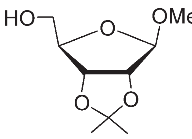
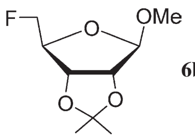
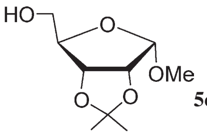
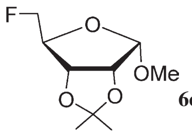
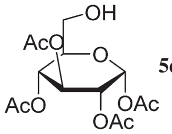
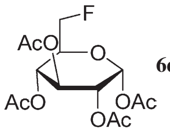
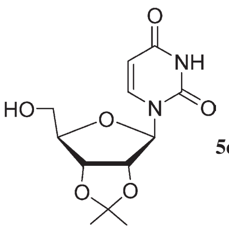
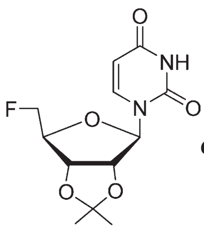


(2)

Reagent	Solvent	Condition	Yield of **6b**, %	Yield of **7**, %
DAST	CH_2Cl_2	−15 °C–rt	—	55[10]
DFMBA	Heptane	MW 10 min	51	20
DFMBA	Heptane	98 °C 3 h	28	11
DFMBA, KF	Dioxane	100 °C 16 h	67	-

Similarly, an α-isomer (**6c**) could be stereospecifically obtained in 63% yield from an α-ribofuranose derivative

Table 3. Deoxyfluorination of hydroxy groups in sugars and a nucleoside using DFMBA **1**[a]

Substrate	Condition	Product	Yield, %[b]
 **5a**	MW 20 min heptane	 **6a**	70
 **5b**	100 °C 16 h dioxane	 **6b**	67[c]
 **5c**	100 °C 24 h dioxane	 **6c**	63[c]
 **5d**	100 °C 6 h dioxane	 **6d**	68[c]
 **5e**	MW 10 min heptane	 **6e**	55

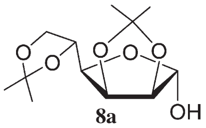
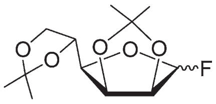
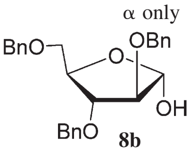
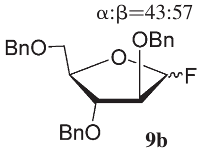
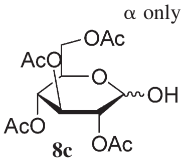
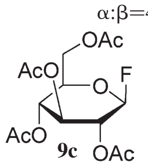
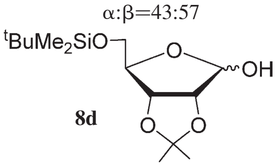
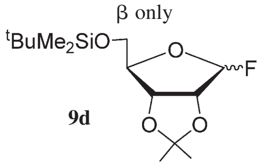
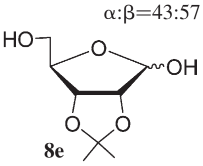
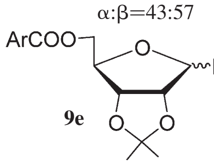
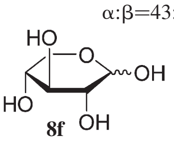
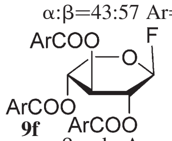
[a] If otherwise not mentioned, 2 equiv. of **1** to substrate was used.
[b] Isolated yield based on substrate was used.
[c] 4 equiv. of KF and 2.5 equiv. of **1** substrate was used.

(**5c**) (Table 3). Under the same conditions, 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranose (**5d**) could be converted to 1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranose (**6d**) in 68% yield. The conversion of 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5a**) to the corresponding fluoride (**6a**) could be achieved in 20 min under the microwave irradiation without affecting an acetonide protecting group. DFMBA **1** can be also used for the deoxyfluorination of nucleosides, and 2′,3′-*O*-isopropylideneuridine (**5e**) could be converted to a 5′-deoxy-5′-fluorouridine derivative (**6e**) in 55% yield without migration of an uracil ring under the microwave irradiation.[11]

2.3. Glycosyl fluorides synthesis using DFMBA

Glycosyl fluorides have been used as a key compound for polysaccharides synthesis and many reagents have been developed for their synthesis from the corresponding sugars.[12] The hydroxy group of the sugars at the 1-position is highly reactive and even HF can be used for the conversion of the sugars to glucosyl fluorides.[13] However, some protecting groups of sugars are sensitive to acidic reagents, and mild reagents for the synthesis of glycosyl fluorides have been desired. Various sugars having protecting groups such as acetonide (**8a**, **d**, **e**), benzyl ether (**8b**), acetate (**8c**) and, silyl ether (**8d**) reacted with **1** at below room temperature quickly without affecting the protecting groups to give the corresponding glycosyl fluorides in good yields as shown in Table 4. Moreover, the hydroxy groups at other than the 1-position were not converted to the fluoride by **1** at below room temperature, and, therefore, the glycosyl fluoride synthesis can be carried out without protection of the hydroxy groups. For instance, 2,3-*O*-isopropylidene-D-ribofuranose (**8e**) reacted with 2.4 equiv. of **1** at 0 °C to give 2,3-*O*-isopropylidene-5-*O*-*m*-methylbenzoyl-D-ribofuranosyl fluoride (**9e**) in 70% yield. Under the reaction conditions, only the hydroxy group at the 1-position was selectively deoxyfluorinated and the hydroxy group at the 5-position was only acylated. Furthermore, D-xylopyranose (**8f**), having four free hydroxy groups, can be directly converted to 2,3,4-tri-*O*-*m*-methylbenzoyl-D-xylopyranosyl fluoride (**9f**) in 60% yield by the reaction with 8 equiv. of **1**. In most of the cases, selectivity for α- or β-isomers was not observed and a mixture of both isomers was obtained regardless of the stereochemistry of the starting materials. Therefore, the reaction proceeds not via an S_N2 mechanism but through an oxonium intermediate.[14] In the cases of a glucose (**8c**) and a xylose derivative (**8f**), the β-isomers (**9c** and **9f**) were selectively formed by the neighboring-group participation of the acyloxy groups at the 2-position.[14]

Table 4. Deoxyfluorination of hydroxy groups at 1-position in sugars using DFMBA **1**[a]

Substrate	Product	Yield, %[b]
 **8a** α only	 **9a** α:β=43:57	90[c]
 **8b** α only	 **9b** α:β=43:57	85
 **8c** α:β=43:57	 **9c** β only	80
 **8d** α:β=43:57	 **9d** α:β=43:57	80[d]
 **8e** α:β=43:57	 **9e** α:β=43:57 Ar=*m*-tolyl	70[d,e]
 **8f**	 **9f** β only Ar=*m*-tolyl	60[c,f]

[a] If otherwise not mentioned, the reaction was carried out in CH_2Cl_2 at room temperature for 1 h with 1.2 equiv. of **1**.
[b] Isolated yield based on sugar used.
[c] The reaction was carried out without solvent.
[d] The reaction was carried out out at 0 °C.
[e] 2.4 equiv. of **1** to sugar was used.
[f] The reaction was carried out for 12 h using 8 equiv. of **1**.

3. Experimental

3.1. General

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400MHz), ^{19}F NMR (376 MHz), and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. A commercially available GoldStar microwave oven (500W, MW-JIK96H5) was modified to accept a port for connecting a reactor to a reflux condenser located outside the oven.[15] A hole of 10 mm diameter was drilled in the oven top and an 80 mm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reactor which is a Teflon™ PFA tube with a diameter of 10 mm and a length of 80 mm sealed at one end. DFMBA **1** was obtained from Mitubishi Gas Chemical Company Inc. and used without further purification. Though handling **1** with glassware is possible, it is recommended to use equipment made of Teflon™. As **1** is slightly moisture-sensitive, it should be handled as quickly as possible in air and kept in a Teflon™ bottle with a tight screw cap. Alcohols **2d**, **2e** were prepared from 1,2-dodecene oxide by the reaction with Et_3N-3HF.[16] Sugar derivatives **5a**, **5d**, **8a** were purchased from

Sigma-Aldrich Co. and **8b**, **8f** were obtained from Junsei Chemical Co. Ltd. Other derivatives **5b**,[17] **5c**,[17] **5e**,[18] **8c**,[19] **8d**,[20] **8e**[21] were prepared from the corresponding sugars or nucleocide according to the literature. The spray dry KF was obtained from Morita Chemical Industries Co. Ltd. and dried before use under the condition of 100 °C/0.01 m Hg for 1 h.

3.2. Fluorination of alcohols using DFMBA

3.2.1. Preparation of 1-fluorododecane (3a).[22] Into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, were introduced heptane (1 ml), **1** (256 mg, 1.2 mmol), and **2a** (186 mg, 1.0 mmol). The open end of the reactor was connected to a port in a microwave oven and the port was connected to a reflux condenser located outside the oven. Then, the reaction mixture was submitted to microwave irradiation for 10 min. During the irradiation, the reaction mixture was refluxed vigorously. After the reaction, the reaction mixture was poured into aq $NaHCO_3$ and extracted with ether three times. The combined ethereal layers were dried over $MgSO_4$, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane) gave 1-fluorododecane **3a** (165 mg, 0.88 mmol) in 88% yield.

IR (neat): 2925, 2855, 1466, 1389, 1050, 1010 cm^{-1}. ^{1}H NMR δ=4.44 (2H, dt, J=47.3, 6.3 Hz), 1.74–1.64 (2H, m), 1.39–1.26 (18H, m), 0.88 (3H, t, J=6.7 Hz). ^{13}C NMR δ=14.07 (1C, s), 22.71 (1C, s), 25.19 (1C, d, J=5.0 Hz), 29.29 (1C, s), 29.39 (1C, s), 29.56 (1C, s), 29.60 (1C, s), 29.67 (1C, s), 29.69 (1C, s), 30.46 (1C, d, J=19.0 Hz), 31.96 (1C, s), 84.11 (1C, d, J=163.8 Hz). ^{19}F NMR δ=−218.36 to −218.75 (1F, m). HRMS (EI) Calcd for $C_{12}H_{25}F$ (M^+) 188.1940. Found 188.1942.

3.2.2. 1-Fluoro-10-undecene (3b).[23] IR (neat): 2927, 2855, 1641, 1465 cm^{-1}. ^{1}H NMR δ=5.86–5.76 (1H, m), 5.02–4.91 (2H, m), 4.44 (2H, dt, J=47.3, 6.1 Hz), 2.07–2.01 (2H, m), 1.75–1.63 (2H, m), 1.39–1.29 (12H, m). ^{13}C NMR δ=25.13 (1C, d, J=4.9 Hz), 28.90 (1C, s), 29.08 (1C, s), 29.21 (1C, s), 29.37 (1C, s), 29.45 (1C, s), 30.40 (1C, d, J=19.0 Hz), 33.78 (1C, s), 84.15 (1C, d, J=164.6 Hz), 114.09 (1C, s), 139.13 (1C, s). ^{19}F NMR δ=−218.37 to −218.75 (1F, m). HRMS (EI) Calcd for $C_{11}H_{21}F$ (M^+) 172.1627. Found 172.1631.

3.2.3. 2-Benzyloxyethyl fluoride (3c).[23] IR (neat): 3031, 2952, 2862, 1496, 1454, 1358 cm^{-1}. ^{1}H NMR δ=7.36–7.28 (5H, m), 4.60 (2H, s), 4.59 (2H, dt, J=47.6, 4.2 Hz), 3.72 (2H, dt, J=29.3, 4.2 Hz). ^{13}C NMR δ=69.12 (1C, d, J=19.8 Hz), 73.31 (1C, s), 83.09 (1C, d, J=168.7 Hz), 127.71 (2C, s), 127.73 (1C, s), 128.41 (2C, s), 137.77 (1C, s). ^{19}F NMR δ=−223.43 to −223.84 (1F, m). HRMS (EI) Calcd for $C_9H_{11}OF$ (M^+) 154.0794. Found 154.0786.

3.2.4. 1,2-Difluorododecane (3d).[24] IR (neat) 2926, 2855, 1467, 1042 cm^{-1}. ^{1}H NMR δ=4.79–4.34 (3H, m), 1.74–1.26 (18H, m), 0.88 (3H, t, J=6.8 Hz). ^{13}C NMR δ=14.09 (1C, s), 15.26 (1C, s), 22.67 (1C, s), 24.74 (1C, d, J=5.0 Hz), 29.31 (1C, s), 29.39 (1C, s), 29.53 (1C, d, J=5.8 Hz), 30.02 (1C, dd, J=20.7, 6.6 Hz), 31.88 (1C, s), 65.84 (1C, s), 84.16 (1C, dd, J=173.7, 23.2 Hz), 91.85 (1C, dd, J=172.0, 19.0 Hz). ^{19}F NMR δ=−189.18 to −189.60 (1F, m), −230.19 to −230.54 (1F, m).

3.2.5. 2-Fluorododecane (3f).[25] IR (neat) 2926, 2855, 1466, 1384, 1130 cm^{-1}. ^{1}H NMR δ=4.65 (dm, 1H, J=50.5 Hz), 1.71–1.26 (20H, m), 0.88 (3H, t, J=6.8 Hz). ^{13}C NMR δ=14.10 (1C, s), 20.99 (1C, d, J=23.2 Hz), 22.69 (1C, s), 25.09 (1C, d, J=5.0 Hz), 29.57 (1C, s), 29.33(1C, s), 29.47(1C, s), 29.55 (1C, s), 29.60 (1C, s), 31.91 (1C, s), 36.95 (1C, d, J=20.7 Hz), 91.06 (1C, d, J=164.6 Hz). ^{19}F NMR δ=−172.45 to −172.89 (1F, m).

3.2.6. 7-Fluorotridecane (3g). IR (neat) 2932, 2859, 1467 cm^{-1}. ^{1}H NMR δ=4.46 (1H, dm, J=49.3 Hz), 1.29–1.67 (20H, m), 0.89 (6H, t, J=6.7 Hz). ^{13}C NMR δ=14.05 (2C, s), 22.60 (2C, s), 25.13 (2C, d, J=5.0 Hz), 29.22 (2C, s), 31.78 (2C, s), 35.22 (2C, d, J=20.7 Hz), 94.53 (1C, d, J=167.1 Hz). ^{19}F NMR δ=−180.76 to −180.38 (m, 1F). HRMS (EI) Calcd for $C_{13}H_{26}$ (M^+−HF) 182.2035. Found 182.2027.

3.2.7. 1,12-Difluorododecane (3h).[23] IR (neat) 2928, 2855, 1467, 1390 cm^{-1}. ^{1}H NMR δ=4.49 (4H, dt, J=47.3, 6.3 Hz), 1.75–1.62 (4H, m), 1.55–1.28 (16H, m). ^{13}C NMR δ=25.13 (2C, d, J=5.0 Hz), 29.22 (2C, s), 29.48 (4C, s), 30.39 (2C, d, J=19.9 Hz), 84.17 (2C, d, J=163.8 Hz). ^{19}F NMR δ=−218.38 to −218.77 (m, 2F). HRMS (EI) Calcd for $C_{12}H_{24}F_2$ (M^+) 206.1846. Found 206.1843.

3.2.8. Butyl 5-fluoropentanoate (3i). IR (neat) 2962, 1736, 1172 cm^{-1}. ^{1}H NMR δ=4.46 (2H, dt, J=47.6, 5.6 Hz), 4.08 (2H, t, J=6.6 Hz), 2.36 (2H, t, J=6.3 Hz), 1.80–1.71 (4H, m), 1.65–1.56 (2H, m), 1.43–1.33 (2H, m), 0.94 (3H, t, J=7.4 Hz). ^{13}C NMR δ=13.58 (1C, s), 19.04 (1C, s), 20.77 (1C, d, J=5.0 Hz), 29.69 (1C, d, J=19.9 Hz), 30.58 (1C, s), 33.64 (1C, s) 64.14 (1C, s) 83.47 (1C, d, J=165.4 Hz), 173.25 (1C, s). ^{19}F NMR δ=−219.25 to −219.66 (m, 1F). HRMS (EI) Calcd for $C_9H_{17}O_2F$ (M^+) 176.1213. Found 176.1216.

3.2.9. Preparation of *p*-bromobenzyl fluoride (3j).[26] DFMBA (256 mg, 1.5 mmol), *p*-bromobenzyl alcohol (187 mg, 1.0 mmol), and $CHCl_3$ (2 ml) were introduced into a reaction vessel made of Teflon™ PFA with a tight screw cap and kept at 50 °C for 2 h in an oil bath. The mixture was poured into aq $NaHCO_3$ and extracted with ether three times. The combined ethereal layers were dried over $MgSO_4$, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–Et_2O) gave **3j** in 95% yield; IR (neat) 2961, 1593, 1487, 1407, 1374, 1213, 1071, 1011 cm^{-1}. ^{1}H NMR δ=7.52 (2H, d, J=7.3 Hz), 7.24 (2H, d, J=7.3 Hz), 5.33 (2H, d, J=47.6 Hz). ^{13}C NMR δ=83.71 (1C, d, J=167.1 Hz), 122.75 (2C, d, J=3.3 Hz), 129.0 (2C, d, J=5.8 Hz), 131.73 (1C, s), 135.13 (1C, d, J=18.2 Hz). ^{19}F NMR δ=−208.64 (1F, t, J=47.6 Hz).

3.3. Deoxyfluorination of sugars using DFMBA

3.3.1. 6-Fluoro-1,2;3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranose (6a).[27,28] IR (neat) 2990, 1384, 1256, 1213, 1072 cm^{-1}. ^{1}H NMR δ=5.56 (1H, d, J=4.9 Hz), 4.65–4.48 (3H, m), 4.35 (1H, dd, J=5.1, 2.4 Hz), 4.27 (1H, dd, $J=8.1$, 2.0 Hz), 4.10–4.07 (1H, m), 1.55 (3H, s), 1.45 (3H, s), 1.34 (6H, s). ^{13}C NMR $\delta=24.39$ (1C, s), 24.88 (1C, s), 25.90 (1C, s), 26.00 (1C, s), 66.60 (1C, d, $J=22.3$ Hz), 70.39 (1C, s), 70.47 (1C, s), 70.55 (1C, s), 82.04 (1C, d, $J=167.9$ Hz), 96.15 (1C, s), 108.78 (1C, s), 109.63 (1C, s). ^{19}F NMR $\delta=-231.73$ (1F, dt, $J=47.6$, 14.0 Hz). HRMS (EI) Calcd for $C_{12}H_{19}O_5F$ (M^+) 262.1216. Found 262.1215.

3.3.2. Preparation of methyl 5-fluoro-2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranoside (6b).[28] DFMBA (533 mg, 2.5 mmol), KF (232 mg, 4.0 mmol), **5b** (204 mg, 1.0 mmol), and 1,4-dioxane (1 ml) were introduced into a reaction vessel made of Teflon™ PFA with a tight screw cap and kept at 100 °C for 16 h in an oil bath. After the reaction, the mixture was poured into aq $NaHCO_3$ and extracted with ether three times. The combined ethereal layers were dried over $MgSO_4$, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–Et_2O) gave **6b** in 67% yield; IR (neat) 2941, 2837, 1458, 1383, 1212, 1090, 871 cm^{-1}. ^{1}H NMR $\delta=4.99$ (1H, d, $J=2.4$ Hz), 4.71 (1H, d, $J=6.1$ Hz), 4.60 (1H, d, $J=5.9$ Hz), 4.39 (3H, dm, $J=37.8$ Hz), 3.33 (3H, s), 1.50 (3H, s), 1.33 (3H, s). ^{13}C NMR $\delta=24.87$ (1C, s), 26.37 (1C, s), 54.85 (1C, s), 81.00 (1C, d, $J=4.1$ Hz), 82.91 (1C, d, $J=172.9$ Hz), 84.36 (1C, s), 84.59 (1C, s), 85.05 (1C, s), 109.21 (1C, s). ^{19}F NMR $\delta=-225.39$ to -225.68 (1F, m). HRMS (EI) Calcd for $C_9H_{14}O_4F$ (M^+-H) 205.0876. Found 205.0869.

3.3.3. Methyl 5-fluoro-2,3-*O*-isopropylidene-5-deoxy-α-D-ribofuranoside (6c).[28] IR (neat) 2939, 1371, 1215, 1098 cm^{-1}. ^{1}H NMR $\delta=4.96$ (1H, s), 4.67–4.62 (2H, m), 4.58 (2H, dm, $J=47.8$ Hz), 4.25 (1H, dm, $J=30.7$ Hz), 3.51 (3H, s), 1.58 (3H, s), 1.37 (3H, s). ^{13}C NMR $\delta=25.56$ (1C, s), 25.89 (1C, s), 56.14 (1C, s), 79.71 (1C, d, $J=26.5$ Hz), 79.66 (1C, s), 80.46 (1C, s), 83.18 (1C, d, $J=172.0$ Hz), 103.17 (1C, s), 115.26 (1C, s). ^{19}F NMR $\delta=-232.72$ (1F, dt, $J=47.8$, 30.7 Hz).

3.3.4. 1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranose (6d).[29] Mp 122–125 °C (lit.[26] 128–129 °C). IR (KBr) 2959, 1757, 1370, 1217, 1079, 1038 cm^{-1}. ^{1}H NMR $\delta=5.74$ (1H, d, $J=8.1$ Hz), 5.32–5.11 (3H, m), 4.60–4.37 (2H, m), 3.89–3.79 (1H, m), 2.12 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 2.03 (3H, s). ^{13}C NMR $\delta=25.55$ (1C, s), 20.76 (1C, s), 67.46 (1C, d, $J=6.6$ Hz), 70.11 (1C, s), 72.70 (1C, s), 73.20 (1C, s), 80.61 (1C, s), 91.55 (1C, s), 168.95 (1C, s), 169.15 (1C, s), 169.28 (1C, s), 170.12 (1C, s). ^{19}F NMR $\delta=-232.73$ (1F, dt, $J=47.0$, 22.6 Hz).

3.3.5. 5′-Fluoro-2′,3′-*O*-isopropylidene-5′-deoxyuridine (6e).[30] IR (neat) 2990, 1687, 1437, 1382, 1274, 1082 cm^{-1}. ^{1}H NMR $\delta=9.18$ (1H, brs), 7.33 (1H, d, $J=8.1$ Hz), 5.84 (1H, s), 5.76 (1H, d, $J=8.1$ Hz), 4.94–4.88 (2H, m), 4.74–4.71 (1H, m), 4.62–4.59 (1H, m), 4.43–4.35 (1H, m), 1.60 (3H, s), 1.36 (3H, s). ^{13}C NMR $\delta=25.15$ (1C, s), 27.02 (1C, s), 79.90 (1C, d, $J=7.4$ Hz), 82.84 (1C, d, $J=172.4$ Hz), 84.50 (1C, s), 85.62 (1C, d, $J=18.2$ Hz), 93.73 (1C, s), 102.66 (1C, s), 114.57 (1C, s), 141.49 (1C, s), 150.19 (1C, s), 163.61 (1C, s). ^{19}F NMR $\delta=-229.973$ to -230.292 (1F, m). HRMS Calcd for $C_{12}H_{15}N_2O_5F$ (M^+) 286.0965. Found 286.0967.

3.4. Glycosyl fluorides synthesis using DFMBA

3.4.1. Preparation of 2,3;5,6-di-*O*-isopropylidene-D-mannofuranosyl fluoride (9a).[31] DFMBA (205 mg, 1.2 mmol), **8a** (187 mg, 1.0 mmol), and CH_2Cl_2 (2 ml) were introduced into a reaction vessel made of Teflon™ PFA with a tight screw cap and the mixture was stirred at room temperature for 1 h. After the reaction, the mixture was poured into aq $NaHCO_3$ and extracted with ether three times. The combined ethereal layers were dried over $MgSO_4$, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–Et_2O) gave **9a** in 90% yield as a mixture of α and β isomers in a ratio of 43:57.

(**9a**-α), IR (neat) 2989, 1374, 1212, 1130, 1070, 972, 849 cm^{-1}. ^{1}H NMR $\delta=5.69$ (1H, d, $J=59.5$ Hz), 4.77–4.43 (2H, m), 4.43–4.38 (1H, m), 4.18–4.05 (3H, m), 1.46 (6H, s), 1.39 (3H, s), 1.35 (3H, s). ^{13}C NMR $\delta=24.49$ (1C, s), 25.14 (1C, s), 25.80 (1C, s), 26.86 (1C, s), 66.64 (1C, s), 72.68 (1C, s), 78.56 (1C, s), 82.60 (1C, s), 84.72 (1C, d, $J=42.2$ Hz), 109.39 (1C, s), 113.20 (1C, s), 113.64 (1C, d, $J=221.6$ Hz). ^{19}F NMR $\delta=-129.25$ (1F, dd, $J=59.5$, 6.7 Hz). HRMS (EI) Calcd for $C_{12}H_{19}O_5F$ (M^++H) 263.1295. Found 263.1317.

(**9a**-β), mp 113–114 °C (lit.[31] 114–115 °C). IR (neat) 2985, 1377, 1263, 1216, 1125, 1089, 1062, 1001, 846, 527 cm^{-1}. ^{1}H NMR $\delta=5.51$ (1H, dd, $J=3.7$, 66.5 Hz), 4.87–4.84 (1H, m), 4.75–4.69 (1H, m), 4.50–4.46 (1H, m), 4.22–4.17 (1H, m), 4.11 (2H, d, $J=3.7$ Hz), 1.57 (3H, s), 1.46 (3H, s), 1.41 (3H, s), 1.39 (3H, s). ^{13}C NMR $\delta=25.24$ (2C, s), 25.67 (1C, s), 26.94 (1C, s), 66.45 (1C, s), 73.52 (1C, s), 77.55 (1C, s), 81.00 (1C, d, $J=1.7$ Hz), 81.23 (1C, d, $J=19.8$ Hz), 107.42 (1C, d, $J=234.9$ Hz), 109.39 (1C, s), 115.74 (1C, s). ^{19}F NMR $\delta=-125.13$ (1F, ddd, $J=66.5$, 15.3, 5.5 Hz). HRMS (EI) $C_{12}H_{20}O_5F$ (M^++H) 263.1295. Found 263.1288

3.4.2. 2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl fluoride (9b-α).[13] IR (neat) 2895, 1725, 1496, 1453, 1376, 1110, 872, 752, 699 cm^{-1}. ^{1}H NMR $\delta=7.30$–7.17 (15H, m), 5.55 (1H, d, $J=67.1$ Hz), 4.63–4.47 (6H, m), 4.18–4.01 (3H, m), 3.56–3.47 (2H, m). ^{13}C NMR $\delta=69.32$ (1C, s), 72.04 (1C, s), 72.09 (1C, s), 73.36 (1C, s), 82.45 (1C, s), 84.07 (1C, s), 86.82 (1C, d, $J=33.9$ Hz), 113.50 (1C, d, $J=225.0$ Hz), 127.66–128.50 (15C, s), 136.89 (1C, s), 137.41 (1C, s), 137.83 (1C, s). ^{19}F NMR $\delta=-127.30$ (1F, ddd, $J=65.3$, 20.8, 5.5 Hz). HRMS (EI) Calcd for $C_{26}H_{27}O_4F$ (M^+) 422.1893. Found 422.1896.

(**9b**-β), mp 78–79 °C (lit.[13] 77–78 °C). IR (neat) 3062, 3030, 2865, 1454, 1115, 1028, 738, 698 cm^{-1}. ^{1}H NMR $\delta=7.30$–7.17 (15H, m), 5.79 (5H, d, $J=61.5$ Hz), 4.73–4.45 (7H, m), 4.17 (1H, dd, $J=9.3$, 2.2 Hz), 3.96 (1H, dd, $J=5.1$, 2.0 Hz), 3.64–3.57 (2H, m). ^{13}C NMR $\delta=71.52$ (1C, s), 72.48 (1C, s), 72.63 (1C, s), 73.45 (1C, s), 81.53 (1C, s), 82.35 (1C, s), 84.52 (1C, d, $J=21.5$ Hz), 108.32 (1C, d, $J=229.9$ Hz), 127.66–128.51 (15C, s), 137.18 (1C, s), 137.73 (1C, s), 137.87 (1C, s). ^{19}F NMR $\delta=-121.23$ (1F, dd, $J=61.6$, 9.2 Hz). HRMS (EI) Calcd for $C_{26}H_{27}O_4F$ (M^+) 422.1893. Found 422.1882.

3.4.3. 2,3,4,5-Tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (9c).[32] Mp 77–78 °C. IR (neat) 2942, 1761, 1439, 1378, 1227, 1109, 1042 cm^{-1}. ^1H NMR δ=5.37 (1H, dd, *J*=52.0, 6.1 Hz), 5.22–5.20 (2H, m), 5.18–5.08 (1H, s), 4.29–4.20 (2H, m), 3.93–3.88 (1H, s), 2.11 (6H, s), 2.05 (6H, s). ^{13}C NMR δ=20.49–20.61 (4C, s), 61.68 (1C, s), 67.36 (1C, s), 71.10 (1C, d, *J*=28.9 Hz), 71.70 (1C, d, *J*=8.3 Hz), 71.96 (1C, d, *J*=4.1 Hz), 106.14 (1C, d, *J*=219.2 Hz), 169.05 (1C, s), 169.23 (1C, s), 169.95 (1C, s), 170.49 (1C, s). ^{19}F NMR δ=−137.83 (1F, dd, *J*=51.9, 10.4 Hz). HRMS (EI) Calcd for $C_{14}H_{20}O_9F$ (M^++H) 351.1091. Found 351.1115.

3.4.4. 2,3-*O*-Isopropylidene-5-*O*-dimethyl^{t}butylsilyl-α-D-ribofuranosiyl fluoride (9d-α). IR (neat) 2932, 1858, 1472, 1381, 1258, 1215, 1108, 838 cm^{-1}. ^1H NMR δ=5.63 (1H, dd, *J*=66.5, 3.7 Hz), 4.70–4.61 (2H, m), 4.47 (1H, brs), 3.75 (2H, d, *J*=2.6 Hz), 1.57 (3H, s), 1.38 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.05 (3H, s). ^{13}C NMR δ=−5.55 (1C, s), −5.36 (1C, s), 18.25 (1C, s), 25.69 (1C, s), 25.71 (1C, s), 25.82 (3C, s), 63.23 (1C, s), 79.52 (1C, s), 81.10 (1C, d, *J*=19.9 Hz), 84.26 (1C, d, *J*=2.5 Hz), 114.84 (1C, s), 108.54 (1C, d, *J*=234.0 Hz). ^{19}F NMR δ=−127.19 (1F, dd, *J*=66.5, 14.6 Hz). HRMS (EI) Calcd for $C_{14}H_{27}O_4FSiNa$ (M^++Na) 329.1561. Found 329.1567.

(**9d**-β), IR (neat) 2932, 1858, 1472, 1381, 1258, 1215, 1108, 838 cm^{-1}. ^1H NMR δ=5.74 (1H, d, *J*=62.9 Hz), 4.80–4.73 (2H, m), 4.39–4.35 (1H, m), 3.75–3.71 (1H, m), 3.56–3.51 (1H, m), 1.47 (3H, s), 1.34 (3H, s), 0.90 (9H, s), 0.07 (3H, s), 0.06 (3H, s). ^{13}C NMR δ=−5.32 (1C, s), −5.30 (1C, s), 18.44 (1C, s), 25.08 (1C, s), 26.01 (3C, s), 26.51 (1C, s), 63.77 (1C, s), 81.19 (1C, s), 85.17 (1C, d, *J*=40.5 Hz), 89.22 (1C, d, *J*=2.5 Hz), 112.81 (1C, s), 115.61 (1C, d, *J*=222.5 Hz). ^{19}F NMR δ=−114.94 (1F, dm, *J*=62.9 Hz).

3.4.5. 2,3-*O*-Isopropylidene-5-*O*-(*m*-methylbenzoyl)-α-D-ribofuranosiyl fluoride (9e-α). IR (neat) 2986, 1723, 1383, 1278, 1200, 1105, 745 cm^{-1}. ^1H NMR δ=7.80–7.78 (2H, m), 7.38–7.23 (2H, m), 567 (1H, dd, *J*=64.9, 3.4 Hz), 4.76–4.67 (3H, m), 4.53–4.34 (3H, m), 2.38 (3H, s), 1.56 (3H, s), 1.36 (3H, s). ^{13}C NMR δ=21.23 (1C, s), 25.67 (1C, s), 25.71 (1C, s), 63.94 (1C, s), 79.41 (1C, s), 81.03 (1C, d, *J*=20.7 Hz), 81.79 (1C, d, *J*=1.7 Hz), 108.01 (1C, d, *J*=235.3 Hz), 116.00 (1C, s), 126.64 (1C, s), 128.37 (1C, s), 129.30 (1C, s), 130.13 (1C, s), 134.11 (1C, s), 138.33 (1C, s), 166.12 (1C, s). ^{19}F NMR δ=−130.22 (1F, dd, *J*=14.6, 65.3 Hz). HRMS (ESI) Calcd for $C_{16}H_{19}O_5F$ (M^+) 310.1217. Found 310.1216.

(**9e**-β), IR (neat) 2990, 1724, 1383, 1278, 1200, 745 cm^{-1}. ^1H NMR δ=7.85–7.83 (2H, m), 7.37–7.29 (2H, m), 5.80 (1H, d, *J*=61.7 Hz), 4.85–4.81 (2H, m), 4.70–4.65 (1H, m), 4.39–4.36 (2H, m), 2.38 (3H, s), 1.47 (3H, s), 1.32 (3H, s). ^{13}C NMR δ=21.23 (1C, s), 24.87 (1C, s), 26.29 (1C, s), 64.50 (1C, s), 80.94 (1C, s), 84.99 (1C, d, *J*=40.5 Hz), 86.37 (1C, d, *J*=2.5 Hz), 113.66 (1C, d, *J*=107.5 Hz), 116.41 (1C, s), 126.87 (1C, s), 128.30 (1C, s), 129.42 (1C, s), 130.25 (1C, s), 134.02 (1C, s), 138.23 (1C, s), 166.20 (1C, s). ^{19}F NMR δ=−116.39 (1F, dt, *J*=61.7, 3.7 Hz).

3.4.6. 2,3,4-Tri-*O*-(*m*-methylbenzoyl)-α-D-xylopyranosyl fluoride (9f). IR (neat) 2957, 1733, 1590, 1185, 739, 681 cm^{-1}. ^1H NMR δ=7.89–7.80 (6H, m), 7.41–7.33 (4H, m), 7.25–7.16 (2H, m), 5.80 (1H, d, *J*=48.8 Hz), 5.67 (1H, s), 5.32 (1H, s), 5.23 (1H, s), 4.60 (1H, d, *J*=15.9 Hz), 4.11 (1H, d, *J*=18.5 Hz), 2.41 (3H, s), 2.26 (3H, s), 2.23 (3H, s). ^{13}C NMR δ=21.02 (1C, s), 21.11 (1C, s), 21.25 (1C, s), 60.70 (1C, s), 68.99 (1C, s), 69.13 (1C, s), 71.23 (1C, d, *J*=24.8 Hz), 104.26 (1C, d, *J*=229.9 Hz), 126.86–138.28 (18C, s), 165.70 (1C, s), 165.77 (1C, s), 165.84 (1C, s). ^{19}F NMR δ=−137.56 (1F, dd, *J*=48.8, 4.9 Hz). HRMS (EI) Calcd for $C_{29}H_{27}O_7F$ (M^+) 506.1741. Found 506.1744.

Acknowledgements

We are grateful to Mitubishi Gas Chemical Company Inc. for their donation of DFMBA and its ARC data.

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SmI_2-Mediated 3-*exo*-trig cyclisation of δ-oxo-α,β-unsaturated esters to cyclopropanols and derivatives

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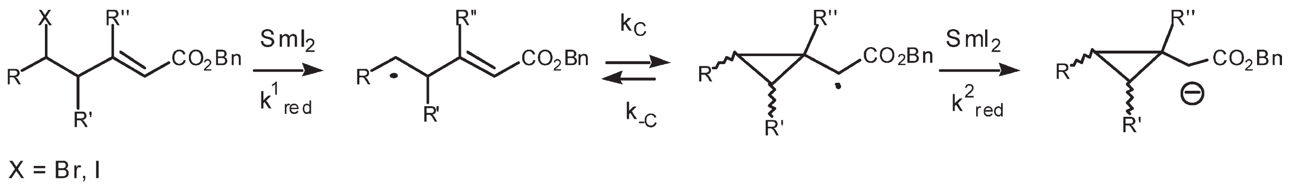
Received 12 March 2004; revised 19 May 2004; accepted 21 May 2004

Abstract—In the presence of samarium diiodide and a proton source, δ-oxo-γ,γ-disubstituted-α,β-unsaturated esters of general formula R–CO–C(R′,R′)–CH=CH–CO_2Bn readily cyclise to *trans*-cyclopropanol products and/or lactones derived from the *cis* isomers. For R=aryl, good stereoselectivities (ca 90%) in favor of the alcohols are generally obtained while a mixture of alcohols and lactones is obtained with R=alkyl or H. For R=cyclopropyl, the lactone is exclusively obtained in more than 90% yield. A mechanistic rationalisation of these variations of diastereoselectivity is proposed.

1. Introduction

In the past 20 to 30 years, radical cyclisations have been extensively used, often with great success, for obtaining carbocycles, especially five-membered and to a lesser extent six-membered ring systems. Meanwhile, few radical cyclisations have been described, which lead to cyclopropanes. This paucity of results is easily accounted for by the fact that, contrary to 5-*exo*-trig cyclisations which are usually fast and irreversible, 3-*exo*-trig radical cyclisations, albeit kinetically feasible, are on the other hand usually thermodynamically strongly disfavored. Indeed, in the parent system, cyclisation of the homoallyl radical is somewhat 10^4 times slower ($k_C=1.0\times10^4\ s^{-1}$ vs $k_{-C}=1.3\times10^8\ s^{-1}$ at 25 °C)[1] than reopening of the cyclopropylmethyl radical. As a result, only homoallylic systems with very specific features have been successfully cyclised to cyclopropane molecules under exclusive radical conditions. Such specific features include structural constraints[2] or the presence of groups able, once the cyclopropylcarbinyl radical is formed, either to stabilise it[3] or to involve it into further fast radical reactions such as cyclisations[2e,f] (cascade processes) or fragmentations (β-elimination of thiyl group).[4]

A few years ago, we reported that δ-bromo and δ-iodo-α,β-unsaturated esters could be cyclised to cyclopropane compounds in the presence of two equivalents of samarium diiodide and a proton donor (typically *tert*-butanol).[5] The success of this procedure was attributed to the known ability of SmI_2 to promote radical-anionic tandem reactions, a property that has extensively been used for various synthetic purposes.[6a,b] In our case, the following mechanism has been proposed[5] (Scheme 1): the homoallylic radical initially formed by monoelectronic reduction of the starting halide cyclises to α-carbalkoxy-substituted cyclopropylcarbinyl radical. Despite the presence of the carbalkoxy substituent, kinetic measurements have shown that this equilibrated process is still in favor of the open radical form, albeit to a lesser extent than in the parent system (k_c/k_{-c}=ca 10).[7] This, however, is of no consequence as the displacement of the overall reaction towards cyclisation is ensured by



Scheme 1.

Keywords: Samarium diiodide; Radical cyclisations; Cyclopropanols; Ketyl radicals.
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doi:10.1016/j.tet.2004.05.074

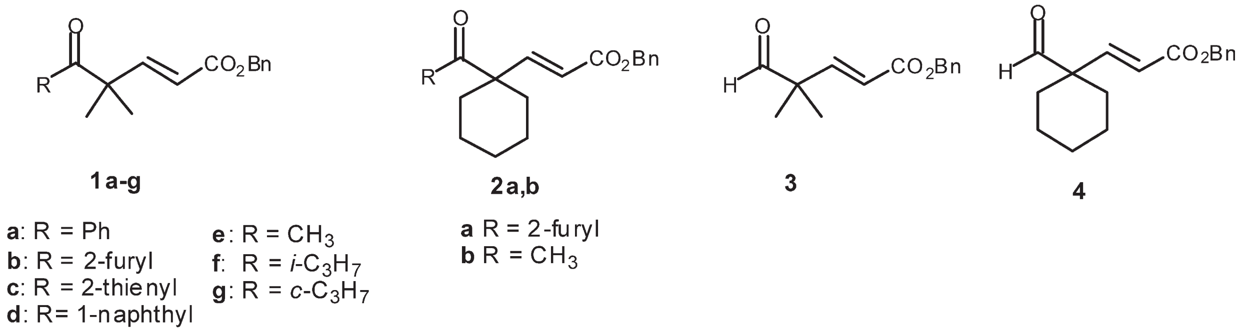
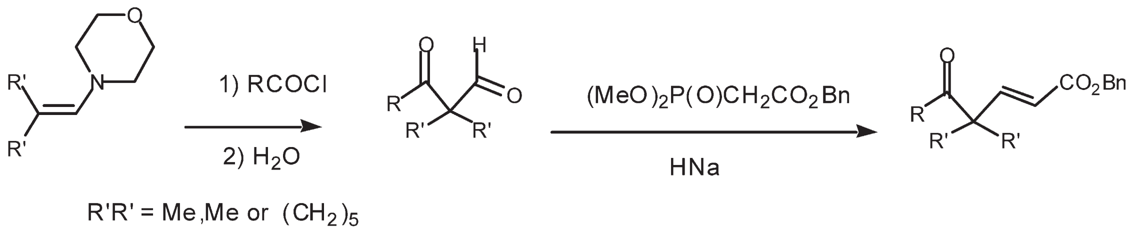


Figure 1.



Scheme 2.

subsequent and irreversible facile monoelectronic reduction of the cyclopropylcarbinyl radical to the corresponding enolate.† We later showed[8] that considerable racemisation was observed in the cyclisation of enantioenriched δ-halo-α,β-unsaturated esters bearing a substituent at the γ-position. Such racemisation was accounted for by assuming that reopening of the cyclopropylcarbinyl radical is probably faster that its reduction to enolate ($k_{-c}>k^2_{red}$ [SmI_2] in Scheme 1).

Notwithstanding the racemisation problem, the SmI_2 mediated cyclisation of δ-halo-α,β-unsaturated esters was found to tolerate the presence of various substituents at the β, γ and δ positions (α-position was not tested in this respect). Unfortunately, the diastereoselectivities of these reactions are low and mixtures of *cis* and *trans* substituted cyclopropanes were usually obtained in comparable amounts. We then turned our attention to the cyclisation of δ-oxo-α,β-unsaturated esters as a way to obtain cyclopropanols through formation of the corresponding ketyl radicals and their subsequent intramolecular addition on the double bond. It was hoped that better diastereoselectivities would be attained in these reactions. Indeed, many examples of related SmI_2 promoted 5-*exo*-trig, 6-*exo*-trig and even 4-*exo*-trig cyclisations of ζ- η- and ϵ-oxo-enoates respectively can be found in the literature. These reactions often display very good stereoselectivities[9] due to the fact that in the transition state, the C–O bond of the ketyl radical and the C=C bond conjugated to the carbalkoxy group adopt preferentially, for stereoelectronic reasons, an antiparallel relationship.[10] Steric effects or coordination to samarium of various functional groups in the substrate molecule may however complicate the stereochemical issue.[11]

A preliminary communication on the cyclisation of δ-oxo-α,β-unsaturated esters had already been issued[12] essentially dealing with aldehydic substrates. We present here a full report of our work which includes aromatic and alkyl ketones. For reasons that will be later specified some cyclisations of aldehydic compounds were also reinvestigated. Several results given in our preliminary communication were thus found erroneous and have been consequently revised.

2. Results

2.1. Synthesis of substrates for cyclisation

In order to avoid any complication which could arise from accidental migration of the double bond from α,β to β,γ position, we have limited our studies to γ,γ-disubstituted δ-keto enoates of general formula **1**–**4** (Fig. 1) Those include aromatic substrates **1a**–**d** and **2a**, alkyl ketones **1e**–**g** and **2b** and aldehydic compounds **3** and **4**. Most ketonic substrates were synthesized by the two-step procedure of Scheme 2. In the first step, acylation of morpholino-enamines derived from isobutyraldehyde or cyclohexane–carboxaldehyde with the appropriate acyl chloride followed by hydrolytic work-up, as described by Inukai and Yoshigawa,[13] gave the corresponding β-keto-aldehydes. In a second step, Wadsworth–Emmons condensation under standard conditions with benzyl dimethoxyphosphono-acetate gave the desired products. Probably due to more severe steric crowding, acylation of isobutyraldehyde morpholino-enamine with isobutyryl chloride and with naphthoyl chloride gave very poor results.

† An analogous radical–anionic tandem process has been proposed to explain the formation of cyclopropyl ring in some nickel complex catalysed electroreductive cyclisations: Ozaki, S.; Matsui, E; Waku, J.; Ohmori, H. *Tetrahedron Lett*. **1997**, *38*, 2705–2708. See also Gassman, P. G.; Lee, C. J. *J. Am. Chem. Soc.*, **1989**, *111*, 739–740.

At this point of our investigation, we became aware of another publication[14] showing that acylation of pyrrolidino-enamines takes place much more readily than that of morpholino-enamines. Indeed, acylation of isobutyraldehyde pyrrolidino-enamine with 1-naphthoyl chloride gave after hydrolytic work-up the desired β-keto-aldehyde in very satisfactory yield. As to 3-oxo-2,2,4-trimethylpentanal, on the way to **1f**, it was prepared by aldol autocondensation of isobutyraldehyde in fair yield[15] followed by oxidation with PCC.

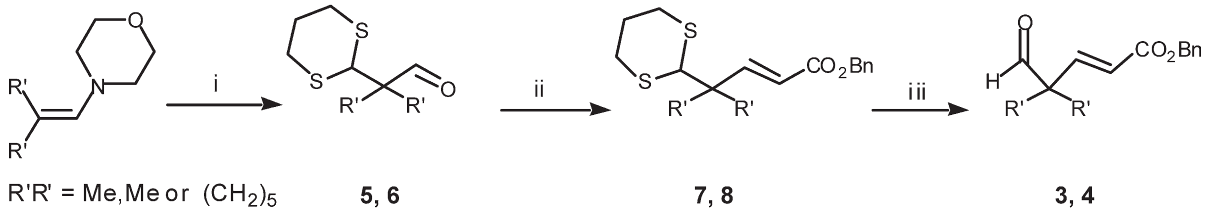
As reported in our preliminary communication, the aldehydic substrates **3** and **4** were prepared in three steps. Morpholino-enamines derived from isobutyraldehyde or cyclohexane–carboxaldehyde were first alkylated with 2-chloro-1,3-dithiane.[16] Hydrolytic work-up gave dithiane aldehydes **5** and **6** that were submitted to Wadsworth–Emmons olefination. The latent aldehydic function was finally unmasked by hydrolysis of the dithiane group in water/acetone in the presence of methyl iodide and collidine[17] (Scheme 3).

2.2. Cyclisations: procedure and experimental results

SmI_2-mediated cyclisations were conducted under inert (argon) dry atmosphere. The procedure was generally as follows: a 0.2 M solution of substrate in THF also containing 4 equiv. of *tert*-butanol was cooled to 0 °C. 2.2 equiv. of a 0.1 M solution of SmI_2 in THF was added dropwise through a cannula over a period of approximately 2 min. The reaction mixture was then stirred at room temperature for several (usually four to twelve) hours until TLC analysis on aliquots showed total consumption of the substrate. The reaction mixture was then quenched with dilute aqueous HCl. After standard work-up, the crude residue was first analysed by NMR and then submitted to column chromatography in order to isolate pure compounds. For a number of substrates, the reaction was carried out twice with different batches of SmI_2 solution with good reproducibility. Experimental procedures other than that described above—especially inverse addition and reactions carried out in the additional presence of four equivalents of HMPA—were also sometimes investigated. Since no significant differences in the outcome of the reaction were observed, they are not reported here.

In most cases only products of reductive cyclisation (Fig. 2) were obtained in our experiments. However, uncyclised products of direct reduction of the carbonyl (alcohol **9**) or of direct reduction of the carbon–carbon double bond (saturated ester **10**) were also found, in minor amounts, in the reaction of methyl ketone **2b** and isopropylketone **1f** respectively. In no cases could products of pinacol coupling be detected. Products of reductive cyclisation were cyclopropanols **11** in which the hydroxyl group and the carbalkoxymethyl group are *trans* to each other relatively to the cyclopropane ring and/or lactones **12** undoubtedly originating from lactonisation of the preliminary formed *cis* stereoisomeric cyclopropanol adducts. In the following of the text, stereoisomers **11** will be referred to as '*trans* cyclopropanols'. On NMR spectra, the methylene protons α to carbonyl of lactones **12** display a very characteristic *AB*X system made of one doublet and one doublet of doublets (J_{AB}=ca 18 Hz, J_{AX}=ca 7 Hz, J_{BX}=0 Hz) while cyclopropanols **11** display the usual pair of doublets of doublets ($J_{BX}\neq 0$ Hz).

The main results of our investigations are summarised in the table. On the NMR spectra of the crude reaction products, only two benzylic signals usually showed up, one corresponding to the *trans* cyclopropanol adduct and the other to benzyl alcohol. If we assume that all benzyl alcohol comes from lactonisation of the primarily formed *cis* cyclopropanol adduct, the *anti*/*syn* selectivity can also be deduced from the relative intensity of the NMR benzylic peaks. In the table, we have therefore reported both *anti*/*syn*



i: 2-chloro-1,3-dithiane, then H_2O; ii: $(MeO)_2P(O)CH_2CO_2Bn$, HNa; iii: H_2O, MeI, collidine, water/acetone.

Scheme 3.

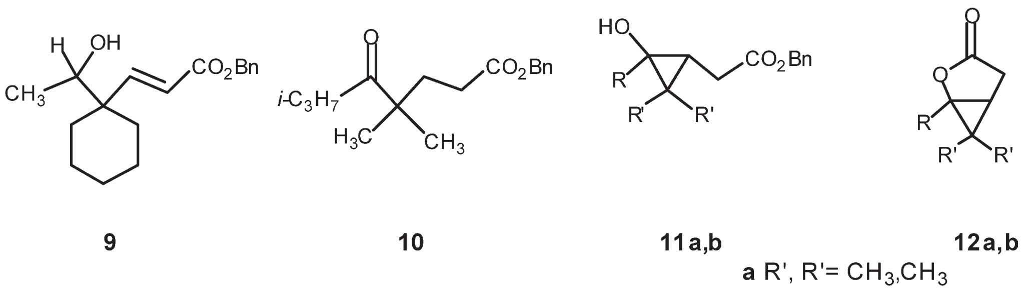
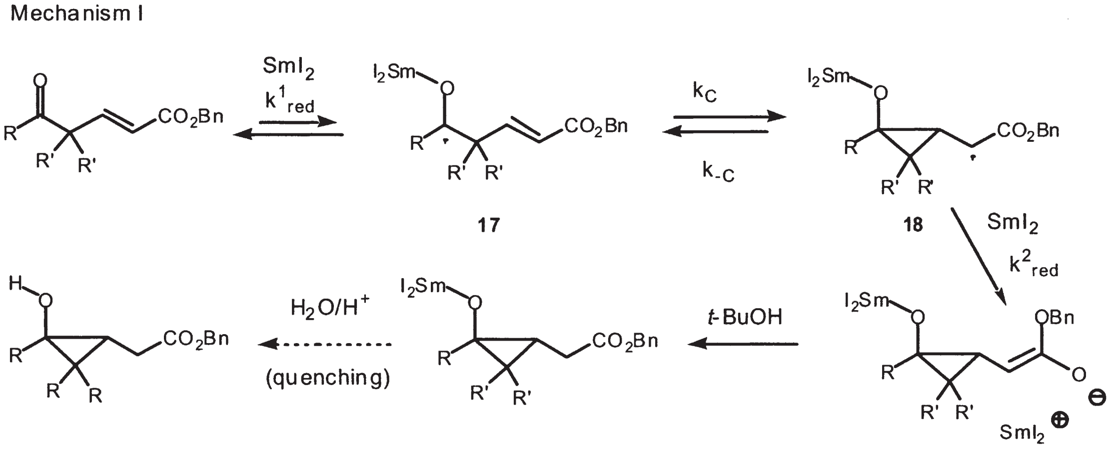


Figure 2.



Scheme 4.

selectivities deduced on the one hand from the respective amounts of *trans* cyclopropanol and lactone isolated by chromatography and on the other hand from NMR of the crude reaction mixture. A fair agreement between the two values was generally observed.

Aromatic ketonic substrates (entries 1–4) were found to give usually in high yield and with complete or very high stereoselectively *trans* cyclopropanols and only small amounts of lactones. With the more sterically encumbered 1-naphthyl substrate **1d** however, the proportion of lactones becomes important (entry 5). Concerning the cyclisation of alkyl ketonic compounds (entries 6–8), a mixture of lactone and of *trans*-cyclopropanol in comparable amounts was obtained not only with isopropyl ketone **1f** but even with the less sterically demanding methyl ketone **1e** and **2b**. Surprisingly, exclusive formation of the lactone in close-to-quantitative yield was observed with the cyclopropyl compound **1g** (entries 9a–c).

Given the results obtained above with non-aromatic ketones, we decided to reinvestigate the cyclisation of some aldehydes because our previous observations that cyclisation takes places with exclusive *anti* selectivity seemed now dubious. Indeed, in this reinvestigation, we found that these substrates also lead to a mixture of *trans* cyclopropanols and of lactones (entries 10, 11). We also found that the yields of the reactions was somewhat poorer than with ketonic compounds, but neither uncyclised products of direct reduction, nor products of pinacol coupling were detected.

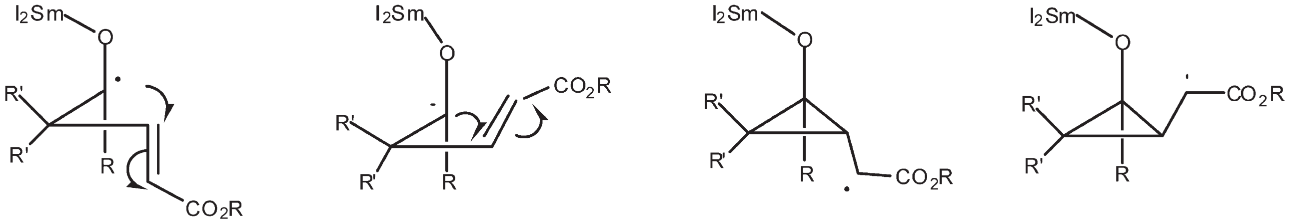
3. Discussion

In our opinion, the collection of results presented here is too limited to allow for a complete understanding of the mechanisms by which δ-oxo α,β-unsaturated esters cyclise in the presence of SmI_2. We will therefore limit ourselves to some broad comments and mechanistic proposals must be considered more as working hypotheses for further investigation rather than as definite statements.

Reduction of ketones to ketyl radicals is notoriously thermodynamically much more favorable with aryl than with alkyl ketones. From a kinetic point of view, recent rate constant measurements with SmI_2 as the one electron reducing agent have shown that the reaction is 10^4 more rapid with acetophenone than with 2-butanone.[18] On the basis of these considerations, the following mechanism (mechanism I, Scheme 4) may be proposed for cyclisation of our arylic substrates. The keto group is first reduced most probably in a reversible way[18,19] to ketyl radical **17** which then adds to the double bond to give the cyclopropylcarbinyl radical **18**.[‡] Further reduction to enolate by a second molecule of SmI_2 followed by protonation completes the reaction. Mechanism I is therefore akin to the one proposed earlier by ourselves for the cyclisation of δ-halo-α,β-unsaturated esters (see Scheme 1). It also corresponds to what is generally invoked for SmI_2 promoted intermolecular condensation of conjugated enoic esters with carbonyl compounds[20] and, as already mentioned, for SmI_2 promoted 4-*exo*, 5-*exo* and 6-*exo*-trig cyclisations of ϵ-,ζ- and η-oxo-enoates.[9] Therefore, in the present 3-*exo*-trig cyclisations, the *anti* stereoselectivity observed with substrates **1a–c** and **2a** could likewise be the result of a preference for a *trans* relationship of the C–O bond of the ketyl radical and the carbon–carbon double bond of the enoate moiety in the transition states of cyclisation (Fig. 3, **A** preferred to **B**). However, an essential difference between 3-*exo*-trig cyclisations and 5- and 6-*exo*-trig-cyclisations is that the former are reversible while the latter are not.[§] As a result, in

[‡] It is thus assumed that cyclisation takes place at the radical stage. A reaction sequence involving first two-electron reduction of the carbonyl group and then cyclisation cannot be totally ruled out. However, the fact that the cyclisation reactions are carried out in the presence of a proton donor renders improbable a cyclisation at an anionic stage. For other arguments in disfavor of anionic cyclisations (including the case where the initial two-electron reduction occurs at the carbon–carbon double bond of the enoate moiety instead of carbonyl) see Ref. 5 and references cited therein.

[§] 4-*exo*-trig cyclisations are potentially reversible but the k_{-c} constant for ring opening of cyclobutyl methyl ketyl radical (2.5×10^4 s^{-1} at 25 °C) is at least three orders of magnitude smaller than that for cyclopropyl methyl ketyl radical.[23] Therefore, the probability for a rapid equilibration between open and cyclised radicals in samarium promoted reductice cyclisation of ϵ-oxo-α,β-unsaturated esters [9a–f] appears low. An isolated example of reductive opening by SmI_2/DMPU, of an α-ketocyclobutane ring within a fused tricyclic system, has been reported (Comins, D. L.; Zheng, X. *J. Chem. Soc.Chem. Commun.* **1994**, 2681–2682). Probably, in this rigid structure, the fragmentation process is greatly facilitated by favorable orbital overlapping.



A B C D

Figure 3.

our case the argument based on stereoelectronic preferences in the transition state of cyclisation holds true only if the retrocyclisation process is slow compared to the irreversible reduction of cyclopropylcarbinyl radical to enolate ($k_{-c} \ll k^2_{red}$ [SmI_2] in Scheme 4). In the reverse limit case ($k_{-c} \gg k^2_{red}$ [SmI_2]), application of the Curtin–Hammet principle[21] leads to the conclusion that the *anti/syn* selectivity depends now on the relative energy of the transition states leading from the *trans* and *cis* cyclopropylcarbinyl radicals **C** and **D** to the corresponding enolates. As pointed out in our preliminary communication,[12] the *trans* (*anti*) selectivity could then be explained by the development of strong repulsive electronic interactions during the reduction of the *cis* radical **D** to carbanion. At the present time of our investigation, it is difficult to ascertain which one (if any) of these two situations prevails. But the second one (fast equilibrium between homoallylic and cyclopropylcarbinyl radicals before further reduction to enolate) seems to us more in keeping with our past results on the cyclisation of δ-halo-α,β-unsaturated esters[8] (*vide supra*) as well as with the relative ease of formation and stability of aromatic ketyl radicals. It may be recalled that the ring opening of (2-phenylcyclopropyl)methyl radical **13** (Fig. 4) is among the fastest radical reactions calibrated to date with $k_{-c}=1.6\times10^{11}\ s^{-1}$ at 20 °C.[22] To the best of our knowledge, no kinetic data are available at the present time concerning the ring opening of 2-phenylcyclopropyl methyl ketyl radical **14**. Meanwhile ring opening of (2-phenylcyclopropyl) phenyl ketyl radical **15** is at least 10^5 to 10^6 faster than that of cyclopropyl phenyl ketyl radical **16** ($k_{-c}=3\times10^5$ to $3\times10^6\ s^{-1}$ vs $\leq 2\ s^{-1}$ at 25 °C).[23]

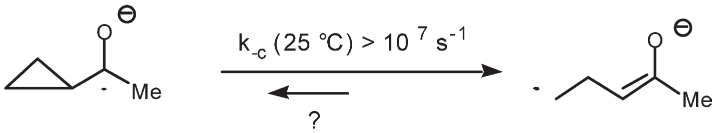
13 X = H
14 X = O$^-$
15 R = Ph
16 R = H

Figure 4.

The increase in the proportion of lactone in the cyclisation of the 1-naphthyl substrate **1d** must be the result of steric effects that may be of two kinds: direct in favouring the formation of the less crowded *cis* cyclopropanol adduct, indirect in preventing coplanarity of the aromatic ring and the ketonic group due to unfavorable steric interactions between the *peri*-hydrogen of the naphthyl group with the carbonyl group on one side and with the *gem*-dimethyl group on the other side. Compound **1d** would thus react more like an alkyl ketonic compound than like an aryl ketonic compound.[24]

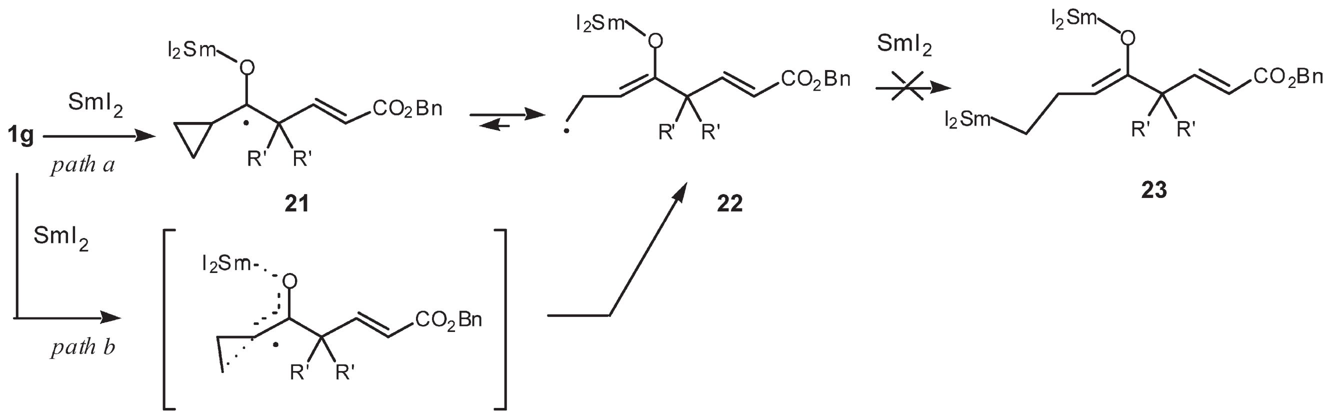
A most intriguing result of our investigation concerns the total selectivity observed in favor of the formation of lactone in the case of the cyclopropylketone substrate **1g**. The cyclisation of this substrate in which a potential cyclopropylcarbinyl-homoallyl type rearrangement is used as a radical probe was undertaken in the hope that it could be give helpful information as to the mechanism of cyclisation. Other examples of utilization of such cyclopropyl radical probes in SmI_2 mediated reactions may be found in the literature.[9e–f,25]

In a recent work,[23] Tanko and co-workers have shown that cyclopropyl-methyl ketyl radicals **19** rapidly open into distonic radical anion **20** with a k_{-c} constant at least equal to and probably higher than $10^7\ s^{-1}$ (25 °C) (Scheme 5). Several examples of ring opening of cyclopropylketones in the presence of one electron reducing system such as Li in NH_3[26] or SmI_2[25a,25c,27] or under photon induced electron transfer[28] may be found in the literature. In our case, we may expect that monoelectronic reduction of the carbonyl group is immediately followed by or takes place concomitantly with (vide infra) ring opening leading to distonic radical **22** (Scheme 6). Probably due to a strong preference for *Z* configuration of the enolate double-bond (the *E*-isomer could cyclise in a 6-*exo*-trig fashion on the enoate moiety), **22** cannot undergo further chemical transformations other than reduction to a homoallylic organosamarium species **23** by a second molecule of SmI_2. Obviously this second reduction does not take place *under our conditions* since we do not observe the corresponding protonated adduct. In other words, in the case of cyclopropyl substrate **1g** the ketyl



19 **20**

Scheme 5.

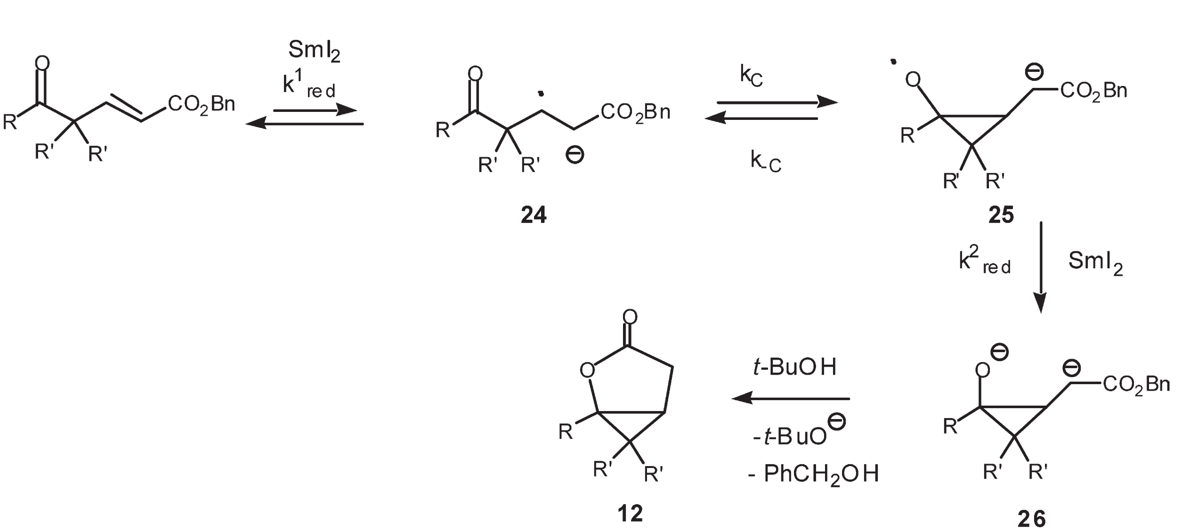


Scheme 6.

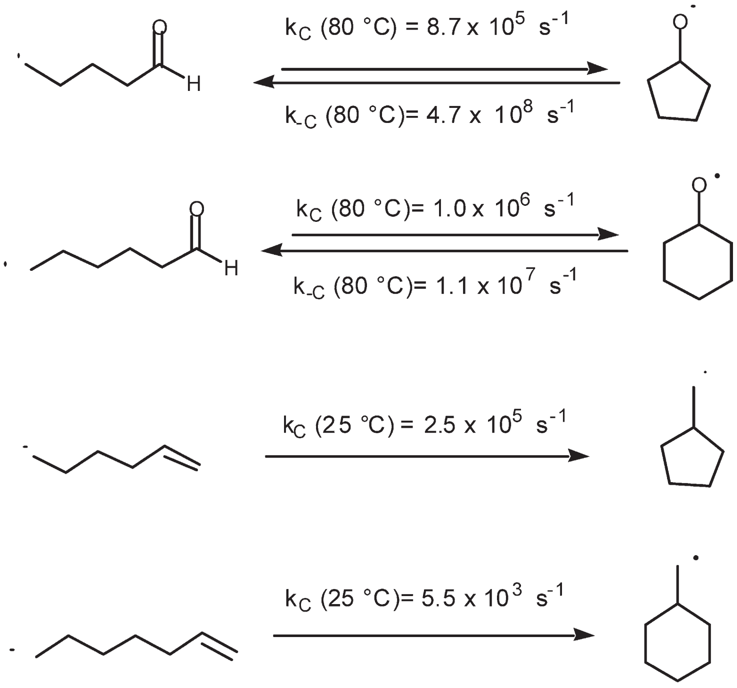
radical pathway is unproductive. We therefore propose for cyclisation of the cyclopropyl substrate a mechanism (mechanism II, Scheme 7) which starts with one electron reduction of the enoate moiety to radical anion **24**. Subsequent radical 3-*exo*-trig cyclisation on the carbonyl group leads to the cyclopropanoxy radical **25**. Finally, reduction of the cyclopropanoxy radical to dianion **26** could be extremely fast, thus displacing the reaction towards cyclisation. The reason why this cyclisation takes place with *syn* selectivity, leading ultimately to lactone **12** will be discussed later.

Before discussing mechanism II in some more details, it should be clearly stated that the proposal of a switch from mechanism I to mechanism II for cyclisation of cyclopropylketone **1g** on the ground that the ketyl radical pathway would now be unproductive relays on two assumptions that would need confirmation. The first one is that ring opening to distonic radical **22** is a reversible process. Reversibility of cyclopropane ring opening in the case of *aryl* cyclopropyl ketyl radical is well established.[23,29] This even includes[23,29b,] aryl cyclopropyl ketones bearing an extra phenyl group at the 2-position of cyclopropane (i.e., **15**, Fig. 4) despite the fact that such substitution induces stabilization of the open distonic form. On another hand, no data concerning putative reversibility of ring opening of *alkyl* cyclopropyl ketyl radical is available at the present time. The second one is that one-electron reduction of the carbonyl group and opening to distonic radical **22** by C–C bond breaking should in some way be concerted (Scheme 6, path b). Indeed, in the case of a stepwise mechanism going through the formation of a discrete ketyl radical **21** (path a), the existence of a further equilibrium between **21** and distonic radical **22** is not supposed to affect the *relative* proportions of ketyl radical **21** and radical anion **24**. Therefore, the reversible formation of **22** should not induce cyclopropyl ketone **1g** to cyclise according to mechanism II rather than mechanism I. Recent electrochemical investigations by Tanko and co-workers,[23] however, have led these authors to consider the stepwise mechanism as more probable.

Concerning now the plausibility of mechanism II itself and in support of it, α,β-unsaturated esters are known to be easily reduced by SmI_2 to radical anions. Those, in turn, can be further reduced to saturated esters[30] or give homo coupling products in dependance of the exact reaction conditions.[31] Intramolecular coupling involving 3-*exo* and



Scheme 7.



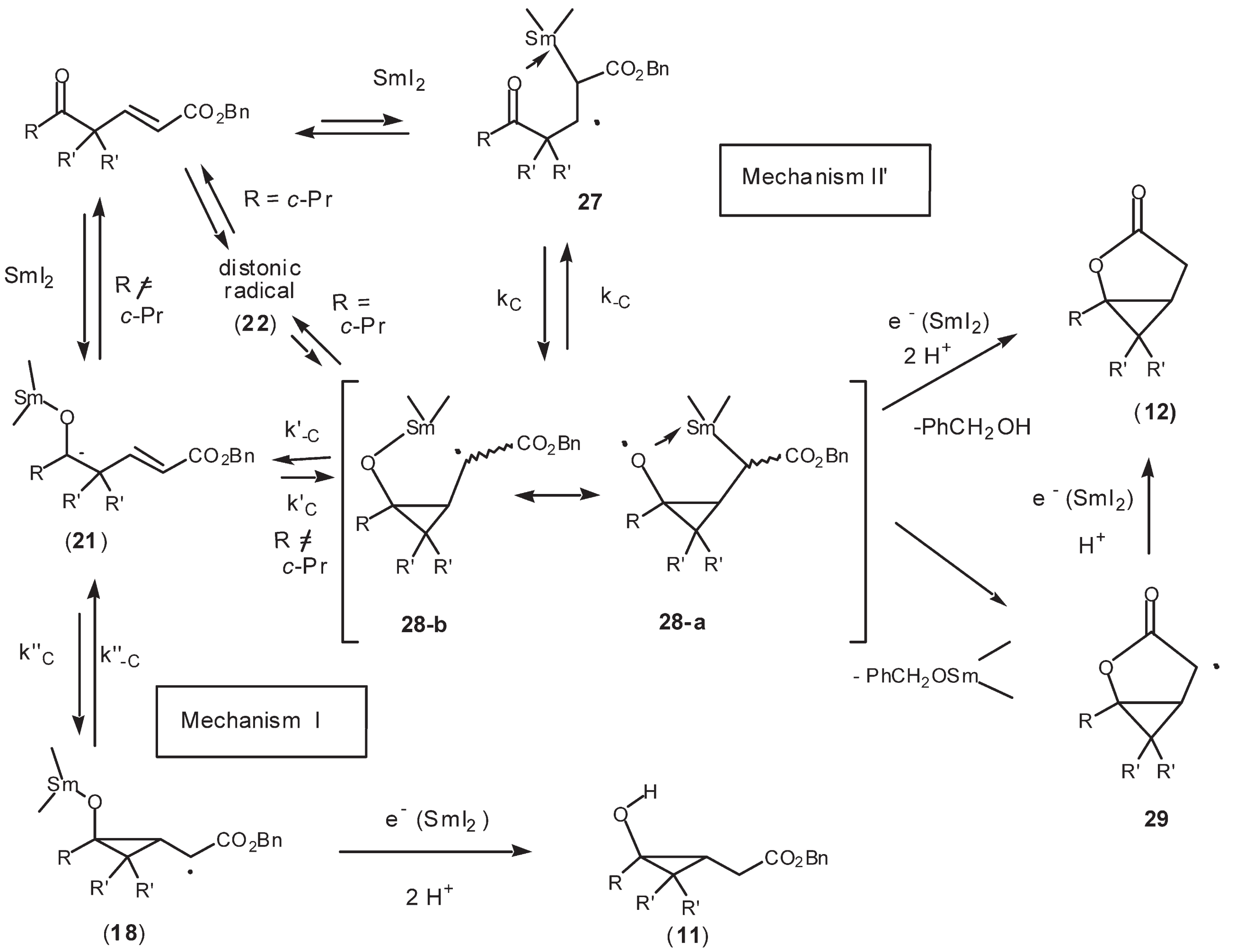
Scheme 8. [33]

6-*exo*-trig cyclisations of bis-enoates have also been reported.[31a] On a different ground, additions of alkyl radical onto carbonyl groups constitute a well-documented class of reactions, even if their utilisation for synthetic purpose[32] is much more limited than radical additions on ethylenic double bonds. This fact can be readily explained by comparison of kinetic data[33] concerning 5- and 6-*exo*-trig cyclisations of ethylenic and aldehydic parent systems as represented in Scheme 8. In both cases, reactions are fast but in the case of carbonyl compounds, the process is less favorable because they are reversible with a k_{-c} cyclo-reversion constant substantially higher than k_c. To the best of our knowledge, no kinetic data concerning either cyclisation of 3-oxo-propyl radical to cyclopropanoxy radical or cycloreversion of the latter species are available in the literature. However it may be inferred that this equilibrium, if it does take place, is largely displaced towards the open form. This of course is not in favor of mechanism II. It should nevertheless be noted that the formation of cyclopropanoxy radical have been postulated in other radical transformations for instance in the tin induced ring expansion of α-halomethyl[34] or other[35] ketones or in some tin induced 1,2 group migrations within radical species that are related to coenzyme B_{12} mediated rearrangements.[36],[¶] Samarium diiodide[37] and more recently zinc and indium powder mediated[38] ring expansion of α-halomethyl cyclic β-keto esters have also been reported but in these cases it is difficult to decide whether these reactions truly involve the formation of cyclopropanoxy intermediates or follow an ionic pathway.

The main problem associated with mechanism II lays in the difficulty to account for *syn* selectivity. We may suspect that, as it is often the case, chelation of samarium plays a crucial role. We tentatively propose mechanism II′ being well aware of its speculative character. Mechanism II′, as represented in the right upper part of Scheme 9 is a further elaboration of mechanism II in which problems of stereochemistry and of coordination to samarium are more specifically addressed. Cyclisation of radical anion **27** under chelation control leads to the cyclopropanoxy radical **28a** tautomeric with the α-carbalkoxy substituted radical form **28b**. **28a**,**b** may undergo cycloreversion back to **27** or to ketyl radical **21** when R≠cyclopropyl. When R is cyclopropyl this last process is replaced by double cycloreversion back to distonic radical **22** which do not react further. Reduction to the dianionic species therefore seems the only possible evolution for the cyclopropyl substrate. After subsequent lactonisation–protonation in situ and/or during work-up, lactone **12** is finally produced. Alternatively, lactonisation may take place within **28a**,**b** to give **29** thus locking at this stage the molecule in the *cis* configuration.

The obtention of mixtures of *trans* cyclopropanols and lactones with aldehyde and alkyl ketone substrates could signify that both mechanisms I and II′ take place concurrently. If so, an additional supposition must however be made for the sake of consistency. Since ketyl radical **21** is the starting point of mechanism I, cycloreversion of **28-a**,**b** to **21** must not be too fast as compared to its further reduction to **12** or its lactonisation to **29**. Otherwise,

¶ Moreover, as pointed out by Curran,[25a] the alkoxy radical is likely to exist not as a free species, but coordinated to samarium(III) as represented in Scheme 9, species **28a** (vide infra). By further electron transfer from samarium, **28a** may also be seen[25a] as a carbo-alkoxy dianionic organic entity coordinated to samarium(IV).



Scheme 9.

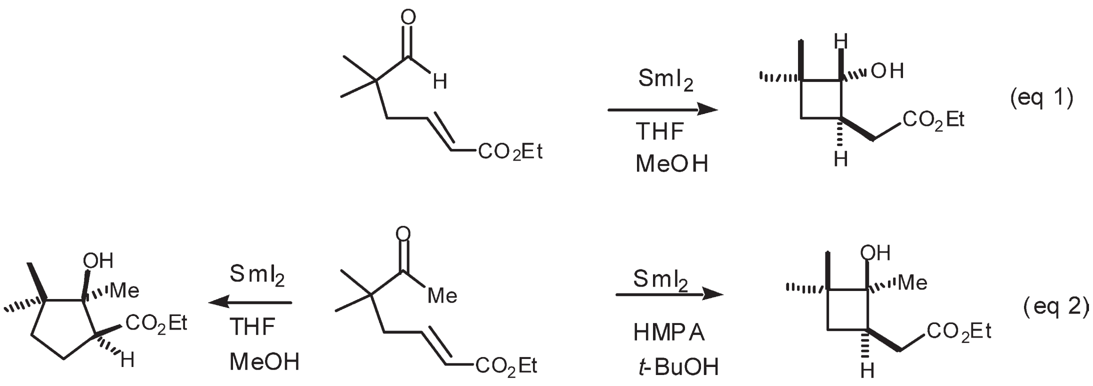
mechanism I (Schemes 4 and 9, left lower part) would ultimately operate.[‖]

The (partial) change of mechanism on going from aromatic ketones to aldehydes and alkyl ketones would reflect the less favorable formation of the ketyl radical. Interestingly an analogous change of mechanism—but this time on going from aldehydes to alkyl ketones—has been proposed by Procter and co-workers in the samarium mediated cyclisation of ϵ-oxo-α,β-unsaturated esters in THF/MeOH.[9e] According to the authors, aldehydic compounds (Eq. 1, Scheme 10) that lead to cyclobutanols with complete *anti*-selectivity, cyclise by addition of the ketyl radical onto the enoate moiety, i.e. according to mechanism I. In the case of methylketone that lead to carbalkoxysubstituted cyclopentanols (Eq. 2), the reaction on the contrary would start by the reduction of the enoate moiety to radical anion. Radical 4-*exo*-trig cyclisations being rather slow,[39] a competitive way would then be preferred. Protonation of the radical anion followed by one electon reduction would give the ester enolate which would finally add to the carbonyl group in a 5-*exo*-trig fashion. Interestingly, if the reaction is conducted in the absence of methanol, but only in THF with 6 equiv. of HMPA and 3 equiv. of *tert*-butanol, a 4-*exo*-trig cyclisation now takes place but with a *syn* stereoselectivity opposite to that observed with aldehydes in THF/MeOH. This switch of reactivity upon change of alcohol cosolvent has, since then, been confirmed on other related substrates by the same authors.[9f]

4. Conclusion

In the presence of SmI_2, δ-oxo-γ,γ-disubstituted-α,β-unsaturated esters readily undergo 3-*exo*-trig cyclisation. High or total diastereoselectivities in favor of the formation of '*trans*' cyclopropanol in which the OH group and the carbalkoxymethyl group are *trans* to each other are generally observed with substrates bearing a terminal aryl substituent. Total opposite stereoselectivity leading ultimately to the lactone derived from '*cis*' cyclopropanol is observed when the terminal substituent is cyclopropyl.

‖ On the contrary, as already discussed, ring opening of **28ab** should be very fast for aryl substrates. Therefore, even if initial reduction should occur at the enoate moiety also for these substrates—for us an unlikely hypothesis—a fast equilibration between radical **28** and **18** would very likely take place rapidly. The *syn*/*anti* stereoselectivity would therefore still be related to the relative energies of the transition states leading from the radical species **28** and **18** to the dianionic species, or alternatively to the relative energies of the transition states leading from **18** to dianionic species on one hand and from **28** to **29** (lactonisation) on the other hand.



Scheme 10. [9e]

Finally when the δ-carbon bears an hydrogen atom (aldehydic substrates) or an alkyl group, a mixture of '*trans*' cyclopropanol and lactone is obtained.

'Trans' cyclopropanols are thought to arise from initial formation of ketyl radicals followed by cyclisation. On the contrary, the favored (but not necessarily exclusive) pathway to lactone would start by one electron reduction of the enoate moiety and the stereochemical issue of the reaction would be the result of samarium chelation in the cyclisation step.

5. Experimental

5.1. General information

^{1}H NMR spectra were recorded at 200 or 250 MHz and ^{13}C spectra at 63 MHz. Chemical shifts are quoted in ppm relative to TMS. High resolution mass spectra (HRMS) were obtained on a Finningan-MAT-95-S spectrometer. Infra-red spectra were taken on a Perkin-Elmer 'Spectrum One' model and in $CHCl_3$ solution.

5.2. Preparation of starting compounds

5.2.1. Preparation of β-keto-aldehydes RCOC(R′R′)-CHO with R′, R′=Me, Me or $(CH_2)_5$. For R=Ph, 2-furyl, 2-thienyl, CH_3, c-C_3H_7 and R′, R′=Me, Me, the β-keto-aldehydes were prepared by condensation of acyl chlorides with the morpholino-enamine of isobutyraldehyde[35] as described by Inukai and Yoshizawa.[13] The acetylation procedure was followed for acylation with aliphatic acyl chlorides and the benzoylation procedure was followed for acylation with aromatic acyl chlorides. The β-ketoaldehyde $CH_3COC(RR')CHO$ ($R'R'=(CH_2)_5$) was prepared in the same way by acetylation of the morpholino-enamine of cyclohexane carboxaldehyde according to the first procedure. i-$C_3H_7COC(CH_3)_3CHO$ was prepared by aldol autocondensation of isobutyraldehyde[15] followed by oxidation of the aldol product with pyridinium chlorochromate.[40] 1-naphthyl-$COC(CH_3)_2CHO$ was prepared by acylation of isobutyraldehyde pyrrolidino-enamine[41] with 1-naphthoyl chloride according to Kuhlmey et al.[14] Probably better yields would have been obtained if other β-ketoaldehydes had similarly been prepared from pyrrolidino-enamines instead of morpholino-enamines.

R′, R′=Me, Me; R=CH_3: 2,2-Dimethyl-3-oxo-butanal. Yield 66% (crude product); oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.60 (s, 1H); 2.09 (s, 3H); 1.34 (s, 6H).

R′, R′=Me, Me; R=i-C_3H_7: 3-Oxo-2,2,4-trimethylpentanal. Yield (over two steps, see above): 38%; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.61 (s, 1H); 2.92 (sept, J=7 Hz, 1H); 1.32 (s, 6H); 1.04 (d, J=7 Hz, 6H).

R′, R′=Me, Me; R=c-C_3H_7: 3-Cyclopropyl-2,2-dimethyl-propanal. Purified by distillation, bp 60 °C, 5 Torr; yield 40%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.58 (s, 1H); 2.07–1.9 (m, 1H); 1.37 (s, 6H); 1.05–0.92 (m, 2H); 0.92–0.80 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 208.9; 201.1; 60.3; 17.7; 10.7; 7.4. IR ($CHCl_3$): 1729.5, 1692 cm^{-1}.

R′, R′=Me, Me; R=Ph: 2,2-Dimethyl-3-oxo-3-phenylpropanal. Purified by column chromatography (AcOEt/cyclohexane 10:90); yield 50%; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H); 7.82–7.25 (m, 5H); 1.45 (s, 6H). IR ($CHCl_3$): 1731.5, 1675.5 cm^{-1}.

R′, R′=Me, Me; R=2-furyl: 2,2-Dimethyl-3-(2-furyl)-3-oxo-propanal. Yield 66% (crude product); oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.4 (s, 1H); 7.54 (d, ^3J=1.0 Hz, 1H); 7.17 (d, ^3J=4.5 Hz, 1H); 6.49 (dd, ^3J=4.5, 2.0 Hz, 1H); 1.4 (s, 6H). IR ($CHCl_3$): 1732, 1664 cm^{-1}.

R′, R′=Me, Me; R=2-thienyl: 2,2-Dimethyl-3-oxo-3-(2-thienyl)-propanal. Yield 74% (crude product); oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (s, 1H); 7.65 (d, ^3J=1.0 Hz, 1H); 7.63 (d, ^3J=5 Hz, 1H)); 7.11–7.07 (m, 1H); 1.49 (s, 6H). IR ($CHCl_3$): 1728, 1653 cm^{-1}.

R′, R′=Me, Me; R=1-naphthyl: 2,2-Dimethyl-3-(1-naphthyl)-3-oxo-propanal. Yield (crude product): 70%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.79 (s, 1H); 9.10 (d, J=8.5 Hz, 1H); 8.75 (d, J=8.5 Hz, 1H), 8.59 (d, J=8 Hz, 1H), 8.19–8.08, 7.96–7.84, 7.77–7.32 (three m, 3H); 1.50 (s, 6H). HRMS (EI) calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.0990. IR ($CHCl_3$): 1687, 1727.5 cm^{-1}.

R′, R′=$(CH_2)_5$; R=CH_3: 1-Acetyl-cyclohexanecarboxaldehyde: Purified by column chromatography (AcOEt/cyclohexane 20:80); yield 30%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.43 (s, 1H); 2.09 (s, 3H); 2.08–1.26 (m, 10H). IR ($CHCl_3$): 1731, 1699 cm^{-1}.

R′, R′=$(CH_2)_5$; R=2-furyl: 1-(2-Furoyl)-cyclohexanecarboxaldehyde: Purified by chromatography; yield 45%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 (s, 1H); 7.43 (d, J=1.5 Hz, 1H); 7.08 (d, J=3.5 Hz, 1H); 6.38 (dd, J=1.5, 3.5 Hz, 1H); 1.48–1.21 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.7; 186.5; 151.2; 146.0; 118.9; 112.1; 49.5; 28.5; 25.5; 21.8.

5.2.2. Preparation of benzyl δ-oxo-α,β-unsaturated esters 1a–g and 2a,b. 1a–g and **2a**,**b** were prepared by Wadsworth–Emmons olefination of β-keto-aldehydes with benzyl dimethoxyphosphonoacetate.[42] The experimental procedure was the same as that used by Nicolaou and co-workers[43] for Wadsworth–Emmons olefination of 3-oxo-2,2-dimethyl-l pentanal with *tert*-butyl diethoxyphosphonoacetate. Purification of crude products was achieved by column chromatography on silica with appropriate mixtures of AcOEt and heptane or cyclohexane as the eluents.

Benzyl 4,4-dimethyl-5-oxo-5-phenyl-pent-2-enoate (**1a**). Purified by column chromatography (AcOEt/cyclohexane 10:90); yield 77%; oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.15 (m, 11H); 6 (d, ^3J=15 Hz, 1H); 5.15 (s, 2H); 1.41 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 202.8; 166.5; 153.8; 136.6; 136.1; 132.6; 129.5; 128.9; 128.8; 128.7; 128.6; 120.4; 66.9; 50.1; 26.3. IR ($CHCl_3$): 1717, 1681.5, 1642 cm^{-1}.

Benzyl 4,4-dimethyl-5-(2-furyl)-5-oxo-pent-2-enoate (**1b**). Purified by column chromatography (AcOEt/cyclohexane 10:90); yield 63%; white solid mp 53 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, J=2 Hz, 1H); 7.29 (m, 6H); 7.13 (d, J=4 Hz, 1H); 6.42 (dd, J=2, 4 Hz, 1H); 5.90 (d, ^3J=16 Hz, 1H); 5.12 (s, 2H); 1.40 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 189.6; 166.2; 152.0; 146.0; 135.2; 128.5; 128.3; 120.1; 119.3; 112.0; 66.1; 48.8; 24.3. IR ($CHCl_3$): 1716.5, 1669, 1645 cm^{-1}.

Benzyl 4,4-dimethyl-5-oxo-5-(2-thienyl)-pent-2-enoate (**1c**). Purified by column chromatography (AcOEt/cyclohexane 10:90); yield 80%; white solid mp: 69 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d, J=4 Hz, 1H); 7.6–7.05 (m, 8H); 6.08 (d, ^3J=16 Hz, 1H); 5.20 (s, 2H); 1.48 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.5; 167.1; 153.4; 142.4; 136.1; 133.9; 133.7; 128.9; 128.7; 128.6; 128.3; 120.7; 66.4; 49.9; 25.9. IR ($CHCl_3$): 1717; 1694 (shoulder), 1646 cm^{-1}.

Benzyl 4,4-dimethyl-5-(1-naphthyl)-5-oxo-pent-2-enoate (**1d**). Purified by column chromatography (AcOEt/cyclohexane 20:80); yield 48%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97–7.28 (m, 13H); 6.03 (d, ^3J=16 Hz, 1H); 5.21 (s, 2H); 1.45 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.5; 167.1; 153.4; 136.1; 133.9; 133.7; 128.9; 128.7; 128.6; 128.3; 120.7; 66.4; 49.9; 25.9. HRMS (EI) calcd for $C_{24}H_{22}O_3$ 358.1569, found 358.1568. IR ($CHCl_3$): 1717, 1693.5, 1645 cm^{-1}.

Benzyl 4,4-dimethyl-5-oxo-hex-2-enoate (**1e**). Purified by column chromatography (AcOEt/cyclohexane 20:80); yield 75%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H); 7.05 (d, ^3J=16 Hz, 1H); 5.90 (d, ^3J=16 Hz; 1H); 5.14 (s, 2H); 2.07 (s, 3H); 1.23 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 208.8; 166.0; 135.6; 128.5; 128.3; 120.5; 66.4; 50.8; 25.9; 23.4. HRMS (EI) calcd for $C_{15}H_{18}O_3$ 246.1260, found 246.1256.

Benzyl 5-oxo-4,4,6-trimethyl-hept-2-enoate (**1f**). Purified by column chromatography (AcOEt/cyclohexane 15:85); yield 72%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H); 7.11 (d, ^3J=16 Hz, 1H); 5.94 (d, ^3J=16 Hz, 1H); 3.01 (sept, ^3J=7 Hz, 1H); 1.26 (s, 6H); 1.04 (d, ^3J=7 Hz, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 215.3; 166.4; 152.1; 136.1; 128.9; 128.6; 120.9; 66.8; 51.5; 36.0; 23.6; 20.3. IR ($CHCl_3$): 1710.5, 1646 cm^{-1}.

Benzyl 5-cyclopropyl-4-4,-dimethyl-5-oxo-pent-2-enoate (**1g**). Purified by column chromatography (AcOEt/heptane 20:80); yield 65%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43–7.12 (m, 5H); 7.16 (d, ^3J=16 Hz, 1H); 5.96 (d, ^3J=16 Hz, 1H); 5.17 (s, 2H); 2.08–1.95 (m, 1H); 1.30 (s, 6H); 1.05–0.92 (m, 2H); 0.92–0.80 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.9; 166.4; 152.6; 136.1; 128.8; 128.5; 128.4; 120.7; 66.6; 51.0; 23.7; 17.4; 12.0 HRMS (EI) calcd for $C_{17}H_{20}O_3$ 166.0993, found 166.0991; IR ($CHCl_3$) 1716.5, 1698, 1647 cm^{-1}.

Benzyl 3-[1-(2-furoyl) cyclohexyl]-prop-2-enoate (**2a**). Purified by column chromatography (AcOEt/heptane 20:80); yield 27%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (d, J=1.5 Hz, 1H); 7.31 (m, 6H); 7.16 (d, J=3.5 Hz, 1H); 6.45 (dd, J=1.5, 3.5 Hz, 1H); 5.90 (d, ^3J=16 Hz, 1H); 5.14 (s, 2H); 2.17–1.41 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 189.3; 166.1; 156.4; 146.4; 135.7; 128.5; 128.1; 121.9; 118.8; 111.8; 65.9; 52.9; 33.4; 25.5; 22.4. HRMS (EI) calcd for $C_{21}H_{22}O_4$ 338.1518, found 338.1512.

Benzyl 3-(1-acetylcyclohexyl)-prop-2-enoate (**2b**). Purified by column chromatography (AcOEt/cyclohexane 10:90); yield 74%; white solid; mp 47 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5H); 6.87 (d, ^3J=16 Hz, 1H); 5.89 (d, ^3J=16 Hz, 1H); 5.16 (s, 2H); 2.08 (s, 3H); 1.99–1.40 (m, 10H) ^{13}C NMR (63 MHz, $CDCl_3$) δ 208.5; 166.3; 151.5; 136.1; 128.9; 128.7; 122.5; 66.8; 55.7; 32.9; 26.5; 25.9; 22.9. HRMS (EI) calcd for $C_{18}H_{22}O_3$: 274.1574, found 274.1574. IR ($CHCl_3$): 1708.5, 1643 cm^{-1}.

5.2.3. Preparation of 2-(1,3-dithian-2-yl)-2-methylpropanal 5 and 1-(1,3-dithian-2-yl) cyclohexane carboxaldehyde 6. 5 and **6** were prepared by alkylation of the morpholino-enamines of isobutyraldehyde and cyclohexanecarboxaldehyde, respectively, with 2-chloro-1,3-dithiane. The procedure of Taylor and LaMattina was followed.[16]

2-(1,3-dithian-2-yl)-2-methylpropanal (**5**). Purified by vacuum distillation bp 56–57 °C, 0.1 Torr; yield 72% on a 40 mmol scale; white solid; mp: 50 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.41 (s, 1H); 4.25 (s, 1H); 3.01–2.58 (m, 4H); 2.07–1.69 (m, 2H); 1.10 (s, 6H). ^{13}C NMR (63 MHz,

$CDCl_3$) δ 202.2; 54.9; 49.9; 30.9; 25.6; 19.3. HRMS (EI) calcd for $C_8H_{14}OS_2$: 190.0485, found 190.0487.

1-(1,3-Dithian-2-yl)cyclohexanecarboxaldehyde (**6**). Purified by Kügelrohr distillation (180 °C, 0.03 Torr); yield 33% on a 20 mmole scale; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.52 (s, 1H); 4.16 (s, 1H); 3.20–2.50 (m, 4H); 2.03–1.17 (m, 12H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.9; 54.8; 52.7; 31.0; 28.6; 25.6; 24.5; 21.9. HRMS (EI) calcd for $C_{11}H_{18}OS_2$: 230.0795, found 230.0799.

5.2.4. Preparation of benzyl 4-(1,3-dithian-2-yl)-4-methylpent-2-enoate 7 and benzyl 4-[1-(1,3-dithian-2-yl)cyclohexyl]-but-2-enoate 8. Benzyl 4-(1,3-dithian-2-yl)-4-methylpent-2-enoate **7**: in a Schlenk tube and under argon atmosphere, 0.22 g (5.5 mmol) of sodium hydride 60% in oil was washed twice with dry pentane and put in suspension in 45 mL of anhydrous THF at 0 °C. To this suspension 1.42 g (5.5 mmol) of benzyl dimethylphosphonoacetate was added dropwise. After cessation of dihydrogen gas evolution a solution of 0.95 g (0.5 mmol) of 2-(1,3-dithian-2-yl)-2-methyl-propanal **5** was slowly added while the temperature was maintained near 0 °C. The reaction mixture was then refluxed for 5 h. The reaction mixture was cooled and water was first cautiously and then more rapidly added. The organic products were extracted with diethyl ether. The organic phase was dried over $MgSO_4$, filtrated and concentrated under vacuum to give 1.45 g (90% yield, oil) of crude benzyl 4-(1,3-dithian-2-yl)-4-methylpent-2-enoate which was found pure by NMR. This crude product was used as such in the following step.

Benzyl 4-(1,3-dithian-2-yl)-4-methylpent-2-enoate (**7**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5H); 7.04 (d, ^3J=14.5 Hz, 1H); 5.84 (d, ^3J=14.5 Hz, 1H); 5.14 (s, 2H); 4.05 (s, 1H); 2.86–2.75 (m, 4H); 2.07–1.76 (m, 2H); 1.23 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.2; 155.2; 135.8; 128.4; 128.0; 118.9; 66.1; 59.0; 41.5; 31.0; 25.6; 24.3; 19.3. HRMS (EI) calcd for $C_{17}H_{22}O_2S_2$: 322.1061, found 322.1063.

Benzyl 4-[1-(1,3-dithian-2-yl)-cyclohexyl]-but-2-enoate **8** was similarly prepared from 1-(1,3-dithian-2-yl)cyclohexanecarboxaldehyde **6**. In this case, the crude product was purified by column chromatography on silica (cyclohexane/AcOEt 95:5).

Benzyl 4-[1-(1,3-dithian-2-yl)-cyclohexyl]-but-2-enoate (**8**). Yield 95%; oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5H); 6.96 (d, ^3J=16 Hz, 1H); 5.90 (d, ^3J=16 Hz, 1H); 5.17 (s, 2H); 4.15 (s, 1H); 2.83 (dd, J=8, 3.5 Hz, 4H); 2.03 (m, 4H); 1.77 (m, 2H); 1.50–1.28 (m, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.2; 153.4; 135.9; 128.5; 128.2; 128.1; 121.7; 66.2; 58.3; 44.3; 33.2; 31.3; 28.95; 25.9; 25.7; 21.9. HRMS (EI) calcd for $C_{20}H_{26}O_2S_2$: 362.1374, found 362.1367.

5.2.5. Preparation of benzyl 4,4-dimethyl-5-oxo-pent-2-enoate 3 and benzyl 3-(1-formyl-cyclohexyl)-prop-2-enoate 4. Heating **7** or **8** in acetone/water in the presence of MeI and *sym*-collidine according to Redlich et al.[17] gave the corresponding aldehydes **3** or **4**.

Benzyl 4,4-dimethyl-5-oxo-pent-2-enoate **3**. Purified by column chromatography (petroleum ether/diethyl ether 80:20); yield 45%; oil. ^{1}NMR (250 MHz, $CDCl_3$) δ 9.33 (s, 1H); 7.26 (m, 5H); 6.92 (d, ^3J=14.5 Hz, 1H); 5.84 (d, ^3J=14.5 Hz, 1H); 5.09 (s, 2H); 1.18 (s, 6H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.7; 165.7; 149.2; 135.6; 128.5, 128.1; 121.5; 66.4; 49.1; 21.0. HRMS (EI) calcd for $C_{14}H_{16}O_3$: 232.1099, found 232.1100.

Benzyl 3-(1-formyl-cyclohexyl)-prop-2-enoate **4**. Purified by column chromatography (petroleum ether/diethyl ether 80:20); yield 74%. ^{1}HNMR (250 MHz, $CDCl_3$) δ 9.32 (s, 1H); 7.33 (m, 5H); 6.77 (d, ^3J=14.5 Hz, 1H); 5.88 d, ^3J=14.5 Hz, 1H); 5.15 (s, 2H); 1.90–1.32 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.8; 165.5; 148.4; 128.5; 128.3; 122.7; 66.4; 53.2; 30.5; 25.2; 22.0. HRMS (EI) calcd for $C_{17}H_{20}O_3$: 272.1412, found 272.1419.

5.3. SmI_2 mediated cyclisations

5.3.1. Preparation of SmI_2 solutions in THF. THF was distilled over benzophenone sodium and under an argon atmosphere. All experiments involving SmI_2 were carried out under an argon atmosphere using standard Schlenk techniques. Diiodoethane, used for preparation of SmI_2, was purified as follows: commercial 1,2 diodoethane was dissolved in diethyl ether and the ethereal solution was washed twice with aqueous sodium thiosulfate to remove any iodine. The organic phase was then dried on magnesium sulfate and then concentrated under vacuum to a small volume. The precipitated white solid was collected by filtration and dried on a vacuum line. All these operations were carried out in the dark.

0.1 M solutions of SmI_2 in THF were prepared in the following way: to 1.80 g (12 mmol) of samarium powder (from Labelcomat Company) was slowly added through a cannula and at room temperature a solution of 2.82 g of freshly purified 1,2-diiodoethane in 100 mL of THF. A blue-green coloration developed immediately and the reaction was somewhat exothermic. Once the addition was completed (after ca 20 min), the suspension was stirred for 12 h, upon which the reaction was considered as complete. The 0.1 M solutions of SmI_2 were of a deep blue color. They were kept as such in the presence of samarium powder in excess and under argon atmosphere for no more than 4 days.

5.3.2. Cyclisation reactions. General procedure: to a solution of 1 mmol of substrate to be cyclised and 4 mmol of *tert*-butanol in 5–6 mL of THF at 0 °C were added dropwise 22 mL (2.2 equiv.) of a 0.1 M solution of SmI_2 in THF. The reaction mixture was then stirred at room temperature with monitoring by TLC or IR spectroscopy on aliquots. Reaction were usually complete within 4–12 h. After quenching with dilute aqueous HCl, the products were extracted in diethyl ether. After drying ($MgSO_4$) and evaporation of ether, the residue was column chromatographied on silica with appropriate mixtures of ethyl acetate and heptane or cyclohexane as the eluents.

5.3.3. Physical and spectroscopic data for cyclisation products. All products were obtained as colorless oils.

5.3.3.1. Cyclopropanols 11a: (R′, R′=CH_3, CH_3). *R=H*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5H); 5.09 (s, 2H); 2.89 (d, ^3J=3 Hz, 1H); 2.29 (d, J=7.6 Hz, 2H); 1.13 (s, 3H); 0.93 (s, 3H); 0.91 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.6; 128.6; 128.2; 66.3; 61.8; 32.6; 27.3; 19.6; 19.3. HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1256. IR ($CHCl_3$): 1732.5 cm^{-1}.

R=Me: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5H); 5.15 (s, 2H); 2.27 (d, ^3J=8 Hz, 2H); 1.10 (s, 3H); 1.07 (s, 3H); 1.03 (t, ^3J=8 Hz, 1H); 0.88 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.3; 135.9; 128.5; 128.1; 66.3; 59.7; 30.6; 29.2; 26.9; 21.3; 17.0; 16.5. HRMS (EI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1423.

R=i-Pr: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H); 5.10 (s, 2H); 2.55–2.40 and 2.28–2.10 (two dd, *AB*X system J_{AB}=16.5 Hz, J_{AX}=6.5 Hz; J_{BX}=8.5 Hz, (1+1)H); 1.62–1.51 (m, 1H); 1.19 (s, 3H); 1.12–1.01 (m, 1H); 1.00–0.98 (m, 9H). HRMS (EI) calcd for $C_{17}H_{24}O_3$: 276.1725, found 276.1723. IR ($CHCl_3$): 1732 cm^{-1}.

R=Ph: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.15 (m, 10H); 5.12 (two d, AB system, J_{AB}=12 Hz, 2H); 2.58–2.41 and 2.18–2.05 (two dd, *AB*X system, J_{AB}=18 Hz, J_{AX}=7 Hz, J_{BX}=6.5 Hz, (1+1)H); 1.4 (s, 3H); 1.4–1.28 (m, 1H); 0.9 (s, 3H). HRMS (EI) calcd for $C_{20}H_{22}O_3$ 310.1569, found 310.1572. IR ($CHCl_3$): 1732 cm^{-1}.

R=2-furyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.31 (m, 6H); 6.31–6.22 (m, 2H); 5.15 (two d, AB system, J_{AB}=12 Hz, 2H); 2.61–2.51 and 2.37–2.26 (two dd, *AB*X system, J_{AB}=17.5 Hz, J_{AX}=7.5 Hz, J_{BX}=8 Hz, (1+1)H); 1.44–134 (m, 1H); 1.37 (s, 3H); 0.95 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.1; 153.5; 142.2; 135.9; 128.6; 128.3; 127.0; 110.1; 109.1; 66.5; 59.2; 31.6; 31.2; 26.2; 21.2; 17.9. IR ($CHCl_3$): 1732.5 cm^{-1}.

R=2-thienyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.20 (m, 6H); 6.87–6.72 (m, 2H); 5.08 (two d, AB system, J_{AB}=12 Hz, 2H), 2.63–2.51 and 2.35–2.23 (two dd, *AB*X system, J_{AB}=17.5 Hz, J_{AX}=7 Hz, J_{BX}=8 Hz, (1+1)H); 1.34 (m, 1H); 1.32 (s, 3H); 0.92 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.4; 142.7; 136.3; 129.0; 128.7; 128.0; 127.1; 126.6; 66.9; 60.9; 32.6; 32.1; 26.9; 21.8; 19.4. IR ($CHCl_3$): 1732.5 cm^{-1}.

R=1-naphthyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.1–7.7, 7.65–7.1 (two m, 12H); 5.25–5.12 (two broad d (app. q), AB system, 2H); 3.0–2.75 and 2.61–2.24 (two broad dd, *AB*X system, $J_{AB}\approx$16 Hz, $J_{BX}\approx$6 Hz; $J_{AX}\approx$8 Hz, (1+1)H); 1.59–1.39 (m, 4H); 0.65 (broad s, 3H). HRMS (EI) calcd for $C_{24}H_{24}O_3$ 360.1725, found 360.1710. IR ($CHCl_3$): 1732 cm^{-1}.

5.3.3.2. Cyclopropanols 11b: R′, R′=$(CH_2)_5$. *R=H*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.11 (s, 2H); 2.98 (d, 1H, ^3J=3.0 Hz); 2.44–2.20 (two close dd, *AB*X system J_{AB}=17 Hz, J_{AX}=7.5 Hz, J_{BX}=8.0 Hz, (1+1)H); 1.65–1.23 (m, 10H); 0.88 (dt, ^3J_d=3, ^3J_t=7.5 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0; 135.7; 128.5; 128.3; 128.0; 66.4; 50.8; 39.7; 25.9; 25.2; 23.4. HRMS (EI) calcd for $C_{17}H_{22}O_3$ 274.1574, found 274.1574. IR ($CHCl_3$): 1732 cm^{-1}.

R=CH_3: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41–7.24 (m, 5H); 5.11 (s, 2H); 2.41–2.14 (two close dd, ABX system J_{AB}=16 Hz, J_{AX}=7.5 Hz, J_{BX}=7.5 Hz, (1+1)H); 1.65–1.15 (m, 13H); 0.91 (t, ^3J=7.5 Hz, 1H). HRMS (EI) calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1723. IR ($CHCl_3$): 1731.5 cm^{-1}.

R=2-furyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (m, 6H); 7.30 (m, 1H); 6.23 (m, 1H); 5.12 (d, J=6 Hz, 2H); 2.60–2.47 and 2.40–2.32 (two dd, *AB*X system, J_{AB}=17 Hz, J_{AX}=7.5 Hz, J_{BX}=7.5 Hz (1+1)H); 1.80–1.12 (m, 11H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.1; 153.4; 142.0; 135.8; 128.5, 128.3; 127.6; 110.0; 108.7; 66.4; 59.7; 32.8; 31.5; 31.1; 31.0; 28.1; 26.3; 25.8; 25.1. HRMS (EI) calcd for $C_{21}H_{24}O_4$ 288.1725, found 288.1723. IR ($CHCl_3$): 1732 cm^{-1}.

5.3.3.3. Lactones 12a: R′, R′=CH_3, CH_3. *R=H*: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.95 (d, ^3J=6.3 Hz, 1H); 2.78–2.67 (dd) and 2.33 (d) (*AB*X system J_{AB}=21 Hz, J_{AX}=8 Hz, J_{BX}=0 Hz, (1+1)H); 1.02 (m, 7H). HRMS calcd for $C_7H_{10}O_2$ 126.0681, found 126.0677. IR ($CHCl_3$): 1775.5 cm^{-1}.

R=Me: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.80 (dd) and 2.11 (d) (*AB*X system J_{AB}=21.0 Hz, J_{AX}=7 Hz, J_{BX}=0 Hz, (1+1)H); 1.23–0.99 (m, 10H). HRMS (EI) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0840. IR ($CHCl_3$): 1772 cm^{-1}.

R=i-Pr: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.80–2.69 (dd) and 2.40 (d) (*AB*X system J_{AB}=19.0 Hz, J_{AX}=7.5 Hz, J_{BX}=0 Hz, (1+1)H); 1.85–1.71 (sept, ^3J=7 Hz, 1H); 1.16–0.99 (m, 13H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.5; 78.2; 31.4; 29.1; 25.5; 24.2; 22.4; 19.6; 18.6; 14.0; HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1148. IR ($CHCl_3$): 1771.5 cm^{-1}.

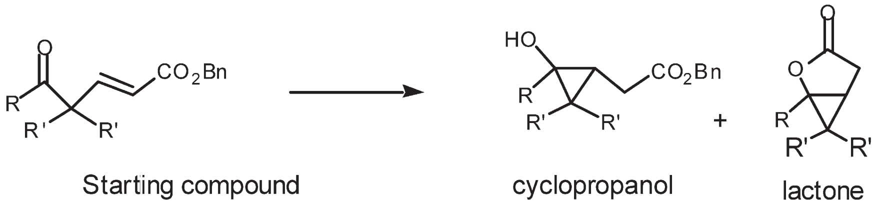
R=c-Pr: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.76–2.58 (dd) and 2.38 (d) (*AB*X system J_{AB}=19 Hz, J_{AX}=7.0 Hz, J_{BX}=0 Hz, (1+1)H); 1.44–1.43 (m, 1H); 1.17 (s, 3H); 1.03 (s, 3H), ca 1.02 (d, partially masked, 1H); 0.77–0.55 (m, 2H); 0.48–0.23 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.9; 76.1; 31.2; 26.1; 22.5; 22.1; 13.9; 9.4; 6.0; 4.0. HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0991. IR ($CHCl_3$): 1772 cm^{-1}.

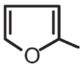
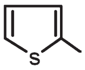
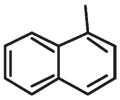
R=2-furyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43–7.35 (m, 1H); 6.45–6.34 (m, 2H); 3.04–2.93 (dd) and 2.54 (d) (*AB*X system J_{AB}=19 Hz, J_{AX}=7.5 Hz, J_{BX}=0 Hz, (1+1)H); 1.78 (d, ^3J=7.5 Hz, 1H); 1.18 (s, 3H); 1.02 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.1; 143.2; 111.2; 110.5; 67.7; 30.6; 27.5; 25.6; 22.8; 13.1. IR ($CHCl_3$): 1783 cm^{-1}.

R=2-thienyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.31 (m, 1H); 7.13–6.98 (m, 2H); 3.07–2.96 (dd) and 2.59 (d) (*AB*X system, J_{AB}=19 Hz, J_{AX}=7.5 Hz, J_{BX}=0 Hz, (1+1)H); 1.77 (d, ^3J=7.5 Hz, 1H); 1.17 (s, 3H); 1.02 (s, 3H). IR ($CHCl_3$): 1773 cm^{-1}.

R=1-naphthyl: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (d, J=8 Hz, 1H); 7.97–7.79, 7.64–7.42 (two m, 6H); 3.25–3.0 and 2.71 (dd and d, ABX system, J_{AB}=19 Hz, J_{AX}=7 Hz, J_{BX}=0 Hz, (1+1)H); 1.92 (d, ^3J=7 Hz, 1H); 1.41 (s, 3H);

Table 1.



Entry	Starting compound				Cyclopropanol **11** (%)[a]	Lactone **12** (%)[a]	*anti/syn* selectivity (S)	
	R	R′R′	No.				(A)[b]	(B)[c]
1	Ph	MeMe	**1a**		85	—	100/0	95/5
2a		MeMe	**1b**	Run 1	73	13	85/15	87/13
2b				Run 2	82	14	85/15	84/16
3		$(CH_2)_5$	**2a**		77	8	91/9	88/12
4		MeMe	**1c**		60	10	86/14	85/15
5a		MeMe	**1d**	Run 1	30	49	38/62	28/72
5b				Run 2	20	47	30/70	26/74
6a	CH_3	MeMe	**1e**	Run 1	60	22	73/27	71/29
6b				Run 2	55	23	70/30	66/33
7		$(CH_2)_5$	**2b**		52	30[d]	63/37	64/66
8a	*i*-C_3H_7	MeMe	**1f**	Run 1	58	35[e]	62/38	61/39
8b				Run 2	58	30[e]	66/34	70/30
9a	*c*-C_3H_7	MeMe	**1g**	Run 1	—	92	0/100	0/100
9b				Run 2	—	95	0/100	0/100
9c				Run 3	—	90	0/100	0/100
10	H	MeMe	**3**		37	30	55/45	53/47
11a				Run 1	30	21	59/61	54/46
11b		$(CH_2)_5$	**4**	Run 2	26	32	44/66	50/50

[a] Yields of pure compounds after separation by chromatography.
[b] Calculated from *S*=yield of **11**/yield of **12**.
[c] Deduced from NMR on crude reaction mixtures by integration of benzylic H peaks of **11** and of benzylic alcohol thus assuming that all benzyl alcohol is produced by lactonisation.
[d] 10% of alcohol of direct reduction **9** was also obtained.
[e] 8–10% of saturated ester **10** was also obtained.

0.79 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.6; 134,7; 134,1; 133.7; 130.2; 128.7; 128.6; 127.2; 126.6; 125.3; 74.6; 31.4; 31.3; 15.6; 13.7. HRMS (EI) calcd for $C_{17}H_{16}O_2$ 252.1147, found 252.1150. IR ($CHCl_3$): 1776 cm^{-1}.

5.3.3.4. Lactones 12b: R′, R′=$(CH_2)_5$. *R=H*: ^1H NMR (200 MHz, $CDCl_3$) δ 3.95 (d, ^3J=6.2 Hz, 1H); 2.80–2.60 (dd) and 2.32 (d) (*AB*X system, J_{AB}=19.0 Hz, J_{AX}=7.5 Hz; J_{BX}=0 Hz, (1+1) H); 1.54–1.16 (m, 11H). HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0985. IR ($CHCl_3$): 1775.5 cm^{-1}.

R=CH₃: ^1H NMR (250 MHz, $CDCl_3$) δ 2.87–2.76 (dd) and 2.40 (d) (*AB*X system, J_{AB}=19.0 Hz, J_{AX}=7.0 Hz; J_{BX}=0), (1+1) H); 1.79–1.15 (m, 13H); 1.06 (d, ^3J=7 Hz, 1H). HRMS (EI) calcd for $C_{11}H_{16}O_2$: 180.1150, found 180. 1147. IR ($CHCl_3$): 1770 cm^{-1}.

R=2-furyl: ^1H NMR (250 MHz, $CDCl_3$) δ 7.39 (m, 1H); 7.31 (m, 1H); 6.40 (m, 1H); 2.91 (dd) and 2.50 (d, *AB*X system, J_{AB}=19.0 Hz, J_{AX}=7.5 Hz, J_{BX}=0 Hz, (1+1) H); 1.72 (d, *J*=7.5 Hz, 1H); 1.65–1.12 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 178.0; 150.6; 143.1; 110.9; 110.4; 56.8; 32.6; 30.2; 26.0; 25.1; 24.7; 24.5; 23.6 (Table 1).

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Tetrahedron 60 (2004) 6945–6958
Tetrahedron

Synthesis of *meta*- and *para*cyclophanes containing unsaturated amino acid residues

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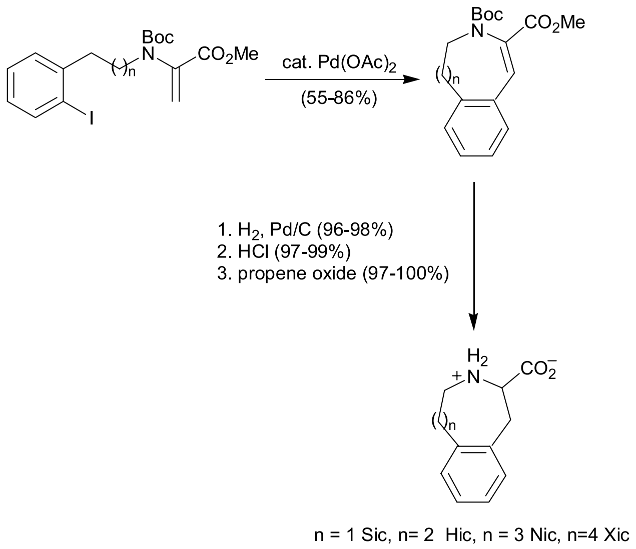
Received 9 February 2004; revised 13 May 2004; accepted 20 May 2004

Abstract—[7.7], [8.8], [9.9] and [13.13] *Para*cyclophanes and [9.9] and [13.13] *meta*cyclophanes containing two unsaturated amino acid residues have been synthesised. An X-ray crystallographic study of three of the *para*cyclophanes and molecular modelling of two *para*cyclophanes and two *meta*cyclophanes revealed two main structural types. The 'staggered' structure appears to be favoured by longer hydrocarbon chains, whilst the 'barrel' structure appears to be more accessible to compounds containing shorter hydrocarbon chains. The [9.9] *para*cyclophane has been hydrogenated and deprotected to give a saturated amino acid, and an alternative approach to key aldehydes is reported.

1. Introduction

The use of conformationally constrained amino acids to probe the binding mode of bioactive molecules to their receptors is a commonly used approach to the design of highly selective and active compounds.[1] Reducing the conformational freedom of a ligand may alter (a) the binding affinity of the ligand at a given receptor, (b) the selectivity of the ligand between different receptors, and (c) the stability of the ligand with respect to enzyme degradation. Examination of the effect of restricting the conformational freedom of a given ligand on these properties may lead to increased insight into the bioactive conformation of the ligand and hence ultimately to the generation of more potent and selective molecules.

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is a conformationally constrained phenylalanine analogue that has been used to considerable effect in medicinal chemistry, its presence in ligands having been shown to influence both affinity and selectivity.[2] We synthesised the seven-, eight-, nine- and ten-membered analogues of Tic that is Sic, Hic, Nic and Xic (Scheme 1), postulating that the incorporation of this novel series of compounds with varying degrees of conformational constraint into biologically active peptides or non-peptides would lead to greater insight into the conformational preferences of the ligand under investigation and the nature of its interaction with the active site. We tested this hypothesis initially on a non-peptide cholecystokinin-2 (CCK_2) receptor antagonist, in which Phe was a key component. Replacement of the Phe in the antagonist with Tic, Sic, Hic, Nic and Xic and subsequent



Scheme 1.

Keywords: Cyclophane; Macrocycle; Heck reaction; Amino acid.

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doi:10.1016/j.tet.2004.05.062

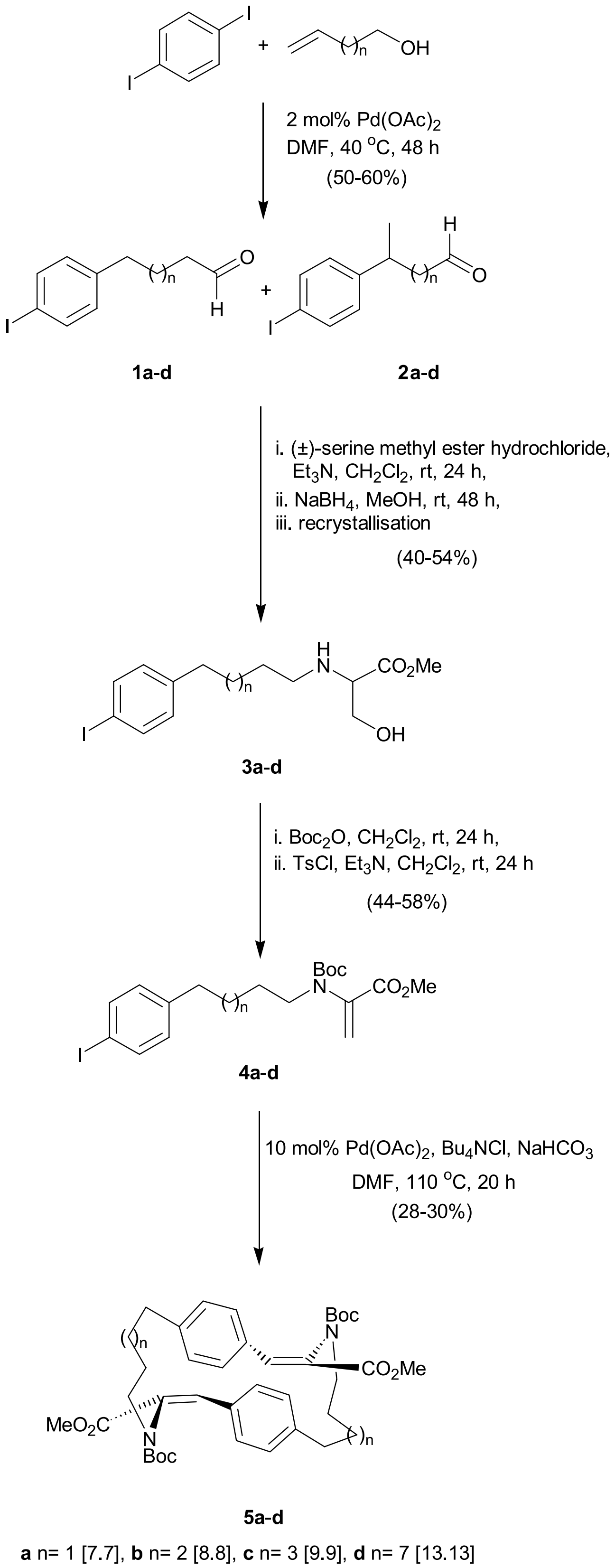
biological analysis revealed that the size of the conformational constraint directly impinged upon the in vitro profile of the constrained ligands.[3]

Sic, Hic, Nic and Xic were synthesised by a reaction sequence in which the key step was an intramolecular palladium-catalysed Heck coupling of iodoarenes tethered to dehydroalanine residues via a bridge between the *ortho*-carbon of the arene, and the nitrogen of the dehydroalanine residue (Scheme 1).[4] (The intermolecular version of this reaction, in which haloarenes are coupled with dehydroalanine derivatives to give dehydrophenylalanine derivatives, which can then be subsequently hydrogenated to phenylalanine derivatives, has been known for some time.[5])

In view of the successful intramolecular coupling of *ortho*-tethered systems, and the promising results obtained in the initial biological application of the amino acids synthesised using this reaction, we decided to undertake a study to determine the outcome of Heck coupling between iodoarenes and dehydroalanine residues tethered via *para* or *meta* bridges of varying lengths that is compounds represented by structures **4** and **17**, respectively. It was anticipated that this would lead to new conformationally constrained analogues of phenylalanine and shed more light on the scope and limitations of the intramolecular coupling of iododarenes and dehydroalanine residues. In view of the spatial constraints placed upon the coupling by the *para* and *meta* relationship between the halide and the tethering chain, it was envisaged that several products may be formed, and that their distribution would depend upon the length of the tether. The anticipated products included (i) the cyclisation products analogous to those observed using the *ortho* bridged systems depicted in Scheme 1, and (ii) acyclic or cyclic products formed by head-to-tail coupling of two or more substrate residues. We present herein a full account of the synthesis of compounds **4** and **17**, the outcome of the subsequent Heck reactions, the X-ray crystallographic and molecular modelling studies performed on the products of the Heck reactions, a hydrogenation study and the development of a new route to key aldehydes. Some of the work on the *para* bridged systems **4** formed the basis of a preliminary communication.[6]

1.1. Synthesis and cyclisation of *para* bridged substrates 4a–d

In order to easily change the tether length between the iodoarene and the dehydroalanine residue to be used in the Heck reaction, we initially proposed to use a method based on a literature Heck reaction between haloarenes and ω-hydroxyalkenes that forms ω-arylaldehydes.[7] As the literature study had been performed on relatively short ω-hydroxyalkenes, we elected to test our approach to the desired substrates **4** using the commercially available four-carbon ω-hydroxyalkene 3-buten-1-ol. Thus 3-buten-1-ol was heated with 1,4-di-iodobenzene in the presence of 2 mol% $Pd(OAc)_2$ (Scheme 2). Analysis of the resultant product mixture revealed that the linear aldehyde **1a** and the branched aldehyde **2a** had been formed (87:13). Thus carbopalladation of 3-buten-1-ol favours arylation of the terminal carbon of the alkene and palladation of the internal carbon.



Scheme 2.

Palladium-hydride elimination then produces the conventional Heck product. Subsequent palladium-hydride-catalysed migration of the alkene formed along the hydrocarbon chain generates an enol that tautomerises to the product aldehyde. Attempts to separate the branched regioisomer **2a** from its linear counterpart **1a** by various purification techniques proved unsuccessful, and experience eventually revealed that the branched isomer was most easily removed at the end of the next stage of the synthesis.

The mixture of aldehydes **1a** and **2a** was thus reacted with serine methyl ester and reduced with sodium borohydride. Crystallisation of the reductive amination product mixture from hexane and diethyl ether provided an analytically pure sample of **3a** uncontaminated with any branched product as determined by analysis of its ^{1}H and ^{13}C NMR spectra. Although crystallisation of **3a** proved to be a viable method for the elimination of the branched regioisomer, it is of note that it was sometimes impeded by facile oil formation. Finally protection of the amine of **3a** with Boc_2O followed by tosylation of the alcohol and a subsequent elimination reaction gave the desired *para* tethered substrate **4a** in which the dehydroalanine residue is connected to the *para*-iodoarene by a chain containing four carbon atoms.

Application of the Jeffery conditions for the Heck reaction[8] to **4a** gave a mixture of products. Careful column chromatography led to the isolation of one of the more mobile components of the mixture, which, after analysis of its spectroscopic and microanalytical data, was tentatively assigned as the cyclophane **5a**. Thus application of the Heck reaction to **4a** had led to head-to-tail coupling of two molecules of substrate. Examination of the crude product using spectroscopic techniques, and attempts to isolate and identify other components of the product mixture failed to provide evidence for a product of a simple intramolecular Heck reaction.

In order to test whether increasing the tether length between the iodoarene and the dehydroalanine residue would facilitate the formation and isolation of the intramolecular Heck product, substrates **4b–d** were synthesised using the commercially available ω-hydroxyalkenes 4-penten-1-ol, 5-hexen-1-ol and 9-decen-1-ol. Formation of **1b–d/2b–d**, **3b–d** and **4b–d** proceeded essentially as described above for **1a/2a**, **3a** and **4a** and all products were fully characterised by spectroscopic and analytical methods (synthetic methods and data available from the author on request).

Application of identical Heck conditions to **4b–d** to those used for **4a** led to the production and isolation of products

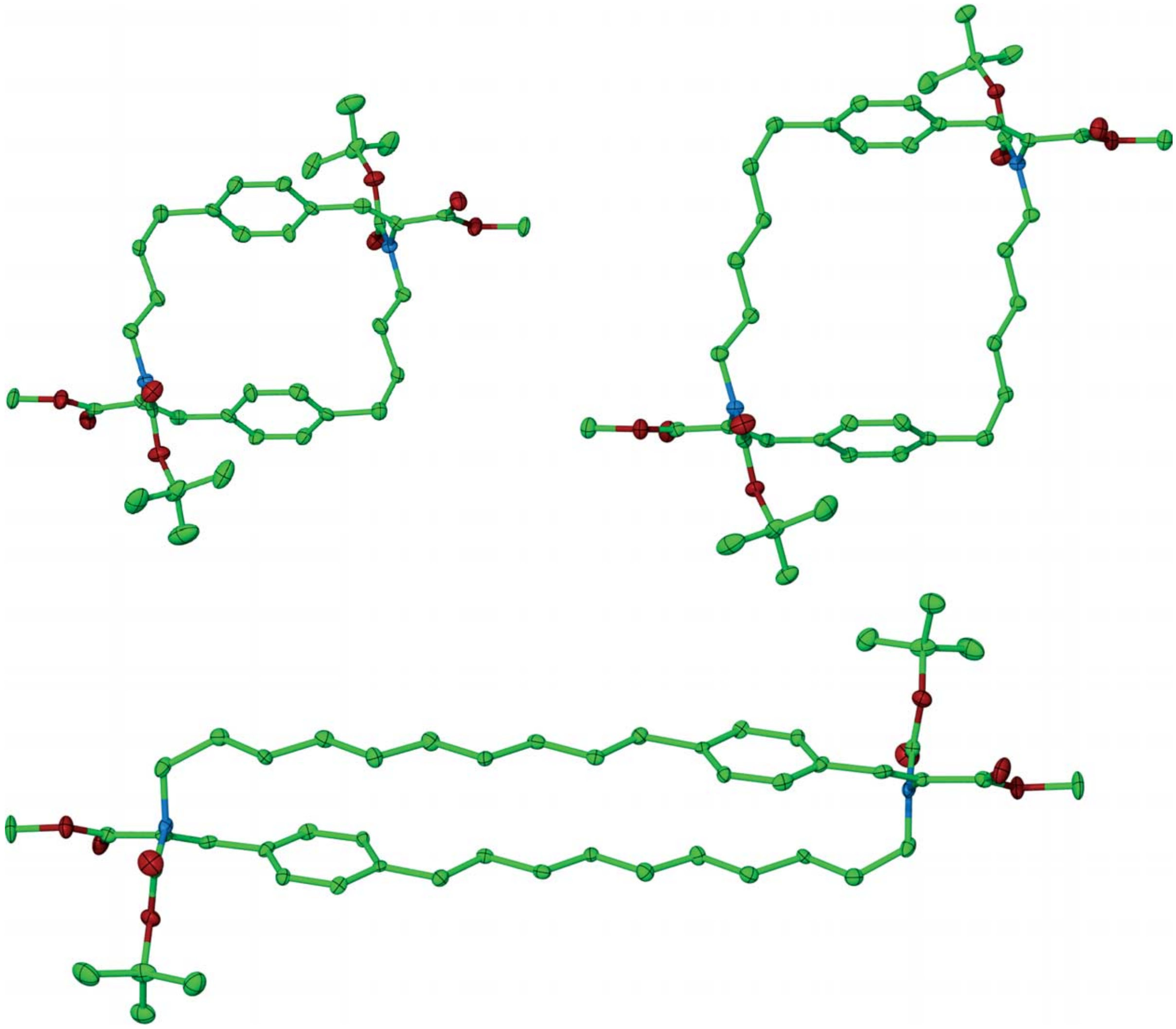


Figure 1. ORTEP diagrams for **5a**, **5c** and **5d**.

that were tentatively identified as cyclophanes **5b–d** on the basis of their spectroscopic and microanalytical data. All attempts to identify and isolate a simple intramolecular Heck product using a range of reaction conditions were unsuccessful.

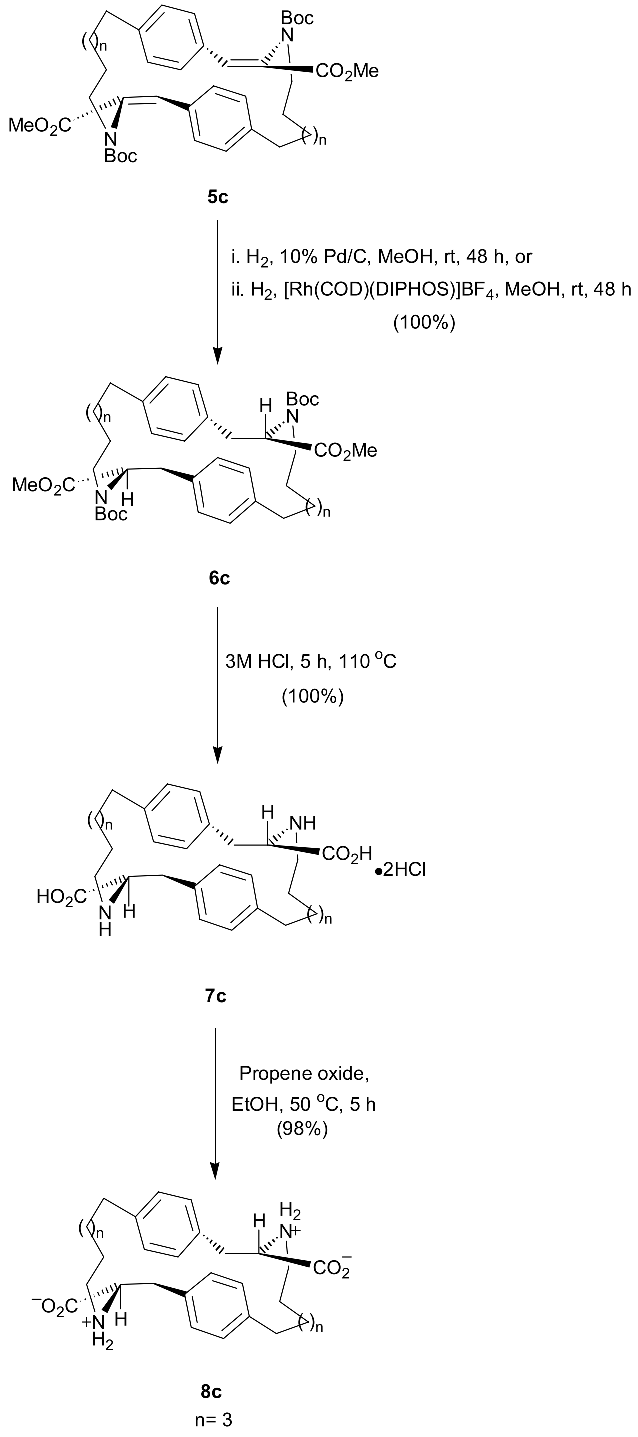
1.2. X-ray crystallographic study of cyclophanes 5a, 5c and 5d (CCDC188015, 188016, 189757)

Crystallisation of **5a**, **5c** and **5d** followed by X-ray crystallographic analysis of the colourless crystals obtained[6] confirmed the structures of **5a–d** and revealed that in the solid state, the larger, more flexible cyclophanes are able to collapse in on themselves in order to minimize void space, while the smaller, more rigid species exhibit small macrocyclic cavities. Thus **5a** and **5c** possess an internal cavity, with that in **5c** approximately large enough to encapsulate methane, and adopt 'barrel-like' shapes (Fig. 1). In contrast the larger **5d** exhibits an extended 'staggered' conformation in which the two alkyl chains lie parallel to one another with a large offset of the aryl rings with essentially no free internal cavity volume.

1.3. Hydrogenation of cyclophane 5c

In view of the current interest in macrocycles, not only as ligands for a wide range of metals,[9] but also as key elements in host–guest chemistry,[10] we were interested in probing whether or not the initially undesired cyclophane synthesis described above could be developed into a new and versatile approach to macrocycles. Moreover it would be attractive to develop this route into a synthesis of chiral macrocycles that could ultimately be applied in the areas of asymmetric catalysis and enantioselective guest recognition. The most alluring way to attempt to introduce asymmetry into **5a–d** would be through an asymmetric hydrogenation procedure, although caution would need to be exercised in this approach in view of the possibility of generating optically inactive meso products. To start to probe the viability of this approach, a hydrogenation study was initiated (Scheme 3).

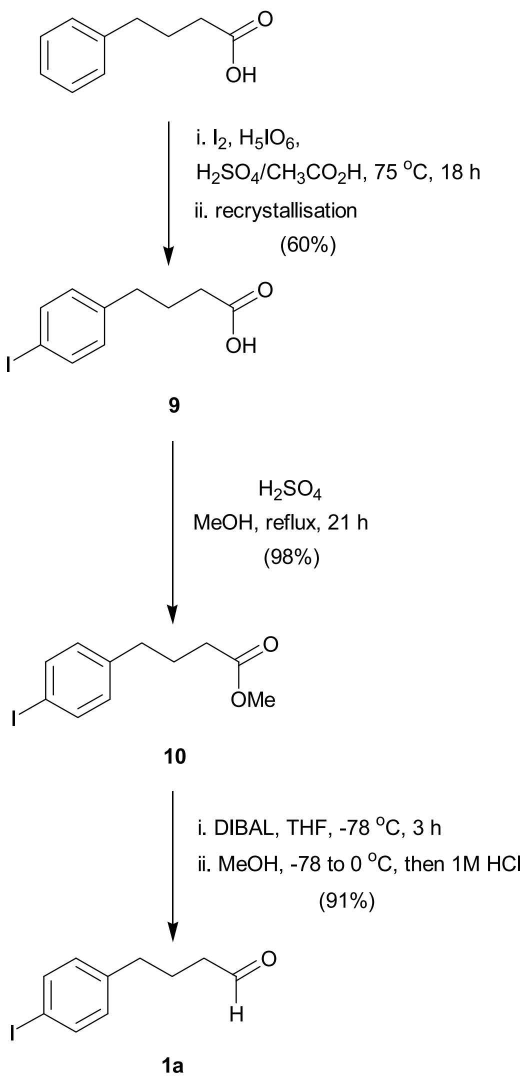
It was anticipated that the hydrogenation of **5a–d** would afford saturated products with two new stereogenic centres. As a representative example, **5c** was chosen for further investigation. Hydrogenation of **5c** using either 10% Pd/C or $[Rh(COD)(DIPHOS)]BF_4$ afforded a product **6c** that 500 MHz ^1H NMR spectroscopy indicated was a single diastereoisomer (Scheme 3). As the product cyclophane did not produce crystals of sufficient quality for X-ray crystallographic analysis, it was subjected to chiral HPLC analysis using several columns, eluents and flow rates, in an attempt to determine its relative stereochemistry. In each case only a single peak was observed. Although not entirely conclusive, these results suggest that the diastereoisomer that has been produced by hydrogenation is more likely to be the *meso RS* compound than the *RR*/*SS* pair.



Scheme 3.

In an attempt to generate compounds more amenable to crystallisation, **6c** was deprotected to give the salt **7c**, and propene oxide treatment was used to remove hydrogen chloride and give the novel amino acid **8c**. Compounds **7c** and **8c** failed to give crystals suitable for crystallographic analysis.

In view of the difficulties associated with the analysis of the hydrogenation product, and the need to eliminate pathways leading to the formation of the *meso* product in any asymmetric version of the reaction, it was concluded that asymmetric hydrogenation would prove to be a non-trivial approach to non-racemic chiral macrocycles from cyclophanes **5** and alternatives were sought.

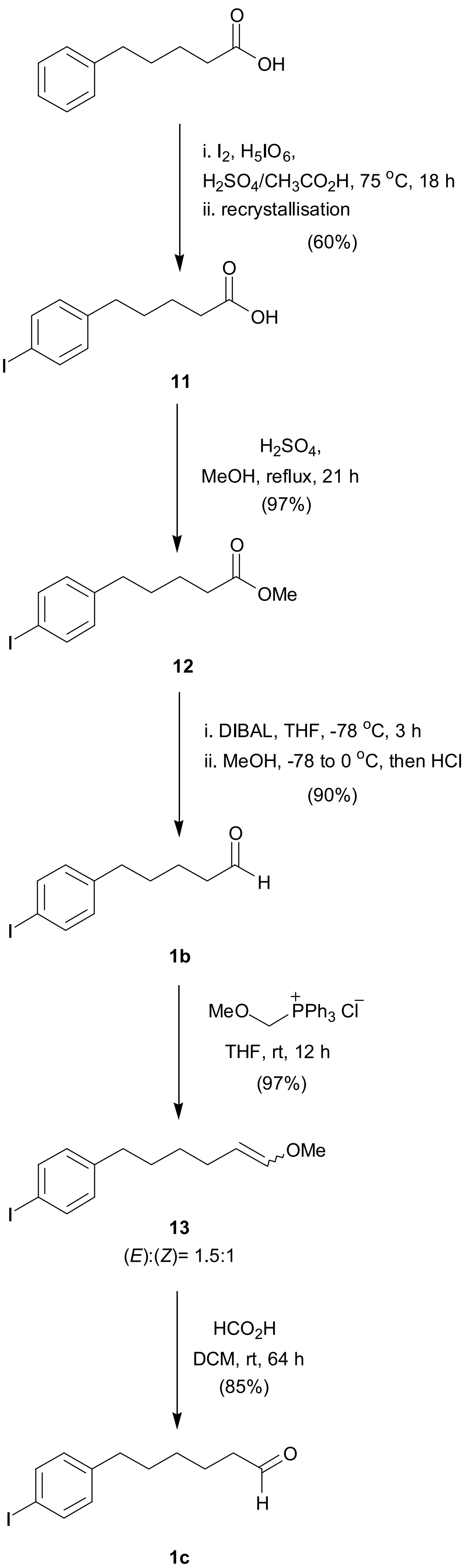


Scheme 4.

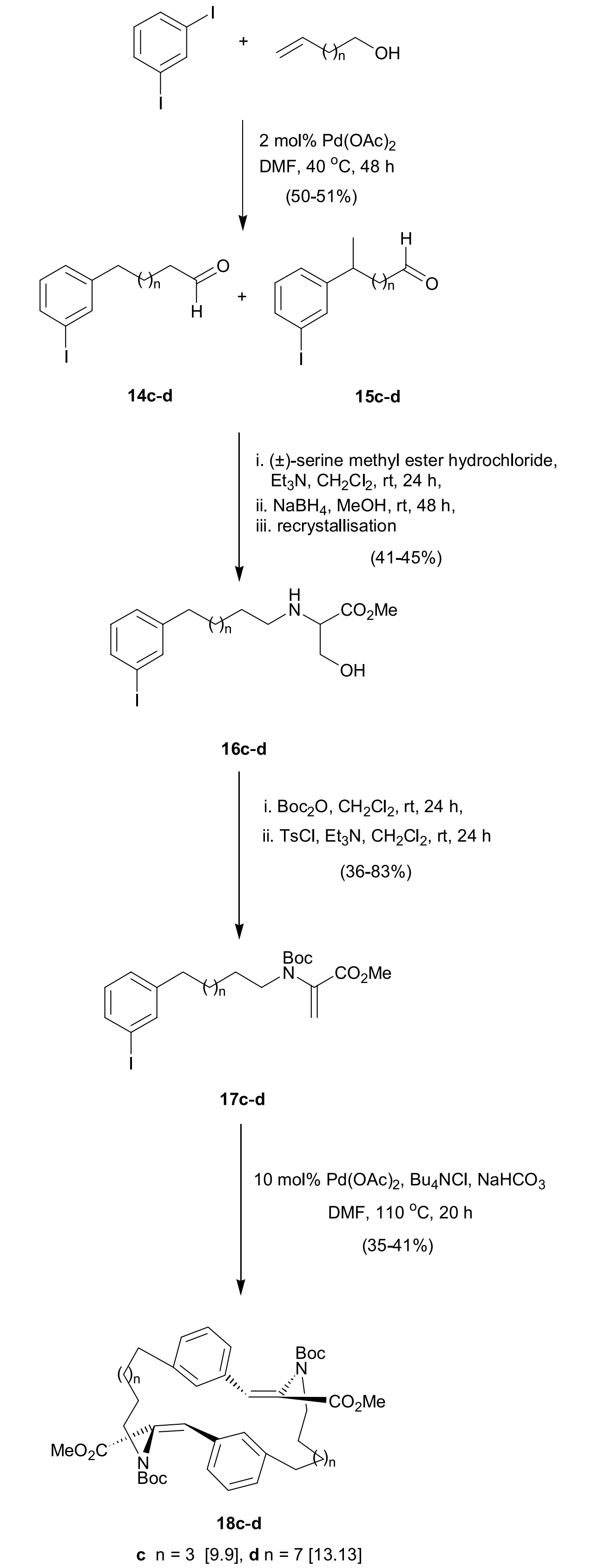
1.4. A second route to aldehydes 1a–c

The problems associated with the production of the branched regioisomers in the synthesis of linear aldehydes **1a–d** led to the development of an alternative approach to the synthesis of the shorter chain aldehydes **1a–c**. Iodination of commercially available 4-phenylbutanoic acid using an established literature procedure[11] gave a 2.5:1 mixture of the desired iodinated acid **9** and its isomer 4-(2-iodophenyl)butanoic acid (Scheme 4). Crystallisation of the mixture readily led to the isolation of pure **9**, which was then converted to its methyl ester **10**. Reduction of **10** using di-*iso*-butylaluminium hydride (DIBAL) gave the desired aldehyde **1a** in good yield. Subjecting commercially available 5-phenylpentanoic acid to the same sequence produced aldehyde **1b** (Scheme 5). The homologous aldehyde **1c** was then generated from **1b** by a Wittig reaction to give vinyl ether **13**, which was subsequently hydrolysed to the desired product.

The use of pure aldehydes in the reductive amination step rendered this step much less problematic. For example, in a typical reaction, reductive amination of an 87:13 linear/branched mixture of **1a** and **1b** gave **3a** in 45%



Scheme 5.



Scheme 6.

yield after purification by crystallisation, whereas repeating the procedure using only **1a** generated using the route described above gave a 78% yield of pure **3a**.

1.5. Synthesis and cyclisation of *meta* bridged substrates 17c–d

The *meta* bridged substrates **17c** and **17d** were synthesised using the same initial approach as that used for the synthesis of the *para* bridged substrates **4a–d**. Reaction of commercially available ω-hydroxyalkenes containing six and 10 carbon atoms with 1,3-di-iodobenzene afforded the desired aldehydes **14c** and **14d** contaminated at levels of 22–25% with their branched isomers **15c** and **15d** (Scheme 6). Reductive amination of the mixtures with serine methyl ester and sodium borohydride followed by crystallisation gave pure samples of **16c** and **16d**. Protection of the amines of **16c** and **16d**, tosylation of their alcohols and elimination produced substrates **17c** and **17d**. Subjecting **17c** and **17d** to the same Heck coupling conditions used for the coupling of **4a–d** led to the production and isolation of macrocycles **18c** and **18d** in significantly better yield than their *para* bridged counterparts **5a–d**. Once again, we were unable to isolate a simple intramolecular Heck product.

1.6. Modelling of *meta*- and *para*cyclophanes

A modelling study was undertaken to probe further the occurrence of 'barrel' and 'staggered' conformations in the cyclophanes produced. The structures of cyclophanes **5c**, **5d**, **18c** and **18d** were examined. Firstly the structures were minimised and partial charges were applied. They were then subjected to molecular dynamics (10 randomisations) at a work temperature of 600 K, and a conformational hunt (using a simulated dielectric constant of 2) that collected all the resulting conformations occurring within a 15 $kcal\ mol^{-1}$ range. The conformations that lay within 3 $kcal\ mol^{-1}$ of the global minimum that is 99% of the conformations that occur at physiological temperature, were then examined. The results of the modelling are depicted in Figure 2. For the [13,13]*para*cyclophane, **5d**, all the conformations examined resembled the crystal structure insomuch as they had the same staggered, extended shape—a typical result is depicted in Figure 2, structure (i). Modelling of the [13,13]*meta*cyclophane **18d** produced a number of conformations within 3 kcal of the global minimum, all of which had the general staggered extended conformation observed in both the X-ray analysis and modelling of **5d** (for a typical example, see Fig. 2, structure (ii)). Modelling of the smaller [9.9]*para*cyclophane **5c** also gave a set of conformations that were all 'staggered' (for a typical example, see Fig. 2, structure (iii)). Finally modelling of the [9.9]*meta*cyclophane **18c** gave mainly 'staggered' conformations (e.g. Fig. 2, structure (iv)) and a couple of conformations that approach the 'barrel' shape seen in the structure determined by X-ray crystallography for **5c** (e.g. Fig. 2, structure (v)). Thus from analyses based on crystalline and in silico environments, it appears that there are two main structural types available to the cyclophanes, barrel and staggered. As X-ray and modelling analyses of *meta*- and *para*[13,13]cyclophanes, have only produced staggered structures, and the same range of analyses of the *meta*- and *para*[9.9]cyclophanes have revealed a mixture of barrel and staggered structures, we tentatively conclude from this study that the staggered structure is favoured by longer hydrocarbon chains whilst the barrel structure is favoured by shorter hydrocarbon

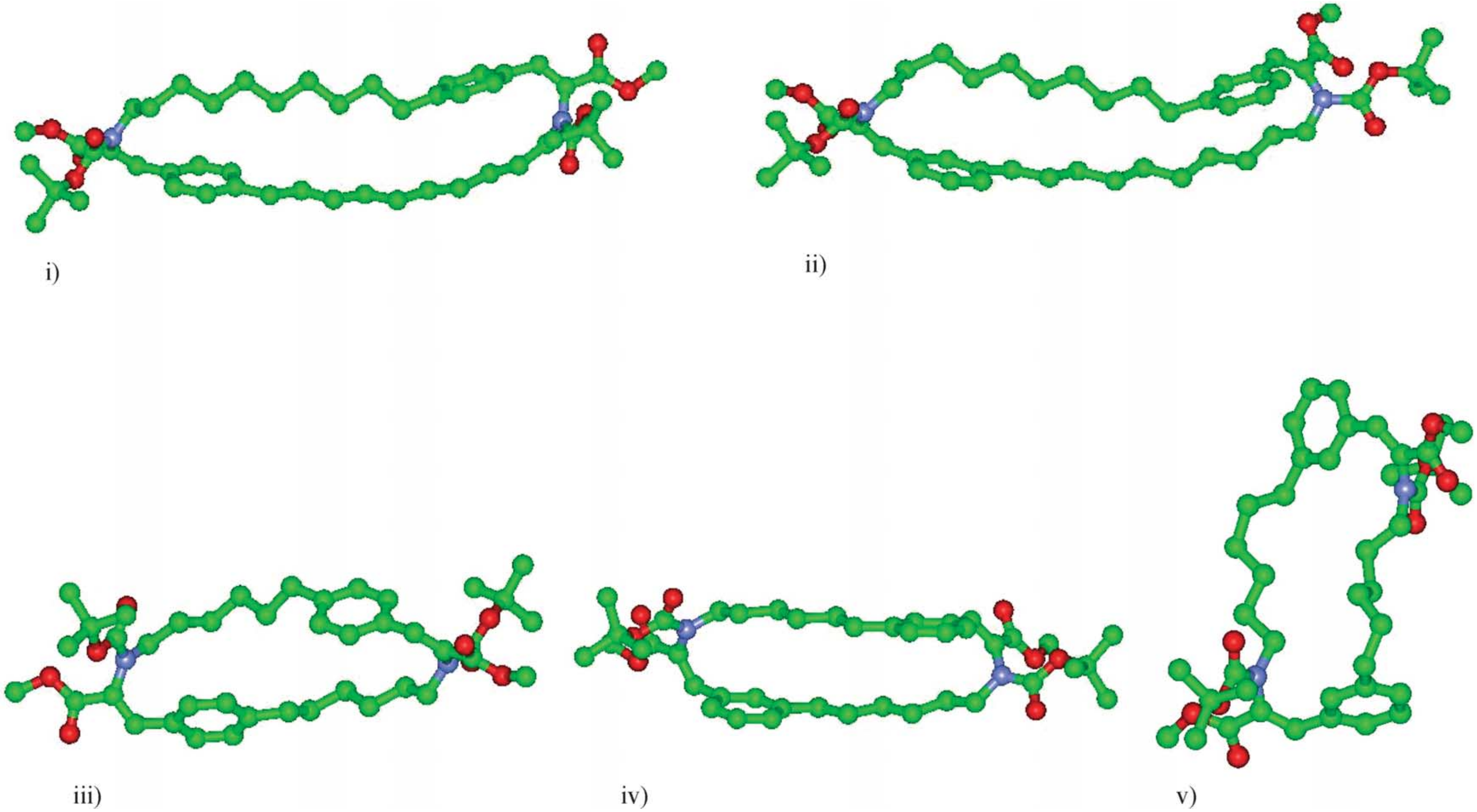


Figure 2. Modelling of *meta*- and *para*cyclophanes; (i) a typical staggered conformation of the [13.13]*para*cyclophane **5d**; (ii) a typical staggered conformation of the [13.13]*meta*cyclophane **18d**; (iii) a typical staggered conformation of the [9.9]*para*cyclophane **5c**; (iv) a typical staggered conformation of the [9.9]*meta*cyclophane **18c**; (v) one of the barrel conformations observed for [9.9]*meta*cyclophane **18c**.

chains. This is consistent with the observation of a barrel structure when the [7.7]*para*cyclophane **5a** was examined by X-ray crystallography.

2. Conclusions

Although, we have failed to isolate *meta* and *para* analogues of the type of compound used to generate Sic, Hic, Nic and Xic, we have discovered a new and versatile approach to macrocycles. The route, based on a new variation of the Heck coupling reaction between iodoarenes and dehydroalanine derivatives, has been used to generate [7.7], [8.8], [9.9], and [13,13] *para*cyclophanes and [9.9] and [13.13] *meta*cyclophanes containing unsaturated amino acid residues. The X-ray crystallographic study of three of the *para*cyclophanes revealed that in the solid state the amino acid residues adopt significantly different relative positions, and molecular modelling of two *para*cyclophanes and two *meta*cyclophanes led to the suggestion that longer hydrocarbon chains may favour the so-called 'staggered' structure, whilst shorter hydrocarbon chains allow a 'barrel' type structure to be accessed. The development of an alternative route to key aldehydes has not only rendered the above synthesis more straightforward, but has also helped to pave the way to the development of a synthesis of non-racemic chiral macrocycles based on head-to-tail Heck couplings that avoids the use of an asymmetric hydrogenation reaction.[12]

3. Experimental

3.1. General

DMF was stirred over barium oxide and then alumina, distilled under reduced pressure and stored over 3 Å molecular sieves. Diethyl ether was stored over sodium wire. DCM was distilled from calcium hydride. THF was distilled from sodium benzophenone ketyl. Triethylamine was distilled from and stored over potassium hydroxide pellets. All remaining chemicals were used as received from commercial sources. The hydrogen used in the hydrogenation experiments was Boc grade 0. Melting points were recorded in open capillaries on a Büchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. NMR spectra were recorded in $CDCl_3$ at room temperature, unless otherwise stated, on Bruker AM 360 (360 MHz ^{1}H NMR, 90 MHz ^{13}C NMR), DRX 400 (400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR) and DRX 500 (500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR) instruments. The carbons were assigned with the aid of DEPT and ^{1}H/^{13}C correlation experiments wherever necessary. Chemical shifts are given in ppm and J values are reported in Hz. Mass spectra were recorded on JEOL AX 505W and Kratos MS890MS spectrometers. Elemental analyses were performed by the University of North London and University College London microanalytical services. Flash chromatography was performed using Merck silica gel (particle size 40–63 μm). Thin layer chromatography was performed on Merck TLC glass sheets on silica gel 60 F_{254} and visualisation was achieved by UV light (254 nm) and/or oxidising the TLC plate with potassium permanganate solution. Analytical HPLC was performed using a Unicam Crystal 200 pump, a Unicam Spectra 100 UV–vis detector (set at 210 nm) and 25 cm×0.46 cm Chiralcel OD-H, AD or AS columns purchased from Daicel Chemical Industries Ltd.

For the sake of clarity in the assignment of the cyclophane spectra, the carbon atoms in the aromatic rings of the iodinated compounds, the cyclised products and their derivatives have been numbered. For the acyclic *para* substituted products, the carbon atom bearing the iodine atom is 'C-4', and the carbon atom bearing the tether is 'C-1'. In the cyclised products and their derivatives the carbon atom bearing the tether remains as 'C-1' and the carbon atom which bore the iodine but is now part of the new carbon–carbon bond becomes 'C-4'. Likewise, for the *meta* substituted products, the carbon atom bearing the iodine atom is 'C-3', and the carbon atom bearing the tether is 'C-1'. In the cyclised products the carbon atom bearing the tether remains as 'C-1' and the carbon atom which bore the iodine becomes 'C-3'.

Experimental detail and analytical data for compounds **2b**, **2c**, **2d**, **3b**, **3c**, **3d**, **4b**, **4c**, **4d**, **5b**, **5d**, **15d**, **16d**, **17d** and **18d**, all of which were made using procedures closely related to one of the procedures described below, are available from the author on request.

3.1.1. 4-(4-Iodophenyl)butanal 1a[13] and 3-(4-iodophenyl)butanal 2a. Sodium hydrogencarbonate (10.5 g, 125.03 mmol, 2.5 equiv), tetra-*n*-butyl ammonium chloride (13.9 g, 50.01 mmol, 1.0 equiv), palladium(II) acetate (0.224 g, 1.0 mmol, 2 mol%) and 1,4-di-iodobenzene (16.5 g, 50.01 mmol, 1.0 equiv) were placed in a Schlenk tube under an atmosphere of nitrogen. 3-Buten-1-ol (6.45 mL, 75.02 mmol, 1.5 equiv) and dry DMF (50 mL, 1.0 M) were added separately via a syringe. The Schlenk tube was lowered into a pre-heated oil bath maintained at 40 °C and stirred for 48 h, during which time the colour was observed to change from pale yellow to black. The Schlenk tube was removed from the oil bath and allowed to cool to room temperature. Diethyl ether (50 mL) was added and the resulting precipitate filtered through Kieselguhr. This process was repeated until no more precipitate was produced. The filtrate was evaporated in vacuo to afford a dark brown oil. Purification via flash chromatography (SiO_2; hexane: ethyl acetate, 5:1, R_f 0.5) afforded the title compounds as a pale yellow oil (6.9 g, 2.52 mmol, 50%; 87:13 linear to branched aldehyde); see below for spectroscopic data for **1a**; discernible spectroscopic data for **2a**: δ_H(360 MHz) 1.33 [3H, d, J=7 Hz, CH(CH_3)], 2.73 [1H, m, CH(CH$_3$)], 6.86–6.87 (2H, m, H-2 and H-6), 7.53–7.55 (2H, m, H-3 and H-5), 9.64 (1H, t, J=2 Hz, CHO); $\delta_C\{^1H\}$ (90 MHz) 22.4 [CH(CH$_3$)], 40.0 [CH(CH$_3$)], 91.6 (C-4), 129.3 (C-2 and C-6), 138.1 (C-3 and C-5), 141.3 (C-1), 201.8 (CHO).

3.1.2. *N*-[4-(4-Iodophenyl)butyl]serine methyl ester 3a. (±)-Serine methyl ester hydrochloride (2.81 g, 18.06 mmol, 1.5 equiv) and 4-(4-iodophenyl)butanal **1a** and 3-(4-iodophenyl)butanal **2a** (3.3 g, 12.04 mmol, 1.0 equiv) were introduced into a reaction vessel which contained anhydrous magnesium sulfate (1.2 g) suspended in dry DCM (24.1 mL, 0.5 M) under nitrogen. Triethylamine

(3.36 mL, 24.08 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 24 h. The contents of the flask were transferred to another reaction vessel via filter cannula under nitrogen and the filtrate was evaporated in vacuo to give a yellow oil. The oil was dissolved in dry methanol (24.1 mL, 0.5 M) and cooled to 0 °C under nitrogen. Sodium borohydride (0.91 g, 24.08 mmol, 2.0 equiv) was added portionwise and the reaction was allowed to warm to room temperature and stirred for 48 h. Demineralised water (25 mL) and ethyl acetate (50 mL) were added and the layers partitioned. The organic layer was extracted with 5% v/v HCl (3×100 mL). The combined aqueous layers were brought to pH 9 by the careful addition of solid potassium carbonate and extracted with ethyl acetate (3×150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to afford a waxy-yellow solid. Purification via crystallisation from hexane–diethyl ether afforded the title compound **3a** as a white solid (2.04 g, 5.41 mmol, 45%), mp 34–35 °C (Found: C, 44.5; H, 5.5; N, 3.9. $C_{14}H_{20}INO_3$ requires C, 44.58; H, 5.34; N, 3.71%); ν_{max}(Nujol)/cm^{-1} 3400–3200br s (NH and OH), 1732vs (C=O); δ_H(360 MHz) 1.48–1.65 (4H, m, $ArCH_2\mathit{CH}_2\mathit{CH}_2$), 2.48–2.73 (6H, br m, $ArCH_2$, CH_2N, NH and OH), 3.35 (1H, dd, J=7, 5 Hz, $C\mathit{H}CO_2CH_3$), 3.57 (1H, dd, J=11, 7 Hz, $C\mathit{H}HOH$), 3.74 (3H, s, CO_2CH_3), 3.74 (1H, dd, J=11, 5 Hz, $CH\mathit{H}OH$), 6.91–6.94 (2H, m, H-2 and H-6), 7.57–7.60 (2H, m, H-3 and H-5); $\delta_C\{^1H\}$ (100 MHz) 29.2, 30.1 ($ArCH_2\mathit{C}H_2\mathit{C}H_2$), 35.6 ($ArCH_2$), 48.5 ($CH_2N$), 52.6 ($CO_2\mathit{C}H_3$), 62.7 ($CH_2OH$), 63.1 ($\mathit{C}HCO_2CH_3$), 91.2 (C-4), 131.0 (C-2 and C-6), 137.8 (C-3 and C-5), 142.3 (C-1), 174.0 ($\mathit{C}O_2CH_3$); m/z (EI) 377 (M^+, 37%), 346 ($M-CH_2OH$, 100), 318 ($M-CO_2CH_3$, 94), 251 (MH−I, 3).

When the above procedure was repeated using 3.3 g of pure **1a**, 3.50 g (9.28 mmol, 78%) of **3a** was isolated.

3.1.3. Methyl 2-{*N*-[(4-(4-iodophenyl)butyl]-*N*-(*tert*-butyloxycarbonyl)-amino}prop-2-enoate 4a. Di-*tert*-butyl dicarbonate (1.46 g, 6.71 mmol, 1.1 equiv) was added in one portion to a stirred solution of *N*-[4-(4-iodophenyl)butyl]serine methyl ester **3a** (2.3 g, 6.10 mmol, 1.0 equiv) in dry DCM (5.4 cm^3) under nitrogen at 0 °C. After 30 min, the reaction was allowed to warm to room temperature and stirred for a further 24 h. The solution was diluted with the addition of dry DCM (8.6 mL). *p*-Toluenesulfonyl chloride (1.74 g, 9.15 mmol, 1.5 equiv) and triethylamine (2.55 mL, 18.30 mmol, 3.0 equiv) were then added. The reaction mixture was stirred for a further 24 h, before being washed with 5% v/v HCl (2×12 mL) and saturated aqueous sodium chloride (1×12 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to afford a brown oil. Purification via flash chromatography (SiO_2; DCM–hexane, 5:1, R_f 0.3) afforded the title compound **4a** as a clear yellow oil (1.55 g, 3.37 mmol, 55%) (Found: C, 49.4; H, 5.7; N, 3.1. $C_{19}H_{26}INO_4$ requires C, 49.68; H, 5.70; N, 3.05%); ν_{max}(neat)/cm^{-1} 1736vs (C=O), 1708vs (C=O), 1632 s (C=C); δ_H(400 MHz) 1.45–1.76 (4H, m, $ArCH_2\mathit{CH}_2\mathit{CH}_2$), 1.47 [9H, s, $C(CH_3)_3$], 2.64 (2H, t, J=7 Hz, $ArCH_2$), 3.56–3.58 (2H, m, CH_2N), 3.84 (3H, s, CO_2CH_3), 5.42 (1H, s, $C{=}C\mathit{H}H$), 5.96 (1H, s, $C{=}CH\mathit{H}$), 6.98–7.00 (2H, m, H-2 and H-6), 7.63–7.65 (2H, m, H-3 and H-5); $\delta_C\{^1H\}$ (100 MHz) 22.7, 28.1 ($ArCH_2\mathit{C}H_2\mathit{C}H_2$), 28.6 [$C(\mathit{C}H_3)_3$], 35.4 ($ArCH_2$), 49.4 ($CH_2N$), 52.7 ($CO_2\mathit{C}H_3$), 81.4 [$\mathit{C}(CH_3)_3$], 91.1 (C-4), 117.6 ($C{=}\mathit{C}H_2$), 131.0 (C-2 and C-6), 137.7 (C-3 and C-5), 140.4 (C-1), 142.4 ($\mathit{C}{=}CH_2$), 154.1 [$\mathit{C}O_2C(CH_3)_3$], 165.8 ($\mathit{C}O_2CH_3$); m/z (CI, NH_3) 477 (MNH_4^+, 100%), 421 [$MNH_4^+-C(CH_3)_3+H$, 31], 360 [$MNH_4^+-C(CH_3)_3-CO_2CH_3-H$, 7], (MH−I, 1).

3.1.4. 6,19-Dicarbomethoxy-5,18-*N*,*N*-di-(*tert*-butyloxycarbonyl)-[7.7]*para*cyclophan-6,19-diene 5a. 3 Å Molecular sieves (0.8 g) were heated in vacuo in a Woods metal bath for 6 h and then added to a Schlenk tube charged with methyl 2-{*N*-[4-(4-iodophenyl)butyl]-*N*-(*tert*-butyloxycarbonyl)-amino}prop-2-enoate **4a** (0.8 g, 1.74 mmol, 1.0 equiv), palladium(II) acetate (391 mg, 0.174 mmol, 10 mol%), sodium hydrogencarbonate (365 mg, 4.35 mmol, 2.5 equiv) and tetra-*n*-butyl ammonium chloride (484 mg, 1.74 mmol, 1.0 equiv). The reaction vessel was evacuated and filled with nitrogen (×5). Dry DMF (35 mL, 0.05 M) was added and the reaction vessel was again evacuated and filled with nitrogen (×5). The Schlenk tube was lowered into a pre-heated oil bath maintained at 110 °C, stirred for 20 h and then allowed to cool to room temperature. Diethyl ether (50 mL) was added and the resulting precipitate filtered off through Kieselguhr. This was repeated until no more precipitate was produced. The filtrate was evaporated in vacuo to afford a dark brown oil. The oil was subjected to flash chromatography (SiO_2; hexane: diethyl ether, 1:1, R_f 0.5) to afford the title compound **5a** as a white solid (0.16 g, 0.242 mmol, 28%), mp 56–57 °C (Found: C, 68.9; H, 7.6; N, 4.2. $C_{38}H_{50}N_2O_8$ requires C, 68.86; H, 7.60; N, 4.23%); ν_{max}(Nujol)/cm^{-1} 1716vs (C=O), 1698vs (C=O), 1632s (C=C); δ_H(400 MHz) 1.19–1.47 (8H, m, $2\times ArCH_2\mathit{CH}_2\mathit{CH}_2CH_2N$), 1.25, 1.27 [18H, 2×s, $2\times C(CH_3)_3$], 2.29–2.59 (4H, m, $2\times ArCH_2$), 2.80–3.36 (4H, m, $2\times CH_2N$), 3.76 (6H, s, $2\times CO_2CH_3$), 6.88–6.90 (4H, m, 2×H-2 and H-6), 7.25–7.30 (4H, m, 2×H-3 and H-5), 7.39 (2H, s, $2\times C{=}CH$); $\delta_C\{^1H\}$ (100 MHz) 23.1, 27.0 ($ArCH_2\mathit{C}H_2\mathit{C}H_2CH_2N$), 27.7, 28.6 [$C(\mathit{C}H_3)_3$ rotamers], 32.0 ($ArCH_2$), 35.4 (CH_2N), 52.7 ($CO_2\mathit{C}H_3$), 80.8 [$\mathit{C}(CH_3)_3$], 129.0 (C-2 and C-6), 130.7 (C-3 and C-5), 130.9 (C-1 and C-4), 137.2 ($C{=}\mathit{C}H$), 144.7 ($\mathit{C}{=}CH$), 155.7 [$\mathit{C}O_2C(CH_3)_3$], 166.8 ($\mathit{C}O_2CH_3$); m/z (FAB positive) 685 (M^++Na, 5%), 562 [$MH-CO_2C(CH_3)_3$, 7], 507 [$MH-CO_2C(CH_3)_3-C(CH_3)_3+2H$, 100], 463 [$MH-CO_2C(CH_3)_3-CO_2C(CH_3)_3+2H$, 14].

3.1.5. 8,23-Dicarbomethoxy-7,22-*N*,*N*-di-(*tert*-butyloxycarbonyl)-[9.9]*para*cyclophan-8,23-diene 5c. 3 Å Molecular sieves (2.8 g) were heated in vacuo in a Woods metal bath for 6 h and then added to a Schlenk tube charged with methyl 2-{*N*-[(6-(4-iodophenyl)hexyl]-*N*-(*tert*-butyloxycarbonyl)-amino}prop-2-enoate **4c** (2.8 g, 5.75 mmol, 1.0 equiv), palladium(II) acetate (130 mg, 0.575 mmol, 10 mol%), sodium hydrogencarbonate (1.21 g, 14.38 mmol, 2.5 equiv) and tetra-*n*-butyl ammonium chloride (1.60 g, 5.74 mmol., 1.0 equiv). The reaction vessel was evacuated and filled with nitrogen (×5). Dry DMF (115 mL, 0.05 M) was added and the reaction vessel was again evacuated and filled with nitrogen (×5). Applying the reaction conditions, work-up (200 mL of diethyl ether), and purification used for **5a** afforded the title compound **5c** as a white solid (0.62 g, 0.864 mmol, 30%), mp 60–61 °C (Found: C, 70.2; H, 8.0; N, 3.8. $C_{42}H_{58}N_2O_8$ requires C, 70.17; H, 8.13; N, 3.90%); ν_{max}($CHCl_3$)/cm^{-1} 1716vs (C=O), 1699vs (C=O), 1640s

(C=C); δ_H(400 MHz) 1.03–1.58 (16H, m, 2×ArCH$_2$C*H*$_2$–C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N), 1.27, 1.29 [18H, 2×s, 2×C(CH$_3$)$_3$], 2.83–2.48 (4H, m, 2×ArCH$_2$), 3.38–3.73 (4H, m, 2×CH$_2$N), 3.75 (6H, s, 2×CO$_2$CH$_3$), 6.99–7.01 (4H, m, 2×H-2 and H-6), 7.37–7.40 (4H, m, 2×H-3 and H-5), 7.40 (2H, s, 2×C=CH); δ_C{1H} (90 MHz) 27.3, 28.1, 28.9, 30.7 (ArCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$CH$_2$N), 28.5, 28.6 [C(*C*H$_3$)$_3$ rotamers], 35.8 (ArCH$_2$), 49.1 (CH$_2$N), 52.6 (CO$_2$*C*H$_3$), 80.7 [*C*(CH$_3$)$_3$], 129.1 (C-2 and C-6), 130.6 (C-3 and C-5), 131.1 (C-1 and C-4), 136.7 (C=*C*H), 145.3 (*C*=CH), 155.7 [*C*O$_2$C(CH$_3$)$_3$], 166.8 (*C*O$_2$CH$_3$); *m/z* (FAB, positive) 741 (M$^+$+Na, 10%), 618 [MH–CO$_2$C(CH$_3$)$_3$, 21], 563 [MH–CO$_2$C(CH$_3$)$_3$–C(CH$_3$)$_3$+2H, 100], 519 [MH–CO$_2$C(CH$_3$)$_3$–CO$_2$C(CH$_3$)$_3$+2H, 31].

3.1.6. 8,23-Dicarbomethoxy-7,22-*N*,*N*-di-(*tert*-butyloxycarbonyl)-[9.9]*para*cyclophane 6c. A pressure vessel was charged with 8,23-dicarbomethoxy-7,22-*N*,*N*-di-(*tert*-butyloxycarbonyl)-[7.7]*para*cyclophan-8,23-diene **5c** (0.050 g, 0.070 mmol, 1 equiv), 10% palladium on charcoal or [Rh(COD)DIPHOS]BF$_4$ (0.015 g, 30% w/w), and dry methanol (10 mL). The reaction vessel was evacuated and filled with nitrogen (×5) and then with hydrogen (×10). The reaction was stirred for 48 h under a hydrogen pressure of 100 psi, followed by filtration through Kieselguhr and evaporation in vacuo to afford the title compound **6c** as a clear oil, which solidified in vacuo to give a white solid (0.050 g, 0.069 mmol, 100%), mp 62–63 °C (Found: C, 69.8; H, 8.8; N, 3.7. C$_{42}$H$_{62}$N$_2$O$_8$ requires C, 69.78; H, 8.64; N, 3.87%); ν_{max}(CHCl$_3$)/cm^{-1} 1720vs, 1701vs (C=O); δ_H (500 MHz, C$_6$D$_5$CD$_3$, 100 °C) 1.01–1.46 (16H, m, 2×ArCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N), 1.47 [18H, s, 2×C(CH$_3$)$_3$], 2.41–2.43 (4H, m, ArCH$_2$), 2.85–2.91 (2H, m, 2×ArCH*H*CHCO$_2$CH$_3$), 3.22–3.28 (2H, m, 2×ArC*H*HCHCO$_2$CH$_3$,), 3.38–3.43 (4H, m, CH$_2$N), 3.52 (6H, s, 2×CO$_2$CH$_3$), 3.93–3.98 [2H, m, 2×C*H*(CO$_2$CH$_3$)], 6.98–6.99 (4H, m, 2×H-2 and H-6), 7.09–7.10 (4H, m, 2×H-3 and H-5); δ_C{^{1}H} (500 MHz, C$_6$D$_5$CD$_3$, 100 °C) 32.0, 34.0, 34.3, 36.1 (ArCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$CH$_2$N), 40.8, 40.9 (Ar*C*H$_2$CH$_2$ and Ar*C*H$_2$CHCO$_2$CH$_3$), 55.6 (CH$_2$N), 55.7 (CO$_2$*C*H$_3$), 69.2 (*C*HCO$_2$CH$_3$), 85.0 [*C*(CH$_3$)$_3$], 133.9 (C-2 and C-6), 135.0 (C-3 and C-5), 135.1, 142.1 (C-1 and C-4), 146.4 [*C*O$_2$(CH$_3$)$_3$], 176.9 (*C*O$_2$CH$_3$); *m/z* (FAB, positive) 746 (MH$^+$+Na, 100%), 667 [MH–C(CH$_3$)$_3$+H, 25], 567 [MH–CO$_2$(CH$_3$)$_3$–C(CH$_3$)$_3$+2H, 75], 507 [MH–CO$_2$(CH$_3$)$_3$–CO$_2$(CH$_3$)$_3$–CH$_3$+2H, 35]. Chiral HPLC analysis using the following conditions gave a single peak: Daicel AD column, ^{n}hexane: propan-2-ol, 90:10, λ=210 nm, flow rate 400 μL/min, rt/min 10.65, 200 μL/min, RT/min 25.23, 100 μL/min, rt/min 35.23; Daicel AS column, ^{n}hexane: propan-2-ol, 90:10, λ=210 nm, flow rate 400 μL/min, rt/min 11.20, 200 μL/min, rt/min 26.24, 100 μL/min, rt/min 36.54; Daicel OD-H column, ^{n}hexane: propan-2-ol, 90:10, λ=210 nm, flow rate 400 μL/min, 12.43 rt/min, 200 μL/min, 28.92, 100 μL/min, rt/min 38.24.

3.1.7. 7,23-Diamino-8,21-dicarboxy[9.9]*para*cyclophane dihydrochloride 7c. 8,23-Dicarbomethoxy-7,22-*N*,*N*-di-(*tert*-butyloxycarbonyl)-[7.7]*para*cyclophane **6c** (0.070 g, 0.097 mmol, 1 equiv) in 3 M HCl (3 mL) was stirred vigorously for 5 h at 110 °C in a 50 mL round-bottomed flask fitted with an air condenser. The solvent was evaporated in vacuo to give the title compound **7c** as a white powder (0.055 g, 0.091 mmol, 100%) mp 190–192 °C (decomp.); (Found: C, 63.7; H, 7.9; N, 5.2. C$_{30}$H$_{44}$N$_2$O$_4$Cl$_2$ requires C, 63.48; H, 7.81; N, 4.94%); ν_{max}(Nujol)/cm^{-1} 3600–3200br s (OH), 1720vs (C=O); δ_H(360 MHz; CD$_3$OD) 1.09–1.80 (16H, m, 2×ArCH$_2$C*H*$_2$–C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N), 2.59–2.85 (8H, m, 2×ArCH$_2$ and 2×ArC*H*$_2$CHCO$_2$H), 3.05–3.45 (4H, m, 2×CH$_2$N), 4.10–4.35 (1H, m, C*H*CO$_2$H), 7.20–7.30 (8H, m, H-2, H-3, H-5, H-6); δ_C{^{1}H} (90 MHz; CD$_3$OD) 26.9, 28.0, 32.9, 33.4 (ArCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$CH$_2$N), 37.0, 37.3 (ArCH$_2$ and Ar*C*H$_2$CHCO$_2$H), 47.9 (CH$_2$N), 62.5 (*C*HCO$_2$H), 129.8 (C-2 and C-6), 130.9 (C-3 and C-5), 134.2, 144.7 (C-1 and C-4), 171.7 (CO$_2$H); *m/z* (FAB, positive) 568 (MH$^+$, 23%), 495 (MH–2HCl, 15), 449 (M$^+$–CO$_2$H–2HCl, 100%).

3.1.8. 7,23-Diamino-8,21-dicarboxy[8.8]*para*cyclophane 8c. The hydrochloride salt **7c** (0.050 g, 0.088 mmol) was dissolved in ethanol (13 mL) in a 100 cm^3 round-bottomed flask fitted with a condenser and propene oxide (1.94 mmol) was added. The solution was stirred at 50 °C for 5 h. The solvent was evaporated in vacuo to give a white solid which was left under vacuum for a day to give the title compound **8c** as an insoluble white solid (0.042 g, 0.085 mmol, 98%), mp 170–172 °C (decomp.) (Found: C, 73.0; H, 8.6; N, 5.5. C$_{30}$H$_{42}$N$_2$O$_4$ requires C, 72.84; H, 8.56; N, 5.66%); ν_{max}(Nujol)/cm^{-1} 1610vs; *m/z* (CI, NH$_3$) 495 (MH$^+$, 100%), 449 (M–CO$_2$H, 35), 404 (M–CO$_2$H–CO$_2$H, 17).

3.1.9. 4-(4-Iodophenyl)butanoic acid 9.[11] A 500 mL round-bottomed flask fitted with a water condenser was placed under an atmosphere of nitrogen. The reaction flask was charged with 4-phenylbutanoic acid (20.0 g, 121.80 mmol, 1.0 equiv), periodic acid (5.55 g, 24.36 mmol, 0.2 equiv), and iodine (12.37 g, 48.72 mmol, 0.4 equiv). A solution of 10 M sulfuric acid (5 mL) and glacial acetic acid (165 mL) in demineralised water (35 mL) was added. The reaction flask was lowered into a pre-heated oil bath maintained at 75 °C and heated for 18 h. The reaction flask was allowed to cool to room temperature and diluted by the addition of demineralised water (100 mL). The precipitate was collected on a sintered funnel and dissolved in DCM (200 mL). The solution was washed with demineralised water (2×100 mL) and saturated aqueous sodium thiosulfate (2×100 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo to give an off-white solid. Purification via crystallisation from hexane–DCM afforded the title compound **9** as white crystals (21.20 g, 72.76 mmol, 60%), mp 80–82 °C (lit. mp 89–90.5 °C[11]); ν_{max}(Nujol)/cm^{-1} 3600–3200br s (OH), 1706vs (C=O); δ_H(360 MHz) 1.96 (2H, qn, *J*=8 Hz, ArCH$_2$C*H*$_2$), 2.39 (2H, t, *J*=8 Hz, C*H*$_2$CO$_2$H), 2.66 (2H, t, *J*=8 Hz, ArCH$_2$), 6.96 (2H, d, *J*=8.0 Hz, H-2 and H-6), 7.62 (2H, d, *J*=8.0 Hz, H-3 and H-5), 11.59 (1H, br s, OH); δ_C{^{1}H} (90 MHz) 26.4 (ArCH$_2$*C*H$_2$), 33.6 (ArCH$_2$), 34.9 (*C*H$_2$CO$_2$H), 91.6 (C-4), 131.0 (C-2 and C-6) 137.1 (C-3 and C-5), 141.2 (C-1), 180.41 (CO$_2$H); *m/z* (EI) 290 (M$^+$, 93%), 231 (M–CH$_2$CO$_2$H, 17), 230 (M–CH$_2$CO$_2$H–H, 100), 217 (M–CH$_2$CH$_2$CO$_2$H, 52).

3.1.10. Methyl 4-(4-iodophenyl)butanoate 10. A 100 mL round-bottomed flask containing 4-(4-iodophenyl)butanoic acid **9** (12.5 g, 43.10 mmol, 1.0 equiv) was fitted with a water condenser and placed under an atmosphere of nitrogen. The reaction flask was charged with sulfuric acid (2.6 mL) and methanol (60 mL). The flask was lowered into a pre-heated oil bath maintained at 70 °C and heated at reflux for 21 h. The reaction flask was allowed to cool to room temperature and the product mixture was concentrated in vacuo to give an orange oil. The oil was dissolved in DCM (100 mL) and the solution was washed with demineralised water (2×50 mL), saturated aqueous sodium hydrogencarbonate (2×50 mL) and saturated aqueous sodium chloride (2×50 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to afford the title compound **10** as a pale yellow oil (12.9 g, 42.43 mmol, 98%) (Found: C, 43.3; H, 4.4. $C_{11}H_{13}IO_2$ requires C, 43.44, H, 4.31%); ν_{max}(neat)/cm^{-1} 1736vs (C=O); δ_H(360 MHz) 1.83 (2H, qn, *J*=8 Hz, ArCH$_2$C*H*$_2$), 2.22 (2H, t, *J*=8 Hz, C*H*$_2$CO$_2$CH$_3$), 2.50 (2H, t, *J*=8 Hz, ArCH$_2$), 3.57 (3H, s, CO$_2$CH$_3$), 6.83 (2H, d, *J*=8.0 Hz, H-2 and H-6), 7.49 (2H, d, *J*=8.0 Hz, H-3 and H-5); $\delta_C\{^1H\}$ (90 MHz) 26.6 (ArCH$_2$*C*H$_2$), 33.6 (ArCH$_2$), 34.9 (*C*H$_2$CO$_2$CH$_3$), 60.0 (CO$_2$*C*H$_3$), 91.4 (C-4), 131.0 (C-2 and C-6), 137.8 (C-3 and C-5), 141.2 (C-1), 174.1 (*C*O$_2$CH$_3$), *m/z* (EI) 304 (M$^+$, 44%), 273 (M−OCH$_3$, 15), 244 (M−*C*O$_2$CH$_3$−H, 100).

3.1.11. 4-(4-Iodophenyl)butanal 1a.[13] A 250 mL round-bottomed flask was placed under an atmosphere of nitrogen and charged with methyl 4-(4-iodophenyl)butanoate **10** (7.4 g, 24.34 mmol, 1.0 equiv) in dry DCM (90 mL). The reaction flask was cooled to −78 °C and a 1 M solution of DIBAL in DCM (36.5 mL, 36.5 mmol, 1.5 equiv) was added dropwise over 1 h. The reaction was stirred at −78 °C for 2 h. Methanol (11 mL) was then added and reaction flask was allowed to warm to 0 °C, before the contents of the flask were poured into 1 M HCl (110 mL) also at 0 °C. The reaction was stirred for 1 h at 0 °C and then extracted with DCM (3×200 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated in vacuo to give an orange oil. Purification via flash chromatography (SiO_2; hexane–ethyl acetate, 5:1, R_f 0.5) afforded the title compound **1a** as a pale yellow oil (6.10 g, 22.26 mmol, 91%); ν_{max}(neat)/cm^{-1} 1726vs (C=O); δ_H(360 MHz) 1.93 (2H, m, ArCH$_2$C*H*$_2$), 2.44 (2H, td, *J*=8, 2 Hz, C*H*$_2$CHO), 2.61 (2H, t, *J*=8 Hz, ArC*H*$_2$), 6.83–6.85 (2H, m, H-2 and H-6), 7.49–7.52 (2H, m, H-3 and H-5), 9.75 (1H, t, *J*=2 Hz, CHO); $\delta_C\{^1H\}$ (90 MHz) 23.4 (ArCH$_2$*C*H$_2$), 34.4 (ArCH$_2$), 42.9 (*C*H$_2$CHO), 91.1 (C-4), 128.9 (C-2 and C-6), 137.5 (C-3 and C-5), 140.1 (C-1), 201.9 (CHO); *m/z* (EI) 274 (M$^+$, 34%), 230 (M−CH$_2$CHO−H, 100), 217 (M−CH$_2$CH$_2$–CHO–H, 27), 147 (M−I, 4), 90 (M−I–CH$_2$CH$_2$CHO, 16).

3.1.12. 5-(4-Iodophenyl)pentanoic acid 11.[11] A 500 mL round-bottomed flask was fitted with a water condenser and placed under an atmosphere of nitrogen. The reaction flask was charged with 5-phenylpentanoic acid (20.0 g, 112.21 mmol, 1.0 equiv), periodic acid (5.11 g, 22.44 mmol, 0.2 equiv), and iodine (11.39 g, 44.88 mmol, 0.4 equiv). A solution of 10 M sulfuric acid (3.6 mL) and glacial acetic acid (120 mL) in demineralised water (24 mL) was added to the flask. Application of the reaction conditions, work-up and purification used for compound **9** afforded the title compound **11** as white crystals (20.50 g, 67.43 mmol, 60%), mp 90–91 °C (lit. mp 109.5–110.5 °C[11]); ν_{max}(Nujol)/cm^{-1} 3600–3200br s (OH), 1700vs (C=O); δ_H(360 MHz) 1.52–1.62 (4H, m, ArCH$_2$–C*H*$_2$C*H*$_2$CH$_2$CO$_2$H), 2.29 (2H, t, *J*=7 Hz, C*H*$_2$CO$_2$H), 2.50 (2H, t, *J*=7 Hz, ArCH$_2$), 6.84–6.86 (2H, m, H-2 and H-6), 7.50–7.52 (2H, m, H-3 and H-5); $\delta_C\{^1H\}$ (90 MHz) 24.5, 30.9 (ArCH$_2$*C*H$_2$*C*H$_2$CH$_2$CO$_2$H), 34.2 (ArCH$_2$), 35.4 (*C*H$_2$CO$_2$H), 91.2 (C-4), 130.9 (C-2 and C-6), 137.7 (C-3 and C-5), 141.9 (C-1), 180.3 (CO$_2$H); *m/z* (EI) 304 (M$^+$, 94%), 286 (M−H$_2$O, 31), 243 (M−CH$_2$CO$_2$H−2H, 11), 217 (M−CH$_2$CH$_2$CH$_2$CO$_2$H, 100).

3.1.13. Methyl 5-(4-iodophenyl)pentanoate 12.[14] A 100 mL round-bottomed flask containing 5-(4-iodophenyl)-pentanoic acid **11** (12.2 g, 39.80 mmol, 1 equiv) was fitted with a water condenser and placed under an atmosphere of nitrogen. Sulfuric acid (2.6 mL) and methanol (60 mL) were added to the reaction flask. Application of the reaction conditions, work-up and purification used for compound **10** afforded the title compound **12** as a pale yellow oil (12.40 g, 38.99 mmol, 97%); ν_{max} (neat)/cm^{-1} 1733vs (C=O); δ_H(360 MHz) 1.66–1.68 (4H, m, ArCH$_2$C*H*$_2$C*H*$_2$CH$_2$CO$_2$–CH$_3$), 2.35 (2H, t, *J*=7 Hz, ArCH$_2$), 2.60 (2H, t, *J*=7 Hz, C*H*$_2$CO$_2$CH$_3$), 3.69 (3H, s, CO$_2$CH$_3$), 6.94–6.97 (2H, m, H-2 and H-6), 7.60–7.63 (2H, m, H-3 and H-5); $\delta_C\{^1H\}$ (90 MHz) 24.8 (ArCH$_2$CH$_2$*C*H$_2$), 31.0 (ArCH$_2$*C*H$_2$), 34.2 (ArCH$_2$), 35.4 (*C*H$_2$CO$_2$CH$_3$), 51.9 (CO$_2$*C*H$_3$), 91.2 (C-4), 130.9 (C-2 and C-6), 137.7 (C-3 and C-5), 142.1 (C-1), 174.3 (*C*O$_2$CH$_3$); *m/z* (EI) 318 (M$^+$, 82%), 286 (M−OCH$_3$–H, 100), 217 (M−CH$_2$CH$_2$CH$_2$CO$_2$CH$_3$, 26).

3.1.14. 5-(4-Iodophenyl)pentanal 1b. A 250 mL round-bottomed flask was placed under an atmosphere of nitrogen and charged with methyl 5-(4-iodophenyl)pentanoate **12** (9.38 g, 29.50 mmol, 1.0 equiv) in dry DCM (90 mL). The reaction flask was cooled to −78 °C and a 1 M solution of DIBAL in DCM (44.3 mL, 44.3 mmol, 1.5 equiv) was added dropwise over 1 h. Application of the reaction conditions, work-up and purification used for compound **1a** afforded the title compound **1b** as a pale yellow oil (7.6 g, 26.39 mmol, 90%) (Found: C, 46.0; H, 4.6. $C_{11}H_{13}IO$ requires C, 45.85; H, 4.55%); ν_{max}(neat)/cm^{-1} 1723vs (C=O); δ_H(500 MHz) 1.55–1.57 (4H, m, ArCH$_2$–C*H*$_2$C*H*$_2$CH$_2$CHO), 2.37 (2H, dt, *J*=8, 2 Hz, C*H*$_2$CHO), 2.50 (2H, t, *J*=8 Hz, ArCH$_2$), 6.84–6.85 (2H, m, H-2 and H-6), 7.50–7.52 (2H, m, H-3 and H-5), 9.67 (1H, t, *J*=2 Hz, CHO); $\delta_C\{^1H\}$ (125 MHz) 21.9, 31.0 (ArCH$_2$*C*H$_2$*C*H$_2$CH$_2$–CHO), 35.5 (ArCH$_2$), 44.1 (*C*H$_2$CHO), 91.3 (C-4), 130.9 (C-2 and C-6), 137.7 (C-3 and C-5), 141.9 (C-1), 202.7 (CHO); *m/z* (EI) 288 (M$^+$, 96%), 244 (M−CH$_2$CHO–H, 17) 217 (M−CH$_2$CH$_2$CH$_2$CHO, 100), 161 (M−I, 2), 143 (M−I–H$_2$O, 21).

3.1.15. (*E*)- and (*Z*)-6-(4-Iodophenyl)-1-methoxyhex-1-ene 13. Potassium *tert*-butoxide (7.91 g, 70.14 mmol, 2 equiv) was added portionwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (25.25 g, 73.65 mmol, 2.1 equiv) in THF (55 mL) at 0 °C under nitrogen. Upon addition a wine-red solution was formed and heat was evolved. The reaction vessel was then allowed to warm to room temperature and stirred for 30 min. A solution of 5-(4-iodophenyl)pentanal **1b** (10.1 g, 35.07 mmol, 1 equiv) in THF (54 mL) was added via cannula under nitrogen. The reaction was stirred at room temperature for 12 h and its colour was observed to change from dark red to an opaque yellow-brown. Saturated aqueous ammonium chloride (100 mL) was added with stirring. The organic layer was decanted and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with demineralised water (200 mL), dried ($MgSO_4$) and evaporated in vacuo to afford a viscous brown oil. Upon addition of hexane, triphenylphosphine oxide precipitated. It was removed by vacuum filtration through Kieselguhr and the filtrate was concentrated in vacuo. The precipitation, filtration and evaporation steps were repeated until no further precipitation of triphenylphosphine oxide occurred. Vacuum distillation of the resultant oil gave the title compound **13** as a pale yellow oil [10.80 g, 34.18 mmol, 97%, (*E*):(*Z*) 1.5:1], bp 140–148 °C at ~1 mmHg [Found (MH^+): 317.0393. $C_{13}H_{19}IO$ requires *M*, 317.0402]; ν_{max}(neat)/cm^{-1} 1650s (C=C), 1206s (C–O–C), 1108s (C–O); δ_H(360 MHz) 1.31–1.39 [4H, m, (*E*)-ArCH$_2$C*H*$_2$C*H*$_2$CH$_2$–CH], 1.53–1.63 [4H, m, (*Z*)-ArCH$_2$C*H*$_2$C*H*$_2$CH$_2$CH], 1.94 [2H, q, *J*=7 Hz, (*E*)-C*H*$_2$C=CH], 2.07 [2H, q, *J*=7 Hz, (*Z*)-C*H*$_2$C=CH], 2.53 [4H, t, *J*=7 Hz, (*E*)- and (*Z*)-ArCH$_2$], 3.48 [3H, s, (*E*)-CH$_3$], 3.56 [3H, s, (*Z*)-CH$_3$], 4.30 [1H, q, *J*=8 Hz, (*Z*)-C*H*=CHOCH$_3$], 4.69 [1H, dt, *J*=8, 12 Hz, (*E*)-C*H*=CHOCH$_3$), 5.86 [1H, d, *J*=8 Hz, (*Z*)-C*H*OCH$_3$], 6.26 [1H, d, *J*=12 Hz, (*E*)-C*H*OCH$_3$], 6.90–6.92 [4H, m, (*E*)- and (*Z*)-H-2 and H-6], 7.55–7.58 [4H, m, (*E*)- and (*Z*)-H-3 and H-5); $\delta_C\{^1H\}$ (90 MHz) 23.96, 29.6 [(*Z*)-ArCH$_2$-*C*H$_2$*C*H$_2$CH$_2$CH], 27.9, 30.6 [(*E*)-ArCH$_2$*C*H$_2$*C*H$_2$CH$_2$CH], 31.0 [(*E*)-*C*H$_2$CH], 31.2 [(*Z*)-*C*H$_2$CH], 35.6 [(*E*)- and (*Z*)-ArCH$_2$], 56.3 [(*E*)-OCH$_3$], 59.9 [(*Z*)-OCH$_3$], 90.9, 91.0 [(*E*)- and (*Z*)-C-4], 103.1 [(*E*)-*C*H=CHOCH$_3$], 106.9 [(*Z*)-*C*H=CHOCH$_3$], 131.0 [(*E*)- and (*Z*)-C-2 and C-6], 137.6 [(*E*)- and (*Z*)-C-3 and C-5], 142.7, 142.9 [(*E*)- and (*Z*)-C-1], 146.6 [(Z)-*C*HOCH$_3$], 147.5 [(*E*)-*C*HOCH$_3$]; *m/z* (EI) 316 (M^+, 100%), 284 (M−OCH$_3$–H, 43).

3.1.16. 6-(4-Iodophenyl)hexanal 1c. Formic acid (52 mL) was added to a pale yellow solution of (*E*)- and (*Z*)-6-(4-iodophenyl)-1-methoxyhex-1-ene **13** (8.6 g, 27.21 mmol) in DCM (40 mL). Upon addition, the solution immediately deepened to a bright yellow colour. The reaction was stirred at room temperature in a foil covered vessel for 64 h. Demineralised water (50 mL) was then added to the reaction and the two layers were partitioned. The organic layer was removed and the aqueous layer extracted with DCM (2×100 mL). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate (2×50 mL) and sodium chloride (50 mL), dried ($MgSO_4$) and evaporated in vacuo to give the title compound **1c** as a pale yellow oil (7.0 g, 23.18 mmol, 85%) (Found: C, 47.4; H, 4.8. $C_{10}H_{11}IO$ requires C, 47.70; H, 5.00%); ν_{max}(neat)/cm^{-1} 1721vs (C=O); δ_H(360 MHz) 1.31–1.39 (2H, m, ArCH$_2$CH$_2$C*H*$_2$), 1.42–1.78 (4H, m, ArCH$_2$C*H*$_2$ and C*H*$_2$–CH$_2$CHO), 2.43 (2H, dt, *J*=8, 2 Hz, C*H*$_2$CHO), 2.55 (2H, t, *J*=8 Hz, ArCH$_2$), 6.91–6.94 (2H, m, H-2 and H-6), 7.58–7.60 (2H, m, H-3 and H-5), 9.71 (1H, t, *J*=2 Hz, CHO); $\delta_C\{^1H\}$ (90 MHz) 22.0, 28.8, 31.2 (ArCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$–CH$_2$CHO), 35.3 (ArCH$_2$), 43.0 (*C*H$_2$CHO), 91.5 (C-4), 130.9 (C-2 and C-6), 137.8 (C-3 and C-5), 142.4 (C-1), 202.8 (CHO); *m/z* (CI, NH$_3$) 320 (MNH_4^+, 100%).

3.1.17. 6-(3-Iodophenyl)hexanal 14c and 5-(3-iodophenyl)hexanal 15c. The procedure was identical to that used for **1a** and **2a** except that 1,3-di-iodobenzene and 5-hexen-1-ol (9.0 mL, 75.02 mmol, 1.5 equiv) were used. The experiment afforded the title compounds **14c** and **15c** as a pale yellow oil (7.75 g, 25.66 mmol, 51%; 78:22 linear to branched aldehyde); spectroscopic data for 6-(3-iodophenyl)hexanal **14c**: ν_{max}(neat)/cm^{-1} 1723vs (C=O); δ_H(360 MHz) 1.35–1.72 (6H, m, ArCH$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$–CHO), 2.46 (2H, dt, *J*=7, 2 Hz, C*H*$_2$CHO), 2.58 (2H, t, *J*=7 Hz, ArCH$_2$), 7.02–7.04 (1H, m, H-5), 7.15–7.17 (1H, m, H-6), 7.53–7.57 (2H, m, H-2 and H-4), 9.79 (1H, t, *J*=2 Hz, CHO); $\delta_C\{1H\}$ (90 MHz) 22.3, 29.1, 31.4 (ArCH$_2$–*C*H$_2$*C*H$_2$*C*H$_2$CH$_2$CHO), 35.7 (ArCH$_2$), 44.2 (*C*H$_2$CHO), 95.1 (C-3), 128.1, 130.5, 135.2, 137.8 (C-2, C-4, C-5, C-6), 145.3 (C-1), 203.0 (CHO); *m/z* (CI, NH$_3$) 320 ($MNH_4{}^+$, 100), 194 (MNH_4^+–I+H, 2); discernible spectroscopic data for 5-(3-iodophenyl)hexanal **15c**: δ_H(360 MHz) 1.21 [3H, d, *J*=7 Hz, CH(C*H*$_3$)], 1.37–1.54 (4H, m, C*H*$_2$C*H*$_2$CH$_2$CHO), 2.46 (2H, dt, *J*=7, 2 Hz, C*H*$_2$CHO), 2.61 [1H, q, *J*=7 Hz, C*H*(CH$_3$)], 7.05–7.06 (1H, m, H-5), 7.17–7.18 (1H, m, H-6), 7.58–7.60 (2H, m, H-2 and H-4), 9.75 (1H, t, *J*=2 Hz, CHO); $\delta_C\{^1H\}$ (90 MHz) 20.6 (*C*H$_2$CH$_2$CH$_2$CHO), 22.6 [CH(*C*H$_3$)], 37.9 (*C*H$_2$CH$_2$-CHO), 40.1 [*C*H(CH$_3$)], 44.2 (*C*H$_2$CHO), 94.9 (C-3), 126.7, 130.7, 135.6, 136.4 (C-2, C-4, C-5, C-6), 149.9 (C-1), 202.8 (CHO).

3.1.18. *N*-[6-(3-Iodophenyl)hexyl]serine methyl ester 16c. (±)-Serine methyl ester hydrochloride (2.32 g, 14.90 mmol, 1.5 equiv), 6-(3-iodophenyl)hexanal **14c** and 5-(3-iodophenyl)hexanal **15c** (3.0 g, 9.93 mmol, 1.0 equiv) were introduced into a reaction vessel which contained anhydrous magnesium sulfate (1.1 g) suspended in dry DCM (19.9 mL, 0.5 M) under nitrogen. Triethylamine (2.77 mL, 19.86 mmol, 2.0 equiv) was added and the reaction was stirred at room temperature for 24 h. The contents of the flask were transferred to another reaction vessel via filter cannula under nitrogen and the filtrate was evaporated in vacuo to give a yellow oil. The oil was dissolved in dry methanol (19.9 mL, 0.5 M) and cooled to 0 °C under nitrogen. Sodium borohydride (0.75 g, 19.86 mmol, 2.0 equiv) was added portionwise and the reaction was allowed to warm to room temperature and stirred for 48 h. Work-up and purification as for **3a** afforded the title compound **16c** as a white solid (1.80 g, 4.48 mmol, 45%), mp 34–35 °C (Found: C, 47.5; H, 6.1; N, 3.4. $C_{16}H_{24}INO_3$ requires C, 47.40; H, 5.97; N, 3.46%); ν_{max}($CHCl_3$)/cm^{-1} 3600–3200br s (NH and OH), 1736vs (C=O); δ_H(400 MHz) 1.25–1.55 (8H, m, ArCH$_2$C*H*$_2$C*H*$_2$–C*H*$_2$C*H*$_2$CH$_2$N), 2.39–2.63 (4H, m, ArCH$_2$ and CH$_2$N), 3.29 (1H, dd, *J*=7, 5 Hz, C*H*CO$_2$CH$_3$), 3.49 (1H, dd, *J*=11, 7 Hz, C*H*HOH), 3.68 (3H, s, CO$_2$CH$_3$), 3.70 (1H, dd, *J*=11, 5 Hz, CH*H*OH), 6.91–6.95 (1H, m, H-5), 7.04–7.06 (1H, m, H-6), 7.42–7.46 (2H, m, H-2 and H-4); $\delta_C\{^1H\}$ (100 MHz) 26.4, 28.4, 29.5, 31.8 (ArCH$_2$*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$–CH$_2$N), 34.8 (ArCH$_2$), 47.6 (CH$_2$N), 51.6 (CO$_2$*C*H$_3$), 61.7 (CH$_2$OH), 62.1 (*C*HCO$_2$CH$_3$), 93.9 (C-3), 127.1, 129.4, 134.1, 136.8 (C-2, C-4, C-5, C-6), 144.6 (C-1), 173.0 (*C*O$_2$CH$_3$); *m/z* (EI) 405 (M^+, 11%), 374 (M−CH$_2$OH, 50), 346 (M−CO$_2$CH$_3$, 84).

3.1.19. Methyl 2-{*N*-[(6-(3-iodophenyl)hexyl]-*N*-(*tert*-butyloxycarbonyl)-amino}prop-2-enoate 17c. Di-*tert*-butyl dicarbonate (3.17 g, 14.53 mmol, 1.1 equiv) was added in one portion to a stirred solution of *N*-[6-(3-iodophenyl)hexyl]serine methyl ester **15c** (5.35 g, 13.21 mmol, 1.0 equiv) in dry DCM (12.0 mL) under nitrogen at 0 °C. After 30 min, the reaction was allowed to warm to room temperature, and stirred for a further 24 h. The solution was diluted with the addition of dry DCM (19.2 mL). *p*-Toluenesulfonyl chloride (3.78 g, 19.82 mmol, 1.5 equiv) and triethylamine (5.5 mL, 39.6 mmol, 3.0 equiv) were added and the reaction was stirred for a further 24 h. Work-up and purification as for **4a** afforded the title compound **17c** as a clear yellow oil (5.35 g, 10.99 mmol, 83%) [Found (M^++Na) 510.1136. $C_{21}H_{30}$–INO_4Na requires for *M*, 510.1117]; ν_{max}(neat)/cm^{-1} 1736vs (C=O), 1709vs (C=O), 1629s (C=C); δ_H(400 MHz) 1.25–1.50 (8H, m, ArCH$_2$*CH$_2$CH$_2$CH$_2$CH$_2$*CH$_2$N), 1.33 [9H, s, C(CH$_3$)$_3$], 2.44 (2H, t, *J*=7 Hz, ArCH$_2$), 3.38 (2H, t, *J*=7 Hz, CH$_2$N), 3.69 (3H, s, CO$_2$CH$_3$), 5.30 (1H, s, C=C*H*H), 5.81 (1H, s, C=CH*H*), 6.89–6.92 (1H, m, H-5), 7.02–7.04 (1H, m, H-6), 7.40–7.44 (2H, m, H-2 and H-4); δ_C{^{1}H} (100 MHz) 26.9, 29.3, 31.6, 35.8, (ArCH$_2$*CH$_2$CH$_2$*–*CH$_2$CH$_2$*CH$_2$N), 28.6 [C(*C*H$_3$)$_3$], 35.8 (ArCH$_2$), 49.8 (CH$_2$N), 52.6 (CO$_2$*C*H$_3$), 81.2 [*C*(CH$_3$)$_3$], 94.8 (C-3), 117.3 (C=*C*H$_2$), 128.1, 130.9, 135.3, 137.8 (C-2, C-4, C-5, C-6), 140.5 (C-1), 145.6 (*C*=CH$_2$), 154.2 [*C*O$_2$C(CH$_3$)$_3$], 165.9 (*C*O$_2$CH$_3$); *m/z* (EI, 20 eV) 487 (M^+, 8%), 431 [MH–C(CH$_3$)$_3$, 100], 372 [MH–CO$_2$CH$_3$–C(CH$_3$)$_3$, 76].

3.1.20. 8,23-Dicarbomethoxy-7,22-*N*,*N*-di-(*tert*-butyloxy-carbonyl)-[7.7]*meta*cyclophan-8,23-diene 18c. 3 Å Molecular sieves (2.81 g) were heated in vacuo in a Woods metal bath for 6 h and then added to a Schlenk tube charged with methyl 2-{*N*-[6-(3-iodophenyl)hexyl]-*N*-(*tert*-butyloxycarbonyl)-amino}prop-2-enoate **17c** (2.81 g, 5.77 mmol, 1.0 equiv), palladium(II) acetate (130 mg, 0.577 mmol, 10 mol%), sodium hydrogencarbonate (1.16 g, 14.43 mmol, 2.5 equiv) and tetra-*n*-butyl ammonium chloride (1.60 g, 5.77 mmol, 1.0 equiv). The reaction vessel was evacuated and filled with nitrogen (×5). Dry DMF (115 mL, 0.05 M) was added and the reaction vessel was again evacuated and filled with nitrogen (×5). Reaction conditions, work-up and purification used for **5a** afforded the title compound **18c** as a white solid (0.84 g, 1.17 mmol, 41%), mp 50–51 °C (Found: C, 70.0; H, 8.2; N, 3.8. $C_{42}H_{58}N_2O_8$ requires C, 70.17; H, 8.13; N, 3.90%); ν_{max}(CHCl$_3$)/cm^{-1} 1717vs (C=O), 1695vs (C=O), 1637s (C=C); δ_H(360 MHz) 1.08–1.65 (16H, m, 2×ArCH$_2$*CH$_2$*–*CH$_2$CH$_2$CH$_2$*CH$_2$N), 1.36 [18H, s, 2×C(CH$_3$)$_3$], 2.49–2.67 (4H, m, 2×ArCH$_2$), 3.16–3.50 (4H, m, 2×CH$_2$N), 3.83 (6H, s, 2×CO$_2$CH$_3$), 7.10–7.18 (2H, m, 2×H-5), 7.20–7.27 (2H, m, 2×H-6), 7.29–7.35 (4H, m, 2×H-2 and H-4), 7.41 (2H, s, 2×C=CH); δ_C{^{1}H} (90 MHz) 27.2, 28.3, 28.9, 31.9 (ArCH$_2$*CH$_2$CH$_2$CH$_2$CH$_2$*CH$_2$N), 28.8 [C(*C*H$_3$)$_3$], 35.8 (ArCH$_2$), 48.7 (CH$_2$N), 80.7 [*C*(CH$_3$)$_3$], 128.2, 129.6, 130.3, 130.6 (C-2, C-4, C-5, C-6), 133.6 (C-1 and C-3), 137.6 (C=*C*H), 143.1 (*C*=CH), 155.4 [*C*O$_2$C(CH$_3$)$_3$], 166.9 (*C*O$_2$CH$_3$); *m/z* (FAB, positive) 741 (M^++Na, 4%), 619 [MH–CO$_2$C(CH$_3$)$_3$+H, 10], 564 [MH–CO$_2$C(CH$_3$)$_3$–C(CH$_3$)$_3$+3H, 89], 520 [MH–CO$_2$C(CH$_3$)$_3$–CO$_2$C(CH$_3$)$_3$+3H, 100], 460 [MH–CO$_2$C(CH$_3$)$_3$–CO$_2$C(CH$_3$)$_3$–CO$_2$CH$_3$+2H, 18], 400 [MH–CO$_2$C(CH$_3$)$_3$–CO$_2$C(CH$_3$)$_3$–CO$_2$CH$_3$–CO$_2$CH$_3$+H, 7].

3.2. Molecular modelling

Molecular modelling was carried out using a Silicon Graphics O2 workstation running under IRIX. The software used was a proprietary package, which incorporated a modified version of COSMIC equipped with XED (eXtended Electronic Distribution) charges[15] rather than the original atom-centred charges.

Acknowledgements

The authors thank James Black Foundation for generous studentship support (J.O.J. and N.M.), the RSC for a Hickinbottom Fellowship student bursary (J.O.J), and EPSRC for an Ear-Marked studentship (J.D.K.).

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