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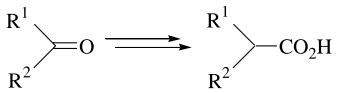
Tetrahedron Vol. 60, No. 1, 2004

Contents

Publisher's Announcement p 9

REPORT

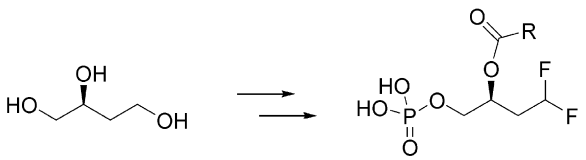
Homologation of ketones into carboxylic acids pp 11–42
Neil F. Badham



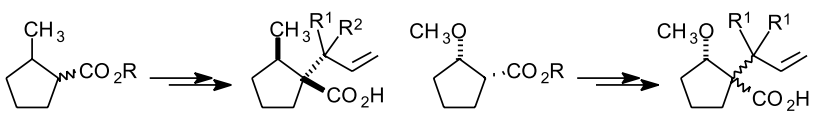
R^1, R^2 = alkyl, aryl, alkenyl

ARTICLES

Synthesis of difluoromethyl substituted lysophosphatidic acid analogues pp 43–49
Yong Xu, Lian Qian, Aaron V. Pontsler, Thomas M. McIntyre and Glenn D. Prestwich*



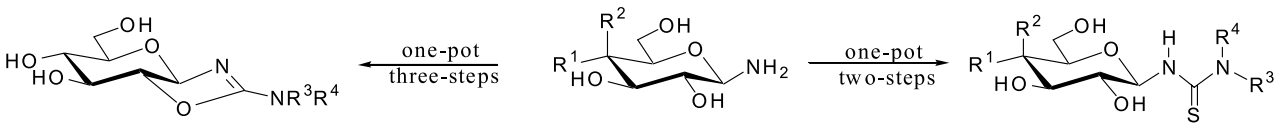
Facial selectivity of the Ireland–Claisen rearrangement of allylic esters of 2-methyl and 2-methoxycyclopentanecarboxylic acids pp 51–60
John C. Gilbert,* Jiandong Yin, Fatima H. Fakhreddine and Matthew L. Karpinski



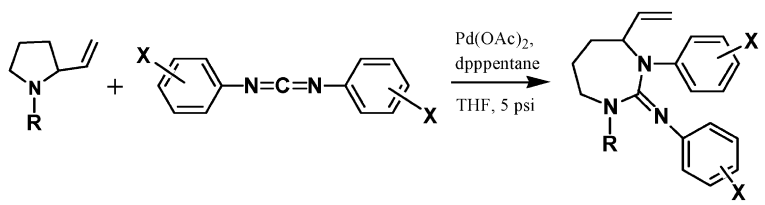
R = *E*- and *Z*-crotyl or prenyl
R^1 = H, R^2 = CH_3 or R^1 = R^2 = CH_3

R = allyl or prenyl
R^1 = H or R^1 = CH_3

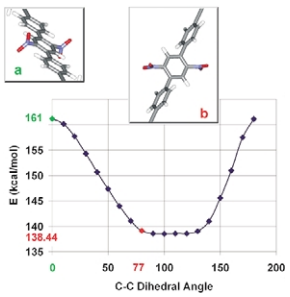
Simple and efficient synthesis of *O*-unprotected glycosyl thiourea and isourea derivatives from glycosylamines **pp 61–72**
Óscar López, Inés Maya, José Fuentes and José G. Fernández-Bolaños*



Regioselective and enantioselective synthesis of seven-membered ring cyclic arylguanidine and urea derivatives **pp 73–79**
Hai-Bing Zhou and Howard Alper*

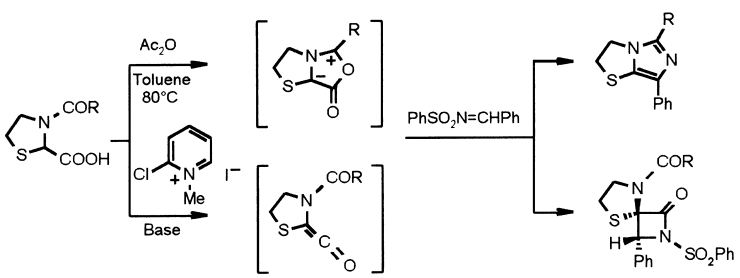


Synthesis of terphenyl oligomers as molecular electronic device candidates **pp 81–92**
Francisco Maya and James M. Tour*

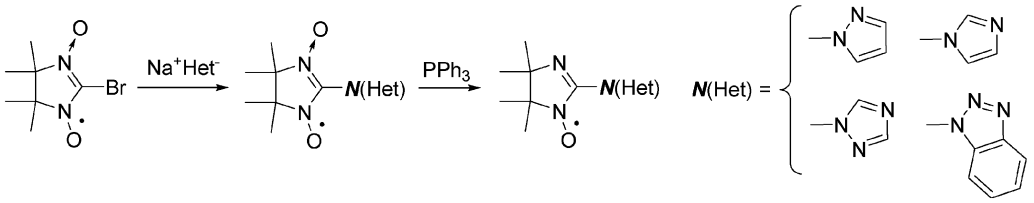


A series of terphenyl-based molecular electronics candidates were synthesized based on known structure–activity relationships and molecular modeling of C–C rotational barriers.

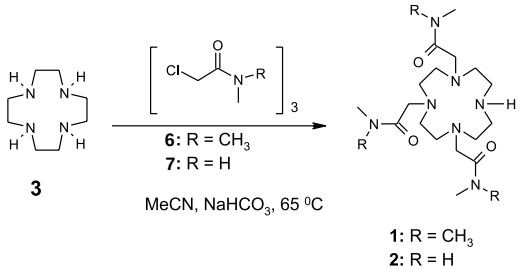
Synthesis of imidazo[5,1-*b*]thiazoles or spiro-β-lactams by reaction of imines with mesoionic compounds or ketenes generated from *N*-acyl-thiazolidine-2-carboxylic acids **pp 93–97**
Giuseppe Cremonesi, Piero Dalla Croce and Concetta La Rosa*



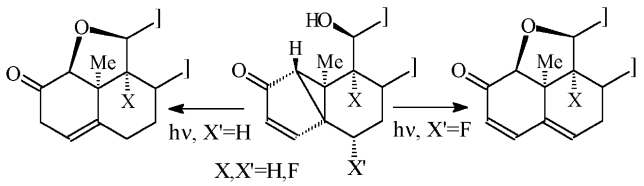
Syntheses and structures of azol-1-yl derivatives of nitronyl and imino nitroxides **pp 99–103**
Eugene V. Tretyakov, Galina V. Romanenko and Victor I. Ovcharenko*



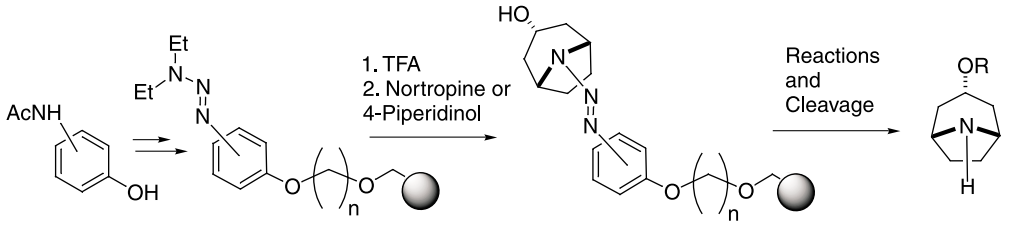
Three step vs one pot synthesis and X-ray crystallographic investigation of heptadentate triamide cyclen (1,4,7,10-tetraazacyclododecane) based ligands and some of their lanthanide ion complexes **pp 105–113**
Thorfinnur Gunnlaugsson,* Joseph P. Leonard,* Sinead Mulready and Mark Nieuwenhuyzen



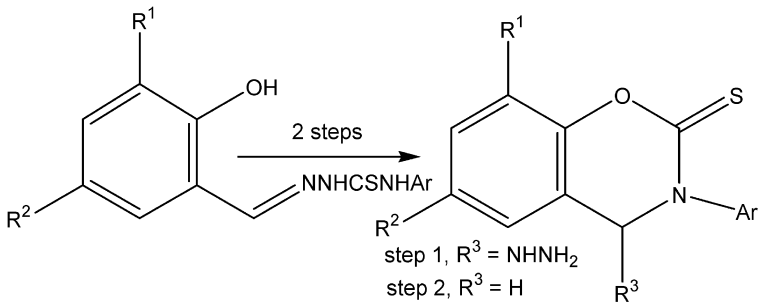
Photochemistry of some steroidal bicyclo[3.1.0]hexenones **pp 115–120**
Andrea Ricci, Elisa Fasani, Mariella Mella and Angelo Albini*



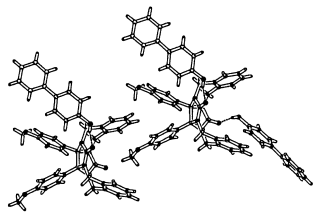
A new strategy for synthesis of polymeric supports with triazene linkers **pp 121–130**
Ryszard Lazny,* Aneta Nodzewska and Piotr Klosowski



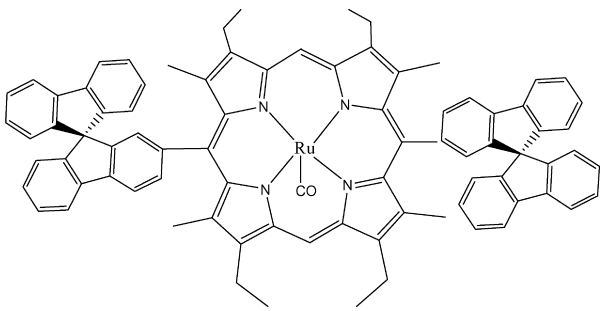
Mineral supported syntheses of benzoxazine-2-thiones under microwave irradiation **pp 131–136**
Lal Dhar S. Yadav,* Beerendra S. Yadav and Suman Dubey



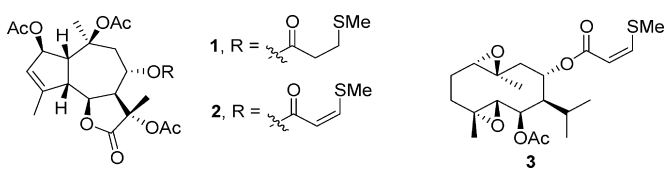
A new binding motif in molecular clips: 1-D polymeric self-inclusion in a phenol complex of a bis(methoxyphenyl)glycoluril **pp 137–143**
Bernadette S. Creaven, John F. Gallagher, John P. McDonagh, John McGinley,* Brian A. Murray* and Giuseppe S. Whelan



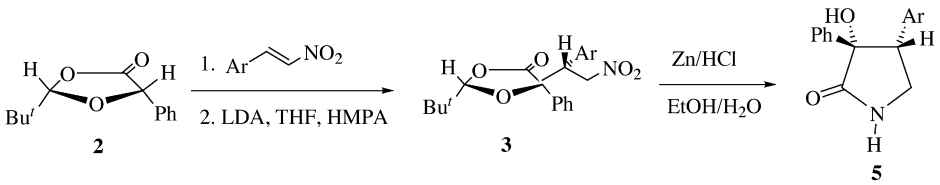
Synthesis and stereochemical studies of di and tetra 9,9′-spirobifluorene porphyrins: new building blocks for catalytic material **pp 145–158**
Cyril Poriel, Yann Ferrand, Sandrine Juillard, Paul Le Maux and Gérard Simonneaux*



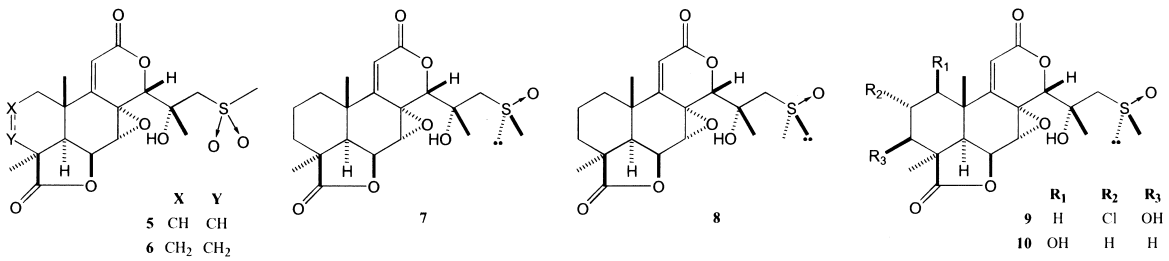
Sulfur-containing sesquiterpenes from *Thapsia villosa* **pp 159–164**
Juan J. Rubal, Francisco M. Guerra, F. Javier Moreno-Dorado, M. Akssira, F. Mellouki, Antonio J. Pujadas, Zacarías D. Jorge and Guillermo M. Massanet*



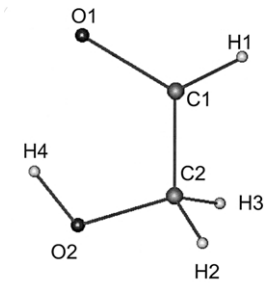
Diastereoselective Michael addition of (*S*)-mandelic acid enolate to nitroalkenes. Enantioselective synthesis of α-hydroxy-α,β-diaryl-γ-lactams **pp 165–170**
Gonzalo Blay, Isabel Fernández, Belén Monje and José R. Pedro*



Rakanmakilactones A–F, new cytotoxic sulfur-containing norditerpene dilactones from leaves of *Podocarpus macrophyllus* var. *maki* **pp 171–177**
Hyun-Sun Park, Naoki Yoda, Haruhiko Fukaya, Yutaka Aoyagi and Koichi Takeya*

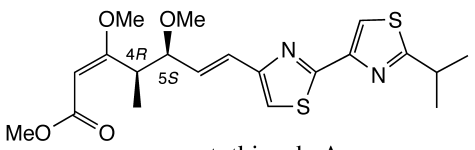


The nature of the rotational barriers in simple carbonyl compounds **pp 179–185**
Tomasz Ratajczyk, Magdalena Pecul and Joanna Sadlej*



Gc-glycolaldehyde

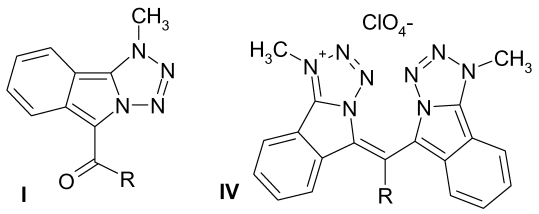
Syntheses of cystothiazole A and its stereoisomers: importance of stereochemistry for antifungal activity **pp 187–194**
Makoto Ojika,* Tatsuya Watanabe, Jianhua Qi, Tomoharu Tanino and Youji Sakagami



cystothiazole A

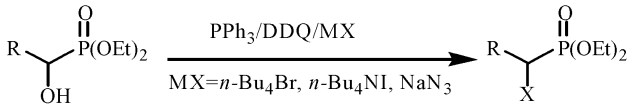
All stereoisomers of cystothiazole A, a myxobacterial antifungal antibiotic, were synthesized enantioselectively, and the importance of the natural 4*R*,5*S* configuration for antifungal activity was unambiguously demonstrated.

New cyanine dyes derived from tetrazolo[5,1-*a*]isoindoles **pp 195–201**
Z. V. Voitenko,* T. V. Yegorova, A. I. Kysil', C. André and J. G. Wolf

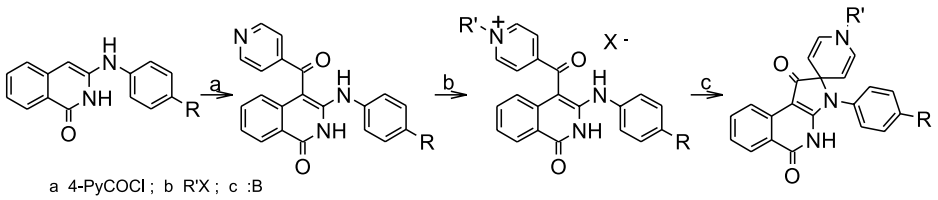


5-Acyl-1-methyltetrazolo[5,1-*a*]isoindoles I and a new type of tetrazoloisoindole based monomethinecyanines IV were isolated in the acylation reaction of 1-methyltetrazolo[5,1-*a*]isoindole with acyl chlorides.

PPh_3/DDQ as a neutral system for the facile preparation of diethyl α-bromo, α-iodo and α-azidophosphonates from diethyl α-hydroxyphosphonates **pp 203–210**
Habib Firouzabadi,* Nasser Iranpoor* and Sara Sobhani

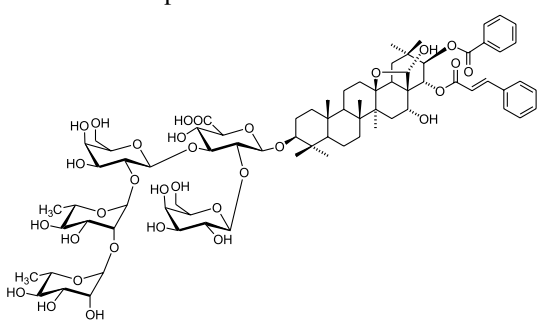


Fused isoquinolines: 3-aryl-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-alkyl-1′,4′-dihydropyridine)s **pp 211–217**
Tat'yana T. Kucherenko,* Roman Gutsul, Vladimir M. Kisel and Vladimir A. Kovtunenko

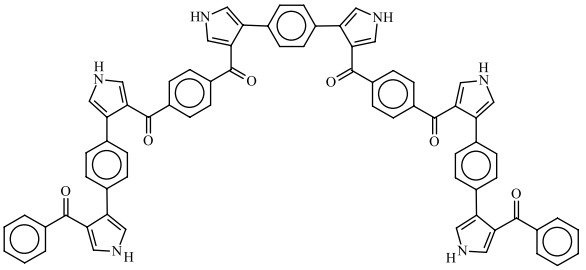


New pentacyclic triterpene saponins with strong *anti*-leishmanial activity from the leaves of *Maesa balansae* **pp 219–228**
Nils Germonprez, Luc Van Puyvelde,* Louis Maes, Mai Van Tri and Norbert De Kimpe*

This article discloses the isolation and structural elucidation of six novel pentacyclic triterpene saponins with strong *anti*-leishmanial activity from the dried leaves of *Maesa balansae*, collected in Vietnam.



Gekreuzt konjugierte oligomere aus pyrrol-, benzol- und carbonyl-Bausteinen **pp 229–233**
Angelina Hormaza, Sabine Hinneschiedt und Herbert Meier*



OTHER CONTENTS

Calendar **I–IX**
Contributors to this issue **XI**
Instructions to contributors **XIII–XVI**

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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

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Tetrahedron

Publisher's Announcement

Tetrahedron continues to seek to improve its service to authors and readers.

- Readership of the Journal via ScienceDirect continues to grow at an impressive rate. During 2003, we have seen over 1 million articles downloaded from *Tetrahedron*. All issues back to volume 1 issue 1 are available. The Journal is read in over 60 countries and 49 of the United States. We also expect readership to grow again in 2004, guaranteeing an even wider international audience for authors' research.
- Publication times continue to shrink. It now takes typically less than 17 weeks to progress an article from first submission to publication on ScienceDirect. Greater usage by authors of electronic submission has helped speed publication. Over half of the submissions are now made electronically.
- *Tetrahedron* remains one of the most highly cited organic chemistry journals. In 2002, the Journal was cited over 32,000 times (ISI Journal Citation Reports®).
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- Our new cover design will allow us to feature structures or colour graphics to draw attention to Symposia-in-Print, Reports or ground-breaking research. The new cover also reflects that the Journal is now published under the Elsevier imprint.
- The graphical contents pages have been designed to give a quicker, clearer overview of the contents of each issue. This layout has also simplified the requirements for authors in preparing a graphical abstract; the templates which were previously provided have now been replaced by the requirement to keep the content of the graphical abstract within an area measuring 5 cm by 17 cm.

Other news regarding the Tetrahedron Publications:

- The website tetrahedron.info continues to attract new readers. The site provides information on a number of initiatives connected with the Tetrahedron journals (for example, the Tetrahedron Prize and Tetrahedron Chair) as well as providing information on submission and content. You can also download free feature articles or enter competitions on the site. Visit the site now at http://www.tetrahedron.info to see what is available.
- The Tetrahedron Symposium 2003 was held in Oxford in July; delegates from academia and industry were attracted by the excellent line-up of speakers. The 2004 Symposium will be held in New York on Friday 18 June and again we have an impressive list of plenary talks. For full details, please go to http://www.tetrahedron.info/symposium

We wish all our readers and authors a Happy New Year and success during 2004.

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Homologation of ketones into carboxylic acids

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Contents

1. Introduction 12
2. Via epoxides 12
   2.1. Unsubstituted epoxides 12
   2.2. α-Cyano epoxides 12
   2.3. α-Ester epoxides 13
   2.4. α-Arylsulfinyl epoxides 15
   2.5. α-Trimethylsilyl epoxides 15
   2.6. α-Chloro α-ester epoxides 16
3. Via nitriles 17
   3.1. Unsubstituted nitriles 17
   3.2. Via cyanohydrins 19
      3.2.1. Trimethylsilyl cyanohydrins 19
      3.2.2. Unsubstituted cyanohydrins 20
4. Via vinyl heteroatoms or halides 20
   4.1. Enol ethers 20
   4.2. Thio enol ethers 21
   4.3. Enamines 22
   4.4. Vinyl boronic esters 23
   4.5. Vinyl isocyanides 23
   4.6. Vinyl halides 24
5. Via alcohols 24
6. Via olefins 25
7. Via acetals/ketals 27
   7.1. Ketene *S*,*S*-acetals 27
   7.2. Ketene *S*,*S*-acetal mono-oxides 29
   7.3. Ketene *O*,*S*-acetals 29
   7.4. Ketene *N*,*O*-acetals 30
   7.5. *O*,*O*-Ketals 30
8. Via acrylonitriles 31
   8.1. α-*tert*-Butoxyacrylonitriles 31
   8.2. α-Aminoacrylonitriles 31
9. Via α-hydroxy acids 32
10. Via homologation/alkylation 32
11. Via enamidines 34
12. Via 1-formylamino-1-arylsulfonyl alkenes 35
13. Miscellaneous 35
14. Conclusion 36

Keywords: Homologation; Carboxylic acids; Ketones.

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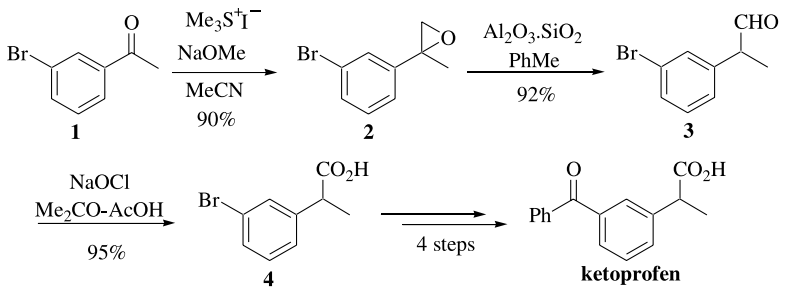


Scheme 1.

1. Introduction

Efficient functional group transformations have been the goal of organic chemists for many years. Reports have appeared on atom economy[1] and towards the ideal synthesis[2] highlighting these goals. The addition of a one carbon unit to a ketone to homologate it to a carboxylic acid is an important transformation that chemists have tackled from many different angles in the hope of achieving this goal. Strategies have used intermediates such as epoxides, vinyl heteroatoms and halides, nitriles or alkenes to give the homologated acids. Generally, only those reactions which do not alter the carbon skeleton next to the ketone will be discussed. The purpose of this article is to provide a general overview of the important synthetic reactions which have been designed to effect this transformation. A wide variety of approaches have been published especially on the preparation of the NSAIDs (e.g. ibuprofen, naproxen, and pranoprofen). A comprehensive discussion of the entire subject is difficult, but a number of excellent reviews have appeared,[3] and references to them will be made wherever possible to allow for a wider scope of synthetic methods. An attempt has been made to survey the relevant literature through June 2003.

2. Via epoxides

Substituted and unsubstituted epoxides have proven to be a popular platform in which to introduce the one carbon unit. Some methods involve epoxide rearrangement to the homologated aldehyde which is then oxidized by a variety of methods to give the corresponding carboxylic acid. Other epoxide rearrangement methods achieve the transformation to the homologated carboxylic acid directly. Representative aldehyde oxidation methods include $KMnO_4$,[4] $K_2Cr_2O_7$,[5] Ag_2O,[6] NaOCl,[7] $NaClO_2$,[8] and Oxone.[9]

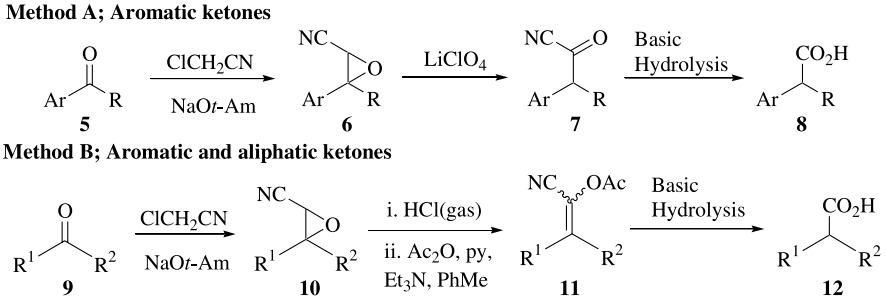
2.1. Unsubstituted epoxides

Corey et al. in 1962 introduced the one carbon unit by using epoxides formed from the reaction of dimethylsulfoxonium methylide and ketones.[10] These epoxides in turn were rearranged under Lewis acid conditions ($BF_3{\cdot}Et_2O$)[11] to give the homologated aldehydes. Other reagents which have been used to rearrange epoxides to aldehydes are, $ZnCl_2$,[12] $InCl_3$,[13] $(t\text{-}Bu_2BrC_6H_2O)_2AlMe$,[14] $MgBr_2{\cdot}Et_2O$[15] and TsOH.[16] Ohta Pharmaceuticals used this type of strategy to prepare ketoprofen,[17] Scheme 1. After rearrangement of epoxide **2** with $Al_2O_3{\cdot}SiO_2$, the aldehyde was oxidized with NaOCl to give the homologated carboxylic acid **4** in 95%. The homologated acid **4** was produced in 3 steps from ketone **1** in 79% yield. Four additional steps from acid **4** gave ketoprofen in 57% from **1**.

2.2. α-Cyano epoxides

White et al. developed methods whereby aromatic or aliphatic ketones could be transformed into α-cyano epoxides by the Darzens reaction[18] and these could be rearranged followed by hydrolysis to give the homologated carboxylic acids,[19] Scheme 2. Method A was found to be only amenable to aromatic ketones and did not work on aliphatic ketones. Aromatic ketones **5** were transformed into glycidic esters **6**, which in turn were converted to acylnitriles **7** by a catalytic amount (4%) of $KHSO_4$, $Li(OOCCF_3)$ or $LiClO_4$ in toluene or xylene at reflux. The acylnitrile was then directly hydrolyzed in aqueous base to give the corresponding homologated acid **8**.

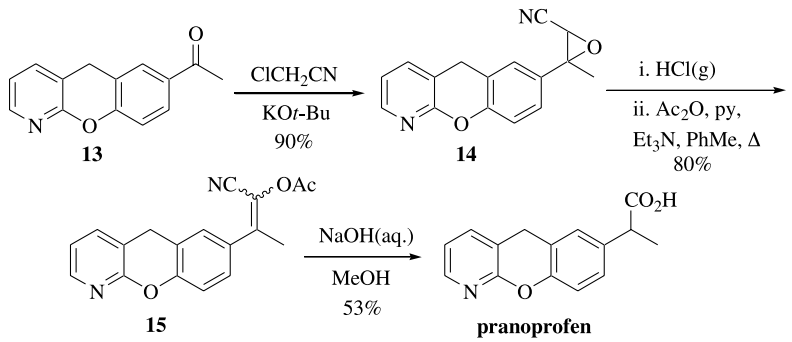
Method B was found to work with both aromatic and aliphatic ketones, although this was a less direct route. Dry HCl converts glycidonitrile **10** into an intermediate α-hydroxy-β-chloronitrile which is acetylated and dehydrohalogenated to give the α-acetoxyacrylonitrile **11**.[20] Basic hydrolysis and acidification gave the desired carboxylic



Scheme 2.

Table 1. Range of substrates transformed using White's methods

Ketone	Homologated acid	Method A yield (%)	Method B yield (%)
p-Isobutylacetophenone	2-(*p*-Isobutylphenyl)propionic acid	72	73
α-Tetralone	1,2,3,4-Tetrahydro-1-naphthoic acid	47	68
Cyclohexanone	Cyclohexane carboxylic acid		57
Cyclopentanone	Cyclopentane carboxylic acid		51
2-Pentanone	2-Methylpentanoic acid		57



Scheme 3.

acids **12**. The range of substrates investigated and yields is shown in Table 1.

Toyo Stauffer Chemical Co., Ltd, Japan used White's method B to prepare pranoprofen,[21] Scheme 3 in 38% overall yield from ketone **13**.

The α-cyano epoxide **14** was prepared in 90% yield from ketone **13** under standard Darzens conditions. Treatment of **13** with HCl(g) converted **14** to an intermediate α-hydroxy-β-chloronitrile, which was then acetylated and dehydrohalogenated to give the α-acetoxyacrylonitrile **15** in 80% yield as a mixture of isomers. Hydrolysis of **15** under basic conditions then gave pranoprofen in 53% yield. An alternative method to hydrolysis is treatment of the α-acetoxyacrylonitriles with piperidine and the corresponding amide is formed,[22] which can be hydrolyzed under the usual conditions to the homologated acid. α,α-Dicyano-epoxides have also been used to effect the homologation of ketones to carboxylic acids.[23]

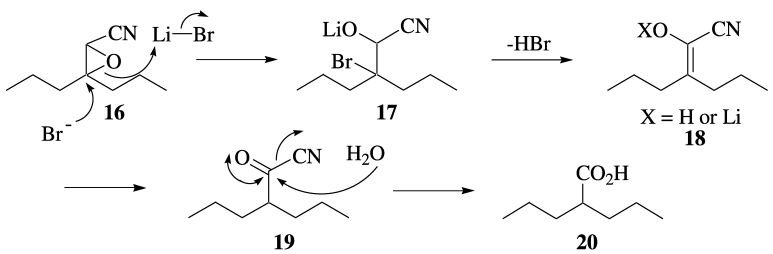
Badham et al.[24] reported an expanded scope of method A developed by White. In the rearrangement, lithium perchlorate in xylene was replaced with safer LiBr, DMF, CH_3CN and water which allowed the rearrangement to work with both aromatic and aliphatic ketones. The intermediate acylnitrile formed during the rearrangement was also hydrolyzed in situ to give the homologated acid directly. One drawback to these methods was that cyanide was liberated during the rearrangement and hydrolysis, and appropriate safety precautions had to be taken when running this chemistry. The rearrangement using LiBr was found not to work if the ketone contained α,α-dialkyl substitution. If the ketone was α,β-unsaturated the rearrangement was found to give an α,β,γ,δ-unsaturated aldehyde instead of the expected acid. In the preparation of SB-207499,[25] this methodology was amenable to multikilo scale.[26] Two mechanisms of the rearrangement of the α-cyano epoxide have been proposed depending on the substrate.[26] The proposed mechanism for the alkylalkyl ketone[27] is shown in Scheme 4.

In the proposed mechanism, bromide attacks the epoxide at the quaternary position either in a S_N1 or S_N2 fashion to give intermediate **17**, which then undergo loss of the elements of HBr to give the enol or enolate **18**. This enol or enolate may be protonated to give **19**, which underwent hydrolysis in situ to give the desired carboxylic acid **20**. The range of substrates investigated is shown in Table 2.

α-Cyano epoxides can also be hydrolyzed to the α-ester epoxide by treatment with K_2CO_3 in MeOH.[28] These α-ester epoxides under alkaline hydrolysis give the homologated acid (see Section 2.3).

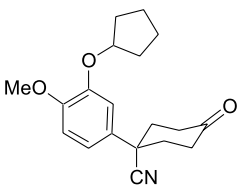
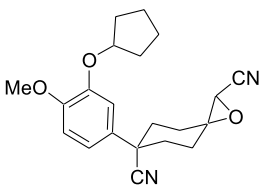
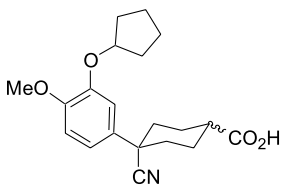
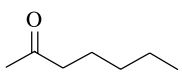
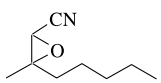
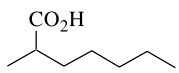
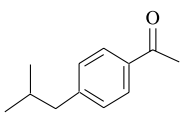
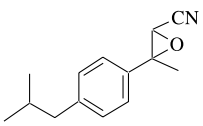
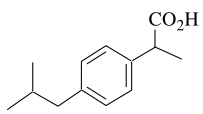
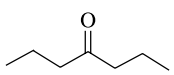
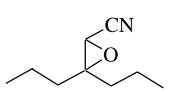
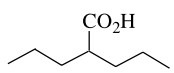
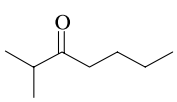
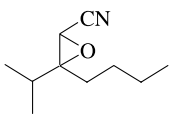
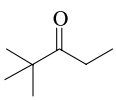
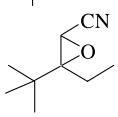
2.3. α-Ester epoxides

The Darzens condensation is a well-established method for



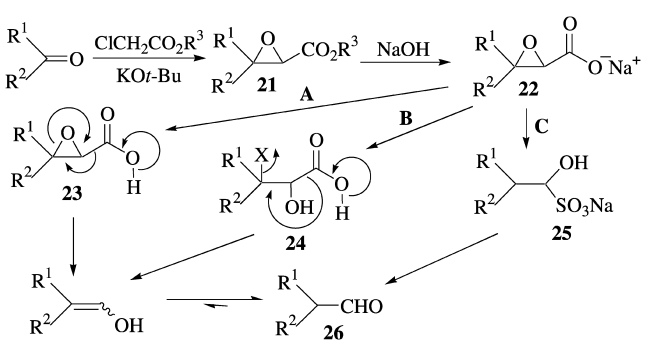
Scheme 4.

Table 2. Range of ketones investigated for the rearrangement of α-cyano epoxides using lithium bromide

Ketone	α-Cyano epoxide	Yield (%)	Homologated acid	Yield (%)
		73		75
		68		63
		73		54
		61		49
		61	No reaction	
		46	No reaction	

the synthesis of α-ester epoxides (glycidic esters).[29] These compounds in turn can be transformed to give the corresponding homologated aldehydes.[30] The first synthesis of a glycidic ester was shown by Erlenmeyer,[31] but Darzens developed and generalized the reaction.[32] The mechanisms of rearrangement of glycidic esters are shown in Scheme 5.

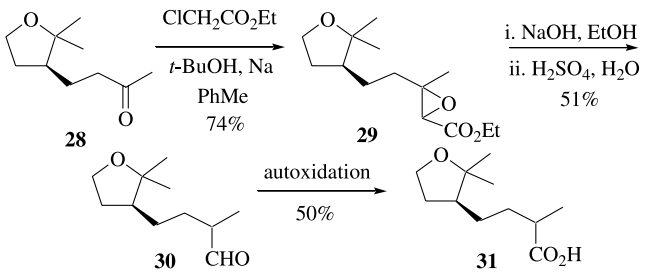
The first step in each of these methods is aqueous hydrolysis of ester **21** to glycidate salt **22**. Path **A** represents the most common sequence for effecting decarboxylation. Compound **22** is transformed into compound **23** which is pyrolyzed to give the homologated aldehyde **26**. Path **B** is the addition of HCl or HBr to the glycidic acid to give **24**, which when treated with alkali decarboxylation occurs with concomitant loss of hydrogen halide to give aldehyde **26**.[33,34] Path **C** occurs when the glycidate **22** is heated with a saturated solution of sodium bisulfite to give the bisulfite adduct of the aldehyde which in turn can give aldehyde **26**.[33] Gora et al. used path **A** to prepare new homoterpenoidal tetrahydrofuran derivatives,[35] Scheme 6.



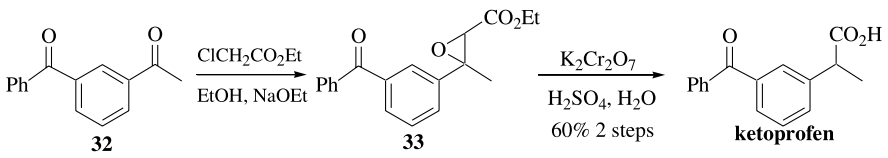
Scheme 5.

Darzens condensation of keto-ether **28** with ethyl chloroacetate in the presence of sodium in toluene gave a diastereomeric mixture of α-ester epoxide **29** in 74% yield. Alkaline hydrolysis of **29** followed by decarboxylation gave aldehyde **30** in 51% yield. On storage at room temperature for 2 months the aldehyde autoxidized to give the homologated acid **31** in 50% yield. Lu et al. also synthesized ketoprofen by use of glycidic esters[36] in 2 steps from ketone **32** in 60% yield, Scheme 7.

The Darzens methodology differentiated the two ketones with subsequent rearrangement of **33** and oxidation of the resultant aldehyde occurring in 1 step. Ketone **32** was prepared in 3 steps from benzoic acid by bromination, a Friedel–Crafts reaction and a Grignard reaction to obtain 3-acetylbenzophenone. The overall yield of ketoprofen from benzoic acid was 32%. Lithium bis(trimethylsilyl)amide can also be used as a base for the Darzens synthesis of



Scheme 6.

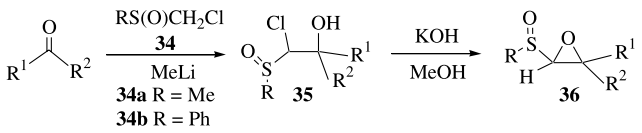


Scheme 7.

glycidic esters.[37] A variety of patents[38–40] and publications[41] has appeared using this methodology especially for the manufacture of NSAIDs and their derivatives.

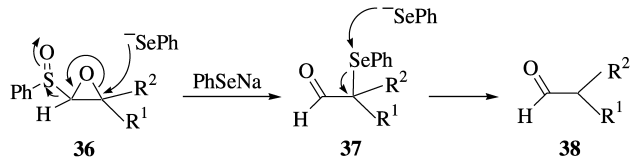
2.4. α-Arylsulfinyl epoxides

α-Arylsulfinyl epoxides were initially reported by Durst in 1969.[42] They were easily prepared from 1-chloroalkyl phenyl sulfoxides[43] and carbonyl compounds via chlorohydrins, Scheme 8.



Scheme 8.

Yamakawa et al.[44] found that the β-carbon of α-arylsulfinyl epoxides was reactive towards PhSeNa to give either dialkyl ketones or aldehydes. The mechanism by which compound **36** was transformed into aldehyde **38** is shown in Scheme 9.



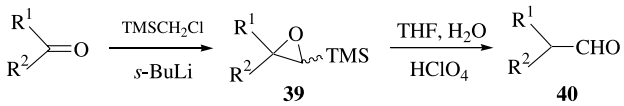
Scheme 9.

The α-arylsulfinyl epoxides were treated with multiple equivalents of sodium benzeneselenoate in ethanol to give the aldehyde. The unreacted sodium benzeneselenoate was recovered as diphenyl diselenide in near quantitative yield, however, the health risks associated with the use of selenium are well known and care should be taken in performing the reactions. A selection of substrates which were investigated is shown in Table 3.

If compound **36** is pyrolyzed the corresponding α,β-unsaturated aldehyde is isolated.[45]

2.5. α-Trimethylsilyl epoxides

α-Trimethylsilyl epoxides were introduced by Stork et al.[46] who showed that epoxidation of a vinylsilane gave an α-trimethylsilyl epoxide. Magnus et al.[48] introduced the formation of α-trimethylsilyl epoxides by chemistry that was closely analogous to the classical Darzens reaction. The mechanism of how α-trimethylsilyl epoxides are transformed into homologated aldehydes has been elucidated by Hudrlik et al.[47] Magnus showed epoxides **39** were rearranged under mild acidic conditions (20% aqueous THF/5–10% $HClO_4$) to give the homologated aldehyde **40**, Scheme 10.



Scheme 10.

Where α-trimethylsilyl epoxides were formed as epimers, the carbon bearing the TMS group the predominant epimer was the one that resulted from having the TMS group in the least sterically encumbered environment. Sterically unhindered aldehydes and ketones posed no problems for formation of the epoxides. Sterically hindered ketones especially nopinone and camphor gave lower yields of the α-trimethylsilyl epoxide. A selection of substrates investigated is shown in Table 4.

When the α-trimethylsilyl epoxide **41**, was rearranged to give homologated aldehyde **42**, a mixture of double bond isomers was obtained in 78% yield. Yamaguchi et al. has used a TES group instead of a TMS group to effect the same rearrangement,[49] Scheme 11. After hydrolysis of **43** with methane sulfonic acid to the aldehyde, the aldehyde was then oxidized with $NaClO_2$ to the corresponding carboxylic acid. No yield was given in the paper, however, for the transformation.

Table 3. Preparation of homologated aldehydes from ketones via α-arylsulfinyl epoxides

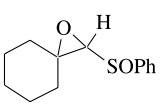
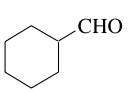
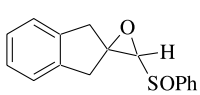
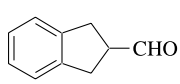
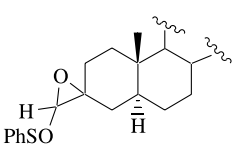
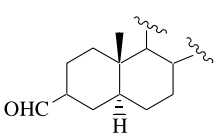
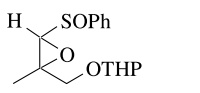
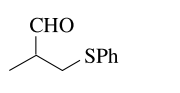
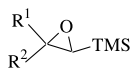
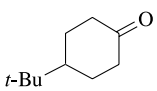
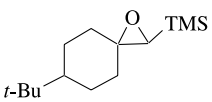
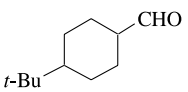
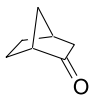
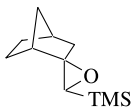
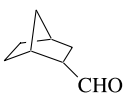
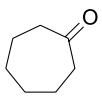
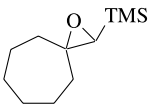
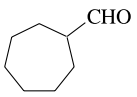
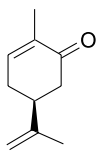
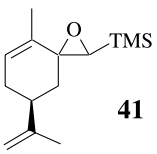
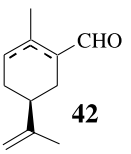
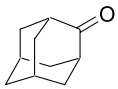
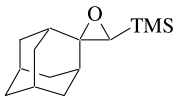
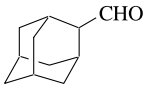
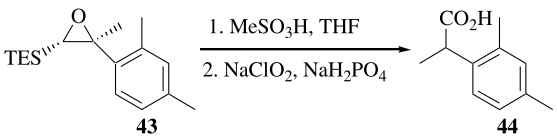
α-Arylsulfinyl epoxide	Homologated aldehyde	Yield (%)	α-Arylsulfinyl epoxide	Homologated aldehyde	Yield (%)
		80			90
		96			75

Table 4. Preparation of homologated aldehydes via α-trimethylsilyl epoxides

Ketone		Yield (%)	Homologated aldehyde	Yield (%)
		88		72
		76		73
		58		98
	 **41**	76	 **42**	78
		95		71

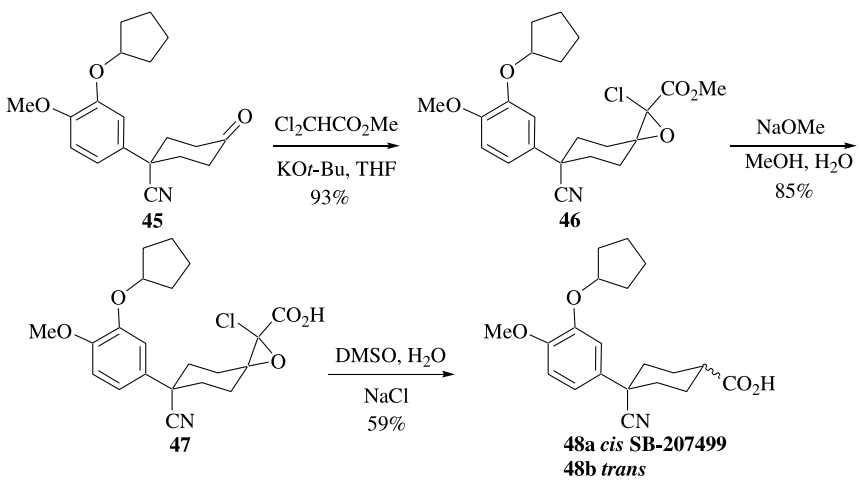


Scheme 11.

2.6. α-Chloro α-ester epoxides

An extension of the methodology in Section 2.3 uses methyldichloroacetate in the Darzens reaction. This was used to prepare SB-207499,[26,50] Scheme 12. Rearrangement of **47** gave the acid directly without the need for further oxidation.

Treatment of ketone **45** with methyl dichloroacetate and potassium *t*-butoxide gave compound **46** as an approximate 3.5:1 ratio of isomers in 93% yield.[51] Hydrolysis of ester **46** then gave the epoxy acid **47** in 85% yield. Treatment of acid **47** under the Krapcho decarboxylation conditions[52] at 150°C in a pressure vessel gave acids **48** (**48a/48b** 1:1) in a crude yield of 59%. A drawback to this method was the use of high temperature and high pressure to effect the transformation. This methodology has also been used to prepare ibuprofen.[53] A variation of this is the rearrangement of the α-cyano α-ester epoxide which can prepared in 2 steps by first forming the α-ester acrylonitrile and then epoxidation.[54]



Scheme 12.

Table 5. Preparation of nitriles from ketones using TosMIC

Ketone	Homologated nitrile	Yield (%)
Adamantanone	2-Cyanoadamantane	93
(+)-Camphor	2-Cyanocamphane	80
t-Butyl methyl ketone	2-Cyano-2,4-dimethyl pentane	70
Estrone 3-methyl ester	17β-Cyano-1,3,5(10)-estratriene-3-ol methyl ester	69
Andostra-1,4-diene-3,17-dione	17-Cyanoandostra-1,4-dien-3-one	47
Di-isopropyl ketone	3-Cyano-2,4-dimethylpentane	65

3. Via nitriles

A variety of methodologies have been developed which are able to transform a ketone into a nitrile thus adding the one carbon. Most methods either use cyanide salts or liquid HCN so care must be taken when performing the chemistry. These nitriles in turn can be hydrolyzed to give the homologated carboxylic acid. There are various methods for the hydrolysis of nitriles to the corresponding carboxylic acid; such methodologies include aqueous HCl,[55] aqueous H_2SO_4,[56] aqueous NaOH,[57] and aqueous $Ba(OH)_2$.[58]

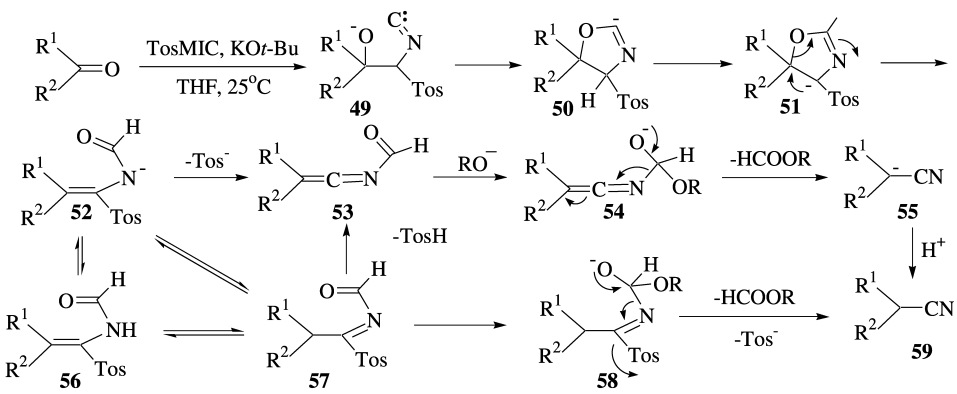
3.1. Unsubstituted nitriles

van Leusen et al. developed a technique of using tosylmethylisocyanide (TosMIC) for the transformation of ketones into nitriles[59] and a selection of substrates is shown in Table 5. The substrates investigated range from simple aliphatic, aromatic and steroidal ketones to sterically hindered ones. The severely hindered carbonyl of di-*t*-butyl ketone did not react, whereas *t*-butyl methyl ketone and di-isopropyl ketone were converted.[60]

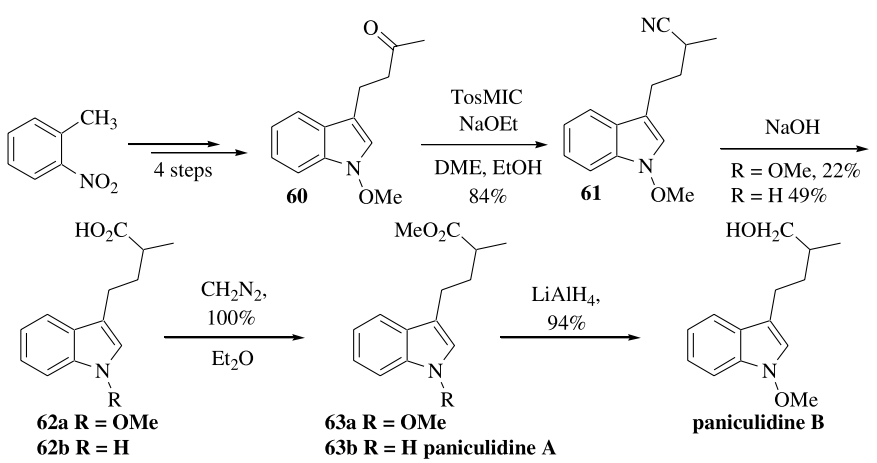
The proposed mechanism of formation of a nitrile from a ketone using TosMIC is shown in Scheme 13.

Somei et al. reported syntheses of paniculidine A and B using TosMIC,[61] Scheme 14. Reaction of **60** gave nitrile **61** in 84% yield. Alkaline hydrolysis of nitrile **61** gave **62a** in 22% yield along with **62b** in 49% yield. Both carboxylic acids (**62a**, **62b**) were methylated quantitatively to yield **63a** and **63b**, paniculidine A. Reduction of ester **63a** yielded paniculidine B in 94%.

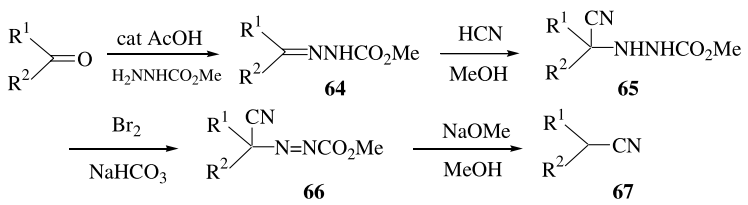
Other publications which have appeared using TosMIC are in the preparation of a spin labeled probe,[62] ketoprofen[63]



Scheme 13.

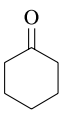
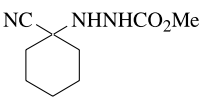
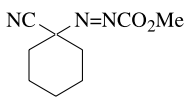
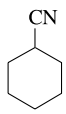
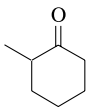
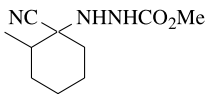
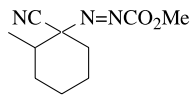
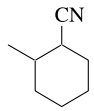
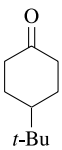
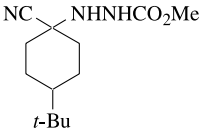
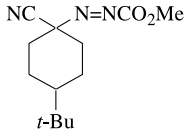
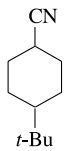
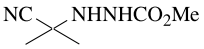


Scheme 14.



Scheme 15.

Table 6. Homologation of ketones to nitriles via methyldialkylcyanodiazene carboxylates

Ketone	Hydrazine	Yield (%)	Diazine	Yield (%)	Homologated nitrile	Yield (%)
		97		95		94
		90		96		n/a
		90		96		96
		98				

and cannabinoid derivatives.[64] A reaction of TosMIC with aldehydes and ketones leading in 2 steps via *N*-(1-tosyl-1-alkenyl)formamides to carboxylic acids has been reported by Schöllkopf et al.[65] (see Section 12) with this reaction later shown to proceed through nitriles.[66] Ziegler et al. describe a method of using methyldialkylcyanodiazene carboxylates as intermediates for transforming aliphatic ketones into nitriles, Scheme 15.[67]

The ketones were first converted to methoxycarbonyl hydrazones **64**, which when reacted with liquid HCN in methanol gave **65**. Bromination and susbequent treatment with catalytic NaOMe gave the corresponding nitriles **67**. Only acetone, cyclo-hexanone and two substituted cyclo-hexanones were reported for this transformation, so it is unknown how general this transformation is Table 6. Chiba et al. expanded on this work showing when acylhydrazones where subjected to electrolytic oxidation in methanol containing NaCN the corresponding nitriles were formed in 1 step.[68] Cacchi et al. reported a procedure using *p*-toluenesulfonyl hydrazone to give compounds similar to **64**.[69] Reese et al. reported the formation of 2,4,6-tri-isopropylbenzenesulfonyl hydrazones of aliphatic and alicyclic ketones.[70] These hydrazones reacted readily with KCN to give the corresponding nitriles. In another method, Kurihara et al. reported the use of diethyl

Table 7. Homologation of ketones via cyanophosphates intermediates

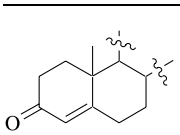
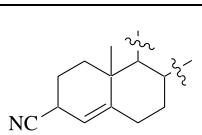
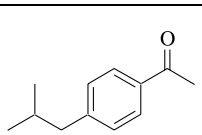
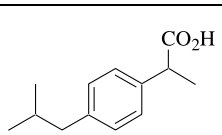
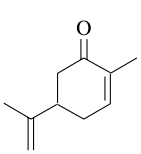
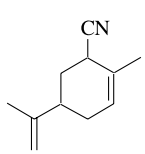
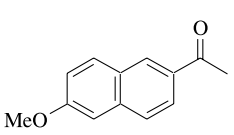
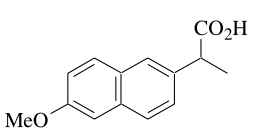
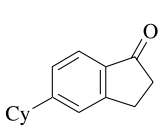
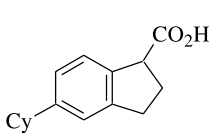
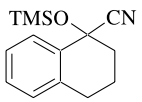
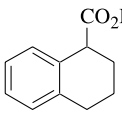
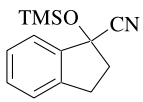
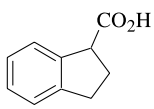
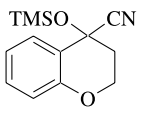
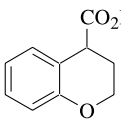
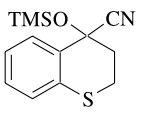
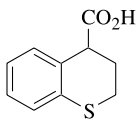
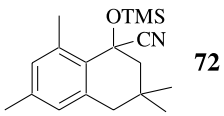
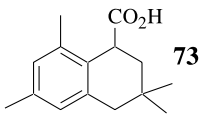
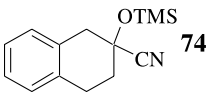
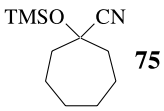
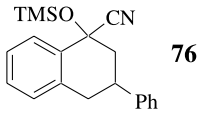
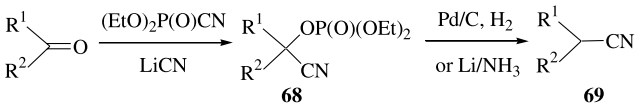
Ketone	Homologated nitrile	Yield (%)	Ketone	Homologated acid	Yield (%)
	 **70**	91			81
	 **71**	89			81
		89			71

Table 8. Preparation of homologated acids from TMS-cyanohydrins

TMS-cyanohydrin	Homologated acid	Yield (%)	TMS-cyanohydrin	Homologated acid	Yield (%)
		68			74
		77			71
 **72**	 **73**	10	 **74**	Complex mixture	
 **75**	Complex mixture		 **76**	Water soluble product	

phosphorocyanidate and LiCN for the transformation of aromatic and α,β-unsaturated carbonyl compounds into nitriles via cyano phosphate intermediates **68**, Scheme 16.[71]



Scheme 16.

Cyano phosphate **68** could be hydrogenated or treated with lithium and ammonia[72] to give nitrile **69**. These nitriles were then hydrolyzed to give the corresponding homologated carboxylic acid, Table 7.

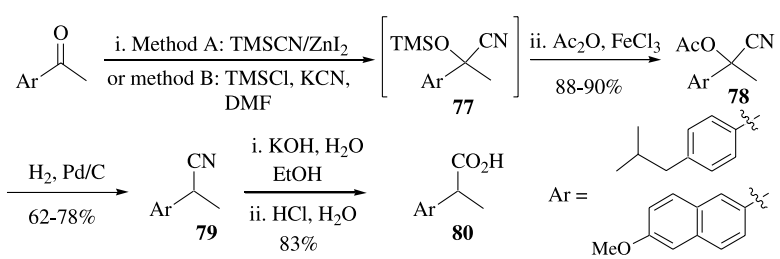
When cyclic enones are used the corresponding unsaturated nitrile **70** and **71** are formed in excellent yield with no isomerization or reduction of the alkene in the Li/NH_3 reduction step. This method however has not been used for aliphatic ketones.

3.2. Via cyanohydrins

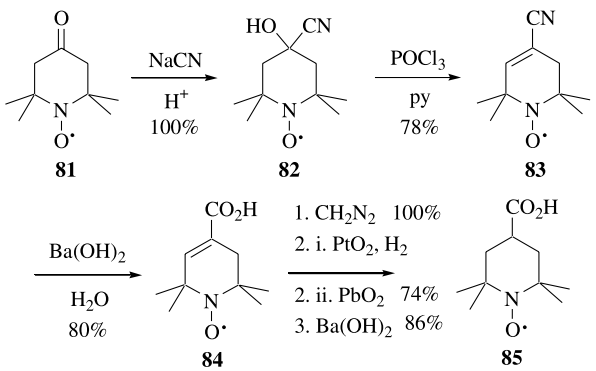
3.2.1. Trimethylsilyl cyanohydrins. TMS-cyanohydrins are easily prepared by treating ketones with TMSCN[73] or TMSCl, KCN[74] to introduce the one carbon unit. The cyanohydrins can then be treated with $SnCl_2$/acid to effect two transformations, reduction of the benzylic oxygen and hydrolysis of the nitrile group to give the desired homologated acid. A variety of substrates investigated are shown in Table 8.[75]

The order of addition of reagents was found to be critical for reducing side product formation (e.g. hydroxy acids)[76] and that the cyanosilyl ether should be treated at room temperature with $SnCl_2$, then acetic acid and finally concentrated HCl followed by vigorous stirring and the rapid application of sufficient heat to bring the heterogeneous mixture to reflux. There were limitations to the method, acid **73** was isolated in only 10% yield from **72** indicating that the reductive hydrolysis was sensitive to steric hindrance. Both cyanohydrins **74** and **75** gave a complex mixture of the corresponding α-hydroxy-acids and unsaturated by-products presumably due to a lack of benzylic stabilization during reduction. A water soluble product from compound **76** resulted in the apparent hydrolysis of the phenyl substituted ether linkage. Hiyama et al. used a similar approach for the preparation of 2-arylpropanoic acids,[77] Scheme 17.

The TMS-cyanohydrins **77** were formed by reaction of a methyl aryl ketone with TMSCN in benzene with ZnI_2 or with TMSCl and KCN in DMF, followed by O-acetylation with Ac_2O in the presence of $FeCl_3$ as catalyst[78] giving the cyanohydrin acetate **78**. Catalytic hydrogenation of **78** gave the corresponding 2-arylpropanenitriles **79** and alkaline



Scheme 17.



Scheme 18.

hydrolysis gave the 2-arylpropanonic acids **80**. Cyanohydrins **77** were converted into their *O*-acetyl derivatives because the cyanohydrins as well as their TMS ethers[75] did not undergo reductive C–O cleavage whereas the acetoxy group did. An alternative method to give **79** was treatment of a TMS-cyanohydrin **77** with TMSCl, NaI in acetonitrile.[79] Other publications using this methodology include preparation of sterically driven anhydrides[80] and methylene bridged benzopyrenes.[81]

3.2.2. Unsubstituted cyanohydrins. Addition of the one carbon unit via cyanohydrins is one of the classical methods for introduction of the one carbon unit. Addition of cyanide to the ketone can occur using sodium[82]/potassium[83] cyanide or diethylaluminum cyanide.[84] Hsai et al. used this methodology to prepare a spin labeled probe,[82] Scheme 18.

Sodium cyanide was added to **81** to give the cyanohydrin **82** in quantitative yield. Dehydration of **82** using $POCl_3$ gives the olefin **83** in 78%. Hydrolysis of the nitrile was achieved using aqueous $Ba(OH)_2$ to give the homologated carboxylic acid **84**. The ester was then formed of the acid, and hydrogenation of the double bond also resulted in the oxygen being hydrogenated to the hydroxyl. Re-oxidation to the radical was achieved with PbO_2 and finally hydrolysis of the ester gave the desired spin probe **85** in 68%. Tabushi et al. has used this strategy to functionalize a bicyclo[3.3.0]-octane,[85] Scheme 19.

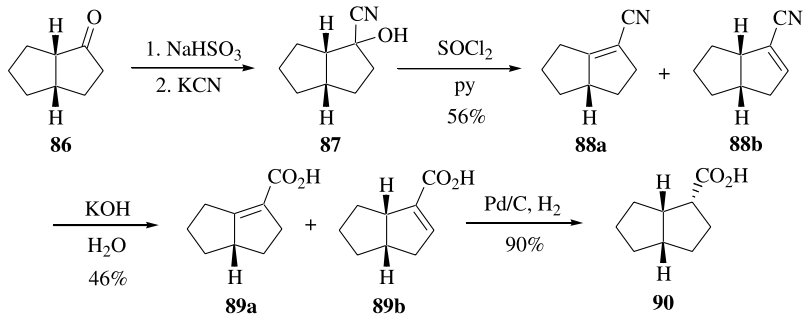
Cyanohydrin **87** was prepared from the sodium bisulfite adduct of **86** with potassium cyanide by Cope's procedure.[83] Dehydration of cyanohydrin **87**[86] produced two products **88a** and **88b** in a 45:55 ratio as determined by NMR or vapor phase chromatography. This mixture was then carried forward to give isomeric carboxylic acids **89a/89b** 44:56, which were both hydrogenated to give quantitatively **90** as a single saturated compound. This approach has also been used in the synthesis of SB-207499[26,87] and for steroids.[88]

4. Via vinyl heteroatoms or halides

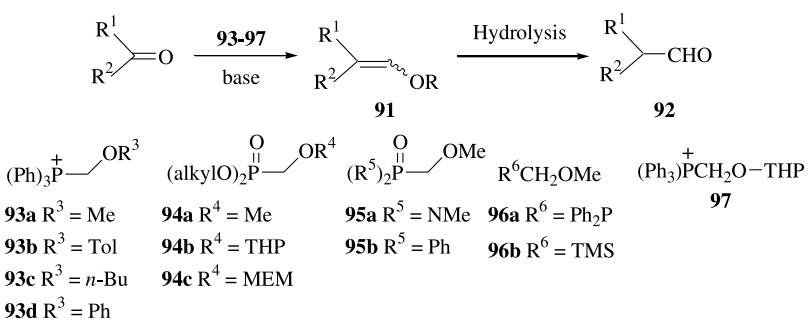
Vinyl heteroatoms or halides are useful moieties in which to introduce the one carbon unit. Hydrolysis or oxidation of these moieties gives the homologated aldehyde or the acid directly.

4.1. Enol ethers

Several reagents have been developed for the transformation of ketones into enol ethers, Scheme 20. Examples include **93a**[89,90] **93b**,[90] **93c**,[91] **93d**,[90,92] **94a**,[93] **94b**,[94] **94c**,[94] **95a**,[93] **95b**,[95] **96a**,[96] **96b**[97] and **97**.[98] Formation of the enol ethers and hydrolysis of them usually occurs in good yield, although there can be some problems. The by-product triphenylphosphine oxide is sometimes difficult to remove,

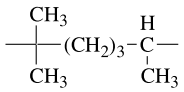
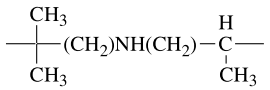


Scheme 19.



Scheme 20.

Table 9. Preparation of homologated aldehydes from ketones via enol ether intermediates

R^1	R^2	OR	Reagent	Enol ether (%)	Homologated aldehyde (%)
Ph	Me	OMEM	**94c**	85	72
	$-(CH_2)_5-$	OTHP	**94b**	88	92
		OMe	**96a**	Not isolated	91
		OMe	**93a**	84	79
	$-(CH_2)_5-$	OMe	**96b**	85	90
Et	Et	OTol	**93b**	72	79

lower yields with hindered ketones and side reactions can occur with enolizable aldehydes and ketones. Hydrolysis of the OR group of the enol ether can also prove difficult in the presence of other sensitive functional groups. To address some of these issues reagents **94b**, **94c** and **97** were introduced to allow for mild hydrolysis of the enol ether. Reagent **96a**[96] and an in situ preparation of **94a**[99] were shown to react with hindered enolizable ketones to give the enol ethers in good yield.

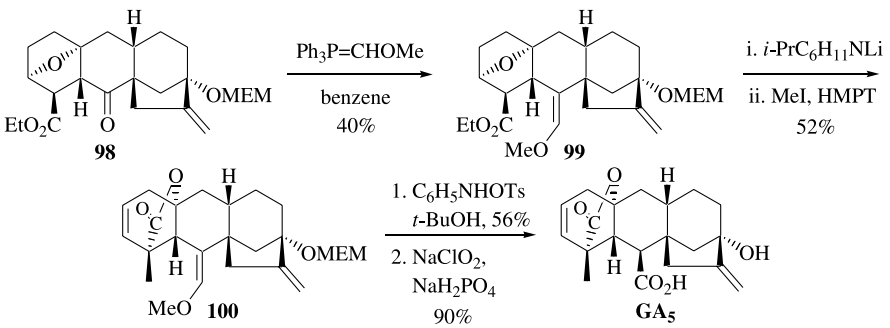
Representative hydrolysis methods of the enol ether **91** to the homologated aldehyde **92** include aqueous $HClO_4$[90,100] *p*TsOH,[101] aqueous HCOOH,[102] TMSI,[103] and aqueous HCl.[104] A selection of substrates investigated is shown in Table 9.

De Clercq et al. used reagent **93a** in the total synthesis of GA_5,[105] Scheme 21. Conversion of **98** to **99** by reaction with $Ph_3P{=}CHOMe$ (**93a**) gave the enol ether **99** in a 90:10 *E*/*Z* ratio in 40% yield along with 50% of a cyclopentanone derivative arising from base induced oxygen bridge opening. Treatment of **99** with lithium isopropylcyclohexylamide followed by addition of methyl iodide resulted in lactone **100** in 52% yield. Acid hydrolysis of **100** to the hydroxyaldehyde (56% yield) followed by sodium chlorite oxidation[8a] (90% yield) gave GA_5.

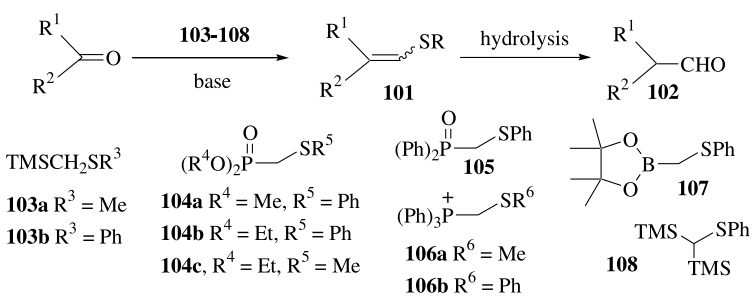
Other strategies where the enol ether has been used as the homologation tool is in preparation of the taxane A and B ring;[106] scaffold for the preparation of pyrethrins;[107] preparation of cyclopropyl precursors;[108] and acetic acid derivatives.[109]

4.2. Thio enol ethers

Thio enol ethers can easily be prepared from the anion of **103a** or **103b**[110,111] **104a**,[112] **104b**,[113] **104c**,[114] **105**,[115] **106a**,[116] **106b**,[117] **107**,[118] and **108**[119] followed by addition of a ketone (or aldehyde) to give the thio enol ether **101**, Scheme 22.

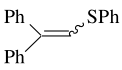
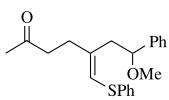
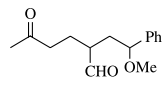
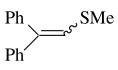
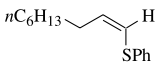
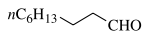
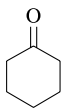
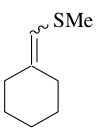
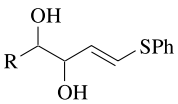
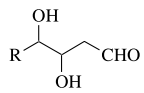


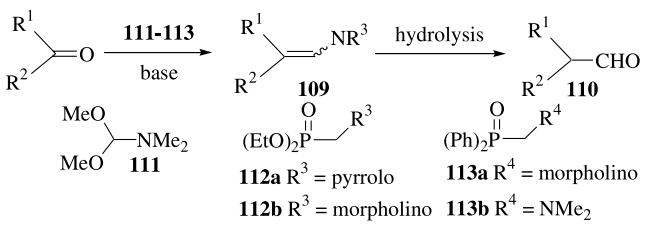
Scheme 21.



Scheme 22.

Table 10. Preparation of homologated aldehydes from thio enol ethers

Ketone	Thio enol ether	Yield (%)	Thio enol ether	Homologated aldehyde	Yield (%)
		83			100
		84			60
		43			50



Scheme 23.

Enolizable ketones can prove problematic with the corresponding vinyl sulfides being isolated in low yield.[120] A number of methods exist for the hydrolysis of **101** with mercury salts,[114b,121] although the hydrolysis can prove problematic and be substrate dependant,[122] Table 10.

Other hydrolysis methods include *p*-TsOH,[123] strong acid,[124] $TiCl_4$[125] and addition of RSH across the double bond to form the *S*,*S*-acetal then hydrolysis.[126]

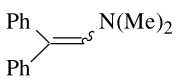
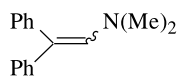
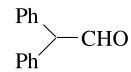
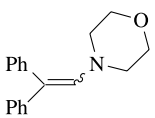
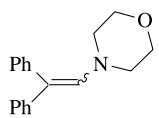
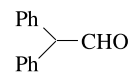
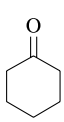
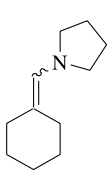
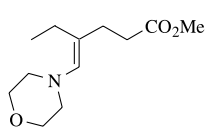
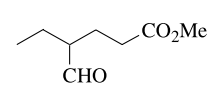
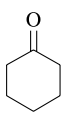
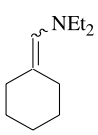
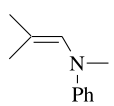
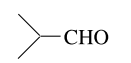
4.3. Enamines

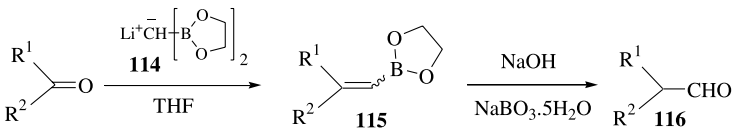
A wide variety of reagents exist for the transformation of carbonyl compounds to enamines in generally good to excellent yield, and the hydrolysis of these enamines is frequently quantitative. Similar problems associated with the formation and hydrolysis of enol ethers may occur with the use of reagents **111**-**113**. Some reagents are limited to aldehydes,[127] but reagents **111**,[128] **112a**,[129] **112b**,[130] **113a**[131] and **113b**[132] react with ketones, Scheme 23. An in situ preparation of reagent **112** with dimethyl(diazomethyl)-phosphonate in the presence of amines (e.g. pyrrole, Et_2NH, *i*-Pr_2NH) also gave good yields of the enamines **109**.[99]

Representative hydrolysis methods of enamine **109** to homologated aldehyde **110** include, aqueous HCl,[133] aqueous AcOH,[134] and aqueous oxalic acid.[135] A selection of substrates that are transformed is shown in Table 11.

Reagents **112a**, **112b** and **113b** have only been used for aromatic ketones, and it is unknown whether they may work

Table 11. Preparation of homologated aldehydes from enamine intermediates

Ketone	Enamine	Yield (%)	Enamine	Homologated aldehyde	Yield (%)
					44, 2 steps
		90			100
		66			45
		70			78



Scheme 24.

Table 12. Homologated of ketones to aldehydes via vinyl boronic acids

Ketone	Homologated aldehyde	Yield (%)
Et_2CO	Et_2CHCHO	74
PhCOMe	PhCH(Me)CHO	80
$Me_2C{=}CHCOMe$	$Me_2C{=}CH(Me)CHO$	81
$EtO_2C(CH_2)_2COMe$	$EtO_2C(CH_2)_2(Me)CHO$	65

for aliphatic ketones. The in situ preparation of **112b** was shown to work with sterically hindered ketones and aliphatic ketones.[99]

4.4. Vinyl boronic esters

Vinyl boronic esters can be prepared from the reaction of lithium bis(ethylenedioxyboryl)methide **114** with ketones or aldehydes.[136] These vinyl boronic esters can then be oxidized to the homologated aldehyde, Scheme 24.[137]

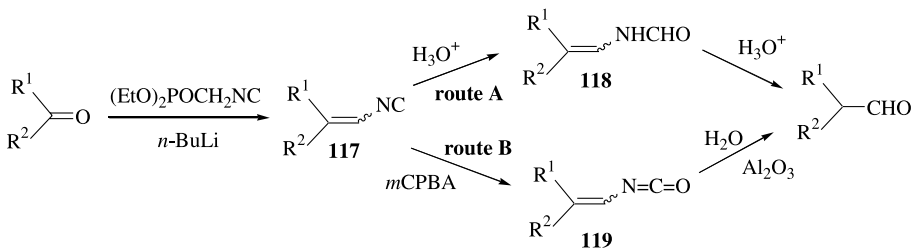
Sodium perborate or buffered hydrogen peroxide were investigated as oxidizing agents for **115** to **116**. Sodium perborate was chosen as the use of hydrogen peroxide may have resulted in aldehyde peroxide by-products which were considered hazardous. A selection of substrates investigated is shown in Table 12.

4.5. Vinyl isocyanides

Schöllkopf et al.[138] showed that ketones and aldehydes reacted via a Wittig–Horner–Emmons reaction using diethyl (isocyanomethyl)phosphonate to give α,β-unsaturated isocyanides **117**. van Leusen et al.[139] showed these can then either hydrolyzed under acidic conditions (route A) or hydrolyzed after oxidation to α,β-unsaturated isocyanate (route B) to give the homologated aldehyde, Scheme 25.

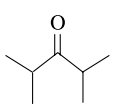
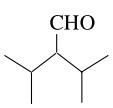
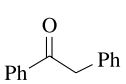
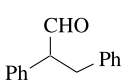
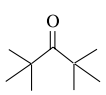
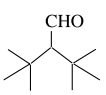
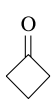
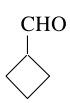
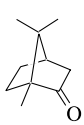
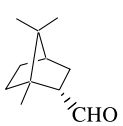
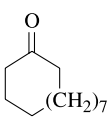
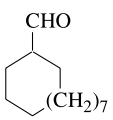
van Leusen's paper describes 20 examples with the yields being good to excellent. A selection of substrates which van Leusen investigated is shown in Table 13.

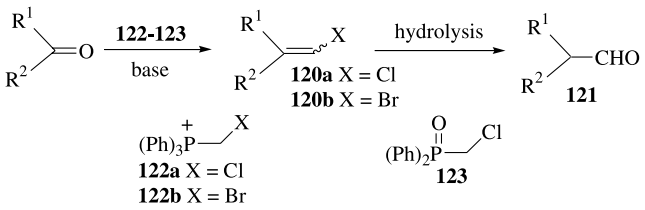
The reactions were found to be clean and intermediates **117**, **118** and **119** need not be isolated. The method has a wide scope and was shown to work on sterically hindered ketones, a strained ketone, large-ring ketone, enolizable ketone an aliphatic aldehyde and an unsaturated aldehyde. Acid-sensitive substrates have also been used and in those cases, route B was the method of choice, since the hydrolysis was essentially achieved under neutral conditions. The hydrolysis in route B was achieved when the entire reaction mixture was passed slowly through a short column of alumina. Care was to be taken with the column to



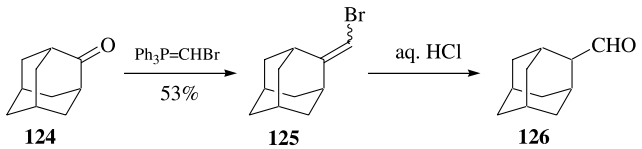
Scheme 25.

Table 13. Homologated aldehydes via Wittig–Horner–Emmons olefination of ketones

Ketone	Homologated aldehyde	Route A yield (%)	Route B yield (%)	Ketone	Homologated aldehyde	Route A yield (%)	Route B yield (%)
		89	90			81	
		54	48			91	
		97	86			98	89



Scheme 26.



Scheme 27.

stop it from cracking due to the gas evolved during hydrolysis.

4.6. Vinyl halides

Ketones and aldehydes may be transformed into vinyl halides by the use of base and reagents **122a**,[116a,140] **122b**,[141,142] and **123**.[116b] These vinyl halides can then be transformed into homologated aldehydes by hydrolysis, Scheme 26.

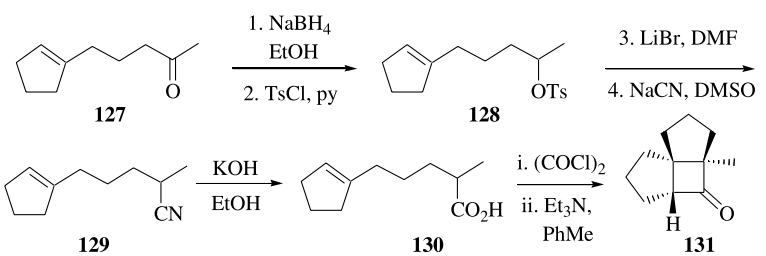
There are limited methods for the hydrolysis of vinyl halides,[143] with most being harsh and not general, leaving this method with limited scope. Sasaki et al. prepared adamantane-2-carbaldehyde **126** from ketone **124** with reagent **122b**, Scheme 27.[142] However, no yield was given for the hydrolysis in the paper.

5. Via alcohols

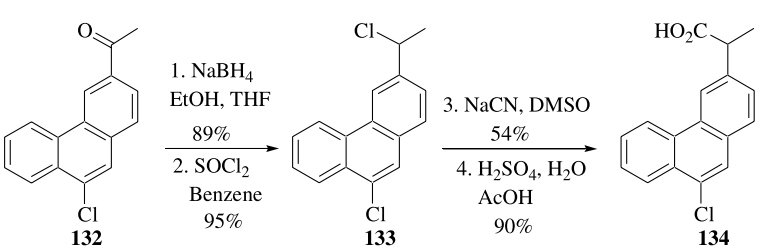
There are several methods by which the initial alcohol is formed such as by reduction or hydrogenation of the ketone. This alcohol in turn can be transformed into a variety of groups for further reaction to introduce the one carbon unit. Yadav et al. tosylated the alcohol and displaced it with cyanide to introduce the one carbon in the preparation of angularly fused triquinane systems,[144] Scheme 28.

Ketone **127** was reduced to the alcohol, and activated as the tosylate **128**. Displacement of the tosylate with LiBr gave the bromide which was displaced by sodium cyanide to give nitrile **129**. Basic hydrolysis of the nitrile gave the desired homologated acid **130**. The overall yield of **130** from **127** was 44%. The acid chloride was obtained from **130** and oxalyl chloride and was immediately reacted with Et_3N in toluene at reflux to give 1-methyl tricyclo[5.3.0.$0^{3,7}$]decan-2-one **131** in 45% yield. Fernandez et al. also used this strategy to synthesis phenanthrylalkanoic acid **134**,[145] Scheme 29. The ketone was reduced to alcohol **133**, transformation to the chloride **133** in 85% over 2 steps and subsequent displacement with sodium cyanide in DMSO gave the nitrile, which was hydrolyzed to give the homologated acid **134** in 49% over 2 steps.

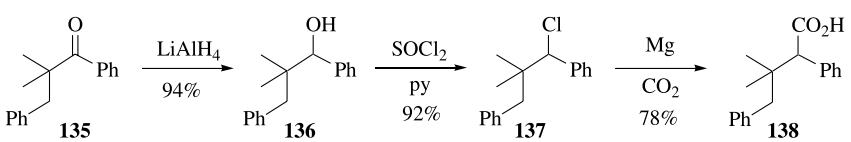
Attempted transformation of ketone **132** into the nitrile directly using TosMIC resulted in only 3% nitrile and 50% of the starting material was recovered in pure form. This methodology has also been used in the preparation of 2-[4-(2-thiazolyloxy)phenyl]propionitrile and analogs,[146] 4-(α-alkyl-α-cyanomethyl)-2,6-disubstituted phenols[147] and NSAIDs.[148] A variation of this methodology involves after the halide is formed, formation of the Grignard and



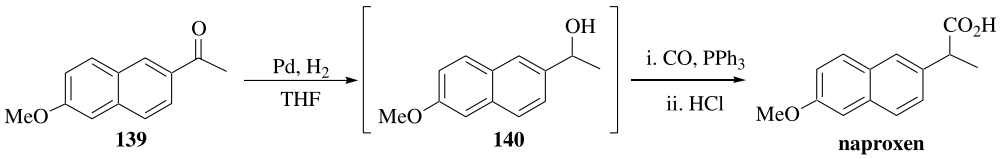
Scheme 28.



Scheme 29.



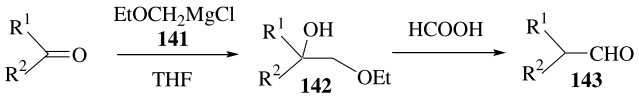
Scheme 30.



Scheme 31.

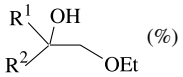
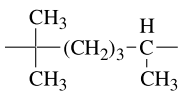
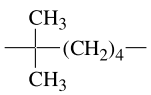
then reaction with CO_2 to introduce the carboxylic acid,[149] Scheme 30.

Reduction of the hindered ketone **135** with $LiAlH_4$ gave alcohol **136** in 94% yield. The alcohol was turned into chloride **137**, which was activated as a Grignard and quenched with CO_2 to give the homologated acid **138** in 78% yield. Maryanoff et al. also reported a similar sequence in the preparation of intermediates in the synthesis of hexahydropyrrolo[2,1-*a*]iso- quinolines.[150] Hiyama et al. reported a sequence where the alcohol was acetylated and then reacted with TosMIC to give the nitrile.[151] The homologated carboxylic acid can also be prepared in 1 step from the ketone by the use of palladium, with a 2 step transformation, one pot sequence. Xie et al. used this to prepare naproxen in 1 step from ketone **139**,[152] Scheme 31.



Scheme 32.

Table 14. Synthesis of homologated aldehydes via α-metallated ethers

R^1	R^2	 (%)	Homologated aldehyde (%)
Me	Me	70	75
Ph	Me	55	88
	$-(CH_2)_4-$	77	76
	$-(CH_2)_5-$	76	75
	$-(CH_2)_6-$	92	77
	$-(CH_2)_7-$	75	81
	$-(CH_2)_{11}-$	94	85
		65	85
		65	75

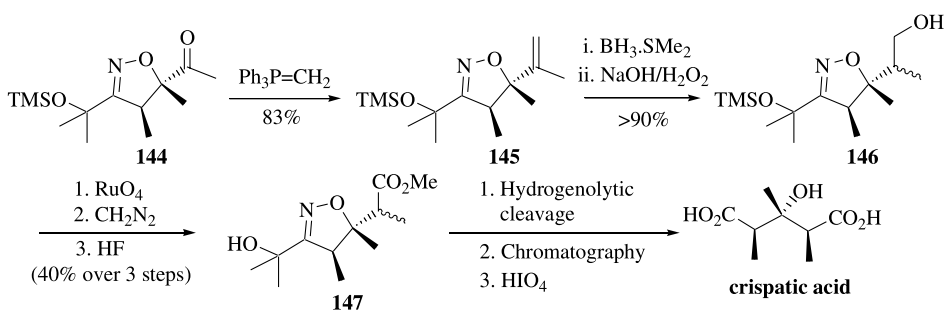
Initially the alcohol was formed by hydrogenation which was then carbonylated to give the homologated acid.

Ketone **139** was reduced with H_2 in the presence of 5–10% Pd/C in THF at 50°C to give in situ alcohol **140**. Triphenylphosphine was then added and addition of CO in THF/HCl at 100–150°C and a CO pressure of 6–10 MPa initially gave the acyl palladium species, which was hydrolyzed by HCl in situ to give naproxen in one step and 90% yield. Seayad et al. used a catalyst system of $PdCl_2(PPh_3)_2$/TsOH/HCl to effect the same transformation in the preparation of ibuprofen.[153] Reaction rates with TOF up to 1200 h^{-1} and ibuprofen selectivity of 95% were achieved at 388 K under a CO partial pressure of 5.4 MPa. An alternative general procedure to homologate ketones into carboxylic acids uses α-metalated ethers, Scheme 32.[154,155]

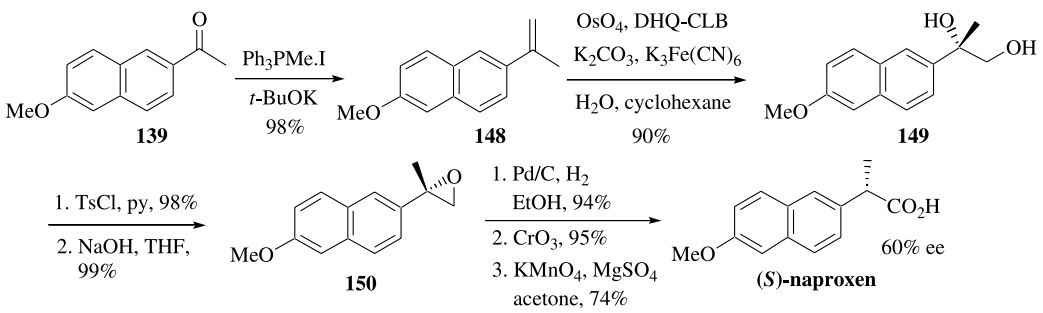
The sequence involves the reaction of Grignard **141** with aldehydes or ketones to give 2-ethoxy alcohols **142**. These alcohols **142** in turn were transformed into the homologated aldehydes **143** by heating with formic acid. A selection of substrates investigated by this method are shown in Table 14.

6. Via olefins

There are several general strategies for formation of the olefin from the ketone, with a variety of strategies then existing to transform the double bond into the homologated carboxylic acid. Such reagents to form the double bond include Wittig reagents;[156] Horner reagents;[157] Wadsworth–Emmons reagents[158] and Peterson reagents.[110] For example the double bond can be hydroborated and the alcohol oxidized to give the homologated acid. There are various methods for the transformation of a primary alcohol into a carboxylic acid, such methods include CrO_3/acid,[159] $KMnO_4$,[160] NaOCl,[161] and RuO_4 or its equivalents.[162] Curran et al. added the one carbon unit using a Wittig/hydroboration/oxidation sequence in the preparation of



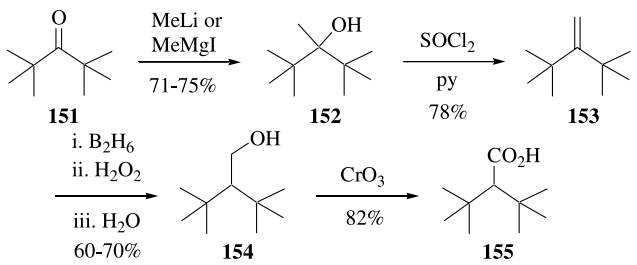
Scheme 33.



Scheme 34.

an intermediate in the synthesis of crispatic acid,[163] Scheme 33.

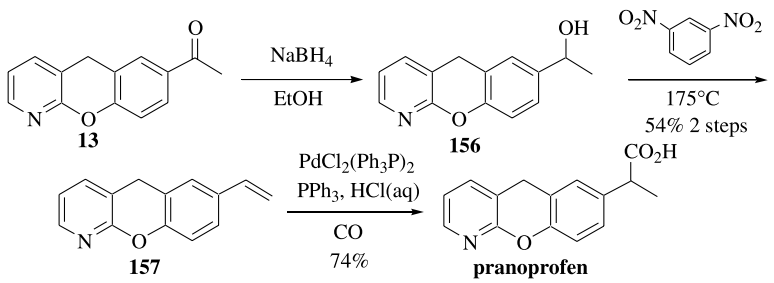
Using a standard Wittig reaction, **145** was produced in 83% yield. Hydroboration of **145** with $BH_3{\cdot}SMe_2$[164] gave a 1:1 mixture of diasterioisomers in >90% yield. Oxidation of alcohol **146** using RuO_4, subsequent ester formation and silyl removal gave **147** in 40% over 3 steps. In three additional steps crispatic acid was produced. Zhao et al.



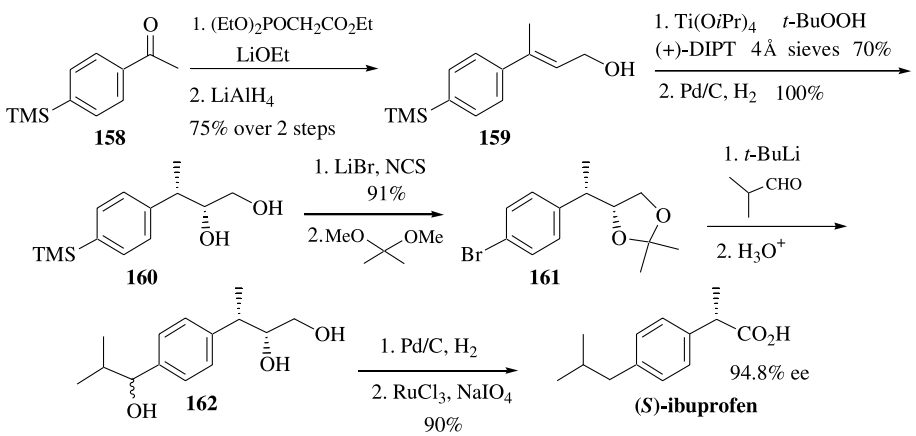
Scheme 35.

published an asymmetric method for the preparation of (*S*)-ibuprofen and (*S*)-naproxen[165] where the stereochemistry was established by a combination of Sharpless asymmetric dihydroxylation[166,167] and catalytic hydrogenation of the chiral terminal epoxide,[168] Scheme 34. Wittig reaction on ketone **139** gave isoprene **148** in 98% yield, which was dihydroxylated[169] to diol **149** in 78% ee as measured by Mosher's monoester.[170] Activation of the primary hydroxyl as a tosylate and then closure to the epoxide gave **150** in 97% over 2 steps. Hydrogenation of the epoxide with 10% Pd/C resulted in inversion of the stereochemistry at the benzylic position, with partial racemization. Subsequent oxidation gave the aldehyde in 95% yield and further oxidation with $KMnO_4$ gave (*S*)-naproxen in 60% ee. (*S*)-Ibuprofen was also synthesized in 60% ee by this method.

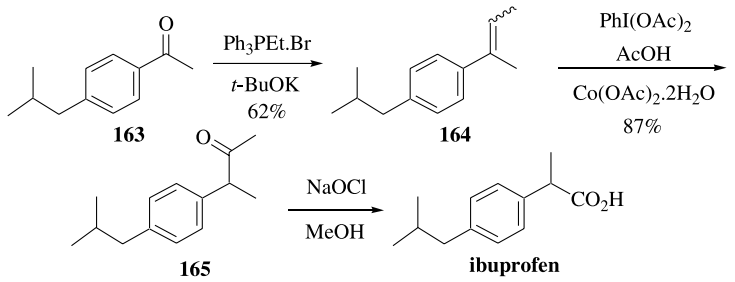
Other publications using the olefination/hydroboration strategy are in the preparation of α,β-disubstituted β-amino acids[171] And Fridamycin E.[172] Newman et al.[173] and others[174] have reported addition of MeLi to ketones



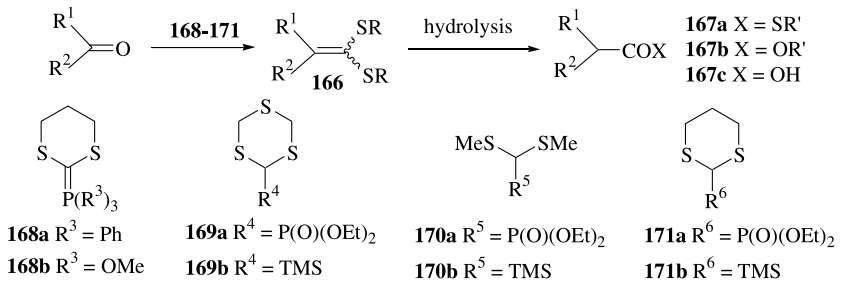
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

then elimination to give the double bond, Scheme 35. Methyl lithium of Grignard was added to ketone **151** to give **152** in 71–75% yield. Alcohol **152** was then dehydrated to give olefin **154** in 78% yield. Hydroboration and oxidation gave the homologated carboxylic acid **155**.

Schaumann et al. extended this to include cyclic hindered ketones for homologation to the carboxylic acid.[175] Mitsubishi Petrochemicals[176] used a similar sequence for the olefin preparation to prepare pranoprofen in 2 steps from ketone **13**, Scheme 36.

Ketone **13** was reduced with $NaBH_4$ and the alcohol eliminated to give styrene **157** in 54% yield over 2 steps. Palladium carbonylation of the styrene[177] gave pranoprofen in 74% yield. Alper et al. have performed an asymmetric carbonylation on a substituted styrene in their preparation of ibuprofen and naproxen.[178]

Hamon et al.[179] prepared (*S*)-ibuprofen and (*S*)-ketoprofen by initially doing a Wittig reaction, to give an α,β-unsaturated ester, Scheme 37.

Reaction of ketone **161** with triethylphosphonoacetate gave mainly the thermodynamically more stable (*E*)-isomer (*E*/*Z* 17:1). Reduction of the mixture of esters with $LiAlH_4$ yielded allylic alcohols **159** which were subjected to the Sharpless epoxidation, giving the epoxide in 70% yield and >98% optical purity after one crystallization. Hydrogenolysis of the epoxy alcohol with 10% Pd/C at −60°C went quantitatively with inversion of configuration to yield diol **160**. Electrophilic substitution of the TMS group and protection of the diol as the acetonide gave **161**. Lithium exchange of the bromide with *t*-BuLi and reaction with 2-methylpropanal, then removal of the protecting group under acidic conditions gave triol **162**. Hydrogenolysis gave the diol, which was cleaved with ruthenium trichloride and sodium periodate to give (*S*)-ibuprofen in 90% yield. Analysis of the derived amide (thionyl chloride, (*S*)-phenylethylamine) by HPLC, compared with diastereomers as standards showed the synthetic ibuprofen to have an optical purity of 96.4%. Shimizu et al. used a different methodology after the Wittig reaction to introduce the carboxylic acid, Scheme 38.[180]

A Wittig reaction with $Ph_3PEt{\cdot}Br$ and *t*-BuOK with ketone **163** gave olefin **164** in 62% yield as a mixture of geometric isomers. Addition of $PhI(OAc)_2$ and $Co(OAc)_2{\cdot}2H_2O$ in AcOH gave ketone **165** in 87% yield at 99% conversion. Oxidation of **165** with aqueous NaOCl transformed the ketone to ibuprofen.

7. Via acetals/ketals

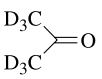
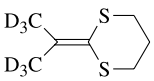
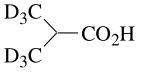
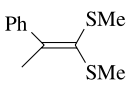
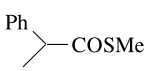
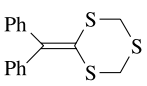
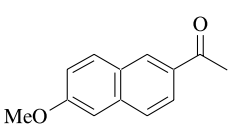
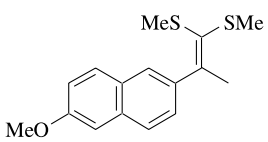
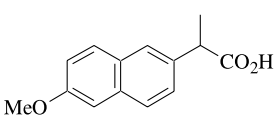
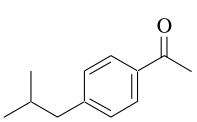
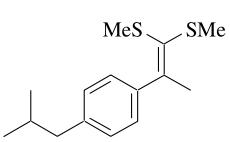
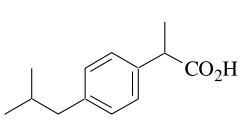
A variety of acetals/ketals have been used to introduce the one carbon unit containing either oxygen, nitrogen or sulfur or a mixture of both. These are versatile intermediates which may be transformed by reduction/hydrolysis to aldehydes, or derivatives of carboxylic acids.

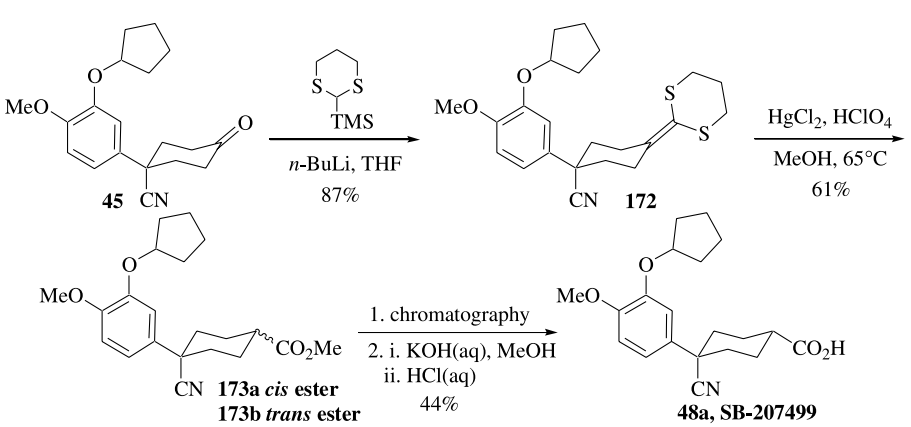
7.1. Ketene *S*,*S*-acetals

The most widely employed methods for the synthesis of ketene *S*,*S*-acetals involve Wittig, or Wittig–Horner reactions of the phosphorus reagents **168a**,[181] **168b**,[182] **169a**,[181,183] **170a**,[183] **171a**[181,183] with carbonyl compounds, Scheme 39.

Alternatively the use of **169b**,[184] **170b**[184,185] and **171b**[186] produces the ketene *S*,*S*-acetals by a variant of the Peterson olefination. Although the reaction of **168a** and **168b** appears to be limited to aldehydes, the more nucleophilic metallated reagent **169a**, **169b**, **170b** and **171** reacted with both aldehydes and ketones giving good to excellent yields of the ketene *S*,*S*-acetal **166**. Similar problems associated with the formation and hydrolysis of enol ethers may occur with the use of reagents **168**-**171**. Depending on the

Table 15. Homologation of ketones using ketene *S*,*S*-acetals as intermediates

Ketone	Ketene *S*,*S*-acetal	Yield (%)	Homologated product	Yield (%)
		88		44
				88
		72		
		78		70
		80		74

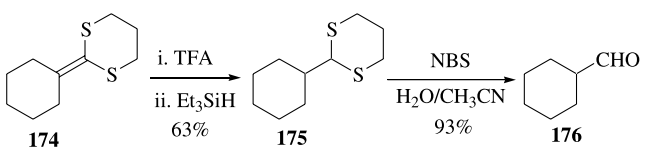


Scheme 40.

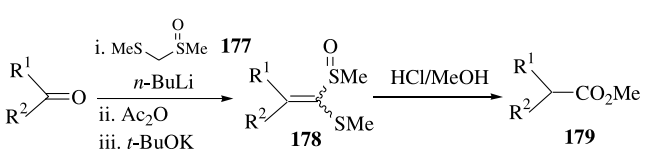
hydrolysis conditions used either the thioester,[185,187] ester[188] or carboxylic acid[189] can be isolated, Table 15.

Christensen et al. used reagent **171b** in the synthesis of SB-207499,[26,190] Scheme 40. Ketone **45** was reacted with the lithium anion of **171b** to give ketene *S*,*S*-acetal **172** in 87% yield. Mercury (II) chloride mediated methanolysis of **172** provided an approximately 11:1 mixture of *cis* and *trans* esters **173** which were separated by flash chromatography. Saponification of ester **173a** with potassium hydroxide gave acid **48a**, SB-207499 in 44% yield.

Alternative hydrolysis methods have been introduced to eliminate the toxicity of mercury salts and risk of using perchloric acid.[191] Copper (II) salts and silica gel or copper (II) sulfate in methanol[192] have been used to give the corresponding homologated esters. Strong acids (glacial AcOH, HCl) have been used to hydrolyze ketene *S*,*S*-acetals to the acids directly,[189b] as well as TFA followed by CaOCl (or hydrogen peroxide) treatment in the preparation of SB-207499.[193] Ketene *S*,*S*-acetals can also be transformed into aldehydes in a 2 step sequence, as shown in the example of the ketene *S*,*S*-acetal of cyclohexanone, Scheme 41.[185a]

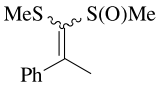
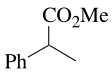
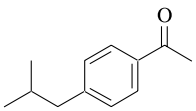
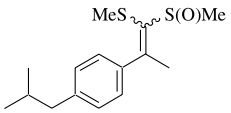
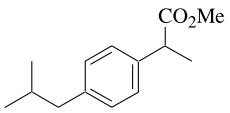
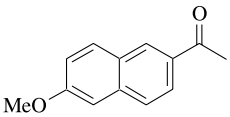
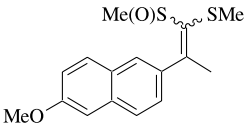
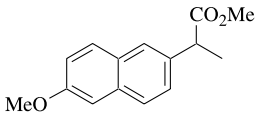
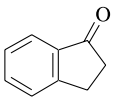
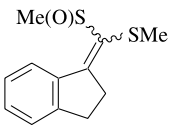
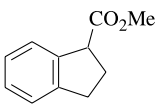
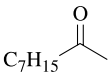
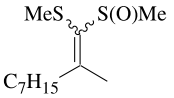
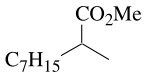


Scheme 41.



Scheme 42.

Table 16. Homologation of ketones using ketene *S*,*S*-acetal mono-oxides

Ketone	Ketene *S*,*S*-acetal mono-oxide	Yield (%)	Homologated ester	Yield (%)
		69		69
		73		92
		67		56
		59		43
		59		44

The double bond was first reduced by a combination of TFA and Et_3SiH. Bromination and hydrolysis then gave homologated aldehyde **176** in 93% yield.

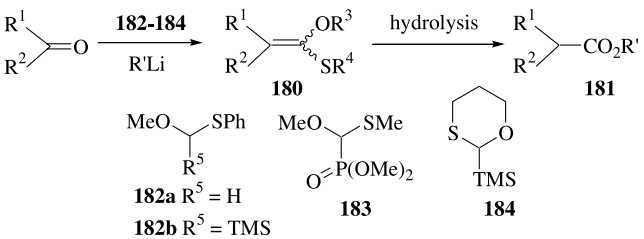
7.2. Ketene *S*,*S*-acetal mono-oxides

Ogura et al. showed ketene *S*,*S*-acetal mono-oxides intermediates could effect the one carbon transformation,[194] Scheme 42. The ketene *S*,*S*-acetal mono-oxides had to be formed as a 3 step sequence.

Using the original process on ketones which worked for aldehydes in the presence of Triton B, product **178** was not obtained.[195] This was thought to be due to enolization and/or fast self-condensation of the starting material in the presence of Triton B. A solution to this problem was after addition of the anion of **177** to the ketone, the resulting tertiary hydroxyl was acylated and then eliminated in the presence of *t*-BuOK to give **178**. Compound **178** can also be prepared from the ketene *S*,*S* acetal by oxidation[196] The ketene *S*,*S* mono-oxides can be hydrolyzed to **179** using methanolic aqueous HCl. A variety of substrates were investigated, and this sequence was shown to work with both aliphatic and aromatic ketones, Table 16.

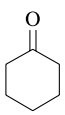
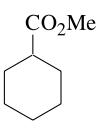
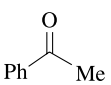
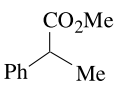
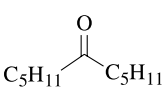
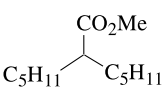
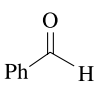
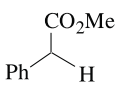
7.3. Ketene *O*,*S*-acetals

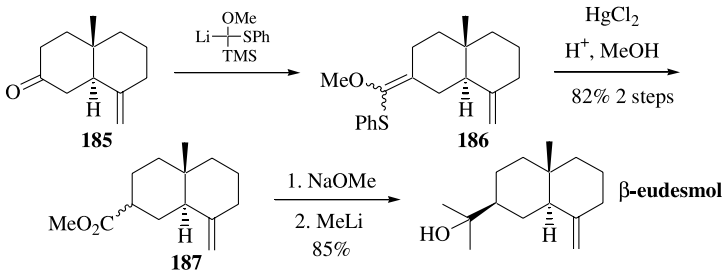
There are various methods for the conversion of carbonyl compounds into ketene *O*,*S*-acetals **180**. These can then be hydrolyzed to the homologated esters,[197] Scheme 43. Reagents **182a**,[198] **182b**,[197,199] **183**[183b] and **184**[200] have been used to effect the transformation of a ketone or aldehyde to a ketene *O*,*S*-acetal.



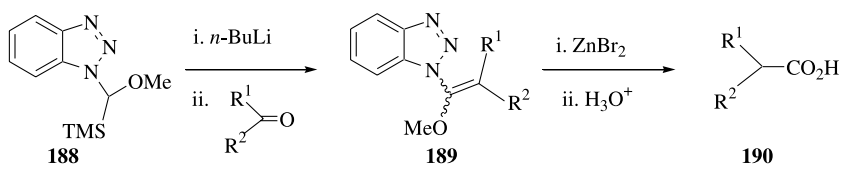
Scheme 43.

Table 17. Preparation of homologated esters from ketones and aldehydes

Ketone	Homologated ester	Yield (%)	Ketone/aldehyde	Homologated ester	Yield (%)
		88			91
		92			89

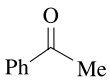
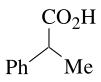
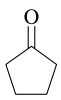
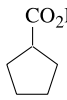
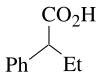
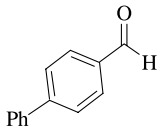
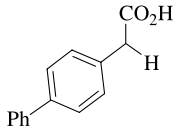
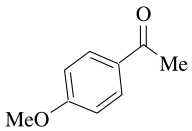
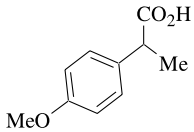
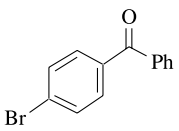
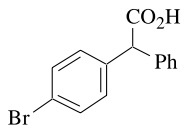


Scheme 44.



Scheme 45.

Table 18. Homologation of ketones to carboxylic acids using ketene *N*,*O*-acetals intermediates

Ketone	Homologated acid	Yield (%)	Ketone/aldehyde	Homologated acid	Yield (%)
		28			55
		55			45
		53			43

Hydrolysis of the ketene *O*,*S*-acetals occurs with the use of $HgCl_2$ and conc. HCl in MeOH,[197] to give the homologated methyl ester. The mechanism of hydrolysis of the ketene *O*,*S*-acetal has been investigated by Schmir et al. using aqueous HCl and aqueous $HClO_4$.[201] A selection of substrates investigated by this procedure using **182b** is shown in Table 17.

de Groot et al. has used this methodology to prepare β-eudesmol, Scheme 44.[197a] Lithiated reagent **182b** was added to ketone **185** to give ketene *O*,*S*-acetals **186**, which was immediately hydrolyzed to give the homologated ester **187** in 82% yield over 2 steps. Methanolysis at reflux of **187** caused isomerization of the exo-methylene double bond into the ring. Equilibration of the esters **187** with NaOMe, followed by addition of MeLi gave β-eudesmol in 85% yield.

Livinghouse et al. has reported procedures for the hydrolysis of ketene *O*,*S*-acetals to the homologated thio ester. These are either using TMSCl, NaI in dry acetonitrile,[199a] and subsequent filtration of the reaction mixture through alumina,[202] or addition of MeSLi to give the thio ester.[203] Representative thio ester hydrolysis methods include aqueous KOH[204] aqueous NaOH,[205] and $LiOH/H_2O_2$.[206]

7.4. Ketene *N*,*O*-acetals

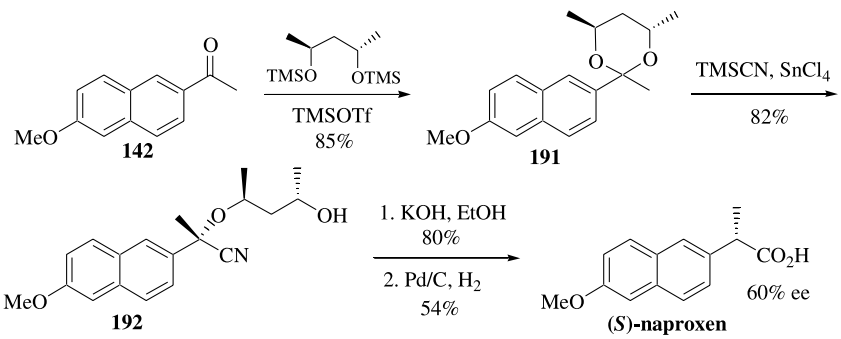
Katritzky et al. reported a method which used trimethylsilyl(methoxy)benzotriazol-1-ylmethane[207] as the Peterson type precursor to give ketene *N*,*O*-acetals, **189**, Scheme 45.[208] These were then hydrolyzed to give the homologated acid **190**.

Lithiation of **188**[207] gave a deep blue solution of the anion which underwent a Peterson olefination with aldehydes and ketones to give **189**. The crude product was then treated with $ZnBr_2$ in the presence of HCl(aq) to provide the corresponding one-carbon homologated acid **190**. The range of substrates varies from aliphatic to aromatic and is shown in Table 18.

7.5. *O*,*O*-Ketals

Sugai et al. reported the formation of aldehyde *O*,*O*-acetals and their conversion into homologated esters.[209] Hiyama et al. used this idea, with the use of a chiral *O*,*O*-ketal to introduce chirality into the homologation sequence,[210] Scheme 46.

Ketone **142**[211] was converted into the chiral *O*,*O*-ketal **191**



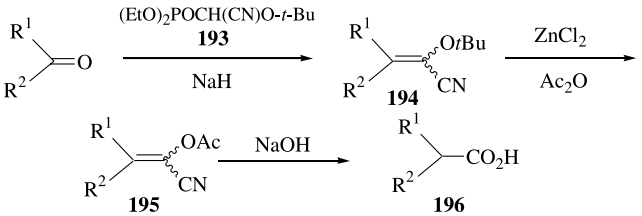
Scheme 46.

by the reaction of (*S*,*S*)-2,4-bis(trimethylsiloxy)pentane in the presence of TMSOTf[212] (84–85% ee diol). TMSCN was then added in the presence of $SnCl_4$ to give a 74% de mixture of nitrile **192** in 89% yield. Alkaline hydrolysis and subsequent hydrogenation gave (*S*)-naproxen in 43% over the 2 steps. The optical purity of the acid was estimated at 60% ee, with the hydrogenation proceeding in inversion of stereochemistry.[213]

8. Via acrylonitriles

8.1. α-*tert*-Butoxyacrylonitriles

Phosphonate **193**[214,215] has been employed as an operational equivalent of a carboxyl anion in a Horner–Emmons modification of the Wittig reaction[216] After formation of **194**, transformation into α-acetoxyacrylonitriles **195** and subsequent hydrolysis affords the homologated carboxylic acid. This method appears to be fairly general, however, acid labile groups, such as acetals do not survive to conditions for the transformation of **195** into **196**, Scheme 47.



Scheme 47.

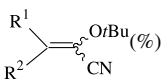
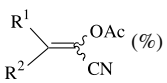
The hydrolysis of the *tert*-butoxy group in **194** proved difficult under a variety of acid conditions. On transforming **194** into **195** by reaction with $ZnCl_2$ in acetic anhydride, the α-acetoxy group was found to be more easily hydrolyzed to give the homologated acid. The steric bulk of diethyl *tert*-butoxy(cyano)methylphosphonate limited the reaction to those ketones which possessed three or more α-hydrogen's. A variety of substrates were found to be transformed in good yield, Table 19. In some cases the α-acetoxyacrylonitrile need not be isolated but taken directly into the hydrolysis stage. Care again must be taken as cyanide is liberated during the hydrolysis. Not only can the phosphonate **193** be used to prepare carboxylic acids, but treatment of the intermediate α-acetoxyacryonitrile **195** with alkoxides or amines, gave esters or amides respectively.[217]

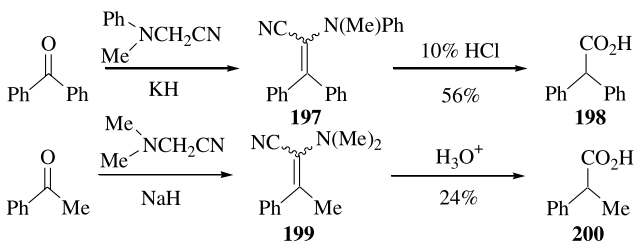
8.2. α-Aminoacrylonitriles

A method for the homologation of aldehydes,[218] acetophenone[218c] and benzophenone[218a] uses α-aminoacrylonitriles[219] to achieve the one carbon transformation. The α-cyano enamine synthon is known to be synthetically equivalent to an acyl cyanide in which the carbonyl group is masked as an enamine.[220] The transformation for each ketone is shown in Scheme 48.

Benzophenone and acetophenone were reacted with the α-aminonitriles to give the α-aminoacrylonitriles **197** and **199**, respectively. Hydrolysis of these gave the homologated carboxylic acids **198** and **200** in 56 and 24%, respectively. No other ketones have been reported for this transformation and it is unknown how general this strategy would be for other substrates.

Table 19. Homologation of ketones to carboxylic acids via α-*tert*-butoxyacrylonitriles

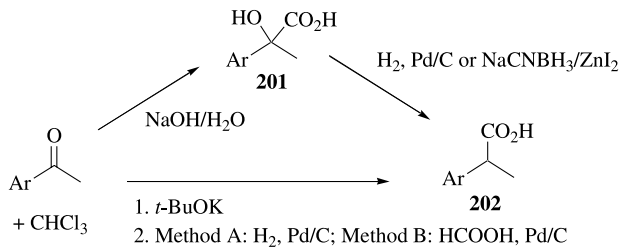
Ketone				Homologated acid (%)
R^1	R^2			
CH_2CH_2Ph	CH_2CH_2Ph	84	90	99
CH_3	Ph	93	94	96
Ph	Ph	86	95	100
$-(CH_2)_5-$		88	88	95
2-Methylcyclohexanone		78	90	92
Cholest-4-en-3-one		86	80	79
Methyl levulinate		74	89	84
5α-Androstane-3,17-dione		92	Not isolated	55



Scheme 48.

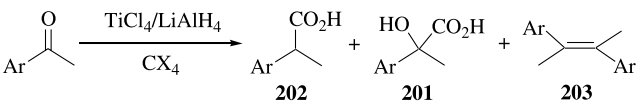
9. Via α-hydroxy acids

This methodology has been developed for aryl methyl ketones and involves two main strategies. The first is addition of dihalocarbenes generated by a base,[221] or low valent titanium.[222] The second is electrolysis of the ketone in the presence of carbon dioxide. Sinisterra et al. developed[221] the addition of dihalocarbenes to aryl ketones using base, Scheme 49.



Scheme 49.

The dihalocarbene was prepared by the addition of base to $CHCl_3$ which when added to the ketone gave hydroxy acid **201** The hydroxy acid was reduced with sodium cyanoborohydride/zinc iodide for a 2 step process or directly by a one pot method by addition of Pd/C using hydrogen or an hydrogen donor such as formic acid to give the acid **202** directly. A selection of substrates investigated is shown in Table 20.



Scheme 50.

The yields are moderate, 35–60% for the one pot procedure. For the low valent titanium procedure,[223] the ratio of $TiCl_4$ to $LiAlH_4$ was found to be critical. Depending on the molar ratio between the two reagents, various products could be formed, Scheme 50.

An excess of $LiAlH_4$ favored the synthesis of the carboxylic acid **202** directly. The optimum conditions were 1/2.5 to 1/3 for $TiCl_4/LiAlH_4$. This was explained that an excess of $LiAlH_4$ decreased the generation of the titanium complex that favored the reductive coupling of the ketone to give **203**, and the hydrogenolysis of the intermediate 2-hydroxy acid **201**. The yields for this procedure are higher 60–78% than the base generated carbene procedure. Another method in which to give the hydroxy acid is by electrochemistry. The ketone is subject to electrolytic reduction and then addition of CO_2 gives the hydroxy acid. Palladium hydrogenation gave the desired homologated carboxylic acid.[224,225] Wang et al. has used this to prepare naproxen in 2 steps from ketone **139** in 85% yield, Scheme 51.[224] Ibuprofen has also been prepared this way.[225]

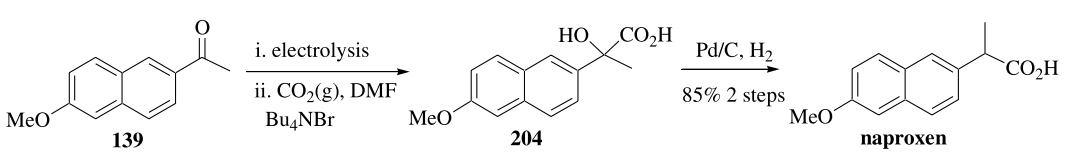
10. Via homologation/alkylation

There are various methods for the homologation of alkyl aryl ketones to introduce the one carbon unit. One strategy consists of treatment of the substrate with $AgNO_3$, $CH(OMe)_3$ and I_2,[226] then alkylation. De Brabander et al. asymmetrically prepared (*S*)-ibuprofen by the $AgNO_3$ method, Scheme 52.[227] Ketone **163** was oxidatively rearranged (I_2, $AgNO_3$, $CH(OMe)_3$) to give the methyl ester **205** in 98% yield. Acylation of (1*S*)-2,10-bornanesultam with ester **205** using Weinreb conditions[228] gave **206** in 79% yield. Deprotonation of **206** resulted in selective formation of the *Z*-(*O*)-lithium enolate which was alkylated at −60°C with MeI. Product **207** was obtained in 83% yield and >95% de. Finally H_2O_2 cleavage gave (*S*)-ibuprofen in 89% yield and 95% ee with recovery of the bornanesultam auxiliary in 95% yield.

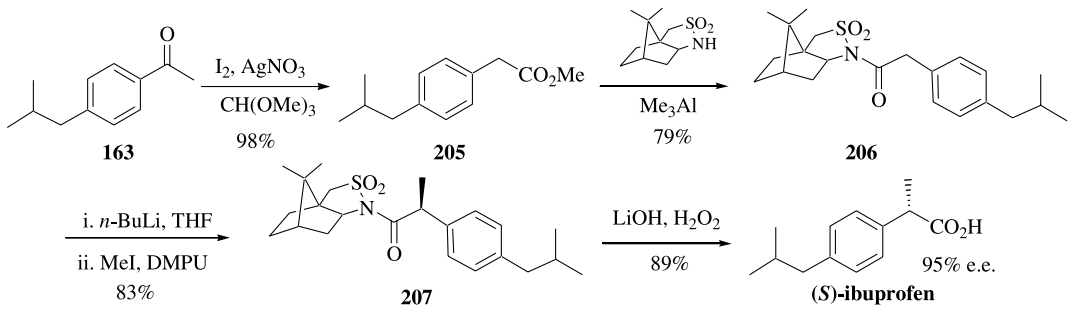
Another variation is the use of $Tl(NO_3)_3$ absorbed onto Montmorillonite K-10 clay[229] to give the homologated ester, which can then be alkylated. Hagmann et al. used this to prepare 11*H*-dibenzo[*b*,*e*][1,4]dioxepinacetic acids,[230] Scheme 53.

Table 20. Preparation of aryl carboxylic acids from aryl ketones via in situ α-hydroxy acids

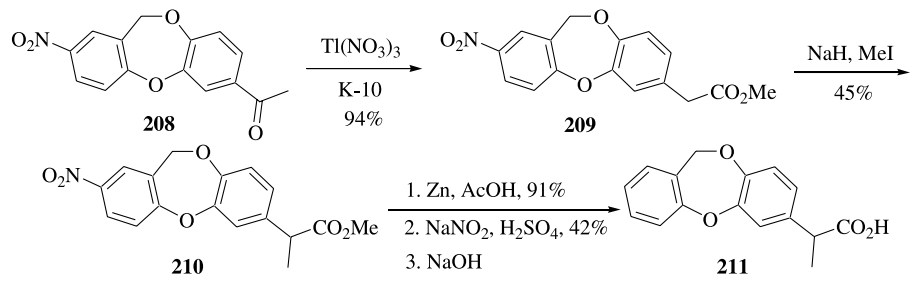
Ar	Method A yield (%)	Method B yield (%)	Ar	Method A yield (%)	Method B yield (%)
C_6H_5	55	60	*p*-$MeOC_6H_4$	45	50
p-Me–C_6H_4	40	45	*p*-ClC_6H_4	35	45
p-*iso*-$C_3H_7C_6H_4$	40	45	6-MeO-2-napthyl	40	45
p-*iso*-$C_4H_9C_6H_4$	40	40	α-Thienyl	35	45



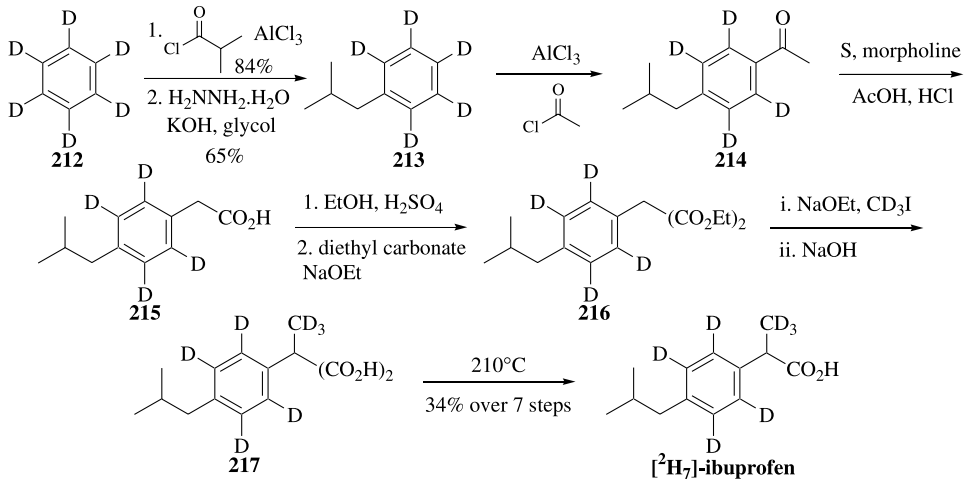
Scheme 51.



Scheme 52.



Scheme 53.

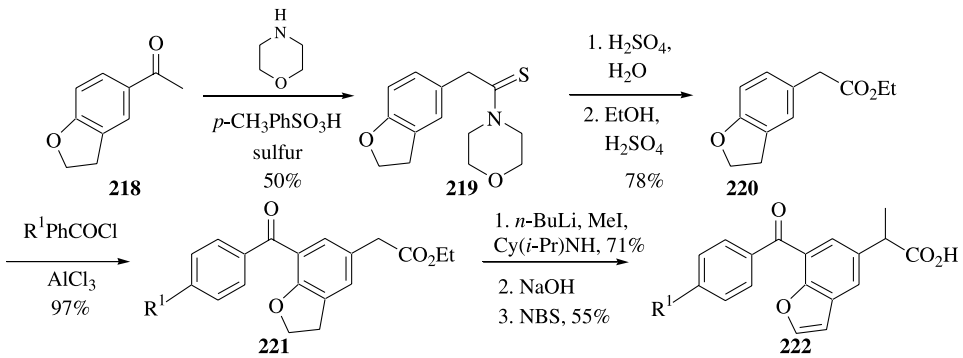


Scheme 54.

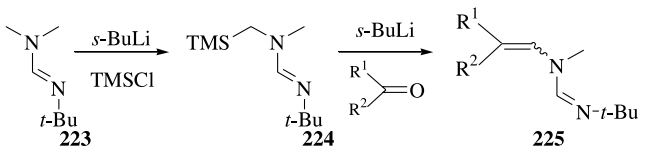
Treatment of ketone **208** with $Tl(NO_3)_3$ on K-10 clay gave ester **209** in 94% yield. Alkylation of **209** with MeI gave **210** in 45% yield. Removal of the nitro group and ester hydrolysis gave the α-methyl acetic acid **211**. This methodology has also been used to prepare (isobutylphenyl)-acetic and propionic acid.[231] Another method is the Willgerodt–Kindler reaction[232] where the ketone is treated with sulfur and a dry primary or secondary amine to give a thioamide which can be hydrolyzed to the acid. Halstead et al. described the preparation of $[^2H_4]$-ibuprofen and $[^2H_7]$-ibuprofen[233] by this method, Scheme 54.

[Ar-$^2H_5$]-isobutyrophenone **213** was prepared by Friedel–Crafts acylation of benzene-d_6 **212** in 84% yield. Reduction of **213** via the Huang–Minlon modification[234] of the Wolff–Kishner reduction yielded [Ar-$^2H_5$]-isobutylbenzene **213** in 65% yield. Friedel–Crafts acylation of **213** gave acetophenone **214** which was converted to the phenyl acetic acid **215** via the Willgerodt–Kindler reaction and hydrolysis of the resulting thiomorpholide. Compound **215** was esterified and on heating with diethyl carbonate and NaOEt gave malonic ester **216**. Deprotonation of **216** and alkylation with either $[^2H_3]$–CH_3I or CH_3I followed by hydrolysis gave **217** or its $[^2H_4]$-analog. Decarboxylation of **217** at 210°C gave $[^2H_7]$-ibuprofen in about 20% overall yield. Dunn et al.[235] used the Willgerodt–Kindler reaction to introduce the one carbon unit in the preparation of analgesic and anti-inflammatory 7-aroylbenzofuran-5-yl-acetic acids **222**, Scheme 55.

For the Willgerodt–Kindler reaction, morpholine was used as the amine to give the thioamide **219** in 50% yield. Subsequent hydrolysis and esterification gave the ethyl ester **220** in 78% yield, which underwent a Friedel–Crafts



Scheme 55.



Scheme 56.

acylation to give **221** in 97% yield. Alkylation of ester **221**, hydrolysis and oxidation with NBS gave the benzofurans **222**. This methodology has also been used to prepare 2-(4-alkylphenyl)propionic acids,[236] and 4-cyclohexylphenyl acetic acids.[237]

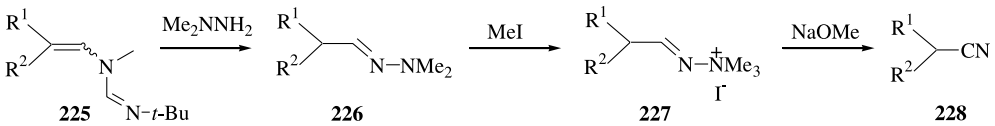
11. Via enamidines

Meyers et al. developed chemistry on the use of enamidines in synthesis.[238] Enamidines were found to react to give either homologated nitriles or aldehydes depending on the reaction conditions used. The general scheme for the preparation of enamidines is shown in Scheme 56.

Enamidines were prepared by metalation/silylation of **223**[239] to give **224**,[240] which are metalated again and treated with various ketones (or aldehydes) to give enamidines **225** as a mixture of geometric isomers. It was found that addition of 2.0 equiv. HMPA prior to addition of enolizable carbonyl compounds to the anion of **224** gave good yields of the Peterson product **225**. In one study, enamidines **225** were shown to give homologated nitriles, Scheme 57.[241]

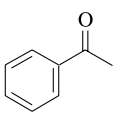
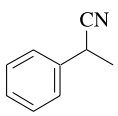
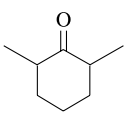
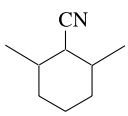
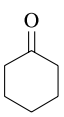
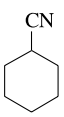
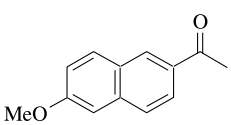
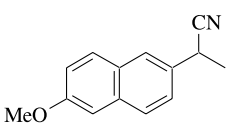
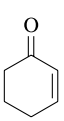
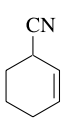
For the preparation of nitriles, enamidines **225** were exchanged to the hydrazone **226** with by *N*,*N*-dimethylhydrazine. These hydrazones **226** were treated with MeI to give the salt **227** and subjected to NaOMe elimination to give nitriles **228** in good yield. A variety of ketones, from aromatic to aliphatic to enones were examined, Table 21.

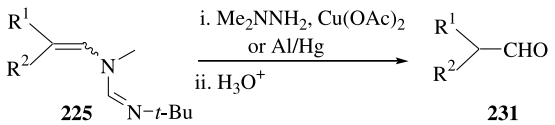
Compound **229** gave nitrile **230** in 66% yield. If TosMIC was used for the same transformation, the corresponding pyrrole was formed.[60] By altering the reaction conditions of compound **225**, homologated aldehydes could be isolated. Enamidine **225** when treated with *N*,*N*-dimethylhydrazine and $Cu(OAc)_2$[242,243] or aluminum amalgam reduction[244] then aqueous acid hydrolysis gave the corresponding aldehydes **231**, Scheme 58.



Scheme 57.

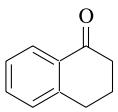
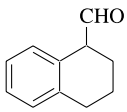
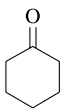
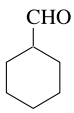
Table 21. Homologation of ketones to nitriles via enamidines

Ketone	Homologated nitrile	Yield (%)	Ketone	Homologated nitrile	Yield (%)
		82			85
		89			65
 **229**	 **230**	66			



Scheme 58.

Table 22. Homologation of ketones to aldehydes via enamidines

Ketone	Homologated aldehyde	Yield (%)
		60[a]
		84[b]
		62[a]

[a] Precursor enamidine **225** was cleaved by hydrazinolysis with 1,1-dimethylhydrazine followed by acid hydrolysis of methiodides obtained from the intermediate hydrazones.
[b] Enamidine was cleaved to diphenylacetaldehyde by using aluminum amalgam in moist ether, giving the corresponding *N*-methyl enamine, which was cleaved with aqueous acid.

Table 22 shows several examples of this method which was shown to work on ketones.

12. Via 1-formylamino-1-arylsulfonyl alkenes

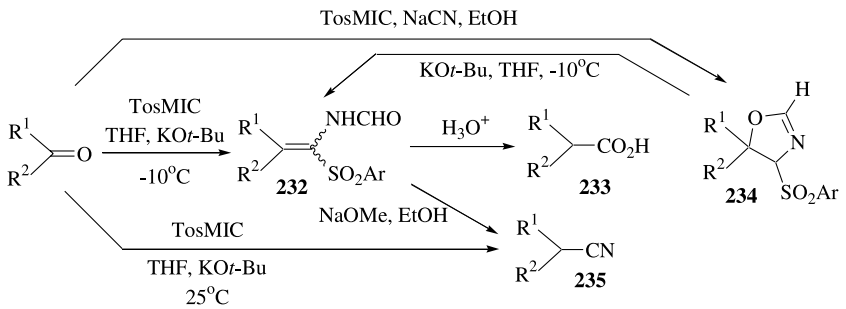
Schöllkopf showed that 1-formylamino-1-arylsulfonyl alkenes were formed when α-metalated isocyanomethylaryl sulfones (e.g. TosMIC) were allowed to react with ketones or aldehydes at −10°C,[65,245] Scheme 59. This is in contrast to van Leusen's results where when the temperature of the reaction was ambient, the homologated nitrile **235** was formed. The 1-formylamino-1-arylsulfonyl alkenes **232** were then converted into carboxylic acids on heating with dilute acid.

Heating the ketone in ethanol with TosMIC in the presence of NaCN as the basic catalyst, 4-arylsulfonyl-2-oxazolines **234** were isolated.[246] Treatment of these compounds with potassium *tert*-butoxide at −10°C gave the 1-formylamino-1-aryl-sulfonyl alkenes **232**. This 2 step approach to compound **232** was sometimes superior to the one step direct method.[245] Heating **232** with NaOMe in ethanol gave the corresponding homologated nitrile **235**.[66] The range of substrates which Schöllkopf reported is shown in Table 23.

13. Miscellaneous

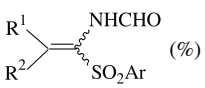
Liebeskind et al. used acetylene to introduce the one carbon unit for homologation of a ketone into a carboxylic acid,[247] Scheme 60, with the reaction sequence being amenable to the sensitive β-lactam ring.

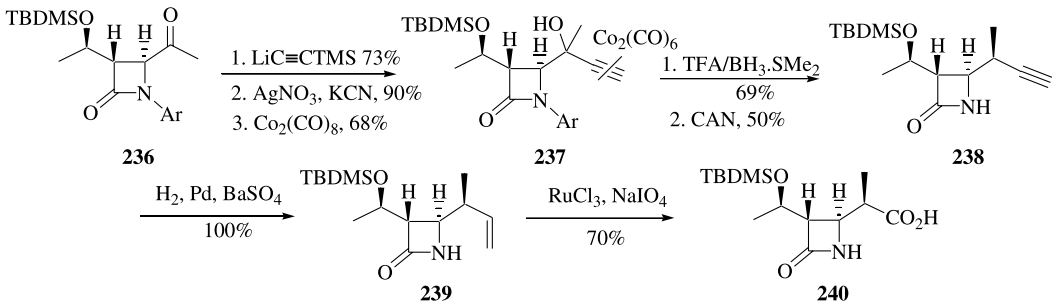
Addition of TMSC≡CLi to **236** gave a 1:1 mixture of alcohols in 73% yield. Desilylation was accomplished with $AgNO_3$/KCN[248] in 90% yield and complexation with $Co_2(CO)_8$ gave **237** in 68% yield. Reduction of the complexed propargyl alcohol was achieved using the Maryanoff modification (BH_3·SMe_2/TFA)[249] of the Nicholas reaction.[250] Simultaneous deprotection of the β-lactam nitrogen and decomplexation of the alkyne using ceric ammonium nitrate gave **238** in 50% yield. Lindlar reduction of the alkyne gave **239** in quantitative yield and oxidative cleavage gave the homologated acid **240** in 70% yield.



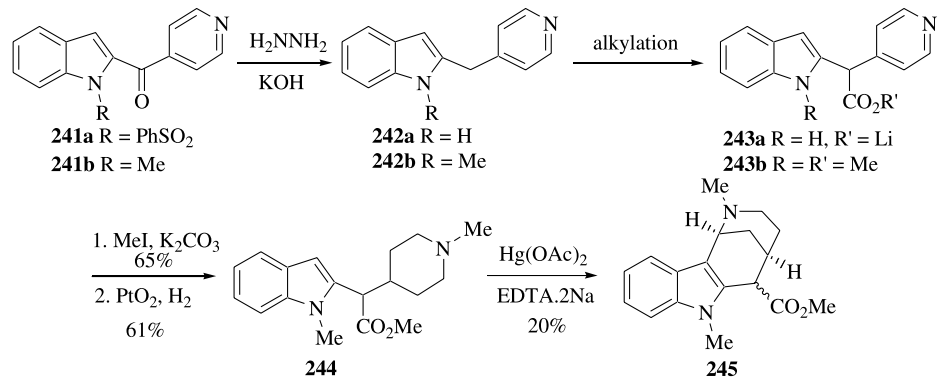
Scheme 59.

Table 23. Homologated acid from ketones/aldehydes via 1-formylamino-1-arylsulfonyl alkenes

R^1	R^2	Ar	 (%)	Homologated acid (%)
C_6H_5	H	C_6H_5	72	65
C_6H_5	CH_3	*p*-CH_3–C_6H_4	42	
α-Napthyl	CH_3	*p*-CH_3–C_6H_4	50	
–$(CH_2)_5$–		*p*-CH_3–C_6H_4	61	85
CH_3	CH_3	*p*-CH_3–C_6H_4	83	62
C_6H_5–CH=CH	H	*p*-CH_3–C_6H_4	73	67



Scheme 60.



Scheme 61.

Hiyama et al. has also used an acetylene to introduce the one carbon unit in the preparation of naproxen.[251] Bosch et al.[252] prepared intermediates in the preparation of the *Strychnos* ring system using a Wolff–Kishner reduction of a ketone and then alkylation, Scheme 61.

Wolff–Kishner reduction of **241a** gave **242a**, with concomitant loss of the $PhSO_2$ group in 64% yield. Compound **242a** was then alkylated using *n*-BuLi and CO_2 to give **243a** in 49% yield. However, without a protecting group on nitrogen it proved difficult to further functionalize. By using the methyl protecting group on nitrogen, compound **242b** was alkylated using KH and dimethyl carbonate to give methyl ester **243b** in 40% yield. With a further 3 steps, **243b** was transformed into the Strychnos ring system **245** in 7.5% yield over the 3 steps.

14. Conclusion

A wide variety of methodologies have been developed to homologate a ketone (or aldehyde) into a carboxylic acid, and which constitute a valuable class of synthetic reactions. These methodologies involve intermediates such as aldehydes, epoxides, nitriles and vinyl heteroatoms, with the synthetic sequences ranging from a single step to multiple transformations. A wide variety of substrates have been transformed both aliphatic, alkenyl and aromatic ketones some of them asymmetrically to give the desired products. Although there are multiple methods and reagents available for this transformation, chemists will still aspire to develop more efficient, practical and broader solutions to overcome some of the limitations with current methodologies.

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Biographical sketch

Neil Badham was born in Paignton, Devon, United Kingdom. He received his BS in Chemistry with Oceanography from the University of Southampton in 1990 and in 1993 obtained his PhD under the supervision of Professor P. J. Parsons from the University of Reading. Subsequently he worked with Professor P. A. Wender at Stanford University (1994–1996) as a postdoctoral fellow. He then joined SmithKline Beecham, UK as an investigator in the Process Research and Development department (1996–1998). He then moved to SmithKline Beecham in King of Prussia, US in the Synthetic Chemistry department (1998–2002). He is currently a senior scientist at Rhodia Pharma Solutions. His current interests are developing practical synthetic processes for scale-up.

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Synthesis of difluoromethyl substituted lysophosphatidic acid analogues

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Abstract—Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) displays an intriguing cell biology that is mediated via interactions both with G-protein coupled seven transmembrane receptors and with nuclear hormone receptor PPARγ. We describe a new and efficient route to enantiomerically homogeneous lysophospholipid analogues from (*S*)-1,2,4-butanetriol to give two 3-difluoromethyl substituted analogues of 2-acyl-*sn*-glycerol 3-phosphate. These compounds are migration-blocked analogues of the liable *sn*-2 LPA species. Preliminary studies were conducted on a nuclear reporter assay in which monocytic cells were transfected with a luciferase construct activated by a PPARγ nuclear receptor response element and have shown that the 3-difluoromethyl substituted analogues are fully active as natural LPA.

1. Introduction

Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) is a naturally occurring phospholipid that shows a variety of biological activities on a wide spectrum of cell types.[1,2] LPA binds and activates four G protein-coupled receptors (GPCRs): LPA_1, LPA_2, LPA_3 and LPA_4 receptors (formerly Edg-2, Edg-4, Edg-7 and an orphan GPCR, p2y9/GPR23).[3,4] LPA plays a critical role as a general growth, survival and pro-angiogenic factor, in the regulation of physiological and pathophysiological processes in vivo and in vitro. Abnormalities in LPA metabolism and function in ovarian cancer patients may contribute to the initiation and progression of the disease.[5] Thus, LPA receptors constitute a potential target for cancer therapy.

LPA receptors exhibit characteristic responses to LPA species with different chain lengths, different instauration patterns, and different acyl positions. The tumor promoter ovarian cancer-activating factor is *sn*-2 LPA rather than the more common *sn*-1 LPA isomer.[6] *sn*-2 LPA activates LPA_2 and LPA_3 receptors,[7] but studies of positional specificity are confounded by a chemical equilibrium favoring the *sn*-1 isomer by almost 6-fold. To circumvent this intramolecular rearrangement, we synthesized *sn*-2 LPA analogues where one hydroxyl group was transformed in the isosteric difluoromethyl moiety to provide LPA analogues that could not undergo acyl migration or further acylation. In addition to GPCR receptors, LPA was recently shown to be an agonist of the nuclear transcription factor PPARγ.[8] PPARγ has long been implicated in atherogenesis.[9,10] PPAR are lipid-activated transcription factors of the nuclear receptor super family that heterodimerize with the retinoic acid X receptor (RXR). PPAR/RXR heterodimers bind to specific peroxisome proliferator response elements (PPRE) to regulate gene expression.[11] Many compounds activate PPARγ, including the anti-diabetes drug rosiglitazone, oxidized phospholipids, fatty acids, eicosanoids, and oxidized LDL. PPARγ is expressed in macrophages and monocytes, vascular smooth muscle cells, endothelial cells, and is highly expressed in atherosclerotic lesions and hypertensive vascular wall.[10,12]

The isosteric substitution of essential hydroxyl groups by fluorine has been a mainstay of analogue design when metabolic stability is desired.[13,14] It is particularly favored as a substitute when the presence of an electronegative atom is sufficient for the interaction of the ligand with the target protein. The difluoromethyl substitution can introduce unexpected biological activity, since the difluoromethyl group has been viewed as being isosteric with a hydroxyl group[15] or as a hydrogen bond donor,[16] allowing for a variety of interactions with solvents and biological molecules.[16,17] Indeed, the high electron density gives rise to the ability of the difluoromethyl substitutent to act as an acceptor in intra- and intermolecular hydrogen bonds, although the acceptor role has not been substantiated. These interactions can result in modified binding to a receptor. Therefore, we decided to test the hypothesis that LPA analogues with a difluoromethyl group in the *sn*-1

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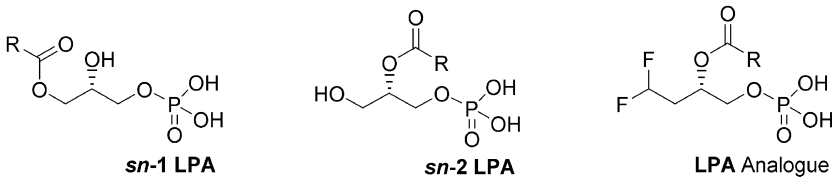


Figure 1. LPA and isosteric analogs.

position might mimic 2-acyl-*sn*-glycerol 3-phosphate as a biological ligand. Such mimics could thus be useful in defining the regiochemical selectivity of LPA receptors for the *sn*-2 acyl position.

Ligand recognition by GPCRs, as well as substrate recognition by enzymes, generally shows a preference for the naturally occurring enantiomer over the unnatural one. However, recognition of LPA by its receptors can be viewed as an exception, as both the natural L (*R*) and unnatural D (*S*) stereoisomers of LPA are equally active in some bioassays.[18] In contrast to the enantiomers of natural LPA, our preliminary biological results have demonstrated that the unnatural D (2*S*) stereoisomers of some *O*-methylated LPA analogues (OMPT)[19] are more active than naturally occurring L (2*R*) enantiomorphs.[20] On the basis of these results, we synthesized the (2*S*) enantiomers of *sn*-2 acyl LPA analogs as the target non-migrating LPA analogues (Fig. 1).

2. Results and discussion

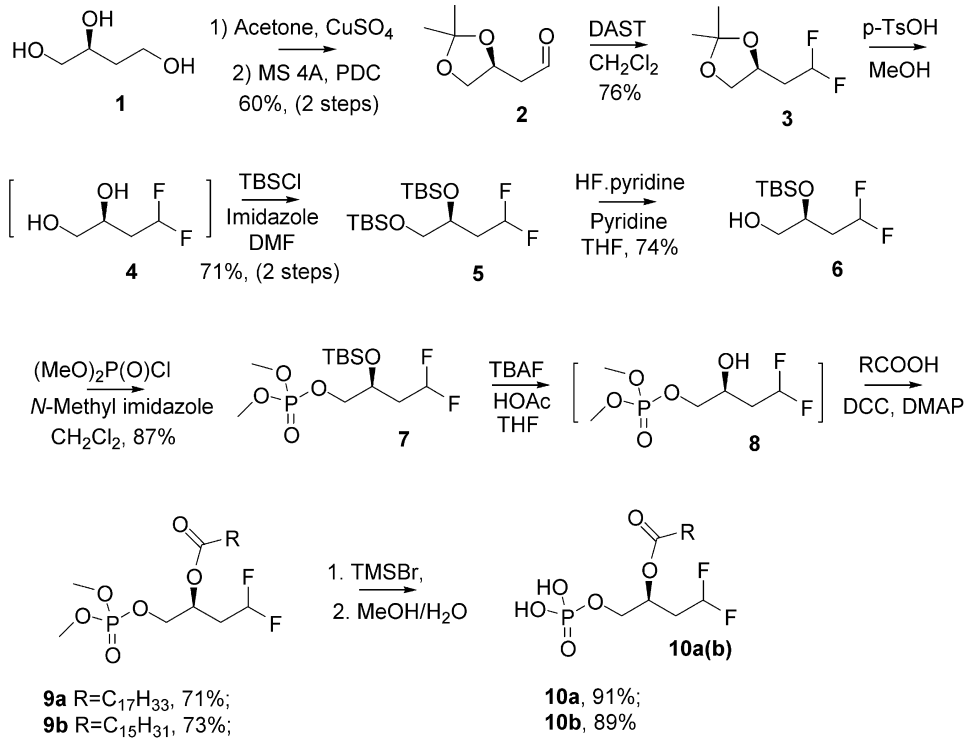
The most general strategy for preparation of difluoromethylated compounds has been conversion of an aldehyde[21] into the corresponding *gem*-difluoride with reagents such as SF_4,[22] aminosulfur trifluorides (DAST,[23] Deoxo-Fluor[24]), and SeF_4.[25] Recently, we synthesized 1,1-difluoro substituted 1-deoxy-(2*S*)-acyl-*sn*-glycerol-3-phosphates as migration-blocked *sn*-2 LPA analogues.[26] However, these analogues failed to show either agonist or antagonist activity when tested in cells expressing LPA_1, LPA_2, or LPA_3 receptors.[8] Since difluoromethyl group can be viewed as isosteric with a hydroxyl group, it could be argued that those analogues had suffered a truncation of the three-carbon glycerol backbone, known to be important for LPA–receptor interactions. Thus, to remedy this unintentional truncation, we designed the four-carbon chain, 1-difluoromethyl-deoxy-(2*S*)-acyl-*sn*-glycerol-3-phosphate **10**, which retains the three-carbon glycerol backbone plus the difluoromethyl group mimicking the C-1 hydroxyl group.

The synthetic routes to the target difluoromethyl compounds 1-difluorodeoxy-2-acyl-*sn*-glycerol-3-phosphate **10** were based on the following design considerations. First, it was necessary to install the fluorine prior to acylation to avoid acyl chain migration during the synthesis. Second, for ease of synthetic manipulations, the deprotection of the penultimate dimethyl phosphate with TMSBr was selected to permit incorporation of unsaturated acyl chains, as well as to reveal the charged phosphate at the final step of the synthesis. Thus, the commercial chiral synthon, (*S*)-1,2,4-butanetriol **1** was chosen as the starting compound. The triol was protected to form the isopropylidene ketal by using $CuSO_4$ as dehydrating agent, and the resulting primary alcohol was oxidized with PDC to provide (*S*)-3,4-dihydroxybutanal acetonide **2**.[27] Nucleophilic fluorination of the aldehyde to difluoromethyl group with DAST gave difluoromethyl intermediate **3** in 76% yield after purification by vacuum distillation.

Next, acidic cleavage of the acetonide with methanolic *p*-TsOH gave the diol intermediate, which was converted to the bis-silyl ether using excess *tert*-butyldimethylsilyl (TBDMS) chloride and imidazole in anhydrous DMF. The more labile primary TBDMS was then cleaved selectively using pyridinium–HF in pyridine–THF at ambient temperature.[28] Phosphorylation of the primary alcohol with dimethylphosphoryl chloride gave phosphate **7**. Initial attempts using potassium *tert*-butoxide as base provided modest yields (56%) of phosphate **7**.[29] Exploration of several organic bases revealed that *N*-methylimidazole was optimal, providing 87% yield after 24 h reaction time.[30] The secondary TBDMS ether then removed with tetrabutylammonium fluoride (TBAF) in THF to give the secondary alcohol;[31] neutralization of TBAF with acetic acid permitted this desilylation to occur without phosphate migration (as monitored by ^{31}P NMR). DCC-promoted esterification of **8** with either oleic acid or palmitic acid provided good yields of esters **9a** and **9b**. Finally, treatment of each ester **9** with bromotrimethylsilane (TMSBr) and subsequent addition of 5% aq. methanol provided the desired fluorinated LPA analogues **10a** and **10b** in nearly quantitative yield (Scheme 1).[32,33]

Since the two fluorines of the difluoromethyl group are diastereotopic, in the aprotic solvent $CDCl_3$, the ^{19}F resonance of compounds **6** and **7** exhibited chemical shifts in the ^{19}F NMR spectra that differed by as much as ~1.0 ppm. In addition, each ^{19}F resonance was split into a dddd peak by the two smaller vicinal $^3J_{FF}$, the intermediate geminal $^2J_{HF}$ and the larger geminal $^2J_{FF}$ couplings. However, in the hydrogen-bonding solvent CD_3OD, the pattern was strikingly different, showing an apparent doublet of triplets and the absence of chemical shift difference between the two CHF_2 fluorines. The spectra changes can be visualized clearly by titration of CD_3OD into $CDCl_3$. As the ratio of CD_3OD increased, the chemical shift difference between the diastereotopic fluorines gradually deceased. One plausible reason is the formation of $C-F\cdots D-O-CD_3$ hydrogen bonds diminished the differences in the chemical environments of the diastereotopic difluoromethyl fluorine atoms.[16]

We have found that the phosphoric acid forms of LPA analogues can be labile during storage or when made as stock solutions for biological evaluation. Thus, we have adopted a standard protocol to obtain a stable sodium salt



Scheme 1.

form of each LPA analogue. For example, **10a** was dissolved in 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed onto a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed neutral sodium salt of **1a** was eluted with Nanopure water. The product solution was lyophilized to give an amorphous white powder, which was stored in solid form at −80 °C under nitrogen atmosphere. Aqueous or DMSO solutions of LPA analogues were prepared and used

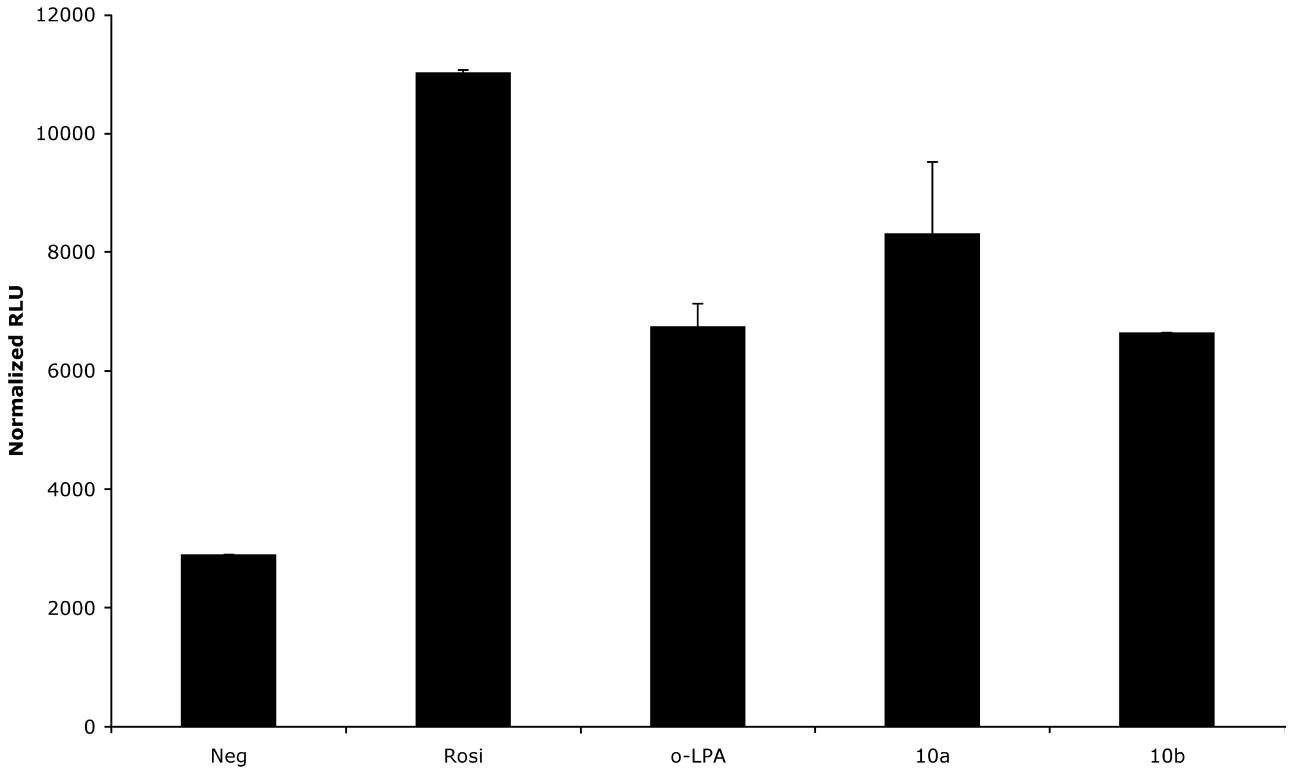


Figure 2. Lipid activation of a peroxisome proliferator responsive element-reporter. Key: RLU, relative light units; Neg, negative control; Rosi, rosiglitazone; o-LPA, *sn*-1-oleoyl lysophosphatidic acid).

within several days to minimize hydrolysis or other decomposition.

2.1. Synthetic LPA analogs activate PPRE function

We found that the fluorodeoxy LPA analogues induced luciferase expression from the acyl-CoAoxidase PPRE reporter (Fig. 2). The effective concentrations for reporter activation by **10a**, **10b**, and LPA were equivalent, so substitution of difluoromethyl for the hydroxyl of LPA was indeed an effective strategy to create stabilized LPA mimetic for this receptor. **10a** has oleyl chain and **10b** has palmitoyl chain, so there was no specificity for the acyl residue. Importantly, the trissulfonamid translocase enhanced the effect of **10a** and **10b** in stimulating the PPRE reporter, as anticipated from the free phosphoryl group of **10a** and **10b**.[8] Since **10a** and **10b** cannot be acylated, intracellular expression of LPA acyltransferase did not change the response to either of these two stable LPA analogues. However, these analogues failed to show either agonist or antagonist activity when tested in insect cells expressing LPA_1, LPA_2, or LPA_3 receptors.[34] The GPCR system is more stereoselective in the requirements for LPA mimetics, and thus the *sn*-3 difluoromethyl substituted LPA analogues elicits different structure–activity profiles with intracellular versus extracellular receptors.

In conclusion, we have demonstrated a concise and efficient synthesis of two acyl-migration blocked 2-acyl LPA analogues. This versatile synthetic route is currently being employed for the synthesis of other migration-blocked and hydrolysis-blocked LPA analogues with different backbones and acyl chains in order to create a panel of LPA analogues that differentiate among the nuclear transcription factor PPARγ and the LPA receptor subtypes.

3. Experimental

3.1. General procedures

Chemicals were obtained from Aldrich and Arcos Chemical Corporation and were used without prior purification. Solvents used were of reagent grade and were distilled before use: THF was distillated from sodium wire. Methylene chloride was distillated from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. ^1H and ^{13}C spectra were recorded at 400 MHz (^1H), 101 MHz (^{13}C), 162 MHz (^{31}P) and 376 MHz (^{19}F), temp. 25 °C. Chemical shifts are given in ppm with TMS as internal standard (δ=0.00); ^{31}P, 85% H_3PO_4 (δ=0.00); ^{19}F, $CFCl_3$ (δ=0.00).

3.1.1. (*S*)-3,4-Dihydroxybutanal acetonide (2). To a solution of (*S*)-1,2,4-butanetriol (20.1 g, 200 mmol) in 380 mL of anhydrous acetone at room temperature were added anhydrous $CuSO_4$ (23 g) and a catalytic amount of *p*-toluenesulfonic acid (0.23 g, 1.211 mmol). The reaction mixture was stirred at room temperature for 3 days and then quenched with solid potassium carbonate (0.33 g, 2.422 mmol). Inorganic salts were filtered and washed with ethyl acetate. All organic solvents were combined and concentrated to give a colorless oil which was purified by flash chromatograph (2% methanol/chloroform) to afford the protected triol, (*S*)-1,2,4-Butanetriol-1,2-acetonide (26.5 g, 182 mmol, 91% yield). The protected triol (8.16 g, 55.9 mmol) was dissolved in 120 mL of anhydrous dichloromethane followed by slow addition of pyridinium dichromate (25.2 g, 67.1 mmol) and powdered 4Å molecule sieves (12.4 g). The suspension was stirred vigorously overnight at room temperature. Hexane/ethyl acetate (1:1, 100 mL) was added to the reaction mixture that was then stirred for 30 min. The black suspension was filtered through a short flash silica gel column to remove excess PDC and its reduced forms. The organic solvents were removed and the residue was distillated under vacuum (22 mm Hg) to give 5.20 g (36.1 mmol, 66% yield) of acetonide **2** as a colorless oil (bp 90 °C/22 mm Hg).

^1H NMR ($CDCl_3$): 9.80 (s, 1H), 4.52 (m, 1H), 4.17 (m, 1H), 3.57 (m, 1H), 2.80 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$): 199.9 (s), 109.5 (s), 70.7 (s), 69.1 (s), 47.8 (s), 26.8 (s), 25.4 (s). $[\alpha]_D^{20}$=+16.1° (2.12, $CHCl_3$); lit.[27] +16.5° (5.32, $CHCl_3$).

3.1.2. 1,2(*S*)-Acetonide-4,4-difluoro-1,2-butanediol (3). To 0.748 g (5.194 mmol) of (*S*)-3,4-dihydroxybutanal acetonide dissolved in dry CH_2Cl_2 (10 mL) was slowly added, with good stirring, (0.824 mL, 6.233 mmol) of diethylaminosulfur trifluoride (DAST). After being stirred at room temperature for 24 h, the reaction mixture was quenched with 10% $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×2), then combined the organic layer and dried with anhydrous Na_2SO_4. The solvent was removed by fractional distillation until the head temperature reached 40 °C. The residue was then distillated at reduced pressure (ca. 20 mm Hg) collecting the fraction distilling at 59–60 °C to give 0.655 g (3.947 mmol, 76%) of acetonide **3** as a colorless liquid.

^1H NMR ($CDCl_3$): 5.93 (tdd, *J*=56.4, 6.4, 2.8 Hz, 1H), 4.23 (m, 1H), 4.08 (dd, *J*=8.0, 6.4 Hz, 1H), 3.57 (dd, *J*=8.4, 7.2 Hz, 1H), 2.15–1.99 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$): 115.5 (t, *J*=238.53 Hz), 109.3 (s), 70.4 (dd, *J*=8.5, 3.8 Hz), 69.1 (s), 38.4 (t, *J*=20.6 Hz), 26.8 (s), 25.5 (s). ^{19}F NMR ($CDCl_3$): −115.71 (1F, dddd, *J*=286.8, 56.1, 25.2, 16.2 Hz), −118.23 (1F, dddd, *J*=286.8, 56.1, 25.2, 16.2 Hz). MS (CI) *m*/*z* 167.1 (M^++1, 100.00), 151.1 (M^+-CH_3, 3.07). HRMS, M^++1. Found: 167.0878. Calcd for $C_7H_{13}O_2F_2$, 167.0884. $[\alpha]_D^{20}$=−7.8° (1.17, MeOH).

3.1.3. 1,2(*S*)-Di[1-(*tert*-butyl)-1,1-dimethylsilyl]-4,4-difluoro-butane-1,2-diol (5). TsOH (34 mg, 0.205 mmol, 0.10 equiv.) was added to a solution of (2*R*)-3,3-difluoro-1,2-propanediol 1,2-acetonide (0.341 g, 2.054 mmol) in MeOH (8 mL), and the solution was stirred at room temperature for 24 h. After addition of NEt_3 (0.2 mL), the solvent was removed under reduced pressure. After addition of anhydrous DMF (3 mL), imidazole (0.420 g, 6.16 mmol, 3.0 equiv.) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.87 g, 5.75 mmol, 2.8 equiv.), the reaction mixture was stirred at room temperature for another 24 h. The solution was diluted with water (10 mL) and ethyl acetate (10 mL), and the aqueous layer was separated and extracted with ethyl acetate (20 mL×3). The combined

organic layers were dried over anhydrous Na_2SO_4, concentrated and the residue was purified by chromatography (*n*-hexane/ethyl acetate 100:1, R_f=0.22) to afford 0.52 g (0.145 mmol, 71%) of diol **5** as a colorless liquid.

^{1}H NMR ($CDCl_3$): 5.93 (tdd, *J*=56.8, 6.0, 3.2 Hz, 1H), 3.86 (m, 1H), 3.57 (dd, *J*=10.4, 5.2 Hz, 1H), 3.40 (dd, *J*=10.4, 7.2 Hz, 1H), 2.13–1.90 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.035 (s, 3H). ^{13}C NMR ($CDCl_3$): 116.4 (t, *J*=237.7 Hz), 68.5 (m), 67.1 (s), 39.2 (t, *J*=21.5 Hz), 25.9 (s), 25.7 (s), 18.3 (s), 18.0 (s), −4.4 (s), −5.2 (s), −5.4 (s), −5.5 (s). ^{19}F NMR ($CDCl_3$): −116.96 (2F, ddd, *J*=56.8, 18.4, 14.7 Hz). MS (CI) *m/z* 355.2 (M^++1, 100.00), 297.1 ($M^+-C_4H_9$, 13.12). HRMS, M^++1. Found: 355.2300. Calcd for $C_{16}H_{37}O_2F_2Si_2$, 355.2300 $[\alpha]_D^{20}=-23.6°$ (1.33, MeOH).

3.1.4. 2(*S*)-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-4,4-difluorobutane-1,2-diol (6). The HF·pyridine complex (70%, 6.02 mmol fluoride, 0.175 mL) was added to a mixture of pyridine (0.53 mL) and a solution of DiTBS ether **5** (0.355 g, 1.003 mmol) in THF (5 mL). The reaction mixture was stirred for 20 h. After completion of the reaction (TLC control), the solution was diluted with ethyl acetate (30 mL), washed with 0.5 M HCl (6 mL×2) and saturated $CuSO_4$ solution (6 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was purified by chromatography (*n*-hexane/ethyl acetate 5:1, R_f=0.30) to give 0.178 g (0.742 mmol, 74%) of diol **6** as a colorless liquid.

^{1}H NMR ($CDCl_3$): 5.89 (tdd, *J*=56.8, 6.0, 3.6 Hz, 1H), 3.96 (m, 1H), 3.60 (m, 1H), 2.14–1.99 (m, 2H), 1.93 (br, 1H), 0.85 (s, 9H), 0.073 (s, 3H), 0.069 (s, 3H). ^{13}C NMR ($CDCl_3$): 116.1 (t, *J*=237.3 Hz), 68.0 (dd, *J*=7.0, 4.0 Hz), 66.3 (s), 38.4 (t, *J*=20.7 Hz), 25.7 (s), 17.9 (s), −4.6 (s), −5.1 (s). ^{19}F NMR ($CDCl_3$): −116.42 (1F, dddd, *J*=286.8, 56.8, 23.7, 14.3 Hz), −117.77 (1F, dddd, *J*=286.8, 56.8, 23.7, 14.3 Hz). MS (CI) *m/z* 241.1 (M^++1, 100.00), 183.0 ($M^+-C_4H_9$, 8.93). HRMS, M^++1. Found: 241.1429. Calcd for $C_{10}H_{23}O_2F_2Si$, 241.1435. $[\alpha]_D^{20}=-16.3°$ (1.79, MeOH).

3.1.5. 1-Phospho-2(*S*)-[1-(*tert*-butyl)-1,1-dimethylsilyl]-4,4-difluoro-butane-1,2-diol dimethyl ester (7). *N*-methylimidazole (26 mg, 0.321 mmol, 1.4 equiv.) was added to a stirred solution of (55 mg, 0.229 mmol) (2*R*)-3,3-difluorine-2-di[[1-(*tert*-butyl)-1,1-dimethylsilyl]oxyl]-1-propanol and dimethyl chlorophosphate (40 mg, 0.275 mmol, 1.2 equiv.) in CH_2Cl_2 (10 mL) at room temperature. After stirring for 24 h, the reaction was complete. A saturated aqueous solution of NH_4Cl (5 mL) was added to the reaction mixture and stirred for 10 min. The aqueous phase was extracted with CH_2Cl_2 (5 mL×3), the organic solution was dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/ethyl acetate 3:2, R_f=0.25) to give 69 mg (0.199 mmol, 87%) of phosphotriester **7** as a colorless oil.

^{1}H NMR ($CDCl_3$): 5.98 (tdd, *J*=56.8, 6.0, 4.4 Hz, 1H), 4.80 (m, 1H), 3.73 (d, *J*=2.8 Hz, 3H), 3.70 (d, *J*=2.8 Hz, 3H), 3.72–3.69 (m, 2H), 2.43–2.13 (m, 2H), 0.84 (s, 9H), 0.024 (s, 3H), 0.021 (s, 3H). ^{13}C NMR ($CDCl_3$): 115.3 (t, *J*=239.2 Hz), 67.8 (dd, *J*=12.3, 5.4 Hz), 64.6 (s), 64.6 (s), 54.3 (d, *J*=5.4 Hz), 36.9 (td, *J*=22.2, 5.3 Hz), 25.7 (s), 18.1 (s), −5.6 (s). ^{19}F NMR ($CDCl_3$): −116.13 (1F, ddd, *J*=286.8, 26.3, 15.8 Hz), −117.16 (1F, ddd, *J*=286.8, 26.3, 15.8 Hz). ^{31}P NMR ($CDCl_3$): 1.473 (s). MS (CI) *m/z* 349.0 (M^++1, 100.00), 241.1 (M^++2-$C_2H_6PO_3$, 14.04). HRMS, M^++1. Found: 349.1419. Calcd for $C_{12}H_{28}F_2O_2PSi$, 349.1412. $[\alpha]_D^{20}=-21.0°$ (0.92, MeOH).

3.1.6. 1-Phospho-2(*S*)-oleoyl-4,4-difluoro-butane-1,2-diol dimethyl ester (9a). A solution of **7** (48 mg, 0.138 mmol) in THF (5 mL) was treated successively with acetic acid (32 μL, 0.552 mmol) and *tetra*-butylammoniumfluoride trihydrate (174 mg, 0.552 mmol) at room temperature. After stirring for 18 h, the reaction was completed (TLC control), then the solvent was evaporated under reduced pressure and the crude product was purified by pass through a short column to afford a colorless liquid. To the alcohol solution and (43 mg, 48 μL, 0.152 mmol) of oleic acid in dry CH_2Cl_2 (1 mL) at room temperature were added dropwise a solution of DCC (43 mg, 0.207 mmol) and DMAP (10 mg, 0.083 mmol) in dry CH_2Cl_2 (2 mL). The solution was stirred at room temperature for 16 h and filtered, the solvent removed, and the residue was purified by chromatography (*n*-hexane/ethyl acetate 1:1, R_f=0.24) to give 49 mg, (0.098 mmol, 71%) of protected analogue **9a** as a waxy solid.

^{1}H NMR ($CDCl_3$): 5.89 (tdd, *J*=56.8, 6.0, 4.4 Hz, 1H), 5.34 (m, 2H), 5.20 (m, 1H), 4.16 (m, 1H), 4.06 (m, 1H), 3.77 (d, *J*=2.8 Hz, 3H), 3.40 (d, *J*=2.8 Hz, 3H), 2.29 (t, *J*=8.0 Hz, 2H), 2.30–2.10 (m, 2H), 1.98 (m, 4H), 1.59 (m, 2H), 1.24 (20H, m), 0.85 (t, *J*=8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): 172.8 (s), 130.0 (s), 129.7 (s), 114.9 (t, *J*=239.3 Hz), 67.6 (s), 67.5 (s), 66.7 (d, *J*=6.9 Hz), 35.3 (t, *J*=22.3 Hz), 34.1 (s), 33.9 (s), 31.9 (s), 29.7 (s), 29.7 (s), 29.5 (s), 29.3 (s), 29.1 (s), 29.1 (s), 29.0 (s), 27.2 (s), 27.1 (s), 24.9 (s), 24.7 (s), 22.7 (s), 14.1 (s). ^{19}F NMR (CDOD): −117.91 (dt, *J*=56.5, 16.9 Hz). ^{31}P NMR ($CDCl_3$): 2.225 (s). MS (CI) *m/z* 499.1 (M^++1, 100.00). HRMS, M^++1. Found: 499.3004. Calcd for $C_{24}H_{46}F_2O_6P$, 499.3000. $[\alpha]_D^{20}=-10.3°$ (0.30, MeOH).

3.1.7. 1-Phospho-2(*S*)-oleoyl-4,4-difluoro-butane-1,2-diol (10a). Thoroughly dried **9a** (15 mg, 0.030 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (1 mL) at room temperature. Bromotrimethylsilane (14 μL, 0.105 mmol) was added with a dry syringe and stirred for 4 h. TLC indicated that all of the reactant had disappeared, then the solvent removed under reduced pressure and dried under vacuum. The residue was dissolved in 95% methanol (1 mL) for 1 h, then the solvent removed under reduced pressure and dried under vacuum, got final product (13 mg, 0.027 mmol, 91% yield.). The labile acid forms of these analogues were then converted to neutral sodium salts. Thus, product **10a** was dissolved in 2 mL of 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed to a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed neutral sodium salt of **10a** was eluted with Nanopure water. The product solution was lyophilized to give sodium salt as white amorphous solid, which was stored in solid form at −80 °C under nitrogen atmosphere.

^{1}H NMR (CD_3OD): 5.99 (tt, J=56.0, 4.0 Hz, 1H), 5.34 (m, 2H), 5.22 (m, 1H), 4.02 (m, 2H), 2.35 (t, J=7.2 Hz, 2H), 2.26–2.03 (m, 2H), 2.03 (m, 4H), 1.58 (m, 2H), 1.32 (m, 20H), 0.89 (t, J=7.2 Hz, 3H). ^{13}C NMR (CD_3OD): 172.5 (s), 128.9 (s), 128.8 (s), 114.9 (t, J=237.7 Hz), 66.5 (d, J=7.6 Hz), 65.8 (d, J=4.6 Hz), 34.3 (t, J=22.2 Hz), 33.0 (s), 32.5 (s), 31.06 (s), 28.8 (s), 28.8 (s), 28.6 (s), 28.5 (s), 28.3 (s), 28.3 (s), 28.2 (s), 28.1 (s), 26.1 (s), 24.0 (s), 23.9 (s), 21.7 (s), 12.5 (s). ^{19}F NMR (CD_3OD): −117.85 (dt, J=58.0, 4.9 Hz). ^{31}P NMR ($CDCl_3$): 0.870 (s). MS (CI) m/z 471.3 (M^++1, 32.34), 421.3 (M^+-CF_2H, 100.00). HRMS, M^++1. Found: 471.2657. Calcd for $C_{22}H_{42}F_2O_6P$, 471.2687. $[\alpha]_D^{20}$=−17.5° (0.04, MeOH).

3.1.8. 1-Phospho-2(*S*)-palmitoyl-4,4-difluoro-butane-1,2-diol dimethyl ester (9b). A solution of **7** (25 mg, 0.064 mmol) in THF (3 mL) was treated successively with acetic acid (15 μL, 0.256 mmol) and *tetra*-butyl-ammoniumfluoride trihydrate (81 mg, 0.256 mmol) at room temperature. After stirring for 4 h, the reaction was completed (TLC control), then the solvent was evaporated under reduced pressure and the crude product was purified by pass through a short column to afford a colorless liquid. To the alcohol and (18 mg, 0.071 mmol) of palmitic acid in dry CH_2Cl_2 (1 mL) at room temperature was added dropwise a solution of DCC (20 mg, 0.096 mmol) and DMAP (5 mg, 0.038 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 16 h and filtered, the solvent removed, and the residue was purified by chromatography (*n*-hexane/ethyl acetate 1:1, R_f=0.26) to give 24 mg (0.052 mmol, 73%) of the protected analogue **9b** as a waxy solid.

^{1}H NMR (CD_3OD): 5.89 (tdd, J=56.8, 6.0, 4.4 Hz, 1H), 5.21 (m, 1H), 4.17 (m, 1H), 4.09 (m, 1H), 3.76 (d, J=2.8 Hz, 3H), 3.73 (d, J=2.8 Hz, 3H), 2.30 (t, J=8.0 Hz, 2H), 2.26–2.12 (m, 2H), 1.57 (m, 2H), 1.22 (m, 26H), 0.85 (t, J=6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 172.8 (s), 114.9 (t, J=239.2 Hz), 67.6 (s), 67.5 (s), 66.7 (m), 35.3 (t, J=22.2 Hz), 34.1 (s), 33.9 (s), 31.9 (s), 29.7 (s), 29.6 (s), 29.6 (s), 29.4 (s), 29.3 (s), 29.2 (s), 29.0 (s), 24.8 (s), 22.7 (s), 14.1 (s). ^{19}F NMR (CD_3OD): −117.51 (dt, J=56.5, 15.6 Hz). ^{31}P NMR (CD_3OD): 2.218 (s). MS (CI) m/z 473.1 (M^++1, 54.60), 225.1 ($M^+-C_5H_{11}-CF_2H$, 100.00). HRMS, M^++1. Found: 473.2835. Calcd for $C_{22}H_{42}F_2O_6P$, 473.2844. $[\alpha]_D^{20}$=−14.6° (0.28, MeOH).

3.1.9. 1-Phospho-2(*S*)-palmitoyl-4,4-difluoro-butane-1,2-diol (10b). Thoroughly dried **9b** (14 mg, 0.030 mmol, 5 h under high vacuum) was dissolved in anhydrous methylene chloride (1 mL) at room temperature. Bromotrimethylsilane (14 μL, 0.104 mmol) was added with a dry syringe and stirred for 4 h. TLC indicated that all of the reactant had disappeared, then the solvent removed under reduced pressure and dried under vacuum. The residue was dissolved in 95% methanol (1 mL) for 1 h and got final product (12 mg, 0.027 mmol, 89%). The LPA analogue **10b** was converted to the corresponding sodium salt using the same procedure as for **10a**. ^{1}H NMR (CD_3OD): 5.81 (td, J=55.2, 4.4 Hz, 1H), 5.03 (m, 1H), 3.96 (m, 2H), 2.20 (t, J=6.8 Hz, 2H), 1.41 (m, 2H), 1.07 (s, 24H), 0.68 (t, J=6.8 Hz, 3H). ^{13}C NMR (CD_3OD): 173.7 (s), 114.4 (t, J=242.3 Hz), 71.2 (td, J=23.7, 8.5 Hz), 63.9 (d, J=4.6 Hz), 34.7 (s), 33.1 (s), 30.8 (s), 30.8 (s), 30.7 (s), 30.6 (s), 30.5 (s), 30.4 (s), 30.1 (s), 25.9 (s), 23.7 (s), 14.5 (s). ^{19}F NMR (CD_3OD): −116.65 (dt, J=58.0, 4.9 Hz). ^{31}P NMR ($CDCl_3$): 0.709 (s). MS (CI) m/z 445.3 (M^++1, 46.30), 323.2 ($M^+-C_5H_{11}-CF_2H$, 100.00). HRMS, M^++1. Found: 445.2510. Calcd for $C_{20}H_{42}F_2O_6P$, 445.2531. $[\alpha]_D^{20}$=−18.8° (0.04, MeOH).

3.2. Synthetic LPA analogs activate PPRE function

CV-1 cells were transiently transfected with a luciferase reporter under the control of the PPAR responsive element of rat acyl-CoA oxidase and SV40 β-galactosidase to normalize transfection efficiency. These cells were stimulated for 18 h with 5 μM of the stated lipid (rosi, rosiglitazone; o-LPA, oleoyl lysophosphatidic acid) before luciferase and β-galactosidase were determined as described in 'Methods'. Data are the range of two determinations and represent the result of two experiments. *Methods*: CV-1 cells were transiently transfected with the PPAR responsive element of rat acyl-CoA oxidase and SV40 β-galactosidase and stimulated production of luciferase was determined as previously described.[35]

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Facial selectivity of the Ireland–Claisen rearrangement of allylic esters of 2-methyl and 2-methoxycyclopentanecarboxylic acids

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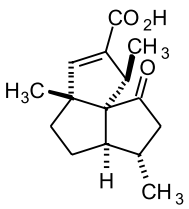
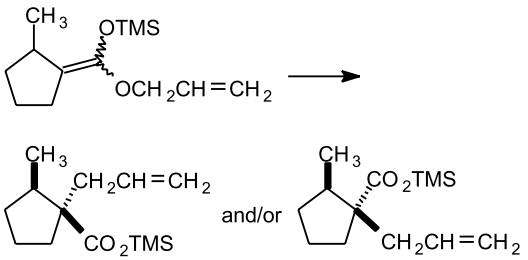
Abstract—Ketene silylacetals derived from prenyl and (*Z*)- and (*E*)-crotyl 2-methylcyclopentanecarboxylates (**9**) were subjected to the Ireland–Claisen rearrangement. All three substrates rearranged with complete facial selectivity, but the (*Z*)- and (*E*)-crotyl systems gave a mixture comprised of the same diastereomers of 1-(1-methyl-2-propenyl)-2-methylcyclopentanecarboxylic acid (**14**) in ratios of 2:1 and 1:2, respectively. In contrast, the ketene silylacetals prepared from allyl and prenyl 2-methoxycyclopentanecarboxylates (**22**) underwent rearrangements with both facial stereochemistries.

1. Introduction[1]

Organic chemists continue to be interested in developing new methodologies for synthesis of polyquinanes[2] due to the aesthetically appealing topologies of this class of compounds and the promising biological activities exhibited by some of its members. As part of a projected synthetic approach to subergorgic acid (**1**), a triquinane first isolated and characterized in 1982,[3,4] it was important to define the facial selectivity of the Ireland–Claisen rearrangement[5] of ketene silylacetals derived from allyl 2-methylcyclopentanecarboxylates (Eq. 1); such an isomerization was a key step for establishing certain stereochemical features in our planned approach to **1**.

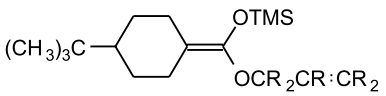


1

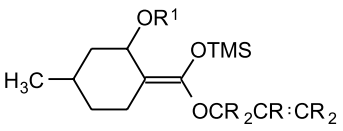


(1)

To our knowledge, there are no literature precedents for predicting the preferred facial selectivity of the Ireland–Claisen rearrangement in 2-substituted cyclopentanecarboxylate systems. The results of studies from our own group offer the closest analogies available, and extrapolating them to the present system is fraught with peril. For example, our previous work involved rearrangements of ketene silylacetals of allyl 4-alkyl and 2-alkoxy-4-alkylcyclohexanecarboxylates **2** and **3**, respectively,[6] so conformational differences between five and six-membered rings become an issue.



2
R = H or alkyl



3
R = H or alkyl, R^1 = alkyl

Keywords: Ireland–Claisen rearrangement; Sigmatropy; Facial selectivity; Diastereoselectivity.
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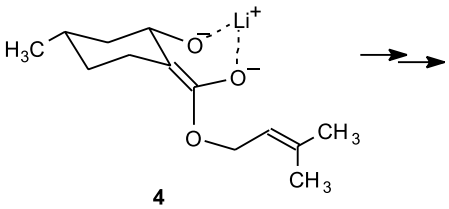
Moreover, although we found the preferred conformation for rearrangement to be chair-like and the orientation of attack of the allyl moiety to be equatorial in all cases, the facial selectivity of the process was dependent on the nature of substituents on the six-membered ring. Thus, the rearrangement of dianion **4** (Eq. 2) involved transfer of the allylic moiety *trans* to the alkoxide, whereas the opposite selectivity was observed with the ketene silylacetal **5** (Eq. 3).[6b–d] The possibility of chelation in **4** was invoked to rationalize the facial selectivity of its rearrangement. The reversal of facial selectivity with **5** presumably reflects operation of the Curtin–Hammett principle,[7] whereby $\Delta H^{\neq}$ to reach the transition state for rearrangement of the less thermodynamically stable conformer **5b** is less than that of **5a** owing to 1,3-interactions between the trimethylsiloxy and 2-alkoxy substituents that develop in the latter conformer during the course of the rearrangement.



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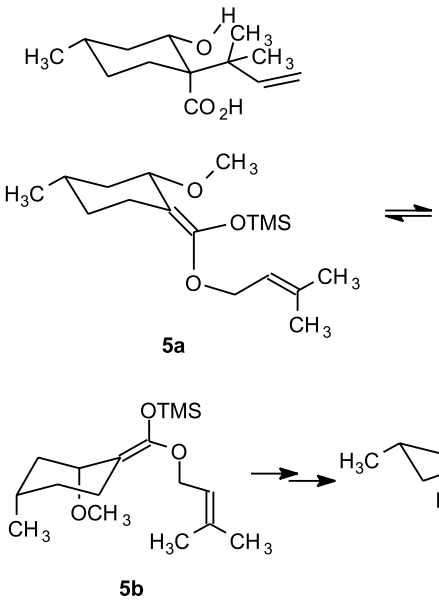
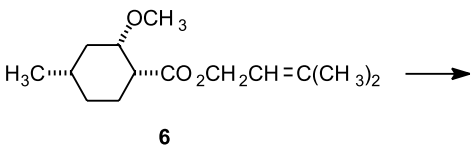


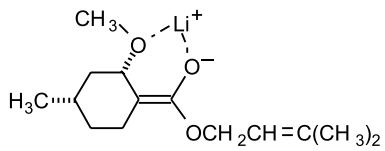
5a (3)

5b

Although the facial selectivity of the Ireland–Claisen rearrangement portrayed in Eq. 1 would presumably mimic that obtained with **5**, subtle conformational factors might well alter this outcome. Thus, whereas the chair conformation of six-membered rings has well-defined axial and equatorial positions, the five-membered analog does not.[8] In addition, the overall stereochemistry of the rearrangement depends not only on the [3,3] sigmatropic process itself, but also on the stereoselectivity for forming the ester enolate that is the precursor to the ketene silylacetal. The 2-methoxy substituent in **6** is available to foster formation of the (*E*)-enolate **7**, which affords **5** upon reaction with TMSCl (Eq. 4). An analogous stereoelectronic factor is unavailable in forming the enolate **8** (Eq. 5); rather, diastereoselectivity of enolate formation in this instance is dependent upon steric factors alone, and predictions of the control that such factors would provide are problematic at best. We, therefore, embarked upon model studies of the Ireland–Claisen rearrangement of allylic esters of 2-methylcyclopentanecarboxylates, and those of 2-methoxycyclopentanecarboxylates as well. The present paper describes the results of our investigations.



6 (4)



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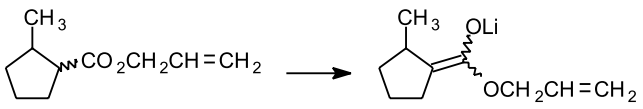


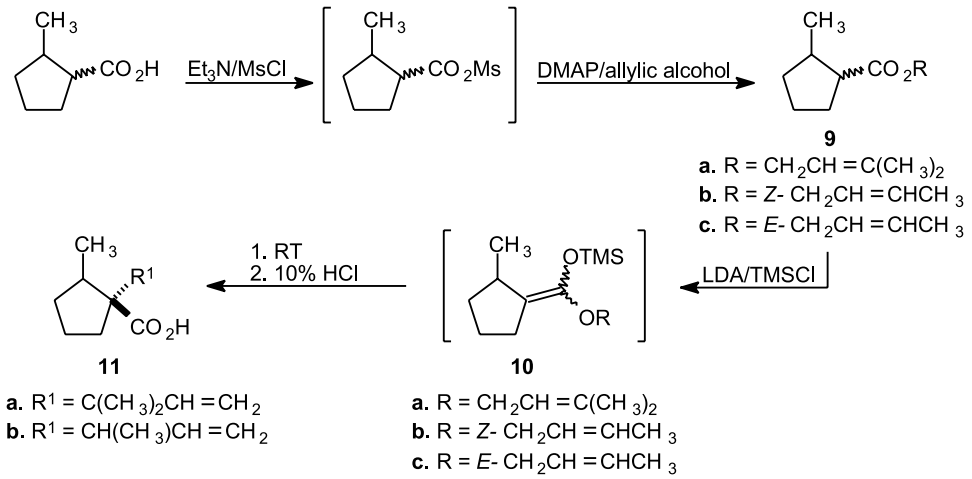
8 (5)

2. Results and discussion

The role of an alkyl group in defining the facial selectivity was explored with substrates **9** (Scheme 1), all of which were prepared in good yield (68–70%) by esterification of a mixture of the diastereomeric 2-methyl-cyclopentane-carboxylic acids[9] according to the unexceptional sequence of Scheme 1. ^{1}H NMR spectroscopic analysis of the esters revealed that each was a 2:1 mixture of diastereomers, a ratio corresponding to that of the mixture of precursor acids. Because the *trans*-isomer predominates in the starting acids, the major diastereomer of **9** is presumably *trans* as well, but since the stereochemistry at C(1) of the ring is destroyed upon formation of the ester enolate from which the ketene silylacetal is derived, separation of the diastereomers was not undertaken. Further conversion of the esters **9** to the ketene silylacetals **10** and rearrangement to the acids **11** were effected via the protocol developed by Ireland and Norbeck (Scheme 1).[10]

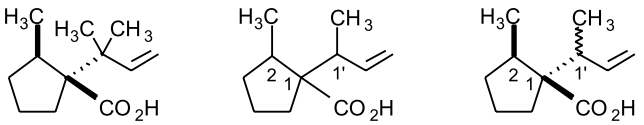
The prenyl ester **9a** afforded a 95% yield of a single carboxylic acid, as determined by ^{13}C and ^{1}H NMR spectral analyses (see Section 3). Through X-ray crystallographic analysis, the stereochemistry of the product was found to be that shown in **12**,[†] demonstrating that the rearrangement involves transfer of the allylic moiety *trans* to the methyl group of the acetal **10a** derived from **9a**. This stereo-chemical outcome suggests that the torsional factors believed to foster the opposite facial selectivity with **5** are not operating in the five-membered ring analog and

[†] Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 218131. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 1.

bespeaks the subtle conformational effects that define the facial selectivity of the Ireland–Claisen rearrangement in such systems.

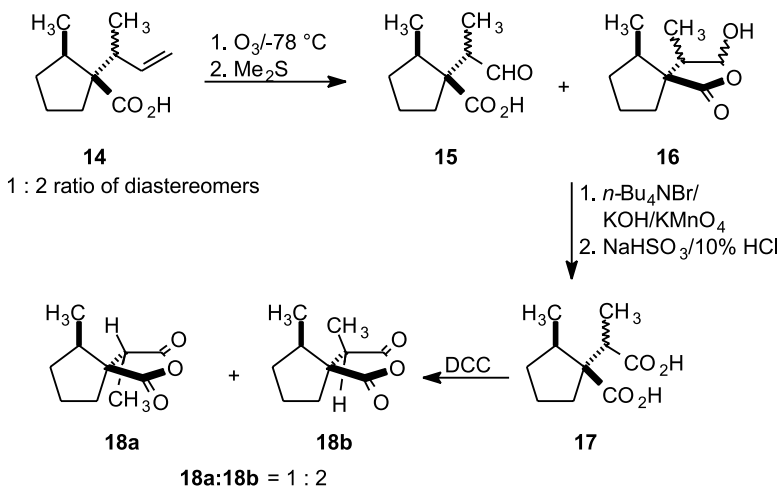


The corresponding rearrangements of **9b** and **c** were more complicated. Exposing **9b** to 2.2 equiv. of LDA according to the usual protocol for forming the ketene silylacetals resulted in the formation of a complex mixture. Decreasing the amount of LDA to 1.1 equiv. afforded a 45% yield of a 2:1 mixture of diastereomeric acids whose spectral properties (MS, IR, ^{13}C and ^{1}H NMR) were consistent with their having the expected carbon skeleton **13**. Subjecting **9c** to identical reaction conditions afforded the same two acids in a 45% yield, but now in a ratio of 1:2.

Either of the two stereocenters, namely C(1) and the allylic carbon atom C(1′), generated via the rearrangement could be the source of diastereomers, but it is the latter that accounts for this, as shown by NOE analyses. Thus, irradiating the allylic proton of the major isomer from both rearrangements provided the same enhancement of the ring methyl group, which suggests that the two diastereomers have the same relative stereochemistries at C(1) and C(2). Given the unambiguous facial selectivity with **9a** and the fact that **9b** and **c**, close steric analogs to **9a**, afford the same pair of diastereomers, the acids were tentatively assigned as having the *cis* stereochemistry shown in **14**.

Confirmation of this and assignment of the configurations of the diastereomers was obtained by converting the 1:2 mixture of the acids **14** to the spiroanhydrides **18** (Scheme 2), whose structural rigidity makes stereochemical definition possible through NMR techniques. Thus, ozonolysis[11] afforded a 1:38 ratio of aldehydes **15** and lactols **16**. Although attempted oxidation of this mixture using Jones reagent,[12] PCC,[13] or PDC[14] proved fruitless, use of basic aqueous potassium permanganate furnished a mixture of diacids **17**.[15] Treating this mixture with dicyclohexylcarbodiimide[16] effected cyclization to the spiroanhydrides **18**, the ratio of which was identical to that of the starting acids **14**.

As seen in Figure 1, there are four diastereomers of **18** that can be formed if no particular facial selectivity is assumed



Scheme 2.

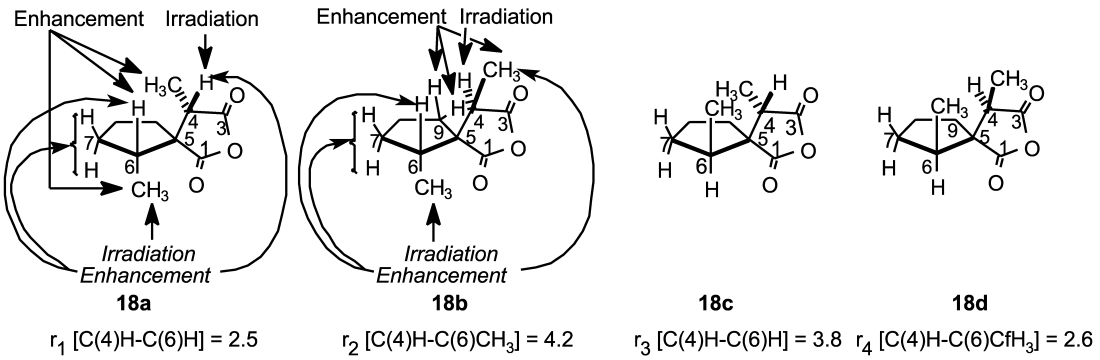


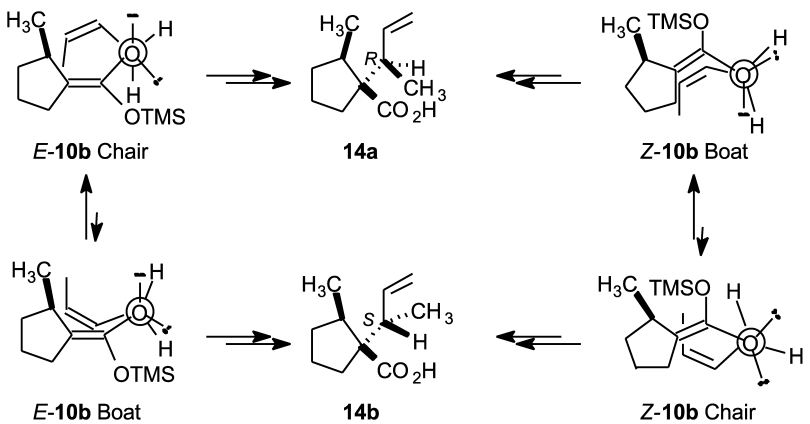
Figure 1. Enhancements from GOESY NMR experiment; r_1 and r_3 are distances (Å) between protons at C(4) and C(6) for **18a** and **18c**, respectively; r_2 and r_4 are distances (Å) for closest approach between proton at C(4) and proton of C(6) methyl group for **18b** and **18d**, respectively.

for the rearrangement of **9bc**. Application of a variety of 1D and 2D NMR spectroscopic techniques, viz. GOESY, ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, and NOESY allowed definitive assignment of stereochemistry to the two diastereomers obtained experimentally. With respect to making a structural assignment for the minor isomer, irradiating the C(4) proton enhanced the resonances for that at C(6) and those of the methyl groups at C(4) and C(6), whereas irradiating the protons of the C(6) methyl group enhanced the absorptions for the C(4), C(6), and C(7) protons. These observations remove **18b** and **18d** as possibilities. Excluding **18c** as the minor isomer is based on data from a NOESY experiment in which no interaction was observed between the proton at C(4) and those of the C(6) methyl group; were the minor isomer **18c**, an interaction would be expected. Thus, a molecular mechanics calculation using the SYBYL force field showed that the most stable conformer for both **18a** and **18c** has the C(4) and C(6) methyl groups quasi-axial and quasi-equatorial, respectively. The distance between the C(4) and C(6) protons in these conformers is 2.5 Å in **18a** and 3.8 Å in **18c** (Fig. 1). These relative distances are consistent with the enhancement of the C(6) proton observed when irradiating that at C(4) in the GOESY experiment if the minor isomer is **18a** rather than **18c**. Assigning **18a** for the structure of the minor isomer is therefore consistent with all the data.

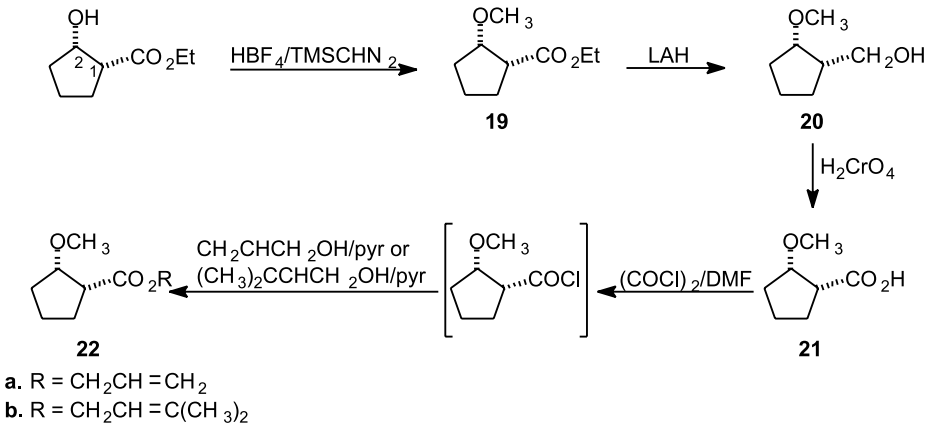
As for the major isomer, irradiating the C(4) proton enhanced the absorptions for the C(9) protons and those of the C(4) methyl group and irradiating the C(6) methyl group enhanced the resonances for the C(6) and C(7) protons and the C(4) methyl protons. Structure **18c** (and **18a**) is thereby eliminated from consideration. Differentiation between **18b** and **18d** as the major isomer comes from the NOESY experiment, wherein a stronger interaction is seen between the C(6) proton and those of the C(4) methyl group than between the protons of the two methyl groups. If the major isomer were **18d**, exactly the reverse would be expected. Applying molecular mechanics calculations to **18b** and **18d** shows that the most stable conformer for **18b** is the one having both methyl groups quasi-equatorial and that for **18d** is that having both methyl groups quasi-axially oriented. The distance between the C(4) proton and those of the C(6) methyl group is computed as 4.2 Å in **18b** and 2.6 Å in **18d**. The distance predicted for **18b** is consistent with the absence of enhancement of the C(4) proton when the C(6) methyl group is irradiated, as seen in the GOESY data; in contrast, enhancement would have been seen if the major isomer were **18d**.

It is highly improbable that epimerization in the step involving formation of **17** would have precisely inverted the ratio of diastereomers **18ab** relative to that of acids **14**. Thus, it is possible to conclude that the major isomer derived from Ireland–Claisen rearrangement of **9c** is **14b** whereas that from **9b** is **14a** (Scheme 3).

There are two obvious ways to rationalize formation of **14ab** from **9bc**. One approach is to assume that a single diastereomer of the ketene silylacetal **10b** is produced from **9b** and that it undergoes the rearrangement through a combination of chair- and boat-like conformations



Scheme 3.



Scheme 4.

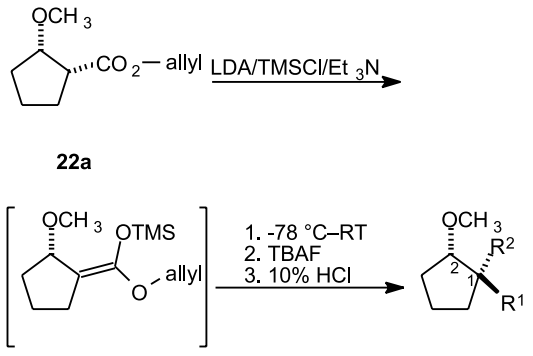
(Scheme 3). For the (*E*)-diastereomer, the two conformations afford the (*R*)- and (*S*)-diastereomers, respectively, at the allylic carbon atom C(1′), whereas in the case of the (*Z*)-diastereomer, the chair- and boat-like conformations yield the (*S*)- and (*R*)-diastereomers, respectively. A comparable analysis can be applied to **10c**.

An alternate approach is to posit that formation of the enolate from **9bc** is not completely diastereoselective, so that an *E*/*Z* mixture of acetals **10** is generated. In this event, even exclusive rearrangement through either a chair- or boat-like conformation is destined to afford **14** as a mixture of diastereomers.

If our earlier results[6b–d] with six-membered ring analogs of **10** serve as a guide, the preference for its rearrangement through a chair-like conformation should be about 9:1. The experimentally observed ratios of 2:1 and 1:2 for **14a/14b** from **9b** and **9c**, respectively, are then clearly less than those that would be expected. This may reflect a differing selectivity between the two reactive conformers for rearrangement, of course, but it may also be the consequence of the ratio of diastereomeric acetals *E*- and *Z*-**10** produced.

To assess the latter possibility, we next explored the Ireland–Claisen rearrangement in a system where it was hoped that chelation would control the selectivity of enolate formation from the starting ester, and thus of the ketene silylacetals as well. Given the apparent success of a 2-methoxy group to control enolate formation in **6** (Eq. 4) cyclopentyl analogs **22** were prepared (Scheme 4). Methylation[17] of ethyl *cis*-2-hydroxy-1-cyclopentane-carboxylate under acidic conditions gave rise to **19**. Reduction[18] to alcohol **20** followed by oxidation[12] afforded carboxylic acid **21**. Its conversion to esters **22ab** was unexceptional,[19] and the products had the expected spectral characteristics (see Section 3). Epimerization at C(1) was not observed for any of the steps in Scheme 4.

Subjecting allyl ester **22a** to the Ireland–Claisen rearrangement, followed by hydrolysis, produced a 53% isolated yield of a mixture of carboxylic acids, whose spectral characteristics were consistent with their being the isomers **24** (Eq. 6). Of particular note were a pair of multiplets at δ 3.92 and 3.60, corresponding to the protons at C(2) of the two isomers, and a pair of doublets of doublets associated with the downfield portions of two AB quartets at δ 2.62 and 2.45 (the centers for each of the doublets of doublets) that were assigned to the diastereotopic allylic protons of the two isomers.[‡] The ratio of the lower field to upper field multiplets of each set of resonances was 1.0:1.1, a result demonstrating that the same diastereomer accounted for the resonances and that the overall course of the rearrangement of **22a** is essentially non-facioselective, that is, the effect of a methoxy group on the facial selectivity of the Ireland–Claisen rearrangement in the six-membered ring system **6** is lost in the five-membered analog.



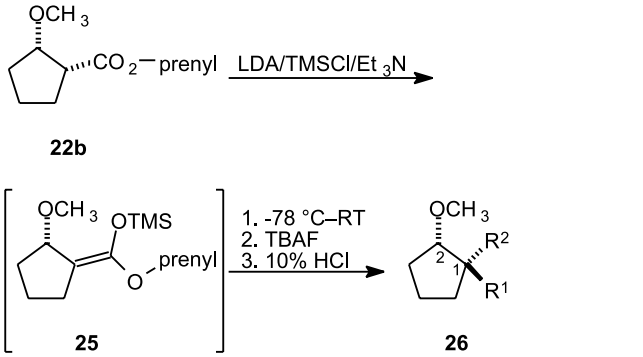
(6)

The major isomer from Ireland–Claisen rearrangement of **22a** was found to be **24b**: Separation of the isomers through column chromatography and GOESY NMR (500 MHz) analyses showed that the lower-field resonances at δ 3.92 and 2.62 are due to the minor isomer **24a**. This assignment was made through the irradiation of the C(2) proton in both the major and minor isomers: In addition to the strong enhancement of the resonance for the methoxy protons in both isomers, the allylic protons of the minor isomer are negligibly enhanced, whereas those of the major isomer are strongly increased. An assignment of the relative stereochemistry of the isomers solely by considering steric compression[20] would have been incorrect because **24b**

[‡] First order splitting patterns were observed for the ABX spin systems in both **24** and **26** based on their $\Delta\nu/J$ values (see Section 3).

would be expected to have resonances for the protons at C(2) and the allylic position at lower field; anisotropic factors associated with the methoxy and carboxy functions account for the observed result.

We had hoped that the increased steric demands of the prenyl moiety in **22b** might improve the facial selectivity in the rearrangement, but this was not to be the case. Treating this ester in the same way as **22a** afforded a 57% isolated yield of a 1.0:1.0 mixture of the carboxylic acids **26**, based on ^{1}H NMR analysis (Eq. 7).



a. $R^1 = CO_2H$, $R^2 = C(CH_3)_2CH=CH_2$
b. $R^1 = C(CH_3)_2CH=CH_2$, $R^2 = CO_2H$

(7)

Particularly diagnostic resonances in this mixture were those of the internal vinylic proton, which appeared as a pair of doublets of doublets centered near δ 6.13 and 5.93, and the C(2) proton, which provided two multiplets at δ 4.09 and 3.88, respectively. One isomer provided the more deshielded resonances of both sets of multiplets, and NMR techniques (GOESY, 500 MHz) on the pure isomers of **26** showed that the lower-field sets of resonances are those of **26a**. Thus, the spectroscopic data for **26** are entirely consistent with those obtained on **24**.[§]

The absence of diastereoselectivity in the overall transformation of **22a** and **22b** to **24** and **26**, respectively, could be associated with the selectivity in forming the ketene silylacetals **23** and **25**, in the faciality of the rearrangement, or with a combination of both factors. An effort to examine these possibilities was undertaken by preparing a sample of **25** and monitoring its rearrangement by NMR spectroscopy. A 5:1 *trans*/*cis* mixture of **22b** afforded a 3:1 mixture of acetals **25** using the conditions shown in Eq. 7, with the exception that the ester enolate was formed and trapped at −110 °C. It appears that there may be some loss of diastereoselectivity in forming **25**, although its lability precludes determining its yield and thereby makes a conclusion on this point ambiguous. By following the disappearance of the resonances at δ 3.19 and 3.21 for the methoxy protons of **25** as a function of time and the concomitant appearance of the corresponding resonances for **26**, it was found that both diastereomers rearranged at the same rate and provided **26** in an unchanging ratio of 55:45 (Table 1). This constancy proves that both diastereomers of **25** have identical and non-discriminant facial selectivity in the rearrangement.

Table 1. Study of rearrangement of **25** at 25 °C as function of time

Time (min)	Ratio of isomers of **25**	Ratio of **25**/**26**	Ratio of **26b**/**26a** (*cis*/*trans*)
30	3:1	95:5	60:40
85	3:1	87:13	55:45
135	3:1	79:21	55:45
195	3:1	70:30	55:45
255	3:1	62:38	55:45
375	3:1	47:53	55:45
2880	N/A	<5:95	55:45

Our observations with the esters **22** clearly show that a 2-methoxy group in the five-membered ring system does not exercise the level of control of enolate diastereoselectivity as it did in the six-membered analog **6**. Even if it is assumed that the major isomer of **25** produced has the *Z*-configuration, the influence of the methoxy group on deprotonation is modest. The reason for this is not particularly obvious and merits further investigation. Moreover, the methoxy group fails to foster the level of facial selectivity that the methyl group in **9** does. This may be due to subtle conformational factors, or may simply reflect the greater steric bulk of a methyl group as compared to a methoxy function.[21]

The generation of isomeric ketene silylacetals from **22b** strongly implies that the formation of diastereomers **14** from **9b** and **9c** results from the formation of a mixture of acetals rather than from competition between chair- and boat-like conformations for the rearrangement. Although the latter may be a factor, we believe it to play a minor role compared to that associated with poor selectivity in forming acetals **10bc**. Whether or not greater diastereoselectivity in keteneacetal formation can be achieved is a subject for future investigations.

3. Experimental

3.1. General information

Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded using spectrometers operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C and $CDCl_3$ served as solvent and internal reference. Chemical shifts (δ) are reported in ppm from TMS. Ratios of isomers were determined from integrated ^{1}H NMR spectra. Infrared spectra were recorded on a Nicolet 510 FT-IR instrument, and were obtained as samples prepared as solutions or thin films between NaCl plates. Low resolution MS measurements were obtained in the chemical ionization mode with a Finnegan-MAT TSQ-70 spectrometer operating at 70 eV with 4 Torr methane gas pressure. High resolution MS measurements were obtained in the chemical ionization mode on a VG ZAB2-E

[§] A shift reagent study using EuFOD was originally applied to define the stereochemistry of **26a** and **26b**. The more upfield of the two methoxy resonances of isomers **26** was shifted downfield faster (see Section 3). Although this result might be interpreted as placing the carboxylic acid and methoxy moieties *cis* to one another as in **26b**, such a conclusion rests on considering only the dependence of lanthanide-induced shifts on distance and neglects that of angle. The upfield methoxy resonance is actually that of **26a**, as determined by GOESY experiments, demonstrating the critical role that angular depenence can play in the interpretation of shift data.

instrument. X-ray structure analysis was carried out by Dr. Vincent Lynch at the Department of Chemistry and Biochemistry at the University of Texas at Austin. Melting ranges were uncorrected. Chromatographic purification of product mixtures refers to purification by flash column chromatography on silica gel, according to the procedure described by Still, et al.[22] All anhydrous reactions were run under a positive pressure of Ar or N_2. All syringes, and hypodermic needles, cannulae, and reaction flasks required for anhydrous reactions were dried for at least 12 h in an oven at 120 °C and cooled under a N_2 atmosphere or in a desiccator. THF was distilled from benzophenone ketyl, under a N_2 atmosphere, just prior to use. Dichloromethane (CH_2Cl_2), *N*,*N*′-dimethylformamide (DMF), pyridine (pyr) and triethylamine (Et_3N) were distilled from CaH_2 under a N_2 atmosphere immediately before use. Benzene (C_6H_6), diisopropylamine (DIPA), and trimethylsilyl chloride (TMSCl) were distilled from CaH_2 and stored over molecular 4 Å sieves. All other reagents and solvents were purified, as necessary, according to standard procedures.[23] Unless noted otherwise, concentration of solutions was accomplished by rotary evaporation at water aspirator pressures.

3.2. Esterification

In a modification of the procedure developed by Chandresekaren and Turner,[24] the diastereomeric 2-methylcyclopentanecarboxylic acids[9] (1 equiv.), CH_2Cl_2, and Et_3N (2 equiv.) were combined in a flask equipped for magnetic stirring under an atmosphere of Ar, and the solution was cooled to 0 °C. Freshly distilled methanesulfonyl chloride (1 equiv.) was added dropwise via syringe to the stirred solution, which was stirred for 1 h at 0 °C. DMAP (0.1 equiv.) and the allylic alcohol (2–4 equiv.) were added to CH_2Cl_2 under an Ar atmosphere, and the solution was cooled to 0 °C. It was then added via syringe to the solution of acid and Et_3N solution. The resulting mixture was held at 0 °C for 1 h. The solution was then stirred for 16 h at room temperature, transferred to a separatory funnel, and diluted with Et_2O. The ethereal solution was sequentially washed with 10% aq. HCl, water, saturated aq. $NaHCO_3$, and dried (Na_2SO_4). Concentration and flash chromatography of the residue afforded the ester as a colorless oil.

3.2.1. 3-Methyl-2-butenyl 2-methylcyclopentanecarboxylate (9a). Flash chromatography (20% EtOAc, 80% hexanes, R_f=0.48) afforded **9a** (414.4 mg, 70% yield), starting with 384.5 mg (3.000 mmol) of acid and 258.4 mg (6.000 mmol) of alcohol. Spectral data (mixture of *trans*/*cis*=2:1): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.31 (m, 1H), 4.54 (m, 2H), 2.75 (q, *J*=7.2 Hz, 0.33H, *cis*-isomer), 2.34–1.08 (m, 13.67H, including peaks for two methyls at 1.73 (s, 1H, *cis*-isomer), 1.68 (s, 2H, *trans*-isomer)), 1.02 (d, *J*=6.5 Hz, 2H, *trans*-isomer), 0.87 (d, *J*=7.1 Hz, 1H, *cis*-isomer); ^{13}C NMR (short of two olefinic carbon resonances due to degeneracy): δ 176.5, 175.3, 138.7, 118.9, 61.2, 60.9, 52.0, 48.3, 39.4, 37.4, 34.8, 33.8, 30.1, 29.7, 27.5, 25.8, 24.4, 23.8, 19.6, 18.0, 16.2, 14.1; HRMS (CI): *m*/*z* calcd for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1541; found 197.1551.

3.2.2. (*Z*)-2-Butenyl 2-methylcyclopentanecarboxylate (9b). Flash chromatography (2.5% EtOAc, 97.5% hexanes, R_f=0.3) afforded **9b** (372.9 mg, 68% yield), starting with 384.5 mg (3.000 mmol) of acid and 865.4 mg (12.00 mmol) of alcohol. Spectral data (2:1 mixture of *trans*/*cis*): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.68 (m, 1H), 5.52 (m, 1H), 4.61 (d, *J*=6.9 Hz, 2H), 2.76 (q, *J*=7.5 Hz, 0.33H, *cis*-isomer), 2.23 (q, *J*=8.4 Hz, 0.67H, *trans*-isomer), 2.16–0.80 (m, 13H, including peaks for three methyls at 1.68 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.3 Hz, 2H, *trans*-isomer), 0.86 (d, *J*=6.5 Hz, 1H, *cis*-isomer)); ^{13}C NMR (lacking two olefinic carbon resonances due to degeneracy): δ 176.1, 175.0, 129.1, 124.6, 59.8, 59.4, 51.8, 48.2, 39.3, 37.4, 34.7, 33.7, 30.0, 27.4, 24.4, 23.7, 21.0, 19.5, 16.1, 13.0; HRMS (CI): *m*/*z* calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1383.

3.2.3. (*E*)-2-Butenyl 2-methylcyclopentanecarboxylate (9c). Flash chromatography (2.5% EtOAc, 97.5% hexanes, R_f=0.3) afforded **9c** (383.8 mg, 70% yield), starting with 384.5 mg (3.000 mmol) of acid and 865.4 mg (12.00 mmol) of alcohol. Spectral data (2:1 mixture of *trans*/*cis*): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.74 (m, 1H), 5.57 (m, 1H), 4.48 (m, 2H), 2.76 (q, *J*=8.1 Hz, 0.33H, *cis*-isomer), 2.23 (q, *J*=8.4 Hz, 0.67H, *trans*-isomer), 2.16–0.80 (m, 13H, including peaks for three methyls at 1.70 (d, *J*=5.4 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 2H, *trans*-isomer), 0.86 (d, *J*=6.3 Hz, 1H, *cis*-isomer); ^{13}C NMR (lacking one olefinic carbon resonance due to degeneracy): δ 176.1, 174.9, 130.9, 130.7, 125.4, 64.8, 64.6, 51.9, 48.3, 39.3, 37.4, 34.8, 33.7, 30.0, 27.4, 24.4, 23.7, 22.0, 19.6, 17.6, 16.2; HRMS (CI): *m*/*z* calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1383.

3.3. General procedure for Ireland–Claisen rearrangements of 9

All rearrangements were run under strictly anhydrous conditions according to procedures developed by Ireland et al.[10] A solution of LDA[25] in THF was prepared in a round-bottomed flask and cooled to −78 °C under a positive pressure of Ar. A dry centrifuge tube was charged with TMSCl/Et_3N/THF (volume ratio of 2.0:0.5:3.7), centrifuged for 10 min, then cooled to −78 °C, and kept under a positive pressure of Ar. The supernatant of the centrifugate (3.0 mL) was transferred via cannula to the LDA solution. The resulting mixture was stirred at −78 °C for 5 min. A solution of the ester in THF, which had been precooled to −78 °C under a positive pressure of Ar, was added dropwise via cannula. This mixture was maintained at −78 °C for 30 min, at which time the solution was allowed to warm to room temperature and stirred at this temperature for 18–48 h. The resulting heterogeneous mixture was diluted with Et_2O (25 mL) and stirred with 10% aq. HCl for 45 min to effect hydrolysis. The resulting biphasic mixture was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The ethereal solutions were combined, washed sequentially with 10 mL each of 10% aq. HCl solution and brine acidified to pH 2, and dried (Na_2SO_4). Concentration afforded a yellow oil that was purified by flash chromatography.

3.3.1. (1*S,2*R**)-1-(1,1-Dimethyl-2-propenyl)-2-methylcyclopentanecarboxylic acid (12).** Following the general procedure and using 196.3 mg (1.000 mmol) of ester **9a**,

2.2 mmol of LDA and an 18-h period of stirring afforded acid **12** (187.1 mg, 95% yield) after flash chromatography (25% EtOAc/hexanes, R_f=0.17). The initially isolated colorless oil solidified to provide X-ray quality crystals: mp 52–53 °C. Spectral data: IR 1691 cm^{-1}; ^1H NMR: δ 6.13 (dd, J=17.7, 10.5 Hz, 1H), 4.99 (m, 2H), 2.40–1.00 (m, 16H, including peaks for three methyl groups at 1.17 (s, 3H), 1.13 (s, 3H), 1.06 (d, J=7.2 Hz, 3H)); ^{13}C NMR: δ 182.2, 146.0, 112.2, 61.8, 41.9, 40.2, 35.9, 33.6, 24.6, 24.1, 23.9, 18.0; HRMS (CI): m/z calcd for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1541; found 197.1534.

3.3.2. (1*S* *,2*R* *)-1-(1-Methyl-2-propenyl)-2-methylcyclopentanecarboxylic acids (14). Following the general procedure and using 182.3 mg (1.000 mmol) of ester **9b**, 1.1 mmol of LDA and a 48-h period of stirring afforded a 2:1 ratio of the acids **14** as a colorless oil (82.6 mg, 45% yield) after flash chromatography (15% EtOAc/hexanes, R_f=0.33). Spectral data (mixture of *trans*/*cis*=2:1): IR 1693 cm^{-1}; ^1H NMR: δ 5.91 (m, 0.67H, *trans*-isomer), 5.67 (m, 0.33H, *cis*-isomer), 5.05 (m, 2H), 2.75 (m, 0.33H, *cis*-isomer), 2.47 (m, 0.67H, *trans*-isomer), 2.30–1.05 (m, 7H), 1.01 (d, J=7.0 Hz, 1H, *cis*-isomer), 1.00 (d, J=6.8 Hz, 2H, *trans*-isomer), 0.95 (d, J=7.0 Hz, 1H, *cis*-isomer), 0.93 (d, J=6.9 Hz, 2H, *trans*-isomer); ^{13}C NMR δ 182.1, 181.7, 141.5, 139.7, 116.3, 114.7, 60.2, 60.1, 42.9, 41.8, 41.1, 41.0, 33.2, 33.1, 30.8, 28.8, 22.4, 22.2, 17.8, 16.3, 15.5, 15.0; HRMS (CI): m/z calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1382. The rearrangement of ester **9c** (182.3 mg, 1.000 mmol) was accomplished according to the same procedure used for **9b** to provide the diastereomeric acids **14** (81.8 mg, 45% yield) in a 1:2 ratio.

3.4. Additional experimental information

3.4.1. (4*R* *,5*S* *,6*R* *)- and (4*S* *,5*S* *,6*R* *)-1,3-Dioxo-2-oxa-4,6-dimethylspiro[4.4]nonane (18ab). A 25-mL two-neck round-bottomed flask, equipped for magnetic stirring, was charged with a solution of **14** (39.4 mg, 0.216 mmol, 1:2 ratio of diastereomers) in CH_2Cl_2 (15 mL) under an N_2 atmosphere. The solution was stirred and cooled to −78 °C and then ozone was bubbled into this solution until it turned a faint blue color, at which time oxygen was bubbled into it to expel excess ozone. Dimethyl sulfide (0.16 mL, 2.18 mmol) was added to the reaction mixture, which was allowed to warm slowly to rt over 3 h with stirring. The mixture was transferred to a 50-mL round-bottomed flask and concentrated to give a pale yellow residue. ^1H NMR spectroscopy indicated that the residue was a mixture of **15** and **16** in a ratio of 1:38. The residue was subjected to the oxidation using a modified procedure as follows.[15] The residue was diluted with CH_2Cl_2 (2.0 mL) in a 10-mL round-bottomed flask and tetrabutylammonium bromide (35.2 mg, 0.108 mmol), 0.10 M aq. KOH (2.8 mL, 0.28 mmol), and $KMnO_4$ (93.5 mg, 0.592 mmol) were added with stirring. The mixture was stirred at rt for 3 h and then cooled in an ice–water bath before slow addition of solid sodium bisulfite (198.0 mg, 1.90 mmol). Aqueous 10% HCl was added dropwise to dissolve MnO_2, then the mixture was further acidified to pH 3 and transferred to a separatory funnel. Diethyl ether (10 mL) and H_2O (2 mL) were added, and the aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated to furnish a pale yellow oil. ^1H NMR spectroscopy of this residue indicated formation of diacids **17**. The crude oil in CH_2Cl_2 (3.0 mL) contained in a 10-mL round-bottomed flask was stirred in the presence of dicyclohexylcarbodiimide (22.5 mg, 0.108 mmol) at rt for 1 h. Water (3 mL) was added, and the mixture was acidified to pH 3 using aq. 10% HCl before being transferred to a separatory funnel. The aqueous layer was separated and extracted with Et_2O (3×10 mL), and the combined organic layers were washed with brine (3×10 mL) and dried (Na_2SO_4). Concentration gave a mixture containing solid and oil, which was washed with hexanes (3×4 mL). The combined washes were concentrated and chromatographed to give anhydrides **18ab** in a ratio of 1:2 as a colorless oil (23.5 mg, 60% for the three steps). ^1H NMR (500 MHz): δ 3.06 (q, J=7.5 Hz, 0.67H), 2.86 (q, J=7.5 Hz, 0.33H), 2.32–1.40 (m, 7H), 1.27 (d, J=7.5 Hz, 1H, CH_3 of **18a**), 1.24 (d, J=7.2 Hz, 2H, CH_3 of **18b**), 1.03 (d, J=6.3 Hz, 1H, CH_3 of **18a**), 0.93 (d, J=6.9 Hz, 2H, CH_3 of **18b**); ^{13}C NMR (125 MHz): δ 175.2, 174.7, 174.0, 173.4, 58.6, 58.4, 44.4, 42.9, 42.6, 39.6, 34.0, 32.4, 32.0, 31.0, 22.0, 21.9, 15.0, 14.3, 12.0, 7.9; HRMS (CI): m/z calcd for $(M+H)^+$ $C_{10}H_{15}O_3$ 183.1022; found 183.1028, 183.1040.

3.4.2. Ethyl *cis*-2-methoxycyclopentanecarboxylate (19). Methylation of ethyl *cis*-2-hydroxycyclopentane-carboxylate (635.6 mg, 3.940 mmol) followed the reported procedure[17] except that $TMSCHN_2$ was added dropwise at 30- rather than 20-min intervals. This afforded **19** (577.2 mg) as a colorless oil in 85% isolated yield. It's spectral data agree with what has been reported in the literature.[26,¶] ^1H NMR: δ 4.24–4.04 (m, 2H), 3.94 (m, 1H), 3.26 (s, 3H), 2.81 (m, 1H), 2.16–1.42 (m, 6H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR: δ 172.8, 84.1, 60.1, 57.1, 49.4, 30.4, 25.2, 21.9, 14.3; HRMS (CI): m/z calcd for $(M+H)^+$ $C_9H_{17}O_3$ 173.1178; found 173.1175.

3.4.3. *cis*-2-Methoxycyclopentanemethanol (20). Reduction of **19** (250.0 mg, 1.452 mmol) followed the reported procedure[18] except that the reaction was performed in THF instead of diethyl ether and afforded **20** (165.1 mg) as a colorless oil in 87% isolated yield. Spectral data: ^1H NMR: δ 3.86 (m, 1H), 3.70 (m, 2H), 3.28 (s, 3H), 2.79 (s, broad, 1H), 2.09 (m, 1H), 1.80–1.40 (m, 6H); ^{13}C NMR: δ 85.3, 63.1, 56.5, 44.7, 30.3, 25.6, 22.2; HRMS (CI): m/z calcd for $(M+H)^+$ $C_7H_{15}O_2$ 131.1072; found 131.1069.

3.4.4. *cis*-2-Methoxycyclopentanecarboxylic acid (21). Oxidation of **20** (165.1 mg, 1.268 mmol) followed the reported procedure[12] except that the reaction mixture was stirred for 5 instead of 2 h and gave **21** (155.6 mg) as a white solid in 85% isolated yield: mp 61–63 °C. Spectral data:[26,‖] ^1H NMR: δ 11.32 (s, broad, 1H), 3.98 (m, 1H), 3.28 (s, 3H), 2.83 (m, 1H), 2.16–1.46 (m, 6H); ^{13}C NMR: δ 178.2, 83.8, 56.9, 49.3, 30.2, 25.4, 21.7; HRMS (CI): m/z calcd for $(M+H)^+$ $C_7H_{13}O_3$ 145.0865; found 145.0859.

¶ The spectral data of ethyl (1*R*,2*S*)-2-methoxycyclopentanecarboxylate previously reported had an additional ^{13}C resonance at δ 22.5 ppm.[26]

‖ The reported[26] spectral data of a 3.4:1 mixture of (1*R*,2*S*) and (1*S*,2*S*)-2-methoxycyclopentanecarboxylic acids are consistent with ours except that the responses at δ 56.9 and 60.0 ppm were assigned to the *trans*- and *cis*-isomers, respectively; this is opposite to our own assignment.

3.4.5. 2-Propenyl *cis*-2-methoxycyclopentanecarboxylate (22a). Esterification of **21** (144.2 mg, 1.000 mmol) followed the reported procedure[19] except that the reagents were mixed at 8–10 °C instead of rt. The reaction mixture was stirred at rt for 16 h to afford **22a** (136.0 mg) as a colorless oil in 74% isolated yield. Spectral data: ^{1}H NMR: δ 5.98–5.82 (m, 1H), 5.36–5.14 (m, 2H), 4.38–4.50 (m, 2H), 3.96 (m, 1H), 3.25 (s, 3H), 2.86 (m, 1H), 2.10 (m, 1H), 1.82–1.46 (m, 5H); ^{13}C NMR: δ 172.4, 132.5, 117.7, 84.0, 64.9, 57.0, 49.5, 30.4, 25.2, 21.9; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1180.

3.4.6. 3-Methyl-2-butenyl *cis*-2-methoxycyclopentanecarboxylate (22b). Esterification of **21** (144.2 mg, 1.000 mmol) followed the same procedure as was used to prepare **22a** and gave **22b** (165.2 mg) as a colorless oil in 78% isolated yield. Spectral data: ^{1}H NMR: δ 5.32 (m, 1H), 4.57 (m, 2H), 3.93 (m, 1H), 3.24 (s, 3H), 2.81 (m, 1H), 2.07 (m, 1H), 1.90–1.44 (m, 11H, including peaks for two methyls at 1.72(s, 3H), 1.67 (s, 3H)); ^{13}C NMR: δ 172.8, 138.6, 118.9, 84.1, 61.2, 57.1, 49.5, 30.5, 25.7, 25.3, 22.0, 18.0; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1489.

3.4.7. (1*R,2*R**)- and (1*S**,2*R**)-1-(2-Propenyl)-2-methoxycyclopentanecarboxylic acid (24a and 24b).** Ester **22a** (93.2 mg, 0.506 mmol), 2.2 equiv. of LDA, and 4.6 equiv. of TMSCl were used in the general procedure for Ireland–Claisen rearrangement. After the reaction mixture had been stirred for 48 h, TBAF (2.33 mL, 1 M solution in THF, 4.6 equiv.) was added at 0 °C, and stirring was continued at rt for 3 h. Water (3.0 mL) was added dropwise at 0 °C, and the pH of the resulting mixture was adjusted to 3–5 by dropwise addition of 10% aq. HCl solution at 0 °C. Normal workup and flash chromatography of the residue afforded a 1.0:1.1 ratio of diastereomers **24** (49.6 mg, 0.269 mmol, 53% yield) as a colorless oil. Further purification by column chromatography (20% EtOAc/hexanes, R_f=0.40, 0.27) effected separation of the isomers. Spectral data for **24a**: ^{1}H NMR: δ 10.40 (s, broad, 1H), 5.77 (m, 1H), 5.04 (m, 2H), 3.92 (m, 1H), 3.32 (s, 3H), 2.62 (dd of downfield portions of AB quartet, *J*=6.3, 13.8 Hz, 1H), 2.28 (dd of upper portions of AB quartet, *J*=7.8, 14.0 Hz, 1H), 2.14–1.52 (m, 6H); ^{13}C NMR: δ 182.3, 134.8, 117.5, 86.0, 57.5, 57.4, 36.3, 32.6, 29.7, 20.7; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1186; spectral data for **24b**: ^{1}H NMR: δ 10.20 (s, broad, 1H), 5.80–5.64 (m, 1H), 5.07 (d, *J*=1.2 Hz, 1H), 5.03 (d, *J*=1.2 Hz, 1H), 3.60 (m, 1H), 3.32 (s, 3H), 2.45 (dd of downfield portions of AB quartet, *J*=7.2, 13.6 Hz, 1H), 2.13 (dd of upper portions of AB quartet, *J*=7.2, 14.0 Hz, 1H), 2.32–1.52 (m, 7H, including doublet of upper portions of AB quartet); ^{13}C NMR: δ 178.7, 133.4, 118.3, 88.4, 58.0, 57.3, 40.0, 30.0, 28.4, 20.3; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1168.

3.4.8. (1*R,2*R**) and (1*S**,2*R**)-1-(1,1-Dimethyl-2-propenyl)-2-methoxycyclopentanecarboxylic acid (26a and 26b).** Following the same procedure as with **22a**, **22b** (143.1 mg, 0.674 mmol) afforded a 1.0:1.0 ratio of diastereomers **26** (81.9 mg, 0.386 mmol, 57%) as a colorless oil. Further purification by column chromatography (20% EtOAc/hexanes, R_f=0.53, 0.42) effected separation of the isomers. Spectral data for **26a**: ^{1}H NMR: δ 10.88 (s, broad, 1H), 6.13 (dd, *J*=18.0, 10.5 Hz, 1H), 4.94–4.84 (m, 2H), 4.09 (d, *J*=4.2 Hz, 1H), 3.24 (s, 3H), 2.18–1.32 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR: δ 181.1, 146.8, 110.6, 86.8, 65.7, 55.8, 40.0, 27.7, 27.1, 25.9, 23.9, 20.4; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1497; spectral data for **26b**: ^{1}H NMR: δ 10.73 (s, broad, 1H), 5.93 (dd, *J*=17.2, 11.1 Hz, 1H), 5.10–5.00 (m, 2H), 3.88 (dd, *J*=9.6, 7.5 Hz, 1H), 3.46 (s, 3H), 2.38–1.40 (m, 6H), 1.14 (s, 3H), 1.08 (s, 3H); ^{13}C NMR: δ 174.6, 143.9, 113.4, 83.8, 62.5, 57.7, 39.6, 29.2, 27.8, 24.6, 23.8, 17.4; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1501.

3.5. Shift reagent study of 26[27]

A 1-dram vial was charged with the mixture of acids **26** (80 mg, 0.40 mmol). Deuteriochloroform (1.5 mL) was added to the vial and the solution was thoroughly shaken. Resolve-Al^{TM} EuFOD (100 mg, 0.100 mmol) was dissolved in $CDCl_3$ (1.0 mL) in a second 1-dram vial. Approximately 0.8 mL of the solution containing **26** was transferred to a 5-mm NMR tube, and a ^{1}H NMR spectrum was obtained. One drop of the EuFOD solution was added to the NMR tube, and another spectrum was obtained. This process was repeated until 15 spectra had been taken. Representative data points for the methoxy resonances are: (1) δ 3.46 (*cis*-isomer), 3.24 (*trans*-isomer); no EuFOD solution; (2) δ 3.46 (*cis*-isomer), 3.37 (*trans*-isomer); two drops of EuFOD solution; (3) δ 3.48 (*cis*-isomer), 3.71 (*trans*-isomer); four drops of EuFOD solution.

3.6. Formation and trapping of the ketene silylacetal intermediate (25)

THF (16 mL) contained in a round-bottomed flask equipped with a stirbar was cooled to −110 °C under Ar and 2 M LDA (0.40 mL) in THF/heptanes was added via syringe and stirred. To this was added 1 mL of the supernatant centrifugate of a solution of TMSCl (2 mL), Et_3N (0.5 mL) and THF (4 mL). The resulting solution was stirred at −110 °C for 3 min. A solution of ester **22b** (80 mg, 0.37 mmol) in THF (1 mL) was cooled to −78 °C and added via cannula to the LDA solution. The mixture was stirred and allowed to warm slowly to −20 °C. At this point, the crude ketene silylacetal could be isolated as a solution in toluene-d_8, in the following manner. The solvents were removed under vacuum (0.5 Torr) at −20 °C, and the residue was suspended in toluene-d_8 (1 mL). The suspension was then quickly passed through a cotton plug into an NMR tube under Ar for immediate analysis by ^{1}H NMR spectroscopy. The *E* and *Z* diastereomers of the ketene silylacetal were observed in approximately a 1:3 ratio. Partial ^{1}H NMR of **25**: δ 5.3–5.4 (m, 1H), 3.21 (s, 3H, −OMe of one acetal), 3.19 (s, 3H, −OMe of other acetal).

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Simple and efficient synthesis of *O*-unprotected glycosyl thiourea and isourea derivatives from glycosylamines

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Abstract—Practical, facile and high-yielding one-pot syntheses of different *O*-unprotected glycopyranosyl thioureas and thioureido bolaamphiphiles (two-step synthesis) and of 2-amino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]oxazoles (three-step synthesis) from glycopyranosylamines are reported. The method involves the preparation of *O*-unprotected β-D-gluco (and D-galacto)pyranosyl isothiocyanates which are in equilibrium with the corresponding 1,2-cyclic thiocarbamates, coupling with amines to afford glycosyl thioureas and treatment with yellow mercury (II) oxide to give *trans*-fused bicyclic isoureas. A D-*gluco* trehazolin analogue is prepared in this way. In situ transformation of *N*,*N*-dialkyl, *N*′-glucopyranosyl thioureas into the corresponding ureas is also reported.

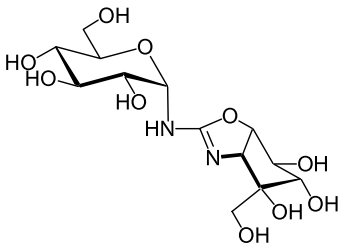
1. Introduction

Isothiocyanates are versatile synthetic intermediates that have been widely used in the synthesis of thiocarbamoyl derivatives. The strong electrophilicity of the NCS group enables these heterocumulenes to take part in addition and cycloaddition reactions, making them extremely useful in the preparation of thioureas and heterocyclic compounds.[1]

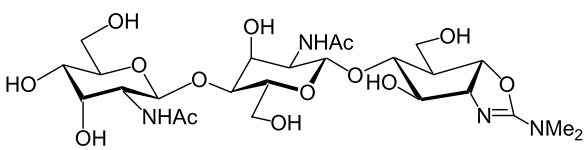
In the last two decades, isothiocyanato derivatives of carbohydrates, mainly *O*-protected glycopyranosyl isothiocyanates have been used to prepare glycoconjugates of biological interest,[2,3] such as thioureidosugars,[4] *N*-nucleosides,[5] *N*-glycopeptides,[6] spiroglycosides,[7] spironucleosides related to (+)-hydantocidin,[8] glycodendrimers and glycoclusters[9] mimetics of natural oligo- and polysaccharides, and bridged thiourea calix-sugars.[10]

Due to the facile reaction between the isothiocyanato and hydroxyl groups, the most readily available isothiocyanato derivatives of sugars are *O*-protected glycosyl isothiocyanates,[2,8] which can be prepared by reaction of *O*-acylated glycosyl halides with silver[11] or potassium thiocyanates,[12] by reaction of per-*O*-acylated aldopyranoses with trimethylsilyl isothiocyanate,[13] by reaction of per-*O*-acylated glycosylamines with thiophosgene,[14] or starting from glycals and potassium thiocyanate in the presence of iodine.[15]

At the same time, 2-amino-2-oxazolines (cyclic isoureas) are biologically active molecules,[16] which are active as imidazoline receptor agonist[17] and as histamine receptor antagonist.[18] They can be used in the treatment of hypertension (e.g. rilmenidine),[19] as appetite suppressant (e.g. aminorex),[20] and to inhibit pheromone synthesis.[21] The isolation of trehazolin[22] **1** and allosamidin[23] **2**, the first natural cyclic isourea derivatives of carbohydrates, with potent activity as threhalase and chitinase inhibitors respectively, has in the last decade encouraged research in the synthesis of trehazolin, allosamidin and related compounds containing modified cyclitol or sugar moieties.[24–26] Syntheses of 2-amino-4,5-dihydro-(1,2-dideoxy-α-D-glucofuranoso)[1,2-*d*]oxazoles from *cis*-fused cyclic sugar thiocarbamates have also been reported.[27]



1 Trehazolin



2 Allosamidin

Recently, we have communicated the preparation of *O*-unprotected glycosyl isothiocyanates and their transformation

Keywords: Isothiocyanates; Thiocarbamates; Thioureas; Isoureas; Thiophosgene; Mercury (II) oxide.
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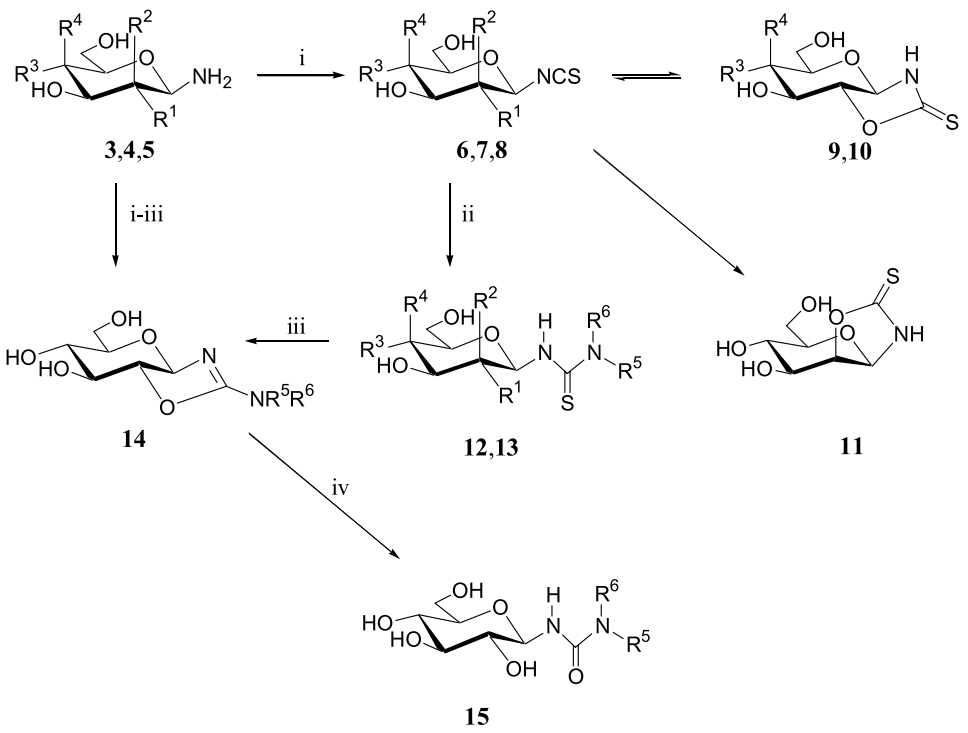


	3,6,12	9	4,7,13	10	5,8
R^1	OH	–	OH	–	H
R^2	H	–	H	–	OH
R^3	OH	OH	H	H	OH
R^4	H	H	OH	OH	H
conf.	D-*gluco*	D-*gluco*	D-*galacto*	D-*galacto*	D-*manno*

Scheme 1. *Reagents and conditions*: (i) $CSCl_2$ (1.2 equiv.), pH 8 ($NaHCO_3/CO_2$), 1:1 water/dioxane, −10 °C, 30 min; (ii) R^5R^6NH (1.2 equiv.), [0.6 equiv. of alkanediamines], pH 9 ($NaHCO_3/CO_2$), rt, 2–5 h; (iii) yellow HgO (3 equiv.), rt, 1–3 h; (iv) yellow HgO (3 equiv.), rt, 2 h.

into glycosyl thioureas[28] and also the preparation of cyclic isourea derivatives.[29] Therein we described the one-pot preparation of the *O*-unprotected glycopyranosyl thioureas **12** and **13** starting from glycopyranosylamines **3** and **4** via intermediate glycopyranosyl isothiocyanates **6** and **7**. The one-pot transformation of the glucosylamine **3** into dihydroglucopyranoso[1,2-*d*]oxazoles **14**, structurally related to trehazolin **1** and allosamidin **2**, was also reported.

2. Results and discussion

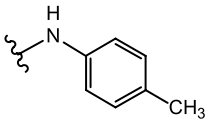
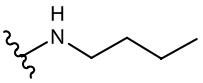
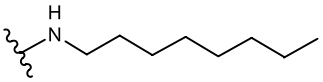
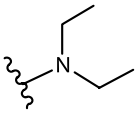
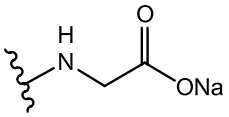
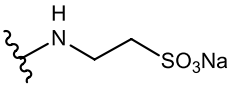
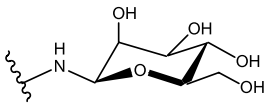
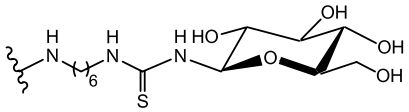
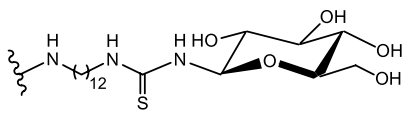
Some data on the reaction of *O*-unprotected glycosyl (glucosyl, maltosyl and lactosyl)amines with thiophosgene to afford the corresponding glycosyl isothiocyanates have been reported.[30] These heterocumulenes were studied as glycosidase inhibitors, and as affinity labels of proteins involved in the transport of carbohydrates through cell membranes, but they were later reported as undergoing ready decomposition under physiological conditions.[31] In the case of β-D-glucopyranosyl isothiocyanate **6**, the synthesis was low-yielding (22%), the characterization was based only on IR spectroscopy, and no further chemistry was reported.[30b]

In our hands, the reaction of β-D-glucopyranosyl amine **3**[32] with thiophosgene leads (Scheme 1) to a mixture of β-D-glucopyranosyl isothiocyanate **6** and 1,2-cyclic thiocarbamate **9** which are in a solvent dependent equilibrium.

The best yield of the mixture of **6** and **9** (64%) was obtained using a buffered ($NaHCO_3/CO_2$, pH 8) suspension in 1:1 water/dioxane, and an excess (20%) of thiophosgene at −10 °C for 40 min. The **6** to **9** ratio, measured by integration of ^1H MNR signals, is 3:2 in D_2O and 1:5 in DMSO-d_6. This behaviour may be explained in terms of the hydrogen bonding of the NH with the solvent, stronger in the case of DMSO than of D_2O.[33]

Similarly, treatment of β-D-galactopyranosyl amine **4**[34] with thiophosgene leads to a mixture of isothiocyanate **7** and thiocarbamate **10** (51%) which were shown to be in a solvent dependent equilibrium that is also shifted towards the thiocarbamate structure in dimethylsulfoxide (1:1 ratio in D_2O and 2:5 in DMSO-d_6). The **6/9** and **7/10** isothiocyanate/thiocarbamate mixtures underwent appreciable decomposition after storage at 0 °C for several days. However, the **6/9** and **7/10** mixtures could be used without further purification in the one-pot synthesis of glucopyranosyl thioureas **12a–k** and galactopyranosyl thioureas **13b** and **13d**, respectively, in good yield (Table 1).

Table 1. Synthesis of thioureas **12**, **13** from β-D-glycopyranosylamines **3**, **4**

Entry	R	**12**, yield (%)	**13**, yield (%)
1		**12a**, 66	—
2		**12b**, 63	**13b**, 53
3		**12c**, 72	—
4		**12d**, 62	**13d**, 69
5		**12e**, 80	—
6		**12f**, 74	—
7		**12g**, 72	—
8		**12h**, 55	—
9		**12i**, 73	—
10		**12j**, 84	—
11		**12k**, 78	—

The reaction of β-D-mannopyranosyl amine[32] **5** with thiophosgene produced the bicyclic thiocarbamate **11**, isolated in a 46% yield. This thiocarbamate is formed through isothiocyanate **8**, but there is no equilibrium between **8** and **11**, as shown by its NMR spectra. Besides that, thiocarbamate **11** did not react with *p*-toluidine as latent isothiocyanate.

The different behaviour of the hydrindane-type systems **9** and **10** on one hand and **11** on the other is due to the differences in the strain of the ring fusion of the tetrahydropyran and the oxazolidine rings. Thiocarbamates **9** and **10** are *trans*-fused bicyclic compounds with unfavourable puckering in the six-member ring due to the decrease of exocyclic equatorial–equatorial angle of the tetrahydropyran unit at the ring junction;[35] the strain of this fusion favours opening with formation of the isothiocyanates **6** and **7**. Compound **11** is a stable *cis*-fused bicyclic system with no tendency to opening, as flattening of the six-membered ring to reduce the exocyclic *cis* torsion angle is relatively facile.

The structures of isothiocyanates **6**, **7** and thiocarbamates

Table 2. Relevant NMR data (δ, ppm; *J*, Hz) for compounds **6**, **7**, **9**–**15**

Compound	Sugar ring					Isothiocyanate, (thio)carbamoyl, isoureido moiety		
	δ H-1	δ H-2	$J_{1,2}$	δ C-1	δ C-2	δ C=X	δ N'–CH_2	δ C-1′[a]
6[b]	4.94	3.43	8.2	86.9	72.5	143.2	—	—
7[b]	4.81	3.63	8.0	87.2	72.9	142.8		
9[b]	5.09	4.08	9.6	88.2	86.8	193.7	—	—
10[b]	4.92	4.35	10.0	89.0	86.1	193.3		
11[b]	5.47	4.98	3.7	82.9	84.7	191.6	—	—
12a[b]	5.42	3.37	8.9	84.6	72.7	183.1	—	—
12b[b]	5.27	3.48	—	84.1	72.7	183.0	45.0	—
12c[c]	5.02	3.14	8.6	83.2	70.1	183.4	43.6	
12d[b]	5.69	3.58	8.8	86.4	73.2	180.0	46.6	
12e[b]	5.62	3.51	8.5	86.6	73.2	180.4	51.4	—
12f[b]	5.33	3.48	8.9	84.2	72.9	183.8	49.2	—
12g[b]	5.29	3.95	9.0	84.0	72.8	183.6	41.1	—
12h[b]	5.49	3.38	9.0	83.9	72.2	—	—	83.9
12i[b]	5.41	3.48	8.9	84.3	72.8	185.0	—	82.4
12j[b]	5.30	3.45	9.0	83.9	72.7	182.0	45.2	83.9
12k[c]	5.02	3.11	8.8	83.3	72.4	183.1	43.6	83.3
13b[b]	5.18	3.75–3.61	—	84.8	70.8	183.1	45.9	—
13d[b]	5.62	3.79	9.0	86.8	70.7	179.9	41.5	—
14a[d]	4.82	3.60	9.6	95.2	85.6	160.0	—	—
14b[b]	4.79	3.54	9.6	94.8	84.6	163.4	41.9	—
14c[d]	4.75	3.49	9.7	96.8	86.7	164.0	43.4	—
14d[d]	4.74	3.48	9.7	97.1	86.8	165.6	43.4	—
14e[d]	4.73	3.49	9.7	96.8	87.2	163.5	47.1	
14h[b]	4.89	3.71	9.8	95.2	86.0	163.0	—	84.3
14j[b]	4.79	3.55	9.5	97.1	86.8	165.6	44.3	97.1
14l[c]	4.59	3.29	9.6	95.9	85.5	161.1	45.4	—
14m[d]	4.69	3.44	9.6	96.9	87.0	164.1	43.9	97.8
15d[b]	4.87	3.42	9.2	81.9	71.9	158.3	41.7	—
15e[b]	4.93	3.48	9.2	83.0	72.9	159.4	46.3	—

[a] C-1′ refers to anomeric carbon of the aglycon part.
[b] In D_2O.
[c] In $(CD_3)_2SO$.
[d] In CD_3OD.

9–**11** were supported on spectroscopic data (Table 2). The most significant difference in the NMR spectra of isothiocyanates **6**, **7** and thiocarbamates **9**–**11** was the ^{13}C chemical shift on the C=S group, which resonated roughly at 143 ppm for **6** and **7**, and about 191–194 ppm for **9**–**11** in agreement with reported data for related isothiocyanato sugars[36] and five-membered thiocarbamate derivatives.[7]

Reaction of the equilibrium mixtures **6/9** and **7/10** in the flask where they were formed, with *p*-tolyl or alkyl primary amines, diethylamine, piperidine, sodium salts of amino-acids glycine and taurine, and *O*-unprotected D-gluco-pyranosyl and D-mannopyranosyl amines afforded the corresponding glycosyl or diglycosylthioureas **12a**–**i**, **13b** and **13d** in moderate to high yields. Similarly, the bola-amphiphiles[37,†] **12j** and **12k** were obtained from **6/9** and 1,6- or 1,12-diamino alkanes, respectively. Thioureas derived from *p*-tolyl, *n*-butyl, *n*-octyl, diethyl amines and piperidine were purified by silica gel column chromatography, whereas the more polar thioureas were isolated by gel filtration chromatography.

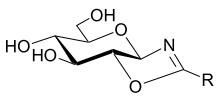
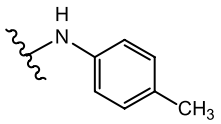
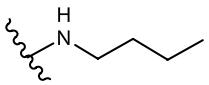
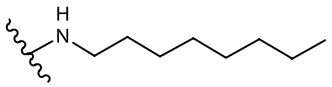
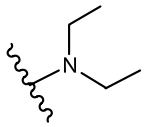
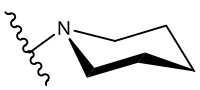
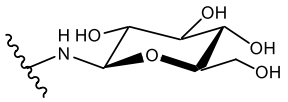
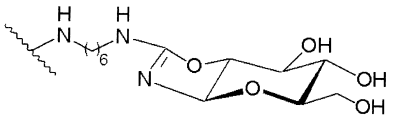
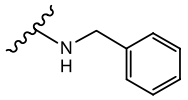
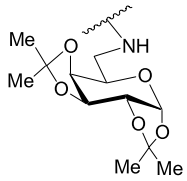
The widely used methodology for the synthesis of glycosyl thioureas involves the coupling of *O*-acylated glycosyl isothiocyanates with amines or aminosugars followed by Zemplen deacetylation.[2,5] However, this reaction has been found to be occasionally unsuccessful or low yielding.[2] In addition, an unexpected base-catalysed anomerization reaction for α and β-D-mannopyranosyl thioureido derivatives has been described upon Zemplen deacetylation.[38] This result contrasts with the preparation of **12i**, which did not show anomerization.

Structures **12** and **13** were supported by analytical and spectroscopic data (Table 2). The chemical shift for the resonance of the C=S group was 180–183 ppm, a value close to that described for *O*-protected acyclic[4] and cyclic[14] glycosylthioureas. The anomeric proton of the D-gluco (**12a**–**k**) and D-galactopyranosyl thioureas **13** resonated in the range 5.0–5.7 ppm, whereas the signal for the corresponding carbon (C-1) was in the range 83–87 ppm in accordance with the presence of a non-strained glycopyranosyl ring in the $^4C_1$ conformation;[39] this conclusion is also supported on the values of the vicinal coupling constants.

The one-pot three-step treatment of β-D-glucopyranosyl-amine **3** successively with thiophosgene (1:1 water/dioxane buffered with $NaHCO_3/CO_2$), then with an amine (*p*-tolyl, *n*-butyl, *n*-octyl, diethylamine, piperidine, 1,6-diamino-hexane, benzylamino, and 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose,[40]) and finally with yellow mercury (II) oxide (3 equiv., 1–3 h, rt), yielded the cyclic isourea derivatives **14** (Table 3) in good yields, 50–70% for the three steps (Scheme 1). The trehazolin analogue

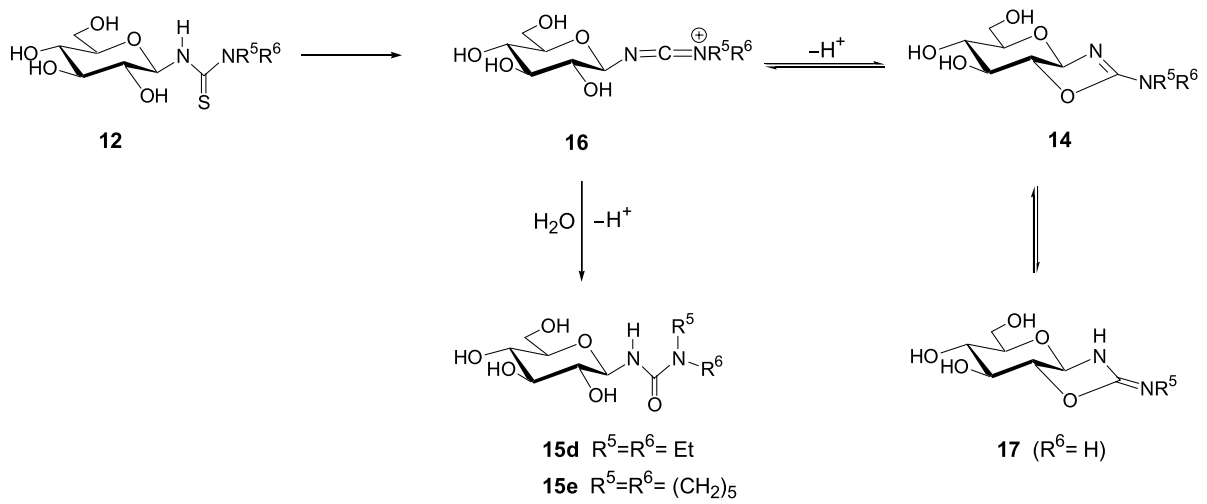
† A bolaamphiphile is defined as a molecule in which two or more hydrophilic groups are connected by one or more hydrophobic chains.

Table 3. Synthesis of cyclic isoureas **14** from β-D-glucopyranosylamine **3** or from β-D-glucopyranosyl thioureas **12**

Entry	R		
		Yield (%)[a]	Yield (%)[b]
1		**14a**, 69	94
2		**14b**, 67	—
3		**14c**, 50	75
4		**14d**, 70	—
5		**14e**, 47	—
6		**14h**, —	89
7		**14j**, 58	—
8		**14l**, 57	—
9		**14m**, 59	—

[a] Isolated yields from **3**.
[b] Isolated yields from **12**.

14h was prepared in a 89% yield starting from the isolated symmetrical *N*,*N*′-bis(β-D-glucopyranosyl) thiourea **12h** by treatment with mercury (II) oxide in 1:1 water/dioxane at rt. Similarly, the *p*-tolyl **14a**, *n*-octyl **14c** derivatives were also obtained from the corresponding isolated thioureas (**12a** and **12c**, respectively) in a 94 and 75% yield using methanol as solvent. Synthesis of **14h** by hydrogenolysis of the derivative of **14h** tetra-*O*-benzylated in the glucopyranose unit has previously been reported by Shiozaki.[41] The reported hydrogenolysis with $Pd(OH)_2$-on-charcoal gave



Scheme 2. Proposed mechanism for the transformation of *N*,*N*-dialkylisoureas into ureas.

an inseparable mixture of **14h** (17%) and *N*,*N*′-bis(β-D-glucopyranosyl)urea (32%).

The isourea derivatives **14** were purified by column chromatography on silica gel, except bolaamphiphile **14j** that was crystallized from ethanol. Attempts to prepare more polar bicyclic isoureas using glycine or taurine as amino compounds were unsuccessful as extensive decomposition took place during the purification by gel filtration chromatography, although the NMR spectra showed the expected isoureas as the major compounds.

Previous results showed that isolated partially *O*-protected sugar thioureas could be cyclodesulfurated to give cyclic isoureas, using freshly prepared dried mercury oxide[42,43] in dried solvents, such as THF,[43] MeCN,[44] Et_2O/Me_2CO,[45] $EtOH/Me_2CO$[42] or using 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in dried MeCN under nitrogen.[41] Our method is experimentally easier as it does not require the isolation of thioureas, and commercial yellow HgO in aqueous dioxane can be used.

The NMR spectra of cyclic isoureas **14** (Table 2) showed significant downfield shifts in the signals of the resonances of C-1 ($\Delta\delta\sim$10 ppm) and C-2 ($\Delta\delta\sim$13 ppm) whereas the resonances for H-1 had a shielding of 0.5–1 ppm, when they were compared with the corresponding signals for the parent thioureas. The $J_{1,2}$ value for **14a**–**m** was 9.5–9.9 Hz, higher than this value for thioureas **12a**–**k** (8.5–9.0 Hz); this might indicate that the pyranoid ring in the *trans*-fused bicyclic compounds is more puckered than that ring in the glycopyranosyl thioureas. Similar behaviour can be observed comparing the *trans*-fused bicyclic thiocarbamates **9** and **10** ($J_{1,2}$=9.6, 10.0 Hz, respectively) with the isothiocyanates **6** and **7** ($J_{1,2}$=8.2, 8.0 Hz, respectively). The chemical shift for the isourea quaternary carbon atom in **14a**–**m** was 160–166 ppm, a value in agreement with that reported for trehazolin and other isourea derivatives.[44]

In situ treatment of crude *N*,*N*-diethyl thiourea **12d** with 3.0 equiv. of yellow HgO for 2 h at rt gave **14d** (70% yield from **3**) together with the glucopyranosyl urea **15d** (18% yield), which was also obtained from **3** using 6.0 equiv of HgO for 4 h (3.0 equiv. each 2 h) in the cyclodesulfurization step (85% yield for the four steps). Under the same conditions piperidine-derived isourea **14e** was not transformed into the corresponding urea. This transformation was achieved in low yield (33%) after 3 months using water as solvent. Attempts at similar transformations involving *N*′-monosubstituted isoureas **14a** and **14b** were unsuccessful, as no evolution from the corresponding isoureas was observed. Relevant NMR data of ureas **15** are included in Table 2. The presence of the urea functional group was confirmed by the characteristic ^{13}C resonance of the carbonyl group (δ 158–159 ppm).[46]

A carbodiimide has been proposed[47] as intermediate in the transformation of thioureas into isourea derivatives; *O*-protected *N*-glycosyl thioureas have been desulfurated with HgO in $CHCl_3$/water to give glycopyranosyl carbodiimides,[48] and desulfuration of sugar derived thioureas with HgO in MeCN/water to give ureas has been reported.[25d] We suggest that the isourea derivatives **14** might be formed via cation **16** (Scheme 2), which undergoes the nucleophilic attack of the *trans* OH-2 to give the isourea derivatives **14**, faster than the attack of H_2O to give ureas **15**. In the case of *N*,*N*-disubstituted thioureas, the positive charge of **16** is stabilized by the two alkyl groups on the nitrogen atom, which provokes the formation of isoureas **14d** and **14e** to be reversible. The attack of H_2O on **16** produces glucosyl ureas **15d**–**e** in an irreversible way. The change from sp^3 hybridized piperidine nitrogen atom to sp^2 for the transformation of **14e** into the intermediate cation **16e** implies a disfavoured strain energy change compared with the acyclic *N*,*N*-diethyl analogues,[35] which might be responsible for the slow formation of urea **15e**.

No presence of the tautomeric tetrahydrooxazole structure **17** was detected by NMR for isoureas **14** in solution, the 2-amino-2-oxazoline **14** being the only possible tautomer for isoureas **14d** and **14e**. As the chemical shifts and coupling constants exhibited by isoureas **14a**–**m** are very close to each other, we can conclude that all of them exist in the 2-amino-2-oxazoline form.

In conclusion, we report expeditious one-pot synthesis in a

buffered aqueous medium of *O*-unprotected glycosyl thioureas (two steps) and dihydroglucopyranoso[1,2-*d*] oxazoles (three steps) starting from easily available β-D-glycopyranosylamines. The *N*/*O* protection–deprotection steps of other described methods to prepare glycosylthioureas, thioureylene oligosaccharides[2] and bolaamphiphiles[49] are avoided. In the case of bicyclic isourea derivatives, not only are the protection–deprotection steps avoided but also we prove that the cyclodesulfuration of the glycosyl thiourea with yellow HgO can be carried out in aqueous media.

3. Experimental

3.1. General procedures

Melting points were recorded on an Electrothermal apparatus and are uncorrected, optical rotations were measured with a Perkin–Elmer 241 polarimeter, and IR spectra (KBr disks) were obtained with an FT-IR Bomem MB-120 spectrophotometer. ^{1}H (300 and 500 MHz) and ^{13}C (75.5 and 125.7 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers. The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. Mass spectra were recorded on Kratos MS 80 RFA and Micromass AutoSpeQ mass spectrometers. TLC was performed on aluminium pre-coated sheets (E. Merck Silica Gel 60 F_{254}); spots were visualized by UV light, by charring with 10% H_2SO_4 in EtOH. Column chromatography was performed using E. Merck Silica Gel 60 (40–63 μm). Microanalysis were performed at the 'Instituto de Investigaciones Químicas', Seville, Spain.

3.1.1. β-D-Glucopyranosyl isothiocyanate (6) and (1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazolidine-2-thione (9). To a suspension of $NaHCO_3$ (281 mg, 3.35 mmol) in 1:1 H_2O/dioxane (5 mL) saturated with CO_2 was added β-D-glucopyranosylamine (250 mg, 1.40 mmol) and thiophosgene (0.13 mL, 1.68 mmol; 1.2 equiv.). The mixture was stirred at −10 °C for 40 min and then it was concentrated to dryness. The residue was dissolved in H_2O (25 mL) and washed with CH_2Cl_2 (3×25 mL). The aqueous layer was concentrated to dryness and the residue was triturated with EtOH and the ethanolic solution was concentrated to dryness and purified by column chromatography (5:1 CH_2Cl_2/MeOH) to give a mixture of **6** and **9** (3:2 ratio in D_2O) together with a small amount of unknown products (198 mg, 64%). R_f=0.39 for both compounds (5:1 CH_2Cl_2/MeOH); IR: ν_{max} 3335, 2027, 1750, 1520, 1364, 1250 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) compound **6**: Table 2 and δ 3.85 (dd, 1H, $J_{5,6a}$=2.3 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.69 (dd, 1H, $J_{5,6b}$=5.6 Hz, H-6b), 3.48 (m, 2H, $J_{2,3}$=8.2 Hz, $J_{3,4}$=8.8 Hz, $J_{4,5}$=8.8 Hz, H-3, H-5), 3.39 (dd, 1H, H-4); compound **9**: Table 2 and δ 4.07–4.09 (m, 2H, H-2, H-3), 3.89 (dd, 1H, $J_{5,6a}$=2.4 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 3.76 (dd, 1H, $J_{5,6b}$=5.5 Hz, H-6b), 3.66 (ddd, 1H, $J_{4,5}$=8.8 Hz, H-5), 3.50 (dd, 1H, H-4); ^{13}C NMR (127.5 MHz, D_2O) compound **6**: Table 2 and δ 79.2 (C-5), 76.8 (C-3), 70.3 (C-4), 61.6 (C-6); compound **9**: Table 2 and δ 82.2 (C-5), 75.4 (C-4) 74.0 (C-3), 61.6 (C-6); EI-MS *m*/*z* 221 ([M]$^+$, 100%); HREI-MS, *m*/*z* calcd for [M]$^+$ $C_7H_{11}NO_5S$: 221.0358, found: 221.0356.

3.1.2. β-D-Galactopyranosyl isothiocyanate (7) and (1,2-dideoxy-β-D-galactopyranoso)[1,2-*d*]-1,3-oxazolidine-2-thione (10). A suspension of $NaHCO_3$ (281 mg, 3.35 mmol) in 1:1 H_2O/dioxane (5 mL) saturated with CO_2 containing β-D-galactopyranosilamine (250 mg, 1.40 mmol) was treated with thiophosgene (0.13 mL, 1.68 mmol; 1.2 equiv.) as described in Section 3.3.1 to give a mixture of **7** and **10** (1:1 ratio in D_2O) together with a small amount of unknown products (158 mg, 51%). R_f=0.33 for both compounds (5:1 CH_2Cl_2/MeOH); IR: ν_{max} 3368, 2060, 1647, 1364, 1115 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) compound **7**: Table 2 and δ 3.88 (d, 1H, $J_{3,4}$=3.0 Hz, $J_{4,5}$=~0.0 Hz, H-4), 3.70–3.65 (m, 3H, H-5, H-6a, H-6b), 3.59 (dd, 1H, $J_{2,3}$=10.5 Hz, H-3); compound **10**: Table 2 and δ 4.21 (dd, 1H, $J_{2,3}$=11.0 Hz, $J_{3,4}$=3.5 Hz, H-3), 4.05 (dd, 1H, $J_{4,5}$=1.0 Hz, H-4), 3.85 (ddd, 1H, $J_{5,6a}$=7.0 Hz, $J_{5,6b}$=4.5 Hz, H-5), 3.80 (dd, 1H, $J_{6a,6b}$=12.0 Hz, H-6a), 3.76 (dd, 1H, H-6b); ^{13}C NMR (127.5 MHz, D_2O) compound **7**: Table 2 and δ 79.6 (C-4), 78.5 (C-5), 73.6 (C-3), 62.0 (C-6); compound **10**: Table 2 and δ 81.9 (C-5), 71.1 (C-3), 70.7 (C-4), 61.8 (C-6); CI-MS *m*/*z* 222 ([M+H]$^+$, 100%); HRCI-MS *m*/*z* calcd for [M+H]$^+$ $C_7H_{12}NO_5S$: 222.0436, found: 222.0436.

3.2. General methods for the synthesis of β-D-glycopyranosyl thioureas 12 and 13

To a suspension of $NaHCO_3$ (281 mg, 3.35 mmol) in 1:1 H_2O/dioxane (5 mL) saturated with CO_2 was added a β-D-glycopyranosilamine (250 mg, 1.40 mmol) and thiophosgene (0.13 mL, 1.68 mmol; 1.2 equiv.). The mixture was stirred at −10 °C for 40 min, then an amine (1.68 mmol, 1.2 equiv.) was added (in the case of α,ω-alkanediamines 0.84 mmol were used) and the mixture was stirred for 3–6 h at rt until TLC showed disappearance of the isothiocyanate **6**. The mixture was concentrated to dryness and the residue was purified by silica gel column chromatography, preparative TLC or by gel-filtration chromatography, as indicated in each case. The following compounds were prepared by this method.

3.2.1. *N*-(β-D-Glucopyranosyl)-*N'*-(*p*-methylphenyl) thiourea (12a). Purification by column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **12a**: 301 mg, 66%. R_f=0.32 (5:1 CH_2Cl_2/MeOH); recrystallization from EtOH/H_2O gave material which shrunk at 98–101 °C and melted at 132–136 °C (dec.); $[\alpha]_D^{25}$ −34° (*c* 1.0, H_2O); IR: ν_{max} 3445, 3327, 1586, 1522, 878, 820, 727 cm^{-1}; ^{1}H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 7.15–7.26 (m, 4H, Ar-H), 3.83 (dd, 1H, $J_{5,6a}$=2.3 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.67 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.49 (ddd, 1H, $J_{4,5}$=9.7 Hz, H-5), 3.48 (t, 1H, $J_{2,3}$=9.1 Hz, $J_{3,4}$=9.0 Hz, H-3), 3.35 (t, 1H, H-4);^{13}C NMR (75.5 MHz, D_2O, 60 °C) Table 2 and δ 138.8, 134.8, 130.6, 126.9 (Ar), 78.0 (C-5), 77.2 (C-3), 70.0 (C-4), 61.4 (C-6), 20,7 (CH_3); FAB-MS *m*/*z* 351 ([M+Na]$^+$, 100%). Anal. calcd for $C_{14}H_{20}N_2O_5S{\cdot}1/2H_2O$: C, 49.84; H, 6.27; N, 8.30, found: C, 49.63; H, 6.33; N, 8.38.

3.2.2. *N*-Butyl-*N'*-(β-D-glucopyranosyl)thiourea (12b).

Purification by column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **12b**: 261 mg, 63%. R_f=0.23 (5:1 CH_2Cl_2/MeOH); crystallization from EtOH gave material which shrunk at 68–72 °C and melted at 102–104 °C (dec.) (from EtOH); $[\alpha]_D^{30}$ −27° (*c* 1.0, H_2O); IR: ν_{max} 3453, 2924, 2872, 1692, 1562, 1352 cm^{-1}; ^1H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 3.84 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.68 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.52 (t, 1H, $J_{2,3}$=8.9 Hz, $J_{3,4}$=8.9 Hz, H-3), 3.48 (ddd, 1H, $J_{4,5}$=9.2 Hz, H-5), 3.52–3.35 (m, 3H, H-2, CH_2), 3.38 (t, 1H, H-4), 1.54 (m, 2H, *J*=7.4 Hz, CH_2), 1.31 (m, 2H, CH_2), 0.86 (t, 3H, CH_3); ^{13}C NMR (75.5 MHz, D_2O, 60 °C) Table 2 and δ 77.9 (C-5) 77.2 (C-3), 70.1 (C-4), 61.4 (C-6), 30.7 ($CH_2\beta$), 19.9 ($CH_2\gamma$), 13.5 (CH_3); FAB-MS *m/z* 317 ($[M+Na]^+$, 100%). Anal. calcd for: $C_{11}H_{22}N_2O_5S\cdot 1/2EtOH$, C, 45.41; H, 7.94; N, 8.82, found: C, 45.55; H, 7.74; N, 8.80.

3.2.3. *N*-(β-D-Glucopyranosyl)-*N′*-octylthiourea (12c). Purification by column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **12c**: 353 mg, 72%. R_f=0.20 (5:1 CH_2Cl_2/MeOH); mp 170–172 °C (dec.) from EtOH/H_2O; $[\alpha]_D^{28}$ −17° (*c* 1.0, MeOH); IR: ν_{max} 3298, 2922, 2855, 1564, 1348, 1074 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 °C) Table 2 and δ 7.49 (d, 1H, $J_{NH,H-1}$=8.2 Hz, NH), 7.42 (t, 1H, J_{NH,CH_2}=5.1 Hz, NH′), 4.64–4.55 (m, 3H, 3OH), 4.02 (m, 1H, OH-6), 3.65 (m, 1H, $J_{6a,6b}$=11.6 Hz, H-6a), 3.56 (m, 1H, H-6b), 3.41 (m, 1H, *J*=6.9 Hz, $CH_2\alpha$), 3.28 (t, 1H, $J_{2,3}$=8.4 Hz, $J_{3,4}$=8.4 Hz, H-3), 3.21–3.11 (m, 1H, H-5), 3.11 (t, 1H, $J_{4,5}$=8.8 Hz, H-4), 1.51 (m, 2H, $CH_2\beta$), 1.28 (m, 10H, $5CH_2$), 0.86 (t, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6, 90 °C) Table 2 and δ 77.5 (C-5), 77.2 (C-3), 72.5 (C-4), 60.9 (C-6), 30.7, 28.2, 28.1, 28.0, 25.9, 21.5, 13.2 (*n*-octyl); FAB-MS *m/z* 373 ($[M+Na]^+$, 100%). Anal. calcd for: $C_{15}H_{32}N_2O_6S\cdot H_2O$: C, 48.89; H, 8.75; N, 7.60, found: C, 49.08; H, 8.61; N, 7.69.

3.2.4. *N,N*-Diethyl-*N′*-(β-D-glucopyranosyl)thiourea (12d). Purification by preparative TLC (5:1 CH_2Cl_2/MeOH, 2 elutions) gave **12d**: 255 mg, 62% as an amorphous solid. R_f=0.23 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ −8.5° (*c* 1.2, H_2O); IR: ν_{max} 3441, 2932, 1533, 1354, 1279, 1071 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 and δ 3.87 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.76–3.63 (m, 4H, *J*=7.0 Hz, $2CH_2$), 3.72 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.55 (t, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=9.0 Hz, H-3), 3.51 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.41 (dd, 1H, H-4), 1.18 (t, 6H, $2CH_3$); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 78.6 (C-5), 78.1 (C-3), 70.6 (C-4), 61.9 (C-6), 12.8 ($2CH_3$); CI-MS *m/z* 295 ($[M+H]^+$, 1%); HRCI-MS: *m/z* calcd for $[M+H]^+$ $C_{11}H_{23}N_2O_5S$: 295.1328, found: 295.1329. Anal. calcd for $C_{11}H_{22}N_2O_5S\cdot H_2O$: C, 49.29; H, 7.74; N, 8.97, found: C, 42.40; H, 7.74; N, 9.26.

3.2.5. *N*-[(β-D-Glucopyranosyl)thiocarbamoyl]piperidine (12e). Purification by column chromatography (CH_2Cl_2→5:1 CH_2Cl_2/MeOH) gave **12e**: 344 mg, 80% as a syrup. R_f=0.25 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{26}$ −34° (*c* 1.0, H_2O); IR: ν_{max} 3368, 2930, 2864, 1755, 1564, 1439, 1329, 1252, 1080, 1040, 880 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 and δ 3.84 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 3.81 (m, 4H, $2CH_2$), 3.70 (dd, 1H, $J_{5,6b}$=5.0 Hz, H-6b), 3.51 (m, 1H, $J_{3,4}$=9.0 Hz, H-3), 3.45 (m, 1H, $J_{4,5}$=9.3 Hz, H-5), 3.38 (t, 1H, H-4), 1.64 (m, 2H, CH_2), 1.57 (m, 4H, $2CH_2$); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 78.6 (C-5), 77.9 (C-3), 70.6 (C-4), 61.9 (C-6), 26.5, 24.9 (CH_2). EI-MS *m/z* 306 ($[M]^+$, 3%); HREI-MS *m/z* calcd for $[M]^+$ $C_{12}H_{23}N_2O_5S$: 306.1294, found: 306.1246.

3.2.6. Sodium [3-(β-D-glucopyranosyl)thioureido]acetate (12f). Purification by gel filtration chromatography gave **12f**: 330 mg, 74% as a syrup. R_f=0.23 (3:2:1 EtOAc/EtOH/H_2O; $[\alpha]_D^{24}$ −32° (*c* 0.7, H_2O); IR: ν_{max} 3362, 1649, 1541, 1516, 1366, 1127, 1013, 629 cm^{-1}; ^1H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 4.06 (m, 2H, CH_2), 3.88 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.72 (dd, 1H, $J_{5,6b}$=5.0 Hz, H-6b), 3.57 (t, 1H, $J_{2,3}$=8.9 Hz, $J_{3,4}$=8.9 Hz, H-3), 3.53 (ddd, $J_{4,5}$=9.4 Hz, H-5), 3.43(t, 1H, H-4); ^{13}C NMR (127.5 MHz, D_2O) Table 2 and δ 177.4 (C═O), 78.0 (C-5), 77.3 (C-3), 70.1 (C-4), 61.4 (C-6); FAB-MS *m/z* 341 ($[M+Na]^+$, 23%); HRFABMS *m/z* calcd for $[M+Na]^+$ $C_9H_{15}N_2Na_2O_7S$: 341.0395, found: 341.0399.

3.2.7. Sodium 2-[3-(β-D-glucopyranosyl)thioureido]ethane sulfonate (12g). Purification by gel filtration chromatography gave **12g**: 371 mg, 72% as a syrup. R_f=0.24 (3:2:1 EtOAc/EtOH/H_2O); $[\alpha]_D^{28}$ −23° (*c* 1.4, H_2O); IR: ν_{max} 3298, 3050, 2922, 1655, 1566, 1437, 1362, 1165, 1040, 991 cm^{-1}; ^1H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 3.95 (m, 2H, *J*=6.5 Hz, CH_2N), 3.91 (dd, 1H, $J_{5,6a}$=2.3 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.75 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.58 (t, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=8.9 Hz, H-3), 3.56 (ddd, 1H, $J_{4,5}$=9.5 Hz, H-5), 3.45 (t, 1H, H-4), 3.21 (t, 2H, CH_2S); ^{13}C NMR (75.5 MHz, D_2O) Table 2 and δ 78.1 (C-5), 77.3 (C-3), 70.1 (C-4), 61.4 (C-6), 50.2 (CH_2S); FAB-MS *m/z* 391 ($[M+Na]^+$, 100%), 759 ($[2M+Na]^+$, 13%); HRFAB-MS *m/z* calcd for $[M+Na]^+$ $C_9H_{17}N_2Na_2O_8S_2$: 391.0222, found: 391.0227.

3.2.8. *N,N′*-Bis(β-D-glucopyranosyl)thiourea (12h). Purification by gel filtration chromatography gave **12h**: 294 mg, 53% as a syrup. R_f=0.38 (3:2:1 EtOAc/EtOH/H_2O); $[\alpha]_D^{24}$ −32° (*c* 0.7, H_2O); IR: ν_{max} 3318, 2899, 1545, 1424, 1364, 1101, 1072 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 2 and δ 3.84 (dd, 1H, $J_{5,6a}$=2.1 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.69 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.53 (t, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=9.0 Hz, H-3), 3.52 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.44 (t, 1H, H-4); ^{13}C NMR (75.5 MHz, D_2O) Table 2 and δ 77.5 (C-5), 76.6 (C-3), 69.4 (C-4), 60.7 (C-6); FAB-MS *m/z* 401 ($[M+H]^+$, 16%), 423 ($[M+Na]^+$, 4%); HRFAB-MS *m/z* calcd for $[M+H]^+$ $C_{13}H_{24}N_2O_{10}S$: 401.1230, found: 401.1232.

3.2.9. *N*-(β-D-Glucopyranosyl)-*N′*-(β-D-mannopyranosyl)thiourea (12i). Purification by gel filtration chromatography gave **12i**: 405 mg, 73% as a syrup; R_f=0.30 (3:2:1 EtOAc/EtOH/H_2O) $[\alpha]_D^{21}$ −24° (*c* 0.5, H_2O); IR: ν_{max} 3380, 2888, 1647, 1541, 1416, 1358, 1099, 1072, 1024, 891 cm^{-1}; ^1H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 5.66 (bs, 1H, H-1′), 4.04 (dd, 1H, $J_{1',2'}$=1.2 Hz, $J_{2',3'}$=3.3 Hz, H-2′), 3.93 (dd, 1H, $J_{5',6a'}$=2.2 Hz, $J_{6a',6b'}$=12.3 Hz, H-6a′), 3.89 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.3 Hz, H-6a), 3.75 (dd, 1H, $J_{5,6a}$=5.2 Hz, H-6b), 3.75 (dd, 1H, $J_{5',6a'}$=5.2 Hz, H-6b′), 3.75 (dd, 1H, $J_{3',4'}$=9.6 Hz, H-3′), 3.64 (t, 1H, $J_{4',5'}$=9.6 Hz, H-4′), 3.60 (m, 1H, $J_{3,4}$=9.0 Hz, H-3), 3.57–3.47 (m, 2H, H-5, H-5′), 3.48 (t, 1H, $J_{2,3}$=9.0 Hz, H-2), 3.45 (t, 1H,

$J_{3,4}$=9.0 Hz, $J_{4,5}$=9.7 Hz, H-4); ^{13}C NMR (75.5 MHz, D_2O, 60 °C) Table 2 and δ 78.1, 78.0 (C-5, C-5′), 77.1 (C-3), 73.9 (C-3′), 70.7 (C-2′), 70.0 (C-4), 67.2 (C-4′), 61.6, 61.3 (C-6, C-6′); FAB-MS *m/z* 401 ([M+H]$^+$, 43%), 423 ([M+Na]$^+$, 76%); HRFAB-MS *m/z* calcd for [M+Na]$^+$ $C_{13}H_{23}N_2NaO_{10}S$: 423.1049, found: 423.1046.

3.2.10. 1,6-Bis[3-(β-D-glucopyranosyl)thioureido]hexane (12j). Purification by gel filtration chromatography gave **12j**: 325 mg, 84% as a syrup. R_f=0.45 (3:2:1 EtOAc/EtOH/H_2O); $[\alpha]_D^{20}$ −15° (*c* 1.0, H_2O); IR: ν_{max} 3295, 2932, 1691, 1660, 1541, 1364, 1103, 1024, 874 cm^{-1}; ^{1}H NMR (300 MHz, D_2O, 60 °C) Table 2 and δ 3.88 (dd, 1H, $J_{5,6a}$=1.9 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.72 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.56 (t, 1H, $J_{2,3}$=8.9 Hz, $J_{3,4}$=8.9 Hz, H-3), 3.53 (ddd, 1H, $J_{4,5}$=9.2 Hz, H-5), 3.51 (m, 2H, CH_2) 3.45 (t, 1H, H-4), 1.60 (m, 2H, CH_2), 1.36 (m, 2H, CH_2); ^{13}C NMR (75.5 MHz, D_2O, 60 °C) Table 2 and δ 77.8 (C-5), 77.2 (C-3), 70.1 (C-4), 61.4 (C-6), 28.4 (CH_2β), 26.1 (CH_2γ); FAB-MS *m/z* 581 ([M+Na]$^+$, 21%); HRFAB-MS *m/z* calcd for [M+Na]$^+$ $C_{20}H_{38}N_2NaO_{10}S_2$: 581.1927, found: 581.1918.

3.2.11. 1,12-Bis[3-(β-D-glucopyranosyl)thioureido]dodecane (12k). Purification by gel filtration chromatography gave **12k**: 345 mg, 77% as a syrup. R_f=0.69 (3:2:1 EtOAc/EtOH/H_2O); $[\alpha]_D^{27}$ +13° (*c* 0.6, DMSO); IR: ν_{max} 3308, 2915, 1689, 1622, 1520, 1456, 1370, 1105, 1024, 872 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) Table 2 and δ 7.43 (d, 1H, $J_{NH,H\text{-}1}$=8.2 Hz, NH), 7.37 (t, 1H, J_{NH,CH_2}=5.0 Hz, NH′), 4.62–4.50 (m, 3H, 3OH), 3.99 (m, 1H, OH-6), 3.66 (m, 1H, $J_{5,6a}$=2.5 Hz, $J_{6a,6b}$=11.6 Hz, H-6a), 3.47 (m, 1H, $J_{5,6b}$=4.8 Hz, H-6b), 3.42 (q, 2H, $J_{H,H}$=7.0 Hz, CH_2), 3.25 (t, 1H, $J_{2,3}$=8.5 Hz, $J_{3,4}$=8.5 Hz, H-3), 3.20 (ddd, 1H, $J_{4,5}$=9.2 Hz, H-5), 3.14 (t, 1H, H-4), 1.51 (m, 2H, CH_2), 1.28 (m, 8H, 4CH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6, 90 °C) Table 2 and δ 77.4 (C-5), 77.2 (C-3), 70.1 (C-4), 60.8 (C-6), 28.4, 28.2, 28.1, 25.9 (CH_2, dodecane); FAB-MS *m/z* 665 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+Na]$^+$ $C_{26}H_{50}N_4NaO_{10}S_2$: 665.2866, found: 665.2869.

3.2.12. *N*-Butyl-*N*′-(β-D-galactopyranosyl)thiourea (13b). Purification by column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **13b**: 218 mg, 53% as a syrup. R_f=0.51. (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{24}$ −1° (*c* 1.1, H_2O); IR: ν_{max} 3331, 2932, 1647, 1557, 1360, 1032 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) Table 2 and δ 3.94 (m, 1H, $J_{4,5}$=~0.0 Hz, H-4), 3.75–3.61 (m, 5H, H-2, H-3, H-5, H-6a, H-6b), 3.51 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.31 (m, 2H, CH_2), 0.87 (t, 3H, *J*=7.3 Hz, CH_3); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 77.5 (C-5), 74.6 (C-3), 69.9 (C-4), 62.2 (C-6), 31.4 (CH_2), 20.6 (CH_2), 14.2 (CH_3); FAB-MS *m/z* 295 ([M+H]$^+$, 52%), 317 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$: 295.1328, found: 295.1326.

3.2.13. *N*,*N*-Diethyl-*N*′-(β-D-galactopyranosyl)thiourea (13d). Purification column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **13d**: 282 mg, 69% as an amorphous solid. R_f=0.51 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{28}$ +15° (*c* 0.5, H_2O); IR: ν_{max} 3324, 2974, 1543, 1424, 1354, 1279, 1121 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) Table 2 and δ 3.96 (m, 1H, $J_{4,5}$=~0.0 Hz, H-4), 3.70 (m, 4H, $J_{2,3}$=9.8 Hz, $J_{3,4}$=2.6 Hz, H-3, H-5, H-6a, H-6b), 3.69 (m, 4H, *J*=7.1 Hz, 2CH_2), 1.17 (t, 6H, 2CH_3); ^{13}C NMR (125.7 MHz, D_2O) Table 2 and δ 77.6 (C-5), 74.9 (C-3), 70.0 (C-4), 62.2 (C-6), 12.7 (2CH_3); FAB-MS *m/z* 295 ([M+H]$^+$, 38%), 317 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$ $C_{11}H_{22}N_2O_5S$: 295.1328, found: 295.1328.

3.3. General methods for the synthesis of cyclic isoureas 14

Method A. To a solution of the crude thiourea **12** prepared as described above starting from β-D-glucopyranosylamine (1.40 mmol) in 1:1 H_2O/dioxane (5 mL) was one-pot added yellow mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.). The mixture was stirred at rt for 1–4 h until TLC showed disappearance of the corresponding thiourea, and then it was filtered through a Celite pad. The filtrate was concentrated to dryness and purified by silica gel column chromatography, except for **14j**, that was crystallized from EtOH.

Method B. To a solution of a purified thiourea **12a**,**c** (0.5 mmol) in MeOH (5 mL) was added yellow mercury oxide (II) (325 mg, 1.5 mmol, 3.0 equiv.). The mixture was stirred at rt for 6 h and then it was filtered through a Celite pad. The filtrate was concentrated to dryness and purified by silica gel column chromatography.

Method C. To a solution of **12h** (0.5 mmol) in 1:1 H_2O/dioxane (5 mL) was added yellow mercury oxide (II) (325 mg, 1.5 mmol, 3.0 equiv.). The mixture was stirred at rt for 3 h and then it was filtered through a Celite pad. The filtrate was concentrated to dryness to give pure **14h**.

3.3.1. 4,5-Dihydro-2-*p*-tolylamino-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14a). *Method A*. Column chromatography (CH_2Cl_2→20:1 CH_2Cl_2/MeOH) gave **14a**: 284 mg, 69% as a yellow solid.

Method B. Filtration through a Celite bed gave **14a**: 138 mg, 94%. R_f=0.80 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ +84° (*c* 1.0, DMSO); IR: ν_{max} 3289, 3073, 1663, 1549, 1518, 1381, 1138, 1096, 1040, 937, 882, 820, 719 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) Table 2 and δ 7.22, 7.09 (m, 4H, Ar-H), 3.90 (dd, 1H, $J_{2,3}$=10.5 Hz, $J_{3,4}$=7.6 Hz, H-3), 3.89 (dd, 1H, $J_{6a,6b}$=12.2 Hz, H-6a), 3.73 (dd, 1H, $J_{5,6b}$=5.3 Hz, H-6b), 3.53 (m, 1H, H-5), 3.40 (dd, 1H, $J_{4,5}$=9.6 Hz, H-4), 2.27 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, CD_3OD) Table 2 and δ 133.9, 130.4, 121.1 (Ar), 83.1 (C-5), 75.6 (C-3), 73.6 (C-4), 62.7 (C-6), 20.8 (CH_3); CI-MS *m/z* 295 ([M+H]$^+$, 46%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{14}H_{19}N_2O_5$: 295.1294, found: 295.1287.

3.3.2. 2-Butylamino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14b). *Method A*. Column chromatography (CH_2Cl_2→8:1 CH_2Cl_2/MeOH) gave **14b**: 244 mg, 67% as a white solid. R_f=0.48 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ +108° (*c* 0.39, DMSO); IR: ν_{max} 3439, 3277, 3090, 2955, 1667, 1592, 1435, 1352, 1289, 1244 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) Table 2 and δ 3.96 (dd, 1H, $J_{2,3}$= 10.6 Hz, $J_{3,4}$=7.9 Hz, H-3), 3.86 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.71 (dd, 1H, $J_{5,6b}$=5.6 Hz, H-6b), 3.59 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.39 (dd, 1H, H-4), 3.10 (t, 2H, $J_{H,H}$=6.9 Hz, CH_2α), 1.46 (m, 2H, CH_2β),

1.28 (m, 2H, $CH_2\gamma$), 0.84 (t, 3H, CH_3); ^{13}C NMR (75.5 MHz, D_2O) Table 2 and δ 81.1 (C-5), 73.7 (C-3), 71.8 (C-4), 61.0 (C-6), 30.7 ($CH_2\beta$), 19.4 ($CH_2\gamma$), 13.1 (CH_3); CI-MS *m/z* 261 ([M+H]$^+$, 100%), 243 ([M+H−H_2O]$^+$, 16%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{11}H_{20}N_2O_5$: 261.1449, found: 261.1450. Anal. calcd for $C_{11}H_{20}N_2O_5$: C, 50.76; H, 7.74; N, 10.76, found: C, 50.61; H, 7.94; N, 11.01.

3.3.3. 4,5-Dihydro-2-octylamino-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14c). *Method A*. Column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **4c**: 221 mg, 50% as a white solid.

Method B. Column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **14c**: 119 mg, 75%. R_f=0.36 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$+82° (*c* 0.83, DMSO); IR: ν_{max} 3312, 2924, 2855, 1651, 1539, 1456, 1373, 1101, 1038, 876 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) Table 2 and δ 3.86 (dd, 1H, $J_{5,6a}$=2.6 Hz, $J_{6a,6b}$=12.1 Hz, H-6a), 3.85 (t, 1H, $J_{2,3}$= 9.8 Hz, $J_{3,4}$=7.7 Hz, H-3), 3,72 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.48 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.37 (dd, 1H, H-4), 3.14 (t, 2H, $J_{H,H}$=7.0 Hz, CH_2), 1.54 (m, 2H, CH_2), 1.31 (m, 10H, 5CH_2), 0.90 (t, 3H, CH_3); ^{13}C NMR (125.7 MHz, CD_3OD) Table 2 and δ 83.1 (C-5), 75.7 (C-3), 73.7 (C-4), 62.7 (C-6), 33.0, 30.5, 30.4, 30.4, 27.8, 23.7 (CH_2), 14.4 (CH_3); CI-MS *m/z* 299 ([M+H−H_2O]$^+$, 35%), 317 ([M+H]$^+$, 100%), 633 ([2M+H]$^+$, 5%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{15}H_{29}N_2O_5$: 317.2076, found: 317.2076.

3.3.4. 2-Diethylamino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14d). *Method A*. Column chromatography (CH_2Cl_2→3:1 CH_2Cl_2/MeOH) gave **14d** (255 mg, 57%) and urea **15d** (70 mg, 18%), which was identical with the product prepared in Section 3.3.10. Data for compound **14d**: R_f=0.69 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ +114° (*c* 0.56, DMSO); IRν_{max} 3324, 2922, 2855, 1642, 1431, 1358, 1314, 1155, 1065, 876, 735 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 2 and δ 3.85 (dd, 1H, $J_{5,6a}$= 2.0 Hz, $J_{6a,6b}$=12.0 Hz, H-6a), 3.86 (dd, 1H, $J_{2,3}$=10.4 Hz, H-3), 3.71 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.49 (ddd, 1H, H-5), 3.33 (m, 5H, H-4, 2CH_2), 1.15 (1, 3H, $J_{H,H}$=7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, CD_3OD) Table 2 and δ 83.1 (C-5), 75.8 (C-3), 73.7 (C-4), 62.8 (C-6), 13.7 (2CH_3); CI-MS *m/z* 225 ([M+H−2H_2O]$^+$, 3%), 243 ([M+H−H_2O]$^+$, 14%), 261 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{11}H_{21}N_2O_5$: 261.1450, found: 261.1454.

3.3.5. 4,5-Dihydro-2-(piperidin-1-yl)-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14e). *Method A*. Column chromatography (CH_2Cl_2→3:1 CH_2Cl_2/MeOH) gave **14e**: 177 mg, 47% as a white solid. R_f=0.48 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{27}$ +107° (*c* 1.0, DMSO); IR: ν_{max} 3376, 3330, 2936, 2855, 1645, 1443, 1356, 1167, 1047, 729 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) Table 2 and δ 3.86 (dd, $J_{2,3}$=10.6 Hz, $J_{3,4}$=7.7 Hz, H-3), 3.85 (dd, 1H, $J_{5,6a}$= 2.3 Hz, $J_{6a,6b}$=12.0 Hz, H-6a), 3.72 (dd, 1H, $J_{5,6b}$=5.2 Hz, H-6b), 3.49 (m, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.36 (dd, 1H, H-4), 1.64 (m, 2H, CH_2), 1.57 (m, 4H, 2CH_2); ^{13}C NMR (125.7 MHz, CD_3OD) Table 2 and δ 83.1 (C-5), 75.8 (C-3), 73.7 (C-4), 62.8 (C-6), 26.4, 25.1 (CH_2); CI-MS *m/z* 273 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{12}H_{21}N_2O_5$: 273.1450, found: 273.1447.

3.3.6. 2-(β-D-Glucopyranosyl)amino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14h). *Method C*. Filtration through a Celite bed gave pure **14h**: 82 mg, 89% as a syrup. R_f=0.25 (3:2:1 EtOAc/EtOH/H_2O); [α] +28° (*c* 0.5, H_2O); IR ν_{max} 3306, 2918, 1651, 1559, 1364, 1125, 993 cm^{-1}; ^1H NMR (500 MHz, D_2O) Table 2 and δ 4.72 (d, 1H, $J_{1',2'}$=8.9 Hz, H-1′), 4.04 (dd, 1H, $J_{2,3}$= 10.6 Hz, $J_{3,4}$=7.9 Hz, H-3), 3.89 (dd, 1H, $J_{5',6a'}$=2.0 Hz, $J_{6a',6b'}$=12.4 Hz, H-6a′), 3.85 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.74 (dd, 1H, $J_{5,6b}$=5.8 Hz, H-6b), 3.71 (t, 1H, H-2), 3.70 (dd, 1H, $J_{5',6b'}$=5.2 Hz, H-6b′), 3.64 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.52 (t, 1H, $J_{2',3'}$=9.4 Hz, $J_{3',4'}$=9.0 Hz, H-3′), 3.47 (ddd, 1H, $J_{4',5'}$=9.4 Hz, H-5′), 3.43 (dd, 1H, H-4), 3.38 (t, 1H, H-2′), 3.35 (t, 1H, H-4′); ^{13}C NMR (125.7 MHz, CD_3OD) Table 2 and δ 86.0 (C-2), 82.3 (C-5), 78.6 (C-5′), 77.6 (C-3′), 74.6 (C-2′), 73.3 (C-3), 72.8 (C-4), 70.4 (C-4′), 62.0, 61.7 (C-6, C-6′); FAB-MS *m/z* 389 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+Na]$^+$ $C_{13}H_{22}N_2NaO_{10}$: 389.1172, found: 389.1185.

3.3.7. 1,6-Bis{4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazol-2-ylamino}hexane (14j). *Method A*. Crystallization from EtOH gave hygroscopic **14j**: 199 mg, 58%. R_f=0.22 (3:2:1 EtOAc/EtOH/H_2O); [α] +43° (*c* 1.0, H_2O); IR: ν_{max} 3347, 2945, 2836, 1651, 1452, 1371, 1026, 712 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 2 and δ 3.97 (dd, 1H, $J_{2,3}$=10.6 Hz, $J_{3,4}$=7.9 Hz, H-3), 3.87 (dd, 1H, $J_{5,6a}$=2.1 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.72 (dd, 1H, $J_{5,6b}$=5.7 Hz, H-6b), 3.60 (ddd, 1H, $J_{4,5}$=9.6 Hz, H-5), 3.40 (dd, 1H, H-4), 3.11 (t, 4H, $J_{H,H}$=6.8 Hz, 2CH_2), 1.49 (m, 4H, 2CH_2), 1.30 (m, 4H, 2CH_2); ^{13}C NMR (75.5 MHz, D_2O) Table 2 and δ 81.6 (C-5), 74.2 (C-3), 72.3 (C-4), 61.5 (C-6), 29.0 ($CH_2\beta$), 26.2 ($CH_2\gamma$); FAB-MS 513 *m/z* ([M+Na]$^+$, 17%); HRFAB-MS *m/z* calcd for [M+Na]$^+$ $C_{20}H_{34}N_4NaO_{10}$: 513.2173, found: 513.2214.

3.3.8. 2-Bencylamino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14l). *Method A*. Column chromatography (CH_2Cl_2→3:1 CH_2Cl_2/MeOH) gave **14l**: 235 mg, 57% as a white solid. R_f=0.62 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ +73° (*c* 1.2, DMSO) IR: ν_{max} 3283, 1633, 1375, 1101, 1040, 874 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) Table 2 and δ 7.34–7.21 (m, 5H, Ar-H), 5.51, 5.29 (bs, 2H, 2OH), 4.65 (bs, 1H, OH-6), 4.22 (s, 2H, CH_2), 3.67 (dd, 1H, $J_{2,3}$=10.2 Hz, $J_{3,4}$=7.6 Hz, H-3), 3.64 (m, 1H, $J_{6a,6b}$= 12.9 Hz, H-6a), 3.46 (m, 1H, H-6b), 3.29 (m, 1H, $J_{4,5}$= 8.9 Hz, H-5), 3.15 (bt, H-4); ^{13}C NMR (300 MHz, DMSO-d_6) Table 2 and δ 139.8, 128.3, 127.2, 126.8 (Ar), 81.9 (C-5), 74.0 (C-3), 72.2 (C-4), 61.0 (C-6); CI-MS *m/z* 277 ([M+H−H_2O]$^+$, 35%), 295 ([M+H]$^+$, 100%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{14}H_{19}N_2O_5$: 295.1294, found: 295.1289. Anal. calcd for $C_{14}H_{18}N_2O_5{\cdot}1/2H_2O$: C, 55.44; H, 6.31; N, 9.24, found: C, 55.50; H, 5.98; N, 9.41.

3.3.9. 2-(6-Deoxy-1,2:3,4-di-*O*-isopropilidene-α-D-galactopyranos-6-yl)amino-4,5-dihydro-(1,2-dideoxy-β-D-glucopyranoso)[1,2-*d*]-1,3-oxazole (14m). *Method A*. Column chromatography (CH_2Cl_2→10:1 CH_2Cl_2/MeOH) gave **14m**: 369 mg, 59% as a syrup. R_f=0.66 (5:1 CH_2Cl_2/MeOH); [α] +50° (*c* 0.9, MeOH); IR: ν_{max} 3312, 2928,

1661, 1373, 1101, 1067, 1005, 874 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) Table 2 and δ 5.43 (d, 1H, $J_{1',2'}$=5.0 Hz, H-1′), 4.58 (dd, 1H, $J_{2',3'}$=2.4 Hz, $J_{3',4'}$=7.9 Hz, H-3′), 4.30 (dd, 1H, H-2′), 4.21 (dd, 1H, $J_{4',5'}$=1.6 Hz, H-4′), 3.97 (m, 1H, H-5′), 3.81 (dd, 1H, $J_{5,6a}$=2.2 Hz, $J_{6a,6b}$=12.1 Hz, H-6a), 3.80 (dd, 1H, $J_{2,3}$=10.6 Hz, $J_{3,4}$=7.6 Hz, H-3), 3.66 (dd, 1H, $J_{5,6b}$=5.4 Hz, H-6b), 3.44 (m, 2H, H-2, H-5), 3.33 (dd, 1H, $J_{5',6a'}$=4.0 Hz, $J_{6a',6b'}$=13.8 Hz, H-6a′), 3.26 (dd, 1H, $J_{4,5}$=9.6 Hz, H-4), 3.22 (dd, 1H, $J_{5',6b'}$=8.5 Hz, H-6b′), 1.45, 1.36, 1.29, 1.28 (4s, 3H each, $4CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD) Table 2 and δ 110.5, 110.0 (Me_2C), 83.2 (C-5), 75.7 (C-3), 73.7 (C-4), 72.7 (C-4′), 72.2 (C-3′), 71.9 (C-2′), 67.4 (C-5′), 62.9 (C-6), 43.9 (C-6′), 26.5, 26.3, 25.2, 24.5 (CH_3); CI-MS *m/z* 429 ($[M+H-H_2O]^+$, 4%); FAB-MS *m/z* 469 ($[M+Na]^+$, 100%), 447 ($[M+H]^+$, 40%); HRFAB-MS *m/z* calcd for $[M+H]^+$ $C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1969.

3.3.10. *N*,*N*-Diethyl-*N*′-(β-D-glucopyranosyl)urea (15d). To a solution of the crude thiourea **12d** prepared as described above starting from β-D-glucopyranosylamine **3** (250 mg, 1.40 mmol) in 1:1 H_2O/dioxane (5 mL) was one-pot added yellow mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.). The mixture was stirred at rt for 2 h and then an extra amount of yellow mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.) was added and the mixture was stirred for other 2 h. After that it was filtered through a Celite pad, the filtrate was concentrated to dryness and purified by silica gel column chromatography to give **15d** (331 mg, 85% from **3**) as a syrup. R_f=0.19 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{24}$ +5° (*c* 1.0, MeOH); IR: ν_{max} 3266, 2947, 2839, 1663, 1543, 1449, 1103, 1022 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 2 and δ 3.84 (dd, 1H, $J_{5,6a}$=1.8 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 3.66 (dd, 1H, $J_{5,6b}$=5.6 Hz, H-6b), 3.50 (t, 1H, $J_{2,3}$=9.2 Hz, $J_{3,4}$=9.2 Hz, H-3), 3.47 (ddd, 1H, $J_{4,5}$=9.7 Hz, H-5), 3.35 (t, 1H, H-4), 3.27 (m, 4H, $2CH_2$), 1.08 (t, 6H, $2CH_3$); ^{13}C NMR (75.5 MHz; D_2O) Table 2 and δ 77.5 (C-5), 77.0 (C-3), 69.8 (C-4), 61.0 (C-6), 12.9 (CH_3); FAB-MS *m/z* 301 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+Na]^+$ $C_{11}H_{22}N_2NaO_6$ 301.1376, found: 301.1384.

3.3.11. *N*-[(β-D-Glucopyranosyl)carbamoyl]piperidine (15e). To a solution of the crude thiourea **12e** prepared as described above starting from β-D-glucopyranosylamine (250 mg, 1.40 mmol) in 1:1 H_2O/dioxane (5 mL) was one-pot added yellow mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.). The mixture was stirred at rt for 2 h and TLC showed disappearance of **12e** and formation of isourea **14e**. An extra amount of yellow mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.) was added, the mixture was stirred for 5 days, and TLC showed no appreciable formation of a new compound. The mixture was filtered through a Celite pad, the filtrate was concentrated to dryness and the residue was dissolved in water (5 mL). Mercury oxide (II) (910 mg, 4.2 mmol, 3.0 equiv.) was added and the mixture was kept at rt for 3 months. Conventional work-up and purification by silica gel column chromatography gave isourea **14e** (52 mg, 14%) as the first eluted compound. Eluted second was **15e** (134 mg, 33% from **3**), R_f=0.18 (5:1 CH_2Cl_2/MeOH); $[\alpha]_D^{27}$ −20° (*c* 1.0, H_2O); IR: ν_{max} 3395, 2940, 1647, 1539, 1454, 1364, 1013 cm^{-1}; ^1H NMR (300 MHz, D_2O) Table 2 and δ 3.92 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=12.3 Hz, H-6a), 3.75 (dd, 1H, $J_{5,6b}$=5.6 Hz, H-6b), 3.58 (t, 1H, $J_{2,3}$=9.2 Hz, $J_{3,4}$=9.2 Hz, H-3), 3.54 (ddd, 1H, $J_{4,5}$=9.9 Hz, H-5), 3.44 (m, 5H, H-4, $2CH_2$), 1.66 (m, 2H, CH_2), 1.58 (m, 4H, $2CH_2$); ^{13}C NMR (75.5 MHz; D_2O) Table 2 and δ 78.4 (C-5), 77.9 (C-3), 70.7 (C-4), 62.0 (C-6), 26.4, 24.9 (CH_2); FAB-MS *m/z* 313 ($[M+Na]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{12}H_{23}N_2O_6$: 291.1556, found: 291.1567.

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Regioselective and enantioselective synthesis of seven-membered ring cyclic arylguanidine and urea derivatives

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Abstract—Cycloaddition reaction of 2-vinylpyrrolidines with carbodiimides in the presence of palladium acetate and dpppentane affords seven-membered ring cyclic arylguanidines in good yields and conversions. When 1-butyl-4-methyl-2-vinylpyrrolidine **1c** was used as a mixture of *trans* and *cis* isomers in a 4:1 ratio, and reacted with bis(2-chlorophenyl)carbodiimide **2a**, high stereoselectivity was achieved and only the *trans* seven-membered cyclic guanidine was obtained. A methyl group in the 4-position of the pyrrolidine ring and the chloro substituent in the *ortho* position of the carbodiimide may be responsible for the enhanced product ratio in favor of the *trans* isomer.

1. Introduction

Seven-membered ring heterocycles have recently attracted attention due to their biologically activities, such as seven-membered ring cyclic ureas DMP 323 and DMP 450, which are notable members of a promising class of highly potent HIV protease inhibitors.[1] Recent reports have also shown that cyclic cyanoguanidines[2] and sulfamide[3] analogues of DMP 323 display high inhibitory activity. In initially reported routes to DMP 323, DMP 450 and related compounds, the urea moiety was formed by reaction of highly toxic phosgene, or a phosgene derivative, with an O-protected diaminediol.[4] Recently, the utility of functionalized 1,4-diamines, produced via a temporary phosphorus tether (P-tethers)/ring-closing metathesis (RCM)/hydrolysis sequence, was demonstrated in the synthesis of a number of structurally diverse DMP 323 analogues, including the seven-membered ring heterocyclic ureas and sulfamides.[5] More recently, catalytic carbonylation of functionalized diamines afforded the core structure of DMP 323 and DMP 450.[6] However, there is still need for further development of metal-catalyzed synthesis methodology, since the direct metal-catalyzed synthesis of seven-membered ring heterocycles could provide an attractive alternative to the multiple step synthetic routes to prepare seven-membered ring ureas and related compounds. There are examples of the reaction of three- or four-membered ring heterocycles such as thiiranes,[7] aziridines,[8] oxiranes,[9] azetidines[10] and oxetanes[11] with heterocumulenes to form five- or six-membered ring heterocycles. Only a few successful metal-catalyzed reactions are known for the preparation of seven-membered cyclic compounds.[12,13]

We previously reported the first use of 2-vinylpyrrolidines and aryl isocyanates for cycloaddition reactions catalyzed by palladium complexes, thus affording 1, 3-diazepan-2-one derivatives in high regioselectivity and good yields.[14] Herein, we describe the first examples of the highly regioselective palladium-catalyzed cyclization reaction of 2-vinylpyrrolidines with carbodiimides for the formation of arylguanidines derivatives. This reaction provides a convenient entry to seven-membered ring cyclic arylguanidines, analogues of 1, 3-diazepan-2-one derivatives that are of interest in the pharmaceutical sector. Moreover, an asymmetric catalytic synthesis of seven-membered ring cyclic ureas and arylguanidines by adding a chiral ligand to the reaction mixture is also described herein.

2. Results and discussion

2.1. Cycloaddition reaction of 2-vinylpyrrolidines with various carbodiimides

The reaction of *N*-butyl-2-vinylpyrrolidines **1a** (0.2 mmol) with bis(*p*-chlorophenyl)-carbodiimide **2c** (0.4 mmol) was first investigated by using reaction conditions similar to those described for the reaction of 2-vinylpyrrolidines with aryl isocyanates. These reaction conditions are not suitable for the present reaction, that is reaction of **1a** with **2c** in the presence of 15 mol% $Pd(OAc)_2$ and 60 mol% PPh_3 in 3 mL

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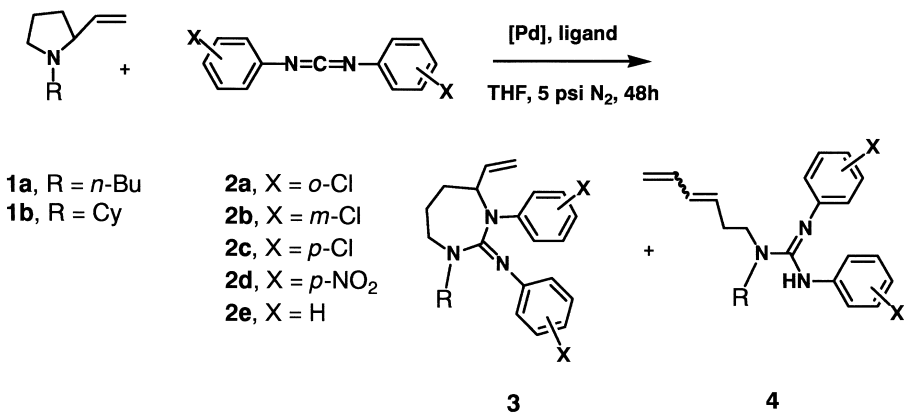


Scheme 1.

Table 1. Optimized cyclization reaction of 1-butyl-2-vinylpyrrolidine **1a** with bis(*p*-chlorophenyl)carbodiimide **2c** catalyzed by palladium[a]

Entry	Equiv. (**2c**/**1a**)	Palladium/ligand (mol%)	Conv. (%)[b]	Yields (%)[c] **3c**, **4c** (ratio)[d]
1	2	$Pd(OAc)_2/PPh_3$ (15:60)	<10	0
2	1.2	$Pd(OAc)_2$/dppf (15:30)	100	0, 35
3	2	$Pd(OAc)_2$/dppp (15:30)	75	14, 56 (20:80)
4	2	$Pd(OAc)_2$/dppb (15:30)	65	11, 42 (21:79)
5	2	$Pd(OAc)_2$/dpppentane (15:30)	97	**56**, **28** (67:33)
6	1.5	$Pd(OAc)_2$/dpppentane (15:30)	95	**70**, **11** (86:14)
7	1.1	$Pd(OAc)_2$/dpppentane (15:30)	51	39, 5 (88:12)
8	2	$Pd_2(dba)_3{\cdot}CHCl_3$/dpppentane (15:30)[e]	33	25, 3 (93/7)

[a] $Pd(OAc)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphine ligand were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1a** and **2c** under 5 psi at 130 °C in a glass autoclave.
[b] The conversion was determined from GC by using biphenyl as an internal standard or was calculated based on the crude ^1H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1a** used.
[d] Based on the isolated yield of **3c** and **4c**, and in most cases **4c** consisted a 1:1 ratio of *trans* and *cis* isomers.
[e] The reaction was conducted at 135 °C.

THF under argon, resulted in no conversion at room temperature (Scheme 1). When the reaction temperature was increased to 130 °C, only 10% conversion was achieved with none of the expected product formed at all (Table 1, entry 1). The bidentate phosphine ligand dppf, which has similar basicity to PPh_3, only gave the ring-opened product **4c** in 35% yield and 100% conversion at 130 °C in 48 h, accompanied by unidentified products (Table 1, entry 2). The alkyl phosphine ligands dppp and dppb showed similar selectivity, affording both the cyclic guanidine **3c** and ring-opened compound **4c**, which can be separated by GC and silica gel chromatography very well. The ring-opened product **4c** was usually formed as the major product (Table 1, entries 3 and 4). We found that the more basic bidentate phosphine dpppentane was the ligand of choice for achieving higher regioselectivity. Under the same reaction conditions as those described above, products **3c** and **4c** were obtained in a 67:33 ratio and in 84% yield and 97% conversion (Table 1, entry 5). This result is also consistent with these we reported previously indicating that phosphine ligands with higher basicity favor the formation of ring-cyclized products.[14]

It is noteworthy that the amount of carbodiimide used has a significant effect on the selectivity of the product formed. When the number of equivalents of **2c** to **1a** was reduced from 2 to 1.1 equiv., the ratio of **3c**/**4c** (88:12) increased, but the yield and conversion were lower (Table 1, entries 6 and 7). Use of 15 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 30 mol% of dpppentane gave **3c**/**4c** in a higher ratio (93/7), but in low yield and conversion (28 and 33%, respectively, Table 1, entry 8).

Based on the reaction conditions above, we concluded that the catalytic system consisting of palladium acetate and dpppentane is preferred for this reaction. Reaction of several 2-vinylpyrrolidines **1a**–**c** and carbodiimides **2a**–**f** was investigated, and the results are summarized in Tables 2 and 3.

Note that in all the reactions of 2-vinylpyrrolidines **1a**–**c** with carbodiimides **2a**–**c** (except **1a** with **2c**), greater regioselectivity was obtained and the desired cyclic arylguanidines **3** were formed exclusively. Only traces, if any, of **4** was observed in these reactions (Table 2). For example, when 1-butyl-2-vinylpyrrolidine **1a** was used as the substrate for reaction with 1.2 equiv. of bis(*o*-chlorophenyl)carbodiimide **2a** and bis(*m*-chlorophenyl)carbodiimide **2b**, in the presence of 10 mol% $Pd(OAc)_2$ and 20 mol% dpppentane at 130 °C for 24 and 36 h, **3a** and **3b** were isolated in 81 and 83% yields with 98 and 99% conversions, respectively, and only a trace of **4a** was observed in both cases (Table 2, entries 1 and 2).

Due to steric effects, 1-cyclohexyl-2-vinylpyrrolidine **1b** exhibited less reactivity compared to **1a**, and slightly higher, and longer, reaction temperature and times, respectively, are needed, affording products in moderate yields and conversions. Reaction of **1b** with 1.5 equiv. of **2a** and **2b** at 145 °C for 48 h gave **3d** and **3e** in 45 and 51% yields, and in 51 and 60% conversions, respectively, (Table 2, entries 4 and 5).

Table 2. Palladium catalyzed cyclization reactions of 2-vinylpyrrolidine **1** with carbodiimides **2** in THF[a]

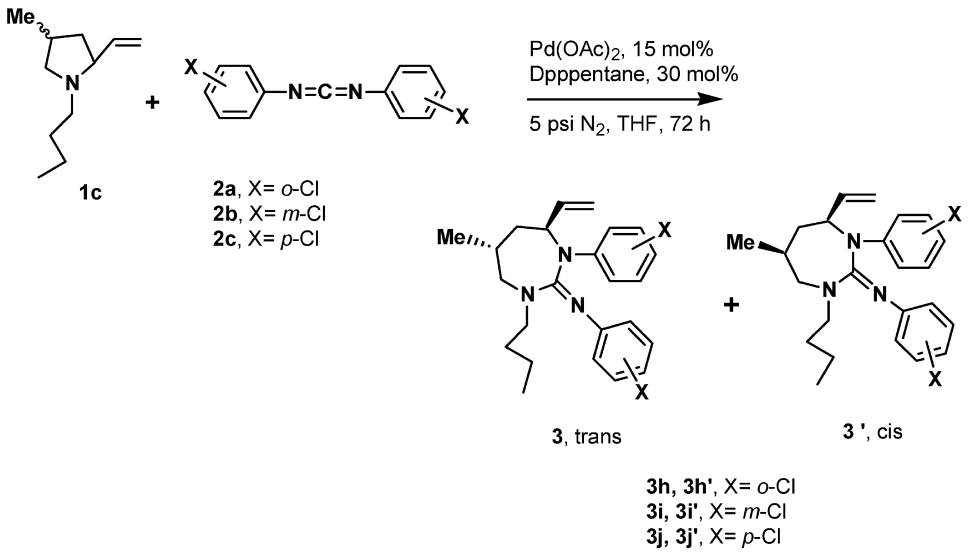
Entry	1	2 (equiv.)	$Pd(OAc)_2$/dpppentane (mol%)	Time (h)	Conv. (%)[b]	3, Yield (%)[c]	4, Yield, %[c] (*trans*/*cis*)[d]
1	**1a**	**2a** (1.2)	(10:20)	24	98	**3a**, 81	Trace
2	**1a**	**2b** (1.2)	(10:20)	36	99	**3b**, 83	0
3	**1a**	**2c** (1.5)	(15:30)	48	95	**3c**, 70	**4c**, 11 (50:50)
4	**1b**	**2a** (1.5)	(15:30)	48	51	**3d**, 45	0
5	**1b**	**2b** (1.5)	(15:30)	48	60	**3e**, 51	0
6	**1b**	**2c** (1.5)	(15:30)	48	35	**3f**, 23	Trace
7	**1a**	**2d** (1.5)	(15:30)	48	98	**3g**, trace	**4g**, 45 (70:30)
8	**1a**	**2e** (2)	(15:30)	48	<20	0	0

[a] $Pd(OAc)_2$ and dpppentane were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1** and **2** under 5 psi at the specified temperature in a glass autoclave.
[b] The conversion was determined by GC using biphenyl as the internal standard or was calculated based on the crude ^{1}H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1** used.
[d] Based on ^{1}H NMR.

When **2c** was used as the reactant, however, the cycloaddition reaction gave **3f** in a lower isolated yield of 23% (Table 2, entry 6). The strength of the electron-withdrawing substituent on an aryl carbodiimide significantly affects the nature of the formed product. When bis(*p*-nitrophenyl)-carbodiimide **2d** was used in the reaction with **1a**, the substrate was nearly fully consumed in 48 h at a relatively lower temperature of 110 °C but gave only traces of **3g** with the ring-opened product **4g** isolated in 45% yield (Table 2, entry 7). Some unknown products were obtained as well. No reaction occurred between bisphenylcarbodiimide **2e** and **1a** at 150 °C for 2 days (Table 2, entry 8). These results may be understood based on the fact that an electron-withdrawing group at the *para*-position of aryl carbodiimides generally enhances the rate of the ring-opening reaction. Aryl carbodiimides with an electron-donating group, or with no substituent, make the electrophilic carbodiimide carbon atom less reactive towards the nucleophilic nitrogen of the (π-allyl)palladium intermediate generated by oxidative addition of pyrrolidine to the palladium-(0) species.

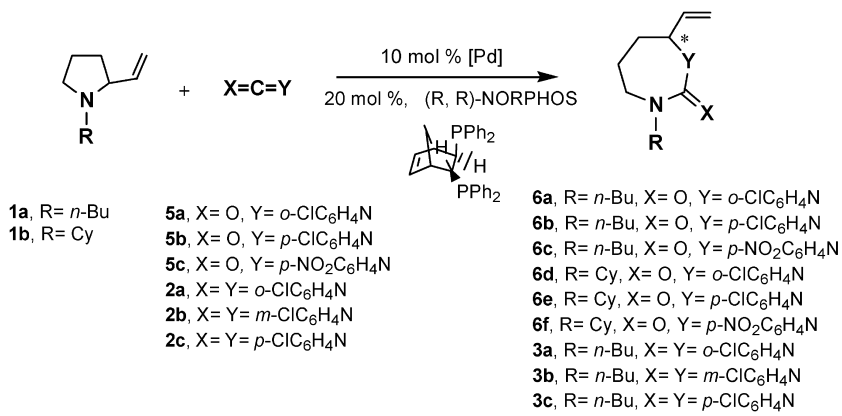
We also investigated the stereoselectivity of the reaction by using 1-butyl-4-methyl-2-vinylpyrrolidine **1c** as the substrate. The latter was a 4:1 mixture of *trans* and *cis* isomers (inseparable by GC and TLC). Reaction of **1c** with bis(chlorophenyl)carbodiimides **2a–c** were sluggish possibly because of the steric hindrance caused by the methyl group in **1c**. Nevertheless, the products were isolated in moderate to good yields (Table 3). Reaction of **1c** with **2c** at 140 °C led to both *trans* and *cis* isomers in 31 and 8%

Table 3. Cyclization reactions of 1-butyl-4-methyl-2-vinylpyrrolidine **1c** with carbodiimides **2** catalyzed by $Pd(OAc)_2$ and dpppentane in THF[a]



Entry	2 (1.5 equiv.)	Conv.[b] (%)	3 (yield, %)[c]	3′ (yield, %)[c]
1	**2a**	42	**3h**, 35	**3h′**, trace
2	**2b**	79	**3i**, 36	**3i′**, 35
3	**2c**	45	**3j**, 31	**3j′**, 8

[a] $Pd(OAc)_2$ and dpppentane were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1c** and **2** under 5 psi N_2 at 140–145 °C in a glass autoclave.
[b] The conversion was determined by GC using biphenyl as the internal standard, or was calculated based on the crude ^{1}H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1c** used.



Scheme 2.

yields (45% conversion), respectively, (Table 3, entry 3). When bis(*m*-chlorophenyl)carbodiimide **2b** was used as the reactant, the total yield of the products increased to 71%, but in low stereoselectivity, and almost the same ratio of *trans* and *cis* isomers was obtained. All the *trans* and *cis* isomers obtained can be easily separated by means of GC and silica gel columns (Table 3, entry 2). Under the same reaction conditions, bis(*o*-chlorophenyl)carbodiimide **2a** gave greater stereoselectivity, with the *trans* product **3h** obtained in 35% yield and in 42% conversion, and only traces of the ring-opened product was observed (Table 3, entry 1). The higher selectivity may be due to steric hindrance by the *ortho* substituents on the phenyl rings, and the methyl group of the pyrrolidine ring. All the reactions may proceed via the formation of a (π-allyl)palladium complex as described previously.[14]

2.2. Asymmetric cyclization reactions of 2-vinylpyrrolidines with aryl isocyanates and carbodiimides using chiral phosphine ligands

The enantioselective variant of the reaction was next investigated (Scheme 2), because this may be a more convenient way to synthesize the biologically relevant targets through one-pot asymmetric catalytic cyclization reactions. To our knowledge, this report is the first example of the asymmetric catalytic synthesis of seven-membered ring diazepan-2-ones and arylguanidines. Several chiral ligands were investigated for the cycloaddition reactions of 1-butyl-2-vinylpyrrolidines **1a** and **1b** with *p*-chlorophenyl isocyanate **5b**. The NORPHOS type ligand with $Pd_2(dba)_3 \cdot CHCl_3$ or $Pd(OAc)_2$ is efficient for the cycloaddition reaction.[16]

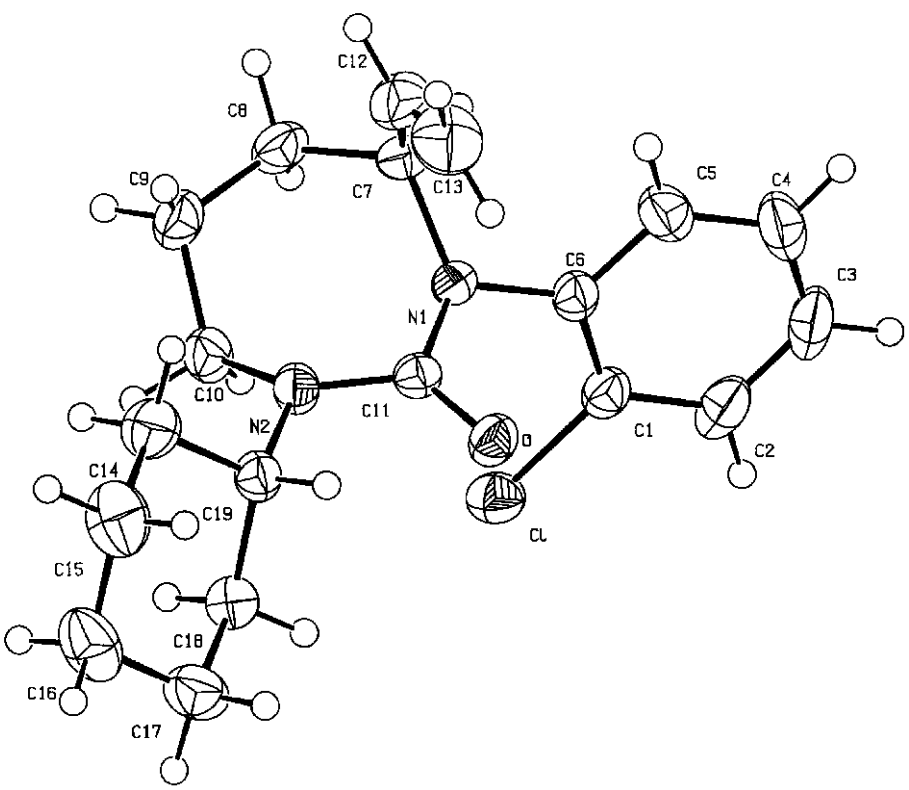


Figure 1. ORTEP view of **6d**.

Table 4. Asymmetric cyclization reactions of 2-vinylpyrrolidine **1** with heterocumulenes catalyzed by palladium and (R,R)-NORPHOS in THF[a]

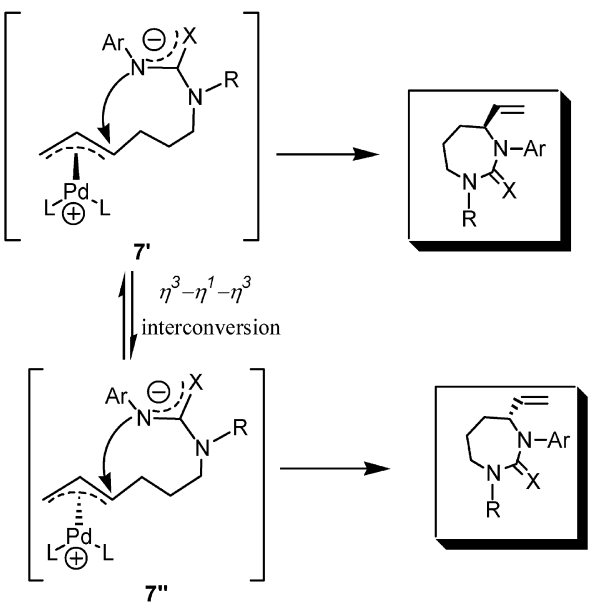
Entry	1	5 or 2	[Pd]	Temp. (°C)	Time (h)	Conv. (%)[b]	Product, yield (%)[c]	ee (%)[d]
1	**1a**	**5a**	$Pd_2(dba)_3{\cdot}CHCl_3$	rt	48	98	**6a**, 65	20
2	**1a**	**5b**	$Pd_2(dba)_3{\cdot}CHCl_3$	rt	24	51	**6b**, 42	23
3	**1a**	**5c**	$Pd_2(dba)_3{\cdot}CHCl_3$	50 (5 psi)	24	96	**6c**, 31	6
4	**1b**	**5a**	$Pd_2(dba)_3{\cdot}CHCl_3$	rt	48	18	**6d**, 15	26
5	**1b**	**5a**	$Pd_2(dba)_3{\cdot}CHCl_3$[e]	50 (5 psi)	24	30	**6d**, 24	16
6	**1b**	**5b**	$Pd_2(dba)_3{\cdot}CHCl_3$	rt	48	15	**6e**, 11	39
7	**1b**	**5b**	$Pd_2(dba)_3{\cdot}CHCl_3$[f]	rt	48	8	**6e**, 6	41
8	**1b**	**5b**	Pd $(OAc)_2$	rt	48	28	**6e**, 21	32
9	**1b**	**5c**	$Pd_2(dba)_3{\cdot}CHCl_3$	40 (5 psi)	24	63	**6f**, 32	7
10	**1a**	**2a**	Pd $(OAc)_2$	130 (5 psi)	48	58	**3a**, 44	6
11	**1a**	**2b**	Pd $(OAc)_2$	130 (5 psi)	48	55	**3b**, 32[g]	8
12	**1a**	**2c**	Pd $(OAc)_2$	130 (5 psi)	48	41	**3c**, 22[h]	14

[a] $Pd_2(dba)_3{\cdot}CHCl_3$ or $Pd(OAc)_2$ and chiral phospine ligands were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of the heterocumulene.
[b] The conversion was determined by GC using biphenyl as the internal standard, or was calculated based on the crude ^1H NMR of the mixture.
[c] Isolated yield.
[d] The ee values were determined by chiral HPLC and the absolute configurations of the products were not determined.
[e] 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol% (R,R)-NORPHOS were used.
[f] 15 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 30 mol% (R,R)-NORPHOS were used.
[g] Ring-opened product **4b** was isolated in 14% yield and in 1:2 ratio of *trans* and *cis* isomers.
[h] Ring-opened product **4c** was isolated in 15% yield and in 1/1.5 ratio of *trans* and *cis* isomers.

The influence of the heterocumulenes on the stereoselectivity of the ring-expansion reaction of **1a** was assessed by using (R,R)-NORPHOS as the ligand (Table 4). *o*-Chlorophenyl isocyanate **5a** gave the diazepan-2-one **6a** in good yield and conversion, but in only 20% ee (Table 4, entry 2). Reaction of **1a** with **5b** afforded **6b** in 23% ee and 42% yield (Table 4, entry 1). *p*-Nitrophenyl isocyanate **5c** was less reactive and **1a** was consumed completely in 24 h with **6c** formed in only 6% ee; a side product was obtained, which, unfortunately, defied attempts to purify (Table 4, entry 3). Substrate **1b** was less reactive toward isocyanates, while relatively higher enantioselectivities were obtained compared to that of **1a**. For example, when *o*-chlorophenyl isocyanate **5a** was used for the reaction, **6d** was obtained in 26% enantiomeric excess and in 15% isolated yield (Table 4, entry 4). Attempts to improve the product yield by increasing the reaction temperature (50 °C, 5 psi) only led to a decrease in the enantioselectivity (Table 4, entry 5). The structure of **6d**, obtained from racemates, was unambiguously established by X-ray diffraction (Fig. 1).[15] In the reaction of **1b** with **5b**, chiral 1-cyclohexyl-3-(*p*-chlorophenyl)-4- vinyl-2*H*-1,3-diazepin-2-one **6e** was isolated in 11% yield and 39% ee (15% conversion) (Table 4, entry 6). The ee value of **6e** can be increased to 41% by increasing the amount of the catalyst, but the yield and conversion decreased significantly (Table 4, entry 7). Further increase in the loading of the catalyst only led to the decomposition of isocyanate, and no reaction occurred at all. Use of $Pd(OAc)_2$ instead of $Pd_2(dba)_3{\cdot}CHCl_3$ had little impact on the enantioselectivity of the reaction. For example, when 10 mol% $Pd(OAc)_2$ and 20 mol% NORPHOS were used for the reaction of **1b** with **5b**, the product was obtained in 32% ee and in 21% yield and 28% conversion (Table 4, entry 8). *p*-Nitrophenyl isocyanate **5c** gave the diazepan-2-one in 32% yield and 63% conversion, however, only 7% ee was obtained (Table 4, entry 9). With the increase in the bulkiness of the heterocumulene in going from aryl isocyanate to carbodiimide, to our surprise, the enantioselectivity was decreased dramatically to give chiral **3a**–**c** in 6, 8 and 14% ee values, respectively, with some ring-opened products also isolated in the cases of **2b** and **2c** (Table 4, entries 10–12). This may be due to the fact that the higher reaction temperature for the cycloaddition process decreased the enantioselectivity. Higher ee values were found in the reaction of carbodiimides with 2-vinylthiiranes[7] and -oxiranes[9a,b] systems compared with the corresponded aryl isocyanate.

Reaction of 1-butyl-4-methyl-2-vinylpyrrolidine **1c** with *p*-chlorophenyl isocyanate **5b** in the presence of 15 mol% $Pd(OAc)_2$ and 30 mol% NORPHOS at room temperature in 20 h, gave both the *trans* and *cis* isomers of 1:2 ratio in 25% yield and 30% conversion. The *trans* and *cis* isomers were obtained in 23 and 19% enantiomeric excess, respectively.

The poor enantioselectivity may be explained by a $\eta^3-\eta^1-\eta^3$ pathway involving intermediate **7′** and **7″**, and this interconversion may be faster than the intramolecular nucleophilic attack of the nitrogen atom, which is a little



Scheme 3.

remote and flexible to C-3 of the (π-allyl)palladium intermediate compared with that of the corresponding three-membered ring system[7,9a,b] (Scheme 3).

In summary, we have successfully demonstrated the scope of the ring expansion reaction of 2-vinylpyrrolidines with carbodiimides, catalyzed by $Pd(OAc)_2$ and dpppentane, for the synthesis of seven-membered cyclic arylguanidines. The products were usually isolated in high yields and conversions. Chiral cyclic ureas and cyclic arylguanidines were produced in up to 41% enantiomeric excess, and in moderate yields from cycloaddition reactions of 2-vinylpyrrolidines with heterocumulenes in the presence of catalytic quantities of a palladium complex and (R,R)-NORPHOS.

3. Experimental

All reactions and manipulations of chemicals were carried out using standard Schlenk techniques under an atmosphere of argon. 2-Vinylpyrrolidines[17] and carbodiimides[18] were prepared according to the literature. THF was dried over Na/benzophenone and distilled prior to use. All NMR spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^1H at 7.24 ppm and ^{13}C at 77.0 ppm). Infrared spectra were recorded on a Fourier transform spectrometer and are reported in wavenumbers (cm^{-1}).

Determination of % ee was achieved using a chiral HPLC equipped with a chiralpak AS column (for compounds **6**, in which the 39% ee for compound **6e** t_R (minor)=13.7 min, t_R=16.5 min) or chiracel OD column (for compounds **3**, in which the 15% ee for compound **3c** t_R (minor)=18.6 min, t_R=20.4 min) with 99:1 or 99.5:0.5 *n*-hexanes: 2-propanol as the mobile phase at a flow rate of 1 mL/min.

3.1. General procedure for the palladium-catalyzed cycloaddition reaction of 2-vinylpyrrolidines (1a, 1b and 1c) with carbodiimides 2

$Pd(OAc)_2$ (4.51 mg, 0.02 mmol, 10 mol% to **1**) was weighed into a Schlenk tube under a stream of argon, 3 mL dry THF was added, and the solution was degassed. Dpppentane (17.6 mg, 20 mol%) was added, followed by 0.2 mmol of **1a**, **1b**, or **1c** and then carbodiimide (0.3 mmol), the mixture was stirred under 5 psi of N_2, at a given temperature. The progress of the reaction was monitored by GC and the crude product was purified by silica chromatography using pentane/ether 2:1 to 1:3 as eluant to afford arylguanidines **3**.

3.1.1. 1-Butyl-3-(3-chlorophenyl)-4-vinyl-2*H*-1,3-diazepin-2-ylidene-(3-chlorophenyl)-amine (3b) (X=*m*-Cl, R=*n*-Bu). 83% yield; colorless oil; IR (neat) ν 3071, 2956, 2930, 2865, 1618, 1578, 1474, 1416, 1369, 1311, 1252, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J*=7.3 Hz), 1.32–1.44 (m, 2H), 1.66–1.93 (m, 6H), 3.18–3.45 (m, 3H), 3.52–3.61 (m, 1H), 4.27 (br, 1H), 5.16 (d, 1H, *J*=18.0 Hz), 5.21 (d, 1H, *J*=11.0 Hz), 5.93 (br, 1H), 6.42 (d, 1H, *J*=7.9 Hz), 6.57 (m, 2H), 6.67–6.70 (m, 3H), 6.80–6.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 145.6, 137.2, 134.2, 133.2, 129.4, 128.8, 122.6, 121.0, 120.8, 120.6, 119.0, 117.3 (two carbons missing as a result of overlap), 61.1, 50.1, 48.1, 30.1, 29.6, 22.9, 20.4, 14.0; MS (*m*/*e*) 415 (M^+), 417 (M^++2), 419 (M^++4); EIHRMS calcd for $C_{23}H_{27}N_3Cl_2$ 415.158195; found, 415.15815.

3.1.2. 1-Cyclohexyl-3-(3-chlorophenyl)-4-vinyl-2*H*-1,3-diazepin-2-ylidene-(3-chlorophenyl)-amine (3e) (X=*m*-Cl, R=Cy). 51% yield; colorless oil; IR (neat) ν 3064, 2930, 2854, 1611, 1595, 1577, 1477, 1410, 1317, 1251, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09–1.15 (m, 1H), 1.39–1.43 (m, 4H), 1.60–2.10 (m, 9H), 3.08 (b, 1H), 3.32 (m, 1H), 4.19–4.32 (m, 2H), 5.15–5.25 (m, 2H), 6.08 (br, 1H), 6.44–6.68 (m, 6H), 6.84–6.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 145.8, 137.2, 134.3, 133.2, 129.6, 128.8, 122.7, 121.0, 120.3, 118.1, 117.2, 116.2 (two carbons missing as a result of overlap), 61.0, 56.2, 42.3, 31.3, 29.9, 29.0, 25.8, 24.4; MS (*m*/*e*) 441 (M^+), 443 (M^++2), 445 (M^++4); EIHRMS calcd for $C_{25}H_{29}N_3Cl_2$ 441.173845; found, 441.17602.

3.1.3. (*trans*) 1-Butyl-6-methyl-3-(3-chlorophenyl)-4-vinyl-2*H*-1,3-diazepin-2-ylidene-(3-chlorophenyl)-amine (3i). 36% yield; colorless oil; IR (neat) ν 3064, 2956, 2927, 2869, 1616, 1593, 1577, 1477, 1465, 1415, 1381, 1369, 1305, 1267, 1257, 1220, 1122, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J*=7.2 Hz), 0.96 (t, 3H, *J*=7.9 Hz), 1.25–1.83 (m, 6H), 1.97–2.09 (m, 1H), 3.03–3.34 (m, 3H), 3.64 (br, 1H), 4.37 (br, 1H), 5.22 (d, 1H, *J*=16.7 Hz), 5.26 (d, 1H, *J*=9.0 Hz), 6.09 (br, 1H), 6.42 (d, 1H, *J*=7.5 Hz), 6.65–6.76 (m, 5H), 6.85 (t, 1H, *J*=6.7 Hz), 6.96 (t, 1H, *J*=9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 150.0, 145.8, 138.1, 137.1, 134.3, 133.3, 129.6, 128.8, 122.5, 121.1, 120.8, 119.8, 117.5, 116.1, 60.7, 55.9, 50.8, 39.0, 30.2, 28.1, 20.4, 18.8, 14.0; MS (*m*/*e*) 429 (M^+), 431 (M^++2), 433 (M^++4); EIHRMS calcd for $C_{24}H_{29}N_3Cl_2$ 429.173845; found, 429.17245.

3.1.4. (*cis*) 1-Butyl-6-methyl-3-(3-chlorophenyl)-4-vinyl-2*H*-1,3-diazepin-2-ylidene-(3-chlorophenyl)-amine (3i′). 35% yield; colorless oil; IR (neat) ν 3064, 2956, 2929, 2872, 1620, 1595, 1581, 1479, 1465, 1437, 1413, 1381, 1309, 1247, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, 3H, *J*=7.3 Hz), 0.97 (t, 3H, *J*=7.3 Hz), 1.33–1.45 (m, 2H), 1.56–1.72 (m, 3H), 1.91–1.95 (m, 2H), 2.77–3.45 (m, 3H), 3.60–4.13 (br, 2H), 5.02–5.11 (m, 2H), 5.65–5.80 (br, 1H), 6.55–6.82 (m, 6H), 6.96 (q, 2H, *J*=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 150.0, 145.8, 138.1, 137.1, 134.3, 133.3, 129.6, 128.8, 122.5, 121.1, 120.8, 119.8, 117.5, 116.1, 60.7, 55.9, 50.8, 39.0, 30.2, 28.1, 20.4, 18.8, 14.0; MS (*m*/*e*) 429 (M^+), 431 (M^++2), 433 (M^++4); EIHRMS calcd for $C_{24}H_{29}N_3Cl_2$ 429.173845; found, 429.17432.

3.1.5. 4c (X=*p*-Cl, R=*n*-Bu). 11% yield; light yellow oil; IR (neat) ν 3391, 3089, 3053, 2958, 2929, 2872, 1643, 1633, 1614, 1585, 1415, 1398, 1309, 1246, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J*=7.3 Hz), 1.19–1.31 (m, 2H), 1.47–1.57 (m, 2H), 2.35–2.51 (m, 2H), 3.16 (t, 2H, *J*=6.8 Hz), 3.35 (t, 2H, *J*=7.0 Hz), 5.01–5.20 (m, 2H), 5.40 (q, 0.5H, *cis*, *J*=8.6 Hz), 5.60–5.71 (m, 0.5H, *trans*), 6.04–6.19 (m, 1H), 6.29–6.36 (m, 0.5H, *trans*), 6.55–6.65 (m, 0.5H, *cis*), 6.74 (d, 4H,*J*=8.1 Hz), 7.13 (d, 4H, *J*=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 150.1, 136.8, 133.1,

131.8, 131.7, 131.2, 129.2, 128.7, 127.1, 121.8, 120.9, 118.1, 116.0, 48.4, 48.0, 47.7, 47.4, 31.1, 30.0, 29.9, 26.4, 20.2, 13.9; MS (*m/e*) 415 (M^+), 417 (M^++2), 419 (M^++2); EIHRMS calcd for $C_{23}H_{27}N_3Cl_2$ 415.158195; found, 415.15921.

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15. Other chiral ligands, i.e. (R)-BINAP type ligands, proved less effective in the reaction of **1a** with **5b**, and only gave 15% ee, in low product yield and conversion. When (R)-DIOP was used, the product was isolated in good yield and conversion, but no enantiodiscrimination was found. However, no reaction occurred when chiral ligands DuPHOS was used as chiral ligands. Use of **1b** as the substrate, and other (R)-Tol-BINAP, (R)-BINAP or (−)-Me-DuPHOS as chiral ligands, gave no reaction with **5b**. Chiral ligands such as (R,R)-DIOP, (S,S)-BDPP and (R,R)-BPPM can give the product in 12–33% yields but in 0% ee.
16. Crystallographic data (excluding structure factors) for the structure **6d** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 219150. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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Synthesis of terphenyl oligomers as molecular electronic device candidates

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Abstract—Six functionalized bis(phenylene ethynylene)-*p*,*p*-terphenyls (BPETs) have been synthesized as potential molecular electronic devices. The molecules containing mono- and dinitro terphenyl cores, were rationally designed based on the electronic properties recently found in oligo(phenylene ethynylene)s (OPEs). From our understanding of the conductance properties in OPEs, improvement of electronic properties may be possible by using BPETs due to a higher rotational barrier between the central aromatic rings of the compounds prepared here. BPETs cores were functionalized with nitro groups and with different metallic adhesion moieties (alligator clips) to provide new compounds for testing in the nanopore and planar testbed structures.

1. Introduction

In the field of molecular electronics, several groups,[1] including our own,[2] have been pursuing the ultimate miniaturization of electronic components, synthesizing diverse organic molecules that can be used as electronic devices. Oligo(phenylene ethynylene)s (OPEs) have been synthesized and tested by new electronic screening methods,[3] engineered nanoscale arrays,[4] and lithographic motifs;[5] thereby recording non-linear conductive properties over metallic[6] and semiconductor layers.[7] Our approach capitalizes on the conformational diversity and functionality of such molecules.[8] Chemical functionalization of OPEs with nitro groups (Fig. 1) has yielded switching properties that were not seen in the unfunctionalized systems.[9–11] The presence of redox groups in the molecule might be responsible for a negative differential resistance (NDR) at room temperature[12] and programmability as memory devices.[13]

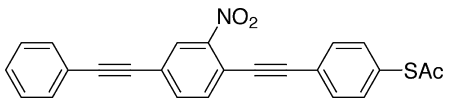

Figure 1. The mononitro OPE that has exhibited NDR in several testbeds.

Several recent studies suggested the conformational characteristics and nitro functionalization are the main sources of the electronic switching characteristics of the molecules.[14,15] Theoretical works have complemented the experimental work with assorted insights,[16,17] suggesting on one hand that high internal rotational energy barriers in linear conjugated molecules are the main causes for the switching effects.[18] On the other hand, the switching phenomenon has been attributed to temporal dipolar moments as the result of electron charges that are facilitated by redox groups on the molecule.[14,15,19] However, newer mechanisms are suggesting that the NDR is not molecularly-inherent, rather the switching is based upon the metal-molecule contact junctions.[14,20]

In this context, terphenyl molecules have recently shown unusual electrical properties,[21] and a high dependence on conformation for electronic conduction.[22] Moreover, terphenyls have shown temperature and solvent effects upon the electronic flow through the systems,[23] high thermal and photo-stability,[24,25] while presenting long-range ordered layers on gold[26] and silver substrates.[27] It is also known that high rigidity and extended π-conjugation of terphenyl thiols result in dense and stable monolayer structures that show lower tunneling barriers when compared to other molecular conjugated structures.[28,29] Finally, their strong dependence on intermolecular forces, conformation, solvent, effective conjugation and geometrical modifications make terphenyl oligomers attractive synthetic targets for further electronic testing.[30] These facts have motivated us to pursue the synthesis of new bis(phenylene ethynylene)-*p*,*p*-terphenyls (BPETs) as molecular device candidates (Fig. 2). The syntheses are presented so as to focus on the commonality of intermediates en route to the targets.

Keywords: Terphenyl; Molecular electronic; Conformational Energy.
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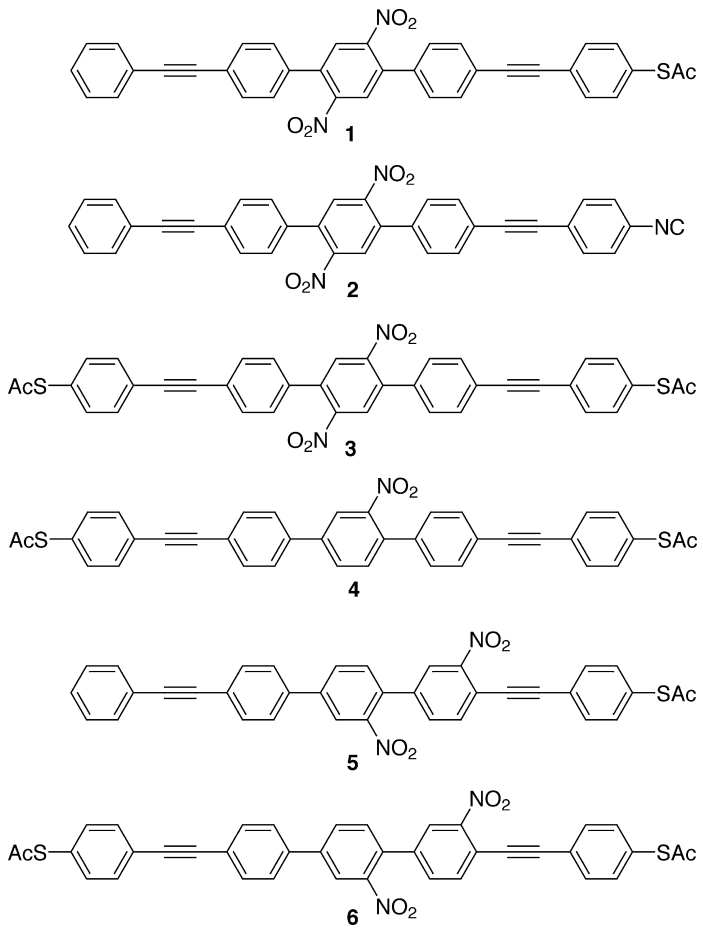


Figure 2. Synthetic targets presented in this work.

BPETs are expected to have a more rigid molecular core with lower conformational freedom, compared with OPEs (Fig. 3). Limited rotations of the C–C bonds between central aromatic rings of the molecule would result in geometrical restrictions. While the OPE pictured in Figure 1 shows no substantial increment in energy from the rotation of the central ring,[16] a biphenyl OPE and terphenyl OPE (Fig. 3(b) and (c), respectively) present significant rotational barriers relative to the OPE (Fig. 3(a)).

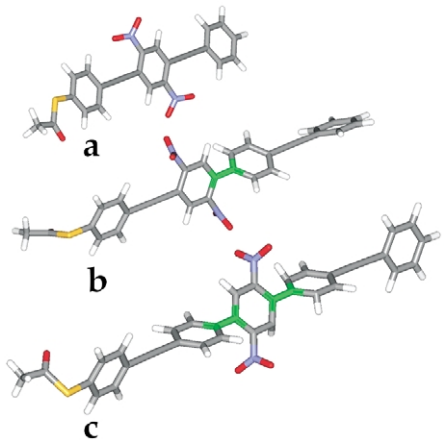


Figure 3. Conformers of different oligomers with (a) zero (b) one, and (c) two rotational barriers from C–C phenyl bonds, highlighted in green.

It is expected that the presence of more than one rotational barrier in the molecule would produce a clear difference between the two conformational states of the molecule: a high energy and a low energy conformation (Fig. 4).

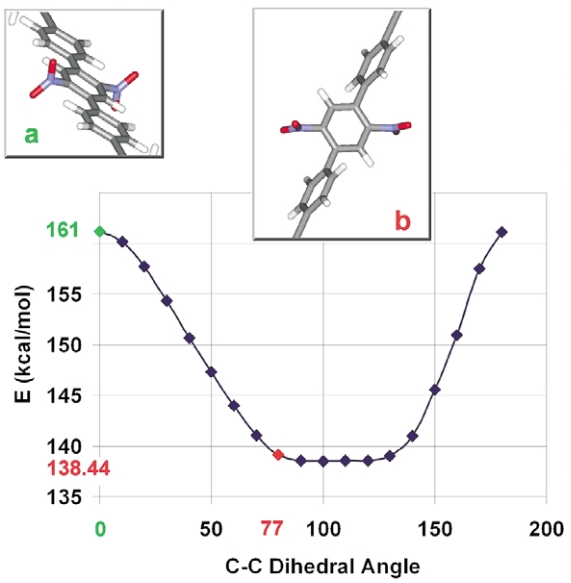


Figure 4. Relative energies at different C–C dihedral angles of optimized structures of **3** by molecular mechanics.[31] Inset a shows the geometry of the central core when the dihedral angles equal zero (values in green). A local minimum shows the geometry of inset b, with a dihedral angle of ca. 77° (values in red).

A high energy conformation of a BPET like **3** would exhibit planar central rings, where overlapping of π-orbitals would impart full conjugation and electron transport to the nitro groups (Fig. 4, inset a). The low energy conformation requires the cancellation of this extended conjugation when the phenyl rings are non-planar and an electron might be more localized in the molecular orbital of one of the electron-withdrawing groups. This localization might have significant effects on the ability of the oligomer to operate as a molecular memory device with extended periods of electron retention, albeit with a larger barrier to electronic transport.

2. Synthesis

The syntheses[32–41] of BPETs start with the functionalization of the central cores. Scheme 1 shows the synthetic route to the nitroaniline precursor **11**.

Nitration of dibromobenzene gave the nitro intermediate **7**. Reduction with tin(II) chloride and subsequent protection of the resulting aniline **8** gave the acetamide **9** in high yield. A second nitration at the 4-position selectively provided **10**, and a final alkaline deprotection of the acetamide afforded the desired nitroaniline **11**.

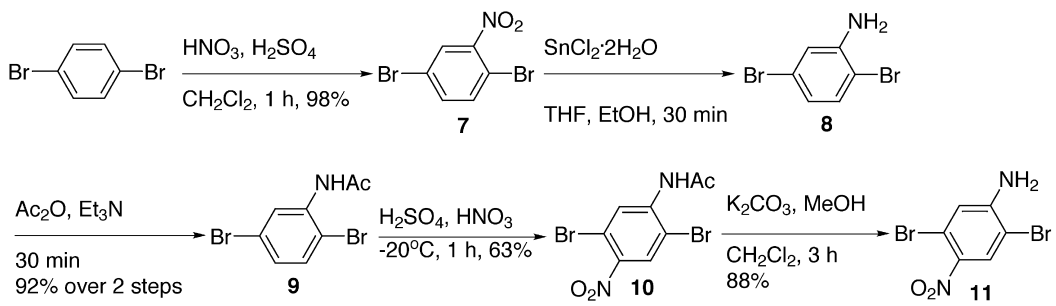
The synthesis of **1** began by coupling commercially available 4-bromoiodobenzene with phenylacetylene at the iodide position as shown in Scheme 2, although inseparable small amounts of the dicoupled byproduct were carried with **12** through the lithium–bromide exchange reaction and stannylation.

The synthesis of the biphenyl backbone is done by a Stille coupling reaction,[42] between the nitroaniline **11** and the stannane **13**. The coupling was chemoselective, undergoing reaction alpha to the more activating nitro group as we have seen in the past,[37] furnishing aniline **14**. The second nitro group for the central ring was introduced by oxidizing the amino group, using HOF generated in situ from water and fluorine,[32] giving **15**.

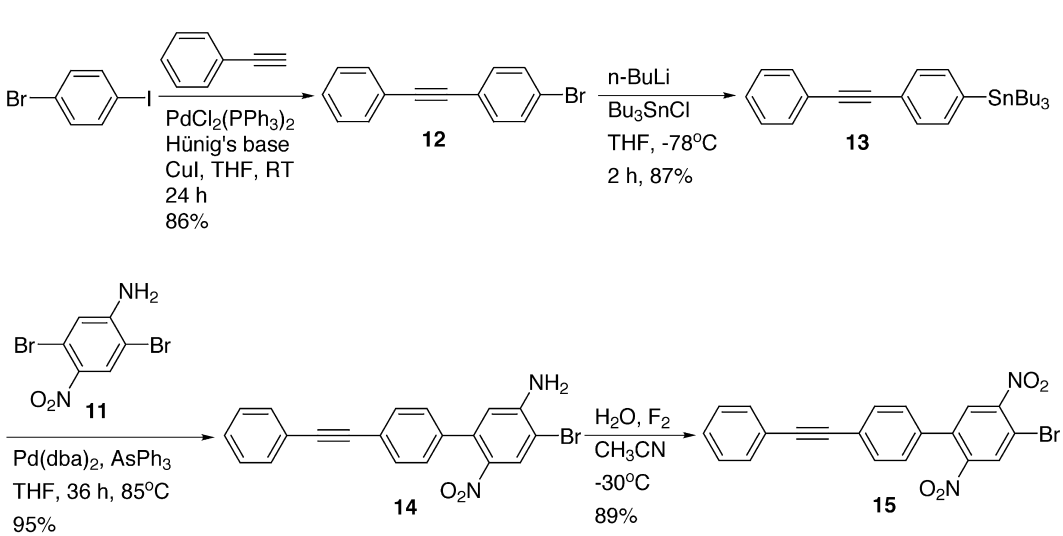
Scheme 3 shows the synthesis of the target BPET **1**.

4-Bromo-1-iodobenzene was selectively coupled with trimethylsilylacetylene (TMSA) to afford **16**, followed by a stannylation to **17**. Stille coupling between **15** and the stannane **17**, afforded **18** which was prepared for a final Sonogashira coupling.[40] 4-(Thioacetyl)iodobenzene **20**,[33] a protected thiol terminus for the metal-molecular junction (or alligator clip), was coupled with **19** to afford the target **1**.

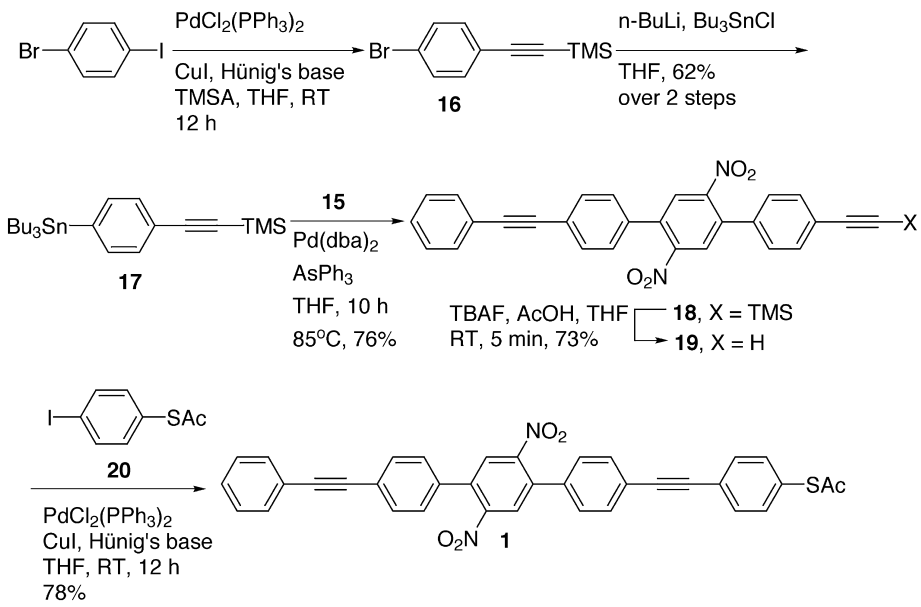
4-Iodoaniline was treated with ethyl formate to yield formamide **21**, a precursor of an isocyanide alligator clip. The formamide could be coupled with the same dinitroterphenyl core, **19**, to afford **22** (Scheme 4). The low yield could be due to the low solubility of **22**, which is a common



Scheme 1.



Scheme 2.



Scheme 3.

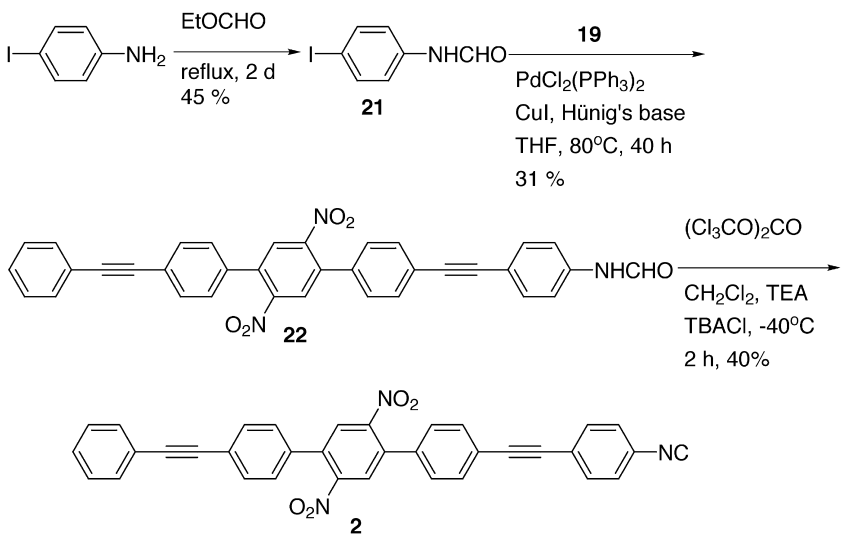
feature of formamides. A final dehydration of **22** using the phosgene precursor, triphosgene,[34] afforded the desired BPET isonitrile **2**.

The convenient nitroaniline intermediate **11** was used in synthetic paths toward several other targets including the symmetric dinitro-terphenyls with alligator clips at both sides as illustrated in Scheme 5.

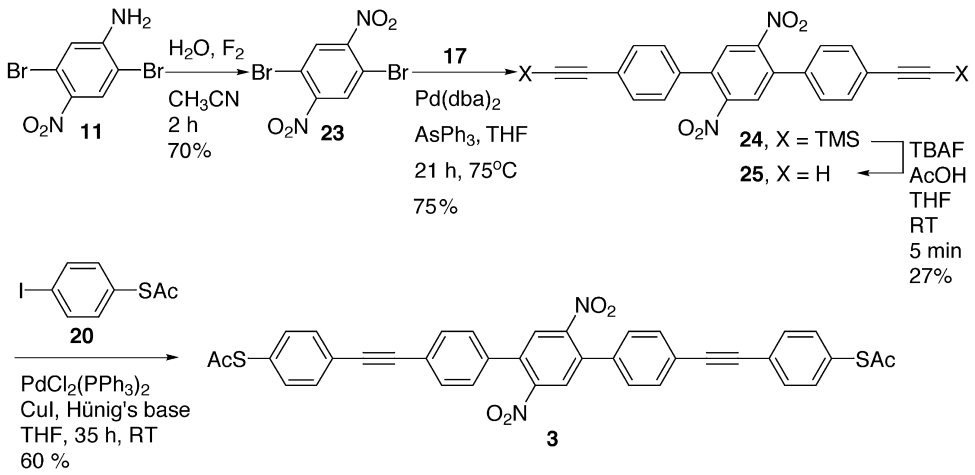
Oxidation of **11** by HOF provided the desired dinitro central precursor **23**. The stannane **17** was used for a double Stille coupling on both halides of **23**, in order to afford **24**. The high yield for this double coupling might indicate the high activation of the bromides toward oxidative addition by the two nitro groups. Bis-deprotection of **24** afforded **25** in low yield, probably due to the poor solubility and instability of bis-terminal alkynes of highly electron deficient systems, a phenomenon that we have consistently observed.[37] A final coupling with the protected-thiol alligator clip **20** yielded the desired symmetric BPET **3**. In the future, it may be advantageous to carry out an in situ TMS-removal and coupling between **20** and **25**, thereby obviating the need to isolate the unstable dialkyne **25**.[35]

Variation of functional groups, both number and location, can have a profound influence on the electronic properties of the oligomers.[15,38] Considering this, the mononitro BPET **4** was prepared using a protocol similar to that described above.

2-Nitroaniline was iodinated at the 4-position, according to a known procedure,[36] affording **26**, followed by diazotization and iodination to give **27** (Scheme 6). A Stille coupling to both iodides gave the mononitro terphenyl **28**, as well as mono-coupled byproducts. Note that if 2,5-dibromonitrobenzene (**7**) was used with **17** to form terphenyl intermediate **28**, the yield decreased to 56%, suggesting that the iodides on this compound are more reactive for Stille coupling than the bromides from compound **7** (Scheme 1).



Scheme 4.



Scheme 5.

Deprotection of both alkynes furnished **29** as the terphenyl intermediate. Once deprotected, both alkynes underwent Sonogashira coupling with the alligator clip **20** in order to give the desired mononitro-BPET **4**. Similar yields were found when Hünig's base was used instead of triethylamine (TEA).

In the synthesis of a dinitro BPET **5**, it was found that nitration of a starting biphenyl core conveniently permitted the exclusion of one carbon–carbon bond formation step in our route toward the construction of the terphenyl moiety; the nitro-functionalization occurred on two aromatic rings,[37] as illustrated in Scheme 7.

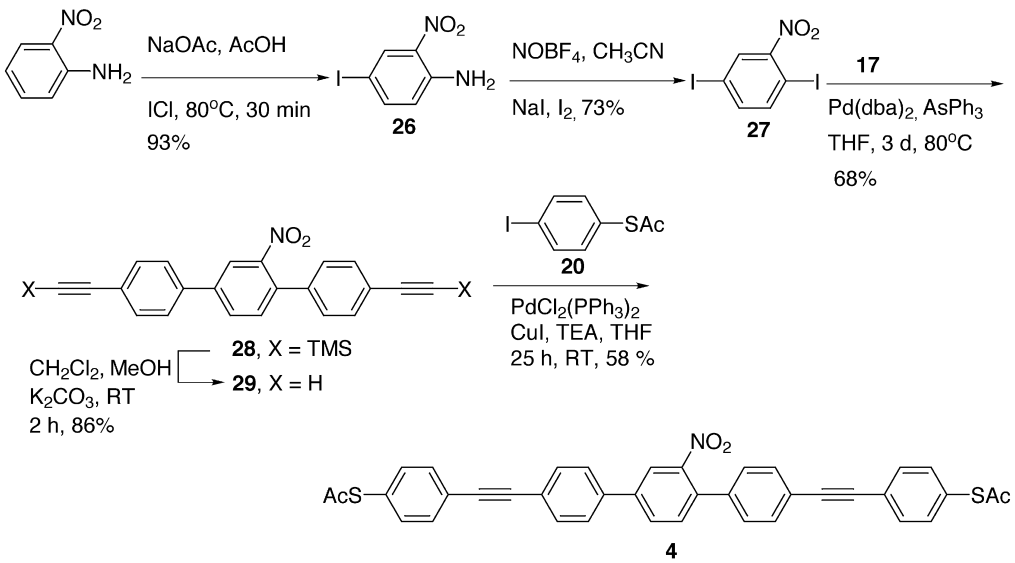
Initial nitric acid treatment of 4,4′-dibromobiphenyl in sulfuric acid gave the 2,3′-dinitrobiphenyl **30**, as the major product, separable from the 2,2′-dinitro isomer by crystallization.[37] TMSA coupled selectively to the bromide at the position *ortho* to the nitro group, yielding **31**. A Stille coupling using the previously synthesized stannane **13** gave a new dinitro terphenyl intermediate **32**. Alkaline deprotection yielded the free alkyne **33**, ready for a final coupling with alligator clip **20**, affording the desired unsymmetrical dinitro BPET **5**.

By using intermediate **31**, it was possible to construct a double functionalized unsymmetrical BPET, as shown in Scheme 8, by just changing the stannane from **13** to **17**.

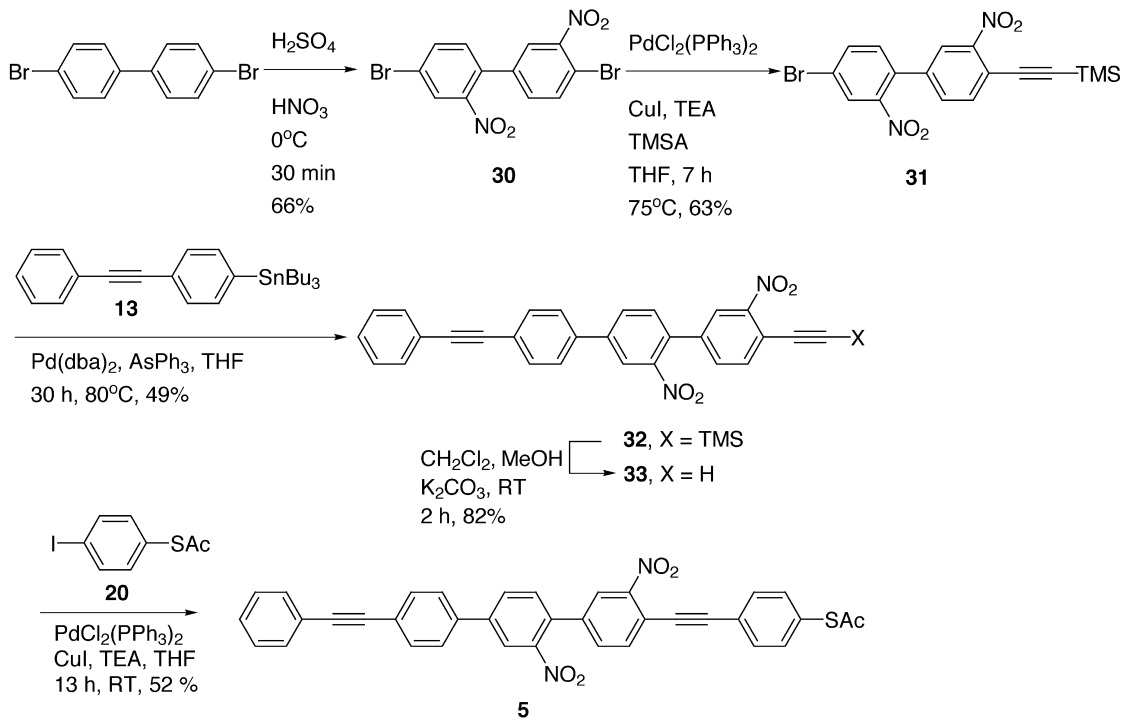
The Stille coupling conditions afforded **34** which was deprotected to form **35** in a higher than expected yield (vide supra). A final double Sonogashira coupling with the alligator clip **20** following typical conditions gave the desired double functionalized unsymmetrical dinitroterphenyl **6**.

3. Summary

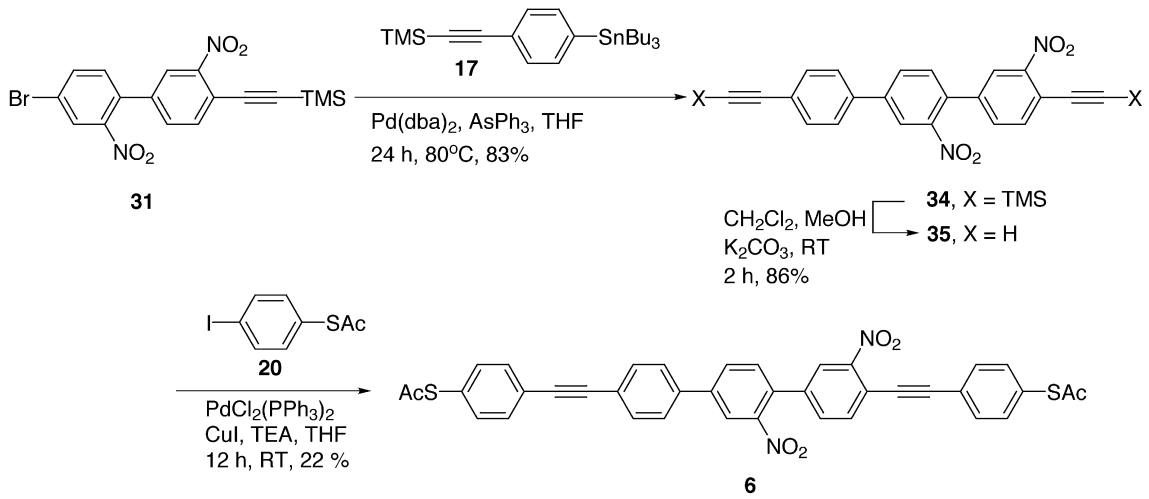
We have developed convergent synthetic methodologies that are based on Sonogashira and Stille couplings for aryl–aryl and aryl–ethynyl bond formations in order to synthesize terphenyl oligomers that are to be probed in molecular electronic device studies. In each case, the oligomers bear at least one nitro moiety for the retention of charge; a feature that has proved efficacious in molecular device activity when the compounds are configured in solid state embodiments. It is hypothesized that the terphenyl



Scheme 6.



Scheme 7.



Scheme 8.

cores, having a greater conformational twist angle at the aryl–aryl junctions, would be able to maintain charges for longer durations, thereby yielding more stable electronic devices. The hypothesis has yet to be tested; however, the syntheses described here provide the molecules, with their affixed alligator clips, making them ready for assembly and testing.

4. Experimental

4.1. Material and general procedures

Unless stated otherwise, reactions were performed in dry, nitrogen-flushed glassware, using freshly distilled solvents. Reagent grade diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. *N*,*N*-Diisopropylethylamine (Hünig's base) and triethylamine (TEA) were distilled from calcium hydride. Reagent grade *n*-hexanes, methylene chloride (CH_2Cl_2), methanol (MeOH), ethanol (EtOH) and ethyl acetate (EtOAc) were used without further distillation. Trimethylsilylacetylene (TMSA) was donated by FAR Research Inc. All other commercially available reagents were used as received. Unless otherwise noted, reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). In general, the chromatography guidelines reported by Still were followed.[39] Flash chromatography (silica gel) was performed with the indicated solvent systems using silica

gel grade 60 (230–400 mesh). All new compounds were named using the Beilstein AutoNom application of Beilstein Commander 2000 software.

4.2. General procedure for the coupling of a terminal alkyne with an aryl halide utilizing a palladium–copper cross-coupling (Castro-Stephens/Sonogashira protocol)[40,41]

To an oven-dried screw cap tube or a round bottom flask equipped with a magnetic stir bar were added the aryl halide, bis(triphenylphosphine)palladium(II) dichloride (5 mol% based on aryl halide), and copper(I) iodide (10 mol% based on aryl halide). The vessel was sealed with rubber septum, evacuated and backfilled with nitrogen (3×). THF was added followed by Hünig's base or TEA. The terminal alkyne was then added and the reaction was heated if necessary. The reaction vessel was cooled to room temperature and the mixture quenched with water or a saturated solution of NH_4Cl. The organic layer was diluted with organic solvent and washed with a saturated solution of NH_4Cl (3×). The combined aqueous layers were extracted with organic solvent (3×), dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The crude product was then purified by flash chromatography.

4.3. General procedure for the coupling of a trialkylaryl stannane with an aryl halide utilizing a palladium–arsine cross-coupling (Stille protocol)[42]

To an oven-dried screw cap tube or a round bottom flask equipped with a magnetic stir bar were added the aryl halide, the stannane, bis(dibenzylideneacetone)palladium(0) (5 mol% based on aryl halide) and triphenylarsine (10 mol% based on aryl halide). The vessel was then sealed with a rubber septum, evacuated and backfilled with nitrogen (3×). THF was added and the reaction heated at 75 °C for at least 48 h. The reaction vessel was cooled to room temperature and the mixture quenched with water and extracted with organic solvents (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The crude product was then purified by flash chromatography.

4.4. General procedure for alkaline deprotection of trimethylsilyl-protected alkynes

The TMS-protected alkyne was added to an open round bottom flask equipped with a stirring bar and a solution of potassium carbonate in MeOH, or tetrabutylammonium fluoride (TBAF) buffered with a mixture of acetic acid (AcOH) and acetic anhydride (Ac_2O). THF or CH_2Cl_2 were added to dissolve the organic compound. The reaction was monitored by TLC every 5 min until deprotection was complete. The reaction was quenched with water and extracted with organic solvents (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The crude product was then purified by flash chromatography.

4.5. General HOF oxidation procedure[32]

CAUTION! Using the dilute form of F_2 in He is highly recommended to minimize potential explosions. The 20% F_2 in He was purchased as a special order mixture from Air Products, Inc., and ordering of the mixture is recommended over mixing the gases in house. F_2-approved fittings should be used throughout the gas manifold system. The entire apparatus should be assembled in a high flow hood.

To a polyethylene bottle was added a mixture of H_2O (1 mL/mmol of substrate) and CH_3CN (30 mL/mmol of substrate) and the vessel was cooled to −20 °C, before bubbling F_2 (20% in He) through the solution at a rate of 80 cubic centimeters per minute (ccpm) for 2 h. The resulting HOF/CH_3CN solution was then purged with pre-purified He for 15 min (**CAUTION!** To avoid explosion, the He purging is essential to ensure that there is no remaining fluorine in the reaction mixture or gas lines) followed by the addition of a solution of the aniline in THF. After stirring for 20 min, the reaction was neutralized by pouring it into aq. $NaHCO_3$ and stirring for 20 min before filtering. The crude was then purified by flash chromatography.

4.5.1. 2,5-Dibromonitrobenzene (7).[43] CAUTION! Nitration of aromatics can lead to polynitrated compounds that are explosive. Although no explosions were seen in this study, we had a previous explosion on related compounds,[43] and blast-protection should therefore be used throughout this process.

Into a 3-neck 1 L round bottom flask fitted with a mechanical stirrer, dibromobenzene (118 g, 0.5 mol) was dissolved in a solution of CH_2Cl_2 (300 mL) and sulfuric acid (200 mL). A mixture of nitric acid (90%, 46 g, 0.7 mol) and sulfuric acid (75 mL) was then added dropwise by an addition funnel, in small batches of about 5 mL every 5 min or until the strong blue color of the reaction mixture turned back into a dark yellow. The reaction mixture was monitored by GC and after 30 min the reaction was complete and quenched with a solution of 25% aq. NaOH (30 mL) to yield a light yellow organic phase. After extractions with CH_2Cl_2 (30 mL), the crude was washed with water (90 mL) and dried over $MgSO_4$. Evaporation in vacuo afforded 140.4 g (98% yield) of **7** as bright light yellow crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=2.2 Hz, 1H), 7.62 (q, J=8.6 Hz, 1H), 7.56 (d, J=8.6, 2.2 Hz, 1H).

4.5.2. 2,5-Dibromoacetanilide (9).[44] To a slurry of **7** (28.1 g, 100 mmol) in a 1 L round bottom flask containing a mixture of EtOH (100 mL) and THF (100 mL), was added tin(II) chloride dihydrate (113 g, 0.5 mol) in small portions, avoiding an excessive increase in the temperature. The yellow slurry was left to cool before a partial evaporation in vacuo, resulting in a white cake. The reaction mixture was transferred into a 1 L beaker containing a solution of 15% aq. NaOH (100 mL) and left for 30 min with stirring at ice bath temperature. Extractions were done with Et_2O (30 mL) and the organic layers were collected and washed with brine (100 mL). Acetic anhydride (30 mL) was added to the organic solution and stirred for 10 min, and TEA (10 mL, 100 mmol) was added followed by heating at 35 °C for 1 h. The afforded white liquid was washed with 50% aq. MeOH (100 mL) and extracted with Et_2O (50 mL). The volume of solvent was reduced, and crystallization with THF (300 mL) and EtOH (300 mL) furnished **8** (27 g, 92% yield) as opaque

white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.58 (br s, 1H), 7.38 (d, J=8.5 Hz, 1H), 7.12 (dd, J=8.5, 2.3 Hz, 1H), 2.25 (s, 3H).

4.5.3. 2,5-Dibromo-4-nitroacetanilide (10).[44] Into a 500 mL 3-neck round bottom flask equipped with mechanical stirring and containing a mixture of nitric acid 90% (55 g, 80 mmol) and sulfuric acid 96% (100 mL), **9** (22 g, 75 mmol) was slowly added at −20 °C. The mixture was stirred until room temperature was reached. Pouring the reaction mixture into an ice bath afforded a light yellow precipitate. The solid was filtered before being washed with saturated aq. sodium bicarbonate (100 mL), water (100 mL) and MeOH (100 mL) yielding **10** (14 g, 63% yield) as a pale white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.20 (s, 1H), 7.76 (br s, 1H), 2.31 (s, 3H).

4.5.4. 2,5-Dibromo-4-nitroaniline (11).[44] Into a 500 mL round bottom flask, **10** (10 g, 30 mmol) was dissolved in CH_2Cl_2 (160 mL). MeOH (160 mL) was added, followed by K_2CO_3 (12 g, 89 mmol). Stirring the light yellow reaction mixture for 3 h resulted into a sunflower-color solution. After evaporation of the methanolic portion, water was used to wash the reaction mixture, and extractions with CH_2Cl_2 (3×30 mL) and EtOAc (3×30 mL) were done before drying over $MgSO_4$. Crystallization from CH_2Cl_2 (10 mL) and MeOH (10 mL) furnished 7.6 g (88% yield) of **11** as bright light orange crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.03 (s, 1H), 4.75 (br s, 2H).

4.5.5. 1-Bromo-4-phenylethynyl-benzene (12).[45] The Sonogashira coupling protocol was followed using 4-bromoiodobenzene (2.8 g, 10 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 2% mol), CuI (76 mg, 4% mol), THF (15 mL), Hünig's base (7 mL, 40 mmol) and phenylacetylene (1.3 mL, 12 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 6:1) afforded **12** (2.2 g, 86% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (m, 2H), 7.38 (m, 5H).

4.5.6. Tributyl-(4-phenylethynyl-phenyl)-stannane (13). Into a 500 mL round bottom flask containing a solution of **12** (2.6 g, 10.1 mmol) in THF (200 mL), *n*-BuLi (4.0 mL, 16.1 mmol) was added dropwise at −78 °C, from an attached addition funnel. The reaction mixture was stirred for 45 min before adding dropwise tri-*n*-butyltin chloride (3 mL, 11.1 mmol). The reaction mixture was allowed to warm up to room temperature, quenched with water (100 mL), extracted with EtOAc (50 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo and purification by flash chromatography (hexanes/CH_2Cl_2 5:1) afforded **13** (4.2 g, 87% yield) as a pale yellow liquid. IR (KBr) 2922, 2328, 2216, 1950, 1904, 1801, 1746, 1657, 1595, 1495, 1454, 1380, 1343, 1299, 1182, 1069, 1015 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.47 (m, 4H), 7.35 (m, 2H), 1.54 (m., 6H), 1.35 (sext, J=7.3 Hz, 6H), 1.0 (t, J=8.0 Hz, 6H), 0.9 (t, J=7.3 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 136.5, 131.8, 130.9, 128.4, 123.7, 123.0, 89.9, 89.7, 29.3, 27.6, 13.9, 9.8. HRMS calcd for $C_{26}H_{36}Sn$: 466.1841, found: 466.1841.

4.5.7. 4-Bromo-6-nitro-4′-phenylethynyl-biphenyl-3-ylamine (14). The Stille coupling procedure was followed using **11** (5.2 g, 17.5 mmol), $Pd(dba)_2$ (502 mg, 5% mol), $AsPh_3$ (536 mg, 10% mol), THF (50 mL), and **13** (9 g, 19.3 mmol) at 85 °C for 36 h. Purification by flash chromatography twice (hexanes/CH_2Cl_2 1:1, then 8:1), yielded the desired adduct **14** (6.5 g, 95% yield) as bright yellow crystals. Mp 172 °C. IR (KBr) 3487, 3390, 3057, 2668, 1961, 1961, 1915, 16709, 1552, 1501, 1302, 1253, 1117, 1034 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.55 (m, 4H), 7.37 (m, 3H), 7.23 (m, 2H), 6.6 (s, 1H), 4.76 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 138.7, 138.5, 138.1, 131.8, 131.7, 130.6, 128.6, 128.5, 127.9, 123.2, 123.2, 116.6, 106.3, 90.5, 89.1. HRMS calcd for $C_{20}H_{13}BrN_2O_2$: 392.0161, found: 392.0154.

4.5.8. 4-Bromo-2,5-dinitro-4′-phenylethynyl-biphenyl (15). The general HOF oxidation procedure was followed using **12** (2.5 g, 6.4 mmol), THF (5 mL) and CH_3CN/H_2O to yield a yellow solid as the desired product (2.4 g, 89% yield). Mp 175 °C. IR (KBr) 3102, 3021, 2873, 2714.5, 2407, 2217, 1538, 1344, 1215, 1099 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.92 (m, 1H), 7.60 (m, 4H), 7.37 (m, 3H), 7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 133.7, 132.5, 131.9, 130.7, 128.9, 128.6, 128.5, 127.9, 122.9, 114.2, 91.8, 88.4. HRMS calcd for $C_{20}H_{11}BrN_2O_4$: 421.9902, found: 421.9910.

4.5.9. (4-Bromo-phenylethynyl)-trimethyl-silane (16).[46] The Sonogashira coupling protocol was followed using 4-bromoiodobenzene (5 g, 17.6 mmol), $PdCl_2(PPh_3)_2$ (62 mg, 5% mol), CuI (33 mg, 10% mol), THF (20 mL), Hünig's base (25 mL, 43 mmol) and TMSA (3 mL, 21.3 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 6:1) afforded **16** (1.9 g, 83% yield) as a pale solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.42 (m, 2H), 0.26 (s, 9H).

4.5.10. Trimethyl-(4-tributylstannanyl-phenylethynyl)-silane (17).[37] Into a 500 mL round bottom flask containing a solution of **16** (16.7 g, 65.8 mmol) in THF (50 mL), *n*-BuLi (30.3 mL, 72 mmol) was added dropwise at −78 °C from an attached addition funnel. The reaction mixture was stirred for 45 min before adding dropwise tri-*n*-butyltin chloride (21 mL, 73 mmol). The reaction mixture was allowed to warm up to room temperature, then quenched with water (100 mL), extracted with Et_2O (50 mL) and dried over $MgSO_4$. Purification by Kugelrhor distillation (130 °C at 0.25 mm Hg) and flash chromatography (hexanes) afforded **17** (27 g, 89% yield) as a clear liquid. IR (KBr) 3438, 3065, 1605, 1532, 1471, 1406, 1381, 1349, 1262, 1072, 1009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 4H), 1.53 (m, 6H), 1.34 (sext, J=7.5 Hz, 6H), 1.08 (m, 6H), 0.91 (t, J=7.5 Hz, 9H), 0.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 136.3, 131,2, 122.8, 29.5, 27.6, 13.9, 9.8, 0.2. HRMS calcd for $C_{23}H_{40}SiSn$: 463.1857, found: 463.1847.

4.5.11. Trimethyl-6,9-dinitro-8-phenylethynyl-triphenyl-ethynyl-silane (18). The Stille coupling procedure was followed using **15** (830 mg, 2 mmol), $Pd(dba)_2$ (56 mg, 5% mol), $AsPh_3$ (16 mg, 6% mol), THF (10 mL), and **17** (1 g, 2.2 mmol) at 85 °C for 36 h. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) yielded the desired adduct **18** (840 mg, 76% yield) as yellow crystals. Mp

235 °C. IR (KBr) 3439, 2959, 2151, 1529, 1476, 13.81, 1250, 851 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.91 (s, 1H), 7.65 (m, 2H), 7.57 (m, 4H), 7.34 (m, 1H), 7.32 (m, 1H), 0.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.0, 134.6, 134.3, 132.8, 128.6, 128.0, 127.9, 127.5, 127.5, 125.0, 124.8, 123.0, 0.2. HRMS calcd for $C_{31}H_{24}N_2O_4Si$: 516.1507, found: 516.1505.

4.5.12. 6′,9′-Dinitro-8′-phenylethynyl-triphenyl-ethynyl (19). The general deprotection protocol was followed using **18** (432 mg, 0.8 mmol), THF (10 mL), acetic acid (0.1 mL, 1.8 mmol) and TBAF (0.9 mL, 0.9 mmol) for 5 min. Purification by flash chromatography (hexanes/CH_2Cl_2 1:3) furnished a pale yellow solid 272 mg (73% yield). Mp 200 °C. IR (KBr) 3482, 3286, 3052, 2914, 2360, 2330, 1552, 1537, 1521, 1521, 1474, 1350, 1261 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.92 (s, 1H), 7.64 (m, 4H), 7.57 (m, 2H), 7.37 (m, 7H), 3.2 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 135.9, 135.0, 134.3, 133.0, 132.5, 131.9, 128.8, 128.6, 128.7, 127.9, 127.6, 127.6, 125.0, 123.8, 123.0, 91.7, 88.5, 82.8, 79.4. HRMS calcd for $C_{28}H_{16}N_2O_4$: 444.1110, found: 444.1111.

4.5.13. Thio-4-16′,19′-dinitro-18′-phenylethynyl-triphenyl-ethynyl-phenyl-acetyl (1). The Sonogashira coupling protocol was followed using **19** (240 mg, 0.5 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 5% mol), CuI (11 mg, 10% mol), **20** (180 mg, 0.6 mmol), THF (20 mL), and Hünig's base (0.3 mL, 2 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 1:3) afforded **1** (250 mg, 78% yield) as a yellow solid. Mp 185 °C (browning). IR (KBr) 3439.0, 2959.3, 2151.2, 1529.7, 1476.1, 13.81.0, 1250.4, 851.3 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.94 (s, 1H), 7.66 (m, 4H), 7.57 (m, 4H), 7.41 (m, 9H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 150.2, 150.2, 136.1, 136.0 134.6, 134.4, 134.3, 132.5, 132.5, 132.4, 131.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.6, 127.5, 125.0, 124.6, 124.2, 123.0, 91.6, 90.8, 90.2, 88.5, 77.5, 77.2, 76.9. HRMS calcd for $C_{36}H_{22}N_2O_5S$: 594.1242, found: 594.1250.

4.5.14. *N*-4-Iodo-phenyl-formamide (21).[47] Into a 500 mL round bottom flask, 4-iodoaniline (10 g, 46 mmol) was dissolved in ethylformate (85 mL). The solution was allowed to reflux overnight, and then partially evaporated in vacuo. An additional portion of ethylformate (85 mL) was added and the process was repeated. A third portion of ethylformate (85 mL) was added and the procedure was repeated. The solvent was evaporated, and a light gray solid was isolated. Flash chromatography (CH_2Cl_2) afforded the desired product (5 g, 45% yield) as a pale white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J=8.7 Hz, 1H), 8.39 (d, J=1.6 Hz, 1H), 7.66 (m, 4H), 7.57 (m, 4H), 7.41 (m, 9H), 2.45 (s, 3H).

4.5.15. *N*-4-16′,19′-Dinitro-18′-phenylethynyl-triphenyl-ethynyl-phenyl-formamide (22). The Sonogashira coupling protocol was followed using **19** (330 mg, 0.7 mmol), $PdCl_2(PPh_3)_2$ (26 mg, 5% mol), CuI (14 mg, 10% mol), **21** (220 mg, 0.9 mmol), THF (8 mL) and Hünig's base (0.4 mL, 2.9 mmol) for 12 h at 70 °C. Purification by flash chromatography (CH_2Cl_2/EtOAc 1:1.2) afforded **22** (130 mg, 31% yield) as a yellow solid with poor solubility. Mp 270 °C (browning). IR (KBr) 3439, 3064, 2919, 2117, 1900, 1792, 1604, 1547, 1519, 1406, 1347, 1273, 1273, 1192, 1104, 1013 cm^{-1}. ^1H NMR (400 MHz, $(CD_3)_2SO$, 2.54) δ 7.95 (s, 1H), 7.94 (s, 1H), 7.66 (m, 4H), 7.57 (m, 4H), 7.41 (m, 9H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 40.4) δ 163.3, 160.7, 150.6, 139.7, 135.4, 135.4, 135.2, 133.6, 133.2, 132.8, 232.6, 133.2, 132.8, 132.3, 129.97, 129.6, 129.2, 129.2, 128.2, 124.3, 124.1, 122.8, 120.0, 118.0, 117.5, 117.5, 91.9, 91.7, 89.4, 88.8. HRMS calcd for $C_{35}H_{21}N_3O_5$: 563.1481, found: 563.1477.

4.5.16. *N*-4-16′,19′-Dinitro-18′-phenylethynyl-triphenyl-ethynyl-phenyl-isocynide (2). Into a large test tube, **22** (220 mg, 0.4 mmol) and triphosgene (58 mg, 0.2 mmol) were added and sealed with septum. The tube was evacuated and nitrogen was introduced before cooling to −40 °C while stirring. Distilled CH_2Cl_2 (7 mL) was added until the suspension was homogeneous. Tetrabutylammonium chloride (11 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (4 mL) and added to the reaction mixture, leaving it for 30 min while monitoring by TLC. The same amount of triphosgene was added in CH_2Cl_2 (0.5 mL) before warming to 0 °C over 1.5 h. The reaction mixture then was quenched with water (10 mL), extracted with CH_2Cl_2 and dried over $MgSO_4$ before removal of the solvent in vacuo. The remaining solid was then recrystallized (CH_2Cl_2/hexanes 1:1) yielding a yellow solid (90 mg, 40% yield) as the desired product. Mp 235 °C. IR (KBr) 3439, 2959, 2151, 1529, 1476, 1381, 1250, 851 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.94 (s, 1H), 7.66 (m, 4H), 7.57 (m, 4H), 7.41 (m, 9H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 150.2, 150.2, 136.1, 136.0 134.6, 134.4, 134.3, 132.5, 132.5, 132.4, 131.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.6, 127.5, 125.0, 124.6, 124.2, 123.0, 91.6, 90.8, 90.2, 88.5, 77.5, 77.2, 76.9. HRMS calcd for $C_{35}H_{19}N_3O_4$: 545.1376, found: 545.1378.

4.5.17. 1,4-Dibromo-2,5-dinitro-benzene (23).[32] The general HOF oxidation procedure was followed using **11** (1.9 g, 6.4 mmol), THF (15 mL) and CH_3CN/H_2O to yield a yellow solid as the desired product (2 g, 70% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 2H).

4.5.18. 1,4-Dinitro-2,5-bis-trimethylsilylethynyl-phenyl-benzene (24). The general Stille coupling procedure was followed using **22** (530 mg, 1.62 mmol), $Pd(dba)_2$ (93 mg, 10% mol), $AsPh_3$ (100 mg, 20% mol), THF (10 mL), **17** (1.65 g, 3.6 mmol) at 75 °C for 21 h. Flash chromatography (hexanes/CH_2Cl_2 5:6) yielded the desired adduct (620 mg, 75% yield) as pale yellow crystals. Mp 250 °C (browning). IR (KBr) 3430, 3267, 2960, 2883, 2155, 1530, 1477, 1411, 1357, 1251, 1223, 1185, 1116, 1014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.91 (s, 1H), 7.65 (m, 2H), 7.57 (m, 4H), 7.34 (m, 1H), 7.32 (m, 1H), 0.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 150.2, 136.1, 134.6, 132.8, 127.9, 127.5, 124.8, 104.0, 96.9, 0.0. HRMS calcd for $C_{28}H_{28}N_2O_4Si_2$: 512.1588, found: 512.1580.

4.5.19. 1,4-Dinitro-2,5-bis-ethynyl-phenyl-benzene (25). The deprotection protocol was followed using **24** (615 mg, 1.2 mmol), THF (20 mL), acetic acid (0.15 mL, 2.6 mmol), and TBAF (2.8 mL, 2.8 mmol). After 10 min a light yellow solid precipitated. After addition of hexanes (10 mL) and filtration, a pale yellow solid was collected (115 mg, 27%

yield) as the desired product **25**. The compound was poorly soluble and it was taken, without complete characterization, onto the next step with no further purification. Mp 270 °C. IR (KBr) 3277, 3052, 2960, 2871, 2359, 1932, 1813, 1675, 1531, 1477, 1355, 1278, 1262, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.62 (m, 4H), 7.35 (m, 4H), 3.20 (s, 2H). HRMS calcd for $C_{22}H_{12}N_2O_4$, 368.0800, found: 368.0797.

4.5.20. Thioacetic acid *S*-{4-[4″-(4-acetylsulfanyl-phenylethynyl)-2′,5′-dinitro-[1,1′;4′,1″]terphenyl-4-ylethynyl]-phenyl} ester (3). The Sonogashira coupling protocol was followed using **24** (110 mg, 0.3 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 10% mol), CuI (11 mg, 20% mol), **20** (200 mg, 0.41 mmol), THF (7 mL) and Hünig's base (0.3 mL, 2.4 mmol) for 12 h at 70 °C. Purification by flash chromatography (hexanes/CH_2Cl_2 1:3) afforded **3** (120 mg, 60% yield) as a yellow solid with poor solubility. Mp 190 °C (browning). IR (KBr) 3399.5, 3062.8, 2956.6, 2924.0, 2853.5, 2357.6, 1909.9, 1707.5, 1603.6, 1587.9, 1536.1, 1484.5, 1351.6, 1117.6 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 2H), 7.62 (m, 8H), 7.41 (m, 8H), 2.45 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 150.2, 136.1, 134.4, 32.5, 132.4, 128.7, 128.1, 127.6, 124.5, 124.2, 90.8, 90.1, 27.1. HRMS calcd for $C_{36}H_{22}N_2O_5S$: 594.1242, found: 594.1249.

4.5.21. 4-Iodo-2-nitro-phenylamine (26).[36] Into a 500 mL round bottom flask were dissolved 2-nitroaniline (30 g, 217 mmol), NaOAc (18.7 g, 228 mmol) and acetic acid (150 mL). A solution of ICl (37 g, 228 mmol) in acetic acid (100 mL) was added and the reaction mixture heated at 90 °C for 30 min. After cooling, the slurry was poured into ice water to afford a brown precipitate that was filtered giving the desired product (53 g, 93% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J=2 Hz, 1H), 7.56 (dd, J=2, 8.2 Hz, 1H), 6.61 (J=8.2 Hz, 1H), 6.1 (br s, 2H).

4.5.22. Nitrosonium tetrafluoroborate ($NOBF_4$).[9] Into a 3-neck 2 L round bottom flask fitted with a mechanical stirrer was added nitrogen purged acetic anhydride (614 mL) and the flask was cooled to −20 °C. HBF_4 (50%, 213 g, 1.2 mol) was added in small portions, so as to maintain the temperature. The emulsion was stirred for 15 min and then warmed to 0 °C. Sodium nitrite (138 g, 2 mol) in H_2O (ca. 100 mL) was slowly and carefully added from an addition funnel to a 1 L 3-neck round bottom flask containing nitric acid 69% (200 g, 2.2 mol) while maintaining rapid stirring. The resulting brown fumes were trapped in a tubing-connected cold finger at −78 °C to afford a blue ink-colored solution. This concentrated NO*x* species was then slowly added to the tetrafluoroboric acid solution until the blue color persisted. The precipitate was filtered and washed with CH_2Cl_2 while kept under a nitrogen atmosphere. The resulted white crystals were left under vacuum overnight and stored under a nitrogen atmosphere, affording the desired product (67 g, 48% yield) as a fluffy white solid, which was used as is for further reactions.

4.5.23. 2,4-Diodo-nitrobenzene (27).[48] Into a 500 mL round bottom flask, $NOBF_4$ (4.87 g, 416 mmol) was added. CH_3CN (180 mL) was added and the mixture was cooled to −40 °C. In a 250 mL round bottom flask was dissolved **25** (10 g, 378 mmol) in CH_3CN (80 mL) and the mixture was slowly transferred via cannula to the first vessel. After 30 min, the reaction mixture was allowed to warm briefly to 0 °C, followed by cooling to −40 °C, and small portions of a mixture of NaI (11.3 g, 76 mmol) and iodine (9.6 g, 38 mmol) were added over 30 min before diluting with CH_2Cl_2, washed with water (2×300 mL), aq. $NaHSO_3$ (2×250 mL) and extracted with CH_2Cl_2. Partial evaporation of the solvent and slow addition of hexanes caused the precipitation of a light pale yellow solid (10.3 g, 73% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=8 Hz, 1H), 7.73 (d, J=8 Hz, 1H), 7.43 (m, 2H), 7.38 (m, 3H), 7.31 (dd, J=8, 2 Hz, 1H).

4.5.24. 1,4-Di(4′-trimethylsilylethynyl-phenyl)-2-nitrobenzene (28). The Stille coupling procedure was followed using **27** (2 g, 6.1 mmol), $Pd(dba)_2$ (107 mg, 3% mol), $AsPh_3$ (114 mg, 6% mol), THF (30 mL), and **17** (6 g, 13 mmol) at 85 °C for 36 h. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) yielded the desired adduct **28** (2.1 g, 68% yield) as a fluffy light yellow solid. Mp 165 °C. IR (KBr) 3017, 2963, 2881, 2400, 2147, 1514.5, 1479, 1425, 1351, 1246, 1215, 1102, 1009 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=2 Hz, 1H), 7.84 (dd, J=2, 8 Hz, 1H), 7.54 (m, 2H), 7.49 (d, J=8 Hz, 1H), 7.28 (m, 2H), 0.28 (s, 9H), 0.27 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 141.2, 138.2, 137.3, 134.8, 133.0, 132.6, 132.6, 130.8, 128.1, 127.0, 123.8, 123.6, 122.8, 104.7, 104.6, 96.4, 95.9, 0.2. HRMS calcd for $C_{28}H_{29}NO_2Si_2$: 467.1737, found: 467.1735.

4.5.25. 1,4-Di(4′-ethynyl-phenyl)-2-nitro-benzene (29). The deprotection protocol was followed using **28** (1.9 g, 4 mmol), CH_2Cl_2 (20 mL), MeOH (25 mL) and K_2CO_3 (2.8 g, 20.3 mmol) for 30 min. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) furnished a yellow solid (1.1 g, 86% yield) as the desired product. Mp 180 °C. IR (KBr) 3297, 3021, 2924.2, 2854, 2431, 2396, 2104, 1526, 1471, 1417, 1355, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=1.6 Hz, 1H), 7.83 (dd, J=1.6, 8 Hz, 1H), 7.62 (m, 4H), 7.56 (m, 2H), 7.51 (d, J=8 Hz, 1H), 7.32 (m, 2H), 3.19 (s, 1H), 3.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 141.1, 138.5, 137.6, 134.7, 133.1, 132.6, 132.5, 130.8, 128.1, 127.1, 122.8, 122.7, 122.5, 83.2, 78.9, 78.6. HRMS calcd for $C_{22}H_{13}NO_2$: 323.0946, found: 323.1155.

4.5.26. 2,5-Bis-thioacetylphenyl-ethynylphenyl-nitrobenzene (4). The Sonogashira protocol was followed using **29** (500 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$ (55 mg, 10% mol), CuI (30 mg, 20% mol), **20** (903 mg, 3.2 mmol), THF (10 mL) and TEA (1.7 mL, 12.4 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) afforded **4** (550 mg, 58% yield) as a light yellow solid. Mp 190 °C (browning). IR (KBr) 3677, 3615, 3017, 2427, 2392, 2205, 1704, 1514, 1421, 1343, 1219, 1110, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=1.6 Hz, 1H), 7.88 (dd, J=1.6, 8 Hz, 1H), 7.68 (s, 4H), 7.59 (m, 6H), 7.54 (d, J=8 Hz, 1H), 7.38 (m, 4H), 7.36 (m, 2H), 2.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.8, 141.3, 138.4, 137.5, 135.0, 149.9, 134.6, 134.6, 132.9, 132.8, 132.6, 132.6, 132.4, 130.9, 128.7, 128.6, 128.4, 127.4, 124.7, 124.6, 123.8, 123.5, 123.0, 90.8, 90.6, 90.2, 30.7, 30.7. HRMS calcd for $C_{36}H_{22}N_2O_5S$: 623.7414, found: 623.1225.

4.5.27. 2,3′-Dinitro-4,4′-dibromobiphenyl (30).[37] Into a 500 mL round bottom flask, 4,4′-dibromo-biphenyl (24 g, 0.3 mol) was dissolved in H_2SO_4 (150 mL) and the flask was cooled to 0 °C, followed by a slow addition of fuming HNO_3 (183 mL). The clear yellow solution turned into a bright yellow suspension, and it was stirred for an additional 30 min. After pouring it into ice water and filtering, the solid was dissolved into EtOH (ca. 300 mL), heated and the volume of the solvent reduced. Crystallization upon cooling and filtration afforded the desired product **30** (18.3 g, 66% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=2 Hz, 1H), 7.81 (m, 6H), 7.32 (m, 4H).

4.5.28. (4′-Bromo-3,2′-dinitro-biphenyl-4-ylethynyl)-trimethyl-silane (31). The Sonogashira protocol was followed using **30** (5 g, 12.4 mmol), $PdCl_2(PPh_3)_2$ (175 mg, 2%), CuI (95 mg, 4%), TEA (8.6 mL, 50 mmol), TMSA (1.85 mL, 13 mmol) and THF (50 mL) at 75 °C for 24 h. Purification by flash chromatography (hexanes/CH_2Cl_2 2:1) gave a light yellow solid that was recrystallized (hexanes/CH_2Cl_2) to yield **31** (3.1 g, 63% yield). Mp 102 °C. IR (KBr) 3013, 2955, 2916, 2846, 2403, 2159, 1600, 1526, 1460, 1355, 1262, 1211, 1157, 1079 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=4 Hz, 1H), 7.98 (d, J=4 Hz, 1H), 7.83 (dd, J=4, 8 Hz, 1H), 7.70 (d, J=8 Hz, 1H), 7.44 (dd, J=4, 8 Hz, 1H), 7.32 (d, J=8 Hz, 1H), 0.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.3, 135.5, 133.1, 132.7, 132.1, 128.0, 124.2, 123.2, 118.7, 105.8, 104.2, 99.0, −0.2. HRMS calcd for $C_{31}H_{24}N_2O_4Si$: 417.9985, found: 414.9990.

4.5.29. (3,2′-Dinitro-4″-phenylethynyl-[1,1′;4′,1″] terphenyl-4-ylethynyl)-trimethyl-silane (32). The Stille coupling procedure was followed using **31** (1.5 g, 3.6 mmol), $Pd(dba)_2$ (178 mg, 5% mol), $AsPh_3$ (110 mg, 10% mol), THF (30 mL) and **13** (1.8 g, 3.7 mmol) at 75 °C for 30 h. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) yielded the desired adduct **32** (0.9 g, 49% yield) as a yellow solid. Mp 235 °C. IR (KBr) 3021, 2963, 2920, 2846, 2400, 2213, 2163, 1600, 1526, 1471, 1413, 1347, 1203, 1079, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=1.6 Hz, 1H), 8.05 (d, J=1.6 Hz, 1H), 7.92 (dd, J=1.6, 8 Hz, 1H), 7.70 (m, 5H), 7.56 (m, 4H), 7.38 (m, 3H), 0.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 149.0, 142.4, 138.5, 137.4, 135.5, 132.6, 132.5, 132.3, 131.8, 131.8, 131.2, 128.8, 128.6, 128.6, 127.1, 124.3, 123.1, 118.4, 105.5, 99.2, 91.4, −0.1. HRMS calcd for $C_{31}H_{24}N_2O_4Si$: 516.1505, found: 516.1511.

4.5.30. 4-Ethynyl-3,2′-dinitro-4″-phenylethynyl-[1,1′;4′,1″]terphenyl (33). The deprotection protocol was followed using **32** (500 mg, 0.9 mmol), CH_2Cl_2 (40 mL), MeOH (40 mL) and K_2CO_3 (640 mg, 4.6 mmol) for 30 min. Purification by flash chromatography (hexanes/CH_2Cl_2 1:1.5) furnished a yellow solid **33** (350 mg, 82% yield). Mp 200 °C. IR (KBr) 3300, 3013, 2434, 2396, 1607, 1526, 1464, 1417, 1343, 1215, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J=2 Hz, 1H), 8.09 (d, J=2 Hz, 1H), 7.93 (dd, J=2, 8.4 Hz, 1H), 7.76 (d, J=2 Hz, 1H), 7.67 (m, 4H), 7.56 (m, 4H), 7.38 (m, 3H), 3.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 142.5, 139.2, 137.4, 135.9, 132.7, 132.57, 132.5, 132.4, 131.9, 131.3, 128.8, 128.6, 127.2, 124.5, 125.4, 123.3, 123.1, 117.5, 91.5, 88.8, 86.5, 78.4. HRMS calcd for $C_{28}H_{16}N_2O_4$: 444.1110, found: 444.1114.

4.5.31. Thioacetic acid *S*-[4-(3,2′-dinitro-4″-phenylethynyl-[1,1′;4′,1″] terphenyl-4-ylethynyl)-phenyl] ester (5). The Sonogashira protocol was followed using **33** (160 mg, 0.4 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 10% mol), CuI (14 mg, 20% mol), **20** (105 mg, 0.4 mmol), THF (10 mL), and TEA (0.3 mL, 1.4 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 1:1.5) afforded **5** (54 mg, 52% yield) as a yellow solid with poor solubility. 150 °C (browning). IR (KBr) 3013, 2438, 2403, 2217, 1712, 1600, 1522, 1417, 1339, 1219, 1110, 1079 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J=1.6 Hz, 1H), 8.14 (d, J=1.6 Hz, 1H), 7.93 (dd, J=1.6, 8.4 Hz, 1H), 7.67 (m, 5H), 7.57 (m, 4H), 7.45 (m, 2H), 7.39 (m, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 136.2, 142.48, 138.5, 135.0, 134.4, 132.8, 132.6, 132.6, 132.5, 131.8, 131.3, 128.8, 128.6, 127.2, 124.6, 124.40, 123.6, 123.3, 123.1, 118.5, 118.3, 91.5, 87.8, 86.4, 83.7, 30.5. HRMS calcd for $C_{36}H_{22}N_2O_5S$: 594.1249, found: 594.1240.

4.5.32. 3,2′-Dinitro-4″-4-di(trimethylsilanylethynyl)-[1,1′;4′,1″]terphenyl (34). The Stille coupling procedure was followed using **31** (2 g, 4.7 mmol), $Pd(dba)_2$ (83 mg, 3% mol), $AsPh_3$ (88 mg, 6% mol), THF (30 mL), and **17** (2.6 g, 5.7 mmol) at 75 °C for 34 h. Purification by flash chromatography (hexanes/CH_2Cl_2 1:1) yielded the desired adduct **34** (2 g, 83% yield) as a fluffy yellow solid. Mp 138 °C. IR (KBr) 3013, 2955, 2920, 2846, 2400, 2155, 1638, 1533, 1464, 1429, 1355, 1219, 1087, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J=1.6 Hz, 1H), 8.04 (d, J=2 Hz, 1.6, 1H), 7.90 (dd, J=1.6, 8 Hz, 1H), 7.71 (d, J=8 Hz, 1H), 7.51 (m, 2H), 0.30 (s, 9H), 0.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 149.1, 142.4, 138.6, 137.7, 135.6, 133.1, 132.7, 132.6, 132.4, 131.4, 127.1, 124.4, 124.2, 123.3, 118.5, 105.6, 104.5, 99.3, 96.7, 0.2, −0.1. HRMS calcd for $C_{28}H_{28}N_2O_4Si_2$: 512.1588, found: 152.1594.

4.5.33. 4″-Ethynyl-3,2′-dinitro-[1,1′;4′,1″]terphenyl-4-ylethyne (35). The deprotection protocol was followed using **34** (1.9 g, 4 mmol), CH_2Cl_2 (20 mL), MeOH (25 mL) and K_2CO_3 (2.8 g, 20.3 mmol) for 30 min. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) furnished a yellow solid (1.1 g, 86% yield) as the desired product. Mp 320 °C (browning). IR (KBr) 3281, 3009, 2924, 2846, 2438, 2400, 2104, 1615, 1522, 1417, 1335, 1211, 1071, 1021 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J=2 Hz, 1H), 8.10 (d, J=2 Hz, 1H), 7.92 (dd, J=2, 8 Hz, 1H), 7.77 (d, J=8 Hz, 1H), 7.65 (m, 4H), 7.54 (m, 2H), 3.62 (s, 1H), 3.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 142.4, 139.1, 138.1, 135.9, 133.2, 133.2, 132.6, 1323.5, 131.4, 127.2, 124.5, 123.4, 123.1, 117.5, 86.5, 83.0, 79.2, 78.4. HRMS calcd for $C_{22}H_{12}N_2O_4$: 368.0797, found: 368.0801.

4.5.34. Thioacetic acid *S*-{4-[4-(4-acetylsulfanyl-phenylethynyl)-3,2′-dinitro-[1,1′;4′,1″] terphenyl-4″-ylethynyl]-phenyl} ester (6). The Sonogashira coupling protocol was followed using **35** (500 mg, 1.3 mmol), $PdCl_2(PPh_3)_2$ (50 mg, 50% mol), CuI (26 mg, 20% mol), **20** (105 mg,

0.3 mmol), THF (10 mL), and TEA (1.5 mL, 11 mmol) for 12 h at room temperature. Purification by flash chromatography (hexanes/CH_2Cl_2 1:2) afforded **6** (150 mg, 22% yield) as a dark yellow solid. Mp 140 °C (browning). IR (KBr) 3013, 2403, 2201, 1704, 1592, 1522, 1429, 1347, 1211, 1122, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J=2 Hz, 1H), 8.15 (d, J=2 Hz, 1H), 7.94 (dd, J=2, 7.6 Hz, 1H), 7.8 (d, J=7.6 Hz, 1H), 7.66 (m, 6H), 7.58 (m, 4H), 7.45 (dd, J=2, 7.6 Hz, 4H), 2.465 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.5, 151.3, 150.1, 142.6, 138.7, 137.9, 135.2, 134.7, 134.7, 133.0, 132.9, 132.8, 132.6, 131.5, 129.9, 129.8, 128.8, 127.4, 124.9, 124.5, 124.2, 123.8, 118.7, 96.4, 90.9, 90.7, 86.4, 30.7, 30.7. HRMS calcd for $C_{38}H_{24}N_2O_6S_2$: 668.1076, found: 668.1096.

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Synthesis of imidazo[5,1-*b*]thiazoles or spiro-β-lactams by reaction of imines with mesoionic compounds or ketenes generated from *N*-acyl-thiazolidine-2-carboxylic acids

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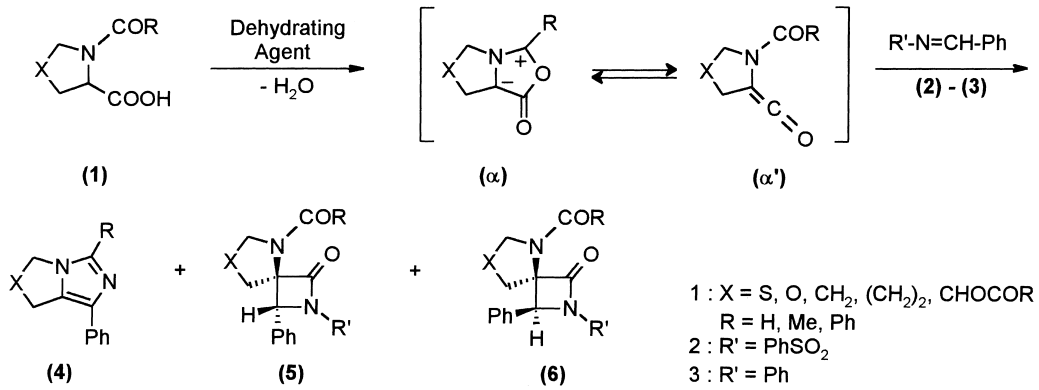
Abstract—New mesoionic compounds (2H, 3H-thiazolo[3,2-*c*]oxazol-7-ones) (β) or ketenes ((3-acyl-1,3-thiazolidin-2-ylidene)methanone) (β′) were generated from *N*-acetyl and *N*-benzoyl-thiazolidine-2-carboxylic acids (**7a**,**b**) using different methods, and their reactivity towards *N*-(phenylmethylene)benzenesulfonamide (**2**) and *N*-(phenylmethylene)aniline (**3**) was tested. When (**7a**,**b**) were treated with (**2**) and acetic anhydride in refluxing toluene solution, only imidazo[5,1-*b*]thiazoles (**8a**,**b**) were obtained from the mesoionic compound intermediates (β). When the ketene intermediates (β′) were generated from (**7a**,**b**) by means of Mukaiyama's reagent, only spiro-β-lactams (**9a**,**b**) were isolated.

1. Introduction

In previous communications, we have reported on the reactivity of bicyclic mesoionic compounds (α) derived from cyclic *N*-acyl-α-amino acids as (*R*)-thiazolidine-4-carboxylic acids, (*S*)-oxazolidine-4-carboxylic acid, (*S*)-prolines, (*R*,*S*)-pipecolinic acids and (2*S*,4*R*)-4-acyloxy-prolines (**1**) (Scheme 1).[1–3] These substrates were cyclo-dehydrated with *N*,*N*′-dicyclohexylcarbodiimide[1] or acetic anhydride[2,3] to the mesoionic compounds (münchnones intermediates) (α) in equilibrium with their ketene valence tautomers (α′). The cycloaddition reactions of (α) and (α′) with *N*-(phenylmethylene)benzenesulfonamide (**2**) and *N*-(phenylmethylene)aniline (**3**) afforded mixtures of imidazole-condensed products (**4**) and diastereoisomeric spiro-β-lactams (**5**)/(**6**), with ratios depending on the nature of R′ ($PhSO_2$ or Ph) and the experimental conditions.

In connection with these results, and as an extension of our studies of the reactivity of new bicyclic mesoionic compounds and their usefulness in the synthesis of condensed heterocycles,[4] we now report on the reactivity



Scheme 1.

Keywords: Mesoionic compounds; Ketenes; Imines; β-Lactams; Mukaiyama's reagent.
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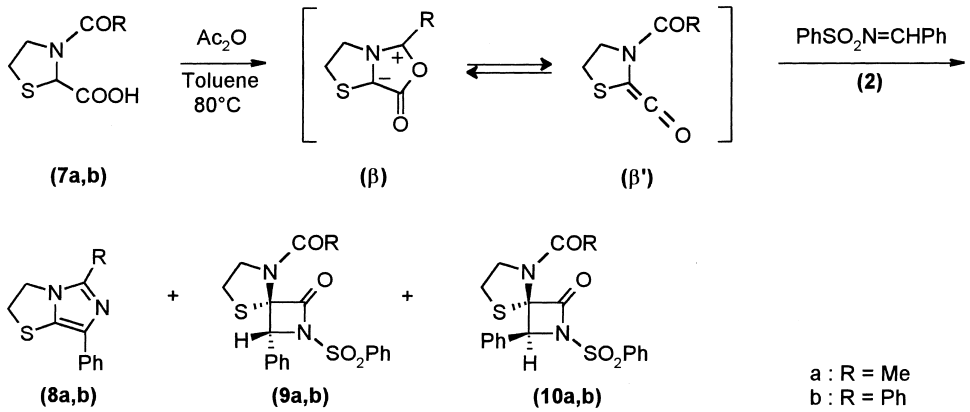


Scheme 2.

of the mesoionic compounds (β) and ketenes (β′) derived from *N*-acetyl and *N*-benzoyl-thiazolidine-2-carboxylic acids (**7a**,**b**) to imines (**2**) and (**3**).

Our interest in compounds (**7a**,**b**) is based on the position of the sulphur atom in relation to the carboxylic group, which is different from that in the previously studied substrates (**1**, X=S): this could modify the reactivity of the corresponding mesoionic or ketene intermediates (β) or (β′) as a result of either electronic or steric factors.

To the best of our knowledge, compounds (**7a**,**b**) have been used as precursors of mesoionic compounds in only one previous study, in which they were reacted with dimethyl-acetylenedicarboxylate in acetic anhydride to afford 2,3-dihydropyrrolo[2,1-*b*]thiazole derivatives.[5]

The 1,3-dipolar cycloaddition reactions between imine (**2**) and the bicyclic mesoionic compounds (β) could produce new condensed bicyclic heterocycles (imidazo[5,1-*b*]thiazoles) that have never previously been prepared by means of 1,3-dipolar cycloaddition reactions.

Another important aim of the study was to obtain only spiro-β-lactams by finding the best experimental conditions for generating only ketenes (β′) from compounds (**7a**,**b**). In our previous experiments using *N*,*N*′-dicyclohexylcarbodiimide or acetic anhydride (specific means of generating mesoionic compounds), spiro-β-lactams were always obtained mixed with (**4**) or, in the cases in which (**4**) did not form, in poor yields. In that case, the formation of spiro-β-lactams such as (**5**)/(**6**) depended on the tautomeric equilibrium between the mesoionic and ketene compounds, and therefore on the stability of the bicyclic mesoionic compounds.

Interest in the synthesis of β-lactams has been renewed by recent discoveries of their activity as inhibitors of cholesterol absorption[6] (in particular those with a spiranic structure[6d]) or thrombin.[7] These heterocycles have also been found to be useful synthons in the synthesis of new polyfunctionalised compounds, as we have demonstrated with our spiro-β-lactams.[8]

2. Results and discussion

The reaction of (**7a**,**b**) with imine (**2**) was run in toluene solution at 80 °C for 28 h with acetic anhydride as the dehydrating agent. This led to a mixture of the imidazo[5,1-*b*]thiazoles (**8a**,**b**) and the diastereoisomeric spiro-β-lactams (**9a**,**b**) and (**10a**,**b**) (Scheme 2), which were separated by means of column chromatography; their structures were confirmed on the basis of analytical and spectroscopic data.

The regiochemistry of compound (**8a**) was confirmed by means of direct comparison with the other theoretical regioisomer called 2,3-dihydro-5-methyl-6-phenyl-imidazo[2,1-*b*]thiazole, which was prepared as previously described.[9]

The relative configuration was assigned to spiro-β-lactams (**9**) and (**10**) on the basis of ^{1}H NMR experiments. In the case of the benzylic proton, the 300 MHz ^{1}H NMR spectra of products (**9a**,**b**) showed a signal with a chemical shift that was 0.5 ppm lower than that of the corresponding diastereoisomers (**10a**,**b**) because of the deshielding effect of the *N*-acyl carbonyl group.

Bicyclic compounds (**8a**,**b**) derive from a typical regio-selective 1,3-dipolar cycloaddition of the mesoionic intermediate (β) to the C=N double bond of imine (**2**) with the subsequent loss of carbon dioxide and benzenesulfinic acid, whereas spiro-β-lactams (**9a**–**b**–**10a**–**b**) are the result of a Staudinger reaction between the imine (**2**) and the ketene intermediate (β′).[10]

As shown in Table 1, the total yields of compounds (**8a**–**b**–**10a**–**b**) were always better than those of the corresponding **4**–**6** (X=S, R′=$PhSO_2$); furthermore, when R=Me, the reaction also affords the bicyclic compound (**8a**).

These results can be explained as being due to the increased stability of mesoionic compounds (β) with respect to (α) as a consequence of the different position of the sulphur atom

Table 1.

Products yield (%) (Ac_2O, toluene, 80 °C)

	(**8**)	(**9**)	(**10**)	(**4**)	(**5**)	(**6**)	(X=S, R′=$PhSO_2$)
R=Me	16	16	4	0	10	6	
R=Ph	29	24	4	22	12	5	

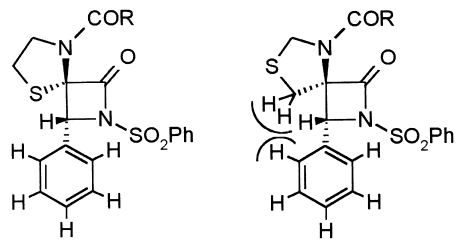


Figure 1.

which, in (β), is adjacent to the negative charge. It is well known that the presence of a sulphur atom increases the acidity of the adjacent CH bonds, an effect that has been attributed to the stabilisation of the carbanion by the sulphur atom.[11] This stabilisation could make up for the cyclisation difficulty of these bicyclic mesoionic compounds.[2]

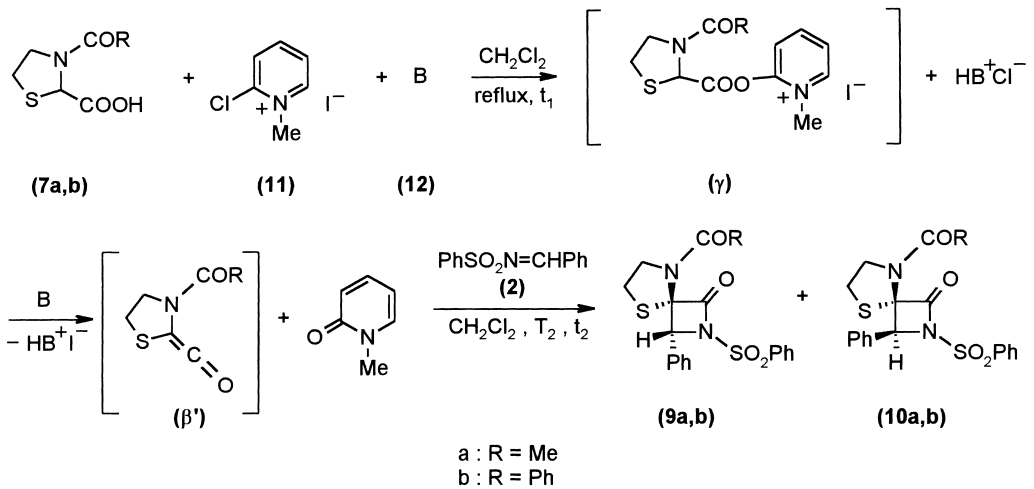
Another difference is the ratio of the diastereoisomeric spiro-β-lactams, which is about 2.5 times in favour of the thermodynamically more stable β-lactam (**9a**,**b**) (3-C phenyl and *N*-acyl groups *trans* to each other). This major diastereoselectivity could also be ascribed to the presence of sulphur, which could favour the formation of products (**9a**,**b**) probably as a result of steric factors: the molecular models show less steric encumbrance between the 3-C phenyl group and the 8-S atom in compounds (**9a**,**b**) in comparison with the same 3-C phenyl group and the 8-CH_2 group in compounds (**5**) (X=S, R′=$PhSO_2$) (Fig. 1).

In order to obtain only imidazo[5,1-*b*]thiazoles (**8a**,**b**), the reactions of (**7a**,**b**) and (**2**) were carried out in boiling toluene for 24 h in the presence of Ac_2O: under these conditions, compounds (**8a**) and (**8b**) were obtained in, respectively, 30 and 50% yields.

On the contrary, it was more difficult to find good conditions for obtaining exclusively spiro-β-lactams. Various methods were tried in order to generate the ketenes (β′) selectively: for example, $SOCl_2$/TEA/toluene, *N*,*N*′-diisopropylcarbodiimide/TEA/THF and 1,1′-carbonyldiimidazole/DBU/THF were all unsuccessful.

With *N*,*N*-dimethylchlorosulfitemethaniminium chloride ($SOCl_2$–DMF), a dehydrating reagent that is also used to prepare β-lactams,[12] the reactions of (**7a**,**b**) with (**2**) led to poor yields (about 15%) of spiro-β-lactams (**9a**,**b**) when run in THF solution at 5–10 °C in the presence of TEA. Better results were obtained using the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide)[13] (**11**) as an acid-activating agent in the presence of a base (**12**) in dichloromethane solution (Scheme 3).

We investigated the effects of different reagent ratios, bases, temperatures and times on reaction yields and stereoselectivity (Table 2). The reactions were run in two steps: first, the aminoacids were refluxed with the Mukaiyama reagent in the presence of 1 equiv. of the base for time t_1, and then the imine and 2 equiv. of the base were added and the reactions continued at temperature T_2 for time t_2.



Scheme 3.

Table 2.

Entry	(**7**)	Ratio (**7**):(**11**):(**12**):(**2**)	Base	t_1 (h)	T_2	t_2 (h)	Total yields (%)	(**9**):(**10**)
1	**7a**	1.0:1.0:2.0:1.0	TPA	1	Reflux	10	17	100:0
2	**7a**	1.0:2.4:6.0:1.0	TPA	1	Reflux	24	34	100:0
3	**7a**	1.5:1.8:4.5:1.0	TPA	1	Reflux	24	52	100:0
4	**7a**	1.8:2.1:4.5:1.0	TPA	1	Reflux	15	55	95:5
5	**7a**	1.8:2.1:5.4:1.0	TPA	10	Reflux	10	70	97:3
6	**7a**	1.8:2.1:5.4:1.0	TEA	10	rt	48	58	100:0
7	**7a**	1.8:2.1:5.4:1.0	TEA	10	Reflux	10	62	95:5
8	**7b**	1.8:2.1:5.4:1.0	TEA	10	rt	20	46	92:8
9	**7b**	1.8:2.1:5.4:1.0	TEA	10	Reflux	10	78	95:5
10	**7b**	1.8:2.1:5.4:1.0	TPA	10	Reflux	10	80	97:3

The best results were obtained using an acid/Mukaiyama reagent/base/imine reagent ratio of 1.8:2.1:5.4:1, with tripropylamine (TPA) as a base, and reflux temperature for 10 h before and after the addition of the imine (entries 5 and 10, Table 2).

In comparison with the preceding method (Table 1) the diastereoselectivity was greatly increased favouring the formation of the more stable spiro-β-lactams (**9a**,**b**). The yield and diastereoselectivity were affected by the reaction time and temperature: for example, at reflux temperature (entry 7, Table 2), spiro-β-lactams (**9a**) and (**10a**) were obtained with a 62% total yield and 95:5 ratio; at room temperature, the yield decreased to 58% but (**9a**) was the only product (entry 6, Table 2). The base also affected the yield and the diastereoselectivity of the reaction (entries 5 and 7, Table 2): in our case, TPA gave higher yields and better stereoselectivity than TEA.[13] A run conducted as in entry 7 but in 1,2-dichloroethane as solvent at 70 °C afforded compound (**9a**) alone, but with a yield of only 36%.

A similar trend was observed with (**7b**) (entries 8–10, Table 2); the bicyclic compound (**8b**) was also detected (about 3–5%), which is in line with the greater stabilisation of the mesoionic tautomer (β) by the phenyl group in comparison with the methyl group.

The same reactions of compounds (**7a**,**b**) with imine (**3**) conducted in toluene solution and acetic anhydride, or in dichloromethane solution and Mukaiyama reagent, led to only NMR-detectable traces of the corresponding spiro-β-lactams, with respectively acetanilide and 3-acetyl-thiazolidine-2-carboxylic acid phenylamide as the main products. Imine (**3**) is scarcely reactive in these kinds of reactions with bicyclic mesoionic compounds.[1]

3. Conclusion

In this study, we generated new mesoionic compounds (2*H*,3*H*-thiazolo[3,2-*c*]oxazol-7-ones) (β) and ketenes ((3-acyl-1,3-thiazolidin-2-ylidene)methanone) (β′) from *N*-acetyl and *N*-benzoyl-thiazolidine-2-carboxylic acids (**7a**,**b**). By reacting these intermediates with imine (**2**), we selectively obtained new imidazo[5,1-*b*]thiazoles and spiro-β-lactams in better yields than the similar mesoionic compounds (α, X=S), possibly because of the different position of the sulphur atom in the starting cyclic amino acid.

The effect of the different position of the sulphur atom on the reactivity of the spiro-β-lactams (**9a**–**b**–**10a**–**b**) is now under investigation.

4. Experimental

4.1. General

Melting points were measured using a Büchi apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC 300 spectrometer. Chemical shifts (δ) are given in ppm in relation to TMS; the solvent was $CDCl_3$ unless otherwise specified. All of the coupling constants (*J*) are in Hertz. The MS spectra were determined using a VG Analytical 7070 EQ mass spectrometer with an attached VG analytical 11/250 data system. The IR spectra were determined using a Perkin–Elmer 1725X FT-IR spectrometer.

Compounds (**2**)[14] and (**7a**,**b**)[5] were prepared according to the reported methods. Mukaiyama's reagent (**11**) was obtained from commercial sources.

4.2. General procedure for the reactions of (7a,b) with (2) and acetic anhydride

Acetic anhydride (25 mmol) was added dropwise under nitrogen to a stirred solution of (**7a**) or (**7b**) (5 mmol) in anhydrous toluene (15 ml). The mixture was heated at 80 °C for 1 h, and then a solution of imine (**2**) (5 mmol) in toluene (10 ml) was added dropwise and the heating continued for 28 h. After evaporation of the solvent, the residue was taken up in dichloromethane (50 ml), and the solution was washed with 10% sodium bicarbonate (2×20 ml) and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated off. The crude mixture was separated using column chromatography (silica gel, toluene/ethyl acetate: 95:5), and the products were recrystallised and identified by means of analytical and spectroscopic data. The relative yields are reported in Table 1.

4.2.1. 2,3-Dihydro-5-methyl-7-phenyl-imidazo[5,1-*b*]thiazole (8a). Colorless solid, mp 130–131 °C (Et_2O/EtOH); ^{1}H NMR δ 2.34 (3H, s, CH_3), 3.83 (2H, t, *J*=6.7 Hz, SCH_2), 4.00 (2H, t, *J*=6.7 Hz, NCH_2), 7.10–7.60 (5H, m, Ph). IR (cm^{-1}, Nujol) 1660, 1600, 1548, 1519, 770. ^{13}C NMR δ 13.5 (CH_3), 38.5 (SCH_2), 44.4 (NCH_2), 124.2–140.9 (5-C, 7-C, 8-C, C_{Ph}). Anal. calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.62; H, 5.47; N, 12.85. MS (*m*/*z*) 216, 201, 188, 147, 121.

4.2.2. *cis*-5-Acetyl-3-phenyl-2-(phenylsulphonyl)-8-thia-2,5-diazaspiro[3.4]octan-1-one (9a). Colorless solid, mp 177–178 °C d. (iPrOH); ^{1}H NMR δ 2.05 (3H, s, CH_3), 2.59 (1H, m, SCH), 2.92 (1H, ddd, *J*=11.4, 7.6, 5.9 Hz, SCH), 3.60 (1H, ddd, *J*=11.4, 7.6, 5.9 Hz, NCH), 3.82 (1H, m, NCH), 5.52 (1H, s, CH), 7.30–7.90 (10H, m, Ph). ^{13}C NMR (DMSO) δ 23.2 (CH_3), 30.1 (SCH_2), 51.4 (NCH_2), 67.6 (CH), 84.6 ($C_{spir.}$), 127.3–136.6 (C_{Ph}), 164.8 (CO), 168.8 (CO). IR (cm^{-1}, Nujol) 1802 (lactam CO), 1657 (amide CO). Anal. calcd for $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.50; N, 6.96. Found: C, 56.62; H, 4.47; N, 6.89. MS (*m*/*z*) 402, 245, 216.

4.2.3. *trans*-5-Acetyl-3-phenyl-2-(phenylsulphonyl)-8-thia-2,5-diazaspiro[3.4]octan-1-one (10a). Colorless solid, mp 160–161 °C d. (iPrOH); ^{1}H NMR δ 1.63 (3H, s, CH_3), 3.07 (2H, m, SCH_2), 3.27 (1H, m, NCH), 3.75 (1H, m, NCH), 5.10 (1H, s, CH), 7.00–8.00 (10H, m, Ph). ^{13}C NMR (DMSO) δ 28.5 (CH_3), 30.7 (SCH_2), 53.2 (NCH_2), 72.9 (CH), 80.9 ($C_{spir.}$), 124.8–142.2 (C_{Ph}), 163.1 (CO), 167.8 (CO). IR (cm^{-1}, Nujol) 1790 (lactam CO), 1668 (amide CO). Anal. calcd for $C_{19}H_{18}N_2O_4S_2$: C, 56.70; H, 4.50; N, 6.96. Found: C, 56.58; H, 4.36; N, 6.81. MS (*m*/*z*) 402, 245, 216.

4.2.4. 2,3-Dihydro-5,7-diphenyl-imidazo[5,1-*b*]thiazole (8b). Colorless solid, mp 155–156 °C (Et_2O); ^1H NMR δ 3.88 (2H, t, J=7.0 Hz, SCH_2), 4.34 (2H, t, J=7.0 Hz, NCH_2), 7.10–7.75 (10H, m, Ph). ^{13}C NMR (DMSO) δ 39.2 (SCH_2), 47.0 (NCH_2), 124.5–134.46 (5-C, 7-C, 8-C, C_{Ph}). IR (cm^{-1}, Nujol) 1602, 1540, 1446, 766. Anal. calcd for $C_{17}H_{14}N_2S$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.19; H, 4.92; N, 10.00. MS (*m*/*z*) 278, 250, 147, 121, 103.

4.2.5. *cis*-5-Benzoyl-3-phenyl-2-(phenylsulphonyl)-8-thia-2,5-diazaspiro[3.4]octan-1-one (9b). Colorless solid, mp 176–177 °C d. (toluene); ^1H NMR δ 2.60 (1H, ddd, J=11.6, 5.0, 2.0 Hz, SCH), 3.0 (1H, m, SCH), 3.67 (1H, m, NCH), 3.84 (1H, ddd, J=11.6, 5.0, 2.0 Hz, NCH), 5.64 (1H, s, CH), 7.20–8.00 (15H, m, Ph). ^{13}C NMR δ 30.7 (SCH_2), 54.6 (NCH_2), 66.7 (CH), 85.1 ($C_{spir.}$), 127.3–137.5 (C_{Ph}), 165.4 (CO), 169.2 (CO). IR (cm^{-1}, Nujol) 1794 (lactam CO), 1638 (amide CO). Anal. calcd for $C_{24}H_{20}N_2O_4S_2$: C, 62.05; H, 4.34; N, 6.03. Found: C, 62.10; H, 4.26; N, 5.94. MS (*m*/*z*) 464, 323, 281, 245.

4.2.6. *trans*-5-Benzoyl-3-phenyl-2-(phenylsulphonyl)-8-thia-2,5-diazaspiro[3.4]octan-1-one (10b). Colorless solid, mp 163–165 °C d. (toluene); ^1H NMR δ 2.85 (1H, ddd, J=11.0, 5.23, 1.7 Hz, SCH), 3.04 (1H, m, SCH), 3.3 (1H, m, NCH), 3.66 (1H, m, NCH), 5.18 (1H, s, CH), 6.70–8.10 (15H, m, Ph). ^{13}C NMR (DMSO) δ 31.7 (SCH_2), 54.2 (NCH_2), 73.8 (CH), 81.4 ($C_{spir.}$), 125.9–143.1 (C_{Ph}), 163.7 (CO), 168.4 (CO). IR (cm^{-1}, Nujol) 1808 (lactam CO), 1644 (amide CO). Anal. calcd for $C_{24}H_{20}N_2O_4S_2$: C, 62.05; H, 4.34; N, 6.03. Found: C, 61.98; H, 4.29; N, 5.91. MS (*m*/*z*) 464, 323, 281, 245.

4.3. General procedure for the reactions of (7a,b) with (2) and Mukaiyama's reagent

A suspension of (**7a**) or (**7b**) (1.8 mmol), 2-chloro-*N*-methylpyridinium iodide (**11**) (2.1 mmol) and tripropylamine (1.8 mmol) in anhydrous methylene chloride (25 ml) were heated at reflux temperature under a nitrogen atmosphere for 10 h. A solution of the imine (**2**) (1 mmol) in anhydrous dichloromethane (10 ml) and tripropylamine (3.6 mmol) were added and the reaction mixture was refluxed for other 10 h. After cooling, the solution was washed with water, 5% HCl aqueous solution, and then with water. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude products were purified by column chromatography (silica gel, toluene/ethyl acetate, 95:5) and recrystallized as indicated above. The relative yields are reported in Table 2.

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Syntheses and structures of azol-1-yl derivatives of nitronyl and imino nitroxides

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Abstract—2-(Pyrazol-1-yl)-, 2-(imidazol-1-yl)-, 2-([1,2,4]triazol-1-yl)-, and 2-(benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl were prepared by reactions of 2-bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (NIT-Br) with the corresponding sodium azolides. In prepared 2-(azol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyls, the NIT–N_{Het} bond is readily hydrolyzed. Reduction of imidazole-3-oxide-1-oxyls leads to corresponding 2-(azol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyls, which are much more stable against hydrolysis. The structures of spin-labeled imidazoles, [1,2,4]triazoles and benzotriazoles are confirmed by X-ray analysis, showing that the paramagnetic molecules form packings with motifs from centrosymmetric dimers to topologically linear chains.

1. Introduction

Molecular ferromagnet design based on complexes of paramagnetic metal ions with nitroxides is becoming an area of active interest, as evidenced by the growing number of experimental works and reviews.[1,2] The demand for highly dimensional heterospin structures has stimulated the development of syntheses of polyfunctional nitroxides. For functional groups, it is desirable to use combinations of donor groups, leading to stereochemically non-rigid complexes with potentialities for higher coordination numbers of the metal ion. Thus, nitroxides with polynitrogen heterocyclic substituents such as imidazole,[3] benzimidazole,[4] pyrazole,[5,6] 1,2,4-triazole,[7] and tetrazole[8] have been prepared.

In all known compounds of this type, the nitronyl nitroxide fragment is bonded to the carbon atom of the heterocyclic substituent. The only published exception is 4,4,5,5-tetramethyl-2-(pyrrol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl,[9] where the nitronyl nitroxide moiety is a poor electron donor. For this reason, we decided to investigate the possibility of synthesizing a series of azol-1-yl derivatives of nitronyl and imino nitroxides containing a nitrogen atom in the *N*-heterocyclic substituent along with the nitrogen atom bonded to the paramagnetic fragment. Nitroxides of this kind are potential polyfunctional spin-labeled ligands. Unexpectedly, we found that nitronyl nitroxides **2a**–**d** are very sensitive to hydrolysis at the C–N_{Het} bond between the heterocycles. Imino nitroxides **3a**–**d** are less liable to this phenomenon. Liability to hydrolysis at the C–N_{Het} bond is an essential obstacle in handling the title nitroxides, and one can think that synthesis of **2b**–**d** and **3b**–**d** in single crystal form, as well as crystal and molecular structure solution, is definite success.

2. Syntheses and structures

The azol-1-yl derivatives of nitronyl and imino nitroxides **2a**–**d** and **3a**–**d** were prepared in a good yield, as shown in Scheme 1. In a typical procedure, an appropriate azole (pyrazole, imidazole, 1,2,4-triazole or benzotriazole) was treated with NaH in DMF, and the resulting sodium azolide was allowed to react with bromoderivative **1**.[9] TLC monitoring indicated that imino nitroxides **3a**–**d** and 4,4,5,5-tetramethylimidazolidin-2-one 1,3-dioxide[10] **4** always formed along with **2a**–**d**. An attempt to isolate **2a**–**d** in individual form led to easy hydrolysis of these nitronyl nitroxides at the C–N_{Het} bond.

Thus, heating in solution above 70 °C or chromatographing on an Al_2O_3 column, or storage in air at room temperature resulted in complete decomposition of **2a**–**d** within 0.5–1.5 h, forming zwitterion **4** and the corresponding heterocycle. Treatment of **2a**–**d** (as well as **4**) with an aqueous alkali or ammonia instantly led to a deep blue solution, whose EPR spectrum is a quintiplet with an unprecedentedly

Keywords: Nitronyl nitroxides; Imino nitroxides; Pyrazole; Imidazole; Triazole; Alkylation.
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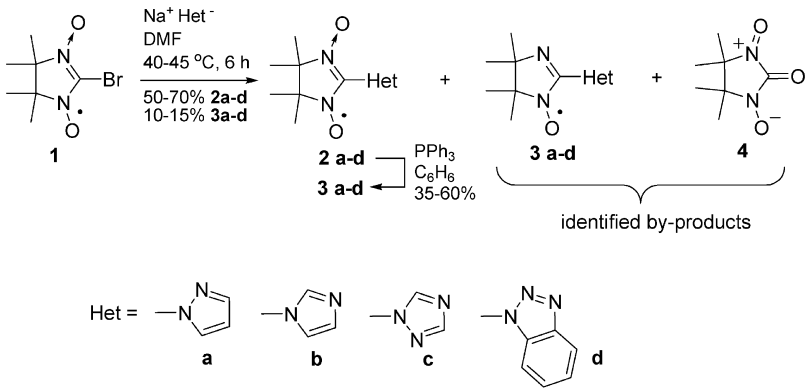
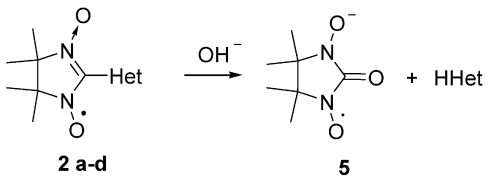


Scheme 1. Preparation of 2-(azol-1-yl)-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyls **2a–d** and 2-(azol-1-yl)-4,4,5,5-tetramethylimidazoline-1-oxyls **3a–d**.



Scheme 2. Alkaline hydrolysis of nitronyl nitroxides **2a–d**.

high nitrogen coupling constant a_N=8.71 G,[8] which is well known and characteristic of hydroxamic acid anion **5** alone (Scheme 2).

The desired nitronyl nitroxides were isolated by column chromatography on SiO_2. Single crystals **2b–d** suitable for an X-ray diffraction study were grown under 'cold' crystallization conditions, as described in Section 4. Numerous attempts to grow crystals **2a** always gave finely disperse polycrystalline concretions, not suitable for an X-ray diffraction study.

Nitronyl nitroxides **2a–d** were reduced to imino nitroxides **3a–d** using PPh_3 in dry benzene (Scheme 1). Compounds **3a–d** are much more kinetically stable. They are not decomposed by water. They may be purified by chromatography on both SiO_2 and Al_2O_3. Imino nitroxides are stored under normal conditions without taking any special safety measures. Nitroxides **3b–d** were grown as crystals suitable for an X-ray diffraction analysis, except **3a**, which precipitated as an oil at −25 °C from hexane.

The molecular structure of **2b–d** and **3b–d** is shown in Figures 1 and 2. Selected bond lengths are given in Tables 1 and 2.

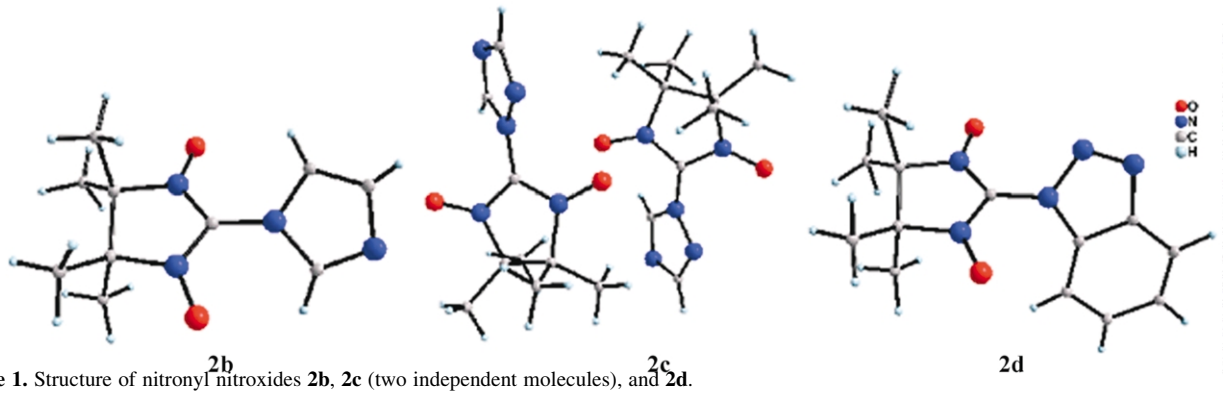


Figure 1. Structure of nitronyl nitroxides **2b**, **2c** (two independent molecules), and **2d**.

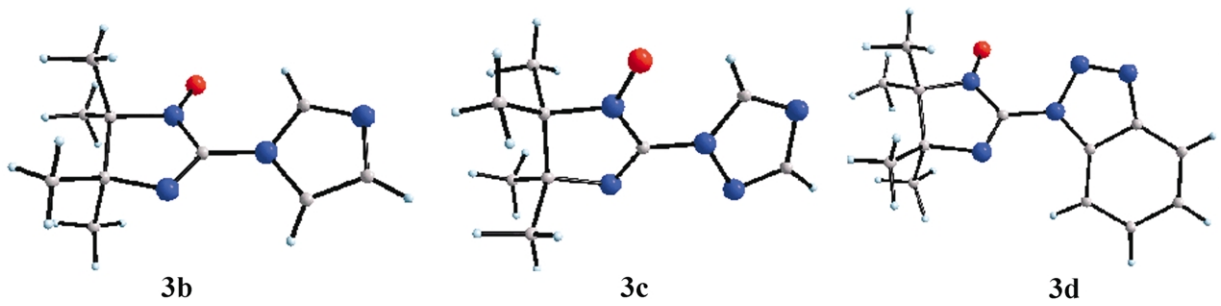


Figure 2. Structure of imino nitroxides **3b**, **3c**, and **3d**.

Table 1. Selected bond lengths (Å) and angles (°) for **2b–d**

Compound	**2b**	**2c**	**2d**
N–O	1.275(2)	1.289(3)	1.282(4)
	1.275(2)	1.267(3)	1.257(5)
C–N	1.333(2)	1.341(4)	1.313(5)
	1.330(2)	1.330(4)	1.346(5)
$C–N_{Het}$	1.374(3)	1.376(4)	1.386(5)
$\angle CN_2–Het$	28.8(2)	44.3(1) 7.8(1)	59.3(2)

Table 2. Selected bond lengths (Å) and angles (°) for **3b–d**, **4**

Compound	**3b**	**3c**	**3d**	**4**
N–O	1.261(3)	1.276(3)	1.265(3)	1.243(4)
				1.249(4)
C–N	1.383(4)	1.383(4)	1.368(3)	1.368(4)
	1.272(4)	1.264(3)	1.257(3)	1.369(4)
$C–N_{Het}$	1.393(4)	1.396(4)	1.387(3)	
$\angle CN_2–Het$	22.2(5)	22.0(4)	36.7(2)	

Note that N–O bond lengths are within the limits characteristic of the nitroxides (~1.27–1.28 Å). The $C–N_{Het}$ bond lengths also vary within a narrow range of values, 1.385±0.015 Å. Within this range of values, however, $C–N_{Het}$ bond lengths for **2d** and **3b–d** markedly exceed those for **2b** and **2c**. This correlates with the significant difference between C–N bond lengths in the imidazoline ring (Tables 1 and 2).

The difference in the C–N bond lengths of the imidazoline ring is quite natural for imino nitroxides **3b–d**, but not for **2d**, for which it proved to be unexpected. This difference in bond lengths must increase polarity of molecules **2d** and **3b–d**. It is not surprising, therefore, that in solids they should typically 'coalesce' into dimers.

Tables 1 and 2 also give the angles between the plane of the N–C–N fragment of the imidazoline ring and the plane of the azole ring, denoted as $\angle CN_2–Het$. They differ substantially from 0° in all compounds, which hinders effective conjugation between the π-systems of the heterocycles.

As noted above, zwitterion **4** is one of hydrolysis products. It was also isolated as qualitative single crystals. As compound **4** was not found in CCDC, here we give its main structural data. Solid compound **4** is formed from two crystallographically independent molecules (Fig. 3), each possessing C_2 symmetry. The N–O distances in the NO groups are virtually the same and equal, on the average, 1.246 Å; i.e. they are much shorter than the typical N–O distances of nitroxides. Molecules **4** also intrinsically have very short C=O distances, 1.200(6) and 1.207(6) Å.

3. Conclusions

In this study, we have synthesized a series of 1-hetaryl derivatives of nitronyl and imino nitroxides and determined their crystal and molecular structure. It has been found that nitronyl nitroxides of this kind are liable to hydrolysis at the

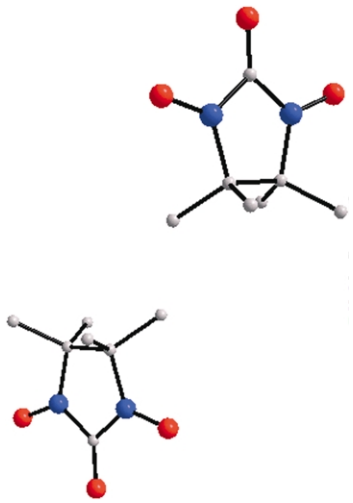


Figure 3. Structure of **4**.

$C–N_{Het}$ bond. This specific feature of nitroxides under study should be taken into account in design of new magnetoactive systems, because, as mentioned in Section 1, synthesis of polyfunctional nitroxides is generally developed for their subsequent application to synthesis of molecular magnets from transition metal heterospin complexes with stable radicals.

4. Experimental

4.1. General

The reactions were monitored by TLC on Silica gel 60 F_{254} aluminum sheets (Merck) using ethyl acetate as eluent. Silica gel 'Merck' (Silica gel 60 0.063–0.200 mm for column chromatography) and Al_2O_3 (neutral, analytical grade, for chromatography, Russia) were used for column chromatography. IR spectra were recorded for KBr pellets on a Vector 22 (Bruker) spectrometer. All reagents and organic solvents were analytical quality and used as purchased. 2-Bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (**1**) was prepared by the procedure described previously.[11]

4.2. General procedure for the preparation of compounds 2a–d

The compounds were synthesized under argon. Azole (4.70 mmol) and DMF (5 mL) were placed in a 50 mL round-bottom flask. To the resulting solution, NaH (60% in mineral oil, 0.20 g, 5.0 mmol) was added with stirring, and the reaction mixture was stirred at room temperature for 10 min. Then **1** (1.0 g, 4.20 mmol) was added, and the reaction mixture stirred at 40–45 °C for 6 h. The flask was connected to a vacuum pump via a trap cooled with liquid nitrogen, and DMF was distilled off at $p<1$ Torr and bath temperature 40–45 °C. The residue was dissolved in benzene (15 mL), and the solid was filtered off. The filtrate was placed on a benzene-wetted SiO_2 column (1.5×30 cm) and chromatographed using a 1:1 mixture of ethyl acetate and benzene as eluent.

The fraction which was collected first was orange colored and contained imino nitroxides **3a–d** and zwitterion **4** (TLC data). This fraction was evaporated on a rotary evaporator and chromatographed on Al_2O_3 (1.5×20 cm) using benzene as eluent. Zwitterion **4** formed a static layer colored blue on Al_2O_3. Imino nitroxides **3a–d** were eluted and recrystallized from hexane. The yields of imino nitroxides **3a–d** were 10–15%.

The second, violet-colored fraction from the SiO_2 column was evaporated on a rotary evaporator at a bath temperature of 25–27 °C. Hexane (~5 mL) was added to the residue, and the product was completely dissolved at room temperature by treatment with ultrasound and benzene addition in sequence. The solution was filtered and stored at −15 °C. Nitronyl nitroxide crystals **2a–d** were filtered off, quickly dried on a filter, and stored in a refrigerator under argon. For an X-ray diffraction study, nitronyl nitroxide crystals **2b–d** were extracted from under the layer of the mother solution and immediately coated with a layer of water-proof glue.

4.2.1. 4,4,5,5-Tetramethyl-2-(pyrazol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2a). Yield 0.48 g (51%), violet crystals, mp 96–97 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 612, 635, 766, 871, 913, 940, 972, 1043, 1078, 1144, 1175, 1201, 1288, 1373, 1399, 1425, 1466, 1576, 1695, 2998, 3118. Anal. found: C, 54.5; H, 6.8; N, 25.0. Calcd for $C_{10}H_{15}N_4O_2$: C, 53.8; H, 6.8; N, 25.1. MS, *m*/*z* (%): 223.11963 (M^+, 44, calcd for $C_{10}H_{15}N_4O_2$ 223.11949), 114 (9), 109 (12), 86 (83), 84 (69), 83 (42), 69 (100), 68 (9), 67 (10), 58 (54).

4.2.2. 2-(Imidazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2b). Yield 0.45 g (48%), violet crystals, mp 125–128 °C. μ_{eff}/β=1.71 (295 K). IR (KBr): [cm^{-1}] 609, 649, 739, 836, 816, 836, 869, 896, 997, 1016, 1067, 1101, 1144, 1173, 1217, 1246, 1273, 1335, 1376, 1409, 1458, 1528, 1582, 1694, 2990, 3148. MS, *m*/*z* (%): 223.11985 (M^+, 73, calcd for $C_{10}H_{15}N_4O_2$ 223.11949), 86 (23), 84 (100), 83 (29), 79 (5), 69 (89), 67 (10), 58 (20). Anal. found: C, 52.5; H, 6.8; N, 24.3. Calcd for $C_{10}H_{15}N_4O_2$: C, 53.8; H, 6.8; N, 25.1.

4.2.3. 4,4,5,5-Tetramethyl-2-([1,2,4]triazol-1-yl)-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2c). Yield 0.48 g (51%), violet crystals, mp 113–114 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 626, 644, 666, 737, 756, 817, 867, 947, 991, 1119, 1140, 1173, 1212, 1271, 1324, 1379, 1421, 1458, 1509, 1578, 1762, 2980, 3095. MS, *m*/*z* (%): 224.11448 (M^+, 71, calcd for $C_9H_{14}N_5O_2$ 224.11474), 157 (22), 110 (28), 84 (100), 83 (29), 70 (27), 69 (80), 56 (86). Anal. found: C, 47.8; H, 6.5; N, 31.2. Calcd for $C_9H_{14}N_5O_2$: C, 48.2; H, 6.3; N, 31.2.

4.2.4. 2-(Benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl (2d). Yield 0.80 g (70%), violet crystals, mp 148–150 °C. μ_{eff}/β=1.73 (295 K). IR (KBr): [cm^{-1}] 609, 756, 766, 780, 845, 865, 919, 972, 998, 1030, 1154, 1177, 1232, 1298, 1312, 1377, 1395, 1426, 1454, 1564, 1612, 2995, 3121. Anal. found: C, 57.1; H, 6.2; N, 25.9. Calcd for $C_{13}H_{16}N_5O_2$: C, 56.9; H, 5.9; N, 25.5.

4.3. General procedure for the preparation of compounds 3a–d

A solution of nitroxide **3a–d** (0.54 mmol) and PPh_3 (140 mg, 0.54 mmol) in benzene (3 mL) was stirred at room temperature for 24 h. TLC (SiO_2, Al_2O_3) showed that the reaction mixture contained Ph_3PO, zwitterion **4**, and iminonitroxide **3a–d**. Ph_3PO was removed from the mixture by chromatography on a silica gel column (1.5×10 cm) with $CHCl_3$. The orange colored fraction was evaporated on a rotary evaporator, and the residue was chromatographed on Al_2O_3 (1.5×15 cm) using benzene as eluent to give nitroxide **3a–d**. An analytical sample was obtained by recrystallization of the product from hexane.

4.3.1. 4,4,5,5-Tetramethyl-2-(pyrazol-1-yl)-4,5-dihydro-1*H*-imidazole-1-oxyl (3a). Yield 61 mg (55%), orange oil. μ_{eff}/β=1.63 (295 K). IR (KBr): [cm^{-1}] 643, 661, 760, 876, 914, 935, 1039, 1073, 1143, 1171, 1201, 1226, 1261, 1347, 1390, 1453, 1531, 1602, 1740, 2935, 2981, 3133. Anal. found: C, 57.3; H, 7.3; N, 26.3. Calcd for $C_{10}H_{15}N_4O$: C, 58.0; H, 7.3; N, 27.1. MS, *m*/*z* (%): 207.12479 (M^+, 5, calcd for $C_{10}H_{15}N_4O$ 207.12458), 152 (10), 134 (10), 124 (5), 120 (18), 114 (12), 109 (38), 94 (8), 85 (6), 84 (95), 83 (10), 79 (15), 70 (5), 69 (100), 68 (12), 67 (15).

4.3.2. 2-(Imidazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl (3b). Yield 40 mg (36%), red crystals, mp 66–67 °C. μ_{eff}/β=1.70 (295 K). IR (KBr): [cm^{-1}] 649, 663, 764, 835, 874, 897, 940, 958, 1002, 1014, 1061, 1108, 1138, 1169, 1221, 1251, 1281, 1318, 1375, 1474, 1524, 1601, 2982, 3126, 3146. Anal. found: C, 58.4; H, 7.4; N, 27.1. Calcd for $C_{10}H_{15}N_4O$: C, 58.0; H, 7.3; N, 27.1.

4.3.3. 4,4,5,5-Tetramethyl-2-([1,2,4]triazol-1-yl)-4,5-dihydro-1*H*-imidazole-1-oxyl (3c). Yield 44 mg (59%), red crystals, mp 75–76 °C. μ_{eff}/β=1.71 (295 K). IR (KBr): [cm^{-1}] 656, 671, 871, 885, 948, 962, 989, 1114, 1139, 1214, 1277, 1308, 1373, 1391, 1454, 1515, 1601, 2977, 3111, 3131. Anal. found: C, 51.8; H, 6.9; N, 33.6. Calcd for $C_9H_{14}N_5O$: C, 51.9; H, 6.8; N, 33.6.

4.3.4. 2-(Benzotriazol-1-yl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-1-oxyl (3d). Yield 36 mg (48%), red crystals, mp 113–114 °C. μ_{eff}/β=1.68 (295 K). IR (KBr): [cm^{-1}] 605, 758, 772, 782, 871, 935, 963, 1001, 1049, 1140, 1156, 1219, 1250, 1287, 1371, 1400, 1449, 1490, 1586, 2980, 3121. Anal. found: C, 60.5; H, 6.4; N, 27.4. Calcd for $C_{13}H_{16}N_5O$: C, 60.5; H, 6.2; N, 27.1.

5. Supplementary material

Crystal data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 217336 for **2b**, 217332 for **2c**, 217333 for **2d**, 217334 for **3b**, 217335 for **3c**, 217331 for **3d**, 217337 for **4**. Copies of this information may be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://ccdc.cam.ak.uk).

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Three step vs one pot synthesis and X-ray crystallographic investigation of heptadentate triamide cyclen (1,4,7,10-tetraazacyclododecane) based ligands and some of their lanthanide ion complexes

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Abstract—The synthesis of several lanthanide complexes from the tris alkylated cyclen (1,4,7,10-tetraazacyclododecane) ligands **1** and **2** is described. The syntheses of **1** and **2** were investigated by means of two different synthetic routes (Method 1 and Method 2). The first of these involves the mono protection of cyclen using 4-methoxyphenylsulfonyl chloride, followed by alkylation of the remaining three secondary amines of cyclen, and deprotection using solvated Na(s). Using this approach only **1** was successfully formed. The X-ray crystal structure of the intermediate, **9** and the corresponding La(III) complex, **9.La** is presented. The second method involved the direct synthesis of the two ligands in a single step. The X-ray crystallography of the Eu(III) complex of one of these ligands is presented. Whereas, Method 1 yielded the product **1** in high purity, but in low overall yield, Method 2 gave higher yields for both ligands (~50% for both).

1. Introduction

The design and synthesis of sensors for anions and neutral molecules has been an area of immense study in recent years.[1] The use of metal complexes as sensors in such situations has been discussed in many of these studies.[1,2] Metal complexes can form metal–ligand interactions with anions that are significantly stronger than hydrogen bonding, or other interactions commonly exploited for anion recognition.[3] For instance Fabrizzi et al. have demonstrated the use of Zn(II) complexes as sensors for aromatic carboxylates such as *p*-nitro benzoic acid.[4] Also Pallavicini et al. have employed Cu(II) complexes with tetraaza ligands that can detect coumarin 343.[5] The use of metal complexes for sensing anions has not been confined to transition metals alone. Lanthanides such as Tb(III) and Eu(III) have been shown to displace cations, such as Ca(II), that can be found in the binding sites of proteins; such binding sites contain anionic groups to complex the cation.[6] Excitation of surrounding aromatic residues (such as tyrosine or phenylalanine) in these proteins can result in sensitization of the lanthanide, producing a lanthanide emission.[7] With the ultimate goal of anion detection in vivo the need for stable lanthanide complexes arises. Yu et al. have demonstrated that stable Tb(III) [2.2.2] cryptates can be sensitized in aqueous solutions when coordinated with acac, a β-diketonate chelate.[8] This requires the displacement of the two labile water molecules from the Tb(III) complex. Nocera et al. have shown aromatic carboxylates to act in a similar manner with Tb(III) [2.2.2] cryptates.[9] In work reported by Diamandis, sensitization of Eu(III) and Tb(III) EDTA complexes at pH 11–12 using a number of aromatic carboxylate compounds such as 5-flurosalicylic acid was demonstrated.[10] Reinhoudt et al. also showed similar results using an EDTA-bis(β-cyclodextrin).[11] Parker et al. have reported the synthesis of heptadentate cyclen based lanthanide complexes, which showed great promise as sensors for bicarbonate.[12] Studies carried out in solutions containing MES buffer with pH ranging between 6.4 and 7.3 demonstrated that stable lanthanide complexes could be produced that can detect the presence of anions under near physiological conditions. As discussed, in many of the above cases, coordination to the anionic species displaces the two bound water molecules from the Tb(III) or Eu(III) complexes. However, in this case the coordinating species was not a sensitizer. Instead, its presence as a coordinated species was detected by changes in the emission lifetimes of the lanthanide ion.

We have been interested in the development of lanthanide luminescent devices and we have synthesized several

Keywords: Supramolecular chemistry; Macrocycles; Lanthanide ions; Cyclen.
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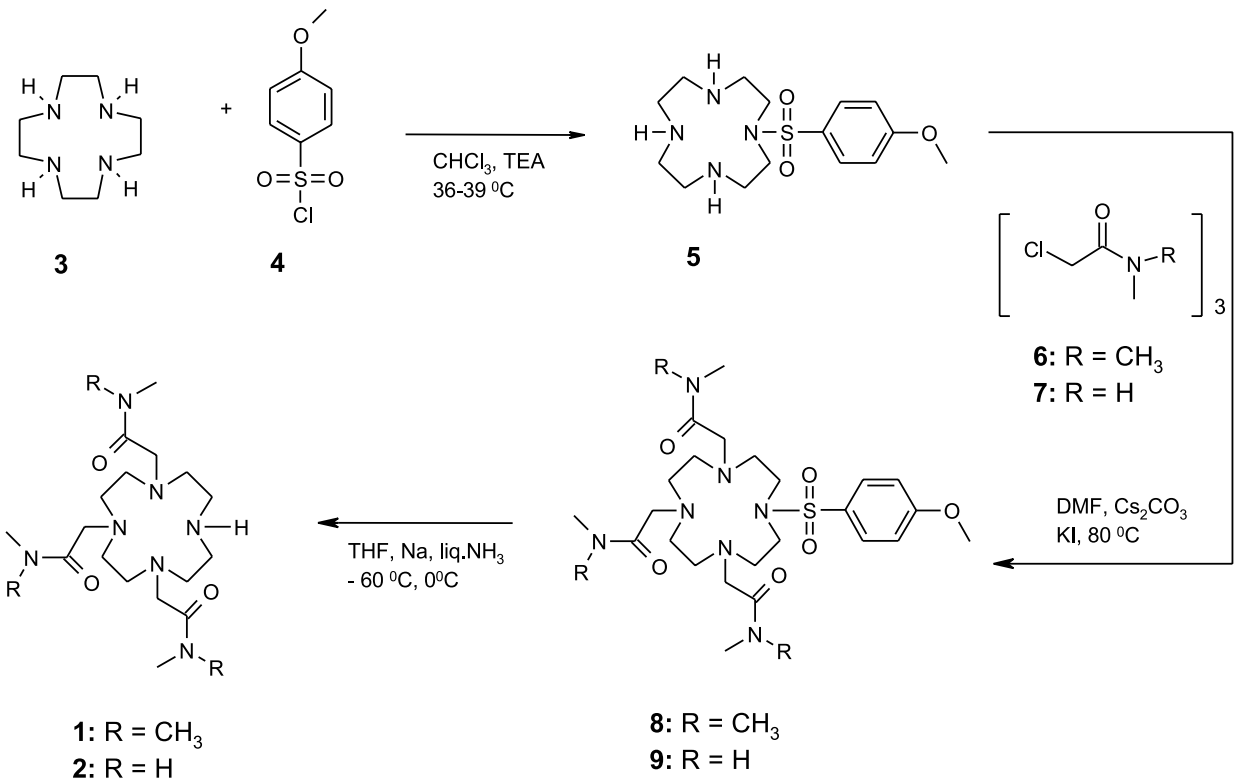
Table 1. Data collection and structural refinement details for **9**, **La.9** and **Eu.2**

Structural formula	$C_{25}H_{42}Cl_3N_7O_6S$ (**9**)	$C_{29}H_{46}F_9N_7O_{16}S_4La$ (**La.9**)	$C_{20}H_{35}F_9N_7O_{16}S_3Eu$ (**Eu.2**)
M	675.07	1186.88	1048.69
Crystal size (mm)	0.18×0.16×0.08	0.34×0.28×0.24	0.36×0.23×0.10
Crystal system	Orthorhombic	Monoclinic	Triclinic
Space group (**Z**)	*Pbca* (**8**)	$P2_1/c$ (**4**)	*P*-1 (**2**)
a (Å)	16.886(2)	13.4113(12)	8.992(4)
b (Å)	9.6598(13)	115527(10)	13.112(5)
c (Å)	38.899(5)	29.089(2)	17.623(7)
α (°)	90	90	79.370(6)
β (°)	90	90.684(2)	82.503(6)
γ (°)	90	90	71.816(6)
U (Å^3)	6345.1(15)	4506.6(7)	1934.3(14)
D_c (g cm^{-3})	1.413	1.749	1.800
F(000)	2848	2396	1048
μ(Mo K$_\alpha$) (mm^{-1})	0.405	1.244	1.899
ω scans; 2θ range (°)	2–45	3–57	2–50
R_{int}	0.1796	0.0359	0.0618
Unique reflections	4150	10295	6732
*wR*2(*R*1)	0.2795(0.0944)	0.0991(0.0364)	0.1688(0.0623)

Eu(III) and Tb(III) complexes as luminescent switches,[13] sensors[14] and logic gate mimics.[15] We have also developed several lanthanide based ribonuclease mimics for the cleavage of mRNA and RNA mimic compounds.[16] These compounds have all been based on tetrasubstitued cyclen complexes, which possess a single metal bound water molecule. The synthesis of such compounds is usually achieved in good yields by reacting 4 equiv. of the pendent arm with cyclen.[17] However, the formation of unsaturated heptadentate ligands is a much more challenging task.[12a,18] The purpose of the work described herein was to synthesis heptadentate ligands **1** and **2** and their Eu(III) and Tb(III) complexes **Eu.1**, **Eu.2**, **Tb.1** and **Tb.2**. Furthermore, these complexes were to be evaluated for their ability to coordinate and sense aromatic carboxylates.[19] All these complexes are expected to be photophysically 'silent' upon excitation as no sensitizing groups have been incorporated into ligands, **1** and **2** and so no indirect excitation of the lanthanides can occur. The work presented herein concerns the synthesis of the two ligands **1** and **2** using two different synthetic methods (Method 1 and Method 2), and the analysis of some of the intermediates and final products using X-ray crystallography (Table 1). We have recently discussed the photophysical properties of these molecules and their ability to detect aromatic carboxylates such as salicylic acid over Aspirin.[19]



Scheme 1. The synthetic route undertaken in Method 1. Whereas, ligand **2** was not obtained by this method, ligand **1** was made in overall 9% yield.

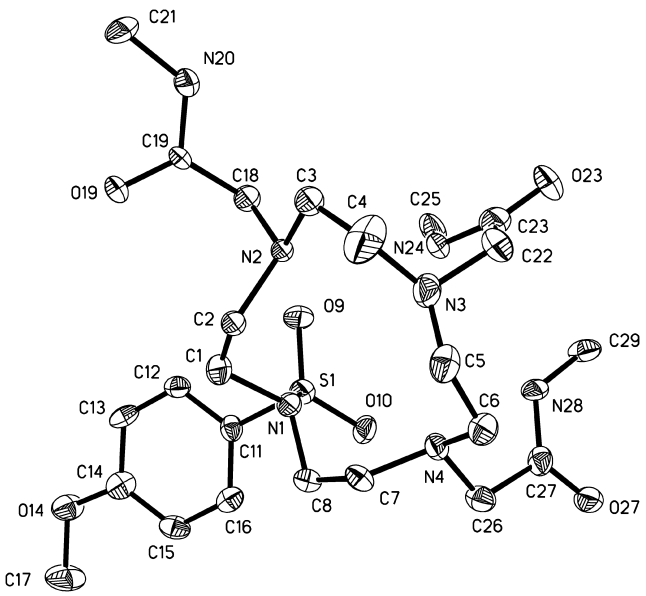


Figure 1. Diagram showing the conformation of ligand **9**. Hydrogen atoms and the disorder are not shown for clarity. Ellipsoids at 30%. A $CHCl_3$ molecule was also found in the unit cell for this structure.

2. Results and discussion

Synthesis of ligands **1** and **2** involved tris *N*-alkylation of cyclen **3**, a macrocycle with four potential alkylation sites. The syntheses of such regioslective *N*-functionalisation of tetraazacycloalkanes is an important area of research.[20] However, often the emphasis has been on developing methods for mono-protection of such macrocyles, which can then be further derivatised, followed by deprotection of the initial protection group.[21] In order to synthesize the proposed ligands herein, two possible synthetic routes were attempted. The first route, Method 1 is shown in Scheme 1, and is based upon the use of a single *N*-protection of cyclen, **3**, in one of its four positions using 1 equiv. of *p*-methoxyphenylsulfonyl chloride, **4**. This technique was first developed by Parker et al.[12a,b] Synthesis of **5** involved dropwise addition of a $CHCl_3$ solution of **4** into a $CHCl_3$ solution of **3** in the presence of triethyl amine at 36–39 °C. The resulting crude product contained a by-product that was determined to be a bis aryl sulfonamide cyclen ligand. Purification by silica gel column chromatography using 90:10 MeCN/MeOH provided **5** in 53% yield. This product was identified from its ^1H NMR spectrum by the presence of two doublets at 7.72 and 7.01 ppm and a singlet at 3.88 ppm resulting from the presence of the aromatic group. Alkylation of **5** using **6** or **7** was carried out in DMF at 80 °C using Cs_2CO_3 as a base and KI to afford **8** or **9**, respectively. The α-chloroamides **6** and **7** were produced from chloroacetyl chloride with the appropriate amine following published procedures.[22] Purification of the tertiary amide **8** was achieved with alumina column chromatography using 97:3 EtOAc/MeOH giving the desired compound as an oil in 50% yield. The secondary amide **9** was purified with alumina column chromatography using CH_2Cl_2/MeOH (1–5%) to give **9** as oil in 41% yield. Both **8** and **9** were characterised by NMR spectroscopy, ESMS, accurate mass and infrared analysis and in the case of **9** by X-ray crystallography. Figure 1 illustrates the crystal structure of **9** and clearly shows the presence of three mono methyl acetamide pendent arms attached to cyclen, along with the *p*-methoxyphenylsulphonamide protection. A summary of selected bond angles and bond lengths is shown in Table 2.

We were also able to form the La(III) complex of **9**, **La.9** by refluxing Lanthanum triflate in EtOH. Upon cooling, hexane was added, ca. 5% and the solution kept cold whereupon crystals were formed. The X-ray crystal structure of this complex is shown in Figure 2, where the ion is coordinated to the four nitrogens of the cyclen ring, the oxygens of the carboxylic amides and to one of the oxygen of the sulfonamide. The average N···La and O···La bond lengths for the coordination of the cyclen ring were 2.855 and 2.494 Å, respectively. Whereas, the distance of the sulfonamide oxygen O···La distance was found to be 2.694 Å. A summary of selected bond angles and bond lengths is shown in Table 2. Furthermore, the lanthanide ion was coordinated to a single triflate (O···La=2.554 Å) and ethanol molecule (O···La=2.577 Å), giving rise to 10 coordinated environments, as expected for La(III) which has

Table 2. Selected bond lengths (Å) and bond angles (°)

(**Tb.1**)		(**9**)		(**Eu.2**)		(**La.9**)		(**Eu.1**)	
Tb1 O15	2.348(3)	C1 C2	1.490(13)	Eu1 O14	2.377(6)	La1 O5	2.458(2)	Eu1 O15	2.342(5)
Tb1 O27	2.326(3)	C3 C4	1.425(13)	Eu1 O22	2.393(6)	La1 O4	2.512(2)	Eu1 O25	2.364(5)
Tb1 O20	2.368(3)	C5 C6	1.520(13)	Eu1 O18	2.399(6)	La1 O3	2.514(2)	Eu1 O19	2.378(5)
Tb1 O1W	2.429(3)	C7 C8	1.494(10)	Eu1 O1W	2.448(6)	La1 O13	2.554(2)	Eu1 O1W	2.418(5)
Tb1 O2W	2.441(3)	N1 C1	1.497(9)	Eu1 O2W	2.485(6)	La1 O1SS	2.577(2)	Eu1 O2W	2.421(5)
Tb1 N1	2.600(4)	N1 C8	1.481(11)	Eu1 N1	2.673(7)	La1 O2	2.694(2)	Eu1 N1	2.605(6)
Tb1 N10	2.656(3)	C19 O19	1.255(10)	Eu1 N10	2.618(7)	La1 N1	2.989(3)	Eu1 N10	2.624(6)
Tb1 N7	2.637(4)	C23 O23	1.247(13)	Eu1 N7	2.670(7)	La1 N10	2.842(3)	Eu1 N7	2.625(6)
Tb1 N4	2.642(4)	C27 O27	1.244(11)	Eu1 N4	2.678(7)	La1 N7	2.808(3)	Eu1 N4	2.647(6)
		C19 N20	1.314(11)			La1 N4	2.784(3)		
		C23 N24	1.334(13)						
O27 Tb1 N10	65.41(11)	C27 N28	1.301(12)	O22 Eu1 N7	65.98(19)	O5 La1 N10	62.57(8)	O25 Eu1 N10	65.39(19)
O20 Tb1 N7	64.53(11)	N1 S1	1.630(8)	O18 Eu1 N4	65.5(2)	O4 La1 N7	61.33(7)	O19 Eu1 N7	64.10(19)
O15 Tb1 N4	65.68(11)	S1 O10	1.440(6)	O14 Eu1 N1	66.1(2)	O3 La1 N4	63.42(7)	O15 Eu1 N4	65.13(19)
01W Tb1 02	71.80	S1 O9	1.431(6)	O1W Eu1 02W	70.9(2)	O2 La1 N1	50.94(7)	O1W Eu1 02W	72.17
N–C–C–O	5.6(7)			N–C–C–O	−30.0(7)	N–C–C–O	−45.0(4)	N–C–C–O	−2.5(11)
N–C–C–O	25.6(6)			N–C–C–O	−32.7(1)	N–C–C–O	−27.8(4)	N–C–C–O	−27.6(10)
N–C–C–O	26.5(6)			N–C–C–O	−36.4(5)	N–C–C–O	31.8(4)	N–C–C–O	−25.4(10)

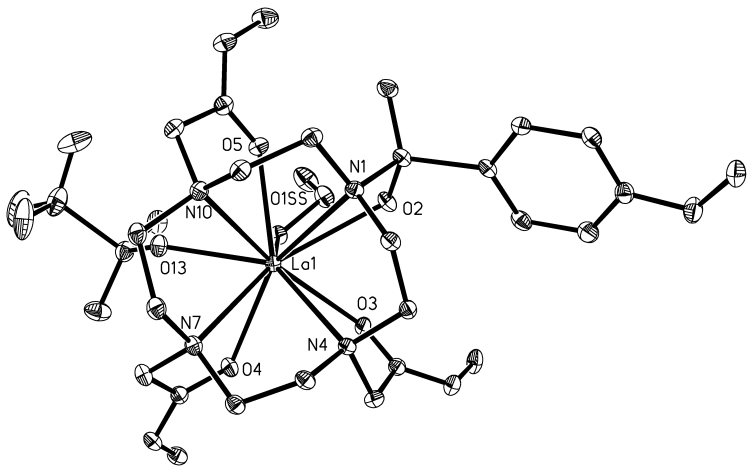
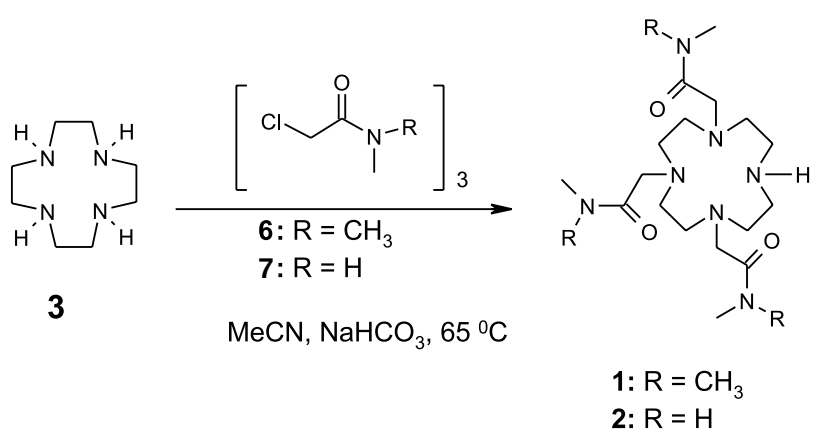


Figure 2. Diagram showing the conformation and binding mode of the La(III) complex **La.9** (**La.9**·$(CF_3SO_3)_3$·EtOH). Hydrogen atoms and lattice anions are not shown for clarity. Ellipsoids at 30%. Three triflate molecules and one ethanol molecuel was also found in the unit cell for this structure.

higher coordination requirements than Eu(III) and Tb(III). Furthermore, the complex adopts a square antiprismatic geometry in solid state, with average N–C–C–N angle of −61.55°. Unfortunately, this complex was found to be unstable and decomposed when dissolved in several solvents, because of this, complete characterizations was not possible. However, it is an important structure since not many La-cyclen structures are known in the literature.[17,23,24]

The final step in the synthesis of **1** and **2** involved deprotection of **8** and **9** using Birch conditions. This was carried out by stirring a THF solution of either **8** or **9** in the presence of Na metal and liquid ammonia at −60 °C.[25] Isolation of these products from the reaction solution involved acid base extraction, which in the case of **2** failed to give the required product, even when continuous extraction techniques were used. However, ligand **1** was isolated in a low yield of 36%, and in 9% overall yield from **3**. The results of this final step in the synthesis of **1** and **2** indicated that this synthetic pathway was not sufficient to synthesize the desired ligands and another method was required. The second route was thus attempted.

The second synthetic route, Method 2, is shown in Scheme 2, and involved direct alkylation of **3** with 3 equiv. of **6** or **7** to yield **1** and **2**, respectively in a single step. A number of variations were attempted using this direct alkylation method, such as high dilution addition of **6** to **3**, by varying the rate addition and concentration of the two reagents, but maintaining the ratio of the reagents (the ratio of **3** to either **6** or **7** was kept as 1:3 or 1:3.1). On many occasions a number of by products were observed and electro spray mass spectral analysis of the reaction mixture showed the presence of mono, bis, tris and tetra-alkylated cyclen. However, these were difficult to isolate successfully and in high purity by column chromatography. Furthermore, the temperature at which these additions were carried out at was also modulated, from 20⟶80 °C, and the use of other solvents such as DMF, were also investigated. However, a successful method was developed, which we present herein. This involved stirring of **3** in a solution of MeCN at 65 °C. To this solution 3 equiv. of **6** or **7** was added in a single addition and the resulting solution was stirred at 65 °C for 72 h. In the case of **1**, the product was isolated as a viscous oil in a 52% yield following purification on an alumina column using 97:3 CH_2Cl_2/MeOH(NH_3), while **2** was isolated in a 59% yield as a white solid following precipitation from ether. Of the two synthetic methods attempted the direct alkylation of **3** was determined to be the most efficient synthetic route for the synthesis of **1** and **2**, with yields over 50% from a one step synthesis compared to total yields of 9% for **1** and 0% for **2** using the initial three step synthesis (Method 1).



Scheme 2. The one-pot syntheses of **1** and **2**.

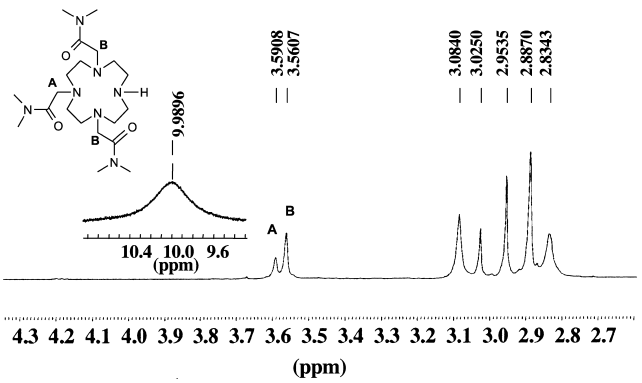
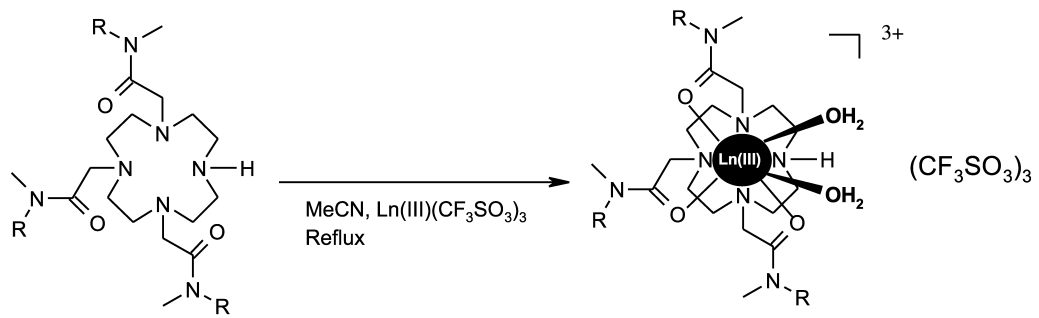


Figure 3. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **1**, showing the C_2-symmetry. (Inset: NH peak at 9.98 ppm.)

Ligands **1** and **2** were characterized using standard techniques. However, both were hygroscopic and elemental analysis of these ligands was not possible. Nevertheless, (ESMS) accurate mass spectroscopy was obtained for both. The ^{1}H NMR spectra of both ligands clearly reflect a C_2 symmetry. This C_2 symmetry runs along an axis through the unalkylated amine in position 1 and the tertiary amine in position 7 of the cyclen ring. The ^{1}H NMR spectrum of **1** shown in Figure 3, revealed the presence of one N–H singlet at 9.98 ppm. The two α-protons for the pendant arms appeared as singlets at 3.59 and 3.56 ppm (in a ratio of 2:4), respectively. From C–H cosy experiments the five singlets observed between 3.08 and 2.83 ppm were representative of both the cyclen CH_2 and methyl acetamide CH_3 protons. The ^{1}H NMR spectrum for **2** showed similar characteristics.[19] The ^{13}C NMR spectra for both **1** and **2** contained 10 signals. For **1** this consisted of two quaternary resonances at 170.3 and 170.2 ppm corresponding to the carboxylic amide carbonyls of the pendant arms. Two CH_2 resonance signals at 55.5 and 53.8 ppm were assigned to the pendant arms. Another four CH_2 signals observed from 51.7 to 46.7 ppm correspond to the cyclen ring. The two final signals were found at 36.4 and 35.3 ppm and correspond to the acetamide methyl groups. A similar ^{13}C NMR spectrum was obtained for **2**.[19] We are currently modifying these two ligands by functionalising the remaining amino moiety with various α-amides such as dipeptides and peptide conjugates, as well as incorporating various chomrophores as antennae and sensors for the population of the Tb(III) and Eu(III) excited states. This work will be the subject of future publications.

The synthesis of the lanthanide complexes **Eu.1**, **Tb.1**, **Eu.2** and **Tb.2** involved refluxing **1** and **2** with Eu(III) and Tb(III) as their triflate salts in freshly dried MeCN (Scheme 3). Upon cooling to room temperature the solutions were poured into stirring solutions of dry ether, and in all cases an oily residue was produced. These oils were collected by decanting the organic layers and the resulting residues were rinsed with either CH_2Cl_2 or $CHCl_3$. The resultant complexes were all isolated as powders in yields of ca. 95% after exhaustive drying under vacuum over P_2O_5 for approximately two weeks. These complexes were characterised by elemental analysis, ESMS, accurate mass, IR and NMR spectroscopy. Similar results were observed for all of these complexes. The ^{1}H NMR spectrum showed the presence of the paramagnetic metal centers, as indicated by several broad resonances appearing over a large ppm range as in the case **Eu.2** where these appeared at 27.04, 14.96, 11.44, 5.20, 3.68, 2.76, 2.41, 1.55, −0.09, −1.84, −4.93, −7.35, −10.77, −12.31, −16.66, respectively. Similar results were observed for the other three complexes. These results indicated that all adapted square antiprismatic geometry in solution.[16,17,24] ESMS and accurate mass analysis proved very useful in characterization of these complexes. All four complexes gave similar spectra, which consisted of M+H peaks for the complex with one and two triflate counter anions present. In some instances M+H peak for the complex along with a large number of $M+H_n+Triflate_x/Z_n$ (x=0–3, n=1–3) peaks were found in the ESMS. The peaks generated compared well with the theoretical isotope model, as shown in Figure 4, for **Eu.1**. It should be noted that the presence of the bound water molecules was not seen during analysis by mass spectroscopy. From IR spectroscopy the single carbonyl stretching frequency occurring at 1643 cm^{-1} in **2** was shifted when complexed to Eu(III) or Tb(III) to 1639 cm^{-1}, an indication that the pendent arms were indeed bound to the metal center.[22] Crystals of **Eu.1** **Eu.2** and **Tb.2** were obtained that were suitable for X-ray crystallographic determination. We have shown the structure of the **Eu.1** and **Tb.2** in our previous publications (selective bond angles and bond lengths are shown for comparison in Table 2).[18,19]



1: R = CH_3 **2:** R = H

Eu.1: R = CH_3, Ln(III) = Eu(III)
Tb.1: R = CH_3, Ln(III) = Tb(III)
Eu.2: R = H, Ln(III) = Eu(III)
Tb.2: R = H, Ln(III) = Tb(III)

Scheme 3. The formation of the Eu(III) and Tb(III) complexes of **1** and **2**.

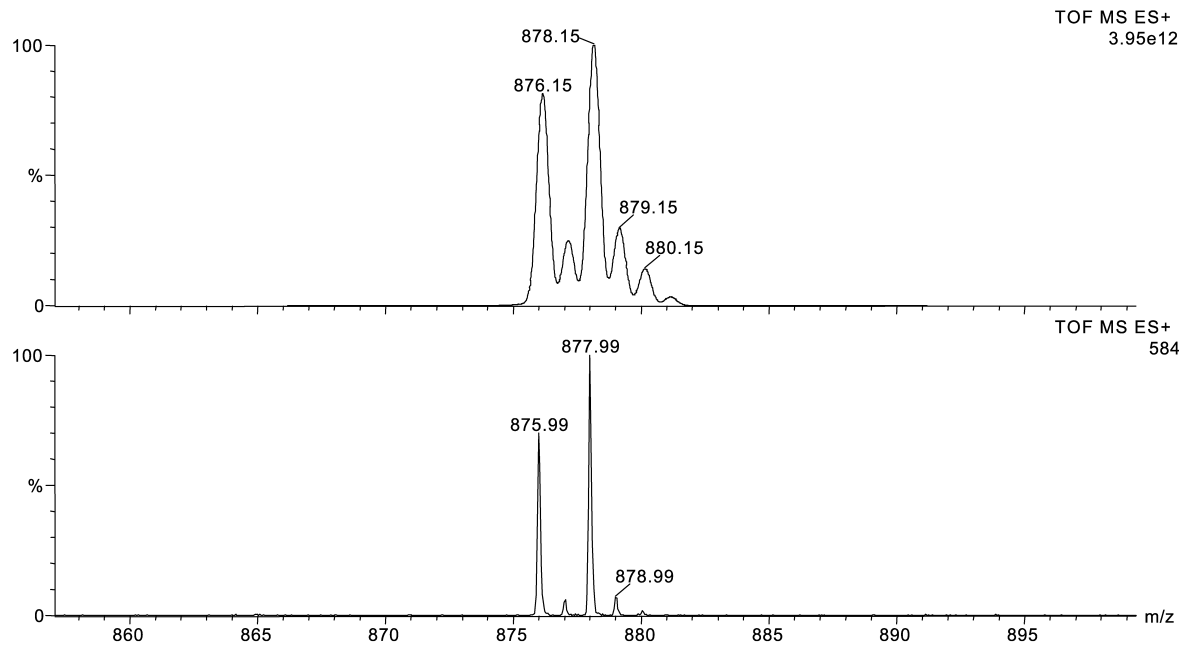


Figure 4. The electro spray mass spectrum of **Eu.1** (bottom) and the calculated isotopic pattern (top).

Crystals of **Eu.2** were obtained by slow evaporation from solutions of MeCN. The structure of **Eu.2** is shown in Figure 5.

All of the structures adopted a square antiprism geometry in the solid state, a common geometry for tetraamide and carboxylate-substituted lanthanide complexes of cyclen, where the metal center was coordinated to the four nitrogens of the macrocycle ring and the three oxygens of the carboxylic amide pendent arms. The Ln(III)–N and Ln(III)–O bond lengths were of similar length in all three complexes with average distances of ca. 2.64 Å and ca. 2.37 Å, respectively. Furthermore, all the crystal structures showed the presence of the two metal bound water molecules. For **Eu.1** and **Tb.1** these bond lengths were similar with an average value of ca. 2.43 Å. This bond length was longer in **Eu.2** with an average of ca. 2.47 Å. The angle that these two water molecules bind to the metal center was also of importance, since the nature of the binding mode with carboxylate anions would depend on the bite angle between the two water molecules. For **Eu.1** the O1W-Eu-O2W bite angle was measured to be 72.17° whereas, for **Tb.1** the O1W-Tb-O2W bite angle was measured to be 71.80° and for **Eu.2** the O1W-Eu-O2W bite angle was measured to be 70.86°. Recently, Dickins et al.[12b,c] reported that related three-arm cyclen complexes can form bidentate adducts with organic anions such as acetate, citrate, glycinate, and lactate through four and five member chelates. The bite angles for all of these complexes

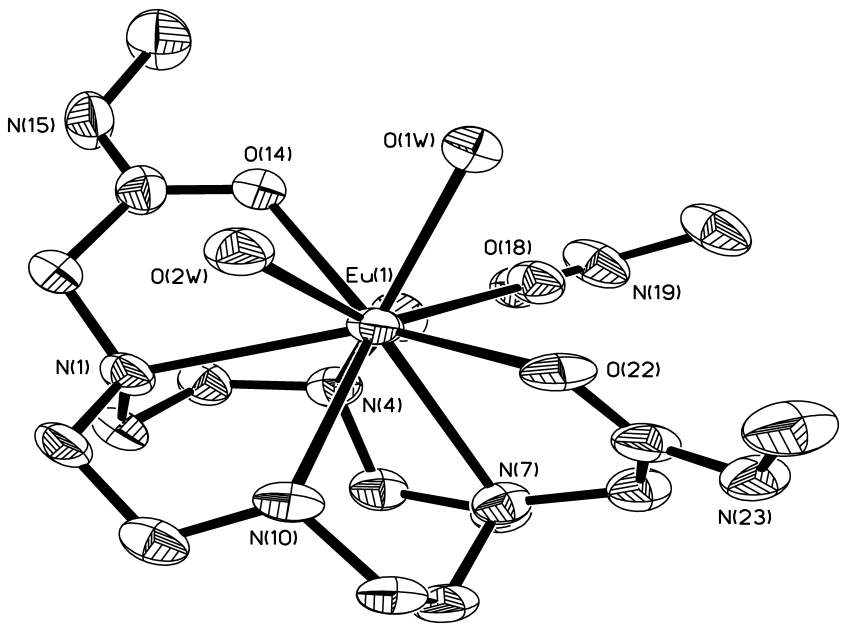


Figure 5. The X-ray crystal structure of **Eu.2** (**Eu2** $(CF_3SO_3)\cdot(H_2O)_2$), showing the seven coordination of the ligand and the two metal bounded water molecules. Hydrogen bonds and lattice anions have been omitted for clarity. Three triflate anions were also found in the unit cell.

were between 54 and 69°. In the case of acetate, this binding was bidentate and occurred through both of the carboxylate oxygens. From these reports and the bite angles calculated for **Eu.1**, **Tb.1** and **Eu.2** it was proposed that aromatic carboxylates would bind in a similar bidentate manner to all the complexes, expelling the two water molecules. This was indeed found to be the case as we have recently reported where the Tb(III) emission of both **Tb.1** and **Tb.2** was 'switched on' (due to the population of the $^5D_4$ excited state of the lanthanide ion through an energy transfer mechanism, involving the excitation of the singlet state of the salicylic acid, followed by intersystem crossing to the triplet state) in the presence of salicylic acid, whereas, no sensitization of the excited state of the lanthanide ion was observed for Aspirin.[19] Furthermore, no binding was found to occur for the Eu(III) complexes, which was caused by much weaker binding to these ions than to the Tb(III) centers.

3. Conclusion

In summary we have synthesized two amide based ligands **1** and **2** using two different synthetic methods. Whereas, the former of these involved three steps, only giving one of the desired products, the second method was quite successful, giving the desired ligands in ca. 50% overall yield in a single step. Even though this method requires elaborate chromatographic purification for one of these products (**1**) the second product was easily obtained by precipitation methods. We were able to obtained both crystals of the ligand **9** the La(III) complex of **9**, one of the intermediates from Method 1. It clearly showed the ability of the ligand to coordinate to the La(III) ion, despite the presence of the sulfonamide. We were also able to grow crystals of three of the four complexes made from **1** and **2**. To the best of our knowledge these were the first examples of such X-ray crystal structures of such heptadentate tri-arm amide based cyclen complexes. The structure of **Eu.2** was reported herein, showing the metal ion coordinating to all the seven coordination sites of the ligand, as well as to two water molecules. As we have demonstrated in our former publication,[18,19] these water molecules could be removed by aromatic carboxylates, in the case of **Tb.1** and **Tb.2**. Of the two synthetic methods investigated herein, Method 2 is superior to Method 1. We are currently improving the use of this method and employing it to develop several peptide based heptadentate tri-arm ligands for the use as molecular sensors and as catalysts for the hydrolysis of mRNA.

4. Experimental

4.1. General

Starting materials were obtained from Sigma Aldrich, Strem Chemicals and Fluka. Columns were run using Silica gel 60 (230–400 mesh ASTM) or Aluminum Oxide (activated, Neutral, Brockmann I STD grade 150 mesh). Solvents were used at GPR grade unless otherwise stated. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Oils were analysed using NaCl plates, solid samples were dispersed in KBr and recorded as clear pressed discs. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. ^{19}F NMR were recorded at 376 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectroscopy was carried out using HPLC grade solvents. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using a Shimadzu HPLC or Water's 9360 to pump solvent. The whole system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation.

4.1.1. 1-(4-Methoxy-phenylsulphonyl)-1,4,7,10-tetraazacyclododecane (5). To a 500 mL three neck RBF, (**3**) 1,4,7,10-tetraazacyclododecane (1.00 g, 5.8 mmol) was added along with $CHCl_3$ (50 mL). To this was added TEA (4.11 g, 40 mmol) which was heated at 36–39 °C. 4-Methoxy phenyl sulphonyl chloride (1.20 g, 5.8 mmol) in $CHCl_3$ (100 mL) was added dropwise over a 5-hour period. The solution was then left stirring overnight. The solution temperature was maintained at 36–39 °C. This solution was reduced to approximately 50 mL upon which a white solid was produced that was removed by filtration and the resulting organic solution was reduced to dryness under vacuum to produce a white solid, 1.6 g (80.0%). This was then purified by silica column chromatography using 90:10, MeCN/MeOH (53% recovery), to yield 0.56 g (28% yield) of **5** as a white solid. Mp=137–140 °C. Calculated for $C_{15}H_{27}N_4O_3S$: [M+H peak] m/z=343.1804. Found: 343.1806; δ_H ($CDCl_3$, 400 MHz) 7.72 (d, J=9.0 Hz, 2H, Ar-H), 7.01 (d, J=8.6 Hz, 2H, Ar-H), 3.88 (s, 3H), 3.40 (d, J=4.5 Hz, 4H, CH_2), 3.18 (d, J=5.0 Hz, 4H, CH_2), 3.00 (d, J=4.0 Hz, 4H, CH_2), 2.87 (d, J=5.0 Hz, 4H, CH_2); δ_C ($CDCl_3$, 100 MHz) 162.9, 128.8, 114.1, 55.2, 49.3, 48.5, 48.2, 45.5; Mass Spec (MeCN, ES+) m/z expected: 342.2. Found: 343.2 (M+H); 365.1 (M+Na); IR ν_{max} (cm^{-1}) 3432, 3095, 3008, 2842, 1712, 1594, 1492, 1438, 1363, 1261, 1222, 1155, 1091, 1052, 1024, 927, 890, 842, 804, 761, 701, 561, 530, 466.

4.2. General synthesis of 1 and 2

Compound **5**, 0.68 g (2.0 mmol) was placed in a 100 mL three neck RBF. To this was added **7**, (0.64 g, 6.0 mmol) [or **6**, 3.1 equiv. in the case of **8**], Cs_2CO_3 (1.95 g, 6.0 mmol) and KI (1.0 g, 5.3 mmol). To this was added dry DMF (12 mL). The reaction was freeze pump thawed twice. The flask was then filled with argon and the reaction was stirred at 80 °C overnight. The resulting solution was then filtered through a celite plug filter and reduced by rotatory evaporation. The resulting residue was dissolved in $CHCl_3$ and washed with water (2×50 mL), and brine (2×50 mL). The organic layer was isolated, dried over K_2CO_3 and reduced under vacuum, to produce a viscous oil. This was then purified by alumina column chromatography using CH_2Cl_2/MeOH (1–5%).

4.2.1. 2-[4,7-Bis-dimethylcarbamoylmethyl-10-(4-methoxy-phenylsulfonyl)-1,4,7,10-tetraaza-cyclododec-1-yl]-*N*,*N*-dimethyl-acetamide (8). 600 mg was purified by

alumina column chromatography using 97:3, EtOAc/MeOH, to yield 320 mg of **8** as a pale yellow viscous oil. Calculated for $C_{27}H_{48}N_7O_6S$: [M+H peak] m/z=598.3387. Found: 598.3389; δ_H ($CDCl_3$, 400 MHz) 7.62 (d, J=9.0 Hz, 2H, Ar-H), 6.94 (d, J=9.0 Hz, 2H, Ar-H), 3.79 (s, 6H), 3.56 (m, 6H), 3.26 (m, 8H), 3.08–2.90 (m, 12H), 2.87–2.81 (m, 10H); δ_C ($CDCl_3$,100 MHz) 173.6, 169.3, 163.1, 129.4, 114.2, 55.3, 55.2, 54.5, 53.8, 53.6, 53.2, 51.1, 36.3, 36.1, 34.9; Mass Spec (MeOH, ES+) m/z expected: 597.78. Found: 598.4 (M+H), 620.6 (M+Na); IR ν_{max} (cm^{-1}) 3438, 2962, 2923, 2854, 1735, 1646, 1508, 1457, 1398, 1340, 1261, 1155, 1091, 1022, 867, 804, 701, 559, 474.

4.2.2. 2-[4-(4-Methoxy-phenylsulfonyl)-7,10-bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl]-*N*-methyl-acetamide (9). 455 mg of **9** was produced as a viscous oil. Calculated for $C_{24}H_{42}N_7O_6S$: [M+H peak] m/z=556.2917. Found: 556.2906; δ_H ($CDCl_3$, 400 MHz); 7.91 (bs, 1H N–H), 7.72 (d, J=8.5 Hz, 2H), 7.63 (bs, 2H, N–H), 7.02 (d, J=9.0 Hz, 2H), 3.88 (s, 3H, OCH_3), 3.47 (s, 4H, CH_2), 3.42 (s, 2H, CH_2) 3.18 (bs, 8H, CH_2), 2.96 (s, 6H), 2.82 (m, 8H, CH_2), 2.08 (s, 3H); δ_C($CDCl_3$, 100 MHz) 171.5, 171.2, 129.4, 114.4, 58.51, 58.10, 55.58, 53.74, 53.33, 53.04, 49.46, 36.35, 31.31, 25.9, 25.8; Mass Spec (MeOH, ES+) m/z expected: 555.3. Found: 556.6, (M+H), 578.6 (M+Na); IR ν_{max} (cm^{-1}) 3421, 3077, 2925, 2854, 1654, 1596, 1542, 1457, 1409, 1338, 1261, 1155, 1093, 1022, 841, 840, 728, 698, 559.

The experimental results for **1** from Method 1 was identical to that obtained for Method 2, which has previously been reported.[19]

4.2.3. 2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethyl-acetamide (1). The ligand **8**, 0.39 g (0.70 mmol) was placed in a 100 mL 3 necked RBF. To this was added dry THF (30 mL) and ethanol (0.3 mL). This was attached to a cold finger condenser and the apparatus was placed into a dry ice/IPA bath where the temperature was dropped to −60 °C. Dry ice and IPA was also added to the condenser. Liquid NH_3 was added to the reaction vessel through the cold finger condenser (approximately 40 mL). Sodium metal (1.2 g, 0.05 mol) was added to this solution. The reaction was left stirring at −60 °C for 4 h during which time the yellow solution turned dark blue. The solution was allowed to warm up to room temperature and left stirring overnight. To this solution THF (20 mL) was added to dissolve the excess (unused) sodium present. Concentrated HCl was added until the solution was at pH 1 and then extracted with DCM. The pH of the solution was then adjusted to pH 14 using KOH pellets and then extracted with chloroform and reduced to yield the desired product. 100 mg (36% yield) of **1** was isolated as a clear residue. Calculated for $C_{20}H_{42}N_7O_3$:[M+H peak] m/z=428.3344. Found: 428.3349; δ_H($CDCl_3$, 400 MHz) 9.98 (broad s, 1H, N–H), 3.59 (s, 2H, CH_2–acetamide), 3.56 (s, 4H, CH_2–acetamide), 3.08 (s, 8H), 3.03 (s, 3H), 2.95 (s, 6H), 2.88 (s, 10H), 2.83 (s, 7H); δ_C($CDCl_3$, 100 MHz) 170.3, 170.2, 55.5, 53.8, 51.7, 50.6, 49.7, 46.7, 36.4, 35.3; Mass Spec (MeOH, ES+) m/z expected: 427.59. Found: 428.33 (M+H), 450.30 (M+Na), 472.30 (M+K); IR ν_{max}(cm^{-1}) 3434, 2927, 2852, 1637, 1508, 1475, 1402, 1338, 1261, 1103, 1064, 1022, 881, 806, 769, 667, 649, 574, 484.

4.2.4. 2-(4,10-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methyl-acetamide Eu(III) (Eu.2). 94.7 mg, (0.22 mmol) of **2** and 0.26 mmol of Eu(III) triflouromethane sulphonate [$Eu(SO_3CF_3)_3$] was added to a 25 mL single necked RBF which contained 10 mL of freshly dried acetonitrile. The solution was freeze thawed three times, placed under an argon atmosphere and left stirring at 82 °C for 24 h. The resulting solution was cooled to room temperature and then dropped slowly onto 100 mL of dry diethyl ether. The diethyl ether was poured off to leave **Eu.2** as oil that was washed with CH_2Cl_2 and dried under high vacuum. Yield >95%. Calculated for $C_{20}H_{35}N_7O_{12}F_9S_3Eu\cdot(H_2O)_2(CH_2Cl_2)_2$: C, 22.19; H, 3.64; N, 8.24. Found: C, 22.29; H, 3.74; N, 8.38. Calculated for $C_{17}H_{36}N_7O_3Eu$:[M+H peak] m/z=539.2092. Found: 539.2087. Calculated for $C_{18}H_{36}N_7O_6F_3SEu$:[M+H(Trif)] m/z=688.1612. Found: 688.1548. Calculated for $C_{19}H_{36}N_7O_9F_6S_2Eu$:[M+H(Trif)$_2$] m/z=837.1133. Found: 837.1181; δ_H(MeOD, 400 MHz) 27.04, 14.96, 11.44, 5.20, 3.68, 2.76, 2.41, 1.55, −0.09, −1.84, −4.93, −7.35, −10.77, −12.31, −16.66; δ_F(MeOD, 376 MHz) −80.45. Mass Spec (MeCN, ES+) m/z expected: 538.2. Found: 539.2 (M+H), 668.1 (M+H(Trif)), 837.1 (M+H(Trif)$_2$); IR ν_{max}(cm^{-1}) 3455, 3386, 3297, 3143, 3000, 2933, 2885, 1639, 1587, 1465, 1419, 1288, 1245, 1160, 1091, 1027, 725, 638, 576, 516.

4.3. X-ray crystallography

Data were collected on a Bruker SMART diffractometer with graphite monochromated Mo K_α radiation. A crystal was mounted on to the diffractometer at low temperature under dinitrogen at ca. 120 K. Cell parameters were obtained from 300 to 500 accurately centered reflections. ω/ϕ Scans were employed for data collection and Lorentz and polarisation corrections were applied.

The structure was solved using direct methods[26] and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were located from difference Fourier maps and fully refined. The function minimised was $\sum[w(|F_o|^2-|F_c|^2)]$ with reflection weights $w^{-1}=[\sigma^2|F_o|^2+(g_1P)^2+(g_2P)]$ where $P=[\max|F_o|^2+2|F_c|^2]/3$. Additional material available from the Cambridge Crystallographic Data Centre comprises relevant tables of atomic coordinates, bond lengths and angles, and thermal parameters Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDCC: copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Photochemistry of some steroidal bicyclo[3.1.0]hexenones

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Abstract—The photochemistry of five 11-hydroxy-1,5-cyclopregn-3-en-2-ones ('lumi' products from the corresponding pregna-1,4-dien-3-ones) has been investigated. In all cases the photoproducts were 1,11-oxy derivatives, resulting from intramolecular attack of the hydroxyl group to the incipient positive charge at C-1. When a fluorine atom was present at C-6, HF elimination took place concurrently with the nucleophilic addition and led to linearly conjugated dienones, rather than the enones obtained in the other cases. Quantum yields were in the range 0.06–0.2, the lower values applying when a fluorine atom was present in position 6 (not in position 9). The results add new evidence on the role of zwitterionic intermediates in the photochemistry of cross-conjugated dienones and the corresponding lumi photoproducts.

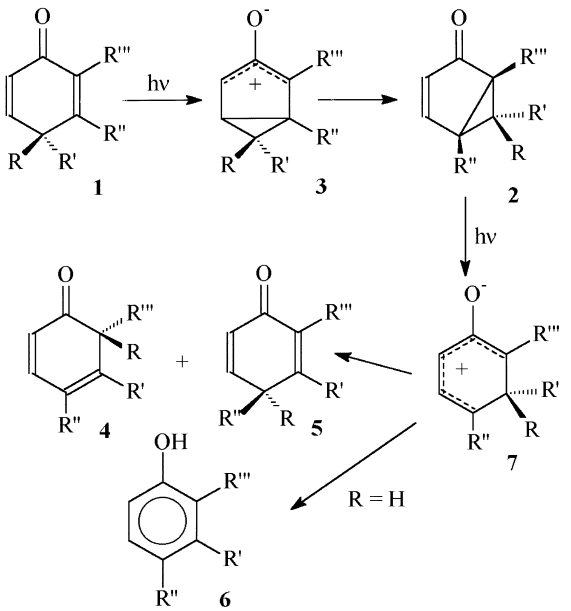
1. Introduction

The complex photochemical reactions of cross-conjugated cyclohexadienones (e.g., **1**, Scheme 1) have fascinated chemists over the past decades and many excellent reviews have been published on this topic.[1] Indeed, the light induced reactions occurring on natural sesquiterpene α-santonin have been among the first photochemical processes investigated[2] and the nature of the primary process occurring in neutral organic solvents has been recognized as rearrangement to bicyclo[3.1.0]hexenones (**2**, the so-called 'lumiproducts') in the 1950s.[3] The process has been envisaged as occurring via a zwitterionic intermediate (**3**)[4] and there is substantial evidence for such a path.[1]

The efficient photoreactions of lumiderivatives themselves complicate these studies. These compounds, in which a cyclopropane ring has replaced one of the double bonds of cross-conjugated dienones, share the high photoreactivity of their precursors. Sequential rearrangements involving a second, third and even fourth photoreactions are not uncommon, particularly with ring-fused cyclohexadienones, and have to be distinguished from thermal (usually acid-catalyzed) reactions. This further photochemistry leading, for example, to products **4**-**6** has been proposed[1a,b,e,g] to involve again a zwitterionic intermediate (**7**), the substitution pattern and the size of the fused ring affecting the course of the photoreaction.

Much work on cross-conjugated ketones has been carried on steroid derivatives,[5] including the exploration of secondary photoreactions. In this case, the rigid polycyclic skeleton further affects the course of the rearrangement and adds complexity. As an example, irradiation of lumidehydrotestosterone 21-acetate has been found to yield two cross-conjugated dienones, one of which with a spirocyclopentane moiety, along with further secondary and tertiary photoproducts, including four new bicyclohexenones, six phenols and three linearly conjugated cyclohexadienones. These arose through 17 different photochemical steps.[6]

Furthermore, intramolecular nucleophilic attack is also possible, as shown for the case of lumiprednisolone



Scheme 1.

Keywords: Photochemistry; Steroids; Ketones; Rearrangements.
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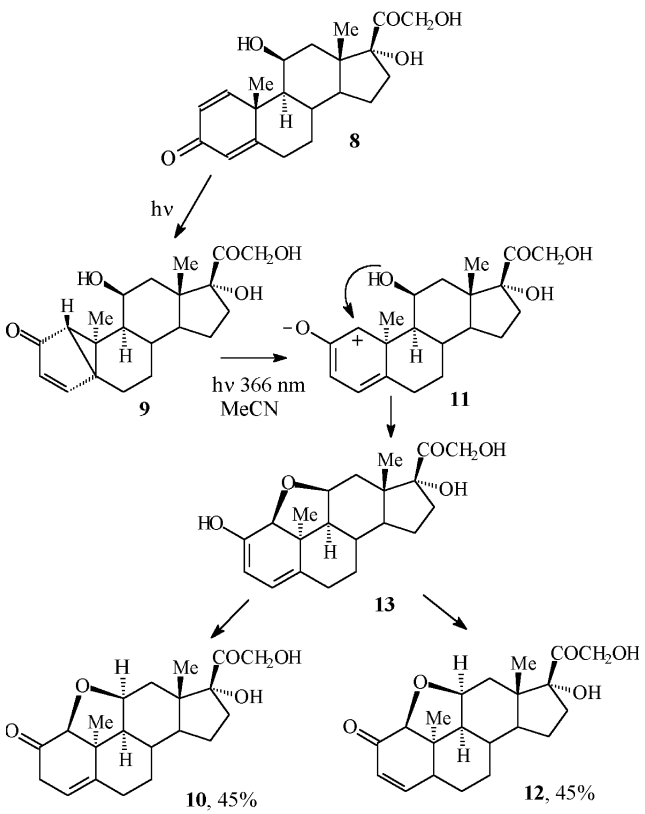
21-acetate **9** (formed in the primary photoreaction from **8**, Scheme 2). The 11β-hydroxyl group traps the (incipient) cation at C-1 (**11**) and yields the 1,11-oxy derivative **10**, while no such reaction occurs with the corresponding epimer, the 11α-hydroxy group apparently being too far away from the cationic site.[7]



Scheme 2.

We recently investigated[8] the photochemistry of a series of halogenated pregnadienones used as anti-inflammatory drugs and found that 'lumi' derivatives were the primary photoproducts, though, particularly at 366 nm, these further reacted at a rate comparable with that of the starting material. Such secondary photochemistry was not initially pursued, but further work that we report here evidenced that a novel photoreaction occurred with some of these derivatives, which supported the zwitterionic nature of the intermediate. In the following, product characterization and quantum yield for such derivatives are discussed.

2. Results and discussion

As mentioned above, the photochemistry of lumiprednisolone (**9**, 11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-ene-2,20-dione) had been previously shown to give **10** in dioxane and ethanol,[7a] although the quantum yield of the reaction had not been measured. In our hands, irradiation of **9** in argon-purged acetonitrile at 366 nm gave both product **10** and a further steroidal enone, each in 45% yield. The spectroscopic characteristics showed that the latter was isomeric with compound **10** and differed in containing a conjugated ketone moiety (structure **12**, Scheme 2).

Separate experiments, carried at low conversion in order to avoid secondary photoreactions, allowed measurement of a quantum yield of 0.2, under these conditions (Table 1). Product **12**, just as product **10**, arose from intramolecular OH addition, differing only for a different tautomerization from dienol **13**. The quantum yield was comparable to that for the rearrangement of the original pregnadienone **8** to the lumi derivative **9**. Furthermore, the latter absorbed more strongly at 366 nm, while the contrary was true at 254 nm. This explained why both with compound **8** and with related dienones[6,7] the best conditions for preparing the lumi derivative involved irradiation at 254 nm, while the use of a longer wavelength led to a mixture and, for a long irradiation time, led directly to the secondary photoproducts.

Table 1. Photoreaction quantum yield and products formed from the irradiation of lumi pregnadienone derivatives at 366 nm

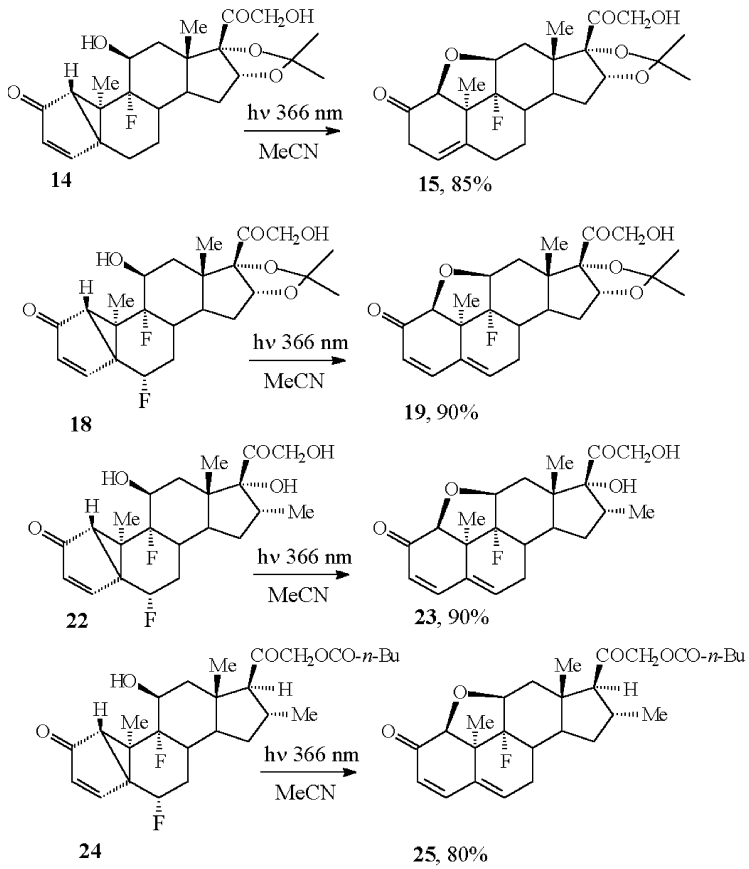
Reagent	Φ	Products (% yield)[a]	Φ (dienone)
9	0.2	**10** (45), **12** (45)	0.3[b]
14	0.2	**15** (85)	0.06[b]
18	0.06	**19** (90)	0.03
21	0.06	**22** (90)	0.03
23	0.06	**25** (80)	0.03[a]

[a] Isolated yield by chromatography calculated on the converted starting material (at ≥80% conversion).
[b] See Ref. 8b.

We next turned to the lumi derivatives of fluorinated pregnadienone drugs. Compound **14**, resulting from the irradiation of triamcinolone 16,17-acetonide, differed from **9** by bearing a fluorine atom in 9 and an acetonide group in 16, 17. This did not change the photochemical pattern and irradiation at 366 nm gave again a 1,11-oxy steroid (**15**, Scheme 3), as indicated by the analytical and spectroscopic properties. Examination of the irradiation mixture suggested that a small amount of an isomeric ketone, with conjugated structure corresponding to **12**, was also present, but the small amount did not allow complete characterization (see Section 3).

The quantum yield was the same as for **9** (0.2). This result can be contrasted with the strong difference in the quantum yield for the rearrangement of the respective pregnadienones (structure of the reactive moiety **16**, Scheme 4). In that case photochemical step a was less efficient in the fluoro derivative (**16**, X=F, Φ 0.06 rather than 0.3 for X=H), a phenomenon that was attributed to the electronegativity of the fluorine atom, which disfavored the positive charge developing during the reaction.[8b] In a structure such as **17**, however, the fluorine atom was too far away from the light-absorbing and reacting enone moiety and the same quantum yield was measured for photochemical step b for both X=H and F.

Lumifluocinolone 16,17-acetonide **18**, which differed from **14** by having a second fluorine atom again in ring B, was found to undergo a new reaction. A single photoproduct was formed, that was again a 1,11-oxy derivative but had lost the 6-fluorine atom and possessed a linearly conjugated dienone

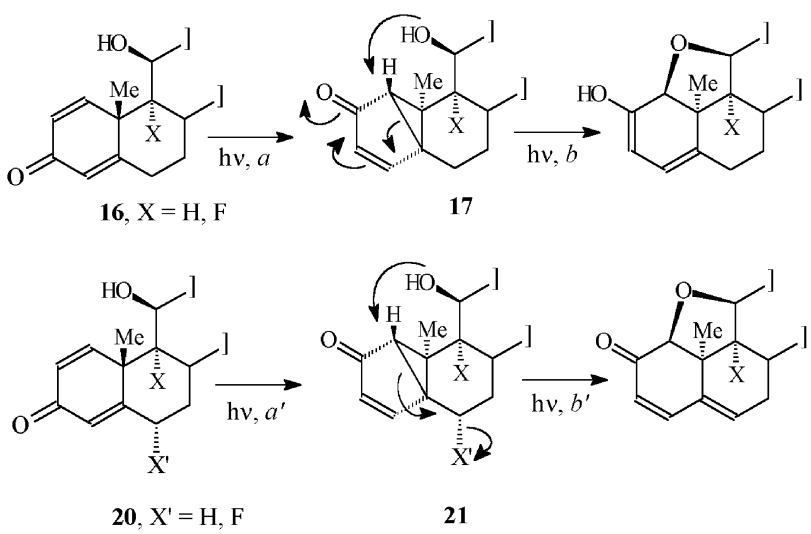


Scheme 3.

structure. Further analytical and spectroscopic evidence supported structure **19** for this compound and in particular NOESY experiments ascertained the stereochemistry. The reaction path was again consistent with an intramolecular attack onto the positive charge developing at C-1, but the presence of a suitably placed nucleofugal group diverted the reaction towards addition–elimination rather than mere addition (step b′ from **21**, Scheme 4).

In this case, the quantum yield was lower, 0.06, reasonably because the second fluorine atom (X′=F in formulae **20**, **21**) was much closer to the photoreacting enone moiety and both photochemical steps, a′ and b′, were affected. The corresponding dienone was in fact found to have a low quantum yield, Φ=0.003 (Table 1).

We then examined two further 6α,9-difluoro derivatives, differing for the substituents on ring D, viz. lumiflumetasone **22** (6α,9-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-ene-2,20-dione) and lumidiflucortolone **24**.



Scheme 4.

In both cases, 1,11-oxy monofluorinated dienones (formulae **23** and **25**) were formed in a high chemical yield. The quantum yield of both rearrangements had the same values as in **18** (0.06), in accord with the fact that the photoreacting moiety (compare formula **21**) remained the same in these derivatives, and the same held true for the rearrangement of the dienones (Table 1).

In conclusion, a clean photorearrangement was found on a series of 11-hydroxy-1,5-cyclopregn-3-en-2-ones. Chemical yields were good and NMR of the raw photolysate did not reveal side-products in substantial amounts. Thus, intramolecular nucleophilic attack by the 11β OH group always overcame other rearrangements from the excited bicyclohexenone (involving C–C bond migration, compare Scheme 1) that are normally observed in the absence of this group. This well fits the postulated development of a positive charge at C-1 upon excitation. Furthermore, a novel photochemical reaction of bicyclo[3.1.0]hexenone was found where nucleophilic attack at position 1 was coupled with elimination of a suitable nucleofugal group, a fluorine in 6, again consistent with the zwitterionic mechanism.

It was also found that a fluorine atom when adjacent to the enone moiety reduced the quantum yield of the bicyclohexenones, just as previously found when adjacent to a cross-conjugated dienone,[8b] while it had no effect when α to the three-membered ring in a cyclopropyl methyl ketone. As it appears from Table 1, the photoreaction of the lumiketones was either about as efficient as or, in most cases, more efficient than the primary photorearrangement of the cyclohexadienones. This made it difficult to avoid the second photochemical step particularly when irradiating above 310 nm, as in this wavelength region this is favored by the higher molar absorptivity of the lumi products. The photoreactivity in the UV–A region has also some bearing on the photostability and possible phototoxicity[9] of these steroids, that are used as topical drugs.

3. Experimental

3.1. Preparative photochemical reactions

Lumiproducts **9**, **14**, **18**, **21**, **23** were obtained by irradiation of the corresponding glucocorticosteroids as already reported.[8] Spectroscopic grade solvents were used for the irradiations.

Preparative irradiations were performed in an immersion well apparatus fitted with a Pyrex filtered 125 W medium pressure mercury arc lamp. Before irradiation argon was flushed under stirring for 30 min and a low gas flux was maintained during reactions. The course of the photoreactions was followed by HPLC (Hypersil ODS2. 4.6×25 mm, 5 μm column, eluting with acetonitrile–water mixtures) and TLC (eluting with cyclohexane–EtOAc mixtures). When the desired conversion was reached, the solvent was rotary evaporated and the products were purified by silica gel (0.040–0.063 mm) column chromatography.

The characterization of the new compounds was based on analytical and spectroscopic techniques, mainly IR and NMR (300 MHz). In every case, examination of the raw photolysate showed no evidence for other products in a significant amount (>5%), except when noted.

3.2. Irradiation of 11β,17α,21-trihydroxy-1,5-cyclopregna-3-en-2,20-dione (lumiprednisolone, 9)

A solution of compound **9** (60 mg, 0.1 mmol) in acetonitrile (100 mL) was irradiated for 20 min, and a 90% conversion was reached. Flash chromatography (cyclohexane–EtOAc (6/4)) gave a single product fraction (49 mg, 90% yield on the converted starting material) as a colorless glassy solid; IR (neat): ν_{max} 3430, 1710, 1660, 1104, 1043, 1011 cm^{-1}; the NMR analysis showed that two compounds were present. ^1H and ^{13}C NMR spectra and heterocorrelation analysis allowed the unambiguous assignment of the structure to the two isomers (ratio ca. 1/1), the first of which corresponded to the one isolated by Williams (only ^1H NMR reported in that case).[7a]

3.2.1. 21-Hydroxy-1β,11β-oxypregna-4-en-2,20-dione (10). ^1H NMR [$(CD_3)_2CO$]: δ, 0.77 (s, 3H), 1.38 (s, 3H), 1.2–2.75 (m, 12H), 2.50 (dd, J=16, 7.5 Hz, 1H), 3.19 (ddd, J=16, 4, 2 Hz, 1H), 4.08 (s, 1H), 4.23 (m, 1H), 4.42 (s, 1H, OH), 4.45 (broad s, 1H, OH), 4.23 and 4.62 (AB q, J=19 Hz, 2H), 5.46 (dt, J=7.5, 2 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$]: δ, 17.5 (CH_3), 23.2 (CH_2), 25.5 (CH_3), 26.8 (CH_2), 27.6 (CH_2), 32.0 (CH), 33.15 (CH_2), 34.9 (CH_2), 38.8 (CH_2), 48.9, 49.6 (CH), 54.1, 55.2 (CH), 67.7 (CH_2), 78.3 (CH), 87.2 (CH), 89.9, 117.3 (CH), 146.4, 204.6 (CO), 212.9 (CO).

3.2.2. 21-Hydroxy-1β,11β-oxypregna-3-en-2,20-dione (12). ^1H NMR [$(CD_3)_2CO$]: δ, 0.68 (s, 3H), 1.32 (s, 3H), 1.2–2.4 (m, 13H), 2.71 (m, 1H), 3.71 (s, 1H), 4.21 (m, 1H), 4.4 (m, 1H, OH), 4.4 (broad s, 1H, OH), 4.22 and 4.61 (ABq, J=19 Hz, 2H), 6.25 (dd, J=10 Hz, 1H), 6.74 (d, J=10 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$]: δ, 18.0 (CH_3), 23.4 (CH_2), 24.8 (CH_3), 27.1 (CH_2), 29.9 (CH), 32.5 (CH), 32.9 (CH_2), 34.9 (CH_2), 40.4 (CH_2), 49.4, 50.5 (CH), 53.9, 57.4 (CH), 67.7 (CH_2), 78.3 (CH), 87.0 (CH), 89.6, 132.4 (CH), 149.6 (CH), 195.1 (CO), 212.9 (CO).

3.3. Irradiation of 9α-fluoro-11β,21-dihydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1,5-cyclopregna-4-en-2,20-dione (lumitriamcinolone acetonide, 14)

A solution of compound **14** (200 mg, 0.46 mmol) in acetonitrile (120 mL) was irradiated for 2 h, and a 95% conversion was reached. A single main product was formed (162 mg, 85%, see below) and was isolated by flash chromatogrphy (cyclohexane–EtOAc (6/4)). However, examination of the crude photolysate evidenced signals at δ 6.33 (d, J=10 Hz) and 6.77 (d, J=10 Hz) which hinted to the presence of the corresponding pregna-3-en-2,20-dione. The small amount did not allow isolation and characterization.

3.3.1. 9α-Fluoro-21-hydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1α,11α-oxy-1,5-cyclopregna-4-en-2,20-dione (15). Colorless crystals, mp 157–159 °C; $[\alpha]_D^{17}$ −11.5 ($CHCl_3$); analysis, found: C, 66.70; H, 6.95;

$C_{24}H_{31}FO_6$ requires C, 66.34; H, 7.19; IR (KBr): ν_{max} 3490, 1725, 1710, 1105, 1045, 1003 cm^{-1}; ^1H NMR ($CDCl_3$): δ, 0.72 (s, 3H), 1.14 (s, 3H), 1.36 (d, J_{HF}=5 Hz, 3H), 1.47 (s, 3H), 1.3–2,5 (m, 10H), 2.75 (dd, J=16, 7 Hz), 3.09 (ddd, J=16, 4, 1.5 Hz, 1H), 4.17 (d, J=20 Hz, 1H), 4.20 (broad d, J=2 Hz, 1H), 4.21 (broad s, 1H), 4.25 (m, 1H), 4.68 (d, J=20 Hz, H-21), 5.01 (d, J=5 Hz, 1H), 5.45 (dt, J=7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ, 16.2 (CH_3), 20.0 (d, J_{CF}=13 Hz, CH_3), 21.0 (d, J_{CF}=5 Hz, CH_2), 24.6 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 30.6 (CH_2), 32.2 (CH_2), 33.1 (d, J_{CF}=21 Hz, CH), 37.5 (CH_2), 41.08 (CH), 45.9, 52.4 (d, J_{CF}=20 Hz), 66.8 (CH_2), 76.9 (d, J=30 Hz, CH), 81.8 (CH), 85.3 (d, J_{CF}=5 Hz, CH), 96.6, 98.5 (d, J=175 Hz), 111.1, 116.5 (CH), 143.3, 203.5 (CO), 210.4 (CO).

3.4. Irradiation of 6α,9α-difluoro-11β,21-dihydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1,5-cyclopregna-3-en-2,20-dione (lumifluocinolone 16,17-acetonide, 18)

A solution of compound **18** (200 mg, 0.44 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 85% conversion was reached. Flash chromatographic separation (cyclohexane–EtOAc (6/4)) afforded 145 mg (90%) of a single product.

3.4.1. 9α-Fluoro-21-hydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1β,11β-oxy-pregna-3,5-dien-2,20-dione (19). Ligh yellow crystals, mp 142–144 °C; $[\alpha]_D^{17}$ −61.6 ($CHCl_3$); analysis: found: C, 66.70; H, 6.70; $C_{24}H_{29}FO_6$ requires C, 66.65; H, 6.76; IR (KBr): ν_{max} 3520, 2845, 1705, 1650 cm^{-1}; ^1H NMR [$(CD_3)_2SO$]: δ 0.54 (s, 3H), 1.1 (s, 3H), 1.23 (d, J_{H-F}=5 Hz, 3H), 1.24 (s, 3H), 1.40 (s, 3H), 1.2–2.5 (m, 9H), 4.02 (s, 1H), 4.11 (dd, J=19, 2 Hz, 2H), 4.50 (dd, J=19, 6 Hz, 1H), 4.17 (m, 1H), 4.9 (broad d, 1H, OH), 5.08 (broad t, J=6 Hz, 1H, OH), 5.91 (d, J=10 Hz, 1H), 6.44 (dd, J=19, 6 Hz, 1H), 7.41 (d, J=10 Hz, 1H); ^{13}C NMR [$(CD_3)_2SO$]: δ 16.7 (CH_3), 22.8 (d, J_{C-F}=5 Hz, CH_2), 23.9 (d, J_{C-F}=18 Hz, CH_3), 25.4 (CH_3), 26.6 (CH_3), 30.7 (CH_2), 32.2 (CH_2), 38.5 (CH), 39.4 (d, J_{C-F}=23 Hz, CH), 46.2 (d, J_{C-F}=20 Hz, CH), 46.7, 66.2 (CH_2), 77.4 (d, J_{C-F}=35 Hz, CH), 81.6 (CH), 84.9 (d, J_{C-F}=5 Hz, CH), 96.9, 98.7 (J_{C-F}=175 Hz), 110.7, 124.7 (CH), 134.5 (CH), 139.2, 148.2 (CH), 192.6 (CO), 210.6 (CO). NOESY experiments confirmed the stereochemical assignment by showing correlation between H-1 at δ 4.02 and Me-18 at 0.72, H-3 at 5.91 and H-11 at 4.17.

3.5. Irradiation of 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-en-2,20-dione (lumiflumetasone base, 22)

A solution of compound **22** (200 mg, 0.49 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 85% conversion was reached. Flash chromatography of the residue (cyclohexane–EtOAc (6/4)) afforded 146 nm (90%) of a single photoproduct.

3.5.1. 6α-Fluoro-17α,21-dihydroxy-16α-methyl-1β,11β-pregna-3,5-dien-2,20-dione (23). Colorless crystals, mp 172–174 °C; $[\alpha]_D^{17}$ +29.4 ($CHCl_3$); analysis found: C, 67.70, H, 6.94; $C_{22}H_{27}FO_5$ requires C, 67.68, H, 6.97; IR (KBr): ν_{max} 3520, 1705, 1658, 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.96 (d, J=7 Hz, 3H), 1.32 (d, J=5 Hz, 3H), 1.25–3.1 (m, 8H), 3.31 (t, J=5 Hz, 1H, OH), 3.93 (s, 1H), 4.15, (m, 1H), 4.25 (dd, J=19, 5 Hz, 1H), 4.65 (dd, J=19, 5 Hz, 1H), 5.95 (d, J=10 Hz, 1H), 6.35 (dd, J=10, 1 Hz, 1H), 7.21 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 17.0 (CH_3), 22.8 (d, J_{C-F}=5 Hz, CH_2), 24.1 (d, J_{C-F}=18 Hz, CH_3), 29.5 (CH_2), 30.8 (CH_2), 36.2 (CH), 40.3 (d, J_{C-F}=21 Hz, CH), 40.4 (CH), 46.4 (d, J_{C-F}=20 Hz), 50.1, 67.4 (CH_2), 78.2 (d, J_{C-F}=30 Hz, CH), 85.5 (d, J_{C-F}=5 Hz, CH), 89.8, 98.3 (d, J_{C-F}=175 Hz), 124.7 (CH), 134.2 (CH), 139.1, 147.8 (CH), 192.8 (CO), 211.8 (CO).

3.6. Irradiation of 6α,9α-difluoro-11β,21-dihydroxy-16α-methyl-1,5-cyclopregna-3-en-2,20-dione 21-pentanoate (lumidiflucortolone 21-valerate, 24)

A solution of compound **24** (200 mg, 0.42 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 80% conversion was reached. Flash chromatographic separation (cyclohexane–EtOAc (7/3)) afforded 120 mg (80%) of a single photoproduct.

3.6.1. 9α-Fluoro-21-hydroxy-16α-methyl-1β,11β-oxy-pregna-3,5-dien-2,20-dione 21-pentanoate (25). Colorless crystals, mp 190 °C; $[\alpha]_D^{17}$ +20 ($CHCl_3$); analysis found: C, 70.67; H, 7.61; $C_{27}H_{35}FO_5$ requires C, 70.72; H, 7.69; IR (KBr): ν_{max} 1720, 1700, 1655, 1195, 1055 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (d, J=7 Hz, 3H), 0.93 (d, J=7 Hz, 3H), 0.98 (t, J=7 Hz, 3H), 1.44 (s, 3H), 3.13 (s, 1H), 4.25 (m, 1H), 5.92 (d, J=10 Hz, 1H), 6.31 (dd, J=10, 1 Hz, 1H), 7.23 (d, J=10 Hz, 1H) 1.0–2.5 all the other protons; ^{13}C NMR: δ 14.6 (CH_3), 15.3 (CH_3), 22.4 (d, J=5 Hz, CH_2), 23.6 (d, J_{C-F}=18 Hz, CH_3), 26.4 (CH_3), 26.8 (CH_2), 30.9 (CH), 31.0 (CH_2), 31.4 (CH_2), 33.2 (CH_2), 36.8(CH), 40.1 (d, J_{CF}=20 Hz, CH), 41.6 (CH_2), 44.3, 45.9 (d, J=20 Hz), 46.0 (CH), 68.2 (CH_2), 77.7 (d, J_{C-F}=20 Hz, CH), 85.1 (d, J_{C-F}=5 Hz, CH), 98.5 (d, J_{CF}=175 Hz), 124.2 (CH), 133.9 (CH), 138.6, 147.4 (CH), 172.4 (COO), 192.4 (CO), 202.7 (CO).

3.7. Quantum yield measurements

Quantum yields measurements were carried out on 3 mL samples of solutions (2.5×10^{-3} M) in spectrophotometric sealed cuvettes. The light source was a focalized 150 W high-pressure mercury arc lamp fitted with a 366 nm interference filter. The fraction of light absorbed was assessed by means of a photon counter. The extent of the reaction was determined by HPLC. The light flow was measured by ferrioxalate actinometry.

Acknowledgements

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A new strategy for synthesis of polymeric supports with triazene linkers

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Abstract—A new strategy based on the use of diethylamine triazenes for stabilization and generation of polymer supported diazonium ions was described. New economical syntheses of four new polymeric supports with 3- and 6-carbon atom spacers and triazene linkers derived from *meta*- and *para*-aminophenol were described and compared to the traditional methods. The possible application of the polymer bound triazene masked diazonium salts as supports for immobilization of secondary amines (nortropine and 4-piperidinole and their esterification and oxidation), and as amine scavengers was shown. The new supports with *meta*-C_3-T2 and *para*-C_3-T2 linkers showed higher loadings and typically gave products with good yields and purities.

1. Introduction

Triazenes are a group of organic compound with a long history.[1] Some of the triazenes showed biological activity and found use in cancer therapy.[2] In recent years triazenes have gained importance as useful tools in organic synthesis[3] such as protecting groups,[4] alkylating agents,[5] ligands for organometallic catalysts,[6] linkers in solid-phase organic synthesis (SPOS).[7] The triazene based linkers are one of the recent and fast growing additions to methodology of supported synthesis, which is one of the workhorses in drug development process based on combinatorial chemistry.[8] The so-called T2 linker originally introduced for anchoring secondary amines[7a] has been used for synthesis of a number of different classes of compounds (amides, thioureas, ureas, hydrazines, alcohols, esters, guanidines, sulfoximines and alkyl halides).[7d] The amine substrates used in solid-phase synthesis were anchored to a support through the T2 type linker by the reaction with a polymer bound diazonium salt (typically tetrafluoroborate) prepared from a polymer bound aromatic amine. In the described preparations of polymer supported diazonium salts and corresponding triazenes *m*-aminophenol[7b] or *p*-nitrophenol[5] served as the precursors of the anchored aromatic amines on Merrifield polymer. In a recent report triazenes were also prepared on polymer from an aromatic amine synthesized directly on polymeric support.[9] In our preliminary communication we have reported on synthesis of spacer-modified triazene linkers and their application in solid-phase reactions of nortropinone with LDA and Grignard reagent.[10]

Herein, we report in detail the strategy for the generation of supported diazonium ions directly from polymer bound triazenes, and a new improved, more economical and less laborious syntheses of four supports with triazene linkers (triazene masked diazonium ions) modified with 3- and 6-carbon atom spacers. The supports could be used for immobilization and derivatization of two important to medicinal chemistry scaffolds: 8-azabicyclo[3.2.1]octan-3-ol (3-nortropine)[11] and 4-hydroxypiperidine (4-piperidinol).[12]

2. Results and discussion

2.1. Preparation of polymers

The typical preparation of triazenes on polymeric support involved anchoring of an aromatic hydroxy amine (specifically *m*-aminophenol) to the Merrifield polymer followed by diazotisation to form the diazonium salt and attachment of amines.[7a] Along this scheme, we prepared *m*-aminophenol-derived precursors of the spacer-modified triazenes **1** by alkylation of *m*-aminophenol with 3-chloropropan-1-ol or 6-chlorohexan-1-ol (Scheme 1). The most suitable solvent for the alkylation of the aminophenol was found to be DMF. The results obtained with three different bases; sodium hydride, solid KOH, and potassium carbonate, did not differ significantly. The major technical problem with this procedure was purification of the products, i.e. removal of DMF and by-products (products of *N*-alkylation and *N*,*O*-bisalkylation) best achieved by distillation. The subsequent

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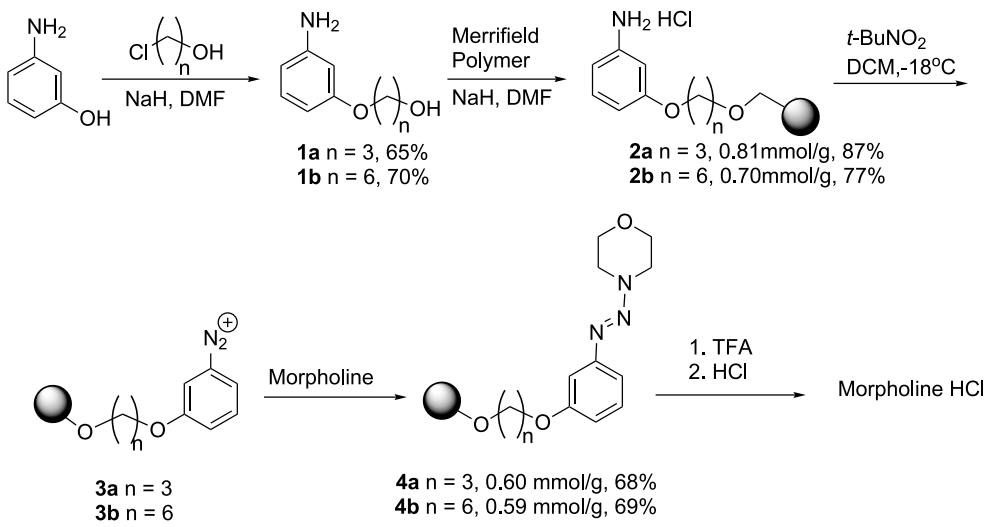
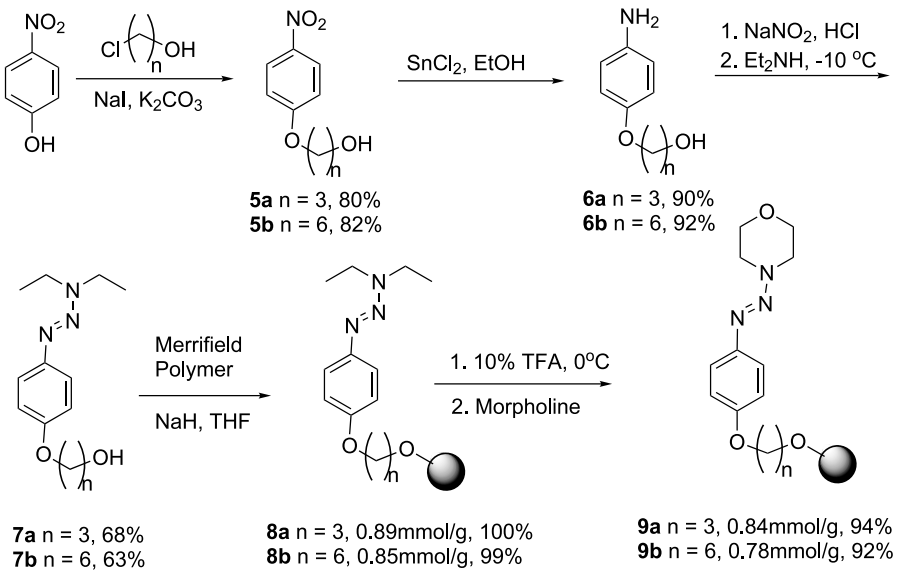


Scheme 1.

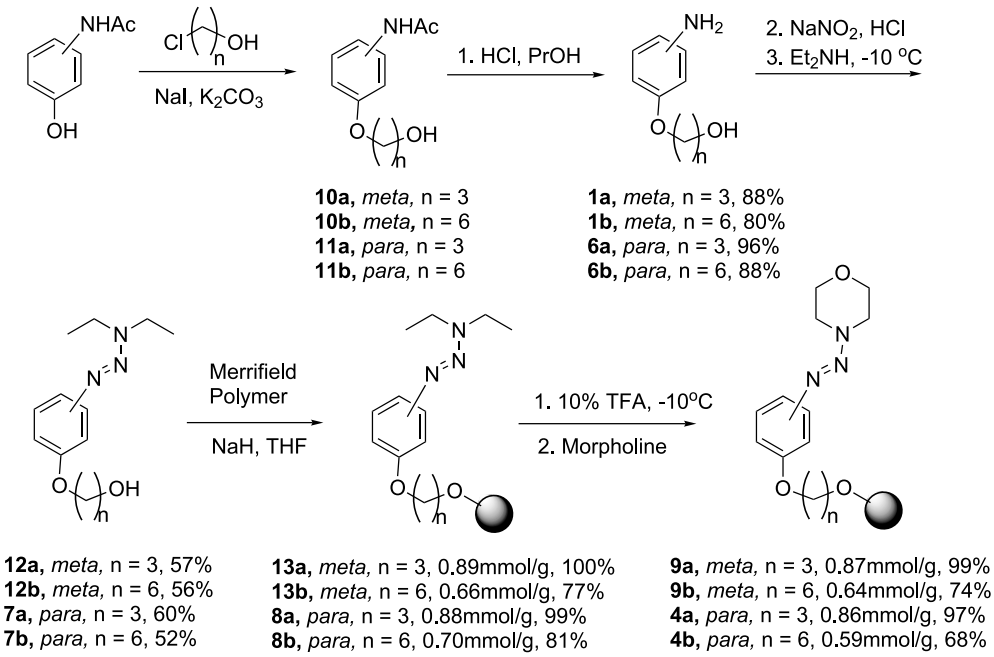
anchoring of the resulting amino alcohols **1** to Merrifield polymer by the Williamson etherification reaction followed by nitrosation of the polymer bound aromatic amines **2** (isolated in the form of hydrochlorides) with *t*-BuONO at −18 °C in dichloromethane provided the polymer bound diazonium salts, which were used for immobilization of amines. Typical test amines were 4-methylpiperidine and morpholine. Morpholine served as an especially useful cheap model of nortropanes because, in our experience, the results obtained for the 'bind and release' process of this amine were very close to those for nortopine and nortropinone. The described traditional approach (Scheme 1) suffered from hard to control chemoselectivity of anchoring of amino alcohols through alkylation with chloromethylpolystyrene as shown by simple model experiments with benzyl chloride in solution. Attempts to optimise the reaction temperature did not improve the loadings and the reaction remained capricious. As a result, the loadings of amines on so prepared supports were usually lower then the loading calculated from the percentage of nitrogen shown by elemental analysis of the triazene loaded polymers. Therefore, a more representative procedure based on direct gravimetric analysis of the obtained amine hydrochloride was used for comparing results.

The sensitivity of ethers of *p*-aminophenol to light and oxygen made the preparation of the *para* analogues more difficult and inefficient. Alkylation of *p*-aminophenol under analogous conditions to those described in Scheme 1 resulted in very low yields of *O*-alkylated products. Therefore, for the preparation of spacer-modified *p*-aminophenol-derived supports we chose to use a different strategy based on use of nitrophenol as synthetic equivalent of aminophenol and protection of amine in the form of triazene. We expected that the polymer bound triazene can serve as a latent diazonium ion. Acidolytic cleavage of the triazenes would regenerate protonated secondary amine and the diazonium ion, which under favourable conditions could be isolated and used for capturing of another amine. Such favourable conditions would be provided by low temperature and solid-phase immobilization. Thus, *p*-nitrophenol was alkylated with iodides (prepared in situ by the Finkelstein reaction) to give the nitro alcohols **5** (Scheme 2). This simple reaction suffered, however, from relatively low nucleophilicity of the nitrophenolate ion and required control of reaction progress (NMR or GC) and rather long reaction times in order to provide satisfactory yields of products. The fairly trivial reduction of nitro group of **5** was achieved with different reductants under variety of conditions ($SnCl_2$/DMF, $SnCl_2$/methanol, $SnCl_2$/ethanol, sodium dithionite/ethanol, $NaBH_4$/Pd/C/methanol) from which the optimal were tin(II) chloride in boiling ethanol. This method gave the best purities and almost quantitative yields in shortest time. In addition, the sensitive amine products **6** were protected by the acidic environment of the reaction medium eliminating the need for protective gas atmosphere. The major drawback of this method was the cumbersome extractive workup of the reaction mixture requiring large excess of potassium hydroxide for dissolving the tin hydroxides precipitate. The amines prepared by reduction of nitro alcohols **5** were promptly protected in the form of triazenes **7** (Scheme 2). Overall yields of the preparation of the key intermediates were 49% for **7a** and 47% for **7b**. These hydroxy triazenes were very effectively attached to a Merrifield polymer under typical conditions i.e. sodium hydride in THF, 60–65 °C. The new approach was proven more successful as indicated by the high loading of diethylamine (Table 1) on polymers **8**, good %N values in elemental analyses and practically quantitative substitution of chlorine by the triazenes (below the detection limit of elemental analysis).[13]

In order to apply the new strategy to the preparation of four polymeric gels (*meta* and *para* C_3 and C_6) on a larger scale we decided to develop an economical, amenable to scaling up and general synthesis of the key triazenes **7** and **12** (Scheme 3). To circumvent the mostly technical problems of preparations (long reaction times, removal of DMF, by-products, tin residues) and to minimize the purification procedures, especially the chromatography, we set up the synthetic plan shown in Scheme 3. The alkylation of the *meta* and *para* hydroxy acetanilides was reasonably fast and efficient. The crude products **10** and **11** were pure enough to be subjected to acidic hydrolysis in boiling ethanol or propanol. Propanol provided for higher reaction temperature and shorter hydrolysis time. The resulting hydroxy



Scheme 2.



Scheme 3.

Table 1. Comparison of loadings of the polymeric supports prepared with two strategies

Support (prepared from)	Theoretical loading of amine (mmol/g)	Experimental loading of amine (mmol/g) (% of theoretical value)	Experimental loading of morpholine (mmol/g)[a] (% of theoretical value)
meta-C_0 (aminophenol)	0.98	0.82 (84)[b]	0.63 (64)
para-C_0 (aminophenol)	0.98	0.79 (81)[b]	0.87 (69)
meta-C_3 (hydroxyamine) **2a**	0.93	0.81 (87)[b]	0.60 (68)
meta-C_6 (hydroxyamine) **2b**	0.89	0.70 (77)[b]	0.59 (69)
para-C_3 (nitrophenol) **8a**	0.89	0.89 (100)[c]	0.84 (94)
para-C_6 (nitrophenol) **8b**	0.86	0.85 (99)[c]	0.78 (92)
meta-C_3 (hydroxyacetanilide) **13a**	0.89	0.89 (100)[c]	0.87 (99)
meta-C_6 (hydroxyacetanilide) **13b**	0.86	0.66 (77)[c]	0.64 (74)
para-C_3 (hydroxyacetanilide) **8a**	0.89	0.88 (100)[c]	0.86 (97)
para-C_6 (hydroxyacetanilide) **8b**	0.86	0.70 (81)[c]	0.59 (68)

[a] Based on mass of morpholine HCl obtained from a weighed sample of polymer after 'bind and release' process.
[b] Loading determined from mass of triethylamine HCl obtained after washing of the gel with triethylamine.
[c] Loading determined from mass of diethylamine HCl obtained after acid cleavage.

anilines were diazotised (sodium nitrite, HCl) and gave corresponding diethylamine triazenes **7** and **12** in fairly good yields (52–60% after chromatographic purification). On larger scale the triazenes could be purified by filtration through pad of silica. The attachment of the hydroxy triazenes to Merrifield gel was accomplished via routine procedure. The overall yields of preparation of the key hydroxy triazenes **12a**, **12b**, **7a** and **7b** via the new method were 50, 45, 58, 46%, respectively. The yields were similar or slightly better then the overall yields of the method based on nitrophenol. However, the new procedure was shorter in time and less laborious. The loadings of polymers with the classical T2 linkers[7] and the new supports prepared through the on polymer diazotisation of amines (Scheme 1) and through the new strategy (Schemes 2 and 3) are shown in Table 1. The comparison suggests that the substitution of reactive sides of chloromethylpolystyrene with amine (diethylamine or morpholine) on polymers prepared by the new method was higher, especially on both of the supports with linkers with 3-carbon atom spacer.

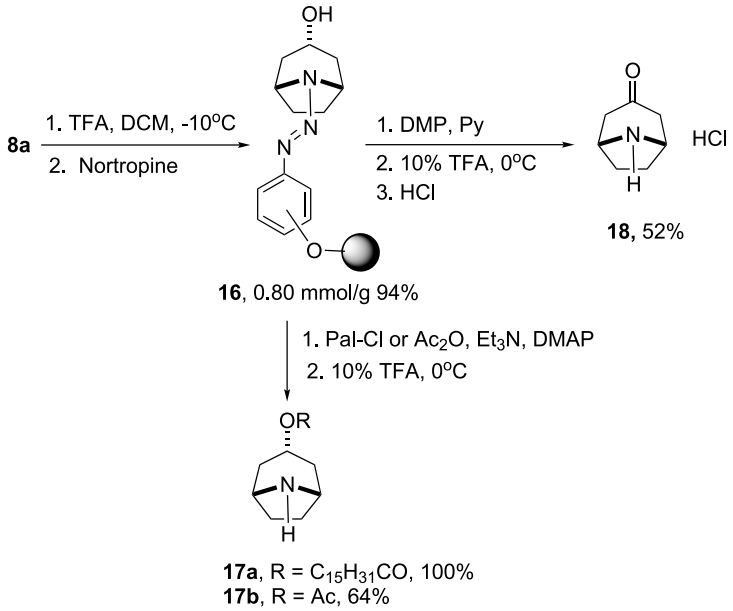
2.2. Polymer supported reactions

As envisaged, simple washing of the triazene gel **8** with a cold 10% solution of trifluoroacetic acid (TFA) in dichloromethane regenerated the supported diazonium salt. The salt could readily anchor another amine as long as the reaction medium remained cold. Such exchange of amines was accomplished with barely noticeable lowering of loadings (Table 1). The loadings of the test amine (morpholine) immobilized on the new polymers **8a** and **13a** through the exchange procedure (97 and 99% of the theoretical value) were significantly better then the loadings of the supports prepared via diazotisation of amines on polymer, i.e. the traditional approach. The data shows however, that both C_6-spacer modified supports **8b**, **13b** had lower loadings than the C_3 supports **8a**, **13a**. In addition to that performance of the *meta*-C_3-T2, *para*-C_3-T2 linkers in Grignard and aldol reactions of supported nortropinone (8-azabicyclo[3.2.1]octan-3-one) was slightly better than the *meta*-C_6-T2 and *para*-C_6-T2 analogues.[10] Encouraged by this results we have further used and tested the polymers with the C_3 linkers.

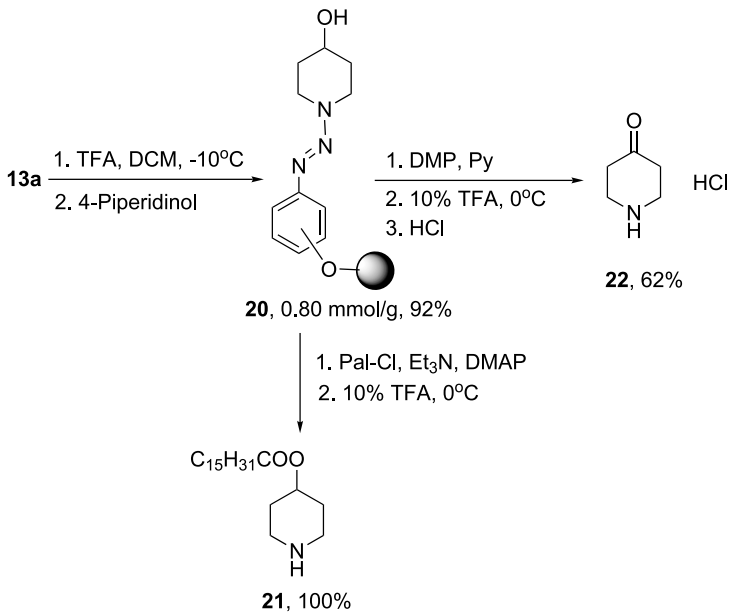
The new polymeric gels were used for immobilization of 3-nortropine and 4-piperidinol with excellent efficiency, (94 and 92% of the theoretical loadings, respectively) and for a few representative reactions of these supported amines (Schemes 4 and 5). The esterification reaction with palmitoyl chloride gave a virtually quantitative yield of esters **17a** and **21**. The simple acetylation was less effective (64 and 62%). Oxidation with Dess–Martin periodinane (DMP) provided ketones with fairly good yields and purities. The gel required thorough washing with basic thiosulfate solutions in order to remove periodinane related by-products. Other oxidants (Py–SO_3 complex) gave incomplete conversion to ketone or even harder to remove impurities (Cr(VI) based oxidants like PDC).

2.3. Stability of triazene linkers and cleavage with TFA

In order to evaluate the stability of the new linkers under reaction conditions model triazenes; *meta* and *para* propyloxy substituted triazenes were treated with the following reagents: Grignard reagent at 0 °C, LDA at −78 °C; potassium *tert*-butoxide, Dess–Martin oxidant, permanganate, hypochloride, peroxides, ethyl iodide and acyl chlorides at room temperature. Analyses of the mixtures showed no significant decomposition of the triazenes by TLC or NMR as long as the solutions remained basic, although the mixtures often discoloured. The observed stability towards strong bases was especially significant in light of recent reports on base induced fragmentation of triazenes.[14] Loadings of the polymers stored in refrigerator remained unchanged for a few months. Thus the stability of the diazonium ions masked in the form of triazenes is high. The *meta*-C_3 triazene linker was proven slightly more stable to acids than the *para* isomer, which was cleaved partially with acetic acid. All of the triazene linkers, as expected, have cleaved under action of acids



Scheme 4.



Scheme 5.

(HCl/THF, HBF_4/THF/, TFA/THF) but the least contaminated amine products were invariably provided by cleavage with TFA in DCM both below 0 °C or at room temperature.

2.4. New polymers as scavengers for amines

We observed that the triazene-loaded polymers could also act as amine scavengers after activation with cold acid solution. When the polymers **8a** or **13a** (twofold molar excess) were pre-treated with cold TFA in DCM, washed free of acid with DCM and added with an equimolar amount of polymer supported tertiary amine (piperidine) to a solution of secondary amine (piperazine or 4-methylpiperidine) the secondary amine was practically removed from the solutions in less than an hour. This observation suggests that the triazene protected polymer supported diazonium salts could also serve as amine scavengers as does the stable polymer supported diazonium tetrafluoroborate.[7e]

3. Conclusions

A new, efficient approach for preparation of resins with bound diazonium ions that are latent and thus stabilized in the form of triazenes has been developed. The masked polymer supported diazonium ions, have good shelf life, and thus can be alternatives to the specially designed thermally stable polymer bound 4-chlorobenzenediazonium tetrafluoroborate (the so-called T2* linker polymer).[7e] Use of the new approach and the three carbon atom spacer modified linkers provided useful polymeric supports with excellent loadings and good purities. The polymers, prepared by pre-loading of triazenes synthesized in solution, could be used, via the amine exchange procedure, for immobilization of secondary amines (as demonstrated on nortropane and piperidine derivatives) and solid-phase synthesis of any class of compounds already prepared with help of the traditional T2 linker.[7] The new polymers can also be used after pre-treatment with cold TFA as amine scavengers in solution.

4. Experimental

4.1. General

All air sensitive reactions were carried out under argon. Tetrahydrofuran was distilled under argon from sodium/benzophenone. Dry dimethylformamide (DMF) was distilled and stored over molecular sieves 4 Å. Chromatographic purifications were achieved by dry-column flash chromatography (DFC).[15] Thin-layer chromatography (TLC) was performed on pre-coated plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), and phosphomolybdic acid followed by charring. Mass spectra were recorded with an AMD-604 spectrometer and are reported as *m/z* ratio (relative intensity). Electron impact (EI) ionisation was accomplished at 70 eV. Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 FTIR Series II Spectrometer as $CHCl_3$ solutions or, in case of polymers, as pressed disks with KBr. Only diagnostic peaks are reported (cm^{-1}). Magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on a Bruker 200 spectrometer in $CDCl_3$ unless otherwise stated. The gel phase ^{13}C NMR spectra of polymers were recorded after at least 1 h swelling in $CDCl_3$. Chemical shifts are reported in ppm downfield of tetramethylsilane.

4.1.1. 3-(3-Aminophenoxy)propan-1-ol (1a). To a solution of 3-aminophenol (3.27 g, 30 mmol) in dry DMF (12 mL), under argon atmosphere, was added sodium hydride (1.21 g, 30 mmol, 60% dispersion in oil) and the mixture was stirred for 10 min. Then the mixture was cooled to 0 °C before addition of 3-chloropropan-1-ol (1.90 g, 20 mmol) and slow warming to room temperature. After stirring for 24 h, the solvent was removed in vacuo and the residue was dissolved in 2 M aqueous hydrochloric acid (60 mL). The solution was extracted with DCM (4×20 mL), alkalised with 2 M potassium hydroxide (80 mL) and extracted with DCM (6×20 mL). The combined alkaline extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The

residue was distilled in Kugelrohr apparatus to remove remaining DMF (ot 120 °C/15 Torr) and to give the product (ot 190–210 °C/0.15 Torr) as a white solid (3.245 g, 65%). Mp 65–67 °C; R_f (5% MeOH/DCM) 0.30; δ_H (200 MHz, $CDCl_3$) 7.05 (t, 8 Hz, 1H), 6.38–6.22 (m, 3H), 4.08 (t, 6 Hz, 2H), 3.85 (t, 7.5 Hz, 2H), 3.67 (br s, 2H), 2.10–1.97 (m, 2H), 1.78 (br s, 1H); δ_C (50.3 MHz, $CDCl_3$) 159.8, 147.6, 130.0, 108.0, 104.5, 101.6, 65.2, 60.0, 31.8; ν_{max}($CHCl_3$) 3624 (OH), 3456, 3340 (NH_2) cm^{-1}; *m/z* (EI) 167 (M^+, 34), 110 (17), 109 (100), 92 (6), 81 (20), 80 (25), 65 (9), 31 (12); HRMS (EI); M^+, found: 167.0939. $C_9H_{13}NO_2$ requires 167.0946.

4.1.2. 6-(3-Aminophenoxy)hexan-1-ol (1b). An analogous procedure to that described for **1a** gave the title compound **1b** (ot 140–250 °C/0.025 Torr) as a yellowish oil (2.845 g, 70%). R_f (10% MeOH/DCM) 0.6; δ_H (200 MHz, $CDCl_3$) 7.05 (t, 8 Hz, 1H), 6.37–6.21 (m, 3H), 3.92 (t, 6.5 Hz, 2H), 3.75–3.58 (m, 4H), 1.98–1.29 (m, 9H); δ_C (50.3 MHz, $CDCl_3$) 159.9, 147.6, 129.7, 107.6, 104.3, 101.5, 67.4, 62.2, 32.3, 28.9, 25.6, 25.2; ν_{max}($CHCl_3$) 3624 (OH), 3455, 3400 (NH_2) cm^{-1}; *m/z* (EI) 209 (M^+, 6), 110 (11), 109 (100), 81 (9), 80 (10), 65 (7), 55 (8), 31 (9); HRMS (EI); M^+, found: 209.1420. $C_{12}H_{19}NO_2$ requires 209.1416.

4.1.3. 3-(3-Aminophenoxy)propyloxymethylpolystyrene hydrochloride (2a). To a solution of 3-(3-aminophenoxy) propan-1-ol (**1a**, 2.896 g, 17.3 mmol, 5.3 equiv.) in dry DMF (20 mL) was added sodium hydride (0.692 g, 60% dispersion in oil, 17.3 mmol) and the mixture was stirred at room temperature for 20 min. After hydrogen evolution have stopped Merrifield gel (3 g, Novabiochem, 1% PS-DVB, 200–400 mesh, 1.1 mmol/g) was added in portions and the mixture was heated to 40 °C for 18 h with intermittent stirring. Then the gel was washed with methanol (1×8 mL, argon), a cold mixture of conc. hydrochloric acid and THF (1:1, 1×8 mL), methanol (2×8 mL), DMF (2×8 mL), methanol (4×8 mL), DCM (4×8 mL) and methanol (2×8 mL). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give yellow, free flowing powder (3.271 g, 96%, 0.81 mmol HCl/g). ν_{max}(KBr) 3442 (NH_3^+) cm^{-1}. Anal. found: C, 75.01; H, 6.35; N, 1.11. $C_{76}H_{81}NO_2Cl$ requires C, 74.58; H, 6.25; N, 1.32.

4.1.4. 6-(3-Aminophenoxy)hexyloxymethylpolystyrene hydrochloride (2b). An analogous procedure to that described for **2a** gave the title polymer **2b** as a light yellow powder (3.192 g, 89%, 0.70 mmol HCl/g). ν_{max}(KBr) 3447 (NH_3^+) cm^{-1}. Anal. found: C, 84.99; H, 7.78; N, 1.04. $C_{79}H_{87}NO_2Cl$ requires C, 84.78; H, 7.75; N, 1.27.

4.1.5. Procedure for anchoring of the test amine morpholine through the *meta*-C_3 linker. Polymer 4a. To a pre-swollen in DCM (8 mL) and cooled to −18 °C suspension of amine hydrochloride polymer **2a** (1 g, 0.81 mmol/g) was added cooled (−18 °C) *tert*-butyl nitrite (1.13 g, 1.3 mL, 11 mmol) and the mixture was agitated for 18 h in a freezer. Then the gel was washed in cold with DCM (6×8 mL) and treated with cold (−18 °C) solution of morpholine (0.233 g, 0.24 mL, 2.37 mmol, 10 equiv.) in DCM (1 mL). The mixture was agitated in a freezer for 3 h and then was allowed to warm up to room temperature. After 16 h the gel was washed successively with DCM and methanol (6×3 mL of each solvent). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give bright, free flowing powder (0.272 g, 0.60 mmol/g, 68% of the theoretical loading of morpholine). ν_{max}(KBr) 1600 (N=N), 1103 (C–N), 1255 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 113.3, 106.2, 66.3, 64.9, 48.0, 29.8. Anal. found: C, 84.75; H, 7.76; N, 2.80. $C_{80}H_{86}N_3O_3$ requires C, 84.46; H, 7.62; N, 3.69.

4.1.6. 3-(4-Nitrophenoxy)propan-1-ol (5a).[16] To a solution of 3-chloropropan-1-ol (7.56 g, 80 mmol) in dry acetone (40 mL), was added sodium iodide (13.2 g, 88 mmol) and the mixture was heated under reflux for 24 h. Then the precipitate was filtered off. To the filtrate was added 4-nitrophenol (13.344 g, 88 mmol) and anhydrous potassium carbonate (16.56 g, 120 mmol) and the mixture was stirred and heated to reflux for 72 h. Then most of the solvent was evaporated and the residue was dissolved in water (100 mL) and alkalised with 2 M solution of potassium hydroxide (pH=14). The alkaline mixture was extracted with DCM (3×70 mL). The combined extracts were washed with 2 M solution of potassium hydroxide (3×40 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was distilled in Kugelrohr apparatus (ot 180–220 °C/0.2 Torr) to give yellowish solid (12.750 g, 80%). R_f (50% AcOEt/Hex) 0.4. Mp 43–45 °C, lit.[16] Mp 48–49 °C; δ_H (200 MHz, $CDCl_3$) 8.24–8.08 (m, 2H), 7.02–6.90 (m, 2H), 4.20 (t, 6 Hz, 2H), 3.92–3.80 (m, 2H), 2.18–1.93 (m, 3H); δ_C (50.3 MHz, $CDCl_3$) 163.9, 140.9, 125.6, 114.2, 65.6, 50.7, 31.5.

4.1.7. 6-(4-Nitrophenoxy)hexan-1-ol (5b). An analogous procedure to that described for **5a** (Kugelrohr distillation ot 200–230/0.05 Torr) gave the title compound **5b** as a light yellow solid (3.927 g, 82%). Mp 80–82 °C (methanol); R_f (50% AcOEt/Hex) 0.35; δ_H (200 MHz, $CDCl_3$) 8.24–8.14 (m, 2H), 7.00–6.90 (m, 2H), 4.06 (t, 6.5 Hz, 2H), 3.79–3.61 (m, 2H), 1.98–1.76 (m, 2H), 1.76–1.37 (m, 7H); δ_C (50.3 MHz, $CDCl_3$) 164.1, 141.0, 125.7, 114.2, 68.6, 62.4, 32.4, 28.7, 25.5, 25.3; ν_{max}($CHCl_3$) 3622, 3442 (OH), 1514 (NO_2) cm^{-1}; *m/z* (EI) 239 (M^+, 12), 139 (16), 123 (24), 109 (21), 101 (29), 83 (65), 55 (100), 41 (32); HRMS (EI): M^+, found: 239.1149. $C_{12}H_{17}O_4N$ requires 239.1158.

4.1.8. 3-(4-Aminophenoxy)propan-1-ol (6a).[17] To a solution of 3-(4-nitrophenoxy)propan-1-ol (**5a**, 4.78 g, 20 mmol) in ethanol (40 mL) was added tin (II) chloride dihydrate (18 g, 80 mmol) and the mixture was stirred and heated under reflux for 20 h. After cooling to room temperature the mixture was diluted with water (150 mL) and basified with an excess of solid potassium hydroxide (35 g). The mixture was extracted with DCM (3×70 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a beige solid (3.006 g, 90%). Mp 88–90 °C ($CHCl_3$), lit.[17b] Mp 90–92 °C; R_f (50% AcOEt/Hex) 0.2; δ_H (200 MHz, $CDCl_3$) 6.83–6.71 (m, 2H), 6.71–6.59 (m, 2H), 4.06 (t, 6 Hz, 2H), 3.86 (t, 6 Hz, 2H), 2.82 (br s, 3H), 2.12–1.96 (m, 2H).

4.1.9. 6-(4-Aminophenoxy)hexan-1-ol (6b).[18] An analogous procedure to that described for **6a** gave the title

compound **6b** as a light red, sensitive to light and oxygen solid (3.846 g, 92%). R_f (10% MeOH/DCM) 0.4; δ_H (200 MHz, $CDCl_3$) 6.83–6.60 (m, 4H), 3.89 (t, 6.5 Hz, 2H), 3.65 (t, 5.5 Hz, 2H), 3.41 (br s, 2H), 1.90–1.70 (m, 2H), 1.70–1.40 (m, 7H); δ_C (50.3 MHz, $CDCl_3$) 152.1, 139.6, 116.4, 115.5, 68.4, 62.4, 32.4, 29.2, 25.7, 25.4; ν_{max}($CHCl_3$) 3624 (OH), 3440, 3366 (N–H), 1238 (C–O–C) cm^{-1}.

4.1.10. 3-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]propan-1-ol (7a). To a cooled (−10 °C) solution of 3-(4-aminophenoxy)propan-1-ol (**6a**, 4.9 g, 29 mmol) and conc. hydrochloric acid (5.3 mL, 63.8 mmol) in ethanol (50 mL) was added portionwise over 20 min. a cold solution of sodium nitrite (2.001 g, 29 mmol) in water (5 mL). After 15 min. the resulting cold solution of the diazonium salt was added to a cold, stirred mixture of diethylamine (8.4 g, 12 mL, 116 mmol, 4 equiv.) water (10 mL) and crushed ice (ca. 20 g). After 15 min the resulting mixture was allowed to warm up to room temperature, strongly basified with potassium hydroxide and extracted with DCM (3×70 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give a crude product. Purification through dry-column flash chromatography (5–50% AcOEt/Hex) gave the triazene product as an orange oil (4.950 g, 68%). R_f (50% AcOEt/Hex) 0.8; δ_H (200 MHz, $CDCl_3$) 7.41–7.33 (m, 2H), 6.91–6.84 (m, 2H), 4.13 (t, 6 Hz, 2H), 3.92–3.80 (m, 2H), 3.73 (q, 7 Hz, 4H), 2.11–1.98 (m, 2H), 1.98–1.91 (m, 1H), 1.26 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 156.4, 144.9, 121.0, 114.4, 65.3, 59.5, br 44.4, 31.8, 12.7; ν_{max}($CHCl_3$) 3430 (OH) cm^{-1}; *m/z* (EI) 251 (M^+, 32), 179 (57), 152 (12), 151 (100), 94 (13), 93 (70), 65 (40), 41 (11). HRMS (EI): M^+, found: 251.1640. $C_{13}H_{21}O_2N_3$ requires 251.1634.

4.1.11. 6-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]hexan-1-ol (7b). An analogous procedure to that described for **7a** gave the title compound **7b** as a light orange oil (5.353 g, 63%). R_f (50% AcOEt/Hex) 0.7; δ_H (200 MHz, $CDCl_3$) 7.39–7.32 (m, 2H), 6.92–6.81 (m, 2H), 3.96 (t, 6.5 Hz, 2H), 3.79–3.60 (m, 6H), 1.90–1.40 (m, 9H), 1.25 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 156.7, 144.8, 121.1, 114.5, 67.9, 62.3, br 44.3, 32.4, 29.1, 25.7, 25.4, 12.7; ν_{max}($CHCl_3$) 3623, 3451 (OH) cm^{-1}; *m/z* (EI) 293 (M^+, 25), 221 (21), 123 (34), 95 (14), 94 (70), 83 (18), 55 (100), 41 (13). HRMS (EI): found: 293.2108 (M^+). $C_{16}H_{27}N_3O_2$ requires 293.2103.

4.1.12. 3-[4-(3,3-Diethyltriaz-1-enyl)phenoxy]propyloxymethylpolystyrene (8a). To a solution of 3-[4-(3,3-diethyltriaz-1-enyl)phenoxy]propan-1-ol (**7a**, 5.522 g, 22 mmol, 5 equiv.) in dry THF (30 mL) was added sodium hydride (0.88 g, 60% dispersion in oil, 22 mmol) and the mixture was heated under argon to 60 °C for 20 min. After the resulting solution was cooled to room temperature Merrifield gel (4 g, Novabiochem, 1% PS-DVB, 200–400 mesh, 1.1 mmol/g) was added and the suspension was heated to 60 °C with intermittent stirring for 72 h. Then the polymer was washed successively with a mixture of water and methanol (1:2, 3×15 mL), methanol (2×15 mL), DCM (2×15 mL), a mixture of water and DMF (1:2, 3×15 mL), DMF (3×15 mL), DCM (3×15 mL) and methanol (3×15 mL). The residual solvent was removed from the gel in vacuo and the gel was dried to a constant mass (ca. 2 h) under high vacuum to give bright yellow, powder (4.676 g, 95%, 0.89 mmol of diethylamine/g, theoretical loading: 0.89 mmol/g). ν_{max}(KBr) 1227 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 156.9, 143.6, 121.3, 114.8, 66.9, 65.3, 46.0, 29.8, 13.0. Anal. found: C, 84.36; H, 7.82; N, 3.73. $C_{80}H_{88}N_3O_2$ requires C, 85.52; H, 7.89; N, 3.74.

4.1.13. 6-[4-(3,3-Diethyltriaz-1-enylo)phenoxy]hexyloxymethylpolystyrene (8b). An analogous procedure to that described for **8a** gave the title polymer **8b** as a light yellow powder (4.958 g, 97%, 0.85 mmol of diethylamine/g, theoretical loading: 0.86 mmol/g). ν_{max}(KBr) 1236 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 156.9, 145.0, 121.3, 114.7, 70.3, 68.1, 46.2, 29.7, 29.3, 26.0, 25.9, 12.9. Anal. found: C, 84.76; H, 8.12; N, 3.44. $C_{83}H_{94}N_3O_2$ requires C, 85.52; H, 8.13; N, 3.60.

4.1.14. *meta*-(3-Hydroxy)propyloxyacetanilide (10a). To a solution of 3-chloropropan-1-ol (2.836 g, 30 mmol) in dry acetone (10 mL), was added sodium iodide (4.946 g, 33 mmol) and the mixture was heated under reflux for 24 h. Then *meta*-hydroxyacetanilide (**9**, 4.989 g, 33 mmol) and anhydrous potassium carbonate (6.22 g, 45 mmol) followed by acetone (10 mL) were added and the mixture was stirred and heated under reflux. After 20 h the solids were filtered off and the filtrate was evaporated in vacuo to give the crude product as a white solid, which was used in the next step. Mp 92–94 °C; R_f (10% MeOH/DCM) 0.50; δ_H (200 MHz, CD_3OD) 7.30–7.22 (m, 1H), 7.21–7.13 (m, 1H), 7.07–6.99 (m, 1H), 6.73–6.62 (m, 1H), 4.05 (t, 6 Hz, 2H), 3.73 (t, 6.5 Hz, 2H), 2.10 (s, 3H), 2.05–1.90 (m, 2H). δ_C (50.3 MHz, $CDCl_3$) 170.0, 159.2, 139.3, 128.9, 111.7, 109.5, 106.0, 64.1, 58.0, 31.7, 22.4. ν_{max}(KBr) 3282 (OH), 1668 (C═O) cm^{-1}; *m/z* (EI) 209 (M^+, 14), 150 (7), 149 (6), 110 (15), 109 (100), 81 (14), 80 (12), 43 (30); HRMS (EI); M^+, found: 209.1060. $C_{11}H_{15}NO_3$ requires 209.1052.

4.1.15. *meta*-(6-Hydroxy)hexyloxyacetanilide (10b). An analogous procedure to that described for **10a** gave the crude title compound **10b** as a white solid, which was used in the next step. Mp 88–90 °C; R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 7.38–7.12 (m, 3H), 7.00–6.85 (m, 1H), 6.74–6.60 (m, 1H), 3.96 (t, 6.5 Hz, 2H), 3.67 (t, 6.5 Hz, 2H), 3.20 (t, 7 Hz, 1H), 2.17 (s, 3H), 1.96–1.24 (m, 8H); δ_C (50.3 MHz, $CDCl_3$) 168.5, 159.6, 139.1, 129.6, 111.8, 110.7, 106.3, 67.9, 62.8, 32.6, 29.1, 25.8. 25.4, 24.5; ν_{max}(KBr) 3307 (OH), 1667 (C═O) cm^{-1}; *m/z* (EI) 251 (M^+, 8), 151 (21), 110 (11), 109 (100), 81 (8), 55 (15), 43 (20), 41 (11); HRMS (EI); M^+, found: 251.1515. $C_{14}H_{21}NO_3$ requires 251.1521.

4.1.16. *para*-(3-Hydroxy)propyloxyacetanilide (11a).[19] An analogous procedure to that described for **10a** gave the crude title compound **11a** as a white solid, which was used in the next step. Mp 93–95 °C; R_f (10% MeOH/DCM) 0.50; δ_H (200 MHz, CD_3OD) 7.44–7.34 (m, 2H), 6.92–6.80 (m, 2H), 4.04 (t, 6 Hz, 2H), 3.73 (t, 6.5 Hz, 2H), 2.08 (s, 3H), 2.02–1.89 (m, 2H); δ_C (50.3 MHz, $CDCl_3$) 170.8, 156.5, 132.2, 122.5, 115.0, 65.3, 59.1, 32.8, 23.2; ν_{max}($CHCl_3$) 3242 (OH), 1655 (C═O) cm^{-1}; *m/z* (EI) 209 (M^+, 25), 167 (12), 110 (9), 109 (100), 108 (33), 80 (12), 53 (8), 43 (26).

4.1.17. *para*-(6-Hydroxy)hexyloxyacetanilide (11b).[20] An analogous procedure to that described for **10a** gave the

crude title compound **11b** as a white solid, which was used in the next step. Mp 92–95 °C; R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 7.40–7.27 (m, 2H), 7.09 (br s, 1H), 6.95–6.78 (m, 2H), 3.94 (t, 6.5 Hz, 2H), 3.67 (t, 6.5 Hz, 2H), 3.26–3.13 (m, 1H), 2.16 (s, 3 h), 1.87–1.34 (m, 8H); δ_C (50.3 MHz, $CDCl_3$) 168.1, 155.9, 130.8, 121.8, 114.7, 68.0, 62.8, 32.6, 30.2, 25.8, 24.6, 24.3; ν_{max}(KBr) 3235 (OH), 1662 (C=O) cm^{-1}; *m/z* (EI) 251 (M^+, 9), 151 (27), 109 (100), 108 (13), 87 (13), 43 (16), 41 (9).

4.2. A general procedure for hydrolysis of acetanilides 10 and 11 (Scheme 3)

A solution of the crude acetanilide **10** or **11** (30 mmol) in a mixture of propanol (10 mL) and conc. hydrochloric acid (7.5 mL, 90 mmol) was heated under reflux for 4 h. Then the solvents were removed in vacuo and the residue was dissolved in water (100 mL), basified with potassium hydroxide to pH=14, and extracted with DCM (3×50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give the hydroxy amines: **1a**: as a light brown solid (4.428 g, 88% after two steps); **1b**: as a light brown solid (5.0066 g, 80% after two steps); **6a**: as a brown solid (4.906 g, 96% after two steps); **6b**: as a brown solid (5.522 g, 88% after two steps).

4.2.1. 3-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]propan-1-ol (12a). An analogous procedure to that described for **7a** gave after dry-column flash chromatography (40–50% AcOEt/Hex) the title compound **12a** as an orange oil (3.737 g, 57%); R_f (50% AcOEt/Hex) 0.50; δ_H (200 MHz, $CDCl_3$) 7.29–7.17 (m, 1H), 7.06–6.99 (m, 2H), 6.75–6.66 (m, 1H), 4.17 (t, 6 Hz, 2H), 3.88 (t, 6 Hz, 2H), 3.77 (q, 7 Hz, 4H), 2.10–1.98 (m, 3 Hz, 2H), 1.27 (t, 7 Hz, 6H); δ_C (50.3 MHz, $CDCl_3$) 159.9, 152.4, 129.0, 113.4, 111.4, 105.7, 65.4, 60.0, br 45.0, 31.9, br 13.0; ν_{max}($CHCl_3$) 3430 (OH) cm^{-1}; *m/z* (EI) 251 (M^+, 18), 151 (100), 94 (22), 93 (72), 72 (18), 65 (65), 58 (19), 41 (18); HRMS (EI): M^+, found: 251.1641. $C_{13}H_{21}O_2N_3$ requires 251.1634.

4.2.2. 6-[3-(3,3-Diethyltriaz-1-enylo)phenoxy]hexan-1-ol (12b). An analogous procedure to that described for **7a** gave after dry-column flash chromatography (45–50% AcOEt/Hex) the title compound **12b** as an orange oil (3.995 g, 56%). R_f (50% AcOEt/Hex) 0.50; δ_H (200 MHz, $CDCl_3$) 7.29–7.19 (m, 1H), 7.07–6.96 (m, 2H), 6.75–6.65 (m, 1H), 4.00 (t, 6.5 Hz, 2H), 3.84–3.59 (m, 6H), 1.95–1.21 (m, 15H); δ_C (50.3 MHz, $CDCl_3$) 156.5, 152.4, 129.2, 113.1, 111.5, 105.8, 67.6, 62.4, br 44.0, 32.4, 29.1, 25.7, 25.3, br 16.3; ν_{max}($CHCl_3$) 3623, 3451 (–OH) cm^{-1}; *m/z* (EI) 293 (M^+, 5), 123 (22), 111 (25), 94 (24), 83 (7), 58 (18), 55 (100), 41 (25). HRMS (EI): M^+, found: 293.2111. $C_{16}H_{27}N_3O_2$ requires 293.2103.

4.2.3. 3-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]propyloxymethylpolystyrene (13a). An analogous procedure to that described for **8a** gave the title polymer **13a** as a light yellow powder (4.688 g, 96%, 0.89 mmol of diethylamine/g, theoretical loading: 0.89 mmol/g). ν_{max}(KBr) 1227 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 160.6, 152.6, 129.4, 113.8, 111.8, 106.0, 66.8, 65.0, 43.9, 29.9, 12.9. Anal. found: C, 84.19; H, 7.79; N, 3.82. $C_{80}H_{88}N_3O_2$ requires C, 85.52; H, 7.89; N, 3.74.

4.2.4. 6-[3-(3,3-Diethyltriaz-1-enyl)phenoxy]hexyloxymethylpolystyrene (13b). An analogous procedure to that described for **8a** gave the title polymer **13b** as a light yellow powder (4.959 g, 98%, 0.66 mmol of diethylamine/g, theoretical loading: 0.86 mmol/g). ν_{max}(KBr) 1236 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 129.4, 113.4, 111.6, 106.0, 70.5, 68.0, 45.3, 29.7, 29.4, 26.1, 25.6, 13.1. Anal. found: C, 84.97; H, 7.93; N, 3.00. $C_{83}H_{94}N_3O_2$ requires C, 85.52; H, 8.13; N, 3.60.

4.2.5. A typical procedure for analysis of loading of a polymeric support: immobilization of a test amine morpholine on the polymer with *meta*-C_3 triazene linker 13a. Polymer 9a. To a swollen in DCM (3 mL) and cooled to −10 °C gel **13a** (0.30 g), was added a cold solution of trifluoroacetic acid in DCM (3 mL, 10% TFA/DCM). After 10 min the gel was washed with cold DCM (2×4 mL), solution of trifluoroacetic acid in DCM (1×3 mL, 10% TFA/DCM) and DCM (3×4 mL). To the collected solutions of diethylamine trifluoroacetate was added conc. hydrochloric acid (0.4 mL, 20 equiv.) and the volatiles were evaporated in vacuo to give pure diethylamine hydrochloride (0.030 g, 0.89 mmol/g, 100% of the theoretical loading). The gel suspension was treated with a solution of morpholine (0.29 mL, 3.3 mmol, 10 equiv.) in DCM (1 mL) and was agitated at −10 °C for 30 min., slowly warmed up to room temperature and left for 12 h. The polymer was washed successively with DCM (6×3 mL), methanol (6×3 mL) and was dried under high vacuum to give yellowish powder (**9a**). Cleavage of morpholine in the same manner as diethylamine gave morpholine hydrochloride (0.034 g, 0.88 mmol/g, 99% of the theoretical loading). ν_{max}(KBr) 1600 (N=N), 1103 (C–N), 1255 (C–O) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 113.3, 106.2, 66.3, 64.9, 48.0, 29.8. Anal. found: C, 84.99; H, 7.50; N, 3.72. $C_{80}H_{86}N_3O_3$ requires C, 84.46; H, 7.62; N, 3.69.

Loadings of anchored amines were calculated from the formula:

$$\text{loading[mmol/g]} = \frac{m_{\text{amine·HCl}}[\text{g}]}{M_{\text{amine·HCl}}[\text{g/mol}]\, m_{\text{gel}}[\text{g}]} \times 10^3$$

4.2.6. Immobilization of nortropine on polymer with *para*-C_3 linker (8a). 3-[4-(3-α-Hydroxynortropanylazo)-phenoxy]propyloxymethylpolystyrene (16). The polymer **8a** (0.70 g, 0.88 mmol/g) was swollen in DCM (5 mL), cooled to −10 °C and washed with a cold solution of TFA (2×3 mL, 10 min. 10% TFA/DCM) followed by DCM (3×3 mL). Then a solution of nortropine (0.78 g, 6.16 mmol, 10 equiv.) in a mixture of DCM/methanol (4:1, 6 mL) was added and the suspension was agitated for 30 min. at −10 °C, warmed up slowly to room temperature, and agitated for 12 h. The polymer was washed with methanol (2×5 mL), DCM (2×5 mL), DMF (2×5 mL), THF (2×5 mL), methanol (2×5 mL), DCM (2×5 mL), methanol (2×5 mL) and dried under high vacuum to a constant mass to give a dark red powder (0.80 mmol/g, 94% of the theoretical loading). ν_{max}(KBr) 338 (OH) cm^{-1}; δ_C (50.3 MHz, $CDCl_3$) 119.7, 114.8, 66.9, 65.1, 55.1, 37.7, 29.8, 26.7. Anal. found: C, 85.19; H, 7.83; N, 3.31. $C_{83}H_{90}N_3O_3$ requires C, 84.65; H, 7.70; N, 3.57.

4.2.7. 3-Palmitoylnortropine (17a). To the swollen in DCM (3 mL), gel **16** (0.35 g,) was added triethylamine (0.32 mL, 2.31 mmol, 6 equiv.), palmitoyl chloride (0.59 mL, 1.9 mmol, 5 equiv.) and a catalytic amount of DMAP (ok. 0.01 g). The mixture was shaken at room temperature for 12 h. Then the gel was washed successively with methanol (2×3 mL), mixture of methanol and diethylamine (1:1, 2×3 mL), methanol (2×3 mL), water (2×3 mL), methanol (2×3 mL), DCM (2×3 mL), methanol (2×3 mL), DCM (2×3 mL) and methanol (2×3 mL). The gel was dried under high vacuum to give a beige powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.105 g, 100% of the theoretical loading) as a white solid. For analyses the free base was obtained by treatment with ammonia solution. Mp 50–53 °C; R_f (10% MeOH/DCM sat. with aq NH_3) 0.45; δ_H (200 MHz, $CDCl_3$) 5.05 (t, 5 Hz, 1H), 3.55–3.47 (m, 2H), 2.29 (t, 7.5 Hz, 2H), 2.10–1.95 (m, 4H), 1.85–1.56 (m, 7H), 1.2–1.10 (m, 24H), 0.88 (t, 6 Hz, 3H); δ_C (50.3 MHz, $CDCl_3$) 173.0, 67.7, 53.3, 37.4, 34.9, 31.9, 29.65, 29.61, 29.55, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 14.1; ν_{max}(CCl_4) 3443 (NH_2), 1731 (C═O), 1169 (C–O), 1076 (C–N) cm^{-1}; *m/z* (EI) 365 (M^+, 0.1), 111 (16), 110 (100), 82 (13), 80 (18), 68 (18), 43 (18), 41 (14). Anal. (hydrochloride) found: C, 68.67; H, 10.77; N, 3.33. $C_{23}H_{44}NO_2Cl$ requires C, 68.71; H, 11.03; N, 3.48.

4.2.8. 3-α-Acetyloxynortropane (nortropine acetate, 17b).[21] An analogous procedure to that described for **17a** (using acetic anhydride instead of palmitoyl chloride) gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound as a white solid (0.095 g, 64% of the theoretical yield). For analysis the free base was obtained by treatment with ammonia solution. R_f (10% MeOH/DCM sat. with aq NH_3) 0.30; δ_H (200 MHz, DMSO-d_6) 4.86 (t, 5 Hz, 1H), 3.38 (br s, 2H), 2.08–1.92 (m, 7H), 1.65–1.42 (m, 5H).

4.2.9. Oxidation of nortropine to nortropinone (18) on polymer with *para*-C_3 triazene linker. Nortropinone hydrochloride.[22] To a suspension of gel **17a** (0.5 g, 0.811 mmol/g) in dry DCM (4 mL) was added finely ground Dess–Martin periodinane (0.86 g, 2.03 mmol, 5 equiv.) and pyridine (0.321 g, 0.33 mL, 4.06 mmol). The mixture was shaken at room temperature for 72 h. Then the gel was washed with methanol (2×4 mL), mixture of 2 M KOH with DMF (1:4, 2×4 mL), mixture of 2 M KOH in methanol (1:4, 2×4 mL), 2 M KOH (2×3 mL), mixture of alkaline aqueous sodium thiosulphate (2 mL) with DMF (2 mL), solution of sodium thiosulphate in aqueous methanol (2 mL), methanol (2×4 mL), THF (2×4 mL), methanol (2×4 mL), DCM (2×4 mL) and methanol (2×4 mL). The gel was dried under high vacuum to give a dark red powder (0.54 g, 88%). Cleavage of the product and conversion to hydrochloride under typical conditions gave the title compound (0.034 g, 52% yield of the oxidation). δ_H (200 MHz, $CDCl_3$) 10.60 (s, br, 1H), 10.25 (s, br, 1H), 4.40 (s, 2H), 3.25 (dd, *J*=4.0, 16.5 Hz, 2H), 2.65–2.38 (m, 4H), 2.10–1.85 (m, 2H).

4.2.10. Immobilization of 4-piperidinol on polymer with *meta*-C_3 linker 13a. 3-[3-(4-Hydroxypiperidinylazo)phenoxy]propyloxymethylpolystyrene (20). The polymer **13a** (0.65 g, 0.89 mmol/g) was swollen in DCM (5 mL), cooled to −10 °C and washed with a cold solution of TFA (2×3 mL, 10 min. 10% TFA/DCM) followed by DCM (3×3 mL). Then was added a solution of anhydrous 4-hydroxypiperydyne (0.72 g, 7.15 mmol, 10 equiv.) in a mixture of DCM/THF/isopropanol (1:2:1) and the suspension was agitated for 30 min. at −10 °C, warmed up to room temperature, and agitated for 12 h. The polymer was washed with methanol (2×5 mL), DCM (2×5 mL), DMF (2×5 mL), THF (2×5 mL), methanol (2×5 mL), DCM (2×5 mL), methanol (2×5 mL) and dried under high vacuum to constant mass to give an orange powder (0.80 mmol/g, 92% of the theoretical loading). ν_{max}(KBr) 3533 (OH), 1232 (C–O) cm^{-1}. Anal. found: C, 85.75; H, 7.60; N, 3.31. $C_{81}H_{88}N_3O_3$ requires C, 84.48; H, 7.70; N, 3.65.

4.2.11. 4-Palmitoyloxypiperidine (21). An analogous procedure to that described for **17a** gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.105 g, 100% of the theoretical yield). The free base for the analyses was obtained by treatment with ammonia. Mp 104–105 °C (hydrochloride); R_f (10% MeOH/DCM) 0.60; δ_H (200 MHz, $CDCl_3$) 5.06 (br s, 1H), 3.22–3.12 (m, 4H), 2.40–2.30 (m, 2H), 2.30–2.12 (m, 1H), 2.12–1.91 (m, 2H), 1.73–1.50 (m, 2H), 1.26 (s, 26H),1.98–1.81 (m, 3H); δ_C (50.3 MHz, $CDCl_3$) 173.2, 43.9, 43.8, 34.6, 32.0, 31.9, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 29.1, 25.0, 22.6, 14.1, 1.0; ν_{max}($CHCl_3$): 1724 (C═O) cm^{-1}; *m/z* (EI) 339 (M^+, 3), 143 (23), 84 (90), 83 (100), 82 (41), 68 (26), 55 (23), 43 (25). Anal. (hydrochloride) found: C, 66.88; H, 11.54; N, 3.66. $C_{21}H_{42}NO_2Cl$ requires C, 67.08; H, 11.26; N, 3.73

4.2.12. 4-Piperidone hydrochloride (22).[23] An analogous procedure to that described for oxidation of **17a** gave the polymer as a red powder. Cleavage of the product under typical conditions followed by addition of conc. hydrochloric acid and evaporation of volatiles gave the title compound (0.034 g, 62% of the theoretical yield). δ_H (200 MHz, CD_3OD) 3.25–3.18 (m, 4H), 2.05–1.95 (m, 4H).

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23. Commercial product (Aldrich) had the same ^{1}H NMR spectrum.

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Mineral supported syntheses of benzoxazine-2-thiones under microwave irradiation

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Abstract—An original montmorillonite K-10 clay catalysed cycloisomerisation of salicylaldehyde 4-arylthiosemicarbazones yields 3,4-dihydro-4-hydrazino-2*H*-benz[*e*]-1,3-oxazine-2-thiones, which on reductive dehydrazination on alumina-supported copper(II) sulfate readily furnish 3,4-dihydro-2*H*-benz[*e*]-1,3-oxazine-2-thiones under solvent-free microwave irradiation. Under the same conditions salicylaldehyde thiosemicarbazones undergo cyclodehydrazination to yield 2*H*-benz[*e*]-1,3-oxazine-2-thiones.

Recently, benzoxazinone derivatisation has attained considerable significance in potential antiviral target compounds.[1–6] The prime driving force in this area is the fight against HIV by developing more efficacious drugs than Efavirenz (Sustiva), a benzoxazinone derivative, which is presently in clinical use for the treatment of AIDS. The hydrazine function is synthetically readily manipulable, thus the present cycloisomerisation expeditiously yielding 4-hydrazinobenzoxazine-2-thiones **6** offers an attractive scaffold to be utilized for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.

Heterogeneous organic reactions have proven useful to chemists both in academia and in industry. Clay-catalysed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attributes under heterogeneous reaction conditions.[7–9] The application of microwave (MW) irradiation as a non-conventional energy source for activation of reactions, in general and on inorganic solid supports in particular, have gained popularity over the usual homogeneous and heterogeneous reactions, as they can be performed rapidly to give pure products in high yields under solvent-free conditions with several eco-friendly advantages in the context of green chemistry.[10–14]

Considering the above reports and in pursuing our work on new cyclisation methods,[15–17] we contemplated an original montmorillonite K-10 clay catalysed MW activated cycloisomerisation of 4-arylthiosemicarbazones **1** to 4-hydrazinobenzoxazine-2-thiones **6** (Scheme 1). Interestingly, this is the first example of the synthesis of 4-hydrazinobenzoxazine-2-thiones **6**, and their reductive dehydrazination to the corresponding benzoxazine-2-thiones **8**. The key element in our approach is the novel utilization of salicylaldehyde as a bifunctional building block whose application to the construction of various benzo-fused oxygen heterocycles of chemical and biological interest is well documented.[18–23]

1. Results and discussion

After some preliminary experimentation, it was found that the cycloisomerisation envisaged (**1**→**6**) can be effected using montmorillonite K-10 clay with intermittent irradiation for 2 min in an unmodified domestic MW oven at 560 W followed by thorough mixing for 2 min outside the oven. This intermittent irradiation-mixing cycle was repeated for the total irradiation time specified in Table 1 to afford benzoxazine-2-thiones **6** in 76–87% yield (Table 1). However, the use of other mineral supports, viz. silica gel, neutral or basic alumina, was far less effective resulting in either no reaction (in the case of basic alumina) or relatively very low yields (14–32%) of **6** (in the cases of silica gel and neutral alumina). Hydrazines **6** readily formed hydrazones with benzaldehyde, further confirmation of their identity. 4-Hydrazinobenzoxazine-2-thiones **6** underwent MW-assisted reductive dehydrazination on alumina-supported copper(II) sulfate under solvent-free conditions to furnish the corresponding benzoxazine-2-thiones **8** (Table 1). When salicylaldehyde thiosemicarbazones **1**, R^3=H, were subjected to MW irradiation under the same conditions as for the synthesis of **6** from **1**, R^3=aryl (Ar), cyclodehydrazination occurred to furnish **7** in 84–92% yield (Table 1).

Keywords: Mineral supported; Microwaves; Solvent free; Benzoxazine-2-thiones; Salicylaldehyde thiosemicarbazones.
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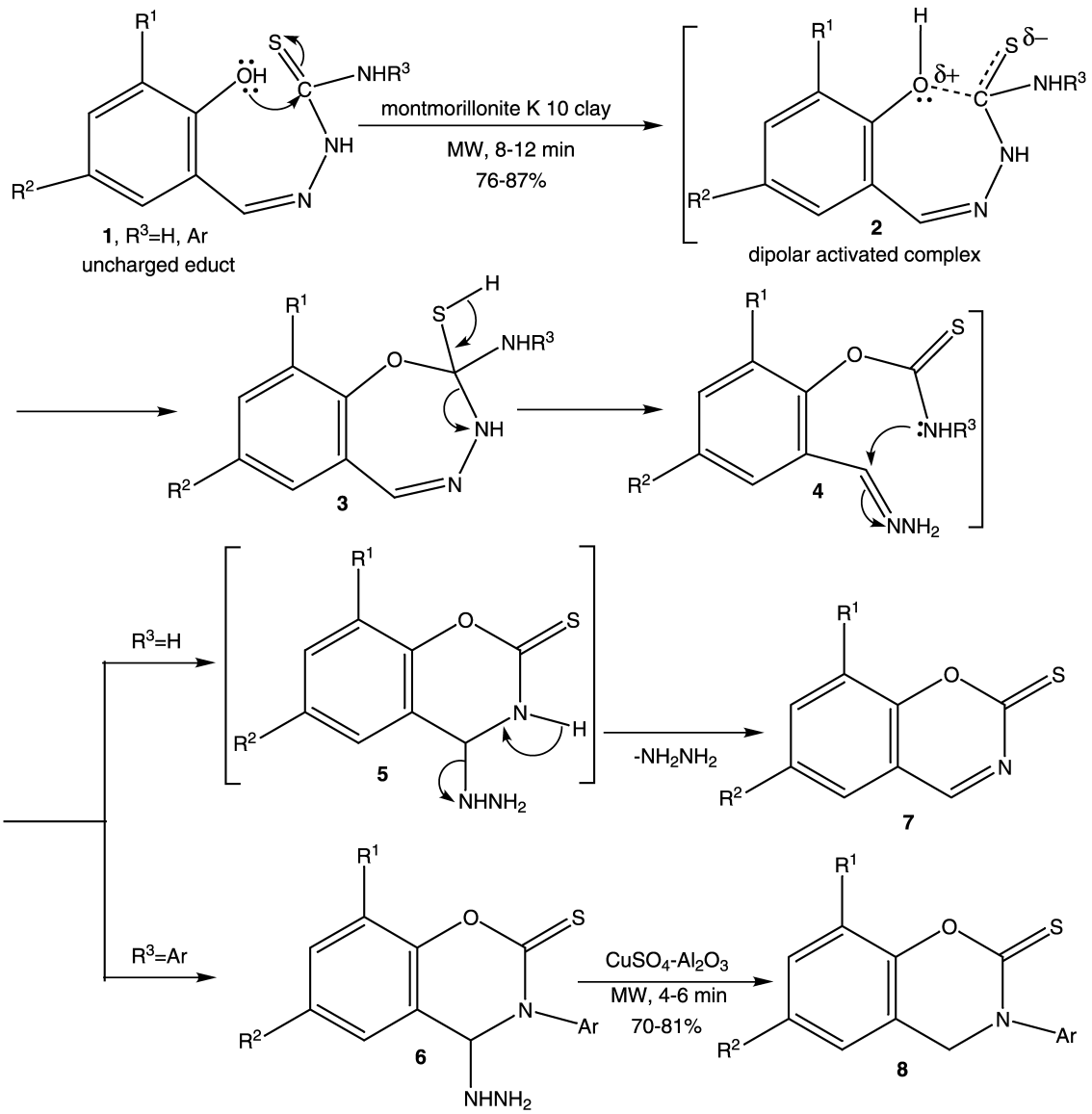

1-8	R^1	R^2	1 Ar	-8	R^1	R^2	Ar
a	H	H	Ph	**f**	H	H	4-MeC_6H_4
b	H	Br	Ph	**g**	H	Br	4-MeC_6H_4
c	Br	Br	Ph	**h**	Br	Br	4-MeC_6H_4
d	H	Cl	Ph	**i**	H	Cl	4-MeC_6H_4
e	Cl	Cl	Ph	**j**	Cl	Cl	4-MeC_6H_4

Scheme 1.

For comparison purposes, the final temperature was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiations and was found to be <90 °C. The cycloisomerisations (**1→6**, R^3=Ar) and cyclodehydrazinations (**1→7**, R^3=H) were also carried out using a thermostated oil bath under the same conditions of time (Table 1) and temperature (90 °C) as for the MW activated method. It was found that significantly lower yields (14–32%) were obtained using oil-bath heating rather than the MW activated method (Table 1). Similar results were obtained in the case of reductive dehydrazination of **6** to **8** (Table 1). These observations may be rationalised on the basis of the formation of a dipolar activated complex from an uncharged educt in these cycloisomerisations (Scheme 1 shows an activated complex **2** as an example) and the greater stabilisation of the more polar activated complex by dipole–dipole interactions with the electromagnetic field of MWs as compared to the less polar educt which may reduce the activation energy ($\Delta G^{\neq}$) resulting in the rate enhancement.[14]

Table 1. Products **6**–**8** prepared on mineral support under solvent-free microwave irradiation

Product	Time[a] (min)	Yield[b] (%)	Product	Time[a] (min)	Yield[b] (%)
6a	10 (10)	82 (22)	**7d**	10 (10)	92 (31)
6b	10 (10)	84 (23)	**7e**	8 (8)	90 (28)
6c	8 (8)	86 (21)	**8a**	5 (5)	76 (14)
6d	10 (10)	87 (25)	**8b**	5 (5)	77 (16)
6e	8 (8)	87 (29)	**8c**	4 (4)	79 (17)
6f	12 (12)	76 (18)	**8d**	5 (5)	75 (15)
6g	12 (12)	78 (19)	**8e**	4 (4)	81 (19)
6h	12 (12)	81 (20)	**8f**	6 (6)	70 (11)
6i	10 (10)	83 (26)	**8g**	6 (6)	71 (13)
6j	8 (8)	85 (27)	**8h**	6 (6)	73 (15)
7a	10 (10)	91 (23)	**8i**	5 (5)	72 (16)
7b	10 (10)	84 (29)	**8j**	4 (4)	78 (15)
7c	8 (8)	87 (26)			

[a] Microwave irradiation time (power=560 W). Parentheses show the time for oil-bath heating at 90 °C.
[b] Yield of isolated and purified product. Parentheses show yield obtained using oil-bath heating.

2. Conclusion

In summary, we have developed original, mineral supported syntheses of various potentially pharmaceutically useful benzoxazine-2-thiones from readily and widely available salicylaldehyde thiosemicarbazones under solvent-free MW irradiation. The present high yielding, expeditious and eco-friendly conversions lead to synthetically readily manipulable products, which may find application in the synthesis of compounds of this class.

3. Experimental

3.1. General

An unmodified domestic MW oven (Kenstar, Model MWO 9808, operating at 2450 MHz) was used at an output of 560 W for all the experiments. Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-d_6 using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser. All chemicals used were reagent grade. Silica gel-G was used for TLC.

3.2. 3,4-Dihydro-4-hydrazino-2*H*-benz[*e*]-1,3-oxazine-2-thiones 6. General procedure

To a solution of salicylaldehyde 4-arylthiosemicarbazone **1** (5.0 mmol) in a small amount of dichloromethane (10 mL) was added montmorillonite K-10 clay (7.5 g), mixed thoroughly and dried under reduced pressure. The contents were taken in a 100 mL conical flask and subjected to MW irradiation at 560 W for 2 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 2 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane–AcOEt, 8:2, v/v), the product was extracted with dichloromethane (3×50 mL), the extract was filtered and the filtrate was evaporated under reduced pressure to leave the crude product which was recrystallised from ethanol to obtain an analytically pure sample of **6**.

3.2.1. Compound 6a. Yellowish needles (1.11 g, 82%), mp 171–172 °C; ν_{max} (KBr) 3362, 3005, 1595, 1578, 1450 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS, 400 MHz) δ: 3.05 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.74 (d, 1H, J=8 Hz, 4-H), 7.18–7.87 (m, 9H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS, 100 MHz) δ: 78.6, 113.1, 114.2, 118.4, 120.3, 122.5, 129.0, 129.6, 130.2,150.0, 166.2, 191.9. MS (*m*/*z*): 271 (M^+). Analysis found: C, 61.68; H, 4.67; N, 15.72%. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49%.

3.2.2. Compound 6b. Yellowish needles (1.47 g, 84%), mp 185–187 °C; ν_{max} (KBr) 3365, 3018, 1596, 1580, 1453 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 3.07 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.75 (d, 1H, J=8.0 Hz, 4-H), 7.29 (d, 1H, J=9.0 Hz, 8-H), 7.90 (dd, 1H, J=9.0, 2.4 Hz, 7-H), 8.22 (d, 1H, J=2.4 Hz, 5-H), 7.16–7.84 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 78.7, 113.1, 114.3, 118.6, 120.1, 122.5, 129.2, 129.8, 130.6, 150.1, 166.3, 192.0. Mass (*m*/*z*): 349 (M^+). Analysis found: C, 47.76; H, 3.32; N, 11.79%. Calcd for $C_{14}H_{12}BrN_3OS$: C, 48.01; H, 3.45; N, 12.00%.

3.2.3. Compound 6c. Yellowish needles (1.84 g, 86%), mp 195–198 °C; ν_{max} (KBr) 3370, 3025, 1598, 1583, 1460 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 3.09 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.78 (d, 1H, J=8.0 Hz, 4-H), 7.88 (d, 1H, J=2.5 Hz, 7-H), 8.17 (d, 1H, J=2.5 Hz, 5-H), 7.18–7.86 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 78.9, 113.2, 114.5, 118.6, 120.3, 122.6, 129.4, 130.1, 130.9, 150.2, 166.5, 192.1. Mass (*m*/*z*): 427 (M^+). Analysis found: C, 38.91; H, 2.69; N, 9.98%. Calcd for $C_{14}H_{11}Br_2N_3OS$: C, 39.18; H, 2.58; N, 9.79%.

3.2.4. Compound 6d. Yellowish needles (1.33 g, 87%), mp 178–179 °C; ν_{max} (KBr) 3368, 3028, 1600, 1582, 1455 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 3.08 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.77 (d, 1H, J=8.1 Hz, 4-H), 7.31 (d, 1H, J=9.2 Hz, 8-H), 7.91 (dd, 1H, J=9.2, 2.5 Hz, 7-H), 8.23 (d, 1H, J=2.5 Hz, 5-H), 7.15–7.86 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 78.8, 113.2, 114.2, 118.7, 120.3, 122.5, 129.1, 129.9, 130.8, 150.3, 166.5, 192.1. Mass (*m*/*z*): 305 (M^+). Analysis found: C, 55.19; H, 3.79; N, 13.89%. Calcd for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96; N, 13.74%.

3.2.5. Compound 6e. Yellowish needles (1.48 g, 87%), mp 189–191 °C; ν_{max} (KBr) 3375, 3030, 1605, 1586, 1462 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 3.11 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.80 (d, 1H, J=8.1 Hz, 4-H), 7.91 (d, 1H, J=2.6 Hz, 7-H), 8.20 (d, 1H, J=2.6 Hz, 5-H), 7.20–7.88 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 79.1, 113.3, 114.7, 118.7, 120.5, 122.7, 129.6, 130.5 131.3, 150.4, 166.7, 192.2. Mass (*m*/*z*): 339 (M^+). Analysis found: C, 49.16; H, 3.10; N, 12.57%. Calcd for $C_{14}H_{11}Cl_2N_3OS$: C, 49.42; H, 3.26; N, 12.35%.

3.2.6. Compound 6f. Yellowish needles (1.08 g, 76%), mp 175–176 °C; ν_{max} (KBr) 3360, 3010, 1592, 1575, 1452 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.31 (s, 3H, Me), 3.03 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.70 (d, 1H, J=7.9 Hz, 4-H), 7.14–7.85 (m, $8H_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.2, 78.5, 113.0, 114.0, 118.3, 120.2, 122.3, 128.8, 129.5, 130.2, 150.0, 166.1, 191.7. Mass (*m/z*): 285 (M^+). Analysis found: C, 62.88; H, 5.18; N, 14.95%. Calcd for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.73%.

3.2.7. Compound 6g. Yellowish needles (1.42 g, 78%), mp 187–189 °C; ν_{max} (KBr) 3362, 3015, 1595, 1578, 1450 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.32 (s, 3H, Me), 3.06 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.72 (d, 1H, J=8.0 Hz, 4-H), 7.27 (d, 1H, J=9.0 Hz, 8-H), 7.88 (dd, 1H, J=9.0, 2.4 Hz, 7-H), 8.21 (d, 1H, J=2.4 Hz, 5-H), 7.14–7.80 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.3, 78.6, 113.0, 114.1, 118.4, 120.0, 122.3, 129.0, 129.8, 130.5, 150.0, 166.2, 191.8. Mass (*m/z*): 363 (M^+). Analysis found: C, 49.66; H, 3.89; N, 11.36%. Calcd for $C_{15}H_{14}BrN_3OS$: C, 49.46; H, 3.87; N, 11.54%.

3.2.8. Compound 6h. Yellowish needles (1.79 g, 81%), mp 198–201 °C; ν_{max} (KBr) 3363, 3028, 1595, 1580, 1458 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.33 (s, 3H, Me), 3.07 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.75 (d, 1H, J=8.0 Hz, 4-H), 7.86 (d, 1H, J=2.5 Hz, 7-H), 8.16 (d, 1H, J=2.5 Hz, 5-H), 7.16–7.83 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.4, 78.7, 113.0, 114.4, 118.5, 120.1, 122.3, 129.2, 130.0, 131.1, 150.0, 166.3, 192.0. Mass (*m/z*): 441 (M^+). Analysis found: C, 40.35; H, 2.79; N, 9.69%. Calcd for $C_{15}H_{13}Br_2N_3OS$: C, 40.65; H, 2.96; N, 9.48%.

3.2.9. Compound 6i. Yellowish needles (1.32 g, 83%), mp 170–171 °C; ν_{max} (KBr) 3365, 3025, 1602, 1579, 1460 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.34 (s, 3H, Me), 3.06 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.74 (d, 1H, J=8.1 Hz, 4-H), 7.30 (d, 1H, J=9.2 Hz, 8-H), 7.90 (dd, 1H, J=9.2, 2.5 Hz, 7-H), 8.21 (d, 1H, J=2.5 Hz, 5-H), 7.16–7.81 (m, 4H, 4-$MeOC_6H_4$). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.3, 78.6, 113.1, 114.0, 118.5, 120.1, 122.4, 129.0, 129.7, 130.6, 150.1, 166.3, 192.0. Mass (*m/z*): 319 (M^+). Analysis found: C, 56.05; H, 4.22; N, 13.28%. Calcd for $C_{15}H_{14}ClN_3OS$: C, 56.33; H, 4.41; N, 13.14%.

3.2.10. Compound 6j. Yellowish needles (1.50 g, 85%), mp 183–185 °C; ν_{max} (KBr) 3371, 3032, 1600, 1585, 1464 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 2.36, (s, 3H, Me), 3.08 (br s, 3H, $NHNH_2$, exchanges with D_2O), 6.77 (d, 1H, J=8.1 Hz, 4-H), 7.90 (d, 1H, J=2.6 Hz, 7-H), 8.18 (d, 1H, J=2.6 Hz, 5-H), 7.16–7.84 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.4, 78.8, 113.1, 114.6, 118.5, 120.4, 122.5, 129.4, 130.6, 131.1, 150.2, 166.6, 192.1. Mass (*m/z*): 353 (M^+). Analysis found: C, 50.98; H, 3.79; N, 11.99%. Calcd for $C_{15}H_{13}Cl_2N_3OS$: C, 50.86; H, 3.70; N, 11.86%.

3.3. 2*H*-Benz[*e*]-1,3-oxazine-2-thiones 7. General procedure

The procedure followed was the same as described above for the synthesis of **6** except that the starting material in this case was **1**, R^3=H, instead of **1**, R^3=aryl (Ar), for **6** (Table 1). Compounds **7a**, **7c**, **7f**, **7g**, **7h**, **7i**, and **7j** are known and their characterisation data agreed well with those reported in the literature.[23]

3.3.1. Compound 7b. Yellow needles (1.01 g, 84%), mp 163–165 °C; ν_{max} (KBr) 3015, 1595, 1579, 1450 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 7.31 (d, 1H, J=9.5 Hz, 8-H), 7.95 (dd, 1H, J=9.5, 2.6 Hz, 7-H), 8.23 (d, 1H, J=2.6 Hz, 5-H), 8.50 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6/TMS) δ: 114.3, 123.2, 125.4, 127.3, 138.1, 150.2, 166.3, 192.2. Mass (*m/z*): 241 (M^+). Analysis found: C, 39.41; H, 1.59; N, 5.90%. Calcd for C_8H_4BrNOS: C, 39.69; H, 1.67; N, 5.79%.

3.3.2. Compound 7d. Yellow needles (0.91 g, 92%), mp 158–159 °C; ν_{max} (KBr): 3032, 1602, 1584, 1458 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 7.33 (d, 1H, J=9.5 Hz, 8-H), 7.98 (dd, 1H, J=9.5, 2.6 Hz, 7-H), 8.27 (d, 1H, J=2.6 Hz, 5-H), 8.51 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6/TMS) δ: 114.9, 125.2, 127.5, 135.1, 138.5, 150.4, 166.4, 192.2. Mass (*m/z*): 197 (M^+). Analysis found: C, 48.86; H, 2.00; N, 7.21%. Calcd for C_8H_4ClNOS: C, 48.62; H, 2.04; N, 7.09%.

3.3.3. Compound 7e. Yellow needles (1.04 g, 90%), mp 170–172 °C; ν_{max} (KBr) 3028, 1603, 1582, 1460 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 7.93 (d, 1H, J=2.6 Hz, 7-H), 8.21 (d, 1H, J=2.6 Hz, 5-H), 8.53 (s, 1H, 4-H). ^{13}C NMR (DMSO-d_6/TMS) δ: 115.1, 125.3, 134.6, 135.3, 138.6, 150.6, 166.6, 192.3. Mass (*m/z*): 231 (M^+). Analysis found: C, 41.11; H, 1.21; N, 6.20%. Calcd for $C_8H_3Cl_2NOS$: C, 41.40; H, 1.30; N, 6.04%.

3.4. 3,4-Dihydro-2*H*-benz[*e*]-1,3-oxazine-2-thiones 8. General procedure

An intimate mixture of **6** (2.5 mmol) and $CuSO_4$–Al_2O_3 (4.4 g, 2.5 mmol of $CuSO_4{\cdot}5H_2O$) was taken in a 100 mL conical flask and subjected to MW irradiation at 560 W for 1 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 1 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane–AcOEt, 9:1, v/v), the product was extracted with dichloromethane (3×25 mL) and the extract was evaporated under reduced pressure to leave the crude product which was recrystallised from ethanol to obtain an analytically pure sample of **8**.

3.4.1. Compound 8a. Yellow needles (0.46 g, 76%), mp 162–163 °C; ν_{max} (KBr) 3012, 1598, 1579, 1455 cm^{-1}. ^1H NMR (DMSO-d_6/TMS, 400 MHz) δ: 6.59 (d, 1H, J=13 Hz, axial H of CH_2), 6.64 (d, 1H, J=13 Hz, equatorial H of CH_2), 7.14–7.80 (m, $9H_{arom}$). ^{13}C NMR (DMSO-d_6/TMS, 100 MHz) δ: 64.3, 112.9, 114.0, 118.3, 120.2, 122.3, 128.9, 129.7, 130.1, 149.9, 166.0, 191.8. Mass (*m/z*): 241 (M^+). Analysis found: C, 69.40; H, 4.42; N, 5.98%. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80%.

3.4.2. Compound 8b. Yellowish needles (0.61 g, 77%), mp 173–174 °C; ν_{max} (KBr) 3025, 1600, 1584, 1460 cm^{-1}. ^1H NMR (DMSO-d_6/TMS) δ: 6.60 (d, 1H, J=13.0 Hz, one of CH_2), 6.65 (d, 1H, J=13.0 Hz, one of CH_2), 7.28 (d, 1H, J=9.0 Hz, 8-H), 7.90 (dd, 1H, J=9.0, 2.4 Hz, 7-H), 8.19 (d,

1H, J=2.4 Hz, 5-H), 7.15–7.81 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 64.4, 113.0, 114.2, 118.5, 120.3, 122.5, 128.8, 129.4, 130.1, 150.0, 166.1, 191.9. Mass (m/z): 319 (M^+). Analysis found: C, 52.36; H, 3.00; N, 4.56%. Calcd for $C_{14}H_{10}BrNOS$: C, 52.51; H, 3.15; N, 4.37%.

3.4.3. Compound 8c. Yellowish needles (0.79 g, 79%), mp 182–184 °C; ν_{max} (KBr) 3032, 1602, 1586, 1465 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 6.61 (d, 1H, J=13.0 Hz, one of CH_2), 6.65 (d, 1H, J=13.0 Hz, one of CH_2), 7.86 (d, 1H, J=2.5 Hz, 7-H), 8.16 (d, 1H, J=2.5 Hz, 5-H), 7.16–7.83 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 64.5, 113.1, 114.2, 118.6, 120.5, 122.6, 128.9, 129.9, 130.6, 150.1, 166.2, 192.1. Mass (m/z): 399 (M^+). Analysis found: C, 42.00; H, 2.09; N, 3.26%. Calcd for $C_{14}H_9Br_2NOS$: C, 42.13; H, 2.27; N, 3.51%.

3.4.4. Compound 8d. Yellowish needles (0.52 g, 75%), mp 168–169 °C; ν_{max} (KBr) 3035, 1604, 1585, 1462 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 6.61 (d, 1H, J=13.0 Hz, one of CH_2), 6.67 (d, 1H, J=13.0 Hz, one of CH_2), 7.28 (d, 1H, J=9.0 Hz, 8-H), 7.92 (dd, 1H, J=9.0, 2.4 Hz, 7-H), 8.21 (d, 1H, J=2.4 Hz, 5-H), 7.16–7.83 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 64.5, 113.2, 114.3, 118.5, 120.4, 122.7, 128.9, 130.0, 135.2, 151.2, 166.2, 192.0. Mass (m/z): 275 (M^+). Analysis found: C, 61.18; H, 3.49; N, 5.29%. Calcd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08%.

3.4.5. Compound 8e. Yellowish needles (0.63 g, 81%), mp 177–179 °C; ν_{max} (KBr) 3033, 1603, 1582, 1460 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 6.62 (d, 1H, J=13.0 Hz, one of CH_2), 6.67 (d, 1H, J=13.0 Hz, one of CH_2), 7.88 (d, 1H, J=2.5 Hz, 7-H), 8.18 (d, 1H, J=2.5 Hz, 5-H), 7.18–7.86 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6/TMS) δ: 64.6, 113.2, 114.4, 118.6, 120.6, 122.8, 129.0, 130.2, 135.4, 151.3, 166.3, 192.1. Mass (m/z): 309 (M^+). Analysis found: C, 53.98; H, 2.79; N, 4.36%. Calcd for $C_{14}H_9Cl_2NOS$: C, 54.21; H, 2.92; N, 4.52%.

3.4.6. Compound 8f. Yellow needles (0.45 g, 70%), mp 150–151 °C; ν_{max} (KBr) 3018, 1595, 1576, 1460 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.30 (s, 3H, Me), 6.57 (d, 1H, J=13.0 Hz, one of CH_2), 6.62 (d, 1H, J=13.0 Hz, one of CH_2), 7.16–7.83 (m, 8H$_{arom}$). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.2, 64.2, 113.1, 114.2, 118.3, 120.4, 122.3, 128.7, 129.4, 130.0, 150.0, 166.0, 191.7. Mass (m/z): 255 (M^+). Analysis found: C, 70.28; H, 4.98; N, 5.28%. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%.

3.4.7. Compound 8g. Yellow needles (0.59 g, 71%), mp 166–167 °C; ν_{max} (KBr) 3022, 1603, 1580, 1456 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.31 (s, 3H, Me), 6.58 (d, 1H, J=13.0 Hz, one of CH_2), 6.63 (d, 1H, J=13.0 Hz, one of CH_2), 7.27 (d, 1H, J=9.0 Hz, 8-H), 7.88 (dd, 1H, J=9.0, 2.4 Hz, 7-H), 8.18 (d, 1H, J=2.4 Hz, 5-H) 7.15–7.81 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.3, 64.2, 113.2, 114.3, 118.4, 120.6, 122.5, 128.9, 129.7, 130.4, 150.2, 166.2, 191.8. Mass (m/z): 333 (M^+). Analysis found: C, 54.14; H, 3.49; N, 4.35%. Calcd for $C_{15}H_{12}BrNOS$: C, 53.90; H, 3.62; N, 4.19%.

3.4.8. Compound 8h. Yellow needles (0.75 g, 73%), mp 181–183 °C; ν_{max} (KBr) 3035, 1598, 1583, 1465 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.32 (s, 3H, Me), 6.59 (d, 1H, J=13.0 Hz, one of CH_2), 6.63 (d, 1H, J=13.0 Hz, one of CH_2), 7.85 (d, 1H, J=2.5 Hz, 7-H), 8.15 (d, 1H, J=2.5 Hz, 5-H) 7.17–7.84 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.3, 64.3, 113.2, 114.2, 118.5, 120.7, 122.7, 128.8, 129.6, 130.5, 150.3, 166.3, 191.9. Mass (m/z): 411 (M^+). Analysis found: C, 43.78; H, 2.50; N, 3.55%. Calcd for $C_{15}H_{11}Br_2NOS$: C, 43.61; H, 2.68; N, 3.39%.

3.4.9. Compound 8i. Yellow needles (0.52 g, 72%), mp 161–162 °C; ν_{max} (KBr) 3038, 1603, 1585, 1470 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.33 (s, 3H, Me), 6.59 (d, 1H, J=13.0 Hz, one of CH_2), 6.65 (d, 1H, J=13.0 Hz, one of CH_2), 7.28 (d, 1H, J=9.0 Hz, 8-H), 7.90 (dd, 1H, J=9.0, 2.4 Hz, 7-H) 8.20 (d, 1H, J=2.4 Hz, 5-H), 7.17–7.83 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.4, 64.3, 113.2, 114.5, 118.5, 120.8, 122.6, 128.9, 130.2, 135.3, 150.3, 166.4, 191.9. Mass (m/z): 289 (M^+). Analysis found: C, 62.01; H, 4.09; N, 5.00%. Calcd for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17; N, 4.83%.

3.4.10. Compound 8j. Yellow needles (0.63 g, 78%), mp 174–176 °C; ν_{max} (KBr) 3040, 1605, 1588, 1475 cm^{-1}. ^{1}H NMR (DMSO-d_6/TMS) δ: 2.34 (s, 3H, Me), 6.61 (d, 1H, J=13.0 Hz, one of CH_2), 6.65 (d, 1H, J=13.0 Hz, one of CH_2), 7.86 (d, 1H, J=2.5 Hz, 7-H) 8.17 (d, 1H, J=2.5 Hz, 5-H) 7.19–7.87 (m, 4H, 4-MeC_6H_4). ^{13}C NMR (DMSO-d_6/TMS) δ: 21.4, 64.4, 113.3, 114.4, 118.5, 120.9, 122.8, 129.1, 130.3, 135.4, 150.4, 166.5, 192.0. Mass (m/z): 323 (M^+). Analysis found: C, 55.28; H, 3.28; N, 4.49%. Calcd for $C_{15}H_{11}Cl_2NOS$: C, 55.57; H, 3.42; N, 4.32%.

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A new binding motif in molecular clips: 1-D polymeric self-inclusion in a phenol complex of a bis(methoxyphenyl)glycoluril

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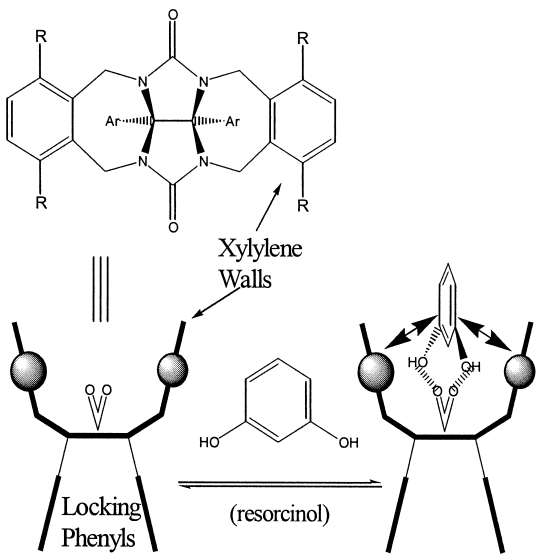
Dedicated to Professor Rory More O'Ferrall in his Emeritus Year

Abstract—Nolte's bis(*o*-xylylenyl)diphenylglycoluril molecular clips, in which the phenyls act as conformational 'locks' of the receptor site, have been modified with *p*-methoxy substituents on the phenyls. While this change does not have a major effect on the complexation of guests such as resorcinol (*m*-dihydroxybenzene) in chloroform solution, it allows for new binding geometries in the solid state. The crystal structure of new host 1,6:3,4-bis(1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)-imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**11**) complexed with 4-phenylphenol (4-PP) has been determined as its toluene solvate [(**11**):2(4-PP):0.5(C_7H_8)]. Molecules of **11** aggregate in 1-D chains through polymeric self-inclusion via C–H···π(aromatic) interactions: 2-D sheets form via aryl stacking of the 1-D chains and the 3-D structure consists of alternating sheets of **11** in between which sheets of (4-PP):0.5(C_7H_8) reside.

1. Introduction

Molecular recognition continues to be of major interest in the fields of host–guest chemistry and biomimetic chemistry.[1] Depending upon the need for selectivity in the recognition process, several types of interactions can play a role. In aqueous solution, the hydrophobic effect is often the main driving force for host–guest complex formation.[2] The selectivity of binding can be improved if additional interactions are involved, such as hydrogen bonding, electrostatic interactions, van der Waals forces, aryl stacking interactions[3] and metal-to-ligand interactions. The approach of using a combination of interactions is particularly important for receptors in organic solvents, because here the hydrophobic effect is lacking. Rebek[4] and Nolte,[5] amongst others, have used this approach to develop host systems that can bind guests based on hydrogen bonding and aryl stacking.

Nolte's bis(*o*-xylylenyl)diphenylglycoluril molecular clip has a cavity which is selective—in terms of shape and binding functions—for resorcinol (1,3-dihydroxybenzene), complexing it via two hydrogen bonds and two aryl stacking interactions in orthogonal dimensions (see Scheme 1).[5] The



Scheme 1.

Keywords: Molecular clip; X-ray crystallography; Co-crystal; Host–guest; Aryl stacking; Hydrogen bonding.
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phenyl substituents act as conformational 'locks', preventing the xylylene 'walls' from populating non-convergent conformations. They have also been able to control the self-assembly of derivatives of the glycoluril building block in such a manner that 3-D architectures of well-defined shape and dimension are formed: when long alkyl chains were attached to the phenyl substituents, interesting self-assembled architectures resulted.[6] The molecules adopt a bilayer structure through a mutual cavity-filling process (dimerisation) which, when combined with aryl stacking interactions, generates malleable crystalline thin films. Similarly, placing pyridine on the locking phenyls gives water-soluble clips that form well-defined nanoscale aggregates.[7] In the case of a naphthalene-walled clip, the complexation-induced NMR shifts observed indicated that two modes of self-association occurred, a 'head-to-head' dimerisation and a 'head-to-tail' one in which the pyridyl groups of one clip are docked in the cavities of a neighbour.[7]

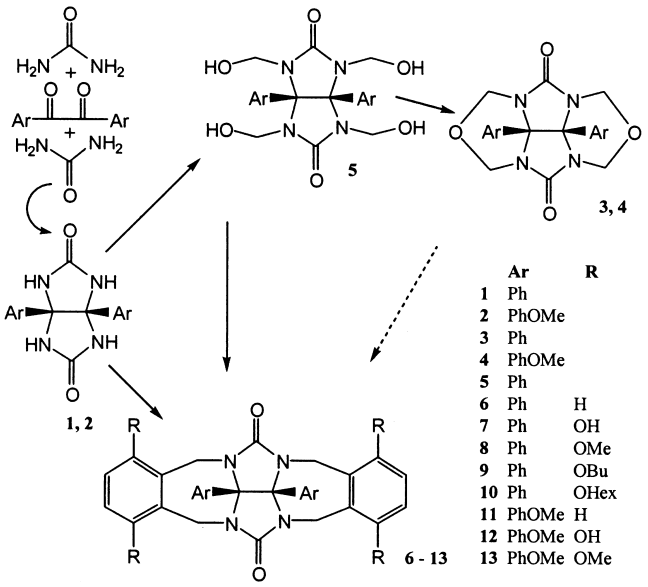
One of the goals of our research has been the design and synthesis of new types of cleft-shaped host molecules that can be functionalised with catalytically active components. Towards this goal, we have designed and studied receptor systems based on diphenylglycoluril (DPG) that can bind dihydroxybenzenes.[8] To examine the binding forces in our host–guest complexes more precisely, we have synthesised a series of new receptor molecules containing *p*-methoxy groups on one or both phenyls of the DPG building block. During this work, we carried out a series of co-crystallisation reactions between the methoxy-clips obtained and various mono- and di-hydroxy benzenes. The crystal structure of one such co-crystallisation is presented here. The new locking group appears to have little adverse effect on binding resorcinol in solution but opens up new intermolecular possibilities in the solid state.

2. Results and discussion

The coupling of DPG **1** (Ar=Ph, prepared from benzil and two ureas), its bis-ether **3** (Ar=Ph) and other tetramethylene derivatives of DPG with aromatic moieties belongs to a type of reaction known as amidoalkylation, or indeed in this case a ureidoalkylation (see Scheme 2). Two literature procedures have been employed in this communication.[5,8] By using these generalised methods the molecular clips **6** (Ar=Ph; R=H), **7** (Ar=Ph; R=OH), and **8** (Ar=Ph; R=OMe), were synthesised in good yields. These clips can then be used as starting points for further derivatisation of the clip structure.

From the tetrahydroxy-clip **7**, butyl- and hexyl-ethers (**9**, **10**; Ar=Ph; R=OBu, OHex) can also be formed by base-catalysed alkylation with the appropriate alkyl bromide.

Another less time-consuming procedure has previously been reported for the synthesis of the bis(xylenyl) clip **6**.[8a] This method cuts out the need to form the tetramethylene derivatives. The synthesis involves heating **1** (DPG) and potassium hydroxide in DMSO with α,α′-dibromo-*o*-xylene for 1–4 h. When the reaction is complete, it is simply added to water and the required product precipitates out in, typically, 80% yield. This reaction has three main



Scheme 2.

advantages: (i) it saves synthesising the tetramethylene derivatives, (ii) a much purer product is obtained more quickly, and (iii) because the tetramethylene compounds will not readily form with all glycolurils, it provides a synthesis for otherwise inaccessible clips. The main limitation, however, is that it is less convenient for clip receptors with substituted xylylene walls, since substituted dibromo-*o*-xylene compounds are not easily accessible.

4,4′-Dimethoxybenzil is commercially available, and we considered it as a potentially interesting alternative to benzil in the synthesis of clips. Besides observing the effects that a *para*-methoxy group would have on the binding properties of a molecular clip, it also opens up a variety of methods for further structural elaboration of the locking groups. Despite its obvious possibilities, it appears to have been bypassed in the literature as a candidate for use as the locking group: the focus elsewhere has been on bipyridyl, halide, and acid functionalities.[6,7] The ring-activating *p*-methoxy group on the locking phenyl could allow the possibility of electrophilic aromatic substitution *ortho*- to it. Alternatively, the methoxy group could be demethylated to give the more reactive hydroxyl for the purpose of immobilising/linking a molecular clip to a solid phase, or for producing phenolate salts to facilitate aqueous solubility, or for binding transition metal cations.

The glycoluril **2** (Ar=Ph-*p*-OMe) which was produced from 4,4′-dimethoxybenzil was synthesised using the same procedure as for **1** (DPG).[8] The substituted benzil was refluxed with urea in trifluoroacetic acid (TFA) and toluene, producing a precipitate. Using this method 4,4′-bis(methoxyphenyl)glycoluril **2** was isolated in 81% yield. The next step with **2** (as for **1**) was to form the tetramethylene derivatives. Proceeding as for **1**, 4,4′-bis(methoxyphenyl)glycoluril **2** and paraformaldehyde were dissolved in DMSO by the careful addition of base and stirred overnight, then following adjustment to pH 1 the tetramethylol intermediate **5** was heated to reflux to form the 4,4′-bis(methoxyphenyl)bisether **4** (Ar=Ph-*p*-OMe). The tetrakis(hydroxymethyl) derivative **5** could not be isolated: any attempts to

isolate this compound from DMSO failed. The bis(xylenyl) clip **11** (Ar=Ph-*p*-OMe; R=H) was formed by reacting **2** with excess dibromo-*o*-xylene under basic conditions, then precipitating the product by adding to water. Reactions of **2** with hydroquinone and 1,4-dimethoxybenzene, respectively, were also carried out to form the clips **12** and **13** (Ar=Ph-*p*-OMe; R=OH, OMe) in 97 and 77% yields.

Clip molecules **6**–**13** contain a cleft with a cavity size of approximately 6.35 Å [6.347(3) Å centroid-to-centroid distance for **11**, 4.167(2) Å for the centroids on the opposite or R group side] which has been shown to be ideal for the binding of aromatic guests.[5a,9] From these studies it is known that the main binding interactions in the formation of complexes of dihydroxybenzenes with molecular clip **6** in chloroform are: (a) hydrogen bonding between the OH groups of the guest and the urea carbonyl functions of the host, and (b) aryl stacking interactions between the aromatic surfaces of the guest and host. While independent research by our[8a,b] and Nolte's[5,9] group has involved the replacement of one or both carbonyl O atoms by S atoms, the design of clip molecules possessing zero, one or two cavity walls and the design of clips containing larger aromatic side-walls has been achieved by Nolte.[5,8,9] Furthermore, when clips with extended walls were built, i.e. naphthalene walls instead of phenyl walls, weak binding was found.[9] This weak binding has been ascribed to a repulsive aryl-stacking interaction between the aromatic guest and the naphthalene side walls. These studies have been carried out on a wide variety of clip molecules, all of which contain unsubstituted phenyl groups as the locking unit.

We have synthesised several molecular clips containing two 4-methoxyphenyl groups as the locking units (see Scheme 2). Complexation of a series of dihydroxybenzene guests with the molecular clips **6**–**13** were investigated by ^{1}H NMR titrations in $CDCl_3$. Table 1 shows the binding strength of the host–guest complex formed. On examination of this data, the two dihydroxy-substituted aromatics resorcinol and catechol show a remarkable difference in K_c, e.g. 3200 M^{-1} for resorcinol, and 95 M^{-1} for catechol when complexed with **13** compared to 200 M^{-1} for resorcinol, and 70 M^{-1} for catechol when complexed with **6**. On comparison with the values obtained for **8**, which has the methoxy groups only present on the walls, we observe quite similar values to **13**, that is 2400 M^{-1} for resorcinol, and 90 M^{-1} for catechol. This suggests that the perturbation of placing methoxy substituents on the locking phenyls has a minimal effect on the binding of resorcinol and catechol in solution. This point is further reinforced when a comparison of the binding of both **6** and **11** with resorcinol shows similar values (200 M^{-1} for **6** and 100 M^{-1} for **11**).

Table 1. The complexation constants, K_c/M^{-1}, of the molecular clips **6**–**13** with resorcinol (1,3-hydroxybenzene), catechol (1,2-hydroxybenzene), and orcinol (5-methyl-1,3-dihydroxybenzene) guests, measured at ~20 °C in $CDCl_3$, by titration of host (typically ~1 mM) with guest

Host	Resorcinol	Catechol	Orcinol
6	200 (±15)	70 (±10)	170 (±15)
7	370 (±40)	45 (±10)	–
8	2400 (±200)	90 (±15)	2300 (±200)
9	5100 (±400)	100 (±15)	4600 (±300)
10	4400 (±300)	60 (±10)	–
11	100 (±15)	–	–
12	350 (±40)	–	–
13	3200 (±250)	95 (±15)	2500 (±200)

Table 1 shows that binding decreased slightly using orcinol (5-methylresorcinol) as guest, as the electron-releasing methyl group decreases the acidity of the OH groups, thus weakening the hydrogen bonding, an effect seen by Nolte with other electron-releasing substituents.[9a,10]

The Table also shows the complexation results for a number of wall-substituted molecular clip receptors with resorcinol. On examination of this data we see an increase in K_c on going from H to OH to OCH_3 substituents in the aromatic walls of the hosts. The aromatic ring of the guest molecule can be considered to be π-rich overall. The position (e.g., *o*-, *m*-, *p*-) of the substituents on the aromatic ring alters the 'π-richness' of the individual atoms on that ring. This can leave some atoms more electron rich than others. The hosts increase in π-richness as we go from H to OH, i.e. **12** is more π-rich than **11**, and the further significant increase in complexation constant going from OH to OCH_3 substituents (i.e. from **12** to **13**) indicates a favourable 'cavity extension' effect. These trends are also seen in the diphenylglycoluril H/OH/OCH_3 series, **6**, **7**, and **8**, reaching a maximum (for the receptors we have prepared) at the tetrabutyloxy derivative, **9**. The lower K_c for tetrahexyloxy clip **10** may be entropic in nature: its melting point is also significantly lower than that of **9**.

The presence of oxy substituents on the cavity walls of some of the receptors (i.e., hydroxy in **7**, and alkoxy in **8**, **9**, and **10**) raises the possibility of: (i) alternative hydrogen bonding modes to dihydroxybenzene guests, with (ii) additional alternatives introduced for the new receptors with methoxies on the 'locking' phenyl moieties (i.e., **11**, **12**, and **13**). However, we did not observe any sign of an incursion of such binding modes in solution in our titration studies, nor—to our knowledge—has Nolte. Specifically, if a significant fraction of the host–guest complex in such a case were to involve a guest OH hydrogen bonding to a host oxygen other than the carbonyls, it is likely to be observed as an anomalous complexation-induced chemical shift change. For the example of hexamethoxy clip **13** and resorcinol, the wall or 'locking phenyl' methoxy singlet might be affected, and its associated aromatic hydrogens, and the induced changes in the aromatic hydrogens of resorcinol attendant on insertion into the cleft would be absent or attenuated. No such anomalous behaviour was observed.

While in theory chloroform's poor donor ability and its inability to act as an acceptor favour all host–guest hydrogen-bonding motifs by default, we believe there are sound theoretical reasons why alternative geometries would be insignificant in our case. Specifically, resorcinol and orcinol (and to a lesser extent catechol) have their hydroxyls optimally placed for the 5.8 Å spacing[8a] of the urea carbonyls of the host, an arrangement which also leaves the guest's aromatic ring sandwiched between the aromatic walls. Alternative hydrogen-bonding modes are unlikely to be as entropically favoured. Enthalpically, they would likely need two hydrogen bonds and two favourable aryl–stacking

interactions to compete. If an alkoxy oxygen accepts a hydrogen bond from resorcinol [alternative (i) above], the second OH cannot reach the opposite wall, and is not optimally placed for one of the carbonyls. An even less favourable arrangement pertains at the locking groups [alternative (ii)], where neither carbonyl can be employed. Ternary complexes—in which resorcinol hydrogen bonds to two separate clip molecules—should be insignificant at our concentrations.

A recent report[11] details measurements for self-association of 15 clips at high concentrations, including two in Table 1: **6** and **8**. The values reported (K_{dimer}=7 and 16 M^{-1}, respectively) suggest that dimerisation is a minor side reaction under our titration conditions. Dilution of 1 mM solutions of representative clips in Table 1 showed negligible changes in chemical shift.

Given the strong binding in many of these cases, we decided to look at the binding of monohydroxybenzenes, to see if reasonable complexation could be attained while sacrificing one host–guest hydrogen bond. In particular, we looked at 4-phenylphenol (4-PP), with the prototypical dimethoxy clip **11**. Attempts to carry out titration studies were thwarted by the poor solubility of this phenol in chloroform (a problem which also occurs for phenol itself). The complexation between two equivalents of 4-PP and one equivalent of the clip **11** was tried in toluene, heated to reflux temperature, since 4-phenylphenol has higher solubility in this solvent. A crystalline material was obtained from the reaction and the X-ray crystal structure determined.[12,13]

The structure of (**11**):2(4-PP):0.5(toluene) (Fig. 1) confirms the 1:2 nature of the interaction between **11** and 4-phenylphenol, with toluene present as a (hemi)solvent of crystallisation. The hydroxyl of each phenol is hydrogen-bonded to a carbonyl oxygen of **11** [O–H···O distances and angles of 2.700(4) and 2.733(4) Å, and 169 and 165°, respectively], but neither 4-PP resides within the cleft/cavity. Instead, a methoxy group from the locking phenyl system of a neighbouring molecule is enclathrated there (see Figure 1b).[14–16] Interestingly, the two methoxy groups are observed as identical in $CDCl_3$ solution in both ^1H and ^{13}C NMR.

The crystal structure of (**11**):2(4-PP):0.5(toluene) can be rationalised as having molecules of **11** aggregate in 1-D chains along the *a*-axis, through polymeric self-inclusion processes via complementary methyl C–H···π(C_6H_4) and phenyl C–H···π(C_6H_4)/offset π···π stacking interactions,[14] (depicted in Figure 2, left): these 1-D chains pack and form 2-D sheets through further π···π stacking contacts while the overall 3-D structure consists of alternating 2-D sheets of **11** (Fig. 2, right) in between which 2-D sheets of the hydrogen-bonded guest/solvate 2(4-PP):0.5(C_7H_8) reside. The 2-D sheets are of course linked by the stronger O–H···O=C bonds.

The complementary self-inclusion process and encapsulation in the crystal structure of (**11**):2(4-PP):0.5(toluene) often arises in macrocyclic hosts e.g. calix[*n*]arenes.[14–18] These systems contain molecular cavities and the inclusion process typically arises when the stronger hydrogen bond donors and acceptors e.g. O–H···O pair off and molecular aggregation and crystal stability is enhanced by multiple weaker C–H···π(aromatic) interactions which ensue on formation of the 3-D crystal structure. In (**11**):2(4-PP):0.5(toluene), two strong C=O acceptors form hydrogen bonds with the two strong O–H (4-PP) donors. The remaining possible donor/acceptors facilitate the filling of the larger molecular cavity of **11** by the *para*-methoxyphenyl group of a symmetry-related molecule **11***: this in turn has its smaller *para*-methoxyphenyl cleft filled by the *o*-phenylene group of **11**. The 1-D chain builds up from these complementary head-to-tail interactions. The crystal structure then aggregates as described above.

In summary, the molecular recognition properties of glycoluril-based molecular clips have prompted many groups to broaden the range of study of these hosts. We have synthesised and studied molecular clips based on the 4,4′-bis(methoxyphenyl)glycoluril. We find an interesting aggregation occurring in the solid state when a monohydroxyaromatic is used as guest rather than the *meta*- or *ortho*-dihydroxyaromatics previously studied. We are currently investigating the solid-state interaction between

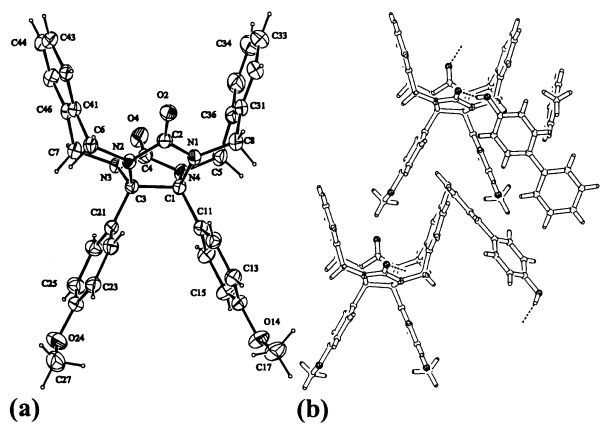


Figure 1. Crystal structure of (**11**):2(4-phenylphenol): (a) labeled structure of molecular clip (**11**) moiety; (b) highlight of clip/clip and clip/4-PP interactions (toluene hemi-solvent of crystallization omitted for clarity).

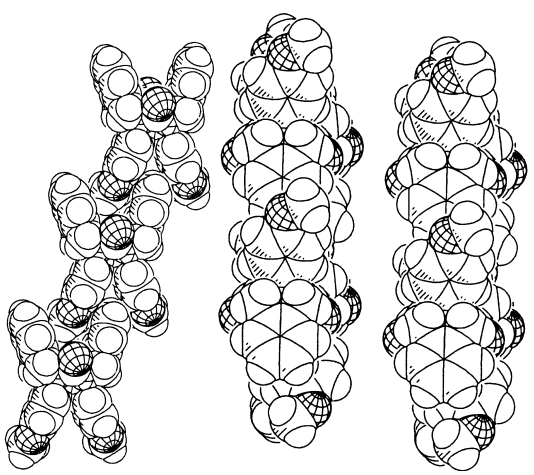


Figure 2. Side-on views of clip moieties in the co-crystal.

the prototype clip **6** and 4-phenylphenol, and also solution studies of the bis(dimethoxyphenyl) clips in toluene. In addition, the minimal effect that the remote methoxy groups have on binding guests in solution holds out considerable promise. Future demethylation of these receptors can provide free phenol functions to facilitate alkaline solubility, complexation of transition metal ions, or covalent attachment to solid-phase support.

3. Experimental

3.1. General

All syntheses were carried out under an inert nitrogen atmosphere. All solvents were distilled using standard procedures. All chemicals were commercial materials used without further purification. Compounds **1**, **3**, **5**, **6**, **7**, and **8** were prepared as described in the literature.[8a] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) with Me_4Si as internal standard using a JEOL JNM-LA300 FT NMR spectrometer, with resolutions of 0.18 Hz and 0.01 ppm, respectively. IR spectra (KBr disc) were measured on a Nicolet Impact 410 FT-IR. Melting points were >300 °C (except **10**). Elemental analyses were carried out at the Microanalytical Laboratory of University College, Dublin.

Table 2 below shows ^{1}H and ^{13}C NMR data for the new compounds, organized by atom type. All were white solids. Details of their syntheses, together with elemental analytical and other data, are also provided below.

3.1.1. 3a,6a-Bis(4-methoxyphenyl)-tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (2).

Urea (3.0 g, 50 mmol), 4,4′-dimethoxybenzil (6.76 g, 25 mmol), TFA (6 mL), and dried toluene (75 mL) were heated to reflux using a Dean and Stark apparatus for 4 h. After cooling, the reaction solution was kept at 0 °C overnight. The resulting precipitate was collected by filtration, washed with IMS (3×100 mL) and acetone (3×50 mL), and then dried to a constant weight under vacuum: yield 7.2 g (81%). IR/cm^{-1}: 3220 (NH), 1684 (C═O). $C_{18}H_{18}N_4O_4$ theory: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.05; H, 5.15; N, 15.92.

3.1.2. 1,6:3,4,-Bis(2-oxapropylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (4).

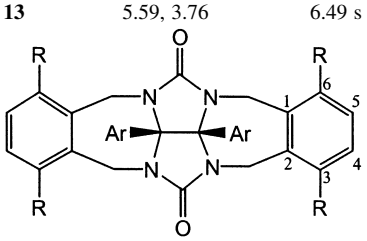
4,4′-Bis(methoxyphenyl)glycoluril (**2**) (0.74 g, 2.1 mmol) and paraformaldehyde (0.33 g, 11 mmol monomer, 30% excess) were stirred in DMSO (6 mL) at ambient temperature. The reaction was adjusted to pH 9 with a 10% aqueous NaOH solution (dropwise, very slowly, until solution is just attained), and stirred at room temperature for 18 h. After this time, the clear solution was brought to pH 1 with conc. HCl and heated to reflux for 2 h. After cooling, the white precipitate that formed was collected by filtration, washed with water (2×100 mL) and ethanol (3×50 mL) and dried to a constant weight under vacuum: yield 0.90 g (99%). IR: 1717 (C═O). $C_{22}H_{22}N_4O_6$ theory: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.45; H, 5.10; N, 12.88.

3.1.3. 1,6:3,4-Bis(3,6-dibutyloxy-(9) and 1,6:3,4-bis(3,6-dihexyloxy-1,2-xylylene)tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (10).

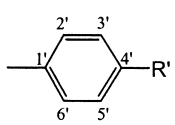
Tetrahydroxy

Table 2. ^{1}H (top) and ^{13}C (bottom) NMR data for **2**, **4**, **9**, **10**, **11**, **12**, and **13**: wall aryl ring numbered 1–6 and locking phenyl numbered 1′–6′, as per structure (centre)

#	H_a–C–H_b	$H_{3,6}/H_{4,5}$	$H_{2',6'}/H_{3',5'}/H_{4'}$	Me
2			6.97/6.64/–	3.62
4	5.65, 4.57		7.08/6.68/–	3.72
9	5.57, 3.87	6.65 s	7.04 (m, 10H)	
10	5.55, 3.89	6.65 s	7.04 (m, 10H)	
11	4.78, 4.19	7.25–7.08m	7.03/6.69/–	3.72
12	5.37, 3.58	6.55 s	6.92/6.77/–	3.65
13	5.59, 3.76	6.49 s	6.98/6.65/–	3.70



Ar =



#	CO	C_qN	H_aCH_b	$C_{1,2}/C_{3,6}/C_{4,5}$	$C_{1'}/C_{2',6'}/C_{3',5'}/C_{4'}$	Me
2	165.9	86.7			130.2/129.2/116.6 /161.6	57.5
4	160.2	79.5	71.9		124.5/129.2/114.1/158.5	55.3
9	157.9	85.1	37.0	135.1/151.3/114.0	128.6/128.2/127.9/127.1*	
10	158.0	85.1	37.1	134.6/150.7/113.5	128.3/128.2/128.1/128.0*	
11	159.9	85.3	45.3	136.9/129.4/127.7	125.6/129.5/114.1/157.9	55.3
12	159.0	84.5	36.5	129.2/146.9/115.1	125.0/128.0/113.9/156.8	55.1
13	160.1	84.5	36.7	128.0/151.5/113.9	126.2/129.5/112.6/157.5	55.9

(a) NMR in $CDCl_3$, at ~20 °C, except DMSO-d_6 for **2**, **12**. (b) ^{1}H coupling constants/Hz for CH_2=11.1, 15.8, 16.0, 15.6, 15.8, 16.0 (**4**, **9**–**13**); for *p*-MeOPh=8.6–8.8 (**2**, **4**, **11**, **12**, **13**). (c) Other NMR signals: NH of **2**=7.64 (exch. D_2O); butyl of **9**=3.95, 1.84, 1.60, 0.98; 69.9, 31.7, 19.3, 13.9; hexyl of **10**=3.81, 1.83, 1.50, 1.35, 1.34, 0.91; 70.3, 31.6, 29.6, 25.8, 22.6, 14.1; OH of **12** not seen; methyl (on aromatic wall) of **13**=3.80; 55.2. *CHs not individually assigned.

clip **7** (0.45 g, 0.80 mmol), 1-bromobutane (0.43 mL, 0.55 g, 4.0 mmol, 25% excess) in DMSO (20 mL) were dissolved at 110 °C. Anhydrous potassium carbonate (1.72 g, 12.5 mmol) was then added in one portion and heating continued for 48 h. The reaction was poured onto water (150 mL) and stirred for 20 min. After addition of Hyflo-Supercel (6 g) to the solution, it was filtered and washed thoroughly with water. Extraction with $CHCl_3$ (50 mL×3), followed by drying with $MgSO_4$ yielded 0.41 g **9** (65%). IR: 1674 (C═O). $C_{48}H_{58}N_4O_6$ theory: C, 73.26; H, 7.43; N, 7.12. Found: C, 73.67; H, 7.55; N, 7.24. Compound **10** was similarly prepared using 1-bromohexane. Yield: 1.17 g (73%); mp 260–265 °C. IR: 1657 (C═O). $C_{56}H_{74}N_4O_6$ theory: C, 74.80; H, 8.29; N, 6.23. Found: C, 75.08; H, 8.33; N, 6.19.

3.1.4. 1,6:3,4-Bis(1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxy-phenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (11). 4,4′-Bis(methoxyphenyl)glycoluril (**2**) (0.49 g, 1.4 mmol) and freshly ground potassium hydroxide (0.80 g, 14 mmol) in DMSO (10 mL) were heated to 120 °C with vigorous stirring for 20 min. α,α′-Dibromo-*o*-xylene (0.80 g, 3.0 mmol) was added in one portion and stirring was continued at this temperature for 2 h. On cooling, the reaction mixture was added to water (100 mL) and stirred for 30 min. The resulting precipitate was collected by filtration, washed with water (3×100 mL) and ether (3×50 mL), and reduced to dryness under vacuum to yield 0.50 g (65%). IR: 1690 (C═O). $C_{34}H_{30}N_4O_4$ theory: C, 73.10; H, 5.41; N, 10.03. Found: C, 72.89; H, 5.36; N, 9.93.

3.1.5. 1,6:3,4-Bis(3,6-dihydroxy-1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (12). 4,4′-Bis(methoxyphenyl)glycoluril bisether (**4**) (0.34 g, 0.78 mmol), *p*-toluenesulfonic acid monohydrate (0.60 g, 3.2 mmol) and 1,2-dichloroethane (7 mL) were placed in a 25 mL round-bottomed flask fitted with a Dean and Stark apparatus containing 4 Å molecular sieves, and heated to reflux with stirring for 10 min. Hydroquinone (0.33 g, 3.0 mmol) was added in one portion and the reaction was further refluxed for 2 h. A brown precipitate formed. On cooling, 1,2-dichloroethane (12 mL) was added. The resulting solid was collected by filtration, washed with water (2×50 mL), ethanol (2×50 mL), and ether (3×30 mL), and dried to constant weight under vacuum to yield 0.47 g (97%). IR: 3400 (OH), 1710 (C═O). $C_{34}H_{30}N_4O_8$ theory: C, 65.59; H, 4.86; N, 9.00. Found: C, 65.17; H, 4.71; N, 8.93.

3.1.6. 1,6:3,4-Bis(3,6-dimethoxy-1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (13). 4,4′-Bis(methoxyphenyl)glycoluril bis-ether (**4**) (0.219 g, 0.50 mmol), acetic anhydride (0.5 mL), and trifluoroacetic acid (0.5 mL) were heated with stirring to 95 °C for 30 min. 1,4-Dimethoxybenzene (0.15 g, 1.1 mmol) was added in one portion; stirring and heating were maintained for 1 h. On cooling, methanol (2 mL) was cautiously added, and the resulting precipitate was collected by filtration, washed with water (2×50 mL), and reduced to dryness under vacuum: yield 0.26 g (77%). IR: 1729 (C═O). $C_{38}H_{38}N_4O_8$ theory: C, 67.25; H, 5.64; N, 8.26. Found: C, 66.99; H, 5.61; N, 7.95.

Acknowledgements

J.F.G. to Dublin City University for the purchase of a Siemens-Bruker P4 diffractometer; J.P.McD. to the Graduate Training Programme; B.S.C., J.Mc.G., and B.A.M. to the Irish Higher Education Authority for its funding of the NCSR; B.A.M. to Syntex, University College Dublin, and Enterprise Ireland, for initial funding of this work.

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12. Crystallographic data: chemical formula $C_{61.5}H_{54}N_4O_6$, molecular weight 945.09 g mol^{-1}, triclinic, space group $P\bar{1}$ (No. 2), a=11.5618(16), b=14.1207(19), c=15.7993(19) Å, α=88.368(10), β=74.618(12), γ=86.119(12),

V=2481.2(6) Å^3, Z=2, T=296(2) K, density=1.265 g cm^{-3} (calc.), F(000)=998, μ=0.082 cm^{-1}, 8615 reflections in the range 2–25°, 8171 unique (4153 with $I>2\sigma I$), 670 parameters, R-factor is 0.066, wR_2=0.136 (based on F^2 for reflections with $I>2\sigma I$), Gof=1.02, density range in final Δ-map is −0.26 to +0.29 e A^{-3}, (solved in SHELXL97, refined in SHELXL97).

13. The crystallographic data for **11**:2($C_{12}H_{10}O$):0.5(C_7H_8) have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 190122. Copies may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).
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Synthesis and stereochemical studies of di and tetra 9,9′-spirobifluorene porphyrins: new building blocks for catalytic material

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Abstract—We report the synthesis and stereochemical properties of a new class of molecules containing a covalently-linked porphyrin and spiro-9,9′-bifluorene derivatives. The large spiro substituents hinder rotation about the *meso* position to give atropisomers which can be detected by ^{1}H NMR after phosphine or isocyanide complexation to the ruthenium spiroporphyrins.

1. Introduction

A series of spiro-bridge polymers based on 9,9′-spirobifluorene have been recently synthesized.[1–4] Since the bifluorene rings are orthogonally arranged through a tetracoordinated carbon, it is expected to enhance the rigidity of the polymer and the thermal stability.[2,3] In addition to model receptors for chiral recognition,[5] spiro derivatives provide a potentially useful stereochemistry[6] that makes the molecules suitable for interconnection in future molecular devices.[7,8] Three dimensional polymers can also be prepared by anodic oxidation of spirobifluorenes.[9,10] Giving the importance of these polymers, incorporation of metalloporphyrins to spirobifluorene polymers is an attractive approach to obtain materials for heterogeneous catalysis. The major synthetic challenge is to prepare a pool of monomers containing a covalently-linked porphyrin and a spirobifluorene. Recently, we reported a preliminary communication on a new class of manganese-porphyrin-polymers as heterogeneous oxidation catalysts.[11] In complement to this work, here we report the synthesis of 9,9′-spirobifluorene porphyrins in which spirobifluorene groups have been attached at the *meso* positions.[12] Two generations of porphyrins, di and tetra 9,9′-spirobifluorene porphyrins, were employed to determine the effect of the bulky spirobifluorene groups on the periphery of the porphyrin ring. Thus, the presence of spirobifluorene groups gives substantial steric hindrance and atropisomers can be detected by ^{1}H NMR.

Keywords: Spirobifluorene; Porphyrins; Ruthenium; Atropisomer; Phosphine.
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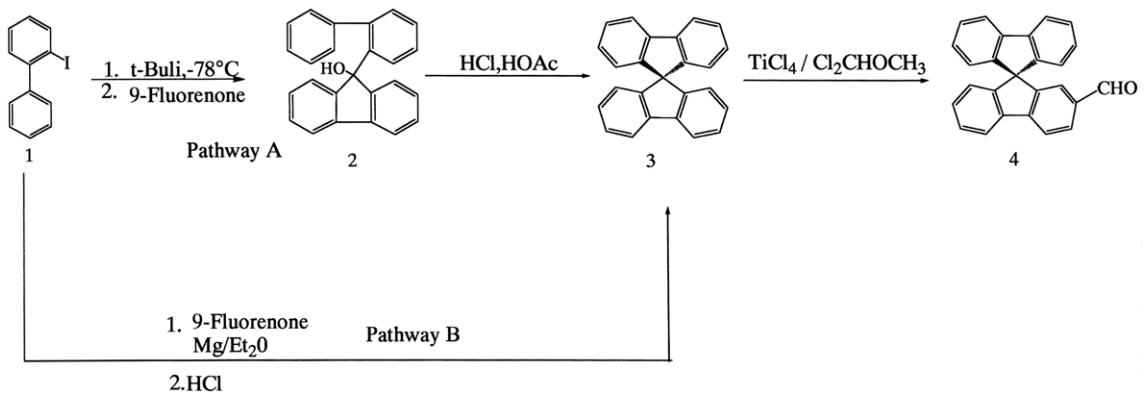
2. Results and discussion

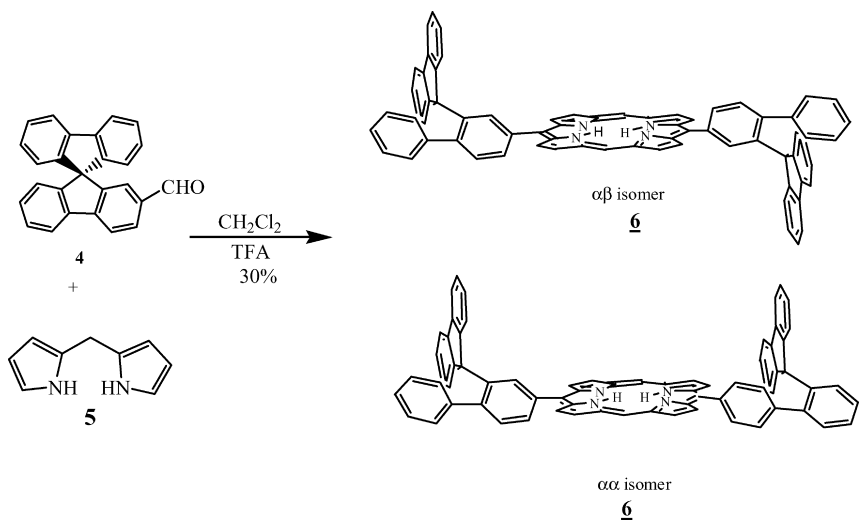
2.1. Synthesis of 9,9′-spirobifluorene-2-carbaldehyde

We decided to explore a method for preparing 9,9′-spirobifluorene-2-carbaldehyde that can be scaled-up to multigram quantities. The synthetic approach to 9,9′-spirobifluorene and then its monoformylated compound is outlined in Scheme 1. 9,9′-Spirobifluorene was prepared from two different ways of synthesis, both of them used 2-iodobiphenyl synthesized from commercially available 2-amino-biphenyl and 9-fluorenone.[13,14] The first way (A), which was described by Tour et al.[13] used a strong base *t*-butyllithium in very drastic conditions has been first tested (Scheme 1). The intermediate 9-(1,1′-biphenyl-2-yl)-9*H*-fluoren-9-ol **2**, obtained before cyclization and dehydratation has been isolated. Thus condensation of 2-iodo-1,1′-biphenyl to 9-fluorenone in *t*-BuLi/pentane solution afforded 9-(1,1′-biphenyl-2-yl)-9-*H*-fluoren-9-ol as an intermediate in 60% yield. Refluxing this intermediate in acetic acid in presence of a few drops of HCl (13N) gave the expected 9,9′-spirobifluorene with 90% yield. However, the second pathway (B) has been preferred giving better yield, in a one pot and mild reaction. This procedure is modified from the one reported by Winter-Werner in 1996.[14]

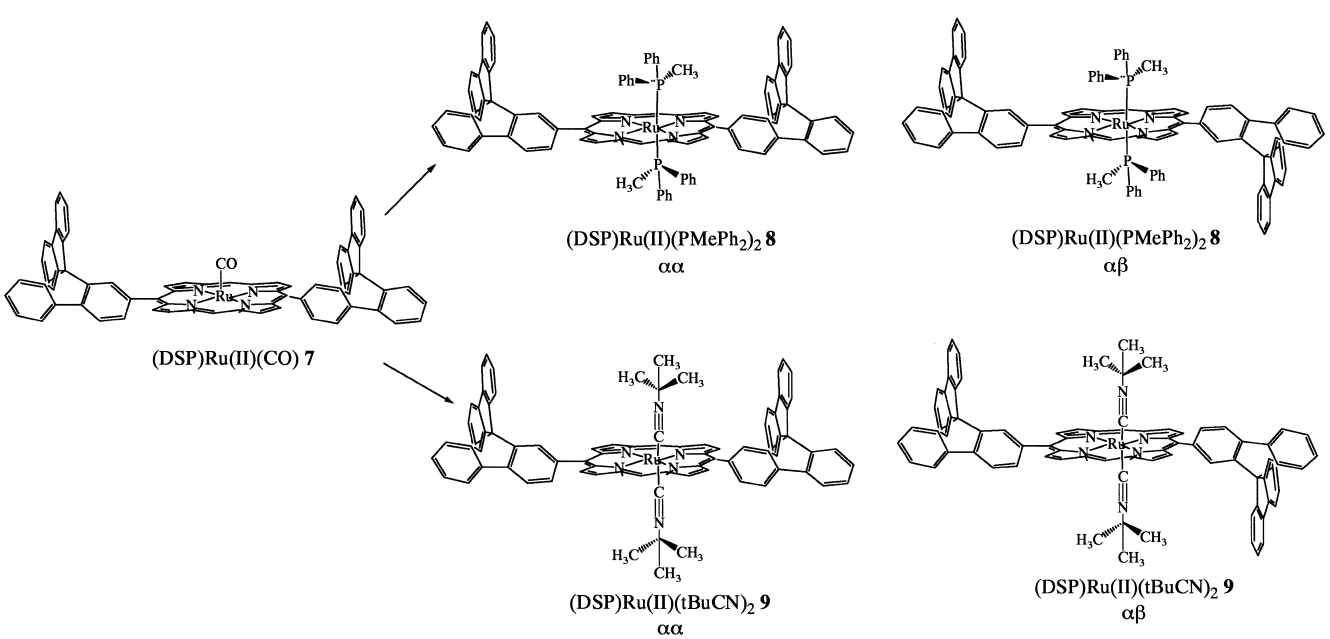
A general synthesis of monosubstituted derivative of 9,9′spirobifluorene via electrophilic substitution is difficult leading to mixture of di and mono substituted compounds.[15] Monoformylation of the spiro compound to prepare 9,9′-spirobi[fluorene]-2-carbaldehyde **4** was however realized using $TiCl_4/Cl_2CHOCH_3$ reagent with 65% yield. A related route to 9,9′-spirobifluorene-2-carbaldehyde has been recently described with a lower yield (30%).[16]



Scheme 1.



Scheme 2.



Scheme 3.

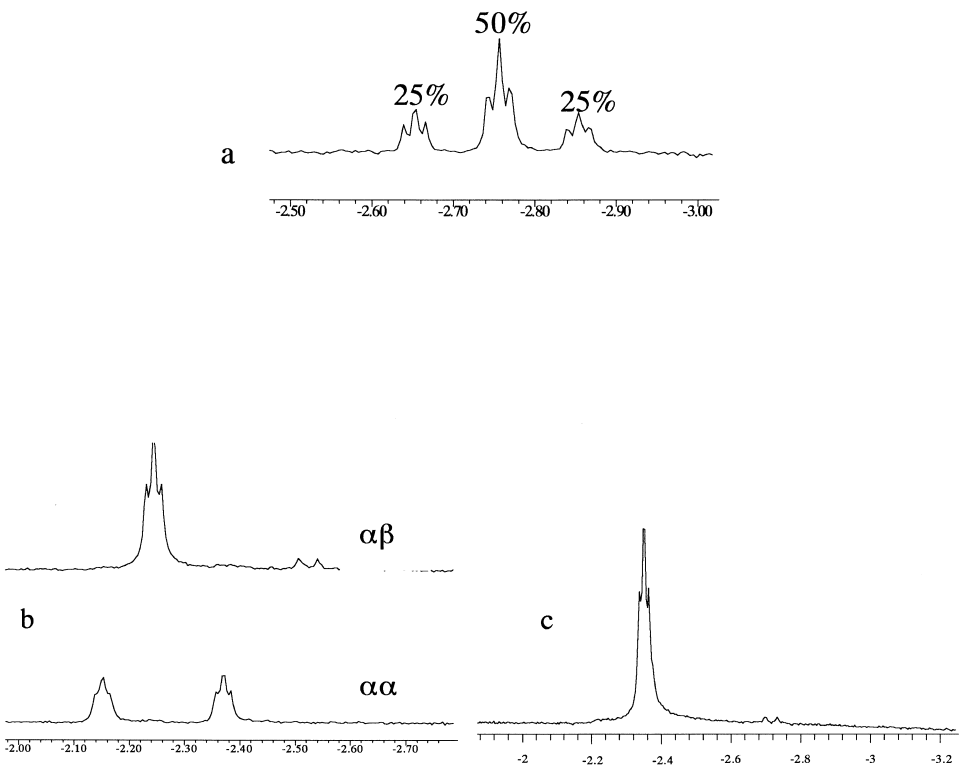
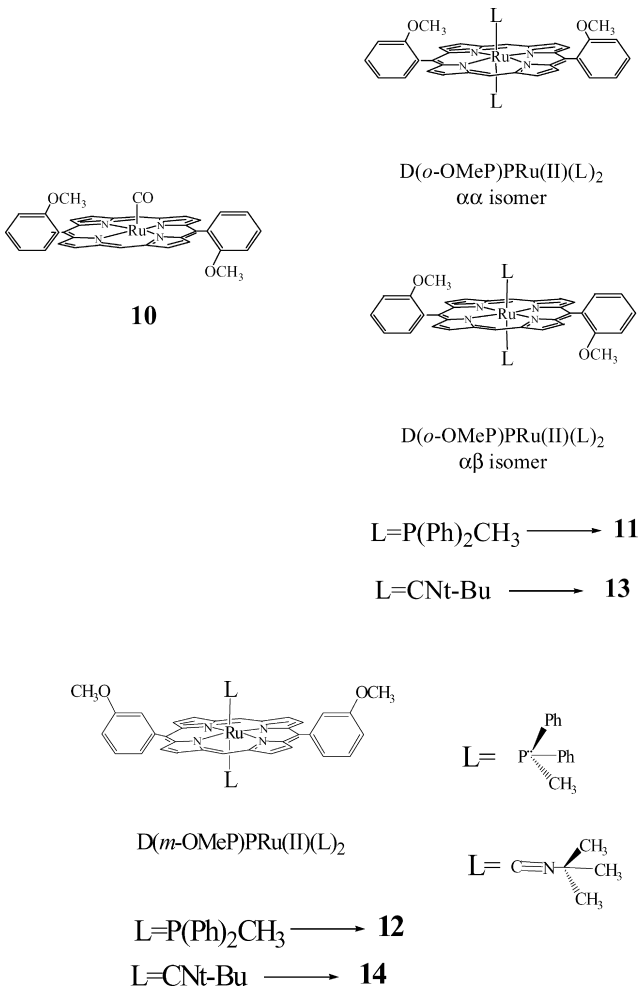


Figure 1. High field portion of the ^{1}H NMR spectrum for compounds **8**, **11** and **12** ($CDCl_3$). (a) Mixture of atropisomers (DSP)Ru(II)$(PMePh_2)_2$ **8**. (b) Separated atropisomers of D(*o*-OMeP)PRu(II)$(PMePh_2)_2$ **11**. (c) D(*m*-OMeP)PRu(II)$(PMePh_2)_2$ **12**.



Scheme 4.

2.2. Syntheses of dispiroporphyrins

Due to possible difficulties with the synthesis of tetraspiroporphyrins bearing bulky substituents such as 9,9′-spirobifluorene, we decided first to target porphyrins bearing only two spirobifluorene groups. Such 5,15-disubstituted porphyrins are typically synthesized from a dipyrromethane derivative and an aldehyde.[17,18] This would be expected to yield a mixture of just two porphyrins if there are atropisomers. The bis-5,15-(9,9′-spirobifluoren-2-yl) porphyrin **6** (called DSP for simplication) was synthesized by condensation of 9,9′-spirobifluorene-2-carbaldehyde **4** and dipyrromethane **5**[19] in dichloromethane with trifluoroacetic acid catalysis. A mixture of porphyrins was isolated and separated by column chromatography and found to contain a small amount of monospiroporphyrin along with another porphyrin that we expected to be the dispiroporphyrin. However, identification of this major product was not straightforward. Mass spectrometry gave a molecular ion consistent with **6** but ^{1}H NMR spectroscopy did not give the simple spectra that we have expected. Furthermore this *meso* free porphyrin is insoluble in a variety of common organic solvents such as dichloromethane, chloroform, acetone and dimethylformamide. Due to this strong insolubility, the ^{1}H NMR spectrum was recorded by adding deuterated trifluoroacetic acid steam in the NMR tube. The ^{1}H NMR (500 MHz) spectrum showed an unusual slight splitting of the *meso* and β pyrrole hydrogen according possibly to two rotational isomers (αα and αβ (Scheme 2).

In the αα atropisomer, the substituents attached to the *meso*-aryl groups lie on the same side of the porphyrin plane, in the α,β atropisomer on opposite sides. Although

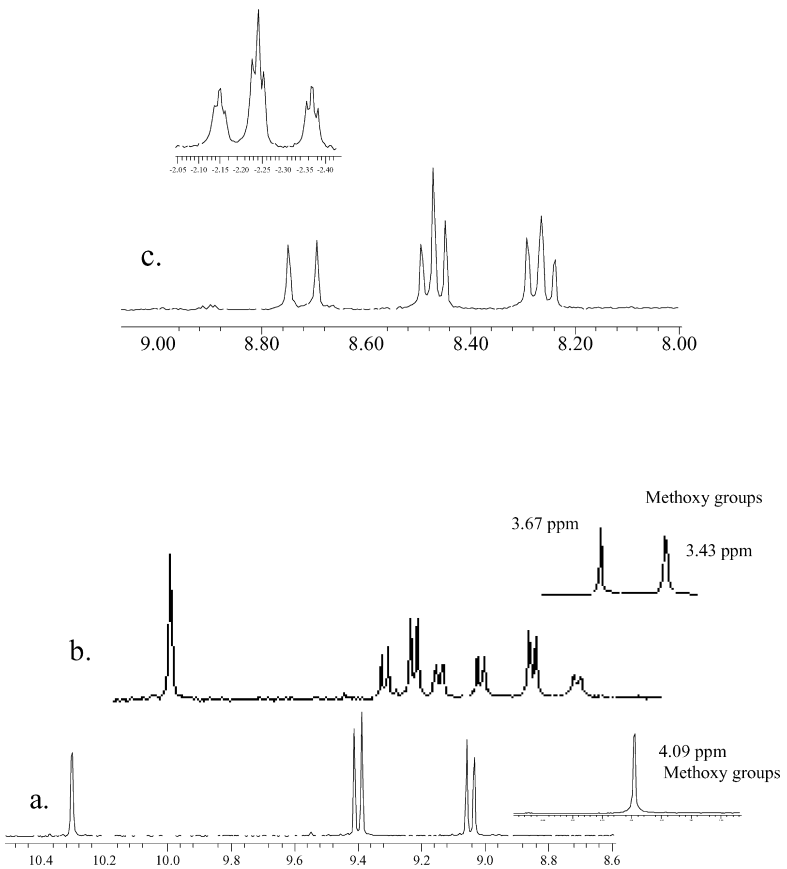


Figure 2. Low field portion of the ^{1}H NMR spectrum: (a) for compound D(*o*-OMeP)PH_2 (αα+αβ); (b) for D(*o*-OMeP)PRu(II)(CO) **10** (αα+αβ); (c) for D(*o*-OMeP)PRu(II)$(PMePh_2)_2$ **11** (αα+αβ) ($CDCl_3$).

atropisomers are not expected when the *meso*-aryl groups are substituted in *meta* position,[20] the large size of the 9,9′-spirobifluorene group may hinder rotation around the $C_{meso}-C_{aryl}$ bond.

2.3. Ruthenium complexation to dispiroporphyrins and stereochemistry

To confirm atropisomerism, the ruthenium complex (DSP)RuII(CO) **7** was first prepared by treatment of **6** with $Ru_3(CO)_{12}$ in highly degassed *o*-dichlorobenzene at 160 °C during 2 h. Then it was decided to study a possible atropisomerism through the complexation of two identical axial ligands. Indeed, complexation of methyldiphenylphosphine or *t*-butylisocyanide offered the greater simplicity because these bis-ligated complexes provided a ruthenium molecule with two topologically identical faces for the α,β isomer and two different faces for the α,α isomer (Scheme 3). The ^{1}H NMR spectrum of the bis(methyldiphenylphosphine) adduct (DSP)Ru(II)$(PMePh_2)_2$ **8** displayed two singlets for the *meso* hydrogens as expected for the presence of two isomers. Moreover the spectrum showed one triplet for the methyl resonance of the axial ligands with the α,β isomer and two triplets of the same intensity for the methyl resonance of $PMePh_2$ for the α,α isomer (Fig. 1(a)). The triplets are due to virtual coupling as reported for similar complexes.[21] These data suggest the presence of a mixture of two conformers, an *anti* (C_{2h} symmetry) and a *syn* isomer (C_{2v} symmetry). It should be underlined that the atropisomerism can also be observed for the *ortho* proton atoms of the phenyl rings of the phosphine ligands for complex **8**.

Since the ^{1}H NMR spectrum showed multiple resonances for the phosphine ligand consistent with atropisomers, variable temperature ^{1}H NMR studies were undertaken to determine the activation energy for aryl rotation in compound **8**. At the coalescence temperature (361 K), free energy of 20.26 kcal/mol was calculated. As recently reported for a porphyrin–carborane system,[22] and a porphyrin–fullerene system,[23] the large size of 9,9′spirobifluorene substituent in meta position increases the energy barrier for aryl rotation; no attempts were made to separate the two atropisomers of compound **8** given the short lifetimes calculated from the activation energy.

To confirm that aryl-porphyrin rotation[24] was the dynamic process being observed, we synthesized the diarylporphyrins bearing methoxy groups in *ortho* position[18] (Scheme 4) and their ruthenium derivatives D(*o*-OMeP)-PRu(II)(CO) **10**. In this case, we were able to separate the mixture of the two atropisomers by silica gel chromatography. As already shown for **6**, the mixture of atropisomers of the free base presented a quite identical ^{1}H NMR (Fig. 2(a)) spectra but the lost of symmetry in the αβ isomer after ruthenium complexation induces a difference in the ^{1}H NMR spectrum (Fig. 2(b)). Indeed the αα isomer exhibits two doublets for β pyrrole protons and four separated doublets can be detected for the αβ isomer in the spectrum.

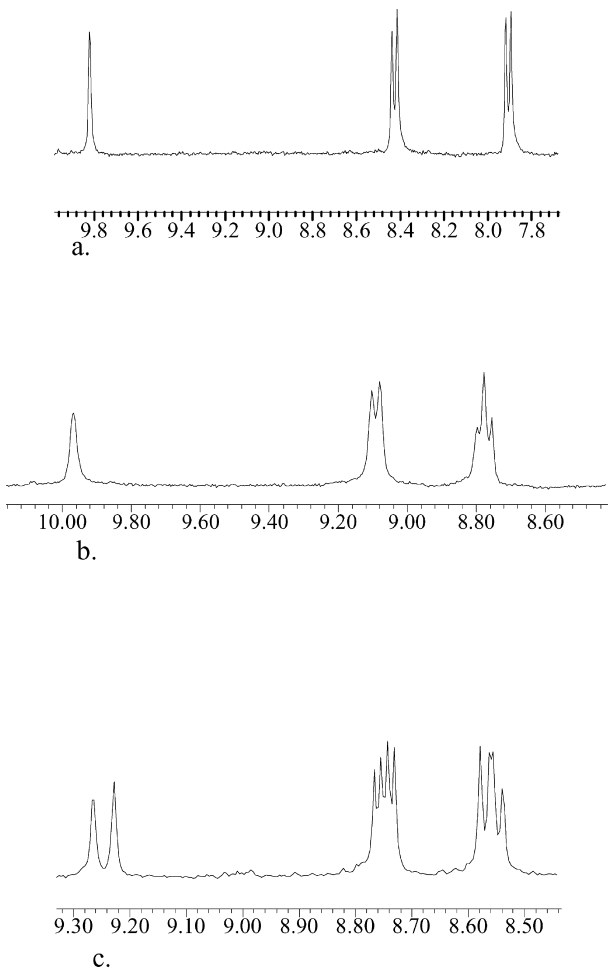


Figure 3. Low field portion of the ^{1}H NMR spectrum: (a) for (DSP)H_2 **6**; (b) for (DSP)RuII(CO) **7**; (c) for (DSP)Ru(II)$(PMePh_2)_2$ **8**.

^{1}H NMR spectrum of the bis(methyldiphenylphosphine) adduct, D(*o*-OMeP)PRu(II) $(PMePh_2)_2$ **11**, was obtained from addition of an excess of ligand to each atropisomer of the D(*o*-OMeP)PRu(II)(CO) precursor **10**. This lead us, in analogy, to assign the two triplets for α,α isomer and the single triplet to the other isomer (Fig. 1(b)). Thermal atropisomerization of each pure isomer in dimethylformamide at 140 °C lead to the statistical mixture 1:1. The synthesis of ruthenium(II) diarylporphyrin complex bearing methoxy groups in *meta* position D(*m*-OMeP)PRu(II)$(PMePh_2)_2$ **12** was also performed. As expected, the spectrum did not show the presence of isomers, displaying only one signal for the methyl group (Fig. 1(c)).

Conformational effect was also established by examining the ^{1}H NMR splitting pattern of the *meso* and pyrrole protons in the low-field part of the spectrum of **8** and **11** which showed two different *meso* protons due to the phosphine complexation (Fig. (3c)). In contrast, only one *meso* proton is detected in **6** and **7** (Fig. (3a,b)).

Observation of phosphorus NMR may be a second possibility to see two different topological faces in theses complexes. The ^{31}P NMR spectra were performed for all the bis phosphine ligated compounds but the sensitivity of this nucleus did not permit to distinguish the different faces of each atropisomer. Indeed, for the (DSP)Ru(II)$(PMePh_2)_2$ **8** complex, only two signals of the same intensity were detected at 2.66 and 2.55 ppm (free ligand: −26.6 ppm), one for αβ isomer and one for the αα isomer. In the later case, the two different faces were not detected by ^{31}P NMR. Such a situation has been already observed for ruthenium picket fence porphyrin.[25]

In order to precise the influence of the steric hindrance caused by the two bulky phenyl groups of the phosphine above the porphyrin ring, *t*-butylisocyanide complexes were also prepared for all compounds previously described. (DSP)Ru(II)(*t*-BuCN)$_2$ **9** was prepared by addition of excess of ligand to the precursor (DSP)Ru(II)(CO) **7** (85%). As expected, the ^{1}H NMR spectrum showed three resonances for the *t*-butyl groups due to the presence of the two conformers (Fig. 4(b)). This complex displayed one singlet for the α,β isomer (−0.70 ppm) and two singlets (−0.57, −0.94 ppm) of the same intensity for the α,α isomer due to inequivalent faces. These results were also compared with the pure αβ and αα D(*o*-OMeP)PRu(II)(*t*-BuCN)$_2$ **13** isomers which exhibit respectively, one and two singlets. As expected, the meta D(*m*-OMeP)PRu(II)(*t*-BuCN)$_2$ complex **14** showed only one singlet for the *t*-butyl groups (Fig. 4(a)).

In order to extend the synthesis and the study of dispiroporphyrins, an other dipyrromethane was synthesized. The choice of 4,4′diethyl-3,3′dimethyl-2,2′dipyrromethane **15** as starting material was not arbitrary. As previously reported by Young and Chang for other *meso*-diphenylporphyrins,[24] the ethyl side chains on β pyrrole

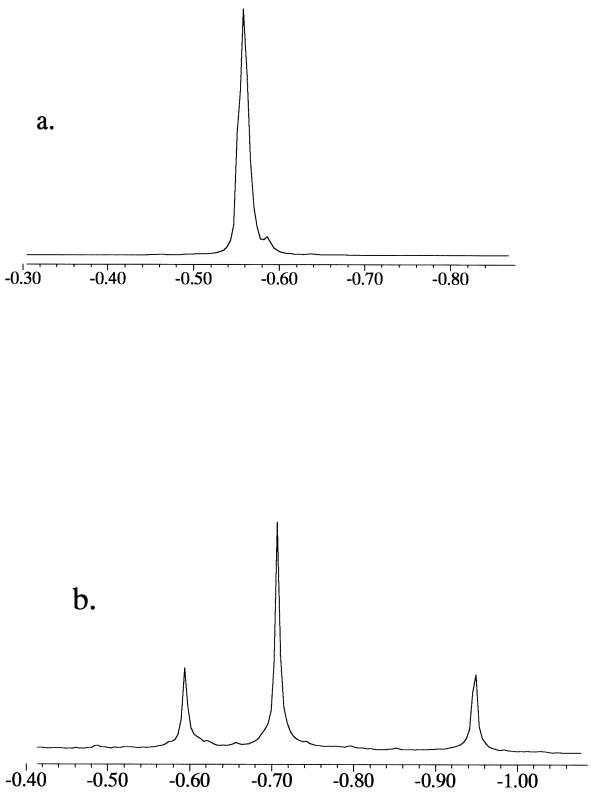


Figure 4. High field portion of the ^{1}H NMR spectrum a for D(*m*-OMeP)PRu(II)(*t*-BuCN)$_2$ **13** and b for (DSP)Ru(II)(*t*-BuCN)$_2$ **9** (mixture of isomers) ($CDCl_3$).

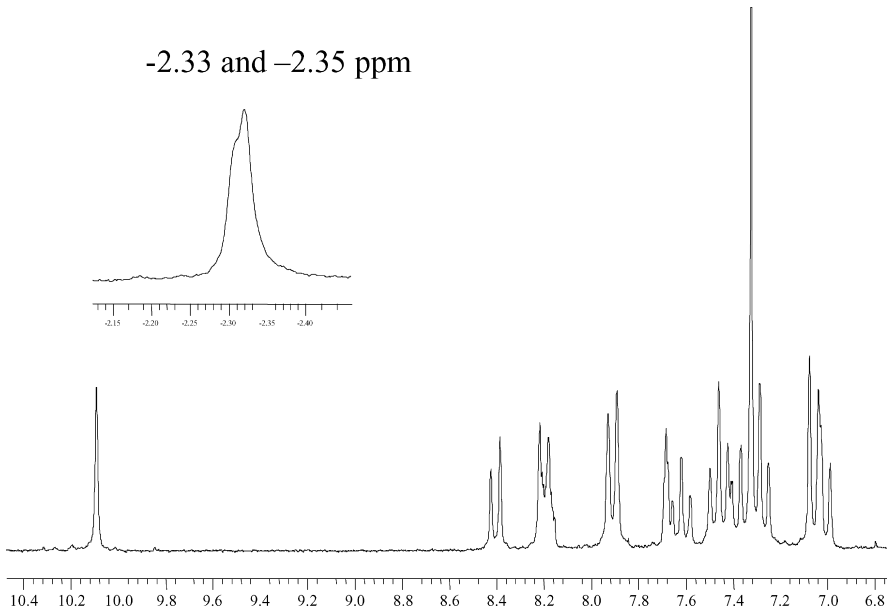
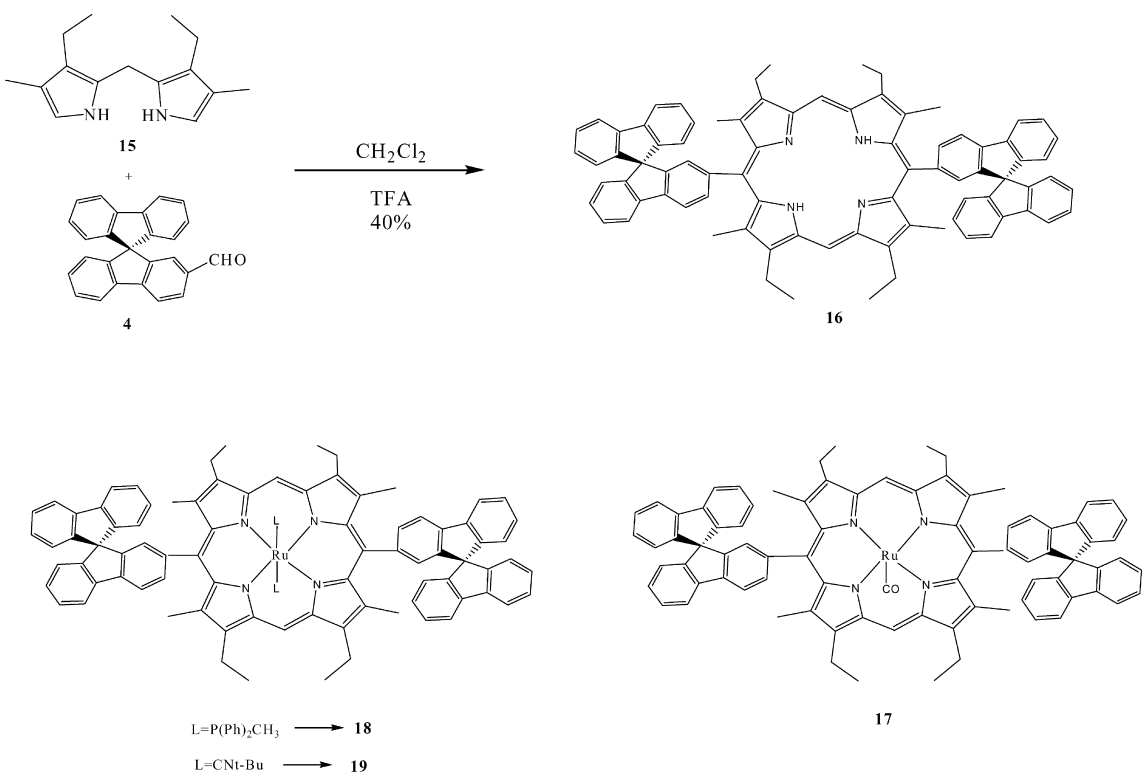


Figure 5. ^{1}H NMR spectrum for compound **16** ($CDCl_3$).

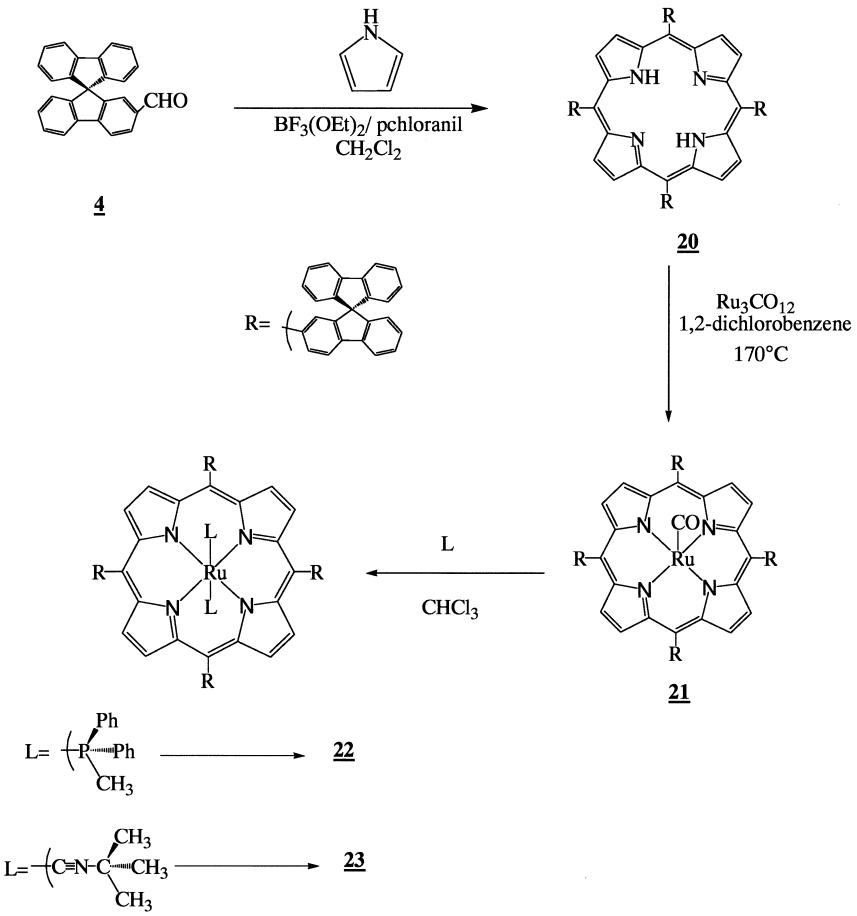
positions rendered dispiroporphyrin more soluble than the non-substituted derivative **6**. Furthermore the methyl group in position 3 constituted a very interesting ^{1}H NMR probe to detect possible atropisomers. Finally, in contrast to previous synthesis of tetramethyldipyrrylmethane,[26] the yields herein were better than 70% in each step.[24]

Mac Donald '2+2' condensation of 4,4′diethyl-3,3′dimethyl-2,2′dipyrromethane **15** with 9,9′-spirobi-[fluorene]-2-carbaldehyde **4** lead to the expected 5,15 bis(spirobifluoren-2-yl)-2,8,18-tetraethyl-3,7,13,17-tetramethyl porphyrin **16** with 40% yield. The increase of solubility compared to porphyrin **6** allowed us to record the ^{1}H NMR spectra of free base **16** in neutral conditions (Fig. 5). The internal NH protons of the porphyrin core were detected as two singlets at −2.33 and −2.35 ppm for the two atropisomers αα and αβ. As expected, signals due to equivalent methyl groups of β pyrrole positions (3, 7, 13 and 17) were separated for each atropisomer (2.16 and 2.17 ppm) and gave a ratio of 1:1 (Scheme 5).

After ruthenium insertion (complex **17**) followed by



Scheme 5.



Scheme 6.

phosphine (complex **18**) or isocyanide (complex **19**) complexation, the presence of two different conformers was also detected by ^{1}H NMR. The complex **18** exhibited three resonances at −2.7, −2.54 and −2.30 ppm corresponding to the phosphine methyl groups, and the complex **19** exhibited three resonances at −0.94, −0.70 and −0.58 ppm, corresponding to the isocyanide methyl groups. Variable temperature ^{1}H NMR spectroscopy was applied to quantify the spirobifluorene interaction with the methyl group in β pyrrole position. By monitoring the coalescence of the free *meso* hydrogen in toluene d_8 between 298 and 378 K, ΔG^* at the coalescence temperature (370 K) was estimated as 20.35 kcal mol^{-1}. This allows us to compare the activation free energy ΔG^* for **18** to that for the unsubstituted complex **8**. The activation free energy for rotation in the compound **18** is similar to that for **8** (20.26 kcal/mol) giving rise to a similar energy of rotation around the single bond between porphyrin and spirobifluorene moieties. Intuitively, the addition of flanking alkyl groups should bring more hindrance than the β-pyrrole protons in preventing rotation. However, the absence of an increase in ΔG^* for **18** suggests that this is not true. Therefore the added steric constraints may be not enough to compensate the remote spiro groups in *meta* position. Similar results were previously observed with *ortho* substituents.[24]

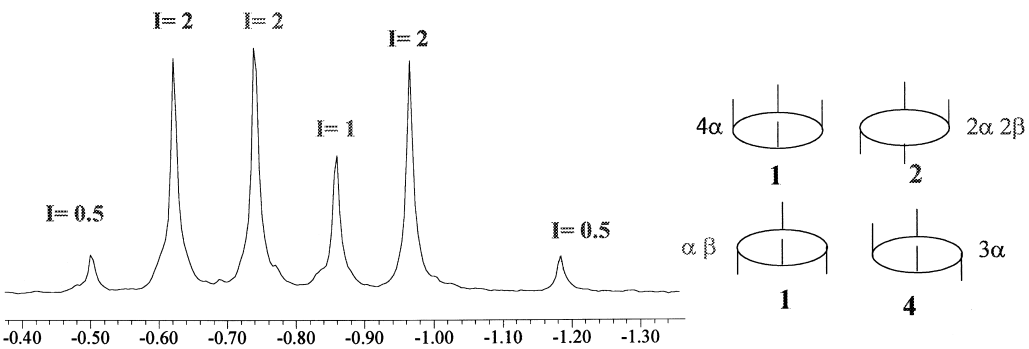


Figure 6. High field portion of the ^{1}H NMR spectrum for compound **23** ($CDCl_3$) with relative intensity of each atropisomer.

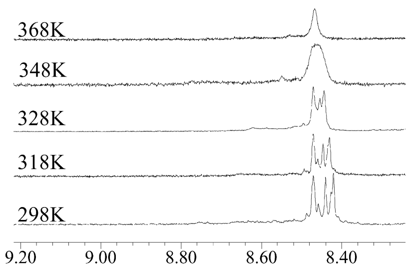


Figure 7. Variable temperature study in toluene d_8 for compound **23** (lowfield part of the spectrum).

2.4. Syntheses and stereochemistry of tetraspiro-porphyrin

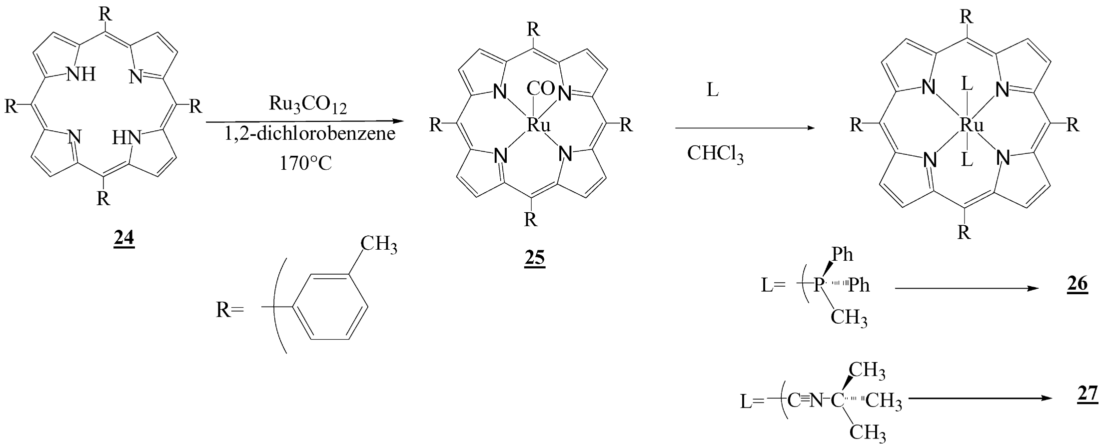
Due to weakness of the *meso* free position toward oxidation process, more resistant tetraspirobifluorene porphyrin ruthenium complexes have also been synthesized for further catalytic studies.[27] Following the Lindsey procedure,[19] condensation of 9,9′-spirobifluorene-2-carbaldehyde **4** and pyrrole led to a satisfactory yield (40%) of *meso*-tetra-(m-9,9′-spirobifluoren-2yl)porphyrin **20** (Scheme 6). Indeed, the ^{1}H NMR spectrum of compound **20** displayed several peaks for the pyrrole resonances between 8.74 and 8.68 ppm, and four resonances at high-field position (−2.43, −2.52, −2.54 and −2.56 ppm) assigned to internal NH. Attempts to isolate these free-base atropisomers by classical chromatography techniques were however unsuccessful, due probably to the *meta* position of the bulky spirobifluorene.

After ruthenium insertion (complex **21**) followed by isocyanide complexation (Scheme 6), the presence of four different conformers was also detected by ^{1}H NMR (Fig. 6). The identification of the various isomers in the ^{1}H NMR spectrum of the tetraspirobifluorene porphyrins was based on a combination of two arguments. First the quantities of each isomer present in the equilibrium mixture should correspond to the statistical composition: 1:2:4:1 respectively for αααα, ααββ, αααβ, αβαβ, as we[25] and others[28] have frequently observed. Secondly, two conformers show identical faces whereas the others show different faces. As expected, the spectrum exhibited six resonances found at high-field position due to the ring current shift and with a relative intensity corresponding to the isocyanide methyl groups of the complex **23**. As presented Figure 6, the statistical mixture of four atropisomers was observed. The αααα isomer has two different faces and exhibit two resonances at −1.18 and −0.50 ppm with relative intensity according with its statistical weight. The two topological faces of this isomer are the more different of all the mixture; one bearing the four spirobifluorene groups and the other completely free. This cause a difference of 0.68 ppm between the two resonances; the interpretation and the assignation of all the signals have been made using this argument. The two resonances at −0.96 and −0.62 have been assigned to the αααβ isomer. The ααββ and αβαβ isomer exhibit both two identical faces according to resonances at respectively, −0.74 and −0.86 ppm.

Variable temperature ^{1}H NMR spectroscopy was applied to detect the spirobifluorene interaction with the proton in β pyrrole position for compound **23**, by monitoring the coalescence of the pyrrole hydrogens in toluene d_8 between 298 and 378 K, (Fig. 7). A coalescence temperature was detected near 350 K. The coalescence temperature was 361 K for **8**, suggesting a similar energy of rotation around the single bond between porphyrin and spirobifluorene moieties for the di and tetraspiro derivatives. As already reported for di-*meso*-substituted compounds, comparison with ruthenium tetraphenylporphyrine derivatives bearing on aryl group *meta* substituents was undertaken. Thus, first T(*m*-MeP)PRu(II)(PPh_2Me)$_2$ **26** and then T(*m*-MeP)-PRu(II)(*t*-BuCN)$_2$ **27** were synthesized from the corresponding Ru(II)(CO) derivatives. As expected, the ^{1}H NMR spectrum exhibits only one resonance at high field for the methyl group of the phosphine for **26** and for the methyl of the isocyanide for **27**, respectively (Scheme 7).

3. Conclusion

The phenomenon of atropisomerism in porphyrins with *meso* aryl substituents in ortho position is well known. It was first described in 1969 by Gottwald and Ullman[29] with tetraphenylporphyrins. This concept has been nicely extended first by Collman[28] and then by others[30,31] with



Scheme 7.

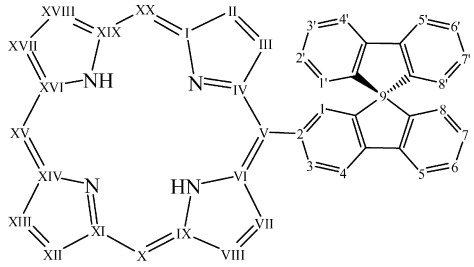
meso-tetraaminophenylporphyrins. Since then atropisomerism has also been reported for ortho di-*meso* substituted aryl-porphyrins.[24,32,33] In contrast, *meta*-substitution rarely shows restricted aryl rotation in tetra and di-arylporphyrins. Thus there are only few examples such as porphyrin carborane system,[22] *meta* aryl fullerene porphyrins[23,34] and multimetallic porphyrin monomers.[35] Therefore the large size of the 9,9′-spirobifluorene group also hinders rotation around the $C_{meso}-C_{aryl}$ bond. Unfortunately, energy barrier was too low to get each atropisomer as a pure compounds. In summary, we have developed new efficient syntheses for preparing in mild conditions and with high yield spirobifluorenylporphyrins. These compounds exhibit atropisomers forms which can be easily detected by ^{1}H NMR though the aryl substituents are in *meta* position. Oxidative electropolymerization of tetraspirobifluorenylporphyrin ruthenium (II) carbonyl complexes **21** can be used to coat Pt electrodes with polymeric films as we already reported for manganese-porphyrin-polymers.[11] When unsticked from the electrode, these polymeric ruthenium materials are able to catalyze the heterogeneous cyclopropanations and 2.3 sigmatropic rearrangements with ethyl diazoacetate.[36]

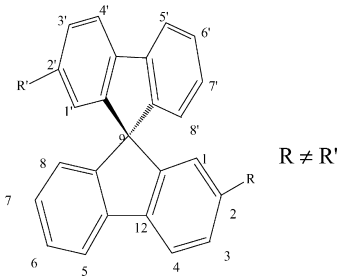
4. Experimental

4.1. General experiments

All reactions were performed under argon and were magnetically stirred. Solvents were distilled from appropriate drying agent prior to use: Et_2O and THF from sodium and benzophenone, toluene from sodium, CH_2Cl_2 from CaH_2, $CHCl_3$ from P_2O_5 and all other solvents were HPLC grade. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Merck pre-coated aluminium foil sheets (Silica gel 60 with fluorescent indicator UV_{254}). Compounds were visualized with UV light at 254 and 365 nm. Column chromatography was carried out using silica gel from Merck (0.063–0.200 mm). ^{1}H NMR and ^{13}C NMR in $CDCl_3$ and toluene d_8 were recorded using Bruker (Advance 500dpx, 300dpx and 200dpx) spectrometers. The assignments have been performed by 2D NMR experiments: COSY (Correlation Spectroscopy), HMBC (Heteronuclear Multiple Bond Correlation), HMQC (Heteronuclear Multiple Quantum Coherence) and NOESY (Nuclear Overhauser Effect Spectroscopy). The rates of conformational interchange (k_c) and the activation free energies ΔG^* at the coalescence temperatures were calculated using approximate equation: $k_c=\pi\Delta\nu/(2)^{1/2}$ for the coalescence of singlets.[37] Although the use of this equation can be criticized, it has been shown that the free energies of activation are in good agreement with the results of complete shape analysis based on equally populated two-site system.[37] High-resolution mass spectra were recorded on a ZabSpec TOF Micromass spectrometer for FAB mode or ESI positif mode and on a Varian MAT 311 for EI mode. The spectra were recorded by the CRMPO at the University of Rennes 1. Infrared spectra were recorded on a Bruker IFS 28. Solid samples were prepared in KBr pellets. Liquid samples were prepared in dichloromethane. Melting points were recorded on WME HEIZBANK KOFLER apparatus. UV-visible spectra were recorded on a UVIKON XL from Biotech.

All electrochemical experiments were performed using a Pt disk electrode (diameter 1 mm), the counter electrode was a vitreous carbon rod and the reference electrode was a silver wire in 0.1 M AgNO3 solution in CH_3CN. Ferrocene was added to the electrolyte solution at the end of a series of experiments. The ferrocene/ferricinium (Fc/Fc+) couple served as internal standard and all reported potentials are referenced to its reversible formal potential. The three electrodes cell was connected to a PAR Model 179 signal coulometer. The cyclic voltammetry traces (CVs) were recorded on a XY SEFRAM-type TGM 164. Acetonitrile with less than 5% of water and dichloromethane with less than 100 ppm of water were used without purification. Tetrabutyl ammonium hexafluorophosphate from FLUKA was used without any purification.





R ≠ R'

4.2. Preparation of spirobifluorene derivatives

4.2.1. 2-Idodo-1,1′-biphenyl 1.[38] To a suspension of 2-amino-1,1′-biphenyl (27 g, 160 mmol) in concentrated hydrochloric acid (32.2 mL) and water (160 mL) cooled at 0 °C was added carefully an aqueous solution of sodium nitrite (13.3 g, 193 mmol) in 10 min. The brown mixture was then stirred at 0 °C for 45 min and added carefully to an aqueous solution of potassium iodide (53.1 g, 320 mmol) in 5 min. The final solution was stirred at room temperature for 12 h and then extracted four times with diethylether. The organic layers were then washed with a solution 3 N of hydrochloric acid, a saturated solution of sodium bicarbonate, sodium chloride, water and dried on magnesium sulphate. The solvents were removed under vacuum to give the 2-idodobiphenyl **1** as purple oil. This compound was used without any other purification (yield: 98%). ^{1}H NMR ($CDCl_3$, ppm): δ 7.1 ($H_{\beta I}$, m, 1H); 7.3–7.6 (m, 7H); 8.03 ($H_{\alpha I}$, m, 1H). ^{13}C NMR ($CDCl_3$, ppm): δ 99.3; 128.2; 128.3; 128.6; 128.8; 129.4; 129.9; 130.7; 131.5; 140.1; 144.7; 147.2. MS (EI) (*m*/*z*): calcd for $C_{12}H_9I$ (M^{+}): 279.97490. Found: 279.9748.

The synthesis of 9,9′-spirobifluorene **3** which was previously described by Tour et al.[13] is not described here. However the spectroscopic data of the intermediate 9-(1,1′-biphenyl-2-yl)-9*H*-fluoren-9-ol **2** are reported.

4.2.2. 9-(1,1′-Biphenyl-2-yl)-9*H*-fluoren-9-ol 2. ^{1}H NMR ($CDCl_3$, ppm): δ 2.28 (OH, s, 1H); 6.01 (dd, 4H); 6.62 (td, 4H); 6.92 (m, 4H); 7.34 (td 1H); 7.6 (td, 2H); 8.1 (dd, 2H). ^{13}C NMR ($CDCl_3$, ppm): δ 82.88; 120.51; 124.79; 125.55; 126.55; 126.71; 127.32; 127.54; 128.35; 129.10; 129.32; 131.7; 140.14; 140.65; 140.79; 151.02. MS (EI) (*m*/*z*): calcd for $C_{25}H_{18}O$ ($M^{\cdot+}$): 334.13577. Found: 334.1368. Mp: 180 °C.

4.2.3. 9,9′-Spirobifluorene 3. Under argon atmosphere 2-iodo-1,1′-biphenyl **1** (44.3 g, 158 mmol) was added dropwise in 30 mn to magnesium turning (5 g, 205 mmol) in 100 mL of diethylether freshly distilled. The addition was controlled to maintained a gentle reflux of diethylether. The mixture was heated to reflux for 90 min and then diluted with 100 mL of diethylether. The mixture was then filtered under argon atmosphere and a solution of 9-fluorenone (37 g, 205 mmol) dissolved in 300 mL of toluene was added dropwise. The mixture was heated to reflux for 24 h. After cooling, the solution was added to 250 g of crushed ice, diluted with 200 mL of toluene and finally 300 mL of concentrated hydrochloric acid was carefully added in 5 min. The solution was stirred for 3 h at room temperature. The two layers were separated and the aqueous layer extracted with dichloromethane. The organic layers were then washed with a saturated solution of sodium bicarbonate, sodium chloride, and water and dried on magnesium sulphate. The solvents were removed under vacuum and the crude product was purified by chromatography on silica gel (first: pentane, second: pentane with a gradient of dichloromethane (from 1 to 30%). Finally the 9,9′-spirobifluorene **3** was washed with a few amount of cold ethanol to afford a white powder (yield: 90%). ^{1}H NMR ($CDCl_3$, ppm): δ 6.79 (H_1, dd, 4H); 7.16 (H_2, td, 4H); 7.42 (H_3, td, 4H); 7.91 (H_4, dd, 4H). ^{13}C NMR ($CDCl_3$, ppm): δ 66 (C_9); 119.87; 123.9; 127.6; 127.7; 141.6; 148.6 (aromatic C). MS (FAB) (*m*/*z*): calcd for $C_{25}H_{16}$ ($M^{\cdot+}$): 316.1252. Found: 316.1249. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 225 (4.79); 236 (4.59); 261 (4.51); 294 (4.11); 305 (4;34). Mp: 202°C. CV (CH_2Cl_2 0.2 M/Bu_4NPF_6, Fc/Fc^+): 1.3 V; 1.42 V.

4.2.4. 9,9′-Spirobifluorene-2-carbaldehyde 4. To a solution of 9,9′-spirobifluorene (12.7 mmol) in 100 mL of distilled and degassed dichloromethane, cooled at 0 °C, was added α,α-dichloro-methyl-methylether (31.6 mmol) in one portion. After 5 min titanium tetrachloride (31.6 mmol in 50 mL dichloromethane) was added drop wise over a period of 45 min. The dark green solution was then stirred at room temperature for 75 min and 250 g of ice was then added and let under vigorous stirring for 30 min. The two layers were then separated and the aqueous layer was extracted two times with 100 mL of dichloromethane. The organic layers were then washed with a saturated solution of sodium bicarbonate, sodium chloride, and water and dried on magnesium sulphate. The solvents were removed under vacuum and the crude product was purified by chromatography on silica gel ($CHCl_3$/Pentane: 6/4) (yield: 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 ($H_{1'}$, ddd, 2H), 6.82 (H_8, ddd, 1H), 7.14 ($H_{2'}$, td, 2H), 7.22 (H_7, td, 1H), 7.30 (H_1, sdd, 1H), 7.43 ($H_{3'}$, td, 2H), 7.47 (H_6, td, 1H), 7.91 ($H_{4'}$, ddd, 2H), 7.94 (H_3, dd, 1H), 7.96 (H_5, ddd, 1H), 8.04 (H_4, dd, 1H), 9.84 (CHO, s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.6 (C_9); 120.2; 120.3; 121.1; 123.8; 124.3; 124.5; 125.2; 127.9; 128; 129.5; 130.2; 135.9; 140.1; 141.8; 147.4; 147.8; 149.7; 150 (C aromatic); 191.6 (C═O). UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 225 (4.59), 282 (4.31), 292 (4.32), 303 (4.38), 328 (4.08). MS (FAB) (*m*/*z*): calcd for $C_{26}H_{16}O$ ($M^{\cdot+}$): 344.1201. Found: 344.1199. Mp: 209 °C. CV (CH_2Cl_2 0.2 M/Bu_4NPF_6, Fc/Fc^+): 1.34 V, 1.66 V.

4.2.5. 2,2′ Dipyrromethane 5. The 2,2′-dipyrromethane **5** was prepared according to the literature procedure and use without other purification (yield: 35%).[19] ^{1}H NMR ($CDCl_3$, ppm): δ 4.01 (CH_2C_2, s, 2H); 6.14 (CH, m, 2H); 6.24 (CH, m, 2H); 6.65 (CH, m, 2H); 7.90 (NH, s br, 2H). MS (EI) (*m*/*z*): calcd for $C_9H_{10}N_2$ ($M^{\cdot+}$):146.0844. Found: 146.0849.

4.2.6. 4,4′-Diethyl-3,3′-dimethyl-2,2′-dipyrromethane 15. 5,5′-Bis(ethoxycarbonyl)-4,4′-diethyl-3,3′-dimethyl-2,2′-dipyrromethane (5.3 mmol) which was obtained from pentan-2,4-dione as previously reported by Lash[39] was dissolved at 100 °C in ethylene glycol (20 mL). The orange solution was degassed for 15 min before adding sodium hydroxide (53 mmol) and heated at 180 °C under an argon atmosphere for 1 h. The mixture was diluted with water and extracted several times with hexane. The organic layers were concentrated, dried over magnesium sulphate and evaporated under reduce pressure. 4,4′-diethyl-3,3′-dimethyl-2,2′-dipyrromethane **15** was stored and protected from light, under an argon atmosphere at −10 °C and used without other purification (yield: 70%). ^{1}H NMR ($CDCl_3$, ppm): δ 1.33 (CH_3C_3, t, 6H); 2.27 (CH_3C_4, s, 6H); 2.67 (CH_2C_3, q, 4H); 3.95 (CH_2C_2, s, 2H); 6.43 (CHC_5, s, 2H); 7.31 (NH, s, 2H). MS (EI) (*m*/*z*): calcd for $C_{15}H_{22}N_2$ ($M^{\cdot+}$): 230.1783. Found: 230.1763.

4.2.7. 5,15-Bis(9,9′-spirobifluoren-2-yl) porphyrin 6. A solution of 2,2′-dipyrromethane **5** (225 mg, 1.54 mmol) and 9,9′-spirobifluorene-2-carbaldehyde **4** (530 mg, 1.54 mmol) in freshly distilled dichloromethane was degassed 10 min. Trifluoroacetic acid (95 μL, 1.22 mmol) was added and the reaction mixture was stirred and protected from light under an argon atmosphere for 15 h. 2.1 mmol (520 mg) of tetrachlorobenzoquinone was added to irreversibly oxidize the di-spiroporphyrinogene and the solution was stirred at air for 60 min and 30 min to reflux. After addition of several drops of triethylamine and the ordinary work-up, concentration, washing, drying, the crude reaction mixture was purified by chromatography on silica gel respectively, with diethyl ether, dichloromethane, mixture of dichloromethane/methanol (8:2) and dichloromethane saturated with concentrated hydrochloric acid. These two last fractions were evaporated and washed with a saturated solution of sodium bicarbonate, sodium chloride, and water and dried on magnesium sulphate. The crude product was dissolved in dichloromethane saturated with concentrated hydrochloric acid and a second chromatography was performed using the same solvents. The last green fraction afforded pure protonated 5,15-bis(9,9′-spirobifluoren-2-yl) porphyrin **6**. The previous work up was performed, the

solvent was removed under vacuum and **6** was crystallized in pentane (yield: 30%). ^{1}H NMR ($CDCl_3$/TFA, ppm) (αα and αβ): δ 7.01 (H_8, dd, 2H); 7.12 ($H_{1'}$, dd, 4H); 7.32 ($H_{2'}$, td, 4H); 7.36 (H_7, td, 2H); 7.5 ($H_{3'}$, td, 4H); 7.6 (H_6, td, 2H); 7.91 (H_1, sd, 2H); 7.94 ($H_{4'}$, dd, 4H); 8.2 (H_5, dd, 2H); 8.41 (H_3, dd, 2H); 8.43 (H_4, dd, 2H); 8.73 ($H_{III,VII,XIII,XVII}$, β pyrrole, d, ^3J=4.83 Hz, 4H); 9.25 ($H_{II,VIII,XII,XVIII}$, β pyrrole, d, ^3J=4.82 Hz, 4H); 10.66 ($H_{X,XX}$ *meso*, s, 2H). ^{13}C NMR ($CDCl_3$/TFA, ppm): δ 66.3 (C_9); 106.6 ($C_{X,XX}$ *meso*); 119.8; 120.5 (C_4); 121.1 ($C_{4'}$); 121.8 (C_5); 124.3 ($C_{1'}$); 125 (C_8); 128.5 ($C_{3'}$); 128.6 ($C_{2'}$); 128.7 (C_6); 129.2 ($C_{II,VIII,XII,XVIII}$, β pyrrole); 129.6 (C_7); 129.8 ($C_{III,VII,XIII,XVII}$, β pyrrole); 133.8 (C_1); 139.7; 140 (C_3); 142; 142.5; 142.7 ($C_{I,IX,XI,XIX}$); 143.7; 146.5 ($C_{IV,VI,XIV,XVI}$); 148; 149.8; 150 (NMR experiments have been performed by adding TFA in the NMR tube due to the insolubility of free base **6**). MS (FAB) (*m*/*z*): calculated for $C_{70}H_{43}N_4$ $(M+H)^+$: 939.3488. Found: 939.3477. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 227 (4.62); 297 (4.13); 307 (4.16); 412 (5.11); 505 (3.92); 541 (3.85); 575 (3.51); 632 (3.38).

4.2.8. 5,15-Bis(9,9′-spirobifluoren-2-yl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 16. A solution of 4,4′-diethyl-3,3′-dimethyl-2,2′-dipyrromethane **15** (354.2 mg, 1.54 mmol) and 9,9′-spirobifluorene-2-carbaldehyde **4** (530 mg, 1.54 mmol) in freshly distilled dichloromethane was degassed 10 min. Trifluoroacetic acid (95 μL, 1.22 mmol) was added and the reaction mixture was stirred protected from light under an argon atmosphere for 15 h, 2.1 mmol (520 mg) of tetrachlorobenzoquinone was added to irreversibly oxidize the di-spiroporphyrinogene and the solution was stirred in air at room temperature for 60 min and then 30 min in refluxing solvent. After addition of several drops of triethylamine and the ordinary work-up, concentration, washing, drying, the crude reaction mixture was purified by chromatography on silica gel (yield: 40%). ^{1}H NMR ($CDCl_3$/TFA, ppm) (αα and αβ): δ −2.35 (NH, s, 1H); −2.33 (NH, s, 1H); 1.30 (CH_3 ethyl, t, 12H); 2.16 (CH_3 methyl, s, 6H); 2.17 (CH_3 methyl, s, 6H); 3.62 (CH_2 ethyl, q, 8H); 6.99 (H spirobifluorene, m, 6H); 7.2–7.45 (H spirobifluorene, m, 10H); 7.59 (H spirobifluorene, m, 4H); 7.85 (H spirobifluorene, dd, 4H); 8.14 (H spirobifluorene, m, 4H); 8.35 (H spirobifluorene, dd, 2H); 10.07 ($H_{X,XX}$ *meso*, s, 2H). MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m*/*z*): calcd for $C_{82}H_{67}N_4$ $(M+H)^+$: 1107, 5366. Found: 1107, 5375. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 227 (4.60); 297 (4.10); 307 (4.13); 410 (5.13); 508 (3.90); 543 (3.81); 577 (3.44); 634 (3.30).

4.2.9. *meso*-5,10,15,20-Tetrakis (9,9′-spirobifluoren-2-yl) porphyrin 20. Pyrrole (524 μL, 7.5 mmol) and 9,9′-spirobifluorene-2-carbaldehyde **4** (2.5 g, 7.5 mmol) were allowed to react at room temperature in dry and degassed dichloromethane (750 mL) under an argon atmosphere and protected from light with trace acid catalysis ($BF_3(OEt)_2$ 48%: 0.75 mmol). Under these conditions, the reaction reaches equilibrium in about 3 h. 6.25 mmol (1.54 g) of p-chloranil was added to irreversibly oxidize the tetraspiroporphyrinogene and the solution was stirred at air for 60 and 30 min to reflux. After addition of several drops of triethylamine and the ordinary work-up, concentration, washing, drying, the crude reaction mixture was purified by chromatography twice on silica gel: first with dichloromethane and then with cyclohexane/dichloromethane: 1/3. Crystallization in distilled toluene for one night at room temperature afforded a purple powder of *meso*-tetrakis 5,10,15,20-(spirobifluoren-2-yl) porphyrin (yield: 40%). ^{1}H NMR ($CDCl_3$, ppm) (4α, 3αβ, 2α2β, αβαβ): δ-3.13 (s, 2H, NH); 6.88 (H_8, d, 4H); 7.07 ($H_{1'}$, m, 8H); 7.21 ($H_{2'}$/H_7, m, 12H), 7.32 ($H_{3'}$, m, 8H); 7.50 (H_6+H_1, m, 8H); 7.71 ($H_{4'}$, m, 8H); 8.07–8.15 (H_5/H_4/H_3, m, 12H); 8.55 (H β pyrrole, m, 4H); 8.57 (H β pyrrole, m, 4H). ^{13}C NMR ($CDCl_3$, ppm): δ 66.1 (C_9); 118; 119.8; 120.1; 120.3; 123.9; 124.2; 127.7; 127.9; 128.1; 128.2; 129; 131(C β pyrrole); 134.9; 141.2; 141.5; 141.7; 141.8; 147.4; 147.6; 148.7; 149.6. MS (FAB) (*m*/*z*): calcd for $C_{120}H_{71}N_4$ $(M+H)^+$: 1567.5634. Found: 1567.5600. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (5.08); 297 (4.58); 309 (4.67); 427 (5.32); 520 (4.17); 556 (4.09); 594 (3.74); 652 (3.76). CV (CH_2Cl_2 0.2 M/Bu_4NPF_6, Fc/Fc^+): 0.585; 0.915; 1.395 (sh); 1.505.

4.3. Typical procedure for ruthenium insertion

Free base porphyrin (313 μmol) was dissolved in distilled 1,2-dichlorobenzene and degassed for 15 min. The reaction mixture was heated at 160 °C and dodecacarbonyl triruthenium was added (830 μmol) over a period of 2 h under an argon atmosphere. The ruthenium insertion was followed by TLC and UV–Vis spectroscopy. The solvents were removed under vacuum, the residue was dissolved in dichloromethane and purified by chromatography on silica gel. The dodecacarbonyl triruthenium was eluted first with pentane and the desired ruthenium complex was eluted with a mixture dichloromethane/diethylether (9:1). Ru(II)(CO) complex was further crystallized from pentane–dichloromethane.

4.3.1. 5,15-Bis(9,9′-spirobifluoren-2-yl) porphyrinato ruthenium carbonyl 7. Yield: 76%. ^{1}H NMR ($CDCl_3$, ppm) (αα and αβ): δ 6.88 (H spirobifluorene, dd, 2H); 7.1–7.26 (H spirobifluorene, m, 8H); 7.29–7.38 (H spirobifluorene, m, 6H); 7.54 (H spirobifluorene, m, 4H); 7.73 (H spirobifluorene, m, 4H); 8.11–8.29 (H spirobifluorene, m, 6H); 8.72 (H β pyrrole, d, 2H); 8.75 (H β pyrrole, m, 2H); 9.04 (H β pyrrole, d, 4H); 9.93 ($H_{X,XX}$ *meso*, s, 2H). MS (FAB) (*m*/*z*): calcd for $C_{71}H_{41}N_4O^{102}Ru$ $(M+H)^+$: 1067.2344. Found: 1067.2349. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (4.80); 296 (4.40); 308 (4.50); 404 (5.11); 521 (4.02); 552 (3.58). IR (KBr, cm^{-1}): ν_{CO} 1943.

4.3.2. 5,15-Bis(2-methoxyphenyl) porphyrinato ruthenium carbonyl 10. Yield: 70%. The free base compound has been synthesized according the procedure described by Manka and Lawrence.[18]

^{1}H NMR ($CDCl_3$, ppm) (αβ isomer): δ 3.45 (s, 6H, methyl group); 7.25–8 (m, 8H, H phenyl ring); 8.54 (Hβ pyrrole, d, ^3J=4.5 Hz, 2H); 8.87 (Hβ pyrrole, d, ^3J=4.6 Hz, 2H); 9.02 (Hβ pyrrole, d, ^3J=4.6 Hz, 2H); 9.25 (Hβ pyrrole, d, ^3J=4.8 Hz, 2H); 10.02 (H *meso*, s, 2H). (αα isomer): δ 3.6 (s, 6H, methyl group); 7.25–8 (m, 8H, H porphyrin phenyl ring); 8.76 (Hβ pyrrole, d, ^3J=4.6 Hz, 4H); 9.15 (Hβ pyrrole, d, ^3J=4.6 Hz, 4H); 9.92 (H *meso*, s, 2H). MS (FAB) (*m*/*z*): calcd for $C_{35}H_{24}N_4O_3^{102}Ru$ (M^+): 650.0898. Found: 650.0902. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 398 (5.28); 517 (4.19). ν_{CO} 1936

4.3.3. 5,15-Bis(9,9′-spirobifluoren-2-yl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrinato ruthenium carbonyl 17. Yield: 75%. ^{1}H NMR ($CDCl_3$, ppm) (αα and αβ): δ 1.73 (CH_3 ethyl, t, 12H); 2.35 (CH_3 methyl, s, 12H); 3.84 (CH_2 ethyl, q, 8H); 6.69–6.91 (H spirobifluorene, m, 6H); 7.12 (H spirobifluorene, m, 4H); 7.36–7.58 (H spirobifluorene, m, 6H); 7.71 (H spirobifluorene, m, 4H); 7.94 (H spirobifluorene, m, 6H); 8.16 (H spirobifluorene, m, 4H); 9.84 ($H_{X,XX}$ *meso*, s, 2H). MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m/z*): calcd for $C_{83}H_{64}N_4O^{102}Ru$ ($M^{\cdot+}$):1234.4124. Found: 1234.4170. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (4.84); 296 (4.47); 308 (4.50); 401 (5.01); 521 (3.99); 552 (3.90). IR (KBr, cm^{-1}): ν_{CO} 1938.

4.3.4. *meso*-5,10,15,20-Tetrakis(9,9′-spirobifluoren-2-yl)porphyrinato ruthenium carbonyl 21. Yield: 82%. ^{1}H NMR(toluene d_8, ppm) (4α, 3αβ,2α2β, αβαβ): 6.90 (H spirobifluorene, dd, 4H); 7.11–7.20 (H spirobifluorene, m, 12H), 7.22–7.30 (H spirobifluorene, m, 12H); 7.50–7.83 (H spirobifluorene, m, 16H); 7.9–8.33 (H spirobifluorene, m, 16H); 8.87 (H β pyrrole, m, 8H). MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m/z*): calcd for $C_{121}H_{68}N_4ONa^{102}Ru$ ($M+Na^+$): 1717.4334. Found: 1717.4330. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (5.1); 298 (4.66); 309 (4.74); 420 (5.31); 533 (4.28); 569 (3.84). IR (KBr, cm^{-1}): ν_{CO} 1938. CV (CH_2Cl_2 0.2 M/Bu_4NPF_6, Fc/Fc^+): 0.46 V; 0.89 V; 1.37 V.

4.3.5. Typical procedure for phsophine ligation: 5,15-bis(9,9′-spirobifluoren-2-yl)porphyrinato ruthenium bis (methyl-diphenyl phosphine) 8. To a solution of ruthenium carbonyl complex (50 μmol) dissolved in distilled and degassed chloroform or dichloromethane was added methyldiphenylphosphine (300 μmol) under an argon atmosphere. The solution was stirred at room temperature until the reaction was completed (5 min). The bis-ligation was checked by monitoring the UV–VIS spectrum. After removal of the solvent, the crude product was crystallized in hexane or pentane to give the Ru(II)bis(methyldiphenylphosphine) complex (yield: 85%). ^{1}H NMR (toluene d_8, ppm) (αα and αβ): δ −2.64 (CH_3 phosphine, t, 1.5H); −2.36 (CH_3 phosphine, t, 3H); −2.14 (CH_3 phosphine, t, 1.5H); 4.19 (H phosphine *o*-phenyl ring, m, 2H); 4.25 (H phosphine *o*-phenyl ring, m, 4H); 4.41 (H phosphine *o*-phenyl ring, m, 2H); 5.96–6.31 (H phosphine *m*-phenyl ring, m, 8H); 6.45–6.61 (H phosphine *p*-phenyl ring, m, 4H); 6.96 (H spirobifluorene, m, 3H); 7.46–8.25 (H spirobifluorene, m, 27H); 8.51 (H *β* pyrrole, m, 4H); 8.69 (H *β*pyrrole, m, 4H); 9.17 ($H_{X,XX}$ *meso*, s, 1H); 9.21 ($H_{X,XX}$ *meso*, s, 1H). ^{31}P NMR (toluene d_8, ppm) (αα et αβ): 2.6 (P phosphine, 1P); 2.7 (P phosphine, 1P). MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m/z*): calcd for $C_{96}H_{66}N_4P_2^{102}Ru$ ($M^{\cdot+}$):1438.3806. Found: 1438.3847. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 426 (5.3); 510 (4).

4.3.6. 5,15-Bis(2-methoxyphenyl) porphyrinato ruthenium bis(methyl-diphenyl phosphine) 11. Yield: 85%. ^{1}H NMR ($CDCl_3$): αα isomer: δ − 2.37 (CH_3 phosphine, t, 3H); −2.15 (CH_3 phosphine, t, 3H); 3.74 (CH_3 methoxy group, s, 6H); 4.16 (H phosphine *o*-phenyl ring, m, 4H); 4.35 (H phosphine *o*-phenyl ring, m, 4H); 6.45 (H phosphine *m*-phenyl ring, m, 8H); 6.76 (H phosphine *p*-phenyl ring, m, 4H); 7.41–7.7 H porphyrin phenyl ring, m, 8H); 8.25 (H β pyrrole, d ^3J=4 Hz, 4H); 8.48 (H β pyrrole, d ^3J=4 Hz, 4H); 8.70 (H*meso*, s, 2H). αβ isomer: δ −2.24 (CH_3 phosphine, t, 6H); 3.68 (CH_3 methoxy group, s, 6H); 4.25 (H phosphine *o*-phenyl ring, m, 8H); 6.43 (H phosphine *m*-phenyl ring, t, 8H); 6.77 (H phosphine *p*-phenyl ring, t, 4H); 7.38–7.67 (H porphyrin phenyl ring, m, 8H); 8.27 (H β pyrrole, d ^3J=4.1 Hz, 4H); 8.45 (H β pyrrole, d ^3J=4.1 Hz, d, 4H); 8.68 (H*meso*, s, 2H). MS FAB (*m/z*): calcd for $C_{47}H_{37}N_4O_2P^{102}Ru$ ($M-P(Ph)_2CH_3^+$)=822.1721. Found: 822.1711. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 423 (5.13), 507 (3.86).

4.3.7. 5,15-Bis(3-methoxyphenyl)porphyrinato ruthenium bis(methyl-diphenyl phosphine) 12. Yield: 84%. ^{1}H NMR ($CDCl_3$): δ −2.35 (CH_3 phosphine, t, 6H); 4.05 (CH_3 methoxy group, s, 6H); 4.15 (H phosphine *o*-phenyl ring, m, 8H); 6.50 (H phosphine *m*-phenyl ring, t, 8H); 6.81 (H phosphine *p*-phenyl ring, t, 4H); 7.32–7.85 (H porphyrin phenyl ring, m, 8H); 8.34 (H β pyrrole, d, ^3J=4.2 Hz, 4H); 8.65 (H β pyrrole, d, ^3J=4.2 Hz, 4H); 9.13 (H*meso*, s, 2H). MS FAB (*m/z*): calcd for $C_{47}H_{37}N_4O_2P^{102}Ru$ ($M-P(Ph)_2CH_3^+$)=822.1721. Found: 822.1711.

4.3.8. 5,15-Bis(9,9′-spirobifluoren-2-yl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl porphyrinato ruthenium bis(methyl-diphenyl phosphine) 18. Yield: 85%. ^{1}H NMR ($CDCl_3$, ppm): (αα and αβ): δ −2.70 (CH_3 phosphine, t, 1, 5H); −2.54 (CH_3 phosphine, t, 3H); −2.30 (CH_3 phosphine, t, 1, 5H); 1.53 (CH_3 ethyl, m, 12H); 2.13 (CH_3 methyl, s, 12H); 3.60 (CH_2 ethyl, m, 8H); 3.80 (H phosphine *o*-phenyl ring, m, 2H); 4.02 (H phosphine *o*-phenyl ring, m, 4H); 4.12 (H phosphine, *o*-phenyl ring, m, 2H); 5.75 (H phosphine *m*-phenyl ring, m, 4H); 6.01–6.10 (H phosphine, *m*-phenyl ring, m, 4H); 6.26 (H phosphine *p*-phenyl ring, m, 2H); 6.39 (H phosphine, *p*-phenyl ring, m, 2H); 6.87–7.93 (Hspirobifluorene, m, 30H); 9 ($H_{X,XX}$ *meso*, s, 1H); 9.1 ($H_{X,XX}$ *meso*, s, 1H). ^{31}P NMR ($CDCl_3$, ppm) (αα and αβ): 3.14 (P phosphine, 1P); 3.16 (P phosphine, 1P). MS (ESI: $CHCl_3$/MeOH: 95/5) (*m/z*): calcd for $C_{108}H_{90}N_4P_2$ ^{102}Ru ($M^{\cdot+}$):1606.5715. Found: 1606.5707. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 426 (5.10); 507 (4.2).

4.3.9. *meso*-5,10,15,20-Tetrakis(9,9′-spirobifluoren-2-yl)porphyrinato ruthenium bis(methyl-diphenyl phosphine) 22. Yield: 88%. ^{1}H NMR (toluene d_8, ppm) (4α, 3αβ, 2α2β, αβαβ): δ −2.90 (CH_3 phosphine, t, 0.37H); −2.64 (CH_3 phosphine, t, 1.5H); −2.36 (CH_3 phosphine, t, 1.5H); −2.31 (CH_3 phosphine, t, 0.75H); −2.04 (CH_3 phosphine, t, 1.5H); −1.82 (CH_3 phosphine, t, 0.37H); 4.09 (H phosphine, *o*-phenyl ring, m, 2H); 4.39 (H phosphine, *o*-phenyl ring, m, 4H); 4.50 (H phosphine, *o*-phenyl ring, m, 2H); 5.84 (H phosphine, *m*-phenyl ring, m, 2H); 6.12 (H phosphine *m*-phenyl ring, m, 6H); 6.52 (H phosphine, *p*-phenyl ring, m, 4H); 6.97–8.32 (H spirobifluorene+H β pyrrole, m, 68H). ^{31}P NMR (toluene d_8, ppm): 2.42 (s, br, 1P); 2.45 (s, br, 0.75P); 2.56 (s, 0.25P). UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 437 (5.43); 522 (3.47).

4.3.10. *meso*-5,10,15,20-Tetrakis(3-methylphenyl)-porphyrinato-rutheniumbis(methyl-diphenyl phosphine) 26. Yield: 85%. ^{1}H NMR ($CDCl_3$, ppm): δ −2.12 (CH_3 phosphine, t, 6H); 2.61 (CH_3, s, 12H); 4.34 (H phosphine *o*-phenyl ring, m, 8H); 6.51 (H phosphine *m*-phenyl ring, t, 8H); 6.80 (H phosphine *p*-phenyl ring, t,

4H); 7.32–7.8 (H porphyrin phenyl ring, m, 16H); 8.1 (H β pyrrole, s, 8H).

4.4. Typical procedure for isocyanide ligation

To a solution of ruthenium carbonyl complex (50 μmol) in distilled chloroform or dichloromethane was added *t*-butylisocyanide (300 μmol) under an argon atmosphere. The solution was stirred at room temperature until the reaction was completed. The bis-ligation was checked by monitoring the UV–VIS spectrum. After filtration, the solvents were removed under vacuum and the residue was dissolved in dichloromethane. Pentane was then added and the solution was set aside for one day for crystallization at 0 °C. Purple crystals of Ru(II) bis(*t*-butylisocyanide) complex were collected by filtration and washed with hexane.

4.4.1. 5,15-Bis(9,9′-spirobifluoren-2-yl)porphyrinato ruthenium bis(*t*-butylisocyanide) 9. Yield: 85%. ^{1}H NMR ($CDCl_3$, ppm) (αα and αβ): δ −0.99 (CH_3 *t*-BuNC, s, 4.5H); −0.76 (CH_3 *t*-BuCN, s, 9H); −0.64 (CH_3 *t*-BuCN, s, 4.5H); 6.86–7.77 (H spirobifluorene, m, 24H); 8.12 (H spirobifluorene, m, 6H); 8.43 ($H_{III,VII,XIII,XVII}$ β pyrrole, m, 4H), 8.75 ($H_{II,VIII,XII,XVIII}$, β pyrrole, d, 4H), 9.42 ($H_{X,XX}$ *meso*, s, 2H).MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m*/*z*): calcd for $C_{80}H_{58}N_6{}^{102}Ru$ ($M^{\cdot+}$):1204.3766. Found: 1204.3780. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (5.10); 296 (4.73); 308 (4.75); 411 (5.28); 525 (3.98); 560 (3.59). IR (liquid, CH_2Cl_2, cm^{-1}): ν_{CN} 2219.

4.4.2. 5,15-Bis(2-methoxyphenyl) porphyrinato ruthenium bis(*t*-butylisocyanide) 13. Yield: 85%. ^{1}H NMR ($CDCl_3$, ppm): αα isomer δ −0.92 (CH_3 *t*-BuNC, s, 9H); −0.21 (CH_3 *t*-BuNC, s, 9H); 4.12 (CH_3 methoxy, s, 6H); 7.3–7.8 (H porphyrin phenyl ring, m, 8H); 8.91 (H β pyrrole, d ^3J=4 Hz, 4H), 9.15 (H, β pyrrole, d ^3J=4 Hz, 4H), 9.7 (H *meso*, s, 2H). αβ isomer: −0.58 (CH_3 *t*-BuNC, s, 18H); 4.07 (CH_3 methoxy, s, 6H); 7.3–7.8 (H phenyl ring, m, 8H); 8.43 (H β pyrrole, d ^3J=4 Hz, 4H), 8.75 (H, β pyrrole, d ^3J=4 Hz, 4H), 9.62 (H *meso*, s, 2H). ν_{CN}: 2112.

4.4.3. 5,15-Bis(3-methoxyphenyl) porphyrinato ruthenium bis(*t*-butylisocyanide) 14. Yield: 80%. ^{1}H NMR ($CDCl_3$, ppm): −0.62 (CH_3 *t*-BuNC, s, 18H); 4.2 (CH_3 methoxy, s, 6H); 7.3–7.8 (H porphyrin phenyl ring, m, 8H); 8.3 (H β pyrrole, d ^3J=4 Hz, 4H), 8.55 (H, β pyrrole, d ^3J=4.3 Hz, 4H), 9.82 (H *meso*, s, 2H). ν_{CN}: 2113.

4.4.4. 5,15-Bis(9,9′-spirobifluoren-2-yl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl porphyrinato ruthenium bis(*t*-butylisocyanide) 19. Yield: 85%. ^{1}H NMR ($CDCl_3$, ppm) (αα and αβ): δ −0.94 (CH_3 *t*-BuCN, s, 4.5H); −0.70 (CH_3 *t*-BuCN, s, 9H); − 0.58 (CH_3 *t*-BuCN, s, 4.5H); 1.62 (CH_3 ethyl, m, 12H); 2.30 (CH_3 methyl, s, 12H); 3.74 (CH_2 ethyl, m, 8H); 7.07–8.12 (H spirobifluorene, m, 30H); 9.39 ($H_{X,XX}$ *meso*, s, 2H). MS (ESI:$CHCl_3$/MeOH: 95/5) (*m*/*z*): calcd for $C_{92}H_{82}N_6{}^{102}Ru$ ($M^{\cdot+}$): 1372.5671. Found: 1372.5702. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 228 (4.92); 296 (4.56); 308 (4.58); 411 (5.11); 520 (3.86); 560 (3.40). IR (KBr, cm^{-1}): ν_{CN} 2113.

4.4.5. *meso*-5,10,15,20-Tetrakis(9,9′-spirobifluoren-2-yl)-porphyrinato-ruthenium bis(*t*-butylisocyanide) 23. Yield: 90%. ^{1}H NMR ($CDCl_3$, ppm) (4α, 3αβ, 2α2β, αβαβ): δ-1.18 (CH_3 *t*-BuCN, s, 1.1H); −0.96 (CH_3 *t*-BuCN, s, 4.5H); −0.86 (CH_3 *t*-BuCN, s, 2.25H); −0.74 (CH_3 *t*-BuCN, s, 4.5H); −0.62 (CH_3 *t*-BuCN, s, 4.5H); −0.50 (CH_3 *t*-BuCN, s, 1.1H); 6.88 (H spirobifluorene, d, 4H); 7.02 (H spirobifluorene, m, 8H), 7.18 (H spirobifluorene, m, 12H); 7.30–7.51 (H spirobifluorene, m, 16H); 7.70 (H spirobifluorene, t, 8H); 8.02 (H spirobifluorene, m, 12H); 8.12 (H β pyrrole, m, 8H). MS (ESI: CH_2Cl_2/MeOH: 9/1) (*m*/*z*): calcd for $C_{130}H_{86}N_6{}^{102}Ru$ ($M^{\cdot+}$): 1832.5957. Found: 1832.6014. UV–VIS (CH_2Cl_2): $\lambda_{max/nm}$ (log ε): 227 (5.21); 297 (4.68); 307 (4.7); 425 (5.52); 532 (3.55). IR (KBr, cm^{-1}): ν_{CN} 2107.

4.4.6. *meso*-5,10,15,20-Tetrakis(3-methylphenyl)porphyrinato-ruthenium bis(*t*-butylisocyanide) 27. Yield: 90%. ^{1}H NMR ($CDCl_3$, ppm) −0.41 (CH_3 *t*-BuNC, s, 18H); 2.65 (CH_3, s, 12H); 7.6 (H porphyrin phenyl ring, m, 8H); 8.01 (H porphyrin phenyl ring, m, 8H); 8.47 (H β pyrrole, s, 8H).

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Sulfur-containing sesquiterpenes from *Thapsia villosa*

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Abstract—Three new sesquiterpenoids bearing sulfurated ester groups have been isolated from the roots of *Thapsia villosa* L. Their structures have been elucidated by spectroscopic means. This is the first time that a methylthiopropionic acid ester is isolated from natural sources.

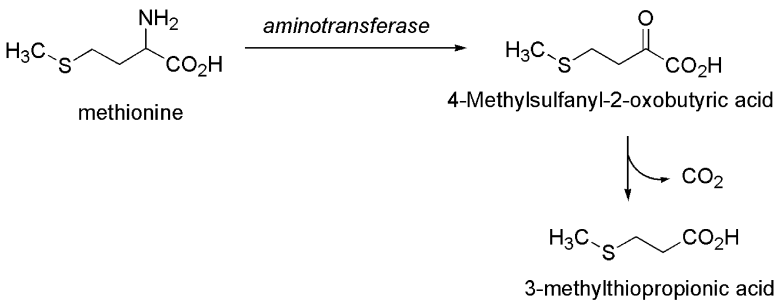
1. Introduction

The presence of sulfur atoms in groups other than sulfates and disulfide bridges in metabolites isolated from natural sources is infrequent. Only certain species belonging to the genus *Petasites* (Compositae),[1] are known to produce sulfurated sesquiterpenes, in higher plants. Sulfur is usually found in ester groups, which biogenetically comes from methionine through the action of an aminotransferase and further decarboxylation to yield 3-methylthiopropionic acid (Scheme 1).[2] Those sulfur-containing compounds isolated from *Petasites* have shown a broad range of activities such as inhibitors of testosterone secretion,[3] calcium channel blockers[4] or anti-inflammatory.[5]

Thapsia villosa L. (Apiaceae) is a perennial herb which grows in uncultured soils of the Western Mediterranean area. Traditionally, it has been used in the folk medicine in Catalonia against scabies.[6] Recently, it has been reported to possess ichthyotoxic activity.[7]

T. villosa displays an extremely variable morphology which often leads to misidentification of the material collected. From a taxonomic point of view, the species is divided into two groups differing in the number of chromosomes and the compounds that they produce. Previous studies of *T. villosa* have provided phenyl propanoids, germacranes, thapsigargin-related guaianolides, slovenolide-type guaianolides and a relatively small group of sesquiterpenes known as thapsanes.[8]

In this work, we report our results on the reinvestigation of the roots of *T. villosa* L. Along with the known phenylpropanoid helmanticine[8b] and the guaianolide thapsivillosine C,[8a] three new sesquiterpenoids bearing sulfur-containing ester groups have been isolated (Fig. 1).



Scheme 1. Formation of 3-methylthiopropionic acid from methionine.

Keywords: *Thapsia villosa*; Sulfur; Sesquiterpene; Methylthiopropanoate ester; Methylthiopropenoate ester.
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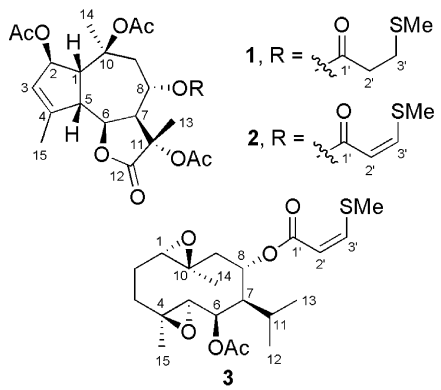

Figure 1. Novel sesquiterpenes from *T. villosa*.

2. Results and discussion

The dichloromethane extract of the roots was subjected to flash chromatography affording **1** (28 mg), **2** (7 mg) and **3** (250 mg).

The presence of a sulfur atom in compound **1** was detected by elemental analysis and confirmed by HREIMS in which a molecular ion [M^+] at *m/z* 526.1860 was in agreement with the molecular formula $C_{25}H_{34}O_{10}S$ (9 degrees of unsaturation). The IR spectrum showed the presence of carbonyl groups at 1791 and 1738 cm^{-1}, the former corresponding to a γ-lactone moiety.

In the ^1H NMR spectrum, some protons, later identified as those of the methylthiopropionate group showed very broad signals. Likewise, the intensity of the ^{13}C NMR signals of their corresponding carbon atoms was also very low. This problem was minimized by running the spectra at −50 °C.

The ^{13}C NMR spectrum displayed twenty five signals, five of which corresponding to carbonyl groups (δ_C 173.9, 170.7, 170.6, 170.1 and 169.9), two were olefinic carbons (δ_C 149.5 and 126.1), and five of them corresponding to carbon atoms bearing oxygenated functionalization (δ_C 79.7, 79.3, 77.8, 75.4 and 65.7).

The five carbonyl groups and the double bond, accounted for 6 degrees of unsaturation. If a γ-lactone ring was present, the compound should be bicyclic. Assuming a bicyclic fused structure, two likely possibilities were considered: a 6.6 or a 5.7 bicyclic compound. The latter possibility was finally confirmed by the different correlations found in the HMBC spectrum.

In the $^1H-^1H$ COSY spectrum, the lactone ring proton, H-6 (δ_H 4.83) was coupled to a C*H* proton (H-7, δ_H 3.60), which in turn was coupled to another C*H* proton (H-8, δ_H 5.80). The chemical shift of C-8 (δ_C 65.7), indicated the presence of an oxygenated group. H-8 was also coupled to two geminal protons at δ_H 2.60 and 1.96 which showed no additional coupling. Thus, the partial structure **A**, shown in Figure 2, was deduced.

A different coupling sequence was found starting from H-6 (partial structure **B**, Fig. 2): H-6 with H-5 (δ_H 3.10), H-5 with H-1 (δ_H 3.42), and H-1 with H-2 (δ_H 5.70). H-2 showed in the HSQC spectrum a cross coupling correlation with C-2 at δ_C 79.4, thus indicating the presence of an ester group at C-2. -2 was finally coupled with a vinylic methine (H-3). Its corresponding carbon, C-3 was correlated in the HMBC spectrum with H-15 (Fig. 2).

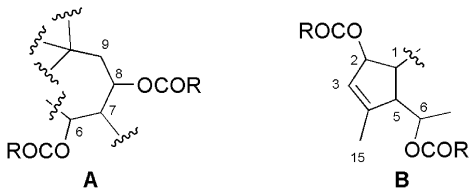

Figure 2. Partial structures found for **1**.

The ^1H NMR spectrum showed additionally the presence of three acetate groups at δ_H 2.10, 2.03, 2.02 which accounted for three of the carbonyl groups. The remaining two carbonyl groups were then assigned to the γ-lactone ring and an additional ester group.

The nature and location of the ester group was deduced as follows. The ^1H NMR spectrum showed two methylene groups coupled each other at δ_H 2.60 (*m*, 2H) and 2.80 (*m*, 2H), assigned to 2H-2′ and 2H-3′ respectively. C-3′ showed a long distance correlation with a $-S-CH_3$ group. The two H-2′ protons were coupled in the HMBC spectrum with C-1′ (δ_C 170.1), which showed additionally a coupling correlation with H-8 at δ_H 5.80. All these correlations were in agreement with a methylthiopropionate ester, $-O-CO-CH_2CH_2-S-CH_3$, located at C-8. His is the first time that this ester group has been reported as part of a natural product.

The HMBC spectrum allowed also to locate the remaining acetoxyl group at C-2 (δ_C 79.4), C-10 (δ_C 79.7) and C-11 (δ_C 77.8) (Fig. 3).

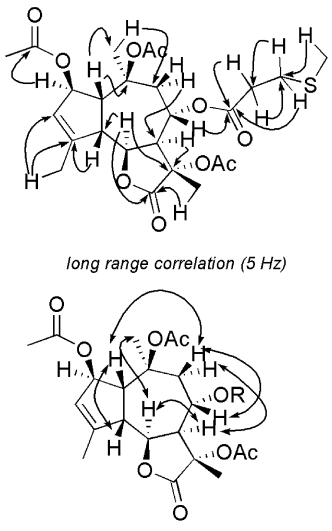

Figure 3. Long range correlations (up) and NOE effects (down) observed in **1** (*J*=5 Hz).

Finally, the relative stereochemistry of the different stereogenic centres was confirmed by NOE experiments and the coupling constant values. The structure of

compound **1** and the observed HMBC correlations are depicted in Figure 3.

Spectral data of compound **2** showed a close resemblance to those of compound **1**. The presence of a sulfur atom was again confirmed by elemental analysis. The HREIMS displayed a peak at *m/z* 464.1500 according to a molecular formula $C_{23}H_{28}O_8S$ and corresponding to $[M-HOAc]^+$ ion. The carbonyl absorptions in the IR spectrum were shown at 1791 and 1734 cm^{-1}. Finally, the ^{13}C NMR showed the presence of an additional double bond in comparison to **1** (δ_C 153.5 and 112.3).

The main difference in the ^1H NMR spectrum consisted on the presence of two mutually coupled doublet signals centered at δ 7.10 and 5.76 respectively. The HSQC spectrum allowed the identification of their corresponding carbons at δ_C 153.5 and 112.3, the former showing a correlation in the HMBC with the S–CH_3 group. These facts led to the identification of the side chain as –O–CO–CH=CH–SMe.[9] The value of the coupling constant $J_{2'-3'}$=10.3 Hz, suggested a *Z*-configuration of the double bond in the chain.

The remaining signals were similar to those in compound **1**. With all these data, the structure of compound **2** is proposed as depicted in Figure 1.

The molecular formula of germacrane **3** was determined by elemental analysis and confirmed by HREIMS (*m/z* 412.1905, $C_{21}H_{32}O_6S$, 6 degrees of unsaturation). The IR spectrum showed an absorption at 1740 cm^{-1}, corresponding to an ester group.

The ^{13}C NMR showed signals corresponding to the presence of two carbonyl groups (δ_C 170.4 and 165.6) and a double bond (δ_C 153.1 and 112.9), which accounted for three degrees of unsaturation. The molecule should be therefore a tricyclic compound.

The presence of six carbons bearing oxygenated groups (δ_C 73.2, 69.3, 66.6, 61.5, 58.8 and 58.7) was also shown in the spectrum. Taking into account that one carbonyl group was located as a part of an acetoxyl group and the other belonged to a different ester group, it left unassigned only two oxygen atoms bonded to four carbons.

From the analysis of the $^1H-^1H$ COSY spectrum, the following correlation sequence could be deduced: The proton H-5 (δ_H 3.16) was coupled to H-6 (δ_H 4.89), which was in turn coupled to H-7 (δ_H 1.60). H-7 was correlated to a methyne at δ_H 1.84 (H-11). Finally H-11 was coupled to two methyl groups at δ_H 1.13 (3 H-12, *J*=6.5 Hz) and 0.95 (3 H-13, *J*=6.5 Hz), respectively. This fact meant that H-11, H-12 and H-13 formed an isopropyl group bonded at C-7 (partial structure B, Fig. 4).

The HSQC spectrum allowed the identification of C-11 (δ_C 26.4), which was correlated in the HMBC spectrum to a C*H* at δ 5.66 (H-8). The chemical shift of C-8 (δ_C 69.3) implied the presence of an oxygenated function at C-8. Surprisingly, no correlation was found between H-7 and H-8 in the $^1H-^1H$ COSY, nor between H-7 and C-8 in the HMBC

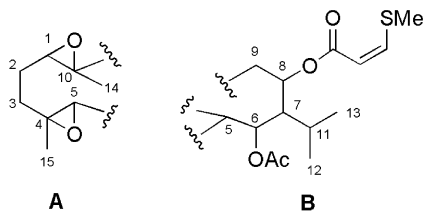

Figure 4. Partial structures found for **3**.

spectrum. Finally, two protons at δ_H 2.23 (H-9α) and 1.85 (H-9β) showed a correlation with C-8 in the HMBC spectrum and confirmed their identity in the HSQC spectrum by a coupling with C-9 (δ_C 42.5).

Another correlation set was also observed in the $^1H-^1H$ COSY spectrum. The proton at δ_H 3.08 (H-1) was coupled to two protons mutually coupled at δ_H 1.45 and 2.07, assigned to H-2β and H-2α. These two protons were coupled to H-3β (δ_H 1.26) and H-3α (2.17), whose corresponding carbon C-3 was shown at δ_C 36.5. -3 showed a correlation in the HMBC spectrum with H-15, which in turn exhibited two additional correlations in the HMBC spectrum with two oxygenated carbons, C-4 (58.8) and C-5 (66.6). This would place an epoxide ring between C-4 and C-5 (partial structure A, Fig. 4).

Similarly, the methyl group located at δ 1.45 (3 H-14) displayed correlations in the HMBC spectrum with carbons at δ_H 58.7 (C-10) and δ_H 61.5, which indicated the presence of a second epoxide ring between C-10 and C-1.

The nature of the ester group was deduced similarly as in **1**. The ^1H NMR showed the presence of an isolated ethylene group as two doublets mutually coupled at δ_H 5.80 (H-2′) and 7.05 (H-3′), whose corresponding carbon atoms were found in the HSQC spectrum at δ_C 112.9 (C-2′) and 153.2 (C-3′). C-3 was correlated with the –S–C*H*$_3$ protons at δ_H 2.38. -2′ showed a correlation with the carbonyl C-1′, which was in turn correlated with H-8 in the HMBC spectrum, confirming the presence of a –O–CO–CH=CH–SCH_3 group located at C-8. The *Z* configuration of the double bond was inferred from the value of the coupling constant (*J*=10.0 Hz).

Finally, the relative configuration of the germacrane was deduced from a NOE study of the molecule. The main effects observed are depicted in Figure 5.

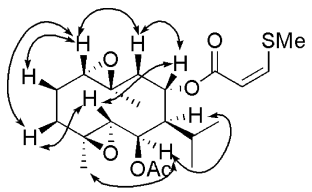

Figure 5. NOE effects observed in **3**

In summary, three new metabolites have been isolated from *Thapsia villosa*. The main novelty of these compounds is the presence of methylthiopropionate or methylthiopropenoate esters. To our knowledge, it is the first time that a methylthiopropionate group is reported as part of a natural

Table 1. ^{1}H and ^{13}C NMR data for compounds **1–3**

Guaianolide 1					Guaianolide 2					Germacrane 3				
H	δ_H	Mult	*J* (Hz)	δ_C	H	δ_H	Mult	*J* (Hz)	δ_C	H	δ_H	Mult	*J* (Hz)	δ_C
1	3.42	dd	$J_{1,5}$=7.8 Hz, $J_{1,2}$=2.1 Hz	50.1	1	3.33	dd	$J_{1,2}$=2.2 Hz, $J_{1,5}$=8 Hz	51.9	1	3.08	d	10.4	61.5
2	5.70	m	–	79.4	2	5.77	m	–	79.6	2α	1.45	m	–	23.8
3	5.60	m	–	126.1	3	5.63	m	–	126.6	2β	2.07	dt	$J_{3\alpha,2\alpha}$=14.6 Hz, $J_{2\alpha-3\alpha}$=3.4 Hz	
4	–	–	–	149.6	4	–	–	–	149.5	3-α	2.17	dt	$J_{3\alpha,2\beta}$=13.2 Hz, $J_{3\alpha-2\alpha}$=3.4 Hz	36.6
5	3.10	m	–	49.6	5	3.1	m	–	50.1	3-β	1.26	m	–	
6	4.83	dd	$J_{6,5}$=11.7 Hz, $J_{6,7}$=9.6 Hz	75.4	6	4.83	dd	$J_{6,5}$=11.9 Hz, $J_{6,7}$=9.7 Hz	76.1	4	–	–	–	58.8
7	3.60	dd	$J_{7,6}$=9.6 Hz, $J_{7,8}$=11.0 Hz	48.3	7	3.68	dd	$J_{7,6}$=9.9 Hz, $J_{7,8}$=11.0 Hz	48.3	5	3.16	d	J_{5-6}=6.8 Hz	66.6
8	5.80	td	$J_{8,7}$=$J_{8,9\alpha}$=11.0 $J_{8,9\beta}$=2.7 Hz	65.7	8	5.73	td	$J_{8,7}$=$J_{8,9\alpha}$=11.2 Hz, $J_{8,9\beta}$=2.8 Hz	65.7	6	4.89	dd	$J_{6,5}$=6.8 Hz, $J_{6,7}$=1.0 Hz	73.2
9α	1.96	dd	$J_{9\alpha,9\beta}$=13.5 $J_{9\alpha,8}$=11.2	44.5	9α	2.14	dd	$J_{9\alpha,9\beta}$=15.4 Hz, $J_{9\alpha,8}$=11.2	44.9	7	1.6	d	$J_{7,11}$=8.7 Hz	48.5
9β	2.60	dd	$J_{9\beta,9\alpha}$=13.5 Hz, $J_{9\beta,8}$=2.7 Hz		9β	2.62	dd	$J_{9\beta,9\alpha}$=15.4 Hz, $J_{9\beta,8}$=2,8 Hz		8	5.66	dd	$J_{8\text{-}9\alpha}$=12.2 Hz, $J_{8\text{-}9\beta}$=5.8 Hz	69.3
10	–	–	–	79.7	10	–	–	–	80.6	9-α	2.23	t	$J_{9\alpha\text{-}8}$=12.2 Hz	
11	–	–	–	77.8	11	–	–	–	78.1	9-β	1.85	dd	$J_{9\beta\text{-}8}$=5.8 Hz, $J_{9\beta-9\alpha}$=13,7 Hz	42.5
12	–	–	–	173.9	12	–	–	–	173.7	10	–	–	–	58.7
13	1.60	s	–	20.3	13	1.62	s	–	20.6	11	1.84	m	–	26.5
14	1.24	s	–	26.9	14	1.38	s	–	26.4	12	1.13	d	J_{12-13}=6.5 Hz	23.2
15	1.90	d	$J_{15,3}$=1.0 Hz	17.3	15	1.95	d	$J_{15,3}$=1.1 Hz	17.4	13	0.95	d	J_{13-12}=6.5 Hz	21.5
1′	–	–	–	170.1	1′	–	–	–	164.8	14	1.45	s	–	22.4
2′	2.60	m	–	34.1	2′	5.76	d	10.3	112.3	15	1.26	s	–	17.2
3′	2.80	m	–	28.34	3′	7.1	d	10.3	153.5	1′	–	–	–	165.6
$-SCH_3$	2.13	s	–	15.3	$-SCH_3$	2.42	s	–	19.3	2′	5.80	d	$J_{2',3'}$=10.0 Hz	112.9
(*C-2*)$-OCOCH_3$	–	–	–	170.7	(*C-2*)$-OCOCH_3$	–	–	–	170.2	3′	7.05	d	$J_{3',2'}$=10.0 Hz	153.1
(*C-2*)$-OCOCH_3$	2.03	s	–	21.0	(*C-2*)$-OCOCH_3$	2.03	s	–	21.2	$-SCH_3$	2.38	s	–	19.6
(*C-10*)$-OCOCH_3$	–	–	–	170.7	(*C-10*)$-OCOCH_3$	–	–	–	170.4	$-OCOCH_3$	–	–	–	170.4
(*C-10*)$-OCOCH_3$	2.02	s	–	21.2	(*C-10*)$-OCOCH_3$	2.03	s	–	20.9	$-OCOCH_3$	1.92	s	–	21.0
(*C-11*)$-OCOCH_3$	–	–	–	170.0	(*C-11*)$-OCOCH_3$	–	–	–	169.9					
(*C-11*)$-OCOCH_3$	2.10	s	–	22.3	(*C-11*)$-OCOCH_3$	2.05	s	–	22.3					

product. Methylthiopropionate esters seems to come from the methylmethionine (MMT) and can be considered as precursors of DMSP (dimethylsulfonium propionate, its thiomethylated derivative). High levels of DMSP in the chloroplasts are related to the control of the saline levels in plants, serving as osmolites.[10] Enzymatic cleavage of DMSP in marine algae has been also reported, to lead to breakdown products that act as scavengers of hydroxyl radicals, thus serving as an antioxidant system.[11] It is noteworthy the fact that the enzymatic pool of *T. villosa* is able to place sulfurated esters on different sesquiterpenoid scaffolds. However, the role of the sulfur atoms in this species remains to be disclosed.

3. Experimental

3.1. General

Melting points are uncorrected and were measured in a Reichert-Jung apparatus. NMR spectra were recorded on a Varian Gemini 300, a Varian Inova 400 or in a Varian Inova 600. H chemical shifts were referenced to the residual $CHCl_3$ signal at δ 7.26 ppm. ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at δ 77.0 ppm. HMBC, HSQC and COSY spectra were recorded with standard Varian pulse gradient sequences. IR spectra were recorded in a Mattson Genesis Series FTIR, using NaCl plates; data are reported in cm^{-1}. Mass spectra were obtained in a Voyager GC–MS or in a VG Autospec-Q. Visualization of the TLC was performed by fluorescence quenching, aqueous ceric ammonium molybdate, anisaldehyde stains or H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Biological material

Specimens of *T. villosa* var *villosa* were collected in Sierra de San Cristóbal, El Puerto de Santa María, Cádiz, in May, 2002. A voucher specimen has been deposited at the Departamento de Ciencias y Recursos Agrícolas y Forestales, University of Córdoba collection (voucher # COA-31092).

3.3. Extraction and isolation

100 g of dried roots were extracted with CH_2Cl_2 in a Soxhlet apparatus for 6 h and concentrated to give a clear yellow oily residue (13.5 g). The extract was subjected to flash chromatography on silica gel. The fraction eluted with hexane–EtOAc (80:20) (4 g) was further chromatographed to give compounds **1** (28 mg) and **3** (250 mg). The fraction eluted with hexane–EtOAc (60:40) yielded **2** (7 mg).

3.3.1. Compound 1. Colorless oil; $[\alpha]_D^{25}=-40$ (*c* 0.13, $CHCl_3$); IR ν_{max} (film) cm^{-1} 2924, 1791, 1738, 1437, 1371, 1241, 1019, 757; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 466 $[M-HOAc]^+$ (1), 244 (16), 226 $[M-3HOAc-C_4H_8O_2S]^+$ (100), 173 (42); HREIMS 526.1860 (calcd for $C_{25}H_{34}O_{10}S$, 526.1873). $C_{25}H_{34}O_{10}S$: calcd. C 57.02, H 6.51, S 6.09; found C 57.35, H 6.64, S 6.21.

3.3.2. Compound 2. Amorphous white powder; $[\alpha]_D^{25}=-24.5$ (*c* 0.25, $CHCl_3$); IR ν_{max} (film) cm^{-1} 2921, 1790, 1733, 1566, 1371, 1240, 1155, 1019, 797; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 464 $[M-HOAc]^+$ (2), 422 $[M-C_4H_6O_3]^+$ (5), 226 $[M-3HOAc-C_4H_6O_2S]^+$ (54), 101 $[C_4H_5OS]^+$ (100); HREIMS 464.1500 $[M-HOAc]^+$ (calcd for $C_{23}H_{28}O_8S$, 464.1505). $C_{25}H_{32}O_{10}S$: calcd. C 57.24, H 6.15, S 6.11; found C 57.11, H 6.17, S 6.31.

3.3.3. Compound 3. Amorphous white powder; $[\alpha]_D^{25}=-18.3$ (*c* 0.25, $CHCl_3$); IR ν_{max} (film) cm^{-1} 2960, 1740, 1698, 1558, 1387, 1235, 1161, 992, 796; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 412 $[M]^+$ (1), 235 $[M-HOAc-C_4H_5O_2S]^+$ (1), 195 $[M-HOAc-C_3H_7-C_4H_6O_2S]^+$ (4), 193 (2), 163 (4), 149 (5), 101 $[C_4H_5OS]^+$ (100); HREIMS 412.1905 (calcd. for $C_{21}H_{32}O_6S$, 412.1920). $C_{21}H_{32}O_6S$: calcd C 61.14, H 7.82, S 7.77; found C 60.81, H 7.85, S 7.97.

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Diastereoselective Michael addition of (*S*)-mandelic acid enolate to nitroalkenes. Enantioselective synthesis of α-hydroxy-α,β-diaryl-γ-lactams

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Abstract—The reaction of the lithium enolate of the (*S*,*S*)-*cis*-1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with several aromatic nitroalkenes in the presence of HMPA proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. Reduction of the nitro group with Zn/HCl/EtOH/H_2O with concomitant intramolecular aminolysis of the acetal moiety leads directly to enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams.

1. Introduction

Recently, we have reported a highly diastereoselective Michael reaction of the (*S*)-mandelic acid enolate with α,β-unsaturated carbonyl compounds and the transformation of the corresponding adducts into highly enantioenriched 2-substituted 1,4-dicarbonyl compounds.[1] In that synthesis the strategy employed to exert stereochemical control in the newly created stereogenic centers involved the use of (*S*)-mandelic acid (**1**) as source of chiral information through its previous conversion into (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** derived from pivalaldehyde (Seebach principle of self-regeneration of stereocenters).[2] We have now extended this methodology to diastereoselective Michael additions using aromatic nitroalkenes as acceptors. The reactions of **2** and related dioxolanones with nitroalkenes have been previously reported, although with low yields and diastereoselectivities.[3] The only described example of such a reaction with **2** has involved nitropropene as Michael acceptor, but no examples with aromatic nitroalkenes have been reported so far.

By reduction of the nitro group in the resulting adducts with concomitant intramolecular aminolysis of the acetal moiety in a further step we have prepared enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams. γ-Lactams and γ-amino acids are important pharmacologically active compounds, as several neurological diseases have been associated with the deficiency of γ-aminobutyric acid (GABA). In fact several unnatural γ-amino acids have found pharmaceutical application as GABA analogues.[4] Although the molecule of GABA is achiral, the prochiral hydrogen atoms at each carbon atom of the GABA framework become mutually different during the interaction of GABA with the chiral biomolecules of the different GABA synaptic mechanisms.[4a,5] Consequently the synthesis of GABA model compounds containing chiral centers with established absolute stereochemistry and in which the conformational and electronic effects can be modified is an important and current target in organic synthesis.[6]

2. Results and discussion

Herein we report on the diastereoselective Michael addition of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** to aromatic nitroalkenes as the key step for a stereoselective synthesis of α-hydroxy-α,β-diaryl-γ-lactams. Nitroalkenes are easily obtained via the Henry reaction[7] and subsequent dehydration, besides they are excellent Michael acceptors due to the strong anion-stabilising effect of the nitro group and in addition the nitro group can be converted into a broad range of functionalities such as the carbonyl group via Nef reaction or an amino group by reduction.[8] However, despite the recent advances in this area,[9] there are very few examples of diastereoselective Michael reactions with nitroalkenes.[10]

At first, the enolate of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** was reacted with nitrostyrene (Scheme 1, Table 1) using an inverse addition protocol,[1] that is to say, a mixture of both compounds in THF was treated at −78 °C with a solution of LDA (1.5 equiv.). After the reaction mixture reached

Keywords: Nitrostyrenes; 1,4-Addition; Dioxolanone; GABA; Self-regeneration of stereocenters.
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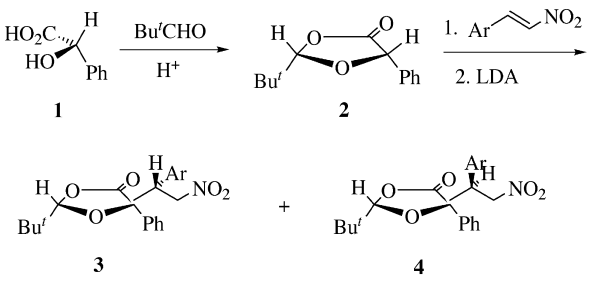


a Ar = Ph; **b** Ar = 4-MeO-Ph; **c** Ar = 3,4-$(MeO)_2$-Ph; **d** Ar = 2,4-$(MeO)_2$-Ph
e Ar = 4-OH, 3-MeO-Ph; **f** Ar = 4-Br-Ph; **g** Ar = 4-CF_3O-Ph; **h** 4-CF_3-Ph

Scheme 1.

Table 1. Michael reaction of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with nitrostyrene

Entry	Additive (eq.)	Product	Yield[a] (%)	dr[b] **3a/4a**
1	None	**3a**+**4a**	36	63/37
2	HMPA (1.5)	**3a**+**4a**	53	84/16
3	HMPA (3.0)	**3a**+**4a**	70	85/15
4	HMPA (6.0)	**3a**+**4a**	71	80/20
5	DMPU (3.0)	**3a**+**4a**	66	89/11
6	TMEDA (3.0)	**3a**+**4a**	25	37/63

[a] Yield refer to isolated diastereoisomeric product mixture.
[b] Ratios determined by ^{1}H NMR.

−40 °C, it was quenched with aqueous NH_4Cl and extracted with ethyl ether. This procedure provided the Michael adducts with poor yield (36%) and moderate diastereoselectivity (**3a**–**4a** ratio 63:37) (entry 1). However the use of HMPA as an additive increased the yield and the diastereoselectivity.[11] Thus the addition of 1.5 equiv. of HMPA (entry 2) improved the reaction yield up to 53% which was much more increased up to 70% with the addition of 3 equiv.. of HMPA (entry 3). In both cases, the reaction took place with a notable increasing of the diastereoselectivity (85:15). Addition of more HMPA (6 equiv.) (entry 4) did not further enhance the yield of the reaction nor modified the diastereoselectivity. The use of DMPU (entry 5) as substitute for HMPA increased slightly the diastereoselectivity but gave a lower yield, while the use of TMEDA decreased both yield and diastereoselectivity.

In order to investigate the effect of the substituents on the aromatic ring of the nitroalkenes and the generality of the method, the reaction was carried out with a range of different substrates (Table 2). The reaction with aromatic nitroalkenes bearing electron-donating groups (entries 2–5) gave products **3**–**4** in good to excellent yields (79–96%) while with aromatic nitroalkenes having electron-withdrawing groups (entries 6–8) gave products **3**–**4** in poor yields. In regard to the diastereoselectivity, the diastereoisomeric ratios range from 85:15 to 90:10 in the case of electron-donating substituted nitroalkenes, while somewhat lower, but still good diastereoisomeric ratios (ranging from 73:27 to 84:16) were observed with electron-withdrawing substituted nitroalkenes.

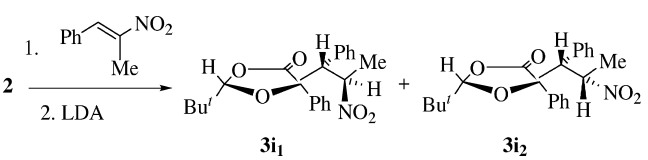
Table 2. Michael reaction of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** with nitroalkenes

Entry	Nitroalkene	Product	Yield[a] (%)	dr[b] **3/4**
1	Nitrostyrene	**3a**+**4a**	70	85/15
2	*p*-Methoxynitrostyrene	**3b**+**4b**	79	90/10
3	3,4-Dimethoxy nitrostyrene	**3c**+**4c**	96	87/13
4	2,4-Dimethoxy nitrostyrene	**3d**+**4d**	94	85/15
5	4-Hydroxy-3-methoxynitrostyrene	**3e**+**4e**	79	85/15
6	*p*-Bromonitrostyrene	**3f**+**4f**	43	84/16
7	*p*-Trifluoromethoxy nitrostyrene	**3g**+**4g**	39	80/20
8	*p*-Trifluoromethyl nitrostyrene	**3h**+**4h**	16	73/27
9	α-Methylnitrostyrene	**3i**+**4i**[c]	66	93/7

[a] Yield refer to isolated diastereoisomeric product mixture.
[b] Ratios determined by ^{1}H NMR.
[c] Compound **3i** is a 50:43 epimer mixture. Compound **4i** is a 4:3 epimers mixture.

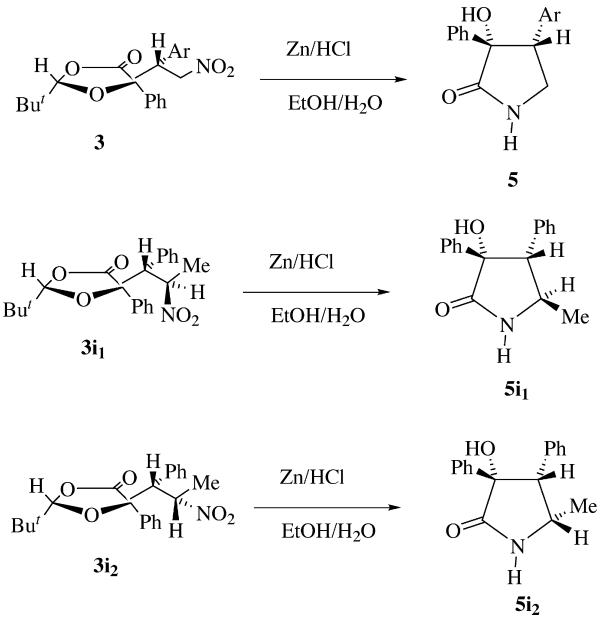
It is important to note that the Michael adducts were obtained as only two diastereoisomers out of the four possible ones for the two newly created stereogenic centers. The stereochemical structures of the Michael adducts **3** and **4** were elucidated by NOEs. These experiments showed in all of the cases the *cis*-relationship between the *t*-Bu group and the phenyl group from the original mandelic acid. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *S*, upon the consideration that the absolute configuration of the acetal carbon bearing the *t*-Bu group in **2** is *S* and it keeps unaltered from **2** to **3** or **4**.[1,2] The assignment of the stereochemistry at the tertiary stereocenter in the side chain was established later, after cyclisation to γ-lactams **5** (see below). These results are compatible with the assumption that the lithium enolate of **2** reacts exclusively from its *Re*-face, the major stereoisomer **3** resulting from the attack to the *Re*-face of the nitroalkenes (relative topicity like) and the minor stereoisomer **4** from the attack to the *Si*-face (relative topicity unlike)

The reaction of the enolate of **2** with α-methylnitrostyrene (entry 9) provides three new stereogenic centers (Scheme 2). Only four out of the eight possible stereoisomers were formed. As in the other cases, the stereogenic centers at β and γ positions with respect to the nitro group are formed during the carbon–carbon bond-forming step, which took place with relative topicity like between the *Re* faces of the enolate and nitroalkene, in the major product **3** and with relative topicity unlike between the *Re* and *Si* faces of the enolate and nitroalkene, respectively, in the minor product **4** (ratio **3i**–**4i** 93:7). The third stereogenic center (α to the nitro group) is formed by a non-diastereoselective protonation of the nitronate intermediate, so that the major adduct is a mixture of epimers at the nitro α position $\mathbf{3i_1}$ and $\mathbf{3i_2}$ (ratio 50:43), which could be separated by HPLC.[12] We would like to remark that the reactions described in this paper are the first examples of addition of **2** to aromatic nitroalkenes, as well as the advantages of our modifications with respect to other procedures,[3] i.e. the inverse addition protocol[1] and the use of HMPA, which allow to obtain good yields (70–96%) and stereoselectivities with nitrostyrenes substituted with electron-donating groups.



Scheme 2.

With the major Michael adducts **3a**-**3f** and **3i$_1$** and **3i$_2$** in hand, we carried out the reduction of the nitro group with Zn/HCl/EtOH/H_2O (Scheme 3). The reaction took place with concomitant intramolecular aminolysis of the acetal moiety leading directly to enantiomerically pure α-hydroxy-α,β-diaryl-γ-lactams **5**.[13]



Scheme 3.

The stereochemical structures of the γ-lactams **5** were established by NOEs. The choice of DMSO-d_6 for these experiments was crucial since it is known that this solvent slows down the exchange of the hydroxyl proton which in our case provided a good starting point for NOE experiments.[14] For instance, in compound **5b** irradiation at δ 5.98 (s) enhanced the signal at δ 7.24 (d) of the phenyl group and the signal at δ 6.96 (d) of the *p*-methoxyphenyl group indicating the *cis*-relationship between the hydroxyl and the *p*-methoxyphenyl groups. In the reverse direction, irradiation at δ 6.96 (d) enhanced the signal at δ 5.98 (s) corresponding to the hydroxyl group and, furthermore gave NOEs with signals at δ 6.74 (d) corresponding to the *meta*-aromatic protons and δ 3.44 (t) of the CH group and δ 3.59 (t) of the *cis*-proton on the CH_2 group (see Figure 1). According to these experiments the absolute configuration of the tertiary carbon atom bearing the aryl group was then assigned to be *R*, upon the consideration that the absolute configuration of the quaternary carbon bearing the phenyl group was *S* in all the cases as explained earlier. These experiments also allowed the assignment of the absolute stereochemistry of the tertiary stereocenter of compounds **3**, i.e. the *R* configuration of this stereocenter in compound **5** was assigned to this carbon in its Michael adduct precursor **3**. The opposite configuration *S* was therefore assigned in adduct **4** since both **3** and **4** are epimers at this position.

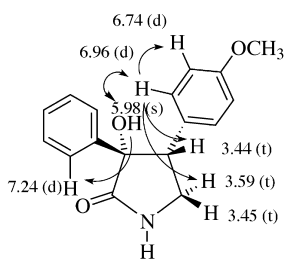


Figure 1. Significative NOEs in compound **5b**.

In summary, we have developed a diastereoselective Michael reaction of a mandelic acid enolate equivalent with aromatic nitroalkenes based on the Seebach principle of self-regeneration of stereocenters.[2] The reaction provides the corresponding adducts with good yields and diastereoisomeric excesses specially with aromatic nitroalkenes bearing electron-donating groups. By reduction with Zn/HCl/EtOH/H_2O, the Michael adducts were converted in the title compounds which constitute interesting enantiomerically pure GABA analogues.

3. Experimental

3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Optical rotations were determined on a Perkin–Elmer 243 polarimeter. NMR spectra were recorded on a Bruker Advance 300 DPX spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz) or a Varian Unity 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) as indicated, and referenced to the residual non-deuterated solvent as internal standard. The carbon type was determined by DEPT experiments. In the case of 3d the ^{13}C NMR was registered in DMSO-d_6 at 70 °C in order to observe all the expected signals. Mass spectra were run by electron impact at 70 eV or by chemical ionisation using methane as ionising gas on a Fisons Instruments VG Autospec GC 8000 series spectrometer. (*S*,*S*)-*cis*-1,3-dioxolan-4-one 2 was prepared according to the literature.[15]

3.2. Michael reaction of nitroalkenes to (*S*,*S*)-*cis*-1,3-dioxolan-4-one 2

A solution of freshly prepared LDA (1.25 mmol) in dry THF (1.3 mL) was slowly added to a solution of (*S*,*S*)-*cis*-1,3-dioxolan-4-one **2** (220 mg, 1 mmol) and the nitroalkene (1.25 mmol) in dry THF–HMPA (5 mL:0.53 mL) at −78 °C. After 1 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl at this temperature, and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel to afford Michael adducts **3** and **4**, which were analysed by ^{1}H NMR in order to determine the ratio of both compounds (yields and diastereoisomeric ratios are included in Table 2). Careful flash chromatography (silica gel, hexane–diethyl ether or hexane–dichloromethane) gave pure adducts **3** and adducts **4** slightly contaminated with minor amounts of **3**. Adducts **3g/4g** and **3h/4h** were not separated.

3.2.1. Michael adduct 3a. Mp 112–114 °C (CH_2Cl_2); $[\alpha]_D^{25}=-64.9$ (*c* 0.8, $CHCl_3$); HRMS *m*/*z* (EI) 369.1571 (M^+, 2.7, $C_{21}H_{23}NO_5$ required 369.1576), 219 (27.7), 191

(6.2), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.70 (9H, s), 4.16 (1H, dd, J=10.9, 4.7 Hz), 4.35 (1H, s), 4.53 (1H, dd, J=13.7, 4.7 Hz), 5.12 (1H, dd, J=13.7, 10.9 Hz), 7.3–7.4 (8H, m), 7.63 (2H, dd, J=8.1, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 53.0 (d), 74.9 (t), 83.5 (s), 110.6 (d), 125.5 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.0 (d), 129.1 (d), 133.4 (s), 136.0 (s), 171.2 (s).

3.2.2. Michael adduct 4a. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.23 (1H, dd, J=15.1, 4.5 Hz), 4.24 (1H, dd, J=13.2, 4.5 Hz), 4.56 (1H, s), 4.93 (1H, dd, J=15.1, 13.2 Hz), 7.3–7.5 (8H, m), 7.82 (2H, dd, J=8.5, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (q), 35.3 (s), 52.3 (d), 74.4 (t), 83.9 (s), 110.9 (d), 125.0 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.0 (d), 129.1 (d), 132.8 (s), 135.8 (s), 171.3 (s).

3.2.3. Michael adduct 3b. Mp 96–98 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−54.2 (c 1.5, $CHCl_3$); HRMS m/z (EI) 399.1677 (M^+, 1.7, $C_{22}H_{25}NO_6$ required 399.1682), 219 (18.8), 180 (26.3), 134 (63.3), 105 (100.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (9H, s), 3.81 (3H, s), 4.10 (1H, dd, J=11.1, 4.8 Hz), 4.44 (1H, s), 4.48 (1H, dd, J=13.6, 4.8 Hz), 5.06 (1H, dd, J=13.6, 11.1 Hz), 6.87 (2H, d, J=8.9 Hz), 7.20 (2H, d, J=8.9 Hz), 7.40 (3H, m), 7.62 (2H, dd, J=7.9, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (q), 35.0 (s), 52.3 (d), 55.2 (q), 75.0 (t), 83.6 (s), 110.6 (d), 114.2 (d), 125.1 (s), 125.5 (d), 128.7 (d), 129.0 (d), 130.2 (d), 136.1 (s), 159.8 (s), 171.3 (s).

3.2.4. Michael adduct 4b. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.82 (3H, s), 4.18 (1H, dd, J=12.8, 4.5 Hz), 4.19 (1H, dd, J=14.1, 4.5 Hz), 4.65 (1H, s), 4.87 (1H, dd, J=14.1, 12.8 Hz), 6.92 (2H, d, J=8.7 Hz), 7.35 (2H, d, J=8.7 Hz), 7.4–7.5 (3H, m), 7.81 (2H, dd, J=7.9, 2.0 Hz).

3.2.5. Michael adduct 3c. Mp 169–171 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−56.0 (c 0.6, $CHCl_3$); HRMS m/z (EI) 429.1784 (M^+, 4.5, $C_{23}H_{27}NO_7$ required 429.1788), 210 (17.4), 164 (100), 105 (67.0); ^{1}H NMR ($CDCl_3$) δ 0.71 (9H, s), 3.86 (3H, s), 3.89 (3H, s), 4.09 (1H, dd, J=11.1, 4.7 Hz), 4.47 (1H, s), 4.48 (1H, dd, J=13.6, 4.7 Hz), 5.09 (1H, dd, J=13.6, 11.1 Hz), 6.76 (1H, d, J=1.7 Hz), 6.85 (1H, m), 6.87 (1H, dd, J=8.3, 1.7 Hz), 7.3–7.4 (3H, m), 7.63 (2H, dd, J=7.7, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 52.7 (d), 55.8 (q), 55.9 (q), 75.0 (t), 83.6 (s), 110.6 (d), 111.1 (d), 112.5 (d), 121.0 (d), 125.5 (d and s, overlaped signals), 128.7 (d), 129.0 (d), 136.1 (s), 148.9 (s), 149.3 (s), 171.3 (s); ^{13}C NMR (acetone-d_6) δ 22.6 (q), 34.8 (s), 52.5 (d), 55.0 (q), 55.2 (q), 75.5 (t), 83.3 (s), 110.0 (d), 111.3 (d), 113.5 (d), 121.4 (d), 125.6 (d), 125.9 (s), 128.2 (d), 128.5 (d), 136.6 (s), 149.1 (s), 149.6 (s), 171.4 (s)

3.2.6. Michael adduct 4c. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.90 (3H, s), 3.91 (3H, s), 4.20 (2H, m), 4.63 (1H, s), 4.88 (1H, dd, J=14.5, 13.2 Hz), 6.8–7.0 (3H, m), 7.4–7.5 (3H, m), 7.81 (2H, dd, J=8.1, 1.1 Hz).

3.2.7. Michael adduct 3d. An oil; $[\alpha]_D^{25}$=+31.2 (c 0.7, $CHCl_3$); HRMS m/z (EI) 429.1776 (M^+, 1.1, $C_{23}H_{27}NO_7$ required 429.1788) 210 (56.8), 164 (100), 105 (21.8); ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.76 (3H, s), 3.80 (3H, s), 4.67 (2H, br s), 4.85 (1H, br s), 5.00 (1H, s), 6.40 (2H, m), 6.74 (1H, d, J=7.5 Hz), 7.35 (3H, m), 7.49 (2H, m); ^{1}H NMR (DMSO-d_6, 70 °C) δ 0.83 (9H, s), 3.57 (3H, s), 3.74 (3H, s), 4.70 (1H, dd, J=9.8, 5.4 Hz), 4.87 (1H, dd, J=13.4, 5.4 Hz), 4.96 (1H, dd, J=13.4, 9.8 Hz), 5.34 (1H, s), 6.41 (1H, d, J=2.4 Hz), 6,47 (1H, dd, J=8.7, 2.4 Hz), 6.74 (1H, d, J=7.5 Hz), 7.00 (1H, d, J=8.7 Hz), 7.35 (3H, m), 7.40 (2H, m); ^{13}C NMR (DMSO-d_6, 70 °C) δ 22.8 (q), 34.4 (s), 43.2 (d), 55.1 (q), 55.4 (q), 75.3 (t), 82.0 (s), 98.4 (d), 105.0 (d), 108.7 (d), 114.0 (s), 125.3 (d), 127.5 (d), 128.1 (d), 129.3(d), 135.5 (s), 158.6 (s), 160.4 (s), 170.8 (s).

3.2.8. Michael adduct 4d. ^{1}H NMR ($CDCl_3$) δ 0.86 (9H, s), 3.80–3.90 (2H, m), 3.81 (3H, s), 3.86 (3H, s), 4.32 (1H, dd, J=12.6, 4.2 Hz), 4.90 (1H, s), 6.46 (2H, m), 7.18 (1H, d, J=9.1 Hz), 7.3–7.4 (3H, m), 7.78 (2H, dd, J=8.1, 1.3 Hz).

3.2.9. Michael adduct 3e. Mp 129–131 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−51.8 (c 0.7, $CHCl_3$); HRMS m/z (EI) 415.1611 (M^+, 3.4, $C_{22}H_{25}NO_7$ required 415.1631), 220 (12.0), 196 (19.7), 150 (74.8), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.72 (9H, s), 3.86 (3H, s), 4.08 (1H, dd, J=10.9, 4.7 Hz), 4.48 (1H, dd, J=13.4, 4.7 Hz), 4.49 (1H, s), 5.06 (1H, dd, J=13.4, 10.9 Hz), 5.65 (1H, s), 6.73 (1H, d, J=1.9 Hz), 6.80 (1H, dd, J=8.1, 1.9 Hz), 6.87 (1H, d, J=8.1 Hz), 7.3–7.4 (3H, m), 7.61 (2H, dd, J=7.9, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.0 (s), 52.7 (d), 56.0 (q), 75.0 (t), 83.6 (s), 110.6 (d), 111.5 (d), 114.7 (d), 122.2 (d), 124.2 (s), 125.5 (d), 128.7 (d), 129.0 (d), 136.0 (s), 146.0 (s), 146.5 (s), 171.4 (s).

3.2.10. Michael adduct 4e. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 3.92 (3H, s), 4.17 (1H, dd, J=12.6, 4.5 Hz), 4.18 (1H, dd, J=14.1, 4.5 Hz), 4.65 (1H, s), 4.87 (1H, dd, J=14.1, 12.6 Hz), 5.69 (1H, s), 6.8–7.0 (3H, m), 7.3–7.5 (3H, m), 7.81 (2H, dd, J=8.1, 1.1 Hz).

3.2.11. Michael adduct 3f. An oil; $[\alpha]_D^{25}$=−58.7 (c 0.6, $CHCl_3$); HRMS m/z (CI) 450.0751 and 448.0740 (M^++1, 11.40 and 12.75, $C_{21}H_{23}NO_5Br$ required 450.0739 and 448.0760 respectively), 364 (98), 362 (100), 317 (52.4), 315 (54), 261 (19.1), 259 (19.6), 219 (57.6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (9H, s), 4.13 (1H, dd, J=11.2, 4.4 Hz), 4.52 (1H, dd, J=13.6, 4.4 Hz), 4.58 (1H, s), 5.04 (1H, dd, J=13.6, 11.2 Hz), 7.13 (2H, d, J=8.5 Hz), 7.39 (3H, m), 7.47 (2H, d, J=8.5 Hz), 7.58 (2H, dd, J=8.1, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (q), 35.2 (s), 52.5 (d), 74.7 (t), 83.2 (s), 110.8 (d), 123.1 (s), 125.4 (d), 128.8 (d), 129.2 (d), 130.7 (d), 132.0 (d), 132.4 (s), 135.7 (s), 170.9 (s).

3.2.12. Michael adduct 4f. ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 4.2–4.3 (2H, m), 4.67 (1H, s), 4.87 (1H, dd, J=14.7, 13.0 Hz), 7.3–7.6 (7H, m), 7.79 (2H, dd, J=8.1, 1.9 Hz).

3.2.13. Michael adduct 3g. ^{1}H NMR ($CDCl_3$) δ 0.72 (9H, s), 4.18 (1H, dd, J=10.9, 4.7 Hz), 4.49 (1H, s), 4.56 (1H, dd, J=13.7, 4.7 Hz), 5.07 (1H, dd, J=13.7, 10.9 Hz), 7.1–7.5 (7H, m), 7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.1 (s), 52.4 (d), 74.7 (t), 83.2 (s), 110.8 (d), 121.0 (d), 125.4 (d), 128.7 (d), 129.2 (d), 130.7 (d), 132.1 (s), 135.6 (s), 149.5 (s), 171.0 (s).

3.2.14. Michael adduct 4g. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.1–4.3 (2H, m), 4.58 (1H, s), 4.88 (1H, dd, J=14.7, 13.0 Hz), 7.1–7.5 (7H, m), 7.80 (2H, d, J=7.2 Hz); ^{13}C

NMR ($CDCl_3$) δ 23.4 (q), 35.3 (s), 51.7 (d), 74.3 (t), 83.7 (s), 111.1 (d), 121.3 (d), 125.0 (d), 129.0 (d), 129.2 (d), 130.8 (d), 131.5 (s), 135.4 (s), 150.5 (s), 171.0 (s).

3.2.15. Michael adduct 3h. ^{1}H NMR ($CDCl_3$) δ 0.73 (9H, s), 4.24 (1H, dd, *J*=10.9, 4.7 Hz), 4.57 (1H, s), 4.58 (1H, dd, *J*=13.7, 4.7 Hz), 5.10 (1H, dd, *J*=13.7, 10.9 Hz), 7.3–7.6 (7H, m), 7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.1 (q), 35.2 (s), 52.7 (d), 74.6 (t), 83.1 (s), 110.8 (d), 125.4 (d), 125.6 (d, J_{C-F}(q)=3.9 Hz), 128,8 (d), 129.2 (d), 129.6 (d), 129.4 (s, J_{C-F}(q)=34.2 Hz), 135,5 (s), 137.6 (s), 170.8 (s).

3.2.16. Michael adduct 4h. ^{1}H NMR ($CDCl_3$) δ 0.83 (9H, s), 4.30 (2H, m), 4.63 (1H, s), 4.93 (1H, dd, *J*=14.5, 12.6 Hz), 7.3–7.8 (9H, m).

3.2.17. Michael adduct 3i$_1$. Mp 133–135 °C (CH_2Cl_2); $[\alpha]_D^{25}$=+35.2 (*c* 0.7, $CHCl_3$); HRMS *m/z* (EI) 383.1737 (M^+, 1.3, $C_{22}H_{25}NO_5$ required 383.1733), 219 (32.2), 191 (5.2), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.84 (9H, s), 1.25 (3H, d, *J*=6.8 Hz), 4.12 (1H, d, *J*=10.4 Hz), 5.06 (1H, s), 5.15 (1H, m), 6.77 (2H, br d, *J*=7.0 Hz), 7.2–7.4 (6H, m), 7.45 (2H, dd, *J*=8.0, 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.3 (q), 23.1 (q), 34.5 (s), 55.2 (d), 81.9 (d), 82.5 (s), 108.8 (d), 127.0 (d), 127.6 (d), 128.0 (d), 128.4 (d), 128.6 (d), 130.9 (d), 132.6 (s), 133.9 (s), 170.6 (s).

3.2.18. Michael adduct 3i$_2$. Mp 110–112 °C (CH_2Cl_2); $[\alpha]_D^{25}$=−98.7 (*c* 0.5, $CHCl_3$); HRMS *m/z* (EI) 383.1737 (M^+, 1.7, $C_{22}H_{25}NO_5$ required 383.1733), 219 (31.5), 191 (5.3), 105 (100.0); ^{1}H NMR ($CDCl_3$) δ 0.78 (9H, s), 1.48 (3H, d, *J*=6.6 Hz), 3.87 (1H, d, *J*=10.2 Hz), 4.76 (1H, s), 5.40 (1H, m), 7.1–7.3 (8H, m), 7.47 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.1 (q), 23.3 (q), 35.1 (s), 58.6 (d), 83.1 (s), 84.7 (d), 110.7 (d), 125.7 (d), 128.18 (d), 128.21 (d), 128.24 (d), 128.5 (d), 130.0 (d), 134.3 (s), 137.4 (s), 172.0 (s).

3.3. Reduction of Michael adducts 3

To a solution of compound **3** (0.49 mmol) in EtOH–H_2O (3.80:0.95 mL) was added Zn dust (361 mg, 5.5 mmol) and conc. HCl (0.75 mL). The reaction mixture was refluxed during 1 hour up to consumption of the starting material (in some cases additional Zn dust and prolonged reaction times until 5–6 h were required). After this time the reaction mixture was filtered, diluted with water and extracted with ethyl acetate (3×20 mL). The organic extracts were combined, washed with brine and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum to give γ-lactam **5**. Yields are included in Table 3.

Table 3. Reduction of Michael adducts **3**

Entry	Michael adduct	γ-Lactam product	Yield (%)
1	**3a**	**5a**	88
2	**3b**	**5b**	93
3	**3c**	**5c**	92
4	**3d**	**5d**	84
5	**3e**	**5e**	76
6	**3f**	**5f**	87
7	**3i$_1$**	**5i$_1$**	99
8	**3i$_2$**	**5i$_2$**	86

3.3.1. γ-lactam 5a. Mp 188–190 °C (AcOEt); $[\alpha]_D^{25}$=+7,3 (*c* 0.9, $CHCl_3$); HRMS *m/z* (EI) 253.1105 (M^+, 3.0, $C_{16}H_{15}NO_2$ required 253.1103), 193 (6.7), 181 (24.8), 169 (38.3), 131 (60.0), 119 (31.3), 69 (100.0); ^{1}H NMR (DMSO-d_6) δ 3.46 (1H, t, *J*=8.4 Hz), 3.54 (1H, t, *J*=8.4 Hz), 3.64 (1H, t, *J*=8.4 Hz), 6.00 (1H, s), 7.03 (2H, m), 7.1–7.3 (8H, m), 8.23 (1H, s); ^{13}C NMR ($CDCl_3$) δ 44.9 (t), 54.5 (d), 79.5 (s), 125.9 (d), 127.5 (d), 127.7 (d), 128.0 (d), 128.2 (d), 129.3 (d), 134.9 (s), 141.1 (s), 177.9 (s).

3.3.2. γ-Lactam 5b. Mp 220–222 °C (AcOEt); $[\alpha]_D^{25}$=−37.9 (*c* 0.5, CH_3OH); HRMS *m/z* (EI) 283.1213 (M^+, 11.8, $C_{17}H_{17}NO_3$ required 283.1208), 265 (40.6), 236 (13.9), 165 (5.6), 134 (100.0); ^{1}H NMR (DMSO-d_6) δ 3.44 (1H, t, *J*=7.5 Hz), 3.45 (1H, t, *J*=7.5 Hz), 3.59 (1H, t, *J*=7.5 Hz), 3.67 (3H, s), 5.98 (1H, s), 6,74 (2H, d, *J*=8.7 Hz), 6.96 (2H, d, *J*=8.7 Hz), 7.15–7.35 (5H, m), 8.22 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.4 (t), 53.8 (d), 55.2 (q), 79.1 (s), 113.3 (d), 126.8 (d), 127.0 (d), 127.7 (d), 128.3 (s), 130.8 (d), 142.8 (s), 158.5 (s), 176.5 (s).

3.3.3. γ-Lactam 5c. $[\alpha]_D^{25}$=−21.5 (*c* 0.6, $CHCl_3$); HRMS *m/z* (EI) 313.1306 (M^+, 41.0, $C_{18}H_{19}NO_4$ required 313.1314), 295 (24.7), 256 (5.4), 164 (100), 148 (9.4), 105 (14.5); ^{1}H NMR (DMSO-d_6) δ 3.45 (2H, m), 3.54 (3H, s), 3.63 (1H, t, *J*=7.0 Hz), 3.66 (3H, s), 5.90 (1H, s), 6.56 (1H, dd, *J*=8.0, 1.9 Hz), 6.59 (1H, d, *J*=1.9 Hz), 6.75 (1H, d, *J*=8,0 Hz), 7.2–7.3 (5H, m), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$) δ 44.7 (t), 54.2 (d), 55.6 (q), 55.7 (q), 79.4 (s), 110.6 (d), 112.6 (d), 121.1 (d), 125.9 (d), 127.0 (s), 127.7 (d), 128.1 (d), 141.1 (s), 148.3 (s), 148.4 (s), 177.8 (s).

3.3.4. γ-Lactam 5d. Mp 171–173 °C (AcOEt); $[\alpha]_D^{25}$=+20.4 (*c* 0.3, CH_3OH); HRMS *m/z* (EI) 313.1317 (M^+, 24.0, $C_{18}H_{19}NO_4$ required 313.1314) 295 (15.1), 256 (5.0), 164 (100),149 (18.9), 121 (17.5), 105 (14.8); ^{1}H NMR (DMSO-d_6) δ 3.23 (3H, s), 3.32 (1H, t, *J*=9.2 Hz), 3.47 (1H, t, *J*=9.2 Hz), 3.70 (3H, s), 3.90 (1H, t, *J*=9.2 Hz), 5.85 (1H, s), 6.33 (1H, d, *J*=2,4 Hz), 6.46 (1H, dd, *J*=8.5, 2.4 Hz), 7.21 (5H, m), 7.41 (1H, d, *J*=8.5 Hz), 8.18 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.1 (t), 45.8 (d), 55.4 (q), 55.6 (q), 78.9 (s), 98.4 (d), 104.7 (d), 117.0 (s), 126.5 (d), 126.7 (d), 127.4 (d), 131.0 (d), 143.2 (s), 158.7 (s), 159.5 (s), 176.5 (s).

3.3.5. γ-Lactam 5e. Mp 232–235 °C (AcOEt); $[\alpha]_D^{25}$=−16,3 (*c* 0.9, CH_3OH); HRMS *m/z* (EI) 299.1168 (M^+, 10.8, $C_{17}H_{17}NO_4$ required 299.1158), 281 (7.7), 150 (100.0), 135 (7.8), 105 (12.8); ^{1}H NMR (DMSO-d_6) δ 3.41 (2H, m), 3.56 (3H, s), 3.62 (1H, dd, *J*=11.8, 12.0 Hz), 5.88 (1H, s), 6.43 (1H, dd, *J*=8.1, 1.9 Hz), 6.55 (1H, d, *J*=1.9 Hz), 6.56 (1H, d, *J*=8.1 Hz), 7.2–7.3 (5H, m), 8.20 (1H, s), 8.74 (1H, s); ^{13}C NMR (DMSO-d_6) δ 44.1 (t), 54.1 (q), 55.7 (d), 79.2 (s), 114.1 (d), 115.0 (d), 122.1 (d), 126.9 (d), 127.0 (d), 127.1 (s), 127.6 (d), 142.9 (s), 145.7 (s), 146.9 (s), 176.5 (s).

3.3.6. γ-Lactam 5f. Mp 261–263 °C (AcOEt); $[\alpha]_D^{25}$=−53.2 (*c* 0.8, CH_3OH); HRMS *m/z* (EI) 333.0164 and 331.0207 (M^+, 31.4 and 28.3, $C_{16}H_{14}NO_2Br$ required 333.0187 and 331.0208 respectively), 315 (16.3), 313 (13.2), 276 (7.8), 274 (7.9), 184 (100), 182 (93.8),105 (53.7); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.40–3.65 (3H, m), 6.10 (1H, s), 7.00 (2H, d, *J*=8.5 Hz), 7.2–7.3 (5H, m),

7.38 (2H, d, J=8.5 Hz), 8.24 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.0 (t), 53.8 (d), 79.0 (s), 120.4 (s), 126.7 (d), 127.2 (d), 127.8 (d), 130.7 (d), 132.0 (d), 136.0 (s), 142.5 (s), 176.1 (s).

3.3.7. γ-Lactam 5i$_1$. Mp 223–225 °C (AcOEt); $[\alpha]_D^{25}$= +38.3 (c 0.7, CH_3OH); HRMS m/z (EI) 267.1252 (M^+, 23.5, $C_{17}H_{17}NO_2$ required 267.1259), 249 (3.6), 196 (13.8), 118 (100) 105 (19.5); ^{1}H NMR (DMSO-d_6) δ 1.08 (3H, d, J=6.0 Hz), 2.92 (1H, d, J=9.2 Hz), 4.05 (1H, m), 6.06 (1H, s), 7.01 (2H, m), 7.1–7.3 (8H, m), 8.29 (1H, s); ^{13}C NMR (DMSO-d_6) δ 19.3 (q), 51.2 (d), 63.8 (d), 80.5 (s), 126.7 (d), 127.0 (d), 127.2 (d), 127.6 (d), 127.8 (d), 130.2 (d), 135.1 (s), 142.6 (s), 175.4 (s).

3.3.8. γ-Lactam 5i$_2$. Mp 187–189 °C (AcOEt); $[\alpha]_D^{25}$= −121.2 (c 0.4, $CHCl_3$); HRMS m/z (EI) 267.1264 (M^+, 31.4, $C_{17}H_{17}NO_2$ required 267.1259), 249 (43.8), 234 (29.3), 220 (13.9), 196 (22.1), 178 (15.2), 118 (100), 105 (34.0); ^{1}H NMR (DMSO-d_6) δ 0.89 (3H, d, J=6.8 Hz), 3.54 (1H, d, J=6.4 Hz), 3.74 (1H, m), 6.03 (1H, s), 7.1–7.4 (10H, m), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ 18.4 (q), 50.5 (d), 57.5 (d), 80.2 (s), 126.5 (d), 126.8 (d), 127.4 (d), 127.8 (d), 128.1 (d), 130.9 (d), 137.0 (s), 143.8 (s), 176.6 (s).

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12. In the case of **3i$_1$** and **3i$_2$** which have an additional stereogenic center the absolute stereochemistry was assigned also by NOEs experiments in compounds **5i$_1$** and **5i$_2$** following a similar reasoning as in compounds **5a**–**5f**.
13. Enantiomeric excesses (>98%) were proven by ^{1}H NMR experiments using the chiral lanthanide shift reagent Eu(hfc)$_3$ under conditions previously optimized for racemic mixtures prepared from (±)-mandelic acid.
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Rakanmakilactones A–F, new cytotoxic sulfur-containing norditerpene dilactones from leaves of *Podocarpus macrophyllus* var. *maki*

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Abstract—Six new S-containing norditerpene dilactones, rakanmakilactones A–F (**5**–**10**), were isolated from the leaves of *Podocarpus macrophyllus* D. Don var. *maki* Endl., along with four known norditerpene dilactones (**1**–**4**). Their structures, stereochemistry and absolute configurations were determined by spectroscopic studies (HRMS, IR, ^{1}H, ^{13}C and 2D NMR), and single-crystal X-ray analyses. Rakanmakilactones were found to have a cytotoxic effect against P388 murine leukemia cells.

1. Introduction

Podocarpus macrophyllus var. *maki* of the family Podocarpaceae is distributed from Australia to the tropical and subtropical areas of eastern Asia.[1] From the plants of the genus *Podocarpus*, a number of nor- and bisnorditerpene dilactones have been isolated,[2–4] which have various biological activities, such as antitumor,[5] insecticidal,[6] antifeedant,[7] allelopathic,[8] and fungicidal activities.[9] In our previous paper, we reported the isolation, structure elucidation, and stereochemistry, two methylsulfoxide containg norditerpene dilactones, podolactone D (**2**) and S_R-podolactone D (**3**).[10] Although sulfur-containing diterpenes are reported in fetal calf serum,[11] only very few are known in higher plants. In the present study, we conducted more thorough survey of norditerpene dilactone fractions of this plant, and separated six new norditerpene dilactones. This paper describes isolation, structural elucidation, stereochemistry, and cytotoxic activities of those new compounds (**5**–**10**).

2. Results and discussion

The $CHCl_3$-soluble portion (619.8 g) derived from a MeOH extract (8 kg) of the leaves of *P. macrophyllus* var. *maki* (46 kg), prepared as described in Section 3, was subjected to silica gel column chromatography and then Diaion HP-20 resin chromatography. The 50% MeOH and 75% MeOH elutes of the Diaion chromatography gave, when further separated and purified by silica gel column chromatography and preparative HPLC with an ODS column, compounds **1**–**4**, **5** (5.8 mg), **6** (7.3 mg), **7** (30.6 mg), **8** (43.2 mg), **9** (50.7 mg), and **10** (20.3 mg). Compounds **1**–**4** were identified as known compounds podolactone C (680 mg),[12] podolactone D (98 mg),[13] S_R-podolactone D (110 mg),[14] and Hallactone B (10.8 mg),[15] respectively, by comparing their physical and spectral data with those in literature (Fig. 1).

Compound **5** (rakanmakilactone A), colorless needles, showed a hydroxyl absorption band at 3582 cm^{-1}, and a γ-lactone carbonyl and δ-unsaturated lactone carbonyl absorption bands at 1767 cm^{-1} and 1704 cm^{-1}, respectively, in its IR spectrum. The molecular formula was assigned to $C_{20}H_{24}O_8S$ on the basis of HRESIMS, which corresponded to the molecular formula of **2** plus one oxygen or to the molecular formula of **4** minus one oxygen. The ^{1}H NMR spectrum was very similar to that of the known compound hallactone B (**4**), both having four methyls (δ 1.13, 1.29, 2.07, and 3.30, all singlets) and two pairs of doublets at δ 3.82 (1H, d, J=15.2 Hz) and δ 4.55 (1H, d, J=15.2 Hz) indicated the presence of two diastereotopic protons on a sulfur-bearing carbon (C-17), suggesting that they had the same basic structures. The major difference between their ^{1}H NMR spectra was that in **5**, there were three olefinic methine protons (δ 5.79, 5.91, 6.22) whereas in **4** there was one. The ^{13}C NMR and HMBC spectra showed the presence of two lactone carbonyl carbons, and assigned the two lactone carbonyls to at C-12 (δ 162.8) and

Keywords: Rakanmakilactones A–F; *Podocarpus macrophyllus*; Podocarpaceae; norditerpene dilactone; single-crystal X-ray analysis; cytotoxicity.
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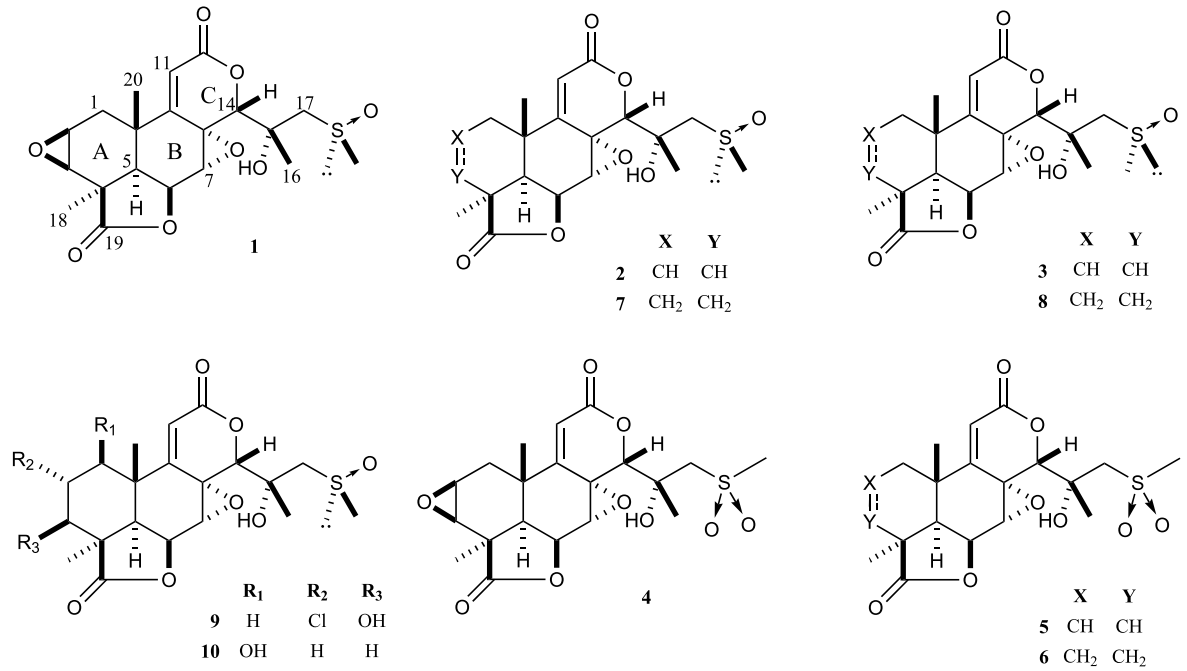


Figure 1. Structures of norditerpene dilactones.

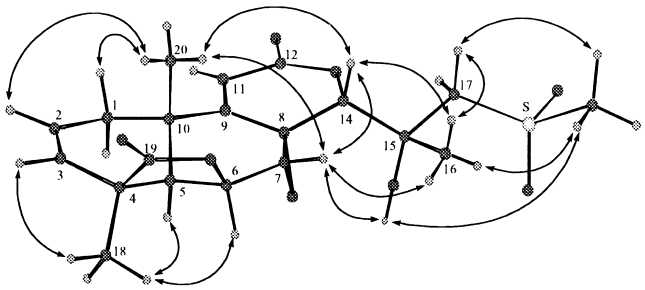


Figure 2. Selected NOESY correlations for **5**.

C-19 (δ 178.0), and assigned one of the olefinic carbon to C-11 (δ 117.6), and the other two to C-2 (δ 126.4) and C-3 (δ 128.4). The comparison of the NMR spectra of **5** with those of **2** and **4** showed that in **5** the chemical shifts of the methyl attached to sulfur in **5** (δ_C 44.4, δ_H 3.30) showed a significant downfield shift compared with the corresponding methylsulfoxide signals of **2**.[16,17] Thus, **5** was shown to the sulfur atom as sulfonyl in side chain. The stereochemistry of compound **5** was determined by the analysis of NOESY spectrum. The correlations were observed between H-7, 20-Me and H-14, between H-5 and 18-Me, H-6 and 18-Me, H-14 and 16-Me (Fig. 2). From these observations, **5** was determined to have the structure shown in Figure 1 (Table 1).

Compound **6** (rakanmakilactone B) was obtained as colorless needles. The molecular formula was assigned to $C_{20}H_{26}O_8S$ on the basis of the $[M+Na]^+$ ion that appeared at *m/z* 449.1272 in the HRESIMS. The IR spectrum showed absorbances at 3565, 1774 and 1729 cm^{-1} due to a hydroxyl and two lactone carbonyl moieties. The ^{13}C NMR spectrum showed 20 signals caused by four methyls including the one

Table 1. ^1H NMR (500 MHz) spectral data for compounds **5**–**10** in pyridine-d_5 at 300 K[a]

Position	5	6	7	8	9	10
1a	2.04 (1H, br s)	1.27–1.35 (1H)	1.24–1.34 (1H)	1.28–1.36 (1H)	1.97 (1H, d, 12.8)	4.07 (1H, dd, 6.1, 11.9)
1b	2.02 (1H, d, 5.9)	1.47–1.55 (1H)	1.46–1.56 (1H)	1.49–1.56 (1H)	2.52 (1H, dd, 4.5, 12.8)	
2a	5.79 (1H, m)	1.41–1.45 (1H, m)	1.39–1.43 (1H, m)	1.42–1.46 (1H, m)		1.84–1.92 (2H)
2b		1.47–1.55 (1H)	1.46–1.56 (1H)	1.49–1.56 (1H)	4.67 (1H, m)	
3a	5.91 (1H, dd, 1.4, 10.0)	1.27–1.35 (1H)	1.24–1.34 (1H)	1.28–1.36 (1H)	3.97 (1H, br t, 9.0)	1.50 (1H, m)
3b		2.17 (1H, m)	2.16 (1H, m)	2.17 (1H, m)		2.40 (1H, m)
5	2.06 (1H)	1.79 (1H, d, 4.5)	1.78 (1H, d, 4.5)	1.81 (1H, d, 4.5)	2.15 (1H, d, 4.1)	1.92 (1H, d, 4.6)
6	5.12 (1H, dd, 0.9, 4.9)	5.03 (1H, dd, 4.5, 1.1)	4.97 (1H, d, 4.5)	5.06 (1H, d, 4.5)	5.07 (1H, dd, 1.2, 4.1)	5.02 (1H, dd, 1.0, 4.6)
7	5.35 (1H, d, 0.9)	5.31 (1H, d, 1.1)	5.23 (1H, s)	5.28 (1H, s)	5.26 (1H, d, 1.2)	5.25 (1H, s)
11	6.22 (1H, s)	6.17 (1H, s)	6.17 (1H, s)	6.18 (1H, s)	6.45 (1H, s)	7.10 (1H, s)
14	4.88 (1H, s)	4.83 (1H, s)	4.88 (1H, s)	4.80 (1H, s)	4.93 (1H, s)	4.94 (1H, s)
16	2.07 (1H, s)	2.06 (3H, s)	1.86 (3H, s)	1.98 (3H, s)	1.86 (3H, s)	1.88 (3H, s)
17a	3.82 (1H, d, 15.2)	3.82 (1H, d, 15.2)	3.42 (1H, d, 13.7)	3.40 (1H, d, 13.7)	3.42 (1H, d, 13.7)	3.45 (1H, d, 13.7)
17b	4.55 (1H, d, 15.2)	4.56 (1H, d, 15.2)	3.79 (1H, d, 13.7)	3.93 (1H, d, 13.7)	3.79 (1H, d, 13.7)	3.81 (1H, d, 13.7)
18	1.29 (3H, s)	1.18 (3H, s)	1.16 (3H, s)	1.19 (3H, s)	1.68 (3H, s)	1.20 (3H, s)
20	1.13 (3H, s)	1.08 (3H, s)	1.09 (3H, s)	1.08 (3H, s)	1.29 (3H, s)	1.44 (3H, s)
SOMe			2.68 (3H, s)	2.71 (3H, s)	2.69 (3H, s)	2.69 (3H, s)
SO_2Me	3.30 (3H, s)	3.31 (3H, s)				

[a] Number of hydrogens, multiplicity, and *J* value in Hz are given in parentheses.

Table 2. ^{13}C NMR (125 MHz) spectral data for compounds **5**–**10** in pyridine-d_5 at 300 K

Position	5	6	7	8	9	10
1	32.5 (t)	29.6 (t)	29.6 (t)	29.5 (t)	40.7 (t)	69.1 (d)
2	126.4 (d)	17.7 (t)	17.7 (t)	17.7 (t)	61.4 (d)	29.4 (t)
3	128.4 (d)	28.6 (t)	28.6 (t)	28.6 (t)	79.2 (d)	28.2 (t)
4	44.2 (s)	41.1 (s)	41.9 (s)	42.0 (s)	47.1 (s)	42.0 (s)
5	42.8 (d)	43.2 (d)	43.4 (d)	43.3 (d)	45.0 (d)	43.8 (d)
6	72.3 (d)	72.8 (d)	72.8 (d)	72.8 (d)	72.2 (d)	72.8 (d)
7	56.0 (d)	56.1 (d)	55.9 (d)	56.0 (d)	55.9 (d)	56.1 (d)
8	58.3 (s)	58.6 (s)	58.7 (s)	58.6 (s)	58.9 (s)	59.1 (s)
9	158.3 (s)	159.4 (s)	159.8 (s)	159.5 (s)	157.7 (s)	157.8 (s)
10	35.7 (s)	36.3 (s)	36.3 (s)	36.2 (s)	38.3 (s)	41.7 (s)
11	117.6 (d)	117.1 (d)	116.9 (d)	117.0 (d)	117.3 (d)	119.9 (d)
12	162.8 (s)	163.0 (s)	163.2 (s)	163.2 (s)	163.0 (s)	163.6 (s)
14	83.7 (d)	83.8 (d)	83.2 (d)	83.8 (d)	83.2 (d)	83.2 (d)
15	72.2 (s)	72.1 (s)	73.4 (s)	72.4 (s)	73.4 (s)	73.3 (s)
16	26.7 (q)	26.7 (q)	27.7 (q)	28.2 (q)	27.6 (q)	27.8 (q)
17	59.5 (t)	59.4 (t)	61.8 (t)	63.0 (t)	61.9 (t)	62.0 (t)
18	22.5 (q)	23.9 (q)	24.0 (q)	23.9 (q)	22.2 (q)	23.7 (q)
19	178.0 (s)	180.5 (s)	180.4 (s)	180.5 (s)	176.4 (s)	180.5 (s)
20	22.7 (q)	24.4 (q)	24.4 (q)	24.4 (q)	23.5 (q)	16.9 (q)
$SOCH_3$			40.3 (q)	40.7 (q)	40.3 (q)	40.3 (q)
SO_2CH_3	44.4 (q)	44.4 (q)				

attached to a sulfonyl group (δ 44.4), four methylenes, five methines, seven quaternary carbons and two lactone carbonyls. Thus, showing that **6** was sulfur-containing norditerpene dilactone. The ^1H NMR spectrum of **6** was generally similar to that of **5**, the major difference being that **6** possessed three methylene protons, whereas **5** had only one. The $^1H-^1H$ COSY and HMBC spectra showed that the three multiplet methylene protons should be at C-1, C-2 and C-3. The NOESY spectrum of **6** showed correlations between H-7, 20-Me and H-14, between H-5, 18-Me and H-6, 18-Me and H-14, 16-ME as observed in **5**. Accordingly, **6** was determined to have the structure shown in Figure 1.

Compounds **7** (rakanmakilactone C) and **8** (rakanmakilactone D) were both obtained as colorless needles. The HRESIMS determined the molecular formulae of **7** and **8** to be $C_{20}H_{26}O_7S$ by the $[M+Na]^+$ ion peaks at *m/z* 433.1335 and *m/z* 433.1313, respectively (Calcd for $C_{20}H_{26}O_7SNa$, 433.1297). Their IR spectra had absorption peaks to be attributed to lactone carbonyl (1777 and 1779 cm^{-1}, respectively), α,β-unsaturated lactone carbonyl (1728, 1735 cm^{-1}, respectively) hydroxyl groups (3583, 3584 cm^{-1}, respectively). These ^1H NMR spectra showed the signals due to γ-lactone ring protons (H-5, H-6), four methylene protons (H-1, H-2, H-3, H-17), an olefinic proton (H-11), a carbinyl proton (H-14), three methyls (16-Me, 18-Me, 20-Me) and methylsulfoxide (side chain). The ^{13}C NMR spectra of these two compounds, together with the information from the DEPT studies, showed the presence of 20 carbons consisting of four methyls, four methylenes, five methines and seven nonprotonated carbons (Table 2). These 1D NMR data and the HMBC studies revealed that **7** and **8** were sulfur-containing norditerpene dilactones of basically the same structure with a methylsulfinyl group at C-14. Their 1D NMR data were almost identical to each other, except that the proton signal of H_b-17 of **8** was to lower than of **7** by 0.14 ppm. This is exactly the same situation that was observed between podolactone D (**2**) and S_R-podolactone D (**3**), which are the epimers at the sulfur atom; when the stereochemistry of the sulfur atom is *R*, the chemical shift of H_b-17 is known to shift to the downfield.[10,18] Accordingly, **7** and **8** were concluded to be epimers at the sulfur atom which was *S* configuration in **7** and *R* configuration in **8**. This conclusion about the structural relationship between **7** and **8** was verified, because when oxidized, they produced the same oxidation product **6** having a sulfonyl moiety on the side chain, at a yield of 85 and 84%, respectively.[19] The X-ray crystallographic analysis on single crystals of **7** and **8** finally proved that **7** had 15*R*,S_S and **8** had 15*R*,S_R configuration as shown by ORTEP representation in Figure 3 (Scheme 1).

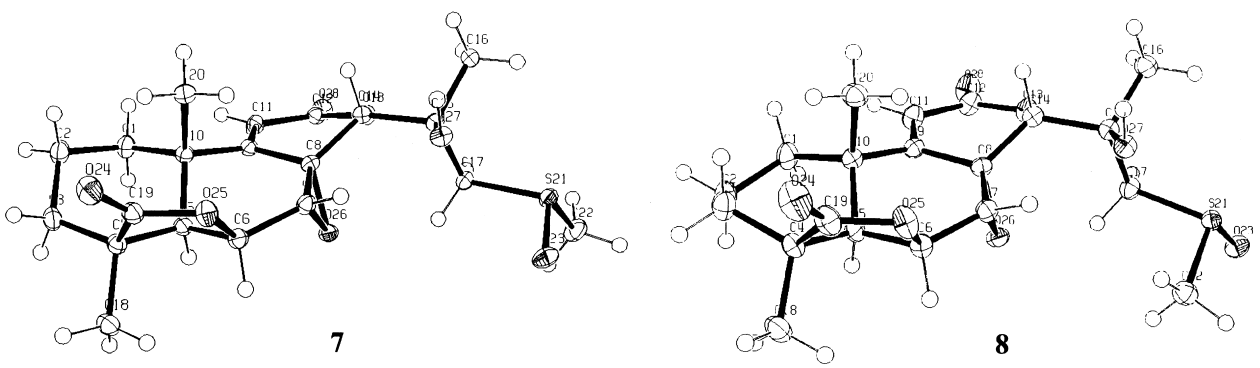
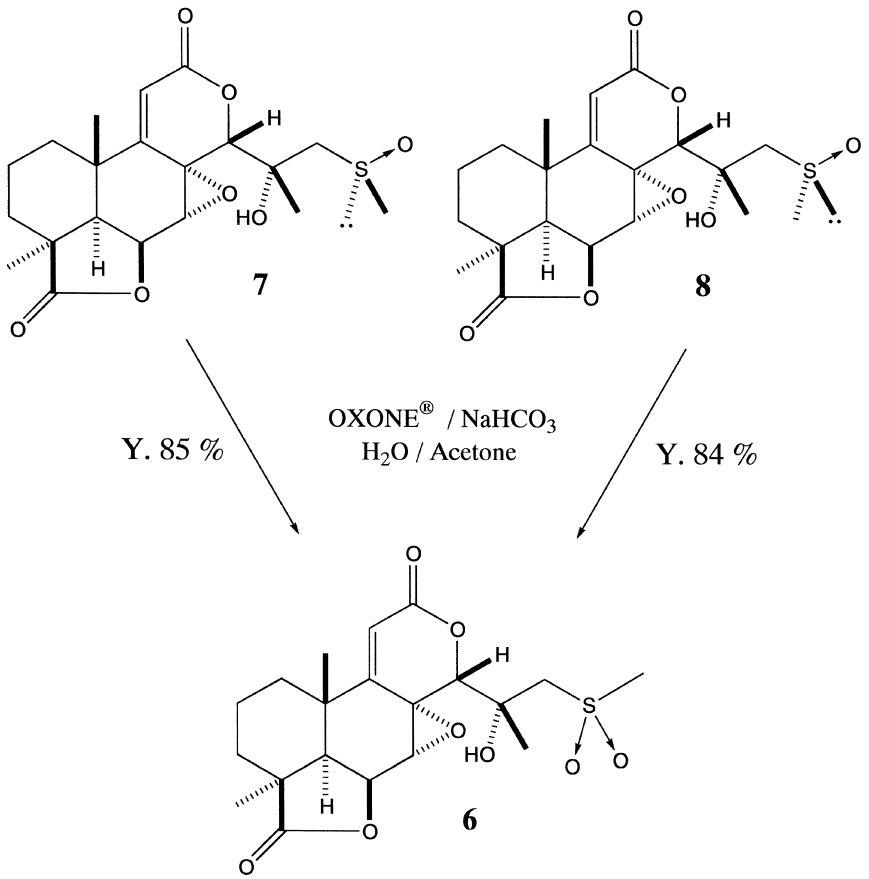


Figure 3. ORTEP representations of **7** and **8** as determined by single-crystal X-ray analysis.



Scheme 1. The oxidation of **7** and **8** to **6**.

Compound **9** (rakanmakilactone E) was isolated as colorless needles, and the IR spectrum indicated the presence of hydroxyl (3528 cm^{-1}) and lactone carbonyl groups (1767, 1725 cm^{-1}). Its elemental analysis showed the presence of a chlorine atom in the molecule (Anal. Calcd for $C_{20}H_{25}O_8ClS$, C, 52.12; H, 5.47; Cl, 7.69; S, 6.96. Found; C, 52.06; H, 5.53; Cl, 7.70; S, 7.31) and the FABMS determined its molecular formula to be $C_{20}H_{25}O_8ClS$ by the $[M+H]^+$ ion peak at *m/z* 461 with an isotope peak at *m/z* 463 (45%). The ^{13}C and ^1H NMR spectral showed the presence of a methylsulfinyl group at δ_C 40.3, δ_H 2.69 (3H, s), and three methine at δ_C 61.9, δ_H 3.42 (1H, d, 13.7) and 3.79 (1H, d, 13.7), δ_C 61.4, δ_H 4.67 (1H, m) and δ_C 79.2, δ_H 3.97 (1H, br t, 9.0) revealed that **9** was norditerpene dilactone with a chlorine atom and a hydroxy group on A ring system. Comparison of the HMBC spectra of **9** with those of the related methylsulfoxide compounds of this series (**1**, **2**, **3**, **7**, and **8**) revealed that **9** had the same basic ring structure and side chain as **1**, **2**, and **7**, and **9** was shown to be an analogue of **7** with substituents at C-2 and C-3. The $^1H-^1H$ COSY correlations observed between H-3 (δ 3.97) and hydroxyl proton (δ 7.40) and the NOESY correlations between 20-Me and H-2, and between H-3 and 18-Me and H-5, implied that **9** was concluded to be 2α-chlorine-3β-hydroxy-rakanmakilactone compound, which was verified by single-crystal X-ray analysis of **9** (Fig. 4). Known halogenated natural products are mostly from in marine organisms and fungi, and this is the first isolation of halogenated norditerpene dilactone from the family Podocarpaceae.

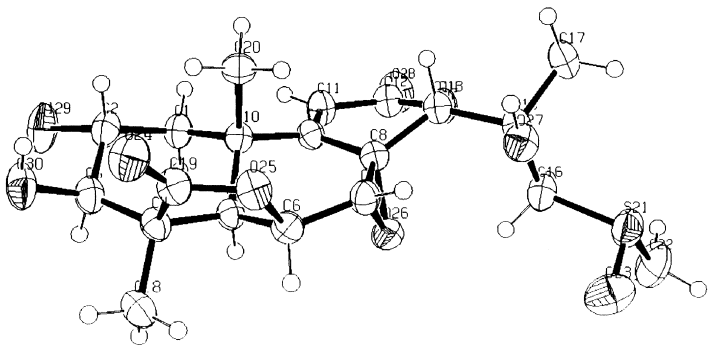


Figure 4. ORTEP representations of **9** as determined by single-crystal X-ray analysis.

Compound **10** (rakanmakilactone F) was obtained as colorless needles. The IR spectral absorptions at 3389, 1767 and 1703 cm^{-1} were assigned to a hydroxyl, a lactone carbonyl, and an α,β-unsaturated lactone carbonyl groups, respectively. Its molecular formula was determined to be $C_{20}H_{27}O_8S$ by the HRFABMS molecular ion peak at *m/z* 442.1426 $[M+H]^+$, which corresponded to those of **7** and **8** with an additional hydroxy group. The ^1H and ^{13}C NMR spectra implied that the basic structure of **10** was same as that of **7** with another hydroxyl group. The oxymethine proton signal at δ 4.07, giving an HMBC correlation with C-10 and C-20, and an NOE correlation with H-5 and Ha-3, was assigned to Ha-1. Thus, the structure of **10** was defined to have a α-hydroxyl group on H-1, as shown in Figure 5.

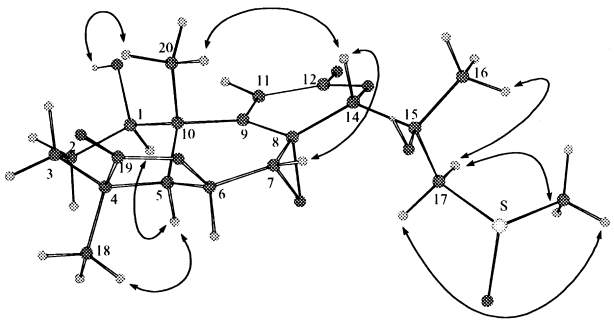


Figure 5. Selected NOESY correlations for **10**.

Many of the sulfur-containing norditerpene dilactones of this series possess a side chain with a methyl sulfinyl group (**1**, **2**, **3**, **7**, **8**, **9**, and **10**), thus producing a steric center at sulfur atom. The chemical shifts of H_a-17 and H_b-17 are summarized in Table 3. In a compound having a S_R configuration, the $\Delta_{(Hb\text{-}17\text{-}Ha\text{-}17)}$ is ca. 0.73–0.76 ppm. On the other hand, in that of compounds having S_S configuration is 0.51–0.58 ppm. This indicated the conformational difference between S_R- and S_S-type. Namely, though the intramolecular hydrogen bond in the compounds **1**, **2**, **7**, **9**, and **10** is possible to form, it may not be formed in **3** and **8** owing to 1,3-diaxial sterical effects between *S*-Me and 16-Me groups. This fact was also confirmed by comparison of single-crystal X-ray analysis data of the S_S compounds (**2**, **7**, and **9**) with those of S_R compounds (**3** and **8**).

The norditerpene dilactones have been reported to show cytotoxic activity against cultured Yoshida sarcoma cells.[5] This suggested that the biological activity of the podolactones is critically dependent on the olefinic system at 9:11, and requires the presence of a dienolide (7:8, 9:11) or the epoxy-enolide (7α:8α-9:11) moiety, and of the dilactones with less number of polar substituents (hydroxyl or ester) show a stronger activity. Compounds **1**–**3** and **5**–**10** showed a cytotoxic activity on P388 leukemia cells with IC_{50} values of 0.16, 0.23, 0.52, 0.31, 0.18, 0.29, 0.25, 5.0, and 4.3 μg/mL, respectively. The result demonstrated that the compounds having a hydroxyl group or a chlorine atom on A ring, had lower cytotoxicity as in **9** and **10**.

3. Experimental

3.1. General

Optical rotations were measured on a JASCO DIP-360 automatic digital polarimeter, IR spectra on a JASCO FT/IR 620 spectrophotometer, and Mass spectra were acquired with VG AutoSpec E and Micromass LCT (Manchester, UK) spectrometers. NMR spectra were obtained on a Brucker DRX-500 spectrometer at 300 K in C_5D_5N. The chemical shifts (δ) of proton signals are given in ppm relative to the resonances of residual C_5D_4HN at 7.21 ppm and those of carbon signals are given in ppm relative to the resonances at 135.5 ppm for C_5D_5N. Elemental analysis was carried out by using an Elemental Vario EL (Hanau, Germany) and a Mettler DL70ES elemental analyzer. Silica gel (Merck Kiesel gel 60, 70–230 μm, Kanto silica gel N 60, 63–210 μm) and Diaion® HP-20 (Mitsubishi Chemical) were used for column chromatography and precoated Kieselgel 60 F_{254} (0.25 mm thick, Merck), RP-18 $F_{254}S$ (0.25 mm thick, Merck) plates for TLC, in which the spots were visualized by spraying of 10% H_2SO_4 solution, followed by heating. Preparative HPLC was carried out on a JASCO PU-986 equipped with a UV-970 UV detector (λ 220 nm) and Inertsil PREP-ODS column (10 μm, 20×250 mm), by using MeOH/H_2O or MeCN/H_2O at a flow rate of 10 mL/min. X-ray single-crystal analysis was taken on a Mac Science DIP diffractometer with Mo Kα radiation (λ=0.71073 Å).

3.2. Plant material

The leaves of *Podocarpus macrophyllus* D. Don var. *maki* Endl. were collected in Chiba, Japan, in October 2000. The botanical identification was made by K. Takeya, Professor of Plant Chemistry of Tokyo University of Pharmacy and Life Science. A voucher specimen has been deposited in the herbarium of Tokyo University of Pharmacy and Life Science (00JCP09).

3.2.1. Extraction and isolation. The air-dried leaves of *P. macrophyllus* var. *maki* (46 kg) were extracted with hot MeOH (180 L×3). Evaporation of the solvent yielded 8 kg of a dark green residue, which was suspended in water (8 L)

Table 3. Chemical shifts (ppm) in $CDCl_3$ for S_S (**1**, **2**, **7**, **9**, **10**) and S_R (**3**, **8**)

S_S-type				S_R-type			
Compound	H_b-17	H_a-17	Δ_{Hb-Ha}	Compound	H_b-17	H_a-17	Δ_{Hb-Ha}
2	3.53	3.02	0.51	**3**	3.63	2.90	0.73
7	3.53	3.00	0.53	**8**	3.66	2.90	0.76
1	3.51	2.99	0.52				
9	3.51	3.00	0.51				
10	3.53	3.00	0.53				

and then treated successively with hexane and $CHCl_3$ (each 8 L). The $CHCl_3$ layer was evaporated in vacuo to give a residue (619.8 g), which was placed on a silica gel column (9.5×35 cm) and eluted sequentially with $CHCl_3$ (15 L), $CHCl_3$/MeOH (20:1,v/v, 25 L), $CHCl_3$/MeOH (7:3, v/v, 20 L) and MeOH (10 L). The $CHCl_3$/MeOH (20:1, v/v) eluate was dried and the residue (200. 4 g) was subjected to Diaion HP-20 (1.4 kg) column chromatography eluting with H_2O (10 L), H_2O/MeOH (1:1, v/v, 25 L), H_2O/MeOH (1:3, v/v, 25 L), MeOH (15 L) and acetone (5 L) to give fractions 1–5, respectively. After removal of solvent, fraction 2 (30.6 g) was chromatographed on silica gel (600 g) eluting stepwise with a serial $CHCl_3$/MeOH mixture (20:1, 10 L; 10:1, 8 L; 5:1, 5 L; 0:1, 3 L) to give fractions I–V with the crystal of **1** (680 mg). Fraction II (9.8 g) was subjected to ODS HPLC eluting with H_2O–MeOH (73:27, v/v) and finally to preparative HPLC using H_2O–MeOH (87:13, v/v) to give **2** (98 mg), **3** (110 mg), **9** (50.7 mg) and **10** (20.3 mg). Fraction 3 gave fractions A–H when subjected to silica gel open chromatography using the same solvent system as in the case of fractions II. Fraction B was further subjected to ODS HPLC eluting with H_2O–MeCN (85:15, 76:24, v/v) to give **4** (10.8 mg), **7** (30.6 mg), and **8** (43.2 mg). Fraction H gave, when subjected to ODS HPLC using the two eluting systems H_2O–MeCN (75:25, v/v) and H_2O–MeOH (70:30, v/v), **5** (5.8 mg) and **6** (7.3 mg).

3.2.2. Rakanmakilactone A (5). Colorless needles (EtOAc–MeOH); mp 274–276 °C; $[\alpha]_D^{24}$=+13.2° (*c* 0.12, MeOH); HRESIMS *m/z* 447.1053 $[M+Na]^+$ (Calcd for $C_{20}H_{24}O_8SNa$, 447.1090); IR (film) ν_{max} 3582, 1767, 1704 cm^{-1}; ^1H, ^{13}C NMR data are given in Tables 1 and 2.

3.2.3. Rakanmakilactone B (6). Colorless needles (EtOAc–MeOH); mp 246–249 °C; $[\alpha]_D^{24}$=+13.4° (*c* 0.11, MeOH); HRESIMS *m/z* 449.1272 $[M+Na]^+$ (Calcd for $C_{20}H_{26}O_8SNa$, 449.1246); IR (film) ν_{max} 3565, 1774, 1729 cm^{-1}; ^1H, ^{13}C NMR data are given in Tables 1 and 2.

3.2.4. Rakanmakilactone C (7). Colorless needles (EtOAc–MeOH); mp 237–240 °C; $[\alpha]_D^{24}$=+61.1° (*c* 0.14, MeOH); HRESIMS *m/z* 433.1335 $[M+Na]^+$ (Calcd for $C_{20}H_{26}O_7SNa$, 433.1297); IR (film) ν_{max} 3583, 1777, 1728, 1590 cm^{-1}; ^1H, ^{13}C NMR data are given in Tables 1 and 2.

Crystal data for **7**. $C_{20}H_{26}O_7S$; orthorhombic; space group $P2_12_12_1$; unit cell dimensions *a*=7.6780(10) Å, *b*=11.0708(4) Å, *c*=22.014(6) Å; *V*=1978.93(9) $Å^3$; *Z*=4; *T*=100 K; d_{cal}=1.378 Mg m^{-3}; μ=0.203 mm^{-1}, *R*(gt)=0.0266, CCDC 216469.

3.2.5. Rakanmakilactone D (8). Colorless needles (EtOAc–MeOH); mp 253–255 °C; $[\alpha]_D^{24}$=+19.4° (*c* 0.20, MeOH); HRESIMS *m/z* 433.1313 $[M+Na]^+$ (Calcd for $C_{20}H_{26}O_7SNa$, 433.1297) IR (film) ν_{max} 3584, 1779, 1735, 1650, 1556 cm^{-1}; ^1H, ^{13}C NMR data are given in Tables 1 and 2.

Crystal data for **8**. $C_{20}H_{26}O_7S$; orthorhombic; space group $P2_12_12_1$; unit cell dimensions *a*=6.554(10) Å, *b*=13.646(4) Å, *c*=22.343(6) Å; *V*=1998.27(12) $Å^3$; *Z*=4; *T*=100 K; d_{cal}=1.364 Mg m^{-3}; μ=0.201 mm^{-1}, *R*(gt)=0.0310, CCDC 216470.

3.2.6. Oxidation of 7 and 8 to 6. Compound **7** (6.0 mg, 0.02 mmol) and sodium bicarbonate (28.0 mg, 0.33 mmol) were dissolved in a mixture of acetone (1 mL) and water (0.8 mL). To this solution was added OXONE® (51 mg) at 0 °C. After stirring at room temperature for 0.5 h, the mixture was treated with H_2O (10 mL) and the whole was extracted with $CHCl_3$ (10 mL, three times). The $CHCl_3$ solution was dried over $MgSO_4$, and evaporated in vacuo to give a residue, which was purified by ODS HPLC (H_2O–MeOH, 70:30, v/v) to afford **6** (5.3 mg, 85%). When **8** (5.1 mg, 0.01 mmol) was treated in the same way as described above, it gave **6** in 84% yield (4.5 mg).

3.2.7. Rakanmakilactone E (9). Colorless needles (EtOAc–MeOH); mp 285–287 °C $[\alpha]_D^{28}$=+11.1° (*c* 0.10, MeOH); FABMS *m/z* 461 $[M+H]^+$(100), 463 $[M+2+H]^+$(45). Anal. Calcd for $C_{20}H_{25}O_8ClS$, C, 52.12; H, 5.47; Cl, 7.69; S, 6.96. Found; C, 52.06; H, 5.53; Cl, 7.70; S, 7.31; IR (film) ν_{max} 3528, 1767, 1725 cm^{-1}; ^1H, ^{13}C NMR data are given in Tables 1 and 2.

Crystal data for **9**. $C_{20}H_{25}O_8ClS$; orthorhombic; space group $P2_12_12_1$; unit cell dimensions *a*=7.842(10) Å, *b*=12.8190(4) Å, *c*=21.9030(6) Å; *V*=2201.83(12) $Å^3$; *Z*=4; *T*=296 K; d_{cal}=1.390 Mg m^{-3}; μ=0.312 mm^{-1}, *R*(gt)=0.0352, CCDC 216471.

3.2.8. Rakanmakilactone F (10). Colorless needles (EtOAc–MeOH); mp 270–272 °C $[\alpha]_D^{28}$=+33.0° (*c* 0.12, MeOH); HRFABMS *m/z* 427.1426 $[M+H]^+$ (Calcd for $C_{20}H_{27}O_8S$, 427.1427); IR (film) ν_{max} 3389, 1767, 1703 cm^{-1}; ^1H, ^{13}C NMR data, see Tables 1 and 2.

3.3. Assay for cytotoxic activity

The cytotoxic assays were performed by using the MTT assay method. The murine P388 leukemia cells were cultured in RPMI 1640 medium (Nissui) supplemented with 5% heat-inactivated fetal bovine serum (FBS) and kanamycin (5.3 mL/L) in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C. The 100 μL of cell suspension was added to each well (3×10^3 cells/well) of a 96-microwell plate (Iwaki, flat bottom, treated polystyrene) and incubated for 24 h. Test compounds were dissolved in DMSO in various concentrations (100, 30, 10, 3, 1, 0.3, 0.1 μg/mL) and 10 μL of the test solution or DMSO (control) was added to each well. The plate was kept in an incubator for 48 h. After termination of cell culture by adding 20 μL MTT (5% in PBS) to each well, the plate was further incubated for 4 h. To each well was added 100 μL of 10% SDS–0.01N HCl. The plate was read on a microplate reader (MPR A4i, Tosoh) at 550 nm. A dose-response curve was plotted for each compound, and the concentrations giving 50% inhibition of the cell growth (IC_{50}) were recorded.

3.4. X-ray single crystallographic analysis

Crystallographic data for **7**, **8** and **9** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, under the reference numbers CCDC 216469, 216470, and 216471, respectively. 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-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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The nature of the rotational barriers in simple carbonyl compounds

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Abstract—The rotational barriers around the CO and CC bonds are investigated in formic acid, ethanedial and glycolaldedyde molecules on the basis of DFT-B3LYP/aug-cc-pVDZ calculations. Natural bond orbitals analysis is applied to enhance physical understanding of rotational barriers. In the case of attractive barriers in formic acid and Gc-glycolaldehyde, the barrier originates from the loss of hyperconjugation that determines the equilibrium structures while for the repulsive barriers in ethanedial and Go-glycolaldehyde, both Lewis and hyperconjugation terms contribute.

1. Introduction

Knowledge of the energy barriers which separate conformers is important for the interpretation of several physical and chemical molecular properties. Experimentally, the potential barrier heights and torsional shape information are accessible from high-resolution FTIR spectroscopy or, for bigger molecules, from the measurement of the NMR spectra, in particular from the spin–spin coupling constants (information on torsional angles). A key problem in the interpretation of the spin–spin coupling constants is the coupling constant-structure correlation. A complementary approach to obtain information on molecular structure and energetics is offered by ab initio calculations. Although the accuracy of the ab initio calculations is still below the state-of-the-art accuracy of the spectroscopic data for molecules of chemical interest, the calculations provide information on the shape of the potential energy surfaces without any initial assumptions.

Glycolaldehyde could be regarded as a prototype for carbohydrates. It has two internal rotational degrees of freedom: the rotation of the hydroxyl group around the C–O bond and the rotation of the $-CH_2$ OH group around the C–C bond, which is attached to the carbonyl group. The rotation about CO or CC bonds adjacent to carbonyl groups is of importance in studying the properties of carbohydrates, lactames and ketones. In particular, the rotation barriers, obtained experimentally, or calculated ab initio, are being used to parametrized potentials utilized for modeling the structures of carbohydrates, their derivatives and complexes, via molecular mechanics. The set of molecules chosen for our study is: formic acid, ethanedial and glycolaldehyde. They can be treated as derivatives of formaldehyde where hydrogen atoms have been substituted by –OH, –CHO and $-CH_2$ OH groups, respectively. For glycolaldehyde, we decided to focus on the rotation around the C–C bond.

The origin of the barrier to rotation has been the subject of many papers.[1,2] According to the electrostatic model,[1] the final value of the energy barrier which separates two conformers is determined by variation of the attractive ($A=V_{ne}$) and the repulsive ($R=T+V_{ee}+V_{nn}$) contributions to the total molecular energy during intramolecular rotation. This lead to the concept of attractive and repulsive rotation barriers.

Very recently, the paper was presented by Pophristic and Goodman on the use of delocalized natural bond orbitals (NBO) model to understand the nature of the barrier to rotation in ethane.[3] The authors used the expansion in terms of Lewis and non-Lewis-type NBO interactions, which identifies distinct physical contributions of 'steric' versus 'hyperconjugation' origin. It was found that, it is hyperconjugation that determines the equilibrium structure of ethane. This is contrary to the textbook explanation that steric repulsion between bonds, due to the overlap of the occupied bond orbitals is the origin of the barrier to rotation in ethane.[4]

In this paper, we present the results of the calculations of rotational barriers about CO and CC bonds adjacent to

Keywords: Natural bond orbitals; Barrier; Hyperconjugation; Glycolaldehyde.
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carbonyl groups in three molecules: formic acid, ethanedial and glycolaldehyde. We analyze the nature of the barrier to rotation on the basis of natural bond orbital methods NBO on the one hand and attractive and repulsive contributions on the other. The method employed is described in Section 2 of this paper. Section 3 presents the results and the summary is presented in Section 4.

2. Methods of calculations

First, let us describe briefly the meaning of the most important terms used in this study. The total energy can be represented as the sum of the kinetic energy T, the electron repulsion V_{ee}, the nuclear repulsion V_{nn} and the attractive nuclear-electron energy V_{ne} terms. The energy difference between the conformers is thus

$$\Delta E = \Delta T + \Delta V_{nn} + \Delta V_{ne} + \Delta V_{ee} \quad (1)$$

The electron repulsion term V_{ee} can be divided into the classic Coulomb repulsion denoted as $1/2\Delta\langle PJ(P)\rangle$, the exchange term ΔE_{ex} and the correlation term ΔE_c. The exchange repulsion involves the Pauli exclusion principle which requires same-spin electrons not to occupy the same spatial region. These three terms are calculated separately[5] at the DFT level of theory and are reported as such in the Gaussian98 package.[6]

$$\Delta V_{ee} = 1/2\Delta\langle PJ(P)\rangle + \Delta E_{ex} + \Delta E_c \quad (2)$$

The NBO model transforms a given wavefunctions into the localized form, corresponding to the one-centre (lone pair) and two-centre (bond) elements of the traditional Lewis structure.[7,8] The set of high-occupancy NBOs is supposed to represent the 'natural Lewis structure' of the molecule. Hyperconjugation, the concept describing electron delocalization, involves electron transfer from an occupied (bonding) to an unoccupied (antibonding) orbital, leading to de-localization of the charge. The effect of the hyperconjugation is obtained by comparison with the results obtained after deletion of selected antibonding orbitals in the NBO description of the molecule. We have used the NOSTAR (NBO 4.0) option for deletion of all non-Lewis orbitals in order to obtain the energy of the idealized natural Lewis structure.[6] In our discussion, complementary to that resulting from Eq. 1, we can picture the barrier to rotation as having a 'Lewis' (localized, covalent) and 'non-Lewis' (delocalized, non-covalent, hyperconjugative) contributions to the energy of the molecule, according to the Eq. 3

$$\Delta E = \Delta E_{Lew} + \Delta E_{del} \quad (3)$$

The non-Lewis contributions are usually much less than 1% of the covalent term.

The calculations of the energy as a function of the HCCH or HCOH dihedral angles at the B3LYP level[9] and NBO analysis have been performed using the Gaussian98 package.[6] DFT–B3LYP is a cheap and increasingly popular method for calculations of the molecular electronic structure[10] and should perform adequately for the barriers to rotation. Moreover, it allowed us to obtain separately several different terms, mentioned above. The basis set employed is aug-cc-pVDZ,[11,12] containing diffuse functions required for the proper description of the outer part of the electron density.

Full geometry optimization have been performed for all the structures. To examine the effect of relaxation of internal molecular modes, we calculated the minimum-energy

Table 1. The selected geometric parameters (in Å, °) for the optimal structures of formic acid, ethanedial, Gc-and Go-glycolaldehyde calculated at B3LYP/aug-cc-pVDZ level

	Formic acid	Ethanodial	Gc-glycolaldehyde	Go-glycolaldehyde
r(C1–C2)	–	1.5267	1.5186	1.5114
r(O1–C1)	1.2049	1.209	1.2237	1.2271
r(H1–C1)	1.1034	1.1134	1.1146	1.1127
r(C2–O2)	–	1.209	1.4307	1.4130
r(C1–O2)	1.3494	–	–	–
r(H2–C2)	–	1.1134	1.1045	1.1078
r(H3–C2)	–	–	1.1048	1.1064
r(H4–O2)	0.9732	–	0.9658	0.9742
α(O1–C1–C2)	–	121.4	122.8	121.8
α(O1–C1–O2)	125.0	–	–	–
α(H1–C1–C2)	–	115.2	115.1	116.8
α(H1–C1–O2)	109.83	–	–	–
α(C1–C2–O2)	–	121.4	107.1	112.0
α(H2–C2–C1)	–	115.1	108.3	107.6
α(H3–C2–C1)	–	–	108.2	108.2
α(H4–O2–C2)	–	–	108.5	105.6
α(H4–O2–C1)	107.5	–	–	–
τ(H1–C1–C2–H2)	–	180.0	−55.6	120.0
τ(H1–C1–O2–H4)	180.0	–	–	–
τ(H1–C1–C2–H3)	–	–	60.0	−122.5
τ(H1–C1–C2–O2)	–	0.0	−178.0	−1.2
τ(O1–C1–C2–O2)	–	180.0	1.8	178.9
τ(O1–C1–O2–H4)	0.0	–	–	–
τ(O1–C1–C2–H2)	–	180.0	–	–
τ(C1–C2–O2–H4)	–	–	−2.1	179.8
τ(H2–C2–O2–H4)	–	–	−123.0	61.2
τ(H3–C2–O2–H4)	–	–	118.1	−61.4

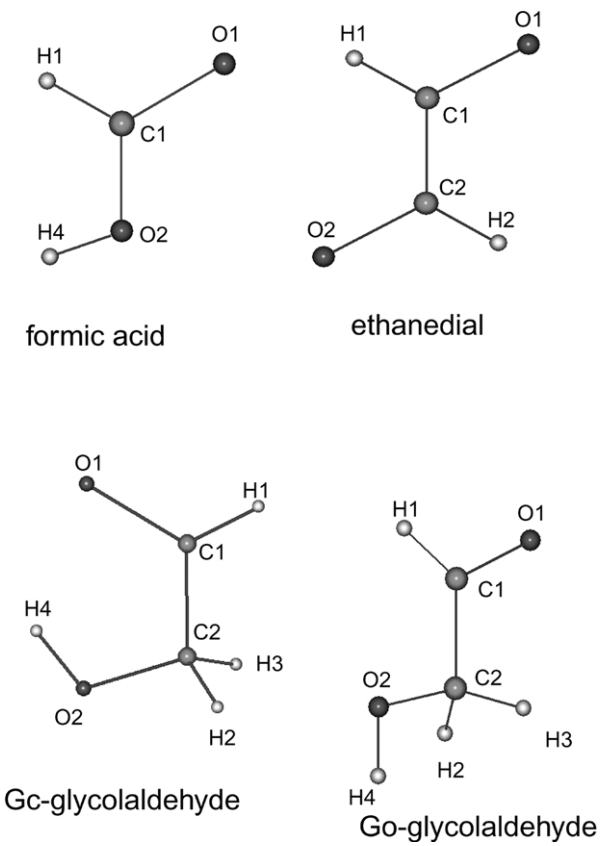

Figure 1. The structures and atom numerations in the systems under study.

paths connecting the structures. The selected geometric parameters of the optimized global minimum structures are presented in Table 1, while the structures themselves are shown in Figure 1.

3. Results and discussion

3.1. Formic acid

Free rotation in formic acid was investigated previously in many papers.[13–15] The molecule can exist in the lowest energy conformer *trans* and in the *cis* conformer of higher energy. We investigated the rotation about the CO bond changing the dihedral angle τ=H4–O2–C1–H1 (see Figure 1 for atom numeration). Table 2 presents the total energy for the conformers *trans* (τ=180 °), *cis* (τ=0 °), and for the transition state at the top of the barrier (τ=90 °). A number of explanations have been proposed for these energy differences.[1,13] The barrier in formic acid is said to be attractive, since the decrease of the A term is faster than the increase of the R term, $|\Delta A|>|\Delta R|$.[1] Our data confirm this statement. Various components of the energy and their changes as the molecule is rotated are displayed in Table 2. The variations of the terms V_{nn}, V_{ne} and V_{ee} during conformational changes are depicted in Figure 2a.

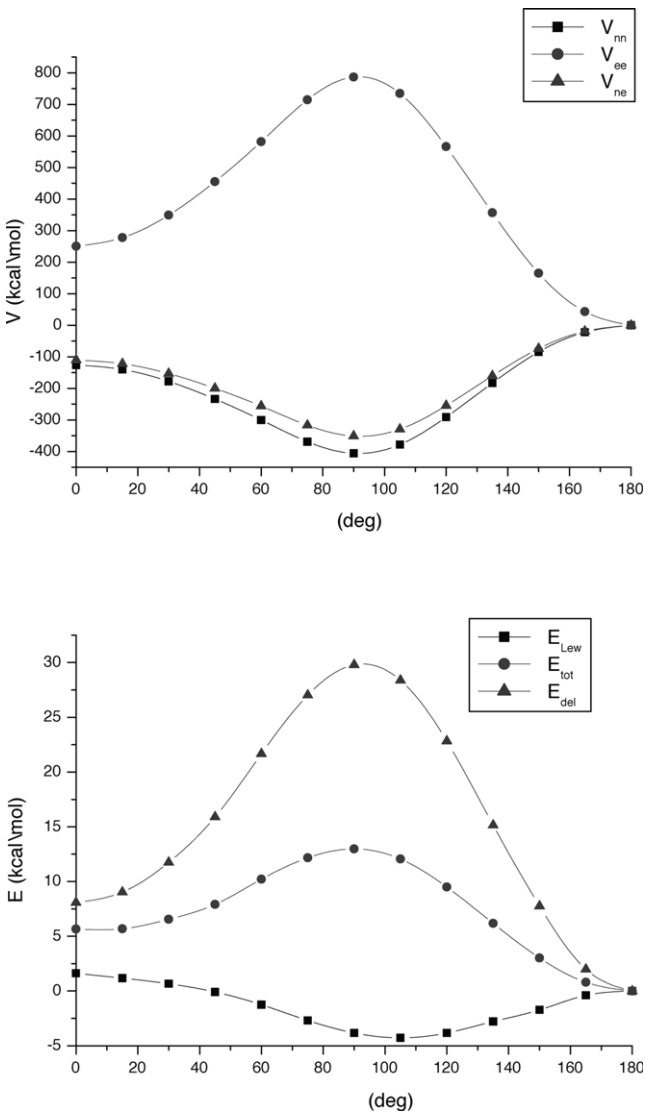

Figure 2. Torsional angle dependence of (a) the electrostatic terms V and (b) Lewis and non-Lewis energy terms for fully relaxed formic acid.

Table 2. The total energy, the Lewis and the hyperconjugation terms and the electrostatic components of the energy of formic acid for the rotation around the CO bond

τ	E_{tot} (a.u.)	ΔE_{tot} (kcal/mol)	E_{Lew} (a.u.)	ΔE_{Lew} (kcal/mol)	E_{del} (a.u.)	ΔE_{del} (kcal/mol)	E_{ex} (a.u.)	ΔE_{ex} (kcal/mol)
180	−189.795331	0.00	−189.521752	0.00	−0.273579	0.00	−17.918756	0.00
90	−189.774639	12.98	−189.527857	−3.83	−0.246782	16.82	−17.896799	13.78
0	−189.788892	4.04	−189.519164	1.62	−0.269727	2.42	−17.918057	0.44
τ	V_{nn} (a.u.)	ΔV_{nn} (kcal/mol)	V_{en} (a.u.)	ΔV_{en} (kcal/mol)	V_{ee} (a.u.)	V_{ee} (kcal/mol)		
180	69.923871	0.00	−586.185340	0.00	138.716749	0.00		
90	69.276915	−405.97	−548.931794	786.61	138.089920	−393.34		
0	69.722991	−126.05	−585.786135	250.50	138.615235	−63.70		

As one can see, the repulsive terms V_{ee} and V_{nn} favor the *cis* conformer of formic acid, not the *trans* one. These terms have the largest values for the most stable *trans* conformer, and decrease by 799 kcal/mol when going to the top of the barrier. On the other hand, the maximum of the attractive term V_{en} is at the barrier top. This value is lower by 786 and 250 kcal/mol, respectively, for *trans* and *cis* conformers. When the dihedral angle is changed from 180 to 90 ° as the barrier is traversed, V_{ne} becomes less negative. The $V_{nn}+V_{ee}$ term, however, becomes less positive, producing a net rise of energy dominated by decreased attraction. Thus, it is the interplay of the repulsive and attractive terms which makes the *trans* conformer the most stable one.

The electronic term V_{ee} is a sum of three terms: Coulomb repulsion energy E_{coul}, exchange energy E_{ex} and correlation energy E_c. These three terms change in a parallel way. The Coulomb term is the most important one, while the last two terms lower the value of electron repulsion, but no more than 15%.

We are now in a position to examine more fully the changes in the energy components as the barrier is traversed. Let us continue with the complementary analysis of the barrier by analyzing Lewis and hyperconjugation (non-Lewis) terms according to Eq. 3. If Lewis energy were the only term taken into account, the energy ordering of the conformers would be: $E_{top}<E_{cis}<E_{trans}$, which is opposite to the actual ordering of the total energy (see Figure 2b). However, delocalization energy of the conformers—called hyperconjugation energy in NBO model—increases in the same order as the total energy. This means that Lewis-like structure, without the hyperconjugation taken into account, would have opposite preferences. This demonstrates that electron delocalization of bonding to antibonding orbitals is the primary cause determining the barrier to rotation in formic acid, same as in ethane molecule.[4]

3.2. Ethanedial

The next molecule studied by us was ethanedial, which differs from formic acid by having the –COH group attached, instead of the –OH group, to the carbonyl group. The minimum energy conformation of this molecule is presented in Figure 1. The *trans* conformer is the global minimum on the molecular energy profile with respect to a change of the dihedral angle τ (H1–C1–C2–H2). Its geometrical parameters calculated at B3LYP/aug-cc-pVDZ level are presented in Table 1. Table 3 contains the total energies and the relative energy terms for different conformers.

The rotation barrier in ethanedial can be classified as repulsive. Inspection of Table 3 shows that the increase of the R term during intramolecular rotation is faster than the decrease of the A term, $|\Delta R|>|\Delta A|$. The relative total energy and the energy decomposition are shown in Figure 3a. The sum of the repulsive energy ($V_{ee}+V_{nn}$) is minimal for the *trans* conformer. On the other hand, the attractive component V_{en} has the lowest absolute value for the *trans* conformer. So, it is evident that the repulsive interactions strongly favor the *trans* conformation.

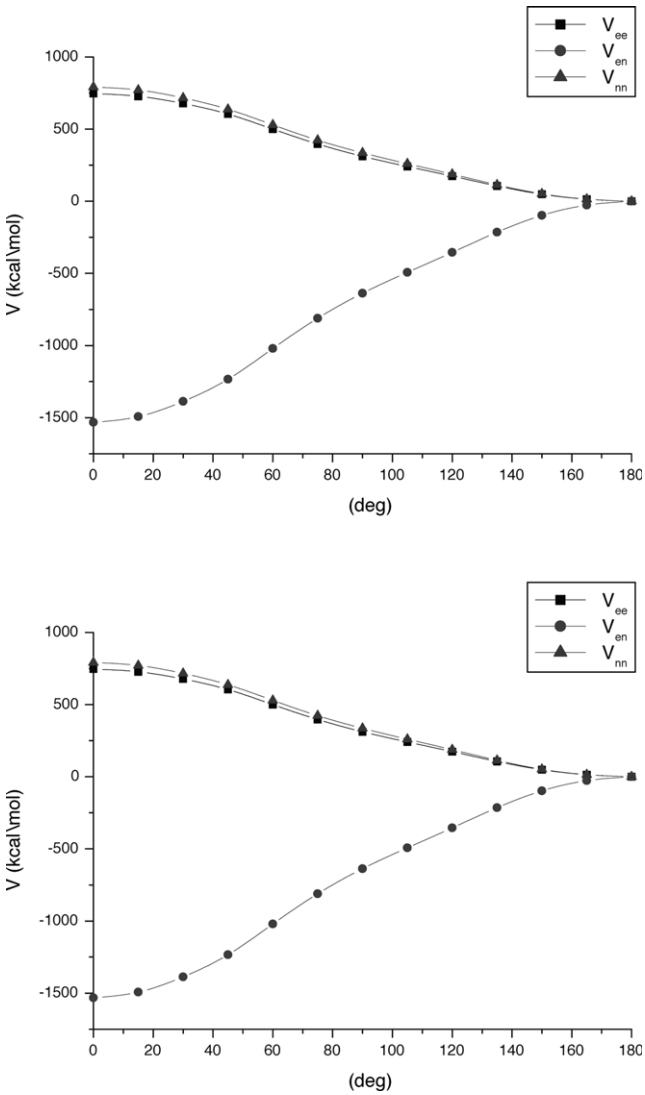

Figure 3. Torsional angle dependence of (a) the electrostatic terms V and (b) Lewis and non-Lewis energy terms for fully relaxed ethanedial.

Table 3. The total energy, the Lewis and the hyperconjugation terms and the electrostatic components of the energy of ethanedial for the rotation around the CC bond

τ	E_{tot} (a.u.)	ΔE_{tot} (kcal/mol)	E_{Lew} (a.u.)	ΔE_{Lew} (kcal/mol)	E_{del} (a.u.)	ΔE_{del} (kcal/mol)	E_{ex} (a.u.)	ΔE_{ex} (kcal/mol)
180	−227.856668	0.00	−227.569961	0.00	−0.286706	0.00	−21.843461	0.00
90	−227.847750	5.60	−227.566952	1.89	−0.28709	3.71	−21.842403	0.274
0	−227.849268	4.64	−227.550227	12.38	−0.299041	−7.74	−21.840054	0.289
τ	V_{nn} (a.u.)	ΔV_{nn} (kcal/mol)	V_{en} (a.u.)	ΔV_{en} (kcal/mol)	V_{ee} (a.u.)	V_{ee} (kcal/mol)		
180	101.573693	0.00	−737.536366	0.00	181.623392	0.00		
90	102.070044	311.46	−738.553006	−637.95	182.157878	335.39		
0	102.762216	745.81	−739.97875	−1532.62	182.885187	791.79		

In order to investigate the energetic preference of the *trans* form over the *cis* one we have carried out the NBO analysis, presented in Figure 3b. This figure shows that the hyperconjugative stabilization is the largest for the dihedral angle equal 0 °. If only that energy were taken into account, the energy ordering should be: $E_{cis}<E_{trans}<E_{top}$, which means that the delocalization of electron density favors the *cis* structure. On the other hand, the Lewis energy favors the *trans* conformer for this molecule. However, the Lewis energy term does not describe the energy sequence properly (the value for the top-of-the barrier conformer is smaller than for the *cis* one). The stabilization of the molecule and the energy ordering of the *trans*, *cis* and top-of-the barrier conformers is determined therefore by the interplay between both Lewis and hyperconjugation terms.

3.3. Glycolaldehyde

The third molecule investigated by us in this paper is glycolaldehyde. It differs from the formic acid by having the $-CH_2COH$ group, instead of the $-OH$ group, attached to the carbonyl group. The global minimum, denoted as the Gc structure, is shown in Figure 1. This structure is stabilized by an intramolecular hydrogen bond involving the carbonyl oxygen and hydroxyl hydrogen. The second minimum under study, named Go-glycolaldehyde, is found for another structure presented in Figure 1. It differs from the global minimum Gc by the position of the $-OH$ group. Actually, there are more local minima on the PES of glyceraldehyde but there are the subject of other paper, where we discuss the potential energy surface and the spin–spin coupling constants for this molecule.[16] The selected optimized structural parameters at the B3LYP/aug-cc-pVDZ have been reported in Table 1 for Gc- and Go-glycolaldehyde structures. The energy difference between Gc and Go structures is 3.38 kcal/mol. We investigated the rotation about the CC bond changing the dihedral torsion angle τ=H1–C1–C2–H2 by 15 ° and carrying out the partial geometry optimization starting from the structures Gc and Go. This results in two different rotation paths. Tables 4 and 5 present the total energy for the stable conformers on each pathway and for the transition state conformers at the top of the barriers for Gc- and Go-glycolaldehyde structures.

Let us discuss first the terms of the energy in Eq. 1. The data of Table 4 are displayed in Figure 4 and the data of Table 5 are shown in Figure 5. The figures present increments of the total energy and the potential energy components. When the dihedral angle τ in Gc-glycolaldehyde structure is changed from 60 to 210 ° (the barrier is traversed at 135 °) the V_{ne} term becomes less negative. The absolute value of the attractive ΔV_{ne} energy is lower by 2431 and 2449 kcal/mol at the barrier top (135 °) than at the most stable structure (60 °) and the second minimum conformer at 210 ° The repulsive terms ($V_{ee}+V_{nn}$) however, become less positive, producing a net rise dominated by decreased attraction. So, for the rotation barrier of Gc-glycolaldehyde the relation is $|\Delta A|>|\Delta R|$, i.e. the barrier is classified as attractive. Contrary to that, the barrier to rotation for the structure Go-glycolaldehyde should be classified as repulsive, because the phases of the two components are reversed. The term V_{ne} becomes more negative when the dihedral angle τ is changed from 120 to 240 °, but the sum of repulsive terms becomes more positive, producing a net rise in energy dominated by increased repulsion: $|\Delta R|>|\Delta A|$.

For the further understanding of the conformation preference let us analyse the decomposition of the total energy to Lewis and hyperconjugation terms. The minimum of the Lewis energy (the highest absolute value) and the maximum of the hyperconjugation term are close to the barrier top at 135 ° (Figure 4b) for the Gc-glycolaldehyde. This means that the hyperconjugation term, not the Lewis energy, is the most important for the energetic ordering of the total energy $E_{60}<E_{210}<E_{top}$. It should be stressed that only the attractive potential V_{ne} is involved in hyperconjugative interactions.

Table 4. The total energy, the Lewis and the hyperconjugation terms and the electrostatic components of the energy of Gc-glycolaldehyde for the rotation around the CC bond

τ	E_{tot} (a.u.)	ΔE_{tot} (kcal/mol)	E_{Lew} (a.u.)	ΔE_{Lew} (kcal/mol)	E_{del} (a.u.)	ΔE_{del} (kcal/mol)	E_{ex} (a.u.)	ΔE_{ex} (kcal/mol)
60	−229.081908	0.00	−228.828213	0.00	−0.253696	0.00	−22.422489	0.00
135	−229.073038	5.57	−228.845153	−10.63	−0.227885	16.19	−22.416268	3.90
210	−229.076213	3.57	−228.837830	−6.03	−0.238383	9.61	−22.416653	3.66
τ	V_{nn} (a.u.)	ΔV_{nn} (kcal/mol)	V_{en} (a.u)	ΔV_{en} (kcal/mol)	V_{ee} (a.u.)	V_{ee} (kcal/mol)		
60	118.635721	0.00	−774.382778	0.00	199.213216	0.00		
135	116.682265	−1225.81	−770.508041	2431.43	197.301846	−1199.40		
210	114.726324	−2453.18	−766.604134	4881.17	195.334604	−2433.86		

Table 5. The total energy, the Lewis and the hyperconjugation terms and the electrostatic components of the energy of Go-glycolaldehyde for the rotation around the CC bond

τ	E_{tot} (a.u.)	ΔE_{tot} (kcal/mol)	E_{Lew} (a.u.)	ΔE_{Lew} (kcal/mol)	E_{del} (a.u.)	ΔE_{del} (kcal/mol)	E_{ex} (a.u.)	ΔE_{ex} (kcal/mol)
120	−229.076515	0.00	−228.844111	0.00	−0.232404	0.00	−22.418822	0.00
240	−229.068604	4.96	−228.839481	2.90	−0.229124	2.06	−22.415421	2.13
300	−229.073930	1.62	−228.821791	14.01	−0.252140	−12.38	−22.417789	0.65
τ	V_{nn} (a.u.)	ΔV_{nn} (kcal/mol)	V_{en} (a.u.)	ΔV_{en} (kcal/mol)	V_{ee} (a.u)	V_{ee} (kcal/mol)		
120	115.000090	0.00	−767.219062	0.00	195.671916	0.0		
240	116.583292	993.47	−770.427780	−2013.50	197.330602	1040.84		
300	117.211512	1387.68	−771.699387	−2811.45	197.970268	1442.24		

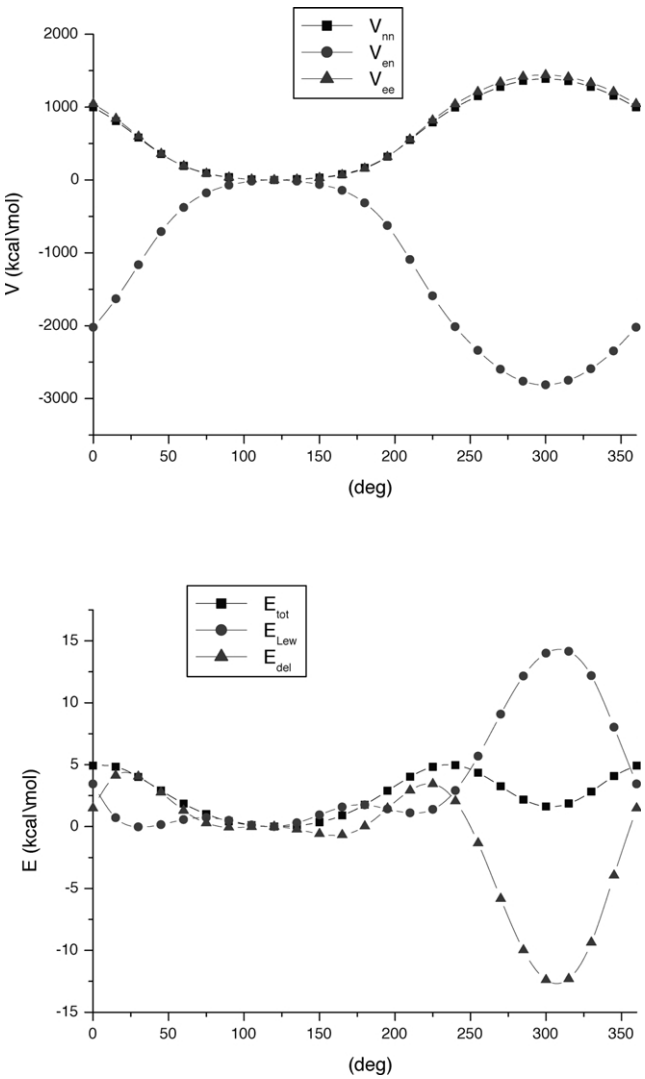

Figure 4. Torsional angle dependence of (a) the electrostatic terms *V* and (b) Lewis and non-Lewis energy terms for fully relaxed Gc-glycolaldehyde.

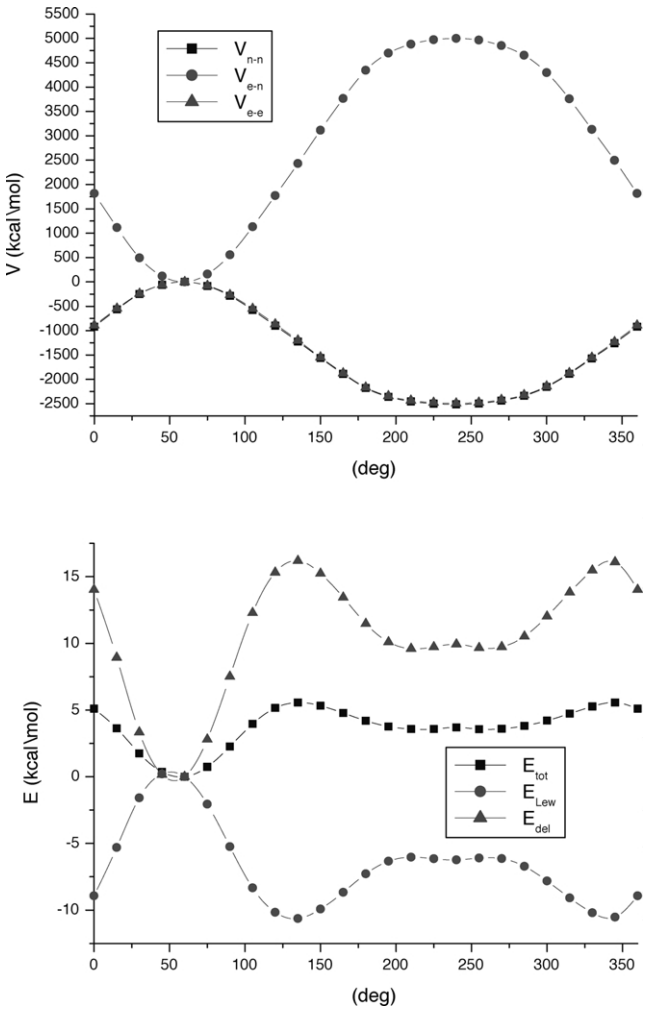

Figure 5. Torsional angle dependence of (a) the electrostatic terms *V* and (b) Lewis and non-Lewis energy terms for fully relaxed Go-glycolaldehyde.

One can conclude that it is the reduction of the attractive electron-nuclear component which determines the structure of Gc-glycolaldehyde. Contrary to that, neither Lewis nor hyperconjugation alone can reproduce the sequence of the total energy in the case of the Go-glycolaldehyde structure (Figure 5b): $E_{120}<E_{300}<E_{top}$. This data illustrate the importance of the interplay of both Lewis and hyperconjugation components, i.e. the importance of the steric as well as the hyperconjugation origin of the conformational preference of the Go-glycolaldehyde structure.

Finally, we notice that the graph in Figure 4b is essentially the same as that in Figure 2b. The decomposition of the energy of the Gc-glycolaldehyde structure does not differ from that in the formic acid: the change of the attractive term (which outweighs the change of the repulsive term) and the hyperconjugation energy are the leading factors. The results in Table 5 suggest also that there is no fundamental difference in the decomposition of the electrostatic energy terms. Similarly, the graph in Figure 5b is essentially the same as the one in Figure 3b, what means the same pattern of the energy decomposition occurs for the ethanedial and for the Go-glycolaldehyde.

4. Conclusions

In this paper, we determined the rotational barriers for a sequence of three molecules with the carbonyl group by ab initio calculations. The results can be summarized as follows:

(1) Decomposition of the total energy into attractive and repulsive components allows for a physical interpretation of the barrier to rotation. Formic acid and Gc-glycolaldehyde have been shown to have a rotational barrier that is predominantly attractive, i.e. arises mainly from reduction of the attractive interaction rather than an increase in the repulsive one. The situation is opposite in ethanedial and Go-glycolaldehyde, where the energy rise is dominated by the increased repulsion. We would like to stress that the nature of the rotation barrier around the C–C bond is completely changed when the –OH group assumes a different conformation.

(2) The predominantly attractive nature of the rotational barrier in formic acid and Gc-glycolaldehyde was confirmed by the analysis of the Lewis and non-Lewis components of the total energy. The prevalent factor determining the nature of this barrier is the loss of the

hyperconjugation when rotation from the most stable to the less stable conformer occurs. This contrasts with the dominance of repulsion for ethanedial and Go-glycolaldehyde barriers, which is due to the balance between the Lewis and the hyperconjugation energetic terms. Neither Lewis nor the hyperconjugation alone can reproduce the sequence of the total energy of these conformers.

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Syntheses of cystothiazole A and its stereoisomers: importance of stereochemistry for antifungal activity

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Abstract—The enantiocontrolled total syntheses of all the stereoisomers of a myxobacterial antibiotic, cystothiazole A, are described. The natural *syn* stereochemistry at the C4–C5 position was controlled by the asymmetric Evans aldol process, whereas the *anti* relationship was introduced by a modified Evans aldol methodology. Starting with a known aldehyde, the common substrate of the aldol reactions, cystothiazole A and its three stereoisomers were synthesized in 9 steps. All three stereoisomers did not show antifungal activity even at a dosage 2500-fold that of cystothiazole A.

1. Introduction

Cystothiazole A (**1**) is an antifungal and cytotoxic antibiotic isolated from the myxobacterium *Cystobacter fuscus* by the authors.[1] The structural features of this antibiotic are the presence of β-methoxyacrylate and bithiazole moieties. This metabolite might be biosynthetically derived via a hybrid process by polyketide synthetases and non-ribosomal peptide synthetases, as supported by incorporation experiments.[2] A number of such natural products has recently been discovered from myxobacteria, e.g. melithiazoles[3,4] and myxothiazol A.[5,6] This family of β-methoxyacrylate type molecules is thought to bind to the cytochrome bc_1 complex of the mitochondrial respiratory chain system to exhibit fungicidal activity, but not inhibit the bacterial system.[7] The mode of action of cystothiazole A (**1**) was demonstrated by an NADH oxidase inhibition experiment using sub-mitochondrial membrane.[1] The derivatives named cystothiazoles B–F were also isolated as minor components from a fermentation broth.[1,8] Cystothiazole A (**1**) was the major and most active principal among the cystothiazole family. Based on the structure-activity relationships (SAR) within the natural cystothiazoles, it was found that the β-methoxyacrylate moiety was essential and the lipophilicity of the terminal alkyl group (isopropyl) is important for the antifungal activity.[8] Although these SAR are informative to some extent, more detailed information should be accumulated prior to developing artificial candidates for agrochemicals or antitumor agents based on **1**. In particular, the importance of the stereochemistry at the C4–C5 position of **1** is of interest for developing achiral simple derivatives.

Two research groups have accomplished the enantiocontrolled total synthesis of cystothiazole A (**1**). Williams and co-workers carried out the first chiral syntheses of **1** and cystothiazole C via the asymmetric Evans aldol process.[9] The second total synthesis of **1** was accomplished by Akita and co-workers.[10,11] The formal syntheses of **1** and cystothiazole C were also reported.[12] The absolute stereochemistry of cystothiazole E, the natural derivative lacking the β-methoxyacrylate moiety, was determined by the total syntheses of both mirror image compounds.[12,13] The syntheses of myxothiazol A, the earliest member of the bithiazole-type β-methoxyacrylate family, were reported in racemic forms.[14,15] We herein describe the first syntheses of all the stereoisomers of cystothiazole A (**1**) to clarify the significance of the C4–C5 stereochemistry of **1** for antifungal activity.

2. Results and discussion

Since the C4–C5 stereogenic centers of cystothiazole A (**1**) is an aldol-type one, the generally applicable methodology toward the stereoisomers of **1** might be the asymmetric Evans aldol condensation[16] and the combined use of the asymmetric *anti* aldol methodology that was a modified version of the Evans aldol process devised by Heathcock and co-workers.[17] The retrosynthetic routes to the stereoisomers as well as the mother compound **1** itself are shown in Scheme 1. The natural **1** and its enantiomer *ent*-**1** are thus obtained by the original Evans aldol process via *syn* aldols from the common aldehyde **2**, whereas, two diastereomers,

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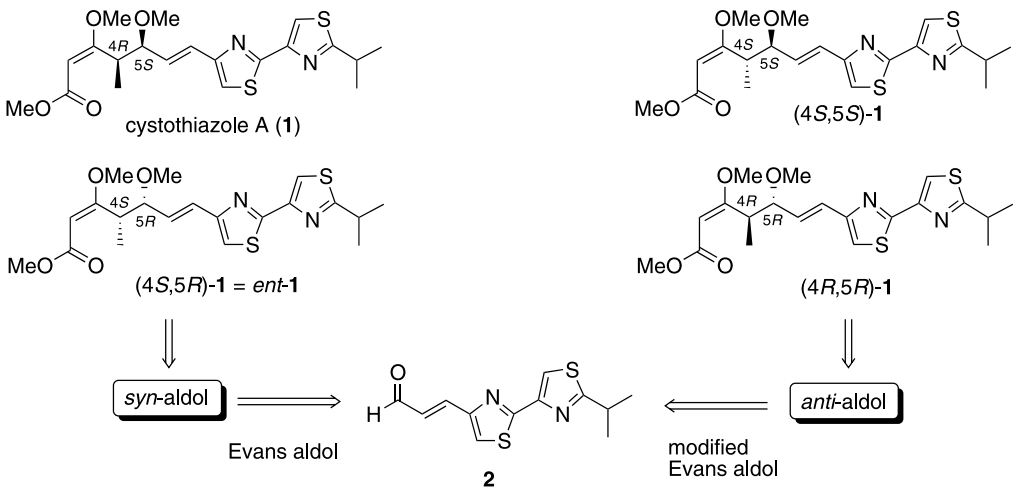
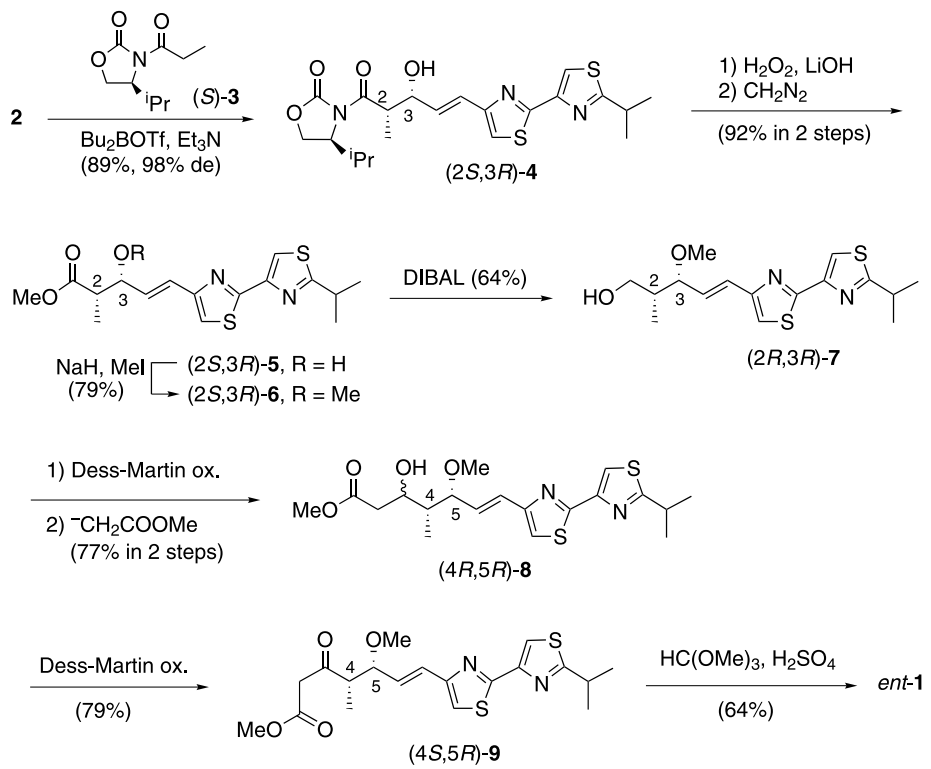


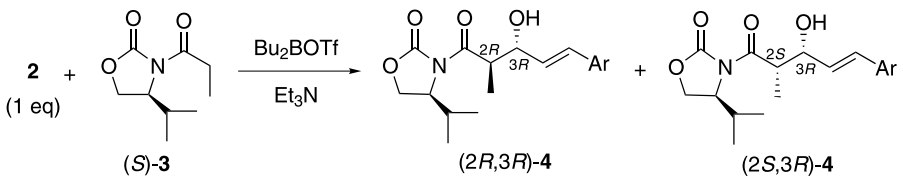
Scheme 1. Synthetic strategy toward all the stereoisomers of cystothiazole A (**1**).

(4*S*,5*S*)-**1** and (4*R*,5*R*)-**1**, could be prepared by the modified Evans aldol methodology via *anti* aldols from **2**. The route for the total synthesis of *ent*-**1** is summarized in Scheme 2. The stereocontrolled formation of (2*S*,3*R*)-*syn*-aldol **4** was performed by the asymmetric Evans aldol reaction[16] with the known aldehyde **2**[9] and (*S*)-oxazolidinone (*S*)-**3** in a high yield and a high diastereoselectivity (Fig. 1, entry 1). Removal of the chiral auxiliary by alkaline hydrogen peroxide followed by diazomethane treatment provided methyl ester **5**, which was then converted to the methyl ether **6**. The yields of **6** varied somewhat due to unknown side products that might arise from β-elimination, although the epimerization at the C-2 position of the isolated product was not observed. Reduction of **6** with DIBAL led to primary alcohol **7**, which, after oxidation to an aldehyde, was subjected to an addition reaction with the carbanion of methyl acetate to afford β-hydroxy ester **8** as a diastereomeric mixture. Dess–Martin periodinane oxidation of **8** gave a β-ketoester, which was finally converted to (−)-**1** (*ent*-**1**) by acid catalyzed enol formation. The total yield of *ent*-**1** from **2** was 16% in 9 steps. The melting point and spectroscopic data of the synthetic *ent*-**1** were identical to those for natural **1** except for the specific rotation: $[\alpha]_D^{25}=-113$ (*c* 0.246, $CHCl_3$) (lit.[1] $[\alpha]_D^{23}=+109$ (*c* 0.24, $CHCl_3$)). Cystothiazole A (**1**) itself was also synthesized in the same manner via aldol (2*R*,3*S*)-**4** that was prepared with the common aldehyde **2** and oxazolidinone (*R*)-**3** (Fig. 1).

The diasteromeric isomers of cystothiazole A, (4*S*,5*S*)-**1** and (4*R*,5*R*)-**1**, were next synthesized from aldehyde **2** by the



Scheme 2. Synthesis of *ent*-cystothiazole A (*ent*-**1**).



entry	(*S*)-**3** (eq)	Et_3N (eq)	Bu_2BOTf (eq)	yield (%)	(2*R*,3*R*)-**4** : (2*S*,3*R*)-**4**[a]
1	2.2	2.8	2.0	90	1:99
2	1.1	2.5	2.2	55	75:25
3	1.0	1.1	2.0	27	99: 1
4	1.0	1.2	1.4	37	95: 5
5	2.0	2.4	2.6	48	21:79

[a] Calculated from isolated yields

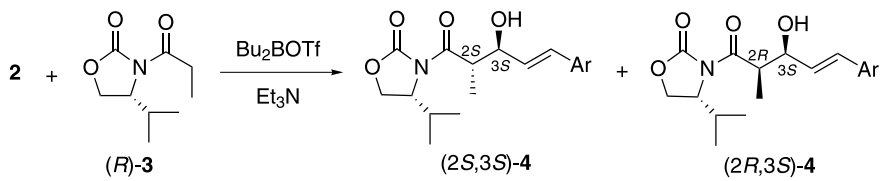
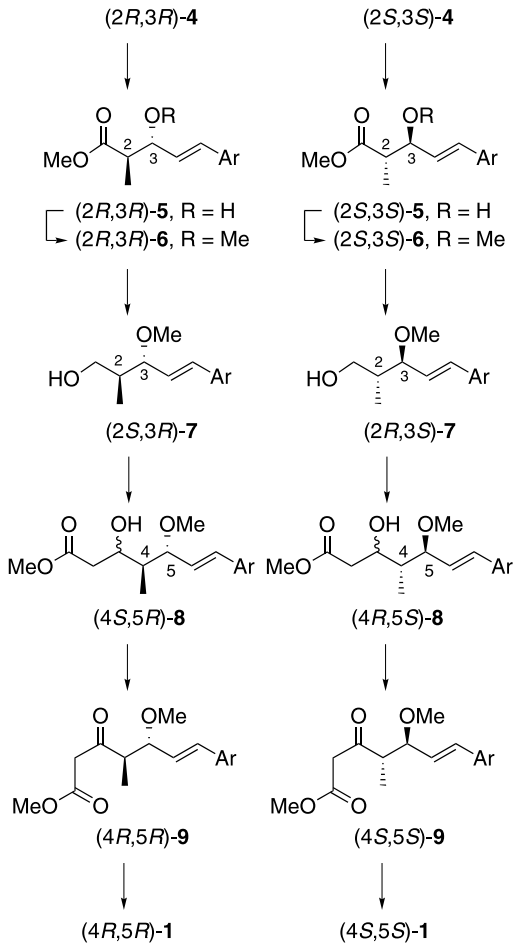


Figure 1. Asymmetric aldol addition reactions under the Evans' conditions (entry 1) and the modified *anti*-selective conditions toward the *anti* aldol (2*R*,3*R*)-**4** (entry 2–5). The second equation represents the aldol reactions to afford the antipodes.

asymmetric *anti* aldol process, although it was reported that the variation of substrate aldehydes was limited.[17] The significant feature of this method is the use of an excess (2 equiv.) of the Lewis acid to oxazolidinone **3**. An open transition state was suggested to account for such *anti* selectivity. An example of the original Evans aldol process conducted for the synthesis of *ent*-**1** (vide supra) is shown in Fig. 1 (entry 1), indicating a high *syn* selectivity as well as a satisfactory chemical yield. On the other hand, when the *anti* aldol conditions were applied to our system by using 2 equiv. of dibutylboron triflate against (*S*)-**3**, the chemical yield and selectivity of the desired *anti* aldol (2*R*,3*R*)-**4** were both low (Fig. 1, entry 2). Reduction of number of equivalents of the base increased the *anti* selectivity, but its yield was much lower than the previous case (entry 3). The low yield of the product might be due to decomposition of the bithiazole moiety of the substrate **2** by the excess Lewis acid. A small excess of the Lewis acid against the base slightly increased the yield and kept a moderate *anti* selectivity (entry 4). A trial was unsuccessful when the amounts of all the reagents were increased to approximately twice those used in entry 4 in order to obtain a higher yield of the *anti* isomer (entry 5). We finally chose the conditions of entry 4 in Fig. 1 to prepare the *anti* aldols. Starting with the *anti* aldols, (2*R*,3*R*)-**4** and (2*S*,3*S*)-**4**, the two diastereomers of cystothiazole A, (4*R*,5*R*)-**1** and (4*S*,5*S*)-**1**, respectively, were synthesized by a series of reactions (Scheme 3), which is the same as that for *ent*-**1** (Scheme 2). Although the *anti* aldols, (2*R*,3*R*)-**4** and (2*S*,3*S*)-**4**, were obviously enantiomers each other from the spectroscopical evidences, their absolute stereochemistry was not very reliable because of the low yields of the *anti* selective Evans aldol process. To confirm the absolute stereochemistry of the *anti* aldols the modified Mosher method[18] was applied to the methyl ester (2*S*,3*S*)-**5** obtained from an *anti* aldol, (2*S*,3*S*)-**4**. Thus, the methyl ester (2*S*,3*S*)-**5** was converted to



Scheme 3. Reaction sequences toward (2*R*,3*R*)-cystothiazole A ((2*R*,3*R*)-**1**) and (2*S*,3*S*)-**1**. The reaction conditions were the same as those for the corresponding steps in Scheme 2.

(*S*)-MTPA ester (**10s**) and (*R*)-MTPA ester (**10r**), and the 5*S* configuration of this compound was demonstrated from the chemical shift differences between these MTPA esters ($\Delta\delta=\delta_{10s}-\delta_{10r}$) as shown in Figure 2.

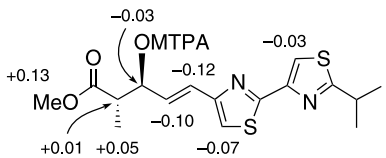


Figure 2. $\Delta\delta$ ($=\delta_{10s}-\delta_{10r}$) values for the MTPA esters (**10r** and **10s**) of (2*S*,3*S*)-**5**.

In antifungal tests using a phytopathogenic fungus *Phytophthora capsici*, synthetic cystothiazole A (**1**) showed an activity until the dose was 0.04 μg/disk, which was the same activity as that of the natural one.[1] However, not only the enantiomer but also the two diastereomers did not show any antifungal activity up to 100 μg/disk. This result was not expected at all, because all the stereoisomers possess the β-methoxyacrylate unit that is regarded as the binding site to the target molecule. The importance of the β-methoxyacrylate moiety in **1** was actually demonstrated by the fact that the synthetic intermediate (4*R*,5*S*)-**9** was inactive, despite its natural stereochemistry. Furthermore, several non-chiral β-methoxyacrylate-type compounds have been developed to the market as pesticides.[19] These findings suggest that unsuitable directions of the substituents at the C4–C5 position completely interfere in the binding of the β-methoxyacrylate moiety to the target molecule.

3. Experimental

3.1. General

Melting points were measured on a Yanaco MP-J3 micro melting point apparatus. Fuji Silysia silica gel BW-300 was employed for open column chromatography. Pre-coated silica gel 60 F_{254} plates (Merck) were used for thin-layer chromatography (TLC). HPLC was performed on a JASCO high-pressure gradient system equipped with PU-980 pumps. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-7000S spectrometer. UV spectra were recorded on a JASCO Ubest-50 UV/VIS spectrophotometer. NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer. NMR chemical shifts were referenced to the solvent peak of δ_H 7.26 (residual $CHCl_3$) for protons and δ_C 77.0 ($CDCl_3$) for ^{13}C. FAB MS (positive) measurements were performed on a JEOL Mstation JMS-700 mass spectrometer using *m*-nitrobenzyl alcohol as a matrix. High-resolution MS were recorded on an Applied Biosystems Mariner Biospectrometry Workstation in the positive ESI mode using an angiotensin I/neurotensin mixture as the internal calibration standard. Antifungal tests were carried out by the previously reported method.[1]

3.1.1. (*S*)-4-Isopropyl-3-[(*E*)-(2*S*,3*R*)-3-hydroxy-5-(2′-isopropyl[2,4′]bithiazol-4-yl)-2-methyl-4-pentenoyl]oxazolidin-2-one ((2*S*,3*R*)-4) and (2*R*,3*S*)-4. To a cooled solution of (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone ((*S*)-**3**) (1.31 g, 7.11 mmol) in dry dichloromethane (14.5 ml) at 0 °C were added a 1 M solution of dibutylboron triflate (6.4 ml) in dichloromethane and then dry triethylamine (1.3 ml, 9.0 mmol). After being stirred for 30 min and then cooled to −78 °C, to the resulting solution was added a solution of **2** (853 mg, 3.25 mmol) in dry dichloromethane (25 ml), and the mixture was stirred at −78 °C for 1 h 40 min and then at 0 °C for 40 min. The reaction mixture was diluted with 0.5 M phosphate buffer (pH 7) (8.6 ml), MeOH (50 ml), and 30% H_2O_2 (8.6 ml), and stirred for an additional 40 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with 5% sodium bicarbonate and then with brine. The solution was dried and concentrated to afford an oil, which was chromatographed on silica gel (4:1 hexane EtOAc) to give (2*S*,3*R*)-**4** (1.29 g, 89% yield, 98% de) and its diastereomer (13 mg, 0.9%). The same procedure with (*R*)-4-isopropyl-3-propionyl-2-oxazolidinone ((*R*)-**3**) gave the enantiomer (2*R*,3*S*)-**4** in 98% yield (99% de based on the yield of a diastereomer).

Compound (2*S*,3*R*)-**4**. Colorless oil; $[\alpha]_D^{24}=+35$ (*c* 0.09, $CHCl_3$); UV (MeOH) 216 (ε 26,400), 249 (20,100), 312 (10,100) nm; IR (film) 3504 (br), 3113, 2967, 2875, 1779, 1698, 1498, 1458, 1386, 1204, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J*=6.9 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H), 1.31 (d, *J*=7.1 Hz, 3H), 1.44 (d, *J*=6.8 Hz, 6H), 2.36 (m, 1H), 3.12 (brs, 1H, OH), 3.37 (sept, *J*=6.8 Hz, 1H), 4.00 (dq, *J*=3.4, 7.1 Hz, 1H), 4.21 (dd, *J*=9.1, 3.1 Hz, 1H), 4.27 (dd, *J*=9.1, 8.3 Hz, 1H), 4.47 (dt, *J*=8.2, 3.5 Hz, 1H), 4.72 (brt, *J*=4.1 Hz, 1H), 6.62 (dd, *J*=15.5, 5.0 Hz, 1H), 6.73 (dd, *J*=15.5, 1.4 Hz, 1H), 7.08 (s, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (q), 14.8 (q), 17.9 (q), 23.1 (q, 2C), 28.4 (d), 33.3 (d), 42.7 (d), 58.3 (d), 63.4 (d), 71.7 (d), 115.0 (d), 115.8 (d), 124.1 (d), 131.7 (d), 148.7 (s), 153.5 (s), 154.2 (s), 162.8 (s), 177.1 (s), 178.6 (s); MS (FAB) *m/z* (rel. int.) 472 ($[M+Na]^+$, 3), 450 ($[M+H]^+$, 73) 432 (43), 406 (2), 364 (3), 340 (8), 303 (12), 275 (72), 265 (60), 237 (65), 219 (13), 176 (4), 136 (85), 77 (43). Anal. found: C, 56.11%; H, 6.00%; N, 9.17%, calcd for $C_{21}H_{27}N_3O_4S_2$: C, 56.10%; H, 6.05%; N, 9.35%.

Compound (2*R*,3*S*)-**4**. $[\alpha]_D^{24}=-38$ (*c* 0.31, $CHCl_3$); HRMS (ESI) *m/z* 450.1531 $(M+H)^+$, calcd for $C_{21}H_{28}N_3O_4S_2$, 450.1516.

3.1.2. (*S*)-4-Isopropyl-3-[(*E*)-(2*R*,3*R*)-3-hydroxy-5-(2′-isopropyl[2,4′]bithiazol-4-yl)-2-methyl-4-pentenoyl]oxazolidin-2-one ((2*R*,3*R*)-4) and (2*S*,3*S*)-4. To a cooled solution of (*S*)-**3** (42 mg, 0.23 mmol) in dry dichloromethane (1 ml) at 0 °C were added a 1 M solution of dibutylboron triflate (0.32 ml) in dichloromethane and then dry triethylamine (0.06 ml, 0.28 mmol). After being stirred for 30 min and then cooled to −78 °C, to the resulting solution was added a solution of **2** (60 mg, 0.23 mmol) in dry dichloromethane (1.1 ml), and the mixture was stirred at −78 °C for 1 h 30 min and then at 0 °C for 90 min. The reaction mixture was diluted with 0.5 M phosphate buffer (pH 7) (0.4 ml), MeOH (2.5 ml), and 30% H_2O_2 (0.4 ml), and stirred for an additional 40 min. Similar procedures for work-up and separation to those for (2*S*,3*R*)-**4** afforded

(2*R*,3*R*)-**4** (35.7 mg, 35%) and its diastereomer (1.9 mg, 2%). (2*S*,3*S*)-**4** was obtained in 23% yield by the same method as that for (2*R*,3*R*)-**4** by using **2** and (*R*)-**3**.

Compound (2*R*,3*R*)-**4**. Colorless oil; $[\alpha]_D^{24}=+3.6$ (*c* 0.14, $CHCl_3$); UV (MeOH) 216 (ε 25,900), 248 (19,000), 311 (10,400) nm; IR (film) 3480 (br), 3111, 2964, 2875, 1773, 1700, 1684, 1199, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=6.9 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 3H), 1.43 (d, *J*=6.9 Hz, 6H), 2.35 (dq, *J*=3.1, 6.9 Hz, 1H), 3.36 (sept, *J*=6.9 Hz, 1H), 4.10 (dq, *J*=3.8, 6.9 Hz, 1H), 4.21 (dd, *J*=9.1, 3.1 Hz, 1H), 4.28 (dd, *J*=9.1, 8.3 Hz, 1H), 4.47 (dt, *J*=8.3, 3.7 Hz, 1H), 4.74 (t, *J*=4.0 Hz, 1H), 6.65 (dd, *J*=15.7, 4.9 Hz, 1H), 6.73 (d, *J*=15.7 Hz, 1H), 7.08 (s, 1H), 7.89 (s, 1H). Anal. found: C, 56.03%; H, 6.33%; N, 9.30%, calcd for $C_{21}H_{28}N_3O_4S_2$: C, 56.10%; H, 6.05%; N, 9.35%.

Compound (2*S*,3*S*)-**4**. $[\alpha]_D^{24}=-3.7$ (*c* 0.10, $CHCl_3$), HRMS (ESI) *m*/*z* 450.1534, calcd for calcd for $C_{21}H_{28}N_3O_4S_2$ 450.1516.

3.1.3. Methyl (*E*)-(2*S*,3*R*)-3-hydroxy-5-(2′-isopropyl[2,4′]bithiazol-4-yl)-2-methyl-4-pentenoate ((2*S*,3*R*)-5), (2*R*,3*S*)-5, (2*R*,3*R*)-5, and (2*S*,3*S*)-5. To a cooled solution of (2*S*,3*R*)-**4** (1.29 g, 2.87 mmol) in 80% aqueous THF (70 ml) at 0 °C was added 30% H_2O_2 (5.9 ml, 59 mmol) and 0.8 M LiOH (30 ml, 24 mmol), and the mixture was stirred for 1 h 15 min. The reaction mixture was diluted with 1.3 M $Ne_2S_2O_3$ (45 ml), acidified with 6 M HCl to pH 1, and extracted with EtOAc (30 ml) five times. The combined extracts were concentrated and the residual oil was treated with diazomethane in ether. The reaction mixture was concentrated, and the residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give (2*S*,3*R*)-**5** (932 mg, 92% in 2 steps). The enantiomer (2*R*,3*S*)-**5** and two diastereomers, (2*R*,3*R*)-**5** and (2*S*,3*S*)-**5**, were obtained in 95%, 91%, and 85% yields, respectively, by the same procedure.

Compound (2*S*,3*R*)-**5**. Colorless needles; mp 45.5–46.5 °C (hexane–EtOAc); $[\alpha]_D^{24}=-17$ (*c* 0.31, $CHCl_3$); UV (MeOH) 220 (ε 24,500), 248 (21,100), 313 (10,500) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J*=7.2 Hz, 3H), 1.44 (d, *J*=6.9 Hz, 6H), 2.76 (dq, *J*=3.9, 7.2 Hz, 1H), 2.83 (d, *J*=4.0 Hz, 1H, OH), 3.37 (sept, *J*=6.9 Hz, 1H), 3.73 (s, 3H), 4.67 (m, 1H), 6.61 (dd, *J*=15.5, 5.2 Hz, 1H), 6.71 (dd, *J*=15.5, 1.2 Hz, 1H), 7.08 (s, 1H), 7.85 (s, 1H). Anal. found: C, 54.52%; H, 5.85%; N, 7.90%, calcd for $C_{16}H_{20}N_2O_3S_2$: C, 54.52%; H, 5.72%; N, 7.95%.

Compound (2*R*,3*S*)-**5**. Colorless oil, $[\alpha]_D^{25}=+15$ (*c* 0.70, $CHCl_3$) (reported data:[9] $[\alpha]_D^{28}=+13.2$ (*c* 0.5, $CHCl_3$)).

Compound (2*R*,3*R*)-**5**. Colorless oil; $[\alpha]_D^{25}=-15$ (*c* 0.40, $CHCl_3$); UV (MeOH) 220 (ε 23,400), 248 (20,300), 312 (10,600) nm; IR ($CHCl_3$) 3120, 2984, 1732, 1174, 1012, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J*=7.0 Hz, 3H), 1.44 (d, *J*=7.0 Hz, 6H), 2.71 (quint, *J*=7.2 Hz, 1H), 2.84 (br, 1H, OH), 3.37 (sept, *J*=7.0 Hz, 1H), 3.73 (s, 3H), 4.41 (dd, *J*=6.0, 7.0 Hz, 1H), 6.62 (dd, *J*=15.5, 6.0 Hz, 1H), 6.68 (d, *J*=15.5 Hz, 1H), 7.10 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q), 23.1 (q, 2C), 33.3 (d), 45.6 (d), 51.9 (d), 74.3 (d), 115.0 (d), 116.2 (d), 125.0 (d), 132.1 (d), 148.6 (s), 153.9 (s), 163.0 (s), 175.9 (s), 178.7 (s); MS (FAB) *m*/*z* (rel. int.) 375 ($[M+Na]^+$, 5), 353 ($[M+H]^+$, 100), 335 (70), 321 (4), 293 (9), 275 (41), 265 (89), 237 (91), 235 (12), 170 (31), 136 (26), 77 (20). Anal. found: C, 54.79%; H, 5.81%; N, 7.92%, calcd for $C_{16}H_{20}N_2O_3S_2$: C, 54.52%; H, 5.72%; N, 7.95%.

Compound (2*S*,3*S*)-**5**. Colorless oil; $[\alpha]_D^{25}=+18$ (*c* 0.41, $CHCl_3$); HRMS (ESI) *m*/*z* 353.0989 $(M+H)^+$, calcd for $C_{16}H_{21}N_2O_3S_2$ 353.0988.

3.1.4. Methyl (*E*)-(2*S*,3*R*)-5-(2′-isopropyl[2,4′]bithiazol-4-yl)-3-methoxy-2-methyl-4-pentenoate ((2*S*,3*R*)-6), (2*R*,3*S*)-6, (2*R*,3*R*)-6, and (2*S*,3*S*)-6. To a cooled solution of (2*S*,3*R*)-**5** (384 mg, 1.09 mmol) in dry DMF (13.6 ml) at 0 °C were added MeI (0.69 ml, 11 mmol) and NaH (60% in mineral oil, 46.0 mg, 1.16 mmol), and the mixture was stirred for 2 h. An additional NaH (45.4 mg, 1.16 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with water (20 ml). The mixture was extracted with ether (30 ml) five times. The combined ethereal extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give (2*S*,3*R*)-**6** (314 mg, 78%). The enantiomer (2*R*,3*S*)-**6** and two diastereomers, (2*R*,3*R*)-**6** and (2*S*,3*S*)-**6**, were obtained in 92, 92, and 82% yields, respectively, by the same procedure.

Compound (2*S*,3*R*)-**6**. Colorless oil; $[\alpha]_D^{24}=-10$ (*c* 0.18, $CHCl_3$); UV (MeOH) 220 (ε 26,000), 248 (21,800), 312 (11,300) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J*=7.1 Hz, 3H), 1.44 (d, *J*=6.8 Hz, 6H), 2.72 (dq, *J*=6.0, 7.1 Hz, 1H), 3.35 (s, 1H), 3.37 (sept, *J*=6.8 Hz, 1H), 3.68 (s, 3H), 4.04 (dd, *J*=6.0, 7.2 Hz, 1H), 6.50 (dd, *J*=15.8, 7.2 Hz, 1H), 6.63 (d, *J*=15.8 Hz, 1H), 7.12 (s, 1H), 7.86 (s, 1H). Anal. found: C, 55.71%; H, 6.13%; N, 7.66%, calcd for $C_{17}H_{22}N_2O_3S_2$: C, 55.71%; H, 6.05%; N, 7.64%.

Compound (2*R*,3*S*)-**6**. Colorless oil; $[\alpha]_D^{25}=+10.3$ (*c* 0.44, $CHCl_3$) (reported data:[9] $[\alpha]_D^{25}=+9.7$ (*c* 2.25, $CHCl_3$)); HRMS (ESI) *m*/*z* 367.1121 $(M+H)^+$, calcd for $C_{17}H_{23}N_2O_3S_2$ 367.1145.

Compound (2*R*,3*R*)-**6**. Mp 65–66 °C; $[\alpha]_D^{25}=-16$ (*c* 0.20, $CHCl_3$); UV (MeOH) 220 (ε 22,300), 249 (19,100), 310 (10,800) nm; IR (KBr) 3127, 1737, 1530, 1221, 1167, 1104, 1092, 978, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, *J*=7.1 Hz, 3H), 1.43 (d, *J*=6.9 Hz, 6H), 2.70 (dq, *J*=9.0, 7.1 Hz, 1H), 3.31 (s, 1H), 3.36 (sept, *J*=6.9 Hz, 1H), 3.72 (s, 3H), 3.90 (t, *J*=8.6 Hz, 1H), 6.38 (dd, *J*=15.6, 8.3 Hz, 1H), 6.64 (d, *J*=15.6 Hz, 1H), 7.13 (s, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (q), 23.1 (q, 2C), 33.3 (d), 45.1 (d), 51.7 (q), 56.8 (q), 84.2 (d), 115.1 (d), 116.1 (d), 127.5 (d), 129.7 (d), 148.6 (s), 153.7 (s), 162.9 (s), 175.4 (s), 178.7 (s); MS (FAB) *m*/*z* (rel. int.) 389 ($[M+Na]^+$, 5), 367 ($[M+H]^+$, 70), 335 (90), 307 (10), 279 (100), 275 (35), 249 (15), 237 (13), 154 (50), 136 (42), 107 (21), 69 (47), 57 (55). Anal. found: C, 55.83%; H, 6.15%; N, 7.84%, calcd for $C_{17}H_{22}N_2O_3S_2$: C, 55.71%; H, 6.05%; N, 7.64%.

Compound (2*S*,3*S*)-**6**. Colorless needles, mp 65–66 °C (hexane–EtOAc); $[\alpha]_D^{25}=+17$ (*c* 0.10, $CHCl_3$); HRMS

(ESI) *m/z* 367.1124 $(M+H)^+$, calcd for $C_{17}H_{23}N_2O_3S_2$ 367.1145.

3.1.5. (*E*)-(2*R*,3*R*)-5-(2′-Isopropyl[2,4′]bithiazolyl-4-yl)-3-methoxy-2-methyl-4-penten-1-ol ((2*R*,3*R*)-7), (2*S*,3*S*)-7, (2*S*,3*R*)-7, and (2*R*,3*S*)-7. To a cooled solution of (2*S*,3*R*)-**6** (176.0 mg, 0.48 mmol) in dry dichloromethane (2.8 ml) at −78 °C was added a 1 M toluene solution of DIBAL (1.0 ml), and the mixture was stirred at −78 °C for 1 h and then 0 °C for 20 min. The reaction was quenched with MeOH (0.3 ml) and the mixture was stirred for 30 min. The mixture was diluted with saturated NH_4Cl (6.5 ml) and water (6.5 ml), and transferred into a separatory funnel with 0.9 M H_2SO_4 and dichloromethane. The organic layer was separated and the aqueous layer was extracted with ether (20 ml) 4 times. The combined organic layers were combined, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give alcohol (2*R*,3*R*)-**7** (104 mg, 64%). The enantiomer (2*S*,3*S*)-**7** and two diastereomers, (2*S*,3*R*)-**7** and (2*R*,3*S*)-**7**, were obtained in 65, 69, and 85% yields, respectively, by the same procedure.

Compound (2*R*,3*R*)-**7**. Colorless oil; $[\alpha]_D^{24}=-42.3$ (*c* 0.23, $CHCl_3$), UV (MeOH) 221 (ε 22,900), 247 (19,700), 313 (10,400) nm; IR (film) 3422 (br), 3105, 2968, 2931, 2874, 2823, 1684, 1618, 1538, 1498, 1464, 1081, 1035, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J*=7.1 Hz, 3H), 1.44 (d, *J*=7.0 Hz, 6H), 2.10 (m, 1H), 2.59 (br, 1H, OH), 3.36 (s, 3H), 3.38 (sept, *J*=7.0 Hz, 1H), 3.60 (brd, *J*=10.7 Hz, 1H), 3.75 (dd, *J*=10.7, 7.7 Hz, 1H), 3.92 (dd, *J*=6.9, 4.2 Hz, 1H), 6.56 (dd, *J*=15.7, 6.9 Hz, 1H), 6.63 (d, *J*=15.7 Hz, 1H), 7.11 (s, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2 (q), 23.1 (q, 2C), 33.6 (d), 39.8 (d), 57.0 (q), 66.0 (t), 85.7 (d), 115.0 (d), 115.7 (d), 126.3 (d), 129.9 (d), 148.6 (s), 154.0 (s), 162.9 (s), 178.7 (s); MS (FAB) *m/z* (rel. int.) 361 ($[M+Na]^+$, 4), 339 ($[M+H]^+$, 90), 307 (55), 279 (100), 277 (48), 265 (25), 249 (20), 237 (15), 224 (13), 170 (30), 136 (77), 115 (15), 91 (46), 69 (56), 55 (68). Anal. found: C, 56.79%; H, 6.68%; N, 8.12%, calcd. for $C_{16}H_{22}N_2O_2S_2$: C, 56.77%; H, 6.55%; N, 8.28%.

Compound (2*S*,3*S*)-**7**. $[\alpha]_D^{25}=+41.5$ (*c* 0.31, $CHCl_3$); HRMS (ESI) *m/z* 339.1213 $(M+H)^+$, calcd for $C_{16}H_{23}N_2O_2S_2$ 339.1196.

Compound (2*S*,3*R*)-**7**. Colorless oil; $[\alpha]_D^{25}=-4$ (*c* 0.18, $CHCl_3$); UV (MeOH) 222 (ε 16,700), 248 (17,500), 313 (9400) nm; IR (film) 3422 (br), 3104, 2822, 1654, 1538, 1183, 1082, 1034, 974, 801, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J*=7.0 Hz, 3H), 1.44 (d, *J*=7.0 Hz, 6H), 1.97 (dq, *J*=3.9, 7.0 Hz, 1H), 3.06 (br, 1H, OH), 3.35 (s, 3H), 3.37 (sept, *J*=7.0 Hz, 1H), 3.65 (m, 3H), 6.45 (dd, *J*=15.7, 8.1 Hz, 1H), 6.59 (d, *J*=15.7 Hz, 1H), 7.12 (s, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (q), 23.1 (q, 2C), 33.3 (d), 40.1 (d), 56.7 (q), 67.4 (t), 88.3 (d), 115.1 (d), 115.8 (d), 126.6 (d), 131.1 (d), 148.6 (s), 153.9 (s), 162.9 (s), 178.7 (s); MS (FAB) *m/z* (rel. int.) 361 ($[M+Na]^+$, 3), 339 ($[M+H]^+$, 92), 307 (55), 279 (100), 277 (49), 265 (26), 248 (18), 237 (12), 224 (13), 170 (30), 154 (92), 136 (80), 107 (33),95 (26), 91 (46), 55 (68). Anal. found: C, 56.78%; H, 6.43%; N, 8.00%, calcd. for $C_{16}H_{22}N_2O_2S_2$: C, 56.77%; H, 6.55%; N, 8.28%.

Compound (2*R*,3*S*)-**7**. $[\alpha]_D^{25}=+5$ (*c* 0.09, $CHCl_3$); HRMS (ESI) *m/z* 339.1183 $(M+H)^+$, calcd for $C_{16}H_{23}N_2O_2S_2$ 339.1196.

3.1.6. Methyl (*E*)-(3*SR*,4*R*,5*R*)-7-(2′-isopropyl-[2,4′]bithiazolyl-4-yl)-3-hydroxy-5-methoxy-4-methyl-6-pentenoate ((4*R*,5*R*)-8), (4*S*,5*S*)-8, (4*S*,5*R*)-8, and (4*R*,5*S*)-8. To a solution of alcohol (2*R*,3*R*)-**7** (104 mg, 0.31 mmol) in dry dichloromethane (4.4 ml) was added dry pyridine (0.40 ml, 4.9 mmol) and Dess–Martin periodinane (223 mg, 0.52 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ether (2 ml), saturated $NaHCO_3$ (2 ml), and saturated $Na_2S_2O_3$ (2 ml), and then stirred at room temperature for 1 h. The reaction mixture was extracted with ether (5 ml) five times. The combined ethereal layers were washed with saturated $NaHCO_3$, water, and brine, successively, dried, and concentrated to give crude aldehyde as an yellow oil.

To a cooled solution of dry diisopropylamine (0.18 ml, 1.33 mmol) in dry THF (1.8 ml) at −78 °C was added a 1.7 M hexane solution of butyllithium (0.74 ml, 1.25 mmol), and the mixture was stirred for 20 min. To the resulting solution was added dry methyl acetate (0.11 ml, 1.4 mmol), and the mixture was stirred at −78 °C for 20 min. To the resulting solution was added a solution of the above crude aldehyde in dry THF (2.3 ml), and the mixture was stirred at −78 °C for 80 min. The reaction mixture was diluted with 10% aqueous citric acid (2.9 ml). The organic layer was separated and the aqueous layer was extracted with ether (6 ml) three times. The combined organic layers were washed with brine, dried, and concentrated. The residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give (4*R*,5*R*)-**8** (97.3 mg, 77%) as a diastereomeric mixture. The enantiomer (4*S*,5*S*)-**8** and two diastereomers, (4*S*,5*R*)-**8** and (4*R*,5*S*)-**8**, were obtained in a diastereomeric mixture in 74, 52, and 84% yields, respectively, by the same procedure.

Compound (4*R*,5*R*)-**8**. Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*=7.1 Hz, 2.4H), 1.04 (d, *J*=7.1 Hz, 0.6H), 1.44 (d, *J*=7.0 Hz, 6H), 1.92 (m, 1H), 2.47 (dd, *J*=15.4, 8.9 Hz, 1H), 2.61 (dd, *J*=15.4, 3.6 Hz, 1H), 3.35 (s, 0.6H), 3.36 (sept, *J*=7.0 Hz, 1H), 3.36 (s, 2.4H), 3.70 (s, 0.6H), 3.72 (s, 2.4H), 3.79 (d, *J*=4.1 Hz, 1H, OH), 3.98 (m, 1H), 4.11 (m, 1H), 4.33 (m, 1H), 6.59 (m, 2H), 7.11 (s, 1H), 7.86 (s, 0.2H), 7.87 (s, 0.8H); ^{13}C NMR (100 MHz, $CDCl_3$, data due to major diastereomer) δ 11.6 (q), 23.1 (q, 2C), 33.6 (d), 39.9 (d), 42.6 (d), 51.7 (q), 57.1 (q), 70.6 (d), 83.6 (d), 115.0 (d), 115.8 (d), 126.0 (d), 130.0 (d), 148.6 (s), 154.0 (s), 162.9 (s), 173.0 (s), 178.6 (s). Anal. found: C, 55.59%; H, 6.49%; N, 6.74%, calcd for $C_{19}H_{26}N_2O_4S_2$: C, 55.58%; H, 6.38%; N, 6.82%.

Compound (4*S*,5*S*)-**8**. The NMR data were the same as those for (4*S*,5*R*)-**8** except for the diastereomeric ratio.

Compound (4*S*,5*R*)-**8** and (4*R*,5*S*)-**8**. Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J*=6.8 Hz, 1.2H), 0.95 (d, *J*=6.8 Hz, 1.8H), 1.44 (d, *J*=6.8 Hz, 6H), 1.85 (m, 1H), 1.95 (m, 1H), 2.41 (dd, *J*=15.4, 3.6 Hz, 0.6H), 2.47 (dd, *J*=16.4, 8.8 Hz, 0.4H), 2.56 (dd, *J*=15.4, 10.0 Hz, 0.6H), 2.61 (dd, *J*=16.4, 2.8 Hz, 0.4H), 3.33 (s, 1.2H), 3.35 (s, 1.8H), 3.36

(septet, 1H), 3.71 (s, 1.8H), 3.72 (s, 1.2H), 3.73 (t, J=8.0 Hz, 0.6H), 3.83 (t, J=8.5 Hz, 0.4H), 4.06 (dt, J=2.0, 8.0 Hz, 0.4H), 4.44 (brd, J=9.6 Hz, 0.6H), 6.43 (dd, J=15.6, 8.2 Hz, 0.4H), 6.47 (dd, J=15.6, 7.6 Hz, 0.6H), 6.61 (d, J=15.6 Hz, 1H), 7.12 (s, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (q, 0.6C), 12.4 (q, 0.4C), 23.1 (q, 2C), 33.3 (d), 39.1 (d, 0.6C), 39.3 (d, 0.4C), 42.3 (d, 0.6C), 42.9 (d, 0.4C), 51.7 (q), 56.5 (q, 0.4C), 56.9 (q, 0.6C), 68.7 (d, 0.6C), 71.3 (d, 0.4C), 85.6 (d, 0.6C), 85.8 (d, 0.4C), 115.1 (d), 115.9 (d), 126.6 (d, 0.6C), 127.0 (d, 0.4C), 130.4 (d, 0.4C), 131.1 (d, 0.6C), 148.6 (s), 153.8 (s), 162.9 (s), 173.0 (s, 0.6C), 173.3 (s, 0.4C), 178.7 (s).

3.1.7. Methyl (*E*)-(4*S*,5*R*)-7-(2′-isopropyl[2,4′]-bithiazolyl-4-yl)-5-methoxy-4-methyl-3-oxo-6-pentenoate ((4*S*,5*R*)-9), (4*R*,5*S*)-9, (4*R*,5*R*)-9, and (4*S*,5*S*)-9. To a cooled solution of (4*R*,5*R*)-**8** (101 mg, 0.25 mmol) in dry dichloromethane (4.3 ml) was added Dess–Martin periodinane (188 mg, 0.45 mmol), and the mixture was stirred at 0 °C for 2 h and then at room temperature for 2 h. The reaction mixture was diluted with ether (1.8 ml), saturated $NaHCO_3$ (1.8 ml), and saturated $Na_2S_2O_3$ (1.8 ml), and then stirred at room temperature for 1 h. The reaction mixture was extracted with ether (8 ml) three times. The combined ethereal layers were washed with brine, dried, and concentrated. The residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give ketoester (4*S*,5*R*)-**9** (79.5 mg, 79%). The enantiomer (4*R*,5*S*)-**9** and two diastereomers, (4*R*,5*R*)-**9** and (4*S*,5*S*)-**9**, were obtained from (4*S*,5*S*)-**8**, (4*S*,5*R*)-**8**, and (4*R*,5*S*)-**8** in 62, 70, and 71% yields, respectively, by the same procedure.

Compound (4*S*,5*R*)-**9**. Pale yellow oil; $[\alpha]_D^{24}=-6.8$ (c 0.60, $CHCl_3$); UV (MeOH) 221 (ε 25,100), 249 (22,000), 312 (11,200) nm; IR (film) 3109, 2874, 2825, 1749, 1715, 1653, 1628, 1088, 975, 801, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J=7.0 Hz, 3H), 1.44 (d, J=6.8 Hz, 6H), 2.99 (dq, J=5.4, 7.0 Hz, 1H), 3.33 (s, 3H), 3.37 (sept, J=6.9 Hz, 1H), 3.56 (d, J=15.7 Hz, 1H), 3.62 (d, J=15.7 Hz, 1H), 3.71 (s, 3H), 4.00 (dd, J=7.4, 5.4 Hz, 1H), 6.42 (dd, J=15.6, 7.4 Hz, 1H), 6.61 (d, J=15.6 Hz, 1H), 7.12 (s, 1H), 7.86 (s, 1H); MS (FAB) m/z (rel. int.) 431 ([M+Na]$^+$, 2), 409 ([M+H]$^+$, 39), 377 (16), 345 (9), 340 (4), 307 (12), 279 (85), 277 (22), 263 (11), 248 (10), 219 (9), 136 (60), 95 (40). Anal. found: C, 55.92%; H, 6.04%; N, 6.90%, calcd for $C_{19}H_{24}N_2O_4S_2$: C, 55.86%; H, 5.92%; N, 6.86%.

Compound (4*R*,5*S*)-**9**. Colorless oil; $[\alpha]_D^{25}=+6.1$ (c 0.51, $CHCl_3$) (reported data:[9] $[\alpha]_D^{30}=+3.8$ (c 0.71, $CHCl_3$); HRMS (ESI) m/z 409.1225 (M+H)$^+$, calcd for $C_{19}H_{25}N_2O_4S_2$ 409.1250.

Compound (4*R*,5*R*)-**9**. Colorless needles; mp 91–92 °C (hexane–EtOAc); $[\alpha]_D^{25}=-51$ (c 0.08, $CHCl_3$); UV (MeOH) 222 (ε 13,400), 250 (18,600), 311 (11,200) nm; IR (KBr) 3090, 2820, 1745, 1711, 1262, 1088, 1008, 962, 799, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J=6.8 Hz, 3H), 1.45 (d, J=6.8 Hz, 6H), 2.94 (dq, J=9.0, 6.8 Hz, 1H), 3.25 (s, 3H), 3.38 (sept, J=6.8 Hz, 1H), 3.58 (d, J=15.6 Hz, 1H), 3.64 (d, J=15.6 Hz, 1H), 3.74 (s, 3H), 3.79 (t, J=9.0 Hz, 1H), 6.39 (dd, J=15.6, 8.4 Hz, 1H), 6.63 (d, J=15.6 Hz, 1H), 7.14 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (q), 23.1 (q, 2C), 33.4 (d), 50.3 (d), 50.7 (t), 52.2 (q), 56.7 (q), 85.3 (d), 115.1 (d), 116.3 (d), 127.6 (d), 129.9 (d), 148.6 (s), 153.6 (s), 163.0 (s), 167.7 (s), 178.7 (s), 205.9 (s); MS (FAB) m/z (rel. int.) 431 ([M+Na]$^+$, 2), 409 ([M+H]$^+$, 29), 377 (25), 345 (7), 340 (6), 307 (12), 279 (60), 277 (17), 219 (10), 136 (62), 55 (85). Anal. found: C, 55.87%; H, 6.02%; N, 6.82%, calcd for $C_{19}H_{24}N_2O_4S_2$: C, 55.86%; H, 5.92%; N, 6.86%.

Compound (4*S*,5*S*)-**9**. Colorless needles; mp 91–92 °C (hexane–EtOAc); $[\alpha]_D^{25}=+52$ (c 0.10, $CHCl_3$); HRMS (ESI) m/z 409.1230 (M+H)$^+$, calcd for $C_{19}H_{25}N_2O_4S_2$ 409.1250.

3.1.8. *ent*-Cystothiazole A (*ent*-1), cystothiazole A (1), (2*S*,3*S*)-1, and (2*R*,3*R*)-1. To a cooled solution of (4*S*,5*R*)-**9** (54.8 mg, 0.15 ml) in trimethyl orthoformate (11 ml) at 0 °C was added concentrated sulfuric acid, and the mixture was stirred at 0 °C for 5 h. The reaction mixture was diluted with saturated $NaHCO_3$ (3 ml) and extracted with ether (7 ml) four times. The combined extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed on silica gel (4:1 hexane–EtOAc) to give *ent*-**1** (39.7 mg, 64%). Cystothiazole A (**1**) and two diastereomers, (4*S*,5*S*)-**1** and (4*R*,5*R*)-**1**, were obtained from (4*R*,5*S*)-**9**, (4*S*,5*S*)-**9**, and (4*R*,5*R*)-**9** in 66, 78, and 75% yields, respectively, by the same procedure.

ent-Cystothiazole A (*ent*-**1**). Colorless needles, mp 112–113 °C (hexane–EtOAc); $[\alpha]_D^{25}=-113$ (c 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J=6.8 Hz, 3H), 1.44 (d, J=6.9 Hz, 6H), 3.33 (s, 3H), 3.37 (sept, J=6.9 Hz, 1H), 3.60 (s, 3H), 3.66 (s, 3H), 3.81 (t, J=7.7 Hz, 1H), 4.17 (dq, J=7.7, 6.8 Hz, 1H), 4.96 (s, 1H), 6.41 (dd, J=15.8, 7.7 Hz, 1H), 6.57 (d, J=15.8 Hz, 1H), 7.08 (s, 1H), 7.86 (s, 1H); HRMS (ESI) m/z 423.1426 (M+H)$^+$, calcd for $C_{20}H_{27}N_2O_4S_2$ 423.1407.

Cystothiazole A (**1**). Colorless needles, mp 111–112 °C; $[\alpha]_D^{25}=+111$ (c 0.24, $CHCl_3$) (reported data:[1] $[\alpha]_D^{25}=+109$ (c 0.24, $CHCl_3$).

(4*R*,5*R*)-Cystothiazole A ((4*R*,5*R*)-**1**). Colorless needles; mp 103–104 °C (hexane–EtOAc); $[\alpha]_D^{25}=+21$ (c 0.09, $CHCl_3$); UV (MeOH) 222 (ε 25,100), 247 (22,000), 313 (11,200) nm; IR (film) 3009, 1716, 1628, 1150, 1096, 977, 821, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J=7.2 Hz, 3H), 1.44 (d, J=6.8 Hz, 6H), 3.28 (s, 3H), 3.38 (sept, J=6.8 Hz, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.85 (dd, J=9.2, 8.4 Hz, 1H), 4.22 (dq, J=9.2, 7.2 Hz, 1H), 5.08 (s, 1H), 6.46 (dd, J=15.7, 8.4 Hz, 1H), 6.63 (d, J=15.7 Hz, 1H), 7.11 (s, 1H), 7.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (q), 23.1 (q, 2C), 33.4 (d), 39.4 (d), 50.8 (q), 55.5 (q), 56.7 (q), 83.8 (d), 91.1 (d), 115.0 (d), 115.3 (d), 122.1 (d), 126.7 (d), 131.5 (d), 148.7 (s), 154.2 (s), 167.9 (s), 177.3 (s), 178.6 (s); MS (FAB) m/z (rel. int.) 445 ([M+Na]$^+$, 2), 423 ([M+H]$^+$, 16), 391 (32), 375 (5), 359 (72), 331 (15), 317 (4), 279 (100), 265 (21), 248 (19), 237 (8), 207 (5), 170 (14), 155 (17), 136 (10), 95 (9), 91 (10), 57 (22). Anal. found: C, 56.77%; H, 6.20%; N, 6.58%, calcd. for $C_{20}H_{26}N_2O_4S_2$: C, 56.85%; H, 6.20%; N, 6.63%.

(4*S*,5*S*)-Cystothiazole A ((4*S*,5*S*)-**1**). Colorless needles; mp 103–104 °C (hexane–EtOAc); $[\alpha]_D^{25}=-22$ (*c* 0.05, $CHCl_3$); HRMS (ESI) *m*/*z* 423.1393 $(M+H)^+$, calcd for $C_{20}H_{27}N_2O_4S_2$ 423.1407.

3.1.9. (*R*)- and (*S*)-MTPA esters (10r and 10s) from (2*S*,3*S*)-5. To a solution containing (2*S*,3*S*)-**5** (0.5 mg, 0.0014 mmol) and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid ((*R*)-MTPA acid, 6.5 mg, 0.028 mmol) in dry dichloromethane (0.5 ml) were added successively 4-(dimethylamino)pyridine (DMAP, 1.7 mg, 0.014 mmol), dicyclohexylcarbodiimide (DCC, 11.5 mg, 0.056 mmol) and 10-camphorsulfonic acid (CSA, 1.9 mg, 0.0084 mmol). After being stirred at room temperature for 12 h, the reaction was quenched by stirring with water (0.5 ml) for 10 min. The mixture was concentrated, the residue was suspended in water (1.5 ml) and extracted with EtOAc (1.5 ml) 3 times. The combined EtOAc extracts were washed successively with saturated aqueous $NaHCO_3$ and H_2O. After evaporation of the solvent, the residue was separated by TLC (silica gel, 3:1 hexane/EtOAc) to give (*R*)-MTPA ester **10r** (0.5 mg). The corresponding (*S*)-MTPA ester (**10s**, 0.6 mg) was prepared from (2*S*,3*S*)-**5** (0.5 mg) by the same way with (*S*)-MTPA acid.

Compound **10r**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J*=7.16 Hz, 3H), 1.45 (d, *J*=6.92 Hz, 6H), 2.916 (dq, *J*=8.6, 7.2 Hz, 1H), 3.38 (sept, *J*=6.9 Hz, 1H), 3.52 (s, 3H), 3.55 (s, 3H), 5.84 (t, *J*=8.61 Hz, 1H), 6.53 (dd, *J*=15.48, 8.61 Hz, 1H), 6.79 (d, *J*=15.48 Hz, 1H), 7.15 (s, 1H), 7.34–7.51 (m, 5H), 7.87 (s, 1H).

Compound **10s**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J*=7.20 Hz, 3H), 1.45 (d, *J*=6.88 Hz, 6H), 2.924 (dq, *J*=8.1, 7.2 Hz, 1H), 3.38 (sept, *J*=6.9 Hz, 1H), 3.52 (s, 3H), 3.68 (s, 3H), 5.81 (t, *J*=8.06 Hz, 1H), 6.43 (dd, *J*=15.46, 8.06 Hz, 1H), 6.67 (d, *J*=15.46 Hz, 1H), 7.08 (s, 1H), 7.31–7.48 (m, 5H), 7.84 (s, 1H).

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New cyanine dyes derived from tetrazolo[5,1-*a*]isoindoles

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Abstract—The investigation of the acylation reaction of 1-methyltetrazolo[5,1-*a*]isoindole with acyl chlorides gave rise to two series of derivatives. 5-Acyl-1-methyltetrazolo[5,1-*a*]isoindoles and a new type of tetrazoloisoindole based monomethinecyanines were isolated. Their structure was confirmed by X-ray diffraction analysis. A mechanism of the formation of these new dyes is proposed. This reaction permit to introduce easily various alkyl, aryl or heteroaryl substituents on the central methine carbon.

1. Introduction

Reactions of simple isoindoles[1–6] have been well studied, but not those of cyclised isoindole systems with a nodal nitrogen atom, mainly in the tetrazoloisoindole series.[1,7]

The interest in tetrazoloisoindoles is both in fundamental chemistry, due to their ability to lead to formal 14π-electrons aromatic systems[8] (in fact they are 10π-electron aromatic systems, like 1,2-substituted isoindole) and in numerous practical applications. For example, biologically active compounds[9] and dyes with tetrazoloisoindole moieties[10–12] are known and tetrazoloisoindole derivatives are used in the chemical modification of biodegradable natural polymers like cellulose.[13]

In a recent review paper[7] we summarised the few contributions to the chemical properties of the tetrazoloisoindoles: only one example of an alkylation reaction[14] is described and it is the same for the cyanoethylation with isocyanates or isothiocyanates or for acylation.[11] Another recent synthesis and reactivity paper of a closely related tetrazoloisoindole system together with an X-ray structure is worthwhile to refer.[15]

There is more information on the formation of dyes, non-substituted mono- and trimethinecyanine chains and also non-symmetrical.[10–12] We recently synthesised potassium hexacyanoferrate (III) and tetracyanonickelate (II) complexes of the cyanine dyes derived from tetrazolo[5,1-*a*]isoindoles.[16] Some general methods to introduce various substituents on the monomethine chain carbon atom are used.[17–22] Moreover, non-symmetrical cyanine dyes with cyclic quinoline, benzoxazole, [5,6]benzoquinoline and benzothiazole substituents in the methine chain were isolated.[20,23] Finally, methods to introduce halide substituents in the chain were proposed.[24–27]

In this contribution, we want to present a new efficient method to introduce alkyl, aryl and heteroaryl substituents on the methine carbon of monomethine cyanine dyes.

2. Results and discussion

2.1. Synthesis

Following the literature,[7] it is clear that the acylation reactions of the tetrazoloisoindoles were not thoroughly studied. Only two examples are described, the acyl derivatives **Ia**,**b** obtained by the reaction of carboxylic acid anhydrides in DMF[11] with the 1-methyl-5*H*-tetrazolo[5,1-*a*]isoindolium salt (Scheme 1). Moreover no spectroscopic characterisation is given.

The goal of our work was the systematic study of the acylation reactions in the tetrazoloisoindole series. We intended to vary the R substituents between large limits, thus it seemed more convenient to use acyl chlorides because of their greater availability than the acid anhydrides.

In the first stage, we studied the acylation of the 1-methyltetrazolo[5,1-*a*]isoindole **II**. The product was obtained in a previously known way,[14] by the action of a base (KOH or NaOH) on 1-methyl-5*H*-tetrazolo[5,1-*a*]isoindolium **III** perchlorate. In spite of its extreme instability,

Keywords: Tetrazoloisoindole; Cyanine dyes; Acylation reactions; X-ray structure determination.
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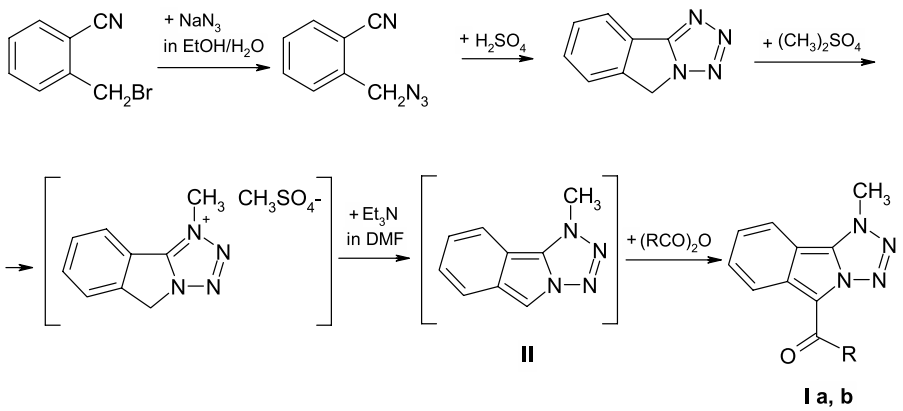


Scheme 1. Synthesis of the acylation products **Ia**,**b**.[11,14]

we were able to isolate the tetrazoloisoindole **II** as an analytically pure sample by sublimation under reduced pressure. UV and ^{1}H NMR spectra were recorded. In the UV, the experimental λ_{max} (362 nm) is in good accordance with the PPP calculated one[8] (λ_{max}=364 nm).(see experimental part). In the following step, the acylation of **II** by the benzoyl chloride to give compound **Ib** was nearly quantitative.

In the second stage, we tried to replace the tetrazoloisoindole **II** by the more readily available perchlorate salt **III**. In this case, we obtained an unexpected result: even in varying the reaction conditions [dioxane+K_2CO_3, dioxane+Et_3N, pyridine] we always obtained, together with the acyl product **I**, a new type of compound, the previously unknown cyanine dyes **IV** (Scheme 2).

The yields and the respective ratios between the final products is greatly dependant of the proportion of the starting materials, i.e. **III**, RCOCl and triethylamine. For the optimal formation of product **I** the best ratio is 1/1/1. The easier formation of the cyanines is obtained with the 2/1/1 ratio but in this case, there is a part of the non-reacted perchlorate salt in the residues. Ratios like 1/1/3 or 2/1/3 lead to the formation of oily residues. Thus, for the best yield in cyanine dyes, the 1/1/2 ratio seems preferable.

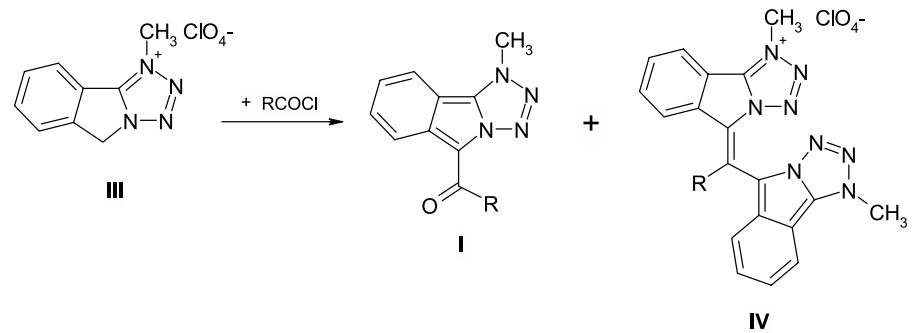
Also, the nature of the R substituent is of great importance. We were unable to isolate the acylated products **I c**,**d**, whereas in this case we obtained the best yields for **IV c**,**d** dyes.

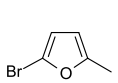
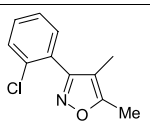
As compared to Scheme 1, we obtained only a small yield of **Ia** with the Scheme 2 type reaction.

On the one hand, the yields of product **I** are high when R is aromatic or heteroaromatic and enhanced by the presence of acceptor substituents on the aromatic site. In this case, the yield of dye are weak, as with **IV e**, **f**, **k**.

On the other hand, the presence of donor groups in the aromatic moieties favour the formation of the dyes in high yield.

The separation and isolation of products **I** and **IV** was always performed by column chromatography, and their



I, IV	**a**	**b**	**c**	**d**	**e**	**f**
R	Me	Ph	$(CH_2)_3Cl$	C_4H_9	2-ClC_6H_4	4-$NO_2C_6H_4$
I, IV	**g**	**h**	**i**	**j**	**k**	
R	4-$CH_3C_6H_4$	2,4-$(MeO)_2C_6H_3$				

Scheme 2. Acylation of the 1-methyl-5*H*-tetrazolo[5,1-*a*]isoindolium **III** perchlorate by acyl chlorides.

structures were confirmed by usual physicochemical methods.

2.2. X-ray structure determination of the dye IVb

Crystal data for **IVb**. $C_{25}H_{19}ClN_8O_4$, M=530.93, monoclinic, $C2/c$, a=22.554(5) Å, b=18.052(4) Å, c=12.349(3) Å, β=101.234(4)°, V=4931.6(19) Å^3, Z=8, ρ_c=1.430 Mg m^{-3}, $F(000)$=2192, λ=0.71073 Å, T=193(2) K, μ (Mo Kα)=0.205 mm^{-1}, crystal size 0.05×0.1×0.5 mm^3, 10898 reflections (3539 independent, R_{int}=0.1531) were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer. The structure was solved by direct methods (SHELXS-97)[28] and 386 parameters were refined using the least-squares method on F^2.[29] Largest electron density residue: 0.458×eÅ^{-3}, R_1(for $I>2\sigma(I)$)=0.0978 and wR_2=0.2754 (all data) with $R_1=\sum||F_o|-|F_c||/\sum|F_o|$ and $wR_2=(\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2)^{0.5}$.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 197823 for **IVb**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB1 1EZ, UK [Fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk] (Fig. 1).

The crystals were obtained from methylene chloride solution.

The cyanine structure is confirmed by the bond length alternation in the planar methine chain, i.e. C11–C13=1.3669 Å, whereas C13–C10=1.4168 Å. Moreover, C8–C10–C11–C13 lies in the same plane with a maximum deviation of 0.009 Å. The aryl substituent forces the chain to adopt a *cis cis* configuration which was already observed in other cases[31] giving a chiral distorted horseshoe shape. The aryl group makes a near 50° angle with the plane of the methine chain whereas the terminal cyanine nitrogen atoms

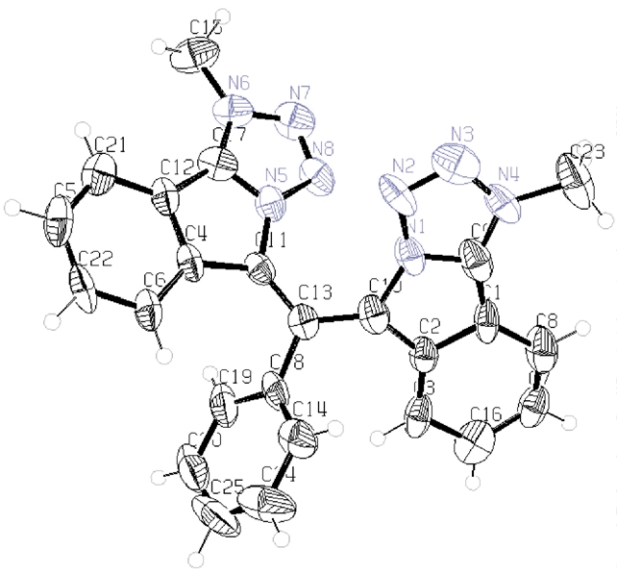


Figure 1. Ortep-3 for Windows[30] Version 1.07 (31st March 2001) drawing of the **IVb** cation with atom numbering.

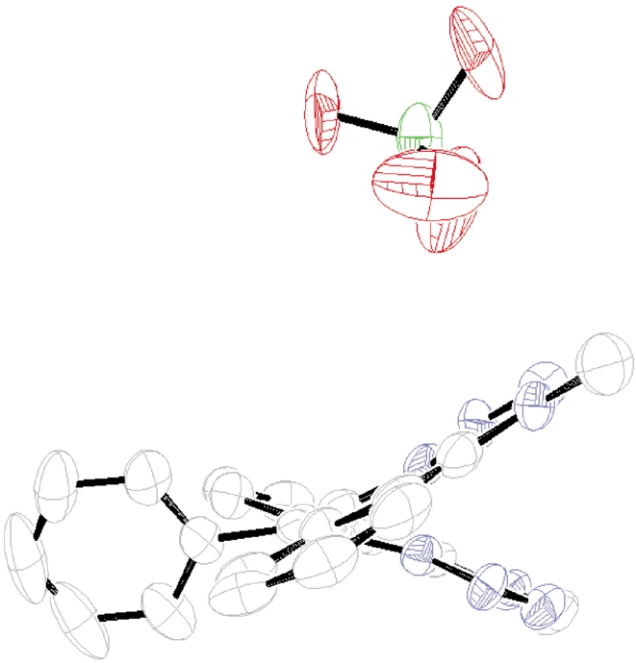


Figure 2. Side view of the **IVb** structure showing the perpendicular R substituent and the angle between the tetrazolo rings.

are respectively 0.916 Å over (N4) and-1.080 Å (N6) under the mean plane. The perchlorate anion is found in two equiprobable rotational conformations centred on the chlorine atom (Fig. 2).

The cartesian coordinates and selected bond length and valence and dihedral angles will be found in Tables 1–4.

2.3. Formation of the cyanine dyes: proposed mechanism

The proposed mechanism for the respective formation of **I** or **IV** is shown in the Scheme 3.

To explain the synthesis of the cyanine **IV**, it is necessary to have at the same time sufficient amounts of compounds **I** and **III**. To confirm this assessment, we have mixed the perchlorate **III** with the acylation product **Ib** and triethylamine in the ratio 1/1/2, respectively. After reaction, by TLC we find only the cyanine **IVb** whose presence is supported by its R_f [R_f=0.42 ($CHCl_3$/MeOH 9/1, 21 °C)]. If we look again to the influence of the ratios of starting products (see Section 2.1) on the respective formation of **I** and **II** it is clear that the lower concentrations of base (1/1/1) are in favour of the direct formation of **I**. On the reverse, excess of triethylamine (1/3/3 or 2/1/3) leads to large quantities of **II** which may be responsible of the great amount of side reactions. In the intermediate case 2/1/1, excess of **III** enhances the formation of **II** due to the le Chatelier principle.

3. Conclusion

We found a new synthetic method for the acylation of the tetrazoloisindoles. In the course of this reaction, we observed the formation of unexpected new monomethine cyanine dyes. Their structure was assessed by an X-ray

Table 1. Fractional coordinates

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
N(1)	0.28802	0.37697	0.31113	C(10)	0.24287	0.43284	0.28143
N(2)	0.30211	0.30932	0.27141	C(11)	0.16724	0.35667	0.16026
N(3)	0.35363	0.28954	0.32882	C(12)	0.11539	0.25693	0.05798
N(4)	0.37120	0.34288	0.40543	C(13)	0.19151	0.42381	0.19590
N(5)	0.17299	0.28903	0.22092	C(14)	0.19371	0.54305	0.09839
N(6)	0.14503	0.17804	0.23950	C(15)	0.11665	0.10572	0.23048
N(7)	0.17746	0.20212	0.33982	C(16)	0.26659	0.60612	0.45900
N(8)	0.19377	0.27029	0.32975	C(17)	0.14210	0.23314	0.16623
C(1)	0.31816	0.46830	0.43139	C(18)	0.16100	0.49168	0.14364
C(2)	0.26336	0.49037	0.35824	C(19)	0.09856	0.49903	0.13381
C(3)	0.23757	0.55939	0.37060	C(20)	0.06851	0.55983	0.07547
C(4)	0.13007	0.33349	0.05376	C(21)	0.08226	0.21860	−0.03406
C(5)	0.06539	0.25934	−0.13021	C(22)	0.07920	0.33497	−0.13442
C(6)	0.11129	0.37246	−0.04603	C(23)	0.43126	0.33537	0.48020
C(7)	0.31994	0.57945	0.53070	C(24)	0.16414	0.60386	0.04038
C(8)	0.34624	0.51476	0.51666	C(25)	0.10306	0.61101	0.03224

Table 2. Selected bond length (Å)

Atom		Distance	Atom		Distance
A	B		A	B	
C1	C9	1.395	C12	C4	1.424
C1	C2	1.438	C13	C18	1.489
C2	C3	1.396	C15	N6	1.449
C2	C10	1.422	C17	N5	1.333
C2	C1	1.438	C17	N6	1.338
C4	C11	1.476	C23	N4	1.489
C9	N4	1.325	N1	N2	1.376
C9	N1	1.346	N2	N3	1.288
C10	C13	1.417	N3	N4	1.354
C10	N1	1.429	N5	N8	1.377
C11	C13	1.367	N6	N7	1.380
C11	N5	1.425	N7	N8	1.297
C12	C17	1.421			

Table 3. selected angles (°)

Atom			Angle	Atom			Angle
A	B	C		A	B	C	
C9	C1	C8	133.39	C11	C13	C10	124.06
C9	C1	C2	105.62	C11	C13	C18	117.88
C3	C2	C10	129.55	C10	C13	C18	118.04
C3	C2	C1	120.27	C14	C18	C13	119.5
C10	C2	C1	110.16	C9	N1	N2	110.04
C2	C3	C16	118.07	C9	N1	C10	112.18
N4	C9	N1	103.55	N2	N1	C10	137.49
N4	C9	C1	147.21	N3	N2	N1	107.22
N1	C9	C1	109.17	N2	N3	N4	107.29
C13	C10	C2	133.93	C9	N4	N3	111.87
C13	C10	N1	123.25	C9	N4	C23	129.55
C2	C10	N1	102.80	N3	N4	C23	118.39

Table 4. Selected dihedral angles (°)

N1	C10	C13	C18	−157.8
N1	C10	C13	C11	24.70
N5	C11	C13	C10	23.55
N5	C11	C13	C18	−154.67

structure determination and we tried to propose a mechanism for this reaction.

4. Experimental

You will find hereafter the numbering scheme of the products **I** and **IV** (Scheme 4).

4.1. General methods

The ^{1}H NMR spectra (400.396 MHz) were recorded with a Varian Mercury 400 with TMS as internal standard. The UV–vis spectra were obtained with a Perkin Elmer Lambda-19 spectrophotometer equipped with a 60 mm integration sphere for solid measurements. Mass spectra were obtained on a Nermag R 10 (in CI with NH_3, the higher peak always correspond to the $[MH]^+$ of the cationic part of the molecule). Elemental analysis were realised with a Carlo Erba analyser. Products **I** and **IV** were purified by column chromatography and possibly crystallised from methylene chloride.

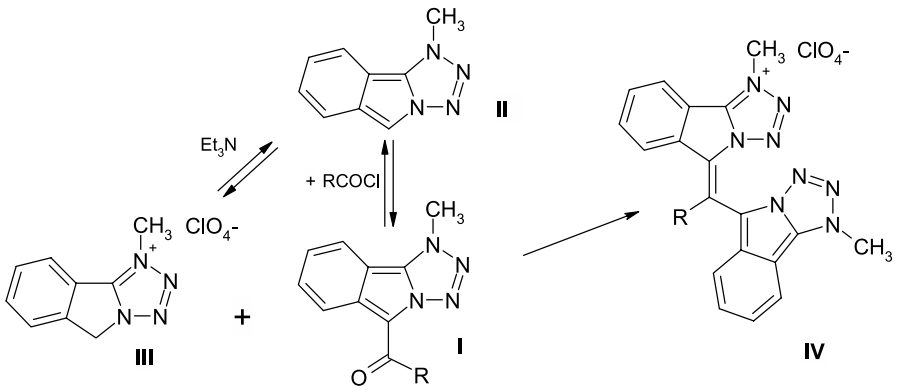
4.1.1. General experimental procedure. The starting products **II** and **III** were obtained by previously described methods.[14] We succeeded in the separation of analytically pure samples of the very unstable 1-methyltetrazoloisoindole by sublimation under reduced pressure (10^{-5} mm Hg). Thus we were able to record for the first time its ^{1}H and UV–vis spectra.

^{1}H NMR δ (CD_3OD) 4.43 (s, 3H, N–CH_3), 6.93 (t, 1H, H_{arom}), 7.26 (t, 1H, H_{arom}), 7.50 (s, 1H, 5-H), 7.55 (d, 1H, H_{arom}), 7.97 (d, 1H, H_{arom}); UV–vis (EtOH) 224 (4.49), 237† (4.23), 248 (4.15), 261† (4.07), 278 (4.09), 330† (3.97), 362 (3.89).

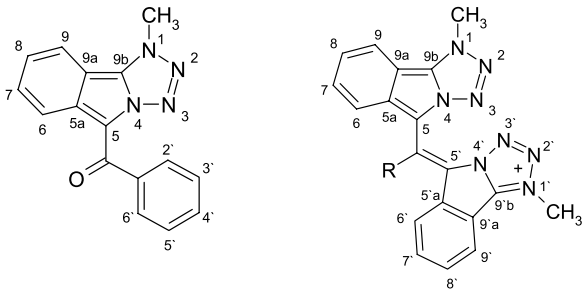
4.2. Synthesis of acylated compounds Ia–b,f–k and of the cyanines IVa–k

Nomenclature for **IVb**. 1-Methyl-5-[(1-methyl-1*H*-tetrazolo[5,1-*a*]isoindol-5-yl)-phenyl-methylene]-5*H*-tetrazolo[5,1-*a*]isoindol-1-ium; perchlorate.

† Shoulder.



Scheme 3. Formation of the cyanine dyes: proposed mechanism.



Scheme 4. Numbering scheme of products **I** and **IV**.

To 0.7 mmol of **III** in 3.5 ml of absolute dioxane were added 0.7 mmol of the corresponding acyl chloride and 1.4 mmol of triethylamine. The mixture was heated at 100 °C for one hour. The resulting mixture was filtered and the precipitate was washed with acetone. The filtrates were combined and dried with a rotatory evaporator. After column chromatography on silicagel (100/250 mesh) with methylene chloride/acetone (3/1) as solvent, the two types of product **I** and **IV** were obtained. Yields of acylation products are between 8.2 (**Ia**) and 78.7 (**Ik**) % whereas the yields of cyanines vary from 0.5 (**IVf**) to 63.8 (**IVc**)%.

Physicochemical constants, melting points, ^{1}H NMR, chromatographic R_f and UV–vis data are given below (structures in Scheme 2).

4.3. Acylated products

4.3.1. Compound Ia. Mp 199 °C; ^{1}H NMR δ (DMSO-d_6) 2.67 (s, 3H, CH_3), 4.55 (s, 3H, N–CH_3), 7.21 (t, 1H, H_{arom}), 7.52 (t, 1H, H_{arom}), 8.11 (d, 1H, H_{arom}), 8.37 (d, 1H, H_{arom}); R_f 0.84 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN)[λ, (log ε) 305 (3.78), 336 (3.85), 338 (3.70). $C_{11}H_{10}N_4O$, M is 214.226. Analysis (calcd, found)% C (61.67, 61.65); H (4.70, 4.78); N (26.15, 26.17). Yield: 8.2%.

4.3.2. Compound Ib. Mp 187 °C; ^{1}H NMR δ (DMSO-d_6) 4.54 (s, 3H, N–CH_3), 7.24 (t, 1H, H_{arom}), 7.45 (t, 1H, H_{arom}), 7.52–7.65 (m, 6H, H_{arom}), 8.22 (d, 1H, H_{arom}); ^{13}C NMR δ (DMSO-d_6) 36.69 (N-Me), 102.90 (C-6), 108.63 (C-9a), 119.95 (C-5), 120.98 (C-9, C-9b), 121.32 (C-8),128.38 (C-3′, C-5′), 128.73 (C-2′, C-6′), 129.57 (C-4′), 130.76 (C-7), 136.66 (C-5a), 141.67 (C-1′), 179.49 (C═O); MS *m/z* 277 $(M+1)^+$(calcd 277.10); R_f 0.82 ($CHCl_3$/MeOH 9/1, 21°C); UV–vis (CH_3CN) [λ, (log ε)] 307 (3.54), 342 (3.62), 389 (3.88), 402† (3.80). $C_{16}H_{12}N_4O$, M is 276.297. Analysis (calcd, found)% C (69.55, 69.59); H (4.38, 4.45); N (20.28, 20.27). Yield: 41.7%.

4.3.3. Compound If. Mp 183 °C; ^{1}H NMR δ (DMSO-d_6) 4.56 (s, 3H, N–CH_3), 7.23–7.32 (m, 1H, H_{arom}), 7.44–7.56 (m, 1H, H_{arom}), 7.89 (d, 2H, H_{arom}), 8.11 (d, 1H, H_{arom}), 8.20 (d, 1H, H_{arom}), 8.38 (d, 2H, H_{arom}); R_f 0.79 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 256 (4.47), 300 (3.92), 329 (3.80), 397 (398). $C_{16}H_{11}N_5O_3$, M is 321.293. Analysis (calcd, found)% C (59.81, 59.85); H (3.45, 3.51); N (21.80, 21.83). Yield: 81.3%.

4.3.4. Compound Ig. Mp 177 °C; ^{1}H NMR δ (DMSO-d_6) 2.47 (s, 3H, CH_3), 4.55 (s, 3H, N–CH_3), 7.17 (t, 1H, H_{arom}), 7.30 (d, 2H, H_{arom}), 7.37 (t, 1H, H_{arom}), 7.52–7.57 (m, 3H, H_{arom}), 8.14 (d, 1H, H_{arom}); MS *m/z* 291 $(M+1)^+$ (calcd 291.11); R_f 0.81 ($CHCl_3$/MeOH 9/1, 21°C); UV–vis (CH_3CN) [λ, (log ε)] 259† (3.94), 307 (3.45), 389 (3.66), 408† (3.50). $C_{17}H_{14}N_4O$, M is 290.323. Analysis (calcd, found)% C (70.33, 70.32); H (4.86, 4.91); N (19.30, 19.32). Yield: 39.8%.

4.3.5. Compound Ih. Mp 182 °C; ^{1}H NMR δ (DMSO-d_6) 3.60 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.53 (s, 3H, N–CH_3), 6.63–6.70 (m, 2H, H_{arom}), 7.16–7.64 (m, 4H, H_{arom}), 8.21 (d, 1H, H_{arom}); R_f 0.79 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 263† (4.18), 281 (3.94), 324 (3.93), 389 (3.75). $C_{18}H_{16}N_4O_3$, M is 336.348. Analysis (calcd, found)% C (64.28, 64.31); H (4.79, 4.81); N (16.66, 16.65). Yield: 27.3%.

4.3.6. Compound Ii. Mp 161 °C; ^{1}H NMR δ (DMSO-d_6) 4.58 (s, 3H, N–CH_3), 7.22 (t, 1H, thiophene), 7.26 (d, 1H, H_{arom}), 7.51 (t, 1H, H_{arom}), 7.78 (d, 1H, thiophene), 7.94 (d, 1H thiophene), 8.15 (d, 1H, H_{arom}), 8.18 (d, 1H, H_{arom}); R_f 0.80 ($CHCl_3$/MeOH 9/1, 21 °C); ^{13}C NMR δ (DMSO-d_6) 36.71 (N-Me), 103.27 (C-6), 107.67 (C-9a), 120.42 (C-9b), 121.45 (C-3′), 121.50 (C-9), 128.18 (C-8), 130.21 (C-4′), 130.44 (C-5′), 131.61 (C-7), 134.09 (C-5a), 137.34 (C-5), 145.26 (C-2′),170.83 (C═O); UV–vis (CH_3CN) [λ, (log ε)] 247 (4.27), 262† (4.19), 308 (3.62), 403 (4.14). $C_{14}H_{10}N_4OS$, M is 282.319. Analysis (calcd, found)% C (59.56, 59.61); H (3.57, 3.62); N (19.85, 19.88); S (11.36, 11.39). Yield: 58.9%.

4.3.7. Compound Ij. Mp 156 °C; ^{1}H NMR δ (DMSO-d_6)

4.60 and 4.68 (2s, 3H, N–CH_3), 6.60 and 6.71 (2d, 1H, furan), 7.21–7.28 (m, 1H, H_{arom}), 7.34 and 7.37 (2d, 1H, furan), 7.50–7.57 (m, 1H, H_{arom}), 8.07 and 8.14 (2d, 1H, H_{arom}), 8.20–8.29 (m, 1H, H_{arom}); MS *m/z* 347 $(M+1)^+$ (calcd 344.99); R_f 0.79 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 288 (4.29), 402 (4.37), 415† (4.35). $C_{14}H_9BrN_4O_2$, M is 345.154. Analysis (calcd, found)% C (48.72, 48.73); H (2.63, 2.70); Br (23.15, 23.18); N (16.23, 16.26). Yield: 47.2%.

4.3.8. Compound Ik. Mp 172 °C; ^{1}H NMR δ (DMSO-d_6) 2.36 (s, 3H, CH_3), 4.52 (s, 3H, N–CH_3), 7.30 (t, 1H, H_{arom}), 7.37–7.46 (m, 4H, H_{arom}), 7.53 (d, 1H, H_{arom}), 7.60 (t, 1H, H_{arom}), 8.25 (d, 1H, H_{arom}); MS *m/z* 392 $(M+1)^+$ (calcd 392.08); R_f 0.78 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 256 (4.49), 263† (4.43), 305 (3.86), 346† (3.96), 384 (4.21), 400 (4.11). $C_{20}H_{14}ClN_5O_2$, M is 391.815. Analysis (calcd, found)% C (61.31, 61.34); H (3.60, 3.68); Cl (9.05, 9.11); N (17.87, 17.91). Yield: 78.7%.

4.4. Cyanine dye

4.4.1. Compound IVa. Mp 166 °C; ^{1}H NMR δ (DMSO-d_6) 3.39, 3.41 and 3.43 (3s, 3H, CH_3), 4.65 and 4.68 (2s, 6H, N–CH_3), 7.22–7.38 (m, 2H, H_{arom}), 7.51–7.68 (m, 4H, H_{arom}), 8.29–8.35 (m, 1H, H_{arom}), 8.43–8.48 (m, 1H, H_{arom}); R_f 0.44 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 313 (4.42), 516† (4.86), 552 (5.31). $C_{20}H_{17}ClN_8O_4$, M is 468.857. Analysis (calcd, found)% C (51.24, 51.29); H (3.65, 3.71); N (23.90, 23.93). Yield: 60.9%.

4.4.2. Compound IVb. Mp 197 °C; ^{1}H NMR δ (DMSO-d_6) 4.68 (s, 6H, N–CH_3), 6.56 (d, 2H, H_{arom}), 7.40–7.48 (m, 4H, H_{arom}), 7.65–7.72 (m, 4H, H_{arom}), 7.80–7.83 (m, 1H, H_{arom}), 8.43 (d, 2H, H_{arom}); R_f 0.42 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 276 (5.23), 305 (5.10), 326 (5.00), 358 (4.84), 522† (5.28), 561 (5.82). $C_{25}H_{19}ClN_8O_4$, M is 530.928. Analysis (calcd, found)% C (56.56, 56.60); H (3.61, 3.67); N (21.11, 21.13). Yield: 51.3%.

4.4.3. Compound IVc. Mp 158 °C; ^{1}H NMR δ (DMSO-d_6) 3.52–3.56 (m, 4H, H_{alk}), 4.29–4.33 (m, 2H, H_{alk}), 4.55 (s, 6H, N–CH_3), 7.20 (t, 2H, H_{arom}), 7.51 (t, 2H, H_{arom}), 8.11 (d, 2H, H_{arom}), 8.40 (d, 2H, H_{arom}); R_f 0.44 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 308 (3.86), 399 (3.20), 527† (4.28), 556 (4.73). $C_{21}H_{18}Cl_2N_8O_4$, M is 517.329. Analysis (calcd, found)% C (48.76, 48.82); H (3.51, 3.56); N (21.66, 21.65). Yield: 63.8%.

4.4.4. Compound IVd. Mp 195 °C; ^{1}H NMR δ (DMSO-d_6) 3.72–4.03 (m, 9H, H_{alk}), 4.65 and 4.70 (2s, 6H, N–CH_3), 7.04–7.11 and 7.17–7.23 (2m, 2H, H_{arom}), 7.49–7.60 (m, 4H, H_{arom}), 8.43–8.47 (m, 2H, H_{arom}); R_f 0.45 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 308 (4.06), 406 (3.58), 519† (4.31), 555 (4.80). $C_{23}H_{23}ClN_8O_4$, M is 510.937. Analysis (calcd, found)% C (54.07, 54.12); H (4.54, 4.58); N (21.93, 21.96). Yield: 62.4%.

4.4.5. Compound IVe. Mp 151 °C; UV–vis (CH_3CN) [λ, (log ε)] 301 (4.90), 343 (5.05), 437† (4.01), 531 (4.71), 564 (5.12). Yield: 2.1%.

4.4.6. Compound IVf. UV–vis (CH_3CN) [λ, (log ε)] 310, 362, 508,† 578. Yield: 0.5%.

4.4.7. Compound IVg. Mp 187 °C; ^{1}H NMR δ (DMSO-d_6) 2.60 (s, 3H, CH_3), 4.61 and 4.67 (2s, 6H, N–CH_3), 6.62–6.70 (m, 2H, H_{arom}), 7.19–7.76 (m, 8H, H_{arom}), 8.41 and 8.46 (2d, 2H, H_{arom}); R_f 0.41 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 307 (4.74), 366 (4.70), 521† (4.94), 561 (5.46). $C_{26}H_{21}ClN_8O_4$, M is 544.954. Analysis (calcd, found)% C (57.31, 57.34); H (3.88, 3.93); N (20.56, 20.59). Yield: 53.2%.

4.4.8. Compound IVh. Mp 181 °C; ^{1}H NMR δ (DMSO-d_6) 3.51 and 3.65 (2s, 3H, OCH_3), 3.85 and 4.00 (2s, 3H, OCH_3), 4.65 and 4.68 (2s, 6H, N–CH_3), 6.50–6.86 (m, 4H, H_{arom}), 7.16–7.54 (m, 5H, H_{arom}), 8.40 and 8.45 (2d, 2H, H_{arom}); R_f 0.40 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 303 (5.12), 361 (5.13), 414† (4.89), 528† (5.22), 564 (5.69). $C_{27}H_{23}ClN_8O_6$, M is 590.979. Analysis (calcd, found)% C (54.87, 54.91); H (3.92, 3.96); N (18.96, 18.97). Yield: 33.7%.

4.4.9. Compound IVi. Mp 185 °C; ^{1}H NMR δ (DMSO-d_6) 4.67 (s, 6H, N–CH_3), 6.80–6.88 (m, 2H, H_{arom}), 7.43–7.62 (m, 6H, H_{arom}), 8.16–8.20 (m, 1H, H_{arom}), 8.43 (d, 2H, H_{arom}); R_f 0.39 ($CHCl_3$/MeOH 9/1, 21 °C);^{13}C NMR δ (DMSO-d_6) 37.25, 104.11, 107.312, 109.44, 121.12, 123.72, 124.99, 127.48, 128.65, 130.32, 132.05, 134.70, 135.34, 135.94, 138.92, 142.29, 145.70; UV–vis (CH_3CN) [λ, (log ε)] 296 (4.91), 388 (4.72), 531† (5.10), 569 (5.57). $C_{23}H_{17}ClN_8O_4S$, M is 536.950. Analysis (calcd, found)% C (51.45, 51.48); H (3.19, 3.23); N (20.87, 20.90). Yield: 29.5%.

4.4.10. Compound IVj. Mp 176 °C; ^{1}H NMR δ (DMSO-d_6) 4.65 (s, 6H, N–CH_3), 6.89–7.08 (m, 2H, H_{arom}), 7.23–7.30 (m, 2H, H_{arom}), 7.51–7.68 (m, 4H, H_{arom}), 8.45 (d, 2H, H_{arom}); R_f 0.39 ($CHCl_3$/MeOH 9/1, 21 °C); ^{13}C NMR δ (DMSO-d_6) 37.29, 105.34, 106.82, 109.63, 112.21, 115.04, 116.70, 120.64, 121.21, 123.03, 123.81, 125.24, 127.36, 128.42, 132.17, 138.61, 142.80;UV–vis (CH_3CN) [λ, (log ε)] 281 (4.77), 307 (4.65), 409 (4.62), 544† (4.87), 582 (5.27). $C_{23}H_{16}BrClN_8O_5$, M is 599.785. Analysis (calcd, found)% C (46.06, 46.11); H (2.69, 2.76); N (18.68, 18.71). Yield: 35.8%.

4.4.11. Compound IVk. R_f 0.39 ($CHCl_3$/MeOH 9/1, 21 °C); UV–vis (CH_3CN) [λ, (log ε)] 309 (3.69), 369 (3.40), 562 (4.26). Yield: 1.7%.

4.5. Synthesis of the acylation product Ib starting from the 1-methyltetrazolo[5,1-*a*]isoindole II

For 0.35 g (0.002 mol) of tetrazoloisoindole II purified by sublimation, we add under inert atmosphere 10 ml of pyridine and 0.24 ml (0.002 mol) of benzoyl chloride. The solution was heathed at 100 °C for 30 min. Pyridine was then evaporated and the residue was crystallized from a mixture of benzene–ethyl acetate to give 0.5 g (89%) of **Ib**.

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PPh_3/DDQ as a neutral system for the facile preparation of diethyl α-bromo, α-iodo and α-azidophosphonates from diethyl α-hydroxyphosphonates

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Abstract—The mixture of triphenylphosphine (PPh_3) and 2,3-dichloro-5,6-dicyanobenzquinone (DDQ) as a neutral system has been used for the preparation of various types of diethyl α-bromo, α-iodo and α-azidophosphonates from their corresponding diethyl α-hydroxyphosphonates in the presence of *n*-Bu_4NBr, *n*-Bu_4NI and NaN_3 in good to high yields.

1. Introduction

α-Functionalized phosphonates are fascinating organophosphorus compounds in biology, pharmacology and organic chemistry.[1] The main interest in the preparation of these compounds arises from their common applications in the Horner–Wadsworth–Emmons (HWE) olefination reaction to produce α-functionalized olefins and acetylenes.[2] α-Hydroxyphosphonates,[3] which are easily prepared from commercially available materials, are useful precursors for the preparation of various types of α-functionalized phosphonates. Although a wide range of procedures exists in the literature for the conversion of ordinary hydroxyl functional groups into other functional groups, these methods are not readily applicable to α-hydroxyphosphonates.[4] Therefore, introduction of new and suitable methods for the preparation of α-functionalized phosphonates by the replacement of hydroxyl functional groups has received wide spread attention from organic chemists.[3a,5]

Preparation of biologically active diethyl α-halogenated phosphonates, which are also good precursors for the preparation of heavily substituted olefines via HWE olefination reaction, is an interesting reaction in organic chemistry.[1g,2a,d–g] A literature survey indicates that in contrast to the existing methods for the conversion of alcohols to their bromides and iodides, few methods are known for the preparation of diethyl α-bromo and α-iodophosphonates from their corresponding diethyl α-hydroxyphosphonates.[6] However, the reported procedures suffered from at least one of the following drawbacks; such as low yields of the products, use of toxic reagents or requiring rather high temperatures. PPh_3/CBr_4 in refluxing benzene and PPh_3/Br_2/Py in CH_3CN at room temperature are the reported procedures that have been used for the preparation of diethyl α-bromophosphonates in low yields (42–67%).[6a] Toxic $SOBr_2$ is the other reported brominating agent that has been applied for this purpose.[6b] In this report, iodination of diethyl α-hydroxyphosphonates has also been tried in the presence of phosphorus triiodide (PI_3).[6b] However, attempts to obtain α-iodophosphonates in reasonable yields failed and the desired products were obtained in poor yields (~10%).[6b] Allyl bromide/carbonyl diimidazole (CDI) and MeI/CDI have been successfully applied for the preparation of diethyl α-bromo and α-iodophosphonates, respectively from diethyl α-hydroxyphosphonates.[6c] These procedures suffer from requiring a high temperature (150 °C).

α-Azidophosphonates are important precursors for the preparation of heterocyclic compounds via 1,3-cycloaddition reactions[7] and also for the preparation of their primary amines.[5e,8] In this view, α-amino phosphonates, which are phosphorus analogues of the corresponding α-aminoacids, are successfully obtained by catalytic hydrogenation of α-azidophosphonates,[5e] or by the Staudinger reaction of the azido compounds with PPh_3.[8a,b] Methods for the direct preparation of diethyl α-azido-phosphonates from diethyl α-hydroxy phosphonates are limited to Mitsunobu reaction using PPh_3/diethyl azodicarboxylate (DEAD) and HN_3 as a source of the azide anion. This reaction requires long reaction times.[5h] Azidation of diethyl α-chloromethylphosphonates[9] and α-tosylatedbenzylphosphonates[10] by means of sodium azide in dimethylformamide (DMF) or dimethylsulfoxide (DMSO), respectively are the other reported

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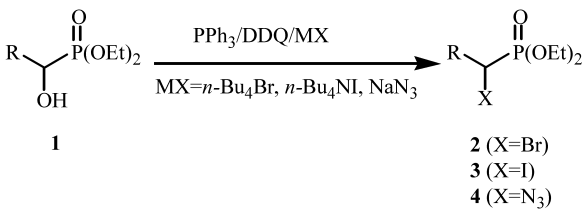
methods for this purpose. Azidation of triethylphosphonoacetate with trifluromethanesulfonyl azide in the presence of Et_3N is the other reported procedure that has been used for the preparation of α-azidophosphonates.[11]

The interaction of quinones as electron-acceptors with derivatives of group VB elements in their trivalent state as electron-donors has been extensively investigated.[12] A number of investigations have dealt more specifically with the structure of the products formed between quinones and tertiary amines, phosphites and phosphines.[13] Although some investigations have been carried out on the reaction of tertiary phosphines with quinones and on their product structures,[12,13] the application of these mixed materials, as reagents in organic synthesis have not been described. Recently we have reported that a mixture of PPh_3 and 2,3-dichloro,5,6-dicanobenzoquinone (DDQ) affords a complex which in the presence of R_4NX (X=CL, Br, I) converts alcohols, selenols and thiols into their corresponding alkyl halides in high yields.[14]

In recent years, we have started extensive studies on the development of new methods for the preparation of diethyl α-functionalized phosphonates from diethyl α-hydroxyphosphonates. Along this line, we have reported mild oxidation and silylation procedures for the preparation of diethyl α-keto and α-trimethylsilyloxyphosphonates in high yields.[15]

We now report that the PPh_3/DDQ system has been successfully applied for the preparation of various types of diethyl α-bromo, α-iodo and α-azidophophonates from their corresponding hydroxyl compounds using MX (*n*-Bu_4NBr, *n*-Bu_4NI and NaN_3) as nucleophilic sources under mild reaction conditions in good to excellent yields (Scheme 1).



Scheme 1.

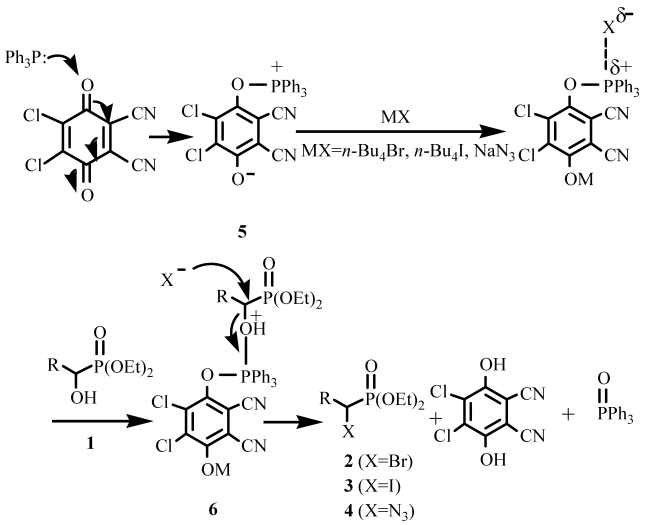
2. Results and discussion

Initially, the halogenation reaction of a variety of diethyl α-hydroxyphosphonates (**1**) with PPh_3/DDQ/*n*-Bu_4NX (X=Br, I) (molar ratio=2:2:2 with respect to **1**) in CH_2Cl_2 at room temperature was studied. The results and the absorption peak of the α-CH group of the products in their ^1H NMR are tabulated in the Tables 1 and 2.

As shown in Tables 1 and 2, various types of diethyl α-bromophosphonates (**2a**–**m**) and diethyl α-iodophosphonates (**3a**, **e**–**g**, **i**–**k**) were obtained in good to excellent yields (60–98%) under similar reaction conditions.

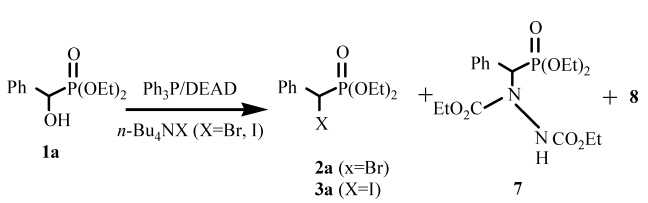
In the second part of our studies, we have applied the PPh_3/DDQ system for the azidation of diethyl α-hydroxyphosphonates. The azidation reaction for the replacement of the hydroxyl functional group of **1a** by PPh_3/DDQ/NaN_3 with the ratio of 2:2:2 equiv. with respect to **1a** in refluxing CH_3CN progressed well in good to high yields (Table 3). The absorption peak of the α-CH group of the products in their ^1H NMR and also the absorption peak of the N_3 group in their IR spectra are tabulated in Table 3.

According to our recent proposed mechanism for the conversion of alcohols, thiols and selenols to their corresponding halides by PPh_3/DDQ/R_4NX (X=Cl, Br, I),[14] we now suggest a similar pathway for the bromination, iodination and azidation of diethyl α-hydroxyphosphonates with *n*-Bu_4NBr, *n*-Bu_4NI and NaN_3 in the presence of PPh_3/DDQ. In the presented method, diethyl α-hydroxyphosphonates react with the adduct formed from the reaction of PPh_3 and DDQ (**5**) to give (**6**). Reaction of **6** with the nucleophile produces the desired products (Scheme 2).



Scheme 2.

In order to show the unique behavior of PPh_3/DDQ system for the preparation of α-functionalized phosphonates, we studied the bromination and iodination of **1a** as a model compound with *n*-Bu_4NBr and *n*-Bu_4NI in the presence of PPh_3/DEAD. The results indicate that under this reaction condition, besides the formation of the desired products **2a** in 41% yield and **3a** in 33% yield, two other by-products **7** and **8** were also isolated. One of the by-products **7** was identified as the alkylated hydrazine derivative and isolated in 5–7% for the bromination and iodination reactions (Scheme 3). The presence of a peak as a doublet for the α-CH at 5.87 ppm with $^2J_{PH}$=13.6 Hz in its ^1H NMR spectra and also two peaks at 3250 and 1730 cm^{-1} for N–H and –C(O)OEt in its IR spectra confirmed the formation of **7**. This type of product is quite familiar in Mitsunobu



Scheme 3.

Table 1. Preparation of diethyl α-bromophosphonates (**2a–n**) from diethyl α-hydroxyphosphonates (**1a–n**) by PPh_3/DDQ/*n*-Bu_4NBr in CH_2Cl_2 at room temperature

Product[Ref]	R–	Time (h)	Yield[a] (%)	^1H NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^2J_{PH}$)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^1J_{PC}$)
2a[6a,16]	C_6H_5–[b]	5	98	4.79 (12.5)	41.85 (159.2)
2b[16]	4-$CH_3C_6H_4$–[b]	5.5	97	4.85 (12.8)	41.80 (159.1)
2c	4-$CH_3OC_6H_4$–	6	97	4.80 (12.7)	41.9 (162.0)
2d	2,4,6-$(CH_3)_3C_6H_2$–	5.5	90	5.65 (14.8)	36.19 (163.2)
2e	2-ClC_6H_4–	7	97	5.53 (13.8)	36.29 (161.6)
2f	3-ClC_6H_4–	9	95	5.36 (13.6)	36.67 (161.5)
2g[16]	4-ClC_6H_4–[b]	8.5	98	5.86 (13.8)	40.91 (159.5)
2h	2,6-$Cl_2C_6H_3$–	6	97	6.1 (13.9)	38.76 (158.0)
2i	2-$O_2NC_6H_4$–	6.5	95	6.01 (14.8)	34.06 (158.2)
2j	3-$O_2NC_6H_4$–	7	94	5.98 (14.6)	38.77 (158.0)
2k[17]	4-$O_2NC_6H_4$–[b]	8.5	96	6.3 (14.8)	40.12 (157.2)
2l	2-Naphthyl	5	94	5.10 (13.9)	41.92 (159.7)
2m	3-Pyridyl	5.5	92	4.91 (13.5)	38.28 (159.5)

[a] Isolated yields.
[b] Registry numbers for **2a**, **b**, **g** and **k**: 23755-78-4, 222850-34-2, 74917-62-7 and 39082-34-3, respectively.

reactions.[18] Therefore, using the PPh_3/DDQ system is a superior method for the high yielding preparation of α-functionalized phosphonates without side product formation.

We have also tried the chlorination of diethyl α-hydroxyphosphonates in the presence of this system with *n*-$Bu_4NCl{\cdot}H_2O$ and *n*-Hex_4NCl. However, chlorination of the phosphonates did not proceed well and the starting materials were isolated intact.

3. Conclusion

In conclusion, in this investigation we have demonstrated the use of PPh_3/DDQ/MX system as a superior and convenient method for the preparation of varieties of diethyl α-bromo-, α-iodo- and α-azidophosphonates from the easily available corresponding diethyl α-hydroxyphosphonates. The ease of handling of the system, mild and neutral reaction conditions, the absence of the formation of the side products and the good to excellent yields of the products are the useful practical points of the presented method.

4. Experimental

Chemicals were either prepared in our laboratories or were purchased from Fluka and Merck Chemical Companies. Products were purified by plate chromatography. The purity determination of the products was accomplished by TLC on silica gel polygram SIL G/UV 254 plates. Mass spectra were run on a Shimadzu GC-Mass-QP 1000 EX at 70 eV. The IR spectra were recorded on a Shimadzu Fourier Transform Infrared Spectrophotometer (FT-IR-8300). The NMR spectra were recorded on a Bruker advance DPX 250 MHz spectrometer. The solvents were purified and dried before use.

4.1. Typical procedure for the preparation of diethyl α-bromobenzylphosphonate (2a) from diethyl α-hydroxybenzylphosphonate (1a)

n-Bu_4NBr (2 mmol, 0.644 g) was added to a stirring mixture of DDQ (2 mmol, 0.454 g) and PPh_3 (2 mmol, 0.524 g) in dry CH_2Cl_2 (10 mL) at room temperature. Then **1a** (1 mmol, 0.244 g) was added to the reaction mixture and the progress of the reaction was monitored by TLC. After 5 h, the reaction mixture was washed with H_2O (3×20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent afforded a crude product that was purified by preparative plate chromatography (silica gel) eluted with CCl_4/EtOAc (2:1) to afford diethyl α-bromobenzylphosphonate (**2a**) in 98% yield (0.3 g) as a yellow oily compound.

4.2. Typical procedure for the preparation of diethyl α-iodobenzylphosphonate (3a) from diethyl α-hydroxybenzylphosphonate (1a)

n-Bu_4NI (2 mmol, 0.738 g) was added to a stirring mixture of DDQ (2 mmol, 0.454 g) and PPh_3 (2 mmol, 0.524 g) in dry CH_2Cl_2 (10 mL) at room temperature. Then **1a** (1 mmol, 0.244 g) was added to the reaction mixture and

Table 2. Preparation of diethyl α-iodophosphonates (**3a**, **e–g**, **i–k**) from diethyl α-hydroxyphosphonates (**1a**, **e–g**, **i–k**) by PPh_3/DDQ/*n*-Bu_4NI in CH_2Cl_2 at room temperature

Product[Ref]	R–	Time (h)	Yield[a] (%)	^1H NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^2J_{PH}$)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^1J_{PC}$)
3a[16]	C_6H_5–[b]	3	84	4.98 (13.4)	15.41 (139.9)
3e	2-ClC_6H_4–	5	68	4.63 (13.2)	9.97 (158.2)
3f	3-ClC_6H_4–	4.5	69	4.92 (13.8)	9.96 (158.5)
3g	4-ClC_6H_4–	3.5	65	4.87 (13.6)	14.28 (156.3)
3i	2-$O_2NC_6H_4$–	5	63	6.16 (15.0)	7.00 (155.8)
3j	3-$O_2NC_6H_4$–	4.5	60	6.05 (14.8)	13.0 (155.1)
3k[17]	4-$O_2NC_6H_4$–[b]	5.5	61	5.80 (13.9)	12.98 (154.6)

[a] Isolated yields.
[b] Registry numbers for **3a** and **k**: 222850-36-4 and 39082-35-4, respectively.

Table 3. Preparation of diethyl α-azidohosphonates (**4a**, **e**–**g**, **i**–**k**) from diethyl α-hydroxyphosphonates (**1a**, **e**–**g**, **i**–**k**) by PPh_3/DDQ/NaN_3 in refluxing CH_3CN

Product[Ref]	R–	Time (h)	Yield[a] (%)	IR (neat) ν_{N3}/cm^{-1}	^{1}H NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^2J_{PH}$)	^{13}C NMR ($CDCl_3$) $\delta_{\alpha CH}$ ($^1J_{PC}$)
4a[1h,8]	C_6H_5–[b]	3	95	2100	4.74 (16.5)	61.96 (158.2)
4e	2-ClC_6H_4–	6	83	2150	5.29 (17.0)	56.35 (161.1)
4f	3-ClC_6H_4–	7.5	89	2123	5.02 (16.4)	47.86 (162.2)
4g	4-ClC_6H_4–	7	80	2110	4.65 (17.0)	61.28 (158.3)
4i	2-$O_2NC_6H_4$–	8.5	76	2125	4.73 (16.4)	56.46 (157.5)
4j	3-$O_2NC_6H_4$–	7.5	83	2140	4.90 (16.4)	61.10 (156.2)
4k[17]	4-$O_2NC_6H_4$–[b]	5.5	75	2134	4.83 (16.7)	61.36 (155.0)

[a] Isolated yields.
[b] Registry numbers for **4a** and **k**: 131523-51-8 and 17986-31-1, respectively.

the progress of the reaction was monitored by TLC. After 3 h, the reaction mixture was washed with H_2O (3×20 mL) and the organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent afforded a crude product that was purified by the preparative plate chromatography (silica gel) eluted with CCl_4/EtOAc (2:1) to afford diethyl α-bromobenzylphosphonate (**3a**) in 84% yield (0.297 g) as a yellow brownish oily compound.

4.3. Typical procedure for the preparation of diethyl α-azidobenzylphosphonate (4a) from diethyl α-hydroxybenzylphosphonate (1a)

NaN_3 (2 mmol, 0.13 g) was added to a stirring mixture of DDQ (2 mmol, 0.454 g) and PPh_3 (2 mmol, 0.524 g) in dry CH_3CN (10 mL). Then **1a** (1 mmol, 0.244 g) was added to the reaction mixture and was refluxed for 3 h (progress of the reaction was monitored by TLC). The resulting reaction mixture was washed with H_2O (3×20 mL), the organic layer was separated and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent afforded a crude product that was purified by preparative plate chromatography (silica gel) eluted with CCl_4/EtOAc (2:1) to afford diethyl α-azidobenzylphosphonate (**4a**) in 95% yield (0.255 g) as a faint yellow oily compound.

4.4. Spectral data and elemental analysis of diethyl α-bromo, α-iodo and α-azidophosphonate are presented bellow

4.4.1. Diethyl α-bromobenzylphosphonate (2a).[6a,16] ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.08 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 1.26 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 3.79–3.82 (m, 1H, 2-OCH_2CH$_3$), 3.93–4.00 (m, 1H, 2-OCH_2CH$_3$), 4.03–4.17 (m, 2H, 2-OCH_2CH$_3$), 4.79 (d, 1H, $^2J_{PH}$=12.5 Hz, –C*H*), 7.25–7.28 (m, 3H, –C_6H_5), 7.47–7.49 (m, 2H, –C_6H_5) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.57 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.78 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 41.85 (d, $^1J_{CP}$=159.2 Hz, –*C*H), 64.46 (d, $^2J_{CP}$=4.2 Hz, 2-O*C*H$_2$CH$_3$), 64.57 (d, $^2J_{CP}$=4.2 Hz, 2-O*C*H$_2$CH$_3$), 129.05–129.95, 134.94, 134.99 (–C_6H_5) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=307, M−Br=227, 227−P(O)(OEt)$_2$=90; $C_{11}H_{16}BrO_3P$ requires C, 43.00; H, 5.21%, found: C, 43.02; H, 5.20%.

4.4.2. Diethyl α-bromo-4-methylbenzylphosphonate (2b).[16] ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.16 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 1.34 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 2.34 (s, 3H, 4-CH_3), 3.85–3.92 (m, 1H, 2-OCH_2CH$_3$), 4.01–4.10 (m, 1H, 2-OCH_2CH$_3$), 4.16–4.27 (m, 2H, 2-OCH_2CH$_3$), 4.85 (d, 1H, $^2J_{PH}$=12.8 Hz, –C*H*), 7.15 (d, 2H, $^3J_{HH}$=6.9 Hz, –C_6H_4), 7.45 (d, 2H, $^3J_{HH}$=6.3 Hz, –C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.50 (d, $^3J_{CP}$=5.7 Hz, 2-OCH$_2$*C*H$_3$), 16.82 (d, $^3J_{CP}$=5.7 Hz, 2-OCH$_2$*C*H$_3$), 22.18 (4-*C*H$_3$), 41.80 (d, $^1J_{CP}$=159.1 Hz, –*C*H), 63.51 (d, $^2J_{CP}$=4.5 Hz, 2-O*C*H$_2$CH$_3$), 64.70 (d, $^2J_{CP}$=4.5 Hz, 2-O*C*H$_2$CH$_3$), 130.0–132.5, 136.4–138.9 (–C_6H_4) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=321, M−Br=241, 241−P(O)(OEt)$_2$=104; $C_{12}H_{18}BrO_3P$ requires C, 44.86; H, 5.61%, found: C, 44.85; H, 5.60%.

4.4.3. Diethyl α-bromo-4-methoxybenzylphosphonate (2c). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.09 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 1.27 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 3.74 (s, 3H, 4-OCH_3), 3.79–3.85 (m, 1H, 2-OCH_2CH$_3$), 3.94–4.04 (m, 1H, 2-OCH_2CH$_3$), 4.10–4.21 (m, 2H, 2-OCH_2CH$_3$), 4.80 (d, 1H, $^2J_{PH}$=12.7 Hz, –C*H*), 6.80 (d, 2H, $^3J_{HH}$=8.6 Hz, –C_6H_4), 7.44 (d, 2H, $^3J_{HH}$=7.5 Hz, –C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.63 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.80 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 41.9 (d, $^1J_{CP}$=162.0 Hz, –*C*H), 55.69 (4-OCH_3), 64.33 (d, $^2J_{CP}$=6.7 Hz, 2-O*C*H$_2$CH$_3$), 64.43 (d, $^2J_{CP}$=6.7 Hz, 2-O*C*H$_2$CH$_3$), 114.49, 126.95, 130.64–131.29, 160.45 (–C_6H_4) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=337, M−Br=257, 257−P(O)(OEt)$_2$=120; $C_{12}H_{18}BrO_4P$ requires C, 42.73; H, 5.34%, found: C, 42.71; H, 5.32%.

4.4.4. Diethyl α-bromo-2,4,6-trimethylbenzylphosphonate (2d). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 0.98 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$*C*H$_3$), 1.31 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$*C*H$_3$), 2.21 (s, 3H, –CH_3), 2.29 (s, 3H, –CH_3), 2.60 (s, 3H, –CH_3), 3.61–3.64 (m, 1H, 2-OCH_2CH$_3$), 3.87–3.91 (m, 1H, 2-OCH_2CH$_3$), 4.13–4.21 (m, 2H, 2-OCH_2CH$_3$), 5.65 (d, 1H, $^2J_{PH}$=14.8 Hz, –C*H*), 6.75 (s, 1H, –C_6H_2), 6.81 (s, 1H, –C_6H_2) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 15.00–15.39 (m, 2-OCH$_2$*C*H$_3$), 20.07 (–*C*H$_3$), 20.71 (–*C*H$_3$), 28.68 (–*C*H$_3$), 36.19 (d, $^1J_{CP}$=163.2 Hz, –*C*H), 62.88–63.36 (m, 2-O*C*H$_2$CH$_3$), 128.02, 130.56 (–C_6H_2) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=349, M−Br=269, 269−P(O)(OEt)$_2$=132; $C_{14}H_{22}BrO_3P$ requires C, 48.14; H, 6.30%, found: C, 48.12; H, 6.28%.

4.4.5. Diethyl α-bromo-2-chlorobenzylphosphonate (2e). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.18 (t, 3H, $^3J_{HH}$=7.5 Hz, 2-OCH$_2$CH_3), 1.36 (t, 3H, $^3J_{HH}$=7.5 Hz, 2-OCH$_2$CH_3), 3.88–4.12 (m, 2H, 2-OCH_2CH$_3$), 4.22–4.31

(m, 2H, 2-OCH_2CH$_3$), 5.53 (d, 1H, $^2J_{PH}$=13.8 Hz, –CH), 7.25–7.37 (m, 3H, –C$_6H_4$), 7.99 (d, 1H, $^3J_{HH}$=7.4 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.19 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.43 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 36.29 (d, $^1J_{CP}$=161.6 Hz, –CH), 64.05 (d, $^2J_{CP}$=6.9 Hz, 2-OCH_2CH$_3$), 64.37 (d, $^2J_{CP}$=6.9 Hz, 2-OCH_2CH$_3$), 127.52–133.56 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=342, M+2=344, M−Br=262, 262−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$BrClO$_3$P requires C, 38.60; H, 4.39%, found: C, 38.60; H, 4.36%.

4.4.6. Diethyl α-bromo-3-chlorobenzylphosphonate (2f). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.08 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 1.28 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 3.78–4.01 (m, 2H, 2-OCH_2CH$_3$), 4.14–4.26 (m, 2H, 2-OCH_2CH$_3$), 5.36 (d, 1H, $^2J_{PH}$=13.6 Hz, –CH), 7.14–7.30 (m, 3H, –C$_6H_4$), 7.89–7.93 (m, 1H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.54 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.78 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 36.67 (d, $^1J_{CP}$=161.5 Hz, –CH), 64.40 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 64.72 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 127.85–133.93 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=342, M+2=344, M−Br=262, 262−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$BrClO$_3$P requires C, 38.60; H, 4.39%, found: C, 38.61; H, 4.41%.

4.4.7. Diethyl α-bromo-4-chlorobenzylphosphonate (2g).[16] ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.11 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 1.26 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 3.79–3.90 (m, 1H, 2-OCH_2CH$_3$), 3.95–4.04 (m, 1H, 2-OCH_2CH$_3$), 4.10–4.21 (m, 2H, 2-OCH_2CH$_3$), 5.86 (d, 1H, $^2J_{PH}$=13.8 Hz, –CH), 7.24 (d, 2H, $^3J_{HH}$=8.4 Hz, –C$_6H_4$), 7.43 (d, 2H, $^3J_{HH}$=8.4 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.62 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.79 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 40.91 (d, $^1J_{CP}$=159.5 Hz, –CH), 64.43 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 64.67 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 129.24–135.33 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=342, M+2=344, M−Br=262, 262−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$BrClO$_3$P requires C, 38.60; H, 4.39%, found: C, 38.59; H, 4.38%.

4.4.8. Diethyl α-bromo-2,6-dichlorobenzylphosphonate (2h). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.12–1.20 (m, 3H, 2-OCH$_2$CH_3), 1.33–1.40 (m, 3H, 2-OCH$_2$CH_3), 3.91–4.06 (m, 2H, 2-OCH_2CH$_3$), 4.19–4.27 (m, 2H, 2-OCH_2CH$_3$), 6.1 (d, 1H, $^2J_{PH}$=13.9 Hz, –CH), 7.16–7.35 (m, 3H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.86 (d, $^3J_{CP}$=6.8 Hz, 2-OCH$_2$CH_3), 16.96 (d, $^3J_{CP}$=6.8 Hz, 2-OCH$_2$CH_3), 38.76 (d, $^1J_{CP}$=158.0 Hz, –CH), 63.35 (d, $^2J_{CP}$=7.1 Hz, 2-OCH_2CH$_3$), 63.60 (d, $^2J_{CP}$=7.1 Hz, 2-OCH_2CH$_3$), 128.60, 129.99, 131.31, 135.73, 136.87 (–C$_6$H$_3$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=376, M+2=378, M+4=381, M−Br=296, 296−P(O)(OEt)$_2$=159; C$_{11}$H$_{14}$BrClO$_3$P requires C, 35.11; H, 3.72%, found: C, 35.08; H, 3.69%.

4.4.9. Diethyl α-bromo-2-nitrobenzylphosphonate (2i). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.15 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 1.36 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 3.91–4.16 (m, 2H, 2-OCH_2CH$_3$), 4.22–4.34 (m, 2H, 2-OCH_2CH$_3$), 6.01 (d, 1H, $^2J_{PH}$=14.8 Hz, –CH), 7.46–7.56 (m, 1H, –C$_6H_4$), 7.63–7.70 (m, 1H, –C$_6H_4$), 7.92 (d, 1H, $^3J_{HH}$=7.9 Hz, –C$_6H_4$), 8.18 (d, 1H, $^3J_{HH}$=8.1 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.10 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.38 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 34.06 (d, $^1J_{CP}$=158.2 Hz, –CH), 64.02 (d, $^2J_{CP}$=7.2 Hz, 2-OCH_2CH$_3$), 64.80 (d, $^2J_{CP}$=7.2 Hz, 2-OCH_2CH$_3$), 124.76, 128.47–129.61, 132.07–132.22, 133.28–133.42 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=352, M−Br=272, 272−P(O)(OEt)$_2$=135; C$_{11}$H$_{15}$BrNO$_5$P requires C, 37.5; H, 4.26%, found: C, 37.8; H, 4.28%.

4.4.10. Diethyl α-bromo-3-nitrobenzylphosphonate (2j). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.14 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 1.28 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$CH_3), 3.92–4.24 (m, 4H, 2-OCH_2CH$_3$), 5.98 (d, 1H, $^2J_{PH}$=14.6 Hz, –CH), 7.49 (t, 1H, $^3J_{HH}$=8.0 Hz, –C$_6H_4$), 7.88 (d, 1H, $^3J_{HH}$=7.7 Hz, –C$_6H_4$), 8.13 (d, 1H, $^3J_{HH}$=7.8 Hz, –C$_6H_4$), 8.32 (s, 1H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 15.26 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 15.40 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 38.77 (d, $^1J_{CP}$=158.0 Hz, –CH), 63.25 (d, $^2J_{CP}$=7.1 Hz, 2-OCH_2CH$_3$), 63.65 (d, $^2J_{CP}$=7.1 Hz, 2-OCH_2CH$_3$), 122.76–123.46, 128.74, 134.48–134.57 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=352, M−Br=272, 272−P(O)(OEt)$_2$=135; C$_{11}$H$_{15}$BrNO$_5$P requires C, 37.5; H, 4.26%, found: C, 37.6; H, 4.27%.

4.4.11. Diethyl α-bromo-4-nitrobenzylphosphonate (2k).[17] ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.10–1.14 (m, 3H, 2-OCH$_2$CH_3), 1.27–1.30 (m, 3H, 2-OCH$_2$CH_3), 3.90–4.05 (m, 2H, 2-OCH_2CH$_3$), 4.12–4.21 (m, 2H, 2-OCH_2CH$_3$), 6.3 (d, 1H, $^2J_{PH}$=14.8 Hz, –CH), 7.66–7.69 (m, 2H, –C$_6H_4$), 8.12–8.15 (m, 2H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.63 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.78 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 40.12 (d, $^1J_{CP}$=157.2 Hz, –CH), 64.60 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 65.05 (d, $^2J_{CP}$=7.0 Hz, 2-OCH_2CH$_3$), 124.09, 130.19–130.96, 142.34–142.40 (–C$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=352, M−Br=272, 272−P(O)(OEt)$_2$=135; C$_{11}$H$_{15}$BrNO$_5$P requires C, 37.5; H, 4.26%, found: C, 37.8; H, 4.29%.

4.4.12. Diethyl α-bromo-2-naphthylphosphonate (2l). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.12 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 1.34 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 3.81–3.91 (m, 1H, 2-OCH_2CH$_3$), 4.00–4.10 (m, 1H, 2-OCH_2CH$_3$), 4.18–4.30 (m, 2H, 2-OCH_2CH$_3$), 5.10 (d, 1H, $^2J_{PH}$=13.9 Hz, –CH), 7.46–7.50 (m, 2H, –C$_{10}H_7$), 7.71–7.83 (m, 4H, –C$_{10}H_7$), 7.97 (s, 1H, –C$_{10}H_7$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.21 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 16.42 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$CH_3), 41.92 (d, $^1J_{CP}$=159.7 Hz, –CH), 64.11 (d, $^2J_{CP}$=7.4 Hz, 2-OCH_2CH$_3$), 64.22 ($^2J_{CP}$=7.4 Hz, 2-OCH_2CH$_3$), 126.04–128.97, 131.90–133.31 (–C$_{10}$H$_7$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=357, M−Br=277, 277−P(O)(OEt)$_2$=140; C$_{15}$H$_{18}$BrO$_3$P requires C, 50.42; H, 5.04%, found: C, 50.4; H, 5.0%.

4.4.13. Diethyl α-bromo-3-pyridylphosphonate (2m). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.20 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 1.35 (t, 3H, $^3J_{HH}$=7.1 Hz, 2-OCH$_2$CH_3), 3.93–4.15 (m, 2H, 2-OCH_2CH$_3$), 4.20–4.31

(m, 2H, 2-OCH_2CH$_3$), 4.91 (d, 1H, $^2J_{PH}$=13.5 Hz, –C*H*), 7.31–7.36 (m, 1H, –C$_5H_4$N), 8.04 (d, 1H, $^3J_{HH}$=8.0 Hz, –C$_5H_4$N), 8.58 (d, 1H, $^3J_{HH}$=4.1 Hz, –C$_5H_4$N), 8.68 (s, 1H, –C$_5H_4$N) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 16.25 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.42 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 38.28 (d, $^1J_{CP}$=159.5 Hz, –*C*H), 64.46 (d, $^2J_{CP}$=7.1 Hz, 2-O*C*H$_2$CH$_3$), 64.80 (d, $^2J_{CP}$=7.1 Hz, 2-O*C*H$_2$CH$_3$), 123.94, 128.70–128.89, 13.56–132.44, 137.64–137.72, 149.96–150.27 (–*C*$_5$H$_4$N) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=308, M−Br=228, 228−P(O)(OEt)$_2$=91; C$_{10}$H$_{15}$BrNO$_3$P requires C, 38.96; H, 4.87%, found: C, 38.90; H, 4.80%.

4.4.14. Diethyl α-iodobenzylphosphonate (3a).[16] ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.13 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.32 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.84–3.90 (m, 1H, 2-OC*H*$_2$CH$_3$), 3.99–3.08 (m, 1H, 2-OC*H*$_2$CH$_3$), 4.18–4.27 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.98 (d, 1H, $^2J_{PH}$=13.4 Hz, –C*H*), 7.28–7.31 (m, 3H, –C$_6H_5$), 7.56–7.59 (m, 2H, –C$_6H_5$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 15.41 (d, $^1J_{CP}$=139.9 Hz, –*C*H), 16.57 (d, $^3J_{CP}$=5.9 Hz, 2-OCH$_2$*C*H$_3$), 16.7 (d, $^3J_{CP}$=5.9 Hz, 2-OCH$_2$*C*H$_3$), 64.42 (d, $^2J_{CP}$=8.6 Hz, 2-O*C*H$_2$CH$_3$), 64.55 (d, $^2J_{CP}$=8.6 Hz, 2-O*C*H$_2$CH$_3$), 128.95–130.04 (–*C*$_6$H$_5$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=354, M−Br=226, 226−P(O)(OEt)$_2$=89; C$_{11}$H$_{16}$IO$_3$P requires C, 37.29; H, 4.52%, found: C, 37.2; H, 4.58%.

4.4.15. Diethyl α-iodo-2-chlorobenzylphosphonate (3e). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.08 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.28 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.81–4.02 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.12–4.24 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.63 (d, 1H, $^2J_{PH}$=13.2 Hz, –CH), 7.10–7.25 (m, 3H, –C$_6H_4$), 7.97 (d, 1H, $^3J_{HH}$=7.9 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 9.97 (d, $^1J_{CP}$=158.2 Hz, –*C*H), 16.55 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.75 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 64.45 (d, $^2J_{CP}$=7.0 Hz, 2-O*C*H$_2$CH$_3$), 64.64 (d, $^2J_{CP}$=7.0 Hz, 2-O*C*H$_2$CH$_3$), 127.98, 128.01, 129.69–130.08, 132.84–133.06, 134.80 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=389, M+2=391, M−Br=261, 261−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$ClIO$_3$P requires C, 33.93; H, 3.86%, found: C, 33.90; H, 3.84%.

4.4.16. Diethyl α-iodo-3-chlorobenzylphosphonate (3f). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.08 (t, 3H, $^3J_{HH}$=6.7 Hz, 2-OCH$_2$C*H*$_3$), 1.29 (t, 3H, $^3J_{HH}$=6.7 Hz, 2-OCH$_2$C*H*$_3$), 3.86–4.00 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.16–4.22 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.92 (d, 1H, $^2J_{PH}$=13.8 Hz, –CH), 7.17–7.23 (m, 3H, –C$_6H_4$), 7.96–7.99 (m, 1H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 9.96 (d, $^1J_{CP}$=158.5 Hz, –*C*H), 16.50 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.75 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 64.51 (d, $^2J_{CP}$=7.1 Hz, 2-O*C*H$_2$CH$_3$), 64.70 (d, $^2J_{CP}$=7.1 Hz, 2-O*C*H$_2$CH$_3$), 128.03, 129.99–130.07, 132.89–132.95, 134.82 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=389, M+2=391, M−Br=261, 261−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$ClIO$_3$P requires C, 33.93; H, 3.86%, found: C, 33.91; H, 3.84%.

4.4.17. Diethyl α-iodo-4-chlorobenzylphosphonate (3g). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.10 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.27 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.78–4.17 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.87 (d, 1H, $^2J_{PH}$=13.6 Hz, –CH), 7.20 (d, 2H, $^3J_{HH}$=8.2 Hz, –C$_6H_4$), 7.44 (d, 2H, $^3J_{HH}$=8.2 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 14.28 (d, $^1J_{CP}$=156.3 Hz, –*C*H), 16.62 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 16.76 (d, $^3J_{CP}$=5.8 Hz, 2-OCH$_2$*C*H$_3$), 64.59 (d, $^2J_{CP}$=6.8 Hz, 2-O*C*H$_2$CH$_3$), 129.33, 131.19, 131.31, 134.78, 135.48 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=389, M+2=391, M−Br=261, 261−P(O)(OEt)$_2$=125; C$_{11}$H$_{15}$ClIO$_3$P requires C, 33.93; H, 3.86%, found: C, 33.94; H, 3.87%.

4.4.18. Diethyl α-iodo-2-nitrobenzylphosphonate (3i). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.23 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.34 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 4.00–4.31 (m, 4H, 2-OC*H*$_2$CH$_3$), 6.16 (d, 1H, $^2J_{PH}$=15.0 Hz, –C*H*), 7.48–7.54 (m, 1H, –C$_6H_4$), 7.66–7.72 (m, 1H, –C$_6H_4$), 7.96 (d, 1H, $^2J_{PH}$=8.2 Hz, –C$_6H_4$), 8.09 (d, 1H, $^2J_{PH}$=8.0 Hz, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 7.00 (d, $^1J_{CP}$=155.8 Hz, –*C*H), 16.50 (d, $^3J_{CP}$=5.9 Hz, 2-OCH$_2$*C*H$_3$), 16.71 (d, $^3J_{CP}$=5.9 Hz, 2-OCH$_2$*C*H$_3$), 63.31 (d, $^2J_{CP}$=8.8 Hz, 2-O*C*H$_2$CH$_3$), 64.50 (d, $^2J_{CP}$=8.8 Hz, 2-O*C*H$_2$CH$_3$), 127.5–129.6 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=399, M−Br=272, 261−P(O)(OEt)$_2$=136; C$_{11}$H$_{15}$INO$_5$P requires C, 33.08; H, 3.76%, found: C, 33.02; H, 3.71%.

4.4.19. Diethyl α-iodo-3-nitrobenzylphosphonate (3j). ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.15 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.28 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.90–4.23 (m, 4H, 2-OC*H*$_2$CH$_3$), 6.05 (d, 1H, $^2J_{PH}$=14.8 Hz, –C*H*), 7.44 (t, 1H, $^3J_{HH}$=8.0 Hz, –C$_6H_4$), 7.89 (d, 1H, $^3J_{HH}$=7.7 Hz, –C$_6H_4$), 8.07 (d, 1H, $^3J_{HH}$=7.6 Hz, –C$_6H_4$), 8.31 (s, 1H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 13.0 (d, $^1J_{CP}$=155.1 Hz, –*C*H), 16.59–16.80 (2-OCH$_2$*C*H$_3$), 64.68–65.02 (2-O*C*H$_2$CH$_3$), 123.70–124.77, 130.24, 136.10, 136.20, 139.25 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=399, M−Br=272, 261−P(O)(OEt)$_2$=136; C$_{11}$H$_{15}$INO$_5$P requires C, 33.08; H, 3.76%, found: C, 33.06; H, 3.74%.

4.4.20. Diethyl α-iodo-4-nitrobenzylphosphonate (3k).[17] ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.04–1.18 (m, 3H, 2-OCH$_2$C*H*$_3$), 1.26–1.31 (m, 3H, 2-OCH$_2$C*H*$_3$), 3.85–4.07 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.12–4.21 (m, 2H, 2-OC*H*$_2$CH$_3$), 5.80 (d, 1H, $^2J_{PH}$=13.9 Hz, –C*H*), 7.65–7.69 (m, 2H, –C$_6H_4$), 8.08–8.18 (m, 2H, –C$_6H_4$) ppm; ^{13}C NMR (CDCl$_3$, TMS, 62.9 MHz): 12.98 (d, $^1J_{CP}$=154.6 Hz, –*C*H), 16.59–16.82 (2-OCH$_2$*C*H$_3$), 64.70–65.09 (O*C*H$_2$CH$_3$), 124.02, 124.27, 130.19, 130.90, 131.01 (–*C*$_6$H$_4$) ppm; IR (neat): peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=399, M−Br=272, 261−P(O)(OEt)$_2$=136; C$_{11}$H$_{15}$INO$_5$P requires C, 33.08; H, 3.76%, found: C, 33.02; H, 3.71%.

4.4.21. Diethyl α-azidobenzylphosphonate (4a).[1h,8] ^{1}H NMR (CDCl$_3$, TMS, 250 MHz): δ 1.21–1.31 (m, 6H, 2-OCH$_2$C*H*$_3$), 3.94–4.14 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.74 (d, 1H, $^2J_{PH}$=16.5 Hz, –C*H*), 7.38–7.45 (m, 5H, –C$_6H_5$) ppm; ^{13}C

NMR ($CDCl_3$, TMS, 62.9 MHz): 16.80 (d, $^3J_{CP}$=6.0 Hz, 2-OCH$_2$*C*H$_3$), 61.96 (d, $^1J_{CP}$=158.2 Hz, –*C*H), 63.91 (d, $^2J_{CP}$=8.6 Hz, 2-O*C*H$_2$CH$_3$), 128.61–129.28 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2100 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=269, M−N_3=227, 227−P(O)(OEt)$_2$=90; $C_{11}H_{16}N_3O_3P$ requires C, 49.07; H, 5.95%, found: C, 49.10; H, 5.90%.

4.4.22. Diethyl α-azido-2-chlorobenzylphosphonate (4e). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.15 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.29 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.85–4.20 (m, 4H, 2-OC*H*$_2$CH$_3$), 5.29 (d, 1H, $^2J_{PH}$=17.0 Hz, –C*H*), 7.19–7.37 (m, 3H, –C$_6$*H*$_4$), 7.61–7.64 (m, 1H, –C$_6$*H*$_4$) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 15.13–15.46 (2-OCH$_2$*C*H$_3$), 56.35 (d, $^1J_{CP}$=161.1 Hz, –*C*H), 62.90–63.32 (2-O*C*H$_2$CH$_3$), 126.31, 128.67–129.17 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2150 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=304, M+2=306, M−N_3=261, 261−P(O)(OEt)$_2$=125; $C_{11}H_{15}ClN_3O_3P$ requires C, 43.42; H, 4.93%, found: C, 43.45; H, 4.95%.

4.4.23. Diethyl α-azido-3-chlorobenzylphosphonate (4f). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.13 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 1.29 (t, 3H, $^3J_{HH}$=7.0 Hz, 2-OCH$_2$C*H*$_3$), 3.85–4.01 (m, 2H, 2-OC*H*$_2$CH$_3$), 4.11–4.22 (m, 2H, 2-OC*H*$_2$CH$_3$), 5.02 (d, 1H, $^2J_{PH}$=16.4 Hz, –C*H*), 7.20–7.33 (m, 3H, –C$_6$*H*$_4$), 7.80–7.85 (m, 1H, –C$_6$*H*$_4$) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 15.13–15.46 (2-OCH$_2$*C*H$_3$), 47.86 (d, $^1J_{CP}$=162.2 Hz, –*C*H), 62.89–63.32 (2-O*C*H$_2$CH$_3$), 126.30–126.41, 128.31–129.08, 130.30, 130.36 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2123 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=304, M+2=306, M−N_3=261, 261−P(O)(OEt)$_2$=125; $C_{11}H_{15}ClN_3O_3P$ requires C, 43.42; H, 4.93%, found: C, 43.40; H, 4.90%.

4.4.24. Diethyl α-azido-4-chlorobenzylphosphonate (4g). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.11–1.29 (m, 6H, 2-OCH$_2$C*H*$_3$), 3.90–4.13 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.65 (d, 1H, $^2J_{PH}$=17.0 Hz, –C*H*), 7.27–7.42 (m, 4H, –C$_6$*H*$_4$) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.70–16.85 (2-OCH$_2$*C*H$_3$), 61.28 (d, $^1J_{CP}$=158.3 Hz, –*C*H), 63.91–64.16 (2-O*C*H$_2$CH$_3$), 129.30–129.96 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2110 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=304, M+2=306, M−N_3=261, 261−P(O)(OEt)$_2$=125; $C_{11}H_{15}ClN_3O_3P$ requires C, 43.42; H, 4.93%, found: C, 43.41; H, 4.92%.

4.4.25. Diethyl α-azido-2-nitrobenzylphosphonate (4i). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.07–1.34 (m, 6H, 2-OCH$_2$C*H*$_3$), 3.92–4.20 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.73 (d, 1H, $^2J_{PH}$=16.4 Hz, –C*H*), 7.44 (t, 1H, $^3J_{HH}$=7.5 Hz, –C$_6$*H*$_4$), 7.61 (t, $^3J_{HH}$=7.5 Hz, 1H, –C$_6$*H*$_4$), 7.77 (d, 1H, $^3J_{HH}$=7.7 Hz, –C$_6$*H*$_4$), 7.92 (d, 1H, $^3J_{HH}$=8.2 Hz, –C$_6$*H*$_4$), ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.56–16.76 (2-OCH$_2$*C*H$_3$), 56.46 (d, $^1J_{CP}$=157.5 Hz, –*C*H), 64.12–64.33 (2-O*C*H$_2$CH$_3$), 125.20–125.53, 129.67–130.39, 133.78, 133.83 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2125 (N_3) cm^{-1}, IR (neat): peak of OH was bsent.; MS (70 eV), *m/e*: M$^+$=314, M−N_3=272, 272−P(O)(OEt)$_2$=135; $C_{11}H_{15}N_4O_5P$ requires C, 42.04; H, 4.78%, found: C, 42.03; H, 4.71%.

4.4.26. Diethyl α-azido-3-nitrobenzylphosphonate (4j). ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.26–1.37 (m, 6H, 2-OCH$_2$C*H*$_3$), 4.06–4.26 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.90 (d, 1H, $^2J_{PH}$=16.4 Hz, –C*H*), 7.55–7.62 (m, 1H, –C$_6$*H*$_4$), 7.80–7.83 (m, 1H, –C$_6$*H*$_4$), 8.21–8.39 (m, 2H, –C$_6$*H*$_4$) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.75 (d, $^3J_{CP}$=5.9 Hz, 2-OCH$_2$*C*H$_3$), 61.10 (d, $^1J_{CP}$=156.2 Hz, –*C*H), 63.1 (d, $^2J_{CP}$=8.2 Hz, 2-O*C*H$_2$CH$_3$), 123.33–123.94, 128.83–130.06, 132.44–132.60, 134.31 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2140 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=314, M−N_3=272, 272−P(O)(OEt)$_2$=135; $C_{11}H_{15}N_4O_5P$ requires C, 42.04; H, 4.78%, found: C, 42.02; H, 4.70%.

4.4.27. Diethyl α-azido-4-nitrobenzylphosphonate (4k).[17] ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ 1.18–1.27 (m, 6H, 2-OCH$_2$C*H*$_3$), 3.99–4.14 (m, 4H, 2-OC*H*$_2$CH$_3$), 4.83 (d, 1H, $^2J_{PH}$=16.7 Hz, –C*H*), 7.57 (m, 2H, –C$_6$*H*$_4$), 8.18 (d, 2H, –C$_6$*H*$_4$) ppm; ^{13}C NMR ($CDCl_3$, TMS, 62.9 MHz): 16.80 (d, $^3J_{CP}$=5.5 Hz, 2-OCH$_2$*C*H$_3$), 61.36 (d, $^1J_{CP}$=155.0 Hz, –*C*H), 64.35 (2-O*C*H$_2$CH$_3$), 124.12–124.30, 129.00–129.33, 131.51 (–*C*$_6$H$_4$) ppm; IR (neat): ν 2134 (N_3) cm^{-1}, Peak of OH was absent.; MS (70 eV), *m/e*: M$^+$=314, M−N_3=272, 272−P(O)(OEt)$_2$=135; $C_{11}H_{15}N_4O_5P$ requires C, 42.04; H, 4.78%, found: C, 42.01; H, 4.72%.

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Tetrahedron

Fused isoquinolines: 3-aryl-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-alkyl-1′,4′-dihydropyridine)s

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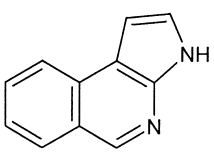
Abstract—Previously unknown 3-arylamino-1,2-dihydro-1-isoquinolones were obtained by condensation of 2-cyanomethylbenzoic acid with arylamines. Isonicotinoylation of the compounds was shown to proceed at the carbon atom in the 4-position to give 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones which were quaternized with alkylating agents and formed the corresponding pyridinium salts. Deprotonation of the latter induced intramolecular conjugated addition with the pyrrole ring closure and formation of spiro compounds. The structure of the products was confirmed by NMR, IR and UV spectroscopy and by synthesis of the model compound, 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione.

The preparative access to 1,4-dihydropyridines via the addition of nucleophilic agents to pyridinium salts was first developed by Kröhnke in 1967.[1] This idea, in its intramolecular version, was used later in the synthesis of the alkaloid nauclefine[2] involving cyclization of quaternized nicotinamides and isonicotinamides induced by coupled addition. Such a cyclization process is of the *exo-trig* type[3] and can be considered as an intramolecular modification of the Michael reaction. Additional examples of the cyclization of similar substrates have been reported.[4,5] This heterocyclization method was extended further, using 4-aryl-substituted pyridinium salts.[6,7] We have shown that quaternary salts of hetaryl 4-pyridyl ketones can also undergo the heterocyclization.[8]

Continuing the study into the *exo-trig* ring closure, we surmised that 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4**) may be appropriate substrates for this purpose.

Using the method proposed earlier for preparation of 3-anilino-1,2-dihydro-1-isoquinolone (2, R=H),[9] we introduced *p*-toluidine, ethyl 4-aminobenzoate, 4-bromoaniline or 4-nitroaniline into reaction with 2-cyanomethylbenzoic acid and obtained the previously unknown 3-arylamino-1,2-dihydro-1-isoquinolones (**2a**–**d**) in good yields.

In their ^{1}H NMR spectra, compounds **2a**–**d** exhibit signals of two exchangeable NH protons, at 10.66–11.35 and 7.78–9.20 ppm, referring to $N^{(2)}H$ and $N^{(3*)}H$, respectively. This assignment is based on the correlation of ^{1}H NMR spectra of **2a**–**d** and their transformation products. Among other spectroscopic peculiarities of compounds **2a**–**d**, there should be intimated the paramagnetic shift (ca. 0.5 ppm)



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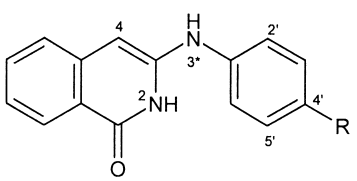
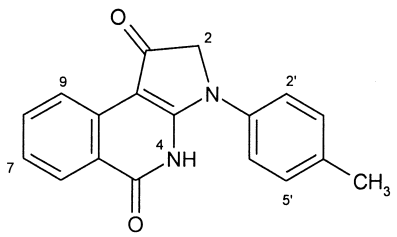


2 a-d

2a : R = Me
2b : R = COOEt
2c : R = Br
2d : R = NO_2



3

Keywords: Acylation; Quaternization; 1,4-Dihydropyridines; Spiro compounds.
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of the doublet signal from the $C^{(8)}H$ proton and the diamagnetic shift (by more than 1 ppm) of the singlet from the $C^{(4)}H$ proton relative to the corresponding signals in isoquinoline. In the first case, this is due to magnetic anisotropy of the neighboring C═O group and in the second—to quasi-aromaticity of the pyridone ring.

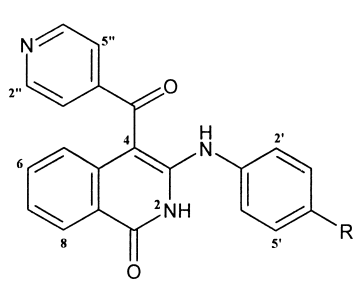
The acylation of 3-anilino-1,2-dihydro-1-isoquinolone was not studied earlier. Since isoquinolones **2a**–**d** have several nucleophilic centers, the acylation, in principle, may proceed at different sites. To determine the main direction of the reaction, we studied first isonicotinoylation of the substrates with isonicotinoyl chloride. The products are formed generally in good yields (60–85%). Based on ^1H NMR spectra, they were identified as 3-arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4a**–**d**), that is, the acylation takes place at the C-4 atom. In the ^1H NMR spectra of compounds **4a**–**d**, the signal of the $C^{(4)}H$ proton, observed in the starting substrates **2a**–**d** at 5.91–6.42 ppm, is absent, but both exchangeable NH protons remain in the molecules and resonate as singlets in the region of 11.52–12.00 and 8.60–9.66 ppm. It should be noted that the effect of the acyl residue at the C-4 atom in **4a**–**d** on chemical shifts is much stronger for the NH than for $C^{(5)}H$ protons. IR spectra of compounds **4a**–**d** show an additional band between 1660 and 1725 cm^{-1} which is absent in starting **2a**–**d** and can be assigned to stretching vibrations of the ketone carbonyl group. Its position in the spectra points to a considerable conjugation of this function with both N-2 and N-3* atoms as is also evidenced in the ^1H NMR spectra. The introduction of the acyl group into molecules **2** causes only a small bathochromic shift (Δ 13 nm) of their long-wave absorption bands in UV spectra. Such a shift as well as a small hyperchromic effect observed are quite predictable for a benzoyl (isonicotinoyl in our case) substituent in the conjugated system.[10] 3-Arylamino-4-isonicotinoyl-1,2-dihydro-1-isoquinolones (**4a**–**d**) are smoothly quaternized in acetonitrile solutions. Although the compounds have several nucleophilic centers, the electrophilic agents attack exclusively the pyridine nitrogen atom to form quaternary salts **5a**–**d** as evidenced by ^1H NMR spectra.

The influence of the acyl residue on the heterocyclic system is more distinct in the salts than in the free bases. Primarily proton-containing groups closest to the substituent suffer considerable paramagnetic shifts: the NMR signals of the $N^{(2')}H$, $N^{(3'*)}$ and $C^{(5')}H$ protons in **5a**–**d** appear already at lower field, in the region of 11.5–12.2, 9.4–9.8 and 7.9–8.3 ppm (as against 11.8–12.0, 8.6–9.3 and 6.8–7.8 ppm in **4a**,**b**), respectively. At the same time, the stretching vibration frequency of the ketone carbonyl in salts **5a**–**d** (near 1670 cm^{-1}) remains unchanged. The color of the solid quaternary salts **5a**–**d** is deeper as compared to the starting compounds **4a**,**b** and **2a**,**b**.

Solutions of **5a**–**d** are instantly decolorized when treated with bases (e.g. triethylamine, piperidine, morpholine or pyridine) and, after dilution with water, easily-crystallizable from DMF precipitates can be isolated. The ^1H NMR and IR spectra of the properly purified products give grounds to suggest that they have the structure of spiro-annelated 1,4-dihydropyridines **7**. The signal of the isoquinoline NH proton remains in structures **7** at 11.51–11.96 ppm, but the proton $N^{(3*)}H$ disappears and a new characteristic pattern corresponding to four α- and β-protons of the 1,4-dihydropyridine moiety arises as two doublets at 6.38–6.59 and 4.33–4.51 ppm. In all cases the coupling constants for these protons are equal to 8 Hz that is typical of olefin *cis*-protons. In the ^{13}C NMR spectra of **7a** and **7c** taken in DMSO-d_6, the signals of the spiro carbon atoms are observed at 88.8 and 88.7 ppm, respectively. The enamine character of the dihydropyridine moiety is reflected in chemical shifts of its C-2′,6′ and C-3′,5′ atoms, i.e. 96.5 and 79.1 ppm for **7a** and 96.8 and 76.0 ppm for **7c**.

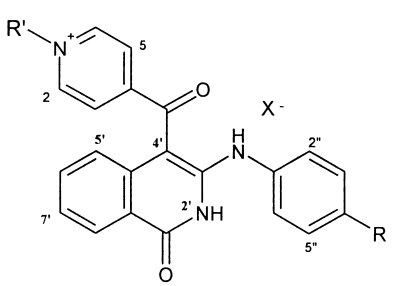
The transformation of quaternary salts **5** into spiro compounds **7** evidently proceeds via intermediates of type **6** which are formed upon deprotonation of the starting salts and then undergo cyclization through intramolecular addition to the electrophilic site in the 4-position of the pyridinium group. It is significant that the sequential transformations **5**→[**6**]→**7** run easily. For example, the contour of the electronic absorption spectrum taken for salt **5a** in methanol reproduces in detail that of spiro compound **7a** but differs in band shape from the spectrum of ketone **4a**. This suggests that the spiro structure is thermodynamically more favorable as compared to the structure of the quaternary salt because even such a weak base as the methanol solvent is able to deprotonate the latter (Scheme 1).

There is no need for preliminary preparation of salts **5** in



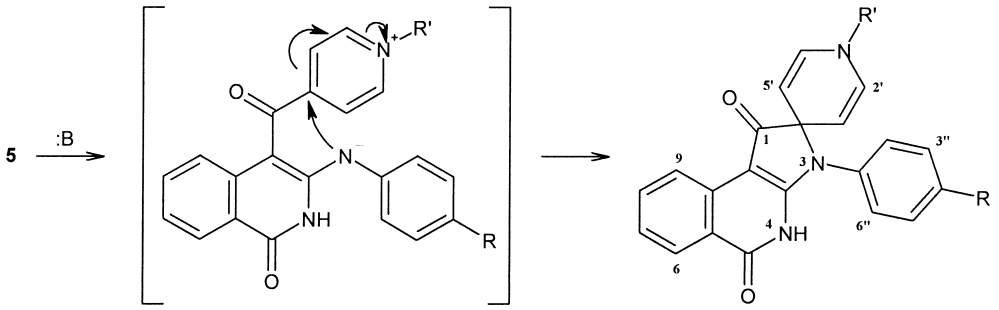
4a-d

4a : R = Me
4b : R = COOEt
4c : R = Br
4d : R = NO_2



5a-d

5a : R = R' = Me , X = TsO
5b : R = Me , R' = Et , X = I
5c : R = COOEt , R' = Et , X = I
5d : R = COOEt , R' = Me , X = I



7a : R = R' = Me
7b : R = Me, R' = Et
7c : R = Me , R' = $PhCH_2$
7d : R = Me , R' = Bz
7e : R = COOEt , R' = Et
7f : R = COOEt , R' = $PhCH_2$
7g : R = Br , R' = Et
7h : R = NO_2 , R' = Me
7i : R = NO_2 , R' = Et

Scheme 1.

order to obtain spiro compounds **7**. It is possible first to treat the isonicotinoylated derivatives **4a–d** with alkylating agents and then, without isolation of the salts **5a–d**, to treat the reaction mixture with a base. In this way compounds **7c** and **7f–i** were obtained in sufficiently high yields. Of particular interest is the one-pot preparation of **7d**, were benzoyl chloride was used in place of the alkylating agent. The benzoyl substituent in the resulting structure **7d** has the strongest effect just on the dihydropyridine ring whose enamine protons exhibit considerable paramagnetic shift in the ^{1}H NMR spectrum.

The basis for the spiro structure **7** is the heterocyclic 3*H*-pyrrolo[2,3-*c*]isoquinoline system (**1**) which is poorly studied. It is known that its derivatives are formed in the reactions of 3-amino-2-methyl-1,2-dihydro-l-isoquinolone with oxalyl chloride[11] and 3-aminoisocarbostyril with *p*-bromophenacyl bromide.[12] In the last case the product is 2-(4-bromophenyl)-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]isoquinolin-5-one which was studied as a selective inhibitor of *c*AMP-dependent proteinkinase.[13] In order to verify the spiro structure of **7**, we synthesized 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione (**3**) as a model compound by the classical method, that is, by reacting 3-(4-toluidino)-1,2-dihydro-l-isoquinolone (**2a**) with chloroacetyl chloride. The comparison of ^{1}H NMR spectra shows a close similarity between chemical shifts of protons in the fused heterocyclic systems of compounds **3** and **7a**. The methylene group $C^{(2)}H_2$ in **3** gives a singlet signal at 4.24 ppm which is absent in **7a**. Also IR spectra of **3** and **7a** are very similar in shapes of absorption bands and vibrational frequencies in the region of 1700–1400 cm^{-1}. The structure similarity of **3** and **7a** having the same chromophore also follows from likeness of their electronic spectra between 250 and 400 nm.

1. Experimental

Melting points of compounds were determined on a Boëtius-type apparatus and are uncorrected. IR spectra were measured with a Pye Unicam SP3-300 instrument in KBr or CsI disks. Electronic spectra of 5×10^{-5} M solutions of **2a**, **3**, **4a**, **5a** and **7a** in methanol were obtained on a Specord M40 spectrophotometer. ^{1}H NMR spectra were taken on a Mercury 400 (Varian) spectrometer (400 MHz) in DMSO-d_6. ^{13}C NMR spectra were measured in DMSO-d_6 on the same instrument at 100 MHz. Chemical shifts are reported in ppm (δ) vs. TMS used as the internal standard. The assignment of signals from aromatic protons was confinned by the COSY HH correlation performed for **7e** and **7h**. In all cases the vicinal coupling constants of aromatic protons are in the range of 7.4–8.4 Hz. TLC on Silufol UV-254 plates was used to monitor the progress of the reactions and to check the purity of the compounds prepared. 2-Cyanomethylbenzoic acid was obtained by the reported procedure.[14]

1.1. General procedure for preparation of 3-arylamino-l,2-dihydro-1-isoquinolones (2a–d)

A suspension of 2-cyanomethylbenzoic acid (10.0 mmol) and the equimolar amount of *p*-toluidine (for **2a**), ethyl 4-aminobenzoate (for **2b**), 4-bromoaniline (for **2c**), or 4-nitroaniline (for **2d**) in chlorobenzene (5 mL) was heated at reflux for 5 h, after which time the solvent was evaporated and the residue was triturated with 2-propanol, filtered, washed with a small amount of 2-propanol, dried, and purified by crystallization from appropriate solvents.

1.1.1. 3-(4-Toluidino)-1,2-dihydro-1-isoquinolone (2a). A colorless solid; (1.5 g, yield 60%); mp 181 °C (from glacial AcOH); [Found: C, 76.68; H, 5.59; N, 11.31. $C_{16}H_{14}N_2O$: requires C, 76.78; H, 5.64; N, 11.19%]; λ_{max} (log ε): 210 (4.37), 370 (3.79) nm; ν_{max} (KBr): 3270 (N–H), 3080, 2959 (C–H), 1650 (C=O), 1600 cm^{-1} (C=C); δ_H: 10.71 (1H, s, NH-2), 7.98 (1H, d, *J*=8.0 Hz, H-8), 7.78 (1H, s, NH-3*), 7.48 (1H, t, *J*=8.0 Hz, H-6), 7.35 (1H, d, *J*=8.0 Hz, H-5), 7.15 (2H, d, *J*=8.2 Hz, H-3′, H-5′), 7.14 (1H, t, *J*=8.0 Hz, H-7); 7.10 (2H, d, *J*=8.2 Hz, H-2′, H-6′), 5.91 (1H, s, H-4), 2.32 (3H, s, CH_3).

1.1.2. 3-(4-Ethoxycarbonylanilino)-1,2-dihydro-1-isoquinolone (2b). A colorless solid; yield (2.22 g, 72%); mp

243 °C (from 2-propanol); [Found: C, 69.98; H, 5.11; N, 8.98. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.09%]; ν_{max} (KBr): 3050 (N–H), 2970 (C–H), 1630 cm^{-1} (C═O); δ_H: 11.10 (1H, s, NH-2), 8.65 (1H, s, NH-3*), 8.07 (1H, d, J=8.2 Hz, H-8), 7.87 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.58 (1H, t, J=8.2 Hz, H-6), 7.51 (1H, d, J=8.2 Hz, H-5), 7.29 (1H, t, J=8.2 Hz, H-7), 7.16 (2H, d, J=8.4 Hz, H-2′, H-6′), 6.31 (IH, s, H-4), 4.26 (2H, q, J=7.6 Hz, OCH_2), 1.30 (3H, t, J=7.6 Hz, CH_3).

1.1.3. 3-(4-Bromoanilino)-1,2-dihydro-1-isoquinolone (2c). A colorless solid; (2.55 g, yield 81%); mp 233 °C (from glacial AcOH); [Found: C, 55.13, Br 25.17; N, 8.72. $C_{15}H_{11}BrN_2O$ requires C, 57.16, Br 25.35; N, 8.89%]; ν_{max} (KBr): 3140 (N–H), 2950 (C–H), 1660 (C═O), 1600, 1560, 1540 cm^{-1}; δ_H: 10.66 (1H, s, NH-2), 8.01 (1H, d, J=8.0 Hz, H-8), 7.93 (1H, s, NH-3*), 7.46 (1H, t, J=8.0 Hz, H-6), 7.40 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.30 (1H, d, J= 8.0 Hz, H-5), 7.14 (1H, t, J=8.0 Hz, H-7), 7.12 (2H, d, J=8.4 Hz, H-2′, H-6′), 5.99 (1H, s, H-4).

1.1.4. 3-(4-Nitroanilino)-1,2-dihydro-1-isoquinolone (2d). A colorless solid; (2.39 g, yield 85%); mp 286 °C (from glacial AcOH); [Found: C, 63.9; H, 4.23; N, 14.08. $C_{15}H_{11}N_3O_3$ requires C, 64.05; H, 3.94; N, 14.94%]; ν_{max} (KBr): 3380 (N–H), 1655 (C═O), 1600, 1560, 1505 cm^{-1} (C═C); δ_H: 11.35 (1H, s, NH-2), 9.20 (1H, s, NH-3*), 8.11 (IH, d, J=8.0 Hz, H-8), 7.64 (IH, t, J=8.0 Hz, H-6), 7.58 (1H, d, J=8.0 Hz, H-5), 7.40 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.14 (1H, t, J=8.0 Hz, H-7), 7.12 (2H, d, J=8.4 Hz, H-2′, H-6′), 6.42 (1H, s, H-4).

1.1.5. Preparation of 3-(4-tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione (3). A suspension of isoquinolone **2a** (0.5 g, 2.0 mmol) in anhydrous dioxane (50 mL) was heated under reflux until it became homogeneous. Chloroacetyl chloride (0.2 mL, 2.5 mmol) was then added to the resultant solution and the mixture was refluxed for 4H, and concentrated. The residue was treated with a concentrated soda solution and the solid was filtered off, washed with water, and crystallized from 2-propanol to give **3** as a light yellow solid. Yield (0.33 g, 58%); mp 285 °C; [Found: C, 73.90; H, 4.83; N, 9.58. $C_{18}H_{14}N_2O_2$ requires C, 74.47; H, 4.86; N, 9.65%]; ν_{max} (log ε): 238 (4.46), 247 (4.45), 284 (4.25), 316 (4.15), 370 (3.91) nm; ν_{max} (KBr): 3140, 3060 (N–H), 1670 infl., 1645 (C═O), 1625, 1580, 1525, 1505, 1445, 1400 cm^{-1}; δ_H: 11.91 (1H, s, NH-4), 8.31 (1H, d, J=7.6 Hz, H-9), 8.02 (1H, d, J=7.6 Hz, H-6), 7.61 (1H, t, J=7.6 Hz, H-8), 7.27 (2H, d, J=8.0 Hz, H-3′, H-5′), 7.23 (2H, d, J=8.0 Hz, H-2′, H-6′), 7.22 (1H, 1, J=7.6 Hz, H-7), 4.24 (2H, s, CH_2), 2.37 (3H, s, CH_3).

1.2. General procedure for preparation of 3-arylamino-4-isonicotinoyl-l,2-dihydro-1-isoquinolones (4a–d)

A mixture of the appropriate isoqiunolone **2a**–**d** (5.0 mmol) and isonicotinoyl chloride (5.1 mmol) in anhydrous dioxane (20 mL) was heated at reflux for 3 h. After evaporation of the solvent in vacuum, the residue was treated with a saturated soda solution, filtered off, washed with water and 2-propanol, and recrystallized from dimethylformamide.

1.2.1. 4-Isonicotinoyl-3-(4-toluidino)-1,2-dihydro-l-isoquinolone (4a). Obtained from **2a** as a light yellow solid; (1.08 g, yield 61%); mp 278 °C; [Found: C, 72.70; H, 4.78; N, 10.89. $C_{22}H_{17}N_3O_2$ requires C, 74.35; H, 4.82; N, 11.82%]; ν_{max} (log ε): 293 (4.34), 383 (4.06) nm; ν_{max} (KBr): 3180, 3050 (N–H), 1675, 1620 (C═O), 1575, 1530 cm^{-1}; δ_H: 11.96 (1H, s, NH-2), 8.69 (2H, d, J=4.4 Hz, H-2″, H-6″), 8.60 (1H, s, NH-3*), 8.15 (1H, d, J=7.4 Hz, H-8), 7.42 (2H, d, J=4.4 Hz, H-3″, H-5″), 7.32 (2H, d, J=7.4 Hz, H-3′, H-5′), 7.22 (1H, t, J=7.4 Hz, H-6), 7.21 (2H, d, J=7.4 Hz, H-2′, H-6′), 7.17 (1H, t, J=7.4 Hz, H-7), 6.83 (1H, d, J=7.4 Hz, H-5), 3.00 (3H, s, CH_3).

1.2.2. 3-(4-Ethoxycarbonylanilino)-4-isonicotinoyl-l,2-dibydro-1-isoquinolone (4b). Obtained from **2b** as a colorless solid; (1.45 g, yield 70%); mp 261 °C; [Found: C, 69.68; H, 4.61; N, 10.11. $C_{24}H_{19}N_3O_4$ requires C, 69.72; H, 4.63; N, 10.16%]; ν_{max} (CsI): 3000 (N–H), 1725, 1670, 1610 (C═O), 1570 cm^{-1}; δ_H: 11.82 (1H, s, NH-2), 9.28 (1H, s, NH-3*), 8.40 (2H, d, J=3.6 Hz, H-2″, H-6″), 8.22 (1H, d, J=7.4 Hz, H-8), 7.79 (1H, d, J=7.4 Hz, H-5), 7.68 (2H, d, J=7.6 Hz, H-3′, H-5′), 7.57 (1H, t, J=7.4 Hz, H-6), 7.38 (1H, t, J=7.4 Hz, H-7), 7.38 (2H, d, J=3.6 Hz, H-3″, H-5″), 6.79 (2H, d, J=7.6 Hz, H-2′, H-6′), 4.24 (2H, q, J= 7.8 Hz, OCH_2); 1.34 (3H, t, J=7.8 Hz, CH_3).

1.2.3. 3-(4-Bromoanilino)-4-isonicotinoyl-1,2-dihydro-1-isoquinolone (4c). Obtained from **2c** as a colorless solid; (1.34 g, yield 64%); mp 305 °C; [Found: C, 59.97; H, 3.32, Br 18.96; N, 9.96. $C_{21}H_{14}BrN_3O_2$ requires C, 60.02; H, 3.36, Br 19.1; N, 10.00%]; ν_{max} (CsI): 3180, 3100 (N–H),1670, 1610 (C═O), 1570, 1505 cm^{-1}; δ_H: 11.52 (1H, s, NH-2), 9.66 (1H, s, NH-3*), 8.47 (2H, d, J=4.0 Hz, H-2″, H-6″), 8.14 (1H, d, J=8.4 Hz, H-8), 7.53 (1H, d, J=8.4 Hz, H-5), 7.42 (1H, t, J=8.4 Hz, H-6), 7.38 (2H, d, J=4.0 Hz, H-3″, H-5″), 7.28 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.27 (1H, t, J=8.4 Hz, H-7), 6.90 (2H, d, J=8.4 Hz, H-2′, H-6′).

1.2.4. 4-Isonicotinoyl-3-(4-nitroanilino)-1,2-dihydro-1-isoquinolone (4d). Obtained from **2d** as a sandy-colored solid; (1.64 g, yield 85%); mp 282 °C; [Found: C, 65.26; H, 3.60; N, 14.47. $C_{21}H_{14}N_4O_4$ requires C, 65.28; H, 3.65; N, 14.50%]; ν_{max} (KBr): 3090 (N–H), 1660, 1640 (C═O), 1595, 1515 cm^{-1}; δ_H: 12.00 (1H, s, NH-2), 9.37 (1H, s NH-3*), 8.42 (2H, d, J=4.8 Hz, H-2″, H-6″), 8.26 (1H, d, J=8.4 Hz, H-8), 7.93 (2H, d, J=8.4 Hz, H-3′, H-5′), 7.84 (1H, d, J=8.4 Hz, H-5), 7.64 (1H, t, J=8.4 Hz, H-6), 7.46 (1H, t, H 8.4 Hz, H-7), 7.44 (2H, d, J=4.8 Hz, H-3″, H-5″), 6.79 (2H, d, J=8.4 Hz, H-2′, H-6′).

1.3. General procedure for preparation of 1-alkyl-4-(3-arylamino-1-oxo-1,2-dihydro-4-isoquinolinoyl)-pyridinium salts (5a–d)

A mixture of isoquinolone **4a** or **4b** and an excess of the appropriate alkylating agent in anhydrous acetonitrile (15–20 mL) was refluxed for 10 h. The volatiles were removed in vacuum and the residue was triturated with 2-propanol and washed on a filter with the same solvent.

1.3.1. 1-Methyl-4-[1-oxo-3-(4-toluidino)-1,2-dihydro-4-isoquinolinoyl]pyridinium tosylate (5a). Obtained from

isoquinolone **4a** (0.7 g, 2.0 mmol) and methyl tosylate (0.42 g, 2.2 mmol) as a bright red solid; yield (0.81 g, 75%); mp 230 °C (from AcOH); [Found: C, 66.48; H, 4.98; N, 7.73. $C_{30}H_{27}N_3O_5S$ requires C, 66.53; H, 5.02; N, 7.76%]; λ_{max} (log ε) 238 (4.66); 247 (4.55); 284 (4.40); 316 (4.25); 370 (3.93) nm; ν_{max} (KBr): 3480, 3080 (N–H), 1675, 1630 (C=O), 1555, 1525 cm^{-1}; δ_H: 11.50 (1H, s, NH-2′), 9.78 (1H, s, NH-3′*), 8.89 (2H, d J=6.4 Hz, H-2, H-6), 8.16 (1H, d, J=8.4 Hz, H-8′), 8.04 (2H, d, J=6.4 Hz, H-3, H-5), 7.88 (1H, d, J=8.4 Hz, H-5′), 7.53 (1H, t, J=8.4 Hz, H-6′), 7.46 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.33 (1H, t, J= 8.4 Hz, H-7′), 7.06 (4H, m, $C_6H_4SO_3$), 6.85 (2H, d, J= 8.0 Hz, H-2″, H-6″), 4.25 (3H, s, NCH_3), 2.31 (6H, s, 4″-CH_3+$CH_3C_6H_4SO_3$.

1.3.2. 1-Ethyl-4-[1′-oxo-3′-(4″-toluidino)-1′,2′-dihydro-4′-isoquinolinoyl] pyridinium iodide (5b). Obtained from isoquinolone **4a** (1.06 g, 3.0 mmol) and ethyl iodide (0.62 g, 4.0 mmol); yield (1.22 g, 80%); mp 246 °C (from DMF); [Found: C, 56.30; H, 4.29; N, 8.19. $C_{24}H_{22}IN_3O_2$ requires C, 56.37; H, 4.34; N, 8.22%]; ν_{max} (KBr): 3500, 3050 (N–H), 1675, 1615 (C=O), 1560, 1525 cm^{-1}; δ_H 11.69 (1H, s, NH-2′), 9.44 (1H, s, NH-3′*), 8.94 (2H, d, J=6.4 Hz, H-2, H-6), 8.18 (1H, d, J=8.4 Hz, H-8′), 8.10 (1H, d, J=8.4 Hz, H-5′), 8.05 (2H, d, J=6.4 Hz, H-3, H-5), 7.60 (1H, t, J= 8.0 Hz, H-6′), 7.37 (1H, t, J=8.0 Hz, H-7′), 7.00 (2H, d, J=8.4 Hz, H-3″, H-5″), 6.75 (2H, d, J=8.4 Hz, H-2″, H-6″), 4.50 2H, (q, J=7.8 Hz, NCH_2), 2.27 (3H, s, 4″-CH_3), 1.31 (3H, t, J=7.8 Hz, CH_2CH_3).

1.3.3. 4-[3-(4-Ethoxycarbonylanilino)-1-oxo-l,2-dihydro-4-isoquinolinoyl]-1-ethylpyridinium iodide (5c). Obtained from isoquinolone **4b** and ethyl iodide taken in the same mole ratio as in Section 1.3.2; (1.02 g, yield 60%); mp 295 °C (from DMF); [Found: C, 54.82; H, 4.22; N, 7.33. $C_{26}H_{24}IN_3O_4$ requires C, 54.85; H, 4.25; N, 7.38%]; ν_{max} (KBr): 3510, 3000 (N–H), 1720, 1675, 1610 (C=O), 1560, 1530 cm^{-1}; δ_H: 12.18 (1H, s, NH-2′), 9.37 (1H, s, NH-3′*), 8.92 (2H, d, J=6.4 Hz, H-2, H-6), 8.34 (1H, d, J=8.4 Hz, H-8′), 8.27 (1H, d, J=8.4 Hz, H-5′), 8.09 (2H, d, J=6.4 Hz, H-3, H-5), 7.72 (1H, t, J=8.4 Hz, H-6′), 7.71 (2H, d, J=8.8 Hz, H-3″, H-5″), 7.49 (1H, t, J= 8.4 Hz, H-7′); 6.75 (2H, d, J=8.8 Hz, H-2″, H-6″), 4.43 (2H, q, J=7.8 Hz, NCH_2), 4.27 (2H, q, J=7.8 Hz, OCH_2), 1.34 (3H, t, J=7.8 Hz, OCH_2CH_3), 1.19 (3H, t, J=7.8 Hz, NCH_2CH_3).

1.3.4. 4-[3-(4-Ethoxycarbonylanilino)-1-oxo-l,2-dihydro-4-isoquinolinoyl]-1-methylpyridinium iodide (5d). Obtained from isoquinolone **4b** (0.5 g, 1.2 mmol) and methyl iodide (0.3 g, 2.1 mmol) added in two equal portions 5H, apart; yield (0.48 g, 72%); mp 228 °C (from AcOH); [Found: C, 54.02; H, 3.93; N, 7.52. $C_{25}H_{22}IN_3O_4$ requires C, 54.07; H, 3.99; N, 7.57%]; ν_{max} (KBr): 3500, 3030 (N–H), 1725, 1670, 1610 (C=O), 1575, 1525 cm^{-1}; δ_H: 12.06 (1H, s, NH-2′), 9.41 (1H, s, NH-3′*), 8.86 (2H, d, J=6.0 Hz, H-2, H-6), 8.26 (1H, d, J=7.8 Hz, H-8′), 8.23 (1H, d, J=7.8 Hz, H-5′), 8.09 (2H, d, J=6.0 Hz, H-3, H-5), 7.75 (2H, d, J= 8.0 Hz, H-3″, H-5″), 7.68 (1H, t, J=7.8 Hz, H-6′), 7.47 (1H, t, J=7.8 Hz, H-7′), 6.82 (2H, d, J=8.0 Hz, H-2″, H-6″), 4.29 (2H, q, J=8.0 Hz, OCH_2), 4.18 (3H, s, NCH_3), 1.36 (3H, t, J=8.0 Hz, CH_2CH_3).

1.4. General and typical procedures for preparation of 3-aryl-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4-[1-alkyl(acyl)-1,4-dihydropyridine]s (7a–i)

Method A (for **7a**, **7b**, **7e**). The appropriate pyridinium salt **5a**, **5b** or **5c** (5 mmol) was dissolved on heating in anhydrous pyridine (about 2 mL) and, after cooling, the resultant solution was diluted with water (30 mL). The precipitate formed was separated by filtration, washed with water, dried, and crystallized from dimethylformamide.

Method B (for **7c**, **7f**–**i**). A mixture of the appropriate isoquinolone **4a**–**d** (5 mmol) and alkylating agent (6 mmol) was refluxed in anhydrous acetonitrile (30 mL) for 6H, and concentrated under a reduced pressure. The residue was dissolved in pyridine (10 mL) on heating and after cooling the resulting solution was diluted with water (30 mL). The precipitate formed was filtered off, washed with water, dried, and crystallized from dimethylformamide.

Method C (for **7d**). To isoquinolone **4a** (1.78 g, 5 mmol) dissolved on heating in anhydrous pyridine (30 mL) was added dropwise benzoyl chloride (1.4 g, 10 mmol). The mixture was heated at reflux for 1H, and concentrated under a reduced pressure. The solid residue was triturated with a saturated solution of soda, washed with water and 2-propanol on a filter, dried, and crystallized from dimethylformamide.

1.4.1. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-c]-isoquinoline-1,5-dione-2-spiro-4′-(1′-methyl-1′,4′-dihydropyridine) (7a). Obtained by Method A from salt **5a** as light yellow crystals; (1.48 g, yield 80%); mp 270 °C; [Found: C, 74.70; H, 5.12; N, 11.32. $C_{23}H_{19}N_3O_2$: requires C, 74.78; H, 5.18; N, 11.37%]; λ_{max} (log ε): 238 (4.72), 247 (4.63), 284 (4.44), 316 (4.20), 370 (4.01) nm; ν_{max} (KBr): 3500, 3140, 3050 (N–H), 1650, 1620 (C=O), 1575, 1518, 1400 cm^{-1}; δ_H: 11.65 (1H, s, NH-4), 8.30 (1H, d, J=8.0 Hz, H-9), 8.05 (1H, d, J=8.0 Hz, H-6); 7.65 (1H, t, J=8.0 Hz, H-8), 7.22 (1H, t, J=8.0 Hz, H-7), 7.20 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.09 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.44 (2H, d, J=7.2 Hz, H-2′, H-6′), 4.33 (2H, d, J=7.2 Hz, H-3′, H-5′), 2.90 (3H, s, NCH_3), 2.39 (3H, s, 4″-CH_3); δ_C,: 96.5 (C-2′.6′), 88.8 (spiro-C), 79.1 (C-3′.5′).

1.4.2. 3-(4-Tolyl)-2,3,4,5-tetrabydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dibydropyridine) (7b). Obtained by Method A from salt **5b**; (1.57 g, yield 82%); mp 331 °C; [Found: C, 75.11; H, 5.48; N, 10.91. $C_{24}H_{21}N_3O_2$ requires C, 75.18; H, 5.52; N, 10.96%]; ν_{max} (KBr): 3510, 3150, 3060 (N–H), 1655, 1625 (C=O), 1585, 1525 cm^{-1}; δ_H: 11.51 (1H, s, NH-4), 8.30 (1H, d, J=7.8 Hz, H-9), 7.99 (1H, d, J=7.8 Hz, H-6), 7.58 (1H, t, J=7.8 Hz, H-8), 7.17 (1H, t, J=7.8 Hz, H-7), 7.14 (2H, d, J=8.0 Hz, H-3″, H-5″), 7.03 (2H, d, J=8.0 Hz, H-2″, H-6″), 6.38 (2H, d, J=7.6 Hz, H-2′, H-6′), 4.34 (2H, d, J= 7.6 Hz, H-3′, H-5′), 3.20 (2H, q, J=7.8 Hz, NCH_2), 2.36 (3H, s, 4″-CH_3), 0.95 (3H, 1, J=7.8 Hz, CH_2CH_3).

1.4.3. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-1,5-dione-2-spiro-4′-(1′-benzyl-1′,4′-dihydropyridine) (7c). Obtained by Method B from

isoquinolone **4a** and benzyl chloride; (1.74 g, yield 78%); mp 340 °C; [Found: C, 78.14; H, 5.11; N, 9.39. $C_{29}H_{23}N_3O_2$ requires C, 78.18; H, 5.20;N, 9.43%]; ν_{max} (KBr): 3490, 3140, 3060, 2950 (N–H), 1645, 1620 (C═O), 1580, 1525, 1495, 1435, 1405 cm^{-1}; δ_H: 11.65 (1H, s, NH-4), 8.30 (1H, d, *J*=7.6 Hz, H-9), 7.99 (1H, d, *J*=7.6 Hz, H-6), 7.64 (1H, t, *J*=7.6 Hz, H-8), 7.22 (1H, t, *J*=7.6 Hz, H-7), 7.19 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.09 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 6.83–7.21 (5H, m, Ph), 6.50 (2H, d, *J*=7.8 Hz, H-2′, H-6′), 4.43 (2H, d, *J*=7.8 Hz, H-3′, H-5′), 4.41 (2H, s, NCH_2), 2.38 (3H, s, 4″-CH_3); δ_C,: 96.8 (C-2′.6′), 88.7 (spiro-C), 79.0 (C-3′.5′).

1.4.4. 3-(4-Tolyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]-isoquinoline-l,5-dione-2-spiro-4′-(1′-benzoyl-1′,4′-dihydropyridine) (7d). Obtained by Method C; (1.68 g, yield 73%); mp 250 °C; [Found: C, 75.75; H, 4.58; N, 9.10. $C_{29}H_{21}N_3O_3$ requires C, 75.80; H, 4.61; N, 9.14%]; ν_{max} (KBr): 3130, 3060, 2950 (N–H), 1670 infl., 1660, 1625 (C═O), 1585, 1525, 1455 cm^{-1}; δ_H: 11.88 (1H, s, NH-4), 8.28 (1H, d, *J*=8.2 Hz, H-9), 8.02 (1H, d, *J*=8.0 Hz, H-6), 7.63 (1H, t, *J*=8.0 Hz, H-8), 7.37–7.56 (5H, m, Ph), 7.24 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 7.23 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.19 (1H, t, *J*=8.0 Hz, H-7), 7.16 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 5.03 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 2.38 (3H, s, 4″-CH_3).

1.4.5. 3-(4-Ethoxycarbonylphenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7e). Obtained by Method A from salt **5c**; (1.74 g, yield 79%); mp 238 °C; [Found: C, 70.70; H, 5.21; N, 9.47. $C_{26}H_{23}N_3O_4$ requires C, 70.74; H, 5.25; N, 9.52%]; ν_{max} (KBr): 3510, 3130, 3010 (N–H), 1730, 1670 infl., 1650, 1620 (C═O), 1588, 1550, 1520, 1500, 1405 cm^{-1}; δ_H: 11.94 (1H, s, NH-4), 8.32 (1H, d, *J*=8.0 Hz, H-9), 8.02 (1H, d, *J*=8.0 Hz, H-6), 7.91 (2H, d, *J*=8.0 Hz, H-3″, H-5″), 7.60 (1H, t, *J*=8.0 Hz, H-8), 7.28 (2H, d, *J*=8.0 Hz, H-2″, H-6″), 7.22 (1H, t, *J*=8.0 Hz, H-7), 6.44 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.39 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 4.34 (2H, q, *J*=7.8 Hz, OCH_2), 3.24 (2H, q, *J*=7.8 Hz, NCH_2), 1.37 (3H, t, *J*=7.8 Hz, OCH_2CH_3), 1.03 (3H, t, *J*=7.8 Hz, NCH_2CH_3).

1.4.6. 3-(4-Ethoxycarbonylphenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-benzyl-1′,4′-dihydropyridine) (7f). Obtained by Method B from isoquinolone **4b** and benzyl chloride; (1.79 g, yield 71%); mp 301 °C; [Found: C, 73.91; H, 4.96; N, 8.29. $C_{31}H_{25}N_3O_4$: requires C, 73.94; H, 5.00; N, 8.34%]; ν_{max} (KBr): 3500, 3140, 3020 (N–H), 1728, 1670 infl., 1650, 1620 (C═O), 1580, 1540, 1520, 1405 cm^{-1}; δ_H 11.85 (1H, s, NH-4), 8.33 (1H, d, *J*=8.2 Hz, H-9), 8.02 (1H, d, *J*=8.2 Hz, H-6), 7.90 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 7.63 (1H, t, *J*=8.2 Hz, H-8), 7.28 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.23 (1H, 1, *J*=8.2 Hz, H-7), 6.907.21 (5H, m, Ph), 6.53 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.43 (2H, s, NCH_2), 4.39 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 4.37 (2H, q, *J*=7.8 Hz, OCH_2), 1.42 (3H, t, *J*=7.8 Hz, CH_3).

1.4.7. 3-(4-Bromopbenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7g). Obtained by Method B from isoquinolone **4c** and ethyl iodide; (1.91 g, yield 85%); mp 291 °C; [Found: C, 61.59; H, 4.01, Br 17.73; N, 9.32. $C_{23}H_{18}BrN_3O_2$: requires C, 61.62; H, 4.05; Br 17.82; N, 9.37%]; ν_{max} (KBr): 3505, 3150, 3060, 3000 (N–H), 1670 infl., 1650, 1620 (C═O), 1580, 1505, 1435, 1405 cm^{-1}; δ_H: 11.73 (1H, s, NH-4), 8.29 (1H, d, *J*=8.0 Hz, H-9), 7.99 (1H, d, *J*=8.0 Hz, H-6), 7.59 (1H, t, *J*=8.0 Hz, H-8), 7.49 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 7.20 (1H, t, *J*=8.0 Hz, H-7), 7.11 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 6.43 (2H, d, *J*=7.2 Hz, H-2′, H-6′), 4.35 (2H, d, *J*=7.2 Hz, H-3′, H-5′), 3.23 (2H, q, *J*=7.8 Hz, NCH_2), 0.97 (3H, t, *J*=7.8 Hz, CH_3).

1.4.8. 3-(4-Nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-1,5-dione-2-spiro-4′-(1′-methyl-1′,4′-dihydropyridine) (7h). Obtained by Method B from isoquinolone **4d** and dimethyl sulfate as an ocher-colored solid; (1.38 g, yield 69%); mp 319 °C; [Found: C, 65.97; H, 3.99; N, 13.92. $C_{22}H_{16}N_4O_4$ requires C, 66.00; H, 4.03; N, 13.99%]; ν_{max} (KBr): 3500, 3420, 3120 (N–H), 1670 infl., 1645, 1620 (C═O), 1575, 1485, 1415 cm^{-1}; δ_H: 11.96 (1H, s, NH-4), 8.30 (1H, d, *J*=8.2 Hz, H-9), 8.18 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 8.04 (1H, d, *J*=8.2 Hz, H-6), 7.61 (1H, t, *J*=8.2 Hz, H-8), 7.46 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.25 (1H, t, *J*=8.2 Hz, H-7), 6.55 (2H, br.s, H-2′, H-6′), 4.52 (2H, br.s, H-3′, H-5′), 3.06 (3H, s, NCH_3).

1.4.9. 3-(4-Nitrophenyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo-[2,3-*c*]isoquinoline-l,5-dione-2-spiro-4′-(1′-ethyl-1′,4′-dihydropyridine) (7i). Obtained by Method B from isoquinolone **4d** and ethyl iodide; (1.76 g, yield 85%); mp 291 °C; [Found: C, 66.58; H, 4.31; N, 13.47. $C_{23}H_{18}N_4O_4$ requires C, 66.66; H, 4.38; N, 13.52%]; ν_{max} (KBr): 3500, 3140, 3040 (N–H), 1670 infl., 1655, 1625 (C═O), 1585, 1535, 1510, 1440, 1405 cm^{-1}; δ_H: 11.96 (1H, s, NH-4), 8.31 (1H, d, *J*=8.2 Hz, H-9), 8.15 (2H, d, *J*=8.2 Hz, H-3″, H-5″), 8.04 (1H, d, *J*=8.2 Hz, H-6), 7.62 (1H, t, *J*=8.2 Hz, H-8), 7.46 (2H, d, *J*=8.2 Hz, H-2″, H-6″), 7.26 (1H, t, *J*=8.2 Hz, H-7), 6.59 (2H, br.s, H-2, H-6(′), 4.51 (2H, br.s, H-3′, H-5′), 3.35 (2H, q, *J*=7.8 Hz, NCH_2), 1.08 (3H, t, *J*=7.8 Hz, CH_3).

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New pentacyclic triterpene saponins with strong *anti*-leishmanial activity from the leaves of *Maesa balansae*

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Abstract—Six new triterpene saponins bearing an oxygen bridge between C-13 and C-28 and with pronounced *anti*-leishmanial activity were isolated from the methanolic extract of leaves of the Vietnamese medicinal plant *Maesa balansae*. The structure was established on the basis of detailed NMR (COSY, NOESY, HMQC, HMBC, TOCSY and DEPT) and FAB-MS studies along with chemical degradation. All saponins identified contained the same pentaglycosidic side chain, but a different esterification pattern on the triterpenoid part. Biological evaluation of the individual compounds against visceral leishmaniasis (*Leishmania infantum* amastigotes) revealed a much better activity in vitro compared to the reference compound Pentostam®, which is currently used as first-line treatment for leishmaniasis.

1. Introduction

Maesa balansae Mez. (Myrsinaceae), a shrub growing in the Northern part of Vietnam,[1] is used in the traditional medicine for the treatment of allergies, sprains, anthelminthic infections, skin ulcers, drunkenness and headache.[2]

Previous chemical investigations on *Maesa* species demonstrated the presence of benzoquinones[3,4] and of triterpenoid compounds.[5,7–10] The present report is the first chemical investigation on *Maesa balansae*.

This paper describes the bioassay-guided isolation and structural elucidation of the main compound, a novel triterpene saponin with strong *anti*-leishmania activity, from the methanolic extract of the leaves of this medicinal plant. All of the isolated saponins possess the same pentasaccharide moiety linked to C-3 of the aglycone.

2. Results and discussion

Following a bio-assay guided screening, the dried leaves of *Maesa balansae* were extracted sequentially with dichloromethane and methanol. The residue obtained after evaporation of the methanol extract was partitioned between *n*-BuOH and water. The *n*-BuOH soluble fraction was evaporated to dryness. After stirring in acetone, the acetone insoluble fraction was repeatedly subjected to semi-preparative reversed-phase HPLC in order to obtain the pure saponins, maesabalides I (**1**), II (**2**), III (**3**), IV (**4**), V (**5**) and VI (**6**) (Fig. 1). These saponins proved to have a very pronounced *anti*-leishmanial activity (vide infra).

Maesabalide I (**1**) was obtained as a white amorphous powder. The molecular formula was established as $C_{76}H_{108}O_{32}$ on the basis of ^{13}C NMR, ^{13}C DEPT NMR and MS. The negative-ion FABMS showed an (M−H (⁻ anion at *m/z* 1531. Fragment peaks occurred at *m/z* 1385 (M−H-146(⁻, *m/z* 1239 (M−H-146-146(⁻, *m/z* 1077 (M−H-146-146-162(⁻ and *m/z* 915 (M−H-146-146-162-162(⁻, corresponding to the subsequent loss of two deoxyhexose and two hexose units.

Of the 76 carbons in the ^{13}C NMR spectrum (pyridine-D_5), 30 were assigned to the triterpenoid skeleton, 30 to the oligosaccharide moiety and the remaining 16 to two acyl groups.

Among the 30 carbons of the triterpene skeleton in the ^{13}C NMR spectrum, seven were assigned to the methyl carbons at δ 28.05, 16.62, 16.37, 18.61, 19.61, 29.80 and 20.60 ppm, and the corresponding methyl protons were identified by an HSQC experiment. Five methine carbons bearing oxygen were found at δ 89.91, 68.33, 80.80, 73.44 and 96.78 ppm.

Keywords: *Maesa balansae*; Myrsinaceae; leaves, isolation; structure elucidation; triterpene saponins; *anti*-leishmanial activity.
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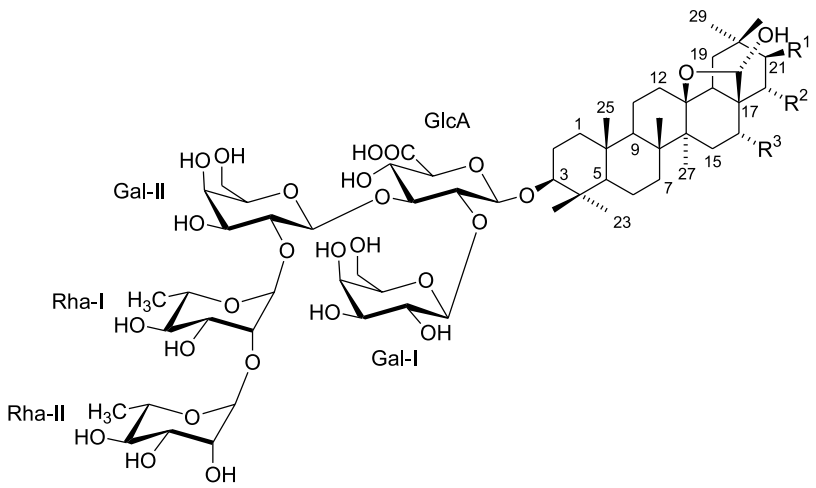

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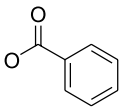
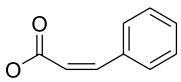
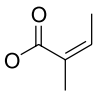
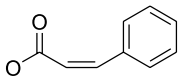
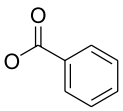
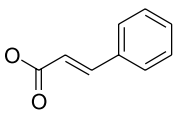
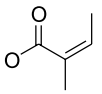
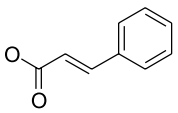
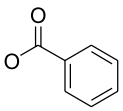
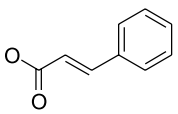
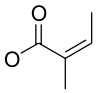
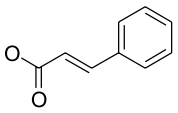
1			OH
2			OH
3			OH
4			OH
5			OAc
6			OAc

Figure 1. Saponins from the leaves of *Maesa balansae*.

The structural assignment was initiated from the long-range coupling networks observed between the methyl protons and the adjacent carbons from the HMBC experiment. Extensive NMR analysis (see Tables 1 and 2) showed that the aglycone was of an oleanane skeleton with an oxygen bridge between C-13 (δ 87.41) and C-28 (δ 96.78). This was also confirmed by comparison of the NMR data with known spectral data for structurally related compounds.[6–9] Besides the two hydroxyls at C-3 and C-28, three other hydroxyl groups were located at C-16, C-21 and C-22. The configuration was determined using the NOE information from a phase-sensitive NOESY experiment. The spatial proximity observed between H-3 and H-23, H-3 and H-5, H-16 and H-26, H-16 and H-28 indicated the β-orientation of the hydroxyl at C-3 and the α-orientation at C-16. The NOEs observed between H-22 and H-18, H-22 and H-30, between H-21 and H-29, between H-28 and H-26 and between H-28 and H-16 indicated the α-orientation of the hydroxyl group at C-22 and C-28, and the β-orientation of the hydroxyl group at C-21.

The two acyl groups, mapped out from COSY and HSQC correlations, were identified as (*Z*)-cinnamoyl and benzoyl. The (*Z*)-cinnamoyl group was attached to C-22 as established from the long-range HMBC coupling (Fig. 2) between H-22 (δ 6.57, d, J=9.9 Hz) and C_c-1 (δ 165.42) of the acyl group, H_c-2 (δ 5.84, d, J=12.8 Hz) and H_c-3 (δ 6.71, d, J=12.8 Hz) of the cinnamoyl group and C_c-1 of the acyl group and confirmed by the lowfield signal of H-22. The *cis*-configuration of the cinnamoyl group was determined from the coupling constant (12.8 Hz) between the olefinic protons H_c-2 and H_c-3. The long-range HMBC coupling between H-21 (δ 6.96, d, J=9.9 Hz) and C_b-1 (δ 166.78) of the acyl group, H_b-3 and H_b-7 (δ 8.36, d, J=7.6 Hz) of the benzoyl group and C_b-1 of the acyl group was in agreement with benzoyl substitution at C-21

Table 1. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and HMBC spectral data of the aglycone part of maesabalide I (**1**) in pyridine-D_5[a]

Position	^{1}H (mult; *J* Hz)	^{13}C[b]	^{1}H–^{1}H COSY	HMBC[c]
1	A: 1.51 m	39.16	H1b	H25
	B: 0.77 m		H1a	
2	A: 2.19 m	26.59	H2b, H3	
	B: 1.80 m		H2a, H3	
3	3.27 brd *J*=10.8 Hz	89.91	H2a, H2b	H23, H24
4		39.86		H23, H24
5	0.73 d *J*=9.6 Hz	55.65	H6a, H6b	H23, H24, H25
6	A: 1.39 m	17.99	H5	H7
	B: 1.55 m		H5	
7	A: 1.60 m	34.38		H26
	B: 1.27 m			
8		42.65		H11, H26, H27
9	1.29 m	50.23		H25, H26
10		36.80		H25
11	A: 1.72 m	19.21	H11b	
	B: 1.45 m		H11a	
12	A: 2.16 m	33.30	H12b	
	B: 1.67 m		H12a	
13		87.41		H27, H28
14		43.76		H16, H26, H27
15	A: 2.12 m	36.39	H15b, H16	H27
	B: 1.63 m		H15a	
16	4.61 m	68.33	H15a	H22, H28
17		54.53		H22, H28
18	2.46 brd *J*=14.3 Hz	46.35	H19a	H28
19	A: 3.18 m	38.12	H19b, H18	
	B: 1.57 m		H19a	
20		37.88		H29, H30
21	6.96 d *J*=9.9 Hz	80.80	H22	H22, H29, H30
22	6.57 d *J*=9.9 Hz	73.45	H21	H21
23	1.29s	28.05		H24
24	1.20s	16.61		H23
25	0.84s	16.37		H26
26	1.35s	18.61		
27	1.65s	19.61		
28	5.20s	96.78		
29	1.18s	29.80		H30
30	1.35s	20.60		H29
Benzoyl				
1b		166.78		H21, H3b, H4b, H6b,H7b
2b		131.35		H4b, H6b
3b	8.36 d *J*=7.6 Hz	130.23	H4b	H7b
4b	7.43 m	128.84	H3b, H5b	H6b
5b	7.52 m	133.16	H4b, H6b	H3b, H7b
6b	7.43 m	128.84	H5b, H7b	H4b
7b	8.36 d *J*=7.6 Hz	130.23	H6b	H3b
Cinnamoyl				
1c		165.42		H22, H2c, H3c
2c	5.84 d *J*=12.8 Hz	120.19	H3c	
3c	6.71 d *J*=12.8 Hz	142.55	H2c	H22, H2c, H5c, H9c
4c		135.20		H2c, H6c, H8c
5c	7.52 d *J*=7.4 Hz	130.29	H6c	H2c, H3c, H6c, H7c, H8c, H9c
6c	7.18 m	128.56	H5c, H7c	H8c
7c	7.25 m	129.11	H6c, H8c	H5c, H9c
8c	7.18 m	128.56	H7c, H9c	H6c
9c	7.52 d *J*=7.4 Hz	130.29	H8c	H2c, H3c, H5c, H6c, H7c, H8c

[a] Chemical shift values are in parts per million relative to TMS. Spectra were recorded at room temperature.
[b] ^{13}C NMR multiplicities were obtained by attached proton test (APT) sequences.
[c] Protons correlated to carbon resonances in the ^{13}C column.

(Fig. 2). This fact was also confirmed by the lowfield signal of H-21.

Structural information about the basic aglycone came also from the spectral data of the aglycone **7** obtained from acid hydrolysis (Scheme 1), in which the original 13β,28 ether bridge in **1** was broken, leading to the formation of a double bond between C-12 (δ_c=125.51, δ_H=5.48, 1H, t, *J*=3.8 Hz) and C-13 (δ_c=140.56) and an aldehyde group at C-28 (δ_c=201.48, δ_H=9.24).

Moreover, the presence of five sugar moieties was evidenced by the ^{1}H and ^{13}C NMR spectra which displayed five anomeric protons at δ 4.98 (d, *J*=5.56 Hz), 5.73 (d, *J*=6.8 Hz), 6.01 (s), 6.12 (d, *J*=7.07 Hz) and 6.17 (s) and carbons at δ 105.27, 103.62, 103.48, 101.28 and 101.37,

Table 2. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and HMBC spectral data of the carbohydrate part of maesabalide I (**1**) in pyridine-D_5[a]

Position	^{1}H (mult; *J* Hz)	^{13}C[b]	^{1}H–^{1}H COSY	HMBC[c]
GlcA				
1′	4.98 d *J*=5.6 Hz	105.27	H2′	H3, H2′, H5′
2′	4.73 m	79.85	H1′, H3′	H1″, H3′
3′	4.75 m	82.97	H2′, H4′	H1‴, H2′, H5′
4′	4.67 m	71.14		H2′, H3′, H4′
5′	4.58 m	77.11		
6′		172.50		H5′
Gal-I				
1″	5.73 d *J*=6.8 Hz	103.62	H2″	H2″
2″	4.52 m	73.45	H1″, H3″	
3″	4.29 m	75.15		H4″
4″	4.44 m	70.16		
5″	4.39 m	76.81		
6″	a: 4.53 m	62.79		H5″
	b: 4.34 m			
Gal-II		101.28		
1‴	6.12 d *J*=7.1 Hz	77.00	H2‴	
2‴	4.66 m	75.84	H1‴, H3‴	H1⁗
3‴	4.49 m	71.14		H2‴
4‴	4.47 m	76.92		H6‴
5‴	4.24 m	61.98		
6‴	4.33 m			H5‴
Rha-I		101.37		
1⁗	6.17 brs	78.01	H2⁗	H2‴
2⁗	4.87 m	72.64	H⁗, H3⁗	H1⁗
3⁗	4.75 m	74.14	H2⁗, H4⁗	H4⁗
4⁗	4.15 t *J*=9.0 Hz	69.70	H3⁗, H5⁗	H2⁗ H3⁗, H5⁗, H6⁗
5⁗	4.84 m	18.22	H4⁗, H6⁗	H1⁗, H4⁗
6⁗	1.43 d *J*=5.3 Hz		H5⁗	H4⁗
Rha-II		103.48		
1⁗′	6.01 brs	72.14	H2⁗′	H2⁗′
2⁗′	4.77 m	72.64	H1⁗′, H3⁗′	
3⁗′	4.54 m	74.14	H2⁗′, H4⁗′	H4⁗′
4⁗′	4.25 t *J*=8.8 Hz	70.16	H3⁗′, H5⁗′	H2⁗′, H6⁗′
5⁗′	4.56 m	18.48	H4⁗′, H6⁗′	H1⁗′, H4⁗′
6⁗′	1.67 d *J*=5.7 Hz		H5⁗′	H4⁗′

[a] Chemical shift values are in parts per million relative to TMS. Spectra were recorded at room temperature.
[b] ^{13}C NMR multiplicities were obtained by attached proton test (APT) sequences.
[c] [c]Protons correlated to carbon resonances in the ^{13}C column.

respectively. The low field chemical shift of C-3 (δ 79.32 for **7** to 89.91 for **1**) indicated that the pentasaccharide chain was connected to this position. This observation was confirmed by the long-range correlation between the anomeric carbon of glucuronic acid and H-3. The complete sequence of pentasaccharide side chain was determined by a combination of DQFCOSY, TOCSY, DEPT, HSQC and HMBC. Starting from the anomeric protons of each sugar unit, all the hydrogens within each spin system were assigned by DQFCOSY and TOCSY. On the basis of the

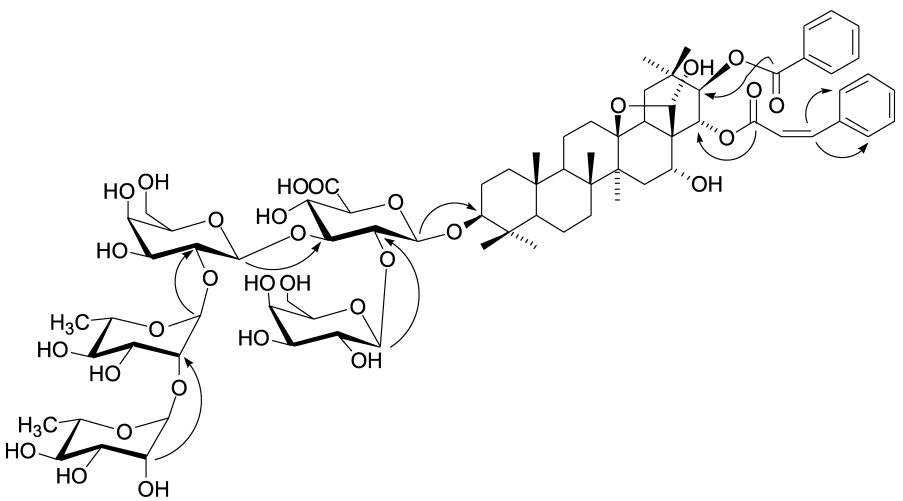
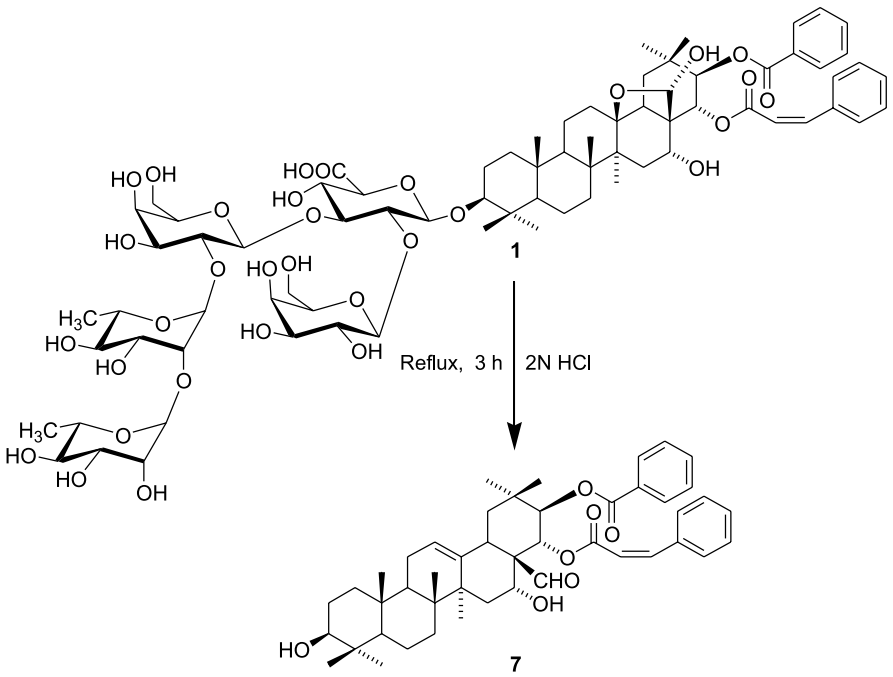


Figure 2. Characteristic long-range ^{13}C–^{1}H correlations observed in a HMBC experiment for maesabalide I (**1**) (pyridine-D_5).



Scheme 1.

assigned protons, the ^{13}C NMR resonances of each sugar unit were identified by HSQC and further confirmed by HMBC. HPTLC and HPLC of the acid hydrolysate of **1** in comparison with reference sugars, mass spectral data, NMR data of related structures[9,10] and applying the rule of Klyne[11] lead to the identification of the five monosaccharide units as β-D-glucuronic acid, β-D-galactose (×2) and α-L-rhamnose (×2). The inter-sugar linkages were established from the following HMBC correlations: H-1 of the terminal rhamnose with C-2 of rhamnose, H-1 of rhamnose with C-2 of galactose, H-1 of galactose with C-3 of glucuronic acid and H-1 of the terminal galactose with C-2 of glucuronic acid. The sugar sequence was also supported from the fragmentation patterns observed in the negative-ion FAB-MS spectra.

The β-anomeric configurations for the galactose and glucuronic acid were based on their $J_{H1,H2}$ coupling constants (5.5–8 Hz). The ^1H NMR nonsplitting pattern and the three-bond strong HMBC correlations from the anomeric proton to C-3 and C-5 (the dihedral angles between H-1 and C-3, H-1 and C-5 are about 180°), indicating the anomeric proton was equatorial, thus possessed an α-configuration. Further evidence for the α-configuration of the rhamnose residues came from the chemical shift of rhamnose C-3 (δ=72.64) and rhamnose C-5 (δ=69.70 and 70.16) in the ^{13}C NMR spectrum in comparison with ^{13}C NMR chemical shift data of the reference compounds β-L-rhamnopyranoside (C-3, δ=75.4; C-5, δ=73.5) and α-L-rhamnopyranoside (C-3, δ=72.5; C-5, δ=69.4).[12] Based upon the above evidence, maesabalide I (**1**) is established as 3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-21β-benzoyloxy-22α-(*Z*)-cinnamoyloxy-13β,28-oxidoolean-16α, 28α-diol (**1**).

Maesabalide II (**2**), an amorphous solid, had a molecular formula of $C_{74}H_{110}O_{32}$, determined from the negative FAB-MS (*m/z* 1509) and ^{13}C DEPT NMR data. ^1H and ^{13}C NMR spectra (see Tables 3–6) indicated that compound **2** had the same sugar arrangement as that of saponin **1** but differed in the acyl group linked to C-21 of the aglycone. NMR analysis established the acyl group linked to C-21 to be angeloyl ((*E*)-2-methyl-2butenoyl(. Signals characteristic for the angeloyl group occurred at δ 5.93 (br q, 1H, *J*=7.2 Hz, H-3), 2.09 (br d, 3H, *J*=7.2 Hz, H-4) and 2.02 (br s, 3H, H-5) in ^1H NMR (pyridine-D_5), and at δ 167.83 (C-1), 128.87 (C-2), 137.53 (C-3), 15.94 (C-4) and 21.02 (C-5) in ^{13}C NMR (pyridine-D_5). The site of esterification was evident from the long-range HMBC correlation between the carbonyl group of angelic acid and H-21 and the lowfield signal of H-21. The structure of saponin **2** was established as 3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-21β-angeloyloxy-22α-(*Z*)-cinnamoyloxy-13β,28-oxidoolean-16α, 28α-diol.

Maesabalide III (**3**) was obtained as a white amorphous powder. The negative-ion FABMS showed a (M−H (⁻ anion at *m/z* 1531. The molecular formula was established as $C_{76}H_{108}O_{32}$ on the basis of ^{13}C DEPT NMR and MS data. The ^1H and ^{13}C NMR spectra (see Tables 3–6) indicated that saponin **3** had the same sugar chain and aglycone moiety as **1**, but differed only in the (*E*)-cinnamoyl group linked to C-22 of the E-ring instead of the (*Z*)-cinnamoyl group in **1**. The *trans*-configuration was determined from the coupling constant (16.0 Hz) between the olefinic protons and the lowfield shift of the olefinic protons δ 6.39 (d, 1H, *J*=16.0 Hz, H_c-2) and δ 7.67 (d, 1H, *J*=16.0 Hz, H_c-3) in the ^1H NMR spectrum. From the above evidence the structure of **3** was elucidated as

Table 3. ^{1}H NMR data (400 MHz, *J* values in hertz) for the aglycone part of maesabalides I–VI (**1**–**6**) (pyridine-D_5) and for the semi-synthetic aglycone (**7**) ($CDCl_3$)

H	1	2	3	4	5	6	7
1	a: 1.51 m	a: 1.49 m	a: 1.52 m	a: 1.50 m	a: 1.48 m	a: 1.44 m	1.64 m
	b: 0.77 m	b: 0.79 m	b: 0.79 m	b: 0.79 m	b: 0.73 m	b: 0.74 m	0.99 m
2	a: 2.19 m	a: 2.16 m	a: 2.19 m	a: 2.16 m	a: 2.14 m	a: 2.13 m	1.60 m
	b: 1.80 m	b: 1.77 m	b: 1.80 m	b: 1.78 m	b: 1.75 m	b: 1.74 m	
3	3.27 brd *J*=10.8 Hz	3.24 brd *J*=11.6 Hz	3.26 brd *J*=12.4 Hz	3.24 brd *J*=11.2 Hz	3.19 brd *J*=11.1 Hz	3.18 brd *J*=11.4 Hz	3.23 brd *J*=11.0 Hz
4							
5	0.73 d *J*=9.6 Hz	0.71 d *J*=11.0 Hz	0.73 d *J*=11.2 Hz	0.71 d *J*=11.7 Hz	0.66 d *J*=8.4 Hz	0.65 d *J*=9.2 Hz	0.72 d *J*=11.8 Hz
6	a: 1.39 m	a: 1.39 m	a: 1.38 m	a: 1.34 m	a: 1.30 m	a: 1.30 m	1.33 m
	b: 1.55 m	b: 1.53 m	b: 1.53 m	b: 1.52 m	b: 1.52 m	b: 1.48 m	1.56 m
7	a: 1.60 m	a: 1.59 m	a: 1.60 m	a: 1.54 m	a: 1.32 m	a: 1.31 m	1.52 m
	b: 1.27 m	b: 1.23 m	b: 1.27 m	b: 1.28 m	b: 1.08 m	b: 1.05 m	1.30 m
8							
9	1.29 m	1.25 m	1.30 m	1.28 m	1.18 m	1.22 m	1.57 m
10							
11	a: 1.72 m	a: 1.71 m	a: 1.75 m	a: 1.73 m	a: 1.63 m	a: 1.73 m	1.89 m
	b: 1.45 m	b: 1.42 m	b: 1.48 m	b: 1.43 m	b: 1.41 m	b: 1.44 m	
12	a: 2.16 m	a: 2.12 m	a: 2.17 m	a: 2.14 m	a: 2.09 m	a: 2.05 m	5.48 t *J*=3.8 Hz
	b: 1.67 m	b: 1.61 m	b: 1.70 m	b: 1.64 m	b: 1.63 m	b: 1.57 m	
13							
14							
15	a: 2.12 m	a: 2.14 m	a: 2.23 m	a: 2.20 m	a: 2.23 m	a: 2.20 m	1.87 m
	b: 1.63 m	b: 1.61 m	b: 1.70 m	b: 1.68 m	b: 1.49 m	b: 1.48 m	1.37 m
16	4.61 m	4.57 m	4.83 m	4.77 m	5.97 m	5.92 m	4.50 m
17							
18	2.46 brd *J*=14.3 Hz	2.38 brd *J*=14.7 Hz	2.49 brd *J*=14.5 Hz	2.42 brd *J*=16.0 Hz	2.52 brd *J*=14.0 Hz	2.45 brd *J*=14.4 Hz	2.85 brd *J*=14.1 Hz
19	a: 3.18 m	a: 3.12 m	a: 3.20 m	a: 3.14 m	a: 2.80 m	a: 2.67 m	2.67 m
	b: 1.57 m	b: 1.51 m	b: 1.60 m	b: 1.55 m	b: 1.65 m	b: 1.60 m	1.36 m
20							
21	6.96 d *J*=9.9 Hz	6.79 d *J*=10.1 Hz	7.04 d *J*=9.8 Hz	6.86 d *J*=10.0 Hz	6.24 d *J*=10.1 Hz	6.07 d *J*=10.2 Hz	5.90 d *J*=10.1 Hz
22	6.57 d *J*=9.9 Hz	6.41 d *J*=10.1 Hz	6.60 d *J*=9.8 Hz	6.43 d *J*=10.0 Hz	6.58 d *J*=10.1 Hz	6.42 d *J*=10.2 Hz	5.51 d *J*=10.1 Hz
23	1.29s	1.27s	1.29s	1.27s	1.26s	1.25s	1.00s
24	1.20s	1.17s	1.18s	1.16s	1.16s	1.15s	0.78s
25	0.84s	0.82s	0.83s	0.81s	0.78s	0.77s	0.90s
26	1.35s	1.33s	1.36s	1.34s	1.26s	1.25s	0.66s
27	1.65s	1.61s	1.67s	1.64s	1.38s	1.35s	1.41s
28	5.20s	5.16s	5.26s	5.21s	5.32s	5.29s	9.24s
29	1.18s	1.15s	1.21s	1.18s	1.16s	1.15s	0.98s
30	1.35s	1.27s	1.37s	1.28s	1.34s	1.25s	1.21s
Acyl (C-16)							
1							
2					2.66s	2.61s	
Acyl (C-21)							
1							
2							
3	8.36 d *J*=7.6 Hz	5.93 q, overlap	8.36 d *J*=7.2 Hz	5.93 q *J*=7.3 Hz	8.30 d *J*=7.7 Hz	5.92 q *J*=7.3 Hz	8.01 d *J*=7.0 Hz
4	7.43 m	2.09 d *J*=7.2 Hz	7.40 m	2.09 d *J*=7.3 Hz	7.40 m	1.98 d *J*=7.3 Hz	7.39 m
5	7.52 m	2.02s	7.45 m	2.02s	7.47 m	1.99s	7.52 m
6	7.43 m		7.40 m		7.40 m		7.39 m
7	8.36 d *J*=7.6 Hz		8.36 d *J*=7.2 Hz		8.30 d *J*=7.7 Hz		8.01 d *J*=7.0 Hz
Acyl (C-22)							
1							
2	5.84 d *J*=12.8 Hz	5.93 d *J*=12.8 Hz	6.39 d *J*=16.0 Hz	5.93 d *J*=16.0 Hz	6.50 d *J*=16.1 Hz	6.68 d *J*=16.1 Hz	5.75 d *J*=12.5 Hz
3	6.71 d *J*=12.8 Hz	6.83 d *J*=12.8 Hz	7.67 d *J*=16.0 Hz	6.83 d *J*=16.0 Hz	7.91 d *J*=16.1 Hz	8.03 d *J*=16.1 Hz	6.86 d *J*=12.5 Hz
4							
5	7.52 d *J*=7.4 Hz	7.79 d *J*=8.1 Hz	7.24 m	7.79 m	7.25 d *J*=7.0 Hz	7.32 m	7.27–7.23 m
6	7.18 m	7.32 m	7.15 m	7.32 m	7.47 m	7.61 m	7.27–7.23 m
7	7.25 m	7.32 m	7.27 m	7.32 m	7.48 m	7.32 m	7.27–7.23 m
8	7.18 m	7.32 m	7.15 m	7.32 m	7.47 m	7.61 m	7.27–7.23 m
9	7.52 d *J*=7.4 Hz	7.79 d *J*=8.1 Hz	7.24 m	7.79 m	7.25 d *J*=7.0 Hz	7.32 m	7.27–7.23 m

3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-21β-benzoyloxy-22α-(*E*)-cinnamoyloxy-13β,28-oxidoolean-16α, 28α-diol.

Maesabalide IV (**4**), a white amorphous powder, had a molecular formula of $C_{74}H_{110}O_{32}$, determined from the negative-ion FAB-MS and ^{13}C DEPT data. As for saponin **3**, compound **4** was an isomer of saponin **2** and differed only in the (*E*)-cinnamoyl group linked to C-22 instead of the (*Z*)-cinnamoyl group in saponin **2** (see Tables 3–6). The *trans*-configuration was again determined from the coupling constant (16.0 Hz) between the olefinic protons and the lowfield shift of the olefinic protons δ 6.50 (d, 1H,

Table 4. ^{1}H NMR data (400 MHz, *J* values in hertz) of the carbohydrate part of maesabalides I–VI (**1**–**6**) in pyridine-D_5

H	1	2	3	4	5	6
GlcA						
1	4.98 d *J*=5.6 Hz	4.97 d *J*=5.6 Hz	4.99 d *J*=5.8 Hz	4.97 d *J*=6.7 Hz	4.95 d *J*=5.9 Hz	4.95 d *J*=5.9 Hz
2	4.73 m	4.73 m	4.74 m	4.72 m	4.75 m	4.74 m
3	4.75 m	4.74 m	4.75 m	4.74 m	4.76 m	4.75 m
4	4.67 m	4.68 m	4.71 m	4.67 m	4.70 m	4.71 m
5	4.58 m	4.57 m	4.59 m	4.57 m	4.57 m	4.60 m
6						
Gal-I						
1	5.73 d *J*=6.8 Hz	5.73 d *J*=7.4 Hz	5.73 d *J*=7.3 Hz	5.72 d *J*=7.0 Hz	5.74 d *J*=6.6 Hz	5.74 d *J*=7.3 Hz
2	4.52 m	4.52 m	4.53 m	4.50 m	4.53 m	4.50 m
3	4.29 m	4.30 m	4.31 m	4.28 m	4.30 m	4.31 m
4	4.44 m	4.41 m	4.42 m	4.40 m	4.37 m	4.39 m
5	4.39 m	4.43 m	4.43 m	4.43 m	4.40 m	4.41 m
6	a: 4.53 m b: 4.34 m	a: 4.55 m b: 4.31 m	a: 4.56 m b: 4.35 m	a: 4.53 m b: 4.31 m	a: 4.57 m b: 4.33 m	a: 4.54 m b: 4.32 m
Gal-II						
1	6.12 d *J*=7.1 Hz	6.09 d *J*=7.7 Hz	6.09 d *J*=7.3 Hz	6.09 d *J*=7.3 Hz	6.13 d *J*=7.3 Hz	6.12 d *J*=7.8 Hz
2	4.66 m	4.66 m	4.66 m	4.65 m	4.67 m	4.67 m
3	4.49 m	4.52 m	4.51 m	4.48 m	4.51 m	4.50 m
4	4.47 m	4.48 m	4.45 m	4.46 m	4.48 m	4.48 m
5	4.24 m	4.23 m	4.31 m	4.22 m	4.25 m	4.26 m
6	4.33 m	4.33 m	4.33 m	4.33 m	4.35 m	4.36 m
Rha-I						
1	6.17 brs	6.17 brs	6.17 brs	6.16 brs	6.18 brs	6.19 brs
2	4.87 m	4.87 m	4.87 m	4.86 m	4.88 m	4.88 m
3	4.75 m	4.76 m	4.76 m	4.75 m	4.76 m	4.76 m
4	4.15 t *J*=9.0 Hz	4.16 t *J*=9.2 Hz	4.15 t *J*=9.2 Hz	4.15 t *J*=9.3 Hz	4.16 t *J*=9.2 Hz	4.16 m
5	4.84 m	4.84 m	4.83 m	4.83 m	4.86 m	4.86 m
6	1.43 d *J*=5.3 Hz	1.45 d *J*=6.1 Hz	1.44 d *J*=5.5 Hz	1.44 d *J*=5.9 Hz	1.44 d *J*=5.6 Hz	1.45 m
Rha-II						
1	6.01 brs	6.02 brs	6.01 brs	6.01 brs	6.02 brs	6.02 brs
2	4.77 m	4.78 m	4.77 m	4.77 m	4.77 m	4.77 m
3	4.54 m	4.55 m	4.56 m	4.55 m	4.55 m	4.56 m
4	4.25 t *J*=8.8 Hz	4.26 t *J*=9.5 Hz	4.26 d *J*=9.9 Hz	4.25 t *J*=9.3 Hz	4.28 t *J*=8.7 Hz	4.26 m
5	4.56 m	4.55 m	4.57 m	4.53 m	4.55 m	4.53 m
6	1.67 d *J*=5.7 Hz	1.68 d *J*=6.1 Hz	1.68 d *J*=6.1 Hz	1.67 d *J*=6.1 Hz	1.68 d *J*=5.6 Hz	1.69 m

J=16.0 Hz, H_c-2) and δ 7.84 (d, 1H, *J*=16.0 Hz, H_c-3). The structure of saponin **4** was determined as 3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-21β-angeloyloxy-22α-(*E*)-cinnamoyloxy-13β,28-oxidoolean-16α, 28α-diol.

Maesabalide V (**5**), an amorphous solid, had a molecular formula of $C_{78}H_{110}O_{33}$ and a molecular weight of 1574, determined from the negative-ion FAB-MS and the ^{13}C DEPT NMR data. ^{1}H and ^{13}C NMR studies (see Tables 3–6) indicated that compound **5** had the same sugar arrangement as that of saponin **1** and the same esters linked to C-21 and C-22 as compound **3** and one acetyl group linked to C-16. Evidence for this fact was found in the extra methyl group (δ_H=2.66, δ_C=22.18) and the ester signal (δ_C=170.12) and in the long-range HMBC coupling of C-1 of the acetyl to H-16. Also the downfield shift of H-16 to δ 5.97 (δ 4.61 for **1**) and C-16 to δ 71.28 (δ 68.33 for **1**) supported this conclusion. From the above evidence, the structure of saponin **5** was established as 3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-16α-acetoxy -21β-benzoyloxy-22α-(*E*)-cinnamoyloxy-13β,28-oxidoolean-28α-ol.

Maesabalide VI (**6**), an amorphous solid as well, had a molecular formula of $C_{76}H_{112}O_{33}$, and a molecular weight of 1552, determined from the negative-ion FAB-MS and the ^{13}C DEPT NMR data. ^{1}H and ^{13}C NMR studies (see Tables 3–6) indicated that compound **6** had the same sugar arrangement of that of saponin **1** and the same ester functions positioned at C-21 and C-22 as compound **4** and one acetoxy group linked to C-16 as in compound **5**. The structure of **6** was established as 3-β-*O*-{[(α-L-rhamnopyranosyl (1→2)-α-L-rhamnopyranosyl (1→2)-β-D-galactopyranosyl (1→3)]-[β-D-galactopyranosyl (1→2)]-β-D-glucuronopyranosyl}-16α-acetoxy-21β-angeloyloxy-22α-(*E*)-cinnamoyloxy-13β,28-oxidoolean-28α-ol.

The isolated saponins were tested against *Leishmania infantum* amastigotes (in vitro). Compounds **3** and **4** showed the highest activity (IC_{50}: 20 ng/mL, 0.013 nM) followed by compound **2** (IC_{50}: 50 ng/mL, 0.033 nM), compound **1** (IC_{50}: 70 ng/mL, 0.046 nM), compound **6** (IC_{50}: 700 ng/mL, 0.45 nM) and compound **5** (IC_{50}: 3400 ng/mL 2.16 nM). In comparison, Pentostam® (sodium stibogluconate), which is currently used as first line drug for the treatment of leishmaniasis[13] had an IC_{50} of 6 μg/mL (8.1 nM), which is 300 times less active than compounds **3** and **4**. In conclusion, extremely potent *anti*-leishmanial

Table 5. ^{13}C NMR data (100 MHz) of the aglycone part of maesabalides I–VI (**1**–**6**) (pyridine-D_5) and for the semi-synthetic aglycone ($CDCl_3$) (**7**)

C	1	2	3	4	5	6	7
1	39.16	39.17	39.18	39.14	39.12	39.09	38.91
2	26.59	26.57	26.57	26.53	26.56	26.56	27.55
3	89.91	89.87	89.84	89.87	89.86	89.83	79.32
4	39.86	39.85	39.86	39.81	39.84	39.83	39.15
5	55.65	55.68	55.67	55.62	55.60	55.57	55.56
6	17.99	18.00	18.01	17.95	17.85	17.82	18.63
7	34.38	34.41	34.43	34.39	34.26	34.25	33.28
8	42.65	42.66	42.68	42.63	42.63	42.60	40.07
9	50.23	50.26	50.26	50.22	50.28	50.27	46.92
10	36.80	36.81	36.82	36.77	36.77	36.75	37.34
11	19.21	19.22	19.24	19.18	19.08	19.05	23.82
12	33.30	33.61	33.33	33.29	33.11	33.10	125.51
13	87.41	87.35	87.37	87.27	86.68	86.61	140.56
14	43.76	43.77	43.80	43.75	43.19	43.17	41.76
15	36.39	36.42	36.49	36.43	33.22	33.19	34.25
16	68.33	68.32	68.50	68.45	71.28	71.24	67.86
17	54.53	54.53	54.76	54.66	53.83	53.74	57.42
18	46.35	46.35	46.27	46.19	45.42	45.39	40.42
19	38.12	38.12	38.15	38.09	37.96	37.92	46.52
20	37.88	37.55	37.85	37.44	37.60	37.25	36.51
21	80.80	79.42	80.84	79.39	79.97	78.59	77.67
22	73.45	73.70	73.92	74.02	72.19	72.33	70.07
23	28.05	28.10	28.10	28.03	28.00	27.99	28.50
24	16.61	16.64	16.63	16.58	16.56	16.55	16.01
25	16.37	16.39	16.39	16.34	16.33	16.32	15.78
26	18.61	18.62	18.64	18.59	18.45	18.44	17.50
27	19.61	19.56	19.61	19.53	19.68	19.62	27.27
28	96.78	96.83	96.88	96.87	96.06	96.05	201.48
29	29.80	29.78	29.82	29.73	29.77	29.74	29.50
30	20.60	20.77	20.62	20.68	20.07	20.22	20.04
Acyl (C-16)							
1					170.12	170.09	
2					22.18	22.16	
Acyl (C-21)							
1	166.78	167.83	166.91	167.96	166.93	167.90	166.75
2	131.35	128.87	131.45	128.97	130.84	128.25	130.36
3	130.23	137.53	130.15	136.94	130.16	138.13	130.14
4	128.84	15.94	128.79	15.81	128.90	15.95	128.79
5	133.16	21.02	133.09	20.94	133.41	20.92	133.39
6	128.84		128.79		128.90		128.79
7	130.23		130.15		130.16		130.14
Acyl (C-22)							
1	165.42	165.46	166.19	166.14	165.43	165.42	165.20
2	120.19	120.48	119.14	119.32	118.39	118.63	119.12
3	142.55	142.32	144.48	144.52	145.36	145.43	145.64
4	135.20	135.43	134.73	134.87	134.84	135.01	135.30
5	130.29	130.58	129.03	129.13	129.15	129.27	129.76
6	128.56	128.37	128.24	128.27	128.54	128.38	128.26
7	129.11	129.35	130.41	130.47	130.56	130.61	129.19
8	128.56	128.37	128.24	128.27	128.54	128.38	128.26
9	130.29	130.58	129.03	129.13	129.15	129.27	129.76

Table 6. ^{13}C NMR data (100 MHz) of the carbohydrate part of maesabalides I–VI (**1**–**6**) in pyridine-D_5

C	1	2	3	4	5	6
GlcA						
1	105.27	105.26	105.24	105.22	105.37	105.38
2	79.85	79.86	79.87	79.81	79.84	79.85
3	82.97	83.12	83.14	83.00	83.08	83.15
4	71.14	71.20	71.12	71.13	71.16	71.12
5	77.11	77.11	77.14	77.02	77.19	77.28
6	172.50	172.59	172.44	172.47	172.50	172.31
Gal-I						
1	103.62	103.73	103.71	103.64	103.70	103.74
2	73.45	73.50	73.46	73.43	73.49	73.50
3	75.15	75.25	75.21	75.18	75.26	75.28
4	70.16	70.21	70.18	70.16	70.21	70.22
5	76.81	76.89	76.83	76.85	76.94	76.95
6	62.79	62.68	62.80	62.81	62.88	62.92
Gal-II						
1	101.28	101.43	101.40	101.36	101.42	101.42
2	77.00	77.11	77.06	77.02	77.09	77.06
3	75.84	75.89	75.87	75.82	75.88	75.91
4	71.14	71.20	71.12	71.13	71.16	71.12
5	76.92	76.89	76.92	76.85	76.94	77.00
6	61.98	61.94	61.93	61.92	61.97	61.94
Rha-I						
1	101.37	101.43	101.40	101.30	101.42	101.42
2	78.01	78.01	77.99	77.99	78.06	78.07
3	72.64	72.54	72.51	72.47	72.51	72.52
4	74.14	74.13	74.09	74.08	74.12	74.14
5	69.70	69.75	69.72	69.68	69.74	69.75
6	18.22	18.29	18.26	18.21	18.28	18.28
Rha-II						
1	103.48	103.54	103.50	103.48	103.54	103.56
2	72.14	72.21	72.17	72.14	72.19	72.21
3	72.64	72.70	72.67	72.64	72.69	72.71
4	74.14	74.21	74.17	74.14	74.19	74.21
5	70.16	70.21	70.18	70.16	70.21	70.22
6	18.48	18.53	18.50	18.46	18.52	18.52

saponins were isolated from the Vietnamese medicinal plant *Maesa balansae*. These compounds are now studied further in view of their high physiological activity and potential to be developed as drug.

3. Experimental

3.1. General experimental procedures

Preparative HPLC was performed on C18 BDS (Hypersil BDS, 8 μm, 200 g) using a column with axial compression (50 mm i.d., packed at 60 bars), gradient elution: water (0.5% m/v NH_4OAc)–methanol–acetonitrile (60:20:20) to (00:50:50) in 50 min; flow rate: 80 mL/min, UV detection (275 nm). TLC on the sugar fraction was carried out on silica HPTLC-plates (Merck, Si 50000 F_{254} s, 0.2 mm layer thickness, 10×10 cm) referenced towards standard monosaccharides. The eluent consisted of $CHCl_3$–MeOH–H_2O (6.4:4.0:0.8). After spraying with 1-naphthol/H_2SO_4 reagent and heating at 110 °C for about 10 min, the spots were visualised.

^1H, ^{13}C and 2D NMR spectra were recorded using a Bruker AVANCE-400 spectrometer. The NMR data of the saponins were measured in pyridine-D_5 and the NMR data for the semi-synthetic aglycone was recorded in $CDCl_3$. Chemical shifts were expressed in δ (ppm) referring to TMS. The negative-ion mode FAB-MS spectra (for the saponins) were recorded on a Micromass VG70SEQ instrument, with glycerol as liquid matrix. The positive-ion ES-MS spectra (for the aglycone) were recorded on a micromass ZMD spectrometer coupled to an Alliance (Waters) HPLC system. Optical rotations were determined on an AA-10 automatic polarimeter (Optical Active Ltd).

3.2. Plant material

Leaves of *Maesa balansae* were collected from Deo Khe,

Dai Tu district, Thai Nguyen province in Vietnam, and were identified by Dr Tran Ngoc Ninh (Institute of Ecology and Biological Resources, NCST, Hanoi, Vietnam). Voucher specimens are deposited at the herbarium of that institute.

3.3. Extraction and isolation

Dried leaves of *Maesa balansae* (3 kg) were extracted exhaustively with dichloromethane and subsequently with methanol. After evaporation, the methanol extract was partitioned between *n*-BuOH and water. The *n*-BuOH soluble fraction was evaporated to dryness. After stirring in acetone, the acetone insoluble fraction was dried to give the crude saponin mixture (100 g). Repeated RP-18 chromatography on 10 g saponin mixture, eluted with 0.5% w/v NH_4OAc in water–methanol–acetonitrile from 60:20:20 to 0:50:50 in 50 min afforded 8 fractions. Further semi-preparative HPLC on the same column using optimised chromatographic conditions afforded six chromatographically pure saponins: maesabalide I (**1**) (230 mg), maesabalide II (**2**) (110 mg), maesabalide III (**3**) (1000 mg), maesabalide IV (**4**) (1000 mg), maesabalide V (**5**) (220 mg) and maesabalide VI (**6**) (230 mg).

3.3.1. Maesabalide I (1). White amorphous powder; FABMS (negative ion mode) *m/z*: 1531 (M−H(⁻; IR (KBr): ν_{max} 3436, 2918, 1725, 1632, 1275, 1073 cm^{-1}; $[\alpha]_D^{18}=-30.5°$ (*c*=0.53, pyridine); λ_{max} 225.0 and 274.5 nm; ^1H NMR and ^{13}C NMR are listed in Tables 1–6. Elemental analysis C: 59.08%, H: 7.33% (calculated C: 59.52%, H: 7.10%).

3.3.2. Maesabalide II (2). White amorphous powder; FABMS (negative ion mode) *m/z*: 1509 (M−H(⁻; IR (KBr): ν_{max} 3368, 2934, 1715, 1628, 1013 cm^{-1}; $[\alpha]_D^{18}=-44.4°$ (*c*=0.59, pyridine); λ_{max} 222.7 and 273.3 nm; ^1H NMR and ^{13}C NMR are listed in Tables 3–6. Elemental analysis C: 58.09%, H: 7.53% (calculated C: 58.80%, H: 7.33%).

3.3.3. Maesabalide III (3). White amorphous powder; FABMS (negative ion mode) *m/z*: 1531 (M−H(⁻; IR (KBr): ν_{max} 3414, 2934, 1719, 1634, 1285, 1074 cm^{-1}; $[\alpha]_D^{18}=-50.4°$ (*c*=0.58, pyridine); λ_{max} 221.5 and 279.2 nm; ^1H NMR and ^{13}C NMR are listed in Tables 3–6. Elemental analysis C: 59.25%, H: 7.24% (calculated C: 59.52%, H: 7.10%).

3.3.4. Maesabalide IV (4). White amorphous powder; FABMS (negative ion mode) *m/z*: 1509 (M−H(⁻; IR (KBr): ν_{max} 3415, 2934, 1705, 1635, 1282, 1079 cm^{-1}; $[\alpha]_D^{18}=-45.3°$ (*c*=0.75, pyridine); λ_{max} 216.8 and 279.2 nm; ^1H NMR and ^{13}C NMR are listed in Tables 3–6. Elemental analysis C: 59.19%, H: 7.24% (calculated C: 58.80%, H: 7.33%).

3.3.5. Maesabalide V (5). White amorphous powder; FABMS (negative ion mode) *m/z*: 1573 (M−H(⁻; IR (KBr): ν_{max} 3438, 2927, 1723, 1636, 1275, 1075 cm^{-1}; $[\alpha]_D^{18}=-61.5°$ (*c*=0.59, pyridine); λ_{max} 222.7 and 278.0 nm; ^1H NMR and ^{13}C NMR are listed in Tables 3–6. Elemental analysis C: 59.42%, H: 7.18% (calculated C: 59.64%, H: 7.04%).

3.3.6. Maesabalide VI (6). White amorphous powder; FABMS (negative ion mode) *m/z*: 1551 (M−H(⁻; IR (KBr): ν_{max} 3385, 2935, 1719, 1635, 1268, 1044 cm^{-1}; $[\alpha]_D^{18}=-54.8°$ (*c*=0.68, pyridine); λ_{max} 221.5 and 278.0 nm; ^1H NMR and ^{13}C NMR are listed in Tables 3–6. Elemental analysis C: 59.03%, H: 7.12% (calculated C: 58.75%, H: 7.27%).

3.4. Acid hydrolysis

Compound **1** (100 mg) was dissolved in 10 mL 2N HCl solution (H_2O–MeOH 1:1) and the mixture was refluxed while stirring for 3 h. After evaporation of the methanol in vacuo, the solution was extracted with EtOAc (3×4 mL). The combined organic layers were washed with H_2O and then evaporated to dryness to give an amorphous powder, which was subjected to HPLC purification obtaining compound **7** (*m/z* 723 (M+H(⁺) (32 mg, 68%). Conditions: column Hypersil C18-BDS, 5 μm, 21.2×250 mm, 30 mL/min, H_2O–MeCN 20:80 to 100% MeCN in 30 min, UV detection at 275 nm. The H_2O layer was concentrated and compared with standard monosaccharides by silica gel TLC, using the mixture $CHCl_3$–MeOH–H_2O (6.4:4.0:0.8) and visualization by spraying with 1-naphthol-H_2SO_4. D-glucuronic acid, D-galactose and L-rhamnose were identified.

3.5. Analysis of the carbohydrate fraction by HPLC

The aqueous fraction obtained after acid hydrolysis of **1** was evaporated to dryness and resolubilized at 100 ppm in water. The chromatogram was compared with those of standard monosaccharides: D-glucose, D-galactose, L-rhamnose, L-arabinose, D-xylose, D-fucose, D-glucuronic acid and D-galacturonic acid injected at a concentration of 50 ppm. D-galactose (×2), D-glucuronic acid and L-rhamnose (×2) were identified after co-elution of the aqueous fraction with the corresponding standard monosaccharides. Conditions: pre-column: PA1 Guard, 10-32, column: CarboPac™ PA1, 10 μm, 250×4 mm, 1 mL/min, 25 μL loop (injection after 10 min), pulsed amperometric detector, solvent A: 100 mM NaOH, solvent B: 100 mM NaOH+0.7 M NaOAc, solvent C: 1 M NaOH, solvent D: H_2O. Linear gradient system: 0.0 min: 100% C, 2.9 min: 100% C, 3.0 min: A–D 5:95, 35.0 min: A–D 5:95, 45.0 min: A–B–D 20:20:60, 55.0 min: A–B 20:80.

3.6. Bioassays

A laboratory strain of *Leishmania infantum* (MHOM/MA(BE)/67), known to be sensitive to the available *anti*-leishmanial reference drug was used. The compounds for biological testing were prepared in 100% dimethyl sulphoxide at 4 concentrations (32–8–2–0.5 μM or μg/mL). Reference drug was sodium-stiboguconate (Pentostam®, GSK). The in vitro sensitivity of amastigotes to the test compounds was determined in primary mouse peritoneal macrophages. These macrophages were induced in mice by intraperitoneal administration of 2% potato starch and harvested about 24 h later in RPMI-1640 medium. Assays were performed in triplicate in 96-well tissue culture plates, each well containing the compound dilutions together with 3×10^4 macrophages and 3×10^5 parasites/well. After 5 days incubation at 37 °C, intracellular amastigote burdens were

microscopically assessed after Giemsa staining. The results are expressed as % reduction of parasite burden compared to untreated control wells. The IC_{50} was lower than 1 μg/mL or μM and no cytotoxicity against MRC-5 cells was observed. Therefore, the compounds were classified as highly active. A detailed account on the bioassays (in vitro and in vivo) will be reported in a medicinal chemistry journal.

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Gekreuzt konjugierte oligomere aus pyrrol-, benzol- und carbonyl-Bausteinen

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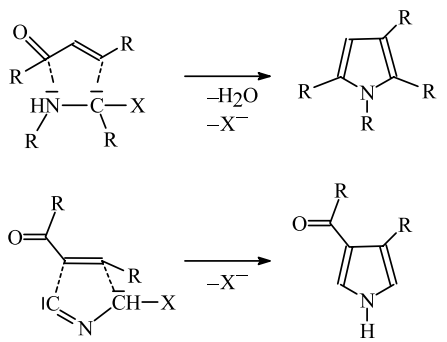
Abstract—Chalcones can serve as C_2 or C_3 components for the formation of 1*H*-pyrroles. In particular the reaction with tosylisocyanid could be applied to the oligochalcones **2d-g** with up to 6 enone units. A series of cross-conjugated oligomers **8d-g** was obtained; these compounds consist of a chain of 1,4-phenylene, carbonyl and 1*H*-pyrrole-3,4-diyl building blocks. The benzene rings bear two propoxy sidechains in order to enhance the solubility.

1. Einleitung

Oligomere aus Arylen- oder Hetarylen-Bausteinen stellen ein aktuelles Arbeitsgebiet in der organischen Synthese und der Materialwissenschaft dar.[1] Die konjugierte oder gekreuzt konjugierte Anordnung dieser Bausteine kann zu linearen, cyclischen, sternförmigen oder dendritischen Strukturen führen. Bei linearen Konjugation tritt in der Regel mit wachsender Zahl der Wiederholungseinheiten ein bathochromer und hyperchromer Effekt auf. Will man einen großen Absorptionsquerschnitt haben, aber dennoch nicht Banden im Vis/NIR-Gebiet, dann bietet sich eine gekreuzte Konjugation an. In den an den Elektronenübergängen beteiligten Orbitalen existieren in diesem Fall Knotenflächen, die den Konjugationseffekt stark schwächen oder ganz zum Erliegen bringen.

Vor einiger Zeit haben wir über gekreuzt konjugierte Oligo(chalkone) berichtet, die über Propoxyseitenketten verfügen und so eine gute Löslichkeit in organischen Solventien aufweisen.[2–4] Längere und vor allem verzweigte Alkoxyketten bewirken zwar eine noch bessere Solubilisierung, haben aber bei materialwissenschaftlichen Anwendungen, z. B. bei der Photoleitfähigkeit Nachteile.[5] Der wichtigste Anwendungsbereich ist auf dem Gebiet der nichtlinearen Optik.[6]

Die Enoneinheit der Chalkone repräsentiert ein bifunktionelles Elektrophil, das für den Aufbau von Heterocyclen hervorragend geeignet ist.[7,8] Damit kann auf einfache synthetische Weise ein neues materialwissenschaftlich interessantes Stoffgebiet erschlossen werden. Die vorliegende Arbeit befasst sich mit der Bildung von Pyrrolringen, wobei die Enoneinheit als C_3- oder als C_2-Komponente dienen kann (Schema 1).



Schema 1. Enone als C_3-Komponente (oben) oder als C_2-Komponente (unten) für die Herstellung von Pyrrolderivaten.

Für die C_3-Komponente benötigt man ein bifunktionelles Nucleophil, das eine NC-Komponente darstellt. Amine mit einer aciden CH-Bindung in α-Stellung kommen dafür in Frage. Die CH-Acidität sollte dabei von einer Gruppe X induziert werden, die gleichzeitig eine gute Abgangsgruppe ist.

Wenn die Enoneinheit als C_2-Komponente fungiert, dann braucht man zur Pyrrolbildung eine NCC- oder CNC-Komponente. Letzteres ist in Schema 1 mit einem Methylisocyanid veranschaulicht, das in α-Stellung eine acidifizierende Gruppe X enthält, die gleichzeitig wieder eine gute Abgangsgruppe ist.

Die Pyrrolring-Synthese sollte in beiden Fällen glatt und mit guten Ausbeuten verlaufen, um bei Oligochalkonen eingesetzt werden zu können.

Keywords: Cross-conjugation; Enones; Oligomers; Pyrrols.
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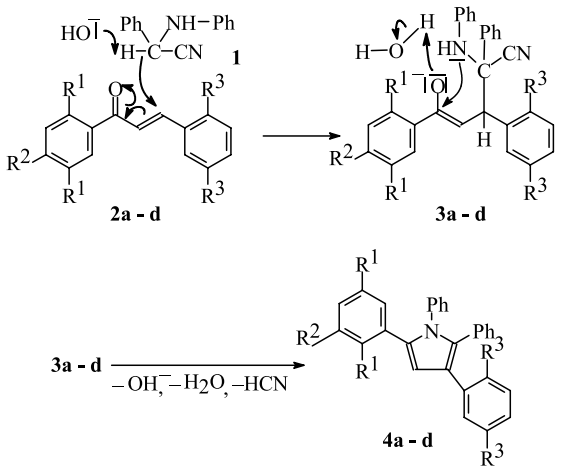
2. Ergebnisse und diskussion

Schon sehr früh wurde gefunden, dass sich α,β-ungesättigte Aldehyde, wie Zimtaldehyd, mit α-Arylamino-phenylacetonitril zu Pyrrolen umsetzen lassen.[9,10] Die Reaktion konnte später auf α,β-ungesättigte Ketone ausgedehnt werden.[11,12] Im alkalischen Medium greift α-Phenylamino-phenylacetonitril (**1**) am β-C-Atom der Chalkone **2** im Sinn einer Michael-Addition an. Die Cyclisierung des linearen Addukts **3** zu einem intermediären Pyrrolidin wird dann durch den Angriff eines Aminstickstoffatoms am Carbonylkohlenstoffatom vollzogen. Beide Schritte folgen dem Weich–Weich/Hart–Hart-Prinzip. Die Eliminierung von Wasser und Blausäure führt schließlich zum gewünschten 1,2,3,5-Tetraarylpyrrol **4**. Die Ausbeuten sind bei Benzalacetophenon (**2a→4a**) und bei seinem 4-Bromderivat (**2b→4b**) brauchbar. Das Dipropoxy-Derivat **2c** reagiert bereits unbefriedigend und aus dem Tetrapropoxy-System **2d** entstehen lediglich Spuren des Pyrrols **4d**. Die 2,5-Dipropoxyphenylreste erhöhen ein wenig die Elektronendichte an der Enoneinheit, und sie bewirken eine sterische Behinderung, so dass die Pyrrolbildung zum Erliegen kommt (Schema 2).

Tabelle 1. ^{13}C NMR-Daten der Verbindungen **4a-c** (Messung in $CDCl_3$ mit TMS als internem Standard)

Verbindung	CH			C_q		
	Pyrrol	Phenyl		C–N	CBr/O	Übrige
		1C	2C			
4a	110.0	125.5	127.8	138.8		123.5
		126.3	128.0	136.1		132.2
		126.9	128.1	134.8		132.7
		127.1	128.2			132.9
			128.5			
			128.6			
			129.1			
			131.5			
4b	110.2	125.6	127.9	138.6	120.4	123.7
		127.1	128.2	135.9		131.9
		127.4	128.2	135.5		132.5
			128.7			132.7
			129.0			
			129.9			
			131.2			
			131.5			
4c	111.2	113.6	127.8	139.3	150.9	123.0
		115.1	127.8	136.5	152.4	123.3
		118.0	128.0	133.1		129.0
		125.2	128.2			131.3
		126.3	128.4			
		126.7	131.5			

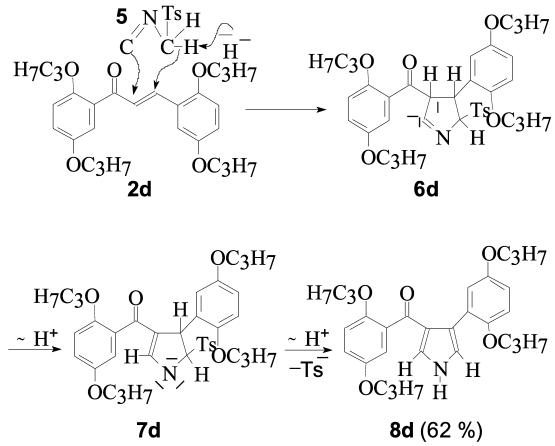


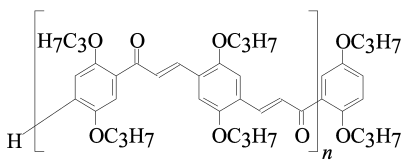
Chalkon	R^1	R^2	R^3	Pyrrol	Ausb. [%]
2a	H	H	H	**4a**	71
2b	H	Br	H	**4b**	62
2c	OC_3H_7	H	H	**4c**	10
2d	OC_3H_7	H	OC_3H_7	**4d**	—

Schema 2. Bildung der Pyrrole **4a-d** aus 2-Phenyl-2-phenylaminoacetonitril (**1**) und den Chalkonen **2a-d** im alkalischen Medium.

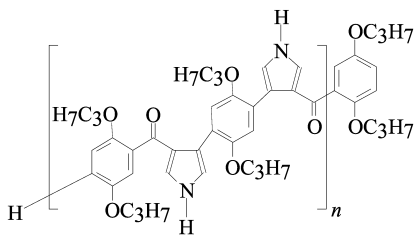
Tabelle 1 enthält eine Zusammenfassung der ^{13}C NMR-Daten der Verbindungen **4a-c**. Die übrigen analytischen und spektroskopischen Charakterisierungen sind im Experimentalteil enthalten.

Die zweite, im Schema 1 diskutierte Variante der Pyrrolbildung verläuft dagegen auch an den propoxy-substituierten Verbindungen mit befriedigenden Ausbeuten.





2	**e**	**f**	**g**
n	**1**	**2**	**3**



8	**e**	**f**	**g**
n	1	2	3
Ausb. [%]	39	63	46

Schema 3. Bildung des Pyrrols **8d** aus dem Chalkon **2d** und dem Isonitril **5** im alkalischen Medium und analoge Umwandlung der Oligochalkone **2e-g** in die Oligomeren **8e-g**.

Sulfonylmethylisocyanide[13] eignen sich hervorragend für die Herstellung von zahlreichen Fünfring-Heterocyclen.[14–17] Das unsubstituierte Chalkon **2a** gibt mit Tosylmethylisocyanid (**5**) im alkalischen Medium 3-Benzoyl-4-phenylpyrrol in einer Ausbeute von 70%.[18] Das Tetrapropoxy-Derivat **2d** reagiert in ähnlicher Weise; das Anion von **5** greift den Michael-Akzeptor **2d** an und bildet nach Protonenverschiebung und Tosylatabspaltung das Pyrrol **8d** (Schema 3). Die Seitenketten beeinträchtigen den Reaktionsablauf kaum, so dass diese Umsetzung auf die Oligochalkone **2e**, **2f** und **2g** übertragen werden kann. Es entstehen die Oligomeren **8e**, **8f** und **8g**, kettenförmige Verbindungen, die jeweils aus Benzol-, Pyrrol- und Carbonyl-Bausteinen zusammengesetzt sind. Die Moleküle **8g** bestehen demgemäß aus 7 Benzolringen, 6 Pyrrolringen und 6 Carbonylgruppen und haben in der gestreckten Konformation eine Länge von ca. 6.5 nm. Eine weitgehend gestreckte Konformation ist unter der Vielzahl der denkbaren Konformeren realistisch, weil Abwinkelungen zur Erhöhung der sterischen Hinderung führen.[4]

Die ^{1}H und ^{13}C NMR Daten von **8d**-**8g** sind im experimentellen Teil enthalten. Die UV-Absorptionen der Verbindungen **8** weisen eine langwellige Bande bei $\lambda_{max}=255\pm2$ nm auf. In der Oligomerenreihe wächst der ε_{max}-Wert von 16.2×10^3 für **8e** über 27.1×10^3 für **8f** auf 43.4×10^3 cm^2 $mmol^{-1}$ für **8g** an.

3. Zusammenfassung

Die Enon-Einheit von Oligochalkonen eignet sich als C_2-Komponente für den Aufbau von Pyrrolringen, wobei Tosylmethylisocyanid als CNC-Komponente dient. Auf diese Weise entstehen gekreuzt konjugierte Oligomere aus 1,4-Phenylenringgliedern, Carbonylgruppen und 1*H*-Pyrrol-3,4-diyl-Bausteinen. Die 2,5-Dipropoxy-Substitution der Benzolringe dient zur Solubilisierung und ermöglicht den Aufbau einer 'Kette' aus 7 Benzolringen, 6 CO-Gruppen und 6 Pyrrolringen.

4. Experimentelles

4.1. Allgemeines

Die Schmelzpunkte wurden mit einem Schmelzpunktapparat SMP/3 der Firma Stuart Scientific bestimmt und sind unkorrigiert. Die ^{1}H und ^{13}C NMR-Spektren wurden an den Geräten AC 300, AMX-400 und Avance-600 der Firma Bruker gemessen. $CDCl_3$ diente, wenn nicht anders angegeben, als Lösungsmittel und TMS als interner Standard. Die Massenspektren wurden mit einem MAT 95 der Firma Finnigan erhalten.

4.2. Ausgangsverbindungen und produkte

Die Ausgangsverbindungen **1**,[9,10] **2d**,[2] **2e**-**g**[3] und **5**[18] wurden entsprechend der angegebenen Literatur hergestellt; **2a** ist käuflich.

4.2.1. (*E*)-1-(4-Bromphenyl)-3-phenyl-2-propen-1-on (2b). 4-Bromacetophenon (3,0 g, 15,1 mmol) werden bei 0 °C unter Rühren zu (0,5 g, 8,9 mmol) KOH in 10 mL CH_3OH gegeben. Nach der Addition von 1,51 mL (1,583 g, 14,9 mmol) Benzaldehyd erwärmt sich das Reaktionsgemisch und nach einigen Minuten beginnt ein Niederschlag auszufallen. Man lässt eine weitere Stunde rühren, filtriert den Niederschlag ab und wäscht ihn mit kaltem Ethanol. Es werden 3,9 g (90%) eines farblosen Feststoffs vom Schmelzpunkt 103 °C erhalten (Schmp. 104–105 °C);[19,20] **2b** kann so direkt weiterverarbeitet werden. ^{1}H NMR ($CDCl_3$): δ=7.41 (m, 3H, *m*-H, *p*-H, Phenyl), 7.45 (d, ^{3}J=15.8 Hz, 2-H), 7.63 (m, 2H, *o*-H, Phenyl), 7.63/7.87 (AA′BB′, 4H, Bromphenyl), 7.79 (d, ^{3}J=15.8 Hz, 1H, 3H). ^{13}C NMR ($D_3C-CO-CD_3$): δ=122.4, 129.5, 129.7 (CH, Phenyl), 128.0 (C_qBr), 131.0, 131.4 (CH, Bromphenyl), 132.7 (C-2), 135.8, 137.9 (C_q), 145.3 (C-3), 189.0 (C-1).

4.2.2. (*E*)-1-(2,5-Dipropoxyphenyl)-3-phenyl-2-propen-1-on (2c). Zu 2,5-Dipropoxyacetophenon[2,3] (1,0 g, 4,2 mmol) und 0,56 mL (587 mg, 5,53 mmol) Benzaldehyd in 20 mL Ethanol tropft man unter Rühren bei Raumtemperatur innerhalb von 5 h 2,0 mL einer 1,5 M KOH. Der pH-Wert darf dabei nicht über 8.0 steigen. Nach 30 h Rühren wird das Lösungsmittel im Vakuum entfernt und der Rückstand durch Säulenchromatographie (40×2 cm SiO_2, Toluol/Ethylacetat 40:1) gereinigt. Man erhält 820 mg (60%) eines viskosen Öls. ^{1}H NMR ($CDCl_3/C_6D_6$ 1:1): δ=0.80 (t, 3H, CH_3), 0.88 (t, 3H, CH_3), 1.55 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 3.64 (t, 2H, OCH_2), 3.68 (t, 2H, OCH_2), 6.63 (d, 1H, Dipropoxyphenyl), 6.89 (dd, 1H, Dipropoxyphenyl), 7.13 (m, 3H, Phenyl), 7.28 (d, 1H, Dipropoxyphenyl), 7.38 (m, 2H, Phenyl), 7.48 (d, ^{3}J=15.6 Hz, 1H, 2-H), 7.68 (d, ^{3}J=15.6 Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3/C_6D_6$ 1:1): δ=10.3, 10.4, (CH_3), 22.5, 22.6 (CH_2), 69.9, 70.8 (OCH_2), 114.3, 115.0, 120.0 (CH, Dipropoxyphenyl), 127.2, 135.3 (C_q), 128.3, 128.7, 129.9 (CH, Phenyl), 129.9 (C-2), 142.2 (C-3), 152.1, 153.2 (C_qO), 191.8 (C-1). FD-MS: *m*/*z* (%)=324 (100) [M^+]. $C_{21}H_{24}O_3$ (324.4): Ber. C 77.75, H 7.46; gef. C 77.78, H 7.28.

4.2.3. 1,2,3,5-Tetraphenyl-1*H*-pyrrol (4a). Zu 500 mg (2,40 mmol) Benzalacetophenon und 550 mg (2,63 mmol) 2-Phenyl-2-phenylamino-acetonitril[9,10] in 14 mL Ethanol tropft man bei 35 °C 1,0 mL einer 1,7 M KOH. Es bildet sich ein Niederschlag des Intermediats **3a**, der mit kaltem Ethanol gewaschen und dann in 30 mL siedendem 1:1-Gemisch aus Methanol und Ethanol aufgelöst wird. Innerhalb von 1 h tropft man 1,5 mL 10 %ige HCl zu. Es beginnt ein Niederschlag auszufallen. Nach weiteren 2 h unter Rückfluß wird filtriert, mit kaltem Ethanol gewaschen und aus Ethanol umkristallisiert. Man erhält 632 mg (71%) **4a** vom Schmelzpunkt 202 °C (lit.:[21] Schmp. 201–202 °C), die durch Vergleich mit einem authentischen Präparat[21–23] identifiziert wurden. ^{13}C NMR ($CDCl_3$): δ=110.0 (C-3), 125.5, 126.3, 126.9, 127.1, 127.8, 127.9, 128.1, 128.2, 128.5, 128.6, 129.1, 131.5 (aromat. CH), 123.5, 132.2, 132.7, 132.9, 134.8, 136.1, 138.8 (C-2, C-4, C-5 und aromat. C_q).

4.2.4. 2-(4-Bromphenyl)-1,4,5-triphenyl-1*H*-pyrrol (4b). Die Herstellung erfolgte wie für **4a** beschrieben. Man erhält in einer Ausbeute von 62% gelbliche Kristalle, die bei 193 °C schmelzen.

^{1}H NMR ($CDCl_3$): δ=6.70 (s, 1H, 3-H), 6.94–7.31 (m, 19H, aromat. H). ^{13}C NMR ($CDCl_3$): δ=110.2 (C-3), 120.4 (C_qBr), 125.6, 127.1, 127.4, 127.9, 128.2, 128.2, 128.7, 129.0, 129.9, 131.2, 131.5 (aromat. CH), 123.7, 131.9, 132.5, 132.7, 133.5, 135.9, 138.6 (C-2, C-4, C-5 und aromat. C_q). FD-MS: *m/z* (%)=449/451 (100) [M^+, Br-Isotopenmuster). $C_{28}H_{20}BrN$ (450.4): Ber. C 74.67, H 4.48, N 3.11; gef. C 74.62, H 4.56, N 3.08.

4.2.5. 2-(2,5-Dipropoxyphenyl)-1,4,5-triphenyl-1*H*-pyrrol (4c). Die Herstellung erfolgte wie für **4a** beschrieben. Man erhält in einer Ausbeute von 10% farblose Kristalle, die bei 81 °C schmelzen. ^{1}H NMR ($CDCl_3$): δ=0.85 (t, 3H, CH_3), 0.94 (t, 3H, CH_3), 1.66 (m, 4H, CH_2), 3.56 (t, 2H, OCH_2), 3.66 (t, 2H, OCH_2), 6.66–6.73 (m, 3H, aromat. H und 3-H), 6.88–6.92 (m, 2H, aromat. H), 7.02–7.31 (m, 14H, aromat. H). ^{13}C NMR ($CDCl_3$): δ=10.3, 10.4 (CH_3), 22.5, 22.6 (CH_2), 70.1, 70.6, (OCH_2), 111.2 (C-3), 113.6, 115.1, 118.0, 125.2, 126.3, 126.7, 127.8, 127.8, 128.0, 128.2, 128.4, 131.3 (aromat. CH), 123.0, 123.3, 129.0, 131.3, 133.1, 136.5, 139.3, 150.9, 152.4 (C-2, C-4, C-5 und aromat. C_q). FD-MS: *m/z* (%)=488 (100) [M^+]. $C_{34}H_{33}NO_2$ (487,6): Ber. C 83.74, H 6.82, N 2.87; gef. C 83.69, H 6.71, N 3.01.

4.2.6. (2,5-Dipropoxyphenyl)[4-(2,5-dipropoxyphenyl)-1*H*-pyrrol-3-yl]methanon (8d). Na-triumhydrid (52 mg, 2,26 mmol) wird in 60 mL wasserfreiem Ether in einem ausgeheizten Kolben unter Argon gerührt, bevor man 250 mg (0,57 mmol) (*E*)-1,3-Bis(2,5-dipropoxyphenyl)-2-propen-1-on (**2d**) und 170 mg (0,87 mmol) Tosylmethylisocyanid (**5**) in 2 mL Diethylether/1 mL DMSO langsam zugibt. Die Reaktionsmischung nimmt eine gelbrote Farbe an. Nach ca. 15 min beginnt ein gelblicher Feststoff auszufallen. Die Dünnschichtchromatographie (SiO_2, Toluol/Essigester 3:1) zeigt nach rund einer weiteren Stunde Rühren das Ende der Reaktion an. Man fügt 200 mL gesättigte wässrige Kochsalzlösung hinzu, filtriert den Niederschlag ab und wäscht ihn gründlich mit Wasser. Der getrocknete gelbe Feststoff wird in möglichst wenig Essigsäureethylester gelöst und an Kieselgel (45×3 cm) mit Toluol/Essigsäureethylester (3:1) chromatographiert. Nach Umkristallisation aus Methanol erhält man 168 mg (62%) farblose Kristalle vom Schmp. 108 °C. (Die Verwendung der basischen Bedingungen $KOC(CH_3)_3$/THF oder K_2CO_3/CH_3OH führt zu Reaktionen, die bei Raumtemperatur über 2–4 Tage laufen und niedrigere Ausbeuten ergeben.)

^{1}H NMR ($CDCl_3$): δ=0.80 (t, 3H, CH_3), 0.85 (t, 3H, CH_3), 0.97 (t, 3H, CH_3), 0.98 (t, 3H, CH_3), 1.58 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 3.70 (t, 2H, OCH_2), 3.73 (t, 2H, OCH_2), 3.79 (t, 2H, OCH_2), 3.81 (t, 2H, OCH_2), 6.63 (m, 2H, *m*-H, *p*-H, Phenyl), 6.66 (d, 1H, *m*-H, Benzoyl), 6.75 (m, 1H, 5-H), 6.76 (dd, 1H, *p*-H, Benzoyl), 6.84 (m, 1H, *o*-H, Phenyl), 6.87 (d, 1H, *o*-H, Benzoyl), 7.04 (dd, ^3J=3.1 Hz, $|^4J|$=2.0 Hz, 1H, 2-H), 8.88 (br. s, 1H, 1-H). ^{13}C NMR ($CDCl_3$): δ=10.4, 10.5, 10.5, 10.5 (CH_3), 22.6, 22.6, 22.7, 22.7 (CH_2), 70.0, 70.2, 70.4, 70.9 (OCH_2), 112.7, 113.9 (*p*-CH, *m*-CH, Phenyl), 113.2 (*m*-CH, Benzoyl), 117.2 (*p*-CH, Benzoyl), 117.9 (*o*-CH, Phenyl), 119.4 (HC-5), 126.7 (HC-2), 121.7, 124.7, 125.2, 131.8 (C_q), 150.6, 150.8, 152.3, 152.5 (C_qO), 190.5 (CO). Die Zuordnung basiert auf einer ^{13}C,^{1}H-Verschiebungskorrelation. FD-MS: *m/z* (%)=480 (100) [M^+]. $C_{29}H_{37}NO_5$ (479.6): Ber. C 72.62, H 7.78, N 2.92, gef. C 72.66, H 7.81, N 2.90.

4.2.7. (2,5-Dipropoxyphenyl)(4-{2,5-dipropoxy-4-[4-(2,5-dipropoxybenzyl)-1*H*-pyrrol-3-yl]-phenyl}-1*H*-pyrrol-3-yl)methanon (8e). Natriumhydrid (100 mg, 4.40 mmol) wird in 15 mL wasserfreiem Ether, wie für **8d** beschrieben, vorgelegt, bevor man Bischalkon **8e** (400 mg, 0,58 mmol) und **5** (341 mg, 1.75 mmol) in 60 mL Diethylether/30 mL DMSO zugibt. Die DC-Kontrolle zeigt nach 1,5 h Rühren das Ende der Reaktion an. Man gibt 300 mL gesättigte, wässrige NaCl-Lösung hinzu, filtriert den Niederschlag ab, wäscht ihn gründlich mit Wasser und kristallisiert ihn aus Isopropanol um. Das hellgelbe Produkt (176 mg, 39%) schmilzt bei 125 °C.

^{1}H NMR (CD_3SOCD_3): δ=0.94 (t, 6H, CH_3), 0.85 (t, 6H, CH_3), 0.77 (t, 6H, CH_3), 1.47–1.54 (m, 4H, CH_2), 1.56–1.63 (m, 4H, CH_2), 1.65–1.72 (m, 4H, CH_2), 3.71 (t, 4H, OCH_2), 3.79 (t, 4H, OCH_2), 3.83 (t, 4H, OCH_2), 6.75 (d, 2H, *o*-H, Dipropoxyphenyl), 6.82 (s, 2H, 1,4-Phenylen), 6.87–6.93 (m, 8H, übrige H an Dipropoxyphenylresten und Pyrrolringen), 11.37 (s, 1H, NH). ^{13}C NMR (CD_3SOCD_3): δ=10.2, 10.3, 10.5 (CH_3), 22.0, 22.1, 22.3 (CH_2), 69.4, 69.7, 70.2 (OCH_2), 114.4, 114.4, 115.7, 116.0, 120.3, 120.3 (CH), 122.8, 123.3, 127.6, 132.6 (C_q), 149.1, 149.7, 151.8 (C_qO), 188.8 (CO). FD-MS: *m/z* (%)=765 (100) [M^+]. $C_{46}H_{56}N_2O_8$ (764.9): Ber. C 72.33, H 7.38, N 3.66, $C_{46}H_{56}N_2O_8 \cdot H_2O$: Ber. C 70.57, H 7.47, N 3.58; gef. C 70.21, H 7.62, N 3.65. Trotz gründlicher Trocknung im Hochvakuum bleibt ein Wassermolekül pro **8e** in den Kristallen enthalten.

4.2.8. Oligomer 8f. Die Herstellung erfolgt nach der für **8e** beschriebenen Vorschrift. Die Umkristallisation aus Essigsäureethylester ergibt ein gelbes Pulver (Ausb. 63%), das bei 302 °C schmilzt. ^{1}H NMR (CD_3SOCD_3): δ=0.76 (t, 6H, CH_3), 0.77 (t, 6H, CH_3), 0.85 (2 t, 12H, CH_3), 0.94 (t, 6H, CH_3), 1.50–1.73 (m, 20H, CH_2), 3.73–3.85 (m, 20H, OCH_2), 6.75–7.04 (m, 20H, aromat. und heteroaromat. H), 11.51 (s, 4H, N–H). ^{13}C NMR (CD_3SOCD_3): δ=10.3, 10.4, 10.5, 10.6, 10.7 (CH_3), 22.2, 22.5 (CH_2, überlagert), 69.6, 69.9, 69.9, 70.3, 70.5 (OCH_2), 113.7, 113.7, 113.7, 114.6, 115.9, 116.2, 120.0, 120.5, 120.5, 120.5 (CH), 122.9, 123.0, 123.4, 123.4, 127.9, 128.2, 132.7, 133.2 (C_q), 149.2, 149.3, 149.3, 149.9, 151.9 (C_qO), 188.6, 189.1 (CO). FD-MS: *m/z* (%)=1335 (100) [M^+] für $C_{80}H_{94}N_4O_{14}$. Auf eine Elementaranalyse wurde verzichtet, da die Verbindung trotz sorgfältiger Trocknung noch beträchtliche Mengen Wasser enthält.

4.2.9. Oligomer 8g. Die Herstellung erfolgt nach der für **8d** beschriebenen Vorschrift. Man isoliert ein dunkelgelbes Pulver (Ausb. 46%), das sich bei 300 °C zu zersetzen beginnt. ^{1}H NMR (CD_3SOCD_3): δ=0.75–0.96 (m, 42H, CH_3), 1.51–1.68 (m, 28H, CH_2), 3.74–3.83 (m, 28H, OCH_2), 6.76–7.04 (m, 28H, aromat. und heteroarom. H), 11.47 (s, 6H, NH). ^{13}C NMR (CD_3SOCD_3): δ=10–11 ppm. (CH_3), 22–23 (CH_2), 69–71 (OCH_2), 113–134 (aromat. CH und C_q), 149–152 (C_qO), 188–191 (CO); die Signale sind stark überlagert und weisen infolge der beschränkten Löslichkeit ein schlechtes Signal-Rausch-Verhältnis auf.

Die Verbindung $C_{114}H_{132}N_6O_{20}$ enthält selbst nach sorgfältiger Trocknung einen hohen Wassergehalt. Im Massenspektrometer fliegt das Molekülion mit einem Wassermolekül. FD-MS: *m/z* (%)=1926 (100) $[C_{114}H_{132}N_6O_{20}+H_3O^+]$. Auf die Elementaranalyse wurde wegen des hygroskopischen Verhaltens verzichtet.

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