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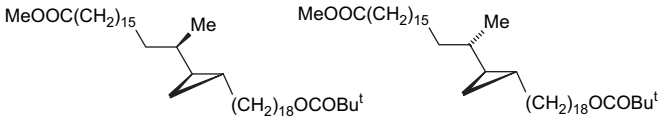
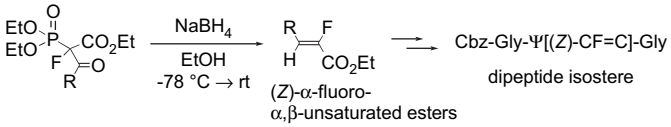
Contents

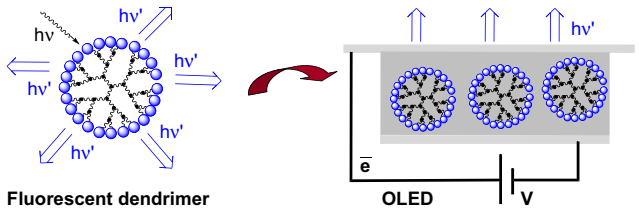
REPORT

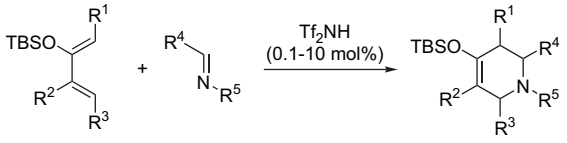
The concept, protocols, instruments of fluorous solid-phase extraction techniques, and their applications for solution-phase parallel and high-throughput synthesis of small molecules and biomolecules are reviewed in this article.

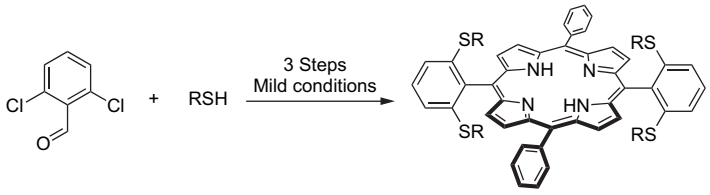
ARTICLES

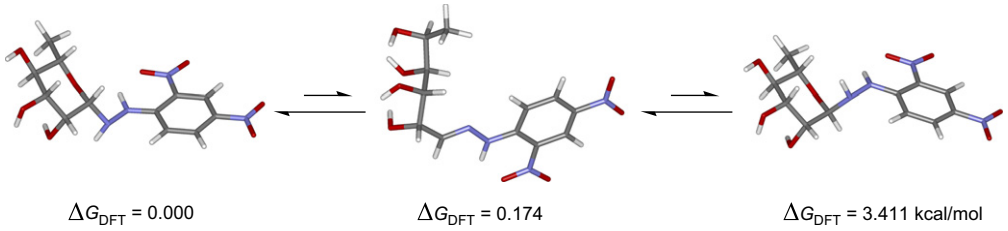


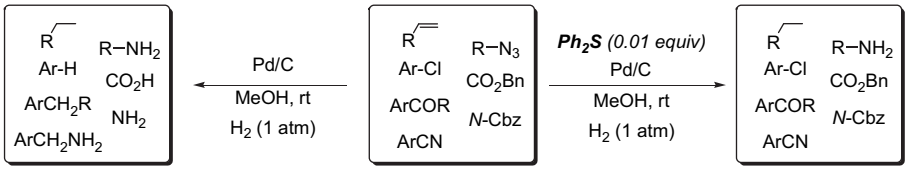


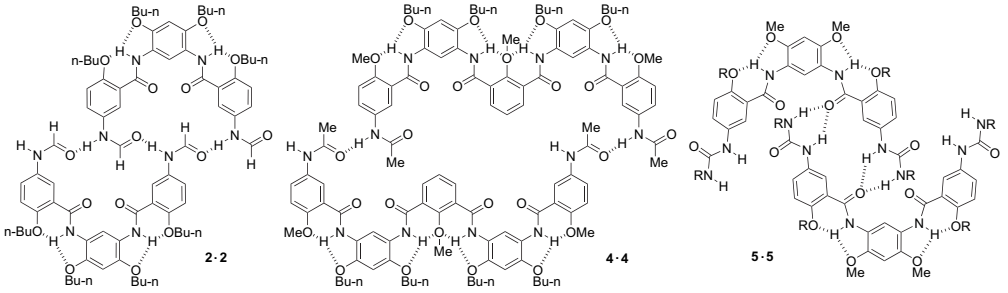


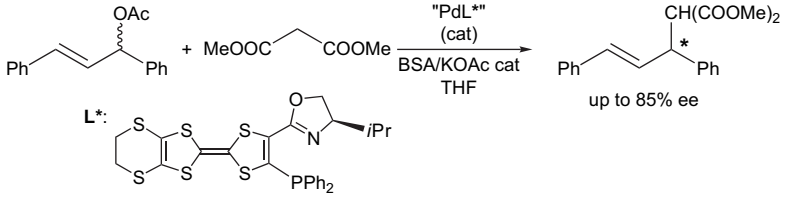


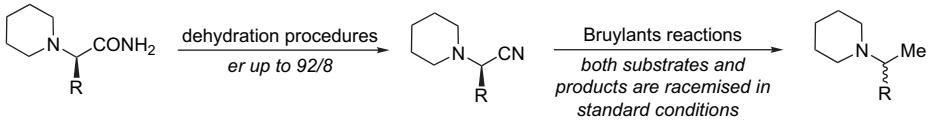


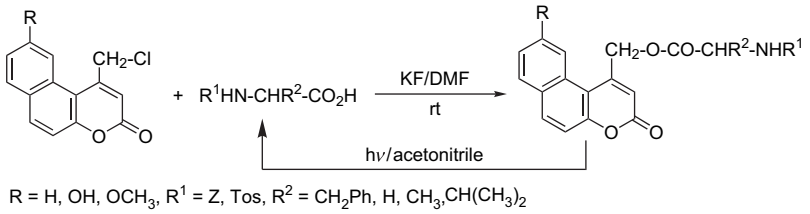


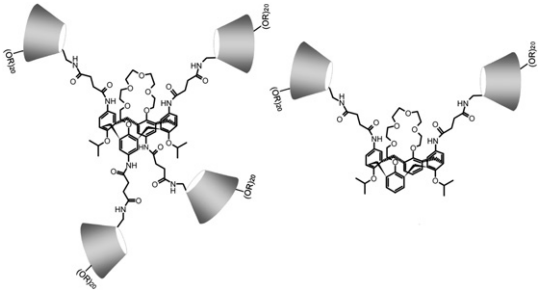




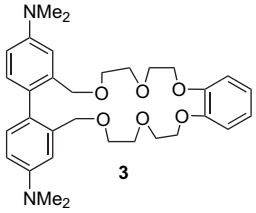




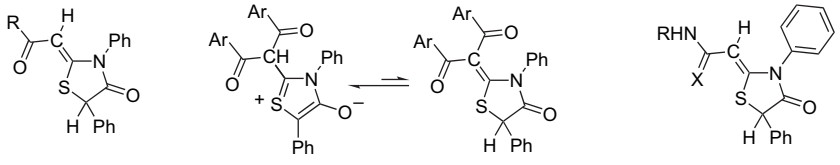


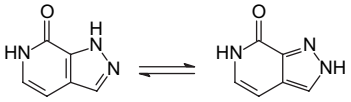


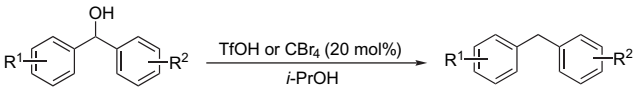
Structures of two main bis- and tetrasubstituted cyclodextrin–calixarene coupling products (R=methyl or H).

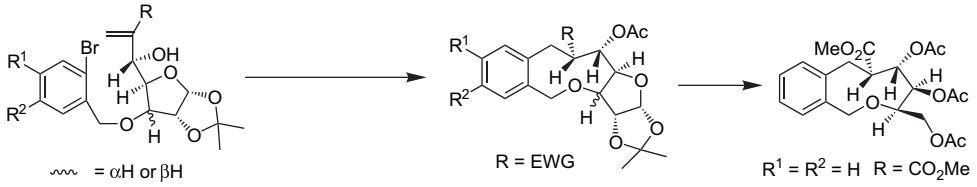


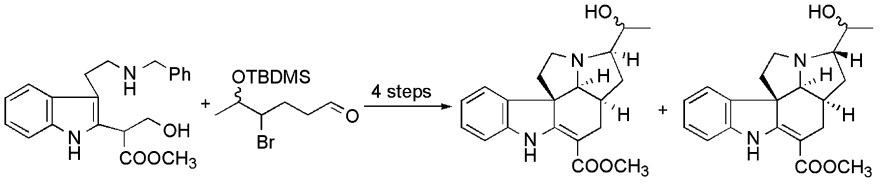
Six new 4,4′-substituted biphenyl coronands have been prepared. The ligands containing dimethylamino groups in the biphenyl moiety have been used in transition metal cations' complexation and one of them (**3**) has demonstrated to be a selective fluorescent sensor for mercury.

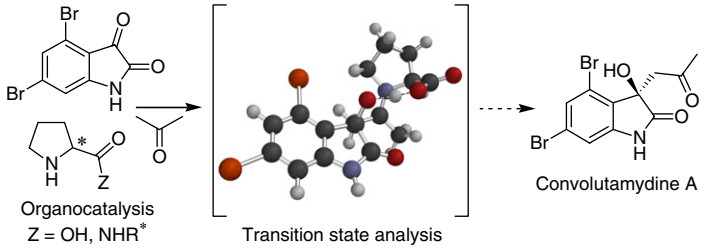


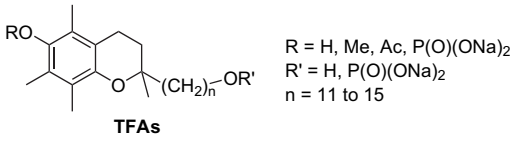




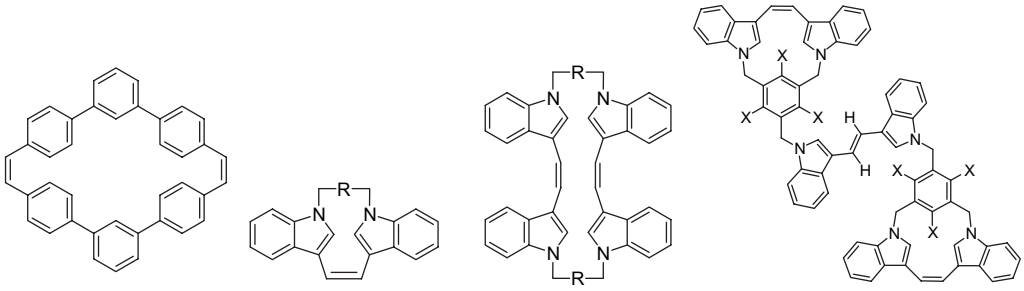


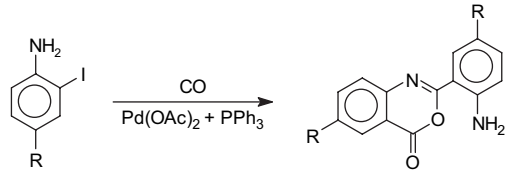


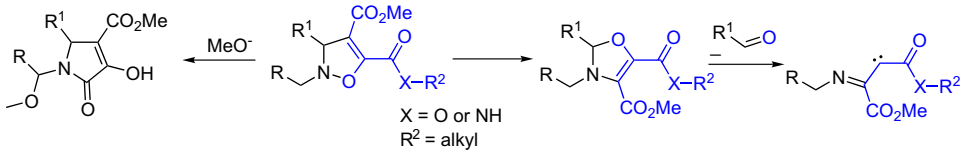


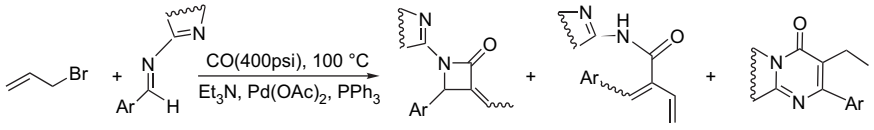


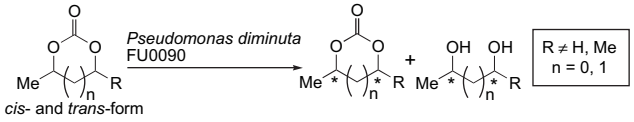
Improved syntheses of several series of tocopherol fatty alcohols (TFAs), modulators of microglial activation as well as their water-soluble prodrug forms are described.

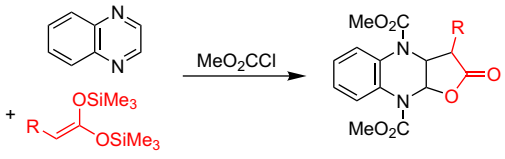


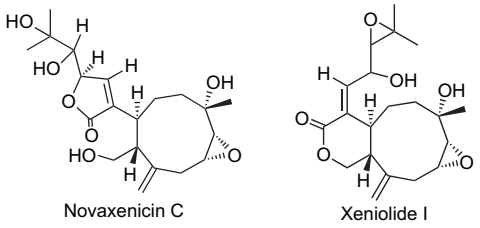




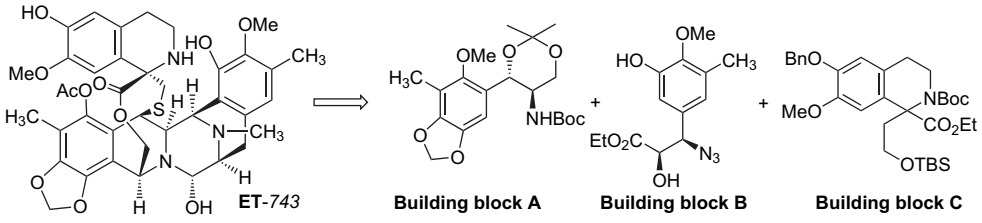


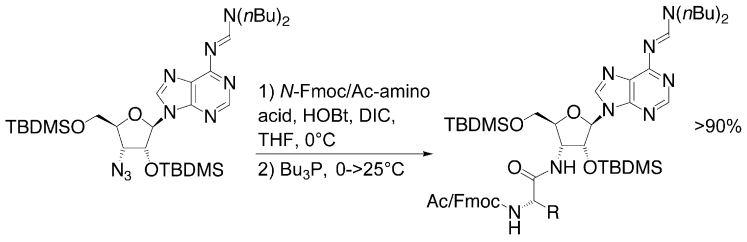






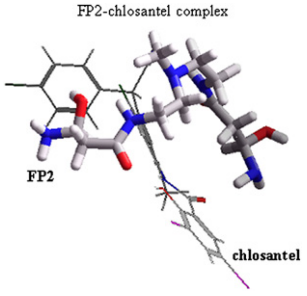
The structure of seven new compounds and their relative stereochemistry were elucidated by NMR and mass spectroscopy data.





An efficient Staudinger–Vilarrasa coupling generates amides from azides in very high isolated yields and purity. New puromycin analogs, mostly putative biosynthetic intermediates, were synthesized in nine steps from adenosine.

Four dendrimeric fragments (FPs) were designed to encapsulate, mainly by H-bonding, a family of drugs known as salicylanilides (acaricides). All geometries were optimized at DFT/LAV3P* level of theory. Amide and alcohol groups were the most efficient to interact with salicylanilides (e.g., FP2–chlosantel complex).



*Corresponding author
Supplementary data available via ScienceDirect

COVER

Several series of phosphorus dendrimers decorated by fluorescent terminal groups are synthesized. A dramatic dependence of the fluorescence properties with the nature of the linkage between the dendrimer and the fluorescent entities is observed. Some of these dendrimers possess electroluminescent properties and were used for the elaboration of Organic Light Emitting Diodes (OLEDs). *Tetrahedron* **2006**, *62*, 11891–11899.

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Synthetic applications of fluorous solid-phase extraction (F-SPE)

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Contents

Keywords: Fluorous; Light fluorous; Fluorous silica gel; Fluorous solid-phase extraction (F-SPE); Reverse F-SPE; Plate-to-plate SPE; Parallel synthesis; High-throughput synthesis; Solution-phase synthesis; Separation; Reagents; Reactants; Catalysts; Chiral auxiliaries; Scavengers; Protecting groups; Displaceable tags; Fluoro*Flash*®; VacMaster®; FlashMaster™; Ex-Block; RapidTrace®; Whatman®.

Abbreviations: BINAP, 2,2′-bis(diphenylphosphineno)-1,1′-binaphthyl; BINOL, 1,1′-bi-2,2′-naphthol; Boc, *tert*-butyloxycarbonyl; BTF, benzotrifluoride; Cbz, benzyloxycarbonyl; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; *m*-CPBA, *meta* chloroperbenzoic acid; DCT, 2,4-dichloro-1,3,5-triazine; dba, dibenzylideneacetone; DEAD, diethyl azodicarboxylate; DIPEA, diisopropylethylamine; DCC, dicyclohexylcarbodiimide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; dppp, 1,2-bis(diphenylphosphineno)propane; DMF, *N*,*N*-dimethylformamide; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; dppf, 1,1′-bis(diphenylphosphineno)ferrocene; FC-72, perfluorohexanes; F-SPE, fluorous solid-phase extraction; FTI, Fluorous Technologies, Inc.; HFE-7100, perfluorobutyl methyl ether; HOAT, 1-hydroxy-7-azabenzotriazole; HOBT, 1-hydroxybenzotriazole; HPLC, high-performance liquid chromatography; LLE, liquid–liquid separation; MOM, methoxymethyl; μw, microwave; NIS, *N*-iodosuccinimide; Oxone, potassium peroxymonosulfate; Rf, perfluoroalkyl group; Rfh, perfluoroalkyl group with CH_2 spacer; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, 2-tetrahydropyranyl; TLC, thin-layer chromatography; TMS, trimethylsilyl; TPP, triphenylphosphine.

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1. Introduction

1.1. Synthesis is reaction and separation

The enterprise of organic synthesis is a collective endeavor involving reaction and separation followed by identification and analysis.[1] The 'reaction and separation stage' produces a new organic molecule while the 'identification and analysis stage' proves what the molecule is and how pure it is. The yield of every organic reaction depends on both the efficiency of the underlying reaction and the ability to recover the target product in pure form from the reaction mixture. Reaction methods have evolved and improved dramatically over the past decades and continue to do so. On the other hand, while they continued to be refined, the core separation methods that synthetic chemists routinely use have not changed for a decade or more.

The concept of the 'ideal reaction' serves as an inspiring, if unattainable, goal for basic research in synthesis.[2] In the trenches (the labs), reactions are usually a means to an end (chemical and drug discovery), and chemists tend to spend more time searching, hoping and wishing for the 'ideal separation'.[1a,b] It is rare that a new, generally applicable separation method comes along.

The purpose of this report is to provide an overview of the increasingly popular new separation technique of fluorous solid-phase extraction (F-SPE). Though it is still less than a decade old,[3] the technique has matured rapidly and is now ready for prime time, as illustrated by the expanding uses over the last 2–3 years.[4] After a brief introduction of two varieties of F-SPE—standard and reverse—we provide comprehensive tabular collections of published uses in small molecule synthesis that are intended to illustrate both the scope of the method and the diverse array of reagents and materials that are now available. We close by providing interested readers with practical information on how to conduct an F-SPE.

1.2. Light fluorous chemistry

The bifurcation of fluorous chemistry into 'heavy' and 'light' branches in 1999 was a direct result of the introduction of F-SPE. The earliest work in the fluorous field focused on introducing large (therefore 'heavy') fluorous tags onto organic and oganometallic reaction components (catalysts, reagents, reactants, etc.).[5,6] These tags then rendered the resulting tagged reaction components soluble in fluorocarbon and other highly fluorinated solvents, and enabled powerful techniques like fluorous biphasic and triphasic reactions, biphasic and triphasic liquid–liquid extractions (LLEs),[7] thermomorphic reactions, and more.[8] The exciting branch of heavy fluorous chemistry, whose techniques are especially suitable for large-scale processes, continues to forge ahead at a rapid pace today.

Heavy fluorous tags are often called ponytails because they usually sprout several fluoroalkyl chains bearing 39 or more (often many more) fluorines. From the outset, workers in the field were bent on giving these ponytails a haircut. The resulting light fluorous molecules (typically with 9–17 fluorines) are cheaper and more readily available, and are much more soluble in common organic solvents. But therein lies the rub—they are also much less soluble in fluorous solvents so the LLE breaks down. The enabling advance for light fluorous molecules was the replacement of the LLE with an SPE.[3,9,10]

Figure 1 compares and contrasts a pair of related heavy and light fluorous alkene metathesis[11] catalysts. The heavy fluorous catalyst **1** is a copolymer of a catalyst component and the fluorous acrylate.[12] (However, many molecular heavy fluorous catalysts are also known.) It is freely soluble in FC-72 but is insoluble in organic solvents like CH_2Cl_2 and EtOAc. Following a reaction with a substrate in $C_6H_5CF_3$–CH_2Cl_2 the catalyst is extracted away from the products with FC-72. Multiple cycles of recovery and reuse were conducted. In principle, it makes little difference that heavy catalysts like **1** have low or even no solubility in the organic

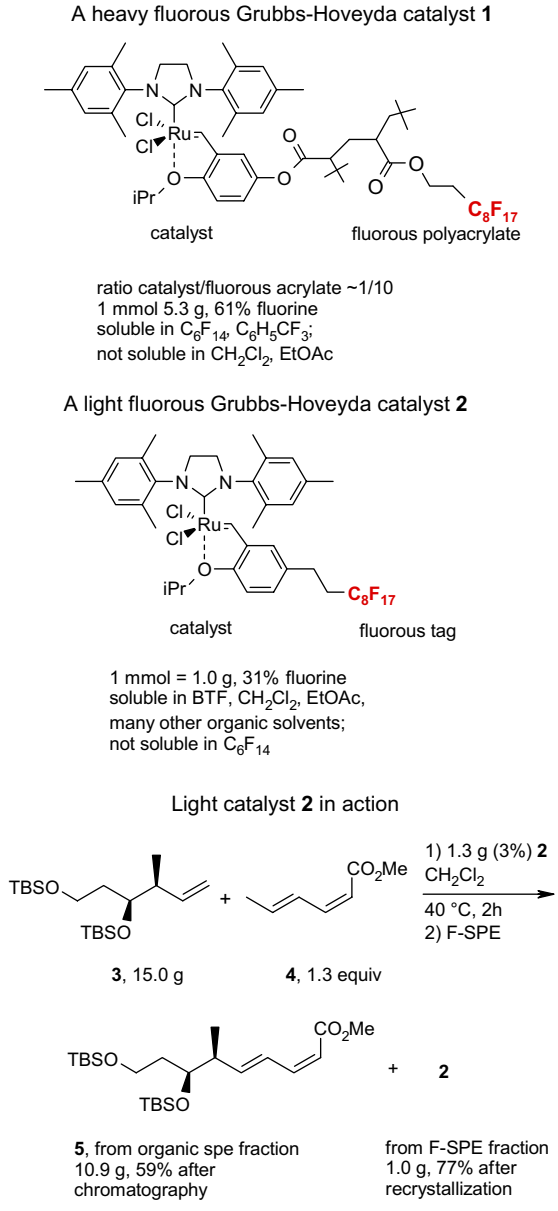


Figure 1. Comparing and contrasting light and heavy fluorous Grubbs–Hoveyda.

reaction solvent, so long as the reaction works. In practice, however, it makes a big difference, especially in small-scale discovery chemistry. Target reactions may fail either because they are too slow to occur at all or because other side reactions occur more rapidly. The rate of a target reaction often depends directly on the concentration of a reactant in the reaction solution—in other words, on its solubility. So having soluble reaction components is a huge advantage, especially when reactions are not understood in great detail, as is always the case with new reactions.

Light fluorous catalyst **2** has very different physical properties from heavy cousin **1**.[13] A green crystalline solid, it is freely soluble in most common organic reaction solvents but has low solubility in fluorous solvents like FC-72. These properties are advantageous for running reactions since one can simply use the standard conditions for non-fluorous reagents without modification.

For example, cross metathesis of **3** and **4** has been conducted at University of Pittsburgh on large scale for a preparative total synthesis of analogs of the anti-cancer agent dictyostatin.[14] In a typical run, 15 g of alkene **3** and diene **4** (1.3 equiv) were combined with 1.3 g of catalyst **2** (3%) in 50 mL of dichloromethane. The homogeneous mixture was warmed to 40 °C for 2 h and cooled prior to evaporation of the reaction solvent. The mixture was then subjected to F-SPE over 50 g of fluorous silica gel to provide an organic fraction of cross- and self-metathesis products. Purification of this fraction provided the cross-coupled product **5** in 60% yield. The fluorous fraction was primarily the recovered catalyst **2** and could be used as such; however, we prefer to recrystallize this product to ensure high catalyst quality for the next use in either the same or a different reaction. Recrystallization of the crude fluorous product from this reaction provided 1.0 g (77%) of recovered catalyst, which was of comparable appearance and purity to the original sample.

Comparing and contrasting this type of light fluorous reaction with traditional solution-phase methods and also solid-phase methods highlights the advantages of the fluorous approach.[15] In reaction, identification, and analysis phases, the light fluorous approach resembles traditional solution-phase methods rather than solid-phase methods because the fluorous reaction components are molecules, not materials. Light fluorous molecules are often soluble in a broad range of standard organic reaction solvents and exhibit reactivity comparable to their non-fluorous parents.[16] In other words, their reaction features are readily predicted. Fluorous molecules can be routinely analyzed by all standard spectroscopic methods and separated by both fluorous and non-fluorous techniques.

The advantage over traditional solution-phase chemistry comes at the separation stage, because the separation of fluorous compounds by F-SPE is a reliable and generic procedure that resembles more a filtration than a chromatography. The separation depends primarily on the presence or absence of a fluorous tag, not polarity or other molecular features that control traditional chromatography. In many respects, light fluorous methods capture the best features of traditional solution-phase chemistry, yet still provide a facilitated separation.

2. Concept of F-SPE

2.1. Classification of F-SPE

F-SPE separations can be grouped into two classes: standard and reverse. The standard or original solid-phase extraction is much more common and involves the partitioning between a fluorous solid phase and a fluorophobic liquid phase.[4] This technique has been used in many settings (manual SPE, automated SPE, plate-to-plate SPE, automated flash chromatography, HPLC) and has proven generality. In contrast, the nascent technique of reverse fluorous solid-phase extraction[17] uses a fluorophobic solid phase (standard silica gel) and a fluorous liquid phase. While there are currently only a few examples, the reverse F-SPE technique has considerable potential. Both techniques have been described in detail[4,17] and we provide here a brief summary. Section 5 of the report on practical aspects is for those planning to use the standard F-SPE technique in the lab.

SPE[18] and chromatography are related because both involve partitioning between solid and liquid phases, and the transition zone between the two techniques is grey. In chemical analysis, an SPE is usually used to help concentrate a very dilute sample; however, in synthesis it is used to partition a concentrated sample rapidly into two fractions. In general, the synthetic SPE resembles a filtration more than a chromatography, and has higher loading levels and lower solvent volumes. After elution of a first fraction with a first solvent, a second solvent of stronger eluting power is added to elute a second fraction. That second fraction is simply too well adsorbed on the solid phase to be eluted by the first solvent in a practical time frame. Multiple fraction collection and analysis are not required—there is one wash for unretained molecules and one wash for retained molecules. In chromatography, elution of successive fractions is typically a 'time-dependent' process—sooner or later, all of the fractions elute. In SPE, elution of successive fractions is a 'solvent-dependent' process.

Among different packing materials for SPE, ion-exchange resins have good retention selectivity, give 'mass-controlled' separation, and are little affected by the volume of the loading solvent. In contrast, polarity-based normal- and reverse-phase silica gels are much less selective and are more sensitive to the polarity and volume of the loading solvent.[18] Fluorous silica gel has strong and selective fluorine–fluorine interaction with fluorous molecules.

2.2. Standard F-SPE

Standard F-SPE was introduced in 1997[3] and involves the use of a fluorous solid phase and a fluorophilic (but not fluorous) solvent, as illustrated in Figure 2. The fluorous solid phase is typically silica gel with a fluorocarbon bonded phase ($–SiMe_2(CH_2)_2C_8F_{17}$), and this is commercially available from Fluorous Technologies, Inc. under the trade name of Fluoro*Flash*®.[19]

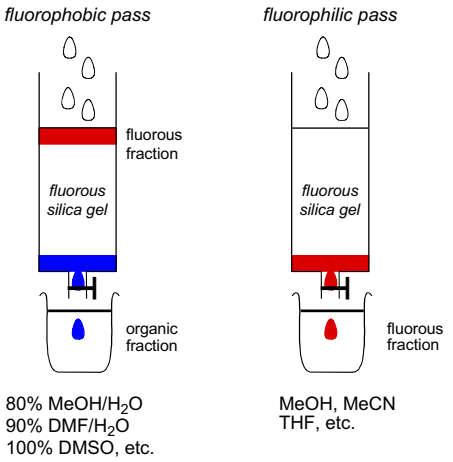


Figure 2. A cartoon of a 'standard' F-SPE. The organic fraction is blue and the fluorous fraction is red.

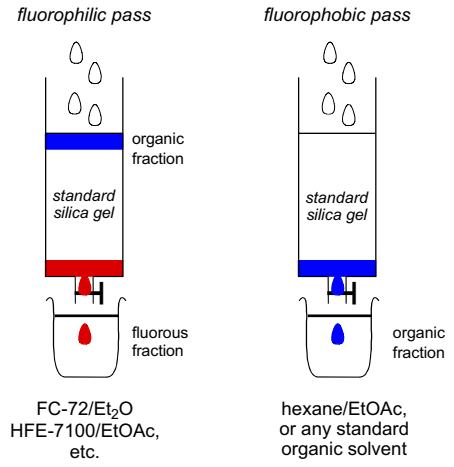


Figure 3. A cartoon of a 'reverse' F-SPE. The organic fraction is blue and the fluorous fraction is red.

Briefly, a crude reaction mixture containing both fluorous and non-fluorous reaction components is charged onto fluorous silica gel and then the silica is eluted with a fluorophobic solvent like 70–80% MeOH–H_2O, 50–60% CH_3CN–H_2O, 80–90% DMF–H_2O, or 100% DMSO. In this 'fluorophobic pass', non-fluorous (organic) compounds typically move at or near the solvent front and elute immediately, while fluorous compounds are retained on the silica gel. In the ensuing 'fluorophilic pass', elution with one of many organic solvents (water-free MeOH or CH_3CN, THF, among others) then provides a fluorous fraction containing those compounds bearing the fluorous tag.

The procedure is simple, general and reliable, and has now been used many times in diverse settings. Importantly, it does not seem to be very sensitive to the polarity of either the fluorous component or the organic component. Thus, the standard F-SPE is a very attractive separation technique in library settings since products with very different characteristics will all exhibit substantially the same behavior.

2.3. Reverse F-SPE

Reverse F-SPE is a new technique with few examples to date,[17] but with considerable potential. The philicities of the solid phase and liquid phase are reversed, and standard silica gel is used as the polar solid phase while blends of fluorous[20] and organic solvents are used as the fluorophilic liquid phase. The concept is illustrated in Figure 3. A sample containing fluorous and non-fluorous components is charged to regular silica gel with standard solvents, and then the silica is eluted with a fluorophilic solvent to remove a fluorous fraction (fluorophilic pass). In our first paper,[17] we used FC-72 (perfluorohexanes) and ether, among other combinations, but we now more often use HFE-7100 (perfluorobutyl methyl ether) blended with ethyl acetate, ether or another organic cosolvent. Following that, a fluorophobic pass can be conducted with any standard organic solvent.

Perfluoroalkyl alkyl ethers like HFE-7100 are preferred over fluorocarbons because the fluorocarbons have very poor eluting power (even for most light fluorous compounds) and they have limited miscibility in organic solvents. Because of this, the range of fluorophilic blends with such solvents is limited.

The reverse F-SPE is attractive for removing fluorous reagents, catalysts, and other byproducts from standard organic target products because after the fluorophilic pass is complete, the organic product absorbed on the head of the silica column can simply be purified by standard flash chromatography. It is also attractive because solvent elution conditions and prospects for success can be readily assessed by using standard silica gel TLC plates.

However, because standard silica gel is used, the behavior of reverse fluorous methods can be significantly affected by the polarity of both the fluorous and the non-fluorous components. While we still have limited experience, we currently feel that reverse F-SPE exhibits the most power when used to separate relatively nonpolar fluorous components from relatively polar organic components. Of course, such kinds of separations might also be conducted by standard chromatography with traditional solvents like hexane–EtOAc. However, the replacement of nonpolar solvent (hexane) of this combination with a fluorous solvent will often provide a better separation because this will significantly retard the elution of the organic fraction without retarding nearly as much (and perhaps even promoting) the elution of the fluorous component.

3. F-SPE methods

3.1. Pressure and gravity F-SPE

Depending on the type of fluorous silica gel that is used, F-SPEs can be driven with light pressure (positive or negative) or by gravity. Commercially available Fluoro*Flash*® SPE silica gel[21] has 40–60 μm particle sizes. Cartridges packed with this size silica gel require positive pressure on the top or negative pressure under the bottom to drive the elution process. When particle size is increased to around 120 μm, gravity SPE is possible.[22]

Figure 4. 2×12 Vacuum SPE manifold.

3.2. Common F-SPE systems

A basic unit for conducting 1–24 SPEs shown in Figure 4 is commercially available from Supelco. Other companies such as Fisher and Waters sell comparable units. The unit is a 2×12 manifold and employs negative pressure, which is convenient for SPE cartridges with 2–10 g silica gel. Fractions are collected in a 10–15 mL test tube. For F-SPE with big cartridges (6–10 g silica gel), more than one tube is needed to collect both non-fluorous and fluorous fractions.

Since the F-SPE process is highly reproducible and functional group independent, it can be easily automated or used in a plate-to-plate format. For parallel synthesis, plate-to-plate F-SPE can significantly increase the throughput. Samples are loaded onto a plate whose cartridges are packed with fluorous silica gel and fractions are collected in a matched receiving plate. The silica gel plate may be cartridge- or well-formatted. Figure 5 shows a 24-cartridge plate and a 24-well plate of VacMaster® from Biotage.[23] Similar systems are also available from United Chemical Technologies, Supelco, and Waters. If 40 μm fluorous silica gel is used, then the receiving plate is connected to a vacuum pump. The 24-channel plate has the following technical features: (1) each cartridge has 6 mL, and each well has 10 mL volume, which can be charged with 3–4 g of fluorous silica gel leaving ~3–5 mL top space for elution solvent; (2) each receiving well has 10 mL volume for collecting fraction; (3) a six-channel pipette is used for parallel sample loading and solvent loading; and (4) the Whatman® receiving plate[24a] has a standard footprint, which can be directly concentrated in a Genevac vacuum centrifuge. The 24-well plate is good for parallel purification of 10–100 mg quantity of products. This system has been demonstrated in the purification of small libraries produced involving amine scavenging reactions with fluorous isatoic anhydride, amide coupling reactions with F-CDMT, and amide coupling reactions with a fluorous Mukaiyama condensation reagent.[25a]

The 96-well F-SPE plate is more suitable for parallel synthesis of larger number but smaller quantity of samples. Figure 6 shows a pair of 96-well Ex-Block plates poised for plate-to-plate F-SPE.[24b] Each well in the top block has 3 mL volume and is charged with 1 g of fluorous silica gel. The bottom receiving well also has 3 mL volume. The 96-well plate F-SPE system has been demonstrated in gravity F-SPE with 120 μm size silica gel for fluorous scavenging reactions and amide coupling reactions.[22] There are several similar 96-well plates commercially available. However, most of them only have 2 mL well volume.

The F-SPE process can also be automated. The RapidTrace® SPE workstation has been widely used in biology labs for sample preparation,[26] but it is less popular in synthetic labs (Fig. 7). The workstation can have up to 10 modules arranged in parallel and attached to a computer to control cartridge conditioning, sample loading, cartridge elution, and fraction collection. The automated sample loading can handle solutions and slurries containing small amounts of solid. Pump-controlled solvent delivery gives accurate solvent volume and flow rate. Each module conducts 10 SPEs sequentially. A maximum of 10×10=100 SPE separations can be finished in 1–2 h unattended. Each SPE cartridge has 3 mL volume, which can be charged with 1.5 g of fluorous silica gel for the separation of 10–100 mg samples. Relative to the plate-to-plate SPE, the RapidTrace® unit has higher upfront instrument cost but significantly saves manpower and provides consistent results.[25b]

Figure 5. 24-Cartridge (left) and 24-well (right) SPE plates.

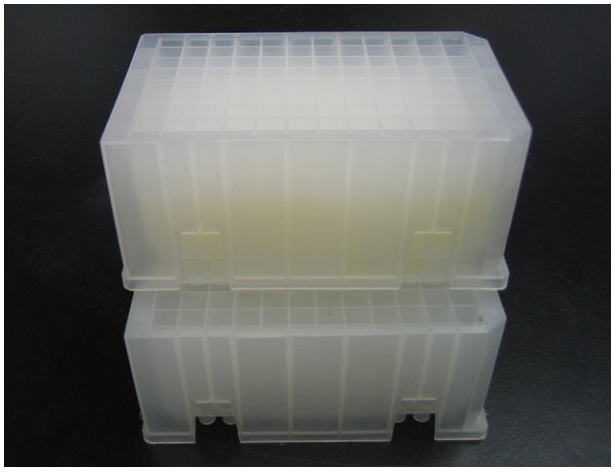


Figure 6. Ex-Block for 96-well plate-to-plate F-SPE.

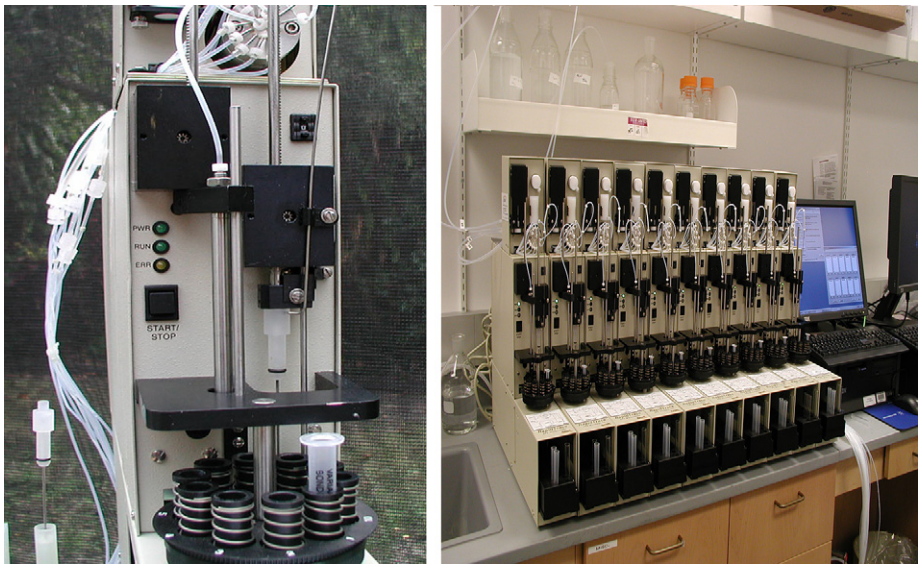


Figure 7. RapidTrace® SPE workstation (left, single unit; right, 10 parallel units).

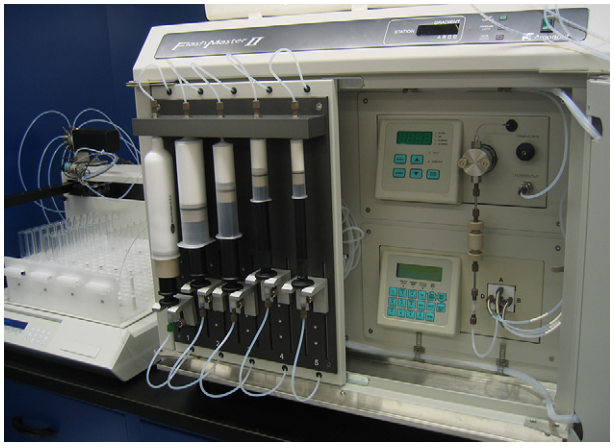


Figure 8. Biotage FlashMaster™ II for variable-scale F-SPE.

Commercial systems from Isco and Biotage are available for large-scale F-SPE or flash chromatography. Among them, the Biotage FlashMaster™ II can handle up to 200 psi back pressure, which is more suitable for fluorous separations using MeOH–H_2O and MeCN–H_2O as the elution solvents. This system has 10 channels; cartridge sizes from 5 to 100 g can be easily fit in (Fig. 8). The FlashMaster™ system also has many features of standard HPLC including gradient solvent mixing, flow control, and UV-trigged fraction collection.

4. Tabular summary of F-SPE

This tabular section is intended to provide a comprehensive collection of the published uses of F-SPE for separation in small molecule synthesis from its inception in 1997 up to early 2006. Small molecule synthesis is not the only use of F-SPE, but applications in oligonucleotide synthesis,[27] peptide synthesis,[28] proteomics[29] and other areas[30] are not covered here. Nor do we cover other uses for fluorous silica gel including HPLC demixing in fluorous mixture synthesis[31] and catalyst/reagent support applications.[32]

The tables are organized so that readers can easily scan them for relevant fluorous reaction components (left column) and allied transformations (center column). References are provided in the right column. In almost all cases, papers report multiple examples of the use of F-SPE, but we often extract only a single representative example. In the case of chiral auxiliaries and protecting groups, for example, the F-SPE may be used in multiple steps, including tagging, reaction of tagged substrate, and detagging. Here, we typically focus on the key reactions. In the case of library synthesis, we summarize the steps and show a generic example of the library core with R groups to give readers a sense of the scope and substitution pattern of the library.

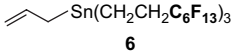
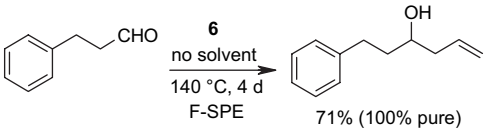
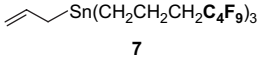
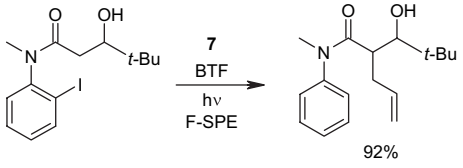
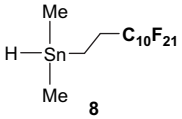
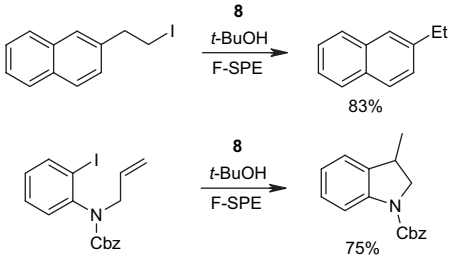
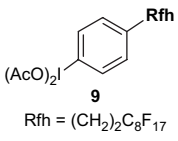
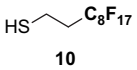
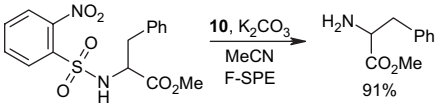
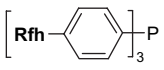
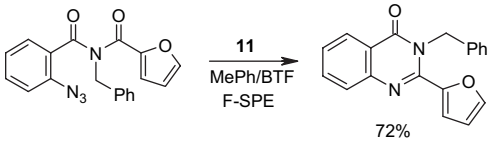
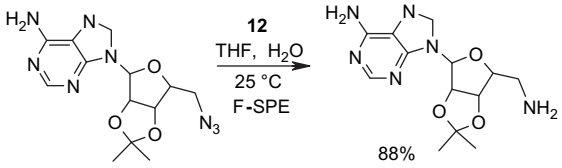
The tables are organized according to fluorous reaction component under the following headings:

- Reagents,[33] Table 1: One or more fluorous reagents are used in at least stoichiometric quantities, providing fluorous byproducts. The precursor and the target product are organic.
- Reactants, Table 2: A fluorous reactant is incorporated into the product, but it is not a chiral auxiliary or a protecting group.
- Catalysts,[34] Table 3: The fluorous reaction component is a catalyst or precatalyst. The precursor and the target product are organic.
- Chiral auxiliary, Table 4: The substrate and product bear a chiral auxiliary with a fluorous tag.
- Scavengers,[35] Table 5: A fluorous reagent is used to consume (scavenge) some undesired reaction component (usually an unreacted starting reagent) and the scavenged product is separated from the organic target product.
- Protecting groups,[36] Table 6: The substrate and/or product bear a fluorous version of a common protecting group.

- Displaceable tags,[36] Table 7: The substrate and derived intermediates bear a tag that is displaced with other functionalities, usually in a diversity oriented synthesis setting.

A number of the more popular fluorous reaction components shown in the tables are commercially available from Fluorous Technologies, Inc.,[19] Aldrich, Fluka, and Wako (in Japan).

Table 1. Reactions with fluorous reagents

Reagent	Transformation	Ref.
 **6**		3
 **7**		37
 **8**		38
 **9** Rfh = $(CH_2)_2C_8F_{17}$		39
 **10**		40
 **11** Rfh = $(CH_2)_3C_8F_{17}$		41
	Staudinger reactions	
$Ph_2P(C_6H_4CH_2CH_2C_6F_{13})$ **12**		42

(*continued*)

Table 1. (*continued*)

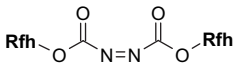
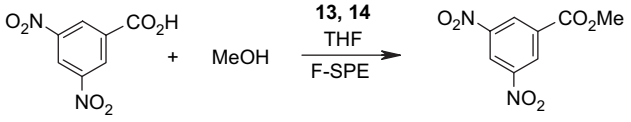
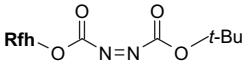
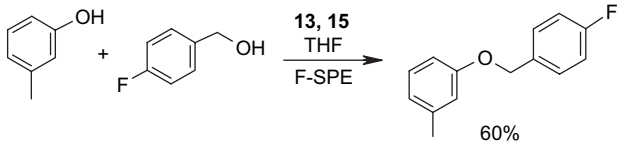
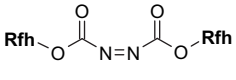
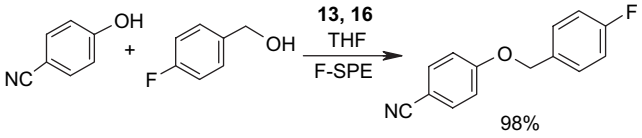
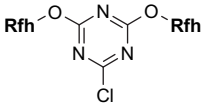
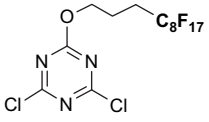
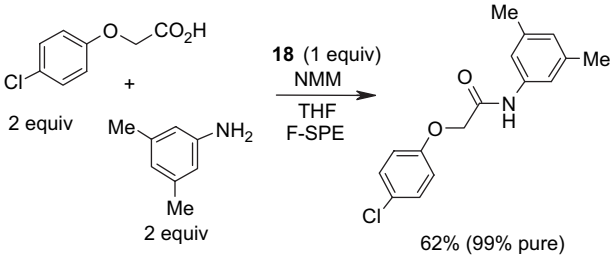
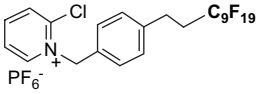
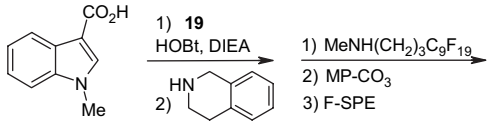
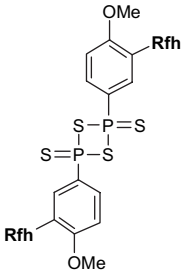
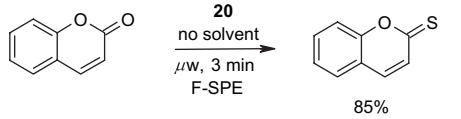
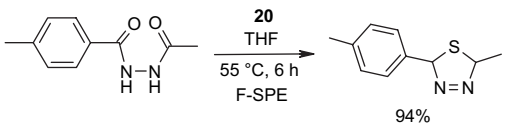
Reagent	Transformation	Ref.
$Ph_2P(C_6H_4CH_2CH_2\mathbf{C_8F_{17}})$ **13, F-TPP**	Mitsunobu reactions	
 **14, F-DEAD-1** Rfh = $(CH_2)_2C_6F_{13}$	 93%	
 **15, F-DEAD-2** Rfh = $(CH_2)_3C_6F_{13}$	 60%	43–45
 **16, F-DEAD-3** Rfh = $(CH_2)_3C_6F_{13}$	 98%	
 **17, F-CDMT** Rfh = $(CH_2)_3C_6F_{13}$	 57% (91% pure)	25
 **18, F-DCT**	 62% (99% pure)	46
 **19,** F-Mukaiyama condensation reagent	 95% (99% pure)	47
 **20,** F-Lawesson's reagent Rfh = $(CH_2)_5C_8F_{17}$ $(CH_2)_4C_8F_{17}$ $(CH_2)_4C_6F_{13}$	 85%  94%	48,49

Table 2. Reactions with fluorous reactants

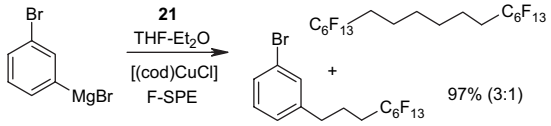
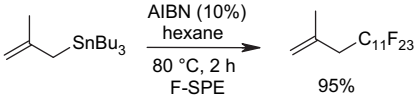
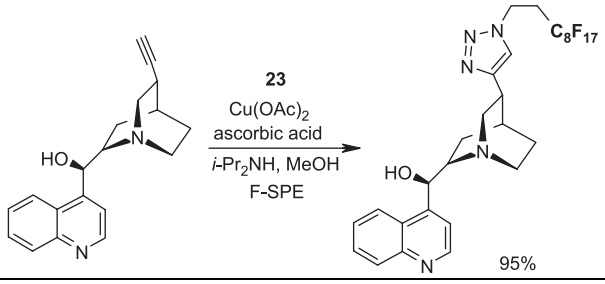
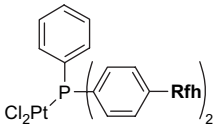
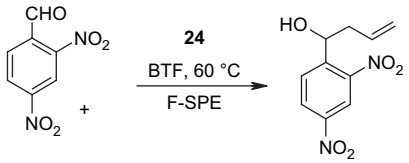
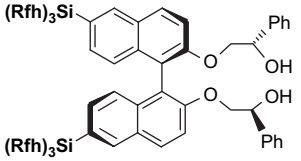
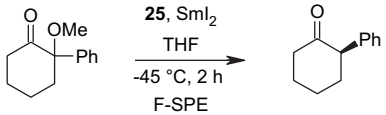
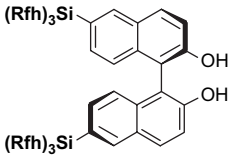
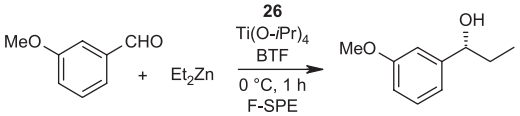
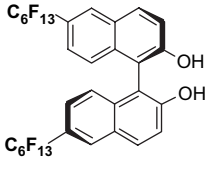
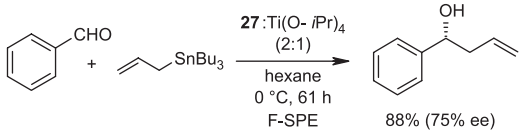
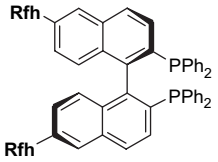
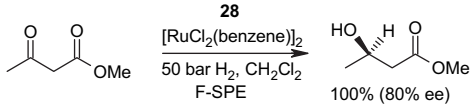
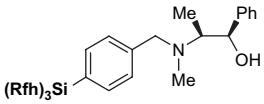
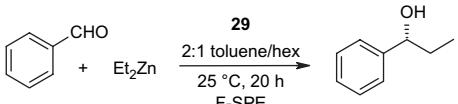
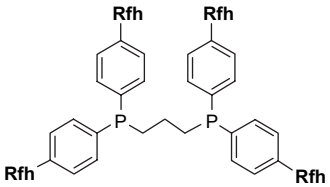
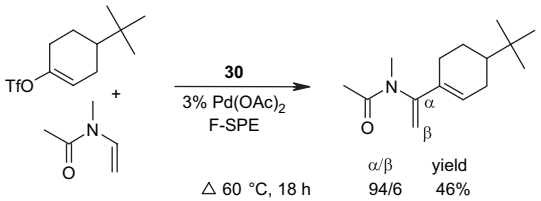
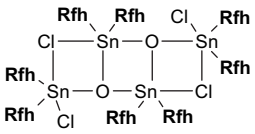
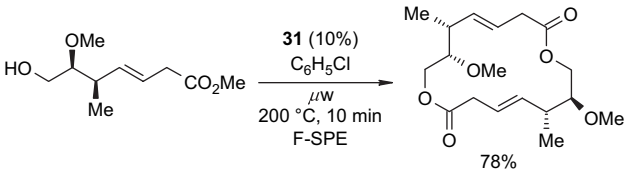
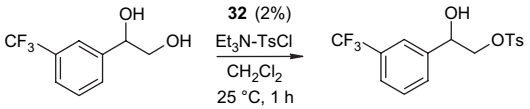
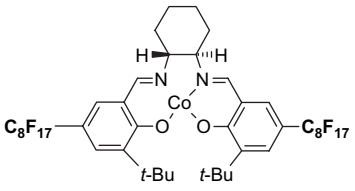
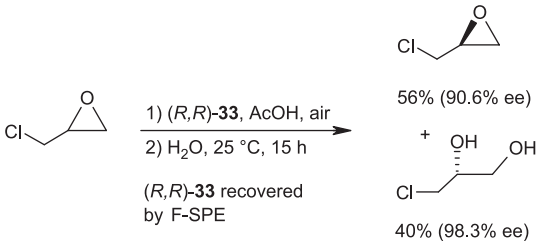
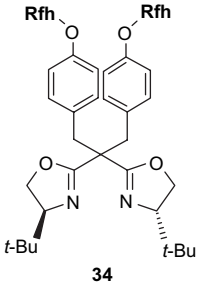
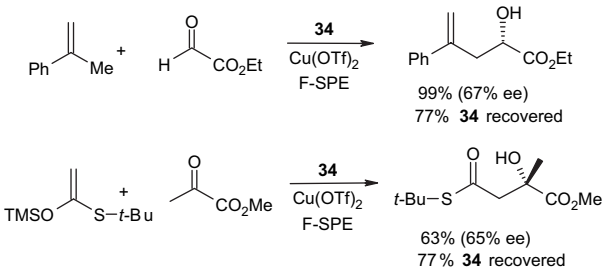
Reactants	Transformation	Ref.
I–C_6F_{13} **21**		50
I–$C_8F_{16}CF(CF_3)_2$ **22**		51
N_3–C_8F_{17} **23**		52

Table 3. Reactions with fluorous catalysts

Catalyst	Transformation	Ref.
 **24** Rfh = $(CH_2)_2C_6F_{13}$	 $[C_6F_{13}(CH_2)_3]_3SnCH_2CH{=}CH_2$ 100% (100% pure)	9
 **25** Rfh = $(CH_2)_2C_6F_{13}$	 82% (81% ee) 98% **25** recovered	53
 **26, (*R*)-F-BINOL** Rfh = $(CH_2)_2C_6F_{13}$	 95% (85% ee) 100% **26** recovered	54
 **27**	 88% (75% ee)	55

(*continued*)

Table 3. (*continued*)

Catalyst	Transformation	Ref.
 **28** Rfh = $(CH_2)_2C_6F_{13}$	 **28** $[RuCl_2(benzene)]_2$ 50 bar H_2, CH_2Cl_2 F-SPE 100% (80% ee)	56
 **29** Rfh = $(CH_2)_2C_6F_{13}$	 **29** 2:1 toluene/hex 25 °C, 20 h F-SPE 91% (83% ee) 100% **29** recovered	57
 **30, F-dppp** Rfh = $(CH_2)_2C_4F_9$	 **30** 3% $Pd(OAc)_2$ F-SPE △ 60 °C, 18 h α/β 94/6 yield 46% μw 90 °C, 15 min 90/10 46%	58
 **31** Rfh = $(CH_2)_2C_6F_{13}$	 **31** (10%) C_6H_5Cl μw 200 °C, 10 min F-SPE 78%	59
$[[C_6F_{13}CH_2CH_2]_2SnO]_n$ **32**	 **32** (2%) Et_3N-TsCl CH_2Cl_2 25 °C, 1 h F-SPE 70%	60
 (*R,R*)-**33**	 1) (*R,R*)-**33**, AcOH, air 2) H_2O, 25 °C, 15 h (*R,R*)-**33** recovered by F-SPE 56% (90.6% ee) 40% (98.3% ee)	61
 **34** Rfh = $(CH_2)_3C_8F_{17}$	 **34** $Cu(OTf)_2$ F-SPE 99% (67% ee) 77% **34** recovered 63% (65% ee) 77% **34** recovered	62

(*continued*)

Table 3. (*continued*)

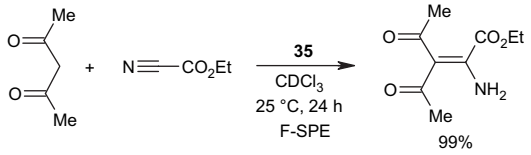
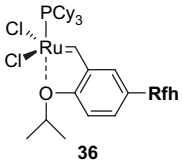
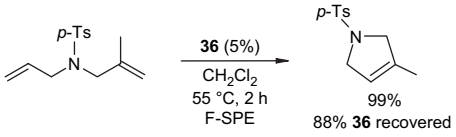
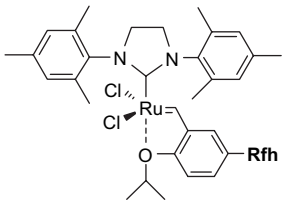
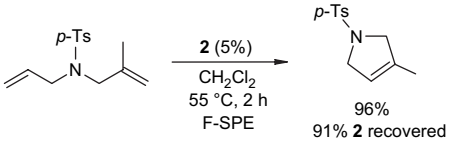
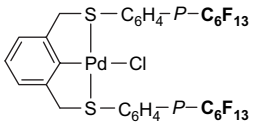
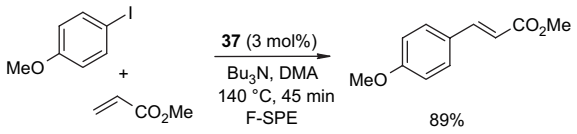
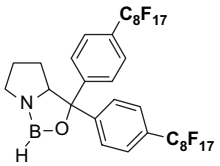
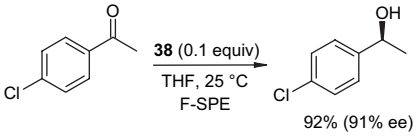
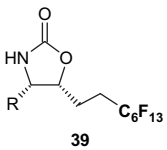
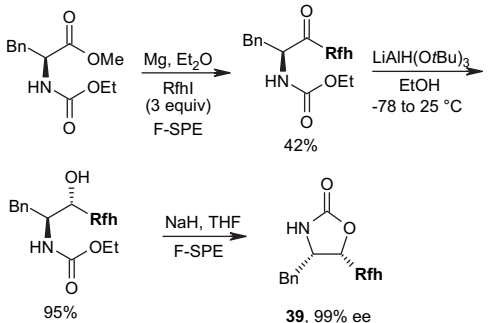
Catalyst	Transformation	Ref.
[Ni{$F_3CC(O)CHC(O)C_6F_{13}$}$_2$] **35**		63
 **36** Rfh = $(CH_2)_3C_6F_{13}$		13
 **2** Rfh = $(CH_2)_3C_8F_{17}$		13
 **37**		64
 **38**		65

Table 4. Reactions with fluorous chiral auxiliaries

Chiral auxiliary	Transformation	Ref.
 **39**		66

(*continued*)

Table 4. (*continued*)

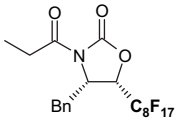
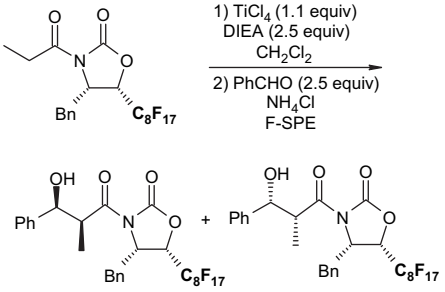
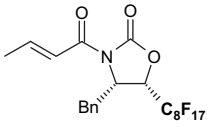
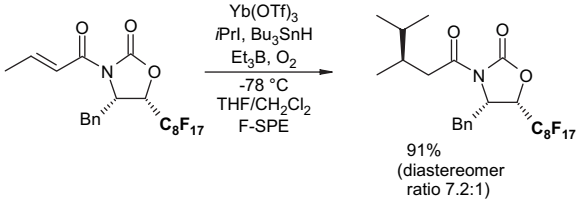
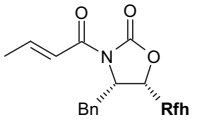
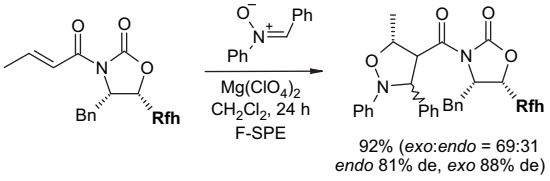
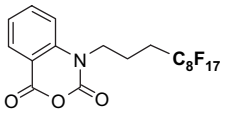
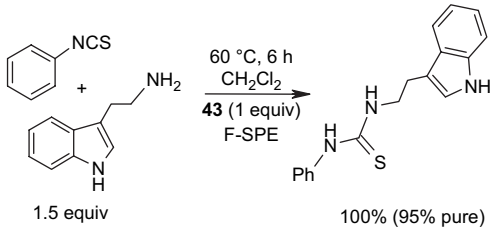
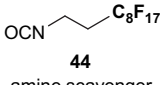
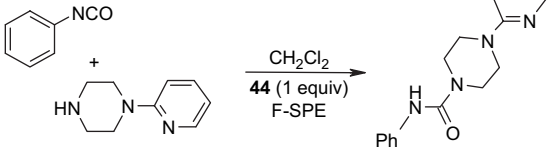
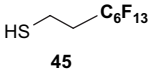
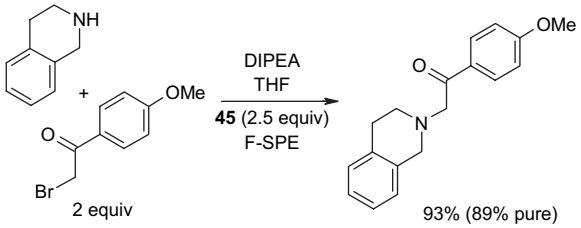
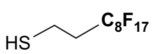
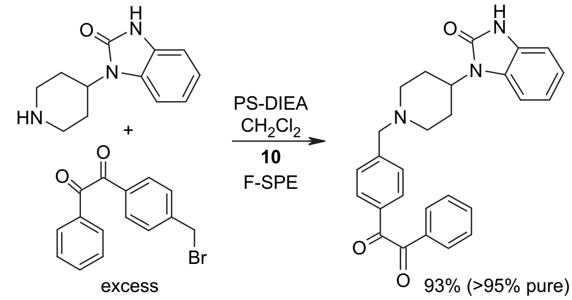
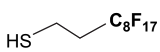
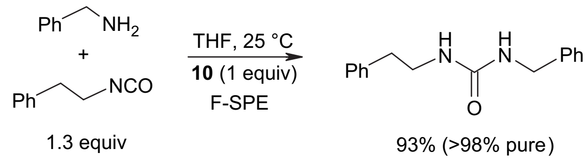
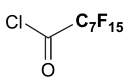
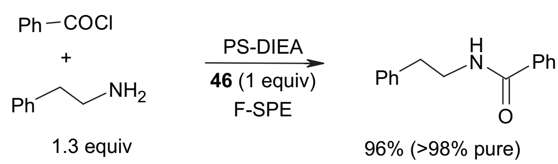
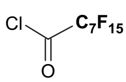
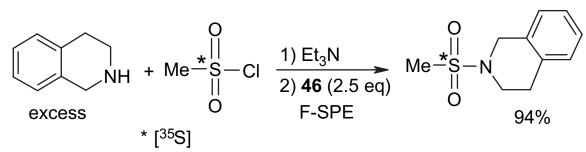
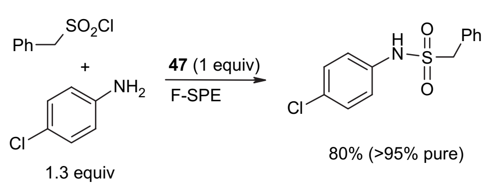
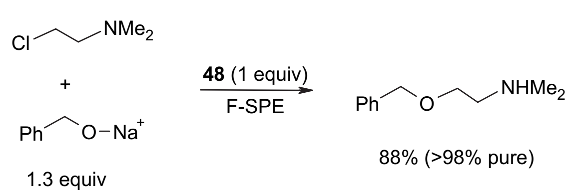
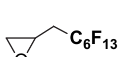
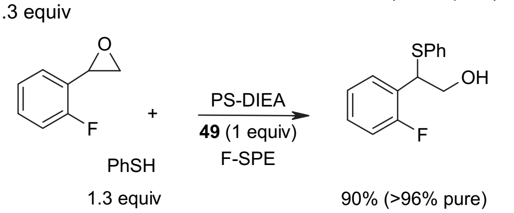
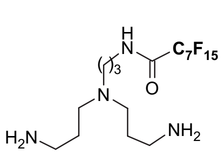
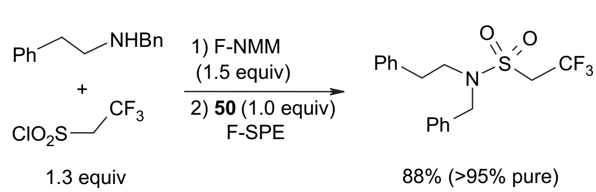
Chiral auxiliary	Transformation	Ref.
 **40**	 1) $TiCl_4$ (1.1 equiv), DIEA (2.5 equiv), CH_2Cl_2; 2) PhCHO (2.5 equiv), NH_4Cl, F-SPE; 94% (>99:1)	67
 **41**	 $Yb(OTf)_3$, *i*PrI, Bu_3SnH, Et_3B, O_2, -78 °C, THF/CH_2Cl_2, F-SPE; 91% (diastereomer ratio 7.2:1)	68
 **42** Rfh = $(CH_2)_2C_6F_{13}$	 $Mg(ClO_4)_2$, CH_2Cl_2, 24 h, F-SPE; 92% (*exo*:*endo* = 69:31, *endo* 81% de, *exo* 88% de)	69

Table 5. Reactions with fluorous scavengers

Scavenger	Transformation	Ref.
 **43** amine scavenger	 1.5 equiv; 60 °C, 6 h, CH_2Cl_2, **43** (1 equiv), F-SPE; 100% (95% pure)	70
 **44** amine scavenger	 1.5 equiv; CH_2Cl_2, **44** (1 equiv), F-SPE; 100% (95% pure)	71
 **45** active halide scavenger	 2 equiv; DIPEA, THF, **45** (2.5 equiv), F-SPE; 93% (89% pure)	72

(*continued*)

Table 5. (*continued*)

Scavenger	Transformation	Ref.
 **10** active halide scavenger		73,74
 **10** isocyanate scavenger		75
 **46** amine scavenger		74
 **46** amine scavenger		75
$HO_3S–C_8F_{17}$ **47** amine scavenger		74
$ClO_2S–C_6F_{13}$ **48** base scavenger		74
 **49** thiol scavenger		74
 **50, F-Tris** sulfonyl chloride scavenger		76

(*continued*)

Table 5. (*continued*)

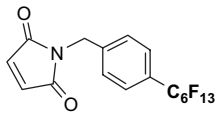
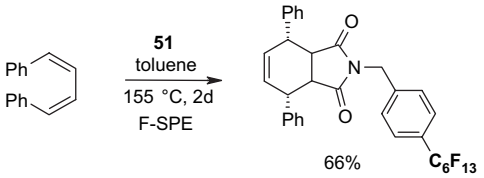
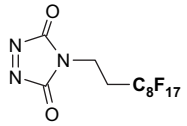
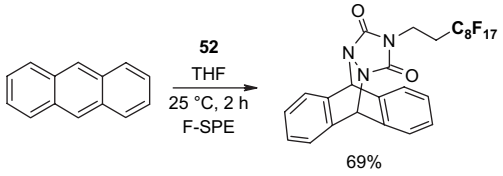
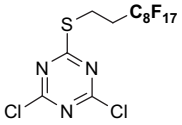
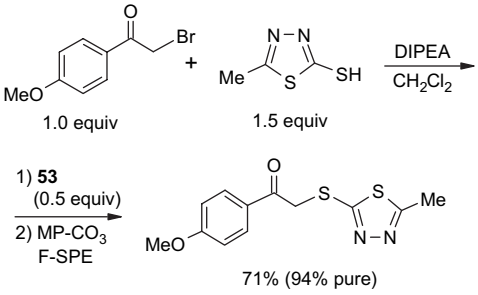
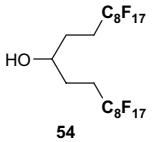
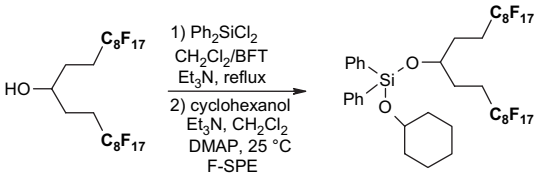
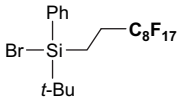
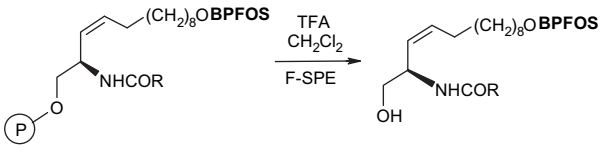
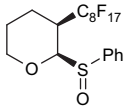
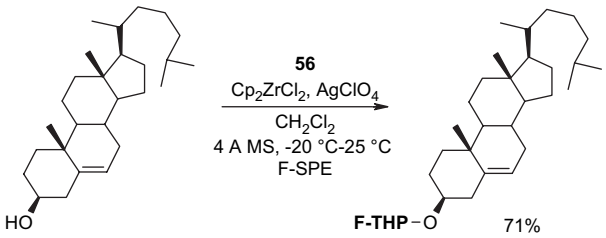
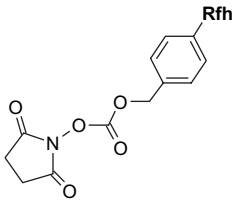
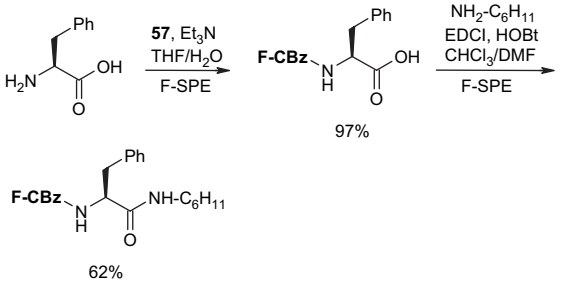
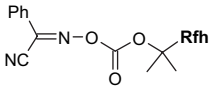
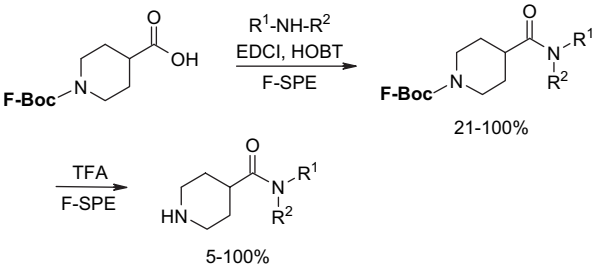
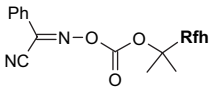
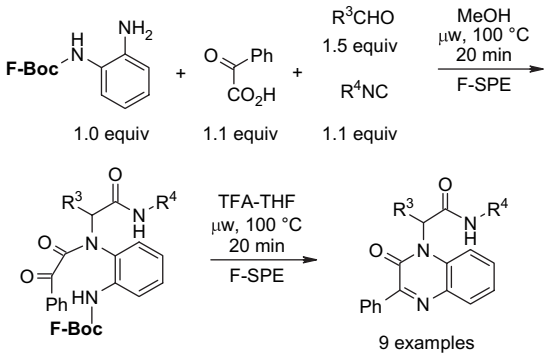
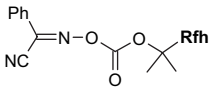
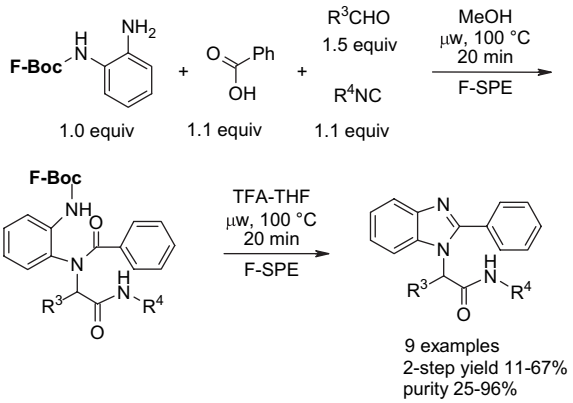
Scavenger	Transformation	Ref.
 **51** dienophile scavenger	 **51**, toluene, 155 °C, 2d, F-SPE; 66%	77
 **52** dienophile scavenger	 **52**, THF, 25 °C, 2 h, F-SPE; 69%	77
 **53, F-DCT** thiol scavenger	 1.0 equiv; 1.5 equiv; DIPEA, CH_2Cl_2; 1) **53** (0.5 equiv) 2) MP-CO_3 F-SPE; 71% (94% pure)	78

Table 6. Reactions with fluorous protecting groups

Protecting group	Transformation	Ref.
 **54**	 1) Ph_2SiCl_2, CH_2Cl_2/BFT, Et_3N, reflux 2) cyclohexanol, Et_3N, CH_2Cl_2, DMAP, 25 °C, F-SPE; 47%	79
 **55, F-BPFOS-Br**	 TFA, CH_2Cl_2, F-SPE	80
 **56**, **F-THP-S(O)Ph**	 **56**, Cp_2ZrCl_2, $AgClO_4$, CH_2Cl_2, 4 A MS, -20 °C-25 °C, F-SPE; 71%	81

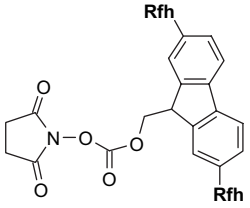
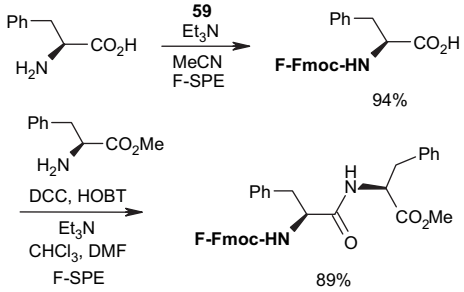
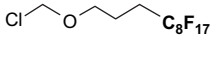
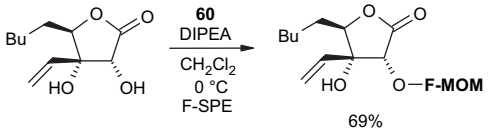
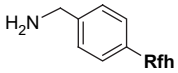
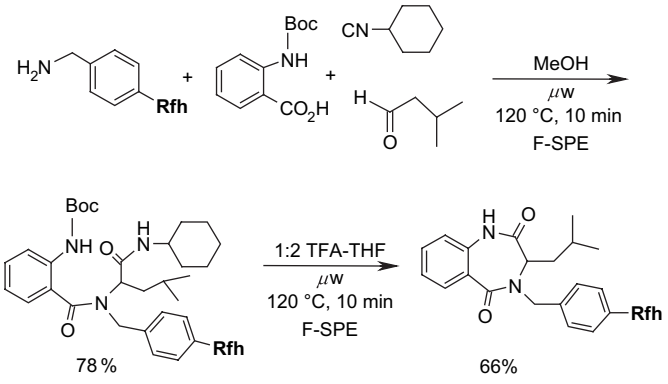
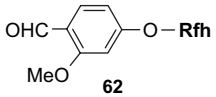
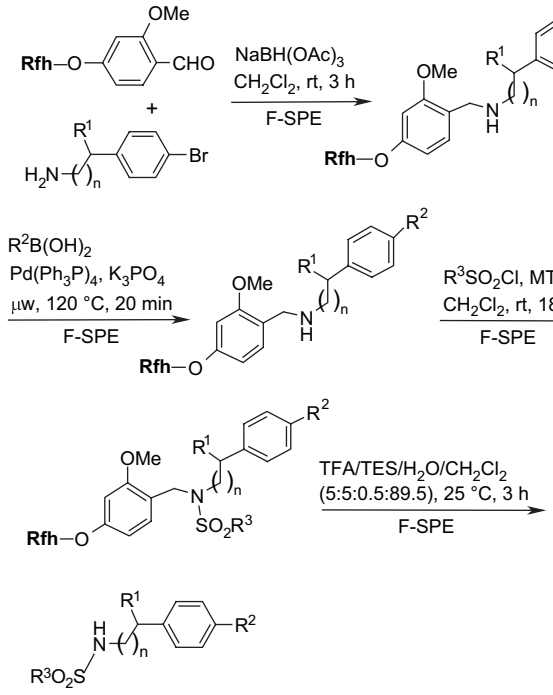
(*continued*)

Table 6. (*continued*)

Protecting group	Transformation	Ref.
 **57, F-CBz-OSu** Rfh = $(CH_2)_2C_8F_{17}$	 97% 62%	82
 **58**, **F-Boc-ON** Rfh = $(CH_2)_2C_6F_{13}$	 21-100% 5-100%	83
 **58**, **F-Boc-ON** Rfh = $(CH_2)_2C_6F_{13}$	 1.0 equiv 1.1 equiv 1.1 equiv 9 examples 2-step yield 51-81% purity 52-85%	84
 **58**, **F-Boc-ON** Rfh = $(CH_2)_2C_6F_{13}$	 1.0 equiv 1.1 equiv 1.1 equiv 9 examples 2-step yield 11-67% purity 25-96%	84

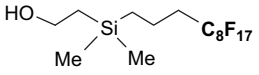
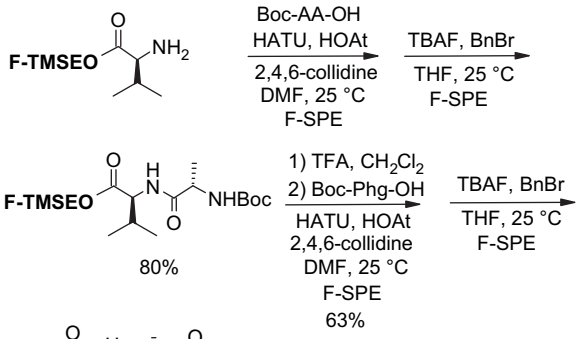
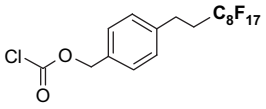
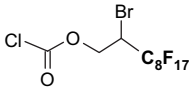
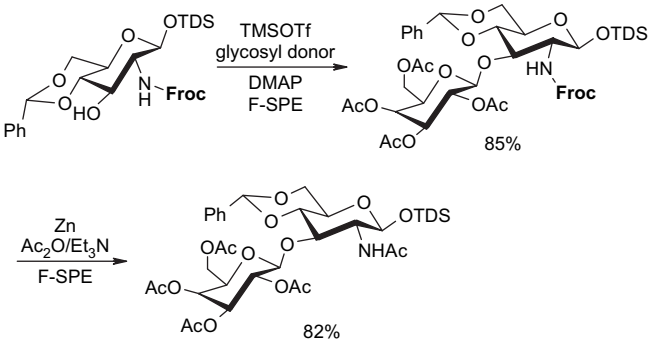
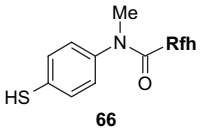
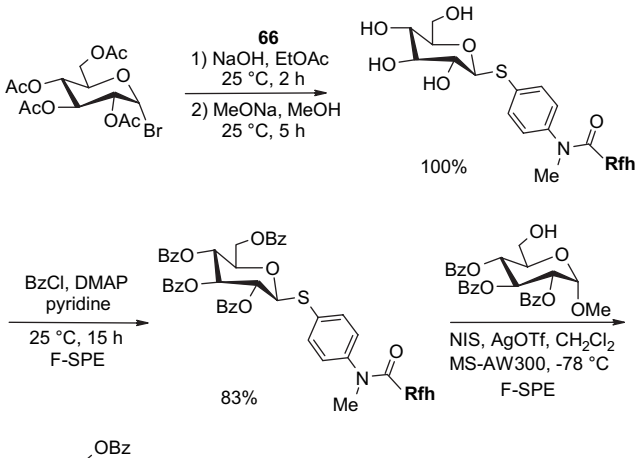
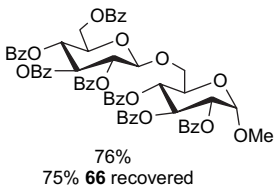
(*continued*)

Table 6. (*continued*)

Protecting group	Transformation	Ref.
 **59, F-Fmoc-OSu** Rfh = $(CH_2)_2C_6F_{13}$		85
 **60, F-MOM-Cl**		86
 **61** Rfh = $(CH_2)_2C_6F_{13}$		87
 **62** Rfh = $(CH_2)_3C_8F_{17}$		88

(*continued*)

Table 6. (*continued*)

Protecting group	Transformation	Ref.
 **63, F-TMS-OH**		89
 **64, F-Cbz-Cl**	Peptides GCCSLPPCALNNPDYCamide 59% (91% pure) RQIKIWFQNRRMKWKKamide 7% (72% pure)	28b
 **65, Froc-Cl**		90
 **66** Rfh = $(CH_2)_2C_8F_{17}$	  76% 75% **66** recovered	91

(*continued*)

Table 6. (*continued*)

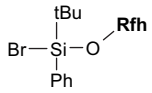
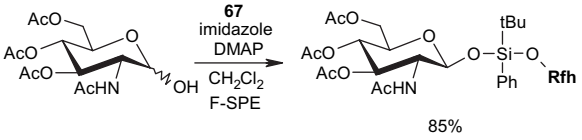
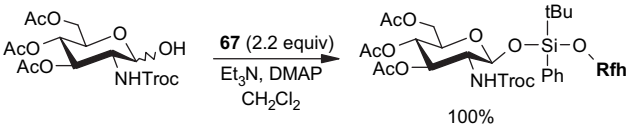
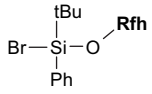
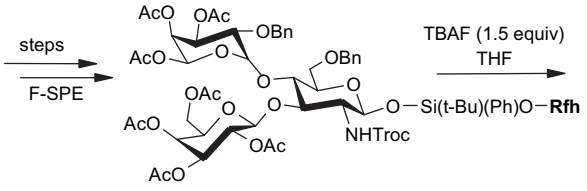
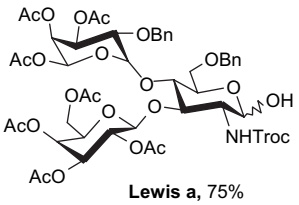
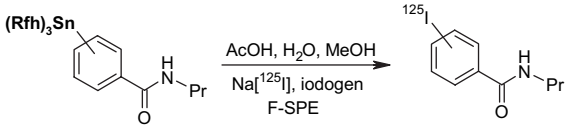
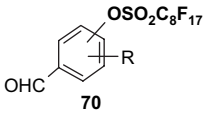
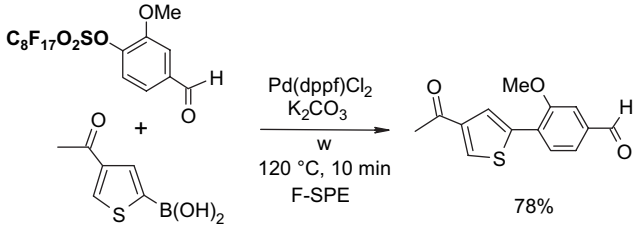
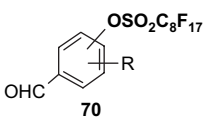
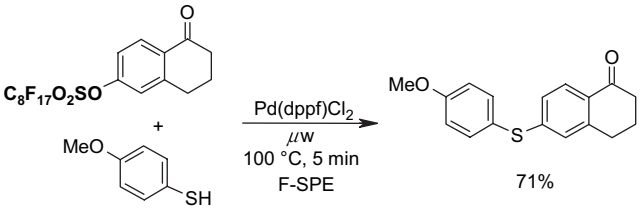
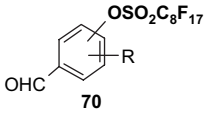
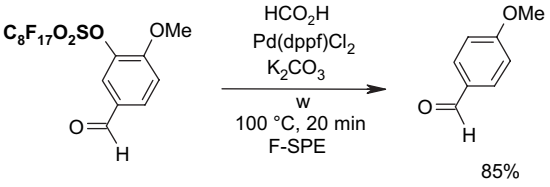
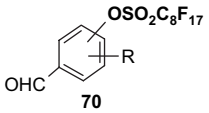
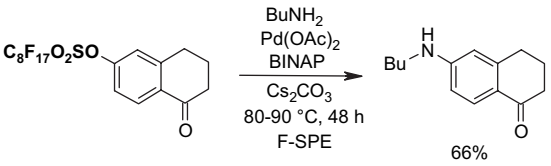
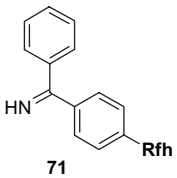
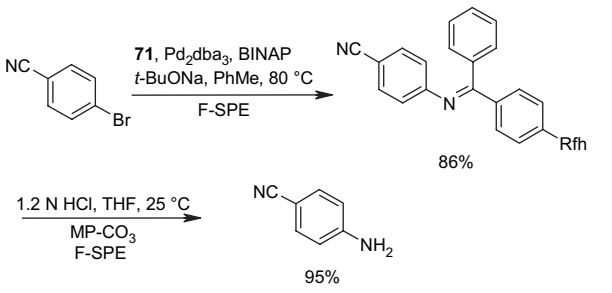
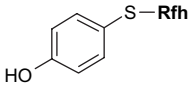
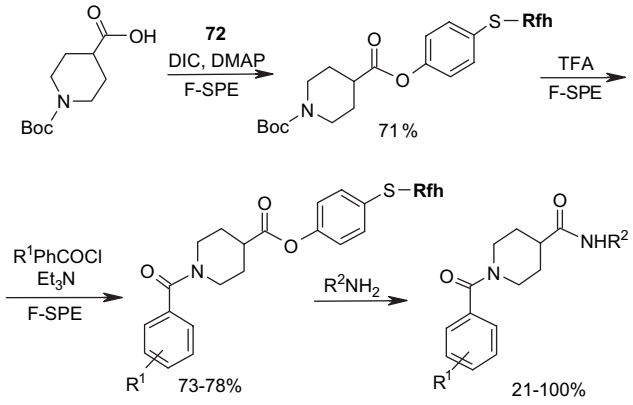
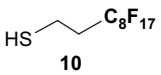
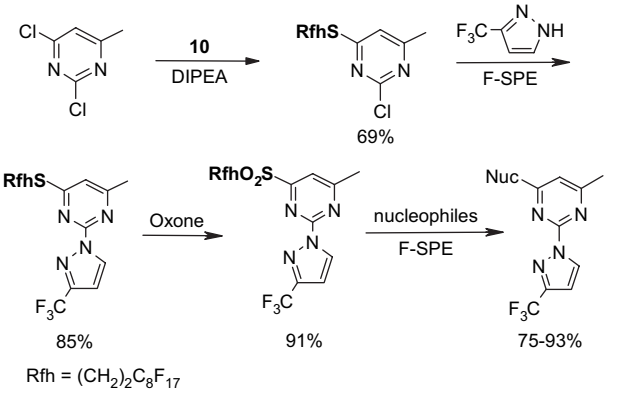
Protecting group	Transformation	Ref.
 **67** Rfh = $(CH_2)_2C_8F_{17}$	 85%	92
	 100%	
 **67** Rfh = $(CH_2)_2C_8F_{17}$	  **Lewis a,** 75%	93

Table 7. Reactions with fluorous displaceable tags

Displaceable tags	Transformation	Ref.
$Br–Sn(CH_2CH_2\mathbf{C_6F_{13}})_3$ **69**	 Rfh = $C_6F_{13}CH_2CH_2$ 85% (>98% pure)	94
	Suzuki reactions	
 **70**	 78%	95
 **70**	 71%	96

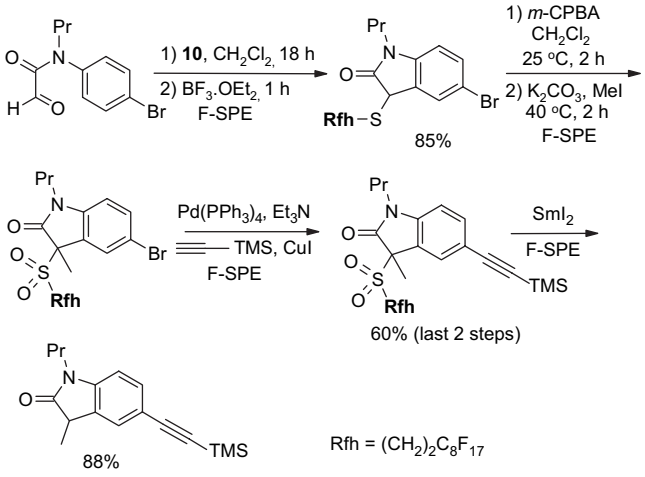
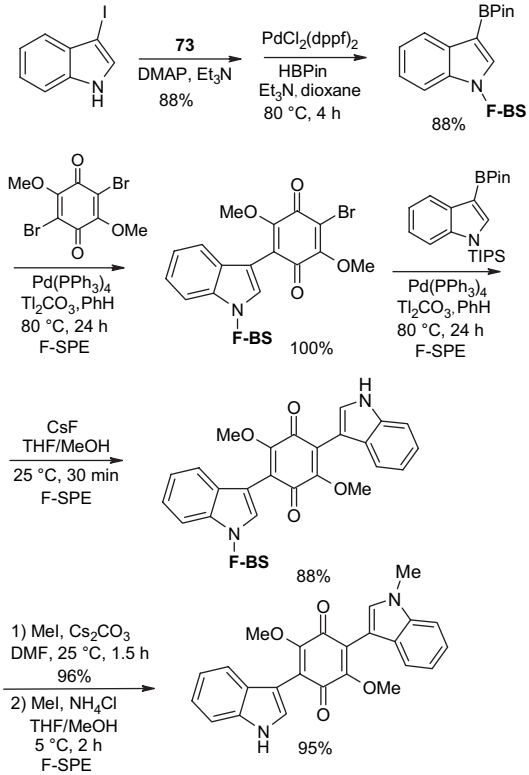
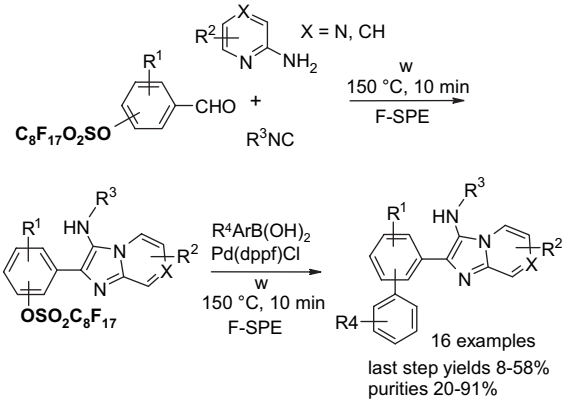
(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
 **70**		97
 **70**		98
 **71** Rfh = $(CH_2)_2C_8F_{17}$		99
 **72, FluoMar** Rfh = $(CH_2)_2C_8F_{17}$		100
 **10**	 Rfh = $(CH_2)_2C_8F_{17}$	101

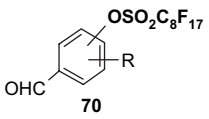
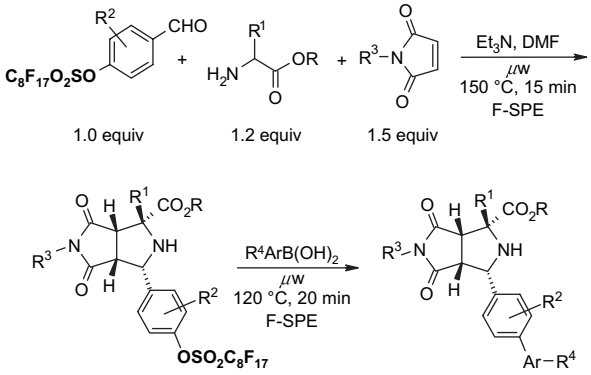
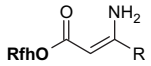
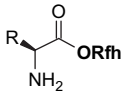
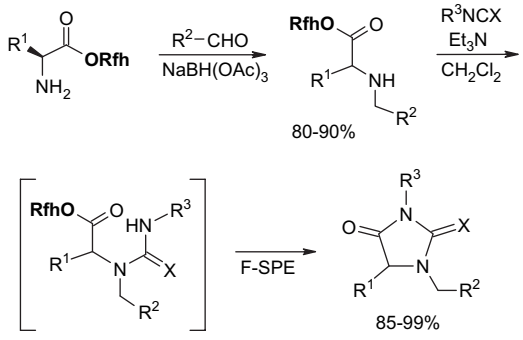
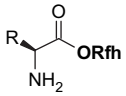
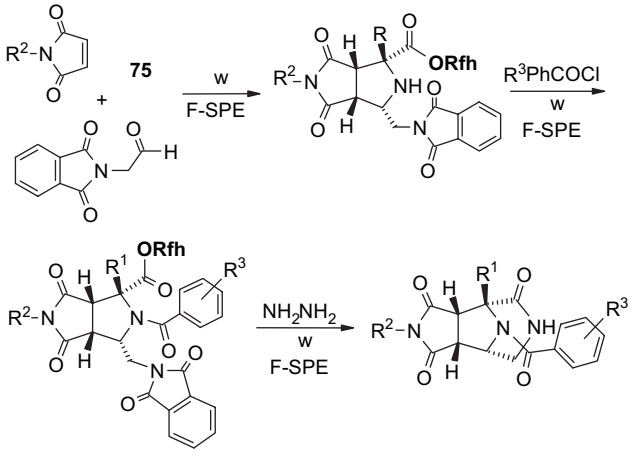
(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
HS–C_8F_{17} **10**		102
C_8F_{17} / SO_2Cl / C_8F_{17} **73, F-BS-Cl**		103
$OSO_2C_8F_{17}$ / R / OHC **70**		104

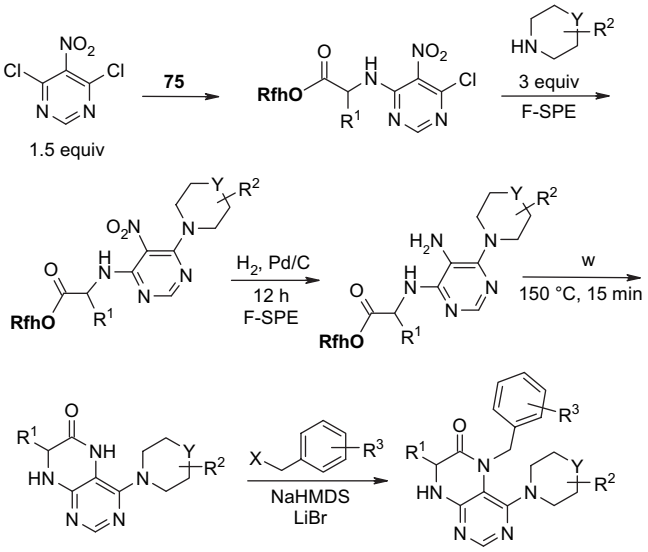
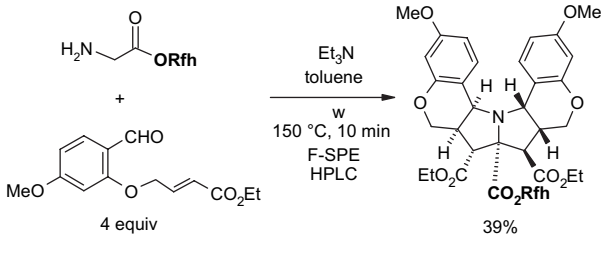
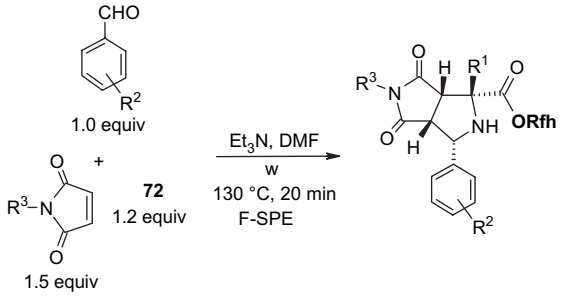
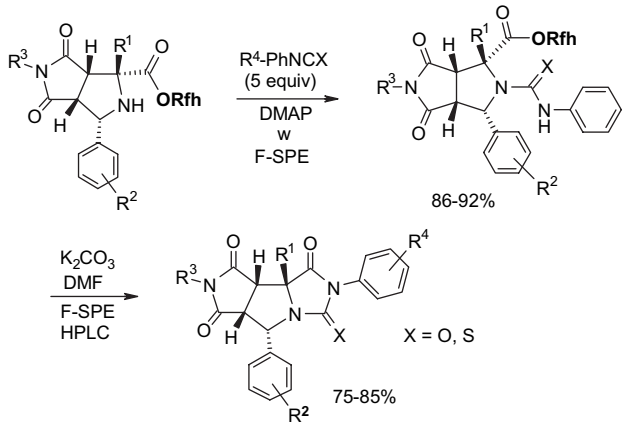
(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
 **70**		105
 **74** Rfh = $(CH_2)_3C_8F_{17}$		106
 **75** Rfh = $(CH_2)_3C_8F_{17}$		107
 **75** Rfh = $(CH_2)_3C_8F_{17}$		108

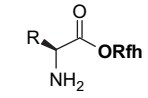
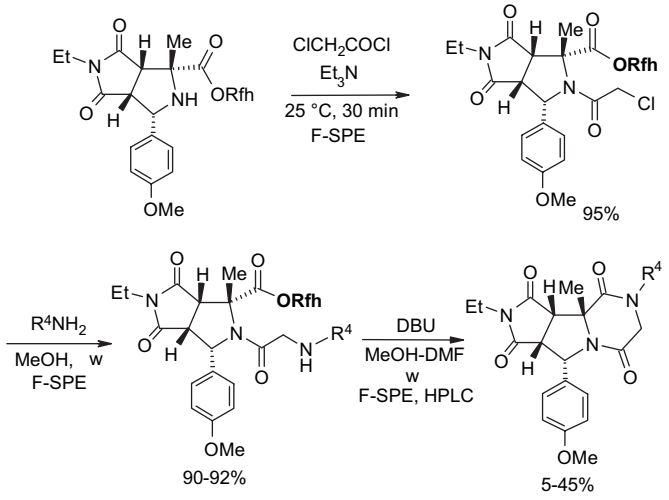
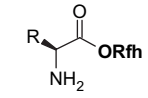
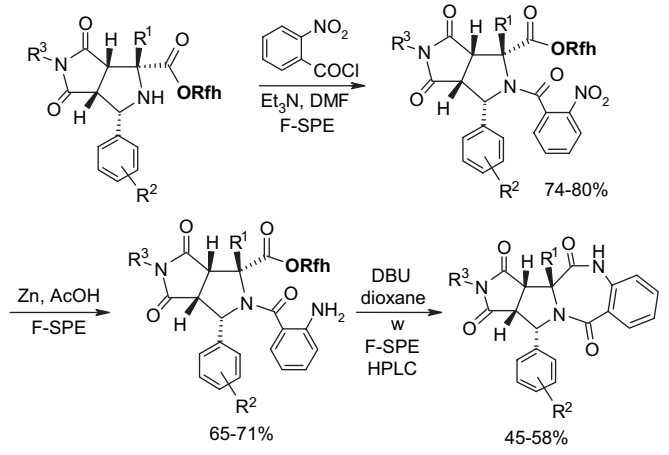
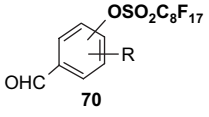
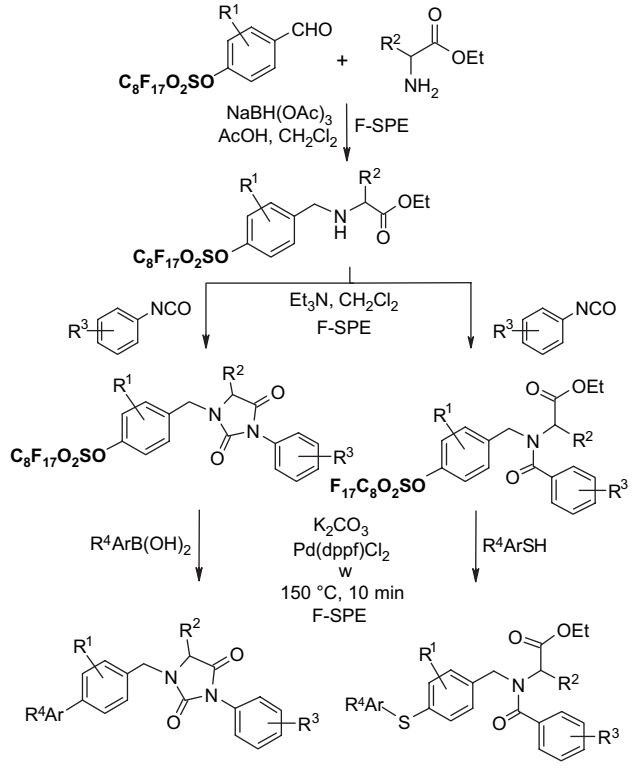
(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
75 Rfh = $(CH_2)_3C_8F_{17}$		109
75 Rfh = $(CH_2)_3C_8F_{17}$		110
75 Rfh = $(CH_2)_3C_8F_{17}$		111
75 Rfh = $(CH_2)_3C_8F_{17}$		111

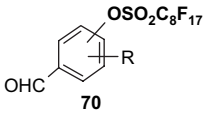
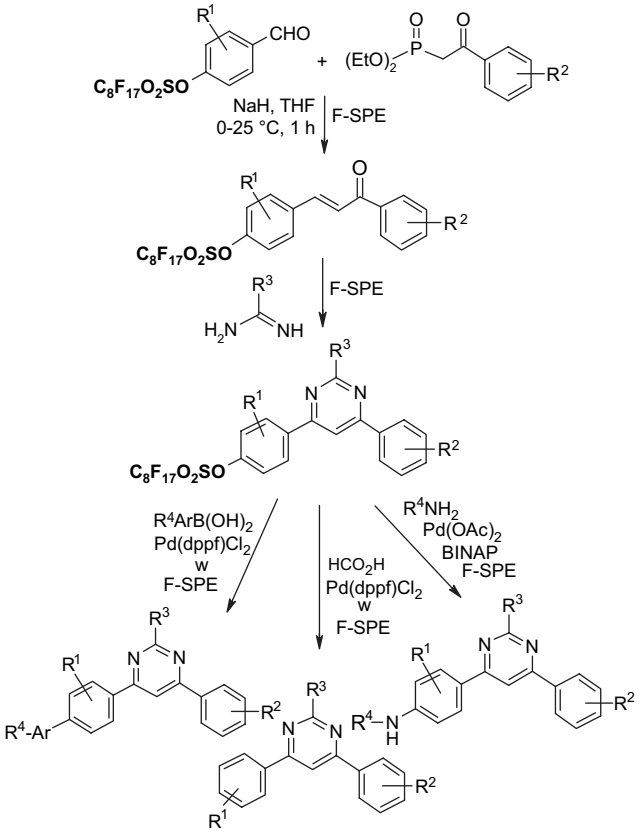
(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
 **75** Rfh = $(CH_2)_3C_8F_{17}$		111
 **75** Rfh = $(CH_2)_3C_8F_{17}$		111
 **70**		95,96

(*continued*)

Table 7. (*continued*)

Displaceable tags	Transformation	Ref.
 **70**		95,97,98

5. Practical aspects of F-SPE[21]

5.1. A typical F-SPE procedure

F-SPEs in cartridge format are very easy to conduct and have the following general steps: cartridge washing (for new cartridges only), preconditioning, sample loading, fluorophobic elution, fluorophilic elution, and final washing for cartridge reuse (optional). A typical F-SPE procedure for the separation of a reaction mixture with a 2 g SPE cartridge is as follows:[21]

Step 1—Cartridge washing: Wash a new cartridge with 1 mL of DMF under a vacuum or positive pressure depending on your SPE manifold. This step can be omitted with recycled cartridges.

Step 2—Preconditioning: Pass through 6 mL of 80:20 MeOH–H_2O to condition the cartridge. Discard the preconditioning eluent.

Step 3—Sample loading: Dissolve sample (100–300 mg) in 0.4 mL of DMF and load onto the cartridge by using vacuum or positive pressure to ensure the sample is completely adsorbed onto the cartridge (see Table 8 for alternative loading solvents).

Step 4—Fluorophobic elution: Wash with 6–8 mL of 80:20 MeOH–H_2O to obtain the fraction containing the organic compounds.

Step 5—Fluorophilic elution: Wash with 8 mL of MeOH to obtain the fraction containing the fluorous compounds.

Step 6—Final washing (optional): To regenerate the SPE cartridge for reuse, wash with 6 mL of THF or acetone and air dry.

5.2. F-SPE demonstration with dyes

The following dye separation demonstrates how F-SPE works. The non-fluorous compound is Solvent Blue® dye; the fluorous compound is F-orange dye. These two dyes have similar polarities. Figure 9 shows fluorous cartridges containing the dye mixture in three different stages of elution. The left-hand test tube illustrates how the F-SPE cartridge appears after loading a mixture of the two dyes and elution with a small amount of 80:20 MeOH–H_2O. The center tube shows how the non-fluorous components (blue fraction) are washed from the cartridge by using more 80:20 MeOH–H_2O. The adsorbed fluorous dye is not eluted even with extensive flushing with 80:20 MeOH–H_2O and remains on the cartridge. Finally, the orange fluorous dye is easily eluted with 100% MeOH or THF, as shown by the third tube.

5.3. Common issues related to F-SPE

5.3.1. Loading solvents. Many different solvents can be used for sample loading; however, the more fluorophilic the solvent is the smaller its volume should be to prevent breakthrough. A list of solvents with increasing fluorophilicity is as follows: H_2O<DMSO<DMF<MeOH<MeCN<THF<HFC-7100 ($C_4F_9OCH_3$)<FC-72. For normal F-SPE,

Table 8. Suggested maximum loading solvent volumes for C_8F_{17}-tagged substrates

Solvent	Maximum loading volume		
	2 g cartridge (mL)	5 g cartridge (mL)	10 g cartridge (mL)
THF	0.2	0.5	1.0
CH_2Cl_2	0.2	0.5	1.0
MeCN	0.2	0.5	1.0
MeOH	0.2	0.5	1.0
DMF	0.4	1.0	2.0
DMSO	0.6	1.5	3.0

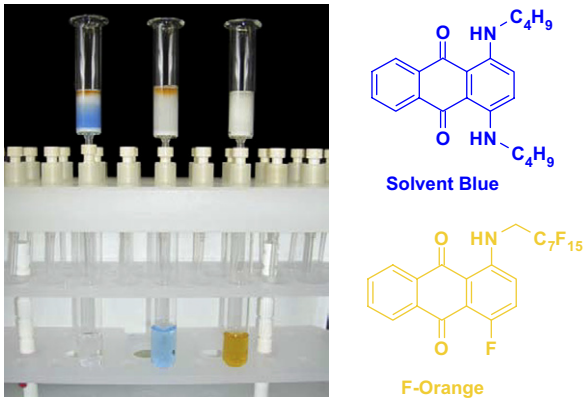


Figure 9. F-SPE with blue (organic) and orange (fluorous) dyes. *Left tube*: beginning of fluorophobic wash (80:20 MeOH–H_2O); *center tube*: end of fluorophobic wash; *right tube*: end of fluorophilic wash (100% MeOH).

the mass loading (weight of crude sample compared to the weight of fluorous silica gel) is suggested to be around 5–10%.[21] With the least fluorophilic DMSO, the solvent loading (volume of solvent compared to the volume of fluorous silica gel) can be as high as 30%, whereas with high fluorophilic THF, the solvent loading should be less than 10% to avoid fluorous sample breakthrough. Table 8 provides recommendations for some common loading solvents and cartridge sizes.

The usual symptom of breakthrough is that a small amount of the fluorous compound comes off early in the organic fraction, but the bulk of the fluorous compound is retained on the cartridge. This happens because the loading solvent elutes the fluorous compounds, but the elution stops as soon as the fluorophobic solvent elutes the loading solvent from the cartridge. Breakthrough problems can often be solved by using less volume of loading solvent. Other solutions are to use a more fluorophobic loading solvent, to use a larger cartridge, or to lower the sample mass loading.

A good loading solvent should have low fluorophilicity and good dissolving power for organic compounds. Direct loading of a reaction mixture onto a fluorous cartridge for SPE is sometimes possible. However, in common practice, the reaction mixture is usually filtered first to remove insoluble solid and catalysts. The concentrated crude mixture is then dissolved in an appropriate loading solvent and loaded onto a cartridge preconditioned with a fluorophobic solvent. In large-scale F-SPE, an aqueous workup of reaction mixture is recommended. This removes water-soluble materials and preserves the lifetime of cartridge for reuse.

5.3.2. Elution solvents. An F-SPE has two solvent passes, the first one uses the fluorophobic solvent and the second one uses the fluorophilic solvent. The fluorophobic solvent is usually a water-miscible organic solvent with certain amount of water to reduce fluorophilicity. Solvents such as 70:30 MeCN–H_2O, 80:20 MeOH–H_2O, and 90:10 DMF–H_2O are the common choices. Acetone–H_2O and THF–H_2O can also serve the purpose. If a component in the reaction mixture is water sensitive, then 100% DMSO can be used for fluorophobic wash. All the non-fluorous components are expected to elute with the fluorophobic solvent in 3–5 column volumes, while fluorous components are retained on the cartridge. If organic components have low solubility in elution solvent, this can occasionally generate a precipitate and block the cartridge during F-SPE. Reduced mass loading and slightly increased the percentage of organic solvent can minimize this problem. After the elution of non-fluorous components, a more fluorophilic solvent such as MeOH, acetone, MeCN, or THF is used to wash out the fluorous component retained on the cartridge in 3–5 column volumes.

5.3.3. Fluorous silica gel reuse. To control the cost spent on fluorous silica gel and reduce waste disposal, the cartridges can be washed thoroughly and conditioned for reuse. The fluorous stationary phase can be cleaned by washing with fluorophilic solvents (acetone, MeCN, and THF) or with a mixture of MeCN–H_2O containing 0.5% TFA. To extend cartridge lifetime, crude samples containing strongly acidic or basic compounds, or having insoluble solids or a large amount of salts are not recommended for directly load onto the cartridge without pretreatment. However, if the cartridge will be discarded after use, the precautions are not necessary.

5.3.4. Gravity F-SPE with large fluorous silica gel. Compared to normal F-SPE with 40 μm fluorous silica gel, the resolution of gravity F-SPE with 120 μm silica gel is reduced to some extent. Cartridges with the large size fluorous silica gel need to be carefully conditioned to remove air bubbles. In the case of plate-to-plate F-SPE, the plate loaded with a high boiling solvent such as DMF or DMSO is degassed in a vacuum chamber (20–30 mmHg) for 3–5 min to remove the air bubbles.

6. Conclusions

The results summarized in this report show that the new separation technique of fluorous solid-phase extraction (F-SPE) has successfully debuted and is now ready for prime time.

While there is still more to be learned, basic F-SPE techniques are well understood and have proven generality. The predictability and generic 'fluorous/non-fluorous' nature of F-SPE's make them especially attractive in research settings with single compounds or compound libraries. The learning curve is not steep; indeed, you can be up and running in the lab with your first F-SPE in as little as 15–30 min. Fluorous silica gel is now commercially available in an assortment of sizes and formats, and an increasing number of fluorous reaction components (reagents, catalysts, tags, scavengers, protecting groups) are also sold commercially. Thus, we expect that the usefulness of F-SPE will continue to expand as it is applied to more and different problems, and we intend that this report will help to fuel that expansion.

Note added in proof

A special issue of fluorous chemistry containing several papers dealing with fluorous solid-phase extraction has just appeared: Zhang, W. *QSAR Comb. Sci.* **2006**, *25*, 679.

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Biographical sketch

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The synthesis of single enantiomers of meromycolic acids from mycobacterial wax esters

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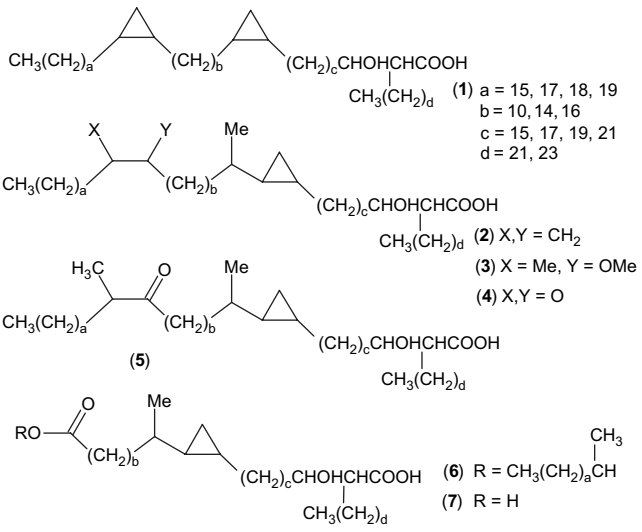
Abstract—Three stereoisomers of a wax ester meromycolate have been prepared starting from mannitol. A detailed comparison of their NMR spectra with those reported for a homologous series of natural wax esters allows the relative configurations of the α-methyl group and adjacent *trans*-cyclopropane to be determined.

1. Introduction

Mycobacterial cell walls show unusually low permeability, a factor which contributes to their resistance to therapeutic agents, apparently due to an exceptionally thick monolayer formed by the packing of esters of C_{60}–C_{90} fatty acids.[1] These 'mycolic acids', exemplified by structures **1**–**5**, contain various structural features including *cis*-cyclopropanes **1**,[2] α-methyl-*trans*-cyclopropanes, α-methyl-β-methoxy and α-methyl-β-keto,[3–6] *cis*-alkene, α-methyl-*trans*-alkene and α-methyl-*trans*-epoxy fragments, e.g., **4**.[7] Each contains a common β-hydroxy acid group[8,9] and they are generally present as mixtures of various chain lengths. Although the hydroxy acid grouping is known to be of *R*,*R*-configuration for a number of bacteria,[10] little is known about the absolute stereochemistries of the other groups. There is some evidence that the 1-methyl-2-methoxy unit at the distal position from the hydroxy acid in mycolic acids **3** is *S*,*S*,[10,6] while other reports identify a *R*-stereochemistry for the three stereocentres of the α-methyl-*trans*-epoxy unit in **4**.[7]

Over 60 years ago, Anderson, in an epic series of papers, initiated studies on mycobacterial lipids and reported[11] that the isolation of two new optically active long-chain alcohols from the neutral fraction of the saponified waxes of the so-called 'timothy bacillus', later classified as *Mycobacterium phlei*.[1] These alcohols were identified as *d*-2-eicosanol [$[\alpha]_D$ +3.5] and *d*-2-octadecanol [$[\alpha]_D$ +5.7]. It was noted that the acidic fraction from these saponified waxes contained a high molecular weight component, tentatively identified as being dibasic.[11] A careful analysis[11a] of the firmly bound lipids from avian tubercle bacilli (*Mycobacterium avium*) again yielded long-chain alcohols, with *d*-2-eicosanol as main component. These lipid fractions also produced a long-chain diacid, recognized for the first time as a mycolic acid and given the title γ-mycolic acid [$[\alpha]_D$ +5.3].[11a] In parallel studies, similar alcohols and acids were characterized from an organism claimed to be the causative agent of leprosy.[11b] It is clear, however, that this bacterium was not the leprosy bacillus as *Mycobacterium leprae* has not been cultivated to date and the mycolic acid composition of *M. leprae* is distinct (Scheme 1).[11c]



Scheme 1.

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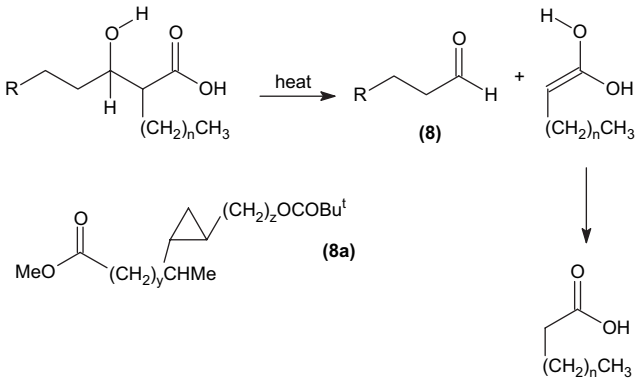
In more recent investigations of mycolic acid structure and distribution, compounds such as **6** or the corresponding diacids **7** were characterized from *Mycobacterium paratuberculosis*[12a] and *Mycobacterium gordonae*,[12b] as a constituent of trehalose mycolates of *M. phlei*,[13–17] including the identification of a trehalose monomycolate ester[13] and *Mycobacterium flavescens*.[17] They are known to be a characteristic component in the *M. avium–Mycobacterium intracellulare* group and other rapidly growing bacteria.[17,28] Their presence in *Mycobacterium smegmatis* has been implied,[19] although not confirmed by a later study.[20] Usually they have been analyzed as the corresponding α-methyl-alkanol and free acid after hydrolysis.[20,21] Some such wax esters do not appear to contain cyclopropanes, while in other cases the composition is not clear.[22–27] The analysis of the intact trehalose monomycolate derivatives by MALDI-TOF mass spectrometry shows ions due to C_{83}, C_{85} and C_{87} wax esters for *M. avium–M. intracellulare* (the italicized species being the major one), and C_{78}, C_{79}, C_{80}, C_{81}, C_{82} and C_{83} for *M. phlei* and *M. flavescens*.[17,18]

Much is now known about the enzymes controlling the biosynthesis of mycolic acids,[3,5,7,29] and a number of proposals have been made as to the relationship between routes to the different types, e.g., that the *cis*-cyclopropane unit, the α-methyl-*trans*-cyclopropane and the α-methyl-β-alkoxy unit are formed from a *Z*-alkene through a common intermediate.[30] A consequence of this would be that the three subunits should have a common absolute stereochemistry at the carbon bearing the methyl group and C-1 of the *cis*-cyclopropane. The number of carbons in the chains of wax esters closely matches with that of the corresponding keto-acids, and they have been shown to be related to them, apparently through a Baeyer–Villiger type process.[21,31,32]

A standard method for characterizing mycolic acids is thermolysis to fragment the hydroxy acid functionality to produce a 'meromycol-aldehyde' (**8**).[23] This can be oxidized to the corresponding 'meromycolic acid' and then protected as a derivative such as **8a** from **7** (Scheme 2).

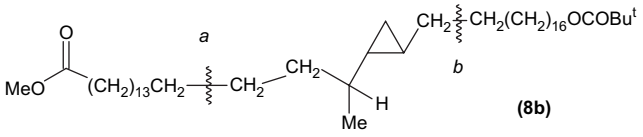


Scheme 2.

In this way, Anderson et al. were able to cleave the diacid ($[\alpha]_D$ in $CHCl_3$ +6.1) from the hydrolysis of timothy bacillus (*M. phlei*) wax ester to produce a mero-compound as a mixture ($[\alpha]_D$ in $CHCl_3$ +3.8).[33]

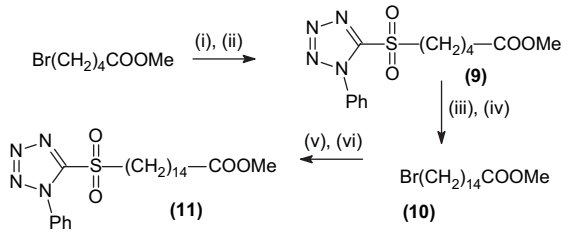
2. Results and discussion

The meromycolates derived from diacids **7** represent interesting synthetic targets because they contain only one group of chiral centres, those of the α-methyl-*trans*-cyclopropane, and may allow the overall chirality of this part of the mycolic acid system to be determined. We have already reported the synthesis of single enantiomers of one example of a di-*cis*-cyclopropane containing mycolic acid **1**,[34] of a corresponding meromycolate,[35] and of one enantiomer of the α-methyl-*trans*-cyclopropane unit present in **6** and **7**.[36] We now report the synthesis of three stereoisomers of the protected derivative **8b**, using a method that can be readily adapted to produce any appropriate chain length. In each case, the synthesis involves forming bonds *a* and *b* in Scheme 3 to a central chiral core derived from mannitol. This was achieved by the use of modified Kocienski–Julia reactions[37] to couple the fragments to produce an *E*/*Z* mixture of alkenes, followed by saturation of the alkene.



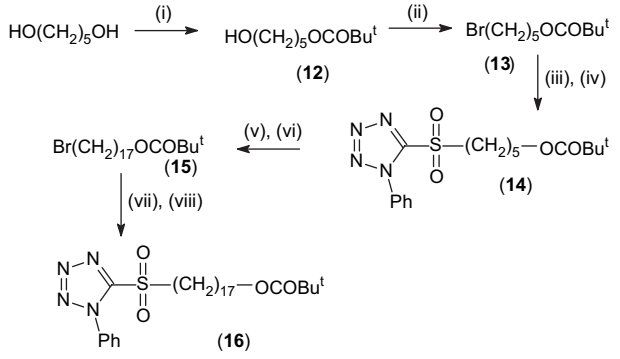
Scheme 3.

The key 15 carbon unit **11** for the left hand fragment was prepared from methyl 5-bromopentanoate as in Scheme 4.



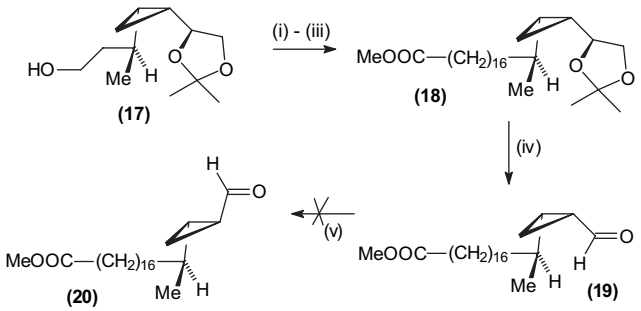
Scheme 4. (i) 1-Phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (92%); (ii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (81%); (iii) LiHMDS, $Br(CH_2)_9CHO$ (80%); (iv) H_2, Pd/C (92%); (v) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (91%); (vi) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (91%).

In a similar way, the 17 carbon unit **16** for the right hand fragment was obtained from pentan-1,5-diol (Scheme 5).



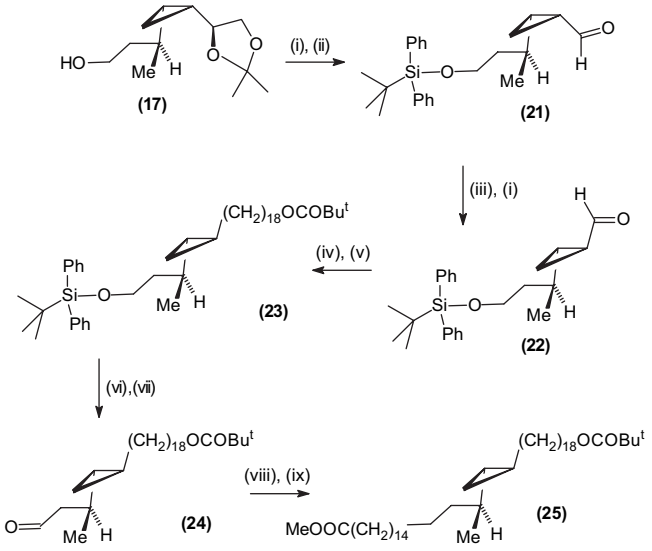
Scheme 5. (i) Pivaloyl chloride, pyridine (84%); (ii) *N*-bromosuccinimide, PPh_3 (92%); (iii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (97%); (iv) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (99%); (v) $Br(CH_2)_{11}CHO$, LiHMDS (72%); (vi) H_2, Pd/C (88%); (vii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (88%); (viii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (98%).

In the first approach, it was hoped to create bond *a* in Scheme 3 first. The alcohol **17**, which we have reported earlier,[36] was oxidized to the corresponding aldehyde then treated with sulfone **11** and a base in a modified Kocienski–Julia reaction,[37] followed by saturation of the intermediate alkene to give ester **18**, introducing the acid chain adjacent to the methyl branch. Cleavage of the acetal gave the *cis*-aldehyde **19**, but this did not give the trans-isomer **20** on attempted epimerization with base (Scheme 6).



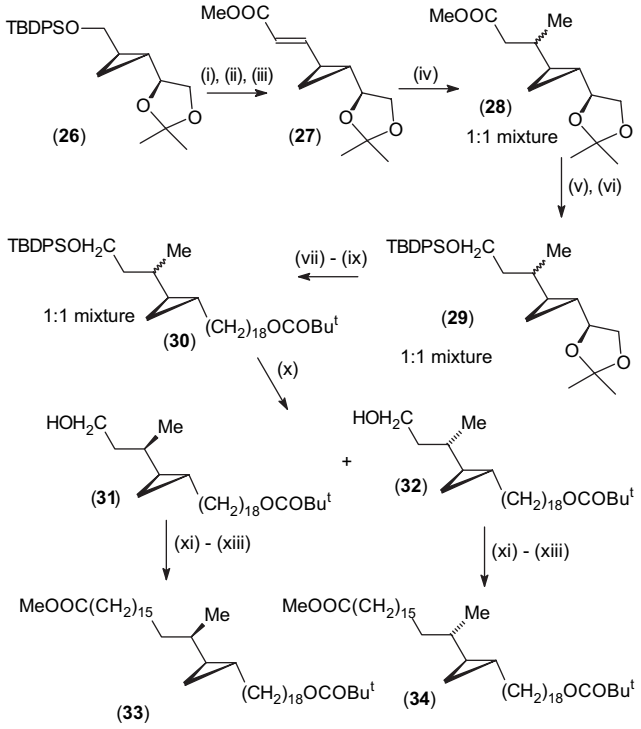
Scheme 6. (i) PCC (88%); (ii) LiHMDS, **11** (48%); (iii) KOOCNNCOOK, AcOH (62%); (iv) HIO_4 (80%); (v) NaOMe.

Given this failure, the other alkyl chain was instead introduced first to create bond *b* in Scheme 3. The alcohol **17** was protected as a silyl ether and then oxidized to *cis*-aldehyde **21**, following a route described earlier.[38,39] Epimerization with NaOMe in MeOH gave the *trans*-aldehyde **22**. Homologation with the sulfone **16** and base by a Julia–Kocienski reaction,[37] and subsequent saturation of the derived *E*/*Z*-alkene mixture using di-imide gave the ester **23** (Scheme 7).



Scheme 7. (i) Bu^tPh_2SiCl, Et_3N, CH_2Cl_2, DMAP (87%); (ii) HIO_4 (96%); (iii) NaOMe (followed by (i), overall 61%); (iv) LiHMDS, **16** (78%); (v) KOOCN=NCOOK, AcOH, MeOH (99.5%); (vi) Bu_4NF, THF (89%); (vii) PCC (83%); (viii) LiHMDS, **11** (55%); (ix) KOOCN=NCOOK, AcOH, MeOH (65%).

Removal of the silyl protecting group from **23**, followed by oxidation gave the aldehyde **24**. Reaction of the sulfone **11** (prepared from methyl 15-bromopentadecanoate) with the aldehyde **24**, again in a modified Julia reaction, led, after saturation of the *E*/*Z*-alkene mixture, to the diester **25**. The diester was converted into the corresponding ester alcohol by hydrolysis with KOH in methanol (95%) followed by re-esterification of the acid with diazomethane (84%). The enantiomer of **25** and **33** and one enantiomer of its diastereoisomer, **34** were prepared from compound **26**, again derived from mannitol (Scheme 8).[38,40]



Scheme 8. (i) Bu_4NF, THF (91%); (ii) PCC, CH_2Cl_2 (91%); (iii) $Ph_3P{=}CHCO_2Me$, toluene (79%); (iv) MeMgBr, CuBr, THF (70%); (v) $LiAlH_4$, THF (92%); (vi) Bu^tPh_2SiCl, imidizole, DMF (87%); (vii) HIO_4 (92%); (viii) LiHMDS, **16** (80%); (ix) KOOCN=NCOOK, AcOH, MeOH (80%); (x) Bu_4NF, THF (88%); (xi) PCC (89%); (xii) LiHMDS, **11** (65%); (xiii) KOOCN=NCOOK, AcOH, MeOH (80%); (xi) PCC (89, 90%) (for **31** and **32**, respectively); (xii) LiHMDS, **11** (65, 70%); (xiii) KOOCN=NCOOK, AcOH, MeOH (80, 80%).

In this case, the addition of methyl magnesium bromide to the alkene gave a ca. 1:1 mixture of the two epimers of acetal **28**, which could not be separated by column chromatography. This mixture was therefore reduced to the corresponding mixture of alcohols and protected as the silyl ethers **29**. Chain extension using sulfone **16** and base followed by saturation of the double bond, and then removal of the silyl ether protection gave a mixture of epimeric alcohols **31** and **32**, which, in this case, could be separated. The two alcohols were then separately chain extended to give **33** and **34** using the same method as described above for **25**.

The ^1H and ^{13}C NMR spectra of **25** and **33** were identical, as were their other spectra; however, they showed opposite specific rotations (+3.7 and −5.1, respectively) as did each of the single intermediates leading to them. The spectra for **34** were very similar to those for **25** and **33** but significant differences were seen in the high field regions in each case. Thus, although the cyclopropane regions of **25** and

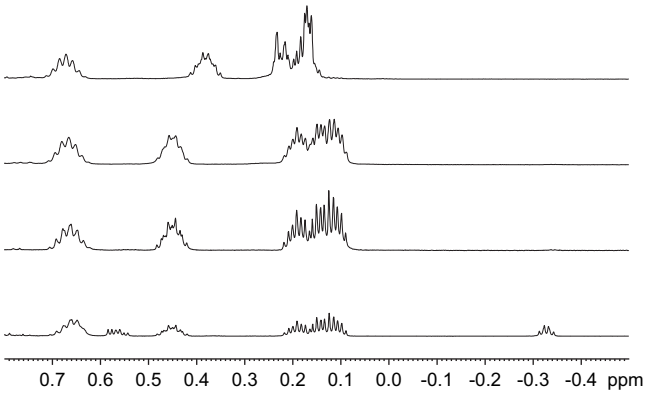
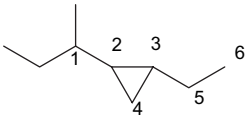


Figure 1. *Cyclopropane region of* ^1H *NMR* of (top to bottom) (i) **34**; (ii) **33**; (iii) **25**; (iv) a natural sample of the dimethyl ester of an ω-carboxy mycolic acid extracted from *M. avium*;[2] this sample contains mainly *trans*-cyclopropanes accompanied by some *cis*-cyclopropanes.

33 were visually identical to those reported for mixtures of wax ester meromycolates, and indeed to the same region in methoxymethylmycolates containing an α-methyl-*trans*-cyclopropane subunit, the same region of **34** was clearly different. Thus, Figure 1 shows the high field region of the ^{1}H NMR spectra of the three synthetic isomers, together with the same region for a natural wax ester—in which there is a mixture of *cis*- and α-methyl-*trans*-cyclopropanes. Moreover, there were small but significant differences in the carbon spectra between **25/33** and **34**; again the published shifts for either mycolic acids or wax esters containing the α-methyl-*trans*-cyclopropane unit were identical to the former. Thus, the relative stereochemistry of this unit is established. The close agreement between the rotation obtained for **25** and that reported by Anderson for a natural mero-wax acid suggests that the natural absolute stereochemistry is that of **25**, though the Anderson product was a mixture obtained well before modern spectroscopic techniques were available.[11] It will be interesting to compare his results with the rotations of mero-wax acids from other bacteria as these become available (Table 1).

Table 1. Selected ^{13}C NMR shifts for α-methyl-*trans*-cyclopropane fragment of natural wax esters and mycolic acids compared to **25/33** and **34**



1	2	3	4	Mycobacterium	Ref.
38.35	26.37	18.85	10.72	*M. tuberculosis*	41
38.13	26.14	18.62	10.50	*M. gordonae*	12b
38.1	18.6	26.1	10.50	*M. avium–M. intracellulare* complex	28
38.11	26.13	18.61	10.48	**25** *SRS*	
38.11	26.11	18.60	10.47	**33** *RSR*	
38.05	26.11	17.34	11.81	**34** *SSR*	

3. Experimental section

3.1. General

Chemicals used were obtained from commercial suppliers or prepared from them by methods described. Solvents, which had to be dry, e.g., ether, tetrahydrofuran, were dried over sodium wire. Petrol was of boiling point 40–60 °C. Reactions carried under inert conditions, were carried out under a slow stream of nitrogen. Those carried out at low temperatures were cooled using a bath of methylated spirit with liquid nitrogen. Silica gel (Merck 7736) and silica plates used for column and thin layer chromatographies were obtained from Aldrich. Organic solutions were dried over anhydrous magnesium sulfate. GLC was carried out on a Perkin–Elmer Model 8410 on a capillary column (15 m×0.53 mm). IR spectra were carried out on a Perkin–Elmer 1600 FTIR spectrometer as liquid films. NMR spectra were recorded on a Bruker AC250 or Advance500 spectrometer; for carbon spectra, +=CH_2, −=CH, CH_3. $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 Optical Activity polarimeter. Mass spectra were recorded on a Bruker Microtof.

3.1.1. 5-(1-Phenyl-1*H*-tetrazol-5-sulfonyl)pentanoic acid methyl ester (9). Anhydrous potassium carbonate (50 g, 362 mmol) was added to a stirred solution of methyl 5-bromovalerate (37.1 g, 190 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (34 g, 190.8 mmol) in acetone (300 ml) at room temperature. After stirring vigorously at 40 °C for 3 h and at room temperature for 16 h, the precipitate was filtered off and washed with acetone, then the filtrate was evaporated to give a brown oil. This was diluted with dichloromethane (250 ml) and water (250 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water (250 ml), dried and evaporated to give 5-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentanoic acid methyl ester as a brown oil (51 g, 92%) [Found $[M+H]^+$: 293.1070; $C_{13}H_{17}N_4O_2S$ requires: 293.1067], which showed δ_H (500 MHz, $CDCl_3$): 7.59–7.52 (5H, m), 3.65 (3H, s), 3.39 (2H, t, *J* 7.25 Hz), 2.36 (2H, t, *J* 7.25 Hz), 1.91–1.84 (2H, m), 1.8–1.74 (2H, m); δ_C (125 MHz, $CDCl_3$): 173.4, 154.2, 133.6, 130.1, 129.7, 51.5, 33.2, 32.8, 28.4, 23.7; ν_{max}: 2950, 1735, 1596, 1500 cm^{-1}. This was used for the next step without purification; to a vigorously stirred solution of the ester (27.8 g, 95 mmol) in tetrahydrofuran (250 ml) and industrial methylated spirits (250 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (18 g, 14.6 mmol) in ice cold 35% w/w hydrogen peroxide (50 ml). After three 30 min intervals a similar solution was added (total 72 g heptamolybdate in hydrogen peroxide (200 ml) was added). The mixture was stirred for 16 h at room temperature, diluted with water (2.5 l) and extracted with dichloromethane (2×400 ml). The combined organic layers were washed with water (1000 ml), dried and evaporated to give a thick yellow oil. Chromatography (1:1 petrol/ethyl acetate) gave 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentanoic acid methyl ester (**9**) (24.8 g, 81%) as a white solid, mp 61–63 °C [Found $[M+H]^+$: 325.0960; $C_{13}H_{17}N_4O_4S$ requires: 325.0965], which showed δ_H (500 MHz, $CDCl_3$): 7.68 (2H, br dd, *J* 1.25, 7.85 Hz), 7.63–7.57 (3H, m), 3.74 (2H, distorted t, *J* 7.85 Hz), 3.66 (3H, s), 2.38 (2H, t, *J* 7.25 Hz), 2.03–1.97 (2H, m), 1.83 (2H, br pent, *J* 7.55 Hz); δ_C (125 MHz, $CDCl_3$): 172.9, 153.3, 132.9, 131.4, 129.6, 125.0, 55.5, 51.7, 33.0, 23.2, 21.6; ν_{max}: 2954, 1734, 1498, 1342, 1153, 766 cm^{-1}.

3.1.2. 15-Bromopentadecanoic acid methyl ester (10). Lithium hexamethyldisilazide (49.2 ml, 49.2 mmol, 1 M

THF) was added dropwise with stirring at −10 °C to ester **9** (14.5 g, 44.68 mmol) and 10-bromodecanal (10 g, 42.55 mmol) in dry tetrahydrofuran (150 ml) under nitrogen. The reaction was exothermic and the temperature rose to −5 °C. The mixture was then stirred for 16 h at room temperature, when TLC showed no starting material, cooled to 0 °C, quenched with satd aq ammonium chloride (100 ml) and extracted with petrol/ether (1:1) (3×60 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (10:2 petrol/ether) gave 15-bromopenta-dec-5-enoic acid methyl ester as a pale yellow oil (11.33 g, 80%). Palladium on carbon (10%) (1 g) was added to a stirred solution of the ester (10.5 g, 31.53 mmol) in tetrahydrofuran (75 ml) and methanol (75 ml) under hydrogen. When no further hydrogen was absorbed, the products were filtered through Celite, which was washed with ethyl acetate. The filtrate was evaporated and the residue was purified by chromatography (5:2 petrol/ether) giving 15-bromopentadecanoic acid methyl ester (**10**) as a white solid (9.7 g, 92%), mp 38–39 °C (lit. 38–39 °C),[42] which showed δ_H (500 MHz, $CDCl_3$): 3.68 (3H, s), 3.42 (2H, t, *J* 7 Hz), 2.32 (2H, t, *J* 7.25 Hz), 1.86 (2H, br pent, *J* 7 Hz), 1.62 (2H, pent, *J* 7.25 Hz), 1.43 (2H, br pent, *J* 7 Hz), 1.28 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.4, 51.4, 34.1, 34.0, 32.8, 29.58, 29.55, 29.4, 29.2, 29.1, 28.8, 28.2, 24.9.

3.1.3. 15-(1-Phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic acid methyl ester (11). Anhydrous potassium carbonate (2.76 g, 20 mmol) was added to a stirred solution of ester **10** (2.75 g, 8.2 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (1.6 g, 9.0 mmol) in acetone (50 ml) at room temperature and stirred vigorously for 16 h. The precipitate was filtered off and washed with acetone, and the filtrate was evaporated to give a brown residue. This was diluted with dichloromethane (75 ml) and water (50 ml). The aqueous layer was re-extracted with dichloromethane (2×25 ml). The combined organic layers were washed with water (50 ml), dried and evaporated to give a yellow solid. Chromatography (5:1 petrol/ether) gave 15-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentadecanoic acid methyl ester (3.25 g, 91%) as a colourless thick oil, which showed δ_H (500 MHz, $CDCl_3$): 7.62 (5H, br s), 3.68 (3H, s), 3.41 (2H, t, *J* 7.6 Hz), 2.32 (2H, t, *J* 7.5 Hz), 1.83 (2H, pent, *J* 7.6 Hz), 1.64 (2H, br pent, *J* 7.6 Hz), 1.46 (2H, br pent, *J* 6.65 Hz), 1.27 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.3, 154.5, 133.8, 130.1, 129.8, 123.9, 51.4, 34.1, 33.4, 29.58, 29.55, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.6, 24.9; ν_{max}: 1732 cm^{-1}.

To a vigorously stirred solution of the above sulfide (3.2 g, 7.4 mmol) in tetrahydrofuran (45 ml) and industrial methylated spirits (45 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (4.2 g, 3.4 mmol) in ice cold 35% w/w hydrogen peroxide (13 ml) at 15 °C. After 1.5 h, a further ice cold solution of heptamolybdate (1.9 g) in hydrogen peroxide (5 ml) was added. The mixture was stirred for 16 h at room temperature then diluted with water (250 ml) and extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water (100 ml), dried and evaporated to give a white solid; chromatography (1:1 petrol/ethyl acetate) gave 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic acid methyl ester (**11**) as a white solid (3.12 g, 91%), mp 78–80 °C [Found $[M+Na]^+$: 487.2343; $C_{23}H_{36}N_4O_4SNa$ requires: 487.2349], which showed δ_H (500 MHz, $CDCl_3$): 7.72 (2H, br dd, *J* 1.9, 8.2 Hz), 7.68–7.61 (3H, m), 3.75 (2H, distorted t, *J* 7.9 Hz), 3.68 (3H, s), 2.32 (2H, t, *J* 7.5 Hz), 1.97 (2H, br pent, *J* 7.55 Hz), 1.64 (2H, br pent, *J* 7.25 Hz), 1.5 (2H, pent, *J* 7.5 Hz), 1.27 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.3, 153.5, 133.1, 131.5, 129.7, 125.1, 56.0, 51.4, 34.1, 29.56, 29.54, 29.50, 29.44, 29.40, 29.20, 29.18, 29.1, 28.9, 28.2, 25.0, 22.0; ν_{max}: 2920, 1731, 1494, 1341, 1151 cm^{-1}.

3.1.4. 2,2-Dimethylpropionic acid 5-hydroxypentyl ester (12). Trimethylacetyl chloride (12 g, 95.39 mmol) was added to a stirred solution of 1,5-pentanediol (20 g, 192 mmol) and pyridine (10 g, 126 mmol) in dichloromethane (100 ml) at 10 °C, then allowed to reach room temperature and stirred for 16 h. A white precipitate was formed, and the mixture was diluted with dichloromethane (200 ml) and washed with dil hydrochloric acid (5%), then the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with satd aq sodium bicarbonate (100 ml) and water (100 ml), dried and evaporated to give a colourless oil. The crude product was columned (5:1 petrol/ethyl acetate) to give 2,2-dimethylpropionic acid 5-hydroxypentyl ester (**12**) as a colourless oil (15.1 g, 84%) [Found $[M+Na]^+$: 211.1302; $C_{10}H_{20}O_3Na$ requires: 211.1305], which showed δ_H (250 MHz, $CDCl_3$): 4.01 (2H, t, *J* 6.4 Hz), 3.58 (2H, t, *J* 6.4 Hz), 2.37 (1H, br s), 1.67–1.49 (4H, m), 1.44–1.32 (2H, m), 1.14 (9H, s); δ_C (62.5 MHz, $CDCl_3$): 178.6, 64.2, 62.3, 38.6, 32.1, 28.3, 27.1, 22.1; ν_{max}: 3379, 2937, 1729 cm^{-1}.

3.1.5. 2,2-Dimethylpropionic acid 5-bromopentyl ester (13). *N*-Bromosuccinimide (15.5 g, 87.2 mmol) was added in portions over 15 min to a stirred solution of ester **12** (13.1 g, 69.6 mmol) and triphenylphosphine (21 g, 80 mmol) in dichloromethane (240 ml) at 0 °C. After stirring at room temperature for 1 h, when TLC showed no starting material, it was quenched with satd aq sodium meta-bisulfate (200 ml). The aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue. This was treated with 1:1 petrol/ether (100 ml) and refluxed for 30 min, then the triphenylphosphine oxide was filtered off and washed with petrol/ether (50 ml). The filtrate was evaporated and the residue chromatographed (10:2 petrol/ether) to give 2,2-dimethylpropionic acid 5-bromopentyl ester (**13**) (16.04 g, 92%) as a colourless oil [Found $[M+Na]^+$: 273.0449; $C_{10}H_{19}O_2{}^{79}BrNa$ requires: 273.0461], which showed δ_H (500 MHz, $CDCl_3$): 4.07 (2H, t, *J* 6.3 Hz), 3.41 (2H, t, *J* 6.65 Hz), 1.88 (2H, pent, *J* 6.9 Hz), 1.66 (2H, pent, *J* 6.9 Hz), 1.52 (2H, pent, *J* 6.9 Hz), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.5, 63.9, 38.7, 33.4, 32.2, 27.7, 27.1, 24.5; ν_{max}: 2959, 2849, 1728, 1480, 1154, 771 cm^{-1}.

3.1.6. 2,2-Dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentyl ester (14). Anhydrous potassium carbonate (18 g, 130 mmol) was added to a stirred solution of ester **13** (15 g, 59.7 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (10.7 g, 60 mmol) in acetone (150 ml) at room temperature. The mixture was stirred vigorously at 40 °C for 3 h, then at room temperature for 16 h, then worked as above to give a pale yellow oil, 2,2-dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentyl ester (20.2 g, 97%) [Found

[M+H]$^+$: 349.1675; $C_{17}H_{25}N_4O_2S$ requires: 349.1693], which showed δ_H (500 MHz, $CDCl_3$): 7.58–7.51 (5H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.39 (2H, t, *J* 7.6 Hz), 1.86 (2H, pent, *J* 7.55 Hz), 1.67 (2H, pent, *J* 6.6 Hz), 1.51 (2H, pent, *J* 6.97 Hz), 1.17 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.5, 154.3, 133.7, 130.0, 129.8, 123.8, 63.8, 38.7, 33.0, 28.7, 28.0, 27.1, 24.9; ν_{max}: 2971, 1725, 1156, 762, 694 cm^{-1}. This was used for next step without purification. To a vigorously stirred solution of the above ester (32.5 g, 93.27 mmol) in tetrahydrofuran (220 ml) and industrial methylated spirits (270 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (18 g, 14.56 mmol) in ice cold 35% w/w hydrogen peroxide (50 ml). A similar solution was added three times at 0.5 h intervals (total 72 g of heptamolybdate in hydrogen peroxide (200 ml) was added). The mixture was stirred for 16 h at room temperature then worked up as above to give a yellow oil. Chromatography (1:1 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentyl ester (**14**) as a thick pale yellow oil (35 g, 99%) [Found [M+H]$^+$: 381.1590; $C_{17}H_{25}N_4O_4S$ requires: 381.1591], which showed δ_H (500 MHz, $CDCl_3$): 7.69–7.67 (2H, m), 7.64–7.57 (3H, m), 4.06 (2H, t, *J* 6.3 Hz), 3.74 (2H, distorted t, *J* 7.9 Hz), 2.03–1.97 (2H, m), 1.7 (2H, pent, *J* 6.3 Hz), 1.58 (2H, pent, *J* 6.95 Hz), 1.18 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.4, 153.4, 132.9, 131.4, 129.7, 125.0, 63.5, 55.8, 38.7, 28.0, 27.1, 24.7, 21.7; ν_{max}: 2968, 1723, 1497, 1343, 1156, 764 cm^{-1}.

3.1.7. 2,2-Dimethylpropionic acid 17-bromoheptadecyl ester (15). Lithium hexamethyldisilazide (38 ml, 40.2 mmol, 1.06 M THF) was added dropwise to a stirred solution of ester **14** (14.1 g, 37 mmol) and 12-bromododecanal (9.58 g, 36.5 mmol) in dry tetrahydrofuran (150 ml) under nitrogen at −10 °C. The reaction was exothermic and the temperature rose to −5 °C. The mixture was allowed to reach room temperature and stirred for 16 h when TLC showed no starting material. Work up as above gave a thick yellow oil; chromatography (10:1 petrol/ether) gave *E*/*Z*-2,2-dimethylpropionic acid 17-bromoheptadec-5-enyl ester in ratio 2.7:1 as a colourless oil (10.9 g, 72%). Palladium on carbon (10%) (0.8 g) was added to a stirred solution of the ester (10.9 g, 26.11 mmol) in ethyl acetate (45 ml) and methanol (110 ml) under hydrogen. When no further hydrogen was absorbed, the reaction mixture was worked up as above. Chromatography (5:2 petrol/ether) gave 2,2-dimethylpropionic acid 17-bromoheptadecyl ester (**15**) as a white solid (9.68 g, 88%), mp 36–38 °C [Found [M+Na]$^+$: 441.2321; $C_{22}H_{43}{}^{79}BrO_2Na$ requires: 441.2339], which showed δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz), 3.41 (2H, t, *J* 6.65 Hz), 1.85 (2H, pent, *J* 7.25 Hz), 1.62 (2H, pent, *J* 6.6 Hz), 1.42 (2H, pent, *J* 7.25 Hz), 1.38–1.22 (24H, m), 1.2 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.7, 64.5, 38.7, 34.0, 32.8, 29.64, 29.60, 29.55, 29.53, 29.51, 29.4, 29.2, 28.8, 28.6, 28.2, 27.2, 25.9; ν_{max}: 1719 cm^{-1}.

3.1.8. 2,2-Dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester (16). Anhydrous potassium carbonate (5 g, 36.2 mmol) was added to a stirred solution of ester **15** (9.28 g, 22.12 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (4 g, 22.4 mmol) in acetone (100 ml) at room temperature. After stirring vigorously for 16 h, work up as above gave a brown oil. Chromatography (5:1 petrol/ether) gave 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)heptadecyl ester (10.07 g, 88%) as a colourless oil [Found [M+H]$^+$: 517.3563; $C_{29}H_{49}O_2N_4S$ requires: 517.3571], which showed δ_H (500 MHz, $CDCl_3$): 7.59–7.51 (5H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.39 (2H, t, *J* 7.25 Hz), 1.81 (2H, pent, *J* 7.55 Hz), 1.61 (2H, pent, *J* 6.65 Hz), 1.43 (2H, pent, *J* 6.6 Hz), 1.37–1.23 (24H, m), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 154.5, 133.7, 130.0, 129.7, 123.8, 64.4, 38.7, 33.3, 29.61, 29.59, 29.58, 29.7, 29.51, 29.49, 29.46, 29.4, 29.2, 29.04, 28.98, 28.6, 28.6, 27.2, 25.9; ν_{max}: 2920, 2851, 1727, 1500, 1159 cm^{-1}.

To a vigorously stirred solution of the above sulfide (9.7 g, 18.77 mmol) in tetrahydrofuran (110 ml) and industrial methylated spirits (110 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (8.5 g, 6.88 mmol) in ice cold 35% w/w hydrogen peroxide (25 ml) at 15 °C. After 1.5 h, further ice cold heptamolybdate (8.5 g) in hydrogen peroxide (25 ml) was added. The mixture was stirred for 16 h at room temperature, diluted with water (250 ml) and worked up as above to give a white solid. Chromatography (1:1 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester (**16**) as a white solid (10.1 g, 98%) [Found [M+Na]$^+$: 571.3271; $C_{29}H_{48}N_4O_4SNa$ requires: 571.32885], mp 51–53 °C, which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.69 (2H, m), 7.65–7.58 (3H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.73 (2H, distorted t, *J* 8.2 Hz), 1.98–1.92 (2H, m), 1.62 (2H, pent, *J* 6.6 Hz), 1.49 (2H, pent, *J* 6.9 Hz), 1.39–1.24 (24H, m), 1.20 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 153.5, 133.1, 131.4, 129.7, 125.1, 64.5, 56.0, 38.7, 29.63, 29.61, 29.53, 29.49, 29.4, 29.20, 29.16, 28.9, 28.6, 28.1, 27.2, 25.9, 21.9; ν_{max}: 2922, 1727, 1497, 1463, 1341, 1284, 1153, 762 cm^{-1}.

3.1.9. (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyraldehyde. (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butanol **17** (1.6 g, 7.47 mmol) in dichloromethane (10 ml) was added to a stirred suspension of pyridinium chlorochromate (4.03 g, 18.7 mmol) in dichloromethane (75 ml) at room temperature and stirred vigorously for 3 h, when TLC showed no starting material, then poured into ether (200 ml), filtered through silica and washed well with ether. The filtrate was evaporated to give an oil; chromatography (5:2 petrol/ether) gave (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyraldehyde (1.4 g, 88%), $[\alpha]_D^{22}$ +10.14 (*c* 1.45, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.9 Hz), 4.07 (1H, dd, *J* 6, 7.85 Hz), 3.87 (1H, br dt, *J* 6.3, 7.85 Hz), 3.67 (1H, t, *J* 7.55 Hz), 2.41–2.39 (2H, m), 1.74–1.67 (1H, m), 1.44 (3H, s), 1.35 (3H, s), 1.1 (3H, d, *J* 6.6 Hz), 0.97 (1H, br dq, *J* 5.65, 8.2 Hz), 0.88 (1H, br dt, *J* 4.75, 8.8 Hz), 0.82–0.75 (1H, m), 0.36 (1H, br q, *J* 5.35 Hz); δ_C (125 MHz, $CDCl_3$): 201.8 (+), 108.6 (+), 76.7 (+), 70.0 (−), 51.3 (−), 28.6 (+), 26.8 (−), 25.7 (+), 23.2 (+), 20.8 (+), 19.2 (+), 8.8 (−); ν_{max}: 1724 cm^{-1}.

3.1.10. (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadecanoic acid methyl ester (18). Lithium hexamethyldisilazide (10.12 ml, 10.1 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester (2.74 g, 6.74 mmol) and (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyraldehyde (1.3 g,

6.13 mmol) in dry tetrahydrofuran (30 ml) under nitrogen at −25 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. The mixture was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with petrol/ether (1:1) (3×40 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick oil; chromatography (10:1 petrol/ether) gave a pale yellow oil, (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadec-15-enoic acid methyl ester (1.2 g, 48%). Dipotassium azodicarboxylate (2.15 g, 11.1 mmol) was added to a stirred solution of the above ester (1 g, 2.22 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Glacial acetic acid (3 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and quenched slowly with satd aq ammonium chloride (5 ml), then extracted with petrol/ether (1:1) (2×50 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; however, the ^{1}H NMR spectra showed that there was still starting material left. The procedure was repeated for another 16 h and the residue was purified by chromatography (10:1 petrol/ethyl acetate) to give (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadecanoic acid methyl ester (**18**) as a colourless oil, which solidified later (0.62 g, 62%) [Found [M+Na]$^+$: 475.3759; $C_{28}H_{52}O_4Na$ requires: 475.3758], $[\alpha]_D^{22}$ −11.75 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.13–4.09 (1H, m), 3.74–3.71 (2H, m), 3.68 (3H, s), 2.32 (2H, t, *J* 7.55 Hz), 1.63 (2H, br pent, *J* 7.25 Hz), 1.46 (3H, s), 1.37 (3H, s), 1.35–1.2 (28H, m), 1.01 (4H, br s), 0.92 (1H, br dq, *J* 5.3, 8.8 Hz), 0.84 (1H, dt, *J* 4.75, 8.85 Hz), 0.71–0.66 (1H, m), 0.24 (1H, br q, *J* 5.35 Hz); δ_C (125 MHz, $CDCl_3$): 174.4, 108.3, 77.9 (−), 70.0 (+), 51.4 (−), 37.4 (+), 34.1 (+), 33.3 (−), 30 (+), 29.7 (+), 29.6 (+), 29.5 (+), 29.3 (+), 29.2 (+), 27.2 (+), 26.9 (−), 25.8 (−), 25.0 (+), 23.9 (−), 20.0 (−), 19.2 (−), 9.1 (+); ν_{max}: 1730 cm^{-1}.

3.1.11. *cis*-(*S*)-18-((1*R*,2*R*)-2-Formylcyclopropyl)nonadecanoic acid methyl ester (19). Periodic acid (0.9 g, 3.98 mmol) was added to a stirred solution of ester **18** (0.6 g, 1.33 mmol) in dry ether (40 ml) under nitrogen at room temperature. After 16 h, TLC showed no starting material. The precipitate was filtered, washed with ether and the solvent was evaporated. Chromatography (10:1 petrol/ethyl acetate) gave *cis*-(*S*)-18-((1*R*,2*R*)-2-formylcyclopropyl)-nonadecanoic acid methyl ester (**19**) (0.4 g, 80%) [Found [M+Na]$^+$: 403.3202; $C_{24}H_{44}O_3Na$ requires: 403.3183], $[\alpha]_D^{22}$ +1.98 (*c* 1.19, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.33 (1H, d, *J* 5.65 Hz), 3.67 (3H, s), 2.3 (2H, t, *J* 7.85 Hz), 1.93–1.87 (1H, m), 1.61 (2H, br pent, *J* 7.2 Hz), 1.44–1.15 (32H, m), 1.05 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 201.8 (−), 174.3, 51.4 (−), 37.4 (+), 34.1 (+), 32.3 (−), 32.0 (−), 29.9 (+), 29.7 (+), 29.64 (+), 29.60 (+), 29.5 (+), 29.3 (+), 29.2 (+), 28.7 (−), 26.8 (+), 24.9 (+), 20.1 (−), 13.6 (+); ν_{max}: 1740, 1706 cm^{-1}.

3.1.12. Attempted epimerization[43] of aldehyde (19). Sodium methoxide (0.13 g, 2.43 mmol) was added to a stirred solution of *cis*-aldehyde **18** (0.37 g, 0.97 mmol) in methanol (30 ml) and tetrahydrofuran (10 ml). This was refluxed for 56 h, cooled to room temperature and quenched with satd aq ammonium chloride (20 ml), and extracted with ether (3×50 ml). The combined organic layers were dried, evaporated and no product was obtained (gave a white gel, which was not soluble in $CDCl_3$).

3.1.13. *tert*-Butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane. Triethylamine (5.66 g, 56.1 mmol) was added to a stirred solution of alcohol **17** (6 g, 28.03 mmol) in dry dichloromethane (150 ml). After 10 min, *tert*-butyldiphenylsilyl chloride (10 g, 36.4 mmol) in dichloromethane (20 ml) was added, followed by dimethylaminopyridine (0.5 g) in dry dichloromethane (5 ml). The mixture was stirred for 4 h, when TLC showed no starting material, quenched with water (50 ml) and extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine and water, and dried to give a residue. This was purified by chromatography (5:1 petrol/ether) to give a colourless oil *tert*-butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (11.02 g, 87%) [Found M$^+$: 452.2747; $C_{28}H_{40}O_3Si$ requires: 452.2747], $[\alpha]_D^{22}$ −7.8 (*c* 1.54, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.69–7.67 (4H, m), 7.47–7.39 (6H, m), 4.19 (1H, dd, *J* 6, 8 Hz), 3.79–3.63 (4H, m), 1.76–1.7 (1H, m), 1.48 (3H, s), 1.41–1.35 (1H, m), 1.35 (3H, s), 1.07 (9H, s), 0.97 (3H, d, *J* 6.3 Hz), 0.96–0.915 (1H, m), 0.91–0.85 (2H, m), 0.74–0.68 (1H, m), 0.29 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 135.6, 135.5, 133.80, 133.78, 129.64, 129.62, 127.68, 127.66, 108.3, 77.8, 70.1, 61.5, 40, 29.7, 26.8, 25.7, 23.9, 19.6, 19.3, 19.2, 9.3; ν_{max}: 2930, 2858, 1111, 1062 cm^{-1}.

3.1.14. *cis*-(1*R*,2*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (21). Periodic acid (12.6 g, 55.3 mmol) was added to a stirred solution of *tert*-butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (10 g, 22.12 mmol) in dry ether (150 ml) under nitrogen at room temperature. The mixture was stirred for 16 h when TLC showed no starting material. The precipitate was filtered then washed with ether and the solvent was evaporated to give a residue; chromatography (10:2 petrol/ether) gave *cis*-(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (**21**) (8 g, 96%) [Found: C 75.5, H 8.6; $C_{24}H_{32}O_2Si$ requires: C 75.74, H 8.47], $[\alpha]_D^{22}$ +3.66 (*c* 1.64, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.32 (1H, d, *J* 6 Hz), 7.69–7.66 (4H, m), 7.47–7.40 (6H, m), 3.73–3.64 (2H, m), 1.91–1.86 (1H, m), 1.72–1.63 (2H, m), 1.5–1.45 (1H, m), 1.33–1.17 (3H, m), 1.07 (9H, s), 1.06 (3H, d, *J* 6.3 Hz); δ_C (125 MHz, $CDCl_3$): 201.5, 135.6, 133.9, 133.8, 129.6, 127.6, 61.4, 39.8, 31.7, 29.3, 28.6, 26.9, 19.9, 19.1, 13.8; ν_{max}: 1703 cm^{-1}.

3.1.15. *trans*-(1*S*,2*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (22). Sodium methoxide (0.937 g, 17.36 mmol) was added to a stirred solution of *cis*-aldehyde **21** (6 g, 15.78 mmol) in methanol (250 ml) and refluxed for 56 h.[43] The mixture was cooled to room temperature and quenched with satd aq ammonium chloride (100 ml), and the product was extracted with ether (3×150 ml). The combined organic layers were

dried and evaporated to give a thick oil, which solidified later. Chromatography (5:2 petrol/ether) gave *trans*-(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (**22**) (1.16 g, 19%) [Found $[M+Na]^+$: 403.2075; $C_{24}H_{32}O_2NaSi$ requires: 403.2064], $[\alpha]_D^{22}$ +22.9 (*c* 1.28, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.00 (1H, d, *J* 5.35 Hz), 7.71–7.67 (4H, m), 7.47–7.39 (6H, m), 3.77 (1H, br dt, *J* 6.3, 10.4 Hz), 3.71 (1H, dt, *J* 6.65, 10.4 Hz), 1.76–1.71 (1H, m), 1.7–1.67 (1H, m), 1.56–1.5 (1H, m), 1.32–1.24 (3H, m), 1.07 (9H, s), 0.99 (3H, d, *J* 6.3 Hz), 0.96–0.93 (1H, m); δ_C (125 MHz, $CDCl_3$): 200.9, 135.6, 135.5, 135.2, 134.8, 133.9, 133.8, 129.6, 127.73, 127.69, 127.66, 61.4, 39.3, 33.3, 30.1, 29.2, 26.9, 26.6, 19.3, 19.2, 19.0, 13.6; ν_{max}: 1707 cm^{-1}. The second fraction (1:1 petrol/ethyl acetate) was (1*S*,2*R*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropanecarbaldehyde (1.16 g, 52%), which showed δ_H (500 MHz, $CDCl_3$): 8.97 (1H, d, *J* 5.65 Hz), 3.73–3.63 (2H, m), 2.15 (1H, br s), 1.76–1.73 (1H, m), 1.71–1.65 (1H, m), 1.59–1.53 (1H, m), 1.35–1.30 (1H, m), 1.29–1.25 (1H, m), 1.21–1.13 (1H, m), 1.03 (3H, d, *J* 7 Hz), 0.95 (1H, m); δ_C (125 MHz, $CDCl_3$): 201.1 (−), 60.2 (+), 39.4 (+), 33.5 (−), 30.3 (−), 28.9 (−), 19.6 (−), 13.3 (+); ν_{max}: 3414 cm^{-1}. The alcohol was protected as before to give the title compound in 81% yield. There was less than 5% of the cis-isomer.

3.1.16. 2,2-Dimethylpropionic acid 18-{(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (23). Lithium hexamethyldisilazide (14.1 ml, 14.1 mmol, 1 M THF) was added dropwise to a stirred solution of sulfone (**16**) (5.15 g, 9.4 mmol) and aldehyde **22** (3.25 g, 8.55 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at −20 °C. The reaction was exothermic and the temperature rose to −10 °C, resulting in a yellow solution. The mixture was allowed to reach room temperature, stirred for 2 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with 1:1 petrol/ether (3×50 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, 2,2-dimethylpropionic acid 18-{(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (4.5 g, 78%), as a 2.7:1 mixture of two isomers [Found $[M+Na]^+$: 725.5303; $C_{46}H_{74}O_3NaSi$ requires: 725.5299]; δ_H (500 MHz, $CDCl_3$) (major isomer): 7.70–7.68 (4H, m), 7.46–7.37 (6H, m), 5.38 (1H, br dt, *J* 6.6, 15 Hz), 4.94 (1H, br dd, *J* 8.5, 15 Hz), 4.1 (2H, t, *J* 6.6 Hz), 3.85–3.74 (2H, m), 1.94 (2H, br q, *J* 6.3 Hz), 1.67–1.58 (4H, m), 1.4–1.26 (25H, br s), 1.23 (9H, s), 1.17–1.12 (1H, m), 1.07 (9H, s), 1.04–0.97 (1H, m), 0.93 (3H, d, *J* 6.6 Hz), 0.89–0.87 (1H, m), 0.47–0.41 (3H, m); δ_H (500 MHz, $CDCl_3$) (minor isomer): 5.26 (1H, br dt, *J* 7.25, 10.8 Hz), 4.73 (1H, br t, *J* 10.8 Hz), 2.13 (1H, m). The remaining signals were obscured by the major isomer.

Method A: dipotassium azodicarboxylate (3.3 g, 17.1 mmol) was added to a stirred solution of 2,2-dimethylpropionic acid 18-{(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (4.5 g, 6.4 mmol) in dry THF (30 ml) and methanol (15 ml) at 10 °C under nitrogen, giving a yellow suspension. Glacial acetic acid (4 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml) and extracted with 1:1 petrol/ether (2×100 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; ^1H NMR showed that there was still starting material left. The procedure was repeated twice for 16 h and the residue was chromatographed (10:1 petrol/ether) to give 2,2-dimethylpropionic acid 18-{(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (**23**) as a white solid (4.5 g, 99.5%) [Found $[M+Na]^+$: 727.5477; $C_{46}H_{76}O_3NaSi$ requires: 727.5456], $[\alpha]_D^{22}$ +5.7 (*c* 1.93, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.69–7.66 (4H, m), 7.43–7.36 (6H, m), 4.07 (2H, t, *J* 6.6 Hz), 3.80–3.72 (2H, m), 1.74–1.68 (1H, m), 1.65–1.59 (2H, br pent, *J* 6.5 Hz), 1.56–1.49 (1H, m), 1.36–1.23 (31H, br s), 1.20 (9H, s), 1.17–1.12 (1H, m), 1.05 (9H, s), 0.94–0.84 (4H, including br s, *δ* 0.88), 0.46–0.40 (1H, m), 0.18–0.137 (2H, m), 0.12–0.09 (1H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 135.6 (+), 134.2, 129.5 (+), 127.5 (+), 64.46 (−), 62.35 (−), 40.21 (−), 38.72, 34.77 (+), 34.34 (−), 29.7 (−), 29.63 (−), 29.58 (−), 29.56 (−), 29.5 (−), 29.2 (−), 28.6 (−), 27.2 (+), 26.9 (+), 25.9 (−), 19.8 (+), 19.2, 18.6 (+), 10 (−); ν_{max}: 2920, 2850, 1730 cm^{-1}.

Method B: triisopropylbenzenesulfonyl hydrazide (0.63 g, 2.13 mmol) was added to the above ester (0.5 g, 0.712 mmol) in tetrahydrofuran (20 ml) at room temperature and stirred for 24 h at 45–50 °C, followed by the addition of another mol. equivalent of triisopropylbenzenesulfonyl hydrazide then stirring for 24 h. After diluting with petrol/ether (1:1) (100 ml) and quenching with aq sodium hydroxide (2%, 20 ml), the organic layer was separated and the aqueous layer was re-extracted with petrol/ether (2×25 ml). The combined organic layers were washed with brine, dried and evaporated. Chromatography on silica eluting with 10:1 petrol/ether gave **23** (0.42 g, 85%), which showed identical spectra to those above.

3.1.17. 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester. Tetra-*n*-butylammonium fluoride (9.6 ml, 9.6 mmol, 1 M solution) was added with stirring to ester **23** (4.5 g, 6.4 mmol) in dry tetrahydrofuran (50 ml) at 5 °C. The mixture was stirred for 16 h at room temperature, when TLC showed no starting material, then evaporated, quenched with water (30 ml) and extracted with dichloromethane (3×50 ml). The combined organic layers were dried and evaporated to give a thick oil. Chromatography (5:0.5 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester (2.63 g, 89%) [Found $[M+Na]^+$: 489.4300; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ +11.02 (*c* 1.27, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 3.77–3.68 (2H, br m), 1.75–1.68 (1H, sext, *J* 6.65 Hz), 1.65–1.60 (2H, m), 1.58–1.51 (1H, m), 1.35–1.24 (32H, br m), 1.19 (9H, s), 1.17–1.11 (1H, m), 0.95 (3H, d, *J* 6.65 Hz), 0.90–0.81 (1H, m), 0.51–0.45 (1H, m), 0.25–0.13 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.5 (+), 61.4 (+), 40.4 (+), 38.7, 35.0 (−), 34.3 (+), 29.7 (+), 29.62 (+), 29.58 (+), 29.54 (+), 29.51 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 19.8 (−), 18.7 (−), 10.6 (+); ν_{max}: 3397, 1731 cm^{-1}.

3.1.18. 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (24). 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester (2.5 g, 5.5 mmol) in dichloromethane (20 ml) was added to a suspension of pyridinium chlorochromate (2.96 g, 13.7 mmol) in dichloromethane (100 ml). The mixture was stirred vigorously at room temperature for 3 h, when TLC showed no starting material, then diluted with ether (250 ml) and filtered through a pad of Celite and then a pad of silica. The silica was washed with ether. The combined filtrate was evaporated to give a residue, which was purified by chromatography (5:0.5 petrol/ethyl acetate) to give a colourless oil, 2,2-dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (**24**) (2.07 g, 83%) [Found [M+Na]$^+$: 487.4100; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ +17.1 (*c* 1.82, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.8 (1H, t, *J* 2.5 Hz), 4.06 (2H, t, *J* 6.6 Hz), 2.52 (1H, ddd, *J* 2.5, 6.0, 15.75 Hz), 2.39 (1H, ddd, *J* 2.5, 7.55, 15.75 Hz), 1.63 (2H, pent, 6.6 Hz), 1.4–1.24 (32H, m), 1.2 (9H, s), 1.20–1.14 (1H, m), 1.03 (3H, d, *J* 6.6 Hz), 0.54–0.47 (1H, m), 0.36–0.23 (3H, m); δ_C (125 MHz, $CDCl_3$): 202.8, 178.6, 64.4 (−), 51.4 (−), 38.7, 34.1 (−), 33.9 (+), 29.7 (−), 29.64 (−), 29.62 (−), 29.58 (−), 29.55 (−), 29.5 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 19.9 (+), 18.8 (+), 11.4 (−); ν_{max}: 2922, 2853, 1729 cm^{-1}.

3.1.19. (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-Dimethylpropionyloxy)-octadecyl]cyclopropyl}nonadecanoic acid methyl ester (25). Lithium hexamethyldisilazide (6.4 ml, 6.4 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)-pentadecanoic methyl ester **11** (1.73 g, 4.26 mmol) and ester **24** (1.8 g, 3.87 mmol) in dry tetrahydrofuran (30 ml) under nitrogen at −30 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. The mixture was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with petrol/ether (1:1) (3×30 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (1.5 g, 55%) as a mixture of two isomers in ratio 2.2:1 [Found [M+Na]$^+$: 725.6446; $C_{46}H_{86}O_4Na$ requires: 725.6418]; δ_H (500 MHz, $CDCl_3$) (major isomer): 5.47–5.37 (2H, m), 4.06 (2H, t, *J* 6.65 Hz), 3.68 (3H, s), 2.3 (2H, t, *J* 7.5 Hz), 2.17–2.12 (1H, m), 2.06–1.92 (3H, m), 1.67–1.61 (5H, m), 1.38–1.25 (51H, m), 1.27 (9H, s), 0.91 (3H, d, *J* 6.6 Hz), 0.78–0.73 (1H, m), 0.50–0.45 (1H, m), 0.30–0.12 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 174.3, 131.4, 128.8, 64.5, 51.4, 34.4, 34.1, 32.7, 29.72, 29.70, 29.68, 29.65, 29.63, 29.60, 29.57, 29.55, 29.53, 29.47, 29.27, 29.24, 29.22, 29.17, 28.6, 27.2, 25.9, 25.7, 25.0, 19.2, 18.6, 10.8; ν_{max}: 2921, 1731, 1479 cm^{-1}; δ_H (500 MHz, $CDCl_3$) (minor isomer): 1.12–1.18 (1H, m), 0.88–0.85 (3H, d, *J* 6.6 Hz), 0.86 (1H, m); δ_C (125 MHz, $CDCl_3$): 130.4, 128.4, 34.7, 34.4, 29.4, 29.1, 27.3, 25.8, 22.65, 22.62, 22.3, 19.4, 15.3, 14.3, 14.1, 14.0, 11.4, 10.7. The remaining signals were obscured by the major isomer. Dipotassium azodicarboxylate (3.3 g, 17.1 mmol) was added to a stirred solution of the above ester (1.2 g, 1.71 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, giving a yellow suspension. Glacial acetic acid (2 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml) and extracted with 1:1 petrol/ether (2×50 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; the ^{1}H NMR spectrum showed that there was still starting material left. The procedure was repeated for another 16 h and the residue was purified by chromatography (10:1 petrol/ether) to give a white solid, (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]-cyclopropyl}nonadecanoic acid methyl ester (**25**) (0.78 g, 65%) [Found [M+Na]$^+$: 727.6560; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ +3.7 (*c* 1.03, $CHCl_3$), mp 47–49 °C; δ_H (500 MHz, $CDCl_3$): 4.06 (2H, t, *J* 6.6 Hz), 3.68 (3H, s), 2.32 (2H, t, *J* 7.6 Hz), 1.64 (4H, m), 1.4–1.24 (60H, br m), 1.2 (9H, s), 0.91 (3H, d, *J* 6.6 Hz), 0.69–0.63 (1H, m), 0.48–0.41 (1H, m), 0.21–0.08 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.62, 174.31, 64.45 (+), 51.39 (−), 38.71, 38.11 (−), 37.41 (+), 34.47 (+), 34.11 (+), 30.06 (+), 29.70 (+), 29.64 (+), 29.56 (+), 29.51 (+), 29.45 (+), 29.25 (+), 29.22 (+), 29.15 (+), 28.61 (+), 27.25 (+), 27.19 (−), 26.13 (−), 25.90 (+), 24.95 (+), 19.67 (−), 18.61 (−), 10.48 (+); ν_{max}: 2918, 1733 cm^{-1}.

3.1.20. (*S*)-18-[(1*R*,2*S*)-2-(18-Hydroxyoctadecyl)cyclopropyl]-nonadecanoic acid methyl ester. (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-Dimethylpropionyloxy)octadecyl]cyclopropyl}-nonadecanoic acid methyl ester (0.27 g, 0.383 mmol) in tetrahydrofuran (5 ml) was added to a stirred solution of potassium hydroxide (0.31 g, 5.59 mmol) in methanol (10 ml), tetrahydrofuran (10 ml) and water (1.5 ml) at room temperature. The mixture was stirred and refluxed at 70 °C for 4 h, when TLC showed no starting material, then cooled to 5 °C, when a white precipitate formed, filtered on a sinter, then washed with ether (2×20 ml). The precipitate was dissolved in hot water and acidified with H_2SO_4 (10%) and the product was extracted with hot petrol/ether (1:1). The organic layer was dried and evaporated to give a white solid, (*S*)-18-[(1*R*,2*S*)-2-(18-hydroxyoctadecyl)-cyclopropyl]nonadecanoic acid (0.22 g, 95%). This was treated with excess diazomethane solution in ether and left to stand for 24 h at room temperature, then the solvent was evaporated to give a solid, which was recrystallized from petrol/ether to give a white solid, (*S*)-18-[(1*R*,2*S*)-2-(18-hydroxyoctadecyl)cyclopropyl]nonadecanoic acid methyl ester (0.19 g, 84%) [Found [M+Na]$^+$: 643.35991; $C_{41}H_{80}O_3Na$ requires: 643.6000], $[\alpha]_D^{22}$ +5.12 (*c* 1.21, $CHCl_3$), mp 65–67 °C; δ_H (500 MHz, $CDCl_3$): 3.67 (3H, s, OCH_3), 3.64 (2H, t, *J* 6.65 Hz, CH_2OH), 2.3 (2H, t, *J* 7.55 Hz, CH_2CO), 1.63–1.54 (6H, m, satd alkane), 1.45–1.21 (57H, m, satd alkane), 1.2–1.15 (2H, br dq, *J* 3.15, 7.2 Hz, satd alkane), 0.9 (3H, d, *J* 6.6 Hz, α-Me), 0.71–0.63 (1H, m, $CHCH_3$), 0.48–0.42 (1H, m, CH-*trans*-cyclopropane), 0.21–0.09 (3H, m, CH and CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 174.36, 63.1 (+), 51.42 (−), 38.12 (−), 37.42 (+), 34.47 (+), 34.12 (+), 32.81 (+), 30.06 (+), 29.71 (+), 29.66 (+), 29.60 (+), 29.46 (+), 29.43 (+), 29.26 (+), 29.15 (+), 27.25 (+), 26.14 (−), 25.73 (+), 24.96 (+), 19.69 (−), 18.62 (−), 10.49 (+); ν_{max}: 3340, 1733 cm^{-1}.

3.1.21. [(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]methanol. Tetra-*n*-butylammonium fluoride (79.2 ml, 79.2 mmol) was added to a stirred solution of *tert*-butyl-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropylmethyl]diphenylsilane (25 g, 60.9 mmol) in dry tetrahydrofuran (150 ml), at 0 °C under nitrogen. The mixture was allowed to reach room temperature, stirred for 16 h when TLC showed no starting material, cooled to 5 °C and quenched with satd aq ammonium chloride (50 ml) and extracted with ethyl acetate (3×200 ml). The combined organic layers were washed with brine (100 ml) and water (100 ml), dried and evaporated to give an oil. Chromatography (1:1 petrol/ethyl acetate) gave [(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (9.54 g, 91%) [Found $[M+NH_4]^+$: 190.1442; $C_9H_{20}O_3N$ requires: 190.1443], $[\alpha]_D^{22}$ −16.2 (*c* 0.995, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.99 (1H, dd, *J* 2.12, 7.6 Hz), 3.6 (1H, br t, *J* 7.3 Hz), 3.52 (1H, dt, *J* 5.5, 7.3 Hz), 3.4 (1H, dd, *J* 6.7, 11.3 Hz), 3.32 (1H, dd, *J* 7, 11.3 Hz), 2.8 (1H, br s), 1.34 (3H, s), 1.25 (3H, s), 1.00–0.86 (1H, m), 0.84–0.74 (1H, m), 0.57 (1H, dt, *J* 4.9, 8.55 Hz), 0.46 (1H, dt, *J* 5.17, 8.55 Hz); δ_C (125 MHz, $CDCl_3$): 108.7, 78.9, 68.9, 65.4, 26.6, 25.4, 18.8, 17.5, 7.8; ν_{max}: 3436, 2984, 2934 cm^{-1}.

3.1.22. (1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-cyclopropanecarbaldehyde. [(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]methanol (9 g, 52.32 mmol) in dichloromethane (50 ml) was added to a suspension of pyridinium chlorochromate (23.7 g, 109.8 mmol) in dichloromethane (400 ml) and stirred vigorously. After 2 h, when TLC showed no starting material, it was cooled to room temperature, poured into ether (500 ml), then the precipitate was filtered through silica and washed with ether. The filtrate was evaporated to give a yellow oil; chromatography (1:1 petrol/ethyl acetate) gave (1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropanecarbaldehyde (8.1 g, 91%) [Found $[M+H]^+$: 171.1023; $C_9H_{15}O_3$ requires: 171.1021], $[\alpha]_D^{22}$ −66 (*c* 1.33, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.08 (1H, d, *J* 4.9 Hz), 4.1 (1H, dd, *J* 5.9, 7.7 Hz), 3.78 (1H, br q, *J* 6.7 Hz), 3.65 (1H, br t, *J* 6.9 Hz), 1.89–1.81 (1H, m), 1.73–1.63 (1H, m), 1.45 (3H, s), 1.37–1.29 (1H, m), 1.33 (3H, s), 1.26–1.16 (1H, m); δ_C (125 MHz, $CDCl_3$): 199.9, 109.4, 76.4, 69.0, 26.52, 26.49, 25.5, 23.7, 11.7; ν_{max}: 1709 cm^{-1}.

3.1.23. (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester (27). Methyl-(triphenylphosphoranylidene)acetate (19.1 g, 47 mmol) was added in portions to a stirred solution of (1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropanecarbaldehyde (8 g, 47 mmol) in toluene (100 ml) at 10 °C. The mixture was allowed to reach room temperature and stirred for 24 h when GLC showed no starting material. The solvent was evaporated and the residue was treated with petrol/ether (1:1) (200 ml) and refluxed for 10 min. The precipitate was filtered off and washed with petrol/ether (100 ml). The solvent was evaporated and the residue was purified by chromatography eluting with petrol/ethyl acetate (5:2) to give (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]acrylic acid methyl ester (**27**) (8.4 g, 79%) [Found $[M+Na]^+$: 249.1095; $C_{12}H_{18}O_4Na$ requires: 249.1097], $[\alpha]_D^{22}$ −75 (*c* 1.16, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 6.43 (1H, dd, *J* 10.1, 15.5 Hz), 5.85 (1H, d, *J* 15.5 Hz), 4.05 (1H, dd, *J* 5.2, 7.3 Hz), 3.76–3.62 (5H, m, including s at δ 3.68), 1.58–1.47 (1H, m), 1.4 (3H, s), 1.32 (3H, s), 1.22–1.15 (1H, m), 1.07 (1H, dt, *J* 5.2, 8.55 Hz), 0.89 (1H, dt, *J* 5, 8.55 Hz); δ_C (125 MHz, $CDCl_3$): 166.8, 151.7, 118.5, 109.1, 77.5, 69.0, 51.3, 26.6, 25.5, 24.4, 18.4, 12.8; ν_{max}: 1720, 1647 cm^{-1}. There was less than 5% of the cis-isomer.

3.1.24. Addition of methyl magnesium bromide to (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester (27). Methyl magnesium bromide (35.4 ml, 106.2 mmol) was added dropwise to a stirred suspension of copper bromide (7.6 g, 53.1 mmol) in dry tetrahydrofuran (250 ml) at −40 °C under nitrogen. The mixture was stirred for 30 min then (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]acrylic acid methyl ester (8 g, 35.4 mmol) in dry tetrahydrofuran (50 ml) was added dropwise at −30 °C. The mixture was allowed to reach −5 °C over 2 h, when GLC showed no starting material, then quenched slowly with satd aq ammonium chloride (50 ml) at −30 °C. The product was extracted with ethyl acetate (3×250 ml). The combined organic layers were washed with brine (100 ml), dried and evaporated to give a brown oil. Chromatography (5:2 petrol/ethyl acetate) gave a mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid methyl ester in ratio 1:1 (**28**) (6 g, 70%) [Found $[M+Na]^+$: 265.1414; $C_{13}H_{22}O_4Na$ requires: 265.1410], $[\alpha]_D^{22}$ −12.3 (*c* 1.14, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 4.05 (1H, dd, *J* 6.3, 7.6 Hz), 4.02 (1H, dd, *J* 6, 12 Hz), 3.67 (3H, s), 3.667 (1H, t, *J* 7.9 Hz), 3.66 (3H, s), 3.62 (1H, t, *J* 7.9 Hz), 3.94 (1H, br dd, *J* 3.45, 7.9 Hz), 3.45 (1H, br dd, *J* 3.15, 7.9 Hz), 2.4 (1H, br dd, *J* 6.3, 15 Hz), 2.35 (1H, br dd, *J* 6.3, 15 Hz), 2.26 (2H, br dd, *J* 7.85, 14.8 Hz), 1.43 (3H, s), 1.42 (3H, s), 1.36–1.30 (2H, m), 1.33 (3H, s), 1.32 (3H, s), 1.03 (3H, d, *J* 6 Hz), 1.02 (3H, d, *J* 6.5 Hz), 0.82–0.77 (1H, m), 0.76–0.71 (1H, m), 0.61–0.55 (2H, m), 0.54–0.50 (3H, m), 0.49–0.44 (1H, m); δ_H (500 MHz, C_6D_6): 3.87 (1H, dd, *J* 6, 7.9 Hz), 3.81 (1H, dd, *J* 6, 7.9 Hz), 3.54 (1H, t, *J* 7.6 Hz), 3.5 (1H, t, *J* 7.6 Hz), 3.36 (1H, dt, *J* 6.3, 7.6 Hz), 3.35 (6H, s), 3.33 (1H, dt, *J* 6, 7.3 Hz), 2.21 (1H, dd, *J* 6.3, 14.8 Hz), 2.15 (1H, dd, *J* 6.3, 14.8 Hz), 2.06 (1H, dd, *J* 7.85, 14.8 Hz), 2.02 (1H, dd, *J* 7.55, 14.8 Hz), 1.54 (6H, s), 1.44 (3H, s), 1.43 (3H, s), 1.32–1.24 (2H, m), 1.00 (3H, d, *J* 6.6 Hz), 0.93 (3H, d, *J* 6.9 Hz), 0.77–0.72 (1H, m), 0.64–0.58 (1H, m), 0.57–0.52 (2H, m), 0.42–0.34 (3H, m), 0.28 (1H, dt, *J* 4.7, 8.2 Hz); δ_C (125 MHz, $CDCl_3$): 173.2, 173.1, 108.9, 108.8, 79.9, 79.8, 69.3, 69.2, 51.43, 51.41, 41.5, 41.4, 34.9, 34.8, 26.8, 25.75, 25.71, 25.69, 22.2, 22.1, 20.3, 20.00, 19.8, 19.7, 9.7, 9.2; ν_{max}: 1738 cm^{-1}.

3.1.25. Reduction of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester. The mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester (5.5 g, 22.7 mmol) in dry tetrahydrofuran (30 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.73 g, 45.4 mmol) in tetrahydrofuran (150 ml) at room temperature under

nitrogen. The mixture was refluxed for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq sodium sulfate (40 ml) until a white solid was formed. The precipitate was filtered off and washed with tetrahydrofuran (2×50 ml). The filtrate was evaporated to give a crude product which was purified by chromatography (1:1 petrol/ethyl acetate) to give a mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (4.47 g, 92%) [Found $[M+Na]^+$: 237.1454; $C_{12}H_{22}O_3Na$ requires: 237.1461], $[\alpha]_D^{22}$ −13.9 (*c* 1.69, $CHCl_3$), which showed δ_H (mixture, C_6D_6, 500 MHz): 3.84 (1H, dd, *J* 5.35, 6 Hz), 3.85 (1H, dd, *J* 5.1, 6 Hz), 3.55 (1H, t, *J* 7.85 Hz), 3.54 (1H, t, *J* 7.6 Hz), 3.48–3.32 (6H, m), 1.49–1.40 (8H, including two s at δ 1.44 and 1.42 (each 3H)), 1.35–1.23 (8H, including two s at δ 1.33 and 1.32 (each 3H)), 0.97 (2H, br s), 0.84 (3H, d, *J* 6.95 Hz), 0.77 (3H, d, *J* 6.3 Hz), 0.74–0.67 (2H, m), 0.66–0.61 (1H, m), 0.53–0.43 (3H, m), 0.33–0.24 (2H, m), 0.21–0.13 (2H, m); δ_C (mixture, C_6D_6, 125 MHz): 109.5, 109.4, 80.5, 79.9, 70.1, 69.9, 61.3, 61.2, 40.9, 40.8, 35.2, 35.0, 27.8, 27.7, 26.7, 26.6, 23.3, 23.2, 21.3, 20.7, 20.4, 10.8, 9.3; ν_{max}: 3410 cm^{-1}.

3.1.26. *tert*-Butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (29). The mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butan-1-ol and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (3 g, 14 mmol) in dry DMF (15 ml) was added to a stirred solution of imidazole (1.43 g, 21 mmol) in dry DMF (40 ml) at 5 °C under nitrogen. The mixture was stirred for 20 min then *tert*-butyldiphenylsilylchloride (4.62 g, 16.8 mmol) was added, then allowed to reach room temperature and stirred for 4 h when TLC showed no starting material. The solvent was evaporated under high vacuum and the residue was diluted with dichloromethane (100 ml) and water (50 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water and brine, dried and evaporated to give a residue, which was purified by chromatography on silica eluting with 5:1 petrol and ethyl acetate to give a mixture of *tert*-butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (**29**) (5.5 g, 87%) [Found $[M+Na]^+$: 475.2628; $C_{28}H_{40}O_3SiNa$ requires: 475.2639], $[\alpha]_D^{22}$ −6.8 (*c* 137, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (8H, m), 7.45–7.38 (12H, m), 4.05 (1H, dd, *J* 6, 8.2 Hz), 3.96 (1H, dd, *J* 6, 8 Hz), 3.79–3.64 (5H, m), 3.57 (1H, t, *J* 8 Hz), 3.46–3.40 (2H, m), 1.70–1.63 (2H, sext, *J* 6.5 Hz), 1.56–1.48 (2H, m), 1.45 (3H, s), 1.43 (3H, s), 1.35 (3H, s), 1.34 (3H, s), 1.30–1.25 (2H, m), 1.06 (9H, s), 1.05 (9H, s), 0.91 (3H, d, *J* 6.3 Hz), 0.907 (3H, d, *J* 6.6 Hz), 0.72–0.63 (2H, m), 0.56–0.47 (3H, m), 0.46–0.34 (3H, m); δ_H (500 MHz, C_6D_6): 7.79–7.76 (8H, m), 7.25–7.22 (12H, m), 3.83 (1H, dd, *J* 6, 7.85 Hz), 3.78 (1H, dd, *J* 6, 7.6 Hz), 3.76–3.67 (4H, m), 3.54 (1H, t, *J* 7.85 Hz), 3.5 (1H, t, *J* 7.6 Hz), 3.42–3.38 (1H, br q, *J* 7.25 Hz), 3.37–3.33 (1H, br dt, *J* 6.3, 7.55 Hz), 1.67–1.60 (2H, m), 1.50–1.44 (2H, m), 1.44 (3H, s), 1.42 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 1.17 (18H, s), 0.86–0.82 (5H, br m), 0.76 (3H, d, *J* 6.6 Hz), 0.63–0.58 (1H, m), 0.54–0.5 (1H, m), 0.49–0.44 (2H, m), 0.36–0.33 (1H, dt, *J* 5.05, 8.2 Hz), 0.35–0.25 (1H, m), 0.21–0.14 (2H, m); δ_C (125 MHz, $CDCl_3$): 135.5, 134.1, 133.9, 129.6, 129.5, 127.60, 127.58, 127.56, 108.8, 108.6, 80.5, 80.0, 69.3, 69.2, 62.0, 61.8, 39.8, 39.7, 34.1, 34.0, 30.9, 26.9, 26.8, 26.5, 25.8, 25.7, 23.5, 22.8, 22.5, 20.2, 19.8, 19.5, 19.4, 19.2, 10.2, 8.8; δ_C (125 MHz, C_6D_6): 136.6, 135.10, 135.05, 130.60, 130.55, 80.5, 79.8, 70.2, 70.1, 63.1, 62.9, 40.9, 40.8, 35.2, 34.9, 27.8, 27.7, 26.74, 26.72, 23.4, 23.22, 21.4, 20.6, 20.5, 20.4, 20.1, 20.0, 10.7, 9.2; ν_{max}: 2932, 2858, 1111, 1062 cm^{-1}.

3.1.27. (1*R*,2*S*)-2-[(*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl] cyclopropanecarbaldehyde. Periodic acid (6.3 g, 27.6 mmol) was added to a stirred mixture of *tert*-butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}-diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxo-lan-4-yl)cyclopropyl]butoxy}diphenylsilane (5 g, 11.1 mmol) in dry ether (100 ml) under nitrogen at room temperature. After stirring for 16 h, TLC showed no starting material. The precipitate was filtered, washed with ether and the solvent was evaporated to give a residue. Chromatography (10:2 petrol/ethyl acetate) gave a mixture of (1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (3.86 g, 92%) [Found $[M+Na]^+$: 403.2048; $C_{24}H_{32}O_2SiNa$ requires: 403.2064], $[\alpha]_D^{22}$ −17.85 (*c* 1.26, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 8.98 (2H, d, *J* 5.65 Hz), 7.68–7.65 (8H, m), 7.45–7.37 (12H, m), 3.82–3.66 (4H, m), 1.74–1.47 (7H, m), 1.35–1.18 (7H, m), 1.06 (18H, s), 0.97 (3H, d, *J* 6.6 Hz), 0.95 (3H, d, *J* 6.65 Hz); δ_H (500 MHz, C_6D_6): 8.74 (1H, d, *J* 3.15 Hz), 8.73 (1H, d, *J* 2.85 Hz), 7.78–7.73 (8H, m), 7.28–7.19 (12H, m), 3.67–3.57 (4H, m), 1.5–1.39 (3H, m), 1.38–1.29 (2H, m), 1.28–1.22 (1H, m), 1.15 (9H, s), 1.14 (9H, s), 0.87–0.76 (6H, m), 0.71 (3H, d, *J* 6.3 Hz), 0.67 (3H, d, *J* 6.3 Hz), 0.49–0.45 (1H, m), 0.35–0.31 (1H, br ddd, *J* 4.4, 6.0, 10.1 Hz); δ_C (125 MHz, $CDCl_3$): 200.9, 200.8, 135.5, 134.8, 133.9, 133.8, 129.6, 127.64, 127.61, 61.5, 61.4, 39.4, 39.3, 33.5, 33.3, 30.1, 29.3, 29.25, 29.19, 26.8, 26.5, 19.5, 19.3, 19.2, 14.6, 13.5; δ_C (125 MHz, C_6D_6): 199.6, 199.5, 136.6, 136.5, 135.8, 134.91, 134.90, 134.8, 130.64, 130.63, 62.6, 62.5, 40.3, 40.26, 34.2, 34.1, 30.6, 29.6, 29.3, 29.0, 27.7, 27.4, 20.1, 20.0, 14.7, 13.3; ν_{max}: 1703 cm^{-1}.

3.1.28. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (30). Lithium hexamethyldisilazide (16.6 ml, 16.6 mmol, 1 M THF) was added dropwise to a stirred solution of 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester **16** (6.06 g, 11.1 mmol) and a mixture of (1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (3.5 g, 9.21 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at −15 °C. The reaction was exothermic and the

temperature rose to −5 °C giving in a yellow solution. The mixture was allowed to reach room temperature and stirred for 2 h when TLC showed no starting material, cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with 1:1 petrol/ether (3×50 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, (*E*/*Z*)-2,2-dimethylpropionic acid 18-{(1*S*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester and 2,2-dimethylpropionic acid 18-{(1*S*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylpropylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (5.17 g, 80%). Dipotassium azodicarboxylate (3.9 g, 20.1 mmol) was added to a stirred solution of the above mixture (4.7 g, 6.69 mmol) in dry THF (30 ml) and methanol (15 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Freshly distilled glacial acetic acid (4 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and quenched slowly with satd aq ammonium chloride (5 ml). The product was extracted with petrol/ether (1:1) (2×100 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; however, the ^{1}H NMR spectrum showed that there was still starting material left. The procedure was repeated twice for 16 h and the residue was purified by chromatography (10:1 petrol/ether) to give 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylpropylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (**30**) as a white solid (3.77 g, 80%) [Found [M+Na]$^+$: 727.5470; $C_{46}H_{76}O_3SiNa$ requires: 727.5456], $[\alpha]_D^{22}$ −6.1 (*c* 1.23, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 7.68–7.67 (8H, m), 7.43–7.37 (12H, m), 4.06 (4H, t, *J* 6.65 Hz), 3.79–3.7 (4H, m), 1.74–1.68 (2H, m), 1.65–1.6 (4H, m), 1.57–1.47 (2H, m), 1.38–1.24 (64H, m), 1.21 (18H, s), 1.18–1.13 (2H, m), 1.06 (9H, s), 1.05 (9H, s), 0.86 (3H, br s), 0.84 (3H, br s), 0.42–0.31 (2H, m), 0.19–0.04 (6H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 135.6, 134.2, 129.4, 127.5, 67.9, 64.5, 62.3, 62.2, 40.2, 40.0, 38.7, 34.8, 34.7, 34.4, 34.35, 29.7, 29.63, 29.56, 29.5, 29.4, 29.2, 28.6, 27.2, 26.9, 25.9, 25.88, 25.6, 20.0, 19.8, 19.2, 18.6, 17.5, 11.8, 10.6; ν_{max}: 2920, 2850, 1732 cm^{-1}.

3.1.29. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (31) and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (32). Tetra-*n*-butylammonium fluoride (7.45 ml, 7.45 mmol) was added to a stirred solution of 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (3.5 g, 4.97 mmol) in dry tetrahydrofuran (50 ml) at 0 °C under nitrogen. The mixture was stirred at room temperature for 16 h when TLC showed no starting material, cooled to 5 °C and quenched with satd aq ammonium chloride (50 ml) and the product extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine (50 ml) and water (50 ml), dried and evaporated to give an oil. Chromatography (5:1 petrol/ethyl acetate) gave as the first fraction 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (**31**) as a white solid (1.1 g, 48%) [Found [M+Na]$^+$: 489.4290; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ −11.29 (*c* 1.08, $CHCl_3$), mp 34–36 °C, which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 3.76–3.67 (2H, m), 1.74–1.68 (1H, br sext., *J* 6.65 Hz), 1.64–1.58 (2H, pent, *J* 6.65 Hz), 1.57–1.51 (1H, m), 1.49 (1H, br s), 1.35–1.23 (31H, br m), 1.19 (9H, s), 1.13 (1H, m), 0.95 (3H, d, *J* 6.65 Hz), 0.88–0.82 (1H, m), 0.51–0.44 (1H, m), 0.25–0.13 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.4 (+), 61.3 (+), 40.4 (+), 38.7, 34.9 (−), 34.3 (+), 29.7 (+), 29.6 (+), 29.57 (+), 29.5 (+), 29.48 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 19.8 (−), 18.7 (−), 10.6 (+); ν_{max}: 3396, 1730 cm^{-1}. The second fraction was 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]-octadecyl ester (**32**), a white solid (0.92 g, 40%) [Found [M+Na]$^+$: 489.4288; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ −4.03 (*c* 1.29, $CHCl_3$), mp 44–46 °C, which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.65 Hz), 3.76 (1H, br dd, *J* 6.3, 10.5 Hz), 3.71 (1H, br dd, *J* 6.9, 10.5 Hz), 1.72–1.65 (1H, br sext., *J* 6.95 Hz), 1.64–1.59 (2H, br pent, *J* 6.6 Hz), 1.56–1.51 (1H, m), 1.46 (1H, br s), 1.36–1.26 (31H, br m), 1.29 (9H, s), 1.09–1.02 (1H, m), 0.99 (3H, d, *J* 6.6 Hz), 0.90–0.82 (1H, m), 0.46–0.39 (1H, m), 0.29–2.00 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.5 (+), 61.4 (+), 40.3 (+), 38.7, 35.2 (−), 34.3 (+), 29.7 (+), 29.6 (+), 29.54 (+), 29.50 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 25.8 (−), 20.3 (−), 17.6 (−), 11.9 (+); ν_{max}: 3396, 1730 cm^{-1}.

3.1.30. 2,2-Dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (0.7 g, 1.5 mmol) was dissolved in dichloromethane (10 ml) and added to a suspension of pyridinium chlorochromate (0.8 g, 3.75 mmol) in dichloromethane (50 ml). The mixture was stirred vigorously at room temperature for 3 h when TLC showed no starting material was left, diluted with diethyl ether (150 ml) and filtered through a pad of Celite and then through a pad of silica. The silica was washed with ether. The combined filtrate was evaporated to give a residue, which was purified by chromatography (5:0.5 petrol/ethyl acetate) to give a colourless oil, 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester, which solidified later (0.62 g, 89%) [Found [M+Na]$^+$: 487.4122; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ −16.4 (*c* 1.82, $CHCl_3$), mp 28–30 °C; δ_H (500 MHz, $CDCl_3$): 9.78 (1H, t, *J* 2.5 Hz), 4.05 (2H, t, *J* 6.6 Hz), 2.50 (1H, ddd, *J* 2.5, 6.0, 15.75 Hz), 2.38 (1H, ddd, *J* 2.5, 7.6, 15.75 Hz), 1.62 (2H, br pent, *J* 6.6 Hz), 1.36–1.25 (32H, m), 1.2 (9H, s), 1.16–1.02 (4H, including d, *J* 6.6 Hz, δ 1.03), 0.53–0.46 (1H, m), 0.35–0.22 (3H, m); δ_C (125 MHz, $CDCl_3$): 202.8 (+), 178.6, 64.4 (−), 51.4 (−), 38.7, 34.1 (−), 33.9 (+), 29.7 (−), 29.63 (−), 29.61 (−), 29.58 (−), 29.5 (−), 29.49 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 19.9 (+), 18.8 (+), 11.4 (−); ν_{max}: 2920, 2850, 1728 cm^{-1}.

3.1.31. 2,2-Dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (0.7 g, 1.5 mmol)

was dissolved in dichloromethane (10 ml) and added to a suspension of pyridinium chlorochromate (0.8 g, 3.75 mmol) in dichloromethane (50 ml). The mixture was stirred vigorously at room temperature for 3 h when TLC showed no starting material, diluted with diethyl ether (150 ml) and worked up as above to give 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (0.63 g, 90%), [Found $[M+Na]^+$: 487.4106; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ −0.011 (*c* 1.23, $CHCl_3$), mp 31–32 °C; δ_H (500 MHz, $CDCl_3$): 9.78 (1H, t, *J* 2.5 Hz), 4.05 (2H, t, *J* 6.6 Hz), 2.49 (1H, ddd, *J* 2.2, 6.0, 15.45 Hz), 2.35 (1H, ddd, *J* 2.5, 7.6, 15.45 Hz), 1.61 (2H, br pent, *J* 6.6 Hz), 1.38–1.24 (32H, m), 1.19 (9H, s), 1.09–1.02 (4H, including d, *J* 6.65 Hz, *δ* 1.05), 0.54–0.48 (1H, m), 0.34–0.29 (1H, m), 0.27–0.21 (2H, m); δ_C (125 MHz, $CDCl_3$): 202.9 (+), 178.6, 64.4 (−), 51.3 (−), 38.7, 34.2 (−), 34.0 (+), 29.7 (−), 29.6 (−), 29.54 (−), 29.51 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 20.3 (+), 18.5 (+), 11.9 (−); ν_{max}: 2920, 2850, 1728 cm^{-1}.

3.1.32. Methyl (*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadecanoate (33). Lithium hexamethyldisilazide (1.87 ml, 1.87 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester (0.558 g, 1.375 mmol) and 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester **11** (0.58 g, 1.25 mmol) in dry tetrahydrofuran (20 ml) under nitrogen at −15 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. This was stirred at room temperature for 1 h when TLC showed no starting material, then cooled to 0 °C, quenched with satd aq ammonium chloride (10 ml) and extracted with 1:1 petrol/ether (3×30 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (10:1 petrol/ether) gave a pale yellow oil, (*E*/*Z*)-(*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (0.57 g, 65%) as a 2.2:1 mixture of isomers. Dipotassium azodicarboxylate (1.38 g, 7.12 mmol) was added to a stirred solution of the ester (0.5 g, 0.712 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Glacial acetic acid (2 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml), then extracted with petrol/ether (1:1) (2×50 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; however, the ^1H NMR spectrum showed that there was still starting material left. The procedure was repeated twice for 24 h and the residue was purified by chromatography (10:1 petrol/ether) to give (*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)-octadecyl]cyclopropyl}nonadecanoic acid methyl ester (**33**) as a white solid (0.4 g, 80%), mp 47–49 °C, [Found $[M+Na]^+$: 727.6579; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ −5.08 (*c* 1.16, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz, CH_2OCO), 3.67 (3H, s, OCH_3), 2.30 (2H, t, *J* 7.27 Hz, CH_2CO), 1.62 (4H, br pent, *J* 7 Hz, $CH_2CH_2CH_2CO$), 1.4–1.22 (59H, br m, satd alkane), 1.2 (9H, s, $COC(CH_3)_3$), 1.18–1.15 (1H, m, satd alkane), 0.90 (3H, d, *J* 6.9 Hz, α-CH_3), 0.693–0.637 (1H, m, $CHCH_3$), 0.48–0.43 (1H, m, CH-*trans*-cyclopropane), 0.216–0.087 (3H, m, CH and CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 178.56, 174.25, 64.42 (+), 51.35 (−), 38.68, 38.11 (−), 37.41 (+), 34.46 (+), 34.07 (+), 30.05 (+), 29.69 (+), 29.63 (+), 29.588 (+), 29.55 (+), 29.51 (+), 29.44 (+), 29.24 (+), 29.21 (+), 29.13 (+), 28.59 (+), 27.24 (+), 27.17 (−), 26.11 (−), 25.88 (+), 24.93 (+), 19.677 (−), 18.60 (−), 10.47 (+); ν_{max}: 2918, 1733 cm^{-1}.

3.1.33. Methyl (*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadecanoate (34). Lithium hexamethyldisilazide (1.6 ml, 1.6 mmol, 1 M) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester **11** (0.48 g, 1.375 mmol) and 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (0.50 g, 1.07 mmol) in dry tetrahydrofuran (20 ml) under nitrogen at −15 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. This was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then worked up as above. Chromatography gave (*E*/*Z*)-(*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (0.52 g, 70%). Hydrogenation and purification as above gave methyl (*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl]-nonadecanoate (**34**) as a white solid (0.4 g, 80%) [Found $[M+Na]^+$: 727.6552; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ −3.87 (*c* 1.16, $CHCl_3$), mp 60–62 °C; δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz, CH_2OCO), 3.67 (3H, s, OCH_3), 2.30 (2H, t, *J* 7.25 Hz, CH_2CO), 1.62 (4H, br pent, *J* 6.3 Hz, $CH_2CH_2CH_2CO$), 1.43–1.23 (59H, br m, satd alkane), 1.2 (9H, s, $COC(CH_3)_3$), 1.07–1.01 (1H, m, satd alkane), 0.93 (3H, d, *J* 6.65 Hz, α-Me), 0.69–0.64 (1H, m, $CHCH_3$), 0.41–0.35 (1H, m, CH-*trans*-cyclopropane), 0.23–0.21 (1H, m, CH-*trans*-cyclopropane), 0.197–0.14 (2H, m, CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 178.61, 174.30, 64.45 (+), 51.38 (−), 38.71, 38.05 (−), 37.34 (+), 34.48 (+), 34.1 (+), 30.08 (+), 29.69 (+), 29.63 (+), 29.588 (+), 29.55 (+), 29.51 (+), 29.44 (+), 29.24 (+), 29.21 (+), 29.13 (+), 28.59 (+), 27.24 (+), 27.17 (−), 26.11 (−), 25.90 (+), 24.95 (+), 19.90 (−), 17.34 (−), 11.81 (+); ν_{max}: 2918, 1733 cm^{-1}.

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Tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates and a synthetic approach to Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly dipeptide isostere

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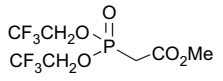
Abstract—(*Z*)-α-Fluoro-α,β-unsaturated esters (*Z*)-**7a–f** were stereoselectively prepared by a tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** with $NaBH_4$ in EtOH. A concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere was achieved via the tandem reduction–olefination of the corresponding 2-acyl-2-fluoro-2-phosphonoacetate **20**.

1. Introduction

There is currently much interest in the synthesis of α-fluoro-α,β-unsaturated carbonyl compounds as valuable building blocks for biologically active compounds.[1–6] Recent efforts in our laboratory have focused on the stereoselective Horner–Wadsworth–Emmons (HWE) reactions for the synthesis of α,β-unsaturated esters or α,β-unsaturated carboxylic acids using HWE reagents,[7–17] such as methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (**1**),[18] bis-(2,2,2-trifluoroethyl)phosphonoacetic acid (**2**),[15,19] triethyl 2-fluoro-2-phosphonoacetate (**3**),[20] and 2-fluoro-2-diethylphosphonoacetic acid (**4**).[3] Although, the stereoselective synthesis of (*E*)-α-fluoro-α,β-unsaturated esters utilizing the HWE reaction of phosphonoacetate **3** with aldehydes is well known,[21–32] there are few reports on the stereoselective HWE reaction, which was successfully employed in the synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters.



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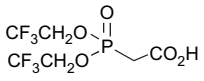

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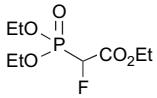

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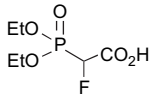

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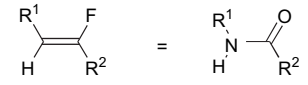
We have demonstrated the HWE reaction of various aldehydes with 2-fluoro-2-diethylphosphonoacetic acid (**4**) with *i*-PrMgBr in THF.[13] However, the HWE reactions resulted in satisfactory *Z*-selectivities only for aromatic and α,β-unsaturated aldehydes. Consequently, we describe herein a tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** for the stereoselective synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters (*Z*)-**7a–f**.[33] In addition, to expand the application of this methodology, we achieved a concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere based on the tandem reduction–olefination. It is well known that fluoroolefins play an important role as amide isosteres, from the standpoint of mimicking of the steric demand, bond lengths, and bond angles.[34–49] Namely, (*Z*)-fluoroolefins mimic the (s-*Z*)-amide bonds, as shown in Figure 1.



(*Z*)-fluoroolefin (s-*Z*)-amide

Figure 1. (*Z*)-Fluoroolefins mimic the (s-*Z*)-amide bonds.

2. Results and discussion

2.1. Tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetate

Triethyl 2-acyl-2-fluoro-2-phosphonoacetates **6a–f** were prepared by the treatment of commercially available triethyl 2-fluoro-2-phosphonoacetate (**3**) with *n*-BuLi (1.05 mol equiv) in THF at 0 °C, followed by acylation of the resulting

Keywords: Reduction; Olefination; Fluorine; Phosphonoacetates; α-Fluoro-α,β-unsaturated esters; Dipeptide isosteres.
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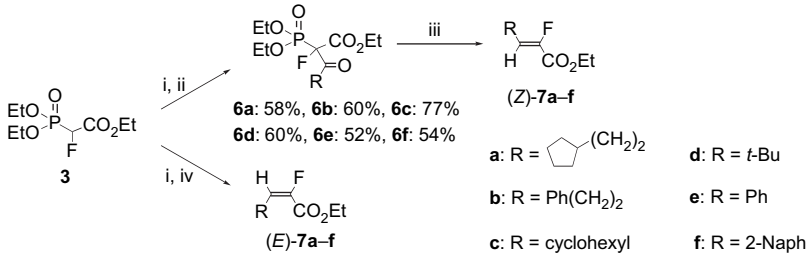


Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, 0 °C, 1 h; (ii) RCOCl **5a–f**, THF, 0 °C, **a**: 2 h, **b**: 1 h, **c**: 5 h, **d**: 6 h, **e**: 1 h, **f**: 1 h; (iii) $NaBH_4$, EtOH, −78 °C to rt (Table 1); (iv) RCHO **8a–f**, THF, rt (Table 2).

lithium enolate with acyl chlorides **5a–f** (1.05 mol equiv) in 52–77% yields (Scheme 1). Tandem reduction–olefination of phosphonoacetates **6a–f** with $NaBH_4$ (1 mol equiv) in EtOH was then examined, as shown in Scheme 1 and Table 1. In the case of phosphonoacetate **6a**, $NaBH_4$ (1 mol equiv) was added to the solution of **6a** in EtOH at −78 °C, and the mixture was then stirred for 2 h, after which the temperature was allowed to rise to room temperature. After 1 h of stirring at room temperature, (*Z*)-α-fluoro-α,β-unsaturated ester (*Z*)-**7a** was obtained in 83% yield as the sole stereoisomer (Table 1, entry 1). Excellent *Z*-selectivity was also achieved in all the other tandem reduction–olefination reactions with phosphonoacetates **6b–f** (Table 1, entries 2–6). The disappearance of the starting phosphonoacetates **6a–f** was conveniently monitored by thin-layer chromatographic (TLC) analysis, and after that the reaction temperature was raised to complete the olefination of the resulting pro-(*Z*)-oxyanion intermediate (Fig. 2). The reduction of phosphonoacetates **6c**,**d** with bulky acyl groups was slower than that of phosphonoacetates **6a**,**b**,**e**,**f**, and the tandem reduction–olefination of phosphonoacetate **6d** was achieved at −78 °C for 18 h without an increase in temperature (Table 1, entries 3 and 4). High volatility of (*Z*)-α-fluoro-α,β-unsaturated ester (*Z*)-**7d** caused an inaccurate yield (Table 1, entry 4). Moderate yields of (*Z*)-α-fluoro-α,β-unsaturated esters (*Z*)-**7e**,**f** were probably attributable to the high lability of the starting phosphonoacetates **6e**,**f** (Table 1, entries 5 and 6).

Table 1. Tandem reduction–olefination of **6a–f** with $NaBH_4$[a]

Entry	Phosphonoacetate	Temperature/time	Yield (%)[b]	*E*:*Z*[c]
1	**6a**	−78 °C/2 h to rt/1 h	83 (**7a**)	0:100 (**7a**)
2	**6b**	−78 °C/2 h to rt/1 h	76 (**7b**)	<1:>99 (**7b**)
3	**6c**	−78 °C/18 h to rt/1 h	84 (**7c**)	9:91 (**7c**)
4	**6d**	−78 °C/18 h	58 (**7d**)[d]	4:96 (**7d**)
5	**6e**[e]	−78 °C/2 h to rt/1 h	59 (**7e**)	0:100 (**7e**)
6	**6f**[e]	−78 °C/1 h to rt/1 h	63 (**7f**)	<1:>99 (**7f**)

[a] EtOH, **6**/$NaBH_4$ (1:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^{1}H NMR (300 or 400 MHz, $CDCl_3$) analysis.
[d] High volatility.
[e] Labile compounds.

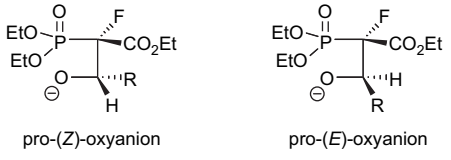


Figure 2. Pro-(*Z*)- and pro-(*E*)-oxyanion intermediate in tandem reduction–olefination of **6a–f**.

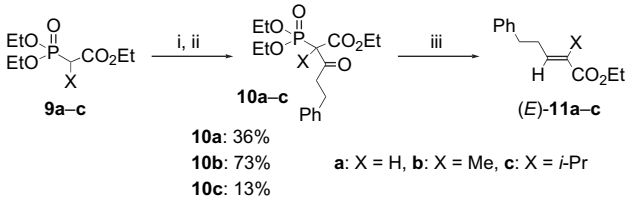
On the other hand, ordinary *E*-selective HWE reactions of phosphonoacetate **3** with aldehydes **8a–f** were performed under *n*-BuLi conditions at room temperature. As anticipated, (*E*)-α-fluoro-α,β-unsaturated esters (*E*)-**7a–f** were obtained as major products in each corresponding reaction (Scheme 1, Table 2). That is to say, a complementarity of stereoselectivity was found between the HWE reaction of phosphonoacetate **3** with aldehydes **8a–f** and the tandem reduction–olefination of phosphonoacetate **6a–f**. The geometry and the diastereomeric ratios of olefins **7a–f** were confirmed on the basis of the coupling constants between fluorine and the adjacent olefinic proton ($^3J_{H,F}$), and the integration of appropriate proton absorptions was obtained by ^{1}H NMR (300 or 400 MHz) analysis, respectively.

Table 2. HWE reactions of 2-fluoro-2-phosphonoacetate **3** with aldehydes **8a–f**[a]

Entry	Aldehyde	Yield (%)[b]	*E*:*Z*[c]
1	**8a**	78 (**7a**)	88:12 (**7a**)
2	**8b**	77 (**7b**)	92:8 (**7b**)[e]
3	**8c**	81 (**7c**)	91:9 (**7c**)
4	**8d**	37 (**7d**)[d]	97:3 (**7d**)[e]
5	**8e**	84 (**7e**)	93:7 (**7e**)
6	**8f**	93 (**7f**)	89:11 (**7f**)

[a] THF, rt, 20 h, **3**/*n*-BuLi/**8** (1.2:1.2:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^{1}H NMR (300 or 400 MHz, $CDCl_3$) analysis.
[d] High volatility.
[e] Determined by ^{1}H NMR (400 MHz, C_6D_6) analysis.

We also subjected a series of phosphonoacetates **9a–c** to the tandem reduction–olefination. Phosphonoacetates **10a–c** were prepared by the treatment of phosphonoacetates **9a–c** with *n*-BuLi (1.05 mol equiv) in THF at 0 °C, followed by acylation of the resulting lithium enolate with 3-phenylpropionyl chloride (**5b**) (1.05 mol equiv) (Scheme 2). Under



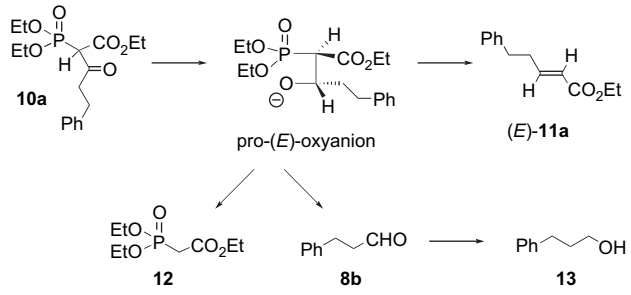
Scheme 2. Reagents and conditions: (i) *n*-BuLi, THF, 0 °C, 1 h; (ii) $PhCH_2CH_2COCl$ (**5b**), THF, 0 °C, **a**: 30 min, **b**: 3 h, **c**: 20 h; (iii) $NaBH_4$, EtOH, −78 °C to rt (Table 3).

Table 3. Tandem reduction–olefination of **10a–c** with $NaBH_4$[a]

Entry	Phosphonoacetate	Temperature/time	Yield (%)[b]	*E*:*Z*[c]
1	**10a**	−78 °C/2 h to rt/1 h	48 (**11a**)[d]	100:0 (**11a**)
2	**10b**	−78 °C/20 h to rt/1 h	49 (**11b**)	93:7 (**11b**)
3	**10c**	−78 °C/6 h	—[e]	—
4	**10c**	0 °C/20 h	9 (**11c**)	56:44 (**11c**)

[a] EtOH, **10**/$NaBH_4$ (1:1 molar ratio).
[b] Isolated yields.
[c] Determined by ^1H NMR (400 MHz, $CDCl_3$) analysis.
[d] 3-Phenyl-1-propanol (19%) was obtained.
[e] No reaction.

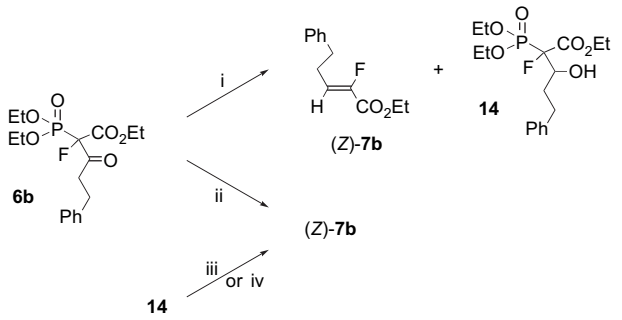
the same reaction conditions of the tandem reduction–olefination described above, phosphonoacetates **10a**,**b** provided α,β-unsaturated esters **11a**,**b** in *E*:*Z* ratios of 100:0 and 93:7, respectively (Table 3, entries 1 and 2). According to Cahn–Ingold–Prelog (CIP) priority, each major stereoisomer of α,β-unsaturated esters **11a**,**b** was assigned as the *E*-configuration, while (*E*)-**11a**,**b** and (*Z*)-**7a–f** refer to the same geometry. Thus, the olefinic proton and the ester moiety of (*E*)-**11a**,**b** and (*Z*)-**7a–f** are on the same side of the double bond. However, the reaction of phosphonoacetate **10c** with a bulky isopropyl group instead of the H, F, or Me group appeared to suffer, as indicated by the low stereoselectivity and the low yield (Table 3, entries 3 and 4). The geometry of olefin **11a** was confirmed on the basis of the coupling constants ($^3J_{H,H}$=15.6 Hz) of ^1H NMR (400 MHz) analysis between both olefinic protons. The geometry of olefins **11b**,**c** was determined on the basis of the chemical shift of the olefinic proton by application of Tobey–Pascual substituent shielding constants.[50–52] The diastereomeric ratios of olefins **11a–c** were also confirmed on the basis of the integration of appropriate proton absorptions by ^1H NMR (400 MHz) analysis. It is worth noting that the tandem reaction of **10a** with $NaBH_4$ afforded 3-phenyl-1-propanol (**13**) in 19% yield as a by-product together with 48% of (*E*)-α,β-unsaturated ester (*E*)-**11a** (Table 3, entry 1). That is to say, reduction of phosphonoacetate **10a** furnished the pro-(*E*)-oxyanion intermediate, from which a retro-aldol type reaction would take place under the basic conditions to give the 3-phenylpropionaldehyde (**8b**). The aldehyde **8b** would be reduced by $NaBH_4$ to 3-phenyl-1-propanol (**13**), immediately (Scheme 3).



Scheme 3. Tandem reduction–olefination of **10a** and by-product **13**.

2.2. Mechanistic consideration of tandem reduction–olefination

As stated above, we performed the reduction step in the tandem reduction–olefination of phosphonoacetates **6a–f** at −78 °C to better differentiate a transition state for the diastereoselective reduction with $NaBH_4$. In fact, Burton and Thenappan reported in 1991 that the use of $NaBH_4$ as a reducing agent of **6e** at room temperature led to a mixture of two geometrical isomers (*E*:*Z*=52:48).[53] In our experiment, an apparent decrease in *Z*-selectivity (*E*:*Z*=16:84, 63% yield) was also found in the tandem reduction–olefination of **6b** at room temperature (Scheme 4).



Scheme 4. Reagents and conditions: (i) $NaBH_4$, EtOH, −78 °C, 18 h; (ii) $NaBH_4$, EtOH, rt, 2 h; (iii) $NaBH_4$, EtOH, rt, 1 h; (iv) *n*-BuLi, THF, rt, 1 h.

Next, we tried to isolate the oxyanion intermediate of the tandem reduction–olefination reaction of **6a–f**. In the case of **6b**, the tandem reduction–olefination at −78 °C gave a fortuitous mixture of (*Z*)-**7b** and alcohol **14**. Chromatographic separation and isolation of the products afforded (*Z*)-**7b** (44%, *E*:*Z*=<1:>99) and alcohol **14** (46%), as shown in Scheme 4. ^{13}C NMR analysis (75 MHz) of alcohol **14** strongly suggested that the alcohol was obtained in a diastereomerically pure form. In addition, treatment of alcohol **14** with $NaBH_4$ (1 mol equiv) in EtOH at room temperature resulted in the formation of (*Z*)-**7b** with an *E*:*Z* ratio of <1:>99 in 80% yield. On the other hand, the addition of *n*-BuLi (1 mol equiv) to a solution of alcohol **14** in THF at room temperature gave (*Z*)-**7b** in 80% yield with a slightly lower stereoselectivity (*E*:*Z*=8:92). It can therefore be presumed that a retro-aldol type reaction is involved here that is similar to the reaction of **10a**. Unfortunately, 3-phenyl-1-propanol (**13**) was not obtained as a by-product in the reaction with $NaBH_4$. A decrease in the stereoselectivity of the olefination of alcohol **14** under *n*-BuLi conditions compared with that under $NaBH_4$ conditions may be ascribed to the ordinary *E*-selective HWE reaction of a small amount of aldehyde **8b** with phosphonoacetate **3** formed by a retro-aldol type reaction of pro-(*Z*)-oxyanion intermediate.

On the basis of the experimental results described above, excellent *Z*-selectivity of this tandem reduction–olefination of **6a–f** to α-fluoro-α,β-unsaturated esters **7a–f** should be the result of highly diastereoselective reduction. When a possible Felkin–Anh type transition state is envisioned,[54–60] the attack of hydride preferentially involves the conformation **A** of phosphonoacetates **6a–f**, not **B**, to minimize steric interactions, as indicated in the Newman projections (Fig. 3). This Felkin–Anh model considers that the transition state mostly resembles the ketones and hydrides.[61] The tandem reduction–olefination of **10a**,**b** to α,β-unsaturated esters **11a**,**b** is also stereoselective, and the stereoselective outcome may be understood in terms of the similar Felkin–Anh type conformation of **10a**,**b** (conformation **C**), as shown in Figure 3. In the case of phosphonoacetate **10c** (X=*i*-Pr),

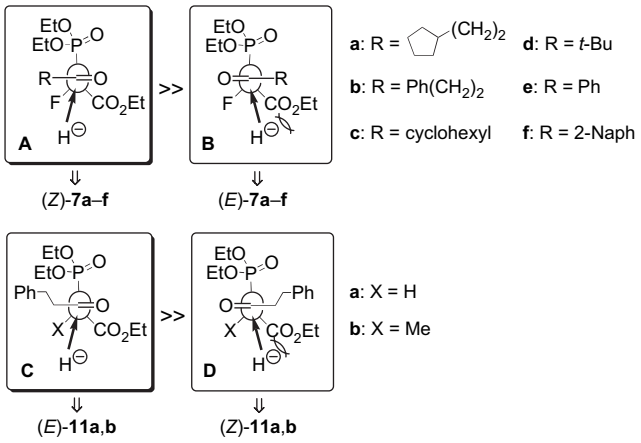


Figure 3. Plausible conformations of **6a**–**f** and **10a**,**b** for diastereoselective reduction with $NaBH_4$.

the reduction is slightly stereoselective because the two possible conformations **C** and **D** are equally important.

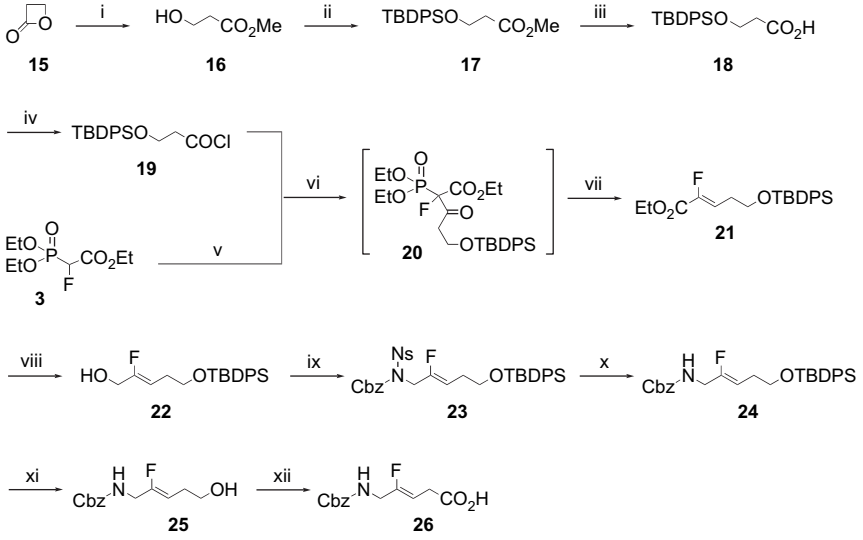
2.3. Synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly as a dipeptide isostere

The chemistry described above was extended to the preparation of dipeptide isosteres. A possible strategy for the synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere via *Z*-selective tandem reduction–olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetate **20** with $NaBH_4$ is shown in Scheme 5. Our synthesis began with a ring opening reaction of the commercially available β-propiolactone (**15**), followed by protection of the resultant alcohol **16** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole according to the procedure of Ley and co-workers (96% yield).[62] Alkaline hydrolysis of the methyl ester **17** with aqueous EtOH solution of NaOH furnished carboxylic acid **18** (99% yield). Upon treatment with oxalyl chloride in CH_2Cl_2, carboxylic acid **18** provided the desired acyl chloride **19** in a quantitative yield. Acylation of phosphonoacetate **3** then afforded triethyl 2-acyl-2-fluoro-2-phosphonoacetate **20** via treatment with acyl chloride **19** under *n*-BuLi conditions at −78 °C in THF. As expected, phosphonoacetate **20** was easily converted to (*Z*)-α-fluoro-α,β-unsaturated ester **21** by the tandem reduction–olefination with $NaBH_4$ in EtOH with excellent stereoselectivity (*E*:*Z*=0:100) at −78 °C in 63% yield (two steps).

Reduction of the (*Z*)-α-fluoro-α,β-unsaturated ester **21** gave the corresponding primary alcohol **22** in 93% yield. The hydroxyl group of **22** was successively transformed to the protected amino group of **23** under Mitsunobu reaction conditions.[63–65] In this reaction, PPh_3, *N*-carbobenzoxy-2-nitrobenzenesulfonamide (*N*-Cbz-NsNH), and alcohol **22** were dissolved in CH_2Cl_2 and diethyl azodicarboxylate (DEAD) in toluene was slowly added to the solution. However, when DEAD was first reacted with the phosphine, a poor result was obtained. Next, Cbz-protected **24** was obtained in 95% yield (two steps) by chemoselective deprotection of the 2-nitrobenzenesulfonyl (Ns) group of **23** with 4-*tert*-butylthiophenol in the presence of K_2CO_3 in DMF. Deprotection of the TBDPS group of **24** with tetra-*n*-butylammonium fluoride (TBAF) in THF cleanly produced the primary alcohol **25** in 92% yield. Finally, oxidation of alcohol **25** with an excess amount of Jones reagent in acetone delivered Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere in 80% yield.

3. Conclusion

We described here the tandem reduction–olefination of 2-acyl-2-fluoro-2-phosphonoacetates **6a**–**f**, as a novel one-pot reaction, for the preparation of α-fluoro-α,β-unsaturated esters **7a**–**f** with excellent *Z*-selectivity. Furthermore, a concise synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (**26**) as a dipeptide isostere was achieved by virtue of an application of this reaction.



Scheme 5. Reagents and conditions: (i) NaOMe, MeOH, 50 °C, 4 h; (ii) TBDPSCl, imidazole, CH_2Cl_2, rt, 14 h; (iii) 1 N NaOH, EtOH, rt, 6 h; (iv) $(COCl)_2$, CH_2Cl_2, rt, 15 h; (v) *n*-BuLi, THF, −78 °C, 1 h; (vi) **19**, THF, −78 °C, 1 h; (vii) $NaBH_4$, EtOH, −78 °C, 2 h to rt, 1 h; (viii) $LiAlH_4$, THF, 0 °C, 30 min; (ix) PPh_3, *N*-Cbz-NsNH, DEAD, CH_2Cl_2, rt, 1 h; (x) 4-*tert*-BuC_6H_4SH, K_2CO_3, DMF, rt, 15 min; (xi) TBAF, THF, rt, 45 min; (xii) Jones reagent, acetone, rt, 30 min.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron impact mass spectra (EIMS) were recorded on a JEOL JMS SX-102A spectrometer. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63–210 μm]. Anhydrous THF, CH_2Cl_2, MeOH, and DMF were used as purchased from Kanto Chemical. Anhydrous EtOH was commercially obtained from Wako Pure Chemical Industry. All aldehydes and acyl chlorides were distilled prior to use. All other reagents were used as purchased.

4.2. Acylation of triethyl 2-fluoro-2-phosphonoacetate (3) with 3-phenylpropionyl chloride (5b)

A 1.6 mol/l solution of *n*-BuLi (4.9 ml, 13.0 mmol) in *n*-hexane was added to a stirred solution of phosphonoacetate **3** (1.5 ml, 12.4 mmol) in anhydrous THF (20 ml) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h, and then 3-phenylpropionyl chloride (**5b**) (1.16 ml, 13.0 mmol) was slowly added to the solution. After being stirred at 0 °C for 1 h, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with AcOEt (50 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (1:1)] to afford **6b** (1.68 g, 60%) as a colorless oil.

4.2.1. Triethyl 5-cyclopentyl-2-fluoro-3-oxo-2-phosphonopentanoate (6a). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.15 (2H, m), 1.31–1.41 (9H, m), 1.45–1.82 (9H, m), 2.77 (2H, dt, J=3.2, 7.3 Hz), 4.23–4.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.1 (s), 28.9 (d, ^3J=2.5 Hz), 32.5 (s), 37.9 (s), 39.4 (s), 63.4 (s), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 65.3 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=208.6 Hz, $^1J_{C,P}$=155.7 Hz), 162.2 (d, $^2J_{C,F}$=23.7 Hz), 199.0 (d, $^2J_{C,F}$=23.0 Hz); IR (neat) 1758, 1733, 1270, 1022 cm^{-1}; EIMS calcd for $C_{16}H_{28}FO_6P$ MW 366.1608, found *m/z* 366.1606 (M^+).

4.2.2. Triethyl 2-fluoro-3-oxo-5-phenyl-2-phosphonopentanoate (6b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.40 (9H, m), 2.90–2.97 (2H, m), 3.07–3.14 (2H, m), 4.18–4.35 (6H, m), 7.15–7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 28.8 (d, ^3J=2.5 Hz), 40.2 (s), 63.3 (s), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 65.3 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=208.6 Hz, $^1J_{C,P}$=154.4 Hz), 126.3 (s), 128.4 (s), 128.5 (s), 140.2 (s), 162.0 (d, $^2J_{C,F}$=22.4 Hz), 197.8 (d, $^2J_{C,F}$=23.0 Hz); IR (neat) 1757, 1732, 1265, 1018 cm^{-1}; EIMS calcd for $C_{17}H_{24}FO_6P$ MW 374.1295, found *m/z* 374.1295 (M^+). Anal. Calcd for $C_{17}H_{24}FO_6P$: C, 54.54; H, 6.46. Found: C, 54.57; H, 6.46%.

4.2.3. Triethyl 3-cyclohexyl-2-fluoro-3-oxo-2-phosphonopropanoate (6c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13–1.49 (14H, m), 1.63–1.96 (5H, m), 2.98–3.10 (1H, m), 4.25–4.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.3 (s), 25.6 (s), 25.7 (s), 28.1 (s), 28.6 (d, ^4J=1.2 Hz), 46.4 (s), 63.3 (s), 65.1 (d, $^2J_{C,P}$=6.9 Hz), 65.2 (d, $^2J_{C,P}$=6.9 Hz), 98.5 (dd, $^1J_{C,F}$=209.3 Hz, $^1J_{C,P}$=156.3 Hz), 162.3 (d, $^2J_{C,F}$=22.4 Hz), 201.8 (d, $^2J_{C,F}$=22.4 Hz); IR (neat) 1756, 1726, 1271, 1097, 1022 cm^{-1}; EIMS calcd for $C_{15}H_{26}FO_6P$ MW 352.1451, found *m/z* 352.1473 (M^+). Anal. Calcd for $C_{15}H_{26}FO_6P$: C, 51.13; H, 7.44. Found: C, 50.97; H, 7.30%.

4.2.4. Triethyl 2-fluoro-4,4-dimethyl-3-oxo-2-phosphonopentanoate (6d). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (9H, d, J=1.7 Hz), 1.25–1.45 (9H, m), 4.25–4.45 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 25.8 (d, $^4J_{C,F}$=5.0 Hz), 45.8 (dd, ^3J=2.5, 3.7 Hz), 63.3 (s), 65.0 (d, $^2J_{C,P}$=6.9 Hz), 65.1 (d, $^2J_{C,P}$=6.9 Hz), 99.9 (dd, $^1J_{C,F}$=214.2 Hz, $^1J_{C,P}$=158.8 Hz), 162.5 (d, $^2J_{C,F}$=22.4 Hz), 203.6 (d, $^2J_{C,F}$=21.8 Hz); IR (neat) 1752, 1716, 1268, 1245, 1022 cm^{-1}; EIMS calcd for $C_{13}H_{24}FO_6P$ MW 326.1295, found *m/z* 326.1308 (M^+). Anal. Calcd for $C_{13}H_{24}FO_6P$: C, 47.85; H, 7.41. Found: C, 47.41; H, 7.18%.

4.2.5. Triethyl 2-fluoro-3-oxo-2-phosphono-3-phenylpropanoate (6e). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.32–1.41 (6H, m), 4.22–4.46 (6H, m), 7.42–7.55 (2H, m), 7.57–7.65 (1H, m), 7.95–8.03 (1H, m), 8.07–8.14 (1H, m); ESIMS calcd for $C_{15}H_{21}FO_6P$ MW 347.1060, found *m/z* 347.1031 (M^++H).

4.2.6. Triethyl 2-fluoro-3-(2-naphthyl)-3-oxo-2-phosphonopropanoate (6f). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J=7.1 Hz), 1.32–1.43 (6H, m), 4.14–4.51 (6H, m), 7.53–7.67 (2H, m), 7.83–7.93 (2H, m), 7.94–8.03 (2H, m), 8.60 (1H, s); ESIMS calcd for $C_{19}H_{23}FO_6P$ MW 397.1216, found *m/z* 397.1190 (M^++H).

4.2.7. Triethyl 3-oxo-5-phenyl-2-phosphonopentanoate (10a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.39 (9H, m, keto- and enol-tautomer), 2.86–3.36 (4H, m, keto- and enol-tautomer), 3.86–4.33 (6H, m, keto- and enol-tautomer), 3.86–4.33 (1H, m, keto-tautomer), 7.14–7.33 (5H, m, keto- and enol-tautomer), 13.70 (1H, s, enol-tautomer); IR (neat) 1738, 1703, 1580, 1433, 1236, 1077, 1025, 976 cm^{-1}; EIMS calcd for $C_{17}H_{25}O_6P$ MW 356.1389, found *m/z* 356.1403 (M^+).

4.2.8. Triethyl 2-methyl-3-oxo-5-phenyl-2-phosphonopentanoate (10b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.36 (9H, m), 1.63 (3H, d, $^3J_{H,P}$=15.6 Hz), 2.89–3.17 (4H, m), 4.08–4.28 (6H, m), 7.15–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.3 (d, $^3J_{C,P}$=6.2 Hz), 16.4 (d, $^3J_{C,P}$=6.2 Hz), 17.1 (d, $^2J_{C,P}$=5.6 Hz),

30.0 (s), 42.0 (s), 62.2 (s), 63.4 (d, $^1J_{C,P}$=133.3 Hz), 63.3 (d, $^2J_{C,P}$=6.9 Hz), 63.5 (d, $^2J_{C,P}$=6.9 Hz), 126.1 (s), 128.4 (s), 128.5 (s), 140.9 (s), 168.5 (d, $^2J_{C,P}$=3.7 Hz), 200.8 (d, $^2J_{C,P}$=1.9 Hz); IR (neat) 1732, 1716, 1455, 1257, 1106, 1048, 1021, 970 cm^{-1}; EIMS calcd for $C_{18}H_{27}O_6P$ MW 370.1545, found *m/z* 370.1546 (M^+).

4.2.9. Triethyl 2-isopropyl-3-oxo-5-phenyl-2-phosphonopentanoate (10c). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, d, *J*=6.8 Hz), 1.19 (3H, d, *J*=6.8 Hz), 1.25–1.38 (9H, m), 2.61–2.77 (1H, m), 2.86–3.05 (4H, m), 4.05–4.31 (4H, m), 4.25 (2H, q, *J*=7.1 Hz), 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (s), 16.3 (d, $^3J_{C,P}$=2.5 Hz), 16.4 (d, $^3J_{C,P}$=1.9 Hz), 19.0 (d, $^3J_{C,P}$=7.5 Hz), 19.1 (d, $^3J_{C,P}$=5.0 Hz), 30.2 (s), 32.7 (d, $^2J_{C,P}$=3.1 Hz), 63.0 (d, $^2J_{C,P}$=6.9 Hz), 63.3 (d, $^2J_{C,P}$=7.5 Hz), 72.1 (d, $^1J_{C,P}$=129.5 Hz), 126.1 (s), 128.42 (s), 128.45 (s), 167.8 (d, $^2J_{C,P}$=3.7 Hz), 201.4 (d, $^2J_{C,P}$=1.9 Hz); IR (neat) 1716, 1255, 1226, 1047, 967 cm^{-1}; EIMS calcd for $C_{20}H_{31}O_6P$ MW 398.1858, found *m/z* 398.1877 (M^+).

4.3. Tandem reduction–olefination of triethyl 5-cyclopentyl-2-fluoro-3-oxo-2-phosphonopentanoate (6a)

To a solution of phosphonoacetate **6a** (100 mg, 0.273 mmol) in EtOH (7 ml) was added a solution of $NaBH_4$ (10.3 mg, 0.273 mmol) in EtOH (3 ml) at −78 °C under argon. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to room temperature and then was stirred for 1 h. The mixture was treated with aqueous solution saturated with NH_4Cl (5 ml) and then extracted with AcOEt (20 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=0:100) was purified by silica gel column chromatography [*n*-hexane–AcOEt (19:1)] to afford (*Z*)-**7a** (48 mg, 83%) as a colorless oil.

4.3.1. Ethyl (*Z*)-5-cyclopentyl-2-fluoro-2-pentenoate [(*Z*)-7a]. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–1.20 (2H, m), 1.33 (3H, t, *J*=7.1 Hz), 1.39–1.68 (6H, m), 1.70–1.87 (3H, m), 2.52 (2H, q, *J*=7.6 Hz), 4.28 (2H, q, *J*=7.1 Hz), 6.13 (1H, dt, $^3J_{H,F}$=33.5 Hz, $^3J_{H,H}$=8.1 Hz); IR (neat) 1735, 1679, 1455, 1371, 1311, 1083 cm^{-1}; EIMS calcd for $C_{12}H_{19}FO_2$ MW 214.1369, found *m/z* 214.1348 (M^+). Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94. Found: C, 66.89; H, 8.82%.

4.3.2. Ethyl (*Z*)-2-fluoro-5-phenyl-2-pentenoate [(*Z*)-7b].[66,67,71] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, *J*=7.1 Hz), 2.51–2.61 (2H, m), 2.76 (2H, t, *J*=7.3 Hz), 4.27 (2H, q, *J*=7.1 Hz), 6.14 (1H, dt, $^3J_{H,F}$=33.2 Hz, $^3J_{H,H}$=7.6 Hz), 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 26.0 (d, $^3J_{C,F}$=2.5 Hz), 34.45 (d, $^4J_{C,F}$=1.9 Hz), 61.5, 119.5 (d, $^2J_{C,F}$=11.2 Hz), 126.29, 128.20, 128.31, 128.53, 140.59, 148.21 (d, $^1J_{C,F}$=256.6 Hz), 160.8 (d, $^2J_{C,F}$=35.5 Hz); IR (neat) 1733, 1679, 1455, 1371, 1313, 1105 cm^{-1}; EIMS calcd for $C_{13}H_{15}FO_2$ MW 222.1056, found *m/z* 222.1051 (M^+). Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 69.79; H, 6.74%.

4.3.3. Ethyl (*Z*)-3-cyclohexyl-2-fluoro-2-propenoate [(*Z*)-7c].[68] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09–1.42 (9H, m), 1.60–1.82 (5H, m), 2.49–2.64 (1H, m), 4.27 (1H, q, *J*=7.2 Hz), 5.98 (1H, dd, $^3J_{H,F}$=33.9 Hz, $^3J_{H,H}$=9.7 Hz); IR (neat) 2929, 2854, 1736, 1673, 1304, 1087 cm^{-1}; EIMS calcd for $C_{11}H_{17}FO_2$ MW 200.1213, found *m/z* 200.1218 (M^+).

4.3.4. Ethyl (*Z*)-2-fluoro-4,4-dimethyl-2-pentenoate [(*Z*)-7d].[69,70] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (9H, d, *J*=0.7 Hz), 1.33 (3H, t, *J*=7.2 Hz), 4.26 (2H, q, *J*=7.2 Hz), 6.06 (1H, d, $^3J_{H,F}$=38.7 Hz); IR (neat) 1735, 1671, 1282, 1205, 1095 cm^{-1}; EIMS calcd for $C_9H_{15}FO_2$ MW 174.1056, found *m/z* 174.1060 (M^+).

4.3.5. Ethyl (*Z*)-2-fluoro-3-phenyl-2-propenoate [(*Z*)-7e].[67,68] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, *J*=7.1 Hz), 4.36 (2H, q, *J*=7.1 Hz), 6.92 (1H, d, $^3J_{H,F}$=35.2 Hz), 7.33–7.44 (3H, m), 7.61–7.68 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.9, 117.5 (d, $^2J_{C,F}$=4.4 Hz), 128.8, 129.7, 130.3 (d, $^4J_{C,F}$=8.1 Hz), 131.2 (d, $^3J_{C,F}$=4.4 Hz), 148.6 (d, $^1J_{C,F}$=267.2 Hz), 161.4 (d, $^2J_{C,F}$=34.3 Hz); IR (neat) 3060, 2983, 2939, 1730, 1660, 1496, 1450, 1371, 1282, 1201, 1101 cm^{-1}; ESIMS calcd for $C_{11}H_{11}NaFO_2$ MW 217.0641, found *m/z* 217.0626 (M^++Na).

4.3.6. Ethyl (*Z*)-2-fluoro-3-(2-naphthyl)-2-propenoate [(*Z*)-7f]. Colorless solid ($CHCl_3$–*n*-hexane), mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (3H, t, *J*=7.1 Hz), 4.38 (2H, q, *J*=7.1 Hz), 7.09 (1H, d, $^3J_{H,F}$=35.2 Hz), 7.45–7.57 (2H, m), 7.75–7.91 (4H, m), 8.10 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 61.9, 117.7 (d, $^2J_{C,F}$=5.0 Hz), 126.6, 126.8 (d, $^4J_{C,F}$=8.1 Hz), 127.3, 127.7, 128.5, 128.6, 128.68, 128.74, 130.8 (d, $^4J_{C,F}$=8.1 Hz), 133.4 (d, $^3J_{C,F}$=33.0 Hz), 147.2 (d, $^1J_{C,F}$=267.8 Hz), 161.5 (d, $^2J_{C,F}$=34.2 Hz); IR (KBr) 3421, 3371, 3062, 2985, 1726, 1655, 1373, 1254, 1099, 1022 cm^{-1}; ESIMS calcd for $C_{15}H_{14}FO_2$ MW 245.0978, found *m/z* 245.0983 (M^++H). Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.43; H, 5.55%.

4.3.7. Ethyl (*E*)-5-phenyl-2-pentenoate [(*E*)-11a].[72] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, *J*=7.1 Hz), 2.45–2.61 (2H, m), 2.71–2.86 (2H, m), 4.18 (2H, q, *J*=7.1 Hz), 5.85 (1H, d, *J*=15.6 Hz), 7.00 (1H, dt, *J*=6.6, 15.6 Hz), 7.14–7.40 (5H, m); IR (neat) 1719, 1653, 1267, 1197, 1039 cm^{-1}; EIMS calcd for $C_{13}H_{16}O_2$ MW 204.1150, found *m/z* 204.1121 (M^+). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.19; H, 7.92%.

4.3.8. Ethyl (*E*)-2-methyl-5-phenyl-2-pentenoate [(*E*)-11b].[73] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7.1 Hz), 1.78 (3H, s), 2.41–2.56 (2H, m), 2.69–2.82 (2H, m), 4.19 (2H, q, *J*=7.1 Hz), 6.81 (1H, dt, *J*=1.2, 7.3 Hz), 7.15–7.33 (5H, m); IR (neat) 1709, 1649, 1266, 1116, 1080 cm^{-1}; EIMS calcd for $C_{14}H_{18}O_2$ MW 218.1307, found *m/z* 218.1281 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.75; H, 8.33%.

4.3.9. Ethyl (*Z*)-2-methyl-5-phenyl-2-pentenoate [(*Z*)-11b].[74] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, *J*=7.1 Hz), 1.89 (3H, d, *J*=1.2 Hz), 2.68–2.83 (4H, m), 4.19 (2H, q, *J*=7.1 Hz), 5.96 (1H, dt, *J*=1.2, 7.1 Hz), 7.15–7.33 (5H, m); IR (neat) 1702, 1652, 1125, 1028 cm^{-1}; EIMS calcd for $C_{14}H_{18}O_2$ MW 218.1307, found *m/z* 218.1304 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.63; H, 8.36%.

4.3.10. Mixture of ethyl (*E*)-2-isopropyl-5-phenyl-2-pentanoate [(*E*)-11c] and ethyl (*Z*)-2-isopropyl-5-phenyl-2-pentanoate [(*Z*)-11c].[75] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (6H, d, J=6.8 Hz, *E*-isomer), 1.11 (6H, d, J=6.8 Hz, *Z*-isomer), 1.30 (3H, t, J=7.1 Hz, *E*- and *Z*-isomer), 2.45–2.91 (5H, m, *E*- and *Z*-isomer), 4.11–4.27 (2H, m, *E*- and *Z*-isomer), 5.73 (1H, t, J=7.3 Hz, *Z*-isomer), 6.61 (1H, t, J=7.1 Hz, *E*-isomer), 7.11–7.36 (5H, m, *E*- and *Z*-isomer); EIMS calcd for $C_{16}H_{22}O_2$ MW 246.1620, found *m/z* 246.1598 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 78.01; H, 9.00. Found: C, 77.66; H, 9.01%.

4.3.11. Ethyl 2-diethylphosphono-2-fluoro-3-hydroxy-5-phenylpentanoate (14). Colorless prism (Et_2O–*n*-hexane), mp 66.5–67.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J=7.0 Hz), 1.32 (3H, t, J=7.0 Hz), 1.34 (3H, t, J=7.0 Hz), 1.54–1.71 (1H, m), 1.93–2.11 (1H, m), 2.60–2.79 (1H, m), 2.85–3.03 (1H, m), 3.40 (1H, br s), 4.09–4.42 (7H, m) 7.10–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (s), 16.25 (d, $^3J_{C,P}$=5.3 Hz), 16.28 (d, $^3J_{C,P}$=5.3 Hz), 31.6 (d, $^4J_{C,F}$=1.3 Hz), 32.2 (dd, $^3J_{C,F}$=4.7 Hz, $^3J_{C,P}$=8.4 Hz), 62.4 (s), 64.2 (d, $^2J_{C,P}$=6.9 Hz), 64.6 (dd, $^4J_{C,F}$=1.3 Hz, $^2J_{C,P}$=6.9 Hz), 71.8 (d, $^2J_{C,F}$=19.9 Hz), 98.0 (dd, $^1J_{C,F}$=204.9 Hz, $^1J_{C,P}$=160.7 Hz), 125.9 (s), 128.3 (s), 128.4 (s), 141.2 (s), 165.8 (dd, $^2J_{C,F}$=22.7 Hz, $^2J_{C,P}$=2.2 Hz); IR (KBr) 3314, 1756, 1601, 1444, 1396, 1255 cm^{-1}; EIMS calcd for $C_{17}H_{26}O_6FP$ MW 379.1451, found *m/z* 376.1439 (M^+). Anal. Calcd for $C_{17}H_{26}O_6FP$: C, 54.25; H, 6.96. Found: C, 54.17; H, 6.84%.

4.4. HWE reaction of triethyl 2-fluoro-2-phosphonoacetate (3) with 3-phenylpropionaldehyde (8b)

To a solution of phosphonoacetate **3** (201 μl, 0.99 mmol) in anhydrous THF (10 ml) was added a solution of *n*-BuLi (1.58 mol/l in *n*-hexane, 0.63 ml, 0.99 mmol) at 0 °C under argon. After being stirred at 0 °C for 1 h, 3-phenylpropionaldehyde (**8b**) (110 μl, 0.83 mmol) was slowly added to the solution at 0 °C. After being stirred at room temperature for 20 h, the reaction mixture was treated with 5% HCl (3 ml) and then extracted with AcOEt (20 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=92:8) was purified by silica gel column chromatography [*n*-hexane–AcOEt–acetone (100:4:1)] to afford a diastereomeric mixture of (*E*)-**7b** and (*Z*)-**7b** (142 mg, 77%) as a colorless oil.

4.4.1. Ethyl (*E*)-5-cyclopentyl-2-fluoro-2-pentenoate [(*E*)-7a]. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01–1.16 (2H, m), 1.35 (3H, t, J=7.1 Hz), 1.39–1.69 (6H, m), 1.70–1.86 (3H, m), 2.52 (2H, q, J=7.8 Hz), 4.30 (2H, q, J=7.1 Hz), 5.94 (1H, dt, $^3J_{H,F}$=21.7 Hz, $^3J_{H,H}$=8.1 Hz); IR (neat) 1729, 1666, 1375, 1342, 1220, 1126 cm^{-1}; EIMS calcd for $C_{12}H_{19}FO_2$ MW 214.1369, found *m/z* 214.1349 (M^+).

4.4.2. Ethyl (*E*)-2-fluoro-5-phenyl-2-pentenoate [(*E*)-7b].[76] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J=7.1 Hz), 2.70–2.93 (4H, m), 4.28 (2H, q, J=7.1 Hz), 5.93 (1H, dt, $^3J_{H,F}$=21.3 Hz, $^3J_{H,H}$=8.1 Hz), 7.15–7.40 (5H, m); IR (neat) 1730, 1455, 1375, 1261, 1024 cm^{-1}; EIMS calcd for $C_{13}H_{15}FO_2$ MW 222.1056, found *m/z* 222.1066 (M^+). Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.08; H, 6.84%.

4.4.3. Ethyl (*E*)-3-cyclohexyl-2-fluoro-2-propenoate [(*E*)-7c].[30,77] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02–1.44 (9H, m), 1.60–1.82 (5H, m), 2.94–3.10 (1H, m), 4.29 (1H, q, J=7.2 Hz), 5.76 (1H, dd, $^3J_{H,F}$=22.0 Hz, $^3J_{H,H}$=10.3 Hz); IR (neat) 2929, 2852, 1729, 1300, 1213 cm^{-1}; EIMS calcd for $C_{11}H_{17}FO_2$ MW 200.1213, found *m/z* 200.1207 (M^+).

4.4.4. Ethyl (*E*)-2-fluoro-4,4-dimethyl-2-pentenoate [(*E*)-7d].[70] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (9H, s), 1.36 (3H, t, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 5.93 (1H, d, $^3J_{H,F}$=28.6 Hz); IR (neat) 1735, 1651, 1374, 1348, 1252 cm^{-1}; EIMS calcd for $C_9H_{15}FO_2$ MW 174.1056, found *m/z* 174.1030 (M^+).

4.4.5. Ethyl (*E*)-2-fluoro-3-phenyl-2-propenoate [(*E*)-7e].[26,71] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 6.92 (1H, d, $^3J_{H,F}$=22.2 Hz), 7.30–7.36 (3H, m), 7.44–7.47 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 61.6, 117.5 (d, $^2J_{C,F}$=25.5 Hz), 128.0, 128.7, 129.6 (d, $^4J_{C,F}$=2.5 Hz), 131.0 (d, $^3J_{C,F}$=9.3 Hz), 147.0 (d, $^1J_{C,F}$=255.3 Hz), 160.5 (d, $^2J_{C,F}$=36.7 Hz); IR (neat) 3058, 2983, 2939, 1732, 1656, 1494, 1448, 1375, 1284, 1230, 1132, 1022 cm^{-1}; ESIMS calcd for $C_{11}H_{11}NaFO_2$ MW 217.0641, found *m/z* 217.0657 (M^++Na).

4.4.6. Ethyl (*E*)-2-fluoro-3-(2-naphthyl)-2-propenoate [(*E*)-7f]. Colorless solid ($CHCl_3$–*n*-hexane), mp 32–34 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 7.07 (1H, d, $^3J_{H,F}$=22.2 Hz), 7.46–7.72 (3H, m), 7.77–7.90 (3H, m), 7.94 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 61.6, 121.6 (d, $^2J_{C,F}$=26.8 Hz), 126.3, 126.7, 127.1 (d, $^4J_{C,F}$=2.5 Hz), 127.5, 127.6, 128.2, 128.3, 128.4, 129.5 (d, $^4J_{C,F}$=3.7 Hz), 133.0 (d, $^3J_{C,F}$=23.7 Hz), 147.1 (d, $^1J_{C,F}$=255.3 Hz), 160.5 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3056, 2983, 1730, 1651, 1506, 1468, 1375, 1336, 1226, 1132, 1020 cm^{-1}; ESIMS calcd for $C_{15}H_{14}FO_2$ MW 245.0978, found *m/z* 245.0970 (M^++H). Anal. Calcd for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.45; H, 5.49%.

4.5. Synthesis of Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly (26)

4.5.1. Methyl 3-hydroxypropionate (16).[62] To a solution of sodium methoxide (146 mg, 2.65 mmol) in anhydrous MeOH (8 ml) was added β-propiolactone (**15**) (1.9 g, 26.5 mmol) at room temperature under argon. After being stirred at 50 °C for 4 h, the reaction mixture was submitted to filtration through a silica gel short column (Et_2O). The filtrate was concentrated in vacuo to afford **16** (2.74 g, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (1H, s, OH), 2.59 (2H, t, J=5.6 Hz), 3.72 (3H, s), 3.88 (2H, t, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 51.7, 58.2, 173.3.

4.5.2. Methyl 3-(*tert*-butyldiphenylsilyloxy)propanoate (17). To a solution of **16** (1.24 g, 11.9 mmol) in anhydrous CH_2Cl_2 (50 ml) were added imidazole (1.62 g, 23.8 mmol) and *tert*-butylchlorodiphenylsilane (3.1 ml, 11.9 mmol) at room temperature under argon. After being stirred at room temperature for 14 h, an aqueous solution saturated with NH_4Cl (20 ml) was added and then extracted with $CHCl_3$ (70 ml×3). The extract was dried over anhydrous $MgSO_4$,

filtered, and evaporated in vacuo to afford an oily residue, which was purified by chromatography on silica gel column [*n*-hexane–AcOEt (15:1)] to give **17** (3.92 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.58 (2H, t, J=6.3 Hz), 3.68 (3H, s), 3.94 (2H, t, J=6.3 Hz), 7.35–7.50 (6H, m), 7.62–7.74 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 37.7, 51.5, 59.8, 127.7, 129.7, 133.5, 135.5, 172.1; IR (neat) 3072, 3049, 2931, 2858, 1745, 1589, 1471, 1429, 1362, 1194, 1111, 1008 cm^{-1}; ESIMS calcd for $C_{20}H_{27}O_3Si$ MW 343.1729, found *m*/*z* 343.1761 (M^++H). Anal. Calcd for $C_{20}H_{26}O_3Si$: C, 70.13; H, 7.65. Found: C, 69.72; H, 7.71%.

4.5.3. 3-(*tert*-Butyldiphenylsilyloxy)propanoic acid (18). To a solution of **17** (3.92 g, 11.4 mmol) in EtOH (15 ml) was added 1 N NaOH (11.4 ml), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated in vacuo, acidified with 10% HCl, and then extracted with $CHCl_3$ (50 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to afford **18** (3.74 g, 99%) as a white powder. Mp 95–97 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.60 (2H, t, J=6.3 Hz), 3.95 (2H, t, J=6.3 Hz), 7.35–7.51 (6H, m), 7.63–7.75 (4H, m), 10.18–11.51 (1H, br s, CO_2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 26.7, 37.6, 59.5, 127.7, 129.7, 133.3, 135.5, 178.3; IR (KBr) 3261, 3070, 2929, 2858, 1587, 1469, 1427, 1390, 1109, 1045, 1008 cm^{-1}; ESIMS calcd for $C_{19}H_{24}NaO_3Si$ MW 351.1392, found *m*/*z* 351.1392 (M^++Na). Anal. Calcd for $C_{19}H_{24}O_3Si$: C, 69.47; H, 7.36. Found: C, 69.36; H, 7.65%.

4.5.4. 3-(*tert*-Butyldiphenylsilyloxy)propanoyl chloride (19). Oxalyl chloride (2.1 ml, 24.4 mmol) was added to a solution of **18** (4.0 g, 12.2 mmol) in anhydrous CH_2Cl_2 (50 ml) under argon. After being stirred at room temperature for 15 h, the reaction mixture was evaporated to dryness in vacuo to afford **19** (4.22 g, quant.) as a white powder, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 3.07 (2H, t, J=5.9 Hz), 3.96 (2H, t, J=5.9 Hz), 7.33–7.51 (6H, m), 7.63–7.75 (4H, m); IR (KBr) 3072, 2931, 2886, 2857, 1793, 1471, 1427, 1390, 1361, 1110 cm^{-1}; ESIMS calcd for $C_{19}H_{24}ClO_2Si$ MW 347.1234, found *m*/*z* 347.1240 (M^++H).

4.5.5. Ethyl (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-fluoropent-2-enoate (21). A 1.6 mol/l solution of *n*-BuLi (7.6 ml, 12.2 mmol) in *n*-hexane was added to a stirred solution of phosphonoacetate **3** (2.4 ml, 11.6 mmol) in anhydrous THF (30 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 1 h, and then a solution of acyl chloride **19** (4.22 g, 12.2 mmol) in anhydrous THF (30 ml) was added to the solution. After being stirred at −78 °C for 1 h, the reaction mixture was treated with 5% HCl (40 ml) and then extracted with $CHCl_3$ (100 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an oily residue.

To a solution of the crude **20** in EtOH (30 ml) was added a solution of $NaBH_4$ (439 mg, 11.6 mmol) in EtOH (30 ml) at −78 °C under argon. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to room temperature and then was stirred for 1 h. The mixture was treated with an aqueous solution saturated with NH_4Cl (50 ml), concentrated in vacuo, and then extracted with $CHCl_3$ (100 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue (*E*:*Z*=0:100) was purified by silica gel column chromatography [*n*-hexane–AcOEt (15:1)] to afford **21** (2.94 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.33 (3H, t, J=7.1 Hz), 2.45–2.54 (2H, m), 3.74 (2H, t, J=6.4 Hz), 4.28 (2H, q, J=7.1 Hz), 6.23 (1H, dt, $^3J_{H,F}$=33.4 Hz, $^3J_{H,H}$=7.6 Hz), 7.33–7.49 (6H, m), 7.62–7.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 26.8, 27.8 (d, $^3J_{C,F}$=2.5 Hz), 61.5, 62.1 (d, $^4J_{C,F}$=2.5 Hz), 117.5 (d, $^2J_{C,F}$=11.8 Hz), 127.7, 129.7, 133.5, 135.5, 148.7 (d, $^1J_{C,F}$=256.0 Hz), 160.7 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3072, 2931, 1732, 1682, 1589, 1471, 1427, 1371, 1313, 1111 cm^{-1}; ESIMS calcd for $C_{23}H_{29}FNaO_3Si$ MW 423.1768, found *m*/*z* 423.1748 (M^++Na). Anal. Calcd for $C_{23}H_{29}FO_3Si$: C, 68.97; H, 7.30. Found: C, 68.67; H, 7.46%.

The geometry and the diastereomeric ratio of **21** were confirmed on the basis of the coupling constant between fluorine and the adjacent olefinic proton ($^3J_{H,F}$=33.4 Hz), and the integration of appropriate proton absorptions was obtained by ^{1}H NMR (400 MHz) analysis. The corresponding *E*-isomer of **21** was prepared by HWE reaction of phosphonoacetate **3** and 3-(*tert*-butyldiphenylsilyloxy)propanal[78,79] utilizing *n*-BuLi as a colorless oil. *E*-Isomer of **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.33 (3H, t, J=7.1 Hz), 2.73–2.82 (2H, m), 3.74 (2H, t, J=6.1 Hz), 4.28 (2H, q, J=7.1 Hz), 6.05 (1H, dt, $^3J_{H,F}$=21.2 Hz, $^3J_{H,H}$=7.8 Hz), 7.33–7.48 (6H, m), 7.62–7.68 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.2, 26.8, 29.0 (d, $^3J_{C,F}$=5.0 Hz), 61.3, 62.7 (d, $^4J_{C,F}$=2.5 Hz), 120.5 (d, $^2J_{C,F}$=19.3 Hz), 127.7, 129.7, 133.5, 135.5, 147.7 (d, $^1J_{C,F}$=251.6 Hz), 160.9 (d, $^2J_{C,F}$=36.1 Hz); IR (neat) 3072, 2931, 2858, 1732, 1427, 1375, 1325, 1217, 1111 cm^{-1}; ESIMS calcd for $C_{23}H_{29}FNaO_3Si$ MW 423.1768, found *m*/*z* 423.1800 (M^++Na). Anal. Calcd for $C_{23}H_{29}FO_3Si$: C, 68.97; H, 7.30. Found: C, 68.80; H, 7.29%.

4.5.6. (*Z*)-5-(*tert*-Butyldiphenylsilyloxy)-2-fluoropent-2-en-1-ol (22). To a solution of **21** (458 mg, 1.14 mmol) in anhydrous THF (10 ml) was added $LiAlH_4$ (91 mg, 2.4 mmol) at 0 °C under argon. After being stirred at 0 °C for 30 min, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with $CHCl_3$ (50 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (4:1)] to afford **22** (380 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 2.28–2.43 (2H, m), 3.69 (2H, t, J=6.6 Hz), 4.08 (2H, dd, $^3J_{H,F}$=15.6 Hz, $^3J_{H,H}$=6.4 Hz), 4.90 (1H, dt, $^3J_{H,F}$=36.9 Hz, $^3J_{H,H}$=7.6 Hz), 7.32–7.48 (6H, m), 7.57–7.72 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.8, 27.0 (d, $^3J_{C,F}$=3.7 Hz), 61.4 (d, $^2J_{C,F}$=32.4 Hz), 63.0 (d, $^4J_{C,F}$=1.9 Hz), 104.6 (d, $^2J_{C,F}$=13.7 Hz), 127.6, 129.6, 133.8, 135.6, 158.4 (d, $^1J_{C,F}$=255.4 Hz); IR (neat) 3356, 3072, 2931, 2858, 1714, 1589, 1471, 1427, 1390, 1111, 1020 cm^{-1}; ESIMS calcd for $C_{21}H_{28}FO_2Si$ MW 359.1843, found *m*/*z* 359.1879 (M^++H). Anal. Calcd for $C_{21}H_{27}FO_2Si$: C, 70.35; H, 7.59. Found: C, 70.06; H, 7.39%.

4.5.7. Benzyl (*Z*)-5-(*tert*-butyldiphenylsilyloxy)-2-fluoropent-2-enylcarbamate (24). To a solution of **22** (500 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (15 ml) were added

PPh_3 (475 mg, 1.81 mmol) and *N*-Cbz-NsNH (610 mg, 1.81 mmol), and then a 2.2 mol/l solution of DEAD (823 μl, 1.81 mmol) in toluene was added slowly at room temperature under argon. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The crude solid was purified by silica gel column chromatography [*n*-hexane–AcOEt (4:1)] to afford crude **23** (1.03 g) as a yellow oil, which was used without further purification.

To a solution of **23** (360 mg) in anhydrous DMF (3 ml) were added K_2CO_3 (220 mg, 1.60 mmol) and 4-*tert*-butylthiophenol (116 μl, 0.69 mmol) at room temperature under argon. After being stirred at room temperature for 15 min, the reaction mixture was treated with 5% HCl (10 ml) and then extracted with $CHCl_3$ (20 ml×3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (7:1)] to afford **24** (230 mg, 95%) as a colorless solid. Mp 44–45 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.16–2.52 (2H, m), 3.66 (2H, t, J=6.6 Hz), 3.86 (2H, dd, $^3J_{H,F}$=14.9 Hz, $^3J_{H,H}$=5.9 Hz), 4.68–4.97 (2H, m, olefinic proton and NH), 5.11 (2H, s), 7.28–7.53 (11H, m), 7.61–7.69 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.8, 27.0 (d, $^3J_{C,F}$=3.7 Hz), 41.7 (d, $^2J_{C,F}$=31.8 Hz), 62.9 (d, $^4J_{C,F}$=2.5 Hz), 66.9, 104.2 (d, $^2J_{C,F}$=13.7 Hz), 127.6, 128.08, 128.11, 128.5, 129.6, 133.7, 135.5, 136.3, 156.10, 156.12 (d, $^1J_{C,F}$=255.4 Hz); IR (neat) 3334, 3070, 2931, 2858, 1714, 1518, 1427, 1390, 1250, 1111 cm^{-1}; ESIMS calcd for $C_{29}H_{35}FNO_3Si$ MW 492.2383, found *m/z* 492.2370 (M^++H). Anal. Calcd for $C_{29}H_{34}FNO_3Si$: C, 70.84; H, 6.97; N, 2.85. Found: C, 70.61; H, 6.98; N, 2.81%.

4.5.8. Benzyl (*Z*)-2-fluoro-5-hydroxypent-2-enylcarbamate (25). A 1.0 mol/l solution of TBAF (927 μl, 0.927 mmol) in THF was added to a stirred solution of **24** (380 mg, 0.77 mmol) in anhydrous THF (20 ml) at room temperature under argon. The mixture was stirred at room temperature for 45 min, after which the reaction mixture was treated with an aqueous solution saturated with $NaHCO_3$ (10 ml) and then extracted with $CHCl_3$ (30 ml×3). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography [*n*-hexane–AcOEt (1:1)] to afford **25** (180 mg, 92%) as a white powder. Mp 55–57 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (1H, br s, OH), 2.29–2.41 (2H, m), 3.65 (2H, t, J=6.1 Hz), 3.90 (2H, dd, $^3J_{H,F}$=14.4 Hz, $^3J_{H,H}$= 6.1 Hz), 4.86 (1H, dt, $^3J_{H,F}$=36.4 Hz, $^3J_{H,H}$=7.3 Hz), 4.95–5.06 (1H, br s, NH), 5.12 (2H, s), 7.29–7.46 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0 (d, $^3J_{C,F}$=3.7 Hz), 41.7 (d, $^3J_{C,F}$=10.0 Hz), 61.5, 67.0, 104.0 (d, $^2J_{C,F}$=13.7 Hz), 128.1, 128.2, 128.5, 136.2, 156.4, 156.6 (d, $^1J_{C,F}$=255.4 Hz); IR (KBr) 3319, 3064, 2945, 1712, 1687, 1547, 1454, 1259, 1138, 1051 cm^{-1}; ESIMS calcd for $C_{13}H_{16}FNNaO_3$ MW 276.1012, found *m/z* 276.1016 (M^++Na). Anal. Calcd for $C_{13}H_{16}FNO_3$: C, 61.65; H, 6.37; N, 5.53. Found: C, 61.42; H, 6.26; N, 5.49%.

4.5.9. (*Z*)-5-(Benzyloxycarbonylamino)-4-fluoropent-3-enoic acid {Cbz-Gly-Ψ[(*Z*)-CF=C]-Gly, 26}. To a solution of **25** (100 mg, 0.395 mmol) in acetone (5 ml) was added Jones reagent (500 μl) at 0 °C. After the reaction mixture was stirred at room temperature for 30 min, 2-propanol (1 ml) was added to it and the resulting mixture was then stirred until the color of the reaction mixture disappeared. After filtration, the filtrate was concentrated in vacuo and then treated with an aqueous solution saturated with $NaHCO_3$ (20 ml), washed with $CHCl_3$ (20 ml). The aqueous layer was acidified with 10% HCl (10 ml) and then extracted with AcOEt (50 ml×5). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford **26** (85 mg, 80%) as a white powder. Mp 74–75 °C ($CHCl_3$–*n*-hexane); ^{1}H NMR (400 MHz, DMSO) δ 3.02 (2H, d, J=7.1 Hz), 3.25–3.43 (1H, br s, NH), 3.76 (2H, dd, $^3J_{H,F}$=12.7 Hz, $^3J_{H,H}$=5.9 Hz), 4.90–5.09 (3H, m), 7.26–7.45 (5H, m), 12.16–12.63 (1H, br s, CO_2H); ^{13}C NMR (75 MHz, CD_3OD) δ 29.7 (d, $^3J_{C,F}$=5.6 Hz), 42.0 (d, $^2J_{C,F}$=33.6 Hz), 67.7, 100.6 (d, $^2J_{C,F}$=12.5 Hz), 128.8, 129.0, 129.5, 138.2, 158.7, 158.9 (d, $^1J_{C,F}$=257.2 Hz), 174.6; IR (KBr) 3313, 2956, 1687, 1550, 1271, 1167, 1140, 1053, 993 cm^{-1}; ESIMS calcd for $C_{13}H_{14}FNNaO_4$ MW 290.0805, found *m/z* 290.0821 (M^++Na). Anal. Calcd for $C_{13}H_{14}FNO_4$: C, 58.42; H, 5.28; N, 5.24. Found: C, 57.98; H, 5.42; N, 4.93%.

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Synthesis of phosphorus dendrimers bearing chromophoric end groups: toward organic blue light-emitting diodes

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Abstract—Several series of phosphorus dendrimers decorated by potential fluorescent end groups (naphthalene, anthracene, and pyrene) have been synthesized. Unexpectedly, we found that it is absolutely necessary to link the fluorophore to the dendrimer through an alkyl link, and not directly through heteroelements such as oxygen or nitrogen, in order to preserve the fluorescence. One series of dendrimers from generation 1 (6 pyrene end groups) to generation 4 (48 pyrene end groups) has been tested for the elaboration of organic light-emitting diodes (OLEDs). The threshold voltage for the emission of light is high (over 20 V), however, electroluminescence is observed in all cases.

1. Introduction

Dendrimers[1–3] constitute a very special type of polymers, whose hyperbranched and perfectly defined structure arouse the interest of thousands of researchers since about 20 years. Their stepwise synthesis allows the grafting where the desired (core, branches, and surface) functional groups were chosen to impart properties in particular in materials science, catalysis, or biology. Among these functional groups, fluorescent entities occupy a special place; they have been grafted to several types of dendrimers and for a lot of purposes,[4,5] including analytical uses such as the detection of dendritic defects[6] or the measurement of hydrodynamic radius,[7] and also for several applications such as labeling of biological entities[8] or elaboration of electroluminescent materials usable as light-emitting diodes. Indeed, organic light-emitting diodes (OLEDs) have key advantages for full-color flat-panel displays, such as high luminescence efficiency, color purity, wide viewing angle, low weight, and lower drive voltages.[9–11] Several types of fluorescent and electroactive dendrimers have already been used for researches in this field, based in particular on fully conjugated dendrimers such as poly(distyrylbenzene),[12] poly(*p*-phenylene),[13] or poly(phenylenevinylene)[14] dendrimer, and also on non-fully conjugated dendrimers (generally of type poly (benzyl ether)) possessing one fluorescent unit at the core.[15,16] However, none of these examples concerns phosphorus-containing dendrimers, despite the known influence of the type of skeleton on the properties (stability, solubility, polarity, density, etc.). We have already reported the grafting of fluorescent entities at the core,[17–19] in the interior,[20] or as end groups of phosphorus dendrimers,[21,22] as well as the synthesis of electroactive phosphorus dendrimers, possessing in most cases ferrocene,[23–25] thiophene,[26] or TTF[27,28] unit. We report here the grafting of several potential fluorescent entities (naphthalene, anthracene, and pyrene) as end groups of several types and generations of phosphorus-containing dendrimers, and the tentative use of one series for the elaboration of organic light-emitting diodes (OLEDs).

2. Results and discussion

2.1. Grafting of fluorescent derivatives on the surface of phosphorus dendrimers

In a first attempt, we decided to use our classical series of phosphorus dendrimers, synthesized by the repetition of two steps (a nucleophilic substitution of hydroxybenzaldehyde on $P(S)Cl_2$ groups and a condensation reaction of a phosphorhydrazide with the aldehydes),[29,30] starting from hexafunctional cyclotriphosphazene core.[31] The simplest way to graft functional groups on the surface of phosphorus-containing dendrimers having $P(S)Cl_2$ end groups consists of using functional phenols in basic conditions, generally as their sodium salts. The grafting of naphthol on the surface of the second generation dendrimer **1-G$_2$** possessing 12 $P(S)Cl_2$ end groups (Scheme 1) is easily monitored by ^{31}P

Keywords: Dendrimers; Fluorescence; Electroluminescence; OLED.
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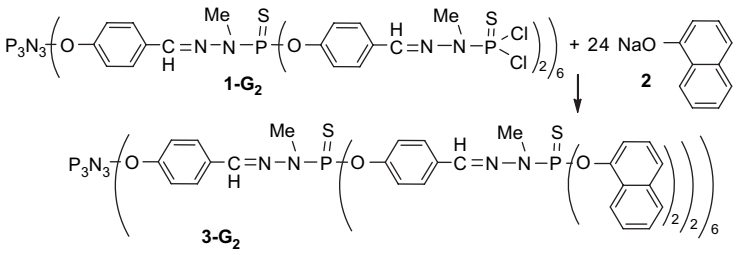


Scheme 1.

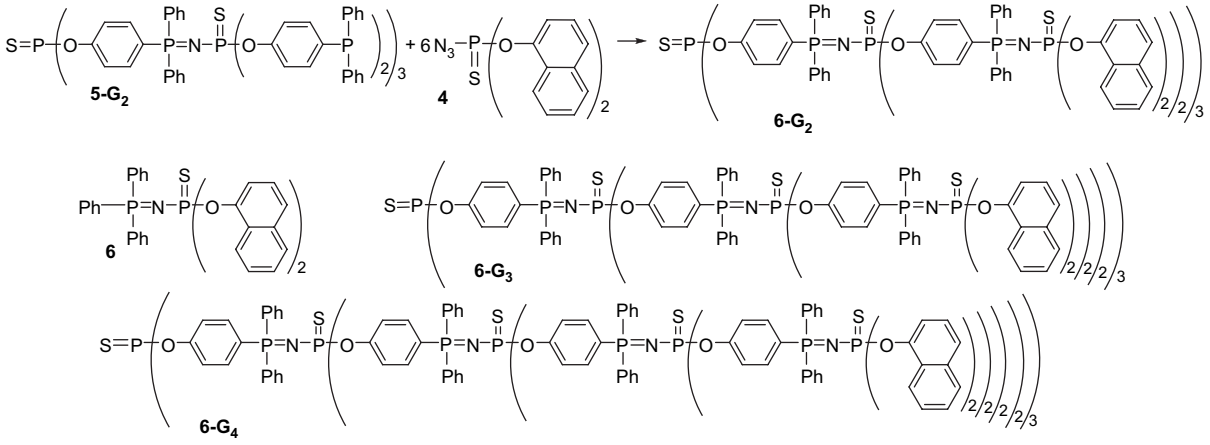
NMR. An intermediate signal at δ=67.5 ppm corresponding to the monosubstitution on each end group is first observed, replaced after the completion of the reaction by a singlet at 61.9 ppm, in addition to the signals corresponding to the core in the first generation. This dendrimer **3-G$_2$** is also characterized by ^{1}H and ^{13}C NMR.

Surprisingly, despite the presence of 24 fluorophores on the surface of dendrimer **3-G$_2$**, this compound is not fluorescent. In order to determine whether the skeleton of the dendrimer could be responsible for this astonishing result, we decided to try to graft naphthol on the surface of another type of phosphorus dendrimers, based on P═N–P═S linkages.[32] This series of dendrimers has free or protected phosphines as end groups at each step. Thus, naphthol cannot be directly linked to these end groups, and we decided to synthesize first the azide **4**, obtained by the reaction of 2 equiv of naphthol on $P(S)Cl_3$, followed by the substitution of the remaining Cl by N_3. The reactivity of this azide toward phosphines was first tested with PPh_3 as a model and with the second generation dendrimer **5-G$_2$**. The Staudinger reactions occur as expected, creating P═N linkages in the model compound **6** and the dendrimer **6-G$_2$** (Scheme 2).

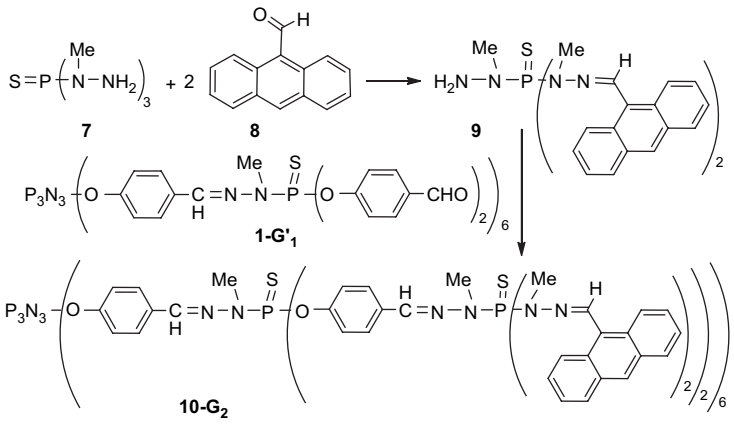
The Staudinger reaction is characterized by ^{31}P NMR, which displays both the disappearance of the singlet corresponding to the phosphine end groups (δ=−6 ppm) and the singlet corresponding to the azide **4** (δ=59.3 ppm), on behalf of the appearance of two doublets at δ=12 ppm (P═N) and 51 ppm (P═S), with $^{2}J_{PP}$=32 Hz. These signals are obtained in addition to two other doublets corresponding to the internal P═N–P═S linkages, and one singlet corresponding to the core of the dendrimer **6-G$_2$**. The azide **4** was also reacted with the third and fourth generations of the dendrimer **5-G$_n$**, to afford dendrimers **6-G$_3$** and **6-G$_4$**, respectively.

The presence of numerous conjugated Ph–P═N–P═S linkages incited us to test the electrochemical behavior of this series of dendrimers. The cyclic voltammogram of the first generation displays a single wave characteristic of an irreversible oxidation. This assumption is supported by the ^{31}P NMR spectrum obtained after electrolysis: the doublets characteristic of **6-G$_2$** disappeared on behalf of a multitude of signals between −10 and +60 ppm. This observation implies the occurrence of an EC process, that is, an electronic transformation followed by a chemical transformation. Such instability under current is incompatible with the use of this series of dendrimers **6-G$_n$** for the elaboration of OLEDs, thus we decided to move back to the first type of dendritic skeleton (shown in Scheme 1), and to modify the type of fluorophore end groups.

In a first attempt, we decided to use the sodium salt of anthracen-9-ol to react with $P(S)Cl_2$ end groups. The reaction is monitored by ^{31}P NMR, which shows the appearance of an intermediate signal at δ=68.8 ppm, corresponding to the substitution of one Cl on each end groups, slowly followed by the appearance of a signal at 63.3 ppm, corresponding to the di-substitution. However, the fully substituted dendrimer could not be isolated, presumably due to a [2+2] photochemical cycloaddition reaction, which induces the precipitation of insoluble compounds. Such behavior has been already observed when two 9-anthryl groups are linked through three atoms,[33] such as the O–P–O linkage in our case.



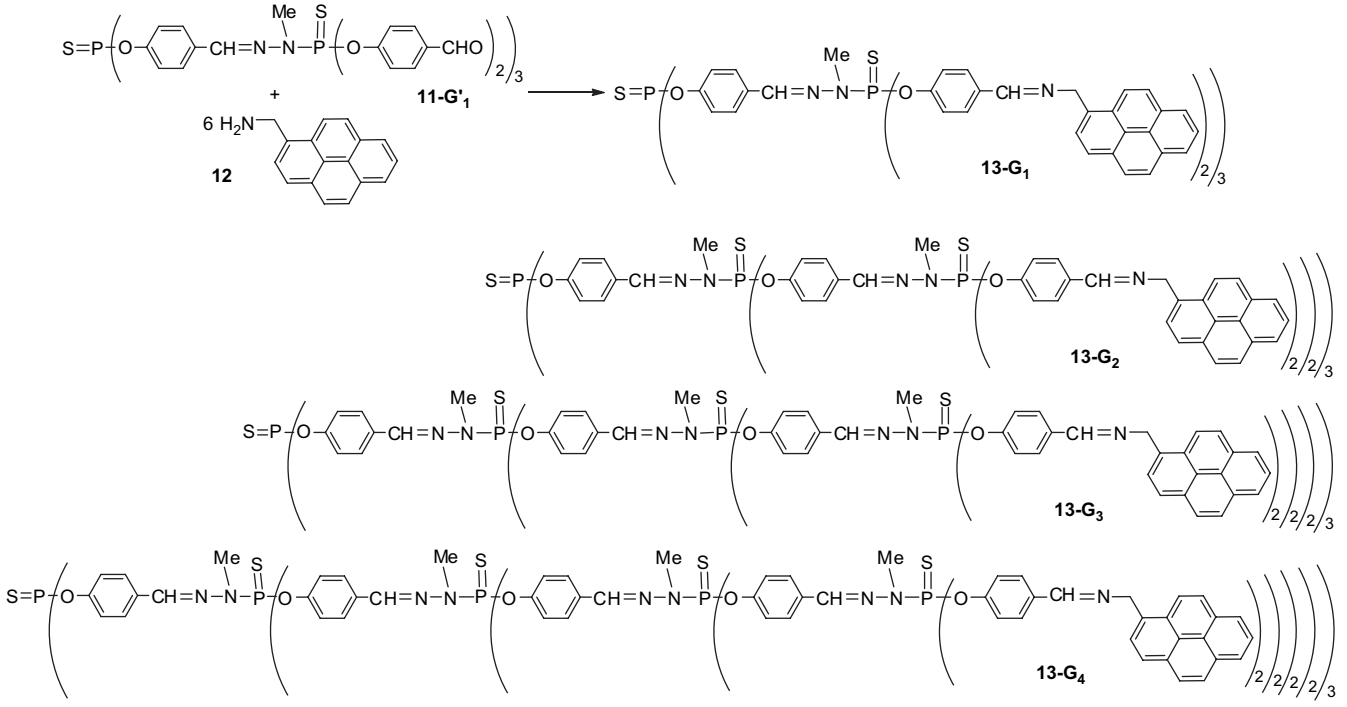
Scheme 2.



Scheme 3.

Thus, we designed another strategy, in order to have a longer linker between both anthryl groups. For such purpose, 2 equiv of 9-anthraldehyde **8** was reacted with 1 equiv of the phosphotrihydrazide **7**, to afford compound **9**, which is isolated in 73% yield. No trace of dimerization is observed for this compound, in which both anthryl groups are separated by seven atoms. The unreacted NH_2 group of compound **9** is used in condensation reactions with the aldehyde end groups of the first generation dendrimer **1-G$_1$′**,[31] to afford the second generation dendrimer **10-G$_2$** (Scheme 3). The completion of the condensation reaction is easily shown by the disappearance of the signals corresponding to the aldehydes by ^{1}H and ^{13}C NMR and by IR spectroscopy.

Unfortunately, this dendrimer also is not fluorescent. In view of all the problems we encountered concerning fluorescence, we reasoned that the presence of several heteroatoms in close proximity to the fluorophores might be the reason, by inducing non-radiative relaxations, in particular due to $n \rightarrow \pi^*$ transitions. Thus, we decided to introduce an alkyl linker to isolate the chromophore from the electronic effects of the dendrimer. Our choice was made on the simplest linker, a CH_2 group, present for instance in 1-pyrenemethylamine **12**. This compound was used in condensation reactions on aldehyde end group of the dendrimer **11-G$_1$′**,[29,30] which differs from **1-G$_1$′** only by the type of core, and the number of end groups. The condensation reactions induce the total disappearance of the signals corresponding to the aldehydes in ^{1}H and ^{13}C NMR and IR spectra. We did not observe hydrolysis of the imine bonds, neither in solution in organic solvents nor when kept as a powder in air. The same condensation reactions were carried out with generations two, three, and four of dendrimer **11-G$_n$′**, to afford dendrimers **13-G$_2$**, **13-G$_3$**, and **13-G$_4$**, respectively (Scheme 4 and Fig. 1).



Scheme 4.

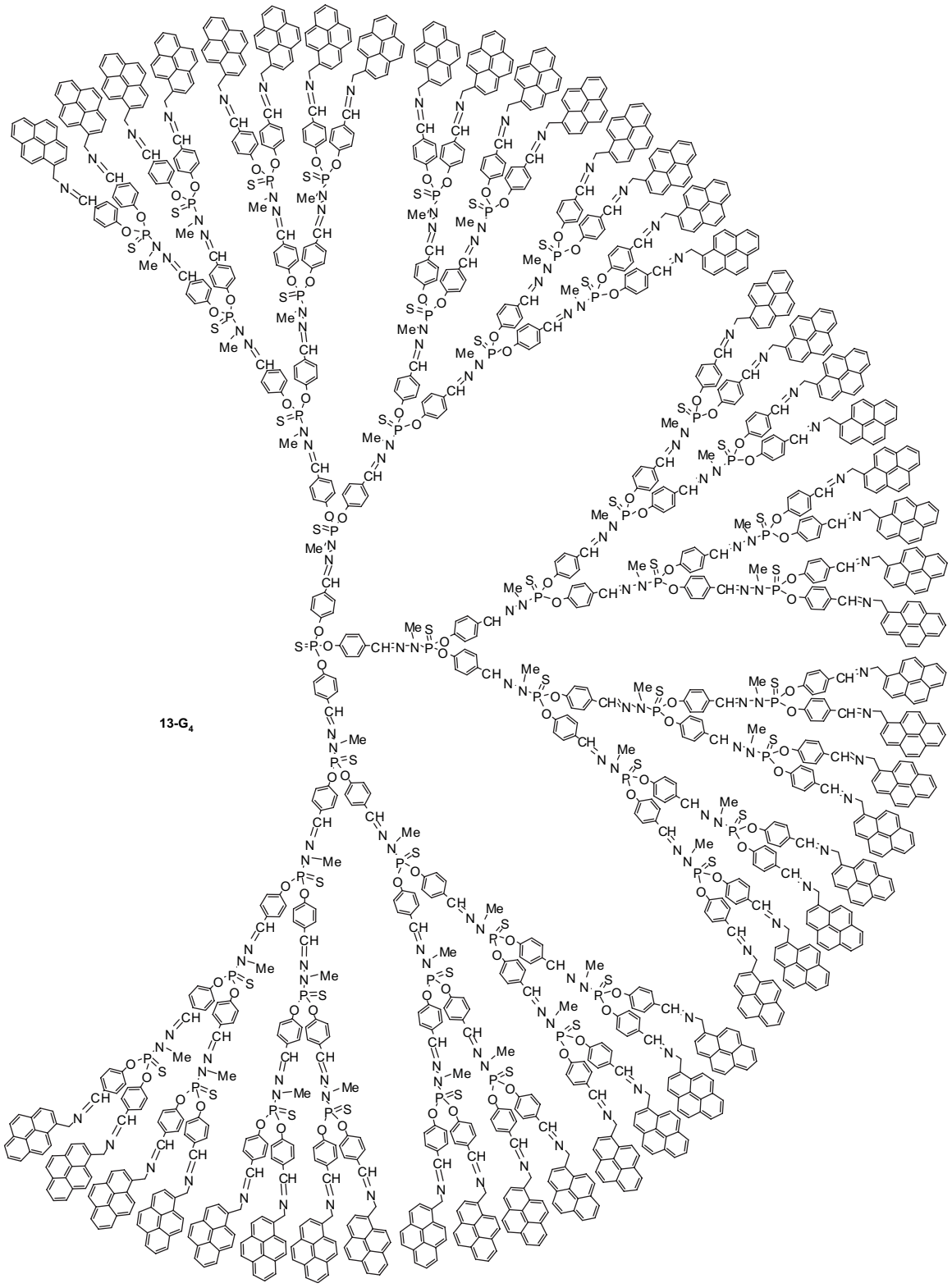


Figure 1. Structure of dendrimer **13-G$_4$**.

Our assumption concerning the negative influence of heteroatoms on the fluorescence properties appears right: the series of dendrimers **13-G$_n$** is fluorescent. Thus, we have carried out a series of tests with these dendrimers, in view of the elaboration of OLEDs. Most of the tests were carried out on the first generation as a model, then on generations three and four to compare with large compounds.

2.2. Photo-physical properties of dendrimers 13-G$_n$

The first property we checked concerns the thermal stability. Thermogravimetric analyses of all compounds display a slight loss of mass (2–7%) between 80 and 180 °C, corresponding to the evaporation of residual solvents, as identified by GC mass. The real decomposition of dendrimers

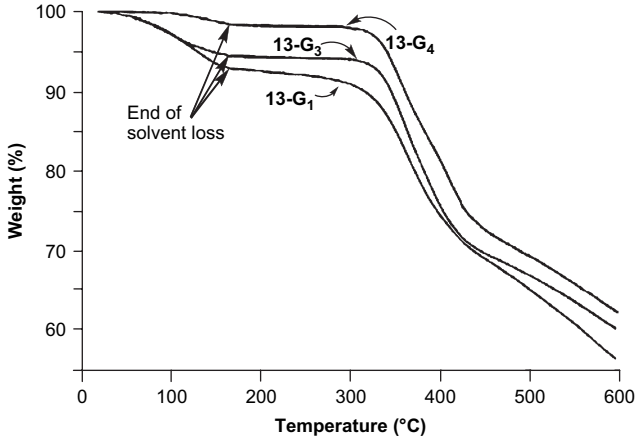


Figure 2. Thermogravimetric analyses of dendrimers **13-G$_n$** (n=1, 3, and 4).

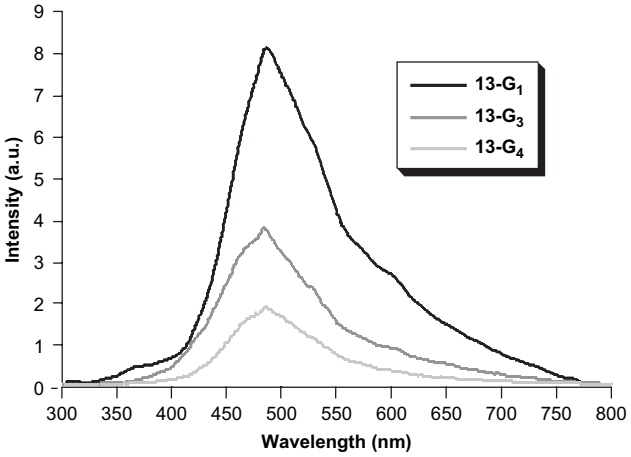


Figure 3. Emission spectra of pyrene excimers of thin films of **13-G$_1$**, **13-G$_3$**, and **13-G$_4$** (intensities in arbitrary units).

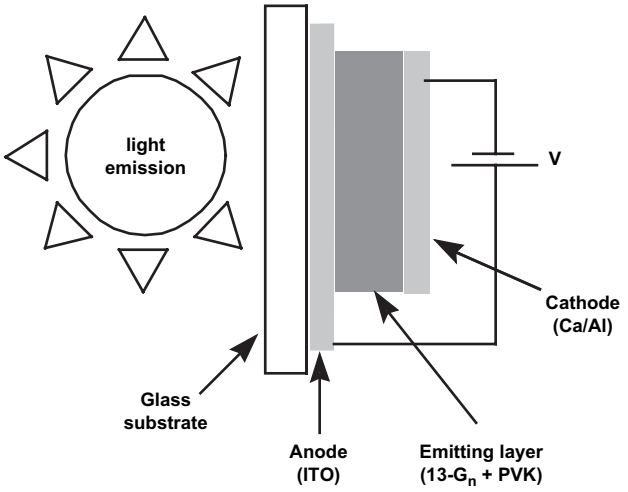


Figure 4. OLED device structure elaborated for electroluminescence experiments.

begins at about 320 °C for all generations (Fig. 2); thus this series of dendrimers is thermally stable enough to be used for the elaboration of OLEDs. The insensitivity of the thermal stability toward generations was already observed for other series of dendrimers having the same skeleton but different end groups.[34]

The second point to be verified concerns the glass transition temperature (T_g). Indeed, the T_g value must be higher than the temperature of the OLED; if not, crystalline microdomains can be formed, inducing a degradation of the performances of the OLED. No glass transition temperature could be detected for **13-G$_1$** between 20 and 300 °C; this result is surprising in view of the value found for the parent compound **11-G$_1$′** (74 °C).[35] The T_g value is 153 °C for **13-G$_3$** and 243 °C for **13-G$_4$**. Thus, OLEDs created from both dendrimers must be used at temperatures lower than 150 and 240 °C, respectively.

The photoluminescence properties of these dendrimers were measured on thin films of **13-G$_1$**, **13-G$_3$**, and **13-G$_4$**. The UV–visible absorption spectra display the bands characteristic of pyrene at 335 and 352 nm, in addition to a very broad band between 230 and 330 nm, corresponding to the aromatic groups of the dendrimers.[36] The fluorescence measured after excitation at 250 nm displays a single emission band in the blue at 484 nm for all three dendrimers. This very broad band corresponds to the emission of excimers of pyrene (Fig. 3). No emission of monomeric pyrene could be detected, in accordance with our previous experiments concerning pyrene derivatives included within the interior of dendrimers.[20]

Electroluminescence was measured on diodes elaborated from a glass substrate covered by a thin film of indium tin oxide (ITO), constituting the transparent anode. The emitting organic layer is deposited by spin coating on the anode of a solution in trichloroethane of dendrimer **13-G$_n$** (5 g/L) in a matrix of poly(vinylcarbazole) (PVK, 20 g/L); then the solvent is eliminated by slow evaporation. The PVK polymer acts as hole transporter and prevents crystallization. The inorganic refractive cathode is constituted by a layer of Ca/Al (Fig. 4).

Application of a voltage between the electrodes should induce the injection of charges into the organic layer (holes from the anode and electrons from the cathode); their recombination will create excitons; a fraction of them will decay radiatively. In the case of the materials elaborated from dendrimers **13-G$_n$**, the threshold tension (V_t) is very high (18 V for **13-G$_1$** and **13-G$_3$**, 20 V for **13-G$_4$**) (Fig. 5). This high value might be due to the trapping of electrons by the dendritic structure, a phenomenon that we already observed.[37] Such high working voltage precludes any practical applications of such devices; however, we decided to determine their brightness.

In all devices, electroluminescence emission peaks are in the blue at about 484 nm, as observed for the photoluminescence spectra of the corresponding dendrimers in thin films. Figure 6 displays the current–luminance characteristics of these OLEDs. The best results are obtained with the fourth generation dendrimer, but even in this case the emission of light is low, only 3.5 cd/m^2. The inset in Figure 6 shows that the threshold voltage for both current and light is similar, indicating a fairly balanced charge injection and transport; furthermore, the luminance is approximately proportional to the current density, indicating that the quantum efficiency is constant over a relatively large range of current.

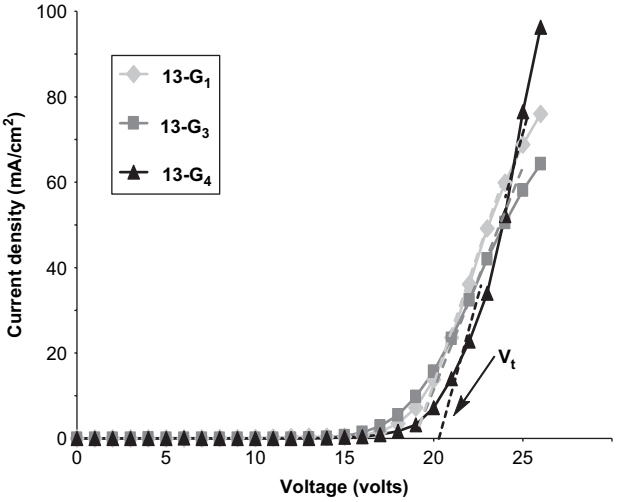


Figure 5. Current–voltage characteristics of **13-G$_n$** (n=1, 3, and 4) dendrimer-based OLEDs with structure of (ITO/**13-G$_n$**:PVK/Ca,Al; V_t: threshold tension).

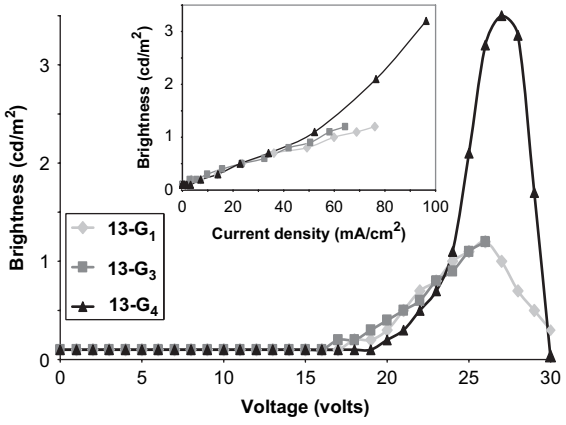


Figure 6. Light–voltage characteristics of **13-G$_n$** (n=1, 3, and 4) dendrimer-based OLEDs with structure of (ITO/**13-G$_n$**:PVK/Ca,Al). Inset: light–current correlation.

3. Conclusion

We have synthesized several series of phosphorus dendrimers bearing potential fluorescent entities as end groups (naphthalene, anthracene, and pyrene). However, the loss of fluorescence observed in several cases led us to the unexpected conclusion that the fluorophore must not be linked to the dendrimer through a heteroelement (oxygen or nitrogen) but through an alkyl linkage. The condensation of 1-pyrenemethylamine with the aldehyde end groups of the dendrimer led to a series of compounds fluorescent even in the solid state, and thermally very stable (up to 320 °C). This series of dendrimers has been tested for the elaboration of organic light-emitting diodes. These OLEDs have a threshold voltage for emission of light that is too high for practical purposes (18–20 V), but they do possess electroluminescent properties.

4. Experimental

4.1. General

All compounds were protected against light by wrapping the vessel in aluminum film. All manipulations were carried out with standard high vacuum and dry-argon techniques. The solvents were freshly dried and distilled (THF and ether over sodium/benzophenone, pentane and CH_2Cl_2 over phosphorus pentoxide). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with Bruker AC 200, AC 250, or DPX 300 spectrometer. References for NMR chemical shifts are 85% H_3PO_4 for ^{31}P NMR, and $SiMe_4$ for ^{1}H and ^{13}C NMR. The attribution of ^{13}C NMR signals has been done using J_{mod}, two-dimensional HMBC, and HMQC, Broad Band or CW ^{31}P decoupling experiments when necessary (br s means broad singlet). The number scheme used for NMR assignments is shown in Figure 7. Compounds **1-G$_n$**,[31] **1-G$_n$′**,[31] **5-G$_n$**,[32] and **11-G$_n$′**[29,30] were synthesized according to published procedures. The OLEDs are elaborated and characterized according to published procedures.[9,38,39]

4.1.1. Synthesis of dendrimer 3-G$_2$. A solution of dendrimer **1-G$_2$** (0.1 g. 20.9 μmol) in THF (30 mL) was added to a suspension of sodium salt of 1-naphthol **2** prepared with 0.1 g (0.69 mmol) of 1-naphthol and 17 mg of sodium hydride in THF (50 mL). The resulting mixture was stirred for 16 h at room temperature, then centrifuged, and the solution was evaporated to dryness to afford a powder, which was washed twice with ether (2×30 mL) to afford dendrimer **3-G$_2$** as a pale beige powder in 96% yield.

^{31}P {^{1}H} NMR ($CDCl_3$): δ=7.8 (s, P_0), 60.7 (s, P_2), 61.9 (s, P_2) ppm. ^{1}H NMR ($CDCl_3$): δ=3.1 (d, $^3J_{HP1}$=10.1 Hz, 18H, Me_1), 3.3 (d, $^3J_{HP2}$=10.6 Hz, 36H, Me_2), 6.9 (d, $^3J_{HH}$=8.5 Hz, 12H, H-C_0^2), 7.1 (d, $^3J_{HH}$=8.1 Hz, 24H, H-C_1^2), 7.2–7.6 (m, 174H, H Arom), 7.7 (d, $^3J_{HH}$=7.5 Hz, 24H, H-C^5), 8.1 (d, $^3J_{HH}$=7.8 Hz, 24H, H-C^8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=32.9 (d, $^2J_{CP1-2}$=13.8 Hz, Me_1, Me_2), 116.0 (d, $^3J_{CP2}$=3.9 Hz, C^2), 121.3 (br s, C_0^2), 121.5 (d, $^3J_{CP1}$=3.9 Hz, C_1^2), 122.5 (s, C^4), 125.2, 125.3 (2s, C^7, C^8), 126.0 (s, C^3), 126.5 (s, C^6), 127.0 (s, C_0^3), 127.1 (s, C_1^3), 127.6 (s, C^5), 128.2 (s, C^9), 132.1 (s, C_0^4), 132.2 (s, C_1^4), 134.7 (s, C^{10}), 138.6 (d, $^3J_{CP1-2}$=13.8 Hz, C_0^5, C_1^5), 147.0 (d, $^2J_{CP2}$=9.8 Hz, C^1), 151.1 (d, $^2J_{CP0-1}$=6.0 Hz, C_0^1, C_1^1) ppm. Anal. Calcd for $C_{384}H_{312}N_{39}O_{66}P_{21}S_{18}$ (7757): C, 59.46; H, 4.05; N, 7.04. Found: C, 59.19; H, 3.88; N, 6.85.

4.1.2. Synthesis of the azide 4. A solution of 1-naphthol (0.94 g, 6.5 mmol) and triethylamine (1 mL, 7.2 mmol) in THF (20 mL) was added dropwise at room temperature to a solution of trichlorothiophosphine (0.33 mL, 3.25 mmol) in THF (30 mL). After stirring for 24 h, the solution was filtered, and then concentrated. Acetone (20 mL) and sodium azide (0.23 g, 3.5 mmol) were added, and the resulting mixture was stirred for 3 days at room temperature, then concentrated and centrifuged. The solution was evaporated to dryness to afford the azide **4** without further purification as maroon oil in 88% yield.

^{31}P {^{1}H} NMR ($CDCl_3$): δ=59.3 (s) ppm. ^{1}H NMR ($CDCl_3$): δ=7.30–7.90 (m, 12H, H_{Ar}), 8.2 (m, 2H, H-C_8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=116.6 (d, $^3J_{CP1}$=4.1 Hz, C^2), 122.0 (s, C^8), 125.4 (d, $^5J_{CP}$=1.0 Hz, C^7), 125.8 (d, $^5J_{CP}$=1.0 Hz, C^4), 126.6 (s, C^3), 126.7 (s, C^6), 126.8 (d, $^3J_{CP}$=5.6 Hz, C^9), 127.8 (s, C^5), 134.8 (s, C^{10}), 146.8 (d, $^2J_{CP}$=10.0 Hz, C^1) ppm. IR (THF): 2160 (ν_{N3}) cm^{-1}.

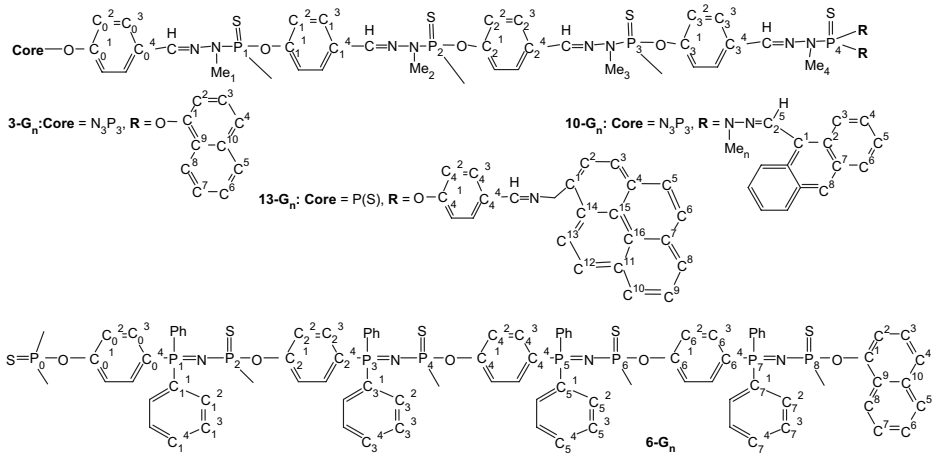


Figure 7. Numbering used for NMR assignments.

4.1.3. Synthesis of the model compound 6. A solution of the azide **4** (100 mg, 0.26 mmol) in THF (10 mL) was added to a solution of triphenylphosphine (70 mg, 0.26 mmol) in THF (10 mL) and stirred at room temperature for 1 h. The resulting solution was evaporated to dryness to afford a powder, which was washed three times with a diethylether/pentane mixture (1/9) to afford **6** as a white powder in 95% yield.

^{31}P {^{1}H} NMR ($CDCl_3$): δ=12.6 (d, $^{2}J_{PP}$=32.0 Hz, P_0), 51.0 (d, $^{2}J_{PP}$=32.0 Hz, P_1) ppm. ^{1}H NMR ($CDCl_3$): δ=7.30–7.39 (m, 10H, H-C^3, H-C^7, H-C$_0^3$), 7.40–7.47 (m, 2H, H-C^6), 7.47–7.57 (m, 9H, H-C$_0^2$, H-C$_0^4$), 7.65 (m, 2H, H-C^4), 7.71 (m, 2H, H-C^2), 7.83 (m, 2H, H-C^5), 8.15 (m, 2H, H-C^8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=117.2 (d, $^{3}J_{CP1}$=4.5 Hz, C^2), 123.8 (s, C^8), 124.4 (d, $^{5}J_{CP1}$=2.0 Hz, C^4), 126.0 (br s, C^3, C^7), 126.6 (s, C^6), 127.8 (s, C^5), 128.3 (d, $^{3}J_{CP1}$=5.0 Hz, C^9), 128.9 (d, $^{3}J_{CP0}$=13.0 Hz, C$_0^3$), 129.1 (dd, $^{3}J_{CP1}$=4.0 Hz, $^{1}J_{CP0}$=107 Hz, C$_0^1$), 132.8 (d, $^{4}J_{CP0}$=3.0 Hz, C$_0^4$), 133.1 (d, $^{2}J_{CP0}$=11.0 Hz, C$_0^2$), 135.2 (s, C^{10}), 148.9 (d, $^{2}J_{CP1}$=10.0 Hz, C1) ppm. Anal. Calcd for $C_{38}H_{29}NO_2P_2S$ (25,618): C, 72.95; H, 4.67; N, 2.24. Found: C, 71.74; H, 4.36; N, 1.99.

4.1.4. General method for the synthesis of the series of dendrimers 6-G$_n$ (n=2, 3, and 4). A stoichiometric amount of azide **4** in dissolved in THF (10 mL) was added dropwise to a solution of dendrimer **5-G$_{n-1}$** (typically 100 mg) in THF (20 mL) and stirred at room temperature for 1 h. The resulting solution was evaporated to dryness to afford a powder, which was washed three times with a diethylether/pentane mixture (1/1) to afford dendrimers **6-G$_n$** as white powders.

4.1.4.1. Compound 6-G$_2$. Yield 89%. ^{31}P {^{1}H} NMR ($CDCl_3$): δ=11.3 (d, $^{2}J_{PP}$=32.5 Hz, P_3), 13.0 (d, $^{2}J_{PP}$=30.5 Hz, P_1), 49.2 (s, P_0), 49.3 (d, $^{2}J_{PP}$=30.5 Hz, P_2), 51.0 (d, $^{2}J_{PP}$=32.5 Hz, P_4) ppm. ^{1}H NMR ($CDCl_3$): δ=7.0–7.6 (m, 186H, C_6H_5, C_6H_4, naphthyl), 7.63 (d, $^{3}J_{H5H6}$=7.9 Hz, 12H, H-C^5), 7.96 (d, $^{3}J_{H7H8}$=8.1 Hz, 12H, H-C^8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=116.7 (d, $^{3}J_{CP6}$=3.6 Hz, C^2), 121.5–121.8 (m, C$_0^2$, C$_2^2$), 123.2 (s, C^8), 123.2 (br d, $^{1}J_{CP}$=111 Hz, C$_2^4$), 123.9 (br s, C^4), 125.5 (br s, C^3, C^7), 126.1 (s, C^6), 127.3 (s, C^5), 127.7 (br d, $^{1}J_{CP1}$=106 Hz, C$_1^1$), 128.2 (br d, $^{1}J_{CP}$=106 Hz, C$_3^1$), 128.4 (d, $^{3}J_{CP4}$=13.5 Hz, C^9), 128.7 (d, $^{3}J_{CP}$=13.1 Hz, C$_1^3$, C$_3^3$), 132.4 (s, C$_1^4$, C$_3^4$), 132.5 (d, $^{2}J_{CP}$=11.3 Hz, C$_1^2$, C$_3^2$), 134.3 (d, $^{2}J_{CP}$=12.1 Hz, C$_0^3$, C$_2^3$), 134.6 (s, C^{10}), 148.3 (d, $^{2}J_{CP4}$=9.7 Hz, C^1), 153.4 (br d, $^{2}J_{CP0}$=8 Hz, C$_0^1$), 155.2 (dd, $^{4}J_{CP3}$=3.69 Hz, $^{2}J_{CP2}$=7.63 Hz, C$_2^1$) ppm. Anal. Calcd for $C_{282}H_{210}N_9O_{21}P_{19}S_{10}$ (4970): C, 68.15; H, 4.26; N, 2.54. Found: C, 67.77; H, 3.92; N, 2.18.

4.1.4.2. Compound 6-G$_3$. Yield 93%. ^{31}P {^{1}H} NMR ($CDCl_3$): δ=11.3 (d, $^{2}J_{PP}$=33.4 Hz, P_5), 13.0 (br d, $^{2}J_{PP}$=31.0 Hz, P_1, P_3), 49.2 (s, P_0), 49.3 (br d, $^{2}J_{PP}$=31.0 Hz, P_2, P_4), 51.0 (d, $^{2}J_{PP}$=33.4 Hz, P_6) ppm. ^{1}H NMR ($CDCl_3$): δ=7.0–7.6 (m, 414H, C_6H_5, C_6H_4, naphthyl), 7.60 (d, $^{3}J_{H5H6}$=7.9 Hz, 24H, H-C^5), 7.95 (d, $^{3}J_{H7H8}$=8.1 Hz, 24H, H-C^8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=116.7 (d, $^{3}J_{CP6}$=3.6 Hz, C^2), 121.5–121.8 (m, C$_0^2$, C$_2^2$, C$_4^2$), 123.2 (s, C^8), 123.2 (br d, $^{1}J_{CP}$=111 Hz, C$_2^4$, C$_4^4$), 123.9 (br s, C^4), 125.5 (br s, C^3, C^7), 126.1 (s, C^6), 127.3 (s, C^5), 127.7 (br d, $^{1}J_{CP1}$=106 Hz, C$_1^1$), 128.2 (br d, $^{1}J_{CP}$=106 Hz, C$_3^1$, C$_5^1$), 128.4 (d, $^{3}J_{CP6}$=13.5 Hz, C^9), 128.7 (d, $^{3}J_{CP}$=13.1 Hz, C$_1^3$, C$_3^3$, C$_5^3$), 132.4 (s, C$_1^4$, C$_3^4$, C$_5^4$), 132.5 (d, $^{2}J_{CP}$=11.3 Hz, C$_1^2$, C$_3^2$, C$_5^2$), 134.3 (d, $^{2}J_{CP}$=12.1 Hz, C$_0^3$, C$_2^3$, C$_4^3$), 134.6 (s, C^{10}), 148.3 (d, $^{2}J_{CP6}$=9.8 Hz, C^1), 153.4 (br m, C$_0^1$), 155.1–155.3 (m, C$_2^1$, C$_4^1$) ppm. Anal. Calcd for $C_{618}H_{462}N_{21}O_{45}P_{43}S_{22}$ (10,940): C, 67.85; H, 4.26; N, 2.69. Found: C, 67.32; H, 3.90; N, 2.25.

4.1.4.3. Compound 6-G$_4$. Yield 93%. ^{31}P {^{1}H} NMR ($CDCl_3$): δ=11.3 (d, $^{2}J_{PP}$=33.7 Hz, P_7), 13.0 (br d, $^{2}J_{PP}$=30.6 Hz, P_1, P_3, P_5), 49.1 (br d, $^{2}J_{PP}$=30.6 Hz, P_2, P_4, P_6), 49.6 (s, P_0), 50.9 (d, $^{2}J_{PP}$=33.7 Hz, P_8) ppm. ^{1}H NMR ($CDCl_3$): δ=7.1–7.5 (m, 822H, C_6H_5, C_6H_4, naphthyl), 7.60 (d, $^{3}J_{H5H6}$=7.9 Hz, 48H, H-C^5), 7.95 (d, $^{3}J_{H7H8}$=8.1 Hz, 48H, H-C^8) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$): δ=116.7 (d, $^{3}J_{CP8}$=3.8 Hz, C^2), 121.5–121.8 (m, C$_0^2$, C$_2^2$, C$_4^2$, C$_6^2$), 123.2 (s, C^8), 123.2 (br d, $^{1}J_{CP}$=111 Hz, C$_2^4$, C$_4^4$), 123.7 (br d, $^{1}J_{CP7}$=109.7 Hz, C$_6^4$), 123.9 (br s, C^4), 125.5 (br s, C^3, C^7), 126.0 (s, C^6), 127.3 (s, C^5), 127.7 (br d, $^{1}J_{CP1}$=106 Hz, C$_1^1$), 128.2 (br d, $^{1}J_{CP}$=106 Hz, C$_3^1$, C$_5^1$), 128.4 (d, $^{3}J_{CP8}$=13.5 Hz, C^9), 128.7 (br d, $^{1}J_{CP}$=105.7 Hz, C$_7^1$), 128.7 (d, $^{3}J_{CP}$=13.1 Hz, C$_1^3$, C$_3^3$, C$_5^3$, C$_7^3$), 132.4 (s, C$_1^4$, C$_3^4$, C$_5^4$, C$_7^4$), 132.5 (d, $^{2}J_{CP}$=11.0 Hz, C$_1^2$, C$_3^2$, C$_5^2$, C$_7^2$), 134.2 (d, $^{2}J_{CP}$=12.1 Hz, C$_0^3$, C$_2^3$, C$_4^3$, C$_6^3$), 134.6 (s, C^{10}), 148.3 (d, $^{2}J_{CP8}$=10.0 Hz, C^1), 153.4 (br m,

C_0^1), 155.1–155.7 (m, C_2^1, C_4^1, C_6^1) ppm. Anal. Calcd for $C_{1290}H_{918}N_{45}O_{93}P_{91}S_{46}$ (22,831): C, 67.86; H, 4.05; N, 2.76. Found: C, 67.29; H, 3.92; N, 2.37.

4.1.5. Synthesis of compound 9. A solution of 9-anthraldehyde **8** (2.80 g, 13.6 mmol) in THF (10 mL) was added to a solution of tris(1-methylhydrazino)thiophosphine **7** (1.1 g, 5.55 mmol) in THF (20 mL) at room temperature and stirred overnight. A precipitate was obtained; it was separated from the solution by filtration. The solution was recovered, and the precipitate was partly dissolved in 40 mL of THF (the trisubstitution product is insoluble). The resulting solution was combined with the previous one, and the solvent was removed under vacuum to afford **9** as a yellow powder in 73% yield.

^{31}P {^1H} NMR ($CDCl_3$): δ=75.5 (s) ppm. ^1H NMR ($CDCl_3$): δ=1.6 (br s, 2H, NH_2), 3.1 (d, $^3J_{HP}$=10 Hz, 3H, Me), 3.5 (d, $^3J_{HP}$=9 Hz, 6H, Me), 7.9, 7.95 (2s, 4H, CH=N, H anthryl), 7.1–7.4, 8.2–8.5 (m, 16H, H anthryl) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=33.2 (d, $^2J_{CP}$=8.5 Hz, Me), 41.6 (d, $^2J_{CP}$=11.5 Hz, Me), 125.6 (s, C^3), 126.5 (s, C^5), 128.0 (s, C^2), 128.5 (s, C^6), 129.1 (s, C^4), 130.3 (s, C^1), 131.9 (s, C^7), 135.8 (s, C^8), 136.5 (s, CH=N) ppm. Anal. Calcd for $C_{33}H_{31}N_6PS$ (574.7): C, 68.97; H, 5.44; N, 14.62. Found: C, 68.60; H, 4.17; N, 14.48.

4.1.6. Synthesis of dendrimer 10-G_2. A solution of dendrimer **1-G_1′** (2.80 g, 13.6 mmol) in THF (10 mL) was added to a solution of compound **9** (1.10 g, 5.55 mmol) in THF (20 mL). After stirring for 4 days at room temperature, the solvent was removed under reduced pressure to afford a powder, which was purified by column chromatography on silica gel with ethyl acetate as eluent. Dendrimer **10-G_2** was isolated as a yellow powder in 73% yield.

^{31}P {^1H} NMR ($CDCl_3$): δ=8.5 (s, P_0), 62.5 (s, P_1), 74.0 (s, P_2) ppm. ^1H NMR ($CDCl_3$): δ=3.0 (d, $^3J_{HP1}$=10.6 Hz, 18H, Me_1), 3.1 (d, $^3J_{HP}$=9.8 Hz, 36H, Me_2), 3.4 (d, $^3J_{HP}$=8.3 Hz, 72H, Me_3), 6.8–8.5 (m, 330H, CH=N, H Ar) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=32.7 (br d, $^2J_{CP}$=9.8 Hz, Me_{1-2-3}), 121.3 (s, C_0^2, C_1^2), 125.6 (s, C^3), 126.5 (s, C^5), 127.7 (s, C_0^3), 128.0 (s, C_1^3), 128.2 (s, C^2), 128.4 (s, C^6), 129.6 (s, C^4), 130.9 (s, C_0^4), 131.0 (s, C^1), 132.1 (s, C^7), 133.0 (s, C_1^4), 135.7 (d, $^3J_{CP1}$=10.2 Hz, C_1^5, C_2^5), 135.8 (s, C^8), 136.6 (d, $^3J_{CP1}$=10.4 Hz, C_0^5), 150.4 (d, $^2J_{CP1}$=7.9 Hz, C_0^1, C_1^1) ppm. Anal. Calcd for $C_{528}H_{456}N_{87}O_{18}P_{21}S_{18}$ (9536): C, 66.51; H, 4.82; N, 12.78. Found: C, 66.33; H, 4.67; N, 12.48.

4.1.7. General method for the synthesis of the series of dendrimers 13-G_n (n=1, 2, 3, and 4). A stoichiometric amount of pyrenemethylamine (freshly prepared from its chlorohydrate by reaction with KOH) in MeOH (10 mL) was added dropwise at room temperature to a solution of dendrimer **11-G_n′** (typically 100 mg) in THF (20 mL). The resulting solution was stirred at room temperature for 1 day (**G_1′**), 3 days (**G_2′**), 5 days (**G_3′**), or 7 days (**G_4′**) until the disappearance of the signal corresponding to the aldehydes in ^1H NMR. The solvent was evaporated to dryness to afford dendrimers **13-G_n** as white powders.

4.1.7.1. Compound 13-G_1. Yield 91%. ^{31}P {^1H} NMR ($CDCl_3$): δ=52.3 (s, P_0), 61.7 (s, P_1) ppm. ^1H NMR ($CDCl_3$): δ=3.3 (d, $^3J_{HP1}$=10.6 Hz, 9H, Me_1), 5.2 (s, 12H, CH_2), 7.2 (br d, $^3J_{HH}$=8.5 Hz, 18H, H-C_0^2, H-C_1^2), 7.5 (s, 3H, C_0^5), 7.6 (d, $^3J_{HH}$=8.6 Hz, 6H, H-C_0^3), 7.7 (d, $^3J_{HH}$=8.6 Hz, 12H, H-C_1^3), 7.8–8.30 (m, 60H, CH=N, pyrene) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=33.0 (d, $^2J_{CP1}$=13.1 Hz, Me_1), 62.2 (s, CH_2-Pyr), 121.5 (d, $^3J_{CP0}$=5.9 Hz, C_0^2), 121.6 (d, $^3J_{CP1}$=4.9 Hz, C_1^2), 123.3 (s, C^{13}), 124.8–125.2 (m, C^2, C^8, C^{10}, C^{15}, C^{16}), 125.9 (s, C^3), 126.7 (s, C^9), 127.0 (s, C^5), 127.4, 127.7 (2s, C^6, C^{12}), 128.4 (s, C_0^3), 128.8 (s, C^{14}), 129.5 (s, C_1^3), 130.7, 130.8 (2s, C^7, C^{11}), 131.2 (s, C^4), 132.5 (s, C_0^4), 132.6 (s, C^1), 133.6 (s, C_1^4), 138.6 (d, $^3J_{CP1}$=14.1 Hz, C_0^5), 151.2 (d, $^2J_{CP0}$=8.2 Hz, C_0^1), 152.4 (d, $^2J_{CP1}$=7.1 Hz, C_1^1), 160.6 (s, CH=N) ppm. Anal. Calcd for $C_{168}H_{120}N_{12}O_9P_4S_4$ (2703): C, 74.65; H, 4.47; N, 6.22. Found: C, 74.54; H, 4.19; N, 6.07.

4.1.7.2. Compound 13-G_2. Yield 93%. ^{31}P {^1H} NMR ($CDCl_3$): δ=52.0 (s, P_0), 61.3 (s, P_2), 61.6 (s, P_1) ppm. ^1H NMR ($CDCl_3$): δ=3.2 (m, 27H, Me_1, Me_2), 5.2 (br s, 24H, CH_2), 7.1–8.3 (m, 213H, pyrene, C_6H_4, CH=N) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=32.9 (d, $^2J_{CP1-2}$=12.8 Hz, Me_1, Me_2), 62.2 (s, CH_2-Pyr), 121.5 (d, $^3J_{CP0-1-2}$=3.4 Hz, C_0^2, C_1^2, C_2^2), 123.2 (s, C^{13}), 124.7–125.1 (m, C^2, C^8, C^{10}, C^{15}, C^{16}), 125.8 (s, C^3), 126.7 (s, C^9), 127.0 (s, C^5), 127.4, 127.6 (2s, C^6, C^{12}), 128.2 (s, C_0^3, C_1^3), 128.7 (s, C^{14}), 129.5 (s, C_2^3), 130.7, 130.8 (2s, C^7, C^{11}), 131.2 (s, C^4, C_1^4), 132.0 (s, C_0^4), 132.6 (s, C^1), 133.5 (s, C_2^4), 138.8 (d, $^3J_{CP0-1}$= 13.0 Hz, C_0^5, C_1^5), 151.3 (d, $^2J_{CP0-1}$=6.9 Hz, C_0^1, C_1^1), 152.3 (d, $^2J_{CP2}$=7.2 Hz, C_2^1), 160.6 (s, CH=N) ppm. Anal. Calcd for $C_{360}H_{264}N_{30}O_{21}P_{10}S_{10}$ (5977): C, 72.35; H, 4.45; N, 7.03. Found: C, 71.98; H, 4.32; N, 7.09.

4.1.7.3. Compound 13-G_3. Yield 94%. ^{31}P {^1H} NMR ($CDCl_3$): δ=51.7 (s, P_0), 61.2 (s, P_3), 61.5 (s, P_2), 61.8 (s, P_1) ppm. ^1H NMR ($CDCl_3$): δ=3.1 (m, 63H, Me_1, Me_2, Me_3), 5.2 (br s, 48H, CH_2), 7.1–8.3 (m, 441H, pyrene, C_6H_4, CH=N) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=32.9 (d, $^2J_{CP1-2-3}$=12.6 Hz, Me_1, Me_2, Me_3), 62.2 (s, CH_2-Pyr), 121.5 (d, $^3J_{CP0-1-2-3}$=3.4 Hz, C_0^2, C_1^2, C_2^2, C_3^2), 123.2 (s, C^{13}), 124.6–125.1 (m, C^2, C^8, C^{10}, C^{15}, C^{16}), 125.8 (s, C^3), 126.6 (s, C^9), 127.0 (s, C^5), 127.4, 127.6 (2s, C^6, C^{12}), 128.2 (s, C_0^3, C_1^3, C_2^3), 128.7 (s, C^{14}), 129.5 (s, C_3^3), 130.7, 130.8 (2s, C^7, C^{11}), 131.2 (s, C^4, C_2^4), 132.0 (s, C_0^4, C_1^4), 132.6 (s, C^1), 133.5 (s, C_3^4), 138.8 (d, $^3J_{CP0-1-2}$=12.5 Hz, C_0^5, C_1^5, C_2^5), 151.3 (d, $^2J_{CP0-1}$=6.1 Hz, C_0^1, C_1^1, C_2^1), 152.3 (d, $^2J_{CP3}$=7.3 Hz, C_3^1), 160.6 (s, CH=N) ppm. Anal. Calcd for $C_{744}H_{552}N_{66}O_{45}P_{22}S_{22}$ (12,524): C, 71.35; H, 4.44; N, 7.38. Found: C, 71.10; H, 4.17; N, 7.57.

4.1.7.4. Compound 13-G_4. Yield 93%. ^{31}P {^1H} NMR ($CDCl_3$): δ=51.7 (s, P_0), 61.2 (s, P_4), 61.5 (s, P_3), 61.9 (s, P_2), 62.2 (s, P_1) ppm. ^1H NMR ($CDCl_3$): δ=3.0 (m, 135H, Me_1, Me_2, Me_3, Me_4), 5.2 (br s, 96H, CH_2), 7.0–8.0 (m, 897H, pyrene, C_6H_4, CH=N) ppm. ^{13}C {^1H} NMR ($CDCl_3$): δ=32.7 (d, $^2J_{CP1-2-3-4}$=13.8 Hz, Me_1, Me_2, Me_3, Me_4), 62.2 (s, CH_2-Pyr), 121.5 (d, $^3J_{CP4}$=4.0 Hz, C_4^2), 121.8 (d, $^3J_{CP0-1-2-3}$=4.0 Hz, C_0^2, C_1^2, C_2^2, C_3^2), 123.2 (s, C^{13}), 124.7 (s, C^2, C^{15}, C^{16}), 125.0 (br s, C^8, C^{10}), 125.8 (s, C^3), 126.5 (s, C^9), 127.0 (s, C^5), 127.3, 127.5 (2s, C^6, C^{12}), 128.2 (br s, C_0^3, C_1^3, C_2^3, C_3^3), 128.6 (s, C^{14}), 129.5 (s, C_4^3), 130.5, 130.6 (2s, C^7, C^{11}), 131.1 (s, C_3^4), 131.2 (s, C^4), 132.0 (s, C_0^4, C_1^4, C_2^4), 132.6 (s, C^1), 133.5 (s, C_4^4), 138.6–139.5 (m, C_0^5, C_1^5, C_2^5, C_3^5), 150.3 (d, $^2J_{CP0-1-2-3}$=7.4 Hz,

C_0^1, C_1^1, C_2^1, C_3^1), 151.3 (d, $^2J_{CP4}$=7.4 Hz, C_4^1), 160.5 (s, CH=N) ppm. Anal. Calcd for $C_{1512}H_{1128}N_{138}O_{93}P_{46}S_{46}$ (25,618): C, 70.89; H, 4.44; N, 7.54. Found: C, 70.64; H, 4.19; N, 7.38.

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Catalytic imino Diels–Alder reaction by triflic imide and its application to one-pot synthesis from three components

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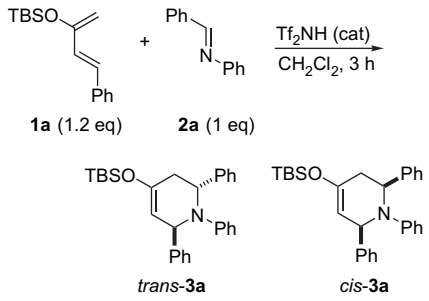
Abstract—An imino Diels–Alder reaction of 2-siloxydienes with aldimines catalyzed by triflic imide (Tf_2NH; 0.1∼10 mol % amount) has been developed leading to substituted piperidin-4-ones. Tf_2NH catalyst is compatible with basic functions, such as pyridine and indole rings in the imino Diels–Alder reaction. Furthermore, X-ray crystallographic analysis indicates that *trans*-2,6-diphenyl-4-piperidinone **4a** obtained by this reaction has a unique conformation in the solid state.

1. Introduction

The piperidine ring system is a ubiquitous structural motif of naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.[1] The imino Diels–Alder reaction is one of the most powerful and useful tools used to prepare heterocycles containing the piperidine nucleus.[2,3] There have been many studies on the imino Diels–Alder reaction, which is typically classified into two variants. One is the reaction of all-carbon 1,3-dienes (C=C–C=C synthon) with imines (C=N synthon). The other is the cycloaddition of azadienes (C=N–C=C or N=C–C=C synthons) with dienophilic alkenes (C=C synthon). The former strategy has been more extensively studied because a variety of imine dienophiles are readily available by the reaction of corresponding aldehydes or ketones with amines. The literature contains many studies of the imino Diels–Alder reaction of imines with Danishefsky's dienes (1-alkoxy-3-siloxybutadienes)[4] to give 2,3-dehydropiperidin-4-ones. Numerous kinds of Lewis acids,[5] including chiral catalysts and Brønsted acids[6] have been developed in the reaction of Danishefsky's dienes. On the contrary, few studies have focused on the reaction of less active 2-siloxydienes with imines, which affords substituted piperidin-4-ones (Scheme 1).[7,8] Although several Lewis acids have been found to activate the imino Diels–Alder reaction of 2-siloxydienes, to the best of our knowledge, the Brønsted acid-catalyzed reaction has not been reported yet.[9] Substituted piperidin-4-one produced in the above reaction would be useful in medicinal chemistry.[10]



Scheme 1.

We have recently reported that triflic imide (Tf_2NH) works as a good catalyst for (2+2)-cycloaddition of silyl enol ethers with α,β-unsaturated esters even in low catalyst loading (∼1 mol %).[11] Furthermore, we have found that Tf_2NH also catalyzes various cycloaddition reactions, such as (2+2)-cycloaddition of allylsilane with acrylates,[12] and the Diels–Alder reaction of 2-siloxydiene and α,β-unsaturated carbonyl compounds.[13,14] In these contexts, silyl triflic imides (R_3SiNTf_2), which are generated from Tf_2NH and silyl enol ether substances, act as an active catalyst of the above cycloadditions.[10,11,14b] Herein, we report the Tf_2NH-catalyzed imino Diels–Alder reaction of 2-siloxydiene with aldimine to give functionalized piperidin-4-one derivatives and its application to the one-pot synthesis of piperidin-4-ones from 2-siloxydiene, aldehyde, and amine.

Keywords: Imino Diels–Alder reaction; Substituted piperidines; Triflic imide; Three component reaction.
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2. Results and discussion

2.1. Imino Diels–Alder reaction of 2-siloxydienes with aldimines

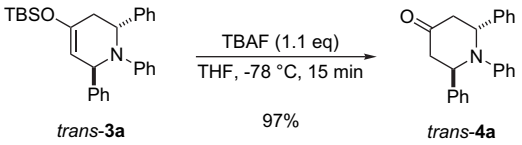
At the outset of this study, the imino Diels–Alder reaction of 2-siloxy-1,3-butadiene **1a** (1.2 equiv) with benzaldimine (**2a**) (1.0 equiv) in the presence of Tf_2NH was examined under various conditions (Scheme 1). With a 2 mol % of Tf_2NH in CH_2Cl_2 at ambient temperature, a diastereomeric mixture of 2,6-diphenyl-4-siloxy-3,4-didehydropiperidine **3a** was obtained in 85% yield, and the diastereomeric ratio was determined to be 4:1 (trans–cis) by ^1H NMR (Table 1, entry 1), whereas no reaction occurred in the absence of the catalyst (entry 2). It is noteworthy that the reaction proceeds smoothly even with 0.1 mol % catalyst loading (entry 3). However, when a stoichiometric amount of Tf_2NH was used, decomposition of siloxydiene owing to its protodesilylation was observed prior to promotion of the desired cycloaddition (entry 4). The Tf_2NH-catalyzed reaction can be successfully performed in various solvents, such as toluene, THF, and acetonitrile (entries 5–7), and the diastereomeric ratio of **3a** was similar within a range of 3:1–4:1 in these solvents. When the reaction of **1a** with **2a** was conducted in CH_3CN, **3a**, which is hardly soluble in the solvent, precipitated. It is noteworthy that **3a** can be isolated with ease only by filtration even in a multi-gram scale (entry 7). The reaction temperature does not affect the diastereomeric ratio, and no desired product was obtained at high temperature (80 °C in a sealed tube) (entries 8 and 9).

The major diastereomer of **3a** was almost quantitatively converted into piperidin-4-one **4a**, which could be crystallized from CH_2Cl_2–hexanes, by treatment with TBAF at −78 °C (Scheme 2). Neither epimerization nor retro-Michael reaction was observed in the process. X-ray crystallographic analysis determined that compound **4a**, derived from the major diastereomer of **3a**, possesses trans-oriented 2,6-substituents (Fig. 1). Fascinatingly, the crystallized form of *trans*-**4a** exists as an unusual conformation. Namely, both phenyl substituents at the C(2) and C(6) positions are oriented axially, and the conformation of the six-membered piperidine ring is a twist-boat form. Three continuous bulky phenyl substituents at N(1), C(2), and C(6) of *trans*-**4a** would prevent the chair-conformation with equatorially oriented bulky substituents at C(2) and C(6).

Table 1. Imino Diels–Alder reaction of **1a** with **2a**

Entry	Cat. (mol %)	Solvent	Temp (°C)	Time (h)	% Yield (trans–cis)[b]
1	Tf_2NH (2.0)	CH_2Cl_2	rt	3	85 (80:20)
2	None	CH_2Cl_2	rt	72	0 (—)
3	Tf_2NH (0.1)	CH_2Cl_2	rt	3	80 (75:25)
4	Tf_2NH (100)	CH_2Cl_2	rt	3	0 (—)
5	Tf_2NH (2.0)	THF	rt	3	69 (63:37)
6	Tf_2NH (2.0)	Toluene	rt	3	82 (67:33)
7	Tf_2NH (2.0)	CH_3CN	rt	0.3	75 (82:18)
8	Tf_2NH (2.0)	CH_2Cl_2	−78	3	61 (79:21)
9[a]	Tf_2NH (2.0)	CH_2Cl_2	80	3	0 (—)

[a] Reaction was carried out in a sealed tube.
[b] Diastereomeric ratios were determined by ^1H NMR.



Scheme 2.

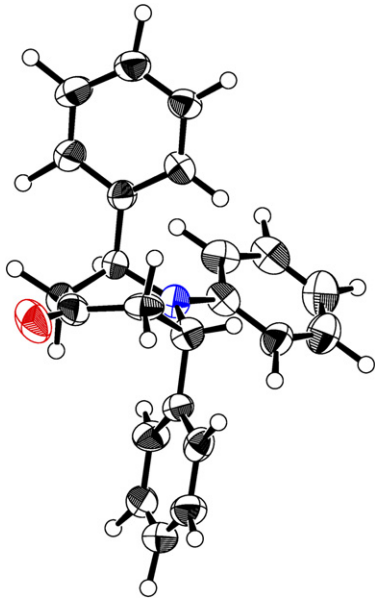
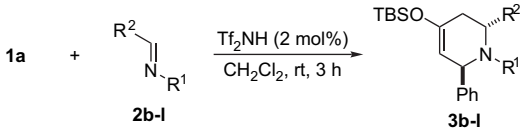


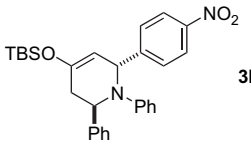
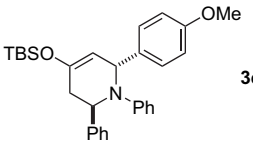
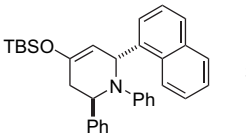
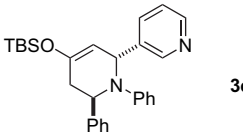
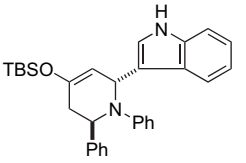
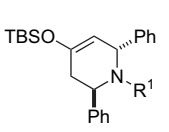
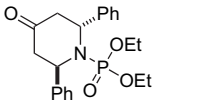
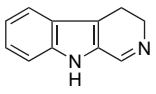
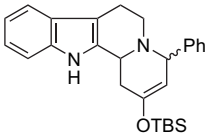
Figure 1. Crystallographic structure of *trans*-**4a** (ORTEP drawing).

Next, the imino Diels–Alder reactions of **1a** with various aldimines **2b**–**2l** under optimal conditions (2 mol % Tf_2NH, CH_2Cl_2, rt) were examined (Scheme 3). Electron-poor (**2b**), electron-rich aromatic (**2c**), and naphthyl substituted (**2d**) aldimines also afforded desired adducts in good yields with a similar stereoselectivity (Table 2, entries 1–3). Substrates with a heterocyclic ring, such as pyridine (**2e**) and indole (**2f** and **2l**), underwent cycloaddition in the presence of Tf_2NH, but their reaction rates were decreased (entries 4, 5, and 11). No protection is necessary for indole N–H in the Tf_2NH-catalyzed reaction (entries 5 and 11). Further studies revealed that aldimines obtained from benzylamine (**2g**) and allylamine (**2h**) afforded the corresponding piperidinone derivatives **3g** and **3h** in good yields, respectively (entries 6 and 7). On the contrary, electrophilic aldimines, which possess an electron-withdrawing function on the nitrogen atom, afforded poor results. Reaction with acyl imine **2i** and sulfonyl imine **2j** resulted in the formation of many side products although trace amounts of cycloadducts **3i** and **3j**, respectively, were produced (entries 8 and 9). The strongly electrophilic imines, such as **2i** and **2j**, may be too reactive to selectively promote the desired cycloaddition in the presence of the Tf_2NH catalyst. Phosphonyl imine **2k** promoted the imino Diels–Alder reaction. However, desilylated piperidinone **4k** was obtained in a moderate yield (entry 10) because of the



Scheme 3.

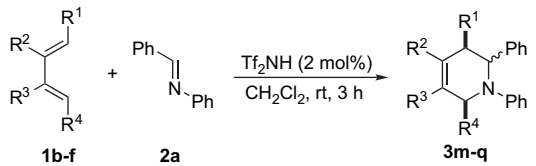
Table 2. Imino Diels–Alder reaction of **1a** with various aldimines

Entry	Imine **2**	Product	% Yield (trans–cis)[e]
1	**2b** (Ph, *p*-$NO_2C_6H_4$)	 **3b**	85 (75:25)
2	**2c** (Ph, *p*-$MeOC_6H_4$)	 **3c**	67 (77:23)
3	**2d** (Ph, 1-naphthyl)	 **3d**	73 (84:16)
4[a]	**2e** (Ph, 3-pyridyl)	 **3e**	61 (73:27)
5[b]	**2f** (Ph, 3-indolyl)	 **3f**	35 (81:19)
6[c]	**2g** (Bn, Ph)	 **3g** (R^1 = Bn)	89 (85:15)
7[c]	**2h** (Allyl, Ph)	**3h** (R^1 = allyl)	88 (80:20)
8	**2i** (CO_2Et, Ph)	**3i** (R^1 = CO_2Et)	Trace (—)
9	**2j** (Ts, Ph)	**3j** (R^1 = Ts)	32 (89:11)
10	**2k** ($PO(OEt)_2$, Ph)	 **4k**	62 (63:37)
11[d]	 **2l**	 **3l**	60 (60:40)[f]

[a] Cat. 5 mol %, 5 h.
[b] Cat. 6 mol %, 24 h.
[c] Cat. 5 mol %
[d] Cat. 10 mol %, CH_3CN, 8 h.
[e] Diastereomeric ratios were determined by ^1H NMR.
[f] Stereochemistry of each diastereomer was not assigned.

poor stability of the corresponding silyl enol ether **3k** (the reason is still unclear).

Results of the imino Diels–Alder reaction of various 2-siloxydienes **1b–1e** and 2-methoxydiene **1f** with aldimine **2a** to give a variety of substituted piperidin-4-ones are summarized in Scheme 4 and Table 3. Whereas 3-methyl-2-siloxydiene **1b** efficiently reacted (86% yield, entry 1), reactions with 1-methyl-2-siloxydiene **1c** and 2-*tert*-butyldimethylsiloxy-1,3-butadiene (**1d**) required 5 mol % of catalyst for complete consumption of aldimine **2a** (entries 2 and 3). Notably, *trans*-**3n** was exclusively obtained as a sole diastereomer in 69% yield, although a mixture of the geometrical isomer (cis–trans=ca. 5:2) of **1c** was conducted in the reaction



Scheme 4.

Table 3. Imino Diels–Alder reaction of **2a** with various dienes

Entry	Diene (R^1, R^2, R^3, R^4)	Cat. (mol %)	Product	% Yield (dr)[a]
1	**1b** (H, OTBS, Me, H)	2	**3m**	86
2	**1c** (Me, OTBS, H, H)	5	**3n**	69 (100:0)[b]
3	**1d** (H, OTBS, H, H)	5	**3o**	69
4	**1e** (H, OTBS, H, OMe)	2	**3p**	0 (—)
5	**1f** (H, OMe, H, Ph)	2	**3q**	48 (79:21)[c]

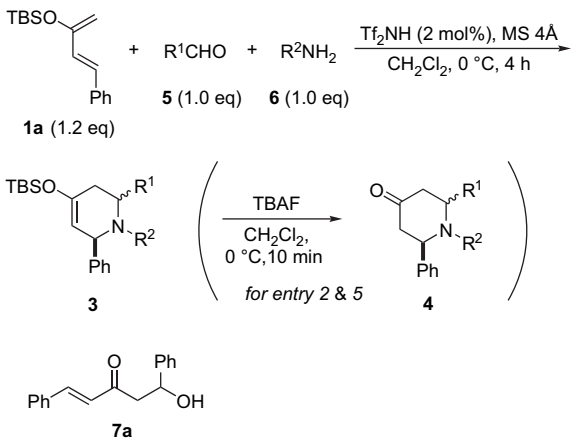
[a] Diastereomeric ratios were determined by ^{1}H NMR.
[b] The relative configuration of the major diastereomer was assigned as *trans*-**3n** because both protons at C(5) and C(6) exist on an equatorial position ($J_{[H(C5)–H(C6)]}$=3.1 Hz in ^{1}H NMR).
[c] The relative configuration of major diastereomer was tentatively assigned as *trans*-**3q** by an analogy to **3a**.

(entry 3). The mechanistic detail including the stereochemical outcome is under investigation. Danishefsky diene **1e** was evaluated as a more electron-rich diene partner, but only decomposition of **1e** by Tf_2NH was observed (entry 4).

We initially considered that the actual catalyst of the imino Diels–Alder reaction would be R_3SiNTf_2, which is formed from Tf_2NH and siloxydiene in situ.[11] However, the reaction of 2-methoxydiene **1f** occurred in the presence of 2 mol % of catalyst to give **3q** in moderate yield (entry 5). This observation indicates that Tf_2NH (pK_a=1.7 in water)[15] directly activates aldimines as a Brønsted acid in the imino Diels–Alder reaction. The action of the Tf_2NH catalyst in the reaction is different from that in the (2+2)-cycloaddition, which was recently established by our group.[11] The following experiment also suggests the catalytic role of Tf_2NH. Thus, when the mixture of **1a** and **2a** was treated with pre-organized $TBSTf_2$ (50 mol %), which was prepared from TBSCl and $AgNTf_2$ in CH_2Cl_2, decomposition of silyl enol ether **1a** quickly occurred prior to imino Diels–Alder reaction with **2a**.

2.2. Application to multicomponent reaction

We have further assessed the one-pot multicomponent reaction (MCR) for the formation of substituted piperidin-4-ones derivatives starting from three components: siloxydiene **1**, aldehyde **5**, and amine **6** (Scheme 5).[16] When a mixture of the whole substrates, **1a**, benzaldehyde (**5a**), and aniline (**6a**) (molar ratio: **1a**:**5a**:**6a**=1.2:1:1), was treated with Tf_2NH (2 mol %), the desired MCR product **3a** was isolated in ca. 20% yield, but the major product was an aldol adduct



Scheme 5.

7a (ca. 60% yield). The result suggests that the undesired reaction of aldehyde **5** with silyl enol ether **1** (Mukaiyama-aldol reaction) competes with imine formation of **5** with amine **6**. On the other hand, sequential addition of the substrates as an alternative protocol was successful (Table 4, entry 1). Namely, after pre-treatment with aldehyde **5a** and amine **6a** in the presence of molecular sieves 4 Å (MS4A) in CH_2Cl_2 for 20 min at ambient temperature, siloxydiene **1a** and Tf_2NH (4 mol %) were added to the resulting mixture at 0 °C to give the desired product **3a** selectively in 78% yield (no formation of **7a** was observed). After completion of the above three component reaction, successive treatment with tetrabutylammonium fluoride (TBAF) in one-pot furnished piperidinone **4b** in a good yield (entry 2). The MCR using aliphatic amine **6b** instead of aromatic amine **6a** also successfully afforded **3g** in good yield (entry 3). On the contrary, the reaction of aliphatic aldehyde **5b** resulted in a poor yield of **3r**[7a] under similar conditions (entries 4 and 5). This is possibly due to the instability of the corresponding imine derived from **5b** and **6b** in the presence of Tf_2NH (Scheme 6).[17]

Table 4. Three component syntheses of **3** and **4**

Entry	Aldehyde	Amine	Product	% Yield (trans–cis)[c]
1	**5a** (PhCHO)	**6a** ($PhNH_2$)	**3a**	78 (80:20)
2[a]	**5a** (PhCHO)	**6a** ($PhNH_2$)	**4a**	72 (82:18)
3	**5a** (PhCHO)	**6b** ($BnNH_2$)	**3g**	74 (80:20)
4[b]	**5b** (^{i}PrCHO)	**6b** ($BnNH_2$)	**3r**	16 (ND[d])
5[a,b]	**5b** (^{i}PrCHO)	**6b** ($BnNH_2$)	**4r**	15 (68:32)

[a] One-pot process involving three component reaction and desilylation was carried out.
[b] Cat. 6 mol %, 24 h.
[c] Diastereomeric ratios were determined by ^{1}H NMR.
[d] ND means 'not determined'.

3. Conclusion

In summary, we have demonstrated that triflic imide (Tf_2NH) works as an effective catalyst for the imino Diels–Alder reaction of 2-siloxydienes and aldimines as well as the three component reaction. Tf_2NH catalyst is compatible for basic functions, such as pyridine and indole rings in the imino Diels–Alder reaction. In the reaction, Tf_2NH would directly activate the imine partner as a Brønsted acid to promote the imino Diels–Alder reaction. It is clearly different from catalytic (2+2)-cycloaddition, in which Lewis acidic silyl triflic imides, generated from Tf_2NH and silylated substrates, act as a real catalyst. Furthermore, X-ray crystallographic analysis indicates that the obtained *trans*-2,6-diphenylpiperidin-4-one **4a** has a unique conformation in the solid state.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere. Anhydrous THF and CH_2Cl_2 were purchased from the Kanto Chemical Co., Inc. Unless otherwise described, other materials were obtained from commercial suppliers and used without further purification. Column chromatography was

performed on Merck silica gel 60 N (230–400 mesh), and flash column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Reactions and chromatography fractions were analyzed employing precoated silica gel plate (Merck silica gel $60F_{254}$). All melting points were determined on Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured on Shimadzu FTIR-8300 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on JEOL AL 400 (400 and 100 MHz) and Varian Gemini 2000 (300 and 75 MHz), respectively, as $CDCl_3$ solutions, and were reported in parts per million downfield from TMS (δ=0) for the ^1H NMR and relative to the central $CDCl_3$ resonance (δ=77.00) for the ^{13}C NMR. Mass spectra were recorded on JEOL DX-303 or AX-500 spectrometer. Elemental analyses were performed on Yanagimoto MT-3 or YANACO CHN CORDER MT-6, and the results (C, H) were within ±0.4% of theoretical values. X-ray crystallographic analysis was performed on Rigaku R-AXIX RAPID.

4.2. General procedure for imino Diels–Alder reaction in the presence of Tf_2NH

To a solution of 2-siloxydiene **1** (1.2 equiv) and aldimine **2** (1.0 equiv) in CH_2Cl_2 (1.0 M) was added Tf_2NH (0.08 M toluene solution, 2–10 mol %) dropwise at ambient temperature. The reaction mixture was stirred for an appropriate time, and then was quenched with saturated $NaHCO_3$ aq. The mixture was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using hexane–AcOEt (including 1% NEt_3) as an eluent to give **3** as a diastereomeric mixture. Several compounds were recrystallized from MeOH to give its *trans*-**3** as a single diastereomer.

4.2.1. *trans*-4-(*tert*-Butyldimethylsiloxy)-1,2,6-triphenyl-3,4-didehydropiperidine (*trans*-3a). Colorless needles. Mp 125–127 °C; IR (KBr) 2930, 1680, 1599, 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.14 (m, 10H), 6.99 (dd, *J*=8.7, 7.5 Hz, 2H), 6.63 (m, 3H), 5.24 (d, *J*=5.3 Hz, 1H), 5.19 (m, 2H), 3.02 (ddt, *J*=16.2, 5.8, 1.9 Hz, 1H), 2.45 (dd, *J*=16.2, 3.6 Hz, 1H), 0.80 (s, 9H), −0.03 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.4, 144.6, 142.8, 128.6, 128.5, 128.2, 127.3, 126.7, 126.6, 126.4, 118.4, 117.8, 106.9, 60.3, 58.0, 37.1, 25.4, 17.8, −4.7, −4.9; LRMS *m*/*z* 441 (M^+); Anal. Calcd for $C_{29}H_{35}NOSi$: C, 78.86; H, 7.99; N, 3.17. Found: C, 78.59; H, 8.00; N, 3.07.

4.2.2. *cis*-4-(*tert*-Butyldimethylsiloxy)-1,2,6-triphenyl-3,4-didehydropiperidine (*cis*-3a). The compound could not be isolated in a pure form. The ^1H NMR spectrum was assigned from a mixture of *trans*-**3a** and *cis*-**3a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.02 (m, 10H), 6.89 (t, *J*=8.3 Hz, 2H), 6.76 (d, *J*=8.3 Hz, 2H), 6.72 (d, *J*=8.3 Hz, 1H), 4.98 (t, *J*=1.9 Hz, 1H), 4.71 (d, *J*=1.9 Hz, 1H), 4.66 (dd, *J*=9.8, 3.9 Hz, 1H), 2.71 (ddt, *J*=16.8, 9.8, 1.9 Hz, 1H), 2.40 (ddt, *J*=16.8, 3.9, 1.7 Hz, 1H), 0.91 (s, 9H), −0.15 (s, 6H).

4.2.3. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-nitrophenyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3b). Colorless needles. Mp 139–140 °C; IR (KBr) 2955, 1681, 1597, 1518, 1346, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.29–7.25 (m, 4H), 7.21–7.17 (m, 1H), 7.01 (t, *J*=7.8 Hz, 2H), 6.69 (t, *J*=7.1 Hz, 1H), 6.58 (d, *J*=8.5 Hz, 2H), 5.27–5.22 (m, 2H), 5.18 (dd, *J*=4.9, 1.5 Hz, 1H), 3.06 (dd, *J*=16.1, 5.4 Hz, 1H), 2.43 (dd, *J*=16.6, 4.1 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.8, 143.6, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 126.8, 126.4, 126.1, 123.5, 119.2, 118.0, 106.7, 60.3, 57.9, 37.0, 25.5, 17.9, −4.4, −4.5; LRMS *m*/*z* 486 (M^+); Anal. Calcd for $C_{29}H_{34}N_2O_3Si$: C, 71.57; H, 7.04; N, 5.76. Found: C, 71.40; H, 7.14; N, 5.59.

4.2.4. *cis*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-nitrophenyl)-1,2-diphenyl-3,4-didehydropiperidine (*cis*-3b). Pale yellow oil. IR (neat) 2930, 1680, 1597, 1521, 1346, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J*=8.7 Hz, 2H), 7.48 (d, *J*=8.7 Hz, 2H), 7.25–7.15 (m, 5H), 6.96 (t, *J*=8.0 Hz, 2H), 6.82 (t, *J*=7.5 Hz, 1H), 6.77 (d, *J*=8.0 Hz, 2H), 5.02 (t, *J*=2.4 Hz, 1H), 4.81 (dd, *J*=9.9, 3.9 Hz, 1H), 4.72 (d, *J*=1.9 Hz, 1H), 2.69 (ddt, *J*=16.4, 9.4, 2.4 Hz, 1H), 2.42 (dd, *J*=16.4, 3.6 Hz, 1H), 0.96 (s, 9H), 0.21 (s, 3H), 0.03 (s, 3H); LRMS *m*/*z* 486 (M^+); HRMS *m*/*z* 486.2316 (calcd for $C_{29}H_{34}N_2O_3Si$: 486.2339).

4.2.5. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(*p*-methoxyphenyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3c). Colorless oil. IR (neat) 2930, 1681, 1597, 1510, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.09 (m, 4H), 7.04–6.99 (m, 3H), 6.92 (d, *J*=8.8 Hz, 2H), 6.84 (t, *J*=8.8 Hz, 2H), 6.60 (d, *J*=8.8 Hz, 2H), 6.48 (t, *J*=6.3 Hz, 1H), 5.02–4.99 (m, 2H), 4.96 (t, *J*=4.6 Hz, 1H), 3.59 (s, 3H), 2.82 (dd, *J*=16.3, 5.6 Hz, 1H), 2.27 (dd, *J*=16.3, 3.9 Hz, 1H), 0.67 (s, 9H), −0.16 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 147.9, 147.5, 144.4, 129.0, 128.5, 128.4, 127.9, 127.8, 126.5, 126.4, 118.6, 113.5, 113.3, 106.9, 60.2, 57.7, 55.2, 37.2, 25.6, 14.7, −4.5; LRMS *m*/*z* 471 (M^+); HRMS *m*/*z* 471.2580 (calcd for $C_{30}H_{37}NO_2Si$: 471.2594).

4.2.6. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(1-naphthyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3d). Colorless crystals. Mp 159–160 °C; IR (KBr) 2928, 1686, 1597, 1502, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.92 (m, 1H), 7.88–7.85 (m, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.42 (d, *J*=7.0 Hz, 2H), 7.36 (t, *J*=7.5 Hz, 2H), 7.30–7.25 (m, 2H), 7.08 (d, *J*=7.0 Hz, 1H), 6.92 (dd, *J*=7.5, 7.2 Hz, 2H), 6.62 (t, *J*=7.2 Hz, 1H), 6.49 (d, *J*=8.0 Hz, 2H), 5.87 (t, *J*=5.1 Hz, 1H), 5.43 (d, *J*=5.8 Hz, 1H), 5.34 (dd, *J*=5.8, 1.9 Hz, 1H), 2.96 (dd, *J*=15.9, 5.8 Hz, 1H), 2.60 (dd, *J*=15.9, 4.3 Hz, 1H), 0.71 (s, 9H), −0.11 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.1, 144.5, 137.7, 133.9, 131.0, 129.0, 128.7, 128.3, 127.6, 126.7, 126.5, 126.0, 125.3, 125.2, 122.9, 118.3, 117.3, 105.9, 61.3, 54.0, 35.0, 25.5, 17.8, −4.5, −4.8; LRMS *m*/*z* 491 (M^+); Anal. Calcd for $C_{33}H_{37}NOSi$: C, 80.60; H, 7.58; N, 2.85. Found: C, 80.55; H, 7.62; N, 2.80.

4.2.7. *trans*-4-(*tert*-Butyldimethylsiloxy)-1,2-diphenyl-6-(3-pyridyl)-3,4-didehydropiperidine (*trans*-3e). Colorless crystals. Mp 116–117 °C; IR (KBr) 2945, 1678, 1597, 1504, 1371, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 8.45 (d, J=2.2 Hz, 1H), 8.42 (dd, J=4.6, 1.4 Hz, 1H), 7.46 (dt, J=8.0, 1.9 Hz, 1H), 7.30–7.24 (m, 4H), 7.19–7.12 (m, 2H), 7.00 (dd, J=8.7, 7.2 Hz, 2H), 6.67 (t, J=7.2 Hz, 1H), 6.61 (d, J=8.9 Hz, 2H), 5.20 (dd, J=5.6, 4.1 Hz, 1H), 5.17 (s, 2H), 3.05 (dd, J=16.4, 5.8 Hz, 1H), 2.42 (dd, J=16.4, 3.9 Hz, 1H), 0.81(s, 9H), 0.00 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.1, 147.2, 146.9, 143.7, 137.8, 134.9, 128.5, 126.7, 126.4, 123.0, 119.3, 118.5, 106.9, 60.1, 56.4, 36.9, 25.5, 17.9, −4.4, −4.6; LRMS m/z 442 (M^+); HRMS m/z 442.2440 (calcd for $C_{28}H_{34}N_2OSi$: 442.2440).

4.2.8. *trans*-4-(*tert*-Butyldimethylsiloxy)-6-(3-indolyl)-1,2-diphenyl-3,4-didehydropiperidine (*trans*-3f). Colorless crystals. Mp 144–145 °C; IR (KBr) 1684, 1595, 1502, 1373, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.33 (d, J=7.1 Hz, 2H), 7.27–7.04 (m, 6H), 6.95–6.87 (m, 4H), 6.67–6.61 (m, 3H), 5.29 (t, J=4.9 Hz, 1H), 5.11 (dd, J=4.1, 1.7 Hz, 1H), 5.02 (d, J=4.1 Hz, 1H), 2.87–2.82 (m, 1H), 2.48 (dd, J=16.6, 4.9 Hz, 1H), 0.77 (s, 9H), −0.03 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 144.4, 136.0, 128.3, 128.1, 127.1, 126.5, 122.5, 121.8, 120.3, 119.6, 119.3, 119.2, 116.7, 110.8, 106.6, 60.0, 51.9, 35.3, 25.6, 18.0, −4.4; LRMS m/z 480 (M^+); Anal. Calcd for $C_{31}H_{36}N_2OSi$: C, 77.45; H, 7.55; N, 5.83. Found: C, 77.64; H, 7.59; N, 5.71.

4.2.9. *trans*-1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2,6-diphenyl-3,4-didehydropiperidine (*trans*-3g). Colorless oil. IR (neat) 2928, 1665, 1371, 1256, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–6.92 (m, 15H), 4.83 (d, J=3.9 Hz, 1H), 4.02 (d, J=3.9 Hz, 1H), 3.83 (dd, J=8.5, 5.6 Hz, 1H), 3.22 (d, J=13.6 Hz, 1H), 3.11 (d, J=13.6 Hz, 1H), 2.25 (m, 2H), 0.74 (s, 9H), −0.21 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 144.1, 141.5, 140.3, 128.9, 128.7, 128.4, 128.2, 128.0, 127.9, 127.0, 126.8, 104.5, 59.3, 54.8, 50.8, 31.3, 25.9, 25.7, 18.2, −4.0, −4.1; LRMS m/z 379 (M^+); HRMS m/z 455.2656 (calcd for $C_{30}H_{37}NOSi$: 455.2644).

4.2.10. *trans*-1-Allyl-4-(*tert*-butyldimethylsiloxy)-2,6-diphenyl-3,4-didehydropiperidine (*trans*-3h). Colorless oil. IR (neat) 2928, 1666, 1362, 1171 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.20 (m, 10H), 5.90–5.83 (m, 1H), 5.14 (dd, J=17.1, 1.7 Hz, 1H), 5.09 (dd, J=7.5, 1.7 Hz, 1H), 4.39 (br s, 1H), 4.06 (t, J=7.2 Hz, 1H), 2.92 (dd, J=14.0, 7.0 Hz, 1H), 2.84 (dd, J=14.0, 5.3 Hz, 1H), 2.43 (d, J=7.2 Hz, 1H), 1.28–1.26 (m, 2H), 0.98 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 144.1, 141.5, 137.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 126.7, 126.6, 116.6, 104.4, 59.1, 54.7, 49.8, 31.1, 25.8, −4.3; LRMS m/z 405 (M^+); Anal. Calcd for $C_{26}H_{35}NOSi$: C, 76.98; H, 8.70; N, 3.45. Found: C, 76.78; H, 8.69; N, 3.21.

4.2.11. *trans*-4-(*tert*-Butyldimethylsiloxy)-2,6-diphenyl-1-(*p*-toluenesulfonyl)-3,4-didehydropiperidine (*trans*-3j). Colorless crystals. Mp 124–126 °C; IR (neat) 1346, 1159, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 7.10 (t, J=3.9 Hz, 2H), 7.00 (dd, J=8.0, 2.2 Hz, 2H), 6.95–6.89 (m, 6H), 5.69 (t, J=2.4 Hz, 1H), 5.31 (d, J=6.8 Hz, 1H), 4.99 (dd, J=4.1, 2.4 Hz, 1H), 2.45 (s, 3H), 2.40 (dd, J=17.4 Hz, 1H), 2.04 (ddt, J=17.4, 7.2, 2.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 143.3, 140.3, 138.4, 138.1, 129.9, 129.8, 128.2, 127.8, 127.5, 127.1, 102.8, 55.2, 52.8, 28.7, 25.7, 25.6, 18.0, −4.6; LRMS m/z 519 (M^+); HRMS m/z 519.2233 (calcd for $C_{30}H_{37}NO_3SSi$: 519.2263).

4.2.12. *trans*-1-(Diethoxyphosphonyl)-2,6-diphenyl-4-piperidone (*trans*-4k). Colorless needles (from hexane–AcOEt). Mp 92–94 °C; IR (neat) 3206, 1686, 1649, 1613, 1227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 3H), 7.39–7.21 (m, 7H), 6.64 (d, J=16.2 Hz, 1H), 4.79–4.71 (m, 1H), 4.06–3.92 (m, 4H), 3.79–3.70 (m, 2H), 3.27 (ds, J=16.2, 6.0 Hz, 1H), 3.15 (dd, J=16.2, 6.0 Hz, 1H), 1.28 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 143.4, 142.7, 134.2, 130.7, 128.9, 128.5, 128.3, 127.3, 126.4, 126.1, 62.5, 62.3, 52.5, 48.4, 16.3, 15.9; LRMS m/z 388 (M^++H); Anal. Calcd for $C_{21}H_{26}NO_4P$: C, 65.11; H, 6.76; N, 3.62. Found: C, 65.15; H, 6.64; N, 3.60.

4.2.13. 2-(*tert*-Butyldimethylsiloxy)-4-phenyl-1,4,6,7,12,12b-hexahydroindolo[2,3a]quinolizine (3l). Pale brown solids (major diastereomer). Mp 155–157 °C; IR (neat) 2930, 1674, 1454, 1201, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.35–7.15 (m, 7H), 7.03–6.94 (m, 2H), 4.91 (d, J=3.4 Hz, 1H), 4.52 (d, J=5.0 Hz, 1H), 4.13 (q, J=5.0 Hz, 1H), 3.06 (m, 1H), 2.83 (m, 1H), 2.59 (d, J=14.5 Hz, 1H), 2.43 (dd, J=16.4, 4.8 Hz, 1H), 2.36–2.24 (m, 2H), 0.85 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 139.9, 136.3, 135.0, 129.9, 128.0, 127.7, 127.5, 121.6, 119.5, 118.2, 110.7, 108.3, 105.2, 63.1, 48.2, 35.5, 25.7, 21.3, 18.0, −4.1, −4.2; LRMS m/z 430 (M^+); HRMS m/z 430.2455 (calcd for $C_{27}H_{34}N_2OSi$: 430.2440).

Colorless oil (minor diastereomer). IR (neat) 3418, 2972, 1672, 1452, 1163, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.46–7.06 (m, 9H), 4.77 (s, 1H), 4.03 (s, 1H), 3.90 (d, J=10.1 Hz, 1H), 2.97 (dd, J=11.4, 4.8 Hz, 1H), 2.77–2.68 (m, 1H), 2.63–2.46 (m, 3H), 2.37 (td, J=11.4, 3.9 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 144.4, 136.6, 134.7, 128.7, 128.4, 128.3, 127.7, 127.2, 126.8, 121.5, 119.5, 118.2, 110.7, 109.0, 67.1, 55.7, 48.7, 35.9, 25.6, 21.7, 18.0, −4.2; LRMS m/z 431 (M^++H); HRMS m/z 430.2467 (calcd for $C_{27}H_{34}N_2OSi$: 430.2440).

4.2.14. 4-(*tert*-Butyldimethylsiloxy)-4-methyl-1,2-diphenyl-4,5-didehydropiperidine (3m). Colorless oil. IR (neat) 2928, 1709, 1597, 1504, 1253 (br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 7H), 6.83 (d, J=7.9 Hz, 2H), 6.74 (t, J=7.2 Hz, 1H), 5.12 (dd, J=6.0, 1.9 Hz, 1H), 3.84 (d, J=15.5 Hz, 1H), 3.55 (d, J=15.0 Hz, 1H), 2.92 (m, 1H), 2.40 (d, J=16.2 Hz, 1H), 1.65 (s, 3H), 0.92 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 142.0, 140.1, 129.0, 128.1, 126.8, 126.7, 117.9, 114.7, 108.5, 60.3, 57.1, 49.3, 35.7, 25.7, 13.8, −3.9, −4.1; LRMS m/z 379 (M^+); Anal. Calcd for $C_{24}H_{33}NOSi \cdot 0.2H_2O$: C, 75.22; H, 8.78; N, 3.66. Found: C, 75.37; H, 8.72; N, 3.56.

4.2.15. *trans*-4-(*tert*-Butyldimethylsiloxy)-3-methyl-1,2-diphenyl-4,5-didehydropiperidine (*trans*-3n). Colorless

oil. IR (neat) 2930, 1668, 1595, 1495, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.13 (m, 7H), 6.81 (d, J=8.1 Hz, 2H), 6.70 (t, J=7.1 Hz, 1H), 4.99 (q, J=3.1 Hz, 1H), 4.92 (d, J=5.8 Hz, 1H), 3.93 (dt, J=15.0, 3.1 Hz, 1H), 3.76 (dt, J=15.0, 3.1 Hz, 1H), 3.11–3.04 (m, 1H), 0.91 (s, 9H), 0.88 (d, J=7.3 Hz, 3H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 138.9, 137.3, 129.4, 129.1, 128.9, 128.7, 128.6, 127.9, 127.8, 117.9, 115.0, 99.2, 63.7, 37.6, 25.7, 18.2, 13.9, 11.2, −3.5, −4.3; LRMS m/z 379 (M^+); Anal. Calcd for $C_{24}H_{33}NOSi$: C, 75.93; H, 8.76; N, 3.69. Found: C, 75.92; H, 8.85; N, 3.67.

4.2.16. 4-(*tert*-Butyldimethylsiloxy)-1,2-diphenyl-4,5-didehydropiperidine (3o). Colorless oil. IR (neat) 2856, 1688, 1597, 1201, 876 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 7H), 6.84 (d, J=8.0 Hz, 2H), 6.75 (t, J=7.4 Hz, 1H), 5.15 (dd, J=6.3, 1.9 Hz, 1H), 4.96 (dd, J=3.3, 1.6 Hz, 1H), 3.96 (dt, J=15.9, 2.7 Hz, 1H), 3.64 (ddd, J=15.7, 3.0, 1.6 Hz, 1H), 2.89 (m, 1H), 2.42 (dd, J=16.5, 1.4 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 147.6, 141.7, 129.1, 128.1, 126.9, 118.0, 114.9, 100.8, 56.6, 44.1, 35.4, 25.7, 18.0, −4.4, −4.5; LRMS m/z 365 (M^+); Anal. Calcd for $C_{23}H_{31}NOSi\cdot 0.3H_2O$: C, 74.46; H, 8.59; N, 3.78. Found: C, 74.23; H, 8.72; N, 3.73.

4.2.17. *trans*-4-Methoxy-1,2,6-triphenyl-3,4-didehydropiperidine (*trans*-3q). Colorless oil. IR (neat) 1682, 1599, 1502, 1371, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 10H), 7.00 (dd, J=8.8, 7.3 Hz, 2H), 6.66–6.59 (m, 3H), 5.29 (d, J=5.1 Hz, 1H), 5.22 (t, J=5.1 Hz, 1H), 4.99 (dd, J=5.1, 1.2 Hz, 1H), 3.44 (s, 3H), 3.08 (dd, J=15.8, 5.1 Hz, 1H), 2.53 (dd, J=15.8, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.6, 144.8, 128.5, 128.4, 128.0, 127.1, 126.6, 126.5, 126.3, 118.2, 117.6, 97.1, 59.7, 58.1, 54.4, 35.0; LRMS m/z 341 (M^+); HRMS m/z 341.1785 (calcd for $C_{24}H_{23}NO$: 341.1780).

4.3. Typical procedure for desilylation of *trans*-3a into *trans*-4a[19]

To a solution of *trans*-**3a** (0.30 mmol) in dry THF (0.5 M) was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.33 mL, 0.33 mmol) dropwise at −78 °C. The reaction mixture was stirred for 15 min at the same temperature, and then diluted with $CHCl_3$. The solution was poured into water, and the mixture was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using hexane–AcOEt (6:1) with 1% NEt_3 as an eluent to afford *trans*-**4a** as white solids. An analytical sample for X-ray crystallography was prepared by recrystallization from dichloromethane–hexane as pillars, mp 206–207 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.22 (m, 10H), 7.10 (dd, J=8.9, 7.5 Hz, 2H), 6.71 (t, J=7.2 Hz, 1H), 6.50 (d, J=8.0 Hz, 2H), 5.48 (dd, J=6.3, 2.1 Hz, 2H), 3.24 (dd, J=17.5, 6.3 Hz, 2H), 2.99 (dd, J=17.5, 2.1 Hz, 2H).

Crystal data for *trans*-**4a**.[16] $C_{23}H_{21}NO$, monoclinic, space group $P2_1/n$, a=13.21(2) Å, b=8.586(13) Å, c=16.02(3) Å, β=106.91(7)°, V=1738.7(50) $Å^3$, Z=4, D=1.251 g/cm^3, R=0.1635, R_w=0.1035, GOF=1.419.

4.3.1. Typical procedure for three component reaction starting from 1a, 5a, and 6a (Table 4, entry 1). To a schlenk round-bottom flask was introduced molecular sieves (4 Å, crushed), **5a** (0.40 mmol) and **6a** (0.40 mmol). Small amount of CH_2Cl_2 was used to wash the wall. The mixture was stirred for 30 min at room temperature, then cooled to 0 °C in an ice bath. To the solution were added **1a** (0.48 mmol) and Tf_2NH (0.08 M toluene solution, 200 μL, 16 μmol, 4 mol %) dropwise. The reaction mixture was stirred for 4 h, and then was quenched with saturated $NaHCO_3$ aq. The mixture was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using hexane–AcOEt with 1% NEt_3 to give **3a**.

4.3.2. Typical procedure for three component reaction, starting from 1a, 5a, and 6a followed by desilylation (Table 4, entry 2). To a schlenk round-bottom flask was introduced molecular sieves (4 Å, crushed), **5a** (0.40 mmol) and **6a** (0.40 mmol). Small amount of CH_2Cl_2 was used to wash the wall. The mixture was stirred for 30 min at room temperature, then cooled to 0 °C in an ice bath. To the solution were added **1a** (0.48 mmol) and Tf_2NH (0.08 M toluene solution, 200 μL, 16 μmol, 4 mol %) dropwise. After the reaction mixture was stirred for 4 h, to the resulting solution was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.48 mmol) at 0 °C. The reaction mixture was stirred for 10 min at the same temperature, and then was quenched with saturated $NaHCO_3$ aq. Work-up and purification was followed as above.

Acknowledgements

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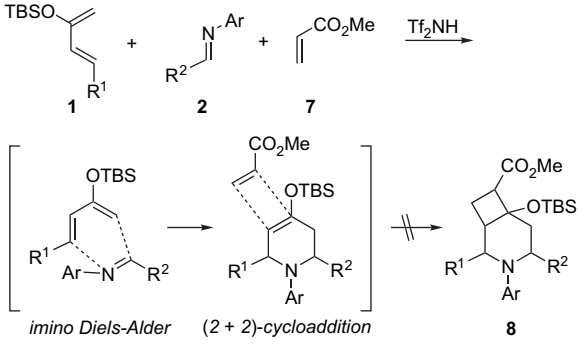
17. Based on our recent finding of the multicomponent (4+2)-(2+2)-cascade cycloaddition of siloxydienes and acrylates,[18] we attempted the imino Diels–Alder variant starting from siloxydienes **1**, imines **2**, and acrylates (Scheme 6). Unfortunately, the desired MCR adduct **8** could not be obtained under various reaction conditions.



Scheme 6.

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A convenient preparation of thioether functionalized porphyrins

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Abstract—This paper describes a convenient and high yielding three-step approach for the synthesis of *trans*-tetraphenylporphyrins possessing two thioethers in the *ortho* positions, which will facilitate the synthesis of more elaborate and complex porphyrin architectures. Their synthesis is realized by a double nucleophilic aromatic substitution of 2 equiv of a thiolate on 2,6-dichlorobenzaldehyde to generate a bis-thioether substituted benzaldehyde. This aldehyde is then condensed with 2 equiv of pyrrole to give a dipyrromethane, which in the final step reacts with an aromatic aldehyde to give a series of thioether-substituted *trans*-tetraphenylporphyrins.

1. Introduction

Porphyrins are a core structural motif that is central to the research of a wide variety of fields including material science,[1] supramolecular chemistry,[2] catalysis,[3] biomimetic chemistry,[3d,4] and small molecule sensing.[5] Among porphyrins, *trans*-substituted *meso*-tetraphenylporphyrins (TPPs) are especially attractive because they reduce the symmetry of the molecule and provide an opportunity for selective functionalization. The resulting linear substitution pattern can be conveniently harnessed for the construction of large, derivatized porphyrinic scaffolds and complex architectures.

Functionalization at the *ortho* positions (R groups, Fig. 1) of the *meso*-aryl group of TPPs is crucial to the successful development of many of these systems.[3,5] This substitution pattern is advantageous because it places the functionality over the porphyrin core, thus enabling the chemists to alter the photophysical or catalytic property of the system by proximity and steric effects.

The low yields universal to the preparation of porphyrins make elaborate multistep synthesis of their precursors unattractive. Nevertheless, the utility of porphyrins decorated with the desired 2,6-disubstituted phenyl groups on the *meso* positions is highlighted by the numerous, often lengthy, and expensive approaches taken by various researchers to prepare these molecules. Recent examples include the work of Jux[6] who described a useful approach to *trans*-TPPs bearing *meso*-2,6-bis(bromomethyl)phenyl groups via 2,6-bis-(methoxymethyl)benzaldehyde (five steps to the aldehyde and nine steps to the functionalized porphyrin). Higuchi et al.[7] described the preparation of 2,6-diamidophenyl *meso* substituted porphyrins, requiring 10 chemical transformations. Starting with 2,6-dimethoxybenzaldehyde, Lindsey et al.[8] reported the preparation of TPPs possessing alkoxy ethers at both *ortho* positions of the *meso*-phenyl groups. Foxon et al.[9] prepared similarly substituted porphyrins substituted by chiral ethers starting from resorcinol (three steps). Additionally, Rose et al.[10] reported a carefully optimized synthesis of the air sensitive *meso*-tetrakis(2,6-diamino-4-*tert*-butylphenyl)porphyrin (five steps), which required 3 weeks for a good yield in its final step.

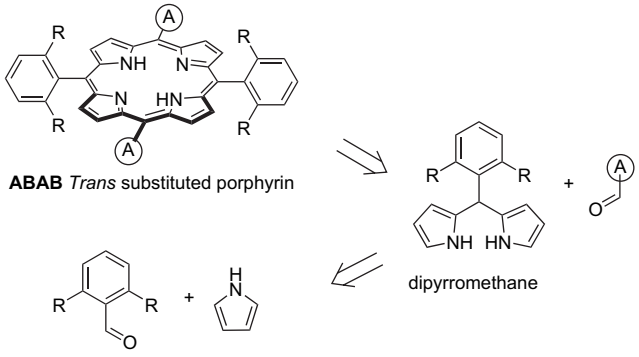

Figure 1. Retrosynthesis for C_2-symmetric **ABAB** *trans*-porphyrins.

Here, we report a conceptually simple, convenient, and efficient method for the preparation of 2,6-dithioether substituted benzaldehydes. These aldehydes are readily converted to dipyrromethanes upon treatment with a Lewis acid, which are then applied in a scrambling free synthesis of C_2-symmetric *trans*-TPPs. We envision that this approach will

Keywords: *trans*-Porphyrins; Thioethers; Synthesis; Dipyrromethanes; 2,6-Disubstituted aldehydes.
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facilitate the synthesis of complex porphyrin architectures, which are useful for broad range of applications in the field of porphyrin chemistry including catalysis, biomimetic chemistry, and material science.

2. Results and discussion

2.1. 2,6-Disubstituted benzaldehydes

We anticipated that starting from the inexpensive 2,6-dichlorobenzaldehyde, a variety of thiols could be introduced at the *ortho* positions via thioethers using nucleophilic aromatic substitution. This was inspired by one example in the literature where Gairns et al.[11] prepared 2,6-bis(phenylsulfanyl)benzaldehyde **2a** from 2,6-dichlorobenzaldehyde and potassium thiophenolate in HMPA over 2 days. We sought to employ mild conditions while avoiding the use of the known carcinogen HMPA.

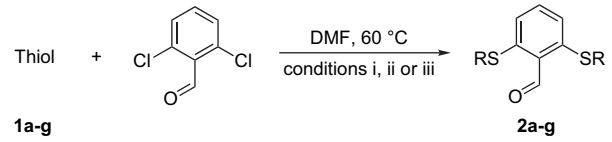
We found that when heated to 60 °C for 30 min, 2,6-dichlorobenzaldehyde reacted smoothly with potassium thiophenolate to give the double substitution product in 93% yield without chromatography (Table 1).

This method also succeeded with aliphatic thiols (Table 1, entries **1b**–**1g**). At 60 °C, over 3 h, 2,6-dichlorobenzaldehyde reacts with 2.2 equiv of KSMe to give dithioether **2b** in excellent yield. The application of similar conditions to other substrates shows how this nucleophilic aromatic substitution is general for many aliphatic thiols. Treatment of dichlorobenzaldehyde with 2.2 equiv of thiols **1c**–**1e** and **1g** and K_2CO_3 in DMF furnished the corresponding dithioether products **2c**–**2e** and **2g** in good to excellent yields, typically without the need for chromatography.

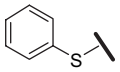
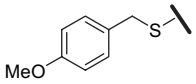
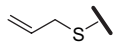
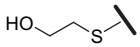
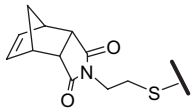
Notably, *tert*-butyl mercaptan (**1f**) was unreactive when the above conditions were employed (Table 1, i and ii), probably due to the lower acidity of this thiol. This transformation proceeded efficiently when the deprotonation of the thiol was performed with NaH in DMF prior to the addition of the aldehyde, affording the product in 88% yield.

The use of only 1 equiv of thiol **1h** in the procedure leads to the selective formation of the monosubstituted product **2h** in 82% isolated yield after recrystallization of the crude reaction product (Fig. 2). ^{1}H NMR analysis of the crude reaction mixture showed 90% conversion to the desired **2h** as well as 6% of the disubstituted product **2e** and 4% starting aldehyde.[12]

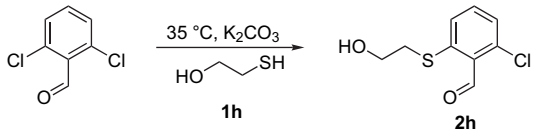
Table 1. Synthesis of 2,6-dithioether aldehydes



1a-g **2a-g**

Thiol	R—	Conditions	Product	Yield (%)
1a		ii	**2a**	93
1b		i	**2b**	93
1c		i	**2c**	89
1d		i	**2d**	71
1e		i	**2e**	83
1f		iii	**2f**	88
1g		i	**2g**	89

Conditions: (i) 2.0 or 2.2 equiv of both thiol and K_2CO_3; (ii) commercially available potassium thiomethoxide was used, and the reaction was done in a glove box; (iii) thiol **1f** was premixed with NaH in DMF before the slow addition of the aldehyde.



1h **2h**

Figure 2. Selective monosubstitution of the dichlorobenzaldehyde.

2.2. Dipyrromethanes

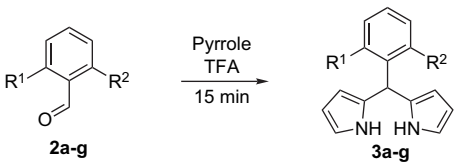
With the series of 2,6-disubstituted aldehydes available, we attempted to prepare the corresponding dipyrromethanes using the conditions developed by Lindsey et al.[13] Treatment of aldehyde **2a** with TFA in excess pyrrole gives dipyrromethane **3a** in 53% yield (Table 2). Application of this procedure to aldehydes **2b**–**2f** followed by flash chromatography gave the desired dipyrromethanes **3b**–**3f**, respectively, in moderate yields ranging from 31–51% with no observed scrambling. These results are typical for dipyrromethanes, which cannot be distilled or selectively precipitated.[13,14] The successful application of the method to aldehyde **2h** bearing an unprotected alcohol highlights the convenience of this method for the rapid access of porphyrin precursors under mild conditions without the need for elaborate protecting group strategy.

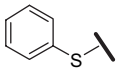
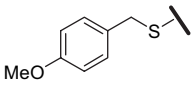
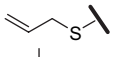
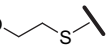
2.3. Porphyrins

Initially, we explored the use of dipyrromethane **2a** in the synthesis of **ABAB** C_2-symmetric *trans*-TPPs. Since standard conditions[15] for the synthesis of *trans*-TPPs typically give significant amounts of scrambling of the *meso* substituents, we employed conditions developed by Lindsey et al. to minimize this for the preparation of porphyrins from 5-(2,6-dichlorophenyl)dipyrromethane and 5-mesityldipyrromethanes.[13]

Treating 1 equiv of **3a** and 1 equiv of *p*-tolualdehyde with 1.78 equiv of TFA in DCM,[13] followed by oxidation with DDQ furnished the **ABAB** *trans*-porphyrin **4a** in 25% yield (Table 3, entry 1). Although the yields initially may seem modest, they are quite reasonable for this type of porphyrin formation.[1a]

Table 2. Preparation of difunctionalized dipyrromethanes



Aldehyde	R^1—	R^2—	Product	Yield (%)
2a	$R^1=R^2=$		**3a**	53
2b	$R^1=R^2=$		**3b**	31
2c	$R^1=R^2=$		**3c**	48
2d	$R^1=R^2=$		**3d**	51
2f	$R^1=R^2=$		**3f**	46
2h	R^1=Cl	R^2 = 	**3h**	40

This procedure was successfully applied to the synthesis of a series of porphyrins. Employing Lindsey's conditions,[13] porphyrins **4b**–**4i** were prepared in moderate to good yields (19–51%). The use of dipyrromethane **3h** in the synthesis gave porphyrin **4h** as a mixture of rotamers, which were separated by careful flash chromatography to give 17% of the α,α-isomer and 16% of the α,β-isomer.

In conclusion, we have developed a quick, convenient, and inexpensive way to prepare *trans*-TPPs bearing thioethers in the 2 and 6 positions of the *meso*-phenyl groups. Considering the mild conditions used, this method should be compatible with a wide range of functionality, making it an attractive approach for the preparation of elaborate porphyrin architectures. Moreover, since these systems also bear multiple thioether functions, it offers the possibility of using these thioether porphyrins for applications requiring their self-assembly on gold surfaces.

3. Experimental

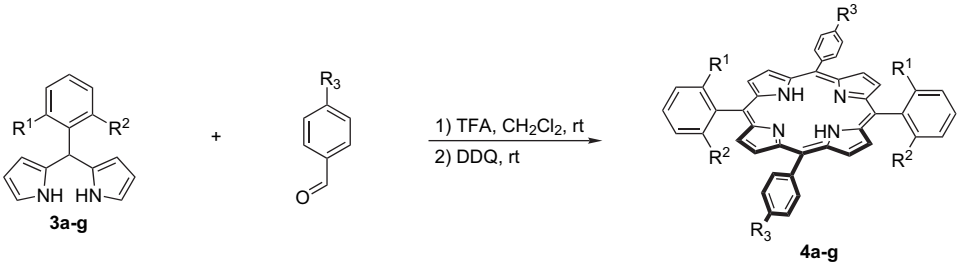
3.1. General remarks

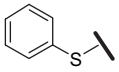
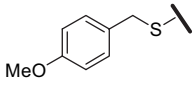
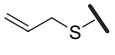
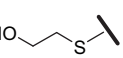
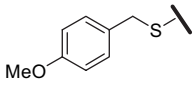
All reagents and solvents used were of ACS grade and were used without further purification unless otherwise mentioned. All processes involving air or moisture sensitive reactants and/or requiring anhydrous conditions were performed under a positive pressure of pre-purified argon using flame-dried glassware. Unless otherwise specified, solutions of Na_2CO_3 and NaOH refer to saturated aqueous solutions.

Compound visualization during TLC analysis was achieved by UV fluorescence, and simply heating on a hot plate for 30 s (this is particularly effective for dipyrromethanes, which develop a green color, which is different from the reaction byproducts).

Infrared spectra (IR) were recorded on a Nicolet Magna 750 FT-IR spectrometer as either a cast or microscope (μscope).

Table 3. Synthesis of C_2-symmetric *trans*-porphyrins



Dipyrromethane	R^1—	R^2—	R^3—	Product	Yield (%)
3a	$R^1=R^2=$		TMS—≡—	**4a**	25
3b	$R^1=R^2=$			**4b**	19
3c	$R^1=R^2=$			**4c**	51
3d	$R^1=R^2=$			**4d**	21
3h	R^1 = 	R^1=Cl		**4h**	33[a] (α,α=17%, α,β=16%)
3c	$R^1=R^2=$			**4i**	21

[a] Due to the hindered rotation around the porphyrin-*meso*-aryl bond, the α,α- and the α,β-isomer could be separated.

Cast refers to the evaporation of a solution on a NaCl plate. Mass spectra (MS) were recorded on a Kratos AEIMS-50 high-resolution mass spectrometer (HRMS), using electron impact ionization (EI), Applied Biosystems (sinapinic acid as the matrix), and Micromass ZabSpec Hybrid Sector-TOF using positive mode electrospray (ES). Microanalyses were obtained on Perkin–Elmer 240 or Carlo Erba 1180 elemental analyzer. Nuclear magnetic resonance (NMR) spectra were obtained on Inova Varian 400 and 500 MHz instruments. ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) using the residual solvent resonance as the reference: $CDCl_3$, δ 7.24; CD_3OD, δ 3.30. The coupling constants reported are within an error range of 0.2–0.4 Hz. ^{13}C NMR shifts are reported relative to: $CDCl_3$, δ 77.0; CD_3OD, δ 49.0. Porphyrin α-carbon signals are typically not reported because of signal broadening due to NH tautomerization.[16] Signals are reported within 0.1 ppm except where close peaks necessitate an additional significant figure.

3.1.1. 5-(3,5-Dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)ethanethiol (1g). Norborn-5-ene-2,3-*endo*-dicarboxylic anhydride[17] (1.64 g, 10.0 mmol), triethylamine (2.02 g, 20.0 mmol), and 2-thioethanolamine hydrochloride (1.13 g, 10.0 mmol) were dissolved in DMF (10 mL) and placed in a sealed tube. The solution was purged with argon (20 min), the reaction vessel was sealed, and then heated at 140 °C for 14 h. The tube was then cooled, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (50 mL), and the organic layer was washed with water (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography eluting with Hex/EtOAc (4/1) afforded a white solid (290 mg, 11%): mp 111–114 °C; IR ($CHCl_3$, cast) 3062, 2989, 2944, 2871, 2559, 1766, 1701, 1395, 1336, 1159, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (t, 1H), 1.50 (dt, 1H, J=9.0, 1.5 Hz), 1.69 (dt, 2H, J=8.5, 1.5 Hz), 2.53 (m, 2H), 3.22 (dd, 2H, J=1.5, 3.0 Hz), 3.35 (m, 2H), 3.47 (m, 2H), 6.07 (t, 2H, J=2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.0, 41.3, 45.0, 45.8, 52.3, 134.4, 177.2; HRMS (EI) calcd for $C_{13}H_{15}O_2NS$: 265.0772, found: 265.0774 [M$^+$] (21.3%).

3.1.2. 2,6-Bis(phenylsulfanyl)benzaldehyde (2a). Thiophenol (2.05 mL, 22.0 mmol) was added to a nitrogen flushed (20 min) stirred mixture of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol), K_2CO_3 (3.04 g, 2.20 mmol), and DMF (5.0 mL). The mixture was stirred for 5 min, and then heated to 60 °C until the reaction was complete as judged by TLC (Hex/EtOAc 6/1) (ca. 30 min). The mixture was diluted with water (15 mL), the product was filtered, rinsed with water (6×10 mL), and dried in vacuo at 55 °C for 3 h to give the aldehyde **2a** (3.11 g, 93%). All spectroscopic data were consistent with the reported data.[11]

3.1.3. 2,6-Bis(methylsulfanyl)benzaldehyde (2b). Under inert atmosphere (glove box), NaSMe (1.46 g, 21.0 mmol) was added portionwise to a stirred solution of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) in DMF (10 mL) (caution, exothermic!). The mixture was stirred for 20 min, then heated to 60 °C, and stirred for 1 h. The mixture was cooled to rt, diluted with EtOAc (25 mL), and washed with water (3×15 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by recrystallization (MeOH) gave **2b** as a white solid (1.85 g, 93%): mp 95–97 °C; IR ($CHCl_3$, cast) 2981, 2921, 2861, 2767, 1670, 1550, 1437, 1416, 1200, 949, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 6H), 7.05 (d, 2H, J=8.0 Hz), 7.36 (t, 1H, J=8.0 Hz), 10.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 121.9, 129.4, 132.9, 145.7, 189.9; HRMS (EI) calcd for $C_9H_{10}OS_2$: 198.0173, found: 198.0175 [M$^+$] (100.0%). Anal. Calcd for $C_9H_{10}OS_2$: C, 54.51; H, 5.08. Found: C, 54.25; H, 5.06.

3.1.4. 2,6-Bis(4-methoxybenzylsulfanyl)benzaldehyde (2c). 4-Methoxybenzylmercaptan (900 μL, 6.00 mmol) was added to an argon flushed (20 min) stirred mixture of 2,6-dichlorobenzaldehyde (525 mg, 3.00 mmol), K_2CO_3 (996 mg, 7.00 mmol), and DMF (3 mL). The mixture was stirred for 5 min, and then heated to 60 °C for 2 h until a light yellow solid precipitated. Water (15 mL) and EtOAc (25 mL) were then added to the reaction mixture, which was then filtered, the solid was washed with cold EtOAc (3×5 mL), and dried in vacuo to give analytically pure **2c** (290 mg). The filtered organic layer was separated, washed with water (5×15 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of this crude residue by recrystallization from Hex/EtOAc (4/1) gave a further 810 mg (total 1.11 g, 90%): mp 142–143 °C; IR (CH_2Cl_2, cast) 2953, 2930, 2833, 2755, 1664, 1609, 1557, 1304, 1257, 1177, 1031, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 6H), 4.11 (s, 4H), 6.86 (AA′BB′, 4H), 7.26 (m, 6H), 7.26 (t, 1H, J=8.0 Hz), 10.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.3, 55.3, 114.1, 126.0, 127.8, 130.1, 131.9, 132.7, 143.6, 159.6, 191.3; HRMS (EI) calcd for $C_{23}H_{22}O_3S_2$: 410.1010, found: 410.1010 [M$^+$] (14.6%). Anal. Calcd for $C_{23}H_{22}O_3S_2$: C, 67.29; H, 5.40; S, 15.62. Found: C, 66.96; H, 5.58; S, 15.40.

3.1.5. 2,6-Bis(allylsulfanyl)benzaldehyde (2d). Allyl mercaptan (5.0 mL, 70% purity; stench!) was added to an argon flushed stirred suspension of 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) and K_2CO_3 (4.14 g, 30.0 mmol) in DMF (10 mL). The mixture was heated to 65 °C for 10 h, cooled, diluted with EtOAc (20 mL), and water (10 mL), and then separated. The organic layer was washed with Na_2CO_3 (2×20 mL), water (4×20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash chromatography (Hex/EtOAc, 7/1) gave **2d** as an oil (1.77 g, 71%); IR (neat film) 3081, 2978, 2858, 1670, 1636, 1561, 1552, 1435, 1406, 1202, 988, 922, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.56 (dt, 4H, J=1.2, 6.8 Hz), 5.13 (dq, 2H, J=1.1, 10.0 Hz), 5.21 (dq, 2H, J=1.4, 17.2 Hz), 5.86 (ddt, 2H, J=17.0, 10.2, 6.8 Hz), 7.23 (AB_2, 2H), 7.36 (AB_2, 1H), 10.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.9, 118.8, 125.9, 132.0, 132.4, 132.5, 143.1, 191.4; HRMS (EI) calcd for $C_{13}H_{14}OS_2$: 250.0486, found: 250.0479 [M$^+$] (14.5%).

3.1.6. 2,6-Bis(2-hydroxyethylsulfanyl)benzaldehyde (2e). 2-Mercaptoethanol (1.72 g, 1.50 mL, 22.0 mmol) was added to a stirred degassed suspension of K_2CO_3 (3.00 g, 22.0 mmol) and 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) in DMF (5 mL). This mixture was heated to 65 °C for 8 h, cooled to rt, filtered, and recrystallized from $CHCl_3$/Hex to give 2.14 g (83%) of a light yellow solid: mp 130–131 °C; IR (μscope) 3231 (br), 2928, 2872, 1670,

1200 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.14 (t, 4H, J=6.3 Hz), 3.83 (t, 4H, J=6.0 Hz), 7.31–7.32 (A_2B, 1H), 7.38–7.41 (A_2B, 2H), 10.76 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 36.9, 61.1, 126.5, 133.4, 134.1, 144.5, 192.5; HRMS (EI) M^+ $C_{11}H_{914}O_3S_2$ calcd: 258.0385, found: 258.0384.

3.1.7. 2,6-Bis(*tert*-butylsulfanyl)benzaldehyde (2f). *tert*-Butyl mercaptan (2.45 mL, 22.0 mmol) was added dropwise to a stirred degassed suspension of NaH (50% in mineral oil, 0.96 g, 20.0 mmol) in DMF (5 mL). After the hydrogen evolution ceased, 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) was added portionwise (caution, exothermic!). This mixture was stirred for 2 h at 60 °C, cooled to rt, diluted with water (ca. 80 mL), and extracted with EtOAc (3×40 mL). The combined organic extracts were washed with water (4×20 ml), and concentrated in vacuo to give an amber oil. This material was heated to 100 °C in vacuo for 20 min, and then cooled to give a yellow solid. This was recrystallized from MeOH to give the title compound as a yellow crystalline solid (2.03 g, 72%). The mother liquor from the recrystallization was concentrated in vacuo, and the solid was again recrystallized to give an additional 452 mg (total yield, 88%): mp 58.0–59.5 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (s, 18H), 7.31–7.32 (A_2B, 1H), 7.38–7.41 (A_2B, 2H), 10.76 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 11.4, 41.1, 126.5, 133.4, 134.2, 146.5, 192.2; HRMS (EI) M^+ $C_{15}H_{22}OS_2$ calcd: 282.1112, found: 282.1115.

3.1.8. 2,6-Bis(2-(3,5-dioxo-4-aza-tricyclo[5.2.1^{2,6}]dec-8-en-4-yl)ethanethio)benzaldehyde (2g). A solution of thiol **1g** (223 mg, 0.842 mmol) and 2,6-dichlorobenzaldehyde (85 mg, 0.49 mmol) in dry DMF (2 mL) was degassed with a stream of argon for 30 min. K_2CO_3 (138 mg, 1.00 mmol) was added under an argon blanket and the mixture was maintained at this temperature for a further 5 min under argon. The mixture was heated to 60 °C and stirred for 4 h. The mixture was cooled, diluted with H_2O (10 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with water (3×20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash chromatography eluting with Hex/EtOAc (2/1 to 1/2) afforded the aldehyde **2g** as a yellow solid (239 mg, 89%): R_f=0.2 (Hex/EtOAc, 4/3), mp 117–119 °C; IR ($CHCl_3$, cast) 2989, 2860, 1764, 1698, 1670, 1562, 1396, 1335, 1203, 1126, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, 2H, J=8.5 Hz), 1.69 (dt, 2H, J=8.5, 1.5 Hz), 2.93 (m, 4H), 3.21 (dd, 4H, J=1.5, 3.0 Hz), 3.34 (m, 4H), 3.54 (m, 4H), 6.07 (t, 2H, J=1.8 Hz), 7.36 (AB_2, 2H), 7.45 (AB_2, 1H), 10.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9, 40.0, 44.9, 45.8, 52.2, 124.9, 131.7, 133.2, 134.5, 142.2, 177.2, 190.6; HRMS (EI) calcd for $C_{29}H_{28}O_5S_2N_2$: 548.14398, found: 548.14340 [M^+] (1.20%).

3.1.9. 2-Chloro-6-(2-hydroxyethylsulfanyl)benzaldehyde (2h). 2-Mercaptoethanol (780 mg, 700 μL, 10.0 mmol) was added to a stirred degassed suspension of K_2CO_3 (1.40 g, 10.0 mmol) and 2,6-dichlorobenzaldehyde (1.75 g, 10.0 mmol) in DMF (5 mL) at 0 °C. This mixture was heated to 40 °C for 3 h, cooled to rt, diluted with water (ca. 70 mL), and filtered. This material was recrystallized from EtOAc/Hex to give a light yellow solid: mp 114–115 °C; IR (CH_2Cl_2, cast) 3253 (br), 2924, 2880, 2767, 1667, 1415 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13 (br s, 1H), 3.15 (t, 2H, J=6.0 Hz), 3.88 (t, 2H, J=6.0 Hz), 7.21 (dd, 1H, J=8.0, 1.0 Hz), 7.31 (d, 1H, J=8.5 Hz), 7.37 (t, 1H, J=8.0 Hz), 10.58 (d, 1H, J=0.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 35.1, 60.2, 124.7, 126.5, 129.5, 133.5, 139.9, 143.9, 190.5; HRMS (EI) M^+ $C_9H_9O_2S^{37}Cl$ calcd: 217.9982, found: 217.9971.

3.1.10. 5-(2,6-Bis(phenylsulfanyl)phenyl)dipyrromethane (3a). TFA (30 μL, 0.40 mmol) was added to a degassed stirred solution of aldehyde **2a** (1.29 g, 4.00 mmol) in pyrrole (10.7 g). The solution was stirred for 15 min, and then the reaction was quenched by the addition of 0.1 M NaOH (4 mL). EtOAc (20 mL) was added and the layers were separated. The organic layer was washed with water (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc=8/1) gave an amber solid (928 mg, 53%); IR (CH_2Cl_2, cast) 3390, 3056, 1674, 1552, 1476, 1438, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.13 (m, 2H), 6.21 (q, 2H, J=3.0 Hz), 6.70 (dd, 2H, J=2.7, 1.5 Hz), 6.78 (s, 1H), 7.18 (t, 1H, J=7.8 Hz), 7.16 (d, 2H, J=7.8 Hz), 7.20–7.35 (m, 10H), 8.63 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.9, 107.8, 108.6, 116.9, 127.2, 127.9, 129.3, 130.9, 131.3 (br), 132.9, 136.5, 137.7 (br), 143.5; HRMS (EI) calcd for $C_{27}H_{22}S_2N_2$: 438.1224, found: 438.1225 [M^+], (100%).

3.1.11. 5-(2,6-Dithiomethoxyphenyl)dipyrromethane (3b). TFA (129 μL, 1.66 mmol) was added to a degassed stirred solution of aldehyde **2b** (990 mg, 5.0 mmol) in pyrrole (20 mL). After the solution was stirred for 25 min, the reaction was quenched by the addition of 0.1 M NaOH (20 mL). The mixture was diluted with EtOAc (30 mL) and separated. The organic layer was washed with water (2×20 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (Hex/EtOAc=5/1) to give a colorless foam (509 mg, 31%): mp 102–104 °C; IR ($CHCl_3$, cast) 3373, 2917, 1557, 1433, 1027, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 6H), 6.08 (m, 2H), 6.19 (m, 2H), 6.52 (s, 1H), 6.72 (m, 2H), 7.13 (d, 2H, J=8.0 Hz), 7.21 (t, 1H, J=7.6 Hz), 8.67 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 39.9, 107.7, 108.3, 116.6, 124.8, 127.6, 130.6, 138.4, 139.1; HRMS (EI) calcd for $C_{17}H_{18}S_2N_2$: 314.0912, found: 314.0907 [M^+] (100.0%). Anal. Calcd for $C_{17}H_{18}S_2N_2C$: 64.97; H, 5.73; N, 8.92. Found: C, 65.12; H, 5.44; N, 8.89.

3.1.12. 5-(2,6-Bis(4-methoxybenzylsulfanyl)phenyl)dipyrromethane (3c). TFA (710 mg μL, 6.23 mmol) was added to a degassed stirred solution of aldehyde **2c** (1.44 g, 3.50 mmol) in pyrrole (35 mL) and CH_2Cl_2 (ca. 5 mL added to dissolve the aldehyde). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (20 mL). EtOAc (50 mL) was added, the layers were separated, and the organic layer was washed with water (2×40 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (Hex/EtOAc, 4/1) to give a light yellow foam (880 mg, 48%): R_f=0.2 (Hex/EtOAc=4/1), mp 65–70 °C (dec); IR (CH_2Cl_2, cast) 3387, 2932, 2834, 1609, 1554, 1511, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.70 (s, 6H), 4.02 (s, 4H), 6.02 (m, 2H), 6.13 (q, 2H, J=3.0 Hz), 6.58 (dt, 2H, J=1.5, 2.7 Hz),

6.72 (s, 1H), 6.82 (AA′BB′, 4H), 7.08–7.18 (m, 6H), 7.89 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.1 (br), 40.7, 55.6, 107.8, 108.6, 114.3, 116.9, 127.6, 129.6, 130.3, 131.0, 131.4, 137.6, 143.7, 159.2; HRMS (EI) calcd for $C_{31}H_{30}O_2N_2S_2$: 526.1749, found: 526.1753 [M^+] (61.3%).

3.1.13. 5-(2,6-Bis(allylsulfanyl)phenyl)dipyrromethane (3d). TFA (30 μL, 0.40 mmol) was added to a degassed stirred solution of aldehyde **2d** (1.00 g, 4.00 mmol) in pyrrole (10.7 g). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (4 mL). The mixture was diluted with EtOAc (20 mL) and separated. The organic layer was washed with water (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc=8/1) gave an amber solid (760 mg, 51%); IR (CH_2Cl_2, cast) 3380, 3080, 2976, 1665, 1634, 1555, 1427, 1027, 922, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49, (d, 4H, J=7.2 Hz), 5.10 (m, 4H), 5.82 (m, 2H), 6.07 (m, 2H), 6.20 (m, 2H), 6.72 (m, 2H), 6.78 (s, 1H), 7.18 (t, 1H, J=8.0 Hz), 7.33 (d, 2H, J=8.0 Hz), 8.65 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.4, 40.4, 107.5, 108.5, 116.5, 118.1, 127.2, 130.1, 131.1, 133.3, 137.0, 143.1; HRMS (EI) calcd for $C_{21}H_{22}S_2N_4$: 366.1224, found: 366.1221 [M^+] (100%).

3.1.14. 5-(2,6-Bis(*tert*-butylsulfanyl)phenyl)dipyrromethane (3f). TFA (23 μL, 0.30 mmol) was added to a degassed stirred solution of aldehyde **2f** (846 mg, 3.0 mmol) in pyrrole (15 mL) and CH_2Cl_2 (ca. 5 mL added to dissolve the aldehyde). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (30 mL). The mixture was diluted with EtOAc (100 mL) and separated. The organic layer was washed with water (2×40 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (Hex/EtOAc) to give **3f** as a light yellow foam (549 mg, 46%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 18H), 5.94–5.96 (m, 2H), 6.12 (q, 2H, J=3.0 Hz), 6.65 (dd, 2H, J=1.5, 3.0 Hz), 7.09 (s, 1H), 7.15 (t, 1H, J=8.0 Hz), 7.61 (d, 2H, J=8.0 Hz), 8.52 (br s, 2H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.5, 41.4, 48.0, 107.2, 108.2, 115.7, 125.9, 131.8, 137.3 (br, 2 overlapping C, supported with the HMBC spectrum), 149.6 (1C not observed); HRMS (EI) calcd for $C_{23}H_{30}N_2S_2$: 398.1850, found: 398.1841 [M^+], (51%).

3.1.15. 5-(2-Chloro-6-(2-hydroxyethylsulfanyl)phenyl)-dipyrromethane (3h). TFA (710 mg μL, 6.23 mmol) was added to a degassed stirred solution of aldehyde **2h** (756 mg, 3.50 mmol) in pyrrole (35 mL) and CH_2Cl_2 (ca. 5 mL added to dissolve the aldehyde prior to the addition of pyrrole). After the solution was stirred for 15 min, the reaction was quenched by the addition of 0.1 M NaOH (20 mL). The mixture was diluted with EtOAc (50 mL) and separated. The organic was washed with water (2× 40 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (Hex/EtOAc, 4/1 to 2/1) to give a light yellow foam (480 mg, 1.45 mmol, 40%); IR ($CHCl_3$, cast) 3358, 1667, 1556, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.83 (br s, 1H), 3.00 (t, 2H, J=5.5 Hz), 3.61 (t, 2H, J=5.5 Hz), 6.01–6.05 (m, 2H), 6.17 (q, 2H, J=3.0 Hz), 6.50–6.67 (br s, 1H), 6.68–6.70 (m, 2H), 7.12 (t, 1H, J=8.0 Hz), 7.26 (d, 1H, J=8.0 Hz), 7.33 (br s, 1H), 8.60–8.80 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.4, 40.3, 59.8, 107.4, 108.6, 117.0, 128.1, 130.2, 135.7, 137.7; HRMS (EI) calcd for $C_{17}H_{17}ON_2S^{35}Cl$: 332.0750, found: 332.0750 [M^+] (100%).

3.1.16. 5,15-Bis(2,6-diphenylsulfanylphenyl)-10,20-bis(*p*-tolyl)porphyrin (4a). TFA (144 μL, 1.78 mmol) was added to a degassed solution of **3a** (438 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.50 mmol) was added. After an additional 1 h, the reaction mixture was filtered through a Florisil column (2 cm× 10 cm), and eluted with CH_2Cl_2. The purple fractions were combined, and concentrated in vacuo to give a purple solid. This solid was purified further by flash chromatography (Hex/EtOAc) to give the title compound (154 mg, 25%); IR (CH_2Cl_2, cast) 3316, 3072, 2956, 2156, 1549, 1248, 797 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ −2.38 (s, 2H), 0.40 (s, 18H), 7.1–7.2 (s, 20H), 7.23 (d, 4H, J=8.0 Hz), 7.45 (t, 2H, J=8.0 Hz), 7.88 (AA′MM′, 4H), 8.22 (AA′MM′, 4H), 8.77 (s, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.09, 95.4, 105.2, 115.8, 119.0, 122.4, 126.2, 127.9, 129.1, 129.4, 130.0 (br), 130.3, 131.4 (br), 133.5, 134.2, 134.5, 139.5, 142.4, 143.1; MS (ES) 1239.4 [MH^+]; UV 432, 524, 559, 598, 660 nm.

3.1.17. 5,15-Bis(2,6-thiomethoxyphenyl)-10,20-bis(*p*-tolyl)porphyrin (4b). TFA (69 μL, 0.89 mmol) was added to a solution of dipyrromethane **3b** (157 mg, 0.500 mmol) and *p*-tolualdehyde (60 mg, 0.50 mmol) in freshly distilled CH_2Cl_2 (50 mL). After the solution was stirred for 30 min, DDQ (170 mg, 0.75 mmol) was added and the mixture was stirred for further 45 min. The crude mixture was filtered through a Florisil column (2.5×15 cm) and eluting with CH_2Cl_2. Concentration in vacuo gave a purple solid (40 mg, 19%); IR (CH_2Cl_2, cast) 3319, 2916, 1555, 1428, 965, 786 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ −2.43 (s, 2H), 2.20 (s, 12H), 2.66 (s, 6H), 7.40 (AA′BB′, 4H), 7.47 (d, 4H, J=8.0 Hz), 7.75 (t, 2H, J=8.3 Hz), 8.06 (AA′BB′, 4H), 8.56 (d, 4H, J=4.5 Hz), 8.82 (d, 4H, J=4.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.2, 21.6, 114.7, 119.7, 120.5, 127.3, 129.5, 129.8 (br), 131.8 (br), 134.5, 137.2, 137.4, 139.0, 143.4; HRMS (ES) calcd for $C_{50}H_{43}N_4S_4$: 827.2371, found: 827.2371 [MH^+].

3.1.18. 5,15-Bis(2,6-bis(4-methoxybenzylsulfanyl)-phenyl)-10,20-bis(*p*-tolyl)porphyrin (4c). TFA (137 μL, 1.78 mmol) was added to a solution of dipyrromethane **3c** (526 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in freshly distilled CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.5 mmol) was added and the mixture was stirred for further 45 min. The crude mixture was filtered through an alumina column (2.5×15 cm) and eluted with CH_2Cl_2. Concentration of the purple eluent gave a purple solid (322 mg, 51%); IR (CH_2Cl_2, cast) 3350, 3317, 2924, 2933, 1609, 1582, 1511, 1249, 798 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −2.36 (s, 2H), 2.75 (s, 6H), 3.64 (s, 12H), 3.82 (s, 8H), 6.57 (AA′BB′, 8H), 6.86 (AA′BB′, 8H), 7.61 (m, 6H), 7.52 (AA′BB′, 4H), 8.05 (AA′BB′, 4H), 8.56 (d, 4H, J=4.5 Hz), 8.82 (d, 4H, J=4.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 37.9, 55.2, 113.6, 115.5, 124.6, 128.6, 129.0, 129.6, 131.3 (br), 134.6, 137.1, 139.2, 140.6, 141.5, 158.4; MS (ES) 1251.4 [MH^+]; λ_{abs} 430, 523, 555, 602, 660 nm.

3.1.19. 5,15-Bis(2,6-diallylsulfanylphenyl)-10,20-bis(*p*-tolyl)porphyrin (4d). TFA (144 μL, 1.78 mmol) was added to a degassed solution of **3d** (467 mg, 1.00 mmol) and 4-(trimethylsilylethynyl)benzaldehyde (202 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.50 mmol) was added. After an additional 1 h, the reaction mixture was filtered through a Florisil column (2 cm×10 cm) and eluted with CH_2Cl_2. The purple fractions were combined, and concentrated in vacuo to give a purple solid. This solid was purified further by flash chromatography (Hex/EtOAc, 6/1) to give the title compound (98 mg, 21%): R_f=0.5 (Hex/EtOAc, 3/1); IR (CH_2Cl_2, cast) 3318, 3021, 2918, 1636, 1553, 1347, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −2.40 (s, 2H, NH), 2.67 (s, 6H), 3.49 (dt, 8H, *J*=5.5, 1.3 Hz), 4.92 (dq, 4H, *J*=10.0, 1.3 Hz), 5.02 (dq, 4H, *J*=17.0, 1.5 Hz), 5.51 (ddt, 4H, *J*=17.5, 10.0, 6.8 Hz), 7.51 (AA′BB′, 8H), 7.67 (t, 2H, *J*=7.5 Hz), 8.10 (AA′BB′, 4H), 8.59 (d, 4H, *J*=5.0 Hz), 8.78 (d, 4H, *J*=4.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 36.5, 115.4, 117.8, 124.2, 127.4, 128.9, 129.8 (br), 131.5 (br), 133.2, 134.6, 137.2, 139.2, 140.6, 141.3; HRMS (ES) calcd for $C_{58}H_{51}S_4N_4$: 931.2997, found: 931.3004 [MH^+].

3.1.20. 5,15-Bis(2,6-diphenylsulfanylphenyl)-10,20-bis(*p*-tolyl)porphyrin (4i). TFA (144 μL, 1.78 mmol) was added to a degassed solution of **3c** (366 mg, 1.00 mmol) and *p*-tolualdehyde (120 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred for 30 min, DDQ (340 mg, 1.50 mmol) was added. After an additional 1 h, the reaction mixture was filtered through a Florisil column (2 cm× 10 cm) and eluted with CH_2Cl_2. The purple fractions were combined, and concentrated in vacuo to give a purple solid. This solid was purified further by flash chromatography (Hex/EtOAc, 6/1) to give the title compound as a purple solid (155 mg, 21%): R_f=0.5 (Hex/EtOAc, 3/1); IR (CH_2Cl_2, cast) 3316, 2930, 1682, 1609, 1511, 1301, 1249, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −2.52 (s, 2H, NH), 3.60 (s, 12H), 3.78 (s, 8H), 6.50 (AA′MM′, 8H), 6.78 (AA′MM′, 8H), 7.47 (d, *J*=7.5 Hz, 4H), 7.59 (t, *J*=7.5 Hz, 2H), 7.97 (AA′MM′, 4H), 8.07 (AA′MM′, 4H), 8.49 (d, *J*=5.5 Hz, 4H), 8.67 (d, *J*=5.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.8, 55.1, 93.9, 113.5, 116.0, 118.1, 124.5, 128.5, 129.1, 129.6, 130 (br), 131 (br), 135.8, 136.3, 140.2, 141.5, 141.7, 158.5, (two carbon signals not observed); MS (ES) 1475.1 [MH^+].

3.1.21. 5,15-Bis(2-chloro-6-(2-hydroxyethylsulfanyl)-phenyl-10,20-bis(4-butoxyphenyl)porphyrin (4h). TFA (144 μL, 1.78 mmol) was added to a solution of **3h** (332 mg, 1.00 mmol) and 4-butoxybenzaldehyde[18] (192 mg, 1.00 mmol) in CH_2Cl_2 (100 mL). After the solution was stirred 30 min, DDQ (340 mg, 1.50 mmol) was added and the mixture was stirred for further 45 min. The crude mixture was filtered through a Florisil column (2.5×15 cm) and eluted with CH_2Cl_2→2% MeOH in CH_2Cl_2 until no further porphyrin was eluted. The eluent was concentrated in vacuo and purified by flash chromatography to give the α,α-isomer (82 mg, 17%) and the α,β-isomer (77 mg, 16%). Data for the α,α-isomer: IR (CH_2Cl_2, cast) 3600–3150, 3316, 2955, 2924, 2854, 1505, 1466, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −2.46 (s, 2H), 1.11 (t, 6H, *J*=7.4 Hz), 1.60 (br s, 2H), 1.67 (Hex, 4H, *J*=7.4 Hz), 1.98 (quin, 4H, *J*=7.0 Hz), 2.72 (t, 4H, *J*=6.0 Hz), 3.39 (t, 4H, *J*=5.8 Hz), 4.24 (t, 4H, *J*=6.4 Hz), 7.25 (d, 4H, *J*=7.8 Hz), 7.58 (dd, 2H, *J*=1.6, 7.8 Hz), 7.66 (t, 2H, *J*=8.0 Hz), 7.69 (dd, 2H, *J*=1.6, 8.0 Hz), 8.09 (dd, 2H, *J*=2.8, 0.4 Hz), 8.15 (dd, 2H, *J*=2.8, 0.4 Hz), 8.63 (d, 4H, *J*=4.8 Hz), 8.89 (d, 4H, *J*=4.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 19.4, 31.5, 36.7, 59.7, 68.0, 112.8, 114.6, 120.1, 125.3, 126.5, 129 (br), 130.0, 132 (br), 133.8, 135.59, 135.63, 138.0, 140.4, 142.0, 144–148 (br), 159.0; HRMS (ES) calcd for $C_{56}H_{53}N_4O_4S_2Cl_2$: 979.2885, found: 979.2884. Data for α,β-isomer: IR (CH_2Cl_2, cast) 3600–3200, 3317, 2956, 2925, 1505, 1472, 1429, 1245, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ −2.42 (s, 2H), 1.27 (t, 6H, *J*=7.4 Hz), 1.39 (br s, 2H), 1.68 (Hex, 4H, *J*=7.4 Hz), 1.98 (quin, 4H, *J*=7.0 Hz), 2.70 (t, 4H, *J*=5.8 Hz), 3.37 (t, 4H, *J*=5.8 Hz), 4.24 (t, 4H, *J*=6.6 Hz), 7.25 (AA′BB′, 4H), 7.53 (d, 2H, *J*=7.8 Hz), 7.61 (t, 2H, *J*=7.9 Hz), 7.67 (d, 2H, *J*=8.0 Hz), 8.14 (AA′BB′, 2H), 8.65 (d, 4H, *J*=4.8 Hz), 8.92 (d, 4H, *J*=4.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 19.4, 31.5, 38.7, 59.7, 68.0, 112.8, 114.6, 120.1, 125.3, 126.5, 129.2 (br), 130.0, 132.0 (br), 133.8, 135.6, 140.0, 142.0, 159.0; HRMS (ES) calcd for $C_{56}H_{53}N_4O_4S_2Cl_2$: 979.2885, found: 979.2886.

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Density functional theory calculations and experimental parameters for mutarotation of 6-deoxy-L-mannopyranosyl hydrazine

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Abstract—The geometry and energy profiles of the mutarotation pathway present in the equilibrium of 6-deoxy-β-L-mannopyranosyl 2,4-dinitrophenylhydrazine (**1a**), 6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**1b**), and 6-deoxy-α-L-mannopyranosyl 2,4-dinitrophenylhydrazine (**1c**) were modeled by DFT calculations at B3LYP/6-31G(d) level affording ΔG_{DFT}=0.000 kcal/mol, ΔG_{DFT}=0.174 kcal/mol, and ΔG_{DFT}=3.411 kcal/mol, respectively. Experimentally, the β-L-pyranose **1a** occurs in 50% followed by the acyclic structure **1b** in 44% as well as by the α-L-anomer **1c** in 6%. The conformations of **1a–c** and their corresponding 2,3,4-triacetyl derivatives **2a–c** were studied by molecular modeling and NMR spectroscopy. IR frequencies, NMR chemical shifts, and X-ray diffraction analysis were employed to compare theoretical with experimental structural parameters.

1. Introduction

Hydrazine derivatives play very important roles in agriculture, pharmaceutical, and chemical industries, and in many aspects of several emerging technologies.[1] This wide class of substances has attracted the attention of both synthetic[2] and theoretical chemists[3] because they represent relevant models for reactivity exploration and the study of the conformational behavior of nitrogen-containing substances. Combination of hydrazine compounds with sugars affords glycosylhydrazine derivatives, which increase the complexity of the chemical structure and properties of the hydrazine moiety. An interesting aspect of glycosylhydrazines, in particular of glycopyranosylhydrazines (e.g., **1a**), is their ability to establish an equilibrium with the corresponding acyclic glycosylhydrazones (**1b**), which leads to the anomeric form of the cyclic glycopyranosylhydrazines (e.g., **1c**) as exemplified in Scheme 1. This equilibrium can be studied under terms comparable to those of sugars mutarotation.[4]

There is no fully delineated systematization that can explain and predict the equilibrium for glycosylhydrazine derivatives. It seems to depend on the structure and stereochemistry of each particular carbohydrate as well as on the acidity or basicity of the solution.[5,6] The mutarotational process has been often described as a tautomerism[6] because of the prevalence of the equatorial *N*-glycosidic anomer and the open chain glycosylhydrazone components, both over that of the anomer carrying the *N*-moiety axially oriented (e.g., **1a** and **1b** over **1c**). In several hydrazine derivatives, particularly for those of rhamnose and mannose, it has also been proved that the predominant isomer in the crystalline state[7–9] is not always the one observed in solution.[5,6,10]

A major part of our ongoing research is directed toward the application of molecular modeling in the stereochemical and conformational elucidation of polyoxygenated molecules derived from 6-deoxyhexoses.[11,12] A theoretical methodology to model and predict the mutarotational equilibrium among the β-L-anomer **1a**, the acyclic component **1b**, and the α-L-anomer **1c** is described and compared to the results obtained by NMR data. The geometric and energetic mutarotational pathways were analyzed by density functional theory calculations at B3LYP/6-31G(d) level.[13] In addition, the same protocols were applied to study the structure and conformation of acetyl derivatives **2a–c** and **3**. Although theoretical approaches on the structure of monosaccharides[4,14–16] and glycopyranosylamines[17] have

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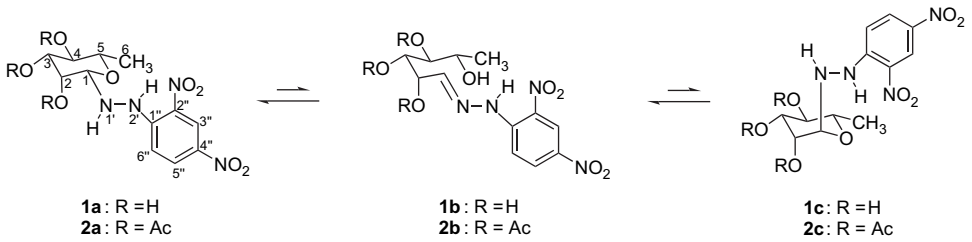


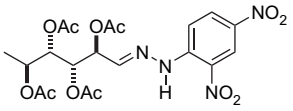
1a: R =H
2a: R = Ac

1b: R =H
2b: R = Ac

1c: R =H
2c: R = Ac

Scheme 1. Mutarotation in glycosylhydrazine derivatives.

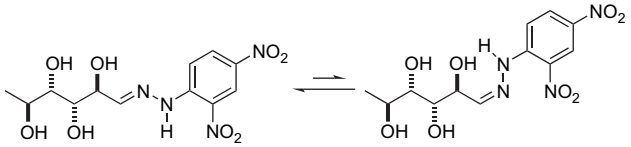
recently been published, there are as yet no DFT structural and mutarotational analyses of glycosylhydrazine derivatives.



3

2. Results and discussion

6-Deoxy-L-mannose (L-rhamnose) treated with 2,4-dinitrophenylhydrazine produced, after crystallization in EtOH, the stable cyclic 1-(6-deoxy-β-L-mannopyranosyl)-2-(2,4-dinitrophenyl) hydrazine (**1a**) with a molecular formula of $C_{12}H_{16}N_4O_8$. Its melting point (165–167 °C) surprisingly matched that previously reported for hydrazone **1b**.[18] However, NMR analysis supported our suspicion that the reported open chain substance is in fact the β-L-pyranose **1a**. The signal for the anilinic NH was recorded at δ 9.65 (s) while the glycosidic NH was registered at δ 5.78 and shown to be coupled with the anomeric proton H-1 at δ 4.16 (*trans*-diaxial coupling constant $J_{NH,1}$=11.5 Hz) in the ^{1}H NMR spectrum in DMSO-d_6. The ^{13}C NMR spectrum was also consistent with that for the pyranoside structure for **1a**, e.g., the anomeric carbon C-1 at δ 87.0. On addition of trace amounts of hydrochloric acid, the DMSO-d_6 solution of **1a** immediately produced a mixture of four major components detectable through their anilinic NH protons at δ 9.66, 9.67, 11.39, and 12.78 in the ^{1}H NMR corresponding to the β-L-anomer **1a**, the α-L-anomer **1c**, and the acyclic component **1b** in its *E* and *Z*-configurations at the C=N double bond, respectively (Scheme 2). The percentage of the isomers **1a** (50%), **1b**-*E* (36%), **1b**-*Z* (8%), and **1c** (6%) was calculated by the signal integrals of selected hydrogen atoms as can be seen in Figure 1. Structural assignments were confirmed through the signals for the anomeric carbon atoms at δ 87.0 for **1a** and 87.9 for **1c**, the signals for the C-1 sp^2 carbon atoms at δ 155.7 for **1b**-*E* and δ 152.9 for **1b**-*Z*. These assignments were further confirmed through a detailed analysis of the 2D NMR spectra of the mutarotational equilibrated mixture, which included COSY, NOESY, gHSQC, and gHMBC experiments. NOESY spectrum was particularly useful in confirming the double bond geometry in the **1b**-*E* and **1b**-*Z*-isomers because of the strong interaction between the anilinic NH and the vinylic H-1 signals only observed in **1b**-*E* but not in **1b**-*Z*. The information provided by the COSY, gHSQC, and gHMBC spectra allowed the individual assignment of signals for the equilibrium components, including the anomeric protons for **1a** and **1c** at δ 5.78 and 4.52, respectively, and the vinylic protons for **1b**-*E* and **1b**-*Z* at δ 8.03 and 7.22, respectively. The interconversion between the α- and β-anomers was also registered by the change in the specific rotation of compound **1a** in acidic solution.



1b-*E* **1b**-*Z*

Scheme 2. *E*-*Z* Isomerization of **1b**.

In order to study the structures of the acyclic components and the α-L-pyranoside form, it was necessary to produce substances that could be isolated for spectroscopic analysis by NMR. Treating pure **1a** with acetic anhydride in pyridine afforded the following such substances: 1-(2,3,4-tri-*O*-acetyl-6-deoxy-β-L-mannopyranosyl)-2-(2,4-dinitrophenyl)-hydrazine (**2a**), 2,3,4-tri-*O*-acetyl-6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**2b**), and 1-(2,3,4-tri-*O*-acetyl-6-deoxy-α-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (**2c**), together with 2,3,4,5-tetra-*O*-acetyl-6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**3**). Additionally, treatment of **1a** with acetyl chloride afforded **3** as the main product. Compounds **2a**, **2b**, and small amounts of **2c** were purified by normal phase HPLC. However, they equilibrated to the original mixture (**2a**–**c**) after standing for 24 h in individual acidic $CDCl_3$ solutions. Linear derivative **2b** was obtained exclusively in its *E*-configuration.

The ^{1}H NMR spectrum of **2a** clearly indicated the presence of a pyranoside ring bearing three acetoxyl substituents. In this case, the signal for the anilinic NH appeared at δ 9.63 while the NH attached to the saccharide was at δ 4.52 and strongly coupled with the anomeric proton H-1 at δ 4.40 ($J_{NH,1}$=11.4 Hz). Adding D_2O permitted the assignment of the labile hydrogen atoms. ^{13}C NMR spectrum exhibited the characteristic signal for the C-1 anomeric carbon at δ 85.7. The X-ray diffraction analysis of **2a** confirmed the structure and stereochemistry of this substance (Fig. 2), which exhibited the 2,4-dinitrophenylhydrazine moiety in a β-equatorial orientation at C_1. The hydrogen atoms H_1–H_2 and H_2–H_3 of this 6-deoxymannose derivative (**2a**) were found in a *syn*-clinal relationship while H_3–H_4 and H_4–H_5 appeared in an *anti*-periplanar orientation (Table 1). The pyranoside ring exists in a conformation close to the classical chair, slightly distorted toward a twist-boat.

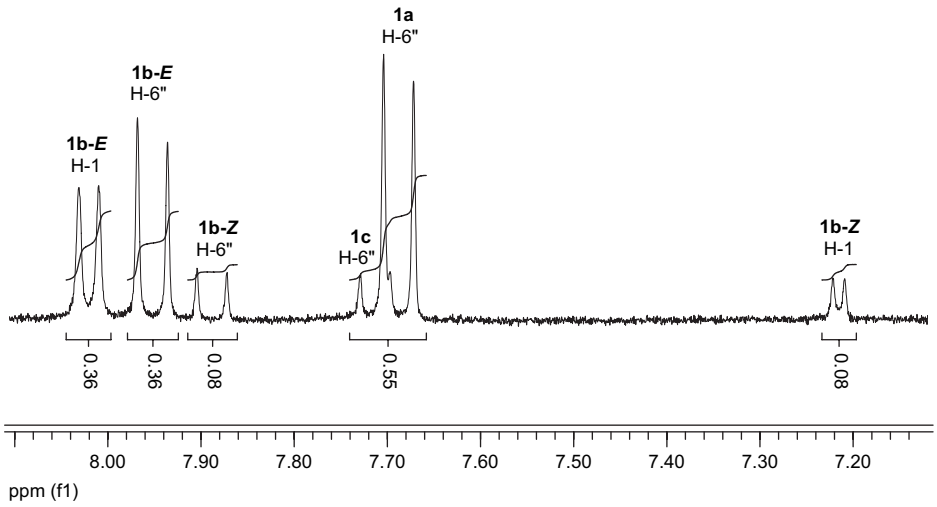


Figure 1. A section of the ^{1}H NMR aromatic region (δ 8.10–7.12) for the equilibrated mixture of 1-(6-deoxy-β-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (**1a**), 6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**1b**, *E* and *Z*-isomers), and 1-(6-deoxy-α-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (**1c**) in DMSO-d_6+HCl at 300 MHz.

Density functional theory calculations were used to analyze the minimum energy pathway and the geometry of each component in the mutarotational equilibrium (Scheme 1). Conformational distribution of compounds **1a**–**c** and **2a**–**c** was individually calculated by molecular mechanics (MMFF) through an extensive Monte Carlo random search.[19] Due to the presence of the hydrazine moiety, the conformational analysis of the pyranoside rings of **1a**, **1c**, **2a**, and **2c** was far more complicated than that expected for simple hexose derivatives. However, in the absence of the usual hydroxymethyl group, normally prominent in the conformational properties of glucopyranosides, the difficulties involved in this analysis were mitigated.[15] A molecular mechanics energy range of 0–10 kcal/mol was selected for these calculations, which yielded a total of 30, 106, and 63 minimum energy conformations for compounds **1a**, **1b**, and **1c**, respectively. Low-energy conformations were correlated to the rotations of the C_1–N_1–N_2–$C_{1'}$ bonds, which defined the conformation of the dinitrophenylhydrazine moiety. The cooperative clockwise or counterclockwise orientations of the hydroxyl groups also played a relevant role in the conformational distribution. Each conformational species was geometry analyzed and selected according to the maximum number of cooperative hydrogen bonds. Using this filtering criteria, 7, 27, and 10 conformations for **1a**, **1b**, and **1c**, respectively, were optimized by DFT calculations employing the B3LYP method with the 6-31G(d) basis set. To ensure a full exploration of the conformational space in linear derivative **1b**, the distribution was additionally calculated through a systematic search model[11] of 54 conformational variants resulting from rotation of the C_2–C_3, C_3–C_4, and C_4–C_5 bonds every 120°, as well as the C_1–C_2 bond by 180°. The minimum energy structures were optimized by DFT calculations by employing the same method and basis set to yield similar results as those obtained from the Monte Carlo method, also within a 0–10 kcal relative range. Analysis of the molecular geometry of each conformer revealed that the physical principles that govern the conformational distribution can be mainly defined by the presence of an intramolecular hydrogen bond patterns as well as steric effects and repulsive 1,3 oxygen–oxygen interactions. Table 2 contains the 27 refined global and local minimum energy structures ordered according to their stability and the corresponding H–C–C–H dihedral angles found in the C_1–C_2–C_3–C_4–C_5 fragment of **1b**. Each rotameric species was named by using the following descriptors: *P* for plus (ca. +60°), *A* for anti (ca.+180°), and *M* for minus (ca. −60°) according to the nearest value for the measured dihedral angles.

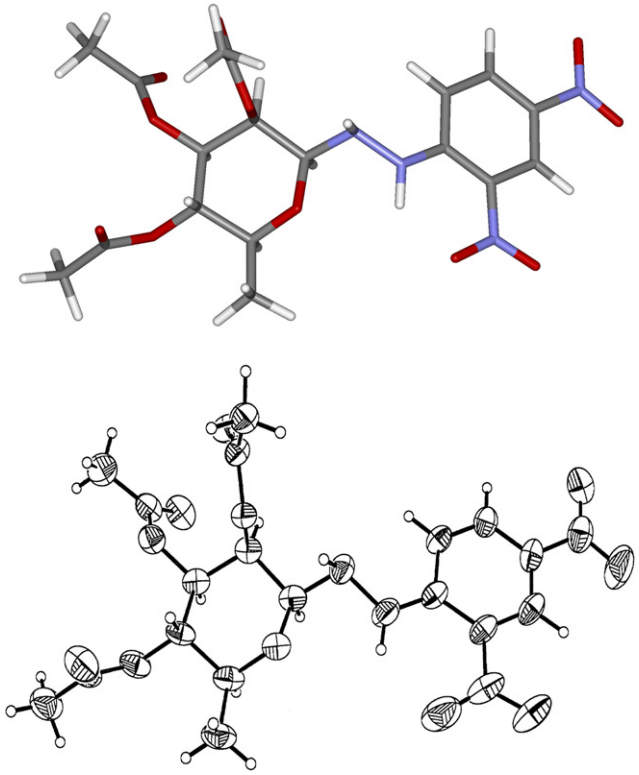


Figure 2. Comparison between the DFT B3LYP/6-31G(d) molecular model of **2a** and its X-ray structure.

Figure 3 illustrates the DFT minimum energy pathway for the mutarotational process from **1a** to **1c** involving six key acyclic conformers of **1b** in the *E*-configuration. The

Table 1. DFT B3LYP/6-31G(d) dihedral angles (in deg) and calculated[a] versus observed[b] ^1H–^1H vicinal coupling constants (in hertz) for the global minimum of pyranosides **1a**, **1c**, **2a**, and four conformations of **2c** (comparison between DFT and X-ray dihedral angles for **2a** is shown)

Compound	$\phi_{H1-C-C-H2}$	$J_{1,2(calcd)}$	$J_{1,2(obsd)}$	$\phi_{H2-C-C-H3}$	$J_{2,3(calcd)}$	$J_{2,3(obsd)}$	$\phi_{H3-C-C-H4}$	$J_{3,4(calcd)}$	$J_{3,4(obsd)}$	$\phi_{H4-C-C-H5}$	$J_{4,5(calcd)}$	$J_{4,5(obsd)}$
1a	−54.1	1.3	0.6	51.2	3.4	3.0	−176.3	9.4	9.3	179.3	9.2	9.2
1c	70.8	1.7	2.0	53.7	3.0	3.3	−172.8	9.1	9.1	177.7	9.2	9.0
2a[c]	−55.0 (−49.3)	1.4	1.2	54.0 (53.5)	3.1	3.3	−173.0 (−174.4)	9.4	10.2	176.0 (−175.3)	9.2	9.3
2c-1	71.3	2.4	—	56.1	4.5	—	−173.0	9.4	—	173.4	9.1	—
2c-2	103.7	1.5	—	59.6	4.1	—	−163.8	8.2	—	116.9	2.8	—
2c-3	168.1	8.4	—	−51.1	5.2	—	−64.7	3.3	—	73.6	1.3	—
2c-4	166.0	8.2	—	−58.3	4.2	—	−103.2	0.6	—	163.2	8.6	—
2c-avg		5.1[d]	4.1		4.5[d]	5.8		5.4[d]	5.0		5.5[d]	6.9

[a] Calculated from DFT dihedral angles via a generalized Karplus-type equation.
[b] Measured in DMSO for **1a** and **1c** and in $CDCl_3$ for **2a** and **2c**.
[c] X-ray dihedral angles are shown in parenthesis.
[d] Averaged value.

β-L-anomer (**1a**) is mainly found in a single conformation with cooperative anticlockwise orientation of the hydroxyl groups and a *trans*-diaxial orientation of the H_1–C_1–N_1–H moiety. For the open chain component **1b**, conformer **1b**-***MPAA***, illustrated, is generated by the pyranoside ring opening at the C_1–O_5 bond of **1a**. The population of this highly energetic conformer (E_{rel}=10.932 kcal/mol) moves toward the more stable rotamer **1b**-***PPPP***, which is in fact the predominant species for the linear component **1b** and contains four optimally-oriented cooperative hydrogen bonds in the tetrahydroxylated chain. However, the rotameric population is distributed to generate an equilibrium involving small amounts of **1b**-***PPPA*** and **1b**-***PPAA***, which ultimately leads to the α-L-anomer **1c**. The rotameric species of **1b** that are not depicted in Figure 3 but listed in Table 2 are also present in the equilibrium according to the Boltzmann distribution, and can be located in branches derived from the main pathway for the mutarotational process. In the α-form, the global minimum **1c** (E_{DFT}=−1287.454180 au, Fig. 3) was followed by a second one (E_{DFT}=−1745.451136 au) arising from the pyranoside chair inversion at the point where the hydrazine moiety and the hydroxyl group at C-2 adopted an equatorial orientation. In this minimum energy conformer, the methyl group at C-5 and the hydroxyl groups at C-3 and C-4 remained axially oriented. This conformational inversion was further studied with peracetylated derivative **2c**.

Table 1 lists the H–C–C–H torsion angles of the global minimum for the cyclic substances **1a** (E_{DFT}=−1287.460165 au) and **2a** (E_{DFT}=−1745.459742 au), both of which showed a prevalent conformation. In contrast, a complex rotameric equilibrium was established in triacetylated derivative **2b** in a similar way as that previously found

Table 2. DFT global and local minimum energy conformers and selected H–C–C–H dihedral angles for the acyclic component **1b**

Conformer[a]	E_{DFT}[b]	E_{rel}[c]	H_1–H_2[d]	H_2–H_3[d]	H_3–H_4[d]	H_4–H_5[d]
1b-*PPPP*	−1287.454425	3.602	81.9	55.5	53.2	51.7
1b-*MPPP*	−1287.453216	4.360	−51.5	53.2	53.9	52.3
1b-*MAMA*	−1287.449155	6.909	−62.7	172.5	−68.9	174.1
1b-*MAPP*	−1287.449031	6.987	−59.2	−176.8	71.7	59.3
1b-*PAAA*	−1287.446925	8.308	77.4	−178.2	177.8	−161.6
1b-*PMPA*	−1287.446698	8.451	80.0	−50.4	83.6	−174.1
1b-*PPPA*	−1287.446668	8.469	72.7	58.8	77.4	−175.5
1b-*MAPM*	−1287.446631	8.493	−62.5	−178.9	80.5	−51.3
1b-*AMPP*	−1287.446391	8.644	167.5	−60.6	54.2	57.7
1b-*PPMP*	−1287.446275	8.716	63.5	64.1	−63.7	56.2
1b-*PPPM*	−1287.445829	8.996	80.6	60.0	59.9	−57.7
1b-*MAAP*	−1287.445533	9.182	−62.3	−168.7	−175.7	85.1
1b-*MAAM*	−1287.445347	9.299	−61.8	−175.9	174.1	−52.7
1b-*PAMP*	−1287.445205	9.388	81.7	164.4	−71.5	47.4
1b-*PPAA*	−1287.444489	9.837	84.4	77.5	−172.6	−165.2
1b-*MPPA*	−1287.444379	9.906	−53.2	53.2	72.7	−177.0
1b-*AMAM*	−1287.443931	10.187	175.2	−54.5	179.7	−53.7
1b-*MAPA*	−1287.443230	10.627	−62.0	173.2	71.7	−177.6
1b-*MPAA*	−1287.442744	10.932	−41.3	80.8	−169.7	−165.2
1b-*AMAA*	−1287.442687	10.968	175.8	−56.0	173.2	−178.0
1b-*PMAP*	−1287.442280	11.223	55.9	−64.7	143.2	55.2
1b-*PPMA*	−1287.441215	11.891	54.4	69.1	−70.7	170.0
1b-*MPAP*	−1287.441208	11.896	−58.1	51.2	169.1	53.9
1b-*AMMA*	−1287.440794	12.156	174.9	−62.8	−64.5	169.8
1b-*AMPM*	−1287.439980	12.666	−161.8	−56.3	60.6	−58.5
1b-*APAA*	−1287.439708	12.837	177.5	52.3	139.5	177.6
1b-*MAMM*	−1287.439604	12.902	−57.3	169.5	−60.1	−62.8

[a] Descriptors are based on H–C–C–H dihedral angles ca. +60°(*P*), ca. 180°(*A*), and ca. −60°(*M*) for the C_1–C_2–C_3–C_4–C_5 fragment.
[b] DFT B3LYP/6-31G(d) total energy in au.
[c] Relative DFT energies (kcal/mol) are in reference to **1a** (E_{DFT}=−1287.460165 au; 1 au=627.51 kcal/mol).
[d] H–C–C–H dihedral angle.

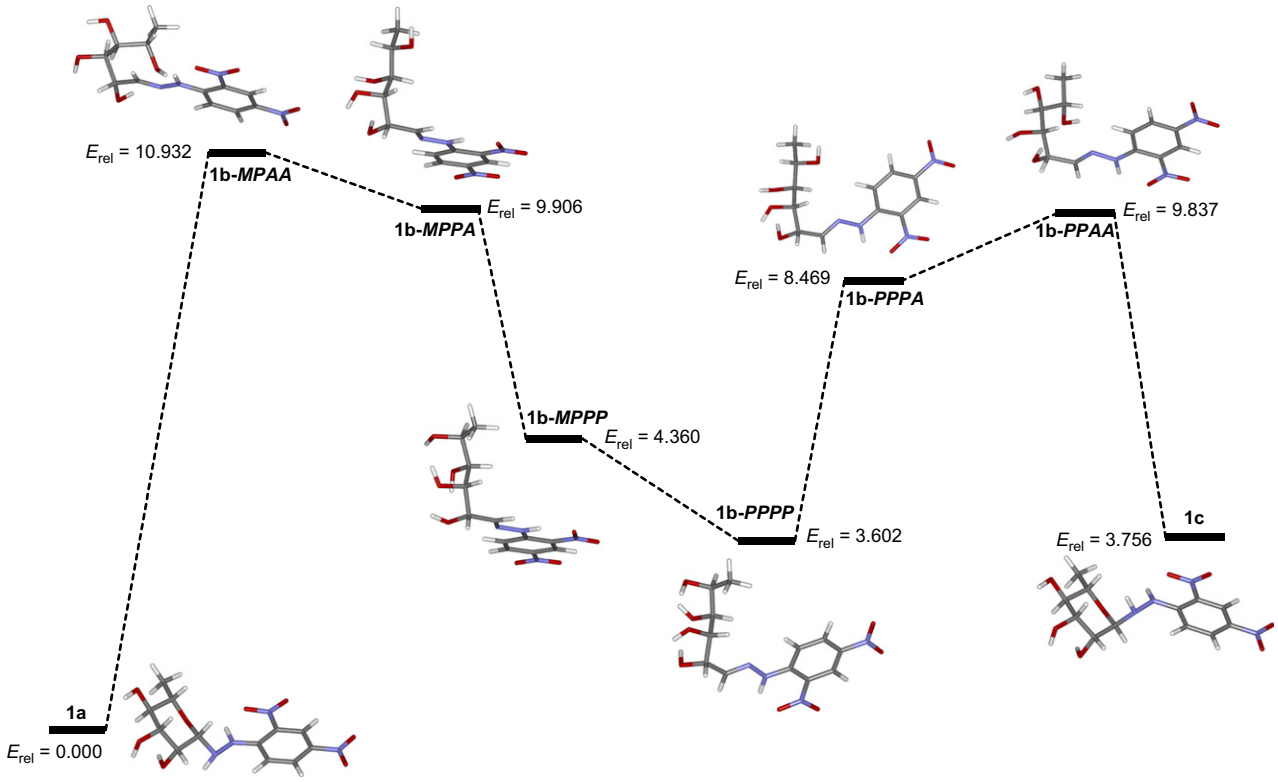


Figure 3. DFT B3LYP/6-31G(d) minimum energy pathway for the mutarotational process from **1a** to **1c**. Relative energies are in kcal/mol referred to the global minimum **1a**.

for tetra-*O*-acetyl-6-deoxy-L-mannose derivatives.[11] This resemblance became evident from the $J_{2,3}$=8.5, $J_{3,4}$=1.9, and $J_{4,5}$=8.5 Hz coupling constant values, which remained very close in all the linear substances derived from this carbohydrate. For pyranoside **2c**, ring inversion occurred between the two possible chair conformations (**2c**-**1** and **2c**-**3**) through two low-energy twisted-boat conformations (**2c**-**2** and **2c**-**4**) as depicted in Figure 4. The equilibrium between the four conformations in **2c** (**2c**-**1**: E_{DFT}= −1745.452419 au; **2c**-**2**: E_{DFT}=−1745.451391 au; **2c**-**3**:

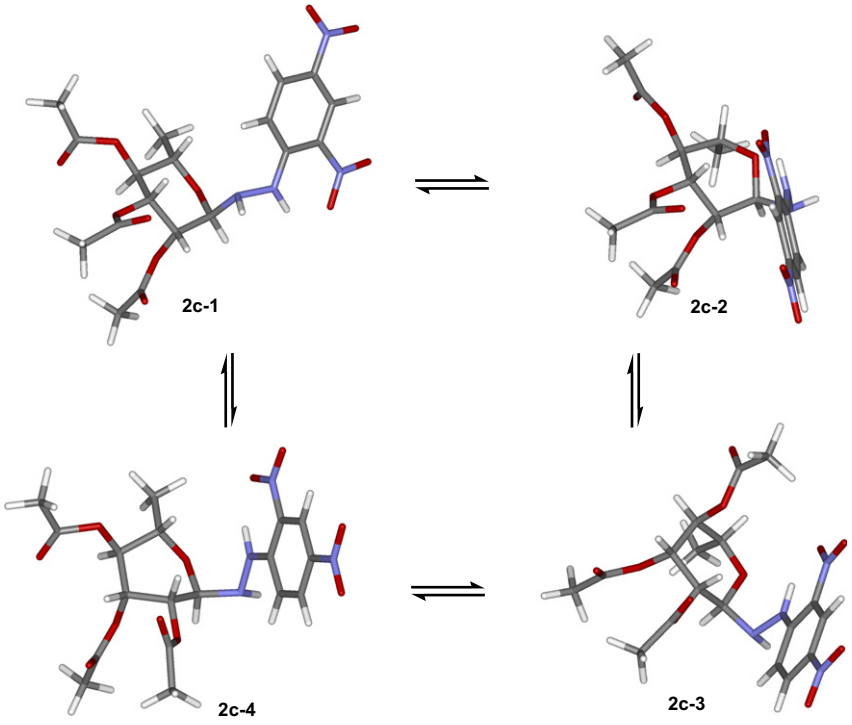


Figure 4. The conformational equilibrium of **2c**.

Table 3. DFT B3LYP/6-31G(d) conformation for the O–C1–C2–C3–C4–C5 rings of **1a**, **1c**, **2a**, and **2c**

Compound	Conformational contributions[a]			Ring conformation	Conformational parameters		
	Chair	Boat	Twist-boat		Q[b]	ϕ[c]	θ[c]
1a[d]	88	2	10	Between chair and half-chair	0.593	24.20	7.75
1c[d]	94	3	3	Distorted chair	0.556	22.88	3.19
2a[d]	93	0	6	Distorted chair	0.545	28.47	4.13
2a[e]	89	9	2	Distorted chair	0.583	4.42	6.77
2c-1[d]	91	6	3	Distorted chair	0.545	19.34	5.26
2c-2[d]	4	61	35	Between boat and twist-boat	0.709	10.73	87.58
2c-3[d]	96	1	3	Chair	0.511	22.53	2.46
2c-4[d]	1	59	40	Between boat and twist-boat	0.731	12.03	89.29

[a] Quantitative contributions of basic conformations in percentage.
[b] Total puckering amplitude in Å.
[c] In degrees.
[d] From density functional theory coordinates.
[e] From X-ray diffraction coordinates.

E_{DFT}=−1745.455161 au; and **2c-4**: E_{DFT}=−1745.451046 au) was detectable from the averaged experimental coupling constants ($J_{1,2}$=4.1, $J_{2,3}$=5.8, $J_{3,4}$=5.0, and $J_{4,5}$=6.9 Hz) measured by spectral simulation. The calculated ^{1}H NMR couplings constants for the four conformations (**2c-1** to **2c-4**) and the averaged values are listed in Table 1. In this equilibrium, the contributing factors to achieve the stability of conformer **2c-3** over **2c-1** were the equatorial orientation of the hydrazine moiety at C_1, the largest group attached to the six-membered ring; the interaction between the hydrogen atom at $N_{1'}$ and the oxygen atom of the pyranoside ring O_1 in the O_1–C_1–$N_{1'}$–H fragment (distance=2.53 Å) and the interaction between the hydrogen atom attached to $N_{2'}$ and the oxygen atom O_1 in the fragment O_1–C_1–$N_{1'}$–$N_{2'}$–H (distance=2.28 Å).

Cremer and Pople polar set of parameters[20] were calculated using the DFT and X-ray coordinates for the quantitative conformational description of the pyranoside minimum energy structures (Table 3). The Altona equation was used to convert dihedral angles into calculated vicinal coupling constants ($^3J_{H-H}$).[21] Calculated and observed ^{1}H–^{1}H vicinal coupling constants showed a good correlation, which validated the DFT conformations for the rigid compounds **1a** and **2a**, and for the mobile pyranoside **2c** (Table 1).

If only the relative DFT energy values of the structures in mutarotation were considered (Fig. 3), the prevalent component according to the Boltzmann distribution would be **1a**. However, by taking into account the thermodynamic factors, a better prediction of the mutarotation composition at the equilibrium was obtained. Table 4 presents the data obtained by a thermochemical analysis in which the corresponding vibrational frequencies and thermal parameters were calculated using the optimized B3LYP/6-31G(d,p) global minimum structures of **1a**, **1b**, and **1c**. The calculated frequencies were scaled by a factor of 0.97 and compared with the experimental frequencies measured in the IR spectrum of the mixture of **1a**, **1b**, and **1c** at equilibrium. Figure 5 shows good agreement between the calculated and observed values, validating the B3LYP/6-31G(d,p) thermodynamic parameters for the mutarotational components. These values were used for estimation of the relative populations of **1a**, **1b**-***PPPP***, and **1c** according to the Gibbs free energy equation $\Delta G=\Delta H-T\Delta S$ and $\Delta G=-RT\ \ln K$. These refined calculations for the three main components also considered the zero-point correction, and the thermal correction to energy and enthalpy, providing more accurate values than those reflected by the relative E_{DFT}. The ΔG values were estimated as ΔG_{DFT}=0.000 kcal/mol for **1a**, ΔG_{DFT}= 0.174 kcal/mol for **1b**-***PPPP***, and ΔG_{DFT}=3.411 kcal/mol for **1c**, which yielded a predicted population at equilibrium of 57.2%, 42.6%, and 0.2% for each species, respectively. These theoretical results were in line with the 50%, 44%,

Table 4. Thermochemical parameters (in kcal/mol) and population (in %) for the mutarotational equilibrium calculated with the B3LYP/6-31G(d,p) global minimum structures of **1a–c**

	ΔE_0[a]	ΔE_{298}[b]	ΔH_{298}[b]	ΔS_{298}[b]	ΔG_{298}[b]	p[b]
1a	0.000	0.000	0.000	0.000	0.000	57.2
1b	1.035	1.462	0.4463	1.734	0.174	42.6
1c	3.591	3.632	0.066	0.287	3.411	0.2

[a] Sum of electronic and zero-point energy.
[b] Calculated at 298.15 K and 1 atm. For the **1a** species the absolute values are E_0=−1287.18993 au, E_{298}=−1287.16810 au, H_{298}=24.890 kcal/mol, S_{298}=158.587 cal/mol K, and G_{298}=−1287.20379 au.

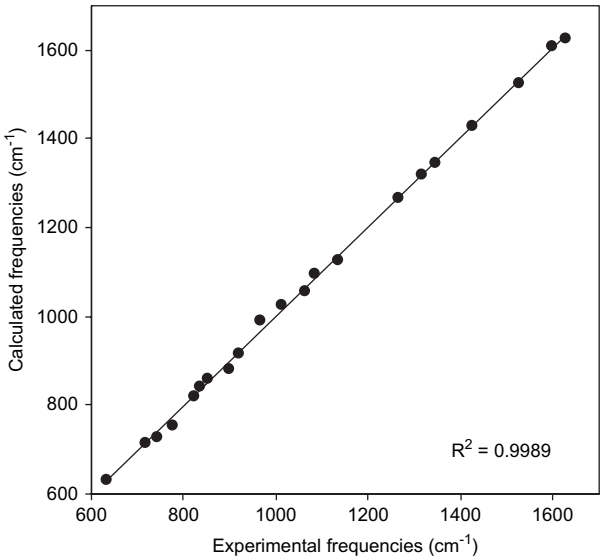


Figure 5. Comparison of the experimental infrared frequencies of compound **1a** with the corresponding calculated values obtained at the B3LYP/6-31G(d,p) level of theory.

Table 5. Comparison between theoretical and experimental ^{13}C NMR chemical shifts for **1a**

Atom	δ_{calcd} [a]	δ_{scaled} [b]	δ_{exp} [c]	$\lvert\delta_{scaled}-\delta_{exp}\rvert$
C-1′	135.1	145.3	149.0	3.7
C-4′	125.0	135.2	135.3	0.1
C-2′	118.7	128.9	128.3	0.6
C-5′	117.1	127.3	129.8	2.5
C-3′	112.2	122.4	123.2	0.8
C-6′	101.0	111.2	116.0	4.8
C-1	80.3	90.5	87.0	3.5
C-3	66.7	76.9	73.7	3.2
C-4	66.5	76.7	73.1	3.6
C-5	65.9	76.1	72.0	4.1
C-2	63.5	73.7	69.8	3.9
C-6	9.3	19.5	18.1	1.4

[a] Calculated at B3LYP/6-31G(d,p) level of theory using GIAO magnetic shielding.
[b] Calculated by linear fit of δ_{calcd} versus δ_{exp}.
[c] Measured at 300 MHz in DMSO-d_6 solution.

and 6% observed NMR ratio (Fig. 1). The entropic contribution, estimated as $\Delta S_{\mathbf{1a},\mathbf{1b}}$=5.814 cal/mol K and agreeing with the PM3 calculations for the mutarotation of glucopyranosylamine derivatives,[22] is notably important for the stability of acyclic structure **1b**. Finally, the experimental ^{13}C NMR chemical shifts for **1a** were compared with these obtained with isotropic magnetic shielding calculations using the SCF GIAO method at DFT/B3LYP level of theory and the basis set 6-31G(d,p). Diagnostic values for C-1 of each species were in close agreement with those obtained experimentally (Table 5).

3. Conclusions

DFT calculations, NMR analysis, and X-ray diffraction studies of 6-deoxy-L-mannopyranosyl hydrazine were performed in order to obtain conformational parameters. The DFT calculated values for the equilibrium among the mutarotational species **1a**, **1b**, and **1c** could be further refined by taking into consideration local conformers including all possible cooperative hydrogen bonded species and the inclusion of solvent modeling. Nevertheless, this work shows that DFT calculations at B3LYP/6-31G(d,p) level represent suitable tools to predict the thermodynamic properties, mutarotational composition, stereochemical features, and conformational preferences of glycosylhydrazines.

4. Experimental

4.1. General

Column chromatography was carried out with silica gel (70–230 mesh) Merck. $CDCl_3$ for NMR spectroscopy was filtered through dry alumina prior to use. HPLC separations were accomplished using an ISCO silica gel column (particle size: 10 μm; column size: 21.2 mm×250 mm) on a Waters (Milford, MA, USA) 600E multisolvent delivery system equipped with a Waters 410 refractive index detector connected to a computer (Optiflex 466/Dell). Control of the equipment, data acquisition, processing, and management of the chromatographic information was performed with the Millennium 2000 software program (Waters). IR spectra were determined on a Perkin–Elmer 16F PC or on a Buck 500 spectrophotometer. ORD was measured on a Perkin–Elmer 341 or JASCO DIP-360 polarimeters. The ^1H (300 MHz), ^{13}C (75.4 MHz), COSY, HMQC, and HMBC experiments were conducted on a Varian Mercury 300 spectrometer. LRMS were measured on a JEOL JMS-AX505HA mass spectrometer. HREIMS was determined on a Kratos concept II H mass spectrometer and HRFABMS were measured on a JEOL DX 300 mass spectrometer.

4.1.1. General procedures for recording the mutarotational equilibria. (a) NMR: solutions of pure samples (5 mg) of **1a** in DMSO-d_6 (0.8 mL) and **2a–c** in $CDCl_3$ (0.8 mL) or DMSO-d_6 (0.8 mL) were treated with 12.1 M HCl in H_2O (1 μL) in 5 mm NMR tubes. (b) Optical activity: specific rotation of a solution of **1a** (5 mg) in DMSO-d_6 (0.8 mL) was monitored at room temperature, $[\alpha]_D$ +35.0. Treatment of this solution with 12.1 M HCl in H_2O (1 μL) provoked an immediate decrease in the optical activity value, $[\alpha]_D$ +0.3. This rotation remained constant during the following 2 h.

4.1.2. pH measurements. The pH values were registered with a VWR Scientific pHmeter (model 8000). A mixture of DMSO-d_6 (4.8 mL) and H_2O (6 μL) has a pH 8.50. The pH of a mixture of compound **1a** (30 mg) in DMSO-d_6 (4.8 mL) and 12.1 M HCl in H_2O (6 μL) was 2.45 after 5 min of stirring while after 90 min it was 2.54. The acidity of the mixture was raised to pH 2.14 after addition of a second portion of HCl (6 μL).

4.1.2.1. (6-Deoxy-β-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (1a). A solution of 2,4-dinitrophenylhydrazine (0.3 g, 1.5 mmol) in sulfuric acid (0.5 mL) was added to a mixture of H_2O (2 mL) and EtOH (7 mL). The mixture was added to a solution of L-rhamnose monohydrate (0.5 g, 2.7 mmol) in EtOH (3 mL), left for 3 h at room temperature and 16 h at 4 °C. The product was crystallized as orange flakes, which were filtered, washed with 5% sodium bicarbonate solution and H_2O and then recrystallized from 90% EtOH in H_2O to afford **1a** (313 mg, 33%). Orange needles; mp 165–167 °C (lit.[18] 164–165 °C); IR (KBr) ν_{max} 3375, 1629, 1598, 1526, 1427, 1348, 1315, 1268, 1135, 1085, 1062, 1012, 968, 920, 900, 853, 835, 822, 777, 744, 718, 635 cm^{-1}; ORD (*c* 0.61, MeOH) $[\alpha]_{589}$ +34, $[\alpha]_{578}$ +37, $[\alpha]_{546}$ +39; ^1H NMR (300 MHz, DMSO-d_6) δ 9.65 (1H, br s), 8.83 (1H, d, *J*=2.5 Hz), 8.30 (1H, dd, *J*=9.6, 2.5 Hz), 7.68 (1H, d, *J*=9.6 Hz), 5.78 (1H, d, *J*=11.5 Hz), 5.01 (1H, d, *J*=4.9 Hz), 4.83 (1H, d, *J*=4.9 Hz), 4.81 (1H, d, *J*=5.2 Hz), 4.16 (1H, br d, *J*=11.5 Hz), 3.83 (1H, br t, *J*=4.5 Hz), 3.28 (1H, m), 3.18 (1H, m), 3.13 (1H, m), 1.20 (3H, d, *J*=5.7 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 149.0, 135.3, 129.8, 128.3, 123.2, 116.0, 87.0, 73.7, 73.1, 72.0, 69.8, 18.1; EIMS *m/z* (rel int.) $[M]^+$ 344 (1), $[M-C_4H_9O_3]^+$ 239 (8), 194 (11), $[239-NO_2]^+$ 193 (100), 184 (28), $[C_6H_5N_3O_4]^+$ 183 (43), 177 (21), 167 (15), 153 (28), 129 (26), 91 (21), 85 (29); HREIMS *m/z* 344.0957 (calcd for $C_{12}H_{16}N_4O_8$, 344.0968).

4.1.2.2. Acetylation of 1a. A solution of **1a** (100 mg) in pyridine (2.5 mL) was treated with acetic anhydride (2.5 mL) at room temperature for 24 h. The reaction mixture was worked-up[11] and the residue was purified by HPLC in

aliquots of 20 mg (*n*-hexane–EtOAc, 1:1, flow rate=6 mL/min) to yield **3** (23.3 mg, 15.7%, t_R=15.5 min), **2a** (50.0 mg, 36.6%, t_R=17.9 min), **2c** (1.6 mg, 1.2%, t_R=21.8 min), and **2b** (36.8 mg, 26.9%, t_R=26.8 min). Treatment of **1a** (100 mg) with acetyl chloride (5 mL) at room temperature for 2 h followed by evaporation under a N_2 flow and HPLC purification gave **3** in better yields (73 mg, 49%).

4.1.2.3. 1-(2,3,4-Tri-*O*-acetyl-6-deoxy-β-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (2a). Yellow prisms; mp 103–105 °C; IR ($CHCl_3$) ν_{max} 3751, 3365, 1750, 1620, 1594, 1524, 1429, 1372, 1339, 1311, 1238, 1226, 1060, 926, 836 cm^{-1}; ORD (*c* 1.29, $CHCl_3$) $[\alpha]_{589}$ +29, $[\alpha]_{578}$ +29, $[\alpha]_{546}$ +31; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (1H, br s), 9.07 (1H, d, *J*=2.7 Hz), 8.27 (1H, dd, *J*=9.6, 2.7 Hz), 7.68 (1H, d, *J*=9.6 Hz), 5.62 (1H, dd, *J*=3.3, 1.2 Hz), 5.08 (1H, dd, *J*=10.2, 9.3 Hz), 5.00 (1H, dd, *J*=3.3, 10.2 Hz), 4.52 (1H, d, *J*=11.4 Hz), 4.40 (1H, dd, *J*=11.4, 1.2 Hz), 3.57 (1H, dq, 1H, *J*=9.3, 6.3 Hz), 2.23, 2.08, 2.00 (3H each, 3s), 1.32 (3H, d, *J*=6.3 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.1, 170.0, 169.8, 148.9, 137.3, 130.1, 129.7, 123.6, 115.6, 85.7, 72.1, 71.5, 70.1, 68.9, 20.7, 20.7, 20.5, 17.4; EIMS *m/z* (rel int.) $[M]^+$ 470 (4), 411 (2), 306 (9), 291 (10), 273 (17), 213 (8), 193 (9), 171 (20), 153 (73), 129 (11), 111 (69), 83 (25), $[C_2H_3O]^+$ 43 (100); HREIMS *m/z* 470.1270 (calcd for $C_{18}H_{22}N_4O_{11}$, 470.1285).

4.1.2.4. X-ray analysis of 2a. The crystal (0.22×0.25×0.46 mm) was obtained from EtOAc–hexane. It was monoclinic, space group *C*2, with *a*=21.017(2), *b*=8.154(2), *c*=13.591(2) Å, cell volume=2254.6 (7) $Å^3$, ρ_{calcd}=1.386 g/cm^3 for *Z*=4, MW=470.40, and *F*(000)e^-= 984. The intensity data were measured using Mo K_α radiation (λ=0.71073 Å). Reflections, measured at 293 K within a 2θ range of 1.55–26.99°, were corrected for background, Lorentz polarization, and absorption (μ=0.116 mm^{-1}), while crystal decay was negligible. The structure was solved by direct methods. For the structural refinement the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Final discrepancy indices were R_F=5.65% and R_W=13.08% using a unit weight for 2947 reflections and refining 306 parameters. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.164 e/A^3. Crystallographic data for **2a** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

*4.1.2.4.1. 2,3,4,-Tri-O-acetyl-6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**2b**)*
Yellow oil; IR ($CHCl_3$) ν_{max} 3559, 3363, 1748, 1619, 1594, 1526, 2511, 1425, 1372, 1342, 1312, 1246, 1138, 1063, 924 cm^{-1}; ORD (*c* 0.66, $CHCl_3$) $[\alpha]_{589}$ +14, $[\alpha]_{578}$ +14, $[\alpha]_{546}$ +17; ^1H NMR (300 MHz, $CDCl_3$) δ 11.10 (1H, s), 9.12 (1H, d, *J*=2.5 Hz), 8.37 (1H, dd, *J*=9.3, 2.5 Hz), 7.91 (1H, d, *J*=9.3 Hz), 7.43 (1H, br d, *J*=5.2 Hz), 5.79 (1H, dd, *J*=8.5, 1.9 Hz), 5.54 (1H, dd, *J*=8.5, 5.2 Hz), 5.11 (1H, dd, *J*=8.5, 1.9 Hz), 3.72 (1H, ddq, *J*=8.5, 6.1, 4.9 Hz), 2.81 (1H, d, *J*=4.9 Hz), 2.13, 2.12, 2.10 (3H each, 3s), 1.20 (3H, d, *J*=6.1 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.5, 170.0, 169.6, 144.6, 143.8, 139.0, 130.3, 129.9, 123.2, 116.7, 73.5, 69.8, 69.0, 65.2, 20.9, 20.8, 20.7, 19.1; FABMS *m/z* $[M+H]^+$ 471, $[M]^+$ 470, $[M-C_2H_3O_2]^+$ 411, $[M-C_2H_3O_2-2C_2H_4O_2]^+$ 291; HRFABMS *m/z* 471.1369 (calcd for $C_{18}H_{22}N_4O_{11}$+H, 471.1363).

*4.1.2.4.2. 1-(2,3,4-Tri-O-acetyl-6-deoxy-α-L-mannopyranosyl)-2-(2,4-dinitrophenyl)hydrazine (**2c**)*
Yellow oil; IR ($CHCl_3$) ν_{max} 3575, 3557, 1790, 1731, 1604, 1487, 1466, 1445, 1390, 1294, 1246, 1103, 1063, 975 cm^{-1}; ORD (*c* 0.15, $CHCl_3$) $[\alpha]_{589}$ −19, $[\alpha]_{578}$ −20, $[\alpha]_{546}$ −22; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, s), 9.11 (1H, d, *J*=2.5 Hz), 8.31 (1H, dd, *J*=9.3, 2.5 Hz), 7.66 (1H, d, *J*=9.3 Hz), 5.29 (1H, dd, *J*=7.1, 4.1 Hz), 5.26 (1H, dd, *J*=5.8, 4.1 Hz), 4.98 (1H, dd, *J*=5.8, 5.0 Hz), 4.72 (1H, dd, *J*=6.9, 5.0 Hz), 4.44 (1H, d, *J*=7.1 Hz), 4.11 (1H, quint, *J*=6.9 Hz), 2.15, 2.12, 2.09 (3H each, 3s), 1.36 (3H, d, *J*=6.9 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.9, 169.6, 169.6, 149.3, 137.5, 130.2, 129.7, 123.8, 115.4, 83.9, 71.1, 70.3, 68.9, 66.8, 20.9, 20.8, 20.7, 16.9; EIMS *m/z* (rel int.) $[M]^+$ 470 (1), 446 (1), 306 (9), 291 (11), 273 (14), 213 (5), 193 (5), 171 (11), 153 (41), 129 (8), 111 (33), 83 (11), $[C_2H_3O]^+$ 43 (100); HREIMS *m/z* 470.1273 $[M]^+$ (calcd for $C_{18}H_{22}N_4O_{11}$, 470.1285).

*4.1.2.4.3. 2,3,4,5-Tetra-O-acetyl-6-deoxy-L-mannose 2,4-dinitrophenylhydrazone (**3**)*
Yellow oil; IR ($CHCl_3$) ν_{max} 3309, 1746, 1619, 1594, 1509, 1437, 1373, 1340, 1235, 1147, 1062, 1038, 924, 837 cm^{-1}; ORD (*c* 1.14, $CHCl_3$) $[\alpha]_{589}$ −14, $[\alpha]_{578}$ −15, $[\alpha]_{546}$ −17; ^1H NMR (300 MHz, $CDCl_3$) δ 11.08 (1H, s), 9.12 (1H, d, *J*=2.5 Hz), 8.35 (1H, dd, *J*=9.5, 2.5 Hz), 7.96 (1H, d, *J*=9.5 Hz), 7.35 (1H, dd, *J*=6.0, 1.0 Hz), 5.58 (1H, dd, *J*=8.0, 3.0 Hz), 5.50 (1H, dd, *J*=8.0, 6.0 Hz), 5.36 (1H, dd, *J*=8.5, 3.0 Hz), 5.04 (1H, dq, *J*=8.5, 6.5 Hz), 2.12 (3H, s), 2.12 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 1.24 (3H, d, *J*=6.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.9, 169.9, 169.8, 169.4, 144.6, 144.0, 138.9, 130.1, 129.8, 123.1, 116.7, 70.9, 69.8, 68.7, 66.8, 21.0, 20.7, 20.7, 20.6, 16.3; EIMS (20 eV) *m/z* (rel int.) $[M]^+$ 512 (0.1), $[M-C_2H_3O_2]^+$ 453 (1), $[453-2C_2H_4O_2]^+$ 333 (2), $[333-C_2H_2O]^+$ 291 (10), 290 (14), 251 (16), 129 (10), 117 (10), 111 (11), $[C_2H_3O]^+$ 43 (100); FABMS *m/z* $[M+Na]^+$ 535; HRFABMS *m/z* 535.1288 $[M+Na]^+$ (calcd for $C_{20}H_{24}N_4O_{12}$+Na 535.1286).

4.1.3. Molecular modeling calculations. Geometry optimizations were carried out using the MMFF94 force-field calculations as implemented in the Spartan'04 program.[23] The systematic conformational search for the pyranoside rings was achieved with the aid of Dreiding models considering torsion angle movements of ca. 30°. The E_{MMFF} values were used as the convergence criterion and a further search with the Monte Carlo protocol was carried without considering energy cut off. All local minima were geometry optimized by DFT at the B3LYP/6-31G(d) level using the Spartan'04 routines. The Altona equation was used to calculate vicinal couplings from dihedral angles for each conformer. Gaussian 03W[24] were used to calculate the ^{13}C NMR chemical shifts at the B3LYP/6-31G(d,p) level. The thermochemical parameters ΔE_0, ΔE_{298}, ΔH_{298}, and ΔS_{298} were calculated at the same level considering vibrational frequencies at 298.15 K and 1 atm. These values were used for

estimation of the relative populations according to the following equations: $\Delta G=\Delta H-T\Delta S$ and $\Delta G=-RT \ln K$.

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Chemoselective hydrogenation method catalyzed by Pd/C using diphenylsulfide as a reasonable catalyst poison

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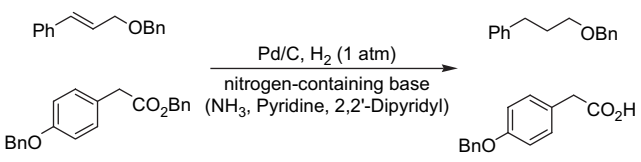
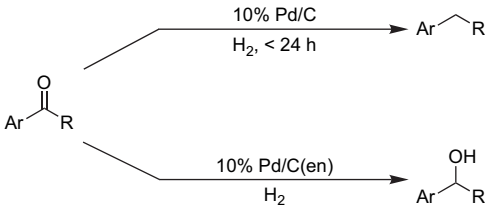
Abstract—While Pd/C is one of the most useful catalysts for hydrogenation, the high catalyst activity of Pd/C causes difficulty in its application to chemoselective hydrogenation between different types of reducible functionalities. In order to achieve chemoselective hydrogenation using Pd/C, we investigated catalyst poison as a controller of the catalyst activity. We found that the addition of Ph_2S (diphenylsulfide) to the Pd/C-catalyzed hydrogenation reaction mixture led to reasonable deactivation of Pd/C. By the use of the Pd/C–Ph_2S catalytic system, olefins, acetylenes, and azides can be selectively reduced in the coexistence of aromatic carbonyls, aromatic halides, cyano groups, benzyl esters, and *N*-Cbz (benzyloxycarbonyl) protecting groups. The present method is promising as a general and practical chemoselective hydrogenation process in synthetic organic chemistry.

1. Introduction

Palladium on activated carbon (Pd/C) is extensively used as a heterogeneous catalyst for hydrogenation in synthetic organic chemistry because of its high catalyst activity, cost-efficiency, easy separation from the reaction mixture, and reusability.[1] However, Pd/C is too active to catalyze selective hydrogenation among the different types of reducible functionalities. Deactivator of the catalyst is recognized as a catalyst poison and it is reported that the deactivation effect depends on the kind or/and amount of the catalyst poison.[1b] Therefore, an appropriate use of the catalyst poison in Pd/C-catalyzed hydrogenation could control the catalyst activity leading to chemoselective hydrogenation.[1] We have reported a method of chemoselective hydrogenation of olefin or benzyl ester functionalities without deprotection of the *O*-benzyl protecting groups by the addition of nitrogenous catalyst poisons such as NH_3, pyridine, or 2,2′-dipyridyl (Scheme 1).[2] We also developed a carbon-supported Pd-ethylenediamine complex [Pd/C(en)],[3] and in the hydrogenation of aromatic ketones using Pd/C(en), a selective partial reduction was achieved to afford the corresponding benzyl alcohol without hydrogenolysis, although Pd/C-catalyzed hydrogenation removed the carbonyl oxygen from the aromatic ketone derivatives (Scheme 2).[3]



Scheme 1.



Scheme 2.

In order to establish a catalytic hydrogenation system possessing a distinct chemoselectivity, we focused on sulfur-containing compounds with the expectation that they should work more effectively as catalyst poisons than nitrogenous compounds. Sulfur-containing catalyst poisons have been reported: quinoline-S is used for Rosenmund reduction in order to avoid the over-reduction of aldehydes to the corresponding alcohols;[4] thiophene or butylmercaptan is used for the selective reduction of olefin tolerating *O*-benzyl protecting groups;[5] platinum sulfide (PtS) catalyzes the conversion from halonitrobenzenes to haloanilines without dehalogenation.[6] During our effort to establish a chemoselective hydrogenation method using Pd/C by the addition of sulfur-containing compounds, we found that the addition

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of diphenylsulfide (Ph_2S) moderately depressed the catalyst activity of Pd/C to acquire distinguishing chemoselectivity on hydrogenation.[7] In this paper, we describe detailed results and discussion about the scope of the chemoselective hydrogenation using the Pd/C–Ph_2S system.

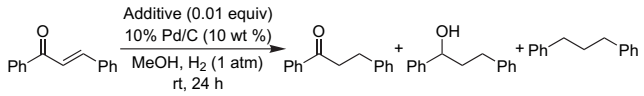
2. Results and discussion

We initially examined the suppressing effect of sulfuric catalyst poisons on the Pd/C-catalyzed hydrogenolysis of chalcone (**1a**) possessing an aromatic ketone and an olefin functionality within the molecule (Table 1). Both olefin and aromatic ketone of **1a** were readily reduced under the Pd/C-catalyzed hydrogenation conditions without any catalyst poison (entry 1); 0.01 equiv of diphenyldisulfide (Ph_2S_2) and thiophenol (PhSH) deactivated the Pd/C completely and no reaction took place (entries 2 and 3). Pd/C-catalyzed hydrogenation with 0.01 equiv of diphenylsulfide (Ph_2S) is the best combination for the chemoselective hydrogenation between olefin and aromatic ketone (entry 5): olefin was reduced to alkane without the reduction of the ketone. The olefin moiety was successfully reducing even with increased amount (to 0.1 equiv) of Ph_2S (entry 6). Unfavorable formation of **3a** was detected, when the amount of Ph_2S was reduced to 0.001 equiv (entry 4). In contrast, diphenylsulfone (Ph_2SO_2) and diphenylsulfoxide (Ph_2SO) were inadequate to inhibit the over-reduction of aromatic ketone to **3a** (entries 7 and 8). Next, we assessed the addition effect of aliphatic sulfur-containing compounds. While the addition of alkyl thiols to the reaction mixture brought about strong inhibition of the reaction of **1a** (entries 9–11), thioether, 2-(methylthio)ethanamine, exerted a milder effect to give **3a** exclusively (entry 12). Dimethylsulfide (Me_2S), dimethylsulfoxide (Me_2SO), and dimethylsulfone (Me_2SO_2) were not effective to achieve the chemoselectivity to **2a** (entries 13–15). Compared with the results in entries 5 and 13, the benzene ring is likely to play an important role as well as the sulfur atom to attain the desired chemoselectivity. The benzene rings of Ph_2S may be able to coordinate with Pd metal in a similar manner to that of a Pd-π-aryl complex or adsorb to the hydrophobic charcoal of Pd/C, leading to the stronger poisoning effect of Pd/C. Eventually, we chose the catalytic amount (0.01 equiv toward the substrate) of Ph_2S as the optimum additive for chemoselective hydrogenation because of its moderate strength as a catalyst poison, cost-efficiency, and odorless nature.

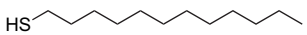
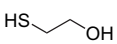
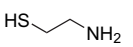
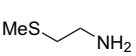
Next, we investigated the chemoselectivity in the hydrogenation of carbonyl compounds containing an alkene or alkyne moiety under our optimal conditions (Table 2). The carbonyl moiety was not reduced in all cases, while the alkene or alkyne moiety within the molecule was smoothly hydrogenated (entries 1–5).

We attempted to apply the reaction conditions to an alkene possessing an aromatic aldehyde in the molecule (Scheme 3). Contrary to our expectation, it was difficult to block the hydrogenation of the aromatic aldehyde to the corresponding benzyl alcohol under the same conditions due to the high reactivity of aromatic aldehyde toward the hydrogenation.

Table 1. Assessment of additives for chemoselective hydrogenation between olefin and aromatic ketone using chalcone (**1a**) as a substrate

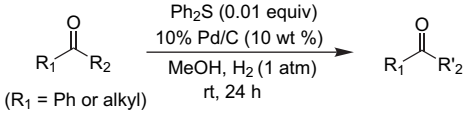


1a **2a** **3a** **4a**

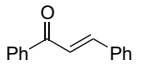
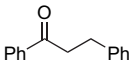
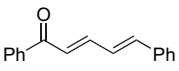
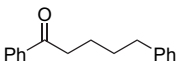
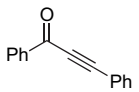
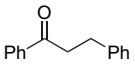
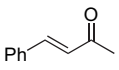
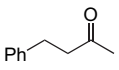
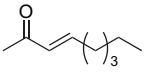
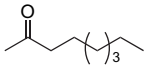
Entry	Additive	**1a**:**2a**:**3a**:**4a**[a]
1	None	0:0:0:100
2	Ph_2S_2	100:0:0:0
3	PhSH	100:0:0:0
4	Ph_2S (0.001 equiv)	0:94:6:0
5	*Ph_2S*	*0:100:0:0*
6	Ph_2S (0.1 equiv)	0:100:0:0
7	Ph_2SO	0:93:7:0
8	Ph_2SO_2	0:0:100:0
9		77:23:0:0
10		100:0:0:0
11		100:0:0:0
12		0:100:0:0
13	Me_2S	0:42:58:0
14	Me_2SO	0:0:100:0
15	Me_2SO_2	0:0:48:52

[a] The ratio was determined based on ^1H NMR analysis.

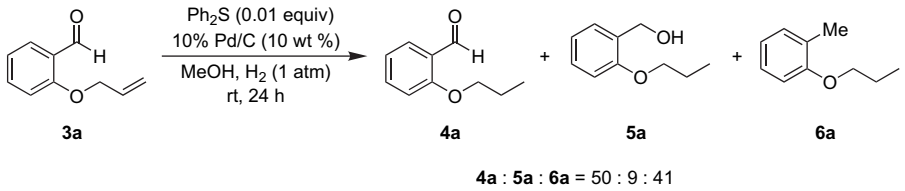
Table 2. Selective hydrogenation of olefin in the presence of aromatic or aliphatic ketone



(R_1 = Ph or alkyl)

Entry	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	quant
2	 **1b**	 **2b**	99
3	 **1c**	 **2a**	quant
4	 **1d**	 **2d**	84[a]
5	 **1e**	 **2e**	68[b]

[a] The reaction was completed within 13 h.
[b] The reaction was completed within 1.5 h. The low isolated yield of **2e** was due to the volatile nature.



Scheme 3. First attempt for chemoselective hydrogenation of olefin in the presence of aromatic aldehyde.

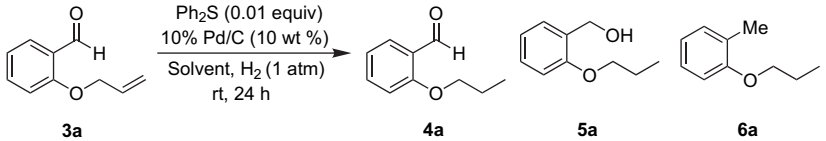
We have reported that the choice of solvent was an important factor to control the chemoselective suppression of epoxides[3c,e] or silyl ethers[8] under the hydrogenation conditions. In the former case, use of THF instead of MeOH as a solvent achieved the Pd/C(en)-catalyzed chemoselective hydrogenation of olefin, nitro, and azide moieties with retention of the epoxide functions. In the latter case, TBDMS (*tert*-butyldimethylsilyl) and TES (triethylsilyl) ethers were cleanly deprotected in MeOH under the Pd/C-catalyzed hydrogenation conditions, while neither TBDMS nor TES ether was cleaved in AcOEt (ethyl acetate) or MeCN (acetonitrile), respectively. With an expectation of complete suppression of the reduction of the aromatic aldehydes, hydrogenolysis of **3a** in a variety of solvents was investigated (Table 3). The hydrogenation of the aldehyde moiety of **3a** proceeded in MeOH (Scheme 3 and Table 3, entry 1), whereas the aldehyde moiety survived completely in THF, AcOEt, MeCN, or 1,4-dioxane (entries 2–5). These solvents made the chemoselective reduction of **3a** possible between the alkene moiety and the aldehyde moiety, because such solvent may be able to coordinate to Pd/C and further reduce the catalyst activity.

The results of the hydrogenation of a variety of aromatic aldehydes in AcOEt are summarized in Table 4. Aromatic aldehydes with an electron-donating group on the benzene ring never hydrogenate (entries 1–3) and a coexisting olefin in the molecule was selectively hydrogenated to the corresponding alkane (entries 2 and 3). Aryl aldehydes bearing an electron-withdrawing group on the benzene ring did also not undergo the reduction under these reaction conditions (entries 4–7).

We next investigated the selectivity of the hydrogenation between olefin and aromatic halide moieties (Table 5). A selective hydrogenation method without hydrogenolysis of aromatic halides could be useful for synthetic organic chemistry. Complete inhibition of the hydrogenolysis of aromatic chlorides using our chemoselective hydrogenation method was achieved (entry 1) and the olefin moiety was hydrogenated smoothly and selectively without dechlorination (entries 2–5). However, the addition of 0.01 equiv of Ph_2S was insufficient to prevent debromination and an increase in the amount of Ph_2S was required (entries 6 and 7). With use of 0.1 equiv of Ph_2S, the olefin moiety was selectively hydrogenated without debromination of the corresponding aromatic bromide (entry 8). In the case of the aromatic iodide as a substrate, no deiodination was also observed (entry 9). These results show that our hydrogenation conditions using Ph_2S are useful in the selective hydrogenation of olefins without the reduction of aromatic halides.

Benzyl ester and *N*-Cbz (benzyloxycarbonyl) protecting groups are widely used due to their easy deprotectable nature.[9] However, the selective hydrogenation of other reducible functionalities without deprotection of benzyl ester or *N*-Cbz protective group is very difficult to attain at a practically useful level. Only a few methods are known in the literature. Zappia et al. reported that use of 3% Pd/C in AcOEt led to the selective hydrogenation of olefin leaving the benzyl ester or *N*-Cbz protective group intact, but these protective groups were time-dependently taken off under their conditions.[10] We also reported that *aliphatic N*-Cbz protective groups were not cleaved by hydrogenolysis using Pd/C(en) as a catalyst, while *aromatic N*-Cbz protective groups could not survive under the same conditions;[3a,f,i] Pd/Fib could also hydrogenate the olefin moiety selectively without the deprotection of both benzyl ester and the *N*-Cbz protective group in THF.[11] We attempted to apply the present Pd/C–Ph_2S system to the selective hydrogenation of olefin in the presence of benzyl ester or the *N*-Cbz protective group (Table 6). The selective hydrogenation of olefin was achieved without hydrogenolysis of the coexisting benzyl ester (entries 1–5). Both aliphatic and aromatic *N*-Cbz

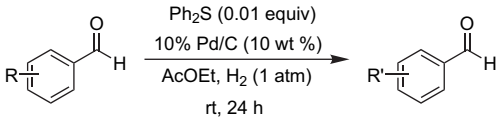
Table 3. Solvent effect on the hydrogenation of an aromatic aldehyde

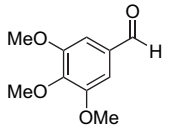
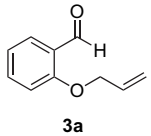
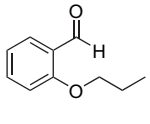
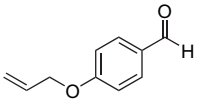
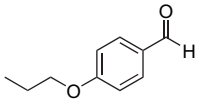
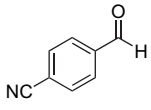
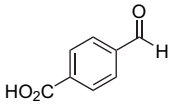
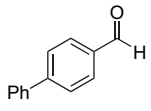
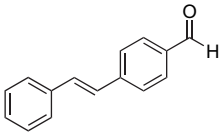
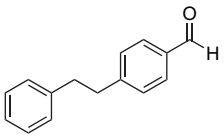


Entry	Solvent	**3a**:**4a**:**5a**:**6a**[a]
1	MeOH	0:50:9:41
2	THF	0:100:0:0
3	AcOEt	0:100:0:0
4	MeCN	0:100:0:0
5	1,4-Dioxane	0:100:0:0

[a] The ratio was determined based on ^{1}H NMR analysis.

Table 4. Suppression of the hydrogenation of aromatic aldehyde and selective hydrogenation of olefin in the presence of aromatic aldehyde



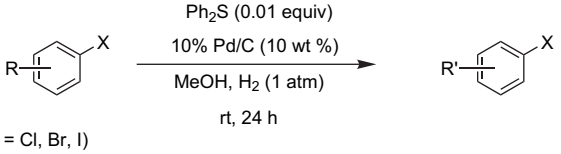
Entry	Substrate	Product	Yield (%)[a]
1	 **3c**	Recovery	99[b]
2	 **3a**	 **4a**	91
3	 **3d**	 **4d**	95
4	 **3e**	Recovery	92[b,c]
5	 **3f**	Recovery	96[b]
6	 **3g**	Recovery	94[b,c]
7	 **3h**	 **4h**	93[b,d]

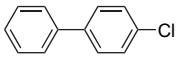
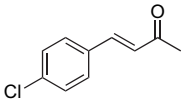
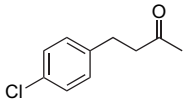
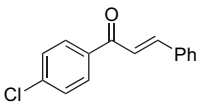
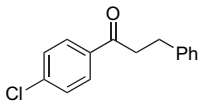
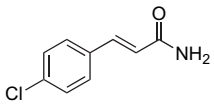
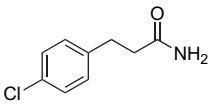
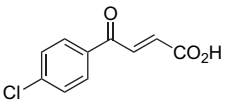
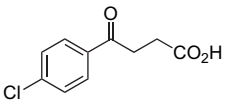
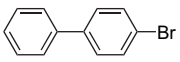
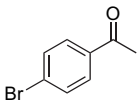
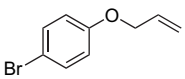
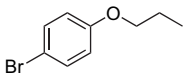
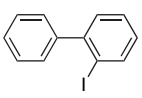
[a] Isolated yield.
[b] Isolated yield of the recovered substrate.
[c] MeCN was used as a solvent.
[d] Small amount of intractable material contained.

protective groups were stable under the hydrogenation conditions (entries 6–8). Our method is proved to be useful for the selective hydrogenation of the alkene moiety in the presence of benzyl ester or the *N*-Cbz protective group.

Aromatic cyano groups are also known as a reducible functionality under Pd/C-catalyzed hydrogenation conditions. We examined if a cyano group could undergo the reduction under our conditions (Table 7). The hydrogenation of an

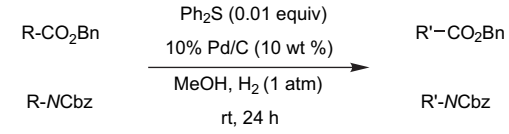
Table 5. Suppression of the hydrogenation of aromatic halide and selective hydrogenation of olefin in the presence of aromatic halide

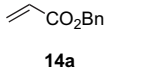
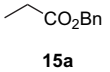
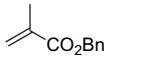
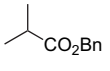
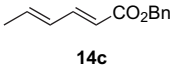
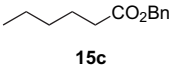
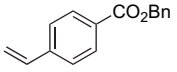
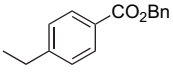
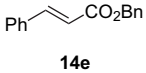
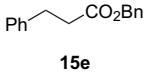
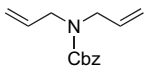
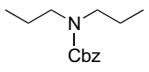
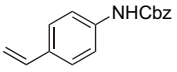
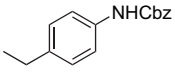
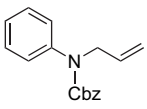
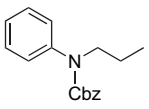


Entry	Substrate	Product	Yield (%)[a]
1	 **9a**	No reaction	75[b]
2	 **9b**	 **10b**	98
3	 **9c**	 **10c**	97
4	 **9d**	 **10d**	90[c]
5	 **9e**	 **10e**	99
6	 **11a**	No reaction	>99[d,e]
7	 **11b**	No reaction	82[b,d]
8	 **11c**	 **12c**	>99[e,f]
9	 **13a**	No reaction	96[b]

[a] Isolated yield.
[b] Isolated yield of the recovered substrate.
[c] The yield was determined based on ^{1}H NMR analysis.
[d] Ph_2S (0.5 equiv) was used.
[e] Determined by GC–MS analysis. A trace of debromination was detected.
[f] Ph_2S (0.1 equiv) was used.

Table 6. Selective hydrogenation of olefin in the presence of benzyl ester or *N*-Cbz protective group



Entry	Substrate	Product	Yield (%)[a]
1	 **14a**	 **15a**	100[b]
2	 **14b**	 **15b**	100[b]
3	 **14c**	 **15c**	quant
4	 **14d**	 **15d**	95
5	 **14e**	 **15e**	94
6	 **16a**	 **17a**	quant
7	 **16b**	 **17b**	98
8	 **16c**	 **17c**	99

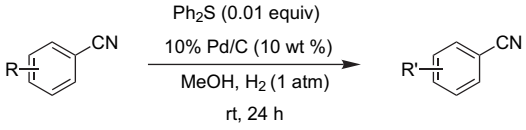
[a] Isolated yield.
[b] The yield was determined based on ^{1}H NMR analysis.

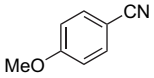
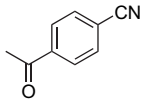
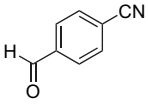
aromatic cyano group did not proceed, regardless of whether the benzene ring was substituted with an electron-donating group or an electron-withdrawing group (entries 1–3).

Next, we investigated the catalyst poison effect of Ph_2S toward an azide functionality (Table 8). The addition of Ph_2S to the reaction mixture did not affect the reduction of azide and the corresponding amine was obtained quantitatively (entries 1 and 2).

Several methods for the selective reduction of the nitro group in the presence of other functionalities such as aromatic carbonyls, aromatic halides, and nitriles have been also reported.[6,12] Application of the present method to nitro compounds was attempted (Table 9). The hydrogenation of **21a** was not complete, but led to the formation of a complex mixture (entry 1). As shown in entries 2 and 3, the hydrogenation of nitro compounds substituted with either an electron-donating (**21b**) or electron-withdrawing group (**21c**) on the benzene ring resulted in incompletion. Hence,

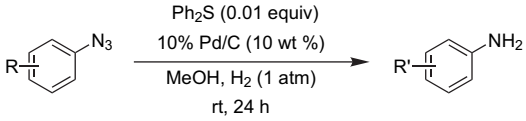
Table 7. Suppression on the hydrogenation of aromatic cyano group

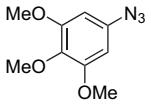
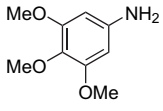
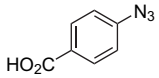
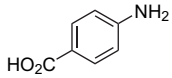


Entry	Substrate	Result
1	 **18a**	Recovery of substrate, 100%[a]
2	 **18b**	Recovery of substrate, 100%[a]
3	 **3e**	Recovery of substrate, 94%[b,c]

[a] Determined by ^{1}H NMR.
[b] Isolated yield of the recovered substrate.
[c] MeCN was used as a solvent.

Table 8. Pd/C–Ph_2S catalyzed hydrogenation of azide



Entry	Substrate	Product	Yield (%)[a]
1	 **19a**	 **20a**	quant
2	 **19b**	 **20b**	quant

[a] Isolated yield.

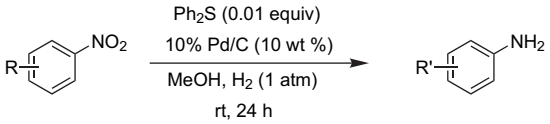
currently it seems difficult to achieve good selectivity in the hydrogenation of nitro groups.

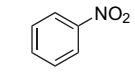
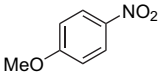
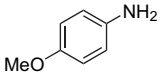
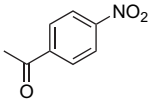
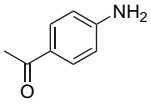
We investigated the reusability of the catalyst without further addition of Ph_2S using benzyl cinnamate (**14e**) as a substrate (Table 10). The hydrogenation using fresh Pd/C and Ph_2S proceeded selectively (Table 6, entry 5 and Table 10, entry 1). The activity of the recycled Pd/C was notably decreased and the reduction of the olefin moiety was even incomplete (entries 2 and 3). These results suggest that recycling the Pd/C used for the hydrogenation seems difficult.

3. Conclusion

During the investigation of the influence of sulfur-containing catalyst poison toward Pd/C in hydrogenation, we found that

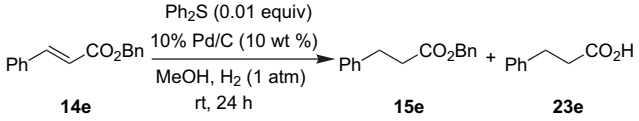
Table 9. Attempt on the Pd/C–Ph_2S catalyzed hydrogenation of nitro compound



Entry	Substrate	Result	Yield (%)[a]
1	 **21a**	Complex mixture[b]	—
2	 **21b**	 **22b**	67[c]
3	 **21c**	 **22c**	53[d]

[a] The yield was determined based on ^{1}H NMR analysis.
[b] Nitro, amine, and diazo compounds were observed by ^{1}H NMR.
[c] Thirty-three percent of the substrate remained intact.
[d] Forty-seven percent of the substrate remained intact.

Table 10. Reuse of Pd/C



Entry	Reuse	**14e**:**15e**:**23e**[a]
1	—	0:100:0
2	First	8:92:0
3	Second	80:20:0

[a] The ratio was determined based on ^{1}H NMR analysis.

Ph_2S was an appropriate catalyst poison to degrade the activity of Pd/C moderately and developed a chemoselective hydrogenation method using the combination of Pd/C and Ph_2S. The addition of only a catalytic amount (0.01–0.1 equiv) of Ph_2S to Pd/C-catalyzed hydrogenation mixtures led to the complete chemoselective hydrogenation of olefin and azide functionalities in the presence of other reducible functional groups, such as aromatic carbonyl, aromatic halide, aromatic cyano group, benzyl ester, and *N*-Cbz protective group. The other distinctive features of this method are the non-use of expensive reagents and the simple and virtually odorless operation. The present chemoselective hydrogenation method should be practically useful in synthetic organic, medicinal, and process chemistry fields.

4. Experimental

4.1. General

Pd/C (10%) was purchased from Aldrich (catalog no. 205699). MeOH and AcOEt for HPLC, dehydrated THF, and dehydrated DMF were purchased from Wako Pure Chemical Industries, Ltd. and used without purification. CH_2Cl_2 was distilled from calcium hydride. All other reagents were purchased from commercial sources and used without further purification. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM), or Kanto Chemical Co., Inc. 60N (63–210 μm spherical, neutral). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in parts per million and are internally referenced (0.00 ppm for TMS for $CDCl_3$ for ^{1}H NMR and 77.0 ppm for $CDCl_3$ for ^{13}C NMR). EI and FAB mass spectra were taken on a JEOL JMS-SX102A instrument.

4.2. Synthesis of the substrate

4.2.1. 1-Bromo-4-(2-propenyloxy)benzene (11c).[13] To a solution of 4-bromophenol (1.73 g, 10.0 mmol) and potassium carbonate (1.52 g, 11.0 mmol) in acetone (10.0 mL) was added allylbromide (0.96 mL, 11.0 mmol) and refluxed for 8 h. Et_2O (30 mL) and water (30 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (30 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford **11c** in 93% yield (1.98 g) as a colorless oil. ^{1}H NMR spectrum of **11c** was identical to that in the literature.[14]

4.2.2. Synthesis of benzyl ester.[11c] To a solution of carboxylic acid (10.0 mmol), EDC·HCl (2.30 g, 12.0 mmol), and DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (15 mL) was added benzyl alcohol (1.04 g, 10.0 mmol). After a certain reaction time, chloroform (50 mL) and water (50 mL) were added and the layers were separated. The aqueous layer was extracted with chloroform (50 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **14c** or **14d**.

4.2.2.1. (2*E*,4*E*)-Benzyl hexa-2,4-dienoate (14c). Obtained from sorbic acid (1.12 g, 10.0 mmol), EDC·HCl (1.92 g, 10.0 mmol), DMAP (122 mg, 1.00 mmol), and benzyl alcohol (1.04 mL, 10.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.2) after 48 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 90% yield (1.82 g) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.38–7.26 (m, 6H), 6.20–6.15 (m, 2H), 5.82 (d, 1H, J=15.9 Hz), 5.19 (s, 2H), 1.85 (d, 3H, J=5.6 Hz); MS (EI) *m*/*z* 202 (M^+, 15), 157 (25), 91 (100); HRMS (EI) Calcd for $C_{13}H_{14}O_2$ (M^+): 202.0994. Found: 202.0985.

4.2.2.2. Benzyl vinylbenzoate (14d).[11c] Obtained from 4-vinylbenzoic acid (500 mg, 3.37 mmol), EDC·HCl (959 mg, 5.00 mmol), DMAP (61.1 mg, 0.500 mmol), and benzyl alcohol (0.350 mL, 3.38 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.2) after 43 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane→*n*-hexane/Et_2O=

4/1) in 92% yield (737 mg) as a colorless oil. ^{1}H NMR spectrum of **14d** was identical to that in the literature.[11c]

4.2.3. Synthesis of *N*-Cbz protecting group.[11c] To a solution of the amine (5.00 mmol) in THF was added *N*-(benzyloxycarbonyloxy)succinimide (1.45 g, 6.00 mmol). After a certain reaction time, AcOEt (150 mL) and water (100 mL) were added and the layers were separated. The organic layer was washed successively with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. If necessary, the residue was applied to flash column chromatography on silica gel to afford **15a**–**15c**.

4.2.3.1. Benzyl diallylcarbamate (16a).[11c] Obtained from diallylamine (1.23 mL, 10.0 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 67 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 97% yield (2.24 g) as a colorless oil. ^{1}H NMR spectrum of **16a** was identical to that in the literature.[11c]

4.2.3.2. Benzyl 4-vinylphenylcarbamate (16b).[11c] Obtained from 4-vinylaniline (1.00 g, 8.39 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.45 g, 10.1 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 7 h of the reaction without any purification in 92% yield (1.99 g) as a pale yellow solid. ^{1}H NMR spectrum of **16b** was identical with that in the literature.[11c]

4.2.3.3. Benzyl allylphenylcarbamate (16c).[11c] Obtained from *N*-allylaniline (1.33 g, 10.0 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 7 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 81% yield (2.18 g) as a colorless oil. ^{1}H NMR spectrum of **16c** was identical with that in the literature.[11c]

4.2.3.4. 5-Azide-1,2,3-trimethoxybenzene (19a).[15] To a solution of 3,4,5-trimethoxyaniline (916 mg, 5.00 mmol) and concentrated hydrochloric acid (11.3 mL) in water (20 mL) was added dropwise a solution of sodium nitrite (362 mg, 5.20 mmol) in water (12.5 mL) at 0–5 °C and the mixture was stirred at 0–5 °C. After 1 h, the mixture was filtered and the filtrate was added to a solution of sodium azide (325 g, 12.5 mmol) in water (12.5 mL) and stirred for 6 h. The mixture was filtered to afford **19a** in 76% yield (795 mg) as a pale yellow solid. ^{1}H NMR spectrum of **19a** was identical with that in the literature.[16]

4.3. Optimization of the reaction conditions (Table 1)

Compound **1a** (208 mg, 1.00 mmol), 10% Pd/C (20.8 mg, 10 wt % of **1a**), an additive (0.01 mmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) to afford the mixture of **1a**–**4a**. The ratio of the mixture was determined by ^{1}H NMR analysis.

4.4. Typical procedure for the chemoselective hydrogenation of olefins in the presence of Ph_2S as a catalyst poison (Tables 2, 5–9, and Scheme 3)

Substrate (500 μmol), 10% Pd/C (10 wt % of the substrate), diphenylsulfide (0.84 μL, 5.00 μmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.5. Procedure for Table 3

Compound **3a** (81.1 mg, 500 μmol), 10% Pd/C (8.2 mg, 10 wt % of **3a**), diphenylsulfide (0.84 μL, 5.00 μmol), and solvent (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.6. Investigation of solvent effect on the hydrogenation of aromatic aldehyde (Table 4)

Substrate (500 μmol), 10% Pd/C (10 wt % of the substrate), diphenylsulfide (0.84 μL, 5.00 μmol), and AcOEt (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.7. Procedure for reuse of Pd/C (Table 10)

In entry 1, **14e** (200 mg, 839 μmol), 10% Pd/C (20 mg, 10 wt % of **14e**), diphenylsulfide (1.38 μL, 8.39 μmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a Kiriyama funnel (8 mm diameter, filter paper 5C, 1 μm, Kiriyama Glass Works Co.), the filtrate was concentrated to provide the product, and filtered Pd/C was dried under reduced pressure for 24 h. In entries 2–4, according to the procedure in entry 1, the reaction was carried out without the addition of Ph_2S.

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Hydrogen bonding-mediated self-assembly of anthranilamide-based homodimers through preorganization of the amido and ureido binding sites

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Abstract—The self-assembly of a novel series of hydrogen bonding-mediated homodimers in chloroform-*d* has been described. Six anthranilamide-based monomers have been prepared, in which two self-binding formamido, trifluoroacetamido, acetamido, butyl or methyl ureido units are introduced at the two ends of the backbones. Quantitative ^{1}H NMR investigations in chloroform-*d* revealed that the formamido and ureido units are more efficient than acetamido to induce the formation of stable homodimers. The association constants of all the new homodimers have been determined by ^{1}H NMR dilution method. Multiply hydrogen bonding-driven binding patterns have been proposed for the homodimers. It is also found that ureido-derived homodimers do not adopt common linear binding pattern observed for simple urea derivatives.

1. Introduction

Self-assembly of linear molecules into duplexes is a common phenomenon in biological systems.[1,2] In recent years, there has been intensive interest in constructing artificial duplexes or dimers of defined structures through the self-assembly of synthetic monomers.[3–5] Particularly, hydrogen bonding has been proved to be ideal non-covalent force for this purpose due to its great directionality and strength.[6] Two general strategies have been developed for the design of hydrogen bonding-mediated molecular building blocks. The first one is based on heterocyclic derivatives, in which hydrogen bonding donors or acceptors are compactly arranged in a designed direction, as demonstrated by the recent self-assembly of quadruply hydrogen bonded binding modes.[7] The second one is to iteratively incorporate simple binding residues into linear backbones. Examples of this family of dimeric aggregates include sheet-like aromatic and aliphatic amide duplexes,[8,9] 3,6-diaminopyridazine-based homodimers[10] and hydrazide-derived heterodimers.[11] To achieve high binding stability and selectivity, both strategies require preorganization and rigidity of the backbones and binding sites of monomers, which is usually realized by making use of intramolecular hydrogen bonding.[12]

In the past decade, the construction of foldamers, linear molecules that are induced by non-covalent forces to adopt well-established secondary structures, has received increasing attention.[13] Also due to its directionality and strength, hydrogen bonding has been widely utilized to construct aromatic oligoamide-based foldamers.[14–23] In addition, some of the synthetic folded structures represent new generation of acyclic receptors for saccharides,[22b,c] alkyl ammoniums[22d] or encapsulation of water.[23b] As part of a program in hydrogen bonding-mediated self-assembly, we had reported the construction of a new series of planar zigzag secondary structures.[24] Recently we also succeeded in utilizing the rigidified structural motif as preorganized backbones to assemble a new family of homoduplex **1**·**1** (Chart 1).[25] In order to explore the assembling diversity and also to screen ideal binding sites for more efficient assembling patterns, we have designed several new monomers. In this paper, we report the synthesis of these new monomers and their self-assembling features in chloroform.

2. Results and discussion

Six monomers **2**–**5** have been designed (Chart 2), which contain two formamido, trifluoroacetamido, acetamido or ureido units, respectively. All these units have been established to be able to self-associate in solvents of low polarity. It was expected that a comparison of their self-associating features would reveal the ideal binding modes for this class

Keywords: Self-assembly; Hydrogen bonding; Aromatic amide; Dimer.
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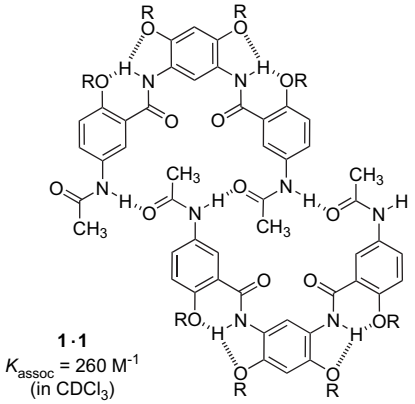


Chart 1.

of homodimers, which should be useful for future design of more elaborate supramolecular architectures.

The synthetic route for **2** is shown in Scheme 1. Thus, ester **6**[25] was first hydrolyzed with lithium hydroxide to give acid **7** in 80% yield. The latter was then treated with formic acetic anhydride in THF to afford **8** in 65% yield. Finally, **8** reacted with diamine **9**[25] in DMF in the presence of HATU and THF produced **2** in 84% yield.

For the synthesis of **3** (Scheme 2), aniline **7** was first treated with trifluoroacetic anhydride in THF to produce **10** in 95% yield. The acid was then coupled with **11**[22b] in DMF and THF in the presence of HATU to afford **3** in 65% yield. For the preparation of **4** (Scheme 3), compound **9** was first coupled with **12**[24a] in THF in the presence of DCC to give intermediate **13** in 65% yield. Then, another intermediate **15** was

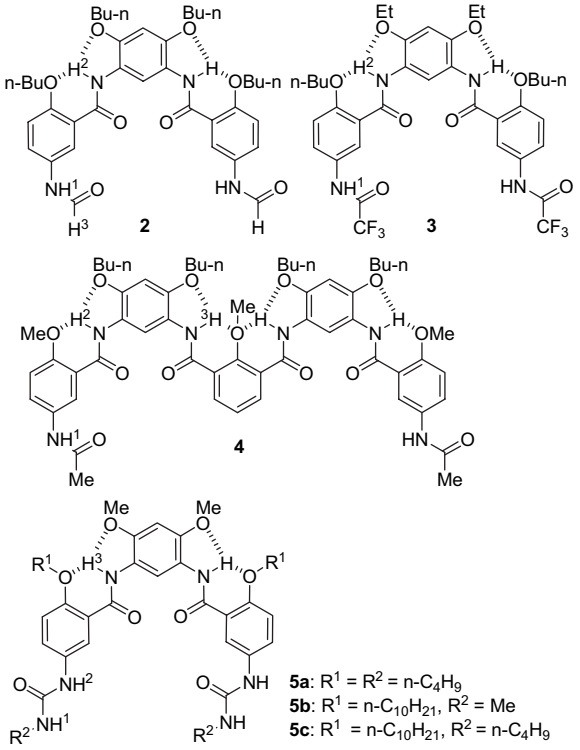
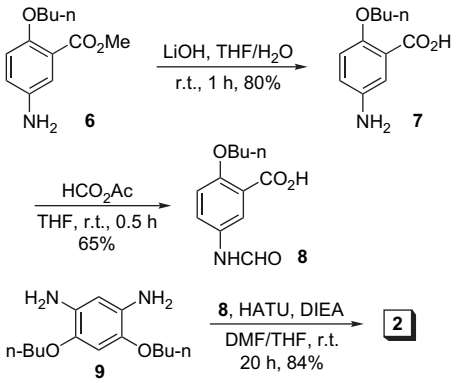
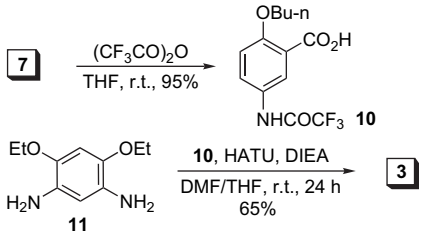


Chart 2.

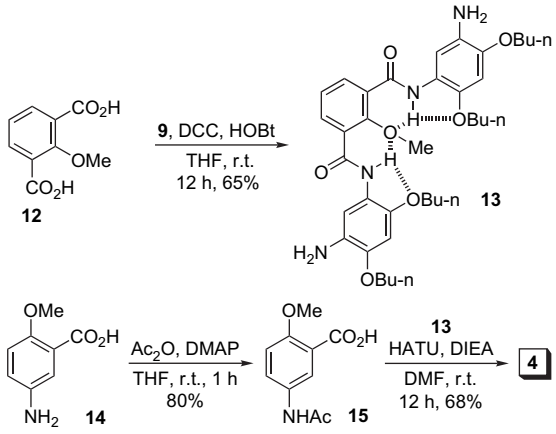


Scheme 1.

obtained in 80% yield from the reaction of **14**[26] with acetic anhydride in THF. Finally, HATU-mediated coupling reaction of **13** with **15** in DMF generated **4** in 68% yield.



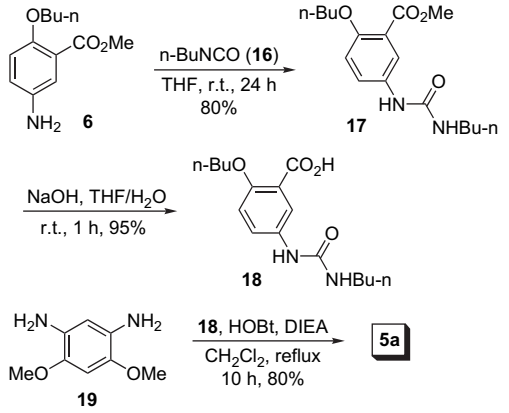
Scheme 2.



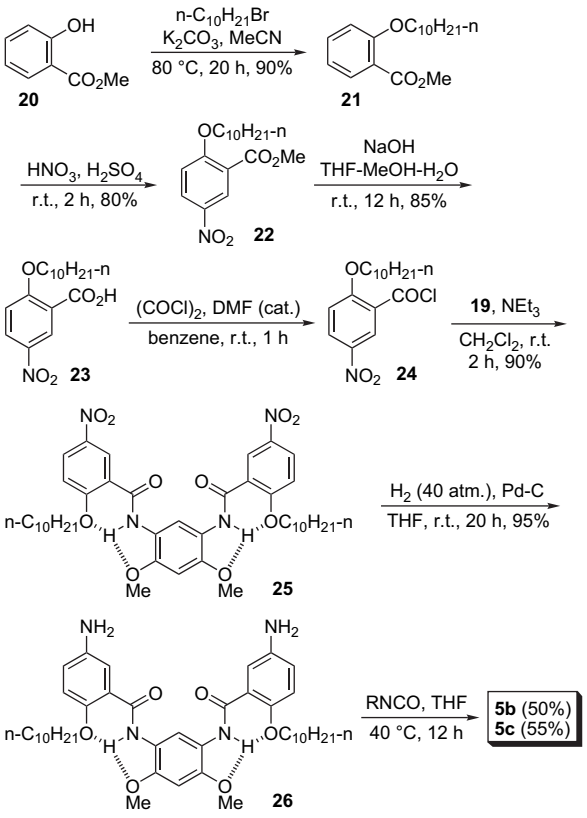
Scheme 3.

To prepare **5a** (Scheme 4), **6** was first treated with butyl isocyanide **16** in THF to give urea **17** in 80% yield. The latter was then hydrolyzed with sodium hydroxide to afford **18** in 95% yield. Compound **18** was again coupled with **19** in dichloromethane in the presence of HOBt to generate **5a** in 80% yield. The synthetic routes for **5b** and **5c** are shown in Scheme 5. Thus, compound **20** was first alkylated in hot acetonitrile with potassium carbonate as base to give **21** in 90% yield. The latter was nitrated in concd sulfuric acid to produce **22** in 80% yield. The intermediate was then hydrolyzed with sodium hydroxide to acid **23** in 85% yield. Treatment of **23** with oxalyl chloride yielded acyl chloride **24**, which was then reacted with compound **19** in dichloromethane in the presence of triethylamine to produce compound **25** in 90% yield. Palladium-catalyzed hydrogenation of **25**

in THF gave diamine **26** in 95% yield. Finally, the reaction of **26** with methyl and butyl isocyanide in THF yielded **5b** and **5c**, respectively.



Scheme 4.



Scheme 5.

Previously, the rigidified preorganized conformation of the anthranilamide backbones of compounds **2**–**5** has been established by the X-ray analysis and ^{1}H NMR techniques.[24a] The ^{1}H NMR spectra of **2**–**5** in $CDCl_3$ are shown in Figure 1. All the linking amide protons display signals at the downfield area, which is consistent with the result observed for their corresponding backbone molecules and suggests the formation of the similar rigidified conformation for **2**–**5**.[24a]

The ^{1}H NMR spectrum of compound **2** in $CDCl_3$ displays one set of sharp signals and the HCON*H* signal appears at

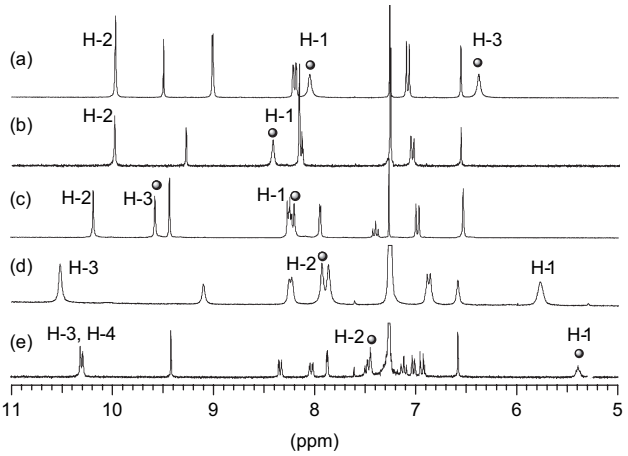


Figure 1. Partial ^{1}H NMR spectrum (400 MHz) of (a) **2**, (b) **3**, (c) **4**, (d) **5c** and (e) **30** in $CDCl_3$ at 25 °C (6.0 mM) (for numbering, see Chart 2).

8.01 ppm. Nevertheless, it has been reported that *N*-phenyl formamide and related derivatives exist as cis and trans isomers as a result of the restricted rotation of the N–C═O bond.[27] The discrepancy suggests that the NH protons were involved in important intermolecular hydrogen bonding, as observed for **1**.[25] ^{1}H NMR dilution experiments were then carried out, which revealed important upfield shifting of both the HCON*H* and HNC*H*O signals (Fig. 2). By fitting the data of the amide proton to a 1:1 binding mode, a K_{assoc} of 2.6 ($\pm$0.3)$\times 10^3$ M^{-1} was obtained for homodimer **2**·**2**.[28] This value is substantially higher than that of **1**·**1** in the same solvent, reflecting the increased efficiency of the self-binding formamide unit obviously as a result of the decreased steric hindrance. Because it has been established that in solution homodimer **1**·**1** mainly adopts a linear binding mode[25] and the X-ray analysis has also revealed a linear assembling pattern for *p*-chlorophenyl-formamide,[29] it is reasonable to propose that dimer **2**·**2** should also adopt a linear self-associating mode (Chart 3), which is stabilized by three intermolecular hydrogen bonds. The upfield shifting of the HCON*H* signal with dilution may be ascribed to the weakening of the intermolecular shielding at reduced concentration. Also based on the ^{1}H NMR dilution experiments, a K_{assoc} of 80 ($\pm$7) M^{-1} was estimated for homodimer **3**·**3** in $CDCl_3$ (Chart 3). The values of **1**·**1** and **3**·**3**

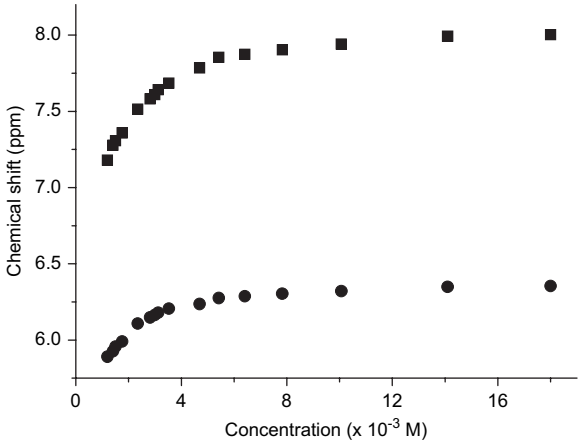


Figure 2. Plot of the chemical shift of the N*H* (■) and O═C*H* (●) protons of **2** (18.2 mM to 1.2 mM) in $CDCl_3$ at 25 °C.

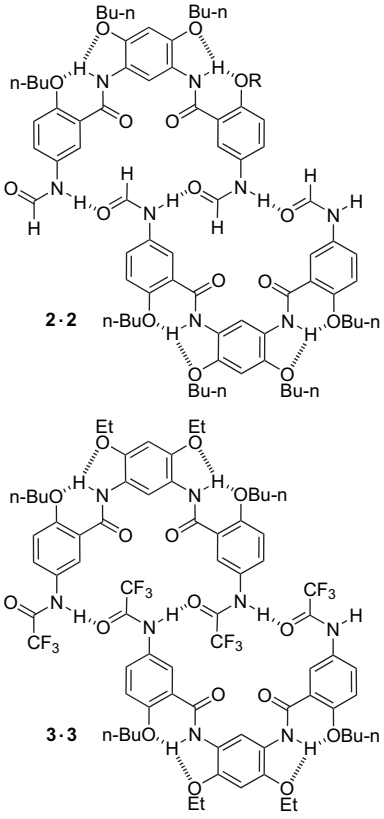


Chart 3.

are pronouncedly smaller than that of **2·2**, which reflect the increased steric hindrance of the CH_3 and CF_3 groups compared to that of the hydrogen atom.

The self-associating property of longer **4** was also investigated by the ^{1}H NMR spectroscopy. 2D-NOESY experiment in $CDCl_3$ revealed modest intermolecular NOE connections between the appended methyl protons and the centrally located benzene protons, which are shown in Chart 4. This observation suggests dimer **4·4** also forms in the solution. The ^{1}H NMR dilution experiments in $CDCl_3$ were then performed, which revealed that the signal of the appended NH protons moved upfield substantially with the decrease of the concentration (Fig. 3). By fitting the data to a 1:1 binding mode, a K_{assoc} of 230 ($\pm$20) M^{-1} could be derived for

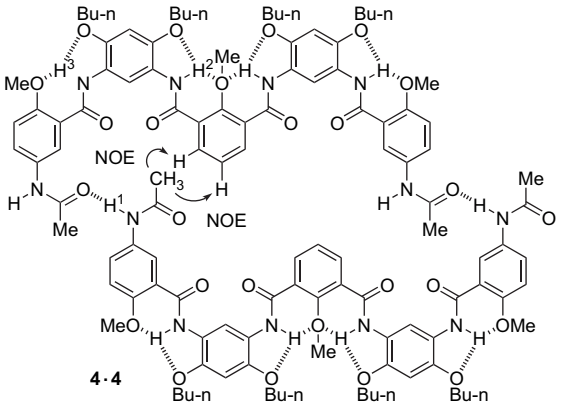


Chart 4.

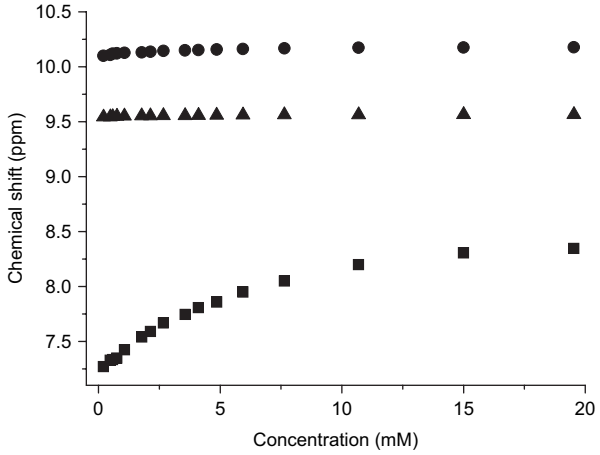


Figure 3. Plot of the chemical shift of the NH-1 (■), NH-2 (▲) and NH-3 (●) protons of **4** (19.5 mM to 0.2 mM) in $CDCl_3$ at 25 °C.

homodimer **4·4**. The value is close to that of homodimer **1·1**, probably as a result of decreased steric hindrance in this dimeric structure, which increases the strength of the single intermolecular hydrogen bond.

Alkyl ureido unit is an efficient self-binding site, which has been widely used for the formation of numerous dimeric capsules.[30] It was envisioned that replacement of the acetamide unit in **1** with the alkyl ureido unit might lead to the formation of more stable homodimers. Therefore, compounds **5a**–**5c** were prepared. Unfortunately, **5a** and **5b** were only slightly soluble in chloroform, which made it impossible to investigate their self-associating property in chloroform. However, a single crystal of **5a** suitable for the X-ray analysis was grown from evaporation of its solution in chloroform. Surprisingly, the solid-state structure revealed a dimeric structure (Fig. 4), in which one of the ureido unit of the monomer was hydrogen bonded to the centrally located C=O oxygen. In addition, the aromatic backbone of the molecule is also twisted considerably. We attribute these results to the large size of the butyl group connected to the ureido unit, which retards the linear self-associating mode (Chart 5). ^{1}H NMR dilution experiments in $CDCl_3$ were carried out for the soluble analogue **5c**, which revealed important upfield shifting of the protons of the two ureido NH groups. Because the signal of the benzene-connected NH protons was

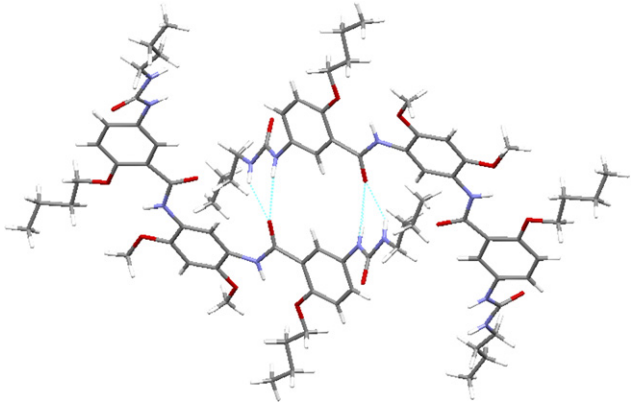


Figure 4. The solid-state structure of **5a**, highlighting the dimeric binding pattern.

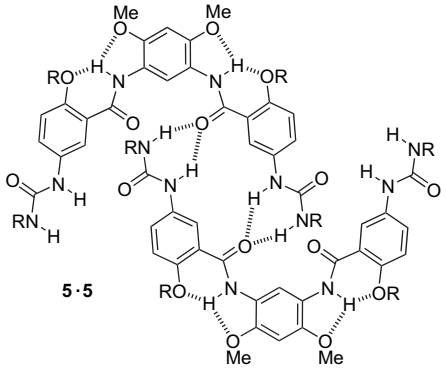


Chart 5.

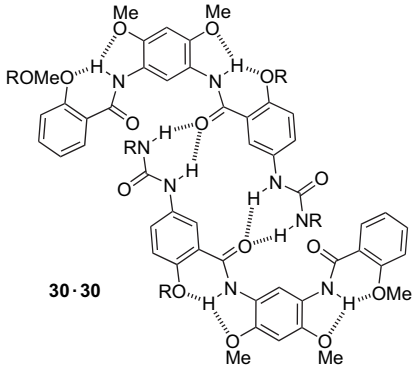
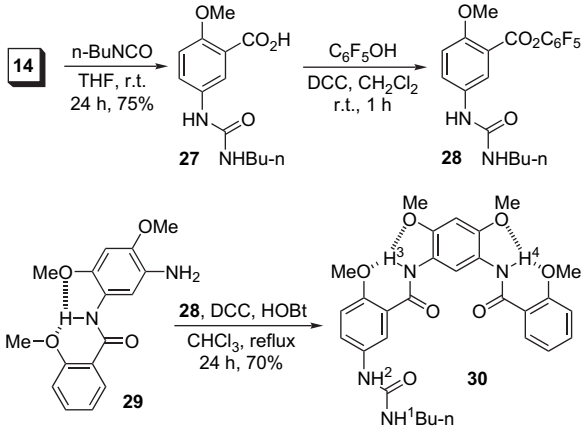


Chart 6.

overlapped with other aromatic signals upon dilution, the signal of the BuNH unit was used as probe for quantitative self-associating study, which gave rise to a K_{assoc} of 1.1 ($\pm$0.1)$\times 10^3$ M^{-1} for homodimer **5c·5c**. This value is also remarkably larger than that of **1·1** probably as a result of the increased number of the intermolecular hydrogen bonds.

It has been reported that simple *N*-alkylated urea derivatives form extended linear stacking structures in the solid state, which are stabilized by intermolecular hydrogen bonding between the ureido units.[31] In order to explore the influence of the rigidified backbone on the self-assembly of the urea derivatives, compound **30** was also prepared according to the route shown in Scheme 6. The ^{1}H NMR spectrum of **30** in $CDCl_3$ is provided in Figure 1. The intramolecular hydrogen bonding is evidenced by the fact that the signals of both amide protons appear in the downfield area. Based on the ^{1}H NMR dilution experiments, we determined the K_{assoc} of the homodimer **30·30** of this molecule in $CDCl_3$ to be approximately 820 M^{-1}. This value is lower than that of homodimer **5c·5c** but notably larger than that of *N*,*N*′-dimethylurea (ca. 400 M^{-1}) in benzene of less polarity.[32] This result indicates that homodimer **30·30** should also mainly adopt the quadruply hydrogen bonded binding pattern, as shown in Chart 6. In principle, if monomers have good solubility, replacement of the ending butyl groups with smaller methyl groups would remarkably reduce the steric hindrance and increase the stability of the corresponding homodimers.



Scheme 6.

3. Conclusion

In summary, we have reported the hydrogen bonding-mediated self-assembly of a new series of homodimers. The key feature of the new supramolecular architectures is the preorganization of their anthranilamide backbones, which is realized by introduction of consecutive three-centered intramolecular hydrogen bonding. The formamido and ureido units display greater binding affinity and may be ideal binding sites for the self-assembly of more stable dimeric structures. Future work will point to the development of longer oligomeric or polymeric monomers, which might lead to the construction of new generation of duplexes of well-ordered structures or self-duplication.

4. Experimental

4.1. General methods

Melting points are uncorrected. All solvents were dried before use following standard procedures. All reactions were performed under an atmosphere of dry nitrogen. The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC analytical center. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification.

4.1.1. Compound 7. A solution of **6**[25] (2.23 g, 10.0 mmol) and lithium hydroxide monohydrate (0.13 g, 30.0 mmol) in THF (50 mL) and water (25 mL) was stirred at room temperature for 1 h and then neutralized with dilute hydrochloric acid (1 N) to pH=7. The solvent was removed under reduced pressure and the resulting residue washed with cold water and ether. The crude product was dried in vacuo and purified by recrystallization from methanol to give **7** as a white solid (1.68 g, 80%). ^{1}H NMR ($CDCl_3$) δ: 7.49–7.48 (m, 1H), 6.89–6.87 (m, 2H), 4.17 (t, *J*=6.8 Hz, 2H), 1.88–1.83 (m, 2H), 1.54–1.47 (m, 2H), 1.00 (t, *J*=6.4 Hz, 3H). MS (EI): *m/z* 209 $[M]^+$. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.05l; H, 7.28; N, 6.54.

4.1.2. Compound 8. To a stirred solution of compound **7** (0.51 g, 2.42 mmol) in THF (10 mL) was added a solution

of formic acetic anhydride (0.26 g, 3.00 mmol) in THF (2 mL). The solution was stirred at room temperature for 0.5 h and then concentrated under reduced pressure. The resulting residue was dissolved in chloroform (20 mL). The solution was then washed with saturated sodium bicarbonate solution (10 mL), water (10 mL×2), brine (10 mL) and dried over sodium sulfate. After the solvent was removed under reduced pressure, the crude product was purified by recrystallization from THF and petroleum ether to give **8** as pale yellow solid (0.37 g, 65%). ^{1}H NMR ($CDCl_3$) δ: 11.07 (br, 1H), 8.40 (d, J=1.7 Hz, 1H), 8.30 (dd, J_1=2.9 Hz, J_2=9.0 Hz, 1H), 7.94 (d, J=2.8 Hz, 1H), 7.61 (s, 1H), 7.05 (d, J=9.0 Hz, 1H), 4.29–4.25 (m, 2H), 1.95–1.86 (m, 2H), 1.57–1.47 (m, 2H), 1.04–0.99 (m, 3H). ^{1}H NMR (DMSO-d_6) δ: 8.63 (s, 1H), 8.22 (s, 1H), 7.87 (d, J=2.7 Hz, 1H), 7.66 (dd, J_1=2.8 Hz, J_2=8.9 Hz, 1H), 7.08 (d, J=9.0 Hz, 1H), 4.01–3.97 (m, 2H), 1.72–1.62 (m, 2H), 1.50–1.37 (m, 2H), 0.93–0.88 (m, 3H). MS (ESI): m/z 238 $[M+H]^+$, 260 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.70; H, 6.28; N, 5.79.

4.1.3. Compound 2. To a stirred solution of compounds **8** (0.24 g, 1.00 mmol) and **9** (0.13 g, 050 mmol) in DMF (10 mL) and THF (10 mL) were added HATU (0.40 g, 1.05 mmol) and DIEA (0.2 mL). The mixture was stirred at room temperature for 20 h and then concentrated in vacuo. The resulting residue was triturated with methanol (10 mL). The mixture was stirred for 0.5 h. The precipitate formed was filtered, washed with ether and recrystallized from methanol and chloroform to give **2** as a yellow solid (0.29 g, 84%). ^{1}H NMR ($CDCl_3$) δ: 10.14 (s, 2H), 9.31 (s, 2H), 9.15 (s, 2H), 8.31 (dd, J_1=2.7 Hz, J_2=8.9 Hz, 2H), 8.25 (d, J=2.7 Hz, 1H), 8.01 (s, 2H), 6.95 (d, J=9.0 Hz, 2H), 6.59 (s, 2H), 4.22–4.18 (m, 4H), 4.19–4.14 (m, 4H), 1.91–1.77 (m, 8H), 1.52–1.43 (m, 8H), 0.99–0.93 (m, 12H). ^{1}H NMR (DMSO-d_6) δ: 10.03 (s, 2H), 9.24 (s, 1H), 8.24 (s, 2H), 8.17 (d, J=2.8 Hz, 2H), 7.83 (dd, J_1=2.8 Hz, J_2=8.9 Hz, 2H), 7.23 (d, J=9.0 Hz, 2H), 6.87 (s, 1H), 4.27–4.23 (m, 4H), 4.17–4.13 (m, 4H), 1.85–1.69 (m, 8H), 1.49–1.35 (m, 8H), 0.94–0.88 (m, 12H). ^{13}C NMR ($CDCl_3$) δ: 162.4, 161.6, 161.5, 159.3, 152.8, 152.3, 145.0, 131.8, 124.0, 122.6, 122.5, 122.0, 120.9, 120.0, 115.0, 114.8, 114.3, 98.6, 69.2, 68.6, 30.7, 30.4, 18.5, 13.6. MS (MALDI-TOF): m/z 691 $[M+1]^+$, 713 $[M+Na]^+$, 729 $[M+K]^+$. HRMS (MALDI-TOF) Calcd for $C_{38}H_{51}N_4O_8$ $[M+H]^+$: 691.3687. Found: 691.3701.

4.1.4. Compound 10. Compound **10** was prepared as a white solid (95%) from the reaction of compound **7** and trifluoroacetic anhydride in THF according to the procedure described above for the preparation of **8**. ^{1}H NMR ($CDCl_3$) δ: 9.07 (s, 1H), 8.29 (dd, J_1=2.8 Hz, J_2=9.0 Hz, 1H), 8.22 (d, J=2.8 Hz, 1H), 7.04 (d, J=9.1 Hz, 1H), 4.23 (t, J=6.8 Hz, 2H), 1.95–1.90 (m, 2H), 1.48–1.43 (m, 2H), 0.96 (t, J=6.5 Hz, 3H). ^{19}F NMR ($CDCl_3$) δ: −76.03. MS (ESI): m/z 305 $[M]^+$. Anal. Calcd for $C_{13}H_{14}F_3NO_4$: C, 51.15; H, 4.62; N, 4.59. Found: C, 51.02; H, 4.70; N, 4.51.

4.1.5. Compound 3. Compound **3** was prepared as a white solid (65%) from the reaction of **10** and **11**[22b] according to the procedure described above for the preparation of **2**. ^{1}H NMR ($CDCl_3$) δ: 10.00 (s, 2H), 9.24 (s, 1H), 9.15 (s, 2H), 8.12–8.16 (m, 4H), 7.02 (d, J=9.8 Hz, 2H), 6.55 (s, 1H), 4.23–4.10 (m, 8H), 1.94–1.86 (m, 4H), 1.51–1.42 (m, 10H), 0.99–0.94 (m, 6H). ^{19}F NMR ($CDCl_3$) δ: −76.01. MS (MALDI-TOF): m/z 771 $[M+1]^+$, 793 $[M+Na]^+$, 809 $[M+K]^+$. HRMS (MALDI-TOF) Calcd for $C_{36}H_{41}N_4O_8F_6$: 771.2802. Found: 771.2823.

4.1.6. Compound 13. A solution of compounds **9** (0.51 g, 2.00 mmol), **12**[24a] (0.20 g, 1.00 mmol), DCC (0.45 g, 2.20 mmol) and HOBt (0.30 g, 2.20 mmol) in THF (25 mL) was stirred at room temperature for 12 h and then concentrated in vacuo. The resulting residue was triturated with chloroform (50 mL). The organic phase was then washed with saturated sodium bicarbonate solution (25 mL), water (25 mL×2), brine (25 mL) and dried over sodium sulfate. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography (dichloromethane/acetone 100:1 to 50:1) to give **13** as a pale yellow solid (0.40 g, 65%). ^{1}H NMR ($CDCl_3$) δ: 9.65 (s, 1H), 8.21 (d, J=7.8 Hz, 2H), 8.04 (s, 2H), 7.39 (t, J=7.8 Hz, 1H), 6.52 (s, 2H), 4.01–3.96 (m, 11H), 3.65 (s, 4H), 1.85–1.72 (m, 8H), 1.59–1.38 (m, 8H), 1.02–0.97 (m, 6H), 0.90–0.85 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 162.4, 155.9, 143.1, 141.2, 134.7, 130.1, 128.6, 125.2, 121.7, 108.7, 99.4, 69.9, 68.8, 64.2, 31.5, 19.4, 19.2, 13.9, 13.8. MS (MALDI-TOF): m/z 687 $[M+Na]^+$. HRMS (MALDI-TOF) Calcd for $C_{37}H_{52}N_4O_7Na^+$ $[M+Na]^+$: 687.3733. Found: 687.3728.

4.1.7. Compound 15. A solution of compound **14** (0.84 g, 5.00 mmol), acetic anhydride (1.02 g, 10.0 mmol) and DMAP (10 mg) in THF (25 mL) was stirred at room temperature for 1 h. After workup, the crude product was subjected to column chromatography (AcOEt/petroleum ether 1:5) to give **15** as a white solid (0.84 g, 80%). ^{1}H NMR ($CDCl_3$) δ: 8.26 (dd, J_1=3.0 Hz, J_2=9.0 Hz, 1H), 7.85 (d, J=3.0 Hz, 1H), 7.06 (d, J=9.0 Hz, 1H), 4.08 (s, 3H), 2.20 (s, 3H). MS (EI): m/z 209 $[M]^+$. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.29; H, 5.25; N, 6.60.

4.1.8. Compound 4. To a stirred solution of compounds **13** (0.14 g, 0.21 mmol) and **15** (0.094 g, 0.45 mmol) in DMF (10 mL) were added HATU (0.17 g, 0.45 mmol) and DIEA (0.1 mL). The mixture was stirred at room temperature for 12 h and then the solvent was removed under reduced pressure. The resulting residue was triturated with methanol (3 mL). The yellow precipitate formed was filtered, dried in vacuo and then subjected to column chromatography (CH_2Cl_2/AcOEt 10:1) to give **4** as a light-yellow solid (0.15 g, 68%). ^{1}H NMR ($CDCl_3$) δ: 10.18 (s, 2H), 9.57 (s, 2H), 9.43 (s, 2H), 8.27–8.20 (m, 6H), 7.94 (d, J=2.6 Hz, 2H), 7.40 (t, J=7.7 Hz, 1H), 6.98 (d, J=9.1 Hz, 2H), 6.53 (s, 2H), 4.06–3.99 (m, 17H), 2.16 (s, 6H), 1.86–1.72 (m, 8H), 1.60–1.39 (m, 8H), 1.02–0.97 (m, 6H), 0.90–0.85 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 169.1, 162.9, 162.3, 155.9, 153.6, 145.9, 134.8, 132.6, 128.5, 125.3, 125.2, 123.6, 122.2, 121.1, 120.3, 116.2, 112.1, 97.3, 69.0, 68.9, 64.3, 56.4, 31.5, 31.4, 24.3, 19.2, 13.8, 13.8. MS (MALDI-TOF): m/z 1047 $[M+H]^+$, 1069 $[M+Na]^+$. HRMS (MALDI-TOF) Calcd for $C_{57}H_{71}N_6O_{13}$ $[M+H]^+$: 1047.5072. Found: 1047.5074.

4.1.9. Compound 17. To a solution of aniline **6** (0.93 g, 4.20 mmol) in THF (20 mL) was added *n*-butyl isocyanide **16** (0.60 mL). The solution was stirred at room temperature

for 24 h and then concentrated in vacuo. The resulting residue was washed with ether thoroughly and the resulting solid subjected to column chromatography (petroleum ether/AcOEt 2:1) to give **17** as a white solid (1.00 g, 75%). ^{1}H NMR ($CDCl_3$) δ: 7.61 (d, J=2.8 Hz, 1H), 7.49 (dd, J_1=8.9 Hz, J_2=2.77 Hz, 1H), 7.27 (s, 1H), 6.92 (d, J=8.9 Hz, 1H), 6.44 (s, 1H), 4.77 (s, 1H), 4.00 (s, 2H), 3.87 (s, 3H), 3.24–3.20 (m, 2H), 1.94–1.75 (m, 2H), 1.57–1.46 (m, 4H), 1.39–1.26 (m, 2H), 0.99–0.88 (m, 6H). MS (EI): m/z 323 $[M+H]^+$. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.20; H, 8.20; N, 8.52.

4.1.10. Compound 18. A solution of compound **17** (0.65 g, 2.00 mmol) and sodium hydroxide (0.24 g, 4.00 mmol) in THF (20 mL) and water (5 mL) was stirred at room temperature for 1 h and then hydrochloric acid (1 N) added to pH=6. The solvent was removed under reduced pressure and the resulting residue washed with cold water and dried in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 20:1) to give **18** as a white solid (0.59 g, 95%). ^{1}H NMR ($CDCl_3$) δ: 11.40 (s, 1H), 8.31 (dd, J_1=9.0 Hz, J_2=2.9 Hz, 1H), 7.71 (d, J=2.9 Hz, 1H), 7.60 (s, 1H), 7.02 (d, J=9.0 Hz, 1H), 5.55 (t, J=5.4 Hz, 1H), 4.27–5.22 (m, 2H), 3.30–3.25 (m, 2H), 1.92–1.84 (m, 2H), 1.59–1.36 (m, 6H), 1.06–0.92 (m, 6H). MS (MALDI-TOF): m/z 309 $[M+H]^+$. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.20; H, 7.94; N, 9.01.

4.1.11. Compound 5a. A solution of compound **18** (0.31 g, 1.00 mmol) and pentafluorophenol (0.18 g, 1.00 mmol), DCC (0.23 g, 1.10 mmol) and DMAP (20 mg) in dichloromethane (20 mL) was stirred at room temperature for 1 h. The solid formed was filtered off and the filtrate added to a stirred solution of diamine **19** (84 mg, 0.50 mmol) and HOBt (0.14 g, 1.00 mmol) in dichloromethane (20 mL). The solution was heated under reflux for 10 h and then cooled to room temperature. After workup, the crude product was purified by column chromatography ($CHCl_3$/MeOH 100:1–20:1) to give **5a** as a white solid (0.24 g, 80%). ^{1}H NMR (DMSO-d_6) δ: 10.52 (s, 2H), 9.45 (s, 1H), 8.47 (s, 2H), 7.93 (d, J=2.8 Hz, 2H), 7.74 (dd, J_1=8.8 Hz, J_2=3.0 Hz, 2H), 7.17 (d, J=9.0 Hz, 1H), 6.92 (s, 1H), 6.07 (t, J=5.9 Hz, 1H), 4.02 (s, 6H), 3.98 (s, 6H), 3.12–3.06 (m, 4H), 1.46–1.27 (m, 8H), 0.92–0.87 (m, 6H). MS (ESI): m/z 665 $[M+H]^+$, 687 $[M+Na]^+$.

4.1.12. Compound 21. To a solution of compound **20** (6.30 g, 41.0 mmol) and *n*-decyl bromide (11.0 g, 49.0 mmol) in acetonitrile (100 mL) was added potassium carbonate (14.0 g, 0.10 mol). The suspension was heated under reflux for 20 h and then concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate (200 mL). The organic phase was washed with saturated sodium bicarbonate solution (100 mL), water (100 mL×2), brine (100 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was purified by column chromatography (petroleum ether/AcOEt 10:1) to afford **21** as colorless oil (11.8 g, 90%). ^{1}H NMR ($CDCl_3$) δ: 7.78 (dd, J=7.8 Hz, 1.6 Hz, 1H), 7.48–7.38 (m, 1H), 6.97 (dd, J_1=7.6 Hz, J_2=3.7 Hz, 1H), 4.05–4.01 (m, 2H), 3.89 (s, 3H), 1.88–1.78 (m, 2H), 1.51–1.28 (m, 14H), 0.89 (t, J=6.5 Hz, 3H). MS (EI): m/z 293 $[M+H]^+$. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.81; H, 9.80.

4.1.13. Compound 22. To a stirred solution of compound **21** (12.9 g, 44.0 mmol) in concd sulfuric acid (98%, 30 mL), cooled in ice bath, was added dropwise a mixture of concd nitric acid (4 mL) and concd sulfuric acid (15 mL). The mixture was stirred at room temperature for 2 h and then poured into ice water (400 mL). The precipitate formed was filtered, washed with water and dissolved with ether (200 mL). The organic phase was washed with aqueous sodium hydroxide solution (0.5 N, 50 mL), water (100 mL× 2), brine (100 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was purified by flash chromatography (petroleum ether/AcOEt 10:1) to give **22** as a yellow solid (10.1 g, 80%). ^{1}H NMR ($CDCl_3$) δ: 8.70 (d, J=2.9 Hz, 1H), 8.34 (dd, J=9.2 Hz, 2.9 Hz, 1H), 7.04 (d, J=9.2 Hz, 1H), 4.15 (t, 2H), 3.93 (s, 3H), 2.14–1.68 (m, 2H), 1.59–1.17 (m, 14H), 0.89 (t, J=6.4 Hz, 3H). MS (EI): m/z 338 $[M+H]^+$. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.92; H, 8.21; N, 4.09.

4.1.14. Compound 23. To a solution of compound **22** (6.76 g, 20.0 mmol) in THF (10 mL) and methanol (100 mL) was added a solution of sodium hydroxide (1.80 g, 40.0 mmol) in water (40 mL). The mixture was added at room temperature for 12 h and then neutralized with hydrochloric acid to pH=5. The solvent was distilled under reduced pressure and the resulting residue triturated with ethyl acetate (100 mL). After workup, the crude product was purified by recrystallization from ethyl acetate to afford **23** as a pale yellow solid (5.49 g, 85%). ^{1}H NMR ($CDCl_3$) δ: 9.05 (d, J=3.0 Hz, 1H), 8.44 (dd, J_1=9.3 Hz, J_2=3.0 Hz, 1H), 7.17 (d, J=9.3 Hz, 1H), 4.38–4.33 (m, 2H), 2.00–1.95 (m, 2H), 1.54–1.30 (m, 14H), 0.90–0.86 (t, J=6.8 Hz, 3H). MS (EI): m/z 323 $[M]^+$. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.95; H, 7.87; N, 4.26.

4.1.15. Compound 24. A solution of compound **23** (3.23 g, 10.0 mmol), oxalyl chloride (6 mL, 24 mmol) and DMF (0.05 mL) in benzene (60 mL) was stirred at room temperature for 1 h and then concentrated under reduced pressure. The resulting residue **24** was dissolved in dichloromethane (40 mL). The solution was used for the next step.

4.1.16. Compound 25. To a stirred solution of **19** (0.84 g, 5.00 mmol) and triethylamine (1.10 mL, 10.0 mmol) in dichloromethane (20 mL) was added the above solution of **24** in dichloromethane. The mixture was stirred at room temperature for 2 h and then another part of dichloromethane was (50 mL) added. The solution was washed with dilute hydrochloric acid (1 N, 20 mL), saturated sodium bicarbonate solution (20 mL), water (25 mL×2), brine (25 mL) and then dried over sodium sulfate. After the solvent was removed under reduced pressure, the resulting residue was subjected to column chromatography (CH_2Cl_2/EtOAc 15:1) to give **25** as a yellow solid (3.50 g, 90%). ^{1}H NMR ($CDCl_3$) δ: 9.93 (s, 2H), 9.66 (s, 1H), 9.30 (d, J=2.7 Hz, 2H), 8.31 (dd, J_1=9.2 Hz, J_2=2.6 Hz, 2H), 7.10 (d, J=9.1 Hz, 2H), 6.57 (s, 1H), 4.33–4.29 (m, 4H), 3.93 (s, 6H), 2.72–1.59 (m, 4H), 1.65–1.14 (m, 32H), 0.86 (t, J=6.4 Hz, 6H). MS (ESI): m/z 779 $[M+H]^+$. Anal. Calcd For $C_{42}H_{58}N_4O_{10}$: C, 64.76; H, 7.51; N, 7.19. Found: C, 64.65; H, 7.62; N, 7.14.

4.1.17. Compound 26. A suspension of compound **25** (2.33 g, 3.00 mmol) and Pd–C (0.2 g, 10%) in THF (100 mL) was stirred under the atmosphere of hydrogen gas (40 atm) in an autoclave for 20 h. The solid was then filtered and the filtrate concentrated under reduced pressure. The resulting residue was subjected to column chromatography (chloroform/methanol 20:1) to give **26** as a pale yellow solid (2.05 g, 95%). ^{1}H NMR ($CDCl_3$) δ: 10.23 (s, 2H), 9.52 (s, 1H), 7.70 (d, J=2.7 Hz, 2H), 6.83–6.79 (m, 4H), 6.55 (s, 1H), 4.12–4.07 (m, 4H), 3.90 (s, 6H), 3.56 (br, 4H), 1.94–1.86 (m, 4H), 1.46–1.25 (m, 28H), 0.89–0.85 (m, 6H). MS (ESI): *m/z* 719 $[M+H]^+$, 741 $[M+Na]^+$, 757 $[M+K]^+$. Anal. Calcd for $C_{42}H_{62}N_4O_6$: C, 70.16; H, 8.69; N, 7.79. Found: C, 69.73; H, 8.68; N, 7.67.

4.1.18. Compound 5c. To a solution of compound **26** (0.19 g, 0.27 mmol) in THF (5 mL) was added *n*-butyl isocyanide **16** (60 mg, 0.60 mmol). The solution was stirred at 40 °C for 12 h and then concentrated under reduced pressure. The resulting residue was washed with ether thoroughly and then purified by recrystallization from methanol and chloroform to afford **5c** as a white solid (0.11 g, 55%). ^{1}H NMR ($CDCl_3$) δ: 10.48 (s, 2H), 9.18 (s, 1H), 8.23 (d, J=8.1 Hz, 2H), 7.96 (s, 2H), 7.86 (s, 2H), 6.88 (d, J=9.0 Hz, 2H), 6.58 (s, 1H), 5.79 (s, 2H), 4.12–4.06 (m, 4H), 3.92 (s, 6H), 2.75 (s, 4H), 1.95–1.90 (m, 4H), 1.60–0.97 (m, 32H), 0.88 (t, J=6.4 Hz, 6H), 0.79 (t, J=6.3 Hz, 6H). MS (ESI): *m/z* 916 $[M]^+$. HRMS (ESI) Calcd for $C_{52}H_{80}N_6O_8$: 916.6038. Found: 916.6054.

4.1.19. Compound 5b. Compound **5b** was prepared as a white solid (50%) from the reaction of compound **26** and methyl isocyanide in THF under similar conditions. ^{1}H NMR ($CDCl_3$) δ: 10.49 (s, 2H), 9.08 (s, 1H), 8.25 (d, J=9.10 Hz, 2H), 8.00 (s, 2H), 7.87 (s, 2H), 6.91 (d, J=9.7 Hz, 2H), 6.63 (s, 1H), 5.53 (s, 2H), 4.15–4.10 (m, 4H), 3.93 (s, 6H), 2.30 (s, 4H), 1.96–1.90 (m, 4H), 1.48–1.26 (m, 30H), 0.89–0.85 (m, 6H). MS (ESI): *m/z* 833 $[M+H]^+$, 855 $[M+Na]^+$, 871 $[M+K]^+$. Anal. Calcd for $C_{46}H_{68}N_6O_8$: C, 66.32; H, 8.23; N, 10.09. Found: C, 66.12; H, 8.25; N, 9.92.

4.1.20. Compound 27. A solution of compound **14** (1.67 g, 10.0 mmol) and *n*-butyl isocyanide **16** (1.22 mL, 10.0 mmol) in THF was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the resulting residue washed with ether thoroughly. The crude product was purified by recrystallization from THF to give **27** as a white solid (1.55 g, 70%). ^{1}H NMR ($CDCl_3$) δ: 8.30 (dd, J_1=9.0 Hz, J_2=3.0 Hz, 1H), 7.72 (d, J=3.0 Hz, 1H), 7.35 (s, 1H), 7.03 (d, J=9.0 Hz, 1H), 5.36–5.32 (m, 1H), 4.08 (s, 3H), 3.31–3.24 (m, 2H), 1.58–1.50 (m, 2H), 1.46–1.36 (m, 2H), 0.97–0.92 (t, J=6.4 Hz, 3H). MS (EI): *m/z* 266 $[M]^+$. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.49; H, 6.85; N, 10.46.

4.1.21. Compound 30. A solution of compound **27** (0.13 g, 1.00 mmol), pentafluorophenol (0.10 g, 1.00 mmol), DCC (0.27 g, 1.00 mmol) and DMAP (10 mg) in chloroform (20 mL) was stirred at room temperature for 1 h. The solid formed was filtered off. The filtrate, the solution of compound **28**, was added to a solution of compound **29**[24a] (0.15 g, 0.50 mmol) and HOBt (0.14 g, 1.00 mmol) in chloroform (20 mL). The solution was heated under reflux for 24 h and then washed with hydrochloric acid (0.5 N, 10 mL), saturated sodium bicarbonate solution (15 mL), water (15 mL), brine (15 mL) and dried over sodium sulfate. After the solvent was removed under reduced pressure, the resulting residue was purified by column chromatography to give **30** as a white solid (0.39 g, 70%). ^{1}H NMR ($CDCl_3$) δ: 10.32 (s, 1H), 10.30 (s, 1H), 9.42 (s, 1H), 8.34 (d, J=8.3 Hz, 1H), 8.04 (dd, J_1=9.1 Hz, J_2=2.9 Hz, 1H), 7.87 (d, J=2.7 Hz, 1H), 7.48 (t, J=7.5 Hz, 2H), 7.12 (t, J=7.6 Hz, 1H), 7.03 (d, J=8.3 Hz, 1H), 6.94 (d, J=8.8 Hz, 1H), 6.58 (s, 1H), 5.41–5.38 (m, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 3.01–2.94 (m, 2H), 1.29–1.14 (m, 4H), 0.82–0.77 (m, 3H). MS (MALDI-TOF): *m/z* 551 $[M+H]^+$. Anal. Calcd for $C_{29}H_{34}N_4O_7$: C, 63.26; H, 6.22; N, 10.18. Found: C, 63.08; H, 6.31; N, 10.14.

4.2. The determination of binding constants

The methods have been reported in a previous paper.[11]

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Chiral tetrathiafulvalene based phosphine- and thiomethyl-oxazoline ligands. Evaluation in palladium catalysed asymmetric allylic alkylation

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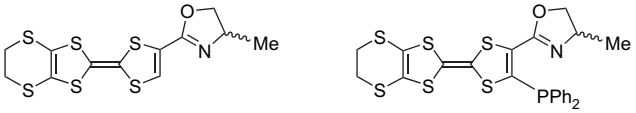
Abstract—New chiral redox active ligands based on ethylenedithio-tetrathiafulvalene (EDT-TTF) bearing racemic or optically pure oxazolines have been synthesised. These auxiliaries possess an additional functionality on the TTF unit, namely a thiomethyl residue or a diphenylphosphino moiety. All ligands have been tested in asymmetric allylic substitutions. The enantioselectivity reached is 85% ee.

1. Introduction

Transition metal catalysed asymmetric allylic alkylations (AAA) provide very useful tools for the formation of stereoselective carbon–carbon bonds.[1] As part of the development of this chemistry, the design and synthesis of new chiral auxiliaries remain a key step. Therefore, a large variety of ligands have been developed for the palladium catalysed AAA[1] and it has been demonstrated that heterobidentate auxiliaries of the P,N type are excellent candidates for that purpose.[1,2] Among those, the phosphine-oxazolines have received increasing attention.[3,4] Within this context, some of us have been involved in the use of chiral aminophosphine-oxazolines in asymmetric catalysis.[5] However, other chiral auxiliaries of the P,S,[6] Se,N[7] and S,N,[8–10] types have been successfully employed as well. On the other hand, some of us have an ongoing interest in the development of electroactive ligands, such as tetrathiafulvalene (TTF) based phosphines[11] or pyridines.[12] Recently, the synthesis of ethylenedithio-tetrathiafulvalene (EDT-TTF) derivatives **1a–c** and **2a–c** based on chiral oxazolines has been reported (Scheme 1).[13] The EDT-TTF-MeOX compounds **1a–c** possess potentially two coordination sites that are the oxazoline unit and the sulfur atoms of the TTF moiety. They have been successfully employed as precursors for chiral molecular metals.[13b] Within the series **2a–c**, the diphenylphosphino moiety tethered to the TTF unit is also able to coordinate a transition metal. Indeed, the X-ray characterisation of the complex (*rac*)-(EDT-TTF-PPh_2-MeOX)$PdCl_2$ showed unambiguously the N,P chelation of racemic **2a** onto the square planar palladium centre.[13a] Because of the potential of N,P type chiral auxiliaries in asymmetric catalysis, we decided to apply them in palladium catalysed AAA. Here, we report on the synthesis of new EDT-TTF based chiral oxazoline ligands and on their use in asymmetric allylic alkylation of the standard substrate (*rac*)-(*E*)-1,3-diphenyl-3-acetoxy-prop-1-ene.



EDT-TTF-MeOX
1a (+/-), **1b** (*R*), **1c** (*S*)

EDT-TTF-PPh_2-MeOX
2a (+/-), **2b** (*R*), **2c** (*S*)

Scheme 1.

2. Results and discussion

In order to increase the steric hindrance on the oxazoline substituent of the chiral auxiliaries of types **1** and **2**, the novel ligands **3a–c** and **4a–c**, bearing an isopropyl residue, have

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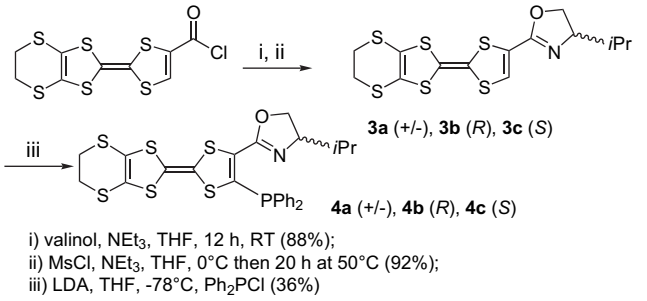
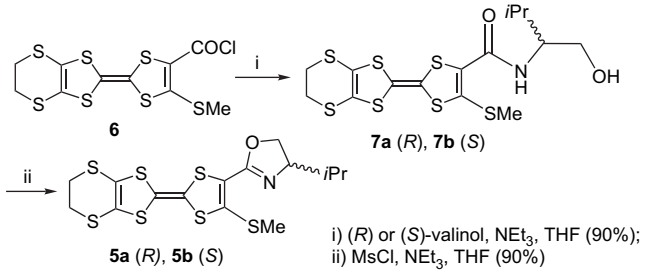
been prepared (Scheme 2). The synthesis of EDT-TTF-*i*PrOX **3a–c** is straightforward following the reported procedure.[14]



Scheme 2.

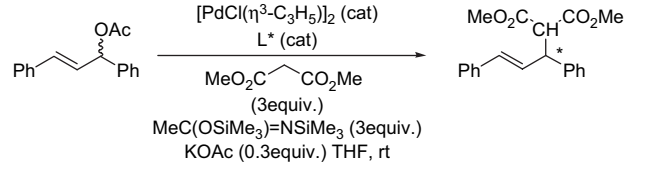
The corresponding phosphinooxazoline ligands EDT-TTF-PPh_2-MeOX **2** and EDT-TTF-PPh_2-*i*PrOX **4** have been prepared following also the procedure described earlier.[13a]

With the aim to examine also the behaviour of auxiliaries containing a thiomethyl residue, rather than a PPh_2 on the TTF unit, we prepared the enantiopure ligands **5a**,**b** according to the route depicted in Scheme 3, the SMe substituent being introduced at an early stage of the synthesis of the acyl chloride **6**.[15] Then, reaction of the latter with the enantiopure (*R*) or (*S*)-valinol afforded the ligands **5a**,**b** via the corresponding β-hydroxy amides **7a**,**b**, thus paralleling the preparation of the non-substituted ligands **3**. The new ligands **4** and **5** have been fully characterised.



Scheme 3.

Next, the mono or bidentate ligands **2–5** were applied in the palladium catalysed asymmetric allylic alkylation of the standard substrate (*rac*)-(*E*)-1,3-diphenyl-3-acetoxy-prop-1-ene with dimethylmalonate (Scheme 4). The results are summarised in Table 1.



Scheme 4.

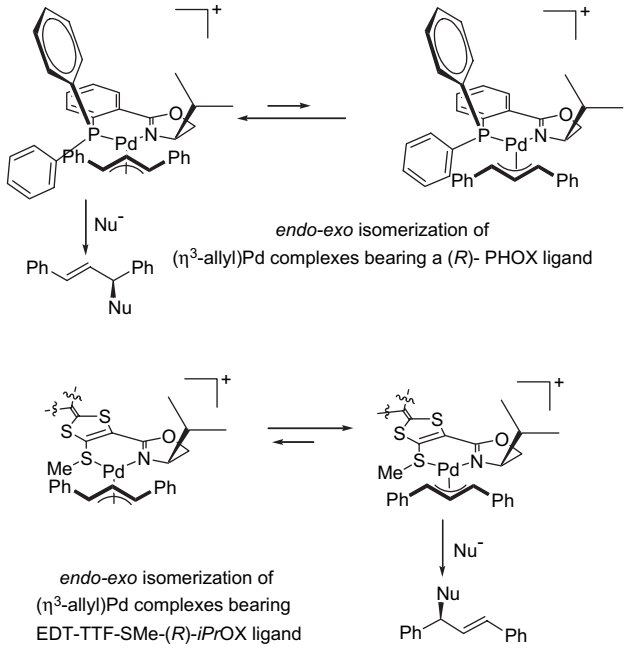
From an experimental standpoint, the precatalysts were generated by reacting $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with the selected optically pure (*R*) and (*S*)-TTF-ligands in THF during 1 h at room temperature. Then, dimethylmalonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate (KOAc) were added in a solution of THF followed by the substrate (*rac*)-(*E*)-1,3-diphenyl-3-acetoxy-prop-1-ene.[16] The auxiliary **3b** bearing only an oxazoline unit induces a very low selectivity of 6% ee (entry 1), that is much lower than the values reported by Bryce and Chesney for an (*S*)-TTF-*i*PrOx ligand, yet measured by a different method.[8f] On the contrary, the chelating auxiliaries **2b** and **4b**, bearing a diphenylphosphino group besides the oxazoline heterocycle, allowed to reach higher enantioselectivities, up to 85% ee (entries 2–4). Note that, as expected, the use of the racemic ligands provided the racemic mixture of the allyl-malonate, with the same activity as the optically pure counterparts. Interestingly, an enhancement of Δee=55% resulted from the use of the isopropyl- (**4b**) rather than the methyl-oxazoline bearing ligand (**2b**) (entry 3 vs 2).[17] A rationale for the difference in behaviour between catalysts bearing ligands **3** and **4**, with an added PPh_2 group, can be easily deduced from the mechanism of the reaction. Indeed, generally, the selectivity exhibited by catalysts bearing bitopic auxiliaries is related both to the conformation of the most stable palladium-allyl intermediates and to the site of addition of the nucleophile to these palladium species (Scheme 5). Thus, for P,N type ligands, the addition is occurring on the palladium-allyl terminus trans to the better π-acceptor atom, that is the phosphorus one.[18] As a result, both the chiral environment of the ligand and the steric congestion provided by the phenyl residue close to the reacting end of the allyl moiety are profitable for a better enantiodiscrimination. This rationale can be taken into account for the palladium catalyst bearing the auxiliary **4**.

Table 1. Asymmetric allylic substitution reactions with chiral EDT-TTF-oxazoline ligands[a]

Entry	Ligand	[Pd] (mol %)	Time (h)	Conv. (%)[b]	ee % (conf.)[c]
1	EDT-TTF-(*R*)-*i*PrOX **3b**	1.5	20	10	6 (*R*)
2	EDT-TTF-PPh_2-(*R*)-MeOX **2b**	3.0	18	25	30 (*R*)
3	EDT-TTF-PPh_2-(*R*)-*i*PrOX **4b**	1.5	18	10	85 (*R*)
4	EDT-TTF-PPh_2-(*R*)-*i*PrOX **4b**	3.0	70	21	80 (*R*)
5	EDT-TTF-SMe-(*R*)-*i*PrOX **5a**	3.0	18	12	26 (*R*)
6	PHOX+EDT-TTF[e]	3.0	18	8	94 (*R*)
7	EDT-TTF-PPh_2-(*R*)-*i*PrOX[d]	3.0	18	11	79 (*R*)

[a] Reactions were carried out by using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.03 or 0.015 mmol), ligand (1.2 equiv/Pd), the substrate (2 mmol), dimethylmalonate (3 equiv, 6 mmol), BSA (3 equiv, 6 mmol), KOAc (0.3 equiv, 0.6 mmol) in THF (20 ml) at room temperature.
[b] Conversions were determined by ^{1}H NMR analysis.
[c] Enantiomeric excesses were determined by HPLC on a Daicel® Chiralpak® AD column. The absolute configuration was assigned by comparing the sign of absolute optical rotation with reported data.
[d] The reaction was carried out with $[Pd(\eta^3\text{-}C_3H_5)$(EDT-TTF-$PPh_2$-*i*PrOX)$]^{2+}$,$PF_6^-$,$SbF_6^-$ in the same conditions as above.
[e] The reaction was performed in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/(*R*)-PHOX/EDT-DMC-TTF in 1/1.5/1.5 ratio.

For the auxiliary **3b**, the two potential coordination sites are the nitrogen and sulfur atoms, although it is well known that TTF sulfur atoms do not possess good coordination properties, and examples of metal$\cdots S_{TTF}$ coordination are scarce.[19] One can consider that the N=C π* orbital is a better π-acceptor than the sulfur atom, all the more since the latter is included in an electron rich heterocycle.[20] Consequently, for the palladium complexes bearing a ligand **3**, the addition



Scheme 5.

of the nucleophile will occur on the allyl-carbon trans to the oxazoline nitrogen of the chiral auxiliary, as suggested by Bryce and Chesney.[8f] The chiral centre of the ligand will be thus away from the reacting site and, moreover, there is not much steric hindrance on the sulfur site where the nucleophile will add. As a result, several conformers of allyl-palladium complexes of similar stability and reactivity are certainly present in the reaction mixture and are likely to provide a lower selectivity.

In the case of the thiomethyl ligand **5b**, the thioether group is a rather poor π-acceptor,[8l] yet better than the S_{TTF}. Again, the nucleophile certainly adds preferentially onto the carbon located trans to the nitrogen of the oxazoline that is also trans to the chiral environment of the catalyst. Furthermore, the low steric congestion around the SMe sulfur atom of the ligand is not prone to highly selective reactions.

The difference of selectivity observed for catalyses performed in the presence of auxiliaries **2b** and **4b** (Δee= 55%) can be attributed to the overall steric crowding discrimination between the corresponding palladium complexes.

The rates of the reactions require some comments. In all our catalytic experiments, the conversions are low even for prolonged reaction times or with higher catalyst loading. This is indicative of the evolution of the catalytic species during catalysis. We suspect an alteration of the catalyst brought into by the TTF unit furnishing an inactive palladium species. In order to check the likely harmful effect of the TTF residue, we carried out an AAA in the presence of the original (*R*)-PHOX auxiliary and of added EDT-dimethylcarboxylate-TTF (EDT-DMC-TTF). Indeed, in the presence of PHOX, the allyl product is obtained with up to 98% ee.[3] In the presence of added amount of EDT-dimethylcarboxylate-TTF (Pd/PHOX/EDT-DMC-TTF=1/1.5/1.5) while using otherwise identical reaction conditions to the ones given in the table, the conversion dropped to 8% while the stereoselectivity remains at a close level of 94% ee (entry 6). Interestingly, enantioselective hydrogenations performed with iridium catalysts bearing EDT-TTF-PPh_2-*i*PrOX **4** are going to completion.[21] The 'poisoning' of the catalyst by TTF species is thus dependent on the metal used.

Finally, the Tsuji–Trost reaction was also carried out in the presence of oxidised TTF-palladium complexes. Indeed, the TTF unit is redox active, showing stable and reversible changes in oxidation states, the corresponding radical cation species being obtained easily upon chemical or electrochemical oxidation.[20] We therefore envisaged that the use of these TTF containing ligands might allow an electromodulation of the catalytic centre upon changing the electronic density around the metal.[22] This concept was nicely demonstrated by Wrighton et al. in the case of the catalytic hydrogenation of cyclohexene using a cobaltocene-diphosphine based rhodium complex as catalyst, which showed a much higher activity in the reduced cobaltocene form than in the oxidised cobaltocenium one.[23] Very recently, Gibson and Long clearly demonstrated that a ferrocenyl based salen titanium (IV) complex is much more active in the ring-opening polymerisation of lactide in the neutral state, as ferrocene, than in the oxidised state, as ferrocenium salt.[24] Therefore, we prepared first the series of (*rac*), (*R*) and (*S*) cationic palladium complexes [Pd(η^3-C_3H_5){EDT-TTF-PPh_2-*i*PrOX}][PF_6]. Next, we performed the chemical oxidation of these compounds with $NOSbF_6$ as oxidising agent.[25]

Note that the oxidation potentials of the TTF-Pd-allyl complexes (0.81 V vs SCE) corresponding to the equilibrium $TTF \leftrightarrows TTF^{+\bullet}$ are about 180 mV higher than those of the free ligands (0.63 V vs SCE), yet showing a full reversibility of this oxidation process. The corresponding oxidised complexes, thus containing TTF radical cations, were obtained as black, paramagnetic powders, for which satisfactory elemental analyses indicate the expected formulation as [Pd(η^3-C_3H_5){EDT-TTF-PPh_2-*i*PrOX}]$^{2+}$$PF_6^-$,$SbF_6^-$. Moreover, the optical activity of the enantiomeric salts has been demonstrated through circular dichroism measurements (Fig. 1). The new species [Pd(η^3-C_3H_5){EDT-TTF-PPh_2-*i*PrOX}]$^{2+}$$PF_6^-$,$SbF_6^-$ were then applied in the test AAA reaction (Table 1, entry 7). The conversion was slightly lower

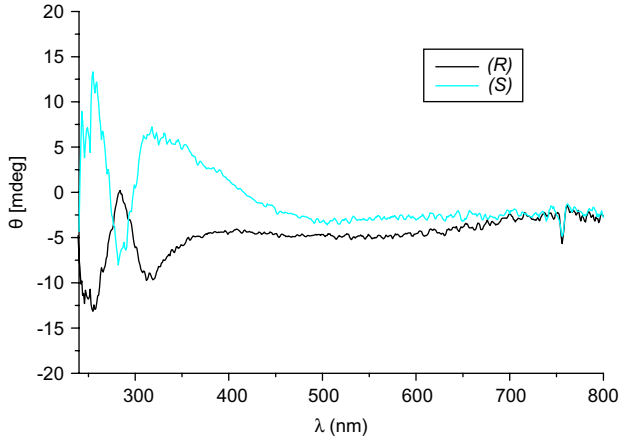


Figure 1. Circular dichroism spectra of the enantiomeric complexes [Pd(η^3-C_3H_5){EDT-TTF-PPh_2-*i*PrOX}]$^{2+}$$PF_6^-$,$SbF_6^-$.

and the enantioselectivity quite similar to those obtained with the non-oxidised counterparts (entry 4), therefore no clear influence, albeit somewhat negative, of the TTF oxidation state can be drawn. The similarity of the results between neutral TTF and radical cation TTF containing precatalysts can be possibly explained by the in situ reduction of $TTF^{+\bullet}$ in TTF, either by Pd(0) species or because of the basicity of the reaction medium. On the other hand, one possible effect of the TTF oxidation would have been the increase of the π-acceptor ability of the phosphino group, leading to a more favourable trans attack. Nevertheless, one could argue that the effect would be similar on the oxazoline nitrogen atom, all the more because of the conjugation between the TTF and oxazoline moieties. Additional experiments, especially aiming at evaluating the stability of ($TTF^{+\bullet}$)Pd(0) complexes, are necessary to clear up these hypotheses.

3. Conclusion

New chiral EDT-TTF-oxazoline type ligands have been synthesised and evaluated in palladium assisted asymmetric allylic substitution. Up to 85% ee could be obtained for the alkylation of (*rac*)-(*E*)-1,3-diphenyl-3-acetoxy-prop-1-ene with dimethylmalonate, using enantiopure bidentate EDT-TTF-PPh_2-*i*PrOxazoline ligands. The low reaction rates and conversions observed are very likely due to a poisoning of the catalyst by the tetrathiafulvalene. Preliminary investigations with (allyl)Pd(II) complexes containing oxidised TTF-PHOX ligands show no sizeable effect on the selectivity of the same catalytic reaction. The use of these new redox active ligands in other enantioselective reactions will be reported in due time.[21]

4. Experimental

4.1. General

All the reactions were carried out under inert gas atmosphere. Solvents were purified by standard techniques: THF was distilled over sodium and benzophenone; acetonitrile was dried over P_2O_5. Triethylamine was distilled over KOH. Nuclear magnetic resonance spectra were recorded on a Bruker Avance DRX 500 spectrometer operating at 500.04 MHz for ^1H, 125.75 MHz for ^{13}C and 202.39 MHz for ^{31}P. Chemical shifts are expressed in parts per million (ppm) downfield from external TMS. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; h, heptuplet; o, octuplet; m, multiplet; br, broad. ^{31}P chemical shifts are reported with positive values downfield from external 85% H_3PO_4 in D_2O. MALDI-TOF MS spectra were recorded on Bruker Biflex-IIITM apparatus, equipped with a 337 nm N_2 laser. Elemental analyses were performed by the 'Service d'Analyse du CNRS' at Gif/Yvette, France. No optical rotations could be measured, as the compounds are highly coloured in deep red. Circular dichroism measurements were recorded on a JASCO J-810 spectropolarimeter.

4.2. General procedure for the synthesis of EDT-TTF-PPh_2-*i*PrOX (4a–c)

To a degassed solution of (*R*)-oxazoline **3b**[14] (600 mg, 1.48 mmol) in 100 mL of dry THF, were added 1.2 equiv of LDA (0.25 mL of $(i\text{-Pr})_2NH$ and 0.89 mL of *n*-BuLi solution 2 M, in 10 mL of THF), at −78 °C. After stirring for 4 h at −78 °C, Ph_2PCl (360 mg, 1.61 mmol) was added dropwise. The reaction mixture was then allowed to warm slowly at room temperature, under stirring overnight. The solvent was removed in vacuo to afford a dark oil, which was diluted in dichloromethane and filtered through a pad of Celite®. After concentration under reduced pressure, the product was purified by chromatography column on silica gel, with CH_2Cl_2/cyclohexane 4/1, to afford 310 mg (36% yield) of **4b** as a red solid, after evaporation of solvent.

^1H NMR ($CDCl_3$, δ) 0.71 (d, *J*=6.7 Hz, 3H, CH_3), 0.78 (d, *J*=6.7 Hz, 3H, CH_3), 1.62 (m, 1H, CH(CH_3)$_2$), 3.25 (s, 4H, SCH_2CH_2S), 3.86 (t, *J*=7.9 Hz, C$H_{syn/i\text{-Pr}}$H′O), 3.92 (m, 1H, NCHCH_2O), 4.16 (dd, *J*=9.2 and 7.9 Hz, 1H, CH$H'_{anti/i\text{-Pr}}$O), 7.34–7.43 (m, 10H, CH_{aro}); ^{13}C NMR ($CDCl_3$, δ) 18.0 (*C*H_3), 18.5 (*C*H_3), 30.1 (S*C*H_2CH_2S), 30.2 (SCH_2*C*H_2S), 32.5 (*C*H(CH_3)$_2$), 71.0 (*C*HN), 72.6 (*C*H_2O), 105.9–113.7–114.1–116.5 (2*C*=*C*), 125.6 (d, J_{C-P}= 20.4 Hz, C=*C*–C=N), 128.5 (2d, J_{C-P}=7.5 Hz, *C*H$_{aro,meta}$), 129.6 (d, J_{C-P}=15.1 Hz, *C*H$_{aro,para}$), 133.5 (2d, J_{C-P}= 21.2 Hz, *C*H$_{aro,ortho}$), 135.4 and 135.8 (d, J_{C-P}=11.3 Hz, *C*$_{ipso}$), 141.2 (d, J_{C-P}=54.5 Hz, C=*C*–PPh_2), 156.8 (d, J_{C-P}= 2.8 Hz, *C*=N); ^{31}P NMR ($CDCl_3$, δ) −10.6; IR (KBr, cm^{-1}): 1628 ($\nu_{C=N}$); *m*/*z* (MALDI-TOF): 588.96 (M^+). Anal. Calcd for $C_{26}H_{24}NOPS_6$: C, 52.94; H, 4.10; N, 2.37. Found: C, 53.01; H, 4.11; N, 2.32.

4.2.1. (+/−)-EDT-TTF-PPh_2-*i*PrOX (4a). From 600 mg of **3a**,[15] red solid (460 mg, 53% yield). Anal. Calcd for $C_{26}H_{24}NOPS_6$: C, 52.94; H, 4.10; N, 2.37. Found: C, 52.95; H, 4.21; N, 2.24.

4.2.2. (*S*)-EDT-TTF-PPh_2-*i*PrOX (4c). From 600 mg of **3c**,[15] red solid (200 mg, 23% yield). Anal. Calcd for $C_{26}H_{24}NOPS_6$: C, 52.94; H, 4.10; N, 2.37. Found: C, 52.78; H, 4.03; N, 2.34.

4.3. General procedure for the synthesis of β-hydroxy amides (7a,b)

(*R*)-2-Amino-3-methyl-1-butanol or (*R*)-valinol (225 mg, 2.14 mmol) and distilled triethylamine (0.48 mL, 3.42 mmol) were placed in 10 mL THF. This colourless solution was stirred for 10 min under N_2 at room temperature, then a freshly prepared solution of EDT-TTF-TM-COCl **6**[15] (690 mg, 1.71 mmol in 70 mL THF, purple colour) was added dropwise. The reaction mixture became orange and a precipitate was formed. After stirring overnight at room temperature, the brown-red mixture was filtrated through Celite and the solvent evaporated. The crude product was purified on silica gel (eluant: THF), then the solvent evaporated. The oil thus obtained was diluted in a small volume of THF (5–8 mL) and dropped onto 400–500 mL petroleum ether to afford **7a** as a brown-pink powder (720 mg, 90% yield).

Mp=136 °C; ^1H NMR ($CDCl_3$, δ): 0.97 (d, ^3J=6.8 Hz, 3H, CH_3), 0.99 (d, ^3J=6.8 Hz, 3H, CH_3), 1.97 (o, ^3J=6.8 Hz, 1H, CH(CH_3)$_2$), 2.55 (s, 3H, SCH_3), 2.75 (br s, 1H, O*H*), 3.29 (s, 4H, SCH_2CH_2S), 3.72 (m, 2H, CH_2O), 3.83 (m, 1H, NH–C*H*–CH_2O), 7.37 (d, ^3J=8.0 Hz, 1H, N*H*); ^{13}C NMR

($CDCl_3$, δ): 18.7 (CH_3), 19.6 (CH_3), 20.0 (SCH_3), 29.0 ($CH(CH_3)_2$), 30.2 (SCH_2CH_2S), 57.8 (CH–NH), 63.8 (CH_2OH), 109.6–111.1–113.5–114.4 (2C=C), 129.9 (=C–SMe), 132.7 (=C–C=O), 160.3 (NH–C=O); *m/z* (MALDI-TOF): 468.89 (M^+) (calcd: 468.95). Anal. Calcd for $C_{15}H_{19}NO_2S_7$: C, 38.35; H, 4.08; N, 2.98. Found: C, 38.39; H, 4.04; N, 2.87.

4.3.1. (*S*)-EDT-TTF-SMe-β-hydroxyamide (7b). From 0.25 mL (2.14 mmol) (*S*)-2-amino-3-methyl-1-butanol or (*S*)-valinol, brown-pink powder (690 mg, 86% yield). Anal. Calcd for $C_{15}H_{19}NO_2S_7$: C, 38.35; H, 4.08; N, 2.98. Found: C, 38.13; H, 4.06; N, 2.85.

4.4. General procedure for the synthesis of EDT-TTF-SMe-*i*PrOX (5a,b)

A solution of hydroxyamide **7a** (670 mg, 1.43 mmol) and distilled NEt_3 (0.34 mL, 2.44 mmol) in 30 mL THF was cooled at 0 °C, and then, mesyl chloride (0.19 mL, 2.43 mmol) was added at once. After 30 min of stirring at 0 °C, more NEt_3 (1.53 mL, 10.98 mmol) was added and the reaction mixture was subsequently heated at 50 °C until the intermediate mesylate disappeared (checked by TLC: AcOEt/cyclohexane 1/1), after ca. 20 h. After filtration through Celite, the solvent was evaporated and the crude product was purified by silica gel chromatography (eluant: AcOEt/cyclohexane 1/1), to afford **5a** as a red powder (580 mg, 90% yield) after evaporation of solvents.

Mp=129 °C; ^1H NMR ($CDCl_3$, δ) 0.88 (d, J=6.7 Hz, 3H, CH_3), 0.97 (d, J=6.7 Hz, 3H, CH_3), 1.78 (o, J=6.7 Hz, 1H, $CH(CH_3)_2$), 2.54 (s, 3H, SCH_3), 3.29 (s, 4H, SCH_2CH_2S), 4.02–4.08 (m, 2H, $NCH(CH_3)$ and $CH_{syn/i\text{-}Pr}$ H′O), 4.32 (dd, J=8.9 and 7.8 Hz, 1H, $CHH'_{anti/i\text{-}Pr}O$); ^{13}C NMR ($CDCl_3$, δ) 18.1 (CH_3), 18.8 (CH_3), 18.6 (SCH_3), 30.2 (SCH_2CH_2S), 32.7 ($CH(CH_3)_2$), 70.9 (CHN), 72.6 (CH_2O), 108.4–112.9–113.5–114.3 (2C=C and C=C–SMe), 137.7 (C=C–C=N), 157.0 (C=N); *m/z* (MALDI-TOF): 450.97 (M^+). Anal. Calcd for $C_{15}H_{17}NOS_7$: C, 39.88; H, 3.79; N, 3.10. Found: C, 39.73; H, 3.79; N, 2.95.

4.4.1. (*S*)-EDT-TTF-SMe-*i*PrOX (5b). From 640 mg (1.36 mmol) hydroxyamide **7c**, red crystalline solid (540 mg, 88% yield). Anal. Calcd for $C_{15}H_{17}NOS_7$: C, 39.88; H, 3.79; N, 3.10. Found: C, 40.02; H, 3.75; N, 2.97.

4.5. Synthesis of the palladium complexes

4.5.1. Synthesis of complexes (+/−), (*R*) and (*S*)-[Pd(η³-C_3H_5)(EDT-TTF-PPh_2-*i*PrOX)]PF_6. The ligand (*R*)-EDT-TTF-PPh_2-*i*PrOX **4b** (59 mg, 0.1 mmol) and the precursor $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (18.6 mg, 0.05 mmol) were dissolved in THF (5 ml). The dark red solution was stirred for 1 h at room temperature followed by the addition of $TlPF_6$ (36 mg, 0.1 mmol). After 15 min of stirring, a filtration through a pad of dry Celite afforded the complex [Pd(η³-C_3H_5)(**4b**)]PF_6 as a dark powder (78.2 mg, 89% yield).

^1H NMR (CD_2Cl_2, δ): 0.55 (d, ^3J=7.1 Hz, 3H, CH_3), 0.89 (d, J=7.1 Hz, 3H, CH_3), 2.03 (dh, J=7.1 and 3.9 Hz, 1H, $CH(CH_3)_2$), 3.02 (br m, 1H, H_{allyl}), 3.29 (m, 4H, SCH_2CH_2S), 3.92 (br m, 1H, H_{allyl}), 4.41 (ddd, J=9.6, 5.1 and 3.9 Hz, 1H, N–CH–(*i*-Pr)–CH_2O), 4.47 (dd, J=9.0 and 5.1 Hz, 1H, $CH_{anti/i\text{-}Pr}H'O$), 4.58 (t, J=9.0 Hz, 1H, $CHH'_{syn/i\text{-}Pr}O$), 4.93 (br m, 1H, H_{allyl}), 5.33 (br m, 1H, H_{allyl}), 5.85 (q, J=10.3 Hz, 1H, $H_{allyl\ central}$), 7.42–7.71 (m, 10H, CH_{aro}); ^{13}C NMR (CD_2Cl_2, δ): 14.5 and 18.3 (s, $2CH_3$), 30.0 (s, $CH(CH_3)_2$), 31.9 (s, SCH_2CH_2S), 68.1 (s, CH–N), 70.5 (s, CH_2O), 76.8 (s, $CH_{2allyl\ trans/N}$), 109.8–113.9–114.3 and 114.6 (s, 2C=C), 123.1 (d, J_{C-P}=6.0 Hz, C=C–C=N), 126.9 and 128.1 (d, J_{C-P}=48.5 Hz, $CH_{2allyl\ trans/P}$), 128.6 (s, $CH_{allyl\ central}$), 130.0 and 130.4 (d, J_{C-P}=11.6 Hz, $CH_{aro,meta}$), 132.2 (d, J_{C-P}=14.0 Hz, C_{ipso}), 132.9 and 133.7 (d, J_{C-P}=14.6 Hz, $CH_{aro,ortho}$), 133.2 and 133.4 (d, J_{C-P}=2.4 Hz, $CH_{aro,para}$), 137.5 (d, J_{C-P}=17.5 Hz, C=C–PPh_2), 159.4 (d, J_{C-P}=6.7 Hz, C=N); ^{31}P NMR (CD_2Cl_2, δ): 16.0; *m/z* (MALDI-TOF): 735.71 (M^+). Anal. Calcd for $C_{29}H_{29}F_6NOP_2PdS_6$: C, 39.48; H, 3.31; N, 1.59. Found: C, 40.82; H, 3.73; N, 1.15 (crude product).

4.5.1.1. [Pd(η³-C_3H_5)(4a)]PF_6. Same amounts of reagents, dark powder (87.2 mg, 99% yield). Anal. Calcd for $C_{29}H_{29}F_6NOP_2PdS_6$: C, 39.48; H, 3.31; N, 1.59. Found: C, 40.92; H, 3.83; N, 1.09 (crude product).

4.5.1.2. [Pd(η³-C_3H_5)(4c)]PF_6. Same amounts of reagents, dark powder (85.2 mg, 97% yield). Anal. Calcd for $C_{29}H_{29}F_6NOP_2PdS_6$: C, 39.48; H, 3.31; N, 1.59. Found: C, 40.87; H, 3.78; N, 1.12 (crude product).

4.5.2. Synthesis of complexes (+/−), (*R*) and (*S*)-[Pd(η³-C_3H_5)(EDT-TTF-PPh_2-*i*PrOX)]$^{2+}$,PF_6^-,SbF_6^-. The complex [Pd(η³-C_3H_5)(**4b**)]PF_6 (80 mg, 0.09 mmol) and the oxidising agent $NOSbF_6$ (24 mg, 0.09 mmol) were dissolved in acetonitrile (8 ml). The solution was stirred for 1 h at room temperature, and then CH_3CN was removed under reduced pressure. The oxidised complex [Pd(η³-C_3H_5)(**4b**)]$^{2+}$, PF_6^-,SbF_6^- was thus isolated as a black powder (88.4 mg, 88% yield). Anal. Calcd for $C_{29}H_{29}F_{12}NOP_2PdS_6Sb$: C, 31.21; H, 2.44; N, 1.26. Found: C, 30.44; H, 3.32; N, 1.45 (crude product).

4.5.2.1. [Pd(η³-C_3H_5)(4a)]$^{2+}$,PF_6^-,SbF_6^-. Same amounts, black powder (80.5 mg, 80% yield). Anal. Calcd for $C_{29}H_{29}F_{12}NOP_2PdS_6Sb$: C, 31.21; H, 2.44; N, 1.26. Found: C, 30.49; H, 3.36; N, 1.41 (crude product).

4.5.2.2. [Pd(η³-C_3H_5)(4c)]$^{2+}$,PF_6^-,SbF_6^-. Same amounts, black powder (81.7 mg, 81% yield). Anal. Calcd for $C_{29}H_{29}F_{12}NOP_2PdS_6Sb$: C, 31.21; H, 2.44; N, 1.26. Found C, 30.51; H, 3.34; N, 1.38 (crude product).

4.6. General procedure for the asymmetric allylic alkylation

In a Schlenk tube, the selected chiral auxiliary (0.036 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (6 mg, 0.016 mmol) were dissolved in anhydrous THF (10 mL). The red solution was stirred for 1 h at room temperature. In a second Schlenk tube, the base KOAc (60 mg), BSA (1.6 mL) and the nucleophile dimethylmalonate (0.7 mL) were mixed in THF (5 mL). The solution containing the palladium precatalyst was transferred onto the above mixture followed by the substrate (505 mg, 2 mmol) in solution in THF (5 mL). The reaction mixture was stirred during the desired reaction time. Then,

a saturated solution of $NaHCO_3$ (20 mL) was added. The product was extracted with diethylether (3×20 mL). The organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvent, an oil was obtained, which was analysed by ^1H NMR in order to determine the conversion and by HPLC (Daicel® Chiralpak® AD column, hexane/isopropanol: 90/10, flow rate=1mL/min; λ=254 nm) to determine the enantiomeric excess.

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Preparation of non-racemic single-stereocentre α-aminonitriles and a study of their fate in Bruylants reactions

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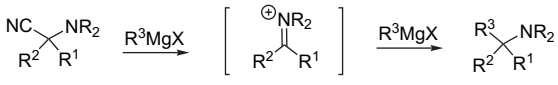
Abstract—A number of chiral carboxamide dehydration methods were investigated for the preparation of four representative enantiomerically enriched α-aminonitriles possessing only one stereogenic centre; best results were observed using Burgess' salt (yield up to 87%, er up to 92/8) or the trifluoroacetic anhydride–triethylamine combination (yield up to 98%, er up to 86/14). Two of the aminonitriles thus obtained were subjected to Bruylants reactions with a methyl Grignard reagent to furnish the corresponding tertiary amines; these products, along with any unreacted starting materials, were obtained essentially in racemic form. In accord with the accepted mechanism for this reaction, a magnesium species is implicated in the formation of an iminium, the common intermediate for both chemical transformation and racemization processes.

1. Introduction

The reaction of a Grignard reagent with an *N*,*N*-disubstituted α-aminonitrile bearing at least one substituent at the α-carbon to give an amine has been known for 80 years, and is generally known as the Bruylants reaction, after its discoverer.[1,2] From the outset, it has always been assumed that the reaction proceeds by initial departure of cyanide to give an iminium intermediate, which then undergoes rapid addition of an organic nucleophile to give the substituted product (Scheme 1). This mechanism is perfectly reasonable, and consistent with a number of experimental observations, including (a) the cases in which the aminonitrile precursors possess nearby chiral centres, in which a high degree of diastereoselectivity is often achieved,[2,3] and (b) modifications of the reaction in which an iminium is specifically generated from an aminonitrile by using a decyanating agent (such as a silver salt), and the Grignard nucleophile is added later in the reaction procedure.[2k,4] It is interesting to note that—perhaps in testimony of the success of the mechanistic proposal—no direct proof for the iminium intermediate in the Bruylants reaction has been either sought nor acquired.



R ≠ H (ie tertiary amine)
R^1, R^2, R^3 = various alkyl or aryl; R^1 or R^2 (but not both) can be H

Scheme 1.

Recently, we carried out a theoretical study of the reaction of a Grignard reagent with a particular aminonitrile system.[5] One intriguing result which emerged from this study was the apparent plausibility of a reaction pathway leading formally to a Bruylants type substitution reaction. Initial formation of an N→Mg Lewis acid–base complex followed by intramolecular substitution of the nitrile group by the complexed alkyl group would give the substitution product (Scheme 2). This transformation appeared feasible on the basis of orbital interactions for the case study and was only slightly less favoured energetically than the experimentally observed addition reaction. While we at no point imagined disproving the intermediacy of an iminium in the Bruylants reaction, we felt that all previous studies or applications thereof had been contented with the fact that the results were compatible with this accepted mechanism; in other words, no detailed search for any evidence of an alternative mechanism, operating even to a minor extent, had been carried out.

Scheme 2.

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We wanted to devise some experiments specifically designed to bring to light any evidence at all concerning an intracomplex substitution mechanism, along the lines of that suggested in Scheme 2. This mechanism should proceed with inversion at the reactive α-carbon centre, so that if the aminonitrile precursor is non-racemic, then the amine product should likewise be obtained in enantiomerically enriched form. In contrast, an iminium intermediate devoid of any chiral information should undergo nucleophilic attack with equal probability on either face of the planar reaction centre leading to racemic material. There is some precedent for a mechanistic investigation based on this rationale: reactions of $Me_2CuLi–BF_3\cdot Et_2O$ with acetals in which the acetal carbon was the only stereogenic centre provided partially enantiomerically enriched ether products, showing that an S_N1 process was operating simultaneously with an S_N2 and/or ion pair mechanism.[6]

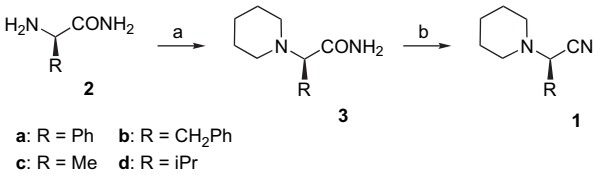
We therefore envisaged the examination of the stereochemical course of the Bruylants reactions of non-racemic α-aminonitriles in which the reacting α-carbon atom was the only stereogenic centre. This in turn presented us with the challenge of preparing appropriate chiral non-racemic substrates for these reactions, for which, surprisingly, almost no precedent existed.

2. Results and discussion

2.1. Selection and preparation of starting materials

The enantioselective preparation of single-stereocentre aminonitriles in which the amine lone pair is free is not a simple matter, since such compounds are expected to be configurationally labile. The literature is bereft of reports on the preparation of such *N*,*N*-dialkylated aminonitriles in enantiomerically enriched form.[7] We are aware of only one such example, (*S*)-1-benzyl-2-cyanopiperidine, prepared in several steps from a non-racemic cyanohydrin.[8] Related structures therefore drew our attention. *N*-Unsubstituted examples (i.e., derivatives of general formula $H_2NCR^1R^2CN$) can be obtained from racemates by resolution (usually with tartaric acid)[9,10] or through enantioselective enzymatic transformations.[10,11] As expected, these materials are stable only as their hydrochlorides (or other salts). Several examples of such compounds have also been prepared from enantiomerically enriched cyanohydrins.[12] Recently, catalytic enantioselective modifications of the Strecker reaction exploiting chiral catalysts have been developed successfully,[13] but the products are invariably *N*-monosubstituted α-aminonitriles (general formula $R^3NHCR^1R^2CN$, or their *N*-acylated derivatives in some applications), since the precursors are preformed imines.[14] Perhaps the most often used approach to obtain non-racemic *N*-monosubstituted aminonitriles is the dehydration of a derivative of the corresponding amino acid carboxamide. $POCl_3$/pyridine,[15] tosyl chloride/pyridine,[16] trifluoroacetic anhydride/triethylamine (TFAA/Et_3N),[17] triflic anhydride/triethylamine,[18] dibutyltin oxide,[19] a number of reagents used for peptide coupling,[20] the cyanuric chloride/dimethylformamide (CyuCl/DMF) combination[21] and Burgess' salt[22] have all been reported as successful dehydrating agents, although, somewhat frustratingly, the enantiomeric purities of the resulting aminonitriles are not always fully determined. More importantly, all of these cases involve amino acid carboxamide starting materials in which the amine nitrogen is protected in some way, usually as a carbamate or an amide, which leads to products of general structure $PNHCR^1R^2CN$, where P is a protecting group. In one exception to this trend, a short series of amino acid carboxamides with free NH_2 groups have been dehydrated with (2-pyridyl)sulfonyl chloride/DMF combination to give the amidine derivatives of the α-aminonitriles; ee values were not reported.[23,24]

We decided to investigate α-aminonitriles of type **1**. The aminonitrile with the aromatic α-substituent (**1a**) was expected to be more prone to racemization and was investigated first. The appropriate tertiary amine carboxamide **3a** was prepared from the readily available[25] (*R*)-phenylglycine carboxamide **2a** by reaction with 1,5-dibromopentane under basic conditions to construct the piperidine ring (Scheme 3).



Scheme 3. For simplicity, only one stereochemical representation is presented here; the absolute configurations of the compounds were: (*R*)-**2a**, (*R*)-**2b**, (*S*)-**2c** and (*S*)-**2d**. Reagents and conditions: (a) $Br(CH_2)_5Br$, K_2CO_3, EtOH, reflux; 96% for **3a**, 79% for **3b**, 62% for **3c**, 56% for **3d**; (b) dehydrating agent (see Tables 1 and 2 and text).

For the key dehydration step, most of the reagents reviewed above were examined. Enantiomeric ratios of the product were determined only in cases where the chemical yield and the optical rotation were considered encouraging. Results are presented in Table 1.

The configurational lability of the target aminonitrile was clearly in evidence. Four of the dehydrating agents tested furnished an extensively or totally racemized product, and were poor-to-moderate performers in terms of chemical yields. CyuCl/DMF gave **1a** with reasonable enantiomeric enrichment, although the isolated yield was moderate. A very good yield but slightly lower enantiomeric enrichment was achieved by using TFAA/Et_3N; it was interesting to note that this reagent performed much better than Tf_2O/Et_3N. Burgess' salt arguably gave the best results, in the combined terms of clean product, decent yield and useful enantiomeric

Table 1. Dehydration reactions of **3a** to give **1a** (see Scheme 3)

Reagent	**3a**→**1a**		
	Yield (%)[a]	OR[b]	er[c]
$POCl_3$/Py	30	+10	—
n-Bu_2SnO	36	0	—
TsCl/Py	64	0	—
Tf_2O/Et_3N	62	+3	—
CyuCl/DMF	53	+39	80/20
TFAA/Et_3N	92	+36	77/23
Burgess' salt	78	+44	92/8

[a] Yields are given for isolated (spectroscopically pure) material.
[b] Optical rotations (OR) are given for $[\alpha]_D^{22}$ (*c* 1.0, $CHCl_3$).
[c] Enantiomeric ratios (er) were determined as indicated in the text.

enrichment. Even so, partial racemization seems unavoidable. Aminonitrile **1a** could be chromatographed on a flash silica gel column with no detectable changes in enantiomeric enrichment; however, crystallization of **1a** from methanol provoked complete racemization.

We then tested the three best methods of dehydration on the three other α-aminonitriles **3b–d**. These compounds were prepared in an analogous fashion to **3a**, starting from the carboxamides of (*R*)-Phe, (*S*)-Ala and (*S*)-Val, respectively (Scheme 3). Results for the dehydration reactions are presented in Table 2. CyuCl/DMF performed poorly in terms of both chemical yield and enantiomeric enrichment. Burgess' salt and TFAA/Et_3N performed reasonably well; chemical yields were more variable with the latter, while enantiomeric ratios for the series of compounds **1** did not differ significantly. In all cases, partial racemization was still evident. Rather surprisingly, this was more the case with the methyl-bearing derivative **1c**, while the other aliphatic derivatives **1b** and **1d** were not less racemized than the aromatic derivative **1a**.

For this work, we required a method for the determination of the enantiomeric ratios. Several options were examined using authentic racemic materials (±)-**1a–d**, which were prepared by standard Strecker condensation procedures. For **1b** and **1c**, a ^1H NMR technique was convenient: in $CDCl_3$ solution, the presence of 7–8 equiv of the chiral resolving agent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol[26] induced complete separation of the methine triplet signals in the spectrum of (±)-**1b** and one of the piperidine C2 methylene signals in the spectrum of (±)-**1c**. This technique failed for **1d**, so we used 1 equiv of (*R*)-Mosher's acid[27] in C_6D_6 to effect the separation of the methine doublet signals in the ^1H NMR spectrum of (±)-**1d**. None of the NMR techniques was suitable for the analysis of **1a**, so we resorted to the use of chiral HPLC, which gave good baseline enantiomer separation. It is noteworthy that we were unable to find a universally convenient analytical technique within this small series of related substances.

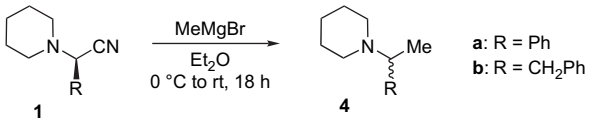
Table 2. Dehydration reactions of **3a–d** to give **1a–d** (see Scheme 3)

Reaction	CyuCl/DMF		TFAA/Et_3N		Burgess' salt	
	Yield (%)[a]	er[b]	Yield (%)[a]	er[b]	Yield (%)[a]	er[b]
3a→1a	53	80/20	92	77/23	78	92/8
3b→1b	45	73/27	98	67/33	71	77/23
3c→1c	10	67/33	44	60/40	80	53/47
3d→1d	Degradation	—	59	86/14	87	81/19

[a] Yields are given for isolated (spectroscopically pure) materials.
[b] Enantiomeric ratios (er) were determined as indicated in the text.

2.2. Bruylants reactions

Enantiomerically enriched samples of **1a** and **1b** were treated with 2 equiv of methyl Grignard reagent under typical Bruylants conditions (Et_2O solution, 0 °C to rt, overnight). Following mild acidic aqueous work-up, the crude product mixture was analyzed; subsequent chromatography on silica gel permitted the isolation of the appropriate products (Scheme 4). Results are presented in Table 3.



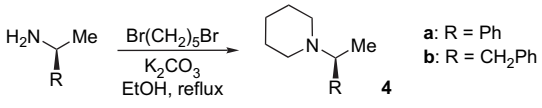
Scheme 4.

Table 3. Bruylants reactions of **1a**,**b** to give **4a**,**b** (see Scheme 4)

Substrate	er[b]	Equiv MeMgBr	Recovered **1**		Product **4**	
			Yield (%)[a]	er[b]	Yield (%)[a]	er[b]
1a	92/8	2	0	—	97	50/50
	92/8	1	45	50/50	44	50/50
	77/23	0	100[c]	75/25	0	—
	77/23	—[d]	100[c]	55/45	0	—
1b	77/23	2	0	—	79	50/50
	77/23	1	44	50/50	46	50/50
	73/27	0	100[c]	67/33	0	—
	73/27	—[d]	100[c]	50/50	0	—

[a] Yields are given for isolated (spectroscopically pure) materials.
[b] Enantiomeric ratios (er) were determined as indicated in the text.
[c] Crude isolate was essentially pure.
[d] Reaction carried out with 2 equiv $MgBr_2 \cdot OEt_2$ instead of MeMgBr.

With 2 equiv of Grignard reagent, the reactions proceeded with excellent chemical yield to give the expected tertiary amines **4a** and **4b**. With only 1 equiv of the Grignard reagent, these amines were obtained in lower yields and were accompanied by unreacted aminonitrile starting materials. In all cases, products and recovered starting materials were isolated in racemic form. Zero-value optical rotations were observed for crude isolates, suggesting that racemization had occurred during the reaction itself.[28] Enantiomerically enriched substrates **1a** and **1b** were submitted to blank control reactions (no Grignard reagents added) and were recovered with no significant loss of enantiomeric enrichment, suggesting that the Grignard reagent had been responsible for racemization. Enantiomerically enriched substrates **1a** and **1b** were submitted to simulated reaction conditions in the presence of 2 equiv of $MgBr_2 \cdot OEt_2$ instead of the Grignard reagent. No amines were obtained, of course, but the recovered starting materials were extensively racemized. We ruled out definitively the (unlikely) possibility that amines **4a** and **4b** had been racemized after their formation in the reaction mixture: authentic samples of enantiomerically pure amines were prepared from the corresponding commercial primary amines according to Scheme 5. When they were subjected to Bruylants conditions and standard work-up, they were recovered intact and without loss of enantiomeric purity. The enantiomeric enrichments of all samples of amines **4a** and **4b** were determined by ^1H NMR spectroscopy in C_6D_6 solution in the presence of 1 equiv of (*S*)-mandelic acid as a chiral solvating agent,[29] which induced complete separation of the methyl doublet signals.

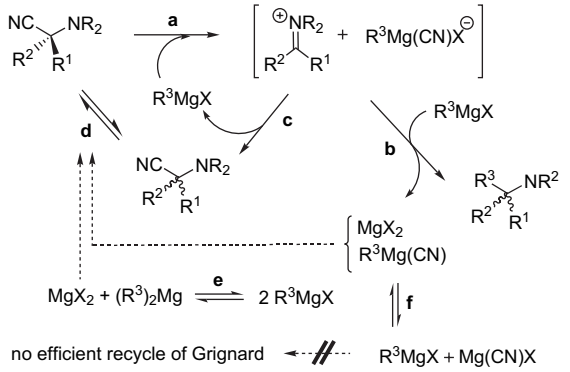


Scheme 5. Yields: 82% for **4a**, 55% for **4b**.

Most preparative applications of the Bruylants reaction are performed using at least 2 equiv of Grignard reagent, and

indeed we observed only partial conversions when 1 equiv was used.[30] We performed a further experiment using racemic **1a** and 1 equiv of methyl magnesium bromide under typical Bruylants conditions (Et_2O solution, 0 °C to rt) then left the stirred mixture at rt for 43 days. After the usual work-up, the product comprised a 77/23 mixture **4a/1a**, obtained with an 83% overall yield, which corresponds to a 64% yield of **4a**. Clearly, the Bruylants reaction proceeds only very slowly beyond 50% conversion in the presence of a single equivalent of Grignard reagent.

Collectively, these results suggest the situation which is summarized in Scheme 6. The first Grignard equivalent generates an iminium by cyanide abstraction (step a), and the privileged source of organic nucleophile is a second Grignard equivalent (step b). The significance of the putative magnesium 'ate' complex generated in the first step remains uncertain; in any case, it appears to be a poor source of organic nucleophile. Racemization of the aminonitrile could occur either by return of cyanide nucleophile to the iminium from the magnesium 'ate' species (step c) or by a parallel cyanide elimination–readdition process mediated by MgX_2 or some related Lewis acid by-product generated from either of the two Grignard equivalents (step d). Another possible source of MgX_2 is the Schlenk equilibrium (step e);[31] the R_2Mg species generated concomitantly might also replace RMgX in step b,[32] although this would not change the net inorganic product component mixture [MgX_2+$R^3Mg(CN)$]. Intriguingly, the regeneration therefrom of a RMgX species (step f), which should be available for recycle and thus facilitate complete conversion with only 1 equiv of Grignard, does not appear to operate effectively. In any event, regardless of the relative rates of these processes, they are collectively faster than any conceivable contribution from an intra-complex substitution mechanism for the Bruylants reaction.



Scheme 6.

3. Conclusions

This work confirms the configurational lability of *N*,*N*-dialkylated aminonitriles in which the amine lone pair is free. Nevertheless, the preparation of single-stereocentre examples in enantiomerically enriched form has been achieved for the first time, and the methods for the determination of enantiomeric purity have been established. The use of these compounds in the Bruylants reaction gives further insight into the mechanism of this transformation and all the evidence obtained is in agreement with the requirement of 2 equiv of Grignard reagent and the intermediacy of a readily formed iminium ion.

4. Experimental

4.1. General methods

Melting points were determined on a Reichert microscope apparatus. NMR spectra were measured on a Bruker AC-400 spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C; chemical shifts (δ) are reported in parts per million. Infrared spectra were recorded as KBr pellets (for solid compounds) or neat (for oils) on a Perkin–Elmer 881 spectrometer or a Perkin–Elmer Paragon 500 FTIR spectrometer; only structurally important peaks (ν) are presented in inverse centimetre. High-resolution mass spectra were recorded in positive electrospray mode on a micro Q-TOF Micromass instrument (3000 V) with an internal lock mass (H_3PO_4) and an external lock mass (Leu-enkephalin). Optical rotations were measured on a Jasco DIP-370 polarimeter. Elemental analyses were carried out by the CNRS Central Microanalytical Laboratory, Lyon. Flash chromatography was carried out on 15 cm length columns of silica gel (40–63 μm). Anhydrous solvents were obtained as follows: ether was distilled from sodium–benzophenone under argon, DMF and dichloromethane were distilled from CaH_2 under argon. Ether solutions of methyl magnesium bromide (3 M) were obtained commercially and used as freshly delivered; dilutions in ether were made immediately before reactions were carried out. Procedures for dehydration test reactions reported in Table 1 followed as closely as possible the literature descriptions (see text for references). Compounds **2a** and **2b** were prepared from the corresponding commercial (*R*)-amino acids using literature procedures.[25] The (*S*)-isomers of compounds **2c** and **2d** were obtained commercially as their hydrochlorides.

4.2. General procedure for piperidine ring construction

1,5-Dibromopentane (5.0 mmol) was added to a solution of primary amine substrate (2.5 mmol) in EtOH (5 mL) in the presence of potassium carbonate (13.5 mmol). The mixture was refluxed overnight and then cooled to rt. The mixture was filtered and the solids were washed through several aliquots of EtOH; combined filtrate and washings were then evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 99/1).

4.2.1. (*R*)-2-Phenyl-2-(1-piperidinyl)ethanamide (3a). Yield 96%. Mp 156 °C (EtOAc); $[\alpha]_D^{25}$ −27.2 (*c* 1.0, $CHCl_3$); IR ν 3240, 1660; ^1H NMR ($CDCl_3$) δ 1.16–1.20 (m, 2H), 1.38–1.49 (m, 4H), 2.26 (m, 4H), 3.72 (s, 1H), 6.79 (s, 1H), 7.01 (s, 1H), 7.20–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 26.4 (CH_2), 52.7 (CH_2), 76.4 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH), 136.5 (C_q), 175.4 (C_q). HRMS *m*/*z* calcd for $C_{13}H_{19}N_2O$ $[MH]^+$: 219.1497; found: 219.1499.

4.2.2. (*R*)-3-Phenyl-2-(1-piperidinyl)propanamide (3b). Yield 79%. Mp 114 °C (H_2O); $[\alpha]_D^{25}$ +45.4 (*c* 1.0, $CHCl_3$); IR ν 3333, 1664; ^1H NMR ($CDCl_3$) δ 1.28–1.44 (m, 6H),

2.33–2.40 (m, 4H), 2.73 (dd, 1H, *J*=6.4 and 14.0 Hz), 3.07 (dd, 1H, *J*=6.6 and 14.0 Hz), 3.20 (t, 1H, *J*=6.5 Hz), 5.57 (br s, 1H), 6.77 (br s, 1H), 7.00–7.14 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 26.7 (CH_2), 32.1 (CH_2), 51.2 (CH_2), 71.2 (CH), 126.0 (CH), 128.3 (CH), 129.2 (CH), 140.4 (C_q), 175.4 (C_q). HRMS: *m/z* calcd for $C_{14}H_{21}N_2O$ $[MH]^+$: 233.1654; found: 233.1652.

4.2.3. (*S*)-2-(1-Piperidinyl)propanamide (3c). Yield 62%. Mp 112 °C (hexane); $[\alpha]_D^{24}$ +22.2 (*c* 1.56, $CHCl_3$); IR ν 3314, 3088, 1666; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3H, *J*=7.2 Hz), 1.41 (m, 2H), 1.51 (m, 4H), 2.38 (m, 2H), 2.47 (m, 2H), 3.01 (q, 1H, *J*=6.8 Hz), 6.18 (s, 1H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.7 (CH_3), 24.1 (CH_2), 26.4 (CH_2), 51.0 (CH_2), 64.4 (CH), 177.6 (C_q). HRMS *m/z* calcd for $C_8H_{17}N_2O$ $[MH]^+$: 157.1341; found: 157.1336. Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.46; H, 10.31; N, 17.82.

4.2.4. (*S*)-3-Methyl-2-(1-piperidinyl)butanamide (3d). Yield 56%. Mp 103 °C (hexane); $[\alpha]_D^{21}$ −9.7 (*c* 1.125, $CHCl_3$); IR ν 3372, 3186, 1661; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J*=6.8 Hz), 1.01 (d, 3H, *J*=6.8 Hz), 1.46 (m, 2H), 1.56 (m, 4H), 2.14 (o, 1H, *J*=6.8 Hz), 2.47 (m, 4H), 2.54 (d, 1H, *J*=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 17.7 (CH_3), 20.0 (CH_3), 24.6 (CH_2), 26.2 (CH), 26.4 (CH_2), 51.7 (CH_2), 75.84 (CH), 174.3 (C_q). HRMS *m/z* calcd for $C_{10}H_{21}N_2O$ $[MH]^+$: 185.1654; found: 185.1667. Anal. Calcd for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20. Found: C, 65.16; H, 10.97; N, 15.25.

4.2.5. (*S*)-1-(1-Phenylethyl)piperidine (4a). Yield 82%. Oil, bp 110–116 °C (4 mmHg); $[\alpha]_D^{25}$ −26.0 (*c* 1.2, $CHCl_3$); IR ν 3040; ^{1}H NMR ($CDCl_3$) δ 1.32–1.38 (m, 2H), 1.44 (d, 3H, *J*=6.8 Hz), 1.56–1.66 (m, 4H), 2.43–2.49 (m, 4H), 3.54 (q, 1H, *J*=6.8 Hz), 7.11–7.23 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_3), 24.6 (CH_2), 26.3 (CH_2), 51.5 (CH_2), 65.2 (CH), 126.6 (CH), 127.7 (CH), 128.0 (CH), 144.0 (C_q). HRMS *m/z* calcd for $C_{13}H_{20}N$ $[MH]^+$: 190.1596; found: 190.1596.

4.2.6. (*S*)-1-(1-Methyl-2-phenylethyl)piperidine (4b). Yield 55%. Oil, bp 120–128 °C (4 mmHg); $[\alpha]_D^{25}$ +15.5 (*c* 1.1, $CHCl_3$); IR ν 3040; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, *J*=6.6 Hz), 1.39–1.45 (m, 2H), 1.63–1.69 (m, 4H), 2.35 (dd, 1H, *J*=12.8 and 10.4 Hz), 2.60–2.63 (m, 4H), 2.84–2.92 (m, 1H), 3.12 (dd, 1H *J*=12.8 and 3.6 Hz), 7.08–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 24.3 (CH_2), 25.5 (CH_2), 38.8 (CH_2), 49.6 (CH_2), 62.5 (CH), 126.1 (CH), 128.3 (CH), 129.2 (CH), 139.7 (C_q). HRMS *m/z* calcd for $C_{14}H_{22}N$ $[MH]^+$: 204.1752; found: 204.1763.

4.3. Strecker synthesis of reference racemic aminonitriles

Piperidine (20 mmol) was treated with exactly 1 equiv of 3.5 M hydrochloric acid solution and the appropriate aldehyde (20 mmol) was then added. A solution of KCN (23 mmol) in a minimum of water (*c* 1 mL) was added dropwise and then the mixture was stirred at rt [2 h for (±)-**1a** and (±)-**1c**, 16 h for (±)-**1b** and 48 h for (±)-**1d**]. Dichloromethane (5 mL) was added and the organic phase was collected, dried over $MgSO_4$ and then evaporated. The residue was purified by crystallization [(±)-**1a**] or by flash chromatography [CH_2Cl_2/cyclohexane 50/50 for (±)-**1b** and (±)-**1d**, CH_2Cl_2/EtOAc 99/1 for (±)-**1c**].

4.3.1. (±)-2-Phenyl-2-(1-piperidinyl)ethanenitrile (1a). Yield 32%. Mp 60 °C (MeOH); IR ν 2220; ^{1}H NMR ($CDCl_3$) δ 1.49–1.70 (m, 6H), 2.53–2.58 (m, 4H), 4.84 (s, 1H), 7.28–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.7 (CH_2), 25.8 (CH_2), 50.9 (CH_2), 63.0 (CH), 115.6 (C_q), 127.8 (CH), 128.2 (CH), 128.7 (CH), 133.5 (C_q). HRMS *m/z* calcd for $C_{13}H_{17}N_2$ $[MH]^+$: 201.1392; found: 201.1397. Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.35; H, 8.11; N, 13.88.

4.3.2. (±)-3-Phenyl-2-(1-piperidinyl)propanenitrile (1b). Yield 27%. Mp 30 °C; IR ν 2222; ^{1}H NMR ($CDCl_3$) δ 1.44–1.62 (m, 6H), 2.36–2.41 (m, 2H), 2.62–2.67 (m, 2H), 2.95–2.98 (m, 2H), 3.55 (dd, 1H, *J*=8.0 and 8.6 Hz), 7.19–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.0 (CH_2), 25.8 (CH_2), 37.7 (CH_2), 51.1 (CH_2), 61.3 (CH), 116.7 (C_q), 127.3 (CH), 128.7 (CH), 129.2 (CH), 136.2 (C_q). HRMS *m/z* calcd for $C_{14}H_{19}N_2$ $[MH]^+$: 215.1548; found: 215.1555. Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.14; H, 8.56; N, 12.49.

4.3.3. (±)-2-(1-Piperidinyl)propanenitrile (1c). Yield 21%. Oil, bp 60 °C (0.6 mmHg); IR ν 2223; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, 3H, *J*=7.2 Hz), 1.45 (m, 2H), 1.58 (m, 4H), 2.36 (m, 2H), 2.61 (m, 2H), 3.59 (q, 1H, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 17.2 (CH_3), 24.1 (CH_2), 25.8 (CH_2), 50.7 (CH_2), 53.1 (CH), 117.7 (C_q). HRMS *m/z* calcd for $C_8H_{15}N_2$ $[MH]^+$: 139.1235; found: 139.1240.

4.3.4. (±)-3-Methyl-2-(1-piperidinyl)butanenitrile (1d). Yield 68%. Mp 54 °C (sublimation); IR ν 2220; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, *J*=6.4 Hz), 1.07 (d, 3H, *J*=6.8 Hz), 1.44 (m, 2H), 1.57 (m, 4H), 1.96 (m, 1H), 2.31 (m, 2H), 2.55 (m, 2H), 2.91 (d, 1H *J*=11.2 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1 (CH_3), 20.2 (CH_3), 24.1 (CH_2), 25.8 (CH_2), 28.8 (CH), 51.0 (CH_2), 66.1 (CH), 117.0 (C_q). HRMS *m/z* calcd for $C_{10}H_{19}N_2$ $[MH]^+$: 167.1548; found: 167.1549. Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.95; H, 10.90; N, 16.91.

4.4. Dehydration procedure using Burgess' salt

Under an argon atmosphere, a solution of the carboxamide (0.46 mmol) in anhydrous dichloromethane (2.5 mL) was stirred at rt while Burgess' salt was added in small portions over 2 h. The reaction mixture was then passed through a flash chromatography column without prior evaporation of the solvent [eluent CH_2Cl_2/cyclohexane 50/50 for (+)-**1a**, (+)-**1b** and (−)-**1d**; CH_2Cl_2/EtOAc 99/1 for (−)-**1c**]. Appropriate fractions were pooled and evaporated to give the required product, which was not further purified.

4.4.1. (*R*)-2-Phenyl-2-(1-piperidinyl)ethanenitrile (1a). Yield 78%. Yellow solid; $[\alpha]_D^{22}$ +44 (*c* 1.0, $CHCl_3$); er (by chiral HPLC): 92/8; ^{1}H and ^{13}C NMR: as for racemic sample.

4.4.2. (*R*)-3-Phenyl-2-(1-piperidinyl)propanenitrile (1b). Yield 71%. Yellow solid; $[\alpha]_D^{22}$ +6.5 (*c* 1.0, $CHCl_3$); er (by

NMR with chiral resolving agent): 62/38; ^{1}H and ^{13}C NMR: as for racemic sample.

4.4.3. (*S*)-2-(1-Piperidinyl)propanenitrile (1c). Yield 80%. Yellow liquid; $[\alpha]_D^{21}$ −24.0 (*c* 1.105, $CHCl_3$); er (by NMR with chiral resolving agent): 53/47; ^{1}H and ^{13}C NMR: as for racemic sample.

4.4.4. (*S*)-3-Methyl-2-(1-piperidinyl)butanenitrile (1d). Yield 87%. White solid; $[\alpha]_D^{25}$ −28 (*c* 1.18, $CHCl_3$); er (by NMR with chiral resolving agent): 81/19; ^{1}H and ^{13}C NMR: as for racemic sample.

4.5. Dehydration procedure using TFAA/Et_3N

Under an argon atmosphere, carboxamide (1.12 mmol) was dissolved in anhydrous dichloromethane (45 mL) and then triethylamine (0.34 mL, 2.44 mmol) was added dropwise. The mixture was cooled at 0 °C and then trifluoroacetic anhydride (0.17 mL, 1.20 mmol) was added dropwise. The mixture was stirred and allowed to return to rt over 3 h and then was washed with a saturated $NaHCO_3$ solution (2×25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to leave the product **1a–d** (see Table 2).

4.6. Dehydration procedure using CyuCl/DMF

Under an argon atmosphere, carboxamide (0.95 mmol) was dissolved in anhydrous DMF (3 mL). The solution was cooled at 0 °C and cyanuric chloride (0.118 g, 0.64 mmol) was added in one portion. The mixture was allowed to return to rt over 8 h and then was quenched by the addition of distilled water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL). The organic phase was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to leave the products **1a–d** (see Table 2).

4.7. Bruylants reactions

Under an argon atmosphere, a solution of methyl magnesium bromide (variable amount; see Table 2) in anhydrous ether (8 mL) was cooled at 0 °C while a solution of aminonitrile **1** (4.00 mmol) in anhydrous ether was added dropwise. The mixture was stirred and allowed to return to rt overnight. A saturated solution of NH_4Cl (10 mL) was added and the ether phase was retained. The aqueous phase was extracted with dichloromethane (3×10 mL). Combined ether and dichloromethane phases were dried over $MgSO_4$ and evaporated. The crude product was checked by NMR and its optical rotation was measured. Products were then separated and purified by flash chromatography (CH_2Cl_2/cyclohexane 50/50). See Table 3 for results. Tertiary amines were obtained as follows.

4.7.1. (±)-1-(1-Phenyl-1-ethyl)piperidine (4a). $[\alpha]_D^{22}$ 0 (*c* 1.0, $CHCl_3$); er (by NMR with chiral resolving agent): 50/50; ^{1}H and ^{13}C NMR: as for (*S*)-enantiomer.

4.7.2. (±)-1-(1-Methyl-2-phenylmethyl)piperidine (4b). $[\alpha]_D^{22}$ 0 (*c* 1.0, $CHCl_3$); er (by NMR with chiral resolving agent): 50/50; ^{1}H and ^{13}C NMR: as for (*S*)-enantiomer.

4.8. Determination of enantiomeric ratios

4.8.1. HPLC analysis. HPLC analysis was performed using a Waters 501 apparatus equipped with a Waters 484 detector and a Chiracel OD column (4.6 mm×250 mm) under the following conditions: hexane/isopropanol 995/5 as mobile phase, rt, λ=254 nm, flow rate=0.5 mL/min. Retention times: (*S*)-**1a**, 13.21 min; (*R*)-**1a**, 14.73 min.

4.8.2. Chiral resolving agents. A solution of test substance (15–35 μmol) in the appropriate solvent (0.5 mL) was treated with: (A) 7–8 equiv of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol, or (B) 1 equiv of (*R*)-Mosher acid, or (C) 1 equiv of (*S*)-mandelic acid. The ^{1}H NMR spectrum was recorded immediately. Diagnostic signals are indicated.

Compound **1b**: $CDCl_3$ (A) δ: 3.54 ppm for (*R*)-**1b** and 3.59 ppm for (*S*)-**1b**.

Compound **1c**: $CDCl_3$ (A) δ: 2.10 ppm for (*R*)-**1c** and 2.22 ppm for (*S*)-**1c**.

Compound **1d**: C_6D_6 (B) δ: 2.93 ppm for (*R*)-**1d** and 2.98 ppm for (*S*)-**1d**.

Compound **4a**: C_6D_6 (C) δ: 1.33 ppm for (*R*)-**4a** and 1.38 ppm for (*S*)-**4a**.

Compound **4b**: C_6D_6 (C) δ: 0.79 ppm for (*R*)-**4b** and 0.82 ppm for (*S*)-**4b**.

Acknowledgements

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Oxobenzo[*f*]benzopyrans as new fluorescent photolabile protecting groups for the carboxylic function

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Abstract—The properties of three oxobenzo[*f*]benzopyrans as new fluorogenic photolabile protecting groups for the carboxylic function of amino acids were studied. Fluorescent amino acid conjugates were efficiently prepared and characterised. Photodeprotection of these compounds was carried out by irradiation at 300, 350 and 419 nm, the most suitable wavelength being 350 nm, on account of short irradiation times and good deprotection yields.

1. Introduction

In organic synthesis protecting groups are many times a laborious necessity, as a convenient and efficient synthesis, chemical stability towards different reagents and selective removal is required.[1] Photochemically releaseable groups have become an important tool in organic synthesis, biotechnology and cell biology, because cleavage only requires light, which is a very mild deprotection strategy that is usually orthogonal to chemical conditions, allowing the removal of protecting groups in sensitive molecules, otherwise incompatible with acidic or basic treatment.[2]

Fluorescent labelling allows easy and reliable detection of target compounds, both qualitatively and quantitatively with improved sensitivity and selectivity, and its application is well reported in many areas including amino acid and peptide chemistry.[3] Fluorescent photolabile protecting groups have advantages over other photolabile groups, because they can act as temporary fluorescent labels, allowing the visualisation of non-fluorescent systems, like most amino acid residues, during the course of organic reactions.

2-Oxobenzopyrans, trivially named as coumarins, represent one of the most widespread and interesting class of heterocyclic compounds. These oxygen heterocycles are the structural units of natural products and many exhibit diverse biological acivity with applications in pharmaceuticals, agrochemicals and insecticides.[4–9] 2-Oxobenzopyran derivatives have been reported as food additives, in cosmetics, as optical brightening agents, disperse fluorescent and laser dyes.[10–12] In addition, these compounds have also been suggested as photolabile protecting groups for biomolecules,[13–15] as well as other polycyclic aromatics such as anthraquinone, phenanthrene and pyrene.[16,17]

Taking these facts into consideration together with our research work related to the area of fluorescent heterocycles synthesis and also amino acid labelling,[18,19] we decided to investigate the possibility of using oxobenzo[*f*]benzopyrans as new fluorescent photocleavable protecting groups for the carboxylic function of organic molecules. Using amino acids as models, the synthesis and characterisation of new fluorescent amino acid conjugates were carried out. Absorption and emission properties of all compounds were measured and the results showed that these conjugates exhibited moderate to excellent fluorescence quantum yields and Stokes' shifts.

Photocleavage of these fully protected amino acids was achieved by using radiation of 300, 350 and 419 nm. The consumption of starting materials as well as the formation of the released amino acid was monitored by RP-HPLC and kinetic data were also obtained.

2. Results and discussion

Chloromethyl oxobenzo[*f*]benzopyrans **1a–c** were prepared through a Pechmann reaction of the corresponding 2-naphthol and its derivatives, and ethyl 4-chloroacetoacetate catalysed by sulfuric acid, at room temperature in good yields.[20] The fluorophores will be designated in this report by a three letter code for simplicity of naming the various amino acid

Keywords: Benzopyrans; Photocleavable groups; Protecting groups; Temporary labels; Fluorophores.
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fluorescent derivatives (1-methylene-3-oxo-3*H*-benzo[*f*]-benzopyran, Obb, 9-hydroxy-1-methylene-3-oxo-3*H*-benzo-[*f*]benzopyran, Obh and 9-methoxy-1-methylene-3-oxo-3*H*-benzo[*f*]benzopyran, Obm).

In order to investigate the linkage of compounds **1a–c** to the carboxylic function of α-amino acids by an ester bond and to compare the influence of the substituent at the oxo-benzo[*f*]benzopyrans, *N*-benzyloxycarbonyl-L-phenylalanine, *Z*-Phe-OH (**2a**) was chosen as model. Derivatisation at the C-terminus of **2a** with heterocycles **1a–c** was carried out with potassium fluoride, in DMF, at room temperature (Scheme 1), yielding derivatives **3a–c**.

By comparing fluorescence data obtained for these derivatives, which will be discussed later, it was concluded that compound **1c** was the most fluorogenic reagent. Thus, using the same method reported above, heterocycle **1c** was reacted with *N*-benzyloxycarbonyl derivatives of glycine (**2b**), alanine (**2c**) and valine (**2d**) and also to *N*-*p*-toluenosulfonyl-phenylalanine (**2e**). After dry chromatography on silica gel, the corresponding fluorescent derivatives **3a–g** were obtained as solid materials in good to excellent yields (71–96%) (Table 1) and were characterised by elemental analysis or high resolution mass spectrometry, IR, ^{1}H and ^{13}C NMR spectroscopies.

The IR spectra of labelled amino acids showed bands due to stretching vibrations of the carbonyl groups from 1757 to 1619 cm^{-1}. ^{1}H NMR spectra showed signals of the amino acid residues, such as a multiplet (δ 4.29–4.82 ppm) or a doublet (δ 4.18 ppm, **3d**) for the α-CH, in addition to the protons of the heterocyclic moiety. In ^{13}C NMR signals of the carbonyl function were found at δ 155.58–156.90 ppm for the carbamate, at δ 159.84–160.10 ppm for C-3 of the heterocycle and at δ 169.4–172.31 ppm for the ester.

Electronic absorption and emission spectra of 10^{-5}–10^{-6} M solutions of compounds **1a–c** and **3a–g** in degassed absolute ethanol were measured; absorption and emission maxima, molar absorptivities and fluorescence quantum yields (Φ_F) are also reported (Table 2). The Φ_F were calculated using 9,10-diphenylanthracene as standard (Φ_F=0.95 in ethanol).[21] For the Φ_F determination, 9,10-diphenylanthracene was excited at the wavelengths of maximum absorption found for each one of the compounds to be tested. The longest wavelength absorption maxima of all compounds were located between 345 and 361 nm, with molar absorptivity ranging from 10,174 to 14,125 M^{-1} cm^{-1}. The wavelengths of maximum absorption obtained for these compounds showed a bathochromic shift when compared with other polycyclic aromatic photocleavable groups, namely 7-methoxycoumarin-4-ylmethoxycarbonyl (Mmoc, λ_{max} 343 nm),[22] anthraquinon-2-ylmethoxycarbonyl (Aqmoc, λ_{max} 327 nm),[16] pyren-1-ylmethoxycarbonyl (Pmoc, λ_{max} 323 nm)[17] and phenanthren-9-ylmethoxycarbonyl (Phmoc, λ_{max} 297 nm).[16] The wavelengths of maximum emission were found between 411 and 478 nm. Emission of compound **3c** was bathochromically shifted when compared to **3a**,**b**, the difference being 67 (**3c/3a**) and 22 nm (**3c/3b**) due to the substituent. Although there was not a significant variation in the maximum wavelengths of emission of compounds **1a–c** in their isolated or conjugated forms, they displayed low Φ_F in their isolated form (the highest value was 0.08, **1a**), which

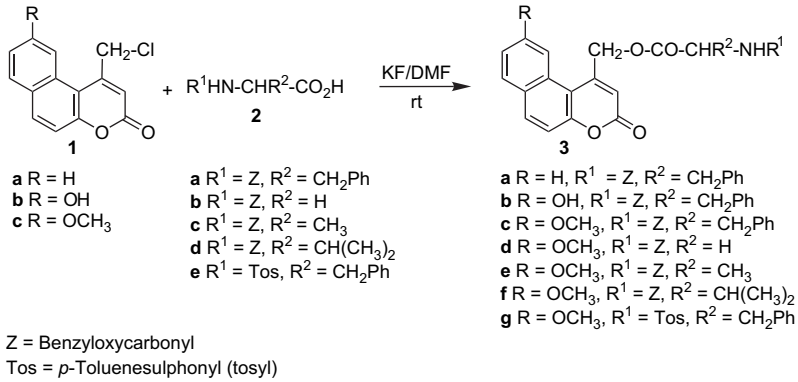
Table 1. Synthesis of compounds **3a–g**

	Compound	Yield (%)	Mp (°C)
3a	*Z*-Phe-Obb	96	127.8–129.8
3b	*Z*-Phe-Obh	81	189.6–190.7
3c	*Z*-Phe-Obm	71	180.8–182.1
3d	*Z*-Gly-Obm	86	181.6–184.0
3e	*Z*-Ala-Obm	83	132.8–134.0
3f	*Z*-Val-Obm	94	122.6–124.0
3g	Tos-Phe-Obm	82	184.8–186.6

Table 2. UV–vis and fluorescence data of compounds **1a**−**c** and **3a**−**g**

	Compound	UV λ_{max}[a] (ε)[b]	Fluorescence λ_{em}[a]	Fluorescence Φ_F	Stokes' shift[a]
1a	Obb-Cl	352 (11,449)	418	0.08±0.01	66
1b	Obh-Cl	361 (12,190)	462	0.02±0.002	101
1c	Obm-Cl	354 (12,826)	472	0.03±0.004	118
3a	*Z*-Phe-Obb	345 (14,125)	411	0.42±0.01	66
3b	*Z*-Phe-Obh	360 (10,174)	456	0.13±0.01	96
3c	*Z*-Phe-Obm	347 (12,075)	478	0.59±0.02	131
3d	*Z*-Gly-Obm	347 (11,436)	471	0.70±0.01	124
3e	*Z*-Ala-Obm	348 (11,640)	477	0.66±0.01	129
3f	*Z*-Val-Obm	348 (11,830)	478	0.58±0.02	130
3g	Tos-Phe-Obm	347 (12,883)	475	0.53±0.01	128

[a] Unit: nm.
[b] Unit: M^{-1} cm^{-1}.



Scheme 1. Synthesis of fluorescent conjugates **3a–g**.

increased upon reaction with the amino acids. All labelled amino acids **3a–g** exhibited moderate to excellent quantum yields ($0.13<\Phi_F<0.70$), compound **3b** having the lowest value probably due to the presence of H-bonds to the solvent, and Stokes' shift from 66 to 131 nm. By comparison of Φ_F of labelled *N*-benzyloxycarbonylphenylalanine **3a–c**, it was possible to see that derivative **3c** exhibited the highest value (0.59) and also the larger Stokes' shift (131 nm), which may be related to the higher electron-donating character of the methoxy substituent on the oxobenzopyran moiety **1c**. Considering these results, oxobenzo[*f*]benzopyrans are promising candidates for fluorescent labelling. In Figure 1, the fluorescence spectra of amino acid conjugates **3a**, **3b**, **3c** and **3g** are shown.

Since our main purpose is the investigation of the potential application of these fluorophores as photocleavable protecting groups in organic synthesis, we decided to evaluate the behaviour of the ester linkage between the fluorescent heterocycles synthesised and the amino acids to photocleavage conditions.

Fully protected phenylalanine derivatives, *Z*-Phe-Obb (**3a**), *Z*-Phe-Obh (**3b**), *Z*-Phe-Obm (**3c**) and Tos-Phe-Obm (**3g**) were used as representative models (Scheme 2). Solutions of the mentioned compounds in acetonitrile (ca. 1×10^{-5} M) were irradiated in a Rayonet RPR-100 reactor, at different wavelengths. As it is desirable to have short irradiation times at the highest irradiation wavelength possible if future bioapplications are to be considered, photolysis was carried out at 300, 350 and 419 nm, in order to determine the best cleavage conditions. The cleavage at different wavelengths was followed by reverse phase HPLC–UV detection.

The plots of peak area versus irradiation time were obtained for each compound, at the considered wavelengths. Peak areas were determined by HPLC and were the average of three runs.

When compounds **3a–c** and **3g** were irradiated at 350 nm, the time necessary for the consumption of the starting materials, until less than 5% of the initial area was detected, varied from 4 to 22 min (Table 3).

At this wavelength, the time cause of the reaction for compound **3b** was similar to that of 350 nm, whereas compounds **3a** and **3g** were photolysed about three times and two times faster, respectively; compound **3c** showed a slower cleavage.

As expected, irradiation at 419 nm resulted in much longer irradiation times for all compounds, with compound **3a** requiring a 29 h photolysis for the consumption of more than 95% of the starting material.

At the same time, the study of the stability of *Z*-Phe-OH (**2a**) and Tos-Phe-OH (**2e**) was carried out under the above reported photolysis conditions. HPLC studies showed that both *N*-blocking groups were stable to the tested conditions, no cleavage being detected. These results supported the fact that the disappearance of the starting materials (**3a**, **3b**, **3c** and **3g**) was associated with the cleavage of the ester linkage between the fluorophore and the C-terminus of the amino acid, as expected.

The formation of *N*-protected phenylalanine, as the expected photolysis product, was also followed by RP-HPLC. The yield of formation of compounds **2a** or **2e** was calculated on the basis of a calibration curve (concentration versus peak area), which was plotted with solutions of these phenylalanine derivatives of known concentration in acetonitrile. In case of compound **3g**, the photorelease yield of the expected product was 73% (300 and 419 nm) and 82% (350 nm). *N*-Protected phenylalanine **2a** was obtained from the photocleavage of compounds **3a–c** in yields ranging

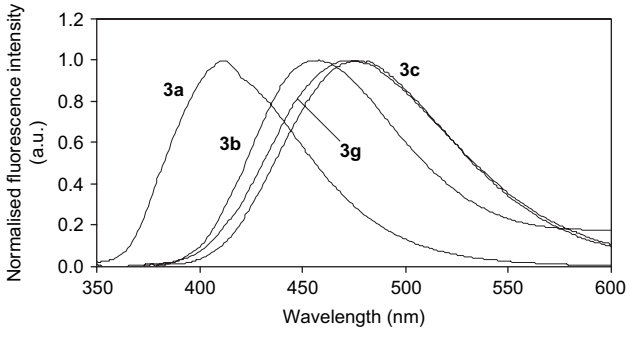
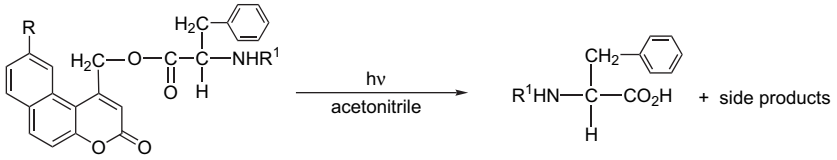


Figure 1. Normalised fluorescence spectra of compounds **3a–c** and **3g**.

Table 3. Photolysis data of compounds **3a–c** and **3g**

Compound		300 nm		350 nm		419 nm	
		Irr time[a]	Release[c]	Irr time[a]	Release[c]	Irr time[b]	Release[c]
3a	*Z*-Phe-Obb	7	79	22	80	29	78
3b	*Z*-Phe-Obh	4	82	4	90	2	92
3c	*Z*-Phe-Obm	12	75	8	81	8	86
3g	Tos-Phe-Obm	4	73	8	82	9	73

[a] Irradiation time (min).
[b] Irradiation time (h).
[c] Yield (%) of the released amino acid as determined by HPLC.



3a R = H, R^1 = Z, **b** R = OH, R^1 = Z
c R = OMe, R^1 = Z, **g** R = OCH_3, R^1 = Tos

2 a R^1 = Z
e R^1 = Tos

Scheme 2. Photocleavage of compounds **3a–c** and **3g**.

from 75 to 92%, the highest value in the case of compound **3b** at 419 nm.

From the obtained data, it was possible to see that the most suitable wavelength of irradiation was 350 nm for compounds **3b**, **3c** and **3g**. Although in the case of compound **3a** the irradiation time was longer at this wavelength, it is preferable to avoid the use of shorter wavelengths of irradiation. The results also indicated an influence of the substituent at position 9 of the heterocycle, as the substituted compounds **3b**, **3c** and **3g** required shorter irradiation times for equal percentage of consumption of the starting material, which was more evident when the wavelength of irradiation was 350 or 419 nm.

Based on HPLC data, the kinetic study of the photocleavage reactions was also carried out. For each compound, the plot of ln *A* versus irradiation time showed a linear correlation for the decrease of the starting material, which suggested a first order reaction. The observed values were calculated by the linear least squares methodology for a straight line (Table 4). Figure 2 summarises the behaviour of conjugates **3a–c** and **3g** at 350 nm.

From these results, it was possible to confirm that the wavelength of irradiation influenced the rate of the photocleavage, 350 nm being the selected wavelength on account of the short irradiation times and the potentially less damaging effect on biological systems. The substituent at the 9-position of the fluorophore was also important in this process, the presence of a hydroxyl group leading to a reduction of the irradiation time.

Although the main purpose of this work was to study the suitability of oxobenzo[*f*]benzopyrans as photocleavable groups for the carboxylic acid function of bifunctional molecules such as amino acids, we also considered their behaviour towards classical chemical cleavage. Therefore, stability tests were carried out using fluorescent *N*-*p*-toluenosulfonylphenylalanine, Tos-Phe-Obm (**3g**) as model. Compound **3g** was submitted to similar conditions to those usually required for cleavage of protecting groups during peptide synthesis, such us catalytic hydrogenation (Pd/C/1,4-cyclohexadiene), acidolysis at room temperature and reflux (TFA, 6 M HCl, aqueous HBr and HBr in acetic acid),[23] reduction with metals (Mg/MeOH)[24] and alkaline hydrolysis (1 M NaOH) (Table 5).

The results showed that under catalytic hydrogenation conjugate **3g** was cleaved, compounds Tos-Phe-OH (**2e**) and 1-methyl-9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran (Obm-H) (**4**) being isolated in low yields.

Table 4. Kinetic data of the photolysis studies of compounds **3a–c** and **3g**

Compound		300 nm		350 nm		419 nm	
		k^a	R^c	k^a	R^c	k^b	R^c
3a	*Z*-Phe-Obb	0.4587	0.9965	0.1175	0.9556	0.1063	0.9965
3b	*Z*-Phe-Obh	0.9416	0.9983	0.8310	0.9940	1.6883	0.9893
3c	*Z*-Phe-Obm	0.2569	0.9998	0.3684	0.9771	0.3841	0.9993
3g	Tos-Phe-Obm	0.8159	0.9980	0.4092	0.9992	0.3353	0.9995

[a] Rate constant (min^{-1}).
[b] Rate constant (h^{-1}).
[c] Correlation coefficient.

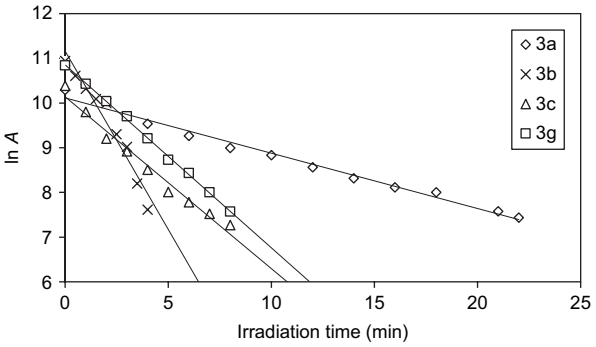


Figure 2. Plot of ln *A* versus irradiation time at 350 nm for compounds **3a–c** and **3g**.

Table 5. Stability tests/chemical cleavage of Tos-Phe-Obm (**3g**)

Cleavage	Time (h)	Yield (%)	
		Tos-Phe-Obm (**3g**)	Tos-Phe-OH (**2e**)
Pd/C/1,4-cyclohexadiene	6	36	11[a,b]
TFA (rt)	2.5	100	—
TFA (reflux)	8.5	100	—
6 M HCl (rt)	4.5	100	—
6 M HCl (reflux)	17	83	—
aq HBr (rt)	4.5	100	—
aq HBr (reflux)	5	—	57[a]
HBr/CH_3CO_2H (rt)[c]	4.5	90	—
HBr/CH_3CO_2H (reflux)[c]	5	—	68[a]
Mg/MeOH	3	—	56[a]
1 M NaOH	9	—	100

[a] Yield of isolated product by dry chromatography.
[b] Obm-H (**4**) was also obtained (25%).
[c] HBr/CH_3CO_2H (45% m/v).

Compound **3g** was stable under acidolysis conditions, at room temperature, and was quantitatively recovered (TFA, 6 M HCl and aqueous HBr) or in 90% yield (HBr in acetic acid). Considering acidolysis at reflux, the fully protected fluorescent conjugate (**3g**) was stable in TFA (9 h, 100% recovery) and 6 M HCl (17 h, 83% recovery). However, in HBr at reflux (5 h), cleavage of the ester linkage between the fluorophore and the amino acid occurred, the expected product **2e** being isolated in moderate yields (57%, aqueous HBr and 68%, HBr in acetic acid).

Reaction of compound **3g** with magnesium gave Tos-Phe-OH (**2e**) in 56%. The stability of tosyl group to this metal was verified with studies of the behaviour of Tos-Phe-OH (**2e**) in the same experimental conditions, which confirmed that it was stable, being recovered quantitatively. As expected, cleavage of the ester bond was achieved by treatment with base (1 M NaOH), resulting in quantitative isolation of compound **2e**.

From the results obtained in these chemical cleavage tests, it was possible to conclude that fluorophore **1c** had the appropriate behaviour to be considered also a suitable conventional protecting group for the carboxylic function of amino acids, in peptide synthesis. All labelled compounds were stable in prolonged storage at room temperature.

3. Conclusions

A series of fluorescent amino acid conjugates were synthesised in excellent yields by a straightforward procedure, between a chloromethylated fluorophore and the C-terminus of several *N*-protected amino acids, through an ester bond. The photophysical properties of these conjugates showed that oxobenzo[*f*]benzopyrans are good fluorogenic reagents for amino acid and peptide chemistry.

The photocleavage studies of the fluorescent phenylalanine derivatives with the three oxobenzo[*f*]benzopyrans showed that the rate of cleavage of the ester bond depended on the wavelength of irradiation as well as on the substituent at the 9-position of the heterocycle. The most suitable wavelength was 350 nm, allowing short irradiation times, which are convenient for possible future biological applications, for example, as caging groups.

In the absence of radiation, we also confirmed that these groups were efficiently chemically cleavable by soft alkaline hydrolysis or in moderate yields by acidolysis with HBr at reflux or with magnesium.

The results obtained, mainly their photophysical properties, allowed us to conclude that the considered functionalised heterocycles are potential candidates as fluorescent labels for biomolecules. Considering the efficient derivatisation reactions and also the good results of the photocleavage process, 1-chloromethyl-3-oxo-3*H*-benzo[*f*]benzopyrans **1a–c** could be used as fluorescent photocleavable protecting groups in organic synthesis. In addition, they can also be used as conventional protecting groups, quantitatively cleavable by basic hydrolysis (1 M NaOH, room temperature).

Bearing in mind the properties displayed by these compounds, further investigations into their applicability in biological systems, for example, as caging groups, will be carried out in the near future.

4. Experimental

4.1. General

All melting points were measured on a Gallenkamp melting point apparatus and were uncorrected. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualised under UV light. Chromatography on silica gel was carried out on Merck Kieselgel (230–240 mesh). IR spectra were determined on a Perkin Elmer FTIR-1600 using KBr discs or Nujol. UV–vis spectra were run on a Hitachi U-2000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 300 spectrometer in $CDCl_3$ or DMSO-d_6 at 300 MHz at 25 °C. All chemical shifts are given in parts per million using δ_H Me_4Si=0 ppm as reference and *J* values are given in hertz. ^{13}C NMR spectra were run in the same instrument at 75.4 MHz using the solvent peak as internal reference. Assignments were made by comparison of chemical shifts, peak multiplicities and *J* values and were supported by spin decoupling-double resonance and bidimensional heteronuclear correlation HMBC and HMQC techniques. Mass spectrometry analyses were performed at the C.A.C.T.I.—Unidad de Espectrometria de Masas of the University of Vigo, Spain, on a Hewlett Packard 5989 A spectrometer for low resolution spectra and a Autospec M spectrometer for high resolution mass spectra. Elemental analyses were carried out on a Leco CHNS 932 instrument. Fluorescence spectra were collected using a Spex Fluorolog 1680 Spectrometer.

4.1.1. *N*-(Benzyloxycarbonyl) phenylalanine (3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Phe-Obb (3a). To a solution of 1-chloromethyl-3-oxo-3*H*-benzo[*f*]benzopyran, Obb-Cl (**1a**) (0.106 g, 4.30×10^{-4} mol) in DMF (1.5 mL), potassium fluoride (0.076 g, 1.30×10^{-3} mol) and *Z*-Phe-OH (**2a**) were added with stirring at room temperature. The reaction mixture was maintained in these conditions for 25 h and monitored by TLC (ethyl acetate/*n*-hexane, 4:6). The precipitate was filtered and the remaining solution was evaporated until dryness. Purification of the residue by dry chromatography using ethyl acetate/*n*-hexane, 3:7 as the eluent, followed by recrystallisation from ethyl acetate/*n*-hexane, gave *Z*-Phe-Obb (**3a**) as a white solid (0.209 g, 96%). Mp=127.8–129.8 °C. TLC (ethyl acetate/*n*-hexane, 4:6): R_f=0.58. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.17 (d, *J*=6.3 Hz, 2H, β-CH_2 Phe), 4.62–4.82 (m, 1H, α-CH Phe), 5.02–5.20 (m, 2H, CH_2 *Z*), 5.30 (d, *J*=7.8 Hz, 1H, α-NH Phe), 5.60–5.76 (m, 2H, CH_2), 6.54 (s, 1H, H-2), 7.10–7.18 (m, 2H, 2×Ar-H Phe), 7.20–7.30 (m, 3H, 3×Ar-H Phe), 7.32–7.40 (m, 5H, 5×Ar-H *Z*), 7.49 (d, *J*=8.7 Hz, 1H, H-5), 7.59 (t, *J*=6.9 Hz, 1H, H-8), 7.67 (dt, *J*=8.3 and 1.5 Hz, 1H, H-9), 7.94 (dd, *J*=8.0 and 1.2 Hz, 1H, H-7), 8.01 (d, *J*=9.0 Hz, 1H, H-6), 8.08 (d, *J*=8.4 Hz, 1H, H-10). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=38.10 (β-CH_2 Phe), 55.17 (α-CH Phe), 64.94 (CH_2), 67.22 (CH_2 *Z*), 112.44 (C-4b), 113.78 (C-2), 117.78 (C-5), 124.54 (C-10), 125.74 (C-8), 127.44 (C-4 Phe), 128.18 (C-4 *Z*), 128.23 (C-3 and C-5 Phe), 128.49 (C-2 and C-6 *Z*), 128.61 (C-9), 128.80 (C-3 and C-5 *Z*), 128.97 (C-6b), 129.04 (C-2 and C-6 Phe), 129.92 (C-7), 131.24 (C-6a), 134.11 (C-6), 135.11 (C-1 Phe), 135.95 (C-1 *Z*), 149.85 (C-1), 154.86 (C-4a), 155.69 (CONH), 159.84 (C-3), 171.10 (CO_2CH_3). IR (KBr 1%, cm^{-1}): ν=3287, 3028, 2963, 2918, 2848, 1740, 1728, 1686, 1553, 1532, 1496, 1455, 1413, 1340, 1290, 1258, 1207, 1198, 1166, 1052, 1019, 822, 803. UV–vis (ethanol, nm): λ_{max} (ε)=345 (14,125 M^{-1} cm^{-1}). Anal. Calcd for $C_{31}H_{25}NO_6$ (507.52): C, 73.36; H, 4.97; N, 2.76. Found: C, 73.28; H, 4.98; N, 2.85.

4.1.2. *N*-(Benzyloxycarbonyl) phenylalanine (9-hydroxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Phe-Obh (3b). The product of reaction of 1-chloromethyl-9-hydroxy-3-oxo-3*H*-benzo[*f*]benzopyran, Obh-Cl (**1b**) (0.100 g, 3.84×10^{-4} mol), with *Z*-Phe-OH (0.115 g, 3.84×10^{-4} mol) (**2a**) was chromatographed using ethyl acetate/*n*-hexane, 3:7 as eluent, to give compound *Z*-Phe-Obh (**3b**) as a white solid (0.163 g, 81%). Mp=189.6–190.7 °C. TLC (acetate/*n*-hexane, 4:6): R_f=0.31. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.00–3.10 (m, 2H, β-CH_2 Phe), 4.40–4.54 (m, 1H, α-CH Phe), 4.95 (d, *J*=12.0 Hz, 1H, CH_2), 5.10–5.20 (m, 2H, CH_2 *Z*), 5.36 (d, *J*=5.1 Hz, 1H, α-NH Phe), 5.48 (d, *J*=11.7 Hz, 1H, CH_2), 6.26 (s, 1H, H-2), 7.14–7.24 (m, 2H, H-8 and 1×Ar-H Phe), 7.28 (d, *J*=8.7 Hz, 3H, H-5 and 2×Ar-H Phe), 7.32–7.42

(m, 7H, 2×Ar-H Phe and 5×Ar-H *Z*), 7.61 (d, *J*=1.8 Hz, 1H, H-10), 7.80 (d, *J*=8.7 Hz, 1H, H-7), 7.91 (d, *J*=9.0 Hz, 1H, H-6), 8.44 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=37.05 (β-CH_2 Phe), 56.26 (α-CH Phe), 66.66 (CH_2), 68.26 (CH_2 *Z*), 107.54 (C-10), 112.30 (C-4b), 114.39 (C-5), 117.79 (C-8), 118.68 (C-2), 125.93 (C-6a), 127.87 (1×Ar-C Phe), 128.39 (1×Ar-C *Z*), 128.65 (2×Ar-C *Z*), 128.96 (2×Ar-C Phe), 129.07 (2×Ar-C *Z*), 130.61 (C-6b), 131.50 (C-7), 134.15 (2×Ar-C Phe), 134.61 (C-6), 134.80 (C-1 Phe and C-1 *Z*), 148.10 (C-1), 155.78 (C-4a), 156.86 (CONH), 157.59 (C-9), 160.07 (C-3), 171.60 (CO_2CH_2). IR (Nujol, cm^{-1}): ν=3346, 3299, 2954, 2924, 2854, 1744, 1710, 1685, 1622, 1553, 1538, 1463, 1456, 1366, 1333, 1290, 1253, 1232, 1215, 1195, 1163, 1140, 1048, 1014, 987, 963, 883. UV–vis (ethanol, nm): λ_{max} (ε)=360 (10,174 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{31}H_{25}NO_7$ [M^+]: 523.1631; found: 523.1611.

4.1.3. *N*-(Benzyloxycarbonyl) phenylalanine (9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Phe-Obm (3c). The product of reaction of 1-chloromethyl-9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran, Obm-Cl (**1c**) (0.104 g, 3.8×10^{-4} mol), with *Z*-Phe-OH (**2b**) (0.113 g, 3.8×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane, 3:7 as the eluent, to give compound *Z*-Phe-Obm (**3c**) as a yellow solid (0.145 g, 71%). Mp=180.8–182.1 °C. TLC (acetate/*n*-hexane, 3:7): R_f=0.45. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.16 (d, *J*=6.6 Hz, 2H, β-CH_2 Phe), 3.95 (s, 3H, OCH_3), 4.72–4.84 (m, 1H, α-CH Phe), 5.02–5.16 (m, 2H, CH_2 *Z*), 5.28 (d *J*=8.1 Hz, 1H, α-NH Phe), 5.66 (s, 2H, CH_2), 6.50 (s, 1H, H-2), 7.08–7.16 (m, 2H, H-3 and H-5 Phe), 7.19–7.28 (m, 3H, H-2, H-4 and H-6 Phe), 7.30–7.40 (m, 7H, H-5, H-8 and 5×Ar-H *Z*), 7.42 (s, 1H, H-10), 7.85 (d, *J*=9.0 Hz, 1H, H-7), 7.93 (d, *J*=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=38.21 (β-CH_2 Phe), 55.17 (α-CH Phe), 55.44 (OCH_3), 64.96 (CH_2), 67.25 (CH_2 *Z*), 105.58 (C-10), 111.82 (C-4b), 113.62 (C-2), 115.28 (C-5), 116.69 (C-8), 126.34 (C-6a), 127.45 (C-4 Phe), 128.19 (C-4 *Z*), 128.26 (C-3 and C-5 Phe), 128.51 (C-2 and C-6 *Z*), 128.80 (C-3 and C-5 *Z*), 129.03 (C-2 and C-6 Phe), 130.51 (C-6b), 131.34 (C-7), 133.81 (C-6), 135.07 (C-1 Phe), 135.95 (C-1 *Z*), 149.64 (C-1), 155.58 (C-4a and CONH), 159.71 (C-9), 160.00 (C-3), 171.16 (CO_2CH_2). IR (Nujol, cm^{-1}): ν=3285, 2954, 2925, 2854, 1746, 1664, 1630, 1549, 1463, 1409, 1378, 1366, 1275, 1248, 1233, 1201, 1183, 1104, 1086, 1038, 1021. UV–vis (ethanol, nm): λ_{max} (ε)=347 (12,075 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{32}H_{27}NO_7$ [M^+]: 537.1788; found: 537.1798.

4.1.4. *N*-(Benzyloxycarbonyl) glycine (9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Gly-Obm (3d). The product of reaction of Obm-Cl (**1c**) (0.100 g, 3.64×10^{-4} mol), with *Z*-Gly-OH (**2b**) (0.076 g, 3.64×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane, 3:7 as the eluent, to give compound *Z*-Phe-Obm (**3c**) as a yellowish solid (0.140 g, 86%). Mp=181.6–184.0 °C. TLC (acetate/*n*-hexane, 4:6): R_f=0.51. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.97 (s, 3H, OCH_3), 4.18 (d, *J*=5.7 Hz, 2H, CH_2 Gly), 5.16 (s, 2H, CH_2 *Z*), 5.35 (br s, 1H, α-NH Gly), 5.77 (s, 2H, CH_2), 6.66 (s, 1H, H-2), 7.24 (dd, *J*=9.0 and 2.4 Hz, 1H, H-8), 7.30–7.40 (m, 6H, H-5 and 5×Ar-H *Z*), 7.42 (s, 1H, H-10), 7.84 (d, *J*=9.0 Hz, 1H, H-7), 7.93 (d, *J*=8.7 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ=42.79 (CH_2 Gly), 55.47 (OCH_3), 64.84 (CH_2), 67.36 (CH_2 *Z*), 105.54 (C-10), 111.77 (C-4b), 112.97 (C-2), 115.31 (C-5), 116.71 (C-8), 126.36 (C-6a), 128.17 (Ar-C *Z*), 128.28 (2×Ar-C *Z*), 128.54 (2×Ar-C *Z*), 130.52 (C-6b), 131.40 (C-7), 133.91 (C-6), 135.95 (C-1 *Z*), 150.20 (C-1), 155.59 (C-4a), 156.34 (CONH), 159.73 (C-9), 160.13 (C-3), 169.43 (CO_2CH_2). IR (Nujol, cm^{-1}): ν=3413, 2954, 2924, 2854, 1757, 1721, 1625, 1553, 1516, 1401, 1368, 1341, 1272, 1232, 1170, 1054, 1016. UV–vis (ethanol, nm): λ_{max} (ε)=347 (11,436 $M^{-1}\,cm^{-1}$). Anal. Calcd for $C_{25}H_{21}NO_7$ (447.43): C, 67.67; H, 5.02; N, 3.03. Found: C, 67.40; H, 5.01; N, 3.06.

4.1.5. *N*-(Benzyloxycarbonyl) alanine (9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Ala-Obm (3e). The product of reaction of Obm-Cl (**1c**) (0.201 g, 7.32×10^{-4} mol), with *Z*-Ala-OH (**2c**) (0.183 g, 8.2×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane mixtures of increased polarity as the eluent, to give compound *Z*-Ala-Obm (**3e**) as a white solid (0.280 g, 83%). Mp=132.8–134.0 °C. TLC (acetate/*n*-hexane, 1:1): R_f=0.45. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.52 (d, *J*=7.2 Hz, 3H, β-CH_3 Ala), 3.97 (s, 3H, OCH_3), 4.48–4.62 (m, 1H, α-CH Ala), 5.06–5.20 (m, 2H, CH_2 *Z*), 5.26 (d, *J*=7.2 Hz, 1H, α-NH Ala), 5.66–5.87 (m, 2H, CH_2), 6.67 (s, 1H, H-2), 7.24 (dd, *J*=9.0 and 2.1 Hz, 1H, H-8), 7.30–7.41 (m, 6H, H-5 and 5×Ar-H), 7.45 (s, 1H, H-10), 7.86 (d, *J*=9.0 Hz, 1H, H-7), 7.95 (d, *J*=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=18.14 (β-CH_3 Ala), 49.74 (α-CH Ala), 55.42 (OCH_3), 64.85 (CH_2), 67.10 (CH_2 *Z*), 105.62 (C-10), 111.66 (C-4b), 112.81 (C-2), 115.21 (C-5), 116.52 (C-8), 126.26 (C-6a), 128.12 (1×Ar-C *Z*), 128.17 (1×Ar-C *Z*), 128.46 (1×Ar-C *Z*), 130.44 (C-6b), 131.32 (C-7), 133.79 (C-6), 135.98 (C-1 *Z*), 150.24 (C-1), 155.48 (C-4a), 155.66 (CONH), 159.63 (C-9), 160.05 (C-3), 172.31 (CO_2CH_2). IR (Nujol, cm^{-1}): ν=3422, 3335, 3065, 2958, 2933, 1732, 1719, 1619, 1543, 1518, 1449, 1418, 1355, 1331, 1249, 1230, 1211, 1168, 1105, 1067, 1024. UV–vis (ethanol, nm): λ_{max} (ε)=348 (11,640 $M^{-1}\,cm^{-1}$). Anal. Calcd for $C_{26}H_{23}NO_7$ (461.45): C, 67.67; H, 5.02; N, 3.03. Found: C, 67.40; H, 5.01; N, 3.06.

4.1.6. *N*-(Benzyloxycarbonyl) valine (9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, *Z*-Val-Obm (3f). The product of reaction of Obm-Cl (**1c**) (0.104 g, 3.8×10^{-4} mol), with *Z*-Val-OH (**2d**) (0.070 g, 2.8×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane mixtures of increasing polarity as the eluent, to give compound *Z*-Val-Obm (**2f**) as a white solid (0.129 g, 94%). Mp=122.6–124.0 °C. TLC (chloroform/methanol, 50:0.5): R_f=0.48. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.95 (d, *J*=7.2 Hz, 3H, γ-CH_3 Val), 1.04 (d, *J*=6.9 Hz, 3H, γ-CH_3 Val), 2.20–2.35 (m, 1H, β-CH Val), 3.98 (s, 3H, OCH_3), 4.40–4.50 (m, 1H, α-CH Val), 5.13 (s, 2H, CH_2 *Z*), 5.25 (d, *J*=8.4 Hz, 1H, α-NH Val), 5.76 (d, *J*=3.9 Hz, 2H, CH_2), 6.70 (s, 1H, H-2), 7.25 (dd, *J*=7.8 and 2.4 Hz, 1H, H-8), 7.30–7.42 (m, 6H, H-5 and 5×Ar-H *Z*), 7.47 (s, 1H, H-10), 7.86 (d, *J*=9.0 Hz, 1H, H-7), 7.95 (d, *J*=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=17.45 (γ-CH_3 Val), 19.17 (γ-CH_3 Val), 30.96 (β-CH Val), 55.43 (OCH_3), 59.28 (α-CH Val), 64.81 (CH_2), 67.25 (CH_2 *Z*), 105.67 (C-10), 111.75 (C-4b), 113.08 (C-2), 115.25 (C-5),

116.58 (C-8), 126.31 (C-6a), 128.17 (1×Ar-C *Z*), 128.22 (2×Ar-C *Z*), 128.50 (2×Ar-C *Z*), 130.49 (C-6b), 131.34 (C-7), 133.82 (C-6), 135.99 (C-1 *Z*), 150.18 (C-1), 155.54 (C-4a), 156.25 (CONH), 159.70 (C-9), 160.07 (C-3), 171.51 (*C*O_2CH_2). IR (KBr 1%, cm^{-1}) ν=3391, 2966, 2928, 1731, 1721, 1625, 1553, 1520, 1456, 1426, 1351, 1306, 1275, 1232, 1180, 1164, 1098, 1059, 1025. UV–vis (ethanol, nm): λ_{max} (ε)=348 (11,838 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{28}H_{27}NO_7$ [M^+]: 489.1788; found: 489.1790.

4.1.7. *N*-(*p*-Toluenesulfonyl) phenylalanine (9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran-1-yl) methyl ester, Tos-Phe-Obm (3g). The product of reaction of Obm-Cl (**1c**) (0.060 g, 2.18×10^{-4} mol), with Tos-Phe-OH (**2e**) (0.069 g, 2.18×10^{-4} mol) was chromatographed using ethyl acetate/*n*-hexane, 3:7 as the eluent, to give compound Tos-Phe-Obm (**3g**) as a yellow solid (0.100 g, 82%). Mp=184.8–186.6 °C. TLC (acetate/*n*-hexane, 4:6): R_f=0.45. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.27 (s, 3H, CH_3), 3.08 (d, *J*=6.9 Hz, 2H, β-CH_2 Phe), 3.93 (3H, s, OCH_3), 4.28–4.40 (m, 1H, α-CH Phe), 5.30–5.53 (m, 3H, CH_2 and α-NH Phe), 6.39 (s, 1H, H-2), 7.02–7.09 (m, 2H, H-3 and H-5 Phe), 7.13–7.19 (m, 5H, H-3 and H-5 Tos, H-2, H-4 and H-6 Phe), 7.23 (dd, *J*=8.7 and 2.4 Hz, 1H, H-8), 7.27–7.32 (m, 2H, H-5 and H-10), 7.61 (d, *J*=8.4 Hz, 2H, H-2 and H-6 Tos), 7.83 (d, *J*=8.7 Hz, 1H, H-7), 7.90 (d, *J*=9.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=21.30 (CH_3 Tos), 39.24 (β-CH_2 Phe), 55.45 (OCH_3), 57.07 (α-CH Phe), 64.88 (CH_2), 105.71 (C-10), 111.64 (C-4b), 113.25 (C-2), 115.20 (C-5), 116.44 (C-8), 126.29 (C-6a), 127.10 (C-2 and C-6 Tos), 127.43 (C-4 Phe), 128.69 (C-3 and C-5 Phe), 129.13 (C-2 and C-6 Phe), 129.60 (C-3 and C-5 Tos), 130.35 (C-6b), 131.37 (C-7), 133.82 (C-6), 134.55 (C-1 Phe), 136.51 (C-1 Tos), 143.73 (C-4 Tos), 149.39 (C-1), 155.45 (C-4a), 159.66 (C-9), 159.98 (C-3), 170.55 (*C*O_2CH_2). IR (KBr 1%, cm^{-1}): ν=3434, 2921, 2846, 1707, 1625, 1550, 1506, 1443, 1349, 1224, 1161, 1080, 1011. UV–vis (ethanol, nm): λ_{max} (ε)=347 (12,883 $M^{-1}\,cm^{-1}$). HRMS (EI): calcd for $C_{31}H_{27}NO_7S$ [M^+]: 557.1508; found: 557.1519.

4.2. General photolysis procedure

A 1×10^{-5} M acetonitrile solution of the compound to be tested (20 mL) was placed in a quartz tube and irradiated in a Rayonet RPR-100 chamber reactor with 10 lamps of different wavelength (300, 350 and 419 nm, 14 W each). Aliquots were taken at regular intervals and analysed by reversed phase HPLC using a Licrospher 100 RP18 (5 μm) column and a system composed by a Jasco PU-980 pump, a UV–vis Shimadzu SPD-GAV detector and a Shimadzu C-RGA Chromatopac register. The eluent was acetonitrile/water, 3:1 (eluent A) or acetonitrile/water, 3:1 with 0.1% TFA (eluent B), previously filtered through a Milipore, type HN 0.45 μm filter and degassed by ultra-sound for 30 min.

The chromatograms were traced by detecting UV absorption (**3a**, λ_{det} 347 nm, flow 1.2 mL min^{-1}, retention time—t_R 4.9 min; **3b**, λ_{det} 360 nm, flow 0.8 mL min^{-1}, t_R 5.2 min; **3c**, λ_{det} 347 nm, flow 1.2 mL min^{-1}, t_R 5.1 min; **3d**, λ_{det} 347 nm, flow 1.0 mL min^{-1}, t_R 5.5 min; **2a**, λ_{det} 240 nm, flow 0.8 mL min^{-1}, t_R 3.3 min; **2e**, λ_{det} 240 nm, flow 0.8 mL min^{-1}, t_R 3.1 min), using eluent A for compounds **3a–c** and **3g** and eluent B for compounds **2a** and **2e**.

The yield of photorelease was calculated by comparison of the HPLC trace (peak area) of the released amino acid with the corresponding standard calibration curve (concentration vs peak area).

4.3. Stability tests with Tos-Phe-Obm (3g)

4.3.1. Catalytic hydrogenation. A suspension of Tos-Phe-Obm (**3g**) (2.90×10^{-2} g, 5.33×10^{-5} mol) in methanol (1.0 mL) and 1,4-cyclohexadiene (1.35×10^{-2} mL, 1.40×10^{-4} mol) was mixed with 10% palladium on charcoal catalyst (1.05×10^{-2} g), and refluxed for 6 h with stirring. The catalyst was filtered off and washed with methanol; the combined liquids were then evaporated under reduced pressure affording the compound as a oily solid (0.185 g, 11%). ^{1}H NMR was well compared with Tos-Phe-OH (**2e**). 1-Methyl-9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran, Obm-*H* (**4**) (3.20×10^{-3} g, 25%) and starting material (**3g**) (1.07×10^{-2} g, 36%) were also isolated.

4.3.1.1. 1-Methyl-9-methoxy-3-oxo-3*H*-benzo[*f*]benzopyran, Obm-*H* (4). TLC (ethyl acetate/*n*-hexane, 6:4): R_f=0.63. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.95 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 6.36 (s, 1H, H-2), 7.23 (dd, *J*=8.7 and 2.4 Hz, 1H, H-8), 7.34 (d, *J*=8.7 Hz, 1H, H-5), 7.84 (d, *J*=8.7 Hz, 1H, H-7), 7.91 (d, *J*=9.0 Hz, 1H, H-6), 7.95 (d, *J*=2.4 Hz, 1H, H-10). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ_C=26.24 (CH_3), 55.42 (OCH_3), 106.35 (C-10), 113.77 (C-4b), 115.40 (C-5), 116.09 (C-2), 116.09 (C-8), 126.47 (C-6a), 131.10 (C-7), 131.73 (C-6b), 133.36 (C-6), 154.02 (C-1), 155.37 (C-4a), 159.11 (C-9), 160.47 (C-3). IR (neat, cm^{-1}): ν=3414, 2918, 2848, 1716, 1623, 1552, 1515, 1455, 1356, 1261, 1228, 1093, 1018, 933 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{12}O_3$ [M^+]: 240.0786; found: 240.0777.

4.3.2. Acidolysis with trifluoracetic acid

(a) To the fully protected amino acid Tos-Phe-Obm (**3g**) (3.00×10^{-2} g, 5.39×10^{-5} mol) were added 0.60 mL of trifluoracetic acid with rapid stirring, at room temperature, over 2.5 h. Evaporation under reduced pressure gave a yellow solid (3.00×10^{-2} g, 100%). ^{1}H NMR confirmed the structure of the starting material.

(b) A solution of Tos-Phe-Obm (**3g**) (2.80×10^{-2} g, 4.97×10^{-5} mol) in TFA (6 mL) was refluxed for 9 h. Evaporation under reduced pressure gave a white-greenish solid (2.80×10^{-2} g, 100%). ^{1}H NMR confirmed the structure of the starting material.

4.3.3. Acidolysis with hydrochloric acid

(a) To the fully protected amino acid Tos-Phe-Obm (**3g**) (2.10×10^{-2} g, 3.77×10^{-5} mol), was added 6 M HCl (0.40 mL) under rapid stirring, at room temperature, over 4.5 h. Evaporation under reduced pressure gave a white solid (2.10×10^{-2} g; 100%). ^{1}H NMR confirmed the structure of the starting material.

(b) A solution of Tos-Phe-Obm (**3g**) (2.10×10^{-2} g; 3.77×10^{-5} mol) in 6 M HCl (0.40 mL) was refluxed

for 17 h. Evaporation under reduced pressure gave a white solid (1.74×10^{-3} g, 83%). ^{1}H NMR confirmed the structure of the starting material.

4.3.4. Acidolysis with hydrobromic acid

(a) To the fully protected amino acid Tos-Phe-Obm (**3g**) (2.20×10^{-2} g, 3.91×10^{-5} mol) was added aqueous HBr (0.2 mL), under rapid stirring over 4.5 h. Evaporation under reduced pressure gave a white solid (2.20×10^{-2} g, 100%). ^{1}H NMR confirmed the structure of the starting material.

(b) A solution of Tos-Phe-Obm (**3g**) (2.20×10^{-2} g, 3.86×10^{-5} mol) in aqueous HBr (0.2 mL) was refluxed for 5 h. Evaporation under reduced pressure, followed by dry chromatography with ethyl acetate/*n*-hexane mixtures of increasing polarity, gave Tos-Phe-OH (**2e**) as a yellow oil (6.80×10^{-3} g, 57%). ^{1}H and ^{13}C NMR well compared with an original sample.

(c) To the fully protected amino acid Tos-Phe-Obm (**3g**) (2.00×10^{-3} g, 3.59×10^{-5} mol), was added a solution of HBr in CH_3CO_2H (45% m/v) (0.008 mL), under rapid stirring over 4.5 h. Evaporation under reduced pressure gave a yellowish white solid (1.80×10^{-2} g, 90%). ^{1}H NMR confirmed the structure of the starting material.

(d) A solution of Tos-Phe-Obm (**3g**) 2.00×10^{-2} g; 3.59×10^{-5} mol), in a solution of HBr in CH_3CO_2H (45% m/v) (0.008 mL), was refluxed for 5 h. Evaporation under reduced pressure followed by dry chromatography ethyl acetate/*n*-hexane, mixtures of increasing polarity, gave Tos-Phe-OH (**2e**) (7.80×10^{-3} g, 68%) as a colourless oil. ^{1}H NMR compared well with an original sample.

4.3.5. Reduction with Mg/MeOH

(a) To a solution of Tos-Phe-Obm (**2g**) (6.00×10^{-2} g, 1.08×10^{-4} mol), in dry methanol (2 mL) magnesium powder (3.90×10^{-2} g, 1.62×10^{-3} mol) was added and the resulting mixture was sonicated for 3 h, at room temperature. The process was monitored by TLC (ethyl acetate/*n*-hexane, 6:4) until all compounds were reacted. The reaction was quenched by addition of saturated aqueous NH_4Cl (4 mL) and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, concentrated to dryness to give Tos-Phe-OH (**2e**) as an off-white oil (1.20×10^{-2} g, 56%). ^{1}H NMR compared well with an original sample.

(b) Starting with Tos-Phe-OH (**2e**) (5.90×10^{-2} g, 1.88×10^{-4} mol), in dry methanol (2 mL) magnesium powder (4.60×10^{-2} g, 1.88×10^{-3} mol) was added and the resulting mixture was sonicated for 3 h, at room temperature. Treatment by following the procedure described above gave a white solid (5.00×10^{-2} g, 84%). ^{1}H NMR confirmed the structure of the compound.

4.3.6. Alkaline hydrolysis. To the fully protected amino acid Tos-Phe-Obm (**3g**) (3.10×10^{-2} g, 5.47×10^{-5} mol), in 1,4-dioxane (2 mL) 1 M NaOH (0.220 mL, 2.19×10^{-4} mol) was added at low temperature. The solution was stirred at 0 °C for 9 h and acidified to pH 3 with 1 M $KHSO_4$. After extraction with ethyl acetate and evaporation of the solvent, Tos-Phe-OH (**2g**) was obtained as an orange solid (4.10×10^{-2} g, 100%). ^{1}H NMR compared well with an original sample.

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Synthesis of calixarene–cyclodextrin coupling products

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Abstract—The coupling of two or four mono-6-amino β-cyclodextrin (amino-CD) units, (unprotected or permethylated hydroxyls), to diisopropoxycalix[4]arene crown-6 (CAL) was realised using the *N*,*N*′-succinyldiamide linker. The resulting molecules in two series were characterised with the help of mass and NMR spectroscopies. The yields of all coupling products were improved for permethylated sugar series compared to the hydroxylated CD series or to our previous studies. The two β-cyclodextrin (β-CD) residues coupled to disubstituted CAL were orientated from the same side of the crown ether.

1. Introduction

In our recent papers of this series,[1,2] we identified several crown calix[4]arene compounds, which could be usefully coupled to β-cyclodextrin (β-CD) (**1**), and then proposed the synthesis of mono-crown and bis-crown calixarene derivatives by coupling them to β-CD through a succinic diamide linker. Such amphiphilic ensembles have a capacity to include a wide variety of molecules according to the availability of three sites: calixarene, crown and cyclodextrin. They represent a new family of compounds to be used as potential drug carriers and have ion affinities.[3] Among several attempts to build β-CD–calixarene systems, in particular seminal work of Reinhoudt's[4–7] and Liu's[8] groups should be mentioned. However, none of these studies used our combination of host molecules or spacer arms.

The synthesis of CD–CAL mixed-derivatives allowed us to construct molecules of new but defined architecture, and also to study their physicochemical properties. This work has some importance in the supramolecular field; the presence of crown, CD and CAL cavities available to different guests is significant in the development of encapsulation devices and molecular containers as a step in nanotechnology, leading to self-assembled, charged molecular capsules.

One difficulty in working with calixarenes is their general poor solubility in organic solvents; this problem is often resolved by the introduction of the crown ether moiety. Likewise, a CD attached to a CAL frame should provide an amphiphilic character to CAL–CD aggregates;[9,10] this would also significantly improve solubility in water, while preserving the supramolecular capacity of each of the three components (CAL, crown and CD).

The use of *n*-octyl mono-crown calix[4]arene (**2**) (a molecule of specific interest as a radioactive Cs^+ extractant in the processing of spent nuclear fuel) as a frame for such a coupling leads to the connection of either two or four CD units to this calixarene.[11] However, the bis-crown calix[4]-arene binds to only two CDs. In both series, the coupling products were obtained with relatively low yield. Purification was laborious, the solubility remained low and NMR spectra were very complex because of many overlapping proton signals. These difficulties led us to modify both the CAL and CD systems in search of friendlier ones (Fig. 1).

The permethylation of CD usually leads to derivatives with increased solubility in organic solvents. The mono-6-amino permethylated β-CD (β-CDmet-NH_2) (**4**) was thus considered as a possible substrate for this CAL–CD coupling,[12,13] according to Scheme 1, together with mono-6-amino β-CD (β-CD-NH_2) (**5**).

We thus propose the coupling of both amino-CDs (**4**, **5**) via the attachment to a free carboxyl of (*N*-succinate monoamide)$_n$CAL (where *n* indicates the number of amino groups attached to the calixarene frame). As we have previously observed, the coupling of the amino-CD to the succ-NH-CAL gives a better yield than does the opposite coupling (that is,

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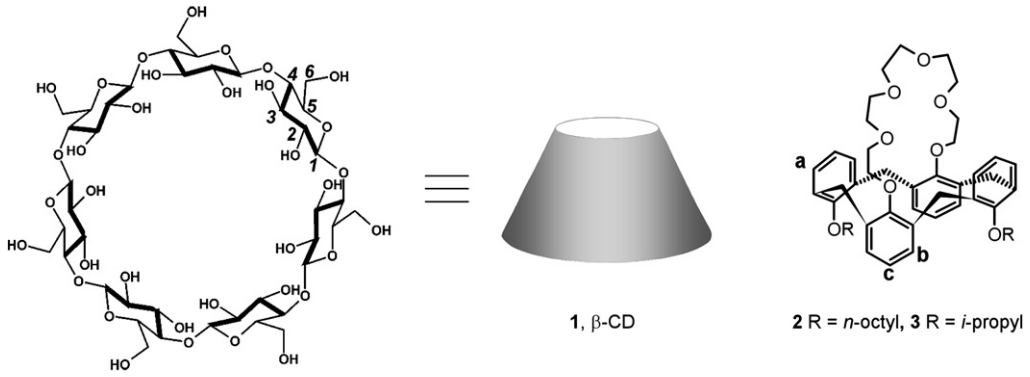


Figure 1. Structures of β-cyclodextrin (**1**) and 25,27-diisopropoxycalix[4]arene-26,28-crown-6 (**3**).

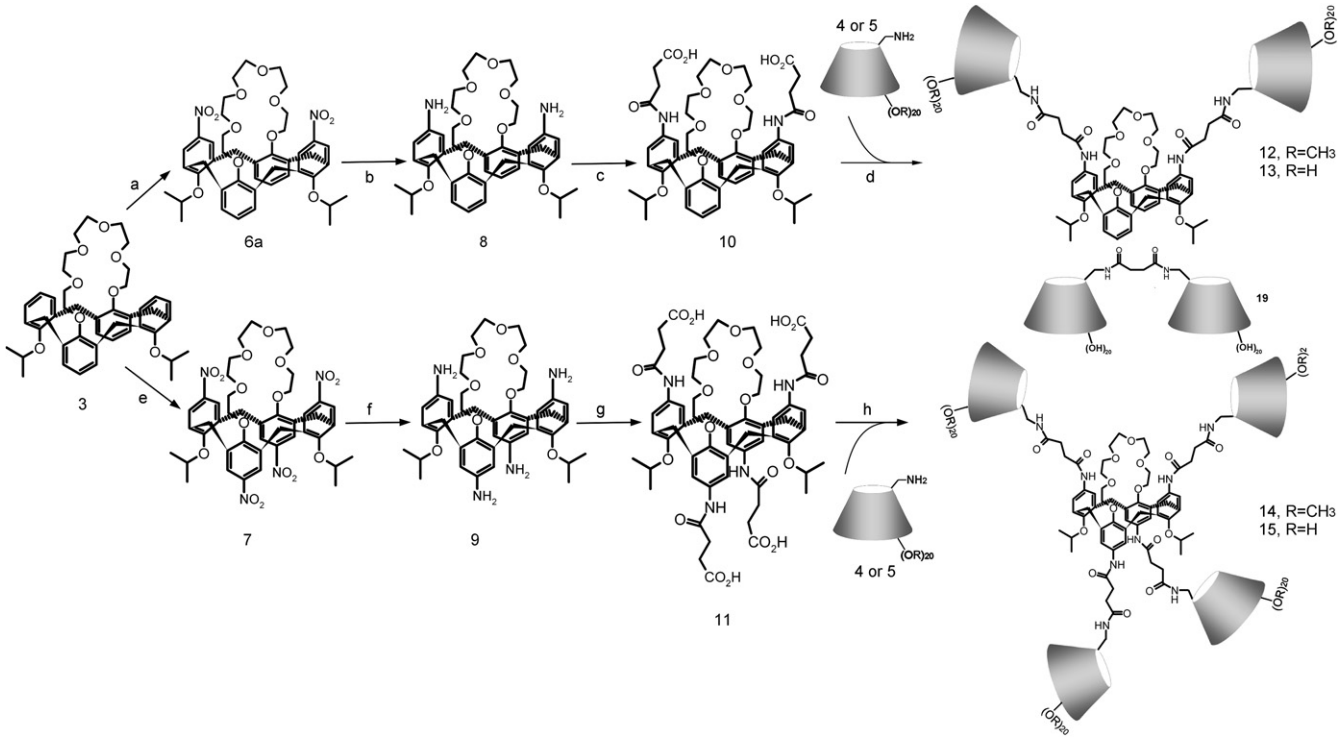
of β-CD-succ to the amino-CAL). This can be explained by the fact that an aromatic amine is less reactive to nucleophilic substitutions than is a primary amine. Furthermore, steric hindrance disfavours the peptidic coupling by this pathway.[14] Consequently, we chose not to follow this second route.

In order to further improve the solubility, we compromised between bis-crown series and compound **2**, and chose the diisopropylcalix[4]arene crown-6 (**3**), since it has a slightly shorter aliphatic chain on two of the phenols of CAL; two others were linked via a mono-crown moiety.

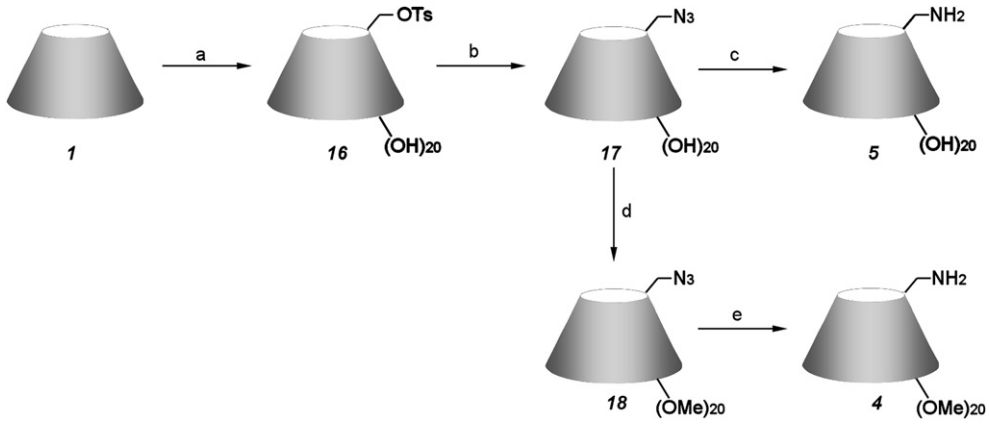
The number of amino groups on the CAL system was controlled by the selective nitration of CAL (**3**).[15] The first compound used was the dinitro cis-to-crown isomer for $CAL(NO_2)_2$ (**6a**), followed by the tetranitro derivative $CAL(NO_2)_4$ (**7**).

The identity of the $CAL(NO_2)_2$ compound was carefully proven from its NMR and X-ray spectra. Both nitro derivatives were then reduced, and coupled to the succinic linkers as per previous procedures[16] (Scheme 1), followed by a final coupling to the amino-CDs **4** and **5**, which we synthesised in parallel (Scheme 2).

The approach proposed in Scheme 1 leads to permethylated CD–CAL coupling products, with a variable number of cyclodextrins attached. Such a methylated CD greatly simplifies the step-by-step synthesis, and the solubility of the final coupling products in organic solvents should be significantly improved for the whole methylated cyclodextrin



Scheme 1. General scheme of coupling of calixarene to cyclodextrins. (a) HNO_3 concd, acetic acid, acetic anhydride, −18 °C, 18 h, 75%; (b) $SnCl_2$, EtOH, 70 °C, 18 h, 75%; (c) succinic anhydride, DMF, 18 h, 86%; (d) DIC, HOBt, DMF, 24 h, 50%; (e) HNO_3 fuming, acetic anhydride, CH_2Cl_2, 1 h, 88%; (f) Ni (Raney), toluene, 70 °C, 4 h, 76%; (g) succinic anhydride, DMF, 18 h, 79%; (h) DIC, HOBt, DMF, 24 h, 63%.



Scheme 2. Synthesis of 6-monoamino-β-cyclodextrins **4** and **5**. (a) β-CD, tosylimidazol, NaOH solution, rt, 45 min, 30%; (b) NaN_3, H_2O, 80 °C, 5 h; (c) Pd/C 10%, H_2, H_2O, 60 °C, overnight, 85%; (d) NaH, MeI, DMF, rt, 6 h, 90%; (e) Pd/C 10%, H_2, H_2O/MeOH, overnight, 85%.

series. As a reference, the hydroxylated CD analogous series was synthesised in parallel. In this last case, dialysis was used to separate the final products from the reagents and other water-soluble compounds.

2. Results and discussion

The tetra *para*-nitration of various calixarenes does not present any particular difficulty. It has already been reported and can be done according to many variations to our exhaustive nitration procedures[15] with a close to quantitative yield (75–90%) in a variety of solvents and within a wide temperature range. The tetranitration, for example, can be easily achieved even in CH_2Cl_2 solution at 0 °C with HNO_3/acetic anhydride. We were able to avoid undesired excess nitration (for instance, the fifth nitro group on the benzylic carbon), as well as the oxidation of the molecule as a whole and its undernitration in a mixture of products. The dinitration was best achieved under trifluoroacetic anhydride, HNO_3 concd at −78 °C (yield: 90%),[15] under low-temperature nitration (−18 °C, 2.2 equiv of fuming HNO_3, yield: 75%[2]), and under random nitration with acetic anhydride–concd HNO_3 (yield: up to 40%). All these methods were followed by column chromatography purifications. Here, the dinitration was performed according to the method described for compound **6a** in Section 4. LC–MS of the crude mixture obtained was recorded showing the presence of isomeric mono, di- and trinitro calixarenes (Fig. 2). For example, for dinitro isomer, the presence of three isomers was detected (**6a**, **6b**,

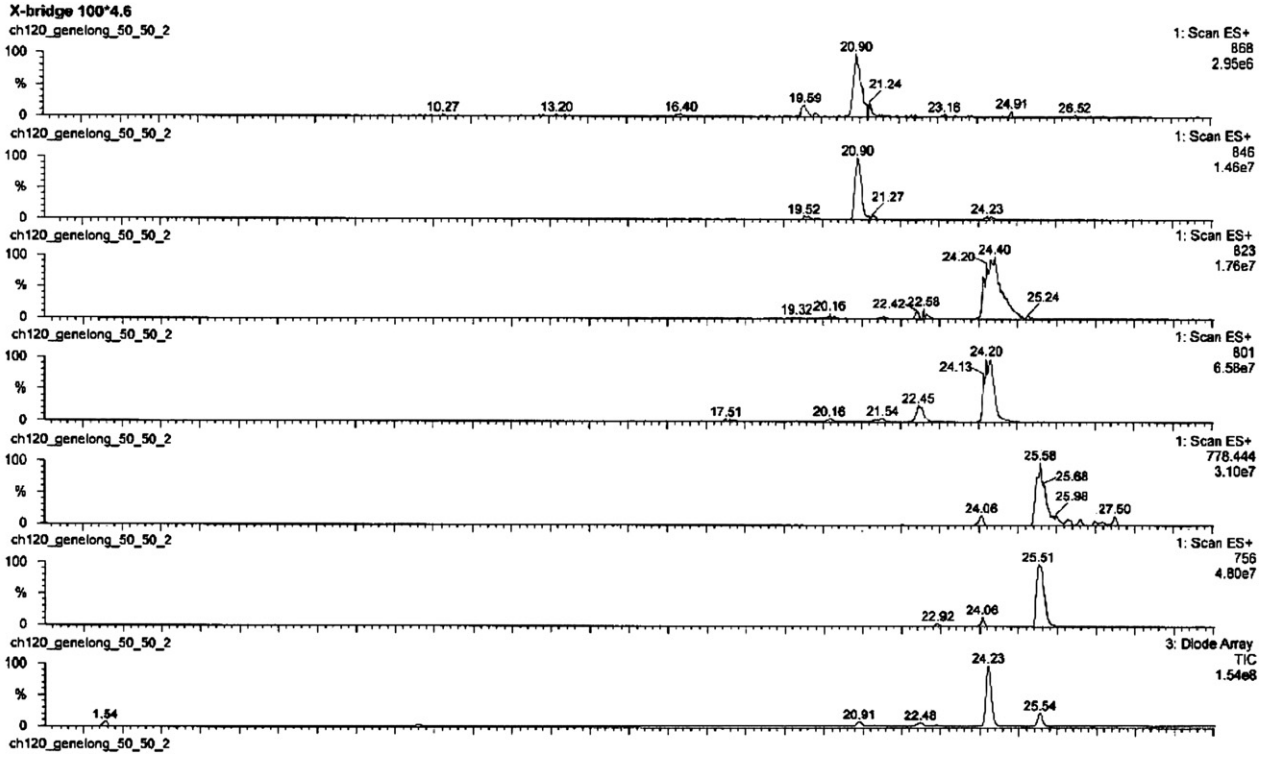


Figure 2. Ion mass chromatograms of polynitrocalixarene derivatives of **1**. Polynitro isomers (*m*/*z*, MH^+ and MNa^+, respectively): mononitro 756 and 778; dinitro 801 and 823; trinitro 847 and 869. Lower run: total ion current, TIC (diode array).

Table 1. LC retention time of nitrocalixarene mixture obtained according to dinitration procedure (see Section 4, compound **6a**)

Number of nitro group	Isomer[a]	Retention time (min)
1	**20a**	25.51
	20b	24.06
2	**6a**[b]	24.20
	6b	22.45
	6c	20.16
3	**21a**	20.90
	21b	19.52

6a: 11,23-Dinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
6b: 11,17-Dinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
6c: 11,29-Dinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
20a: 11-Nitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
20b: 17-Nitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
21a: 11,17,23-Trinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
21b: 11,17,29-Trinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6.
[a] Identification of isomers was done assuming similar behaviour of *n*-octyl mono-crown series and *i*-PrCAL series under LC conditions applied (see Section 4); pure compound **1**, t_R=25.71 min and dinitro compound **6a** were used as references for this determination. Traces of $CAL(NO_2)_4$, t_R=9.6 min were also observed.
[b] Major isomer.

6c). The major isomer (**6a**) ratio, as estimated from its MH^+ and MNa^+ mass chromatogram, was in the vicinity of 95% (Table 1).

The dinitro calixarene isomers were fully characterised for the *n*-octyl mono-crown series, using NMR and LC methods.[11] The polynitro diisopropoxy mono-crown series was also characterised using electrospray mass spectrometry (ESI-MS) and liquid chromatography.

The identity of the $CAL(NO_2)_2$ compound was carefully proven from its NMR and X-ray spectra. The NMR of this particular molecule showed some interesting features: the most characteristic proton signals were those associated with the aryl protons—two types of protons for the phenyl moiety without NO_2 group (7.06 ppm (d, 4H, H_b), 6.88 ppm (t, 2H, H_c)) with $^3J_{H_{b-c}} = 7.5$ Hz and a singlet at 8.02 ppm for *meta* protons on phenyls bearing NO_2. This is in conjunction with the ^{13}C signals, which follow the similar deshielding trend (C–NO_2 at 142.0 ppm), and confirmed the proposed structure. The geometry of the two nitro groups in $CAL(NO_2)_2$ was also established with 2D NMR as being in cis-to-crown orientation (compound **6a**), (that is, both NO_2 groups were orientated on the crown side of the molecule (Fig. 3)); this was confirmed via X-rays.

The exact identification of the two NO_2 groups is important because the next steps of the coupling will maintain the relative spatial orientation of both nitrogens throughout the entire scheme.

The separate reduction of both nitrated compounds, dinitro **6a** and tetranitro **7** led to the corresponding amines **8** and **9**, respectively, with high yield varying from 70% for $SnCl_2$ reduction of dinitro, to 76% for Raney nickel reduction of tetranitro derivatives.[17]

The reduction of dinitrocalix[4]arene (**6a**) to the corresponding diamino compound **8** (Scheme 1), however, was better achieved by the $SnCl_2$ reduction. When the Raney nickel

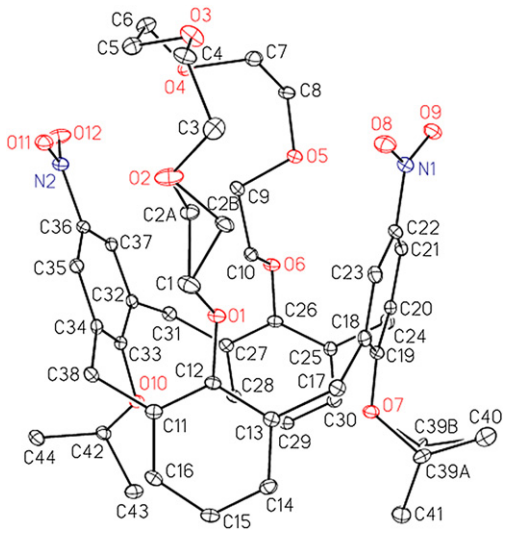


Figure 3. View of compound **6a**. Hydrogen atoms are omitted. Displacement ellipsoids are drawn at the 20% probability level.

reduction was performed on the compound **6a**, a persistent and difficult-to-purify green crystalline residue was observed: this was probably due to the complexation of the amine by Ni^{2+} cation. This difficulty was overcome by using $SnCl_2$ reduction instead;[18] however, this observation alone fully justified the relatively low yield of reduction obtained.

Electrospray mass spectrometry, using mostly Cs^+ but also occasionally Na^+ cationisation agents via the crown-metal complex, allowed us to easily follow the progress of these reactions and of the purification of compounds in the crown series.

For the amines **8** and **9**, the most significant proton shift is the singlet signal at ca. 8 ppm, which disappeared in the compounds **8** and **9**, giving singlet signal deshielded at 6.71 ppm for **8**, and at 6.51 ppm for **9**. The key control signal in NMR spectrum was the shift of the C–NH_2 signal to ca. 133.2 ppm in ^{13}C spectrum (*ipso-para* carbon), thus confirming the reduction to diamine; this was less pronounced for compound **9**.

The amidation of the two amines with succinic anhydride in DMF led to the production of the last synthetic intermediates before the final coupling of the β-CD-NH_2 (**8**) and β-CDmet-NH_2 (**9**) to the $CAL(succ)_n$ molecules (n=2, **10**, n=4, **11**).

From the opposite side of the synthetic scheme, the β-CD-NH_2 (**5**) and β-CDmet-NH_2 (**4**) were synthesised according to the following sequence of reactions (Scheme 2). The common starting product obtained by supramolecular tosylation of β-CD (β-CD-OTs) (**16**) was then transformed into the azide **17**. Direct reduction of compound **17** gave β-CD-NH_2 (**5**), and methylation of **17** with methyliodide in sodium hydride, followed by similar reduction with Pd/C led to β-CDmet-NH_2 (**4**) with challenging yields. The use of Pd/C for reduction of the azido group avoids an important difficulty related to Staudinger method[19,20] where the inclusion of triphenylphosphine or its oxide in the CD cavity is observed.[21]

The full NMR and ESI-MS (Na^+ cationisation) spectra give some interesting features in this series, confirming the expected structures obtained. In order to succeed in the remaining part of the synthesis, both β-CD-NH_2 and β-CDmet-NH_2 should be obtained as very high-purity compounds. This objective was realised by the combined use of column chromatography and ion exchange resin. Their purity was confirmed by NMR and ESI-MS techniques and was in the vicinity of 90–95%.[22] The most interesting signal in the NMR spectra of these amines were the dd at 2.95 ppm (CH_2–N) confirming that the mono 6-amination was overwhelmingly achieved.

2.1. Coupling of (succ)$_n$CAL to β-CD-NH_2

The coupling reactions between the two components were realised for the di- and tetrasubstituted calix[4]arene series. When the activated ester method (DIC, HOBt) was used, two expected coupling products in methylated β-CD series were respectively obtained (yields up to 50% for di-coupled product **12**, 65% for tetrasubstituted product **14**). In hydroxylated CD series the corresponding yields of compounds **13** and **15** were lower (approximately at 20% level). It should be noted that starting from this point, MALDI-TOF-MS was used for mass determination of the coupling compounds.

As in previous work in this series,[1] dimers containing the β-CDmet-succ skeleton were also detected. Their structures should be rationalised on the basis of coupling of two CD derivatives: the β-CDmet-NH_2 and the β-CDmet-succ (HOOC–CH_2–CH_2–NH)$_n$ CDmet. The coupling reaction seems to be affected by the presence of residual succinic acid, which also can react with amines **4** and **5**. Their structures will be characterised separately.

A detailed characterisation of these coupling products for the disubstituted (**12**) and tetrasubstituted calix[4]arene crown-6 (**14**), in methylated β-CD series, is presented in Section 4. However, in the hydroxylated CD series the usual impurities, in particular β–β CD dimer (**19**) and two coupling products with two or three CD residues attached to the calixarene instead of the expected four, were observed. Their separation by classical chromatography was impossible, the attempt of isolation and purification by dialysis resulted in a mixture, which when analysed by MALDI clearly indicated the presence of the above mentioned by-products.

The yield of both CDmet–CAL coupling products is however greater than in the natural CD series, the coupling in natural β-CD remains relatively low; however, the solubility of the aggregates synthesised was significantly improved and their purification was much easier (e.g., column chromatography could be used for purification).

3. Conclusion

The coupling of permethylated and hydroxylated CD series to amino-CAL was accomplished using succinic linkers for separation between two molecules.

With the help of diamino- and/or tetramino calixarene as a base, we can reasonably consider that the in-space orientation of β-CD is properly controlled, and that the calixarene–crown system represents a good example of a frame molecule for the construction of carbohydrate tubes 'dangling' from such a frame.

As it was mentioned in previous cases that were examined, the hydroxylated CD moiety is large enough to overturn the calixarene crown and form some H-bonds over the CAL–crown systems. Once again, molecular modelling calculations showed that this important stabilising interaction, absent for the CDmet series, enabled the correct orientation of both linker and CD moieties, improved the total yield of coupling product[23] and eventually involved chiral linker to target a more organised system.

In order to further develop the use of CAL frames for construction of peptide chains in a rigorously space-orientated direction, a similar synthetic scheme should be attempted for peptide–succ-NH CAL systems. This might allow the formation of interpeptide chain interactions,[24,25] and the organisation of the resulting molecules into multihelix systems; in particular, this may lead to quadruple peptide helices.[23]

In this respect, the attempts to bond various diamino-CD derivatives to a CAL frame seem particularly appealing, and could lead to dendrimeric structures. It seems, from our observations in this field, that the crown-6 system attached to CAL is small, hidden and 'crushed' by a large CD. However, we can consider its selective removal, because of its phenolic ether character, by various ablation techniques.[26]

4. Experimental

4.1. General

All calixarene derivatives were purchased from Acros Organics. The starting cyclodextrins are given from Roquette Frères (France). Most of the reagents and solvents used in this study came from the Sigma–Aldrich and used without further purification. TLC was performed on Silica Gel 60 F_{254} plates (E. Merck) followed by charring with 10% (v/v) H_2SO_4 or UV revelation. NMR experiments were performed using a Bruker DRX500 spectrometer operating at 500 and 125 MHz for ^1H and ^{13}C, respectively. In all cases, the samples were prepared in deuterium oxide, DMSO-d_6 (Euriso-Top, Saclay, France) and measurements were performed at 25 °C. Chemical shifts are given relative to external Me_4Si (0 ppm) and calibration was performed using the signal of the residual protons of the solvent as a secondary reference. Selected 2D experiments were run on these compounds in order to unambiguously assign signals. Molecular modelling calculations were done with HyperChem 6.03 Mm+ (Hypercube, USA, 2000) in gas-phase only. The X-ray diffraction determination was done on dinitrocalix[4]arene (**6a**). The data were collected at 100(2) K on a Nonius Kappa-CCD area detector diffractometer using graphite-monochromated Mo Kα radiation (0.71073 Å). The data were processed with HKL2000.[27] The structure was solved by direct methods with SHELXS-97 and subsequent Fourier-difference synthesis and refined by full-matrix

least-squares on F^2 with SHELXL-97.[28] All non-hydrogen atoms were refined with anisotropic displacement parameters.

Crystal data and refinement details: $C_{44}H_{52}N_2O_{12}$, M=800.88, triclinic, space group $P\bar{1}$, a=9.4077(9), b=12.6984(8), c=17.5132(15) Å, α=75.357(5), β=86.167(4), γ=83.820(5)°, V=2010.8(3) Å^3, Z=2, μ=0.096 mm^{-1}, F(000)=852. Refinement of 545 parameters on 6982 independent reflections out of 15247 measured reflections (R_{int}=0.081) led to R_1=0.069, wR_2=0.161 and S=1.054, CCDC 612684.

The mass spectra were recorded on triplequad Quattro II Micromass ESI-MS system as solutions of ca. 0.1 mg mL^{-1} in methanol/water (1:1) introduced with Harward Apparatus syringe-pump. The working range of the instrument was from m/z 100 to 2000. For the details of ESI analytical conditions see Ref. 11. The MALDI-TOF spectra were recorded for superior than 1500 mass compounds only on MALDI-TOF Voyager DE, Applied Biosystem of Université de Lille using DHB matrix and usual protein calibration standards within 1200 to 5700 mass range. The acceleration voltage was fixed at 20 kV and the number of laser shots at 100.

For LC–MS experiment, the mass spectrometer is the Waters Micromass® ZQ™ (quadrupole with ESI source) and the UV detector is the Waters 2996 photodiode array. The instrumental parameters were: capillary voltage at 3.5 kV, source temperature at 120 °C and cone voltage was fixed at 20 V. The column is a Waters XBridge™ C18, 4.6×100 mm, 3.5-μm particle size. Elution solvents are: A, acetonitrile (containing 0.1% formic acid) and B, water (containing 0.1% formic acid). A linear gradient elution was used: from A/B, 50:50 (v:v) to A, 100 (v) in 25 min at a flow rate of 1 mL/min. Spectra were recorded in continuum mode by scanning the quadripole between m/z 130 and 2000.

4.2. Synthesis

4.2.1. 6^{I}-(*O*-*p*-Tolylsulfonyl)-cyclomaltoheptaose (16). This compound was synthesised from β-CD (**1**) according to the Bittman method.[29] Yield: 26%. Mp=179 °C; R_f=0.6 (BuOH/MeOH/H_2O/NH_3 3:3:3:1); ^{1}H NMR (500 MHz, DMSO-d_6, 298 K): δ=7.75 (d, 2H; $H_{b/b'}$), 7.42 (d, 2H; $H_{c/c'}$), 5.6–5.9 (14O*H*, O*H*-2, O*H*-3), 4.81–4.86 (m, 6H; H-1$^{II-VII}_{CD}$), 4.76 (d, 1H; H-1$^{I}_{CD}$), 4.33 (d, 1H; H-6$^{I}_{CD}$), 4.18 (dd, 1H; H-6′$^{I}_{CD}$), 3.4–3.7 (m, 18H; H-5$^{I-VII}_{CD}$/H-6$^{II-VII}_{CD}$/H-6′$^{II-VII}_{CD}$/H-3$^{I-VII}_{CD}$), 3.2–3.4 (m, 14H; H-2$^{I-VII}_{CD}$/H-4$^{I-VII}_{CD}$), 2.42 (s, 3H; C$_e$*H*); ESI-MS+: m/z 1290.2 [M+H]$^+$ (calcd for $C_{49}H_{77}O_{37}S$: 1290.2).

4.2.2. 6^{I}-Azido-6^{I}-deoxy-cyclomaltoheptaose (17). This azide was obtained with sodium azide according to Ueno method.[30] R_f=0.5 (BuOH/MeOH/H_2O/NH_3 3:3:3:1); ^{1}H NMR (500 MHz, D_2O): δ=5.10 (d; H-1$_{CD}$), 3.99 (t; H-3$_{CD}$), 3.86–3.97 (m; H-5$_{CD}$/H-6$_{CD}$/H-6′$_{CD}$), 3.68 (dd; H-2$_{CD}$), 3.61 (d; H-4$_{CD}$); ESI-MS+: m/z 1166.5 [M+H]$^+$ (calcd for $C_{42}H_{70}O_{34}N_3$).

4.2.3. 6^{I}-Azido-6^{I}-deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis (2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose (18). The compound **17** is dissolved in dry DMF (100 mL) and cooled down at 0 °C. NaH is added in portions (1.55 g, 65 mmol, dispersed in oil 60%). After 20 min, iodomethane (18.35 g, 129 mmol) is slowly added. The reaction is stirred overnight at room temperature under argon. Salts formed are filtered off, washed with dichloromethane and the filtrate is concentrated. Oily residue is dissolved in a minimum amount of water and extracted with chloroform (3×50 mL). The organic phase is washed with water (2×50 mL), dried with sodium sulfate, filtered and evaporated. Removal of the oily residue was achieved by filtration through a silica bed yielding 1.65 g (90%) of compound **18**. R_f=0.8 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.31–5.36 (H-1$_{CD}$), 3.88–3.96 (H-5$_{CD}$/H-6$_{CD}$), 3.69–3.84 (H-4$_{CD}$/H-6′$_{CD}$/H-3$_{CD}$), 3.65 (OCH_3-6$_{CD}$), 3.56 (OCH_3-3$_{CD}$), 3.43 (OCH_3-2$_{CD}$), 3.38–3.42 (H-2$_{CD}$); ESI-MS+: m/z 1462.8 [M+Na]$^+$ (calcd for $C_{62}H_{109}N_3NaO_{34}$).

4.2.4. 6^{I}-Amino-6^{I}-deoxy-2^{I},3^{I}-di-*O*-methyl-hexakis (2$^{II–VII}$,3$^{II–VII}$,6$^{II–VII}$-tri-*O*-methyl) cyclomaltoheptaose (4). This compound was synthesised according to the method described by Carofliglio[22] from compound **18** and purified using ionic exchange resin BioRad AG 50W-X_4 (50–100 mesh), the residue was acidified at a pH of 4–5. The aqueous solution was put into the resin column, eluted with 900 mL of water and then with 400 mL of aqueous ammonia (10%). The pure compound appeared in ammonia fractions. These fractions were evaporated almost to dryness and lyophilised. Yield: 86% of the desired compound **4**. R_f=0.2 (CH_2Cl_2/MeOH 8:2); ^{1}H NMR (500 MHz, D_2O): δ_H=5.36 (d, 1H; H-1$^{I}_{CD}$, $^3J_{1^I-2^I}$=3.6 Hz), 5.30–5.35 (m, 6H; H-1$^{II-VII}_{CD}$), 3.86–3.96 (m; H-5$^{II-VII}_{CD}$), 3.87–3.92 (m; H-6$^{II-VII}_{CD}$), 3.83 (H-5$^{I}_{CD}$), 3.75–3.83 (m; H-4$^{II-VII}_{CD}$), 3.76 (H-3$^{I}_{CD}$), 3.69–3.79 (m; H-3$^{II-VII}_{CD}$), 3.71 (H-4$^{I}_{CD}$), 3.65–3.73 (m; H-6′$^{II-VII}_{CD}$), 3.64–3.66 (m; OCH_3-6$_{CD}$), 3.55–3.57 (m; OCH_3-3$_{CD}$), 3.43 (H-2$^{I}_{CD}$), 3.42–3.43 (m; OCH_3-2$_{CD}$), 3.36–3.44 (m; H-2$^{II-VII}_{CD}$), 3.05 (dd, 1H; H-6$^{I}_{CD}$, $^3J_{6^I-5^I}$=5.5 Hz, $^3J_{6^I-6'^I}$=14.2 Hz), 2.96 (dd, 1H; H-6′$^{I}_{CD}$, $^3J_{6'^I-5^I}$=3.0 Hz, $^3J_{6'^I-6^I}$=14.2 Hz); ^{13}C NMR (125 MHz, D_2O): δ_C=97.1–97.8 (C-1$^{I-VII}_{CD}$), 80.9–81.6 (C-3$^{I-VII}_{CD}$), 80.2–80.6 (C-2$^{I-VII}_{CD}$), 76.7–78.6 (C-4$^{I-VII}_{CD}$), 71.0–71.4 (C-6$^{II-VII}_{CD}$), 70.7–71.7 (C-5$^{I-VII}_{CD}$), 59.8–60.4 (O*C*H$_3$-6$_{CD}$), 58.3–59.0 (O*C*H$_3$-3$_{CD}$/O*C*H$_3$-2$_{CD}$), 41.6 (C-6$^{I}_{CD}$); ESI-MS+: m/z 1414.8 [M+Na]$^+$ (calcd for $C_{62}H_{112}NNaO_{34}$).

4.2.5. 11,23-Dinitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (6a). 1,3-Diisopropoxycalix[4]arene-crown-6 (200 mg, 0.281 mmol) **3** was dissolved in 10 mL of acetic anhydride and maintained under −15 °C. A mixture of 5 mL of acetic anhydride, 5 mL of acetic acid and fuming nitric acid (26 μL, 2.2 equiv) is added dropwise to the calixarene solution. After addition, the reaction mixture is warmed at room temperature and stirred overnight. The mixture is then poured into ice water and extracted twice with ether. Organic phases were extracted with a solution of saturated $NaHCO_3$ three times, dried over $MgSO_4$, filtered and evaporated. The residue is purified on silica gel column chromatography eluted with cyclohexane/ethyl acetate 9:1 to 8:1 to give 168 mg of the desired product. Yield: 75%. R_f=0.5 (cyclohexane/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=8.02 (s, 4H; H_a); 7.06 (d, 4H; H_b, J_{b-c}=7.5 Hz), 6.88 (t, 2H; H_c, J_{b-c}=7.5 Hz), 4.40 (sept., 2H; C*H*(CH$_3$)$_2$, J=6 Hz), 3.91 (d, 4H; ar–H_αCH$_\beta$–ar, $J_{\alpha-\beta}$=16.1 Hz), 3.85 (d, 4H; ar–H$_\alpha$CH_β–ar, $J_{\alpha-\beta}$=16.1 Hz), 3.61 (t, 4H; ar–OCH_2, J=6.3 Hz), 3.58 (s, 4H; O–CH$_2$), 3.51 (m, 4H; O–CH$_2$),

3.48 (m, 4H; O–CH_2), 3.22 (t, 4H; ar–OCH_2CH_2–O, J=6.3 Hz), 0.91 (d, 12H; CH_3, J=6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=160.7, 156.6 (C–O), 142.0 ($C_{arom.}NO_2$), 135.5, 132.4 ($C_{arom.}CH_2$), 130.8 (C_c), 125.2 (C_a), 122.7 (C_b), 71.9 ($CH(CH_3)_2$), 71.5, 71.1, 70.6, 69.6, 69.4 (CH_2–O), 38.9 (ar–CH_2–ar), 22.0 (CH_3); ESI-MS+: m/z measured at 933.5 $[M+Cs]^+$ (calcd for $C_{44}H_{52}N_2O_{12}Cs$).

4.2.6. 11,23-Diamino-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (8). A suspension of 62 mg of compound **6a** (0.077 mmol) and 175 mg of $SnCl_2\cdot 2H_2O$ (0.77 mmol) in 3.7 mL of ethanol was refluxed overnight. The reaction mixture is poured into ice water. The solution is adjusted to pH=9 with 1 N NaOH and extracted three times with dichloromethane. Organic phases were washed with distilled water and dried over $MgSO_4$, filtered and evaporated. The product is used without further purification. Yield: 75%. R_f=0.5 (chloroform/methanol 9:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=6.93 (d, 4H; H_b, J_{b-c}=7.5 Hz), 6.71 (s, 4H; H_a), 6.61 (t, 2H; H_c, J_{b-c}=7.5 Hz), 4.12 (sept., 2H; C$H(CH_3)_2$), 3.86–3.96 (m, 16H; OCH_2), 3.70 (s, 4H; OCH_2), 3.54 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=13.1 Hz), 3.41 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=13.1 Hz), 1.25 (d, 12H; CH_3, J=6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=156.1, 133.8 (C–O), 133.2 ($C_{arom.}NH_2$), 130.1 (C_c), 128.3 ($C_{arom.}CH_2$), 121.8 (C_b), 120.1 (C_a), 73.9 ($CH(CH_3)_2$), 72.4, 72.0, 71.7, 71.6, 69.4 (CH_2–O), 36.1 (ar–CH_2–ar), 22.8 (CH_3); ESI-MS+: m/z measured at 873.5 $[M+Cs]^+$ (calcd for $C_{44}H_{56}N_2O_8Cs$).

4.2.7. 11,23-Diamidosuccinyl-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (10). $CAL(NH_2)_2$ **8** (95 mg, 128 μmol) is dissolved in 3 mL of DMF together with 26.9 mg of succinic anhydride (269 μmol). The reaction mixture is stirred overnight, evaporated and the 140 mg of product is used without further purification. Yield: 86%. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H=9.67 (s, 2H; C(O)NH), 7.33 (s, 4H; H_a), 7.00 (d, 4H; H_b, J_{b-c}=7.4 Hz), 6.74 (t, 2H; H_c, J_{b-c}=7.4 Hz), 4.10 (sept., 2H; C$H(CH_3)_2$, J=5.8 Hz), 3.77 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=15.9 Hz), 3.65 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=15.9 Hz), 3.5 (s, 4H; O–CH_2), 3.43–3.48 (m, 4H; O–CH_2), 3.36–3.40 (m, 4H; O–CH_2), 3.12–3.19 (m, 4H; O–CH_2), 3.05–3.12 (m, 4H; OCH_2), 2.43–2.57 (m, 4H; CH_{2succ}), 0.76 (d, 12H; CH_3, J=5.6 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C=173.8 (C(O)NH), 169.1 (C(O)OH), 156.3, 149.9 (C–O), 134.0 ($C_{arom.}NH$), 133.2, 133.0 ($C_{arom.}CH_2$), 129.8 (C_c), 121.3 (C_b), 119.5 (C_a), 69.9, 69.7 (CH_2–O), 69.6 ($CH(CH_3)_2$), 69.4, 68.7, 68.4 (CH_2–O), 39.4 (ar–CH_2–ar), 30.9, 28.9 (CH_{2succ}), 21.3 (CH_3); ESI-MS+: m/z measured at 963.4 $[M+Na]^+$ (calcd for $C_{53}H_{65}O_{14}N_2Na$).

4.2.8. 5,11,17,23-Tetranitro-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (7). 1,3-Diisopropoxycalix[4]arene-crown-6 **3** (200 mg, 294 μmol) is dissolved in 5 mL of dichloromethane and cooled to 0 °C. A mixture of 400 μL of nitric acid, 500 μL acetic anhydride dissolved in 2 mL of dichloromethane is cooled to 0 °C and added dropwise to the calix[4]arene solution. After several minutes the reaction is stopped by addition of 4 mL of triethylamine and diluted with 50 mL of dichloromethane. The mixture is extracted twice with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. The residue is purified on silica gel column. The elution with cyclohexane/AcOEt, 6:4 gives 230 mg of the desired product. Yield: 88%. R_f=0.6 (cyclohexane/AcOEt 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=8.07 (s, 4H; $H_{arom.}$), 8.02 (s, 4H; $H_{arom.}$), 4.47 (sept., 2H; C$H(CH_3)_2$; J=6.5 Hz), 3.96 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=16 Hz), 3.91 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=16 Hz), 3.60 (t, 4H; O–CH_2–, J=5.5 Hz), 3.53 (s, 4H; O–CH_2–), 3.31 (br s, 8H; O–CH_2–CH_2–O), 3.47 (t, 4H; O–CH_2–, J=5.5 Hz), 1.05 (d, 12H; CH_3, J=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=161.8 (2C–NO_2), 160.2 (2C–NO_2), 142.3 (4C–CH_2), 134.5 (2C–O), 133.9 (2C–O), 126.6 (4$CH_{arom.}$), 126.1 (4$CH_{arom.}$), 73.1 (2$CH(CH_3)_2$), 71.6 (2CH_2–O), 71.3 (2CH_2–O), 71.1 (2CH_2–O), 70.8 (2CH_2–O), 69.7 (2CH_2–O), 38.2 (4ar–CH_2–ar), 22.0 (4CH_3); ESI-MS+: m/z measured at 1023 $[M+Cs]^+$ (calcd for $C_{44}H_{50}N_4O_{16}Cs$).

4.2.9. 5,11,17,23-Tetramino-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (9). $CAL(NO_2)_4$ **7** (78 mg, 88 μmol) is dissolved in 3 mL of methanol and one spatula of Raney nickel. The mixture is placed under hydrogen atmosphere and stirred vigorously overnight. The mixture is filtered under Celite® pad and evaporated to dryness. The residue is purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH, 9:1 to give 51 mg of the desired product. Yield: 76%. R_f=0.3 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=6.52 (s, 4H; $H_{arom.}$), 6.41 (s, 4H; $H_{arom.}$), 4.11 (sept., 2H; C$H(CH_3)_2$; J=6.0 Hz), 3.81–3.80 (m, 16H; 4O–CH_2), 3.76 (s, 4H; O–CH_2–), 3.55 (se, 8H; $4NH_2$), 3.46 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=13.5 Hz), 3.38 (d, 4H; ar–$H_\alpha CH_\beta$–ar, $J_{\alpha-\beta}$=13.5 Hz), 1.25 (d, 12H; CH_3, J=6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=149.6 (2C–O), 146.8 (2C–O), 140.6 (2C–NH_2), 139.9 (2C–NH_2), 134.3 (2$C_{arom.}$–CH_2), 133.8 (2$C_{arom.}$–CH_2), 118.42 (2$CH_{arom.}$), 118.0 (4$CH_{arom.}$), 73.3 (2$CH(CH_3)_2$), 72.3 (2CH_2–O), 71.9 (2CH_2–O), 71.6 (2CH_2–O), 71.4 (2CH_2–O), 69.7 (2CH_2–O), 36.7 (4ar–CH_2–ar), 22.6 (4CH_3); ESI-MS+: m/z measured at 903 $[M+Cs]^+$ (calcd for $C_{44}H_{58}N_4O_8Cs$).

4.2.10. 5,11,17,23-Tetramido-25,27-diisopropoxycalix[4]arene-26,28-crown-6 (11). $CAL(NH_2)_4$ **9** (60 mg, 77.8 μmol) is dissolved in 4 mL of DMF together with 31.2 mg of succinic anhydride (311 μmol). The reaction mixture is stirred overnight, evaporated and the 72 mg of product is used without further purification. Yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$), δ_H=12.03 (se, 2H; C(O)OH), 9.65 (s, 2H; C(O)NH), 9.60 (s, 2H; C(O)NH), 7.31 (s, 8H; $H_{arom.}$), 4.07 (sept., 2H; C$H(CH_3)$), 3.08–3.65 (OCH_2/ar–CH_2–ar), 0.79 (s, 12H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=173.3 (C(O)NH), 168.7 (C(O)OH), 151.3, 149.5 (C–O), 133.6, 132.8, 132.7, 132.4 ($C_{arom.}CH_2$/$C_{arom.}NH$), 120.0, 119.2 ($C_{arom.}H$), 69.6, 69.5, 69.2, 69.1, 68.3 (CH_2–O, $CH(CH_3)_2$), 38.3 (ar–CH_2–ar), 30.5, 28.6 (CH_{2succ}), 20.8 (CH_3); ESI-MS+: m/z measured at 1193.40 $[M+Na]^+$ (calcd for $C_{60}H_{74}N_4O_{20}Na$).

4.2.11. Calix di-β-CDmet (12). $CAL(succ)_2$ (83 mg, 88 μmol) was dissolved in 2 mL of DMF. DIC (109 μL, 705 μmol) and 95 mg of HOBt (705 μmol) were added successively. Then 249 mg of **4** (176 μmol) was added. After 30 h, the mixture was evaporated, diluted in CH_2Cl_2 and extracted with HCl 0.1 M. The product is purified on silica gel column, eluted with CH_2Cl_2, then CH_2Cl_2/MeOH 95:5,

to give 120 mg of the desired compound **12**. Yield: 35%. R_f=0.5 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ_H=9.61 (t, 2H; CONH), 7.61 (t, 2H; CONH), 7.33 (s, 4H; Ha), 6.99 (d, 4H; Hc), 6.74 (t, 2H; Hb), 5.21–5.03 (m, 14H; H-1_{CD}), 4.09 (m, 2H; C*H*CH_{3calix}), 3.57–3.83 (m; H-5_{CD}), 3.14–3.58 (H-6_{CD}/H-4_{CD}/H-3_{CD}/CH_2–O_{calix}/ar–CH_2–ar), 3.0–3.1 (m; H-2_{CD}), 0.75 (s, 12H; CH_{3calix}); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C=171.3, 169.4 (C(O)NH), 156.3, 149.8 (C–O), 134.0 ($C_{arom.}$NH), 133.2, 133.0 ($C_{arom.}CH_2$), 129.9 (C_c), 121.5 (C_b), 119.5 (C_a), 97.9–97.1 (C-1_{CD}), 81.0–79.0 (C-3_{CD}/C-2_{CD}/C-4_{CD}), 68.4–71.1 (C-6_{CD}/C-5_{CD}/CH_2–O_{calix}/*C*H$(CH_3)_{2calix}$), 60.3–60.8 (OCH_3-6_{CD}), 57.6–58.3 (OCH_3-3_{CD}/OCH_3-2_{CD}), 30.4 (CH_{2succ}), 21.2 (CH_{3calix}); MALDI-TOF MS: *m*/*z* measured at 3756.3 $[M+Na]^+$ (calcd for $C_{176}H_{282}N_4O_{80}Na$).

4.2.12. Calix tetra-β-CDmet (14). CAL(succ)$_4$ **11** (60 mg, 51 μmol) was dissolved in 5 mL of DMF. DIC (127 μL, 820 μmol) and 111 mg of HOBt (820 μmol) were added successively. Then 297 mg of **4** (210 μmol) was added. After 30 h, the mixture was evaporated, diluted in CH_2Cl_2 and extracted with HCl 0.1 M. The product is purified via silica gel column chromatography, eluted with CH_2Cl_2/acetone 1:1, then another column chromatography is done with CH_2Cl_2/MeOH 95:5 to give 217 mg of **14**. Yield: 63%. R_f= 0.5 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (500 MHz, DMSO-d_6), δ_H=9.61 (s, 2H; C(O)NH), 9.55 (s, 2H; C(O)NH), 7.61 (se, 4H; NH_{CD}C(O)), 7.24–7.34 (m, 8H; $H_{arom.}$), 5.00–5.22 (m; H-1_{CD}), 4.04 (m, 2H; CH$(CH_3)_2$), 3.64–3.75 (m; H-5_{CD}), 3.18–3.55 (H-6_{CD}/H-4_{CD}/H-3_{CD}/CH_2–O_{calix}/ar–CH_2–ar), 3.0–3.1 (m; H-2_{CD}), 2.30–2.50 (m; CH_{2succ}), 0.76 (s, 12H; CH_{3calix}); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C=97.7–97.9 (C-1_{CD}), 81.5–81.6 (C-3_{CD}), 81.1–81.2 (C-2_{CD}), 69.7–71.0 (C-6_{CD}/C-5_{CD}/CH_2–O_{calix}/*C*H$(CH_3)_{2calix}$), 60.6–60.7 (OCH_3-6_{CD}), 57.7–58.2 (OCH_3-3_{CD}/OCH_3-2_{CD}), 31.2 (CH_{2succ}), 21.1 (CH_{3calix}); MALDI-TOF MS: *m*/*z* measured at 6780.4 $[M+Na]^+$ (calcd for $C_{308}H_{510}N_8O_{152}Na$).

4.2.13. Calix di-β-CD (13) and calix tetra-β-CD (15). CAL(succ)$_n$ (n=2, 36 mg and n=4, 24 mg) was dissolved in 4 mL of DMF. DIC (for **13**, 47 μL and for **15**, 51 μL) and HOBt (for **13**, 41 mg and for **15**, 44 mg) were added successively. Then **5** (for **13**, 91.1 mg and for **15**, 95.3 mg) dissolved in DMF was added. After three days, the mixture was evaporated, diluted in water and precipitated in acetone. The residues were dialysed with ester cellulose membrane MWCO=2000 for **13** and MWCO=3000 for **15**. MALDI-TOF spectra proved the existence of compound **19** ($[M+Na]^+$, 2372.6) in the synthesis of compound **13**, 3195.4 $[M+Na]^+$. For synthesis of compound **15**, presence of 2373 $[M+Na]^+$ of compound **19**, 5657.1 $[M+Na]^+$ of compound **15** and partially substituted calixarene structures such as 3433.9 (calix di-β-CD disucc) and 4523.0 (calix tri-β-CD monosucc) was detected.

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4,4′-Substituted biphenyl coronands. Preparation of a new selective fluorescent sensor for mercury salts

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Abstract—Six new 4,4′-substituted biphenyl coronands have been prepared. The ligands containing dimethylamino groups in the biphenyl moiety have been used in transition metal cations' complexation and one of them (**3**) has demonstrated to be a selective fluorescent sensor for mercury. Stoichiometries of the formed complexes and complexation constants have been determined by titration experiments. In addition, the extractant ability of some ligands has also been studied. Finally, the electrochemical properties of some of these ligands are also described.

1. Introduction

Molecular systems that combine binding ability and photochemical or photophysical properties are of great interest for designing chemosensors.[1] Recently it has been established that conformational restriction is a viable mechanism for transducing ion binding into enhanced fluorescence emission in organic fluorophores.[2] Among the systems studied it is possible to find biphenyl and bipyridyl derivatives that experiment fluorescence enhancement after complexation. It is well established that more rigid fluorophores are more fluorescent[3] even though this restriction is due to complex formation.[4] On the other hand, it is also known that substituents in the biphenyl systems have strong influence on its fluorescent properties.[5] For all these reasons, we have been interested in using the 4,4′-bis(*N*,*N*-dimethylamino)-biphenyl (TMB, tetramethylbenzidine) subunit in the design and synthesis of red-ox and fluorescent sensors.[6] In particular our interest has been directed toward the preparation of crown ether and azacrown ether derivatives covalently attached to the 2,2′ position of TMB[7] and their use as fluorescent and red-ox chemosensors. Among all the possible target cations our interest has been mainly directed toward Cd^{2+}, Hg^{2+} and Pb^{2+} because they are highly toxic environmental pollutants and they are generated from both natural and industrial sources. In addition Zn^{2+} has been also studied due to its electronic configuration that makes it similar to Cd^{2+} and Hg^{2+}.

The studied ligands are shown in Chart 1 and in addition to the TMB moiety they contend an *ortho*-disubstituted benzene system. The presence of this additional aromatic ring has the goal of increasing the rigidity of the cavity to improve cation selectivity. In addition, several heteroatoms and functional groups are present in these ligands to study the influence of the donor atom nature.

On the other hand, solvent extraction belongs to one of the most important processes in water treatment and the use of complexing agents plays an important role in such processes. In solvent extraction of metallic ions it is possible to use a variety of ligands as extracting agents and among

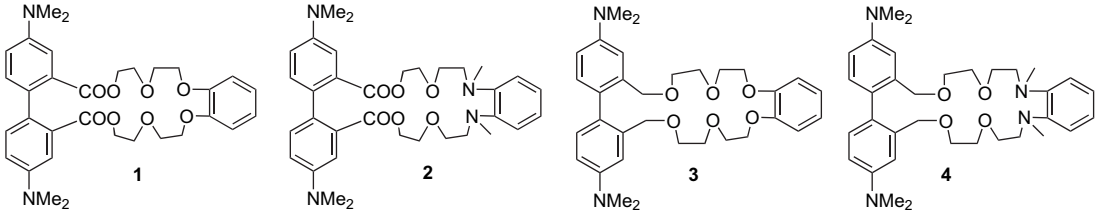

Chart 1.

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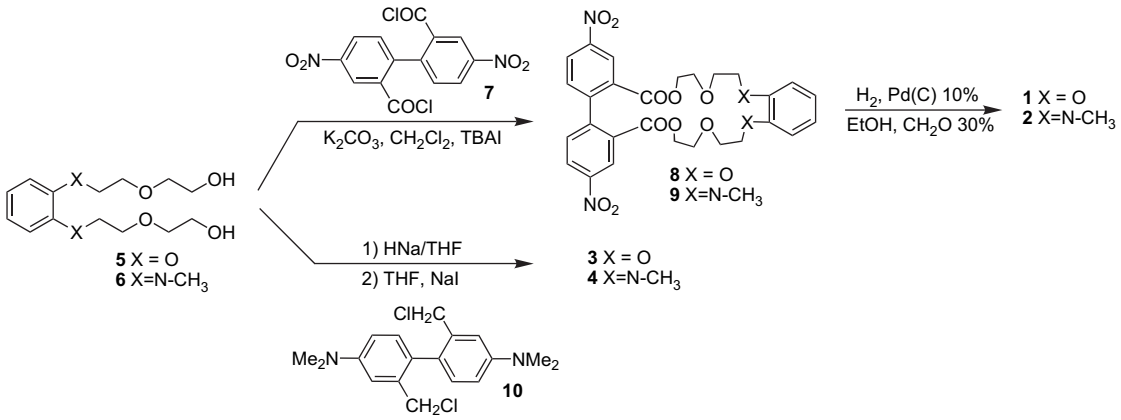


Scheme 1.

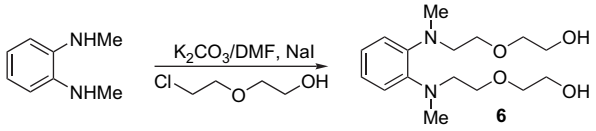
these complexing agents, macrocyclic polyethers have been widely used and the strong influence of the ligand topology on the extraction efficiency has been well established.[8] For this reason, we have been also interested in evaluating the ability of the prepared ligands in cation extraction.

2. Results and discussion

2.1. Synthesis

Ligands **1** and **2** were easily prepared as described in Scheme 1 starting, respectively, from 2,2′-bis(chlorocarbonyl)-4,4′-dinitrobiphenyl (**7**)[9] and the corresponding phenyl derivative compounds **8** and **9** could be isolated. Reductive amination of the nitro groups gave rise to the corresponding dimethylamino ligands **1** and **2**, respectively, almost with quantitative yields. On the other hand, direct reaction between 4,4′-bis(dimethylamino)-2,2′-bis(chloromethyl)biphenyl (**10**)[7] and the corresponding chains gave rise to **3** and **4**.

To carry out the syntheses described above, compound **5** was prepared from catechol as is described in the literature.[10] The synthesis of **6** was accomplished from *o*-*N*,*N*′-dimethylphenylenediamine[11] by alkylation with 2-[2-chloroethoxy]-ethanol (Scheme 2).



Scheme 2.

2.2. Complexation studies

Due to the presence of the TMB moiety in the prepared ligands, they present fluorescent properties. The influence of the cyclic systems directly bound to the 2,2′ positions of the TMB gives rise to the expected changes in the emission bands.[12] Thus, **1** and **2** present the emission band at λ_{max}=487 and 481 nm, respectively, whereas both **3** and **4** show values of 372 nm.

Complexation experiments were carried out in CH_3CN with solutions of Zn^{2+}, Cd^{2+}, Pb^{2+}, Ni^{2+}, Hg^{2+} as triflate salts. The results obtained with ligands **1**, **2** and **4** and all the studied cations were very similar, since a quenching of the fluorescence was observed after the salt addition (results obtained for ligand **4** are reflected in Fig. 1, as an example; for the other ligands, refer to Supplementary data). This behaviour could be due not only to the presence of the transition metal cation in the solution,[13] but also to the modifications in the dihedral angle between both aromatic rings or the conformational restriction induced by the complexation event.[14]

By contrast ligand **3** showed a more interesting behaviour when complexation experiments were carried out with the studied salts. Thus, even though all the cations are complexed by the ligand the fluorescent properties in each case were different. Three types of fluorescent behaviours were observed with this ligand (Fig. 2 for Zn^{2+}, Cd^{2+} and Hg^{2+} and Supplementary data for Ni^{2+} and Pb^{2+}) the most interesting result being those obtained with Hg^{2+}. In the presence of this cation a new band at λ=464 nm that could be attributed to the formation of intermolecular excimers[15,12] appears. Oppositely, Cd^{2+} and Ni^{2+} did not give rise to any modification of the fluorescence and the intensity of the new band was very small in the presence of Zn^{2+} and Pb^{2+}.

The different behaviour observed in the presence of Hg^{2+} makes compound **3** able to act as a selective fluorescent sensor for this cation. As Zn^{2+}, Cd^{2+} and Hg^{2+} have the same electronic configuration, selectivity experiments were

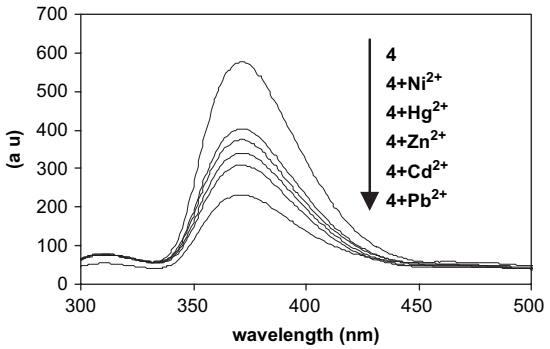


Figure 1. Fluorescent response of ligand **4** in CH_3CN in the presence of 1 equiv of Ni^{2+}, Hg^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} as triflate salts.

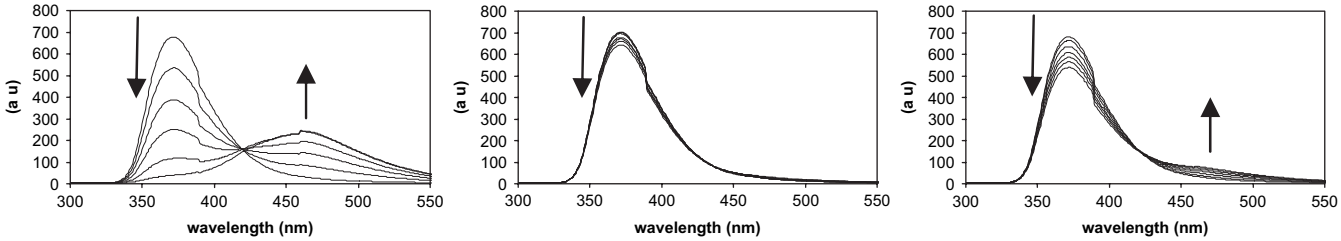


Figure 2. (From left to right) Complexation experiments with ligand **3** in CH_3CN with Hg^{2+}, Cd^{2+} and Zn^{2+}, all of them as triflate salts.

carried out with an equimolecular mixture of these three cations. The results obtained with the mixture were the same observed in the presence of pure Hg^{2+} samples (Fig. 3).

Titration experiments with the different cations using fluorescence showed that the stoichiometries of the formed complexes were always 1:1 (see Supplementary data). Complexation constants for these complexes were determined as described in Section 4 and they are reflected in Table 1.

The values of the complexation constants suggest that substitution of the ester groups for the corresponding ether groups gives rise to very small changes in Ni^{2+} and Zn^{2+} complexation and slightly larger in Cd^{2+} complexation. On the other hand, complexation of Hg^{2+} and Pb^{2+} was stronger with **3** ($\log K$=6.8±0.4 and 6.2±0.2, respectively) than with **1** ($\log K$=5.6±0.2 and 5.3±0.1, respectively) but shows the opposite tendency when **2** ($\log K$=6.3±0.4 and 6.2±0.2, respectively) and **4** ($\log K$=4.9±0.2 and 5.9±0.1, respectively) were compared. When complexation constants with ligands **3** and **4** were compared it was observed that substitution of oxygen by nitrogen atoms gives rise to stronger complexes with Ni^{2+} and Cd^{2+} and keeping similar strength with Zn^{2+}. The opposite behaviour was observed with Pb^{2+} and even more with Hg^{2+}. This behaviour agrees with both the preference of Hg^{2+} for being complexated by crown ether containing six oxygen atoms[16] and the usual coordination properties in divalent lead complexes.[17]

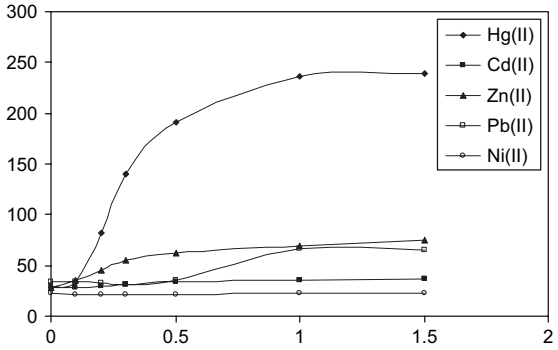


Figure 3. Effect of 1 equiv of metal ions on the emission at 470 nm for solutions of **3** (3.0×10^{-5} M) in acetonitrile.

Table 1. Complexation constants ($\log K$) for ligands **1**–**4** in acetonitrile determined by fluorescence titrations

	Ni^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	Pb^{2+}
1	5.1±0.5	5.9±0.3	5.8±0.2	5.6±0.2	5.3±0.1
2	6.1±0.4	5.8±0.3	5.4±0.3	6.3±0.4	6.2±0.2
3	5.7±0.5	5.9±0.2	5.7±0.2	6.8±0.4	6.2±0.2
4	6.9±0.3	5.6±0.2	7.0±0.5	4.9±0.2	5.9±0.1

2.3. Extraction experiments

Extraction experiments were carried out with ligands **2**, **4**, **8** and **9** that were chosen to study the influence of different functional groups in extraction ability. Thus, comparison between ligands **2** and **4** results allows knowing the influence that ester or ether groups have in extraction properties. The preliminary extraction experiments were carried out with alkaline cations as their picrate salts. Extraction constants for these ligands determined by using the Cram's method are shown in Table 2.[18]

As can be seen in Figure 4 substitution of ester by ether groups gives rise to a big increase of the extraction properties. This behaviour could be related to two factors: (a) the higher flexibility and size showed by the cavity and (b) the much more donor character of the ether oxygen atom. Comparison between ligands **2** and **9** demonstrates that the type of substitution in the biphenyl moiety has a very small influence on extraction of Li^+ and Na^+. However, larger effects were observed with Cs^+ and even more with K^+. Thus the extraction constants for these cations were around 20 and 10 times higher, respectively, when ligand **9** was used. One explanation to this fact can be found in the higher

Table 2. $-\log K_e$ (water/chloroform) determined by using Cram's method

	2	**4**	**8**	**9**
Li^+	2.46	4.77	4.76	2.83
Na^+	2.38	4.75	4.66	2.75
K^+	2.77	5.19	4.52	4.05
Cs^+	2.13	3.79	4.13	3.22

All the salts were picrates.

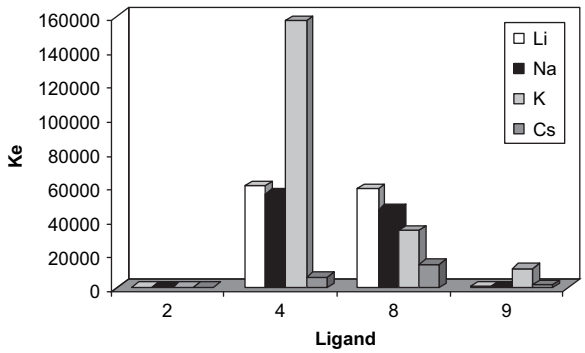


Figure 4. Comparison of alkaline cation extraction (water/chloroform) with ligands **2**, **4**, **8** and **9**.

lipophilic character of the nitro group, which is an important point for the extraction properties.

Finally, comparison between ligands **8** and **9** indicates that substitution of nitrogen atoms by oxygen atoms give rise to higher extraction, which can be related to the hard character of the alkaline cations that make stronger interactions with the harder oxygen atoms than the softer nitrogen atoms. In addition, ligand **4** extracts preferably K^+ that agrees with the relation cavity size/cation radium. By contrast, both ligands **8** and **9** show a small K^+ extraction that could be related to the smaller cavity of this ligand due to the presence of the two ester groups. As it is shown in Figure 4, extraction of Li^+ by ligands **4** and **8** is very similar. The small size of this cation allows it to form strong complexes using only four oxygen atoms. For this reason it fits as well in ligand **4** as in ligand **8**.

2.4. Electrochemical experiments

The electrochemical response of compound **4** in MeCN solution has been studied, as well as the electrochemistry of such macrocyclic receptor in the presence of an excess of different metal ions, namely, Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Ni^{2+} and Zn^{2+}. The electrochemical response at glassy carbon and platinum electrodes is dominated by two successive one-electron-transfer processes involving the oxidation of the diaminobiphenyl moiety above +1.0 V versus AgCl/Ag. The obtained results were compared with those previously reported for ligand **11**[7] (Chart 2) and the corresponding potential data are shown in Table 3.

As shown in Figure 5, corresponding to a 10^{-3} mM solution of **11** in 0.10 M Bu_4NPF_6/MeCN, the CV response of that receptor at platinum electrode consists of three overlapped anodic peaks at +0.74 (Ia), +0.92 (IIa), and +1.09 V (IIIa) coupled with their cathodic counterparts at +0.72 (Ic), +0.84 (IIc). The voltammetric profile varies slowly with the potential scan rate and remains essentially identical for

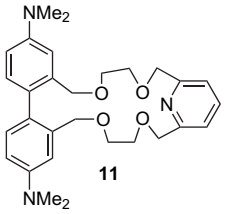


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Chart 2.

Table 3. Peak potential data in V versus AgCl/Ag for ligands **4** and **11** in MeCN solution (0.10 M Bu_4NPF_6)

Ligand	Anodic peaks			Cathodic peaks		
	Ia	IIa	IIIa	Ic	IIc	IIIc
4	+0.62	+0.91	—	+0.51	+0.74	—
4+K^+	+0.58	+0.82	—	+0.49	+0.67	—
4+Zn^{2+}	+0.85		+1.02	+0.75		+0.96
4+Cd^{2+}	+0.88		+1.04	+0.85		0.99
11	+0.74	+0.92	+1.09	+0.72	+0.84	—
11+Zn^{2+}	+0.81		—	+0.72		—
11+Cd^{2+}	+0.86		—	+0.77		—

From CVs at 100 mV/s at platinum electrode.

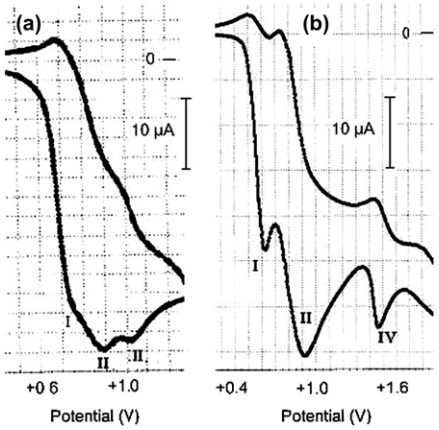

Figure 5. CVs of (a) a 2.0 mM **11** solution in 0.10 M Bu_4NPF_6/MeCN. (b) A 2.0 mM **4** solution in 0.10 M Bu_4NPF_6/MeCN. Potential scan rate 100 mV/s.

experiments performed at glassy carbon electrodes, thus denoting that no adsorption processes occur. The voltammetric behaviour at platinum and glassy electrodes in DMSO solutions was almost identical to that described in MeCN. All three pairs Ia/Ic, IIa/IIc and IIIa/IIIc, can be described as essentially reversible one-electron-transfer processes as judged by the variation of anodic-to-cathodic peak potential separation with the potential scan rate, $E_{pa}-E_{pc}$. The value of this parameter tends to 60 mV at low sweep rates, as expected for a one-electron reversible process. The response of this bis(dimethylamino)biphenyl-containing receptor is consistent with that reported for the oxidation of aromatic compounds.[19] Thus, the parent neutral ligand, L, is reversibly oxidized to the corresponding radical cation $L^{\bullet+}$ and a dication, L^{2+}, in two successive one-electron-transfer steps. Consistently, the value of the peak current function (peak current/(sweep rate)$^{1/2}$) determined for the receptors studied here was almost identical to that reported for different biphenyl-type receptors at the same concentration. These correspond to the Ia/Ic and IIa/IIc couples. The presence of an additional couple IIIa/IIIc is rationalized taking into account that the overall oxidation process is accompanied by a significant stereochemical modification: there is a transition from the dihedral neutral molecule, to the planar dication. Accordingly, the first electron-transfer step yields a nonplanar cation radical ($L^{\bullet+}$) that undergoes to some extent a relatively slow pre-organization process.[20] Under similar conditions, ligand **4** shows the Ia/Ic (0.62 V) and IIa/IIc (0.91 V) couples but not the pair IIIa/IIIc. The absence of these peaks suggests that the oxidation process of ligand exclusively occurs through the nonplanar dication. In addition, a new couple (IVa/IVc) around 1.5 V due to the oxidation of the *o*-phenylenediamine appears (Fig. 5b).

The most remarkable facts for compounds **11** and **4** were their different behaviours in the presence of Zn^{2+} and Cd^{2+}. For ligand **11**, the preferred way for the oxidation was through the nonplanar radical cation and thus, peak III disappeared totally and overlapping of peaks II and I was observed. The small size of this ligand precludes the rotation toward the planar radical cation. By contrast, the larger size of ligand **4** allows the transition metal cations to be located close to the softer nitrogen atoms of the *o*-phenylenediamine moiety and now the oxidation through the planar geometry is

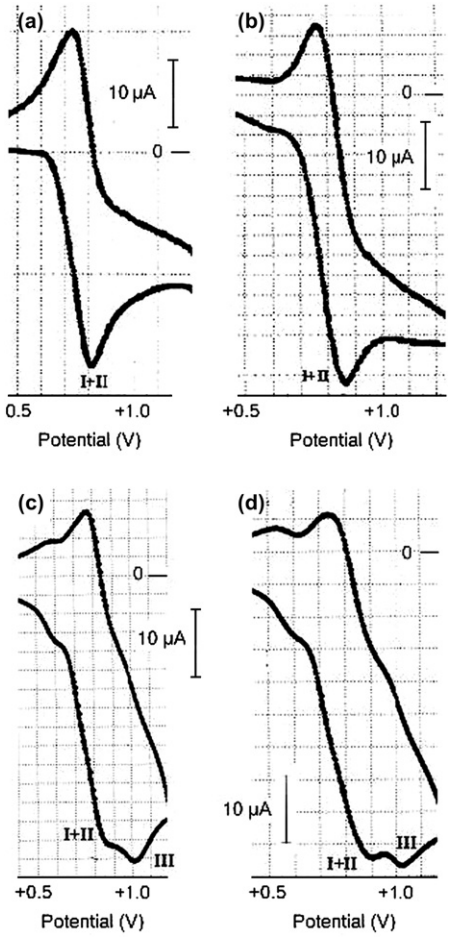

Figure 6. CVs of (a) a 2.0 mM **11**+4 times excess of Zn^{2+} solution in 0.10 M Bu_4NPF_6/MeCN. (b) A 2.0 mM **11**+4 times excess of Cd^{2+} solution in 0.10 M Bu_4NPF_6/MeCN. (c) A 2.0 mM **4**+4 times excess of Zn^{2+} solution in 0.10 M Bu_4NPF_6/MeCN. (d) A 2.0 mM **4**+4 times excess of Cd^{2+} solution in 0.10 M Bu_4NPF_6/MeCN. Potential scan rate 100 mV/s.

possible (Fig. 6). When the cation is large enough to be coordinated by the six donor atoms (for example, K^+, radio 1.33 Å) the dihedral/planar interconversion of the radical cation is precluded and only peaks I and II appear in the cyclovoltamogramme (Fig. 7).

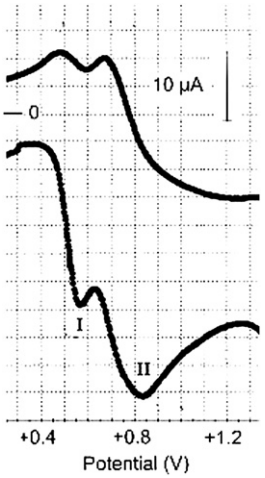

Figure 7. CVs of a 2.0 mM **4**+K^+ solution in 0.10 M Bu_4NPF_6/MeCN. Potential scan rate 100 mV/s.

3. Conclusions

Several new coronands derived from 4,4′-disubstituted biphenyl have been synthesized. Extraction experiments with alkaline cations demonstrated that these ligands showed the expected behaviour. Thus, ligand **4** was the best extractant for potassium salts. In relation to the electrochemical properties of the studied ligands, it is possible to conclude that the oxidation mechanism is strongly dependent on the cation and the cavity size. Thus, with small cations or with soft cations that are close to the nitrogen atoms the planar radical cation can be observed. By contrast with larger cations like K^+ the formation of this type of cation radical is precluded and consistently with that coordination, the couple IIIa/IIIc disappears.

In relation to the sensing properties of these ligands we can conclude that **3** showed to be a selective fluorescent sensor for Hg^{2+}. The new band observed in the fluorescent spectra of this ligand in the presence of mercury salts can be related to the formation of an excimer as it has been observed in other related compounds. Finally, it can be concluded that the presence of six oxygen atoms in the cavity gives rise to the stronger complexes with this mercury whereas ligand **4** where two oxygen atoms have been substituted by nitrogen give rise to its stronger complexes with Cd^{2+} and Ni^{2+}.

4. Experimental

4.1. General methods

All commercially available reagents were used without further purification. Water sensitive reactions were performed under argon. Column chromatography was carried out on silica gel Merck 60 (230–400 mesh) and on SDS activated neutral aluminium oxide (0.05–0.2 mm; activity degree 1). IR spectra were recorded on a Perkin–Elmer 1750 FT-IR and a Bruker Equinox 55 FT-IR. NMR spectra were recorded with Bruker Avance 300/500 and Varian Unity-300/400 spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Spectra were referenced to residual undeuterated solvent. High resolution mass spectra were taken with a Fisons VG-AUTOSPEC and those using the electrospray ionizing technique were recorded on an HPLC-MS with ion trap Bruker 3000-Esquire Plus. UV spectra were run at 20 °C (thermostated) on a Shimadzu UV-2102 PC. Fluorescence spectra were carried out in a Varian Cary Eclipse Fluorimeter.

4.1.1. Synthesis of *N*,*N*′-dimethyl-*N*,*N*′-bis(ethoxyethanol)-*o*-phenylenediamine (6). *N*,*N*′-Dimethyl-*o*-phenylenediamine (2.795 g, 20.4 mmol) was added over a solution of 2-(2-chloroethoxy)ethanol (17.2 ml, 204 mmol), potassium carbonate (18 g, 130.5 mmol) and sodium iodide (5 mg) in dry toluene (160 ml). The mixture was refluxed using a Dean–Stark until the thin layer chromatography did not show starting material (72 h). After the reaction was finished, the mixture was allowed to cool at room temperature and filtered off. Solvent was evaporated under reduced pressure and the remaining oil was distilled (230 °C, 0.4 mmHg) to give **6** as a yellow oil (5.601 g, 88%). IR (KBr): 3350 (OH), 2859, 1588 (C=C), 1493, 1449, 1118 (C–O–C), 748 cm^{-1}.

^{1}H NMR ($CDCl_3$) δ (ppm): 6.92 (4H, m, Ar–H), 3.64 (4H, t, J=5.9 Hz, CH_2–O), 3.59 (4H, t, J=5.9 Hz, CH_2–O), 3.48 (4H, t, J=5.9 Hz, CH_2–OH), 3.42 (4H, t, J=5.9 Hz, CH_2–NR_2), 2.8 (6H, s, N–CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.0, 122.0, 119.2, 72.3, 68.5, 61.5, 52.4, 40.3. HRMS (EI): M^+ calcd for $C_{16}H_{24}N_2O_4$ 312.2050; found 312.2037.

4.1.2. Synthesis of 2,2′-(4,4′-dinitrobiphenyl)-10,11-benzo-2,19-dicarboxy-22-crown-6 (8). The reaction was carried out under dry conditions. Two solutions were prepared.

Solution A: 1,2-Bis(5-hydroxy-3-oxy-1-pentyloxy)benzene **5** (0.286 g, 1 mmol) in dry dichloromethane (18 ml).

Solution B: 4,4′-Dinitro-2,2′-bis(chlorocarbonyl)-biphenyl (**7**) (0.406 g, 1.1 mmol) in dry dichloromethane (18 ml).

Both solutions were added dropwise, simultaneously and at the same rate over a stirring, cold (0 °C) solution of anhydrous potassium carbonate (0.692 g, 5 mmol) and tetrabutylammonium iodide (4 mg) in dry dichloromethane (165 ml). The solution was stirred during 5 days at room temperature. Then, the suspension was filtered off, washed with ethyl acetate and the solvent was evaporated under vacuum. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH 99:1) gave **8** as an orange oil (0.214 g, 37%). IR (KBr): 3418, 2928 (CH_2), 1731 (C═O), 1607 (C═C), 1504 (N═O), 1360 (N═O), 746 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.90 (2H, d, J=2.1 Hz, Ar–H), 8.43 (2H, dd, J_1=2.1 Hz, J_2=8.1 Hz, Ar–H), 7.42 (2H, d, J=8.1 Hz, Ar–H), 6.90–6.82 (4H, m, Ar–H), 4.36–4.20 (4H, m, CH_2–O), 4.11–4.06 (4H, m, CH_2–O), 3.76–3.58 (8H, m, CH_2–O). ^{13}C NMR ($CDCl_3$) δ (ppm): 149.3, 147.8, 131.4, 131.2, 126.8, 125.9, 123.5, 122.2, 120.4, 115.1, 70.1, 69.6, 69.1, 65.7. HRMS (EI): M^+ calcd for $C_{28}H_{26}N_2O_{12}$ 582.1486; found 582.1483.

4.1.3. Synthesis of 2,2′-TMB-10,11-benzo-22-crown-6 (1). An heterogeneous solution of **8** (0.384 g, 0.66 mmol), formaldehyde (0.3 ml, 30% in water) and Pd/C 10% (0.1 g) in anhydrous ethanol (50 ml) was stirred under hydrogen (30 lib/inch^2). The mixture was followed by thin layer chromatography until the reaction was finished (45 min), then the reaction was filtered off and the solid was washed with HCl 10%. The aqueous layer was basified accurately with potassium carbonate, extracted with ethyl acetate (3×25 ml) and washed with brine. Organic layers were joined, dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give compound **1** as a yellow-orange solid without further purification (0.323 g, 85%). Mp: 66–68 °C. IR (KBr): 3060, 2874, 1722 (C═O), 1608 (C═C), 1503, 1255 (C–O), 741 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.28 (2H, d, J=2.8 Hz, Ar–H), 7.09 (2H, d, J=9.0 Hz, Ar–H), 6.92–6.82 (6H, m, Ar–H), 4.24 (4H, t, J=5.1 Hz, CH_2–O), 4.09 (4H, m, CH_2–O), 3.75 (4H, m, CH_2–O), 3.61 (4H, m, CH_2–O), 2.96 (6H, s, $(CH_3)_2$–N). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.9, 149.5, 142.4, 132.1, 131.1, 122.0, 122.0 115.6, 115.0, 113.9, 70.0, 69.7, 69.5, 64.5, 40.9. HRMS (EI): M^+ calcd for $C_{32}H_{38}N_2O_8$ 578.2628; found 578.2628.

4.1.4. Synthesis of 2,2′-(4,4′-dinitrobiphenyl)-*N*,*N*′-dimethyl-2,19-dicarboxy-9,12-diaza-10,11-benzo-22-crown-6 (9). Using the same procedure employed in the preparation of **8**, *N*,*N*′-dimethyl-*N*,*N*′-bis(ethoxyethanol)-*o*-phenylenediamine (**6**) (0.395 g, 1.27 mmol) and 4,4′-dinitro-2,2′-bis(chlorocarbonyl)-biphenyl **7** (0.467 g, 1.27 mmol) gave ligand **9** after chromatographic purification (neutral alumina, CH_2Cl_2/MeOH 97:3) as a pale brown oil (0.1338 g, 18%). IR (KBr): 3005, 2867, 1727 (C═O), 1608 (C═C), 1524 (N═O), 1348 (N═O), 1270, 1122, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.96 (2H, d, J=2.4 Hz, Ar–H), 8.44 (2H, dd, J_1=2.4 Hz, J_2=8.4 Hz, Ar–H), 7.38 (2H, d, J=8.4 Hz, Ar–H), 6.92 (4H, m, Ar–H), 4.19 (4H, t, J=4.5 Hz, CH_2OOC), 3.54–3.29 (12H, m, CH_2–N+CH_2–O), 2.75 (6H, s, $(CH_3)_2N$). ^{13}C NMR ($CDCl_3$) δ (ppm): 164.7, 148.1, 147.8, 145.8, 131.1, 130.9, 126.6, 122.5, 119.8, 119.8, 69.0, 68.4, 65.5, 53.1, 40.3. HRMS (EI): M^+ calcd for $C_{30}H_{32}N_4O_{10}$ 608.2118; found 608.2155.

4.1.5. Synthesis of 2,2′-TMB-*N*,*N*′-dimethyl-2,19-dicarboxy-9,12-diaza-10,11-benzo-22-crown-6 (2). Following the same procedure employed in the synthesis of **1**, ligand **9** (0.2137 g, 0.35 mmol) by reductive methylation, gave compound **2** as a yellow oil without further purification (0.167 g, 80%). IR (KBr): 3002, 2868, 1714 (C═O), 1613 (C═C), 1495, 1125, 752 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.23 (2H, d, J=8.4 Hz, Ar–H), 6.92 (4H, m, Ar–H), 6.88 (2H, d, J=3 Hz, Ar–H), 6.64 (2H, dd, J=8.4 Hz, J=3 Hz, Ar–H), 4.68 (4H, dd, CH_2OOC), 4.17 (4H, dd, O–CH_2CH_2OOC), 3.67–3.34 (8H, CH_2–O+CH_2–N), 2.97 (12H, s, CH_3N), 2.95 (6H, s, CH_3N). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.7, 144.8, 132.6, 132.2, 125.9, 123.1, 117.0, 117.0, 107.2, 106.3, 69.0, 66.2, 64.6, 64.3, 39.2, 35.8. HRMS (EI): M^+ calcd for $C_{34}H_{44}N_4O_6$ 604.3261; found 604.3232.

4.1.6. Synthesis of 2,2′-TMB-10,11-benzo-22-crown-6 (3). In a two-neck round bottom flask, under argon, a stirred solution of 1,2-bis(5-hydroxy-3-oxy-1-pentyloxy)benzene (**5**) (0.286 g, 1 mmol) and NaH 60% mineral oil (0.120 g, 3 mmol) in THF (50 ml) was refluxed for 2 h. 2,2′-Bis(chloromethyl)-4,4′-bis(dimethylamine)biphenyl (**10**) (0.335 g, 1 mmol) and sodium iodide (5 mg) in THF (50 ml) was added dropwise over this solution. The mixture was heated for 48 h and quenched with water. THF was removed under vacuum, the aqueous layer was extracted with ethyl acetate (3×25 ml) and organic layers were washed with brine, dried with anhydrous sodium sulfate and evaporated under reduced pressure. Column chromatography (silica gel, EtOAc to EtOAc/MeOH 95:5) gave compound **3** as pale yellow oil (0.2036 g, 37%). IR (KBr): 3080, 2867 (CH_3, CH_2), 1681 (C═O), 1608 (C═C), 1126 (C–O–C), 744 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 6.93 (2H, d, J=8.5 Hz, Ar–H), 6.87 (6H, m, Ar–H), 6.67 (2H, dd, J_1=2.5 Hz, J_2=8.5 Hz, Ar–H), 4.35 (4H, s, CH_2–O), 4.11 (4H, t, J=3.9 Hz, CH_2–O), 3.83–3.49 (12H, m, CH_2–O), 2.96 (12H, s, $(CH_3)_2N$). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.2, 149.5, 137.9, 131.4, 128.6, 121.9, 114.9, 112.7, 111.7, 71.8, 71.2, 70.3, 70.1, 69.8, 41.1. HRMS (EI): M^+ calcd for $C_{32}H_{42}N_2O_6$ 550.3043; found 550.3056.

4.1.7. Synthesis of 2,2′-TMB-*N*,*N*′-dimethyl-9,12-diaza-10,11-benzo-22-crown-6 (4). Proceeding as in the synthesis of **3**, *N*,*N*′-dimethyl-*N*,*N*′-bis(ethoxyethanol)-*o*-phenylenediamine (**6**) (0.312 g, 1 mmol) and 2,2′-bis(chloromethyl)-4,4′-bis(dimethylamine)biphenyl (**10**) (0.335 g, 1 mmol) gave compound **4** after chromatographic purification (neutral alumina, hexane/EtOAc 50:50 to EtOAc) as a brown oil

(0.276 g, 48%). IR (KBr): 3080, 2852, 2792, 1607.82, 1493 (C=C), 1448, 1347, 1118, 1090 and 804 (C–N) cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 6.94–6.89 (8H, m, Ar–H), 6.67 (2H, dd, J_1=3.0 Hz, J_2=8.4 Hz, Ar–H), 4.33 (4H, s, CH_2–O), 3.58–3.42 (12H, m, CH_2–O), 3.3 (4H, t, J=6.6 Hz, CH_2–N), 2.96 (12H, s, $(CH_3)_2N$), 2.73 (6H, s, CH_3–N). ^{13}C NMR ($CDCl_3$) δ (ppm): 150.2, 145.9, 138.0, 131.3, 128.4, 122.4, 119.7, 112.3, 111.6, 71.7, 70.5, 70.0, 69.2, 53.3, 41.1, 40.4. HRMS (EI): M^+ calcd for $C_{34}H_{48}N_4O_4$ 576.3675; found 576.3679.

4.2. Fluorescence titrations with cations. General procedure

The spectrum of free ligand (3.0 ml, 10^{-5} M) in acetonitrile was recorded. Then, an aliquot of a solution 10^{-3} M in the metallic salt and 10^{-5} M in the ligand was added (0.1 equiv), the mixture was stirred for 30 s and the spectrum was recorded. This procedure was repeated several times until the concentration of the salt was larger than the ligand and no variation of the signals was observed. The plot of the variation of the absorbance/emission versus the ratio between the salt and the complex gave the titration curve and so the stoichiometry of the complex. The constant value was calculated making use of the program Specfit.[21]

4.3. Electrochemical experiments

Electrochemical measurements were performed at 298 K in a conventional three-electrode cell under argon atmosphere. Nominal ca. 2.0 mM concentrations of the ligand were used in dry MeCN and DMSO using tetrabutylammonium hexafluorophosphate (0.10 M) as a supporting electrolyte. A 4 times excess of metallic salts was used in each case (triflate salts for the transition metal cations and perchlorate for alkaline cations). Experiments were performed using a BAS CV 50 W equipment using a BAS MF2012 glassy carbon electrode (GCE) (geometrical area 0.071 cm^2), and a BAS MF2014 platinum electrode (geometrical area 0.018 cm^2) as a working electrode. A platinum wire auxiliary electrode and a AgCl (3 M NaCl)/Ag reference electrode separated from the test solution by a salt bridge only containing supporting electrolyte completed the electrode arrangement. The potential of such reference electrode was −35 mV versus the saturated calomel reference electrode (SCE).

4.4. Extraction experiments

These experiments were carried out as described in Ref. 9.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.084.

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On the reactivity of 2-alkyl-1,3-thiazolium-4-olates toward electrophiles

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Dedicated to the memory of Professor Marcial Moreno-Mañas

Abstract—On the basis of our synthetic methodologies employing mesoionic synthons, the nucleophilic character of 2-alkyl-1,3-thiazolium-4-olates (2-alkylthioisomünchnones) has been envisaged and developed, at the expenses of their common role as masked 1,3-dipoles. Reactions with aliphatic acid chlorides lead to monoketones derived from thiazolidin-4-ones, whose structure can be rationalized in terms of orbital interactions by computational studies. Aromatic acid chlorides invariably produce 1,3-dicarbonyl compounds, yet maintaining the mesoionic core. Unlike [3+2]-cycloadditions reported previously for thioisomünchnones with isocyanates and isothiocyanates, these heterocumulenes react with 2-alkylthioisomünchnones affording conjugated amides or thioamides.

1. Introduction

The mesoionic heterocycles have become useful and versatile synthons en route to varied and functionalized heterocyclic systems or advanced materials with extended conjugation.[1,2] The reactivity stems from their masked 1,3-dipolar character, thus interacting with a wide range of dipolarophiles in cycloaddition reactions. In some cases, such as in our previously reported selective reactions with 1,3-thiazolium-4-olates (thioisomünchnones), the mesoionic ring triggers a sequential process in which the initial cycloadduct is not stable enough and undergoes further ring opening leading to novel heterocyclic or acyclic structure. The protocol can be tailored by a careful choice of the substitution pattern on the mesoionic ring.[1]

In general, the presence of aromatic groups largely stabilizes the mesoionic system and has a profound effect on the dipolar character. An acyl group at a vicinal position to the exocyclic heteroatom markedly decreases the ability of these dipolar species as cycloadditive partners. Conversely, an electron-releasing substituent at C-2 not only enhances rates, but it is also responsible for the subsequent cycloadduct evolution.[1,3] It is therefore surprising that the scarce number of monocyclic mesoionics alkylated at C-2. The first derivative of a 2-methylthioisomünchnone was reported by Robert et al. in 1978 proving spectroscopically that this substance coexists in solution with its non-mesoionic tautomer of 2-methylenethiazolidine-4-one.[4]

Recently, we envisaged the possibility of generating other alkylated derivatives of thioisomünchnones at C-2 and set out to prepare them. Their tautomeric equilibria were equally elucidated by spectroscopy and computation.[5] The present study is aimed at exploring the reactivity of 2-alkylthioisomünchnones against a range of electrophiles that include acid chlorides, isocyanates, and isothiocyanates and demonstrating the methodology can be an efficient diversity oriented functionalization in organic synthesis.

2. Results and discussion

In a logical fashion theory should be preceding experiments. Our preliminary calculation of the charge distribution, at the B3LYP/6-31G(d) level of theory, of 2-methyl-1,3-thiazolium-4-olate (**1**) and its tautomer 2-methylenethiazolidine-4-one (**2**) (Scheme 1) reveals the nucleophilic character of the exocyclic carbon at C-2 of both heterocycles. The nucleophilicity manifests itself regardless of the computational methodology employed to estimate the charges (Table 1):[6] Mulliken population analysis (MPA), natural population analysis (NPA), electrostatic potential-derived charges using

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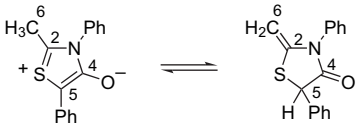
the CHelpG scheme of Breneman (CHelpG), or electrostatic potential-derived charges using the Merz–Kollman–Singh algorithm (MKS).



1 **2**

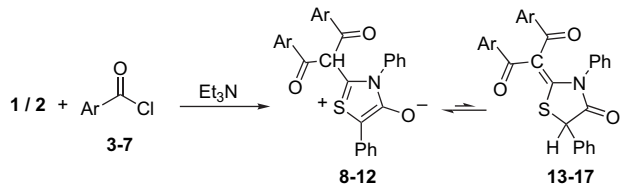
Scheme 1.

Table 1. Charge distribution at the B3LYP/6-31G(d) level on the carbon atoms of compounds **1** and **2**

Heterocycle	Position	MPA	NPA	CHelpG	MKS
1	2	0.13	0.05	0.22	0.28
	4	0.60	0.59	0.52	0.49
	5	−0.37	−0.38	−0.31	−0.32
	6	−0.51	−0.72	−0.15	−0.42
2	2	0.17	0.01	0.24	0.13
	4	0.61	0.71	0.48	0.46
	5	−0.49	−0.47	0.16	−0.17
	6	−0.43	−0.52	−0.47	−0.54

2.1. Reactions with acid chlorides

The simultaneous behavior of the exocyclic double bond of compound **2** as both enamine and vinyl thioether unravels its reactivity toward electrophiles. Thus, when the tautomeric system **1/2** reacts with the aromatic acid chlorides (**3–7**) in CH_2Cl_2 at ambient temperature and in the presence of Et_3N, the resulting 2-heteroaryl-1,3-diketones were obtained as mixtures of tautomers **8–12** and **13–17** (Scheme 2). The process does not stop at monosubstitution, but adds a second molecule of acid chloride, regardless of the amounts of acid chloride and Et_3N employed. The best yields (42–78%) were obtained by using 1 equiv of **1/2** and 2 equiv of both acid chloride and Et_3N. Larger excesses did not improve the above yields to a significant extent. The tautomeric equilibrium is entirely shifted to the mesoionic form in the case of compounds **8**, **9**, and **12**; however, aryl groups with an electron-withdrawing substituent at *para* position still favor the mesoionic structures (**10** and **11**) over the thiazolidinones (**15** and **16**) in a 2.5:1 ratio.



3-7 **8-12** **13-17**

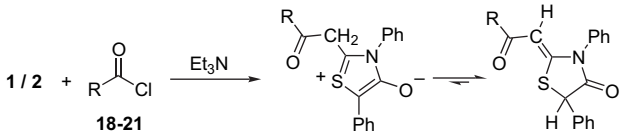
3, 8, 13 Ar = Ph
4, 9, 14 Ar = 4-$MeOC_6H_4$
5, 10, 15 Ar = 4-$NO_2C_6H_4$
6, 11, 16 Ar = 4-ClC_6H_4
7, 12, 17 Ar = 2-FC_6H_4

Scheme 2.

The above procedure represents a novel entry to α,β-unsaturated 2-heteroaryl ketones, which could also be applied to the functionalization of 2-alkyl imidazolidines.[7] In this context, the selective synthesis of α,β-unsaturated ketones remains an interesting challenge in view of their synthetic utility,[8] and some syntheses have been recently reported.[9] Furthermore, the formation of such 2-heteroaryl-1,3-diketones occurs under mild conditions and constitutes an alternative to the use of enolates. In fact, it is known that vinyl or aryl halide does not react with enolates unless strong electron-withdrawing groups are present at *ortho* or *para* position, or under drastic conditions leading to benzynes as intermediates.[10]

1,3-Diketones **8–12** exhibit a singlet at 6.20 ppm attributed to the only non-aromatic proton. For compounds **10** and **11** an additional singlet at 5.30 ppm (H-5 of tautomers **15** and **16**) can also be observed. Striking differences also emerge from their ^{13}C NMR spectra: the exocyclic carbon linked to C-2 lies in the range 88.2–93.2 ppm for **8–12**, whereas that carbon resonates at 144.6 and 141.4 ppm for **15** and **16**, respectively.

When the tautomeric system **1/2** was exposed to aliphatic acid chlorides (**18–21**, 2 equiv) and Et_3N (2 equiv), compounds **26–29** were obtained (Scheme 3) with satisfactory yields (51–70%). Unlike the aryl derivatives, this transformation stops invariably at a monosubstitution stage. The use of acid chloride excess, higher temperatures, or prolonged reaction times did not afford the corresponding 1,3-dicarbonyl compounds at all. Moreover, when **26** was treated with benzoyl chloride (as well as with acetyl chloride), the starting material was recovered unaffected.



18-21 **22-25** **26-29**

18, 22, 26 R = Me
19, 23, 27 R = Et
20, 24, 28 R = Pr
21, 25, 29 R = CH_2OCH_3

Scheme 3.

Only one signal set was observed for **26–29** in their proton NMR spectra. The H-5 proton invariably resonates at 5.10 ppm whereas the olefinic proton lies in the range 5.60–5.90 ppm, substantially more deshielded than those of the methylene group in **2** (4.27 and 4.39 ppm). The ^{13}C resonances for C-4 and C-5 at 173.3 and 50.1 ppm, respectively, also support the tautomeric structure of thiazolidine-4-one of compounds **26–29**. As noted in our preliminary communication,[11] both the *Z* configuration of the exocyclic double bond and the *s-Z* conformational arrangement of the enone moiety were established by X-ray diffraction analysis. Further semiempirical (at the PM3 level) and DFT calculations reveal the greater stability of the non-mesoionic tautomers **26–29** (Table 2).

Although acylation of the exocyclic carbon appears to occur with a complete stereoselection leading to *Z*-configured products, we were also intrigued by the fact that the *Z*- and

Table 2. Energy differences (kcal/mol) between mesoionic (**22–25**) and non-mesoionic tautomers (**26–29**)

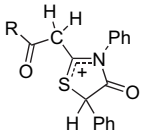
Tautomeric systems	ΔE (PM3)	ΔE (B3LYP/6-31G(d))
22/26	14.58	18.88
23/27	14.83	18.54
24/28	14.14	18.44
25/29	14.83	19.79

Table 3. Energy differences (kcal/mol) between *E*- and *Z*-diastereomer of **26–29**

Compound	ΔE_{E-Z} (PM3)
26	1.18
27	0.94
28	1.05
29	0.60

E-diastereomer of **26–29** are separated by small energy differences as evidenced by a rapid computational screening at the PM3 level (Table 3).

We then sought a stereoelectronic effect forcing the intermediate **30** to adopt a conformation capable of minimizing the steric repulsion between the N–Ph group and the substituent at C-2. The latter would be favored by a non-bonding intramolecular interaction S···O arising from the overlapping of $n_{(C=O)}$ and $\sigma^*_{(C=S)}$ orbitals.[12]



30

Structures **26–29** were first optimized at B3LYP/6-31G(d) level. When energies were plotted against the dihedral angle O=C–C=C, two minima having *Z,s-Z* and *Z,s-E* conformations could be detected (Fig. 1), which display a coplanar arrangement between the carbonyl group and the double bond. The former (*Z,s-Z*) is stabilized by 6.1 kcal/mol with respect to the *Z,s-E* conformer. Furthermore, the non-bonded S···O length is 2.684 Å, in close agreement with crystallographic data (2.699 Å).

2.2. Reactions with heterocumulenes

Pioneering work by Potts et al. in the 1970s showed that 1,3-thiazolium-4-olates may react either with isocyanates or with isothiocyanates affording stable cycloadducts.[13] Hamaguchi and Nagai noted that for thioisomünchnones lacking substituents at C-5 the resulting cycloadducts further evolved to the starting heterocycle after undergoing acylation at C-5.[14] A polycyclic 2-aminothioisomünchnone followed a different pathway nevertheless, leading to six-membered betaines after sulfur extrusion.[15]

When mesoionic compound **1** as well as **31–34** were treated with an equimolar amount of chlorosulfonylisocyanate (**39**) or chlorocarbonylisocyanate (**40**) in CH_2Cl_2 at room temperature for 1–4 h, the resulting conjugated amides **41–45** could be isolated (Scheme 4). It is worth pointing out the absence of chlorosulfonyl or chlorocarbonyl functionalities in products; such labile groups were most likely removed during work-up protocols, which involve chromatographic purification. Moreover, an excess of isocyanate does not add another carboxamido group.

Heterocycles **41–45** do not show the NMR pattern found for the mesoionic tautomers, whilst a series of resonances are consistent with a thiazolidinone moiety: two singlets in the range 4.88–5.54 ppm characteristic of the H-5 proton and the olefinic one (when R^1=H) along with a typical tertiary carbon (C-5) at approximately 50 ppm.

Remarkably, other less reactive isocyanates (**46–48**) and isothiocyanates (**49** and **50**) led likewise to 2-carbamoyl (or 2-thiocarbamoyl)methylenethiazolidin-4-ones (**51–55**) as the sole tautomers, although reactions were only practical in refluxing toluene (Scheme 5). These findings evidence again that an alkyl group at C-2 of 1,3-thiazolium-4-olates has a substantial chemoselective effect enhancing the nucleophilicity of these heterocycles at the expenses of their cycloadditive ability.

The overall process involving 2-alkylthioisomünchnones and iso(thio)cyanates can easily be interpreted as depicted in Scheme 6, i.e., nucleophilic addition of the exocyclic double bond to the heterocumulene carbon giving rise to a dipolar intermediate (**52**) followed by a fast proton exchange that produces the conjugated (thio)amide.

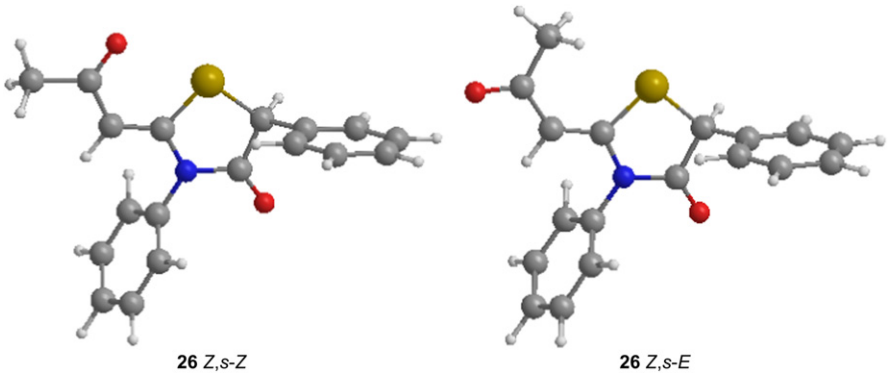
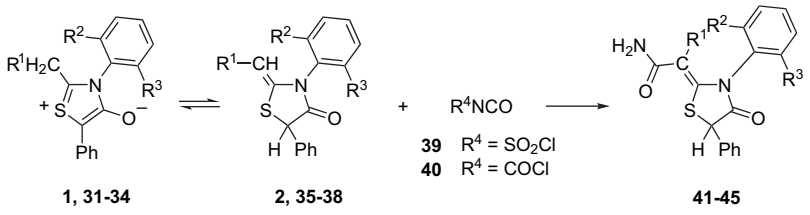
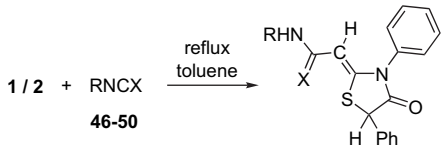


Figure 1. Conformational arrangements (*Z,s-Z* and *Z,s-E*) for compound **26**, whose energies have been refined at the B3LYP/6-31G(d) level.



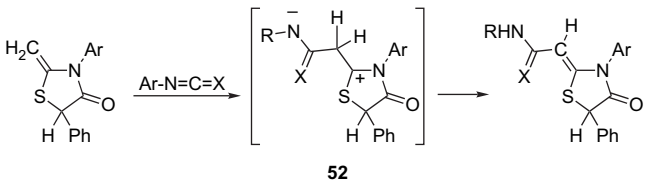
1, 2, 41 $R^1 = R^2 = R^3 = H$
31, 35, 42 $R^1 = H$, $R^2 = R^3 = Me$
32, 36, 43 $R^1 = H$, $R^2 = Me$, $R^3 = Et$
33, 37, 44 $R^1 = Me$, $R^2 = R^3 = H$
34, 38, 45 $R^1 = Et$, $R^2 = R^3 = H$

Scheme 4.



46, 51 R = Ph, X = O
47, 52 R = 2-$NO_2C_6H_4$, X = O
48, 53 R = 4-$NO_2C_6H_4$, X = O
49, 54 R = COOEt, X = S
50, 55 R = 4-$NO_2C_6H_4$, X = S

Scheme 5.



Scheme 6.

Since the amide functionality represents a ubiquitous motif in syntheses oriented to drug discovery,[16] the aforementioned strategy allows for a facile construction of amides and thioamides conjugated with ketene *N*,*S*-ketals, whose synthetic utility will further be pursued in our laboratories.

In conclusion, we have reported the distinctive behavior of 2-alkylthioisomünchnones toward a series of common and reactive electrophiles producing a major functionalization of the parent heterocycle with extended conjugation. These reactions also unmask the nucleophilic character of mesoionics, rather than their usual 1,3-dipolar behavior, which can now be harnessed in a practical way.

3. Experimental

3.1. General methods

Melting points were determined on Gallenkamp and/or Electrothermal apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on precoated Merck 60 GF_{254} silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. Flash chromatography was conducted on Merck 60 silica gel (230–400 mesh). IR spectra were recorded in the range 4000–600 cm^{-1} on a FT-IR MIDAC spectrophotometer. NMR spectra were recorded on Bruker spectrometers operating at 400 MHz for ^1H nuclei or 100 MHz for ^{13}C resonances, in $CDCl_3$ or DMSO-d_6 solutions. Tetramethylsilane (TMS) was used as the internal standard (δ=0.00 ppm). Combustion microanalyses were performed at the University of Extremadura and high-resolution mass spectra at the University of Santiago de Compostela (*Servicio de Espectrometría de Masas*). Geometry optimizations of reactants and transition structures were carried out at the PM3[17] and density functional theory (DFT) levels, the latter using the B3LYP[18] functional and the 6-31G(d)[19] basis set. All calculations were performed using the Gaussian03 package.[20]

3.2. General procedure for the preparation of 1,3-dicarbonyl compounds (8–12/13–17)

To a stirred solution of **1** (50 mg, 0.187 mmol) in CH_2Cl_2 (5.0 mL) were added the corresponding aroyl chloride (0.374 mmol) and Et_3N (52.2 μL, 0.374 mmol). After 48 h at room temperature, analytical TLC (ethyl acetate/hexane 1:2) revealed the disappearance of **1**; the organic phase was then washed with brine (3× 40.0 mL), dried ($MgSO_4$), and evaporated until crystallization was started. Then it was kept into the refrigerator favoring crystals to be formed. They were filtered and washed with diethyl ether to give the title compounds.

3.2.1. 2-Dibenzoylmethyl-3,5-diphenyl-1,3-thiazolium-4-olate (8). Following the above general procedure, the title compound was obtained in 38% yield (yellow crystals). Mp: 204 °C; IR (cm^{-1}): 1759, 1629, 1562; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.26 (m, 18H, Ar-H), 6.21 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.88 (C2), 163.04 (C4), 159.86 (CO), 139.32, 135.14, 134.56, 134.45, 130.53, 130.17, 130.02, 129.74, 129.01, 128.72, 128.23, 128.14, 127.71, 126.93, 126.77, 126.65 (Ar-C), 108.39 (C5), 88.45 (CH) ppm. Anal. Calcd for $C_{30}H_{21}NO_3S$: C, 75.77; H, 4.45; N, 2.95; S, 6.74. Found: C, 75.64; H, 4.51; N, 2.80; S, 6.50.

3.2.2. 2-(Di-4-methoxybenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (9). Following the above general procedure, the title compound was obtained in 73% yield (yellow crystals). Mp: 197 °C (dec); IR (KBr) ν_{max} 1749,

1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–6.84 (m, 18H, Ar-H), 6.15 (s, 1H, CH), 3.83, 3.80 (s, 3H, CH_3O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.03 (C2), 164.56 (C4), 162.59, 161.52 (CO), 159.41, 135.23, 134.23, 132.43, 132.11, 129.96, 129.89, 128.89, 128.71, 128.26, 127.47, 126.48, 118.83, 114.00, 113.28 (Ar-C), 107.85 (C5), 87.95 (CH), 55.49, 55.21 (CH_3O) ppm. Anal. Calcd for $C_{32}H_{25}NO_5S$: C, 71.76; H, 4.70; N, 2.62; S, 5.99. Found: C, 71.98; H, 4.79; N, 2.54; S, 5.83.

3.2.3. 2-(Di-4-nitrobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (10) and 2-(di-4-nitrobenzoyl)methylene-3,5-diphenyl-1,3-thiazolidine-4-one (15). Following the above general procedure, the title tautomers were obtained in 78% yield (red crystals). Mp: 197 °C; IR (KBr) ν_{max} 1772, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25, 8.20, 8.00, 7.90 (d, 8H, Ar-H), 7.54–7.36 (m, 10H, Ar-H), 6.20 (s, 1H, CH, **10**), 5.30 (s, 1H, C5H, **15**) ppm, ratio **10/15**=2:1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.05 (C2), 161.41 (C4), 160.92, 159.89 (CO), 148.79, 134.66, 133.84, 131.29, 130.68, 130.38, 129.26, 128.96, 128.44, 128.03, 127.83, 126.87, 123.96, 123.53 (Ar-C), 144.58 (C2=*C*), 88.89 (CH) ppm. Anal. Calcd for $C_{30}H_{19}N_3O_7S$: C, 63.71; H, 3.39; N, 7.43; S, 5.67. Found: C, 63.92; H, 3.60; N, 7.23; S, 5.66.

3.2.4. 2-(Di-4-chlorobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (11) and 2-(di-4-chlorobenzoyl)-methylene-3,5-diphenyl-1,3-thiazolidine-4-one (16). Following the above general procedure, the title tautomers were obtained in 72% yield (yellow crystals). Mp: 235 °C (dec); IR (KBr) ν_{max} 1757, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07, 7.77, 7.71 (d, 8H, Ar-H), 7.52–7.26 (m, 10H, Ar-H), 6.14 (s, 1H, CH, **11**), 5.29 (s, 1H, C5H, **16**) ppm, ratio **11/16**=2.5:1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.40 (C2), 162.23 (C4), 161.26, 160.11 (CO), 141.39, 137.60, 136.54, 134.96, 134.17, 131.84, 131.47, 130.23, 130.11, 129.47, 129.34, 129.23, 129.08, 128.33, 128.14, 127.93, 126.99, 126.65, 125.04 (Ar-C), 141.39 (C2=*C*), 108.84 (C5), 88.16 (CH) ppm. Anal. Calcd for $C_{30}H_{19}Cl_2NO_3S$: C, 66.18; H, 3.52; N, 2.57; S, 5.89. Found: C, 66.26; H, 3.52; N, 2.31; S, 5.80.

3.2.5. 2-(Di-2-fluorobenzoyl)methyl-3,5-diphenyl-1,3-thiazolium-4-olate (12). The residue obtained after evaporation was purified by flash chromatography (ethyl acetate/hexane, gradient from 1:3 to 1:1), the title compound was obtained as yellow crystals in 49% yield. Mp: 185 °C (ethyl acetate); IR (KBr) ν_{max} 1766, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–6.96 (m, 18H, Ar-H), 6.27 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.65 (C2), 163.41 (C4), 161.75, 160.78 (CO), 160.41, 159.75, 159.26, 136.33, 136.24, 134.93, 134.08, 132.20, 131.72, 131.63, 130.67, 130.06, 129.93, 129.54, 129.02, 128.17, 127.87, 127.62, 127.50, 126.80, 124.27, 127.09, 117.37, 117.16, 116.04, 115.79, 115.37 (Ar-C), 108.90 (C5), 93.19 (CH) ppm. Anal. Calcd for $C_{30}H_{19}F_2NO_3S$: C, 70.44; H, 3.74; N, 2.74; S, 6.27. Found: C, 70.61; H, 3.76; N, 2.58; S, 5.98.

3.3. General procedure for the synthesis of α,β-unsaturated ketones (26–29)

To a stirred solution of **1** (50 mg, 0.187 mmol) in CH_2Cl_2 (5.0 mL) were added the corresponding acid chloride (0.374 mmol) and Et_3N (52.2 μL, 0.374 mmol). After 48 h at room temperature, the solvent was evaporated and the residue was purified by preparative thin-layer or flash chromatography afforded the title compounds.

3.3.1. (*Z*)-2-Acetylmethylene-3,5-diphenyl-1,3-thiazolidin-4-one (26). Following the above general procedure and purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:3) compound **26** was obtained, which was further crystallized from ethyl acetate (52%). Mp: 156 °C (ethyl acetate); IR (KBr) ν_{max} 1720, 1647, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.25 (m, 10H, Ar-H), 5.60 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.11 (CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.14 (*C*OCH_3), 173.30 (C4), 158.04 (C2), 135.57, 130.13, 129.77, 129.11, 128.65, 128.29, 127.93 (Ar-C), 100.88 (=CH), 50.03 (C5), 30.14 (CO*C*H_3) ppm. Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53; S, 10.36. Found: C, 70.09; H, 5.17; N, 4.38; S, 10.51.

3.3.2. (*Z*)-3,5-Diphenyl-2-propanoylmethylene-1,3-thiazolidin-4-one (27). Following the above procedure and purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:2) compound **27** was obtained, which was further crystallized from ethyl acetate (46%). Mp: 219 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3048, 1714, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.34 (m, 10H, Ar-H), 5.65 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.36 (CH_2CH_3), 1.05 (CH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.57 (CO), 173.30 (C4), 157.63 (C2), 135.66, 135.17, 130.13, 129.75, 129.11, 128.65, 128.32, 127.96 (Ar-C), 100.21 (=CH), 50.09 (C5), 36.12 (CO*C*H_2CH_3), 8.47 ($COCH_2CH_3$) ppm. Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; S, 9.91. Found: C, 70.45; H, 5.37; N, 3.98; S, 9.81.

3.3.3. (*Z*)-2-Butanoylmethylene-3,5-diphenyl-1,3-thiazolidin-4-one (28). Purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:1) yielded **28**, which was further crystallized from ethyl acetate (70%). Mp: 153 °C (ethyl acetate); IR (KBr) ν_{max} 1738, 1718, 1649, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.25 (m, 10H, Ar-H), 5.64 (s, 1H, =CH), 5.09 (s, 1H, H-5), 2.32 (t, 2H, $CH_3CH_2CH_2$–), 1.59 (m, 2H, $CH_3CH_2CH_2$–), 0.88 (t, 3H, $CH_3CH_2CH_2$–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.11 (CO), 173.33 (C4), 157.68 (C2), 135.66, 135.18, 130.14, 129.75, 129.11, 128.65, 128.32, 127.96 (Ar-C), 100.56 (=CH), 50.10 (C5), 45.03 (CO*C*H_2–CH_2–CH_3), 18.03 ($COCH_2$–*C*H_2–CH_3), 13.83 ($COCH_2$–CH_2–*C*H_3) ppm. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15; S, 9.50. Found: C, 70.97; H, 5.71; N, 4.26; S, 9.38.

3.3.4. (*Z*)-3,5-Diphenyl-2-methoxyacetylmethylene-1,3-thiazolidin-4-one (29). Purification by preparative thin-layer chromatography (ethyl acetate/hexane 1:3) yielded **29**, which was further crystallized from ethyl acetate (65%). Mp: 147 °C (ethyl acetate); IR (KBr) ν_{max} 1717, 1638, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.26 (m, 10H, Ar-H), 5.92 (s, 1H, =CH), 5.12 (s, 1H, H-5), 3.93 (s, 2H, CH_3OCH_2–), 3.32 (s, 3H, CH_3OCH_2–) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.53 (CO), 173.32 (C4), 159.92 (C2), 135.38, 134.93, 130.17, 129.86, 129.17, 128.74, 128.32, 127.86 (Ar-C), 96.71

(=CH), 50.16 (C5) ppm. Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found: C, 67.34; H, 5.12; N, 3.90; S, 9.52.

3.4. Synthesis of carbamoylalkylidene-1,3-thiazolidine-4-ones (41–45)

To a stirred solution of **1** or **31–34** (1.0 mmol) in CH_2Cl_2 (5.0 mL/g) was added chlorosulfonylisocyanate or chlorocarbonylisocyanate (1.2 mmol). After 4 h at room temperature, the solvent was evaporated and the residue was subjected to chromatographic purification.

3.4.1. (*Z*)-2-Carbamoylmethylene-3,5-diphenyl-1,3-thiazolidine-4-one (41). This compound was obtained from **1** following the above procedure, purification by flash chromatography (ethyl acetate/hexane, gradient from 1:5 to 1:1), and further crystallization from ethyl acetate in 58% yield. Mp: 243 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3472, 3344, 1726, 1659 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.61–7.33 (m, 10H, Ar-H), 7.24 (bs, 1H, NH), 6.73 (br s, 1H, NH), 5.38 (s, 1H, =CH), 5.17 (s, 1H, H-5); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.07 (C4), 168.15 ($CONH_2$), 152.75 (C2), 138.00, 136.01, 130.21, 129.59, 129.09, 128.76, 128.71, 128.29 (Ar-C), 95.01 (=CH), 49.24 (C5). Anal. Calcd for $C_{17}H_{14}N_2O_2S\cdot 1/2H_2O$: C, 63.93; H, 4.73; N, 8.77; S, 10.04. Found: C, 64.24; H, 4.64; N, 8.54; S, 10.18.

Compound **41** could also be obtained from **1** and chlorocarbonylisocyanate after chromatographic purification (ethyl acetate/hexane 1:3), and further crystallization from ethyl acetate in 65% yield.

3.4.2. (*Z*)-2-Carbamoylmethylene-3-(2,6-dimethyl)-phenyl-5-phenyl-1,3-thiazolidine-4-one (42). The solution obtained by applying the general procedure to **31** and chlorosulfonylisocyanate was evaporated, and the resulting white crystals were filtered and washed with cold CH_2Cl_2. The title compound isolated in 45% yield was pure enough and had mp: 166 °C (dec); IR (KBr) ν_{max} 3070, 1625, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.45–7.28 (m, 10H, Ar-H), 7.56 (s, 1H, NH), 7.18 (s, 1H, NH), 5.54 (s, 1H, =CH), 5.02 (s, 1H, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.45 (C4), 168.11 ($CONH_2$), 150.07 (C2), 137.45, 136.18, 135.93, 135.75, 133.42, 130.23, 129.72, 129.17, 128.87, 127.99, 127.84, 126.20 (Ar-C), 94.86 (=CH), 48.89 (C5), 17.17, 17.02 (CH_3-Ar) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.24; H, 5.64; N, 8.50; S, 9.38.

3.4.3. (*Z*)-2-Carbamoylmethylene-3-(2-ethyl-6-methyl)-phenyl-5-phenyl-1,3-thiazolidine-4-one (43). The solution obtained by applying the general procedure to **32** and chlorosulfonylisocyanate was evaporated and the residue purified by preparative thin-layer chromatography (ethyl acetate/hexane 1:1). White crystals of **43** (42% yield) were obtained from ethyl acetate. Mp: 183 °C (dec); IR (KBr) ν_{max} 3450, 1735, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.15 (m, 10H, Ar-H), 6.36 (br s, 1H, NH), 5.55 (bs, 1H, NH), 5.12 (s, 1H, H-5), 4.88 (s, 1H, =CH), 2.48 (m, 2H, CH_3CH_2-Ar), 2.10 (s, 3H, CH_3-Ar), 1.05 (t, 3H, CH_3CH_2-Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.56 (C4), 167.25 ($CONH_2$), 150.2 (C2), 135.45, 134.86, 132.64, 131.58, 130.48, 130.12, 128.95, 127.48, 127.05, 125.23 (Ar-C), 94.80 (=CH), 50.15 (C5), 28.9 (CH_3CH_2-Ar), 19.9 (CH_3-Ar), 13.25 (CH_3CH_2-Ar) ppm. Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.10; H, 5.68; N, 8.04; S, 9.28.

3.4.4. (*Z*)-2-(1-Carbamoyl)ethylidene-3,5-diphenyl-1,3-thiazolidine-4-one (44). The solution obtained by applying the general procedure to **33** and chlorosulfonylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:4). The title compound was obtained in crystalline form (60% yield) from ethyl acetate. Mp: 189 °C (dec); IR (KBr) ν_{max} 3148, 1715, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, 1H, NH), 8.38 (d, 1H, NH), 7.67–7.38 (m, 10H, Ar-H), 5.29 (s, 1H, H-5), 2.15 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.30 (C4), 172.18 ($CONH_2$), 149.52 (C2), 137.08, 134.63, 132.63, 129.36, 128.36, 126.86, 126.68, 124.01 (Ar-C), 89.58 (=C), 51.12 (C5), 11.48 (CH_3) ppm. Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.68; H, 4.56; N, 8.84; S, 10.12.

3.4.5. (*Z*)-2-(1-Carbamoyl)propylidene-3,5-diphenyl-1,3-thiazolidine-4-one (45). The solution obtained by applying the general procedure to **34** and chlorosulfonylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:4). Crystals of **45** were isolated from ethyl acetate in 58% yield. Mp: 176 °C (dec); IR (KBr) ν_{max} 3210, 1735, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, 1H, NH), 8.27 (d, 1H, NH), 7.67–7.30 (m, 10H, Ar-H), 5.29 (s, 1H, H-5), 2.65 (q, 2H, CH_2CH_3), 1.19 (t, 3H, CH_2CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.63 (C4), 170.89 ($CONH_2$), 150.85 (C2), 138.25, 137.61, 133.18, 132.47, 129.73, 127.45, 127.08, 124.49, 124.23 (Ar-C), 90.05 (=C), 51.28 (C-5), 14.67 (CH_3CH_2), 11.40 (CH_3CH_2) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28; S, 9.47. Found: C, 67.25; H, 5.51; N, 8.34; S, 9.61.

3.5. Synthesis of 2-(*N*-arylcarbamoyl)alkylidene-1,3-thiazolidine-4-ones (51–55)

To a stirred solution of **1** (1.11 mmol) in toluene (5.0 mL) was added the corresponding arylisocyanate (2.2 mmol) and the reaction mixture was refluxed until TLC analysis (ethyl acetate/hexane 1:2) revealed the disappearance of **1** (48–72 h).

3.5.1. (*Z*)-3,5-Diphenyl-2-(*N*-phenylcarbamoyl)methylene-1,3-thiazolidine-4-one (51). The solution obtained by applying the general procedure to **1** and phenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). The title compound was isolated as white crystals from ethyl acetate in 45% yield. Mp: 174 °C (ethyl acetate); IR (KBr) ν_{max} 3205, 1720, 1632, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.55 (s, 1H, NH), 7.57–6.94 (m, 15H, Ar-H), 5.14 (s, 1H, =CH), 4.73 (s, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.41 (C4), 169.81 (CONH), 159.81, 152.15, 138.02, 137.90, 135.26, 134.47, 129.71, 129.41, 129.20, 129.10, 128.86, 128.41, 128.23, 127.38, 123.80, 120.10, 116.67 (Ar-C), 94.80 (=CH), 50.34 (C5). Anal. Calcd for $C_{23}H_{18}N_2O_2S$:

C, 71.48; H, 4.69; N, 7.25; S, 8.30. Found: C, 71.25; H, 4.62; N, 7.34; S, 8.35. HRMS-FAB$^+$, found: 409.0981 ($C_{23}H_{18}N_2O_2S$+Na requires 409.0987), Δ=−0.44 ppm.

3.5.2. (*Z*)-3,5-Diphenyl-2-[*N*-(2-nitrophenyl)carbamoyl]-methylene-1,3-thiazolidine-4-one (52). The solution obtained by applying the general procedure to **1** and *o*-nitrophenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). Compound **52** was isolated as yellowish crystals from ethyl acetate in 58% yield. Mp: 212 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3338, 1720, 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H, NH), 8.85 (d, 1H, Ar-H), 8.16 (dd, 1H, Ar-H), 7.63–7.09 (m, 7H, Ar-H), 5.32 (s, 1H, =CH), 5.16 (s, 1H, H5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.81 (C4), 165.38 (CONH), 158.13 (C2), 135.87, 134.90, 130.35, 130.04, 129.10, 128.71, 128.23, 127.95, 125.68, 122.71, 122.01 (Ar-C), 94.92 (=CH), 50.22 (C5). Anal. Calcd for $C_{23}H_{17}N_3O_4S$: C, 64.03; H, 3.97; N, 9.74; S, 7.43. Found: C, 63.89; H, 3.65; N, 10.09; S, 7.33. HRMS-CI$^+$, found: 454.0826 ($C_{23}H_{17}N_3O_4S$+Na requires 454.0832), Δ=1.39 ppm.

3.5.3. (*Z*)-3,5-Diphenyl-2-[*N*-(4-nitrophenyl)carbamoyl]-methylene-1,3-thiazolidine-4-one (53). The solution obtained by applying the general procedure to **1** and *p*-nitrophenylisocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane 1:5). Yellow crystals of **53** (from ethyl acetate) were collected in 55% yield. Mp: 234 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3337, 1726, 1597, 1554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H, NH), 8.85 (d, 1H, Ar-H), 8.16 (dd, 1H, Ar-H), 7.63–7.09 (m, 7H, Ar-H), 5.35 (s, 1H, =CH), 5.15 (s, 1H, H5) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.951 (C4), 168.45 (CONH), 158.02 (C2), 134.57, 133.59, 132.84, 131.08, 130.10, 129.51, 128.89, 127.39, 125.18, 123.91, 123.05 (Ar-C), 95.63 (=CH), 51.85 (C5). Anal. Calcd for $C_{23}H_{17}N_3O_4S$: C, 64.03; H, 3.97; N, 9.74; S, 7.43. Found: C, 64.25; H, 3.75; N, 9.45; S, 7.22.

3.6. Synthesis of 2-(*N*-thiocarbamoyl)alkylidene-1,3-thiazolidine-4-ones (54 and 55)

To a stirred solution of **1** (1.86 mmol) in toluene (8.0 mL) was added the corresponding isothiocyanate (2.2 mmol) and the reaction mixture was refluxed for approximately 36 h (TLC monitoring, ethyl acetate/hexane 1:2, revealed the disappearance of **1**).

3.6.1. (*Z*)-2-(*N*-Ethoxycarbonylthiocarbamoyl)methylene-1,3-thiazolidine-4-one (54). The solution obtained by applying the above procedure to **1** and ethoxycarbonyl isothiocyanate was subsequently cooled at 0 °C. Yellow crystals of the title compound were collected and washed with Et_2O (65% yield). Mp: 223 °C (dec); IR (KBr) ν_{max} 3184, 1739, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H, NH), 7.58–7.24 (m, 10H, Ar-H), 7.55 (s, 1H, =CH), 5.10 (s, 1H, H-5), 4.06 (q, 2H, CH_3CH_2O), 1.19 (t, 3H, CH_3CH_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.25 (CSNH), 173.38 (CONH), 165.77 (C4), 149.73, 130.20, 130.01, 129.23, 128.74, 128.41, 127.86 (C-Ar), 104.45 (=CH), 62.12 (CH_3CH_2O), 51.40 (C5), 14.13 (CH_3CH_2O) ppm. Anal. Calcd for $C_{20}H_{18}N_2O_3S_2$: C, 60.28; H, 4.55; N, 7.03; S, 16.09. Found: C, 60.56; H, 4.75; N, 7.27; S, 15.93. HRMS-CI$^+$, found: 398.076984 ($C_{20}H_{18}N_2O_3S_2$ requires 398.07588), Δ=−2.8 ppm.

3.6.2. (*Z*)-2-[*N*-(4-Nitrophenyl)thiocarbamoyl]methylene-1,3-thiazolidine-4-one (55). The solution obtained by applying the general procedure to **1** and *p*-nitrophenyl isothiocyanate was evaporated and the residue purified by flash chromatography (ethyl acetate/hexane, gradient from 1:5 to 1:1). Yellow crystals of **55** in 55% yield were obtained in ethyl acetate cooled at −15 °C. Mp: 261 °C (dec, ethyl acetate); IR (KBr) ν_{max} 3316, 2360, 1723 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H, NH), 8.20–7.36 (m, 14H, Ar-H), 6.17 (s, 1H, =CH), 5.44 (s, 1H, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.13 (CSNH), 166.47 (C4), 159.98, 145.73, 143.06, 136.93, 135.81, 130.32, 130.20, 129.72, 129.02, 128.87, 128.23, 124.32, 121.59 (Ar-C), 105.67 (=CH), 50.07 (C5) ppm. Anal. Calcd for $C_{23}H_{17}N_3O_3S_2$: C, 61.73; H, 3.83; N, 9.39; S, 14.33. Found: C, 61.44; H, 3.88; N, 9.29; S, 14.51. HRMS-CI$^+$, found: 447.071481 ($C_{23}H_{17}N_3O_3S_2$ requires 447.07113), Δ=−0.8 ppm.

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Synthesis and tautomerism study of 7-substituted pyrazolo[3,4-*c*]pyridines

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Abstract—A number of 7-substituted pyrazolo[3,4-*c*]pyridine derivatives have been synthesized in order to investigate the N1–N2 tautomerism within this class of biologically interesting compounds. Tautomeric equilibrium has been studied using NMR ^{13}C, ^{15}N chemical shifts and heteronuclear ^{1}H–^{15}N and ^{1}H–^{13}C spin–spin couplings, in conjunction with X-ray crystallography. The N1 tautomer predominates in DMF solution in all the compounds tested.

1. Introduction

Biomolecules are often characterized by the presence of more than one basic atom and can exist in multiple tautomeric and protonated states, which should be considered in the study of their mode of interaction with their substrates, where hydrogen bonding between donor and acceptor motifs are usually involved. Within this context, the structure and the 7*H*–9*H* prototropic tautomeric equilibrium of isolated nucleic acid bases and several purine derivatives have been extensively investigated, both theoretically and experimentally.[1–5] Among a large number of purine-related heteroaromatic compounds that have also been studied, all five isomers of pyrazolopyridines have received much attention, as concerns their pharmacological activity. Some pyrazolopyridines are well-known non-sedative anxiolytic agents,[6] while some others can act as human enzyme inhibitors, for example, a number of differently substituted pyrazolopyridines have been recently shown to be potent inhibitors of phosphodiesterases,[7] matrix metalloproteinases,[8] glycogen synthase kinase-3,[9] and of cyclin-dependent kinases.[10]

We are involved in the synthesis and structure–activity relationship studies of some pyrazolo[3,4-*c*]pyridine nucleosides (Fig. 1, I and II, respectively), which can be viewed as singly modified (4-deaza) formycins.[11] Formycin A and formycin B (Fig. 1) are potent antibiotics with proven antiviral, immunodepressant, antitumor, and antimetabolic activities.[12]

The presence of the pyrazole ring in the formycins results in a N1–H/N2–H prototropic tautomerism and consequently at physiological pH they exist as mixture of tautomers. Concerning formycin A, it has been shown that in aqueous solution the N1–H tautomer is the predominant one (>94%), although protonation at N-4 was accompanied with the migration of the hydrogen from N-1 to N-2.[13] A shift in the tautomeric equilibrium for both formycins towards the

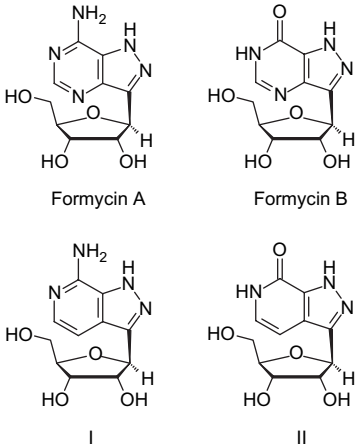

Figure 1. Structures of purine-like C-nucleosides.

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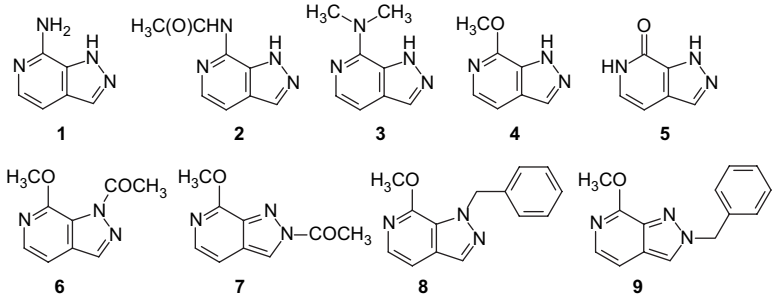


Figure 2. Structures of the examined pyrazolo[3,4-*c*]pyridines.

minor N2–H form was also observed upon complex formation with purine nucleoside phosphorylase (PNP), suggesting the preferential binding of a specific tautomer to this biologically important enzyme.[14]

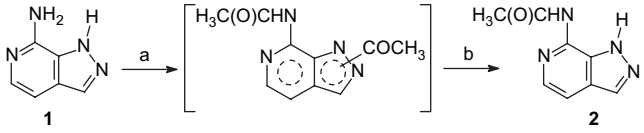
During initial studies, a peak broadening in the ^{1}H NMR spectra of compounds I and II was observed, which was attributed in the coexistence of tautomers, in accordance with the findings reported for the formycins.[15] In order to further investigate this phenomenon, we have selected a number of pyrazolo[3,4-*c*]pyridine derivatives (Fig. 2) and we have decided to study their tautomerism by low-temperature NMR spectroscopy.[16]

Relative populations of individual tautomers are generally influenced by temperature, solvent, and substitution pattern, which modifies the electronic distribution within the molecule. We have thus prepared compounds **1**–**5**, which bear 7-substituents with various electronic and steric properties. Moreover, since the ^{13}C and ^{15}N NMR chemical shifts were utilized to specify the protonation site of purines[16,17] we have considered the syntheses of N-1 and N-2 substituted analogues **6**–**9** as models for the determination of the spectral data. In addition to chemical shift analysis, heteronuclear coupling constants were revealed to be a useful tool for tautomeric equillibria studies, consequently all compounds lack a 3-substituent, in order to utilize the $J_{H3–Cx}$ and $J_{H3–Ny}$ couplings to accomplish the study.

2. Results and discussion

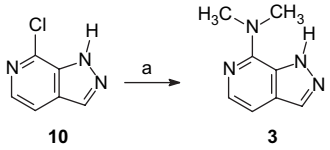
2.1. Synthesis

The syntheses of compounds **1**, **4**, and **5** (Fig. 2) has already been reported starting from 2-amino-3-nitro-4-picoline, which was suitably substituted and ring-closed in the presence of nitrosyl chloride or isoamylnitrite.[18] Compound **2** was prepared by acetylation of **1** and treatment of the resulting mixture of regio-isomers with methanolic ammonia (Scheme 1).



Scheme 1. Reagents and conditions: [a] acetic anhydride, rt, 12 h; [b] NH_3/CH_3OH, rt, 1 h, 92% (overall).

Compound **3** was prepared from 7-chloropyrazolo[3,4-*c*]-pyridine (**10**)[18b] upon treatment with an ethanolic solution of dimethylamine (Scheme 2).



Scheme 2. Reagents and conditions: [a] $(CH_3)_2NH/CH_3CH_2OH$, reflux, 12 h, 75%.

Compounds **6** and **7** were prepared by direct acetylation of **4**,[18a] whereas the benzyl substituted regio isomers **8** and **9**, resulted upon treatment of compound **4** with NaH, followed by addition of benzyl bromide to the generated anion. The substitution occurs readily at position 2, when the reaction is carried out at room temperature and this is probably due to the steric hindrance, exerted by the 7-substituent. On the other hand, analogous treatment of a DMF solution of **4** with acetic anhydride or benzyl bromide at reflux provided both 1- and 2-isomers, and from this mixture the 1-substituted analogue was isolated by column chromatography.

During the preparation of the 1-benzyl isomer **8**, a minor amount of a third product, apart from the 2-regio isomer **9**, was also isolated. This derivative was identified as the 2,6-dibenzylpyrazolo[3,4-*c*]pyridine-7-one (**11**, Fig. 3a), based on NMR analysis. Furthermore, compound **11** furnished crystals from methanol suitable for an X-ray diffraction

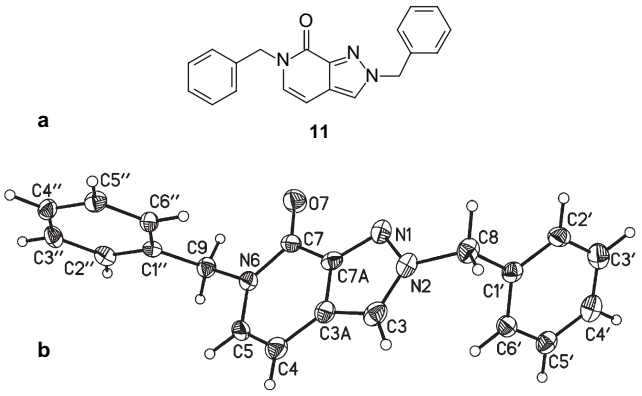
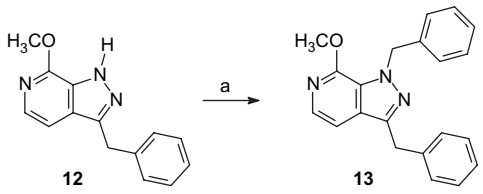


Figure 3. (a) Structure of compound **11** and (b) perspective view of the X-ray structure of compound **11**.

analysis, which provided the unambiguous assigment of its structure (Fig. 3b).

Taking into account the regioselective formation of the N-2 substituted isomers, we have also prepared the 3-benzyl analogue **13** (Scheme 3), in order to study the influence of a bulky 3-substituent in the N-alkylation. Thus, reaction of 3-benzyl-7-methoxypyrazolo[3,4-*c*]pyridine (**12**)[19] with benzyl bromide in the presence of sodium hydride, provided exclusively the 1-benzyl analogue **13**. This regio-isomer was identified by the use of the corresponding HMBC spectrum, where a cross-peak between the NCH_2Ph and C-7a is obvious and additionally, this methylene presented NOE with the 7-methoxy group.



Scheme 3. Reagents and conditions: [a] NaH, benzyl chloride, DMF, rt, 1 h, 68%.

2.2. NMR spectroscopy

Low-temperature NMR represents an important tool for examining tautomeric equilibrium.[16] Fast chemical exchange among the individual components usually occurs at laboratory temperatures. The resulting NMR spectra correspond to a time-averaged contribution, which reflects Boltzmann populations of the individual tautomers.[20] Decreasing the temperature slows down the chemical exchange process. At low temperatures, separated signals of individual tautomers could be detected, however, this methodology has rarely been used in the field of purine chemistry since exchange studies of purine derivatives have been performed primarily in water.[21] Separation of the NMR signals of individual tautomers of purine derivatives at low temperatures has been recently described in DMF and DMSO/acetonitrile solutions.[16,22]

The ^{1}H NMR spectra of compounds **1**–**9** in DMF solution are characterized by four main signals: the AX system of H-4 and H-5 at 7.11–7.57 ppm and 7.50–7.93 ppm, respectively, a singlet at 8.20–8.65 ppm attributed to H-3 and a broad signal at ~14 ppm attributed to the proton suspected for tautomerism exchanging between N-1 and N-2. In all cases, except pyrazolopyridinone **5** and 7-dimethylamino derivative **3**, the H-3, H-4, and H-5 signals were sharp at room temperature.

The assignment of ^{13}C and ^{15}N spectra was performed using the corresponding 2D gHMBC and gHSQC[23] spectra and chemical shifts are summarized in Table 1.

Heteronuclear coupling constants were determined using the GSQMBC spectra[24] from the anti-phase doublets of the corresponding cross-peaks and the most important are summarized in Table 2.

The spectroscopic data concerning the pair of compounds **6**–**7** and **8**–**9** show that C-7a, C-3a, C-3, N-1, and N-2 chemical shifts and the J_{H-C} and J_{H-N} coupling constants can be a useful tool for the determination of the substitution site and/or the tautomeric form, as previously seen in the case of formycin and purine derivatives.[16,25] When N-1 is substituted, N-2 is deshielded (at ~326 ppm), as well as C-3 and C-3a (~135 ppm). When N-2 is substituted, N1 and C-7a are deshielded (at ~291 ppm and 138 ppm, respectively). Moreover, indirect spin–spin coupling constants of H-3 with N-1, N-2, and C-7a exhibit characteristic differences between N-1 and N-2 substitution and can be additionally used for tautomer discrimination.

Considering the above results the qualitative inspection of the spectroscopic data concerning compounds **1**–**5** and mainly N-1 and N-2 chemical shifts, suggests that in all cases the N1–H tautomer should be predominant in DMF solution.

In order to study the tautomeric equilibrium concerning compounds **1**–**5**, variable temperature studies have been performed, in a temperature range of 213–303 K. In the case of compound **5**, on lowering the temperature to 213 K, a second set of signals appeared in the ^{1}H NMR spectrum with relative intensities 100 and 7, which corresponds to the ratio of major and minor components 93.5:6.5.

2D ^{1}H–^{13}C and ^{1}H–^{15}N gHSQC, gHMBC, and GSQMBC spectra recorded at this temperature, allowed for the complete resonance assignment and determination of coupling constants. ^{1}H–^{15}N GSQMBC spectrum of compound **5** is shown in Figure 4. All characteristic NMR spectroscopic data are summarized in Table 3, along with the corresponding data for compounds **6** and **7**, in order to facilitate the comparison. All data suggest that the major component corresponds to the N1–H tautomer, while the minor component corresponds to N2–H.

No significant changes in the ^{1}H NMR patterns were observed on decreasing the temperature in all other derivatives **1**–**4**. One set of signals was detected, even if signals were

Table 1. ^{13}C and ^{15}N NMR chemical shifts (ppm) for compounds **1**–**9** and **11** in DMF-d_7 at 303 K

Compounds	C3	C3a	C4	C5	C7	C7a	N1	N2	N6
1	133.65	127.54	104.79	138.25	147.73	128.77	190.5	309.6	248.9
2	134.30	130.42	112.64	137.54	139.03	130.16	188.0	322.1	276.6
4	134.68	129.79	109.82	136.49	151.66	128.23	184.4	322.1	252.7
5	134.0	125.5	98.6	126.1	155.1	133.1	not obsd	not obsd	155.2
6	139.71	135.46	109.87	141.30	152.51	125.52	222.5[a]	325.7[a]	263.1[a]
7	123.46	126.73	109.78	137.94	157.93	140.44	291.5[a]	252.5[a]	252.3[a]
8	133.58	130.34	109.64	135.98	150.89	126.43	191.1	327.4	252.1
9	125.49	127.25	109.42	136.08	156.65	137.97	292.2	233.9	247.9
11	125.74	124.13	99.25	130.71	157.90	142.29	307.1	230.5	160.5

[a] Chemical shifts determined at 273 K.

Table 2. Characteristic J_{H-C} and J_{H-N} scalar coupling constants (Hz) of compounds **1–9** and **11** in DMF-d_7 at 303 K

	$^1J_{H3-C3}$	$^2J_{H3-C3a}$	$^3J_{H3-C7a}$	$^3J_{H3-N1}$	$^2J_{H3-N2}$
1	188.9	11.3	4.4	7.2	12.3
2	190.2	11.7	3.9	7.6	12.9
4	190.2	11.5	4.5	8.2	13.2
5	189.0	10.7	3.7	[a]	[a]
6	196.6	11.1	3.2	8.0	14.0
7	198.8	8.2	6.8	2.3	4.4
8	192.1	11.0	3.7	7.5	12.9
9	194.2	8.8	7.6	0.9	4.5
11	192.9	8.5	7.2	—	4.7

[a] Not observed.

Table 3. Characteristic ^{15}N and ^{13}C chemical shifts (δ in ppm) and indirect spin–spin coupling constants (J in Hz) of tautomers **5** *major* and **5** *minor* in DMF-d_7 at 213 K along with the corresponding spectroscopic data for derivatives **6** and **7**

	6	**7**	***5** major*	***5** minor*
	Chemical shifts			
N1	222.5	291.5	196.7	298.7
N2	325.7	252.5	319.1	221.7
C3	139.32	124.34	134.98	124.34
C3a	134.97	123.67	126.06	123.67
C7a	124.92	142.29	132.82	142.29
	Coupling constants			
J_{H3-N1}	8.0	2.3	6.9	[a]
J_{H3-N2}	14.0	4.4	13.2	6.4
J_{H3-C3a}	11.1	8.2	11.0	8.2
J_{H3-C7a}	3.2	6.8	5.5	6.4

[a] Not observed.

sharpened. In the case of compound **3** the two N-7 methyl group signals were clearly observed at 213 K, while a broad signal exists at room temperature (thus not considered in the tables), showing that an additional conformational equilibrium exists around the C7–N7 bond, due to the steric hindrance imposed by the bulk of the two methyl groups.

As mentioned above, from a qualitative point of view, the spectroscopic data for compounds **1–4** are in good agreement with the N1–H tautomer predominance. Simple AM1 semi-empirical calculations showed that the energy difference between N1–H and N2–H tautomers is ~3 kcal/mol in the case of the pyridinone **5**, while this difference is >5 kcal/mol for all other derivatives. These theoretical calculations are in agreement with the experimental observations described above, predicting that the population of N2–H tautomer should be undetectable by NMR. The calculated energy differences present an analogy to those performed on adenine and guanine[26] predicting that in both cases the N9–H was the most stable tautomer, followed by N7–H, however, concerning adenine, the N7–H was considerably less stable. In the case of derivative **4**, the experimental ^{15}N chemical shifts existing for the acetyl- and benzyl- derivatives **6–9** permit the theoretical calculation of the population ratio of the two tautomers at room temperature, according to equations similar to those described for the purine tautomerism.[5] The ratio was calculated to be 97/3 and, as the reliability of the approaches for determining the tautomeric ratios using averaged chemical shifts is approximately 10% and substitution at N-1 and N-2 is not the same as in compounds **6–9** and **4**, we conclude that the N2–H tautomer population is very low and undetectable by NMR at low temperature.

7-Methoxy-1*H*-pyrazolo[3,4-*c*]pyridine (**4**) furnished crystals from methanol suitable for a single-crystal X-ray analysis, which provided the unambiguous assignment of its structure (Fig. 5). The crystallographic analysis reveals that, in the solid state the proton is also localized at the nitrogen atom N1, confirming the NMR analysis.

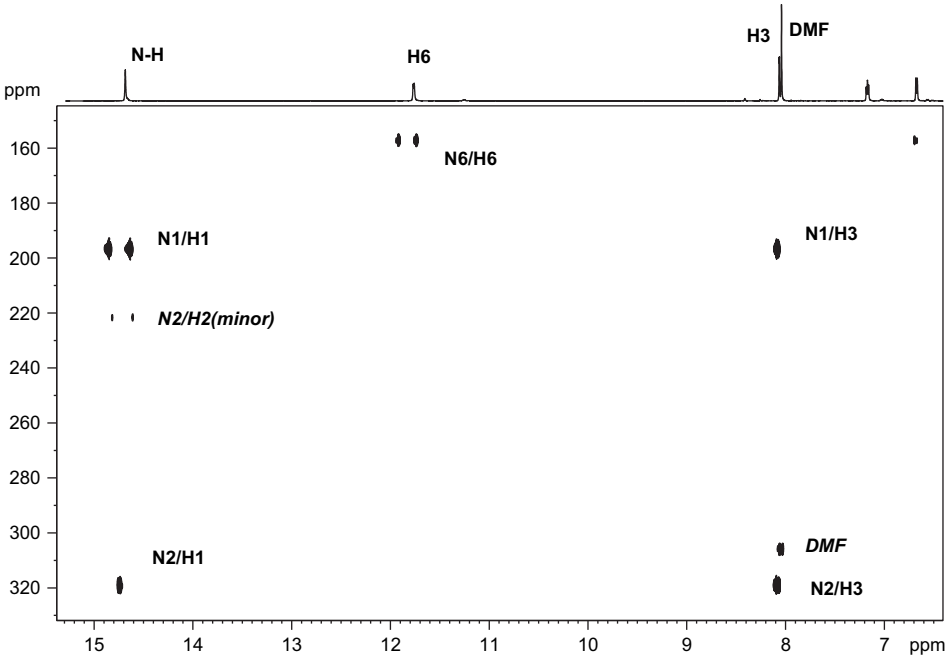


Figure 4. $^1H-^{15}N$ GSQMBC spectrum of compound **5** in DMF-d_7 at 213 K.

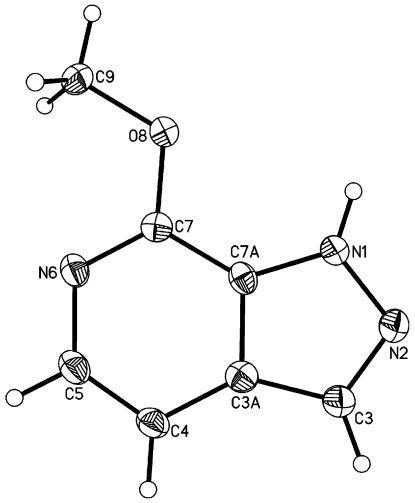


Figure 5. Perspective view of the X-ray structure of compound **4**.

3. Conclusions

In conclusion, we have shown that the N1–H tautomer of the 7-substituted pyrazolo[3,4-*c*]pyridines is predominant in solution. Only in the case of the pyrazolopyridinone **5** could the N2–H tautomer be clearly detected at appropriate NMR spectra, probably due to the rather small energy difference of the N1–H and N2–H pair of tautomers, which could be attributed to the relatively reduced aromatic character of the pyridine ring in both tautomers. On the other hand, the reduced aromaticity of the pyridine ring of the N2–H tautomer of compounds **1**–**4**, when compared to the corresponding N1–H tautomer, results in a high energy difference between them and this is in favor of the existence of the N1–H species. N-substitution of the 7-substituted pyrazolo[3,4-*c*]pyridine ring system occurs predominantly at the less hindered N-2. However, the presence of a 3-bulky substituent favors the regioselective formation of the N-1 isomer.

4. Experimental

4.1. Chemistry

All chemicals were purchased from Aldrich Chemical Co. Melting points were determined on a Büchi apparatus and are uncorrected. Flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Analytical thin layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Elemental analyses were performed on a Perkin–Elmer PE 240C Elemental Analyzer (Norwalk, CT, USA) and were within ±0.4% of the theoretical values.

4.1.1. 7-Acetamido-1*H*-pyrazolo[3,4-*c*]pyridine (2). 7-Aminopyrazolo[3,4-*c*]pyridine[18b] (200 mg, 1.49 mmol) was stirred overnight with 5 ml of acetic anhydride, at room temperature. Acetic anhydride was removed under reduced pressure and the residue was dissolved in a saturated solution of ammonia in methanol. The solution was stirred at room temperature for 1 h, the solvent was vacuum evaporated and the residue was purified by column chromatography (silica gel) using a mixture of cyclohexane/ethylacetate 20/80 (v/v) as the eluent to give **2** (240 mg, 92%) as white crystals. Mp 263 °C (CH_2Cl_2). ^{1}H NMR (DMF-d_7, 300 MHz) δ 2.32 (s, 3H, CH_3), 7.57 (d, 1H, H-4, J_{4-5}=5.38 Hz), 7.93 (d, 1H, H-5, J_{5-4}=5.38 Hz), 8.22 (s, 1H, H-3). ^{13}C NMR (DMF-d_7, 50 MHz) δ 24.02 (CH_3), 112.64 (C-4), 130.16 (C-7α), 130.42 (C-3α), 134.30 (C-3), 137.54 (C-5), 139.03 (C-7), 171.10 (CO). Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.62; H, 4.43; N, 31.98.

4.1.2. 7-Dimethylamino-1*H*-pyrazolo[3,4-*c*]pyridine (3). 7-Chloro-1*H*-pyrazolo[3,4-*c*]pyridine[18b] (**10**, 150 mg, 0.98 mmol) was added to a saturated solution of dimethylamine in ethanol (15 ml) and the resulting solution was refluxed for 12 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) using a mixture of methylenechloride/methanol 90/10 (v/v) as the eluent, to give **3** (120 mg, 75%) as white crystals. Mp 260 °C (dec) (Et_2O/MeOH). ^{1}H NMR (DMF-d_7, 300 MHz) δ 3.65 [br s, 6H, $(CH_3)_2N$], 7.11 (br d, 1H, H-4), 7.50 (br, 1H, H-5), 8.46 (br s, 1H, H-3). Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.51; H, 6.16; N, 34.32.

4.1.3. 1-Benzyl-7-methoxypyrazolo[3,4-*c*]pyridine (8). 7-Methoxy-1*H*-pyrazolo[3,4-*c*]pyridine[18a] (50 mg, 0.34 mmol) was dissolved in anhydrous DMF (7 ml) under argon. A suspension of NaH (60% in paraffin oil, 20 mg, 0.51 mmol), which had previously been washed with pentane, was added to the solution, under cooling and the mixture was stirred at room temperature for 30 min. Then, a solution of benzyl bromide (0.05 ml, 0.37 mmol) in anhydrous DMF (1 ml) was added and the reaction mixture was heated at reflux for 1 h. The solvent was vacuum evaporated and the product was purified by column chromatography (silica gel) using a mixture of cyclohexane/ethylacetate 80/20 (v/v) as the eluent, to give compounds **8**, **9**, and **11**.

4.1.4. Data for 1-benzyl-7-methoxypyrazolo[3,4-*c*]pyridine (8). Yield: 28%. Mp 147 °C (white crystals). ^{1}H NMR (DMF-d_7, 300 MHz) δ 4.13 (s, 3H, CH_3), 5.85 (s, 2H, CH_2), 7.26–7.36 (m, 5H, Ph), 7.37 (d, 1H, H-4, J_{4-5}=5.85 Hz), 7.75 (d, 1H, H-5, J_{5-4}=5.85 Hz), 8.20 (s, 1H, H-3). ^{13}C NMR (DMF-d_7, 50 MHz) δ 53.30 (CH_3), 54.73 (CH_2), 109.64 (C-4), 126.43 (C-7α), 127.79 [*C*H(Ph)], 128.04 [*C*H(Ph)], 128.82 [*C*H(Ph)], 130.34 (C-3α), 133.58 (C-3), 135.98 (C-5), 138.29 [*C*(Ph)], 150.89 (C-7). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.35; H, 5.62; N, 17.38.

4.1.5. Data for 2-benzyl-7-methoxypyrazolo[3,4-*c*]pyridine (9). Yield: 32%. Oil. ^{1}H NMR (DMF-d_7, 300 MHz) δ 4.06 (s, 3H, CH_3), 5.80 (s, 2H, CH_2), 7.25 (d, 1H, H-4, J_{4-5}=6.06 Hz), 7.36–7.49 (m, 5H, Ph), 7.62 (d, 1H, H-5, J_{5-4}=6.06 Hz), 8.65 (s, 1H, H-3). ^{13}C NMR (DMF-d_7, 50 MHz) δ 53.61 (CH_3), 58.09 (CH_2), 109.42 (C-4), 125.49 (C-3), 127.25 (C-3α), 129.25 [*C*H(Ph)], 129.79 [*C*H(Ph)], 136.08 (C-5), 137.97 (C-7α), 138.02 [*C*(Ph)], 156.65 (C-7). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.43; H, 5.38; N, 17.32.

4.1.6. Data for 2,6-dibenzylpyrazolo[3,4-*c*]pyridin-7-one (11). Yield: 15%. Mp 148 °C (white crystals). ^{1}H NMR

(DMF-d_7, 300 MHz) δ 5.23 (s, 2H, N^6–CH_2), 5.65 (s, 2H, N^2–CH_2), 6.53 (d, 1H, H-4, J_{4-5}=7.31 Hz), 7.23 (d, 1H, H-5, J_{5-4}=7.31 Hz), 7.25–7.44 (m, 10H, 2×Ph), 8.31 (s, 1H, H-3). ^{13}C NMR (DMF-d_7, 50 MHz) δ 50.74 (N^6–CH_2), 57.26 (N^2–CH_2), 99.25 (C-4), 124.13 (C-3α), 125.74 (C-3), 128.00 [*C*H(Ph)], 128.35 [*C*H(Ph)], 128.67 [*C*H(Ph)], 128.76 [*C*H(Ph)], 129.17 [*C*H(Ph)], 129.30 [*C*H(Ph)], 130.71 (C-5), 137.51 [*C*(Ph)], 139.12 [*C*(Ph)], 142.29 (C-7α), 157.90 (C-7). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32. Found: C, 76.38; H, 5.54; N, 13.07.

4.1.7. 1,3-Dibenzyl-7-methoxypyrazolo[3,4-*c*]pyridine (13). 3-Benzyl-7-methoxypyrazolo[3,4-*c*]pyridine[19] (**12**, 40 mg, 0.17 mmol) was dissolved in anhydrous DMF (7 ml) under argon. A suspension of NaH (60% in paraffin oil, 10 mg, 0.26 mmol) was added to the solution, under cooling and the mixture was stirred at room temperature for 30 min. A solution of benzyl bromide (0.03 ml, 0.19 mmol) in anhydrous DMF (1 ml) was then added and the reaction mixture was stirred at room temperature for 1 h. The solvent was vacuum evaporated and the product was purified by column chromatography (silica gel) using a mixture of cyclohexane/ethylacetate 85/15 (v/v) as the eluent, to give **13** (38 mg, 68%) as white crystals. Mp 89 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (s, 3H, CH_3), 4.29 (s, 2H, C^3–CH_2), 5.78 (s, 2H, C^3–CH_2), 6.87 (d, 1H, H-4, J_{4-5}=5.85 Hz), 7.16–7.30 (m, 10H, 2×Ph), 7.60 (d, 1H, H-5, J_{5-4}=5.86 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.77 (C^3–*C*H$_3$), 53.50 (CH_3), 54.84 (N^1–*C*H$_2$), 108.89 (C-4), 126.52 [*C*H(Ph)], 127.55 [*C*H(Ph)], 127.69 (C-7α), 128.63 [*C*H(Ph)], 128.64 (C-3α), 128.80 [*C*H(Ph)], 135.27 (C-5), 138.05 [*C*(Ph)], 138.89 [*C*(Ph)], 144.60 (C-3), 150.93 (C-7). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.29; H, 5.76; N, 12.88.

4.2. NMR spectroscopy

NMR spectra were recorded using a Bruker Avance DRX 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H), 125.77 MHz (^{13}C), and 50.68 MHz (^{15}N), a Bruker Avance DRX 400 spectrometer operating at frequencies of 400.13 MHz (^{1}H), 100.61 MHz (^{13}C), and 40.54 MHz (^{15}N) and a Bruker Avance 300 spectrometer operating at frequencies of 300.13 MHz (^{1}H), 75.48 MHz (^{13}C), and 30.41 MHz (^{15}N). NMR spectra were measured at various temperatures specified in the text or in the tables. The ^{1}H and ^{13}C NMR chemical shifts (δ in ppm) were referenced to the signal of the solvent. The ^{15}N chemical shifts were referenced to liquid CH_3NO_2 (381.7 ppm)[27] and are reported relative to liquid NH_3. The 2D NMR experiments gHSQC, gHMBC, and GSQMBC were recorded as described previously[23,24] and were used for assigning the individual ^{1}H, ^{13}C, and ^{15}N resonances and for determining the ^{1}H–^{13}C and ^{1}H–^{15}N coupling constants.

4.3. X-ray diffraction analysis

The diffraction data were collected with a KM4CCD four-circle area-detector diffractometer (KUMA Diffraction, Poland) equipped with an Oxford Cryostream Cooler (Oxford Cryosystems, UK). Mo Kα radiation (monochromator Enhance, Oxford Diffraction, UK) was used in all measurements. We performed the ω-scan technique with different κ and φ offsets in order to cover the entire independent part of reflections in the 3–25° θ range. Cell parameters were refined from all the strong reflections. Data reduction was carried out using the program CrysAlis RED (Oxford Diffraction, UK). Direct methods in SHELXS-97,[28] were used to solve the structures, and the structures were refined by using SHELXL-97.[29] The tables were prepared for publication by using SHELXL and PARST,[30] and the figures were generated with ORTEP-III.[31] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

4.3.1. Crystal data for 4. CCDC Ref. No. 608944. Crystallized from methanol, $C_7H_7N_3O$, M_{rel}=149.16, T=120(2) K, Orthorhombic, λ=0.71073 Å, space group P_{bac}, a=11.3022(8) Å, b=7.4180(6) Å, c=16.2981(12) Å, V=1366.43(18) Å^3, Z=8, D_{calcd}=1.450 Mg/m^3, crystal size 0.40×0.30×0.20 mm, GOF=1.140, R=0.0402/0.0453 ($I>2\sigma(I)$/all data).

4.3.2. Crystal data for 11. CCDC Ref. No. 608945. Crystallized from methanol, $C_{20}H_{17}N_3O$, M_{rel}=315.37, T=120(2) K, Orthorhombic, λ=0.71073 Å, space group $P2_12_12_1$, a=5.8111(6) Å, b=10.0362(10) Å, c=26.568(3) Å, V=1549.5(3) Å^3, Z=4, D_{calcd}=1.352 Mg/m^3, crystal size 0.50×0.25×0.20 mm, GOF=0.948, R=0.0343/0.0480 ($I>2\sigma(I)$/all data).

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Disproportionation reaction of diarylmethylisopropyl ethers: a versatile access to diarylmethanes from diarylcarbinols speeded up by the use of microwave irradiation

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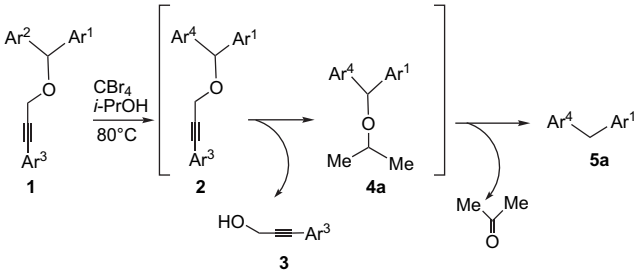
Abstract—An efficient synthesis of diarylmethanes under classical thermal conditions and under microwave heating is described from diarylcarbinols via a new disproportionation reaction. The key step involves a selective hydride transfer of isopropyl ether intermediates. Mild reaction conditions i.e., catalytic CBr_4 or TfOH in *i*-PrOH and good yields render this method useful and competitive to the conventional approaches relying on application of external reducing agents.

1. Introduction

During our research on the synthesis of low generation poly(arylpropargylether) dendrimers,[1] we hoped to cleave a methoxyethoxymethyl- (MEM-) protected phenol under mild conditions as previously described by Lee.[2] However, when ether **1** was reacted with a catalytic amount of CBr_4 in *i*-PrOH at 80 °C, the expected triarylether **2** was not detected. Instead, the only products isolated were the propargylic alcohol **3** (92%) and the diarylmethane **5a** (70%). On the contrary, performing the reaction at a lower temperature (55 °C; 24 h) resulted in the formation of **3** and unsymmetrical ether **4a** (90%).

To explain the formation of **5a** from **1**, we believe that the deprotection of the MEM group occurred and subsequently, the intermediate **2**, unstable under these acidic conditions, cleaved to give the propargylic alcohol **3** together with **5a** having a free phenolic group. The formation of the latter compound would probably result from a selective disproportionation reaction of the unsymmetrical ether **4a** via a concerted selective hydride transfer as in the Meerwein–Ponndorf–Verley-reduction[3] (Scheme 1). The high selectivity of this dismutation requiring catalytic acidic conditions,[4] could be explained by a preferable hydride transfer to the more electrophilic bis-benzylic carbon centre.



Ar^1= 4-$MeOC_6H_4$; Ar^2= 4-$MEMOC_6H_4$; Ar^3= 4-$EtO_2CC_6H_4$; Ar^4= 4-HOC_6H_4

Scheme 1. Plausible mechanism for the formation of **5a** from **1**.

The simplicity of this transformation and the interest of diarylmethane derivatives in organic chemistry led us to investigate this reaction.

Diarylmethane derivatives are of considerable interest as biological and medicinal substrates,[5] models for analogous thermally robust linkages present in fuel resources such as coal[6] and components in acid- or alkali-treated lignins.[7] Besides this, some diarylmethanes are frequently used as subunits in the design of supramolecular structures.[8] A number of methods have been proposed for their synthesis including transition metal-catalyzed cross coupling between aryl or benzyl nucleophiles with benzyl or aryl halides, respectively.[9,10] Alternative routes consist in the reduction of diaryl ketones[11] or benzhydrols[12] using, in most cases, a hydride donor agent (e.g., Et_3SiH, $NaBH_4$, H_2, PMHS, $LiAlH_4$,…) in the presence of TFA or a Lewis acid ($BF_3 \cdot Et_2O$, $AlCl_3$, $InCl_3$…).

Keywords: Disproportionation; Diarylcarbinols; Diarylmethanes; *i*-PrOH; CBr_4; TfOH; Microwave heating.
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Some examples of disproportionation reactions giving access to diarylmethane derivatives[13] were mentioned in the literature. Most of the described methods are sometimes harsh, need strong acidic activations and are often associated with low yields. In this letter, we report a simple and convenient procedure for the synthesis of a range of substituted diarylmethane derivatives from diarylcarbinols mediated by CBr_4 or TfOH (triflic acid) in *i*-PrOH.

2. Results and discussion

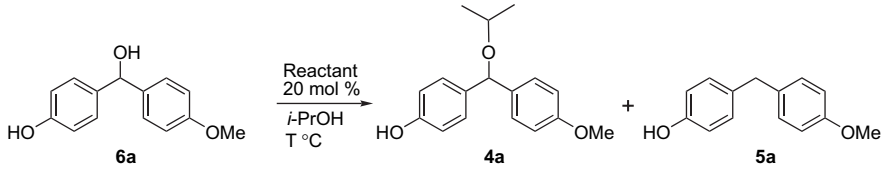
At the outset of this work, we evaluated the effect of a variety of catalysts on the disproportionation of carbinol **6a** chosen as a model substrate. Table 1 summarizes the results of our investigations.

After screening a series of catalysts, we were delighted to find that the use of catalytic amount of CBr_4, PTSA (*p*-toluenesulfonic acid), TfOH and aqueous HBr (entries 1, 2, 4 and 7), in contrast to TFA (trifluoroacetic acid), HCO_2H and Amberlyst 15 (entries 3, 5 and 6) allowed complete conversion of intermediate **4a** into **5a**. The best yield (83%, entry 1) was obtained with CBr_4 (20 mol %) in boiling *i*-PrOH for 24 h.

Next, in the continuation of our work to develop rapid and efficient methodologies, we choose to promote and accelerate the synthesis of **5a** using microwave-assisted irradiation.[14] Because heating was not foreseen to cause any serious decomposition problems, we gradually increased the temperature. We were pleased to observe that, in the presence of CBr_4 (20 mol %) and using microwave irradiation at 140 °C, **6a** was totally transformed into **5a** in only 15 min with a good yield (78%, entry 9). Under these conditions (microwave heating at 140 °C), **6a** was reacted with the other previously tested catalysts (TFA, HCOOH, Amberlyst 15) and the disappearance of the ether **4a** occurred in favour of the diarylmethane **5a** (compare entries 3 and 11, 5 and 13, 6 and 14). Moreover, when using CBr_4, PTSA, TfOH under microwave irradiation, the yields obtained at 140 °C were similar to or better than those observed under classical thermal conditions (compare entries 1 and 9, 2 and 10, 4 and 12). Finally, the amount of the catalyst was then studied. With 5 mol % of either CBr_4 or PTSA, the transformation was efficient and no starting material or intermediate ether **4a** was detected (entries 15, 16). As a control experiment, **6a** was heated in *i*-PrOH with CBr_4 (5 mol %) in a sealed tube at 140 °C for 15 min. Comparison of the results obtained using convectional or microwave heating indicated clearly the efficiency of the latter method (70%, entry 15 vs 40%, entry 17).

Having optimized the reaction parameters, we then examined the reaction with a wide variety of benzhydrols **6**, prepared from Grignard reagents and aromatic aldehydes (Table 2). All benzhydrols subjected to the CBr_4/*i*-PrOH system produced the corresponding diarylmethane derivatives but with variable amounts of their corresponding ether intermediate **4** except in the case of **5b** (entry 1). Thus, when using CBr_4 (20 mol %) in *i*-PrOH for 15 min under microwave irradiation at 140 °C, **5c** and **5d** were obtained together with their isopropylether precursors (entries 2 and 4). On the contrary, replacing CBr_4 by TfOH resulted in a complete disproportionation reaction with higher yields and easier purifications (entries 3 and 5). In this way, reduced phenstatin[15]

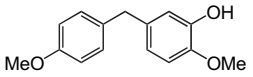
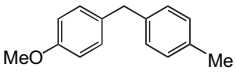
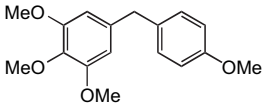
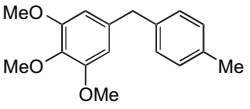
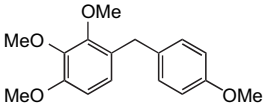
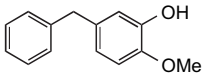
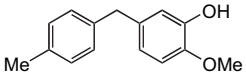
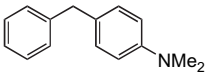
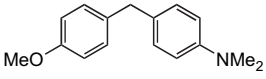
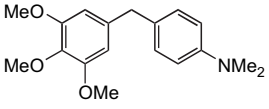
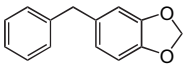
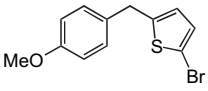
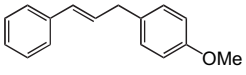
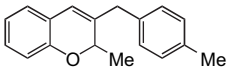
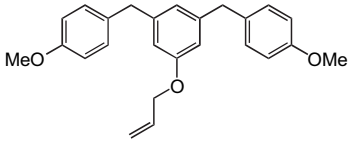
Table 1. Reduction of **6a** in *i*-PrOH



Entry	Reactant	Temperature (°C)	Conditions[a]	Time (h)	**4a**/**5a**[b]	**5** Yield[c] (%)
1	CBr_4	80	A	24	0/100	83
2	PTSA	80	**A**	24	0/100	74
3	TFA	80	A	24	100/0[d]	—
4	TfOH	80	A	24	0/100	70
5	HCO_2H	80	A	24	100/0[d]	—
6	Amberlyst 15	80	A	24	30/70	—
7	Aqueous HBr	80	A	24	0/100	57
8	CBr_4	100	B	0.25	0/100[e]	40
9	CBr_4	140	B	0.25	0/100	78
10	PTSA	140	B	0.25	0/100	80
11	TFA	140	B	0.25	22/78	—
12	TfOH	140	B	0.25	0/100	81
13	HCO_2H	140	B	0.25	50/50	—
14	Amberlyst 15	140	B	0.25	0/100	60
15	CBr_4[f]	140	B	0.25	0/100	70
16	PTSA	140	B	0.25	0/100	65
17	CBr_4[f]	140	C	0.25	0/100	40

[a] Method: **A**: thermal conditions; **B**: microwave irradiation; **C**: sealed tube.
[b] Ratio determined by ^1H NMR analysis ($CDCl_3$) of the crude reaction mixtures.
[c] Yield of isolated product after column chromatography.
[d] Isolated yield of **4a**: 82% (TFA); 76% (HCO_2H).
[e] The ^1H NMR spectrum of the crude mixture revealed the presence of an unidentified by-product.
[f] The reaction was carried out using 5 mol % of CBr_4.

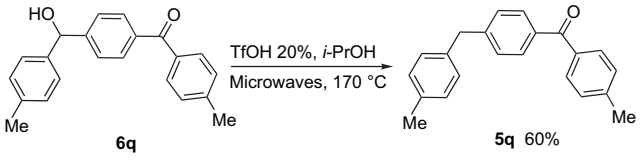
Table 2. Synthesis of diarylmethanes **5** from diarylcarbinols **6** under microwave irradiation

Entry	Alcohols **6**	Diarylmethanes **5**		Reactant (20 mol %)	Yield[a] (%)
1	**6b**		**5b**	CBr_4	70
2 3	**6c**		**5c**	CBr_4 TfOH	61[b] 85
4 5	**6d**		**5d**	CBr_4 TfOH	62[b] 70
6	**6e**		**5e**	TfOH	72
7	**6f**		**5f**	TfOH	80
8	**6g**		**5g**	TfOH	64
9	**6h**		**5h**	TfOH	78
10	**6i**		**5i**	TfOH	87
11	**6j**		**5j**	TfOH	64
12	**6k**		**5k**	TfOH	86
13	**6l**		**5l**	TfOH	75[c]
14	**6m**		**5m**	TfOH	86
15	**6n**		**5n**	TfOH	80[d]
16	**6o**		**5o**	TfOH	51[e]
17	**6p**		**5p**	TfOH	67

[a] Yield of isolated product after column chromatography.
[b] Unsymmetrical diarylmethylisopropyl ether (15–20%) was also isolated.
[c] Reaction time: 1 h.
[d] Obtained as a 1/1 mixture of double bond transposed isomers.
[e] Obtained as a 1/4 mixture of double bond transposed isomers.

analogues **5e** and **5f** were prepared with 72% and 80% isolated yields, respectively (entries 6 and 7). As shown with the model benzhydrol **6a** (Table 1), phenolic benzhydrols as well as amino derivatives afforded the expected diarylmethanes **5g–5k** with good yields (entries 8–12). We have also noticed that the disproportionation was efficient with methylenedioxyaryl analogue, but required a prolonged reaction time (1 h, entry 13). Because various functional groups survived under the reaction conditions, we have applied this process to the brominated thiophene **6m** and we were pleased to observe its total transformation affording the reduced compound **5m** with an excellent yield (86%, entry 14). The protocol was also applied to alcohols **6n**, **6o**. The expected diarylmethane derivatives **5n**, **5o** were then obtained with fair to good yields accompanied by isomers resulting in the double bond migration (entries 15 and 16). Disproportionation was also successful (67% entry 17) with compound **6p** containing two benzydrol units. In that case, we were delighted to find that this process took place with only 10% of TfOH per hydroxyl and preserved the allylic ether function (entry 17).

Finally, we have tested this microwave protocol (catalytic TfOH in *i*-PrOH) with the hydroxyketone **6q**. After stirring for 2 h at 170 °C[16] using microwave heating, we were pleased to observe that the disproportionation process occurred (60%). Careful examination of the crude mixture by ^{1}H NMR did not reveal the presence of reduced by-products (alcohols or diarylmethanes), demonstrating in this manner the selectivity of the present reductive method (Scheme 2).



Scheme 2. Reduction of **6q** preserving the ketone function.

To confirm the selectivity of this process, we have carried out the following experiment. When the model **6a** and benzophenone (as external carbonyl compound) were reacted together for 30 min at 140 °C using microwave heating, we were pleased to observe that the disproportionation of **6a** occurred without affecting the benzophenone, which was recovered totally unchanged (95%). However, we have noticed that under these conditions (TfOH 20%, *i*-PrOH, microwaves, 140 °C) several benzaldehydes were partially reduced under these conditions even in the absence of **6a**.

3. Conclusion

We have described herein a fast and efficient synthesis of functionalized diarylmethane derivatives under classical thermal conditions and in a faster way under microwave irradiation.[17] This process is chemoselective since several functional groups are tolerated (hydroxy, allyl, ketone) in contrary to some of the previously reported methods.[11,12] The key step involves a highly selective disproportionation reaction of diarylmethylisopropyl ether intermediates obtained from the corresponding carbinols. Further developments will be disclosed in due course.

4. Experimental

4.1. Materials

All glasswares were oven-dried at 140 °C. THF was distilled from sodium-benzophenone ketyl.

4.2. Instrumentation

All microwave experiments were performed using an Emrys Optimizer in 2–5 mL Pyrex reaction vessels. Each contained a Teflon stir bar and Teflon coated reaction vessel cap.

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker Avance 300. ^{1}H chemical shifts are reported in parts per million from the peak of residual chloroform (7.27 ppm). ^{13}C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14 ppm). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a Perkin–Elmer 240 analyser. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

4.3. Typical procedure for the preparation of diarylcarbinols 6

At −40 °C, a 1 M solution of Grignard reagent (1.5 mL; 1.5 mmol) was added dropwise to a solution of aldehyde (1 mmol) in THF (10 mL). The mixture was then stirred for 12 h at rt and then hydrolyzed with H_2O (10 mL). The organic phase was separated and the water phase was extracted with ether (2×10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give alcohols **6**, which were further purified by flash chromatography on silica gel.

Alcohols **6a**, **6c**, **6d**, **6g**, **6i**, **6j**, **6k**, **6l** and **6n** are known and gave satisfactory data. All new compounds were characterized by ^{1}H, ^{13}C NMR, IR and elemental analysis.

4.3.1. (4-Methoxyphenyl)-(3-hydroxy-4-methoxyphenyl)-methanol 6b. Yield: 78%.

Mp: 96 °C.

TLC: R_f 0.34 (cyclohexane/AcOEt 60/40, SiO_2).

Anal. Calcd for **6b** ($C_{15}H_{16}O_4$): C, 69.22; H, 6.20. Found: C, 69.10; H, 6.33.

IR (neat) ν_{max}/cm^{-1}: 3447, 3204, 1610, 1510, 1247, 1127, 1025.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10 (d, 1H, J=3.3 Hz), 3.78 (s, 3H), 3.86 (s, 3H), 5.59 (s, 1H), 5.71 (d, 1H, J=3.3 Hz), 6.78–6.92 (m, 5H), 7.27 (d, 2H, J=8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3 (OCH_3), 55.9 (OCH_3), 75.4 (CH), 110.4 (CH), 112.9 (CH), 113.8 (2CH), 118.0

(CH), 127.7 (2CH), 136.2 (C), 137.6 (C), 145.5 (C), 145.6 (C), 159.0 (C).

4.3.2. (3,4,5-Trimethoxyphenyl)-(4-tolyl)methanol 6e. Yield: 76%.

Mp: 95 °C.

TLC: R_f 0.63 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **6e** ($C_{17}H_{20}O_4$): C, 70.81; H, 6.99. Found: C, 70.89; H, 7.13.

IR (neat) ν_{max}/cm^{-1}: 3349, 1590, 1509, 1459, 1422, 1326, 1266, 1128, 1059, 1039, 1004.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.15 (d, 1H, J=3.3 Hz), 2.34 (s, 3H), 3.82 (s, 3H), 3.83 (s, 6H), 5.75 (d, 1H, J=3.3 Hz), 6.61 (s, 2H), 7.16 (d, 2H, J=7.8 Hz), 7.27 (d, 2H, J=7.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1 (CH_3), 56.0 ($2OCH_3$), 60.7 (OCH_3), 76.0 (CH), 103.4 (2CH), 126.4 (2CH), 129.1 (2CH), 137.1 (C), 137.3 (C), 139.6 (C), 140.7 (C), 153.1 (2C).

4.3.3. (3,4,5-Trimethoxyphenyl)-(4-methoxyphenyl)-methanol 6f. Yield: 83%.

TLC: R_f 0.44 (cyclohexane/AcOEt 60/40, SiO_2).

Anal. Calcd for **6f** ($C_{17}H_{20}O_5$): C, 67.09; H, 6.62. Found: C, 66.65; H, 6.86.

IR (neat) ν_{max}/cm^{-1}: 3500, 1601, 1510, 1493, 1462, 1243, 1172, 1092, 1009.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.86 (d, 1H, J=5.7 Hz), 3.68 (s, 3H), 3.81 (s, 3H), 3.87 (s, 6H), 5.91 (d, 1H, J=5.7 Hz), 6.66 (d, 1H, J=8.7 Hz), 6.88 (d, 2H, J=8.7 Hz), 7.00 (d, 1H, J=8.7 Hz), 7.29 (d, 2H, J=8.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.2 (OCH_3), 55.9 (OCH_3), 60.6 ($2OCH_3$), 71.9 (CH), 106.9 (CH), 114.4 (2CH), 122.0 (CH), 128.6 (2CH), 130.1 (C), 136.2 (C), 142.1 (C), 151.2 (C), 153.3 (C), 158.7 (C).

4.3.4. (3-Hydroxy-4-methoxyphenyl)-(4-tolyl)methanol 6h. Yield: 73%.

Mp: 101–102 °C.

TLC: R_f 0.55 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **6h** ($C_{15}H_{16}O_3$): C, 73.75; H, 6.60. Found: C, 73.61; H, 6.78.

IR (neat) ν_{max}/cm^{-1}: 3412, 3229, 1509, 1445, 1277, 1125, 1038, 947.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.07 (d, 1H, J=3.3 Hz), 2.32 (s, 3H), 3.87 (s, 3H), 5.57 (s, 1H), 5.73 (d, 1H, J=3.3 Hz), 6.79–6.94 (m, 3H), 7.13 (d, 2H, J=7.8 Hz), 7.26 (d, 2H, J=7.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1 (CH_3), 55.9 (OCH_3), 79.2 (CH), 110.4 (CH), 113.6 (CH), 118.9 (CH), 126.3 (2CH), 129.1 (2CH), 136.0 (C), 136.8 (C), 139.5 (C), 145.4 (C), 145.8 (C).

4.3.5. (5-Bromothiophen-2-yl)-(4-methoxyphenyl)-methanol 6m. Yield: 61%.

TLC: R_f 0.62 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **6h** ($C_{12}H_{11}BrO_2S$): C, 48.17; H, 3.71. Found: C, 48.37; H, 3.68.

IR (neat) ν_{max}/cm^{-1}: 1610, 1509, 1439, 1244, 1172, 1029, 966.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.91 (s, 1H), 3.80 (s, 3H), 5.83 (s, 1H), 6.57 (d, 1H, J=3.8 Hz), 6.86 (m, 3H), 7.30 (d, 2H, J=8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.3 (OCH_3), 72.1 (CH), 112.1 (C), 114.0 (2CH), 124.9 (CH), 127.7 (2CH), 129.4 (CH), 134.8 (C), 150.1 (C), 159.5 (C).

*We have noticed that after few days **6m** was not stable in $CDCl_3$.*

4.3.6. (2-Methyl-2*H*-chromenyl)-(4-tolyl)methanol 6o. Yield: 80% (mixture of diastereoisomers).

TLC: R_f 0.61 (cyclohexane/AcOEt 70/30, SiO_2).

Anal. Calcd for **6o** ($C_{18}H_{18}O_2$): C, 81.17; H, 6.81. Found: C, 80.87; H, 6.95.

IR (neat) ν_{max}/cm^{-1}: 3404, 1605, 1513, 1485, 1364, 1235, 1206, 1142, 1105, 1040, 1022.

^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (d, 1.5H, J=6.6 Hz), 1.27 (d, 1.5H, J=6.6 Hz), 2.02–2.10 (br s, 1H), 2.36 (s, 3H), 4.69 (q, 0.5H, J=6.6 Hz), 4.94 (q, 0.5H, J=6.6 Hz), 5.25 (s, 0.5H), 5.32 (s, 0.5H), 6.32 (s, 0.5H), 6.58 (s, 0.5H), 6.70–7.30 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: (the presence of diastereoisomers complicates the spectrum; only the most significant resonances are listed) 19.5 (CH_3), 20.0 (CH_3), 21.2 ($2CH_3$), 71.7 (2CH), 74.0 (CH), 75.0 (CH), 116.3 (CH), 116.4 (CH), 118.1 (CH), 120.0 (CH), 121.2 (CH), 121.3 (CH), 122.2 (2C), 126.6 (2CH), 126.8 (2CH), 129.1 (2CH), 129.3 (2CH), 129.5 (2CH), 130.0 (2CH), 137.7 (C), 138.2 (2C), 138.4 (C), 140.1 (C), 140.2 (C), 153.6 (2C).

4.3.7. Compound 6p. Compound **6p** was prepared from 5-allyloxy-isophthalic acid dimethyl ester in three steps as follows.

4.3.7.1. 3,5-Bis(hydroxymethyl)-(1-allyloxy)-phenyl. Under argon, were mixed $LiAlH_4$ in 110 mL of THF (8.7 g; 230.4 mmol) and 5-allyloxy-isophthalic acid dimethyl ester (14.4 g; 57.6 mmol) in 80 mL of THF. The stirred solution was then refluxed for 3 h. After cooling at 0 °C, the solution was hydrolyzed dropwise with H_2O

(100 mL), filtered and concentrated under vacuo to give 10.7 g (55.1 mmol) of the diol.

Yield: 96%.

TLC: R_f 0.52 (CH_2Cl_2/MeOH 90/10, SiO_2).

Mp: 54–55 °C.

IR (neat) ν_{max}/cm^{-1}: 3335, 3251, 3015, 2930, 2876, 1594.

^1H NMR (300 MHz, MeOD) δ: 4.54 (dt, 2H, J=5.1 Hz, J=1.6 Hz), 4.56 (s, 4H), 5.23 (dq, 1H, J=10.5 Hz; J=1.6 Hz), 5.39 (dq, 1H, J=17.2 Hz, J=1.6 Hz), 6.02 (m, 1H), 6.84 (s, 2H), 6.91 (s, 1H), (OH not seen).

^{13}C NMR (75 MHz, MeOD) δ: 65.1 (CH_2), 69.7 ($2CH_2$), 113.0 (CH), 117.4 (CH_2), 118.7 (2CH), 135.0 (CH), 144.4 (2C), 160.4 (C).

4.3.7.2. 5-Allyloxyisophthalaldehyde. A solution of the diol (350 mg; 1.80 mmol) in CH_2Cl_2 (11 mL) was mixed with PCC (1.24 g; 5.7 mmol) and stirred for 2 h at rt. The mixture was then diluted in Et_2O (15 mL) and filtered over SiO_2. The filtrate was concentrated under vacuo to give 5-allyloxyisophthalaldehyde (280 mg, 1.47 mmol) as a white solid.

Yield: 85%.

TLC: R_f 0.33 (cyclohexane/AcOEt 80/20, SiO_2).

Mp: (cyclohexane) 67–68 °C.

IR (neat) ν_{max}/cm^{-1}: 3000, 2832, 1681, 1592.

^1H NMR (300 MHz, $CDCl_3$) δ: 4.59 (dt, 2H, J=5.2 Hz, J=1.4 Hz), 5.27 (dq, 1H, J=10.5 Hz; J=1.4 Hz), 5.39 (dq, 1H, J=17.2 Hz, J=1.4 Hz), 6.00 (m, 1H), 7.59 (s, 2H), 7.89 (s, 1H), 9.98 (s, 2H).

^{13}C NMR (75 MHz, MeOD) δ: 69.3 (CH_2), 118.4 (CH), 120.0 (2CH), 124.1 (CH), 132.0 (CH), 138.2 (2C), 157.9 (C), 190.7 (2C).

4.3.7.3. 3,5-Bis[(4-methoxyphenyl)hydroxymethyl]-1-allyloxy-benzene 6p. Yield: 50%.

Mp: 101–103 °C.

TLC: R_f 0.13 (cyclohexane/AcOEt 60/40, SiO_2).

Anal. Calcd for **6p** ($C_{25}H_{26}O_5$): C, 73.87; H, 6.45. Found: C, 73.71; H, 6.48.

IR (neat) ν_{max}/cm^{-1}: 3347, 1611, 1509, 1441, 1282, 1247, 1168, 1111, 1028.

^1H NMR (300 MHz, $CDCl_3$) δ: 3.03 (s, 6H), 3.77 (d, 2H, J=5.0 Hz), 3.88 (d, 2H, J=4.0 Hz), 4.47 (d, 1H, J=10.4 Hz), 4.64 (d, 1H, J=17.2 Hz), 4.97 (d, 2H, J=4.0 Hz), 5.21–5.40 (m, 1H), 6.10–6.14 (m, 6H), 6.34 (s, 1H), 6.57 (d, 4H, J=8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.5 ($2OCH_3$), 70.2 (CH_2), 76.8 (2CH), 112.9 (2CH), 115.2 (4CH), 118.3 (CH), 118.9 (CH), 129.6 (4CH), 135.8 (CH), 139.5 (2C), 149.1 (2C), 160.5 (2C), 160.7 (C).

4.3.8. {4-[(4-Tolyl)-hydroxymethyl]-phenyl}-(4-tolyl)-methanone 6q. Compound **6q** was obtained as a by-product (22%) of the reaction between *p*-tolyl magnesium bromide (1 equiv) and terephthaldicarboxaldehyde (2 equiv) as follows: to a solution of terephthaldicarboxaldehyde (2.68 g, 22 mmol) in 40 mL of THF was added dropwise at −40 °C under argon, 11 mL (11 mmol) of a 1 M solution of *p*-tolyl magnesium bromide. After stirring for a night at rt, the mixture was treated with H_2O (30 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were then dried with $MgSO_4$ and evaporated to dryness. Purification by flash chromatography afforded **6q** as a white solid.

Yield: 22% (not optimized).

Mp: 108 °C.

TLC: R_f 0.63 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **6q** ($C_{22}H_{20}O_2$): C, 83.51; H, 6.37. Found: C, 83.29; H, 6.22.

IR (neat) ν_{max}/cm^{-1}: 3483, 2918, 1637, 1604, 1569, 1413, 1316, 1279, 1177, 1043, 1017.

^1H NMR (300 MHz, $CDCl_3$) δ: 1.75 (s, 3H), 1.84 (s, 3H), 2.40 (s, 1H, OH), 5.25 (s, 1H), 6.56 (d, 2H, J=7.8 Hz), 6.67 (d, 4H, J=7.8 Hz), 6.88 (d, 2H, J=8.4 Hz), 7.10 (d, 2H, J=7.8 Hz), 7.13 (d, 2H, J=8.4 Hz).

^{13}C NMR (75 MHz) δ: 21.1 (CH_3), 21.6 (CH_3), 60.4 (CH), 126.6 (2CH), 127.2 (2CH), 128.9 (2CH), 129.8 (2CH), 130.1 (2CH), 130.2 (2CH), 134.8 (C), 136.7 (C), 137.5 (C), 140.5 (C), 143.1 (C), 148.3 (C), 196.2 (C).

4.4. Typical procedure for the disproportionation of carbinols under thermal conditions

To a flask containing **6a** (1 mmol) was added CBr_4 (66 mg, 0.2 mmol) in *i*-PrOH (8 mL). The mixture was then stirred at 80 °C for 24 h. After cooling to rt, the crude mixture was hydrolyzed with H_2O (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried with $MgSO_4$ and evaporated to dryness. Purification by flash chromatography afforded the diarylmethane derivative **5a**.

4.5. Typical procedure for the disproportionation of carbinols under microwave irradiation

To an Emrys Optimizer 2–5 mL Pyrex reaction vessel were added 0.2 mL of a 1 M solution of TfOH in *i*-PrOH, 1 mmol of diarylcarbinol and *i*-PrOH (3 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 140 °C, time 900 s, fixed hold time: on, sample absorption: high, pre-stirring: 60 s. After cooling to rt, the crude mixture was treated as above.

Diarylmethanes **5a**, **5c**, **5d**, **5f**, **5g**, **5i**, **5j**, **5l** and **5n** are known and gave satisfactory data.

4.5.1. (4-Methoxyphenyl)-(3-hydroxy-4-methoxyphenyl)-methane 5b. Yield: 70%.

Mp: 61–62 °C.

TLC: R_f 0.48 (cyclohexane/AcOEt 60/40, SiO_2).

Anal. Calcd for **5b** ($C_{15}H_{16}O_3$): C, 73.75; H, 6.60. Found: C, 73.71; H, 6.67.

IR (neat) ν_{max}/cm^{-1}: 3467, 1609, 1586, 1508, 1463, 1444, 1271, 1223, 1202, 1178, 1130, 1020.

^1H NMR (300 MHz, $CDCl_3$) δ: 3.78 (s, 3H), 3.83 (s, 2H), 3.85 (s, 3H), 5.56 (s, 1H), 6.66 (dd, 1H, J=8.2 Hz, J=1.8 Hz), 6.76 (d, 1H, J=1.8 Hz), 6.77 (d, 1H, J=8.2 Hz), 6.82 (d, 2H, J=8.4 Hz), 7.10 (d, 2H, J=8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.4 (CH_2) 55.2 (OCH_3), 56.0 (OCH_3), 110.6 (CH), 113.8 (2CH), 115.1 (CH), 120.0 (CH), 129.7 (2CH), 133.5 (C), 135.0 (C), 144.9 (C), 145.5 (C), 157.9 (C).

4.5.2. (4-Tolyl)-(3,4,5-trimethoxyphenyl)methane 5e. Yield: 80%.

Mp: 53 °C.

TLC: R_f 0.40 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **5e** ($C_{17}H_{20}O_3$): C, 74.97; H, 7.40. Found: C, 74.89; H, 7.29.

IR (neat) ν_{max}/cm^{-1}: 1588, 1506, 1465, 1421, 1324, 1240, 1120, 1001.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 3.90 (s, 2H), 6.42 (s, 2H), 7.12 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.9 (CH_3), 41.7 (CH_2), 56.0 ($2OCH_3$), 60.8 (OCH_3), 105.8 (2CH), 128.6 (2CH), 129.1 (2CH), 135.6 (C), 136.2 (C), 136.9 (C), 137.8 (C), 153.1 (2C).

4.5.3. (4-Tolyl)-(3-hydroxy-4-methoxyphenyl)methane 5h. Yield: 64%.

Mp: 80–81 °C.

TLC: R_f 0.20 (cyclohexane/AcOEt 70/30, SiO_2).

Anal. Calcd for **5h** ($C_{15}H_{16}O_2$): C, 78.92; H, 7.06. Found: C, 78.87; H, 7.05.

IR (neat) ν_{max}/cm^{-1}: 3435, 1587, 1502, 1468, 1446, 1351, 1302, 1238, 1127, 1020.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 3.86 (s, 5H), 5.56 (s, 1H, OH), 6.67 (dd, 1H, J=10.0 Hz, J=2.1 Hz), 6.76–6.80 (m, 2H), 7.09 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0 (CH_3), 40.9 (CH_2), 56.0 (OCH_3), 110.6 (CH), 115.1 (CH), 120.1 (CH), 128.7 (2CH), 129.1 (2CH), 134.8 (C), 135.4 (C), 138.3 (C), 144.9 (C), 145.5 (C).

4.5.4. (4-Methoxyphenyl)-(4-*N*,*N*-dimethylaminophenyl)-methane 5k. Yield: 86%.

Mp: 77 °C.

TLC: R_f 0.26 (cyclohexane/AcOEt 80/20, SiO_2).

Anal. Calcd for **5k** ($C_{18}H_{23}NO_3$): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.55; H, 7.95; N, 4.50.

IR (neat) ν_{max}/cm^{-1}: 1614, 1588, 1521, 1505, 1461, 1421, 1237, 1123, 1006.

^1H NMR (300 MHz, $CDCl_3$) δ: 2.93 (s, 6H), 3.82 (s, 9H), 3.84 (s, 2H), 6.41 (s, 2H), 6.73 (d, 2H, J=8.7 Hz), 7.08 (d, 2H, J=8.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.8 ($2NCH_3$), 41.2 (CH_2), 56.0 ($2OCH_3$), 60.8 (OCH_3), 105.7 (2CH), 113.0 (2CH), 129.3 (2CH), 136.1 (C), 137.7 (2C), 149.1 (C), 153.1 (2C).

4.5.5. 2-Bromo-5-(4-methoxybenzyl)thiophene 5m. Yield: 86%.

TLC: R_f 0.59 (cyclohexane/AcOEt 50/50, SiO_2).

Anal. Calcd for **5m** ($C_{12}H_{11}BrOS$): C, 50.90; H, 3.92; S, 11.32. Found: C, 50.20; H, 3.78; S, 11.08.

IR (neat) ν_{max}/cm^{-1}: 1614, 1588, 1521, 1505, 1461, 1421, 1237, 1123, 1006.

^1H NMR (300 MHz, $CDCl_3$) δ: 3.78 (s, 3H), 3.99 (s, 2H), 6.52 (d, 1H, J=4.0 Hz), 6.82–6.85 (m, 3H), 7.13 (d, 2H, J=8.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.6 (CH_2), 55.2 (OCH_3), 109.9 (C), 114.0 (2CH), 125.1 (CH), 129.5 (CH), 129.6 (CH), 130.9 (CH), 131.6 (C), 146.6 (C), 158.4 (C).

4.5.6. 2-Methyl-3-(4-methylbenzyl)-2*H*-chromene 5o. Yield: 51%.

TLC: R_f 0.40 (cyclohexane/AcOEt 80/20, SiO_2).

IR (neat) ν_{max}/cm^{-1}: (mixture of isomers) 2922, 1766, 1657, 1607, 1578, 1514, 1487, 1456, 1370, 1236, 1207, 1108, 1039.

^1H NMR (300 MHz, $CDCl_3$) (obtained as an inseparable mixture (4/1) with its minor double bond transposed isomer) *major isomer* ***5o*** δ: 1.33 (d, 3H, J=6.6 Hz), 2.35 (s, 3H), 3.36 (d, 1H, J=15.9 Hz), 3.46 (d, 1H, J=15.9 Hz), 4.79 (q, 1H, J=6.6 Hz), 6.07 (s, 1H), 6.78 (d, 1H, J=8.1 Hz), 6.84 (t, 1H, J=16.0 Hz), 6.93 (dd, 1H, J=6.0 Hz, J=1.3 Hz), 7.05–7.13 (m, 5H). *2-Methyl-3-(4-methylbenzylidene)chromane (minor isomer)*: (only the most significant resonances are listed) δ: 1.50 (d, 3H, J=6.6 Hz), 2.36 (s, 3H), 3.38

(d, 1H, J=19.0 Hz), 3.87 (d, 1H, J=19.0 Hz), 5.37 (d, 1H, J=6.6 Hz), 6.56 (s, 1H), 6.89 (d, 2H, J=7.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) *major isomer* ***5o*** δ: 18.9 (CH_3), 29.9 (CH_3), 39.3 (CH_2), 73.7 (CH), 115.9 (CH), 119.6 (CH), 120.9 (CH), 122.5 (C), 125.9 (CH), 128.4 (CH), 129.0 (2CH), 129.2 (2CH), 134.8 (C), 136.0 (C), 138.5 (C), 151.5 (C). ^{13}C NMR (75 MHz, $CDCl_3$) *minor isomer*: (only the most significant resonances are listed) δ: 21.1 (CH_3), 29.6 (CH_3), 31.6 (CH_2), 70.1 (C), 117.1 (CH), 120.3 (CH), 125.4 (CH), 127.4 (CH), 128.5 (CH), 153.0 (C).

4.5.7. 3,5-Bis(4-methoxybenzyl)-1-allyloxybenzene 5p. Yield: 67%.

TLC: R_f 0.47 (cyclohexane/AcOEt 90/10, SiO_2).

Anal. Calcd for **5p** ($C_{25}H_{26}O_3$): C, 80.18; H, 7.00. Found: C, 80.12; H, 6.98.

IR (neat) ν_{max}/cm^{-1}: 1592, 1509, 1453, 1241, 1175, 1107, 1034.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 6H), 3.86 (s, 4H), 4.44 (dt, 2H, J=5.7 Hz, J=1.5 Hz), 5.28 (dq, 1H, J=10.5 Hz, J=1.5 Hz), 5.36 (dq, 1H, J=17.4 Hz, J=1.5 Hz), 5.95–6.08 (m, 1H), 6.56 (s, 2H), 6.65 (s, 1H), 6.83 (d, 4H, J=8.7 Hz), 7.10 (d, 4H, J=8.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.0 ($2CH_2$), 55.2 ($2OCH_3$), 68.6 (CH_2), 112.9 (2CH), 113.8 (4CH), 117.6 (CH_2), 122.1 (CH), 129.8 (4CH), 133.0 (2C), 133.3 (CH), 143.0 (2C), 157.9 (2C), 158.9 (C).

4.5.8. [4-(4-Methylbenzyl)-phenyl]-(4-tolyl)methanone 5q. Yield: 61%.

TLC: R_f 0.55 (cyclohexane/AcOEt 90/10, SiO_2).

Anal. Calcd for **5q** ($C_{22}H_{20}O$): C, 87.96; H, 6.71. Found: C, 87.94; H, 6.66.

IR (neat) ν_{max}/cm^{-1}: 1652, 1605, 1312, 1276, 1177, 1114.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 2.53 (s, 3H), 4.11 (s, 2H), 7.21 (s, 4H), 7.35–7.40 (m, 4H), 7.79–7.83 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0 (CH_3), 21.6 (CH_3), 41.5 (CH_2), 120.1 (2CH), 129.3 (4CH), 130.1 (2CH), 130.2 (2CH), 130.3 (2CH), 135.1 (C), 135.7 (C), 135.8 (C), 137.1 (C), 143.0 (C), 146.1 (C), 196.1 (C).

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16. At 140 °C, the disproportionation was incomplete (30% of **4q** was observed in the crude mixture).
17. The experimental microwave experiments described in this letter are well established and controlled and can be safely and beneficially reproduced.

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Sequential Baylis–Hillman reaction and radical cyclization of furanose derivatives: expeditious approach to enantiopure benzo-fused nine-membered oxacycles

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Abstract—A regioselective 9-*endo-trig* aryl radical cyclization of D-glucose derived diastereomeric Baylis–Hillman reaction products with Bu_3SnH led to highly functionalized tricyclic benzannulated ethers incorporating *cis*- and *trans*-9,5 bicyclic systems in good yields. Degradation of one of the products afforded an enantiopure multifunctionalized benzoxonine derivative.

1. Introduction

Benzo-fused cyclic molecules are often referred to as 'privileged structures' owing to their ubiquitous appearance in natural products as well as modern pharmaceuticals.[1] Recently, benzannulated medium-ring heterocycles and related bicyclic analogues have been reported[2] to be useful as CCR-5 antagonists and as anti-HIV agents. The abundance of annulated oxonine rings in biologically important compounds[3] continues to ensure that they are important synthetic targets. This has prompted the use of a large number of methods for their synthesis.[4] Compared to benzoxepines or benzoxocines, synthetic routes to benzoxonine rings are not reported. We had earlier reported successful preparation of the benzannulated seven- and eight-membered oxacycles through radical cyclization on unsubstituted olefins (Fig. 1).[5,6] Unfortunately, this method could not be extended to the synthesis of nine-membered ring system despite repeated attempts with variations in reagents or conditions.

We envisaged that the presence of an electron withdrawing group conjugated to the olefinic bond might help the ring closure by 1,4 addition, leading to the formation of the desired ring system.[7] Starting from our carbohydrate derived chirons **1a–c** and **1d**, suitably designed substrates **2a–e**, **3a–e**, **2f**, and **3f** for the cyclization could be accessible by application of the Baylis–Hillman reaction.

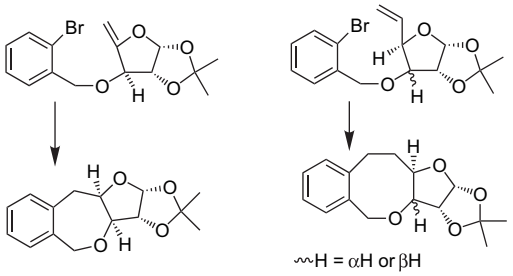

Figure 1. Syntheses of seven- and eight-membered ring ethers.

In this paper we report a sequential Baylis–Hillman reaction and intramolecular radical cyclization[8] to the synthesis of sugar annulated benzoxonine derivatives. Cleavage of the sugar ring of one of these tricyclic derivatives provides multifunctionalized enantiopure benzoxonine.

2. Results and discussion

Initially, *O*-2-bromobenzylated-1,2:5,6-di-*O*-isopropylidene glucofuranoside **1a**,[5] its analogues **1b–c**,[5] and the 3-*O*-epimeric sugar derivative **1d**[5,9] were converted to the noraldehydes through selective deketalization and sodium periodate oxidation. Subsequent Baylis–Hillman reactions of the crude aldehydes were carried out with suitable acrylates

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and acrylonitriles (3 equiv) in the presence of 100 mol % of DABCO in dioxane–water (7:3).[10] The reactions afforded mixtures of the adducts **2a–f** and **3a–f** in approximately 70–80% yield (Table 1) along with small amounts of the unreacted aldehydes (Scheme 1). Subsequently, the isomeric mixtures of **2a–d** and **2f** with **3a–d** and **3f** were separated by flash chromatography. The relative stereochemistries of **2a–d**, **2f**, **3a–d**, and **3f** are based upon comparison of the observed chemical shifts and *J* values with those reported for the corresponding *O*-methyl analogues by Krishna et al.[11]

Radical cyclization of each of the diastereoisomeric alkenes **2a–d** and **3a–d** in refluxing benzene with Bu_3SnH (1.5 equiv) and AIBN (5 mol %) followed by separation of the tin compounds,[12] acetylation, and chromatography furnished (Scheme 2) the respective tricyclic ethers **4a–d** and **5a–d** as the only isolable products (Table 2). Similar treatment of the diastereomeric mixture of **2e+3e** furnished **4e** and **5e**, which could be resolved chromatographically.

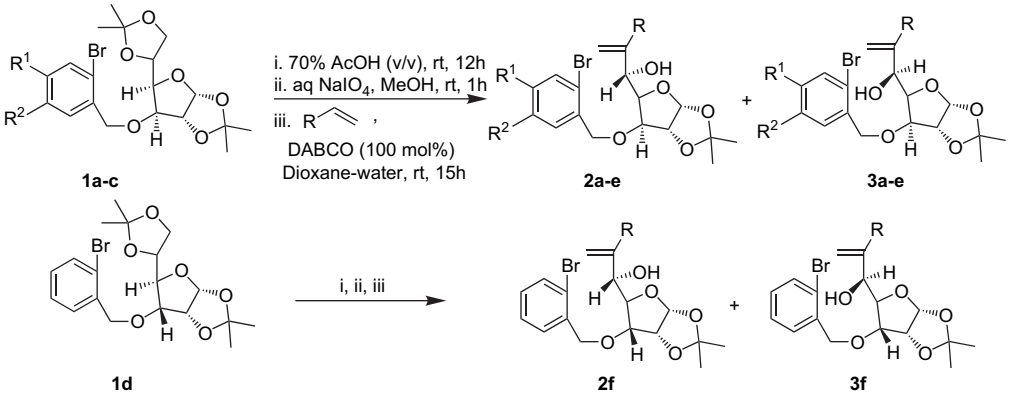
Table 1. Preparation of diastereomeric alkenes **2a–f** and **3a–f**

Entry	Substrate	R	R^1	R^2	Products (yield %)
1	**1a**	$-CO_2Me$	H	H	**2a** (31), **3a** (46)
2	**1b**	$-CO_2Me$	–OMe	–OMe	**2b** (34), **3b** (46)
3	**1c**	$-CO_2Me$	$-OCH_2O-$	—	**2c** (31), **3c** (45)
4	**1a**	$-CO_2Et$	H	H	**2d** (32), **3d** (43)
5	**1a**	–CN	H	H	**2e+3e** (76)[a]
6	**1d**	$-CO_2Me$	H	H	**2f** (18), **3f** (60)

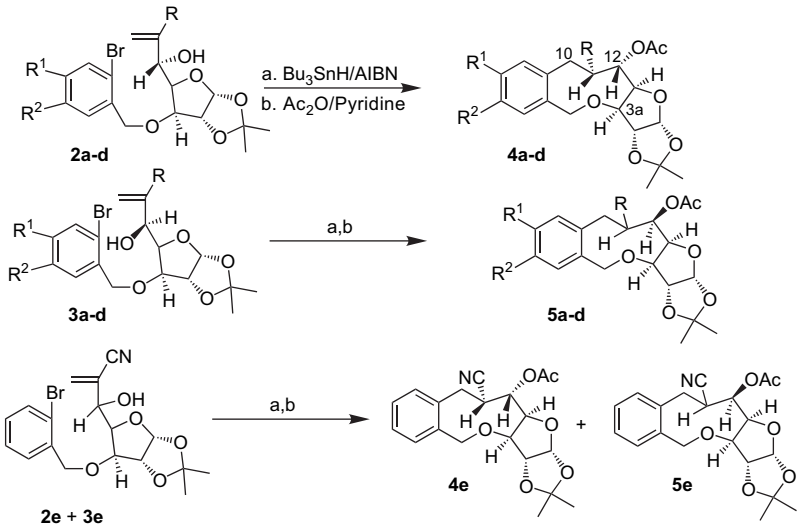
[a] Attempts to separate the diastereomeric mixture of **2e** and **3e** were unsuccessful. We therefore used the mixture for the next step.

The stereochemistry of the oxonine derivatives **4a–e** could not be established by ^1H NMR spectroscopy due to their poorly resolved spectra. However, the structure of **4a**[13] was determined by X-ray diffraction study (Fig. 2), which clearly established a cis-orientation of the acetoxy and carbomethoxy groups at the C_{11}–C_{12} bond. The gross structures of **5a–e** were ascertained by ^1H NMR spectroscopy as well as by adequate ^{13}C NMR, ^1H–^1H COSY, and mass spectral analyses.

We next focused our attention on the corresponding D-allose derived olefins **2f** and **3f** where the ring forming bonds are trans-oriented. The radical cyclization of **2f** and **3f** could indeed be effected under similar condition as described above. Usual work up and chromatographic purification gave the respective tricyclic ethers **6** and **7** in 47% and 52% yields (Scheme 3).



Scheme 1. Baylis–Hillman reaction of sugar derived aldehydes with activated olefins.



Scheme 2. Radical cyclization of alkenes.

Table 2. Syntheses of tricyclic benzannulated ethers **4a–e** and **5a–e**

Entry	Substrate	Product	Yield (%)
1	**2a**	**4a**	64
2	**2b**	**4b**	57
3	**2c**	**4c**	58
4	**2d**	**4d**	53
5	**3a**	**5a**	71
6	**3b**	**5b**	67
7	**3c**	**5c**	63
8	**3d**	**5d**	67
9	**2e+3e**	**4e**,[a] **5e**[a]	42, 37

[a] The isomeric mixture of **4e** and **5e** was separated by flash chromatography.

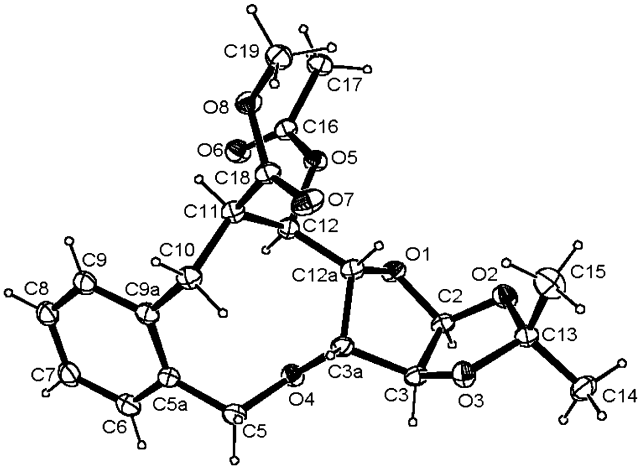
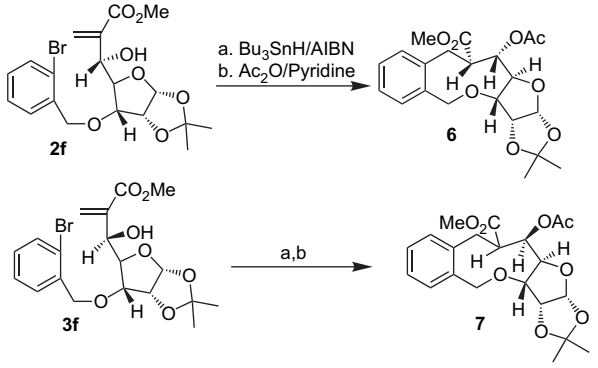
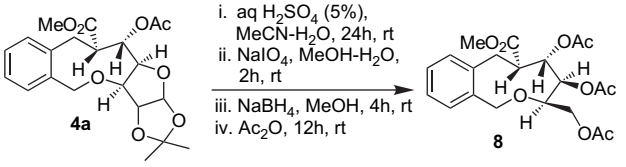


Figure 2. ORTEP diagram of **4a**.



Scheme 3. Radical cyclization of alkenes **2f** and **3f**.

The assigned structures of **6** and **7** were based upon spectroscopic data. These studies showed that the cyclization preferred the 9-*endo-trig* pathway in agreement with the general trend observed in the radical cyclization of medium and large rings, where *endo* cyclization modes are favored,[14] and with other experimental results on ring closures.[6] The feasibility of synthesizing benzoxonine derivatives from the annulated sugar derivatives could also be realized. Thus, **4a** was converted (Scheme 4) into the multifunctionalized benzoxonine **8** (overall yield 22%) through a sequence of reactions involving removal of the 1,2-*O*-isopropylidene group with 5% H_2SO_4 (v/v) in CH_3CN–H_2O (3:1), $NaIO_4$ cleavage of the resulting diol, $NaBH_4$ reduction of the generated carbonyl group and acetylation.



Scheme 4. Conversion of **4a** to the benzoxonine derivative **8**.

3. Conclusion

In summary, we have developed a straightforward and an efficient synthetic route to benzannulate nine-membered oxacycles using sequential Baylis–Hillman reaction and radical cyclization on appropriate furanose derivatives. The reaction worked on a variety of D-glucose derived substrates and could be extended to other sugar derived products. The findings open up the possibility of obtaining enantiopure multifunctionalized benzoxonine derivatives starting from an appropriate sugar derivatives.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in a Bruker AM 300L or ADVANCE 600 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra were obtained using either JEOL AX-500 or Micromass Q-Tofmicro™ spectrometers. IR spectra were obtained from JASCO FT/IR Model 410. Elemental analyses were carried out with a C,H,N analyzer. Specific rotations were measured at 589 nm on a JASCO P-1020 polarimeter. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography and flash chromatography were carried out using commercial-grade silica gel (60–120 mesh or 230–400 mesh). PS and EA are abbreviated for petroleum spirit (60–80 °C) and ethyl acetate, respectively.

4.2. General procedure for the syntheses of compounds 1a–d[5]

To a magnetically stirred solution of 1,2:5,6-di-*O*-isopropylidene glucofuranoside (1 mmol) and the appropriate 2-bromobenzyl bromide (1.2 mmol) in CH_2Cl_2 (20 mL) was added Bu_4NBr (50 mg) followed by aqueous NaOH (50%, 20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h and extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were washed with H_2O (3×25 mL), dried (Na_2SO_4), and evaporated to afford a syrup, which on column chromatography over silica gel yielded the corresponding bromobenzyl derivatives.

4.2.1. (3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (1a). Thick oil (300 mg, 70%); $[\alpha]_D^{27}$ −21.6 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 4.00 (dd, *J* 5.8, 8.4 Hz, 1H), 4.07–4.18 (m, 3H), 4.39 (dd, *J* 13.6, 6.0 Hz, 1H), 4.65–4.69 (d-like, 2H), 4.76 (d, *J* 12.8 Hz, 1H), 5.92 (d, *J* 3.6 Hz, 1H), 7.15–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 26.6, 27.1, 27.2, 67.8, 70.0, 72.8,

81.7, 82.6, 82.9, 105.7, 109.4, 112.2, 123.0, 127.7, 129.5, 129.6, 132.9, 137.4; IR (Neat) ν_{max} 2985, 1450, 1376 cm^{-1}; Anal. Calcd for $C_{19}H_{25}BrO_6$: C, 53.16; H, 5.87. Found: C, 53.00; H, 5.75; ESIMS: *m/z* 451, 453 (MNa^+ for Br^{79}, Br^{81}).

4.2.2. (3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (1b). Thick oil (366 mg, 75%); $[\alpha]_D^{27}$ −30.5 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.03–4.18 (m, 4H), 4.39 (dd, *J* 13.6, 5.9 Hz, 1H), 4.60 (d, *J* 12.1 Hz, 1H), 4.65 (d, *J* 3.7 Hz, 1H), 4.71 (d, *J* 12.1 Hz, 1H), 5.90 (d, *J* 3.7 Hz, 1H), 6.98 (s, 1H), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 26.6, 2×27.2, 56.5, 56.6, 67.7, 71.9, 73.0, 81.6, 82.3, 82.9, 105.6, 109.4, 112.2, 112.9, 113.4, 115.9, 129.4, 148.9, 149.6; IR (Neat) ν_{max} 2946, 1509, 1269 cm^{-1}; Anal. Calcd for $C_{21}H_{29}BrO_8$: C, 51.54; H, 5.97. Found: C, 51.40; H, 5.85; ESIMS: *m/z* 511, 513 (MNa^+ for Br^{79}, Br^{81}).

4.2.3. (3a*R*,5*R*,6*S*,6a*R*)-5-Bromo-6-[5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole-6-yloxymethyl]-benzo[1,3]dioxole (1c). Thick oil (330 mg, 70%); $[\alpha]_D^{27}$ −29.3 (*c* 0.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 3.99 (dd, *J* 6, 8 Hz, 1H), 4.03–4.15 (m, 3H), 4.37 (dd, *J* 6, 13.8 Hz), 4.56 (d, *J* 12.6 Hz, 1H), 4.64 (d, *J* 3.7 Hz, 1H), 4.67 (d, *J* 12.6 Hz, 1H), 5.91 (d, *J* 3.6 Hz, 1H), 5.96 (s, 2H), 6.99 (s, 1H), 7.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.7, 27.2, 68.0, 71.8, 72.8, 81.8, 82.3, 82.9, 102.1, 105.7, 109.5, 109.8, 112.3, 113.0, 113.5, 130.6, 147.9, 148.3; IR (Neat) ν_{max} 2983, 2925, 1728 cm^{-1}; Anal. Calcd for $C_{20}H_{25}BrO_8$: C, 50.75; H, 5.32. Found: C, 50.42; H, 5.29; MS (EI): *m/z* 472, 474 (40%, M^+ for Br^{79}, Br^{81}).

4.2.4. (3a*R*,5*R*,6*R*,6a*R*)-6-(2-Bromo-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (1d). White solid (317 mg, 74%); mp 54 °C; $[\alpha]_D^{27}$ +99.1 (*c* 1.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.37 (s, 3H), 1.59 (s, 6H), 3.93 (dd, *J* 4.5, 8.5 Hz, 1H), 4.03 (d, *J* 7.0 Hz, 2H), 4.16 (dd, *J* 3.4, 8.5 Hz, 1H), 4.36 (dt, *J* 3.4, 6.9 Hz, 1H), 4.68 (d, *J* 12.8 Hz, 1H), 4.71 (t-like, 1H) 4.85 (d, *J* 12.8 Hz, 1H), 5.79 (d, *J* 3.8 Hz, 1H), 7.16–7.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.2, 26.2, 26.7, 26.8, 65.2, 71.3, 74.9, 75.0, 77.9, 78.3, 104.0, 109.6, 113.0, 122.7, 127.5, 129.2, 129.7, 132.5, 137.0; IR (Neat) ν_{max} 2979, 1439, 1374 cm^{-1}; Anal. Calcd for $C_{19}H_{25}BrO_6$: C, 53.15; H, 5.87. Found: C, 52.96; H, 5.84; MS (EI): *m/z* 413, 415 (45%, M^+-15 for Br^{79}, Br^{81}).

4.3. General procedure for the syntheses of olefins 2a–f and 3a–f

The appropriate bromobenzyl derivative **1a–d** (1 mmol) was stirred overnight with 70% aqueous HOAc (v/v, 50 mL) at room temperature (monitored by TLC till disappearance of starting material). Removal of HOAc on a rotary evaporator under reduced pressure (temp 40 °C) using dry toluene (4×25 mL) afforded the intermediate diol as viscous syrup. A solution of the intermediate diol in the minimum volume of methanol was cooled to 0 °C and treated with aqueous $NaIO_4$ (1.2 mmol, dissolved in 20 mL of water) dropwise with stirring (45 min). The reaction mixture was evaporated under reduced pressure and the residual syrup was extracted with $CHCl_3$ (4×25 mL). The combined organic layers were washed with water (3×25 mL), dried (Na_2SO_4), and evaporated to furnish the crude aldehyde.[5] To a solution of this crude aldehyde in dioxane–water [(7:3), 10 mL], DABCO (100 mol %) and methylacrylate (3 mmol) [or ethylacrylate (3 mmol) or acrylonitrile (3 mmol)] were added and stirred for 15 h at room temperature. After the completion of reaction (TLC), the mixture was extracted with ethyl acetate (3×15 mL). The extract was washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford a residue, which was purified by flash chromatography on silica gel (230–400 mesh) using 30–40% ethyl acetate in petroleum ether (60°–80 °C) to furnish corresponding Baylis–Hillman adducts **2a–f** and **3a–f**.

4.3.1. 2-{(*R*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (2a). Colorless liquid (137 mg, 31%); $[\alpha]_D^{27}$ −10.8 (*c* 3.70 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.48 (s, 3H), 3.52 (d, *J* 3.1 Hz, 1H), 3.73 (s, 3H), 4.14 (d, *J* 3.6 Hz, 1H), 4.50 (t, *J* 3.5 Hz, 1H), 4.57 (d, *J* 12.0 Hz, 1H), 4.71 (d, *J* 3.7 Hz, 1H), 4.78 (d, *J* 12.0 Hz, 1H), 4.92 (s, 1H), 6.02 (d, *J* 3.7 Hz, 1H), 6.06 (s, 1H), 6.38 (s, 1H), 7.19 (t-like, 1H), 7.32 (t-like, 1H), 7.41 (d-like, 1H), 7.58 (d-like, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 51.8, 68.7, 71.5, 80.1, 82.0, 84.2, 104.9, 112.0, 123.0, 127.6, 127.8, 129.5, 129.7, 132.7, 135.8, 138.3, 166.4; IR (Neat) ν_{max} 3497, 2985, 2936, 1713, 1631 cm^{-1}; Anal. Calcd for $C_{19}H_{23}BrO_7$: C, 51.48; H, 5.23. Found: C, 51.43; H, 5.19; ESIMS: *m/z* 465, 467 (MNa^+).

4.3.2. 2-{(*R*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (2b). Colorless liquid (170 mg, 34%); $[\alpha]_D^{27}$ −31.8 (*c* 0.53 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.47 (s, 3H), 3.56 (s, 1H), 3.73 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.13 (d, *J* 3.5 Hz, 1H), 4.48 (m, 1H), 4.51 (d, *J* 11.7 Hz, 1H), 4.70 (s, 1H), 4.72 (d, *J* 11.7 Hz, 1H), 4.91 (s, 1H), 6.02 (d, *J* 3.6 Hz, 1H), 6.08 (s, 1H), 6.39 (s, 1H), 6.91 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.7, 51.7, 56.0, 56.1, 68.4, 71.4, 79.9, 82.0, 84.0, 104.8, 111.9, 112.5, 113.5, 115.4, 127.6, 127.7, 138.3, 148.4, 149.4, 166.3; IR (Neat) ν_{max} 3502, 2988, 2944, 2887, 1725, 1607 cm^{-1}; Anal. Calcd for $C_{21}H_{27}BrO_9$: C, 50.11; H, 5.41. Found: C, 49.89; H, 5.39; ESIMS: *m/z* 525, 527 (MNa^+).

4.3.3. 2-{(*R*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(6-Bromo-benzo[1,3]-dioxol-5-ylmethoxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (2c). Colorless liquid (150 mg, 31%); $[\alpha]_D^{27}$ −17.7 (*c* 0.92 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.48 (s, 3H), 3.75 (s, 3H), 4.10 (d, *J* 3.3 Hz, 1H), 4.13 (m, 2H), 4.49 (m, 2H), 4.67 (m, 2H), 5.99 (m, 3H), 6.07 (s, 1H), 6.39 (s, 1H), 6.88 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.3, 26.7, 51.7, 68.6, 71.4, 80.0,

81.7, 83.8, 101.9, 105.1, 109.6, 111.8, 112.7, 113.9, 127.8, 128.9, 138.3, 147.4, 148.3,166.3; IR (Neat) ν_{max} 3501, 2987, 2934, 1722, 1628 cm^{-1}; Anal. Calcd for $C_{20}H_{23}BrO_9$: C, 49.30; H, 4.76. Found: C, 49.41; H, 4.73; ESIMS: *m/z* 509, 511 (MNa^+).

4.3.4. 2-{(*R*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid ethyl ester (2d). Colorless liquid (145.9 mg, 32%); $[\alpha]_D^{27}$ −16.2 (*c* 5.35 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (m, 6H), 1.48 (s, 3H), 4.13 (d, *J* 3.6 Hz, 1H), 4.19 (q, *J* 7.1 Hz, 2H), 4.51–4.80 (m, 5H), 4.91 (s, 1H), 6.02 (m, 2H), 6.38 (s, 1H), 7.12–7.58 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 26.8, 27.3, 61.2, 69.2, 71.9, 80.7, 82.5, 84.6, 105.4, 112.4, 123.4, 127.9, 128.0, 130.0, 130.1, 133.2, 136.4, 139.1, 166.4; IR (Neat) ν_{max} 3507, 2985, 2935, 1713, 1631 cm^{-1}; Anal. Calcd for $C_{20}H_{25}BrO_7$: C, 52.53; H, 5.51. Found: C, 52.59; H, 5.43; ESIMS: *m/z* 479, 481 (MNa^+).

4.3.5. 2-{(*R*)-[(3a*R*,5*R*,6*R*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (2f). Colorless liquid (79.6 mg, 18%); $[\alpha]_D^{27}$ +64.5 (*c* 1.63 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.56 (s, 3H), 2.80 (d, *J* 7.2 Hz, 1H), 3.65 (s, 3H), 3.99 (dd, *J* 4.2, 8.7 Hz, 1H), 4.20 (dd, *J* 3.2, 8.7 Hz, 1H), 4.58–4.81 (m, 4H), 5.80 (d, *J* 3.4 Hz, 1H), 5.99 (s, 1H), 6.36 (s, 1H), 7.12–7.53 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.6, 26.9, 51.8, 69.4, 71.2, 76.9, 78.7, 80.7, 104.4, 113.3, 122.2, 126.9, 127.4, 129.0, 132.3, 136.9, 139.1, 166.6; IR (Neat) ν_{max} 3452, 2985, 2936, 1720, 1631 cm^{-1}; Anal. Calcd for $C_{19}H_{23}BrO_7$: C, 51.48; H, 5.23. Found: C, 51.37; H, 5.26; ESIMS: *m/z* 465, 467 (MNa^+).

4.3.6. 2-{(*S*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (3a). Colorless liquid (203 mg, 46%); $[\alpha]_D^{27}$ −28.2 (*c* 2.25 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 3.79 (s, 3H), 4.17 (d, *J* 2.7 Hz, 1H), 4.42 (m, 1H), 4.56–4.80 (m, 5H), 5.92 (s, 1H), 5.96 (d, *J* 3.6 Hz, 1H), 6.34 (s, 1H), 7.18 (d-like, 1H), 7.32 (m, 1H), 7.47 (d-like, 1H), 7.56 (d-like, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 51.9, 69.5, 71.7, 80.2, 81.9, 82.5, 105.1, 111.9, 122.9, 127.6, 128.0, 129.5, 129.6, 132.6, 136.5, 139.0, 166.8; IR (Neat) ν_{max} 3489, 2987, 2941, 1724, 1630 cm^{-1}; Anal. Calcd for $C_{19}H_{23}BrO_7$: C, 51.48; H, 5.23. Found: C, 51.40; H, 5.16; ESIMS: *m/z* 465, 467 (MNa^+).

4.3.7. 2-{(*S*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (3b). Colorless liquid (230 mg, 46%); $[\alpha]_D^{27}$ −26.5 (*c* 1.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.48 (s, 3H), 3.51 (d, *J* 8.7 Hz, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.15 (d, *J* 2.8 Hz, 1H), 4.41 (dd, *J* 2.8, 7.8 Hz, 1H), 4.57 (d, *J* 12.0 Hz, 1H), 4.69 (d, *J* 3.6 Hz, 1H), 4.74 (d, *J* 12.0 Hz, 1H), 4.80 (d, *J* 7.8 Hz, 1H), 5.92 (s, 1H), 5.95 (d, *J* 3.6 Hz, 1H), 6.35 (s, 1H), 7.00 (s, 1H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.7, 51.8, 56.0, 56.1, 69.5, 71.5, 80.2, 81.8, 82.3, 105.1, 111.8, 112.6, 113.2, 115.3, 127.8, 128.3, 138.9, 148.4, 149.2, 166.8; IR (Neat) ν_{max} 3502, 2987, 2944, 2889, 1725, 1608 cm^{-1}; Anal. Calcd for $C_{21}H_{27}BrO_9$: C, 50.11; H, 5.41. Found: C, 50.19; H, 5.46; ESIMS: *m/z* 525, 527 (MNa^+).

4.3.8. 2-{(*S*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(6-Bromo-benzo[1,3]-dioxol-5-ylmethoxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (3c). Colorless liquid (218 mg, 45%); $[\alpha]_D^{27}$ −30.4 (*c* 0.81 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 3.79 (s, 3H), 4.13 (d, *J* 3.0 Hz, 1H), 4.40 (dd, *J* 3.0, 7.8 Hz, 1H), 4.54 (d, *J* 12.0 Hz, 1H), 4.67 (m, 2H), 4.76 (d, *J* 7.8 Hz, 1H), 4.94 (m, 2H), 5.99 (s, 2H), 6.36 (s, 1H), 6.97 (s, 1H), 7.01 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.4, 26.9, 52.0, 69.7, 71.7, 80.2, 82.0, 82.3, 101.9, 105.2, 109.8, 111.9, 112.8, 113.8, 128.2, 129.6, 138.8, 147.5, 148.2, 166.9; IR (Neat) ν_{max} 3495, 2987, 2934, 1716, 1630 cm^{-1}; Anal. Calcd for $C_{20}H_{23}BrO_9$: C, 49.30; H, 4.76. Found: C, 49.32; H, 4.71; ESIMS: *m/z* 509, 511 (MNa^+).

4.3.9. 2-{(*S*)-[(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid ethyl ester (3d). Colorless liquid (196 mg, 43%); $[\alpha]_D^{27}$ −45.8 (*c* 0.65 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 6H), 1.48 (s, 3H), 3.55 (d, *J* 7.8 Hz, 1H), 4.17 (d, *J* 2.9 Hz, 1H), 4.24 (q, *J* 7.1 Hz, 2H), 4.42 (dd, *J* 3.0, 7.7 Hz, 1H), 4.67 (m, 2H), 4.78 (d, *J* 12.1 Hz, 1H), 5.91 (s, 1H), 5.95 (d, *J* 3.6 Hz, 1H), 6.34 (s, 1H), 7.18 (t-like, 1H), 7.33 (d, *J* 7.3 Hz, 1H), 7.47 (d, *J* 7.3 Hz, 1H), 7.56 (d, *J* 7.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 26.3, 26.8, 60.9, 69.5, 71.6, 80.2, 81.9, 82.4, 105.1, 111.8, 122.9, 127.5, 127.6, 129.4, 129.5, 132.6, 136.4, 139.1, 166.4; IR (Neat) ν_{max} 3494, 2986, 2936, 1714, 1629 cm^{-1}; Anal. Calcd for $C_{20}H_{25}BrO_7$: C, 52.53; H, 5.51. Found: C, 52.42; H, 5.48; ESIMS: *m/z* 479, 481 (MNa^+).

4.3.10. 2-{(*S*)-[(3a*R*,5*R*,6*R*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl]-hydroxy-methyl}-acrylic acid methyl ester (3f). Colorless liquid (265 mg, 60%); $[\alpha]_D^{27}$ +81.2 (*c* 1.07 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.58 (s, 3H), 2.94 (br s, 1H), 3.68 (s, 3H), 3.83 (dd, *J* 4.5, 8.4 Hz, 1H), 4.46 (m, 2H), 4.66 (m, 2H), 4.84 (s, 1H), 5.80 (d, *J* 3.4 Hz, 1H), 5.96 (s, 1H), 6.26 (s, 1H), 7.13 (t-like, 1H), 7.30 (t-like, 1H), 7.43 (d-like, 1H), 7.50 (d-like, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 26.9, 51.6, 68.8, 70.6, 76.9, 77.8, 80.3, 104.4, 113.2, 122.0, 125.7, 127.1, 128.8, 129.2, 132.1, 136.9, 137.5, 165.9; IR (Neat) ν_{max} 3440, 2991, 2950, 1727, 1631 cm^{-1}; Anal. Calcd for $C_{19}H_{23}BrO_7$: C, 51.48; H, 5.23. Found: C, 51.32; H, 5.22; ESIMS: *m/z* 465, 467 (MNa^+).

4.4. General procedure for radical cyclization of the olefins 2a–d, 2f, 3a–d, 3f, and 2e+3e

To a gently refluxing (400 W lamp) solution of the olefins **2a–d**, **2f**, **3a–d**, **3f** or **2e+3e** (1 mmol) and AIBN (2.5 mol %) in dry benzene (120 mL) under N_2 atmosphere was added a solution of Bu_3SnH (1.5 mmol) and AIBN (2.5 mol %) in dry benzene (150 mL) slowly over a period of 3 h. After complete addition the mixture was heated at reflux for another 3 h. The solvent was removed under

vacuum and the residue was dissolved in diethyl ether (100 mL) and stirred vigorously for 10 h with a saturated solution of aqueous KF (75 mL). The white precipitate was filtered off and washed with diethyl ether. After separation of ether layer, the aqueous layer was extracted with diethyl ether (6×25 mL), the combined organic layers were washed with water (3×30 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a thick oil. This was purified by flash chromatography on silica gel using 30–40% ethyl acetate in petroleum ether (60°–80 °C) to furnish **4a–e**, **5a–e**, **6**, and **7**.

4.4.1. Compound 4a. White crystalline solid (260 mg, 64%); mp 191 °C; $[\alpha]_D^{27}$ +28.4 (*c* 0.62 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 2.04 (s, 3H), 2.92 (br s, 1H), 3.06 (br s, 1H), 3.25 (br s, 1H), 3.74 (s, 3H), 4.30 (br s, 1H), 4.45 (br s, 1H), 4.62 (m, 2H), 4.88 (d, *J* 12.6 Hz, 1H), 5.12 (br s, 1H), 5.85 (s, 1H), 7.14–7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 26.3, 26.7, 31.6, 48.4, 51.9, 78.9, 84.6, 104.0, 111.7, 126.9, 128.9, 129.4, 130.6, 136.8, 137.5, 169.7, 173.7; IR (KBr) ν_{max} 2987, 2932, 1739 cm^{-1}; Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.13; H, 6.43; ESIMS: *m*/*z* 429 (MNa^+).

4.4.2. Compound 4b. White crystalline solid (266 mg, 57%); mp 154 °C; $[\alpha]_D^{27}$ +21.9 (*c* 2.19 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.51 (s, 3H), 2.04 (s, 3H), 2.91 (br s, 1H), 2.98 (br s, 1H), 2.26 (br s, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.30 (br s, 1H), 4.52 (m, 2H), 4.62 (d, *J* 3.6 Hz, 1H), 4.81 (d, *J* 12.6 Hz, 1H), 5.08 (br s, 1H), 5.85 (d, *J* 3.6 Hz, 1H), 6.60 (s, 1H), 6.76 (s, 1H); ^{13}C NMR (75 MHz) δ 21.0, 26.7, 27.2, 32.0, 49.0, 52.3, 56.3, 56.4, 70.3, 71.7, 79.3, 85.3, 104.4, 112.1, 113.2, 113.9, 129.7, 147.8, 149.5, 170.1, 173.4; IR (KBr) ν_{max} 2937, 1742, 1720 cm^{-1}; Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.22; H, 6.48. Found: C, 58.98; H, 6.41; ESIMS: *m*/*z* 489 (MNa^+).

4.4.3. Compound 4c. Foamy solid (261 mg, 58%); $[\alpha]_D^{27}$ +16.9 (*c* 1.25 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 2.04 (s, 3H), 2.89 (br s, 2H), 3.19 (br s, 1H), 3.75 (s, 3H), 4.28 (br s, 1H), 4.37 (d, *J* 12.6 Hz, 2H), 4.61 (d, *J* 3.3 Hz, 1H), 4.76 (d, *J* 12.1 Hz, 1H), 5.11 (br s, 1H), 5.85 (s, 1H), 5.94 (d, *J* 1.9 Hz, 2H), 6.64 (s, 1H), 6.75 (s, 1H); ^{13}C NMR (150 MHz) δ 21.1, 26.3, 26.8, 31.5, 48.4, 51.9, 71.5, 73.1, 83.5, 101.2, 109.7, 111.8, 128.0, 146.2, 148.0, 169.8, 173.2; IR (Neat) ν_{max} 2987, 2937, 2924, 1742 cm^{-1}; Anal. Calcd for $C_{22}H_{26}O_{10}$: C, 58.66; H, 5.82. Found: C, 58.61; H, 5.87; ESIMS: *m*/*z* 473 (MNa^+).

4.4.4. Compound 4d. Colorless liquid (223 mg, 53%); $[\alpha]_D^{27}$ +18.1 (*c* 1.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (m, 6H), 1.50 (s, 3H), 2.03 (s, 3H), 2.95 (m, 1H), 3.05 (m, 1H), 3.24 (m, 1H), 4.12–4.32 (m, 3H), 4.46 (m, 1H), 4.62 (m, 2H), 4.87 (d, *J* 12.5 Hz, 1H), 5.09 (br s, 1H), 5.86 (d, *J* 3.3 Hz, 1H), 7.14–7.29 (m, 4H); ^{13}C NMR (150 MHz) δ 14.2, 21.1, 26.3, 26.8, 31.7, 48.7, 61.0, 77.1, 103.8, 111.8, 127.0, 129.0, 129.5, 137.6, 169.9; IR (Neat) ν_{max} 2984, 2947, 1728 cm^{-1}; Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.71. Found: C, 62.77; H, 6.74; ESIMS: *m*/*z* 443 (MNa^+).

4.4.5. Compound 4e. Foamy solid (157 mg, 42%); $[\alpha]_D^{27}$ −2.5 (*c* 0.31 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.48 (s, 3H), 2.11 (s, 3H), 3.02 (t, *J* 12.7, 1H), 3.29 (dd, *J* 2.3, 14.1 Hz, 1H), 3.44 (d, *J* 11.4 Hz, 1H), 4.09 (s, 1H), 4.46 (dd, *J* 3.1, 8.9 Hz, 1H), 4.54 (d, *J* 13.2 Hz, 1H), 4.62 (d, *J* 3.5 Hz, 1H), 4.98 (d, *J* 13.2 Hz, 1H), 5.09 (d, *J* 7.2 Hz, 1H), 5.90 (d, *J* 3.5 Hz, 1H), 7.17–7.41 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 26.3, 26.8, 32.6, 35.5, 80.0, 84.0, 104.5, 112.3, 128.1, 129.2, 129.9, 134.8, 170.1; IR (Neat) ν_{max} 2987, 2933, 2245, 1736 cm^{-1}; Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.47; H, 6.24; N, 3.76; ESIMS: *m*/*z* 396 (MNa^+).

4.4.6. Compound 5a. Colorless liquid (288 mg, 71%); $[\alpha]_D^{27}$ +16.2 (*c* 1.92 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.42 (s, 3H), 1.85 (s, 3H), 2.89 (dd, *J* 4.2, 14.0 Hz, 1H), 3.51 (dd, *J* 7.0, 14.0 Hz, 1H), 3.63 (m, 1H), 3.69 (s, 3H), 4.07 (s, 1H), 4.16 (s, 1H), 4.59 (m, 2H), 4.98 (d, *J* 13.2 Hz, 1H), 5.17 (d, *J* 8.0 Hz, 1H), 5.92 (d, *J* 3.5 Hz, 1H), 7.09–7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 26.3, 26.8, 32.8, 44.9, 51.8, 71.2, 74.7, 79.8, 83.0, 84.2, 104.4, 112.0, 126.8, 126.9, 128.6, 128.7, 131.7, 136.2, 170.0, 173.9; IR (Neat) ν_{max} 2987, 2938, 1738 cm^{-1}; Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.17; H, 6.34; ESIMS: *m*/*z* 429 (MNa^+).

4.4.7. Compound 5b. Colorless liquid (319 mg, 67%); $[\alpha]_D^{27}$ +19.9 (*c* 1.46 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.42 (s, 3H), 1.90 (s, 3H), 2.85 (d, *J* 14.4 Hz, 1H), 3.45 (m, 1H), 3.65 (br s, 1H), 3.68 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.00 (s, 1H), 4.12 (s, 1H), 4.50 (d, *J* 13.2 Hz, 1H), 4.56 (s, 1H), 4.93 (d, *J* 13.2 Hz, 1H), 5.13 (br s, 1H), 5.93 (s, 1H), 6.61 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8, 26.2, 26.7, 32.1, 51.7, 55.8, 56.0, 71.1, 74.0, 76.7, 80.0, 82.2, 84.1, 104.3, 111.7, 111.9, 112.3, 115.0, 128.0, 147.2, 148.6, 169.8, 174.2; IR (Neat) ν_{max} 2941, 1738 cm^{-1}; Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.22; H, 6.48. Found: C, 59.13; H, 6.39; ESIMS: *m*/*z* 489 (MNa^+).

4.4.8. Compound 5c. Colorless liquid (284 mg, 63%); $[\alpha]_D^{27}$ +21.1 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.41 (s, 3H), 1.93 (s, 3H), 2.77 (dd, *J* 3.2, 14.2 Hz, 1H), 3.39 (dd, *J* 7.7, 14.2 Hz, 1H), 3.59 (m, 1H), 3.72 (s, 3H), 3.98 (s, 1H), 4.15 (s, 1H), 4.41 (d, *J* 12.9 Hz, 1H), 4.55 (d, *J* 3.5 Hz, 1H), 4.85 (d, *J* 13.0 Hz, 1H), 5.11 (d, *J* 7.8 Hz, 1H), 5.94 (br s, 3H), 6.60 (s, 1H), 6.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8, 26.2, 26.7, 32.6, 44.3, 51.7, 71.4, 73.9, 79.5, 82.1, 84.0, 101.1, 104.3, 108.8, 111.7, 111.9, 129.3, 131.4, 146.3, 147.7, 169.7, 174.1; IR (Neat) ν_{max} 2989, 2941, 2881, 1731, 1726 cm^{-1}; Anal. Calcd for $C_{22}H_{26}O_{10}$: C, 58.66; H, 5.82. Found: C, 58.78; H, 5.74; ESIMS: *m*/*z* 473 (MNa^+).

4.4.9. Compound 5d. Colorless liquid (281 mg, 67%); $[\alpha]_D^{27}$ +11.4 (*c* 1.16 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* 7.1 Hz, 3H), 1.31 (s, 3H), 1.42 (s, 3H), 1.84 (s, 3H), 2.88 (dd, *J* 3.7, 13.2 Hz, 1H), 3.56 (m, 2H), 4.08–4.18 (m, 4H), 4.51 (m, 2H), 4.99 (d, *J* 13.3 Hz, 1H), 5.20 (d, *J* 7.5 Hz, 1H), 5.92 (d, *J* 3.6 Hz, 1H), 7.10 (d, *J* 7.1 Hz, 1H), 7.16–7.32 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 20.8, 26.3, 26.8, 32.7, 45.2, 60.7, 71.2, 74.8, 76.9, 84.2, 104.3, 111.9, 126.8, 128.5, 128.6, 136.2, 170.0, 173.3; IR (Neat) ν_{max} 2985, 2936, 1733 cm^{-1}; Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.71. Found: C, 62.89; H, 6.69; ESIMS: *m*/*z* 443 (MNa^+).

4.4.10. Compound 5e. Colorless liquid (138 mg, 37%); $[\alpha]_D^{27}$ +19.9 (*c* 1.46 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.43 (s, 3H), 2.11 (s, 3H), 3.04 (dd, *J* 2.6, 14.0 Hz, 1H), 3.66 (dd, *J* 7.7, 14.0 Hz, 1H), 3.97 (s, 2H), 4.11 (s, 1H), 4.48 (d, *J* 13.5 Hz, 1H), 4.56 (d, *J* 3.3 Hz, 1H), 4.75 (d, *J* 8.2 Hz, 1H), 5.02 (d, *J* 13.5 Hz, 1H), 5.95 (d, *J* 3.2 Hz, 1H), 7.13 (d-like, 1H), 7.27 (t-like, 1H), 7.37 (t-like, 1H), 7.48 (d-like, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.9, 26.2, 26.7, 31.1, 33.4, 69.5, 74.0, 79.7, 82.0, 83.6, 104.7, 112.3, 120.4, 127.8, 128.5, 129.2, 132.2, 135.5, 135.7, 170.0; IR (Neat) ν_{max} 2987, 2933, 2243, 1747 cm^{-1}; Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.35; H, 6.34; N, 3.68; ESIMS: *m*/*z* 396 (MNa^+).

4.4.11. Compound 6. Foamy solid (191 mg, 47%); $[\alpha]_D^{27}$ +69.8 (*c* 0.81 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.70 (s, 3H), 2.03 (s, 3H), 2.99 (dd, *J* 6.1, 13.6 Hz, 1H), 3.28 (m, 1H), 3.59 (m, 2H), 3.74 (s, 3H), 4.64 (m, 2H), 4.82 (m, 2H), 5.24 (d, *J* 13.4 Hz, 1H), 5.61 (d, *J* 3.5 Hz, 1H), 7.12–7.31 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.0, 26.4, 26.7, 29.2, 49.2, 52.1, 72.5, 73.2, 74.2, 78.6, 79.0, 103.1, 113.1, 127.0, 129.2, 129.9, 130.6, 135.6, 137.8, 169.9, 172.5; IR (Neat) ν_{max} 2982, 2928, 1741 cm^{-1}; Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.01; H, 6.39; ESIMS: *m*/*z* 429 (MNa^+).

4.4.12. Compound 7. Colorless liquid (251.7 mg, 62%); $[\alpha]_D^{27}$ +85.9 (*c* 1.38 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.40 (s, 3H), 1.62 (s, 3H), 3.05 (dd, *J* 4.9, 13.6 Hz, 1H), 3.50 (m, 1H), 3.77 (m, 4H), 3.99 (dd, *J* 4.3, 8.8 Hz, 1H), 4.45 (d, *J* 8.8 Hz, 1H), 4.66 (m, 2H), 5.28 (d, *J* 13.6 Hz, 1H), 5.51 (d, *J* 2.5 Hz, 1H), 5.58 (d, *J* 3.3 Hz, 1H), 7.10–7.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.6, 26.3, 26.8, 30.1, 46.6, 52.5, 70.6, 72.4, 73.6, 77.9, 78.1, 103.4, 113.4, 126.3, 128.8, 129.4, 130.7, 136.3, 141.1, 170.0, 173.9; IR (Neat) ν_{max} 2989, 2935, 1734 cm^{-1}; Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.21; H, 6.42; ESIMS: *m*/*z* 429 (MNa^+).

4.5. Synthesis of benzoxonine derivative 8

Compound **4a** (1 mmol) was dissolved in CH_3CN–H_2O (1:1) containing 5% H_2SO_4 and kept at room temperature for 24 h. The acidic solution was neutralized with solid $NaHCO_3$, filtered, and the filtrate was evaporated in vacuum. The residue was dissolved in MeOH (20 mL) and treated dropwise at 0 °C with an aqueous solution (25 mL) of $NaIO_4$ (1.2 mmol) with stirring for 1 h. Usual work up followed by $NaBH_4$ reduction in MeOH afforded the diol. This was acetylated with Ac_2O (0.5 mL) and pyridine (2 mL) at room temperature for 12 h to furnish a crude product, which was purified by silica gel flash chromatography using 10% ethyl acetate in petroleum ether (60–80 °C) to afford **8**.

4.5.1. Benzoxonine 8. Colorless liquid (93 mg, 22%); $[\alpha]_D^{27}$ +6.20 (*c* 0.61 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 2.81 (d, *J* 13.4 Hz, 1H), 3.17 (dd, *J* 7.1, 14.2 Hz, 1H), 3.36 (m, 1H), 3.74 (s, 3H), 4.22 (m, 3H), 4.71 (d, *J* 11.7 Hz, 1H), 4.89 (d, *J* 11.7 Hz, 1H), 5.22 (br s, 1H), 5.30 (s, 1H), 7.18–7.42 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.06, 20.07, 20.08, 20.09, 27.8, 46.6, 51.9, 52.4, 64.2, 69.9, 71.9, 75.8, 126.5, 128.8, 129.0, 130.6, 136.4, 169.4, 169.9, 170.7, 174.0; IR (Neat) ν_{max} 2953, 1743 cm^{-1}; Anal. Calcd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.20. Found: C, 59.67; H, 6.26; MS (ESI^+): *m*/*z* 445 (MNa^+).

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Supplementary data

^1H NMR and ^{13}C NMR spectra for all new compounds are provided in the supplementary data files. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.080.

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13. Crystal data of **4a**: $C_{21}H_{26}O_8$, M=406.4, orthorhombic, space group $P2_12_12_1$, a=8.659 (1), b=11.419 (1), c=20.395 (3) Å, V=2016.6 (4) Å^3, Z=4, F(000)=864, T=293 (2)K, μ (μ_0 K_α)=0.103 mm^{-1}. A total of 2692 unique reflection were measured (θ_{max}=25.0°) on a MacScience DIP Labo 32001 diffractometer using graphite monochromatised Mo Kα radiation (λ=0.71073 Å). The structure was determined by direct methods with SHELXS 97[15]and refined by full-matrix least-squares method on F^2 using SHELXL 97.[15] Non-hydrogen atoms were refined anisotropically and the hydrogen atoms located from the difference Fourier maps were treated as riding on their parent atoms. Final R_1=0.0704, ωR_2=0.1932, a goodness of fit=0.862 for all 2692 reflections; for the 2087 observed data [$I>2\sigma(I)$] only, R_1=0.0601. CCDC 295094.
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Synthesis of vinca alkaloids and related compounds. Part 105: Efficient convergent synthetic pathway to the ibophyllidine skeleton and synthesis of (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine☆

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Abstract—Starting from methyl-5-oxohexanoate we produced the appropriately functionalized aldehyde, which, after having been allowed to react with the tryptamine derivative in a [4+2] cycloaddition reaction as the final step, yielded the molecule containing a D-seco-aspidospermane skeleton. From the latter we could successfully produce a 1:1 mixture of protected epimers, the desilylation reaction of the protected molecules gave the alkaloids (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine in good yield.

1. Introduction

The ibophyllidine alkaloids, as pentacyclic monoterpenoid indole alkaloids, can be biogenetically classified into the ψ-aspidospermane skeleton group.[2,3] The precursors of their biosynthesis are pandoline (**1a**) and 20-epipandoline (**1b**)[4] (Fig. 1). The title alkaloids were isolated in 1980 by French researchers from the trunk of *Tabernaemontana albiflora*.[5] In our earlier publications we described an efficient convergent synthetic pathway to build up the aspidospermane and ψ-aspidospermane skeletons, in the course of which compounds with a D-seco-aspidospermane skeleton were obtained from an N_b-benzyltryptamine derivative (**3**) and appropriately built up aldehydes (or aldehyde equivalents), respectively. In the final reaction step involving intramolecular acylation or alkylation, the synthesis of several alkaloids and alkaloid-like molecules was achieved.[6,7]

2. Results and discussion

In the present synthesis we again used the well-proven tryptamine derivative **3**.[6] We anticipated that aldehyde **4**, used as a reaction partner would yield in a reaction with **3** a molecule with a D-seco-aspidospermane skeleton from which pentacyclic alkaloids can be easily formed (Fig. 2).

The starting material for the preparation of **4** was methyl-5-oxohexanoate (**5**) (Scheme 1).[8] In the first step, **5** was

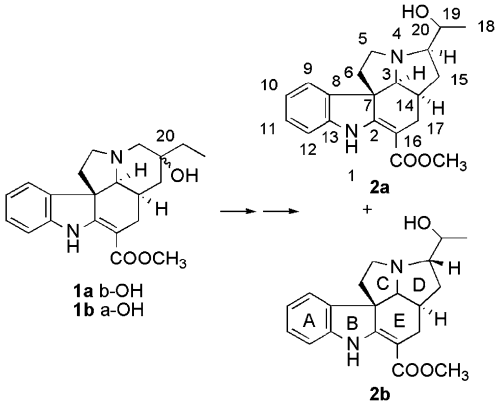

Figure 1. Biosynthesis of **2a** and **2b**.

☆ See Ref. 1.
Keywords: 19-Hydroxy-ibophyllidine; 19-Hydroxy-20-epiibophyllidine; Indole alkaloids; Natural products.
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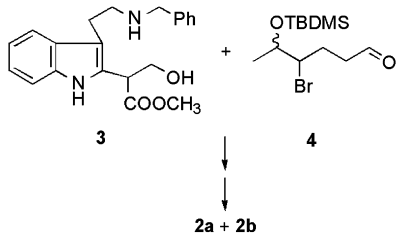
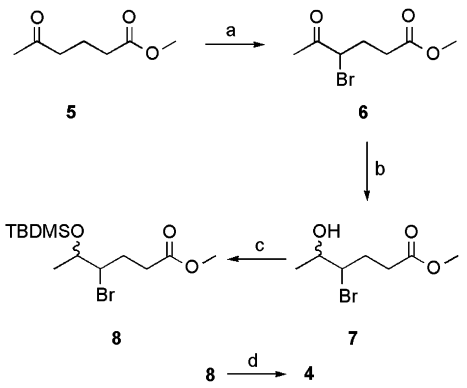
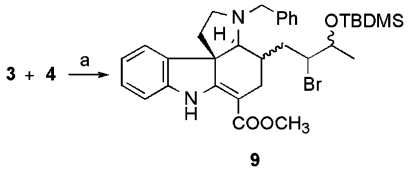


Figure 2. Planned synthesis of **2a** and **2b**.



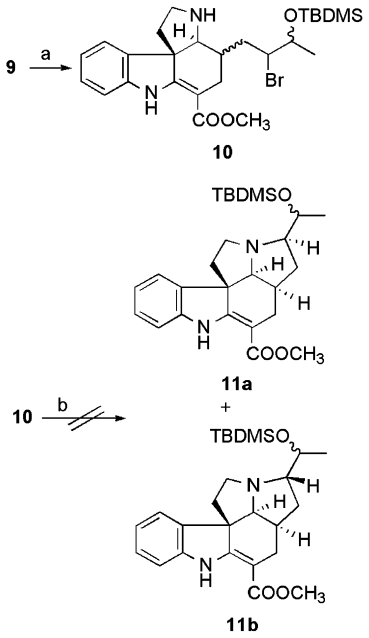
Scheme 1. Reagents and conditions: (a) Br_2, $(C_2H_5)_2O$, 0 °C (67%); (b) $NaBH_4$, CH_3OH, 0 °C (86%); (c) TBDMSCl, imidazole, CH_2Cl_2, Δ (78%); (d) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −60 °C (72%).

brominated to give **6**, then the ketone group was reduced with sodium borohydride to **7**. Subsequently, we protected the alcohol **7** in dichloromethane with *tert*-butyldimethylsilyl chloride in the presence of imidazole **8**. In the next step, ester **8** containing the protecting group was converted into aldehyde **4** in a good yield. The secondary amine **3** was allowed to react with aldehyde **4** in toluene in the presence of *p*-toluenesulfonic acid monohydrate (Scheme 2). From the reaction mixture the D-seco-aspidospermane **9** was isolated. As a continuation of the synthesis we intended to form the D-ring of the ibophyllidine skeleton. The benzyl group was removed from the tertiary amine **9** by catalytic hydrogenolysis, then **10** was boiled in toluene, xylene, or decalin, but the expected pentacyclic molecules (**11a** and **11b**) were not obtained in any of the cases (Scheme 3).



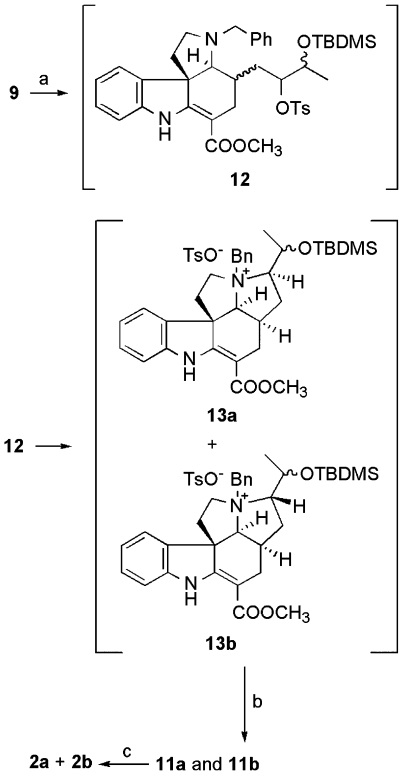
Scheme 2. Reagent and conditions: (a) *p*-TsOH·H_2O, toluene, Δ (47%).

Modifying our synthesis strategy, we intended to create the *p*-toluenesulfonyloxy group instead of the bromine function in the intramolecular alkylation reaction. We wished to achieve the halogen→tosyloxy change by boiling compound **9** in acetonitrile with silver *p*-toluenesulfonate, which is a method known in the literature (Scheme 4).[9] Surprisingly, the reaction did not result in the expected product mixture (**12**). In our opinion, during conversion, the tosyloxy group attaches to molecule **12**, resulting under the applied reaction conditions in the formation via alkylation of



Scheme 3. Reagents and conditions: (a) 10% Pd/C, H_2, CH_3COOH, (92%); (b) toluene, xylene or decalin, Δ.

a mixture of the quaternary salts **13a** and **13b**, accompanied by the earlier described full epimerization.[10] The salt mixture was catalytically debenzylated and in this step a mixture of the alcohols containing the protecting group (**11a** and **11b**) was obtained as a product. By removing the protecting group in the final step, (±)-19-hydroxy-ibophyllidine (**2a**) and (±)-19-hydroxy-20-epiibophyllidine (**2b**) can be isolated from the reaction mixture with a good yield.



Scheme 4. Reagents and conditions: (a) AgOTs, CH_3CN, Δ; (b) 10% Pd/C, H_2, CH_3COOH (48%); (c) 1 M HCl, THF (**2a**, 42%, **2b**, 39%).

3. Conclusion

We have worked out a new, biomimetic synthesis pathway for the construction of the ibophyllidine skeleton. Starting from methyl-5-oxohexanoate **5**, we produced aldehyde **4**, which was then used as a reaction partner in the course of the planned synthesis. In the final step the [4+2] cycloaddition reaction of the tryptamine derivative **3** and the aldehyde **4** resulted in **9** with a D-seco-aspidospermane skeleton. The hydrogenolysis of the tertiary amine **9** led to a mixture of the secondary amine epimers **10** from which the pentacyclic alkaloid skeleton was attempted to be formed by intramolecular alkylation. Due to lack of formation of the D-ring of the ibophyllidine skeleton we modified our strategy as a result of which a 1:1 mixture of the molecules containing the protective groups (**11a** and **11b**) was produced. As a final step, following removal of the protective group, we arrived at the (±)-19-hydroxy-ibophyllidine (**2a**) and (±)-19-hydroxy-20-epiibophyllidine (**2b**) alkaloids.

4. Experimental

4.1. General

Melting points were determined on a hot-stage microscope Boetius and are uncorrected. IR spectra were recorded on a Specord JR-75 spectrophotometer. NMR spectra were recorded on a Varian Unity INOVA-400 instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All NMR spectra were recorded at rt. Chemical shifts are reported relative to Me_4Si (δ=0 ppm). Mutual ^{1}H–^{1}H couplings are given only once. MS spectra were recorded on a PE Sciex API 2000 triple-quadrupole mass spectrometer equipped with a Turbo Ion Spray source and VG ZAB2-SEQ tandem mass spectrometer (high resolution mass spectra). Preparative TLC analyses were performed on silica gel F_{254} plates, and column chromatography was carried out on Merck Kieselgel 60 (0.063–0.200 mm).

4.1.1. Methyl 4-bromo-5-oxohexanoate (6). Compound **5** (2.00 g, 17.5 mmol) was dissolved in ether (50 mL) and it was cooled to 0 °C. Bromine (3.19 g, 20 mmol, 1.02 mL) was added to the solution at 0 °C over 20 min period. After the addition, the reaction mixture was allowed to warm up to rt and then stirred for 30 min. The suspension was extracted with 5% aqueous solution of $NaHCO_3$ (2×10 mL) and brine (2×10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:2, R_f=0.45) to afford 1.33 g (67%) of the product **6** as a yellow oil: IR (neat) ν 2961, 1736, 1714, 1440, 1273, 1178 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.19+2.35 (2×1H, 2×m; CH–CH_2–CH_2), 2.39 (3H, s; $COCH_3$), 2.51+2.55 (2×1H, 2×ddd, J_{gem}= 16.6 Hz, J_{vic}=7.0+7.0 and 7.6+6.4 Hz; CH_2COOCH_3), 3.70 (3H, s; OCH_3), 4.43 (1H, dd, J=8.4+5.6 Hz; CH–Br); ^{13}C NMR ($CDCl_3$) δ 26.28 (COCH_3), 28.19+31.22 (CH_2CH_2COOCH_3), 51.86 (OCH_3), 52.75 (*C*H–Br), 172.74 (*C*OOCH_3), 201.30 (CH_3*C*O); MS *m/z* (relative intensity) 223 (40.0, [M]$^+$), 221 (41.0, [M]$^+$), 209 (29.0), 207 (29.0), 191 (26.0), 121 (45.0), 42 (100.0); HRMS (EI) calcd for $C_7H_{14}{}^{79}BrO_3$ 223.0658, found for [M$^+$] 223.0654.

4.1.2. Methyl 4-bromo-5-hydroxyhexanoate (7). $NaBH_4$ (0.40 g, 9 mmol) was added to a solution of **6** (2.00 g, 9 mmol) in dry methanol (50 mL) at 0 °C. After the addition, the reaction mixture was allowed to warm up to rt, and was stirred for 1 h. It was then poured into brine (20 mL) and extracted with dichloromethane (2×50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1:2, R_f= 0.4) to afford 1.74 g (86%) of the product **7** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 3472, 2952, 1736, 1440, 1260, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J=6.1 Hz; CHCH_3), 2.01 (1H, d, J=7.0 Hz; OH), 2.10–2.32 (2H, m; CHCH_2CH$_2$), 2.48–2.68 (2H, m; CH_2COOCH_3), 3.69 (3H, s; OCH_3), 3.77 (1H, m; C*H*OH), 4.07 (1H, td, J=10.0+4.0 Hz; CH–Br); ^{13}C NMR ($CDCl_3$) δ 21.3 (*C*H_3CH), 30.6 (CH*C*H_2CH$_2$), 32.1 (*C*H_2COOCH_3), 51.8 (OCH_3), 64.8 (*C*H–Br), 70.3 (*C*HOH), 173.2 (*C*OOCH_3); MS *m/z* (relative intensity) 227 (21.0, [M]$^+$), 225 (21.0, [M]$^+$), 209 (35.0), 207 (35.0), 181 (25.0), 179 (25.0), 127 (33.0), 74 (100.0); HRMS (EI) calcd for $C_7H_{14}{}^{79}BrO_3$ 225.0126, found for [M+H$^+$] 225.0143.

4.1.3. Methyl 4-bromo-5-(*tert*-butyl-dimethyl-silanyloxy) hexanoate (8). Imidazole (1.21 g, 17.8 mmol) was added to a solution of **7** (2.00 g, 8.9 mmol) in dry dichloromethane (40 mL). Then *tert*-butyldimethylsilyl chloride (2.68 g, 17.8 mmol) in 10 mL dry dichloromethane was added dropwise to a stirred solution at rt. After the addition the mixture was refluxed over 24 h. Then it was cooled, the salts were separated by filtration and the organic phase was washed with water (2×15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1:1, R_f=0.9) to afford 2.35 g (78%) of the product **8** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 2952, 2936, 1744, 1440, 1256, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (6H, s; $Si(CH_3)_2$), 0.90 (9H, s; $C(CH_3)_3$), 1.26 (3H, d, J=6.2 Hz; CH_3CH), 2.01+2.28 (2×1H, 2×m; CHCH_2CH$_2$), 2.49+2.63 (2×1H, 2×ddd, J_{gem}=16.4 Hz, J_{vic}=8.0+7.5 and 8.5+5.5 Hz; CH_2COOCH_3), 3.68 (3H, s; OCH_3), 3.92 (1H, td, J=10.6+3.5 Hz; C*H*Br), 3.98 (1H, qd, J=6.2 and 3.5 Hz; C*H*O–); ^{13}C NMR ($CDCl_3$) δ −4.8 and −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.6 (*C*H_3CH), 25.8 (C(CH_3)$_3$), 28.6 (CH*C*H_2CH$_2$), 32.5 (*C*H_2COOCH_3), 51.7 (OCH_3), 60.5 (CH–Br), 71.1 (*C*HO–), 173.3 (*C*OOCH_3); MS *m/z* (relative intensity) 341 (2.0, [M]$^+$), 339 (2.0, [M]$^+$), 309 (18.0), 307 (18.0), 283 (69.0), 281 (39.0), 259 (31.0), 209 (67.0), 207 (67.0), 159 (79.0), 127 (55), 85 (100.0); HRMS (EI) calcd for $C_{13}H_{28}{}^{79}BrO_3Si$ 339.0991, found for [M+H$^+$] 339.0986.

4.1.4. 4-Bromo-5-(*tert*-butyl-dimethyl-silanyloxy) hexanal (4). The ester **8** (2.00 g, 5.9 mmol) was dissolved in 50 mL dry dichloromethane and cooled to −60 °C. A solution of 1.0 M diisobutyl aluminum hydride in hexane (7.1 mL, 7 mmol) was added dropwise, and the resulting solution was stirred at −60 °C for 45 min. Then saturated aqueous NH_4Cl was added, and the solution was allowed to warm up to rt. After stirring for 30 min the white precipitate was filtered, and the solvent was extracted with water (2×20 mL) and brine (15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo.

The residue was purified by column chromatography (eluting with ether/hexane=1:4, R_f=0.6) to afford 1.31 g (72%) of the product **4** as a colorless oil (8:2 mixture of the diastereoisomers): IR (neat) ν 2952, 2944, 1732, 1468, 1152, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07+0.08 (2×3H, 2×s; $Si(CH_3)_2$), 0.90 (9H, s; $C(CH_3)_3$), 1.26 (3H, d, J=6.2 Hz; CH_3CH), 2.00+2.32 (2×1H, 2×m; $CHCH_2CH_2$), 2.66+2.77 (2×1H, 2×m; CH_2COOCH_3), 3.89 (1H, td, J=10.6+3.5 Hz; CHBr), 3.99 (1H, qd, J=6.2 and 3.5 Hz; CHO–), 9.81 (1H, t, J=1.0 Hz; HC=O); ^{13}C NMR ($CDCl_3$) δ −4.8 and −4.4 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 19.5 (CH_3CH), 25.8 ($C(CH_3)_3$), 25.8 ($CHCH_2CH_2$), 42.5 (CH_2CHO), 60.4 (CHBr), 71.1 (CHO–), 201.1 (HC=O); MS m/z (relative intensity) 309 (4.0, $[M]^+$), 307 (4.0, $[M]^+$), 283 (15.0), 281 (15.0), 253 (25.0), 251 (32.0), 209 (56.0), 207 (56.0), 171 (23.0), 159 (82.0), 73 (100.0); HRMS (EI) calcd for $C_{12}H_{24}{}^{79}BrO_2Si$ 307.0729, found for $[M-H^+]$ 307.0744.

4.1.5. 3-Benzyl-4-[2-bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo [2,3-*d*]carbazole-6-carboxylic acid methyl ester (9). A solution of 1.00 g (2.85 mmol) of **3**, 1.08 g (3.45 mmol) **4**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 50 mL of dry toluene was refluxed under argon over 24 h. The reaction mixture was extracted with brine (2×40 mL), and the combined aqueous phases were extracted with dichloromethane (2×40 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluent: ethylacetate/hexane=1:4, R_f=0.6) to yield 0.84 g (47%) **9** as a yellow oil: IR (neat) ν 3381, 2928, 1680, 1612, 1464, 1440, 1248, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.19, −0.08, −0.03, and 0.07 (6H, 4×s; $Si(CH_3)_3$), 0.69 and 0.77 (9H, 2×s; $C(CH_3)_3$), 1.10 and 1.12 (3H, 2×d, J=6.5 Hz; CH_3CH), 1.17–1.57 (2H, m; 14-CH_2), 1.68+2.05 (2×1H, 2×m; 6-H_2), 2.22–2.40 (1H, m; 14-H), 2.50–2.75 (3H, m; 17-H_2+5-H_A), 2.85–3.03 (2H, m; 5-H_B+3-H), 3.76 and 3.78 (3H, 2×s; OCH_3), 3.65–3.90 (3H, m; CH–O+CH-Br+NCH_ACH_B), 4.18–4.32 (1H, 2×d; NCH_ACH_B), 6.76–6.86 (2H, m; 12-H+10-H), 6.95 (1H, br; 9-H), 7.09–7.16 (1H, m; 11-H), 7.26–7.45 (5H, m; Ph), 8.88 and 8.95 (1H, 2×br s; N1-H). ^{13}C NMR ($CDCl_3$) δ −4.9, −4.9, −4.8, and −4.7 ($Si(CH_3)_3$), 17.9 and 17.9 ($C(CH_3)_3$), 18.9 and 19.1 (CH_3CH), 20.7 and 24.8 (C17), 25.6 and 25.7 ($C(CH_3)_3$), 32.6 and 34.1 (C14–CH_2), 36.8 and 37.4 (C14), 42.3 and 42.5 (C6), 50.1 and 50.4 (C5), 50.9 (OCH_3), 55.2 (C7), 57.7 and 58.0 (NCH_2Ph), 59.3 and 59.6 (CH–Br), 69.9 and 72.3 (C3), 70.9 and 71.1 (CH–O), 90.1 and 91.3 (C16), 109.2 and 109.3 (C12), 120.6 and 120.7 (C10), 122.2 (C9), 127.1 (C4′), 127.9 and 127.9 (C11), 128.4 (C3′+C5′), 129.0 (C2′+C6′), 137.7 (C8), 139.1 (C1′), 142.9 and 143.0 (C13), 164.9 and 165.3 (C2), 168.7 and 168.9 ($COOCH_3$); MS m/z (relative intensity) 626 (12.0, $[M]^+$), 624 (12.0, $[M]^+$), 412 (40.0), 410 (31.0), 295 (11.0), 171 (16.0), 127 (45.0), 91 (100.0); HRMS (EI) calcd for $C_{33}H_{45}{}^{79}BrN_2O_3Si$ 624.2382, found for $[M^+]$ 624.2397.

4.1.6. 4-[2-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*] carbazole-6-carboxylic acid methyl ester (10). A mixture of **9** (0.5 g, 0.8 mmol) and 10% palladium/charcoal (0.25 g) in glacial acetic acid (10 mL) was hydrogenated for 2 h at rt and then filtered. The filtrate was poured into ice-water (50 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with dichloromethane (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The main component was separated by preparative TLC (eluting with dichloromethane/methanol=20:1, R_f=0.35) to yield **10** (0.39 g, 92%) as a yellow oil: IR (neat) ν 3376, 2952, 1680, 1608, 1464, 1440, 1248, 1204, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.18, −0.09, −0.07, and −0.03 (6H, 4×s; $Si(CH_3)_3$), 0.68 and 0.78 (9H, 2×s; $C(CH_3)_3$), 1.11 and 1.12 (3H, 2×d, J=6.3 Hz; CH_3CH), 1.14+1.41 (2×1H, 2×m; 14-CH_2), 1.82+1.92 (2×1H, 2×m; 6-H_2), 2.13 (1H, m;14-H), 2.33 and 2.43+2.64 and 2.70 (2×1H, 2×dd; 17-H_2), 3.10–3.20 (2H, m; 5-H_2), 3.47 and 3.49 (1H, 2×s; 3-H), 3.76 and 3.78 (3H, 2×s; OCH_3), 3.78–3.94 (2H, m; CH–O+CH–Br), 6.75–6.95 (2H, m; 12-H+10-H), 7.10–7.20 (1H, m; 11-H), 7.20–7.25 (1H, m; 9-H), 8.96 and 9.01 (1H, s; N1-H). ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, −4.8, and −4.7 ($Si(CH_3)_3$), 17.8 ($C(CH_3)_3$), 19.1 (CH_3CH), 20.4 and 24.4 (C17), 25.6 and 25.7 ($C(CH_3)_3$), 32.8 and 35.4 (C14-CH_2), 39.1 and 39.8 (C14), 44.1 and 44.5 (C6), 45.1 and 45.4 (C5), 51.0 (OCH_3), 55.9 and 56.0 (C7), 59.0 and 59.3 (CH–Br), 65.4 and 67.1 (C3), 70.6 and 70.9 (CH–O), 89.5 and 90.5 (C16), 109.2 and 109.3 (C12), 120.8 and 120.9 (C10), 121.9 (C9), 127.9 and 128.0 (C11), 137.5 (C8), 143.1 (C13), 165.2 and 165.6 (C2), 168.6 and 168.9 ($COOCH_3$); MS m/z (relative intensity) 536 (3.0, $[M]^+$), 534 (3.0, $[M]^+$), 456 (53.0), 295 (78.0), 242 (55.0), 215 (85.0), 168 (15.0), 154 (15.0), 110 (100.0); HRMS (EI) calcd for $C_{26}H_{39}{}^{79}BrN_2O_3Si$ 534.1913, found for $[M^+]$ 534.1897.

4.1.7. 19-(*tert*-Butyl-dimethyl-silanyloxy)-ibophyllidine (11a) and 19-(*tert*-butyl-dimethyl-silanyloxy)-20-epi-ibophyllidine (11b). Silver *p*-toluenesulfonate (0.45 g, 1.6 mmol) was added to a solution of **9** (0.5 g, 0.8 mmol) in acetonitrile (10 mL), and the mixture was refluxed for 48 h. After heating the solvent was evaporated in vacuo. The residue was dissolved in glacial acetic acid (10 mL) and 0.25 g 10% palladium/charcoal was added. The reaction mixture was hydrogenated for 4 h at rt and then filtrated. The filtrate was poured into ice-water (50 mL) and neutralized with saturated Na_2CO_3 solution. The mixture was extracted with dichloromethane (3×50 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1:2, R_f=0.75) to afford 0.17 g (48%) of the mixture of **11a** and **11b** as a colorless oil: IR (neat) ν 3376, 2952, 2912, 1680, 1612, 1468, 1440, 1248, 744 cm^{-1}; **11a** component (~45%): ^1H NMR ($CDCl_3$) δ 0.092 and 0.10 (2×3H, 2×s; $Si(CH_3)_3$), 0.90 (9H, s; $C(CH_3)_3$), 1.38 (3H, d, J=6.0 Hz; 18-H_3), 1.50 (1H, ddd, J_{gem}=12.0 Hz, J_{vic}=11.8+6.7 Hz; 15-H_A), 1.82+3.15 (2×1H, 2×dd, J_{gem}=15.0 Hz, J_{vic}=11.0 and 7.00 Hz; 17-H_2), 2.04 (1H, m; 14-H), 2.10–2.32 (3H, m; 6-H_2+15-H_B), 2.83 (1H, m; 5-H_A), 3.08–3.15 (2H, m; 5-H_B+20-H), 3.51 (1H, br d, J=8.3 Hz; 3-H), 3.76 (3H, s; OCH_3), 3.99 (1H, m; 19-H), 6.81 (1H, d, J=8.0 Hz; 12-H), 6.93 (1H, m; 10-H), 7.14 (1H, m; 11-H), 7.51 (1H, br d, J=7.0 Hz; 9-H), 9.11 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ −4.6 and −3.8 ($Si(CH_3)_2$), 18.1 ($C(CH_3)_3$), 23.4 (C18), 25.9

(C(CH_3)$_3$), 31.9 (C17), 32.6 (C15), 37.4 (C14), 41.7 (C6), 48.0 (C5), 50.9 (OCH_3), 55.4 (C7), 70.4 (C19), 70.8 (C20), 76.1 (C3), 92.2 (C16), 108.8 (C12), 121.4 (C10), 123.3 (C9), 127.7 (C11), 138.7 (C8), 143.3 (C13), 164.9 (C2), 168.6 (COOCH$_3$); **11b** component (~55%): ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s; Si(CH_3)$_3$), 0.90 (9H, s; C(CH_3)$_3$), 1.23 (3H, d, J=6.2 Hz; 18-H$_3$), 1.64+2.04 (2×1H, 2×ddd, J_{gem}=12.0 Hz, J_{vic}=5.2+~1 and 7.2+12.0 Hz; 6-H$_2$), 1.86–2.00 (4H, m; 17-H$_A$+15-H$_2$+14-H), 2.74 (1H, dd, J_{gem}=14.4 Hz, J_{vic}=4.6 Hz; 17-H$_B$), 2.85 (1H, ddd, J=6.0+7.1+8.1 Hz; 20-H$_\beta$), 2.98+3.36 (2×1H, 2×ddd, J_{gem}=12.4 Hz, J_{vic}=7.2+~1 and 5.2+12.0 Hz; 5-H$_2$), 3.70 (1H, qd, J=6.2 and 6.0 Hz; 19-H), 3.76 (3H, s; OCH_3), 3.84 (1H, d, J=6.2 Hz; 3-H), 6.83 (1H, d, J=8.0 Hz; 12-H), 6.89 (1H, m; 10-H), 7.16 (1H, m; 11-H), 7.32 (1H, d, J=7.3 Hz; 9-H), 9.05 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ −4.4 and −4.3 (Si(CH_3)$_2$), 18.2 (C(CH$_3$)$_3$), 21.9 (C18), 25.9 (C(CH$_3$)$_3$), 26.8 (C17), 34.9 (C15), 38.9 (C14), 39.4 (C6), 50.9 (OCH_3), 53.2 (C5), 57.9 (C7), 73.0 (C19), 73.3 (C20), 74.1 (C3), 91.9 (C16), 109.1 (C12), 120.9 (C10), 122.6 (C9), 127.9 (C11), 136.9 (C8), 143.6 (C13), 164.9 (C2), 168.6 (COOCH$_3$); MS m/z (relative intensity) 454 (6.0, [M]$^+$), 296 (22.0), 295 (100.0), 263 (9.0); HRMS (EI) calcd for $C_{26}H_{38}N_2O_3Si$ 454.2652, found for [M$^+$] 454.2652.

4.1.8. 19-Hydroxy-ibophyllidine (2a) and 19-hydroxy-20-epiibophyllidine (2b). Aqueous HCl solution (2N, 0.5 mL) was added to a solution of **11a** and **11b** (0.20 g, 0.44 mmol) in tetrahydrofuran (5 mL), and the mixture was stirred for 30 min at rt. After stirring the mixture was concentrated in vacuo, then the residue was dissolved in dichloromethane (20 mL) and worked with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The two main components were separated by preparative TLC (eluting with acetone/hexane=2:1). The less polar compound (**2a**, R_f=0.53) was obtained (60 mg, 42%) as a colorless oil: IR (neat) ν 3376, 2952, 1672, 1612, 1480, 1464, 1248, 1224, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J=7.5 Hz; 18-H$_3$), 1.74+2.13 (2×1H, m; 15-H$_2$), 1.71+2.08 (2×1H, m; 6-H$_2$), 1.83+2.88 (2×1H, dm, dd, J_{gem}=11 Hz, J_{vic}=6.9 Hz; 17-H$_2$), 2.10 (1H, m; 14-H), 2.95+3.28 (2×1H, 2×dd, J_{gem}=11.5 Hz, J_{vic}=6.9 Hz; 5-H$_2$), 3.06 (1H, ddd, J=6.1+7.1+8.0 Hz; 20-H$_\alpha$), 3.81 (1H, br d, J=8.0 Hz; 3-H), 3.76 (3H, s; OCH_3), 3.89 (1H, m; 19-H), 6.85 (1H, d, J=8.0 Hz; 12-H), 7.01 (1H, m; 10-H), 7.19 (1H, m; 11-H), 7.49 (1H, br d, J=7.1 Hz; 9-H), 9.07 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 23.0 (C18), 29.5 (C17), 33.1 (C15), 37.8 (C14), 41.7 (C6), 48.2 (C5), 50.7 (OCH_3), 55.4 (C7), 70.8 (C19), 76.1 (C3), 91.5 (C16), 108.9 (C12), 121.4 (C10), 123.3 (C9), 128.0 (C11), 138.5 (C8), 143.2 (C13), 164.8 (C2), 168.7 (COOCH$_3$); MS (FAB) m/z (relative intensity) 341 (100.0, [M+H$^+$]), 327 (37.0), 149 (46.0). HRMS (FAB) calcd for $C_{20}H_{25}N_2O_3$ 341.1782, found for [M+H$^+$] 341.1772. The more polar component (**2b**, R_f=0.55) was obtained (55 mg, 39%) as a colorless oil: IR (neat) ν 3368, 2928, 1688, 1612, 1480, 1456, 1248, 1228, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, J=8.0 Hz; 18-H$_3$), 1.66+2.14 (2×1H, m; 15-H$_2$), 1.81+2.90 (2×1H, dm, dd, J_{gem}=12.0 Hz, J_{vic}=7.0 Hz; 17-H$_2$), 1.83+2.27 (2×1H, 2×dd, J_{gem}=11.9 Hz, J_{vic}=8.0 Hz; 6-H$_2$), 2.07 (1H, m; 14-H), 2.64+2.93 (2×1H, 2×dd, J_{gem}=12.0 Hz, J_{vic}=7.0 Hz; 5-H$_2$), 3.11 (1H, ddd, J=6.0+7.1+8.0 Hz; 20-H$_\beta$), 3.67 (1H, d, J=8.0 Hz; 3-H), 3.77 (3H, s; OCH_3), 3.84 (1H, qd, J=6.1 and 6.0 Hz; 19-H), 6.82 (1H, dm, J=8.0 Hz; 12-H), 6.98 (1H, m; 10-H), 7.14 (1H, m; 11-H), 7.38 (1H, d, J=7.5 Hz; 9-H), 9.05 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 22.2 (C18), 24.9 (C17), 34.6 (C15), 38.8 (C14), 41.7 (C6), 50.7 (OCH_3), 51.2 (C5), 55.4 (C7), 71.5 (C19), 73.4 (C20), 74.3 (C3), 90.3 (C16), 109.5 (C12), 120.8 (C10), 122.4 (C9), 128.1 (C11), 136.9 (C8), 143.2 (C13), 164.5 (C2), 169.1 (COOCH$_3$); MS (FAB) m/z (relative intensity) 341 (100.0, [M+H$^+$]), 327 (35.0), 149 (38.0); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_3$ 341.1782, found for [M+H$^+$] 341.1778.

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Supplementary data

Supplementary data contains ^{1}H, ^{13}C, and 2D NMR spectra of **6**, **7**, **8**, **4**, **9**, **10**, **11a**, **11b**, **2a**, and **2b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.079.

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The first total synthesis of (*R*)-convolutamydine A

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Abstract—The first total synthesis of (*R*)-convolutamydine A has been achieved by the organocatalytic addition of acetone to 4,6-dibromoisatin. The absolute configuration was determined by single crystal X-ray diffraction. DFT studies were used to model the transition states for the aldol reaction and equilibrium geometries of the post-aldol reaction intermediates. The DFT study revealed that the aldol bond forming reaction was considerably endothermic.

1. Introduction

Convolutamydines A–E are alkaloids that were isolated from the Floridian marine bryozoan *Amathia convoluta* in 1995.[1] These compounds have a 4,6-dibromo-3-hydroxyoxindole as a common skeleton and contain a quaternary stereocenter on C-3. Each convolutamydine differs in the side chain moiety at C-3, and for an enantioselective synthesis of these interesting natural products, the introduction of an asymmetric quaternary center is required. Several racemic syntheses of convolutamydines A–E have been proposed in the past,[2] and only very recently the enantioselective synthesis of convolutamydines B and E has been reported by Kobayashi and co-workers.[3] Here we report the first enantioselective synthesis of (*R*)-convolutamydine A (Fig. 1).

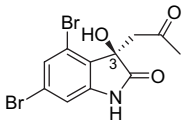

Figure 1. Structure of (*R*)-convolutamydine A.

2. Results and discussion

Recently, we reported the first example of the enantioselective addition of acetone to isatin using organocatalysis.[4] Of the several prolinamides tested as catalysts, the best results were obtained using 10 mol % of D-Pro-(*R*)-β^3-hPhg-OBn at −15 °C (up to 73% ee, (*R*)). In contrast, the results obtained with L-Pro-OH were quite unsatisfactory, affording the new stereogenic center with a maximum of 33% ee.

Interestingly, when L-Pro was used as catalyst, the *S* enantiomer was preferentially obtained. This outcome is opposite to that generally observed in the aldol addition of acetone to aldehydes when catalyzed by proline or prolinamides.[5] Moreover, the reaction catalyzed with our prolinamides afforded the new stereogenic center with greater ee and an absolute configuration that was dependent upon the absolute configuration of the proline moiety of the catalysts. In addition, the choice of the amino acid in the second position either enhances or reduces the enantiomeric excess and the yield.

Thus, we reasoned that, utilizing the same synthetic approach, we could readily obtain enantiomerically pure convolutamydine A. In this case, the starting material for the addition of acetone is 4,6-dibromoisatin, which is not commercially available, but can be obtained through a five-step sequence starting from *p*-nitroaniline, as previously reported for the total synthesis of racemic convolutamydine A[2b] (Scheme 1).

First, we investigated the D-Pro-OH catalyzed addition of acetone to **4** using various reaction conditions (Table 1).

Keywords: Convolutamydine A; Aldol reaction; Organocatalysis; DFT calculations.
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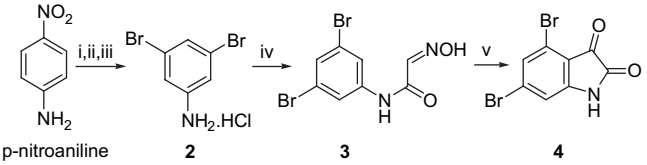
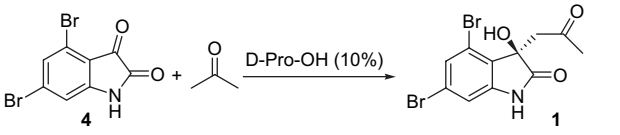


Scheme 1. Reagents and yields: (i) AcOH, Br_2, 98%; (ii) EtOH, $NaNO_2$, H_2SO_4, 97%; (iii) EtOH, Raney Ni, H_2, then HCl in H_2O/EtOH, 86–96%; (iv) chloral, $(H_2NOH)_2H_2SO_4$, Na_2SO_4, H_2O/EtOH (3:l, v/v), 82–88%; (v) 86% H_2SO_4, 80–86%.

Table 1. Enantiomeric excesses and yields of **1** obtained from the aldol reaction of 4,6-dibromoisatin with acetone catalyzed by D-proline[a]



Entry	Catalyst	Time (h)	Temp (°C)	Yield (%)	ee (%)[b]	Configuration
1	H-D-Pro-OH	17	20	Quant	3.5	*R*
2	H-D-Pro-OH	17	−15	86	55	*S*
3	H-D-Pro-OH[c]	16	−15	Quant	52	*S*
4	H-D-Pro-OH[d]	17	−15	45	35	*S*
5	H-D-Pro-OH	17	−30	0	—	—

[a] Conditions: the concentration of **4** in acetone was 0.15 M and 10 mol % of the catalyst was used.
[b] ee values were determined by HPLC.
[c] The concentration of **4** in acetone was 75 mM and 10 mol % of the catalyst was used.
[d] Dry acetone was used as the solvent.

As previously reported for isatin, the proline-catalyzed reaction afforded the desired product in good to excellent overall yield but with a moderate enantiomeric excess: at room temperature the reaction is very poorly enantioselective (entry 1), while the ee reaches 55% at −15 °C (entry 2). Furthermore, by lowering the temperature, the initial very poor (*R*)-enantioselectivity turns into a moderate (*S*)-enantioselectivity. This outcome is opposite to what we observed with the addition of acetone to isatin and is in agreement with the previously reported addition of acetone to aldehydes[4,5]. The proline catalyzed addition of acetone to 4-bromoisatin was therefore studied in detail by DFT calculations, as discussed later. As **4** is less soluble than isatin in acetone, the yield substantially improved when a lower concentration was used (entry 3 vs entry 2); on the other hand, when dry acetone was used, both a reduced yield and ee were obtained, thus suggesting that water may play a role in the reaction mechanism.

Owing to the unsatisfactory results, we tested the catalytic activity of a small library of dipeptides, which we considered to be the most interesting structures among those tested for the addition of acetone to isatins[4] (Fig. 2 and Table 2).

From Table 2 it can be seen that the optimal reaction temperature is −15 °C. The yields are always very high, with the exception of entry 7, where catalyst **9** was used, and of entry 16, where the catalyst loading was only 1 mol %. In general, catalysts containing the L-Pro-moiety preferentially afforded the (*S*)-enantiomer (entries 1, 2 and 7), while D-Pro-containing catalysts preferentially gave the (*R*)-enantiomer (entries 3, 4 and 8−17). An exception to this generalization was the reaction catalyzed by H-D-Pro-(*S*)-αMeChg-OBn **8**, which preferentially afforded the (*S*)-enantiomer (entries 5 and 6), but the ee is very low.

Finally, the total synthesis of (*R*)-convolutamydine A (**1**) was achieved using H-D-Pro-(*R*)-β^3Phg-OBn **10** as the catalyst and by performing the reaction at a low concentration of **4** (entry 12). This favours the complete dissolution of **4** in the solvent (Scheme 2). Highly enantiomerically enriched (*R*)-**1**

Table 2. Enantiomeric excesses and yields of convolutamydine A (**1**) obtained in the aldol reaction of **4** with acetone as catalyzed by dipeptides **5**–**11**[a]

Entry	Cat.[b]	Solvent	Time (h)	Temp (°C)	Yield	ee (%)[c]	Configuration
1[d]	**5**	Acetone	96	20	Quant	21	*S*
2[d]	**6**	Acetone	96	20	Quant	28	*S*
3	**7**	Acetone	65	20	Quant	33	*R*
4[e]	**7**	Acetone	16	−15	70	39	*R*
5	**8**	Acetone	65	20	Quant	4.5	*S*
6[e]	**8**	Acetone	16	−15	82	9	*S*
7[d]	**9**	Acetone	17	20	33	46	*S*
8	**10**	Acetone	17	20	Quant	54	*R*
9	**10**	Acetone	17	−15	Quant	62	*R*
10[d]	**10**	Acetone	17	−15	90	60	*R*
11[d]	**10**	Acetone	17	−30	91	50	*R*
12[e]	**10**	Acetone	17	−15	Quant	68	*R*
13	**10**	Acetone/toluene	17	20	Quant	48	*R*
14	**10**	Acetone/toluene	17	−15	Quant	61	*R*
15[f]	**10**	Acetone	17	−15	66	50	*R*
16[g]	**10**	Acetone	17	−15	31	—	
17[d]	**11**	Acetone	96	20	Quant	34	*R*

[a] Unless otherwise specified, the concentration of **4** in acetone was 0.15 M.
[b] Unless otherwise stated, the catalyst loading was 10 mol %.
[c] ee values were determined by HPLC.
[d] Dry acetone was used as solvent.
[e] The concentration of **4** in acetone was 75 mM.
[f] The catalyst loading was 5 mol %.
[g] The catalyst loading was 1 mol %.

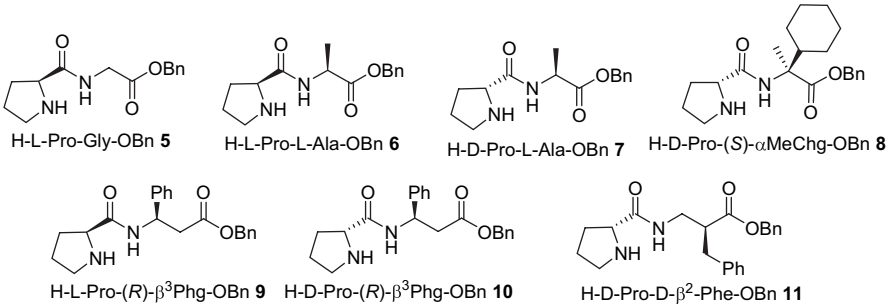
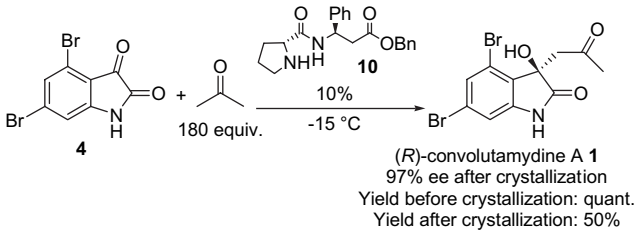


Figure 2. Dipeptides evaluated in this study.

(97% ee) was obtained after (a) elimination of the catalyst by filtration on silica; (b) partial crystallization resulting in the elimination of *rac*-**1** (due to the strong tendency of *rac*-**1** to self aggregate), thus reducing its solubility and enantiomerically enriching the solution in (*R*)-**1**; and (c) concentration of the mother liquors and crystallization. Several solvents were tested for the final crystallization, including methanol, diethyl ether, methyl *tert*-butyl ether, ethyl acetate, THF and toluene. Diethyl ether proved to be the most suitable solvent. The enantiomeric enrichment was analyzed by HPLC analysis (see Supplementary data). This process is quite simple and reproducible, and may therefore be applied for the production of larger quantities of **1**.



Scheme 2. Optimized synthesis of (*R*)-convolutamydine A.

Previously, the absolute configuration of natural convolutamydine A had only been assigned by CD correlation with similar compounds.[6] We have unambiguously determined the absolute configuration of our compound as (*R*) by single crystal X-ray diffraction (Fig. 3).

Comparison of the optical rotation of synthetic **1**, $[\alpha]_D^{20}$ +41.4 (*c* 0.14, MeOH), with the data for the optical rotation of the natural sample, $[\alpha]_D^{20}$ +27.4 (*c* 0.06, MeOH),[1b] confirms that the naturally occurring compound has the (*R*) configuration. However, we observed differences in the CD spectrum of **1** in methanol (Fig. 4) in comparison to the data reported in the literature.[1b] For the natural sample CD λ_{ext} (MeOH) at 228.20 nm was $\Delta\varepsilon$ −2.86, while we found $\Delta\varepsilon$ +25.86 at the same wavelength. The complete CD spectrum of **1** is reported in Figure 4 and is very similar to the CD spectrum of convolutamydine B.[3]

The organocatalytic asymmetric proline-catalyzed aldol reaction has recently received considerable attention. In addition to the experimental results,[5b,7] DFT calculations have been found to be a persuasive argument for the nucleophilic addition of an enamine to the carbonyl group in preference to other reaction mechanisms and have been used to successfully predict and rationalize enantioselectivities.[8]

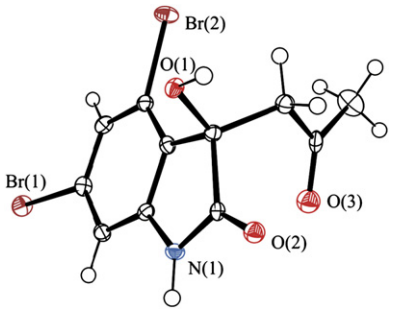


Figure 3. ORTEP drawing of the (*R*)-enantiomer of convolutamydine A.

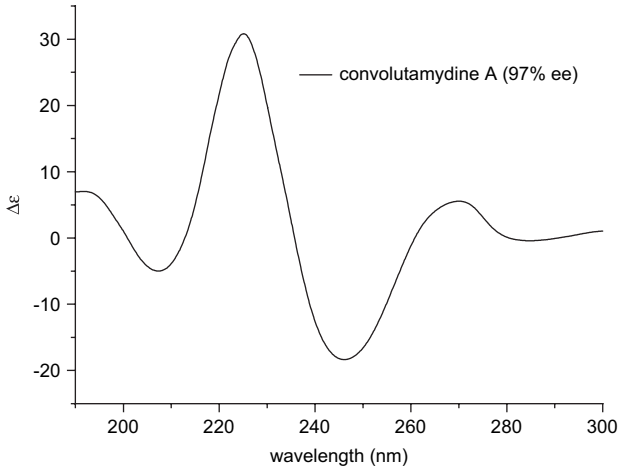


Figure 4. CD spectrum of a sample of **1** (concentration 5 mM in methanol).

Our experimental studies have revealed that the substrate 4,6-dibromoisatin gives an excellent yield with moderate enantiomeric excess for the (*S*)-enantiomer when using D-proline. In principle, this result could be explained using either a Houk–List transition state, involving an *anti*-enamine,[5,9] or via a *syn*-enamine.[8i] By simple examination of the structures, it was not immediately obvious how the presence of the adjacent amide group would affect the reaction outcome, although it was to be expected that the 4-bromo-substituent would impart a steric effect. Therefore, in order to obtain more insight into the proline-catalyzed addition of acetone to 4,6-dibromoisatin, combined semi-empirical (PM3)[10] followed by geometry/energy optimization using density functional theory (DFT, B3LYP)[11] 6-311G*,[12] calculations were performed.

Previous DFT calculations have revealed the importance of a hydrogen bond between the carboxylic acid and the aldehyde or ketone carbonyl group. As the reaction progresses through the C···C bond forming transition state, this proton is simultaneously transferred to the forming alkoxide, ultimately giving rise to a zwitterionic, iminium, intermediate.

Initially, a PM3 conformer search of diastereoisomeric, zwitterionic, iminium intermediates was performed. A hydrogen bond between the carboxylate group and the tertiary alcohol was present as a result of the addition of the *anti*- or *syn*-hydrogen bonded L-proline enamines to the *Re* and *Si* faces of the keto-carbonyl group of isatin. The resulting unique lowest energy conformers were then modified by introduction of a 4-bromo-substituent, so as to model any steric effect of this substituent upon the aldol reaction, and subjected again to PM3 equilibrium geometry minimizations. These equilibrium geometry structures were then used as starting points for B3LYP/6-311G* calculations, where the bromine atom was described by use of a pseudopotential. From the initial eight inputs, seven unique equilibrium geometry structures (characterized as minima by the lack of any imaginary vibrations) were found (see Fig. 5 and Supplementary data).

In addition, the PM3 geometries of the 4-bromoisatin zwitterionic intermediates were used as starting points for determining PM3 transition state geometries for the retro-aldol

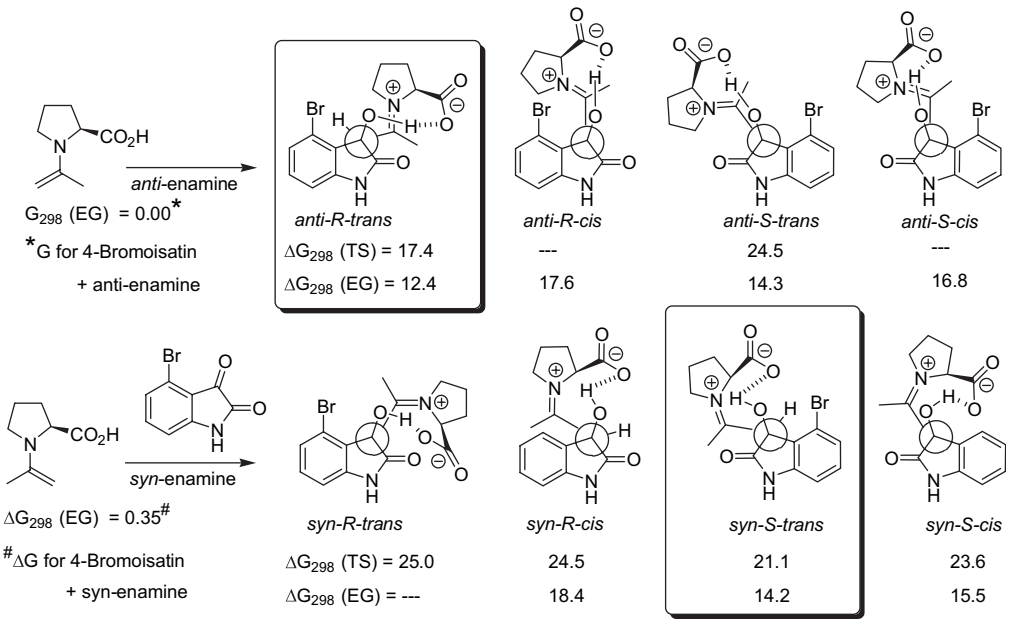


Figure 5. Schematic Newman projections of the eight lowest energy conformations resulting from the reaction of the *syn*-, and *anti*-, acetone L-proline enamines with 4-bromoisatin.[13]

reaction, which in turn were used as starting points for the B3LYP/6-311G* transition state calculations. From the initial eight inputs, six unique transition states were found and were characterized by a single imaginary frequency that corresponded to simultaneous formation of the C–C bond and proton transfer from the acid to the forming alkoxide (see Supplementary data). The values of ΔG for the respective transition states are presented in Figure 5.

If the reaction of the acetone L-proline enamine with 4-bromoisatin was kinetically controlled, in accord with the calculated transition states, the *anti-R-trans* TS and *syn-S-trans* TS transition states would result in the (*R*)- and (*S*)-enantiomers, respectively, where the (*R*)-enantiomer would predominate.[13] This is consistent with the experimentally observed result. However, the calculated difference in free energy (ΔG) between these gas phase transition states would result in an enantiomeric excess considerably greater than that experimentally observed. This difference may in part be due to solvation effects reducing the energy difference between the transition states in solution.[8i] Interestingly, the calculations predict that the *syn*-enamine (*syn-S-trans* TS conformation) would be responsible for the formation of the minor enantiomer. Previous studies of proline-catalyzed intermolecular aldol reactions have generally attributed the formation of both major and minor products to the addition of the *anti*-enamine to the *Re* and *Si* faces of the aldehyde.[8g] Recently, Clemente and Houk, using DFT methods, have demonstrated for the Hajos–Parrish–Eder–Sauer–Wiechert reaction[14] that the respective *anti*-enamine leads to the major product and the respective *syn*-enamine to the minor product. In this case too, ΔG was slightly overestimated by the theoretical model.[8b,e] Barbas et al. have also observed the importance of a *syn*-enamine (called *s-cis*, their work) in a diastereo- and enantioselective Mannich reaction.[15] In addition, our calculations show that the *syn-S-cis* TS structure is also lower in energy than the *anti-S-trans* TS.

Comparing our calculated transition structures, notable differences can be appreciated. The lowest energy transition state, *anti-R-trans* TS, has a staggered conformation of the substituents bonded to the carbons of the forming C···C bond. The *anti*-configuration of the enamine results in the proline moiety having a minimal steric interaction with both the bromine substituent of the aromatic ring and the amide group of the oxindole moiety. The O–C···C angle (112.3°) reflects considerable bond formation. This is consistent with the short bond length (1.661 Å) reflecting that the transition state resembles the product structure. In addition two electrostatic interactions can be identified:[16] (i) the forming alkoxide oxygen is stabilized by a proximal hydrogen of the pyrrolidine ring (2.258 Å) that is adjacent to the developing iminium ion ($^{\delta+}$HCN···O$^{\delta-}$); (ii) the amide carbonyl interacts with a methyl group hydrogen atom (2.503 Å), $^{\delta-}$O···CH$_3$C=N$^{\delta+}$.

In the *syn-S-trans* TS the substituents bonded to the carbons involved in the forming C···C bond are staggered. This conformation further results in a minimal interaction with the bromine substituent. At the same time a possible steric interaction of the enamine methyl group with the amide carbonyl is minimized by the enamine being inclined away from the plane of the bromoisatin substrate (the angle of the forming C···C–O bond is 108.1° and the C···C distance is 1.975 Å), thus maximizing orbital overlap for the nucleophilic addition to the keto-carbonyl.[17] There are no notable secondary electrostatic interactions involved between the polar groups.

An unusual feature of this reaction is that the C···C bond forming step was found to be considerably endothermic, approximately 13 kcal/mol (Fig. 6). Therefore, the aldol reaction in this case could be reversible depending upon the energetics of the hydrolysis reaction. Clemente and Houk[8e] found that the hydrolysis transition state was 13 kcal/mol (ΔH_0) higher in energy than the initial reaction reagents

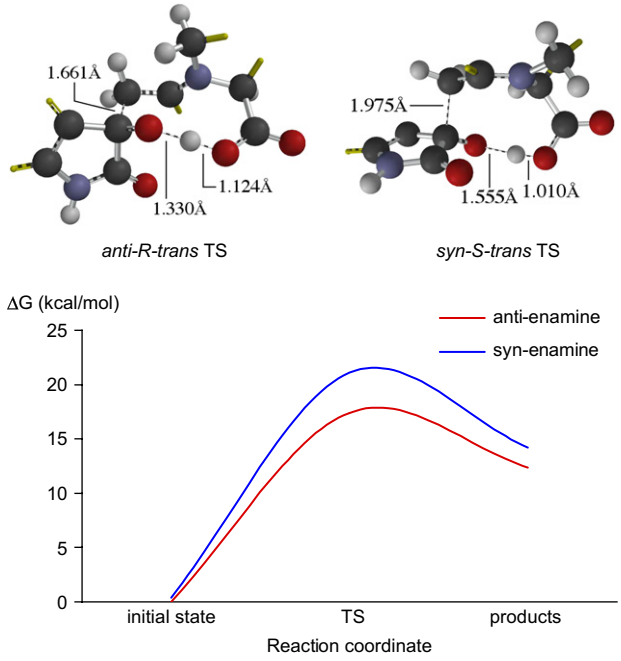


Figure 6. Reaction coordinate for the reaction of the *syn*- and *anti*-enamines.

but that this transition state was approximately 10 kcal/mol lower in energy than the aldol transition state.

Therefore, given the differences in the methodology between the studies, the activation energies (ΔG_{298}) for the aldol reaction are less than or similar to the previously cited aldol activation energy. Examining two extreme cases: (i) if the transition state for the hydrolysis reaction is lower in energy, then the transition state for the aldol reaction will not be reversible and the enantioselectivity of the reaction would be controlled by the aldol step. This is not in agreement with our experimental results. (ii) If the hydrolysis reaction passes through a transition state that is higher in energy than the aldol transition state, the C–C bond forming step can be reversible.

In this case, there are now two further situations that can result in control of the enantioselectivity: (i) the hydrolysis reaction and (ii) the intermediate zwitterionic iminium product ratio. Our calculations of the equilibrium geometry structures for the intermediate zwitterionic iminium products reveal a $\Delta\Delta G$ of 1.45 kcal/mol favouring the *anti-R-trans*-EG.[18] This energy difference would correspond to an enantioselectivity of approximately 80%, which is much closer to the experimental result. Water has recently been observed to impart a beneficial effect upon the enantioselectivity of some amino acid catalyzed aldol reactions and is, evidently, involved in the hydrolysis step and at this point we cannot rule out the importance of the participation of water in the reaction mechanism.[19] Thus, the calculated reaction of the acetone L-proline enamine with 4-bromoisatin reveals several features: (i) the principal transition states have free energies of activation of 17 and 21 kcal/mol; (ii) the aldol bond forming reaction is endothermic; (iii) in the case of the transition state leading to the principle intermediate (*anti-R-trans* EG), the transition state has a resemblance to the product[20] greater than that found in previously studied reactions of the acetone proline enamine with aldehydes, as proved by a shorter C···C bond forming length.

In the case of the D-prolinamide dipeptides studied in this work, the (*R*)-aldol product was obtained, whereas with D-proline the (*S*)-aldol product was obtained. Due to the steric requirements of the catalyst **10**, we speculate that there must be a change in the reaction coordinate that inverts both the energy profile and the equilibrium geometries of the *syn-S-trans* (or *anti-S-trans*) and the *anti-R-trans* transition states.[21]

3. Conclusion

In conclusion, we have reported the first enantioselective synthesis of convolutamydine A (**1**), an alkaloid having interesting biological activity. The absolute configuration of the natural compound has been confirmed by an X-ray diffraction analysis of the synthetic sample. An initial theoretical investigation suggests that the major enantiomer can be explained as being formed via a Houk–List transition state involving the *anti*-enamine but the minor enantiomer is the result of reaction of the *syn*-enamine. In addition, the enantioselectivity of the reaction does not appear to be controlled by the aldol transition states.

4. Experimental

4.1. General

Routine NMR spectra were recorded with spectrometers at 400, 300 or 200 MHz (^{1}H NMR) and at 100, 75 or 50 MHz (^{13}C NMR). Chemical shifts are reported in δ values relative to the solvent peak of $CHCl_3$, set at 7.27 ppm. Infrared spectra were recorded with an FTIR spectrometer. Melting points were determined in open capillaries and are uncorrected. The CD spectra were obtained using cylindrical fused quartz cells of 0.1 cm path length. The values are expressed in terms of molecular CD.

D-Proline is commercially available. L-α-Methylcyclohexylglycine has been prepared by hydrogenation of L-(α-methyl)-phenylglycine as described previously.[22] The β-amino acids *R*-β^3-hPhg (L-β^3-homophenylglycine) and L-β^2-hPhe (L-β^2-homophenylalanine) were prepared at DSM Research as described in PCT Pat. Appl. WO 01/42173 and Eur. Pat. Appl. No. 04075597.7 (patent pending), respectively. Peptide bond formation was accomplished via standard solution-phase procedures, with HBTU [*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate] and triethylamine in acetonitrile on Boc-protected prolines. The removal of the Boc group was accomplished via reaction with trifluoroacetic acid in dichloromethane.

Analytical high performance liquid chromatograph (HPLC) was performed on an HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm), using an AD column (0.46 cm I.D.× 25 cm) (Daicel Inc.) for the analysis of ee values of convolutamydine A. Elution conditions: flow rate 0.7 mL/min, solvent hexane/isopropanol 80:20, retention time: 16.7 min for isomer *S* and 21.5 min for isomer *R*, detection wavelength 225 and 230 nm. Hexane CHROMASOLV® and isopropanol CHROMASOLV® for HPLC were used as the eluting solvents.

4.2. Optimized synthesis of (*R*)-convolutamydine A

H-D-Pro-*R*-β[3]-hPhg-OBn (0.03 mmol, 11 mg) was stirred in acetone (4 mL) for 15 min at −15 °C. Solid 4,6-dibromoisatin[2b] (0.3 mmol, 91 mg) was added and the mixture was stirred for 17 h. After this time, acetone was removed under reduced pressure and the mixture was purified by flash chromatography (cyclohexane/ethyl acetate 1:1), to eliminate the catalyst and enhance the enantiomeric excess.[23] The enantiomeric excesses were determined by HPLC prior to purification. Pure (*R*)-convolutamydine A was obtained from the enriched enantiomeric mixture, by crystallization from diethyl ether. Yield before crystallization: quantitative. Yield after crystallization: 50%; mp=196–201 °C, lit.[2] 190–195 °C; $[\alpha]_D^{20}$ +41.4 (*c* 0.14, MeOH) lit.[2]: $[\alpha]_D^{20}$ +27.4 (*c* 0.06, MeOH); IR ($CHCl_3$, 3.10^{-3} M): ν=3428, 3244, 1740, 1720, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 3.35 (d, 1H, *J*=17.1 Hz), 3.74 (d, 1H, *J*=17.1 Hz), 7.01 (s, 1H), 7.33 (s, 1H), 7.84 (br s, 1H); ^1H NMR (300 MHz, CD_3OD): δ 2.13 (s, 3H), 3.31 (d, 1H, *J*=17.7 Hz), 4.01 (d, 1H, *J*=17.7 Hz), 7.06 (d, 1H, *J*=1.8 Hz), 7.33 (d, 1H, *J*=1.8 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 28.9, 74.5, 112.6, 119.3, 123.3, 128.0, 128.4, 146.3, 178.9, 206.0; ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 47.7, 75.2, 113.3, 129.5, 144.2, 162.5, 177.2, 182.6; MS (EI) *m*/*z* (rel intensity) 365, 363, 361, 320, 308, 306, 304, 277, 275, 254, 168; HRMS (EI) calcd for $C_{11}H_9{}^{79}Br_2NO_3$ (M^+): 360.8949; found: 360.8941.

The enantiomeric excess could be further improved by the crystallization of *rac*-**1** from Et_2O, leaving an ethereal solution of (*R*)-**1**. Concentration of this solution gave a crystalline product of 97% ee as determined by HPLC and crystals suitable for X-ray diffraction were obtained.

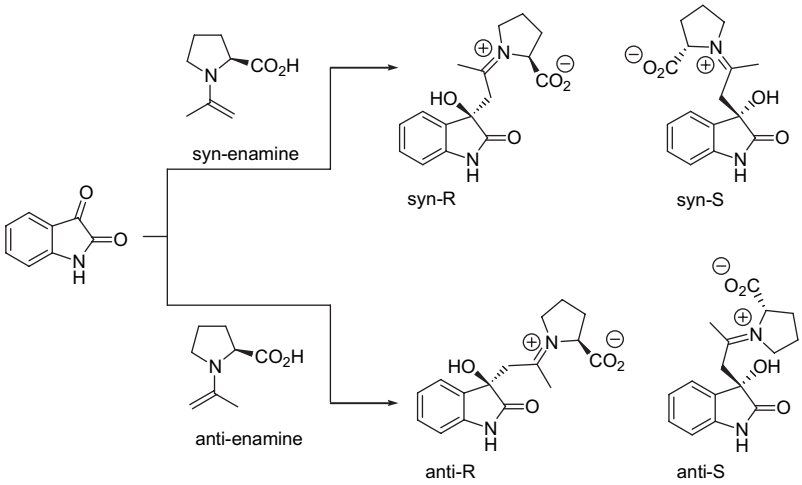
4.3. X-ray crystallography

The X-ray intensity data for convolutamydine A[24] were measured on an AXS ApexII diffractometer, equipped with a CCD detector. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For both crystals, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program, and an empirical absorption correction was applied using SADABS. The structure was solved by direct methods and subsequent Fourier syntheses in the orthorhombic crystal system (space group *P*212121) and refined by full-matrix least-squares on F2 (SHELXTL), using anisotropic thermal parameters for all non-hydrogen atoms. All hydrogens, except those attached to the nitrogen and oxygen atoms, which were located in the Fourier map, were added in calculated positions, included in the final stage of refinement with isotropic thermal parameters, $U(H)=1.2U_{eq}(C)$ [$U(H)=1.5U_{eq}$(C–Me)], and allowed to ride on their carrier carbons. The absolute configuration was determined (Flack parameter −0.006(8)).

4.4. Methodology for obtention of the initial inputs for the DFT calculations—semi-empirical PM3 calculations

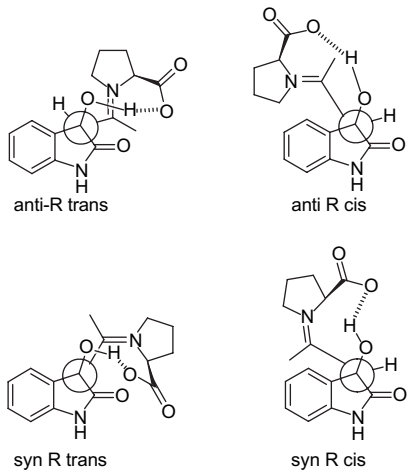
Initially, a PM3 conformer search on two of the four possible diastereoisomeric zwitterionic iminium intermediates (*syn-S*, attack of the *syn*-enamine on the *Re*-face of the ketone, and *anti-R*, attack of the *anti*-enamine on the *Si* face of the ketone) was performed (Scheme 3).

In each case, two structurally different, lowest energy, conformers were found. In short, these isomers can be described as having the proline moiety cis or trans to the aromatic ring of the oxindole nucleus. These isomers are related by rotation around the C–C bond formed in the aldol reaction and the carboxylate group forms a hydrogen bond to the alcohol that is either proximal (cis) or distal (trans) to the aromatic ring. These isomeric structures could, in principle, be traced back to initial reactant Van der Waals complexes where a hydrogen bond from the carboxylic acid could occur to either side of the keto-carbonyl group. The four isomers were then used to model the *syn-R* and *anti-S* structures by inverting the stereochemistry of the tertiary alcohol and performing equilibrium geometry PM3 calculations (Scheme 4). Thus, a total of eight equilibrium geometry zwitterionic intermediates were obtained. 4,6-Dibromoisatin was modeled as the 4-bromoisatin to ensure that any steric effect



Scheme 3. Reaction of the *syn*-, and *anti*-, acetone L-proline enamines with isatin resulting in four diastereomeric zwitterionic intermediates.

due to the bromine was incorporated. The eight equilibrium geometry PM3 structures obtained for isatin were modified by substitution of 4-H for 4-Br and subjected to PM3 equilibrium geometry calculations. These equilibrium geometry structures were then used as starting points for B3LYP 6-311G* calculations, where the bromine atom was described by use of a pseudopotential. From the initial eight inputs, seven unique equilibrium geometry structures (characterized as minima by the lack of any imaginary vibrations) were found.



Scheme 4. Schematic Newman projections of the four conformations for the zwitterionic intermediates *anti-R* and *syn-R* that would lead to formation of the *R*-enantiomer of the aldol product. Hydrogens behind the plane of the oxindole nucleus bonded to the carbon of the enamine have been omitted for clarity. The descriptors 'trans' and 'cis' are used, subjectively, to indicate the position of the proline nucleus relative to the aromatic ring of the oxindole nucleus.

In addition, the PM3 geometries of the 4-bromoisatin zwitterionic intermediates were used as starting points for determining PM3 transition state geometries for the retro-aldol reaction. The eight PM3 aldol transition states were used as starting points for the B3LYP 6-311G* transition state calculations. From the initial eight inputs, six unique transition states were found that were characterized by a single imaginary frequency that corresponded to simultaneous formation of the C–C bond and proton transfer from the acid to the forming alkoxide.

Acknowledgements

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Supplementary data

Experimental details and characterization data of the catalysts **5**–**11**. Cartesian coordinates, structures, and tables of thermodynamic data from the DFT calculations. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.077.

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13. The corresponding values of ΔG for the diastereomeric aldol transition states (TS) and for the respective intermediate zwitterionic iminium ion product equilibrium geometries (EG) are given relative to ΣG for the substrates 4-bromoisatin+*anti*-enamine. The hydrogens behind the plane of the oxindole moiety bonded to the carbon of the enamine and the 4-bromo-atom of the products *syn-R-cis* and *syn-S-cis* have been omitted for clarity. The descriptors trans and cis are used, subjectively, to indicate the position of the proline nucleus relative to the aromatic ring of the oxindole nucleus.
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18. Where there is thermodynamic control then the product ratio is given by the respective equilibrium constants. $\Delta\Delta G/RT=-\ln(K_1/K_2)$.
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24. Crystal data for convolutamydine A. The crystals were obtained from diethyl ether. Formula weight: 363.01; orthorhombic, $P2_12_12_1$; Z=4; a=7.61 Å; b=7.91 Å; c=19.83 Å; $\alpha=\beta=\gamma=90^\circ$; V=1193.14 Å^3; 2884 unique reflections; R=0.0168. The structure has been deposited with the Cambridge Crystallographic Data Centre and has received the deposition number CCDC 610173.

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Improved synthesis of tocopherol fatty alcohols and analogs: microglial activation modulators

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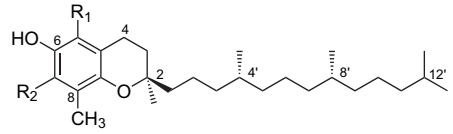
Abstract—The synthesis of tocopherol fatty alcohols (TFAs), potent microglial activation modulators, was achieved via *C*-alkylation of trimethylhydroquinone. Several analogs, in particular water-soluble prodrugs, have been synthesized using a Wittig reaction and their antioxidant activities have been evaluated.

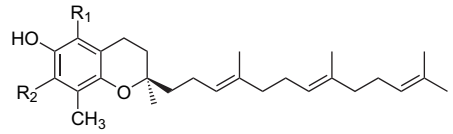
1. Introduction

Vitamin E, the most important fat-soluble antioxidant in biological systems, occurs naturally in eight main isoforms: α, β, γ, and δ-tocopherols and four corresponding tocotrienols (Scheme 1).[1] Both groups are composed of differentially methylated 2-substituted 3,4-dihydro-2*H*-1-benzopyrans, the chromans and a phytyl side chain for the tocopherols and an unsaturated farnesyl chain for the tocotrienols.[2]



Tocopherol

α : $R_1 = R_2 = CH_3$ γ : $R_1 = H$, $R_2 = CH_3$
β : $R_1 = CH_3$, $R_2 = H$ δ : $R_1 = R_2 = H$



Tocotrienol

Scheme 1. Tocopherols and tocotrienols.

Although γ-tocopherol is generally the most abundant form in the diet, α-tocopherol accounts for over 90% of the total vitamin E retained in the body.[1] Naturally occurring α-tocopherol is optically active, having three chiral centers whereas most synthetic supplements are mixtures of the eight possible stereoisomers.

Several groups have identified an α-tocopherol transfer protein (α-TTP) acting mainly in the liver.[3] Studies on the distribution and chiral discrimination of deuterated tocopherols have shown that the 2*R*-isomer of the trimethylated chroman ring dominates the biokinetics. The naturally occurring α-tocopherol is as such preferentially retained by the liver and then redistributed to the tissues.[3b]

α-Tocopherol is therefore the member of the vitamin E family presenting the highest biological activities. Besides its well-known role of being the most effective chain-breaking phenolic antioxidant in mammalian tissues,[4] α-tocopherol has numerous important clinical effects. It acts as a regulator of heme synthesis and an inhibitor of platelet aggregation.[5] Vitamin E plays also an important role in the brain immune system and thus in the prevention of degenerative neuropathies by acting mainly as a neuroprotective agent.[6]

Previous studies showed that *n*-hexacosanol, a long chain primary alcohol extracted from *Hygrophila erecta*, a plant known in the traditional Chinese medicine for its wound healing properties, increases the survival rate and induces the differentiation of fetal mice neurons in vitro.[7] The chain length and the ω-hydroxyl function are crucial factors for this biological activity which is similar to that of naturally occurring growth factors, namely neurotrophic factors.

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In order to combine the neurotrophic activity and the neuroprotective effects of antioxidant molecules, we investigated hybrid compounds composed of a neurotrophic ω-alkanol structure and an antioxidant moiety. This approach led to the syntheses of 3-(15-hydroxy-pentadecyl)-2,4,4-trimethyl-cyclohexen-1-one (tCFA-15)[7b] and 18-(5-methoxy-1*H*-indol-3-yl)octadecane-1-ol.[8] These compounds are strong neural stem cells differentiation inducers, which present antioxidant and neuroprotective activities. In addition, they increase the axonal outgrowth and counteract the axonal growth inhibitory properties of semaphorin 3A and myelin-associated proteins[9] and can therefore be considered as compounds suitable for the treatment of neurological diseases.

In a previous study, we showed that tocopherol fatty alcohols (TFAs), combining the trimethylated chroman ring of α-tocopherol and an ω-alkanol side chain, modulate microglial activation.[10] Microglial cells, the brain resident monocyte-macrophage cell population are found as quiescent cells throughout the brain parenchyma, where they represent around 15% of the cell population.[11] Upon appropriate stimulation, typically after brain injury or infection, as well as during the development of neuropathies like Alzheimer's disease and multiple sclerosis, microgliocytes continue their previously halted differentiation process to become immunocompetent phagocytic cells. Activated microglia produces pro-inflammatory cytokines and a series of free radicals which induce neurodegenerative events comparable to those observed in Alzheimer's disease.[12] TFAs (Scheme 2), specifically the 2-(12-hydroxy-dodecyl)-2,5,7,8-tetramethyl-chroman-6-ol, the TFA bearing 12 carbon atoms on the side chain (n=12), significantly decreases the production of TNF-α and NO radicals by activated microglial cells.[10] In order to further investigate these potent anti-neuroinflammatory properties and their possible applications in the treatment of degenerative neuropathies, larger quantities of TFAs and their water-soluble prodrug forms as well as their optically pure isomers are required.

2. Results and discussion

Here we report an optimized synthesis of different TFAs based on *C*-alkylation of trimethylhydroquinone (THQ) as well as the syntheses of optically active isomers. Several analog compounds are also synthesized in order to investigate the roles of the side chain and the nucleus. Finally, the syntheses of a range of highly water-soluble prodrug forms designed for animal testings are described (Scheme 2).

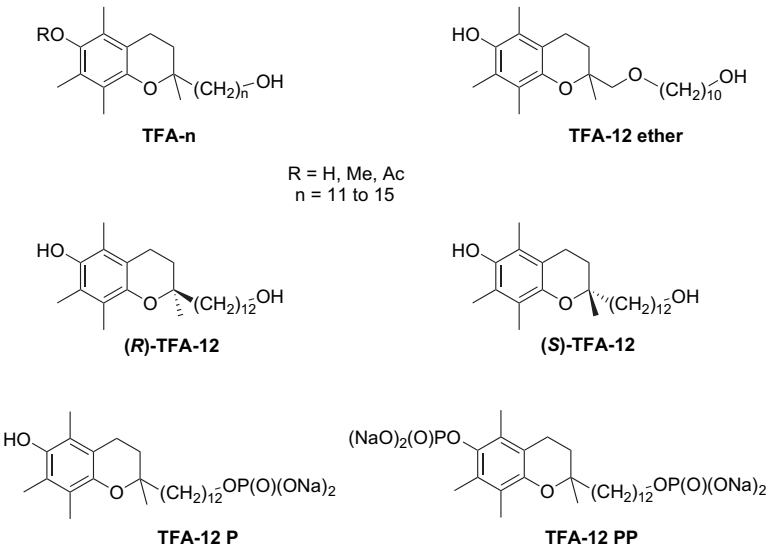
TFAs being able to modulate microglial activation,[10] we wanted to investigate if and to what extend the antioxidative capacity provided by the chroman ring takes part in this activity. In this aim, two new series AcTFAs and MeTFAs were synthesized. Both series have the phenol function, essential for their antioxidant activity, protected by a more or less stable group in biological environment.

In order to investigate the importance of the linking atom between the chroman ring and the ω-alkanol side chain, TFA-12 ether having an oxygen-linking atom was synthesized.

As previously described, the 2*R*-isomer of vitamin E dominates the biokinetics. In order to determine a possible stereogenic effect in the modulation of microglial activation, (*R*)-TFA-12 and (*S*)-TFA-12 were synthesized.

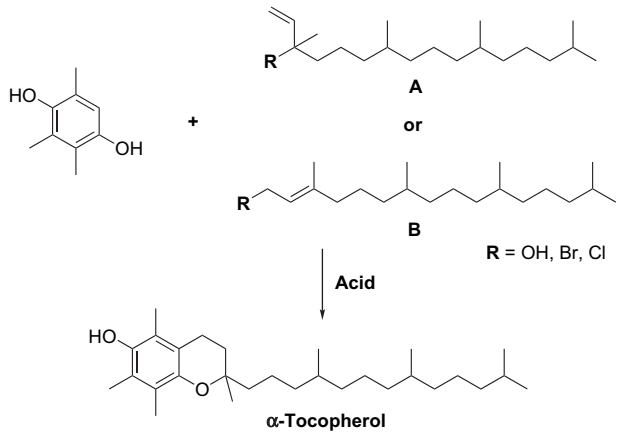
Finally, in order to determine the ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of TFA-12 and to study its effects on an animal model of multiple sclerosis, the syntheses of water-soluble prodrugs TFA-12 P and TFA-12 PP were developed.

Vitamin E is a very common antioxidant used for food conservation and has thus evoked large synthetic interest.[13] Most industrial preparation processes of (all-*rac*)-α-tocopherol are based on a Lewis or Broensted acid catalyzed condensation of THQ with isophytol **A** (R=OH),[14] phytol



Scheme 2. Different tocopherol fatty alcohols.

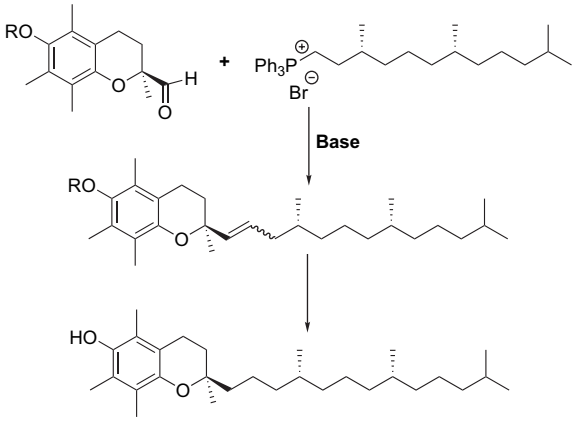
B (R=OH),[15] or the corresponding halides **A** (R=Br or Cl)[16] or **B** (R=Br or Cl)[17] (Scheme 3).



Scheme 3. Industrial synthesis of (all-*rac*)-α-tocopherol.

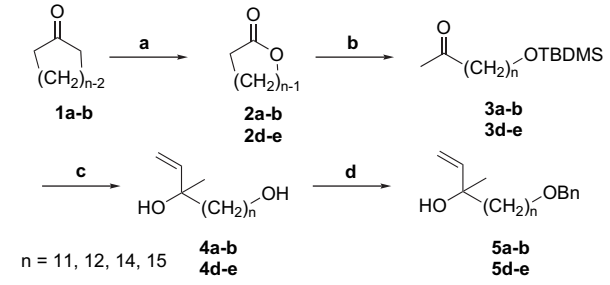
Industrial chroman ring formation can also be achieved by a regioselective Rh(I)-catalyzed arylation of β-springene with THQ.[18]

Several methods have been developed to synthesize chiral chromans or optically active α-tocopherol.[19] Most procedures are based on Wittig[2,3b,20] (Scheme 4) or Julia[6] type couplings of an activated chroman moiety with the corresponding side chain.



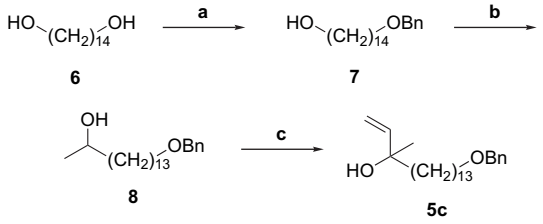
Scheme 4. Synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol.

TFAs were first synthesized through *C*-alkylation of THQ using ω-benzyloxy allylic alcohols **5a–e** (Scheme 5). These



Scheme 5. Reagents and conditions: (a) *m*-CPBA, CF_3CO_2H, CH_2Cl_2, reflux (80–85%); (b) (i) NHMeOMe·HCl, MeLi, (ii) MeLi, (iii) TBDMSCl, imidazole, THF, 0 °C to rt (68–76%); (c) (i) $CH_2CHMgBr$, THF, 0 °C to rt, (ii) TBAF (66–88%); (d) NaH, BnBr, THF, reflux (73–81%).

key intermediates were obtained starting either from the corresponding cyclic ketones and lactones (Schemes 5 and 6) or from the corresponding 1,ω-diol (Scheme 6).



Scheme 6. Reagents and conditions: (a) NaH, BnBr, NBu_4Br, THF, reflux (32%); (b) $(CO)_2Cl_2$, DMSO, NEt_3, MeMgBr, THF, −78 to 0 °C (66%); (c) $(CO)_2Cl_2$, DMSO, NEt_3, $CH_2CHMgBr$, THF, −78 to 0 °C (75%).

A Baeyer–Villiger type oxidation of ketones **1a–b** in the presence of trifluoroacetic acid gave lactones **2a–b** (Scheme 5).[21] Lactones **2d** and **2e** are commercially available. Formation of the Weinreb methyl hydroxamate using its salt in the presence of methyllithium followed by a subsequent addition of methyllithium gave the methylketones.[22] Finally silylation of the generated ω-hydroxyl function allowed us to obtain the protected hydroxyketones **3a–b,d–e** from the corresponding lactones **2a–b,d–e** in a one-step procedure with satisfactory overall yields.

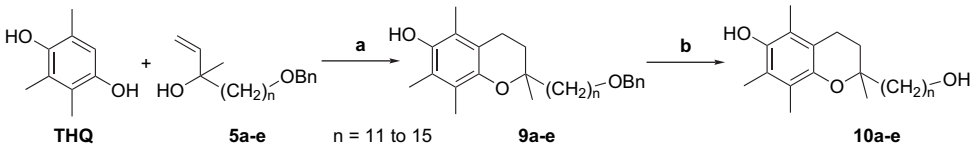
Nucleophilic addition of vinylmagnesium bromide followed by an *in situ* desilylation gave the corresponding ω-hydroxyl allylic alcohols **4a–b,d–e** which were then submitted to a regioselective benzylation in order to generate ω-benzyloxy allylic alcohols **5a–b,d–e**. The use of silylethers as temporary protecting groups remained necessary as all attempts to benzylate the ω-hydroxyl methylketones resulted in low yields. The silyl groups had nevertheless to be replaced by benzylethers as the *C*-alkylation of THQ using silyloxy allylic alcohols did not proceed.

The synthesis of ω-benzyloxy allylic alcohol **5c** was achieved by a monobenzylation of 1,14-tetradecandiol **6** followed by two subsequent Swern–Ireland[23] reactions using, respectively, methylmagnesium bromide and vinylmagnesium bromide as nucleophiles (Scheme 6).

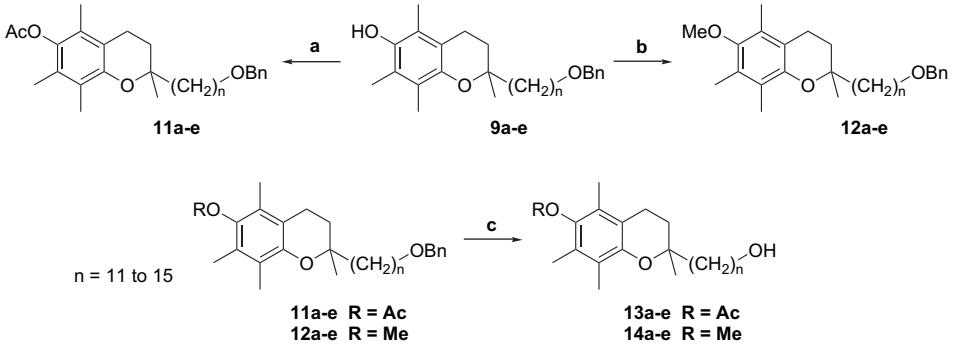
With the ω-benzyloxy allylic alcohols **5a–e** in hand, ω-benzylated TFAs **9a–e** were obtained by an acid catalyzed *C*-alkylation of THQ (Scheme 7). TFAs **10a–e** were finally obtained after treatment with hydrogen over palladium catalyst of compounds **9a–e**.

In order to generate the AcTFA and MeTFA series, the free phenol function of ω-benzylated TFAs **9a–e** was either acetylated in the presence of acetic anhydride in pyridine or methylated using sodium hydride and methyl iodide (Scheme 8). Both series were then submitted to treatment with hydrogen over palladium catalyst to give AcTFAs **13a–e** and MeTFAs **14a–e**, respectively.

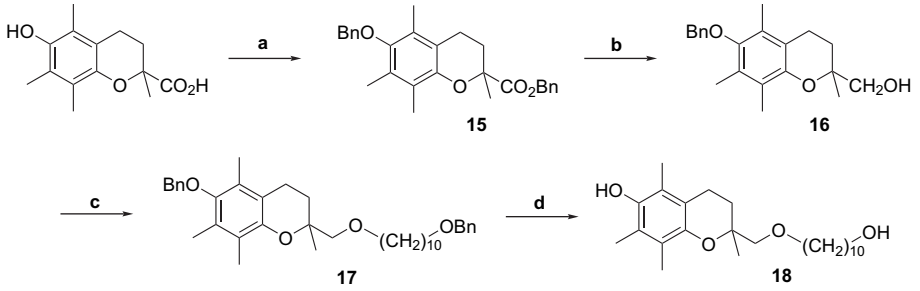
TFA-12 ether **18** was obtained starting from the short chain α-tocopherol analog Trolox® which was dibenzylated using benzyl bromide and potassium carbonate (Scheme 9). Benzyl ester **15** was reduced to its alcohol **16** which in the presence of sodium hydride and 10-iodo-1-(benzyloxy)-decane



Scheme 7. Reagents and conditions: (a) $ZnCl_2$, HCl, EtOAc, rt (68–76%); (b) H_2, Pd/C 5%, EtOH, rt (82–96%).



Scheme 8. Reagents and conditions: (a) Ac_2O, pyridine, rt (85–99%); (b) NaH, MeI, THF, 0 °C (81–99%); (c) H_2, Pd/C 5%, EtOH, rt (83–97%).



Scheme 9. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (95%); (b) $LiAlH_4$, THF, 0 °C (96%); (c) NaH, 10-iodo-1-(benzyloxy)-decane, THF, reflux (42%); (d) H_2, Pd/C 5%, EtOH, rt (64%).

afforded compound **17**. TFA-12 ether **18** was finally obtained by hydrogenation of **17**.

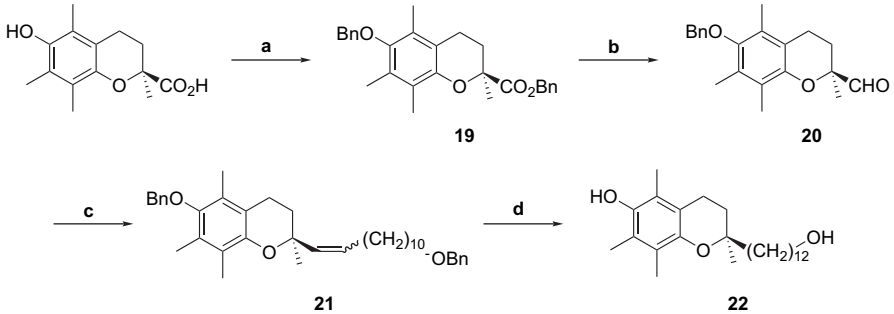
(*R*)-TFA-12 **22** and its enantiomer (*S*)-TFA-12 were synthesized starting either from (*S*)- or (*R*)-Trolox®, respectively.

(*S*)-Trolox® was dibenzylated as previously described (Scheme 10). The benzyl ester **19** was then reduced to its aldehyde **20** using DIBAL-H. A Wittig type coupling using Schlosser's conditions gave alkene **21** which after hydrogenation afforded (*R*)-TFA-12 **22**.

(*S*)-TFA-12 was obtained following the same procedure with identical yields starting from (*R*)-Trolox®.

As TFA-12 is highly lipophilic and thus needs the use of cosolvents (ethanol, dimethyl isosorbide) to achieve a maximum solubility of 1 mg/mL, we synthesized several prodrug forms of TFA-12 which have improved water solubility, namely hemisuccinate or phosphate salts[24] which are readily cleaved by esterases or phosphatases.

In a first attempt, a synthesis of the hemisuccinates prodrugs of TFA-12 was considered (data not shown).[25] Maximum



Scheme 10. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (95%); (b) DIBAL-H, heptane, −78 °C (79%); (c) *t*-BuLi, *t*-BuOK, 11-benzyloxy-undecanyltriphenylphosphonium bromide, THF, −78 to 0 °C (93%); (d) H_2, Pd/C 5%, EtOH, rt (73%).

water solubility of the bis-hemisuccinate prodrug (4 mg/mL in saline) was insufficient to study the acute toxicity of TFA-12 and so we turned to the synthesis of phosphate prodrugs.

The sodium salt of the phosphoric acid monoester TFA-12 P **25** was synthesized in three steps starting from TFA-12 **10b** (Scheme 11). After protection of the phenolic moiety, the aliphatic alcohol was phosphorylated using the phosphoramidite method developed by Fraser-Reid.[26] The benzyl groups of compound **24** were removed by treatment with hydrogen over palladium catalyst. However, the disodium salt **25**, obtained reacting the corresponding phosphoric acid with NaOH 1 N, still had poor aqueous solubility (<1 mg/mL in saline).

We thus turned to the synthesis of bisphosphate monoester TFA-12 PP **28**. Using the phosphoramidite method resulted in a mixture of by-products due to the oxidation of the chroman ring in the presence of *m*-chloroperoxybenzoic acid.

The method developed by Silverberg[27] which first phosphorylates the phenol group using dibenzyl phosphonate, carbon tetrachloride, *N*,*N*-diisopropylethylamine, and catalytic dimethyl aminopyridine in acetonitrile did not proceed efficiently probably due to the poor solubility of TFA-12 in acetonitrile. Surprisingly, running the reaction in dichloromethane, resulted in complete regioselective phosphorylation of the aliphatic alcohol yielding phosphate **26**. Hence, we then used the phosphoramidite method in order to obtain the bisphosphate **27** (Scheme 12).

After treatment with hydrogen over palladium catalyst, the tetrasodium salt of the bisphosphate monoester TFA-12 PP **28** was obtained with a yield of 82%. This compound has appreciable aqueous solubility (15 mg/mL in saline) and sufficient stability to allow its development for intravenous administration.

In order to determine the antioxidant activity of the different TFAs, their free radical scavenging activity was evaluated by determining the corresponding IC_{50} using the DPPH (2,2′-di(4-*tert*-octylphenyl)-1-picrylhydrazyl)[28] test (Table 1).

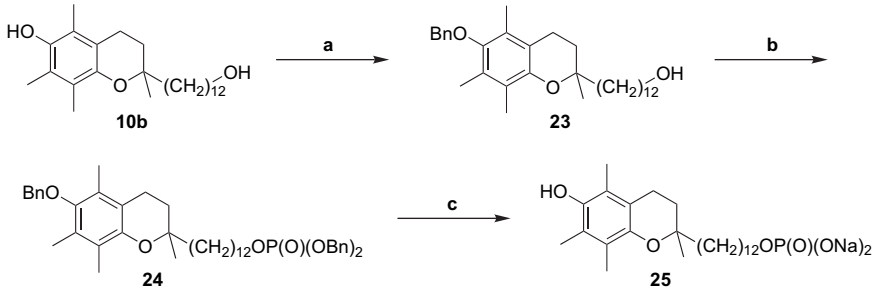
Table 1. IC_{50} of the different TFAs after 15 min in the presence of DPPH

Entry	Compound	IC_{50} (mM)	Error
1	Trolox®	0.08	±0.03
2	α-Tocopherol	0.90	±0.06
3	TFA-12 **10b**	0.90	±0.03
4	TFA-12 ether **18**	1.51	±0.07
5	AcTFA-12 **13b**	>10	—
6	MeTFA-12 **14b**	>10	—
7	TFA-12 PP **28**	>10	—

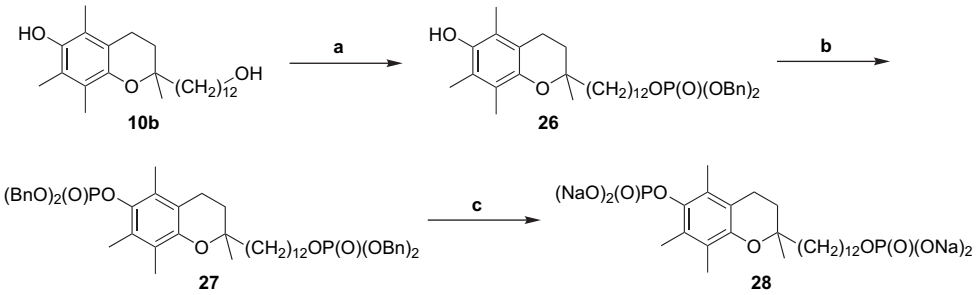
The IC_{50}s of a given series of TFAs were not affected by the length of the side chain (data not shown).

Trolox® and α-tocopherol (entries 1 and 2) were used as control compounds. Trolox® generally has better antioxidant activity because of its increased ethanol solubility compared to α-tocopherol. Vitamin E and TFA-12 (entries 2 and 3) have identical IC_{50}s, whereas AcTFA-12, MeTFA-12, and TFA-12 PP (entries 5–7) did not show any antioxidant activity (IC_{50}>10 mM).

These findings are consistent with the fact that the phenol function of the chroman moiety is crucial for the antioxidant activity.



Scheme 11. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux (73%); (b) (i) $iPr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, rt, (ii) *m*-CPBA, CH_2Cl_2, 0 °C (85%); (c) (i) H_2, Pd/C 5%, EtOH, rt, (ii) NaOH 1 N, EtOH, rt (74%).



Scheme 12. Reagents and conditions: (a) $(BnO)_2P(O)H$, CCl_4, DIEA, DMAP, CH_2Cl_2, −10 °C (78%); (b) (i) $iPr_2NP(OBn)_2$, tetrazole, CH_2Cl_2, rt, (ii) *m*-CPBA, CH_2Cl_2, 0 °C (89%); (c) (i) H_2, Pd/C 5%, EtOH, rt, (ii) NaOH 1 N, EtOH, rt (82%).

3. Conclusion

In order to further investigate the potent neurobiological activities of the TFAs, several series of TFAs have been synthesized. TFAs, AcTFAs, and MeTFAs were prepared via *C*-alkylation of THQ whereas (*R*)-TFA-12, its enantiomer, and the different water-soluble prodrugs were obtained through a Wittig coupling reaction. Both syntheses allowed us to obtain sufficient quantities of products to carry on the biological testings on microglial activation and on animal models of multiple sclerosis.

4. Experimental

4.1. General

Tetrahydrofuran was distilled from sodium/benzophenone under argon prior use. Dichloromethane was distilled from calcium hydride. All reactions involving moisture sensitive reactants were executed under an argon atmosphere using oven dried and/or flame dried glassware. ^{1}H NMR spectra were recorded on a Bruker Advance 300 (300 MHz) spectrometer as solutions in $CDCl_3$ or CD_3OD. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm) or CH_3OH (3.31 ppm) as internal standard. *J* values are expressed in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker Advance 300 (75 MHz) spectrometer as solutions in $CDCl_3$ or CD_3OD. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (77.4 ppm) or CH_3OH (49.0 ppm) as internal standard. The attribution of different carbons (C, CH, CH_2, CH_3) was determined by ^{13}C to ^{1}H polarization transfer (DEPT). ^{31}P NMR spectra were recorded on a Bruker Advance 300 (121.5 MHz) spectrometer as solutions in $CDCl_3$ or D_2O. Chemical shifts are expressed in parts per million (ppm, δ) downfield with a positive sign relative to external 85% H_3PO_4 in H_2O. Mass spectra (MS) were measured on a MicroTOF Daltonics Electrospray apparatus by direct introduction (a positive ion polarity, a set nebulizer at 1.20 bar, a set capillary at 4500 V, an exit at 120 V, a heater at 150 °C, at 5.5 L/min). Optical rotations was obtained in the indicated solvent at ambient temperature on a Perkin–Elmer 241. Routine monitoring of reactions were performed using 60 F_{254} silica gel TLC plates (Merck), which were dipped in a solution of vanillin (1 g) in EtOH–H_2SO_4 (95:5) and heated on a hot plate. Merck silica gel 60 F_{254} was used for column chromatography.

4.1.1. Oxacyclotridecan-2-one (2a).[29] To a solution of cyclododecanone (3.0 g, 16.44 mmol, 1 equiv) in dry CH_2Cl_2 (35 mL) were added *m*-chloroperbenzoic acid (6.80 g, 39.44 mmol, 2.4 equiv) and acetic acid (1.28 mL, 39.44 mmol, 1 equiv) and the mixture was refluxed in the dark for 24 h. A saturated solution of Na_2CO_3 (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 95:5) to give 2.77 g of a colorless oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (br s, 14H, H-5 to H-11), 1.64 (m, 4H, H-4, H-12), 2.35 (m, 2H, H-3), 4.13 (m, 2H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.3–27.6 (C-4 to C-12), 34.4 (C-3), 63.2 (C-13), 173.9 (C-2).

4.1.2. Oxacyclotetradecan-2-one (2b).[30] Yield 85% (2.53 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (br s, 16H, H-5 to H-12), 1.65 (m, 4H, H-4, H-13), 2.35 (m, 2H, H-3), 4.12 (m, 2H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4–27.6 (C-4 to C-13), 34.4 (C-3), 63.3 (C-14), 173.9 (C-2).

4.1.3. 13-(*tert*-Butyldimethylsilyloxy)tridecan-2-one (3a). To a solution of dimethylhydroxylamine hydrochloride (2.04 g, 20.95 mmol, 1.5 equiv) in dry THF (70 mL) cooled to 0 °C was slowly added MeLi 1.6 M in THF (25.3 mL, 40.51 mmol, 2.9 equiv). After 5 min at 0 °C, a solution of compound **2a** (2.77 g, 13.97 mmol, 1 equiv) in dry THF (40 mL) was slowly added and the resulting mixture was allowed to warm to rt. After 1 h at rt, the mixture was cooled to 0 °C and MeLi 1.6 M in THF (26.2 mL, 41.91 mmol, 3 equiv) was slowly added and the mixture was warmed to rt. After 2 h at rt, *tert*-butyldimethylsilyl chloride (3.16 g, 20.95 mmol, 1.5 equiv) and imidazole (1.43 g, 20.95 mmol, 1.5 equiv) were added. After 2 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 3.11 g of a white solid (68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.83 (s, 9H, CH_3C), 1.23 (br s, 14H, H-5 to H-11), 1.52 (m, 4H, H-4, H-12), 2.11 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9 (CSi), 23.8 (C-4), 25.7 (C-11), 26.5 (CH_3C), 29.1–29.8 (C-1, C-5 to C-10), 32.8 (C-12), 43.3 (C-3), 63.0 (C-13), 209.5 (C-2).

4.1.4. 14-(*tert*-Butyldimethylsilyloxy)tetradecan-2-one (3b). Yield 73% (2.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.82 (s, 9H, CH_3C), 1.24 (br s, 16H, H-5 to H-12), 1.50 (m, 4H, H-4, H-13), 2.13 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9 (CSi), 23.8 (C-4), 25.7 (C-12), 26.5 (CH_3C), 29.0–29.8 (C-1, C-5 to C-11), 32.8 (C-13), 43.3 (C-3), 63.0 (C-14), 209.5 (C-2).

4.1.5. 16-(*tert*-Butyldimethylsilyloxy)hexadecan-2-one (3d). Yield 70% (2.72 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.82 (s, 9H, CH_3C), 1.26 (br s, 20H, H-5 to H-14), 1.51 (m, 4H, H-4, H-15), 2.12 (s, 3H, H-1), 2.40 (t, *J* 7.4 Hz, 2H, H-3), 3.63 (t, *J* 6.6 Hz, 2H, H-16). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.8 (CSi), 23.8 (C-4), 25.7 (C-14), 26.5 (CH_3C), 29.0–29.8 (C-1, C-5 to C-13), 32.8 (C-15), 43.3 (C-3), 63.0 (C-16), 209.5 (C-2).

4.1.6. 17-(*tert*-Butyldimethylsilyloxy)heptadecan-2-one (3e). Yield 76% (2.4 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.04 (s, 6H, CH_3Si), 0.83 (s, 9H, CH_3C), 1.23 (br s, 22H, H-5 to H-15), 1.52 (m, 4H, H-4, H-16), 2.11 (s, 3H, H-1), 2.39 (t, *J* 7.4 Hz, 2H, H-3), 3.61 (t, *J* 6.6 Hz, 2H, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ: −4.5 (CH_3Si), 18.9

(CSi), 23.8 (C-4), 25.7 (C-15), 26.5 (CH_3C), 29.1–29.8 (C-1, C-5 to C-14), 32.8 (C-16), 43.3 (C-3), 63.0 (C-17), 209.5 (C-2).

4.1.7. 12-Methyltetradec-13-ene-1,12-diol (4a). To a solution of compound **3a** (2.14 g, 3.04 mmol, 1 equiv) in dry THF (30 mL) cooled to 0 °C was slowly added vinylmagnesium bromide 1 M in THF (9.1 mL, 9.13 mmol, 3 equiv) and the resulting mixture was allowed to warm to rt. After 3 h at rt, tetrabutylammonium fluoride 1 M in THF (4.6 mL, 4.56 mmol, 1.5 equiv) was added. After 15 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.55 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.24 (br s, 18H, H-3 to H-11), 1.53 (m, 4H, H-2, H-10), 3.60 (t, 2H, J 6.4 Hz, H-1), 5.03 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-14), 5.17 (dd, 1H, J_E 17.4 Hz, H-14′), 5.91 (dd, 1H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-10), 25.8 (C-9), 27.5 (CH_3), 29.4–30.1 (C-3 to C-8), 32.8 (C-2), 42.3 (C-11), 63.0 (C-1), 73.4 (C-12), 111.4 (C-14), 145.3 (C-13).

4.1.8. 13-Methylpentadec-14-ene-1,13-diol (4b). Yield 66% (0.98 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, CH_3), 1.24 (br s, 20H, H-3 to H-12), 1.50 (m, 4H, H-2, H-11), 3.60 (t, 2H, J 6.4 Hz, H-1), 5.03 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-15), 5.17 (dd, 1H, J_E 17.4 Hz, H-15′), 5.89 (dd, 1H, H-14). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-11), 25.8 (C-10), 27.5 (CH_3), 29.4–30.1 (C-3 to C-9), 32.7 (C-2), 42.3 (C-12), 63.0 (C-1), 73.4 (C-13), 111.4 (C-15), 145.2 (C-14).

4.1.9. 15-Methylheptadec-16-ene-1,15-diol (4d). Yield 81% (0.38 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, CH_3), 1.24 (br s, 24H, H-3 to H-14), 1.51 (m, 4H, H-2, H-13), 3.61 (t, 2H, J 6.4 Hz, H-1), 5.02 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-17), 5.18 (dd, 1H, J_E 17.4 Hz, H-17′), 5.89 (dd, 1H, H-16). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.8 (C-13), 25.8 (C-12), 27.6 (CH_3), 29.3–30.1 (C-3 to C-11), 32.7 (C-2), 42.3 (C-14), 63.1 (C-1), 73.3 (C-15), 111.5 (C-17), 145.3 (C-16).

4.1.10. 16-Methyloctadec-17-ene-1,16-diol (4e). Yield 88% (0.35 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, CH_3), 1.25 (br s, 26H, H-3 to H-15), 1.51 (m, 4H, H-2, H-14), 3.62 (t, 2H, J 6.4 Hz, H-1), 5.02 (dd, 1H, J 1.1 Hz, J_Z 10.7 Hz, H-18), 5.18 (dd, 1H, J_E 17.4 Hz, H-18′), 5.90 (dd, 1H, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-14), 25.7 (C-13), 27.5 (CH_3), 29.4–30.0 (C-3 to C-12), 32.8 (C-2), 42.4 (C-15), 63.0 (C-1), 73.3 (C-16), 111.4 (C-18), 145.3 (C-17).

4.1.11. 14-(Benzyloxy)-3-methyltetradec-1-ene-3-ol (5a). To a solution of compound **4a** (0.40 g, 1.65 mmol, 1 equiv) in dry THF (20 mL) was added sodium hydride (0.16 g, 6.60 mmol, 4 equiv) and the resulting suspension was refluxed. After 30 min, benzyl bromide (0.24 mL, 1.98 mmol, 1.2 equiv) was added and the refluxing was continued. After 3 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 85:15) to give 0.40 g of a colorless oil (73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 19H, H-5 to H-12, CH_3), 1.58 (m, 4H, H-4, H-13), 3.48 (t, 2H, J 6.6 Hz, H-14), 4.50 (s, 2H, CH_2Ph), 5.03 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1′), 5.91 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.8 (CH_3), 29.5–30.1 (C-7 to C-14), 42.3 (C-4), 70.5 (C-15), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.12. 15-(Benzyloxy)-3-methylpentadec-1-ene-3-ol (5b). Yield 76% (0.85 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 21H, H-5 to H-12, CH_3), 1.58 (m, 4H, H-4, H-14), 3.48 (t, 2H, J 6.6 Hz, H-15), 4.50 (s, 2H, CH_2Ph), 5.03 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1′), 5.91 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.8 (CH_3), 29.5–30.1 (C-7 to C-14), 42.3 (C-4), 70.5 (C-15), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.13. 17-(Benzyloxy)-3-methylheptadec-1-ene-3-ol (5d). Yield 79% (0.89 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (br s, 25H, H-5 to H-14, CH_3), 1.58 (m, 4H, H-4, H-16), 3.49 (t, 2H, J 6.6 Hz, H-17), 4.51 (s, 2H, CH_2Ph), 5.05 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.21 (dd, 1H, J_E 17.3 Hz, H-1), 5.90 (dd, 1H, H-2), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.7 (CH_3), 29.6–30.1 (C-7 to C-16), 42.3 (C-4), 70.5 (C-18), 72.7 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.3, 127.6, 128.5 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.14. 18-(Benzyloxy)-3-methyloctadec-1-ene-3-ol (5e). Yield 89% (1.06 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 27H, H-5 to H-16, CH_3), 1.59 (m, 4H, H-4, H-17), 3.47 (t, 2H, J 6.6 Hz, H-18), 4.51 (s, 2H, CH_2Ph), 5.04 (dd, 1H, J 1.2 Hz, J_Z 10.6 Hz, H-1), 5.20 (dd, 1H, J_E 17.3 Hz, H-1), 5.91 (dd, 1H, H-2), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.2 (C-6), 27.7 (CH_3), 29.5–30.0 (C-7 to C-17), 42.4 (C-4), 70.5 (C-18), 72.8 (CH_2Ph), 73.3 (C-3), 111.4 (C-1), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 145.3 (C-2).

4.1.15. 14-(Benzyloxy)tetradecan-1-ol (7). To a suspension of tetradecan-1,14-diol (3.43 g, 14.89 mmol, 1 equiv) in dry THF (30 mL) was added sodium hydride (0.50 g, 20.84 mmol, 1.4 equiv) and the resulting suspension was refluxed. After 30 min, benzyl bromide (1.80 mL, 14.89 mmol, 1 equiv) and tetrabutylammonium fluoride (0.96 g, 2.98 mmol, 0.2 equiv) were added and the refluxing was continued. After 12 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 1.52 g of a white solid (32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 20H, H-3 to H-12), 1.59 (m, 4H, H-2,

H-13), 3.48 (t, *J* 6.6 Hz, 2H, H-14), 3.63 (t, *J* 6.4 Hz, 2H, H-1), 4.52 (s, 2H, C*H*$_2$Ph), 7.32 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.7–29.3 (C-3 to C-13), 32.8 (C-2), 63.0 (C-1), 70.5 (C-14), 72.8 (*C*H$_2$Ph), 126.9, 127.4, 128.3 (Ar-CH), 138.7 (Ar-C).

4.1.16. 15-(Benzyloxy)pentadecan-2-ol (8). To a solution of oxalyl chloride (0.68 mL, 8.03 mmol, 1.05 equiv) in dry THF (15 mL) cooled to −78 °C was slowly added anhydrous DMSO (0.60 mL, 8.41 mmol, 1.1 equiv). The solution was allowed to reach −35 °C and stirred for 5 min at this temperature before being cooled to −78 °C again. A solution of compound **7** (2.45 g, 7.65 mmol, 1 equiv) in THF (18 mL) was slowly added and the resulting mixture was warmed to −35 °C. After 15 min at this temperature, triethylamine (6.4 mL, 45.86 mmol, 6 equiv) was added and stirring was continued at 0 °C for 2 h. The resulting suspension was cooled to −78 °C and methylmagnesium bromide 3 M in ether (12.8 mL, 38.22 mL, 5 equiv) was slowly added. After 2 h at rt, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 1.69 g of a white solid (66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, 3H, *J* 6.2 Hz, H-1), 1.32 (br s, 20H, H-4 to H-13), 1.40 (m, 2H, H-3), 1.65 (m, 2H, H-14), 3.49 (t, *J* 6.6 Hz, 2H, H-15), 3.80 (t, *J* 5.3 Hz, 2H, H-2), 4.53 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.7 (C-1), 27.1–31.0 (C-4 to C-14), 40.6 (C-3), 69.4 (C-2), 71.8 (C-15), 74.1 (*C*H$_2$Ph), 128.7, 128.9, 129.6 (Ar-CH), 140.0 (Ar-C).

4.1.17. 16-(Benzyloxy)-3-methylhexadec-1-ene-3-ol (5c). To a solution of oxalyl chloride (1.42 mL, 16.57 mmol, 2.4 equiv) in dry THF (16 mL) cooled to −78 °C was slowly added anhydrous DMSO (1.2 mL, 16.92 mmol, 2.45 equiv). The solution was allowed to reach −35 °C and stirred for 5 min at this temperature before being cooled to −78 °C again. A solution of compound **8** (2.31 g, 6.90 mmol, 1 equiv) in THF (22 mL) was slowly added and the resulting mixture was warmed to −35 °C. After 15 min at this temperature, triethylamine (5.76 mL, 41.33 mmol, 6 equiv) was added and stirring was continued at 0 °C for 2 h. The resulting suspension was cooled to −78 °C and vinylmagnesium bromide 1 M in ether (48.33 mL, 48.33 mL, 7 equiv) was slowly added. After 2 h at rt, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 1.86 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 23H, H-5 to H-14, C*H*$_3$), 1.61 (m, 4H, H-4, H-15), 3.45 (t, *J* 6.6 Hz, 2H, H-16), 4.50 (s, 2H, C*H*$_2$Ph), 5.02 (dd, *J* 1.3 Hz, J_Z 10.7 Hz, 1H, H-1), 5.19 (dd, J_E 17.3 Hz, 1H, H-1′), 5.90 (dd, 1H, H-2), 7.34 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9 (C-5), 26.5 (C-6), 27.7 (*C*H$_3$), 29.5–30.0 (C-7 to C-15), 42.4 (C-4), 70.5 (C-16), 72.8 (*C*H$_2$Ph), 73.3 (C-3), 111.5 (C-1), 127.5, 127.6, 128.7 (Ar-CH), 138.7 (Ar-C), 145.4 (C-2).

4.1.18. 2-(11-(Benzyloxy)undecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9a). To a solution of THQ (0.12 g, 0.75 mmol, 1 equiv) in EtOAc (20 mL) were added compound **5a** (0.25 g, 0.75 mmol, 1 equiv), zinc chloride (0.08 g, 0.60 mmol, 0.8 equiv), and HCl 37% aq (0.013 mL, 0.15 mmol, 0.2 equiv) and the resulting mixture was stirred at rt. After 48 h, a saturated solution of $NaHCO_3$ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 85:15) to give 0.26 g of a white solid (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.24 (br s, 16H, H-2′ to H-9′), 1.57 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-11′), 4.18 (s, 2H, C*H*$_2$Ph), 7.32 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-10′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-11′), 72.7 (*C*H$_2$Ph), 74.5 (C-2), 117.3 (C-5), 118.3 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 144.6 (C-4a), 145.6 (C-8b).

4.1.19. 2-(12-(Benzyloxy)dodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9b). Yield 68% (0.20 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.56 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 4.18 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.7 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-11′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-12′), 72.7 (*C*H$_2$Ph), 74.4 (C-2), 117.2 (C-5), 118.3 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.20. 2-(13-(Benzyloxy)tridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9c). Yield 70% (0.23 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.26 (br s, 20H, H-2′ to H-11′), 1.59 (m, 4H, H-1′, H-12′), 1.79 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 4.19 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-12′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-13′), 72.7 (*C*H$_2$Ph), 74.4 (C-2), 117.2 (C-5), 118.5 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.21. 2-(14-(Benzyloxy)tetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9d). Yield 69% (0.42 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 22H, H-2′ to H-12′), 1.59 (m, 4H, H-1′, H-13′), 1.79 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 4.19 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.8 (C-2a), 26.3 (C-3′), 29.5–30.0 (C-4′ to C-13′), 31.5 (C-3), 39.4 (C-1′), 70.5 (C-14′), 72.8

(CH_2Ph), 74.4 (C-2), 117.2 (C-5), 118.5 (C-6), 120.9 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.5 (Ar-C), 144.7 (C-4a), 145.6 (C-8b).

4.1.22. 2-(15-(Benzyloxy)pentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (9e). Yield 76% (0.29 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.58 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.6 (t, 2H, *J* 6.8 Hz, H-4), 3.46 (t, 2H, *J* 6.6 Hz, H-15′), 4.18 (s, 2H, CH_2Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 72.8 (CH_2Ph, C-16′), 74.5 (C-2), 117.3 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 127.4, 127.6, 128.3 (Ar-CH), 138.7 (Ar-C), 144.5 (C-4a), 145.6 (C-8b).

4.1.23. 2-(11-Hydroxyundecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10a). To a solution of compound **9a** (0.45 g, 0.96 mmol, 1 equiv) in EtOH (15 mL) was added palladium on charcoal (5%, 0.20 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 6:4) to give 0.35 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.26 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.7 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-10′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-11′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 399 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{24}H_{40}O_3Na$ (MNa$^+$) 399.2870. Found 399.2864.

4.1.24. 2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10b). Yield 92% (0.24 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.55 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.6 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.1 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-12′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 413 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{25}H_{42}O_3Na$ (MNa$^+$) 413.3026. Found 413.3017.

4.1.25. 2-(13-Hydroxytridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10c). Yield 82% (0.41 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 20H, H-2′ to H-11′), 1.55 (m, 4H, H-1′, H-12′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.6 (C-7a), 12.3 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.6–30.1 (C-4′ to C-12′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-13′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 427 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{44}O_3Na$ (MNa$^+$) 427.3183. Found 427.3138.

4.1.26. 2-(14-Hydroxytetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10d). Yield 87% (0.31 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.24 (br s, 22H, H-2′ to H-12′), 1.55 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.15 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.2 (C-5a), 11.6 (C-7a), 12.3 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.4–30.1 (C-4′ to C-13′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-14′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{46}O_3Na$ (MNa$^+$) 441.3339. Found 441.3319.

4.1.27. 2-(15-Hydroxypentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (10e). Yield 88% (0.12 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.56 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.6 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 74.5 (C-2), 117.3 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{48}O_3Na$ (MNa$^+$) 455.3496. Found 455.3519.

4.1.28. 2-(11-(Benzyloxy)undecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11a). To a solution of compound **9a** (0.50 g, 1.07 mmol, 1 equiv) in dry pyridine (4 mL) was added acetic anhydride (0.52 mL, 2.36 mmol, 2.2 equiv) and the mixture was stirred at rt. After 24 h, a saturated solution of HCl 1 M (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.52 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 16H, H-2′ to H-9′), 1.58 (m, 4H, H-1′, H-10′), 1.78 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.34 (s, 3H, CH_3C=O), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.48 (t, 2H, *J* 6.6 Hz, H-11′), 4.52 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.4–30.1 (C-4′ to C-10′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-11′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.3 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.8 (*C*=O).

4.1.29. 2-(12-(Benzyloxy)dodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11b). Yield 85% (0.44 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 18H, H-2′ to H-10′), 1.59 (m, 4H, H-1′, H-11′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.35 (s, 3H, CH_3CO_2), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 4.52 (s, 2H, CH_2Ph),

7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.4–30.0 (C-4′ to C-11′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-12′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.4 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.6 (C=O).

4.1.30. 2-(13-(Benzyloxy)tridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11c). Yield 89% (0.25 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.28 (br s, 20H, H-2′ to H-11′), 1.59 (m, 4H, H-1′, H-12′), 1.77 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.36 (s, 3H, CH_3C=O), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.3 (C-5a, C-7a, C-8a, CH_3C=O), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.3–30.0 (C-4′ to C-12′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-13′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.5 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.4 (C=O).

4.1.31. 2-(14-(Benzyloxy)tetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11d). Yield 97% (0.71 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H, H-2a), 1.30 (br s, 22H, H-2′ to H-12′), 1.60 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.13 (s, 6H, H-5a, H-7a), 2.17 (s, 3H, H-8a), 2.36 (s, 3H, CH_3C=O), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 4.53 (s, 2H, CH_2Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.4 (C-5a, C-7a, C-8a, CH_3CO_2), 20.5 (C-4), 20.6 (C-2′), 23.7 (C-2a), 26.2 (C-3′), 29.2–30.0 (C-4′ to C-13′), 31.5 (C-3), 39.6 (C-1′), 70.5 (C-14′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.5 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.4 (C=O).

4.1.32. 2-(15-(Benzyloxy)pentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (11e). Yield 99% (0.11 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.29 (br s, 24H, H-2′ to H-13′), 1.59 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.34 (s, 3H, CH_3C=O), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.48 (t, 2H, *J* 6.6 Hz, H-15′), 4.52 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3–12.2 (C-5a, C-7a, C-8a, CH_3C=O), 20.5 (C-4), 20.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.0 (C-4′ to C-14′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-15′), 72.9 (CH_2Ph), 76.5 (C-2), 117.3 (C-5), 123.1 (C-6), 124.9 (C-7), 126.7 (C-8), 127.7–128.3 (Ar-CH), 138.7 (Ar-C), 140.5 (C-4a), 149.8 (C-8b), 169.8 (C=O).

4.1.33. 2-(11-(Benzyloxy)undecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12a). To a solution of compound **9a** (0.53 g, 1.13 mmol, 1 equiv) in dry THF (12 mL) cooled to 0 °C were added sodium hydride (0.04 g, 1.58 mmol, 1.4 equiv) and methyl iodide (0.21 mL, 3.39 mmol, 3 equiv). After 1 h at 0 °C, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.50 g of a white solid (93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.26 (br s, 16H, H-2′ to H-9′), 1.60 (m, 4H, H-1′, H-10′), 1.77 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.21 (s, 3H, H-8a), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-11′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.6 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.9 (C-2a), 26.2 (C-3′), 29.4–31.4 (C-4′ to C-10′), 31.7 (C-3), 39.8 (C-1′), 60.4 (OCH_3), 70.6 (C-11′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.34. 2-(12-(Benzyloxy)dodecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12b). Yield 87% (0.41 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.27 (br s, 18H, H-2′ to H-10′), 1.61 (m, 4H, H-1′, H-11′), 1.77 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.20 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-12′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–31.2 (C-4′ to C-11′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-12′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.35. 2-(13-(Benzyloxy)tridecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12c). Yield 81% (0.47 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 20H, H-2′ to H-11′), 1.61 (m, 4H, H-1′, H-12′), 1.78 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.17 (s, 3H, H-5a), 2.19 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-13′), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–31.3 (C-4′ to C-12′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-13′), 72.9 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.36. 2-(14-(Benzyloxy)tetradecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12d). Yield 99% (0.72 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 22H, H-2′ to H-12′), 1.61 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.12 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.19 (s, 3H, H-8a), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.47 (t, 2H, *J* 6.6 Hz, H-14′), 3.64 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2Ph), 7.30 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.4–31.3 (C-4′ to C-13′), 31.7 (C-3), 39.8 (C-1′), 60.3 (OCH_3), 70.6 (C-14′), 72.8 (CH_2Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.37. 2-(15-(Benzyloxy)pentadecyl)-6-methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene (12e). Yield 96% (0.52 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3H, H-2a), 1.26 (br s, 24H, H-2′ to H-13′), 1.60 (m, 4H, H-1′, H-14′), 1.78 (m, 2H, H-3), 2.11 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.20 (s, 3H, H-8a), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.48

(t, 2H, *J* 6.6 Hz, H-15′), 3.65 (s, 3H, OC*H*$_3$), 4.52 (s, 2H, C*H*$_2$Ph), 7.31 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.8 (C-7a), 12.6 (C-8a), 20.7 (C-4), 23.7 (C-2′), 23.9 (C-2a), 26.2 (C-3′), 29.5–31.3 (C-4′ to C-14′), 31.7 (C-3), 39.8 (C-1′), 60.4 (O*C*H$_3$), 70.6 (C-15′), 72.9 (*C*H$_2$Ph), 74.8 (C-2), 117.5 (C-5), 122.9 (C-6), 125.7 (C-7), 127.6 (C-8), 138.8 (Ar-C), 147.8 (C-4a), 149.4 (C-8b).

4.1.38. 2-(11-Hydroxyundecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13a). To a solution of compound **11a** (0.54 g, 1.06 mmol, 1 equiv) in EtOH (15 mL) was added palladium on charcoal (5%, 0.11 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 6:4) to give 0.43 g of a white solid (97%). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.76 (m, 2H, H-3), 1.99 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.12 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7–12.9 (C-5a, C-7a, C-8a, C*H*$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.4–30.1 (C-4′ to C-10′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-11′), 75.4 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.8 (*C*═O). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{42}O_4Na$ (MNa$^+$) 441.2975. Found 441.2909.

4.1.39. 2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13b). Yield 83% (0.35 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.55 (m, 4H, H-1′, H-11′), 1.75 (m, 2H, H-3), 1.98 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.12 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7–12.8 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-11′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-12′), 75.3 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.3 (C-8b), 169.7 (*C*═O). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{44}O_1Na$ (MNa$^+$) 455.3132. Found 455.3111.

4.1.40. 2-(13-Hydroxytridecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13c). Yield 85% (0.17 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.24 (s, 3H, H-2a), 1.26 (br s, 20H, H-2′ to H-11′), 1.54 (m, 4H, H-1′, H-12′), 1.74 (m, 2H, H-3), 1.98 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.11 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.8 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.4 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-12′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-13′), 75.3 (C-2), 117.4 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.9 (*C*═O). *m*/*z* (ESI$^+$) 469 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{46}O_4Na$ (MNa$^+$) 469.3288. Found 469.3218.

4.1.41. 2-(14-Hydroxytetradecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13d). Yield 97% (0.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.24 (s, 3H, H-2a), 1.25 (br s, 22H, H-2′ to H-12′), 1.54 (m, 4H, H-1′, H-13′), 1.75 (m, 2H, H-3), 2.00 (s, 3H, H-7a), 2.01 (s, 3H, H-8a), 2.11 (s, 3H, C*H*$_3$C═O), 2.59 (t, 2H, *J* 6.8 Hz, H-4), 3.64 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.9 (C-5a, C-7a, C-8a, *C*H$_3$CO), 20.4 (C-4), 20.6 (C-2a), 23.7 (C-2′), 25.7 (C-3′), 29.5–30.1 (C-4′ to C-13′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-14′), 75.3 (C-2), 117.5 (C-5), 123.1 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.7 (*C*═O). *m*/*z* (ESI$^+$) 483 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{29}H_{48}O_4Na$ (MNa$^+$) 483.6782. Found 483.6775.

4.1.42. 2-(15-Hydroxypentadecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl acetate (13e). Yield 87% (0.54 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 24H, H-2′ to H-13′), 1.55 (m, 4H, H-1′, H-14′), 1.76 (m, 2H, H-3), 1.99 (s, 3H, H-7a), 2.00 (s, 3H, H-8a), 2.10 (s, 3H, C*H*$_3$C═O), 2.58 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.8–12.9 (C-5a, C-7a, C-8a, *C*H$_3$C═O), 20.5 (C-4), 20.6 (C-2a), 23.6 (C-2′), 25.7 (C-3′), 29.5–30.0 (C-4′ to C-14′), 32.8 (C-3), 39.5 (C-1′), 63.1 (C-15′), 75.4 (C-2), 117.4 (C-5), 123.0 (C-6), 124.9 (C-7), 126.6 (C-8), 140.5 (C-4a), 149.4 (C-8b), 169.8 (*C*═O). *m*/*z* (ESI$^+$) 497 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{30}H_{50}O_4Na$ (MNa$^+$) 497.3601. Found 497.3592.

4.1.43. 11-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)undecan-1-ol (14a). Yield 87% (0.34 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.22 (s, 3H, H-2a), 1.25 (br s, 16H, H-2′ to H-9′), 1.56 (m, 4H, H-1′, H-10′), 1.77 (m, 2H, H-3), 2.12 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-11′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.7 (C-7a), 12.4 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.4–31.3 (C-4′ to C-10′), 32.8 (C-3), 39.7 (C-1′), 60.4 (O*C*H$_3$), 63.1 (C-11′), 74.5 (C-2), 117.5 (C-5), 118.5 (C-6), 121.0 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 413 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{25}H_{42}O_3Na$ (MNa$^+$) 413.3026. Found 413.3005.

4.1.44. 12-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecan-1-ol (14b). Yield 85% (0.22 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.57 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.3 (C-4′ to C-11′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-12′), 74.5 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 427 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{26}H_{44}O_3Na$ (MNa$^+$) 427.3183. Found 427.3215.

4.1.45. 13-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)tridecan-1-ol (14c). Yield 93% (0.27 g). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.23 (s, 3H, H-2a), 1.25 (br s, 20H, H-2′ to H-11′), 1.58 (m, 4H, H-1′, H-12′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.65

(t, 2H, *J* 6.6 Hz, H-13′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.3 (C-4′ to C-12′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-13′), 74.6 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 441 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{27}H_{46}O_3Na$ (MNa$^+$) 441.3339. Found 441.3317.

4.1.46. 14-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)tetradecan-1-ol (14d). Yield 95% (0.45 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.26 (br s, 22H, H-2′ to H-12′), 1.58 (m, 4H, H-1′, H-13′), 1.78 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.61 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OCH$_3$), 3.65 (t, 2H, *J* 6.6 Hz, H-14′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.5–31.4 (C-4′ to C-13′), 32.8 (C-3), 39.7 (C-1′), 60.5 (O*C*H$_3$), 63.1 (C-14′), 74.6 (C-2), 117.5 (C-5), 118.5 (C-6), 121.1 (C-8), 122.6 (C-7), 144.4 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{28}H_{48}O_3Na$ (MNa$^+$) 455.3496. Found 455.3516.

4.1.47. 15-(6-Methoxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)pentadecan-1-ol (14e). Yield 89% (0.29 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.26 (br s, 24H, H-2′ to H-13′), 1.57 (m, 4H, H-1′, H-14′), 1.77 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.18 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.63 (s, 3H, OC*H*$_3$), 3.64 (t, 2H, *J* 6.6 Hz, H-15′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (C-5a), 11.8 (C-7a), 12.5 (C-8a), 20.7 (C-4), 23.5 (C-2′), 23.9 (C-2a), 25.7 (C-3′), 29.4–31.2 (C-4′ to C-14′), 32.8 (C-3), 39.7 (C-1′), 60.4 (O*C*H$_3$), 63.1 (C-15′), 74.5 (C-2), 117.5 (C-5), 118.4 (C-6), 121.0 (C-8), 122.6 (C-7), 144.5 (C-4a), 145.6 (C-8b). *m*/*z* (ESI$^+$) 455 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{29}H_{50}O_3Na$ (MNa$^+$) 469.3652. Found 469.3689.

4.1.48. Benzyl 6-(benzyloxy)-2,5,7,8-tetramethylchroman-2-carboxylate (15). To solution of Trolox® (0.60 g, 2.40 mmol, 1 equiv) in acetone (35 mL) were added potassium carbonate (2.98 g, 21.57 mmol, 9 equiv) and benzyl bromide (0.87 mL, 7.19 mmol, 3 equiv) and the resulting mixture was refluxed. After 40 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 2.58 g of a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (s, 3H, H-2a), 1.87 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.46 (m, 2H, H-4), 2.58 (m, 1H, H-3), 4.50 (s, 2H, C*H*$_2$Ph), 5.04 (d, *J* 12.5 Hz, 1H, C═OC*H*H′Ph), 5.16 (d, 1H, C═OCH*H*′Ph), 7.29 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.9 (C-4), 25.5 (C-2a), 30.7 (C-3), 66.4 (C═O*C*H$_2$Ph), 74.7 (*C*H$_2$Ph), 77.1 (C-2), 117.3 (C-5), 123.1 (C-6), 126.0 (C-7), 127.8 (C-8), 127.6–128.5 (Ar-CH), 135.8 (Ar-C), 137.9 (Ar-C), 148.1 (C-4a), 148.9 (C-8b), 173.8 (*C*═O).

4.1.49. (6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methanol (16). To a solution of compound **15** (0.50 g, 1.15 mmol, 1 equiv) in dry THF (10 mL) cooled to 0 °C was added lithium aluminum hydride (0.05 g, 1.15 mmol, 1 equiv). After 1 h at this temperature, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.36 g of a colorless oil (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.75 (m, 2H, H-3), 2.11 (s, 3H, H-7a), 2.18 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.60 (d, *J* 11.3 Hz, 1H, CH_2OH), 2.67 (d, *J* 11.3 Hz, 1H, CH_2OH), 4.70 (s, 2H, C*H*$_2$Ph), 7.40 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.2 (C-4), 20.5 (C-2a), 27.7 (C-3), 65.4 (*C*H$_2$OH), 69.4 (*C*H$_2$Ph), 74.8 (C-2), 117.6 (C-5), 122.9 (C-6), 126.3 (C-7), 127.0–128.6 (Ar-CH), 137.9 (Ar-C), 147.2 (C-4a), 148.6 (C-8b).

4.1.50. 10-Iodo-1(benzyloxy)-decane. To a suspension of 1,10-decandiol (3 g, 17.21 mmol, 1 equiv) in toluene (45 mL) was added HI 57% aq (6.8 mL, 51.63 mmol, 3 equiv) and the resulting mixture was heated at 90 °C. After 6 h, a saturated solution of $Na_2S_2O_3$ (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 3.82 g of a colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (br s, 12H, H-3 to H-8), 1.54 (m, 2H, H-2), 1.82 (m, 2H, H-9), 3.18 (t, *J* 7.1 Hz, 2H, H-10), 3.62 (t, *J* 6.4 Hz, 2H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.3 (C-10), 25.5 (C-9), 28.5–32.7 (C-3 to C-8), 33.5 (C-2), 63.0 (C-1). To a solution of 10-iododecan-1-ol (3.85 g, 13.55 mmol, 1 equiv) in dry THF (15 mL) was added sodium hydride (0.45 g, 18.97 mmol, 1.4 equiv) and the resulting mixture was refluxed. After 30 min, benzyl bromide (1.97 mL, 16.27 mmol, 1.2 equiv) was added and refluxing was continued. After 24 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 8:2) to give 4.81 g of a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (br s, 12H, H-3 to H-8), 1.62 (m, 2H, H-2), 1.78 (m, 2H, H-9), 3.35 (t, *J* 6.7 Hz, 2H, H-10), 3.45 (t, *J* 6.4 Hz, 2H, H-1), 4.49 (s, 2H, C*H*$_2$Ph), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.5 (C-10), 26.3 (C-3), 27.8 (C-8), 29.6–29.9 (C-2, C-4 to C-6), 32.9 (C-9), 70.6 (C-1), 73.0 (*C*H$_2$Ph), 127.3, 128.2, 128.4 (Ar-CH), 141.3 (Ar-C).

4.1.51. 6-(Benzyloxy)-2-((10-(benzyloxy)decyloxy)-methyl)-2,5,7,8-tetramethyl-3,4-tetrahydroxy-2*H*-chromene (17). To a solution of compound **16** (0.20 g, 0.62 mmol, 1 equiv) in dry THF (6 mL) was added sodium hydride (0.02 g, 0.80 mmol, 1.3 equiv) and the resulting mixture was refluxed. After 30 min, a solution of 10-iodo-1(benzyloxy)-decane (0.58 g, 1.55 mmol, 2.5 equiv) was added and the refluxing was continued. After 20 h, a saturated solution of NH_4Cl (100 mL) was added to the reaction

mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 9:1) to give 0.19 g of a colorless oil (42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 15H, H-3′ to H-8′, H-2a), 1.55 (m, 4H, H-2′ to H-9′), 1.75 (m, 3H, H-3, H-10′), 1.96 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.11 (s, 3H, H-5a), 2.15 (s, 3H, H-8a), 2.61 (t, *J* 6.8 Hz, 2H, H-4), 3.48 (m, 4H, C*H*$_2$O-alkyl, H-1′), 4.47 (s, 2H, alkyl-OC*H*$_2$Ph), 4.65 (s, 2H, Ar-OC*H*$_2$-Ph), 7.53 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.9 (C-7a), 12.3 (C-8a), 20.3 (C-4), 20.4 (C-2a), 25.7–29.7 (C-2′ to C-9′), 32.8 (C-3), 63.1 (C-10′), 72.0 (C-1′), 72.9 (alkyl-OCH$_2$Ph), 74.7 (Ar-OCH$_2$Ph), 74.8 (*C*H$_2$O-alkyl), 74.8 (C-2), 117.5 (C-5), 118.7 (C-6), 121.3 (C-7), 122.5 (C-8), 127.5–128.7 (Ar-CH), 137.3 (Ar-C), 144.8 (C-4a), 145.4 (C-8b).

4.1.52. 2-((10-Hydroxydecyloxy)methyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (18). To a solution of compound **17** (0.14 g, 0.24 mmol, 1 equiv) in EtOH (8 mL) was added palladium on charcoal (5%, 0.03 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 72 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc: 7:3) to give 0.06 g of a colorless oil (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (br s, 15H, H-3′ to H-8′, H-2a), 1.55 (m, 4H, H-2′, H-9′), 1.75 (m, 1H, H-3), 1.96 (m, 1H, H-3), 2.10 (s, 3H, H-7a), 2.11 (s, 3H, H-5a), 2.15 (s, 3H, H-8a), 2.61 (t, *J* 6.8 Hz, 2H, H-4), 3.48 (m, 6H, C*H*$_2$O-alkyl, H-1′, H-10′), 4.55 (br s, 1H, Ph-O*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.9 (C-7a), 12.3 (C-8a), 20.3 (C-4), 20.4 (C-2a), 25.7–29.7 (C-2′ to C-9′), 32.8 (C-3), 63.1 (C-10′), 72.0 (C-1′), 74.8 (*C*H$_2$O-alkyl), 74.8 (C-2), 117.5 (C-5), 118.7 (C-6), 121.3 (C-7), 122.5 (C-8), 144.8 (C-4a), 145.4 (C-8b). *m*/*z* (ESI$^+$) 415 (M+Na$^+$). HRMS (ESI$^+$) calcd for $C_{24}H_{40}O_4Na$ (MNa$^+$) 415.2819. Found 415.2635.

4.1.53. (*S*)-Benzyl 6-(benzyloxy)-2,5,7,8-tetramethylchroman-2-carboxylate (19).[31] Compound **19** ($[\alpha]_D^{20}$ −3.5 (*c* 0.5, $CHCl_3$)) and its (*R*)-enantiomer ($[\alpha]_D^{20}$ +3.4 (*c* 0.5, $CHCl_3$)) were obtained as described for the racemic mixture **15**. All analytical data were identical to that of **15**.

4.1.54. (*S*)-6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromene-2-carbaldehyde (20). To a solution of compound **19** (0.87 g, 2.03 mmol, 1 equiv) in dry heptane (30 mL) cooled to −78 °C was added over a period of 1.5 h 30 DIBAL-H 1 M in hexane (2.19 mL, 2.19 mmol, 1.08 equiv). After an additional hour at −78 °C, a saturated solution of sodium tartrate (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 0.52 g of a colorless oil (79%). $[\alpha]_D^{20}$ −0.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H, H-2a), 1.85 (m, 1H, H-3), 2.14 (s, 3H, H-7a), 2.21 (s, 3H, H-5a), 2.25 (s, 3H, H-8a), 2.29 (m, 1H, H-3), 2.58 (m, 2H, H-4), 4.71 (s, 2H, C*H*$_2$Ph), 7.41 (m, 5H, Ar-H), 9.65 (s, 1H, C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.3 (C-4), 21.6 (C-2a), 27.8 (C-3), 74.7 (*C*H$_2$Ph), 80.5 (C-2), 117.8 (C-5), 123.2 (C-6), 126.4 (C-7), 127.8–128.6 (Ar-CH), 128.5 (C-8), 137.8 (Ar-C), 147.5 (C-4a), 149.2 (C-8b), 204.4 (*C*HO).

4.1.55. 11-Benzyloxyundanyltriphenylphosphonium bromide. To a solution of 11-bromo-1-(benzyloxy)-undecane (13.6 g, 39.48 mmol, 1 equiv) in CH_3CN (50 mL) was added triphenylphosphine (12.5 g, 47.81 mmol, 2 equiv) and the resulting mixture was refluxed. After 44 h, CH_3CN was evaporated and several washings of the residue in hexane and ether gave 22.85 g of a white solid (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (br s, 14H, H-3 to H-9), 1.56 (m, 4H, H-2, H-10), 3.42 (t, *J* 6.6 Hz, 2H, H-11), 3.69 (m, 2H, H-1), 4.45 (s, 2H, C*H*$_2$Ph), 7.28 (m, 5H, Ar-H), 7.73 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7 (C-1), 23.4 (C-2), 26.2 (C-9), 29.2–30.6 (C-3 to C-8, C-10), 70.6 (C-11), 72.9 (*C*H$_2$Ph), 117.6, 119.3 (Ar-CH), 127.5, 127.6, 128.4 (Ar-CH), 130.4, 130.7, 133.6, 133.8, 135.1 (Ar-CH), 138.7 (Ar-C).

4.1.56. (*S*)-6-(Benzyloxy)-2-(12-(benzyloxy)dodec-1-enyl)-2,5,7,8-tetramethyl-3,4-tetrahydro-2*H*-chromene (21). To a suspension of 11-benzyloxyundanyltriphenylphosphonium bromide (0.49 g, 0.82 mmol, 1.2 equiv) in dry THF (5 mL) cooled to −78 °C was slowly added *t*-BuLi 1.6 M in hexane (0.51 g, 0.82 mmol, 1.2 equiv). The resulting mixture was allowed to warm to rt and after 15 min was cooled to 0 °C and potassium *tert*-butoxide (0.10 g, 0.82 mmol, 1.2 equiv) was added. After 15 min to the solution cooled to −78 °C was slowly added a solution of compound **20** (0.22 g, 0.68 mmol, 1 equiv) in dry THF (5 mL). After 1 h at −78 °C, the solution was allowed to warm to 0 °C. After 1.5 h 30, a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and the aqueous layer was extracted with ether (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–CH_2Cl_2: 9:1) to give 0.36 g of a colorless oil (93%). $[\alpha]_D^{20}$ −6.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 14H, H-3′ to H-10′), 1.48 (s, 3H, H-2a), 1.59 (m, 2H, H-11′), 1.78 (m, 1H, H-3), 2.01 (m, 1H, H-3), 2.16 (s, 3H, H-7a), 2.21 (s, 3H, H-5a), 2.26 (s, 3H, H-8a), 2.59 (m, 2H, H-4), 3.46 (t, *J* 6.6 Hz, 2H, H-12′), 4.50 (s, 2H, alkyl-OC*H*$_2$Ph), 4.69 (s, 2H, Ar-OC*H*$_2$Ph), 5.34 (m, 2H, H-1′, H-2′), 7.45 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.0 (C-5a), 12.1 (C-7a), 12.9 (C-8a), 21.1 (C-4), 26.2 (C-3′), 27.3–29.9 (C-4′ to C-11′), 27.3 (C-2a), 33.3 (C-3), 70.5 (C-12′), 72.9 (alkyl-OCH$_2$Ph), 74.7 (Ar-OCH$_2$Ph), 75.8 (C-2), 118.0 (C-5), 122.8 (C-6), 125.9 (C-8), 127.8 (C-7), 127.5–128.5 (Ar-CH), 132.7, 133.2 (C-1′, C-2′), 137.0, 137.8 (Ar-C), 147.5 (C-4a), 149.2 (C-8b).

4.1.57. (*R*)-2-(12-Hydroxydodecyl)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-ol (22). To a solution of compound **21** (0.36 g, 0.64 mmol, 1 equiv) in EtOH (14 mL) was added palladium on charcoal (5%, 0.08 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 48 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel

(hexane–EtOAc: 7:3) to give 0.18 g of a white solid (73%). $[\alpha]_D^{20}$ −0.4 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.54 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.14 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.60 (t, 2H, *J* 6.8 Hz, H-4), 3.65 (t, 2H, *J* 6.6 Hz, H-12′). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.4 (C-5a), 11.6 (C-7a), 12.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 26.2 (C-3′), 29.5–30.2 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 70.5 (C-12′), 74.5 (C-2), 117.4 (C-5), 118.4 (C-6), 121.0 (C-8), 122.7 (C-7), 144.5 (C-4a), 145.6 (C-8b).

4.1.58. 12-(6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecan-1-ol (23). To a solution of compound **10b** (450 mg, 1.15 mmol, 1 equiv) in dry acetone (12 mL) were added potassium carbonate (0.478 mg, 3.46 mmol, 3 equiv) and benzyl bromide (0.25 mL, 3.46 mmol, 3 equiv). The stirred mixture was refluxed under argon. After 10 h, a saturated solution of NH_4Cl (50 mL) was added to the reaction mixture and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (heptane–EtOAc: 8:2) to give 0.402 g of a colorless oil (73%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (s, 3H, H-2a), 1.27 (br s, 18H, H-2′ to H-10′), 1.39–1.61 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 3H, H-7a), 2.17 (s, 3H, H-5a), 2.22 (s, 3H, H-8a), 2.59 (t, *J* 6.9 Hz, 2H, H-4), 3.64 (t, *J* 6.6 Hz, 2H, H-12′), 4.70 (s, 2H, Ar-OC*H*$_2$Ph), 7.42 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.7 (C-10′), 29.4–30.2 (C-3′ to C-9′, C-11′), 31.3 (C-3), 39.7 (C-1′), 63.1 (C-12′), 74.7 (C-2, Ar-O*C*H$_2$Ph), 117.6 (C-5), 122.9 (C-7, C-8), 126.0 (C-4a), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.4 (Ar-CH), 138.0 (Ar-C), 147.9 (C-8b), 148.1 (C-6).

4.1.59. Dibenzyl 12-(6-(benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (24). To a solution of compound **23** (0.385 g, 0.80 mmol, 1 equiv) in CH_2Cl_2 (4 mL) were added 1*H*-tetrazole (0.112 g, 1.60 mmol, 2 equiv) and dibenzyl diisopropyl phosphoramidite (0.32 mL, 0.96 mmol 1.2 equiv) and the resulting mixture was stirred at rt. After 3 h, the mixture was cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (0.27 g, 77% w/w, 1.20 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) was added, maintaining the temperature at 0 °C. After 1 h, a saturated solution of $Na_2S_2O_3$ (30 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were successively washed with H_2O (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL) before being dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (heptane–EtOAc: 85:15 to 8:2) to give 0.503 g of a colorless oil (85%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (br s, 21H, H-2a, H-2′ to H-10′), 1.39–1.61 (m, 4H, H-1′, H-11′), 1.78 (m, 2H, H-3), 2.10 (s, 3H, H-7a), 2.16 (s, 3H, H-5a), 2.22 (s, 3H, H-8a), 2.59 (t, *J* 6.6 Hz, 2H, H-4), 3.97 (q, *J* 6.9 Hz, 2H, H-12′), 4.69 (s, 2H, Ar-OC*H*$_2$Ph), 5.03 (dd, *J* 8.1, 2.1 Hz, 4H, P-OC*H*$_2$Ph), 7.36 (m, 15H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8 (C-5a), 12.0 (C-7a), 12.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.9 (C-2a), 25.6 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.3 (C-3), 39.8 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 74.7 (C-2, Ar-O*C*H$_2$Ph), 117.6 (C-5), 122.9 (C-7, C-8), 126.0 (C-4a), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-CH), 138.0 (Ar-C), 147.9 (C-8b), 148.1 (C-6). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: −3.56.

4.1.60. Sodium 12-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (25). To a solution of compound **24** (0.48 g, 0.65 mmol, 1 equiv) in EtOH (5 mL) was added palladium on charcoal (10%, 0.096 g, 20% w/w). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. A saturated solution of $NaHCO_3$ (50 mL) was added to the residue and the aqueous layer was extracted with EtOAc (3×50 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was diluted in water (5 mL), treated with a solution of NaOH (1 M) until pH 7.5 was reached. The mixture was lyophilized to give 0.327 g of a white solid (74%). ^1H NMR (300 MHz, CD_3OD) δ: 1.26 (br s, 21H, H-2a, H-2′ to H-10′), 1.36–1.62 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.04 (s, 3H, H-7a), 2.08 (s, 3H, H-5a), 2.12 (s, 3H, H-8a), 2.57 (t, *J* 6.8 Hz, 2H, H-4), 3.94 (q, *J* 6.9 Hz, 2H, H-12′). ^{13}C NMR (75 MHz, CD_3OD) δ: 10.8 (C-5a), 11.0 (C-7a), 11.7 (C-8a), 20.5 (C-4), 23.4 (C-2′), 25.3 (C-2a, C-3′), 29.0–30.1 (C-4′ to C-11′), 31.6 (C-3), 39.1 (C-1′), 65.7 (C-12′), 74.2 (C-2), 117.0 (C-5), 120.7 (C-8), 121.8 (C-7), 123.1 (C-4a), 147.8 (C-6), 148.1 (C-8b). ^{31}P NMR (121.5 MHz, D_2O) δ: 3.89. *m*/*z* (ESI^+) 515 ($M+H^+$). HRMS (ESI^+) calcd for $C_{25}H_{42}O_6Na_2P$ (MH^+) 515.2509. Found 515.2505.

4.1.61. Dibenzyl 12-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)dodecyl phosphate (26). To a solution of compound **10b** (0.40 mg, 1.02 mmol, 1 equiv) in CH_2Cl_2 (10 mL) cooled to −10 °C, were added carbon tetrachloride (1 mL, 10.24 mmol, 10 equiv), *N*,*N*-diisopropylethylamine (0.90 mL, 5.15 mmol, 5 equiv), and *N*,*N*-dimethyl aminopyridine (0.50 g, 0.41 mmol, 0.4 equiv). Dibenzyl phosphite (0.70 mL, 3.1 mmol, 3 equiv) was then added dropwise and the temperature was kept at or below −10 °C. After 3 h, a solution of KH_2PO_4 (0.5 M, 30 mL) was added and the mixture was allowed to warm to rt. After 30 min, the mixture was extracted with EtOAc (3×50 mL). The combined extracts were washed successively with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give 0.518 g of a white solid (78%). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.39–1.56 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.11 (s, 6H, H-5a, H-7a), 2.16 (s, 3H, H-8a), 2.60 (t, *J* 6.6 Hz, 2H, H-4), 3.97 (q, *J* 6.9 Hz, 2H, H-12′), 5.03 (m, 4H, P-OC*H*$_2$Ph), 7.34 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3 (C-5a), 11.8 (C-7a), 12.2 (C-8a), 20.8 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.8 (C-3′), 29.1–30.1 (C-4′ to C-11′), 31.5 (C-3), 39.5 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 69.2 (P-O*C*H$_2$Ph), 74.5 (C-2), 117.3 (C-5), 118.5 (C-8), 121.0 (C-7), 122.6 (C-4a), 127.9 (Ar-CH), 128.5 (Ar-CH), 136.0 (Ar-C), 144.6 (C-6), 145.5 (C-8b). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: −3.43.

4.1.62. Dibenzyl 2-(dibenzyl 12-dodecyl phosphate)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl phosphate (27). To a solution of compound **26** (0.50 g, 0.77 mmol, 1 equiv) in CH_2Cl_2 (2 mL) were added 1*H*-tetrazole (0.108 g, 1.54 mmol, 2 equiv), dibenzyl diisopropyl phosphoramidite (0.30 mL, 0.92 mmol 1.2 equiv) and the resulting mixture was stirred at rt. After 3.5 h, the mixture was cooled to 0 °C and a solution of *m*-chloroperoxybenzoic acid (0.190 g, 77% w/w, 0.85 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL) was added, maintaining the temperature at 0 °C. After 1 h, a saturated solution of $Na_2S_2O_3$ (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were successively washed with H_2O (30 mL), a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (heptane–EtOAc: 85:15 to 80:20) to give 0.625 g of a colorless oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H, H-2a), 1.25 (br s, 18H, H-2′ to H-10′), 1.40–1.62 (m, 4H, H-1′, H-11′), 1.76 (m, 2H, H-3), 2.05 (s, 3H, H-7a), 2.14 (s, 3H, H-5a), 2.18 (s, 3H, H-8a), 2.54 (t, *J* 6.6 Hz, 2H, H-4), 3.98 (q, *J* 6.6 Hz, 2H, H-12′), 5.04 (m, 8H, P-OC*H*$_2$Ph), 7.31 (m, 20H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.9 (C-5a), 13.0 (C-7a), 13.9 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.6 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.2 (C-3), 39.7 (C-1′), 68.0 (C-12′), 69.1 (P-O*C*H$_2$Ph), 69.7 (P-O*C*H$_2$Ph), 75.0 (C-2), 117.6 (C-5), 123.2 (C-8), 125.3 (C-7), 127.2 (Ar-CH), 127.9 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 135.8 (Ar-C), 135.9 (Ar-C), 140.7 (C-6), 148.8 (C-8b). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 0.49, −3.67.

4.1.63. Sodium 2-(12-dodecyl phosphate)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-6-yl phosphate (28). To a solution of compound **27** (0.58 mg, 0.64 mmol, 1 equiv) in EtOH (3 mL) was added palladium on charcoal (10%, 0.058 g). The mixture was stirred under an atmosphere of hydrogen at rt. After 4 h, the mixture was filtered on Celite and concentrated under reduced pressure. The residue was dissolved in water (5 mL), treated with a solution of NaOH (1 M) until pH 8 was reached. The mixture was then purified by DEAE-Trisacryl ion-exchange column with a NaCl solution (step gradient 0.5 M, 1 M, 2 M), subjected to size exclusion chromatography and then lyophilized to give 0.333 g of a white solid (82%). ^{1}H NMR (300 MHz, D_2O) δ: 1.27 (br s, 21H, H-2a, H-2′ to H-10′), 1.41–1.62 (m, 4H, H-1′, H-11′), 1.85 (m, 2H, H-3), 2.09 (s, 3H, H-7a), 2.19 (s, 3H, H-5a), 2.23 (s, 3H, H-8a), 2.65 (t, *J* 6.6 Hz, 2H, H-4), 3.78 (q, *J* 6.9 Hz, 2H, H-12′). ^{13}C NMR (75 MHz, D_2O) δ: 11.1 (C-7a), 12.6 (C-5a), 13.2 (C-8a), 20.7 (C-4), 23.6 (C-2′), 23.8 (C-2a), 25.4 (C-3′), 29.1–30.2 (C-4′ to C-11′), 31.5 (C-3), 39.1 (C-1′), 65.7 (C-12′), 74.2 (C-2), 117.6 (C-5), 123.2 (C-8), 125.3 (C-7), 127.2 (C-4a), 140.5 (C-6), 148.6 (C-8b). ^{31}P NMR (121.5 MHz, D_2O) δ: 0.57, 4.01. *m*/*z* (ESI^-) 549 ($M-3Na^+ + 3H^+$). HRMS (ESI^-) calcd for $C_{25}H_{43}O_9NaP_2$ ($M-3Na^+ + 3H^+$) 549.2377. Found 549.2378.

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Synthesis, complexation studies and biological applications of some novel stilbenophanes, indolophanes and bisindolostilbenophanes via McMurry coupling

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Abstract—Various types of stilbenophanes, indolophanes and bisindolostilbenophanes were synthesized by intra-, inter- and tandem intra-, intermolecular McMurry coupling. Some of the indolophanes and bisindolostilbenophanes exhibited significant activity against the growth of various bacteria. Complexation of some of the cyclophanes with TCNQ has also been studied.

1. Introduction

The synthesis of [2,2]paracyclophane[1] by Cram and Steinberg was a revolutionary breakthrough in the field of cyclophane chemistry. In the synthesis of cyclophanes, the ring-closing step is often crucial[2] and various reagents and reaction conditions have been developed for this purpose. Many reagents containing transition metals were used for the ring-closing step in cyclophane synthesis. Samarium-catalyzed intramolecular pinacol coupling has been used in the synthesis of planar and chiral paracyclophanes.[3] Macrocyclic pyridinophanes[4] from α,ω-diynes were synthesized by cobalt-mediated [2+2+2] cycloaddition. Biaryl type cyclophanes[5] were synthesized from [2,5]metacyclophanebromides and triflates by Suzuki coupling. Electro-active tris-(tetrathiafulvaleno)dodecadehydro[18]annulenes[6] with ester substituents were synthesized by palladium-mediated cyclotrimerization of 4,5-diethynyl-tetrathiafulvalenes. Recently, ruthenium-catalyzed ring-closing metathesis proved to be a straightforward method to synthesize allenic cyclophanes.[7]

Microwave technology has been used for the synthesis of cationic cyclophanes.[8] The synthesis of thiacyclophanes by a one-pot reaction, utilizing a suitable dibromide and methanedithiolate generated from the double reduction of CS_2 with $NaBH_4$ has also been reported from this laboratory.[9] Recently, indolophanes and cylindrical indolophanes were synthesized by tandem alkylation methodology using NaH.[10] Ring-closing metathesis has been successfully used to synthesize symmetrical and unsymmetrical pyridinophanes.[11]

Use of low valent titanium for the synthesis of supramolecular structures has gained great impetus during recent times. An intramolecular McMurry coupling reaction was used as a key step in the enantiospecific synthesis of (+)-ipalbidine.[12] Molecular clocks[13] and artificial molecular devices such as light-driven molecular motors[14] were synthesized by the application of McMurry coupling. Symmetrical and unsymmetrical stilbenes[15] and highly distorted cone calyx-[4]arenes[16] and porphyrin derivatives[17] from tetrapyrroledialdehyde have also been synthesized using intramolecular McMurry coupling. Stilbenophanes are an interesting class of compounds and are synthesized by inter-[18] and intramolecular[19] McMurry coupling technique.

The synthesis of biologically active cyclophanes[20] has attracted supramolecular chemists in recent times. The indole moiety is present in a number of natural products[21] and known to be a bioactive nucleus.[22] Cyclophanes with an indole moiety, which are also called indolophanes[23] have received attention during recent times due to their applications in various fields. The synthesis of stilbene based indolophanes, bisindolostilbenophanes,[24] were reported recently from this laboratory by using McMurry coupling. We wish to report herein the synthesis and host–guest complexation studies of various types of stilbenophanes **4a–4d** and indolophanes **6a–6c**, **6d–6f**, **8a–8d** and **11a**-**11b** with TCNQ. We also wish to report the antimicrobial properties of various indolophanes towards three important types of pathogenic bacteria viz. *Salmonella typhi*, *Serratia marcensis* and *Streptococcus pneumoniae*.

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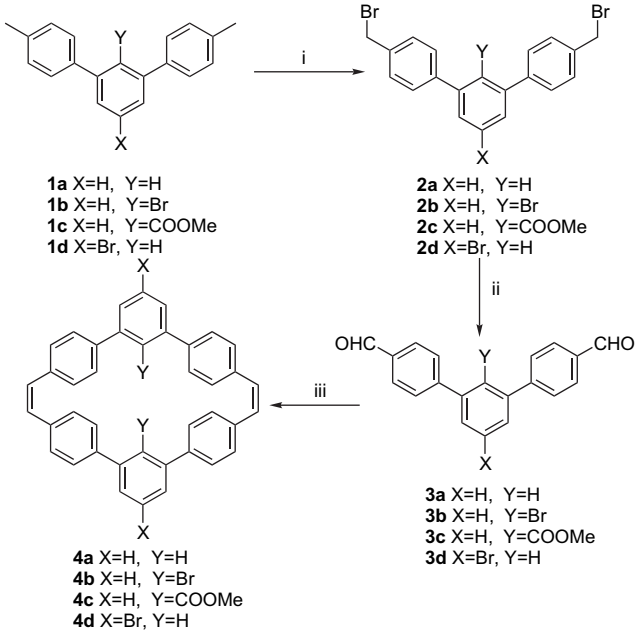
2. Results and discussion

2.1. Stilbenophanes with *m*-terphenyl moiety

m-Terphenyldibromide **2a**[25] obtained by the radical bromination of *m*-terphenyl **1a** was oxidized with tetrabutylammonium dichromate TBADC in $CHCl_3$ to give dialdehyde **3a** in 69% yield. Addition of 1 equiv of the dialdehyde to a solution of 20 equiv of $TiCl_4$ and 40 equiv of Zn in THF, followed by refluxing for 6 h resulted in the formation of stilbenophane **4a** (Scheme 1). Stilbenophanes **4b** and **4c** were synthesized by using similar methodology from the corresponding dialdehydes **3b** and **3c**. Reaction of *p*-tolylmagnesiumbromide with 2,4,6-tribromoiodobenzene in THF gave *m*-terphenyl **1d** in 78% yield. *m*-Terphenyl **1d**[25] on NBS bromination afforded the corresponding dibromide **2d**. Treatment of dibromide **2d** with TBADC in $CHCl_3$ gave dialdehyde **3d** in 69% yield. Dialdehyde **3d** underwent intermolecular McMurry coupling to give the stilbenophane **4d**.



Scheme 1. Reagents and conditions: (i) NBS (2.1 equiv), benzoyl peroxide, CCl_4, reflux, 40 h, 80% (**2a**), 80% (**2b**), 78% (**2c**), 80% (**2d**); (ii) TBADC, $CHCl_3$, reflux, 6 h, 69% (**3a**), 67% (**3b**), 60% (**3c**), 69% (**3d**); (iii) $TiCl_4$ (20 equiv), Zn (40 equiv), pyridine, THF, reflux, 6 h, 24% (**4a**), 18% (**4b**), 25% (**4c**), 24% (**4d**).

2.2. Synthesis of indolophanes with a smaller cavity

The synthetic utility of McMurry coupling has been investigated for the synthesis of indolophanes, another rare class of cyclophanes. *o*-Xylyl dibromide was reacted with indole-3-aldehyde in CH_3CN and 25% NaOH for 2 days to give preindolophane dialdehyde **5a** in 70% yield. Formation of **5a** was confirmed by ^1H NMR, ^{13}C NMR, mass spectral data and elemental analysis. When 1 equiv of dialdehyde **5a** was treated with 20 equiv of $TiCl_4$ and 40 equiv of Zn in THF under reflux, indolophane **6a** was obtained in 19% yield through intramolecular McMurry coupling. The structure of indolophane **6a** was further confirmed by ^1H NMR, ^{13}C NMR, FABMS spectral data and elemental analysis. Similarly *m*-xylyl dibromide and 2,6-bis(bromomethyl)pyridine

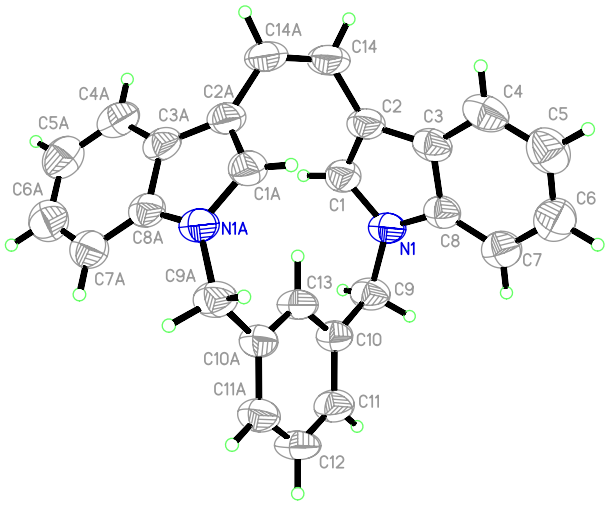


Figure 1. ORTEP diagram for the indolophane **6b**.

were treated with indole-3-aldehyde to give dialdehydes **5b** and **5c** in 72 and 74% yields, respectively. Dialdehydes **5b** and **5c** underwent intramolecular McMurry coupling to give indolophanes **6b** and **6c**. The structures of indolophanes **6b**[26] and **6c**[27] were thoroughly characterized by spectral and analytical data and further confirmed by single crystal X-ray analysis. The ORTEP diagrams of the cyclophanes **6b** and **6c** are shown in Figs. 1 and 2, respectively. However, the dialdehydes **5d–5f** with spacer units such as *p*-xylyl, 2,5-dimethoxy-*p*-xylyl and 4,4′-bis(methylene)-1,1′-biphenyl underwent intermolecular McMurry coupling to yield the indolophanes **6d–6f** (Scheme 2). From the above observation it is clear that dialdehydes **5a–5f** underwent coupling either intramolecularly or intermolecularly depending upon the spacer unit.

2.3. Synthesis of indolophanes with *m*-terphenyl spacer unit

The McMurry coupling was next used for the synthesis of indolophanes with a *m*-terphenyl spacer. Dibromide **2a** on N-alkylation with indole-3-aldehyde in 25% NaOH in CH_3CN afforded dialdehyde **7a**. The ^1H and ^{13}C NMR

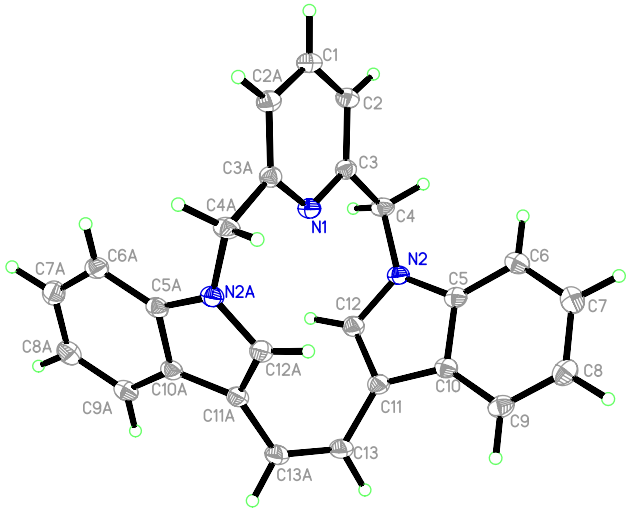
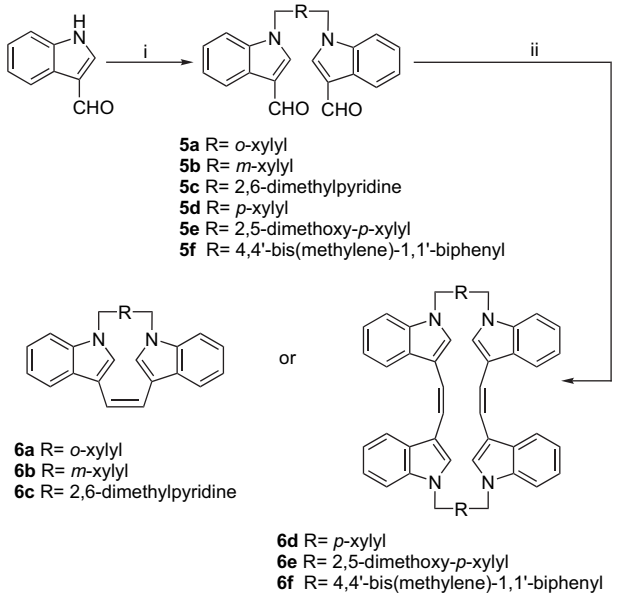
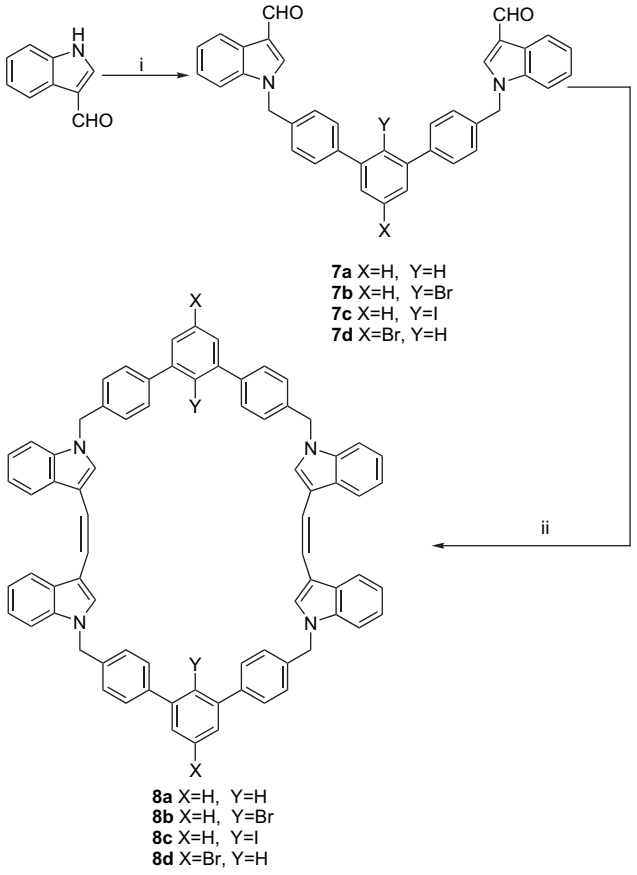


Figure 2. ORTEP diagram for the indolophane **6c**.



Scheme 2. Reagents and conditions: (i) *o*,*m*,2,6-dimethylpyridine, *p*-2,5-dimethoxy-*p*-xylyl, 4,4′-bis(bromomethyl)-1,1′-biphenyl dibromide, CH_3CN, 25% NaOH, 48 h, 70% (**5a**), 72% (**5b**), 74% (**5c**), 74% (**5d**), 66% (**5e**), 68% (**5f**); (ii)$TiCl_4$ (20 equiv), Zn (40 equiv), THF, pyridine, reflux overnight, 19% (**6a**), 24% (**6b**), 36% (**6c**), 20% (**6d**), 23% (**6e**), 18% (**6f**).

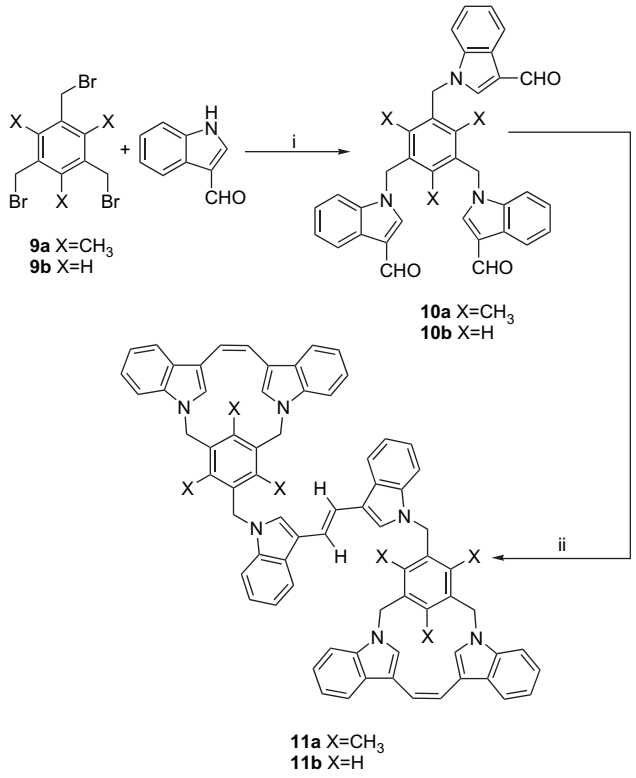
spectra are in accordance with the proposed structure. In the ^{1}H NMR spectrum, the NCH_2 and aldehydic protons appeared as a singlet at δ 5.40 and 10.01 in addition to aromatic protons. In the ^{13}C NMR spectrum, the NCH_2 carbons appeared at δ 54.8 and aldehydic carbons appeared at δ 184.8. Dialdehyde **7a** on treatment with low valent titanium under the conditions described earlier afforded indolophane **8a** in 8% yield. In the ^{1}H NMR spectrum, two singlets were observed for indolophane **8a** at δ 5.23 and 6.86 for NCH_2 and olefinic protons, in addition to aromatic protons. In the ^{13}C NMR spectrum, cyclophane **8a** showed 13 signals and the structure was further confirmed by FABMS spectrum and elemental analysis. Similar methodology was used to synthesize the indolophanes **8b**–**8d** with a *m*-terphenyl spacer unit (Scheme 3).



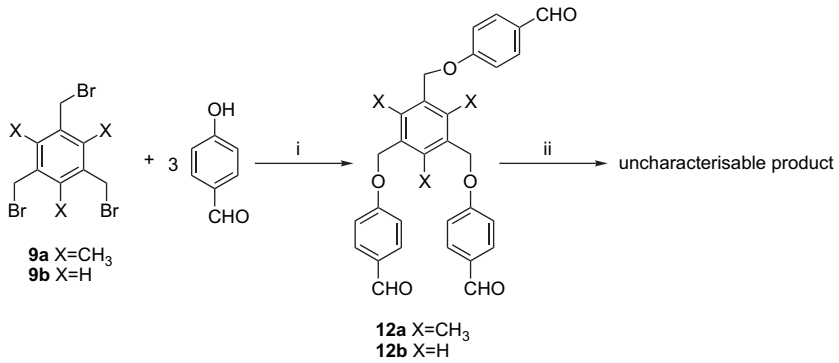
Scheme 3. Reagents and conditions: (i) **2a/2b/2c/2d**, CH_3CN, 25% NaOH, 48 h, 78% (**7a**), 76% (**7b**), 77% (**7c**), 70% (**7d**); (ii) $TiCl_4$ (20 equiv), Zn (40 equiv), THF, pyridine, reflux overnight, 8% (**8a**), 6% (**8b**), 5% (**8c**), 8% (**8d**).

2.4. Synthesis of bisindolostilbenophanes by using tandem intra- and intermolecular McMurry coupling

Encouraged by the versatility of the McMurry coupling technique for the synthesis of stilbenophanes and indolophanes with various spacer units, the technique was further extended for the synthesis of cylindrical cyclophanes, which are a very rare class of cyclophanes. 1,3,5-Trimethyl-tris(bromomethyl)benzene[28] was N-alkylated by using indole-3-aldehyde to give the trialdehyde **10a** (Scheme 4). The trialdehyde **10a** on treatment with low valent titanium underwent both intra- and intermolecular McMurry coupling to afford only the bisindolostilbenophane **11a** in 24% yield and not the cylindrical cyclophane. The structure was further confirmed by ^{1}H NMR,[24b] ^{13}C NMR,[24b] FABMS spectra and elemental analysis. By similar methodology, 1,3,5-tris(bromomethyl)benzene was N-alkylated with indole-3-aldehyde to give trialdehyde **10b** in 78% yield. Trialdehyde **10b** also



Scheme 4. Reagents and conditions: (i) CH_3CN, 25% NaOH, rt, 48 h, 80% (**10a**), 78% (**10b**); (ii) $TiCl_4$ (30 equiv), Zn (60 equiv), THF, pyridine, reflux overnight, 24% (**11a**), 22% (**11b**).

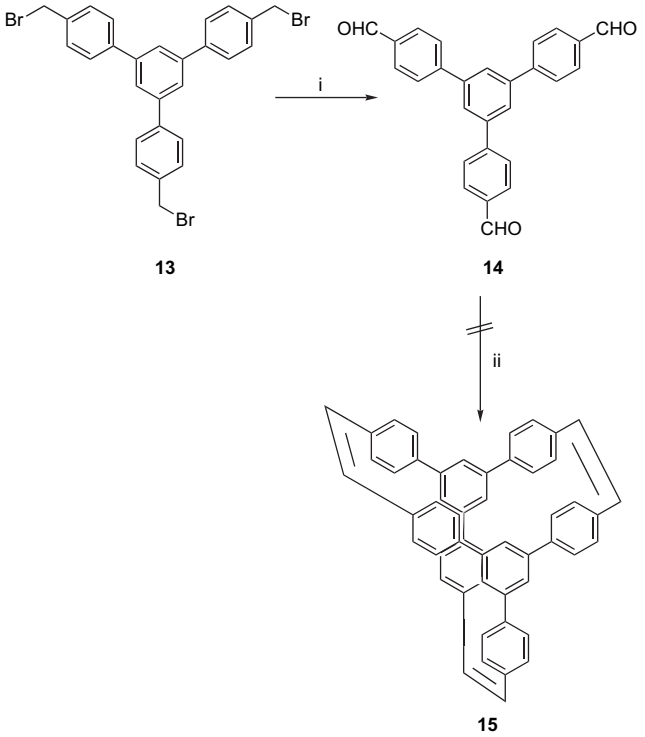


Scheme 5. Reagents and conditions: (i) DMF, K_2CO_3, 80 °C, 48 h, 65% (**12a**), 67% (**12b**); (ii) $TiCl_4$ (30 equiv), Zn (60 equiv), THF, pyridine, reflux, overnight.

underwent cyclization intra- and intermolecularly with low valent titanium in tandem nature to give bisindolostilbenophane **11b** in 22% yield. Tandem intra- and intermolecular McMurry coupling technique for the synthesis of bisindolostilbenophanes **11a** and **11b** is the first of its kind in the literature.

2.5. Synthesis of dioxastilbenophanes

McMurry coupling has been successfully used in the synthesis of dioxastilbenophanes.[29] Encouraged by such earlier reports from our laboratory, we focused our attention on the synthesis of cyclophanes from trialdehydes **12a** and **12b**. O-Alkylation of 1,3,5-trimethyl-tris(bromomethyl)benzene with *p*-hydroxybenzaldehyde afforded the trialdehyde **12a** in 65% yield. Similarly, O-alkylation of 1,3,5-tris(bromomethyl)benzene with *p*-hydroxybenzaldehyde afforded trialdehyde **12b**.[30] **12a** (1 equiv) was treated with $TiCl_4$ (30 equiv) and Zn (60 equiv) in THF under reflux gave uncharacterizable products (Scheme 5). This may be due to the non-rigidity of the trialdehyde due to the ether linkage, which can give some flexibility and hence could lead to polymerization. It is noteworthy to mention that trialdehydes **10a** and **10b** could undergo both intra- and intermolecular McMurry coupling to give cyclophanes **11a** and **11b**, whereas trialdehydes **12a** and **12b** gave only uncharacterizable products.



Scheme 6. Reagents and conditions: (i) TBADC, $CHCl_3$, reflux, 6 h, 69%; (ii) $TiCl_4$ (30 equiv), Zn (60 equiv), pyridine, THF, reflux, overnight.

2.6. Attempted synthesis of cylindrical stilbenophanes

Intermolecular McMurry coupling of dialdehydes **3a–3d** to give stilbenophanes **4a–4d** prompted us to explore this technique for the synthesis of cylindrical stilbenophane **15**. Tribromide **13**[31] on oxidation with TBADC in $CHCl_3$ afforded trialdehyde **14** in 69% yield. The structure of trialdehyde **14** was confirmed by ^1H NMR, ^{13}C NMR spectra and elemental analysis. Trialdehyde **14** on treatment with $TiCl_4$ and Zn under refluxing conditions afforded uncharacterizable products (Scheme 6).

3. Antibacterial studies of the indolophanes

S. No.	Indolophanes	Concentration (μg/mL)	Zone of inhibition[a] (mm)		
			Salmonella typhi	*Serratia marcescens*	*Streptococcus pneumoniae*
1	**6b**	25	4.4	6.0	5.0
		50	6.2	8.4	6.5
		75	9.6	10.4	9.7
2	**6c**	25	5.2	5.6	5.2
		50	8.2	8.2	6.2
		75	11.2	10.6	8.8
3	**8a**	25	4.9	5.3	4.9
		50	7.8	7.8	5.8
		75	10.9	10.3	8.5
4	**8d**	25	5.0	5.4	5.1
		50	8.0	8.0	6.0
		75	11.1	10.4	8.7
5	**11a**	25	5.0	5.4	5.8
		50	9.2	8.8	7.0
		75	12.0	10.2	10.2
6	**11b**	25	5.2	5.6	5.2
		50	8.2	8.2	6.2
		75	11.2	10.6	8.8

[a] Values of zone of inhibition are the mean of six replicates.

Bacterial cultures such as *S. typhi*, *S. marcensis* and *S. pneumoniae* were obtained from Madras Medical College, Chennai, India. All the cultures were maintained on nutrient agar medium. The activity was tested by disc diffusion method.[32]

3.1. Methodology

Each of the bacterium was inoculated in 50 mL of nutrient broth individually and was incubated in an environ shaker for 10 h at 150 rpm. About 150 μL of each of the broth culture was amended with 125 mL of molten nutrient agar medium and was plated. Indolophanes **6b**, **6c**, **8a**, **8d**, **11a** and **11b** each at 25, 50 and 75 μg/mL were prepared in $CHCl_3$ and were loaded onto filter paper disc. The discs were then dried and placed on each of the bacterium amended medium. The assay plates were incubated at 35 °C for 48 h. The zone of inhibition was measured, which was expressed in millimetre.

3.2. Results

While screening on nutrient agar medium, all the six indolophanes **6b**, **6c**, **8a**, **8d**, **11a** and **11b** at all the concentrations produced noteworthy inhibition against *S. typhi*, *S. marcensis* and *S. pneumoniae*. However, **6c**, **8a**, **8d**, **11a** and **11b** inhibited *S. typhi* significantly followed by *Serratia marcensis* when compared with *S. pneumoniae*. On the contrary, **6b** inhibited effectively *Serratia marcensis* than the others.

4. Complexation studies

Cyclophanes **6a–6c**, **11a** and **11b** exhibited charge transfer complexes with TCNQ among all the cyclophanes reported in this paper. Complexation studies of **6a–6c**, **11a** and **11b** with TCNE and PQT were not successful. Cyclophanes **6a–6c**, **11a** and **11b** show UV–vis absorption maxima at 241.3, 234, 274, 232 and 230 nm, respectively. However, the acceptor TCNQ shows absorption maxima at 274 nm. Cyclophanes **6a–6c**, **11a** and **11b** form a charge transfer complex with TCNQ as evidenced by the appearance of absorption maxima at 395, 398, 396, 398 and 397, respectively. The studies were carried out as outlined below.

In a typical experiment, 3 mL aliquot of a standard stock solution of the cyclophane in 1:1 mixture of $CHCl_3/CH_3CN$ was placed in a quartz cuvette. A known amount of the electron deficient guest molecule was added in incremental amounts and changes in absorbance of the CT bands were recorded. Table 1 shows the CT complexation studies of **6b** with various concentrations of TCNQ. A plot of [concn of cyclophane]/absorbance versus 1/concentration of guest was linear (Fig. 3). From the slope and the intercept values K_a (K_a=intercept×slope^{-1}) and ε (ε=intercept^{-1}) were evaluated. The plots were linear and suggest that the predominant species in the solution was 1:1 complex. K_a and ε values of CT complexes formed from **6a–6c**, **11a** and **11b** are shown in Table 2.

Table 1. Benesi–Hildebrand treatment data of the CT complex formed between the cyclophane **6b** and TCNQ λ_{max}=398 nm. Concentration of cyclophane **6b**=10^{-5} M

Concentration of guest, [X] (M)	Absorbance (*A*)	[Y]/*A* (M)	1/[X] (M^{-1})
4.9×10^{-6}	0.500	0.00002	204,081
9.8×10^{-6}	0.978	0.0000102	102,040
14.7×10^{-6}	1.424	0.000007	68,027
19.6×10^{-6}	1.811	0.0000055	51,020
24.5×10^{-6}	2.088	0.0000047	40,816

K_a=7.14×10^2 M^{-1}, ε=2×10^7 M^{-1} cm^{-1}, SD=99.97 (%).

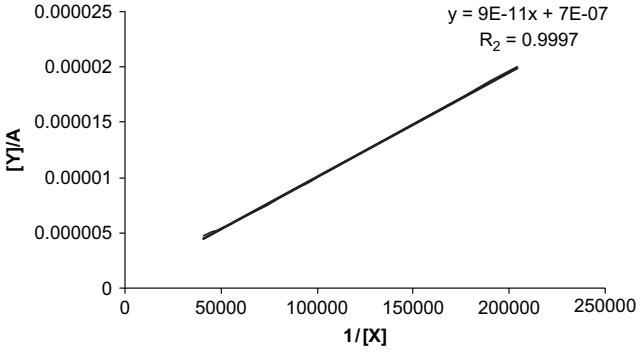


Figure 3. Plot between 1/[*X*] and [*Y*]/*A* for compound **6b**.

Table 2. Complexation of TCNQ with cyclophanes **6a–6c**, **11a** and **11b**

Cyclophane	K_a	ε
6a	1×10^3	2×10^8
6b	7.14×10^2	2×10^7
6c	7.936×10^3	1.4×10^6
11a	2.5×10^4	2×10^5
11b	2.00×10^3	1.66×10^5

Cyclophane **6c** complexes with TCNQ more strongly than **6b**, which is followed by **6a**. In the case of **11a** and **11b**, the former one complexes more effectively than the latter.

5. Conclusion

Various types of stilbenophanes, indolophanes and bisindolostilbenophanes were obtained by intra-, inter-, tandem intra- and intermolecular McMurry coupling. Some of the indolophanes exhibited noteworthy inhibition against *S. typhi*, *S. marcescens* and *S. pneumoniae.* Charge transfer studies were carried out with some indolophanes and TCNQ.

6. Experimental

6.1. General

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL 400 and JEOL 500 spectrometers at 500, 400, 125 and 100 MHz, respectively. Mass spectra were recorded on a JEOL DX 303 HF spectrometer and FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer.

6.2. Procedure A for NBS bromination

Freshly recrystallized *N*-bromosuccinimide (NBS) (92 mmol/135 mmol) was added in 5–6 equal portions at

6 h apart to a solution of methyl aryl compound (44 mmol) in CCl_4 (350 mL) heated at reflux; each addition was immediately followed by adding a few milligrams of benzoyl peroxide. After 40 h of total reaction time at reflux the mixture was cooled and the precipitated succinimide was removed by filtration. The solvent was removed and the residue was chromatographed (SiO_2) from hexane/$CHCl_3$ and then recrystallized.

6.3. General procedure B for oxidation of dibromide to dialdehyde

Tetrabutylammonium dichromate (TBADC) was prepared by stirring a heterogeneous mixture of tetrabutylammonium hydrogen sulfate (100 mmol) in CH_2Cl_2 (100 mL) and K_2CrO_4 (250 mmol) in water (100 mL) at room temperature for 2 h. The reagent was obtained from the organic layer as orange coloured pasty mass. The dibromide was dissolved in $CHCl_3$, mixed with TBADC (1.32 equiv) and refluxed for 6 h. $CHCl_3$ was removed under reduced pressure and the resulting pasty mass was mixed with column silica gel and chromatographed. Elution with a mixture of $CHCl_3$/hexane (2:3) gave the respective dialdehyde.

6.4. General procedure C for N-alkylation

To a solution of indole-3-aldehyde (7.5 mmol) in CH_3CN (50 mL), NaOH (25%) solution was added and stirred for 10 min. The bromide (15.9 mmol/22.5 mmol) in acetonitrile (20 mL) was added at once and stirred at room temperature for 48 h. After completion of the reaction CH_3CN was removed under reduced pressure and the reaction mixture was extracted with CH_2Cl_2 (300 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed using hexane and ethyl acetate (3:2) as eluent.

6.5. General procedure D for McMurry coupling

A solution of zero valent titanium prepared from $TiCl_4$ (20 equiv/30 equiv) with zinc (40 equiv/60 equiv) in dry THF (75 mL) under a nitrogen atmosphere at 0 °C was allowed to attain room temperature after 0.5 h and then refluxed for 1 h. Aldehyde was added in one lot to the freshly prepared low valent titanium. After the addition, the reaction mixture was refluxed overnight. The reaction mixture was cooled and then quenched with saturated K_2CO_3 solution. The precipitated inorganic material was removed by filtration. The precipitate was thoroughly washed with THF for several times and the combined THF extract was removed under reduced pressure. The residue was then dissolved in water and extracted in $CHCl_3$ (200 mL), washed with water (2×200 mL), brine (100 mL) and dried over Na_2SO_4. Crude product, obtained after evaporation of $CHCl_3$, was purified by column chromatography.

6.5.1. Compound 1d. To a stirred solution of *p*-tolylmagnesiumbromide (prepared from 31.1 g, 18.1 mmol of *p*-bromotoluene and 4.41 g, 18.1 mmol of Mg in 40 mL of THF) under N_2 atmosphere was added dropwise 2,4,6-tribromobenzene in THF (150 mL) (5.6 mmol) over 1 h at reflux. Stirring was continued for 6 h, after which the reaction was quenched with cold, dilute HCl (40 mL). Then THF was removed under reduced pressure and the aqueous solution was extracted several times with CH_2Cl_2. Combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The residue obtained after solvent removal was chromatographed in hexane to give **1d** as a white solid in 78% (15 g); mp 126–130 °C; [found: C, 71.25; H, 5.10. $C_{20}H_{17}Br$ requires C, 71.23; H, 5.08%]; δ_H (500 MHz, $CDCl_3$) 7.67–7.66 (m, 3H, Ph); 7.51–7.49 (m, 4H, Ph); 7.27–7.25 (m, 4H, Ph); 2.41 (s, 6H, C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 143.6, 138.0, 137.0, 129.7, 128.5, 127.1, 124.5, 123.3, 21.3; *m*/*z* (EI) 337 (M^+), 339 (M^++2).

6.5.2. Compound 2d. Following the general procedure A, dibromide **2d** was obtained as a light yellow colour solid in 80% yield; mp 148–151 °C; [found: C, 48.51; H, 3.02. $C_{20}H_{15}Br_3$ requires C, 48.52; H, 3.05%]; δ_H (500 MHz, $CDCl_3$) 7.70–7.65 (m, 3H, Ph); 7.58–7.55 (m, 4H, Ph); 7.49–7.47 (m, 4H, Ph); 4.54 (s, 4H, C*H*$_2$); δ_C (125 MHz, $CDCl_3$) 143.0, 139.8, 137.8, 129.8, 129.2, 127.7, 127.5, 124.8, 33.1; *m*/*z* (EI) 495 (M^+), 497 (M^++2), 499 (M^++4).

6.5.3. Compound 3a. Following the general procedure B, dialdehyde **3a** was obtained as a white solid in 69% yield; mp 204–208 °C; [found: C, 83.92; H, 4.95. $C_{20}H_{14}O_2$ requires C, 83.90; H, 4.93%]; IR (KBr) ν_{max}: 1686 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.08 (s, 2H, C*H*O); 7.99 (d, 4H, *J* 8.6 Hz, Ph); 7.87 (s, 1H, Ph); 7.81 (d, 4H, *J* 8.0 Hz, Ph); 7.69–7.67 (m, 2H, Ph); 7.62–7.60 (m, 1H, Ph); δ_C (125 MHz, $CDCl_3$) 191.9, 146.7, 140.6, 135.4, 130.4, 129.7, 127.8, 127.4, 126.5; *m*/*z* (EI) 286 (M^+).

6.5.4. Compound 3b. Following the general procedure B, dialdehyde **3b** was obtained as a light yellow colour solid in 67% yield; mp 215–217 °C; [found: C, 65.75; H, 3.56. $C_{20}H_{13}BrO_2$ requires C, 65.77; H, 3.59%]; IR (KBr) ν_{max}: 1696 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.06 (s, 2H, C*H*O); 7.95–7.91 (m, 4H, Ph); 7.85–7.81 (m, 7H, Ph); δ_C (125 MHz, $CDCl_3$) 191.6, 145.0, 143.1, 137.9, 132.6, 130.2, 129.8, 127.3, 124.9; *m*/*z* (EI) 365 (M^+), 367 (M^++2).

6.5.5. Compound 3c. Following the general procedure B, dialdehyde **3c** was obtained as a light yellow colour solid in 60% yield; mp 209–211 °C; [found: C, 76.70: H, 4.73. $C_{22}H_{16}O_4$ requires C, 76.73; H, 4.68%]; IR (KBr) ν_{max}: 1699, 1720 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.06 (s, 2H, C*H*O); 7.93 (d, 4H, *J* 8.0 Hz, Ph); 7.61–7.55 (m, 3H, Ph); 7.45–7.44 (m, 4H, Ph); 3.37 (s, 3H, COOC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 192.0, 169.2, 146.5, 139.6, 135.6, 132.6, 130.0, 129.9, 129.2, 52.2, 30.5; *m*/*z* (EI) 345 (M^+).

6.5.6. Compound 3d. Following the general procedure B, dialdehyde **3b** was obtained as a light yellow colour solid in 69% yield; mp 223–226 °C; [found: C, 65.79; H, 3.61. $C_{20}H_{13}BrO_2$ requires C, 65.77; H, 3.59%]; IR (KBr) ν_{max}: 1703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.07 (s, 2H, C*H*O); 7.99 (s, 2H, Ph); 7.97 (s, 2H, Ph); 7.79–7.75 (m, 7H, Ph); δ_C (125 MHz, $CDCl_3$) 191.7, 145.2, 142.5, 135.9, 130.5, 130.2, 127.9, 125.2, 123.8; *m*/*z* (EI) 365 (M^+), 367 (M^++2).

6.5.7. Compound 4a. Following the general procedure D, stilbenophane **4a** was obtained as a light yellow colour solid in 24% yield; mp >300 °C; [found: C, 94.42; H, 5.53. $C_{40}H_{28}$ requires C, 94.45; H, 5.55%]; δ_H (400 MHz,

$CDCl_3$) 7.50–7.42 (m, 8H, Ph); 7.36 (d, 8H, *J* 8.2 Hz, Ph); 7.06 (d, 8H, *J* 8.2 Hz, Ph); 6.74 (s, 4H, C*H*=C*H*); δ_C (100.4 MHz, $CDCl_3$) 141.6, 140.2, 136.6, 131.0, 129.8, 129.2, 126.9, 125.0, 124.9; *m/z* (FABMS) 508 (M^+).

6.5.8. Compound 4b. Following the general procedure D, stilbenophane **4b** was obtained as a light yellow colour solid in 18% yield; mp >300 °C; [found: C, 72.08; H, 3.97. $C_{40}H_{26}Br_2$ requires C, 72.04; H, 3.93%]; δ_H (400 MHz, $CDCl_3$) 7.42–7.32 (m, 6H, Ph); 7.25 (d, 8H, *J* 8.3 Hz, Ph); 6.91 (d, 8H, *J* 8.3 Hz, Ph); 6.78 (s, 4H, C*H*=C*H*); δ_C (100.4 MHz, $CDCl_3$) 142.7, 139.6, 135.5, 130.7, 128.9, 128.1, 127.1, 125.2, 124.7; *m/z* (FABMS) 666 (M^+), 668 (M^++2), 670 (M^++4).

6.5.9. Compound 4c. Following the general procedure D, stilbenophane **4c** was obtained as a light yellow colour solid in 25% yield; mp >300 °C; [found: C, 84.62; H, 5.20. $C_{44}H_{32}O_4$ requires C, 84.59; H, 5.16%]; δ_H (400 MHz, $CDCl_3$) 7.48–7.41 (m, 6H, Ph); 7.36 (d, 8H, *J* 7.8 Hz, Ph); 7.22 (d, 8H, *J* 7.8 Hz, Ph); 6.86 (s, 4H, C*H*=C*H*); 3.37 (s, 6H, COOCH_3); δ_C (100.4 MHz, $CDCl_3$) 205.5, 140.5, 139.7, 138.1, 130.4, 129.4, 127.2, 127.0, 126.4, 125.7, 51.5; *m/z* (FABMS) 624 (M^+).

6.5.10. Compound 4d. Following the general procedure D, stilbenophane **4d** was obtained as a light yellow colour solid in 24% yield; mp >300 °C; [found: C, 72.02; H, 3.91. $C_{40}H_{26}Br_2$ requires C, 72.04; H, 3.93%]; δ_H (400 MHz, $CDCl_3$) 7.64–7.42 (m, 6H, Ph); 7.31 (d, 8H, *J* 8.3 Hz, Ph); 7.04 (d, 8H, *J* 7.8 Hz, Ph); 6.74 (s, 4H, C*H*=C*H*); δ_C (100.4 MHz, $CDCl_3$) 143.9, 139.0, 133.4, 128.7, 127.0, 126.6, 126.0, 123.6, 123.3; *m/z* (FABMS) 666 (M^+), 668 (M^++2), 670 (M^++4).

6.5.11. Compound 5a. Following the general procedure C, dialdehyde **5a** was obtained as a light brown colour solid in 70% yield; mp 156–158 °C; [found: C, 79.59; H, 5.11; N, 7.18. $C_{26}H_{20}N_2O_2$ requires C, 79.57; H, 5.14; N, 7.14%]; IR (KBr) ν_{max}: 1647 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.90 (s, 2H, C*H*O); 8.05 (d, 2H, *J* 8.1 Hz, Ar); 7.42 (s, 2H, Ar); 7.41–7.40 (m, 2H, Ar); 7.27–7.24 (m, 4H, Ar); 7.16–7.11 (m, 4H, Ar); 5.24 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.8, 137.5, 137.4, 133.2, 129.9, 129.8, 125.5, 124.6, 123.6, 122.4, 118.9, 110.0, 48.4; *m/z* (EI) 392 (M^+).

6.5.12. Compound 5b. Following the general procedure, C dialdehyde **5b** was obtained as a light brown colour solid in 72% yield; mp 130–132 °C; [found: C, 79.55; H, 5.12; N, 7.19. $C_{26}H_{20}N_2O_2$ requires C, 79.57; H, 5.14; N, 7.14%]; IR (KBr) ν_{max}: 1631 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.97 (s, 2H, C*H*O); 8.31 (d, 2H, *J* 7.5 Hz, Ar); 7.65 (s, 2H, Ar); 7.33–7.31 (m, 4H, Ar); 7.29–7.25 (m, 4H, Ar); 7.20–7.18 (m, 1H, Ar); 6.89 (s, 1H, Ar); 5.27 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.7, 138.3, 137.3, 136.7, 130.1, 127.1, 125.6, 124.4, 123.3, 122.3, 118.7, 110.3, 50.7; *m/z* (EI) 392 (M^+).

6.5.13. Compound 5c. Following the general procedure C, dialdehyde **5c** was obtained as a light brown colour solid in 74% yield; mp 178–182 °C; [found: C, 76.34; H, 4.89; N, 10.65. $C_{25}H_{19}N_3O_2$ requires C, 76.32; H, 4.87; N, 10.68%]; IR (KBr) ν_{max}: 1652 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.01 (s, 2H, C*H*O); 8.32 (d, 2H, *J* 7.7 Hz, Ar); 7.79 (s, 2H, Ar); 7.54 (m, 1H, Ar); 7.33–7.30 (m, 2H, Ar); 7.28–7.25 (m, 4H, Ar); 6.89 (d, 2H, *J* 7.7 Hz, Ar); 5.44 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.8, 155.8, 138.9, 138.7, 137.4, 124.4, 123.3, 122.3, 120.7, 110.4, 52.5; *m/z* (EI) 393 (M^+).

6.5.14. Compound 5d. Following the general procedure C, dialdehyde **5d** was obtained as a light brown colour solid in 74% yield; mp 187–190 °C; [found: C, 79.58; H, 5.16; N, 7.11. $C_{26}H_{20}N_2O_2$ requires C, 79.57; H, 5.14; N, 7.14%]; IR (KBr) ν_{max}: 1657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.00 (s, 2H, C*H*O); 8.33 (m, 2H, Ar); 7.74 (s, 2H, Ar); 7.52 (d, 4H, *J* 8.4 Hz, Ar); 7.35–7.30 (m, 2H, Ar); 7.25–7.22 (m, 4H, Ar); 5.39 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.8, 140.5, 138.6, 137.5, 134.7, 127.8, 125.6, 124.3, 123.3, 122.3, 118.7, 110.5, 50.7; *m/z* (EI) 392 (M^+).

6.5.15. Compound 5e. Following the general procedure C, dialdehyde **5e** was obtained as a light brown colour solid in 66% yield; mp 196–200 °C; [found: C, 74.30; H, 5.37; N, 6.21. $C_{28}H_{24}N_2O_4$ requires C, 74.32; H, 5.35; N, 6.19%]; IR (KBr) ν_{max}: 1647 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.98 (s, 2H, C*H*O); 8.31–8.28 (m, 2H, Ar); 7.72 (s, 2H, Ar); 7.39–7.38 (m, 2H, Ar); 7.31–7.30 (m, 2H, Ar); 7.25 (s, 2H, Ar); 6.51 (s, 2H); 5.30 (s, 4H, NCH_2); 3.64 (s, 6H, OCH_3); δ_C (125 MHz, $CDCl_3$) 184.8, 151.2, 138.8, 137.6, 125.5, 124.5, 124.2, 123.1, 122.2, 118.4, 111.8, 110.4, 56.1, 46.0; *m/z* (EI) 452 (M^+).

6.5.16. Compound 5f. Following the general procedure C, dialdehyde **5f** was obtained as a light brown colour solid in 68% yield; mp 136–140 °C; [found: C, 82.05; H, 5.19; N, 5.99. $C_{32}H_{24}N_2O_2$ requires C, 82.03; H, 5.16; N, 5.98%]; IR (KBr) ν_{max}: 1651 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.01 (s, 2H, C*H*O); 8.34–8.32 (m, 2H, Ar); 7.74 (s, 4H, Ar); 7.54–7.51 (m, 2H, Ar); 7.35–7.30 (m, 4H, Ar); 7.25–7.20 (m, 6H, Ar); 5.39 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.7, 140.5, 138.5, 137.5, 134.8, 127.8, 125.6, 124.3, 123.2, 122.3, 118.7, 110.5, 50.7; *m/z* (EI) 468 (M^+).

6.5.17. Compound 6a. Following the general procedure D, indolophane **6a** was obtained as a light yellow colour solid in 19% yield; mp 126 °C; [found: C, 86.61, H, 5.63; N, 7.79. $C_{26}H_{20}N_2$ requires C, 86.64; H, 5.59; N, 7.77%]; δ_H (400 MHz, $CDCl_3$) 8.17 (d, 2H, *J* 7.4 Hz, Ar); 7.79 (d, 2H, *J* 8.6 Hz, Ar); 7.64 (t, 2H, *J* 7.5 Hz, Ar); 7.46 (d, 4H, *J* 8.6 Hz, Ar); 7.29 (t, 2H, *J* 7.5 Hz, Ar); 6.72 (s, 2H, C*H*=C*H*); 6.30 (s, 2H, Ar); 5.80 (s, 4H, NCH_2); δ_C (100.4 MHz, $CDCl_3$) 153.9, 136.4, 130.3, 129.5, 128.9, 125.1, 124.2, 120.0, 119.4, 112.0, 108.5, 46.2; *m/z* (FABMS) 360 (M^+).

6.5.18. Compound 6b. Following the general procedure D, indolophane **6b** was obtained as a light yellow colour solid in 24% yield; mp 297 °C; [found: C, 86.68; H, 5.61; N, 7.77. $C_{26}H_{20}N_2$ requires C, 86.64; H, 5.59; N, 7.77%]; δ_H (400 MHz, $CDCl_3$) 7.59 (d, 2H, *J* 7.3 Hz, Ar); 7.23 (d, 2H, *J* 7.8 Hz, Ar); 7.18–7.14 (m, 3H, Ar); 7.12 (d, 2H, *J* 7.8 Hz, Ar); 7.07 (d, 2H, *J* 7.3 Hz); 6.79 (s, 2H, C*H*=C*H*); 6.49 (s, 2H, Ar); 6.09 (s, 1H); 4.98 (s, 4H, NCH_2); δ_C (100.4 MHz, $CDCl_3$) 139.0, 138.0, 128.5, 128.1, 126.1, 125.0, 122.2, 120.1, 119.7, 114.2, 110.1, 49.6; *m/z* (FABMS) 360 (M^+).

6.5.19. Compound 6c. Following the general procedure D, indolophane **6c** was obtained as a light yellow colour solid in 36% yield; mp 228–232 °C; [found: C, 83.09; H, 5.32; N, 11.64. $C_{25}H_{19}N_3$ requires C, 83.08; H, 5.30; N, 11.63%]; δ_H (500 MHz, $CDCl_3$) 7.72 (d, 2H, *J* 7.7 Hz, Ar); 7.54 (t, 1H, *J* 7.6 Hz, Ar); 7.31–7.29 (m, 2H, Ar); 7.19 (m, 1H, Ar); 7.17–7.13 (m, 4H, Ar); 7.11 (s, 1H, Ar); 6.86 (s, 2H, Ar); 6.82 (s, 2H, C*H*=C*H*); 5.17 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 155.2, 136.9, 136.6, 131.2, 128.9, 122.9, 121.1, 120.2, 119.4, 119.0, 111.7, 108.9, 49.8; *m*/*z* (FABMS) 361 (M^+).

6.5.20. Compound 6d. Following the general procedure D, indolophane **6d** was obtained as a light yellow colour solid in 20% yield; mp 135 °C; [found: C, 86.68; H, 5.61; N, 7.76. $C_{52}H_{40}N_4$ requires C, 86.64; H, 5.59; N, 7.77%]; δ_H (400 MHz, $CDCl_3$) 7.50 (d, 8H, *J* 7.8 Hz, Ar); 7.14 (d, 8H, *J* 8.3 Hz, Ar); 7.03 (d, 4H, *J* 7.8 Hz, Ar); 7.07 (d, 4H, *J* 7.8 Hz); 6.94 (s, 4H, Ar); 6.77 (s, 4H, C*H*=C*H*); 5.13 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 140.0, 137.1, 136.7, 129.0, 127.4, 127.3, 125.9, 121.7, 119.2, 118.9, 111.1, 109.5, 49.6; *m*/*z* (FABMS) 720 (M^+).

6.5.21. Compound 6e. Following the general procedure D, indolophane **6e** was obtained as a light yellow colour solid in 23% yield; mp 134 °C; [found: C, 79.94; H, 5.77; N, 6.68. $C_{56}H_{48}N_4O_4$ requires C, 79.98; H, 5.75; N, 6.66%]; δ_H (400 MHz, $CDCl_3$) 7.48 (d, 4H, *J* 7.8 Hz, Ar); 7.21 (d, 4H, *J* 8.3 Hz, Ar); 7.09 (m, 8H, Ar); 7.02 (t, 4H, *J* 7.3 Hz, Ar); 6.80 (s, 4H, C*H*=C*H*); 6.24 (s, 4H, Ar); 5.11 (s, 8H, NCH_2); 3.49 (s, 12H, OCH_3); δ_C (100.4 MHz, $CDCl_3$) 150.8, 136.8, 128.8, 126.0, 125.9, 121.5, 118.9, 118.6, 111.1, 110.6, 109.5, 55.9, 55.8, 44.5; *m*/*z* (FABMS) 840 (M^+).

6.5.22. Compound 6f. Following the general procedure D, indolophane **6f** was obtained as a light yellow colour solid in 18% yield; mp 137 °C; [found: C, 88.06; H, 5.55; N, 6.43. $C_{64}H_{48}N_4$ requires C, 88.04; H, 5.54; N, 6.42%]; δ_H (400 MHz, $CDCl_3$) 7.52 (d, 8H, *J* 7.3 Hz, Ar); 7.38 (d, 8H, *J* 8.3 Hz, Ar); 7.18–7.07 (m, 20H, Ar); 6.84 (s, 4H, C*H*=C*H*); 5.20 (s, 8H, NCH_2); δ_C (100.4 MHz, $CDCl_3$) 137.0, 136.7, 129.0, 127.3, 127.2, 125.8, 121.7, 119.1, 118.8, 110.5, 109.4, 49.5; *m*/*z* (FABMS) 872 (M^+).

6.5.23. Compound 7a. Following the general procedure C, dialdehyde **7a** was obtained as a light brown colour solid in 78% yield; mp 218–220 °C; [found: C, 83.84; H, 5.16; N, 5.16. $C_{38}H_{28}N_2O_2$ requires C, 83.80; H, 5.18; N, 5.14%]; IR (KBr) ν_{max}: 1650 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.01 (s, 2H, C*H*O); 8.34–8.32 (m, 2H, Ar); 7.75 (s, 2H, Ar); 7.59 (d, 4H, *J* 8.6 Hz, Ar); 7.54–7.49 (m, 4H, Ar); 7.37–7.34 (m, 2H, Ar); 7.33–7.30 (m, 4H, Ar); 7.26–7.25 (m, 4H, Ar); 5.40 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.8, 141.3, 141.0, 137.5, 134.6, 128.0, 127.8, 126.5, 126.0, 125.6, 124.3, 123.3, 122.3, 118.6, 110.5, 50.8; *m*/*z* (EI) 545 (M^+).

6.5.24. Compound 7b. Following the general procedure C, dialdehyde **7b** was obtained as a light brown colour solid in 76% yield; mp 132–134 °C; [found: C, 73.24; H, 4.39; N, 4.51. $C_{38}H_{27}N_2O_2Br$ requires C, 73.20; H, 4.36; N, 4.49%]; IR (KBr) ν_{max}: 1651 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.99 (s, 2H, C*H*O); 8.35–8.33 (m, 2H, Ar); 7.76 (s, 2H, Ar); 7.39–7.37 (m, 6H, Ar); 7.33–7.31 (m, 6H, Ar); 7.25–7.21 (m, 5H, Ar); 5.54 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.9, 143.1, 138.8, 137.6, 130.5, 130.4, 130.3, 126.9, 126.8, 125.6, 118.7, 110.6, 110.5, 50.7; *m*/*z* (EI) 623 (M^+), 625 (M^++2).

6.5.25. Compound 7c. Following the general procedure C, dialdehyde **7c** was obtained as a brown colour solid in 77% yield; mp 128–132 °C; [found: C, 68.09; H, 4.09; N, 4.20. $C_{38}H_{27}N_2O_2I$ requires C, 68.07; H, 4.06; N, 4.18%]; IR (KBr) ν_{max}: 1652 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.02 (s, 2H, C*H*O); 8.34–8.33 (m, 2H, Ar); 7.77 (s, 2H, Ar); 7.41–7.36 (m, 5H, Ar); 7.35–7.30 (m, 6H, Ar); 7.25–7.20 (m, 6H, Ar); 5.36 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.8, 143.1, 142.0, 138.7, 137.6, 134.9, 130.4, 130.3, 130.8, 130.2, 126.9, 126.8, 125.6, 118.7, 97.6, 94.8, 50.7; *m*/*z* (EI) 670 (M^+).

6.5.26. Compound 7d. Following the general procedure C, dialdehyde **7d** was obtained as a brown colour solid in 70% yield; mp 218–222 °C; [found: C, 73.22; H, 4.33; N, 4.53. $C_{38}H_{27}N_2O_2Br$ requires C, 73.20; H, 4.36; N, 4.49%]; IR (KBr) ν_{max}: 1646 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.01 (s, 2H, C*H*O); 8.33–8.30 (m, 2H, Ar); 7.75 (s, 4H, Ar); 7.65 (s, 2H, Ar); 7.54 (d, 4H, *J* 8.0 Hz); 7.35–7.30 (m, 4H, Ar); 7.26–7.24 (m, 5H, Ar); 5.40 (s, 4H, NCH_2); δ_C (125 MHz, $CDCl_3$) 185.3, 142.1, 141.9, 139.6, 137.7, 135.4, 131.4, 131.1, 130.9, 130.6, 128.9, 128.6, 127.9, 125.9, 119.8, 110.9, 50.9; *m*/*z* (EI) 623 (M^+), 625 (M^++2).

6.5.27. Compound 8a. Following the general procedure D, indolophane **8a** was obtained as a light yellow colour solid in 8% yield; mp 224–229 °C; [found: C, 89.01; H, 5.53; N, 5.46. $C_{76}H_{56}N_4$ requires C, 89.03; H, 5.51; N, 5.46%]; δ_H (500 MHz, $CDCl_3$) 7.60 (s, 2H, Ar); 7.53–7.52 (m, 4H, Ar); 7.46–7.42 (m, 12H, Ar); 7.22–7.20 (m, 6H, Ar); 7.18–7.13 (m, 12H, Ar); 7.12–7.04 (m, 8H); 6.86 (s, 4H, C*H*=C*H*); 5.23 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 140.4, 129.0, 127.6, 127.4, 126.2, 126.0, 125.9, 121.8, 119.2, 118.9, 110.1, 109.5, 49.6; *m*/*z* (FABMS) 1025.

6.5.28. Compound 8b. Following the general procedure D, indolophane **8b** was obtained as a light yellow colour solid in 6% yield; mp 231–233 °C; [found: C, 77.20; H, 4.58; N, 4.78. $C_{76}H_{54}Br_2N_4$ requires C, 77.16; H, 4.60; N, 4.74%]; δ_H (500 MHz, $CDCl_3$) 7.64–7.52 (m, 6H, Ar); 7.47–7.27 (m, 8H, Ar); 7.25–7.22 (m, 12H, Ar); 7.19–7.15 (m, 8H, Ar); 7.10–7.08 (m, 8H, Ar); 6.88 (s, 4H, C*H*=C*H*); 5.25 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 131.1, 130.5, 128.8, 127.6, 126.9, 126.5, 126.2, 122.8, 121.7, 119.9, 118.9, 114.1, 110.5, 50.2; *m*/*z* (FABMS) 1180 (M^+), 1182 (M^++2), 1184 (M^++4).

6.5.29. Compound 8c. Following the general procedure D, indolophane **8c** was obtained as a light yellow colour solid in 5% yield; mp 218–220 °C; [found: C, 71.50; H, 4.28; N, 4.36. $C_{76}H_{54}I_2N_4$ requires C, 71.48; H, 4.26; N, 4.39%]; δ_H (500 MHz, $CDCl_3$) 7.53–7.48 (m, 6H, Ar); 7.35–7.27 (m, 8H, Ar); 7.22–7.18 (m, 12H, Ar); 7.16–7.14 (m, 8H, Ar); 7.12–7.11 (m, 8H, Ar); 6.94 (s, 4H, C*H*=C*H*); 5.29 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 130.3, 129.9, 127.7, 127.3, 126.9, 126.4, 126.0, 121.7, 120.9, 119.1, 118.9, 111.1, 109.5, 49.6; *m*/*z* (FABMS) 1276.

6.5.30. Compound 8d. Following the general procedure D, indolophane **8d** was obtained as a light yellow colour solid in 8% yield; mp 215–217 °C; [found: C, 77.18; H, 4.57; N, 4.76. $C_{76}H_{54}Br_2N_4$ requires C, 77.16; H, 4.60; N, 4.74%]; δ_H (500 MHz, $CDCl_3$) 7.44–7.36 (m, 6H, Ar); 7.34–7.27 (m, 8H, Ar); 7.21-7.13 (m, 12H, Ar); 7.11–7.05 (m, 8H, Ar); 7.01–6.97 (m, 8H, Ar); 6.87 (s, 4H, C*H*=C*H*); 5.24 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 131.9, 131.1, 129.3, 128.7, 127.9, 127.4, 127.1, 126.8, 123.4, 122.7, 121.2, 120.6, 119.8, 117.8, 111.2, 50.4; *m/z* (FABMS) 1180 (M^+), 1182 (M^++2), 1184 (M^++4).

6.5.31. Compound 10a. Following the general procedure C, trialdehyde **10a** was obtained as a light brown colour solid in 80% yield; mp 199–201 °C; [found: C, 79.14; H, 5.63, 6.99. $C_{39}H_{33}N_3O_3$ requires C, 79.16; H, 5.62; N, 7.10]; IR (KBr) ν_{max}: 1649 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.89 (s, 3H, C*H*O); 8.28 (d, 3H, *J* 7.5 Hz, Ar); 7.51 (d, 3H, *J* 8.0 Hz, Ar); 7.41–7.34 (m, 6H, Ar); 7.27 (s, 3H, Ar); 5.43 (s, 6H, NCH_2); 2.28 (s, 9H, CH_3); δ_C (125 MHz, $CDCl_3$) 184.6, 140.5, 137.4, 135.2, 130.9, 125.9, 124.5, 123.7, 122.1, 118.6, 109.9, 45.5, 16.6; *m/z* (EI) 591 (M^+).

6.5.32. Compound 10b. Following the general procedure C, trialdehyde **10b** was obtained as a brown colour solid in 78% yield; mp 174–178 °C; [found: C, 78.65; H, 4.96; N, 7.66. $C_{36}H_{27}N_3O_3$ requires C, 78.67; H, 4.95; N, 7.65%]; IR (KBr) ν_{max}: 1653 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.90 (s, 3H, C*H*O); 8.28 (d, 3H, *J* 8.0 Hz, Ar); 7.55 (s, 3H, Ar); 7.30–7.28 (m, 3H, Ar); 7.21–7.18 (m, 3H, Ar); 7.04 (d, 3H, *J* 8.6 Hz, Ar); 6.80 (s, 3H, Ar); 5.22 (s, 6H, NCH_2); δ_C (125 MHz, $CDCl_3$) 184.6, 138.0, 137.1, 125.5, 125.2, 124.4, 123.3, 122.4, 118.8, 110.2, 50.4; *m/z* (EI) 549 (M^+).

6.5.33. Compound 11a. Following the general procedure D, indolophane **11a** was obtained as a light yellow colour solid in 24% yield; mp 222–226 °C; [found: C, 86.11; H, 6.05; N, 7.68. $C_{78}H_{66}N_6$ requires C, 86.15; H, 6.12; N, 7.73%]; δ_H (500 MHz, $CDCl_3$) 7.62 (d, 2H, *J* 7.5 Hz, Ar); 7.53 (d, 4H, *J* 8.0 Hz, Ar); 7.47 (d, 2H, *J* 8.0 Hz, Ar); 7.38 (d, 4H, *J* 8.1 Hz, Ar); 7.29 (t, 2H, *J* 8.0 Hz, Ar); 7.25 (s, 2H, Ar); 7.20–7.17 (m, 6H, Ar); 7.08 (t, 4H, *J* 7.5 Hz, Ar); 6.87 (s, 4H, Ar); 6.42 (s, 4H, CH=CH); 6.35 (s, 2H, CH=CH); 5.50 (d, 4H, *J* 14.3 Hz, NCH_2); 5.35 (s, 4H, NCH_2); 5.23 (d, 4H, *J* 14.3 Hz, NCH_2); 2.48 (s, 12H, CH_3); 2.26 (s, 6H, CH_3); δ_C (125 MHz, $CDCl_3$) 141.2, 137.4, 137.2, 136.7, 135.1, 130.8, 129.2, 128.0, 127.5, 127.4, 123.0, 121.7, 119.8, 119.7, 119.3, 119.1, 111.9, 110.8, 109.0, 108.9, 44.7, 44.6, 16.7, 16.2; *m/z* (FABMS) 1087 (M^+).

6.5.34. Compound 11b. Following the general procedure D, indolophane **11b** was obtained as a light yellow colour solid in 22% yield; mp 282–289 °C; [found: C, 86.12; H, 5.37; N, 8.34. $C_{72}H_{54}N_6$ requires C, 86.20; H, 5.43; N, 8.38%]; δ_H (500 MHz, $CDCl_3$) 7.67 (d, 4H, *J* 7.5 Hz, Ar); 7.61 (d, 2H, *J* 7.5 Hz); 7.25–7.11 (m, 20H, Ar); 6.85 (s, 6H, Ar); 6.81 (s, 4H, Ar); 6.50 (s, 4H, C*H*=C*H*); 6.01 (s, 2H, C*H*=C*H*); 5.17 (s, 4H, NCH_2); 4.95 (s, 8H, NCH_2); δ_C (125 MHz, $CDCl_3$) 139.3, 137.8, 137.5, 136.7, 129.5, 129.0, 128.2, 128.1, 125.2, 125.1, 124.7, 124.2, 121.9, 119.8, 119.4, 119.2, 119.0, 113.8, 111.2, 109.8, 109.5, 49.5, 49.0; *m/z* (FABMS) 1002 (M^+).

6.5.35. Compound 12a. A mixture of *p*-hydroxybenzaldehyde (2 mmol) and tribromide **9a** (7.7 mmol) and K_2CO_3 (3.46 g) in anhydrous DMF (30 mL) were stirred under nitrogen for 48 h at 60 °C. The reaction mixture was poured into water (1 L) and stirred. The resulting precipitate was filtered, washed with water (3×150 mL) and dissolved in CH_2Cl_2 (350 mL). The organic layer was washed with NaOH solution (5% w/v, 2×100 mL), dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed (SiO_2) using hexane/$CHCl_3$ (1:2) to give the trialdehyde **12a** in 65% yield; mp 140–142 °C [found: C, 75.81; H, 5.81. $C_{33}H_{30}O_6$ requires C, 75.84; H, 5.79%]; IR (KBr) ν_{max}: 1680 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.90 (s, 3H, C*H*O); 7.88 (d, 6H, *J* 8.4 Hz, Ph); 7.13 (d, 6H, *J* 8.4 Hz, Ph); 5.21 (s, 6H, PhCH_2); 2.45 (s, 9H, CH_3); δ_C (125 MHz, $CDCl_3$) 190.9, 164.0, 139.8, 132.2, 131.4, 130.4, 114.9, 65.3, 16.2; *m/z* (EI) 522 (M^+).

6.5.36. Compound 12b. Following the procedure as mentioned for compound **12a** trialdehyde **12b** was obtained in 67% yield; mp 141–143 °C [found: C, 75.01; H, 5.01. $C_{30}H_{24}O_6$ requires C, 74.99; H, 5.03]; IR (KBr) ν_{max}: 1682 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.88 (s, 3H, C*H*O); 7.83 (d, 6H, *J* 8.4 Hz, Ph); 7.49 (s, 3H, Ph); 7.06 (d, 6H, *J* 8.4 Hz, Ph); 5.18 (s, 6H, PhCH_2); δ_C (125 MHz, $CDCl_3$) 190.9, 163.5, 137.4, 132.1, 130.4, 126.3, 115.2, 69.81; *m/z* (EI) 480 (M^+).

6.5.37. Compound 14. Following the general procedure B, trialdehyde **14** was obtained as a white colour solid in 69% yield; mp 230–234 °C; [found: C, 83.04; H, 4.64. $C_{27}H_{18}O_3$ requires C, 83.06; H, 4.65%]; IR (KBr) ν_{max}: 1691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 10.09 (s, 3H, C*H*O); 8.02 (d, 6H, *J* 8.4 Hz, Ph); 7.90 (s, 3H, *J* 8.4 Hz, Ph); 7.86 (d, 6H, *J* 7.7 Hz, Ph); δ_C (125 MHz, $CDCl_3$) 191.9, 146.4, 141.7, 135.8, 130.5, 128.1, 126.6; *m/z* (EI) 390 (M^+).

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Palladium-catalysed carbonylation of 4-substituted 2-iodoaniline derivatives: carbonylative cyclisation and aminocarbonylation

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Abstract—2-Iodoaniline derivatives were used as bifunctional substrates in palladium-catalysed carbonylation. Depending on the substituents, two types of compounds were synthesised: having methyl or hydrogen in 4-position 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives have been formed, chloro, bromo, cyano or nitro groups in the same position resulted in the formation of dibenzo[*b*,*f*][1,5]-diazocine-6,12-dione derivatives. In the presence of various primary and secondary amines (*tert*-butylamine, amino acid methyl esters) as *N*-nucleophiles 2-keto-carboxamides were obtained as major products in aminocarbonylation reaction with double carbon monoxide insertion.

1. Introduction

Palladium-catalysed carbonylation reactions including amino- and alkoxycarbonylation and carbonylative coupling reactions are widely used in synthetic chemistry.[1,2] Aminocarbonylation plays a special role among these reactions, since those carboxamides which are hardly available in conventional synthetic methods (e.g., with bulky substituents at the amide nitrogen, the application of weak amine nucleophiles) can be synthesised from easily available starting materials. The synthesis of a wide variety of unsaturated carboxamides or aryl carboxamides with various structures has been reported using enol-triflates/iodo-alkenes or aryl triflates/aryl halides as substrates in aminocarbonylation, respectively.[3]

Due to the amino and iodo functionalities, 2-iodoaniline is a versatile building block for organic synthesis. Among them, functionalised iodoaromatics have been applied in many homogeneous catalytic reactions. The allylation of 2-iodoaniline and its consecutive alkoxycarbonylation resulted in the mixture of substituted indol- and 4-oxo-quinoline derivatives.[4] The palladium-catalysed carbonylation of 2-iodoaniline has been used in a multistep reaction for the synthesis of pentacyclic compounds.[5] 2-(2′-Phenyl-ethinyl)-phenol and 2-iodoaniline have been reacted in carbonylation reaction in the presence of $Pd(PPh_3)_4$ resulting in the formation of 2-benzofuranyl-benzo[*d*][1,3]oxazin-4-one derivatives.[6] A carbonylative coupling reaction of 2-iodoaniline and a nucleophile in a zinc complex has been carried out resulting in 3-(2′-amino-benzoyl)-alanine.[7] 3-Keto-2-benzylidene-indol has been synthesised by reacting 2-iodoaniline with phenylacetylene under carbon monoxide in palladium(0)-catalysed reaction.[8] The carbonylative Sonogashira coupling of 2-iodoaniline with 1-octyne resulted in the corresponding 2-amino-aryl-alkinyl ketone in high yield.[9] Various esters possessing enol-triflate moieties and iodo-benzenes have been reacted with 2-iodoaniline in palladium-catalysed carbonylative ring-closure reaction resulting in 2-cycloalkenyl and 2-aryl-benzofuranyl-benzo[*d*]-[1,3]oxazin-4-one derivatives, respectively.[10]

Although 2-iodoaniline derivatives may act both as an iodoarene substrate and as a *N*-nucleophile, to the best of our knowledge, no precedence for their use as a bifunctional substrate has been reported. In this study, catalytic carbonylation on 2-iodoaniline and its 4-substituted derivatives is described.

2. Results and discussion

2.1. Intramolecular aminocarbonylation reactions with 2-iodoaniline derivatives

2-Iodoaniline (**1a**) and its analogues (**1b–f**) were reacted under carbon monoxide pressure (100 bar) in DMF in the presence of in situ generated palladium(0)-triphenylphosphine catalysts *without* adding any further nucleophiles like amines or alcohols (Scheme 1). Palladium(II) acetate was used as catalytic precursor. The formation of neutral

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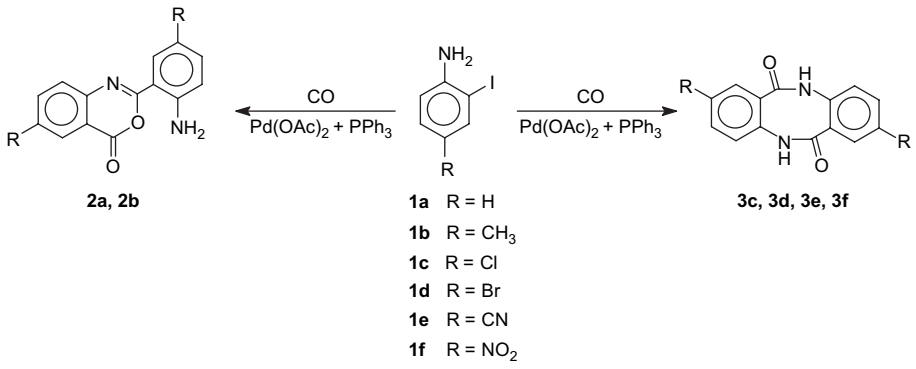


Scheme 1. Carbonylative cyclisation of 2-iodoanilines.

and anionic Pd(0) species from $Pd(OAc)_2/PPh_3$ system has been shown by cyclic voltammetry and ^{31}P NMR spectroscopy.[11–14] The reduction of Pd(II) to Pd(0) is due to PPh_3, which is itself oxidised to triphenylphosphine oxide.

The aim of the work was the application of a substrate family, which possesses both the iodoaryl moiety that can readily be oxidatively added to palladium(0) as well as an amino functionality that can act as a *N*-nucleophile in the product-forming step. The substrates can be divided into two groups according to the chemoselectivity of the reaction. Compounds **1a** and **1b** were transformed to the corresponding 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives (**2a** and **2b**) via double carbon monoxide insertion, while only one of the amino groups reacts. However, symmetric 5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione ('dianthranilide') type compounds (**3c**–**f**) have been obtained as major product when **1c**–**f** have been used as substrates (Scheme 1). It should be noted that due to extremely low solubilities of the latter dianthranilide-type derivatives and consequently, the difficulty in obtaining good quality NMR spectra, IR and MS spectroscopy play a crucial role in the structure determination. The structures have been proved by the typical vibrations in the ν(CO) region (see Section 4).

The products (**2a**, **2b**, **3c**–**f**) have been obtained with practically complete conversion and isolated in 74–85% yields. High chemoselectivities towards both 2-aryl-benzoxazin-4-ones (**2a**, **2b**) and dibenzo-diazocine-6,12-diones (**3c**–**f**) were obtained. The target compounds were formed with higher than 96% chemoselectivities in both cases. The major strength of these reactions could be their simplicity providing the target compounds without organic side products. The formation of both types of compounds can be rationalised by a simple reaction: two substrates (iodoaniline derivative)+two CO provide the cyclic product. The parent compounds of both families (dianthranilide[15–17] and **2a**[18–20]) are known and there are several conventional synthetic methods for their synthesis. The Beckmann rearrangement of anthraquinone dioxime (yield 85%)[17] and heating of 1,2,3-benzotriazin-4-one in inert solvents (yield 71%)[18] can be considered as high-yielding procedures of preparative importance, respectively.

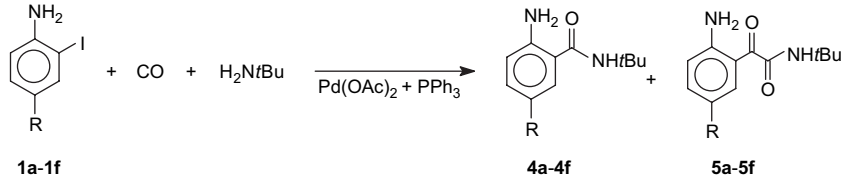
2.2. Aminocarbonylation reactions of 2-iodoaniline derivatives in the presence of primary and secondary amines

The carbonylative dimerisation products (**2a**, **2b**, **3c**–**f**) have been formed only in traces (<5%) in the presence of primary amines. The iodoaniline derivatives (**1a**–**f**) were thus reacted under carbon monoxide pressure (40 bar) in DMF at 50 °C in the presence of $Pd(OAc)_2$ and triphenylphosphine as the in situ catalyst and *tert*-butylamine as nucleophile (Scheme 2, Table 1). The corresponding 2-keto-*tert*-butylcarboxamides

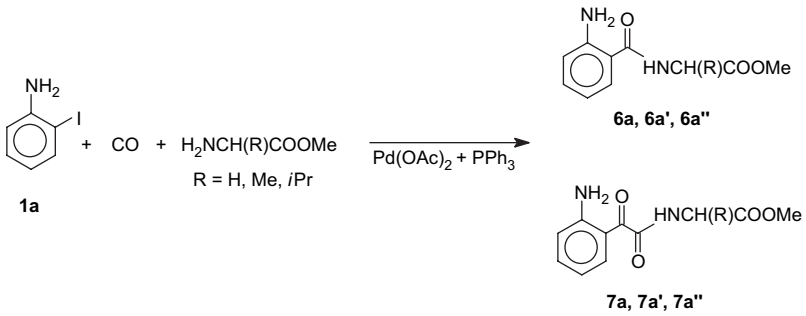
Table 1. Aminocarbonylation of 2-iodoanilines (**1a**–**f**) with primary and secondary amines[a]

Substrate	Amine	t_R[b] [h]	Products[c] [%]	
			Carboxamide	Ketocarboxamide
1a	*t*-BuNH_2	20	0 (**4a**)	100 (**5a**)
1b	*t*-BuNH_2	20	38 (**4b**)	62 (**5b**)
1c	*t*-BuNH_2	20	5 (**4c**)	95 (**5c**)
1d	*t*-BuNH_2	20	0 (**4d**)	100 (**5d**)
1e	*t*-BuNH_2	20	0 (**4e**)	100 (**5e**)
1f	*t*-BuNH_2	20	0 (**4f**)	100 (**5f**)
1a	GlyOMe	70	5 (**6a**)	95 (**7a**)
1a	AlaOMe	70	0 (**6a′**)	100 (**7a′**)
1a	ValOMe	6	0 (**6a″**)	100 (**7a″**)
1a	ProOMe	6	0 (**8a**)	100 (**9a**)
1b	ProOMe	6	0 (**8b**)	100 (**9b**)
1c	ProOMe	6	0 (**8c**)	100 (**9c**)
1f	ProOMe	6	0 (**8f**)	100 (**9f**)

[a] Reaction conditions: 0.025 mmol $Pd(OAc)_2$; 0.05 mmol PPh_3, 1 mmol 2-iodoaniline derivative (**1a**–**f**); 5 mmol *tert*-butylamine (or 1.25 mmol amino acid methylester hydrochloride), 10 ml DMF; 40 bar carbon monoxide, reaction temperature: 50 °C.
[b] Practically complete conversion (>98%) was obtained in all cases.
[c] Determined by GC–MS.

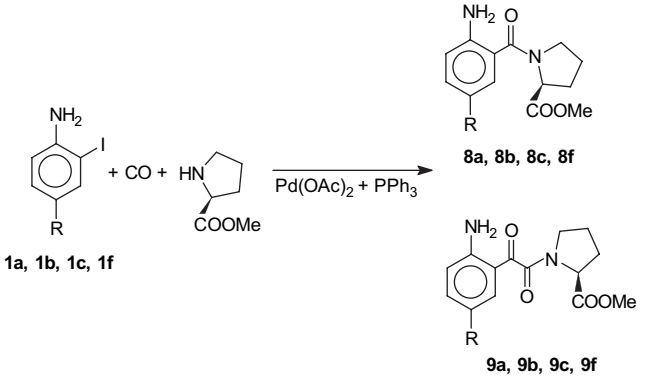


Scheme 2. Aminocarbonylation of 2-iodoanilines with *tert*-butylamine.



Scheme 3. Aminocarbonylation of 2-iodoaniline with amino acid esters as primary amines.

(**5a–f**) were obtained as major products in all cases (Table 1). The amount of the carboxamide in the reaction mixture was the highest (38% yield; **4b**) when **1b** was used as a substrate. Similarly high yields of ketocarboxamides were obtained with glycine methylester, alanine methylester and valine methylester as amine, so methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-glycinate (**7a**), methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-alaninate (**7a′**) and methyl *N*-{(2′-amino-phenyl)-glyoxyloyl}-valinate (**7a″**) were formed by double carbon monoxide insertion, respectively (Scheme 3). The carboxamide formed by single carbon monoxide insertion was detected by GC–MS only in the case of methyl glycinate. Similarly, exclusive ketocarboxamide formation (**9a**, **9b**, **9c**, **9f**) was observed with methyl prolinate as secondary amine (Scheme 4). A similar prevalence of 2-oxo-carboxamides over carboxamides in aminocarbonylation of iodoaromatics has been reported.[21]



Scheme 4. Aminocarbonylation of 2-iodoanilines with methyl prolinate as secondary amine.

3. Conclusions

It has been shown that 2-iodoaniline derivatives can be transformed into two different types of 'dimeric' ring-closure products in palladium-catalysed carbonylation. The reactions need rather severe conditions due to the weak arylamine nucleophile. However, by using various alkylamines for the aminocarbonylation of the same substrates under similar carbonylation conditions, the iodoaryl moiety of iodoanilines reacts exclusively (i.e., the adjacent amino group bound to the aryl ring remained intact). Due to double carbon monoxide insertion, 2-ketocarboxamides of practical interest have been isolated as major products in all cases. As for their potential biological importance, various 2-oxoamides are reported as potent inhibitors of digestive lipases[22–24] and phospholipases A2.[25] Furthermore, 2-oxoamides based on γ-amino acids inhibit Group VIA phospholipase A2 and exhibit interesting in vivo anti-inflammatory and analgesic activity.[26]

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1. The FTIR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg.

2-Iodoaniline (**1a**) and amino acid esters were purchased from Aldrich. The other substituted 2-iodoanilines (**1b**,[27] **1c**,[27] **1d**,[27] **1e**,[28] **1f**[29]) were synthesised according to the known procedures.

4.2. Aminocarbonylation experiments with 2-iodoaniline derivatives

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1 mmol iodo substrate (**1a–f**) and 0.5 ml triethyl amine were dissolved in DMF (10 ml) under argon in a 100 ml autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurised to 100 bar with carbon monoxide. The reaction was conducted for 140 h upon stirring at 50 °C. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and washed with water (20 ml). The organic phase was thoroughly washed twice with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml), dried over Na_2SO_4 and concentrated to powder-like crystalline material in case of **2a** and **2b**. Due to low solubility of the substituted dianthranilides (**3c–f**), they have been crystallised mainly from the catalytic mixture and washed with ethanol.

4.3. Aminocarbonylation experiments of 2-iodoaniline derivatives with *tert*-butylamine

In a typical experiment, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 1 mmol iodo substrate (**1a–f**), *tert*-butylamine (0.53 ml, 5 mmol) and 0.5 ml triethyl amine were dissolved in DMF (10 ml) under argon. The homogeneous yellow solution was transferred into a 100 ml autoclave and it was pressurised to 40 bar with carbon monoxide. The reaction was conducted for 20 h upon stirring at 50 °C. A sample of this solution was immediately analysed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and washed with water (20 ml). The organic phase was thoroughly washed twice with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), brine (20 ml), dried over Na_2SO_4 and concentrated to a yellow waxy material or a thick oil. Chromatography (silica, chloroform, than chloroform/ethanol=1:1) yielded the desired compounds as yellow solids.

4.4. Characterisation of the products

4.4.1. 2-(2′-Amino-phenyl)-benzo[*d*][1,3]oxazin-4-one (2a). ^{1}H NMR ($CDCl_3$) δ: 8.21 (dd, 7.9 Hz, 0.9 Hz, 1H); 8.10 (dd, 8.4 Hz, 1.4 Hz, 1H); 7.85 (dt, 7.7 Hz, 1.4 Hz, 1H); 7.57 (d, 8.0 Hz, 1H); 7.45 (t, 7.9 Hz, 1H); 7.26 (dt, 7.9 Hz, 1.4 Hz, 1H); 6.73 (m, 2H); 6.42 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ: 159.5; 158.0; 149.8; 146.6; 136.4; 133.8; 129.7; 128.7; 127.9; 126.3; 116.7; 116.5; 110.1. IR (KBr, cm^{-1}): 3439, 3309, 1750, 1742, 1625, 1593, 1550, 1473. MS (*m*/*z*/rel int.): 238 (M^+)/100; 194/17; 120/86; 92/51; 65/30. Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.25): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.77; H, 4.43; N, 11.48. Yield: 74%. Isolated as pale yellow powder-like crystalline material. Mp 172 °C.

4.4.2. 2-(2′-Amino-4′-methyl-phenyl)-7-methyl-benzo[*d*]-[1,3]oxazin-4-one (2b). ^{1}H NMR ($CDCl_3$) δ: 8.00 (s, 1H); 7.88 (s, 1H); 7.55 (dd, 8.2 Hz, 1.6 Hz, 1H); 7.47 (d, 8.2 Hz, 1H); 7.07 (dd, 8.4 Hz, 1.6 Hz, 1H); 6.63 (d, 8.4 Hz, 1H); 6.25 (br s, 2H, NH_2); 2.46 (s, 3H, CH_3); 2.27 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 159.7; 157.4; 147.3; 144.4; 138.0; 137.8; 134.6; 129.2; 128.3; 126.2; 117.0; 116.5; 110.2; 21.4; 20.2. IR (KBr, cm^{-1}): 3453 (br, diffuse), 1738, 1629, 1620, 1592, 1556, 1492. MS (*m*/*z*/rel int.): 266 (M^+)/100; 222/12; 134/47; 106/28; 77/27. Anal. Calcd for $C_{16}H_{14}N_2O_2$ (266.30): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.52; N, 10.25. Yield: 85%. Isolated as pale yellow powder-like crystalline material. Mp 191–193 °C.

4.4.3. 2,8-Dichloro-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3c). ^{1}H NMR (DMSO-d_6) δ: 8.30 (s, 2H, Ar-H); 7.30 (d, 8 Hz, 2H, Ar-H); 6.90 (d, 8 Hz, 2H, Ar-H); 6.75 (br s, 2H, CON*H*). IR (KBr, cm^{-1}): 3451 (weak, diffuse), 1680, 1618, 1601, 1492. MS (*m*/*z*/rel int.): 306, 308, 310 (M^+)/15, 10, 2; 153/54; 73/100; 44/67. Anal. Calcd for $C_{14}H_8N_2O_2Cl_2$ (307.14): C, 54.75; H, 2.63; N, 9.12. Found: C, 54.53; H, 2.87; N, 9.01. Yield: 78%. Isolated as yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.4. 2,8-Dibromo-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3d). ^{1}H NMR (DMSO-d_6) δ: 7.82 (s, 2H, Ar-H); 7.30 (d, 8 Hz, 2H, Ar-H); 6.62 (d, 8 Hz, 2H, Ar-H); 6.50 (br s, 2H, CON*H*). IR (KBr, cm^{-1}): 3451 (weak, diffuse), 1681, 1612, 1598, 1506, 1487. MS (*m*/*z*/rel int.): 394, 396, 398 (M^+)/28, 55, 27; 197, 199/100, 99; 171/53. Anal. Calcd for $C_{14}H_8N_2O_2Br_2$ (396.04): C, 42.46; H, 2.04; N, 7.07. Found: C, 42.20; H, 1.95; N, 6.89. Yield: 80%. Isolated as yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.5. 2,8-Dicyano-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3e). ^{1}H NMR (DMSO-d_6) δ: 8.55 (s, 2H, Ar-H); 7.40 (d, 8 Hz, 2H, Ar-H); 7.11 (s, 2H, CON*H*); 6.69 (d, 8 Hz, 1H, Ar-H). IR (KBr, cm^{-1}): 3455, 3345, 2214, 1621, 1588, 1497. MS (*m*/*z*/rel int.): 288 (M^+)/16; 145/100; 117/29. Anal. Calcd for $C_{16}H_8N_4O_2$ (288.27): C, 66.67; H, 2.80; N, 19.44. Found: C, 66.50; H, 2.94; N, 19.17. Yield: 77%. Isolated as pale yellow powder-like crystalline material. Mp >330 °C (decomposed).

4.4.6. 2,8-Dinitro-5*H*,11*H*-dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (3f). ^{1}H NMR (DMSO-d_6) δ: 8.68 (s, 2H, Ar-H); 7.94 (d, 8 Hz, 2H, Ar-H); 6.86 (br s, 2H, CON*H*); 6.73 (d, 8 Hz, 2H, Ar-H). IR (KBr, cm^{-1}): 3440 (br, diffuse), 1653, 1648, 1622, 1455, 1399. MS (*m*/*z*/rel int.): 382 (M^+)/15; 368/6; 256/12; 213/14; 174/28; 129/35; 97/50; 57/88; 44/93; 43/100. Anal. Calcd for $C_{14}H_8N_4O_6$ (328.24): C, 51.23; H, 2.46; N, 17.07. Found: C, 51.11; H, 2.63; N, 16.87. Yield: 85%. Isolated as orange powder-like crystalline material. Mp >330 °C (decomposed).

4.4.7. *N*-*tert*-Butyl-(2-amino-phenyl)-glyoxylamide (5a). ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 8.0 Hz, 1H, Ar-H); 7.18 (d, 8 Hz, 1H, Ar-H); 6.65 (br s, 1H, CON*H*); 6.50–6.60 (m, 2H, Ar-H); 6.32 (br s, 2H, N*H*$_2$); 1.38 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.0; 163.5; 151.8; 135.0; 133.4; 116.3; 115.0; 113.4; 51.0; 27.8. IR (KBr, cm^{-1}): 3440 (br, diffuse), 1693, 1642. MS (*m*/*z*/rel int.): 220 (M^+)/15; 120/100; 93/22; 92/23. Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.56; H, 7.60; N, 12.61. Yield: 78%. Isolated as pale brown crystalline material. Mp 155–157 °C.

4.4.8. *N*-*tert*-Butyl-(2-amino-5-methyl-phenyl)-glyoxylamide (5b). ^{1}H NMR ($CDCl_3$) δ: 8.13 (s, 1H, Ar-H); 7.10 (d, 8 Hz, 1H, Ar-H); 6.62 (br s, 1H, CON*H*); 6.55 (d, 8 Hz, 1H, Ar-H); 6.10 (br s, 2H, N*H*$_2$); 2.20 (s, 3H, CH_3); 1.42 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.1; 163.6; 150.4; 137.3; 133.4; 125.1; 116.9; 114.5; 51.6; 28.5. IR (KBr, cm^{-1}): 3480, 3345 (br, diffuse), 1698, 1652, 1602. MS (*m*/*z*/rel int.): 234 (M^+)/15; 134/100; 107/18; 106/22. Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.30): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.40; H, 7.83; N, 11.77. Yield: 72%. Isolated as pale brown crystalline material. Mp 165 °C.

4.4.9. *N*-*tert*-Butyl-(2-amino-5-chloro-phenyl)-glyoxylamide (5c). ^{1}H NMR ($CDCl_3$) δ: 8.45 (s, 1H, Ar-H); 7.20 (d, 8 Hz, 1H, Ar-H); 6.70 (br s, 1H, CON*H*); 6.58 (d, 8 Hz, 1H, Ar-H); 6.25 (br s, 2H, N*H*$_2$); 1.40 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$) δ: 190.2; 162.4; 151.2; 138.3; 136.2; 118.6; 115.7; 107.2; 51.7; 28.4. IR (KBr, cm^{-1}): 3490, 3350 (br, diffuse), 1700, 1655, 1605. MS (*m*/*z*/rel int.): 254(256) (M^+)/15(5); 154(156)/100(34); 127/20. Anal. Calcd for $C_{12}H_{15}N_2O_2Cl$ (254.72): C, 56.59; H,

5.94; N, 11.00. Found: C, 56.41; H, 5.73; N, 10.81. Yield: 80%. Isolated as pale brown crystalline material. Mp 169–171 °C.

4.4.10. *N*-*tert*-Butyl-(2-amino-5-bromo-phenyl)-glyoxylamide (5d). ^{1}H NMR ($CDCl_3$) δ: 8.62 (s, 1H, Ar-H); 7.33 (d, 8 Hz, 1H, Ar-H); 6.70 (br s, 1H, CONH); 6.52 (d, 8 Hz, 1H, Ar-H); 6.25 (br s, 2H, NH_2); 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.8; 162.6; 150.9; 135.9; 133.1; 120.5; 118.3; 114.9; 51.8; 28.4. IR (KBr, cm^{-1}): 3490, 3350 (br, diffuse), 1690, 1650, 1611. MS (*m*/*z*/rel int.): 300(298) (M^+)/27(26); 200(198)/96(95); 57/100. Anal. Calcd for $C_{12}H_{15}N_2O_2Br$ (299.17): C, 48.18; H, 5.05; N, 9.36. Found: C, 48.05; H, 5.22; N, 9.17. Yield: 83%. Isolated as brown crystalline material. Mp 187–189 °C.

4.4.11. *N*-*tert*-Butyl-(2-amino-5-cyano-phenyl)-glyoxylamide (5e). ^{1}H NMR ($CDCl_3$) δ: 8.95 (s, 1H, Ar-H); 7.42 (d, 8 Hz, 1H, Ar-H); 7.22 (s, 1H, CONH); 6.70 (br s, 2H, NH_2); 6.62 (d, 8 Hz, 1H, Ar-H); 1.43 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.6; 161.8; 154.4; 140.5; 137.3; 119.0; 117.6; 114.1; 51.9; 28.4. IR (KBr, cm^{-1}): 3480, 3340 (br, diffuse), 2240, 1700, 1652, 1605. MS (*m*/*z*/rel int.): 245 (M^+)/20; 145/65; 118/94; 57/100. Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.55; H, 6.37; N, 16.97. Yield: 68%. Isolated as pale brown crystalline material. Mp 170–171 °C.

4.4.12. *N*-*tert*-Butyl-(2-amino-5-nitro-phenyl)-glyoxylamide (5f). ^{1}H NMR ($CDCl_3$) δ: 9.60 (s, 1H, Ar-H); 8.13 (d, 8 Hz, 1H, Ar-H); 7.05 (br s, 2H, NH_2); 6.80 (br s, 1H, CONH); 6.70 (d, 8 Hz, 1H, Ar-H); 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 188.9; 161.7; 156.1; 137.1; 132.3; 130.2; 117.0; 112.5; 52.0; 28.4. IR (KBr, cm^{-1}): 3440 (br, diffuse), 1690, 1653. Anal. Calcd for $C_{12}H_{15}N_3O_4$ (265.27): C, 54.33; H, 5.70; N, 15.84. Found: C, 54.20; H, 5.88; N, 15.67. Yield: 86%. Isolated as orange crystalline material. Mp 219 °C.

4.4.13. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-glycinate (7a). ^{1}H NMR ($CDCl_3$) δ: 8.20 (d, 8 Hz, 1H, Ar-H); 7.40 (t, 8 Hz, 1H, Ar-H); 6.62–6.74 (m, 3H, Ar-H+CONH); 6.35 (br s, 2H, NH_2); 4.18 (d, 5.6 Hz, 2H); 3.71 (s, 3H, OCH_3). MS (*m*/*z*/rel int.): 236 (M^+)/21; 208/6; 120/100; 92/28. Anal. Calcd for $C_{11}H_{12}N_2O_4$ (236.23): C, 55.93; H, 5.12; N, 11.86. Found: C, 55.80; H, 5.31; N, 11.69. Yield: 46%. Isolated as waxy yellow material.

4.4.14. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-alaninate (7a′). ^{1}H NMR ($CDCl_3$) δ: 8.30 (d, 8 Hz, 1H, Ar-H); 7.43 (t, 8 Hz, 1H, Ar-H); 6.60–6.72 (m, 3H, Ar-H+CONH); 6.23 (br s, 2H, NH_2); 4.60 (qi, 7.5 Hz, 1H, $CHCH_3$); 3.71 (s, 3H, OCH_3); 1.45 (d, 7.5 Hz, 3H, $CHCH_3$). ^{13}C NMR ($CDCl_3$) δ: 188.5; 172.5; 163.3; 151.7; 136.0; 134.1; 132.0; 116.7; 116.0; 52.5; 48.0; 18.0. IR (KBr, cm^{-1}): 3480, 3370 (br, diffuse), 1745, 1688, 1632. MS (*m*/*z*/rel int.): 250 (M^+)/17; 120/100; 92/20. Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.30; H, 5.81; N, 10.95. Yield: 48%. Isolated as waxy yellow material.

4.4.15. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-valinate (7a″). ^{1}H NMR ($CDCl_3$) δ: 8.25 (d, 8 Hz, 1H, Ar-H); 7.42 (t, 8 Hz, 1H, Ar-H); 6.65–6.75 (m, 3H, Ar-H+CONH); 6.34 (br s, 2H, NH_2); 4.50 (dd, 8.2 Hz, 5.2 Hz, 1H, NHCH); 3.68 (s, 3H, OCH_3); 2.20 (m, 1H, $CH(CH_3)_2$); 0.87 (d, 6.8 Hz, 3H, CH_3); 0.84 (d, 6.8 Hz; 3H, CH_3). MS (*m*/*z*/rel int.): 278 (M^+)/10; 120/100; 92/21. Anal. Calcd for $C_{14}H_{18}N_2O_4$ (278.31): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.32; H, 6.76; N, 10.02. Yield: 48%. Isolated as brown powder-like crystalline material. Mp 121–123 °C.

4.4.16. Methyl *N*-{(2′-amino-phenyl)glyoxyloyl}-prolinate (9a). ^{1}H NMR ($CDCl_3$) δ: 7.70 (d, 8 Hz, 1H, Ar-H); 7.23 (t, 8 Hz, 1H, Ar-H); 6.58–6.70 (m, 2H, Ar-H); 6.35 (br s, 2H, NH_2); 4.60 (m, 1H, $CHCOOCH_3$); 3.76 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.2; 172.0; 165.3; 152.0; 136.0; 133.8; 132.0; 116.9; 116.2; 58.0; 52.4; 47.3; 19.3; 14.5. IR (KBr, cm^{-1}): 3480, 3340 (br, diffuse), 1726, 1656. MS (*m*/*z*/rel int.): 276 (M^+)/10; 120/100; 92/20. Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.98; N, 10.02. Yield: 68%. Isolated as yellow powder-like crystalline material. Mp 143 °C.

4.4.17. Methyl *N*-{(2′-amino-5′-methyl-phenyl)glyoxyloyl}-prolinate (9b). ^{1}H NMR ($CDCl_3$) δ: 7.50 (s, 1H, Ar-H); 7.13 (d, 8 Hz, 1H, Ar-H); 6.58 (d, 8 Hz, 1H, Ar-H); 6.15 (br s, 2H, NH_2); 4.63 (m, 1H, $CHCOOCH_3$); 3.80 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 2.24 (s, 3H, $ArCH_3$); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.3; 171.9; 165.8; 149.8; 137.4; 133.0; 125.5; 116.8; 113.4; 58.0; 52.3; 47.0; 24.6; 20.2. IR (KBr, cm^{-1}): 3490, 3370 (br, diffuse), 1776, 1676. MS (*m*/*z*/rel int.): 290 (M^+)/13; 134/100; 106/22. Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.32): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.01; H, 6.38; N, 9.47. Yield: 71%. Isolated as yellow crystalline material. Mp 155–157 °C.

4.4.18. Methyl *N*-{(2′-amino-5′-chloro-phenyl)glyoxyloyl}-prolinate (9c). ^{1}H NMR ($CDCl_3$) δ: 7.70 (s, 1H, Ar-H); 7.23 (d, 8 Hz, 1H, Ar-H); 6.62 (d, 8 Hz, 1H, Ar-H); 6.35 (br s, 2H, NH_2); 4.63 (m, 1H, $CHCOOCH_3$); 3.82 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 192.5; 171.9; 165.0; 150.3; 136.0; 132.4; 128.4; 120.8; 118.4; 58.3; 52.2; 47.0; 29.1; 24.4. IR (KBr, cm^{-1}): 3480, 3355 (br, diffuse), 1772, 1674. MS (*m*/*z*/rel int.): 312(310) (M^+)/3(1); 128/100. Anal. Calcd for $C_{14}H_{15}N_2O_4Cl$ (310.74): C, 54.11; H, 4.87; N, 9.02. Found: C, 54.23; H, 4.98; N, 9.17. Yield: 65%. Isolated as yellow crystalline material. Mp 155–156 °C.

4.4.19. Methyl *N*-{(2′-amino-5′-nitro-phenyl)glyoxyloyl}-prolinate (9f). ^{1}H NMR ($CDCl_3$) δ: 8.60 (d, 1.4 Hz, 1H, Ar-H); 8.03 (dd, 1.4 Hz, 8 Hz, 1H, Ar-H); 7.3 (br s, 2H, NH_2); 6.73 (d, 8 Hz, 1H, Ar-H); 4.61 (m, 1H, $CHCOOCH_3$); 3.82 (s, 3H, OCH_3); 3.40–3.50 (m, 2H, NCH_2); 1.9–2.3 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$) δ: 192.1; 171.7; 164.2; 156.0; 137.1; 131.4; 131.0; 117.5; 112.0; 58.8; 52.6; 47.0; 29.1; 24.1. IR (KBr, cm^{-1}): 3430, 3300 (br, diffuse), 1722, 1654. MS (*m*/*z*/rel int.): 321 (M^+)/2; 253/9; 128/100. Anal. Calcd for $C_{14}H_{15}N_3O_6$ (321.29): C, 52.34; H, 4.71; N, 13.08. Found: C, 52.22; H, 4.78; N, 13.19. Yield: 58%. Isolated as red-brown powder-like crystalline material. Mp 188–190 °C.

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Synthesis and new rearrangements of 4-isoxazolin-4,5-dicarboxylic acid derivatives

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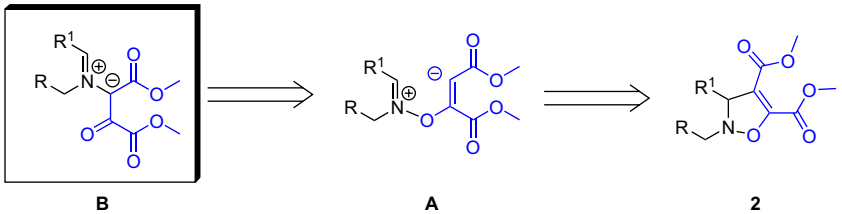
Abstract—Acyclic nitrones react with dimethyl acetylenedicarboxylate (DMAD) to give stable isoxazolines, from which the ones that contain electron-donating aromatic rings at the C3 position (R^1) were shown to undergo unprecedented fragmentation at room temperature, giving the R^1-aldehyde and inseparable product mixtures, probably due to the formation of highly reactive species such as iminocarbenes. Attempts to convert the isoxazolines to the corresponding stable azomethine ylides, by refluxing in toluene, again led to the same product mixtures as above (e.g., the room temperature decomposition). Isoxazolines when reacted with methoxide at room temperature afforded highly functionalised diastereomeric mixtures. Also, isoxazolines, when reacted with propylamine, gave the corresponding amides regioselectively, all of which were more stable than the parent isoxazolines.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and the scope of targets that can be prepared by this chemistry. In this context, nitrones are the most useful through their ability to generate nitrogen- and oxygen-based functionalities from the cycloaddition reactions.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with a variety of dipolarophiles[3] are bicyclic compounds with potentially interesting biological activities. On the other hand, they are a source of new heterocyclic compounds via interesting ring-opening reactions.[4] Previously we reported the synthesis of stable adducts of 3-imidazolin-3-oxides with dimethyl acetylenedicarboxylate (DMAD)[3d,e] and 3-phenylpropanoic acid alkyl esters.[3f] Thermally and base-induced ring-opening reactions of these adducts were demonstrated.

In a recent report from our laboratory, we described the utility of isoxazolo[3,2-*a*]isoquinolines as stable azomethine ylides.[3h] The substituent effects observed in this rearrangement prompted us to propose a mechanism, which did not involve the largely accepted intermediate, acylaziridine.[5] The way involves scission of the C3–C4 bond to give intermediates **A**, which rearrange to **B** (see Scheme 1). To assess the scope of this reaction for the synthesis of acyclic azomethine ylides **B**, we developed the retrosynthetic analysis described in Scheme 1. This would first require the preparation of *N*-benzyl(methyl)-*C*-aryl nitrones **1**. This would then be subjected to the cycloaddition with DMAD to give isoxazolines **2**. It was envisaged that the rearrangements of isoxazolines **2** would produce azomethine ylides **B**. It is well known that nitrones generally react with alkynes to give unstable adducts. However, those which are stable can be subjected to rearrangements under thermal conditions. The synthesis and rearrangements of the alkyne adducts of some nitrones have been reviewed.[1a,5] 4,5-Dihydroimidazole *N*-oxides undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles and the cycloadducts were shown to convert into the corresponding ene-1,1-diamines.[6] There is still a large interest for



Scheme 1. Retrosynthetic analysis of acyclic azomethine ylides **B**.

Keywords: Dipolar cycloaddition; Nitrones; Acyclic azomethine ylides; 4-Isoxazolines; Pyrrole derivative; 1*H*-Pyrrole-3-carboxylic acid methyl ester; Rearrangement.
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4-isoxazolines due to their biological activities[7a] and as a source of interesting rearrangements.[7b,c]

2. Results and discussion

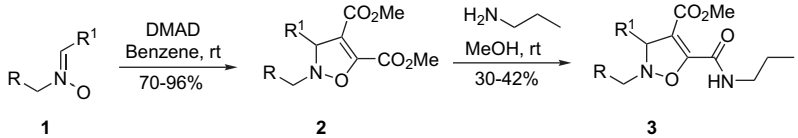
Nitrones **1a–f** were prepared in moderate yields (50–75%) according to the methods reported[8] and their geometry was proved to be (*Z*) by NOESY 1D experiments as the irradiation of benzylic methylene (or the methyl in the case of **1f**) gave enhancements for the imine hydrogens' signals. The reaction of nitrones **1a–e** with DMAD was then investigated in benzene at room temperature. This gave the corresponding isoxazolines **2** in good yields (70–96%) (Scheme 2). Isoxazolines **2** were characterised by spectroscopy as soon as purified by column chromatography.

The IR spectra of isoxazolines **2** have similar C=O and C=C bond profiles as the adducts of imidazolin-3-oxides or 3,4-dihydroisoquinolin-2-oxides with DMAD. The absorption at 1750 cm^{-1} was assigned to the C=O at C5. The characteristic ^{13}C NMR assignments for the C=C bonds of the isoxazolines **2** are ca. 107 and 156 ppm for C4 and C5, respectively. The C3 carbon signal appears about 70 ppm.

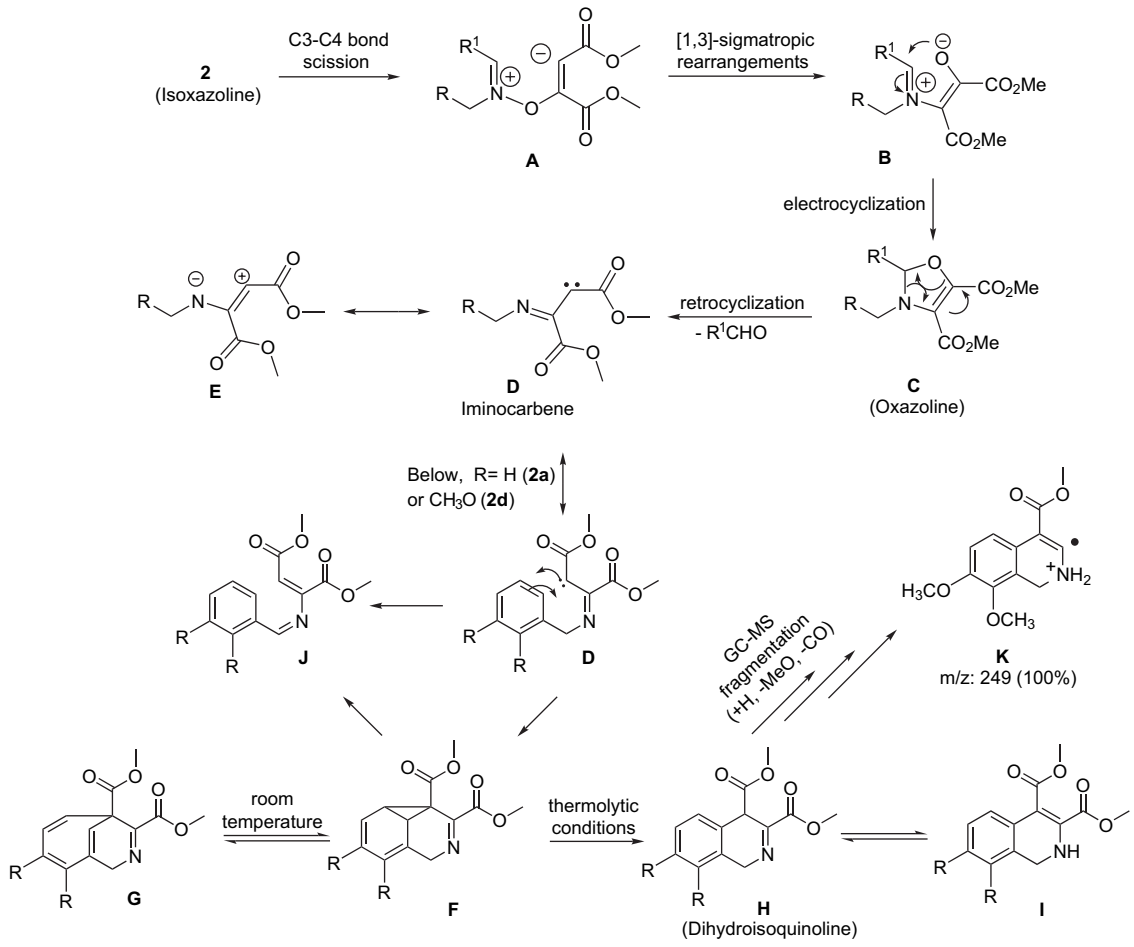
Isoxazolines **2** were stable in the condensed phase for prolonged periods of time (remained unchanged for months in a refrigerator). However, when kept in solution at 20 °C for two weeks, some decomposition was observed for **2a** and **2b** (50% and 75%, respectively). On the other hand, **2d** was fully decomposed. Surprisingly, **2c** and **2e** were stable within this period of time. This observation was in good agreement with those of isoxazolo[3,2-*a*]isoquinolines reported.[3h] It seems that the driving force for the rearrangements of simple isoxazolines **2** is the scission of the C3–C4 bond, as in the case of isoxazolo[3,2-*a*]isoquinolines. This gives rise to the formation of zwitterion **B**, as depicted in Scheme 1. However, the differences begin here. In all of the cases studied, one of the decomposition products of isoxazoline **2** was an aldehyde derived from the R^1 at the C3 position of **2**. The probable mechanism for the conversion of isoxazoline **2** into the corresponding R^1-aldehyde is depicted in Scheme 3 and could be rationalised as follows: the initial C3–C4 bond scission gives zwitterions **A**. That electron-donating groups favour the rearrangement supports this assumption. The 1,3-sigmatropic rearrangement of **A** could produce the iminium enolate **B**, the electrocyclization of which gives oxazoline **C**. The retrocyclization of the latter could produce the R^1-aldehyde and an extremely reactive intermediate, like iminocarbene **D** which will serve as a new dipole **E** isomeric with the corresponding azomethine ylide. Although the use of in situ formed oxazolines as precursors of in situ formed azomethine ylides is known,[9] conversion of isoxazoline **2** into the corresponding R^1-aldehyde and probable isoazomethine ylide via oxazoline is reported for the first time.

Since iminocarbene **D** is a very reactive intermediate, intramolecular carbene insertion would occur to generate products, such as **H** (or **I**). This became evident when **2a** was refluxed in dichloroethane. Although a complex mixture was formed, the ^1H NMR analysis indicated two doublets at 4.29 (1H, d, J=16.0) and 4.67 (1H, d, J=16.0) and a singlet at 5.26 ppm. These are characteristic peaks for dimethyl 1,4-dihydroisoquinoline-3,4-dicarboxylate **H**, corresponding to the C-1 and C-4 hydrogens. The attempts to separate the mixture by column chromatography resulted in a much more complex mixture, probably due to the known disproportionations of the dihydroisoquinolines.[10] Further experiments to trap the in situ formed iminocarbene **D** (or isoazomethine ylides) are underway. However, we were lucky to detect the first examples of products pointing to the formation of proposed intermediate **H** (or **I**). Subjecting the isoxazoline **2d** to GC–MS analysis at 200 °C injection temperature clearly revealed that the fragmentation occurs to give the corresponding R^1-aldehyde (isolated in a separate experiment) and a main product **K**, with an *m*/*z* value of 249 amu (100%). This base peak is easily deduced, with the loss of MeO and CO, from the molecular ion of dihydroisoquinoline **H**. Under thermolytic conditions, the formation of **H** (or **F**) is more probable and could readily result from norkaradine **F**, a product of intramolecular carbene insertion **D** and probably is in equilibrium with tropilidene **G** at room temperature. The presence of fragment peaks in the mass spectrum of a minor product implies that the product **J** also formed. These are all summarised in Scheme 3.

The treatment of isoxazolines **2** with methoxide in methanol at room temperature for 28 h gave complex mixtures. However, in the case of **2a**, highly functionalized diastereomeric compounds (**10** and **11**) were successfully isolated as 1:1 mixture upon chromatography (Scheme 4). These compounds are pyrrole derivatives and could be further elaborated to give some biologically active pyrroles. 2-Phenylpyrrolidines are nicotine analogues.[11a] Well-known 1β-methylcarbapenem antibiotics having a (3*S*,5*S*)-*cis*-disubstituted pyrrolidine ring as the C-2 side chain, such as meropenem,[11b] S-4661,[11c] have a broad antibacterial spectrum covering Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. In contrast, J-114.870, a novel carbapenem, shows ultra-broad antibacterial activity against MRSA as well as *P. aeruginosa*, which contains (3*S*,5*R*)-*trans*-disubstituted pyrrolidine ring C-2 side chain.[11d] (−)-Codonopsinine and (−)-codonopsine (Fig. 1) are two 2-arylpyrrolidine alkaloids isolated from *Codonopsis clematidea*[12] in 1969. They are attractive for both synthetic and medicinal chemists due to the challenging penta-substituted pyrrolidine nucleus and varied biological activities as antibiotics and as antihypertensive agents without any effects

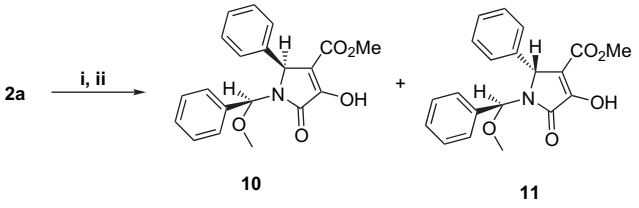


Scheme 2. Synthesis of 4-isoxazolines **2** and amides **3**. Reagents and conditions: (a) R=Ph, R^1=Ph; (b) R=Ph, R^1=2,3-$(MeO)_2$Ph; (c) R=Ph, R^1=2-NO_2Ph; (d) R=2,3-$(MeO)_2$Ph, R^1=2,3-$(MeO)_2$Ph; (e) R=2,3-$(MeO)_2$Ph, R^1= 2-NO_2Ph; (f) R=H, R^1=3,4-$(MeO)_2$Ph; (g) R=2,3-$(MeO)_2$Ph, R^1=Ph.



Scheme 3. Rearrangements of 4-isoxazoline **2** to an R^1-aldehyde and a very reactive iminocarbene **D**, which gives intramolecular cyclisation.

on the central nervous system.[13] The structures of **10** and **11** were elucidated using elemental and detailed NMR analysis (details are given in Section 4).



Scheme 4. Reagents: (i) MeO^-, MeOH, rt, 28 h; (ii) H^+.

The formation of **10** and **11** could be rationalised in the following way and summarised in Scheme 5: a methoxide-induced elimination of **2a** gives resonance stabilised imine enolate **4**. This then, itself or its protonated form **5**, reacts with methoxide to give the diastereoisomers **6** and **7**. The intramolecular cyclisation of **6** and **7** finally gives phenyl-2,5-dihydro-1*H*-pyrrol-3-olates **8** and **9**, the acidification of which affords the diastereoisomers **10** and **11**.

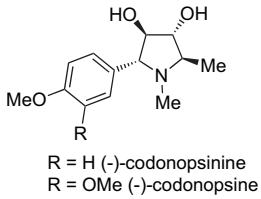
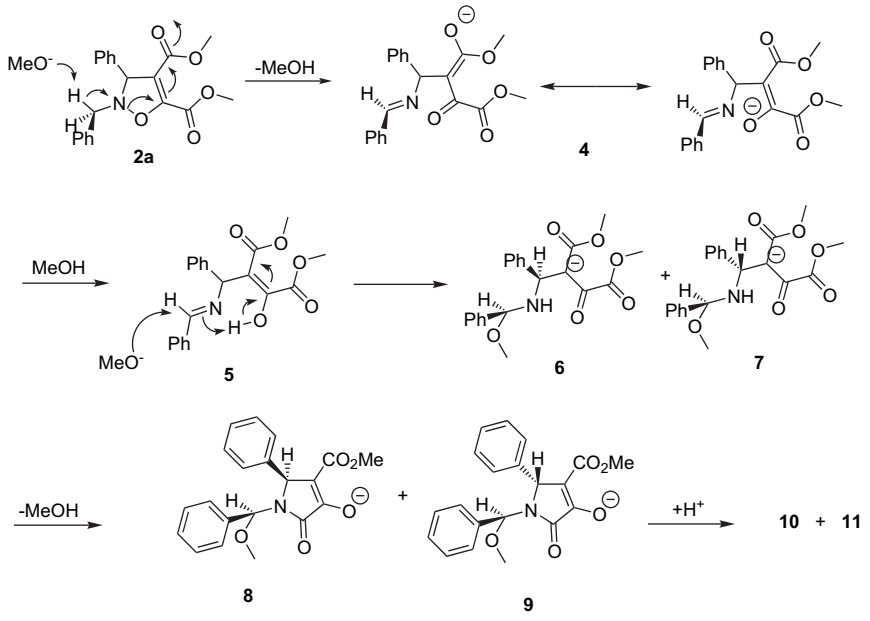


Figure 1. Structures of (−)-codonopsinine and (−)-codonopsine.

The treatment of isoxazolines **2** with propylamine in methanol at room temperature led to selective formation of amides **3** in low yields (30–42%), as depicted in Scheme 2. Selective amide formation was supported by the absence of both the IR absorption peak at 1750 cm^{-1} (corresponds to the ester C═O at the C-5 of **2**) and the ^1H NMR signals at 3.91 ppm (corresponds to the ester CH_3O at the C-5 of **2**). The enhanced reactivity of C-5 carbonyl was similar to those observed in our chemoselective alkyl bromoacetate–Zn mediated transesterification of imidazoisoxazolines[14] and chemoselective alkoxyzinc salts catalysed transesterifications.[15] This preference can be explained in terms of the formation of a hydrogen bonded pre-complex between the amine and the isoxazoline, where the nucleophile ($^nPrNH_2$) and the electrophilic C═O centre are orientated in a geometrically favourable position, as depicted in Figure 2.

Amides **3** were much more stable than their precursors and could be stored at room temperature for months without any significant decomposition. The replacement of the methoxy group by propylamine at the C5 position decreases the electron-withdrawing capacity of the ester carbonyl by resonance effect. This is another important factor determining the formation of zwitterion **B** shown in Scheme 1.



Scheme 5. Mechanism for the rearrangement of isoxazolines **2** into diastereoisomers **10** and **11**.

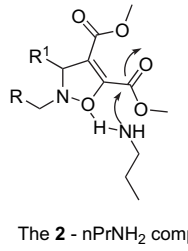
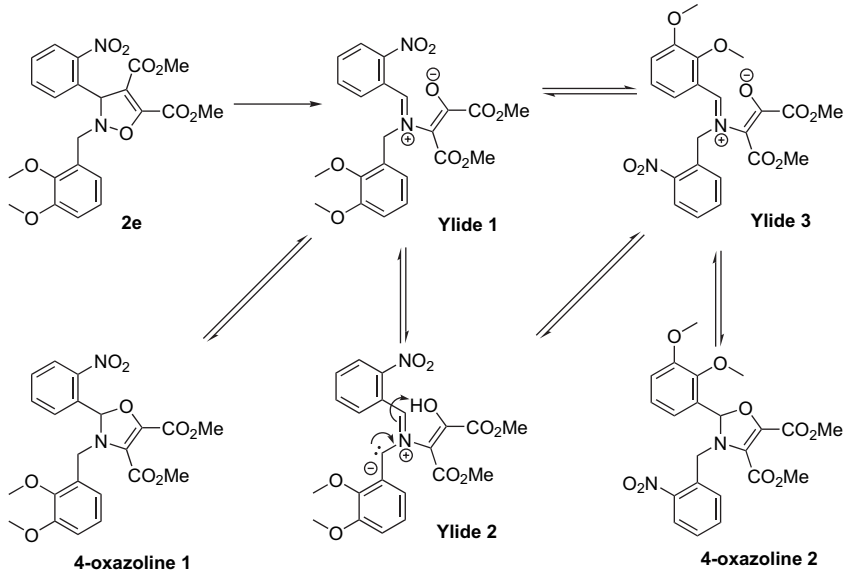


Figure 2. Complex formation between **2** and propylamine, which would lead to selective amide formation **3**.

Although stable at room temperature, amide **3b**, when refluxed in THF, again led to the formation of R^1-aldehyde (2,3-dimethoxybenzaldehyde). Thermal treatment of amide **3d** led to similar results, as above and with those of **2d**, where R^1-aldehyde (2,3-dimethoxybenzaldehyde) and base peak formations with an *m*/*z* value of 249 amu were detected by GC–MS. This time, the loss of $PrNH_2$ and CO (in the case of **3d**), instead of MeO and CO (in the case of **2d**), would account for the formation of base peak (for detailed discussion, refer to Scheme 3).

The thermolysis of asymmetric isoxazoline **2e** in the injection of GC–MS led to the formation of two different aldehydes, the expected R^1-aldehyde (2-nitrobenzaldehyde) and the unexpected R-aldehyde (2,3-dimethoxybenzaldehyde) in the 1:5 ratio, respectively. The other two peaks in the chromatogram corresponded to the products obtained from cyclisations of the minor carbene (*N*-2,3-dimethoxybenzyliminocarbene) and the main carbene (2-nitrobenzyliminocarbene). The rationale for these results is presented in Scheme 6. Isoxazoline **2e** first rearranges to give the **ylide 1**, electrocyclization of which produces **4-oxazoline 1**.



Scheme 6. Probable mechanism for the rearrangement of initially formed azomethine **ylide 1** to the thermodynamically more stable azomethine **ylide 3**.

Due to electron-deficient character of the dipolarophile (2-nitrobenzaldehyde), retrocyclization of the **4-isoxazoline 1** seems to be less favourable than the retrocyclization of **4-oxazoline 2**, where the electron-rich dipolarophile (2,3-dimethoxybenzaldehyde) is present.

How the precursor of the latter **4-oxazoline 2** is formed deserves discussion. Initially formed **ylide 1**, less stable due to the electron-withdrawing nitro group at the phenyl ring, rearranges to give isomeric **ylide 3**. The rearrangement may be assumed as a 1,3-hydride shift to give directly **ylide 3** or as intramolecular proton shift to give **ylide 2**, the concerted rearrangement of which as seen in Scheme 6 would produce the more stable **ylide 3**.

3. Conclusion

Isoxazolines **2**, prepared from the reaction of nitrones **1** with DMAD, underwent a substituent-dependent rearrangement involving consecutive C3–C4 bond scission and 1,3-sigmatropic shift to give the corresponding iminium enolates **B** (azomethine ylides). Isoxazoline amides **3** were obtained selectively and proved to be more stable at room temperature than the corresponding **2**. Electron-donating groups facilitated effectively the rearrangement process of **2**. This was in good agreement with the results we have recently reported for the formation of azomethine ylides from DMAD adducts with 3,4-dihydroisoquinolin-1-oxides.[3h] In situ formed azomethine ylides from the thermolysis of **2** and **3**, for the first time, underwent further transformations, such as electrocyclization to 4-oxazolines **C** and retrocycloaddition to an R^1-aldehyde and a reactive intermediate, iminocarbene **D**. In the case of an asymmetrical ylide, the initially formed **ylide 1** with an electron-deficient aromatic ring at the imine carbon isomerised to thermodynamically more stable one (**ylide 3**), where electron-rich aromatic ring ended up at the imine carbon. Some NMR and mass spectral data for the products of intramolecular cyclisation provided evidences for the structure to be iminocarbene **D**. However, the full elucidation of the structures of more cyclised products is required and investigation to solve this challenging problem is underway. The treatment of isoxazolines **2** with methoxide at room temperature gave a new entry to highly functionalized pyrrolidines, which could serve as precursors for the synthesis of biologically active 2-arylpyrrolidine derivatives.

4. Experimental

4.1. General

Melting points were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. 1D and 2D NMR experiments were performed on a Varian Mercury Plus 400 MHz spectrometer. Nitrones **1a–f** were prepared according to the methods we have recently reported.[8] The elemental analyses were performed on a EuroEA 3000 CHNS analyser.

4.1.1. *C*-(2,3-Dimethoxyphenyl)-*N*-2,3-dimethoxybenzylnitrone 1d. Yield 75%; white crystals; mp 122–124 °C; IR (KBr) $\nu_{C=N}$ 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s), 3.86 (3H, s), 3.80 (3H, s), 3.88 (3H, s) 5.13 (2H, s), 6.93–6.98 (2H, m), 7.05–7.11 (3H, m), 7.91 (1H, s), 8.8 (1H, dd, J=8.0, 1.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1; 56.1; 61.2; 61.7; 66.5; 113.7; 114.9; 120.9; 123.2; 124.4; 125.0; 127.5; 129.6; 147.3; 148.0; 152.1; 152.9.

Anal. Calcd for $C_{18}H_{21}NO_5$ (331.36): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.30; H, 6.41; N, 4.22.

4.2. Synthesis of 2-benzyl-3-aryl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl esters 2. General procedure

DMAD (1 mmol) was added to a solution of nitrone **1** (1 mmol) in benzene (8 mL) and the reaction mixture was stirred for 22 h in the cases of **1a**,**b**,**d**,**f** and 28 h in the cases of **1c**,**e** at room temperature. The solvent was evaporated and the residue was subjected to column chromatography over silica gel eluting with a mixture of ethyl acetate–petroleum ether.

4.2.1. 2-Benzyl-3-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2a. Yield 80%; oil; IR (KBr) $\nu_{C=O}$ 1759, 1713, $\nu_{C=C}$ 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (3H, s), 3.91 (3H, s), 4.12 (1H, d, J=13.2), 4.44 (1H, d, J=13.2), 5.23 (1H, s), 7.12–7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.6; 63.7; 72.9; 109.5; 127.5; 128.3; 128.4; 128.8; 128.8; 129.7; 134.9; 139.6; 152.1; 159.7; 162.9.

Anal. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.93; H, 5.45; N, 3.93.

4.2.2. 2-Benzyl-3-(2,3-dimethoxyphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2b. Yield 73%; oil; IR (KBr) $\nu_{C=O}$ 1750, 1710, $\nu_{C=C}$ 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (3H, s), 3.72 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.19 (1H, d, J=13.6), 4.36 (1H, d, J=13.6), 5.75 (1H, s), 6.84–6.88 (2H, m), 7.04 (1H, t, J=7.6), 7.27–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.5; 56.0; 61.0; 63.0; 67.1; 108.9; 112.7; 120.1; 124.6; 128.1; 128.6; 129.8; 132.9; 135.4; 147.2; 152.7; 152.8; 159.8; 162.8.

Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C, 63.91; H, 5.61; N, 3.39. Found: C, 63.90; H, 5.60; N, 3.42.

4.2.3. 2-Benzyl-3-(2-nitrophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2c. Yield 85%; oil; IR (KBr) $\nu_{C=O}$ 1753, 1716, $\nu_{C=C}$ 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (3H, s), 3.92 (3H, s), 4.31 (1H, d, J=14.0), 4.41 (1H, d, J=14.0), 6.21 (1H, s), 7.29–7.46 (6H, m), 7.55–7.69 (2H, m), 7.88 (1H, d, J=8.4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3; 53.7; 64.4; 67.6; 108.9; 124.7; 128.3; 128.7; 129.2; 129.7; 129.8; 133.8; 134.8; 134.9; 148.7; 153.3; 159.2; 162.2.

Anal. Calcd for $C_{20}H_{18}N_2O_7$ (398.37): C, 60.30; H, 4.55; N, 7.03. Found: C, 60.34; H, 4.57; N, 7.00.

4.2.4. 2-(2,3-Dimethoxybenzyl)-3-(2,3-dimethoxyphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2d. Yield 96%; oil; IR (KBr) $\nu_{C=O}$ 1755,

1712, $\nu_{C=C}$ 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.91 (3H, s), 4.23 (1H, d, J=13.6), 4.45 (1H, d, J=13.6), 5.81 (1H, s), 6.83–6.87 (3H, m), 6.97–7.04 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0; 53.4; 56.0; 58.3; 61.0; 61.1; 67.5; 109.2; 112.3; 112.6; 120.2; 123.1; 124.1; 124.4; 129.6; 133.1; 147.3; 148.0; 152.6; 152.8; 152.9; 159.9; 162.9.

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.47): C, 60.88; H, 5.75; N, 2.96. Found: C, 60.80; H, 5.79; N, 2.85.

4.2.5. 2-(2,3-Dimethoxybenzyl)-3-(2-nitrophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2e. Yield 70%; oil; IR (KBr) $\nu_{C=O}$ 1753, 1717, $\nu_{C=C}$ 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 3.91 (3H, s) 4.31 (1H, d, J=13.26), 4.53 (1H, d, J=13.26), 6.27 (1H, s), 6.85–6.90 (1H, m), 7.01–7.07 (2H, m), 7.41–7.45 (1H, m), 7.57–7.87 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3; 53.5; 56.0; 58.6; 61.1; 67.8; 109.3; 112.6; 122.9; 124.1; 124.7; 128.5; 129.0; 129.1; 129.8; 131.2; 133.6; 133.7; 135.0; 148.1; 153.0; 153.0; 159.3; 162.3.

Anal. Calcd for $C_{22}H_{22}N_2O_9$ (458.42): C, 57.64; H, 4.84; N, 6.11. Found: C, 57.61; H, 4.89; N, 6.09.

4.2.6. 3-(3,4-Dimethoxyphenyl)-2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2f. Yield 80%; oil; IR (KBr) $\nu_{C=O}$ 1752, 1714, $\nu_{C=C}$ 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.00 (3H, s), 3.66 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 4.77 (1H, s), 4.99 (1H, s), 6.83 (1H, d, J=8.8), 6.90–6.93 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1; 51.9; 53.3; 55.8; 55.9; 76.0; 109.8; 110.2; 111.1; 119.7; 149.1; 149.2; 150.8; 159.5; 162.7.

Anal. Calcd for $C_{17}H_{21}NO_7$ (351.35): C, 58.11; H, 6.02; N, 3.99. Found: C, 58.13; H, 6.07; N, 3.88.

4.2.7. 2-(2,3-Dimethoxybenzyl)-3-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2g. Yield 85%; oil; IR (KBr) $\nu_{C=O}$ 1750, 1706, $\nu_{C=C}$ 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (3H, s), 3.76 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 4.23 (1H, d, J=13.2), 4.35 (1H, d, J=13.2), 5.29 (1H, s), 6.86–6.88 (1H, m), 7.00–7.04 (2H, m), 7.26–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.5; 56.0; 57.9; 61.2; 73.2; 109.7; 112.5; 123.1; 124.2; 127.6; 128.3; 128.6; 128.7; 129.0; 129.8; 140.0; 148.1; 151.97; 153.0; 159.8; 162.9.

Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C, 63.91; H, 5.61; N, 3.39. Found: C, 63.94; H, 5.67; N, 3.35.

4.3. Synthesis of 2-benzyl-3-aryl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl esters 3. General procedure

Propylamine (1.5 mmol) was added to a solution of isoxazoline **2** (0.5 mmol) in methanol and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under vacuum and the product was purified by preparative TLC.

4.3.1. 2-Benzyl-3-phenyl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3a. Yield 42%; oil; IR (KBr) $\nu_{C=O}$ 1688, 1669, ν_{NH} 3283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6), 1.64 (2H, hex, J=7.6), 3.40 (2H, m), 3.63 (3H, s), 4.12 (1H, d, J=13.26), 4.46 (1H, d, J=13.26), 5.86 (1H, s), 7.13–7.16 (2H, m), 7.24–7.36 (8H, m), 9.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.5; 41.8; 52.5; 63.0; 73.4; 107.1; 127.5; 128.2; 128.3; 128.7; 128.8; 129.9; 134.7; 140.4; 156.2; 156.6; 165.9.

Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.44): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.50; H, 6.31; N, 7.40.

4.3.2. 2-Benzyl-3-(2,3-dimethoxyphenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3b. Yield 37%; oil; IR (KBr) $\nu_{C=O}$ 1688, 1669, ν_{NH} 3283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6), 1.60 (2H, hex, J=7.6), 3.34–3.48 (2H, m), 3.56 (3H, s), 3.59 (3H, s), 3.84 (3H, s), 4.16 (1H, d, J=13.2), 4.37 (1H, d, J=13.2), 5.80 (1H, s), 6.75–6.85 (2H, m), 7.00 (1H, t, J=8.0), 7.27–7.40 (5H, m), 9.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.6; 41.8; 52.6; 55.9; 60.8; 63.4; 67.5; 106.6; 112.4; 120.2; 124.4; 128.1; 128.7; 130.2; 133.7; 135.0; 147.0; 152.7; 156.7; 165.9.

Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.49): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.47; H, 6.43; N, 6.40.

4.3.3. 2-Benzyl-3-(2-nitrophenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3c. Yield 33%; oil; IR (KBr) $\nu_{C=O}$ 1694, 1678, ν_{NH} 3282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.5), 1.63 (2H, hex, J=7.5), 3.40 (2H, m), 3.56 (3H, s), 4.30 (1H, d, J=13.26), 4.42 (1H, d, J=13.26), 6.28 (1H, s), 7.22–7.75 (9H, m), 9.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.5; 41.8; 52.8; 63.8; 67.6; 107.0; 124.1; 128.4; 128.7; 129.1; 130.1; 130.3; 133.7; 134.1; 135.7; 148.5; 156.1; 157.0; 165.0.

Anal. Calcd for $C_{22}H_{23}N_3O_6$ (425.43): C, 62.11; H, 5.45; N, 9.88. Found: C, 62.10; H, 5.48; N, 9.93.

4.3.4. 2-(2,3-Dimethoxybenzyl)-3-(2,3-dimethoxyphenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3d. Yield 40%; oil; IR (KBr) $\nu_{C=O}$ 1691, 1673, ν_{NH} 3287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.2), 1.64 (2H, hex, J=7.2), 3.40 (2H, m), 3.60 (3H, s), 3.66 (3H, s), 3.78 (3H, s), 3.83 (3H, s), 4.22 (1H, d, J=13.3), 4.42 (1H, d, J=13.3), 5.86 (1H, s), 6.75–6.78 (1H, m), 6.82–6.84 (2H, m), 6.96–7.05 (3H, m), 9.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.6; 41.7; 52.5; 55.9; 56.0; 57.5; 60.9; 61.2; 68.0; 106.7; 112.4; 120.3; 123.7; 124.2; 124.4; 129.2; 133.9; 147.1; 148.1; 152.8; 152.9; 156.7; 156.9; 165.9.

Anal. Calcd for $C_{26}H_{32}N_2O_8$ (500.54): C, 62.39; H, 6.44; N, 5.60. Found: C, 62.43; H, 6.45; N, 5.65.

4.3.5. Methyl 2-(2,3-dimethoxybenzyl)-3-(2-nitrophenyl)-5-(propylcarbamoyl)-2,3-dihydroisoxazole-4-carboxylate 3e. Yield 30%; oil; IR (KBr) $\nu_{C=O}$ 1694, 1678, ν_{NH} 3280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t,

J=7.41), 1.61 (2H, hex, J=7.41), 3.34 (2H, m), 3.63 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 4.25 (1H, d, J=13.3), 4.52 (1H, d, J=13.3), 6.31 (1H, s), 6.85 (1H, m), 6.86–7.02 (2H, m), 7.37–7.77 (4H, m), 9.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.5; 41.8; 53.1; 56.0; 57.8; 61.2; 68.1; 107.0; 112.7; 123.5; 124.2; 124.3; 128.5; 129.0; 130.1; 133.6; 135.6; 148.1; 148.6; 152.9; 156.4; 157.1; 164.9.

Anal. Calcd for $C_{24}H_{27}N_3O_8$ (485.49): C, 59.37; H, 5.61; N, 8.66. Found: C, 59.39; H, 5.63; N, 8.73.

4.3.6. 2-(2,3-Dimethoxybenzyl)-3-phenyl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3g. Yield 42%; oil; IR (KBr) $\nu_{C=O}$ 1691, 1672, ν_{NH} 3280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.5), 1.63 (2H, hex, J=7.5), 3.40 (2H, m), 3.63 (3H, s), 3.76 (3H, s), 3.85 (3H, s), 4.24 (1H, d, J=12.9), 4.43 (1H, d, J=12.9), 5.35 (1H, s), 6.86 (1H, m), 7.00 (2H, m), 7.19–7.25 (5H, m), 9.69 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.5; 41.8; 52.5; 56.0; 57.0; 61.3; 73.7; 107.3; 112.4; 123.5; 124.3; 127.6; 128.2; 128.6; 128.8; 140.8; 148.1; 152.9; 156.1; 156.8; 166.0.

Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.49): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.45; H, 6.48; N, 6.31.

4.3.7. 4-Hydroxy-1-(methoxyphenylmethyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid methyl esters 10 and 11. Yield 55%; mp 132 °C; IR (KBr) $\nu_{C=O}$ 1694; 1678, ν_{OH} 3282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (3H, s, CHOMe), 3.45 (3H, s, CHOMe), 3.56 (3H, s, CO_2Me), 3.62 (3H, s, CO_2Me), 4.71 (1H, s, C-3H), 5.27 (1H, s, C-3H), 6.40 (2H, s, MeOC*H*N), 6.76–6.78 (2H, m), 6.87–6.94 (6H, m), 7.00–7.03 (3H, m), 7.22–7.29 (6H, m), 7.36–7.38 (3H, m), 9.0 (2H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, MeO, ether; 52.2, MeO, ester; 56.1, MeO, ester; 57.0, MeO, ester; 57.8, C-3; 58.4, C-3, 84.28, NCO; 84.33, N*C*O; 114.1, C-4; 114.6, C-4; 126.2; 126.5; 127.7; 127.8; 127.9; 128.0; 128.4; 128.6; 128.7; 128.8; 134.9; 135.8; 136.3; 137.7; 156.5, C-5; 156.6, C-5; 165.6, C=O, 165.7, C=O; 165.8, C=O; 165.9, C=O.

Anal. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.95; H, 5.40; N, 3.93.

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Synthesis and isomerization of *N*-α-aza-heteroaryl-β-lactams

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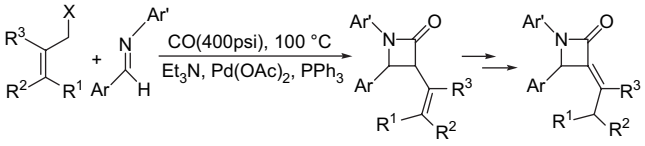
Abstract—The [2+2] carbonylative cycloaddition of *N*-α-aza-heteroaryl substituted imines with allyl bromide led partially to β-lactams, which underwent isomerization to the more stable α,β-unsaturated carbonyl compound. Pyrimidinone derivatives together with doubly unsaturated amides represent the remaining isolated products. The strong electron-withdrawing effect of the two α-aza-heterocycles linked to the nitrogen atom and to the C4 of the 2-azetidinone structure could give a ring expansion, through a 2-azetinone intermediate that affords the pyrimidinone compounds. The substituted amides, instead, should result from a ring-opening reaction of the β-lactam.

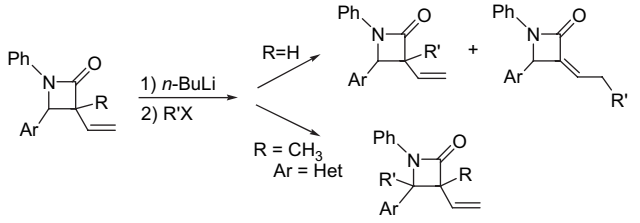
1. Introduction

β-Lactams show a wide range of pharmacological activities and synthetic routes to such compounds continue to be developed.[1–4] The use of 2-azetidinones as starting materials in organic synthesis is based on the impressive variety of transformations that can be derived from this system. For instance, Alcaide and Almendros described the selective bond cleavage and rearrangement of the β-lactam nucleus with applications in the stereocontrolled synthesis.[5] Thus, compounds such as alkaloids,[6,7] carbohydrates[8,9] and different kinds of heterocycles[10–14] have been produced from β-lactams. Recently, we reported the stereoselective synthesis of β-lactams by an improved Pd-catalyzed [2+2] carbonylative cycloaddition of allyl halides with various imines,[15] where the catalytic species involved was Pd(0)[16] (Scheme 1). Moreover, we found that the presence of an α-aza-heterocycle attached to the iminic carbon, for example, where Ar=2-benzothiazole or 2-thiazole or 2-pyridine, led partially to β-lactams having a vinylic moiety conjugated to the carbonyl group.[16] The high electron-withdrawing effect of the α-aza-heterocycle should increase the acidity of the proton linked to C3, favouring isomerization in the presence of Et_3N.



Scheme 1.

The deprotonation and the stereoselective functionalization of the C3 carbon atom of β-lactams have been also reported by us.[17] It has been shown that the deprotonation of the C4 carbon could be achieved only with a structure showing no protons at C3 and having an α-aza-heterocycle linked at C4, which increased the acidity of the directly attached hydrogen (Scheme 2).



Scheme 2.

In order to thoroughly investigate the electron-withdrawing effect of various heterocycles linked at the different positions of the β-lactam nucleus, we thought to perform, under the same conditions, the [2+2] carbonylative cycloaddition of *N*-α-aza-heteroaryl substituted imines with allyl bromide.

Keywords: β-Lactams; Pyrimidinones; Carbonylative cycloaddition; Isomerization.
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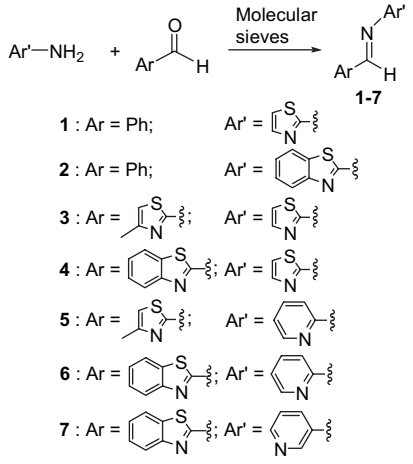
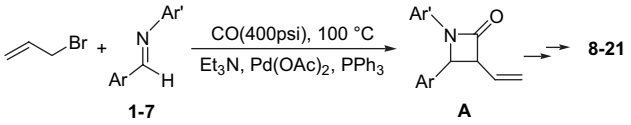
2. Results and discussion

The reacting *N*-α-aza-heteroaryl imines **1–7** were prepared by coupling reactions of the appropriate amines with the corresponding aldehydes according to the Taguchi's methodology (Scheme 3).[18]



Scheme 3.

According to previous results,[15] the [2+2] carbonylative cycloaddition of the imines **1–7** with allyl bromide under CO pressure, in the presence of Et_3N and $Pd(OAc)_2/Ph_3P$, should afford β-lactams **A** (Scheme 4).

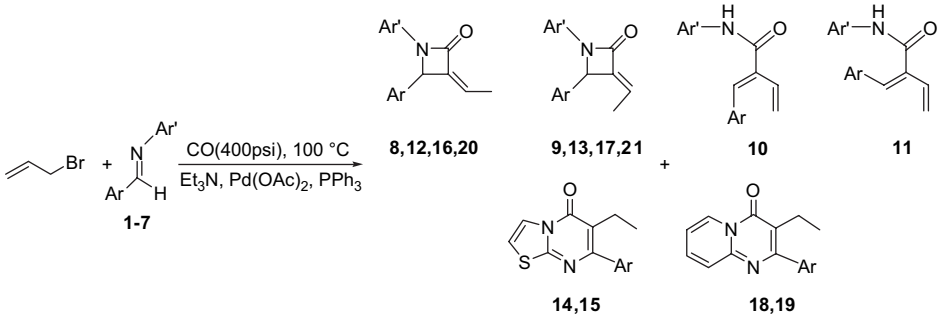


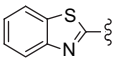
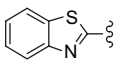
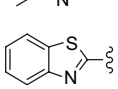
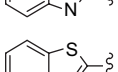
Scheme 4.

Surprisingly, such structures were not obtained but, from the reaction mixtures compounds **8–21** listed in Table 1 were isolated.

The relative configuration of the α,β-unsaturated β-lactams was assigned from their ^1H NMR spectra: the *Z* isomers displayed vinylic protons with an upfield chemical shift, whereas the *E* compounds showed a downfield chemical shift as these protons are in the deshielding region of the neighbouring carbonyl group.[19–21] The structures of compounds **10** and **11** have been assigned by ^1H NMR spectra on the basis of spectroscopic data reported in literature for analogous structures.[22] The structures of compounds **14**

Table 1. [2+2] Carbonylative cycloaddition of imines **1–7** with allyl bromide



Entry	Ar	Ar′	Total yield (%)[a]	Product distributions (%)[b]				
1	Ph		80	**8** (traces)	**9** (54)	—	**10** (24)	**11** (21)
2	Ph		85	**12** (32)	**13** (68)	—	—	—
3			97	—	—	**14** (100)	—	—
4			50	—	—	**15** (100)	—	—
5			98	**16** (traces)	**17** (traces)	**18** (99)	—	—
6			40	—	—	**19** (100)	—	—
7			30	**20** (80)	**21** (20)	—	—	—

[a] Isolated yields.
[b] Diasteromeric ratios evaluated by GC and ^1H NMR spectroscopy.

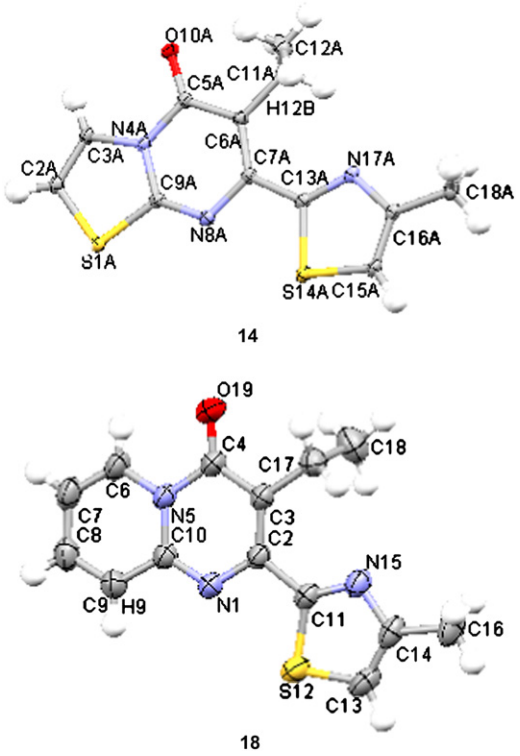
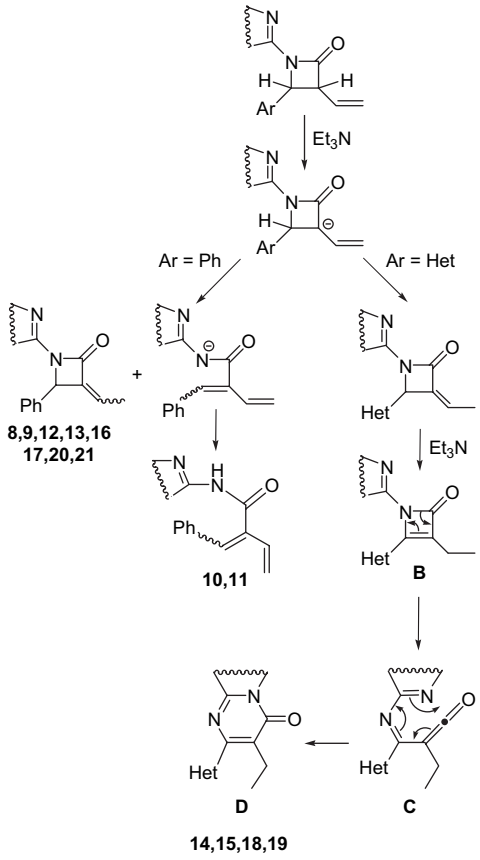


Figure 1. Molecular structure of compound **14** at 90 K, ellipsoids at 50% probability level, H atoms not to scale. Molecular structure of compound **18** at room temperature, ellipsoids at 50% probability level, H atoms not to scale.



Scheme 5.

and **18** have been assigned by X-ray[23] measurements and their molecular structures are reported in Figure 1.

The remaining structures **15** and **19** were assigned comparing the spectroscopic data with those obtained for compounds **14** and **18**.

Scheme 5 shows a possible rearrangement of the β-lactam **A**, obtained by the [2+2] carbonylative cycloaddition reaction, and leading to the compounds listed in Table 1.

Products **8**, **9**, **12**, **13**, **16**, **17**, **20** and **21** should derive from a first deprotonation of **A** at the C3, and a subsequent isomerization of the carbanion to the more stable α,β-unsaturated carbonyl compound. The generation of products **10** and **11** could be explained by a C4–N1 bond breakage in the same intermediate carbanion, which occurs under basic conditions. This latter behaviour is reported in the literature as one of the possible bond cleavages of the β-lactam nucleus.[24] The 2-azetinone **B** should result from a double isomerization: a first deprotonation at the C3 should lead to the α,β-unsaturated β-lactam, while a subsequent deprotonation at the C4 should shift the double bond inside the β-lactamic ring, affording the 2-azetinone. This behaviour could be due to the strong electron-withdrawing effect by both heterocycles directly linked to the ring. The 2-azetinone is often proposed as a short-lived intermediate,[25–28] which evolves to a ketene, for which only in few cases has it been isolated and characterized.[29,30] The high antiaromatic character of this small ring, in fact, does not confer enough thermal stability to the molecule, which rapidly leads to the ketenic form initially, and then finally to the pyrimidinonic product. The proposed relative stability of the three forms is confirmed by free energy quantum chemical calculations of the structures **B**, **C** and **D**, respectively. Calculations were performed at the 6-311G*/B3LYP level (in the gas phase).[31] According to the calculations, the ketenic structure **C** is only 5.3 kcal/mol more stable than **B**, which is strongly antiaromatic, while the stable structure **D** has a free energy 36.1 kcal/mol lower than **C**.

The transformation of **B** to the ketene **C** first, and then to the pyrimidinone **D**, could be related to the presence of two α-aza-heterocycles linked to the nitrogen atom and to the C4 of the 2-azetidinone structure, respectively. A similar rearrangement has been recently described by Alajarin and co-workers on 4-acyloxy-β-lactams resulting in a final cycle broadening, through a 2-azetinone intermediate formation and C2–N1 bond cleavage.[32] Moreover, when C4 does not link a heterocycle (Ar=Ph), the deprotonation at C3, described above, led to a ring-opening reaction of the β-lactamic systems, the cleavage of the C4–N1 bond affording the doubly unsaturated amides **10** and **11**.

3. Conclusion

In summary, we have prepared *N*-α-aza-heteroaryl β-lactams, which underwent isomerization. Novel α,β-unsaturated 2-azetidinones were prepared together with new pyrimidinone derivatives and doubly unsaturated amides. The pyrimidinone compounds seem to be produced from ring expansion

of the rearranged β-lactams through a 2-azetinone intermediate. This behaviour has been observed only for structures showing two heterocyclic moieties linked to the nitrogen atom and to the C4 carbon, respectively. The unsaturated amides are the result of a ring-opening reaction of the β-lactam systems having the heterocycle linked only to the nitrogen atom. The electron-withdrawing effect of the various heterocycles linked at the different positions of the β-lactam nucleus has been thoroughly exploited. A mechanism has been proposed through structures of different relative stabilities, confirmed by free energy quantum chemical calculations. The selective bond cleavage and the rearrangement of the β-lactam nucleus afforded novel structures of potential use in the organic synthesis of biologically and pharmacologically interesting compounds.

4. Experimental

4.1. General

THF, triethylamine, palladium(II)acetate, triphenyl-phosphine, allyl bromide, 4-formylmorpholine, 2-pyridinecarboxaldehyde, 2-aminothiazole, 2-aminopyridine, 3-aminopyridine, 4-methyl-thiazole, 2-aminothiophenol, glycolic acid and all other chemicals were of commercial grade (Aldrich) and were used without further purification. Benzaldehyde and allyl bromide of commercial grade (Aldrich), were purified by distillation prior to use. 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 MHz 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 with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC–MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV (EI). The electrospray ionization (HR-ESI-MS) experiments were carried out in a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), dissolved in a solution 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. 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. TLC was 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.

4.2. General procedure for the preparation of *N*-α-aza-heteroaryl imines 1–7

The *N*-α-aza-heteroaryl imines were prepared by coupling reactions of 1 mmol of the appropriate amine with the corresponding aldehyde (1 mmol) in anhydrous Et_2O, in the presence of 7 g of molecular sieves (Aldrich, 4 Å, 1.6 mm pellets) for 24 h, according to Taguchi's method.[18]

4.2.1. Benzylidene-thiazol-2-yl-amine 1. Yield 150 mg (80%), yellow solid, mp 116–117 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.23 (d, J=3.5 Hz, 1H), 7.46–7.56 (m, 3H), 7.68 (d, J=3.5 Hz, 1H), 7.97–7.99 (m, 2H), 9.04 (s, 1H). ^{13}C NMR (100.62 MHz): δ 118.3, 128.9, 129.8, 132.6, 135.0, 141.4, 163.3, 173.1, 192.0. GC–MS (70 eV) *m*/*z* (rel int.): 188 (96) M^+, 187 (100), 161 (10), 104 (14), 85 (24), 58 (42). IR ($CHCl_3$): 3060, 3020, 2997, 1607, 1577, 1484, 1451, 1365, 1312, 1194, 1135 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.86; H, 4.26; N, 14.86.

4.2.2. Benzothiazol-2-yl-benzylidene-amine 2. Yield 202 mg (85%), yellow solid, mp 82–84 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.35 (t, J=8.2 Hz, 1H), 7.46–7.63 (m, 4H), 7.84 (d, J=8.0 Hz, 1H), 7.99 (d, J=7.9 Hz, 1H), 8.03 (d, J=7.0 Hz, 2H), 9.10 (s, 1H). ^{13}C NMR (100.62 MHz): δ 121.7, 123.1, 125.1, 126.4, 129.0, 130.2, 133.2, 135.0, 137.5, 153.1, 166.1, 172.0. GC–MS (70 eV) *m*/*z* (rel int.): 238 (47) M^+, 237 (100), 211 (11), 210 (12), 135 (16), 108 (13). IR ($CHCl_3$): 3060, 3001, 2980, 1605, 1315, 1150 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.75. Found: C, 70.50; H, 4.25; N, 11.80.

4.2.3. (4-Methyl-thiazol-2-yl-methylene)-thiazol-2-yl-amine 3. Yield 203 mg (97%), yellow solid, mp 80–82 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.56 (s, 3H), 7.18 (s, 1H), 7.31 (d, J=3.4 Hz, 1H), 7.73 (d, J=3.4 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100.62 MHz): δ 17.1, 119.2, 119.6, 142.0, 155.2, 155.8, 166.7, 171.2. GC–MS (70 eV) *m*/*z* (rel int.): 209 (100) M^+, 182 (52), 125 (73), 111 (55), 99 (20), 72 (60). IR ($CHCl_3$): 3019, 2977, 2825, 1522, 1423 cm^{-1}. Anal. Calcd for $C_8H_7N_3S_2$: C, 45.91; H, 3.37; N, 20.08. Found: C, 45.98; H, 3.36; N, 20.15.

4.2.4. Benzothiazol-2-yl-methylene-thiazol-2-yl-amine 4. Yield 196 mg (80%), yellow solid, mp 172–174 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 7.39 (d, J=3.4 Hz, 1H), 7.51–7.58 (m, 2H), 7.78 (d, J=3.4 Hz, 1H), 7.97 (d, J=7.5 Hz, 1H), 8.16 (d, J=7.6 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 120.6, 122.2, 124.7, 126.8, 127.8, 135.9, 142.3, 154.2, 155.9, 165.8, 170.7. GC–MS (70 eV) *m*/*z* (rel int.): 245 (100) M^+, 218 (41), 161 (24), 135 (19), 108 (19). IR ($CHCl_3$): 3067, 2999, 2928, 2857, 1698, 1586, 1477, 1262 cm^{-1}. Anal. Calcd for $C_{11}H_7N_3S_2$: C, 53.85; H, 2.88; N, 17.13. Found: C, 53.76; H, 2.85; N, 17.10.

4.2.5. (4-Methyl-thiazol-2-yl-methylene)-pyridin-2-yl-amine 5. Yield 199 mg (98%), yellow solid, mp 66–67 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 7.11 (s, 1H), 7.21 (dd, J=5.0, 7.0 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.76 (t, J=7.9 Hz, 1H), 8.51 (d, J=5 Hz, 1H), 9.3 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 17.1, 118.0, 120.3, 122.7, 138.2, 149.0, 155.3, 155.5, 159.5, 165.9. GC–MS (70 eV) *m*/*z* (rel int.): 203 (77) M^+, 175 (8), 158 (19), 125 (24), 79 (100), 78 (71). IR ($CHCl_3$): 3057, 2992, 2927, 1689, 1589, 1510, 1428, 1241 cm^{-1}. Anal. Calcd for $C_{10}H_9N_3S$: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.15; H, 4.48; N, 20.62.

4.2.6. Benzothiazol-2-yl-methylene-pyridin-2-yl-amine 6. Yield 232 mg (97%), yellow solid, mp 140–141 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.24–7.27 (m, 1H), 7.42–7.60 (m, 3H), 7.80 (td, J=1.8, 7.7 Hz, 1H), 7.95 (d, J=7.8 Hz, 1H), 8.15 (d, J=7.9 Hz, 1H), 8.55 (d, J=3.5 Hz, 1H), 9.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 120.9, 122.1, 123.3, 124.5, 126.5, 127.0, 135.6, 138.2, 149.1, 154.1, 156.3, 159.0, 167.0. GC–MS (70 eV) *m/z* (rel int.): 239 (88) M^+, 238 (25), 211 (22), 186 (4), 135 (20), 79 (100), 78 (50). IR ($CHCl_3$): 3063, 2998, 2860, 1698, 1615, 1587, 1485, 1460, 1436, 1320, 1237 cm^{-1}. Anal. Calcd for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.56. Found: C, 65.30; H, 3.80; N, 17.58.

4.2.7. Benzothiazol-2-yl-methylene-pyridin-3-yl-amine 7. Yield 225 mg (94%), yellow solid, mp 165–167 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.37 (dd, J=4.7, 8.0 Hz, 1H), 7.47–7.56 (m, 2H), 7.63 (d, J=8.0 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.0 Hz, 1H), 8.56 (d, J=4.7 Hz, 1H), 8.63 (d, J=2.2 Hz, 1H), 8.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 122.1, 123.8, 124.4, 126.7, 127.1, 127.7, 135.5, 143.2, 145.4, 148.7, 153.7, 155.2, 166.4. GC–MS (70 eV) *m/z* (rel int.): 239 (41) M^+, 238 (100), 212 (27), 186 (7), 135 (12), 78 (22). IR ($CHCl_3$): 3065, 2994, 2860, 1699, 1622, 1498, 1475, 1420, 1319, 1240 cm^{-1}. Anal. Calcd for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.56. Found: C, 65.18; H, 3.76; N, 17.50.

4.3. General procedure for the preparation of compounds 8–21

A mixture of 1.0 mmol of **1–7**, 1.5 mmol of allyl bromide, 0.08 mmol of PPh_3, 0.02 mmol of $Pd(OAc)_2$ 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 of CO), and then heated to 100 °C for 18–65 h. The reaction was then cooled to room temperature, worked up by addition of water (15 mL) and extracted with Et_2O (3×5 mL). The combined organic layers 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 products (**8–21**); yields: 30–98%.

4.3.1. (*Z*)-3-Ethylidene-4-phenyl-1-thiazol-2-yl-azetidin-2-one 8. Traces measured by GC–MS (70 eV) *m/z* (rel int.): 256 (100) M^+, 241 (14), 227 (24), 179 (95), 129 (36), 115 (25).

4.3.2. (*E*)-3-Ethylidene-4-phenyl-1-thiazol-2-yl-azetidin-2-one 9. Yield 110 mg (43%), white solid, mp 158–159 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.83 (d, J=7.4 Hz, 3H), 5.78 (s, 1H), 6.08 (d, J=5.3 Hz, 1H), 7.13 (d, J=5.3 Hz, 1H), 7.27–7.35 (m, 7H). ^{13}C NMR (100.62 MHz): δ 14.7, 61.1, 105.6, 120.6, 126.6, 126.7, 127.9, 128.8, 140.8, 142.1, 155.9, 160.0. GC–MS (70 eV) *m/z* (rel int.): 256 (100) M^+, 241 (15), 227 (26), 179 (93), 129 (34), 115 (31). IR ($CHCl_3$): 3019, 1670, 1540, 1205 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.65; H, 4.76; N, 10.89.

4.3.3. (*E*)-*N*-Thiazol-2-yl-2-benzylidene-but-3-enamide 10. Yield 49 mg (19%), yellow solid, mp 96–98 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 5.61 (d, J=11.3 Hz, 1H), 5.74 (d, J=17.9 Hz, 1H), 6.83 (ddd, J=1.2, 11.3, 17.9 Hz, 1H), 6.95 (d, J=3.6 Hz, 1H), 7.34–7.45 (m, 8H). ^{13}C NMR (100.62 MHz): δ 113.7, 122.1, 128.5, 129.1, 130.1, 130.5, 132.8, 134.7, 136.7, 137.3, 159.2, 165.9. GC–MS (70 eV) *m/z* (rel int.): 256 (44) M^+, 157 (68), 129 (85), 128 (100). IR ($CHCl_3$): 3399, 3020, 2967, 1676, 1530, 1212 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.53; H, 4.70; N, 10.96.

4.3.4. (*Z*)-*N*-Thiazol-2-yl-2-benzylidene-but-3-enamide 11. Yield 43 mg (17%), yellow solid, mp 104–108 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 5.27 (d, J=10.7 Hz, 1H), 5.29 (d, J=17.4 Hz, 1H), 6.54 (ddd, J=0.8, 10.7, 17.4 Hz, 1H), 6.70 (s, 1H), 6.96 (d, J=3.6 Hz, 1H), 7.15–7.22 (m, 6H), 7.28 (d, J=3.6 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 113.3, 117.5, 128.3, 128.5, 129.0, 133.0, 134.4, 135.3, 135.9, 136.8, 159.3, 166.4. GC–MS (70 eV) *m/z* (rel int.): 256 (38) M^+, 157 (65), 129 (85), 128 (100). IR ($CHCl_3$): 3399, 3020, 2967, 1676, 1530, 1212 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.69; H, 4.74; N, 10.87.

4.3.5. (*Z*)-1-Benzothiazol-2-yl-3-ethylidene-4-phenyl-azetidin-2-one 12. Yield 83 mg (27%), yellow solid, mp 155–156 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 2.19 (d, J=7.2 Hz, 3H), 5.41 (s, 1H), 6.21 (q, J=7.2 Hz, 1H), 7.23–7.70 (m, 8H), 8.32 (d, J=7.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 16.6, 66.3, 117.8, 121.7, 121.8, 125.6, 126.3, 126.9, 127.0, 127.7, 128.3, 128.4, 128.7, 140.1, 154.0, 161.9. GC–MS (70 eV) *m/z* (rel int.): 306 M^+ (100), 291 (15), 277 (25), 229 (72). IR ($CHCl_3$): 3060, 2990, 1650, 1500, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14. Found: C, 70.62; H, 4.59; N, 9.19.

4.3.6. (*E*)-1-Benzothiazol-2-yl-3-ethylidene-4-phenyl-azetidin-2-one 13. Yield 177 mg (58%), yellow solid, mp 142–144 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.87 (d, J=7.1 Hz, 3H), 5.82 (s, 1H), 7.18 (q, J=7.1 Hz, 1H), 7.29–7.59 (m, 8H), 8.33 (d, J=7.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 14.6, 60.3, 117.9, 121.5, 123.4, 125.5, 126.3, 126.6, 127.7, 128.8, 129.1, 135.9, 140.4, 141.2, 154.8, 161.7. GC–MS (70 eV) *m/z* (rel int.): 306 M^+ (100), 291 (15), 277 (23), 229 (70). IR ($CHCl_3$): 3060, 2990, 1650, 1500, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.60; N, 9.14. Found: C, 70.45; H, 4.58; N, 9.11.

4.3.7. 3-Ethyl-2-(4-methyl-thiazol-2-yl)-thiazolo[3,2-α]-pyrimidin-4-one 14. Yield 269 mg (97%), yellow solid, mp 169–171 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.23 (t, J=7.3 Hz, 3H), 2.54 (s, 3H), 3.32 (q, J=7.3 Hz, 2H), 6.96 (d, J=4.5 Hz, 1H), 7.08 (s, 1H), 7.95 (d, J=4.5 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 12.8, 17.5, 18.8, 111.3, 117.6, 118.8, 121.8, 148.8, 155.0, 158.4, 160.0, 166.5. GC–MS (70 eV) *m/z* (rel int.): 277 M^+ (100), 262 (18), 248 (41), 234 (59). IR ($CHCl_3$): 3123, 3007, 2970, 2931, 2873, 1661, 1561, 1520, 1341, 1194, 1062, 980, 918 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_3OS_2$: C, 51.96; H, 4.00; N, 15.15. Found: C, 51.99; H, 3.98; N, 15.20.

4.3.8. 2-Benzothiazol-2-yl-3-ethyl-thiazolo[3,2-α]pyrimidin-4-one 15. Yield 156 mg (50%), yellow solid, mp 236–238 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.30 (t, J=7.3 Hz, 3H), 3.43 (q, J=7.3 Hz, 2H), 7.01 (d, J=4.8 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.96–8.00 (m, 2H), 8.13 (d, J=8.9 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 13.0, 19.0, 111.9, 120.9, 121.6, 121.9, 124.4, 126.0, 126.2, 136.4, 148.8, 154.7, 158.5, 159.9, 167.6. GC–MS (70 eV) *m/z* (rel int.): 313 M^+ (100), 298 (37), 284 (51), 270 (56), 186 (15). IR ($CHCl_3$): 3030, 3000, 2928, 2855, 1664, 1560, 1496, 1458 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.40; H, 3.52; N, 13.37.

4.3.9. 3-Ethylidene-4-(4-methyl-thiazol-2-yl)-1-pyridin-2-yl-azetidin-2-one 16 and 17. Traces measured by GC–MS (70 eV) *m/z* (rel int.): 271 M^+ (47), 256 (24), 242 (88), 228 (100), 78 (51).

4.3.10. 3-Ethyl-2-(4-methyl-thiazol-2-yl)-pyrido[1,2-α]-pyrimidin-4-one 18. Yield 265 mg (98%), yellow solid, mp 149–150 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.27 (t, J=7.3 Hz, 3H), 2.54 (d, J=0.8 Hz, 3H), 3.41 (q, J=7.3 Hz, 2H), 7.01–7.05 (m, 1H), 7.08 (q, J=0.8 Hz, 1H), 7.57–7.60 (m, 2H), 8.95–8.97 (m, 1H). ^{13}C NMR (100.62 MHz): δ 12.8, 17.5, 19.5, 114.7, 117.6, 118.1, 126.1, 126.9, 134.6, 148.0, 149.7, 154.8, 159.3, 167.3. GC–MS (70 eV) *m/z* (rel int.): 271 M^+ (89), 256 (29), 242 (76), 228 (100), 78 (81). IR ($CHCl_3$): 3009, 2971, 2930, 2873, 1666, 1637, 1538, 1489, 1243 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.48. Found: C, 61.85; H, 4.80; N, 15.53.

4.3.11. 2-Benzothiazol-2-yl-3-ethyl-pyrido[1,2-α]pyrimidin-4-one 19. Yield 123 mg (40%), yellow solid, mp 217–218 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.34 (t, J=7.3 Hz, 3H), 3.52 (q, J=7.3 Hz, 2H), 7.01–7.11 (m, 1H), 7.44 (t, J=7.3 Hz, 1H), 7.52 (t, J=7.0 Hz, 1H), 7.66 (d, J=3.5 Hz, 2H), 7.98 (d, J=8.0 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 9.01 (d, J=7.3 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 13.1, 19.7, 115.2, 120.0, 121.5, 124.4, 125.9, 126.1, 126.4, 127.1, 134.9, 136.5, 148.1, 149.8, 154.8, 159.4, 168.6. GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 292 (78), 278 (83), 264 (86), 78 (60). IR (KBr): 3100, 3060, 2973, 2924, 2874, 1662, 1632, 1536, 1483, 1210, 922, 771, 753, 729, 701 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.35; H, 4.25; N, 13.70.

4.3.12. (*Z*)-4-Benzothiazol-2-yl-3-ethylidene-1-pyridin-3-yl-azetidin-2-one 20. Yield 24% (evaluated by GC analysis of the crude product), brown oil. ^{1}H NMR (400.13 MHz): δ 2.16 (d, J=7.2 Hz, 3H), 5.87 (s, 1H), 6.03 (q, J=7.2 Hz, 1H), 7.10–7.24 (m, 1H), 7.43 (t, J=7.2 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.83–7.87 (m, 2H), 8.06 (d, J=8.2 Hz, 1H), 8.31–8.34 (m, 1H), 8.68 (d, J=2.0 Hz, 1H). ^{13}C NMR (100.62 MHz): δ 29.7, 60.4, 122.0, 123.5, 123.80, 123.83, 126.0, 126.5, 131.1, 134.2, 135.1, 138.27, 139.3, 145.4, 153.0, 161.0, 168.2. GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 278 (48), 186 (67), 78 (18). IR ($CHCl_3$): 3064, 2992, 2927, 2855, 1757, 1486, 1435, 1366 cm^{-1}. HR-ESI-MS: *m/z* calcd for $C_{17}H_{13}N_3OS$: 307.0781, $[M+H]^+$; found: 307.0790.

4.3.13. (*E*)-4-Benzothiazol-2-yl-3-ethylidene-1-pyridin-3-yl-azetidin-2-one 21. Compound characterized only by ^{1}H NMR as it was isolated in low quantity containing an inseparable mixture of the two *Z* and *E* isomers (**20**+**21**). Yield 6% (evaluated by GC analysis of the crude product). ^{1}H NMR (400.13 MHz): δ 1.91 (d, J=7.0 Hz, 3H), 7.55 (q, J=7.0 Hz, 1H), 7.10–7.24 (m, 1H), 7.43 (t, J=7.2 Hz, 1H), 7.52 (t, J=8.0 Hz, 1H), 7.83–787 (m, 2H), 8.06 (d, J=8.2 Hz, 1H), 8.31–8.34 (m, 1H), 8.68 (d, J=2.0 Hz, 1H). GC–MS (70 eV) *m/z* (rel int.): 307 M^+ (100), 278 (53), 186 (72), 78 (14).

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Enantioselective microbial hydrolysis of dissymmetrical cyclic carbonates with disubstitution

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Abstract—Enantioselective microbial hydrolysis of C_1 and C_2 dissymmetrical cyclic carbonates with disubstitution (methyl and another groups) has been developed. *Pseudomonas diminuta* (FU0090), a bacterium, efficiently catalyzes the hydrolysis of five-membered cyclic carbonates. While the trans-substrates are hydrolyzed with low enantioselectivities and/or reactivities, the microbe hydrolyzes the cis-substrates with very high enantioselectivities to afford the corresponding almost optically pure *anti*-(2*R*,3*S*)-diols. On the other hand, six-membered *trans*-cyclic carbonates are enantioselectively hydrolyzed to afford the corresponding optically active *syn*-(2*R*,4*R*)-diols, although the hydrolysis of the cis-substrates gives racemic compounds. In all cases, the enzyme prefers the (*R*)-enantiomer for the carbon atom bearing a methyl group.

1. Introduction

Optically active diols are important intermediates for the synthesis of natural products, and many synthetic procedures for such compounds have been developed. Although the asymmetric dihydroxylation of olefins is one of the most popular ways to prepare chiral 1,2-diols,[1] this method does not always satisfactorily work in terms of the enantioselectivity in some cases. For example, the oxidation of (*Z*)-disubstituted olefins is not a suitable tool for the preparation of optically active *anti*-1,2-diols.[2] On the other hand, optically active 1,3-diols are not easily synthesized by direct preparation methods.

The use of enzymes in the preparation of such optically active compounds is especially attractive due to the remarkable stereoselectivity and its benign effect on the environment. Enzymatic hydrolysis of diacetates and esterification of diols are the representative biochemical methods to prepare such compounds.[3] The reactions, however, produce a mixture of more than two compounds (diol, diacetate, and two monoacetates), which causes difficulty with the purification, and the almost examples have been limited to the reaction of *meso*- and C_2-symmetrical compounds. Recently, the kinetic resolution of cyclic carbonates with hydrolytic enzymes is one of the attractive methods for preparing optically active diols.[4] We have already reported the enzyme-mediated hydrolysis of cyclic carbonates, and have accomplished the efficient preparation of various kinds of optically active diols.[5,6] Commercially available porcine pancreas lipase (PPL, Type II from Sigma) catalyzes the hydrolysis of monosubstituted cyclic carbonates to afford the corresponding optically active 1,2- and 1,3-diols.[5] On the other hand, *Pseudomonas diminuta* (FU0090), which is a bacterium isolated from the soil and classified by NCIMB Japan Co. Ltd, hydrolyzes the C_2-symmetrical five- and six-membered cyclic carbonates with a dimethyl group, and then optically active 2,3-butanediol and 2,4-pentanediol were obtained.[6a] This type of reaction proceeds irreversibly because the acyl moiety of the substrate leaves the reaction system as carbon dioxide. The enzyme, however, has a high substrate specificity for the side chain of the substrate, and the reaction of the substrate bearing a diethyl group was not hydrolyzed at all. During our studies on this microbial reaction, we observed that even C_1- and C_2-dissymmetrical disubstituted substrates could be enantioselectively hydrolyzed when one of the substituent was a methyl group. Herein, we reported the application of the microbial hydrolysis to various five- and six-membered cyclic carbonates bearing methyl and another groups, and then prepared the corresponding optically active 1,2- and 1,3-diols with two chiral centers

Keywords: Cyclic carbonates; Enantioselective hydrolysis; Enzymes; Microbial reaction; Optically active diols.
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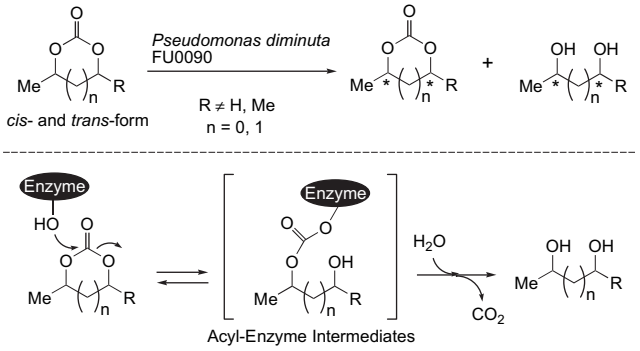
(Scheme 1). In particular, the optically pure *anti*-1,2-diols were obtained from the five-membered *cis*-substrates with high enantioselectivities.[6b]



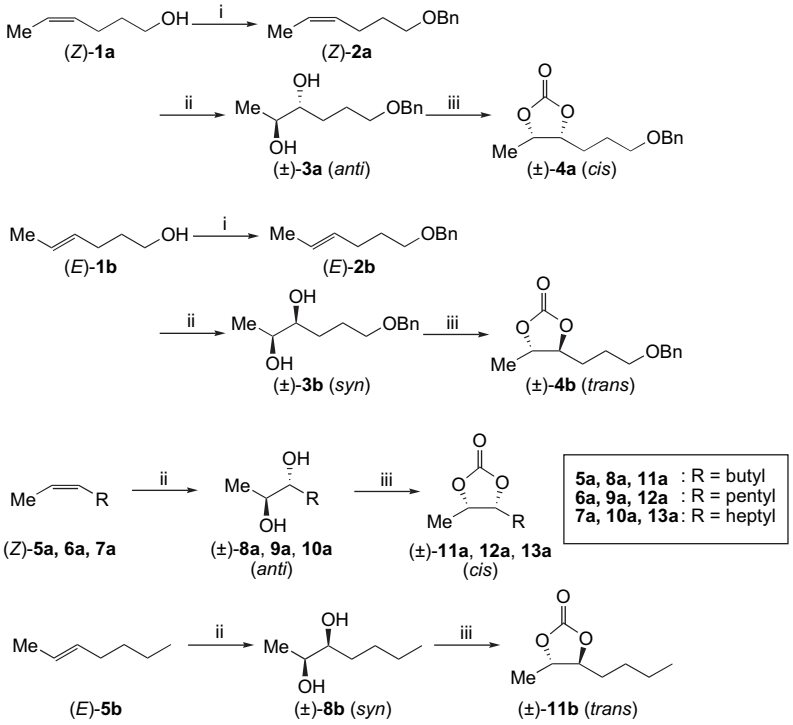
Scheme 1.

2. Results and discussion

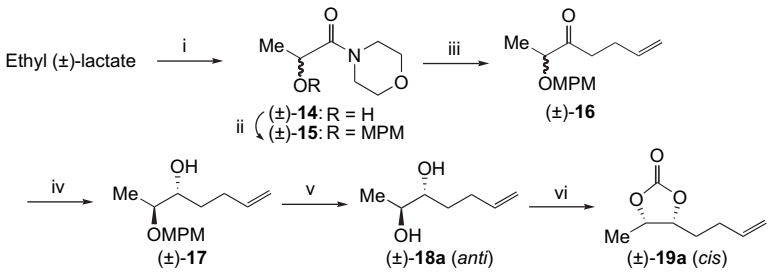
The diastereomeric *anti*- and *syn*-racemic diols, which were the precursors of cyclic carbonates, were readily synthesized. The compounds 1,2-diols are selectively prepared starting from (*Z*)- and (*E*)-olefins, respectively, as shown in Schemes 2 and 3. On the other hand, selective reduction of β-hydroxy ketones followed by separation with column chromatography on silica gel afforded *anti*- and *syn*-1,3-diols (Scheme 4). In all cases, successive treatment of the diols with pyridine and bis(trichloromethyl)carbonate (triphosgene) resulted in the corresponding racemic substrates.

First, we selected the racemic five-membered cyclic carbonates, diastereomers of the *cis*- and *trans*-4-(3-benzyloxy)propyl-5-methyl-1,3-dioxolan-2-ones ((±)-**4a** and **4b**, respectively) as the representative substrates. After the reaction of (±)-**4** (ca. 84 mg, 10 mM) with *P. diminuta* in 50 mL of glucose medium at 30 °C, the bacterium catalyzed the hydrolysis of both substrates, and the corresponding *anti*- and *syn*-6-benzyloxy-2,3-diols (**3a** and **3b**, respectively) were obtained, as expected (Scheme 5). The transform substrate ((±)-**4b**) was enantioselectively hydrolyzed to give the optically active (2*R*,3*R*)-**3b** ($[\alpha]_D^{22}$ +11.5 (*c* 0.72, MeOH), 75% ee) in 23% yield and the remaining (4*S*,5*S*)-**4b** ($[\alpha]_D^{22}$ −10.0 (*c* 0.35, MeOH), 54% ee) in 44% yield. In this case, the enzyme preferentially hydrolyzed the (4*R*,5*R*)-form in the same stereoselective manner as in the case of the C_2-symmetrical (±)-*trans*-4,5-dimethyl-1,3-dioxolan-2-one (**38b**) bearing a dimethyl group.[6a] The hydrolysis, however, proceeded with moderate enantioselectivity, and the conversion and *E* value of the reaction for 48 h were 0.42 and 12, respectively,[7] while **38b** was hydrolyzed with high enantioselectivity (*E* value=70). To determine the stereochemistry of the resulting (2*R*,3*R*)-**3b**, the sign of the optical rotation was compared with that of the authentic sample (2*S*,3*S*)-**3b** ($[\alpha]_D^{27}$ −13.8 (*c* 1.16, MeOH), 77% ee), which was transformed from (*E*)-**2b** by the asymmetric dihydroxylation method with AD-mix-α and $CH_3SO_2NH_2$ in *t*-BuOH/H_2O (Scheme 6).[1]

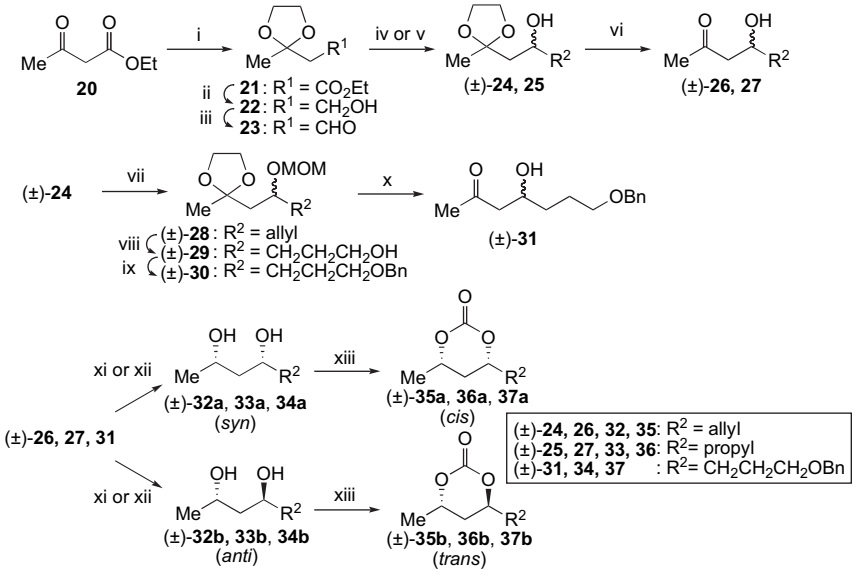
On the other hand, the enantioselectivity of the hydrolysis of the *cis*-substrate ((±)-**4a**) was almost perfect. The reaction of (±)-**4a** for 48 h produced the remaining cyclic carbonate (4*R*,5*S*)-**4a** ($[\alpha]_D^{26}$ +10.9 (*c* 1.68, MeOH), 97% ee) in 43% yield and the resulting optically pure diol (2*R*,3*S*)-**3a** ($[\alpha]_D^{25}$ −14.0 (*c* 2.54, MeOH)) in 40% yield (conv.=0.49, *E* value[3]=>200). Although, we have already reported the hydrolysis of *cis*-4,5-dimethyl-1,3-dioxolan-2-one (**38a**; the *meso*-cyclic carbonate bearing a dimethyl group) as the C_1-symmetrical substrate,[6a] this is the first



Scheme 2. (i) BnBr, NaH/THF, reflux ((*E*)-**2b**, 98%); (ii) cat. OsO_4, NMO/acetone/H_2O, rt (**3a**, 86% from **1a**; **3b**, 63%; **8a**, 49%; **8b**, 87%; **9a**, 82%; **10a**, 55%); (iii) triphosgene, Py/CH_2Cl_2, −78→0 °C (**4a**, 92%; **4b**, 96%; **11a**, 78%; **11b**, 85%; **12a**, 60%; **13a**, 97%).

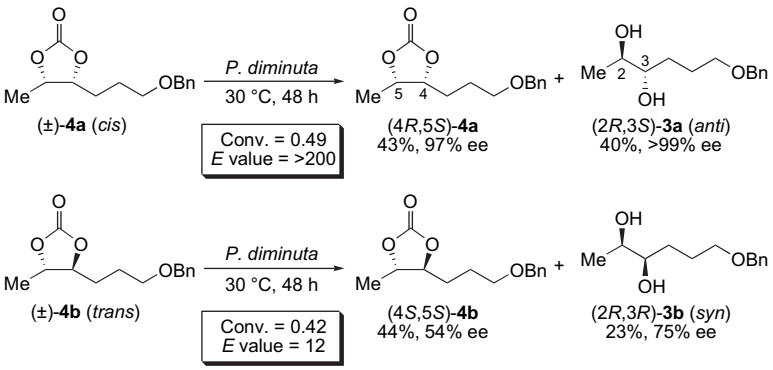


Scheme 3. (i) Morpholine, reflux (69%); (ii) MPMCl, NaH/THF, rt (87%); (iii) $CH_2{=}CHCH_2CH_2MgBr$/THF, rt (74%); (iv) $ZnBH_4/Et_2O$ (48%); (v) cat. *p*-TsOH/MeOH (76%); (vi) triphosgene, Py/CH_2Cl_2, −78→0 °C (51%).

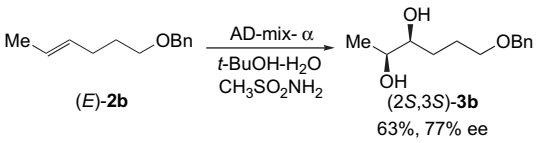


Scheme 4. (i) cat. *p*-TsOH, ethylene glycol/benzene, reflux (73%); (ii) $LiAlH_4$/THF, rt (91%); (iii) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78 °C→rt (75%); (iv) $CH_2{=}CHCH_2MgBr$/THF, rt (**24**, 88%); (v) propylmagnesium bromide/THF, rt (**25**, 76%); (vi) 2 M HCl aq/THF (**26**, 71%; **27**, 79%); (vii) MOMCl, *i*-Pr_2NH/CH_2Cl_2 (89%); (viii) $BH_3\cdot$THF/THF then 2 M NaOH aq, H_2O_2 (90%); (ix) BnBr, NaH/THF (88%); (x) 2 M HCl aq/THF (71%); (xi) *Procedure A*, $NaBH_4$/MeOH (**32a** (56%)+**32b** (28%); **33a** (64%)+**33b** (32%); **34a** (50%)+**34b** (34%)); (xii) *Procedure B*, $MeNB(OAc)_3H$/AcOH/CH_3CN (**32a** (24%)+**32b** (73%); **33a** (16%)+**33b** (78%); **34a** (37%)+**34b** (56%)); (xiii) triphosgene, Py/CH_2Cl_2, −78 °C→rt (**35a**, 78%; **35b**, 55%; **36a**, 30%; **36b**, 42%; **37a**, 79%; **37b**, 76%).

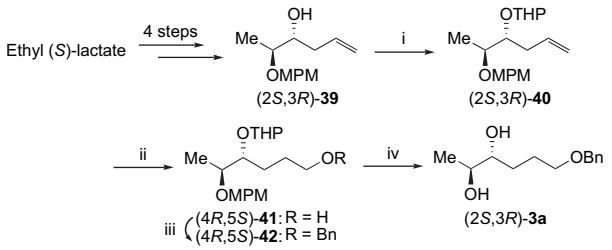
example of the enantioselective hydrolysis of the *cis*-disubstituted carbonates. The absolute configuration of the *anti*-diol was determined by comparing the optical rotation with that of the optically active authentic (2*S*,3*R*)-**3a** ($[\alpha]_D^{25}$ +12.9 (*c* 1.34, MeOH)), which was prepared from ethyl (*S*)-lactate in seven steps (Scheme 7). In the case of *anti*-1,2-diol, the asymmetric dihydroxylation of (*Z*)-**2a** with AD-mix-α proceeded with very low enantioselectivity to give (2*R*,3*S*)-**3a** in only 18% ee. These show that the microbial hydrolysis apparently has some advantage for the preparation of optically active *anti*-1,2-diol with high ee.



Scheme 5.

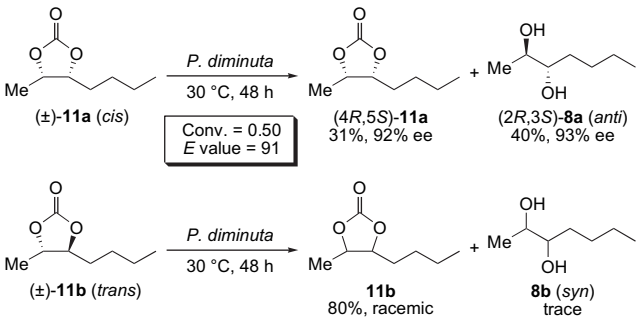


Scheme 6.



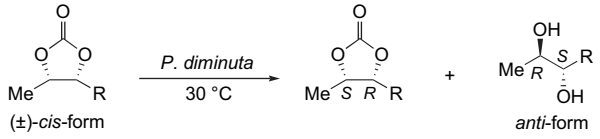
Scheme 7. (i) DHP, *p*-TsOH/CH_2Cl_2 (64%); (ii) BH_3·THF/THF then 2 M NaOH aq, H_2O_2 (62%); (iii) BnBr, NaH/THF (81%); (iv) *p*-TsOH/MeOH (38%).

The difference in the reactivity between the diastereomers is noticeably observed during the hydrolysis of the substrates bearing a butyl group ((±)-**11a** and **11b**) as a substituent (Scheme 8). The hydrolysis of the *cis*-substrate (±)-**11a** smoothly proceeded to give optically active compounds, (4*R*,5*S*)-**11a** (92% ee, $[\alpha]_D^{22}$ +14.6 (*c* 1.04, MeOH)) in 31% yield and (2*R*,3*S*)-**8a** (93% ee, $[\alpha]_D^{23}$ −22.0 (*c* 0.82, MeOH)) in 40% yields (reaction for 48 h; conv.=0.50, *E* value=91). Interestingly, in the case of the *trans*-isomer (±)-**11b**, the enzyme scarcely catalyzed the substrate at all.



Scheme 8.

Then, we applied the microbial reaction to several five-membered *cis*-cyclic carbonates (Scheme 9, Table 1). As expected, all the substrates were hydrolyzed with high enantioselectivity. The reaction of the substrate bearing an unsaturated substituent (R=3-butenyl, (±)-**19a**, entry 3) gave a result similar to that of (±)-**11a**, which has the corresponding saturated group. The bacterium smoothly catalyzed the hydrolysis of (±)-**19a** for 48 h to give the optically active (4*R*,5*S*)-**19a** (63% ee) and (2*R*,3*S*)-**18a** (95% ee) in 46 and 42% yields, respectively (conv.=0.40, *E* value=75). The optically active **18a** is an important precursor for the synthesis of a biologically active deoxysugar, D-amicetose.[8] On the other hand, the substrates bearing a longer chain, (±)-**12a** (R=pentyl, entry 1) and **13a** (R=heptyl, entry 2) showed excellent enantioselectivities, although the reactivities were low. For the reactions going for 96 h, the resulting (2*R*,3*S*)-**9a** and **10a** were obtained in their optically pure forms, and the *E* values were over 200.



Scheme 9.

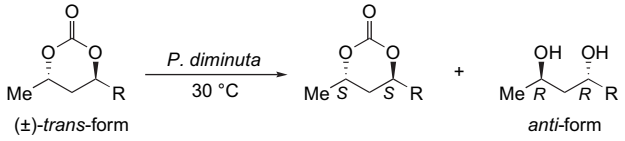
Next, our attention focused on the ring size of the substrate, and we tried the reaction of racemic six-membered cyclic carbonates (Scheme 10, Table 2). As expected, *P. diminuta* catalyzed the hydrolysis of all the substrates examined to afford the corresponding 1,3-diols. The stereoselective manner, however, was quite different from that of the five-membered substrates. In the case of the *trans*-substrate bearing an allyl group (**35b**, entry 1), the substrate was smoothly hydrolyzed with good enantioselectivity to give the optically active remaining (4*S*,6*S*)-**35b** (72% ee) in 39% yield and the resulting (2*R*,4*R*)-**32b** (84% ee, $[\alpha]_D^{21}$ −29.7 (*c* 0.66, $CHCl_3$)) in 26% yield (reaction for 48 h; conv.=0.46, *E* value=25). The absolute configuration of the diol **32b** was determined by comparing the optical rotation with that reported; (2*R*,4*R*)-**32b** (96% ee), lit.[9] $[\alpha]_D^{23}$ −34.1 (*c* 1.13, $CHCl_3$). The reaction for 72 h (entry 2) gave optically pure (4*S*,6*S*)-**35b** in 27% yield. It is noteworthy that the enzyme preferentially catalyzes the hydrolysis of (*R*)-enantiomer at the asymmetric center bearing a methyl group as

Table 1. Microbial hydrolysis of several five-membered (±)-*cis*-cyclic carbonates[a]

Entry	R	Time (h)	Carbonate			Diol			Conv.[b]	*E*[c]
				Yield (%)	ee (%)		Yield (%)	ee (%)		
1	Pentyl	96	**12a**	77	18[d]	**9a**	14	>99[e]	0.15	>200
2	Heptyl	96	**13a**	84	13[f]	**10a**	11	>99[g]	0.12	>200
3	3-Butenyl	48	**19a**	46	63[h]	**18a**	42	95[i]	0.40	75

[a] The reaction was performed using 10 mM of the substrate.
[b] Calculated by ee(carbonate)/[ee(carbonate)+ee(diol)].
[c] Calculated by ln[(1−conv.)(1−ee(carbonate))]/ln[(1−conv.)(1+ee(carbonate))].
[d] $[\alpha]_D^{28}$ +6.10 (*c* 1.08, MeOH).
[e] $[\alpha]_D^{28}$ −20.4 (*c* 0.89, MeOH).
[f] $[\alpha]_D^{29}$ +3.58 (*c* 0.79, MeOH).
[g] $[\alpha]_D^{24}$ −10.1 (*c* 0.39, MeOH).
[h] $[\alpha]_D^{23}$ +7.93 (*c* 1.20, MeOH).
[i] $[\alpha]_D^{23}$ −19.1 (*c* 1.31, MeOH).

well as that in the case of the five-membered substrates. Changing the substituent from allyl to propyl (**36b**, entry 3) and 3-benzyloxypropyl (**37b**, entry 4) decreased the reactivity and the enantioselectivity. For example, the reaction of **36b** for 48 h gave the optically active (2*R*,4*R*)-**33b** in 84% ee, but the conversion and *E* value were only 0.10 and 13, respectively. The longer reaction time scarcely improved the conversion at all. Interestingly, although the enzyme accelerated the hydrolysis of the cis-substrates and the reactions for 48 h gave the remaining carbonates (**35a**, 37%; **36a**, 48%; **37a**, 47%) and the corresponding diols (**32a**, 31%; **33a**, 28%; **34a**, 18%), all of the products were almost racemates.



Scheme 10.

Based on all of our observations, we can formulate an empirical rule for predicting the enantioselectivity in this microbial reaction.[10] For the rigid five-membered substrates, the active site model is illustrated in Figure 1. First, a methyl group at C-5 position of the substrates is necessary for the enantioselective reaction because we have also found that monosubstituted cyclic carbonates (R^1=H), such as 4-methyl-1,3-dioxolan-2-one (**43**) and 4-(2-benzyloxy)ethyl-1,3-dioxolan-2-one (**44**) in Figure 2, are smoothly hydrolyzed without enantioselectivity. Second, the enzyme prefers (5*R*)-substrates in all cases. These results indicate that the enzyme apparently distinguishes the stereochemistry at the asymmetric center substituted with a methyl group and the *cis*-(5*R*)-substrate is most suitable for the active site of the enzyme (R^1=Me, R^2=alkyl, R^3=H). In the case of the fast reactive enantiomer, the methyl group would locate at the *S* (small)-pocket, with hydrogen in *H*-site, and with R^2 group in *L* (large)-pocket. In the reaction of *trans*-substrates, the elongation of the substituent (R^3) at the C-4 position decreases both the reactivity and the enantioselectivity. Because the introduction of a benzyloxy group on the side chain could improve the reactivity, the oxygen atom of the substrates could play an important role for the interaction between the substrates and the enzyme.

On the other hand, for the six-membered *trans*-cyclic carbonates, R group at the pseudo-equatorial position could turn to *L*-pocket when the pseudo-axial methyl group locates

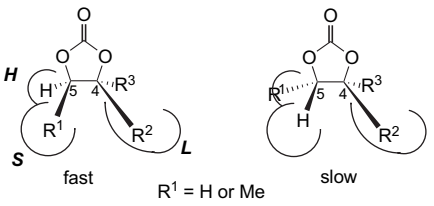


Figure 1.

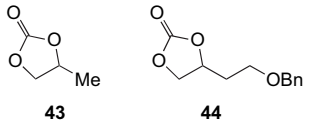


Figure 2.

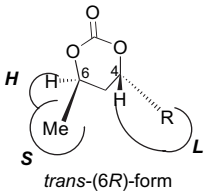


Figure 3.

at the *S*-pocket (Fig. 3). This indicates that the *trans*-(6*R*)-substrate might be a most preferable isomer. But, it is difficult to understand the stereoselective mode because the six-membered ring is very flexible in comparison with the five-membered ring. Consequently, the enantio- and diastereoselectivity of the hydrolysis was lower than those in the case of the five-membered substrates.

3. Conclusion

In this paper, we have established the microbial enantioselective hydrolysis of five- and six-membered cyclic carbonates bearing two substituents, which are methyl and another groups, as a new route to optically active diols. In particular, this is the first report for the enantioselective hydrolysis of five-membered *cis*-cyclic carbonates, which are favorably hydrolyzed with high enantioselectivity to give the corresponding optically pure *anti*-1,2-diols. Furthermore, we can postulate the active site model for the hydrolase through the microbial reaction for various substrates.

Table 2. Microbial hydrolysis of several six-membered (±)-*trans*-cyclic carbonates[a]

Entry	R	Time (h)	Carbonate			Diol			Conv.[b]	*E*[c]
				Yield (%)	ee (%)		Yield (%)	ee (%)		
1	Allyl	48	**35b**	39	72	**32b**	26	84	0.46	25
2	Allyl	72	**35b**	27	>99[d]	**32b**	29	61	0.62	>20
3	Propyl	48	**36b**	80	10	**33b**	16	84[e]	0.10	13
4	$-(CH_2)_3OBn$	48	**37b**	71	6	**34b**	7	84	0.07	12

[a] The reaction was performed using 10 mM of the substrate.
[b] Calculated by ee(carbonate)/[ee(carbonate)+ee(diol)].
[c] Calculated by ln[(1−conv.)(1−ee(carbonate))]/ln[(1−conv.)(1+ee(carbonate))].
[d] $[\alpha]_D^{20}$ −75.7 (*c* 1.00, $CHCl_3$).
[e] $[\alpha]_D^{22}$ −8.91 (*c* 0.63, $CHCl_3$).

4. Experimental

4.1. General

^{1}H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR spectra were measured on a JEOL JNM AL-300 and α-500 with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with Shimadzu FTIR-8300 and IR Prestige-21 spectrometers. Mass spectra were obtained with a JEOL EI/FAB mate BU25 Instrument by the EI method. Optical rotations were measured with a Jasco DIP-1000 polarimeter. HPLC data were obtained on Shimadzu LC-10AD$_{VP}$, SPD-10A$_{VP}$, and sic 480II data station (System Instruments Inc.). GLC data were taken on GL Sciences GC 353B and sic 480II data station (System Instruments Inc.). E. Merck Kieselgel 60 F_{254} Art. 5715 was used for analytical TLC. Preparative TLC was performed on E. Merck Kieselgel 60 F_{254} Art. 5744. Column chromatography was performed with Silica Gel 60N (63–210 mm, Kanto Chemical Co. Inc.). Melting points were obtained on a Yanako melting point apparatus and were not corrected. All other chemicals were also obtained from commercial sources.

4.2. Preparation of 1,2-diols

4.2.1. (2*RS*,3*SR*)-(6-Benzyloxy)hexane-2,3-diol ((±)-3a (*anti*)). Under an argon atmosphere, to a suspension of NaH (60% in oil, 900 mg, 22 mmol) in THF (10 mL) was added a solution of (*Z*)-4-hexen-1-ol (**1a**, 2.0 g, 20 mmol) in THF (15 mL) and benzyl bromide (2.9 mL, 24 mmol) at 0 °C. The mixture was stirred for 6 h under reflux, and the reaction was quenched with 0.1 M phosphate buffer (pH 6.5). The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=2/1) to give (*Z*)-(6-benzyloxy)-2-hexene (**2a**) as a colorless oil (3.7 g).

To a solution of (*Z*)-**2a** (3.7 g, 19.6 mmol) in acetone (7 mL) and H_2O (3 mL) were added 4-methylmorpholine *N*-oxide (10.0 g, 80 mmol), *t*-BuOH (0.3 mL), and a catalytic amount of OsO_4, and the mixture was stirred for 2 h at room temperature. After addition of NaS_2O_4, stirring for 30 min, and filtration through a Celite pad, the products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give (±)-**3a** as a colorless oil (3.9 g, 86% from **1a**); IR (neat) 3399, 2930, 1714, 1454, 1277, 1099, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.15 (d, J=6.5 Hz, 3H), 1.41–1.85 (m, 4H), 3.50–3.82 (m, 4H), 4.53 (s, 2H), 7.28–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=17.0, 26.5, 28.9, 70.3, 70.5, 73.1, 74.7, 127.7, 128.4, 129.5, 137.9; MS *m*/*z* (rel intensities) 224 (M^+, 5.6%), 206 (2.5), 107 (100), 91 (100); HRMS *m*/*z* 224.1419 (224.1413 calcd for $C_{13}H_{20}O_3$, M^+).

4.2.2. (2*RS*,3*RS*)-(6-Benzyloxy)hexane-2,3-diol ((±)-3b (*syn*)). According to the procedure for the preparation method described above, (*E*)-4-hexen-1-ol (**1b**, 1.02 g, 10.2 mmol) was converted to (*E*)-(6-benzyloxy)-2-hexene (**2b**, 1.90 g, 98%) as a colorless oil. Then, (*E*)-**2b** (56.5 mg, 0.30 mmol) was converted to (±)-**3b** as a colorless oil (41.7 mg, 63%); IR (neat) 3399, 2926, 2857, 1454, 1098, 1072, 737, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.18 (d, J=6.0 Hz, 3H), 1.45–1.52 (m, 1H), 1.62 (br s, 2H), 1.64–1.72 (m, 1H), 1.79 (td, J_1=J_2=6.0 Hz, 1H), 3.34 (ddd, J_1=3.0 Hz, J_2=6.5 Hz, J_3=9.5 Hz, 1H), 3.54 (t, J=6.0 Hz, 2H), 3.56–3.62 (m, 1H), 4.23 (s, 2H), 7.26–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.3, 26.0, 30.9, 70.5, 70.9, 73.2, 75.8, 127.8, 128.5, 137.9; MS *m*/*z* (rel intensities) 224 (M^+, 1.7%), 206 (0.6), 107 (34), 91 (100); HRMS *m*/*z* 224.1412 (224.1413 calcd for $C_6H_{14}O_2$, M^+).

4.2.3. (2*RS*,3*SR*)-Heptane-2,3-diol ((±)-8a (*anti*)). According to the procedure for the preparation of **3a** described above, (*Z*)-2-heptene (**5a**, 564 mg, 5.75 mmol) was converted to (±)-**8a** as a colorless oil (375 mg, 49%); IR (neat) 3379, 2932, 1462, 1379, 1055, 984, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.92 (t, J=7.0 Hz, 3H), 1.14 (d, J=6.5 Hz, 3H), 1.24–1.43 (m, 5H), 1.43–1.53 (m, 1H), 2.39 (br s, 2H), 3.54–3.65 (m, 1H), 3.79 (qd, J_1=3.0 Hz, J_2=6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 16.5, 22.7, 28.2, 31.4, 70.4, 74.9; MS *m*/*z* (rel intensities) 132 (M^+, 5.6%), 113 (37), 104 (28), 83 (46), 71 (90), 57 (100); HRMS *m*/*z* 132.1137 (132.1150 calcd for $C_7H_{16}O_2$, M^+).

4.2.4. (2*RS*,3*RS*)-Heptane-2,3-diol ((±)-8b (*syn*)). According to the procedure for the preparation of **3a** described above, (*E*)-2-heptene (**5b**, 1.01 g, 10.4 mmol) was converted to ((±)-**8b** as a colorless oil (1.18 g, 87%); IR (neat) 3370, 2957, 2934, 2872, 1458, 1375, 1057 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.92 (t, J=7.0 Hz, 3H), 1.20 (d, J=6.0 Hz, 3H), 1.33–1.52 (m, 6H), 2.29 (br s, 2H), 3.31–3.36 (m, 1H), 3.60 (qd, J_1=J_2=6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 19.5, 22.7, 27.7, 33.1, 70.9, 76.2; MS *m*/*z* (rel intensities) 132 (M^+, 12%), 114 (11), 107 (31), 91 (100), 71 (51); HRMS *m*/*z* 132.1151 (132.1150 calcd for $C_7H_{16}O_2$, M^+).

4.2.5. (2*RS*,3*SR*)-Octane-2,3-diol ((±)-9a (*anti*)). According to the procedure for the preparation of **3a** described above, (*Z*)-2-octene (**6a**, 2.02 g, 18.1 mmol) was converted to (±)-**9a** as a colorless oil (2.15 g, 82%); IR (neat) 3285, 2955, 2940, 2916, 2857, 1485, 1069, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.90 (t, J=7.0 Hz, 3H), 1.15 (d, J=6.5 Hz, 3H), 1.25–1.36 (m, 5H), 1.37–1.43 (m, 2H), 1.46–1.55 (m, 1H), 1.70 (br s, 1H), 1.98 (br s, 1H), 3.61–3.64 (m, 1H), 3.77–3.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.0, 16.6, 22.6, 25.7, 31.7, 31.9, 70.4, 74.9; MS *m*/*z* (rel intensities) 146 (M^+, 6.9%), 128 (18), 110 (16), 101 (100), 99 (42), 85 (39); HRMS *m*/*z* 146.1361 (146.1307 calcd for $C_8H_{18}O_2$, M^+).

4.2.6. (2*RS*,3*SR*)-Decane-2,3-diol ((±)-10a (*anti*)). According to the procedure for the preparation of **3a** described above, (*Z*)-2-decene (**7a**, 656 mg, 4.68 mmol) was converted to (±)-**10a** as a colorless oil (446 mg, 55%); IR (neat) 3293, 2955, 2916, 2853, 1487, 1468, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.88 (t, J=7.0 Hz, 3H), 1.15 (d, J=6.5 Hz, 3H), 1.21–1.51 (m, 12H), 1.82 (br s, 2H), 3.59–3.64 (m, 1H), 3.76–3.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.1, 16.6, 22.6, 26.0, 29.2, 29.6, 31.8, 70.4,

74.9; MS *m/z* (rel intensities) 174 (M^+, 7.6%), 156 (4.8), 138 (6.3), 129 (100), 113 (14), 99 (15); HRMS *m/z* 174.1625 (174.1620 calcd for $C_{10}H_{22}O_2$, M^+).

4.2.7. (2*RS*,3*SR*)-6-Heptene-2,3-diol ((±)-18a (*anti*)). To ethyl (±)-lactate (10.0 g, 0.08 mol) was added morpholine (14.8 g, 0.17 mol), and the mixture was stirred overnight under reflux. After removal of the excess morpholine in vacuo, the residue was purified by distillation under reduced pressure to afford (±)-2-hydroxy-1-morpholinopropan-1-one (**14**) as a colorless oil (9.35 g, 69%); bp 109–110 °C/3 mmHg; IR (neat) 3420, 2858, 2341, 1643, 1439, 1273, 1115, 845, 571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.33 (d, *J*=6.5 Hz, 3H), 3.38–3.76 (m, 8H), 3.87 (br s, 1H), 4.45 (q, *J*=6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.1, 42.6, 45.2, 63.9, 66.2, 66.6, 173.6.

Under an argon atmosphere, to a suspension of NaH (553 mg, 13.8 mmol, 60% in oil) in THF (20 mL) was added a solution of (±)-**14** (2.0 g, 12.6 mmol) in THF (10 mL) and *p*-methoxybenzyl chloride (1.9 mL, 2.2 g, 13.8 mmol) at 0 °C. After the mixture was stirred for 24 h at room temperature, the reaction was stopped with 0.2 M phosphate buffer (pH 6.5). The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give (±)-2-(4-methoxybenzyloxy)-1-morpholinopropan-1-one (**15**) as a colorless oil (3.06 g, 87%); IR (neat) 2961, 2903, 2857, 1647, 1514, 1464, 1437, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.43 (d, *J*=7.0 Hz, 3H), 3.60–3.67 (m, 8H), 3.80 (s, 3H), 4.30 (q, *J*=7.0 Hz, 1H), 4.40 (d, *J*=11.5 Hz, 1H), 4.52 (d, *J*=11.5 Hz, 1H), 6.88 (d, *J*=8.5 Hz, 2H), 7.25 (dd, J_1=2.5 Hz, J_2=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=17.8, 42.4, 45.6, 55.2, 66.7, 67.0, 70.8, 75.0, 113.8, 129.4, 129.5, 159.4, 170.7.

Under an argon atmosphere, to a solution of (±)-**15** (4.6 g, 16.5 mmol) in THF (40 mL) was added 3-butenylmagnesium bromide (90 mL, 2.2 M in THF) at 0 °C and stirred for 24 h at room temperature. After the reaction was stopped with satd NH_4Cl aqueous solution, the products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give (±)-2-(4-methoxybenzyloxy)-6-hepten-3-one (**16**) as a colorless oil (3.03 g, 74%); IR (neat) 2978, 2936, 2837, 1717, 1514, 1250, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.32 (d, *J*=7.0 Hz, 3H), 2.28–2.35 (m, 2H), 2.63 (td, J_1=7.5 Hz, J_2=17.5 Hz, 1H), 2.67 (td, J_1=7.5 Hz, J_2=17.5 Hz, 1H), 3.80 (s, 3H), 3.91 (q, *J*=6.5 Hz, 1H), 4.44 (d, *J*=11.5 Hz, 1H), 4.47 (d, *J*=11.5 Hz, 1H), 4.91–5.07 (m, 2H), 5.81 (tdd, J_1=6.5 Hz, J_2=10.5 Hz, J_3=17.0 Hz, 1H), 6.86–6.91 (m, 2H), 7.23–7.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=17.4, 27.2, 36.5, 55.3, 71.6, 80.3, 113.9, 115.2, 129.4, 129.6, 137.2, 159.4, 212.2.

Under an argon atmosphere, to a solution of (±)-**16** (2.0 g, 8.06 mmol) in Et_2O (30 mL) was slowly added $Zn(BH_4)_2$ (120 mL, ca. 0.13 M in Et_2O) at −30 °C, and the mixture was stirred for 24 h. The reaction was quenched with 0.2 M phosphate buffer (pH 6.5). The products were extracted with AcOEt (×4), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give (2*RS*,3*SR*)-2-(4-methoxybenzyloxy)-6-hepten-3-one ((±)-**17**) as a colorless oil (962 mg, 48%). The diastereoselectivity was not determined, but the amount of the minor isomer was very small; IR (neat) 3447, 2928, 2855, 1613, 1514, 1248, 1080, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.15 (d, *J*=6.5 Hz, 3H), 1.41–1.59 (m, 2H), 1.63 (br s, 1H), 2.03–2.18 (m, 1H), 2.20–2.34 (m, 1H), 3.49 (dq, J_1=3.5 Hz, J_2=6.5 Hz, 1H), 3.69–3.78 (m, 1H), 3.80 (s, 3H), 4.44 (d, *J*=11.5 Hz, 1H), 4.53 (d, *J*=11.5 Hz, 1H), 4.94–5.07 (m, 2H), 5.83 (tdd, J_1=6.5 Hz, J_2=10.5 Hz, J_3=17.0 Hz, 1H), 6.85–6.90 (m, 2H), 7.23–7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 22.6, 31.6, 55.3, 60.4, 70.3, 72.4, 113.8, 114.8, 129.2, 138.4, 157.8.

To a solution of (±)-**17** (195 mg, 0.78 mmol) in MeOH (30 mL) was added a catalytic amount of *p*-TsOH at room temperature, and stirred overnight. The reaction was stopped with satd $NaHCO_3$ aqueous solution, and the products were extracted with AcOEt (×3), and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=5/1) to give (±)-**18a** (*anti*) as a colorless oil (77.4 mg, 76%); IR (neat) 3377, 3077, 2974, 2926, 2855, 1641, 1449, 1065, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.16 (d, *J*=6.5 Hz, 3H), 1.52 (dt, J_1=6.5 Hz, J_2=7.5 Hz, 2H), 1.96 (br s, 2H), 2.04–2.30 (m, 2H), 3.64 (dt, J_1=3.5 Hz, J_2=6.5 Hz, 1H), 3.81 (qd, J_1=3.5 Hz, J_2=6.5 Hz, 1H), 5.07 (tdd, J_1=J_2=1.5 Hz, J_3=17.0 Hz, 2H), 5.85 (tdd, J_1=6.5 Hz, J_2=10.5 Hz, J_3=17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=16.7, 30.2, 30.7, 70.4, 74.4, 115.1, 138.3; MS *m/z* (rel intensities) 130 (M^+, 2.0%), 112 (6.1), 94 (4.4), 85 (8.4), 83 (15), 73 (13); HRMS *m/z* 130.0946 (130.0994 calcd for $C_7H_{14}O_2$, M^+).

4.3. Preparation of 1,3-diols

4.3.1. (2*RS*,4*SR*)- and (2*RS*,4*RS*)-6-Heptene-2,4-diol ((±)-32a (*syn*) and (±)-32b (*anti*)). To a solution of ethyl 3-oxobutanoate (**20**, 30.0 g, 231 mmol) in benzene (60 mL) were added a solution of ethylene glycol (42.9 g, 691.6 mmol) in benzene (60 mL) and a catalytic amount of *p*-TsOH at room temperature. After the mixture was stirred for 20 h under reflux, the reaction was stopped with satd $NaHCO_3$ aqueous solution at 0 °C. The organic layer was washed with satd $NaHCO_3$ aqueous solution (×3) and brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by distillation to give ethyl (2-methyl-1,3-dioxolan-2-yl)acetate (**21**) as a colorless oil (29.4 g, 73%); bp 90–120 °C (23 mmHg); IR (neat) 3468, 2889, 1744, 1377, 1225, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.27 (t, *J*=7.0 Hz, 2H), 1.51 (s, 3H), 2.67 (s, 2H), 3.99 (s, 4H), 4.16 (q, *J*=7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 24.5, 44.2, 60.5, 64.8, 107.6.

Under an argon atmosphere, to a suspension of $LiAlH_4$ (15.0 g, 86.2 mmol) in THF (150 mL) was added a solution of **21** (3.30 g, 86.2 mmol) in THF (90 mL) at 0 °C. The mixture was stirred for 1 h. The reaction was quenched slowly

with H_2O (3.3 mL), 15% NaOH (3.3 mL), H_2O (6.6 mL) at 0 °C, and the mixture was stirred for 24 h. After filtration through a Celite pad and evaporation under reduced pressure, the residue was purified by distillation to give 2-(2-methyl-1,3-dioxolan-2-yl)ethanol (**22**) as a colorless oil (10.3 g, 91%); bp 100–114 °C (24 mmHg); IR (neat) 3383, 1651, 1381, 1150, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.37 (s, 3H), 1.95 (t, J=5.5 Hz, 2H), 2.94 (t, J=5.5 Hz, 1H), 3.76 (dt, J_1=J_2=5.5 Hz, 2H), 4.0 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=23.8, 40.3, 59.0, 64.5, 110.0.

Under an argon atmosphere, to a solution of oxalyl chloride (5.77 g, 45.5 mmol) in CH_2Cl_2 (30 mL) was added a solution of DMSO (7.09 g, 90.1 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 5 min, a solution of **22** (5.01 g, 37.9 mmol) in THF (40 mL) was added to the mixture at −78 °C, and the mixture was stirred for 10 min. After an addition of triethylamine (13.8 g, 136.4 mmol) to the solution at −78 °C, the mixture was warmed up to 0 °C. The reaction was stopped with 0.1 M phosphate buffer (pH 6.5). The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=6/1→5/1→3/1) to give 3-(1,3-dioxolan-2-yl)-butanal (**23**) as a colorless oil (3.71 g, 75%); IR (neat) 1715, 1418, 1385, 1360, 1132, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.43 (s, 3H), 2.72 (d, J=3.0 Hz, 2H), 3.93–4.07 (m, 4H), 9.76 (t, J=3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=25.0, 52.5, 64.8, 107.6, 200.2.

Under an argon atmosphere, to a solution of **23** (610 mg, 4.69 mmol) in THF (80 mL) was added a solution of allylmagnesium bromide (9.38 mL, 1.0 M THF solution) at 0 °C. After the mixture was stirred for 1 h, the reaction was stopped with satd NH_4Cl aqueous solution at 0 °C. The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=5/1) to give (±)-2-methyl-2-(2-hydroxy-4-penten)-1,3-dioxolane (**24**) as a colorless oil (700 mg, 88%); IR (neat) 2982, 1641, 1217, 1107, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.37 (s, 3H), 1.70–1.95 (m, 2H), 2.10–2.35 (m, 2H), 3.57 (s, 1H), 3.92–4.03 (m, 1H), 3.98–4.03 (s, 4H), 5.02–5.18 (m, 2H), 5.85 (tdd, J_1=7.0 Hz, J_2=10 Hz, J_3=17 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=24.1, 41.7, 44.2, 64.3, 64.7, 67.5, 110.4, 117.3, 134.8.

To a solution of (±)-**24** (1.00 g, 5.83 mmol) in THF (20 mL) was added a solution of 2 M HCl aq (20 mL) at 0 °C. The mixture was stirred for 6 h and the reaction was stopped with H_2O at 0 °C. The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=5/1) to give (±)-4-hydroxy-6-hepten-2-one (**26**) as a colorless oil (530 mg, 71%); IR (neat) 3429, 2924, 1709, 1420, 1167, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.18 (s, 3H), 2.20–2.33 (m, 2H), 2.58 (dd, J_1=8.5 Hz, J_2=17.5 Hz, 1H), 2.63 (dd, J_1=4.0 Hz, J_2=17.5 Hz, 1H), 3.13 (br s, 1H), 4.05–4.20 (m, 1H), 5.02–5.20 (m, 2H), 5.70–5.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=30.7, 40.8, 49.1, 66.9, 118.0, 134.1, 209.6.

Procedure A: to a solution of (±)-**26** (810 mg, 6.33 mmol) in MeOH (40 mL) was added sodium borohydride (479 mg, 12.7 mmol) at 0 °C. After the mixture was stirred for 2 h at room temperature, the reaction was stopped with brine at 0 °C. The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=3/1) to give (±)-**32a** (*syn*) and (±)-**32b** (*anti*) as colorless oils (**32a**, 446 mg, 56%; **32b**, 223 mg, 28%).

Procedure B: under an argon atmosphere, to Me_4NBH_4 (1.07 g, 12.0 mol) were slowly added AcOH (4 mL) at 0 °C and CH_3CN (11 mL) at room temperature, and the mixture was stirred for 30 min. After the addition of (±)-**26** (699 mg, 5.46 mmol) in CH_3CN (10 mL) at 0 °C and stirring for 3 h, the reaction was quenched with 0.5 M $C_4H_4KNaO_6$ aqueous solution (10 mL). The products were extracted with AcOEt (×3), and the organic layer was washed with satd $NaHCO_3$ aqueous solution, brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=3/1) to give (±)-**32a** (*syn*) and (±)-**32b** (*anti*) as colorless oils (**32a**, 172 mg, 24%; **32b**, 516 mg, 73%).

Compound (±)-**32a** (*syn*): IR (neat) 3339, 3077, 2969, 2932, 1641, 1418, 1375, 1325 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.21 (d, J=6.0 Hz, 3H), 1.51 (td, J_1=10.0 Hz, J_2=14.5 Hz, 1H), 1.61 (td, J_1=2.5 Hz, J_2=14.0 Hz, 1H), 2.17–2.25 (m, 2H), 3.10 (br s, 1H), 3.29 (br s, 1H), 3.83–3.97 (m, 1H), 3.98–4.17 (m, 1H), 5.10–5.20 (m, 2H), 5.76–5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=24.0, 42.6, 44.1, 68.9, 71.8, 118.3, 134.2; MS *m*/*z* (rel intensities) 131 (M^++H, 11%), 112 (36), 94 (41), 89 (100), 87 (69), 73 (28); HRMS *m*/*z* 131.1060 (131.1072 calcd for $C_7H_{15}O_2$, M^++H).

Compound (±)-**32b** (*anti*): IR (neat) 3368, 3077, 2970, 2932, 1641, 1412, 1375, 1350 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.24 (d, J=6.0 Hz, 3H), 1.62 (dd, J_1=J_2=6.0 Hz, 2H), 2.18–2.32 (m, 2H), 2.64 (br s, 2H), 4.00 (tt, J_1=J_2=6.0 Hz, 1H), 4.16 (tq, J_1=J_2=6.0 Hz, 1H), 5.05–5.20 (m, 2H), 5.74–5.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=23.5, 41.9, 43.5, 65.4, 68.1, 118.3, 134.6; MS *m*/*z* (rel intensities) 130 (M^+, 5.5%), 112 (20), 94 (13), 89 (11), 85 (54), 71 (95); HRMS *m*/*z* 130.0995 (130.0994 calcd for $C_7H_{14}O_2$, M^+).

4.3.2. (2*RS*,4*SR*)- and (2*RS*,4*RS*)-heptane-2,4-diol ((±)-33a (*syn*) and (±)-33b (*anti*)). According to the procedure for the preparation of **24** described above, the aldehyde **23** (1.15 g, 8.82 mmol) was converted to (±)-1-(2-methyl-1,3-dioxolan-2-yl)-2-pentanol (**25**) as a colorless oil (1.17 g, 76%); IR (neat) 3526, 2957, 2934, 2874, 1377, 1256, 1219, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=7.0 Hz, 3H), 1.22–1.60 (m, 4H), 1.37 (s, 3H), 1.76 (dd, J_1=9.0 Hz, J_2=14.5 Hz, 1H), 1.82 (dd, J_1=2.0 Hz, J_2=14.5 Hz, 1H), 3.56 (s, 1H), 3.85–3.95 (m, 1H),

3.95–4.06 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.1, 18.6, 24.1, 39.5, 44.8, 64.2, 64.7, 67.7, 110.4.

According to the procedure for the preparation of **26** described above, **25** (602 mg, 3.46 mmol) was converted to (±)-4-hydroxy-2-heptanone (**27**) as a colorless oil (356 mg, 79%); IR (neat) 3441, 2959, 2932, 2874, 1713, 1418, 1362, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.93 (t, J=7.0 Hz, 3H), 1.20–1.57 (m, 4H), 2.18 (s, 3H), 2.54 (dd, J_1=9.0 Hz, J_2=17.5 Hz, 1H), 2.61 (dd, J_1=3.0 Hz, J_2=17.5 Hz, 1H), 2.97 (br s, 1H), 3.90–4.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.9, 18.6, 30.7, 38.5, 49.9, 67.3, 210.0.

Procedure A: according to the procedure for the preparation of **32** described above, (±)-**27** (645 mg, 4.96 mmol) was converted to (±)-**33a** (*syn*) and (±)-**33b** (*anti*) as colorless oils (**33a**, 420 mg, 64%; **33b**, 210 mg, 32%).

Procedure B: according to the procedure for the preparation of **32** described above, (±)-**27** (566 mg, 4.35 mmol) was converted to (±)-**33a** (*syn*) and (±)-**33b** (*anti*) as colorless oils (**33a**, 89.0 mg, 16%; **33b**, 445 mg, 78%).

Compound **33a** (*syn*): IR (neat) 3349, 2961, 2932, 2872, 1418, 1375, 1323 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.93 (t, J=7.0 Hz, 3H), 1.21 (d, J=6.5 Hz, 3H), 1.29–1.62 (m, 6H), 2.97 (br s, 2H), 3.86–3.88 (m, 1H), 4.01–4.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.0, 18.4, 24.2, 40.4, 44.6, 69.2, 72.8; MS *m*/*z* (rel intensities) 132 (M^+, 6.1%), 114 (100), 101 (6.7), 96 (41), 87 (20), 71 (100); HRMS *m*/*z* 132.1119 (132.1150 calcd for $C_7H_{16}O_2$, M^+).

Compound **33b** (*anti*): IR (neat) 3348, 2961, 2932, 2872, 1456, 1418, 1377, 1325 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.94 (t, J=7.0 Hz, 3H), 1.24 (d, J=6.0 Hz, 3H), 1.10–1.81 (m, 4H), 1.61 (dd, J_1=5.0 Hz, J_2=6.0 Hz, 2H), 2.50 (br s, 2H), 3.90–4.01 (m, 1H), 4.08–4.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 18.9, 23.5, 39.5, 43.9, 65.5, 69.1; MS *m*/*z* (rel intensities) 132 (M^+, 2.0%), 114 (28), 101 (17), 96 (25), 87 (13), 71 (90); HRMS *m*/*z* 132.1141 (132.1150 calcd for $C_7H_{16}O_2$, M^+).

4.3.3. (2*RS*,4*SR*)- and (2*RS*,4*RS*)-7-benzyloxyheptane-2,4-diol ((±)-34a (*syn*) and (±)-34b (*anti*)). Under an argon atmosphere, to a solution of (±)-**24** (2.00 g, 11.6 mmol) in CH_2Cl_2 (30 mL) was added a solution of diisopropylamine (6.1 mL, 34.9 mmol) and chloromethylmethylether (1.8 mL, 23.3 mmol). The mixture was stirred for 17 h at room temperature and the reaction was stopped with 0.1 M phosphate buffer (pH 6.5) at 0 °C. The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1→7/1→4/1) to give (±)-2-(2-methoxymethoxypent-4-enyl)-2-methyl-1,3-dioxolane (**28**) as a colorless oil (2.2 g, 89%); IR (neat) 2934, 1639, 1377, 1146, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.36 (s, 3H), 1.86 (dd, J_1=5.0 Hz, J_2=14.5 Hz, 1H), 1.91 (dd, J_1=6.0 Hz, J_2=14.5 Hz, 1H), 2.25–2.48 (m, 2H), 3.39 (s, 3H), 3.79–3.87 (m, 1H), 3.89–3.98 (m, 4H), 4.67 (d, J=7.0 Hz, 1H), 4.68 (d, J=7.0 Hz, 1H), 5.02–5.14 (m, 2H), 5.84 (tdd, J_1=7.0 Hz, J_2=10.0 Hz, J_3=17.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=24.3, 40.1, 43.1, 55.7, 64.3, 64.4, 73.6, 95.6, 109.0, 117.3, 134.7.

Under an argon atmosphere, to a solution of (±)-**28** (1.00 g, 4.63 mol) in THF (15 mL) was added BH_3·THF (9.3 mL, 9.26 mol) at 0 °C. The mixture was stirred for 40 min and the reaction was quenched with 2 M NaOH (9.3 mL) and H_2O_2 (9.3 mL). After 1 h, the products were extracted with Et_2O (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give (±)-4-methoxymethoxy-5-(2-methyl-1,3-dioxolan-2-yl)-1-pentanol (**29**) as a colorless oil (900 mg, 90%); IR (neat) 3476, 2886, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.35 (s, 3H), 1.55–2.05 (m, 7H), 3.40 (s, 3H), 3.66 (t, J=7.0 Hz, 2H), 3.75–3.85 (m, 1H), 3.86–4.01 (m, 4H), 4.63 (d, J=7.0 Hz, 1H), 4.72 (d, J=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=24.3, 28.1, 32.0, 43.5, 55.7, 62.9, 64.3, 64.5, 73.9, 95.5, 108.9.

Under an argon atmosphere, to a solution of NaH (890 mg, 22.2 mmol) in THF (30 mL) was added a solution of (±)-**29** (2.59 g, 11.1 mmol) in THF (25 mL) and benzyl bromide (1.3 mL, 11.1 mmol) at 0 °C. The mixture was stirred for 48 h under reflux and the reaction was stopped with 0.1 M phosphate buffer (pH 6.5) at 0 °C. The products were extracted with AcOEt (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1) to give (±)-2-(5-benzyloxy-2-methoxymethoxypentyl)-2-methyl-1,3-dioxolane (**30**) as a colorless oil (3.2 g, 88%); IR (neat) 2932, 2880, 1454, 1375, 1038, 947, 916, 737, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.35 (s, 3H), 1.50–2.05 (m, 6H), 3.37 (s, 3H), 3.49 (t, J=6.0 Hz, 2H), 3.70–3.81 (m, 1H), 3.82–4.00 (m, 4H), 4.50 (s, 2H), 4.62 (d, J=7.0 Hz, 1H), 4.70 (d, J=7.0 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=24.3, 25.1, 32.2, 43.6, 55.7, 64.3, 64.4, 70.3, 72.8, 73.8, 95.4, 108.9, 127.4, 127.5, 128.3, 138.6.

To a solution of (±)-**30** (1.00 g, 3.09 mmol) in THF (50 mL) was added a solution of 2 M HCl aq (20 mL) at 0 °C. The mixture was stirred for 24 h and the reaction was stopped with 0.2 M phosphate buffer (pH 6.5) at 0 °C. The products were extracted with Et_2O (×3), and the organic layer was washed with brine, and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=5/1) to give (±)-7-benzyloxy-4-hydroxy-heptan-2-one (**31**) as a colorless oil (510 mg, 71%); IR (neat) 3433, 2926, 2859, 1711, 1454, 1362, 1099, 739, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.45–1.85 (m, 4H), 2.17 (s, 3H), 2.53–2.63 (m, 2H), 3.29 (br s, 1H), 3.51 (t, J=6.0 Hz, 2H), 4.00–4.10 (m, 1H), 4.51 (s, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=25.9, 30.8, 33.5, 50.1, 67.4, 70.2, 73.0, 127.6, 127.7, 128.4, 138.3, 209.7.

Procedure A: according to the procedure for the preparation of **32** described above, (±)-**31** (500 mg, 2.12 mmol) was

converted to (±)-**34a** (*syn*) and (±)-**34b** (*anti*) as colorless oils (**34a**, 252 mg, 50%; **34b**, 168 mg, 34%).

Procedure B: according to the procedure for the preparation of **32** described above, (±)-**31** (315 mg, 1.34 mmol) was converted to (±)-**34a** (*syn*) and (±)-**34b** (*anti*) as colorless oils (**34a**, 118 mg, 37%; **34b**, 177 mg, 56%).

Compound **34a** (*syn*): IR (neat) 3383, 2928, 2857, 1454, 1406, 1323, 1099, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.18 (d, J=6.0 Hz, 3H), 1.43–1.80 (m, 6H), 3.52 (t, J=6.0 Hz, 2H), 3.66 (br s, 2H), 3.80–3.92 (m, 1H), 3.97–4.09 (m, 1H), 4.53 (s, 2H), 7.22–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=23.0, 25.2, 33.8, 44.8, 68.9, 70.0, 72.3, 72.8, 127.6, 127.8, 128.3, 138.5; MS *m/z* (rel intensities) 238 (M^+, 4.9%), 179 (9.2), 149 (100), 107 (66), 99 (43), 91 (100); HRMS *m/z* 238.1570 (238.1569 calcd for $C_{14}H_{22}O_3$, M^+).

Compound **34b** (*anti*): IR (neat) 3377, 2928, 2857, 1454, 1408, 1312, 1099, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.22 (d, J=6.0 Hz, 3H), 1.50–1.82 (m, 6H), 2.80 (br s, 1H), 3.42 (br s, 1H), 3.46–3.59 (m, 2H), 3.90–4.00 (m, 1H), 4.08–4.21 (m, 1H), 4.53 (s, 2H), 7.24–7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.4, 26.5, 34.9, 44.0, 65.4, 69.2, 70.5, 73.1, 127.7, 127.8, 128.4, 137.9; MS *m/z* (rel intensities) 238 (M^+, 7.7%), 179 (79), 147 (21), 131 (77), 107 (100), 91 (100); HRMS *m/z* 238.1572 (238.1569 calcd for $C_{14}H_{22}O_3$, M^+).

4.4. Preparation of five-membered cyclic carbonates

4.4.1. (4*RS*,5*SR*)-4-(3-Benzyloxy)propyl-5-methyl-1,3-dioxolan-2-one ((±)-4a (*cis*)). Under an argon atmosphere, pyridine (7.9 g, 0.10 mmol) was added to a solution of (±)-**3a** (3.9 g, 17.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C, followed by addition of a solution of triphosgene (3.1 g, 10.3 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The mixture was then slowly warmed to 0 °C and stirred for 1 h. The reaction was stopped with a satd NH_4Cl aqueous solution and the products were extracted with CH_2Cl_2 (×3). The organic layer was washed with 1 M HCl (×2), brine, satd $NaHCO_3$ aqueous solution, and brine, and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give (±)-**4a** as a colorless oil (3.96 g, 92%); IR (neat) 2938, 2859, 1798, 1717, 1452, 1368, 1184, 1074, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.36 (d, J=7.0 Hz, 3H), 1.66–1.90 (m, 4H), 3.48–3.53 (m, 1H), 3.53–3.60 (m, 1H), 4.51 (s, 2H), 4.65 (ddd, J_1=4.0 Hz, J_2=5.5 Hz, J_3=7.0 Hz, 1H), 4.82 (dq, J_1=J_2=7.0 Hz, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.5, 25.9, 69.1, 72.9, 75.9, 79.7, 127.6, 127.7, 128.4, 138.2, 154.6; MS *m/z* (rel intensities) 250 (M^+, 18%), 173 (15), 107 (56), 91 (100); HRMS *m/z* 250.1187 (250.1205 calcd for $C_{14}H_{18}O_4$, M^+).

4.4.2. (4*RS*,5*RS*)-4-(3-Benzyloxy)propyl-5-methyl-1,3-dioxolan-2-one ((±)-4b (*trans*)). According to the procedure for the preparation of **4a** described above, (±)-**3b** (445 mg, 1.99 mmol) was converted to (±)-**4b** (*trans*) as a colorless oil (478 mg, 96%); IR (neat) 2934, 2859, 1798, 1454, 1373, 1186, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.43 (d, J=6.5 Hz, 3H), 1.59–1.87 (m, 4H), 3.45–3.60 (m, 2H), 4.22 (ddd, J_1=2.0 Hz, J_2=6.5 Hz, J_3=12.0 Hz, 1H), 4.38 (dq, J_1=J_2=6.5 Hz, 1H), 4.50 (s, 2H), 7.27–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=19.5, 25.1, 30.2, 69.1, 73.0, 78.4, 83.3, 127.6, 127.7, 128.4, 138.1, 154.5; MS *m/z* (rel intensities) 250 (M^+, 28%), 173 (19), 71 (22), 43 (100); HRMS *m/z* 250.1200 (250.1205 calcd for $C_7H_{12}O_3$, M^+).

4.4.3. (4*RS*,5*SR*)-4-Butyl-5-methyl-1,3-dioxolan-2-one ((±)-11a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**8a** (375 mg, 2.84 mmol) was converted to (±)-**11a** (*cis*) as a colorless oil (350 mg, 78%); IR (neat) 2959, 1788, 1462, 1371, 1190, 1070, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.93 (t, J=7.0 Hz, 3H), 1.30–1.42 (m, 3H), 1.36 (d, J=6.5 Hz, 3H), 1.49–1.60 (m, 2H), 1.67–1.78 (m, 1H), 4.64 (ddd, J_1=3.5 Hz, J_2=7.0 Hz, J_3=10.0 Hz, 1H), 4.84 (qd, J_1=J_2=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 14.5, 22.3, 28.4, 75.9, 79.9, 154.7; MS *m/z* (rel intensities) 159 (M^++H, 4.5%), 101 (46), 85 (100), 72 (100), 57 (100); HRMS *m/z* 159.1046 (159.1021 calcd for $C_8H_{15}O_3$, M^++H).

4.4.4. (4*RS*,5*RS*)-4-Butyl-5-methyl-1,3-dioxolan-2-one ((±)-11b (*trans*)). According to the procedure for the preparation of **4a** described above, (±)-**8b** (1.07 g, 8.10 mmol) was converted to (±)-**11b** (*trans*) as a colorless oil (1.09 g, 85%); IR (neat) 2959, 2934, 2872, 1798, 1454, 1377, 1188, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.93 (t, J=6.5 Hz, 3H), 1.31–1.55 (m, 4H), 1.46 (d, J=6.5 Hz, 3H), 1.60–1.83 (m, 2H), 4.19 (dt, J_1=5.0 Hz, J_2=6.5 Hz, 1H), 4.38 (dq, J_1=J_2=6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=13.8, 19.1, 22.3, 26.7, 32.8, 78.4, 83.5, 154.6; MS *m/z* (rel intensities) 159 (M^++H, 2.0%), 101 (17), 85 (36), 71 (61), 57 (100); HRMS *m/z* 159.0966 (159.1021 calcd for $C_8H_{15}O_3$, M^++H).

4.4.5. (4*RS*,5*SR*)-4-Methyl-5-pentyl-1,3-dioxolan-2-one ((±)-12a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**9a** (2.08 g, 18.6 mmol) was converted to (±)-**12a** (*cis*) as a colorless oil (1.63 g, 60%); IR (neat) 2957, 2932, 2860, 1798, 1466, 1370, 1186, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.91 (t, J=7.0 Hz, 3H), 1.23–1.45 (m, 5H), 1.36 (d, J=6.5 Hz, 3H), 1.45–1.64 (m, 2H), 1.64–1.80 (m, 1H), 4.63 (ddd, J_1=3.5 Hz, J_2=7.0 Hz, J_3=10.0 Hz, 1H), 4.82 (dq, J_1=J_2=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.9, 14.5, 22.4, 25.2, 28.8, 31.4, 75.9, 79.9, 154.6; MS *m/z* (rel intensities) 173 (M^++H, 3.9%), 157 (4.8), 129 (13), 110 (21), 99 (78), 85 (68); HRMS *m/z* 173.1174 (173.1178 calcd for $C_9H_{17}O_3$, M^++H).

4.4.6. (4*RS*,5*SR*)-4-Heptyl-5-methyl-1,3-dioxolan-2-one ((±)-13a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**10a** (418 mg, 2.01 mmol) was converted to (±)-**13a** (*cis*) as a colorless oil (405 mg, 97%); IR (neat) 2953, 2928, 2857, 1798, 1370, 1180, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.89 (t, J=6.0 Hz, 3H), 1.24–1.44 (m, 9H), 1.36 (d, J=6.5 Hz, 3H), 1.45–1.64 (m, 2H), 1.64–1.81 (m, 1H), 4.63 (ddd, J_1=3.5 Hz, J_2=6.5 Hz, J_3=10.0 Hz, 1H), 4.82 (dq, J_1=J_2=6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 14.5, 22.6, 25.6, 28.8, 29.0, 29.2, 31.7, 75.9, 79.9, 154.7; MS *m/z* (rel intensities) 201 (M^++H, 2.1%), 156 (1.9), 138

(29), 127 (33), 113 (17), 99 (11); HRMS *m/z* 201.1490 (201.1491 calcd for $C_{11}H_{21}O_3$, M^++H).

4.4.7. (4*RS*,5*SR*)-4-(3-Butenyl)-5-methyl-1,3-dioxolan-2-one ((±)-19a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**18a** (325 mg, 2.50 mmol) was converted to (±)-**19a** (*cis*) as a colorless oil (200 mg, 51%); IR (neat) 2982, 2926, 2853, 1798, 1370, 1186, 1074, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.37 (d, J=6.5 Hz, 3H), 1.55–1.69 (m, 1H), 1.75–1.93 (m, 1H), 2.07–2.24 (m, 1H), 2.24–2.75 (m, 1H), 4.61–4.73 (m, 1H), 4.84 (dq, J_1=J_2=6.5 Hz, 1H), 5.00–5.18 (m, 2H), 5.80 (tdd, J_1=6.5 Hz, J_2=10.5 Hz, J_3=17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.5, 28.1, 29.5, 75.8, 78.9, 116.4, 136.2, 154.5; MS *m/z* (rel intensities) 156 (M^+, 13%), 114 (16), 112 (6.8), 97 (39), 85 (12), 84 (51); HRMS *m/z* 156.0736 (156.0787 calcd for $C_8H_{12}O_3$, M^+).

4.5. Preparation of six-membered cyclic carbonates

4.5.1. (4*RS*,6*SR*)-4-Allyl-6-methyl-1,3-dioxan-2-one ((±)-35a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**32a** (100 mg, 0.77 mmol) was converted to (±)-**35a** (*cis*) as a colorless oil (93.2 mg, 78%); IR (neat) 2980, 2936, 1748, 1643, 1400, 1248, 1229, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.42 (d, J=6.0 Hz, 3H), 1.64 (td, J_1=12.0 Hz, J_2=14.0 Hz, 1H), 2.07 (td, J_1=3.0 Hz, J_2=14.0 Hz, 1H), 2.38–2.45 (m, 1H), 2.49–2.56 (m, 1H), 4.48 (ddt, J_1=3.0 Hz, J_2=J_3=6.0 Hz, 1H), 4.56 (ddq, J_1=3.0 Hz, J_2=6.0 Hz, J_3=11.5 Hz, 1H), 5.12–5.22 (m, 2H), 5.76–5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.1, 33.9, 75.1, 77.9, 119.4, 131.2, 149.1; MS *m/z* (rel intensities) 157 (M^++H, 3.7%), 141 (3.2), 129 (4.4), 112 (5.0), 97 (15), 87 (8.8); HRMS *m/z* 157.0864 (157.0865 calcd for $C_8H_{13}O_3$, M^++H).

4.5.2. (4*RS*,6*RS*)-4-Allyl-6-methyl-1,3-dioxan-2-one ((±)-35b (*anti*)). According to the procedure for the preparation of **4a** described above, (±)-**32b** (403 mg, 3.10 mmol) was converted to (±)-**35b** (*anti*) as a colorless oil (265 mg, 55%); IR (neat) 2980, 2938, 1746, 1643, 1387, 1254, 1202, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=1.45 (d, J=6.0 Hz, 3H), 1.90 (ddd, J_1=4.5 Hz, J_2=6.0 Hz, J_3= 9.0 Hz, 1H), 2.03 (ddd, J_1=4.5 Hz, J_2=7.0 Hz, J_3= 14.0 Hz, 1H), 2.38–2.44 (m, 1H), 2.57–2.63 (m, 1H), 4.56–4.61 (m, 1H), 4.68–4.74 (m, 1H), 5.16–5.23 (m, 2H), 5.75–5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.8, 31.5, 39.0, 77.0, 77.3, 119.5, 131.5, 149.2; MS *m/z* (rel intensities) 157 (M^++H, 30%), 141 (2.1), 129 (4.4), 112 (11), 97 (26), 84 (13); HRMS *m/z* 157.0873 (157.0865 calcd for $C_8H_{13}O_3$, M^++H).

4.5.3. (4*RS*,6*SR*)-4-Methyl-6-propyl-1,3-dioxan-2-one ((±)-36a (*cis*)). According to the procedure for the preparation of **4a** described above, (±)-**33a** (383 mg, 2.9 mmol) was converted to (±)-**36a** (*cis*) as a colorless oil (139 mg, 30%); IR (neat) 2961, 2936, 2874, 1744, 1400, 1248, 1198, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.96 (t, J= 7.0 Hz, 3H), 1.35–1.83 (m, 6H), 1.42 (d, J=6.0 Hz, 3H), 4.30–4.49 (m, 1H), 4.49–4.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.7, 17.7, 21.2, 34.8, 37.3, 75.1, 78.6, 149.4; MS *m/z* (rel intensities) 159 (M^++H, 34%), 143 (2.7), 130 (42), 114 (43), 86 (77), 72 (100); HRMS *m/z* 159.1022 (159.1021 calcd for $C_8H_{15}O_3$, M^++H).

4.5.4. (4*RS*,6*RS*)-4-Methyl-6-propyl-1,3-dioxan-2-one ((±)-36b (*anti*)). According to the procedure for the preparation of **4a** described above, (±)-**33b** (650 mg, 4.93 mmol) was converted to (±)-**36b** (*anti*) as a colorless oil (323 mg, 42%); IR (neat) 2961, 2938, 2874, 1746, 1387, 1252, 1204, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=0.96 (t, J=7.5 Hz, 3H), 1.41 (d, J=6.5 Hz, 3H), 1.42–1.79 (m, 6H), 4.39–4.49 (m, 1H), 4.49–4.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.7, 18.2, 20.8, 32.4, 36.9, 72.7, 75.9, 149.4; MS *m/z* (rel intensities) 159 (M^++H, 51%), 129 (6.1), 115 (12), 99 (6.1), 86 (7.1), 71 (100); HRMS *m/z* 159.1047 (159.1021 calcd for $C_8H_{15}O_3$, M^++H).

4.5.5. (4*RS*,6*SR*)-4-(3-Benzyloxypropyl)-6-methyl-1,3-dioxan-2-one ((±)-37a (*syn*)). According to the procedure for the preparation of **4a** described above, (±)-**34a** (100 mg, 0.42 mmol) was converted to (±)-**37a** (*syn*) as a colorless oil (87.8 mg, 79%); IR (neat) 2932, 2857, 1746, 1042, 1244, 1194, 1113, 737, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.39 (d, J=6.0 Hz, 3H), 1.50–1.90 (m, 4H), 1.98–2.10 (m, 2H), 3.44–3.58 (m, 2H), 4.38–4.58 (m, 2H), 4.50 (s, 2H), 7.24–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.2, 24.7, 32.3, 34.7, 69.4, 72.9, 75.1, 78.6, 127.6, 128.4, 138.3, 149.1; MS *m/z* (rel intensities) 264 (M^+, 4.2%), 221 (5.8), 160 (100), 130 (15), 107 (96), 91 (100); HRMS *m/z* 264.1373 (264.1362 calcd for $C_{15}H_{20}O_4$, M^+).

4.5.6. (4*RS*,6*RS*)-4-(3-Benzyloxy-propyl)-6-methyl-1,3-dioxan-2-one ((±)-37b (*anti*)). According to the procedure for the preparation of **4a** described above, (±)-**34b** (520 mg, 2.19 mmol) was converted to (±)-**37b** (*anti*) as a colorless oil (437 mg, 76%); IR (neat) 2934, 2859, 1746, 1387, 1252, 1207, 1115, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.40 (d, J=6.5 Hz, 3H), 1.65–2.10 (m, 6H), 3.44–3.60 (m, 2H), 4.44–4.60 (m, 1H), 4.50 (s, 2H), 4.62–4.74 (m, 1H), 7.24–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.7, 25.2, 31.9, 32.4, 69.3, 72.7, 72.9, 75.9, 127.6, 128.4, 138.2, 149.3; MS *m/z* (rel intensities) 264 (M^+, 6.9%), 173 (6.5), 159 (4.6), 107 (46), 91 (100), 71 (100); HRMS *m/z* 264.1336 (264.1362 calcd for $C_{15}H_{20}O_4$, M^+).

4.6. Typical procedure for the hydrolysis of cyclic carbonates with *P. diminuta*

The basal medium for the microbial reaction consists of glucose (10 g), polypeptone (7 g), and yeast extract (5 g) in 1 L of 0.1 M phosphate buffer (pH 6.5). A 500-mL Erlenmeyer flask each containing 100 mL of sterilized basal medium was inoculated with a loopful of *P. diminuta*, and incubated for 48 h at 30 °C. To the broth was added 80 μL (84 mg) of (±)-**4a** (*cis*) and the cultivation was continued. After 50 mL of acetone was added to the mixture followed by saturation with NaCl and filtration through a Celite pad, the products were extracted with AcOEt, and the organic layer was dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel (hexane/AcOEt=5/1) to afford (4*R*,5*S*)-**4a** (36.1 mg, 43%; 97% ee) and (2*R*,3*S*)-**3a** (30.1 mg, 40%; >99% ee) as colorless oils. The ee of (2*R*,3*S*)-**3a** was determined by HPLC analysis of the

corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm, DuPont Instruments); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 30 (2*R*,3*S*) and 32 (2*S*,3*R*) min. To determine the ee of (4*R*,5*S*)-**4a**, the cyclic carbonate was hydrolyzed with K_2CO_3 to afford the corresponding (2*S*,3*R*)-**3a**. The absolute configuration was confirmed by comparing its optical rotation sign with that of the authentic sample (2*S*,3*R*)-**3a**, and the preparation method is described in the following section.

Enantioselective reactions of the other substrates were carried out by the same procedure. The results were shown in the text. All the spectral data (^{1}H and ^{13}C NMR, IR, and MS) were in full agreement with those of the racemates. The ee's of diols were determined by HPLC or ^{1}H NMR analysis. The ee's of cyclic carbonates were determined by similar analyses of the corresponding diols derived from the carbonates with K_2CO_3. The methods and the conditions are given below:

Compound **3b**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm, Agilent Technologies); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 36 (2*S*,3*S*) and 39 (2*R*,3*R*) min.

Compound **8a**: ^{1}H NMR (500 MHz) analysis of the corresponding bis-(+)-MTPA ester. Signals at δ 3.42 (d, J=1.0 Hz)+3.50 (d, J=1.0 Hz) (CH_3O×2, (2*S*,3*R*)) and 3.46 (t, J=1.0 Hz) (CH_3O×2, (2*R*,3*S*)).

Compound **9a**: ^{1}H NMR (500 MHz) analysis of the corresponding bis-(+)-MTPA ester. Signals at δ 3.42 (s)+3.50 (d, J=1.0 Hz) (CH_3O×2, (2*S*,3*R*)) and 3.45 (s)+3.46 (s) (CH_3O×2, (2*R*,3*S*)). The absolute configuration was confirmed by comparing its optical rotation sign with that reported; (2*S*,3*R*)-**9a**, lit.[11] $[\alpha]_D^{18}$ +22.73 (*c* 1.10, MeOH).

Compound **10a**: ^{1}H NMR analysis of the corresponding bis-(+)-MTPA ester. Signals at δ 3.42 (d, J=1.0 Hz)+3.50 (s) (CH_3O×2, (2*S*,3*R*)) and 3.45 (d, J=1.0 Hz)+3.46 (s) (CH_3O×2, (2*R*,3*S*)).

Compound **18a**: ^{1}H NMR analysis of the corresponding bis-(+)-MTPA ester. Signals at δ 3.42 (s)+3.49 (s) (CH_3O×2, (2*S*,3*R*)) and 3.45 (s)+3.46 (s) (CH_3O×2, (2*R*,3*S*)).

Compound **32a**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 16 and 17 min.

Compound **32b**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 14 (2*R*,4*R*) and 16 (2*S*,4*S*) min.

Compound **33a**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 13.6 and 14.4 min.

Compound **33b**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 13 (2*R*,4*R*) and 14 (2*S*,4*S*) min.

Compound **34a**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 30 and 32 min.

Compound **34b**: HPLC analysis of the corresponding bis-(+)-MTPA ester. Conditions of the HPLC analysis: column, Zorbax-Sil (0.46 mm×25 cm); eluent, hexane/AcOEt=90/10; flow rate, 0.5 mL/min; retention time, 26 (2*R*,4*R*) and 32 (2*S*,4*S*) min.

4.7. Preparation of the authentic sample (2*S*,3*R*)-3a

According to the procedure described above for the preparation of (±)-**17**, (2*S*,3*R*)-2-(4-methoxybenzyloxy)-5-hexen-3-ol (**39**) was prepared from ethyl (*S*)-lactate in four steps.

Under an argon atmosphere, to a solution of (2*S*,3*R*)-**39** (502 mg, 2.13 mmol) in $CHCl_2$ (10 mL) were added 3,4-dihydro-2*H*-pyran (2.0 mL, 1.8 g, 21 mmol) and a catalytic amount of *p*-TsOH at 0 °C, and stirred overnight at room temperature. The reaction was stopped with satd $NaHCO_3$ aqueous solution, and the products were extracted with $CHCl_2$ (×3). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=10/1→5/1) to give (4*R*,5*S*)-5-(4-methoxybenzyloxy)-4-tetrahydropyranyloxy-1-hexene (**40**) as a colorless oil (433 mg, 64%). This compound included some impurity, but this was used without further purification.

Under an argon atmosphere, to a solution of (2*S*,3*R*)-**40** (400 mg, 1.25 mmol) in THF (10 mL) was added BH_3·THF (1.25 mL, 2.0 M in THF) at 0 °C and stirred for 4 h at room temperature. The reaction was quenched with a drop of water, followed by the addition of 2 M NaOH aqueous solution (2.5 mL) and 35% H_2O_2 (2.5 mL), and the mixture was stirred overnight at room temperature. After the mixture was saturated with NaCl, products were extracted with Et_2O (×3), and the organic layer was dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1→AcOEt) to give (4*R*,5*S*)-5-(4-methoxybenzyloxy)-4-tetrahydropyranyloxy-1-hexanol (**41**) as a colorless oil (262 mg, 62%).

According to the procedure for the preparation of (*Z*)-**2a** described above, (4*R*,5*S*)-**41** (329 mg, 0.973 mmol) was converted to (4*R*,5*S*)-1-benzyloxy-5-(4-methoxybenzyloxy)-4-tetrahydropyranyloxyhexane (**42**, 337 mg, 81%) as a colorless oil.

According to the procedure for the preparation of (±)-**18a** described above, (4*R*,5*S*)-**42** (259 mg, 0.605 mmol) was converted to (2*S*,3*R*)-**3a** (51.6 mg, 38%) as a colorless oil; $[\alpha]_D^{25}$ +12.9 (*c* 1.34, MeOH). All the spectral data (^{1}H and

^{13}C NMR, IR, and MS) of (2*S*,3*R*)-**3a** were in full agreement with those of (±)-**3a**.

4.8. Preparation of the authentic sample (2*S*,3*S*)-3b

Under an argon atmosphere, to a solution of (2*S*,3*R*)-**24** (400 mg, 1.25 mmol) in *t*-BuOH (5 mL)/H_2O (5 mL) mixed solvent was added AD-mix-α (1.4 g), and the mixture was stirred at room temperature. After the mixture changed to a biphasic clear solution, to the solution were added $CH_3SO_2NH_2$ (95 mg) and (*E*)-**2b** (190 mg, 1.0 mmol) at 0 °C, and stirred overnight at room temperature. After addition of NaS_2O_4 and stirring for 30 min, the products were extracted with AcOEt (×4), and the organic layer was washed with 2 M NaOH aqueous solution (×2). After the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/1) to give (2*S*,3*S*)-**3b** as a colorless oil (148 mg, 66%); $[\alpha]_D^{27}$ −13.8 (*c* 1.16, MeOH); $[\alpha]_D^{23}$ −8.0 (*c* 1.87, $CHCl_3$). All the spectral data (^{1}H and ^{13}C NMR, IR, and MS) of (2*S*,3*S*)-**3b** were in full agreement with those of (±)-**3b**.

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Synthesis of 1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones by cyclization of 1,1-bis(trimethylsiloxy)ketene acetals with pyrazine and quinoxaline

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Abstract—1,4-Diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones were prepared by cyclization of 1,1-bis(trimethylsiloxy)ketene acetals with pyrazine and quinoxaline.

1. Introduction

1,1-Bis(trimethylsiloxy)ketene acetals represent interesting synthetic building blocks, which can be regarded as masked carboxylic acid dianions.[1–3] Rudler et al. were the first to report the use of 1,1-bis(trimethylsiloxy)ketene acetals as 1,3-dinucleophiles in cyclization reactions: In 1999, they reported the synthesis of lactones by reaction of 1,1-bis(trimethylsiloxy)ketene acetals with chromium(0) complexes.[4] In 2000, Rudler et al. developed the palladium(0) catalysed reaction of 1,1-bis(trimethylsiloxy)ketene acetals with allyl acetates to give γ-unsaturated carboxylic acids, which were transformed into 5-(hydroxymethyl)-γ-lactones by addition of H_2O_2 in the presence of catalytic amounts of methyltrioxorhenium (MTO).[5] Rudler et al. also reported interesting reactions of 1,1-bis(trimethylsiloxy)ketene acetals with tropylium derivatives.[6] We reported the cyclocondensation of 1,1-bis(trimethylsiloxy)ketene acetals with oxalyl chloride[7] and 3-(siloxy)alk-2-en-1-ones to give maleic anhydrides and pyran-2-ones, respectively.[8]

Pyridinium salts represent important synthetic building blocks, which can be generated in situ by acylation of pyridines.[9] They have been used in various reactions with Grignard reagents, cyanide (Reissert reaction), trimethylsilylacetonitrile, allylsilanes, silyl enol ethers or diazoesters.[10] We reported the cyclization of 1,3-bis(silyl enol ethers)[11]—masked 1,3-dicarbonyl dianions—with isoquinoline.[12] In 2002, Rudler et al. reported the first cyclocondensations of 1,1-bis(trimethylsiloxy)ketene acetals with pyridine[13a] and later extended this interesting concept to other *N*-heterocycles.[13b] We reported the cyclocondensation of 1,1-bis(trimethylsiloxy)ketene acetals with isoquinoline.[14] Recently, Rudler et al. reported the first cyclizations of 1,1-bis(trimethylsiloxy)ketene acetals with pyrazine[13b,15] and quinoxaline.[15] These reactions provide a facile access to 2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones and 1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones, respectively. Herein, we report our own findings in this field. With regard to the previous report of Rudler et al.,[15] we extensively studied the preparative scope of the reactions. In addition, 2-monosubstituted 1,1-bis(trimethylsiloxy)ketene acetals have been employed by us, which give rise to questions of stereochemistry. The isomeric products could be successfully separated for the first time and their structure unambiguously assigned.

2,3-Benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones and 1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones are of biological relevance as they represent analogues of clofazimine, riboflavin (vitamin B_2) and lumiflavin. The substituted dihydrophenazine clofazimine represents an important drug against leprosy and is also effective against a number of diseases related to the autoimmune system.[16] However, there are serious problems, such as bacterial resistance.[16] Therefore, the development of suitable clofazimine analogues is of pharmacological relevance.

Keywords: Cyclizations; Heterocycles; Iminium salts; Pyrazine; Quinoxaline; Silyl enol ethers.
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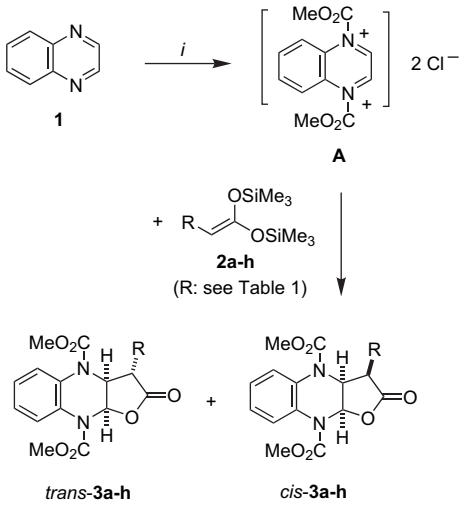
2. Results and discussion

The reaction of 1,1-bis(trimethylsiloxy)ketene acetal **2a** (1.4 equiv)[17] with quinoxaline (**1**) (1.0 equiv) in the presence of methyl chloroformate (4.0 equiv) afforded the 2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-one **3a** as a separable mixture of diastereomers *trans*-**3a** and *cis*-**3a** (Scheme 1 and Table 1). During the optimization of the cyclocondensation, the activating agent, stoichiometry, temperature and concentration played an important role. The formation of **3a** can be explained by formation of bis(iminium salt) **A**, attack of the carbon atom of **2a** onto **A** and subsequent cyclization. Alternatively, the reaction may proceed by formation of a simple iminium salt, reaction of the latter with **2a**, acylation of the second nitrogen atom and subsequent cyclization.



Scheme 1. Cyclization of 1,1-bis(siloxy)ketene acetals **2a–h** with **1**. *i*, **1** (1.0 equiv), **2** (1.4 equiv), $ClCO_2Me$ (4.0 equiv), CH_2Cl_2, 20 °C, 12 h.

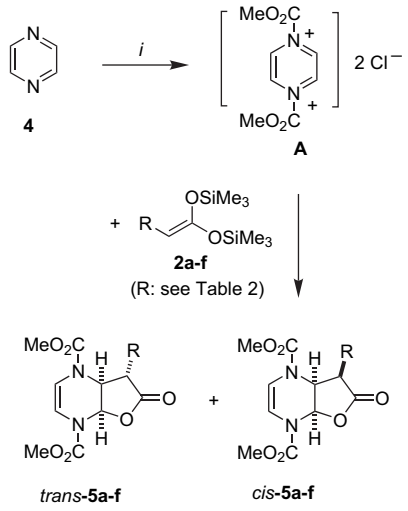
The preparative scope of the methodology was studied (Scheme 1 and Table 1). The reaction of **1** with 1,1-bis(trimethylsiloxy)ketene acetals **2b–h**, prepared from the corresponding alkanoic acids, afforded the 2,3-benzo-1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones **3b–h** as separable mixtures of diastereomers. As expected, a cis-annulation was observed for all 5,6-bicyclic products, due to steric reasons. In contrast to the reaction of isoquinoline with 1,1-bis(trimethylsiloxy)ketene acetals, the reaction of the latter with quinoxaline proceeded with low 1,2-diastereoselectivity. However, the isomers could be separated by chromatography, due to their different polarity.

Table 1. Products and yields

3	R	% (*trans*-**3**)[a]	% (*cis*-**3**)[a]
a	Et	19	28
b	^{n}Pr	29	21
c	^{n}Bu	11	25
d	^{n}Dodec	30	15
e	^{i}Pr	27	33
f	^{c}Hex	28	27
g	$CH_2(^{c}Pent)$	32	24
h	$(CH_2)_2(^{c}Hex)$	25	12

[a] Yields of isolated products.

The reaction of 1,1-bis(trimethylsiloxy)ketene acetal **2a** (1.4 equiv) with pyrazine (**4**) (1.0 equiv) in the presence of methyl chloroformate (4.0 equiv) afforded the 1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-one **5a** as a separable mixture of diastereomers *trans*-**5a** and *cis*-**5a** (Scheme 2 and Table 2). The reaction of **4** with 1,1-bis(trimethylsiloxy)-ketene acetals **2b–f** afforded the 1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones **5b–f** as separable mixtures of diastereomers.



Scheme 2. Cyclization of 1,1-bis(siloxy)ketene acetals **2a–f** with **4**: *i*, **4** (1.0 equiv), **2** (1.4 equiv), $ClCO_2Me$ (4.0 equiv), CH_2Cl_2, 20 °C, 12 h.

The relative configurations for chinoxalines **3** and pyrazines **5** were proved by NOESY experiments. In the NOESY spectra recorded for **3b**, **3f**, **3g** and **5e** cross peaks could be observed for the hydrogen atoms H-2 with H-9 (**3b**, **3f**, **3g**) and H-2 with H-7 (**5e**), respectively, only in the case of cis-compounds. The atom numbering for NMR assignment of **3** and **5** is given in Scheme 3. The cis- or trans-configuration of the other compounds **3** and **5** could be confirmed based on chemical shifts. Thus, the H-3 signals for the cis-compounds are generally shifted downfield compared to the trans-compounds. It should be noted that some signals in the ^{1}H and ^{13}C spectra appeared as broadened or doubled signals due to dynamic processes (hindered rotation about the NCO bonds).

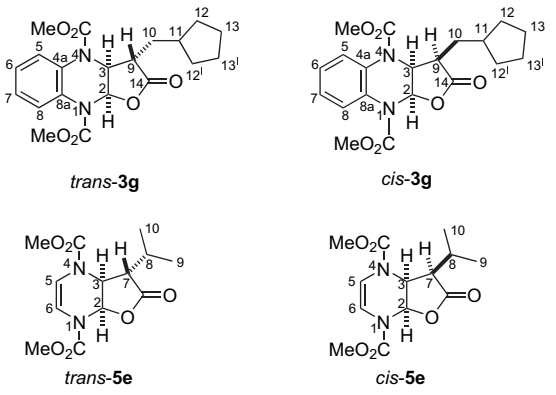
The configuration of *cis*-**5e** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[18] The trans-isomers generally proved to be less polar (R_f value) than the cis-isomers.

In conclusion, we have reported—based on previous work of Rudler et al.[15]—the synthesis of a number of

Table 2. Products and yields

5	R	% (*trans*-**5**)[a]	% (*cis*-**5**)[a]
a	Et	24	0
b	^{n}Pr	40	26
c	^{n}Bu	30	39
d	^{n}Dodec	26	20
e	^{i}Pr	20	35
f	^{c}Hex	38	11

[a] Yields of isolated products.



Scheme 3. Atom numbering of quinoxaline **3g** and pyrazine **5e** for NMR assignment.

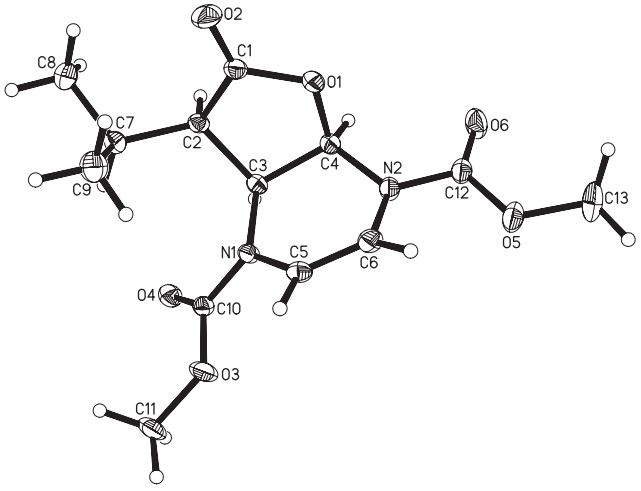


Figure 1. Ortep plot of *cis*-**5e**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.

1,4-diaza-7-oxabicyclo[4.3.0]non-2-en-6-ones by cyclization of 1,1-bis(trimethylsiloxy)ketene acetals with pyrazine and quinoxaline.

3. Experimental

3.1. General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR, the deuterated solvents indicated were used. The ^{1}H NMR (250.13 and 300.13 MHz) and ^{13}C NMR (62.9 and 75.5 MHz) were recorded on Bruker spectrometers AC 250 and ARX 300, respectively, at 300 K. In addition to the routine measurements, the spectra of **3b**, **3f**, **3g** and **5e** were recorded on a Bruker spectrometer AVANCE 500 (^{1}H: 500.13 MHz and ^{13}C: 125.8 MHz). Calibration of spectra was carried out on solvent signals ($CDCl_3$: δ ^{1}H=7.25, δ ^{13}C=77.0; DMSO-d_6: δ ^{1}H=2.50, δ ^{13}C=39.7). The NMR signals were assigned by DEPT and two-dimensional $^{1}H,^{1}H$ COSY, $^{1}H,^{1}H$ NOESY and $^{1}H,^{13}C$ correlation spectra (HSQC, HMBC). Mass spectrometric data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.1.1. Typical procedure for the synthesis of 2-oxo-3,3a-dihydrofuro[2,3-*b*]quinoxalines 3a–h and 6-oxo-7,7a-dihydrofuro[3,2-*b*]pyrazines 5a–f. To a CH_2Cl_2 solution (50 mL) of quinoxaline (0.325 g, 2.5 mmol) and 2-methylcyclopentyl-1,1-bis(trimethylsilyloxy)ethene (1.003 g 3.5 mmol) was slowly added methyl chloroformate (0.945 g, 10.0 mmol) at 20 °C. The solution was stirred for 12 h at 20 °C. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, *n*-heptane/EtOAc 20:1 to 5:1) to give *trans*-**3g** (0.315 g, 32%) and *cis*-**3g** (0.225 g, 24%) as colourless solids. Due to the restricted rotation in the urethane moiety, compounds **3** and **5** appeared as mixtures of two rotamers. All compounds were formed as racemates.

3.1.1.1. Dimethyl 3-ethyl-2-oxo-3,3a-dihydrofuro[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3a). Starting with quinoxaline (**1**) (0.261 g, 2.00 mmol), 2-ethyl-1,1-bis-(trimethylsilyloxy)ethene (**2a**) (0.650 g, 2.80 mmol) and methyl chloroformate (0.67 mL, 8.00 mmol), *trans*-**3a** (0.125 g, 19%) was isolated as a colourless solid, mp 147 °C; *cis*-**3a** (0.185 g, 27%) was isolated as a colourless solid, mp 147 °C.

Data of *trans*-**3a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.52 (br, 1H, Ar), 7.33 (br, 1H, Ar), 7.23–7.17 (m, 2H, Ar), 6.70 (d, 1H, $^{3}J_{2,3}$=8.8 Hz, H-2), 5.50 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.45–2.36 (m, 1H, H-9), 1.92–1.84 (m, 1H, CH_2), 1.82–1.65 (m, 1H, CH_2), 1.03 (t, 3H, ^{3}J=7.3 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.6 (COO), 153.9 (br) (2NCO), 130.5, 130.3 (C_{Ar}), 126.5, 126.2, 126.1, 125.9 (CH_{Ar}), 86.0 (C-2), 59.1 (C-3), 53.9, 53.7 (OCH_3), 43.2 (C-9), 22.7 (CH_2), 10.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3422 (br), 2965 (m), 1715 (s), 1506 (m), 1325 (s), 1165 (s), 950 (s), 755 (w). MS (EI; 70 eV): *m*/*z* (%)=334 ([M]$^+$, 100), 306 (39), 247 (43), 235 (54), 145 (25), 59 (21). HRMS (EI) calcd for $C_{16}H_{18}N_2O_6$ ([M]$^+$): 334.1159; found: 334.1154.

Data of *cis*-**3a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.43 (br, 1H, Ar), 7.33 (br, 1H, Ar), 7.30–7.19 (m, 2H, Ar), 6.92 (d, 1H, $^{3}J_{2,3}$=8.0 Hz, H-2), 5.73 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.77 (br s, 3H, OCH_3), 2.66 (m, 1H, H-9), 1.71–1.50 (m, 2H, CH_2), 1.12 (t, 3H, ^{3}J=7.3 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.3 (COO), 155.0, 153.6 (2NCO), 130.9, 130.3 (C_{Ar}), 126.8, 126.4, 126.3, 125.6 (CH_{Ar}), 86.4 (C-2), 58.9 (C-3), 53.9, 53.8 (OCH_3), 44.7 (C-9), 19.1 (CH_2), 12.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3422 (br), 2965 (m), 1715 (s), 1506 (m), 1325 (s), 1165 (s), 950 (s), 755 (w). MS (EI; 70 eV): *m*/*z* (%)=334 ([M]$^+$, 100), 306 (39), 247 (43), 235 (54), 145 (25), 59 (21). HRMS (EI) calcd for $C_{16}H_{18}N_2O_6$ ([M]$^+$): 334.1159; found: 334.1153.

3.1.1.2. Dimethyl 3-propyl-2-oxo-3,3a-dihydrofuro-[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3b). Starting with quinoxaline (**1**) (0.325 g, 2.50 mmol), 2-propyl-1,1-bis-(trimethylsilyloxy)ethene (**2b**) (0.863 g, 3.5 mmol) and methyl

chloroformate (0.78 mL, 10.25 mmol), *trans*-**3b** (0.252 g, 29%) was isolated as a colourless solid, mp 99–100 °C; *cis*-**3b** (0.183 g, 21%) was isolated as a colourless solid, mp 142–143 °C.

Data of *trans*-**3b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ=7.51–7.48 (m, 1H, H-8), 7.41 (br, 1H, H-5), 7.28–7.23 (m, 2H, H-6,7), 6.73 (d, 1H, $^3J_{2,3}$=8.8 Hz, H-2), 5.53 (br t, 1H, H-3), 3.78 (s, 3H, OCH_3), 3.73 (br s, 3H, OCH_3), 2.34 (m, 1H, H-9), 1.70–1.59 (m, 2H, CH_2), 1.45–1.36 (m, 2H, CH_2), 0.84 (t, 3H, ^3J=7.3 Hz, CH_3). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ=175.1 (COO), 153.8, 153.5 (br) (2NCO), 130.8 (C-4a), 130.6 (C-8a), 126.5 (br), 126.3 (br), 126.2, 125.6 (C-5,6,7,8), 86.6 (C-2), 59.6 (C-3), 53.9, 53.5 (OCH_3), 41.6 (C-9), 31.4, 19.2 (CH_2), 13.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3427 (br, w), 2961 (m), 2974 (w), 1792 (s), 1730 (br, s), 1596 (w), 1505 (s), 1441 (s). MS (EI, 70 eV): *m*/*z* (%)=348 ([M]$^+$, 100), 320 (68), 291 (97), 261 (34), 235 (77), 145 (30). Anal. Calcd for $C_{17}H_{20}N_2O_6$ (348.35): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.37; H, 5.81; N, 7.85.

Data of *cis*-**3b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ=7.47–7.43 (m, 1H, H-8), 7.39 (br, 1H, H-5), 7.27–7.22 (m, 2H, H-6,7), 6.92 (d, 1H, $^3J_{2,3}$=8.0 Hz, H-2), 5.61 (br t, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.70 (br s, 3H, OCH_3), 3.00 (ddd, 1H, $^3J_{3,9}$=9.5 Hz, $^3J_{9,10a}$=7.5 Hz, $^3J_{9,10b}$=6.3 Hz, H-9), 1.53–1.30 (m, 4H, CH_2), 0.87 (t, 3H, ^3J=7.3 Hz, CH_3). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ=175.1 (COO), 154.3 (br, NCO), 153.4 (NCO), 131.2 (C-4a), 130.7 (C-8a), 126.6 (br), 126.5 (br), 126.2 (C-5,6,7), 125.3 (C-8), 86.8 (C-2), 59.1 (C-3), 53.9 (OCH_3), 53.7 (br, OCH_3), 41.9 (C-9), 27.2, 20.3 (CH_2), 13.9 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3422 (br, w), 2963 (m), 2867 (w), 1774 (s), 1713 (br, s), 1597 (m), 1508 (s), 1441 (s), 1330 (br, s). MS (EI, 70 eV): *m*/*z* (%)=348 ([M]$^+$, 94), 320 (55), 291 (100), 261 (25), 235 (55), 145 (37). Anal. Calcd for $C_{17}H_{20}N_2O_6$ (348.35): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.23; H, 5.91; N, 7.97.

3.1.1.3. Dimethyl 3-butyl-2-oxo-3,3a-dihydrofuro[2,3-*b*]-quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3c). Starting with quinoxaline (**1**) (0.261 g, 2.00 mmol), 2-butyl-1,1-bis(trimethylsilyloxy)ethene (**2c**) (0.728 g, 2.80 mmol) and methyl chloroformate (0.67 mL, 8.00 mmol), *trans*-**3c** (0.083 g, 11%) was isolated as a colourless solid, mp 125–126 °C; *cis*-**3c** (0.180 g, 25%) was isolated as a colourless oil.

Data of *trans*-**3c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.50 (br, 1H, Ar), 7.32 (br, 1H, Ar), 7.25–7.17 (m, 2H, Ar), 6.69 (d, 1H, $^3J_{2,3}$=8.8 Hz, H-2), 5.48 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.48–2.34 (m, 1H, H-9), 1.90–1.78 (m, 1H, CH_2), 1.71–1.56 (m, 1H, CH_2), 1.46–1.22 (m, 4H, CH_2), 1.03 (t, 3H, ^3J=7.3 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.0 (COO), 154.0 (2NCO), 130.6, 130.3 (C_{Ar}), 126.5, 126.2 (2), 126.0 (CH_{Ar}), 86.0 (C-2), 59.6 (C-3), 54.0, 53.7 (OCH_3), 41.8 (C-9), 29.4, 28.2, 22.2 (CH_2), 13.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3425 (br), 2960 (m), 1789 (s), 1507 (s), 1332 (s), 1162 (s), 971 (s), 745 (w). MS (EI; 70 eV): *m*/*z* (%)=362 ([M]$^+$, 100), 291 (65), 275 (33), 235 (55), 189 (14), 145 (26), 59 (20). HRMS (EI) calcd for $C_{18}H_{22}N_2O_6$ ([M]$^+$): 362.1472; found: 362.1461.

Data of *cis*-**3c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.43 (br, 1H, ArH), 7.23–7.19 (m, 3H, ArH), 6.92 (d, 1H, $^3J_{2,3}$=8.2 Hz, H-2), 5.74 (br, 1H, H-3), 3.87 (s, 3H, OCH_3), 3.78 (br s, 3H, OCH_3), 2.75–2.66 (m, 1H, H-9), 1.59–1.29 (m, 6H, CH_2), 0.91 (t, 3H, ^3J=7.3 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.4 (COO), 154.9 (br) (2NCO), 131.0, 130.3 (C_{Ar}), 126.8, 126.4, 126.3, 125.6 (CH_{Ar}), 86.5 (C-2), 58.8 (C-3), 53.9, 53.7 (OCH_3), 43.0 (C-9), 29.7, 25.2, 22.5 (CH_2), 13.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3420 (br), 2954 (m), 1715 (s), 1508 (s), 1331 (s), 1160 (s), 965 (s), 754 (w). MS (EI; 70 eV): *m*/*z* (%)=362 ([M]$^+$, 100), 291 (63), 275 (32), 235 (51), 189 (17), 145 (28), 59 (21). HRMS (EI) calcd for $C_{18}H_{22}N_2O_6$ ([M]$^+$): 362.1472; found: 362.1462.

3.1.1.4. Dimethyl 3-dodecyl-2-oxo-3,3a-dihydrofuro-[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3d). Starting with quinoxaline (**1**) (0.325 g, 2.50 mmol), 2-dodecyl-1,1-bis-(trimethylsilyloxy)ethene (**2d**) (1.304 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**3d** (0.355 g, 30%) was isolated as a colourless solid, mp 100–101 °C; *cis*-**3d** (0.178 g, 15%) was isolated as a colourless solid, mp 119–120 °C.

Data of *trans*-**3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.52 (br, 1H, Ar), 7.31 (br, 1H, Ar), 7.26–7.21 (m, 2H, Ar), 6.70 (d, 1H, $^3J_{2,3}$=8.7 Hz, 1H, H-2), 5.49 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.82 (br s, 3H, OCH_3), 2.47–2.42 (m, 1H, H-9), 1.85–1.60 (br m, 2H, CH_2), 1.46–1.39 (m, 2H, CH_2), 1.38–1.24 (m, 18H, CH_2), 0.88 (t, 3H, ^3J=6.7 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.0 (COO), 154.1, 154.0 (NCO), 130.6, 130.4 (C_{Ar}), 126.6, 126.2 (2), 125.9 (CH_{Ar}), 86.0 (C-2), 59.7 (C-3), 53.9, 53.7 (OCH_3), 41.8 (C-9), 31.9, 29.7, 29.6 (3), 29.5, 29.4, 29.3, 29.2, 26.1, 22.7 (CH_2), 14.1 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3413 (br, w), 2919 (s), 2849 (m), 1771 (s), 1716 (br, s), 1595 (w), 1508 (s), 1441 (m). MS (EI, 70 eV): *m*/*z* (%)=474 ([M]$^+$, 100), 387 (19), 291 (62), 235 (55), 145 (20). HRMS (EI) calcd for $C_{26}H_{38}N_2O_6$ ([M]$^+$): 474.27244; found: 474.27190.

Data of *cis*-**3d**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.43 (br, 1H, Ar), 7.26–7.19 (m, 3H, Ar), 6.92 (d, 1H, $^3J_{2,3}$=8.3 Hz, H-2), 5.73 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.77 (br s, 3H, OCH_3), 2.71 (m, 1H, H-9), 1.62–1.52 (m, 4H, CH_2), 1.47–1.13 (m, 18H, CH_2), 0.87 (t, 3H, ^3J=6.7 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.4 (COO), 153.6 (2NCO), 131.0, 130.4 (C_{Ar}), 126.8, 126.4 (2), 125.6 (CH_{Ar}), 86.4 (C-2), 58.8 (C-3), 53.8, 53.7 (br) (OCH_3), 43.1 (C-9), 31.9, 29.6 (3), 29.5 (2), 29.3 (2), 27.5, 25.6, 22.7 (CH_2), 14.1 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3419 (br, w), 2918 (s), 2849 (m), 1773 (s), 1715 (br, s), 1596 (w), 1509 (s), 1472 (m). MS (EI, 70 eV): *m*/*z* (%)=474 ([M]$^+$, 100), 387 (13), 291 (40), 235 (34), 145 (15). Anal. Calcd for $C_{17}H_{20}N_2O_6$ (474.58): C, 65.80; H, 8.07; N, 5.90. Found: C, 66.00; H, 8.20; N, 5.59.

3.1.1.5. Dimethyl 3-isopropyl-2-oxo-3,3a-dihydrofuro-[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3e). Starting with quinoxaline (**1**) (0.261 g, 2.00 mmol), 2-isopropyl-1,1-bis(trimethylsilyloxy)ethene (**2e**) (0.728 g, 2.80 mmol) and methyl chloroformate (0.67 mL, 8.00 mmol), *trans*-**3e** (0.185 g, 27%) was isolated as a brownish solid, mp

159–160 °C; *cis*-**3e** (0.232 g, 33%) was isolated as a brownish solid, mp 168–169 °C.

Data of *trans*-**3e**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.50 (br, 1H, Ar), 7.26–7.19 (m, 3H, Ar), 6.67 (d, 1H, $^3J_{2,3}$=8.9 Hz, H-2), 5.60 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.80 (br s, 3H, OCH_3), 2.40 (dd, 1H, $^3J_{3,9}$=7.6 Hz, $^3J_{9,CH}$=4.2 Hz, H-9), 2.32–2.22 (m, 1H, CH), 1.03 (d, 3H, ^3J=7.0 Hz, CH_3), 1.00 (d, 3H, ^3J=6.8 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.1 (COO), 153.8 (2NCO), 130.7, 130.4 (C_{Ar}), 126.5, 126.2 (2), 125.7 (CH_{Ar}), 86.2 (C-2), 56.2 (C-3), 53.9, 53.6 (OCH_3), 48.0 (C-9), 28.2 (CH), 19.5, 18.1 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3413 (br), 2959 (m), 1715 (s), 1507 (m), 1330 (s), 1165 (s), 959 (s), 766 (w). MS (EI; 70 eV): *m*/*z* (%)=348.1 ([M]$^+$, 100), 320 (48), 305 (49), 261 (73), 235 (64), 145 (27). HRMS (EI) calcd for $C_{17}H_{20}N_2O_6$ ([M]$^+$): 348.13159; found: 348.13137.

Data of *cis*-**3e**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.44 (br, 1H, Ar), 7.26–7.14 (m, 3H, Ar), 6.84 (d, 1H, $^3J_{2,3}$=7.8 Hz, H-2), 5.77 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.75 (br s, 3H, OCH_3), 2.56 (dd, 1H, $^3J_{3,9}$=9.2 Hz, $^3J_{9,CH}$=6.1 Hz, H-9), 2.08–2.00 (m, 1H, CH), 1.11 (d, 3H, ^3J=6.8 Hz, CH_3), 1.04 (d, 3H, ^3J=6.8 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.3 (COO), 153.8 (2NCO), 130.8, 130.5 (C_{Ar}), 127.1, 127.0, 126.0, 125.4 (CH_{Ar}), 85.4 (C-2), 59.7 (C-3), 53.8 (2 OCH_3), 49.0 (C-9), 25.5 (CH), 22.7, 19.6 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3428 (br), 2954 (m), 1711 (s), 1507 (m), 1328 (s), 1161 (s), 1008 (s), 765 (w). MS (EI; 70 eV): *m*/*z* (%)=348.1 ([M]$^+$, 100), 320 (81), 305 (58), 261 (78), 235 (68), 145 (29). Anal. Calcd for $C_{19}H_{22}N_2O_6$ (348.35): C, 58.61; H, 5.79, N, 8.04. Found: C, 58.98; H, 5.86; N, 7.83.

3.1.1.6. Dimethyl 3-cyclohexyl-2-oxo-3,3a-dihydrofuro-[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3f). Starting with quinoxaline (**1**) (0.190 g, 1.45 mmol), 2-cyclohexyl-1,1-bis(trimethylsilyloxy)ethene (**2f**) (0.580 g, 2.03 mmol) and methyl chloroformate (0.54 mL, 5.80 mmol), *trans*-**3f** (0.160 g, 28%) was isolated as a colourless solid, mp 169–170 °C; *cis*-**3f** (0.150 g, 27%) was isolated as a colourless solid, mp 205–206 °C.

Data of *trans*-**3f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.60 (br, 1H, Ar), 7.27 (br, 1H, Ar), 7.23–7.18 (m, 2H, Ar), 6.66 (d, 1H, $^3J_{2,3}$=8.5 Hz, H-2), 5.62 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.40 (dd, 1H, $^3J_{3,9}$=7.0 Hz, $^3J_{9,10}$=4.5 Hz, H-9), 1.89–1.55 (m, 6H, ring CH, ring CH_2), 1.31–1.15 (m, 5H, ring CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=174.2 (COO), 153.9 (br, 2NCO), 130.7, 130.4 (C-4a,8a), 126.7, 126.5, 126.2, 125.9 (CH_{Ar}), 86.3 (C-2), 56.9 (C-3), 53.9, 53.7 (OCH_3), 48.2 (C-9), 38.4 (CH), 30.0, 28.5, 26.3, 26.0, 25.8 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (br), 2927 (m), 1715 (s), 1506 (m), 1329 (s), 1157 (s), 960 (s), 751 (w). MS (EI; 70 eV): *m*/*z* (%)=388.1 ([M]$^+$, 100), 360 (21), 301 (21), 252 (25), 192 (19), 145 (18). Anal. Calcd for $C_{20}H_{24}N_2O_6$ (388.41): C, 61.84; H, 6.23; N, 7.21. Found: C, 61.81; H, 6.16; N, 6.77.

Data of *cis*-**3f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.45 (br, 1H, Ar), 7.30 (br, 1H, Ar), 7.24–7.15 (m, 2H, Ar), 6.83 (d, 1H, $^3J_{2,3}$=7.9 Hz, H-2), 5.76 (br s, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.57 (dd, 1H, $^3J_{3,9}$=9.5 Hz, $^3J_{9,10}$=5.4 Hz, H-9), 1.75–1.61 (m, 6H, ring CH, ring CH_2), 1.28–1.12 (m, 5H, ring CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=172.5 (COO), 155.2, 153.5 (NCO), 131.1, 130.5 (C-4a,8a), 127.0 (br), 126.8 (br), 126.0, 125.5 (CH_{Ar}), 85.6 (C-2), 59.5 (C-3), 53.8 (2C, OCH_3), 48.2 (C-9), 35.5 (CH), 32.7, 29.1, 26.6, 26.2, 25.9 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3428 (br), 2928 (m), 1714 (s), 1506 (s), 1327 (s), 1159 (m), 966 (s), 753 (w). MS (EI; 70 eV): *m*/*z* (%)=388.1 ([M]$^+$, 100), 360 (25), 301 (19), 252 (24), 235 (40), 192 (20), 145 (22). Anal. Calcd for $C_{20}H_{24}N_2O_6$ (388.41): C, 61.84; H, 6.23; N, 7.21. Found: C, 61.80; H, 6.08; N, 6.62.

3.1.1.7. Dimethyl 3-(cyclopentylmethyl)-2-oxo-3,3a-dihydrofuro[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3g). Starting with quinoxaline (**1**) (0.325 g, 2.5 mmol), 2-methylcyclopentyl-1,1-bis(trimethylsilyloxy)ethene (1.003 g, 3.5 mmol) and methyl chloroformate (0.945 g, 10.0 mmol), *trans*-**3g** (0.315 g, 32%) was isolated as a colourless solid, mp 129 °C; *cis*-**3g** (0.225 g, 24%) was isolated as a colourless solid, mp 174 °C.

Data of *trans*-**3g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.51 (br, 1H, Ar), 7.30 (br, 1H, Ar), 7.24–7.19 (m, 2H, Ar), 6.69 (d, 1H, $^3J_{2,3}$=8.5 Hz, H-2), 5.50 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.80 (br s, 3H, OCH_3), 2.43 (m, 1H, H-9), 2.06 (br m, 1H, H-11), 1.82–1.48 (m, 8H, H-10,12a,12′a,13,13′), 1.09–0.97 (m, 2H, H-12b,12′b). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=175.2 (C-14), 154.1 (br, NCO), 154.0 (NCO), 126.6 (CH_{Ar}), 126.3 (br, CH_{Ar}), 126.2, 125.9 (CH_{Ar}), 86.0 (C-2), 60.1 (C-3), 53.9 (OCH_3), 53.7 (br, OCH_3), 40.9 (C-9), 36.7 (C-11), 36.3 (C-10), 32.9, 31.8 (C-12,12′), 25.1, 25.0 (C-13,13′). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3421 (br, w), 2958 (m), 2870 (w), 1787 (s), 1725 (s), 1593 (m), 1507 (s). MS (EI, 70 eV): *m*/*z* (%)=388 ([M]$^+$, 99), 291 (100), 235 (45), 189 (25), 145 (28). Anal. Calcd for $C_{20}H_{24}N_2O_6$ (388.41): C, 61.84; H, 6.23; N, 7.21. Found: C, 62.16; H, 6.43; N, 6.84.

Data of *cis*-**3g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.44 (br, 1H, Ar), 7.27 (br, 1H, Ar), 7.23–7.17 (m, 2H, Ar), 6.92 (d, 1H, $^3J_{2,3}$=8.2 Hz, H-2), 5.73 (br, 1H, H-3), 3.76 (br s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.76 (m, 1H, H-9), 2.16 (m, 1H, H-11), 1.78 (m, 2H, H-12a,12′a), 1.65–1.43 (m, 6H, H-10,13,13′), 1.08 (m, 2H, H-12b,12′b). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=174.5 (C-14), 155.0, 153.5 (NCO), 126.8 (br, CH_{Ar}), 126.5 (br, CH_{Ar}), 126.3, 125.6 (CH_{Ar}), 86.4 (C-2), 59.0 (C-3), 53.8 (OCH_3), 53.7 (br, OCH_3), 42.1 (C-9), 37.1 (C-11), 32.5, 32.4 (C-12,12′), 31.6 (C-10), 25.1, 25.0 (C-13,13′). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3427 (br, w), 2955 (m), 2867 (w), 1785 (s), 1719 (s), 1594 (m), 1506 (s). MS (EI, 70 eV): *m*/*z* (%)=388 ([M]$^+$, 100), 291 (97), 235 (43), 189 (20), 145 (23). Anal. Calcd for $C_{20}H_{24}N_2O_6$ (388.41): C, 61.84; H, 6.23; N, 7.21. Found: C, 61.90; H, 6.38; N, 6.90.

3.1.1.8. Dimethyl 3-(2-cyclohexylethyl)-2-oxo-3,3a-dihydrofuro[2,3-*b*]quinoxaline-4,9(2*H*,9a*H*)-dicarboxylate (3h). Starting with quinoxaline (**1**) (0.325 g, 2.50 mmol), 4-cyclohexyl-1,1-bis(trimethylsilyloxy)but-1-ene (**2h**) (1.100 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**3h** (0.258 g, 25%) was isolated as a

colourless solid, mp 128–130 °C; *cis*-**3h** (0.123 g, 12%) was isolated as a colourless solid, mp 115–116 °C.

Data of *trans*-**3h**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.52 (br, 1H, Ar), 7.33 (br, 1H, Ar), 7.24–7.20 (m, 2H, Ar), 6.70 (d, 1H, $^3J_{2,3}$=8.8 Hz, 1H, H-2), 5.49 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.81 (br s, 3H, OCH_3), 2.47–2.33 (m, 1H, H-9), 1.99–1.80 (br m, 1H, CH), 1.78–1.51 (m, 6H, CH_2), 1.39–1.05 (m, 6H, CH_2), 1.00–0.75 (m, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.0 (COO), 154.0 (br, 2NCO), 130.6, 130.4 (C_{Ar}), 126.5, 126.2 (2), 125.9 (CH_{Ar}), 86.0 (C-2), 59.5 (C-3), 53.9, 53.6 (br) (OCH_3), 41.9 (C-9), 37.2 (CH), 33.4, 33.1, 32.8, 26.9, 26.4, 26.2, 26.1 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3448 (br, m), 2923 (s), 2852 (m), 1771 (s), 1716 (br, s), 1593 (w), 1507 (s), 1441 (s). MS (EI, 70 eV): *m*/*z* (%)=416 ([M]$^+$, 100), 357 (3), 291 (11), 235 (27), 188 (30), 145 (16). HRMS (EI) calcd for $C_{22}H_{28}N_2O_6$ ([M]$^+$): 416.19419; found: 416.19472.

Data of *cis*-**3h**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.44 (br, 1H, Ar), 7.31 (br, 1H, Ar), 7.23–7.20 (m, 2H, Ar), 6.93 (d, 1H, $^3J_{2,3}$=8.0 Hz, 1H, H-2), 5.75 (br, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.78 (br s, 3H, OCH_3), 2.75–2.61 (br m, 1H, H-9), 1.77–1.53 (m, 7H, CH, CH_2), 1.38–1.05 (m, 6H, CH_2), 1.01–0.75 (m, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.3 (COO), 155.0, 153.5 (NCO), 131.0, 130.4 (C_{Ar}), 126.8 (br), 126.5 (br), 126.3, 125.6 (CH_{Ar}), 86.5 (C-2), 58.8 (C-3), 53.8, 53.7 (br) (OCH_3), 43.4 (C-9), 37.6 (CH), 33.2, 33.1, 32.9, 26.5, 26.3, 26.2 (2) (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3420 (br, m), 2920 (s), 2851 (s), 1773 (s), 1717 (br, s), 1597 (w), 1508 (s), 1440 (s), 1338 (br, s). MS (EI, 70 eV): *m*/*z* (%)=416 ([M]$^+$, 100), 388 (3), 291 (11), 235 (26), 145 (17). HRMS (EI) calcd for $C_{22}H_{28}N_2O_6$ ([M]$^+$): 416.19419; found: 416.19437. Anal. Calcd for $C_{22}H_{28}N_2O_6$ (416.47): C, 63.45; H, 6.78; N, 6.73. Found: C, 64.11; H, 7.07; N, 6.44.

3.1.1.9. Dimethyl 7-ethyl-6-oxo-7,7a-dihydrofuro[3,2-*b*]-pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5a). Starting with pyrazine (**4**) (0.200 g, 2.5 mmol), 2-ethyl-1,1-bis(trimethylsilyloxy)ethene (**2a**) (0.650 g, 2.80 mmol) and methyl chloroformate (0.67 mL, 8.00 mmol), *trans*-**5a** (0.170 g, 24%) was isolated as a colourless oil.

Data of *trans*-**5a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.20 (br, 3H, H-2,5,6), 4.72 (br, 1H, H-3), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.84 (br, 1H, H-7), 1.85–1.79 (m, 1H, CH_2), 1.62–1.53 (m, 1H, CH_2), 1.10 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.5 (COO), 153.1 (NCO), 152.7 (NCO), 108.7 (br, 2CH), 80.4 (C-2), 56.0 (br, C-3), 53.8, 53.7 (OCH_3), 46.0 (br, C-7), 21.4 (CH_2), 10.6 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (br), 2960 (s), 1716 (s), 1443 (s), 1339 (s), 1127 (s), 974 (s), 766 (w). MS (EI; 70 eV): *m*/*z* (%)=284.1 ([M]$^+$, 100), 240 (10), 185 (76), 139 (44), 95 (44), 59 (30). Anal. Calcd for $C_{12}H_{16}N_2O_6$ (284.00): C, 50.70; H, 6.63; N, 9.85. Found: C, 50.86; H, 6.09; N, 9.21.

3.1.1.10. Dimethyl 7-propyl-6-oxo-7,7a-dihydrofuro-[3,2-*b*]pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5b). Starting with pyrazine (**4**) (0.200 g, 2.50 mmol), 2-propyl-1,1-bis(trimethylsilyloxy)ethene (**2b**) (0.863 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**5b** (0.299 g, 40%) was isolated as a colourless oil; *cis*-**5b** (0.196 g, 26%) was isolated as a colourless solid, mp 71–72 °C.

Data of *trans*-**5b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.24 (br, 3H, H-2,5,6), 4.66 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.91 (br, 1H, H-7), 1.81–1.71 (m, 2H, CH_2), 1.64–1.45 (m, 2H, CH_2), 0.97 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.8 (COO), 153.0 (br, NCO), 152.7 (NCO), 108.8 (br), 108.0 (br) (CH), 80.5 (C-2), 57.1 (br, C-3), 54.0, 53.7 (OCH_3), 46.2 (br), 45.0 (br) (C-7), 30.6, 19.7 (CH_2), 13.9 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3546 (br, w), 3160 (s), 2960 (br, s), 2875 (s), 1785 (br, s), 1717 (br, s), 1540 (w), 1443 (br, s). MS (EI, 70 eV): *m*/*z* (%)=298 ([M]$^+$, 73), 198 (12), 185 (100), 139 (68), 95 (48). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.29): C, 52.34; H, 6.08; N, 9.39. Found: C, 52.06; H, 6.19; N, 9.19.

Data of *cis*-**5b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.27 (br, 3H, H-2,5,6), 5.28 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.83 (br m, 1H, H-7), 1.71–1.39 (m, 4H, CH_2), 0.92 (t, 3H, ^3J=7.3 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.7 (COO), 153.1 (2NCO), 110.6 (2CH), 81.7 (br, C-2), 54.0 (C-3), 54.0, 53.9 (OCH_3), 42.3 (C-7), 28.4, 20.5 (CH_2), 13.9 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3545 (br, w), 3138 (m), 2960 (br, s), 2874 (s), 1783 (br, s), 1717 (br, s), 1540 (w), 1438 (br, s). MS (EI, 70 eV): *m*/*z* (%)=298 ([M]$^+$, 27), 198 (15), 185 (61), 139 (49), 95 (43), 59 (100). HRMS (EI) calcd for $C_{13}H_{18}N_2O_6$ ([M]$^+$): 298.11594; found: 298.11537. Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.29): C, 52.34; H, 6.08; N, 9.39. Found: C, 51.83; H, 6.09; N, 8.84.

3.1.1.11. Dimethyl 7-butyl-6-oxo-7,7a-dihydrofuro[3,2-*b*]pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5c). Starting with pyrazine (**4**) (0.200 g, 2.50 mmol), 2-butyl-1,1-bis(trimethylsilyloxy)ethene (**2c**) (0.912 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**5c** (0.234 g, 30%) was isolated as a colourless oil; *cis*-**5c** (0.297 g, 39%) was isolated as a colourless oil.

Data of *trans*-**5c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.24 (br, 3H, H-2,5,6), 4.68 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.90 (br m, 1H, H-7), 1.82–1.73 (m, 2H, CH_2), 1.63–1.25 (m, 4H, CH_2), 0.93 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.8 (COO), 153.0 (br, NCO), 152.7 (NCO), 108.9 (br), 108.8 (br) (CH), 80.5 (C-2), 56.9 (C-3), 54.0, 53.7 (OCH_3), 46.5 (br), 44.9 (br) (C-7), 28.4, 28.2, 22.5 (CH_2), 13.8 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (br, s), 3140 (m), 2959 (s), 2863 (s), 1792 (br, s), 1734 (br, s), 1539 (w), 1437 (br, s), 1368 (br, s). MS (EI, 70 eV): *m*/*z* (%)=312 ([M]$^+$, 100), 268 (10), 185 (79), 139 (61), 95 (21), 59 (17). HRMS (EI) calcd for $C_{14}H_{20}N_2O_6$ ([M]$^+$): 312.13159; found: 312.13168. Anal. Calcd for $C_{14}H_{20}N_2O_6$ (312.32): C, 53.84; H, 6.45; N, 8.97. Found: C, 53.20; H, 6.42; N, 8.63.

Data of *cis*-**5c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.27 (br, 3H, H-2,5,6), 5.29 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.82 (br m, 1H, H-7), 1.64-1.24 (m, 6H, CH_2), 0.89 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.8 (COO), 153.4 (br, NCO), 153.1 (NCO), 110.6 (2 CH), 81.6 (br, C-2), 54.0 (C-3), 54.0, 53.8 (OCH_3), 42.5 (C-7), 29.4, 26.0, 22.5 (CH_2), 13.7 (CH_3). IR (KBr, cm^{-1}):

$\tilde{\nu}$ = 3545 (br, w), 3435 (br, w), 3137 (m), 2958 (br, s), 2871 (s), 1782 (br, s), 1716 (br, s), 1540 (w), 1444 (br, s). MS (EI, 70 eV): *m/z* (%)=312 ([M]$^+$, 100), 198 (19), 185 (83), 139 (46), 95 (23), 59 (21). HRMS (EI) calcd for $C_{14}H_{20}N_2O_6$ ([M]$^+$): 312.13159; found: 312.13136.

3.1.1.12. Dimethyl 7-dodecyl-6-oxo-7,7a-dihydrofuro-[3,2-*b*]pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5d). Starting with pyrazine (**4**) (0.200 g, 2.50 mmol), 2-dodecyl-1,1-bis(trimethylsilyloxy)ethene (**2d**) (1.304 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**5d** (0.275 g, 26%) was isolated as a colourless oil; *cis*-**5d** (0.214 g, 20%) was isolated as a colourless oil.

Data of *trans*-**5d**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.23 (br, 3H, H-2,5,6), 4.67 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.89 (m, 1H, H-7), 1.82–1.71 (m, 2H, CH_2), 1.67–1.45 (br m, 2H, CH_2), 1.38–1.21 (m, 18H, CH_2), 0.88 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.8 (COO), 153.0 (br, NCO), 152.7 (NCO), 108.9 (br, 2CH), 80.5 (C-2), 56.9 (C-3), 54.0, 53.7 (OCH_3), 46.6, 45.1 (br) (C-7), 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 26.3, 22.7 (CH_2), 14.1 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3140 (w), 2924 (s), 2854 (s), 1790 (s), 1724 (br, s), 1540 (w), 1444 (s), 1344 (br, s). MS (EI, 70 eV): *m/z* (%)=424 ([M]$^+$, 100), 380 (5), 281 (4), 185 (20), 139 (15). HRMS (EI) calcd for $C_{22}H_{36}N_2O_6$ ([M]$^+$): 424.25679; found: 424.25793.

Data of *cis*-**5d**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.27 (br, 3H, H-2,5,6), 5.28 (br, 1H, H-3), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.81 (br m, 1H, H-7), 1.75–1.55 (m, 2H, CH_2), 1.55–1.37 (m, 2H, CH_2), 1.37–1.18 (m, 18H, CH_2), 0.88 (t, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.8 (COO), 153.3 (br, NCO), 153.0 (NCO), 110.6, 110.3 (br) (CH), 81.6 (C-2), 54.1 (C-3), 54.0, 53.8 (OCH_3), 42.5 (br, C-7), 31.9, 29.6 (3), 29.5, 29.4, 29.3 (2), 27.3, 26.3, 22.6 (CH_2), 14.1 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3447 (br, w), 3144 (w), 2957 (m), 2920 (s), 2850 (s), 1763 (s), 1748 (s), 1678 (m), 1449 (s), 1349 (br, s). MS (EI, 70 eV): *m/z* (%)=424 ([M]$^+$, 100), 380 (1), 280 (3), 185 (40), 139 (28). HRMS (EI) calcd for $C_{22}H_{36}N_2O_6$ ([M]$^+$): 424.25679; found: 424.25795.

3.1.1.13. Dimethyl 7-isopropyl-6-oxo-7,7a-dihydrofuro-[3,2-*b*]pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5e). Starting with pyrazine (**4**) (0.200 g, 2.50 mmol), 2-isopropyl-1,1-bis-(trimethylsilyloxy)ethene (**2e**) (0.616 g, 3.5 mmol) and methyl chloroformate (0.78 mL, 10.25 mmol), *trans*-**5e** (0.146 g, 20%) was isolated as a colourless solid, mp 102–103 °C; *cis*-**5e** (0.265 g, 35%) was isolated as a colourless solid, mp 92–93 °C.

Data of *trans*-**5e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.30–6.05 (br, 3H, H-2,5,6), 4.79 (br, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.77 (br s, 3H, OCH_3), 2.75 (br s, 1H, H-7), 2.17 (br s, 1H, H-8), 1.12 (d, 3H, ^3J=7.0 Hz, CH_3), 1.04 (d, 3H, ^3J= 7.0 Hz, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=173.7 (COO), 152.9 (br, NCO), 152.6 (NCO), 108.7 (br, C-5,6), 80.5 (C-2), 55.4 (br), 54.6 (br) (C-3), 53.9, 53.5 (OCH_3), 52.1 (br), 50.1 (br) (C-7), 27.7 (C-8), 19.7, 18.9 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (br, w), 3139 (w), 2964 (m), 1783 (s), 1727 (br, s), 1683 (m), 1441 (s), 1347 (br, s). MS (EI, 70 eV): *m/z* (%)=298 ([M]$^+$, 100), 211 (40), 198 (15), 185 (74), 139 (60). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.29): C, 52.34; H, 6.08; N, 9.39. Found: C, 52.14; H, 6.08; N, 9.05.

Data of *cis*-**5e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.25–6.18 (br, 3H, H-2,5,6), 5.25 (br s, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.79 (br s, 1H, H-7), 1.96 (br s, 1H, H-8), 1.13 (d, 3H, ^3J=7.0 Hz, CH_3), 0.94 (d, 3H, ^3J=7.0 Hz, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=173.1 (COO), 153.4 (br, NCO), 153.0 (NCO), 110.8 (br), 110.2 (C-5,6), 81.2 (C-2), 54.4 (C-3), 53.9, 53.8 (OCH_3), 48.5 (C-7), 25.0 (C-8), 23.0, 18.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (br, m), 3137 (w), 2965 (m), 1780 (s), 1728 (br, s), 1442 (s), 1337 (br, s). MS (EI, 70 eV): *m/z* (%)=298 ([M]$^+$, 92), 211 (24), 198 (45), 185 (100), 139 (67). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.29): C, 52.34; H, 6.08; N, 9.39. Found: C, 52.24; H, 6.10; N, 9.20.

3.1.1.14. Dimethyl 7-cyclohexyl-6-oxo-7,7a-dihydrofuro-[3,2-*b*]pyrazine-1,4(4a*H*,6*H*)-dicarboxylate (5f). Starting with pyrazine (**4**) (0.200 g, 2.50 mmol), 2-cyclohexyl-1,1-bis(trimethylsilyloxy)ethene (**2f**) (0.989 g, 3.46 mmol) and methyl chloroformate (0.94 mL, 10.0 mmol), *trans*-**5f** (0.320 g, 38%) was isolated as a colourless solid, mp 129–130 °C; *cis*-**5f** (0.060 g, 11%) was isolated as a colourless oil.

Data of *trans*-**5f**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.22 (br, 3H, H-2,5,6), 4.73 (br, 1H, H-3), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.76 (br, 1H, H-7), 1.78–1.64 (m, 6H, CH_2, ring CH), 1.46–1.11 (m, 5H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=174.0 (COO), 153.0, 152.7 (NCO), 109.4 (br) (C-5,6), 80.9 (C-2), 56.4 (br, C-3), 54.0, 53.6 (br) (OCH_3), 48.2 (br, C-7), 37.7 (ring CH), 30.2, 29.6, 26.3, 26.2, 25.8 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (br), 2931 (s), 1721 (s), 1449 (s), 1341 (s), 1120 (s), 956 (s), 765 (w). MS (EI; 70 eV): *m/z* (%)=388.1 ([M]$^+$, 100), 211 (26), 185 (59), 139 (37), 95 (15), 59 (12). HRMS (EI) calcd for $C_{16}H_{22}N_2O_6$ ([M]$^+$): 338.1472; found: 338.1466.

Data of *cis*-**5f**: ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.29–6.12 (br m, 3H, H-2,5,6), 5.22 (br, 1H, H-3), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.75 (br, 1H, H-7), 1.76–1.53 (m, 6H, CH_2, ring CH), 1.24–1.12 (m, 5H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.3 (COO), 153.1 (2NCO), 110.1 (C-5,6), 81.0 (C-2), 53.9 (C-3), 53.9 (2 OCH_3), 48.4 (C-7), 35.5 (CH), 33.2, 28.8, 27.0, 26.4, 25.7 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3434 (br), 2931 (s), 1733 (s), 1428 (s), 1341 (s), 1121 (s), 957 (s), 766 (w). MS (EI; 70 eV): *m/z* (%)=388.1 ([M]$^+$, 100), 211 (26), 185 (59), 139 (37), 95 (15), 59 (12). HRMS (EI) calcd for $C_{16}H_{22}N_2O_6$ ([M]$^+$): 338.14724; found: 338.14659.

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Novaxenicins A–D and xeniolides I–K, seven new diterpenes from the soft coral *Xenia novaebrittanniae*

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Abstract—Seven new diterpenes, novaxenicins A–D (**1**–**4**) and xeniolides I–K (**5**–**7**), have been isolated from the Kenyan soft coral *Xenia novaebrittanniae*. The structures and relative stereochemistry of the compounds were elucidated by interpretation of MS, COSY, HSQC, HMBC, and NOESY experiments. The structure of novaxenicin A (**1**) was secured by X-ray diffraction analysis. Compound **5** possesses anti-bacterial activity at a concentration of 1.25 μg/ml and compound **2** induces apoptosis in transformed mammalian cells at a concentration of 1.25 μg/ml.

1. Introduction

Octocorals of the genera *Xenia* (order Alyconaceae, family Xeniidae) are a rich source of diterpenoids containing nine-membered carbocylic rings.[1–3] Xenicin isolated from *Xenia elongata* was the first reported compound.[4] Soon after additional members of the group were reported from the Red Sea *Xenia macrospiculata*.[5,6] The structures of the *Xenia* diterpenoids have been divided by us into three groups: xenicins or xenicane type (containing a dihydropyran-cyclononane skeleton), xeniolides (possessing a δ-lactone-cyclononane skeleton), and xeniaphyllanes (possessing a prenylated caryophyllene skeleton).[7]

Dozens of *Xenia*-isoprenoides have since been reported (53 reports)[3] with all kinds of modifications in the ring system as well as in the prenyl side chain. More recently two additional types of compound have been added, i.e., the xeniaethers[8] and the azamilides.[9] Antheliolide A isolated from *Anthelia glauca*, is an example of a more complex penta cyclic secondary metabolite of mixed-biogenesis (C_{20}+C_4) incorporating the xeniaphyllane ring system.[10]

The present work describes the isolation and structural elucidation of seven new *Xenia* diterpenes, designated as novaxenicins A–D (**1**–**4**) and xeniolides I–K (**5**–**7**) according to their structures (Figs. 1 and 2). The compounds were isolated from the Kenyan soft coral *X. novaebrittanniae* (Ashworth, 1900) collected in Kitagamwa, southern Kenya (04° 48′ 49″ S, 39° 21′ 60″ E, February, 2004). The collection was done on a reef, at a depth of 8 m, characterized by highly diverse soft coral fauna. The colonies there form large patches, growing mainly on dead colonies of stony corals. The type locally of species is New Britain and Loyalty Islands; later it was recorded in the northern Red Sea.[11] Further records, not yet verified, are from Philippines, the Malay Archipelago, the Great Barrier Reef Australia, and New Caledonia.[12]

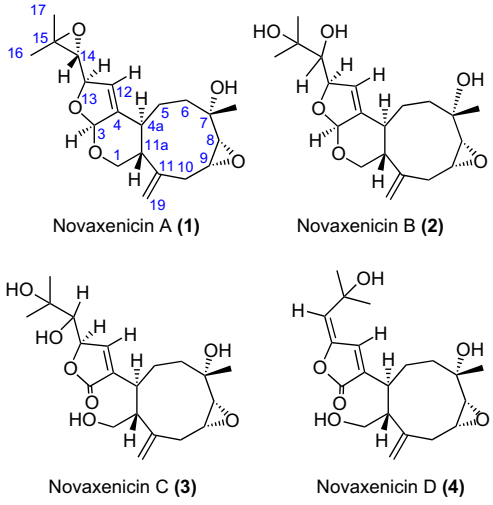

Figure 1. Novaxenicins A–D (**1**–**4**).

Keywords: Soft coral; Diterpenes; Novaxenicins; Xeniolides.
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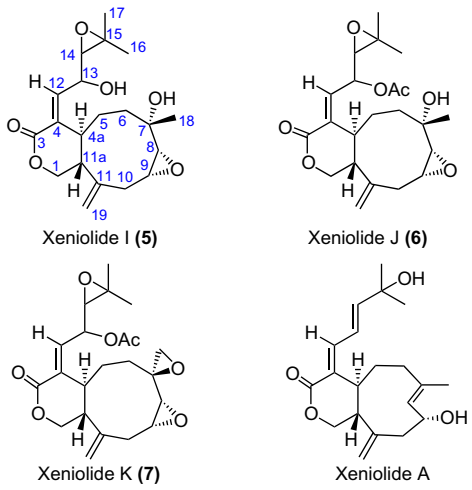

Figure 2. Xeniolides A and I–K (**5**–**7**).

2. Results and discussion

The ethyl acetate extract of the *Xenia* (35 g, dry weight) was repeatedly chromatographed over Sephadex LH-20 columns, followed by vacuum–liquid chromatography (VLC) over silica gel to yield the seven new compounds.

The CIMS spectrum of **1** exhibited a pseudo molecular ion $[M+H]^+$ at *m/z* 349. The molecular formula $C_{20}H_{28}O_5$ was suggested by the ^{13}C NMR data and later confirmed by X-ray diffraction analysis (see below). Both the ^1H NMR and the ^{13}C NMR spectra of **1** and most other herewith described compounds, were well resolved in C_6D_6 (Tables 1–3). The ^{13}C and ^1H NMR experiments revealed the presence of an exocyclic double bond (δ_C 142.1 s, 118.7 t and δ_H 4.90 t, 4.97 br s), one tri-substituted double bond (δ_C 142.1 s, 118.7 d and δ_H 5.75 br s), two epoxides (δ_C 61.7 d, 60.9 d and 64.9 d, 58.5 s and δ_H 2.36 d, 2.84 ddd and 3.06 d),

Table 1. ^{13}C NMR spectral data of compounds **1**–**7**[c]

C	**1**[a]	**2**[a]	**3**[b]	**4**[a]	**5**[a]	**6**[a]	**7**[a]
1	69.4 t	69.7 t	64.6 t	63.9 t	69.9 t	70.5 t	69.4 t
3	108.0 d	107.4 d	173.1 s	169.5 s	169.1 s	169.9 s	168.7 s
4	143.3 s	143.8 s	136.8 s	136.2 s	135.8 s	137.8 s	136.3 s
4a	35.2 d	36.1 d	33.0 d	32.1 d	36.2 d	35.4 d	33.9 d
5	25.7 t	28.9 t	29.1 t	28.2 t	32.5 t	31.6 t	32.9 t
6	33.9 t	34.8 t	35.7 t	33.8 t	32.7 t	31.9 t	27.8 t
7	72.2 s	72.3 s	72.1 s	71.8 s	70.9 s	70.6 s	54.7 s
8	61.7 d	62.4 d	61.8 d	61.3 d	62.5 d	62.5 d	55.7 d
9	60.9 d	61.7 d	60.5 d	60.3 d	59.1 d	59.4 d	58.0 d
10	29.1 t	29.1 t	28.5 t	27.3 t	34.8 t	33.9 t	33.1 t
11	142.1 s	143.4 s	147.1 s	144.2 s	144.3 s	143.0 s	142.4 s
11a	53.9 d	55.0 d	54.1 d	53.5 d	44.4 d	44.6 d	43.7 d
12	119.9 d	118.6 d	151.1 d	137.6 d	141.0 d	134.9 d	135.8 d
13	85.0 d	89.3 d	82.6 d	147.3 s	66.3 d	69.4 d	69.6 d
14	64.9 d	78.1 d	78.3 d	122.0 d	65.0 d	62.8 d	62.6 d
15	58.5 s	71.1 s	72.0 s	70.9 s	59.5 s	59.7 s	59.0 s
16	18.5 q	25.3 q	28.4 q	30.9 q	19.1 q	18.4 q	18.0 q
17	24.2 q	26.2 q	27.2 q	31.0 q	24.1 q	24.6 q	24.5 q
18	31.8 q	32.1 q	32.6 q	31.5 q	32.7 q	32.5 q	48.4 t
19	118.7 t	119.7 t	118.9 t	119.8 t	119.8 t	116.8 t	116.4 t
Ac						169.6 s, 20.8 q	169.0 s, 20.7 q

[a] Recorded in $CDCl_3$ solution measured at 100 MHz.
[b] Recorded in d_6-DMSO solution measured at 100 MHz.
[c] Multiplicities were determined by DEPT and HSQC experiments.

one methylenoxy group (δ_C 69.4 t, and δ_H 3.39 t, 3.80 dd), one methineoxy group (δ_C 85.0 d and δ_H 5.75 s), one methinedioxy group (δ_C 108.0 d, δ_H 5.58 s), and one *tert*-alcohol (δ_C 72.2 s).

The above functionalities account for four of the seven degrees of unsaturation of **1**, suggesting three additional rings. The COSY spectrum revealed the presence of three spin systems (I–III) depicted in Figure 3. HMBC correlations connected the latter three spin systems enabling the construction of the planar structure of **1** as shown in Figure 3.

The relative stereochemistry of most of **1** was determined by the analysis of coupling constants and from NOESY cross-peaks (Fig. 4). A cis-configuration for the 8(9) epoxy moiety, a trans-configuration for H-4a and H-11a and a ca. 90° dihedral angle between H-12 and H-13, were determined from the measured 4.4,[13,14] 11.0,[14] and 0 Hz coupling constants, respectively.

Further support for the suggested stereochemistry came from NOE cross-peaks depicted in Figure 4. NOEs between CH_3-18 and H-6β (the same side as H-11a) suggested that this methyl group was also β, an NOE between H-3 and H-13 determined them to be cis-oriented and an NOE between CH_3-16 and H-14 distinguished between the geminal methyl pair. The suggested stereochemistry of the nine-membered ring is the same as in known *Xenia* diterpenes as, e.g., in isoxeniatin C[9] and in the blue coral secondary metabolites, helioxenicins A–C.[14] Helioxenicin C, possessing the same ring system as compound **1**, is closest in structure to **1**, as seen from the NMR data. Novaxenicin A differs from helioxenicin C in C-1 (a CH_2O group against a lactol) and in the configuration of C-3.

The full relative stereochemistry of **1** was secured by X-ray diffraction analysis (Fig. 5 and Section 4). The absolute configuration of this light atom structure cannot be reliably determined from diffraction data. Yet, it is more likely (based on the Flack parameter)[15] to be the one shown in Figure 5 and known for the other *Xenia* diterpenoids in the series.

The sensitivity of the conformation of the nine-membered ring to small structural changes is revealed by changes in the proton chemical shifts and coupling constants, e.g., (δ_H 2.63 d, 2.43 d; H-8), (δ_H 3.03 m, 3.12 ddd; H-9), (δ_H 3.52 br t, δ_H 3.85 dd; H-4a) and (δ_H 2.64 br t, δ_H 3.21 dd; H-11a) (Table 2), for compounds **3** and **4**, respectively.

The CIMS spectrum of novaxenicin B (**2**) exhibited a pseudo molecular ion at *m/z* 367 $[M+H]^+$. The molecular formula $C_{20}H_{30}O_6$ was determined by HRCIMS. ^{13}C and ^1H NMR revealed high similarity to **1**, namely, **2** possessing the same tricyclic ring system, but differing in the side chain. The 14(15) epoxide of **1** is exchanged by a 14,15-diol in **2** (δ_C, 78.1 d and 71.1 s for C-14 and C-15, respectively) (Fig. 1). The latter change of functionality brought about a change in the vicinal coupling constant between H-13 and H-14, from 8.7 Hz for **1** to 3.3 Hz for **2**. The expected conformational mobility of the side chain prevented the determination of the chirality of C-14. Moreover, as it is unknown if the 14,15-epoxide of **1**, that is, expected to be obtained from the 14(15) double bond, is the precursor

Table 2. ^{1}H NMR spectral data of novaxenicins A–D (**1**–**4**)[c]

H	**1**[a]	**2**[a]	**3**[b]	**4**[a]
1	3.80 dd (11.4, 4.6)	3.65 dd (11.8, 4.6)	3.21 ddd (11.2, 4.3, 0.9)	3.63 dt (11.4, 4.1)
	3.39 t (11.4)	3.32 t (11.8)	3.05 m	3.48 dd (11.4, 4.1)
3	5.58 s	5.43 s		
4a	3.51 br t (11.2)	3.45 br t (11.2)	3.52 br t (11.8)	3.85 dd (11.6, 8.6)
5	1.65 m	1.81 m	1.85 t (14.1)	1.92 dt (1.6, 14.9)
	1.50 dt (2.6, 14.9)	1.49 dt (1.9, 14.1)	1.43 m	1.67 m
6	1.83 dt (2.8, 14.9)	1.73 m	1.64 t (14.1)	1.23 m
	1.30 dq (14.9, 2.6)	1.25 m	1.35 m	1.21 m
8	2.36 d (4.0)	2.29 d (4.2)	2.63 d (4.4)	2.43 d (4.0)
9	2.84 ddd (12.0, 5.0, 4.0)	2.78 ddd (10.0, 5.1, 4.2)	3.03 m	3.12 ddd (11.3, 5.1, 4.0)
10	2.61 dt (1.5, 12.0)	2.45 ddd (12.4, 10.0, 0.9)	2.75 t (12.1)	2.90 dt (5.1, 11.3)
	2.54 dd (12.0, 5.0)	2.48 dd (12.4, 5.1)	2.52 br t (12.1)	2.78 br dt (1.7, 12.9)
11a	2.40 dt (4.6, 11.2)	2.35 dt (4.6, 11.2)	2.64 br t (11.8)	3.21 dd (11.6, 4.1)
12	5.75 br s	6.04 s	7.28 s	8.31 s
13	4.78 dddd (8.7, 3.9, 2.6, 0.9)	5.20 br t (3.3)	5.19 br s	
14	3.06 d (8.7)	3.74 d (3.3)	3.48 d (4.6)	5.70 s
16	1.37 s, 3H	1.20 s, 3H	1.19 s, 3H	1.34 s, 3H
17	1.22 s, 3H	1.42 s, 3H	1.12 s, 3H	1.38 s, 3H
18	1.23 s, 3H	1.21 s, 3H	1.24 s, 3H	1.23 s, 3H
19	4.97 br s	4.89 s	5.14 s	5.28 s
	4.90 d (1.3)	4.83 s	5.08 s	5.18 s

[a] Recorded in C_6D_6 solution measured at 400 MHz.
[b] Recorded in d_6-DMSO solution measured at 400 MHz.
[c] The *J*-values in hertz are indicated in parentheses.

Table 3. ^{1}H NMR spectral data of xeniolides I–K (**5**–**7**)[c]

H	**5**[a]	**6**[b]	**7**[b]
1	3.96 dd (10.6, 4.2)	4.18 dd (10.7, 4.0)	4.32 dd (11.1, 4.5)
	3.75 t (10.6)	3.94 t (10.7)	4.05 dd (11.1, 9.2)
4a	3.56 ddt (11.0, 1.5, 4.0)	3.89 m	3.82 dd (11.6, 5.6)
5	1.89 m	1.82 m	1.79 m
	1.49 m	1.64 m	1.75 m
6	2.08 ddd (15.0, 11.1, 3.6)	2.18 ddd (14.6, 10.6, 2.6)	2.10 ddd (15.2, 7.2, 4.6)
	1.23 m	1.60 m	1.93 ddd (15.2, 9.3, 4.8)
8	2.20 d (3.8)	2.82 d (3.9)	3.23 d (3.8)
9	2.58 dt (10.9, 3.8)	2.99 dt (11.3, 3.9)	3.07 dt (11.1, 3.8)
10	2.85 dd (13.4, 10.9)	3.08 dd (13.2, 11.3)	2.97 dd (14.0, 11.1)
	2.51 dd (13.4, 3.8)	2.85 dd (13.2, 3.9)	2.80 dd (14.0, 3.8)
11a	2.41 m	2.64 br dt (4.0, 11.9)	2.77 m
12	6.84 dd (9.4, 1.5)	6.29 dd (1.5, 10.1)	6.43 dd (10.9, 0.8)
13	4.56 dd (9.4, 8.1)	5.40 dd (10.1, 8.4)	5.32 dd (10.9, 8.4)
14	2.70 d (8.1)	2.96 d (8.4)	2.98 d (8.4)
16	1.39 s, 3H	1.39 s, 3H	1.37 s, 3H
17	1.18 s, 3H	1.35 s, 3H	1.36 s, 3H
18	1.13 s, 3H	1.36 s, 3H	2.83 d (5.6)
			2.57 d (5.6)
19	4.81 s	5.19 br s	5.20 s
	4.59 s	5.01 d (1.2)	5.06 d (1.5)
Ac		2.01 s, 3H	2.01 s, 3H

[a] Recorded in C_6D_6 solution measured at 400 MHz.
[b] Because of the better resolution, the NMR of **6** and **7** were taken in $CDCl_3$ at 400 MHz.
[c] The *J*-values in hertz are indicated in parentheses.

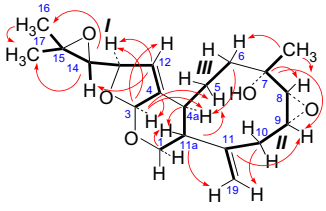

Figure 3. ^{1}H–^{1}H COSY (I–III) and selected HMBC correlations for novaxenicin A (**1**).

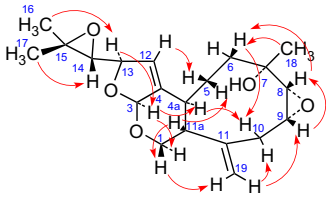

Figure 4. Selected NOESY for novaxenicin A (**1**).

of **2**, no conclusion about the configuration of C-14 could be reached.

Novaxenicin C (**3**) was found to possess a molecular formula $C_{20}H_{30}O_7$ as established from its HRESIMS (*m*/*z* 405.1907, $[M+Na]^+$), implying six degrees of unsaturation. The NMR data of compound **3**, the most polar compound among the seven (several OH groups, ν_{max} 3560 cm^{-1}) had to be determined in d_6-DMSO. The NMR data revealed the presence of the following functionalities: an exocyclic double bond (δ_C 118.9 t, 147.0 s), an α,β-unsaturated butenolide (δ_C 173.1 s, 136.8 s, 151.1 d, 82.6 d), an epoxide (δ_C 61.8 d, 60.5 d), a methyleneoxy group (δ_C 64.6 t), one methineoxy group

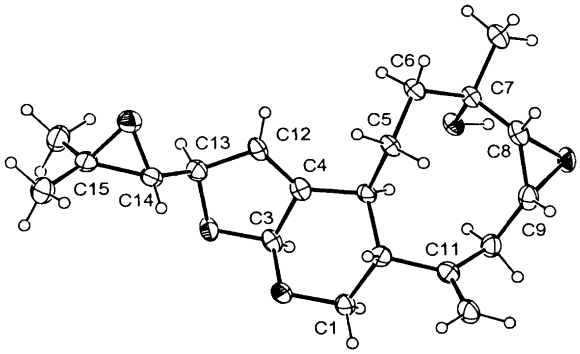

Figure 5. ORTEP representation of novaxenicin A (**1**) as determined by signal-crystal X-ray analysis.

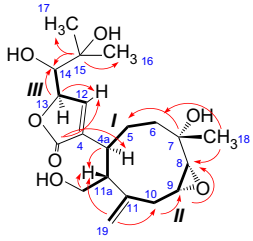

Figure 6. ^{1}H–^{1}H COSY (I–III) and HMBC correlations for novaxenicin C (**3**).

(δ_C 78.3 d), and two tertiary alcohols (δ_C 72.1 s, 72.0 s) carrying, together, three methyl groups (δ_H 1.19 s, 1.12 s, and 1.24 s).

The above functionalities account for five of the six degrees of unsaturation of **3** suggesting one additional ring. The COSY spectrum revealed the presence of three spin systems (I–III, Fig. 6), which could be linked together by CH-correlations (HMBC) to establish the planar structure of **3** (Fig. 1). Novaxenicin C possesses two of the three rings constructing the ring system of novaxenicins A and B (**1** and **2**). The relative stereochemistry of **3** was established, as for **1** and **2**, from the coupling constants and NOEs (Fig. 7), i.e., the chirality of the five asymmetric centers of the nine-membered ring is the same as in **1** and **2**. Additionally, a 13*R** configuration is assumed on the basis of common biogenesis of **1**–**4**. The configuration of C-14 on the other hand, as in the case of **2**, remains unsolved.

The CIMS spectrum of **4** exhibited a pseudo molecular ion $[M+H]^+$ at *m*/*z* 365. The molecular formula was determined by HRMS to be $C_{20}H_{28}O_6$, which agrees with the loss of a molecule of water from **3**. The ^{13}C and ^{1}H NMR spectra of **4** are almost identical to those of **3**, the only major difference being an additional $\Delta^{13(14)}$ double bond (δ_C 147.3 s, 122.0 d) instead of the 14-hydroxy group. NOEs between CH_3-16 and CH_3-17 to H-12 and H-14, respectively, established the $\Delta^{13(14)}$ *E* configuration and point to a preferred conformation around the 14(15) double bond. Notable in the ^{1}H NMR spectrum of **4** is the low field chemical shift of H-12 (δ_H 8.31 s) due to its β-position to the lactone carbonyl group and its allylic position to the Δ^{13} bond.

The three additional isolated compounds (**5**–**7**) possessing the ring system of xeniolide A were designated xeniolides I–K (Fig. 2).

The CIMS spectrum of xeniolide I (**5**) exhibited a molecular ion $[M+H]^+$ at *m*/*z* 365. The molecular formula was determined by HRCIMS to be $C_{20}H_{28}O_6$. The NMR data of **5** revealed, in addition to the same substituted nine-membered rings of **1**–**4**, a δ-lactone conjugated to an exocyclic

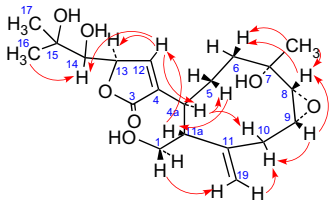

Figure 7. Observed NOESY for novaxenicin C (**3**).

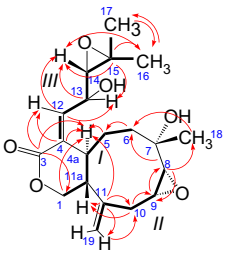

Figure 8. COSY (I–III) and selected HMBC correlations for xeniolide I (**5**).

tri-substituted double bond (δ_C 69.9 t, 169.1 s, 135.8 s, 141.0 d) condensed to the nine-membered ring, a methineoxy group (C-13, δ_C 66.3 d), and a tri-substituted epoxide (C-14,15, δ_C 65.0 d, 59.5 s) with two substituting CH_3 groups (Me-16,17, δ_C 19.1 q, 24.1 q). The COSY spectrum (Fig. 8) revealed for **5** the presence of three spin systems (I–III) that were joined together by long-range CH-correlations (HMBC) (Fig. 8), establishing its planar structure (Fig. 2). The *E* configuration of the 4(12)-double bond as in xeniolide A was established from the low field chemical shift of H-12 (δ_H 6.84, against 6.40 in case of the *iso*-isomer)[16] and NOEs between H-13 and H-5. Proton H-13 in all three new xeniolides (**5**–**7**) possesses two large coupling constants (ca. 8 and 10 Hz) with its neighbors, H-12 and H-14, pointing to two anti-conformations but, because of conformational mobility of the side chain, it was impossible to suggest unambiguously the stereochemistry of C-13 and C-14.

Xeniolide J (**6**), $C_{22}H_{30}O_7$ (HRCIMS), is the 13-acetoxy derivative of **5** (Fig. 2). Comparison of the ^{1}H NMR spectrum of **6** with that of **5**, Table 3, showed a downfield shift of H-13 from 4.56 dd (*J*=9.4, 8.1) to 5.40 dd (*J*=10.1, 8.4).

Xeniolide K (**7**), $C_{22}H_{28}O_7$ (HRCIMS), possesses, according to the NMR data, the same side chain (C-4 to CH_3-16, CH_3-17) and butanolide (C-1, C-4a, and C-11a) as **6**, but differs in the substitution of the nine-membered ring. Namely, the 18-methyl group disappeared and instead showed up a new 1,1-disubstituted epoxide (δ_C 54.7 s, 48.4 t), as in the havannahines,[17,18] as confirmed by HMBC correlations from C-6 and C-7 to H-18,18′.

Comprehensive comparison of the NMR data of **7** with that of the havannahine isomers (xenicins possessing the 7(18), 8(9) diepoxy moieties),[18] exhibited good agreement with havannahine itself, over the other isomers. The suggested structure is also in good agreement with the NOESY cross-peaks (Fig. 9), though, the epimeric 7(18) epoxide cannot

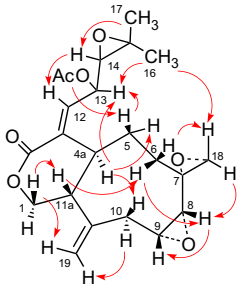

Figure 9. Selected NOESY correlations for xeniolide K (**7**).

unambiguously be excluded. Change of the epoxide stereochemistry is not expected to significantly influence the observed NOEs.

All new compounds and especially xeniolide K are very acid sensitive because of the epoxy groups.

Compound **5** possesses anti-bacterial activity at a concentration of 1.25 μg/ml (*Escherichia coli* and *Bacillus subtilis*) and compound **2** induces apoptosis in transformed mammalian cells at a concentration of 1.25 μg/ml.[19]

Noteworthy is an earlier report on *X. novaebrittanniae* collected at Laing Island, Papua-New Guinea, affording three different compounds, a xenicin derivative and two *iso*-xeniolide A derivatives. Isolation of divergent secondary metabolites from the same soft coral collected from different localities is well known—the reason for this still being a source for debate.[20]

3. Conclusion

The four novaxenicins (**1**–**4**) together with helioxenicin C[14] build an interesting group of compounds related to the *Xenia* diterpenoids. Biogenetically, the novaxenicins and the xeniolides (Figs. 1 and 2) may be obtained from a similar precursor, regarding the common two xeniolide rings,[7] namely, a metabolite possessing a 1-methyleneoxy and a 3-carboxaldehyde group. The latter can then undergo different routes that will lead to either xeniolides (oxidation of C-3, before or after C-1 to C-3 cyclization), or form a dihydrofurane or a butenolide ring, from C-3 to C-13, by the attack of the C-3 lactol OH or carboxylic group on C-13, to create the novaxenicins. It is unlikely that during the isolation process the two stable ring systems will convert one to the other.

4. Experimental

4.1. General experimental procedures

Optical rotations were obtained with a Jasco P-1010 polarimeter. IR spectra were obtained with a Bruker FTIR Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-500 and Avance-400 spectrometers. ^{1}H, ^{13}C, COSY, HSQC, NOESY, and HMBC were recorded using standard Bruker pulse sequences. EIMS, CIMS, and HRMS measurements were recorded on a Fisons, Autospec Q instrument. Electrospray MS measurements were performed on an AppliedBiosystems Q-STAR Pulsar instrument (ESI-QqTOF).

4.2. Biological material

The soft coral *X. novaebrittanniae* (Ashworth, 1900) was collected at Kitagamwa in February, 2004. A voucher specimen is deposited at the Zoological Museum, Tel Aviv University, Israel (ZMTAU CO 32253).

4.3. Extraction and isolation

Freeze-dried soft coral (KB-2177, 35 g) was homogenized and extracted with ethyl acetate (0.2 l×3) to give after evaporation a brown gum (3.5 g). The gum was chromatographed on a Sephadex LH-20 column, eluting with hexane–$CHCl_3$–MeOH (2:1:1), 12 fractions of 20 ml were collected.

Interesting fractions from the Sephadex column were further separated on the methanol-washed silica gel (VLC) as follows: fraction 5 (46 mg) afforded with hexane–ethyl acetate (7:3) compound **1** (18.5 mg 0.052% dry weight) and with 2:3 compounds **6** (3.9 mg 0.011% dry weight) and **7** (4.5 mg 0.012% dry weight). Fractions 7 and 8 (98 mg) afforded with hexane–ethyl acetate (2:3) compounds **2** (19 mg 0.0547% dry weight) and **5** (6.2 mg 0.017% dry weight). Fractions 9 and 10 (49 mg) afforded with hexane–ethyl acetate ratio 3:7 compound **4** and with 2:8 compound **3**. Compound **4** (9.4 mg 0.026% dry weight) was further purified by HPLC (RP-18) eluted with CH_3CN–H_2O (85:15), and compound **3** (3.2 mg 0.009% dry weight) with CH_3CN–H_2O (80:20).

4.3.1. Novaxenicin A (1). Colorless crystals (crystallized from acetone); mp 168–172 °C; $[\alpha]_D^{22}$ −34 (*c* 0.98, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3436, 3023, 2838, 1729, 1426, 1331, 1219, 1016, 929 cm^{-1}; ^{1}H and ^{13}C NMR see Tables 1 and 2; CIMS *m/z* 349 $[M+H]^+$ (86), 331 (35) ($[M+H]^+-H_2O$), 259 (55) ($[M+H]^+-C_4H_{10}O_2$), 71 (75) (C_4H_7O), 277 (100) ($[M+H]^+-C_4H_8O$).

4.3.2. Novaxenicin B (2). Pale yellow oil; $[\alpha]_D^{22}$ −37 (*c* 1.81, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3684, 3500, 3019, 1731, 1425, 1215, 1031, 928 cm^{-1}; ^{13}C and ^{1}H NMR see Tables 1 and 2; CIMS *m/z* 367 $[M+H]^+$ (8), 365 (10) ($[M+H]^+-H_2$), 347 (16) ($[M+H]^+-H_2-H_2O$), 278 (85) ($[M+H]^+-C_4H_9O_2$), 151 (100) ($[M+H]^+-C_{13}H_{12}O_3$); HRCIMS *m/z* 367.2042 (Calcd for $C_{20}H_{30}O_6$, 367.2046).

4.3.3. Novaxenicin C (3). Pale yellow oil; $[\alpha]_D^{22}$ −12 (*c* 0.3, MeOH); IR (MeOH) ν_{max} 3684, 3480, 3018, 1754, 1424, 1211, 1030, 922 cm^{-1}; ^{13}C and ^{1}H NMR see Tables 1 and 2; ESIMS *m/z* 405.17 $[M+Na]^+$; HRESIMS *m/z* 405.1907 (Calcd for $C_{20}H_{30}O_7Na$, 405.1883).

4.3.4. Novaxenicin D (4). Pale yellow oil; $[\alpha]_D^{22}$ −77 (*c* 0.94, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3680, 3019, 1754, 1426, 1216, 1031, 927 cm^{-1}; ^{13}C and ^{1}H NMR see Tables 1 and 2; CIMS *m/z* 365 $[M+H]^+$ (20), 347 (85) ($[M+H]^+-H_2O$), 83 (100) (C_5H_7O); HRCIMS *m/z* 365.1881 (Calcd for $C_{20}H_{28}O_6$, 365.1885).

4.3.5. Xeniolide I (5). Pale yellow oil; $[\alpha]_D^{22}$ +41 (*c* 0.17, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3480, 3020, 1750, 1616, 1216, 1032, 926 cm^{-1}; ^{13}C and ^{1}H NMR see Tables 1 and 3; CIMS *m/z* 365 $[M+H]^+$ (20), 329 (100) ($[M+H]^+-2H_2O$), 347 (40) ($[M+H]^+-H_2O$), 293 (40) ($M+H]^+-C_4H_8O$); HRCIMS *m/z* 365.1963 (Calcd for $C_{20}H_{28}O_6$, 365.1964).

4.3.6. Xeniolide J (6). Pale yellow oil; $[\alpha]_D^{22}$ +10 (*c* 0.13, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3627, 3020, 1751, 1630, 1204, 1015, 922 cm^{-1}; ^{13}C and ^{1}H NMR see Tables 1 and 3; CIMS *m/z* 407 $[M+H]^+$ (15), 347 (82) ($[M+H]^+-C_2H_4O_2$), 329 (100) ($[M+H]^+-C_3H_{10}O_2$); HRCIMS *m/z* 407.2067 (Calcd for $C_{22}H_{30}O_7$, 407.2069).

4.3.7. Xeniolide K (7). Pale yellow oil; $[\alpha]_D^{22}$ −27 (*c* 0.28, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3475, 3011, 1745, 1640, 1204, 1160, 970 cm^{-1}; ^{13}C and ^1H NMR see Tables 1 and 3; EIMS *m/z* 404 $[M]^+$ (12), 345 (100) ($[M]^+-C_2H_3O_2$), 287 (55) ($[M]^+-C_5H_9O_3$); HREIMS *m/z* 404.1831 (Calcd for $C_{22}H_{28}O_7$, 404.1835).

4.4. X-ray crystallographic analysis

The measurements were carried out on a Nonius KappaCCD diffractometer at low temperature (ca. 110 K) in order to optimize the precision of the crystallographic determination, with Mo Kα radiation.

Crystal data: $C_{20}H_{28}O_5$, *M*=348.42, monoclinic, space group $P2_1$, *a*=10.9750(11), *b*=7.7323(4), *c*=11.9516(12) Å, β=114.545(3)°, *V*=922.59(14) $Å^3$, *Z*=2, *T*=110(2) K, D_c=1.254 g cm^{-3}, μ(Mo Kα)=0.09 mm^{-1}, 2245 unique reflections to $2\theta_{max}$=51.4°, 229 refined parameters, R_1=0.058 for 3191 observations with $I>2\sigma(I)$, R_1=0.095 (wR_2=0.119).

The molecule geometry, including that of epoxide fragments, revealed common bond lengths and bond angle characteristics, and the polar space group of the crystal is consistent with the chiral nature of this compound. The central six-membered ring adopts a chair conformation, the unsaturated five-membered ring is planar, and the eight-membered ring has a strain-optimized conformation. In the crystal, neighboring molecules displaced along **b** in both directions are O–H···O hydrogen bonded to one another, thus forming supramolecular chains along the polar direction. These bonds involve the ethereal *O*-atom of the six-membered ring of one species as proton acceptor and the hydroxyl group of another unit as proton donor [O···O 2.940(3) Å, O–H···O 151°]. Side-packing of these chains perpendicular to **b** is stabilized by van der Waals forces.

Crystal data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CDCC deposition number 613498. The supplementary crystallographic data for this paper can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

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Synthetic studies on Ecteinascidin-743: synthesis of building blocks through Sharpless asymmetric dihydroxylation and aza-Michael reactions☆

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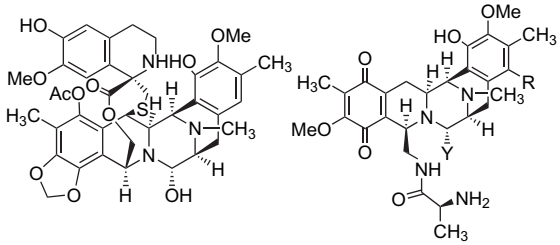
Abstract—A practical and an efficient synthesis of three building blocks of tetrahydroisoquinoline alkaloid Ecteinascidin-743 was accomplished, starting from readily available piperonal, 2-methyl anisole, and veratraldehyde. A combination of Vilsmeier–Haack reaction and Sharpless asymmetric dihydroxylation was employed for the synthesis of building blocks **A** and **B** whereas a Heck reaction in PEG-2000 and aza-Michael reactions were employed for the synthesis of building block **C**.

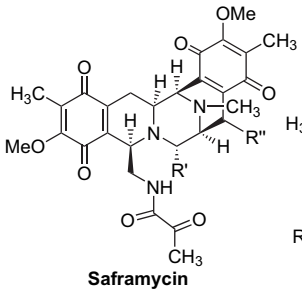
1. Introduction

The chemistry of tetrahydroisoquinoline alkaloids has attracted considerable interest over the years due to their potent biological properties.[1] Ecteinascidin-743 (ET-743) is a marine tetrahydroisoquinoline natural product isolated from *Ecteinascidia turbinata* by Rinehart et al.,[2] in 1990, which has been demonstrated to be a highly promising, exceedingly potent anti-tumor agent currently in phase II/III clinical trials and also attracting considerable attention owing to its unique mechanism of action.[3] The novel structure of ET-743 combined with the natural scarcity and remarkable biological activities make it an attractive and important synthetic target. ET-743 is structurally related to Safracin,[4] Saframycin,[5] and Reniaramycins,[6] which are also potent anti-tumor antibiotics that contain densely functionalized tetrahydroisoquinoline ring systems constituted from similar amino acid components.[7]

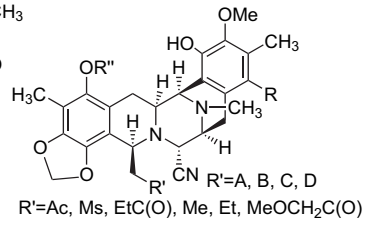


Ecteinascidin-*743*

safracin A : R=Y=H; R=Br, Y=H
B : R=H, Y=OH; R=H, Y=CN



Saframycin



R'=A, B, C, D
R'=Ac, Ms, EtC(O), Me, Et, MeOCH$_2$C(O)

Phthalascidin analogs

The first total synthesis was achieved by Corey[8] and later Fukuyama[9] and Zhu[10] have achieved two total syntheses. Cuevas and co-workers at pharmaMar have developed a semi-synthesis of ET-743 from Cyanosafracin B.[11] Corey and co-workers prepared a similar synthetic analogue of ET-743 (Phthlascidin, Pt-650) that exhibited virtually the same cytotoxicity as the natural product.[12] Other synthetic approaches have been reported from a number of research groups including those of Kubo,[13] Danishefsky,[14] Williams,[15] Liu,[16] and Magnus.[17]

2. Results and discussion

Our continued interest in the development of new protocols for the synthesis of nitrogen containing heterocycles[18] and hybrid natural products[19] related to anti-tumor compounds prompted us to adopt a convergent strategy for the synthesis of ET-743 and identify the three building blocks **A**–**C**. The retrosynthetic analysis revealed that the fully functionalized

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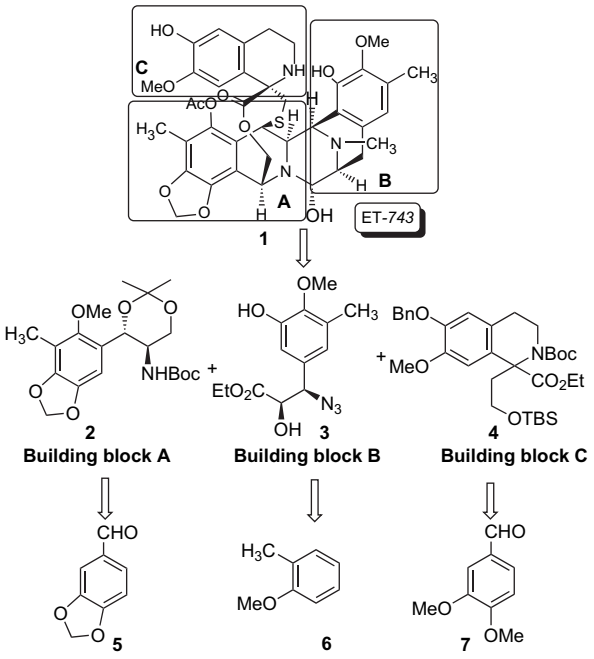
dihydroxy cinnamate esters could be useful chiral materials, which should furnish the desired stereochemistry at C-2 and C-3 in the target building blocks **A** and **B**. Building block **C** could be obtained from a Heck reaction, aza-Michael reaction, and carboxylation of a phenyl ethylamine derivative. Synthesis of these building blocks commenced with inexpensive and readily available starting materials piperonal, 2-methyl anisole, and veratraldehyde (Scheme 1), respectively.

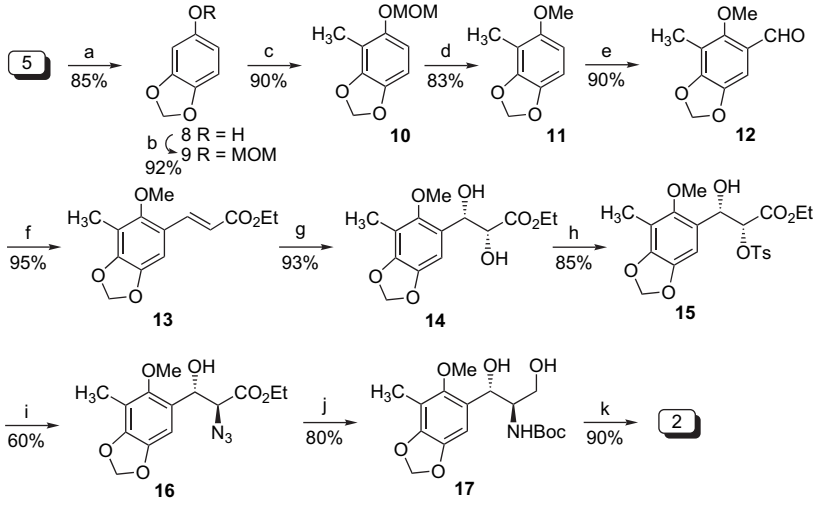


Scheme 1.

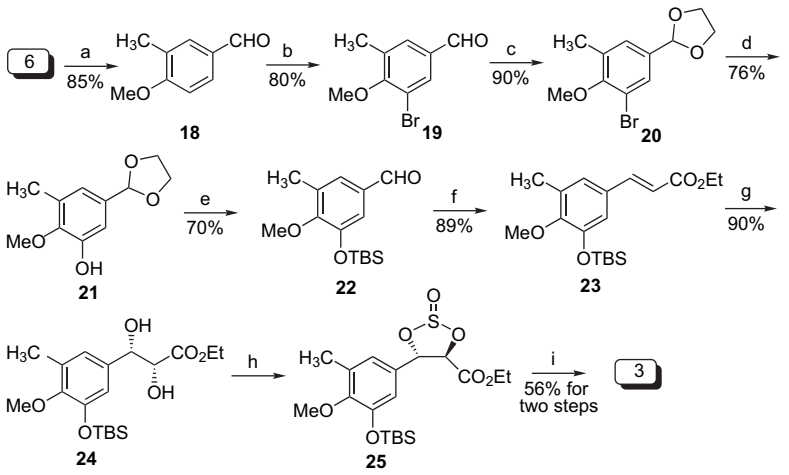
The chemical route for the synthesis of building block **A** (**2**) is shown in Scheme 2. The Baeyer–Villiger oxidation[20] of piperonal **5** using *m*-chloroperoxybenzoic acid followed by base hydrolysis gave the phenol **8**, which was protected as its MOM ether **9** using diisopropylethylamine (DIPEA) and methoxymethyl chloride (MOMCl). Selective monomethylation of compound **9** carried out at −78 °C using ^{n}BuLi, tetramethylethylenediamine (TMEDA) followed by methyl iodide gave the compound **10**. The MOM ether group in **10** was converted to methyl ether **11** by two-step sequence viz., deprotection of MOM group of the compound **5** using concd HCl in refluxing ethanol[21] followed by methylation using K_2CO_3 and methyl iodide in acetone. The Vilsmeier–Haack formylation[22,20b] of compound **11** using $POCl_3$/dimethylformamide gave the aldehyde **12**. Two-carbon homologation of aldehyde **12** using ethoxycarbonylmethylene triphenylphosphine in benzene at room temperature gave the unsaturated ester **13**.

The Sharpless asymmetric dihydroxylation[23] of unsaturated ester **13** using AD mix-α in ^{t}BuOH–H_2O (1:1) for 12 h gave the diol **14** with 97% ee. The aim of selective α-tosylation of diol **14** was achieved with tosyl chloride and triethyl amine in CH_2Cl_2 to yield the mono-tosylated compound **15**.[24] α-Azido ester **16** was synthesized from mono-tosylated compound **15** using sodium azide in *N*,*N*-dimethylformamide at 65 °C. *N*-Boc protected amino diol **17** was obtained from the α-azido ester **16** by the two-step sequence; lithium aluminum hydride reduction followed by in situ Boc protection using $(Boc)_2O$ to give the Boc protected amino diol **17**. Selective 1,3-acetonide protection of compound **17** using 2,2-dimethoxypropane, camphor sulfonic acid in acetone gave the building block **A** (**2**) (Scheme 2).

Building block **B** was synthesized from 2-methyl anisole **6**. Vilsmeier–Haack formylation of 2-methyl anisole **6** using $POCl_3$/DMF gave the aldehyde **18**. Bromination of aldehyde **18** using *N*-bromosuccinamide in acetonitrile at room temperature for 24 h gave the bromo compound **19**.[25] Ethylene glycol protection of bromo compound **19** with cat. PTSA afforded the compound **20**. This was converted to TBS ether **22** by a three-step sequence: conversion of the bromide to phenol **21** using ^{n}BuLi, trimethyl borate, and 4-methyl morpholine *N*-oxide in tetrahydrofuran under refluxing conditions,[26] cleavage of the ethylene glycol moiety, which was followed by protection of phenol **21** as its TBS ether **22** using *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2. This is concise method for the synthesis of aldehyde **22**



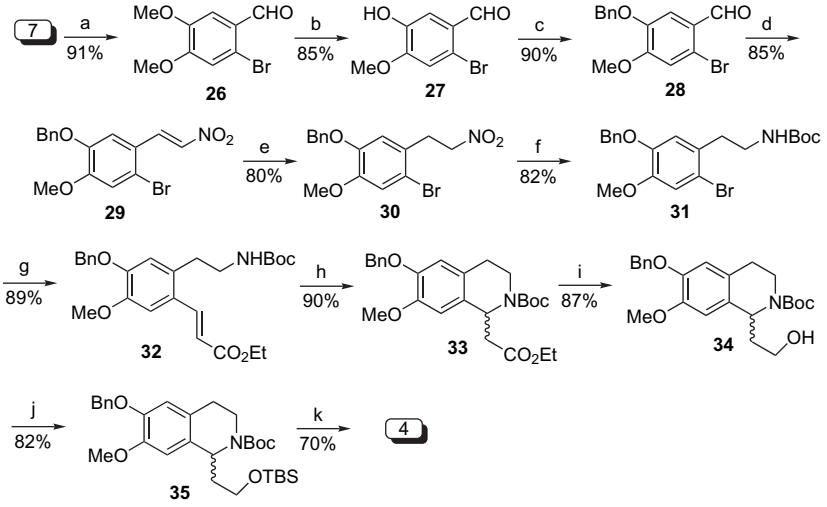
Scheme 2. (a) *m*-CPBA, CH_2Cl_2, aq KOH; (b) DIPEA, MOMCl; (c) ^{n}BuLi, TMEDA, MeI, −78 °C, THF; (d) (i) HCl, EtOH; (ii) K_2CO_3, MeI, acetone; (e) DMF–$POCl_3$; (f) ethoxycarbonylmethylenetriphenyl phosphine, benzene; (g) AD mix-α, ^{t}BuOH–H_2O (1:1); (h) TsCl, TEA, CH_2Cl_2; (i) NaN_3, DMF, 65 °C; (j) LAH, $(Boc)_2O$, THF; (k) 2,2-DMP, CSA, acetone.



Scheme 3. (a) DMF–$POCl_3$; (b) NBS, acetonitrile; (c) ethylene glycol, PTSA, benzene; (d) ^{n}BuLi, $B(OMe)_3$, NMO, THF; (e) (i) HCl, THF–H_2O; (ii) TBSCl, imidazole, CH_2Cl_2; (f) ethoxycarbonylmethylenetriphenyl phosphine, benzene; (g) AD mix-α, ^{t}BuOH–H_2O (1:1); (h) $SOCl_2$, TEA, CH_2Cl_2; (i) NaN_3, DMF, 65 °C.

from inexpensive 2-methyl anisole **6**. The two-carbon homologation of compound **22** was carried out by Wittig olefination protocol using ethoxycarbonylmethylene triphenylphosphine in benzene to give the unsaturated ester **23**. The Sharpless asymmetric dihydroxylation of unsaturated ester **23** using AD mix-α furnished the diol **24** in high enantiomeric purity (98% ee). Both the dihydroxylation reactions proceeded smoothly at room temperature in the absence of methane sulfonamide. To get the β-azido functionality, diol **24** was converted as its cyclic sulfite **25** using $SOCl_2$ and TEA followed by regioselective opening of this cyclic sulfite **25** using NaN_3 in DMF to get the β-azido ester (building block **B**) exclusively (Scheme 3).[27] This building block not only is a key intermediate for the synthesis of Ecteinascidin analogs but also for the synthesis of substituted α-hydroxy-β-phenyl alanines.[28]

Synthesis of building block **C** (**4**) started from veratraldehyde **7**. Selective bromination of veratraldehyde **7** using Br_2 in MeOH at <40 °C temperature gave the bromo compound **26**. The 5-methoxy group was selectively deprotected in the compound **26**, which was carried out using H_2SO_4 at 90 °C to give **27**.[29] Phenol **27** was protected as its benzyl ether using K_2CO_3 and benzyl bromide in acetone under reflux conditions to yield the aldehyde **28**. The next step was nitro-aldol condensation of aldehyde **28** with nitro methane and ammonium acetate in acetic acid to afford the unsaturated nitro compound **29**. Conversion of unsaturated nitro compound **29** to saturated nitro compound **30** was achieved with sodiumborohydride in EtOH at 0 °C. Lithium aluminum hydride reduction of nitro compound **30** gave the amine, which was in situ protected with $(Boc)_2O$ to yield the compound **31**. The palladium catalyzed Heck reaction of compound **31** with ethyl acrylate in polyethylene glycol (PEG-2000) gave the unsaturated ester **32**.[30] The compound **32** was subjected to aza-Michael reaction after –Boc deprotection followed by reprotection with $(Boc)_2O$ to yield tetrahydroisoquinoline **33**. Reduction of ester group to primary alcohol **34** followed by TBS protection and carboxylation yielded building block **C** (**4**) (Scheme 4).



Scheme 4. (a) Br_2, MeOH, <40 °C; (b) H_2SO_4, 90 °C; (c) K_2CO_3, BnBr, acetone; (d) nitro methane, ammonium acetate, acetic acid; (e) $NaBH_4$, EtOH; (f) LAH, $(Boc)_2O$, THF; (g) ethyl acrylate, $Pd(OAc)_2$, TEA, PEG-2000, 80 °C; (h) TFA, CH_2Cl_2, Na_2CO_3, $(Boc)_2O$; (i) $NaBH_4$, LiCl, EtOH–THF (1:1); (j) TBSCl, imidazole, CH_2Cl_2; (k) ^{n}BuLi, $ClCO_2Et$, THF.

3. Conclusion

In conclusion, we have successfully achieved the synthesis of three building blocks of ET-743 from piperonal, 2-methyl anisole, and veratraldehyde. Simple and efficient methods like Baeyer–Villiger oxidation, Vilsmeier–Haack formylation, Sharpless asymmetric dihydroxylation, and Heck reaction in PEG-2000 and aza-Michael reactions have been employed for the synthesis of these building blocks. These building blocks are also useful for the synthesis of other tetrahydroisoquinoline natural products like Saframycin, Safracin, etc. The building blocks will be utilized in the construction of hybrid natural products toward creating diverse scaffolds for screening against biological targets. The work in this direction is currently underway in our group.[31]

4. Experimental section

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 meshes. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometer. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in hertz. HPLC was recorded on SHIMADZU HPLC using chiralcel OB-H column, and hexane and isopropyl alcohol as eluents. Melting points (uncorrected) were obtained using a Buchi 535 melting point apparatus. Mass spectra were obtained on Finnegan MAT 1020B or micromass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

4.1.1. 5-Methoxy methoxy benzo[*d*][1,3] dioxole (9).[21] Piperonal **5** (5.0 g, 33 mmol) and *m*-CPBA (8.4 g, 48 mmol) were refluxed in dry CH_2Cl_2 (75 mL) for 18 h. Most of the CH_2Cl_2 was removed by distillation under reduced pressure and the residue was dissolved in ethyl acetate (75 mL). The solution was washed with aq $NaHCO_3$ until effervescence ceased, then with brine, and dried over anhydrous sodium sulfate. Removal of the solvent left crude formate. The crude formate was dissolved in a little MeOH and hydrolyzed under nitrogen with a slight excess of 10% aq KOH at room temperature. After the completion of the reaction, the reaction mixture was acidified with dilute HCl and extracted with ethyl acetate twice (2×100 mL). The combined organic layers were washed with water, brine, and removal of the solvent gave phenol **8** (3.9 g, 85%), which was used further without purification. The crude phenol **8** (3.9 g, 28 mmol) and DIPEA (7.35 mL, 42 mmol) were taken in dry CH_2Cl_2 (50 mL) at 0 °C. After 10 min methoxymethyl chloride (2.27 g, 28 mmol) was added and the mixture stirred for 8 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water and aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by silica gel column chromatography to give the MOM ether **9** (4.7 g, 92%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.65 (d, J=13.0 Hz, 1H, Ar), 6.57 (s, 1H, Ar), 6.45 (d, J=13.0 Hz, 1H, Ar), 5.90 (s, 2H, OCH_2O), 5.05 (s, 2H, OCH_2OCH_3), 3.48 (s, 3H, OCH_3); EIMS *m*/*z* 182 (M^+); IR (neat): 3080, 1300, 900 cm^{-1}.

4.1.2. 5-Methoxy methoxy-4-methyl benzo[*d*][1,3] dioxole (10).[21] A solution of MOM ether **9** (4.5 g, 24 mmol) in dry THF (75 mL) at −78 °C was treated with *n*-butyl lithium (23.1 mL, 1.6 M solution in hexane, 37 mmol) under inert atmosphere. The mixture was stirred at −78 °C for 10 min, added tetramethylethylenediamine (3.71 mL, 24 mmol) followed by MeI (1.53 mL, 24 mmol), and allowed it to warm to room temperature over a period of 2 h. Stirring was continued for another 10 h, reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (75 mL). Organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to yield the alkylated product **10** (4.36 g, 90%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.51 (d, J=8.6 Hz, 1H, Ar), 6.46 (d, J=8.6 Hz, 1H, Ar), 5.88 (s, 2H, OCH_2O), 5.07 (s, 2H, OCH_2OCH_3), 3.46 (s, 3H, OCH_3), 2.10 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 196 (M^+); IR (neat): 3065, 1590, 890 cm^{-1}.

4.1.3. 5-Methoxy-4-methyl benzo[*d*][1,3] dioxole (11).[21,32] Concd HCl (0.5 mL) was added to a stirred solution of MOM ether **10** (4.0 g, 25 mmol) in ethanol (40 mL) and the resulting solution was refluxed for 1–3 h. After completion of the reaction (monitored by TLC) the solvent was removed in vacuo and residue was diluted with 5% $NaHCO_3$ and extracted with ethyl acetate (50 mL). Organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the phenol. To this phenol (3.0 g, 19 mmol) in acetone (30 mL) was added K_2CO_3 (5.44 g, 39 mmol) followed by MeI (2.45 mL, 39 mmol). The reaction mixture was heated to reflux (under cold water circulation) for 5 h. Reaction mixture was filtered, filtrate was concentrated in vacuo and the crude product was purified by silica gel column chromatography to afford the methyl ether **11** (3.0 g, 83% for two steps) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.53 (d, J=8.0 Hz, 1H, Ar), 6.18 (d, J=8.0 Hz, 1H, Ar), 5.85 (s, 2H, OCH_2O), 3.74 (s, 3H, OCH_3), 2.06 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 166 (M^+); IR (neat): 3072, 1580, 760 cm^{-1}.

4.1.4. 6-Methoxy-7-methyl benzo[*d*][1,3] dioxole-5-carbaldehyde (12). The Vilsmeier complex was prepared by the drop wise addition of freshly distilled $POCl_3$ (1.98 mL) to dry *N*,*N*-dimethylformamide (6 mL) during 15 min with stirring and cooling in ice bath. The complex was allowed to warm to room temperature and was then added drop wise to a stirred solution of the methyl ether **11** (3.0 g, 18 mmol) in dry DMF (6 mL) at 100–110 °C. Heating and stirring were continued till completion of the reaction

(1–2 h). The mixture was poured into ice water, made just basic by the addition of aq sodium carbonate, and exhaustively extracted with ethyl acetate (3×40 mL), the combined extracts were washed successively with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to yield the aldehyde **12** (3.15 g, 90%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.18 (s, 1H, C*H*O), 7.12 (s, 1H, Ar), 6.05 (s, 2H, OCH_2O), 3.86 (s, 3H, OCH_3), 2.21 (s, 3H, ArCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.4, 160.0, 152.5, 144.0, 123.2, 113.5, 103.2, 102.0, 63.7, 8.6; EIMS: *m*/*z* 196 (M^++2), 194 (M^+), 151, 121, 67, 65; HRMS-EI calcd for $C_{10}H_{10}O_4$: 194.0579; found: 194.0576; mp 74–76 °C; IR (KBr): 2915, 1672, 1610, 1416, 1279, 927, 580 cm^{-1}.

4.1.5. Ethyl-3-(6-methoxy-7-methyl benzo[*d*][1,3] dioxol-5-yl)-(*E*)-2-propionate (13). To a stirred solution of aldehyde **12** (3.0 g, 15 mmol) in benzene (60 mL) was added ethoxycarbonylmethylene triphenylphosphine (8 g, 23 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred at room temperature for 24 h. Solvent was removed under reduced pressure and residue was purified by silica gel column chromatography using hexane–ethyl acetate system to afford the unsaturated ester **13** (3.87 g, 95%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, *J*=16.3 Hz, 1H, ArC*H*=), 6.86 (s, 1H, Ar), 6.25 (d, *J*=16.3 Hz, 1H, =C*H*CO_2Et), 5.96 (s, 2H, OCH_2O), 4.27 (q, *J*=7.4 Hz, 2H, OC$H_2$$CH_3$), 3.72 (s, 3H, OC$H_3$), 2.18 (s, 3H, ArC$H_3$), 1.33 (t, *J*=7.4 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.2, 154.2, 148.8, 143.6, 139.3, 120.5, 116.5, 113.6, 102.6, 101.5, 62.1, 60.2, 14.3, 9.0; EIMS: *m*/*z* 264 (M^+), 234, 206, 178, 176, 147; HRMS-EI calcd for $C_{14}H_{16}O_5$: 264.0997; found: 264.1002; mp 98–100 °C; IR (KBr): 2982, 1708, 1617, 1474, 1278 cm^{-1}.

4.1.6. Ethyl-(2*R*,3*S*)-dihydroxy-3-(6-methoxy-7-methyl-benzo[*d*][1,3] dioxol-5-yl) propionate (14). To a stirred solution of AD mix-α (18.0 g) in *tert*-butyl alcohol (50 mL) and water (50 mL) at room temperature was added unsaturated ester **13** (3.5 g, 13 mmol). The reaction was stirred at room temperature for 12 h. Sodium sulfite (18.0 g) was added as a solid at 0 °C and the mixture was stirred for 30 min. Ethyl acetate (100 mL) was added; organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The pure product **14** (3.67 g, 93%) was obtained as a white solid by silica gel column chromatography with hexane–ethyl acetate (70:30) as an eluent. Enantiomeric excess was determined by HPLC using chiralcel OB-H column, and isopropanol and hexane as eluents (1:9); flow rate 1 mL/min; major isomer t_R 40.54 min, minor enantiomer t_R 42.39 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.79 (s, 1H, Ar), 5.92 (s, 2H, OCH_2O), 5.10–5.05 (m, 1H, ArC*H*OH), 4.28–4.20 (m, 3H, OC$H_2$$CH_3$, C*H*$CO_2$Et), 3.73 (s, 3H, OC$H_3$), 3.12–3.06 (br s, 1H, OH), 2.92–2.86 (br s, 1H, OH), 2.15 (s, 3H, $ArCH_3$), 1.28 (t, *J*=6.4 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 150.6, 146.4, 143.2, 125.2, 113.0, 104.1, 101.1, 74.3, 69.9, 62.0, 61.1, 13.9, 9.2; EIMS: *m*/*z* 298 (M^+), 196, 180, 165, 137; HRMS-EI calcd for $C_{14}H_{18}O_7$: 298.1052; found: 298.1058; mp 114 °C; $[\alpha]_D^{25}$ −12.35 (*c* 1.00, $CHCl_3$); IR (KBr): 3500, 2926, 1733, 1412, 1208, 1091 cm^{-1}.

4.1.7. Ethyl-(3*S*)-hydroxy-3-(6-methoxy-7-methyl-benzo-[*d*][1,3] dioxol-5-yl)-2-(4-methyl phenyl sulfonyloxy)-(2*R*)-propionate (15). To a stirred solution of diol **14** (3.5 g, 11 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen was added triethyl amine (2.39 mL, 17 mmol) followed by tosyl chloride (2.24 g, 17 mmol). After being stirred for 15 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to afford the tosylated product **15** (4.50 g, 85%) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, *J*=8.2 Hz, 2H, Ar), 7.16 (d, *J*=8.2 Hz, 2H, Ar), 6.57 (s, 1H, Ar), 5.93 (s, 1H, OCH_2O), 5.88 (s, 1H, OCH_2O), 5.19–5.15 (m, 1H, ArC*H*OH), 4.94 (d, *J*=3.5 Hz, 1H, C*H*CO_2Et), 4.20 (q, *J*=7.0 Hz, 2H, OC$H_2$$CH_3$) 3.66 (s, 3H, OC$H_3$), 2.72–2.68 (m, 1H, O*H*), 2.42 (s, 3H, tosyl CH_3), 2.02 (s, 3H, ArCH_3), 1.26 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.0, 150.1, 146.5, 144.5, 142.9, 132.5, 129.2, 127.7, 122.7, 112.8, 104.1, 101.1, 80.4, 69.6, 62.0, 60.8, 21.5, 13.9, 9.1; EIMS: *m*/*z* 452 (M^+); HRMS-EI calcd for $C_{21}H_{24}O_9S$: 452.1141; found: 452.1143; mp 113 °C; $[\alpha]_D^{25}$ +47.8 (*c* 1.00, $CHCl_3$); IR (KBr): 3520, 2931, 1760, 1472, 1368, 1091, 794 cm^{-1}.

4.1.8. Ethyl-2-azido-(3*S*)-hydroxy-3-(6-methoxy-7-methyl-benzo[*d*][1,3] dioxol-5-yl)-(2*S*)-propionate (16). To a stirred solution of tosylate **15** (4.5 g, 9 mmol) in DMF (30 mL) was added NaN_3 (1.94 g, 29 mmol) as a solid in one portion. The temperature was raised to 65 °C for 12 h and then cooled to room temperature and the mixture was diluted with water, and extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was removed and the crude product was purified by silica gel column chromatography (ethyl acetate–hexane 20:80) to yield the azide **16** (1.90 g, 60%) as pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.67 (s, 1H, Ar), 5.94 (s, 2H, OCH_2O), 5.10 (d, *J*=6.0 Hz, 1H, ArC*H*OH), 4.24 (q, *J*=7.0 Hz, 2H, OC$H_2$$CH_3$), 4.07 (d, *J*=6.0 Hz, 1H, C*H*CO_2Et), 3.75 (s, 3H, OCH_3), 2.99–2.95 (br s, 1H, O*H*), 2.17 (s, 3H, ArCH_3), 1.29 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.1, 151.4, 146.9, 143.3, 124.0, 113.3, 103.8, 101.2, 69.5, 65.9, 61.9, 61.4, 14.0, 9.3; EIMS: *m*/*z* 323 (M^+), 196, 165, 137, 67, 38; HRMS-EI calcd for $C_{14}H_{17}N_3O_6$: 323.1117; found: 323.1120; mp 109 °C; $[\alpha]_D^{25}$ −13.16 (*c* 0.60, $CHCl_3$); IR (KBr): 3500, 2931, 2108, 1736, 1472, 1090 cm^{-1}.

4.1.9. [2*S*-Hydroxy-1*R*-hydroxymethyl-2-(6-methoxy-7-methyl-benzo[1,3] dioxol-5-yl)-ethyl]-carbamic acid *tert*-butyl ester (17). To an ice-cold suspension of LAH (0.7 g, 18 mmol) in dry THF (15 mL) under nitrogen was added azido ester **16** (1.5 g, 4.6 mmol) in THF (20 mL).

The reaction mixture was stirred at room temperature for 2 h and then refluxed for 2 h until no starting material was observed. Reaction mixture was quenched with aq NaOH and water, then $(Boc)_2O$ (1.5 g, 6.9 mmol) in THF (15 mL) was added and stirring was continued for 4 h at room temperature. After completion of the reaction, the reaction mixture was filtered over the Celite and washed with ethyl acetate, filtrate was concentrated in vacuo and crude residue was purified by silica gel column chromatography to give the amino diol **17** (1.30 g, 80%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.76 (s, 1H, Ar), 5.92 (s, 2H, OCH_2O), 5.20 (d, J=7.8 Hz, 1H, ArC*H*OH), 5.08 (br s, 1H, N*H*), 4.12–4.02 (m, 1H, C*H*NH), 3.90–3.50 (m, 5H, OCH_3, CH_2OH), 3.20 (br s, 1H, O*H*), 2.17 (s, 3H, $ArCH_3$), 1.40 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.3, 150.4, 146.2, 143.3, 130.0, 128.2, 126.0, 104.0, 101.1, 70.8, 62.7, 61.1, 56.3, 28.2, 9.2; ESI-MS: *m*/*z* 378 (M^++Na), 355 (M^+); HRMS-EI calcd for $C_{17}H_{25}NO_7$: 355.1631; found: 355.1628; $[\alpha]_D^{25}$ +13.6 (*c* 1.00, $CHCl_3$); IR (KBr): 3502, 2930, 1620, 1320, 895 cm^{-1}.

4.1.10. [4*S*-(6-Methoxy-7-methyl-benzo[1,3] dioxol-5-yl)-2,2-dimethyl[1,3] dioxan-5*R*-yl]ethyl]-carbamic acid *tert*-butyl ester (2). The amino diol **17** (1.0 g, 2.8 mmol) was dissolved in a mixture of acetone (10 mL) and 2,2-DMP (0.34 mL, 2.8 mmol) and a catalytic amount of CSA was added. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of triethyl amine and solvent was removed in vacuo to give the crude product, which was purified by silica gel column chromatography to give **2** (1.0 g, 90%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83 (s, 1H, Ar), 5.91 (s, 2H, OCH_2O), 4.93 (d, J=8.8 Hz, 1H, ArC*H*O), 4.63 (br s, 1H, N*H*), 4.16–4.10 (m, 1H, C*H*NH), 3.80–3.50 (m, 5H, OCH_3, CH_2O), 2.17 (s, 3H, $ArCH_3$), 1.60 (s, 3H, $CH(CH_3)_2$), 1.46 (s, 3H, $CH(CH_3)_2$), 1.35 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.6, 151.0, 146.2, 143.2, 129.5, 127.7, 123.3, 103.9, 100.6, 98.6, 68.1, 63.5, 60.8, 50.2, 28.5, 27.8, 27.6, 8.7; ESI-MS: *m*/*z* 418 (M^++Na); Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.47; H, 7.28; N, 3.62; $[\alpha]_D^{25}$ −9.16 (*c* 3.00, $CHCl_3$); IR (KBr): 2995, 1608, 1400, 960 cm^{-1}.

4.1.11. 4-Methoxy-3-methyl benzaldehyde (18).[33] This compound was prepared in the same way as aldehyde **12**, from 2-methyl anisole **6** (3.10 g, 25 mmol). The crude product was purified by column chromatography to afford **18** (3.13 g, 85%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.84 (s, 1H, C*H*O), 7.72 (d, J=9.0 Hz, 1H, Ar), 7.61 (s, 1H, Ar), 6.84 (d, J=9.0 Hz, 1H, Ar), 3.89 (s, 3H, OCH_3), 2.26 (s, 3H, $ArCH_3$); FABMS: *m*/*z* 150 (M^+); IR (KBr): 2350, 1670, 1580, 1260, 730 cm^{-1}.

4.1.12. 3-Bromo-4-methoxy-5-methyl benzaldehyde (19).[34] To a stirred solution of aldehyde **18** (3.0 g, 20 mmol) in acetonitrile (30 mL) was added *N*-bromosuccinimide (7.12 g, 40 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred for 24 h at room temperature, after completion of the reaction (monitored by TLC), diluted with ethyl acetate (60 mL), washed with water, brine, dried over anhydrous Na_2SO_4, removal of the solvent under vacuo, and purified by silica gel column chromatography to give the bromo compound **19** (3.66 g, 80%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.95 (s, 1H, C*H*O), 7.90 (s, 1H, Ar), 7.64 (s, 1H, Ar), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 228 (M^+), 149, 77, 51; IR (KBr): 2352, 1660, 1570, 1210, 675 cm^{-1}.

4.1.13. 2-(3-Bromo-4-methoxy-5-methyl phenyl)-1,3-dioxolane (20). A 250 mL RB flask was charged with aldehyde **19** (3.6 g, 16 mmol), ethylene glycol (1.73 g, 27 mmol), benzene (100 mL) and catalytic amount of PTSA mono-hydrate. The flask was attached to a water separator under reflux condenser fitted with drying tube. An oil bath was placed under the flask and the reaction mixture was refluxed until close to theoretical amount of water collected in the trap, this requires about 9 h. The reaction a mixture was cooled to room temperature, solvent was removed, basified with $NaHCO_3$, extracted with ethyl acetate (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Crude residue was purified by silica gel column chromatography to give the product **20** (3.86 g, 90%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar), 7.16 (s, 1H, Ar), 5.66 (s, 1H, OC*H*O), 4.10–3.90 (m, 4H, OCH_2CH_2O), 3.76 (s, 3H, OCH_3), 2.32 (s, 3H, $ArCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.8, 131.7, 130.2, 129.3, 126.6, 112.0, 108.8, 66.2, 55.5, 14.0; FABMS: *m*/*z* 272 (M^+); HRMS-FAB calcd for $C_{11}H_{13}BrO_3$: 272.0048; found: 272.0043; IR (KBr): 3030, 1598, 1330, 720, 682 cm^{-1}.

4.1.14. 2-(3-Hydroxy-4-methoxy-5-methyl phenyl)-1,3-dioxolane (21). A solution of bromo compound **20** (3.8 g, 13 mmol) in THF (40 mL) at −78 °C was treated with *n*-butyl lithium (1.06 g, 16 mmol). The mixture was stirred at −78 °C for 15 min, treated with trimethyl borate (4.3 g, 41 mmol) and allowed to warm to room temperature over a period of 2 h. An excess of anhydrous NMO (4.38 g, 41 mmol) was then added to the solution under a positive pressure of nitrogen and the resulting suspension was refluxed for 12 h. After dilution in ether the reaction mixture was hydrolyzed with water and the organic phase washed with water to reach pH −7. The solvent was removed under reduced pressure and crude residue was purified by silica gel column chromatography to afford the pure product **21** (2.2 g, 76%) as colorless viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88 (s, 1H, Ar), 6.80 (s, 1H, Ar), 6.68 (s, 1H, O*H*), 5.60 (s, 1H, OC*H*O), 4.20–4.00 (m, 4H, OCH_2CH_2O), 3.80 (s, 3H, OCH_3), 2.33 (s, 3H, $ArCH_3$); FABMS: *m*/*z* 209 (M^+); IR (KBr): 3620, 3040, 1400, 960 cm^{-1}.

4.1.15. 3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-benzaldehyde (22). Compound **21** (2.0 g, 9.5 mmol) was dissolved in 20 mL of THF containing 10 mL of 5% HCl. After 20 h at 25 °C the solvent was removed under reduced pressure to yield the aldehyde (1.3 g). To the aldehyde (1.3 g, 8.3 mmol) in dry CH_2Cl_2 (15 mL) was added imidazole (0.849 g, 12 mmol) at 0 °C

under inert atmosphere. After being stirred for 15 min TBDMSCl (1.25 g, 12 mmol) was added and stirring was continued for 6 h, then the reaction mixture was filtered with water and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and crude residue was purified by silica gel column chromatography to afford the pure product **22** (1.9 g, 70% for two steps) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.80 (s, 1H, C*H*O), 7.28 (s, 1H, Ar), 7.18 (s, 1H, Ar), 3.82 (s, 3H, OCH_3), 2.35 (s, 3H, ArCH_3), 1.05 (s, 9H, SiCH(CH_3)$_3$), 0.22 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.19; H, 8.60; FABMS: *m/z* 280 (M^+); IR (KBr): 2947, 1695, 1578, 1499, 735 cm^{-1}.

4.1.16. Ethyl-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(*E*)-2-propionate (23). This unsaturated ester was prepared in the same way as unsaturated ester **13** from the aldehyde **20** (1.0 g, 3.5 mmol). Solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford **23** (1.12 g, 89%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (d, J=16.3 Hz, 1H, ArC*H*=), 6.95 (s, 1H, Ar), 6.83 (s, 1H, Ar), 6.25 (d, J=16.3 Hz, 1H, =C*H*CO_2Et), 4.24 (q, J=7.4 Hz, 2H, OCH_2CH$_3$), 3.76 (s, 3H, OCH$_3$), 2.26 (s, 3H, ArCH$_3$), 1.34 (t, J=7.4 Hz, 3H, OCH$_2$CH_3), 1.05 (s, 9H, SiCH(CH_3)$_3$), 0.22 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.07; H, 8.65; FABMS: *m/z* 350 (M^+); IR (KBr): 2978, 1712, 1610, 1480, 1260 cm^{-1}.

4.1.17. Ethyl-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(2*R*,3*S*)-dihydroxy-propionate (24). This was prepared in the same way as diol **14** from unsaturated ester **23** (1.0 g, 2.8 mmol) to afford **24** (1.0 g, 90%) as viscous oil. Enantiomeric excess was determined by HPLC using chiralcel OB-H column, and isopropanol and hexane as eluents (1:9); flow rate 1 mL/min; major isomer t_R 36.91 min, minor enantiomer t_R 38.53 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.75 (s, 1H, Ar), 6.72 (s, 1H, Ar), 4.76 (br s, 1H, ArC*H*OH), 4.29–4.20 (m, 3H, OCH_2CH$_3$, C*H*CO_2Et), 3.72 (s, 3H, OCH_3), 2.24 (s, 3H, ArCH_3), 1.29 (t, J=7.7 Hz, 3H, OCH$_2$CH_3), 1.00 (s, 9H, SiCH(CH_3)$_3$), 0.19 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 149.3, 148.5, 135.3, 132.0, 121.4, 117.0, 74.7, 74.1, 61.9, 59.6, 29.6, 25.6, 16.0, 14.0, −4.6; EIMS: *m/z* 384 (M^+), 196, 180, 165, 137; Anal. Calcd for $C_{19}H_{32}O_6Si$: C, 59.34; H, 8.39. Found: C, 59.52; H, 8.26; $[\alpha]_D^{25}$ +2.83 (*c* 0.60, $CHCl_3$); IR (KBr): 3427, 2930, 1735, 1588, 1432, 1326, 1235, 1073, 840 cm^{-1}.

4.1.18. Ethyl-(3*R*)-azido-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(2*R*)-hydroxy-propionic acid ethyl ester (3). To an ice-cold solution of diol **24** (0.5 g, 1.3 mmol) and triethyl amine (0.53 mL, 3.9 mmol) in CH_2Cl_2 was added thionyl chloride (0.23 g, 1.9 mmol) drop wise over a period of 10 min, stirring was continued for another 5 min at 0 °C. The reaction mixture was diluted with cold ether and washed with cold water. The aqueous phase was extracted with ether and the combined organic phases washed with cold brine and concentrated in vacuo gave the cyclic sulfite **25**. The cyclic sulfite **25** was used further without any purification. The crude cyclic sulfite **25** (0.5 g, 1.1 mmol) was taken in dry DMF, added NaN_3 (0.22 g, 3.5 mmol) as a solid and the reaction mixture was heated to 65 °C for 10 h. After completion of the reaction, reaction mixture was diluted with ether and washed with water. Solvent was removed and the crude product purified by silica gel column chromatography yielded the azide **3** (0.3 g, 56% for two steps) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.74 (s, 1H, Ar), 6.66 (s, 1H, Ar), 5.60 (br s, 1H, O*H*), 4.67 (d, J=4.0 Hz, 1H, ArC*H*N_3), 4.42–4.38 (m, 1H, C*H*CO_2Et), 4.20 (q, J=7.5 Hz, 2H, OCH_2CH$_3$), 3.80 (s, 3H, OCH_3), 2.30 (s, 3H, ArCH_3), 1.28 (t, J=7.5 Hz, 3H, OCH$_2$CH_3); FABMS: *m/z* 409 (M^+); $[\alpha]_D^{25}$ +3.86 (*c* 1.00, $CHCl_3$); Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.96; H, 5.76; N, 14.12; IR (KBr): 3418, 2928, 2107, 1732, 1460, 1040 cm^{-1}.

4.1.19. 2-Bromo-4,5-dimethoxy benzaldehyde (26).[29] A 250 mL RB flask was charged with MeOH (40 mL) and 3,4-dimethoxy benzaldehyde **7** (4.0 g, 24 mmol) was added with stirring. Bromine (1.35 mL, 26 mmol) was added with cooling (T<40 °C), and stirring continued at the same temperature for 1 h. Solvent was removed under vacuo, at this point the product may start to precipitate from solution. After cooling to 20 °C water was added with stirring, the resultant slurry was filtered using Buckner funnel, washed with water and cold methanol. The obtained colorless to slightly yellowish product **26** is dried in vacuo (5.30 g, 91%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.17 (s, 1H, C*H*O), 7.38 (s, 1H, Ar), 7.00 (s, 1H, Ar), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.2, 154.2, 148.6, 126.2, 120.1, 115.2, 110.1, 56.3, 55.9; EIMS: *m/z* 245 (M^+); mp 143–145 °C; IR (KBr): 2350, 1670, 1580, 740 cm^{-1}.

4.1.20. 2-Bromo-5-hydroxy-4-methoxy-benzaldehyde (27).[29] A 500 mL RB flask charged with 98% sulfuric acid (25 mL) under nitrogen was heated with stirring at 90 °C. Stirring was stopped and 2-bromo-4,5-dimethoxybenzaldehyde **26** (5.0 g, 20 mmol) was added within 2 min and the reaction was allowed to proceed at 90 °C for 6 h. This mixture was then added quickly to a beaker containing ice and water to precipitate the product. The reaction mixture was cooled to 20 °C and filtered through Buckner funnel and washed with water, dried in vacuum desiccator to give the phenol **27** (4.0 g, 85%) as gray powder.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.02 (s, 1H, C*H*O), 7.26 (s, 1H, Ar), 6.95 (s, 1H, Ar), 3.86 (s, 3H, OCH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 189.9, 152.9, 145.8, 125.8, 117.1, 114.9, 114.1, 55.6; EIMS: *m/z* 231 (M^+); mp 104–106 °C; IR (KBr): 3600, 3050, 1590, 1450, 980 cm^{-1}.

4.1.21. 5-Benzyloxy-2-bromo-4-methoxy-benzaldehyde (28).[35] To a stirred solution of phenol **27** (3.0 g, 12 mmol) in acetone (30 mL) was added K_2CO_3 (3.58 g, 25 mmol), followed by benzyl bromide (1.5 mL, 12 mmol). The reaction mixture was refluxed for 4 h. After completion of the

reaction, the reaction mixture was filtered, and washed with acetone. The filtrate was concentrated in vacuo and purified by silica gel column chromatography to yield the compound **28** (3.75 g, 90%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.06 (s, 1H, C*H*O), 7.24–7.12 (m, 6H, Ar, Ph), 7.00 (s, 1H, Ar), 5.06 (s, 2H, CH_2Ph), 3.96 (s, 3H, OCH_3); EIMS: *m*/*z* 320 (M^+), 91; mp 139–141 °C; IR (KBr): 2357, 1678, 1586, 1501, 1262, 738 cm^{-1}.

4.1.22. 1-Benzyloxy-4-bromo-2-methoxy-5-[2-nitro-(*E*)-1-ethenyl] benzene (29). A mixture of aldehyde **28** (3.5 g, 10 mmol), nitro methane (1.18 mL, 21 mmol) and ammonium acetate (2.5 g, 32 mmol) in acetic acid (40 mL) was heated at 100 °C for 4 h under nitrogen atmosphere. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into a beaker containing ice, the yellowish solid product was separated out. The solid was filtered and washed with water several times to remove the excess acid and dried in vacuo to give the pure unsaturated nitro compound **29** (3.37 g, 85%) as yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, *J*=14.1 Hz, 1H, =CH), 7.23–7.16 (m, 5H, Ph), 7.15 (d, *J*=14.1 Hz, 1H, =C*H*), 7.06 (s, 1H, Ar) 7.00 (s, 1H, Ar), 5.07 (s, 2H, CH_2Ph), 3.97 (s, 3H, OCH_3); FABMS: *m*/*z* 364 (M^+), 363, 321, 154, 137; Anal. Calcd for $C_{16}H_{14}BrNO_4$: C, 52.77; H, 3.87; N, 3.85. Found: C, 52.74; H, 3.83; N, 3.80; mp 164 °C; IR (KBr): 2928, 1544, 1506, 1381, 1158, 1023 cm^{-1}.

4.1.23. 1-Benzyloxy-4-bromo-2-methoxy-5-(2-nitro ethyl) benzene (30). Unsaturated nitro compound **29** (3.0 g, 8 mmol) was dissolved in ethanol (50 mL) cooled to 0 °C, then $NaBH_4$ (0.939 g, 24 mmol) was added portion wise and stirred for 2 h at the same temperature. Solvent was removed under reduced pressure and the residue was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica gel column chromatography to give the saturated nitro compound **30** (2.38 g, 80%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.28 (m, 5H, Ph), 7.02 (s, 1H, Ar), 6.74 (s, 1H, Ar), 5.08 (s, 2H, CH_2Ph), 4.52 (t, *J*=7.3 Hz, 2H, CH_2NO_2), 3.88 (s, 3H, OCH_3), 3.30 (t, *J*=7.3 Hz, 2H, ArCH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.9, 147.7, 136.3, 128.5, 128.0, 127.4, 126.7, 116.5, 116.4, 114.8, 74.5, 71.4, 56.2, 33.4; FABMS: *m*/*z* 366 (M^+), 365, 319, 260, 184, 137; HRMS-FAB calcd for $C_{16}H_{16}BrNO_4$: 365.0263; found: 365.0259; mp 95 °C; IR (KBr): 2921, 1588, 1500, 1325, 1264, 1206 cm^{-1}.

4.1.24. 2-[2-Bromo-4-methoxy-5-benzyloxy]-1-(*tert*-butoxycarbonyl amino)-ethane (31). To an ice-cold suspension of LAH (0.209 g, 5 mmol) in dry THF (30 mL) under nitrogen was added nitro compound **30** (2.0 g, 5 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 1–2 h. The reaction mixture was quenched with aq NaOH and water, then $(Boc)_2O$ (1.2 g, 5 mmol) in THF (15 mL) was added and stirring was continued for 4 h at room temperature. After completion of the reaction the reaction mixture was filtered over Celite and washed with ethyl acetate, the filtrate was concentrated in vacuo and crude residue was purified by silica gel column chromatography to give the compound **31** (1.90 g, 82%) as yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.25 (m, 5H, Ph), 7.00 (s, 1H, Ar), 6.75 (s, 1H, Ar), 5.08 (s, 2H, CH_2Ph), 4.55–4.40 (m, 1H, N*H*), 3.85 (s, 3H, OCH_3), 3.30 (q, *J*=7.0 Hz, 2H, NHCH_2), 2.80 (t, *J*=7.0 Hz, 2H, ArCH_2), 1.40 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.2, 149.5, 148.0, 137.1, 130.6, 129.0, 128.3, 127.8, 116.9, 116.8, 115.5, 79.6, 71.7, 56.6, 40.8, 36.2, 28.8; FABMS: *m*/*z* 436 (M^+); HRMS-FAB calcd for $C_{21}H_{26}BrNO_4$: 435.1045; found: 435.1041; mp 88 °C; IR (KBr): 3375, 2923, 1706, 1504, 1255, 1025 cm^{-1}.

4.1.25. 2-[2-(Ethylpropionoate)-4-methoxy-5-benzyloxy]-1-(*tert*-butoxy-carbonyl-amino)-ethane (32). A mixture of bromo compound **31** (1.50 g, 3.4 mmol), ethyl acrylate (0.56 mL, 5 mmol), palladium acetate (0.0038 g, 0.17 mmol), and triethyl amine (0.5 mL, 5 mmol) in PEG-2000 (6.0 g) was heated at 80 °C for 18 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled, extracted with cold diethyl ether (3×50 mL), washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and the crude residue was purified by silica gel column chromatography to afford the unsaturated ester **32** (1.39 g, 89%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (d, *J*=15.2 Hz, 1H, ArC*H*=), 7.44–7.25 (m, 5H, Ph), 7.05 (s, 1H, Ar), 6.73 (s, 1H, Ar), 6.22 (d, *J*=15.2 Hz, 1H, =C*H*CO_2Et), 5.14–5.09 (m, 3H, CH_2Ph, N*H*), 4.24 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 3.30–3.15 (m, 2H, NHCH_2), 2.90 (t, *J*=7.0 Hz, 2H, ArCH_2), 1.41 (s, 9H, Boc), 1.36 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 167.0, 155.7, 150.2, 148.6, 141.1, 136.5, 132.3, 128.5, 128.2, 128.0, 127.4, 118.5, 117.7, 115.5, 109.7, 79.3, 60.3, 56.1, 41.8, 32.9, 28.4, 14.3; FABMS: *m*/*z* 455 (M^+), 400, 354, 154, 137; HRMS-FAB calcd for $C_{26}H_{33}NO_6$: 456.2386; found: 456.2381; mp 135 °C; IR (KBr): 3381, 2925, 1713, 1601, 1515, 1269, 1167, 1028 cm^{-1}.

4.1.26. 6-Benzyloxy-1-ethoxycarbonylmethyl-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (33). A 100 mL RB flask was charged with unsaturated ester **32** (1.2 g, 2.6 mmol) and 30 mL 50% TFA in CH_2Cl_2 mixture at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (30 mL), basified with Na_2CO_3, and allowed to stir for 12 h. After completion of the reaction (monitored by TLC), $(Boc)_2O$ (0.574 g, 2.6 mmol) in CH_2Cl_2 was added and stirred for further 4 h. The reaction mixture was filtered, washed with CH_2Cl_2, filtrate was concentrated in vacuo, and crude residue was purified using silica gel column chromatography to give the tetrahydroisoquinolines **33** (1.0 g, 90%) as light yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.20 (m, 5H, Ph), 6.72–6.55 (m, 2H, Ar), 5.56–5.36 (m, 1H, ArC*H*N), 5.08 (s, 2H, CH_2Ph), 4.10 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 3.85 (s, 3H,

OCH_3), 3.40–3.09 (m, 1H, NC*H*), 2.90–2.50 (m, 5H, NC*H*, ArCH_2, CH_2CO$_2$Et), 1.45 (s, 9H, Boc), 1.35 (t, J=7.3 Hz, 3H, OCH$_2$CH_3); FABMS: *m*/*z* 455 (M^+); Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.32; H, 7.19; N, 3.19; mp 105 °C; IR (KBr): 2977, 1693, 1620, 1259 cm^{-1}.

4.1.27. 6-Benzyloxy-1-(2-hydroxy-ethyl)-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (34). To a stirred solution of LiCl (0.28 g, 6.5 mmol) and sodiumborohydride (0.25 g, 6.5 mmol) in ethanol (20 mL) was added ester **33** (1.0 g, 2.1 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, solvent was removed under reduced pressure. Reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure and the crude product was purified by silica gel chromatography (hexane–EtOAc 70:30) to yield the alcohol **34** (0.78 g, 87%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.25 (m, 5H, Ph), 6.65 (s, 1H, Ar), 6.54 (s, 1H, Ar), 5.23–5.17 (m, 1H, ArC*H*N), 5.07 (s, 2H, CH_2Ph), 4.11–3.96 (m, 2H, CH_2OH), 3.85 (s, 3H, OCH_3), 3.70–3.42 (m, 2H, CH_2NH), 3.14–3.04 (m, 1H, ArCH_2), 2.85–2.73 (m, 1H, ArCH_2), 2.59–2.50 (m, 1H, CH_2CH$_2$OH), 2.10–2.00 (m, 1H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc); Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.67; H, 7.52; N, 3.42; FABMS: *m*/*z* 413 (M^+); IR (KBr): 3437, 2933, 1513, 1425, 1255 cm^{-1}.

4.1.28. 6-Benzyloxy-1-[2-(*tert*-butyl-dimethyl-silanyl-oxy)-ethyl]-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (35). This compound was prepared in the same way as aldehyde **22**, from the alcohol **34** (0.7 g, 1.69 mmol). The crude material was purified by silica gel chromatography to afford **35** (0.732 g, 82%) as thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.20 (m, 5H, Ph), 6.60 (s, 1H, Ar), 6.55 (s, 1H, Ar), 5.20–4.98 (m, 3H, ArC*H*N, CH_2Ph), 4.20–3.60 (m, 6H, OCH_3, CH_2OH, CH_2NH), 3.30–2.98 (m, 1H, CH_2NH), 2.95–2.60 (m, 1H, ArCH_2), 2.58–2.45 (m, 1H, ArCH_2), 2.08–1.80 (m, 2H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc), 0.92 (s, 9H, SiCH(CH_3)$_3$), 0.02 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{30}H_{45}NO_5Si$: C, 68.27; H, 8.59; N, 2.65. Found: C, 68.24; H, 8.55; N, 2.61; FABMS: *m*/*z* 527 (M^+).

4.1.29. 6-Benzyloxy-1-[2-(*tert*-butyl-dimethyl-silanyl-oxy)-ethyl]-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-dicarboxylic acid-2-*tert*-butyl ester-1-ethyl ester (4). To a stirred solution of compound **35** (0.5 g, 0.94 mmol), in THF (10 mL) at −78 °C under inert atmosphere was added *n*-butyl lithium (0.093 g, 1.3 mmol). The mixture was stirred at −78 °C for 15 min and ethyl chloroformate (0.136 mL, 1.3 mmol) was added drop wise. Stirring was continued for 2 h at the same temperature and allowed to warm to room temperature. Reaction mixture was quenched with saturated NH_4Cl and extracted with diethyl ether twice (2×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography to give the product **4** (0.40 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.10 (m, 5H, Ph), 6.90 (s, 1H, Ar), 6.75 (s, 1H, Ar), 5.30–5.10 (m, 2H, CH_2Ph), 4.35 (q, J=7.5 Hz, 2H, OCH_2CH$_3$), 4.28–4.10 (m, 1H, CH_2OH), 3.90–3.59 (m, 5H, OCH_3, CH_2OH, CH_2NH), 3.30–2.40 (m, 3H, CH_2NH, ArCH_2), 2.15–1.85 (m, 2H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc), 1.35 (t, J=7.5 Hz, 3H, OCH$_2$CH_3) 0.90 (s, 9H, SiCH(CH_3)$_3$), 0.10 (s, 6H, Si(CH_3)$_2$); FABMS: *m*/*z* 600 (M^++1), 599 (M^+), 600 (M^+−1); Anal. Calcd for $C_{33}H_{49}NO_7Si$: C, 66.08; H, 8.23; N, 2.34. Found: C, 66.17; H, 8.12; N, 2.42; IR (KBr): 2945, 1692, 1520, 1259, 750 cm^{-1}.

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Shorter puromycin analog synthesis by means of an efficient Staudinger–Vilarrasa coupling

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Abstract—An efficient Staudinger–Vilarrasa coupling generates amides from azides and 1-hydroxybenzotriazole esters of amino- or hydroxy acid derivatives in very high isolated yields and purity. New puromycin analogs, mostly putative biosynthetic intermediates, were synthesized in nine steps from adenosine.

1. Introduction

1.1. Puromycin's mode of action as an antibiotic

Puromycin (**1**) is long known as an antibiotic agent produced by *Streptomyces alboniger*. This molecule is a 3′-amino-3′-deoxynucleoside derivative bearing an amide linked L-α-aminoacid. From a structural point of view, it strongly resembles the 3′-terminus of any aminoacylated transfer RNA (Fig. 1, left).

Like the natural substrate, puromycin is recognized by the ribosomal A-site, albeit independently of the codon, where the antibiotic's α-amino group accepts a nascent peptide chain from the neighboring P-site bound peptidyl transfer RNA, which leads to truncated, dysfunctional puromycyl peptides. Hence, its mode of action consists in irreversibly inhibiting the ribosomal bacterial protein synthesis. However, puromycin metabolism is accompanied by the formation of the toxic deacylated aminodeoxynucleoside, PAN.[1] Therefore, this natural antibiotic cannot be used for medical purposes for humans. Moreover, puromycin suffers somewhat from a lack of selectivity toward prokaryotic cells in the sense that both bacterial and mammalian systems recognize puromycin and in vitro binding affinity differences between prokaryotic and eukaryotic ribosomes are sometimes arguably significant.[2] In addition, bacterial resistance toward puromycin may arise.[3] Thus, the search for new puromycin analogs may serve simultaneously several aims: to find a novel broad band antibiotic agent, to better comprehend the ribosomal protein synthesis mechanism[4] and to validate a putative biosynthetic pathway of puromycin in *S. alboniger*.

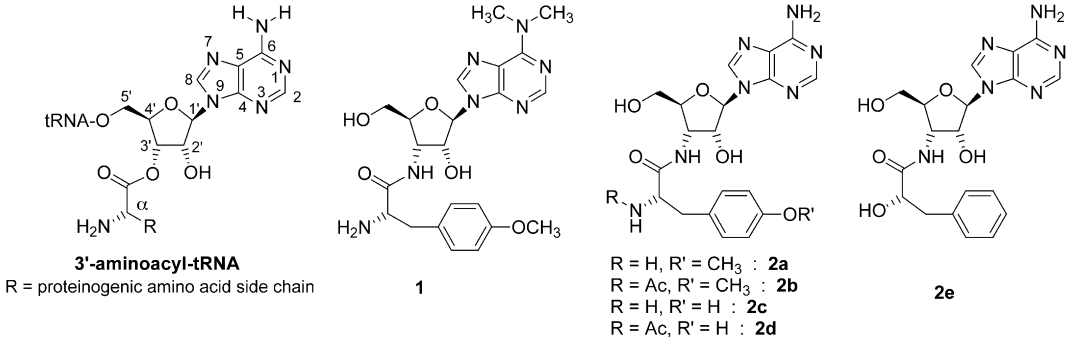

Figure 1. Natural compounds (left) and putative biosynthetic or other mimics (**2a–e**).

Keywords: Nucleosides; Amide coupling; Antibiotic; Biosynthesis.
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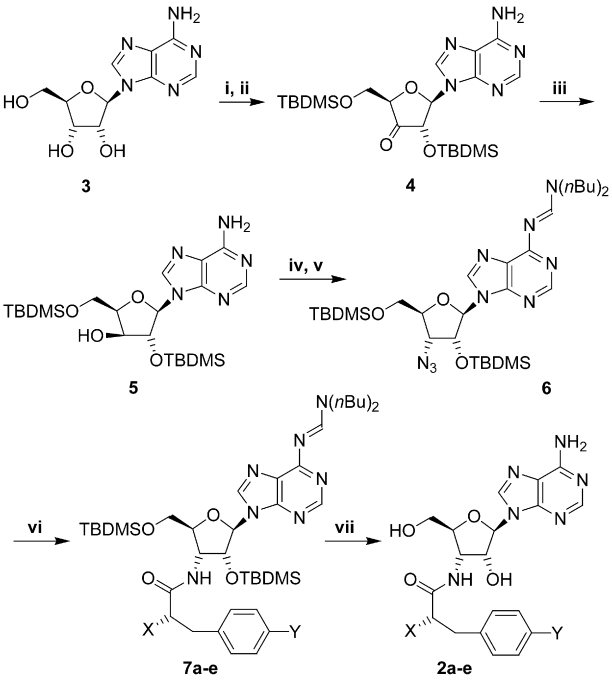
Several syntheses of a variety of puromycin analogs have already been described.[5]

1.2. Puromycin's biosynthesis and detoxification

The main aim of this work was to synthesize putative biosynthetic intermediates of puromycin that could validate a biosynthetic pathway in *S. alboniger* that was proposed by Jiménez and collegues.[6] The remaining uncertainties of the biosynthesis reside, on the one hand, on the order of the addition of three methyl groups—two onto the 6-amino group of puromycin's adenine moiety and one onto the phenol function of the attached tyrosine moiety. On the other hand, the biosynthesis of puromycin requires two enzymes that interfere with α-*N*-acetylated puromycin derivatives, in order to protect the host organism from its own metabolite. Since puromycin's α-amino group functions as the bioactive nucleophilic center in the ribosomal A-site, the inhibition or perturbation of the order of addition and hydrolysis of an *N*-acetyl group would pose severe autotoxicity problems.[3a,7] It was also shown that *S. alboniger* developed a different kind of resistance against the action of puromycin by way of the transmembrane protein Pur8, possibly by promoting an active efflux energized by a proton-dependent electrochemical gradient.[8] Actually, this is also how other bacteria, mutants of the *Klebsiella pneumoniae* strain ECL8 or *Enterobacter cloacae*,[3] manage to develop some resistance against puromycin. Moreover, *K. pneumoniae* shows an *N*-acetyl transferase activity as well,[9] which may contribute to this resistance phenomenon. Through the in-depth knowledge about these detoxification processes it should be nowadays possible to develop a rational biomedical strategy against both resistance mechanisms, in order to eventually use some puromycin analog as a new broad band antibiotic—it would be one of the suicidal kind, an irreversible inhibitor that would provoke the accumulation of truncated prokaryotic peptides, which should provoke an enhanced human immune response to additionally fight the infection.

1.3. Synthesis of puromycin analogs

To first study the proposed biosynthetic pathway of puromycin, we decided to synthesize three new puromycin analogs **2b–d** (Fig. 1) using an efficient synthetic procedure developed in our labs. We already synthesized analog **2a**,[5m] while α-hydroxy-α-deamino analog **2e** will serve a different purpose. One key-step of the synthesis is the usage of the so-called modified Staudinger reaction uncovered by Vilarrasa and collegues and developed by Vilarrasa and others,[10] an attractive water-compatible variant of which has recently become known through Bertozzi and collegues as the Staudinger ligation,[11] and that we should like to call the Staudinger–Vilarrasa coupling. It proceeds from organoazide **6** and a suitably activated *N*-protected α-aminoacid or unprotected α-hydroxy acid (Scheme 1). The formerly used reduction of the 3′-azido group to an amino group becomes obsolete. We gain one synthetic step, obtain most of time a higher coupling yield and need not care about the chemical stability of the 3′-amino derivative, which is difficult to stock owing to a slow cleavage of the base-sensitive nucleobase protecting group. Other optimized protocols also contributed to a more efficient synthesis with respect to the one we published.[5m]



7a: X = NHFmoc, Y = OCH_3
7b: X = NHAc, Y = OCH_3
7c: X = NHFmoc, Y = OH
7d: X = NHAc, Y = OH
7e: X = OH, Y = H

2a: X = NH_2, Y = OCH_3
2b: X = NHAc, Y = OCH_3
2c: X = NH_2, Y = OH
2d: X = NHAc, Y = OH
2e: X = OH, Y = H

Scheme 1. (i) TBDMSCl, Py, rt, 72 h; SiO_2, 48%; (ii) CrO_3, Py, Ac_2O, CH_2Cl_2, rt, 3 h; SiO_2, 81%; (iii) $NaHB(OAc)_3$, CH_3CN/AcOH (50:3 v/v), −18 °C, 5 h; CH_2Cl_2/$NaHCO_3$–H_2O_2 workup, 90%; (iv) $(CH_3O)_2CH$–$N(n\text{-}Bu)_2$, MeOH, rt, 2 h; SiO_2, 98%; (v) 1: TfCl, DMAP, CH_2Cl_2, rt, 2 h, CH_2Cl_2/$NaHCO_3$ workup; 2: LiN_3, DMF, rt, overnight; EtOAc/$NaHCO_3$ workup, SiO_2, 85%; (vi) 1: *N*-Fmoc/Ac α-aminoacid or α-hydroxy acid, HOBt, DIC, THF, 0 °C; 2: $(n\text{-}Bu)_3P$, from 0 °C to rt within 30 min, overnight; CH_2Cl_2/$NaHCO_3$ workup, SiO_2, 54–100%; (vii) 1: $NEt_3 \cdot 3HF$ (TBAF for **2e**), THF, rt, overnight; 2: 33% CH_3NH_2 in EtOH, 4 h, rt; EtOAc/CH_2Cl_2/$NaHCO_3$ workup, RP-HPLC.

From a general synthetic point of view, our coupling procedure takes advantage of a classical peptide synthesis activation of carboxylic acids that allows for inexpensive, mild, efficient, and epimerization-free couplings with in situ-generated iminophosphoranes. It demonstrates the compatibility of the Staudinger–Vilarrasa coupling with unprotected phenol and, in part, hydroxyl groups and is the first such protocol to be so simple and high yielding under stoichiometric solution reaction conditions.

2. Results and discussion

2.1. Optimized synthesis of azide 6

We begin the analog's synthesis with the protection the 2′- and 5′-positions as *tert*-butyldimethylsilyl ethers, which gives a mixture of 2′,5′- and 3′,5′-*O*-TBDMS regioisomers. The undesired regioisomer is separated and submitted to isomerizing conditions (2.5% Et_3N in MeOH). A three day-long silylation reaction affords 48% isolated yield of pure 2′,5′-*O*-TBDMS regioisomer. One can rise its overall yield to 85% through two isomerization steps.

The inversion of the configuration at the 3′-position is carried out by an oxidation/reduction sequence. For the oxidation the Garegg reagent proves best (CrO_3 in Ac_2O and pyridine). We found better reduction conditions through the use of commercial $NaHB(OAc)_3$ in CH_3CN containing a minimal amount of AcOH at −18 °C. The much shortened reaction time leads to better yields when compared to the formerly published procedure (90% after 4 h reaction time instead of 84% from $NaBH_4$ in AcOH at 15–16 °C then 12–13 °C after 2.5 days reaction time).[5m] An important advantage is that there is no need for a flash chromatography after the reaction, which proceeds cleanly. A simple workup was found sufficient to obtain crude **5** pure enough for the next step; the small amounts of the non-desired *ribo* isomer (2–5% with respect to **5**) are eliminated during the purification processes of the following steps.

These steps consist in protecting the exocyclic amino group on the adenine moiety (98%), the activation of the 3′-hydroxyl group with help of triflic chloride and the nucleophilic displacement of the triflate intermediate with lithium azide leading to azide **6** (85% yield, scale ≤3 g).

2.2. The synthetic key step: classical amino acid activation combined with optimized Staudinger conditions

Inspired by the pioneering coupling studies on solid support by Tóth and colleagues,[10q] and Piccialli and colleagues,[10r] we developed a coupling protocol that replaces the usual reduction of the organoazide into an amine, which would be the usual substrate for a coupling reaction. The protocol consists in mixing the amino acid derivative (or hydroxy acid) with HOBt (1-hydroxybenzotriazole), DIC (diisopropylcarbodiimide), and **6** at 0 °C. The coupling begins with the dropwise addition of commercial Bu_3P to the reaction mixture and then rising the temperature to ambient within approximately 30 min. Freshly distilled Bu_3P, other coupling conditions—unactivated amino acid, amino acid activated by DEPBT/NMM, DEPBT/DIEA,[12] iminophosphorane formation using Me_3P—[13] other reagents' amounts or a different order of addition[10p] were tested but did not lead to better results.

The reported optimized protocol gives easy access to amides free of residual[14] Bu_3P or Bu_3PO and without partial cleavage of the Fmoc protection[13b] in close to quantitative yields: **7a**, **7b**, **7c**, and **7d** are obtained in 94, 93, 91, and 100 % isolated yields, respectively. Only the yield of **7e** was 54%. For this compound a slight modification of the protocol (evaporation of THF before workup) gives rise to the formation of two by-products as determined by MS: an acyltriazene and a product of β-elimination of HN_3. The combined coupling yields for amide and acyltriazene then reaches 65% and the three final products are detected by ^{1}H NMR with the ratio **2e**/acyltriazene/(2′,3′)-elimination product: 0.68/0.16/0.16.

2.3. Deprotection and purification

With the exception of **2e**, all compounds are deprotected and purified the same way. Desilylation with $NEt_3 \cdot 3HF$ (2.0 equiv) and subsequent deprotection of Fmoc and formamidine groups in 33% ethanolic methylamine. For **2e**, we replaced $NEt_3 \cdot 3HF$ by TBAF (4 equiv).

The final, highly polar compounds were purified by preparative reversed-phase HPLC (eluants: A=10 mM aq NH_4OAc, pH 6.5, B=CH_3CN/H_2O 9:1) and obtained in part (**2a** and **2c**) as lyophilized α-ammonium acetate salts. The products were considered sufficiently pure when the content of acetate shown by ^{1}H NMR was below 5 equiv.

3. Conclusion

Four new puromycin analogs were synthesized for which an optimized nine-step procedure is presented, one that includes a very efficient Staudinger–Vilarrasa coupling reaction that combines standard epimerization-free amino acid activation with optimized Staudinger reaction conditions on organoazides. Mechanistic studies on some aspects of the Staudinger–Vilarrasa coupling are underway. The analogs will be subjected to biological assays.

Many organoazides are usually chemically stable,[15a] readily and stereospecifically accessible and easy to handle (non-hygroscopic, conveniently apolar, and pH-neutral) if, during their synthesis, contact of inorganic azide salts with halogenated solvents[15b–d] and acidification[15e] are avoided. Staudinger reaction conditions are orthogonally compatible with quite a variety of otherwise reducible functional and protecting groups such as, for instance, alkenes, imines, amidines, guanidines, *O*- or *N*-benzyl, *O*-allyl, *N*-allyloxy-, and *N*-benzyloxycarbonyl groups some of which are enjoying widespread usage in nucleoside and peptide syntheses. This version of the Staudinger–Vilarrasa coupling, being a simpler alternative than some others,[16a] opens way to mild and efficient access to other[16b,c] carboxamide target compounds, such as sterically hindered peptides,[16d–h] for instance—one more element that adds to the attractivity of organoazides.[17]

4. Experimental

4.1. General

LiN_3 was prepared from NaN_3 and LiCl (1:1) in EtOH (residual NaN_3 and LiCl were filtered off after treatment with EtOH and then Et_2O); *Caution*: *Do not acidify, do not heat as a dry solid!*[15] ^{1}H NMR spectra (300 MHz) were obtained from solutions in $CDCl_3$, with the residual protonated solvent signal as an internal reference (7.26 ppm for $CHCl_3$). The chemical shifts δ_H are given in ppm; the coupling constants *J* are given in Hertz (Hz); the signals are described as follows: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{1}H NMR spectra (500 MHz) of the analogs **2a–e** were obtained from solutions in H_2O/D_2O 9:1 using residual acetate as internal standard (1.94 ppm for CH_3COO^-). The water signal at ~4.7 ppm was suppressed using the WET pulse sequence. ^{13}C NMR spectra (125 MHz) were measured in $CDCl_3$; δ_C (central signal)=77.0 ppm. The assignments of ^{1}H- and ^{13}C NMR signals were achieved with the help of D/H exchange, HSQC, COSY, and DEPT experiments if necessary. H(2′) and sometimes H(3′) ^{1}H NMR signals of **2a–e** are close to 4.7 ppm, thus, missing in the corresponding signal listing owing to the water suppression through the WET pulse sequence.

They could be identified by COSY. Mass spectra (MS and HRMS) were obtained using Fast Atomic Bombardment (FAB from CH_2Cl_2 or H_2O/MeOH 9:1) and Electro Spray Ionization (ESI from CH_2Cl_2 or H_2O/MeOH 9:1). Thin Layer Chromatography (TLC) was performed on a precoated silica gel F_{254} plates with fluorescent indicator. The compounds were visualized using UV light (254 nm). Free amines were visualized on TLC plates by spraying with 20% ninhydrin solutions in ethanol, followed by heating. Nucleosides were visualized on TLC plates by subsequent spraying with concentrated H_2SO_4 and 2% naphthoresorcinol solutions in ethanol, followed by heating. Column chromatography was performed with flash silica gel (0.04–0.063 mm).

4.1.1. Preparative RP-HPLC purification. Isocratic conditions were used for the purification of the analogs **2a–e**: A/B 85:15. 250×8 mm Eurospher® 100/5 RP_{18} column, flow rate: 2 mL/min; UV detection at 260 nm. The following eluants were used. A: 10 mM aq NH_4OAc pH ~6.5; B: CH_3CN/H_2O 9:1. Eluants for HPLC were prepared with water purified through the *Milli-Q* system. NH_4OAc was biochemical quality and CH_3CN was HPLC grade.

4.2. Optimized synthetic procedures

4.2.1. Compound 4. See Ref. 5m, reaction time of silylation: 3 days.

4.2.2. 9-[2′,5′-Bis-(*O*-*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]-9*H*-adenine (5). To a suspension of **4** (5 g, 0.010 mol) in dry CH_3CN (200 mL) at room temperature was added just enough AcOH (12 mL) to dissolve all the solid. The mixture was cooled down to −78 °C and $NaHB(OAc)_3$ (2.54 g, 0.012 mol) was added portionwise. After 2 h, the reaction stopped and the same quantity of $NaHB(OAc)_3$ was added to reach total conversion of the material **3**. After 2 more hours, the solution was taken up by 3% H_2O_2/saturated $NaHCO_3/CH_2Cl_2$ (1:100:200 v/v/v) and extracted. The organic layers were combined and washed with saturated $NaHCO_3$ solution and then with H_2O until pH 7–8 was reached. The resulting organic layer was dried over anhydrous $MgSO_4$ and evaporated. Compound **5** (4.46 g, 90%) was obtained as a pale yellow foam. $C_{22}H_{41}N_5O_4Si_2$ (495.77). R_f (AcOEt)=0.49. ^{1}H NMR ($CDCl_3$): δ=0.04, 0.06, 0.07 (3s, 12H, Si–CH_3); 0.87, 0.88 (2s, 18H, Si–C(CH_3)$_3$); 3.98 (dd, 1H, ^3J=5.8 Hz, ^2J=11.3 Hz, H_A(5′)); 4.08 (m, 1H, H(3′)); 4.12 (dd, 1H, ^3J=4.1 Hz, ^2J=11.3 Hz, H_B(5′)); 4.20–4.26 (m, 1H, H(4′)); 4.50 (m, 1H, H(2′)); 5.76 (d, 1H, ^3J=1.2 Hz, H(1′)); 6.18 (br s, 2H, NH_2(6)); 6.72 (br s, 1H, OH(3′)); 7.96 (s, 1H, H(8)); 8.29 (s, 1H, H(2)).[18]

4.2.3. Compound 6. See Ref. 5m.

4.3. General procedure for the coupling of *N*-protected amino acids with the azide 6 to give amides 7a–d

The *N*-protected amino acid (0.096 mmol) was co-evaporated three times with 2 mL freshly distilled THF under reduced pressure and dissolved in 1.75 mL dry THF at 0 °C. To this solution was added HOBt (17 mg, 0.128 mmol). The solution was allowed to stir for 10 min at 0 °C. Then, DIC (20.0 μL, 0.128 mmol) was added dropwise. After having stirred for 10 more minutes at 0 °C, a solution of **6** (49 mg, 0.074 mmol) dissolved in 1.5 mL anhydrous THF was added via syringe, followed by commercial (97%, *Aldrich*) tri-*n*-butylphosphine (40 μL, 0.161 mmol) and the reaction was allowed to pursue overnight with the temperature increasing to rt within approximately 30 min. After evaporation to dryness, the solid was then taken up with 0.7 mL water. The product was extracted three times with 15 mL CH_2Cl_2. The combined organic layers were washed by 35 mL saturated $NaHCO_3$ solution and 35 mL water, dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (EtOAc/hexanes 1:1) gave **7a–e** as colorless oils.

4.3.1. 6-*N*-[(Di-*n*-butylamino)methylene]-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-[α-*N*-(9-fluorenyl)methoxycarbonyl-(*p*-methoxy-L-phenylalanyl)amino]-3′-deoxyadenosine (7a). Yield: 67 mg, 94%. $C_{56}H_{80}N_8O_7Si_2$ (1033.48). R_f (AcOEt/petrol ether 50:50)=0.5. ^{1}H NMR ($CDCl_3$): δ=−0.14, −0.13, 0.14 (3s, 12H, Si–CH_3); 0.74 (s, 9H, Si–C(CH_3)$_3$); 0.95 (m, 15H, Si–C(CH_3)$_3$, N($CH_2CH_2CH_2CH_3$)$_2$); 1.31–1.45 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.59–1.71 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 2.83–2.94 (br, 1H, H(β1)-*O*–MeTyr); 3.10–3.20 (br m, 1H, H(β2)-*O*-MeTyr); 3.38 (t, 2H, ^3J=7.2 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.70 (m, 2H, N($CH_2CH_2CH_2CH_3$)$_2$); 3.77 (s, 3H, CH_3-*O*-MeTyr); 3.83–3.99 (m, 3H, H(5′), H(9″)-Fmoc); 4.20 (t, 1H, ^3J=6.7 Hz, H(α)-*O*-MeTyr); 4.30–4.50 (m, 4H, H(4′), H(3′), (*O*-CH_2)–Fmoc); 4.57 (t, 1H, ^3J=6.7 Hz, 5.0 Hz, H(2′)); 5.45 (br, 1H, NH-carbamate); 5.90 (d, 1H, ^3J=3.7 Hz, H(1′)); 6.08 (br, 1H, NH-amide), 6.88 (d, 2H, ^3J=8.5 Hz, H arom.-Tyr); 7.11 (br, 2H, H arom.-*O*-MeTyr); 7.30 (t, 2H, ^3J=7.5 Hz, H(2″)); 7.39 (t, 2H, ^3J=7.5 Hz, H(3″)); 7.55 (dd, 2H, ^4J=3.4 Hz, ^3J=7.5 Hz, H(1″)); 7.76 (d, 2H, ^3J=7.5 Hz, H(4″)); 8.26 (s, 1H, H(8)); 8.50 (s, 1H, H(2)); 8.98 (s, 1H, N^6=CH).[18]

4.3.2. 3′-[α-*N*-Acetyl-(*p*-methoxy-L-phenylalanyl)amino]-6-*N*-[(di-*n*-butylamino)methylene]-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-deoxyadenosine (7b). Yield: 59 mg, 93%. $C_{43}H_{72}N_8O_6Si_2$ (853.26). R_f (AcOEt)=0.48. ^{1}H NMR ($CDCl_3$): δ=−0.10, 0.14 (2s, 12H, Si–CH_3); 0.78 (s, 9H, Si–C(CH_3)$_3$); 0.96 (s, 15H, Si–C(CH_3)$_3$, N($CH_2CH_2CH_2CH_3$)$_2$); 1.38 (hex, 4H, ^3J=7.6 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 1.59–1.71 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 2.00 (s, 3H, CH_3–Ac); 2.80 (dd, 1H, ^3J=9.2 Hz, ^2J=13.7 Hz, H(β1)-*O*-MeTyr); 3.14 (dd, 1H, ^3J=5.1 Hz, ^2J=13.7 Hz; H(β2)-*O*-MeTyr); 3.40 (t, 2H, ^3J=7.3 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.71 (m, 2H, N($CH_2CH_2CH_2CH_3$)$_2$); 3.77 (s, 3H, CH_3-*O*-MeTyr); 3.78–3.82 (m, 2H, H(5′)); 3.90 (m, 1H, H(4′)); 4.42 (q, 1H, ^3J=6.1 Hz, H(3′)); 4.48–4.57 (m, 2H, H(α)-*O*-MeTyr, H(2′)); 5.85 (d, 1H, ^3J=4.0 Hz, H(1′)); 5.89 (d, 1H, ^3J=6.1 Hz, NH–C(3′)); 6.21 (d, 1H, ^3J=7.2 Hz, NH–Ac); 6.88, 7.15 (2d, 4H, ^3J=8.6 Hz, H arom.-*O*-MeTyr); 8.27 (s, 1H, H(8)); 8.52 (s, 1H, H(2)); 9.04 (s, 1H, N^6=CH). ^{13}C NMR ($CDCl_3$): δ=−5.32 (Si–CH_3); 13.70, 13.95 (N($CH_2CH_2CH_2CH_3$)$_2$); 17.81, 18.50 (Si–*C*(CH_3)$_3$); 19.77, 20.20 (N($CH_2CH_2CH_2CH_3$)$_2$); 22.77 (CH_3–Ac); 25.58, 26.07 (Si–C(*C*H_3)$_3$); 29.29, 32.04 (N($CH_2CH_2CH_2CH_3$)$_2$); 39.04 (C(β)-*N*-AcTyr); 45.37 (N($CH_2CH_2CH_2CH_3$)$_2$); 50.79 (C(3′)); 52.19 (N($CH_2CH_2CH_2CH_3$)$_2$); 55.13 (C(α)-*O*-MeTyr); 55.29 (CH_3-*O*-MeTyr); 63.34 (C(5′)); 76.08 (C(2′)); 84.82 (C(4′));

89.2 (C(1′)); 92.72 (C arom.-*O*-MeTyr); 114.33 (C arom.-*O*-MeTyr); 126.07 (C(5)); 130.20 (C arom.-*O*-MeTyr); 139.95 (C(8)); 150.47 (C(4)); 153.06 (C(2)); 155.51 (C arom.-*O*-MeTyr); 157.26 (C(6)); 158.83 (N^6=CH(*n*-Bu)$_2$); 169.63, 170.83 (amide C=O). HRMS (ESI$^+$): Exact mass calculated for $C_{43}H_{73}N_8O_6Si_2$: 853.5191. Found: 853.5196.

4.3.3. 6-*N*-[(Di-*n*-butylamino)methylene]-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-[α-*N*-(9-fluorenyl)methoxycarbonyl-(*p*-hydroxy-L-phenylalanyl)amino]-3′-deoxyadenosine (7c). Yield: 69 mg, 91%. $C_{55}H_{78}N_8O_7Si_2$ (1019.44). R_f (AcOEt/petrol ether 50:50)=0.31. ^{1}H NMR ($CDCl_3$): δ=−0.07, −0.06, 0.11, 0.12 (4s, 12H, Si–CH_3); 0.75 (s, 9H, Si–C(CH_3)$_3$); 0.94 (s, 15H, Si–C(CH_3)$_3$, N($CH_2CH_2CH_2CH_3$)$_2$); 1.33–1.44 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.61–1.72 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 2.83 (m, 1H, H(β1)-*N*-FmocTyr); 2.91–2.97 (m, 1H, H(β2)-*N*-FmocTyr); 3.43 (t, 2H, ^3J=7.2 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.67 (t, 2H, ^3J=7.6 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.71–3.77 (m, 2H, H(5′)); 3.93–4.00 (m, 1H, H(4′)); 4.48 (t, 1H, ^3J=5.3 Hz, H(α)-*N*-FmocTyr); 4.56 (t, 1H, ^3J=6.2 Hz, H(3′)); 4.67–4.72 (m, 1H, H(2′)); 6.03 (d, 1H, ^3J=3.3 Hz, H(1′)); 6.70, 7.05 (2d, 4H, ^3J=8.1 Hz, H arom.-*N*-FmocTyr); 7.21–7.26 (m, 2H, H(2″)); 7.32 (t, 2H, ^3J=7.4 Hz, H(3″)); 7.53–7.56 (m, 2H, H(1″)); 7.76 (d, 2H, ^3J=7.5 Hz, H(4″)); 8.41 (s, 1H, H(8)); 8.47 (s, 1H, H(2)); 8.94 (s, 1H, N^6=CH). ^{13}C NMR ($CDCl_3$): δ=−5.46, −5.28 (Si–CH_3); 13.65, 13.66 (N($CH_2CH_2CH_2CH_3$)$_2$); 17.61, 18.40 (Si–*C*(CH_3)$_3$); 19.77, 20.18 (N($CH_2CH_2CH_2CH_3$)$_2$); 26.06, 26.09 (Si–C(*C*H_3)$_3$); 29.70, 30.95 (N($CH_2CH_2CH_2CH_3$)$_2$); 42.27 (C(β)-Tyr); 45.69 (N($CH_2CH_2CH_2CH_3$)$_2$); 47.21 (C(9″)-Fmoc); 51.92 (N($CH_2CH_2CH_2CH_3$)$_2$); 52.98 (C(α)-*N*-FmocTyr); 57.25 (C(3′)); 63.10 (C(5′)); 67.03 ((*O*-CH_2)–Fmoc); 74.91 (C(2′)); 85.11 (C(4′)); 86.79 (C(1′)); 119.17 (C arom.-*N*-FmocTyr); 120.00, 125.13 (C arom.-*N*-Fmoc); 126.00 (C(5)); 127.08, 127.75 (C arom.-*N*-Fmoc); 129.00, 130.12 (C arom.-*N*-FmocTyr); 139.43 (C(8)); 141.32, 143.79 (C arom.-*N*-Fmoc); 150.95 (C(4)); 152.42 (C(2)); 155.92 (C arom.-*N*-FmocTyr); 156.96 (C(6)); 158.47 (N^6=CH(*n*-Bu)$_2$); 160.64 (carbamate C=O); 170.28 (amide C=O). HRMS (ESI$^+$): Exact mass calculated for $C_{55}H_{79}N_8O_7Si_2$: 1019.5610. Found: 1019.5616.

4.3.4. 3′-[α-*N*-Acetyl-(*p*-hydroxy-L-phenylalanyl)amino]-6-*N*-[(di-*n*-butylamino)methylene]-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-deoxyadenosine (7d). Yield: 62 mg, 100%. $C_{42}H_{70}N_8O_6Si_2$ (839.23). R_f (AcOEt/petrol ether 70:30)=0.82. ^{1}H NMR ($CDCl_3$): δ=−0.37, −0.21, 0.12, 0.13 (4s, 12H, Si–CH_3); 0.71 (s, 6H, N($CH_2CH_2CH_2CH_3$)$_2$); 0.94 (s, 18H, Si–C(CH_3)$_3$); 1.31–1.44 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.59–1.72 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 2.03 (s, 3H, CH_3–Ac); 3.37–4.51 (m, 9H, N($CH_2CH_2CH_2CH_3$)$_2$, H(5′), H(α)-*N*-AcTyr, H(4′), H(3′)); 4.54 (t, 1H, ^3J=6.9 Hz, H(2′)); 5.39 (d, 1H, ^3J=3.7 Hz, NH–C(3′)); 5.60 (d, 1H, ^3J=6.9 Hz, H(1′)); 6.52 (d, 1H, ^3J=7.1 Hz, NH–Ac); 7.06, 7.17 (2d, 4H, ^3J=8.3 Hz, H arom.-*N*-AcTyr); 8.23 (s, 1H, H(8)); 8.59 (s, 1H, H(2)); 8.98 (s, 1H, N^6=CH). ^{13}C NMR ($CDCl_3$): δ=−5.74 (Si–CH_3); 13.56, 13.80 (N($CH_2CH_2CH_2CH_3$)$_2$); 17.43, 18.22 (Si–*C*(CH_3)$_3$); 19.57, 19.97 (N($CH_2CH_2CH_2CH_3$)$_2$); 23.27 (CH_3–Ac); 25.13, 25.84 (Si–C(*C*H_3)$_3$); 28.98, 30.66 (N($CH_2CH_2CH_2CH_3$)$_2$); 39.14 (C(β)-*N*-AcTyr); 45.01 (N($CH_2CH_2CH_2CH_3$)$_2$); 51.75 (N($CH_2CH_2CH_2CH_3$)$_2$); 52.76 (C(α)-*N*-AcTyr); 55.50 (C(3′)); 63.98 (C(5′)); 74.61 (C(2′)); 84.82 (C(4′)); 86.50 (C(1′)); 93.00 (C arom.-*N*-AcTyr); 118.93 (C arom.-*N*-AcTyr); 125.65 (C(5)); 129.87 (C arom.-*N*-AcTyr); 139.26 (C(8)); 150.53 (C(4)); 152.11 (C(2)); 155.65 (C arom.-*N*-AcTyr); 156.81 (C(6)); 158.25 (N^6=CH(*n*-Bu)$_2$); 169.27, 170.16 (amide C=O). HRMS (ESI$^+$): Exact mass calculated for $C_{42}H_{71}N_8O_6Si_2$: 839.5035. Found: 839.5034.

4.3.5. (2*S*)-6-*N*-[(Di-*n*-butylamino)methylene]-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-[(2-hydroxy-3-phenylpropionyl)amino]-3′-deoxyadenosine (7e). To a solution of L-phenyllactic acid (126 mg, 0.76 mmol) in 6 mL freshly distilled dry THF at 0 °C was added HOBt (97 mg, 0.72 mmol). The solution was allowed to stir for 10 min at 0 °C. Then, DIC (115.8 μL, 0.74 mmol) was added dropwise. After having stirred for 10 more minutes at 0 °C, a solution of **6** (241 mg, 0.37 mmol) dissolved in 6 mL freshly distilled anhydrous THF was added via syringe, followed by tri-*n*-butylphosphine (180 μL, 0.70 mmol) and the reaction was allowed to pursue overnight with a temperature increasing until rt within approximately 30 min. After evaporation to dryness, the solid was then taken up by 3 mL water. The product was extracted three times with 100 mL CH_2Cl_2. The organic layers were washed by 150 mL saturated $NaHCO_3$ solution and 150 mL water, dried over anhydrous $MgSO_4$, filtered, and evaporated. Purification by flash chromatography (EtOAc/hexanes 1:1) gave **7e** as a colorless oil. Yield: 321 mg, 54%. $C_{40}H_{67}N_7O_5Si_2$ (782.17). R_f (AcOEt/petrol ether 50:50)=0.29. ^{1}H NMR ($CDCl_3$): δ=−0.03, −0.01 (m, 6H, Si–CH_3); 0.15–0.19 (m, 6H, Si–CH_3); 0.85 (m, 9H, Si–C(CH_3)$_3$); 0.96 (m, 15H, Si–C(CH_3)$_3$, N($CH_2CH_2CH_2CH_3$)$_2$); 1.65 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 1.36 (m, 4H, N($CH_2CH_2CH_2CH_3$)$_2$); 2.84 (dd, 1H, ^3J=9.1 Hz, ^2J=13.9 Hz, Hβ1); 3.26 (dd, 1H, ^3J=3.6 Hz, ^2J=13.9 Hz, Hβ2); 3.39 (t, 2H, ^3J=7.2 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.72 (t, 2H, ^3J=7.6 Hz, N($CH_2CH_2CH_2CH_3$)$_2$); 3.74 (m, 1H, H(5′)); 4.10 (m, 1H, Hα); 4.20 (m, 1H, H(4′)); 4.22 (m, 1H, H(3′)); 4.61 (m, 1H, H(2′)); 6.07 (d, 1H, ^3J=3.7 Hz, H(1′)); 7.18–7.33 (m, 5H, H arom.-L-phenyllactic acid); 8.31 (s, 1H, H(8)); 8.54 (s, 1H, H(2)); 9.01 (s, 1H, N^6=CH). ^{13}C NMR ($CDCl_3$): δ=−5.38, −5.31, −5.06, −4.97 (Si–CH_3); 13.67, 13.91 (N($CH_2CH_2CH_2CH_3$)$_2$); 17.82, 18.38 (Si–*C*(CH_3)$_3$); 19.76, 20.17 (N($CH_2CH_2CH_2CH_3$)$_2$); 25.54, 26.01 (Si–C(*C*H_3)$_3$); 29.18, 30.91 (N($CH_2CH_2CH_2CH_3$)$_2$); 45.02 (N($CH_2CH_2CH_2CH_3$)$_2$); 50.70 (C(3′)); 40.98 (C(β)); 51.77 (N($CH_2CH_2CH_2CH_3$)$_2$); 64.10 (C(5′)); 76.02 (C(2′)); 82.09 (CH(α)); 84.37 (C(4′)); 88.89 (C(1′)); 125.89 (C(5)); 128.56, 128.77, 129.41, 129.58 (C arom.-L-phenyllactic acid); 140.20 (C(8)); 151.19 (C(4)); 152.68 (C(2)); 158.32 (N^6=CH(*n*-Bu)$_2$); 160.10 (C(6)); 171.09 (amide C=O). HRMS (ESI$^+$): Exact mass calculated for $C_{40}H_{68}N_7O_5Si_2$: 782.4821. Found: 782.4823.

4.4. General procedure for the deprotection of analogs 7a–d to give 3′-(α-amino/*N*-acetylamidoacyl)amino-3′-deoxyadenosines 2a–d

To a solution of **7a–d** (0.08 mmol) in THF (1.0 mL) was added $Et_3N\cdot 3HF$ (~37% HF, 25 μL, 0.15 mmol). The solution was stirred at rt overnight. The THF was evaporated on a rotatory evaporator under reduced pressure and a solution (1.0 mL) of 33% (v/v) methylamine in EtOH was added. The mixture was stirred at rt for 4 h, taken up by 3 mL water.

Organic impurities were extracted successively three times with 7 mL EtOAc and three times with 7 mL CH_2Cl_2. The combined organic layers were extracted successively with 3 mL $NaHCO_3$, then 3 mL water. The combined aqueous phases were concentrated, re-diluted with HPLC eluant A, filtered (0.7 μm) and injected to purify by RP-HPLC. The fractions containing **2a–d** were concentrated in a $Si(CH_3)_2Cl_2$-treated glass flask on a rotatory evaporator under reduced pressure, then repeatedly lyophilized in Eppendorf tubes under 'high-vacuum' (SpeedVac) until NH_4OAc was present in lower than 5 molar equivalent amounts with respect to the analogs **2a–d**, as determined by ^1H NMR. The analogs **2a–d** were thus isolated as white fluffy solids.

4.4.1. 3′-(*p*-Methoxy-L-phenylalanylamino)-3′-deoxyadenosine (2a). ^1H NMR (H_2O/D_2O 9:1): δ=3.00–3.10 (m, 1H, H(β1)-*O*-MeTyr); 3.27 (dd, 1H, ^3J=6.1 Hz, ^2J=13.9 Hz, H(β2)-*O*-MeTyr); 3.45 (dd, 1H, ^3J=3.8 Hz, ^2J=13.4 Hz, $H_A(5')$); 3.71 (dd, 1H, ^3J=1.6 Hz, ^2J=13.4 Hz, $H_B(5')$); 3.84 (s, 3H, CH_3-*O*-MeTyr); 3.85–3.88 (m, 1H, H(4′)); 4.24 (dd, 1H, $^3J_{H(\alpha)-H(\beta2)}$=6.9 Hz, $^3J_{H(\alpha)-H(\beta1)}$=10.2 Hz, H(α)-*O*-MeTyr); 5.96 (d, 1H, $^3J_{H(1')-H(2')}$=3.6 Hz, H(1′)); 7.05, 7.28 (2d, 4H, ^3J=8.5 Hz, H arom.-*O*-MeTyr); 8.26 (s, 1H, H(2)); 8.34 (s, 1H, H(8)).[18]

4.4.2. 3′-[α-*N*-Acetyl-(*p*-methoxy-L-phenylalanylamino)]-3′-deoxyadenosine (2b). $C_{22}H_{27}N_7O_6$ (485.49). ^1H NMR (H_2O/D_2O 9:1): δ=1.86 (s, 3H, CH_3–Ac); 2.84–2.88 (m, 1H, H(β1)-*N*-AcTyr); 3.00 (dd, 1H, ^3J=7.1 Hz, ^2J=14.7 Hz, H(β2)-*N*-AcTyr); 3.32–3.37 (m, 2H, H(5′)); 3.69 (s, 3H, CH_3-*O*-MeTyr); 3.78 (m, 1H, H(4′)); 5.83 (d, 1H, $^3J_{H(1')-H(2')}$=2.2 Hz, H(1′)); 6.86, 7.12 (2d, 4H, ^3J=8.4 Hz, H arom.-*O*-MeTyr); 8.11 (s, 1H, H(2)); 8.21 (s, 1H, H(8)). HRMS (ESI^+): Exact mass calculated for $C_{22}H_{28}N_7O_6$: 486.2101. Found: 486.2106.

4.4.3. 3′-(*p*-Hydroxy-L-phenylalanylamino)-3′-deoxyadenosine (2c). $C_{19}H_{23}N_7O_5$ (429.43). ^1H NMR (H_2O/D_2O 9:1): δ=2.67–2.73 (m, 1H, H(β1)-Tyr); 2.95 (dd, 1H, ^3J=6.2 Hz, ^2J=13.1 Hz, H(β2)-Tyr); 3.29 (dd, 1H, ^3J=3.9 Hz, ^2J=13.0 Hz, $H_A(5')$); 3.56 (dd, 1H, ^3J=1.7 Hz, ^2J=13.0 Hz, $H_B(5')$); 3.69 (m, 1H, H(4′)); 3.77 (m, 1H, H(3′)); 4.38 (dd, 1H, $^3J_{H(\alpha)-H(\beta2)}$=6.2 Hz, $^3J_{H(\alpha)-H(\beta1)}$=7.6 Hz, H(α)-Tyr); 5.88 (d, 1H, $^3J_{H(1')-H(2')}$=3.1 Hz, H(1′)); 6.80, 7.07 (2d, 4H, ^3J=8.6 Hz, H arom.-Tyr); 8.15 (s, 1H, H(2)); 8.23 (s, 1H, H(8)). HRMS (ESI^+): Exact mass calculated for $C_{19}H_{24}N_7O_5$: 430.1839. Found: 430.1829.

4.4.4. 3′-[α-*N*-Acetyl-(*p*-hydroxy-L-phenylalanylamino)]-3′-deoxyadenosine (2d). $C_{21}H_{25}N_7O_6$ (471.47). ^1H NMR (H_2O/D_2O 9:1): δ=1.98 (s, 3H, CH_3–Ac); 2.87 (dd, 1H, ^3J=9.3 Hz, ^2J=13.7 Hz, H(β1)-*N*-AcTyr); 3.02 (dd, 1H, ^3J=7.0 Hz, ^2J=13.7 Hz, H(β2)-*N*-AcTyr); 3.41 (dd, 1H, ^3J=4.0 Hz, ^2J=13.0 Hz, $H_A(5')$); 3.66 (m, 1H, $H_B(5')$); 3.87–3.90 (m, 1H, H(4′)); 4.46 (dd, 1H, $^3J_{H(3')-H(2')}$=5.9 Hz, $^3J_{H(3')-H(4')}$=7.8 Hz, H(3′)); 4.53 (dd, 1H, $^3J_{H(\alpha)-H(\beta2)}$=7.0 Hz, $^3J_{H(\alpha)-H(\beta1)}$=9.3 Hz, H(α)-*N*-AcTyr); 4.68 (dd, 1H, $^3J_{H(2')-H(1')}$=3.1 Hz, $^3J_{H(2')-H(3')}$=5.9 Hz, H(2′)); 5.98 (d, 1H, $^3J_{H(1')-H(2')}$=3.1 Hz, H(1′)); 6.78, 7.11 (2d, 4H, ^3J=8.5 Hz, H arom.-*N*-AcTyr); 8.22 (s, 1H, H(2)); 8.31 (s, 1H, H(8)). HRMS (ESI^+): Exact mass calculated for $C_{21}H_{26}N_7O_6$: 472.1944. Found: 472.1947.

4.4.5. (2*S*)-3′-[(2-Hydroxy-3-phenylpropionyl)amino]-3′-deoxyadenosine (2e). To a solution of **7e** (0.08 mmol) in THF (1.0 mL) was added TBAF (320 μL, 0.32 mmol). The solution was stirred at rt for 2 h. THF was evaporated on a rotatory evaporator under reduced pressure and a solution (1.0 mL) of 33% (v/v) methylamine in EtOH was added. The mixture was stirred at rt for 4 h and then taken up by 3 mL water. Organic impurities were extracted successively three times with 7 mL EtOAc and three times with 7 mL CH_2Cl_2. The organic layers were both washed by 3 mL $NaHCO_3$, then 3 mL water. The aqueous phase was directly purified by RP-HPLC with use of the same conditions as described for the analogs **2a–d**. The fractions containing **2e** were concentrated in a $Si(CH_3)_2Cl_2$-treated glass flask on a rotary evaporator under reduced pressure, then repeatedly lyophilized in Eppendorf tubes under 'high-vacuum' (SpeedVac), until NH_4OAc was present in lower than 5 molar equivalent amounts with respect to the analog **2e**, as determined by ^1H NMR. The analog **2e** was thus isolated as white fluffy solid. $C_{19}H_{22}N_6O_5$ (414.42). ^1H NMR (H_2O/D_2O 9:1): δ=2.95 (dd, 1H, ^3J=4.1 Hz, ^2J=8.1 Hz, H(β1)-L-3-phenyllactic acid); 3.00 (dd, 1H, ^3J=4.1 Hz, ^2J=8.1 Hz, H(β2)-L-3-phenyllactic acid); 3.50 (dd, 1H, ^3J=4.3 Hz, ^2J=13.5 Hz, $H_A(5')$); 3.70 (dd, 1H, ^3J=2.4 Hz, ^2J=13.5 Hz, $H_B(5')$); 3.96–4.02 (m, 1H, H(4′)); 4.41–4.49 (m, 2H, H(3′), H(α)-L-3-phenyllactic acid); 4.52–4.57 (m, 1H, H(2′)); 5.96 (d, 1H, $^3J_{H(1')-H(2')}$=2.8 Hz, H(1′)); 7.16–7.33 (m, 5H, H arom.-L-3-phenyllactic acid); 8.15 (s, 1H, H(2)); 8.25 (s, 1H, H(8)). HRMS (ESI^+): Exact mass calculated for $C_{19}H_{23}N_6O_5$: 415.1730. Found: 415.1730.

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Theoretical design of dendrimeric fractal patterns for the encapsulation of a family of drugs: salicylanilides

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Abstract—Four dendrimeric fragments (FPs) were designed to encapsulate a family of drugs known as salicylanilides (importantly acaricides/anthelminthics), mainly by H-bonding. The experimental system: PAMAM–DBNP (2,6-dibromo-4-nitrophenol) was also calculated as a reference. The efficiency of encapsulation is related to the presence of functional groups like amide and alcohol, the flexibility of the aliphatic chains, and efficient pre-organization before the encapsulation. All the geometry optimizations were carried out at DFT/LAV3P* level of theory. Two hybrid functionals were tested: B3LYP and BHandHLYP. The last one shows improved performance in describing close contacts as well as better agreement with experimental observations for the complex PAMAM–BDNP.

1. Introduction

Dendrimers, studied so far and for more than two decades, are described as well-defined, highly branched macromolecules. Several research groups have discussed the great potential of dendrimers as advanced materials in many different areas including medicine[1,2] and catalysis,[1–3] among others. Particularly, the use of dendrimers as drug delivery vehicles has attracted much attention. Due to their globular structures and internal cavities, dendrimers resemble the globular proteins observed in nature with a remarkable difference: the internal cavities of proteins are the natural consequence of self-stabilization processes, while in the case of dendrimers, such cavities can be designed in a rational way. Such possibility of designing has been a starting point of numerous studies, trying to find 'the best' fractal patterns† for specific applications.[4]

In the pharmaceutical area, the most important characteristic of any drug is its medical efficiency and, unfortunately, it often drops because, even though the drug reaches the target site, it occurs in very small amounts mainly due to solubility problems.[5] Therefore, the development of drug carriers has been of great importance and many works have been done so far in an interdisciplinary way.

Some polymers and copolymers, as well as micelle vehicles, have been already used as drug delivery systems; however, they have had limited applications due to their polydispersities, poor stability, and aggregation problems when the solvent is not the appropriate one.[6] In this sense, features like monodispersity and inherent micelle-like structure of dendrimers, among other properties, justify their attractiveness in pharmaceutical and medicinal applications.[7]

One of the most studied dendrimers, so-called PAMAM (poly(amidoamine)),[8] has been already tested as host for some biologically important molecules like quinoline, quinazoline, and nicotine, as well as for a variety of drugs.[9] Since favorable biological properties like low in vitro and in vivo toxicities, low immunogenicity (degree to which a substance induces an immune response), and known biodistribution were observed for PAMAM starburst dendrimers,[10] this family of molecules has been systematically chosen to be tested as drug delivery systems. Thus, amine- and ester-terminated PAMAM dendrimers were used to increase the solubility of drugs like ibuprofen,[5] nifedipine, salicylic acid, and 2,6-dibromo-4-nitrophenol.[11] PEG-attached PAMAM dendrimers of third and fourth generations were designed to encapsulate anticancer drugs like adriamycin and methotrexate,[12] with an efficiency depending on the dendrimeric generation and the flexibility of the chains of the poly(ethylene glycol) grafts. Other drugs like piroxicam,[13] anti-inflammatory drugs such as ketoprofen, diflunisal, and naproxen[14] as well as nicotinic acid[15] have been also encapsulated by PAMAM dendrimers.

Beyond the PAMAM family, so far explored, the challenge now is the designing of new and more specific dendrimeric

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† Fractal pattern in this context is defined as each repetitive unit forming the branches of a dendrimer.

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fractal patterns to be used as hosts, including a more detailed structural description of the inclusion complexes and the interactions involved in their formation. Interesting examples of different designs of delivery systems can be found in the literature.[16]

1.1. Specific problem to be solved

In veterinary, a set of high-spectral drugs, known as salicylanilides (Fig. 1), are used as acaricides and antihelmithycs. These drugs are highly active against adult flukes and immature flukes[17] such as *Fasciola hepatica* and *Fasciola gigantica* as well as cestode infection.

In spite of their activity, these hydrophobic drugs lose effectiveness due to their low solubility; therefore, an encapsulation process appears as a very attractive alternative. Basically three ways of interaction have been described considering dendritic hosts: (i) physical entrapment, (ii) covalent attachment onto the dendrimeric surface (dendrimer–drug conjugates), and (iii) non-covalent binding of drug molecules inside the dendrimers by H-bonding and/or hydrophobic interactions. It has been observed that the host designs involving this last option (H-bonding) represent the most suitable way, considering not only the ease to form complexes but also the convenience for the posterior delivery process,[18] since no covalent bonds have to be broken.

The computational chemistry applied to the host's design emerges as an excellent tool to evaluate different combinations of functional groups and lengths of fractal patterns, which can be used later as building blocks to construct dendrimeric hosts, more specific to encapsulate particular guests.

In the present study, taking advantages of computational tools, different fractal patterns (molecular fragments) were rationally designed to encapsulate molecules of salicylanilides, considering H-bonding as one of the main interactions. The interaction energies were evaluated in order to find 'ideal' fractal patterns for the posterior construction of dendrimeric architectures. The conformations of the designed fractal patterns (FPs) were obtained in gas-phase as well as in aqueous medium to explore the pre-organization condition of these hosts (prior to encapsulation processes) in a more realistic environment. For comparative purposes, the encapsulation system formed between a PAMAM derivative and 2,6-dibromo-4-nitrophenol (*DBNP*) (antifungal/antibacterial agent),[19] was considered here as an experimental reference system (see Section 3.2).

2. Computational details

All the initial structures (FPs, drugs, and the inclusion complexes formed between them) were equilibrated by conformational search (Force Field OPLS2001),[20] using the Monte Carlo statistical method[21] included in the Macromodel software. The algorithm of Monte Carlo Multiple Minima (MCMM)[22] without limits on the number of variable torsion allowed in the search was used. In all the cases redundant conformers (two to four splice structures) were found to have the lowest energy, hence they were grouped to be taken as single minimal energy conformers to carry out subsequent calculations. The rejected second conformers (clearly different in structure) have higher energy (3–4 kcal/mol). The geometry optimization of all minimal energy conformers was carried out at B3LYP/LAV3P* level of theory. The LAV3P* basis set, included in the Jaguar 5.5 program,[23] considers effective core potentials (ECPs) generated to replace the innermost core electrons for third-row (K–Cu), fourth-row (Rb–Ag), and fifth-row (Cs–Au), integrating relativistic effects (important for heavy atoms) and reducing in this way the computational efforts comparing with all-electron calculations.[24] Natural charges were calculated in gas phase by Natural Bond Orbital analysis.[25] For comparative purposes (see Section 3.6), another hybrid functional, BHandHLYP (exchange: 50% exact HF exchange, 50% Slater local exchange functional; correlation: Lee–Yang–Parr local and non-local functional[26]) was used instead of B3LYP, for the calculation of interaction energies, considering only one of the host molecules and its interaction with all the guests under study.

The conformational search, as well as the geometry optimization of the designed hosts was also carried out in aqueous medium to evaluate the conformational changes due to the environment. The solvated molecules were calculated using the self-consistent reaction field method with its own Poisson–Boltzmann solver,[27] which represents the solvent as a layer of charges at the molecular surface (providing in this way a dielectric continuum boundary). These solvent point charges are returned to a SCF algorithm to calculate

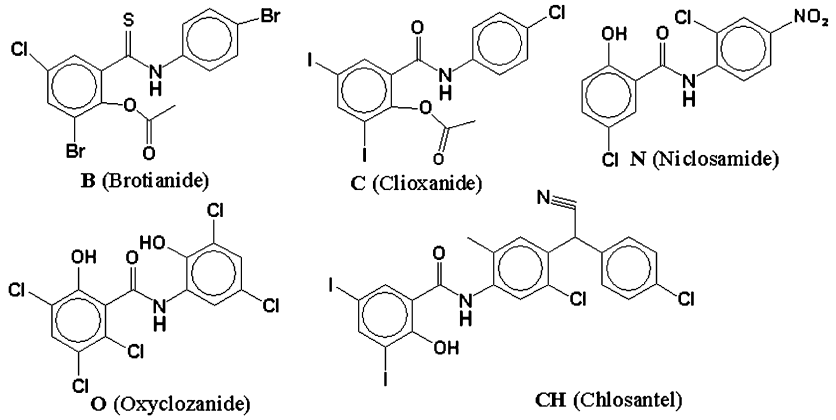

Figure 1. Salicylanilides (capital letters in bold style will be used as labels).

again the wave function incorporating the solvent charges. The process is repeated until the convergence is achieved.

3. Results and discussion

3.1. Design of fractal patterns

Twenty different fractal patterns (FPs) were designed, incorporating some polar functional groups (e.g., –NHCO, –NHR, ROH, –NHOH, etc.) into their chains, in order to induce the non-covalent interactions like H-bonds. The length of the aliphatic chains was also modified since it was observed earlier that the flexibility is a critical factor to take into account when encapsulation hosts are designed.[4]

All the constructed fractal patterns, as well as their complexes with the salicylanilides, were minimized by conformational analysis (MCMM). A first discrimination of fractal patterns was carried out, based on the number and directionality of H-bonds formed with the encapsulated drugs in a range of distances from 1.5 to 2.5 Å. It was observed that, as the aliphatic chains in the FPs become more flexible, the formation of H-bonds is favored. The most efficient functional groups were the amide, alcohol, and sulfonic acid interacting with the drugs forming H-bonds. Thus, after rational elimination, four of the most suitable FPs to encapsulate the drugs under study are illustrated in Figure 2.

For further analyses (including the calculation of host–guest interaction energies), the geometry optimizations of the FPs, the salicylanilides, and the host–guest complexes formed between them were carried out at B3LYP/LAV3P* level of theory. The interaction energies were calculated according to the variation method,[28] as the difference between the energy of the host–guest complex and the sum of total energies of their isolated parts ($\Delta E = E_{complex} - (E_{fractal\ pattern} + E_{drug})$).

Table 1 shows the interaction energies (in kcal/mol) between FPs and drug molecules.

From Table 1, the efficiency of encapsulation of FPs follows the next general order: FP1>FP2>FP3>FP4.

All the interaction energies between FPs and drugs are schematically plotted in Figure 3. With the exception of the complexes FP4-**B** and FP4-**N**, all the interactions resulted favorable. In general, the flexibility and chemical nature of

Table 1. Interaction energies (kcal/mol) calculated at B3LYP/LAV3P* level of theory

FP	1	2	3	4
Brotianide	−17.431	−11.721	−0.383	8.130
Clioxanide	−23.255	−9.973	−5.626	−11.424
Chlosantel	−31.121	−25.364	−18.465	−10.450
Niclosamide	−24.304	−30.668	−9.627	0.090
Oxyclozanide	−50.362	−43.438	−34.276	−36.501

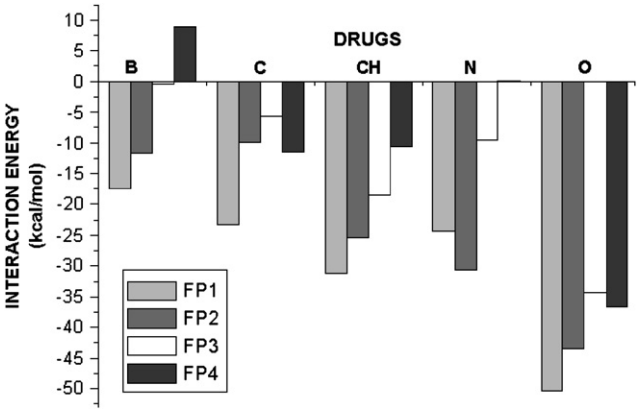

Figure 3. Interaction energies of FPs–drugs.

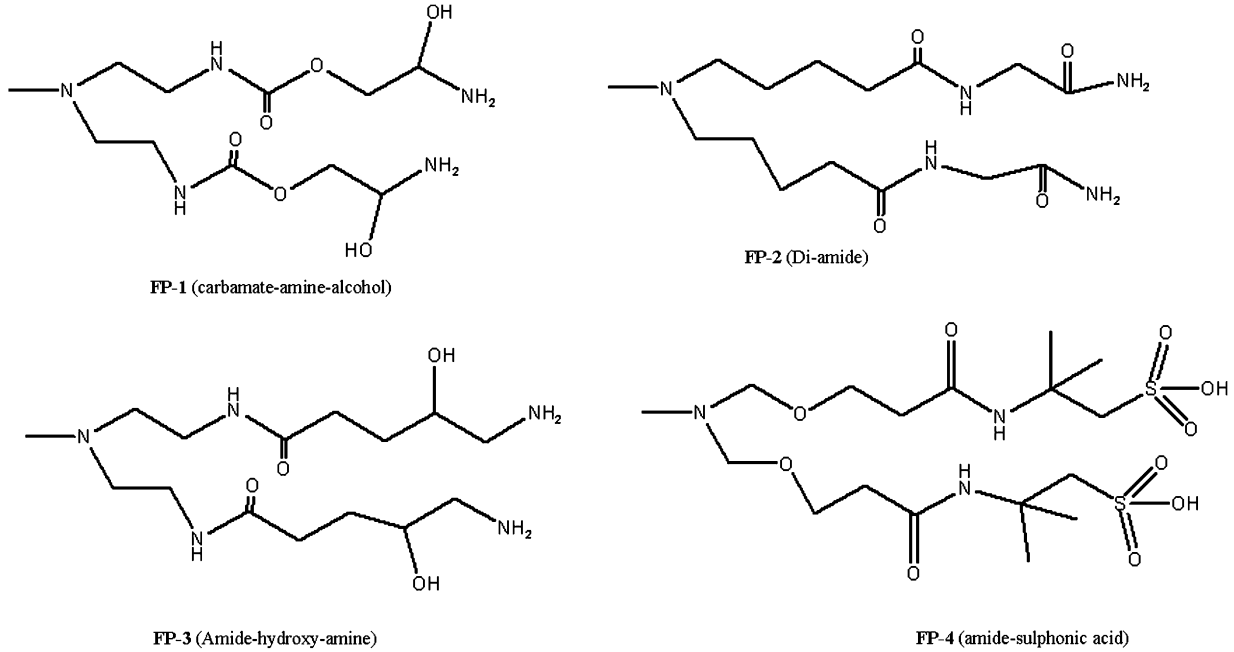

Figure 2. Suitable fractal patterns (FPs) to interact with salicylanilides.

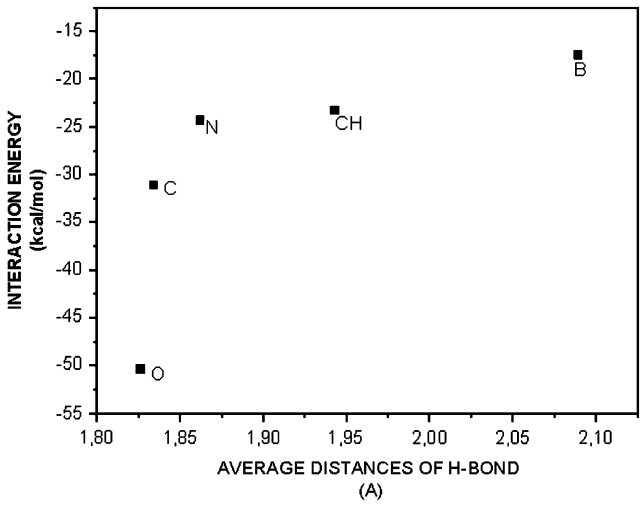

Figure 4. FP1–drug complexes (**O**: oxyclozanide; **C**: clioxanide; **N**: niclosamide; **CH**: chlosantel; **B**: brotianide).

the designed FPs were appropriate to shelter the salicylanilides in a specific way.

A clear relationship was observed between the H-bonding distances and the interaction energies. The average H-bond distances versus the interaction energies of the FP1–drugs complexes are plotted in Figure 4. Even though a linear relationship was not observed, the tendency is straightforward: the shorter is the distance, the more favorable is the interaction energy between the host and the guests.

The correlation observed in Figure 4 is an evidence of the important role of H-bonding as a driving force for the complex formation. Due to their high directionality and the amplest range of strength of interaction (e.g., $[F–H–F]^-$ and $NH_3–H–Cl^-$; ~40 and ~15 kcal/mol, respectively), the H-bonds are present in many examples of molecular tectonics where the formation of molecular assemblies is directed by them.[29] The assemblage by H-bonding is illustrated in Figure 5 where the encapsulation of the drugs by the fractal pattern FP1 is shown.

An additional important remark about the H-bonding is that the H-bond length is more important than their number.

Considering such short distances, in any host–guest complex there is, to some extent, a superposition of molecular orbitals. These orbitals are theoretically described by a basis set. Since the complete description of each orbital of each part of the complex by a basis set is operationally difficult, a superposition of basis sets to achieve the complete description occurs, resulting in the error known as the basis set superposition error (BSSE), which overestimates the interaction energy.

In order to illustrate the magnitude of the BSSE, it was calculated only for the complexes formed between FP1 and the drugs. The standard estimation was done by the counterpoise correction of Boys and Bernardi.[30] In Table 2 are shown the corrected interaction energies (final column) and the magnitude of the error due to the superposition of the basis when the complexes are formed.

Even when the calculated BSSE values are significant (for comparison see Ref. 31), the stability order of the complexes is maintained since the error is quite similar in all the cases, and, even considering this error, the interaction energies are still favorable.

In Section 3.2 an experimental encapsulation system reported in the literature is described and the host–guest interaction energy calculations are presented in order to validate the used theoretical methods.

3.2. Experimental reference system: PAMAM–DBNP

In 2003 Twyman et al. (see Ref. 19a) reported a set of neutral water-soluble PAMAM derivatives with hydroxyl terminal groups (e.g., Fig. 6) as potential drug carriers.

Some water-insoluble molecules were tried to be encapsulated, particularly by the dendrimer with 24 terminal OH groups (Gen 1.5). The insoluble antifungal/antibacterial compound 2,6-dibromo-4-nitrophenol (DBNP) was encapsulated and totally solubilized. The binding mechanism proposed by the authors involves ion-pairing interactions with the internal tertiary nitrogens.[32] No H-bonding interactions were observed.

Trying to reproduce the unambiguous complexation manifested by the infinite solubilization of DBNP (independent of the interaction mechanism), a fragment of the PAMAM dendrimer (without hydroxyl terminal groups, not involved anyway in the encapsulation process) was constructed and its host–guest complex with DBNP was considered. To avoid interactions with amino-terminal groups, the terminal amines were di-substituted with methyl groups. The same theoretical methodology described above for the designed fractal patterns and their complexes with salicylanilides was used to calculate the reference system. Figure 7 shows the structure of the model inclusion complex in vacuum (pure host–guest interaction): B3LYP/LAV3P* model (Table 3) was able to reproduce the encapsulation of the DBNP by the PAMAM fragment since favorable interaction energy (−4.442 kcal/mol) was obtained. To compare the encapsulation efficiencies, the FP1–DBNP complex is also calculated and the interaction energy is included in Table 3. The FP1 interacts more efficiently with DBNP than the PAMAM fragment does, by H-bonding, which is desirable in terms of facilitation of the posterior release of the guest molecules. The difference observed in energies of interaction can be taken as an indication for the presence of more interacting sites in the designed fractal pattern.

Taking into account the presence of aliphatic amines (terminal-primary amines and internal-tertiary amines) as part of the fractal patterns FP1, FP2, and FP3, and also present in the PAMAM reference system, their possible protonation in aqueous media, thus competing with the encapsulation process, is an issue that will be discussed below. In the case of the fractal patterns FP1, FP2, and FP3, the primary amines as terminal groups are irrelevant since all these fractal patterns were designed as simple models to be eventually incorporated, as building blocks, in a dendrimeric framework, hence, such terminal groups will be totally substituted to give rise to dendrimeric drug carriers. As in the PAMAM

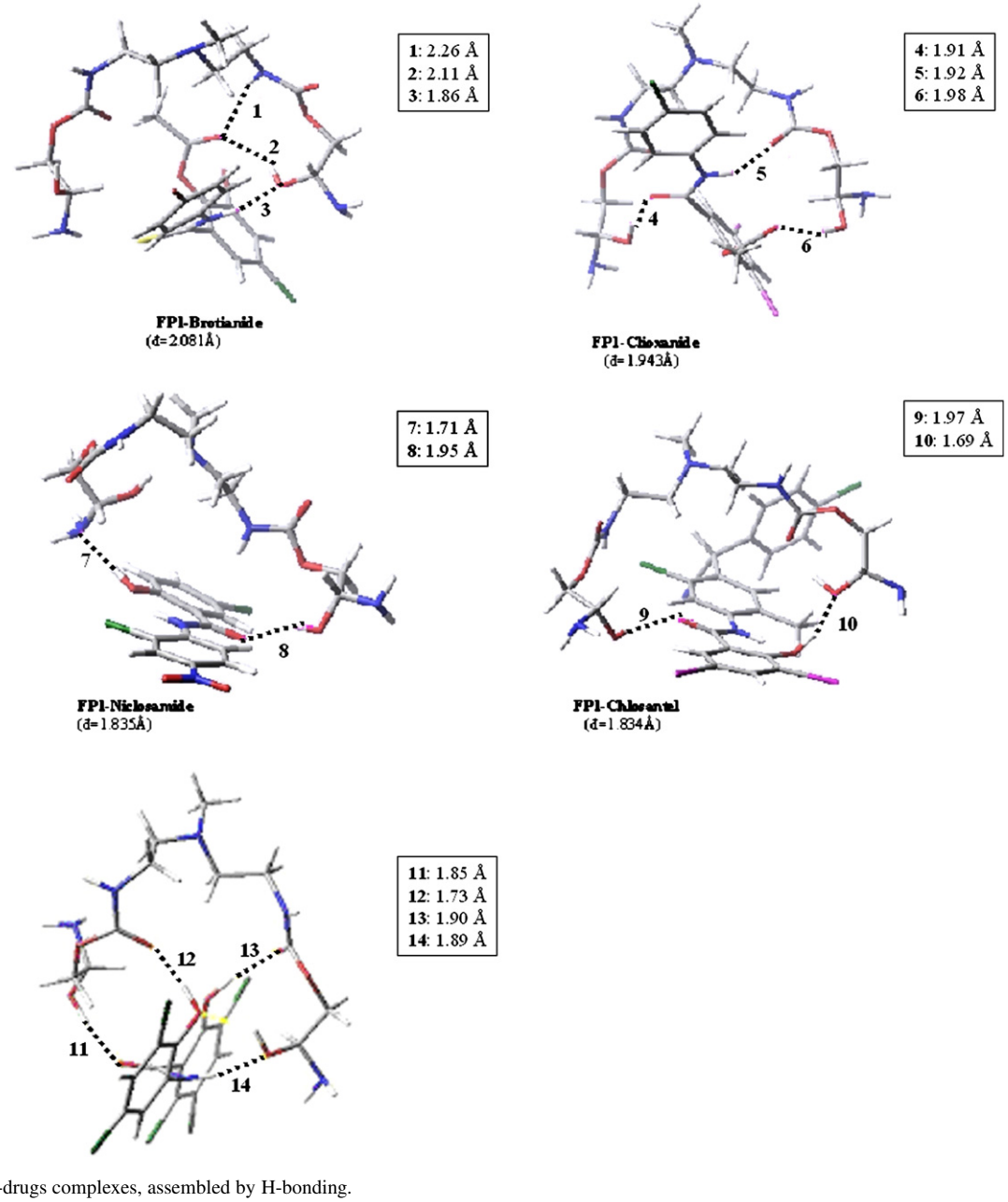

Figure 5. FP1-drugs complexes, assembled by H-bonding.

Table 2. BSSE and corrected interaction energies (kcal/mol) for FP1–drugs complexes

FP1–drug	BSSE (kcal/mol)	E_{corr} (kcal/mol)
Brotianide	−10.17	−7.25834731
Clioxanide	−10.32	−12.93569904
Niclosamide	−6.65	−17.65654303
Chlosantel	−9.53	−21.59453124
Oxyclozanide	−12.01	−38.35508542

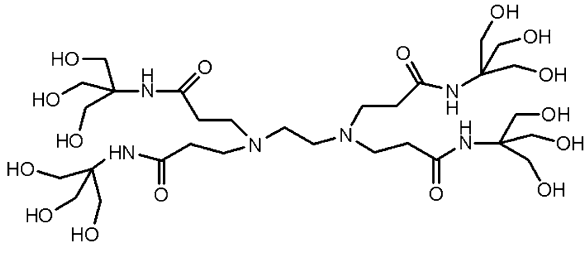

Figure 6. PAMAM derivative.

reference system, as it was mentioned above, the terminal amino groups were methyl-substituted in order to avoid any possible interaction. Thus, the remaining aliphatic amines, inside the dendrimer, in both FPs and PAMAM reference systems, are all tertiary amines. In order to ensure that the protonation of these internal amines by water can be discarded as possible competing event, the equilibrium concentration of protonated amines was estimated using pK_a values of the conjugated acids of tertiary amines (pK_a data compiled by R. Williams) as well as the ionic product K_w. As a result (pK_a value of the conjugated acid of trimethylamine (pK_a=9.76) and $K_w=10^{-14}$), the fraction of free tertiary amine in aqueous solution is more than 99%. It is

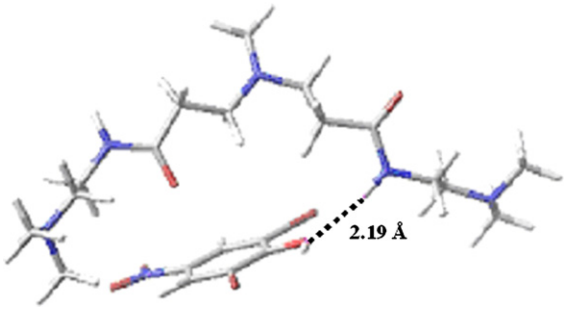

Figure 7. Reference system: model inclusion complex PAMAM–DBNP in vacuum.

Table 3. Reference system calculated at B3LYP/LAV3P* level of theory

Reference system	Interaction energy (kcal/mol)	BSSE (kcal/mol)	E_{corr} (kcal/mol)
PAMAM–DBNP	−9.5716	−5.1290	−4.4425
Comparison			
FP1–DBNP	−18.2102	−4.4400	−13.7702

important to mention that, as the dendrimeric drug carriers achieve globular structures at higher generations, the discussion about possible protonations becomes even less important due to the reduction of solvent accessibility. Soluble globular macromolecules with a hydrophobic interior, to shelter the hydrophobic drugs are the most probable scenario.

3.3. Electrostatic maps

Since H-bonding is involved, the electrostatic potential in aqueous medium was mapped onto a surface of electron density to get a description of the electrostatic characteristics of both drugs and FPs (Fig. 8a and b, respectively). The colors toward blue and red represent positive and negative regions, respectively.

Regarding the results of interaction energies from Table 1, brotianide and clioxanide were the worst drugs to encapsulate by the hosts and they are actually the drugs whose electrostatic potential surfaces show little 'variety of regions' to interact: clioxanide exhibits mainly well defined negative zones and brotianide does not even exhibit defined regions at all. The other three drugs have both, negative and positive well defined regions, which increase the interaction possibilities from the electrostatic point of view.

A similar situation was found in the case of the FPs (Fig. 8b). The FP4 was the poorest host for the salicylanilides and it is precisely the one with fewest variety of regions at the electrostatic surfaces.

Thus, specially when H-bonding (electrostatic in nature) is involved, the calculation of the electrostatic surfaces can be very useful to visualize the sites of interaction in both hosts and guests in order to predict their affinities.

3.4. Pre-organized conformations

When a host–guest complex is formed, there are several operating factors that modulate the affinity of the interaction. The shape, size, conformation, and charge distribution of the host entities are key 'controllers' to take into account when a design is carried out. In this sense, it is very important to examine the pre-organization of the designed fractal patterns, before the complexation occurs, starting from their conformations.

The optimized conformations of the FPs in both gas phase and solution (water) phase are shown in Figure 9a and b.

This schematic comparison shows that in the cases of FP1 and FP2 there are no big differences in conformation when the solvent is present, upholding their cavity shapes to shelter the guest molecules.

An orientation of the carbonyl groups is observed in the case of solvated FP2, pointing the oxygen atoms toward the interior of the cavity, but still maintaining the enough room to encapsulate one drug molecule. This behavior is convenient in terms of encapsulation in aqueous media since the host conformations do not change drastically, preserving a relative independence of the environment. Undoubtedly the drugs, hydrophobic in nature, will prefer any environment less polar than water, such as the interior of the FPs.

Analyzing the other two FPs (Fig. 9b), particularly the FP3 showed a notable change when the structure is exposed to solvent, evidencing its affinity to polar environments. The FP4, similar to FP1 and FP2, essentially maintains its conformation in both media. Thus, the inspection of the conformations leads to an intuitive idea of the accessibility inside the cavities of the designed fractal patterns, which coincides with the efficiency of encapsulation stated before in terms of the energy of interaction. The fractal pattern labeled as FP3 showed a solvated structure with the lowest level of pre-organization and the energetic trade off for that is reflected in the unfavorable interaction energies with some of the drug molecules, compared with other fractal patterns. Therefore, a compromise between the number of sites of interaction and the pre-organization conditions must be settled in order to have better hosts for specific applications.

The flexibility of the dendrimeric architectures has to be highlighted (Fig. 9a and b), which is notoriously different from that observed for conventional host systems like cyclodextrins, cyclophanes, calixarenes, etc.

3.5. NBO analysis

From the analysis of the atomic charges (NBO calculations) it is possible to locate, not only the donor sites of the host molecules but also the hydrogen atoms with a deficit of charge, susceptible to form H-bonds with some electronegative atom from the guest molecules (salicylanilides in this case), increasing in this way the sites of interaction between the drugs and the fractal patterns (see Fig. 10).

Thus, well pre-organization, suitable electrostatic environment, flexibility, and the negative charge distribution lying on the heteroatoms are some of the features founded in the designed FPs. Specially the fractal pattern FP1 brings together most of the favorable features and it is the host interacting with the highest efficiency with the salicylanilides.

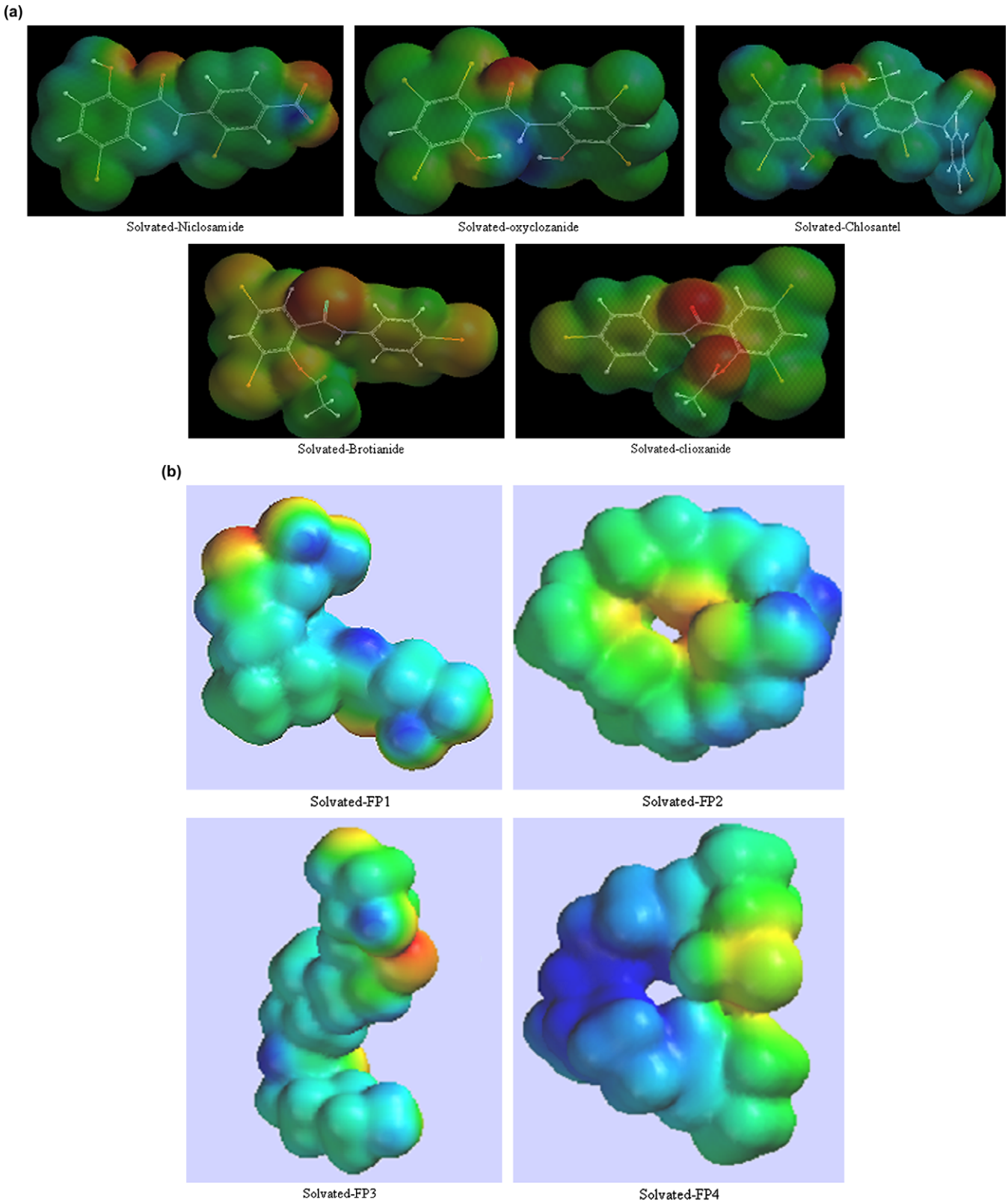

Figure 8. Electrostatic potential surfaces of (a) solvated salicylanilides; (b) solvated FPs.

3.6. DFT functionals: B3LYP versus BHandHLYP describing H-bonding

The theoretical treatment of non-covalent interactions has been widely discussed and some methods have been very successful reproducing both weak and strong interactions.[33] Within the DFT framework, the hybrid functional labeled as BHandHLYP, developed in 1993, shows good performance, in describing the non-covalent interactions with an important electrostatic contribution.[34] This functional, with higher

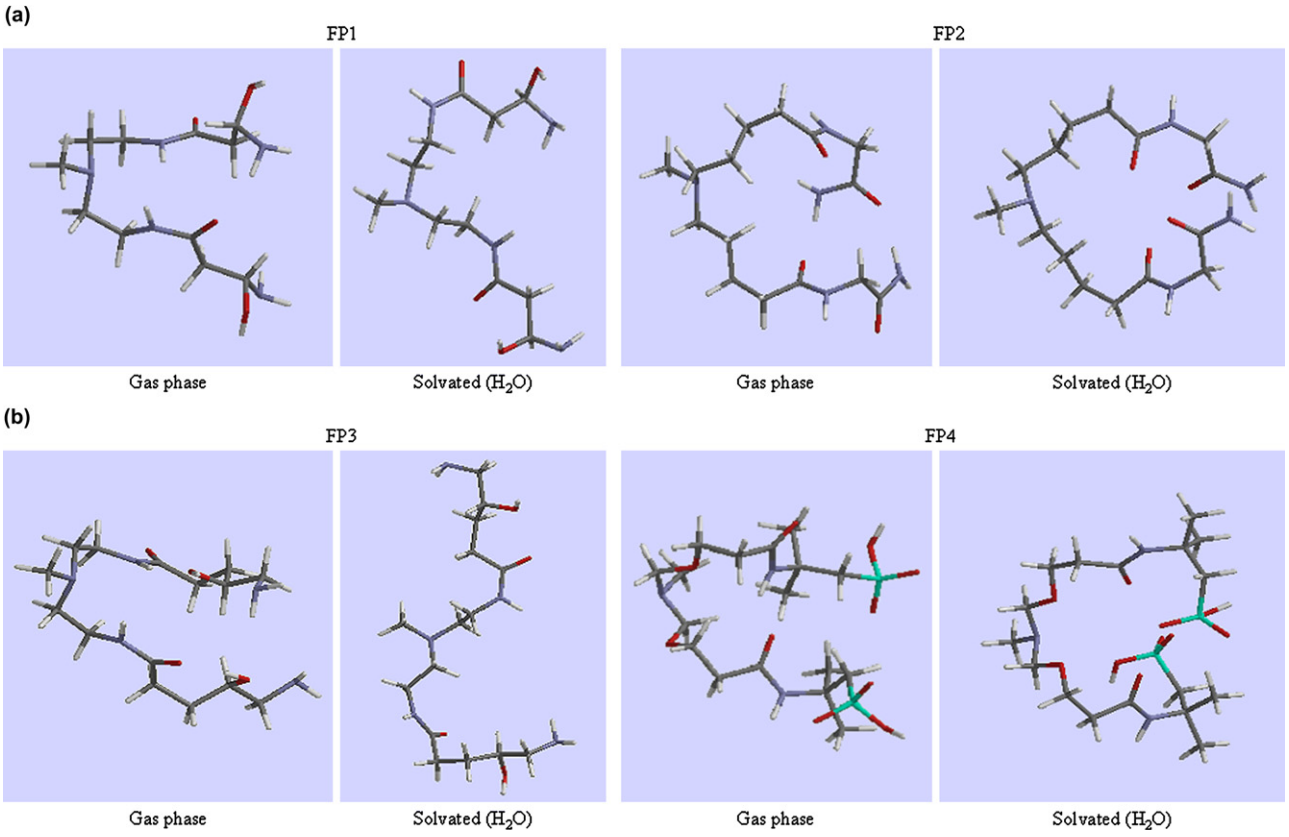

Figure 9. Conformations of fractal patterns in gas phase and aqueous phase: (a) FP1 and FP2; (b) FP3 and FP4.

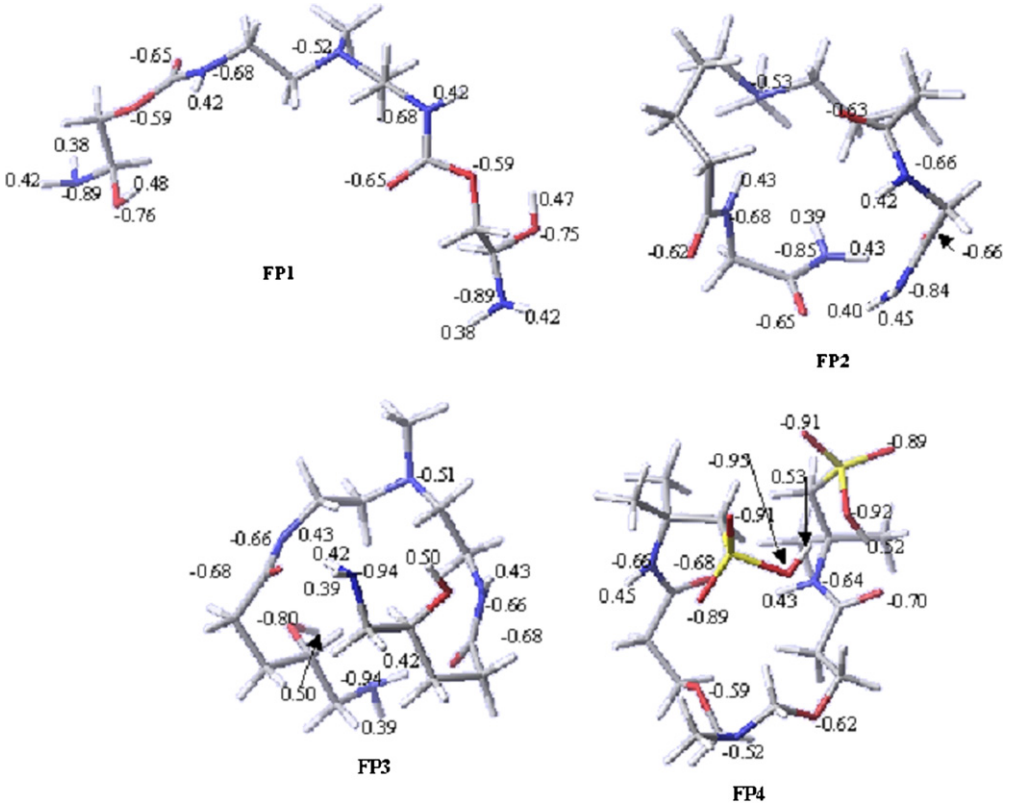

Figure 10. Atomic charges from the NBO analysis.

percent of Hartree–Fock (exact) exchange contribution (50%) has shown superior, in comparison with other hybrid functionals like B3LYP (with 20%), particularly reproducing H-bonding interactions. A comparison of these two hybrid functionals (B3LYP and BHandHLYP) was carried out by the calculation of interaction energies of the host–guest systems formed between the fractal pattern FP1 and the studied drugs, using the same basis set as it is shown in Table 4 (BSSE correction was included). The corrected energies are those in parentheses.

Table 4. FP1–drugs interaction energies (kcal/mol)

	B3LYP/LACVP*	BHandHLYP/LACVP*
Brotianide	−17.431 (−7.258)	−28.515 (−19.052)
Clioxanide	−23.255 (−12.935)	−36.426 (−24.459)
Niclosamide	−24.304 (−17.656)	−38.233 (−28.864)
Chlosantel	−31.121 (−21.594)	−45.847 (−33.750)
Oxyclozanide	−50.362 (−38.355)	−35.542 (−23.534)
PAMAM–DBNP	**−9.5716 (−4.4425)**	**(−15.1215)**

In parentheses are included the corrected interaction energies.

As seen from Table 4, except for the complex FP1–oxyclozanide, the interaction energies become 30–40% more negative when the functional BHandHLYP is used (roughly the same percentage corresponding to the 'extra' Hartree–Fock exchange contribution considered in this functional). According to the results obtained for the experimental system PAMAM–DBNP (in bold style at the end of Table 4), the functional BHandHLYP reproduces the experimental observation even better than B3LYP since a more negative energy was obtained, which is more in accordance with the infinite solubility of the hydrophobic molecule of DBNP after its encapsulation. The H-bond distances are shorter when the BHandHLYP functional is used in the calculation, comparing with those obtained with the B3LYP functional (see Table 5). Clearly, the treatment of exchange-correlation contributions by the functional BHandHLYP is better than that obtained by B3LYP, since the short distances (below 3 Å) correspond to more favorable interaction energies.

The interaction energies of the FP1–drug complexes show a polynomial (second-order) fit as a function of the exchange-correlation contribution (XC). The plots in Figure 11

Table 5. Number of H-bonds and their average distances (Å) in FP1–drugs complexes

	B3LYP	BHandHLYP
Brotianide	(3) 2.089	(3) 1.933
Clioxanide	(3) 1.943	(3) 1.836
Niclosamide	(2) 1.862	(2) 1.779
Chlosantel	(2) 1.834	(2) 1.744
Oxyclozanide	(5) 1.889	(5) 1.824

In parentheses are expressed the number of H-bonds.

make evident that the treatment of the XC energetic term is the main difference between the two hybrid functionals BHandHLYP and B3LYP. While the functional BHandHLYP (Fig. 11a) enclose all the FP1–drug complexes with a very good fit (R^2: 0.997), the functional B3LYP (Fig. 11b) do not describe the complete series (oxyclozanide did not fit). The calculated interaction energies as a function of all other energetic contributions showed a good linear fit, regardless of the hybrid functional used.

Therefore, although both functionals describe nearly the same order of stability of the complexes under study, the functional BHandHLYP showed two important skills: a better description of close contacts and a wider spectrum of systems that it can depict.

4. Conclusions

Using computational chemistry tools, four dendrimeric fragments (fractal patterns, FPs) were designed as simple models to encapsulate a family of drugs known as salicylanilides (important acaricides/antihelmithycs), mainly by H-bonding. The incorporation of different polar functional groups as part of the FPs as well as the modification of the length of the aliphatic chains were both aspects taken into account to get good candidates as hosts for the drugs under study. There is a compromise between flexibility and sites of interaction by polar groups but generally speaking, as the aliphatic chains in the FPs become more flexible, the formation of H-bonds is favored. The pre-organization of any host is an essential attribute to participate in encapsulation events; a bad pre-organization of the hosts results in a poorer interaction with the guests. In this terms, the studied fractal

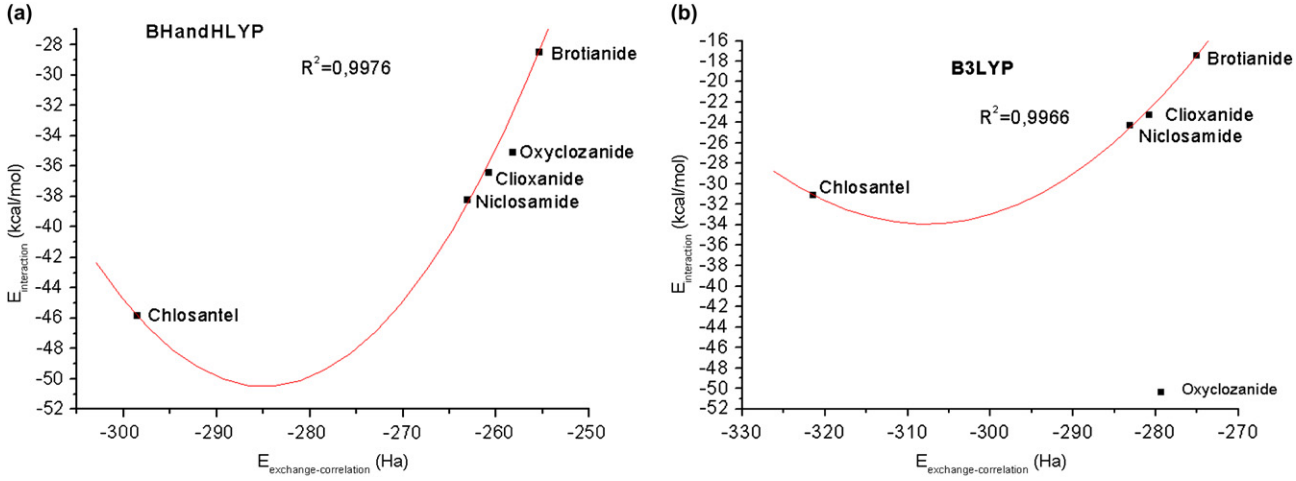

Figure 11. Interaction energy versus exchange correlation energy term: (a) BHandHLYP treatment; (b) B3LYP treatment.

patterns in both, gas phase and aqueous phase, exhibited generally good pre-organization to shelter the drugs as guest molecules, in accordance with the negative energies of interaction obtained theoretically. Two hybrid functionals, B3LYP and BHandHLYP, were used to calculate the interaction energies between FPs and salicylanilides. Both functionals describe nearly the same order of stability of the complexes under study; however, the functional BHandHLYP described in a better way the close contacts and also reproduced in a more realistic manner the favorable interaction between PAMAM and DBNP (reference system) observed experimentally.

In accordance with all the obtained results for the designed fractal patterns, the rational construction of hosts for specific guests seems to be useful to get major efficiency in encapsulation processes thus, this philosophy will be kept for further work.

Finally, both, the synthesis of the designed fractal patterns to corroborate their skills experimentally as well as the study of the salicylanilides delivery from the interior of the dendrimeric hosts are two important issues that will be address in future work. It is known that the primary action of salicylanilides as acaricides is the uncoupling of oxidative phosphorylation,[35,36] which means that they are the chemicals that decrease the efficiency of ATP production at mitochondrial level, causing the cellular death.[37,38] The carrier-mediated mechanism of transport follows a trans-membranal pathway; thus, once the carrier–drug complex reaches the target site (which is enclosed for the highly hydrophobic mitochondrial membrane), the release of the drug (hydrophobic in nature) is possible due to a major affinity, leaving the carrier (e.g., a dendrimer) behind, which is more alike to the aqueous environment mainly due to its globular shape. Theoretical and experimental works will be done about these subjects.

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