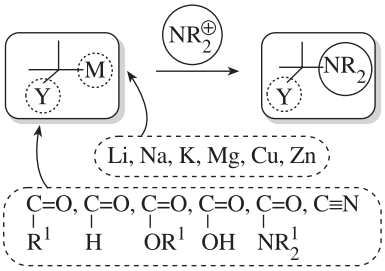
ELSEVIER

Tetrahedron

Tetrahedron Vol. 60, No. 40, 2004

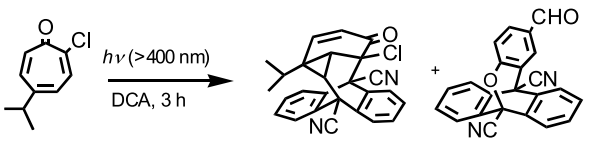
Contents

REPORT

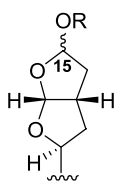


Electrophilic amination is a valuable protocol for the regio- and stereospecific formation of C–N bonds. This review focuses on the reagents and methods for the synthesis of α-aminocarbonyl compounds using α-metallocarbonyl compounds and electrophilic nitrogen-transfer reagents.

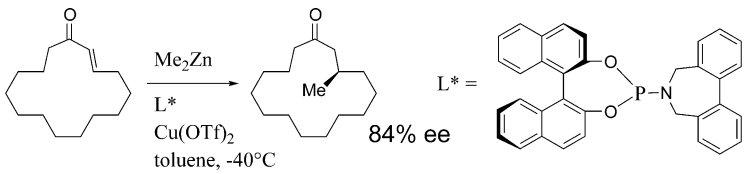
ARTICLES

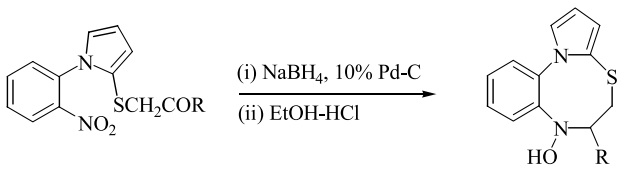


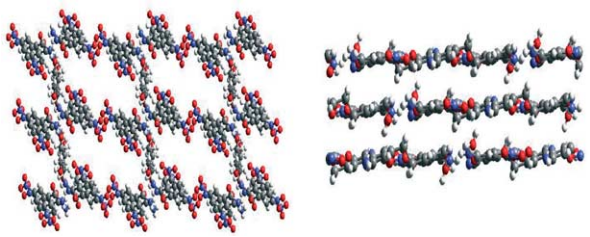
A *meta*-adduct was formed via a bicyclo[4.4.1]undecenediyl biradical intermediate and an aldehyde having an oxabicyclo[3.2.2]nonane system was obtained with the elimination of the isopropyl group.

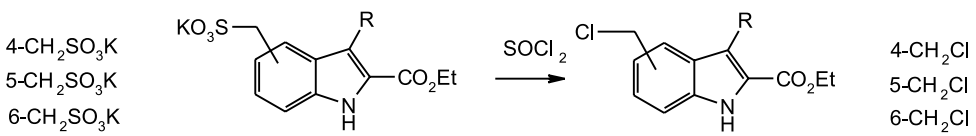


R = H, Me, Et

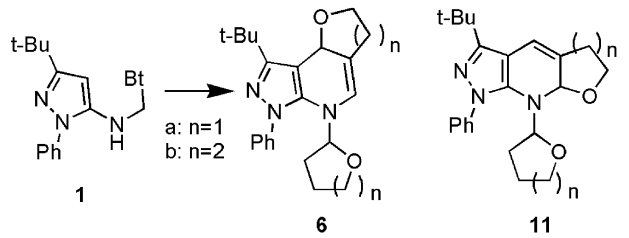


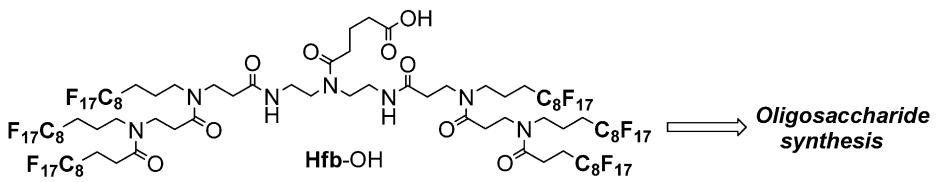


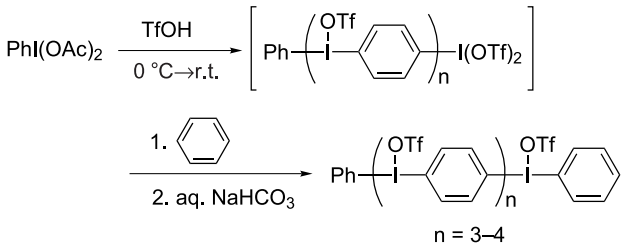


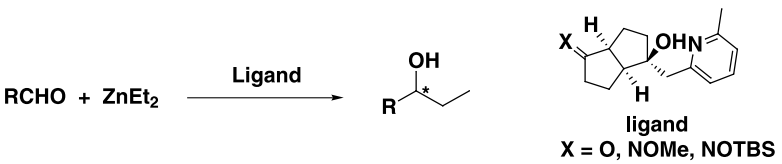


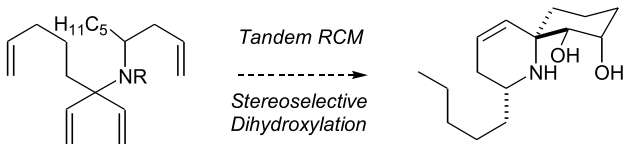
4-, 5- and 6-(Chloromethyl)indoles were prepared from indole-4-, 5- and 6-methanesulfonic acids, respectively, by replacement of the sulfo group with chlorine. The indole-methanesulfonic acids were prepared by Fischer synthesis.

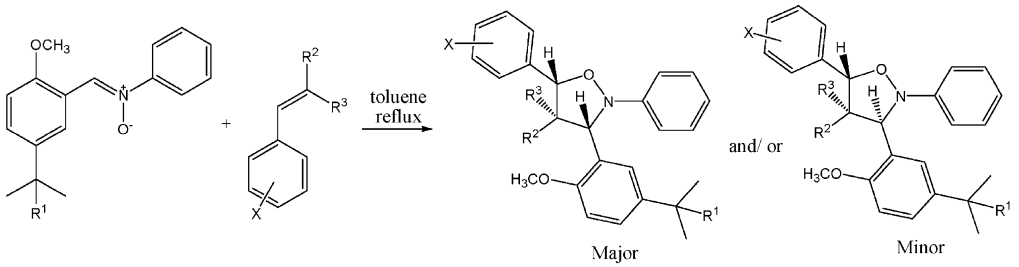


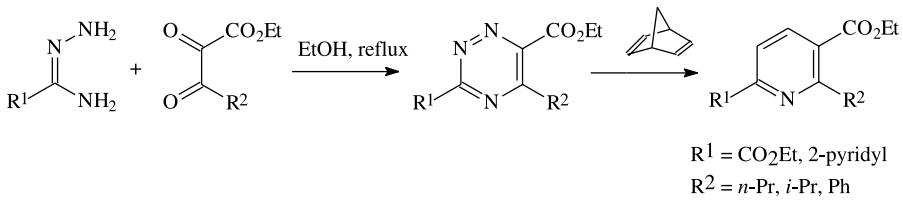


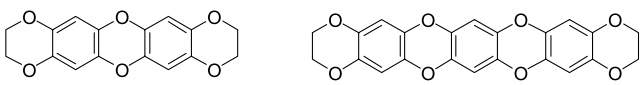


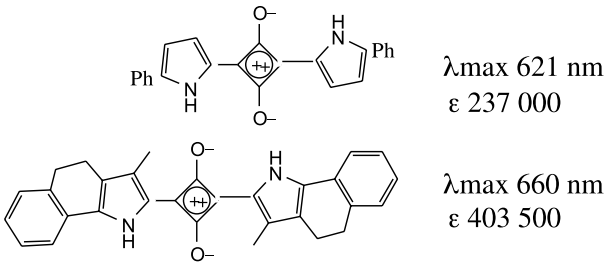


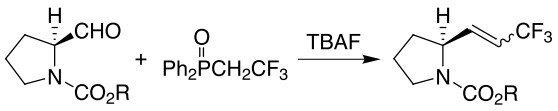


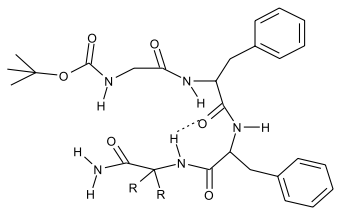


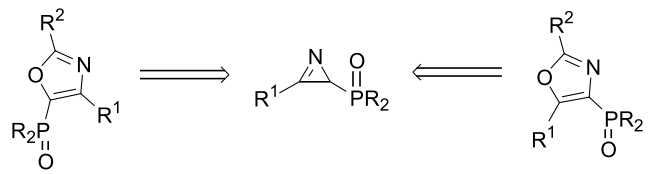


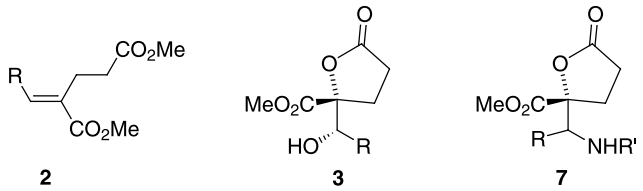




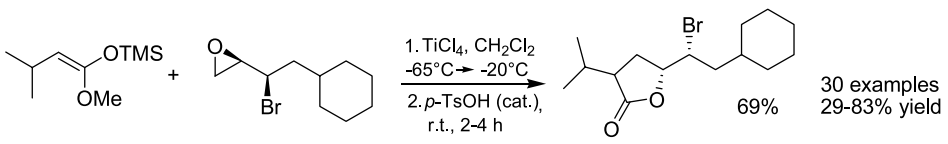


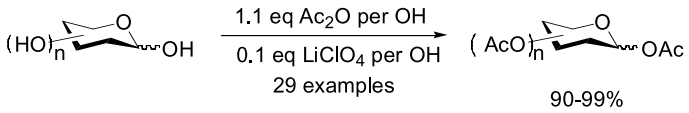


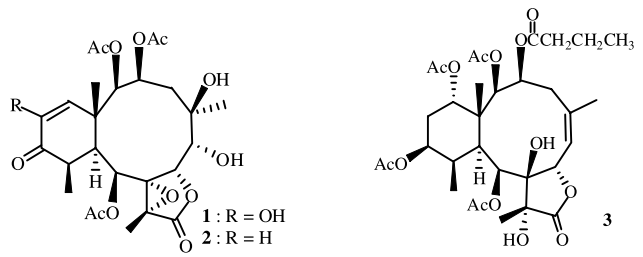




Asymmetric dihydroxylation and amino-hydroxylation of (*E*)-dimethyl-2-alkylidene glutarates **2** provide enantio-enriched to enantiopure highly functionalized γ-butyrolactones **3** and **7**.







OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

SCIENCE DIRECT™

Full text of this journal is available, on-line from **ScienceDirect**. Visit **www.sciencedirect.com** for more information.

CONTENTS direct

This journal is part of **ContentsDirect**, the ***free*** alerting service which sends tables of contents by e-mail for Elsevier books and journals. You can register for **ContentsDirect** online at: **http://contentsdirect.elsevier.com**

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

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 8747–8782

Tetrahedron report number 690

Electrophilic α-amination of carbonyl compounds

Ender Erdik*

Department of Chemistry, Science Faculty, Ankara Üniversity, Besevler, Ankara 06100, Turkey

Received 17 June 2004

Available online 20 August 2004

Contents

1. Introduction

Electrophilic amination is an important synthetic reaction in which an electrophilic nitrogen carried by the reagent is transferred to a nucleophilic atom of the substrate to form Nu–N bond in the product. This methodology provides an important route for C–N bond formation in organic synthesis. In this context, a variety of synthetic equivalents of the NH_2^+ synthon have been developed over the years[1–6] for the transfer of nitrogen to ordinary carbanions and enolates derived from organometallic compounds of Group 1, 2, 11 and 12 and resulting in a conceptually simple method for the synthesis of amines and α-aminocarbonyl compounds, respectively (Scheme 1). The direct C–N bond-forming reactions using electrophilic aminating reagents also constitutes one of the simplest procedures for the construction of a stereogenic carbon centre attacked to an amino group.

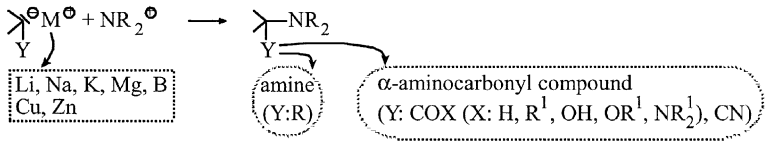
The introduction of a nitrogen functionality adjacent to a carbonyl group using electrophilic aminating reagents is a topical area of research, particularly with respect to the synthesis of α-amino acids, esters and ketones. The biological and synthetic importance of racemic and stereomeric α-amino acids has stimulated the development of numerous methods[7–9] for their synthesis and, among these, electrophilic amination is one of the most important and general methods for the direct formation of chiral C–N bonds in optically active α-amino acids.

In an earlier review.[1] I surveyed electrophilic aminating reagents for the amination of ordinary carbanions and enolates. Later, electrophilic amination methods used in the

Keywords: Electrophilic amination; Enolates; α-Amino carbonyl compounds; α-Amino acids; Chiral catalyst; Chiral auxiliary.

* Tel.: +90-312-212-6720; fax: +90-312-223-2395; e-mail: erdik@science.ankara.edu.tr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.001



Scheme 1.

synthesis of amines and α-aminocarbonyl compounds have been well documented.[2–7] The literature associated with the electrophilic amination of enolates has not been reviewed separately and extensively, however, except for a report on the synthetic methods for α-amino-β-hydroxyacids, which are an important class of α-amino acids.[5]

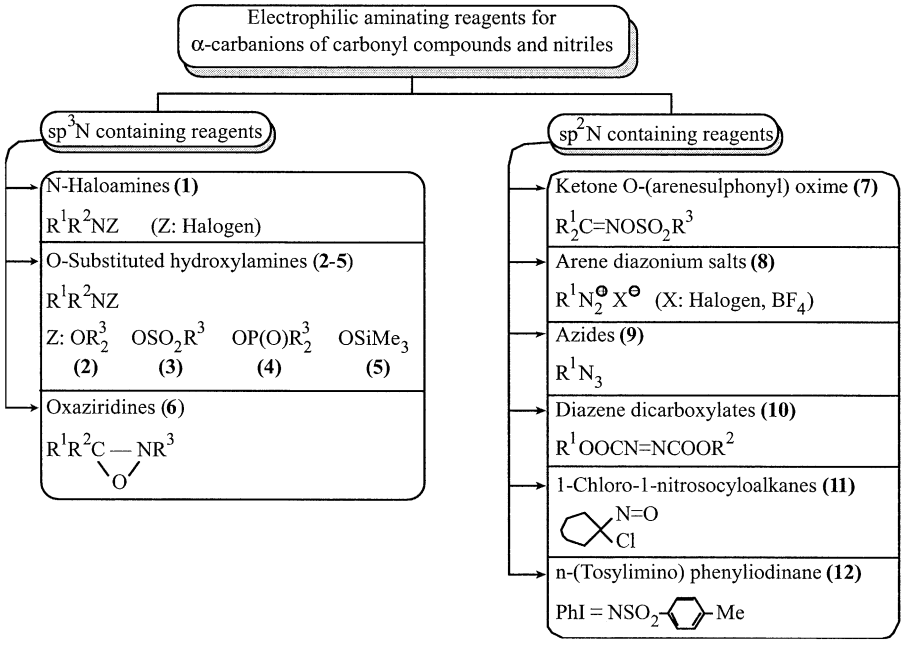
In continuation of our long-term interest in electrophilic amination strategies for C–N bond formation, we now survey electrophilic aminating reagents for the amination of enolates and eniminates, i.e, α-carbonions derived from carbonyl compounds and nitriles, respectively. This review summarises the literature published until the end of 2003, with the major emphasis being placed on the synthetic applications of electrophilic amination methods for α-aminocarbonyl compounds and nitriles without a detailed mechanistic interpretation. For the format of the review, a reagent-based division and a method-based subdivision have been used. Asymmetric versions of these methods have been discussed at the end of each division. Electrophilic aminating reagents **1–12** used in the synthesis of α-aminocarbonyl compounds and nitriles are summarised in Scheme 2. Methods for the preparation of aminating reagents are included but only key references are given. In the discussion of the amination methods, the main synthetic aspects including reaction conditions and some relevant data have been included. Further details of the experimental conditions are available from the primary literature.

In this review, in order to provide an easy discussion of the methods for the synthesis of nonchiral and chiral α-amino carbonyl compounds, a classification was drawn up according to whether

(i) the starting materials, that is, the enolate, or carbonyl compound and the base for the deprotonation of the carbonyl compound and the aminating reagent are nonchiral or chiral,
(ii) the enolate is prepared by using a stoichiometric base or a catalytic base (merged enolisation), and
(iii) the stereodirecting group is incorporated into the enolate, base or aminating reagent or a chiral catalyst is used.

The analysis given in Scheme 3 indicates the five types of established methods for nonstereoselective (Method A) and stereoselective (Methods B–E) electrophilic C–N bond forming at the α-C of carbonyl compounds. As may be seen, chiral induction is generated by using one of the following methods as the stereodifferentiating event: (i) Chiral transition metal catalysts in the amination of enolates (Method B) where a transition metal salt is used either complexed with a chiral ligand or in the presence of a chiral ligand. (ii) chiral nitrogen bases or transition metal salts for merged chiral enol or enamine formation from carbonyl compounds (Method C), (iii) chiral carbonyl compounds orenolates (Method D), and (iv) chiral aminating reagents (Method E).

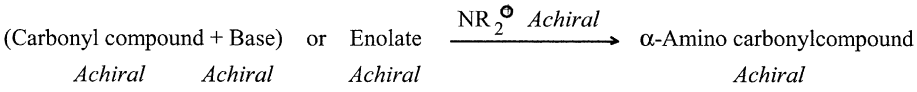
In the discussion of enolate amination with each type of reagent (Sections 2.1–2.7), a tabulation has been given for



Scheme 2.

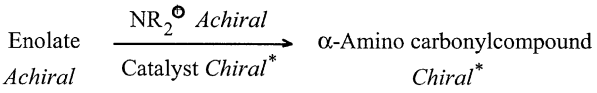
Division of established nonstereoselective and stereoselective electrophilic amination methods for α-carbanions of carbonyl compounds and nitriles ($NR_2^{\oplus}$: aminating reagent)

Method A



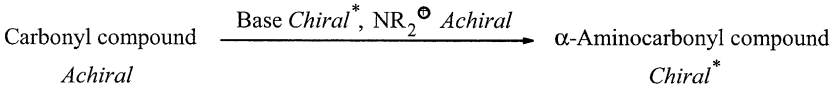
A transition metal salt can be used as a catalyst and also for deprotonation (direct amination)

Method B



Catalyst: A transition metal salt complexed with a *chiral* ligand or a transition metal salt in the presence of a *chiral* ligand.

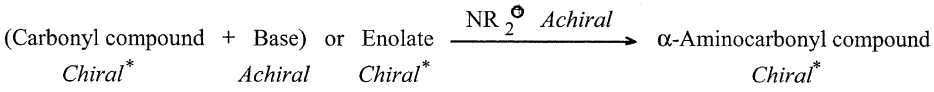
Method C



Base : A catalytic *chiral* nitrogen base or a transition metal salt complexed with a *chiral* ligand (merged enolization).

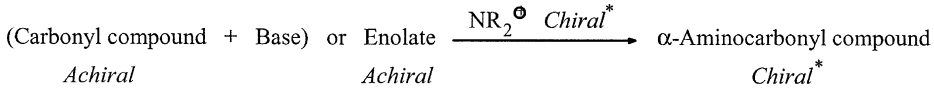
This method is also knows as "direct asymmetric α-amination of carbonyl compounds."

Method D



The carbonyl compound incorporates a *chiral* auxiliary which requires removal later.

Method E



Scheme 3.

the application of the above methods illustrating the related schemes and/or equations and references. At the end the review, a carbonyl compound-based tabulation has also been arranged to show all the reagents for electrophilic nitrogen-transfer and to list related schemes and/or equations and references.

2. Reagents and methods for electrophilic α-amination of carbonyl compounds

2.1. *N*-Haloamines, O-substituted hydroxylamines and their N-substituted derivatives

A list of *N*-haloamines (**1**) and O-substituted hydroxylamines (**2**) as electrophilic nitrogen-transfer reagents to enolates and eniminates and related amination methods are given in Table 1.

N-Halomines have not been utilised extensively for amination procedures because of their instability, and cumbersome preparation,[10] leading to unreproducible yields. Among the *N*-haloamines, only the monochloroamine (**1a**) was used for enolate amination and a few examples have been reported.[11–13] Amination of α-lithiated carboxylic acid with (**1**) gave a very low yield[11,12] although high yields were obtained in the amination of carbanions prepared from substituted diethyl malonates (Scheme 4).[13]

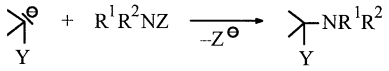
O-Methylhydroxylamine (methoxyamine) (**2a**) and *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) (**2b**) are the most extensively used *O*-organyl hydroxylamine type reagents (**2**) for electrophilic amination of carbanions. Several methods have appeared for the synthesis *O*-alkyl hydroxylamines.[14–16] *O*-Methylhydroxylamine (**2a**) can be prepared by a one-step procedure [15] or can be obtained from its commercially available hydrochloride salt.[17,18] Methods for the preparation of *O*-(nitrophenyl)hydroxylamines and *O*-acylhydroxylamines have been reviewed.[19] *O*-(Nitrophenyl)-hydroxylamines (**2b**) are stable and commercially available. *O*-Acylhydroxylamines (**2c**) are generally unstable with the exception of the 2,4,6-trimethylbenzoyl derivatives.

Table 1. Amination of enolates and eiminates with *N*-chloroamine (**1a**) and O-substituted hydroxylamines (**2–5**)

R^1R^2NZ (**1-5**)

	R^1	R^2	Z
1a	H	H	Cl
2a	H	H	OMe
2b	H	H	O-(2,4-$(NO_2)_2$C$_6$H$_3$) (DPH)
2c	H	H	OCOR-(4-NO_2C$_6$H$_4$)
3a	H	H	OSO_2-(2,4,6-Me_3C$_6$H$_2$) (MSH)
3b	H	H	OSO_2OH (HOSA)
3c	H	COOt-Bu	OSO_2-(4-MeC$_6$H$_4$)
	(Li derivative is known as LiBTOC.)		

	R^1	R^2	Z
3d	H	COOEt	OSO_2-(4-NO_2C$_6$H$_4$)
3e	H	COOEt	OSO_2-(4-MeC$_6$H$_4$)
3f	H	COOt-Bu	OSO_2-(2-pyridyl)
4a	H	H	$OPOPh_2$
4b	Me	Me	$OPOPh_2$
4c	H	H	$OPO(OC_6H_4Me)_2$
4d	Me	Me	2-Ph-3-Me-1,3,2-oxazaphosphetidine 2-oxide
5	H	$SiMe_3$	$OSiMe_3$



Y: COX (X: R, OH, OR, NH_2), CN

Aminating reagent	Method[a]	Scheme, Eq.	Reference
1a	A	Scheme 4	12,13
2a	A	Schemes 5 and 6	11,12,20,21
2b	A	Scheme 7 and 8, Eq. 1	22–24
2c	A	Scheme 9	11,25
3a	A	Eqs.2–4	27–29
3b	A	—	12,30
3c	A	Eq. 5, Eq. 6	38
	D	Scheme 16	55
3d	A	Schemes 10 and 12, Eq. 7, 8a and 8b	39–43
	D	Scheme 17, Eqs. 12–14	41,56
3e	A	Scheme 12	42
3f	A	Scheme 13	48
4a	A	Scheme 15, Eqs. 9–11	25,51,52
	D	—	57
	E	Scheme 18	58,59
4b	A	Scheme 14	52
4c	A	Scheme 15	25
4d	E	Eq. 15	60

[a] See Scheme 3.

The suitability of several *O*-alkyl- and *O*-benzylhydroxylamines and *O*-(2-tetrahydropyranyl) hydroxylamine for the amination of α-lithiated carboxylic acids was investigated by Yamada et al.[11,12] and the highest yield was obtained by aminating with *O*-methylhydroxylamine (**2a**). The procedure was used for the preparation of a series of α-aminocarboxylic acids, and except for α-phenylglycine, quite low yields were obtained (Scheme 5).

RCH_2COOH —(1. LDA, THF-HMPA; 2. **2a**, −15°C; 3. H_2O)→ $RCH(NH_2)COOH$

7-11% (R: alkyl, $PhCH_2$)

56% (R: Ph)

Scheme 5.

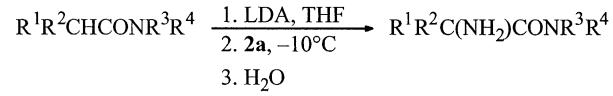
$RCH(COOEt)_2$ —(1. NaH, benzene; 2. **1a**, Et_2O; 3. H_2O)→ $RC(NH_2)(COOEt)_2$ 70-92%

R : H, Me, Et, i,Pr, s-Bu, $PhCH_2$, Ph

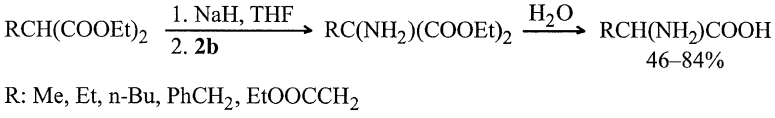
Scheme 4.

Attempts to aminate α-lithiated derivatives of *t*-butyl acetate and phenylacetamide with **2a** failed although the preparation of *N*-mono- or *N*,*N*-disubstituted α-aminocarboxamides resulted in good yields (Scheme 6).[21]

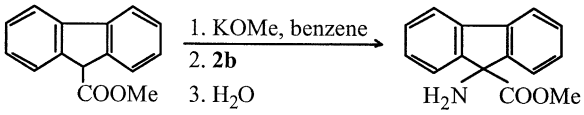
The use of *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) (**2b**) as an aminating reagent for enolates was first studied by Sheradsky and co-workers in the amination of methyl 9-fluorene carboxylate and diethyl α-phenylmalonate (Eqs. 1a and 1b).[22,23]



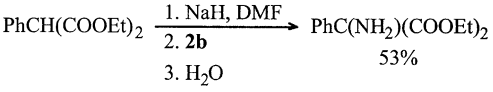
Scheme 6.



Scheme 7.



(1a)

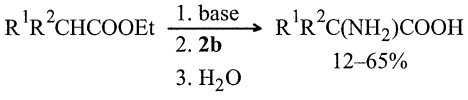


(1b)

Radhakrishna et al. converted the sodium enolates of substituted diethyl malonates into α-aminocarboxylic acids in good yields by amination with DPH (**2b**) and then hydrolysis and decarboxylation (Scheme 7).[24] The method was also found to be useful in the amination of various ester enolates (Scheme 8) and the amination yield was found to decrease with increasing basicity of the enolate. Additionally, DPH (**2b**) could be successfully used in the amination of the lithium eniminate of phenylacetonitrile, but amination of the Reformatsky reagent and the trimethylsilyl enol ether of ethyl phenylacetate with DPH (**2b**) failed. The unsuccessful use of DPH (**2b**) in the amination of carbanions derived from β-diketones and 3-methylbutanoic acid has already been reported.[12]

O-Acylhydroxylamines (**2c**) were reported to give traces of amination product in their reaction with an α-lithiated carboxylic acid.[12]

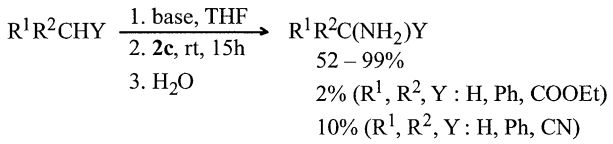
Recently, Smulik and Vedejs have proved *O*-(4-nitrobenzoyl)hydroxylamine (**2c**) to be quite effective for



base: NaH or i-Pr(c–C_6H_{11})NH

R^1,R^2: Ph, COOEt; H, COOEt; Ph,CN; H, Ph; Me, Ph

Scheme 8.



base: NaH / rt; KOt-Bu/–78°C

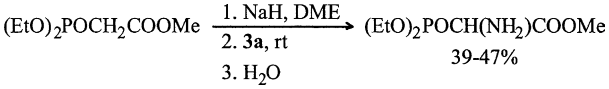
R^1, R^2, Y: H, COOEt, COOEt; Ph, COOEt, COOEt; Ph, CN, COOEt; Ph, Ph, CN; Ph, H, COOEt; Ph, H, CN

Scheme 9.

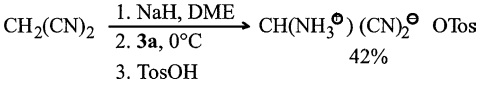
amination of the more highly stabilized enolates in comparison of enolates of ethyl phenyl acetates and phenylacetonitrile (Scheme 9).[25]

O-Sulphonylhydroxylamines (**3**) have found numerous applications in the amination of enolates as well as carbanions. Methods for the prepartion of *O*-(arenesulphonyl)hydroxylamines (**3**) and their *N*-mono- and *N*,*N*-diorganyl-substituted derivatives have been reviewed.[10] *O*-(Mesitylenesulfonyl) hydroxylamine (**3a**) is stable and can be kept below 0 °C for a month without any change. However, its preparation just before the use is however strongly recommended.[26]

A few examples have been reported for the synthesis of α-aminocarbonyl compounds by the amination of enolates and eniminates with **3a**. The sodium enolate of methyl diethylphosphonoacetate (Eq. 2).[27] and eniminate of malonodinitrile (Eq. 3)[28] reacted with **3a** to give the α-aminated products with moderate yields.

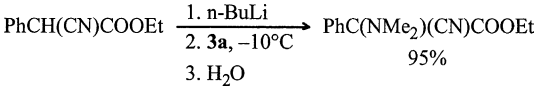


(2)



(3)

Amination of the lithium enolate of ethyl phenylcyanoacetate with *N*,*N*-dimethyl derivative of **3a** was also reported to give a high yield (Eq. 4).[29]



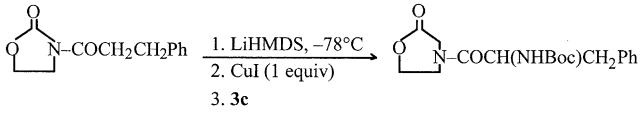
(4)

Due to the complete insolubility of hydroxylamine *O*-sulfphonic acid, HOSA (**3b**), in all nonaqueous solvents, amination with HOSA is restricted to aqueous solutions. In one attempt, its reaction with some β-diketo compounds in alkaline solution was investigated and symmetrically substituted pyrroles were obtained.[30] The successful amination of α-lithiated carboxylic acids with **3b** [12] has been reported.[12]

N-Alkoxycarbonyl *O*-(arenesulphonyl)hydroxylamines [alkyl *N*-(arenesulfonyloxy)carbamates)] (**3c**) and (**3d**) have found numerous applications in the electrophilic amination of enolates and eniminates. They are useful aminating reagents since (i) they can be easily prepared[31,32] and can be stored at 0 °C for many months without decomposition, (ii) arenesulphonyloxy groups are good leaving groups, and (iii) alkoxycarbonyl groups are widely used[33,34] and easily removable protecting groups for amino functions.[35,36] Genet et al. have used *N*-*t*-butoxycarbonyl *O*-tosylhydroxylamine, NHBocOTos (**3c**), as its N-lithiated derivative LiNBocOTos (LiBTOC) for the direct transfer of an LiNBoc⊕ group[35] since the N-lithiated derivatives of O-substituted hydroxylamines (**2**–**5**) have already been indicated as the actual aminating reagents.[18,37] LiBTOC can be easily prepared by the deprotonation of **3c** with 1 equiv. of *n*-butyllithium just before use.[32]

In the amination of metal enolates derived from carboxylic esters, **3c** reacted with lithium enolates, but not with zinc enolates, more readily (Eq. 5).[38] The lithium enolates of *N*-acyloxazolidinones have been successfully aminated in the presence of a stoichiometric amount of CuI (Eq. 6).

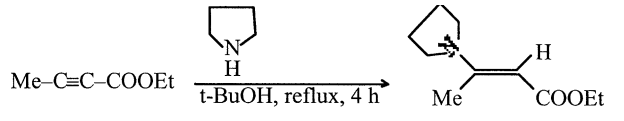
$$PhCH_2COOi\text{-}Pr \xrightarrow[2.\ \mathbf{3c}]{1.\ LiHMDS,\ -78°C} PhCH(NHBoc)COOi\text{–}Pr \qquad (5)$$

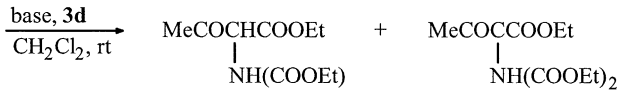


(6)

Pellaconi et al. have reported that *N*-ethoxycarbonyl *O*-(4-nitrobenzenesulphonyl) hydroxylamine, NH(COOEt)ONs (**3d**) provides an easy access for the synthesis of α-amino β-oxoesters from β-enamino esters in the absence of added bases[39,40] and for the direct amination of β-oxoesters in the presence of CaO.[41,42]

They observed that the β-enaminoester prepared by treating ethyl 2-butynoate with pyrrolidine reacts with **3d** to give a monoaminated product **A** in the absence of a base with a much higher yield than that in the presence of an organic or inorganic base (Scheme 10).[39,40] They pointed out that a bis-functionalised product **B** forms, probably by amination at the α-position to the ester group in the presence of a base,[43] but the formation of **A** as a single product in the absence of base shows that the substrate itself or pyrrolidine either formed or present in trace amounts in the reaction medium might act as a base.

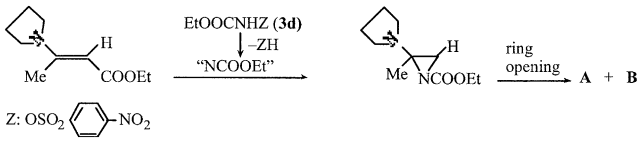




Base	Molar ratios substrate:base:**3c**	Reaction time, h	Yields, % **A**	**B**
Et_3N	1:1:2	14	18	5
CaO	1:3:3	48	26	8
——	1:–:1	45	40	–

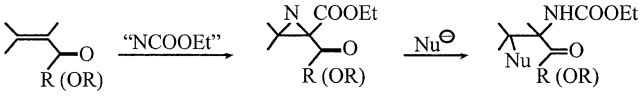
Scheme 10.

As far as the mechanism is concerned, the above data do not indicate whether aziridination of the double bond, that is, ethoxycarbonyl nitrene, 'NCOOEt', transfer to the double bond, takes place (Eq. 7), as also verified by the authors.[40]



(7)

Aziridination is an elegant way of introducing an α-amino function into α,β-unsaturated carbonyl compounds (Eq. 8a) and enol and enamine derivatives of carbonyl compounds (Eq. 8b). Transferring a nitrene or nitrenoid species to the double bond and then ring opening leads to the N-protected α-aminocarbonyl compounds.

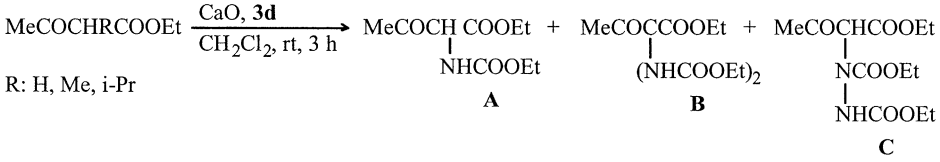


(8a)

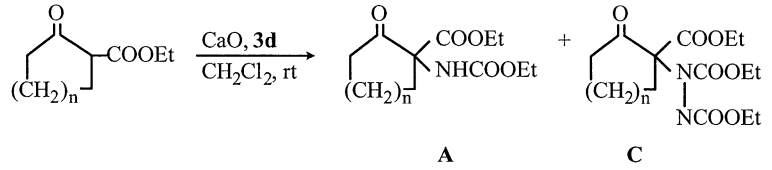
Y: RO or R_2N

(8b)

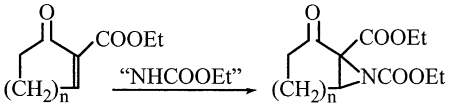
Fiorovanti et al. showed that *N*-alkoxycarbonyl *O*-(arenesulphonylhydroxylamines [alkyl *N*-(arenesulphonyloxy)-carbamates) (**3c**), (**3d**) and (**3e**) can be used for the direct nucleophilic or electrophilic aziridination of the olefinic double bond of α, β-unsaturated carboxylates[44,45] and, very recently, γ-lactones[46] in the presence of CaO. In another study, they reported that a chiral *N*-alkoxycarbonyl *O*-nosylhydroxylamine produced diastereomeric aziridines of 2-acyl- or 2-ethoxycarbonyl substituted cycloalkanones and crotonates in good yields and with high diastereomeric ratios[47] in the presence of CaO. Later, Pellacani's group reacted β-oxoesters with **3d** in the presence of CaO and aminated products were obtained in medium yields (Scheme 11a).[41] Depending on the relative amounts of the reagent and the reaction time, ethyl acetylacetate (R:H) can be easily monoaminated (**A**) or bisaminated (**B**). Its monoalkylated derivate, however gave N-aminated product (**C**) as the second product. Amination of β-oxoesters having a ring also gave the aziridines (**E**) as the reaction products (Scheme 11b). As a mechanistic interpretation for their formation, the authors offered hydrogen abstraction by the nitrene 'NCOOEt' to give **D** and then aziridation of **D** by the nitrene.



R	Molar ratios substrate:base:**3d**	Yields, % **A**	**B**	**C**
H	1:3:1	4	41	—
H	1:2:1	58	8	—
Me	1:6:2	42	—	14
	1:6:6	22	—	43



n: 1, 2

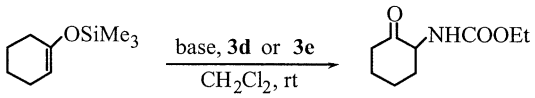


n	Molar ratios substrate: base: **3d**	yields, % **A**	**C**	**E**
1	1 : 6 : 2	35	4	19
2	5 : 2 : 1	49	–	4

Scheme 11.

Pellacani et al. have compared the reactivities of *N*-ethoxycarbonyl derivatives of *O*-(tosyl)-hydroxylamine (**3e**) and *O*-(nosyl)hydroxylamine (**3d**) in the amination of the trimethylsilyl enol ether of cyclohexanone in the presence of an organic or inorganic base (Scheme 12).[42] Replacing the tosyl group with nosyl group decreased the reaction time and increased the amination yield, although *O*-(tosyl)hydroxylamine (**3e**) is approximately 50-fold times less expensive than *O*-(nosyl)hydroxylamine (**3d**).

N-*t*-Butoxycarbonyl *O*-(2-pyridylsulphonyl)hydroxylamine (**3f**) was used by Hanessian[48] for the amination of



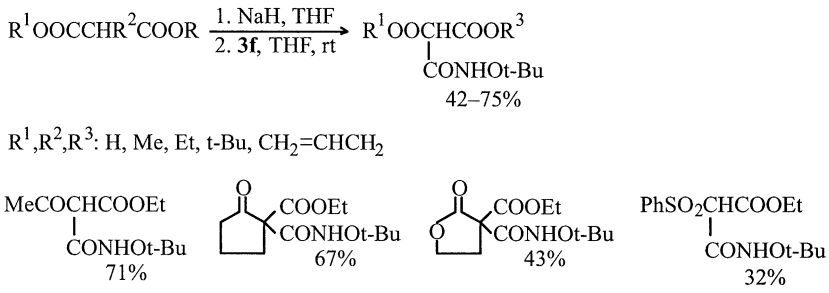
Ar	Base	Reaction time, h	Yield, %
3e	Cs_2O_3	24	51
	Et_3N	24	—
3d	CaO	3,5	67
	Et_3N	3	—

Scheme 12.

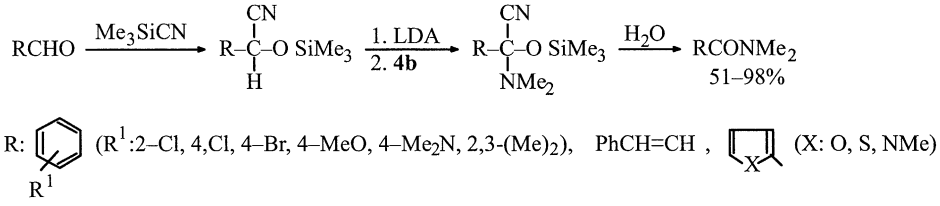
β-dicarbonyl compounds due to the enhanced leaving group reactivity of the 2-pyridyl sulphonyloxy group, but the 2-*t*-butoxyaminocarbonyl derivatives were obtained instead of the expected *N*-*t*-butoxycarbonyl protected amino acids (Scheme 13). Malonates, acyclic and cyclic β-ketoesters, α-alkoxycarbonyl lactones, and β-ketosulphones proved to be good substrates for this reaction and THF, diethyl ether, ether/hexanes, benzene and toluene were found to be suitable solvents. In the presence of HMPA, TMED and additives such as lithium chloride or bromide, however, lower yields were obtained. Lithium and potassium enolates were also found to be less reactive than sodium enolates. The use of **3c** instead of **3f** gave lower yields. A Lossen-type rearrangement was offered as the likely mechanism for the *t*-butoxyaminocarbonylation of β-dicarbonyl compounds.

O-(Diphenylphosphinyl)hydroxylamine (**4a**) and its *N*,*N*-dimethyl-derivative (**4b**) have been used for the successful amination of enolates. Methods for the preparation of *O*-(phosphinyl)hydroxylamines are available,[49,50] **4a** and **4b** being stable compounds which can be stored at −20 °C.

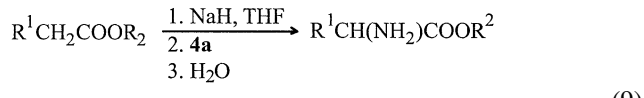
A report describes the amination of sodium enolates of phosphonoacetate and malonate esters and malononitrile with **4a** in moderate yields (Eqs. 9 and 10).[51]



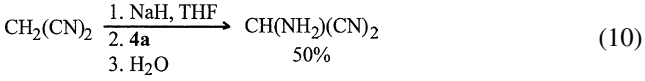
Scheme 13.



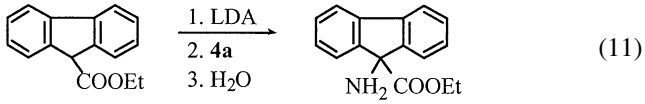
Scheme 14.

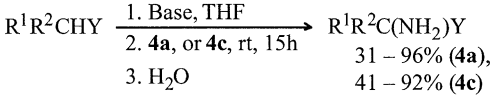


R^1, R^2	yield, %
$(EtO)_2PO$, CH_2Ph	57
EtOOC, Et	60



Amination of the lithium enolate of 9-fluorenecarboxylic acid ethyl ester with **4d** was also found to be successful (Eq. 11).[52]

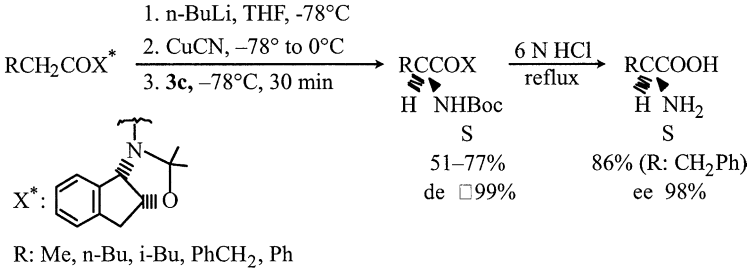




base: NaH / rt; KOt-Bu/–78°C

R^1, R^2, Y: H, COOEt, COOEt; Ph, COOEt, COOEt; Ph, CN, COOEt; Ph, Ph, CN; Ph, H, COOEt; Ph, H, CN

Scheme 15.



R: Me, n-Bu, i-Bu, $PhCH_2$, Ph

Scheme 16.

In another report, anions derived from *O*-(trimethylsilyl)-cyanohydrins reacted with **4b** to yield *N*,*N*-dimethylcarboxamides in medium to high yields (Scheme 14).[53]

Recently, Smulik and Vedejs have shown that *O*-(diphenylphosphinyl)hydroxylamine (**4a**) and *O*-(di-4-methoxyphenylphosphinyl)hydroxylamine (**4c**) react efficiently with enolates derived from malonates, phenylacetates and phenylacetonitriles at-78 °C (Scheme 15).[25] **4c** was found to be more soluble than **4a** and sufficiently reactive for use in low temperature electrophilic amination. Comparative amination results show an advantage for **4c** with the more basic enolates derived from phenylacetates and phenylacetonitrile.

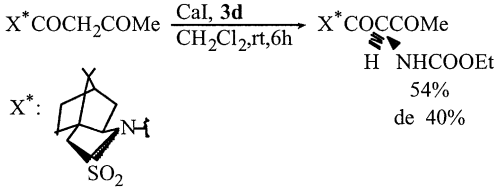
N,*O*-Bis (trimethysilyl)hydroxylamine, NH(TMS)OTMS, (**5**), which is an efficient and mild reagent for organocuprates[54] has not been used for the amination of enolates to

date. The use of **5** for the α-amination of carbonyl compounds is now in progress in our group.

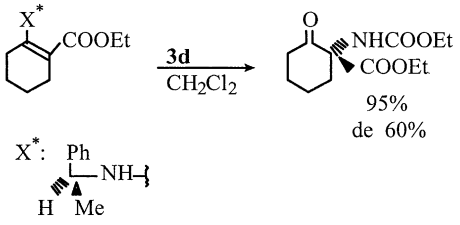
2.1.1. Asymmetric versions of amination with *N*-alkoxycarbonyl *O*-(arenesulphonyl)hydroxylamines (3c), (3d) and *O*-(diphenylphosphinyl)hydroxylamine (4a). Among the methods for chiral induction in the amination of enolates with **3**, Method D, that is, the use of chiral carbonyl compounds as stereodirecting events (Scheme 3), was attempted and successful results were obtained. There is also one report on the use of a chiral aminating reagent, that is, Method E.

The use of **3c** for the amination of chiral copper enolates derived from carboxamides with *N*-chiral aminoindanol groups provides a useful approach to the asymmetric synthesis of α-amino acids (Scheme 16)[55] The direct reaction of lithium or zinc enolates with **3c** did not yield the expected products.

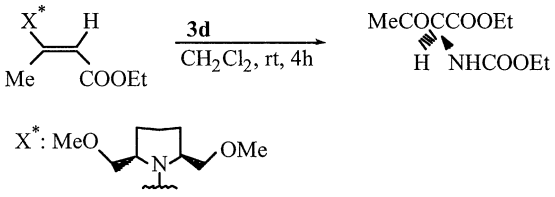
Fiorovanti et al. have used **3d** in the presence of CaO for amination of a chiral β-ketocarboxamide carrying bornane [10,2] sultam (Oppolzer sultam) as chiral auxiliary (Eq. 12).[41] They also attempted the amination of a chiral β-enaminoester derived from 2-(ethoxycarbonyl)cyclohexanone and (*R*)-1-phenylethylamine (Eq. 13)[38] or prepared by treating ethyl 2-butynoate with chiral pyrrolidines (Eq. 14).[40]



(12)

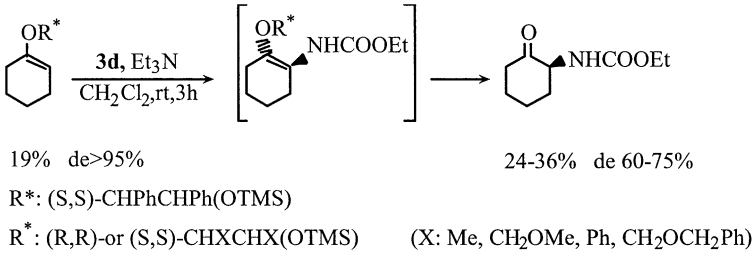


(13)

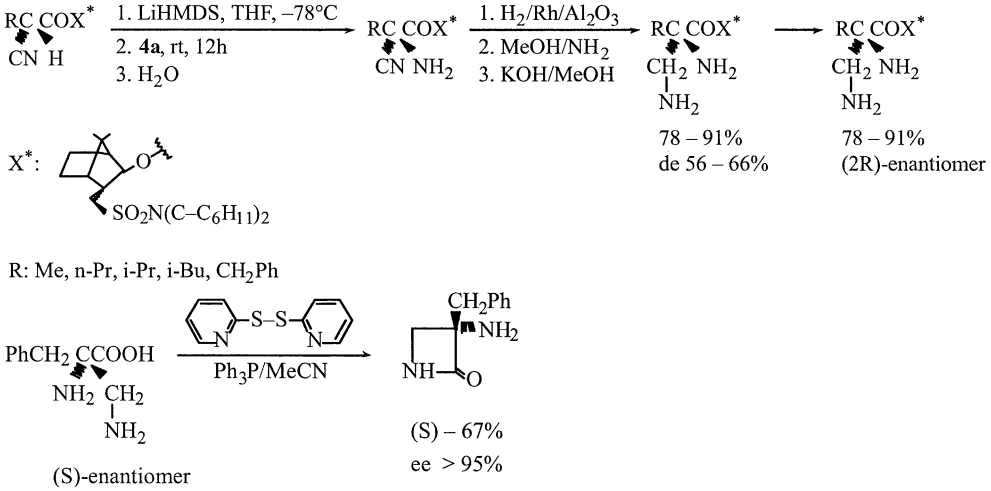


(14)

Fioravanti et al. were additionally interested in the asymmetric formation of C–N bonds in chiral enol ethers using their reaction with **3d** (Scheme 17)[56] and they obtained the α-aminoketones in low yields and



Scheme 17.



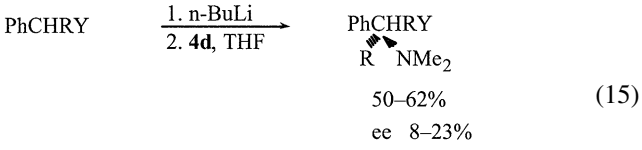
Scheme 18.

diastereomeric ratios. They showed, however, that the amination takes place via an aziridination route and they could isolate the expected aziridine intermediate **A** in a very high diastereomeric excess, confirming that the following hydrolysis step is responsible for partial recemization leading to the observed low diastereoselectivity.

Chiral 3-hydroxybutanoic acid methyl and ethyl esters were already used as the substrates in an unsuccessful asymmetric amination with *O*-(diphenylphoshinylhydroxylamine **4a** and with its *N*,*N*-diisopropyl derivative, that is, Method D.[57]

However, an efficient synthesis of enantiomerically pure antibiotic-related α,β-diaminopropionic acids by stereoselective amination of chiral α-cyanoesters with **4a** followed by appropriate reduction could be succeded (Scheme 18).[58] Cyclisation of (*S*)-α,β-diamino-α-benzylacetic acid allows the asymmetric synthesis of (*S*)-β-amino-β-benzyl α-azetidinone.[59]

A chiral phosphinylhydroxylamine, (2*R*,4*S*,*R*)-2-[*O*-(*N*,*N*-dimethylamino)]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**4d**) was also reported to react with lithium enolates, that is, Method E in low enantiomeric ratio (Eq. 15).[60]



R, Y: H, COOEt ; Me, COOEt; H, CN

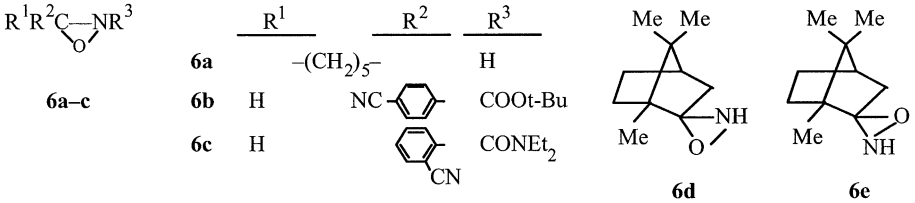
2.2. Oxaziridines

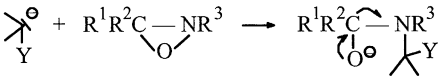
Oxaziridines (**6**) are attacked by nucleophiles at either the oxygen or nitrogen atoms, depending upon the nature of the nucleophile and the substituents on the oxaziridine, especially at the nitrogen atom. N–H, *N*-organyl (alkyl, aryl), *N*-acyl, *N*-alkoxycarbonyl (N–COOR) and *N*-carboxamido (N–$CONR_2$) oxaziridines have been used as electrophilic nitrogen transfer reagents to C-nucleophiles (Table 2). Oxaziridines are crystalline, stable both at room temperature and under reflux and are easy-to-use reagents and the amination products of *N*-alkoxycarbonyl- and *N*-carboxamidoaziridines are the desired N-protected amino compounds such as N–COOMe (N-Moc), N–COO*t*-Bu (N-Boc) and N–$CONR_2$.

The preparation and utilisation of oxaziridines as electrophilic aminating reagents have been extensively reviewed by Vidal et al.[61]

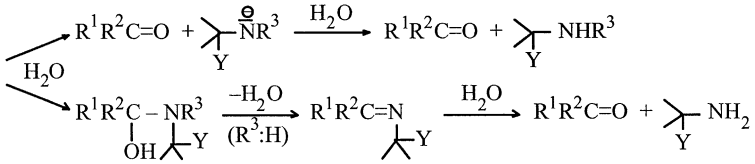
The synthetic applications of cyclohexanespiro-3′-oxaziridine [(3,3-pentamethyleneoxaziridine (**6a**)] for amination of various nucleophiles have already been discussed by Schmitz and Andrea.[62] The same authors and their co-workers have also investigated the amination of carbanions with **6a**.[63] *N*-Alkoxycarbonyloxaziridines have been used as aminating reagents for enolates[64] and for enantiomeric enolates of ketones.[65] The preparation and use of *N*-carboxamidoaziridines (**6b**) and (**6c**) for the amination of enolates have been also reported.[66] Chiral N–H oxazridines derived from camphor and fenchone have been also prepared[67] and have recently been used for asymmetric nitrogen transfer to enolates.[68]

Table 2. Amination of enolates and eniminates with oxaziridines (**6**)



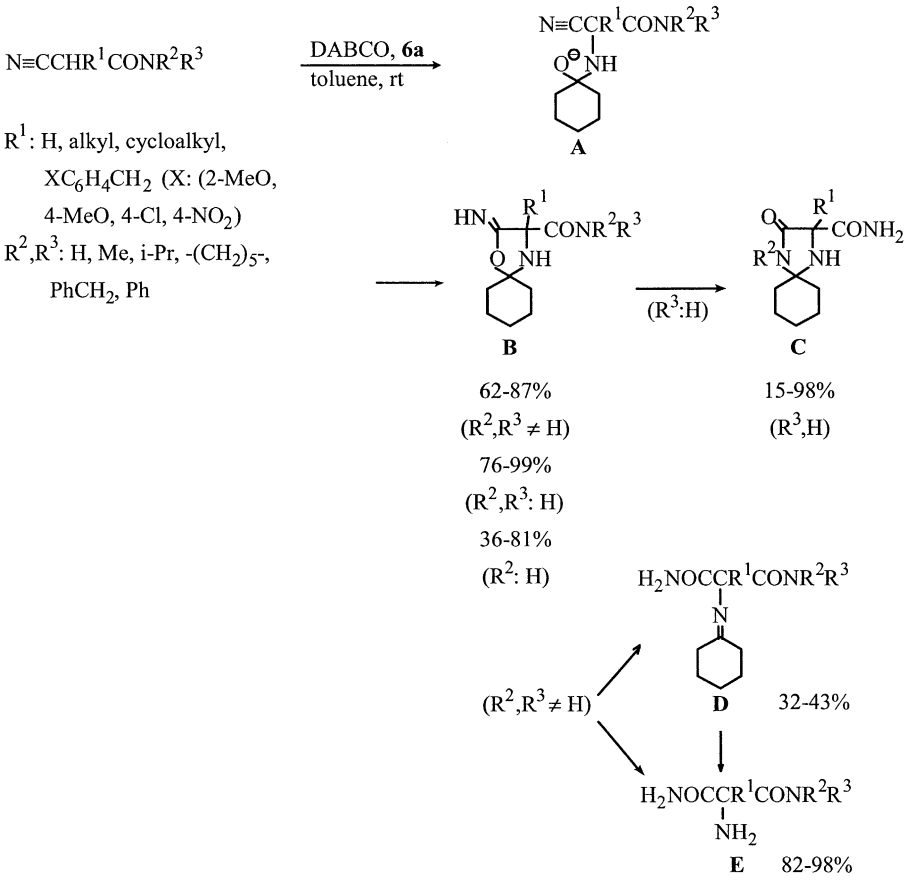


Y: COX (X: R, OR, NR_2),CN

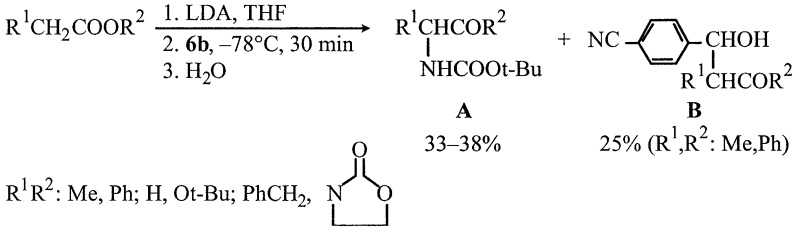


Aminating reagent	Method[a]	Scheme	Reference
6a	A	Scheme 19	63
6b	A	Scheme 20	64
6c	A	Scheme 21	65
6d	E	Schemes 23,24	66
6e	E	Schemes 23,24	67
6e	E	Schemes 23,24	68

[a] See Scheme 3.



Scheme 19.

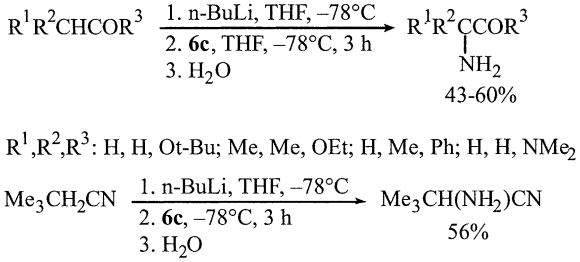


Scheme 20.

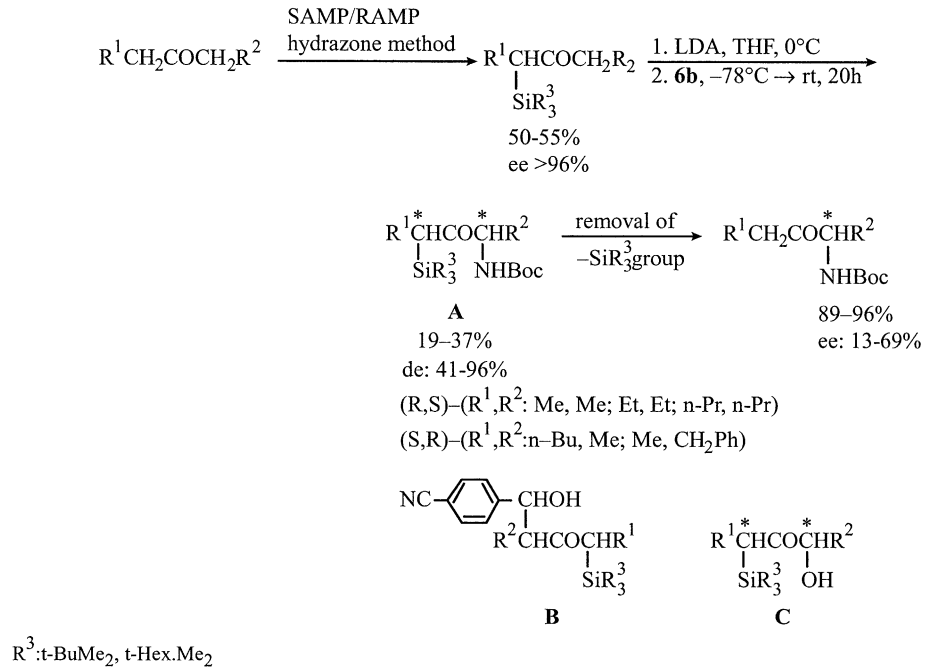
The reactions of 3,3-pentamethyleneoxaziridine (**6a**) with malonic acid amides, cyanoacetic acid amides and a number of cylic carboxylic amides resulted in the formation of the substitution products **A** formed by transfer of a 1-hydroxycyclohexylamino group to the enolates (Scheme 19).[63] In the amination of substituted cyanoacetamides, however ring closure compounds formed by the intromolecular attack on a nitrile group, the substituted 1,4-diazaspiro [4,5] decanones **B**, were obtained as the reaction products in good yields. Ring transformation of these products yielded **C** as the new products. Dehydration of **A** and following or direct elimination of cylohexanone gave the expected amination products **D** and **E**, respectively, in the reaction of N,N-disubstituted cyanoacetamides.

N-Boc-3-(4-cyanophenyl)oxaziridine (**6b**), which is a stable and commercially available reagent has been used for N-Boc transfer to ketone, carboxylic ester and carboxamide enolates by Collet and co-workers (Scheme 20).[64] They pointed out that enolate amination gives the expected product **A** in low yields due to competing aldol reaction product **B** formed between starting enolate and 4-cyanobenzaldehyde, which is released in the N-Boc transfer reaction.

Later, Armstrong and co-workers, in common with Vidal



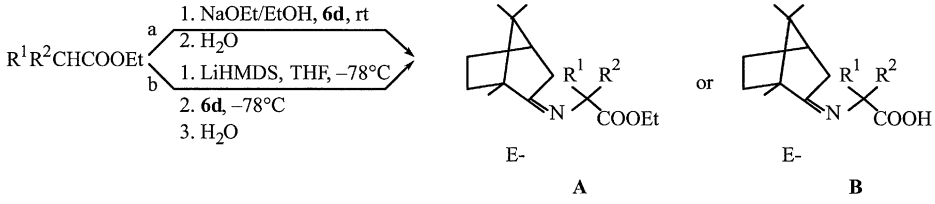
Scheme 21.



Scheme 22.

and Collet, thought that varying the aldehyde portion by the incorporation of *o*-substituents would reduce the amount of aldol product and possibly increase the yield of the desired amination product.[66] and this was indeed shown to be the case. In the amination of *t*-butyl acetate with a series of 3-aryl-*N*-carboxamidooxaziridines, to asses the effect of the aromatic substituents on the yield of the amination product and on the ratio of the amination to aldol product, 3-(2-cyanophenyl)oxaziridine (**6c**) was found to be the most effective reagent.

N-Carboxamidoaziridine **6c** was also used successfully to



R1,R2	Conditions	Reaction time, h	Products	Yield, %
H, COOEt	a	3	A	68
	b	6	A	50
Me, COOEt	a	4	A[a]	89
	b	56	A	20
n-Bu, COOEt	b	49	A[b]	14
Ph, COOEt	b	60	–	–
H, H	b	8	–	–
H n–Pr	b	6	–	–
H Ph	b	29	B	30
H, COMe	b	48	A[b]	43

[a] 1:1 diastereomeric mixture.

[b] Same product obtained in the amination of malonate anion (R1,R2:H, COOEt)

Scheme 23.

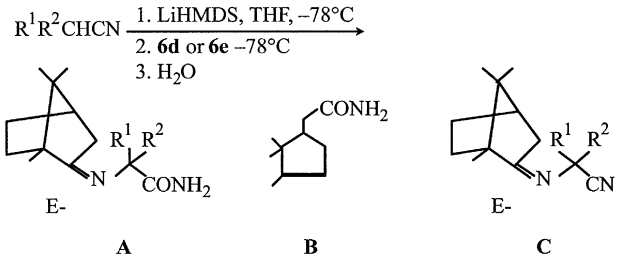
aminate a variety of α-lithiated carboxylic esters, ketones, carboxamides and nitriles (Scheme 21).[66]

2.2.1. Asymmetric versions of amination with oxaziridines (6b), (6d) and (6e). Only Methods D and E, that is, the use of carbonyl compounds or aminating reagents, respectively, as stereodirecting events (Scheme 3) were studied for chiral induction in the amination of enolates with **6**.

Enders and co-workers synthesised chiral α-aminoketones by the amination of enolates of enantiomeric α-silylketones with **6b**. (Scheme 22).[65] α-Silylketones, which serve as ketone equivalent in asymmetric synthesis, can be prepared by SAMP/RAMP hydrazone methodology and regioselectively deprotonated in the α′-position. Reacting the enantiomeric enolates with **6b** yielded the α-N-Boc-α′-silyl substituted ketones **A** in low yields. Cleavage of the silyl group gives the N-Boc α-aminoketones. Two competing side reactions, aldol reaction and hydroxylation gave the side products **B** and **C**, respectively, causing a decrease in the yield of the amination product **A**.

Page and co-workers reported the preparation of the first stable chiral N–H oxaziridines, derived from (1*R*)-(+)-camphor (**6d**) and (1*R*)-(−)-fenchone (**6e**)[67] and explored the use of these reagents for the asymmetric amination of ester enolates and nitrile eniminates.[68] The compound **6d** is a crystalline solid and **6e** is an oily liquid, both are stable, even under reflux, and each consist of a pair of diastereomers in a ratio of about 60:40. In the amination of ester enolates with (*R*)-camphoryloxaziridine (**6d**) (Scheme 23), the reactivity of the reagent toward malonate anions was first tested under thermodynamic and kinetic conditions, that is, the amination was carried out either by adding the ester to a mixture of sodium ethoxide and **6d** at room temperature and stirring or by adding **6d** to enolate prepared by lithiation of ester with LiHMDS in THF at −78 °C and stirring, respectively. Under thermodynamic conditions, the reaction times were found to be much shorter than those for the kinetic conditions and the yields were higher.

The expected products that is, the (*R*)-camphor imines of ethyl carboxylates **A**, were obtained, with one ester group



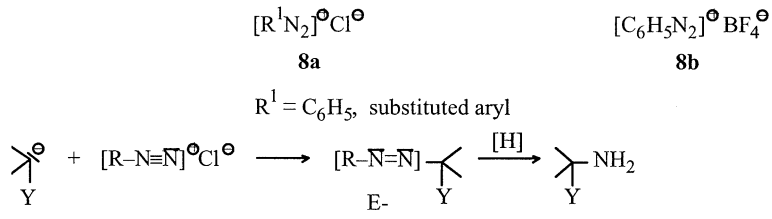
A **B** **C**

R^1,R^2	Aminating reagent	Reaction time, h	Products[a]	Yield, %
H, Ph	**6d**	5	A	78
	6e	5	A	55
H, 2-Naphthphyl	**6d**	5	A	73
	6e	9	A	31
H, 1-Naphthhyl	**6d**	5	A	80
	6e	4	A	48
H, 4-ClC_6H_4	**6d**	5	A	80
H, 4-$MeOC_6H_4$	**6d**	9	A	75
H, 4-$NO_2C_6H_4$	**6d**	6	B	21
H, Me	**6d**	5	B	36
H, Et	**6d**	7	B	83
H, CN	**6d**	6	A	82
H, CH_2=CH	**6d**	27	A[b]	45
H, COOEt	**6d**	6	A[c]	17
Ph, COOEt	**6d**	31	C	68

[a] de:0-33%.
[b] Isomerisation of the terminal double bond gave enamide.
[c] Decarboxylated nitrile (R^1:H).

Scheme 24.

Table 3. Amination of enolates and eniminates with arenediazonium salts (**8**)



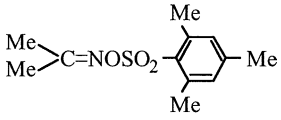
Aminating Reagent	Method[a]	Scheme. Eq.	Reference
8a	A	Scheme 25	73
8b	A	Scheme 26, Eqs. 16a and 16b	74,75
	D	Eq. 17	77

[a] See Scheme 3.

being lost during the reaction process. While amination of the malonate anion gave only one diastereomer, the methyl malonate anion gave a diastereomeric mixture. No product was obtained in the amination of malonate anions with bulky α-substituents such as phenyl. Monoesters, the enolates of which are less stabilised and more reactive than those of malonates, were investigated under kinetic conditions. No reaction was observed with ethyl acetate and ethyl butyrate, suggesting a successful transformation with stabilised carbanions. Amination of ethyl acetylacetate, however, gave surprisingly the (*R*)-camphorimine of ethyl glycinate as the reaction product formed by the loss of an acetyl group, instead of decarboxylation of the ester group. As no diastereomeric excess of the imine products derived from the aminaton of ester enolates with **6d**, was obtained, the amination of nitrile eniminates with **6d** and **6e** was investigated as the next target to improve the diastereoselectivity. Diastereomeric mixtures of the carboxyamides **A** were obtained (Scheme 24), except for 4-nitrophenylacetamide which yielded the α-campholenic amide **B** through a rearrangement. The observed diastereomeric excesses in amination of ester enolates and nitrile eniminates with (*R*)-camphoryloxaziridine (**6d**) were, however, found lower than 33% and attempts to obtain a better diastereosselectivity by using (*R*)-fenchonyloxaziridine (**6e**) as aminating reagent resulted in a 23–52% diastereomeric excess. A mechanism was also offered for the reaction at the oxaziridine unit.

2.3. Ketone *O*-(arenesulfonyl)oximes

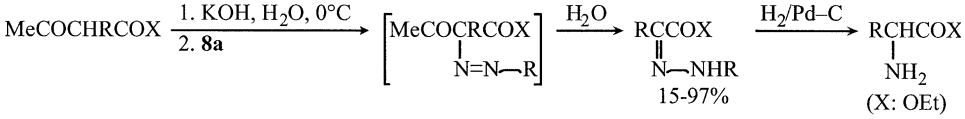
There is no published work in the literature on the use of ketoxime and their O-substituted derivatives for enolate amination. As part of our ongoing project on the electrophilic amination of carbanions, we are investigating the use of acetone *O*-(mesitylenesulfonyl)oxime (**7a**) as an aminating reagent for the lithium and zinc enolates of carboxylic acids and carboxylic esters. The *O*-(sulfonyl)oxime **7a** has been developed in our laboratories[69] and its uses for the amination of pre-prepared[70] or in situ prepared Grignard reagents[71] and for organozinc reagents[72] have been already reported.



2.4. Arenediazonium salts

Arenediazonium salts (**8**) were also used as the electrophilic nitrogen source for active methylene compounds in protic media and for also lithum and silicon enolates (Table 3). The reaction of β-dicarbonyl compounds with **8a** in alkaline solution is known as the Japp–Klingemann reaction (Scheme 25).[73] The hydrazono or azo esters can be easily reduced to the α-amino acid esters and hydrolyzed to the α-amino acids. However, only β-dicarbonyl compounds and their α-monosubstituted derivatives, however, provide an effective method for preparation of α-aminoketones and esters.

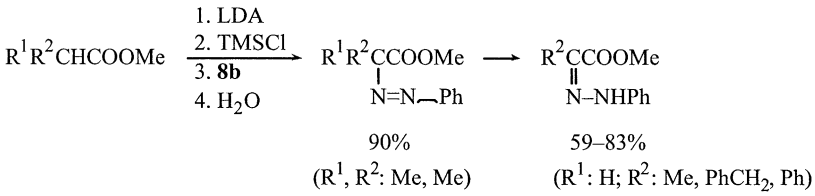
There are only three reports in literature on the amination of lithium and trimethylsilyl enolates of ketones[74] and esters[75] with benzenediazonium tetrafluoroborate (**8b**). Two ketones are reported to give α-azoketones (Eqs. 16a and 16b).[74] Ester enolates give α-azo or hydrazo esters in good yields, which are converted to the α-amino esters (Scheme 26).[75]



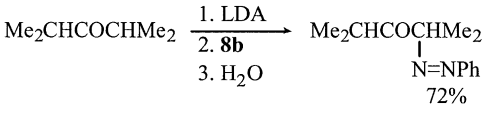
X: Me, OEt

R[1]: C_{1-4} alkyl, $PhCH_2$, $EtOOC(CH_2)_2$, $MeCOCH_2$, $NC(CH_2)_2$, Cl, CN

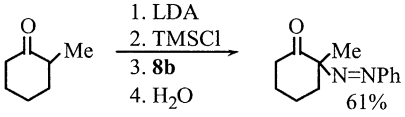
Scheme 25.



Scheme 26.



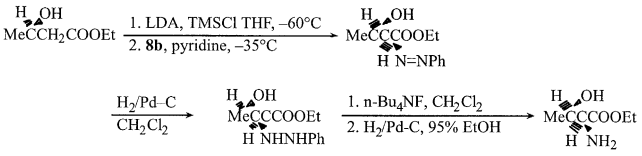
(16a)



(16b)

In our group, we have developed a procedure for amination of triarylzincates with **8b**[76] and the amination ester enolates is currently in progress.

An asymmetric version of amination with **8b** is exemplified by one published report.[77] Trimethysilyl enolate prepared from ethyl (3*S*)-3-hydroxy butanoate reacts with **8b** in pyridine to provide the (2*R*,3*S*)-α-azoester in low yield, but with a high diastereoselectivity (Eq. 17). The syn selective reaction of the enolate with imines was also confirmed.

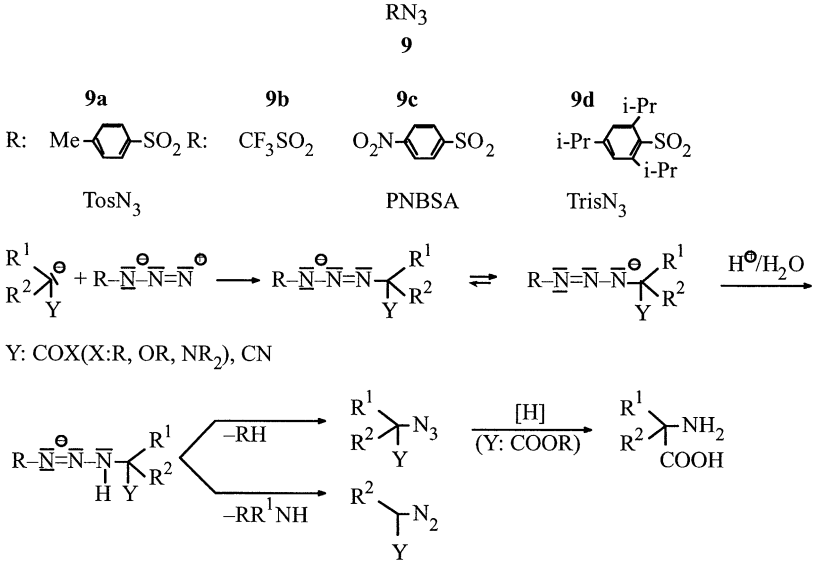


(17)

2.5. Azides

Organic azides (**9**) have found their numerous applications in the electrophilic amination of carbanions, and methods for their preparation and synthetic uses have been reviewed.[78] however, Methods for the electrophilic azide transfer to enolates and eniminates are, however, still limited. The problem related to the use of azides is that these reagents also react to function as diazo transfer reagents.[79] For this reason, the reaction parameters in the synthesis of α-azidocarbonyl compounds using sulphonyl azides were modified in all attempts to afford maximum the azide transfer with minimal competing diazo transfer. So far, *p*-toluensulphonyl azide (tosyl azide) (**9a**), *p*-nitrobenzene-sulphonyl azide (nosyl azide) (**9c**) and 2,4,6-triisopropyl-benezensulfonyl azide (trisyl azide) (**9d**) were used for

Table 4. Amination of enolates and eniminates with azides (**9**)

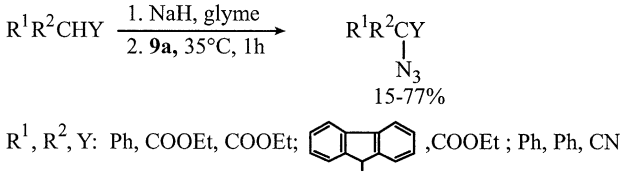


Aminating reagent	Method[a]	Scheme, Eq.	Reference
9a	A	Scheme 27	80
	D	Scheme 29	88,89
9b	A	—	81
9c	D	Scheme 27	88,89
9d	A	Scheme 28, Eqs. 18 and 19	82–87,91
	D	Schemes 29–31	88–90,92,93

[a] See Scheme 3.

electrophilic azidation of enolates and eniminates (Table 4). The azide **9a** is a shock-sensitive reagent, and great caution is always necessary in the handling of azides. The structure of the sulphonyl azide has a major influence on the reaction between the azide and diazo transfer routes. Early approaches for the amination of enolates with azides involve reaction of resonance stabilised enolates with **9a**[80] and **9b**,[81] or, according to Kühlein and Jensen procedure,[82] the reaction of nonstabilized enolates with **9a**.[83–87] Recently, a method for azide transfer to chiral carboximide enolates and procedures for the derivatisation of α-azido carboximides to α-amino acids have been reported by Evans et al.[88–92]

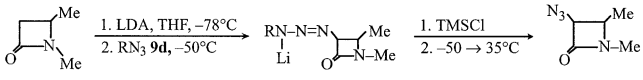
The reaction of sodium enolates of substituted malonates and 9-fluorenecarboxylates with **9a** gave medium yields of α-azidocarbonyl compounds, but the azidation of the sodium eniminate of diphenylacetonitrile resulted in a low yield (Scheme 27).[80]



Scheme 27.

Trifluoromethanesulphonyl azide **9b**, prepared in situ from trifluoromethanesulphonyl chloride and sodium azide, reacted with enolates derived from β-dicarbonyl compounds and phosphonoacetates to yield the α-azidocarbonyl compounds in good yields.[81]

In an important study by Kuhlein and Jensen, the lithum enolate o a γ, β-propiolactam, *N*-methyl 4-methyl-2-azetidinone was treated with azide (**9d**) to yield the lithium salt of the triazene adduct (Eq. 18).[82] Treatment of the adduct with the quenching reagent TMSCl and decomposition by heating yielded the 3-azido azetidines as a 3:2 mixture of stereoisomers.



(18)

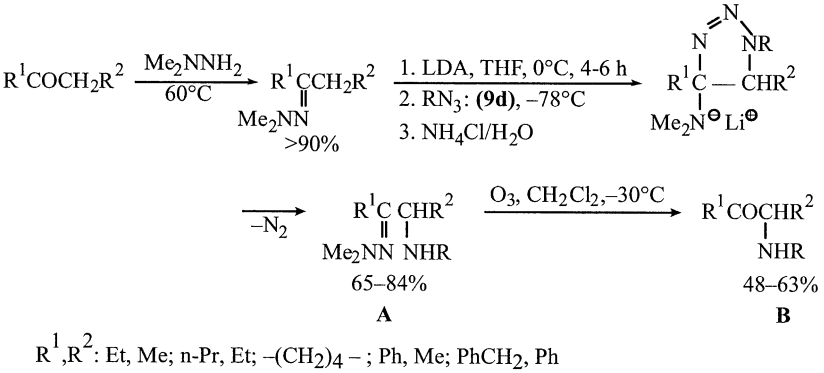
Azide transfer to β-lactam lithium enolates and TMSCl quenching resulted in the application of this method to the synthesis of a number of 3-aminoazetidinones in good yields,[81–86] and it has also been successfully adapted for the direct azidation of a γ-lactam lithium enolate.[87]

Enders and co-workers have recently used trisyl azide **9d** for the syntheses of α-azidohydrazones from the corresponding ketone *N*,*N*-dimethydrazones (Scheme 28).[91] Instead of the expected azide transfer product, however, the N-protected α-aminohydrazones **B** formed using NH_4Cl as quench reagent following amination. 1,3-Dipolar cycloaddition of the azide dipole reagent with the enolate in an opposite regioselectivity was proposed by Evans for the formation of the triazoline adduct **A**,[89] which, upon subsequent loss of N_2, yielded the reaction product **B**, which can be oxidatively cleaved to give the α-amino ketones in good yields.

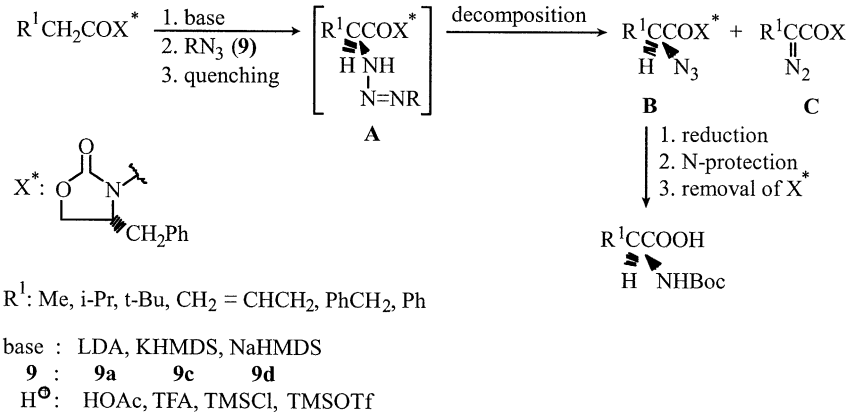
2.5.1. Asymmetric versions of amination with azides (9a), (9c) and (9d). For chiral induction in the amination of enolates with azides **9**, only Method **D**, that is, the use of chiral carbonyl compound as a stereodirecting event (Scheme 3), was successfully tried.

Evans and co-workers have explored the azidation of chiral carboximide enolates systematically and developed a method for the synthesis of enantiomeric α-amino acids.[88–90] They have studied the reaction parameters, that is, enolate metal, azide transfer reagent, and quenching reagent on the yield of electrophilic enolate azidation in conjunction with the development of asymmetric syntheses of (*R*) and (*S*)-α-azidocarboxylic acids (Scheme 29).[88,89]

They found that the yield of the azide transfer product **B** increases at the expense of the competing diazo transfer product **C** (i) as the enolate counterion becomes more electropositive (Li ≪ Na < K), (ii) as the transfer reagent becomes more electron rich and sterically demanding (**9c** < **9a** < **9d**) and (iii) when glacial acetic acid is used instead of the more reactive trifluoroacetic acid or silylating agents, TMSCl or TMSOTf, for quenching. Under reaction optimisation conditions, using KHDMS for deprotonation of carboximides containing (4*R*)- or (4*S*)-4-benzyl-2-oxazolidinone, that is, *N*-acyloxazolidinones as chiral anxiliaries, reacting the enolates with an azide **9** at −78 °C, quenching the reaction with HOAc and heating gently yielded the α-azidocarboximides in high yield and

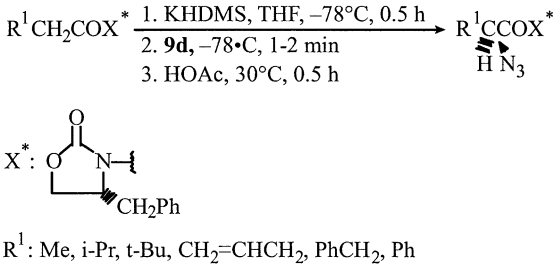


Scheme 28.



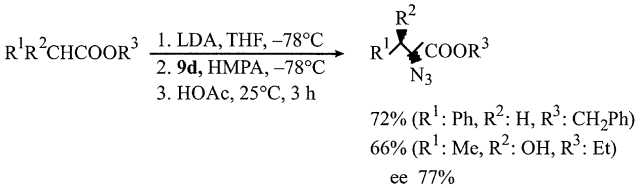
Scheme 29.

diastereomeric excess (Scheme 30).[88,89] The triazene adduct **A** formed by the addition of enolate to the electrophile azide as shown in Scheme 29 is not isolated, but decomposes to the azide upon warming the mixture following quenching.[89] Based on the decomposition studies on the intermediate triazene **A**, the weak insoluble base KOAc, generated as a result of the reaction quenching was established as the key compound for triazene decomposition to the azide.[89]



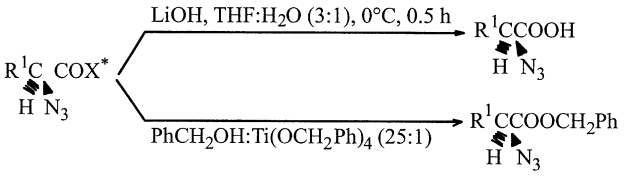
Scheme 30.

The reaction of **9d** with ester enolates was also investigated and the yield was found to be less sensitive to the enolate metal than that in the azidation of chiral amide enolates. The effect of the azide transfer reagent on the azide transfer product **A** to diazo transfer product **B** ratio (see Scheme 29 for products **A** and **B**) did not, however, change in the azidation of ester and chiral amide enolates (Eq. 19).[89]



(19)

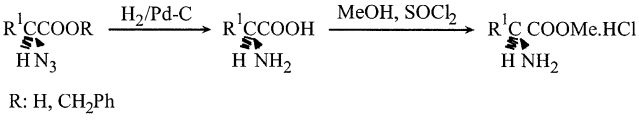
Derivatives of α-azidocarboximides were also investigated. They undergo selective hydrolysis for removal of the chiral auxiliary[89,90] and, for conventional substrates, transesterification without racemisation (Eq. 20).[90]



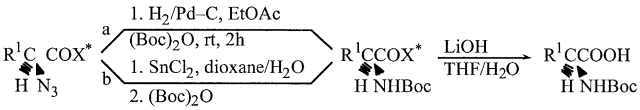
(20)

Hydrolysis (saponification) with LiOH or, more effectively, with H_2O_2–LiOH (2:1) gave the corresponding α-azidocarboxylic acids in high yield and in high enantiomeric purity. For transesterification, benzyl alcohol in the presence of its titanium tetraalkoxide was used to provide benzyl esters in high yields.

α-Azidoacids or esters can be reduced to α-amino acids and the resulting α-amino acids are then esterified to provide the methyl ester hydrochorides (Eq. 21).[90] Reduction and N-protection can, however, also be carried out before hydrolysis and conditions have been discovered by Evans group to achieve this transformation in good yield.[89,90] The protocol can be applied by either hydrogenation, in situ N-protection to prepare N-Boc derivative and then hydrolysis (path a) or alternatively reduction with $SnCl_2$, in methanol[85] or dioxane[86], N-protection and then hydrolysis (path b) (Eq. 22).

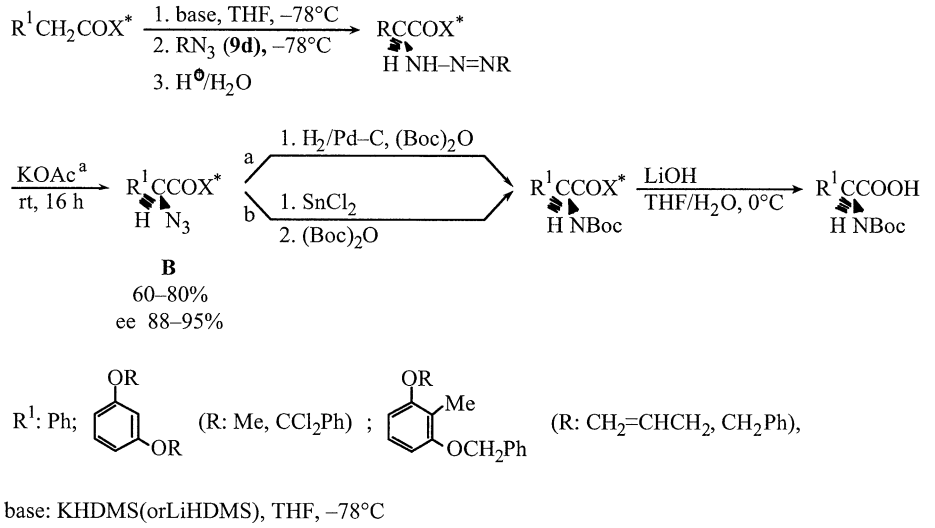


(21)



(22)

Williams and co-workers used Evans' electrophilic amination method for asymmetric synthesis of antibiotic related arylglycines and they reported that the triazene **A** (Scheme 29) could not be broken down to the α-azidocarboximide **B** in certain cases.[92] The optimisation of the conditions for enolate formation, azide transfer to enolate, the stability and isolation of triazene **A** and the decomposition of the triazene to the desired azide **B** were discussed in detail again by Evans and co-workers.[90] They applied the



Scheme 31.

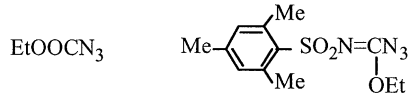
method for the asymmetric azidation of enolates derived from arylacetamides containing a chiral oxazolidinone moiety to prepare nonproteinogenic arylglycines, in conjunction with the syntheses of vancomycin-related antibiotics (Scheme 31). KOAc was again reported to be the best reagent for the transformation of triazene **A** to α-azidocarboximide **B** with the highest diastereoselectivity. α-Azido carboximides **B** can be successfully reduced and N-protected according to the reported procedure.[85] Subsequent cleavage of the chiral auxiliary the provides N-Boc arylglycines in almost quantitative yield in high enantiomeric excess.

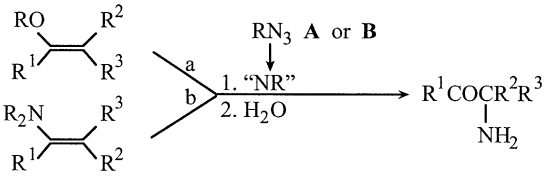
Evans' electrophilic amination method was also used in the asymmetric synthesis of another antiobiotic-related arylglycine; that is (*S*)-*N*-boc-3,5-bis(isopropoxy)-4-methoxypenylgycine with 95% yield and 95% enantiomeric excess.[93]

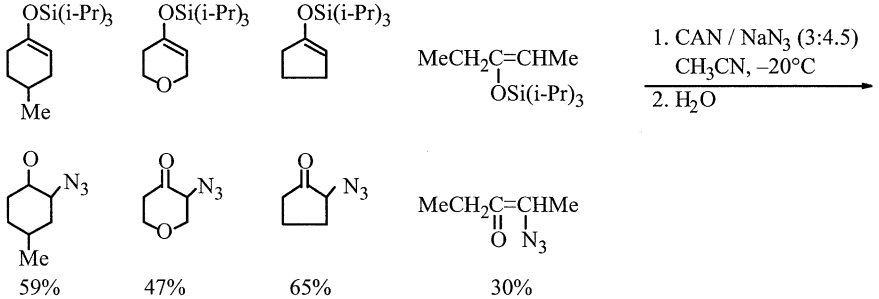
As summarised in Section 2.2, aziridination, that is, nitrene transfer to a double bond, is one of the established methods for introducing an α-amino function to enols and enamines (Eq. 8). Loreto and co-workers also showed that the amination of enols with NH(COOEt)ONs (**3d**) takes place via the aziridination route (Eq. 7)[40,41] (Scheme 18).[56]

The formation of aziridines from the addition of thermally or photochemically generated nitrenes to olefins has been well documented.[94,95]

Loreto et al. have published procedures for the amination of ketones[96,97] and esters[98] by the addition of nitrenes to silyl enolates (Eq. 23, path a) and they used the photolysis or thermolysis of ethyl azidoformate **A**. Successful asymmetric amination of carbonyl compounds by nitrene transfer[56] to enol ethers carrying chiral auxiliaries has also been reported[99] by the same group however. For nitrene formation in enol ethers, however they found photolysis of **A** unsuccessful, contrary to its thermolysis. Danishefsky attempted asymmetric aziridination of enol ethers using[100] prior to this work. Pellacani's group recently tried both ethyl azidoformate **A** and (*N*-mesitylenesulphonyl)azido formimidate **B** for the aziridination of cyclopentanone and cyclohexanone enamines derived from chiral pyrrolidines and observed that the asymmetric induction was higher in the reaction of cyclopentanone enamines with **A** and **B** and that the cyclohexanone enamines did not undergo aziridination (Eq. 23 path b).[101,102]







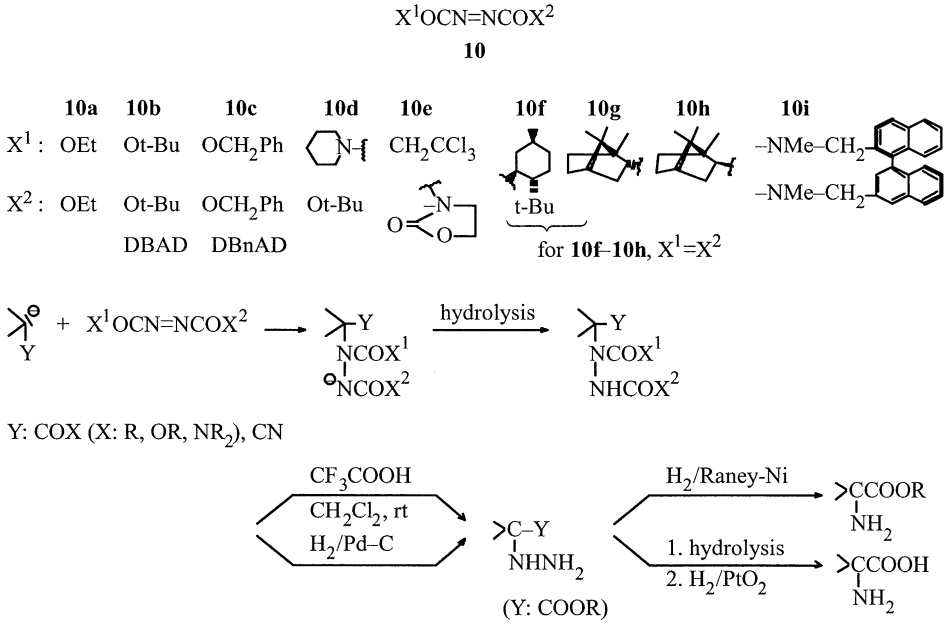
Scheme 32.

Magnus and co-workers used the reagent combination ceric ammonium nitrate (CAN)/NaN_3, as an electrophilic aminating reagent for triisopropyl silylenol ethers and reported a direct method for the synthesis of α-azidoketones in medium to good yields (Scheme 32).[103] The method is described as electrophilic α-azidonation, since the reagent combination PhIO/$TMSN_3$ leads to β-azidonation.[104] α-Azidoketones are useful synthetic intermediates and they can be reduced to α-aminoketones. Triisopropylsilyl enol ethers are easily prepared from the ketone and triisopropylsilyl triflate in the presence of triethylamine.

2.6. Diazene dicarboxylates

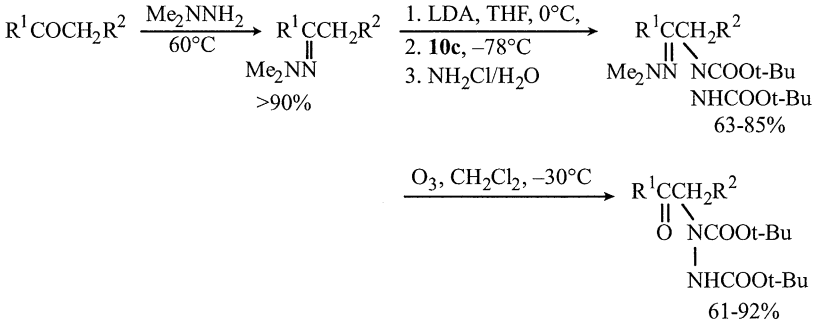
Electrophilic amination of enolates with diazene dicarboxylates (**10**) is as a particularly attractive method for α-aminocarbonyl compounds and especially for α-amino acids. In addition, a number of papers have appeared on the asymmetric synthesis of α-amino acids and α-amino-β-hydroxyacids using different methods for chiral induction in the amination. The choice of diazene dicarboxylates (**10**) for the α-amination of enolates, especialy enolates derived from carboxylic acids and esters, depends on several factors, although the synthesis of α-aminocarbonyl compounds requires three or four steps (Table 5). Diazene dicarboxylates (**10**) are stable and commercially available reagents and di *t*-butyl azodicarboxylate (**10b**) is the most-used reagent, due to its high reactivity. A number of methods are available for clean removal of the *t*-butoxycarbonyl group[105] in addition to methods for N–N bond cleavage. The products of the 1,4-conjugate addition of enolates to diazene dicarboxylates are the α-hydrazido adducts of carbonyl compounds. For the synthesis of α-amino esters and acids, removal of the *N*-acyl groups, followed by hydrogenolysis of the α-hydrazino adducts, is the most common route. For the first step, hydrolysis by trifluoroacetic acid is used more than hydrogenolysis and, for the second step, hydrogenolysis with Raney-Ni or with Pt are the methods of choice for the α-amino esters and α-amino acids, respectively.

Table 5. Amination of enolates and eniminates with diazene dicarboxylates (**10**)



Aminating reagent	Method[a]	Scheme, Eq.	Reference[a]
10a	A	Scheme 34, Eqs. 26 and 27	112,113,116,117
	C	Schemes 39, 41, 43 and 44	121–123,125,126
	D	Scheme 56	113
10b	A	Scheme 34	116
	C	Schemes 38 and 44	120,126
	D	Schemes 45–47, 49–55, Eq. 29	128,133,134,146
10c	A	Schemes 33 and 34, Eq. 25	91,110,111,116
	B	Scheme 37	116
	C	Schemes 39–42	121,133,124
	D	Scheme 56	113
10d	A	Eq. 28	118
10e	A	Eqs. 24 and 28	106–109,118
	B	Scheme 36	119
10f	E	Scheme 57	146,147
10g	E	Scheme 57	146,147
10h	D	Eq. 30	141,142
	E	Scheme 57, Eq. 30	142,143,146,147
10i	E	Scheme 58	145

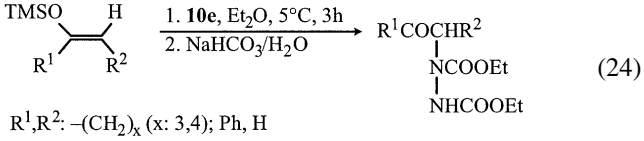
[a] See Scheme 3.



Scheme 33.

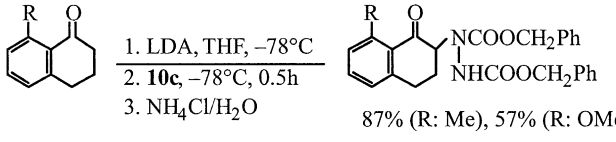
Hydrolysis of α-aminoesters is generally carried out before hydrogenolysis.

The first reports on the use of diazene dicarboxylates (**10e**) for the electrophilic amination of achiral enolates describe the reactions of diethyl malonate,[106] acetylacetone and ethyl acetoacetate[107] and cyclohexanone-derived enolates[108] with **10a**. The amination of trimethylsilyl enolates of cyclohexanone, cyclopentanone and acetophenone with **10a** was also found to be successful (Eq. 24).[109]



(24)

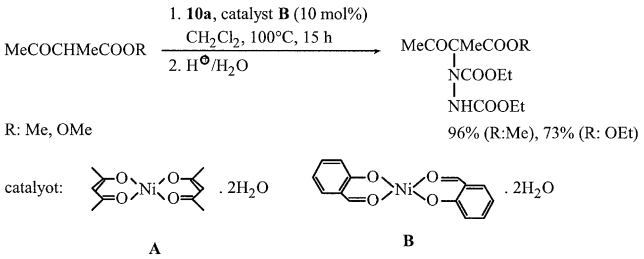
Gmeiner and Bollinger applied the amination of ketone enolates with **10c** in the synthesis of some pharmacologically active compounds and α-tetralones were aminated in good yields (Eq. 25).[110,111]



(25)

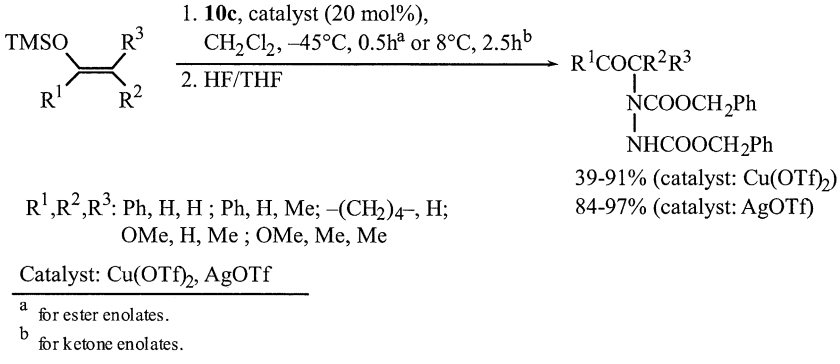
Enders and co-workers used **10c** for the syntheses of α-hydrazidohydrazones from the corresponding enolates of ketone *N*,*N*-dimethylhydrazones (Scheme 33).[91] The products were cleaved to α-hydrazidoketones in high yields.

In recent years, two reports have appeared on the direct transition metal-catalysed amination of active methylene compounds with diazene dicarboxylates (**10**).[112,113] It is well known that transition metal-catalysed conjugate additions of active methylene compounds to Michael acceptors are attractive, since secondary reactions are minimised by avoiding basic catalysis.[114,115] Moreno-Marias and co-workers reported that, in the reactions of 2-methyl-substituted derivatives of acetylacetone and ethyl acetoacetate with **10a**, nickel salicylaldehydate **B** showed a better catalyic activity than nickel acetylacetonate **A** (Eq. 26).[112] This reaction also provides the first example of a direct catalytic amination of 1,3-diketones and 3-ketoesters with diazene dicarboxylates.

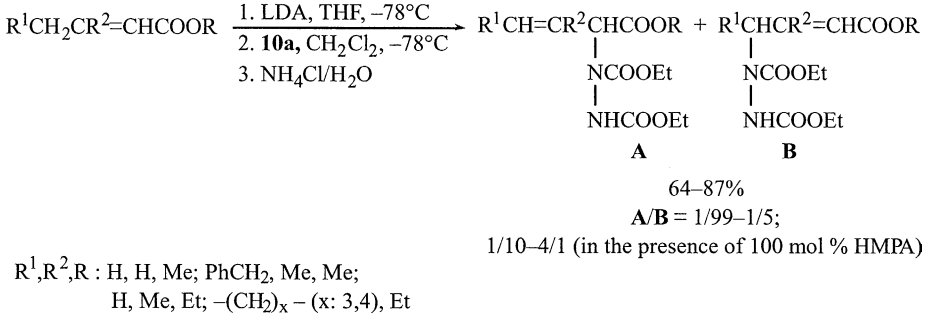


(26)

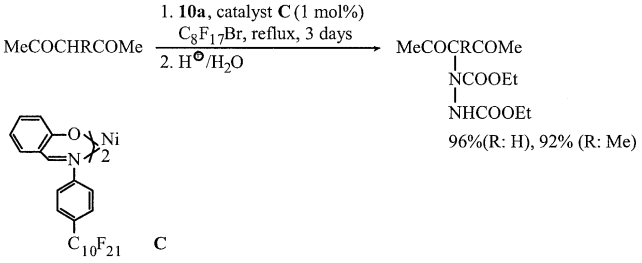
Although catalysis by the complex of salicylaldehyde **B** does not lead to side products, as in the case of catalysis by the complex of acetylacetone **A**, **B** was found to contaminate the final product after work-up. The authors therefore decided to use the Ni(II) complex of the Schiff base of salicylaldehyde and 4-perfluorodecylaniline as catalyst **C** in a polyfluorinated solvent for the recovery of the catalyst and also for easy isolation of the product (Eq. 27).[113] The recovered catalyst **C** could be used four times without a noticeable drop in the yield.



Scheme 34.



Scheme 35.

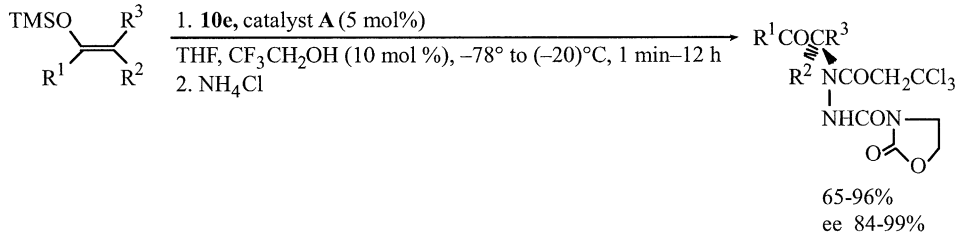


(27)

Kobayashi and co-workers investigated transition metal catalysis in the amination of enolates with **10c** (Scheme 34).[116] They observed that copper and silver triflates have a higher catalytic activity than the other transition metals and also tin(II) triflates and they reported silver triflate to be the most efficient catalyst. Catalytic amination of silyl enolates derived from ketones, esters and thioesters proceeded cleanly and highs yield were obtained. The optimizaton studies showed that the amination proceeded cleanly in CH_2Cl_2 and, not only **10c**, but also **10a** and **10b** gave the corresponding amination adducts in high yields and *t*-butyldimethysilyl group performed well as a silyl moiety instead of the trimethylsilyl group.

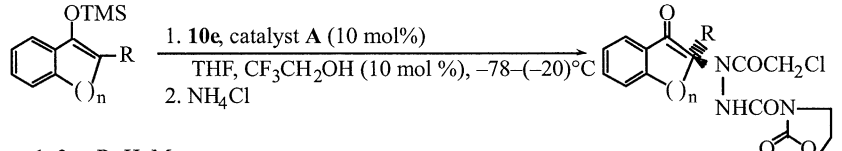
Yamamoto and co-workers reported interesting results on the regiocontrol of amination of dienolates with diazene dicarboxylates **10**.[117] Lithium dienolates derived from α, β-unsaturated carboxylates reacted with **10a** to give either exclusively or predominantly γ-amino acid derivatives (**B**) and the addition of HMPA increased the α-selectivity (**A**) (Scheme 35). In the presence of a Lewis acid, γ-Sn masked dienolates produced α-adducts, while α-Si or α-Ge masked dienolates gave γ-adducts.

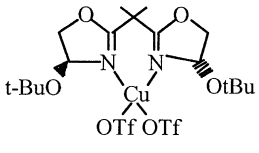
In addition, they observed that a diazene ester–amide



R1, R2, R3: Ph, H, C1-4 -alkyl ; Ph, H, CH_2 = $CHCH_2$; 4-$MeOC_6H_4$, H, Ph; t-BuS, Me, H; t-Bu, H, Me;

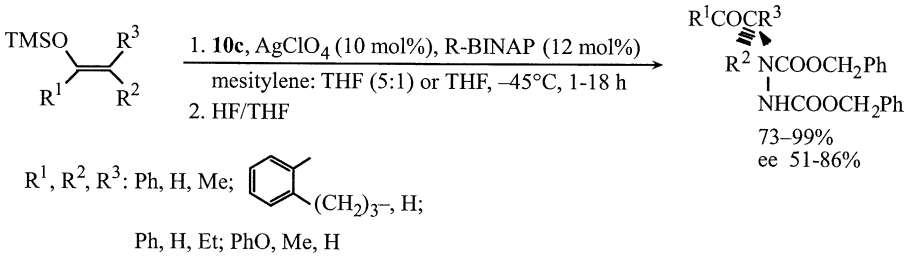
N–, H, C2-4 alkyl; N–, H, CH_2=$CHCH_2$





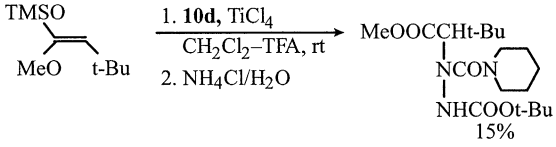
A

Scheme 36.



Scheme 37.

reagent reacts with ethylzinc, -lithium, -aluminium or -copper reagents at the nitrogen atom attached to the ester group, whereas it reacts with the same organometallic compounds at the atom attached to the amide group in the presence of a Lewis acid in high yield.[118] The explanation depended on the formation of different chelated intermediates in the absence or presence of Lewis acids to be attacked by the carbanion. Amination of an enolate, however gave a low yield (Eq. 28).



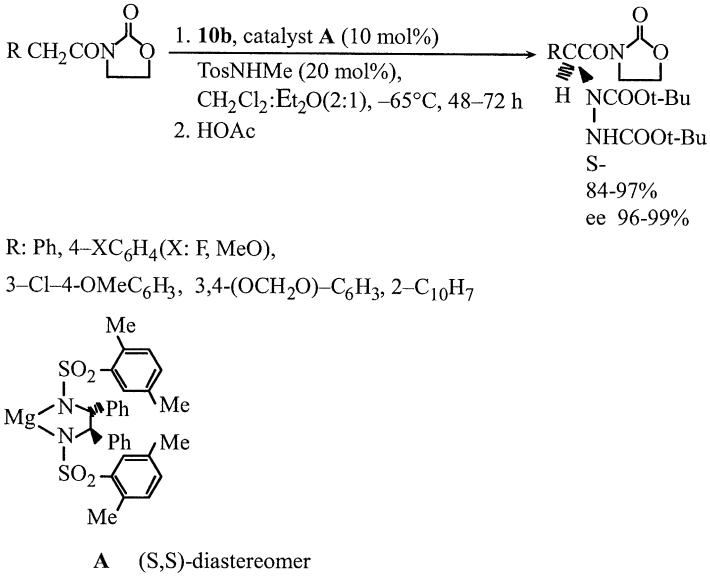
(28)

2.6.1. Asymmetric versions of amination with diazene dicarboxylates (10a–i). All methods outlined in Scheme 3 have been used for chiral induction in the amination of enolates with **10**. Methods B, C and D, that is, the use of chiral catalysts, bases or enolates, respectively as stereo-directing events, generally provided successful routes for the asymmetric synthesis of α-amino acids and esters. In addition, Method E, that is, the use of chiral aminating reagents, has also been investigated.

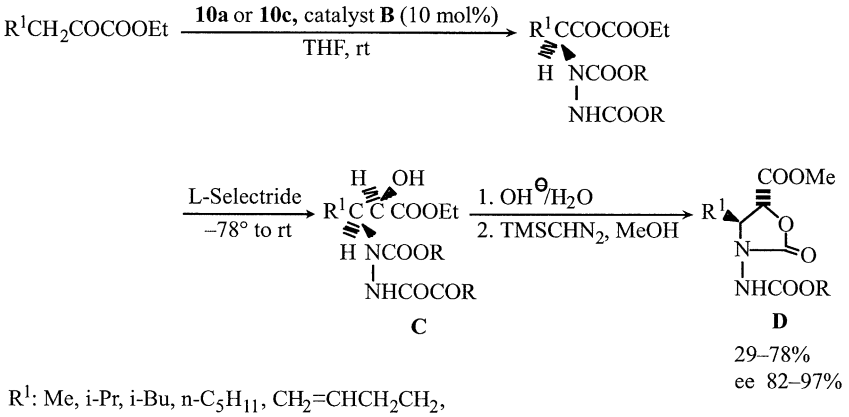
There are two reports on the asymmetric amination of enolates using chiral transition metal catalysis.[116,119] Evans and co-worker used a chiral Cu(II) complex, $Cu(OTf)_2L^*_2$ for the enantioselective amination of silyl enolates derived from ketones, acylpyrroles and thioesters with **10e** and obtained high enantiomeric excesses (Scheme 36).[119] An alcohol additive appeared to be critical to promote the catalyst turnover. As diazene dicarboxylate, **10e** was selected over **10c** and **10d** because of its favourable solubility properties. The complete regioselectivity of **10e** suggested its activation through chelation with the complex **A**.

Kobayashi and co-workers used a silver salt/chiral ligand system as a catalyst in the amination of silyl enolates with **10c** (Scheme 37).[116] The best chiral induction was obtained with $AgClO_4$/(*R*)-BINAP in mesitylene–THF.

A recent and very attractive use of diazene dicarboxylates **10** for the asymmetric α-amination of carbonyl compounds involves preparing catalytic chiral enolate derivatives[120–122] or enamine derivates[123–126] to be aminated. The enolate derivatives were prepared by using a chiral magnesium sulphonamide complex $Mg(NR^*_2)_2$ **A** by Evans and co-workers (Scheme 38)[120] and by using a chiral bisoxazoline–Cu(II) complex **B** by Jorgensen and co-workers (Scheme 39).[121] (Scheme 40)[122] as catalysts. Enamine derivatives were prepared by using L-proline by List (Scheme 41)[123] and by Jorgensen (Scheme 42)[124] and (Scheme 43)[125] and very recently, by Brase (Scheme 44).[121] These seven reports[120–126] provide examples for the direct catalytic (or organo-catalytic as named by Jorgensen[120]) asymmetric α-amination of carbonyl compounds. Generation of catalytic enol and enamine intermediates by using transition

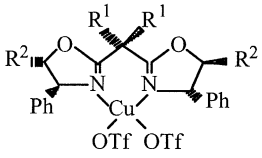


Scheme 38.



R^1: Me, i-Pr, i-Bu, n-C_5H_{11}, CH_2=$CHCH_2CH_2$, CH_2=CH CH_2, c–$C_6H_{11}CH_2$, CH_2Ph

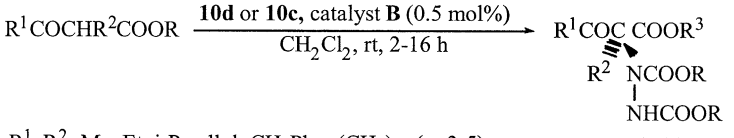
R: Et with **10a**, CH_2Ph with **10c**



R^1, R^2: Me, H; H, Ph; Me, Ph

B

Scheme 39.



R^1, R^2: Me, Et, i-Pr, allyl, CH_2Ph, –$(CH_2)_n$–(n: 3-5)

R^3: Et, t-Bu

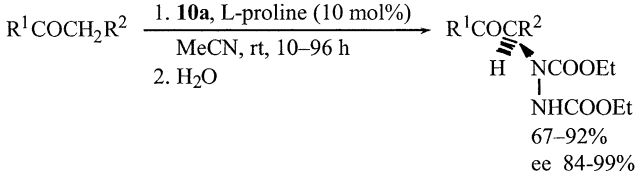
R: Et with **10a**, CH_2Ph with **10c**

catalyst **B**: R^1, R^2: H, H

Scheme 40.

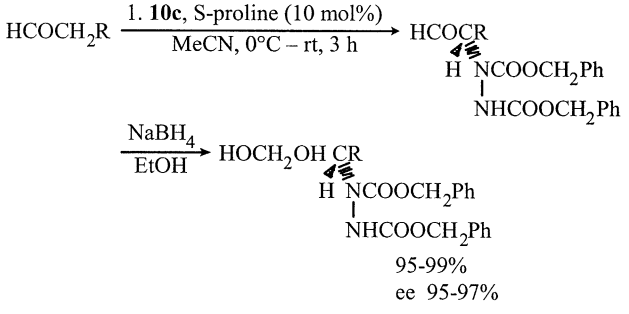
metal complexes[120–122] or L-proline[123–126], respectively, has been reported as 'merged enolisation' by Evans.[120]

α-Amination of carboximides with **10b** in the presence of **A** (Scheme 38)[120], and α-amination of α-ketoesters (Scheme 39)[121] and β-ketoesters (Scheme 40)[122] with **10c** in the presence of **B**, proceed with low loading (0.5–10 mol%) of the catalysts and give the desired 2-, 3- and 2-hydrazido adduct, respectively, in high yields and excellent enantiomeric excesses. In the α-amination of α-ketoesters, however the keto functionality was stereoselectively reduced to the syn-2-hydroxy-3-hydrazido adduct (**C**) in order to solve the problem of loss of enantioselectivity and subsequent cyclization–ester hydrolysis and reesterification steps gave the *N*-amino-oxazolidinones (**D**) in good yields and high diastereoselectivity.[121] The use of THF instead of CH_2Cl_2[122] increased the amination yield and several chiral bisoxazoline–Cu(II) complexes[121] have been found to be successful.



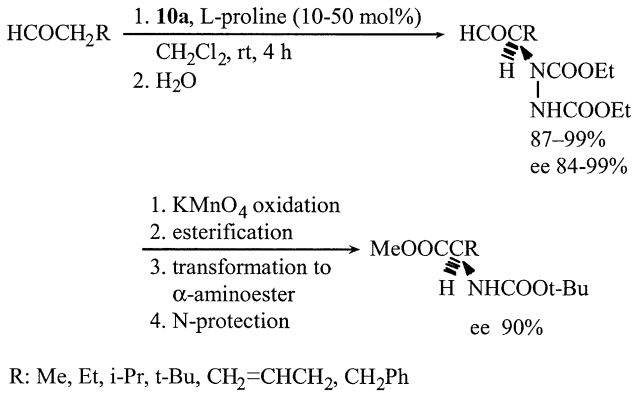
R^1, R^2: Me, Me; Me, Et; Me, i-Pr; Me, CH_2Ph; Et, Me

Scheme 41.



R: Me, Et, i-Pr, n-Pr, n-Bu, CH_2Ph

Scheme 42.



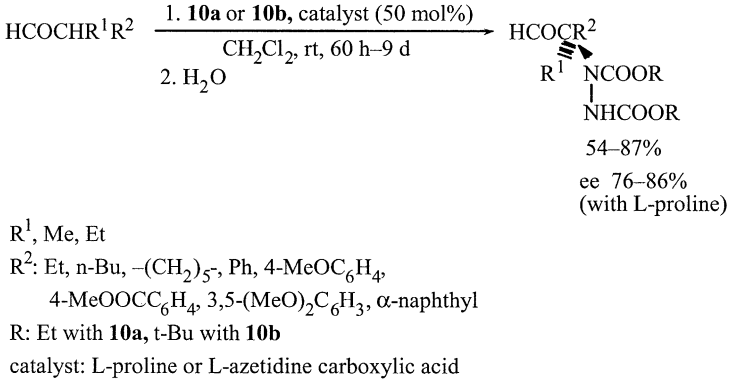
Scheme 43.

α-Amination of ketones (Scheme 41)[123] and aldehydes (Scheme 42)[124] (Scheme 43)[125] and (Scheme 44)[126] catalysed by L-proline[123–125] or L-oxazolidinone[126] give access to enantiomeric α-hydrazidoketones and aldehydes, respectively. These reactions are conducted at room temperature in either CH_2Cl_2 or MeCN and an easy isolation procedure provides products in good yields and excellent enantioselectivities. L-Oxazolidinone catalysis resulted in lower enantioselectivities. The potential and scope of the electrophilic amination of catalytically formed enamine intermediates of ketones and aldehydes has been demonstrated by the synthesis of different valuable optically active products. The reduction of the keto functionality gave either syn or anti α-aminoalcohols. The reduction or oxidation–esterification of the aldehyde functionality provided α-aminoalcohols and N-protected esters of α-amino acids, respectively, and cyclisation of the corresponding alcohols gave the oxazolidinones.[124,126]

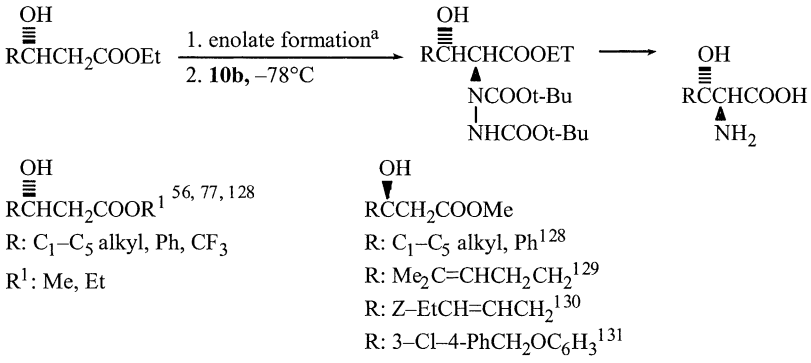
Attractive features of the L-proline-catalysed direct asymmetric α-amination of ketones and aldehydes have been recently reviewed[127] and these include readily available and inexpensive achiral starting materials, operationally simple reaction conditions, high yields and enantiomeric excess and accesses to α-aminoalcohols, α-amino acids and oxazolidinones.

Diazenedicarboxylates **10** have found many applications in the asymmetric synthesis of α-aminocarbonyl compounds by the amination of enolates derived from chiral carbonyl compounds or from carbonyl compounds containing a chiral auxiliary group.

Amination of chiral β-hydroxyester enolates with **10b** is the method of choice for the preparation of anti α-amino-β-hydroxyesters. Greck and Genet have prepared a number of these reagents and have used the amination products as precursors for other biologically active compounds.[57,128–131] They also have a reviewed the applications of this amination procedure.[5] Since the amination procedure simply consists of the preparation of the lithium enolates,[56,77] silyl enolates[130] or zinc enolates[128,129,131] of the

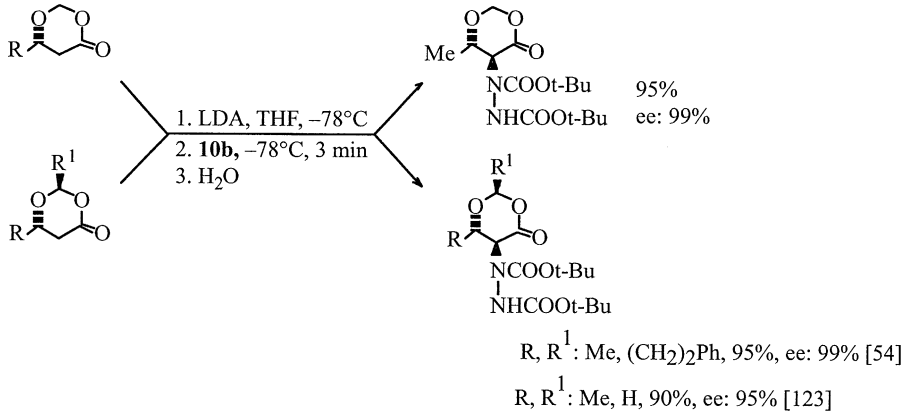


Scheme 44.



[a] LDA or 1. LDA, 2.R_3SiCl (R_3Si: MeSi, Me_2 (t–Bu)Si) or 1. LDA, 2. $ZnCl_2$

Scheme 45.



Scheme 46.

esters and their reactions with **10b**. Only the starting β-hydroxyesters and the related references are given[54,77,128–131] here. The products anti α-hydrazide adducts, are obtained in medium or good yields with diastereomeric excesses higher than 60% (Scheme 45) The anti stereoselectivity could be increased by preparing zinc enolates which have chelating properties, and potassium and titanium enolates gave exclusively the anti diastereomer.[128]

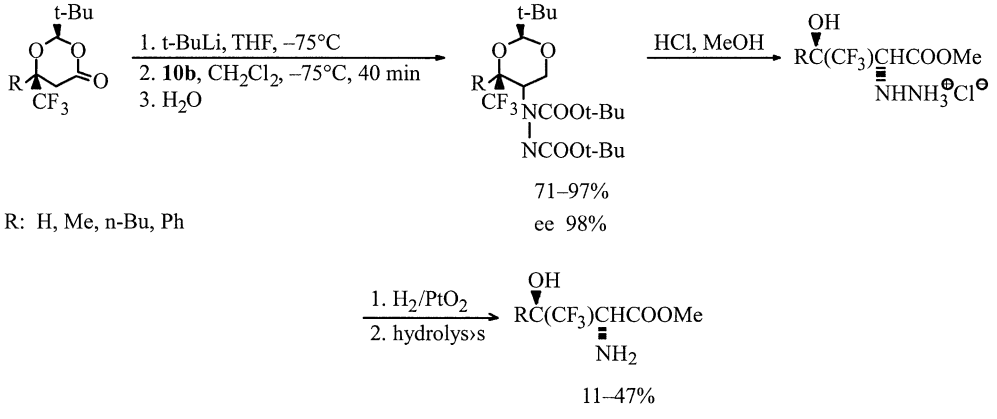
Genet and co-workers anticipated that the modest diastereoselectivites obtained in the amination of 3-hydroxyalkanoate enolates were due to the acyclic nature of these substrates[56] and reported that the amination of 3-hydroxyalkanoic acids protected as the dioxanones gives high yields and diastereomeric excesses (Scheme 46).[56,128] The methylene dioxanones were derived from 3-phenylpropanal[56] or formaldehyde.[125]

Seebach and co-workers have also investigated the amination of enolates derived from dioxanones for the syntheses of diastereomerically pure 2-amino-3-trifluoromethyl-3-hydroxyalkanoic acids (Scheme 47).[132,133] Trifluoro substituted dioxanones were prepared by cuprate addition to the corresponding dioxinone.

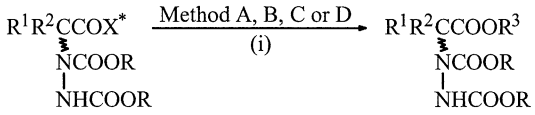
Amination of enolates derived from carbonyl compounds containing chiral auxiliary groups in good yields and high diastereoselectivities provides another successful route for the asymmetric transfer of electrophilic nitrogen to the α-carbon of carbonyl compounds. This method for the asymmetric synthesis of α-amino acids or esters has been well investigated using different units as the stereocontrolling elements in carbonyl compounds. For this purpose, di-*t*-butyl azodicarboxylate (**10b**) was found to be the reagent of choice due to its high diastereofacial selection with chiral enolates, as well its high reactivity.

Preliminary studies were reported by Gennari,[134] Vederas,[135] Evans[136] and Oppolzer and their co-workers[137,138] in 1986. Later, Evans[139] and Oppolzer[140] published extension of their work which were complementary to their preliminary reports. Recently, Page and co-workers have published an enantioselective synthesis of a α-amino acids using the amination of ketone enolates mediated by an asymmetric building block.[141,142]

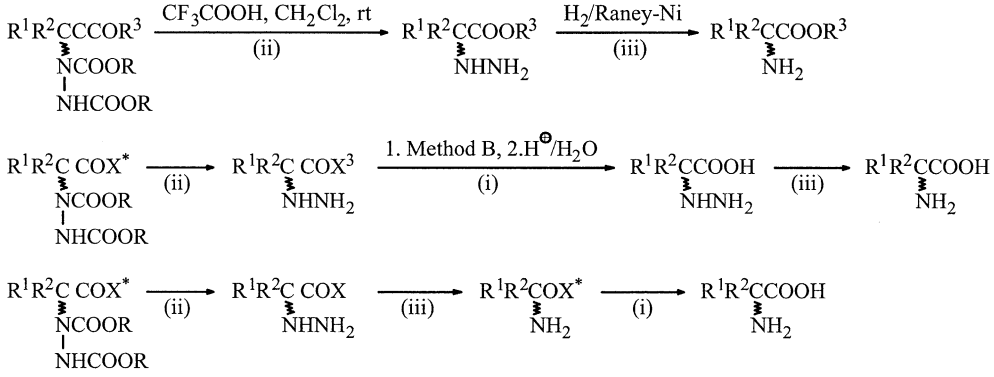
There are some routes for the transformation of diastereomeric α-hydrazido adducts of chiral stereodirecting group-containing esters and amides into enantiomerically pure α-amino acids or their N-protected derivatives. These all consist of methods for carrying out the following reactions: (i) Removal of the chiral auxiliary, (ii) removal of the *N*-acyl groups of the α-hydrazido adduct by hydrolysis or hydrogenolysis, (iii) hydrogenolysis of the α-hydrazino adduct to the α-amino acid or ester. These reactions are generally carried out in the order (i), (ii), and (iii),[135,136,139] but the order (ii), (i), and (iii)[134] or (ii), (iii) and (i)[137–139] can also be applied. α-Hydrazido adducts are subjected to these reactions with equal success in high yields. The



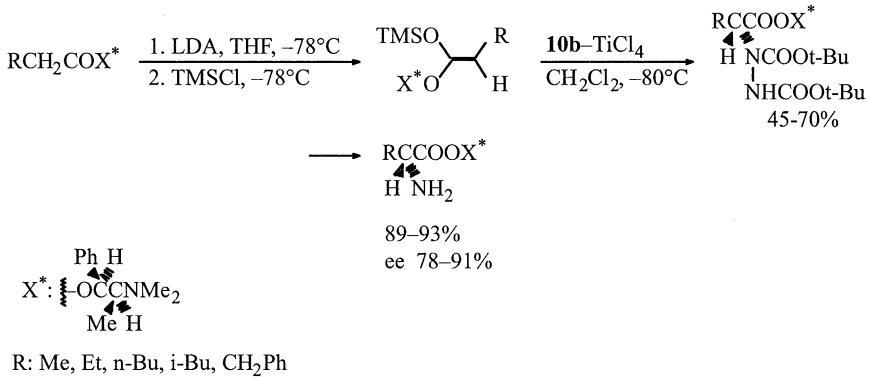
Scheme 47.



Method	Reagent and reaction conditions	R^3
A	LiOH, THF/H_2O(2:1), 0°C, 2–16 h	H
B	MeOMgBr, MeOH, 0°C, 0.5–22 h	Me
C	$LiOCH_2Ph$, $PhCH_2OH$, 0°C, 2–50 h	CH_2OH
D	LiOOH, THF/H_2O (3:1), 0°C, 3.2 h	H



Scheme 48.

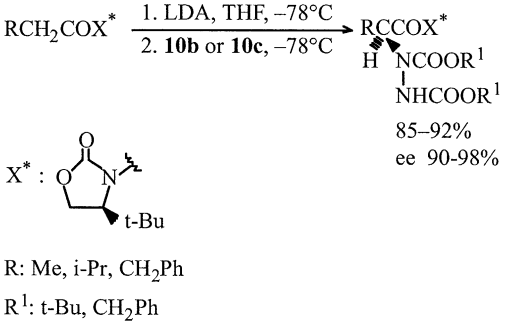


Scheme 49.

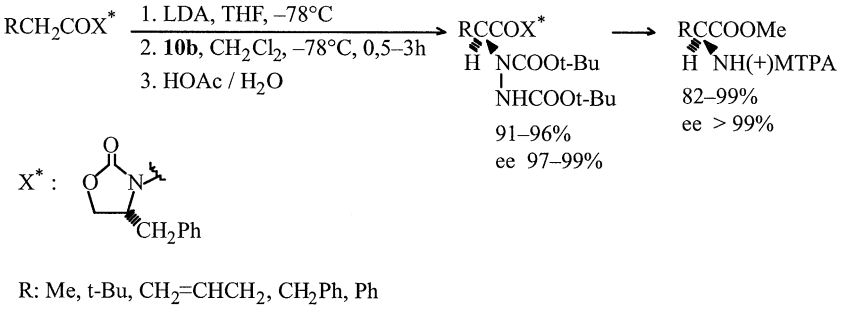
methods for (ii) and (iii) have already been outlined in the introduction to this section. In Scheme 18, the methods for (i)[139] are shown and the routes for the transformation of α-hydrazido adducts of esters to α-amino acids under mild and nonracemising conditions are demonstrated. In this review, only the yields and diastereoselectivities of the α-hydrazido adducts and α-amino acids or esters are therefore given, but the routes for this transformation are not included (Scheme 48).

Gennari prepared α-hydrazido compounds by the reaction of a **10b**–$TiCl_4$ complex with silyl enolates of chiral esters containing (1*R*,2*S*)-*N*-methylephedrine as the auxiliary (Scheme 49).[134] No reaction occurred without $TiCl_4$. Reasonably good chemical yields and high enantiomeric excesses were obtained in the synthesis of α-amino acids.

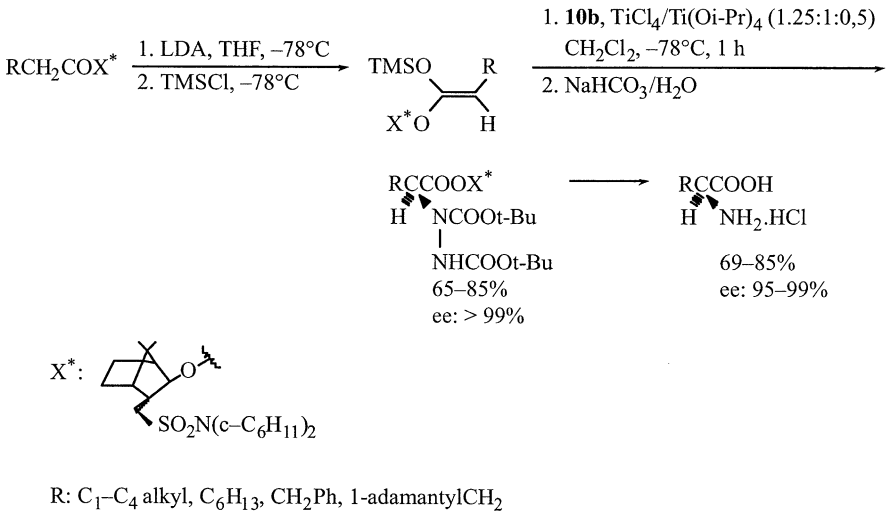
Vederas et al. used (4*R*)-*t*-butyl-2-oxazolidinone as the chiral auxiliary for the asymmetric amination of chiral carboximide-derived enolates with **10** (Scheme 50).[135] They found that the diasteromeric excess improves as the



Scheme 50.



Scheme 51.



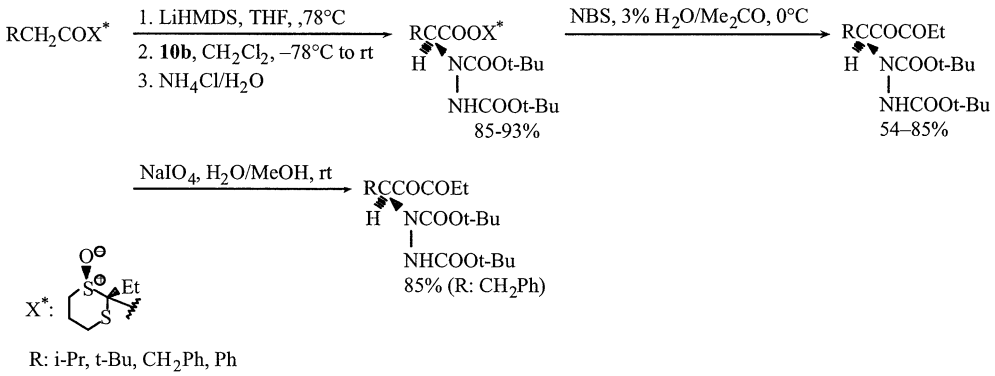
Scheme 52.

substitution on **10** and on the acyl side chain of the chiral auxiliary increases. The highest diastereoselectivites were obtained by using **10b** as the aminating reagent and 4-*t*-butyl- or benzyl-substituted oxazolidin-2-one as chiral auxiliary.

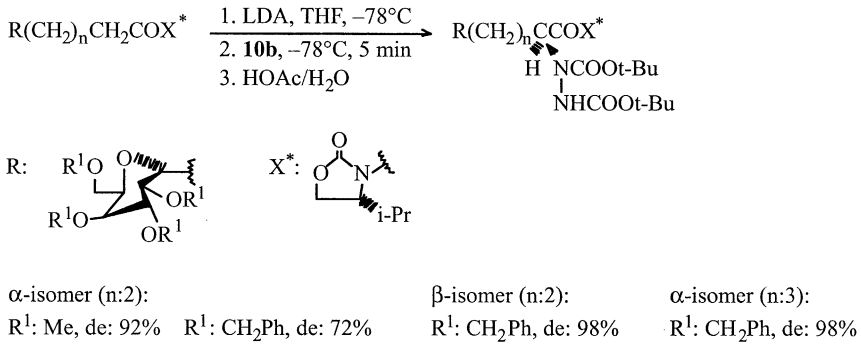
Evans also chosen (4*S*)-4-benzyl-2-oxazolidinone containing carboximides as the chiral substrates to be lithiated and aminated with **10b** for the asymmetric synthesis of α-hydrazido adducts in high yields, with high diastereomeric excesses (Scheme 51).[136,139] The amination of a glutaryl imide (R: $MeOOCCH_2CH_2$) derived enolate afforded the diastereomerically pure α-hydrazido adduct with a yield of 51%.

Oppolzer used **10b** in the presence of $TiCl_4(Ti(Oi\text{-}Pr)_4$ (2:1) to aminate the silyl enolates of chiral esters containing bornane [10.2] sultam (Oppolzer sultam as the chiral auxiliary (Scheme 52).[137,138,140] The high yield reaction gave diastereomerically pure α-hydrazido adducts which were transformed into (2*S*)-α-amino acid hydrochlorides in good overall yields and high enantiomeric purity.

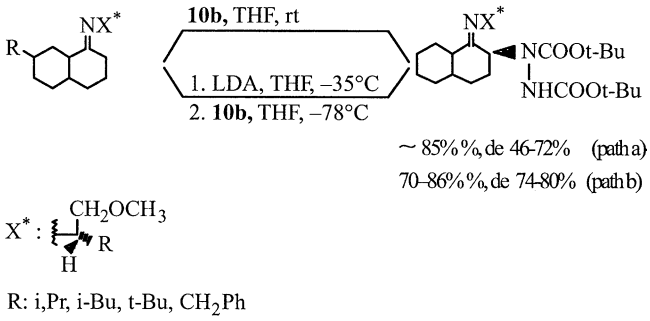
Enolates containing *syn* and *anti* 2-ethyl-1,3-dithiane 1-oxide as the chiral auxiliary have been aminated with **10b** by Page and co-workers and the successful application of this process to the synthesis of α-hydrazidocarboxylic acids with limited enantiomeric excess has been described (Scheme 53).[141,142]



Scheme 53.



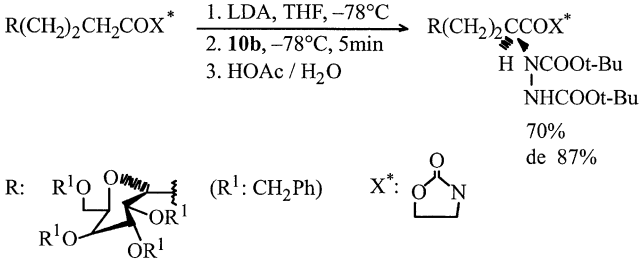
Scheme 54.



Scheme 55.

Asymmetric induction by a chiral oxazolidinone auxiliary in the electrophilic amination of enolates was also used by Arya and co-workers for the synthesis of C-linked isostereomers of α- or β-glycoconjugates starting from the 4-α- or 4-β-glycosyl derivatives of carboximides (Scheme 54).[143,144]

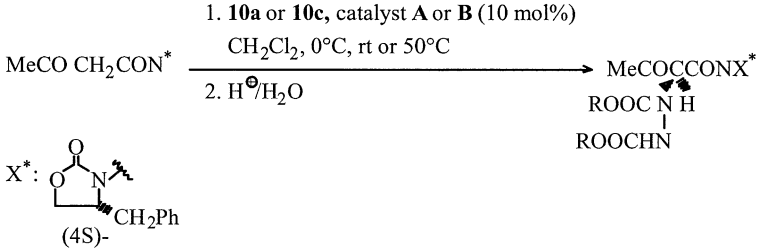
They proposed that the low diastereoselectivity for the amination of the perbenzylated α-galactosyl derivative could be due to the steric hindrance by the benzyl group at the 2-position of the α-galactosyl moiety and, in fact, they obtained high diastereoselectivities during the aminations of both permethylated α-galactosyl derivative and the perbenzylated β-galactosyl derivative. They also found that adding an extra methylene unit in the starting perbenzylated α-galactosyl derivative did not cause steric hindrance and, in addition, removing the chirality of the oxazolidinone auxiliary additionally influenced the diastereoselectivity, indicating the effect of the α-galactosyl moiety on inducing the remote asymmetric induction (Eq. 29).[144] This is the first report on the stereoselective control of electrophilic amination by a remote chirality on the carbonyl compound derived enolates.



(29)

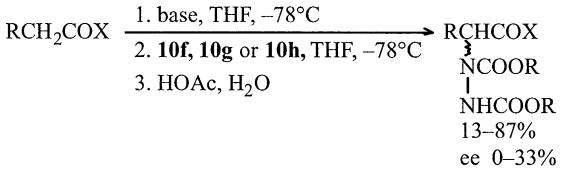
Enamines including a chiral auxiliary were employed by Gmeiner and Bollinger to aminate α-tetralones by using **10b**. The starting materials were obtained from α-tetralone and a chiral amino ether. Due to imine–enamine tautomerism, they could be also successfully subjected to direct amination (Scheme 55) (path a and b).[145]

Moreno-Marias and co-workers, who reported the transition metal-catalysed direct amination of active methylene



Reagent	Catalyst	Reaction temp. and time	Yield, %	de, %
10a	**A**	rt, 18 h	94	64
	B	rt, 12 h	97	48
10c	**A**	0°C, 4 days	100	78
	B	rt, 17 h	100	40
	B	0°C, 3 days	100	38

Scheme 56.



R^1; X : Ph, OEt; CH_2COOEt, OEt; Et, NMe_2; i-Pr, NMe_2

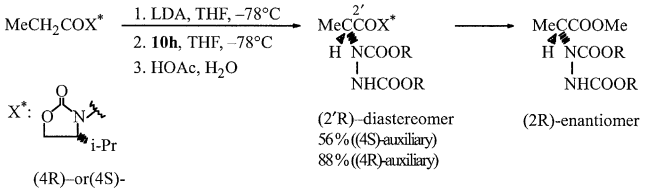
base: LiHMDS for X: OEt, LDA for X: NMe_2

R: (+)-menthyl (–)-bornyl, (–)-isobornyl

Scheme 57.

compounds with **10** (Scheme 56),[123] also carried out the catalytic asymmetric direct amination of acetylacetamide including (4*S*)- or (4*R*)-4-benzyl-2-oxazolidinone in the presence of the catalysts **A** and **B** (Eq. 26). When **10a** and **10c** were used as aminating reagents, the diastereomeric excesses changed, depending on the catalyst, reaction temperature, time and the aminating reagent.

Vederas and co-workers have reported the asymmetric amination of enolates with the chiral diazene dicarboxylates **10f**-**10h**.[146,147] They prepared the di (+)-menthyl, di (−)-borrnyl, and di (−)-isobornyl diazene dicarboxylates, **10f**, **10g** and **10h**, respectively, and reacted them with achiral carboxylic ester and carboxamide enolates (Scheme 57).[146] The α-hydrazido adducts were obtained with little or no stereoselectivity. The possibility of double stereoselection was also tested by aminating enantiomeric carboximide enolates containing a chiral oxazolidinone auxiliary (Evans enolates) with **10h**, to obtain diastereomeric α-hydrazido adducts (Eq. 30). In both cases, however only one diastereomer formed indicating the control of stereoselectivity by the chiral auxiliary on the enolate.



(30)

As Vederas thought that control of amination stereochemistry is possibly prevented by the conformational mobility of **10f**–**10h** around the bonds to O and also by the equal exposition of both faces of their azo moiety to electrophilic attack, the Vederas' group prepared a bridged chiral diazene dicarboxamide **10i** with one face shielded and each nitrogen atom in a different steric environment.[147] Amination of carboxamides containing achiral oxazolidinone gave α-hydrazido adducts with high diastereoselectivity as expected (Scheme 58).

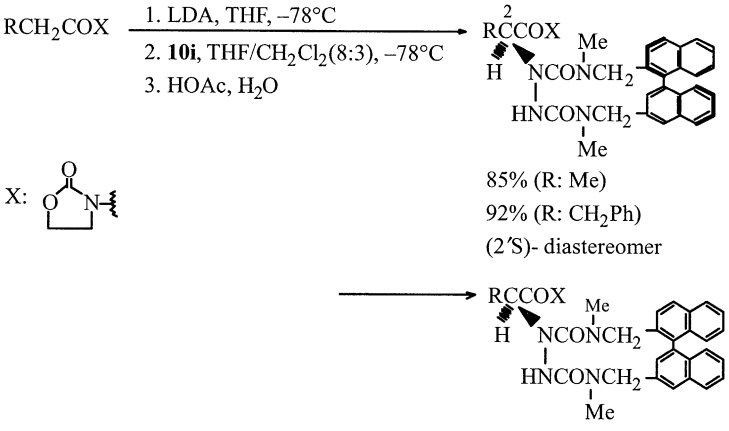
2.7. 1-Chloro-1-nitroso cycloalkanes and *N*-(tosylimino) phenyliodinane

Oppolzer and co-workers offered successful solutions for asymmetric electrophilic nitrogen transfer to ketone and carboxylic amide enolates by using achiral or chiral 1-chloro-1-nitrosocycloalkanes (**11**) (Table 6).[148,149]

A high valent iodine compound; (*N*-tosylimino)phenyliodinane (**12**) was also used efficiently for the electrophilic amination of achiral and chiral α-tosylaminoketones.[150,151] (*N*-Tosylimino)-phenyliodinane (**12**) acts as a nitrene precursor and reacts with a C=C bond to form an aziridine. Following the aziridination of the enol derivatives, ring opening of the aziridine intermediate affords the corresponding α-aminocarbonyl compound.

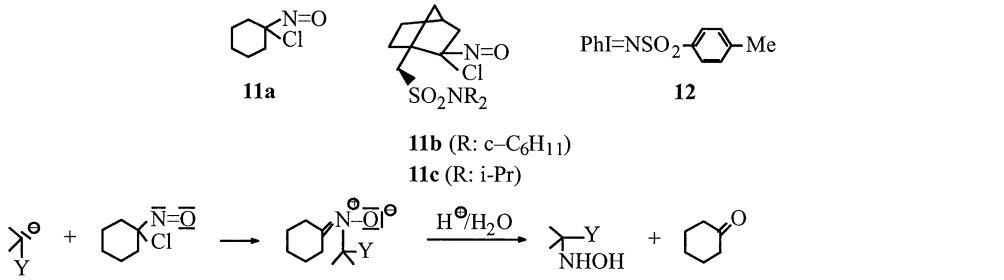
Evans[152] and Jacobsen[153] extended the scope of the aziridination process independently by using chiral copper catalysts in the reaction of **12** with styrene and cinnamate derivatives and developed an asymmetric metal-catalysed aziridination method.

1-Chloro-1-nitrosocylohexane (**11a**) was used for the amination of chiral carboxamides, which are converted to enantiomerically pure α-amino acids (Scheme 59).[148] Carboxamides containing the bornane [10,2] sultam (Oppolzer sultam) as the chiral auxiliary reacted with **11a** following deprotonation and afforded the crude β-keto-hydroxylamines with sultam (**A**) as single diastereomers in high yield. Hydrogenoloysis of **A** provided the crude α-aminocarboxamides with sultam (**B**) which were hydrolysed to give enantiomerically pure α-amino acids. The use



Scheme 58.

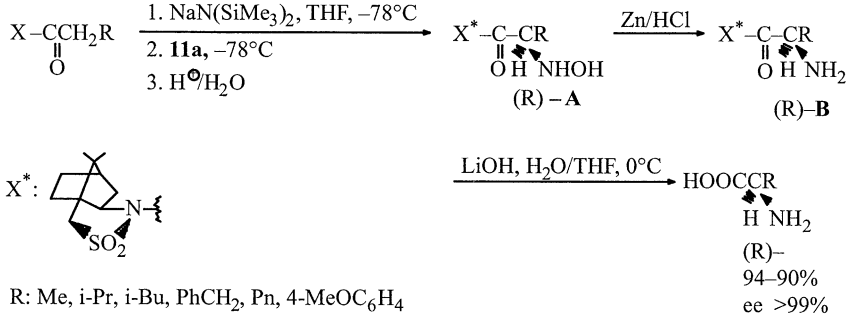
Table 6. Amination of enolates and eniminates with 1-chloro-1-nitrosocycloalkanes (**11**) and *N*-(tosylimino)phenyliodinane (**12**)



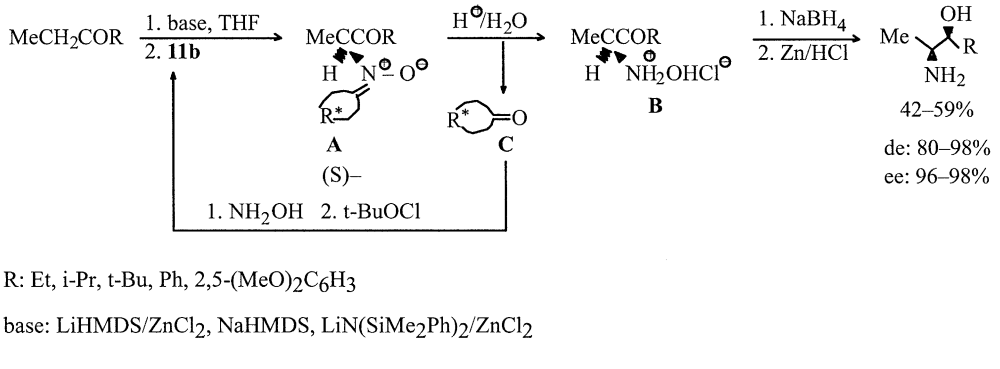
of carboxamides containing antipode of sultam gives the other enantiomer of the α-amino acid by applying the same procedure.

Treatment of the enolates derived from *N*-acylsultams with **11a** provides an easy-to-use and effective method for the asymmetric preparation of α-amino acids due to the commercial availability of the antipodes of the chiral auxiliary sultam, the easily crystallisable products **A** and **B** and no epimerization during the conversion of **A** to **B**.

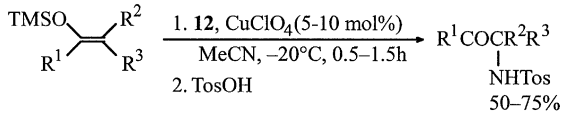
As an extension of this procedure, the successful preparation of an α-amino acid with two stereogenic centre with high diastereomeric excess was also reported (Eq. 31). The chiral enolate was prepared by the conjugate addition of ethylmagnesium bromide to an enamide containing the Oppolzer sultam.



Scheme 59.

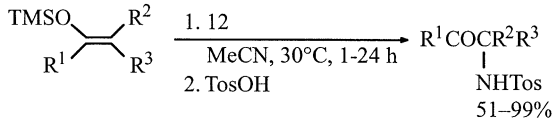


Scheme 60.



R^1, R^2, R^3: n-Bu, H, H ; Ph, H, H ; Ph, Me, H ; $-(CH_2)_4-$, H; PhO, H, n-Bu; MeO, H, n-Bu (no reaction)

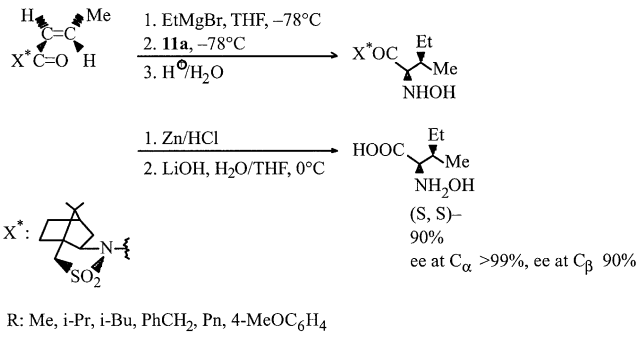
Scheme 61.



R^1, R^2, R^3: Et, Me, H ; H, H, CH_2=CH; Ph, H, H ; Ph, H, Me

XC_6H_4 (X: 2-Me, 3-Me, 4-Me, 4-MeO, 4-NO_2, 4-Cl), H,

Scheme 62.



R: Me, i-Pr, i-Bu, $PhCH_2$, Pn, 4-$MeOC_6H_4$

(31)

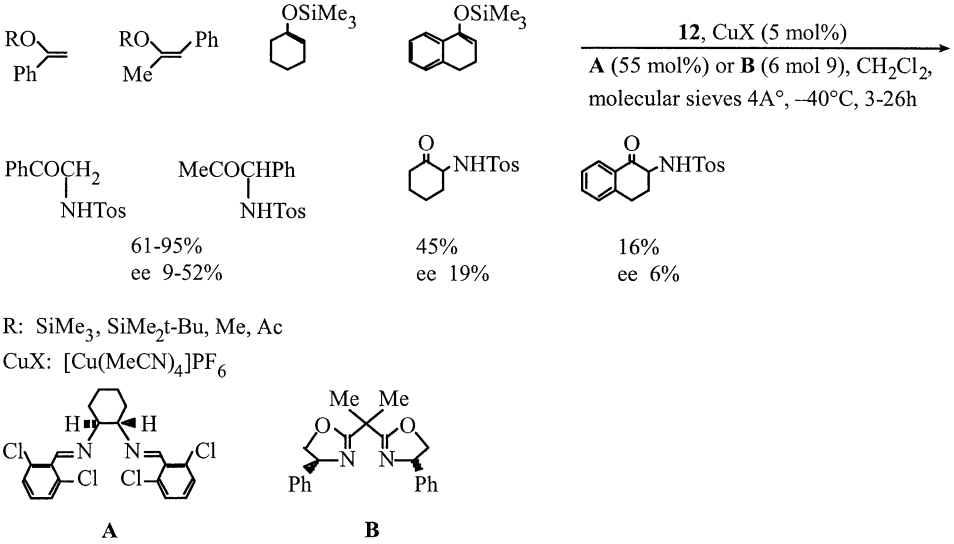
The chiral 1-chloro-1-nitroso reagents (**11b**) and (**11c**), can be prepared as both antipodal reagents for the preparation of diastereo- and enantiomerically pure α-aminoketones (Scheme 60).[149] The reaction consists of amination of ketone enolates with **11b** to give the (*S*)-nitrones (**A**), which are hydrolysed to the (*S*)-β-keto hydroxylamines (**B**) and chiral ketones (**C**). Erythro-selective reduction of **B** followed by hydrogenolysis, yields the erythro-β-amino alcohols in good yields with high diastereselectivity. **C** could be recycled to the aminating reagent **11b**.

Evans and co-workers have evaluated *N*-(tosylimino)-phenyliodinane (**12**) as an effective reagent for the copper-catalysed amination of enolsilanes and silylketene acetals in good yields (Scheme 61).[150]

The reaction was found to be sensitive to the Cu(I) or Cu(II) catalysts, the silyl moiety and the ester group. $CuClO_4$ afforded the best yield, (trimethylsilyl)- and (*t*-butyldimethylsilyl) ketene acetals afforded similar yields of the α-aminoesters, while no reaction was observed with a (phenyldimethylsilyl) ketene acetal. The authors speculated that the metal catalysis might be unnecessary and they reported no expected α-aminoketone formation in the absence of catalysis. Lim and Ahn, however reported that **12** reacts with enolsilanes at room temperature to provide α-tosylaminoketones in medium to high yields (Scheme 62).[151] The influence of the position and electronic effects of substituents on the reaction time was also evaluated and a long reaction time was required in the amination of enolsilanes of phenylketones containing electron-withdrawing substituents at the *o*-position.

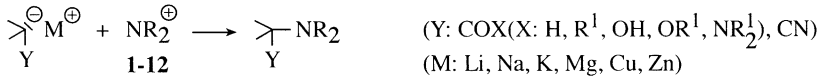
Adam and co-workers have used the methods of Evans[152] and the Jacobsen[153] for the asymmetric amination of a series of enol ethers (Scheme 63).[154] The chiral copper catalysts were prepared in situ from $[Cu(MeCN)_4]PF_6$ and the optically active ligands **A** and **B**. The enantioselectivity was found to depend upon the electronic properties of the oxygen atom of the enol and appreciable enantiomeric excesses have been obtained with the less electron-rich enol acetate.

Table 7 is given to show all electrophilic nitrogen-transfer



Scheme 63.

Table 7. Electrophilic α-amination of carbonyl compounds and nitriles with reagents **1–12**



Reagents : **1, 2a-c, 3a-f, 4a-c** **6a-d** **8a-b** **9a-b** **10a-i** **11a, b** **12**

Table : Table I Table I Table III Table IV Table V Table VI

$NH_2^{\oplus}$	Carbonyl compounds and nitriles to be aminated					
	Aldehyde	Ketone	Carboxylic acid	Carboxylic ester	Carboxylic amide	Nitrile
1			Scheme 4[13]			
2a			Scheme 5[11,12]		Scheme 6[21]	
2b				Eqs. 1a and 1b,[22,23] Scheme 7[24] Scheme 8[24]		
2c				Scheme 9[25]		Scheme 9[25]
3a				Eq. 2,[27] Eq. 4[29]		Eq. 3,[28] Eq. 4[29]
3b			—[12]			
3c		Eq. 6[38]		Eq. 5[38]	Scheme 16[a55]	
3d		Scheme 12,[42] Eq. 12,[a41] Scheme 17[a56]		Scheme 10,[39,40,43] Eq. 7,[40] Scheme 11[41] Eq. 13,[a40] Eq. 14[a40]		
3e		Scheme 12[42]				
3f				Scheme 13[48]		
4a				Eq. 9,[51] Scheme 15,[25] Eq. 11[52]		Eq. 10,[51] Scheme 15[25]
4b						Scheme 14[53]
4c				Scheme 15[25]		Scheme 15[25]
4d				Eq. 15,[60] Scheme 18[58,59]		Eq. 15[60]
6a					Scheme 19[63]	
6b		Scheme 22[65]		Scheme 20[64]		
6c				Scheme 21[66]	Scheme 21[66]	
6d				Scheme 23,[68] Scheme 24[68]		Scheme 24[68]
8a		Scheme 25[73]		Scheme 25[73]		
8b		Eqs. 16a and 16b[74]		Scheme 26,[75] Eq. 17[a77]		
9a				Scheme 27[80]	Scheme 29[88,89]	Scheme 27[80]
9b				—[81]		
9d		Scheme 28[91]		Eq. 19[89]	Eq. 18,[82] Scheme 29[88,89] Scheme 30,[88,89] Scheme 31[92]	
10a	Scheme 43,[125] Scheme 44,[126] Scheme 50,[135] Scheme 56[123]	Scheme 34,[116] Scheme 39,[a121] Scheme 41[123]		Eq. 26,[112] Eq. 27,[113] Scheme 39,[a121] Scheme 35,[117,118] Eq. 28[117,118]		
10b	Scheme 44[126] Scheme 50[135]	Scheme 34,[116] Scheme 53,[141,142] Scheme 54,[143,144] Eq. 29,[a144] Scheme 55[a145]		Eq. 29,[a121] Scheme 45,[a56,77,128–131] Scheme 46,[a56,128] Scheme 47,[a132,133] Scheme 49,[a134] Scheme 52,[a137,138,140]	Scheme 38,[a120] Scheme 51[a136,139]	
10c	Scheme 42,[124] Scheme 56[123]	Eq. 25,[110,111] Scheme 33,[31] Scheme 34,[116] Scheme 37,[116] Scheme 39,[121] Scheme 40[a122]		Scheme 40[a122]		[a]
10d		Scheme 40[a122]		Scheme 40[a122]		
10e		Eq. 24,[109] Scheme 36[a119]				
10f, g, h	Scheme 57,[a146] Eq. 30[146]					
10i	Scheme 58[a147]					
11a	Scheme 59,[a148] Eq. 31[a148]					
11b		Scheme 60[a149]				
12	Scheme 63[152,153]	Scheme 61,[150] Scheme 62,[151] Scheme 63[152,153]				

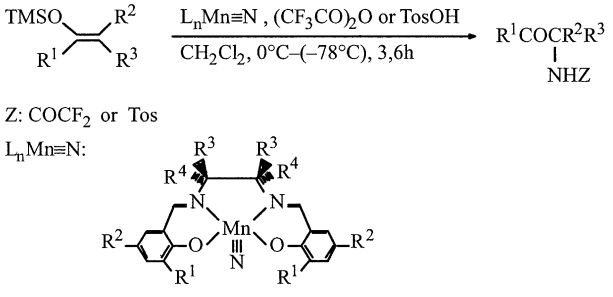
[a] Note. Scheme and/or equation numbers for asymmetric versions of electrophilic amination.

reagents used for α-amination of carbonyl compounds and nitriles, and to list the numbers of related schemes, equations in the review and references.

2.8. Miscellaneous

Successful aziridination reactions for the electrophilic amination of ketone and ester silyl enolates employed a nitrogen source, *N*-(tosylimino)phenyliodinane (**12**) in the presence of copper catalysis.[155,156] On the other hand, it is of interest to carry out the aziridination of silyl enolates using stoichiometric metal-mediated nitrogen transfer reactions.

An approach for the direct aziridination of an olefinic double bond with a nitridomanganese (V) complex[154] was extended by Carreira and co-workers[156] to the amination of silyl enol ethers with new types of nitridomanganese (V) complexes, $L_nMn{\equiv}N$. For this purpose, the nitrido manganese (V) complexes are activated by trifluoroacetic anhydride or *p*-toluenesulphonic acid in the presence of silyl enol ethers and α-aminoketones can be prepared in good yields (Eq. 32). In recent years, the enantioselective α-amination of ketones has also been reported by using chiral nitridomanganese (V) complexes.[157,158] The amination yields are medium to high and enantioselectivities are dependent on the nature of the complex.



(32)

3. Concluding remarks

Electrophilic amination is an important strategy for C–N bond formation in organic synthesis and provides a potentially powerful method for the introduction of a nitrogen functionality to carbanions.

The development of new reagents and methods has increased the versatility of electrophilic amination in the last 15 years. The stereoselective direct amination methodology also seems to be interesting and very promising for the formation of chiral α-C–N bonds in carbonyl compounds and the importance of optically active α-amino acids has stimulated an enormous development in synthetic strategies by electrophilic amination.

The intention here has been to arrange the reagents and illustrate the methods for nonchiral and chiral synthesis of α-aminocarbonyl compounds by the amination of stoichiometric and catalytic α-carbanions derived from carbonyl compounds. I think this review will reflect the current rapid increase in this area.

Acknowledgements

I am grateful to Dr. P. Smith for careful reading of the manuscript. I am also grateful to Turkish Scientific and Technical Research Council (Grant No. TBAG-1983 (100T087)) and Ankara University (Research Grant No. 2001-07-05-063) for supporting my research group (Dr. Fatma Eroğlu, Dr. Didem Kâhya, Melike Koçoğlu and Özgen Ömür) who have been trying for contribution to electrophilic α-amination of carbonyl compounds.

References and notes

1. Erdik, E.; Ay, M. *Chem. Rev.* **1987**, *29*, 1947.
2. Mulzer, J.; Altenbach, H. J.; Brown, M.; Krohn, K.; Reissing, H.U. In *Organic Synthesis Highlights*, VCH: Weinheim, 1991; p 45.
3. Boche, G. In *Houben-Weyl, Methods of Organic Chemistry*, Helmchen, G.; Hoffman, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, p 5153.
4. Askani, R.; Taber, D. F. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; 1996; Vol. 7, Pergamon: Oxford, p 1881.
5. Genet, J. P.; Greck, C. *Synlett* **1997**, 741.
6. Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281.
7. *Modern Amination Methods*, Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000.
8. Williams, R. M. In *Synthesis of Optically Active α-Aminoacids Organic Chemistry Series*, Pergamon: Oxford, 1984; Vol. 7.
9. Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
10. Kovacic, P.; Lowry, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639.
11. Yamada, S.; Oguri, T.; Shioiri, T. *J. Chem. Soc. Chem. Commun.* **1972**, 623.
12. Oguri, T.; Shiori, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, 23167.
13. Horiike, M.; Oda, J.; Inouye;, Y.; Ohno, M. *Agric. Biol. Chem.* **1969**, *33*, 292. *Chem. Abstr.* **1969**, *71*, 2929r.
14. Theilacker, W.; Ebbe, K. *Angew. Chem.* **1956**, *68*, 303.
15. Cnimiak, A.; Kolasa, T. *Bull. Acad. Pol. Sci.* **1974**, *22*, 195.
16. Hjeds, H. *Acta Chem. Scand.* **1965**, *19*, 1764.
17. Beak, P.; Basha, A.; Kokko, B. *J. Am. Chem. Soc.* **1982**, *47*, 2822.
18. Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.
19. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
20. Oguri, T.; Shiori, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 173.
21. Yamada, S.; Oguri, T.; Shiori, T. *Jpn. Kokai Tokkyo Koho* **1974**, *74*, 116004. *Chem. Abstr.* **1975**, *82*, 15888n.
22. Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833.
23. Sheradsky, T.; Nir, Z. *Tetrahedron Lett.* **1969**, 77.

24. Radhakrishna, A. S.; Loudon, G. M.; Miller, M. J. *J. Org. Chem.* **1979**, *44*, 4836.
25. Smulik, J. A.; Vedejs, A. *Org. Lett.* **2003**, *5*, 4187.
26. Taylor, E. C.; Sun, J. H. *Synthesis* **1980**, 801.
27. Scopes, D. I. C.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 376.
28. Taylor, E. C.; Sun, J. H. *Synthesis* **1980**, 801.
29. Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K. *Angew. Chem. Int. Ed.* **1978**, *17*, 687.
30. Tamura, Y.; Katu, S.; Ikeda, M. *Chem. Ind. (London)* **1971**, 787.
31. Carpino, L. A.; Giza, C. A.; Carpino, B. A. *J. Am. Chem. Soc.* **1959**, *81*, 955.
32. Greck, C.; Bischoff, L.; Girard, A.; Hajicek, J.; Genet, J. P. *Bull. Soc.Chim. Fr.* **1994**, *131*, 429.
33. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 327.
34. Kocienski, P. J. In *Protecting Groups*, Georg Thieme: Stuttgart, 1994; p 192.
35. Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035.
36. Shaikh, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385.
37. Boche, G.; Wagner, H. U. *J. Chem. Soc., Chem. Commun.* **1984**, 1591.
38. Genet, J. P.; Mallart, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359.
39. Fiorouanti, S.; Olivieri, L.; Pellancani, L.; Terdella, P. A. *Tetrahedron Lett.* **1998**, *39*, 6391.
40. Felice, E.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1999**, *40*, 4413.
41. Barani, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 11235.
42. Fioravanti, So.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **2001**, *42*, 1171.
43. Fioravanti, S.; Olivieri, L.; Pellacani, L.; Tardella, P. A. *J. Chem. Res. Synop.* **1998**, 338.
44. Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A.; Ballini, R. *Tetrahedron* **1998**, *54*, 6169.
45. Carducci, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1996**, *37*, 3777.
46. Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Veri, E. *Tetrahedron Lett.* **2003**, *44*, 4953.
47. Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **2003**, *44*, 3031.
48. Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *64*, 5896.
49. Harger, M. J. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3284. Harger, M. J. P. *J. Chem. Soc. Chem. Commun.* **1979**, 768.
50. Yaguanc, J. J.; Masse, G.; Sturtz, G. *Synthesis* **1985**, 807.
51. Calvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835.
52. Boche, G.; Bernheim, M.; Schrott, W. S. *Tetrahedron Lett.* **1982**, *23*, 5399.
53. Boche, G.; Bosold, F.; Niebner, M. *Tetrahedron Lett.* **1982**, *23*, 3255.
54. Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620.
55. Zheng, N.; Armstrong, J. D.; McWilliams, J. C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817.
56. Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. *Tetrahedron* **1991**, *30*, 5877.
57. Genet, J. P.; Juge, S.; Mallart, S. *Tetrahedron Lett.* **1988**, *29*, 6765.
58. Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787.
59. Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1465.
60. Boche, G.; Schrodt, W. *Tetrahedron Lett.* **1982**, *23*, 5403.
61. Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691.
62. Andrea, S.; Schmitz, E. *Synthesis* **1991**, 327.
63. Andrea, S.; Schmitz, E.; Wulf, J.-P.; Schutz, B. *Liebigs Ann. Chem.* **1992**, 239.
64. Vidal, J.; Gay, L.; Steron, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791.
65. Enders, D.; Poiesz, C.; Joseph, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3709.
66. Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247.
67. Page, P. C. B.; Murrel, V. L.; Lirrousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204.
68. Page, P. C. B.; Limousin, C.; Murrel, V. L. *J. Org. Chem.* **2002**, *67*, 7787.
69. Erdik, E. In *Encylopedia for Organic Synthesis*, Paguette, L. A., Ed.; Wiley: New York, 1955; Vol. 1, p 41.
70. Erdik, E.; Ay, M. *Synth. React. Inorg. Metal-Org. Chem.* **1989**, *19*, 663.
71. Erdik, E.; Daskapan, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3139.
72. Erdik, E.; Daskapan, T. *Tetrahedron Lett.* **2002**, *43*, 6237.
73. Phillips, R. R. *Org. React.* **1959**, *10*, 143.
74. Garst, M. E.; Lukton, D. *Synth. Commun.* **1980**, *10*, 155.
75. Sakakura, T.; Hara, M.; Tara, M. *J. Chem. Soc. Perkin Trans. 1* **1994**, 289.
76. Erdik, E.; Koçoğlu, M. *Main Group Metal Chem.* **2002**, *25*, 621.
77. Guanti, G. J.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553.
78. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298.
79. Regitz, M.; Mass, G.; In *Diazo Compounds, Properties and Synthesis*, Academic: New York, 1986; Chapter 13.
80. Weininger, S. J.; Kohen, S.; Matako, S.; Kaya, G.; Anselme, J. P. *J. Org. Chem.* **1974**, *39*, 1591.
81. Hakimelahi, G. H.; Just, G. *Synth. Commun.* **1980**, *10*, 429.
82. Kühein, R.; Jensen, H. *Liebigs Ann. Chem.* **1974**, 369.
83. Wasserman, H. H.; Hlasta, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 6780.
84. Golding, B. T.; Smith, A. J. J. *Chem. Commun.* **1980**, 702.
85. Bevilacaua, P. F.; Keith, D. D.; Roberts, J. L. *J. Org. Chem.* **1984**, *49*, 1430.
86. Nishida, A.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1984**, *27*, 765.
87. Nitta, H.; Hatanaka, M.; Ishimaru, T. *J. Chem. Soc. Chem. Commun.* **1987**, 51.
88. Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.
89. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.
90. Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; Devries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189.
91. Enders, D.; Joseph, R.; Poiesz, C. *Tetrahedron* **1998**, *54*, 10065.
92. Stone, M. J.; Maplestone, R. A.; Rahman, S. K.; Williams, D. H. *Tetrahedron Lett.* **1991**, *32*, 2663.

93. Vergne, C.; Bouillon, J. P.; Chastanet, J.; Bois-Choussy, M.; Zhu, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3095.
94. (a) Lwowski, M. In *Nitrenes*, Lwowski, M., Ed.; Interscience: New York, 1970; p 185. (b) Edwards, O. E. In *Nitrenes*, Lwowski, M., Ed.; Interscience: New York, 1970; p 225.
95. Lwowski, M. In *Azides and Nitrenes*, Scriven, E. F. V., Ed.; Academic: New York, 1984, p 205.
96. Laciuro, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1983**, *24*, 593.
97. Cipollone, A.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **1987**, *52*, 2584.
98. Pellaconi, L.; Pulcini, P.; Tardelle, P. A. *J. Org. Chem.* **1982**, *47*, 5023.
99. Loreta, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1989**, *30*, 2975.
100. Griffith, D. A.; Danishefsky, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5811 and references cited therein.
101. Fİoravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 2261.
102. Fioravanti, S.; Pellacani, L.; Ricci, D.; Tardella, P. A. *Tetrahedron: Asymmetry* **1990**, *1*, 931.
103. Magnus, P.; Barth, L. *Tetrahedron Lett.* **1995**, *51*, 11075.
104. Magnus, P.; Roe, H. C. *J. Chem. Soc. Chem. Commun.* **1995**, 263.
105. Shaika, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385 and references cited therein.
106. Diels, O.; Behncke, H. *Chem. Ber.* **1924**, *57*, 653.
107. Huisgen, R.; Jakab, F. *Liebigs Ann. Chem.* **1954**, 590. 3T.
108. Diels, O. *Liebgs Ann. Chem.* **1992**, 429.
109. Moriarity, R. M.; Prakash, I. *Synth. Commun.* **1985**, *15*, 649.
110. Gmeiner, P. *Tetrahedron Lett.* **1991**, *32*, 5927.
111. Gmeiner, P.; Bollinger, B. *Liebigs Ann. Chem.* **1992**, 273.
112. Clariana, J.; Galvez, N.; Marchi, C.; Moreno-Marias, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331.
113. Mesegver, M.; Moreno-Marias, M.; Vallribera, A. *Tetrahedron Lett.* **2000**, *41*, 4093.
114. Moreno-Marias, M.; Marquet, J.; Vallribera, A. *Tetrahedron* **1996**, *52*, 3377.
115. Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259.
116. Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *78*, 666.
117. Yamamoto, Y.; Hatsuya, S.; Yamada, J.-i. *Tetrahedron Lett.* **1989**, *30*, 3445.
118. Yamamoto, Y.; Yumoto, M.; Yamada, J.-i *Tetrahedron Lett.* **1991**, *32*, 3079.
119. Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.
120. Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.
121. Juhl, K.; Jorgenson, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420.
122. Marigo, M.; Juhl, J.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1367.
123. List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
124. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.
125. Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790.
126. Vogh, H.; Vanderheiden, S.; Brase, S. *J. Chem. Soc. Chem. Comm.* **2003**, 2448.
127. Duthaler, R. *Angew. Chem. Int. Ed.* **2003**, *42*, 975.
128. Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Genet, J.-P. *Synlett* **1993**, 475.
129. Greck, C.; Ferreirra, F.; Genet, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2031.
130. Greck, C.; Bischoff, L.; Genet, J.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 1989.
131. Girard, A.; Greck, C.; Ferroad, D.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 7967.
132. Gautschi, M.; Seebach, D. *Angew. Chem. Int. Ed.* **1992**, *31*, 1083.
133. Sting, A. R.; Seebach, D. *Tetrahedron* **1996**, *52*, 279.
134. Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394.
135. Trimble, L.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397.
136. Evans, D.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395.
137. Oppolzer, W.; Moretti, R. *Helv. Chem. Acta* **1986**, *69*, 1923.
138. Oppolzer, W.; Pedrosa, M. R. *Tetrahedron Lett.* **1986**, *27*, 831.
139. Evans, D.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525.
140. Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541.
141. Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *Tetrahedron Lett.* **1994**, *35*, 2427.
142. Page, P. C. B.; McKenzie, M. J.; Allin, S. M.; Buckle, D. R. *Tetrahedron* **2000**, *56*, 9683.
143. Ben, R. N.; Orellana, O.; Arya, P. *J. Org. Chem.* **1998**, *63*, 4817.
144. Arya, P.; Ben, R. N.; Qin, H. *Tetrahedron Lett.* **1998**, *39*, 6131.
145. Gineiner, P.; Bollinger, B. *Tetrahedron* **1994**, *37*, 10909.
146. Harris, J. M.; Bolessa, E. A.; Mendonca, A. J.; Feng, S.-C.; Vederas *J. Chem. Soc. Perkin Trans. 1* **1995**, 1945.
147. Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc. Perkin* **1996**, *1*, 2669.
148. Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991.
149. Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900.
150. Evans, D. A.; Faul, M. A.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.
151. Lim, B.-W.; Ahn, R.-H. *Synth. Commun.* **1996**, *26*, 3417.
152. Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
153. Li, Z.; Conser, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.
154. Adam, W.; Roschmann, R. J.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2000**, 557.
155. Groves, J. T.; Takahaski, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073.
156. DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364 and references cited therein.
157. Svenstrup, N.; Bogevig, A.; Harzell, R. G.; Jorgensen, K. A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1559 and references cited therein.
158. Minakuta, S.; Ando, T.; Nishimura, M.; Ryu, I.; Komatsu, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3392 and references cited therein.

Biographical sketch

Ender Erdik is a Professor of Chemistry at Ankara University, Science Faculty, Turkey. She received her PhD degree from Ankara University completing her doctoral thesis in Professor C. Tüzün's group in 1971. She conducted her postdoctoral studies in Professor G. M. Whitesides' group at MIT, USA (1974–1976) as a Fulbright Research Fellow and in Professor R. Baker's group at Southampton University, England (1981–1982) as a British Council Fellow. She carried out NATO Research programs with Professor E.-i Negishi at Purdue University, USA (1991) and with Professor D. S. Matteson at Washington State University, USA (1981, 1986, 1999). Her research interests concentrate in the area of synthetic and mechanistic aspects of Grignard, organolithium, -copper and -zinc reagents, and mainly in the transition metal catalyzed C–C and C–N coupling reactions.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8783–8790

meta-Photoaddition reactions of 2-chloro-, 2,5-dichloro-, and 2-halo-5-isopropyl-tropones with 9,10-dicyanoanthracene

Akira Mori,[a,*] Hiroki Yokoo[b] and Toshihide Hatsui[a]

[a]*Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*
[b]*Graduate School of Engineering Sciences, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*

Received 27 May 2004; revised 22 July 2004; accepted 22 July 2004

Available online 21 August 2004

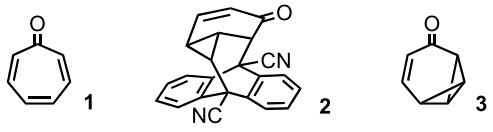
Abstract—Photoreactions of 2-halotropones with the excited 9,10-dicyanoanthracene gave a *meta*-adduct and substitution products occurred at the C-2 position of troponoids. The mechanism of the *meta*-adduct was proved by the product analysis of the reaction of 3,7-dideuterio-2-bromo-5-isopropyltropone and 9,10-dicyanoanthracene. In the photoreaction of 2-chloro-5-isopropyltropone and 9,10-dicyanoanthracene in a mixed solvent of benzene and methanol, a benzaldehyde with a dibenzo-2-oxabicyclo[3.2.2]nonane system was obtained to support occurrence of an [8+4] cycloaddition reaction between them.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The 9,10-dicyanoanthracene (DCA) sensitized photoreactions were widely investigated from the mechanistic[1] and synthetic viewpoints.[2] These reactions are usually controlled by redox potentials, excitation energy, and solvent polarity. In some cases, the cycloaddition reactions between DCA and olefins have been observed.[3–7]

Previously, we have reported the photochemical reactions of tropone (**1**) and the excited state of DCA, which gave a [4+2] and a [4+2]–[4+4] cycloadduct, a *meta*-adduct (**2**), and a dibenzocycloheptatriene derivative in non-polar benzene.[8] In a mixed solvent of polar acetonitrile and dichloromethane, however, an [8+4] adduct was obtained via an electron-transfer process together with the products obtained in the photoreaction in benzene although ΔG value of the electron-transfer process was +1.2 kcal/mol. In the reaction, we have tentatively proposed the mechanism of the formation of the *meta*-adduct (**2**) via tricyclo[4.1.0.0^{2,7}]-hept-3-en-5-one, tropovalene (**3**), from the structure of the *meta*-adduct (Scheme 1).

Furthermore, we extended the reaction to halotropones such as 2-bromotropone and 2,7-dibromotropone, which yielded anthracene, dihydroanthracene, and anthracenone derivatives and solvent-incorporated products.[9] From the results of solvent effects, we proposed an ionic mechanism in polar solvents and a radical mechanism in non-polar solvents in the reaction of halotropones with DCA. In this paper, we report the photoreaction of the excited DCA with 2-chloro-, 2,5-dichloro-, and 2-halogeno-5-isopropyltropones to propose the mechanism of the *meta*-adduct via a bicyclo[4.4.1]undecenediyl biradical from the product analysis of the reaction of 3,7-dideuterio-2-bromo-5-isopropyltropone and DCA, which excluded a tropovalene mechanism. The reaction of 2-chloro-5-isopropyltropone and DCA in a mixed solvent of benzene and methanol yielded an aldehyde with an oxabicyclo[3.2.2]nonane system, which supported occurrence of an [8+4] cycloaddition reaction between them.



Scheme 1.

2. Results and discussion

2.1. Irradiation of 2-chlorotropone

When a benzene solution of 2-chlorotropone (**4**) and DCA was irradiated by means of a 400 W mercury lamp through a filter to cut off light with <400 nm using 0.7 M $NaNO_2$ solution, two products (**5**, **6**) were obtained in 19 and 3% yields, respectively. Before the irradiation, the reaction

Keywords: Photoreactions; 9,10-Dicyanoanthracene; Troponoids; *meta*-Addition; [8+4] Cycloaddition; Bicyclo[4.4.1]undecenyl biradical intermediate.
* Corresponding author. Tel.: +81-92-583-7806; fax: +81-92-583-7810; e-mail: mori-a@cm.kyushu-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.049

mixture was deoxygenated by bubbling dry nitrogen gas. The yield was based on the consumed starting material. The mass spectrum of product **5** showed that it has a molecular weight with a value corresponding to a chloride ion and a cyano group being eliminated from a 1:1 adduct between **4** and DCA. The spectral data are similar to a bromo derivative of **5**, which has been obtained in the reaction of 2,7-dibromotropone and DCA.[9] Therefore, the structure of **5** was assigned to be an anthracenone derivative. The structure of **6** was determined to be a 1,1a,8,8a-tetrahydro-9-oxo-2,7(1′,2′)-benzeno-1,8-propenobenzo[*a*]cyclopropa[*d*]cycloheptene-2,7-dicarbonitrile derivative, a *meta*-adduct by the ^{1}H and ^{13}C NMR spectroscopic data by comparison of the *meta*-adduct (**2**) obtained from the reaction of **1** and DCA.[8] Similarly, products **5** and **6** were obtained in 33 and 5% yields from irradiation in dichloromethane.

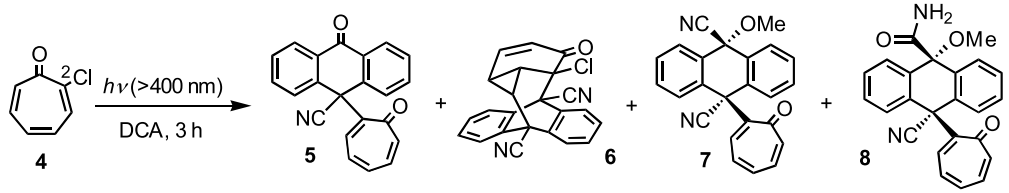
While **4** was irradiated with DCA in the presence of methanol in dichloromethane, two new products **7** and **8** were obtained in 18% yields, respectively, together with **6** in 7% yield. The molecular weight of compound **7** indicated that the chlorine atom of a 1:1-adduct between **4** and DCA was replaced by a methoxyl group. The ^{13}C NMR spectrum showed that **7** has a symmetry in a molecule, three sp^3-carbon atoms including a methoxyl group, two cyano groups, and a tropone ring. These data supported structure **7** although the stereochemistry is tentatively assigned. The molecular weight of compound **8** indicated that **8** was a hydration product of **7**. Since the ^{1}H NMR spectrum of **8** is similar to that of **7** except for the existence of two signals at δ 5.27 (1H, br) and 5.53 (1H, br), which are assigned to an amide NH_2, the structure of **8** was determined to be an amide derivative of **7**. When compared their ^{13}C NMR chemical shifts of sp^3-carbon atoms between **7** and **8**, the methoxyl group of **8** appeared at the lower field by 9 ppm than **7** and the others were not so much different between them, which could conclude that the cyano group close to the methoxyl group of **7** was hydrated. An intramolecular hydrogen bonding between the amide proton and the methoxyl group of **8** caused to differentiate the chemical shifts of the amide protons although the structure of **8** is symmetrical and to decrease electron density of the methoxyl group to make the chemical shift lower than that of **7** (Scheme 2).

2.2. Irradiation of 2,5-dichlorotropone

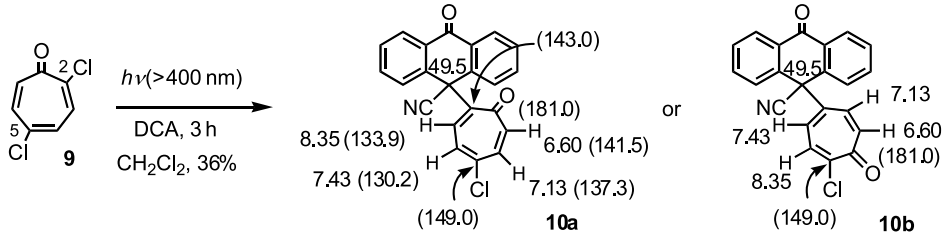
Similarly, irradiation of a dichloromethane solution of 2,5-dichlorotropone (**9**) and DCA gave product **10** in 36% yield. The ^{1}H NMR spectrum indicated that two structures **10a** and **10b** are possible since the four tropone ring protons appeared as two sets of the AB quartet. The assignment of the tropone ring protons is shown in Scheme 3, which is based on the consideration of the values of the vicinal and *meta* coupling constants.[10] We measured the heteronuclear multiple bond correlation (HMBC) spectrum to distinguish between structures **10a** and **10b**. In the HMBC spectrum, the proton at δ 8.35 correlated with the signals at δ 49.5, 149.0, and 181.0, which are assigned to be the sp^3-carbon atom, the sp^2-carbon atom with a chlorine atom, and the tropone carbonyl group, respectively. In **10b**, however, the proton at δ 8.35 has no correlation with the sp^3-carbon atom and the protons, which correlate to the sp^3-carbon atom, are the protons at δ 7.43 and 7.13 in structure **10b**. Therefore, structure **10b** should be excluded and product **10a** was a chloro derivative at the C-5 position of **5**. The similar type of products has been observed in the reaction of 2,7-dibromotropone and the excited DCA.[9]

2.3. Irradiation of 2-halo-5-isopropyltropones

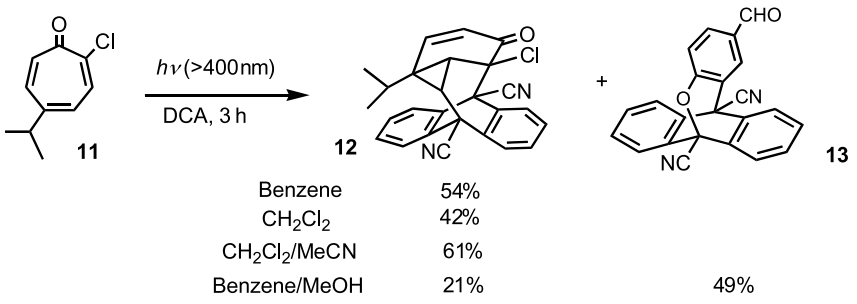
When a benzene solution of 2-chloro-5-isopropyltropone (**11**)[11] and DCA was irradiated, a single product (**12**) was obtained in 54% yield. The structure of **12** was determined to be a *meta*-adduct by the ^{1}H and ^{13}C NMR spectroscopic



Scheme 2.



Scheme 3.



Scheme 4.

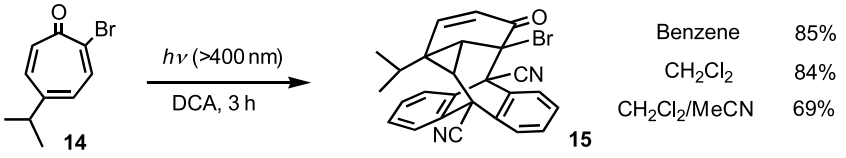
data by comparison of the *meta*-adduct (**2**) obtained from **1** and DCA. Similarly, adduct **12** was obtained in 42% yield from irradiation in dichloromethane and in 61% in a mixed solvent of acetonitrile and dichloromethane. While **11** and DCA were irradiated in the presence of methanol in benzene, a new product (**13**) was obtained in 49% yield together with **12** in 21% yield. From NMR spectra, compound **13** is a benzaldehyde derivative with a symmetrical structure. An isomer of **13** has been obtained as one of the photoproducts in the reaction of 2,7-dibromotropone and DCA.[9] The chemical shifts [6.86 (1H, d, $J=8.3$ Hz), 7.43 (1H, dd, $J=8.3$, 2.0 Hz), 8.25 (1H, d, $J=2.0$ Hz)] of the benzaldehyde ring protons indicated that a formyl group is at the *para* position of the oxygen substituent (Scheme 4).

Similarly, 2-bromo-5-isopropyltropone (**14**) gave a bromo derivative **15** of **12** in 85 and 84% yields in benzene and in dichloromethane, respectively and in 69% yield in a mixed solvent of acetonitrile and dichloromethane (Scheme 5).

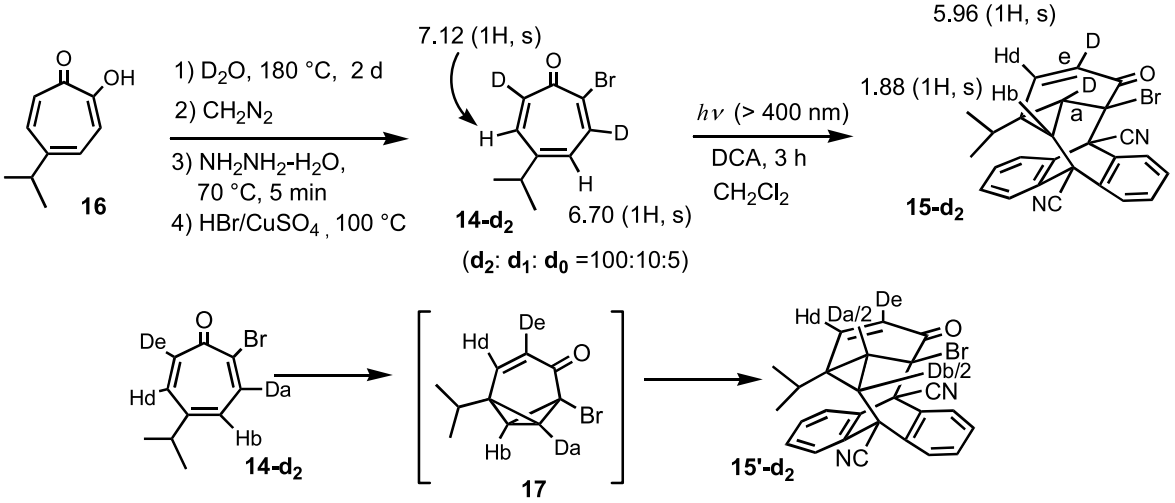
2.4. Mechanistic considerations

The fluorescence quenching of DCA with **4** and **14** was efficient in acetonitrile and was obeyed in the Stern–Volmer equation. From the slope of the plot of Io/I vs. [**4**] and life time of DCA ($\tau=15.3$ ns in acetonitrile),[12] the k_q value for **4** was $6.5\times10^{10}\ M^{-1}\ s^{-1}$. Similarly the value for **14** was $8.5\times10^{10}\ M^{-1}\ s^{-1}$. These values show the reaction to be close to diffusion control.

We have tentatively proposed the mechanism involving a symmetrical tropovalene in the formation of the *meta*-adducts.[8] In order to elucidate the mechanism of the *meta*-adducts, we prepared 3,7-dideuterio-2-bromo-5-isopropyltropone (**14**-d_2). Deuteration of 5-isopropyltropolone (**16**) in D_2O at 180 °C for 2 d gave 3,7-dideuterio-5-isopropyltropolone (**16**-d_2). After methylation of **16**-d_2 with diazomethane, the methyl ether was reacted with hydrazine hydrate and the resultant hydrazine derivative was heated at 100 °C in hydrobromic acid in the presence of $CuSO_4$ to



Scheme 5.



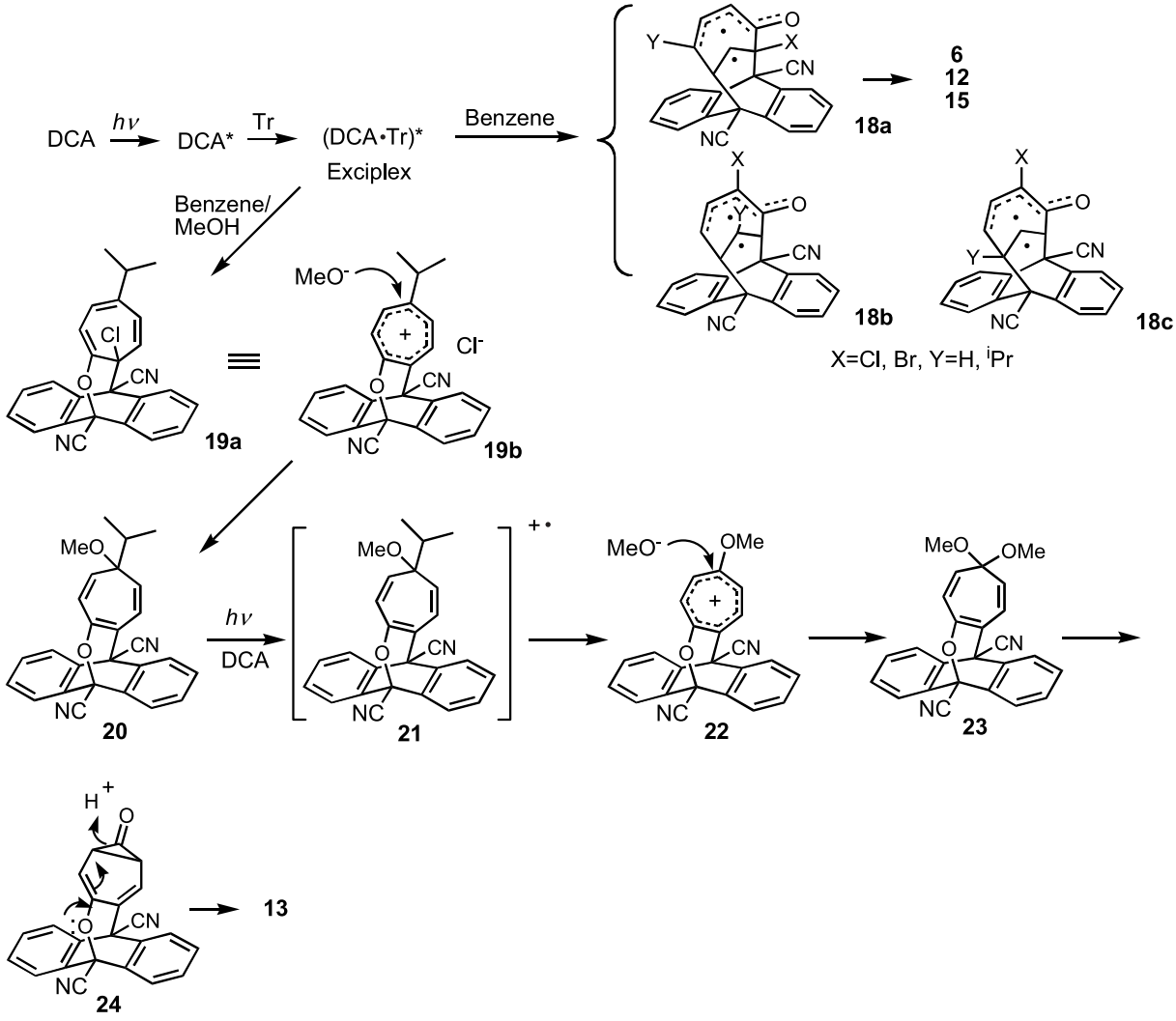
Scheme 6.

give **14**-d_2. The distribution of deuterium atoms of **14**-d_2 was determined by ^{1}H NMR spectral data, which are summarized in Scheme 6. The ratio of d_2:d_1:d_0 of **14**-d_2 was 100:10:5.

Irradiation of **14**-d_2 under the similar conditions gave **15**-d_2, whose ^{1}H NMR spectrum indicated that two deuterium atoms were located at the C-a and C-e positions. If the symmetrical tropovalene (**17**) were concerned in the photoreaction, the deuterium atoms should distribute on C-a, C-b, and C-e positions in a ratio of 1/2:1/2:1 as shown in **15′**-d_2. Since the ^{1}H NMR spectrum of **15**-d_2 showed that the deuterium atom is located at the C-a and C-e in a ratio of 1:1, this excluded the tropovalene mechanism.

It is known that the *meta*-cycloaddition reactions proceeded commonly in the photoreaction of arenes and olefins.[13] Although the mechanism is still only partly understood, a bicyclo[3.2.1]octenyl biradical should be involved in the reactions of arenes and ethenes. Taking the mechanism of the reactions of arenes and ethenes into account, we proposed a mechanism involving a bicyclo[4.4.1]undecenyl biradical (**18**). Since the troponoids used in the reactions are unsymmetrical, there are three reaction modes to generate biradical intermediates (**18a–c**). Biradical **18b** and **18c**, which have a halogen atom on the conjugated system, seem to be more stable than biradical **18a** with a halogen atom at the bridgehead position. From the reaction of 2-halo-5-isopropyltropones, only the *meta*-adduct via **18a** was obtained in a reasonable yield in the absence of a nucleophile. The position bearing a halogen atom preferred to form a bond. This is parallel to that a monosubstituted **4** gave only the *meta*-product **6** together with the other products although the yield is low.

In the *meta*-cycloaddition reactions in monosubstituted arenes and olefins,[13] donor substituents on the benzene ring prefer the position C-1 of the *meta*-adduct, a tricyclo-[3.3.0.0^{2,8}]oct-3-ene system, and acceptors the positions C-2 and C-4. The selectivity of reactions is depending on the reaction systems. Usually the *meta*-cycloaddition reactions yielded a mixture of products. In the photoreaction of chlorobenzene and 1,2-dichloroethene,[14] however, it gave a single product with a chloro atom at the position C-1 as an electron-donating group. This is explained by that halogens are inductively withdrawing and mesomerically donating.



Scheme 7.

In the present case, DCA reacted with 2-halo-5-isoropyltropones as a diene moiety to give only the *meta*-adducts with a halogen atom on the position corresponding to the C-8 of tricyclo[3.3.0.0^{2,8}]oct-3-ene in a reasonable yield. The *meta*-addition reactions in halotroponoids proceeded with different selectivity in the reaction of chlorobenzene and 1,2-dichloroethene. Furthermore, it is known that the selectivity in the reactions of arenes with dienes is reversed to the reactions of arenes and alkenes. Thus, the reaction modes are dependent on the reaction systems and the product distributions are sensitive to the reaction conditions (Scheme 7).

The isolation of aldehyde **13** is quite informative to propose the mechanism of dihydroanthracenes and anthracenones in the photoreaction of 2-halotropones and DCA, which suggested the formation of a 2-oxabicyclo[3.2.2]nonadiene derivative (**19a**), equivalent to a cycloheptarienylium ion (**19b**).[15] The similar mechanism has been proposed in the reaction of 2,7-dibromotropone and the excited DCA.[9] Next, a methoxide ion attacks the cycloheptatrienyl ion (**19b**) to give a 7-isopropyl-7-methoxycycloheptatriene derivative (**20**). Since the oxidation potential of cycloheptatriene **20** should be lower than 2-halotropones,[9,16] an electron-transfer reaction would occur from **20** to DCA to give a cation radical (**21**). Elimination of a propyl radical from the cation radical (**21**) and an attack of a methoxide ion to the resultant methoxycycloheptatrienyl ion (**22**) gave a 7,7-dimethoxycycloheptatriene derivative (**23**). Finally, aldehyde **13** is formed from a norcaradiene derivative (**24**) by an assistance of electron donation of the oxygen atom.

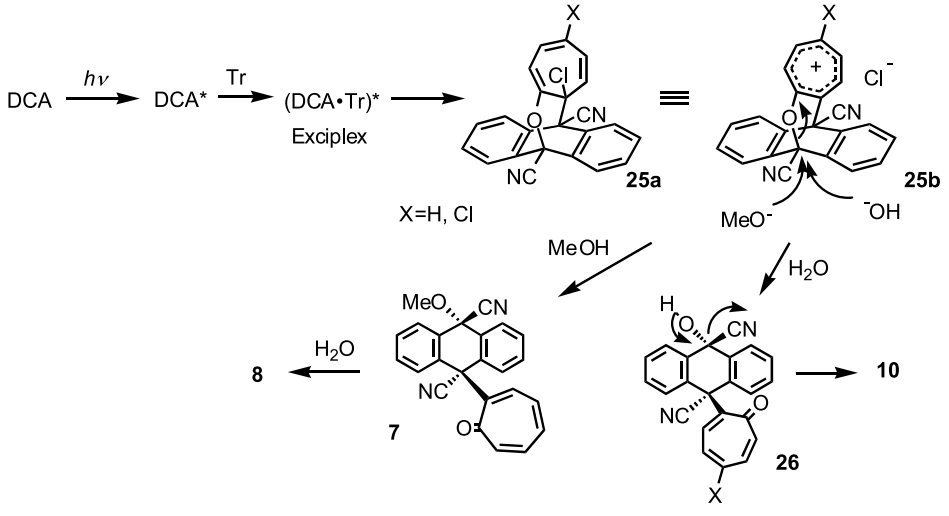
The mechanisms of the formation of **10**, **7**, and **8** are shown in Scheme 8. As has been reported in the reaction of halotropones and the excited DCA, we proposed the mechanism involving an [8+4] adduct, which was derived through an energy transfer process.[9] An attack of water to a cycloheptatrienylium ion (**25b**) gave a cyanohydrin (**26**), from which an elimination of HCN gave anthracenone **10**. On the other hand, an attack of methanol on **25b** gave **7**. A cyano group was hydrated to give amide **8**. From the mechanism proposed, the stereochemistry of **7** and **8** should be reasonable as shown in the Schemes.

3. Conclusion

The tropovalene mechanism was excluded from the experimental results using deuterated 2-bromo-5-isopropyltropone. By considering the mechanism of the photoreactions of arenes and olefins, we proposed the mechanism involving the bicyclo[4.4.1]undecenediyl biradical to form the *meta*-adduct. We have reported the reactions of 2-bromo- and 2,7-dibromo-tropones and the excited DCA, where they yielded mainly anthracene and anthracenone derivatives by attack of water contaminated in the solvent or by attack of the solvent used in the reaction on a [8+4] intermediate.[9] They did not give any *meta*-adducts.[17] In the present study, 2,5-dichlorotropone (**9**) gave an anthracenone derivative, which is parallel to the result of 2,7-dibromotropone. 2-Chlorotropone (**4**) afforded both the *meta*-adduct and the anthracenones together with the products via an [8+4] adduct. 2-Halo-5-isopropyltropones gave only the *meta*-adduct except for the reaction in the presence of a nucleophile such as methanol, where a benzaldehyde derivative obtained via an [8+4] adduct became a major product (Table 1).

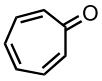
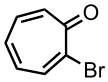
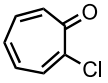
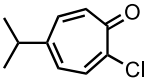
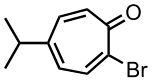
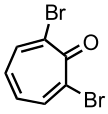
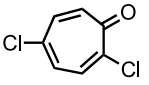
It has been known in photoreactions of benzenoids and alkenes that powerful donor and acceptor alkenes gave *ortho*-photoaddition[18] and alkenes having poor electron-donor or poor electron-acceptor abilities preferentially yielded *meta*-adducts.[19] The reactions are dependent on the redox potentials. In the present case, dihalotropones did not give any *meta*-adducts while the reaction of monohalotropones became likely to be a *meta*-addition reaction. The electron-donor or electron-acceptor abilities of substituents reflected the product distribution.

The selectivity of the *meta*-addition is quite high. Only one isomer formed exclusively in the reaction of unsymmetrical troponoids. The preferred reaction site is on the carbon atom bearing a halogen atom, the C-2 position. The bulkiness of the isopropyl group at the C-5 position assisted to determine the reaction site of the *meta*-addition. In the presence of a nucleophile, the isopropyl group was eliminated to give aldehyde **13** through concomitant electron-transfer reaction, which proved the contribution of the [8+4] intermediate.



Scheme 8.

Table 1. Product distribution of photoreactions

	meta-Adduct	[8+4]-Adduct or products via [8+4]-adduct
	Yes	Yes
	Yes[17]	Yes
	Yes	Yes
	Yes	Yes
	Yes	No
	No	Yes
	No	Yes

4. Experimental

4.1. General

The elemental analyses were performed at the elemental analysis laboratory of Kyushu University. The melting points were obtained on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The NMR spectra were measured on JEOL GSX 270H, LA 400, and LA 600 spectrometers in $CDCl_3$; the chemical shifts are expressed in δ units. The mass spectra were measured with JEOL 01SG-2 and JMS-700 spectrometers. The IR spectra were recorded on a JASCO IR-A102 spectrometer with KBr disks. The stationary phase for the column chromatography was Wakogel C-300 and the elution solvents were mixtures of hexane and ethyl acetate. The solvent used in photoreactions was bubbled by dried nitrogen gas for 30 min.

4.1.1. Synthesis of 2-chloro-5-isopropyltropone (11). 5-Isopropyl-2-methoxytropone, obtained from 5-isopropyltropolone (1.64 g) and diazomethane, was reacted with hydrazine hydrate at 80 °C for 5 min to give 2-hydrazino-5-isopropyltropone (1.4 g). To a solution of copper sulfate (2.5 g) dissolved in hot water (10 ml), a mixture of conc. HCl (1 ml) and 2-hydrazino-5-isopropyltropone (274 mg) was added at one time. After cooling to room temperature, the mixture was extracted by chloroform. The chloroform layer was dried with Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (hexane/AcOEt) to give 2-chloro-5-isopropyltropone (**11**)[11] (oil, 100.4 mg, 36%). *Compound* **11**: ^{1}H NMR δ 1.24 (6H, t, J=6.8 Hz), 2.82 (1H, sept, J=6.8 Hz), 6.79 (1H, dd, J=9.9, 1.7 Hz), 7.16 (1H, dd, J=12.6, 1.7 Hz), 7.24 (1H, d, J=12.6 Hz), and 7.74 (1H, d, J=9.9 Hz).

4.1.2. Synthesis of 2-bromo-5-isopropyltropone (14). Similarly, to a solution of copper sulfate (4.1 g) dissolved in hot water (10 ml), a mixture of conc. HBr (4 ml) and 2-hydrazino-5-isopropyltropone (500 mg) was added at one time. After cooling to room temperature, the mixture was extracted by chloroform. The chloroform layer was dried with Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (hexane/AcOEt) to give 2-bromo-5-isopropyltropone (**14**) (brown oil, 365 mg, 57%). *Compound* **14**: ^{1}H NMR δ 1.24 (1H, 6H, t, J=6.8 Hz), 2.78 (1H, sept, J=6.8 Hz), 6.70 (1H, dd, J=9.9, 1.7 Hz), 7.12 (1H, dd, J=12.7, 1.7 Hz), 7.24 (1H, d, J=12.7 Hz), and 8.03 (1H, d, J=9.9 Hz). ^{13}C NMR δ 22.7 (2C), 37.6, 127.8, 137.0, 137.6, 139.9, 140.4, 156.0, and 180.4. EA Found: C, 52.87; H, 4.49%. Calcd for $C_{10}H_{11}OBr$: C, 52.89; H, 4.89%.

4.1.3. Photoreaction of 2-chlorotropone (4) and DCA. *In benzene.* A benzene solution (300 ml) of **4** (71.2 mg) and DCA (114 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **5** (25.6 mg, 19%) and **6** (5.1 mg, 3%) together with recovered DCA (17.1 mg). *Compound* **5**: yellow plates; mp 233–235 °C. ^{1}H NMR δ 6.71 (1H, dd, J=11.6, 0.8 Hz), 7.07 (1H, ddd, J=11.6, 7.9, 0.8 Hz), 7.17 (1H, ddd, J=10.5, 7.9, 0.8 Hz), 7.30 (1H, ddd, J=10.5, 9.0, 0.8 Hz), 7.37–7.43 (2H, m), 7.53–7.60 (4H, m), 8.43–8.47 (2H, m), and 8.53 (1H, dd, J=9.0, 0.8 Hz). ^{13}C NMR δ 49.9, 120.4, 126.5, 128.4, 129.3, 131.7, 132.3, 133.7, 135.7, 135.9, 136.0, 137.8, 143.0, 150.4, 182.2, and 182.4. IR (KBr) 3414, 3070, 3034, 2988, 2230, 1734, 1634, 1455, 1243, 1042, 930, 789, 756, 737, and 680 cm^{-1}. MS *m/z* (%) 325 (8), 324 (58), 323 (100), 322 (12), 295 (35), 294 (38), 269 (40), 218 (49), and 190 (62). HM Found: 323.0951. Calcd for $C_{22}H_{13}NO_2$: 323.0946. *Compound* **6**: colorless crystals; mp 265–267 °C. ^{1}H NMR δ 1.88 (1H, tdd, J=9.5, 4.0, 1.0 Hz), 1.94 (1H, td, J=9.5, 0.8 Hz), 2.17 (1H, t, J=9.5 Hz), 5.45 (1H, dd, J=9.9, 1.0 Hz), 6.08 (1H, ddd, J=9.9, 4.0, 0.8 Hz), 7.38–7.46 (2H, m), 7.55–7.59 (1H, m), 7.60–7.62 (2H, m), 7.83–7.86 (1H, m), 7.92–7.94 (1H, m), and 8.18–8.20 (1H, m). ^{13}C NMR δ 19.5, 25.7, 34.8, 45.9, 58.4, 68.9, 116.2, 118.5, 123.6, 126.9, 127.4, 129.0 (2C), 129.1, 129.9, 130.0, 130.2, 130.4, 130.9, 132.6, 137.4, 137.6, and 189.0. IR (KBr) 3410, 3064, 2244, 1690, 755, 730, and 712 cm^{-1}. MS *m/z* (%) 368 (1), 242 (20), 241 (100), and 228 (40). HM Found: 368.0715 and 370.0697. Calcd for $C_{23}H_{13}N_2OCl$: 368.0717 and 370.0687.

In dichloromethane. A dichloromethane solution (300 ml) of **4** (71.2 mg) and DCA (114 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **5** (37 mg, 33%) and **6** (6 mg, 5%) together with recovered DCA (34.8 mg).

In a mixed solution of dichloromethane and methanol. A mixed solution of dichloromethane (300 ml) and methanol (3 ml) of **4** (71.2 mg) and DCA (114 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W

high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **6** (10.8 mg, 7%), **7** (28.6 mg, 18%), and **8** (28.6 mg, 18%) together with recovered DCA (17.1 mg). *Compound* **7**: colorless needles; mp 224–225 °C. ^{1}H NMR δ 3.09 (3H, s), 6.78 (1H, dm, J=10.1 Hz), 7.09–7.17 (3H, m), 7.45–7.47 (2H, m), 7.54–7.57 (4H, m), 7.94 (1H, d, J=8.3 Hz), and 8.02 (2H, dd, J=9.2, 1.3 Hz). ^{13}C NMR δ 50.5, 52.3, 73.2, 118.7, 119.3, 127.3, 128.9, 129.7, 130.6, 130.7, 132.1, 133.6, 135.4, 135.7, 137.0, 142.3, 150.2, and 182.9. IR (KBr) 3414, 3064, 3030, 2972, 2940, 2234, 1731, 1634, 1594, 1527, 1483, 1462, 1447, 1403, 1288, 1237, 1084, 1046, 987, 909, and 764 cm^{-1}. MS *m/z* (%) 365 (18), 364 (70), 333 (19), 229 (20), 228 (100), 136 (31), and 77 (24). HM Found: 364.1210. Calcd for $C_{24}H_{16}N_2O_2$: 364.1212. *Compound* **8**: yellow crystals; mp 271–272 °C. ^{1}H NMR δ 3.08 (3H, s), 5.27 (1H, br), 5.53 (1H, br), 6.81 (1H, dd, J=10.2, 1.9 Hz), 7.06–7.16 (3H, m), 7.38 (2H, td, J=7.5, 1.3 Hz), 7.43 (2H, dd, J=7.9, 1.3 Hz), 7.51 (2H, dd, J=7.5, 1.3 Hz), 7.83 (1H, d, J=9.0 Hz), and 7.97 (2H, dd, J=7.9, 1.3 Hz). ^{13}C NMR δ 51.6, 61.4, 71.4, 119.7, 127.8, 128.9, 129.7, 130.2, 130.3, 132.6, 134.7, 134.9, 137.3, 138.5, 141.9, 154.5, 182.7, and 185.2. IR (KBr) 3482, 3202, 2236, 1684, 1554, 1338, 1082, 786, and 759 cm^{-1}. MS *m/z* (%): 382 (2), 333 (22), 307 (72), 290 (19), 279 (100), 252 (19), 239 (17), 228 (16), and 123 (16). HM Found: 382.1319. Calcd for $C_{24}H_{18}N_2O_3$: 382.1317.

4.1.4. Photoreaction of 2,5-dichlorotropone (9) and DCA. A dichloromethane solution (100 ml) of **9** (43.8 mg) and DCA (57.6 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **10** (26.2 mg, 36%) together with recovered DCA (11.5 mg). *Compound* **10**: yellow crystals; mp 229–231 °C. ^{1}H NMR δ 6.60 (1H, d, J=12.8 Hz), 7.13 (1H, dd, J=12.8, 2.4 Hz), 7.39–7.41 (2H, m), 7.43 (1H, dd, J=9.9, 2.4 Hz), 7.55–7.60 (4H, m), 8.35 (1H, d, J=9.9 Hz), and 8.44–8.45 (2H, m). ^{13}C NMR δ 49.5, 120.1, 126.5, 128.2, 129.3, 130.2, 131.5, 133.7, 133.9, 137.3, 137.4, 141.5, 143.0, 149.1, 181.0, and 181.9. IR (KBr) 3416, 3064, 2234, 2210, 1670, 1626, 1589, 1517, 1453, 1323, 1304, 1022, 758, 736, and 679 cm^{-1}. MS *m/z* (%) 360 (8), 359 (35), 358 (25), 357 (100), 329 (10), 294 (10), 218 (21), and 190 (20). HM Found: 357.0554 and 359.0540. Calcd for $C_{22}H_{12}NO_2Cl$: 357.0557 and 359.0527.

4.1.5. Photoreaction of 2-chloro-5-isopropyltropone (11) and DCA. *In benzene*. A benzene solution (100 ml) of **11** (56.0 mg) and DCA (70.8 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **12** (35.6 mg, 54%) together with recovered DCA (34.1 mg). *Compound* **12**: colorless crystals; mp 262–264 °C. ^{1}H NMR δ 0.76 (3H, t, J=6.6 Hz), 1.00 (1H, sept, J=6.6 Hz), 1.10 (3H, t, J=6.6 Hz), 1.60 (1H, dd, J=10.3, 1.3 Hz), 1.91 (1H, d, J=10.0 Hz), 5.47 (1H, d, J=10.0 Hz), 5.93 (1H, dd, J=10.3, 1.3 Hz), 7.38–7.46 (2H, m), 7.55 (1H, dd, J=7.4, 1.5 Hz), 7.58–7.61 (2H, m), 7.81–7.83 (1H, m), 7.89–7.92 (1H, m), and 8.15–8.17 (1H, m). ^{13}C NMR δ 18.8, 18.9, 32.5, 35.2, 38.3, 41.3, 46.4, 58.4, 69.2, 116.2, 118.6, 123.4, 126.7, 127.3, 128.9, 129.8, 129.9 (2C), 130.0, 130.2, 130.3, 131.0, 132.7, 137.5, 138.4, and 189.2. IR (KBr) 3474, 3068, 2234, 2244, 1690, 1457, 1229, 848, 761, and 743 cm^{-1}. MS *m/z* (%) (FAB): 411 (M^++1, 2), 241 (10), 183 (13), and 107 (10). HM (FAB) Found: 411.1264 and 413.1246 $(M+H)^+$. Calcd for $C_{26}H_{19}N_2OCl$ $(M+H)^+$: 411.1265 and 413.1235.

In dichloromethane. A dichloromethane solution (100 ml) of **11** (45.4 mg) and DCA (57.6 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **12** (38.4 mg, 42%) together with recovered DCA (6.8 mg).

In a mixed solvent of dichloromethane and acetonitrile. A mixed solution of dichloromethane (50 ml) and acetonitrile (50 ml) of **11** (30 mg) and DCA (37.5 mg) was irradiated for 3 h under nitrogen atmosphere by means of 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **12** (32.2 mg, 61%) together with recovered DCA (8 mg).

In a mixed solvent of benzene and methanol. A mixed solution of benzene (100 ml) and methanol (3 ml) of **11** (45.4 mg) and DCA 57.6 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **12** (9.5 mg, 21%) and **13** (18.3 mg, 49%) together with recovered DCA (33.0 mg). *Compound* **13**: colorless crystals; mp 294–296 °C. ^{1}H NMR δ 6.86 (1H, d, J=8.3 Hz), 7.55–7.58 (4H, m), 7.43 (1H, dd, J=8.3, 2.0 Hz), 7.94–7.96 (2H, m), 8.06–8.07 (2H, m), 8.25 (1H, d, J=2.0 Hz), and 9.89 (1H, s). ^{13}C NMR δ 51.9, 78.3, 114.7, 116.1, 121.9, 122.9, 123.9, 126.7, 127.4, 129.0, 130.0, 130.9, 131.3, 131.8, 137.4, 154.9, and 189.7. IR (KBr) 3412, 3066, 2252, 1697, 1604, 1476, 1310, 1233, 1116, 964, 768, and 635 cm^{-1}. MS *m/z* (%): 349 (37), 348 (100), 323 (19), 322 (73), 319 (13), 291 (14), 264 (17), and 228 (44). HM Found: 348.0895. Calcd for $C_{23}H_{12}N_2O_2$: 348.0899.

4.1.6. Photoreaction of 2-bromo-5-isopropyltropone (14) and DCA. *In benzene*. A benzene solution (100 ml) of **14** (56.8 mg) and DCA (57.6 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **15** (74.0 mg, 85%) together with recovered DCA (14.2 mg). *Compound* **15**: colorless crystals; mp 259–260 °C. ^{1}H NMR δ 0.77 (3H, d, J=6.8 Hz), 0.97 (1H, sept, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz), 1.88 (1H, d, J=10.0 Hz), 1.94 (1H, dd, J=10.0, 1.3 Hz), 5.47 (1H, d, J=10.0 Hz), 5.96 (1H, dd, J=10.0, 1.3 Hz), 7.38–7.44 (2H, m), 7.55–7.56 (1H, m), 7.60–7.61 (2H, m), 7.80–7.81 (1H, m), 7.91–7.92 (1H, m), and 8.20–8.22 (1H, m). ^{13}C NMR δ 18.6, 18.9, 33.3, 35.2, 38.3, 41.4, 46.4, 58.0, 64.9, 117.0, 118.5, 123.3, 126.6,

127.3, 128.7, 129.1, 129.8, 129.9, 130.1, 130.2 (2C), 130.8, 132.4, 137.5, 138.7, and 189.0. IR (KBr): 3072, 2958, 1688, 1457, 1227, 844, 762, and 742 cm^{-1}. MS *m/z* (%) (FAB): 457 (2), 455 (2), 241 (19), 229 (15), and 107 (11). EA Found: C, 68.45; H, 4.20; N, 6.18%. Calcd for $C_{26}H_{19}N_2OBr$: C, 68.58; H, 4.21; N, 6.15%.

In dichloromethane. A dichloromethane solution (100 ml) of **14** (56.8 mg) and DCA (57.6 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **15** (75.0 mg, 84%) together with recovered **15** (13.2 mg).

In a mixed solution of dichloromethane and acetonitrile. A mixed solvent of dichloromethane (50 ml) and acetonitrile (50 ml) of **14** (60.3 mg) and DCA (60.3 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **15** (49.8 mg, 69%) together with recovered DCA (24.2 mg).

4.1.7. Preparation of 3,7-dideuterio-2-bromo-5-isopropyltropone (14-d_2). A D_2O (3 ml) solution of 5-isopropyltropolone (210 mg) was heated at 180 °C for 24 h in a sealed tube. After the reaction, the reaction mixture was extracted by ether. The ether solution was dried and evaporated in vacuum. The residue was treated by diazomethane to give methyl ether, which was heated at 80 °C in the presence of hydrazine hydrate for 5 min to give 3,7-dideuterio-2-hydrazino-5-isopropyltropone (224 mg). To a solution of copper sulfate (2 g) dissolved in hot D_2O (3 ml), a mixture of conc. HBr (2 ml) and 2-hydrazino-5-isopropyltropone (224 mg) was added at one time. After cooling to room temperature, the mixture was extracted by chloroform. The chloroform layer was dried with Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (hexane/AcOEt) to give 3,7-dideuterio-2-bromo-5-isopropyltropone (**14**-d_2) (brown oil, 33.3 mg, 12%). *Compound* **14**-d_2: brownish oil; ^{1}H NMR δ 1.24 (6H, d, J=6.8 Hz), 2.80 (1H, sept, J=6.8 Hz), 6.70 (1H, s), and 7.12 (1H, s). MS *m/z* (%): 231 (4), 230 (97), 229 (22), 228 (M^+, 100), 227 (10), and 226 (5).

4.1.8. Photoreaction of 3,7-dideuterio-2-bromo-5-isopropyltropone (14-d_2) and DCA. A dichloromethane solution (100 ml) of **14**-d_2 (33.3 mg) and DCA (33.1 mg) was irradiated for 3 h under nitrogen atmosphere by means of a 400 W high-pressure mercury lamp through 0.7 M $NaNO_2$ solution. After evaporation of the solvent, the residue was chromatographed on a silica gel column (hexane/AcOEt) to give **15**-d_2 (11.0 mg, 43%) together with recovered DCA (20.3 mg). *Compound* **15**-d_2: colorless crystals; ^{1}H NMR δ 0.77 (3H, d, J=6.8 Hz), 0.97 (1H, sept, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz), 1.88 (1H, s), 5.96 (1H, s), 7.38–7.44 (2H, m), 7.55–7.56 (1H, m), 7.60–7.61 (2H, m), 7.80–7.81 (1H, m), 7.91–7.92 (1H, m), and 8.20–8.22 (1H, m). MS *m/z* (%) (FAB): 459 (2), 457 (2), 241 (19), 229 (15), and 107 (11).

4.1.9. Fluorescence quenching. Fluorescence spectra and measurement of fluorescence quenching were recorded on JSC, FP-700 spectrometer. The fluorescence quenching of DCA was measured by various concentrations of **4** and **14** in acetonitrile. The intensities at E_{ex}=400 nm and E_{em}=448 nm were obtained three times for each cell and an average value for each sample was used. The quenching results were analyzed according to the Stern–Volmer equation.

References and notes

1. For example: Gould, I. R.; Boiani, J. A.; Gaillard, E. B.; Goodman, J. L.; Farid, S. *J. Phys. Chem. A* **2003**, *107*, 3515.
2. For example: Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Org. Chem.* **1997**, *62*, 5966.
3. Brown-Wensley, K. A.; Mattes, S. L.; Farid, S. *J. Am. Chem. Soc.* **1978**, *100*, 4162.
4. Mizuno, K.; Ichinose, N.; Otsuji, Y. *J. Org. Chem.* **1992**, *57*, 1855.
5. Müller, F.; Mattey, J. *Chem. Rev.* **1993**, *93*, 99.
6. Ikeda, H.; Aburakawa, N.; Tanaka, F.; Fukushima, T.; Miyashi, T. *Eur. J. Org. Chem.* **2001**, 3445.
7. Photocycloreactions of cyanoarenes: see (a) Mangion, D.; Arnold, D. R.; Cameron, T. S.; Robertson, K. N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 48. (b) Sakamoto, M.; Yagi, T.; Mino, T.; Yamaguchi, K.; Fujita, T. *J. Am. Chem. Soc.* **2000**, *122*, 8141. (c) Boggeri, E.; Fasani, E.; Mella, M.; Albini, A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 2097.
8. Wu, S.-P.; Mori, A.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1994**, 919. Mori, A.; Wu, S.-P.; Kato, N.; Takeshita, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3045.
9. Mori, A.; Kawakami, H.; Kato, N.; Wu, S.-P.; Takeshita, H. *Org. Biomol. Chem.* **2003**, *1*, 1730.
10. Sato, M.; Ebine, E.; Tsunetsugu, J. *J. Chem. Soc., Chem. Commun.* **1978**, 215. Tsuda, T.; Sugiyama, S.; Mori, A.; Takeshita, H. *Bull. Chem. Soc. Jpn* **1987**, *60*, 2695.
11. Doering, W. von E.; Knox, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 297.
12. Eriksen, J.; Foote, C. S. *J. Phys. Chem.* **1978**, *82*, 2659.
13. Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615.
14. Gilbert, A.; Heath, P.; Rodwell, P. W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1867. Drew, M. G. B.; Gilbert, A.; Rodwell, P. W. *Tetrahedron Lett.* **1985**, *26*, 949.
15. Doering, W. von E.; Knox, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 3203.
16. Jacobi, D.; Abraham, W.; Pischel, U.; Grubert, L.; Stösser, R.; Schnabel, W. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1695.
17. The photoreaction of 2-bromotropone and DCA was undertaken in a mixed solvent of dichloromethane and acetonitrile (1:1) to give the *meta*-adduct in 32% yield. Kawakami, H.; Mori, A, unpublished result.
18. Bryce-Smith, D.; Gilbert, A.; Orger, B.; Tyrrell, H. *J. Chem. Soc., Chem. Commun.* **1974**, 334.
19. Mattay, J. *Tetrahedron* **1985**, *41*, 2393. Mattay, J. *Tetrahedron* **1985**, *41*, 2405.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8791–8800

Assigning the C-15 configuration of 15-hydroxy-, 15-methoxy-, 15-ethoxy-hexahydrofurofuran neoclerodane diterpenoids

Sergio Rosselli, Antonella Maggio, Franco Piozzi and Maurizio Bruno*

Dipartimento di Chimica Organica, Università di Palermo, Viale delle Scienze, 90128 Palermo, Italy

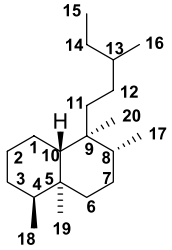
Received 21 May 2004; revised 24 June 2004; accepted 15 July 2004

Available online 21 August 2004

Abstract—Examination of ^{1}H and ^{13}C NMR spectra allows the establishment of rules for assigning the correct configuration at C-15 of 15-hydroxy-, 15-methoxy-, 15-ethoxy-hexahydrofurofuran neoclerodane diterpenoids. The structure of several diterpenoids has been assigned or ammended.
© 2004 Elsevier Ltd. All rights reserved.

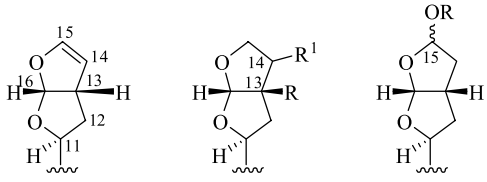
1. Introduction

The neoclerodanes are a class of diterpenoids based on the skeleton **1** and many of its derivatives show interesting biological properties. The most investigated is the antifeedant and related insecticidal activity against several pest insects.[1–4] Some products were tested with positive results for antiviral,[5] antitumour,[5–10] antibiotic,[11,12] antimicrobial[13,14] and amoebicidal[15] activity. Other products are part of traditional drugs used for the treatment of tumours, hepatitis, cirrhosis, urinary diseases[7] and peptic ulcers.[16] In two cases even an hallucinogen activity was observed.[17,18] However, cases of severe hepatotoxicity in man were reported.[19,20]



1

Frequently, the C-11/C-16 chain contains an oxygenated pentacyclic ring, or a bicyclic furofuranic system **2**, variously hydrogenated. In several cases, this system shows an oxygen function on C-15 forming an hemiacetalic or acetalic bond. Such natural products occur in species of the genera *Scutellaria* and *Ajuga* (Lamiaceae) and *Clerodendron* and *Caryoptis* (Verbenaceae). Consequentially, carbon C-15 can have a *R* or *S* configuration. Usually, its attribution is not easy, especially as there exists the possibility of an equilibration through an open structure for hemiacetals. In fact, often the 15*R* and 15*S* hemiacetalic epimers are isolated in a 1:1 mixture.



R = R^1 = H
R = H, R^1 = OAcyl
R = OH, R^1 = H

R = H, Me, Et

2

2. Results and discussion

Scutecyprol A is a neoclerodane diterpenoid with a 15-hydroxy-hexahydrofurofuran system, deriving from the structure **2**. It was isolated the first time from *Scutellaria cypria*[21] as a 1:1 mixture of the two C-15 epimers **3a** and **3b**; in fact, the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ solution (Tables 1 and 2) indicated that some protons and carbons gave a double signal due to the occurrence of the two epimers.

Keywords: Natural products; Diterpenoids; Neoclerodanes; Configuration; 15-Oxygenated-hexahydrofurofuranes.
* Corresponding author. Tel.: +39-091-596905; fax: +39-091-596825; e-mail: bruno@dicpm.unipa.it

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.033

Table 1. ^{1}H NMR data of compounds **3a**, **3b**, **19**, **20**, **29** and **30**

H	**3a** (15*R*)	**3b** (15*S*)	**19** (15*R*)	**20** (15*S*)	**29** (15*R*)	**30** (15*S*)
2β	—	—	4.08 m	4.08 m	—	—
3α	—	—	2.54 dt	2.54 dt	—	—
6β	4.68 brdd	4.68 brdd	4.62 dd	4.62 dd	4.68 dd	4.68 dd
10β	—	—	2.18 dd	2.18 dd	—	—
11α	4.00 dd	4.59 dd	3.99 dd	4.29 dd	4.02 dd	4.44 dd
13β	3.09 m	2.82 m	2.94 m	2.76 m	2.98 m	2.82 m
15α	5.64 d	—	5.10 d	—	5.23 d	—
15β	—	5.53 d	—	4.97 d	—	5.09 d
16β	5.80 d	5.78	5.70 d	5.79 d	5.72 d	5.78 d
Me17	0.86 d	0.88 d	0.89 d	0.91 d	0.87 d	0.89 d
18a	2.98 dd	2.98 dd	2.94 d	2.94 d	2.99 brd	2.99 brd
18b	2.21 d	2.21 d	2.35 d	2.35 d	2.21 d	2.21 d
19a	4.89 d	4.89 d	—	—	4.90 d	4.91 d
19b	4.37 brd	4.37 brd	—	—	4.38 brd	4.38 brd
19α	—	—	5.11 s	5.11 s	—	—
Me20	0.95 s	0.94 s	1.10 s	1.07 s	0.97 s	0.94 s
Ac	2.10 s	2.10 s	2.01 s	2.01 s	2.11 s	2.11 s
Ac	1.95 s	1.95 s	—	—	1.95 s	1.95 s
OCH_3	—	—	3.33 s	3.33 s	—	—
OCH_3	—	—	3.50 s	3.50 s	—	—
OCH_2a	—	—	—	—	3.75 m	3.75 m
OCH_2b	—	—	—	—	3.44 m	3.44 m
CH_3	—	—	—	—	1.18 t	1.19 t
J (Hz)						
1α,3α	—	—	2.9	2.9	—	—
1α,10β	—	—	13.2	13.2	—	—
1β,10β	—	—	9.5	9.5	—	—
2β,3α	—	—	2.9	2.9	—	—
3α,18a	2.4	2.4	—	—	—	—
3α,3β	—	—	14.1	14.1	—	—
6β,7α	11.4	11.4	10.9	10.9	11.5	11.5
6β,7β	4.9	4.9	4.5	4.5	4.6	4.6
6β,19b	<0.5	<0.5	—	—	<0.5	<0.5
8β,Me17	6.3	5.8	6.4	5.9	6.4	6.4
11α,12a	11.7	10.6	11.5	10.7	11.6	11.0
11α,12b	4.4	5.9	4.7	6.2	4.5	5.6
13β,16β	5.3	5.3	5.4	5.4	5.5	5.6
14a,15α,	4.0	—	4.1	—	4.9	—
14b,15α	0	—	0	—	0	—
14a,15β	—	0	—	0	—	0
14b,15β	—	5.6	—	5.5	—	5.7
18a,18b	4.0	4.0	4.3	4.3	4.1	4.1
19a,19b	12.2	12.2	—	—	12.3	12.3
CH_2–Me	—	—	—	—	7.0	7.0

Now, we isolated a product from *Scutellaria sieberi* having the identical structure of scutecyprol A; its NMR spectra gave only a signal for the protons and carbons that had previously appeared as double signals and corresponding to the chemical shift of one of the two signals. It meant that only an epimer was present.

Considering the three-dimensional structure of the two epimers, it was clear that only in the case of a 15*R* configuration a NOE experiment of irradiation of H-11 could produce a clear increase in the intensity of H-15. This is not possible in the 15*S* configuration. Actually, a clear NOE (8%) increase was observed in our product, thus proving the 15*R* configuration, with 15β-OH and 15α-H orientation, and hence structure **3a**.

To confirm this hypothesis, repeated carbon NMR spectra on the $CDCl_3$ solution of **3a** were run: after 20 min, a second signal of minor intensity appeared for those same carbons that gave two signals in the mixture. The intensity of these new signals increased in the course of time, until the same signals of the mixture of epimers **3a** and **3b** extracted from *S. cypria* were obtained.

A similar behaviour was observed by Ohno for ^{13}C NMR spectrum of a sample of 15*R*-scutecyprol A in pyridine-d_5 solution, obtained as a pure epimer from *Scutellaria discolor*.[22]

The chance of having isolated pure 15*R*-scutecyprol A **3a** gave us the opportunity of reporting in this paper its exact configuration and of describing a rule for the attribution of proton and carbon resonances to many hemiacetals at C-15, having 15*R* or 15*S* configuration and usually isolated as a 1:1 mixture of the two epimers. In the same way, this rule allows to assign the configurations of stable acetalic derivatives carrying $-OCH_3$ or $-OC_2H_5$ groups. Thus, we performed a critical check of the whole literature concerning such products.

The reinvestigation of the data concerning H-11, H-13, H-15 and H-16 in papers published by us and by other authors for products with the 15-OH group led us to either confirm or amend former attributions; the correct ones are reported in Table 3.

Table 2. ^{13}C NMR data of compounds **3a**, **3b**, **19**, **20**, **29** and **30**

C	**3a** (15*R*)	**3b** (15*S*)	**19** (15*R*)	**20** (15*S*)	**29** (15*R*)	**30** (15*S*)
1	22.17 t	22.20 t	28.88 t	28.83 t	24.97	25.03
2	24.95 t	25.01 t	66.71 d	66.71 d	22.18	22.16
3	32.70 t	32.74 t	36.89 t	36.89t	32.76	32.73
4	65.01 s	65.05 s	60.72 s	60.72 s	65.03	65.06
5	45.55 s	45.55 s	42.67 s	42.67 s	45.55	45.55
6	71.95 d	72.10 d	68.18 d	68.31 d	71.95	72.11
7	33.40 t	33.40 t	33.48 t	33.48 t	33.38	33.45
8	36.06 d	36.16 d	35.60 d	35.37 d	36.18	36.13
9	40.13 s	40.18 s	40.93 s	40.99 s	40.11	40.17
10	48.48 d	48.30 d	41.11 d	41.11d	48.51	48.30
11	83.61 d	83.55 d	84.55 d	84.20 d	83.56	83.54
12	32.08 t	32.47 t	33.10 t	33.55 t	32.21	32.73
13	40.01 d	41.03 d	39.67 d	40.17 d	40.06	40.72
14	38.83 t	39.86 t	38.07 t	39.57 t	38.23	39.60
15	98.67 d	98.41 d	104.93 d	104.72 d	103.60	103.85
16	107.46 d	109.50 d	107.67 d	109.70 d	107.20	109.13
17	16.47 q	16.40 q	16.67 q	16.67 q	16.45	16.45
18	48.32 t	48.44 t	48.82 t	49.82 t	48.48	48.43
19	61.71 t	61.81 t	100.20 s	100.28 s	61.73	61.82
20	13.98 q	14.01 q	14.13 q	13.92 q	14.02	14.09
Ac	170.11 s	171.00 s	170.43 s	170.43 s	170.13	170.13
Ac	170.11 s	171.00 s			170.95	170.92
Ac	21.18 q	21.14 q	21.25 q	21.25 q	21.18	21.21
Ac	21.18 q	21.14 q			21.18	21.21
OMe			55.25 q	55.25 q		
OMe			54.73 q	54.50 q		
OEt					62.85	63.07
OEt					15.12	15.10

Indeed, clear differences occur for the signals of H-11, H-13, H-15 and H-16. The resonance of H-11 in the 15*R* configuration occurs at higher fields than in the 15*S* configuration: average chemical shift is 3.94–4.07 ppm for 15*R*, versus 4.48–4.60 ppm for 15*S*. In contrast, the resonance of H-13 occurs in the 15*R* configuration at lower fields than in the 15*S* configuration: average chemical shift 2.90–3.10 ppm for 15*R* against 2.78–2.85 ppm for 15*S*.

Minor differences occur for H-15: the average chemical shift is 5.61–5.66 ppm for 15*R*, versus 5.48–5.56 ppm for 15*S*. Finally, H-16 occurs at 5.76–5.83 ppm for 15*R*, versus 5.75–5.79 ppm for 15*S*. A similar trend was observed in the literature values[22,23] for the proton spectra run in pyridine-d_5 solution. All these values refer to spectra run in $CDCl_3$ and in pyridine-d_5, as reported in Table 9. An analogous rule can be suggested for the chemical shift values of ^{13}C NMR spectra, concerning carbon atoms C-12 to C-16.

In the case of scutecyprol A and of other similar diterpenoids, the chemical shifts of the carbon atoms C-12, C-13, C-14, C-15, C-16 show constant differences comparing 15*R* versus 15*S* configuration. The values of C-12, C-13 and C-14 occur at slightly higher fields for the 15*R* configuration, whereas the values of C-15 occur at slightly lower fields. However, the greatest difference is observed for C-16: the values for the 15*R* configuration fall about 2 ppm upfield. For 15*R* epimers, C-16 resonates in the range 107.2–107.9 ppm, for 15*S* epimers between 109.1 and 110.0 (see Table 9).

Applying this rules to other pairs of C-15 hemiacetalic epimers, we have now been able to assign the values of ^{13}C NMR spectra of the two epimers of 14,15-dihydro-15-hydroxyajugapitin (**5**) and chamaepitin (**6**) and to assign or reverse the values of ^{1}H NMR spectra of the two epimers of 14,15-dihydro-15-hydroxyajugachin A (**4**), 14,15-dihydro-15-hydroxyajugapitin (**5**), chamaepitin (**6**), scupontin D (**8**), scupontin F (**9**), scutalbin C (**10**), scutecyprol B (**11**), scutalbin B (**12**), scutalsin (**13**), scutalpin O (**14**) and scupolin K (**15**). The correct values of ^{1}H NMR spectra and ^{13}C NMR spectra for compounds **3**-**18** are reported in the Tables 3 and 4, respectively.

Afterwards, we analysed the data reported in the literature for the 15-OCH_3 derivatives. The first example was scupolin I (**19**), isolated from *Scutellaria polyodon*.[24] Its 15*R* stereochemistry was proved by its NOE enhancement between the C-11 and C-15 protons. However, the ^{13}C NMR spectrum reported in the paper was in complete disagreement with the rule proposed by us in the present paper. In order to clarify the problem we decided to synthesize it and its C-15 epimer by dissolving scutalbin C (**10**) in a 1:1 mixture of MeOH and AcOH. Scupolin I (**19**) and its C-15 epimer (**20**) were obtained in a 11:9 ratio. The ^{1}H and ^{13}C NMR spectra of the two compounds, run in $CDCl_3$, are reported in Tables 1 and 2, and they are in perfect agreement with our rule. Our rule confirms the correct stereochemistry at C-15 of hativenes A–C (**21**-**23**),[25] whose structures were also determined by NOESY experiments. On the other hand, the structures reported in the literature for clerodinin A (**24**) isolated from *Clerodendron brachyanthum*,[26] lupulins A (**25**), B (**26**) and D (**27**) isolated from *Ajuga lupulina*,[27] and 15-methoxy-14,15-dihydro-3-epicaryoptin (**28**) isolated from *Clerodendron inerme*,[28] have to be revised. Thus, we assign to clerodinin A, lupulin A and 15-methoxy-14,15-dihydro-3-epicaryoptin a 15*S* stereochemistry and the structures **24**, **25** and **28**,

Table 3. ^{1}H NMR data of 15-OH derivatives

Compound	No.	Ref.	Solvent	Ratio	H-11	H-13	H-15	H-16
Scutecyprol A 15*R*	**3a**		$CDCl_3$	Pure	4.00	3.09	5.64	5.80
Scutecyprol A 15*S*	**3b**		$CDCl_3$	Mixture	4.59	2.82	5.53	5.78
14,15-Dihydro-15-hydroxyajugachin A 15*R*	**4a**	34	$CDCl_3$	Mixture	3.96[a]	3.05[a]	5.60[a]	5.81[a]
14,15-Dihydro-15-hydroxyajugachin A 15*S*	**4b**	34	$CDCl_3$	1:1	[b]	[b]	5.49[a]	5.77[a]
14,15-Dihydro-15-hydroxyajugapitin 15*R*	**5a**	33	$CDCl_3$	Mixture	4.05[a]	[b]	5.56[a]	5.80[a]
14,15-Dihydro-15-hydroxyajugapitin 15*S*	**5b**	33	$CDCl_3$	1:1	[b]	[b]	[b]	5.76[a]
Chamaepitin 15*R*	**6a**	35	$CDCl_3$	Mixture	4.07[a]	[b]	5.48[a]	5.81[a]
Chamaepitin 15*S*	**6b**	35	$CDCl_3$	1:1	[b]	[b]	[b]	5.77[a]
Scutelaterin C 15*R*	**7a**	36	$CDCl_3$	Mixture	4.02	3.02	5.66	5.79
Scutelaterin C 15*S*	**7b**	36	$CDCl_3$	2:3	4.56	2.78	5.54	5.75
Scupontin D 15*R*	**8a**	37	$CDCl_3$	Mixture	3.96	3.07[a]	5.61[a]	5.81[a]
Scupontin D 15*S*	**8b**	37	$CDCl_3$	1:1	4.57	2.84[a]	5.50[a]	5.76[a]
Scupontin F 15*R*	**9a**	37	$CDCl_3$	Mixture	3.98	3.10[a]	5.63[a]	5.83[a]
Scupontin F 15*S*	**9b**	37	$CDCl_3$	1:1	4.60	2.85[a]	5.52[a]	5.79[a]
Scutalbin C 15*R*=scutaltasin 15*R*	**10a**	38	$CDCl_3$	Mixture	3.94	3.00	5.62[c]	5.77[c]
Scutalbin C 15*S*=scutaltasin 15*S*	**10b**	38	$CDCl_3$	1:1	4.48	2.80	5.51[c]	5.76[c]
Scutaltasin 15*R*	**10a**	39	$CDCl_3$	Mixture	3.95	2.90	5.63[c]	5.79
Scutaltasin 15*S*	**10b**	39	$CDCl_3$	1:1	4.50	2.78	5.53[c]	5.77
Scutecyprol B 15*R*	**11a**	38	$CDCl_3$	Mixture	3.99	3.10	5.64[c]	5.80[c]
Scutecyprol B 15*S*	**11b**	38	$CDCl_3$	1:1	4.52	2.82	5.53[c]	5.78[c]
Scutalbin B 15*R*	**12a**	40	$CDCl_3$	Mixture	3.95	[b]	5.61[a]	5.76[a]
Scutalbin B 15*S*	**12b**	40	$CDCl_3$	1:1	4.50	[b]	5.51[a]	5.75[a]
Scutalsin 15*R*	**13a**	40	$CDCl_3$	Mixture	3.95	[b]	5.62[a]	5.77[a]
Scutalsin 15*S*	**13b**	40	$CDCl_3$	1:1	4.49	[b]	5.51[a]	5.76[a]
Scutalpin O 15*R*	**14a**	41	$CDCl_3$	Mixture	4.00[a]	3.10[a]	5.63[a]	5.80[a]
Scutalpin O 15*S*	**14b**	41	$CDCl_3$	1:1	[b]	2.85[a]	5.53[a]	5.78[a]
Scupolin K 15*R*	**15a**	42	$CDCl_3$	Mixture	3.99	3.10	5.66[c]	5.81[c]
Scupolin K 15*S*	**15b**	42	$CDCl_3$	1:1	4.54	2.85	5.54[c]	5.78[c]
Scutecyprol A 15*R*	**3a**	22	Py-d_5	Pure	4.16	3.16	6.04	6.12
Scutecyprol A 15*S*	**3b**	22	Py-d_5	Mixture	4.93	2.80	5.80	5.98
No name 15*R*	**16a**	22	Py-d_5	Mixture	4.15	3.14	6.03	6.10
No name 15*S*	**16b**	22	Py-d_5		4.94	2.78	5.80	5.96
No name 15*R*	**17a**	22	Py-d_5	Mixture	4.14	3.14	6.06	6.15
No name 15*S*	**17b**	22	Py-d_5		4.88	2.80	5.82	6.02
No name 15*R*	**18a**	22	Py-d_5	Mixture	4.11	3.13	6.06	6.13
No name 15*S*	**18b**	22	Py-d_5		4.85	2.78	5.82	6.01
Scutecyprol B 15*R*	**11a**	23	Py-d_5	Mixture	4.12	3.12	6.06[c]	6.13[c]
Scutecyprol B 15*S*	**11b**	23	Py-d_5		4.86	2.78	5.82[c]	6.01[c]
Scutalbin B 15*R*	**12a**	23	Py-d_5	Mixture	4.10	[b]	6.06	6.13
Scutalbin B 15*S*	**12b**	23	Py-d_5		4.85	[b]	5.82	6.01
Scutalsin 15*R*	**13a**	23	Py-d_5	Mixture	4.10	[b]	6.05	6.13
Scutalsin 15*S*	**13b**	23	Py-d_5		4.85	[b]	5.82	6.01

[a] These values were not assigned in the original paper.
[b] Not reported in the original paper.
[c] The assignments of these values have been reversed with respect to those reported in the original paper.

respectively. Lupulin D, whose structure had been already correct by Chen et al. who determined the relative configuration of the molecules by X ray diffraction analysis,[29] and lupulin B belong instead to the 15*R* series and their structures are showed in formulae **27** and **26**. The definitive correct data for compounds **19**-**28** are reported in Tables 5 and 6.

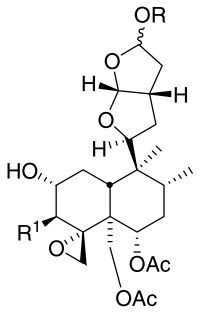
In the same way, we extended our study to the 15-OC_2H_5 compounds. Clerodinin C and clerodinin D, epimeric at C-15, were first isolated from *C. brachyanthum* and they were also reported as products of AcOH catalysed ethanolysis of clerodin.[30] Clerodinin C was assigned the 15 β-OEt stereochemistry (15*R*) on the basis of mechanistic considerations. Successively, they were isolated from *Ajuga parviflora*[31] and the authors confirmed the stereochemistry previously reported since they could not observe significant NOE enhancement between H-11 proton and the CH_2 of the OEt group. Finally, the same compounds were isolated from *Scutellaria grossa*;[22] in this case the stereochemistry at C-15 was given based on NOE enhancement observed between H-15/H-11 and CH_2 of the OEt group/H-16 for the 15*R* isomer and CH_2 of the OEt group/H-11 for the 15*S* isomer. Since in this last paper ^{1}H and ^{13}C NMR spectra were run in pyridine-d_5, it was not possible to compare these spectra with those reported in the two previous papers where they were run in $CDCl_3$. In order to assign the correct stereochemistry to clerodinin C and D we synthesized them by treatment of clerodin (**38**) with EtOH and AcOH; two isomeric compounds were obtained in a 9:11 ratio. The ^{1}H and ^{13}C NMR spectroscopy data of spectra run in pyridine-d_5 of the most abundant one were in perfect agreement with those reported for the 15*R* epimer[22] as well as the ^{1}H and ^{13}C NMR spectra run in pyridine-d_5 of the less abundant one were in perfect agreement with those reported for the 15*S* epimer.[22] On the other hand, the spectra registered in $CDCl_3$ (Tables 1 and 2) were identical to those reported for the two epimers with reversed stereochemistry at C-15. Finally, ROESY experiments on our compounds proved that the correct stereochemistry at C-15 is that described by Ohno[22]

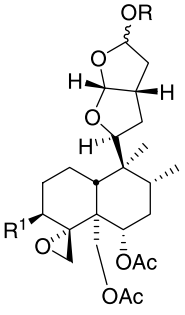
and consequently the structures previously reported for clerodinin C and D,[30,31] have to be reversed. Therefore, we assign to clerodinin D the structure of (15*R*)-15β-ethoxy-14,15-dihydroclerodin (**29**) and to clerodinin C the structure of (15*S*)-15α-ethoxy-14,15-dihydroclerodin (**30**).

Based on the peculiar differences observed between the two 15*R* and 15*S* isomers (Table 9) and on the data reported in literature we can correct several structures previously reported.

Clerodiol, isolated from *C. brachyanthum*,[30] 3β-acetoxy-clerodinin C and 15β-ethoxy-14,15-dihydro-ajugapitin isolated from *A. parviflora*,[31] all indicated as 15*R* isomers, instead have the structures **31**, **32** and **33** respectively, with a 15*S* stereochemistry, 15α-ethoxy-14,15-dihydro-ajugapitin isolated from *A. parviflora*[31] and indicated as the 15*S* isomer, instead has the structure **34** with a 15*R* stereochemistry. Furthermore, we can assign to ivain III, isolated from *Ajuga iva*,[32] and to 15-ethoxy-14,15-dihydro-ajugapitin, isolated from *Ajuga chamaepitys*,[33] whose stereochemistries at C-15 was not ascertained, the 15*S* configurations and the structures **35** and **33**, respectively. The definitive correct data for compounds **29**-**37** are reported in Tables 7 and 8.

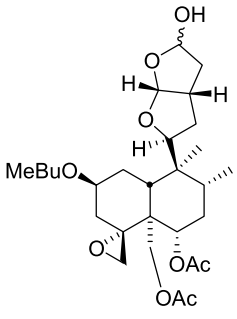
In summary, we believe that our observations and the rules proposed herein can allow an accurate attribution of the configurations of the 15-OH and of the structures of the 15-OCH_3 and 15-OC_2H_5 natural and semisynthetic neoclerodane derivatives (Table 9).





3a R = H 15*R* R^1 = H
3b R = H 15*S* R^1 = H
24 R = Me 15*S* R^1 = H
26 R = Me 15*R* R^1 =
27 R = Me 15*R* R^1 = H
28 R = Me 15*S* R^1 = OAc
29 R = Et 15*R* R^1 = H
30 R = Et 15*S* R^1 = H
32 R = Et 15*S* R^1 = OAc

4a R = H 15*R* R^1 =
4b R = H 15*S* R^1 =
21 R = Me 15*R* R^1 =
22 R = Me 15*S* R^1 =
5a R = H 15*R* R^1 =
5b R = H 15*S* R^1 =
25 R = Me 15*S* R^1 =
33 R = Et 15*S* R^1 =
34 R = Et 15*R* R^1 =
6a R = H 15*R* R^1 =
6b R = H 15*S* R^1 =



7a 15*R*
7b 15*S*

Table 4. ^{13}C NMR data of 15-hydroxy epimers

Compounds	No.	Ref.	Solvent	Ratio	C11	C12	C13	C14	C15	C16
Scutecyprol A 15*R*	**3a**		$CDCl_3$	Pure	83.61	32.08	40.01	38.83	98.67	107.46
Scutecyprol A 15*S*	**3b**		$CDCl_3$	Mixture	83.55	32.47	41.03	39.86	98.41	109.50
14,15-Dihydro-15-hydroxyajugapitin 15*R*	**5a**	33	$CDCl_3$	Mixture	83.3[a]	32.0[a]	40.1	33.2[a]	98.6[a]	107.2[a]
14,15-Dihydro-15-hydroxyajugapitin 15*S*	**5b**	33	$CDCl_3$	1:1	82.8[a]	32.1[a]	40.1	33.3[a]	98.3[a]	109.1[a]
Chamaepitin 15*R*	**6a**	35	$CDCl_3$	Mixture	83.2	32.2	40.0[a]	33.2[a]	98.6[a]	107.2[a]
Chamaepitin 15*S*	**6b**	35	$CDCl_3$	1:1	83.2	32.2	40.1[a]	33.3[a]	[b]	109.1[a]
Scutelaterin C 15*R*	**7a**	36	$CDCl_3$	Mixture	83.7	32.7	42.3	[b]	98.7	107.4
Scutelaterin C 15*S*	**7b**	36	$CDCl_3$	2:3	82.7	33.2	42.0	[b]	98.4	109.3
Scutalbin C 15*R*	**10a**	38	$CDCl_3$	Mixture	84.4	33.0	39.7	38.8	98.7	107.9
Scutalbin C 15*S*	**10b**	38	$CDCl_3$	1:1	84.6	33.7	40.5	39.9	98.4	110.0
Scutecyprol B 15*R*	**11a**	38	$CDCl_3$	Mixture	84.4	33.1	39.7	38.8	98.7	107.9
Scutecyprol B 15*S*	**11b**	38	$CDCl_3$	1:1	84.6	33.6	40.7	39.9	98.4	110.0
Scutalpin O 15*R*	**14a**	42	$CDCl_3$	Mixture	83.6	32.0	39.9	38.7	98.6	107.3
Scutalpin O 15*S*	**14b**	42	$CDCl_3$	1:1	83.6	32.3	41.3	39.8	98.3	109.3
Scupolin K 15*R*	**15a**	42	$CDCl_3$	Mixture	84.6	32.8	39.9	38.8	98.7	107.9
Scupolin K 15*S*	**15b**	42	$CDCl_3$	1:1	84.9	33.3	40.7	39.7	98.4	110.0
Scutecyprol A 15*R*	**3a**	22	Py-d_5	Mixture	83.8	32.6	41.0	39.9	99.3	107.6
Scutecyprol A 15*S*	**3b**	22	Py-d_5		83.4	33.0	41.7	40.7	98.7	109.5
No name 15*R*	**16a**	22	Py-d_5	Mixture	83.6	32.7	41.0	39.9	99.3	107.6
No name 15*S*	**16b**	22	Py-d_5		84.0	33.0	41.7	40.6	98.7	109.4
No name 15*R*	**17a**	22	Py-d_5	Mixture	84.4	33.3	40.8	39.9	99.4	108.0
No name 15*S*	**17b**	22	Py-d_5		85.0	33.9	41.4	40.7	98.7	109.8
No name 15*R*	**18a**	22	Py-d_5	Mixture	84.4	33.3	40.8	39.9	99.4	107.9
No name 15*S*	**18b**	22	Py-d_5		85.0	33.9	41.4	40.7	98.7	109.8
Scutalbin C 15*R*	**10a**	22	Py-d_5	Mixture	84.5	33.4	40.8	39.9	99.3	108.0
Scutalbin C 15*S*	**10b**	22	Py-d_5		85.0	34.0	41.4	40.7	98.7	109.9
Scutecyprol B 15*R*	**11a**	23	Py-d_5	Mixture	84.3	33.3	40.7	39.9	99.4	107.9
Scutecyprol B 15*S*	**11b**	23	Py-d_5		84.9	33.9	41.4	40.7	98.7	109.8
Scutalbin B 15*R*	**12a**	23	Py-d_5	Mixture	84.3	33.3	40.7	39.8	99.4	107.9
Scutalbin B 15*S*	**12b**	23	Py-d_5		84.9	33.9	41.4	40.7	98.7	109.8
Scutalsin 15*R*	**13a**	23	Py-d_5	Mixture	84.3	33.3	40.7	39.9	99.4	107.9
Scutalsin 15*S*	**13b**	23	Py-d_5		84.9	33.9	41.4	40.7	98.7	109.8

[a] These values were not assigned in the original paper.
[b] Not reported in the original paper.

Table 5. ^{1}H NMR data of 15-methoxy derivatives in $CDCl_3$

Compound	No.	Ref.	H-11	H-13	H-15	H-16
Scupolin I 15*R*	**19**		3.99	2.94	5.10	5.70
Scupolin I 15*S*	**20**		4.29	2.76	4.97	5.79
Hativene A	**21**	25	3.99	2.97	5.08	5.72
Hativene B	**22**	25	4.37	2.78	4.95	5.80
Hativene C	**23**	25	4.37	2.83	4.95	5.79
Clerodinin A[a]	**24**	26	4.34	2.77	4.94	5.76
Lupulin A[a]	**25**	27	4.37	2.81	4.96	5.81
Lupulin B[a]	**26**	27	4.02	3.01	5.11	5.72
Clerodinin B[a]=lupulin D	**27**	26	3.98	2.95	5.07	5.67
Lupulin D[a]	**27**	27	3.99	2.98	5.08	5.68
15-Methoxy-14,15-dihydro-3-epicaryoptin[a]	**28**	28	4.40	2.80	4.98	5.80

[a] The stereochemistry at C-15 of these compounds have been reversed with respect to that reported in the original paper.

Table 6. ^{13}C NMR data of 15-methoxy derivatives in $CDCl_3$

Compound	**No**	Ref.	C-11	C-12	C-13	C-14	C-15	C-16
Scupolin I 15*R*	**19**		84.55	33.10	39.67	38.07	104.93	107.67
Scupolin I 15*S*	**20**		84.20	33.55	40.17	39.57	104.72	109.70
Hativene A 15*R*	**21**	25	82.8	32.4	40.0	38.1	104.7	107.4
Hativene B 15*S*	**22**	25	82.7	32.6	40.5	39.4	104.5	108.8
Clerodinin A[a]	**24**	26	83.2	32.6	40.5	32.7[b]	104.7	109.2
Lupulin A[a]	**25**	27	82.8	32.7	40.5	39.5	104.8	109.2
Lupulin B[a]	**26**	27	83.4	32.2	39.9	38.1	104.9	107.2
Clerodinin B[a]=lupulin D	**27**	26	83.5	32.7	40.5	32.6[b]	104.9	107.2
Lupulin D[a]	**27**	27	83.5	32.2	39.9	32.7[b]	104.8	107.2
15-Methoxy-14,15-dihydro-3-epicaryoptin[a]	**28**	28	83.0	32.5	40.4	39.4	104.7	109.0

[a] The stereochemistry at C-15 of these compounds have been reversed with respect to that reported in the original paper.
[b] Wrong assignment in the original paper.

Table 7. ^{1}H NMR data of 15-ethoxy derivatives

Compound	No	Ref.	Solvent	H-11	H-13	H-15	H-16
Clerodinin D	**29**		$CDCl_3$	4.02	2.98	5.23	5.72
Clerodinin D[a]	**29**	31	$CDCl_3$	3.99	2.95	5.20	5.69
Clerodinin C	**30**		$CDCl_3$	4.44	2.82	5.09	5.78
Clerodinin C[a]	**30**	31	$CDCl_3$	4.37	2.80	5.06	5.75
Clerodiol[a]	**31**	30	$CDCl_3$	4.40	2.82	5.06	5.74
3β-Acetoxy-clerodinin C[a]	**32**	31	$CDCl_3$	4.42	2.80	5.06	5.76
15-Ethoxy-14,15-dihydroajugapitin[b] (15*S*)	**33**	33	$CDCl_3$	4.48	[c]	5.09	5.81
15-Ethoxy-14,15-dihydroajugapitin[a] (15*S*)	**33**	31	$CDCl_3$	4.40	2.80	5.05	5.78
15-Ethoxy-14,15-dihydroajugapitin[a] (15*R*)	**34**	31	$CDCl_3$	3.98	2.99	5.18	5.72
Ivain III[b]	**35**	32	$CDCl_3$	4.48	[c]	5.12	5.86
No name	**29**	22	Py-d_5	4.09	2.99	5.32	5.84
No name	**30**	22	Py-d_5	4.55	2.73	5.08	5.90
No name	**36**	22	Py-d_5	4.09	3.00	5.37	5.94
No name	**37**	22	Py-d_5	4.54	n.r.	5.10	5.96

[a] The stereochemistry at C-15 of these compounds have been reversed with respect to that reported in the original paper.
[b] The stereochemistry at C-15 of these compounds have been assigned.
[c] Not reported in the original paper.

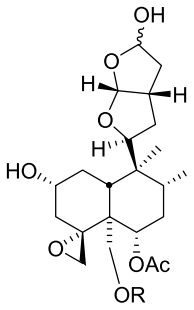
Table 8. ^{13}C NMR data of 15-ethoxy derivatives

Compound	No.	Ref.	Solvent	C-11	C-12	C-13	C-14	C-15	C-16
Clerodinin D	**29**		$CDCl_3$	83.56	32.21	40.06	38.23	103.60	107.20
Clerodinin D[a]	**29**	31	$CDCl_3$	83.6	32.7	40.0	38.2	103.6	107.1
Clerodinin C	**30**		$CDCl_3$	83.54	32.73	40.72	39.60	103.85	109.13
Clerodinin C[a]	**30**	31	$CDCl_3$	83.5	32.7	40.7	39.6	103.8	109.1
Clerodiol[a]	**31**	30	$CDCl_3$	83.6	32.2	40.0	32.7[b]	103.9	109.0
3β-Acetoxy-clerodinin C[a]	**32**	31	$CDCl_3$	83.4	32.7	40.7	39.6	103.9	109.1
15-Ethoxy-14,15-dihydroajugapitin[a] (15*S*)	**33**	31	$CDCl_3$	83.2	32.6	40.6	39.5	103.8	109.1
15-Ethoxy-14,15-dihydroajugapitin[a] (15*R*)	**34**	31	$CDCl_3$	83.0	32.4	40.0	38.2	103.5	107.1
No name	**29**	22	Py-d_5	83.7	32.4	40.5	38.3	104.2	107.7
No name	**30**	22	Py-d_5	83.7	33.0	41.1	39.7	104.3	109.6
No name	**36**	22	Py-d_5	85.0	33.3	40.4	38.4	104.4	108.2
No name	**37**	22	Py-d_5	85.1	33.6	40.8	39.8	104.0	110.0

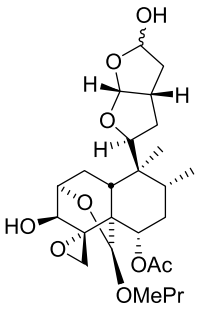
[a] The stereochemistry at C-15 of these compounds have been reversed with respect to that reported in the original paper.
[b] Wrong assignment in the original paper.

Table 9. Range of chemical shift of H-11, H-13, H-15, H-16 and C-16

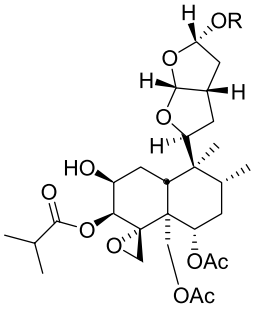
In $CDCl_3$	H-11	H-13	H-15	H-16	C-16
15 R-OH epimers	3.94–4.07	2.90–3.10	5.61–5.66	5.76–5.83	107.2–107.9
15 S-OH epimers	4.48–4.60	2.78–2.85	5.48–5.56	5.75–5.79	109.1–110.0
In pyridine-d_5	H-11	H-13	H-15	H-16	C-16
15 R-OH epimers	4.10–4.16	3.12–3.16	6.03–6.06	6.10–6.15	107.6–108.0
15 S-OH epimers	4.85–4.94	2.78–2.80	5.80–5.82	5.96–6.02	109.4–109.9
In $CDCl_3$	H-11	H-13	H-15	H-16	C-16
15 R-OMe epimers	3.98–4.02	2.94–3.01	5.07–5.11	5.67–5.72	107.2–107.7
15 S-OMe epimers	4.29–4.40	2.76–2.83	4.94–4.98	5.76–5.81	108.8–109.7
In $CDCl_3$	H-11	H-13	H-15	H-16	C-16
15 R-OEt epimers	3.98–4.00	2.95–2.99	5.18–5.20	5.69–5.72	107.1
15 S-OEt epimers	4.37–4.48	2.78–2.82	5.04–5.12	5.74–5.86	109.1
In pyridine-d_5	H-11	H-13	H-15	H-16	C-16
15 R-OEt epimers	4.09	2.99–3.00	5.32–5.44	5.94–5.84	107.7–108.2
15 S-OEt epimers	4.54–4.55	2.73	5.08–5.10	5.96–5.90	109.6–110.0



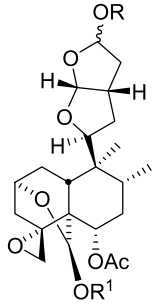
8a	15*R*	R = HBuHBuAc
8b	15*S*	R = HBuHBuAc
9a	15*R*	R = HBuHBuHBu
9b	15*S*	R = HBuHBuHBu



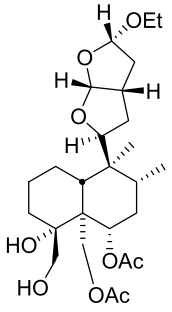
15a	15*R*
15b	15*S*



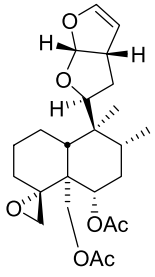
23	R = Me
35	R = Et



10a	R = H	15*R*	R^1 = H
10b	R = H	15S	R^1 = H
11a	R = H	15*R*	R^1 = Tig
11b	R = H	15*S*	R^1 = Tig
12a	R = H	15*R*	R^1 = MeBu
12b	R = H	15S	R^1 = MeBu
13a	R = H	15*R*	R^1 = MePr
13b	R = H	15*S*	R^1 = MePr
17a	R = H	15*R*	R^1 = Et
17b	R = H	15*S*	R^1 = Et
18a	R = H	15*R*	R^1 = Ac
18b	R = H	15*S*	R^1 = Ac
19	R = Me	15*R*	R^1 = Me
20	R = Me	15*S*	R^1 = Me
36	R = Et	15*R*	R^1 = Et
37	R = Et	15*S*	R^1 = Et



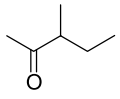
31



38

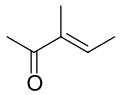
Acyl groups :

Ac

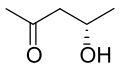


MeBu

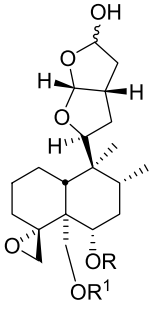
MePr



tig



HBu



14a	15*R*	R = Ac	R^1 = MePr
14b	15*S*	R = Ac	R^1 = MePr
16a	15*R*	R = H	R^1 = Ac
16b	15*S*	R = H	R^1 = Ac

3. Experimental

3.1. General

Optical rotations were measured on a Perkin–Elmer 141 polarimeter. IR spectra were obtained on a Perkin–Elmer 1310 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained

on Bruker AMX-600 a operating at 600.13 and 150.9 MHz for proton and carbon, respectively. DEPT experiments were acquired on a Bruker AMX-300 spectrometer. Measurements were made on solution in $CDCl_3$ and pyridine-d_5, chemical shifts were referenced to TMS set at 0 ppm, and coupling constants are given in Hz. MS were recorded on a Finnigan TSQ70 instrument (70 eV, direct inlet). Elemental analysis was carried out with a Perkin–Elmer 240 apparatus. Merck Si gel (70–230 mesh) was used for column chromatography.

3.2. Isolation of (15*R*)-scutecyprol A (3a)

(15*R*)-Scutecyprol A (**3a**) (200 mg) was isolated from *S. sieberi* cultivated in the Orto Botanico 'G. E. Ghirardi' dell'Università of Milan, at Toscolano (Garda Lake, Brescia) and collected in June 2002.

3.3. Isolation of scutalbin C (10) and clerodin (38)

Scutalbin C (**10**) and clerodin (**38**) were isolated from *Scutellaria albida* and the purification procedures have been previously reported.[38]

3.4. Preparation of scupolin I (19) and 15-*epi*-scupolin I (20)

To a solution of scutalbin C (**10**) (25 mg, 0.0591 mmol) was dissolved in a mixture 1:1 of MeOH and AcOH (1 mL). The mixture was left standing at room temperature overnight. The mixture was added with 10 mL of ethyl acetate and washed in turn with saturated aqueous $NaHCO_3$ and H_2O. The organic layer was separated, dried (Na_2SO_4), concentrated and chromatographed on a column (silica gel not deactivated, petroleum ether–ethyl acetate 3:2) to provide 15-*epi*-scupolin I (**20**) (9 mg, 0.0203 mmol) and scupolin I (**19**) (11 mg, 0.0251 mmol).

3.4.1. 15-*epi*-Scupolin I (20). Amorphous solid. $[\alpha]_D^{25} = +52.4$ ($c=0.22$ $CHCl_3$). IR (KBr) $\nu_{max}=3040$, 2950, 1720, 1450, 1370, 1250, 1145, 1090, 940 cm^{-1}. ^1H NMR ($CDCl_3$, 600.12 MHz): see Table 1. ^{13}C NMR ($CDCl_3$, 150.9 MHz), see Table 2. EIMS: *m/z* (%)=452 $[M]^+$ (1), 421 $(M-MeO)^+$ (3), 420 $(M-MeOH)^+$ (3), 392 $(M-AcOH)^+$ (2), 360 $(M-MeO-AcOH)^+$ (3), 143 (35), 111 (100). $C_{24}H_{36}O_8$ (452.54): calcd C, 63.70; H, 8.02; found C, 63.61; H, 7.91.

3.5. Preparation of clerodinin D (29) and clerodinin C (30)

To a solution of clerodin (**38**) (25 mg, 0.0578 mmol) was dissolved in a mixture 1:1 of EtOH and AcOH (1 mL). The mixture was left standing at room temperature overnight. The mixture was added with 10 mL of ethyl acetate and washed in turn with saturated aqueous $NaHCO_3$ and H_2O. The organic layer was separated, dried (Na_2SO_4), concentrated and chromatographed on a column (silica gel not deactivated, petroleum ether–ethyl acetate 3:2) to provide clerodinin C (**30**) (9 mg, 0.0195 mmol) and clerodinin D (**29**) (11 mg, 0.0238 mmol).

Acknowledgements

This work was supported by Italian Government project PRIN 2003.

References and notes

1. van Beek, T. A.; de Groot, Ae. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 513–568.
2. Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243–287.
3. Klein Gebbink, E. A.; Jansen, B. J. M.; de Groot, Ae. *Phytochemistry* **2002**, *61*, 737–770.
4. Bruno, M.; Piozzi, F.; Rosselli, S. *Nat. Prod. Rep.* **2002**, *19*, 357–378.
5. Wagner, H.; Seitz, R.; Lotter, H.; Herz, W. *J. Org. Chem.* **1978**, *43*, 3339–3345.
6. Nagao, Y.; Ito, N.; Kohno, T.; Kuroda, H.; Fujita, E. *Chem. Pharm. Bull.* **1982**, *30*, 727–729.
7. Lin, Y.-L.; Kuo, Y.-H.; Cheng, M.-C.; Wang, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2642–2646.
8. Itokawa, H.; Totsuka, N.; Takeya, K.; Watanabe, K.; Obata, E. *Chem. Pham. Bull.* **1988**, *36*, 1585–1588.
9. Tamamura, T.; Sawa, T.; Isshiki, K.; Masuda, T.; Homma, Y.; Iinuma, H.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1664–1669.
10. Isshiki, K.; Tamamura, T.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1819–1821.
11. Andersen, N. R.; Rasmussen, P. R. *Tetrahedron Lett.* **1984**, *25*, 465–468.
12. Andersen, N. R.; Rasmussen, P. R.; Falshaw, C. P.; King, T. J. *Tetrahedron Lett.* **1984**, *25*, 469–472.
13. Tsuji, H.; Tani, Y.; Ueda, H. *Bokin Bobai* **1978**, *6*, 170–172.
14. Tsuji, H.; Tani, Y.; Ueda, H. *Nippon Nogei Kagaku Kaishi* **1977**, *51*, 609–615.
15. Rojas-Garciduenas, M.; Dominguez, X. A. *Turrialba* **1976**, *26*, 10–13.
16. Kitazawa, E.; Sato, A.; Takahashi, S.; Kuwano, H.; Ogiso, A. *Chem. Pharm. Bull.* **1980**, *28*, 227–234.
17. Ortega, A.; Blunt, J. F.; Manchand, P. S. *J. C. S. Perkin Trans. 1* **1982**, 2505–2508.
18. Valdes, L. J.; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716–4719.
19. Kouzi, S. A.; McMurtry, R. J.; Nelson, S. D. *Chem. Res. Toxicol.* **1994**, *7*, 850–856 and bibliography therein.
20. Loeper, J.; Descatoire, V.; Letteron, P.; Moulis, C.; Degott, C.; Dansette, P.; Fau, D.; Pessayre, D. *Gastroenterology* **1994**, *106*, 464–472 and bibliography therein.
21. Bruno, M.; Fazio, C.; Arnold, N. A. *Phytochemistry* **1996**, *42*, 555–557.
22. Ohno, A.; Kizu, H.; Tomimori, T. *Chem. Pharm. Bull.* **1996**, *44*, 1540–1545.
23. Ohno, A.; Kizu, H.; Tomimori, T. *Chem. Pharm. Bull.* **1997**, *45*, 1097–1100.
24. de la Torre, M. C.; Rodriguez, B.; Bruno, M.; Vassallo, N.; Bondì, M. L.; Piozzi, F.; Servettaz, O. *J. Nat. Prod.* **1997**, *60*, 1229–1235.
25. Ben Jannet, H.; Harzallah-Skhiri, F.; Mighri, Z.; Simmonds, M. S. J.; Blaney, W. M. *Fitoterapia* **2000**, *71*, 105–112.

26. Lin, Y.-L.; Kuo, Y.-H.; Chen, Y.-L. *Chem. Pharm. Bull.* **1989**, *37*, 2191–2193.
27. Chen, H.; Tan, R. X.; Liu, Z. L.; Zhang, Y. *J. Nat. Prod.* **1996**, *59*, 668–670.
28. Achari, B.; Giri, C.; Saha, C. R.; Dutta, P. K.; Pakrashi, S. C. *Phytochemistry* **1992**, *31*, 338–340.
29. Chen, H.; Tan, R.-X.; Liu, Z.-L.; Zhao, C.-Y.; Sun, J. *Acta Crystallogr. Sect. C* **1997**, *53*, 814–816.
30. Lin, Y.-L.; Kuo, Y.-H.; Chen, Y.-L. *Heterocycles* **1989**, *29*, 1489–1495.
31. Beauchamp, P. B.; Bottini, A. T.; Caselles, M. C.; Dev, V.; Hope, H.; Larter, M.; Lee, G.; Mathela, C. S.; Melkani, A. B.; Millar, P. D.; Miyatake, M.; Pant, A. K.; Raffel, R. J.; Sharma, V. K.; Wyatt, D. *Phytochemistry* **1996**, *43*, 827–843.
32. Camps, F.; Coll, J.; Cortel, A. *Chem. Lett.* **1982**, 1053–1056.
33. Camps, F.; Coll, J.; Dergallo, O. *Phytochemistry* **1984**, *23*, 2577–2579.
34. Bozov, P. I.; Papanov, G. Y.; Malakov, P. Y.; de la Torre, M. C.; Rodriguez, B. *Phytochemistry* **1993**, *34*, 1173–1175.
35. Camps, F.; Coll, J.; Dergallo, O.; Ruis, J.; Miravitlles, C. *Phytochemistry* **1987**, *26*, 1475–1479.
36. Bruno, M.; Cruciata, M.; Bondì, M. L.; Piozzi, F.; de la Torre, M. C.; Rodriguez, B.; Servettaz, O. *Phytochemistry* **1998**, *48*, 687–691.
37. Rodriguez, B.; de la Torre, M. C.; Jimeno, M. L.; Bruno, M.; Vassallo, N.; Bondì, M. L.; Piozzi, F.; Servettaz, O. *J. Nat. Prod.* **1997**, *60*, 348–355.
38. Bruno, M.; Vassallo, N.; Simmonds, M. S. J. *Phytochemistry* **1999**, *50*, 973–976.
39. Malakov, P. Y.; Papanov, G. Y.; Boneva, I. M. *Phytochemistry* **1996**, *41*, 855–857.
40. Bruno, M.; Piozzi, F.; Rodriguez, B.; de la Torre, M. C.; Vassallo, N.; Servettaz, O. *Phytochemistry* **1996**, *42*, 1059–1064.
41. Malakov, P. Y.; Papanov, G. Y. *Phytochemistry* **1998**, *49*, 2449–2452.
42. Bruno, M.; Bondì, M. L.; Rosselli, S.; Piozzi, F.; Servettaz, O. *J. Nat. Prod.* **2000**, *63*, 1032–1034.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8801–8806

Asymmetric activation of tropos catalysts in the stereoselective catalytic conjugate additions of R_2Zn to α,β-enones: an efficient synthesis of (−)-muscone

Patrizia Scafato, Giovanni Cunsolo, Stefania Labano and Carlo Rosini*

Dipartimento di Chimica, Università degli Studi della Basilicata, via N. Sauro 85, 85100 Potenza, Italy

Received 7 May 2004; revised 23 June 2004; accepted 15 July 2004

Available online 21 August 2004

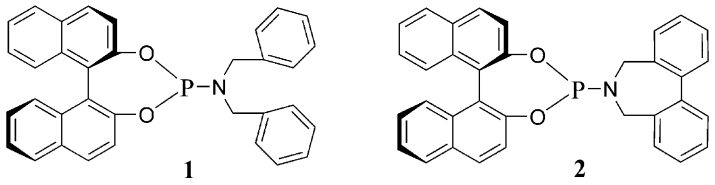
Abstract—The preparation of a new phosphoramidite starting from (*R*)-BINOL and a biphenylamine is presented. In such a compound the chirality is due only to atropisomerism and this molecule possesses a flexible biphenylamine residue. Therefore it can work as a tropos catalyst. The catalytic efficiency of this new phosphoramidite has been tested in some asymmetric conjugate additions of dialkylzinc reagents to α,β-enones and compared with that of an analogous already known non-tropos ligand. Interestingly, while comparable results were obtained in the addition of $ZnEt_2$ to chalcone and cyclohexenone, in the case of the addition of $ZnMe_2$ to (*E*)-cyclopentadec-2-en-1-one, the new ligand provides (−)-muscone, a valuable ingredient of the perfume industry, in 84% ee, while the non-tropos ligand gives a much lower (57%) ee value.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Configurationally stable biaryl compounds (i.e. 2,2′,6,6′-tetrasubstituted biphenyls and 2,2′-disubstituted-1,1′-binaphthyls) have received a lot of attention as chiral[1] ligands and catalysts in asymmetric synthesis. More recently, even non-atropisomerically stable, flexible biaryl compounds have been employed towards the same end.[2] From this point of view, excellent results have been obtained by Mikami and co-workers who introduced[2] the concept of 'asymmetric activation of tropos catalysts': here, if a tropos species (say a flexible biphenyl compound) is linked to a metal which, in turn, is linked to a stable enantiopure ligand (the chiral activator) a single diastereoisomeric compound can be formed, since a preferred sense of twist is induced in the tropos moiety by the stable chiral activator. This may cause an increase of the catalytic activity and of the asymmetric induction: many examples of highly enantioselective processes carried out within this scheme have been described. Interestingly, the same concept has also been applied[3] in a related topic: the assignment of the absolute configuration of aliphatic 1,*n*-diols ($n=2$–4) by exploiting the sense of twist induced in a biphenyl moiety when a diol, reacting with a suitable flexible biphenyl ketone, forms the corresponding ketal. Herein, we want to show a further example of this concept in which it becomes possible to carry out a highly enantioselective synthesis of (−)-muscone,[4] a valuable ingredient of the perfume industry, by means of the asymmetric conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one.[5] The last few years have witnessed significant progresses[6] in the field of the catalytic asymmetric conjugate addition of organozinc compounds to α,β-unsaturated ketones, allowing the construction of C–C bonds in high chemical yields and efficient stereocontrol, thus providing the synthetic organic chemist with a very powerful tool to assemble even large and polyfunctional molecules.[7] The success obtained in such of process relies mainly in the development of efficient catalytic precursors which are constituted by Cu(II) or Cu(I) salts coordinated by enantiopure phosphorus ligands. The family of phosphoramidites, the use of which has been pioneered by Feringa and co-workers,[6a,7a,b,8] has been particularly successful in this respect. In these ligands the chiral source is often derived from enantiopure 2,2′-dihydroxy-1,1′-binaphthyl, BINOL, or modified binaphthols, coupled to another achiral or chiral residue, so the phenomenon of double asymmetric induction may also result.[9] Our attention was captured by a recent paper of Feringa et al. where a systematic study of the relationship between structure of the chiral ligand and asymmetric induction was carried out:[8a] of the several ligands tested, compound **1** (Scheme 1) seemed to us particularly attractive because we immediately saw in it the possibility to make a

Keywords: (−)-Muscone; Asymmetric conjugate addition; Organozinc compounds; Asymmetric copper catalysis; Asymmetric activation; Phosphoramidites; α,β-Enones.
* Corresponding author. Tel.: +39-0971-202241; fax: +39-0971-202223; e-mail: rosini@unibas.it

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.034



Scheme 1.

comparison with the properties of the structurally related ligand **2** (Scheme 1).

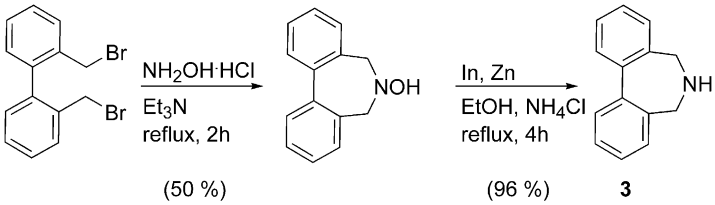
The possibility of asymmetric activation exists in compound **2** and this is not possible in **1**.[2,5e] Previous examples of phosphoramidite catalysts based on the principle of asymmetric activation made use[5e] of a centrochiral amine residue and phenolic part derived from flexible biphenol. Interestingly, ligand **2** derives from a part coming from enantiopure BINOL and an achiral, flexible biphenyl amine; in other words **2** shows a completely new design: chiral phenol, flexible biphenyl amine and overall chirality only due to atropisomerism.

2. Results and discussion

We synthesized the phosphoramidites **1** and **2** simply by adding a solution of (*R*)-BINOL in THF to a solution of dichloroamidite of dibenzylamine or amine **3** respectively, prepared in situ by treating the suitable amine with PCl_3 and NEt_3, according to the Alexakis procedure.[10] Amine **3** was prepared (Scheme 2) starting from 2,2′-bis(bromomethyl)-biphenyl,[11a,b] obtained from diphenic acid, by transforming it in the corresponding hydroxylamine and successive reduction with In/Zn in boiling ethanol.[11c]

It is well known[3,12] that biphenyl compounds like **3** present an M–P equilibrium and that the activation energy for this transformation is about 14–15 kcal/mol, so the inversion of the biphenyl sense of twist is really fast at room temperature and the two enantiomers of **3** cannot be isolated. In principle, starting from (*R*)-BINOL two diastereoisomeric phosphoramidites could be obtained, taking into account that the biphenyl group could be P or M twisted, i.e. (*R*,P)-**2** and (*R*,M)-**2**. However, also in compounds where the biphenyl moiety is linked to a chiral group, a fast P–M interconversion still occurs:[3,12] thus, this fact ensures that the stereoisomeric ratio between (*R*,P)-**2** and (*R*,M)-**2** is only determined by their thermodynamic stability. The ^{31}P NMR spectrum of **2** showed the presence of only one peak (δ= 146.38). Taking into account that diastereoisomeric phosphoramidites[8a] (and phosphites[13]) show different ^{31}P signals, it is tempting to assume that in the case of **2** a single diastereoisomer is present in solution. We also measured the CD spectrum of **1** and **2**: the difference spectrum, CD(**2**)–CD(**1**), could afford a reasonable estimate[14] of the CD coming from a distorted biphenyl group. Interestingly, in the spectrum (Fig. 1) two Cotton effects can be recorded below 280 nm (i.e. in the region where the biphenyl chromophore absorbs): a broad positive one (220–260 nm), which clearly results from the contribution of two bands of the same positive sign at about 220 and 240 nm, and a negative one at about 215 nm. The Cotton effect at 240 nm is reasonable due to the A transition of the biphenyl chromophore which is a probe of the sense of twist of the biphenyl group: a positive Cotton effect from the A band indicates[3,12] a negative (M) torsion of the biphenyl.

Asymmetric conjugate additions of dialkylzinc reagents to the enones **4**–**6** (Scheme 3) were carried out in toluene (at −40 °C for **4** and **5** and at 0 °C for **6**) with a catalytic precursor deriving from $Cu(OTf)_2$/**1** or **2** (ratio substrate/Cu/chiral ligand = 1/0.03/0.06). The results are collected in Table 1. In the presence of **1** diethyl zinc adds quickly (4 h) and smoothly to both **4** (run 1) and **5** (run 2) affording the corresponding ketones in high yields and moderate enantiomeric excesses. It is noteworthy that the same results have been obtained[8a] by Feringa et al. who used slightly different experimental conditions (CuOTf instead of $Cu(OTf)_2$, −10 °C for 16 h instead of −40 °C for 4 h). A moderate value of enantiomeric excess has also been obtained with the same ligand for ketone **6**[15] (run 3): (−)-muscone is prepared in 57% ee, i.e. a value which is not of practical interest for the perfume industry. Then the same reactions were repeated (under the same experimental conditions) using phosphoramidite **2**. Also, ligand **2** gives rise to an efficient catalytic system: in the cases of **4** (run 4) and **5** (run 5) the addition products are obtained in good yields and short reaction times (2 h ca.), but we could not observe a substantial 'asymmetric activation' effect. In fact, while in the case of chalcone (Table 1, run 1 vs run 4) we had an increase from 52 to 65%, in the case of cyclohexenone (Table 1, run 2 vs run 5) we had a slight reduction of stereoselectivity (from 54% with **1** to 45% with **2**). However, much to our delight, significant increase of ee was observed just in the case of ketone **6**: in fact, (run 6) with **2** derived from (*R*)-BINOL, (−)-muscone having 84% ee was obtained. Of course, using (*S*)-BINOL for the preparation of **2**, the (+) antipode is obtained with the same



Scheme 2.

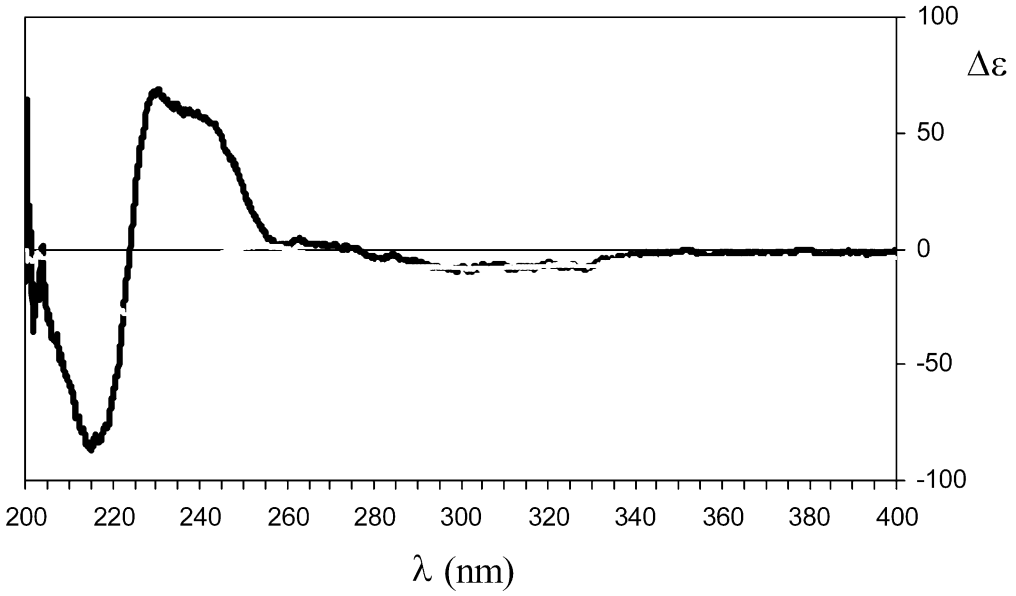
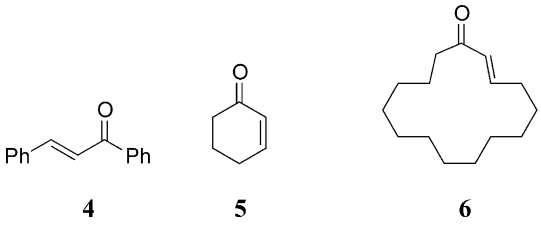


Figure 1. Difference spectrum (CD-2)–(CD-1) in THF.

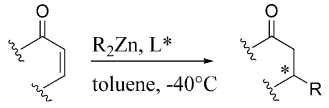


4 **5** **6**

Scheme 3.

enantiomeric excess (run 7). Another interesting observation is the result with a different amount of $Cu(OTf)_2$. Using enone/$Cu(OTf)_2$/L^* = 1/0.01/0.02 (i.e. with only 1% of metal) the ee goes to 61% ee (run 8). These results are very important from a practical point of view: the use of (*R*)-**2** guarantees a truly catalytic synthesis of the natural antipode of (−)-muscone having high enantiomeric purity and this certainly constitutes an economic access to this valuable fine chemical. From a more theoretical point of view, this result demonstrates the importance of the concept of asymmetric activation: here the (*R*)-chirality of BINOL imposes the biphenyl moiety of the ligand **2** to assume a preferred M sense of twist. The pair (*R*,M) obtained in this way allows an efficient enantioselective conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one. On the other hand, the same ligand **2** does not work with the same efficiency in the cases of **4** and **5**, indicating that the asymmetric activation effect is strongly dependent on the substrate employed. However, it is interesting to note that, if the results provided by **2** are compared with those obtained in the case of **1**, an increase of the ee is observable for addition to **4** and **6** (13 and 27%, respectively) whilst a small

Table 1. Asymmetric conjugated addition of R_2Zn to α,β-enones in the presence of ligands **1** and **2**



Run	Enone	Ligand	R_2Zn	Yield[a]	ee (a.c.)[b]
1	**4**	**1**	Et_2Zn	68	52[c] (*S*)
2	**5**	**1**	Et_2Zn	95	54[d] (*R*)
3	**6**	**1**	Me_2Zn	60[e]	57[f] (*R*)
4	**4**	**2**	Et_2Zn	70	65[c] (*S*)
5	**5**	**2**	Et_2Zn	98	45[d] (*R*)
6	**6**	**2**	Me_2Zn	72[e]	84[f] (*R*)
7	**6**	**2**[g]	Me_2Zn	68[e]	84[f] (*S*)
8	**6**	**2**[h]	Me_2Zn	50[g]	61[f] (*R*)

[a] Carried out at −40 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.03/0.06; yield calculated on the isolated and purified product.
[b] Determined by the sign of optical rotatory power.
[c] Determined by HPLC on chiral column Chiralcel OJ, hexane/isopropanol 99.5: 0.5, 1.0 ml/min, 254 nm.
[d] Determined by HPLC on chiral column Chiralcel OD, hexane/isopropanol 99.7: 0.3, 0.5 ml/min, 254 nm, on the corresponding dioxolane obtained with (*R*,*R*)-1,2-diphenylethane-1,2-diol.
[e] Carried out at 0 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.03/0.06; yield calculated on isolated and purified product.
[f] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as described by Yamamoto.[16] When the same measurament has been carried out by polarimetry [for (−)-muscone: $[\alpha]_D = -12.7$ (c = 0.9, MeOH), lit. 4g] the slightly higher value of 89% is obtained.
[g] **2** has been prepared from (*S*)-BINOL.
[h] Carried out at 0 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.01/0.02.

reduction (9% ca.) is observed in the case of **5**. Therefore, (*R*,M)-**2** behaves like a matched pair of the BINOL and biphenyl chiralities in the cases of chalcone and (*E*)-cyclopentadec-2-en-1-one, while it looks like a mismatched pair in the case of cyclohexenone. This different outcome could be related to a different conformational behavior[6c] of the α,β-unsaturated ketones. In fact, whilst **4** and **6** are flexible compounds, **5** is fixed in a pure *s-trans* situation. In other words, a pure *s-trans* system is not a very good substrate for the Cu/**2** catalyst since the enantioselectivity is only moderate, on the contrary flexible α,β-unsaturated ketones afford higher values of asymmetric induction, the macrocyclic ketone **6** providing the highest ee. It is noteworthy that the present results are at variance with those reported by Alexakis et al.[5e] who employed a phosphoramidite ligand where the amine part was centro chiral and the phenolic part derived from the flexible biphenol. Here, in fact, ketone **5** is a good substrate whilst **4** and **6** are not, giving rise only to moderate enantioselectivities (27 and 49%, respectively).

3. Conclusions

This work describes some important results in the field of the asymmetric conjugate addition to α,β-unsaturated ketones: first, the completely new designed phosphoramidite ligand **2**, where the chirality is due only to atropisomerism and where the amine residue constitutes the tropos part, has been prepared and tested. In this way, a protocol has been set up by which a valuable fine chemical, (−)-muscone, can be easily prepared. Second, it has been possible to make a comparison between the previously reported ('asymmetrically activated') phosphoramidites (where the amine moiety was centrochiral and the phenolic counterpart a flexible biphenol) and **2** (without stereogenic centers, deriving from enantiopure BINOL and showing the flexible biphenyl amine **3**). This comparison shows that the two kinds of phosphoramidites have opposite behavior versus rigid or flexible ketones. Understanding the origin of this correlation could be an extremely useful key to understand the reaction stereochemistry and thus to reliably predict the enantioselectivity of this reaction.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Aspect300 300 MHz NMR and Varian AS500 500 MHz NMR spectrometers, using TMS as external standard. The ^{31}P NMR spectrum was recorded at the frequency of 242.88 MHz with an Inova 600 instrument. The sample was dissolved in CD_2Cl_2 and the chemical shift of the signals were calculated with respect to H_3PO_3 85% (0 ppm) by replacement. TLC analyses were performed on silica gel 60 Macherey–Nagel sheets; flash chromatography separations were carried out on suitable columns using silica gel 60 (230–400 mesh) or neutral aluminum oxide. HPLC analyses were performed on a JASCO PU-1580 intelligent HPLC pump equipped with a Varian 2550 UV detector. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Melting points were taken using a Kofler Reichert–Jung Thermovar apparatus and are uncorrected. Mixture compositions were determined by GC–MS on a Hewlett Packard 6890 chromatograph equipped with a HP-5973 mass detector. IR spectra were performed with a Perkin–Elmer 883 spectrometer. Toluene and dichloromethane were refluxed over sodium–benzophenone and calcium hydride respectively and distilled before the use. Unless otherwise specified the reagents were used without any purification.

4.1.1. Synthesis of 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl (3). 2,2′-Bis(bromomethyl)-1,1′-biphenyl was prepared by PBr_3 bromination of 2,2′-bis(hydroxymethyl)-1,1′-biphenyl, in turn obtained by Red-Al reduction of dimethyl ester of commercially available diphenic acid.

To a solution of Et_3N (53 ml) and hydroxylamine hydrochloride (3.7 g, 54 mmol), under nitrogen atmosphere, 2,2′-bis(bromomethyl)-1,1′-biphenyl (5.4 g, 16 mmol) was added and the mixture was heated to reflux for 2 h. The mixture was filtered under vacuum and the resulting solution was distilled to remove the Et_3N. The crude product was purified on silica gel (petroleum ether/ethyl ether 4:1–petroleum ether/ethyl ether 2:1) affording the pure 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl-*N*-hydroxide (1.7 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (d, J= 12.1 Hz, 2H), 3.95 (d, J=12.1 Hz, 2H), 7.5 (m, 9H); ^{13}C NMR (75 Mz, $CDCl_3$): δ 60.44, 127.81, 129.51, 130.15, 133.92, 149.50.

To a 1:1 solution of EtOH/satd. NH_4Cl (40 ml, pH≅6) 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl-*N*-hydroxide (1.7 g, 8 mmol) was added. Indium (5%, 46 mg, 0.4 mmol) and zinc (1.04 g, 16 mmol) were then added and the mixture was refluxed for 7 h. After cooling, the mixture was filtered on Celite and concentrated. A satd. Na_2CO_3 solution was added and the mixture was extracted with ethyl acetate. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo to afford the biphenylazepine **3** (1.5 g, 7.6 mmol, 95%) as a white solid. Mp=229–231 °C; IR (neat): ν_{max} 3310, 3140, 2910, 1450, 1380, 1200, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.04 (s, 5H), 7.47–7.49 (m, 2H), 7.55–7.60 (m, 4H), 7.64 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 Mz, $CDCl_3$): δ 45.90, 128.61, 129.22, 129.54, 130.50, 131.27, 140.81.

4.1.2. Synthesis of O,O′-(*R*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*′-dibenzylphosphoramidite (1). Under nitrogen atmosphere, at 0 °C, to a stirred mixture of freshly distilled PCl_3 (174 μL, 20 mmol) and Et_3N (3.9 mL, 28 mmol) in dry THF (4 mL) freshly distilled dibenzylamine (384 μL, 2.0 mmol) was added and the mixture was stirred for 3 h at room temperature. Slowly, a solution of enantiopure (*R*)-BINOL (572 mg, 2.0 mmol) in dry THF (6 mL) was added at 0 °C. After stirring (19 h) at room temperature, the resulting mixture was diluted with toluene and filtered on neutral aluminum oxide. The solution was concentrated and purified by flash chromatography on neutral aluminum oxide using CH_2Cl_2 as eluent obtaining 417 mg (0.81 mmol, 41%) of the pure ligand as a foamy white solid. Stripping with petroleum ether gave the product as white solid.

Mp = 132–134 °C. Spectroscopic data (NMR and $[\alpha]_D^{20}$) were in good agreement with data reported in literature.[8a]

4.1.3. Synthesis of O,O′-(*R*)-(−)-(1,1′-dinaphthyl-2,2′-diyl)-*N*-2-[2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenylyl] phosphoramidite (2). Under nitrogen atmosphere, at 0 °C, to a stirred solution of PCl_3 (174 μL, 20 mmol) and Et_3N (3.9 mL, 28 mmol) in dry THF (4 mL) the biphenylazepine **3** (390 mg, 2.0 mmol) was added and the mixture was stirred for 3 h at room temperature. Slowly, a solution of enantiopure (*R*)-BINOL (572 mg, 2.0 mmol) in dry THF (6 mL) was added at 0 °C. After 18 h of stirring at room temperature, the resulting mixture was diluted with toluene and filtered on neutral aluminum oxide. The solution was concentrated and purified by flash chromatography on neutral aluminum oxide using CH_2Cl_2 as eluent obtaining 630 mg (1.24 mmol, 62%) of the pure ligand as a foamy solid. Stripping with petroleum ether gave the phosphoramidite **2** as a white solid. Mp = 152–154 °C; $[\alpha]_D^{20} = -246$ ($c = 0.45$; CH_2Cl_2); IR (neat): ν_{max} 3080, 2860, 1580, 1460, 1230, 1050, 930, 820, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.67 (dd, 2H, $J_1 = 13.0$ Hz, $J_2 = 9.5$ Hz), 4.00 (dd, 2H, $J_1 = 13.0$ Hz, $J_2 = 6.5$ Hz), 7.08 (d, 1H, $J = 8.5$ Hz), 7.19–7.21 (m, 1H), 7.27–7.30 (m, 4H), 7.35 (d, 1H, $J = 9.0$ Hz), 7.39–7.48 (m, 8H), 7.57 (d, 1H, $J = 8.5$ Hz), 7.80 (d, 1H, $J = 8.5$ Hz), 7.88 (d, 1H, $J = 7.5$ Hz), 7.95 (d, 1H, $J = 8.5$ Hz), 8.01 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.65, 47.82, 122.21, 122.31, 124.83, 125.06, 126.32, 127.18, 127.30, 128.06, 128.43, 128.50, 128.59, 129.51, 130.25, 130.56, 131.05, 131.67, 133.20, 135.20, 141.25, 149.29, 149.90; ^{31}P NMR (242.88 MHz, CD_2Cl_2) δ 146.38. Anal. calcd for $C_{34}H_{24}NO_2P$: C 80.14; H 4.75; N 2.74; P 6.08. Found: C, 80.85; H, 5.10; N 2.90; P 6.30.

4.1.4. Synthesis of cyclopentadec-2-en-1-one (6). To a solution of 30% H_2O_2 (2.0 mL, 18 mmol) and 1,1,1-trifluoromethylacetone (0.3 mL, 3.3 mmol) a solution of 2-phenylthiocyclopentadecanone (obtained from 2-cyclopentadecanone as reported)[15] (5.0 g, 15 mmol) in $CHCl_3$ (15 ml) was added at 0 °C. After 1 h of stirring at 0 °C, the mixture was diluted with $CHCl_3$ and the organic layer was separated, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude sulfoxide was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 3/1) obtaining the pure product (4.2 g, 12 mmol, 80%) and the starting sulfide (300 mg, 6%).

Under nitrogen atmosphere, the sulfoxide (4.2 g, 12 mmol) was dissolved in anhydrous toluene (100 mL) and calcium carbonate (160 mg, 1.6 mmol) was added. The mixture was stirred 12 h at room temperature and refluxed for 2 h. After cooling at room temperature, water (50 mL) was added and the organic layer was separated, washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 3/1) affording 2.38 g (89%) of 2-cyclopentadecenone.

4.1.5. Enantioselective conjugate addition of diethylzinc to chalcone (4). A solution of $Cu(OTf)_2$ (5 mg, 0.014 mmol) and chiral ligand (0.030 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. To this catalyst solution, chalcone (104 mg, 0.5 mmol) was added and, after cooling to −40 °C, diethylzinc (1.0 M in hexane, 1.0 mL, 2 equiv) was added dropwise. The reaction was monitored by TLC. After stirring for 2 h at −40 °C the reaction mixture was poured in 10 mL of 1.0 M HCl solution and extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl ether 8:2), affording pure 1,3-diphenyl-pentanone (70%). The ee was determined by HPLC analyses: Daicel Chiralcel OJ, hexane/2-propanol 99.5:0.5, 1.0 mL/min, $\lambda = 254$ nm, $t_r = 18.63$ min (*S*); $t_r = 28.29$ min (*R*).

4.1.6. Enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one (5). A solution of $Cu(OTf)_2$ (5 mg, 0.014 mmol) and chiral ligand (0.03 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The solution was cooled to −40 °C and 2-cyclohexen-1-one (48 mg, 0.5 mmol) followed by Et_2Zn (1.0 M in hexane, 1.0 mL, 2 equiv) were added slowly. The reaction was monitored by GC–MS. After stirring for 2 h at −40 °C the reaction mixture was poured in 10 mL of 1 M HCl solution and extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered. Removal of ethyl ether under reduced pressure, 700–350 mbar, at room temperature yielded the crude product in toluene which was purified by flash column chromatography (SiO_2, pentane/ethyl ether 5:1) to afford 3-ethylcyclohexanone (98%) as a colorless liquid. The ee was determined by HPLC analyses after derivatization with (*R*,*R*)-1,2-diphenylethan-1,2-diol: to a solution of 3-ethylcyclohexanone (62 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) actived 4 Å molecular sieves were added at room temperature followed by (*R*,*R*)-1,2-diphenylethan-1,2-diol (128 mg, 0.6 mmol) and by traces of *p*-toluensulfonic acid. After stirring for 2 h the 4 Å molecular sieves were removed by filtration and the reaction mixture was dried with anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl ether 98:2) to afford the desired ketal as a colorless liquid. The ee was determined by HPLC analyses: Daicel Chiralcel OD, hexane/2-propanol 99.7:0.3, 0.5 mL/min, $\lambda = 254$ nm, $t_r = 8.0$ min (*R*,*R*,*R*), $t_r = 10.0$ min (*S*,*R*,*R*).

4.1.7. Enantioselective conjugate addition of dimethylzinc to 2-cyclopentadecen-1-one (6). A solution of $Cu(OTf)_2$ (5.6 mg, 0.015 mmol) and chiral ligand (0.03 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. After cooling to 0 °C, Me_2Zn (2.0 M in toluene, 0.38 mL, 1.5 equiv) was added followed by 2-cyclopentadecenone (111 mg, 0.5 mmol). The reaction was monitored by GC–MS analysis. After stirring for 1.5 h at 0 °C 1 M HCl solution (10 mL) and ethyl ether (5 mL) were added and stirred for a few minutes. Then, the solution was extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash column chromatography (SiO_2, petroleum ether/ethyl ether 95:5), affording (−)-muscone (70%) as colorless oil. $[\alpha]_D = -11.3$ ($c = 0.85$, MeOH). The ee was determined

by the following NMR method:[16] a solution of $Eu(hfc)_3$ (107 mg) and (+) or (−)-muscone (3.6 mg) in 0.5 ml of $CDCl_3$ was subjected to analysis by NMR. The peak (doublet) caused by methyl group of the (*R*) enantiomer shifted to 3.72 ppm, while that of the (*S*) shifted to 3.59 ppm. The ee were calculated from the area peak ratio.

Acknowledgements

The authors thank Università degli Studi della Basilicata and MIUR-COFIN 2002 'Sintesi di aromi e fragranze' for their financial support. The authors thank the NMR laboratory of the Università di Bologna for recording the ^{31}P NMR spectrum.

References and notes

1. (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (c) Putala, M. *Enantiomer* **1999**, *4*, 243. (d) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809. (e) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.
2. (a) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561. (b) Delogu, G.; Vallée, Y. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 1. (c) Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369.
3. Superchi, S.; Casarini, D.; Laurita, A.; Bavoso, A.; Rosini, C. *Angew. Chem., Int. Ed.* **2002**, *40*, 451.
4. (a) Fujimoto, S.; Yoshikawa, K.; Itoh, M.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1389. (b) Kraft, V. P.; Bajgrowitz, J. A.; Denis, C.; Frater, G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2980. (c) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1. (d) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *95*, 925. (e) Kamat, V. P.; Hagiwara, H.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2253. (f) Kamat, V. P.; Hagiwara, H.; Katsumi, T.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, *56*, 4397. (g) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593.
5. (a) Alexakis, A.; Benhaim, C.; Fornioux, X.; van der Heuvel, A.; Leveque, J. M.; March, S.; Rosset, S. *Synlett* **1999**, *11*, 1811. (b) Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 153. (c) Choi, H. C.; Choi, J. Y.; Yang, H. Y.; Kim, Y. H. *Tetrahedron: Asymmetry* **2002**, *13*, 801. (d) Fraser, P. K.; Woodward, S. *Chem. Eur. J.* **2003**, *9*, 776. (e) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, *9*, 1375. (f) Scafato, P.; Labano, S.; Cunsolo, G.; Rosini, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3873.
6. (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Krause, N.; Hoffmann-Roeder, A. *Synthesis* **2001**, *2*, 171. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.
7. (a) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc* **1999**, *121*, 1104. (b) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841. (c) Alexakis, A.; March, S. *J. Org. Chem.* **2002**, *67*, 8753. (d) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835. (e) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. (f) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. (g) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362. (h) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779. (i) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192. (j) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009. (k) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276. (l) Reetz, M. T.; Neugebauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 1799.
8. (a) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865. (b) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374.
9. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.
10. Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.
11. (a) Bergmann, E. D.; Pelchowicz, Z. *J. Am. Chem. Soc.* **1953**, *75*, 2663. (b) Dholakia, S.; Gillard, R. D.; Wimmer, F. L. *Polyhedron* **1985**, *4*, 791. (c) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.
12. (a) Sutherland, I. O.; Ramsay, M. V. J. *Tetrahedron* **1965**, *21*, 3401. (b) Carter, R. E.; Dahlqvis, K.-I.; Berntsson, U. P. *Org. Magn. Res.* **1977**, *9*, 44. (c) Rashidi-Ranjbar, P.; Sandstroem, J. *Proceedings of the 4th Conference on Circular Dichroism, Bochum, Germany*, 1991, p 152.
13. (a) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8737. (b) Iuliano, A.; Scafato, P. *Tetrahedron: Asymmetry* **2003**, *14*, 611.
14. Mikami, K.; Yusa, Y.; Aikawa, K.; Hatamo, M. *Chirality* **2003**, *15*, 105.
15. To prepare (*E*)-cyclopentadec-2-en-1-one, the procedure of Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1445 has been followed. Here, the C═C bond of **6** derives from an elimination reaction involving an intermediate sulfoxide, in turn produced by oxidation of the corresponding sulfide by oxone. However, instead of using oxone to oxidize the sulfide to sulfoxide, we used the method of H_2O_2/CF_3COCH_3, described by Lupattelli, P.; Ruzziconi, R.; Scafato, P.; Degl'Innocenti, A.; Paolobelli, A. *Synth. Commun.* **1997**, *27*, 441. In this way, no sulfone is formed; this allows an easy separation of the desired sulfoxide from the starting sulfide which can be recycled, increasing the overall conversion.
16. Yamamoto, T.; Ogura, M.; Kanisawa, T. *Tetrahedron* **2002**, *58*, 9202.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8807–8815

Novel pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine ring synthesis. Unusual Truce–Smiles type rearrangement of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl(or sulfinyl)}acetone

Athanasios Kimbaris,[a] Jonathan Cobb,[b] Georgios Tsakonas[a] and George Varvounis[a,*]

[a]*Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece*
[b]*Department of Chemistry, King's College London, University of London, Strand, London WC2R 2LS, UK*

Received 5 January 2004; revised 23 June 2004; accepted 15 July 2004

Available online 21 August 2004

Abstract—Reaction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone with sodium hydroxide with or without zinc gave 1-(2-nitrophenyl)(1*H*-pyrrol-2-ylsulfonyl)methane by a Truce–Smiles type of transformation and 1-(2-nitrophenyl)-2-methylsulfonylpyrrole by deacetylation. Similar treatment of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfinyl}acetone gave only 1-(2-nitro-phenyl)(1*H*-pyrrol-2-ylsulfinyl)methane. 1-{[1-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone, 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenyl-ethan-1-one or 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetonitrile were reductively cyclised with sodium borohydride and 5% palladium-on-carbon into 6-methyl(or phenyl)-5,6-dihydro-7*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocin-7-ol or 6-amino-5*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine-7-oxide, respectively.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Diaryl and arylheterocyclic sulfones are an emerging class of non-nucleoside HIV-1 reverse transcriptase inhibitors.[1–10] Compounds with the sulfonyl group not part of a ring seem to be the most potent, although related cyclic counterparts such as 5*H*-pyrrolo[1,2-*b*][1.2.5]pyrrolobenzothiadiazepin-11(10*H*)-one-5,5-dioxides[6] are important members of these bioactive compounds. Artico and coworkers have recently synthesised 9*H*-pyrrolo[2,1-*b*][1.3.6]benzothiadiazocin-10-(11*H*)-one-4,4-dioxide[4] as a potential anti-HIV-1 agent. The compound was prepared by reacting 2-aminothiophenol with ethyl 2-(1*H*-pyrrol-1-yl) acetate, hydrolysing ethyl 2-{2-[(2-amino-phenyl)sulfanyl]-1*H*-pyrrol-1-yl}acetate, cyclising 2-{2-[(2-aminophenyl)-sulfanyl]-1*H*-pyrrol-1-yl}acetic acid and oxidising 9*H*-pyrrolo[2,1-*b*][1.3.6]benzothiadiazocin-10-(11*H*)-one. The synthesis of 10*H*-pyrrolo[1,2-*b*][1.2.5]benzothiadiazocine-5,5-dioxide[11] has been carried out by intramolecular cyclisation of *N*-[2-(1*H*-pyrrol-1-ylsulfonyl)benzyl]methanamide, prepared from the reaction of [2-(1*H*-pyrrol-1-ylsulfonyl)phenyl]methanamine with ethyl chloroformate, followed by treatment with triphosgene. An isomer, 10*H*-pyrrolo[1,2-*b*][1.2.6]benzothiadiazocin-11-(12*H*)-one-5,5-dioxide,[12] was prepared by intramolecular cyclisation of 2-{1-[(2-aminophenyl)sulfonyl]-1*H*-pyrrol-2-yl}acetic acid. Fifteen years ago Cheeseman et al. reported the synthesis of the 5,6-dihydropyrrolo[1,2-*a*]-[3.1.6]benzothiadiazocine ring system.[13,14] Two routes were employed that utilized 1-(2-aminophenyl)-1*H*-pyrroles as starting materials. These compounds were derived from the reaction between 2-nitroanilines and 2,5-dimethoxytetrahydrofuran followed by reduction of the resulting 1-(2-nitrophenyl)-1*H*-pyrroles. The first route involved reaction of 1-(2-aminophenyl)-1*H*-pyrroles with chloroacetic anhydride or α-chloropropionyl chloride, thiocyanation of the *N*1-[2-(1*H*-pyrrol-1-yl)-phenyl]-2-chloroacetamides with copper(II) thiocyanate and reductive cyclisation of the resulting *N*1-[2-(2-thiocyanato-1*H*-pyrrol-1-yl)phenyl)-2-chloroacetamides in the presence of sodium borohydride.[13] The second route involved treatment of 1-(2-aminophenyl)-1*H*-pyrrole with trifluoroacetic anhydride, thiocyanation of *N*1-[2-(1*H*-pyrrol-1-yl)-phenyl]-2,2,2-trifluoroacetamide, reductive alkylation of *N*1-[2-(2-thiocyanato-1*H*-pyrrol-1-yl)-phenyl]-2,2,2-trifluoroacetamide with ethyl bromoacetate and concomitant cleavage of the amide group in the presence of sodium borohydride, followed by cyclisation of the resulting ethyl 2-{[1-(2-aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate in the presence of trimethylaluminium.[14]

Keywords: Pyrroles; Pyrrolobenzothiadiazocines; Cyclisation; Reduction; Truce–Smiles rearrangement.
* Corresponding author. Tel.: +30-26510-98382; fax: +30-26510-98799; e-mail: gvarvoun@cc.uoi.gr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.036

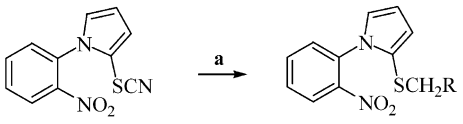
2. Results and discussion

With an extension of this work in mind, we decided to exploit the intramolecular capture of in situ generated nitroso species by carbanions and the intramolecular addition of hydroxyl-amines to carbonyl groups or nitriles in order to effect ring closure by carbon–nitrogen bond formation. To this end, we prepared ketones **2** and **3**,[14] ester **4** and nitrile **5**[15] by selectively reducing 1-(2-nitrophenyl)-2-thiocyanato-1*H*-pyrrole **1**[15] with sodium borohydride and then treating the resulting thiol, that was not isolated, with 2-chloroacetone, phenacyl bromide, ethyl bromoacetate or chloroacetonitrile, respectively (Scheme 1).

A few examples, where intramolecular capture of in situ generated nitroso species is used for the synthesis of fused heterocycles, are given below. Reductive cyclisation of *N*1-(alkyl or aryl)-2-nitrobenzamides into 2-(alkyl or aryl)-2,3-dihydro-1*H*-3-indazolones has been accomplished via treatment with zinc dust and sodium hydroxide.[16] Milder reaction conditions, zinc dust and ammonium chloride, have been used for the cyclisation of substituted 3-(2-nitrophenoxy)phenols to 3*H*-phenoxazin-3-ones[17] and of ethyl 2-nitrophenylacetate to 4-hydroxy-1,4-benzoxazine-3(4*H*)-one.[18] Recently, we reported the reductive cyclisation of (2-nitrophenyl)(1*H*-pyrrol-2-yl)methanone with zinc and ammonium chloride or sodium hydroxide which gave 5,10-dihydropyrrolo[1,2-*b*]cinnolin-10-one.[19]

Selective reduction of compounds **2**, **3** and **4** with zinc dust and ammonium chloride in aqueous ethanol from 0 °C to room temperature respectively afforded mixtures of the corresponding amines **7**, **9**[14] and **11**,[14] and hydroxylamines **8**, **10** and **12** (Scheme 2). No trace of the anticipated pyrrolobenzothiadiazepines **6** was detected. This could be due to the weakly basic reaction conditions that were ineffective in deprotonating the methylene group in the intermediate nitroso compounds. On the other hand when compounds **2** and **3** were subjected to selective reduction using zinc dust and sodium hydroxide in refluxing aqueous ethanol, a complex mixture was produced in each case that appeared as a streak on TLC. All attempts to separate the components of these mixtures proved unsuccessful.

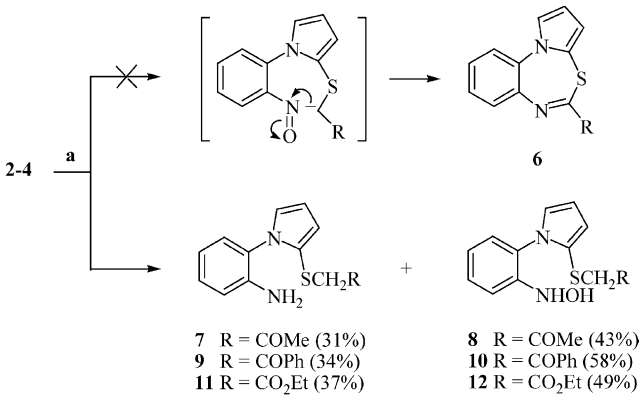
Oxidation of **2** and **3** to their sulfones would increase the acidity of the methylene hydrogens in these compounds. Thus, compounds **2** and **3** were oxidized smoothly into their corresponding sulfones **13** and **15** by 2-chloroperbenzoic acid (Scheme 3). However, the required reductive cyclisation of **13** and **15** by treatment with zinc and ammonium



1

2 R = COMe (72%)
3 R = COPh (76%)
4 R = CO_2Et (49%)
5 R = CN (62%)

Scheme 1. Reagents: (a) (i) $NaBH_4$, EtOH, NaOH, (ii) $ClCH_2COMe$, $BrCH_2COPh$, $BrCH_2CO_2Et$ or $ClCH_2CN$.



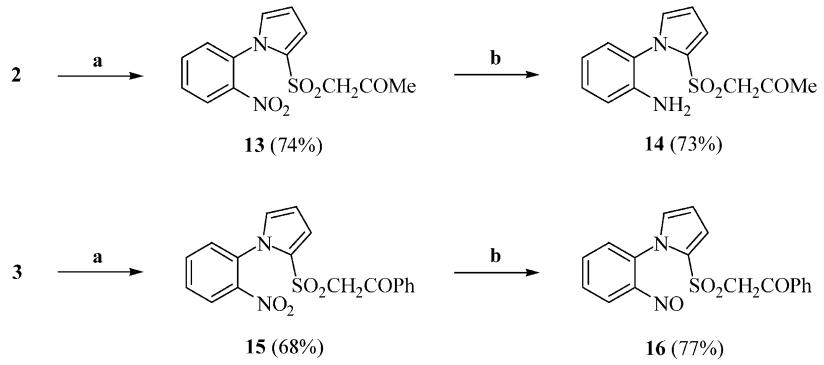
7 R = COMe (31%)
9 R = COPh (34%)
11 R = CO_2Et (37%)

8 R = COMe (43%)
10 R = COPh (58%)
12 R = CO_2Et (49%)

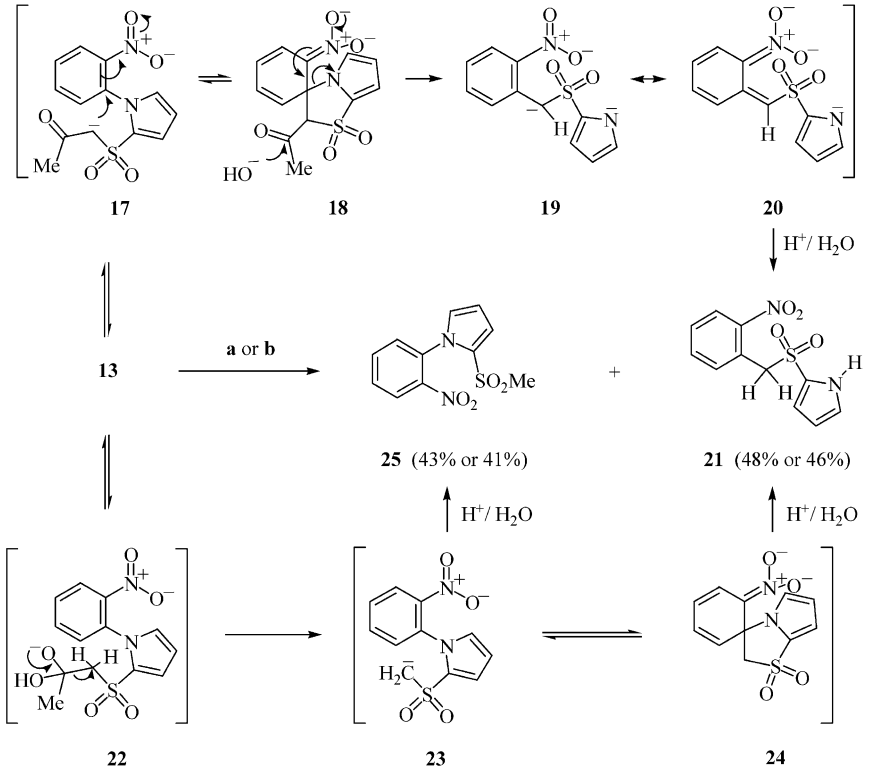
Scheme 2. Reagents: (a) Zn, NH_4Cl, H_2O, EtOH, 0–22 °C.

chloride failed, yielding instead the amine **14** and nitroso compound **16**, respectively.

We anticipated that by using a stronger base such as sodium hydroxide in the reduction of sulfone **13**, the abstraction of the relatively acidic methylene proton should be accelerated according to the mechanism of Scheme 2, and would lead to the sulfone derivative of pyrrolobenzothiadiazepine **6** (R = COMe). However, heating **13** in aqueous ethanolic sodium hydroxide containing zinc dust yielded a mixture of two new compounds, **21** and **25**, in 48 and 43% yield, respectively. A speculative mechanism for this reaction is shown in Scheme 4. In line with the proposed mechanism, hydroxide ion could react on compound **13** both as a base and as a nucleophile. Intramolecular nucleophilic attack on the benzene ring by carbanion **17** would give the Meisenheimer-type intermediate **18** that could ring-open prior or after addition of hydroxide anion to the acetyl group to give, after loss of acetate anion, pyrrolyl dianion **19**. On the other hand, addition of hydroxide ion to the acetyl group of **13** would give intermediate **22** from which loss of acetate anion would lead to carbanion **23**. After acidification, the reaction would lead to products **21** and **25**. The formation of **21** is considered to be an unusual case of a Truce–Smiles rearrangement. The reason that the nitro groups of compounds **21** and **25** are not reduced by the reductive reaction conditions is probably due to the rapid interconversion between **19** and **21** and **23** and **25**, before acidification. The structure of **25** was confirmed by its unambiguous synthesis from thiocyanate **1**. The latter was alkylated with methyl iodide in the presence of sodium borohydride to give 1-(2-nitrophenyl)-2-methylthio-1*H*-pyrrole, which was then oxidised directly to sulfone **25** by reaction with oxone® in acetone at room temperature. Heating compound **13** in aqueous ethanolic sodium hydroxide gave a mixture of **21** and **25** in 46 and 41% yield, respectively. Furthermore when compounds **21** and **25** were heated in aqueous sodium hydroxide with or without the presence of zinc dust, starting material was recovered unchanged. These results confirm beyond doubt that zinc dust plays no role in the reaction and that the formation of **21** and **25** occurs independently from **13**. Cheeseman and Hawi have proposed a mechanism similar in some respects to that of Scheme 4 to explain the rearrangement of methyl 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]thio}acetate into 2,3-dihydro-2-(2-nitrophenyl)-3-oxo-pyrrolo[2,1-*b*]thiazole. The reaction took place in dimethyl sulfoxide with potassium *t*-butoxide as base.[15]



Scheme 3. Reagents: (a) 3-chloroperbenzoic acid, CH_2Cl_2, reflux; (b) Zn, NH_4Cl, H_2O, EtOH, 0–22 °C.

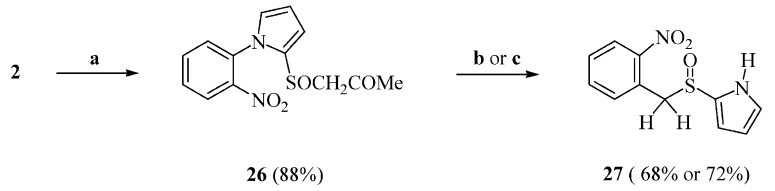


Scheme 4. Reagents: (a) Zn, NaOH, H_2O, EtOH, reflux; (b) NaOH, H_2O, EtOH, reflux.

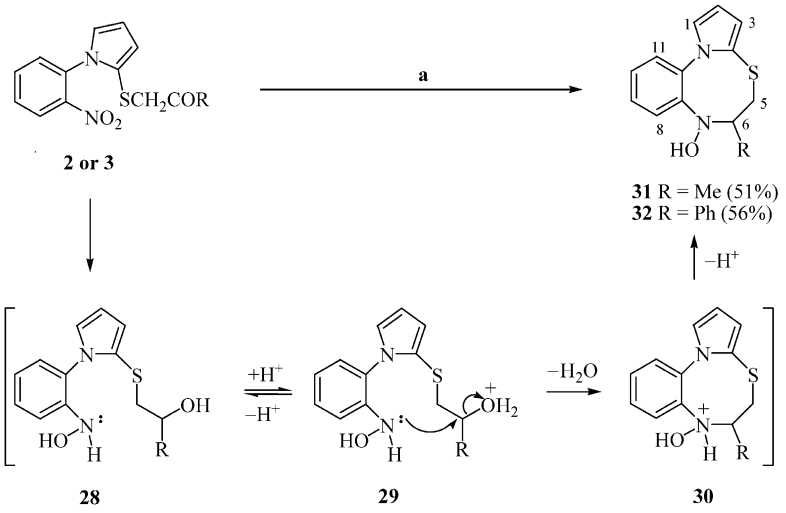
In order to acquire further insight into the reaction of Scheme 4 it was decided to prepare sulfoxide **26**. The first attempt involved the oxidation of sulfide **2** by 3-chloroperbenzoic acid at room temperature for several days. This however resulted in a mixture of starting material and sulfoxide **26** but reaction of **2** with oxone® in acetone at ambient temperature afforded sulfoxide **26** as a single product in 88% yield (Scheme 5). When **26** was heated in aqueous ethanolic sodium hydroxide containing zinc dust pyrrolylsulfinylmethane **27** was obtained in 68% yield. Repeating the reaction without zinc dust gave **27** in 72% yield. An analogous mechanism to that described for the transformation of **13** to **21** in Scheme 4 is proposed. A likely explanation for 1-(2-nitrophenyl)-2-methylsulphinylpyrrole not being formed is that the sulfoxide analogue of carbanion **23** (Scheme 4) is less stabilised than **23** itself and is therefore not formed.

Compounds **2**, **3** and **5** were found to be useful precursors to the novel pyrrolo[1,2-*a*][3.1.6]benzothiadiazocin-7-ols **31** and **32**, and, pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine-7-oxide **36**, respectively. Thus ketones **2** or **3** were reductively cyclised in the presence of sodium borohydride and 5% palladium-on-carbon to give the corresponding tricycles **31** and **32** in 51 and 56% yield respectively (Scheme 6). It is proposed that the initial step in this reaction is reduction of both nitro and keto groups of compounds **2** or **3** leading intermediate **28**. After addition of ethanolic hydrogen chloride, protonation of **28** gives intermediate **29**. The latter may deprotonate back to **28** or intramolecularly cyclise to **30** by displacement of water. Loss of a proton from intermediate **30** gives either **31** or **32**.

In the ^{1}H NMR spectrum of **31** at 24 °C, the broad signal at 2.24 ppm contains the upfield signal of the methylene



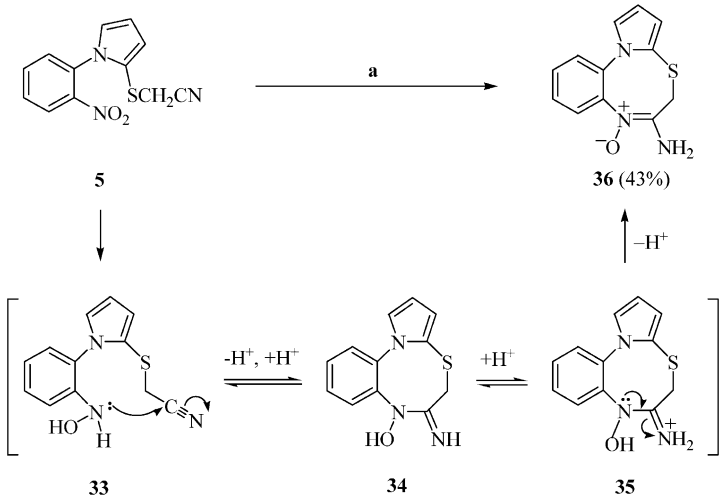
Scheme 5. Reagents: (a) oxone®, $(Me)_2CO$, 30 min; (b) Zn, NaOH, H_2O, EtOH, reflux; (c) NaOH, H_2O, EtOH, reflux.



Scheme 6. Reagents: (a) (i) $NaBH_4$, 10% Pd–C, H_2O, 1,4-dioxane, 2% aq. NaOH, (ii) EtOH–HCl, pH = 5–6.

group, assigned to H-5a, overlapping with the hydroxyl group. This was verified by D_2O addition which showed a remaining broad signal at 2.24 ppm. H-5b appears as a doublet at 2.48 ppm and H-6 appears as a multiplet in the region 3.65–3.70. Line narrowing is known to occur when the conformational equilibrium of a methylene group is fast on the NMR time-scale.[20] The fine structure of these signals was revealed by recording the spectrum at 60 °C. At this temperature the OH signal shifted upfield by 0.22 ppm, H-5a and H-5b are double doublets at 2.35 and 2.51 ppm, respectively, and H-6 is a double doublet of a quartet at 3.69 ppm. In the ^1H NMR spectrum of **32** at 24 °C, the broad signal at 2.50 ppm, assigned to H-5a, overlaps with the hydroxyl group. After D_2O addition the remaining signal at 2.50 ppm is broad. H-5b and H-6 appear as double doublets at 2.69 and 4.57 ppm, respectively. In the spectrum of **32** at 60 °C, H-5a has sharpened to a double doublet at 2.55 ppm whereas the OH signal is so broad that its chemical shift cannot be recorded.

Treatment of nitrile **5** with sodium borohydride and 5% palladium-on-carbon gave tricyclic-*N*-oxide **36** in 43% yield (Scheme 7). The proposed mechanism for this transformation involves reduction of **5** to intermediate hydroxylamine **33**, intramolecular nucleophilic addition to the nitrile group, protonation of resulting imine **34** to iminium cation **35** and conversion of the later to *N*-oxide **36** by lone pair electron delocalisation and deprotonation. The



Scheme 7. Reagents: (a) (i) $NaBH_4$, 10% Pd–C, H_2O, 1,4-dioxane, 2% aq. NaOH, (ii) EtOH/HCl, pH = 5–6.

carbon and proton atoms of compounds **31**, **32** and **36** were fully characterised with the aid of DQF-COSY, DEPT, HMQC and HMBC spectra.

In summary, it has been shown that substituted pyrroles such as 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone are reduced by zinc and ammonium chloride to the corresponding hydroxylamine and amine derivatives, without the observation of any intramolecular interaction. A similar result was obtained with 1-{[1-(2-nitro-phenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone where only the corresponding amine was isolated. However, treatment of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone with zinc and sodium hydroxide gave a mixture of two products resulting from a Truce–Smiles type of transformation and a simple deacetylation. Remarkably, no reduction of the nitro group in these compounds had occurred. Reduction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone or -1-phenylethan-1-one with sodium borohydride and 5% palladium-on-carbon, lead to two novel pyrrolo[1,2-*a*]-[3.1.6]benzothiadiazocine derivatives. The N-oxide function of these compounds suggests transient hydroxyl-amine intermediates This novel synthetic method was successfully applied.

3. Experimental

3.1. General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls and liquids between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Nuclear magnetic resonance spectra were measured at 360 MHz on a Brüker AM 360 spectrometer or at 400 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained using a JEOL JMS-AX 505W high resolution instrument under EI or CI conditions, or a Bruker Apex III high resolution instrument under ESI conditions. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers except for dichloromethane, ethanol, ethyl acetate, light petroleum (bp 40–60 °C) and methanol that were purified and dried according to recommended procedures.[21]

3.2. Alkylation of 1-(2-nitrophenyl)-1*H*-pyrrol-2-ylthiocyanate. General procedure A

To a stirred solution of **1** (1.22 g, 5 mmol) in dry ethanol (50 mL), kept under a continuous stream of argon, sodium borohydride (0.28 g, 7.5 mmol) was added in portions and the mixture stirred at room temperature for 45 min. A solution of sodium hydroxide (0.42 g, 7.5 mmol) in dry ethanol (10 mL) was then added followed by chloroacetone, phenacyl bromide, ethyl chloroacetate or chloroacetonitrile (7.5 mmol). The mixture was stirred at 60–65 °C for 1.5 h and at room temperature for 12 h. The solvent was removed in vacuo up to 15 mL and to this oily residue, water (45 mL) was added and extracted with dichloromethane (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (12, 25% ethyl acetate/light petroleum) to give 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone **2**, 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one **3**, ethyl 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate **4** or [1-(2-nitrophenyl)-1*H*-pyrrol-2-ylsulfanyl]acetonitrile **5**, respectively.

3.2.1. 1-{[1-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-acetone (2). (0.5 g, 72%) as pale yellow oil, bp 112–114 °C/12 mm Hg; ν_{max}(liquid film) 1720, 1540, 1360 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 2.07 (3H, s, Me), 3.12 (1H, s, br, CH_2), 6.33 (1H, dd, J=3.6, 3.1 Hz, H-4), 6.59 (1H, dd, J=3.6, 1.7 Hz, H-3), 6.88 (1H, dd, J=3.1, 1.7 Hz, H-5), 7.50 (1H, dd, J=7.9, 1.3 Hz, H-6′), 7.61 (1H, ddd, J=9.0, 8.0, 1.3 Hz, H-4′), 7.74 (1H, ddd, J=9.0, 7.9, 1.6 Hz, H-5′), 8.05 (1H, dd, J=8.0, 1.6 Hz, H-3′); δ_C (90.5 MHz; $CDCl_3$) 28.3, 47.3, 110.9, 120.3, 120.8, 125.1, 125.9, 129.3, 131.2, 132.9, 133.5, 146.6, 202.9; *m/z* (EI) 276 (65, M^+), 260 (10) 187 (33), 171 (38), 143 (12), 83 (100%); HRMS (EI): (M^+), found 276.0563. $C_{13}H_{12}N_2O_3S$ requires 276.0569.

3.2.2. 2-{[1-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one (3). (1.27 g, 76%) as yellow needles (ethanol); mp=96–97 °C; (lit.[14] mp=97–98 °C), identical in all respects to an authentic sample.

3.2.3. Ethyl 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate (4). (0.68 g, 49%) as a yellow oil, bp 123–128 °C/12 mm Hg; ν_{max} (liquid film) 1740, 1540, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.20 (3H, t, J=7.0 Hz, Me), 3.03 (2H, d, J=7.8, Hz, SCH_2), 4.01–4.12 (2H, m, CH_2), 6.35 (1H, dd, J=3.3, 3.0 Hz, H-4), 6.67 (1H, dd, J=3.3, 1.7 Hz, H-3), 6.89 (1H, dd, J=3.0, 1.7 Hz, H-5), 7.48 (1H, dd, J=7.8, 1.4 Hz, H-6′), 7.60 (1H, ddd, J=8.1, 7.9, 1.5 Hz, H-4′), 7.71 (1H, ddd, J=7.9, 7.8, 1.5 Hz, H-5′), 8.04 (1H, dd, J=8.1, 1.5 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 12.8, 33.8, 60.3, 106.3, 115.9, 117.7, 119.0, 124.4, 125.3, 126.5, 128.0, 131.2, 142.8, 171.4; *m/z* (EI) 306 (35, M^+), 275 (68), 173 (100), 140 (25%); HRMS (EI): (M^+), found 306.0671 $C_{14}H_{14}N_2O_4S$ requires 306.0674.

3.2.4. [1-(2-Nitro-phenyl)-1*H*-pyrrol-2-ylsulfanyl]acetonitrile (5). (0.76 g, 62%) as pale yellow oil; (lit.[15]), identical in all respects to an authentic sample.

3.3. Reduction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]-sulfanyl}acetone, 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]-sulfanyl}-1-phenylethan-1-one and ethyl 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate with zinc dust and ammonium chloride in aqueous ethanol. General procedure B

To a stirred solution of compounds **2**, **3** or **4** (1.2 mmol) in ethanol (15 mL) at 0 °C was added zinc dust (0.24 g, 3.6 mmol) followed by a solution of ammonium chloride (0.38 g, 7.2 mmol) in water (8 mL). The reaction mixture was left to stir at room temperature for 1.5 h, filtered the residue washed with hot ethanol (15 mL). The solvents were evaporated in vacuo to near dryness, water (35 mL) was added and extracted with dichloromethane (3×10 mL). The

combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. The oily residue was purified by flash chromatography (12% ethyl acetate/light petroleum) to give two fractions. The first fraction gave 1-{[1-(2-aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone **7**, 2-{[1-(2-aminophenyl)-1*H*-pyrrol-2-yl]-sulfanyl}-1-phenylethan-1-one **9** or ethyl 2-{[1-(2-aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate **11** and the second fraction gave 1-{[1-(2-hydroxylaminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone **8**, 2-{[1-(2-hydroxylaminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one **10** or ethyl 2-{[1-(2-hydroxylaminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate **12**, respectively.

3.3.1. 1-{[1-(2-Aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone (7). (90 mg, 31%) as pale yellow oil, bp 152–155 °C/12 mm Hg; ν_{max} (liquid film) 3525, 3420, 1685 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, Me), 3.69 (2H, s, br, NH_2), 3.71 (2H, d, $J=13$ Hz, SCH_2), 6.27 (1H, t, $J=3.6$ Hz, H-4), 6.81 (1H, dd, $J=3.6$, 1.8 Hz, H-3), 6.91 (1H, dd, $J=7.9$, 1.4 Hz, H-3′), 7.11 (1H, dd, $J=3.6$, 1.8 Hz, H-5), 7.29 (1H, ddd, $J=9.0$, 7.9, 1.4 Hz, H-5′), 7.48 (1H, ddd, $J=7.9$, 1.3 Hz, H-4′), 7.52 (1H, dd, $J=9.0$, 1.3 Hz, H-6′); δ_C (100 MHz; $CDCl_3$) 28.8, 41.7, 106.2, 115.6, 116.5, 116.8 (2C), 126.4 (2C), 128.7, 129.5, 202.2; *m/z* (EI) 246 (63, M^+), 229 (18) 153 (75), 69 (100%); HRMS (EI): (M^+), found 246.0826. $C_{13}H_{14}N_2OS$ requires 246.0833.

3.3.2. 1-{[1-(2-Hydroxylaminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone (8). (0.13 g, 43%) as pale yellow oil, bp 143–145 °C/12 mm Hg; ν_{max} (liquid film) 3380, 1710 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.07 (3H, s, Me), 3.18 (2H, s, SCH_2), 5.62 (2H, s, br, NHOH), 6.28 (1H, t, $J=3.1$ Hz, H-4), 6.48 (1H, dd, $J=3.1$, 1.4 Hz, H-3), 6.87 (1H, dd, $J=3.1$, 1.4 Hz, H-5), 6.97 (1H, ddd, $J=8.0$, 7.2, 2.4 Hz, H-5′), 7.16 (1H, dd, $J=7.8$, 2.4 Hz, H-3′), 7.52 (1H, ddd, $J=7.8$, 7.2, 1.4 Hz, H-4′), 7.79 (1H, dd, $J=8.0$, 1.4 Hz, H-6′); δ_C (100 MHz; $CDCl_3$) 28.7, 41.8, 106.3, 110.7, 117.1, 118.3, 122.2, 126.5, 128.2, 129.0, 140.1, 202.1; *m/z* (EI) 263 (45, M^+), 188 (58) 169 (65), 83 (100%); HRMS (EI): (M^+), found 263.0854. $C_{13}H_{14}N_2O_2S$ requires 263.0845.

3.3.3. 2-{[1-(2-Aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one (9). (0.12 g, 34%) as an oil (lit.[14]), identical in all respects to an authentic sample.

3.3.4. 2-{[1-(2-Hydroxylaminophenyl)-1*H*-pyrrol-2-yl]-sulfanyl}-1-phenylethan-1-one (10). (0.22 g, 58%) as a pale yellow oil, bp 168–172 °C/12 mm Hg; ν_{max} (liquid film) 3400, 1680 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.53 (1H, d, $J=12.4$ Hz, *H*CH), 3.69 (1H, d, $J=12.4$ Hz, HC*H*), 5.83 (2H, s, br, NHOH), 6.26 (1H, t, $J=3.3$ Hz, H-4), 6.38 (1H, dd, $J=3.3$, 1.4 Hz, H-3), 6.86 (1H, dd, $J=3.3$, 1.4 Hz, H-5), 6.98 (1H, dd, $J=7.1$, 2.4 Hz, benzenoid), 7.15 (1H, d, $J=7.6$ Hz, benzenoid), 7.37–7.44 (5H, m, benzenoid), 7.55 (1H, d, $J=7.5$ Hz, benzenoid), 7.82 (1H, dd, $J=7.6$, 1.4 Hz, benzenoid); δ_C (100 MHz; $CDCl_3$) 37.8, 115.8, 116.1, 116.9, 118.4, 119.2, 122.4, 126.7 (2C), 128.6 (2C), 130.4 (2C), 131.8, 132.2, 134.6, 142.2, 193.5; *m/z* (EI) 324 (3, M^+), 281 (39), 267 (22), 221 (49), 187 (67), 147 (100), 133 (21%); HRMS (EI): (M^+), found 324.0937. $C_{18}H_{16}N_2O_2S$ requires 324.0932.

3.3.5. Ethyl 2-{[1-(2-aminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate (11). (0.12 g, 37%) as an oil (lit.[14]), identical in all respects to an authentic sample.

3.3.6. Ethyl 2-{[1-(2-hydroxylaminophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetate (12). (0.17 g, 49%) as pale yellow oil, bp 151–154 °C/12 mm Hg; ν_{max} (liquid film) 2430, 1760 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.19 (3H, t, $J=7.1$ Hz, Me) 3.04 (2H, d, $J=7.8$ Hz, SCH_2), 4.02 (2H, q, CH_2), 5.5 (2H, s, br, NHOH), 6.29 (1H, t, $J=3.3$ Hz, H-4), 6.57 (1H, dd, $J=3.3$, 1.8 Hz, H-3), 6.86 (1H, dd, $J=3.3$, 1.8 Hz, H-5), 7.03 (1H, ddd, $J=8.0$, 7.0, 2.2 Hz, H-5′), 7.17 (1H, dd, $J=7.8$, 2.2 Hz, H-3′), 7.38–7.42 (2H, m, H-4′, H-6′); δ_C (100 MHz; $CDCl_3$) 12.9, 33.7, 60.3, 105.1, 115.1, 116.2, 116.5, 118.5, 122.3, 126.9, 128.0, 129.5, 140.4, 171.4; *m/z* (EI) 292 (14, M^+), 276 (67), 187 (57), 173 (100), 156 (70), 140 (20), 119 (10%); HRMS (EI): (M^+), found 292.0888. $C_{14}H_{16}N_2O_3S$ requires 292.0882.

3.4. Oxidation of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone and 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one with 2-chloroperbenzoic acid. General procedure C

To a solution of compound **2** or **3** (1.45 mmol) in dichloromethane (30 mL) was added 2-chloroperbenzoic acid (0.25 g, 1.45 mmol) and the resulting mixture was heated under reflux for 12 h. Heating was continued for 10 h during which time 2-chloroperbenzoic acid (0.03 g, 0.15 mmol) was added at hourly intervals. The solvent was evaporated under reduced pressure and to the oily residue water (30 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed in vacuo. Purification of the oily residue by flash chromatography (11%, 50% ethyl acetate/light petroleum) afforded 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone **13** or 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}-1-phenylethan-1-one **15**.

3.4.1. 1-{[1-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}-acetone (13). (0.33 g, 74%) as a yellow oil, bp 159–162 °C/12 mm Hg; ν_{max} (liquid film) 1710, 1545, 1340, 1290, 1140 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, Me), 3.84 (1H, d, $J=13.2$ Hz, *H*CH), 4.06 (1H, d, $J=13.2$ Hz, HC*H*) 6.45 (1H, dd, $J=3.9$, 2.8 Hz, H-4), 6.96 (1H, dd, $J=3.9$, 2.2 Hz, H-3), 7.14 (1H, dd, $J=3.9$, 2.2 Hz, H-5), 7.63 (1H, dd, $J=7.6$, 1.5 Hz, H-6′), 7.70 (1H, ddd, $J=8.0$, 7.6, 1.5 Hz, H-4′), 7.75 (1H, ddd, $J=8.0$, 7.6, 1.6 Hz, H-5′), 8.14 (1H, dd, $J=8.0$, 1.6 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 31.0, 65.7, 111.4, 114.5, 125.3, 128.0, 130.5, 131.3, 131.5, 133.8, 134.2, 146.4, 199.3; *m/z* (EI) 308 (1, M^+), 279 (10) 235 (3), 210 (13), 188 (42), 168 (53), 143 (40), 129 (47), 102 (63), 83 (100%); HRMS (EI): (M^+), found 308.0454. $C_{13}H_{12}N_2O_5S$ requires 308.0466).

3.4.2. 2-{[1-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}-1-phenylethan-1-one (15). (0.36 g, 68%) as colourless plates (ethyl acetate); mp 143–144 °C [Found: C, 58.31; H, 3.85; N, 7.61. $C_{18}H_{14}N_2O_5S$ requires C, 58.37; H, 3.81; N, 7.57%]; ν_{max} (liquid film) 1680, 1540, 1340, 1325, 1240 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.84 (1H, d, $J=13.1$ Hz, *H*CH), 4.28 (1H, d, $J=13.1$ Hz, HC*H*), 6.32 (1H,

t, J=3.3 Hz, H-4), 6.81–6.84 (2H, m, H-3, benzenoid), 7.15 (1H, dd, J=3.3, 1.8 Hz, H-5), 7.35–7.39 (5H, m, benzenoid), 7.52 (1H, d, J=7.4 Hz, benzenoid), 7.72 (2H, m, benzenoid); δ_C (100 MHz; $CDCl_3$) 47.8, 117.2, 117.9, 119.8, 120.9, 124.1, 128.0, 130.0, 130.3 (2C), 130.6, 131.1 (2C), 133.2, 134.9, 135.3, 144.8, 180.7; *m/z* (EI) 370 (14, M^+), 317 (18), 267 (26), 198 (100), 155 (60), 113 (72%).

3.5. Reduction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}acetone and 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfonyl}-1-phenylethan-1-one with zinc dust and ammonium chloride in aqueous ethanol

Compound **13** or **15** (0.9 mmol) was dissolved in ethanol (10 mL), the solution cooled to 0 °C and treated with zinc dust (0.18 g, 2.7 mmol) and ammonium chloride (0.29 g, 5.4 mmol) according to General procedure B. The oily residue after work-up was purified by column chromatography (33% ethyl acetate/light petroleum) to give 1-{[1-(2-aminophenyl)-1*H*-2-pyrrol-2-yl]sulfonyl}acetone **14** or 2-{[1-(2-nitrosophenyl)-1*H*-pyrrol-2-yl]-sulfonyl}-1-phenylethan-1-one **16**.

3.5.1. 1-{[1-(2-Aminophenyl)-1*H*-2-pyrrol-2-yl]sulfonyl}acetone (14). (0.18 g, 73%) as colourless needles (ethanol); mp 100–101 °C; [Found: C, 56.16; H, 4.99; N, 10.02. $C_{13}H_{14}N_2O_3S$ requires C, 56.10; H, 5.07; N, 10.07%]; ν_{max} (Nujol) 3460, 3360, 1705, 1320, 1125 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, Me), 3.91 (2H, s, br, NH2), 4.14 (2H, s, CH2), 6.33 (1H, dd, J=3.9, 2.6 Hz, H-4), 6.87 (1H, dd, J=2.6, 1.8 Hz, H-3), 6.91 (1H, dd, J=7.9, 1.4 Hz, H-3′), 7.11 (1H, dd, J=3.9, 1.8 Hz, H-5), 7.28 (1H, ddd, J=8.8, 7.9, 1.4 Hz, H-5′), 7.47 (1H, ddd, J=8.8, 7.7, 1.3 Hz, H-4′), 7.52 (1H, dd, J=7.9, 1.3 Hz, H-6′); δ_C (100 MHz; $CDCl_3$) 31.0, 57.8, 109.3, 112.7, 113.3, 116.9, 117.6, 125.49, 126.2, 128.1, 131.4, 140.1, 197.1; *m/z* (EI) 278 (75, M^+), 221 (62), 169 (100), 142 (35%).

3.5.2. 2-{[1-(2-Nitrosophenyl)-1*H*-pyrrol-2-yl]sulfonyl}-1-phenylethan-1-one (16). (0.25 g, 77%) as pale-yellow solid (ethyl acetate/hexane); mp 49–50 °C; ν_{max} (Nujol) 1670, 1320, 1100 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.31 (1H, d, J=13.0 Hz, HCH), 4.44 (1H, d, J=13.0 Hz, HC*H*), 6.33 (1H, t, J=3.4 Hz, H-4), 6.81–6.84 (2H, m, H-3, benzenoid,), 6.96 (1H, s, br, benzenoid), 7.16 (1H, s, br, H-5), 7.35–7.40 (4H, m, benzenoid), 7.52 (1H, t, J=7.3 Hz, benzenoid), 7.71 (2H, s, br, benzenoid); δ_C (100 MHz; $CDCl_3$) 53.7, 112.8, 116.5, 119.6, 120.1, 121.6, 124.3, 127.5, 130.1, 130.3 (2C), 130.7, 131.2 (2C), 134.2, 134.9, 145.8, 188.7; *m/z* (EI) 355 (1, M^++1), 323 (24), 272 (74), 257 (70), 218 (59), 187 (50), 156 (80), 131 (55), 105 (100), 69 (98%); HRMS (EI): (M^++1), found 355.0730. $C_{18}H_{15}N_2O_4S$ requires 355.0752.

3.5.3. Oxidation of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone with oxone®. To a stirred solution of **2** (0.4 g, 1.4 mmol) in acetone (30 mL) was added dropwise a solution of oxone® (0.87 g, 2.6 mmol) in water (5 mL). The mixture was left stirring for 20 min, water (40 mL) was added and extracted with chloroform (3x30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give an oily residue that was purified by column chromatography (ethyl acetate) to give 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfinyl}acetone **26** (0.36 g, 88%) as an orange oil, bp 147–152 °C/12 mm Hg; ν_{max} (liquid film) 1710, 1520, 1330, 1220 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.15 (3H, s, Me) 3.86 (1H, d, J=14.2 Hz, *H*CH), 3.94 (1H, s, br, HC*H*), 6.39 (1H, t, J=3.3 Hz, H-4), 6.82 (1H, s, H-3), 6.89 (1H, d, J=3.3 Hz, H-5), 7.59–7.72 (3H, m, H-4′, H-5′, H-6′). 7.99 (1H, d, J=8.0 Hz, H-3′); *m/z* (EI) 293 (75, M^++1), 277 (53), 235 (100), 188 (65%); HRMS (EI): (M^+), found 292.0525. $C_{13}H_{12}N_2O_4S$ requires 292.0518.

3.6. Reaction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]-sulfonyl}acetone and 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfinyl}acetone with zinc dust and sodium hydroxide in aqueous ethanol. General procedure D

To a stirred solution of **13** or **26** (1.2 mmol) in ethanol (15 mL) was added a solution of sodium hydroxide (0.19 g, 4.8 mmol) in water (8 mL) and zinc dust (0.24 g, 3.6 mmol). The resulting mixture was heated under reflux over a period of 3 h, filtered, washed with hot ethanol and the filtrate evaporated to near dryness. Water (35 mL) was added to the oily residue and then extracted with dichloromethane (3× 10 mL). The combined organic extracts were dried (Na_2SO_4), evaporated in vacuo, and the oily residue was purified by column chromatography (12% ethyl acetate/light petroleum) to give in the first fraction 1-(2-nitrophenyl)(1*H*-pyrrol-2-ylsulfonyl)methane **21** and in the second fraction 1-(2-nitrophenyl)-2-methylsulfonylpyrrole **25** or (ethyl acetate) to give 1-(2-nitrophenyl)(1*H*-pyrrol-2-ylsulfinyl)methane **27**.

3.6.1. 1-(2-Nitrophenyl)(1*H*-pyrrol-2-ylsulfonyl)-methane (21). (0.15 g, 48%) as colourless needles (toluene); mp 116–118 °C; [Found: C, 49.57; H, 3.81; N, 10.57. $C_{11}H_{10}N_2O_4S$ requires C, 49.62; H, 3.79; N, 10.52%]; ν_{max} (Nujol) 3440, 1550, 1365, 1345, 1135 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.99 (2H, s, CH_2), 6.26 (1H, dd, J=3.8, 2.8 Hz, H-4), 6.60 (1H, dd, J=3.8, 2.6 Hz, H-3), 6.97 (1H, dd, J=2.8, 2.6 Hz, H-5), 7.39 (1H, dd, J=7.5, 1.6 Hz, H-6′) 7.54 (1H, ddd, J=9.0, 8.0, 1.6 Hz, H-4′), 7.59 (1H, ddd, J=9.0, 7.5, 1.5 Hz, H-5′), 7.99 (1H, dd, J=8.0, 1.5 Hz, H-3′), 9.18 (1H, s, br, NH); δ_C (90.5 MHz; $CDCl_3$) 59.07, 110.4, 116.8, 123.4, 124.1, 124.9, 125.3, 129.8, 133.1, 134.0, 149.4; *m/z* (EI) 266 (28, M^+), 185 (37), 154 (16), 130 (75), 78 (100%); HRMS (EI): (M^+), found 266.0358. $C_{11}H_{10}N_2O_4S$ requires 266.0361.

3.6.2. 1-(2-Nitrophenyl)-2-methylsulfonylpyrrole (25). (0.15 g, 43%) as colourless needles (toluene); mp 90–92 °C; [Found: C, 49.66; H, 3.75; N, 10.59. $C_{11}H_{10}N_2O_4S$ requires C, 49.62; H, 3.79; N, 10.52%]; ν_{max} (Nujol) 1540, 1330, 1310, 1140 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.93 (3H, s, Me), 6.43 (1H, dd, J=3.9, 2.8 Hz, H-4), 6.86 (1H, dd, J=2.8, 1.9, Hz, H-3), 7.13 (1H, dd, J=3.9, 1.9 Hz, H-5), 7.63 (1H, dd, J=7.7, 1.5 Hz, H-6′), 7.68 (1H, ddd, J=8.0, 6.3, 1.5 Hz, H-4′), 7.74 (1H, ddd, J=7.7, 6.3, 1.5 Hz, H-5′), 8.09 (1H, dd, J=8.0, 1.5 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 39.3, 112.9, 117.9, 118.7 (2C), 123.5, 128.1, 129.8, 132.7, 133.7, 143.7; *m/z* (EI) 266 (16, M^+), 185 (23), 136 (64), 82 (100%).

3.6.3. 1-(2-Nitrophenyl)(1*H*-pyrrol-2-ylsulfinyl)methane (27). (0.21 g, 68%) as colourless needles (toluene); mp

143–144.5 °C; [Found: C, 52.76; H, 4.05; N, 11.18. $C_{11}H_{10}N_2O_3S$ requires C, 52.79; H, 4.03; N, 11.20%]; ν_{max} (Nujol) 3450, 1510, 1230, 1040 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.79 (1H, d, J=12 Hz, *H*CH), 4.85 (1H, d, J=12 Hz, HC*H*), 6.14 (1H, dd, J=3.7, 2.6 Hz, H-4), 6.43 (1H, dd, J=2.6, 1.7 Hz, H-3), 6.97–7.01 (2H, m, H-5, H-6′), 7.39–7.46 (2H, m, H-4′ και H-5′), 8.06 (1H, dd, J=8.2, 1.7 Hz, H-3′), 11.34 (1H, s, br, NH); δ_C (100 MHz; $CDCl_3$) 59.5, 109.2, 114.7, 124.8, 125.3, 125.7, 125.8, 129.5, 133.5, 134.0, 148.5; *m/z* (CI) 268 (100, $M^+ + NH_3$), 251 (28, M^+), 235 (9), 203 (15).

3.7. Reaction of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]-sulfonyl}acetone and 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfinyl}acetone with sodium hydroxide in aqueous ethanol

Compound **13** or **26** (1.2 mmol) was dissolved in ethanol (15 mL) and treated with a solution of sodium hydroxide (0.19 g, 4.8 mmol) in water (8 mL) and heated under reflux over a period of 3 h. After work-up according to General procedure C, compounds **21** (0.14 g, 46%), **25** (0.14 g, 41%) or **27** (0.22 g, 72%), prepared by this method, were identical in all respects to the corresponding compounds obtained by General procedure D.

3.8. Reductive cyclisation of 1-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetone, 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}-1-phenylethan-1-one and 2-{[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl]sulfanyl}acetonitrile with sodium borohydride and 5% palladium-on-carbon. General procedure E

A suspension of 5% palladium-on-carbon (0.06 g) in water (3 mL) was added to a stirred solution of sodium borohydride (0.3 g, 7.8 mmol) in water (6 mL) while purging with argon. A solution of **2**, **3** or **5** (1.8 mmol) in 1,4-dioxane (20 mL) was added and the mixture stirred for 30 min. After that time an aqueous solution of 2% sodium hydroxide (18 mL) was added and the mixture was stirred for 20 min. The reaction mixture was then filtered and the pH adjusted to 5–6 by the addition of ethanolic hydrogen chloride. Water (20 mL) was added to the oily solution and then extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo, and the oily residue was purified by column chromatography (20% ethyl acetate/light petroleum) to give in the first fraction 6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocin-7-ol **31**, 6-phenyl-5,6-dihydro-7*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocin-7-ol **32** or 6-amino-5*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine-7-oxide **36**.

3.8.1. (±)-6-Methyl-5,6-dihydro-7*H*-pyrrolo[1,2-*a*]-[3.1.6]benzothiadiazocin-7-ol (31). (0.21 g, 51%) as yellow oil, bp 136–139 °C/12 Torr; ν_{max} (liquid film) 3400 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.10 (3H, d, J=6.3 Hz, Me), 2.24 (2H, s, br, OH, H-5a), 2.48 (1H, d, J=12.2 Hz, H-5b), 3.65–3.70 (1H, m, H-6), [at 60 °C: 2.02 (1H, s, br, OH), 2.35 (1H, dd, J=13.2, 8.1 Hz, H-5a), 2.51 (1H, dd, J=13.2, 4.0 Hz, H-5b), 3.69 (1H, ddq, J=8.1, 6.3, 4.0 Hz, H-6)] 6.35 (1H, dd, J=3.6, 3.1 Hz, H-2), 6.58 (1H, dd, J=3.6, 1.7 Hz, H-3), 6.87 (1H, dd, J=3.1, 1.7 Hz, H-1), 7.55 (1H, dd, J=7.9, 1.4 Hz H-8), 7.61 (1H, ddd, J=9.0, 8.0, 1.4 Hz, H-10), 7.73 (1H, ddd, J=9.0, 7.7, 1.6 Hz, H-9), 8.03 (1H, d, J=8.0 Hz, H-11); δ_C (100 MHz; $CDCl_3$) 21.4 (Me), 45.6 (C-5), 65.5 (C-6), 110.1 (C-2), 110.6 (C-3), 115.9 (C-1), 119.8 (C-11), 121.4 (C-3a), 125.0 (C-8), 125.4 (C-10), 129.2 (C-9), 132.9 (C-11a), 146.7 (C-7a); *m/z* (EI) 248 (32, $M^+ + 2$), 246 (5, M^+), 173 (61), 157 (55), 131 (17), 84 (83), 49 (100%); HRMS (EI): (M^+), found 246.0825 $C_{13}H_{14}N_2OS$ requires 246.0827.

3.8.2. (±)-6-Phenyl-5,6-dihydro-7*H*-pyrrolo[1,2-*a*]-[3.1.6]benzothiadiazocin-7-ol (32). (0.33 g, 56%) as yellow oil, bp 141–145 °C/12 Torr; ν_{max} (liquid film) 3420 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.50 (2H, s, br, OH, H-5a), [at 60 °C: 2.55 (1H, dd, J=13.5, 9.5 Hz, H-5a), 2.69 (1H, dd, J=13.5, 3.3 Hz, H-5b), 4.57 (1H, dd, J=9.5, 3.3 Hz, H-6)], 6.36 (1H, dd, J=3.3, 3.0 Hz, H-2), 6.64 (1H, dd, J=3.3, 1.7 Hz, H-3), 6.88 (1H, dd, J=3.0, 1.7 Hz, H-1), 7.22–7.75 (9H, m, benzenoid), 8.03 (1H, d, J=7.1 Hz, H-11); δ_C (100 MHz; $CDCl_3$) 46.1 (C-5), 71.3 (C-6), 110.9 (C-2), 120.2 (C-3a), 125.1 (C-3), 125.6 (C-1), 125.9 (4C, benzenoid), 127.8 (1C, benzenoid), 128.5 (3C, benzenoid), 129.2 (1C, benzenoid), 131.2 (1C, benzenoid), 133.3 (1C, benzenoid), 142.2 (C-7a); *m/z* (CI) 343 [18, $(M+NH_4+NH_3)^+$], 340 (100), 272 (20), 221 (20), 187 (57), 171 (24), 107 (21), 83 (39%); HRMS (ESI): ($M^+ + 1$), found 309.1052. $C_{18}H_{17}N_2OS$ requires 309.1056.

3.8.3. 6-Amino-5*H*-pyrrolo[1,2-*a*][3.1.6]benzothiadiazocine-7-oxide (36). (0.21 g, 43%) as yellow powder (ethyl acetate); mp 94–96 °C [Found: C, 58.75; H, 4.53; N, 17.12. $C_{12}H_{11}N_3OS$ requires C, 58.76; H, 4.52; N, 17.14%]; ν_{max} (Nujol) 3430, 1220 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.14 (1H, d, J=12.2 Hz, H-5a), 3.56 (1H, d, J=12.2 Hz, H-5b), 3.90 (2H, s, br, NH_2), 6.27 (1H, dd, J=3.6, 3.0 Hz, H-2), 6.57 (1H, dd, J=3.6, 1.7 Hz, H-3), 6.80 (1H, dd, J=3.0, 1.7 Hz, H-1), 7.35–7.55 (3H, m, H-9, H-10 και H-11), 7.61 (1H, d, J=7.7 Hz, H-8); δ_C (100 MHz; $CDCl_3$) 30.7 (C-5), 109.9 (C-2), 118.2 (C-3), 119.1 (C-3a), 124.0 (C-1), 126.3 (C-11), 127.5 (C-10), 128.2 (C-7), 129.0 (C-6), 129.9 (C-8), 130.6 (C-9), 136.3 (C-11a), 139.1 (C-7a); *m/z* (EI) 245 (5, M^+), 229 (38), 156 (100), 113 (30), 70 (9%).

Acknowledgements

This work supported by a PENED grant (91ED102) from the General Secretariat of Research and Technology, Athens (to A.K.). We thank Professor N. Hadjiliadis for elemental analyses, which were obtained on a machine financed by the Section of Inorganic and Analytical Chemistry of the University of Ioannina. We are particularly grateful to A. Cakebread and R. Tye for mass spectra obtained on machines funded by the University of London Intercollegiate Research Services Scheme.

References and notes

1. McMahon, J. B.; Gulakowsky, R. J.; Weislow, O. S.; Schultz, R. J.; Narayanan, V. L.; Clanton, D. J.; Pedemonte, R.;

Wassmundt, F. W.; Buckheit, R. W.; Decker, C. D.; White, L.; Bader, J. P.; Boyd, M. R. *Antimicrob. Agents Chemother.* **1993**, *37*, 754.
2. Williams, T. M.; Ciccarone, T. M.; Mactough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291.
3. Young, S. D.; Amblard, M. C.; Britcher, S. F.; Grey, V. E.; Tran, L. O.; Lumma, W. C.; Huff, J. R.; Schleif, W. A.; Emini, E. E.; O'Brien, J. A.; Pettibone, D. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 491.
4. Silvestri, R.; Pagnozzi, E.; Artico, M.; Stefancich, G.; Massa, S.; La Colla, P. *J. Heterocycl. Chem.* **1995**, *32*, 683.
5. Artico, M.; Silvestri, R.; Stefancich, G.; Massa, S.; Pagnozzi, E.; Musu, D.; Scintu, F.; Pinna, E.; Tinti, E.; La Colla, P. *Arch. Pharm. (Weinheim)* **1995**, *328*, 223.
6. Artico, M.; Silvestri, R.; Stefancich, G.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. *J. Med. Chem.* **1996**, *39*, 522.
7. Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A. G.; Putzolu, M.; Corrias, S.; Spiga, G. M.; La Colla, P. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 837.
8. Artico, M.; Di Santo, R.; Costi, R.; Massa, S.; Scintu, F.; Loi, A. G.; De Montis, A.; La Colla, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1931.
9. Silvestri, R.; Artico, M.; Massa, S.; Stefancich, G.; Congeddu, E.; Putzolu, M.; La Colla, P. *Farmaco* **1997**, *52*, 323.
10. Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, A. G.; Scintu, F.; La Colla, P. *J. Med. Chem.* **2000**, *43*, 1886.
11. Di Santo, R.; Costi, R.; Artico, M.; Massa, S. *J. Heterocycl. Chem.* **1995**, *32*, 1779.
12. Di Santo, R.; Costi, R.; Artico, M. *J. Heterocycl. Chem.* **1996**, *33*, 2019.
13. Cheeseman, G. W. H.; Hawi, A. A.; Varvounis, G. *J. Heterocycl. Chem.* **1985**, *22*, 423.
14. Cheeseman, G. W. H.; Varvounis, G. *J. Heterocycl. Chem.* **1987**, *24*, 1157.
15. Cheeseman, G. W. H.; Hawi, A. *J. Heterocycl. Chem.* **1983**, *20*, 591.
16. Bruneau, P.; Delvare, C. *J. Med. Chem.* **1991**, *34*, 1028.
17. Bird, C. W.; Latif, M. *Tetrahedron* **1980**, *36*, 529.
18. Sicker, D.; Prätorius, B.; Mann, G.; Meyer, L. *Synthesis* **1989**, 211.
19. Kimbaris, A.; Varvounis, G. *Tetrahedron* **2000**, *56*, 9675–9683.
20. Katritzky, A. R.; Akhmedov, N. G.; Ghiviriga, I.; Maimait, R. *J. Chem. Soc., Perkin Trans. 2* **2002**, *12*, 1986.
21. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; Butterworth-Heinemann: Oxford, 1996.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8817–8827
Tetrahedron

Synthesis and analysis of some adducts of 3,5-dinitrobenzamide

J. PrakashaReddy and V. R. Pedireddi*

Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Received 25 March 2004; revised 22 June 2004; accepted 15 July 2004

Available online 24 August 2004

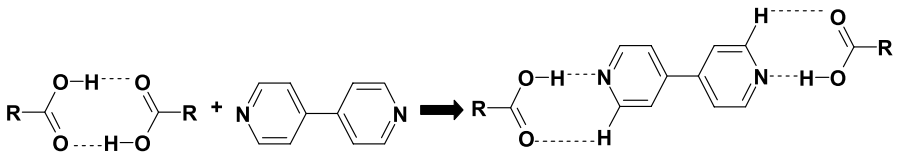
Abstract—Adducts of 3,5-dinitrobenzamide, **1**, with dimethylsulfoxide (DMSO), water and aza donor molecules like 4,4′-bipyridyl, **3**, 1,2-bis(4-pyridyl)ethene, **4** and 1,2-bis(4-pyridyl)ethane, **5** are reported. While DMSO adduct was obtained by crystallization of **1** from DMSO, all other adducts were obtained by co-crystallization of **1** with the respective substrates from CH_3OH, except the water adduct. The water adduct, however, was obtained during the co-crystallization of **1** with 4-chloro or 4-aminobenzamide, but not upon crystallization from water directly. The adducts of aza donor compounds, **3**–**5** crystallize as solvates, incorporating solvent of crystallization. All these adducts were characterized by single crystal X-ray diffraction methods. All the adducts crystallize in centrosymmetric space groups with the amide moiety forming cyclic hydrogen bonds.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Synthesis of supramolecular assemblies (also referred as adducts, co-crystals, molecular complexes) using a knowledge of intermolecular interactions, alternately noncovalent bonds[1,2] (for instance, hydrogen bonds), observed in a variety of crystal structures of both organic and organometallic compounds, has become a focal point for the synthesis of complex materials with tailor-made properties such as polymorphs,[3] host–guest systems,[4] self-assembled mono and multi layers,[5] pillared materials[6] etc. Systematic studies directed towards the analysis of topological arrangement of the noncovalent bonds in terms of building blocks (motifs, synthons, couplings etc.) facilitated the employment of successful strategies for the synthesis of targeted supramolecular assemblies.[2b,7,8] In fact, the synthesis proceeds through the reorganization or transformation of the building blocks present in the reactant structures.[9] For instance, insertion of aza aromatic molecules between acid molecules, as shown in Scheme 1, could be regarded as the transformation of centrosymmetric 8-membered O–H···O dimer into a 7-membered pair-wise hydrogen bonded dimer.[8a,10]

In a majority of instances, such processes yield desired and anticipated structural assemblies, as is evident from the reports on numerous assemblies in the recent literature.[1–10] Some organic functional groups, however, form more than one type of motif in practice. As a result, structural modifications depend upon the nature of the substrates employed to synthesize supramolecular assemblies.[11] For example, cyanuric acid, a cyclic imide, with two types of patterns (cyclic and acyclic) in its solid state structure,[12] forms different assemblies with DMSO and melamine as shown in Scheme 2. Thus, we are interested in evaluating the features of functional groups that are capable of forming different types of networks to utilize them in the synthesis of novel molecular complexes (adducts) by co-crystallization with different substrates.

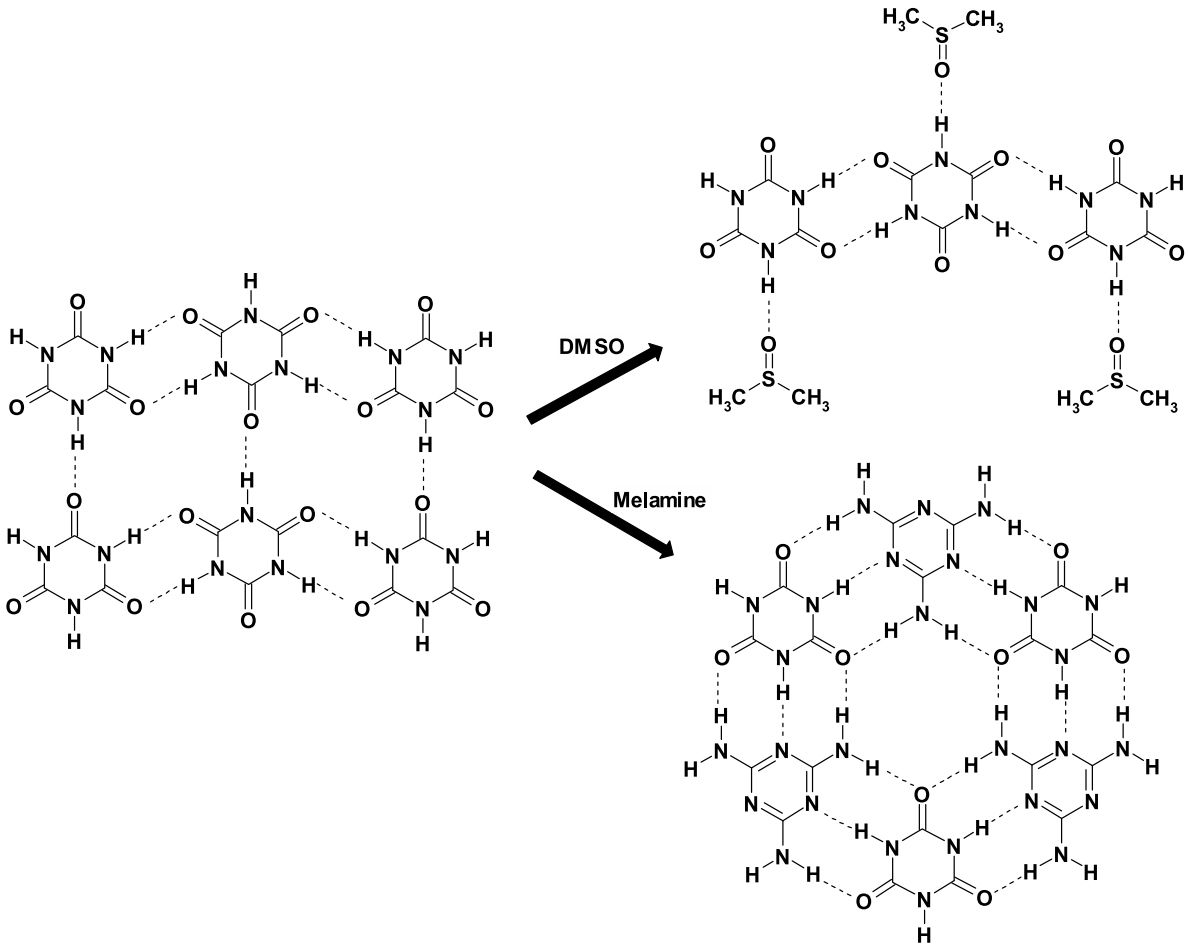
In this process, the amide ($-CONH_2$) group, which, in a way, is comparable to both imides and carboxylic acids with



Scheme 1. An adduct formation between the carboxylic acid and 4,4′-bipyridyl.

Keywords: 3,5-Dinitrobenzamide; Host–guest complexes; Channel structures; Layered structures.
* Corresponding author. Tel.: +91-20-2589-3300x2097; fax: +91-20-2589-3153; e-mail: pediredi@ems.ncl.res.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.039

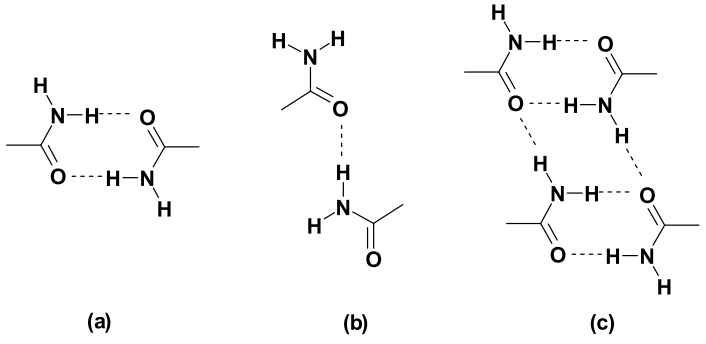


Scheme 2. Adducts of cyanuric acid with (a) DMSO and (b) melamine.

respect to the topology of the hydrogen bond patterns[13] and also forms different types of hydrogen bonding networks, dimers and catemers (see Scheme 3) has been chosen for its evaluation to form different types of adducts using both features of hydrogen bonding patterns (a) and (b).

For this purpose, our initial efforts of co-crystallization of aliphatic amides with 4,4′-bipyridyl to mimic the interaction between carboxylic acids and 4,4′-bipyridyl systems, did not yield any complexes, perhaps due to the incompatibility between the patterns in the reactants and products.[14] Hence, we focused our attention on aromatic amides, and in this respect we considered 3,5-dinitrobenzamide, **1**, as our main reactant to synthesize numerous supramolecular assemblies.

We initiated our studies with the determination of the crystal structure of **1**, as it was not known in the literature.[15] Based on the knowledge of the parent crystal structure,[16] we then chose various substrates to form supramolecular assemblies and the preliminary results with 4,4′-bipyridyl, **3**, were quite intriguing with the formation of adducts incorporating crystallization of solvent into the crystal lattice.[17] These results encouraged us to evaluate the ability of **1** to form different types of supramolecular assemblies including



Scheme 3. Different types of hydrogen bond motifs formed in amide compounds. (a) Cyclic (b) catemeric and (c) two-dimensional motif through the association of adjacent cyclic motifs.

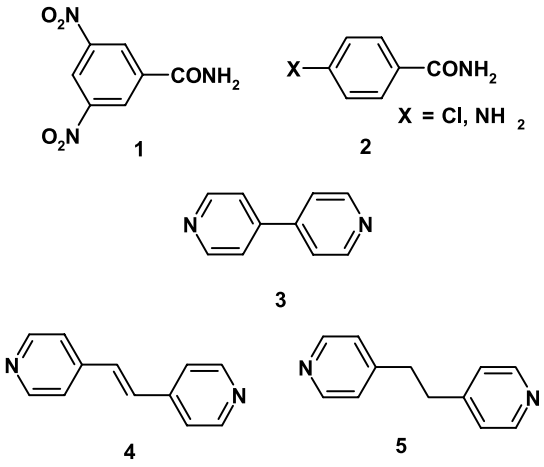


Chart 1.

Reactants	Solvent	Product and Composition	
1	dmso	1a	(1:1)
1	dmso	1b	(1:1)
1+2	methanol	1c	(4:1)
1+3	water	3a	(2:1:2)
1+3	methanol	3b	(2:1:2)
1+4	methanol	4a	(2:1:2)
1+4	water	4b	(2:2:2)
1+5	methanol	5a	(2:1:2)
1+5	water	5b	(1:1:1)

solvated structures. For this purpose, crystallization of **1** from various solvents and also co-crystallization with 1,2-bis(4-pyridyl)ethene, **4** and 1,2-bis(4-pyridyl)ethane, **5**, have been carried out. A detailed account of these results will be presented in this article (Chart 1).

2. Results and discussion

In the crystal structure of **1**[16] determined using crystals obtained from methanol, the dimers of amides that are formed by centrosymmetric N–H···O hydrogen bonds (H···O, 2.05 Å) are held together by the formation of single N–H···O hydrogen bonds (H···O, 2.17 Å), as shown in Figure 1, in contrast to the generally known dimeric association (Scheme 3(c)) except for the amides with bulky substituents.[18] This kind of unusual arrangement of intermolecular interactions, generally, facilitates the formation of polymorphs. Hence, we carried out crystallization of **1** from various solvents like benzene, ethylacetate, chloroform, dichloromethane, carbontetrachloride, etc. but all the crystals thus obtained gave a unit cell corresponding

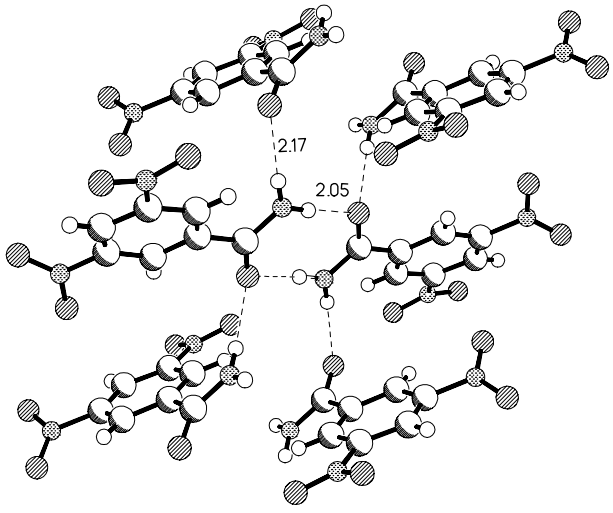
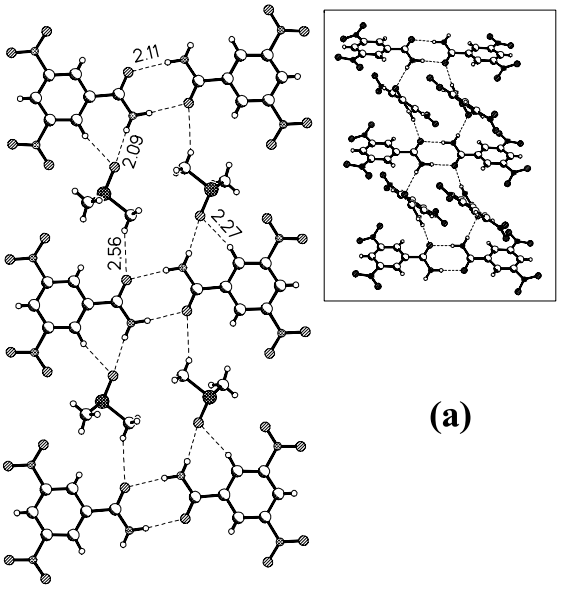


Figure 1. Arrangement of molecules of 3,5-dinitrobenzamide, **1**, in its crystal lattice.



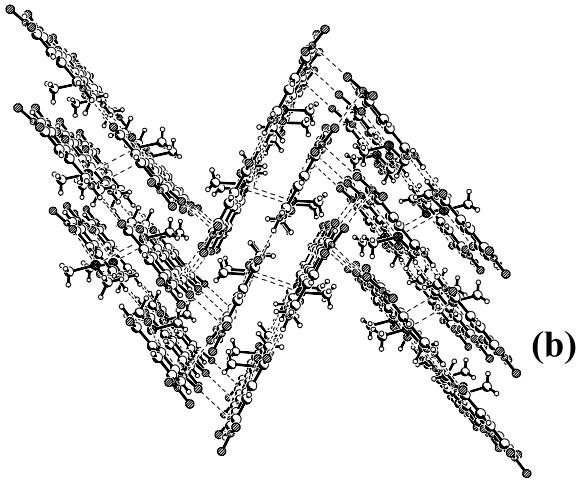


Figure 2. (a) Recognition pattern between amide, **1** and DMSO molecules and the arrangement of the molecules in the adduct, **1a**. (b) Three-dimensional packing of molecules in the adduct, **1a**.

to the form obtained from methanol. However, crystals from dimethylsulfoxide (DMSO), a highly polar solvent as well as hydrogen bond acceptor, gave a different unit cell.

2.1. Adducts of 3,5-dinitrobenzamide with DMSO and water

3,5-Dinitrobenzamide, **1** upon crystallization from a dimethylsulfoxide (DMSO) solution, yields rectangular plate shaped single crystals and the structure determination reveals that solvent of crystallization is also present in the crystal lattice. We labeled this compound as **1a**. The recognition pattern and interactions among the molecules in a two-dimensional arrangement are shown in Figure 2(a). Structure analysis discloses that, interaction between **1** and DMSO is established through a N–H···O hydrogen bond formed between *anti*-hydrogen atom of amide group and S═O group of DMSO with a H···O distance of 2.09 Å. Other characteristics of the hydrogen bonds are listed in Table 2. The adjacent molecules of **1** interact with each other forming a 8-membered cyclic network mediated by N–H···O hydrogen bonds. The H···O distance is 2.11 Å with an N–H···O angle of 174° (Table 2). In fact, this arrangement shows a close relationship to the parent crystal structure of **1**[16] with the replacement of molecules of **1** related by pseudo-glide symmetry with DMSO molecules. For comparison purposes, the packing of molecules in **1** is shown as an inset in Figure 2(a). In the three-dimensional packing, the adduct, **1a**, yield a herringbone structure as shown in Figure 2(b). In addition, the DMSO molecules also form C–H···O hydrogen bonds (H···O, 2.27, 2.56 Å) with the molecules of **1**.

In our further efforts to compare **1a** with the other related adducts of DMSO known in the literature, it has been noted that DMSO molecules exist in a disordered form in some of the adducts (for example, adduct of cyanuric acid and DMSO[12]). Hence, we have performed a search on the Cambridge Structural Database (CSD),[15] using version 5.24, to find the probability of the occurrences of the two forms of DMSO in the crystal lattices.

The search retrieved a total of 229 organic compounds with DMSO in their crystal lattices with a majority of structures (158 compounds) possessing ordered DMSO molecules. In the remaining structures, 45 compounds have disordered DMSO molecules and 26 compounds have both ordered and disordered DMSO molecules within a crystal lattice. However, one compound, 1,1′-binaphthyl-2,2′-bicarboxylic acid,[19] has been found to have two crystal structures (Refcodes: CIWJEX01,[19] CIWJEX10[20]) possessing exclusively either an ordered or a disordered DMSO

Table 1. Crystallographic data of adducts **1a**-**1c**, **4a**, **4b**, **5a** and **5b**

	1a	1b	1c	4a	4b	5a	5b
Formula	$C_7H_5N_3O_5$: $C_2H_6O_1S_1$	$C_7H_5N_3O_5$: $C_2H_6O_1S_1$	4($C_7H_5N_3O_5$): (H_2O)	2($C_7H_5N_3O_5$): ($C_{12}H_{10}N_2$): 2($C_1H_4O_1$)	2($C_7H_5N_3O_5$): 2($C_{12}H_{10}N_2$): 2(H_2O)	2($C_7H_5N_3O_5$): ($C_{12}H_{12}N_2$): 2($C_1H_4O_1$)	$C_7H_5N_3O_5$: $C_{12}H_{12}N_2$: H_20
Fw	289.27	289.27	860.56	334.29	822.75	335.30	390.39
Crystal shape		needles	blocks	Blocks		blocks	
Crystal color	colorless	colorless	colorless	colorless	colorless	colorless	colorless
Crystal system	monoclinic	monoclinic	tetragonal	triclinic	triclinic	triclinic	triclinic
Space group	$P2_1/c$	$P2_1/c$	$P4_2/n$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	10.720(2)	10.874(1)	17.217(5)	7.319(3)	7.240(2)	6.946(1)	7.592(1)
b (Å)	19.642(4)	6.243(1)	17.217(5)	7.625(4)	13.294(1)	7.832(2)	9.965(1)
c (Å)	5.952(1)	18.915(3)	5.999(3)	14.420(7)	20.483(2)	14.764(1)	13.927(2)
α (deg)	90	90	90	76.32(1)	75.65(1)	83.97(1)	76.45(1)
β (deg)	94.37(1)	94.72(1)	90	75.85(1)	85.19(1)	76.50(1)	75.55(1)
γ (deg)	90	90	90	75.03(1)	84.16(1)	79.28(1)	72.42(1)
V (Å^3)	1249.6(4)	1279.7(3)	1778.3(12)	740.8(6)	1896.5(2)	765.8(5)	958.1(5)
Z	4	4	2	2	2	2	2
D_{calc} (g cm^{-3})	1.538	1.501	1.607	1.499	1.441	1.454	1.433
T (K)	293	293	293	133	293	133	293
Mo Kα	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
μ (mm^{-1})	0.287	0.280	0.141	0.120	0.110	0.116	0.109
2θ range (deg)	46.54	46.48	46.44	46.66	46.58	46.76	46.56
Limiting indices	$-9\le h\le 11$ $-21\le k\le 19$ $-6\le l\le 6$	$-10\le h\le 12$ $-6\le k\le 6$ $-20\le l\le 20$	$-19\le h\le 7$ $-18\le k\le 16$ $-6\le l\le 6$	$-8\le h\le 8$ $-8\le k\le 8$ $-16\le l\le 16$	$-7\le h\le 8$ $-14\le k\le 14$ $-22\le l\le 21$	$-7\le h\le 7$ $-8\le k\le 8$ $-16\le l\le 16$	$-8\le h\le 8$ $-11\le k\le 11$ $-15\le l\le 15$
F(000)	600	600	880	348	856	350	432
No. reflns measured	5344	5242	3442	6082	8259	6198	7764
No. unique reflns [R(int)]	1794 [0.0256]	1819 [0.0414]	1274[0.0452]	2133 [0.0212]	5393 [0.0305]	2211 [0.0270]	2746 [0.0205]
No. reflns used	1584	1157	1023	1958	3194	1963	2686
No. parameters	216	226	150	273	677	278	347
parameter/ parameter	8.30	8.05	8.49	7.81	7.97	7.95	7.91
GOF on F^2	1.058	0.845	1.242	1.063	1.000	1.707	1.178
$R1[I>2\sigma(I)]$	0.0511	0.0466	0.0608	0.0362	0.0540	0.0582	0.0393
wR2	0.1369	0.1166	0.1630	0.0999	0.1141	0.1879	0.1000
Final diff. Fourier map (e$^-$ Å^{-3}) max, min	0.95, −0.24	0.19, −0.13	0.69, −0.23	0.25, −0.21	0.25, −0.20	0.70, −0.27	0.31, −0.31

molecule. Interestingly, these two modifications were reported to be obtained by varying the temperature of crystallization process, with the ordered structure obtained at room temperature and the disordered structure at high temperature (50 °C). This has encouraged us to carry out crystallization of **1** in the presence of DMSO at high temperature also.

2.1.1. Form II of 3,5-dinitrobenzamide and DMSO, 1b. Crystallization of **1**, from DMSO, by warming on a water bath for about 40 min and subsequently cooling to ambient temperature and allowing for slow-evaporation, gave single crystals of long needle shaped geometry, which we labeled as **1b**.

The unit cell determination gave cell parameters which are different from that of **1a**, (Table 1). Hence, we proceeded further with the crystal structure determination and found that in **1b**, DMSO molecules are disordered as anticipated. The asymmetric unit of **1b** is shown in Figure 3(a) along with the ordered DMSO structure, **1a** (Figure 3(b)).

Packing analysis reveals that **1a** and **1b**, indeed, are identical in all the aspects of two- and three-dimensional arrangements except for the length of the hydrogen bonds. It is apparent from Figures 2(a) and 4 that molecules in **1b** are more densely packed than in **1a** as similar hydrogen bonds are formed with shorter distances (Table 2) in **1b** than in **1a**. For example, the N–H···O hydrogen bond that holds **1** and DMSO molecules is 1.99 Å in **1b**, whereas it is 2.09 Å in **1a**. Similarly, the N–H···O hydrogen bond in the centrosymmetric coupling is 2.00 Å, but this distance in **1a** is 2.11 Å (Table 2).

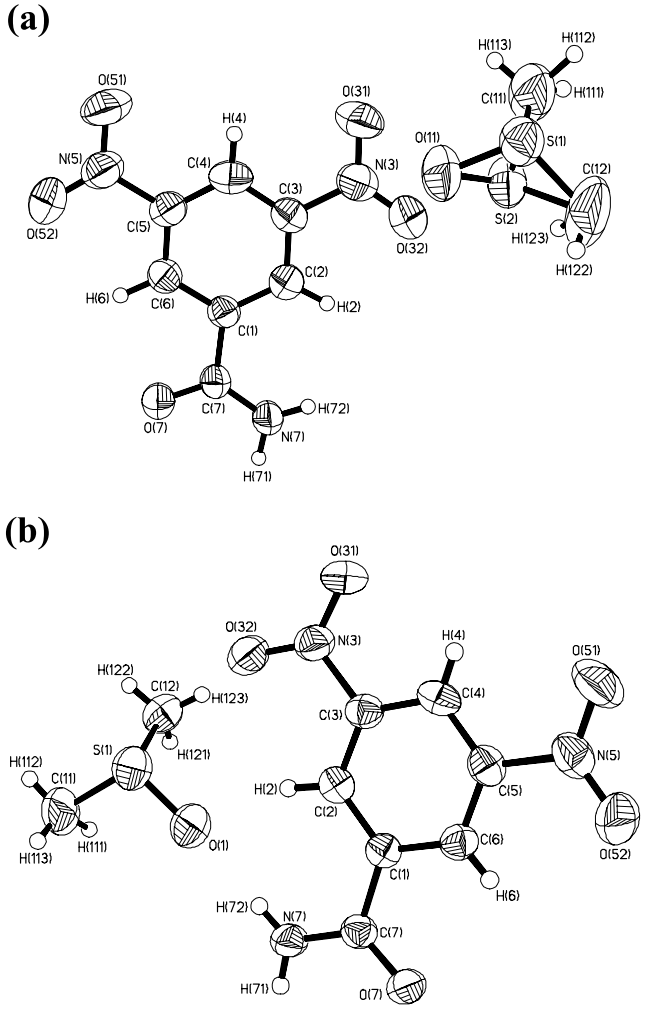


Figure 3. (a) ORTEP drawing of adduct **1b** showing disordered DMSO molecules against the ordered molecules found in the adduct, **1a** as shown in (b).

Thus, establishing the affinity of the anti-hydrogen atom of the amide moiety of **1** to form adducts with hydrogen bond receptors, we carried out crystallization of **1** from solvents like dimethylformamide and dimethylamine, which possess hydrogen bond donor/acceptor groups. However, none of these solvents gave any adducts, except pure crystals of **1**. Nevertheless, our attempts to co-crystallize **1** with various substrates, as discussed in the later sections, co-crystallisation of **1** with 4-chloro or 4-aminobenzamides, from a CH_3OH solution, a water adduct of **1** was obtained instead of molecular adducts with the substrates employed. In fact, water was not present in the reaction medium but was absorbed from the atmosphere, which is a well-known process in many crystallization studies. Further, it is more surprising to note that, the water adduct could not be synthesized by crystallization of **1** directly from water.

2.1.2. 3,5-Dinitrobenzamide and water, 1c. Analysis of crystal data discloses that **1** and water molecules are in a 4:1 molar ratio in the adduct **1c** and crystallizes in a higher symmetry space group, $P4_2/n$ (tetragonal lattice, Table 1). Packing analysis reveals several exciting features.

The adduct **1c** forms a channel structure as shown in Figure 5(a). Analysis of each channel reveals that they are octagonal in nature, rather than the usually observed hexagonal channels in organic structures.[21] In each octagon, as shown in Figure 5(b), the amide molecules form centrosymmetric dimers held together by N–H···O hydrogen bonds with an H···O distance of 2.05 Å (Table 2). Four such dimers are held together by C–H···O hydrogen bonds

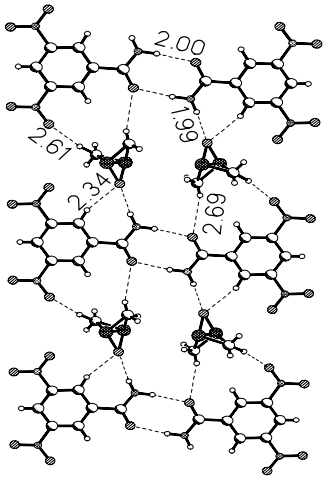


Figure 4. Arrangement of molecules of amide, **1** and disordered DMSO in the crystal structure of adduct, **1b**. Compare with Figure 2(a) for similarity between ordered and disordered structures along with parent structure of amide, **1**.

Table 2. Characteristics of hydrogen bonds (distances, Å and angles, deg)[a]

Hydrogen bonds	1a	1b	1c	4a	4b	5a	5b
O–H···N				1.85 2.77 170.9	1.78 2.81 170.0 2.05 2.88 167.1 2.10 3.03 166.8	1.74 2.76 168.2	2.01 2.89 164.3 2.08 2.93 158.3
N–H···O	2.09 2.87 164.5 2.11 2.96 174.1	1.99 2.84 170.8 2.00 2.92 171.8	2.05 2.90 169.8	1.99 2.82 157.3 2.11 2.99 170.4	1.96 2.89 171.4 1.99 2.93 177.4 2.03 2.95 172.4 2.11 3.01 170.7	1.97 2.82 156.0 2.04 2.95 176.8	1.91 2.84 178.1 1.95 2.86 171.9
C–H···O	2.27 3.18 164.7 2.56 3.35 154.5 2.83 3.57 147.5 2.89 3.73 163.0	2.34 3.24 161.7 2.61 3.76 169.4 2.69 3.43 152.3	2.52 3.44 171.7	2.31 3.28 164.8 2.42 3.38 169.2 2.56 3.47 170.5 2.56 3.48 173.9 2.61 3.46 158.9 2.69 3.59 161.8 2.73 3.57 154.5 3.00 3.64 123.6	2.39 3.28 160.4 2.45 3.26 159.0 2.45 3.30 149.5 2.49 3.39 167.7 2.61 3.65 176.6 2.63 3.64 165.1 2.64 3.51 161.3 2.68 3.59 163.7 2.75 3.60 154.2 2.76 3.60 152.2 2.77 3.69 164.1 2.79 3.66 147.8 2.82 3.62 144.3 2.83 3.67 158.6 2.89 3.72 145.3	2.36 3.27 154.0 2.50 3.38 169.1 2.60 3.47 144.4 2.65 3.48 159.4 2.68 3.67 149.3 2.73 3.64 164.7 2.82 3.70 150.9 2.86 3.58 117.3	2.39 3.28 155.2 2.48 3.34 148.4 2.53 3.48 176.1 2.56 3.44 156.5 2.58 3.39 146.0 2.63 3.47 151.0 2.68 3.56 156.2 2.98 3.47 114.2
C–H···N					2.55 3.49 174.2 2.79 3.64 161.1	2.90 3.85 177.6	2.81 3.70 168.3 2.94 3.77 147.2

[a] The three numbers in each column represent H···O(N), O(N/C)···O(N) and angles, respectively.

(H···O, 2.52 Å) constituting octagonal cavities, which are being filled by water molecules. The adjacent octagons are held together by C–H···O hydrogen bonds (H···O, 2.52 Å) to yield two-dimensional sheets. These sheets, in turn, are stacked through π–π interactions and form three-dimensional structure with channels. Interestingly, the water molecules do not have any interaction with the host molecules, as the interaction between the O atoms of water and $–NO_2$ groups (protruded into the channel) is 3.48 Å (see Figure 5(b)).

It suggests that **1** may also be a potential host to accommodate large guest species provided the channel dimension is increased. Taking into account the versatility of 4,4′-bipyridine, **3**, as a spacer ligand in the molecular complexes of benzoic acid derivatives, we targeted the synthesis of a molecular complex between **1** and **3** envisaging formation of large channels with the insertion of **3** between the amide molecules related by inversion symmetry by forming N–H···N hydrogen bonds.[22]

2.2. Adducts of 3,5-dinitrobenzamide, 1 with aza-donor compounds

Co-crystallization of **1** with 4,4′-bipyridyl, **3**, from water, gave a complex, **3a** forming a three-dimensional channel structures as shown in Figure 6(a).[17] However, in contrast to our expectations, the molecules of **3** were inserted as guest molecules in the host lattice formed by **1** in association with water molecules rather than being involved in enhancement of the channel dimensions. In fact, a similar arrangement was observed in complex, **3b** (Figure 6(b)) obtained by crystallization of **1** and **3** from methanol.[17] Complexes **3a** and **3b** are iso-structural except for the solvent of crystallization. Also, it is worth mentioning that topology of the host-network is different around the channels in both the complexes with planar sheets and helical arrangement in **3a** and **3b**, respectively (Figure 7).

Encouraged by the unusual structural features of **1**, observed in the complexes **3a** and **3b**, further experiments were carried out to rationalize its host features by co-crystallizing with 1,2-bis(4-pyridyl)ethene, **4** and 1,2-bis(4-pyridyl)-ethane, **5**. These results are described in the following sections.

2.2.1. 3,5-Dinitrobenzamide and 1,2-bis(4-pyridyl)-ethene from methanol, 4a. Co-crystallization of **1** and bipyridyl, **4** from a methanol solution gave single crystals in a 2:1 composition along with the solvent of crystallization in the asymmetric unit (Table 1). The packing analysis reveals that the three-dimensional structure (Figure 8(a)) is due to the stacking of two-dimensional planar sheets. The arrangement of the molecules in a typical sheet is shown in Figure 8(b).

The molecules of **1** form the centrosymmetric cyclic hydrogen bond (H···O, 2.11 Å), while the methanol molecules interact with it through a N–H···O hydrogen bond (H···O, 1.99 Å, Table 2). This assembly further interacts with the adjacent units by forming centrosymmetric cyclic C–H···O hydrogen bonds (H···O, 2.56 Å) between the amide dimers and acyclic C–H···O hydrogen bonds (H···O, 2.31, 3.00 Å) between methanol and $–NO_2$ groups, thus leading to the formation of a cavity, which is filled by the molecules of **4**. The bipyridyl molecules interact with the host network through the formation of O–H···N hydrogen bonds (H···N, 1.85 Å) with the methanol molecules. This ensemble forms channels due to the stacking of sheets along a crystallographic axis (Figure 8(c)).

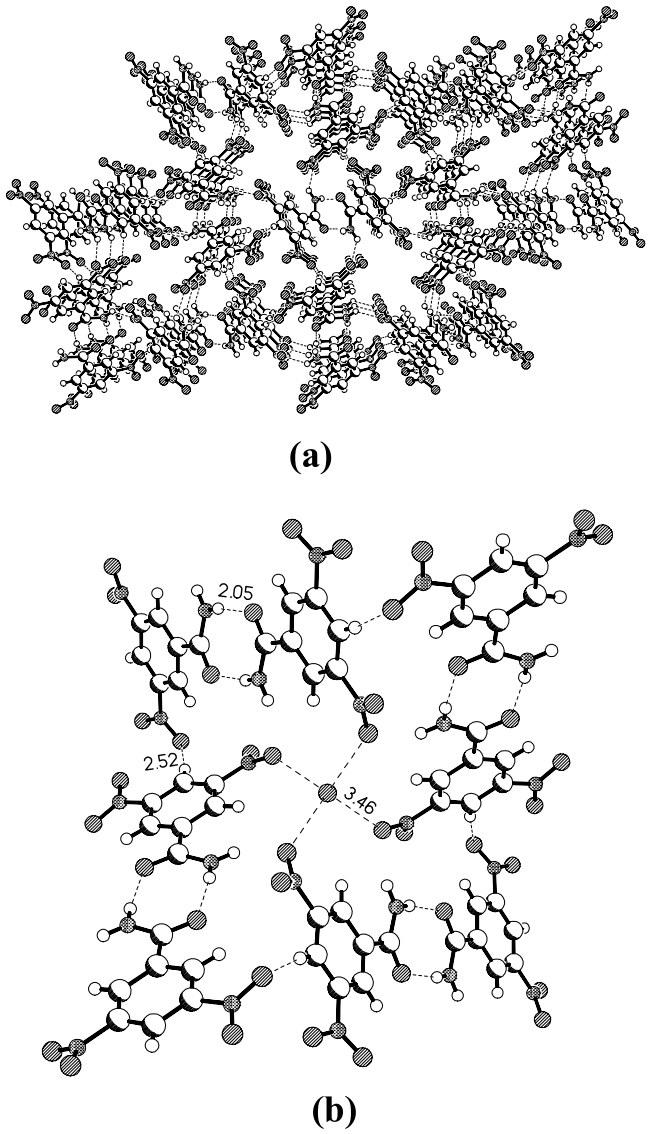


Figure 5. (a) Three-dimensional view of channels observed in the adduct **1c**. (b) Packing of molecules constituting octagonal channels in the adduct **1c**.

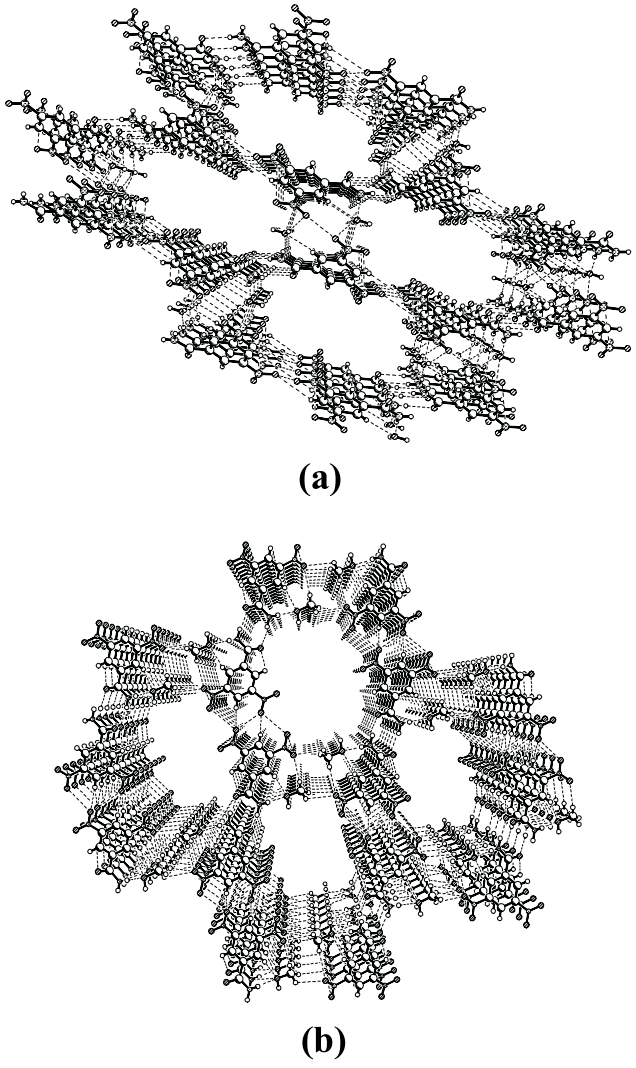


Figure 6. Channel structures observed in the adducts, **3a** (a) and **3b** (b). Guest molecules are removed for the purpose of clear vision of the channels.

2.2.2. 3,5-Dinitrobenzamide and 1,2-bis(4-pyridyl)-ethene from water, 4b. In the molecular complex, **4b**, the constituent compounds **1** and **4** co-crystallize in a 1:1 molar ratio with two molecules each in the asymmetric unit. We labeled the molecules of **1** as A and B whereas molecules of **4** as C and D. The interaction among the molecules and recognition pattern between the constituents is shown in Figure 9(a).

It is apparent from the molecular packing analysis that both the molecules of **1** (A and B) interact with each other through the generally known centrosymmetric cyclic motifs in amide compounds. The hydrogen bond distances are 1.96 and 1.99 Å. Surprisingly, the recognition, between **1** and **4**, occurs through pyridyl nitrogen, $-NO_2$ groups and phenyl hydrogens, without the involvement of amide functionality. As a result, a unique recognition pattern is evolved with three hydrogen bonds, as shown in Scheme 4, consisting of two C–H···O and one C–H···N hydrogen bonds. The other related motifs, known in the literature, consist either of

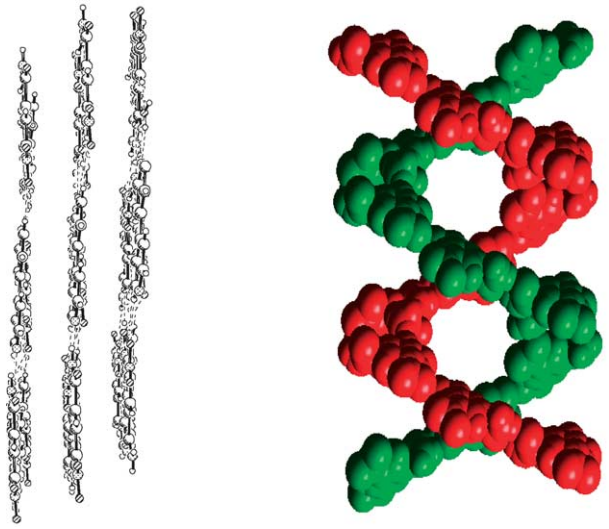


Figure 7. Packing arrangement of the molecules around the channels in **3a** (left) and **3b** (right).

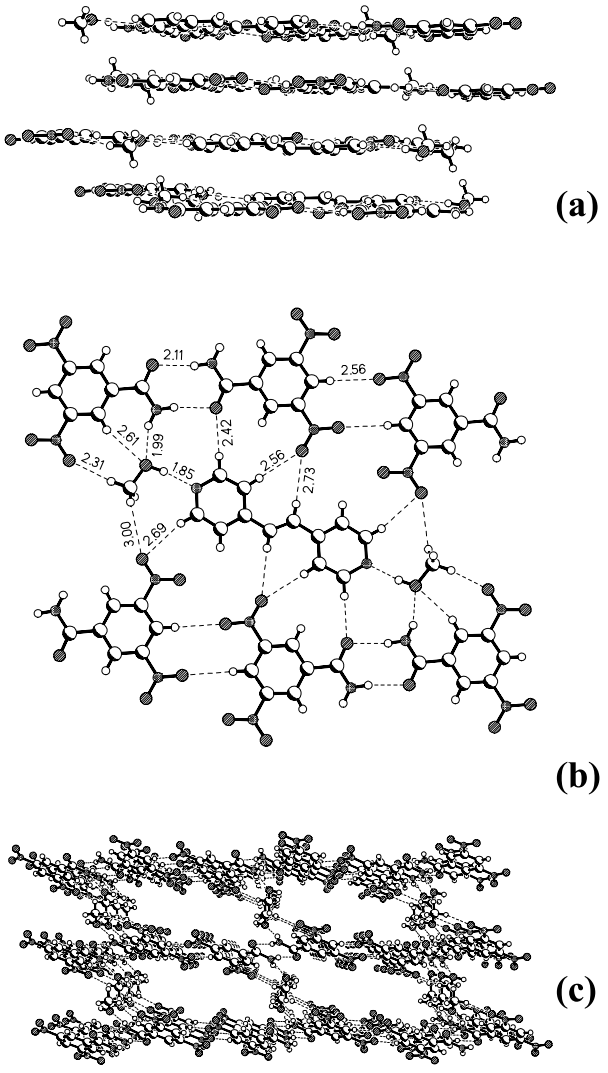


Figure 8. (a) Stacking of the two-dimensional sheets. (b) Two-dimensional arrangement of constituent molecules **1** and **4** in the crystal structure of **4a**. Notice the formation of host network by amide and methanol molecules forming a cavity, which is occupied by the molecules of **4**. (c) Projection of three-dimensional packing showing the channels. Guest molecules have been omitted.

strong hydrogen bonds (for example, cyanuric acid and melamine complex,[4a,23] Scheme 2(b)) or a combination of weak and strong hydrogen bonds (for example, a molecular complex of N-methylcyanuric acid and 9-ethyladenine[24]). However, in complex, **4b**, all the hydrogen bonds in the recognition pattern are weak hydrogen bonds. Another interesting feature is that only one of the pyridyl nitrogens of **4** is involved in this unique pattern, while the other nitrogen is attached to a water molecule through O–H···N hydrogen bond with an H···N distance of 1.78 Å (Table 2).

Thus, in the two-dimensional arrangement, a supermolecule, comprising of four molecules (two from each **1** and **4**), is established, which are shown by straight lines in Figure 9(a). Such adjacent supermolecules interact with each other through water molecules by forming N–H···O hydrogen bonds (H···O, 2.03 and 2.11 Å). In addition, the interaction between the supermolecules is further strengthened by C–H···O hydrogen bonds (H···O range

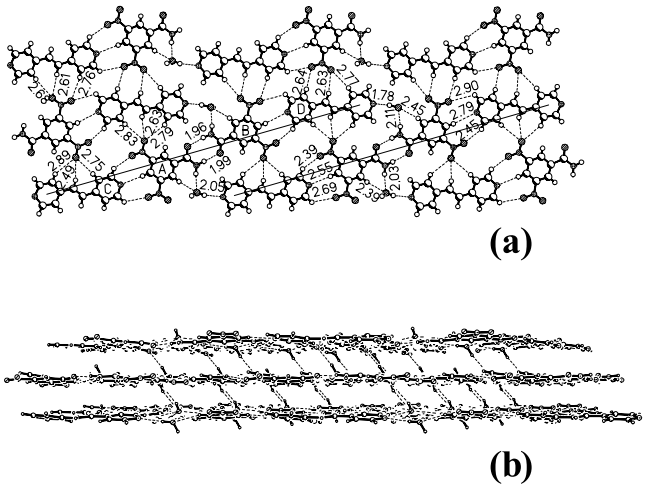


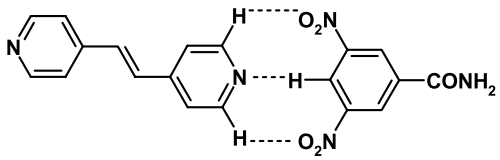
Figure 9. (a) Two-dimensional arrangement of molecules in the crystal structure of **4b**. Lines across the molecules show the basic supermolecules formed between the constituent molecules **1** and **4**. (b) Stacking of the two-dimensional sheets.

2.49–2.89 Å), formed between the $-NO_2$ groups and hydrogen atoms of ethene and aromatic moieties. These two-dimensional sheets stack to yield three-dimensional structure stabilized by O–H···N hydrogen bonds (H···N, 2.10 Å), formed by water molecules, as well as π–π interaction (3. 36 Å), as shown in Figure 9(b).

2.2.3. 3,5-Dinitrobenzamide and 1,2-bis(4-pyridyl)-ethane from methanol, 5a. Crystallization of **1** and 1,2-bis(4-pyridyl)ethane, **5** gave co-crystals, **5a** along with the solvent of crystallization, methanol, in the crystal lattice. The two-dimensional arrangement of molecules and formation of channels are shown in Figure 10. Comparison of Figures 8 and 10 reveals that **5a** is iso-structural with **4a** in all respects except for the length of the hydrogen bonds.

2.2.4. 3,5-Dinitrobenzamide and 1,2-bis(4-pyridyl)-ethane from water, 5b. Molecular complex, **5b** is identical to that of **4b** in almost all the aspects including the recognition pattern between the constituents and the formation of supermolecules, except the number of molecules in the asymmetric unit. **5b** is a 1:1 complex with only one molecule of each reactant in the asymmetric unit. As a result, all the molecules are related to each other by an appropriate symmetry. The arrangement of molecules is shown in Figure 11 and straight lines joining the individual molecules represent each supermolecule.

However, **4b** and **5b** differ with respect to the interaction between the supermolecules. The adjacent supermolecules in **5b** are connected together by centrosymmetric cyclic C–H···N hydrogen bonds, with an H···N distance of 2.94 Å (Table 2). As a consequence of this, the supermolecules



Scheme 4. A new triplet supramolecular recognition pattern.

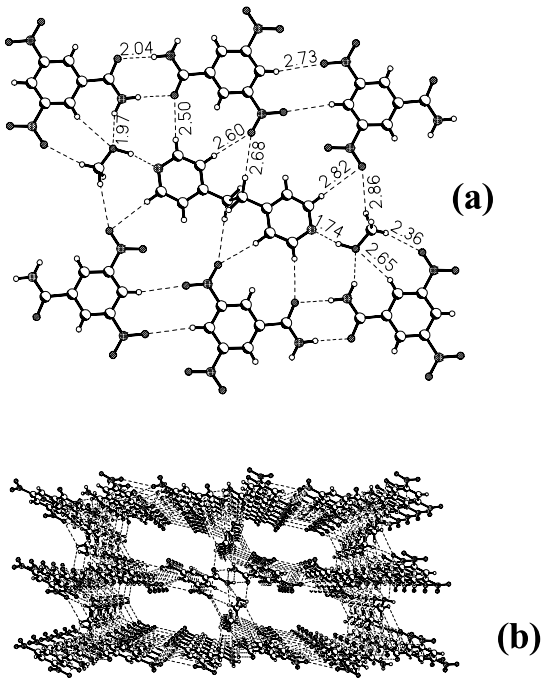


Figure 10. (a) Two-dimensional arrangement of constituent molecules **1** and **5** in the crystal structure of **5a**. Notice the formation of a host network by amide and methanol molecules forming a cavity, which is occupied by the molecules of **5**. (b) Projection of three-dimensional packing showing the channels. Guest molecules have been omitted.

constitute infinite molecular tapes. The adjacent tapes in two-dimensional arrangement are held together by C–H···O hydrogen bonds formed between $-NO_2$ groups and aromatic hydrogen atoms. These two-dimensional sheets further stack to yield a three-dimensional crystal structure, stabilized by O–H···N hydrogen bonds (H···N, 2.08 Å, Table 2) and π–π interactions in the same manner to that observed in **4b**. The three-dimensional arrangement is shown in Figure 11(b).

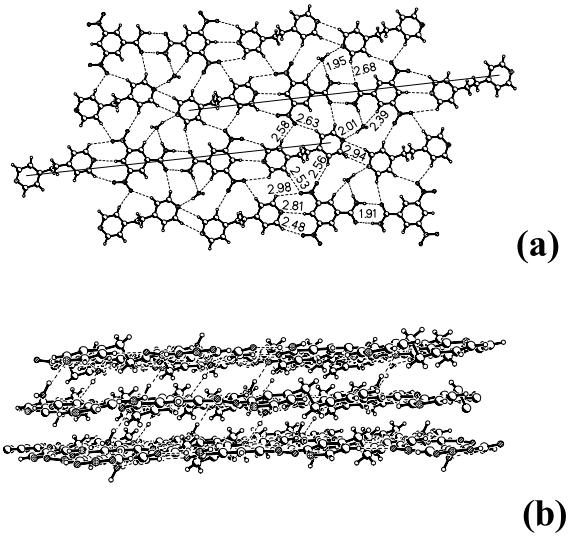


Figure 11. (a) Arrangement of molecules of **1** and **5** in the crystal structure of **5b**. Notice the C–H···N hydrogen bond dimers between the adjacent supermolecules unlike in the **4b**. (b) Three-dimensional arrangement obtained by the stacking of the planar sheets. Dashed lines between sheets are O–H···N hydrogen bonds formed by water molecules.

2.3. Comparison of complexes 4a, 4b, 5a and 5b

It is apparent from the description of the structural features of **4a**, **4b**, **5a** and **5b** that, the structures possessing the same solvent of crystallization (**4a** and **5a**; **4b** and **5b**) are isostructural rather than structures with the same bipyridyl molecules (**4a** and **4b**; **5a** and **5b**). This feature, in fact, supports the involvement of solvent molecules within the host frame-work for the creation of a fixed void space to accommodate appropriate guest molecules. Hence, CH_3OH, which is bigger in dimension than H_2O, able to create the required space to accommodate **4** and **5** in **4a** and **5a**, respectively. Another, noteworthy feature is the formation of different types of interactions by the pyridyl nitrogens of **4** and **5**, despite being the same, chemically. For example, in **4a** and **5a**, both the pyridyl nitrogen atoms of **4** and **5** form same type of O–H···N hydrogen bonds (Figs. 8(a) and 10(a)) with CH_3OH molecules, whereas in **4b** and **5b**, each pyridyl nitrogen atom have different interactions (Figs. 9(b) and 11(b)), with one of them forming O–H···N hydrogen bond with water molecule and the other one forming a triplet recognition pattern (Scheme 4) with molecules of **1**. Further, in none of these structures, interaction between the amide group and aza group is observed, and the centrosymmetric N–H···O hydrogen bonded motif of amide moiety is always retained.

In conclusion, we have reported the synthesis of various adducts of 3,5-dinitrobenzamide, **1**, by co-crystallizing it with different substrates. In this study, we have mainly observed that the amide moiety of **1** has always shown preference to form dimeric unit and its anti hydrogen atom is associated with a solvent molecule (DMSO in **1a** and **1b**; H_2O in **3a**, **4b** and **5b**) CH_3OH in **3b**, **4a** and **5a**). It is noteworthy to mention an intriguing feature that in none of the complexes **4a**, **4b**, **5a** and **5b**, aza donor compounds, did participate as spacer ligand as observed in the molecular complexes of acids. It is further interesting to note that the channel dimensions are tuned with the aid of the solvent of crystallization to accommodate the guest molecules unlike other known host–guest complexes, wherein this feature is totally dominated by the nature of host compound alone. Thus, several host–guest type complexes could be synthesized with **1** by choosing appropriate solvent in accordance with the dimension of the guest molecule.

3. Experimental

3.1. Synthesis of molecular adducts

All the chemicals used in this study were obtained commercially and used as such without any further purification. HPLC grade solvents were used for the recrystallization/co-crystallization experiments. The synthesis of co-crystals was carried out, by dissolving the reactants in the appropriate solvents either at room temperature or by warming on a water bath and subsequently cooling by a slow-evaporation method. In a typical experiment, 50 mg (0.5 mmol) of 3,5-dinitrobenzamide and 90 mg (0.5 mmol) of 1,2-bis(4-pyridyl)ethene were dissolved in a methanol solution at the boiling temperature of methanol and then

subsequently cooled to room temperature. Colorless rectangular block shaped single crystals of good quality were obtained over a period of 3 days and were used for X-ray diffraction studies.

3.2. Crystal structure determination by X-ray diffraction methods

Good quality single crystals of adducts (**1a**-**1c**, **4a** **4b**, **5a** and **5b**) of 3,5-dinitrobenzamide have been carefully selected looking under a polarized Leica microscope equipped with CCD camera and glued to a glass fiber using an adhesive (cyano acrylate). In all the cases, the crystals were smeared in the adhesive solution to prevent decay of crystals due to solvent evaporation or direct exposure to ambient atmosphere. The intensity data were collected on a Bruker single crystal X-ray diffractometer, equipped with an APEX detector, at room temperature (293 K), except for **4a** and **5a**, which were collected at the temperature 133 K due to the instability of the crystals. Subsequently, the data were processed using Bruker suite of programmes (SAINT[25]) and the convergence was found to be satisfactory with good R_{ini} parameters. The details of the data collection and crystallographic information are given in Table 1. The structure determination by direct methods and refinements by least-squares methods on F^2 were performed using SHELXTL-PLUS[25] package. The processes were so smooth without any complications. All non-hydrogen atoms were refined anisotropically. The hydrogen atom positions were taken from a difference Fourier maps and were refined isotropically. All the intermolecular interactions were computed using PLATON.[26] Full details of crystallographic information are deposited at Crystallographic Data Centre as supplementary publication (CCDC 234371-234377 for **1a**-**1c**, **4a**, **4b**, **5a** and **5b**, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk].

4. Supplementary data

A total of 83 pages, X-ray data with the details of refinement procedures (cif files), ORTEP diagrams, lists of bonding parameters (bond lengths and angles), structure factors of molecular complexes **1a**-**1c**, **4a**, **4b**, **5a** and **5b** and a table of refcodes of CSD analysis of DMSO structures. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2004.07.039.

Acknowledgements

We thank Department of Science and Technology, New Delhi for the financial assistance. Also, we thank Dr. S. Sivaram, Director, NCL, and Dr. K. N. Ganesh, Head of the Division, NCL for their encouragement. One of us (J. P.) thanks CSIR for the award of a Junior Research Fellowship (JRF).

References and notes

1. (a) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*. Elsevier: Amsterdam, 1989. (b) *Crystal Design: Structure and Function.* Desiraju, G. R., Ed.; Wiley: New York, 2003. (c) Desiraju, G. R. *Nature* **2001**, *412*, 397–400. (d) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*. VCH: Weinheim, 1995. (e) Comprehensive Supramolecular Chemistry; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vogtle, F., Lehn, J.-M., Eds.; Pergamon: Oxford, 1996; Vol. 6. (f) *Comprehensive Supramolecular Chemistry, Solid-State Supramolecular Chemistry: Crystal Engineering*; MacNicol, D. D., Toda, F., Bishop, R., Eds.; Pergamon: New York, 1996; Vol. 6.
2. (a) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D. N.; Mammen, M.; Gordon, D. M. *Acc. Chem. Res.* **1995**, 28, 37–44. (b) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, 94, 2383–2420. (c) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999.
3. (a) Bernstein, J. *Polymorphism in Molecular Crystals*; Oxford University Press: New York, 2002. (b) Pedireddi, V. R. *Cryst. Eng. Commun.* **2001**, 15, 1–3. (c) McCrone, W. C. *Polymorphism in Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Eds.; Interscience: New York; Vol. 2, 1965. (d) Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res.* **1995**, 28, 193–200. (e) Brittain, H. G. *Polymorphism in Pharmaceutical Solids*; Marcel Dekker Inc.: New York, 1999. (f) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid State Chemistry of Drugs*, 2nd ed.; SSCI Inc.: West Lafayette, IN, 1999; pp 489–498. (g) Threlfall, T. L. *Analyst* **1995**, 120, 2435–2460. (h) Kumar, V. S. S.; Addlagatta, A.; Nangia, A.; Robinson, W. T.; Broder, C. K.; Mondal, R.; Evans, I. R.; Howard, J. A. K.; Allen, F. H. *Angew. Chem., Int. Ed.* **2002**, 41, 3848–3851. (i) Jetti, R. K. R.; Boese, R.; Sarma, J. A. R. P.; Reddy, L. S.; Vishweshwar, P.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2003**, 42, 1963–1967. (j) Henck, J.-O.; Bernstein, J.; Ellern, A.; Boese, R. *J. Am. Chem. Soc.* **2001**, 123, 1834–1841.
4. (a) Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A.; Rao, C. N. R. *J. Am. Chem. Soc.* **1997**, *119*, 10867–10868. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018–1033. (c) Swift, J. A.; Pivovar, A. M.; Reynolds, A. M.; Ward, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 5887–5894. (d) Endo, K.; Ezuhara, T.; Koyanagi, M.; Masuda, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1997**, *119*, 499–505. (e) Pedireddi, V. R.; Jones, W.; Charlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 987–988. (f) *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. D., Eds.; Academic London, 1984; Vols. 2 and 3. (g) Hollingsworth, M. D.; Harris, K. D. M.; Jones, W.; Thomas, J. *J. Inclusion Phenom.* **1987**, *5*, 273–277. (h) Pedireddi, V. R. *Cryst. Growth Des.* **2001**, *1*, 383–385. (i) Hagrman, P. J.; Hagrman, D.; Zubieta, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2639–2684. (j) Nangia, A. *Curr. Opin. Solid State Mater. Sci.* **2001**, *5*, 115–122.
5. (a) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533–1554. (b) Hofer, R.; Textor, M.; Spencer, N. D. *Langmuir* **2001**, *17*, 4014–4020. (c) Bonhote, P.; Moser, J.-E.; Humphry-Baker, R.; Vlachopoulos, N.; Zakeeruddin, S. M.; Walder, L.; Graetzel, M. *J. Am. Chem. Soc.* **1999**, *121*, 1324–1336. (d) Addadi, L.; Moradian, J.; Shay, E.; Maroudas, N. G.; Weiner, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2732–2736. (e) Raz, S.; Weiner, S.; Addadi, L. *Adv. Mater.* **2000**, *12*, 38–42.

(f) Laibinis, P. E.; Whitesides, G. M.; Allara, D. L.; Tao, Y. T.; Parikh, A. N.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7152–7167. (g) Brown, S. P.; Spiess, H. W. *Chem. Rev.* **2001**, *101*, 4125–4156.

6. (a) Suh, M. P.; Min, K. S.; Ko, J. W.; Choi, H. J. *Eur. J. Inorg. Chem.* **2003**, 1373–1379. (b) Chatterjee, S.; Pedireddi, V. R.; Rao, C. N. R. *Tetrahedron Lett.* **1998**, *39*, 1803–1806. (c) Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A.; Rao, C. N. R. *Tetrahedron* **1998**, *32*, 9457–9474. (d) Rusanov, E. B.; Ponomarova, V. V.; Komarchuk, V. V.; Stoeckli-Evans, H.; Fernadez-Ibanez, E.; Stoeckli, F.; Sieler, J.; Domasevitch, K. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 2499–2501. (e) Moulton, B.; Lu, J.; Hajndl, R.; Hariharan, S.; Zaworotko, M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2821–2824. (f) Eddaoudi, J.; Kim, J.; Vodak, D.; Sudik, A.; Wachter, J.; O' Keeffe, M.; Yaghi, O. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4900–4904. (g) Brooker, S.; de Geest, D. J.; Kelly, R. J.; Plieger, P. G.; Moubaraki, B.; Murray, K. S.; Jameson, G. B. *J. Chem. Soc., Dalton Trans.* **2002**, 2080–2087.
7. (a) Desiraju, G. R. *Angew. Chem., Int. Ed.* **1995**, *34*, 2311–2327. (b) Lehn, J.-M. *Science* **1986**, *225*, 849–858. (c) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48. (d) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988–1011.
8. (a) Pedireddi, V. R.; Jones, W.; Charlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 997–998. (b) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126. (c) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601–4610. (d) Bernstein, J.; Davey, R. J.; Henck, J.-O. *Angew. Chem., Int. Ed.* **1999**, *38*, 3440–3461.
9. (a) Pedireddi, V. R.; Ranganathan, A.; Chatterjee, S. *Tetrhedron Lett.* **1998**, *39*, 9831–9834. (b) Pedireddi, V. R.; PrakashaReddy, J. *Tetrhedron Lett.* **2002**, *43*, 4927–4930.
10. (a) Sharma, C. V. K.; Zaworotko, M. J. *Chem. Commun.* **1996**, 2655–2656. (b) Chatterjee, S.; Pedireddi, V. R.; Rao, C. N. R. *Tetrahedron Lett.* **1998**, *39*, 2843–2846. (c) Pedireddi, V. R.; Chatterjee, S.; Ranganathan, A.; Rao, C. N. R. *Tetrahedron.* **1998**, *32*, 9457–9474. (d) Vishweshwar, P.; Nangia, A.; Lynch, V. M. *J. Org. Chem.* **2002**, *67*, 556–565. (e) Walsh, R. D. B.; Bradner, M. W.; Fleischman, S.; Morales, L. A.; Moulton, B.; Rodriguez-Hornedo, N.; Zaworotko, M. J. *Chem. Commun.* **2003**, 186–187.
11. Ranganathan, A.; Pedireddi, V. R.; Sanjayan, G.; Ganesh, K. N.; Rao, C. N. R. *J. Mol. Struct.* **2000**, *522*, 87–94.
12. Pedireddi, V. R.; Belhekar, D. *Tetrahedron* **2002**, *58*, 2937–2941.
13. (a) Leiserowitz, L.; Tuval, M. *Acta Crystallogr. Sect. B.* **1978**, *34*, 1230–1247. (b) Lewis, F. D.; Yang, J.; Stern, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 12029–12037. (c) Weinstein, S.; Leiserowitz, L.; Gil-Av, E. *J. Am. Chem. Soc.* **1980**, *102*, 2768–2772. (d) Harkema, S.; Gaymans, R. J. *Acta Crystallogr. Sect. B* **1977**, *33*, 3609–3611. (e) Harkema, S.; Gaymans, R. J.; van Hummel, G. J.; Zylberlicht, D. *Acta Crystllogr. Sect. B* **1979**, *35*, 506–508. (f) Adams, W. W.; Fratini, A. V.; Wiff, D. R. *Acta Crystallogr. Sect. B.* **1978**, *34*, 954–956. (g) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265–9269. (h) Brisson, J.; Gagne, J.; Brisse, F. *Can. J. Chem.* **1989**, *67*, 840–849. (i) Lewis, F. D.; Yang, J.-S. *J. Phys. Chem. B* **1997**, *101*, 1775–1781.
14. Pedireddi, V. R. *Cryst. Eng. Comm.* **2002**, *4*, 315–317.
15. Allen, F. H.; Kennard, O. *Chem. Des. Automat. News* **1993**, *8*, 31–37.
16. Pedireddi, V. R.; PrakashaReddy, J.; Arora, K. K. *Tetrahedron Lett.* **2003**, *44*, 4857–4860.
17. Pedireddi, V. R.; PrakashaReddy, J. *Tetrahedron Lett.* **2003**, *44*, 6679–6681.
18. Kuduva, S. S.; Craig, D. C.; Nangia, A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1999**, *121*, 1936–1944.
19. Csoregh, I.; Sjogren, A.; Czugler, M.; Cserzo, M.; Weber, E. *J. Chem. Soc., Perkin Trans. 2* **1986**, 507–509.
20. Makhkamov, K. K.; Ibragimov, B. T.; Weber, E.; Beketov, K. M. *J. Phys. Org. Chem.* **1999**, *12*, 157–164.
21. (a) Herbstein, F. H. *Top. Curr. Chem.* **1987**, *140*, 107–139. (b) Russell, V. A.; Ward, M. D. *New J. Chem.* **1998**, *22*, 149–153. (c) Russell, V. A.; Evans, C. C.; Li, W. J.; Ward, M. D. *Science* **1997**, *276*, 575–579. (d) Darlow, S. F. *Acta Crystllogr.* **1961**, *14*, 159–166. (e) Liu, R.; Mok, K.-M.; Valiyaveettil, S. *New J. Chem.* **2001**, *25*, 890–892.
22. We are aware that such an exercise with aliphatic amide was futile, but still we proceeded with aromatic amides in the same directions, with a presumption that π–π interaction between either aromatic amides or amide$\cdots$bipyridine would facilitate the formation of the desired architecture
23. (a) Zerkowski, J. A.; MacDonald, J. C.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 2382–2391. (b) Zerkowski, J. A.; Seto, C. T.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025–9026. (c) Zerkowski, J. A.; Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1992**, *114*, 5473–5475.
24. Pedireddi, V. R.; Ranganathan, A.; Ganesh, K. N. *Org. Lett.* **2001**, *3*, 99–102.
25. (a) *Siemens*, *SMART System*, Siemens Analytical X-ray Instruments Inc., Madison, WI, USA, 1995. (b) Sheldrick, G. M. *SHELXTL*, *Users manual*; Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 2001.
26. Spek, A. L. *PLATON, Molecular Geometry Program*; University of Utrecht: The Netherlands, 1995.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8829–8837

A facile synthesis of 4-, 5- and 6-chloromethyl-1*H*-indole-2-carboxylates: replacement of a sulfonic acid functionality by chlorine☆

Béla Pete[a,*] and Gyula Parlagh[b]

[a]*Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*
[b]*Department of Physical Chemistry, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

Received 11 August 2003; revised 21 June 2004; accepted 15 July 2004

Abstract—Valuable new synthetic intermediates, 4-, 5- or 6-chloromethyl-1*H*-indole-2-carboxylates, were prepared by the facile elimination of SO_2 from 2-ethoxycarbonyl-1*H*-indole-4-, 5- or 6-methanesulfonic acids, respectively, easily accessible by Fischer-type indolization.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The synthesis of functionalized indoles has been of interest to organic chemists for many years due to the large number of natural products that contain this structural element.[2] More importantly, indole containing compounds have pronounced effects in many physiological processes.

The synthesis of 4- or 6-substituted indoles as reactive synthetic intermediates is an important aspect in the chemistry of this heterocycle. Due to the enormous interest in ergot alkaloids a significant amount of work have appeared dealing with 3,4-disubstituted indoles[3] also present in the antibiotic nosiheptide.[4] The 4-vinyl-6,7-(dihydroxy)indole-2-carboxylates are key intermediates for the synthesis of the antitumor agent CC-1065 and of the inhibitors of cyclic adenosine-3′,5′-monophosphate phosphodiesterase PDE-I and PDE-II.[5] Indoles substituted at the 6 position are also important intermediates for the synthesis of a wide range of indolic alkaloids, such as members of the neoechinulin[6] and teleocidine[7] families.

Indoles having 5-HT receptor activity as agonists[8] or antagonists[9] have aroused considerable synthetic interest during the last decade in many research groups. Although the 5-indolylcarbinyl unit is a common structural element of these compounds, their synthesis is carried out in a different way: the latent 5-substituent had been introduced prior to the indolization step.[9,10] This approach is impractical; instead a common advanced intermediate suitable for facile derivatization to generate a diverse group of 5-substituted indoles is required. An obvious target to fulfill these requirements would be the 5-halomethyl indoles.

Two main approaches have been utilized in the synthesis of indoles carrying substituents on the benzenoid part of the heterocycle: (a) direct introduction of substituents onto an already constructed indole and (b) construction of a suitably functionalized benzenoid ring followed by annulation of the pyrrole portion to generate the indole system.

Methods following route (a) always raise the question of appropriate regioselectivity. This is well known from works dealing with the Friedel–Crafts-type acylation of indoles.[11] In most cases it seems more useful to introduce the desired functionalities prior to the elaboration of the indole ring (route b). The Reissert,[12] Fischer,[13] and Batcho–Leimgruber[14] indole syntheses have been the primary methods for the synthesis of these indoles. Due to the rather harsh conditions required by the indolization step it is necessary to utilize fairly robust benzenoid precursors compatible with the required conditions. Elaboration to the more reactive functionalities actually found in the targeted indoles is then often multistep and inefficient in yield.

☆ See Ref. 1.

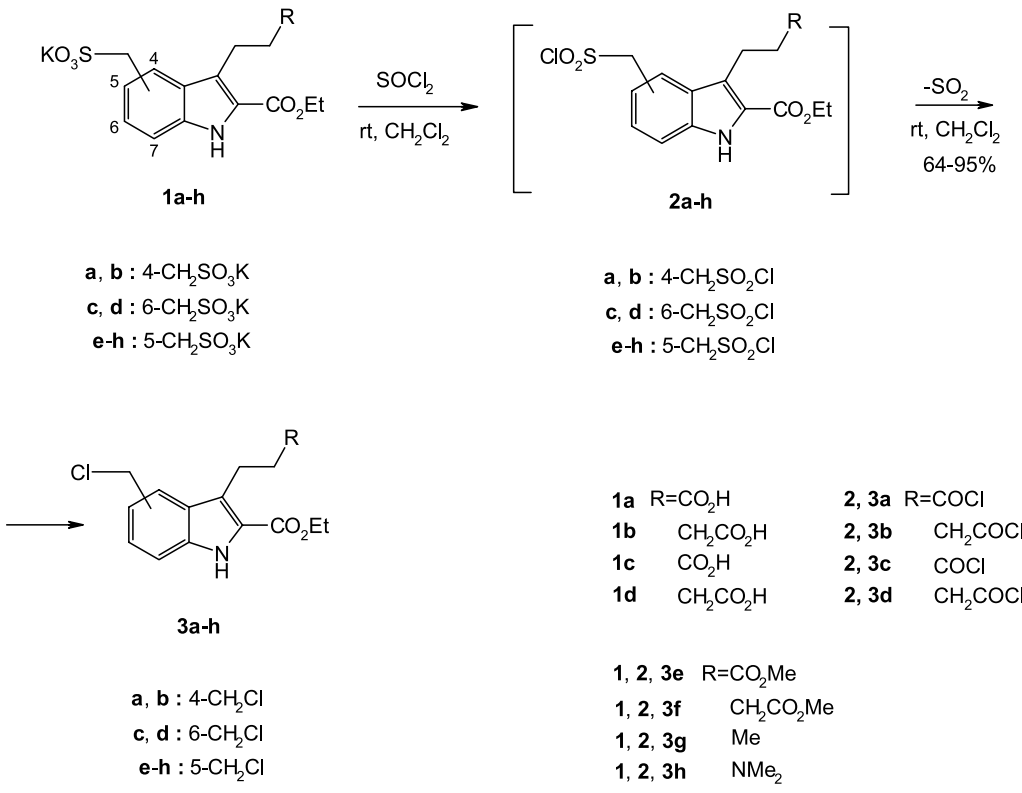
Keywords: Fischer synthesis; Japp-Klingemann reaction; 4-(Chloromethyl) indoles; 5-(Chloromethyl)indoles; 6-(Chloromethyl)indoles; Desulfination.
* Corresponding author. Tel.: +36-1-4631111/58-26; fax: +36-1-4633648; e-mail: bpete@mail.bme.hu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.038

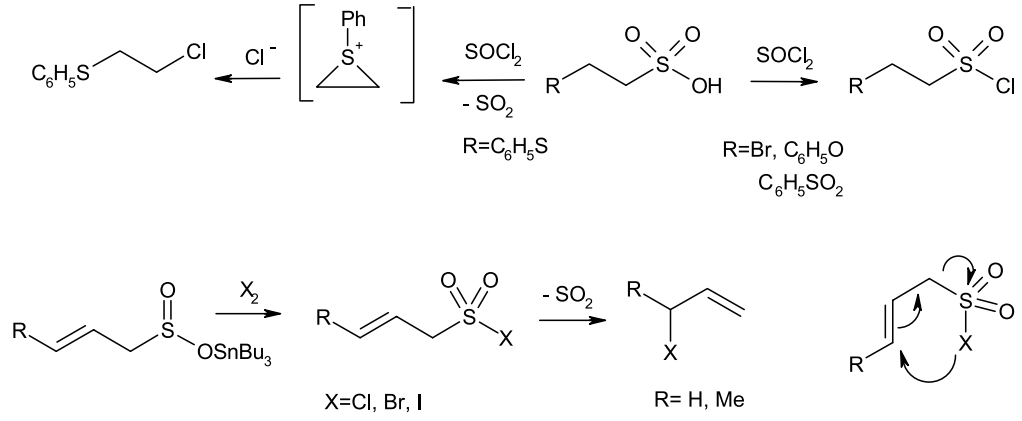
1.1. Synthesis of chloromethyl-indoles

In this paper we demonstrate that the sulfomethyl group while being extremely stable as a benzenoid or indole substituent, can easily be transformed into a 4-, 5- or 6-chloromethyl group in 2-ethoxycarbonyl-1*H*-indole-4-, 5- or 6-methanesulfonic acids, respectively. This transformation is based on our observation that the SO_3H group of the indole-4-, 5- or 6-methanesulfonic acids **1a–h** is easily replaced by chlorine under the circumstances of the formation of sulfonyl chlorides (Scheme 1). The elimination and replacement of the SO_3H group by chlorine in **1a–h** is actually so facile that the SO_3H group may be regarded as a kind of latent chlorine atom. This type of 'functional group chemistry' is little known in the literature, and unprecedented in the chemistry of the indoles. To the best of our knowledge, only two examples exist where this type of transformation has been used for preparative purposes: Barber and co-workers developed a general method for the preparation of aryloxymethyl chlorides from aryloxymethanesulfonates and PCl_5 at rt.[15] Moreover, a number of 2-benzimidazolyl chlorides were prepared in good yields from the corresponding 2-benzimidazolyl sulfonic acids by treatment with PCl_5 and $POCl_3$.[16]

The formation of alkyl chlorides (Scheme 2) and even alkyl amines has been observed by the elimination of SO_2 from alkyl sulfonyl chlorides[17] or sulfonamides,[18] respectively,



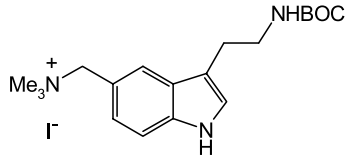
Scheme 1.



Scheme 2.

but the reactions have not been shown to have any synthetic utility.

We have observed this type of transformation first in case of the indole-5-methanesulfonic acids.[1a] Castro and Matassa[19] have already demonstrated that the 5-indolylcarbinyl carbon has a high reactivity, similar to that of the 3-indolylcarbinyl carbon (e.g., in gramine) by synthesizing the tryptamine **4** (Scheme 3). This high reactivity toward nucleophilic substitution is the result of resonance interaction, quite similar to that accepted to operate in the case of the 3-indolylcarbinyl carbon (Scheme 4, **c**, **f**, **j**). The same type of resonance interaction can also operate in case of 4-, 6- and 7-indolylcarbinyl carbons stabilizing electron-deficiency on these atoms (Scheme 4, **i**, **h**, **d**). These resonance structures[20] are important contributors to the overall π-electron structure of indole, but **h** and **i** must be smaller in weight than **c** and **d**. This is because both **h** and **i** develops through **f** or **j**, which are known to be the most important among resonance structures with charge separation, thus decreasing the weight of **h** and **i**. The total π-electron-density calculations of indole show the same picture: there is a higher proportion of negative charge on C-5 and C-7 compared to C-4 and C-6.[21] This build-up of negative charge on C-4, C-5, C-6 (and C-7) must facilitate the loss of SO_2 from sulfonyl chlorides **2a**–**h**, if elimination proceeds through an ionic intermediate. Evidence has already been presented for the intermediacy of an episulfonium ion in the thermal desulfination of 2-(phenylthio)ethanesulfonyl chloride by McManus et al (Scheme 2).[17a] The probable driving force for the loss of SO_2 on attempted chlorination of aryloxymethane-sulfonates[15] is the formation of the resonance-stabilized intermediate $[ArO^+=CH_2]$. In case of an ionic intermediate, the preferred compounds that undergo SO_2 elimination would be indole-5- and indole-7-methanesulfonic acids.[22] To prove this mechanism we have synthesized indole-4- and indole-6-methanesulfonic acids **1a**–**d**, with the expectation that they will behave like normal sulfonic acids yielding sulfonyl chlorides with $SOCl_2$.



4

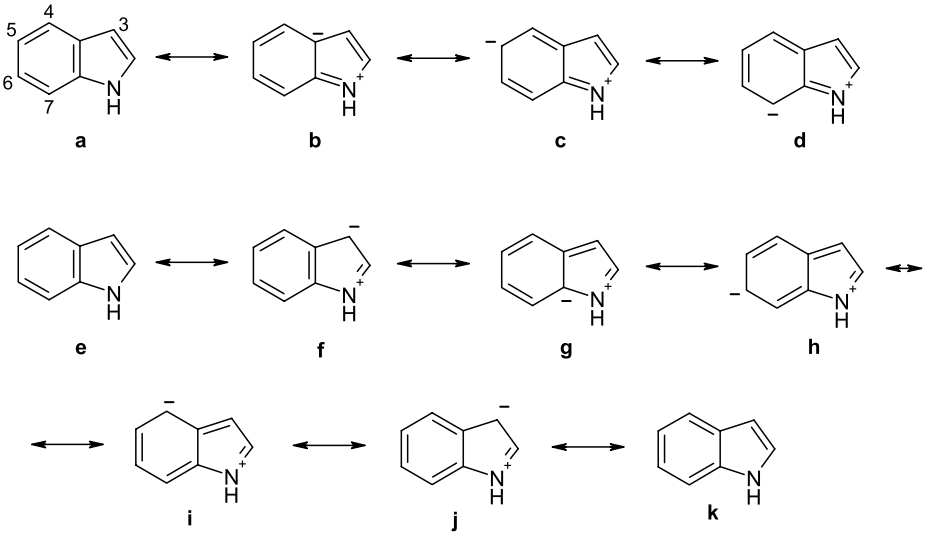
Scheme 3.

Suprisingly, we found that **1a**–**d** underwent SO_2 elimination, under the influence of $SOCl_2$, more readily than the indole-5-methanesulfonic acids, with concomitant formation of 4- and 6-(chloromethyl)indoles **3a**–**d** (Scheme 1).[1b] The fact that the position of the sulfomethyl group does not play an important role in the loss of SO_2 suggest that resonance interaction may not be the governing factor in this process. However, it does have a role in the reactivity of the CH_2Cl groups: while the 5-chloromethyl-indoles **3e**–**h** react instantaneously with MeOH at rt yielding 5-methoxymethyl-indoles,[22] the 4- and 6-chloromethyl-indoles **3a**–**d** do not show the signs of methoxymethyl ether formation in MeOH after 20 min at rt (Scheme 5). The difference in the rate of hydrolysis of **3e**–**h**[23] and **5a**–**d**[24] is even more pronounced.

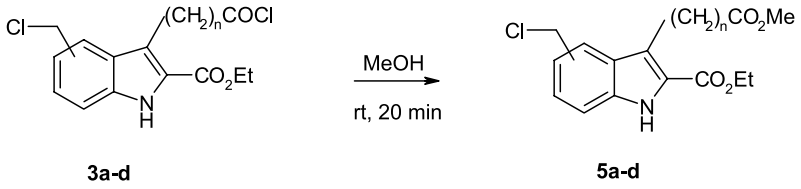
Substituted benzyl chlorides are known to prefer S_N1 mechanism in nucleophilic substitution reactions. The differences observed in the rate of methanolysis and hydrolysis correspond to that suggested by resonance structures **c**, **d**, **h**, and **i**.

To the best of our knowledge there are no data available in the literature comparing the reactivity of 4-, 5-, 6- and 7-indolylcarbinyl carbons.

On the other hand, precedent for the concerted loss of SO_2 and formation of halides is also known: the thermal desulfination of allylic sulfonyl halides takes place by a concerted mechanism (Scheme 2).[25] Whether the displacement of the chlorosulfonyl group of **2a**–**h** by chloride follows a nucleophilic path, or occurs simultaneously, is not yet clear and needs further investigation.



Scheme 4.



3a-d **5a-d**

3, 5a	n=2, 4-CH_2Cl	yield: 85%
3, 5b	n=3, 4-CH_2Cl	88%
3, 5c	n=2, 6-CH_2Cl	83%
3, 5d	n=3, 6-CH_2Cl	92%

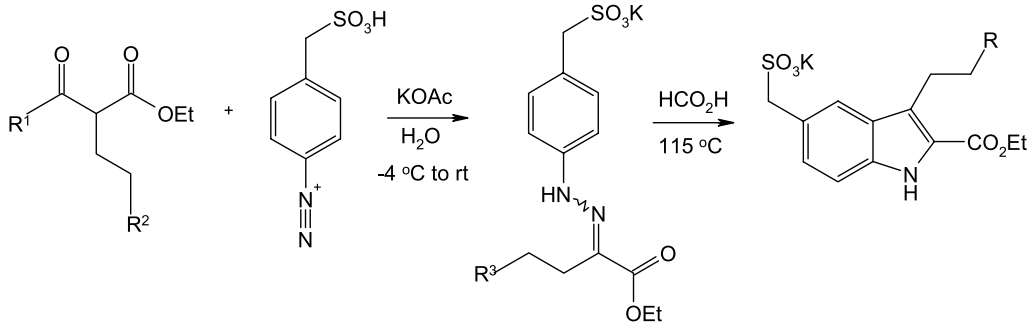
Scheme 5.

1.2. Synthesis of indole-methanesulfonic acids

The preparation of indole-methanesulfonic acids **1a**–**h** and indole-ethanesulfonic acid **16** has started by the Japp-Klingemann reaction of diazotized aminophenyl-sulfonic acids **7**, **11** or **14** and β-oxoester derivatives **6e**–**h** to yield hydrazones **8e**–**h** and **12**, **13**, **15** (Schemes 6–8). KOAc or $KHCO_3$ was used to adjust the pH to 4–5 during condensation, the hydrazones either separated from the reaction mixture (**8f**, **h**, **13**, **15**) or were isolated by evaporating the aqueous solution to dryness and extracting the solid residue with MeOH (**8e**, **g**, **12**). The regiochemical structure of the hydrazones was not investigated. The Fischer indolisation was carried out either in formic acid (**8e**, **f**, **g**, **15**) or in AcOH–$HCl_{(g)}$ at reflux (**12**, **13**) or ambient temperature (**8h**). The sulfonic acids were isolated by evaporating the solvent and were purified by crystallization from water in good overall yield (60–70%). The *meta*-substituted phenylhydrazones usually lead to the concomitant formation of 4- and 6-substituted indoles when subjected to Fischer-type rearrangement. The formation of mixtures of regioisomers can be avoided by blocking the appropriate *ortho*-position of the phenylhydrazone with Cl or Br which is then removed from the indole by hydrogenolysis.[26] In our case the two regioisomeric indoles **1a**, **c** and **1b**, **d** were produced in a 1:1 ratio (Scheme 7) and were easily separated by fractional crystallization from water, as **1a** or **1d** are more soluble in polar solvents than **1c** or **1b**, respectively. As the sulfonic acids, and their salts, possess very good crystallization properties the easy separation of the regioisomers is an important feature of the above process.

The Fischer indolization of hydrazones **8e** and **8f** gave the carboxylic acids **9** and **10**, respectively. As the CH_2Cl groups of **3e**–**h** have the same reactivity as a COCl group, the formation of acid chlorides has to be avoided during chlorination. This was accomplished by protection of CO_2H as CO_2Me to give **1e** and **1f**, respectively, prior to the reaction with $SOCl_2$ (Scheme 6). In case of 4- and 6-methanesulfonic acids **1a**–**d** the protection of CO_2H can be carried out after the chlorination as the COCl of **3a**–**d** undergoes methanolysis much faster than the CH_2Cl group (Scheme 5).

We were curious about whether this peculiar behavior of



6 e - h **7** **8 e - h** **9**, **10**, **1g**, **1h**

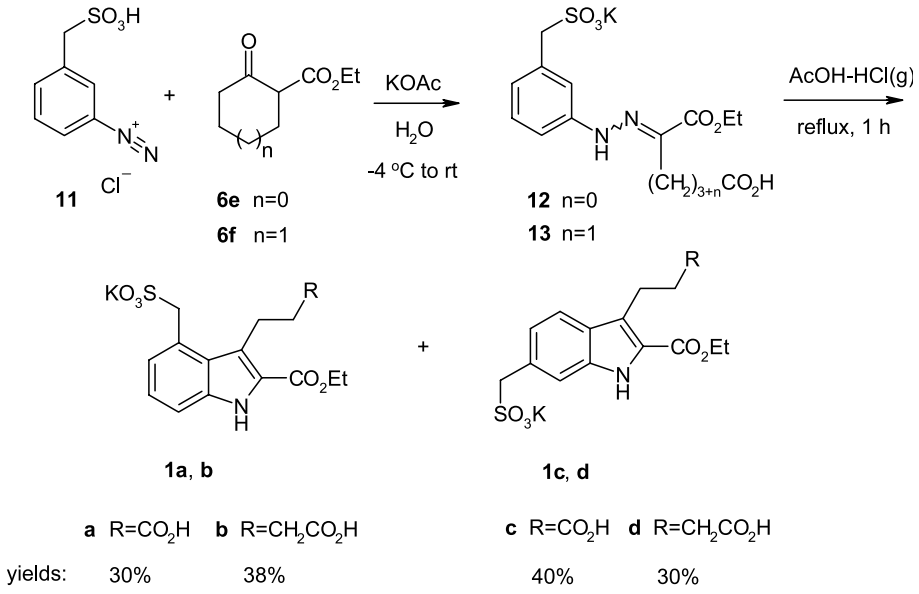
6 e $R^1+R^2=CH_2$
f $R^1+R^2=(CH_2)_2$
g $R^1=OH$, $R^2=Et$
h $R^1=Me$, $R^2=CH_2NMe_2$

8 e $R^3=CH_2CO_2H$
f $(CH_2)_2CO_2H$
g Et
h CH_2NMe_2

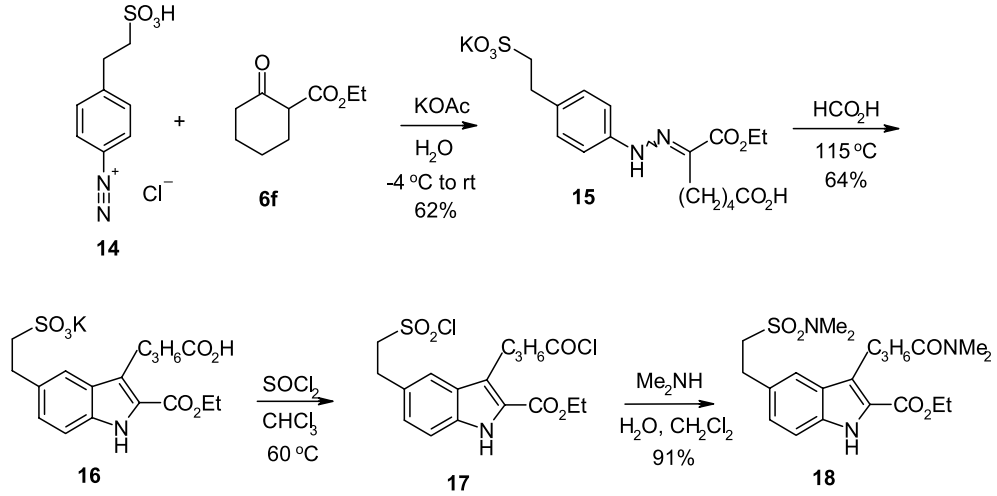
9 $R=CO_2H$ (i) → **1 e** CO_2Me
10 CH_2CO_2H (i) → **1 f** CH_2CO_2Me
1 g Me
1 h NMe_2

yields: **9**=63%; **10**=68%; **1g**=54%; **1h**=40%; **1e**, **1f**=quant.

Scheme 6. (i) MeOH, $SOCl_2$, −25 °C to rt, 24 h, quant.



Scheme 7.



Scheme 8.

indole-methanesulfonic acids is also possessed by the homologs. The indolyl-5-ethanesulfonic acid **16**, synthesized according to Scheme 8, however, behaved like normal sulfonic acids yielding sulfonyl chloride **17** with $SOCl_2$.

In summary, a new synthesis of 4-, 5- and 6-(chloromethyl)-indoles **3a–h** featuring the transformation of the CH_2SO_3H group to CH_2Cl has been developed. The advantages related to our process are obvious: the sulfo-group of **1a–h**, as one of the chemically most stable, allows a broad range of transformations of the indole nucleus. The chloromethyl functionality can then be introduced under mild conditions.

2. Experimental

^1H NMR and ^{13}C NMR spectra were recorded at 250 or 62.5 MHz, respectively, on a Bruker AC 250 spectrometer. All δ values are given in ppm, TMS was used as an internal standard. IR spectra were measured on Perkin–Elmer 1600 series FTIR spectrophotometer. All chemicals were reagent grade and used without further purification. (4-Aminophenyl)methanesulfonic acid,[1a] (3-aminophenyl)methanesulfonic acid,[1b] and (4-aminophenyl)ethanesulfonic acid[27] were prepared as described previously. Compound **6h** was prepared according to Ref. 9a. Most sulfonic acid derivatives did not have definite melting points but ranges instead.

2.1. General procedure for the preparation of hydrazones 8e–h, 12, 13, and 15

To the suspension of (4-aminophenyl)methanesulfonic acid (**7**) (9.35 g, 50 mmol) or (4-aminophenyl)ethanesulfonic acid (**14**) (10.0 g, 50 mmol) or to the solution of (3-aminophenyl)methanesulfonic acid (**11**) (9.35 g, 50 mmol) in water (80 ml) and concd HCl (25 ml), was added $NaNO_2$ (ca. 3.1 g, 45 mmol, as the sulfonic acids always contain inorganic salt) in small portions over a period of 0.5 h at −4

to −2 °C until the starch–iodine test showed blue. Ethyl 2-oxo-cyclopentanecarboxylate **6e** (55 mmol) or ethyl 2-oxo-cyclohexanecarboxylate **6f** (55 mmol) or ethyl 2-(3-dimethylamino-propyl)-3-oxo-butanoate **6h** (55 mmol) was added without solvent at the same temperature while stirring vigorously. Butylmalonic acid monoethyl ester **6g** was added in EtOH prepared as follows: diethyl *n*-butyl-malonate (10 g, 46 mmol) in dry EtOH (20 ml) was cooled to 5 °C then KOH (3 g, 53 mmol) in dry EtOH (50 ml) was added at the same temperature over a period of 1 h. The reaction mixture was kept at rt for 8 h, cooled to 0 °C then added to the diazonium solution over a period of 0.5 h. Having introduced the β-oxoester, KOAc (ca. 15 g) was added over a period of 15 min at 0 °C until the pH reached 4–5. In case of **8h**, $KHCO_3$ was used instead of KOAc. The yellow solution was allowed to reach rt while stirring vigorously and additional KOAc was added to keep the pH at around 4. The solution was stirred for 2 h at rt then kept at 5 °C in case of **8f**, **8h**, **13**, **15** for 18 h to complete the precipitation of hydrazones which were isolated by filtration, but still contained 3–6% inorganic salts (in case of **8h** ca. 25%). The solution of hydrazones **8e**, **8g**, **12** was evaporated to dryness and the solid residue triturated with MeOH (300 ml) to separate the hydrazones from inorganic salts. The suspension was filtered and the filtrate rotary evaporated to give hydrazones which contained 10–30% KOAc but were used without further purification. Because of the inorganic contamination up to 30%, the exact yields of **8e**, **8g**, **8h**, **12** are not known. These amorphous materials were purified by slow evaporation of aqueous solutions at ambient temperature to obtain crystalline materials suitable for analysis.

2.1.1. 2-{[4-(Sulfomethyl)-phenyl]-hydrazono}-hexane-dioic acid 1-ethyl ester (8e). Orange powder, mp 180–190 °C. ^{1}H NMR (D_2O) δ 1.38 (3H, t, J=7 Hz), 1.70 (2H, m), 2.30 (2H, s), 2.54 (2H, s), 4.17 (2H, s), 4.28 (2H, q, J=7 Hz), 7.29 (2H, d, J=8 Hz), 7.39 (2H, d, J=8 Hz). ^{13}C NMR (D_2O) δ 11.50, 18.53, 22.06, 32.81, 54.28, 59.89, 112.01, 122.90, 129.16, 133.47, 140.98, 164.18, 178.68. IR: 3471, 1665, 1521, 1211 cm^{-1}. Anal Calcd for $C_{15}H_{18}K_2N_2O_7S$: C, 40.16; H, 4.04; N, 6.24. Found: C, 40.10; H, 4.11; N, 6.15.

2.1.2. 2-{[4-(Sulfomethyl)-phenyl]-hydrazono}-heptane-dioic acid 1-ethyl ester (8f). Yellow crystals, (15.7 g, 68%), mp 204–214 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.43 (3H, t, J=7 Hz), 1.70 (4H, s), 2.43 (2H, s), 2.52 (2H, s), 4.24 (2H, s), 4.31 (2H, q, J=7 Hz), 7.25 (2H, d, J=8 Hz), 7.44 (2H, d, J=8 Hz). ^{13}C NMR (DMSO-d_6) δ 15.04, 26.28, 28.30, 33.63, 36.97, 57.94, 63.05, 115.04, 126.55, 131.41, 132.96, 144.40, 165.41, 182.07. IR: 3465, 1668, 1198 cm^{-1}. Anal Calcd for $C_{16}H_{20}K_2N_2O_7S$: C, 41.54; H, 4.36; N, 6.06. Found: C, 41.59; H, 4.42; N, 5.99.

Compounds **8g**, **h** were not sufficiently pure for analysis.

2.1.3. 2-{[3-(Sulfomethyl)-phenyl]-hydrazono}-hexane-dioic acid 1-ethyl ester (12). Yellow crystals, mp 220–230 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.50 (3H, t, J=7 Hz), 1.90 (2H, m), 2.50 (2H, m), 2.73 (2H, m), 4.31 (2H, s), 4.45 (2H, q, J=7 Hz), 7.20 (1H, d, J=7.2 Hz), 7.41 (2H, m), 7.51 (1H, d, J=7.2 Hz). ^{13}C NMR (D_2O) δ 11.54, 18.27, 22.03, 32.25, 54.78, 59.53, 111.28, 113.74, 121.60, 127.24, 130.93, 133.11, 141.43, 163.97, 177.85. IR: 3471, 1668, 1231 cm^{-1}. Anal Calcd for $C_{15}H_{18}K_2N_2O_7S$: C, 40.16; H, 4.04; N, 6.24. Found: C, 40.03; H, 4.00; N, 6.19.

2.1.4. 2-{[3-(Sulfomethyl)-phenyl]-hydrazono}-heptane-dioic acid 1-ethyl ester (13). Yellow crystals, (14.3 g, 62%), mp 185–190 °C (H_2O, dec). ^{1}H NMR (DMSO-d_6) δ 1.28 (3H, t, J=7 Hz), 1.55 (4H, s), 2.23 (2H, s), 2.48 (2H, s), 3.75 (2H, s), 4.23 (2H, q, J=7 Hz), 6.86 (1H, d, J=8 Hz), 7.08 1H, m), 7.21 (2H, m), 11.90 (1H, s). ^{13}C NMR (DMSO-d_6) δ 14.47, 25.27, 27.59, 32.73, 35.83, 57.68, 61.12, 112.31, 115.82, 124.32, 128.99, 129.32, 135.62, 143.38, 163.69, 177.40. IR: 3478, 1670, 1193, 1047 cm^{-1}. Anal Calcd for $C_{16}H_{20}K_2N_2O_7S$: C, 41.54; H, 4.36; N, 6.06. Found: C, 41.48; H, 4.30; N, 5.97.

2.1.5. 2-{[4-(2-Sulfo-ethyl)-phenyl]-hydrazono}-heptane-dioic acid 1-ethyl ester (15). Yellow crystals, (14.8 g, 62%), mp 190–200 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.37 (3H, t, J=7 Hz), 1.60 (4H, m), 2.37 (4H, m), 3.10 (2H, m), 3.22 (2H, m), 4.14 (2H, q, J=7 Hz), 7.10 (2H, d, J=8 Hz), 7.26 (2H, J=8 Hz). ^{13}C NMR (D_2O) δ 11.53, 22.02, 24.45, 27.74, 29.85, 31.59, 50.53, 58.58, 111.36, 125.46, 127.00, 130.38, 139.54, 161.27, 175.46. IR: 3443, 1672, 1520, 1204 cm^{-1}. Anal Calcd for $C_{17}H_{22}K_2N_2O_7S$: C, 42.84; H, 4.65; N, 5.88. Found: C, 42.61; H, 4.70; N, 5.80.

2.2. General procedure for the preparation of 9, 10, 1g and 16

The hydrazone **8e**, **f**, **g** (prepared from **7**, 50 mmol) or **15** (prepared from **14**, 50 mmol), respectively, was added to formic acid (100 ml, 98%) in small protions while keeping the temperature at 5–10 °C then refluxed for 1 h. After cooling to rt, the precipitated inorganic material was filtered off, the filtrate was evaporated to dryness and the solid residue crystallized from water to give **9**, **10**, **1g** and **16**. Yields refer to the aminophenyl-sulfonic acids.

2.2.1. 3-(2-Carboxy-ethyl)-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (9). Beige crystals, (11 g, 63%), mp 272–276 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.48 (3H, t, J=7 Hz), 2.66 (2H, m), 3.32 (2H, m), 4.37 (2H, q, J=7 Hz), 4.40 (2H, s), 7.42 (2H, s), 7.73 (1H, s). ^{13}C NMR (DMSO-d_6) δ 14.42, 20.35, 35.40, 57.87, 60.60, 111.91, 121.72, 122.01, 123.48, 126.38, 126.99, 128.36, 135.69, 162.04, 174.42. IR: 3325, 1685, 1250, 1040 cm^{-1}. Anal Calcd for $C_{15}H_{17}NO_7S$: C, 50.70; H, 4.82; N, 3.94. Found: C, 50.92; H, 4.83; N, 3.92.

2.2.2. 3-(3-Carboxy-propyl)-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (10). Beige crystals, (12.5 g, 68%), mp 237–240 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.34 (3H, t, J=7 Hz), 1.80 (2H, m), 2.30 (2H, m), 2.88 (2H, m), 4.20 (2H, s), 4.26 (2H, q, J=7 Hz), 7.29 (2H, s), 7.54 (1H, s). ^{13}C NMR (D_2O) δ 11.37, 21.02, 23.14, 31.29, 55.06, 59.40, 109.98, 120.10, 120.73, 121.08, 121.66, 124.93, 125,67, 133.53, 161.38, 176.48. IR: 3329, 1688, 1207, 1044 cm^{-1}. Anal Calcd for $C_{16}H_{18}KNO_7S$: C, 47.16; H, 4.45; N, 3.44. Found: C, 46.94; H, 4.35; N, 3.52.

2.2.3. 3-Propyl-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1g). Orange crystals, (9.7 g, 54%), mp

238–242 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.17 (3H, t, J= 7 Hz), 1.67 (3H, t, J=7 Hz), 1.83 (2H, m), 3.18 (2H, m), 4.50 (2H, s), 4.56 (2H, q, J=7 Hz), 7.60 (2H, s), 7.92 (1H, s). ^{13}C NMR (D_2O) 13.72, 13.84, 24.10, 26.34, 57.49, 61.82, 112.41, 122.91, 123.16, 123.32, 126.23, 127.60, 128.18, 136.05, 164.13. IR: 3272, 1692, 1261 cm^{-1}. Anal Calcd for $C_{15}H_{18}KNO_5S$: C, 49.57; H, 4.99; N, 3.85. Found: C, 49.61; H, 4.97; N, 3.80.

2.2.4. 3-(3-Carboxy-propyl)-5-(2-sulfo-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (16). Beige crystals, (13.4 g, 63.5%), mp 268–272 °C (H_2O, dec). ^{1}H NMR (D_2O) δ 1.47 (3H, t, J=7 Hz), 1.81 (2H, m), 2.35 (2H, m), 2.83 (2H, m), 3.22 (2H, m), 3.33 (2H, m), 4.33 (2H, q, J=7 Hz), 7.26 (1H, d, J=8.4 Hz), 7.35 (1H, d, J=8.4 Hz), 7.45 (1H, s). ^{13}C NMR (DMSO-d_6) δ 14.85, 24.02, 26.69, 32.15, 34.20, 54.27, 60.78, 113.20, 119.52, 123.00, 123.90, 128.07, 132.44, 135.72, 162.50, 175.41. IR: 3331, 1685, 1244 cm^{-1}. Anal Calcd for $C_{17}H_{20}KNO_7S$: C, 48.44; H, 4.78; N, 3.32. Found: C, 48.14; H, 4.70; N, 3.37.

2.2.5. 3-(2-Methoxycarbonyl-ethyl)-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1e) and 3-(3-methoxycarbonyl-propyl)-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1f). To MeOH (200 ml) cooled to −25 °C was added $SOCl_2$ (10 ml) at the same temperature over a period of 0.5 h and kept for additional 0.5 h at −25 °C. Indole-methanesulfonic acid **9** or **10** (30 mmol) was added as a solid and the reaction mixture was allowed to reach rt and stirred for 24 h. The clear solution was evaporated to dryness to give **1e** or **1f** quantitatively. Pure materials suitable for analysis were obtained by neutralizing the aqueous solutions of **1e** or **1f** by $KHCO_3$ and recrystallizing the precipitated material from MeOH.

Compound **1e**. Beige crystals, mp 275–280 °C (MeOH, dec). ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, t, J=7 Hz), 2.54 (2H, m), 3.27 (2H, m), 3.60 (3H, s), 3.84 (2H, s), 4.32 (2H, q, J=7 Hz), 7.28 (2H, m), 7.53 (1H, s), 11.52 (1H, s). ^{13}C NMR (DMSO-d_6) δ 13.89, 19.79, 34.49, 51.06, 57.31, 59.96, 111.40, 120.82, 121.08, 122.93, 125.53, 126.28, 127.77, 135.11, 161.30, 172.47. IR: 3273, 1732, 1679, 1263, 1194 cm^{-1}. Anal Calcd for $C_{16}H_{18}KNO_7S$: C, 47.16; H, 4.45; N, 3.44. Found: C, 46.87; H, 4.52; N, 3.46.

Compound **1f**. Beige crystals, mp 245–250 °C (MeOH, dec). ^{1}H NMR (DMSO-d_6) δ 1.33 (3H, t, J=7 Hz), 1.85 (2H, m), 2.30 (2H, m), 3.04 (2H, m), 3.56 (3H, s), 3.92 (2H, s), 4.30 (2H, q, J=7 Hz), 7.30 (2H, m), 7.55 (1H, s), 11.48 (1H, s). ^{13}C NMR (DMSO-d_6) δ 13.95, 23.13, 25.52, 32.68, 50.93, 57.38, 59.85, 111.36, 121.15, 121.92, 122.86, 125.70, 126.63, 127.72, 135.20, 161.51, 172.99. IR: 3269, 1733, 1682, 1255 cm^{-1}. Anal Calcd for $C_{17}H_{20}KNO_7S$: C, 48.44; H, 4.78; N, 3.32. Found: C, 48.23; H, 4.84; 3.25.

2.2.6. 3-(2-Dimethylamino-ethyl)-5-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1h). To glacial acetic acid (100 ml) was added hydrazone **8h** (prepared from **7**, 50 mmol) then HCl(g) (3–4 g) was introduced to the vigorously stirred suspension to dissolve the solid while keeping the temperature at 5–10 °C. After standing for 24 h at rt, the precipitated crystals were filtered off and were dissolved in water (40 ml) at rt. The solution was neutralized by solid $KHCO_3$, the precipitated material was filtered off to give **1h**, as colorless powder (7.1 g, 40%), mp 280–285 °C (H_2O). ^{1}H NMR (D_2O) δ 1.29 (3H, t, J=7 Hz), 2.69 (6H, s), 2.8–3.2 (4H, m), 3.96 (2H, s), 4.25 (2H, q, J= 7 Hz), 7.22 (1H, d, J=8.5 Hz), 7.33 (1H, d, J=8.5Hz), 7.62 (1H, s); ^{13}C NMR (D_2O) δ 13.56, 20.80, 43.29, 57.04, 58.01, 61.61, 112.21, 120.44, 121.77, 123.12, 123.38, 126.80, 127.92, 135.56, 162.91. IR: 3447, 1701, 1256, 1034 cm^{-1}. Anal Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26; N, 7.90. Found: C, 54.20; H, 6.29; N, 7.81.

2.2.7. 3-(2-Carboxy-ethyl)-4-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1a) and 3-(2-carboxy-ethyl)-6-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1c). The hydrazone **12** (prepared from **11**, 30 mmol) was added to glacial acetic acid (100 ml) containing 3 g HCl(g) at rt then kept at 90–95 °C for 1 h. After cooling to rt, the precipitated inorganic material was filtered off, the filtrate was evaporated to dryness and the solid residue crystallized from water (25 ml) to give **1c** as beige powder (3.0 g, 28%), mp 265–270 °C (H_2O, dec). The filtrate was evaporated to dryness and triturated with MeOH (30 ml). The suspension was filtered to give a solid containing both isomers while the filtrate gave after evaporation to dryness pure **1a** as beige powder (2.2 g, 21%), mp 278–282 °C (H_2O, dec). Repeating the above procedure, the overall yield for **1c**: 40% and for **1a**: 30%. **1a**. ^{1}H NMR (D_2O) δ 1.49 (3H, t, J=7 Hz), 2.54 (2H, m), 3.52 (2H, m), 4.41 (2H, q, J=7 Hz), 4.54 (2H, s), 7.18 (1H, d, J=8 Hz), 7.38 (1H, t, J=8 Hz), 7.43 (1H, d, J=8 Hz). ^{13}C NMR (DMSO-d_6) δ 11.54, 18.84, 33.29, 52.09, 59.61, 110.30, 120.23, 121.63, 122.47, 122.76, 123.08, 123.39, 134.76, 161.09, 175.37. IR: 3325, 1680, 1255 cm^{-1}. Anal Calcd for $C_{15}H_{16}KNO_7S$: C, 45.79; H, 4.10; N, 3.56. Found: C, 45.54, H, 4.20, N, 3.48.

Compound **1c**. ^{1}H NMR (DMSO-d_6) δ 1.35 (3H, t, J= 7 Hz), 2.49 (2H, m), 3.25 (2H, m), 3.87 (2H, s), 4.32 (2H, q, J=7 Hz), 7.05 (1H, d, J=8 Hz), 7.37 (1H, s), 7.53 (1H, d, J=8 Hz), 11.42 (1H, s). ^{13}C NMR (DMSO-d_6) δ 12.32, 18.30, 33.29, 56.08, 58.15, 111.91, 117.28, 119.73, 120.90, 121.03, 123.80, 130.00, 134.39, 159.80, 172.11. IR: 3331, 1683, 1250 cm^{-1}. Anal Calcd for $C_{15}H_{16}KNO_7S$: C, 45.79; H, 4.10; N, 3.56. Found: C, 45.63, H, 4.11, N, 3.52.

2.2.8. 3-(3-Carboxy-propyl)-4-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1b) and 3-(3-carboxy-propyl)-6-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (1d). The hydrazone **13** (prepared from **11**, 30 mmol) was added to glacial acetic acid (100 ml) containing 3 g HCl(g) at rt then kept at 90–95 °C for 1 h. After cooling to rt, the precipitated inorganic material was filtered off, the filtrate was evaporated to dryness and the solid residue crystallized from water (30 ml) to give **1b** (4.2 g, 38%) as beige crystals, mp 275–280 °C (H_2O, dec). The filtrate was kept at 5 °C for a few days, the separated crystals were filtered out to give **1d** (3.3 g, 30%) as beige crystals, mp 235–240 °C (H_2O, dec). **1b**. ^{1}H NMR (D_2O) δ 1.53 (3H, t, J=7 Hz), 1.86 (2H, m), 2.54 (2H, m), 3.37 (2H, m), 4.48 (2H, q, J=7 Hz), 4.59 (2H, s), 7.23 (1H, d, J= 8 Hz), 7.45 (1H, t, J=8 Hz), 7.54 (1H, d, J=8 Hz). ^{13}C NMR (DMSO-d_6) δ 14.95, 24.75, 27,75, 34.28, 55.31, 60.72, 111.63, 123.80, 124.31, 124.52, 124.74, 126.22,

129.71, 137.74, 162.58, 175.08. IR: 3326, 1688, 1256 cm^{-1}. Anal Calcd for $C_{16}H_{18}KNO_7S$: C, 47.16; H, 4.45; N, 3.44. Found: C, 46.98; H, 4.37; N, 3.37.

Compound **1d**. ^1H NMR (DMSO-d_6) δ 1.34 (3H, t, J=7 Hz), 1.83 (2H, m), 2.21 (2H, m), 3.05 (2H, m), 3.84 (2H, s), 4.32 (2H, q, J=7 Hz), 7.05 (1H, d, J=8 Hz), 7.36 (1H, s), 7.53 (1H, d, J=8 Hz), 11.44 (1H, s). ^{13}C NMR (DMSO-d_6) δ 14.88, 24.21, 26.59, 33.96, 58.63, 60.76, 114.50, 119.84, 123.13, 123.47, 123.59, 126.67, 132.65, 137.00, 162.56, 175.09. IR: 3330, 1687, 1252 cm^{-1}. Anal Calcd for $C_{16}H_{18}KNO_7S$: C, 47.16; H, 4.45; N, 3.44. Found: C, 47.10; H, 4.51; N, 3.36.

2.3. General procedure for the preparation of chloromethyl-indoles (3a–h) and (5a–d)

Appropriate sulfonate salt (**1a**–**g**, 5 mmol) was stirred in dry CH_2Cl_2 (25 ml) containing $SOCl_2$ (2 ml, 28 mmol) and DMF (0.06 ml) at rt for 4 h. The solution was filtered and the filtrate was evaporated to dryness to give **3a**–**g** as crystalline solids, in near quantitative yields. In case of **1h** the procedure was the same, but dry $CHCl_3$ was used at reflux temperature for 3 h, then **3h** precipitated from the reaction mixture on cooling. The chloromethyl-indoles **3e**–**h** decomposed quickly when exposed to atmospheric moisture. Acid chlorides **3a**–**d** were dissolved in MeOH and kept at rt for 20 min then evaporated to dryness to give **5a**–**d** as white crystalline solids relatively stable on air. Recrystallization of **5a**–**d** did not yield pure materials probably because of slow hydrolysis therefore elemental analysis could not be carried out.

2.3.1. 3-(2-Methoxycarbonyl-ethyl)-5-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (3e). Brown solid (1.54 g, 95%). ^1H NMR ($CDCl_3$) δ 1.35 (3H, t, J=7 Hz), 2.63 (2H, m), 3.32 (2H, m), 3.62 (3H, s), 4.34 (2H, q, J=7 Hz), 4.67 (2H, s), 7.27 (2H, m), 7.64 (1H, s), 8.90 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.29, 20.35, 35.13, 47.56, 51.63, 61.02, 112.61, 120.81, 122.49, 124.30, 126.48, 127.39, 129.37, 135.72, 162.07, 173.56.

2.3.2. 3-(3-Methoxycarbonyl-propyl)-5-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (3f). Brown solid (1.53 g, 91%). ^1H NMR ($CDCl_3$) δ 1.33 (3H, t, J=7 Hz), 1.96 (2H, m), 2.32 (2H, m), 3.06 (2H, m), 3.59 (3H, s), 4.32 (2H, q, J=7 Hz), 4.64 (2H, s), 7.24 (1H, d, J=7 Hz), 7.33 (1H, d, J=7 Hz), 7.58 (1H, s), 9.72 (1H, s). ^{13}C NMR ($CDCl_3$) δ 13.94, 23.47, 25.55, 33.17, 47.27, 51.11, 60.54, 112.28, 120.49, 123.14, 123.87, 126.03, 127.31, 128.82, 135.58, 161.99, 173.73.

2.3.3. 3-(3-Propyl)-5-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (3g). Brown solid (1.30 g, 93%). ^1H NMR ($CDCl_3$) δ 0.96 (3H, t, J=7.3 Hz), 1.41 (3H, t, J=7 Hz), 1.67 (2H, m), 3.05 (2H, m), 4.41 (2H, q, J=7 Hz), 4.73 (2H, s), 7.35 (2H, s), 7.66 (1H, s), 8.22 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.16, 14.33, 24.20, 26.60, 47.67, 60.75, 112.26, 120.72, 123.78, 124.66, 125.93, 127.52, 128.64, 135.43, 162.24.

2.3.4. 3-(2-Dimethylamino-ethyl)-5-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (3h). Colorless crystals (1.1 g, HCl salt, 64%). ^1H NMR ($CDCl_3$) δ 1.44 (3H, t, J=7 Hz), 2.91 (3H, s), 2.93 (3H, s), 3.20 (2H, m), 3.46 (2H, m), 4.33 (2H, q, J=7 Hz), 4.81 (2H, s), 7.38 (2H, s), 7.85 (1H, s), 9.12 (1H, s). ^{13}C NMR (DMSO-d_6) δ 14.96, 20.24, 42.47, 48.34, 56.87, 61.29, 113.80, 117.85, 121.52, 125.25, 127.06, 127.17, 129.77, 136.62, 161.94.

2.3.5. 3-(2-Methoxycarbonyl-ethyl)-4-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (5a). Colorless crystals (1.37 g, 85%), mp 130–132 °C (MeOH). ^1H NMR ($CDCl_3$) δ 1.40 (3H, t, J=7 Hz), 2.74 (2H, m), 3.65 (2H, m), 3.68 (3H, s), 4.42 (2H, q, J=7 Hz), 5.00 (2H, s), 7.07 (1H, d, J=7 Hz), 7.21 (1H, t, J=8 Hz), 7.37 (1H, d, J=7.8 Hz), 9.60 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.29, 21.64, 36.03, 45.22, 51.68, 61.18, 113.38, 122.35, 123.34, 124.39, 124.44, 125.16, 131.45, 136.78, 162.10, 173.55. IR: 3303, 1731, 1690, 1321 cm^{-1}.

2.3.6. 3-(3-Methoxycarbonyl-propyl)-4-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (5b). Colorless crystals (1.50 g, 88%), mp 122–124 °C (MeOH). ^1H NMR ($CDCl_3$) δ 1.43 (3H, t, J=7 Hz), 2.00 (2H, m), 2.49 (2H, m), 3.36 (2H, m), 3.69 (3H, s), 4.41 (2H, q, J=7 Hz), 5.00 (2H, s), 7.12 (1H, d, J=7 Hz), 7.26 (1H, t, J=8 Hz), 7.37 (1H, d, J=7.8 Hz), 8.88 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.40, 25.18, 27.42, 33.96, 45.08, 51.61, 60.96, 113.08, 123.22, 123.81, 124.23, 124.69, 124.24, 131.59, 136.63, 162.05, 174.00. IR: 3301, 1733, 1682, 1321 cm^{-1}.

2.3.7. 3-(2-Methoxycarbonyl-ethyl)-6-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (5c). Colorless crystals (1.34 g, 83%), mp 104–106 °C (MeOH). ^1H NMR ($CDCl_3$) δ 1.41 (3H, t, J=7 Hz), 2.66 (2H, m), 3.39 (2H, m), 3.63 (3H, s), 4.40 (2H, q, J=7 Hz), 4.69 (2H, s), 7.17 (1H, d, J=8.4 Hz), 7.39 (1H, s), 7.68 (1H, d, J=8.4 Hz), 9.02 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.14, 20.22, 34.93, 46.94, 51.42, 60.91, 111.96, 120.83, 120.95, 122.26, 124.27, 127.38, 134.73, 135.66, 162.04, 173.45. IR: 3306, 1731, 1689, 1322 cm^{-1}.

2.3.8. 3-(3-Methoxycarbonyl-propyl)-6-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (5d). Colorless crystals (1.55 g, 92%), mp 92–94 °C (MeOH). ^1H NMR ($CDCl_3$) δ 1.42 (3H, t, J=7 Hz), 2.00 (2H, m), 2.36 (2H, m), 3.14 (2H, m), 3.69 (3H, s), 4.40 (2H, q, J=7 Hz), 4.70 (2H, s), 7.16 (1H, d, J=7 Hz), 7.39 (1H, s), 7.66 (1H, d, J=8.3 Hz), 8.92 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.39, 23.89, 25.84, 33.55, 47.09, 51.46, 60.91, 111.89, 121.00, 121.26, 123.59, 124.30, 127.94, 134.94, 135.63, 162.14, 174.00. IR: 3304, 1730, 1692, 1322 cm^{-1}.

2.3.9. 3-(3-(Dimethylcarbamoyl)-propyl)-5-(2-(dimethylsulfamoyl)-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (18). To the solution of $SOCl_2$ (2 ml, 28 mmol) and DMF (0.06 ml) in CH_2Cl_2 (30 ml) was added **16** (1.15 g, 3 mmol) and the reaction mixture was stirred for 24 h at rt. The solvent was evaporated and the remaining oil dissolved in dry CH_2Cl_2 (20 ml). This solution was added to Me_2NH (3 ml, 22 mmol, 33% in H_2O) at 0 °C over a period of 1 h. The reaction mixture was allowed to reach rt and stirred for additional 4 h then the layers were separated, the aqueous phase extracted with CH_2Cl_2 (10 ml). The combined organic phase was dried ($MgSO_4$) and the solvent

evaporated to give **18** as a semicrystalline brown solid (1.2 g, 91%), mp 110–112 °C (EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, $J=7$ Hz), 2.00 (2H, m), 2.36 (2H, m), 2.87 (6H, s), 2.91 (3H, s), 2.92 (3H, s), 3.16 (2H, m), 3.19 (4H, s), 4.37 (2H, q, $J=7$ Hz), 7.13 (1H, dd, $J=8.5$, 1.5 Hz), 7.30 (1H, d, $J=8.4$ Hz), 7.51 (1H, s), 8.93 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.38, 24.04, 26.05, 29.37, 32.82, 35.32, 37.14, 37.45, 50.11, 60.72, 112.17, 120.01, 123.80, 123.89, 126.21, 128.28, 129.68, 134.84, 162.19, 172.87. IR: 1670, 1242 cm^{-1}. Anal. Calcd for $C_{21}H_{31}N_3O_5S$: C, 57.65; H, 7.14; N, 9.60. Found: C, 57.60; H, 7.17; N, 9.49.

Acknowledgements

The authors would like to thank the National Fund for Science and Research (OTKA Project No. T038329) for financial support.

References and notes

1. This work has been published as preliminary communication: (a) Pete, B.; Tőke, L. *Tetrahedron Lett.* **2001**, *42*, 3373. (b) Pete, B.; Parlagh, Gy. *Tetrahedron Lett.* **2003**, *44*, 2537.
2. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
3. (a) Pérez-Serrano, L.; Casarrubios, L.; Domınguez, G.; Freire, G.; Pérez-Castells, J. *Tetrahedron* **2002**, *58*, 5407. (b) Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267.
4. Shin, C.; Yamada, Y.; Hayashi, K.; Yonezawa, Y.; Umemura, K.; Tanji, T.; Yoshimura, J. *Heterocycles* **1996**, *43*, 891.
5. Castedo, L.; Marcos, C. F.; Ruiz, M.; Tojo, G. *Heterocycles* **1990**, *31*, 37.
6. Rahman, A.; Basha, A. In *Biosynthesis of Indole Alkaloids The International Series of Monographs on Chemistry*; Baldwin, J. E., Goodenough, J. B., Halpern, J., Rowlinson, J. S., Eds.; Clarendon: Oxford, 1983; p 176.
7. Gerwick, W. H.; Tan, L. T.; Sitachitta, N. Nitrogen-containing metabolites from marine cyanobacteria. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 2001; p 136.
8. Xu, Y. C.; Schaus, J. M.; Walker, C.; Krushinski, J.; Adham, N.; Zgombick, J. M.; Liang, S. X.; Kohlman, D. T.; Audia, J. E. *J. Med. Chem.* **1999**, *42*, 526.
9. (a) Moloney, G. P.; Robertson, A. D.; Martin, G. R.; MacLennan, S.; Mathews, N.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Glen, R. C. *J. Med. Chem.* **1997**, *40*, 2347. (b) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dodsworth, S.; Sang, P. Y.; Knight, C.; Williams, M.; Maxwell, M.; Glen, R. C. *J. Med. Chem.* **1999**, *42*, 2504.
10. Chen, C. Y.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738.
11. (a) Yeung, K. S.; Farkas, M. E.; Qiu, Z.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 5793. (b) Cruz, R. P. A.; Ottoni, O.; Abella, C. A. M.; Aquino, L. B. *Tetrahedron Lett.* **2001**, *42*, 1467. (c) Demopoulos, V. J.; Nicolaou, I. *Synthesis* **1998**, 1519. (d) Nakatsuka, S.; Teranishi, K.; Goto, T. *Tetrahedron Lett.* **1994**, *35*, 2699. (e) Tani, M.; Aoki, T.; Ito, S.; Matsumoto, S.; Hideshima, M.; Fukushima, K.; Nozawa, R.; Maeda, T.; Tashiro, M.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3261. (f) Murakami, Y.; Tani, M.; Tanaka, K.; Yokoyama, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2023.
12. Uhle, F. C.; McEwen, C. M.; Schroter, H.; Yuan, C.; Baker, B. W. *J. Am. Chem. Soc.* **1960**, *82*, 1200.
13. Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.
14. Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.
15. Barber, H. J.; Fuller, R. F.; Green, M. B.; Zwartouw, H. T. *J. Appl. Chem.* **1953**, *3*, 266.
16. Hinkley, J. M.; Porcari, A. R.; Walker, J. A.; Swayze, E. E.; Townsend, L. B. *Synth. Commun.* **1998**, *28*, 1703.
17. (a) McManus, S. P.; Smith, M. R.; Herrmann, F. T.; Abramovitch, R. A. *J. Org. Chem.* **1978**, *43*, 647. (b) King, J. M.; Khemani, K. C. *Can. J. Chem.* **1985**, *63*, 619.
18. Takahashi, M.; Muta, S. *Synthesis* **1997**, 866.
19. Castro, J. L.; Matassa, V. G. *Tetrahedron Lett.* **1993**, *34*, 4705.
20. Remers, W. A. Properties and reactions of indoles. In *The Chemistry of Heterocyclic Compounds. Indoles, Part One*; Houlihan, W. J., Ed.; Wiley-Interscience, New York, 1972; p 55.
21. Remers, W. A. Properties and reactions of indoles. In *The Chemistry of Heterocyclic Compounds. Indoles, Part One*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; p 59.
22. We have also prepared 2-ethoxycarbonyl-1*H*-indole-7-methanesulfonic acids which gave 7-chloromethyl-indoles when treated with $SOCl_2$.[24] The reactivity of 7-chloromethyl-indoles in nucleophilic substitution reactions was the same as that observed in case of 5-chloromethyl-indoles.[24]
23. Pete, B.; Parlagh, Gy.; Tőke, L. *Heterocycles* **2003**, *60*, 2761.
24. Pete, B. et al. Unpublished results.
25. King, M. D.; Sue, R. E.; White, R. H.; Young, D. J. *Tetrahedron Lett.* **1997**, *38*, 4493.
26. Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638.
27. Pete, B.; Simig, Gy.; Poszávácz, L.; Tőke, L. *Heterocycles* **2003**, *60*, 2441.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8839–8843

Synthesis of novel hydropyrazolopyridine derivatives in solvent-free conditions via benzotriazole methodology

Rodrigo Abonia,[a,*] Emerson Rengifo,[a] Jairo Quiroga,[a] Braulio Insuasty,[a] Justo Cobo[b] and Manuel Nogueras[b]

[a]*Grupo de Investigación de Compuestos Heterocíclicos, Department of Chemistry, Universidad del Valle, A.A. 25360 Cali, Colombia*
[b]*Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain*

Received 15 June 2004; revised 9 July 2004; accepted 14 July 2004

Available online 21 August 2004

Abstract—The reaction between 5-[*N*-(benzotriazol-1-ylmethyl)amino]-3-*tert*-butyl-1-phenylpyrazole or 5-amino-4-(benzotriazol-1-ylmethyl)-3-*tert*-butyl-1-phenylpyrazole with some unactivated and electron-rich alkenes has followed heterocyclization reactions to yield hydropyrazolopyridines, under solvent-free conditions, as predicted by benzotriazole methodology in contrast with those results obtained under solution. The reaction mechanism was proposed after fully spectroscopic analysis of final products and intermediates.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Pyrazolopyridines and its hydroderivatives are target compounds because of the displayed interesting biological activities.[1–4] In our ongoing search for new preparation methods of these derivatives with diverse substitution, and or fused with other rings, we have already reported different preparation methods of such derivatives from 5-amino-3-methyl-1-phenylpyrazole and chalcones or Mannich bases, what have been proved as versatile methods in heterocyclic synthesis.[5,6]

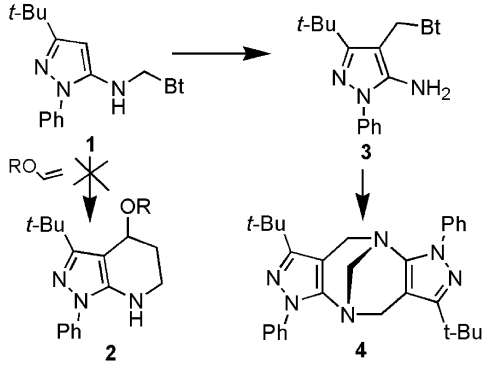
Recently, we have described two attempts for preparing tetrahydropyrazolopyridines **2** using benzotriazole methodology,[7–9] by reaction of the benzotriazolyl 5-aminopyrazole **1** with electron-rich alkenes in methanolic solution (see Scheme 1).

Both attempts failed in the obtention of target compounds **2**, but alternatively, the isomerization to product **3** and the unexpected isolation of the pyrazole Tröger's base analogue **4** have been important to understand the behavior and evolution of this kind of compounds.[10]

Using such results as starting point, we have successfully prepared the target tetrahydropyrazolopyridine derivatives following the benzotriazole methodology under solvent-free conditions with *p*-toluenesulfonic acid as catalyst. So, we are reporting here the preparation of diverse tetrahydropyrazolopyridines including the novel triaza-indacene and triaza-cyclopentanaphthalene derivatives.

2. Results and discussion

Taking into account that the reactions between 5-[*N*-(benzotriazol-1-ylmethyl)amino]-3-*tert*-butyl-1-phenylpyrazole **1** and electron-rich alkenes failed to render the predicted products **2** when they were carried out in solution (Scheme 1), we decided to heat, in an oil bath, a mixture of compound **1** with an excess (5 equiv.) of the corresponding



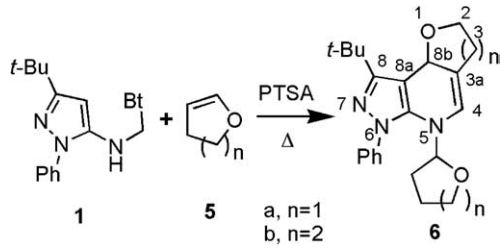
Scheme 1. Reaction evolution of benzotriazolyl 5-aminopyrazole **1** in alcoholic solution.

Keywords: 5-Aminopyrazole; Hydropyrazolopyridines; Benzotriazole; Alkenes; Cyclization; Triaza-indacenes; Triaza-cyclopentanaphthalenes.
* Corresponding author. Address: Departamento de química, Universidad del Valle, A. A. 25360, Cali, Colombia. Tel./fax: +57-2-3392440; e-mail: abonia@univalle.edu.co

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.028

alkene (both cyclic **5a(b)** and terminal **7**, **9** were used), in the presence of catalytic amounts of *p*-toluenesulfonic acid.

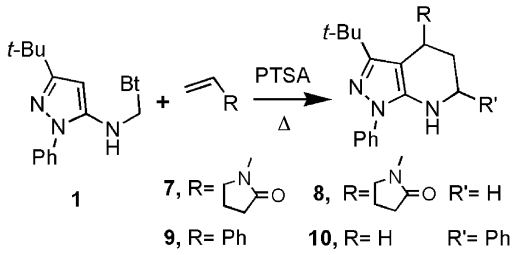
This approach, in the case of the cyclic alkenes **5a(b)**, afforded well 3,5,6,8b-tetrahydro-2*H*-furo[2,3-*d*]pyrazolo[3,4-*b*]pyridine (triaza-*as*-indacene) **6a**, or 2,3,4,6,7,9a-hexahydropyrano[2,3-*d*]pyrazolo[3,4-*b*]pyridine (triaza-cyclopenta[*a*]naphthalene) **6b**, both isolated as oily residues in moderate to good yields (see Scheme 2).



1 5 6

Scheme 2. Reaction products **6** from pyrazole **1** and cyclic alkenes **5** in solvent-free conditions. Numbering is displayed for **6a**.

This methodology was extended to the reaction of **1** with terminal alkenes **7** and **9** (Scheme 3).



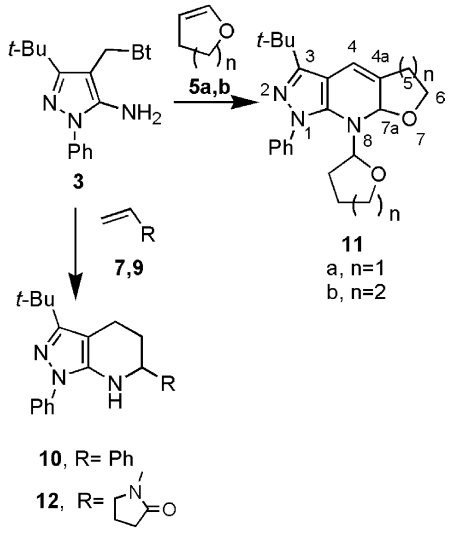
1

Scheme 3. Pyrazolopyridines from reaction of pyrazole **1** and terminal alkenes **7**, **9** in solvent-free conditions.

In both cases, although pyrazolopyridines **8** and **10** are, respectively, formed, several features are pointed out as important to understand this kind of reactions: (i) there is no introduction of a second molecule on nitrogen at pyridine moiety due to the less activated double bond, (ii) there is no oxidation at pyridine moiety as happens with **6**, and (iii) regiochemistry changes when styrene **9** is used.

After the confirmation of the structures **6**, **8** and **10**, we decide to apply this approach to the (less reactive) benzotriazolyl isomer **3**,[11,12] and hence try to control the regiochemistry of the final products. As predicted, the reaction of **3** with the cyclic **5a(b)** affords the corresponding 1,5,7a,8-tetrahydrofuro[2,3-*b*]pyrazolo[4,3-*e*]pyridine (triaza-*s*-indacene) **11a** and 1,5,6,7,8a,9-hexahydropyrano[2,3-*b*]pyrazolo[4,3-*e*]pyridine (triaza-cyclopenta[*b*]-naphthalene) **11b**, respectively. From the terminal alkenes **7** and **9** the corresponding tetrahydropyrazolopyridines **12** and **10** were obtained, which were isolated as oily materials in acceptable to good yields as well (Scheme 4). It is remarkable that just in the case of reaction with the unactivated styrene **9** the final product was the same both from **1** and **3**.

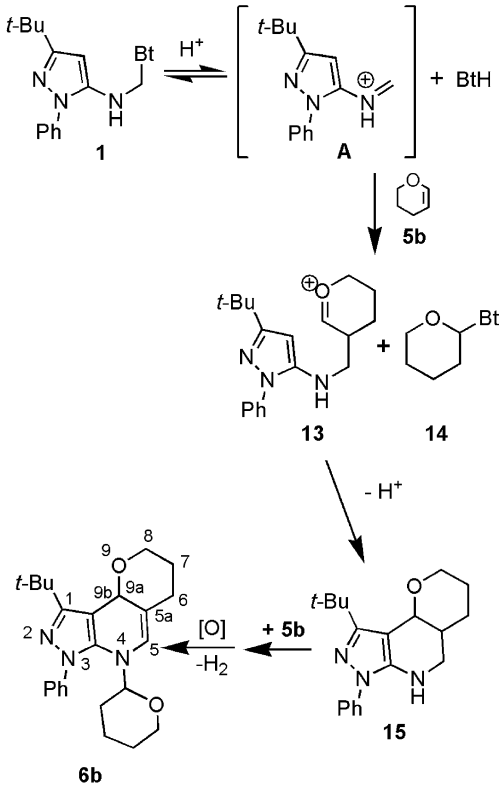
Compounds **6/11** (1:2-adducts) result from a first



3 11

Scheme 4. Pyrazolopyridines from pyrazole **3** via benzotriazole methodology in solvent-free conditions. Numbering is displayed for **11a**.

heterocyclization step between one equivalent of the cyclic alkenes **5** and compound **1/3**, respectively, to give the analogue intermediates type **15**, which give final products after N-alkylation on its free N–H with a second equivalent of the corresponding alkene and further oxidation (Scheme 5 shows the pathway to form **6b**). It is difficult to point out if the oxidative process, to form **6** and **11**, happens before or after the N-alkylation step. However, it seems to proceed after the N-alkylation as indicated in Scheme 5, because it would preclude the complete aromatization of the hydropyridinic ring, that could take place under the reaction conditions. The reaction progress was monitored by TLC,



1 A 13 14 15 6b

Scheme 5. Stepwise formation of compounds **6b** and related products.

showing that in all cases by-products type **14** were produced, what is in accordance with this methodology, confirming the pathway shown above.

Although compounds **6** and **11** are obtained as mixtures of two racemates, as consequence of the generation of two stereogenic centers from the reaction, that is, C-8b(9a) and C-2′(2′) for **6a**(**b**) and C-7a(8a), C-2′(2′) for **11a**(**b**), it was not possible to separate them and the raw mixtures were characterized just as they were.

Structures **6a(b)** and **11a(b)** were fully characterized by spectroscopic and analytical data, and apart from other absorptions in ^{1}H NMR, the main signals correspond to a set of a couple of two doublets, one between 8.35 and 8.37 ppm (J=1.8–3.0 Hz) assigned to H-8b(9a) for **6a**(**b**); and H-7a(8a) for **11a**(**b**), and the other one between 8.52 and 8.53 ppm (J=1.8–3.0 Hz) corresponding to H-4(5) for **6a**(**b**); and H-4 for **11a(b)**, which appear coupled each other through allylic coupling. These coupling along with the absence of N–H absorption in IR spectra, and the relatively low-field chemical shift of H-4(5) (in aromatic region) for both type of compounds **a**(**b**), are in accordance with the proposed structures for **6** and **11**. The most relevant signals observed in the ^{13}C NMR correspond again with that allylic moiety CH–C=CH: that is, absorptions between 128.1 and 129.0 ppm assigned to central quaternary C at mentioned allylic moiety; between 130.5 and 131.1 ppm for the allylic CH position C-9a for **6b**, and finally between 149.6 and 152.9 ppm for the vinyl CH of such residue. Signals for both hydrofuran-2-yl and hydropyran-2-yl substituents are also remarkable, confirming in this way the N-alkylation in these reactions. Regiochemistry is also confirmed by HMBC experiments, in which are observed correlation between H-4(5)↔C-8b(9a), H-8b(9a)↔C-8(1) and H-4(5)↔C-2′(2′) for **6a**(**b**) and between H-4(4)↔C-7a(8a), H-4(4)↔C-3(3) and H-7a(8a)↔C-2′(2′) for **11a**(**b**). NOESY experiments also determinant for complete characterization agreed with proposed structures observing the following remarkable correlations: H-8b(9a)↔H-2′(2′) in compounds **6** and H-4↔H(*t*-Bu) in compounds **11**. Other NOE correlations like between H's$_{ortho}$ of phenyl and H-3′ at furan or pyran residues were also observed for both **6** and **11** compounds, which agree with the commented N-alkylation.

Concerning to the pyrrolidinonyl tetrahydro-1*H*-pyrazolo [3,4-*b*]pyridines **8/12**, which result from reaction between pyrazoles **1/3** and terminal 1-vinyl-2-pyrrolidinone **7**, that were isolated as white solid and light oil, respectively, spectroscopic findings are pointed out herein after, and are in complete agreement with the proposed structures for both compounds (Schemes 3 and 4). These findings are mainly referred to the regiochemistry and the related intramolecular hydrogen bonding. So, the stretching vibrations bands at 3381/3315 cm^{-1}, and at 1658/1652 cm^{-1}, for the IR spectra of **8/12**, respectively, confirms the presence of the secondary amide group and so the pyrrolidinonyl fragment. The notorious appearance of the 7-NH and C-2′=O stretching vibrations for compound **12** at relatively lesser wave-numbers than those for compound **8**, suggests an appreciable intramolecular hydrogen bonding between 7-NH and C-2′=O groups in **12**, which is precluded in compound **8**. In the ^{1}H NMR spectra, the 7-NH groups at 5.92 and 8.30 ppm are clearly observed as broad and sharp singlets for **8** and **12**, respectively. The shape and chemical shift of 7-NH in **12** also confirm the intramolecular hydrogen bonding. On the contrary that happens with compounds **6/11**, in compounds **8/12** the oxidative process towards the dihydropyridinic rings were not observed, and so, signals for the saturated protons H-4, H-5 and H-6 appear between 1.66 and 6.65 ppm in the aliphatic region. Signals for the pyrrolidinonyl residue also appear in above region for both compounds. As expected, signal for H-6 in **12** appears at lower field (6.62 ppm) than its analogue H-4 in **8** (5.18 ppm), due to the deshielding effect of both nitrogen atoms bonded to C-6 in **12**. In the ^{13}C NMR spectra, all the above observations are confirmed: C-2′=O absorptions at 172.9 and 174.8 ppm for **8** and **12**, respectively; C-4, C-5- and C-6 appear between 18.1 and 60.6 ppm (aliphatic region). Mass spectra are also consistent with the proposed structures, where, the formation of the stable aromatic pyrazolopyridinium ion with loss of pyrrolidinonyl residue is the main fragmentation process being the base-peak.

Finally, compound **10** was obtained in comparable yields from the reaction both of **1** and **3** with the unactivated styrene **9**, what suggests a first isomerization step from **1** to **3** during the reaction course if it started from **1**. This was confirmed by TLC detection and further isolation of the isomer **3** from the reaction mixture. Such isomerization process from **1** to **3** was also described in ethanolic solution.[10] Probably, the styrene **9** behaves more as a solvent than as reactant, due to its relatively less reactivity compared with the other alkenes, allowing the initial isomerization from **1** towards the more stable isomer **3** when mixture is heated.[11] Then, **3** reacts with **9** slowly yielding product **10**. Compound **10** was fully characterizated by spectroscopic methods. So in the IR spectrum, a stretching vibration band at 3371 cm^{-1} confirms the free NH group. In the ^{1}H NMR spectrum, signals for H-4, H-5 and H-6 are also observed in the aliphatic region, what confirms the non-oxidative process on the pyridinic moiety like in compounds **8** and **12**. The N(7)–H appears at 5.81 ppm as a narrow doublet (J=3.4 Hz), coupled with H-6, in accordance with the proposed structure. The presence of four new aromatic signals (from the styrene), in the ^{13}C NMR spectrum, as well as, a COSY correlation between H-6 and 7-NH, corroborate the orientation of this reaction and the structure for compound **10**. Mass spectrum shows the molecular ion with m/z=331 as base-peak, contrary to that observed for their analogues **8** and **12**. This fact could be explained by a relatively lesser tendency of a molecule of benzene to be lost from compound **10**, when comparing with a pyrrolidinone one from compounds **8** and **12**.

For compounds **8**, **10** and **12** the N-alkylation step was not observed like occurs for compounds **6** and **11**. This fact can mainly be explained on the basis of the lesser reactivity of styrene and 1-vinyl-2-pyrrolidinone than vinyl ehers towards nucleophilic addition, more than owing to differences in nucleophilicity or steric effects of the pyrazolopyridine intermediates type **15** versus structures **8**, **10** and **12**.

3. Conclusions

It is remarkable that this simple solvent-free methodology readily allows the synthesis of novel hydropyrazolopyridines, such triaza-*s*-(*as*)-indacene or cyclopenta[*a*]([*b*])-naphthalene derivatives, which are not reported elsewhere, and are not easy to obtain from other methods. Undoubtedly, the exchange of the reaction conditions (solvent-free vs. methanol) was the critical point to accomplish the synthesis of the expected products. We can conclude that solvent promotes isomerization or even other processes but not the desired heterocyclization reaction. Finally, compounds **6** and **11** (1:2-adducts) that were initially non-desired by-product of target ones, are of particular interest owing to their structures are closely related to the framework of some naturally occurring products.[13,14]

4. Experimental

4.1. General methods

All melting points were determined on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX 300 (300 and 75.5 MHz, for ^{1}H and ^{13}C respectively), DMSO-d_6 (δ_H=2.5; δ_C=39.5) as solvent, TMS as internal standard. Silica gel plates (Merk F_{254}) were used for analytical TLC. The IR spectra were recorded on a SHIMADZU FTIR-8400 spectrophotometer in KBr discs. The Mass spectra were run on a Hewlett Packard 5989-B spectrometer (EI, 70 eV). The starting 5-amino-3-*tert*-butyl-1-phenylpyrazole was prepared from 4,4-dimethyl-3-oxopentanonitrile and phenylhydrazine following a general procedure.[15]

4.2. General procedure for preparing the compounds (6,11)a, (6,11)b, 8, 10 and 12

A mixture of 5-[*N*-(benzotriazol-1-ylmethyl)amino]-3-*tert*-butyl-1-phenylpyrazole **1**[10] or 5-amino-4-(benzotriazol-1-ylmethyl)-3-*tert*-butyl-1-phenylpyrazole **3**[4] (200 mg, 0.58 mmol), the respective alkene **5a(b)**), **7** or **9** (2.9 mmol) and *p*-toluenesulfonic acid (50 mg) was heated in an oil bath (until melting), for 3–5 min (TLC monitoring). After cooling, each mixture was dissolved in ethyl acetate (5 mL) and washed with aq NaOH solution (5%, 10 mL) and water, and organic extract dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the oily residues were purified by column chromatography on silica gel and (gradient hexane/ethyl acetate) as eluent.

4.2.1. 8-*tert*-Butyl-6-phenyl-5-(tetrahydrofuran-2-yl)-3,5,6,8b-tetrahydro-2*H*-1-oxa-5,6,7-triaza-*as*-indacene (6a). This compound was obtained from 2,3-dihydrofuran **5a** and pyrazole **1** as light oil, 70% yield; ^{1}H NMR (DMSO-d_6): 1.53 (s, 9H, 3 CH_3 *t*-Bu), 1.75–1.77 (m, 2H, H-4′), 1.79–1.85 (m, 2H, H-3′), 3.00 (m, 2H, H-3), 3.60–3.65 (m, 2H, H-5′), 3.67–3.88 (m, 2H, H-2), 5.11 (d, J=3.0 Hz, 1H, H-2′), 7.30 (t, J=6.0 Hz, 1H, H_{para}), 7.54 (t, J=6.0 Hz, 2H, H_{meta}), 8.29 (d, J=9.0 Hz, 2H, H_{ortho}), 8.37 (d, J=1.8 Hz, 1H, H-8b), 8.52 (d, J=1.8 Hz, 1H, H-4); ^{13}C NMR (DMSO-d_6): δ 23.0 (C-4′), 29.4 (3 CH_3 *t*-Bu), 31.8 (C-3′), 32.4 (C-3), 33.8 (C_q *t*-Bu), 66.1 (C-5′), 67.1 (C-2), 103.1 (C-2′), 114.2 (C-8a), 119.8 (Ph–C_{ortho}), 125.0 (Ph–C_{para}), 128.2 (C-3a), 129.0 (Ph–C_{meta}), 131.1 (C-8b), 139.3 (Ph–C_{ipso}), 149.8 (C-4- and C-5a), 152.9 (C-8); MS *m*/*z* (%): 365 (42) [M^+], 277 (36), 265 (30), 71 (100), 57 (13), 43 (39). Anal. calcd for $C_{22}H_{27}N_3O_2$ (365.48): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.45; H, 7.38; N, 11.64.

4.2.2. 1-*tert*-Butyl-3-phenyl-4-(tetrahydropyran-2-yl)-3,4,6,7,8,9a-hexahydro-9-oxa-2,3,4-triaza-cyclopenta[*a*]-naphthalene (6b). This compound was obtained from 3,4-dihydro-2*H*-pyran **5b** and pyrazole **1** as light oil, 75% yield; ^{1}H NMR (DMSO-d_6): 1.00–1.65 (m, 14H, 3 CH_3 *t*-Bu, H-4′, H-5′ and one H-7), 1.85–1.97 (m, 3H, H-3′a and one H-7), 2.85 (br t, 2H, H-6), 3.36–3.42 (m, 1H, one H-8), 3.62–3.79 (m, 3H, one H-8, H-6′), 4.54 (br s, 1H, H-2′), 7.29 (t, J=6.0 Hz, 1H, H_{para}), 7.53 (t, J=7.3 Hz, 2H, H_{meta}), 8.27 (d, J=7.7 Hz, 2H, H_{ortho}), 8.35 (d, J=1.8 Hz, 1H, H-9a), 8.52 (d, J=1.8 Hz, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ 19.2 (C-4′), 25.0 (C-5′), 28.7 (C-7), 29.5 (3 CH_3 *t*-Bu), 30.3 (3′-C), 31.2 (C-6), 33.9 (C_q *t*-Bu), 61.4 (C-6′), 65.7 (C-8), 98.1 (C-2′), 114.3 (C-9b), 119.9 (Ph–C_{ortho}), 125.1 (Ph–C_{para}), 128.9 (C-5a), 129.0 (Ph–C_{meta}), 130.6 (C-9a), 139.4 (Ph–C_{ipso}), 149.6 (C-5), 149.8 (C-3a), 152.9 (C-1); MS *m*/*z* (%): 393 (95) [M^+], 291 (42), 278 (44), 276 (57), 234 (24), 179 (24), 85 (90), 57 (38), 43 (27), 41 (100). Anal. calcd for $C_{24}H_{31}N_3O_2$ (393.53): C, 73.25; H, 7.94; N, 10.68. Found: C, 73.14; H, 8.09; N, 10.62.

4.2.3. 3-*tert*-Butyl-1-phenyl-8-(tetrahydrofuran-2-yl)-5,6,7a,8-tetrahydro-1*H*-7-oxa-1,2,8-triaza-*s*-indacene (11a). This compound was obtained from 2,3-dihydrofuran **5a** and pyrazole **3** as light oil, 62% yield; ^{1}H NMR (DMSO-d_6): 1.53 (s, 9H, 3 CH_3 *t*-Bu), 1.70–1.78 (m, 2H, H-4′), 1.80–1.89 (m, 2H, H-3′), 3.01 (t, J=6.7 Hz, 2H, H-5), 3.61–3.66 (m, 2H, H-5′), 3.68–3.73 (m, 2H, H-6), 5.13 (d, J=3.0 Hz, 1H, H-2′), 7.30 (t, J=6.2 Hz, 1H, H_{para}), 7.54 (br t, J=6.5 Hz, 2H, H_{meta}), 8.28 (br d, J=6.5 Hz, 2H, H_{ortho}), 8.37 (d, J=1.9 Hz, 1H, H-7a), 8.52 (d, J=2.0 Hz, 1H, H-4); ^{13}C NMR (DMSO-d_6): δ 23.0 (C-4′), 29.4 (3 CH_3 *t*-Bu), 31.8 (C-3′), 32.3 (C-5), 33.8 (C_q *t*-Bu), 66.0 (C-5′), 67.1 (C-6), 103.0 (C-2′), 114.2 (C-3a), 118.2 (Ph–C_{ortho}), 125.0 (Ph–C_{para}), 126.7 (Ph–C_{meta}), 128.1 (C-4a), 131.1 (C-7a), 139.3 (Ph–C_{ipso}), 149.8 (C-4 and C-8a), 152.9 (C-3); MS *m*/*z* (%): 365 (17) [M^+], 277 (21), 265 (21), 262 (19), 77 (14), 71 (100), 57 (13), 43 (48), 41 (39). Anal. calcd for $C_{22}H_{27}N_3O_2$ (365.48): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.19; H, 7.37; N, 11.66.

4.2.4. 3-*tert*-Butyl-1-phenyl-9-(tetrahydropyran-2-yl)-1,5,6,7,8a,9-hexahydro-8-oxa-1,2,9-triaza-cyclopenta[*b*] naphthalene (11b). This compound was obtained from 3,4-dihydro-2*H*-pyran **5b** and pyrazole **3** as light oil, 68% yield; ^{1}H NMR (DMSO-d_6): 1.38–1.60 (m, 13H, 3 CH_3 *t*-Bu, H-4′ and H-5′), 1.65–1.73 (m, 2H, H-6), 1.85–2.05 (m, 2H, H-3′), 2.85 (t, J=6.0 Hz, 2H, H-5), 3.40–3.51 (m, 1H, one H-7), 3.65–3.82 (m, 3H, H-6′, one H-7), 4.55 (br s, 1H, H-2′), 7.28 (t, J=6.0 Hz, 1H, H_{para}), 7.54 (t, J=7.0 Hz, 2H, H_{meta}), 8.27 (d, J=7.0 Hz, 2H, H_{ortho}), 8.35 (d, J=3.0 Hz, 1H, H-8a), 8.53 (d, J=3.0 Hz, 1H, H-4); ^{13}C NMR (DMSO-d_6): δ 19.2 (C-4′), 25.0 (C-5′), 28.7 (C-6), 29.4 (3 CH_3 *t*-Bu), 30.3 (3′-C), 31.1 (C-5), 33.8 (C_q *t*-Bu), 61.3 (C-6′), 65.7 (C-7), 98.0 (C-2′), 114.2 (C-3a), 119.8 (Ph–C_{ortho}), 125.0

(Ph–C_{para}), 128.9 (Ph–C_{meta}), 129.0 (C-4a), 130.5 (C-8a), 139.2 (Ph–C_{ipso}), 149.6 (C-4), 149.7 (C-9a), 152.9 (C-3); MS *m/z* (%): 393 (60) [M^+], 378 (10), 278 (40), 276 (56), 234 (23), 85 (100), 57 (44), 41 (97). Anal. calcd for $C_{24}H_{31}N_3O_2$ (393.53): C, 73.25; H, 7.94; N, 10.68. Found: C, 73.14; H, 7.81; N, 10. 63.

4.2.5. 3-*tert*-Butyl-1-phenyl-4-(*N*-pyrrolidin-2-onyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine (8). This compound was obtained from 1-vinyl-2-pyrrolidinone **7** and pyrazole **1** as white solid, 66% yield; mp 75–6 °C; IR (cm^{-1}): 3381 (NH), 1658 (C═O); ^{1}H NMR (DMSO-d_6): 1.17 (s, 9H, 3 CH_3 *t*-Bu), 1.66–1.98 (m, 4H, H-4′, H-5), 2.14–2.39 (m, 2H, H-3′), 3.03–3.15 (m, 2H, H-6), 3.22–3.38 (m, 2H, H-5′), 5.18 (br s, 1H, H-4), 5.92 (br s, 1H, 7-NH), 7.26 (t, J=7.4 Hz, 1H, H_{para}), 7.45 (t, J=8.4 Hz, 2H, H_{meta}), 7.60 (d, J=8.6 Hz, 2H, H_{ortho}); ^{13}C NMR (DMSO-d_6): δ 18.1 (C-5), 29.3 (3 CH_3 *t*-Bu), 29.4 (C-4′), 31.3 (C-3′), 33.0 (C_q *t*-Bu), 38.7 (C-6), 42.5 (C-4), 46.5 (C-5′), 93.0 (C-3a), 121.4 (Ph–C_{ortho}), 125.4 (Ph–C_{para}), 129.1 (Ph–C_{meta}), 139.2 (Ph–C_{ipso}), 146.1 (C-7a), 157.3 (C-3), 172.9 (C-2′═O); MS *m/z* (%): 338 (41) [M^+], 281 (39), 253 (73), 252 (100), 196 (36), 77 (45), 41 (91). Anal. calcd for $C_{20}H_{26}N_4O$ (338.46): C, 70.98; H, 7.74; N, 16.55. Found: C, 71.05; H, 7.79; N, 16.63.

4.2.6. 3-*tert*-Butyl-1,6-diphenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine (10). This compound was obtained from styrene **9** and pyrazoles **1** and **3** as light oil, 80% yield; IR (cm^{-1}): 3354 (NH); ^{1}H NMR (DMSO-d_6): 1.30 (s, 9H, 3 CH_3 *t*-Bu), 1.81–2.02 (m, 2H, H-5), 2.28–2.62 (m, 1H, one H-4), 2.65–2.78 (m, 1H, one H-4), 4.31 (br d, 1H, H-6), 5.81 (d, J=3.4 Hz, 1H, 7-NH), 7.12–7.29 (m, 2H, Ph–H), 7.35 (br t, 2H, Ph–H), 7.39–7.46 (m, 4H, Ph–H), 7.70 (br d, 2H, Ph–H); ^{13}C NMR (DMSO-d_6): δ 20.3 (C-5), 29.3 (3 CH_3 *t*-Bu), 31.2 (C-4), 32.8 (C_q *t*-Bu), 56.0 (C-6), 96.5 (C-3a), 121.2, 124.9, 126.6, 126.8, 128.2, 129.0, 139.7 (Cq Ph), 144.2 (Cq Ph), 145.1 (Cq Ph), 156.6 (C-3); MS *m/z* (%): 331 (100) [M^+], 316 (23), 289 (65), 223 (36), 194 (33), 180 (39), 105 (51), 91 (22), 77 (73). Anal. calcd for $C_{22}H_{25}N_3$ (331.46): C, 79.72; H, 7.60; N, 12.68. Found: C, 79.83; H, 7.64; N, 12.59.

4.2.7. 3-*tert*-Butyl-1-phenyl-6-(*N*-pyrrolidin-2-onyl)-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine (12). This compound was obtained from 1-vinyl-2-pyrrolidinone **7** and pyrazole **3** as light oil, 50% yield; IR (cm^{-1}): 3478 (NH), 1670 (C═O); ^{1}H NMR (DMSO-d_6): 1.24 (s, 9H, 3 CH_3 *t*-Bu), 1.73–2.35 (m, 6H, H-4, H-4′, H-5), 2.75–3.00 (m, 2H, H-3′), 3.10–3.25 (m, 2H, H-5′), 6.63 (m, 1H, H-6), 7.37–7.47 (m, 2H, one H_{ortho}, one H_{meta}), 7.55 (t, 1H, H_{para}), 7.74 (dd, 1H, one H_{meta}), 8.05 (d, 1H, one H_{ortho}), 8.30 (s, 1H, 7-NH); ^{13}C NMR (DMSO-d_6): δ 18.4 (C-5), 29.2 (*t*-Bu-Cq), 29.7 (3 CH_3 *t*-Bu), 30.67 (C-4′), 31.2 (C-3′), 34.2 (C-4), 42.1 (C-5′), 61.0 (C-6), 79.2 (C-3a), 119.1 (Ph–C_{meta}), 121.2 (Ph–C_{para}), 124.4 (Ph–C_{ortho}), 132.2 (Ph–C_{ipso}), 132.5 (C-7a), 145.1 (C-3), 174.8 (C-2′═O); MS *m/z* (%): 339 (80) [M^++H], 338 (49) [M^+], 281 (44), 254 (72), 253 (53), 252 (100), 196 (25), 77 (29), 41 (31).

Acknowledgements

Authors thank COLCIENCIAS, Universidad del Valle, Universidad de Jaén and Consejería de Educación y Ciencia (Junta de Andalucía, Spain) for financial support.

References and notes

1. Hardy, C. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 343–409.
2. Orth, R. E. *J. Pharm. Sci.* **1968**, *57*, 537–556, and references cited therein.
3. Yu, G.; Mason, H.; Wu, X.; Wang, J.; Chong, S.; Dorough, G.; Henwood, A.; Pongrac, R.; Seliger, L.; He, B.; Normandin, D.; Adam, L.; Krupinski, J.; Macor, J. *J. Med. Chem.* **2001**, *44*(7), 1025–1027.
4. El-Ahl, A. A. S.; Metwally, M. A.; Amer, F. A. *Boll. Chim. Farm.* **1995**, *7*, 369–374.
5. Quiroga, J.; Insuasty, B.; Cruz, S.; Hernández, P.; Bolaños, A.; Moreno, R.; Hormaza, A.; De Almeida, R. H. *J. Heterocycl. Chem.* **1998**, *35*, 333–338.
6. Insuasty, B.; Quiroga, J.; Meier, H. *Trends Heterocycl. Chem.* **1997**, *5*, 83–89.
7. Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 3993–4001.
8. Katritzky, A. R.; Abonia, R.; Yang, B.; Qi, M.; Insuasty, B. *Synthesis* **1998**, 1487–1490.
9. Abonia, R.; Albornoz, A.; Insuasty, B.; Quiroga, J.; Meier, H.; Hormaza, A.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. *Tetrahedron* **2001**, *57*, 4933–4938.
10. Abonia, R.; Rengifo, E.; Quiroga, J.; Insuasty, B.; Sánchez, A.; Cobo, J.; Low, J. N.; Nogueras, M. *Tetrahedron Lett.* **2002**, *43*, 5617–5620.
11. In reference 10, we demonstrated that compound **3** is formed from **1** in methanolic solution, and hence the thermodynamic product. Its unreactivity towards heterocyclization reaction was also confirmed.
12. Low, J. N.; Cobo, J.; Nogueras, M.; Sánchez, A.; Rengifo, E.; Abonia, R. *Acta Crystallogr. Sect. E* **2002**, *58*, o53–o54.
13. Horaguchi, T.; Miyazawa, K.; Hasegawa, E.; Shimizu, T.; Suzuki, T.; Tanemura, K. *J. Heterocycl. Chem.* **1990**, *27*(4), 941–948.
14. Mehta, G.; Narayana Murthy, A.; Siva Kumar Reddy, D. *Tetrahedron Lett.* **1987**, *28*(13), 1467–1468.
15. Grandberg, I. I.; Ting, W.-P.; Kost, A. N. *Zhurn. Obsch. Khim.* **1961**, *31*, 2311–2315. *Chem. Abstr.* **1962**, *56*, 4746h.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8845–8854

Rapid oligosaccharide synthesis on a fluorous support

Kohtaro Goto,[a] Tsuyoshi Miura,[a,†,*] Daisuke Hosaka,[a] Hiroharu Matsumoto,[a] Mamoru Mizuno,[a] Hide-ki Ishida[a] and Toshiyuki Inazu[a,b,*]

[a]*The Noguchi Institute, Labolatry of Glycoorganic Chemistry, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan*
[b]*Department of Applied Chemistry, School of Engineering, and Institute of Glycotechnology, Tokai University, Kitakaname 1117, Hiratsuka, Kanagawa 259-1292, Japan*

Received 27 May 2004; revised 13 July 2004; accepted 13 July 2004

Available online 21 August 2004

Abstract—The novel fluorous support **Hfb** (hexakisfluorous chain-type butanoyl) was easily prepared. The **Hfb** group was readily introduced into the anomeric hydroxyl group of a carbohydrate, and was recyclable after cleavage. The use of the **Hfb** group was applicable for the rapid oligosaccharide synthesis in which the synthetic intermediates could be purified using fluorous and normal organic solvents. Each synthetic intermediate could be monitored by TLC, NMR and mass spectrometry.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Recently, it has been gradually revealed that oligosaccharides on cell surfaces play important roles in various biological processes such as cell-cell interaction, cell adhesion and immunogenic recognition.[1] In order to better understand the functions of oligosaccharides, it is necessary to rapidly and efficiently synthesize oligosaccharides. However, it is difficult to synthesize oligosaccharides because of two crucial problems. First, a multitude of hydroxyl groups have similar reactivity of each monomer, and the effective differentiation of each hydroxyl group is required to afford the glycosyl donors and acceptors. Secondly, a control of stereoselectivity at anomeric position in each glycosylation is not easy. Due to these problems, the synthesis of oligosaccharides needs a lengthy process that requires the exact optimization of the reaction conditions and chromatographic purification of the reaction mixture in each step. Therefore, there is no commercially available automatic synthesizer of an oligosaccharide. On the other hand, peptides and nucleotides are easily prepared by a commercially available automatic synthesizer using a solid-phase synthesis. The solid-phase synthesis of oligosaccharides has also been extensively studied,[2] however, the usual solid-phase method suffers from some serious disadvantages, such as the difficulty in large-scale synthesis and the inability to monitor the reaction by TLC, NMR spectroscopic analysis and mass spectrometry. The solid-phase synthesis of oligosaccharide that uses a soluble polymer support (PEG) has also been reported.[2] This strategy can overcome some of these disadvantages, however, it cannot be monitored by TLC and the intermediates cannot be purified by silica-gel column chromatography. To rapidly and efficiently synthesize oligosaccharides, we adopted another concept such as fluorous chemistry that was reported by Horváth and Rabái as the fluorous biphasic system in 1994.[3] A fluorous (highly fluorinated) solvent such as perfluorohexane and perfluoromethylcyclohexane is immiscible in most organic solvents and water, and three layers are formed. A fluorous compound exhibits a high solubility for fluorous solvents, and is readily separated from non-fluorinated compounds by a simple fluorous-organic solvent partition. Since Horváth and Rabái reported this concept, it has been developed for use in a combinatorial chemistry, a parallel synthesis and a catalytic chemistry.[4,5] In addition, since Curran and co-workers described the fluorous synthesis[5] (fluorous-tag method) as a strategic alternative to solid-phase synthesis, fluorous chemistry has become more popular in organic synthesis, such as the Baeyer–Villigar[6] or Swern[7] oxidation, Heck[8] or Suzuki[9] coupling, the Mitsunobu reaction,[10] Friedel–Crafts acylation[11] and so on.[12] Furthermore, they have also reported a fluorous mixture synthesis using a fluorous silica-gel.[13] The fluorous protecting groups are essential for the fluorous synthesis performance. Several fluorous hydroxy protecting groups such as acetal, silyl and benzyl groups have already been reported.[14,15] Other

Keywords: Fluorous; Glycosylation; Oligosaccharide; Synthetic method; Support.
* Corresponding authors. Tel.: +81-3-5944-3215; fax: +81-3-5944-3214 (T.M.); tel.: +81-463-58-1211; fax: +81-463-50-2012 (T.I.); e-mail: tmiura@cis.ac.jp
† Current address: Faculty of Pharmaceutical Sciences, Chiba Institute of Science, Japan.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.027

fluorous protecting groups for amino or carboxyl groups have also been reported.[16] Curran and co-workers adapted the fluorous-tag method to the fluorous disaccharide synthesis using the fluorous benzyl protecting group by a glycal method.[15] Unfortunately, their glycosylation method gave only the 2-deoxy disaccharides and could not synthesize the longer chain oligosaccharides in order to introduce the fluorous benzyl groups to the glycosyl donor. In addition, the yield for the reaction step to introduce the fluorous benzyl group to the hydroxyl group was not satisfactory. Recently, we reported a method for the fluorous oligosaccharide synthesis involving the novel fluorous acyl protecting group **Bfp** (bisfluorous chain-type propanoyl).[17,18] We also reported the fluorous support **Hfb** (hexakisfluorous chain-type butanoyl) in a preliminary communication.[19] Herein we describe the full details of the development of a novel fluorous support **Hfb** and its application to the rapid synthesis of oligosaccharides. Moreover, several glycosylation methods using the fluorous support **Hfb** was studied. Our concept of fluorous oligosaccharide synthesis is shown in Figure 1. We adopted the introduction of a fluorous support only at the anomeric hydroxyl group of the glycosyl acceptor in order to more efficiently synthesize the longer chain oligosaccharides. The glycosyl acceptor containing the fluorous support couples with the glycosyl donor to afford the fluorous disaccharide. After partition of the reaction mixture with fluorous and normal organic solvents, the fluorous disaccharide is extracted by the fluorous layer, and the excess amount of the glycosyl donor is extracted by the organic layer. After selective deprotection, repeating this procedure gives the fluorous oligosaccharide, which is able to be purified only by liquid–liquid extraction without column chromatography. Finally, the fluorous support is removed to give the desired oligosaccharide extracted with an organic solvent. The fluorous support is extracted by a fluorous solvent and is recyclable.

2. Results and discussion

We designed and synthesized compound **10** with six fluorous chains as a novel fluorous support. Compound **4**, which contains three fluorous chains, was prepared as a precursor (Scheme 1). The reaction of **Bfp**-OH[17] (**1**) with a fluorous amine **2**[17] provided compound **3** in 96% yield. The treatment of **3** with aqueous sodium hydroxide gave the fluorous carboxylic acid **4**, which contains three fluorous chains, in 98% yield.

We synthesized compound **10** by two methods using compound **4**, and first attempted to prepare compound **10** using route A (Scheme 2).[19]

The two primary amino groups of diethylenetriamine (**5**) were protected with the triphenylmethyl group to provide the amine **6**[20] in 95% yield. Compound **6** was coupled with methyl hydrogen glutarate to afford compound **7** in 98% yield. Removal of the triphenylmethyl groups from **7** were performed by treatment of HCl in dioxane to give compound **8**. Compound **8** was reacted with fluorous carboxylic acid **4** (2 equiv.) to afford a fluorous ester **9**, which contains six fluorous chains, in 82% yield. The treatment of **9** with aqueous sodium hydroxide gave a fluorous support **10** in 98% yield. The acyl moiety of **10** was

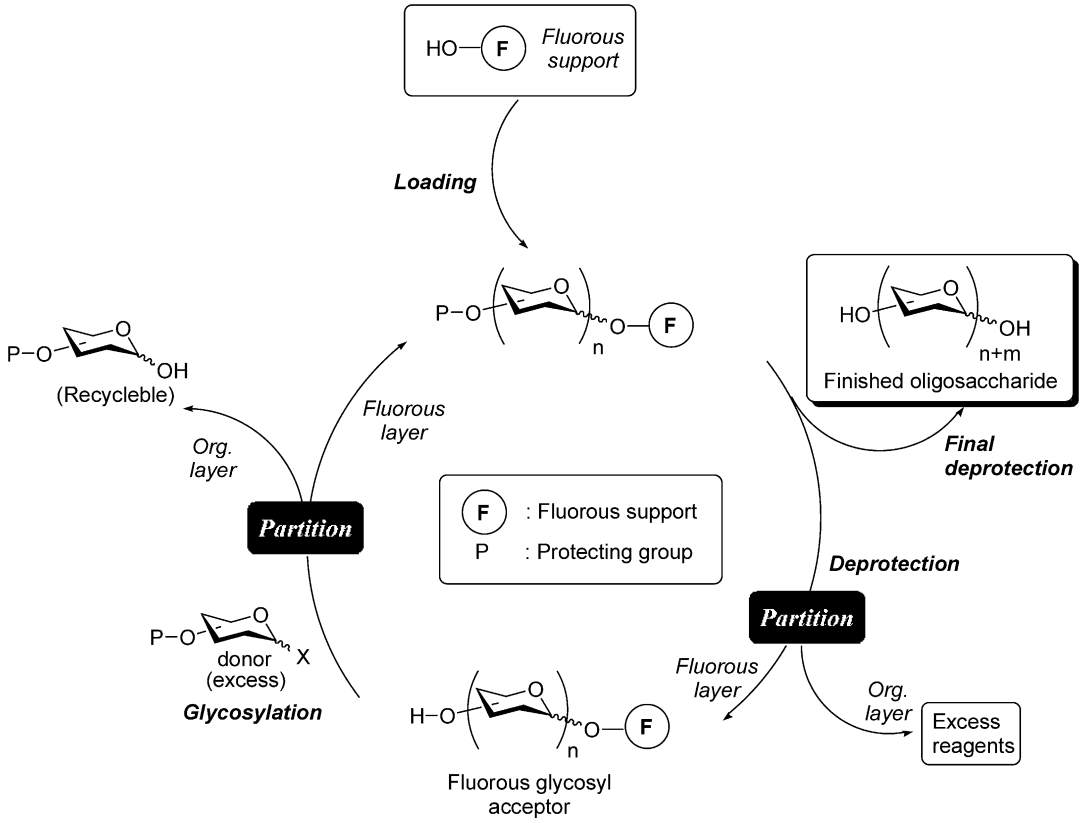
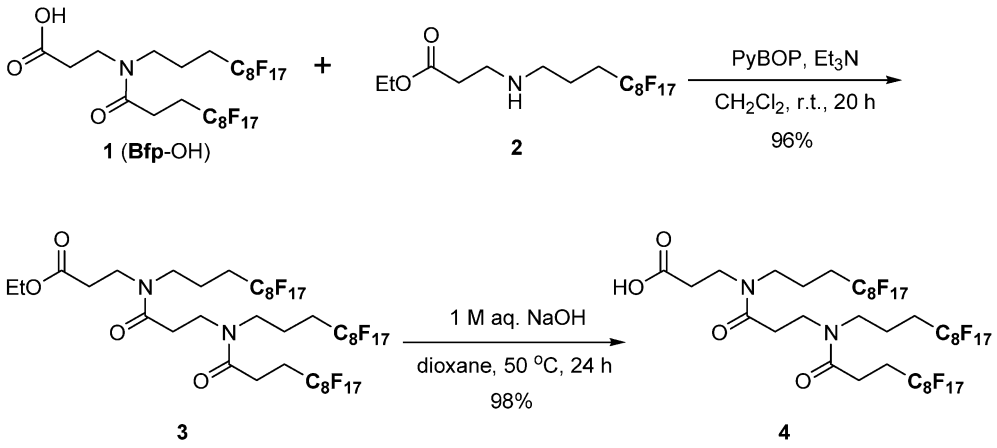


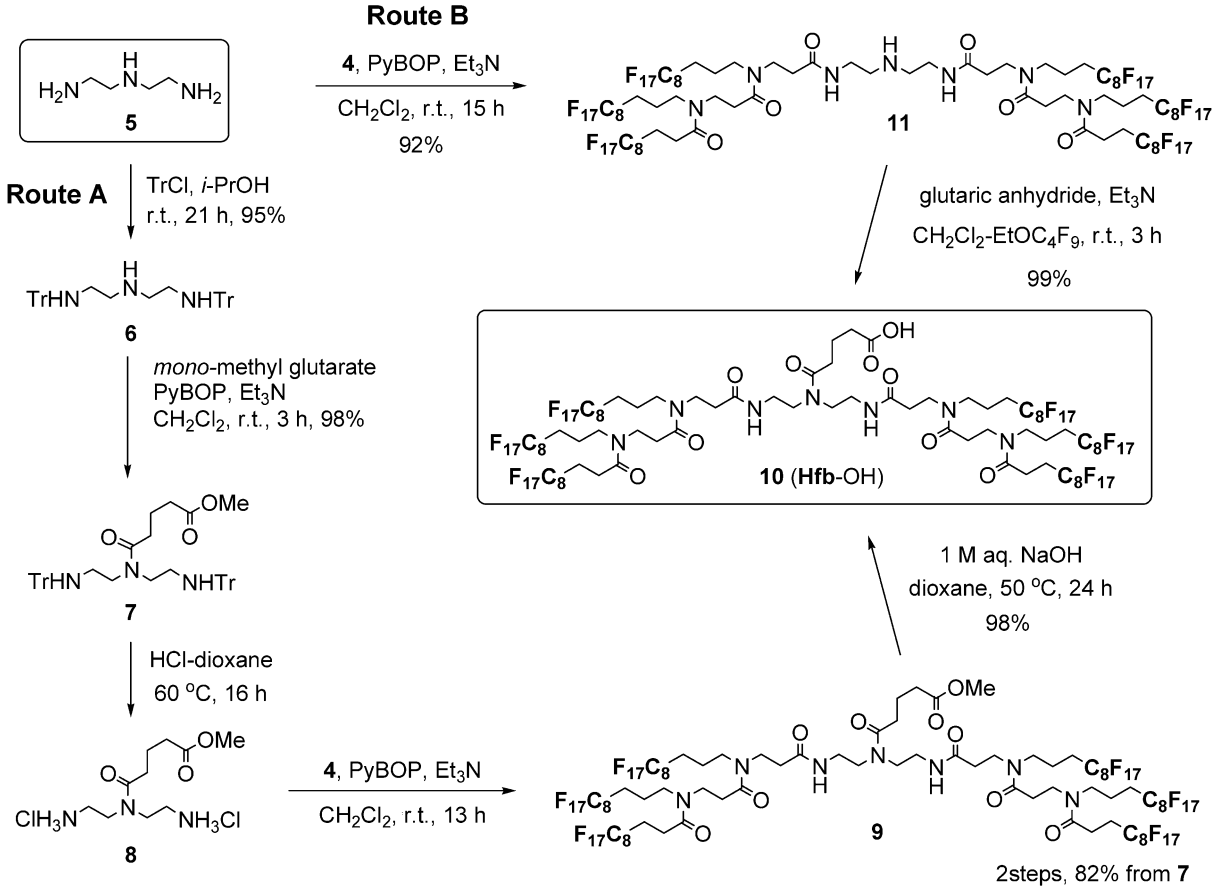
Figure 1. Concept of oligosaccharide synthesis.



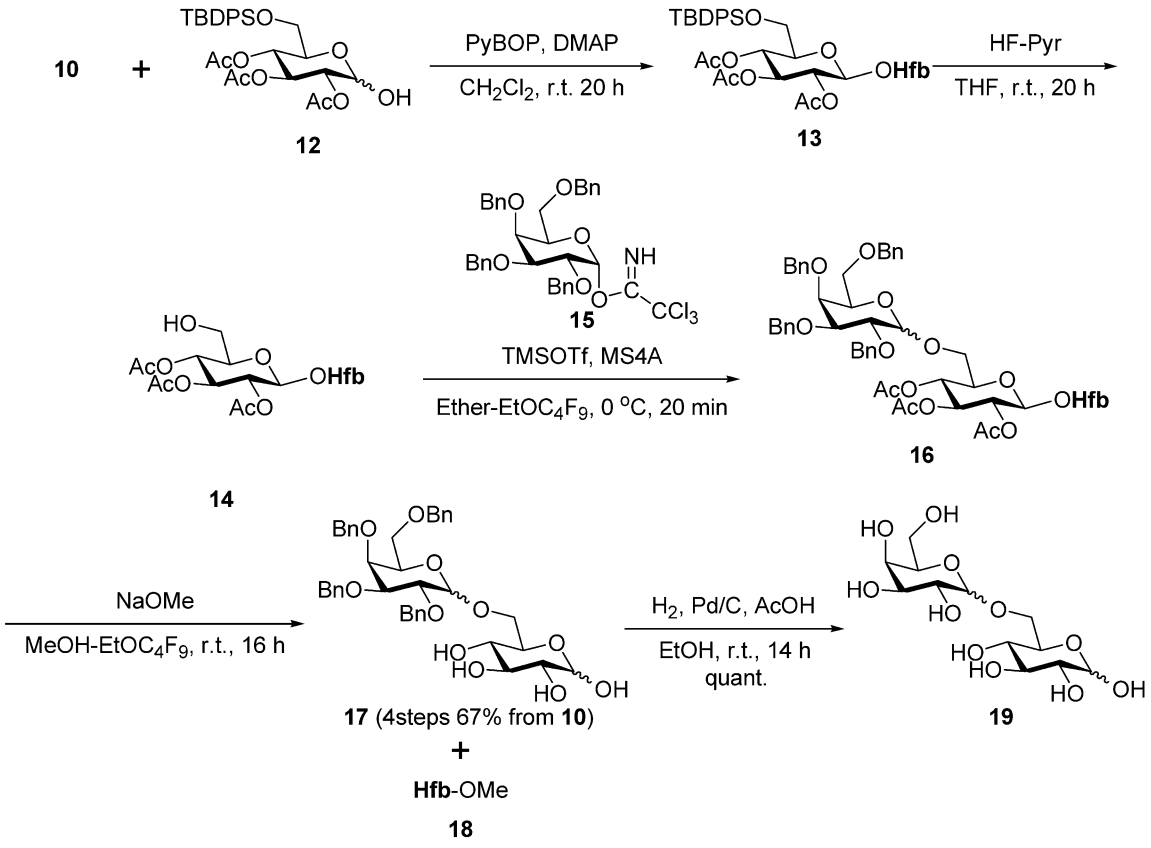
Scheme 1. Preparation of fluorous carboxylic acid **4**.

named **Hfb** (hexakisfluorous chain-type butanoyl). We thought that the six fluorous chains of **10** enhance the efficiency of the liquid–liquid extraction better than the **Bfp** group containing two fluorous chains. Thus we achieved the synthesis of **Hfb**-OH (**10**) by route A. However, route A is unsuitable for the rapid and convenient synthesis of **Hfb**-OH (**10**) due to the lengthy steps. We planned route B as shown in Scheme 2. The two primary amino group of diethylenetriamine (**5**) were directly reacted with **4** (2 equiv.) to provide a fluorous amine **11**, which contains six fluorous chains, in 92% yield. Compound **11** was coupled with glutaric anhydride to produce **Hfb**-OH (**10**) in high yield. Route A is 5 steps with a 75% overall yield from **5**, on the other hand, route B is only 2 steps with 90% yield. As a result, we improved the synthesis of **Hfb**-OH (**10**) marking it more efficient and produced a higher yield than the preliminary communication.[19]

At first, a synthesis of the disaccharide **17** was performed (Scheme 3). Among the many useful methods for glycosylation we selected Schmidt method as one of the most major synthetic methods to prepare an oligosaccharide.[21] The fluorous support **Hfb** was easily introduced into the anomeric hydroxyl group of the glucose derivative **12**



Scheme 2. Synthesis of Hfb-OH (**10**).



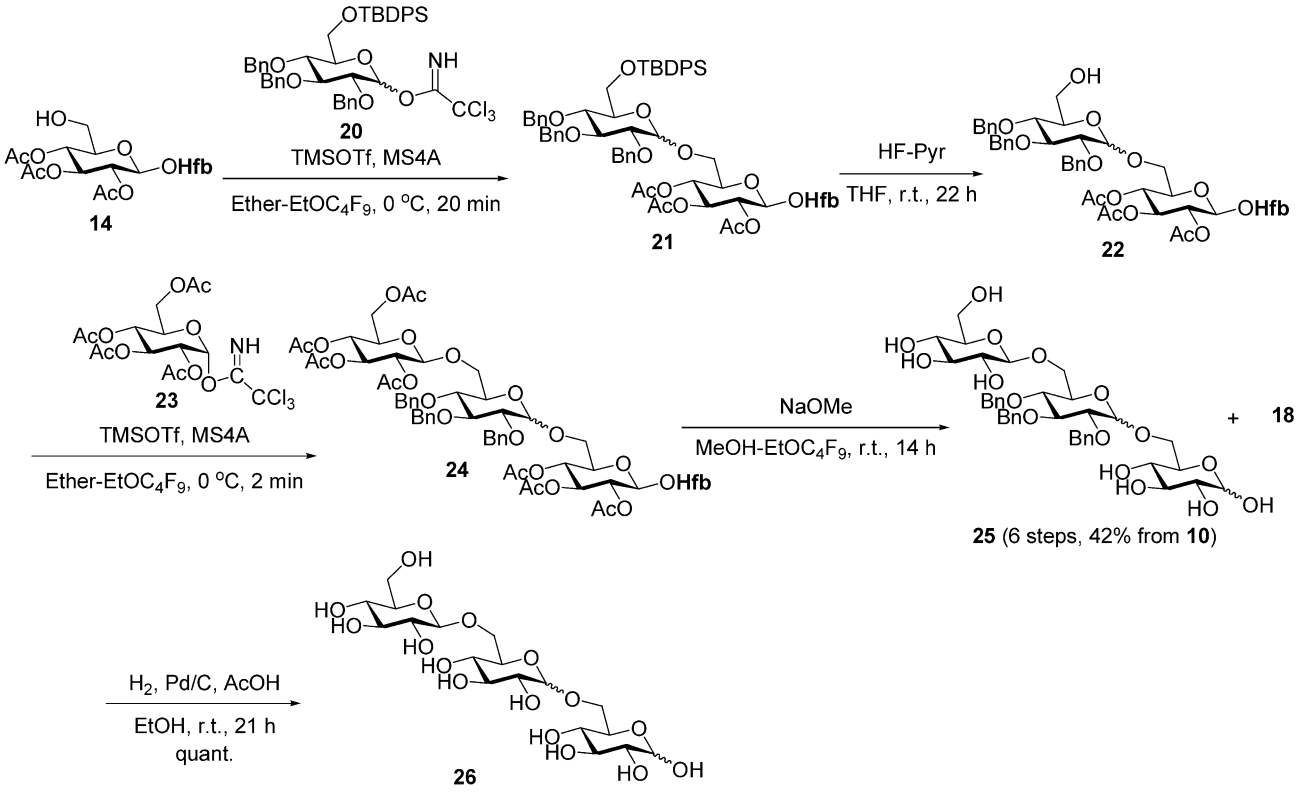
Scheme 3. Disaccharide synthesis on fluorous support **Hfb**.

using PyBOP and 4-dimethylaminopyridine (DMAP) to give the fluorous compound **13**.[22] Removal of the TBDPS group from **13** was achieved by treatment with HF-pyridine in THF to afford the flourous glycosyl acceptor **14**.[22] The fluorous disaccharide **16**[22] was obtained by the reaction of **14** with the excess glycosyl donor **15**[21] in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) in ether–$EtOC_4F_9$.[23] $EtOC_4F_9$ is miscible in most organic solvents and fluorous solvents. The fluorous intermediates **13**, **14** and **16** were respectively extracted with the fluorous solvent FC-72[24] by partitioning the product mixtures between FC-72 and an organic solvent such as MeOH, MeCN and toluene. No further purification such as silica-gel column chromatography was carried out. The **Hfb** group of **16** was easily removed by treatment with NaOMe in MeOH–$EtOC_4F_9$ to afford crude **17**, which was extracted with MeOH by partitioning the mixture between FC-72 and MeOH. The methyl ester of **Hfb** (**Hfb**-OMe, **18**) was recovered from the FC-72 layer in 81% yield. Compound **18** was treated with aqueous sodium hydroxide to give **Hfb**-OH (**10**), which was reused. After a single silica-gel column chromatographic purification step, the disaccharide **17** was obtained in 67% overall yield from **12** (4 steps). The benzyl groups of compound **17** were removed by hydrogenation in the presence of Pd/C to afford compound **19**.[25,26]

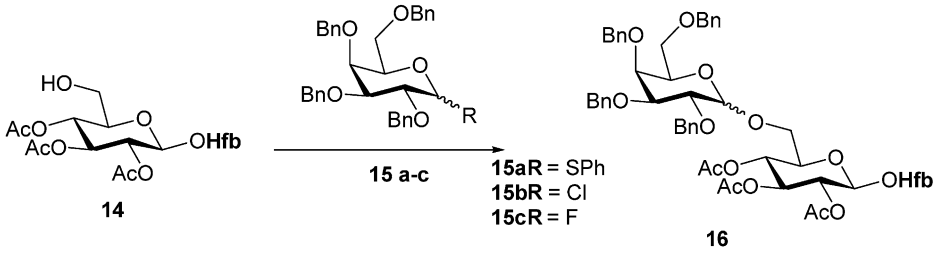
Next, we synthesized the longer chain oligosaccharide, and the fluorous glycosyl acceptor **14** was reacted with the glycosyl donor **20**[27] to afford the fluorous disaccharide **21** (Scheme 4).[22,28] Removal of the TBDPS group from **21** was achieved by treatment with HF-Pyr in THF to afford the fluorous compound **22**.[22] The reaction of the glycosyl acceptor **22** with the glycosyl donor **23**[21] under similar glycosidation conditions afforded the fluorous trisaccharide **24**.[22,28] The fluorous intermediates **21**, **22** and **24** were respectively extracted with the fluorous solvent FC-72 by partitioning the product mixtures between FC-72 and the organic solvents. No further purification such as silica-gel column chromatography was performed. The **Hfb** group of **24** was removed by the same method, as described above. After a single silica-gel column chromatographic purification step, the trisaccharide **25** was obtained in 42% overall yield from **10** (6 steps). The benzyl groups of compound **25** were removed by hydrogenation in the presence of Pd/C to afford compound **26**.[29,30]

Among the many useful methods for glycosylation, we attempted only Schmidt method as the major synthetic method to provide oligosaccharide.[21] Therefore, we applied other glycosylation methods to the fluorous acceptor **14** (Scheme 5).

We performed the thioglycoside method,[31] the Köenigs–Knorr method[32] and the Suzuki method[33] (Table 1). All these methods gave the corresponding disaccharides as a white solid in good yield. Especially, entry 5 (Suzuki method) and entries 7 and 8 (thioglycoside method) show that these methods gave the corresponding disaccharide in good yields with the use of a small excess of the glycosyl donor. As a result, it was found that the major glycosylation



Scheme 4. Trisaccharide synthesis on fluorous support **Hfb**.



Scheme 5.

Table 1. Study of glycosylation using various glycosylation methods on fluorous support **Hfb**

Entry	Temperature (°C)	Time	Solvent	R	Donor (equiv.)	Activator	Yield (%)[a]	α/β ratio[b]
1	0	24 h	Ether–$EtOC_4F_9$	Cl	10	AgOTf–$AgCl_4$	61	2.5:1
2	0	25 h	Ether–$EtOC_4F_9$	Cl	3	AgOTf–$AgCl_4$	39	2.0:1
3	−20	2.5 h	Ether–$EtOC_4F_9$	F	10	Cp_2ZrCl_2–$AgClO_4$	93	1.3:1
4	−20	2.5 h	Ether–$EtOC_4F_9$	F	5	Cp_2ZrCl_2–$AgClO_4$	77	1.5:1
5	−20	4 h	Ether–$EtOC_4F_9$	F	3	Cp_2ZrCl_2–$AgClO_4$	70	1.6:1
6	0	20 min	CH_2Cl_2–$EtOC_4F_9$	Sph	5	NIS–TfOH	72	1.4:1
7	0	50 min	CH_2Cl_2–$EtOC_4F_9$	Sph	3	NIS–TfOH	80	1.6:1
8	0	2.5 h	CH_2Cl_2–$EtOC_4F_9$	Sph	1.5	NIS–TfOH	81	1.4:1

[a] Isolated yield.
[b] Detected by ^1H NMR spectra of products after deprotection.

methods were available for the fluorous oligosaccharide synthesis.

3. Conclusion

The use of the **Hfb** group as a fluorous support made it possible to rapidly synthesize an oligosaccharide by minimal column chromatography purification. We achieved the synthesis of **Hfb**-OH (**10**) quite efficiently and rapidly compared it with the previous method.[19] The **Hfb** group was readily introduced into the anomeric hydroxyl groups of the glycosyl acceptor, and removed in high yield by the usual procedure. Moreover, it was recyclable after cleavage. Each fluorous synthetic intermediate could be obtained in a straightforward manner by simple FC-72-organic solvent extraction. The reaction conditions for each synthetic step could be rapidly optimized, because the reactions could be

monitored by TLC and mass spectrometry in contrast to the usual solid-phase reactions. Although the fluorous intermediates could also be measured by NMR spectroscopic analysis, the peaks in the NMR of the fluorous compounds containing the **Hfb** group are somewhat broad due to the influence of the amide linkages and the fluorous groups.[15] Although the fluorous intermediates could also be subjected to silica-gel column chromatography, only the final compounds were purified by chromatography. This fluorous oligosaccharide synthesis should be applicable for a large-scale synthesis. Furthermore, it was found that major glycosylation methods were available to the fluorous oligosaccharide synthesis. Thus the oligosaccharide synthesis using the fluorous support **Hfb** is an excellent alternative strategy to solid-phase method. Further application for the synthesis of a bioactive carbohydrate and glycoconjugate is now in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded using JEOL JNM-EX-400 (400 MHz) or JEOL JNM-ECA-600 (600 MHz) spectrometers. MALDI-TOF MS. were recorded using Voyager-DE STR, and α-cyano-4-hydroxy cinnamic acid was used as a matrix. ESI-TOF MS. were recorded on Mariner™. Part of the product was isolated by column chromatography on silica-gel (Kanto Chemical, silica-gel 60 N, spherical, neutral, 40–50 μm). The fluorous solvent FC-72 and Novec HFE-7200 were purchased from 3 M Tokyo. The aqueous NH_3 was 28% aqueous solution purchased from Wako Pure Chemical Industries, Ltd.

4.1.1. Compound 3. Triethylamine (4.0 mL, 29.2 mmol) and PyBOP (6.08 g, 17.7 mmol) were added to a solution of compound **1** (**Bfp**-OH; 10.0 g, 9.77 mmol) and **2** (5.64 g, 9.77 mmol) in CH_2Cl_2 (120 mL) at room temperature. After stirring for 20 h at room temperature, the reaction mixture was added to water, and then extracted with $CHCl_3$. The $CHCl_3$ layers were washed with water, 2 M aq. HCl, saturated aq. $NaHCO_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica-gel (hexane–AcOEt, 1:1) to give compound **3** (14.9 g, 96%) as a white amorphous solid. R_f=0.56 (hexane–AcOEt, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.20–1.30 (m, 3H), 1.80–1.95 (m, 4H), 2.01–2.17 (m, 4H), 2.46–2.79 (m, 8H), 3.36–3.54 (m, 4H), 3.56–3.76 (m, 4H), 4.09–4.20 (m, 2H); MALDI-TOF MS: Calcd for $C_{41}H_{30}F_{51}N_2O_4$ *m/z* $[M+H]^+$: 1583.1, Found: 1583.7; Calcd for $C_{41}H_{29}F_{51}N_2O_4Na$ *m/z* $[M+Na]^+$: 1605.1, Found: 1606.1; Calcd for $C_{41}H_{29}F_{51}N_2O_4K$ *m/z* $[M+K]^+$: 1621.1, Found: 1622.4.

4.1.2. Compound 4. To a solution of compound **3** (22.2 g, 14.0 mmol) in 1,4-dioxane (300 mL) was added 1 M aq. NaOH (150 mL) at room temperature. After stirring for 4 h at 50 °C, 2 M aq. HCl was added and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4, and concentrated. Compound **4** (21.5 g, 99%) was obtained as a white amorphous solid. R_f=0.56 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.81–1.96 (m, 4H), 2.01–2.17 (m, 4H), 2.47–2.79 (m, 8H), 3.39–3.55 (m, 4H), 3.57–3.75 (m, 4H); MALDI-TOF MS; Calcd for $C_{39}H_{25}F_{51}N_2O_4Na$ *m/z* $[M+Na]^+$: 1577.1, Found: 1576.5; Calcd for $C_{39}H_{25}F_{51}N_2O_4K$ *m/z* $[M+K]^+$: 1593.1, Found: 1592.3.

4.1.3. Compound 6.[20] Diethylamine (6.0 mL, 61.2 mmol) and chlorotriphenylmethane (17.0 g, 61.2 mmol) were added to a solution of compound **5** (diethylenetriamine; 3.0 mL, 27.8 mmol) in 2-propanol (60 mL) at room temperature. After stirring for 21 h at room temperature, 1 M aq. NaOH was added, and the reaction mixture was adjusted to pH 11. The reaction mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica-gel ($CHCl_3$–MeOH, 20:1) to give compound **6** (15.5 g, 95%) as a white amorphous solid.

4.1.4. Compound 7. Triethylamine (51 μL, 0.37 mmol) and PyBOP (143 mg, 0.275 mmol) were added to a solution of compound **6** (108 mg, 0.184 mmol) and methyl hydrogen glutarate (28 μL, 22 μmol) in CH_2Cl_2 (2 mL) at room temperature. After stirring for 3 h at room temperature, the reaction mixture was added to water, and then extracted with AcOEt. The AcOEt layers were washed with water, 2 M aq. HCl, saturated aq. $NaHCO_3$, and brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica-gel (hexane–AcOEt, 3:2) to give compound **7** (129 mg, 98%) as a white amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.64 (brs, 2H), 1.96 (t, J=7.6 Hz, 2H), 2.22 (t, J=6.2 Hz, 2H), 2.26 (t, J=6.2 Hz, 2H), 2.39 (t, J=7.6 Hz, 2H), 2.45 (t, J=7.6 Hz, 2H), 3.33 (t, J=6.2 Hz, 2H), 3.38 (t, J=6.2 Hz, 2H), 3.33 (s, 3H), 7.12–7.44 (m, 30H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=20.60, 32.28, 33.58, 42.09, 42.34, 45.91, 48.47, 51.50, 70.77, 70.94, 126.24, 126.79, 128.00, 128.41, 128.52, 145.62, 146.00, 172.61, 173.77; HRMS (ESI-TOF MS.): Calcd for $C_{48}H_{50}N_3O_3$ *m/z* $[M+H]^+$: 716.3847, Found: 716.3811.

4.1.5. Compound 8. A solution of 4 M HCl in dioxane (55 mL) was added to compound **7** (3.82 g, 5.43 mmol) at room temperature. After stirring for 16 h at 60 °C, AcOEt was added to the reaction mixture, and then filtered. The crude product of **8** (1.64 g) was obtained as a white solid, and used in the next step without further purification.

4.1.6. Compound 9. Triethylamine (3.87 mL, 27.9 mmol) and PyBOP (12.5 g, 24.0 mmol) were added to a solution of the crude compounds **8** (1.47 g) and **4** (17.2 g, 11.1 mmol) in CH_2Cl_2 (400 mL) at room temperature. After stirring for 13 h at room temperature, toluene was added to the reaction mixture and CH_2Cl_2 was concentrated. The toluene solution was partitioned three times with FC-72. The combined FC-72 layers were then concentrated. The residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH, 20:1) to give compound **9** (13.1 g, 82%) as a white amorphous solid. R_f=0.54 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.76–1.98 (m, 10H), 1.99–2.17 (m, 8H), 2.34–2.88 (m, 20H), 3.31–3.53 (m, 16H), 3.54–3.78 (m, 11H); MALDI-TOF MS: Calcd for

$C_{88}H_{68}F_{102}N_7O_9$ *m/z* $[M+H]^+$: 3304.3, Found: 3305.8; Calcd for $C_{88}H_{67}F_{102}N_7O_9Na$ *m/z* $[M+Na]^+$: 3326.3, Found: 3327.5; Calcd for $C_{88}H_{67}F_{102}N_7O_9K$ *m/z* $[M+K]^+$: 3342.3, Found: 3342.6.

4.1.7. Compound 10. *Route A*. To a solution of compound **9** (1.55 g, 0.454 mmol) in 1,4-dioxane (80 mL) was added 1 M aq. NaOH (40 mL) at room temperature. After stirring for 24 h at 50 °C, 2 M aq. HCl was added, and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4 and concentrated. Compound **10** (1.44 g, 97%) was obtained then used in the next step without further purification. R_f=0.54 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.80–1.99 (m, 10H), 2.00–2.17 (m, 8H), 2.34–2.80 (m, 20H), 3.35–3.55 (m, 16H), 3.56–3.75 (m, 8H); MALDI-TOF MS; Calcd for $C_{87}H_{66}F_{102}N_7O_9$ *m/z* $[M+H]^+$: 3290.3, Found: 3291.5; Calcd for $C_{87}H_{65}F_{102}N_7O_9Na$ *m/z* $[M+Na]^+$: 3312.3, Found: 3315.5.

Route B. Triethylamine (197 μL, 1.42 mmol) and glutaric anhydride (81.0 mg, 0.708 mmol) were added to a solution of compound **11** (450 mg, 0.142 mmol) in $EtOC_4F_9$ (4.5 mL) and CH_2Cl_2 (4.5 mL) at room temperature. After stirring for 3 h at room temperature, 2 M aq. HCl was added and the reaction mixture was adjusted to pH 2. The reaction mixture was extracted three times with AcOEt–$EtOC_4F_9$ (2:1), dried over anhydrous Na_2SO_4 and concentrated. The crude product of **10** (464 mg, 99%) was used in the next step without further purification.

4.1.8. Compound 11. Diethylenetriamine (81 μL, 0.75 mmol) and PyBOP (935 mg, 1.80 mmol) were added to a solution of crude compound **4** (1.47 g) and triethylamine (416 μL, 3.00 mmol) in CH_2Cl_2 (25 mL) at room temperature. After stirring for 15 h at room temperature, the reaction mixture was concentrated. The residue was partitioned between MeOH and FC-72 (×3). The combined FC-72 layers were concentrated. The crude product was purified by column chromatography on silica-gel ($CHCl_3$–MeOH–aq. NH_3=85:15:0.6) to give compound **11** (2.20 g, 92%) as a white amorphous solid. R_f=0.46 ($CHCl_3$–MeOH–aq. NH_3=8:2:0.2); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.78–1.97 (m, 8H), 2.00–2.17 (m, 8H), 2.42–2.64 (m, 12H), 2.66–2.82 (m, 8H), 3.26–3.52 (m, 12H), 3.55–3.74 (m, 8H); MALDI-TOF MS: Calcd for $C_{82}H_{60}F_{102}N_7O_6$ *m/z* $[M+H]^+$: 3176.3, Found: 3177.6; Calcd for $C_{82}H_{59}F_{102}N_7O_6Na$ *m/z* $[M+Na]^+$: 3198.3, Found: 3197.1.

4.1.9. Compound 13. 4-Dimethylaminopyridine (243 mg, 1.98 mmol) and PyBOP (1.03 g, 1.98 mmol) were added to a solution of compound **12** (1.00 g, 1.84 mmol) and **Hfb**-OH (**10**, 2.17 g, 0.660 mmol) in CH_2Cl_2 (110 mL). After stirring for 20 h at room temperature, MeOH (110 mL) was added to the reaction mixture and only CH_2Cl_2 was concentrated. The reaction mixture was extracted three times with FC-72 (110 mL). The combined FC-72 layers were then concentrated. The crude product of **13** (2.45 g) was used in the next step without further purification. R_f=0.47 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.03 (s, 9H) 1.76–2.19 (m, 27H), 2.30–2.85 (m, 20H), 3.26–3.82 (m, 27H), 5.07–5.17 (m, 1H), 5.18–5.27 (m, 2H), 5.69–5.76 (m, 1H, H-1), 6.73–7.21 (m, 1H), 7.30–7.74 (m, 11H); MALDI-TOF-MS: Calcd for $C_{115}H_{99}F_{102}N_7O_{17}Na$ *m/z* $[M+Na]^+$: 3838.5, Found: 3837.1.

4.1.10. Compound 14. HF-Pyr (4.45 mL, 159 mmol) was added to a solution of crude **13** (2.45 g) in THF (38 mL). After stirring for 20 h at room temperature, the reaction mixture was added to saturated aq. $NaHCO_3$ (150 mL). Toluene (150 mL) was then added to the reaction mixture. The reaction mixture was extracted three times with FC-72 (150 mL). The FC-72 layers were washed with brine, then dried over anhydrous Na_2SO_4 and concentrated. The crude product of **14** (2.30 g) was used in the next step without further purification. R_f=0.36 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.71–2.21 (m, 28H), 2.27–2.87 (m, 20H), 3.27–3.83 (m, 27H), 5.04–5.18 (m, 2H), 5.27–5.38 (m, 1H), 5.69–5.82 (m, 1H, H-1), 6.75–7.23 (m, 1H), 7.29–7.96 (m, 1H); MALDI-TOF MS: Calcd for $C_{99}H_{82}F_{102}N_7O_{17}Na$ *m/z* $[M+Na]^+$: 3600.4, Found: 3600.9.

4.1.11. Compound 16. *Using the Schmidt method.*[21] Molecular sieves 4A powder (1.4 g) was added to a solution of the crude compound **14** (395 mg) and compound **15** (680 mg, 0.992 mmol) in ether (6.0 mL)–$EtOC_4F_9$ (3.2 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (140 μL, 0.773 mmol) was added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, triethylamine (0.5 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16** (372 mg), and this residue was used in the next step without further purification. R_f=0.47 ($CHCl_3$–MeOH–H_2O=9:1:0.08); ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.76–2.16 (m, 27H), 2.20–2.83 (m, 20H), 3.16–4.06 (m, 33H), 4.29–5.33 (m, 12H), 5.66–5.71 (m, 1H, H-1), 6.69–7.17 (m, 2H), 7.02–7.44 (m, 20H); MALDI-TOF MS: Calcd for $C_{133}H_{115}F_{102}N_7O_{22}Na$ *m/z* $[M+Na]^+$: 4122.6, Found: 4121.4.

General procedure for disaccharide **16** *using thioglycoside method.*[30] Molecular sieves 4A powder (1.6 g) was added to a solution of compound **14** (133 mg, 37.2 μmol) and compound **15a** (70.6 mg, 0.112 mmol) in CH_2Cl_2 (2.0 mL)–$EtOC_4F_9$ (1.0 mL) under an argon atmosphere. After stirring for 2 h at room temperature, NIS (50.0 mg, 0.223 mmol) and TfOH (2 μL, 22 μmol) were added to the reaction mixture at 0 °C. After stirring for 50 min at 0 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$, and extracted three times with AcOEt. The AcOEt layers were washed with saturated aq. $NaHCO_3$, saturated aq. $Na_2S_2O_3$ and brine. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (122 mg, 80%) as a white amorphous solid.

General procedure for disaccharide **16** *using the Köenigs–Knorr method.*[31] Molecular sieves 4A powder (1.5 g) was added to a solution of compound **14** (131 mg, 36.5 μmol) and AgOTf (204 mg, 0.365 mmol), $AgClO_4$ (188 mg, 0.365 mmol) in ether (1.0 mL)–$EtOC_4F_9$ (1.5 mL) under an argon atmosphere. After stirring for 2 h at room temperature, compound **15b** (204 mg, 0.365 mmol) in ether (2.0 mL) was added to the reaction mixture at 0 °C. After stirring for 24 h at 0 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (91.4 mg, 61%) as a white amorphous solid.

General procedure for disaccharide **16** *using the Suzuki method.*[32] A mixture of Cp_2ZrCl_2 (161 mg, 0.55 mmol), $AgClO_4$ (114 mg, 0.55 mmol) and molecular sieves 4A powder (1.0 g) in ether (2.5 mL) was stirred at −20 °C under an argon atmosphere. After stirring for 10 min at −20 °C, compound **14** (165 mg, 46.1 μmol) and compound **15c** (75.1 mg, 0.138 mmol) in ether (5.0 mL)–$EtOC_4F_9$ (2.5 mL) were added to the reaction mixture. After stirring for 4 h at −20 °C, the reaction mixture was filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **16**, and this residue was purified by column chromatography on silica-gel ($CHCl_3$–MeOH=40:1) to give compound **16** (132 mg, 70%) as a white amorphous solid.

4.1.12. Compound 17. A sodium methoxide solution (28%) in methanol (10 μL) was added to a solution of the crude compound **16** (349 mg) in $EtOC_4F_9$ (8 mL)–MeOH (16 mL). After stirring for 16 h at room temperature, Amberlite IR-120 (H^+ form) was added and the reaction mixture was neutralized. After filtration, the filtrate was concentrated. The residue was partitioned between MeOH and FC-72 (×3). The MeOH layer was concentrated to give the crude product of **17**. The FC-72 layers were concentrated to afford the pure compound **18**. The crude product of **17** was purified by column chromatography on silica-gel to give pure compound **17** (50 mg, 67% in 4 steps) as a white powder. HRMS (ESI-TOF MS.): Calcd for $C_{40}H_{46}O_{11}Na$ *m/z* $[M+Na]^+$: 725.2932, Found: 725.2959.

4.1.13. Compound 19.[25,26] A solution of **17** (31.0 mg) in EtOH (9.0 mL) was added to a suspension 10% Pd/C (40.0 mg) in EtOH (1.0 mL)–AcOH (1.0 mL). After bubbling with hydrogen for 14 h at room temperature, the reaction mixture was filtered. After the filtrate was concentrated, the compound **19** (16.0 mg, quant.) was obtained as a white powder.

Melibiose. ^{1}H NMR (600 MHz, D_2O): δ=4.53 (d, J=7.6 Hz), 4.84 (d, J=4.1 Hz), 4.85 (d, J=3.4 Hz), 5.09 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=61.06, 61.08, 65.82, 65.92, 68.41, 68.44, 69.20, 69.42, 69.45, 69.57, 70.06, 70.90, 71.39, 72.92, 74.03, 74.31, 75.85, 92.10, 96.03, 98.13, 98.17.

Arolactose. ^{1}H NMR (600 MHz, D_2O): δ=4.29 (d, J=9.6 Hz), 4.31 (d, J=8.3 Hz), 4.52 (d, J=8.3 Hz), 5.10 (d, J=4.1 Hz); ^{13}C NMR (150 MHz, D_2O): δ=60.97, 68.57, 68.63, 68.65, 68.68, 69.42, 69.48, 70.44, 70.74, 71.39, 72.64, 74.01, 74.86, 75.11, 75.14, 75.62, 92.10, 95.94, 103.25.

4.1.14. Compound 21. Molecular sieves 4A powder (3.3 g) was added to a solution of the crude compound **14** (953 mg) and compound **20** (1.86 g, 2.23 mmol) in ether (14 mL)–$EtOC_4F_9$ (8 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (338 μL, 1.86 mmol) was added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, triethylamine (0.8 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeCN and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **21** (1.07 g), and was used in the next step without further purification.

4.1.15. Compound 22. HF-Pyr (1.75 mL, 62.4 mmol) was added to a solution of the crude **21** (1.07 g) in THF (15 mL). After stirring for 22 h at room temperature, the reaction mixture was added to saturated aq. $NaHCO_3$ (200 mL), then toluene (200 mL) was added to the reaction mixture. The reaction mixture was extracted three times with FC-72 (200 mL). The FC-72 layers were washed with brine, then dried over anhydrous Na_2SO_4 and concentrated. The crude product of **22** (952 mg) was used in the next step without further purification.

4.1.16. Compound 24. Molecular sieves 4A powder (6.0 g) was added to a solution of the crude compound **22** (360 mg) and compound **23** (884 mg, 1.79 mmol) in ether (29 mL)–$EtOC_4F_9$ (3 mL) under an argon atmosphere. After stirring for 2 h at room temperature, TMS-OTf (163 μL, 0.898 mmol) was added to the reaction mixture at 0 °C. After stirring for 2 min at 0 °C, triethylamine (0.5 mL) was added to the reaction mixture. The reaction mixture was then filtered. The filtrate was added to saturated aq. $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was partitioned between MeOH and FC-72 (×3). The FC-72 layers were concentrated to give the crude product of **24** (360 mg), and this residue was used in the next step without further purification.

4.1.17. Compound 25. A sodium methoxide solution (28%) in MeOH (10 μL) was added to a solution of the crude compound **24** (360 mg) in $EtOC_4F_9$ (8 mL)–MeOH (16 mL). After stirring for 14 h at room temperature, Amberlite IR-120 (H^+ form) was added and the reaction mixture was neutralized. After filtration, the filtrate was concentrated. The residue was partitioned between MeOH

and FC-72. The methanol layer was concentrated to give the crude compound **25**. The FC-72 layer was concentrated to afford pure compound **18**. The crude compound **25** was purified by column chromatography on silica-gel to give pure compound **25** (34.0 mg, 43% in 6 steps) as a white powder. HRMS (ESI-TOF MS.): Calcd for $C_{39}H_{50}O_{16}Na$ *m/z* $[M+Na]^+$: 797.2991, Found: 797.2969.

4.1.18. Compound 26.[29,30] A solution of **25** (15.0 mg) in EtOH (4.0 mL) was added to a suspension 10% Pd/C (20.0 mg) in EtOH (1.0 mL)–AcOH (1.0 mL). After bubbling with hydrogen for 21 h at room temperature, the reaction mixture was filtered. After the filtrate was concentrated, the compound **26** (10.0 mg, quant.) was obtained as a white powder.

O-(β-D-Glucopyranosyl)-(1→6)-*O*-(α-D-glucopyranosyl)-(1→6)-D-glucopyranose. ^{1}H NMR (600 MHz, D_2O): δ= 4.34 (d, J=8.3 Hz), 4.51 (d, J=7.6 Hz), 4.79 (d, J= 3.4 Hz), 4.80 (d, J=4.1 Hz), 5.08 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=92.14, 96.03, 97.96, 98.00, 102.57.

O-(β-D-Glucopyranosyl)-(1→6)-*O*-(β-D-glucopyranosyl)-(1→6)-D-glucopyranose. ^{1}H NMR (600 MHz, D_2O): δ= 4.34 (d, J=8.3 Hz), 4.35 (d, J=5.5 Hz), 4.36 (d, J= 8.3 Hz), 4.38 (d, J=6.9 Hz), 4.50 (d, J=10.3 Hz), 5.07 (d, J=3.4 Hz); ^{13}C NMR (150 MHz, D_2O): δ=92.07, 95.90, 102.65, 102.70, 102.77, 102.79.

Acknowledgements

This work was partly supported by Grants-in-Aid for Scientific Research (C) (No. 13680680) and a Grant-in-Aid for Encouragement of Young Scientists (No. 13771349) from the Japan Society for the Promotion of Science, by a grant for Hi-Tech Research from Tokai University, and by the Takeda Science Foundation. This work was performed through the Noguchi Fluorous Project by our institute.

References and notes

1. (a) Varki, A. *Glycobiology* **1993**, *3*, 97. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (c) Blithe, D. L. *Trends Glycosci. Glycotechnol.* **1993**, *5*, 81.
2. (a) Manabe, S.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12638. (b) Ando, H.; Manabe, S.; Nakahara, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3848. (c) Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523. (d) Eichler, E.; Yan, F.; Sealy, J.; Whitfield, D. M. *Tetrahedron* **2001**, *57*, 6679. (e) Ito, Y.; Kanie, O.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2510. (f) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 2116 and references cited therein.
3. Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.
4. (a) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (b) Nishikido, J.; Kamishima, M.; Matsuzawa, H.; Mikami, K. *Tetrahedron* **2002**, *58*, 8345. (c) Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, *4*, 1993. (d) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohga, Y. *Tetrahedron* **2001**, *57*, 5565. (e) Barrett, A. G. M.; Braddock, D. C.; Catterick, D.; Chadwick, D.; Henschke, J. P.; McKinnell, R. M. *Synlett* **2000**, 847. (f) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641 and references cited therein.
5. (a) Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866. (b) Curran, D. P. *Pure Appl. Chem.* **2000**, *72*, 1649. (c) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174 and references cited therein.
6. Hao, X.; Yamazaki, O.; Yoshida, A.; Nishikido, J. *Tetrahedron Lett.* **2003**, *44*, 4977.
7. Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.* **2001**, *123*, 7449.
8. (a) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (b) Moineau, J.; Pozzi, G.; Quici, S.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 7683.
9. Chen, D.; Qing, F.; Huang, Y. *Org. Lett.* **2002**, *4*, 1003.
10. (a) Dandapani, S.; Curran, D. P. *Tetrahedron Lett.* **2002**, *58*, 3855. (b) Dobbs, A. P.; McGregor-Johnson, C. *Tetrahedron Lett.* **2002**, *43*, 2807. (c) Rábai, J.; Szabó, D.; Borbás, E. K.; Kövesi, I.; Kövesdi, I.; Csàmpai, A.; Gömöry, A.; Pashinnik, V. E.; Shermolovich, Y. G. *J. Fluorine Chem.* **2002**, *114*, 199. (d) Markowicz, M. W.; Dembinski, R. *Org. Lett.* **2002**, *4*, 3785.
11. Barrett, A. G. M.; Braddock, D.; Catterick, C. D.; Chadwick, D.; Heschke, J. P.; McKinnell, R. M. *Synlett* **2000**, 847.
12. (a) Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4500. (b) Markert, C.; Bannwarth, W. *Helv. Chim. Acta* **2002**, *85*, 1887. (c) Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341. (d) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480.
13. (a) Zhang, W.; Luo, Z.; Chen, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443. (b) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233. (c) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774. (d) Curran, D. P. *Synlett* **2001**, 1488. (e) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766.
14. (a) Manzoni, L. *Chem. Commun.* **2003**, 2930. (b) Wipf, P.; Reeves, J. T.; Balachandran, R.; Giuliano, K. A.; Hamel, E.; Day, B. W. *J. Am. Chem. Soc.* **2000**, *122*, 9391. (c) Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667. (d) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 5139. (e) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 4649. (f) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681.
15. Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937.
16. (a) Curran, D. P.; Amatore, M.; Guthrie, D.; Campbell, M.; Go, E.; Luo, J. Z. *J. Org. Chem.* **2003**, *68*, 4643. (b) Schwinn, D.; Bannwarth, W. *Helv. Chim. Acta* **2002**, *85*, 255. (c) Filippov, D. V.; Zoelen, J. D.; Oldfield, S. P.; Marel, G. A.; Overkleeft, H. S.; Drijfhout, J. W.; Boom, J. H. *Tetrahedron Lett.* **2002**, *43*, 7809. (d) Pardo, J.; Cobas, A.; Guitlán, E.; Castedo, L. *Org. Lett.* **2001**, *3*, 3711. (e) Luo, Z.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261.
17. Miura, T.; Hirose, Y.; Ohmae, M.; Inazu, T. *Org. Lett.* **2001**, *3*, 3947.
18. Miura, T.; Inazu, T. *Tetrahedron Lett.* **2003**, *44*, 1819.
19. Miura, T.; Goto, K.; Hosaka, D.; Inazu, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2047.
20. Zang, E.; Sadler, P. J. *Synth. Commun.* **1997**, *27*(18), 3145.
21. Schmidt method: Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343.
22. The product mixtures containing the fluorous compounds **13**,

16 and **24** were partitioned between FC-72 and MeOH. Those containing the fluorous compound **14** and **22** were partitioned FC-72, toluene and water. The product containing the fluorous compound **21** was partitioned between FC-72 and acetonitrile. None of the fluorous compounds were detected by TLC of the organic layer after three times extraction with FC-72, which shows that these compounds were quantitatively extracted with FC-72.

23. $EtOC_4F_9$ is a commercially available fluorocarbon solvent (3 M, Tokyo), which is called Novec™ HFE-7200.
24. FC-72 is a commercially available fluorocarbon solvent (3M, Tokyo), which consists of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.
25. The anomer ratio of compound **19** (the newly formed anomeric position) was determined to be $\alpha/\beta=60{:}40$ by NMR spectroscopic analysis. Moreover, the correlation between anomeric protons of galactose residue and 6-position carbons of glucose residue of the compound **19** was observed by HMQC and HMBC of NMR spectroscopic analysis.
26. Compound **19** was identified by comparison of spectroscopic data of the authentic samples (melibiose and arolactose).
27. Xu, W.; Springfield, S. A.; Koh, J. T. *Carbohydr. Res.* **2000**, *325*, 169.
28. The starting materials **14** and **22** were not observed by TLC after the glycosylation.
29. The anomer ratio of compound **26** (the newly formed anomeric position) was determined to be $\alpha/\beta=78{:}22$ based on NMR spectroscopic analysis. The glycoside linkages of compound **26** were analyzed using the above NMR spectroscopic analysis in Ref. 25.
30. Compound **26** was identified by comparison of spectroscopic data of an authentic sample: Koto, S.; Morishima, N.; Shichi, S.; Haigoh, H.; Hirooka, M.; Okamoto, M.; Higuchi, T.; Shimizu, K.; Hashimoto, Y.; Irisawa, T.; Kawasaki, H.; Takahashi, Y.; Yamazaki, M.; Mori, Y.; Kudo, K.; Ikegaki, T.; Suzuki, S.; Zen, S. *Bull. Chem. Soc. Jpn* **1992**, *65*, 3257.
31. Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.
32. Köenigs, W.; Knurr, E. *Chemische Berichte* **1901**, *34*, 957.
33. (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567. (b) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571. (c) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3575. (d) Suzuki, K.; Maeta, H.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 4853. (e) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8855–8860

Reaction of (diacetoxyiodo)benzene with excess of trifluoromethanesulfonic acid. A convenient route to *para*-phenylene type hypervalent iodine oligomers

Tsugio Kitamura,[a,*] Daisuke Inoue,[a] Ichiro Wakimoto,[b] Tetsu Nakamura,[b] Ryoji Katsuno[b] and Yuzo Fujiwara[b]

[a]*Department of Chemistry and Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi, Saga 840-8502, Japan*
[b]*Department of Applied Chemistry, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka 812-8581, Japan*

Received 2 June 2004; accepted 9 July 2004

Available online 21 August 2004

Abstract—Reaction of (diacetoxyiodo)benzene [$PhI(OAc)_2$] in trifluoromethanesulfonic acid (TfOH) resulted in oligomerization of $PhI(OAc)_2$. Quenching with NaBr gave the bromide salts of hypervalent iodine oligomers that were determined by thermolysis with KI to be a *para* phenylene type of oligomers. Neutralization of the reaction mixture of $PhI(OAc)_2$ and TfOH with aqueous $NaHCO_3$ yielded the triflate salts of iodine oligomers. Furthermore, quenching the reaction mixture with aromatic substrates afforded arylated iodine oligomers. These iodine oligomers were found to be 3–4 of the number average degree of polymerization (P_n) by GC analysis of the thermolysis products and ^{1}H NMR analysis. The major products, trimer and tetramer, were synthesized independently.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Applications of hypervalent iodine compounds to organic chemistry have recently attracted a great deal of attention because they show high reactivity and have come into wide use in organic synthesis.[1] Since Hartmann and Meyer[2] reported the formation of (*p*-iodophenyl)(phenyl)iodonium salt (**1**) in Figure 1 as a stable hypervalent iodine compound, many diaryliodonium salts have been prepared. The preparation and chemistry of diaryliodonium salts have been summarized in early reviews.[3] An extended type of the salts, *p*-phenylenebis(aryliodonium) salts (**2**), has been prepared recently by arylation of 1,4-bis(trifluoroacetoxyiodo)benzene.[4] Okawara and his coworkers studied the synthesis of the tetramers of iodonium salts[5] and suggested that the structure of the tetramers was composed of a *meta*-phenylene skeleton. However, no further extended polymeric iodonium salts (**3**) have been prepared.

On the other hand, we found that the self-condensation of PhIO takes place in the presence of 2 equiv. of TfOH to give a bisiodine(III) reagent, 1-[(hydroxy)(trifluoromethylsulfonyloxy)iodo]-4-[(phenyl)(trifluoromethylsulfonyloxy)iodo]benzene (**4**),[6] as shown in Scheme 1. This reagent **4** showed high reactivity to aromatic substrates and afforded

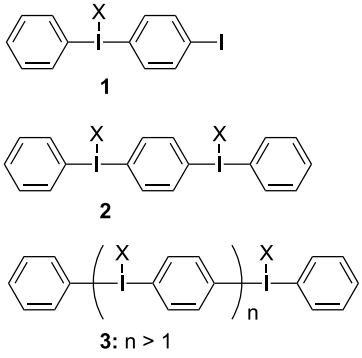
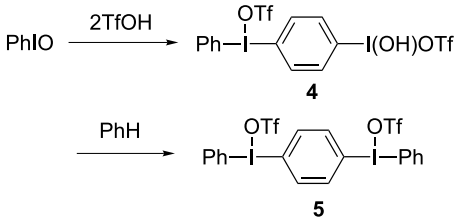


Figure 1.



Scheme 1.

Keywords: Hypervalent iodine oligomer; (Diacetoxyiodo)benzene; Trifluoromethanesulfonic acid; *para*-Phenylene structure.
* Corresponding author. Tel.: +81-952-28-8550; fax: +81-952-28-8548; e-mail: kitamura@cc.saga-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.026

(*p*-phenylene)bis(phenyliodonium) ditriflate (**5**) in the reaction with benzene. Furthermore, the reaction of **4** with diphenyl ether also gave oxygen-bridged tetraiodonium salt (**6**).[6a] On the basis of the self-condensation of PhIO, the mechanism on the transformation of PhIO into **1** was elucidated.[7]

However, bisiodine(III) reagent **4** did not undergo polymerization to afford polymeric iodonium salts **3** although **4** had a reactive hypervalent iodonio group. The failure in polymerization was considered to be due to the reduced reactivity of the phenyl ring by the electron-withdrawing hypervalent iodine[8] and to the insolubility of **4** in the organic solvent employed. Thus, we conducted the reaction of $PhI(OAc)_2$ using excess of TfOH and found that $PhI(OAc)_2$ underwent polymerization to give the oligomers.[9] In this paper, we report in detail our findings on the formation and structure of the hypervalent iodine oligomers, and the independent synthesis of the hypervalent iodine trimer and tetramer to confirm the structure of the oligomers obtained by the reaction of $PhI(OAc)_2$.

2. Results and discussion

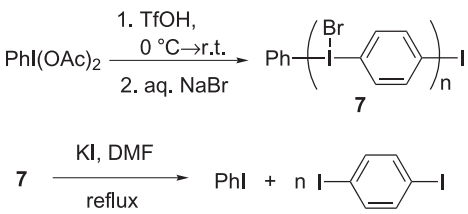
2.1. Oligomerization of $PhI(OAc)_2$ with TfOH. Isolation of hypervalent iodine oligomers as the bromide salts

$PhI(OAc)_2$ was treated with excess of TfOH and then the reaction was quenched with ice-water. However, no precipitates were formed on standing. When NaBr was added to the reaction mixture according to an early procedure[10] to isolate diaryliodonium salts, pale yellow precipitates were formed. For example, the reaction of $PhI(OAc)_2$ (2.5 mmol) with TfOH (50 mmol) followed by treatment with aqueous NaBr gave 0.5–0.7 g of a pale yellow solid of the bromide (**7**), mp 149–157 °C (dec), as shown in Table 1 and Scheme 2. However, the solid bromide **7** did not dissolve even in a polar organic solvent such as DMF, DMSO, or MeOH. To elucidate the structure of the solid, we conducted thermolysis with KI affording the corresponding organic iodides according to the conventional method[11] and analyzed the iodides with a capillary GC.

Table 1. Reaction of $PhI(OAc)_2$ with TfOH followed by treatment with NaBr[a]

Entry	Reaction time (h)	Yield of **7** (g)	P_n[b]
1	1	0.55	3.0
2	2	0.64	3.1
3	8	0.66	3.2
4	24	0.68	3.4
5	48	0.65	3.6
6	64	0.72	3.9
7	96	0.58	3.2
8	168	0.62	3.1

[a] Reaction conditions: $PhI(OAc)_2$ (0.80 g, 2.5 mmol), TfOH (4.5 mL, 50 mmol) at room temperature.
[b] Determined by GC after the decomposition with KI.



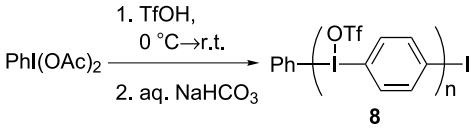
Scheme 2.

When the solid bromide **7** were reacted with KI in DMF under reflux conditions, iodobenzene and 1,4-diiodobenzene were formed. No isomers other than 1,4-diiodobenzene were detected. Therefore, the formation of 1,4-diiodobenzene strongly indicates that the structure of bromide **7** is composed of a *para*-phenylene unit. On the basis of the quantitative GC analysis of iodobenzene and 1,4-diiodobenzene, the number average degree of polymerization (P_n) was calculated to be 3–4 as shown in Table 1. Therefore, the solid bromides were determined to be hypervalent iodine oligomers bearing a *p*-phenylene structure.

This result is different from Okawara's report[5] that iodine oligomers (tetramers) have *meta*-phenylene units. However, our previous study[6] on the dimerization of PhIO with TfOH supports this *para* orientation. It is, therefore, considered that the lone pairs on the iodine(III) atom govern the orientation of the oligomerization in the same way as the effect of halogen on electrophilic aromatic substitution of halobenzenes.

2.2. Isolation of hypervalent iodine oligomers as triflate salts

The bromide salt **7** of hypervalent iodine oligomers could not be analyzed by NMR since the solubility of **7** in organic solvents was extremely low. Then, we tried to isolate the hypervalent iodine oligomers as triflate salts and found that the neutralization of the reaction mixture with $NaHCO_3$ resulted in the formation of the precipitates of triflate (**8**), as shown in Scheme 3.



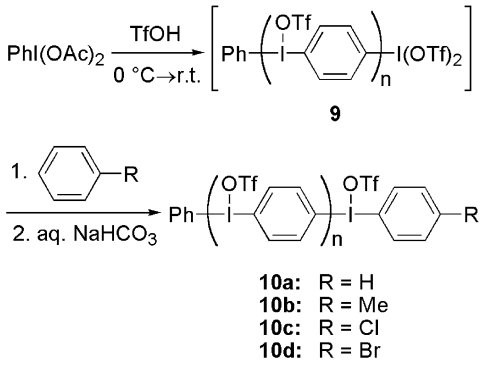
Scheme 3.

For example, the reaction of $PhI(OAc)_2$ (2.5 mmol) with TfOH (50 mmol) for 8–48 h followed by neutralization with aqueous $NaHCO_3$ afforded white solids (0.5–0.6 g) of hypervalent iodine oligomers as shown in Table 2. The triflate salt **8** of oligomers dissolved in polar solvents such as DMSO and MeOH and this enabled the analysis by NMR. The ^1H NMR spectrum of **8** showed characteristic chemical shifts of hypervalent iodine compounds bearing a *p*-phenylene structure, indicating that the aromatic protons between the hypervalent iodines in the *p*-phenylene ring were observed around 8.32 ppm as a singlet. The terminal *p*-iodophenyl group showed a typical A_2B_2 pattern at 7.9–8.0 ppm and the *ortho* protons of the phenyl group appeared around 8.26 ppm as a doublet. The number average degree of polymerization P_n was determined to be 3.5–3.8 (entries

Table 2. Reaction of $PhI(OAc)_2$ with TfOH followed by treatment with $NaHCO_3$[a]

Entry	TfOH (mmol)	Reaction time (h)	Yield of **8** (g)	P_n[b]
1	12.5	24	0.26	2.3
2	25	24	0.48	3.3
3	50	24	0.64	3.7
4	75	24	0.55	3.7
5	50	8	0.53	3.5
6	50	48	0.62	3.8

[a] Reaction conditions: $PhI(OAc)_2$ (0.80 g, 2.5 mmol) at room temperature.
[b] Determined by ^1H NMR.



Scheme 4.

3–6 in Table 2) by the calculation of the integrals of these protons. This result is almost identical to that determined by the GC analysis of the thermolysis of **7** with KI. Therefore, the hypervalent iodine oligomers obtained in this study were found to be mostly composed of a trimer and a tetramer bearing a *p*-phenylene structure.

2.3. Arylation of hypervalent iodine oligomers

In the reaction mixture of $PhI(OAc)_2$ and TfOH, before quenching with NaBr or H_2O, it is presumed that there exists an intermediate hypervalent iodine species (**9**) having a reactive terminal site such as a bis(trifluoromethylsulfonyloxy)iodanyl group.[12] Since a $PhI(OAc)_2$/2TfOH reagent system shows high reactivity to aromatic substrates to give diaryliodonium salts,[13] it is expected that this terminal iodine group can react with aromatic substrates to provide arylated hypervalent iodine oligomers.

Thus, $PhI(OAc)_2$ was treated with excess of TfOH and then allowed to react with benzene, toluene, chlorobenzene, or bromobenzene, as shown in Scheme 4. The quenching and neutralization of the reaction mixture yielded the corresponding arylated hypervalent iodine oligomers (**10**) in good yields. The fact that the reaction with less reactive halobenzenes proceeds readily suggests that the terminal hypervalent iodine of **9** has a highly electrophilic character. The ^1H NMR spectra, however, showed that arylated iodine oligomers **10** were contaminated by small amounts of unarylated iodine oligomers **8**.

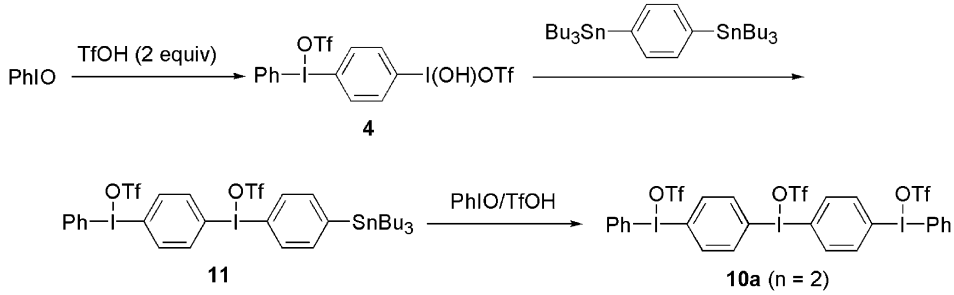
The thermolysis of phenylated iodine oligomers **10a** with KI similarly gave iodobenzene and 1,4-diiodobenzene. The quantitative GC analysis of iodobenzene and 1,4-diiodobenzene indicated that the number average degree of polymerization P_n was 3.5.

2.4. Independent synthesis of hypervalent iodine trimer and tetramer

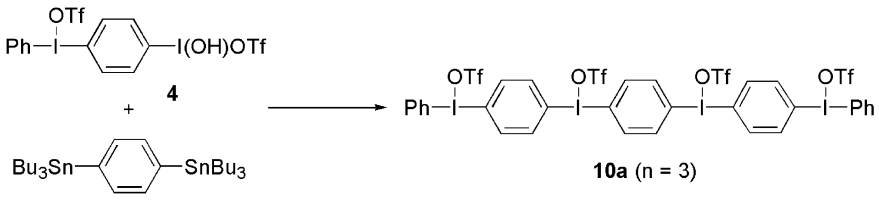
From the above results, it is found that the reaction of $PhI(OAc)_2$ with excess of TfOH gives hypervalent iodine oligomers **7**, **8**, and **10** which are mostly composed of the trimer and the tetramer. Thus, we conducted an independent synthesis of the hypervalent iodine trimer, as illustrated in Scheme 5, to confirm its existence in the iodine oligomers **10a**.

The self-condensation of PhIO with 2 equiv. of TfOH in CH_2Cl_2 gave bisiodine(III) reagent **4** in 84% yield. Arylation of **4** with 1,4-bis(tributylstannyl)benzene provided 4-(tributylstannyl)phenyl-substituted bisiodine(III) compound (**11**) in 61% yield. Reaction of **11** with a PhIO/TfOH reagent followed by repeated recrystallization afforded hypervalent iodine trimer [**10a** ($n=2$)] in 26% yield. The ^1H NMR spectrum of **10a** ($n=2$) is almost identical with that of phenylated hypervalent iodine oligomers **10a**. The triplet signals at 7.53 and 7.70 ppm are attributed to the *meta* and *para* protons of the terminal phenyl rings, respectively, and the doublet signal at 8.25 ppm to the *ortho* protons. Specially, the single peak observed at 8.34 ppm corresponds to all protons of the *p*-phenylene units. The ^{13}C NMR spectrum showed characteristic high-field signals of *ipso* carbons bound to iodine(III) at 116.7, 120.3, and 120.5 ppm.

p-Phenylene-type hypervalent iodine tetramer [**10a** ($n=3$)]



Scheme 5.



Scheme 6.

was prepared by the reaction of **4** with excess of 1,4-bis(tributylstannyl)benzene, as shown in Scheme 6. However, the procedure also provided *mono*-substituted compound **11**. Accordingly, tetramer **10a** ($n=3$) was isolated in 3% yield by repeated recrystallization. The ^{1}H NMR spectrum of tetramer **10a** ($n=3$) was almost the same as that of trimer **10a** ($n=2$), giving signals at 7.54 (triplet), 7.69 (triplet), and 8.26 (doublet) ppm corresponding to the *meta*, *para*, and *ortho* protons of the terminal phenyl rings, and the single peak at 8.34 ppm due to the protons of the *para* phenylene rings. The ^{13}C NMR spectrum of **10a** ($n=3$) indicated similarly high-field signals of the *ipso* carbon bound to iodine(III) at 116.7, 120.3, 120.5, and 120.6 ppm. The ^{1}H NMR spectra of trimer **10a** ($n=2$) and tetramer **10a** ($n=3$) are very similar except for higher integration of the *p*-phenylene signal. Comparison of these spectra with phenylated oligomers **10a** indicates that the ^{1}H NMR spectrum of **10a** is close to that of tetramer **10a** ($n=3$).

3. Conclusion

We have demonstrated that reaction of $PhI(OAc)_2$ in excess of TfOH gives hypervalent iodine oligomers comprising 3 or 4 units of $-C_6H_4I(X)-$. The structure of the oligomers was characterized by GC analysis of the decomposition products with KI and by NMR. The oligomers obtained in this study have a *para* phenylene structure and 3–4 of P_n. Functionalization of the iodine oligomers **9** with aromatic substrates was readily performed to give aryl-substituted oligomers **10**. As the practical applications, it has been reported that several types of diaryliodonium salts show strong biological activity.[1] Preliminarily, we examined the biological activity of the hypervalent iodine oligomers. Evaluation results of the biological activity indicate that these iodine oligomers show toxicity toward fungi and bacteria.[14] Particularly, hypervalent iodine oligomers **10** exhibit in vitro toxicity against *Aureobasidium pullulans* and *Penicillium funiculosum* at the 50 ppm level and strong toxicity at the 25 ppm level against bacterial species such as *Bacillus subtilis*, *Enterobacter aerogenes*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Micrococcus luteus* and *Enterococcus faecalis*. Independent syntheses of trimer **10a** ($n=2$) and tetramer **10a** ($n=3$) confirm the structure of the hypervalent iodine oligomers. As a future subject of study on hypervalent iodine oligomers, it will be very interesting to see the structure and property of these new types of hypervalent iodine oligomers because these oligomers contain many hypervalent iodines in the molecule.

4. Experimental

4.1. General

Melting points are uncorrected. Analytical GC evaluations of the product mixture were performed on a capillary gas chromatography using 30 m×0.25 mm capillary column (DB-5, J&J Scientific). Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

4.2. Oligomerization of $PhI(OAc)_2$ with TfOH. Isolation of hypervalent iodine oligomers 7 as bromide salts

(Diacetoxyiodo)benzene (0.80 g, 2.5 mmol) was added to TfOH (4.5 mL, 50 mmol) at 0 °C and the mixture was stirred at room temperature for the time given in Table 1. The reaction mixture was poured onto ice (45 g) and NaBr (7.72 g, 75 mmol) was added. The resulting precipitates were collected by suction, washed with water and methanol, and dried in vacuo. The oligomers **7** (0.55–0.72 g) were obtained as a pale yellow solid as shown in Table 1. The oligomers **7** decomposed in the range of 149–157 °C.

4.3. Decomposition of the oligomers 7 with KI

A mixture of oligomers **7** (50 mg) and KI (1.5 g, 9.0 mmol) in DMF (5 mL) was heated under reflux (163 °C) for 1 h. Water was added to the mixture and the products were extracted with ether. The organic layer was washed with water and aqueous sodium thiosulfate, and dried over anhydrous Na_2SO_4. The GC analysis of the products was performed on a Shimadzu gas chromatograph equipped with a capillary column (DB-5, J&W Scientific) using hexamethylbenzene as an internal standard. The products formed were iodobenzene and 1,4-diiodobenzene. The number average degree of polymerization (P_n) was calculated on the basis of the concentration of these products. Since the decomposition of **7** by KI affords a 1: *n* stoichiometric ratio of iodobenzene and 1,4-diiodobenzene, the P_n value is obtained by the following equation; $P_n=n-1$, where $n=$ [1,4-diiodobenzene]/[iodobenzene]. The results are given in Table 1. Because of the insolubility of **7** in organic solvents other methods for determination of P_n could not be applied.

4.3.1. Isolation of hypervalent iodine oligomers 8 as triflate salts. (Diacetoxyiodo)benzene (0.80 g, 2.5 mmol) was added to TfOH (the quantity described in Table 2) at 0 °C and the mixture was stirred at room temperature for the time given in Table 2. The reaction mixture was poured onto ice (50 g) and $NaHCO_3$ was carefully added until the solution was neutralized. The solution was kept standing for

3 d. The resulting white precipitates were collected by suction, washed with water, and dried in vacuo to give oligomers **8** as a white solid as shown in Table 2. Mp 241–248 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (t, J=7.8 Hz, ArH), 7.68 (t, J=7.5 Hz, ArH), 7.90 (d, J=8.4 Hz, ArH), 8.00 (d, J=8.4 Hz, ArH), 8.26 (d, J=7.8 Hz, ArH), 8.32 (s, ArH).

4.3.2. Arylation of hypervalent iodine oligomers. (Diacetoxyiodo)benzene (0.80 g, 2.5 mmol) was added to TfOH (4.5 mL, 50 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. An aromatic substrate (10 mmol) was added and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured onto ice (50 g) and $NaHCO_3$ (4.41 g, 52.5 mmol) was added carefully. The solution was kept standing for 3 d. The resulting precipitates were collected by suction, washed with water, and dried in vacuo to give white solids of arylated oligomers **10**. Phenylated oligomers **10a**, 0.81 g, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (t, J=8 Hz, ArH), 7.62–7.72 (m, ArH), 8.26 (d, J=8 Hz, ArH), 8.33 (s, ArH). 4-Methylphenylated oligomers **10b**, 0.64 g, ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, Me), 7.35 (d, J=8 Hz, ArH), 7.54 (t, J=8 Hz, ArH), 7.68 (t, J=8 Hz, ArH), 8.13 (d, J=8 Hz, ArH), 8.26 (d, J=8 Hz, ArH), 8.34 (s, ArH). 4-Chlorophenylated oligomers **10c**, 0.85 g, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51–7.56 (m, ArH), 7.62–7.72 (m, ArH), 8.26–8.29 (m, ArH), 8.33 (s, ArH). 4-Bromophenylated oligomers **10d**, 0.81 g, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51–7.56 (m, ArH), 7.66–7.78 (m, ArH), 8.17–8.27 (m, ArH), 8.33 (s, ArH).

The phenylated iodine oligomers **10a** were also characterized by decomposition with KI. A mixture of oligomers **10a** (50 mg) and KI (1.5 g, 9.0 mmol) in DMF (5 mL) was refluxed for 1 h. After workup of the reaction mixture, the products were analyzed by GC using hexamethylbenzene as an internal standard. The products formed were iodobenzene and 1,4-diiodobenzene. The number average degree of polymerization (P_n) was calculated to be 3.5.

4.4. Preparation of hypervalent iodine trimer 10a (n=2) and tetramer 10a (n=3)

4.4.1. Preparation of 1-[(hydroxy)(trifluoromethylsulfonyloxy)iodo]-4-[(phenyl)(trifluoromethylsulfonyloxy)iodo]benzene (4). To a suspension of PhIO (1.1 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added TfOH (0.89 mL, 10 mmol) dropwise at 0 °C and the mixture was stirred for 4 h at room temperature. The solvent was removed by a rotary evaporator and ether was added to the residue. The resulting crystals were collected by suction, washed with ether, and dried in vacuo to afford 1.5 g (84%) of **4**,[6] mp 126–129 °C (dec).

4.4.2. Preparation of 1-[(phenyl)(trifluoromethylsulfonyloxy)iodo]-4-[(4-(tributylstannyl)phenyl)(trifluoromethylsulfonyloxy)]benzene (11). To a solution of 1,4-bis(tributylstannyl)benzene[15] (0.656 g, 1.0 mmol) in MeCN (10 mL) was added **4** (0.722 g, 1.0 mmol) at 0 °C and the mixture was stirred for 1 h at room temperature. The evaporation of the solvent gave crystals, which were collected by suction, washed with ether, and dried in vacuo to give 0.683 g (64%) of **11**: mp 238–242 °C (dec), ^{1}HMR (300 MHz, DMSO-d_6) δ 0.80 (t, J=7.2 Hz, 9H), 1.05 (t, J=7.5 Hz, 6H), 1.24 (m, 6H), 1.46 (m, 6H), 7.50–7.69 (m, 5H), 8.17 (d, J=8.1 Hz, 2H), 8.26 (d, J=7.8 Hz, 2H), 8.33 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.31, 13.47, 26.57, 28.43, 116.77, 117.02, 119.99, 120.24, 131.91, 132.38, 134.18, 135.38, 137.63, 137.71, 139.24, 148.58.

4.4.3. Preparation of hypervalent iodine trimer, bis[4-[(phenyl)(trifluoromethylsulfonyloxy)iodo]phenyl](trifluoromethylsulfonyloxy)iodine [10a (n=2)]. To a suspension of PhIO (0.33 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was added TfOH (0.13 mL, 1.5 mmol) dropwise at 0 °C and the mixture was stirred for 2 h at room temperature. A solution of **11** (0.536 g, 0.5 mmol) in MeCN (40 mL) was added to the resulting solution of PhIO/TfOH reagent at 0 °C and then the mixture was heated with stirring at 40 °C for 22 h. The solvent was evaporated by a rotary evaporator and ether was added to crystallize the residue. The crystals obtained from ether were recrystallized repeatedly from MeCN and ether to give 0.15 g (26%) of **10a** (n=2): mp 241–243 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (t, J=7.8 Hz, 4H), 7.70 (t, J=7.2 Hz, 2H), 8.25 (d, J=7.8 Hz, 4H), 8.34 (s, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.67, 120.34, 120.48, 131.84, 132.34, 135.27, 137.70, 137.77. Anal. Calcd for $C_{27}H_{18}F_9I_3O_9S_3$: C, 28.59; H, 1.60. Found: C, 28.59; H, 1.69.

4.4.4. Preparation of hypervalent iodine tetramer, 1,4-bis[[4-[(phenyl)(trifluoromethylsulfonyloxy)iodo]phenyl](trifluoromethylsulfonyloxy)iodo]benzene [10a (n=3)]. To a solution of 1,4-bis(tributylstannyl)benzene (0.328 g, 0.5 mmol) in MeCN (100 mL) was added **4** (1.083 g, 1.5 mmol) at 0 °C and the mixture was stirred for 3 d at room temperature. At the end of the reaction, crystals were precipitated. The crystals were collected by suction, washed with ether, and finally recrystallized repeatedly from MeCN and ether to give 0.020 g (2.6%) of **10a** (n=3). Mp 235–238 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (t, J=7.8 Hz, 4H), 7.69 (t, J=7.5 Hz, 2H), 8.26 (d, J=7.8 Hz, 4H), 8.34 (s, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 116.69, 120.28, 120.48, 120.58, 131.87, 132.37, 135.30, 137.70, 137.80, 137.93. Anal. Calcd for $C_{34}H_{22}F_{12}I_4O_{12}S_4$: C, 27.47; H, 1.49. Found: C, 27.64; H, 1.65.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also thank the Agricultural Chemical Research Laboratory of Sumitomo Chemical Co., Ltd., for biological evaluations of some hypervalent iodine oligomers.

References and notes

1. For recent reviews and books, see: Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Patai, S.,

Rappoport, Z., Eds.; Wiley: New York, 1983, Chapters 18 and 25. Varvoglis, A. *Synthesis*; 1984, 709–726. Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244–250. Merkushev, E. B. *Russ. Chem. Rev. (Engi. Transl.)* **1987**, *56*, 826–845. Moriarty, R. M.; Vaid, R. K. *Synthesis*; 1990, 431–447. Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett*; 1990, 365–383. Varvoglis, A. The Organic Chemistry of Polycoordinated Iodine.. VCH: New York, 1992. Kita, Y.; Tohma, H.; Yakura, Y. *Trends Org. Chem.* **1992**, *3*, 113–128. Prakash, O.; Saini, N.; Sharma, P. K. *Synlett*; 1994, 221–227. Kitamura, T. *Yuki Gosei Kagaku Kyokai Shi* **1995**, *53*, 893–905. Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. Varvoglis, A. Hypervalent Iodine in Organic Synthesis. Academic: New York, 1997. Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409–458. Ochiai, M. Akiba, K., Ed.; *Chemistry in Hypervalent Compounds*. Wiley-VCH: New York, 1999. Chapter 12. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584.

2. Hartman, C.; Meyer, V. *Chem. Ber.* **1894**, *27*, 426–432.
3. (a) Willgerodt, C. *Die Organishen Vervindungen mit Mehrwertigen Jod*; Ferdinand Enke Verlag: Stuttgart, 1914. (b) Sandin, R. B. *Chem. Rev.*, *32*, 249–276. (c) Beringer, F. M.; Gindler, E. M. *Iodine Abstr. Rev.*, 370. (d) Banks, D. F. *Chem. Rev.*, *66*, 243–266. (e) Olah, G. A. *Halonium Ions*; Wiley: New York, 1975.
4. Gallop, P. M.; Paz, M. A.; Flückiger, R.; Stang, P. J.; Zhdankin, V. V.; Tykwinski, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 11702–11704.
5. Yamada, Y.; Kashima, K.; Okawara, M. *Polym. Lett. Ed.* **1976**, *14*, 65–71.
6. (a) Kitamura, T.; Furuki, R.; Nagata, K.; Taniguchi, H.; Stang, P. J. *J. Org. Chem.* **1992**, *57*, 6810–6814. (b) Kitamura, T.; Furuki, R.; Nagata, K.; Zheng, L.; Taniguchi, H. *Synlett* **1993**, 193–194.
7. Kitamura, T.; Nagata, K.; Nakamura, T.; Furuki, R.; Taniguchi, H. *Tetrahedron* **1995**, *51*, 6229–6236.
8. Hansh, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *19*, 165–195.
9. For a preliminary report, see: Kitamura, T.; Wakimoto, I.; Nakamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 253–356.
10. Beringer, F. M.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2705–2708.
11. Beringer, F. M.; Falk, R. A.; Karniol, M.; Lollien, I.; Masullo, G.; Mausner, M.; Sommer, E. *J. Am. Chem. Soc.* **1959**, *81*, 342–351.
12. Zefirov, N. S.; Safronov, S. O.; Kaznacheev, A. A.; Zhdankin, V. V. *J. Org. Chem. USSR (Engl. Transl.)* **1990**, 1633–1634. *Zh. Org. Khim.* 1989, *25*, 1807–1808.
13. Kitamura, T.; Matsuyuki, J.; Taniguchi, H. *Synthesis* **1994**, 147–148.
14. Biological evaluations have been conducted at the Agricultural Chemical Research Laboratory of Sumitomo Chemical Co., Ltd., Takarazuka, Japan.
15. Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 715–720.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8861–8868
Tetrahedron

Bifunctional pyridyl alcohols with the bicyclo[3.3.0]octane scaffold in the asymmetric addition of diethylzinc to aldehydes

Yu-Wu Zhong, Chang-Sheng Jiang, Ming-Hua Xu* and Guo-Qiang Lin*

Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

Received 28 June 2004; revised 8 July 2004; accepted 8 July 2004

Available online 18 August 2004

Abstract—Some new pyridyl alcohols with the *cis*-bicyclo[3.3.0]octane scaffold were synthesized and used as chiral ligands for the enantioselective addition of diethylzinc to aldehydes. Ligands **4** were found to be far superior to the C_2-symmetric ligands **2** in terms of enantioselectivities. Quantitative yields and enantiomeric excesses of up to 92% were obtained when the ligand **4** was used. The carbonyl function in **4** proved to be beneficial for the high enantioselectivities in the addition of diethylzinc to aldehydes. Conversion of the carbonyl group into oxime or oxime ether group led to a sort of more active ligands, which catalyzed the same reaction with rate acceleration.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Over the past decade, much attention has been paid to the design and synthesis of novel chiral ligands for the asymmetric processes.[1] Among them, the development of bifunctional ligand systems for the asymmetric construction of C–C bonds is of great interest.[2,3] The secondary basic sites in chiral ligands provided an additional interaction between the ligand and the reagent, which usually resulted in an improved reactivity and stereoselectivity.[4]

Amino alcohols catalyzed addition of diethylzinc to aldehydes was so extensively explored that it has become as one of the model reactions in the asymmetric catalysis.[5] It is generally accepted that this reaction proceeds via a dual activation of the aldehyde electrophile and the diethylzinc nucleophile,[6] as shown in transition state **A** in Figure 1. It occurred to us that if there is a secondary basic site (represented as Nu in **B** in Figure 1) in the same ligand well positioned to coordinate with zinc atom Zn(2), the dissociation of Zn(2)–O(2) bond in **A** might occur. Accordingly, the transition state would shift from **A** to **B**, which included a chair-like six-membered ring structure.[7]

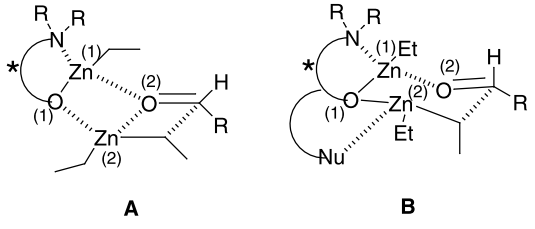


Figure 1.

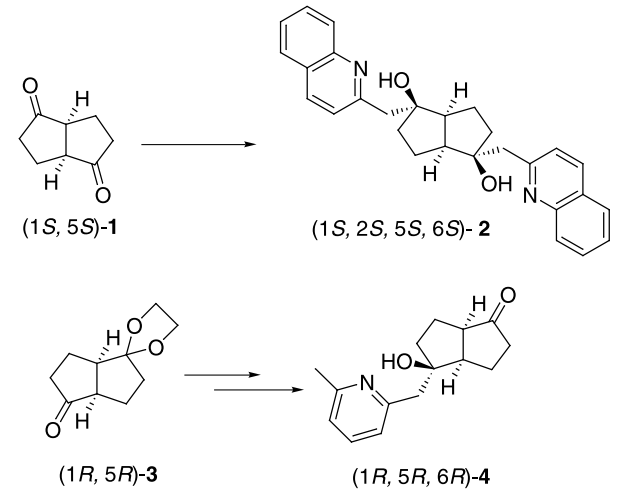
In our laboratory, we are interested in the application of some structurally interesting molecules for asymmetric synthesis.[8] Synthesis of new chiral ligands bearing the *cis*-bicyclo[3.3.0]octane scaffold and their applications in asymmetric reactions are one of our recent projects.[8c,d] The appealing semi-caged structure of the *cis*-bicyclo[3.3.0]octane framework is anticipated to provide a peculiar chiral environment in asymmetric processes.

In our previous work,[8c] we reported the synthesis of the C_2-symmetric bis-pyridyl alcohol **2** (Scheme 1) and mono-pyridyl alcohol **4** from the chiral diketone **1**[9] which was easily obtained from 1,5-cyclooctadiene, and their application as novel chiral ligands in the enantioselective addition of diethylzinc to aldehydes. To our surprise, C_2-symmetric ligand **2** was found to only induce very low enantioselectivity (7% ee) in the diethylzinc addition to benzaldehyde, while ligand **4**, with a carbonyl group in the bicyclo[3.3.0]octane scafflod, was found much more efficient in catalyzing the same reaction and provided the product with 92% ee in quantitative yield. Similar good ees (89–92%) were observed in the reaction with other aldehydes. To explain these results, we envisioned that the carbonyl group in ligand **4** might be involved in the

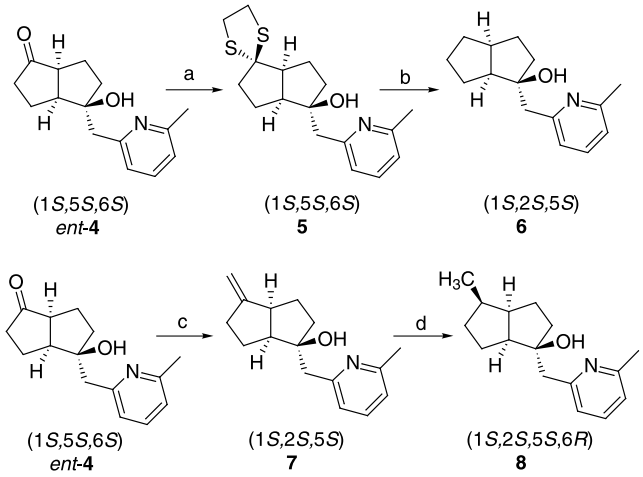
Keywords: Bicyclo[3.3.0]octane; Bifunctional ligand; Pyridyl alcohol; Diethylzinc; Secondary basic site.

* Corresponding authors. Tel.: +86-21-64163300x3206; fax: +86-21-64166263; e-mail addresses: xumh@mail.sioc.ac.cn; lingq@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.015



Scheme 1. The synthesis of compounds **2** and **4**.



Scheme 2. The synthesis of compounds **5**, **6**, **7**, and **8**. (a) $HSCH_2CH_2SH$, BF_3OEt_2, CH_2Cl_2, Quant. (b) Raney-nickel, EtOH, reflux, Quant. (c) CH_3PPh_3I, *t*-BuOK, 82%. (d) Pd/C, MeOH, H_2 (1 atm), 85%.

coordination with zinc atom and stabilize the reaction transition state, as depicted in Figure 1.

In this paper, we wish to report our detailed studies. We found that the unmasked carbonyl group in ligand **4** acted as a secondary basic group in this reaction, and was important for maintaining the high stereoselectivities. The modification of **4** by converting the carbonyl function into oxime or oxime ether group led to a kind of more efficient ligands, which catalyzed the addition of diethylzinc to aldehydes with an obvious acceleration effect.

2. Results and discussion

To address whether the carbonyl group in ligand **4** had contribution to the high enantioselectivity observed in the diethylzinc addition to aldehydes, we first consider to convert the carbonyl group into other functions to see if it would result in an apparent impact on the stereoselectivity when applied to the reaction. Reduction of the carbonyl group into methylene moiety was certainly the first choice.

Unfortunately, direct reduction, including Wolff-Kishner–Huang reduction[10] and reduction of tosylhydrazone by sodium cyanoborohydride,[11] was proved to be unsuccessful. Thus, a different approach was then taken. As shown in Scheme 2, by converting the *ent*-**4** (the enantiomer of **4**) into its dithioketal counterpart **5**, followed by the reaction with Raney-nickel in 2-propanol,[12] we successfully obtained the designed compound **6**. In addition, compound **7** and **8**[13] were also synthesized via Wittig reaction of *ent*-**4** with CH_3PPh_3I, followed by the hydrogenation reaction.

With compounds **5**, **6**, **7** and **8** in hand, we investigated their efficiency as chiral ligand respectively in the diethylzinc addition to aldehydes under the same conditions[8c] as ligand

Table 1. Comparison of the stereoselectivity of the product induced by ligand **4** and **5**–**8**[a]

Entry	Ligand	Aldehyde	Yield (%)[b]	ee (%)[c]
1	**4**	Benzaldehyde	>98	92
2	**4**	*p*-Chlorobenzaldehyde	84	91
3	**4**	*p*-Anisaldehyde	>98	91
4	**4**	*p*-Tolualdehyde	>98	91
5	**4**	1-Naphthaldehyde	>98	89
6	**4**	*trans*-Cinnamaldehyde	>98	51
7	**5**	Benzaldehyde	90	78
8	**5**	*p*-Chlorobenzaldehyde	90	76
9	**5**	*p*-Anisaldehyde	85	77
10	**6**	Benzaldehyde	>98	79
11	**6**	*p*-Chlorobenzaldehyde	95	77
12	**7**	Benzaldehyde	88	77
13	**7**	*p*-Chlorobenzaldehyde	93	79
14	**7**	*p*-Anisaldehyde	>98	77
15	**7**	*p*-Tolualdehyde	>98	78
16	**7**	1-Naphthaldehyde	>98	76
17	**7**	*trans*-Cinnamaldehyde	98	33
18	**8**	Benzaldehyde	>98	77
19	**8**	*p*-Chlorobenzaldehyde	>98	78
20	**8**	*p*-Anisaldehyde	>98	75
21	**8**	*p*-Tolualdehyde	98	79
22	**8**	1-Naphthaldehyde	>98	74
23	**8**	*trans*-Cinnamaldehyde	90	33

[a] The absolute configuration of products catalyzed by **4** is *R*, while it is *S* when catalyzed by **5**–**8**.
[b] Isolated yield after the column chromatography.
[c] Determined by chiral HPLC analysis.

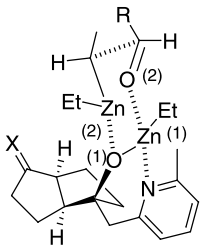


Figure 2. Proposed transition state.

To gain some insight into this interesting phenomena, X-ray analysis of **2** and **4** were performed (Figs. 3 and 5).[14] X-ray analysis of **2** (Fig. 3) revealed that there was a hydrogen bonding between hydroxyl O(2)H and oxygen atom O(1), and the distance between two oxygen atoms was 2.74 Å. The two nitrogen atoms in the quinoline ring were hidden in the back side of the bicyclo[3.3.0]octane framework, and neither of them had a hydrogen bonding with the hydroxy moiety. It was reasonable to assume when **2** was used to catalyze the addition of diethylzinc to aldehyde, the real catalyst could be depicted in Figure 4, wherein zinc atom

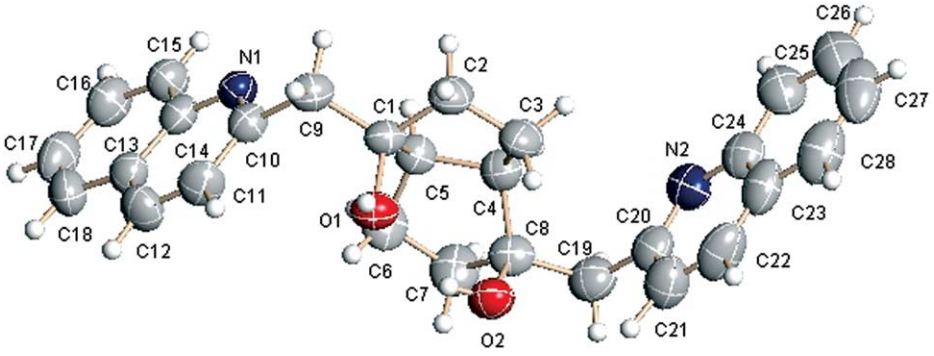


Figure 3. X-ray analysis of ligand **2**.

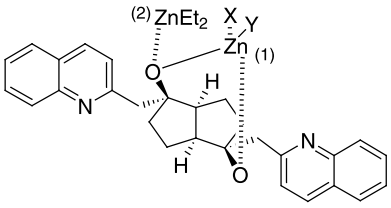


Figure 4. Proposed catalyst when **2** was used as the ligand. X, Y may be the ethyl, aldehyde group, or as part of the oligmer form.

4 was used. The experimental results were summarized in Table 1. As we can see, when the ligand **5**, **6**, **7** or **8** was used, the obtained ee value of the corresponding product was 10% or more lower than that obtained by using ligand **4**. For benzaldehyde (entries 7, 10, 12, 18), substituted benzaldehydes (entries 8, 9, 11, 13, 14, 15, 19, 20, 21) and 1-naphthaldehyde (entries 16, 22), the ee value of the product decreased from 90% level (entries 1–5) to 77% or so. For *trans*-cinnamaldehyde (entries 17, 23) a similar decrease from 51% (entry 6) to 33% was observed. These results indicate that the presence of the carbonyl group in ligand **4** is indeed important for maintaining the high ee in this reaction.

Considering the differences between ligand **4** and **6**–**8**, it might be reasonable to postulate that the carbonyl group in ligand **4** was employed as a secondary basic site, in other words, the reaction might proceed via a transition state as shown in Figure 2 (X=O), where the carbonyl group coordinated with zinc atom Zn(2) to act as a secondary basic group. In the case of ligand **5**, although the sulfur atom could be a secondary basic site, it was still not as effective as ligand **4**, which suggested that the planar conformation of the carbonyl group of ligand **4** was also an important factor for inducing the high enantioselectivity.

Zn(2) did not coordinate with the nitrogen atom. It was obvious that the surroundings of zinc atoms Zn(1) and Zn(2) was free from steric hindrance, which resulted in the low stereo-induction.

On the other hand, the X-ray analysis of **4** (Fig. 5) showed a

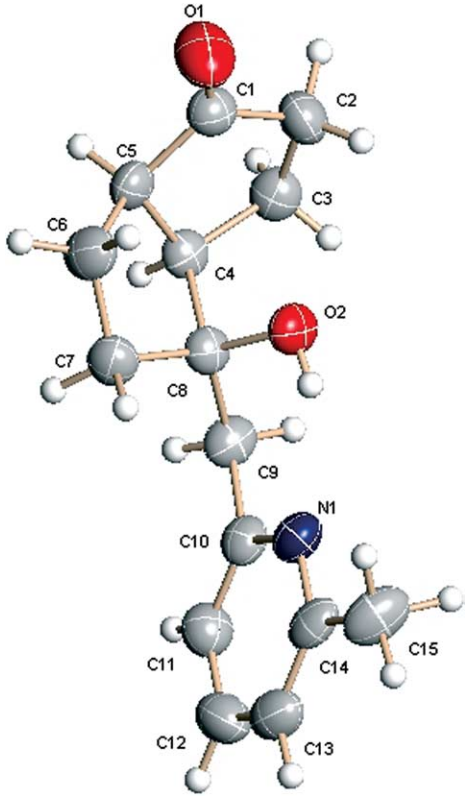
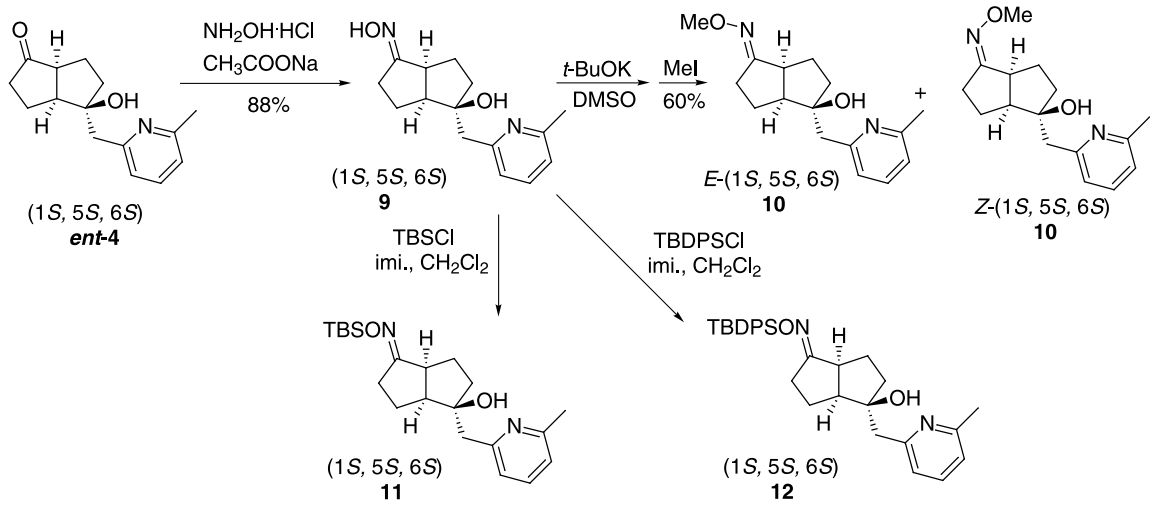


Figure 5. X-ray analysis of ligand **4**.



Scheme 3. The synthesis of ligands **9**–**12**.

hydrogen bonding between the hydroxyl O(2)H and the nitrogen atom in the pyridine ring. When **4** was used to catalyze the addition of diethylzinc to aldehyde, the real catalyst was possible as described in Figure 2. Zinc atom Zn(1) combined with hydroxyl oxygen atom, and coordinated with the nitrogen atom in the pyridine ring. Zinc atom Zn(2) coordinated with hydroxyl oxygen atom. The carbonyl oxygen was also possibly involved in the stabilizing the six-membered chair-like transition state. Taking advantage of the steric hindrance of bicyclo[3.3.0]-octane backbone and methyl group in the pyridine ring, the reaction using ligand **4** gave higher enantioselectivities.

To further prove our hypothesis, we envisioned that if X in the proposed transition state (Fig. 2) is replaced by sulfur atom or nitrogen atom, which will have a more electron-donating potential and thus the ethyl group bound to Zn(2) atom would be more nucleophilic. As a result, an accelerated reaction rate could be observed in the same reaction. Disappointingly, we were unsuccessful in converting the carbonyl group of ligand *ent*-**4** into thiocarbonyl group with Lawesson' reagent or P_2S_5.[15,16] Efforts to convert the carbonyl group into imine analogous also failed, presumably due to the presence of the hydroxy and pyridine moiety within the molecule.

We then turned our attention to the oxime and oxime ether group which were reluctantly used in chiral ligands or auxiliaries due to the usual formation of a mixture of geometric isomers.[17] However, two advantages of oxime and oxime ether are appealing: (1) they are more electron-donating than imine; (2) the high stability toward hydrolytic conditions would allow them for separation via flash column chromatography easily. Keeping these in mind, we prepared the oxime ligand **9** from ligand *ent*-**4**. Methylation of **9** afford the *O*-methyl oxime ether ligand **10** (Scheme 3). The *E*/*Z* isomers of oxime **9** were inseparable by column chromatography. However, the corresponding oxime ether *E*-**10** and *Z*-**10** could be separated by flash column chromatography.[18]

Interestingly, when oxime ligand **9** was used to catalyze the

Table 2. Comparison of the reaction rational catalyzed by ligands **4**, **9**–**12**[a]

Entry	RCHO	Ligand	Catalyst loading (mol%)	Temperature (°C)	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	Benzaldehyde	**4**	10	0 to rt	24	>98	92
2	Benzaldehyde	**9**	5	0	10	>98	81
3	Benzaldehyde	**9**	10	−20	24	>98	84
4	Benzaldehyde	*Z*-**10**	3	0	10	>98	83
5	Benzaldehyde	*E*-**10**	4	0	10	>98	85
6	Benzaldehyde	**11**	3	0	10	>98	88
7	Benzaldehyde	**11**	5	−20	44	>98	90
8	Benzaldehyde	**12**	2	0	10	>98	86
9	Benzaldehyde	**12**	6	−20	30	>98	88
10	*p*-Chlorobenzl-dehyde	**11**	3.5	0	11	94	87
11	*p*-Anisaldehyde	**11**	4	0	12	>98	88
12	*trans*-Cinnamal-dehyde	**11**	4	0	8	88	51
13	Cyclohexane-carboxyalde-hyde	**11**	4.5	0	11	>98	69[d]

[a] The absolute configuration of all products is *S* except in entry 1 which is *R*.
[b] Isolated yield after the column chromatography.
[c] The ee was determined by chiral HPLC analysis unless otherwise noted.
[d] The ee was determined by comparison of the specific optical rotation with the literature, see Ref. 19.

addition of diethylzinc to benzaldehyde, a distinctive acceleration phenomenon was observed. The reaction was completed in only 10 h at 0 °C with 5 mol% of loading (entry 2, Table 2). In comparison, the reaction needed 24 h at rt for completion when 10 mol% of ligand **4** was used (entry 1, Table 2). Considering a relatively lower ee of 81% was observed, the reaction temperature was reduced to −20 °C (entry 3), which resulted in a prolonged reaction time (24 h) and a slight enhancement of ee to 84%. Similar acceleration effect was also observed when oxime ether *Z*-**10** or *E*-**10** was used as the ligands (entries 4 and 5). It was worth noting that the addition reaction catalyzed by *Z*-**10** or *E*-**10** afforded the product with the same sense and almost the same ee value, which indicated the geometry (*Z* or *E*) of the oxime ether played a minor role in the stereoinduction of this reaction.

Comparison of entry 2 and entries 4, 5 revealed that the oxime ether ligand was more efficient than the corresponding oxime ligand in terms of the enantioselectivity. Therefore, we turned to prepare other oxime ethers with the hope to find more efficient ligands. As shown in Scheme 3, TBS (*t*-butyldimethylsilyl) oxime ether ligand **11** and TBDPS (*t*-butyldiphenylsilyl) oxime ether ligand **12** were synthesized from oxime **9** in quantitative yields. When 3 mol% of **11** was employed as the ligand (entry 6), the reaction was completed within 10 h to furnish the product with a slight increase of ee (88%) than ligand **10**. A decrease in temperature from 0 to −20 °C resulted in a further increase of ee to 90%, in sacrifice of the reaction time (44 h) (entry 7). Attempts to employ compound **12** with a bulkier silyl ether group as the ligand to further increase the ee proved to be unsuccessful (entries 8 and 9). Extension of the substrate to substituted benzaldehydes (entries 10 and 11) and aliphatic aldehydes (entries 12 and 13) using TBS–oxime **11** as ligand also showed an acceleration effect, though the ee of the product decreased slightly in comparison with that induced by ligand **4**.

This acceleration effect is in accordance with our hypothesis. When the carbonyl group in **4** (or *ent*-**4**) was converted into oxime or oxime ether group that had a more electron-donating potential, the ethyl group bound to Zn(2) atom should be more nucleophilic. As a result, an accelerated reaction occurred. Considering the relative position of the carbonyl group and the hydroxyl group in ligand **4** (see X-ray analysis in Figure 5), the lone pair electrons of the carbonyl oxygen atom are almost bisected by the O(1)–O(2) line. So unlikely they could be directed to one zinc atom at the same time. The experimental fact that both *E*- and *Z*-oxime ether (entries 4 and 5, Table 2) gives the same enantioselectivities with the same sense also implies that the lone pair electrons would not be involved in the transition state. Most likely it is the π electrons of the carbonyl group that interact with the zinc atom Zn(2) in the supposed transition state **B** in Figure 1. Clarification of the real mechanism calls for further investigation.

3. Conclusion

In summary, some new pyridyl alcohols with the *cis*-bicyclo[3.3.0]octane scaffold were synthesized and used to catalyze the enantioselective addition of diethylzinc to aldehydes. C_2-symmetric ligand **2** was found less effective than unsymmetric ligand **4**. Over 90% ees were found when **4** was used to catalyze the reactions. The carbonyl group in pyridyl alcohol **4** was evidenced to be important in achieving the high enantioselectivity. Conversion of this carbonyl group into oxime or oxime ether motif led to a kind of more efficient ligand, which catalyzed the same reaction with a higher reaction rate. The work to expand the use of these ligands in other asymmetric reactions is in progress.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on 300 and 75 MHz FT-spectrometers, respectively, using $SiMe_4$ as the internal reference. IR spectra were recorded on a Bio-Rad FTS-185 IR spectrometer. Mass spectra were recorded by the EI method, and HRMS were measured on a Finnigan MAT-8430 mass spectrometer. Elemental analyses were performed on Heraeus Rapid-CHNO. Enantiomeric excess (ee) determination was carried out using HPLC with Chiralcel OD, AS, AD, OJ columns. The silica gel used for flash chromatography was 300–400 mesh. All solvents were dried by standard methods. Unless otherwise noted, commercially available reagents were used without further purification.

4.1.1. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-ylmethyl)-bicyclo[3.3.0]octan-2-one, ethylene thioketal, 5. Pyridyl alcohol *ent*-**4** (490 mg, 2 mmol) was dissolved in anhydrous dichloromethane (50 mL) in a 100 mL flame-dried three-necked flask under an argon atmosphere, followed by the addition of Boron trifluoride diethyl etherate (1.33 mL, 10 mmol) and 1,2-ethanedithiol (0.32 mL, 4 mmol). This solution was stirred at rt overnight and quenched by the saturated aqueous $NaHCO_3$. The organic layer was separated, and the water layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over with anhydrous Na_2SO_4. Purification by flash column chromatography afforded 630 mg of **5** as a white solid in quantitative yield. Mp 72 °C; $[\alpha]_D^{20}$ +5.3° (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.99 (m, 7H), 2.16 (m, 1H), 2.32 (m, 1H), 2.49 (s, 3H), 2.76 (m, 1H), 2.87 (s, 2H), 3.23 (m, 4H), 6.00–6.60 (br, 1H), 6.89 (d, J= 7.8 Hz, 1H), 7.00 (d, J=8.1 Hz, 1H), 7.50 (td, J=7.8, 1.2 Hz, 1H); FT-IR (KBr, cm^{-1}): 3367, 3062, 2922, 1594, 1576, 1459, 1416; EIMS (*m*/*z*, %): 321 (M^+, 12.85), 303 (M^+-H_2O, 1.93), 262 (15.30), 260 (30.29), 228 (30.13), 162 (12.89), 149 (33.32), 134 (13.55), 107 (100.00), 106 (26.84); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.26, 25.40, 30.08, 38.32, 38.75, 39.94, 42.99, 46.35, 51.26, 56.91, 75.82, 81.90, 120.88, 121.03, 137.11, 157.05, 158.86; HRMS for $C_{17}H_{23}NOS_2$ (M^+), calcd: 321.1221, found 321.1211.

4.1.2. (1*S*,2*S*,5*S*)-2-(6-Methylpyridin-2-ylmethyl)-bicyclo-[3.3.0]octan-2-ol, 6. Thioketal **5** (360 mg, 1.1 mmol) was dissolved in ethanol (20 mL), followed by

the addition of 1 g of Raney nickel. The resulting mixture was then refluxed for 2 h. The cooled solution was filtered through celite and washed with ethanol. Purification by flash column chromatography provided 260 mg of pyridyl alcohol **6** as an oil in quantitative yield. $[\alpha]_D^{20}$ +4.4° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (m, 5H), 1.63 (m, 5H), 2.13 (m, 1H), 2.45 (m, 1H), 2.52 (s, 3H), 2.90 (m, 2H), 6.16 (br, 1H), 6.92 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.49 (m, 1H); FT-IR (film, cm^{-1}): 3348, 3068, 2948, 1579, 1459, 798; EIMS (*m/z*, %): 231 (M^+, 1.82), 162 (21.33), 149 (34.49), 134 (10.72), 108 (10.59), 107 (100.00), 106 (12.04), 79(6.97), 41(7.16); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.27, 27.31, 27.57, 30.15, 34.43, 39.82, 43.22, 46.46, 52.46, 81.67, 120.85, 120.92, 136.97, 157.04, 159.36; HRMS for $C_{15}H_{21}NO$ (M^+), calcd: 231.1623, found 231.1641.

4.1.3. (1*S*,2*S*,5*S*)-6-Methylene-2-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-ol, 7. To a 100 mL three-necked round-bottomed flask was added PPh_3CH_3I (606 mg, 1.5 mmol) and THF (20 mL) under argon atmosphere at 0 °C. While the mixture was stirred, *t*-BuOK (168 mg, 1.5 mmol) was added. The resulting yellow solution was stirred for 30 min, followed by the slow addition of a solution of 245 mg of pyridyl alcohol *ent*-**4** (1 mmol) in 10 mL of THF. Stirring was continued for 10 h at 0 °C. Then, 10 mL water was added to quench the reaction. Usual workup followed by flash column chromatography afforded **7** (200 mg, yield 82%) as a colorless oil. $[\alpha]_D^{20}$ +80.0° (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.53 (m, 2H), 1.73 (m, 3H), 1.95 (m, 1H), 2.23 (m, 2H), 2.45 (m, 1H), 2.51 (s, 3H), 2.92 (m, 3H), 4.74 (m, 1H), 4.83 (m, 1H), 6.20 (br, 1H), 6.92 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H); FT-IR (film, cm^{-1}): 3335, 3068, 2951, 1654, 1579, 1459, 877; EIMS (*m/z*, %): 243 (M^+, 8.09), 107 (100.00), 149 (16.99), 162 (16.91), 134 (14.74), 108 (12.09), 79 (10.79), 77 (8.79); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.20, 25.97, 30.51, 34.86, 39.36, 46.05, 47.62, 52.95, 82.04, 103.67, 121.03, 121.05, 137.14, 157.09, 159.17, 159.26; HRMS for $C_{16}H_{19}N$ (M^+-H_2O), calcd.: for 225.1529, found 225.1518.

4.1.4. (1*S*,2*S*,5*S*,6*R*)-6-Methyl-2-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-ol, 8. To a solution of **7** (410 mg, 1.68 mmol) in methanol (20 mL) was added 57 mg of 10% Pd/C. The mixture was hydrogenated for 48 h under 1 atm of H_2, and then filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography to give **8** (348 mg, yield 85%) as a colorless oil. $[\alpha]_D^{20}$ +21.8° (*c* 1.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (d, J=6.3 Hz, 3H), 1.13 (m, 2H), 1.39 (m, 4H), 1.56 (m, 2H), 1.75 (m, 1H), 2.14 (t, J=7.5 Hz, 1H), 2.34 (m, 1H), 2.45 (s, 3H), 2.85 (s, 2H), 5.84 (br, 1H), 6.8 (d, J=7.8 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 1H); FT-IR (film, cm^{-1}): 3352, 3065, 1595, 1579, 1459, 1097, 795; EI-MS (*m/z*, %): 245 (M^+, 1.19), 227 (M^+-H_2O, 3.74), 162 (18.99), 149 (36.55), 134 (9.67), 108 (10.73), 107 (100.00), 106 (13.13), 79 (5.89), 41 (5.87); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.02, 23.09, 23.31, 25.15, 32.82, 36.54, 39.78, 46.24, 47.27, 51.68, 80.97, 119.85, 119.89, 135.97, 156.12, 158.53; HRMS for $C_{16}H_{23}NO$ (M^+), calcd.: 245.1780, found: 245.1794.

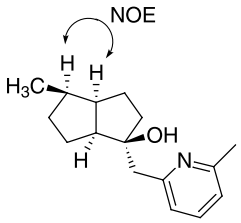


Figure 6. The establishment of the relative configuration of ligand **8** by NOESY analysis.

The relative configuration of **8** was confirmed by its NOESY analysis, see Figure 6.

4.1.5. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-one oxime, 9. To a solution of 37 mg of hydroxylamine hrdrochloride in 5 mL of ethanol was added *ent*-**4** (65 mg, 0.26 mmol) and sodium acetate (43 mg, 0.53 mmol). The resulting mixture was stirred at rt for 30 min. After evaporation of the solvent, the residue was partitioned between CH_2Cl_2 (10 mL) and brine (10 mL). The water layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purification by flash column chromatography to give **9** (61 mg, yield 88%) as a white solid. $[\alpha]_D^{20}$ +136.7° (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.56–2.05 (m, 6H), 2.06–2.37 (m, 2H), 2.52 (s, 3H), 2.63 (m, 1H), 2.87 (m, 1H), 3.03 (m, 1.5H), 3.40 (m, 0.5H), 6.21 (br, 1H), 6.93 (d, J=7.5 Hz, 1H), 7.02 (d, J=8.1 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 8.41 (br, 1H); FT-IR (KBr, cm^{-1}): 3393, 3188, 3075, 2957, 1674, 1597, 1579, 1459, 950; EIMS (*m/z*, %): 260 (M^+, 1.67), 243 (M^+-OH, 19.24), 225 (8.88), 163 (7.04), 162 (17.64), 134 (12.90), 108 (10.95), 107 (100.00), 106 (12.45). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.05; H, 7.72; N, 10.62.

4.1.6. 4.6. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo[3.3.0]octan-2-one *O*-methyl oxime, 10. Potassium *tert*-butoxide (166 mg, 1.48 mmol) was added into a solution of oxime **9** (350 mg, 1.34 mmol) in 15 mL of DMSO. The mixture was stirred at rt for 30 min, followed by the addition of the iodomethane (0.094 mL, 1.48 mmol). After 1 h, the mixture was diluted with ethyl acetate (300 mL) and washed with brine. The residue after concentration was subjected to flash chromatography to afford *Z*-**10** (40 mg), *E*-**10** (50 mg) and a mixture of *Z*-**10** and *E*-**10** (100 mg) with a total yield of 60%. The ratio of *Z*-**10**/*E*-**10** was confirmed to be 1:2 by ^1H NMR analysis of the crude product.

Minor isomer (*Z*, *less polar*). $[\alpha]_D^{20}$ +217.6° (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.49–1.81 (m, 5H), 2.08 (m, 1H), 2.27 (m, 2H), 2.50 (s, 3H), 2.61 (m, 1H), 2.81–2.98 (AB, δ_A=2.84, δ_B=2.96, J_{AB}=14.4 Hz, 2H), 3.30 (m, 1H), 3.80 (s, 3H), 6.24 (br, 1H), 6.90 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H); FT-IR (film, cm^{-1}): 3324, 2945, 1595, 1577, 1459, 1056; EIMS (*m/z*, %) 275 (M^++H, 100.00), 276 (13.75), 257 (4.67), 244 (3.23), 243 (17.61), 226 (3.74), 225 (10.30), 107 (15.18); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.15, 24.28, 27.68, 31.23, 39.56, 43.72, 45.77, 52.19, 61.22, 82.07, 120.96, 121.12, 137.18, 157.25, 159.07, 170.47.

Major isomer (*E*, *more polar*). $[\alpha]_D^{20}$ +124.3° (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.59–1.71 (m, 3H), 1.87 (m, 2H), 2.05 (m, 1H), 2.35 (m, 1H), 2.40–2.70 (m, 2H), 2.50 (s, 3H), 2.81–3.02 (AB, $\delta_A=2.83$, $\delta_B=2.99$, $J_{AB}=14.4$ Hz, 2H), 3.10 (m, 1H), 3.83 (s, 3H), 6.92 (d, $J=$ 7.8 Hz, 1H), 7.02 (d, $J=7.8$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H); FT-IR (film, $^{-1}$): 3325, 2953, 1596, 1579, 1460, 1053, 756; EIMS (*m*/*z*, %) 275 (M^++H, 7.27), 243 (27.01), 225 (23.85), 162 (21.51), 134 (17.88), 108 (13.61), 107 (100.00), 79 (9.12), 65 (8.12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.78, 24.27, 28.37, 29.09, 39.70, 45.65, 46.16, 61.27, 82.17, 120.99, 121.12, 137.16, 157.27, 159.10, 171.05; HRMS for $C_{16}H_{22}N_2O_2$ (M^+), calcd: 274.1681, found: 274.1719.

4.1.7. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-one *O*-(*tert*-butyldimethylsilyl) oxime, 11. To a solution of oxime **9** (130 mg, 0.5 mmol) and imidazole (140 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added *tert*-butyldimethylsilyl chloride (151 mg, 1 mmol). The stirring was continued for 4 h at rt. The resulting mixture was diluted with CH_2Cl_2 and washed with brine. Purification by flash column chromatography provided 190 mg of **11** as a colorless oil in quantitative yield. $[\alpha]_D^{20}$ +97.0° (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.08 (s, 6H), 0.85 (s, 4.5H), 0.86 (s, 4.5H), 1.20–1.90 (m, 5H), 1.95–2.20 (m, 1H), 2.26–2.32 (m, 1H), 2.44 (s, 3H), 2.50 (m, 1H), 2.84 (dd, $J=14.7$ Hz, 3.6 Hz, 1H), 2.95 (dd, $J=14.3$, 5.7 Hz, 1H), 3.05 (m, 0.5H), 3.33 (m, 0.5H), 6.25 (br, 1H), 6.85 (m, 1H), 6.96 (d, $J=8.1$ Hz, 1H), 7.45 (t, $J=7.8$ Hz, 1H); FT-IR (film, cm^{-1}): 3335, 2956, 1596, 1579, 1461, 1249, 915, 837, 781; EIMS (*m*/*z*, %): 374 (M^+, 3.01), 318 (18.35), 317 ($M^+-C_4H_9$, 73.64), 225 (35.67), 162 (13.53), 108 (16.21), 107 (100.00), 106 (18.35), 75 (40.24); HRMS. for $C_{21}H_{34}N_2O_2Si$ (M^+), calcd: 374.2390, found 374.2359.

4.1.8. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo[3.3.0]octan-2-one *O*-(*tert*-butyldiphenylsilyl) oxime, 12. Prepared from oxime **9** and *tert*-butyldiphenylsilyl chloride in a similar way as described in Section 4.1.7. $[\alpha]_D^{20}$ +84.8° (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (s, 9H), 1.50–2.00 (m, 6H), 2.34 (m, 2H), 2.53 (s, 3H), 2.63–3.09 (m, 3.5H), 3.54 (m, 0.5H), 6.00–6.50 (br, 1H), 6.92 (m, 1H), 7.03 (d, $J=7.2$ Hz, 1H), 7.36 (m, 6H), 7.50 (m, 1H), 7.72 (m, 4H); FT-IR (film, cm^{-1}): 3323, 3072, 2959, 1595, 1579, 1460, 1429, 1114, 914, 740, 701, 506; EIMS (*m*/*z*, %): 498 (M^+, 0.57), 442 (21.89), 441 ($M^+-C_4H_9$, 62.21), 225 (80.36), 199 (70.68), 198 (19.12), 197 (22.14), 107 (100.00), 106 (23.60); HRMS for $C_{31}H_{38}N_2O_2Si$ (M^+), calcd: 498.2703, found 498.2710.

4.2. General procedure for the asymmetric addition of diethyl zinc to arylaldehydes

To a solution of ligand (0.05 mmol) in toluene (2.3 mL) at 0 °C was added 15% wt solution of diethylzinc in hexane (2.3 mL, 2.0 mmol). The resulting mixture was stirred for 30 min at 0 °C, followed by the addition of the freshly distilled benzaldehyde (1.0 mmol). The reaction mixture was stirred at 0 °C to completion, and then quenched with saturated aqueous NH_4Cl. The water layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over with anhydrous Na_2SO_4. Purification by flash column chromatography afforded the addition product. The enantiomeric excess of the obtained product was determined by chiral HPLC analysis.

Acknowledgements

We are grateful to the financial assistance by the NSFC (20172063 and 203900506), the Major State Basic Development Program (6200077506) and Chinese Academy of Sciences. We are also grateful to the suggestion given by the referees during the review of this article.

References and notes

1. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999.
2. For selective reviews, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236. (b) Groger, H. *Chem. Eur. J.* **2001**, *7*, 5247. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (d) Steinhagen, H.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339.
3. For recent examples, see: (a) Dimauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (b) Dimauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (c) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3. (d) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.
4. (a) Schinnerl, M.; Bohm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765. (b) Dimauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053.
5. For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
6. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (b) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (d) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605. (e) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (f) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.
7. (a) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2003**, *125*, 5130. (b) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464. (c) Xu, Q.-Y.; Wang, G.-X.; Pan, X.-F.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 381. (d) Cherng, Y.-J.; Fang, J.-M.; Lu, T.-J. *J. Org. Chem.* **1999**, *64*, 3207.
8. (a) Wang, J.-Q.; Xu, M.-H.; Zhong, M.; Lin, G.-Q. *Chin. Chem. Lett.* **1998**, *9*, 325. (b) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (c) Zhong, Y.-W.; Lei, X.-S.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2002**, *13*, 2251. (d) Zhong, Y.-W.; Tian, P.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771.
9. (a) Mehta, G.; Srinivas, K. *Tetrahedron Lett.* **2001**, *42*, 2855. (b) Perard-Viret, J.; Rassat, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1. (c) Lemke, K.; Ballschuh, S.; Kunath, A.; Theil, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2051. (d) Moriarty, R. N.; Duncan, M. P.; Vaid, P. K.; Prakash, R. *Org. Synth.* **1990**, *68*, 175.
10. Huang, M.-L. *J. Am. Chem. Soc.* **1946**, *68*, 2487.

11. Caglioti, L.; *Organic Syntheses*, Collect. Vol. 6; Wiley: New York, 1988 p 62.
12. Paquette, L. A.; *Encyclopedia of Reagents for Organic Synthesis*, Vol. 6; Wiley: New York, 1995 p 4401.
13. Shown in Scheme 2 is the major isomer of **8** whose relative configuration has been evidenced by the NOESY analysis, see Section 4.
14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 242959 and 242960, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk
15. (a) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158. (b) Scheibye, S.; Shabana, R.; Lawesson, S.-O. *Tetrahedron* **1982**, *38*, 993. (c) Deng, S.-L.; Chen, R.-Y. *Synthesis* **2002**, 2527. (d) Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N. *Tetrahedron* **1985**, *41*, 2567.
16. Paquette, L. A.; *Encyclopedia of Reagents for Organic Synthesis*, Vol. 6; Wiley: New York, 1995 p 4138.
17. (a) Brunner, H.; Schonherr, M.; Zabel, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2671. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841. (c) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 841.
18. *O*-methylation of oxime (1*S*,5*S*,6*S*)-**9** afforded a mixture of *E* and *Z* isomers of (1*S*,5*S*,6*S*)-**10** in a ratio of 2:1 as determined by ^{1}H NMR analysis. Attempts to assign their configuration by NOESY analysis proved unsuccessful. ^{13}C NMR correlation method adopted by many authors[20] was also abortive in our case. So we tentatively assumed that the major isomer of **10** had the *E* form oxime ether with the methoxy group *anti* to the bridged carbon, and the minor isomer had the *Z* form oxime ether.
19. $[\alpha]_D^{20}$ +3.93° (*c* 3.50, $CHCl_3$). Literature: $[\alpha]_D^{20}=+5.6°$ (*c* 1.09, $CHCl_3$) for *R* enantiomer with 96% ee. Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929.
20. (a) Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1028. (b) Farser, R. R.; Dhawan, K. L. *J. Chem. Soc. Chem. Commun.* **1976**, 674. (c) Miller, R. J.; Kuliopulos, A.; Coward, J. K. *J. Org. Chem.* **1989**, *54*, 3436.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8869–8880
Tetrahedron

A diastereoselective tandem RCM approach to spiropiperidines

Robert A. J. Wybrow,[a] Andrew S. Edwards,[a] Neil G. Stevenson,[a] Harry Adams,[a] Craig Johnstone[b] and Joseph P. A. Harrity[a,*]

[a]*Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK*
[b]*Department of Medicinal Chemistry, AstraZeneca, Mereside, Alderley Park, Cheshire SK10 4TG, UK*

Received 24 May 2004; revised 21 June 2004; accepted 8 July 2004

Available online 23 August 2004

Abstract—This paper outlines the stereocontrolled synthesis of a functionalised spiropiperidine through a diastereoselective tandem RCM reaction. The diastereoselectivity of this process was found to be strongly dependant on the nature of the catalyst; the less active first generation Ru–carbene complexes provided the desired spirocycle in high yield and with good stereocontrol. Additionally, the further functionalisation of the spiropiperidine was carried out through a regio- and stereoselective dihydroxylation reaction employing Donohoe's OsO_4-TMEDA conditions.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Olefin metathesis is now established as one of the most prominent and widely applied synthetic transformations in organic chemistry.[1] Indeed, this technique is now commonly employed as a key carbon–carbon bond forming step in the assembly of naturally occurring compounds and, more recently, for the preparation of functionalised synthetic intermediates in enantiomerically enriched form.[2] Our own research efforts in this area have focused on exploiting selective metathesis reactions of polyolefinic systems.[3,4] Accordingly, we have found that this technique provides an efficient method for the preparation of spirocyclic and angularly fused tricyclic compounds (Fig. 1).

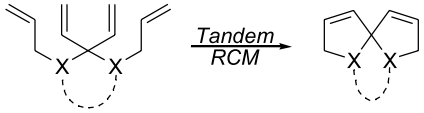


Figure 1.

A notable feature of metathesis reactions is that the products are generated with an alkene motif, which permits further elaboration of the end products. However, in the context of the spiro- and tricycles from our tandem RCM approach, the exploitation of these intermediates towards synthetic targets would likely necessitate the differentiation of the two alkene functional groups. In this regard, we have recently been investigating techniques for the selective manipulation of spirocyclic dienes and wish to report herein a diastereoselective assembly of a nitrogen-containing spirodiene that permits alkene functionalisation to take place in a regio- and stereoselective fashion.[5] Furthermore, we report our progress toward the elaboration of such intermediates to histrionicotoxin analogues[6] (Fig. 2).

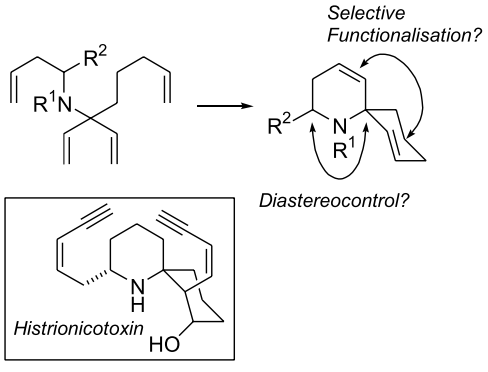


Figure 2.

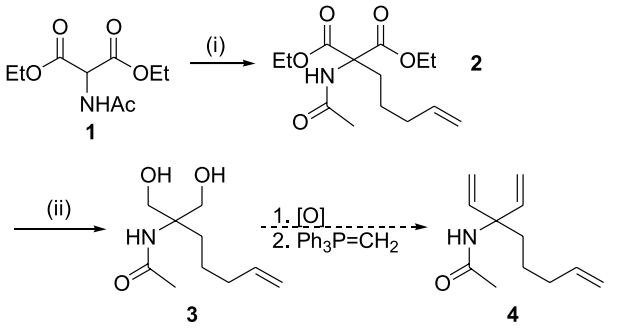
2. Results and discussion

In our previously reported studies of the tandem RCM approach to spirocyclic systems, the requisite tetraene substrates were prepared from malonate derivatives that allowed the straightforward appendage of alkene moieties together with the opportunity to carry out a subsequent

Keywords: Tandem RCM approach; Metathesis reactions; Tetraene substrates.
* Corresponding author. Fax: +44-114-222-9346;
e-mail: j.harrity@sheffield.ac.uk

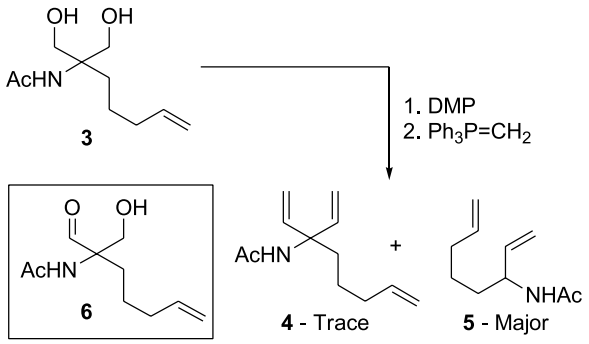
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.025

conversion of the 1,3-dicarbonyl unit to a 1,4-pentadiene.[3a] This route was found to be simple and reliable therefore we embarked on the synthesis of our nitrogen containing tetraene substrate from commercially available acetamidomalonate **1** as outlined in Scheme 1.



Scheme 1. (i) NaOEt, EtOH, $CH_2{=}CH(CH_2)_3Br$, 93%; (ii) LAH, THF, 98%.

Alkylation of **1** with 5-bromopent-1-ene proceeded smoothly to provide diester **2** which was reduced to the corresponding diol **3**. We prepared to convert the diol moiety to the desired 1,4-pentadiene **4** using an oxidation/Wittig olefination protocol. Unfortunately, the use of the Dess–Martin periodinane (DMP) followed by addition of the phosphorus ylid furnished diene **5** as the major product together with minor quantities of the desired triene **4**. It is likely that this apparent decarbonylation process occurs via a retro-aldol reaction of the product of mono-oxidation **6** (Scheme 2).



Scheme 2.

Recourse to various common oxidants did not alleviate this problematic side reaction and we therefore sought to circumvent the double oxidation process.[7] More specifically, we envisaged that the use of a carbamate protecting group would allow differentiation of the 1,3-diol moiety by offering the opportunity to conduct a cyclisation reaction to the oxazolidinone. This process would protect the system against retro-aldol elimination and leave the remaining primary alcohol for elaboration to the requisite olefin (Chart 1). The alkylation and reduction reactions on

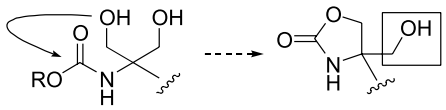
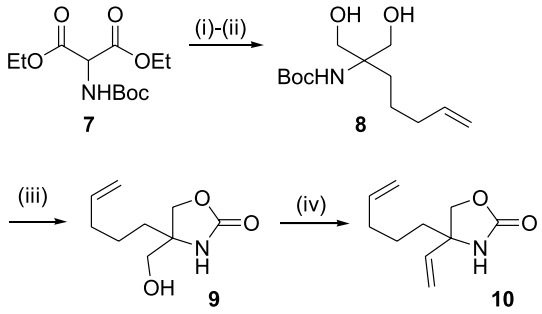


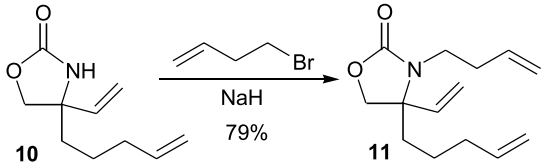
Chart 1.

commercially available Boc-protected aminomalonate **7** proceeded without incident and treatment of diol **8** with NaH resulted in an efficient cyclisation to oxazolidinone **9**. We were pleased to find that the oxidation/Wittig process now took place efficiently to give **10** in 85% overall yield (Scheme 3).

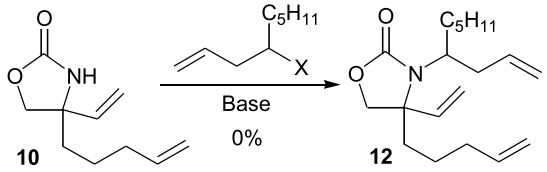


Scheme 3. (i) NaOEt, EtOH, $CH_2{=}CH(CH_2)_3Br$, 100%; (ii) LAH, THF, 78%; (iii) NaH, THF, 71%; (iv) (a) Swern; (b) $Ph_3P{=}CH_2$, 85% over two steps.

We next decided to install the third olefin motif through the N-alkylation of oxazolidinone **10**. Indeed, alkylation of **10** with 4-bromopent-1-ene proceeded smoothly to provide **11**, however, all attempts to perform a similar alkylation with secondary alkyl halides and triflates failed to furnish the more substituted oxazolidinone **12** and starting **10** was returned in all cases (Eqs. 1 and 2).



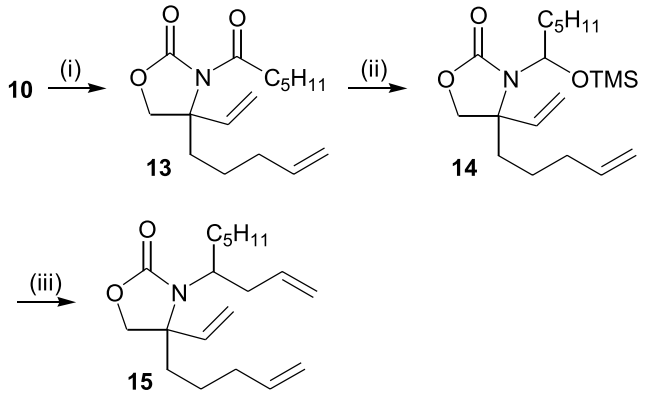
(1)



(2)

During our attempts to promote the alkylation reaction, we became aware of an intriguing approach to α-allylated amines from the corresponding amides developed by Suh and co-workers.[8] We decided to employ this strategy to construct the secondary amine motif by the method outlined in Scheme 4. Acylation of **10** followed by the partial reduction and silylation of **13** allowed N,O-acetal TMS ether **14** to be isolated in high yield as a stable oil. Finally, Lewis acid mediated allylation of **14** proceeded smoothly to furnish the desired oxazolidinone **15** as a 1:1 mixture of diastereoisomers.

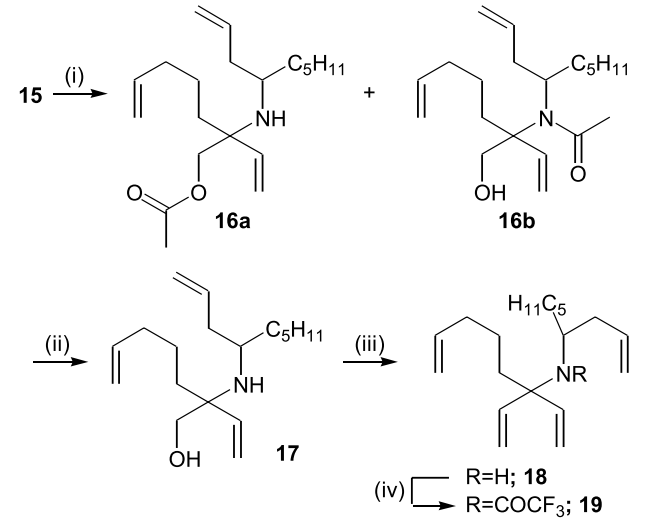
The final steps towards the target tetraene required hydrolysis of the oxazolidinone followed by oxidation and methylenation of the remaining alcohol. Unfortunately, **15** proved to be remarkably resistant to acid or base mediated hydrolysis. In the event, ring cleavage was achieved upon addition of MeLi to **15** and a mixture of acetate **16a** and acetamide **16b** were obtained in high yield.[9] We were pleased to find that both the acetate **16a** and the acetamide



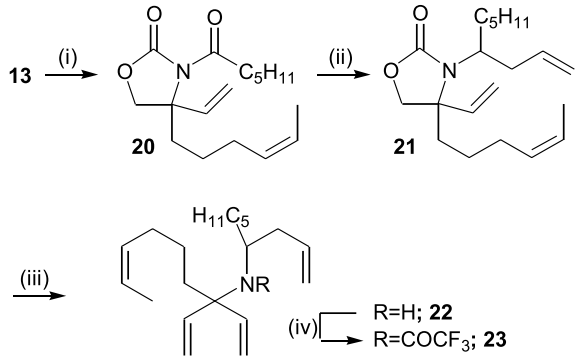
Scheme 4. (i) (a) BuLi, THF, −78 °C; (b) $C_5H_{11}COCl$, 95%; (ii) (a) DIBAL-H, CH_2Cl_2, −100 °C; (b) TMSOTf, 2,6-lutidine, 76%; (c) CH_2=$CHCH_2SiMe_3$, $BF_3.OEt_2$, CH_2Cl_2, 72%.

16b could be hydrolysed in acceptable yield to the desired alcohol **17**. Finally, oxidation and Wittig methylenation using conditions developed during our preliminary studies[5] generated the substrate tetraene **18** in high yield. Finally, since Ru-metathesis catalysts are known to be incompatible with unprotected amine functionality[10] we prepared trifluoroacetamide **19** for our tandem RCM studies.

Tetraene **19** contains four different alkene moieties and therefore four possible sites of initiation by the Ru-catalyst. However, previous studies in our laboratories[3a] and elsewhere[11] suggested that initiation would not take place at the alkenes adjacent to the quaternary alkyl sites. Of the two remaining alkenes, we anticipated that optimum levels of diastereocontrol would be obtained if the first RCM reaction involved the alkene chain bearing the stereogenic centre. We therefore decided to prepare a second class of tetraene substrates that would bear appropriate alkene substitution so as to direct Ru–carbene initiation towards the N-containing alkene chain. Accordingly, and as outlined in Scheme 6, stepwise oxidative cleavage of the more remote olefin[12] in **13** provided (*Z*)-substituted alkene **20** after the Wittig reaction. Conversion of **20** to tetraene **23** was then carried



Scheme 5. (i) (a) MeLi, Et_2O, −78 °C; (ii) NaOH, H_2O/EtOH (1:1), 80 °C, 60% over two steps; (iii) (a) TFA, CH_2Cl_2, 0 °C; (b) Swern; (c) Ph_3P=CH_2, 88%; (iv) TFAA, Et_3N, Et_2O, 89%.



Scheme 6. (i) (a) AD-mix-β, *t*-BuOH/H_2O; (b) $NaIO_4$, THF/H_2O; (c) Ph_3P=$CHCH_3$; 43% over three steps; (ii) (a) DIBAL-H, CH_2Cl_2, −100 °C; (b) TMSOTf, 2,6-lutidine, 79%; (c) CH_2=$CHCH_2SiMe_3$, $BF_3 \cdot OEt_2$, CH_2Cl_2, 50%; (iii) (a) MeLi, Et_2O, −78 °C; (b) NaOH, H_2O/EtOH (1:1), 80 °C, 63% over two steps; (c) TFA, CH_2Cl_2, 0 °C; (d) Swern; (e) Ph_3P=CH_2, 41% over three steps; (iv) TFAA, Et_3N, Et_2O, 89%.

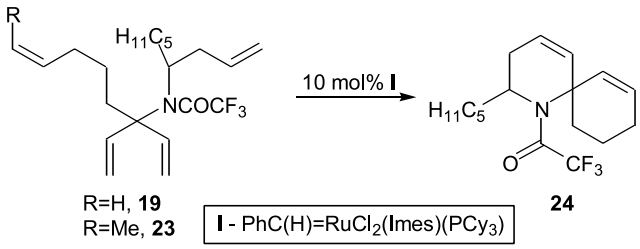
out using an analogous procedure to that outlined in Schemes 4–6.

With tetraenes **19** and **23** in hand the stage was set to investigate the tandem RCM reaction, the results are shown in Table 1. We initially investigated the tandem RCM reaction in DCM and toluene at elevated temperatures using Grubbs' 2nd generation catalyst **I** and were pleased to find that spiropiperidine **24** was formed in excellent yield, however, unfortunately as an almost equal mixture of diastereoisomers. Disappointingly, the diastereoselectivity was not improved by reducing the reaction temperature or when more substituted tetraene **23** was employed.

As an alternative means of increasing reaction diastereoselectivity, we opted to examine the less active first generation Grubbs' catalyst **II** in the spiro-forming process. As outlined in Scheme 7, we subjected **19** to 10 mol% **II** in toluene at elevated temperature and were surprised to find that the major product was the monocyclic piperidine **25**. Additionally, and importantly, **25** was isolated as a 16:1 diastereomeric mixture. Subjection of **25** to **I** provided spiropiperidine **24** in a 16:1 ratio that favoured the corresponding minor diastereomer produced in the tandem RCM process described in Table 1.[13] Finally, we were pleased to find that the tandem RCM process could be accomplished with high levels of diastereocontrol when **II** was employed in refluxing DCM to generate the same major diastereomer of spirodiene **24** in 99% yield. The relative stereochemistry of the product was assigned on the free amine **26** by NOE and this was later corroborated by X-ray crystallography (vide infra).

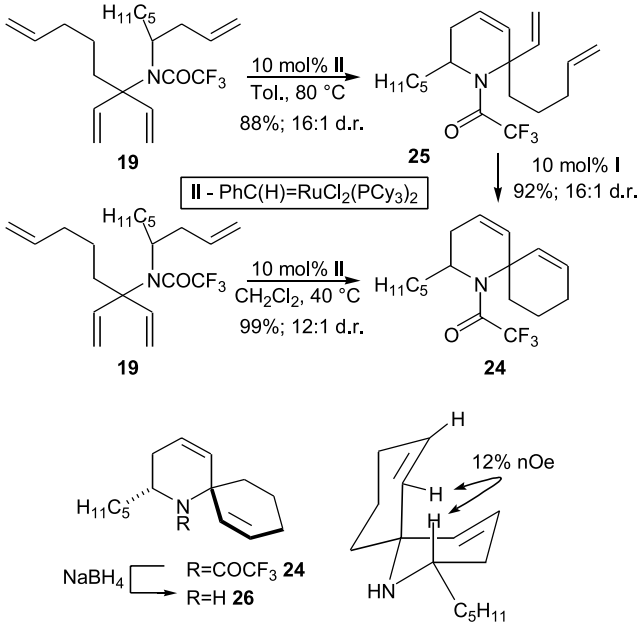
Our rationale for the observed diastereoselectivity in the tandem RCM process is depicted in Figure 3.[14] Whilst there are two possible alkenes available for Ru–carbene initiation, we believe that Thorpe-Ingold effects promote RCM toward the heterocycle ring over the potentially competing carbocycle formation. As mentioned earlier, this is envisaged to provide the optimum relay of stereochemical information as the RCM reaction takes place on the diene unit bearing a stereogenic centre. This assumption is supported by the

Table 1.



Entry	R	Solvent	Temperature	Yield (d.r.[a])
1	H	Tol	80 °C	100% (1.2:1)
2	H	CH_2Cl_2	40 °C	95% (1.5:1)
3	H	Tol	25 °C	95% (1.4:1)
4	H	CH_2Cl_2	25 °C	65% (1.3:1)
5	Me	Tol	80 °C	88% (1:1)

[a] As estimated by GC-MS.



Scheme 7.

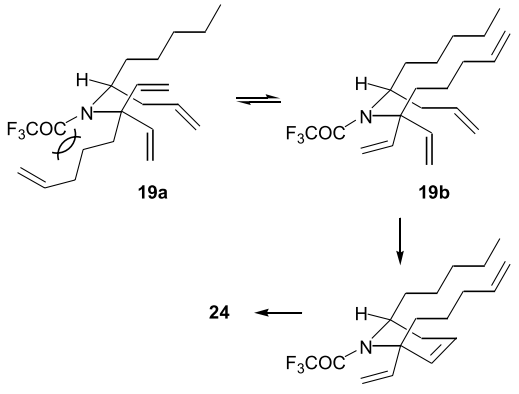
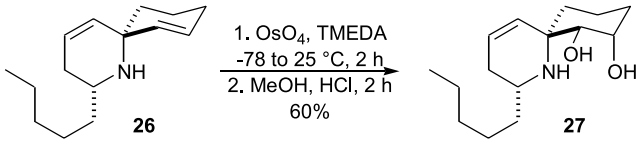


Figure 3.

observation that piperidine **25** is the only single-ring closed product that we have isolated after subjection of tetraene **19** to Grubbs' catalysts. Clearly however, this does not rule out a slow carbocycle ring closure followed by rapid piperidine closure in the spiroforming RCM reactions. This latter issue notwithstanding, we anticipate that two reactive conformations **a** and **b** are available to the tetraene **19**. Both conformations have the *n*-pentyl chain in an axial orientation because of the well established preference for N-acylated 2-alkyl piperidines to adopt an axial alkyl group in order to minimise A(1,3)-strain.[15] Indeed. this effect has been exploited recently by Martin and co-workers in the formation of bridged azabicycles using RCM reactions.[16] We believe therefore that this unfavourable interaction reduces the propensity of the tetraene to exist in conformation **19a** and permits the piperidine forming RCM reaction to proceed via conformation **19b**.

With a diastereoselective synthesis of the spirodiene in hand, we turned our attention to the problem of regio- and stereoselective alkene functionalisation. Earlier studies had shown that good selectivities could be achieved using N-directed epoxidation[5a] but unfortunately the product epoxide was not amenable to further elaboration towards histrionicotoxin based targets. We therefore, decided to investigate an alternative functionalisation process and were attracted to alkene dihydroxylation. Specifically, the highly significant observation by Donohoe and co-workers that a TMEDA-OsO_4 complex permits the dihydroxylation reaction to be directed with respect to carbon-heteroatom bonds[17] suggested that we could exploit a similar strategy for regio- and stereoselective functionalisation of the requisite alkene in **26**. However, the N-directed dihydroxylation thus far has been restricted to primary amides. Nonetheless, and as outlined in Scheme 8, we subjected spirodiene **26** to the TMEDA-OsO_4 complex and were delighted to isolate the corresponding diol **27** in good yield as a single diastereoisomer. Single crystal X-ray diffraction allowed us to establish that dihydroxylation had taken place *cis*-to the C–N bond, therefore confirming that the tandem RCM-dihydroxylation sequence had successfully set three



Scheme 8.

of the four stereogenic centres required for elaboration to histrionicotoxin targets (Fig. 4).[18,19]

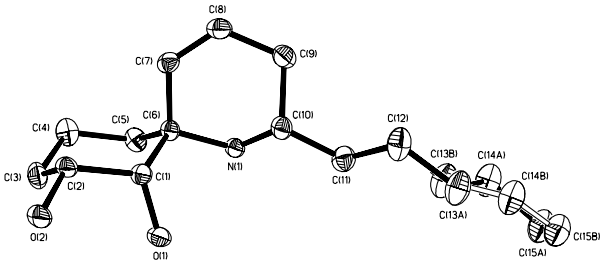


Figure 4. ORTEP diagram of diol **27** with thermal ellipsoids shown at 50% probability level, H-atoms omitted for clarity. (C13, C14 and C15 were found to be disordered and refined to 89.5:10.5 occupancy).

It is not clear at this stage whether this regio- and stereoselective dihydroxylation is the result of a directed reaction or steric/electronic activation of one olefin face in **26**. Nonetheless, the further elaboration of **27** to histrionicotoxin analogues is the subject of active research within our laboratories.

3. Conclusion

We have developed a diastereoselective spiropiperidine synthesis through a tandem RCM reaction of tetraene **19** in the presence of Grubbs' 1st generation Ru-catalyst **II** and have shown that this compound can be further functionalised in a regio- and stereoselective manner through Donohoe's OsO_4-TMEDA dihydroxylation reaction.

4. Experimental

4.1. General

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen. Flash chromatography was performed on silica gel (BDH Silica Gel 60 43–60). The solvent system used was a gradient of petroleum ether, increasing in polarity to ethyl acetate. Very polar compounds required DCM/MeOH/NH_3 mixes in the ratio 10:0.5:0.5–10:4:0.5. Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) which were developed using standard visualizing agents: Ultraviolet light or potassium permanganate.

^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (J) in Hz, and assignment. ^{13}C NMR spectra were recorded on a Bruker AC-250 (62.9 MHz) or AMX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm). Infrared (FTIR) spectra were recorded on a Perkin–Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films using sodium chloride plates, as a DCM solution or as a KBr disc. Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin–Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in either FAB (FAB^+), EI (EI^+) or CI (CI^+) mode. Elemental microanalysis performed using a Perkin–Elmer 2400 CHNS/O Series II Elemental Analyser. Melting points were performed on recrystallised solids and recorded on a Gallenkamp melting point apparatus and are uncorrected. All solvents and reagents were purified using standard, laboratory techniques according to methods published in 'Purification of Laboratory Chemicals' by Perrin, Armarego, and Perrin (Pergamon Press, 1966).

4.1.1. 2-Acetylamino-2-pent-4-enyl-malonic acid diethyl ester 2. To absolute ethanol (15 mL) at 0 °C was added sodium (466 mg, 20.25 mmol, washed with petroleum ether). After dissolution of the sodium, commercially available diethyl acetoaminomalonate **1** (4.0 g, 18.41 mmol) was added as one portion and the resultant mixture stirred at 0 °C. After 5 min, 5-bromopent-1-ene (8.0 mL, 67.6 mmol) was added via syringe. The reaction was heated at reflux for 2 h after which time it was quenched with water and the product extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue was carried out by filtration through celite/silica with ethyl acetate and then stirring the crude filtrate in cold hexane, affording **2** as a white solid (4.89 g, 93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.15–1.30 (2H, m, $CH_2CH_2CH_2$-$CH{=}CH_2$), 1.27 (6H, t, J=7.0 Hz, OCH_2CH_3), 1.98–2.09 (2H, m, $CH_2CH_2CH_2CH{=}CH_2$), 2.03 (3H, s, $C(O)CH_3$), 2.25–2.37 (2H, m, $CH_2CH{=}CH_2$), 4.27 (4H, q, J=7.0 Hz, OCH_2CH_3), 4.90–5.05 (2H, m, $CH_2CH{=}CH_2$), 5.74 (1H, ddt, J=17.0, 10.5, 6.5 Hz, $CH_2CH{=}CH_2$), 6.77 (1H, br s, N*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 22.9, 23.0, 31.7, 33.2, 62.4, 66.4, 114.9, 137.8, 168.1, 168.9. FTIR (DCM/cm^{-1}) ν_{max}: 2981 (m), 2935 (w), 1741 (s), 1666 (s), 1507 (m), 1445 (w), 1371 (w), 1302 (w), 1266 (m), 1198 (s), 1096 (w), 859 (w). HRMS (TOF ES^+) Calculated for $C_{14}H_{24}NO_5$ (MH^+): 286.1654. Found 286.1640. Melting point/°C: 42–43.

4.1.2. *N*-(1,1-*Bis*-hydroxymethyl-hex-5-enyl)-acetamide 3. To a stirred solution of lithium aluminium hydride (690 mg, 17.29 mmol) in THF (50 mL) at 0 °C was added 2-acetylamino-2-pent-4-enyl-malonic acid diethyl ester **2** (1.0 g, 3.5 mmol) in THF (5 mL) via cannula. The reaction was stirred for a further half hour at room temperature before being carefully quenched with water and the product extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded **3** as a waxy solid (690 mg, 98%).

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29–1.44 (2H, m, CH_2-$CH_2CH_2CH{=}CH_2$), 1.55–1.66 (2H, m, $CH_2CH_2CH_2$-$CH{=}CH_2$), 1.95–2.11 (2H, m, $CH_2CH{=}CH_2$), 2.02 (3H, s, $C(O)CH_3$), 3.56 (2H, br d, J=11.5 Hz, CH_2OH), 3.77 (2H, br d, J=11.5 Hz, CH_2OH), 4.00 (2H, br s, O*H*), 4.90–5.08 (2H, m, $CH_2CH{=}CH_2$), 5.77 (1H, ddt, J=11.0, 10.0, 7.0 Hz, $CH_2CH{=}CH_2$), 5.94 (1H, br s, N*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.5, 24.0, 32.4, 34.0, 61.3, 65.7, 115.1, 138.1, 171.9. FTIR (DCM/cm^{-1}) ν_{max}: 3306 (br vs), 3081 (w), 2935 (s), 1641 (s), 1558 (s), 1461 (m), 1440 (m), 1376 (m), 1307 (w), 1056 (s), 912 (m). HRMS (TOF ES$^+$) Calculated for $C_{10}H_{20}NO_3$ (MH^+): 202.1443. Found 202.1450. Melting point/°C: 56–58.

4.1.3. (1,1-*Bis*-hydroxymethyl-hex-5-enyl)-carbamic acid *tert*-butyl ester 8. To absolute ethanol (55 mL) at 0 °C was added sodium (1.49 g, 64.7 mmol, washed with petroleum ether). After dissolution of the sodium, commercially available diethyl 2-[*N*-(*tert*-butoxycarbonyl)-amino]malonate **7** (15 mL, 58.8 mmol) was added via syringe and the resultant mixture stirred at 0 °C. After 5 min, 5-bromopent-1-ene (8 mL, 67.6 mmol) was added via syringe. The reaction mixture was heated at reflux for 12 h after which time it was quenched with water and the product extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue was carried out by filtration through celite/silica with ethyl acetate, to afford alkylated malonate as a colourless oil (20.2 g, 100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.20–1.30 (2H, m, CH_2-$CH_2CH_2CH{=}CH_2$), 1.24 (6H, t, J=7.0 Hz, OCH_2CH_3), 1.42 (9H, s, $C(CH_3)_3$), 2.06 (2H, dt, J=7.0, 7.0 Hz, $CH_2CH{=}CH_2$), 2.27 (2H, br t, J=8.0 Hz, $CH_2C(CO_2Et)_2$-NHBoc), 4.13–4.30 (4H, m, OCH_2CH_3), 4.90–5.05 (2H, m, $CH_2CH{=}CH_2$), 5.76 (1H, ddt, J=17.0, 10.5, 7.0 Hz, $CH_2CH{=}CH_2$), 5.90 (1H, br s, N*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.8, 28.2, 33.2, 60.4, 62.3, 66.4, 114.9, 138.0, 153.8, 159.3, 168.3. FTIR (film/cm^{-1}) ν_{max}: 3429 (m), 2980 (m), 2934 (w), 1740 (s), 1722 (s), 1488 (s), 1368 (w), 1258 (m), 1205 (w), 1169 (s), 1027 (m). HRMS (TOF ES$^+$) Calculated for $C_{17}H_{30}NO_6$ (MH^+): 344.2073. Found 344.2058.

To a stirred solution of lithium aluminium hydride (1.15 g, 29.12 mmol) in THF (20 mL) at 0 °C was added alkylated malonate (4.0 g, 11.65 mmol) in THF (20 mL) via cannula. The mixture was allowed to warm to room temperature and stirred for 12 h, after which time it was quenched with NH_4Cl (saturated aq.). The product was extracted with DCM/MeOH (10:1), the organic layer was separated and dried over $MgSO_4$ and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded **8** as a colourless solid (2.35 g, 78%). (NB: larger quantities of diol were prepared by multiple small-scale reactions rather than a large-scale reaction for safety purposes) ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30–1.46 (2H, m, $CH_2CH_2CH_2CH{=}CH_2$), 1.43 (9H, s, $C(CH_3)_3$), 1.49–1.59 (2H, m, $CH_2C(CH_2OH)_2NHBoc$), 2.04 (2H, dt, J=7.0, 7.0 Hz, $CH_2CH{=}CH_2$), 3.57 (2H, br d, J=11.0 Hz, $CH_\alpha H_\beta OH$), 3.82 (2H, br d, J=11.0 Hz, $CH_\alpha H_\beta OH$), 4.90 (1H, br s, N*H*), 4.92–5.07 (2H, m, $CH{=}CH_2$), 5.78 (1H, ddt, J=17.0, 10.0, 7.0 Hz, $CH{=}CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.3, 28.3, 32.9, 33.7, 59.3, 60.4, 66.4, 115.0, 138.2, 156.5. FTIR (DCM/cm^{-1}) ν_{max}: 3355 (br s), 2978 (m), 2930 (s), 1694 (s), 1642 (w), 1504 (m), 1367 (m), 1170 (s), 1048 (m). HRMS (TOF ES$^+$) Calculated for $C_{13}H_{26}NO_4$ (MH^+): 260.1862. Found 260.1849. Melting point/°C: 87–88.

4.1.4. 4-Hydroxymethyl-4-pent-4-enyl-oxazolidin-2-one 9. To THF (120 mL) at 0 °C was added NaH (60% w/w in mineral oil) (1.4 g, 34.91 mmol). After several minutes, diol **8** (8.23 g, 31.73 mmol) in THF (10 mL) was added via cannula and the mixture was allowed to warm to room temperature and stir for 12 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded the oxazolidinone **9** as a colourless solid (4.14 g, 71%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36–1.59 (4H, m, $CH_2CH_2CH_2$-$CH{=}CH_2$), 2.12 (2H, dt, J=7.0, 7.0 Hz, $CH_2CH{=}CH_2$), 3.44 (1H, d, J=12.0 Hz, $CH_\alpha H_\beta OH$), 3.58 (1H, d, J=12.0 Hz, $CH_\alpha H_\beta OH$), 4.07 (1H, d, J=8.5 Hz, $CH_\alpha H_\beta$-OC(O)), 4.32 (1H, d, J=8.5 Hz, $CH_\alpha H_\beta OC(O)$), 4.90–5.07 (2H, m, $CH_2CH{=}CH_2$), 5.75 (1H, ddt, J=17.0, 10.0, 7.0 Hz, $CH_2CH{=}CH_2$), 6.62 (1H, br s, N*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.5, 33.7, 34.8, 62.0, 66.2, 71.4, 115.4, 137.7, 160.6. FTIR (DCM/cm^{-1}) ν_{max}: 3306 (br s), 2927 (m), 2854 (w), 1738 (s), 1403 (w), 1257 (w), 1166 (w), 1047 (m). HRMS (TOF ES$^+$) Calculated for $C_9H_{16}NO_3$ (MH^+): 186.1130. Found 186.1123. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.13; H, 8.34; N, 7.49. Melting point/°C: 80–81.

4.1.5. 4-Pent-4-enyl-4-vinyl-oxazolidin-2-one 10. To DCM (35 mL) at −78 °C was added oxalyl chloride (0.92 mL, 10.48 mmol) via syringe. DMSO (1.55 mL, 21.87 mmol) in DCM (60 mL) was then added via cannula into this mixture and left to stir for 2 min at −78 °C. After this time the oxazolidinone **9** (1.69 g, 9.11 mmol) in DCM (35 mL) was added via cannula into the reaction. The reaction mixture was left to stir for one hour. Et_3N (5.08 mL, 36.45 mmol) was added via syringe and the mixture allowed to warm to room temperature. The reaction was quenched with water and $NaHCO_3$ (saturated aq.) and the product extracted with DCM. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. The crude aldehyde was carried through to the next step without further purification. To a stirred solution of methyltriphenylphosphonium bromide (4.82 g, 13.50 mmol) in THF (100 mL) at room temperature was added potassium ^{t}butoxide (1.51 g, 13.50 mmol) in one portion. The mixture was stirred until dissolution, after which time the crude aldehyde in THF (30 mL) was added via cannula. The reaction was left to stir for 1 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded vinyl oxazolidinone **10** as a colourless oil (1.4 g, 85%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26–1.44 (2H, m, $CH_2CH_2CH_2CH{=}CH_2$), 1.53–1.67 (2H, m, CH_2CH_2-$CH_2CH{=}CH_2$), 2.01 (2H, dt, J=7.0, 7.0 Hz, CH_2-$CH{=}CH_2$), 4.07 (1H, d, J=8.0 Hz, $CH_\alpha H_\beta OC(O)$), 4.10 (1H, d, J=8.0 Hz, $CH_\alpha H_\beta OC(O)$), 4.85–5.00 (2H, m,

$CH_2CH{=}CH_2$), 5.18 (1H, d, $J=11.0$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.23 (1H, d, $J=17.5$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.65 (1H, ddt, $J=16.5$, 10.0, 7.0 Hz, $CH_2CH{=}CH_2$), 5.75 (1H, dd, $J=17.5$, 11.0 Hz, $CCH{=}CH_{cis}H_{trans}$), 6.82 (1H, br s, N*H*). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.6, 33.5, 38.4, 62.0, 74.3, 114.8, 115.1, 137.8, 139.3, 160.0. FTIR (film/cm^{-1}) ν_{max}: 3268 (br m), 2934 (m), 1753 (s), 1392 (m), 1276 (w), 1038 (m), 923 (m). HRMS (TOF ES$^+$) Calculated for $C_{10}H_{16}NO_2$ (MH^+): 182.1181. Found 182.1185.

4.1.6. 3-But-3-enyl-4-pent-4-enyl-4-vinyl-oxazolidin-2-one 11. To a stirred solution of NaH (60% w/w in mineral oil) (110 mg, 2.76 mmol) in DMF (8 mL) at room temperature was added vinyl oxazolidinone **10** (500 mg, 2.76 mmol) in DMF (4 mL) via cannula. After stirring for 5 min, 4-bromo-but-1-ene (0.3 mL, 3 mmol) was added via syringe under nitrogen and left to stir for 30 min. This was followed by sequential addition of NaH and 4-bromobut-1-ene respectively until vinyl oxazolidinone **10** was no longer present by TLC analysis. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded the alkylated oxazolidinone **11** as a yellow oil (510 mg, 79%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.19–1.82 (4H, m, $CH_2CH_2CH_2CH{=}CH_2$), 2.10 (2H, dt, $J=7.0$, 7.0 Hz, $CH_2CH_2CH_2CH{=}CH_2$), 2.35 (2H, dt, $J=7.5$, 7.5 Hz, $NCH_2CH_2CH{=}CH_2$), 2.96–3.22 (2H, m, NCH_2CH_2), 4.04 (1H, d, $J=9.0$ Hz, $CH_\alpha H_\beta O$), 4.10 (1H, d, $J=9.0$ Hz, $CH_\alpha H_\beta O$), 4.92–5.14 (4H, m, $CH_2CH{=}CH_2$), 5.25 (1H, d, $J=17.5$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.32 (1H, d, $J=10.5$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.65–5.88 (2H, m, $CH_2CH{=}CH_2$), 5.84 (1H, dd, $J=17.5$, 10.5 Hz, $CCH{=}CH_{cis}H_{trans}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.2, 33.4, 33.7, 34.1, 40.6, 64.1, 71.5, 115.6, 117.0, 117.2, 135.0, 137.6, 138.9, 158.1. FTIR (film/cm^{-1}) ν_{max}: 3078 (w), 2978 (m), 2928 (s), 2858 (m), 1748 (s), 1642 (w), 1440 (w), 1402 (m), 1368 (w), 1053 (m), 916 (m). HRMS (TOF ES$^+$) Calculated for $C_{14}H_{22}NO_2$ (MH^+): 236.1651. Found 236.1643.

4.1.7. 3-Hexanoyl-4-pent-4-enyl-4-vinyl-oxazolidin-2-one 13. To a stirred solution of oxazolidinone **10** (798 mg, 4.40 mmol) in THF (55 mL) at -78 °C was added BuLi (1.94 mL, 4.84 mmol, 2.5 M in hexane). After 20 min stirring, hexanoyl chloride (0.92 mL, 6.60 mmol) was added via syringe and left to stir for 5 min, after which time the solution was left to warm to room temperature. The reaction was quenched with water and the product extracted with ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded acylated oxazolidinone **13** as a colourless oil (1.16 g, 95%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (3H, t, $J=6.5$ Hz, CH_2CH_3), 1.09–1.51 (6H, m), 1.52–1.72 (2H, m), 1.82 (1H, ddd, $J=13.5$, 12.5, 4.0 Hz, $NCCH_\alpha H_\beta CH_2$), 2.08 (2H, dt, $J=7.0$, 7.0 Hz, $CH_2{=}CHCH_2$), 2.28 (1H, ddd, $J=13.5$, 12.5, 4.0 Hz, $NCCH_\alpha H_\beta CH_2$), 2.89 (2H, t, $J=7.5$ Hz, $NC(O)CH_2$), 4.11 (1H, d, $J=9.0$ Hz, $CH_\alpha H_\beta OC(O)$), 4.18 (1H, d, $J=9.0$ Hz, $CH_\alpha H_\beta OC(O)$), 4.91–5.09 (2H, m, $CH_2CH{=}CH_2$), 5.19 (1H, d, $J=17.5$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.26 (1H, d, $J=11.0$ Hz, $CCH{=}CH_{cis}H_{trans}$), 5.75 (1H, ddt, $J=17.0$, 10.0, 6.5 Hz, $CH_2CH{=}CH_2$), 6.11 (1H, dd, $J=17.5$, 11.0 Hz, $CCH{=}CH_{cis}H_{trans}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.3, 22.4, 23.9, 31.1, 33.3, 34.5, 36.5, 65.1, 71.1, 115.1, 115.3, 137.5, 138.6, 153.9, 173.7. FTIR (film/cm^{-1}) ν_{max}: 2991 (s), 1782 (s), 1708 (s), 1642 (m). HRMS Calculated for $C_{16}H_{25}NO_3$ (MH^+): 279.1834. Found: 279.1834.

4.1.8. 4-Pent-4-enyl-3-(1-trimethylsilanyloxy-hexyl)-4-vinyl-oxazolidin-2-one 14. To a stirred solution of acylated oxazolidinone **13** (2.09 g, 7.50 mmol) in DCM (45 mL) at -100 °C was added DIBAL-H (11.25 mL, 11.25 mmol, 1 M in DCM) dropwise and left to stir for an hour. After this time, TMSOTf (3.39 mL, 18.75 mmol) and 2,6-lutidine (2.62 mL, 22.50 mmol) were simultaneously added via syringe and the reaction allowed to stir at -100 °C for 20 min before quenching with dilute $NaHCO_3$ (45 mL). After warming to room temperature, the product was extracted with ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded reduced oxazolidinone **14** as a yellow oil (2.02 g, 76%) and as an inseparable 1:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ -0.2–0.19 (18H, m, $OSi(CH_3)_3$), 0.59–0.89 (6H, m, CH_2CH_3), 0.96–1.43 (16H, m), 1.46–1.87 (8H, m), 1.96 (4H, dt, $J=7.0$, 7.0 Hz, $CH_2CH{=}CH_2$), 3.85–4.05 (4H, m, $CH_2OC(O)$), 4.72–5.32 (10H, m), 5.50–5.79 (2H, m, $CH_2CH{=}CH_2$), 5.79–6.08 (2H, m, $CCH{=}CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ -0.1, 0.0, 13.7, 21.9, 22.3, 25.3, 25.6, 30.9, 31.1, 33.5, 33.7, 35.5, 36.0, 36.3, 63.8, 64.0, 70.9, 71.0, 79.4, 80.2, 115.1, 115.6, 115.9, 137.5, 139.8, 139.9, 156.5, 156.9. FTIR (film/cm^{-1}) ν_{max}: 2956 (s), 2931 (s), 2861 (m), 1754 (s). HRMS Calculated for $C_{19}H_{35}NO_3SiNa$ (MNa^+): 376.2284. Found: 376.2302.

4.1.9. 4-Pent-4-enyl-3-(1-pentyl-but-3-enyl)-4-vinyl-oxazolidin-2-one 15. To a stirred solution of reduced silyl ether **14** (0.27 g, 0.76 mmol) in DCM (12 mL) at -78 °C was added $BF_3{\cdot}OEt_2$ (88 μL, 0.84 mmol) and allyl trimethylsilane (0.18 mL, 1.15 mmol) simultaneously via syringe. After 10 min the mixture was transferred to a cold bath at -20 °C, where it was left for 20 min. After this time, the reaction was quenched with dilute $NaHCO_3$ (12 mL). After warming to room temperature, the product was extracted with DCM. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded allylated oxazolidinone **15** as a yellow oil (168 mg, 72%) and as an inseparable 1:1 mixture of diastereomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.68–0.94 (6H, m, CH_2CH_3), 1.04–1.89 (24H, m), 1.91–2.16 (4H, dt, $J=7.0$, 7.0 Hz, $CH_2CH_2CH{=}CH_2$), 2.30–2.64 (4H, m, $CHCH_2CH{=}CH_2$), 2.72–2.92 (2H, quintet, $J=7.0$ Hz, $CH_2CH(NH)CH_2$), 3.89–4.12 (4H, m, $CH_2OC(O)$), 4.81–5.39 (12H, m), 5.49–5.89 (6H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.4, 22.5, 26.7, 30.2, 31.9, 32.5, 33.8, 34.4, 36.7, 37.2, 52.9, 53.1, 64.0, 64.5, 70.9, 115.6, 117.0, 117.6, 135.9, 137.6, 138.4, 138.8, 170.6. FTIR (film/cm^{-1}) ν_{max}: 3077 (m), 2929 (s), 2860 (s), 1748 (s), 1641 (s). HRMS Calculated for $C_{19}H_{32}NO_2$ (MH^+): 306.2433. Found: 306.2428.

4.1.10. Ring opening of 4-pent-4-enyl-3-(1-pentyl-but-3-enyl)-4-vinyl-oxazolidin-2-one 15. To a stirred solution of

allylated oxazolidinone **15** (35 mg, 0.12 mmol) in diethyl ether (0.35 mL) at −78 °C was added MeLi (72 μL, 0.12 mmol, 1.6 M in diethyl ether) dropwise. The reaction was left to warm to room temperature and monitored by TLC analysis to determine whether all starting material had been consumed. If not then the reaction was again cooled to −78 °C and another equivalent of MeLi (72 μL, 0.12 mmol) added. This process was repeated until all starting material had been consumed. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded ester **16a** as a yellow oil (22 mg, 59%) and amide **16b** as a yellow oil (8 mg, 21%).

Compound **16a**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (6H, t, J=6.5 Hz, CH_2CH_3), 1.05–1.54 (28H, m), 1.88–2.15 (12H, m), 2.45–2.59 (2H, m), 4.0 (4H, s, $CH_2OC(O)CH_3$), 4.82–5.16 (12H, m), 5.55–5.81 (6H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1, 20.9, 22.6, 22.7, 25.4, 32.0, 34.1, 36.0, 36.4, 36.7, 40.6, 40.9, 50.7, 50.8, 58.9, 66.2, 114.2, 114.7, 116.8, 117.0, 135.9, 136.1, 138.5, 142.3, 170.9. FTIR (film/cm^{-1}) ν_{max}: 2929 (m), 2859 (m), 1744 (s). HRMS Calculated for $C_{20}H_{36}NO_2$ (MH^+): 322.2746. Found: 322.2732.

Compound **16b**. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.73–0.89 (6H, m, CH_2CH_3), 1.09–1.90 (26H, m), 1.91–2.06 (4H, m, $CH_2CH{=}CH_2$), 2.11 (6H, s, $N(CO)CH_3$), 2.34–2.50 (4H, m, $CHCH_2CH{=}CH_2$), 3.26–3.48 (2H, m, $CH_2CH(NH)CH_2$), 3.67 (2H, d, J=12.0 Hz, $CH_\alpha H_\beta OH$), 3.93 (2H, d, J=12.0 Hz, $CH_\alpha H_\beta OH$), 4.82–5.28 (12H, m), 5.43–5.99 (6H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 22.5, 22.8, 23.4, 26.1, 27.5, 28.0, 31.8, 33.1, 33.3, 34.2, 36.5, 37.1, 40.9, 41.3, 57.8, 67.3, 71.1, 114.9, 115.0, 117.3, 135.4, 135.6, 135.8, 138.4, 140.7, 174.4. FTIR (film/cm^{-1}) ν_{max}: 3370 (br), 2957 (s), 2930 (s), 2860 (m), 1745 (m), 1608 (s). HRMS Calculated for $C_{20}H_{36}NO_2$ (MH^+): 322.2746. Found: 322.2740.

4.1.11. 2-(1-Pentyl-but-3-enylamino)-2-vinyl-hept-6-en-1-ol 17. To a stirred solution of ester **16a** and amide **16b** (188 mg, 0.58 mmol) in 1:1 ethanol/H_2O (6 mL) was added NaOH (700 mg, 17.51 mmol) upon which the mixture was heated at reflux for 16 h. After cooling, the product was extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded amino alcohol **17** as a colourless oil (145 mg, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.82 (6H, t, J=6.5 Hz, CH_2CH_3), 1.07–1.58 (26H, m), 1.87–2.26 (10H, m), 2.49–2.66 (2H, quintet, J=6.0 Hz, $CH_2CH(NH)CH_2$), 3.35 (4H, s, CH_2OH), 4.80–5.19 (12H, m), 5.56–5.85 (6H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.6, 22.9, 25.3, 25.6, 31.9, 32.0, 34.1, 35.7, 35.9, 36.6, 40.4, 40.7, 50.4, 50.6, 60.6, 63.0, 114.4, 114.7, 117.2, 117.6, 135.7, 135.9, 138.5, 142.4. FTIR (film/cm^{-1}) ν_{max}: 3432 (br), 2929 (s), 2858 (m), 1640 (s). HRMS Calculated for $C_{18}H_{34}NO$ (MH^+): 280.2640. Found: 280.2638.

4.1.12. (1,1-Divinyl-hex-5-enyl)-(1-pentyl-but-3-enyl)-amine 18. To DCM (3 mL) at −78 °C was added oxalyl chloride (52 μL, 0.60 mmol) via syringe. DMSO (88 μL, 1.24 mmol) in DCM (5.5 mL) was then added via cannula into this mixture. During this time, amino alcohol **17** (145 mg, 0.52 mmol) was stirred with TFA (44 μL, 0.57 mmol) in DCM (3 mL) at 0 °C for 30 min and then added via cannula to the above mixture. Stirring was continued at −78 °C for 1 h. Et_3N (0.29 mL, 2.07 mmol) was added via syringe and the reaction mixture allowed to warm to room temperature. The reaction was quenched with water and the product extracted with DCM. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. The crude aldehyde was carried through to the next step without purification. To a stirred solution of methyl triphenylphosphonium bromide (277 mg, 0.78 mmol) in THF (9 mL) at room temperature was added potassium ^{t}butoxide (87 mg, 0.78 mmol) in one portion. The mixture was stirred until dissolution, after which time the crude aldehyde in THF (3 mL) was added via cannula. The reaction was left to stir for 1 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded tetraene **18** as a colourless oil (126 mg, 88%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (3H, t, J=6.5 Hz, CH_2CH_3), 0.98–1.55 (14H, m), 1.96 (2H, dt, J=7.0, 7.0 Hz, $CH_2CH_2CH{=}CH_2$), 2.02–2.12 (2H, m, $CHCH_2CH{=}CH_2$), 2.55 (1H, quintet, J=5.5 Hz, $CH_2CH(NH)CH_2$), 4.79–5.13 (8H, m), 5.59–5.83 (4H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.6, 23.2, 25.4, 32.0, 34.2, 36.2, 37.3, 40.5, 51.2, 61.8, 113.7, 114.5, 116.9, 136.2, 138.8, 143.7. FTIR (film/cm^{-1}) ν_{max}: 2929 (s), 2859 (s), 1730 (m), 1640 (m). HRMS Calculated for $C_{19}H_{34}N$ (MH^+): 276.2691. Found: 276.2700.

4.1.13. *N*-(1,1-Divinyl-hex-5-enyl)-2,2,2-trifluoro-*N*-(1-pentyl-but-3-enyl)-acetamide 19. To a solution of tetraene **18** (73 mg, 0.27 mmol) in diethyl ether (4 mL) was added Et_3N (74 μL, 0.53 mmol). The solution was cooled to 0 °C and stirred for 5 min before the addition of trifluoroacetic anhydride (TFAA) (75 μL, 0.53 mmol) via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded protected tetraene **19** as a yellow oil (88 mg, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (3H, t, J=6.5 Hz, CH_2CH_3), 0.98–1.46 (8H, m), 1.48–1.87 (2H, m), 1.88–2.31 (4H, m), 2.33–2.61 (2H, m), 3.57–3.88 (1H, m, $CH_2CH(NH)CH_2$), 4.78–5.31 (8H, m), 5.51–5.83 (2H, m), 5.86–6.23 (2H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0, 22.4, 24.0, 27.5, 31.7, 33.9, 35.1, 35.9, 41.0, 59.7, 69.9, 114.9, 115.7, 116.8 (q, J=291 Hz, CF_3), 117.7, 135.3, 138.2, 138.9, 157.3 (q, J=36 Hz, C=O). FTIR (film/cm^{-1}) ν_{max}: 2958 (s), 2933 (s), 2862 (m), 1694 (s), 1643 (m), 1436 (m), 1196 (s), 1142 (s). HRMS Calculated for $C_{21}H_{33}NOF_3$ (MH^+): 372.2514. Found: 372.2524.

4.1.14. 4-(4,5-Dihydroxy-pentyl)-3-hexanoyl-4-vinyl-oxazolidin-2-one 20. To a stirring solution of acylated oxazolidinone **13** (1 g, 3.58 mmol) in 1:1 *t*-butanol/H_2O (36 mL) was added AD-mix-β (5.02 g). The reaction was monitored by TLC analysis, until all the starting material

had been consumed. The reaction was quenched with water and sodium sulfite and the product extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded an inseparable 1:1 mixture of diol diastereomers as a colourless oil (709 mg, 63%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (6H, t, $J=6.5$ Hz, CH_2CH_3), 1.03–1.64 (20H, m), 1.69–1.94 (2H, m, $NCCH_\alpha H_\beta CH_2$), 2.04–2.40 (2H, m, $NCCH_\alpha H_\beta CH_2$), 2.84 (4H, t, $J=7.5$ Hz, $CH_2C(O)N$), 2.96–3.44 (6H, m), 3.46–3.73 (4H, m), 4.14 (4H, s $CH_2OC(O)$), 5.16 (2H, d, $J=17.5$ Hz, $CH{=}CH_{trans}H_{cis}$), 5.23 (2H, d, $J=11.0$ Hz, $CH{=}CH_{trans}H_{cis}$), 6.06 (2H, ddd, $J=17.5$, 11.0, 1.5 Hz, $CH{=}CH_{cis}H_{trans}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 19.1, 19.3, 22.3, 22.4, 24.0, 24.4, 31.2, 32.6, 32.7, 34.1, 34.9, 35.1, 35.3, 36.6, 64.4, 64.6, 66.5, 66.7, 70.6, 71.2, 71.5, 71.8, 138.4, 154.2, 160.5, 174.0. FTIR (film/cm^{-1}) ν_{max}: 3402 (br), 2932 (s), 2871 (s), 1779 (s), 1707 (s), 1643 (w). HRMS Calculated for $C_{16}H_{28}NO_5$ (MH^+): 314.1967. Found: 314.1977.

To a stirred solution of diol (923 mg, 2.95 mmol) in THF (30 mL) was added $NaIO_4$ (1.26 g, 5.89 mmol) in an aqueous solution of THF (40 mL, 10% H_2O) via cannula. The reaction was left to stir for 16 h and then quenched with water. The product was extracted with diethyl ether. The organic layer was separated, dried over $MgSO_4$ and the solvent removed in vacuo. The crude aldehyde was carried through to the next step without further purification. To a stirred solution of ethyl triphenylphosphonium bromide (3.5 g, 9.45 mmol) in THF (80 mL) was added potassium ^{t}butoxide (1.06 g, 9.45 mmol). The mixture was stirred until dissolution, after which time the crude aldehyde in THF (20 mL) was added via cannula. The reaction was left to stir for 1 h, quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded diene **20** as a yellow oil (927 mg, 68%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.82 (3H, t, $J=6.5$ Hz, CH_2CH_3), 0.99–1.41 (6H, m), 1.45–1.64 (5H, m), 1.76, (1H, ddd, $J=14.0$, 12.5, 4.0 Hz, $NCCH_\alpha H_\beta CH_2$), 2.01 (2H, dt, $J=7.0$, 7.0 Hz, $CH_2CH{=}CHCH_3$), 2.22 (1H, ddd, $J=13.5$, 12.5, 4.5 Hz, $NCCH_\alpha H_\beta CH_2$), 2.82 (2H, t, $J=7.5$ Hz, CH_2CON), 4.05 (1H, d, $J=9.0$ Hz, $CH_\alpha H_\beta OC(O)$), 4.12 (1H, d, $J=9.0$ Hz, $CH_\alpha CH_\beta OC(O)$), 5.13 (1H, d, $J=17.5$ Hz, $CH{=}CH_{trans}H_{cis}$), 5.19 (1H, d, $J=11$ Hz, $CH{=}CH_{trans}H_{cis}$), 5.22–5.50 (2H, m, $CH_3CH{=}CHCH_2$), 6.06 (1H, dd, $J=17.5$, 11.0 Hz, $CCH{=}CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.8, 13.9, 22.4, 23.1, 23.9, 26.5, 31.2, 34.7, 36.6, 65.2, 71.2, 115.2, 125.0, 129.3, 138.6, 154.1, 173.8. FTIR (film/cm^{-1}) ν_{max}: 2931 (m), 2861 (m), 1781 (s), 1708 (s). HRMS Calculated for $C_{17}H_{27}NO_3$ (NaM^+): 316.1889. Found: 316.1880.

4.1.15. 4-Hex-4-enyl-3-(1-pentyl-but-3-enyl)-4-vinyl-oxazolidin-2-one 21. To a stirred solution of acylated oxazolidinone **20** (927 mg, 3.16 mmol) in DCM (25 mL) at -100 °C was added DIBAL-H (4.74 mL, 4.74 mmol, 1 M in DCM) dropwise and left to stir for 1 h. After this time, TMSOTf (1.43 mL, 7.90 mmol) and 2,6-lutidine (1.10 mL, 9.48 mmol) were simultaneously added via syringe and the reaction allowed to stir at -100 °C for 20 min before quenching with dilute $NaHCO_3$ (25 mL). After warming to room temperature, the product was extracted with ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded an inseparable 1:1 mixture of diastereotopic silyl ethers as a yellow oil (923 mg, 79%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.13–0.18 (18H, m, $OSi(CH_3)_3$), 0.66–0.82 (6H, m, CH_2CH_3), 0.99–1.84 (32H, m), 1.94 (4H, dt, $J=7.0$, 7.0 Hz, CH_2CH_2-$CH{=}CHCH_3$), 3.82–3.95 (4H, m, $CH_2OC(O)$), 4.98–5.44 (8H, m), 5.81–6.03 (2H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 0.09, 0.14, 12.7, 12.8, 13.9, 22.5, 22.8, 23.2, 25.5, 25.7, 26.6, 26.8, 31.3, 31.3, 35.7, 35.8, 36.3, 36.6, 64.0, 64.2, 71.1, 71.2, 79.7, 80.3, 115.7, 116.2, 124.6, 124.7, 129.4, 129.5, 140.0, 156.8, 157.1. FTIR (film/cm^{-1}) ν_{max}: 2956 (s), 2931 (s), 2861 (m), 1754 (s), 1708 (w). HRMS Calculated for $C_{20}H_{37}NO_3SiNa$ (NaM^+): 390.2440. Found: 390.2431.

To a stirred solution of reduced silyl ether (923 mg, 2.51 mmol) in DCM (40 mL) at -78 °C was added $BF_3.OEt_2$ (0.29 mL, 2.76 mmol) and allyl trimethylsilane (0.60 mL, 3.76 mmol) simultaneously via syringe. After 10 min stirring the mixture was immediately transferred to a cold bath at -20 °C, where it was left for 20 min. After this time, the reaction was quenched with dilute $NaHCO_3$ (40 mL). After warming to room temperature, the product was extracted with DCM. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded an inseparable 1:1 mixture of diastereotopic allylated oxazolidinone **21** as a yellow oil (402 mg, 50%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (6H, t, $J=6.5$ Hz, CH_2CH_3), 1.05–1.89 (30H, m), 2.03 (4H, dt, $J=7.0$, 7.0 Hz, $CH_2CH_2CH{=}CHCH_3$), 2.30–2.64 (4H, m, $CHCH_2CH{=}CH_2$), 2.82 (2H, quintet, $J=7.0$ Hz, CH_2-$CHCH_2CH{=}CH_2$), 3.98 (2H, d, $J=9.0$ Hz, $CH_\alpha H_\beta OC(O)$), 4.02 (2H, d, $J=9.0$ Hz, $CH_\alpha H_\beta OC(O)$), 4.85–5.09 (4H, m), 5.13–5.84 (12H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.7, 13.8, 14.0, 22.6, 23.0, 26.8, 26.9, 31.8, 32.0, 32.5, 34.5, 36.6, 37.3, 53.0, 53.1, 64.6, 70.9, 117.2, 117.6, 117.7, 125.0, 129.2, 135.8, 136.0, 138.5, 138.8, 156.3. FTIR (film/cm^{-1}) ν_{max}: 3011 (m), 2929 (s), 2859 (m), 1750 (s), 1641 (w). HRMS Calculated for $C_{20}H_{34}NO_2$ (MH^+): 320.2590. Found: 320.2580.

4.1.16. (1,1-Divinyl-hept-5-enyl)-(1-pentyl-but-3-enyl)-amine 22. To a stirred solution of allylated oxazolidinone **21** (402 mg, 1.26 mmol) in diethyl ether (5 mL) at -78 °C was added MeLi (0.79 mL, 1.26 mmol, 1.6 M in diethyl ether) dropwise. The reaction was left to warm to room temperature and monitored by TLC analysis to determine whether all starting material had been consumed. If not then the reaction was again cooled to -78 °C and another equivalent of MeLi (0.79 mL, 1.26 mmol) added. This process was repeated until all starting material had been consumed. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded the ester as a yellow oil (172 mg, 41%) and the amide as a yellow oil (76 mg, 18%).

Ester. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (6H, t, J= 6.5 Hz, CH_2CH_3), 1.05–1.63 (32H, m), 1.82–2.18 (14H, m), 2.43–2.65 (2H, m, $CH_2CHCH_2CH{=}CH_2$), 3.99 (4H, s, $CH_2OC(O)CH_3$), 4.83–5.15 (8H, m), 5.19–5.50 (4H, m), 5.52–5.82 (4H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.7, 14.0, 20.9, 22.6, 23.3, 25.4, 27.1, 32.0, 32.8, 35.9, 36.3, 36.7, 40.6, 40.9, 50.6, 50.7, 58.9, 66.2, 114.1, 116.8, 116.9, 124.0, 125.0, 130.1, 130.9, 135.9, 136.0, 142.3, 170.8. FTIR (film/cm^{-1}) ν_{max}: 2930 (s), 2858 (m), 1744 (s), 1639 (w). HRMS Calculated for $C_{21}H_{38}NO_2$ (MH^+): 336.2903. Found: 336.2898.

Amide. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.79–0.93 (6H, m, CH_2CH_3), 1.10–2.20 (42H, m), 2.37–2.59 (4H, m, $NCHCH_2CH{=}CH_2$), 3.35–3.53 (2H, m, CH_2CHCH_2-$CH{=}CH_2$), 3.62–3.80 (2H, m, $CC_\alpha H_\beta OH$), 3.90–4.08 (2H, m, $CCH_\alpha H_\beta OH$), 4.94–5.52 (12H, m), 5.55–5.81 (2H, m, $NCHCH_2CH{=}CH_2$), 5.94 (2H, dd, J=11.0, 18.0 Hz, $NCCH{=}CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.8, 13.9, 22.5, 24.0, 27.1, 27.7, 28.1, 28.3, 29.4, 29.5, 31.8, 33.0, 33.2, 33.3, 37.1, 37.3, 40.9, 41.4, 47.6, 57.8, 66.9, 67.1, 69.8, 71.5, 114.9, 115.2, 117.2, 117.4, 124.3, 124.5, 129.8, 130.3, 135.3, 140.6, 177.1. FTIR (film/cm^{-1}) ν_{max}: 3377 (br), 2958 (s), 2931 (s), 1606 (s). HRMS Calculated for $C_{21}H_{38}NO_2$ (MH^+): 336.2903. Found: 336.2912.

To a stirred solution of ester and amide (172 mg, 0.51 mmol) in 1:1 ethanol/H_2O (6 mL) was added NaOH (615 mg, 15.38 mmol) upon which the mixture was refluxed for 16 h. After cooling, the product was extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded amino alcohol as a colourless oil (150 mg, 100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.69–0.92 (6H, t, J=6.5 Hz, CH_2CH_3), 1.06–1.64 (34H, m), 1.81–2.23 (8H, m), 2.47–2.71 (2H, quintet, J=5.5 Hz, CH_2CHCH_2-$CH{=}CH_2$), 3.34 (4H, s, CH_2OH), 4.79–5.17 (8H, m), 5.19–5.47 (4H, m), 5.54–5.83 (4H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.7, 13.9, 17.8, 22.5, 23.5, 25.3, 25.5, 27.1, 31.9, 32.9, 33.7, 35.7, 35.9, 36.5, 40.4, 40.7, 50.4, 50.5, 60.5, 62.3, 63.1, 114.2, 117.1, 117.4, 123.9, 130.2, 135.7, 135.8, 142.5. FTIR (film/cm^{-1}) ν_{max}: 3442 (br), 2930 (s), 2859 (m), 1638 (w). HRMS Calculated for $C_{19}H_{36}NO$ (MH^+): 294.2797. Found: 294.2796.

To DCM (4.5 mL) at −78 °C was added oxalyl chloride (80 μL, 0.91 mmol) via syringe. DMSO (0.14 mL, 1.91 mmol) in DCM (9 mL) was then added via cannula into this mixture and left to stir for 2 min. During which time, amino alcohol (233 mg, 0.79 mmol) was stirred with TFA (67 μL, 0.87 mmol) in DCM (4.5 mL) at 0 °C for 30 min and then added via cannula to the above mixture. This was allowed to stir at −78 °C for 1 h. Et_3N (0.44 mL, 3.18 mmol) was added via syringe and allowed to warm to room temperature. The reaction was quenched with water and the product extracted with DCM. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. The crude aldehyde was carried through to the next step without purification. To a stirred solution of methyl triphenylphosphonium bromide (426 mg, 1.19 mmol) in THF (14 mL) at room temperature was added potassium ^{t}butoxide (134 mg, 1.19 mmol) in one portion. The mixture was stirred until dissolution, after which time the crude aldehyde in THF (4.5 mL) was added via cannula. The reaction was left to stir for 1 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded tetraene **22** as a colourless oil (95 mg, 41%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.81 (3H, t, J= 6.5 Hz, CH_2CH_3), 0.94–1.69 (16H, m), 1.95 (2H, dt, J=7.0, 7.0 Hz, $CH_2CH_2CH{=}CHCH_3$), 2.01–2.19 (2H, m, CH_2-$CH(NH)CH_2CH{=}CH_2$), 2.55 (1H, quintet, J=5.5 Hz, $CH_2CHCH_2CH{=}CH_2$), 4.89–5.15 (6H, m), 5.22–5.46 (2H, m), 5.61–5.82 (3H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.8, 14.1, 22.7, 23.7, 25.4, 27.2, 32.1, 36.3, 37.4, 40.6, 51.1, 61.7, 113.4, 116.8, 123.9, 130.5, 136.2, 143.9. FTIR (film/cm^{-1}) ν_{max}: 2930 (s), 2858 (s), 1638 (w). HRMS Calculated for $C_{20}H_{36}N$ (MH^+): 290.2848. Found: 290.2841.

4.1.17. *N*-(1,1-Divinyl-hept-5-enyl)-2,2,2-trifluoro-*N*-(1-pentyl-but-3-enyl)-acetamide 23. To a solution of tetraene **22** (95 mg, 0.33 mmol) in diethyl ether (5.5 mL) was added Et_3N (92 μL, 0.66 mmol). The solution was cooled to 0 °C and stirred for 5 min before the addition of trifluoroacetic anhydride (TFAA) (93 μL, 0.66 mmol) via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with water and the product extracted with diethyl ether. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded protected tetraene **23** as a yellow oil (123 mg, 98%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81 (3H, t, J=6.5 Hz, CH_2CH_3), 1.06–1.43 (8H, m), 1.47–2.66 (11H, m), 3.72 (1H, m, $CH_2CHCH_2CH{=}CH_2$), 4.89–5.50 (8H, m), 5.53–5.77 (1H, m), 5.88–6.26 (2H, m). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 12.8, 13.9, 22.4, 24.6, 26.9, 30.3, 32.7, 34.9, 35.9, 41.1, 59.7, 69.8, 115.8, 116.9 (q, J= 289 Hz, CF_3), 117.7, 124.5, 129.9, 135.3, 138.9. FTIR (film/cm^{-1}) ν_{max}: 2958 (s), 2933 (s), 2862 (m), 1691 (s), 1642 (w), 1197 (s), 1142 (s). HRMS Calculated from $C_{22}H_{35}NOF_3$ (MH^+): 386.2671. Found: 386.2663.

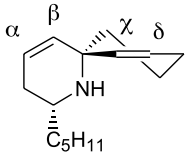
4.1.18. Synthesis of 2,2,2-trifluoro-1-(6-pent-4-enyl-2-pentyl-6-vinyl-3,6-dihydro-2*H*-pyridin-1-yl)-ethanone 25. To a solution of protected tetraene **24** (100 mg, 0.269 mmol) in toluene (2.5 mL) was added Grubbs' ruthenium catalyst **II** ($PhC(H){=}RuCl_2(PCy_3)_2$) (22.2 mg, 27 μmol). The reaction was stirred at 80 °C and monitored by TLC analysis until all starting material had been consumed. The solvent was removed in vacuo and analysis by NMR showed formation of a single-closed product. Purification of the resulting residue by silica gel chromatography afforded mono-closed system **25** as a colourless oil (85 mg, 92%) and a mixture of diastereomers (16:1). ^{1}H NMR (250 MHz, C_6D_6): δ 0.76–1.73 (15H, m), 1.80–2.29 (4H, m), 3.95 (1H, br t, J=5.0 Hz, $CH_2CH(CH_2)NH$), 4.86–5.15 (4H, m), 5.28 (1H, dd, J=10.0, 3.0 Hz, CH_2-$CH{=}CHC$), 5.41 (1H, ddd, J=10.0, 7.5, 2.0 Hz, CH_2-$CH{=}CHC$), 5.69 (1H, ddt, J=17.0, 10.5, 6.5 Hz, $CH_2CH{=}CH_2$), 6.38 (1H, dd, J=17.5, 11.0 Hz, $CCH{=}CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 22.6, 24.3, 26.4, 26.8, 31.6, 33.9, 35.2, 35.6, 52.8, 63.7, 113.9,

114.9, 116.7 (q, $J=289$ Hz, CF_3), 121.5, 131.6, 138.3, 140.2, 156.1 (q, $J=31$ Hz, C=O). FTIR (film/cm^{-1}) ν_{max}: 2933 (s), 2871 (m), 1694 (s), 1201 (s), 1136 (s). HRMS Calculated for $C_{19}H_{29}NOF_3$ (MH^+): 344.2201. Found: 344.2199.

4.1.19. Synthesis of 2,2,2-trifluoro-1-(2-pentyl-1-aza-spiro[5.5]undeca-4,7-dien-1-yl)-ethanone 24 from 2,2,2-trifluoro-1-(6-pent-4-enyl-2-pentyl-6-vinyl-3,6-dihydro-2*H*-pyridin-1-yl)-ethanone 25. To a solution of spiropiperidine **25** (42 mg, 0.123 mmol) in toluene (1.2 mL) was added Grubbs' ruthenium catalyst **I** ($PhC(H)=RuCl_2(Imes)(PCy_3)$) (10.4 mg, 12.2 μmol). The reaction was heated to 80 °C for 1 h before cooling and removal of the solvent in vacuo. Purification of the resulting residue by silica gel chromatography afforded protected spirocycle **24** as a colourless oil (85 mg, 92%) as a mixture of diastereomers (16:1). ^{1}H NMR (250 MHz, C_6D_6): δ 0.66 (3H, t, $J=7.0$ Hz, CH_2CH_3), 0.73–2.08 (16H, m), 2.26–2.50 (1H, m), 3.67–3.85 (1H, br m, $NCH(CH_2)CH_2$), 4.87–4.96 (1H, m, CCH_2CHCH_2), 5.05 (1H, ddd, $J=10.0$, 7.0, 2.5 Hz, $CCHCH_\delta CH_2$), 5.34 (1H, dd, $J=10.5$, 2.5 Hz, $CCH_\beta CHCH_2$), 5.51 (1H, ddd, $J=10.0$, 5.5, 2.5 Hz, $CCHCH_\alpha CH_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9, 19.9, 22.5, 23.3, 26.5, 27.2, 30.6, 31.6, 34.5, 52.3, 59.2, 116.6 (q, $J=290$ Hz, CF_3), 118.4, 127.1, 130.1, 130.4, 155.4 (q, $J=34$ Hz, C=O). FTIR (film/cm^{-1}) ν_{max}: 2933 (s), 2871 (m), 1694 (s), 1201 (s), 1136 (s). HRMS Calculated for $C_{17}H_{25}NOF_3$ (MH^+): 316.1888. Found: 316.1889.

4.1.20. Direct synthesis of 2,2,2-trifluoro-1-(2-pentyl-1-aza spiro[5.5]undeca-4,7-dien-1-yl)-ethanone 24. To a solution of protected tetraene **23** (50 mg, 0.14 mmol) in DCM (0.5 mL) was added Grubbs[1] ruthenium catalyst **II** ($PhC(H)=RuCl_2(PCy_3)_2$) (11.5 mg, 13 μmol). The reaction was heated to reflux for 16 h before cooling and removal of the solvent in vacuo. Purification of the resulting residue by silica gel chromatography afforded protected spirocycle **24** as a colourless oil (42 mg, 99%) and a mixture of diastereomers (12:1).

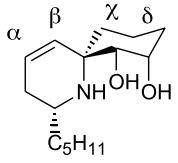
4.1.21. 2-Pentyl-1-aza-spiro[5.5]undeca-4,7-diene 26.



26

To a solution of protected spirocycle **24** (175 mg, 0.56 mmol) in absolute ethanol (3 mL) was added sodium borohydride (84 mg, 2.22 mmol). The reaction was heated to reflux for 16 h, before quenching with 1 M HCl (3 mL) and stirring for 30 min. The solution was then basified with 1 M NaOH until alkaline before extraction with ethyl acetate. The organic layer was separated and dried over $MgSO_4$, and the solvent removed in vacuo. Purification of the resulting residue by silica gel chromatography afforded spirodiene **26** as a yellow oil (89 mg, 88%). ^{1}H NMR (250 MHz, C_6D_6): δ 0.87 (3H, t, $J=6.5$ Hz, CH_2CH_3), 1.08–1.94 (17H, m), 2.95–3.09 (1H, br m, $NCH(CH_2)CH_2$), 5.57 (1H, dt, $J=10.0$, 3.5 Hz, $CH_2CH_\alpha=CH_\beta C$), 5.69 (2H, br s, $CCH_\chi CH_\delta CH_2$), 5.97 (1H, dt, $J=10.0$, 1.5 Hz, $CH_2CH_\alpha=CH_\beta C$). ^{13}C NMR (62.9 MHz, CD_6D_6): δ 14.3, 19.6, 22.9, 25.5, 25.8, 32.4, 32.8, 375, 38.2, 48.2, 53.4, 124.3, 125.9, 132.9, 134.1. FTIR (film/cm^{-1}) ν_{max}: 3020 (m), 2926 (s), 2856 (s), 1455 (m). HRMS: Calculated for $C_{15}H_{26}N$ (MH^+): 220.2065. Found: 220.2074.

4.1.22. 2-Pentyl-1-aza-spiro[5.5]undec-4-ene-7,8-diol 27.



27

To a solution of spiropiperidine **26** (25.5 mg, 0.116 mmol) was added DCM (12 mL) and Et_3N (19.2 μL, 0.128 mmol). The solution was cooled to −78 °C for 10 min, after which time OsO_4 (31 mg, 0.122 mmol) in DCM (1 mL) was added via cannula. The solution was left to stir at −78 °C for 2 h during which time the colour changed from clear to orange to red-brown. When all starting material had been consumed the reaction was warmed to room temperature. The organic solvent was removed in vacuo, resulting in a brown solid. To this was added methanol (5 mL) and 2 drops of concentrated HCl and the reaction was allowed to stir overnight. Removal of the solvent in vacuo and purification of the resulting residue by silica gel chromatography afforded diol **27** as a yellow solid (17 mg, 60%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (3H, t, $J=6.5$ Hz, CH_2CH_3), 0.99–1.95 (17H, m), 1.98–2.22 (1H, m, $CH_2CH(CH_2)NH$), 2.91–3.15 (1H, m, $CH_2CH(CH_2)NH$), 3.46–3.62 (1H, m, $CH_\chi OHCH_\delta OHCH_2$), 3.77–3.96 (1H, m, $CH_\chi OHCH_\delta OHCH_2$), 5.51–5.76 (1H, dd, $J=10.5$, 1.0 Hz, $CH_2CH_\alpha=CH_\beta C$), 5.91 (1H, ddd, $J=10.5$, 6.0, 2.0 Hz, $CH_2CH_\alpha=CH_\beta C$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1, 17.3, 22.6, 25.7, 30.3, 31.6, 31.9, 34.9, 37.1, 48.8, 57.7, 70.5, 73.1, 118.8, 127.3. FTIR (film/cm^{-1}) ν_{max}: 3355 (br), 2927 (s) 2858 (s) 1459 (m). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53; Found: C, 70.52; H, 11.13; N, 5.50. HRMS Calculated for $C_{15}H_{28}NO_2$ (MH^+): 254.2120. Found: 254.2119.

Acknowledgements

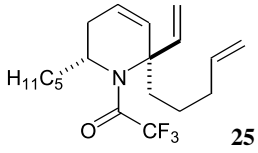
The authors are grateful to the EPSRC for a studentship to ASE (GR/M46259) and RAJW. Financial support from AstraZeneca is also gratefully acknowledged. We thank Dr. Tim Donohoe for helpful discussions during the preparation of this manuscript.

References and notes

1. For reviews see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (d) Fürstner, A. *Angew. Chem., Int. Ed.*

2000, *39*, 3012. (e) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.

2. (a) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (c) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502.
3. (a) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247. (b) Bassindale, M. J.; Edwards, A. S.; Hamley, P.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2000**, 1035. (c) Wybrow, R. A. J.; Johnson, L. A.; Auffray, B.; Moran, W. J.; Adams, H.; Harrity, J. P. A. *Tetrahedron Lett.* **2002**, *43*, 7851.
4. For other examples of tandem RCM reactions on polyolefin systems see: (a) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027. (b) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *Org. Lett.* **2001**, *3*, 671. (c) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817. (d) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421. (e) Fukuda, Y.; Sasaki, H.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2002**, *43*, 2047. (f) Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749.
5. For preliminary accounts of this work see: (a) Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542. (b) Wybrow, R. A. J.; Stevenson, N. G.; Harrity, J. P. A. *Synlett* **2004**, 140.
6. (a) For a recent approach to histrionicotoxin using a single RCM reaction see: Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427. (b) For lead references and an elegant two-directional approach to histrionicotoxin analogues see: Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598.
7. This transformation has recently been accomplished on a tris-1,1,1-(hydroxymethyl)ethane derivative using IBX: Clarke, P.; Jeffery, M. J.; Boydell, A. J.; Whiting, S.; Linclau, B. *Tetrahedron* **2004**, *60*, 3625.
8. Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commun.* **2002**, 1064.
9. For a related process see: Jones, S.; Norton, H. C. *Synlett* **2004**, 338.
10. For a recent example see: Wright, D. L.; Schulte, J. P.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.
11. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
12. The use of OsO_4 led to over oxidation and poor selectivity for dihydroxylation of the more remote alkene.
13. We were unable to unambiguously establish the stereochemistry of the major piperidine **25**. However, we have carried out the conversion of **25** to **24** using both Ru-catalysts **I** and **II** under a variety of conditions and have found the diastereomeric ratio of starting **25** to be conserved in the spirodiene product **24**. We therefore conclude that the major diastereoisomer of **25** produced from the reaction in Scheme 7 to be that shown below:



25

14. For examples of catalyst dependant diastereoselectivity see: (a) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376. (b) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129.
15. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445.
16. Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.
17. For a recent review see: Donohoe, T. J. *Synlett* **2002**, 1223.
18. Crystallographic data (excluding structure factors) for structure **27** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 237218. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. Surprisingly, treatment of **26** with osmium tetroxide in the absence of TMEDA additive (1 equiv OsO_4, acetone/H_2O, RT, 18 h) did not lead to dihydroxylation of either olefin and starting material was recovered.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8881–8892

Diastereoselective synthesis of 2,3,4,5-tetrasubstituted isoxazolidines via 1,3-dipolar cycloaddition

Vellaisamy Sridharan,[a] Shanmugam Muthusubramanian,[a,*] Shanmugaperumal Sivasubramanian[a] and Kurt Polborn[b]

[a]*Department of Organic Chemistry, Madurai Kamaraj University, Palkalai Nagar, Madurai 625 021, India*
[b]*Department of Chemistry, Ludwig-Maximilians-University, Butenandt Street 5-13, D-81377 Munich, Germany*

Received 19 April 2004; revised 21 June 2004; accepted 8 July 2004

Available online 18 August 2004

Abstract—The 1,3-dipolar cycloaddition reactions of α-2-methoxyaryl nitrones with nitrostyrenes and chalcones have been investigated. The regiochemistry and stereochemistry of the resultant cycloadducts have been determined with the help of NMR spectroscopy and X-ray analysis. β-Nitrostyrenes add to nitrones to give two geometrical isomers, while the β-methyl-β-nitrostyrene gives a single isomer in relatively low yield. The chalcones give a single cycloadduct upon 1,3-dipolar addition.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

1,3-Dipolar cycloaddition reactions have been employed for the synthesis of heterocyclic compounds.[1] High stereospecificity/stereoselectivity associated with these reactions make them synthetically important.[2–5] It has been found that 1,3-dipolar cycloaddition reactions proceed through a concerted mechanism.[6] The nitrone-olefin 1,3-dipolar cycloaddition reaction is interesting, as it can create as many as three new contiguous stereogenic centers in a single step.[7,8] Both inter and intramolecular nitrone–alkene cycloaddition reactions have received attention because they are useful methods for the formation of heterocycles of biological interest.[9–12]

It has been known that diarylnitrones form isoxazolidines upon cycloaddition with suitable dipolarophiles. Recently, we have synthesized a set of new diaryl nitrones with a hydroxyl group in the *ortho* position of the α-aryl ring and investigated their spectral characteristics.[13] The reactivity of these nitrones and their methylated derivatives towards cycloaddition is presented in this article. Two sets of dipolarophiles have been chosen for this investigation—β-nitrostyrenes and chalcones.

2. Results and discussion

The α-2-hydroxyaryl-*N*-aryl nitrones,[13] are interesting substrates for cycloaddition in the sense that the presence of a hydroxyl group in the *ortho* position can influence the course of the reaction due to electronic and steric effects apart from its ability to form hydrogen bonding wherever possible. Hence, a cycloaddition involving this dipole and the said dipolarophiles is of interest regarding the rate as well as the resultant stereo- and regiochemistry of the products. The α-2-hydroxylaryl-*N*-aryl nitrones, under conventional conditions in toluene undergo the cycloaddition with 1,3-diphenyl-2-propen-1-one very slowly giving poor yields of the resultant isoxazolidines. It took approximately 20 h for a conversion of just below 4% formation of the expected isoxazolidines. Change of solvent, increase in reaction time, change of the dipolarophile or even the use of microwaves has not improved the yield. In fact, under microwave radiation, no product formation was observed. The yield of the product has been arrived at by comparing the signal intensity from ^{1}H NMR spectra of the crude reaction product in which the unreacted nitrone dominates. It is very difficult to isolate the isoxazolidine from the crude product by column chromatography. In the case of cycloaddition of α-(2-hydroxy-5-isopropylphenyl)-*N*-phenyl nitrone **1** with 1,3-diphenyl-2-propen-1-one as noticed from the ^{1}H NMR spectrum of the crude product, three less, equally intense one hydrogen signals at 4.81 ppm (t, $J=9.6$ Hz), 5.12 ppm (d, $J=9.6$ Hz) and 5.64 ppm (d, $J=9.6$ Hz) have been noticed which can be attributed to the CH signals of the isoxazolidine. By comparision with the cycloadducts obtained from

Keywords: 1,3-Dipolar cycloaddition; α-2-Methoxyaryl nitrones; Stereoselectivity; NMR and X-ray analysis.
* Corresponding author. Tel.: +91-452-2458246; fax: +91-452-2459139; e-mail: muthumanian2001@yahoo.com

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.021

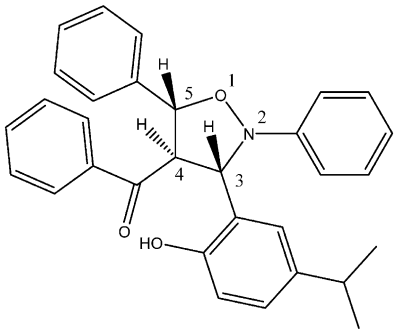


Figure 1.

α-2-methoxyaryl-*N*-aryl nitrones, vide infra, it can be safely assigned that the signal at 4.81 ppm is due to H-4, the signal at 5.12 ppm is due to H-5 and that at 5.64 ppm is due to H-3 (Fig. 1) and an all *trans* stereochemistry to the substituents.

The poor reactivity of the α-2-hydroxyaryl nitrones towards cycloaddition may be due to the decrease in the dipolar character of the dipole by hydrogen bonding. As the respective methylated nitrones undergo cycloaddition effectively, vide infra, steric hindrance due to the *ortho* hydroxyl may not be a reason for this poor reactivity. The dipolar character of the nitrone moiety is also affected by resonance as shown in Figure 2. The colour of the nitrone **1** is bright yellow in contrast to the other simple diaryl nitrones supporting such resonance contribution.

As the reason for the poor reactivity of the hydroxyl nitrones is attributed to the hydrogen bonding, it has been planned to prepare the respective methylated nitrones, **2** such as the one reported already[13] and investigate their behavior towards dipolarophiles. These methylated nitrones were prepared from the respective methoxy arylaldehydes and phenylhydroxylamine. The cycloaddition was carried out on these nitrones **2** with β-nitrostyrenes, **3** and chalcones, **4** in conventional solution medium and also under solvent free microwave condition. Though, the reaction does not proceed in the solid state under microwave, the reaction is complete in reasonable time in toluene with very good yields. The cycloaddition of **2** with nitrostyrene proceeds within 8 h, while that with chalcones requires little more time, up to 16 h.

The cycloaddition of nitrones **2** with β-nitrostyrenes **3** have been carried out in toluene in 1:1 ratio under reflux conditions (Scheme 1). The *ortho* substituted styryl systems require more time for completion of the reaction. The crude product mixture in all the cases shows the presence of two products by TLC with close R_f values. The ^{1}H and ^{13}C NMR spectra of the crude also exhibit two sets of signals corresponding to two isomeric products. The two products were separated by column chromatography using silica gel with pet ether and ethyl acetate as the eluent. The overall yield in all the cases is around 90% and the yield of the major isomer (**5**) is around 85% of the overall yield, the remaining being the minor isomer (**6**). The minor isomer is obtained in relatively better yield in the case of **6e**. All the major isomers are white crystalline solids while the minor isomers are viscous liquids.

The systematic structure analysis for the major isomer to arrive at the exact regio and stereochemistry was carried out using ^{1}H, ^{13}C and several 2D NMR spectroscopic techniques. The assignment of signals and the regio and stereochemistry for a representative case (**5a**) is discussed here. The doublet of doublets at 5.19 ppm (J=6.3, 2.7 Hz), H-4, has a C–H COSY contour with a carbon at 102.4 ppm. Hence this must be the C-4 carbon. There is one hydrogen doublet at 7.82 ppm with coupling constant 1.8 Hz which can be confidently assigned H-6″ (Fig. 3), as there is no other hydrogen in the system with a single *meta* coupling. This appears relatively downfield due to steric effect with the nearby N–Ph ring and *t*-butyl group in the *ortho* position. H-6″ has a HMBC contour with the carbon at 70.7 ppm and hence this carbon must be C-3, leaving the carbon at 85.4 ppm to be C-5. The former carbon has a C–H COSY with the doublet at 6.01 ppm (J=2.7 Hz) indicating this hydrogen to be H-3. The latter carbon has a C–H COSY contour with the signal at 5.56 ppm (J=6.3 Hz) and hence this hydrogen is H-5. The H-5 hydrogen has HMBC contours with aromatic carbons 135.4 and 127.4 ppm out of which the latter one is a CH carbon (DEPT 90) and hence this C-5 carbon carries a phenyl group and not a nitro group. Thus the major isomer **5a** is 3-[5-(*t*-butyl)-2-methoxyphenyl]-4-nitro-2,5-diphenyltetrahydroisoxazole (Fig. 3).

The stereochemistry of the ring substituents is arrived at from the coupling constants between H-3 and H-4 and H-4

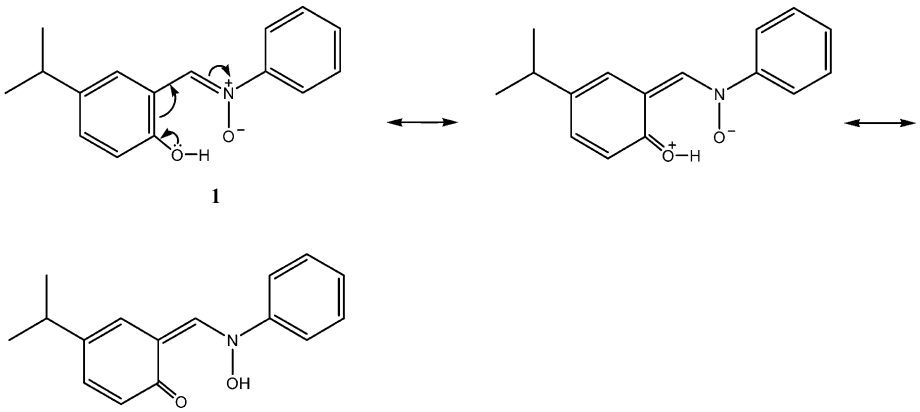
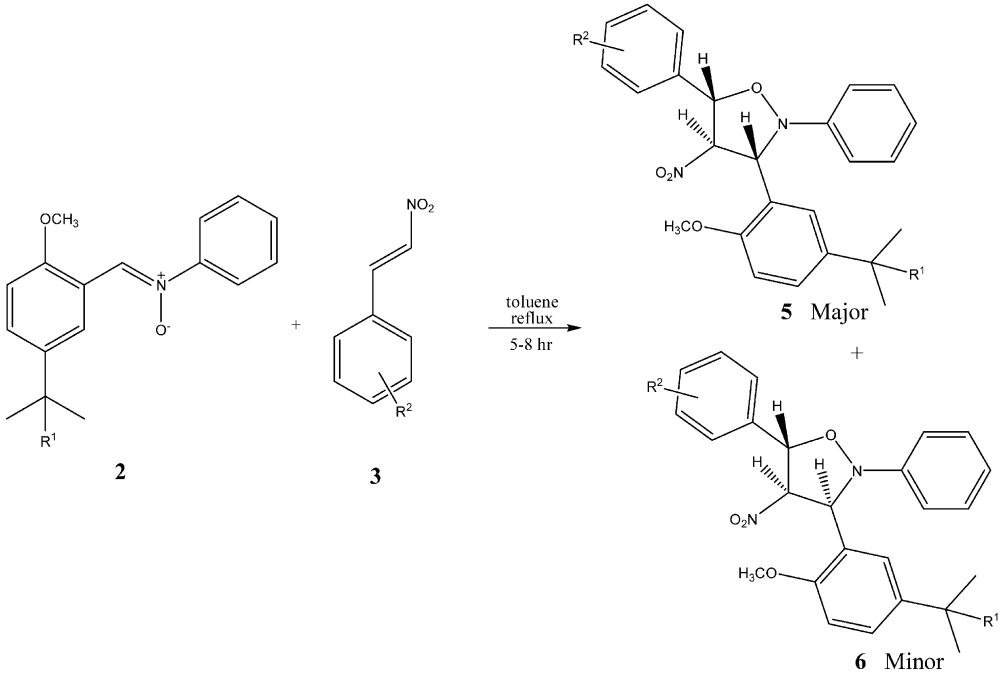


Figure 2.



	R^1	R^2	Total yield (%)
a	CH_3	H	88
b	CH_3	4-CH_3	93
c	CH_2CH_3	H	85
d	CH_2CH_3	4-CH_3	84
e	CH_2CH_3	2-OCH_3	80
f	Ph	H	92
g	Ph	4-CH_3	89
h	Ph	2-Cl	92
i	Ph	2-OCH_3	86
j	CH_2CH_3	2-Cl	94

Scheme 1.

and H-5. The $J_{3,4}$ is 2.7 Hz is small enough to consider these hydrogens to be *trans* to each other in a five membered ring. The $J_{4,5}$ is 6.3 Hz relatively higher than $J_{3,4}$ but still not high enough for a *cis* geometry in a five membered system. Hence the stereochemistry around H-4 and H-5 has to be *trans*. Obviously the dihedral angle between H-4 and H-5 may be smaller than that between H-3 and H-4 suggesting that H-4 is closer to H-5 than H-3. This is also confirmed from the NOESY spectrum, H-4 has a strong NOE contour with H-5, but a weak NOE contour with H-3. The variation in the *J* value between H-3 and H-4 and H-4 and H-5 may not only due to the change in the dihedral angle but also due

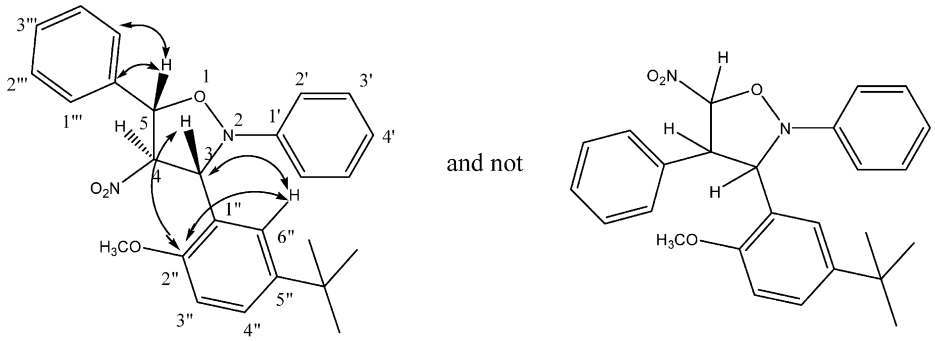


Figure 3. Correct regio- and stereochemistry and selected HMBC correlations of **5a**.

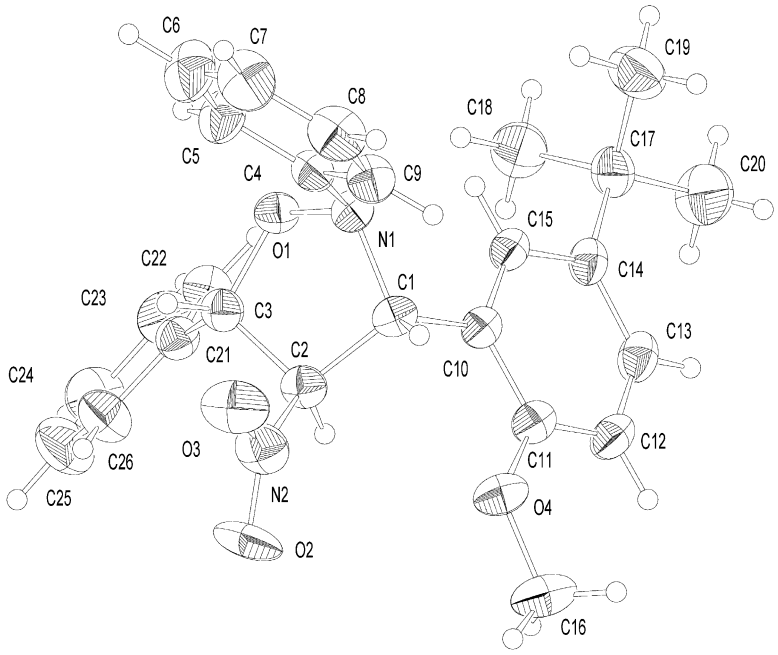


Figure 4. ORTEP diagram of 3-*r*-[5-(*t*-butyl)-2-methoxyphenyl]-4-*trans*- nitro-2-phenyl-5-*cis*-tetrahydroisoxazole (**5a**).

to the electronegativity differences of the attached atoms, oxygen to C-5 and N–Ph to C-3. The correct stereochemistry of the major isomer is shown in Figure 3.

To confirm the assigned stereochemistry of **5a**, single crystal X-ray analysis of **5a** (Fig. 4) has been carried out. The X-ray structure of the molecule possesses an envelope structure with the nitrogen atom being out of plane from the rest of the ring atoms and the *N*-phenyl ring occupying the axial position. The all *trans* stereochemistry around C-3, C-4 and C-5, as suggested by NMR spectroscopy, has been confirmed by the X-ray structure. However, the distance between H-4 and H-5 is 2.787 Å while that between H-3 and H-4 is 2.681 Å, in contrast to the observation made in solution by NMR spectroscopy (vide supra). It is interesting to note that the chemical shift and the coupling constants for H-3, H-4 and H-5 are almost same for **5a**, **b**, **c**, **d**, **f** and **g**. But for **5e**, **h**, **i** and **j**, where the aryl group at C-5 is *ortho* substituted, the chemical shift values are not in the same trend. While the chemical shift of H-4 has not changed much, that of H-3 moves to upfield by ~0.2 ppm and H-5 moves to downfield by ~0.5 ppm compared to the former series. The deshielding of the H-5 can be accounted due to the presence of an *ortho* substituent in the attached aryl group and the shielding of the H-3 may be attributed to a forced orientation of the C-5 aryl ring due to the *ortho*-substituent in which the H-3 comes under the shielding cone. The change in orientation of the C-5 aryl is also evidenced by the change in the coupling constant $J_{4,5}$ reflecting the change in the dihedral angle involved. In ^{13}C NMR spectra the C-4 and C-3 are not much affected, though the C-5 alone gets shielded by ~5 ppm due to the steric hindrance in the *ortho*-substituted systems, **5e**, **h**, **i** and **j** compared to **5a**, **b**, **c**, **d**, **f** and **g**. Though the NMR spectroscopic features differ markedly for these two sets of compounds, the crystal structures of **5e** (Fig. 5) and **5a** do not differ widely.

The minor isomer **6** could be a regioisomer or a stereoisomer of the major isomer **5**. The ^1H NMR spectrum of **6e** exhibits two doublets at 5.19 ppm ($J=7.8$ Hz) and 6.16 ppm ($J=5.4$ Hz) and one doublet of doublets at 5.57 ppm ($J=7.8$, 5.4 Hz) accounting for the isoxazolidine moiety. The one hydrogen singlet at 7.44 ppm can be easily assigned to the proton H-6″ as in the case of the major isomer **5**. This signal at 7.44 ppm makes HMBC cross peaks with the carbon at 67.1 ppm and hence it must be C-3. The C–H COSY spectrum shows correlation between the signal at 67.1 ppm and the doublet at 5.19 ppm, so it is H-3. Consequently the other doublet at 6.16 ppm is due to H-5 and the doublets of doublet at 5.57 ppm is due to H-4. In the C–H COSY experiment the former signal makes contours with 78.8 ppm and the latter with 97.3 ppm and hence the former is C-5 and the latter is C-4. The ^1H NMR spectrum of **6e** also shows two singlets at 3.74 and 3.80 ppm for the presence of two methoxy signals.

The H-3 signal at 5.19 ppm makes HMBC contours with the downfield carbon at 154.6 ppm, which in turn correlates with the signal at 3.80 ppm. This clearly shows that the carbon signal is due to C-2″ and the proton signal is due to the methoxy group attached with the C-2″ carbon. Consequently the other downfield signal at 156.5 ppm is due to C-2‴ carbon and the signal at 3.74 ppm is due to the C-2‴ attached methoxy protons. This carbon at 156.5 ppm exhibits HMBC correlations with the downfield doublet at 7.53 ppm accounting for one hydrogen with coupling constant 7.2 Hz and therefore this signal is due to H-6‴ and it makes HMBC cross peaks with the C-5 carbon and not with the C-4 carbon. This clearly confirms the regiochemistry of the compound, that is, the 2-methoxy aryl ring is attached with the C-5 carbon and the nitro group is attached with the C-4 carbon suggesting that the minor isomer **6e** is a stereoisomer of the major isomer **5e** and not a regioisomer.

The stereochemistry of the minor isomer **6e** has been

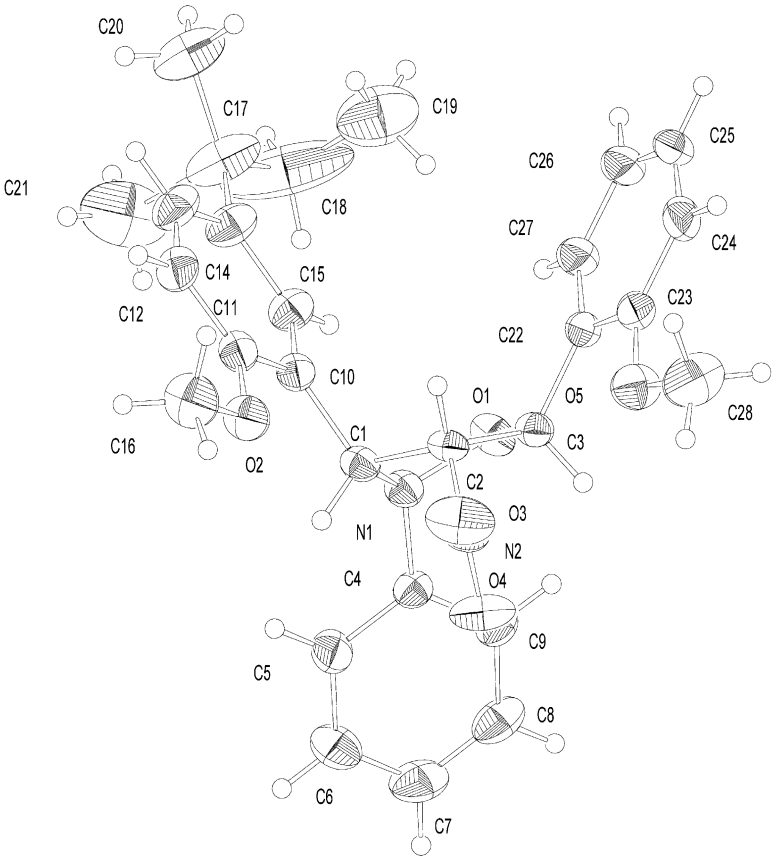
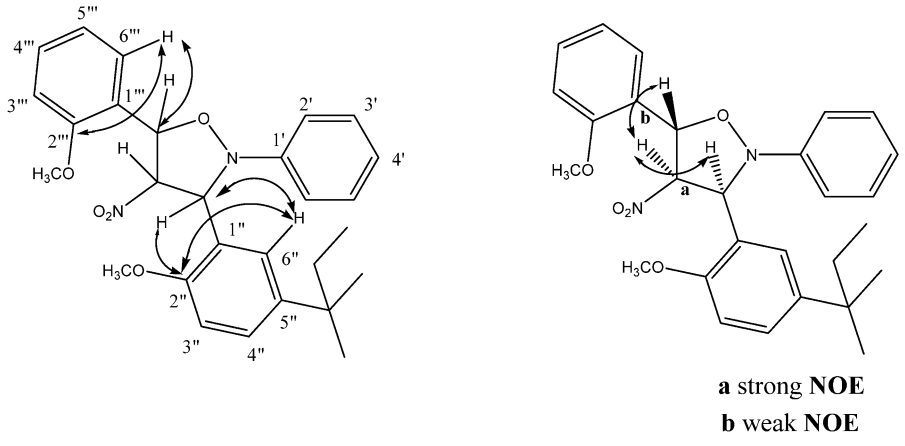


Figure 5. ORTEP diagram of 3-*r*-[2-methoxy-5-(*t*-pentyl)phenyl]-5-*cis*-(2-methoxyphenyl)-4-*trans*-nitro-2-phenyltetrahydroisoxazole (**5e**).

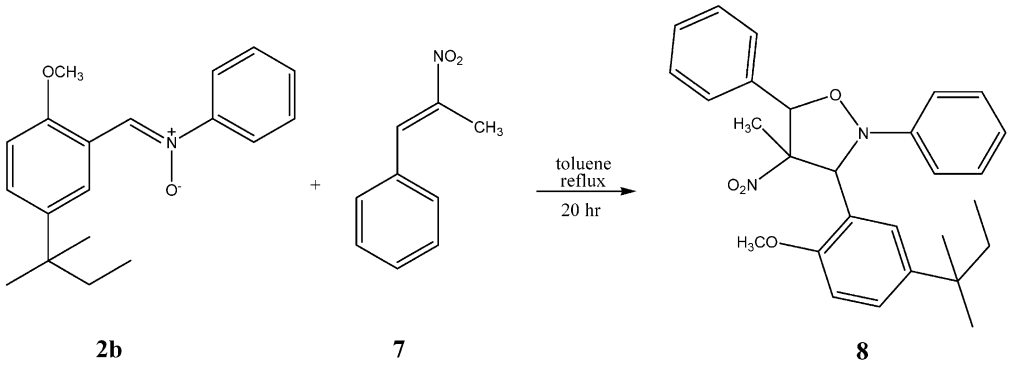
assigned from the combined use of coupling constants and NOESY spectrum. The $J_{4,5}$ is 5.4 Hz for **6e**, which is almost equal to the $J_{4,5}$ values of the major isomer **5**. Therefore, the stereochemistry between C-4 and C-5 is *trans* as observed in the major isomer. The $J_{3,4}$ is much higher (7.8–8.7 Hz) for the minor isomer than the major one (2.4–3.0 Hz). This higher coupling constant can be accounted in terms of the *cis* stereochemistry between C-3 and C-4. The NOESY spectrum of **6e** shows an intense contour between H-3 and H-4 as the two hydrogens are *cis* to each other and forms a weak contour between H-4 and H-5 since these two hydrogens are *trans* to each other. The stereochemical structure of **6e** is shown in Figure 6.

Since β-nitrostyrenes act as good dipolarophiles in the 1,3-dipolar cycloaddition reactions, it was planned to use β-methyl-β-nitrostyrene also as a dipolarophile towards cycloaddition. When α-(5-*t*-pentyl-2-methoxyphenyl)-*N*-phenyl nitrone (**2b**) was treated with β-methyl-β-nitrostyrene (**7**) in toluene as described in the previous cycloaddition reactions, it gave only one isomer. The conversion was only 24% even after 20 h. The ^{1}H NMR spectrum of the crude reaction mixture exhibits only two singlets between 5.0 and 6.5 ppm indicating the formation of a single isomer. After completion of the reaction, the separation of the product from the mixture was difficult through column chromatography as both unreacted β-methyl-β-nitrostyrene and the



a strong **NOE**
b weak **NOE**

Figure 6. Selected HMBC correlations and NOE correlations of **6e**.



2b **7** **8**

Scheme 2.

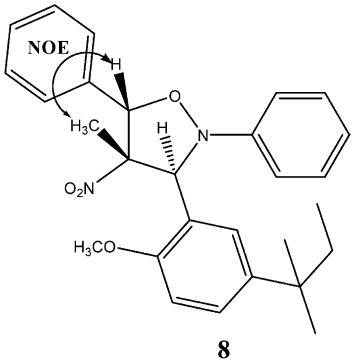
product formed have the same R_f value. As the β-methyl-β-nitrostyrene crystallizes well in petroleum ether, it was removed from the reaction mixture by careful recrystallization. As the nitrone and the product have different R_f values, they were separated easily by column chromatography (Scheme 2).

The ^{1}H NMR spectrum of **8** shows two singlets at 5.05 and 6.46 ppm each accounting for one hydrogen. This helps to fix the regiochemistry at the isoxazolidine moiety suggesting that **8** is 3-[2-methoxy-5-(*t*-pentyl)phenyl]-4-methyl-4-nitro-2,5-diphenyltetrahydroisoxazole. The *meta* coupling doublet at 7.66 ppm has been assigned for H-6″ and it makes no HMBC correlation with any of the singlets like the previous β-nitrostyrene cycloadducts. This hydrogen makes a HMBC contour with the downfield carbon at 154.9 ppm (C-2″), which in turn makes correlation with the singlet at 5.05 ppm. Therefore, the singlet at 5.05 ppm is due to H-3 and consequently the other singlet at 6.46 ppm is due to H-5.

The NOESY experiment helps to assign the orientation of the methyl group. The methyl group at 1.50 ppm makes a poor NOESY contour with the H-5 hydrogen at 6.46 ppm and no contour with the H-3 hydrogen at 5.05 ppm. This shows that the methyl group is closure to H-5 and could be *trans* to H-3. Therefore, the correct stereochemistry around C-4 in the isoxazolidine **8** could be as shown in Figure 7.

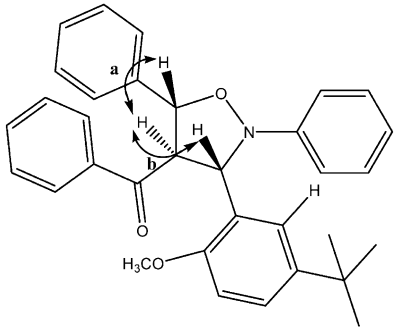
Interestingly, the cycloaddition reaction of the α-(5-substituted-2-methoxyphenyl)-*N*-phenyl nitrones with different substituted chalcones yields only one isomer with good yield but the reaction time is higher when compared to the cycloaddition involving β-nitrostyrenes. The regiochemistry of the cycloadducts has been confirmed by spectral analysis. For a representative case, the spectral details of the only product, **9a** have been discussed here. The one hydrogen signal at 8.01 ppm (*meta* coupling doublet, H-6″) makes HMBC correlation with the carbon signal at 72.2 ppm indicating the latter to be C-3, which makes C–H COSY cross peaks with the doublet at 5.60 ppm (J=5.7 Hz) and hence it must be H-3. Therefore, the other doublet at 5.30 ppm (J=9.0 Hz) is H-5 and the doublets of doublet at 4.40 ppm (J=9.0, 5.7 Hz) is H-4. The C–H COSY experiment helps to identify the respective carbons (86.1 and 69.0 ppm as C-5 and C-4, respectively). The H-3 proton at 5.60 ppm makes HMBC correlation with the carbonyl group at 197.9 ppm showing that the COAr unit is attached to the C-4 carbon and not with the C-5 carbon. Obviously the correct regiochemistry of the product is **9** and not its regioisomer (Scheme 3).

By logic, the stereochemistry of **9a** can be expected to be all *trans* as in the case of the major isomer of nitrostyrene system. The $J_{3,4}$ and $J_{4,5}$ are 5.7 and 9.0 Hz, while that for the major isomer of nitrostyrene adducts are 2.7 and 6.3 Hz. The trend shows an increase by about 3.0 Hz in both $J_{3,4}$ and $J_{4,5}$ values in chalcone adducts compared to the nitrostyrene adducts. This may be attributed to the change in the electronegativity at C-4 as the vicinal coupling constants are much dependent on electronegativity of the attached groups



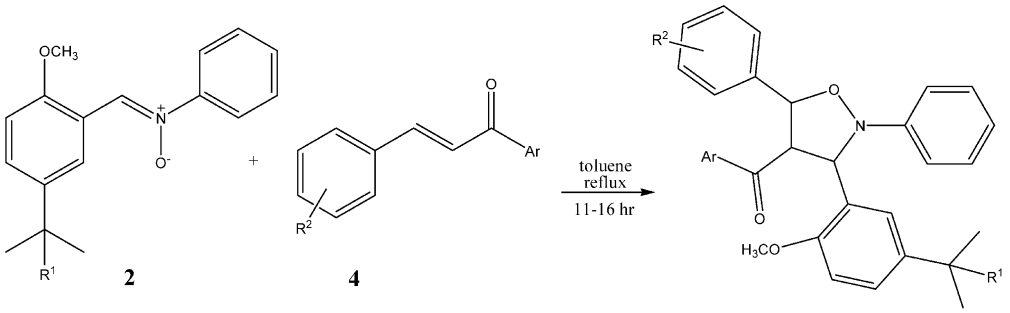
8

Figure 7.



a strong **NOE**
b weak **NOE**

Figure 8. Stereochemistry of **9a** with NOE correlations.



	R^1	R^2	Ar	Total yield (%)
a	CH_3	H	Ph	71
b	CH_3	4-CH_3	2-Thienyl	72
c	CH_3	4-CH_3	Ph	74
d	Ph	4-CH_3	Ph	76
e	Ph	H	Ph	73
f	Ph	2-OCH_3	Ph	65
g	CH_2CH_3	H	Ph	73
h	CH_2CH_3	4-CH_3	Ph	75

Scheme 3.

apart from dihedral angle. Hence the stereochemistry of **9a** can be safely taken to be similar to that of the major isomer of the β-nitrostyrene adducts, **5**. The NOE effect as noticed in **5** is noticed in **9a** also (strong NOE with H-4 and H-5 and weak NOE with H-3 and H-4), again supporting the same stereochemistry in these two cases (Fig. 8). The assigned all *trans* structure was confirmed by X-ray analysis of **9d** (Fig. 9). The distances between H-3 and H-4 and that between H-4 and H-5 in **9d** are slightly higher than the respective distances in **5a**.

Another interesting feature in these adducts is the nonequivalent methyl carbons (and methyl hydrogens in some cases) of 5-*t*-pentyl and 5-1-methyl-1-phenylethyl substituted aryl at C-3 of the isoxazolidines **9**. The significant difference in chemical shifts may be due to the diastereotopic nature of these groups with respect to the chiral carbon, C-3. All the chalcone adducts **9** have the methoxy signal at 3.2 ppm in their NMR spectra. This is slightly upfield than normal, which can probably due to the anisotropic effect of the nearby COPh group. This is

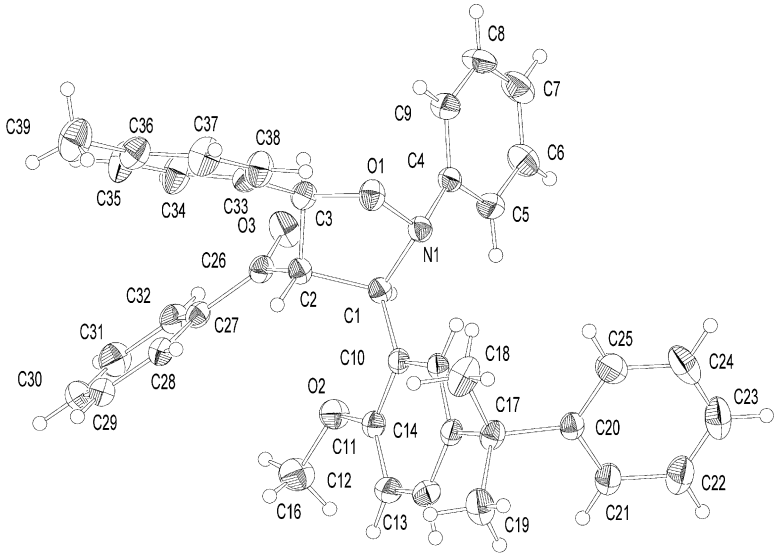


Figure 9. ORTEP diagram of [3-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(4-methylphenyl)-2-phenyl tetrahydro-4-isoxazolyl](phenyl)methanone (**9d**).

supported by the fact that the methoxy hydrogens of *o*-OMe aryl at C-5 (**9f**) also appear in the same region experiencing the same effect due to similar orientation.

The major adduct formed with β-nitrostyrenes and the only adduct formed with chalcones are well in agreement with the regio and stereochemistry for these type of 4,5-disubstituted cycloadducts obtained by 1,3-dipolar cycloadditions reported earlier.[1] The course of the addition has been governed by the inherent dipole of the dipolarophiles and the *trans* stereochemistry of the dipolarophiles have been retained in the adducts, major isomer **5** and the only isomer **9**.

3. Experimental

Melting points are uncorrected. ^{1}H, ^{13}C, DEPT, H–H COSY, C–H COSY, HMBC and NOESY spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and CCl_4 in case of liquids). The single crystal X-ray data set was collected on a Nonius MACH3 Kappa diffractometer with Mo K_α radiation ($\lambda=0.71073$ Å). The structure was solved by direct methods using SHELXS-86 and refined by full matrix least squares on F^2 by SHELXL-93. The molecular views were realized by ZORTEP. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication numbers CCDC 235731, 235732 and 235733 for **5a**, **5e** and **9d** respectively. Column chromatography was carried out in silica gel (60–120 mesh) using pet ether–ethyl acetate as eluent.

3.1. Cycloaddition of α-(5-substituted-2-methoxyphenyl)-*N*-phenyl nitrones with β-nitrostyrenes

General procedure. A mixture of α-(5-substituted-2-methoxyphenyl)-*N*-phenyl nitrone **2** (5 mmol) and β-nitrostyrene **3** (5 mmol) was refluxed in dry toluene (50 mL) for a period specified below. The solvent was evaporated under reduced pressure and the diastereoisomers **5** and **6** were separated through silica column using petroleum ether–ethyl acetate as eluent. The solid diastereoisomer **5** was recrystallised from petroleum ether–ethyl acetate mixture. The individual yields of **5** and **6** have been arrived at from the ^{1}H NMR spectra.

3.1.1. Diastereoisomers of 3-[5-(*t*-butyl)-2-methoxyphenyl]-4-nitro-2,5-diphenyltetrahydro isoxazole (5/6a). Reaction time, 6 h; overall yield, 88%; percentage yield of **5a**, 88; percentage yield of **6a**, 12.

3.1.2. 3-*r*-[5-(*t*-Butyl)-2-methoxyphenyl]-4-*trans*-nitro-2-phenyl-5-*cis*-phenyltetrahydro isoxazole (5a). Isolated yield: 1.52 g (70%), white solid, mp 162–63 °C [Found: C, 72.1; H, 6.5; N, 6.4. $C_{26}H_{28}N_2O_4$ requires C, 72.20; H, 6.53; N, 6.48%]; ν_{max}(KBr) 2962, 1596, 1552, 1494, 1454, 1357, 1249, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (9H, s), 3.76 (3H, s), 5.19 (1H, dd, $J=6.3$, 2.7 Hz, H_4), 5.56 (1H, d, $J=6.3$ Hz, H_5), 6.01 (1H, d, $J=2.7$ Hz, H_3) 6.84 (1H, d, $J=8.4$ Hz), 7.03 (1H, t $J=7.5$ Hz) 7.15 (2H, d, $J=7.8$ Hz); 7.26–7.39 (8H, m), 7.82, (1H, d, $J=1.8$ Hz); δ_C (75 MHz, $CDCl_3$) 32.0, 34.8, 55.7, 70.7 (C_3), 85.4 (C_5), 102.4 (C_4), 110.1, 114.5, 122.7, 124.7, 126.2, 126.3, 127.4, 129.4, 129.7, 129.8, 135.4, 144.1, 150.4, 154.3; crystal data: $C_{26}H_{28}N_2O_4$, $M=432.50$, triclinic, $a=10.5569$ (12), $b=11.341$ (2), $c=11.379$ (2), $\alpha=109.402$ (13), $\beta=96.960$ (12), $\gamma=109.118$ (12)°, volume=1173.0 (3) Å^3, $z=2$, $Dc=1.225$ mg/m^3, $\mu=0.083$ mm^{-1}, crystal dimensions $0.37\times0.43\times0.57$ mm, $F(000)=460$, $T=295$ (2) K, $\theta=2.11$–23.97°, 3890 reflections measured, 3645 unique [R(int)=0.0058], minimum and maximum transmission 0.9627 and 1.000, $R1=0.0409$ and $wR2=0.1110$ for all 3645 observed reflections and $R1=0.0479$ and $wR2=0.1178$ for all reflections and 314 refined parameters and 4 restrains, final electron density 0.222 and −0.171 e/Å^3.

3.1.3. 3-*r*-[5-(*t*-Butyl)-2-methoxyphenyl]-4-*cis*-nitro-2-phenyl-5-*trans*-phenyltetrahydro isoxazole (6a). Isolated yield: 0.19 g (9%), viscous liquid [Found: C, 72.3; H, 6.6; N, 6.4. $C_{26}H_{28}N_2O_4$ requires C, 72.20; H, 6.53; N, 6.48%]; ν_{max}(CCl_4) 2958, 1590, 1550, 1492, 1457, 1359, 1253, 1033 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (9H, s), 3.83 (3H, s), 5.37 (1H, d, $J=8.7$ Hz, H_3), 5.61 (1H, dd, $J=8.7$, 6.6 Hz, H_4), 5.99 (1H, d, $J=6.6$ Hz, H_5) 6.78 (1H, d, $J=8.7$ Hz), 7.03–7.52 (12H, m).

3.1.4. Diastereoisomers of 3-[5-(*t*-butyl)-2-methoxyphenyl]-5-(4-methylphenyl)-4-nitro-2-phenyltetrahydroisoxazole (5/6b). Reaction time, 6 h; overall yield, 93%; percentage yield of **5b**, 88; percentage yield of **6b**, 12.

3.1.5. 3-*r*-[5-(*t*-Butyl)-2-methoxyphenyl]-5-*cis*-(4-methylphenyl)-4-*trans*-nitro-2-phenyl tetrahydroisoxazole (5b). Isolated yield: 1.61 g (72%), white solid, mp 132–33 °C [Found: C, 72.6; H, 6.7; N, 6.4. $C_{27}H_{30}N_2O_4$ requires C, 72.62; H, 6.77; N, 6.27%]; ν_{max}(KBr) 2960, 1598, 1554, 1498, 1450, 1355, 1253, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (9H, s), 2.32 (3H, s), 3.77 (3H, s), 5.16 (1H, dd, $J=6.6$, 2.7 Hz, H_4), 5.51 (1H, d, $J=6.6$ Hz, H_5), 6.00 (1H, d, $J=2.7$ Hz, H_3) 6.84 (1H, d, $J=8.7$ Hz), 7.02 (1H, t $J=7.5$ Hz) 7.13–7.22 (6H, m), 7.31–7.37 (3H, m), 7.82, (1H, d, $J=1.8$ Hz); δ_C (75 MHz, $CDCl_3$) 21.7, 32.0, 34.8, 55.6, 70.8 (C_3), 85.4 (C_5), 102.5 (C_4), 110.1, 114.4, 122.6, 124.7, 126.1, 126.4, 127.4, 129.7, 123.0, 132.2, 139.8, 144.1, 150.5, 154.3.

3.1.6. 3-*r*-[5-(*t*-Butyl)-2-methoxyphenyl]-5-*trans*-(4-methylphenyl)-4-*cis*-nitro-2-phenyl tetrahydroisoxazole (6b). Isolated yield: 0.22 g (10%), viscous liquid [Found: C, 72.7; H, 6.8; N, 6.2. $C_{27}H_{30}N_2O_4$ requires C, 72.62; H, 6.77; N, 6.27%]; ν_{max}(CCl_4) 2962, 1597, 1559, 1497, 1453, 1358, 1250, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.24 (9H, s), 2.37 (3H, s), 3.83 (3H, s), 5.36 (1H, d, $J=8.7$ Hz, H_3), 5.59 (1H, dd, $J=8.7$, 6.9 Hz, H_4), 5.94 (1H, d, $J=6.9$ Hz, H_5) 6.80 (1H, d, $J=8.4$ Hz), 7.05–7.61 (11H, m).

3.1.7. Diastereoisomers of 3-[2-methoxy-5-(*t*-pentyl)phenyl]-4-nitro-2,5-diphenyl tetrahydroisoxazole (5/6c). Reaction time, 5 h; overall yield, 85%; percentage yield of **5c**, 82; percentage yield of **6c**, 18.

3.1.8. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-4-*trans*-nitro-2-phenyl-5-*cis*-phenyltetrahydro isoxazole (5c). Isolated

yield: 1.39 g (62%), white solid, mp 118–19 °C [Found: C, 72.7; H, 6.7; N, 6.2. $C_{27}H_{30}N_2O_4$ requires C, 72.62; H, 6.77; N, 6.27%]; ν_{max}(KBr) 2965, 1596, 1552, 1494, 1464, 1359, 1243, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.67 (3H, t, J=7.5 Hz), 1.26 (3H, s), 1.27 (3H, s), 1.62 (2H, q, J=7.5 Hz), 3.77 (3H, s), 5.18 (1H, dd, J=6.3, 2.4 Hz, H_4), 5.56 (1H, d, J=6.3 Hz, H_5), 6.02 (1H, d, J=2.4 Hz, H_3) 6.84 (1H, d, J=8.4 Hz), 7.03 (1H, t J=7.5 Hz) 7.15 (2H, d, J=7.8 Hz), 7.25–7.37 (8H, m), 7.74, (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 9.6, 29.0, 29.1, 37.3, 38.0, 55.6, 70.6 (C_3), 85.3 (C_5), 102.5 (C_4), 110.0, 114.5, 122.6, 125.3, 126.1, 127.0, 127.4, 129.3, 129.7, 129.7, 135.6, 142.3, 150.3, 154.2.

3.1.9. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-4-*cis*-nitro-2-phenyl-5-*trans*-phenyltetrahydro isoxazole (6c). Isolated yield: 0.29 g (13%), viscous liquid [Found: C, 72.6; H, 6.8; N, 6.3. $C_{27}H_{30}N_2O_4$ requires C, 72.62; H, 6.77; N, 6.27%]; ν_{max}(CCl_4) 2960, 1596, 1550, 1497, 1460, 1355, 1240, 1032 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.58 (3H, t, J=7.5 Hz), 1.18 (3H, s), 1.22 (3H, s), 1.63 (2H, q, J=7.5 Hz), 3.83 (3H, s), 5.36 (1H, d, J=8.7 Hz, H_3), 5.61 (1H, dd, J=8.7, 6.6 Hz, H_4), 5.99 (1H, d, J=6.6 Hz, H_5) 6.81 (1H, d, J=8.7 Hz), 7.08–7.58 (12H, m).

3.1.10. Diastereoisomers of 3-[2-methoxy-5-(*t*-pentyl)-phenyl]-5-(4-methylphenyl)-4-nitro-2-phenyltetrahydroisoxazole (5/6d). Reaction time, 6 h; overall yield, 84%; percentage yield of **5d**, 85; percentage yield of **6d**, 15.

3.1.11. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-5-*cis*-(4-methylphenyl)-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5d). Isolated yield: 1.50 g (65%), white solid, mp 106–07 °C [Found: C, 73.1; H, 7.1; N, 6.1. $C_{28}H_{32}N_2O_4$ requires C, 73.03; H, 7.00; N, 6.08%]; ν_{max}(KBr) 2963, 1598, 1550, 1490, 1452, 1358, 1240, 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.67 (3H, t, J=7.5 Hz), 1.26 (3H, s), 1.27 (3H, s), 1.62 (2H, q, J=7.5 Hz), 2.32 (3H, s), 3.77 (3H, s), 5.16 (1H, dd, J=6.3, 2.7 Hz, H_4), 5.51 (1H, d, J=6.3 Hz, H_5), 6.01 (1H, d, J=2.7 Hz, H_3) 6.84 (1H, d, J=8.7 Hz), 7.02 (1H, t J=7.5 Hz) 7.14–7.37 (9H, m), 7.75 (1H, d, J=1.5 Hz); δ_C (75 MHz, $CDCl_3$) 9.6, 21.7, 29.0, 29.1, 37.3, 38.0, 55.6, 70.6 (C_3), 85.4 (C_5), 102.6 (C_4), 111.0, 114.4, 122.5, 125.3, 126.2, 126.9, 127.4, 129.7, 130.0, 132.4, 139.7, 142.3, 150.4, 154.2.

3.1.12. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-5-*trans*-(4-methylphenyl)-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6d). Isolated yield: 0.28 g (12%), viscous liquid [Found: C, 73.0; H, 6.9; N, 6.2. $C_{28}H_{32}N_2O_4$ requires C, 73.03; H, 7.00; N, 6.08%]; ν_{max}(CCl_4) 2960, 1660, 1545, 1486, 1448, 1352, 1245, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.57 (3H, t, J=7.5 Hz), 1.18 (3H, s), 1.22 (3H, s), 1.62 (2H, q, J=7.5 Hz), 2.41 (3H, s), 3.83 (3H, s), 5.35 (1H, d, J=8.7 Hz, H_3), 5.59 (1H, dd, J=8.7, 6.6 Hz, H_4), 5.94 (1H, d, J=6.6 Hz, H_5) 6.80 (1H, d, J=8.7 Hz), 7.03–7.60 (11H, m).

3.1.13. Diastereoisomers of 3-[2-methoxy-5-(*t*-pentyl)-phenyl]-5-(2-methoxyphenyl)-4-nitro-2-phenyltetrahydroisoxazole (5/6e). Reaction time, 8 h; overall yield, 80%; percentage yield of **5e**, 70; percentage yield of **6e**, 30.

3.1.14. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-5-*cis*-(2-methoxyphenyl)-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5e). Isolated yield: 1.24 g (52%), white solid, mp 133–34 °C [Found: C, 70.4; H, 6.8; N, 5.9. $C_{28}H_{32}N_2O_5$ requires C, 70.53; H, 6.77; N, 5.88%]; ν_{max}(KBr) 2960, 1598, 1560, 1492, 1451, 1355, 1249, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.62 (3H, t, J=7.5 Hz), 1.22 (6H, s), 1.60 (2H, q, J=7.5 Hz), 3.67 (3H, s), 3.77 (3H, s), 5.20 (1H, dd, J=5.7, 2.7 Hz, H_4), 5.78 (1H, d, J=2.7 Hz, H_3), 5.92 (1H, d, J=5.7 Hz, H_5), 6.81 (1H, d, J=8.4 Hz), 6.84 (1H, d, J=7.8 Hz), 6.93 (1H, t J=7.5 Hz), 7.03 (1H, t, J=7.2 Hz), 7.14 (2H, d, J=7.8 Hz), 7.20–7.36 (4H, m), 7.49 (1H, d, J=7.5 Hz), 7.64 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 9.6, 29.0, 29.1, 37.3, 37.9, 55.5, 55.6, 71.4 (C_3), 80.8 (C_5), 101.6 (C_4), 109.9, 110.7, 114.9, 121.0, 122.5, 124.5, 125.3, 126.6, 126.8, 127.0, 129.5, 130.3, 142.2, 150.5, 154.3, 157.1; crystal data: $C_{28}H_{32}N_2O_5$, M=476.56, triclinic, a=9.7540 (14), b=12.694 (2), c=12.797 (2), α=100.176 (13), β=111.387 (11), γ=111.519 (13)°, volume=1281.4 (3) Å^3, z=2, Dc=1.235 mg/m^3, μ=0.085 mm^{-1}, crystal dimensions 0.53×0.43×0.37 mm, F(000)=508, T=295 (2) K, θ=2.33–23.97°, 3222 reflections measured, 4014 unique [R(int)=0.0081], minimum and maximum transmission 0.9996 and 0.9560, $R1$=0.0559 and $wR2$=0.1518 for all 4014 observed reflections and $R1$=0.0689 and $wR2$=0.1641 for all reflections and 322 refined parameters and 0 restrains, final electron density 0.462 and −0.522 e/Å^3.

3.1.15. 3-*r*-[2-Methoxy-5-(*t*-pentyl)phenyl]-5-*trans*-(2-methoxyphenyl)-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6e). Isolated yield: 0.53 g (22%), viscous liquid [Found: C, 70.5; H, 6.8; N, 5.8. $C_{28}H_{32}N_2O_5$ requires C, 70.53; H, 6.77; N, 5.88%]; ν_{max}(CCl_4) 2955, 1600, 1563, 1490, 1458, 1352, 1240, 1028 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.54 (3H, t, J=7.2 Hz), 1.16 (3H, s), 1.20 (3H, s), 1.53 (2H, q, J=7.2 Hz), 3.74 (3H, s), 3.80 (3H, s), 5.19 (1H, d, J=7.8 Hz, H_3), 5.57 (1H, dd, J=7.8, 5.4 Hz, H_4), 6.16 (1H, d, J=5.4 Hz, H_5), 6.77 (1H, d, J=8.7 Hz), 6.90 (1H, d, J=8.1 Hz), 6.98 (1H, t J=7.5 Hz), 7.02–7.22 (6H, m), 7.33 (1H, t, J=7.8 Hz), 7.44 (1H, s), 7.53 (1H, d, J=7.2 Hz); δ_C (75 MHz, $CDCl_3$) 9.4, 28.8, 28.9, 37.3, 37.8, 55.4, 56.0, 67.1 (C_3), 78.8 (C_5), 97.3 (C_4), 109.9, 110.6, 120.6, 120.9, 121.0, 125.3, 126.0, 126.6, 127.2, 127.6, 128.9, 129.9, 141.8, 148.2, 154.6, 156.5.

3.1.16. Diastereoisomers of 3-[2-methoxy-5-(1-methyl-1-phenylethyl) phenyl]-4-nitro-2,5-diphenyltetrahydroisoxazole (5/6f). Reaction time, 6 h; overall yield, 92%; percentage yield of **5f**, 83; percentage yield of **6f**, 17.

3.1.17. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-4-*trans*-nitro-2-phenyl-5-*cis*-phenyltetrahydroisoxazole (5f). Isolated yield: 1.76 g (71%), white solid, mp 89–90 °C [Found: C, 75.3; H, 6.2; N, 5.7. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; ν_{max}(KBr) 2958, 1590, 1555, 1494, 1452, 1359, 1250, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.66 (6H, s), 3.76 (3H, s), 5.15 (1H, dd, J=6.3, 3.0 Hz, H_4), 5.53 (1H, d, J=6.3 Hz, H_5), 6.00 (1H, d, J=3.0 Hz, H_3), 6.79 (1H, d, J=8.7 Hz), 7.02 (1H, t, J=7.2 Hz), 7.10–7.35 (15H, m), 7.72 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 31.2, 31.3, 42.9, 55.7, 70.4 (C_3), 85.3 (C_5), 102.5 (C_4), 110.2, 114.6, 122.7, 125.9, 126.1, 126.2, 127.1, 127.3, 128.2, 128.5, 129.4, 129.7, 129.9, 135.6, 143.6, 150.2, 151.1, 154.4.

3.1.18. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-4-*cis*-nitro-2-phenyl-5-*trans*-phenyltetrahydroisoxazole (6f). Isolated yield: 0.35 g (14%), viscous liquid [Found: C, 75.2; H, 6.2; N, 5.7. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; $\nu_{max}(CCl_4)$ 2962, 1593, 1562, 1497, 1458, 1362, 1242, 1022 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.60 (3H, s), 1.61 (3H, s), 3.82 (3H, s), 5.32 (1H, d, J=8.7 Hz, H_3), 5.59 (1H, dd, J=8.7, 6.6 Hz, H_4), 5.91 (1H, d, J=6.6 Hz, H_5), 6.77 (1H, d, J=8.7 Hz), 7.02–7.48 (17H, m).

3.1.19. Diastereoisomers of 3-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(4-methylphenyl)-4-nitro-2-phenyltetrahydroisoxazole (5/6g). Reaction time, 5 h; overall yield, 89%; percentage yield of **5g**, 85; percentage yield of **6g**, 15.

3.1.20. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-*cis*-(4-methylphenyl)-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5g). Isolated yield: 1.80 g (71%), white solid, mp 140–41 °C [Found: C, 75.5; H, 6.4; N, 5.5. $C_{32}H_{32}N_2O_4$ requires C, 75.57; H, 6.34; N, 5.51%]; ν_{max}(KBr) 2959, 1592, 1552, 1498, 1464, 1355, 1258, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.67 (6H, s), 2.34 (3H, s), 3.75 (3H, s), 5.13 (1H, dd, J=6.3, 3.0 Hz, H_4), 5.49 (1H, d, J=6.3 Hz, H_5), 5.99 (1H, d, J=3.0 Hz, H_3), 6.79 (1H, d, J=8.7 Hz), 7.01 (1H, t, J=7.2 Hz), 7.09–7.35 (14H, m), 7.73 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 21.7, 31.2, 31.3, 42.9, 55.6, 70.5 (C_3), 85.3 (C_5), 102.5 (C_4), 110.2, 114.5, 122.6, 125.8, 126.0, 126.3, 127.1, 127.3, 128.2, 128.4, 129.6, 123.0, 132.4, 139.7, 143.6, 150.3, 151.1, 154.4.

3.1.21. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-*trans*-(4-methylphenyl)-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6g). Isolated yield: 0.31 g (12%), viscous liquid [Found: C, 75.6; H, 6.4; N, 5.6. $C_{32}H_{32}N_2O_4$ requires C, 75.57; H, 6.34; N, 5.51%]; $\nu_{max}(CCl_4)$ 2962, 1596, 1550, 1494, 1452, 1357, 1249, 1031 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.61 (3H, s), 1.62 (3H, s), 2.33 (3H, s), 3.81 (3H, s), 5.31 (1H, d, J=8.7 Hz, H_3), 5.58 (1H, dd, J=8.7, 6.6 Hz, H_4), 5.87 (1H, d, J=6.6 Hz, H_5), 6.76 (1H, d, J=8.7 Hz), 7.01–7.47 (16H, m).

3.1.22. Diastereoisomers of 5-(2-chlorophenyl)-3-[2-methoxy-5-(1-methyl-1-phenylethyl) phenyl]-4-nitro-2-phenyltetrahydroisoxazole (5/6h). Reaction time, 7 h; overall yield, 92%; percentage yield of **5h**, 85; percentage yield of **6h**, 15.

3.1.23. 5-*cis*-(2-Chlorophenyl)-3-*r*-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5h). Isolated yield: 1.93 g (73%), white solid, mp 127–28 °C [Found: C, 70.5; H, 5.4; N, 5.3. $C_{31}H_{29}ClN_2O_4$ requires C, 70.38; H, 5.53; N, 5.30%]; ν_{max}(KBr) 2960, 1592, 1554, 1490, 1452, 1358, 1240, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.62 (6H, s), 3.74 (3H, s), 5.23 (1H, dd, J=5.1, 2.7 Hz, H_4), 5.73 (1H, d, J=2.7 Hz, H_3), 6.03 (1H, d, J=5.1 Hz, H_5), 6.78 (1H, d, J=8.7 Hz), 7.02–7.36 (14H, m), 7.42 (1H, dd, J=8.7, 2.1 Hz), 7.57 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 31.1, 31.2, 42.8, 55.7, 71.4 (C_3), 81.4 (C_5), 101.4 (C_4), 110.3, 115.4, 123.2, 125.8, 126.0, 126.1, 127.0, 127.6, 128.2, 128.4, 128.4, 129.6, 130.1, 130.4, 133.3, 134.2, 143.5, 149.9, 151.0, 154.5.

3.1.24. 5-*trans*-(2-Chlorophenyl)-3-*r*-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6h). Isolated yield: 0.34 g (13%), viscous liquid [Found: C, 70.4; H, 5.4; N, 5.4. $C_{31}H_{29}ClN_2O_4$ requires C, 70.38; H, 5.53; N, 5.30%]; $\nu_{max}(CCl_4)$ 2963, 1589, 1549, 1493, 1449, 1361, 1243, 1032 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.62 (3H, s), 1.63 (3H, s), 3.84 (3H, s), 5.28 (1H, d, J=7.8 Hz, H_3), 5.62 (1H, dd, J=7.8, 4.5 Hz, H_4), 6.29 (1H, d, J=4.5 Hz, H_5), 6.78 (1H, d, J=8.7 Hz), 7.03–7.65 (16H, m).

3.1.25. Diastereoisomers of 3-[2-methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(2-methoxyphenyl)-4-nitro-2-phenyltetrahydroisoxazole (5/6i). Reaction time, 8 h; overall yield, 86%; percentage yield of **5i**, 84; percentage yield of **6i**, 16.

3.1.26. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-*cis*-(2-methoxyphenyl)-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5i). Isolated yield: 1.78 g (68%), white solid, mp 125–26 °C [Found: C, 73.2; H, 6.2; N, 5.4. $C_{32}H_{32}N_2O_5$ requires C, 73.26; H, 6.15; N, 5.34%]; ν_{max}(KBr) 2959, 1590, 1557, 1494, 1456, 1360, 1242, 1038 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.63 (6H, s), 3.65 (3H, s), 3.75 (3H,s), 5.16 (1H, dd, J=5.7, 2.7 Hz, H_4), 5.76 (1H, d, J=2.7 Hz, H_3), 5.90 (1H, d, J=5.7 Hz, H_5), 6.75 (1H, d, J=8.7 Hz), 6.83 (1H, d, J=8.1 Hz), 6.92 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.05–7.36 (12H, m), 7.64 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 31.2, 31.3, 42.8, 55.5, 55.6, 71.4 (C_3), 80.7 (C_5), 101.6 (C_4), 110.1, 110.7, 115.0, 121.1, 122.6, 124.6, 125.8, 126.0, 126.6, 126.8, 127.1, 128.0, 128.4, 129.5, 130.2, 143.5, 150.4, 151.1, 154.5, 157.0.

3.1.27. 3-*r*-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-*trans*-(2-methoxyphenyl)-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6i). Isolated yield: 0.34 g (13%), viscous liquid [Found: C, 73.3; H, 6.1; N, 5.3. $C_{32}H_{32}N_2O_5$ requires C, 73.26; H, 6.15; N, 5.34%]; $\nu_{max}(CCl_4)$ 2958, 1590, 1555, 1496, 1458, 1362, 1240, 1036 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.61 (3H, s), 1.62 (3H, s), 3.78 (3H, s), 3.82 (3H,s), 5.16 (1H, d, J=8.1 Hz, H_3), 5.55 (1H, dd, J=8.1, 5.4 Hz, H_4), 6.10 (1H, d, J=5.4 Hz, H_5), 6.76 (1H, d, J=8.7 Hz), 6.79 (1H, d, J=8.4 Hz), 7.04–7.52 (15H, m).

3.1.28. Diastereoisomers of 5-(2-chlorophenyl)-3-[2-methoxy-5-(*t*-pentyl)phenyl]-4-nitro-2-phenyltetrahydroisoxazole (5/6j). Reaction time, 6 h; overall yield, 94%; percentage yield of **5j**, 87; percentage yield of **6j**, 13.

3.1.29. 5-*cis*-(2-Chlorophenyl)-3-*r*-[2-methoxy-5-(*t*-pentyl)phenyl]-4-*trans*-nitro-2-phenyltetrahydroisoxazole (5j). Isolated yield: 1.86 g (77%), white solid, mp 108–09 °C [Found: C, 67.3; H, 6.1; N, 5.9. $C_{27}H_{29}ClN_2O_4$ requires C, 67.42; H, 6.08; N, 5.82%]; ν_{max}(KBr) 2962, 1598, 1559, 1498, 1451, 1358, 1243, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.60 (3H, t, J=7.5 Hz), 1.21 (6H, s), 1.57 (2H, q, J=7.5 Hz), 3.76 (3H, s), 5.27 (1H, dd, J=5.1, 3.0 Hz, H_4), 5.76 (1H, d, J=3.0 Hz, H_3), 6.06 (1H, d, J=

5.1 Hz, H_5), 6.83 (1H, d, J=8.4 Hz), 7.05 (1H, t, J=7.5 Hz), 7.14 (2H, d, J=7.8 Hz), 7.22–7.36 (6H, m), 7.54–7.59 (2H, m); δ_C (75 MHz, $CDCl_3$) 9.6, 29.0, 29.0, 37.3, 37.9, 55.6, 71.4 (C_3), 81.4 (C_5), 101.5 (C_4), 110.2, 115.2, 123.1, 125.4, 125.7, 127.1, 127.6, 128.5, 129.6, 130.2, 130.5, 133.4, 134.2, 142.2, 150.0, 154.3.

3.1.30. 5-*trans*-(2-Chlorophenyl)-3-*r*-[2-methoxy-5-(*t*-pentyl)phenyl]-4-*cis*-nitro-2-phenyltetrahydroisoxazole (6j). Isolated yield: 0.27 g (11%), viscous liquid [Found: C, 67.4; H, 6.2; N, 5.9. $C_{27}H_{29}ClN_2O_4$ requires C, 67.42; H, 6.08; N, 5.82%]; ν_{max}(CCl_4) 2958, 1590, 1558, 1494, 1452, 1358, 1250, 1022 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.51 (3H, t, J=7.5 Hz), 1.15 (3H, s), 1.21 (3H, s), 1.51 (2H, q, J=7.5 Hz), 3.82 (3H, s), 5.31 (1H, d, J=7.8 Hz, H_3), 5.64 (1H, dd, J=7.8, 4.5 Hz, H_4), 6.35 (1H, d, J=4.5 Hz, H_5), 6.79 (1H, d, J=8.4 Hz), 7.08 (1H, t, J=7.2 Hz), 7.19–7.65 (10H, m).

3.1.31. Cycloaddition of α-(5-*t*-pentyl-2-methoxyphenyl)-*N*-phenyl nitrone with β-methyl-β-nitrostyrene. A mixture of 1.49 g (5 mmol) of α-(5-*t*-pentyl-2-methoxyphenyl)-*N*-phenyl nitrone, **2b** and 0.82 g (5 mmol) of β-methyl-β-nitrostyrene, **7** was refluxed in dry toluene (50 mL) for 20 h. The solvent was evaporated under reduced pressure and the unreacted β-methyl-β-nitrostyrene was removed by recrystallization from petroleum ether. The pure 3-[2-methoxy-5-(*t*-pentyl)phenyl]-4-methyl-4-nitro-2,5-diphenyl tetrahydroisoxazole **8** was separated through silica column using petroleum ether–ethyl acetate as eluent and recrystallised from petroleum ether–ethyl acetate mixture. White solid, Yield: 0.55 g (24%), mp 158–59 °C [Found: C, 73.1; H, 6.9; N, 6.2. $C_{28}H_{32}N_2O_4$ requires C, 73.02; H, 7.00; N, 6.08%]; ν_{max}(KBr) 2962, 1598, 1546, 1494, 1455, 1378, 1253, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.61 (3H, t, J=7.5 Hz), 1.22 (3H, s), 1.25 (3H, s), 1.50 (3H, s), 1.59 (2H, q, J=7.5 Hz), 3.81 (3H, s), 5.05 (1H, s, H_3), 6.46 (1H, s, H_5), 6.81 (1H, d, J=8.7 Hz), 6.99–7.05 (3H, m), 7.19–7.25 (3H, m), 7.35–7.41 (5H, m), 7.66 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 9.4, 22.2, 28.9, 37.4, 37.9, 55.9, 74.5 (C_3), 84.0 (C_5), 101.0 (C_4), 110.2, 117.9, 122.9, 123.9, 127.0, 127.4, 127.5, 128.9, 129.0, 129.1, 134.2, 142.1, 149.2, 154.9.

3.2. Cycloaddition of α-(5-substituted-2-methoxyphenyl)-*N*-phenyl nitrones with chalcones

General procedure. A mixture of α-(5-substituted-2-methoxyphenyl)-*N*-phenyl nitrone **2** (5 mmol) and chalcones **4** (5 mmol) was refluxed in dry toluene (50 mL) for a period specified below. The solvent was evaporated under reduced pressure and the cycloadduct **9** was separated from the reaction mixture through silica column using petroleum ether–ethyl acetate as eluent and recrystallised from petroleum ether–ethyl acetate mixture.

3.2.1. 3-[5-(*t*-Butyl)-2-methoxyphenyl]-2,5-diphenyltetrahydro-4-isoxazolyl(phenyl) methanone (9a). Reaction time: 12 h, White solid, Yield: 1.74 g (71%), mp 139–40 °C [Found: C, 80.5; H, 6.8; N, 2.8. $C_{33}H_{33}NO_3$ requires C, 80.62; H, 6.77; N, 2.85%]; ν_{max}(KBr) 2958, 1675, 1594, 1492, 1452, 1359, 1247, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (9H, s), 3.21 (3H, s), 4.40 (1H, dd, J=9.0, 5.7 Hz, H_4), 5.30 (1H, d, J=9.0 Hz, H_5), 5.60 (1H, d, J=5.7 Hz, H_3) 6.68 (1H, d, J=8.7 Hz), 6.97 (1H, t J=7.2 Hz) 7.12 (2H, d, J=7.8 Hz); 7.19–7.34 (10H, m), 7.42 (1H, t, J=7.5 Hz), 7.50 (2H, d, J=7.2 Hz), 8.01 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 32.1, 34.8, 54.7, 69.0 (C_4), 72.2 (C_3), 86.1 (C_5), 109.6, 114.2, 121.7, 124.2, 125.2, 127.4, 128.7, 128.8, 129.1, 129.2, 129.5, 130.2, 133.5, 136.9, 137.2, 144.1, 152.3, 154.0, 197.9.

3.2.2. [3-[5-(*t*-Butyl)-2-methoxyphenyl]-5-(4-methylphenyl)-2-phenyltetrahydro-4-isoxazolyl](2-thienyl)methanone (9b). Reaction time: 12 h, white solid, yield: 1.84 g (72%), mp 140–41 °C [Found: C, 75.0; H, 6.6; N, 2.6. $C_{32}H_{33}NO_3S$ requires C, 75.11; H, 6.50; N, 2.74%]; ν_{max}(KBr) 2958, 1656, 1596, 1494, 1409, 1359, 1243, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (9H, s), 2.30 (3H, s), 3.33 (3H, s), 4.16 (1H, dd, J=9.3, 5.7 Hz, H_4), 5.29 (1H, d, J=9.3 Hz, H_5), 5.63 (1H, d, J=5.7 Hz, H_3) 6.72 (1H, d, J=8.4 Hz), 6.86 (1H, dd, J=4.8, 3.9 Hz) 6.94–6.98 (2H, m), 7.08–7.11 (4H, m), 7.20–7.33 (5H, m), 7.52 (1H, dd, J=4.8, 0.9 Hz); 8.00 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$) 21.7, 32.1, 34.8, 54.7, 70.7 (C_4), 71.8 (C_3), 85.7 (C_5), 109.6, 114.2, 121.7, 124.2, 125.2, 127.4, 128.4, 129.5, 129.8, 130.2, 132.9, 133.7, 134.8, 139.1, 144.1, 145.0, 152.3, 154.0, 190.4.

3.2.3. [3-[5-(*t*-Butyl)-2-methoxyphenyl]-5-(4-methylphenyl)-2-phenyltetrahydro-4-isoxazolyl](phenyl)methanone (9c). Reaction time: 11 h, white solid, yield: 1.87 g (74%), mp 150–51 °C [Found: C, 80.8; H, 7.0; N, 2.8. $C_{34}H_{35}NO_3$ requires C, 80.76; H, 6.98; N, 2.77%]; ν_{max}(KBr) 2958, 1675, 1594, 1492, 1440, 1359, 1247, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (9H, s), 2.29 (3H, s), 3.20 (3H, s), 4.40 (1H, dd, J=9.3, 5.7 Hz, H_4), 5.28 (1H, d, J=9.3 Hz, H_5), 5.60 (1H, d, J=5.7 Hz, H_3) 6.68 (1H, d, J=8.4 Hz), 6.96 (1H, t J=7.2 Hz) 7.06–7.33 (11H, m), 7.41 (1H, t, J=7.5 Hz), 7.51 (2H, d, J=8.1 Hz) 8.01 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 21.7, 32.1, 34.9, 54.7, 68.8 (C_4), 72.3 (C_3), 86.1 (C_5), 109.6, 114.2, 121.6, 124.2, 125.2, 127.4, 128.7, 128.8, 129.5, 129.8, 130.3, 133.5, 133.7, 137.3, 139.0, 144.1, 152.4, 154.0, 198.0.

3.2.4. [3-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(4-methylphenyl)-2-phenyl tetrahydro-4-isoxazolyl](phenyl)methanone (9d). Reaction time: 13 h, white solid, yield: 2.15 g (76%), mp 169–70 °C [Found: C, 82.4; H, 6.5; N, 2.6. $C_{39}H_{37}NO_3$ requires C, 82.51; H, 6.57; N, 2.47%]; ν_{max}(KBr) 2969, 1673, 1592, 1490, 1450, 1355, 1238, 1020 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.71 (3H, s), 1.73 (3H, s), 2.31 (3H, s), 3.22 (3H, s), 4.35 (1H, dd, J=9.0, 5.4 Hz, H_4), 5.27 (1H, d, J=9.0 Hz, H_5), 5.58 (1H, d, J=5.4 Hz, H_3) 6.63 (1H, d, J=8.4 Hz), 6.96 (1H, t J=7.2 Hz) 7.05–7.32 (16H, m), 7.42 (1H, t, J=7.5 Hz), 7.49 (2H, d, J=7.5 Hz) 7.93 (1H, d, J=1.5 Hz); δ_C (75 MHz, $CDCl_3$)* 21.7, 31.3, 31.4, 43.0, 54.8, 69.0 (C_4), 71.8 (C_3), 85.7 (C_5), 109.7, 114.3, 121.6, 125.4, 126.0, 127.2, 127.4, 128.4, 128.7, 128.9, 129.4, 129.8, 130.2, 133.5, 133.9, 137.2, 138.9, 143.6, 151.4, 152.2, 154.1, 198.0; crystal data: $C_{39}H_{37}NO_3$, M=567.70, triclinic, a=8.748 (3), b=9.972 (2), c=18.744 (4), α=100.79 (2), β=94.44 (2), γ=102.46 (2)°, volume=1556.5 (7) $Å^3$, z=2, Dc=1.211 mg/m^3, μ=0.076 mm^{-1}, crystal dimensions 0.57×0.33×0.23 mm, F(000)=604, T=295 (2) K, θ=2.61–23.97°, 5036

reflections measured, 4868 unique [R(int)=0.0107], minimum and maximum transmission 0.9993 and 0.9749, $R1$=0.0422 and $wR2$=0.1070 for all 4868 observed reflections and $R1$=0.0652 and $wR2$=0.1167 for all reflections and 393 refined parameters and 0 restrains, final electron density 0.156 and −0.164 e/Å^3. * one CH carbon merged with others.

3.2.5. 3-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-2,5-diphenyltetrahydro-4-isoxazolyl(phenyl)methanone (9e). Reaction time: 13 h, white solid, yield: 2.02 g (73%), mp 92–93 °C [Found: C, 82.4; H, 6.4; N, 2.6. $C_{38}H_{35}NO_3$ requires C, 82.43; H, 6.37; N, 2.53%]; ν_{max}(KBr) 2957, 1668, 1590, 1492, 1445, 1358, 1246, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.71 (3H, s), 1.72 (3H, s), 3.21 (3H, s), 4.37 (1H, dd, J=9.0, 5.4 Hz, H_4), 5.30 (1H, d, J=9.0 Hz, H_5), 5.60 (1H, d, J=5.4 Hz, H_3) 6.63 (1H, d, J=8.7 Hz), 6.95 (1H, t J=7.2 Hz) 7.08–7.32 (17H, m), 7.40 (1H, t, J=7.5 Hz), 7.48 (2H, d, J=7.5 Hz) 7.93 (1H, d, J=2.4 Hz); δ_C (75 MHz, $CDCl_3$) 31.4, 31.5, 43.0, 54.8, 69.2 (C_4), 71.8 (C_3), 85.8 (C_5), 109.8, 114.4, 121.6, 125.4, 126.0, 127.1, 127.2, 127.4, 128.5, 128.6, 128.8, 128.9, 129.2, 129.5, 130.2, 133.6, 137.1, 137.2, 143.7, 151.4, 152.2, 154.1, 197.9.

3.2.6. [3-[2-Methoxy-5-(1-methyl-1-phenylethyl)phenyl]-5-(2-methoxyphenyl)-2-phenyltetrahydro-4-isoxazolyl](phenyl)methanone (9f). Reaction time: 16 h, white solid, yield: 1.89 g (65%), mp 128–29 °C [Found: C, 80.2; H, 6.3; N, 2.3. $C_{39}H_{37}NO_4$ requires C, 80.25; H, 6.39; N, 2.40%]; ν_{max}(KBr) 2959, 1673, 1592, 1490, 1455, 1350, 1241, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.70 (3H, s), 1.71 (3H, s), 3.16 (3H, s), 4.21 (1H, dd, J=8.4, 4.8 Hz, H_4), 5.56 (2H, m, $H_{3,5}$), 6.60 (1H, d, J=8.4 Hz), 6.94–7.33 (16H, m) 7.44 (1H, t, J=7.2 Hz), 7.53 (1H, d, J=7.5 Hz) 7.62 (2H, d, J=7.2 Hz), 7.89 (1H, d, J=2.1 Hz); δ_C (75 MHz, $CDCl_3$)* 31.3, 31.5, 42.9, 54.3, 54.6, 67.4 (C_4), 72.3 (C_3), 80.6 (C_5), 109.4, 110.0, 114.6, 121.1, 121.6, 125.2, 125.9, 126.0, 127.0, 127.2, 128.4, 128.5, 128.6, 129.3, 129.4, 130.6, 133.0, 137.8, 143.4, 151.4, 152.0, 154.0, 156.3, 198.5. * one quaternary carbon merged with others.

3.2.7. 3-[2-Methoxy-5-(*t*-pentyl)phenyl]-2,5-diphenyltetrahydro-4-isoxazolyl(phenyl) methanone (9g). Reaction time: 12 h, white solid, yield: 1.84 g (73%), mp 58–59 °C [Found: C, 80.7; H, 6.9; N, 2.8. $C_{34}H_{35}NO_3$ requires C, 80.76; H, 6.98; N, 2.77%]; ν_{max}(KBr) 2955, 1670, 1591, 1493, 1452, 1359, 1247, 1027 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.73 (3H, t, J=7.5 Hz), 1.31 (3H, s), 1.32 (3H, s), 1.68 (2H, q, J=7.5 Hz), 3.23 (3H, s), 4.39 (1H, dd, J=9.0, 5.4 Hz, H_4), 5.31 (1H, d, J=9.0 Hz, H_5), 5.60 (1H, d, J=5.4 Hz, H_3), 6.68 (1H, d, J=8.4 Hz), 6.98 (1H, t, J=7.2 Hz), 7.12 (2H, d, J=7.5 Hz), 7.20–7.35 (10H, m), 7.43 (1H, t, J=7.2 Hz), 7.49 (2H, d, J=7.2 Hz) 7.94 (1H, d, J=1.8 Hz); δ_C (75 MHz, $CDCl_3$) 9.7, 29.0, 29.1, 37.4, 38.0, 54.7, 69.1 (C_4), 72.0 (C_3), 85.9 (C_5), 109.6, 114.3, 121.7, 124.8, 126.0, 127.4, 128.7, 128.8, 129.1, 129.2, 129.5, 130.0, 133.5, 137.1, 137.2, 142.4, 152.3, 153.8, 197.9.

3.2.8. [3-[2-Methoxy-5-(*t*-pentyl)phenyl]-5-(4-methylphenyl)-2-phenyltetrahydro-4-isoxazolyl](phenyl)-methanone (9h). Reaction time: 13 h, white solid, yield: 1.95 g (75%), mp 64–65 °C [Found: C, 80.8; H, 7.2; N, 2.8. $C_{35}H_{37}NO_3$ requires C, 80.89; H, 7.18; N, 2.70%]; ν_{max}(KBr) 2957, 1672, 1590, 1489, 1448, 1350, 1242, 1023 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.73 (3H, t, J=7.2 Hz), 1.30 (3H, s), 1.32 (3H, s), 1.64 (2H, q, J=7.2 Hz), 2.23 (3H, s), 3.22 (3H, s), 4.38 (1H, dd, J=9.0, 5.4 Hz, H_4), 5.29 (1H, d, J=9.0 Hz, H_5), 5.60 (1H, d, J=5.7 Hz, H_3), 6.68 (1H, d, J=8.4 Hz), 6.96 (1H, t, J=7.2 Hz), 7.06–7.34 (11H, m), 7.42 (1H, t, J=7.5 Hz), 7.51 (2H, d, J=7.5 Hz), 7.93 (1H, d, J=1.5 Hz); δ_C (75 MHz, $CDCl_3$) 9.7, 21.6, 29.0, 29.1, 37.4, 38.0, 54.6, 69.9 (C_4), 72.1 (C_3), 85.9 (C_5), 109.5, 114.2, 121.6, 124.8, 125.9, 127.4, 128.7, 128.8, 129.5, 129.8, 130.1, 133.4, 133.9, 137.2, 139.0, 142.4, 152.3, 153.9, 198.1.

References and notes

1. Padwa, A., Ed.; *Dipolar Cycloaddition Chemistry*; Vols. 1–2. Wiley-Interscience: New York, 1984.
2. Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. *J. Org. Chem.* **1999**, *64*, 4990.
3. Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 4865.
4. Young, D. G.; Gomez-Bengoa, E.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 692.
5. Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778.
6. Huisgen, R.; 1,3-Dipolar cycloaddition. Introduction, survey, mechanics. Padwa, A., Ed.; *1,3-Dipolar-cycloaddition Chemistry*; Vol. 1. Wiley-Interscience: New York; 1984. p. 1–176.
7. Dondas, H. A.; Cummins, J. E.; Grigg, R.; Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 7951.
8. Alibes, R.; Blanco, P.; de March, P.; Figueredo, M.; Font, J.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron Lett.* **2003**, *44*, 523.
9. Kumar, K. R. R.; Mallesha, H.; Rangappa, K. S. *Eur. J. Med. Chem.* **2003**, *38*, 613.
10. Gothelf, K. V.; Jorgenson, K. A. *Chem. Rev.* **1998**, *98*, 863.
11. Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905.
12. Mulzer, J. *Organic Synthesis Highlights*; Verlag Chemie: Weinheim, 1991 p 77.
13. Sridharan, V.; Muthusubramanian, S.; Sivasubramanian, S. *Indian J. Chem.* **2004**, *42B*, p. 857.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8893–8897
Tetrahedron

Synthesis of pyridine and 2,2′-bipyridine derivatives from the aza Diels–Alder reaction of substituted 1,2,4-triazines

Stephen P. Stanforth,[a,*] Brian Tarbit[b] and Michael D. Watson[a]

[a]*Department of Chemical and Life Sciences, School of Applied Sciences, University of Northumbria, Newcastle upon Tyne NE1 8ST, UK*
[b]*Seal Sands Chemicals Ltd., Seal Sands Road, Seal Sands, Middlesbrough TS2 1UB, UK*

Received 10 May 2004; revised 16 June 2004; accepted 8 July 2004

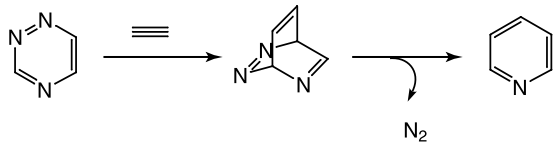
Available online 23 August 2004

Abstract—Amidrazone **1a** and the tricarbonyl derivatives **2b–d** reacted in boiling ethanol in the presence of 2,5-norbornadiene **5** giving the pyridine derivatives **6b–d** respectively (59–72%) and in the presence of 2,3-dihydrofuran **7** yielding the lactones **10b–d** (39–44%). The 2,2′-bipyridine derivatives **6e–g** were similarly obtained in good yield (81–87%) from the reaction of amidrazone **1b** and tricarbonyl derivatives **2b–d** in the presence of 2,5-norbornadiene **5**.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Pyridine derivatives occupy a pivotal position in modern heterocyclic chemistry and consequently facile methods for the synthesis of this ring system from readily available starting materials is of contemporary interest.[1] 2,2′-Bipyridine and its derivatives have also been the subject of numerous studies, principally because of their well developed coordination chemistry.[2] They have found applications in many areas of chemistry including supramolecular chemisty,[3] artificial photosynthesis systems,[4] luminescent sensor materials,[5] non-linear optical materials[6] and when they bear pendant chiral substituents, they have found use as ligands in metal catalysed asymmetric reactions.[7] The aza Diels–Alder reaction has become an important and versatile method for the preparation of pyridine derivatives and several recent reviews have discussed the scope and application of this useful reaction.[8] One important theme in aza Diels–Alder methodology is the reaction between a 2-azadiene and a suitable dienophile to form either the dihydro- or tetrahydro-pyridine skeleton as depicted in Scheme 1. A diverse range of 2-azadienes and dienophiles have been utilised in this reaction enabling the preparation of a wide variety of pyridine derivatives. 1,2,4-Triazines[9] have been used as 2-azadiene equivalents on many occasions and these heterocycles have been reacted with suitable acetylene equivalents yielding pyridine derivatives (Scheme 2). Recent examples of the aza Diels–Alder reaction of 1,2,4-triazines giving pyridine and/or 2,2′-bipyridine derivatives include their reaction with 2,5-norbornadiene[10] and enamines as acetylene equivalents.[11]

Scheme 1.

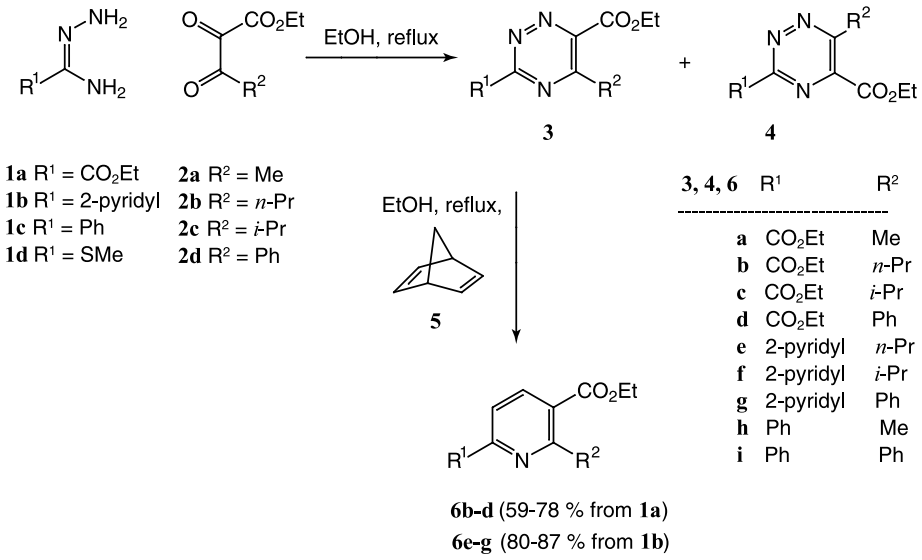


Scheme 2.

1,2,4-Triazines can be readily prepared from 1,2-dicarbonyl derivatives and amidrazones [$RC(=NHNH_2)NH_2$] and many 1,2,4-triazines have been prepared using this methodology.[9] The 1,2-dicarbonyl compounds that have been used in this reaction have generally been symmetrical and problems with the formation of regioisomeric triazines cannot occur. α-Ketoaldehydes also react with amidrazones giving single products derived from attack of the amidrazone's hydrazine group at the aldehyde carbonyl group. The reaction of amidrazones with symmetrical 1,2,3-triketones similarly yields 1,2,4-triazine derivatives. Interestingly, only a few examples of the reaction of amidrazones with α,β-diketoesters have been reported (Scheme 3). Thus, the reaction between the amidrazone **1c** and the ester **2d** was

Keywords: Pyridines; 2,2′-Bipyridines; Aza Diels–Alder reaction; 1,2,4-Triazines.
* Corresponding author. Tel.: +44-191-2274784; fax: +44-191-2273519; e-mail: steven.stanforth@unn.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.024



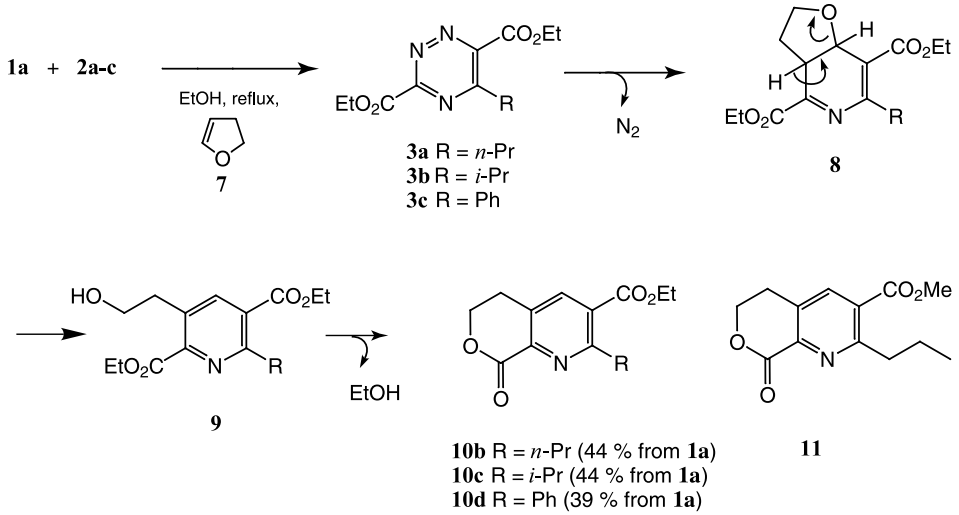
Scheme 3.

reported to give only ethyl 3,5-diphenyl[1,2,4]triazine-6-carboxylate **3i** in 70% yield[12] whereas Ohsumi and Neunhoeffer reacted this amidrazone **1c** with ester **2a** and obtained a mixture of the corresponding regioisomeric triazines **3h** and **4h** in unspecified yields.[13] The reaction of amidrazone **1a** with ester **2a** was investigated by Synder and co-workers who obtained a 10.5:1 mixture of the regioisomeric triazines **3a** and **4a** in 46% overall yield.[14] An α,β-diketoester bearing a pendant protected amino acid moiety has been reacted with *S*-methylisothiosemicarbazide **1d** giving a mixture of regioisomeric triazines in low overall yield.[15]Thus, the reactions between amidrazones and α,β-diketoester **2a** gave mixtures of 1,2,4-triazines whereas only one 1,2,4-triazine product was obtained when a more sterically demanding R^2 group was present i.e. the α,β-diketoester **2d** was used.

In view of the current interest in pyridine and 2,2′-bipyridine synthesis, we envisaged that the reaction of amidrazones **1a**[16] and **1b**[17] with α,β-diketoesters **2**[18] in the presence of an appropriate aza-dienophile might be developed as a useful method for the preparation of pyridine and bipyridine derivatives via the aza Diels–Alder reaction of 1,2,4-triazine intermediates.

2. Results and discussion

Amidrazone **1a** (prepared from ethyl thioamido oxalate[16] and hydrazine hydrate) and compound **2b** reacted in boiling ethanol in the presence of an excess of 2,5-norbornadiene **5** to give a single pyridine derivative, compound **6b**, in 78% yield. Under similar conditions, the pyridine derivatives **6c** (72%) and **6d** (59%) were prepared from the appropriate α,β-diketoesters and 2,5-norbornadiene **5**. We assumed that the amidrazone **1a** had reacted regioselectively with the α,β-diketoesters **2b–d** yielding the corresponding triazine intermediates **3b–d** and not the isomeric heterocycles **4b–d**. This assumption was confirmed by selective hydrolysis of the less sterically crowded 6-ester substituent in pyridines **6b** and **6d** and subsequent decarboxylation



Scheme 4.

yielding the known ethyl 2-propylpyridine-3-carboxylate[19] and ethyl 2-phenylpyridine-3-carboxylate[20] respectively.

The methodology described above for the synthesis of pyridines **6b–d** was readily extended to the preparation of the bipyridine derivatives **6e–g**. Thus, amidrazone **1b** was reacted with each of the α,β-diketoesters **2b–d** in the presence of an excess of 2,5-norbornadiene **5** in boiling ethanol yielding the bipyridines **6e** (81%), **6f** (80%) and **6g** (87%) respectively.

2,3-Dihydrofuran **7** has been used by Gilchrist and co-workers[21] as an acetylene equivalent in the aza Diels–Alder reaction of triazines. Amidrazone **1a** was reacted with each of the α,β-diketoesters **2b–d** and an excess of 2,3-dihydrofuran **7** in ethanol at reflux in a 'one-pot' reaction yielding the lactones **10b** (44%), **10c** (44%) and **10d** (39%) respectively as shown in Scheme 4. Ring-opening of the ether ring in intermediates **8** yields the pyridines **9** which could not be isolated but underwent lactonisation giving the products **10b–d**. The proposed regioselectivity depicted in formula **8** was confirmed by starting with the methyl ester analogue of the α,β-diketoester **2b**. Reaction of this compound with the amidrazone **1a** in the presence of 2,3-dihydrofuran **7** gave the methyl ester analogue of lactone **10b**, compound **11**, indicating that the 2-ester substituent in the triazine intermediate **3b** was involved in lactonisation.

The observed regioselectivity of the cycloaddition of triazine **3b** and 2,3-dihydrofuran **7** was also predicted by PM3 semi-empirical molecular orbital calculations (Fig. 1).[22] The HOMO (2,3-dihydrofuran)/LUMO (triazine) energy difference (8.21 eV) is significantly smaller than the HOMO (triazine)/LUMO (2,3-dihydrofuran) energy difference (11.50 eV) indicating that the former interaction will determine the outcome of this inverse electron demand cycloaddition reaction. The coefficients of the HOMO (2,3-dihydrofuran)/LUMO (triazine) at the reaction centres are shown in Figure 1. The most efficient frontier molecular orbital overlap will occur when the largest frontier molecular orbital coefficients of the two reactants interact and this corresponds to the C3-position of the 2,3-dihydrofuran **7** interacting with the C2-position of the triazine **3b** and the C2-position of the 2,3-dihydrofuran **7** interacting with the C5-position of the triazine **3b**. This situation corresponds with the observed regioselectivity of the cycloaddition reaction.

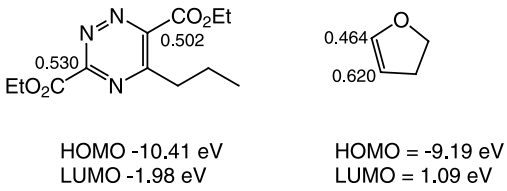


Figure 1.

In conclusion we have developed a useful 'one pot' method for the preparation of pyridine and 2,2′-bipyridine derivatives from α,β-diketoesters **2b–d** under mild conditions. Thus, we have shown that amidrazones **1a** and **1b** reacted in boiling ethanol with unsymmetrical tricarbonyl derivatives **2b–d** in the presence of 2,5-norbornadiene **5** giving pyridines **6b–d** and 2,2′-bipyridines **6e–g** in good overall yields and that lactones **10b–d** could be prepared in moderate overall yields from amidrazone **1a** and α,β-diketoesters **2b–d** in the presence of 2,3-dihydrofuran **7**.

3. Experimental

Amidrazone **1a** was prepared from ethyl thioamido oxalate [$EtO_2CC(=S)NH_2$] [16] and hydrazine hydrate. Ethyl thioamido oxalate was prepared from commercially available ethyl oxamate and Lawesson's reagent following a literature proceedure.[16] Amidrazone **1b** was prepared from 2-cyanopyridine and hydrazine hydrate.[17] ^{1}H NMR spectra were determined at 270 MHz.

3.1. Synthesis of pyridines 6b–d and 10b–d. General method

To a stirred solution ethyl thioamido oxalate[16] (0.5 g, 3.75 mmol) in ethanol (25 mL) was added hydrazine hydrate (0.19 g, 3.75 mmol). After 20 min at room temperature, the appropriate α,β-diketoester **2**[18] (3.75 mmol) and either 2,5-norbornadiene **5** (3.46 g, 37.5 mmol) or 2,3-dihydrofuran **7** (7.9 g, 133 mmol) were added in one portion. The solution was heated at reflux for 20 h, allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The product was isolated by columchromatography over silica gel.

3.1.1. Diethyl 6-propylpyridine-2,5-dicarboxyate 6b. This compound was obtained as an orange oil (78%) (eluent: ethyl acetate/petroleum ether bp 60–80 °C 1:1). ^{1}H NMR: ($CDCl_3$) δ 8.23 (d, 1H, $J=8$ Hz, py-*H*), 7.97 (d, 1H, $J=8$ Hz, py-*H*), 4.49–4.40 (overlapping quartets, 4H, 2× ester-CH_2–), 3.19 (t, 2H, $J=7$ Hz, –CH_2–), 1.75 (sextet, 2H, $J=7$ Hz, –CH_2–), 1.44 (overlapping triplets, 6H, 2×ester-CH_3) and 0.95 (t, 3H, $J=7$ Hz, –CH_3) ppm, HRMS (CI): calcd for $C_{14}H_{20}NO_4$ (M+H) 266.1392, found 266.1392.

3.1.2. Diethyl 6-isopropylpyridine-2,5-dicarboxyate 6c. This compound was obtained as an orange oil (72%) (eluent: ethyl acetate/petroleum ether bp 60–80 °C 1:1). ^{1}H NMR: ($CDCl_3$) δ 8.12 (d, 1H, $J=8$ Hz, py-*H*), 7.92 (d, 1H, $J=8$ Hz, py-*H*), 4.42 (overlapping quartets, 4H, 2×ester-CH_2–), 3.77 (septet, 1H, $J=7$ Hz, –C*H*–), 1.43 (overlapping triplets, 6H, 2×ester-CH_3) and 1.35 (d, 6H, $J=7$ Hz, 2×-CH_3) ppm, HRMS (CI): calcd for $C_{14}H_{20}NO_4$ (M+H) 266.1392, found 266.1388.

3.1.3. Diethyl 6-phenylpyridine-2,5-dicarboxylate 6d. This compound was obtained as a yellow oil (59%) (eluent: ethyl acetate/petroleum ether bp 60–80 °C 4:6). ^{1}H NMR: ($CDCl_3$) δ 8.19 (d, 1H, $J=8$ Hz, py-*H*), 8.10 (d, 1H, $J=8$ Hz, py-*H*), 7.57 (m, 1H, Ph-*H*), 7.44 (m, 4H, Ph-*H*), 4.49 (q, 2H, $J=7$ Hz, –CH_2–), 4.17 (q, 2H, $J=7$ Hz, –CH_2–), 1.45 (t, 3H, $J=7$ Hz, –CH_3) and 1.05 (t, 3H, $J=7$ Hz, –CH_3) ppm, HRMS (CI): calcd for $C_{17}H_{18}NO_4$ (M+H) 300.1124, found 300.1234.

3.1.4. Ethyl/methyl 8-oxo-2-propyl-5,6-dihydro-8*H*-pyrano[3,4-*b*]pyridine-3-carboxylate 10b/11. This

compound was obtained as an orange oil (44%) (eluent, petroleum ether bp 60–80 °C/ethyl acetate 4:6). ν_{max} (KBr): 1724 and 1187 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.08 (s, 1H, py-*H*), 4.60 (t, 2H, $J=6$ Hz, ring-CH_2–), 4.43 (q, 2H, $J=7$ Hz, ester-CH_2–), 3.17 (overlapping triplets, 5H, ester-CH_3, ring-CH_2–), 1.72 (m, 2H, –CH_2–), 1.43 (t, 2H, $J=7$ Hz, –CH_2–) and 0.99 (t, 3H, $J=7$ Hz, –CH_3) ppm, ^{13}C NMR: ($CDCl_3$) δ 165.9 (CO), 163.4 (CO), 162.3 (C), 143.8 (C), 138.2 (*CH*), 132.9 (C), 129.5 (C), 66.9 (CH_3), 62.1 (CH_3), 38.7 (CH_2), 29.7 (CH_2), 26.9 (CH_2), 23.6 (CH_2) and 14.2 (CH_2) ppm, HRMS (CI): calcd for $C_{14}H_{18}NO_4$ (M+H) 264.1236, found 264.1234. When the experiment was repeated using methyl 2,3-dioxohexanoic acid in place of compound **2b**, the methyl ester **11** was obtained which had the following ^1H NMR spectral data ($CDCl_3$): δ 8.09 (s, 1H, py-*H*), 4.60 (t, 2H, $J=7$ Hz, ring-CH_2–), 3.96 (s, 3H, –CH_3), 3.16 (m, 4H, 2×-CH_2–), 1.72 (sextet, 2H, $J=7$ Hz, –CH_2–) and 0.98 (t, 3H, $J=7$ Hz, –CH_3) ppm.

3.1.5. Ethyl 8-oxo-2-isopropyl-5,6-dihydro-8*H*-pyrano[3,4-*b*]pyridine-3-carboxylate 10c. The ethyl ester was obtained as an orange oil (44%) (eluent: petroleum ether bp 60–80 °C/ethyl acetate 4:6). ν_{max} (KBr): 1722 and 1187 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 7.94 (s, 1H, py-*H*), 5.85 (t, 2H, $J=6$ Hz, ring-CH_2–), 4.42 (q, 2H, $J=7$ Hz, ester-CH_2–), 3.74 (septet, 1H, –*CH*–), 3.13 (t, 2H, $J=6$ Hz, ring-CH_2–), 1.43 (t, 3H, $J=7$ Hz, ester-CH_3) and 3.39 (d, 6H, $J=7$ Hz, 2×isopropyl-CH_3) ppm, ^{13}C NMR: ($CDCl_3$) δ 167.0 (CO), 166.4 (CO), 162.2 (C), 143.8 (C), 137.4 (*CH*), 132.8 (C), 129.4 (C), 66.8 (–CH_3), 62.1 (CH_3), 32.9 (CH_2), 27.0 (CH_2), 22.2 (CH_2), 21.1 (CH_2) and 14.2 (CH_2) ppm, HRMS (CI): calcd for $C_{14}H_{18}NO_4$ (M+H) 264.1236, found 264.1233.

3.1.6. Ethyl 8-oxo-2-phenyl-5,6-dihydro-8*H*-pyrano[3,4-*b*]pyridine-3-carboxylate 10d. This compound was obtained as a an orange oil which crystallised from ethanol giving a white crystalline solid (39%), mp 162 °C. ν_{max} (KBr): 1736, 1701, 1182 and 1139 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.01 (s, 1H, py-*H*), 7.60 (m, 1H, Ph-*H*), 7.40 (m, 4H, Ph-*H*), 4.65 (t, 2H, $J=5$ Hz, ring-CH_2–), 4.19 (q, 2H, $J=7$ Hz, ester-CH_2–), 3.22 (t, 2H, $J=5$ Hz, ring-CH_2–) and 1.03 (t, 3H, $J=7$ Hz, ester-CH_3) ppm, ^{13}C NMR: ($CDCl_3$) δ 167.4 (CO), 161.9 (CO), 158.8 (*CH*), 143.5 (C), 138.8 (C), 137.6 (*CH*), 133.8 (C), 131.0 (C), 129.2 (C), 128.8 (C), 128.3 (C), 66.8 (CH_3), 62.1 (CH_2), 27.1 (CH_2) and 13.6 (CH_2) ppm, Anal. for $C_{17}H_{15}NO_4$: calcd C, 68.68; H, 5.09; N, 4.71, found C, 68.54; H, 4.84; N, 4.60.

3.1.7. 6-Propylpyridine-2,5-dicarboxylic acid 5-ethyl ester and ethyl 2-propylpyridine-3-carboxylate. 6-Propylpyridine-2,5-dicarboxylic acid 5-ethyl ester (0.15 g, 56%) was synthesised from diethyl 6-propyl-pyridine-2,5-dicarboxylate **6b** following the procedure described below for the preparation of 6-phenylpyridine-2,5-dicarboxylic acid 5-ethyl ester and was obtained as a brown oil. ^1H NMR: ($CDCl_3$) δ 8.40 (d, 1H, $J=8$ Hz, py-*H*), 8.12 (d, 1H, $J=8$ Hz, py-*H*), 4.44 (q, 2H, $J=7$ Hz, ester-CH_2–), 3.18 (t, 2H, $J=7$ Hz, –CH_2–), 1.08 (m, 2H, –CH_2–) 1.43 (t, 3H, $J=7$ Hz, ester-CH_3) and 1.02 (t, 3H, $J=7$ Hz, –CH_3). Ethyl 2-propylpyridine-3-carboxylate (0.17 g, 70%) was synthesised from 6-propylpyridine-2,5-dicarboxylic acid 5-ethyl ester following the procedure described below for the preparation of ethyl 2-phenylpyridine-3-carboxylate and was obtained as a brown oil. ^1H NMR: ($CDCl_3$) δ 8.67 (dd, 1H, $J=5$, 2 Hz, py-*H*), 8.17 (dd, 1H, $J=8$, 2 Hz, py-*H*) 7.24 (dd, 1H, $J=8$, 2 Hz, py-*H*), 4.40 (q, 2H, $J=7$ Hz, ester-CH_2–) 3.14 (t, 2H, $J=7$ Hz, –CH_2–), 1.76 (m, 2H, –CH_2–), 1.41 (t, 3H, $J=7$ Hz, ester-CH_3) and 1.00 (t, 3H, $J=7$ Hz, –CH_3) ppm. This ^1H NMR spectral data is consistent with that reported in the literature.[19]

3.1.8. 6-Phenylpyridine-2,5-dicarboxylic acid 5-ethyl ester and ethyl 2-phenylpyridine-3-carboxylate. To a solution of diethyl 6-phenylpyridine-2,5-dicarboxylate **6d** (0.3 g, 1.00 mmol) in ethanol (20 mL) was added a solution of KOH (0.12 g, 1.00 mmol, in 2 mL of water) and the mixture was stirred at room temperature for 3 h. The pH was then adjusted to 1 and the mixture was extracted with dichloromethane (25 mL), washed with water (2×5 mL) and evaporated to give the 6-phenylpyridine-2,5-dicarboxylic acid 5-ethyl ester as a brown oil (0.22 g, 81%). ^1H NMR: ($CDCl_3$) δ 8.32 (d, 1H, $J=8$ Hz, py-*H*), 8.27 (d, 1H, $J=8$ Hz, py-*H*), 7.53–7.48 (m, 5H, Ph-*H*), 4.20 (q, 2H, $J=7$ Hz, ester-CH_2–) and 1.08 (t, 3H, $J=7$ Hz, ester-CH_3) ppm. 6-Phenylpyridine-2,5-dicarboxylic acid 5-ethyl ester (0.22 g, 0.81 mmol) was placed in a round bottom flask and heated gently by means of a Bunsen burner for 2 min. The resulting distillate was collected giving ethyl 2-phenyl-pyridine-3-carboxylate as a brown oil (0.08 g, 42%). ^1H NMR: ($CDCl_3$) δ 8.76 (dd, 1H, $J=5$, 2 Hz, py-*H*), 8.10 (dd, 1H, $J=8$, 2 Hz, py-*H*), 7.50–7.54 (m, 2H, Ph-*H*), 7.40–7.44 (m, 3H, Ph-*H*), 7.34 (dd, 1H, $J=8$, 5 Hz, py-*H*), 4.14 (q, 2H, $J=7$ Hz, ester-CH_2–) and 1.04 (t, 3H, $J=7$ Hz, ester-CH_3) ppm. This ^1H NMR spectral data is consistent with that reported in the literature.[20]

3.2. Synthesis of bipyridine derivatives 6e–g. General method

To a stirred solution of amidrazone **1b**[17] (0.5 g, 3.68 mmol) in ethanol (15 mL) was added appropriate α,β-diketoester **2**[18] (3.38 mmol) and 2,5-norbornadiene **5** (3.46 g, 36.8 mmol). This solution was heated at reflux under an atmosphere of nitrogen for 20 h, allowed to cool to room temperature, and evaporated under reduced pressure giving the crude product which was purified by column chromatography over silica gel.

3.2.1. Ethyl 6-propyl-2,2′-bipyridine-5-carboxylate 6e. This compound was obtained as an orange oil (81%) (eluent: ethyl acetate/petroleum ether bp 60–80 °C 1:1). ν_{max} (KBr): 1718, 1252 and 1093 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.70 (dd, 1H, $J=5$, 2 Hz, py-*H*), 8.52 (d, 1H, $J=8$ Hz, py-*H*), 8.28 (s, 2H, py-*H*), 7.84 (dt, 1H, $J=8$, 2 Hz, py-*H*), 7.33 (m, 1H, py-*H*), 4.40 (q, 2H, $J=7$ Hz, ester-CH_2–), 3.22 (m, 2H, –CH_2–), 1.83 (sextet, 2H, $J=7$ Hz, –CH_2–), 1.43 (t, 3H, $J=7$ Hz, ester-CH_3) and 1.04 (t, 3H, $J=7$ Hz, –CH_3) ppm, HRMS (CI): calcd for $C_{16}H_{19}N_2O_2$ (M+H) 271.1446, found 271.1443.

3.2.2. Ethyl 6-isopropyl-2,2′-bipyridinyl-5-carboxylate 6f. This compound was obtained as an orange waxy solid (80%), mp 66–70 °C, (eluent: ethyl acetate/petroleum ether bp 60–80 °C 1:1). ^1H NMR: ($CDCl_3$) δ 8.69 (d, 1H, $J=5$ Hz, py-*H*), 8.59 (d, 1H, $J=8$ Hz, py-*H*), 8.28 (d, 1H,

$J=8$ Hz, py-*H*), 8.20 (d, 1H, $J=8$ Hz, py-*H*), 7.85 (t, 1H, $J=8$ Hz, py-*H*), 7.32 (m, 1H, py-*H*), 4.40 (q, 2H, $J=7$ Hz, ester-CH_2–) 3.93 (septet, 1H, $J=7$ Hz, –C*H*–), 1.42 (t, $J=7$ Hz, ester-CH_3) and 1.38 (d, 6H, $J=7$ Hz, 2×isopropyl-CH_3) ppm, HRMS (CI): calcd for $C_{16}H_{19}N_2O_2$ (M+H) 271.1446, found 271.1445.

3.2.3. Ethyl 6-phenyl-2,2′-bipyridine-5-carboxylate 6g. This compound was obtained as an orange oil (87%) (eluent: ethyl acetate/petroleum ether bp 60–80 °C 6:4). ν_{max} (KBr): 1717, 1250 and 1092 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 8.70 (ddd, 1H, $J=5$, 2, 1 Hz, py-*H*), 8.57 (dd, 1H, $J=7$, 2 Hz, py-*H*), 8.45 (d, 1H, $J=8$ Hz, py-*H*), 8.23 (d, 1H, $J=8$ Hz, py-*H*), 7.8 (dt, 1H, $J=8$ Hz, py-*H*), 7.67–7.63 (m, 1H, Ph-*H*), 7.49–7.43 (m, 4H, Ph-*H*), 7.33 (m, 1H, py-*H*), 4.40 (q, 2H, $J=7$ Hz, –CH_2–) and 1.09 (t, 3H, $J=7$ Hz, –CH_3) ppm, HRMS (CI): calcd for $C_{19}H_{16}N_2O_2$ (M+H) 305.1290, found 305.1289.

Acknowledgements

We thank Seal Sands Chemicals Ltd. for generous financial support and the EPSRC mass spectrometry service for high resolution mass spectra.

References and notes

1. (a) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523–1526. (b) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682–1683. (c) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331–8334. (d) Bagley, M. C.; Hughes, D. D.; Sabo, H. M.; Taylor, P. H.; Xiong, X. *Synlett* **2003**, 1443–1446.
2. (a) Constable, E. C.; Steel, P. J. *Coord. Chem. Rev.* **1989**, *93*, 205–223. (b) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553–3590.
3. (a) Lawrence, D. S.; Jiang, T.; Levett, M. *Chem. Rev.* **1995**, *95*, 2229–2260. (b) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2003**, 235–254. (c) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87–95.
4. Sun, L.; Hammarström, L.; Åkermark, B.; Styring, S. *Chem. Soc. Rev.* **2001**, *30*, 36–49.
5. Keefe, M. H.; Benkstein, K. D.; Hupp, J. T. *Coord. Chem. Rev.* **2000**, *205*, 201–228.
6. Maury, O.; Guégan, J.-P.; Renouard, T.; Hilton, A.; Dupau, P.; Sandon, N.; Toupet, L.; Le Bozec, H. *New. J. Chem.* **2001**, *25*, 1553–1566.
7. (a) Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kočovskú, P. *Organometallics* **2001**, *20*, 673–690. (b) Puglisi, A.; Benaglia, M.; Annunziata, R.; Bologna, A. *Tetrahedron Lett.* **2003**, *44*, 2947–2951. (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831–1842. (d) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teply, F.; Meghani, P.; Kočovskú, P. *J. Org. Chem.* **2003**, *68*, 4727–4742.
8. (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138. (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939.
9. Neunhoeffer, H.; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; *Comprehensive Heterocyclic Chemistry II*; Vol. 6. Pergamon: New York; 1996. p. 507–573. Chapter 6.11 and references therein.
10. (a) Pabst, G. R.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 6687–6690. (b) Pabst, G. R.; Schmid, K.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 6691–6694. (c) Pabst, G. R.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8817–8820. (d) Pfüller, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8821–8824. (e) Pabst, G. R.; Pfüller, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8825–8828. (f) Pabst, G. R.; Pfüller, O. C.; Sauer, J. *Tetrahedron* **1999**, *55*, 8045–8064.
11. (a) Rykowski, A.; Branowska, D.; Kielak, J. *Tetrahedron Lett.* **2000**, *41*, 3657–3659. (b) Branowska, D.; Rykowski, A. *Synlett* **2002**, 1892–1894. (c) Branowska, D.; Kielak, J. *Pol. J. Chem.* **2003**, *77*, 1149–1155. (d) Kozhevnikov, D. M.; Kozhevnikov, V. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. N.; Neunhoeffer, H. *Mendeleev Commun.* **2002**, 30–32. (e) Raw, S. A.; Taylor, R. J. K. *Chem. Commun.* **2004**, 508–509.
12. Sagi, M.; Wada, K.; Konno, S.; Yamanaka, H. *Heterocycles* **1990**, *30*, 1009–1021.
13. Ohsumi, T.; Neunhoeffer, H. *Tetrahedron* **1992**, *48*, 651–662.
14. Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257–3269.
15. Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 668–679.
16. Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623–2625.
17. Case, F. H. *J. Org. Chem.* **1965**, *30*, 931–933.
18. The α,β-diketoesters **2** were prepared from their commercially available β-ketoesters ($R^2COCH_2CO_2Et$) by a diazo-transfer reaction giving the corresponding diazocompounds [$R^2COC(N_2)CO_2Et$] and subsequent treatment of these diazo-compounds with ^{t}BuOCl. For example, see: Detering, J.; Martin, H.-D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 695–698.
19. Jørgensen, A. S.; Jacobsen, P.; Christiansen, L. B.; Bury, P. S.; Kanstrup, A. PCT Int. Appl. WO 98 55,483; *Chem. Abstr.* **1999**, *130*, 52323e. We thank Dr Jørgensen for providing us with ^1H NMR spectral data of ethyl 2-propylnicotinate.
20. Yamauchi, M.; Shirota, M.; Tsugane, A. *J. Heterocycl. Chem.* **1997**, *34*, 93–96.
21. Rocha Gonsalves, A. M.d'A.; Pinho e Melo, T. M. V. D.; Gilchrist, T. L. *Tetrahedron* **1993**, *49*, 5277–5290.
22. Calculations were performed using 'Hyperchem' software (HyperChem™, Hyypercube Inc., 1115 NW 4th Street, Gainesville, Florida 32601-4256, USA). An initial geometry optimisation was carried out using the MM^+ molecular mechanics program and the resulting structures were then geometry optimised using the semi-empirical PM3 RHF method. The molecular orbitals' energies and coefficients were determined from the geometry optimised structures.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8899–8912

Synthesis of annulated dioxins as electron-rich donors for cation radical salts

Jonas Hellberg,* Emma Dahlstedt and Margit E. Pelcman

Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

Received 23 January 2004; revised 16 June 2004; accepted 8 July 2004

Available online 18 August 2004

Abstract—The synthesis of a series of new alkoxylated linearly annulated dioxins is described together with their cyclic voltammetric behavior and some preliminary result on their ability to form cation radical salts. Of these dioxins, seven (**8**, **12**, **19**, **21**, **27**, **33**, **34**) are the first representatives of entirely new heterocyclic systems. Dioxins **8**, **21**, **22** and **27** gave good quality cation radical salts upon electrocrystallization.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

In the field of organic electroactive materials, many different interesting applications can be envisaged and realized with slight alterations in the molecular structure. By designing and substituting the constituting π-system, properties like solubility, crystallinity, intramolecular π-overlap etc can be manipulated.

Low crystallinity together with high charge carrier mobility is a prerequisite for obtaining LED-characteristics. A good solubility together with large π-overlap is needed to get a good candidate for liquid phase processable materials for field-effect transistors.[1]

We have previously presented alkoxylated dibenzofurans[2] and naphthalenes[3] as donors for cation radical salts. These systems have in general generated interesting results, although conductivities have been modest and electron–electron repulsion high. ESR-signals have on the other hand been very narrow and intense, indicative of a high stability of the cation radical, a low spin–orbit coupling due to the presence of only lighter elements (C, H, O), and a good charge-carrier mobility because of regular π-stacking.

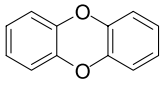
In order to reduce the electron–electron repulsion one must enlarge the communicative π-system (keep it planar), but one side effect is that the system usually gets more insoluble and therefore less useful.

We anticipated that a possible solution to this problem was to use annulated benzodioxins as the core π-system.

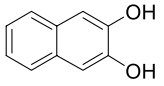
Dibenzodioxin **1** is a heterocyclic system whose halogenated derivatives form a notorious class of compounds, infamous for their ecotoxicity. Less is known about more electron-rich derivatives, although the stability of the corresponding cation radicals had been noted quite early.[4] This stability and the planarity of the dibenzodioxin[5] system prompted us to synthesize a series of substituted dibenzodioxins for evaluation of this class of compounds as potential donors for cation radical salts and as candidates for the active electrolyte in field-effect transistors. We were also encouraged by initial calculations,[6] that showed that dibenzodioxins should be more flexible than the corresponding anthracenes, thereby making them more soluble and easier to study.

Furthermore, recent interest in pharmacological applications of dihydrodioxins[7] and dibenzodioxins[8] should render the synthesis of these products interest to a larger audience.

We have previously published a preliminary report on these systems[9] and now want to present more results on our synthetic efforts in this project.



1



2

2. Results and discussion

Published syntheses of dibenzodioxins are either aimed at preparing electron-poor halogenated structures[10] or use

Keywords: Dioxines; Dibenzodioxines; Cyclovoltammetry.
* Corresponding author. Tel.: +4687908127; fax: +4687912333; e-mail: jhel@kth.se

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.017

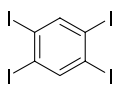
carcinogenic hexamethylphosphoramide (HMPA) as solvent.[11] Low yields are common when the substrate is not activated towards nucleophilic aromatic substitution.[12]

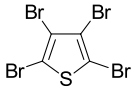
Our first strategy is based on the use of 2,3-dihydroxynaphthalene **2** as a nucleophile in a modification of the Ullmann ether synthesis.[13] Diiodinated electrophiles were readily available by Suzuki iodination[14] or the corresponding dibromo-derivatives by bromination with bromine in dichloromethane. We chose 1,3-dimethyl-3,4,5,6-tetrahydro2(1*H*)-pyrimidinone (DMPU) as a non-carcinogenic alternative to HMPA and copper(I) iodide as catalyst. No optimizations were made for each substrate. The yields and structures of dioxins **8**-**12** prepared from the diiodinated electrophiles are given in Table 1 and the corresponding dioxins **11**, **12** and **19**-**22** from the dibrominated electrophiles in Table 2.

As seen from the tables a series of new annulated dioxins could be synthesized in low to modest yields.

Although this method is relatively inefficient, it provides a fast way into highly substituted pentacyclic dioxins. All of these (except dinaphthodioxin **9**) are new compounds, and structures **8**, **12**, **19**, **20** and **21** are representatives of entirely new heterocyclic systems. Both sterically demanding and very electron-rich electrophiles (like **5** and **6**) can be forced to react under this protocol. We could not identify any clear difference between diiodinated or dibrominated electrophiles in terms of yield.

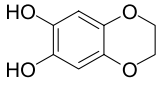
Attempts to make a fourfold etherification with substrates like 1,2,4,5-tetraiodobenzene **23** or 2,3,4,5-tetrabromothiophene **24** were unsuccessful.

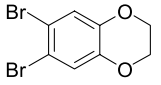

23


24

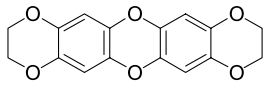
Although useful, 2,3-naphthalenediol (**2**) as the nucleophilic part is limiting the target structure to a napththodioxin, rendering all these donors a limited solubility and an 'unused' side for substitution. We therefore wished to explore the possibility of using other nucleophiles in the reaction protocol used for 2,3-naphthalenediol **2**.

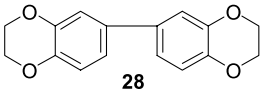
Unfortunately, we were unsuccessful when applying this procedure with nucleophiles other than 2,3-dihydroxynaphthalene (**2**). Thus, 6,7-dihydroxybenzo-1,4-dioxane **25** failed to react with 2,3-diiodonaphthalene (**4**) and also with both 6,7-dibromo or 6,7-diiodobenzo-1,4-dioxane (**26** and **3** respectively).

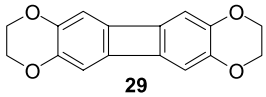

25


26

The latter reaction should have given access to a very interesting, symmetrical and electron-rich tri-dioxin **27**, that we envisaged to have interesting properties.

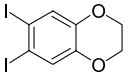
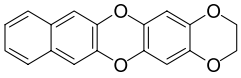
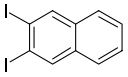
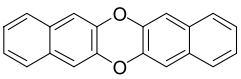
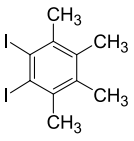
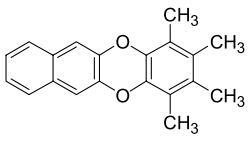
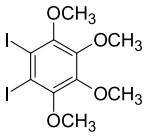
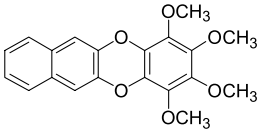
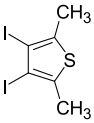
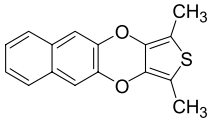

27


28


29

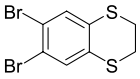
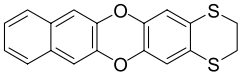
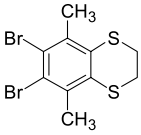
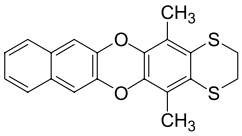
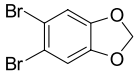
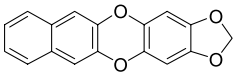
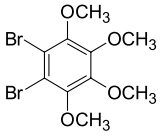
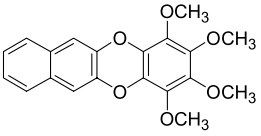
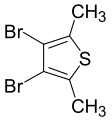
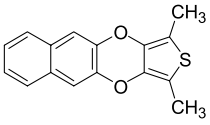
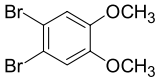
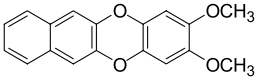
However, the only products that we could find in the reaction mixture had spectroscopic properties indicating

Table 1. Products **8**-**12** yielded from reaction of 2,3-dihydoxynaphthalene (**2**) with various diiodinated electrophiles[a]

Electrophile		Product		Yield (%)
	**3**		**8**	8
	**4**		**9**	25
	**5**		**10**	21
	**6**		**11**	2
	**7**		**12**	9

[a] The reaction was conducted in anoxic conditions.

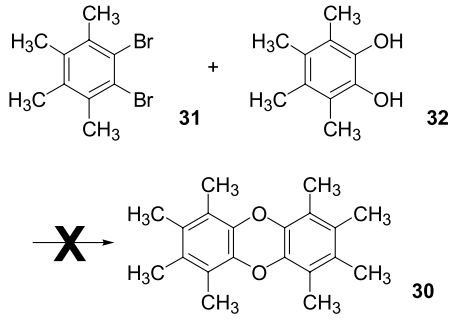
Table 2. Products **11**, **12** and **19**-**22** yielded from reaction of 2,3-dihydoxy-naphthalene (**2**) with various dibrominated electrophiles[a]

Electrophile		Product		Yield (%)
	**13**		**19**	34
	**14**		**20**	8
	**15**		**21**	4
	**16**		**11**	1
	**17**		**12**	9
	**18**		**13**	43

[a] The reaction was conducted in anoxic conditions.

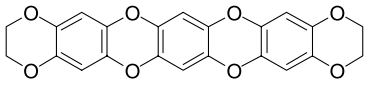
mainly dimer of benzo(1,4)dioxane, **28**, and traces of the biphenylene structure **29**.

Similarly unsuccessful was the attempt to synthesize the permethylated dibenzodioxin **30**, from dibromoprehnitene **31** and dihydroxyprehnitene **32** (Scheme 1).

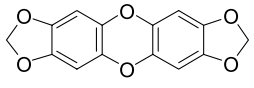


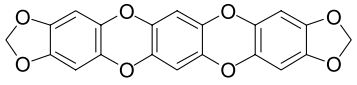
Scheme 1. Unsuccessful attempt to prepare compound **30**.

The results gained so far clearly showed that we needed heavier chalcogen substitution to get more electron-rich and thereby more easily oxidized donors. There was also an obvious need to alter the nucleophile to be able to synthesize dioxins other than ones with naphthalene substitution, since this substitution pattern led to more insoluble donor structures. Furthermore, we wished to synthesize both electron-rich and symmetrical structures since these reduce the risk for structural disorder in the solid state.

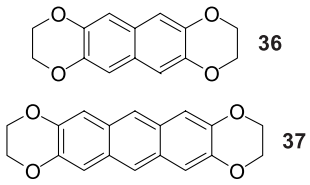


Inspired by the results so far we set up a new series of target molecules. We chose the highly symmetric tri-dioxin **27** and its higher homologue tetra-dioxin **33** as the prime targets.



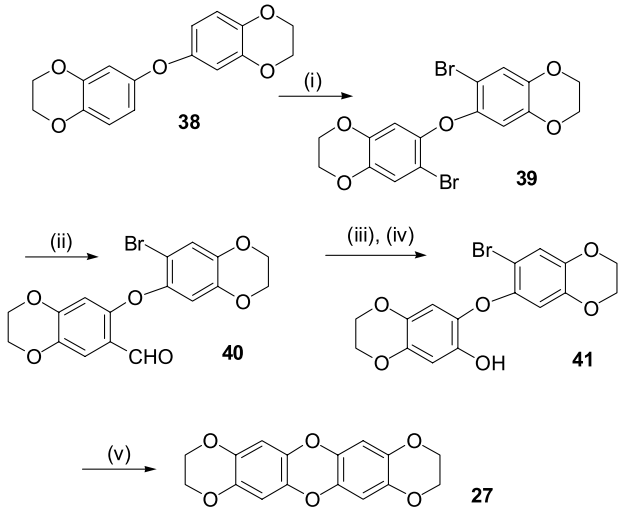


The ethylenedioxo substitution is often a good compromise between donating ability and steric demand. In comparison the methoxy group lowers the oxidation potential more effectively, but prevents good stacking of the π-donors in the cation radical salt, due to its relatively unrestricted rotation of the methoxy group. The methylenedioxy group is even less sterically demanding and has been shown to provide possibilities for hydrogen-bonding in the solid state.[15] Compounds **34** and **35** were therefore also included as target structures as a valuable isomer that should be possible to synthesize by the methodology we developed for the ethylenedioxy-analogues.



If our hypothesis was right, these structures should be both soluble and have a comparably low oxidation potential as well as a lower separation between the first and second half-wave in their cyclic voltammograms. In order to effectively compare the effect of one dioxin moiety inserted into the linear acene, we decided to synthesize the corresponding bis(dihydrodioxino)-substituted naphthalene and anthracene (**36** and **37**) respectively.

The first goal was the elusive tri-dioxin **27**. The synthesis is shown in Scheme 2.

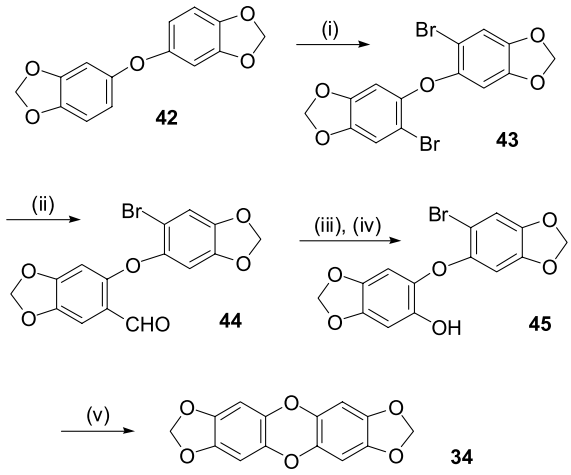


Scheme 2. Reagents and conditions: (i) Br_2, CH_2Cl_2, rt, 94% (ii) *n*-BuLi, THF, −70 °C, DMF, 49% (iii) MCPBA, CH_2Cl_2, reflux, 84% (iv) KOH, MeOH, rt, quant. (v) NaH, Cu(I)I, DMPU, 140 °C 31%.

The corresponding diaryl ether of benzodioxane, (or 6,6′-oxybis[2,3-dihydroyl-1,4-benzodioxin]) **38** could be conveniently dibrominated to give compound **39** in 94% yield. Monolithiation with n-butyllithium in THF and quenching with DMF gave the monoaldehyde **40** in 49% yield after chromatography. Bayer–Villiger oxidation with MCPBA gave the formate in 84% yield, which was hydrolyzed without purification in quantitative yield to the corresponding phenol **41**.

When treated with our standard Ullmann conditions we could isolate the target tri-dioxin **27** in 42% yield.

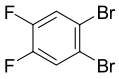
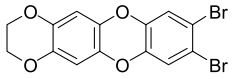
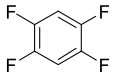
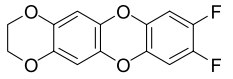
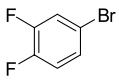
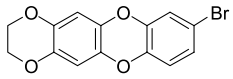
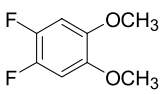
Analogously, we could synthesize the dioxolo-derivative **34** from the corresponding diaryl ether **42** in five steps and 14% yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) Br_2, CH_2Cl_2, rt, quant. (ii) *n*-BuLi, THF, −70 °C, DMF, 47% (iii) MCPBA, CH_2Cl_2, reflux, quant (iv) KOH, MeOH, rt, 86% (v) NaH, Cu(I)I, DMPU, 140 °C, 36%.

Although successful for the construction of the pentacyclic structures **27** and **34**, we thought that this stepwise procedure would be impractical when constructing the higher homologues, and decided therefore to adopt another strategy for these structures. We envisaged that aromatic nucleophilic substitution could be useful in the construction of these systems and that proved to be correct. The results are shown in Table 3.

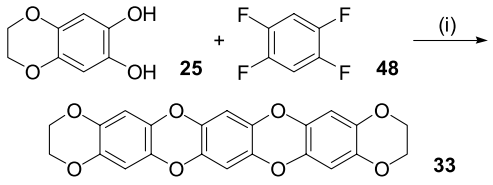
Table 3. Products **47**, **49** and **51** yielded from reaction[a] of 6,7-dihydroxy-benzo-1,4-dioxane (**25**) with some electrophiles

Electrophile		Product		Yield (%)
	**46**		**47**	Quant.
	**48**		**49**	72
	**50**		**51**	43
	**52**	No reaction		—

[a] Reactants and conditions: NaH, DMPU, 140 °C.

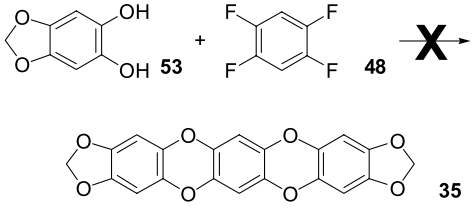
Reaction of 6,7-dihydroxybenzo-1,4-dioxane **25** with 1,2-dibromo-4,5-difluorobenzene **46** proceeded smoothly to give a quantitative yield of the dibrominated dibenzodioxin **47**, a reaction that nicely demonstrates the difference in reactivity of the halogen substituents. Analogously the difluorodibenzodioxin **49** could be synthesized in useful yields from 6,7-dihydroxybenzo-1,4-dioxane **25** and 1,2,4,5-tetrafluorobenzene **48**. However, when we used 4,5-difluorobromobenzene **50** for this reaction, we could isolate the monobromodibenzodioxin **51** in a modest 43% yield, and 4,5-difluoroveratrol **52** was completely unreactive under these conditions, once again showing the importance of the para-substituents influence on the reactivity.

By replacing the DMPU with N-methylpyrrolidinone (NMP), increasing the temperature to 205 °C, and using 2 equiv. of 6,7-dihydroxybenzo-1,4-dioxane (**25**) versus 1,2,4,5-tetrafluorobenzene (**48**), we could perform a fourfold aromatic nucleophilic substitution, and isolate the higher homologous tetra-dioxin **33** in 81% yield (Scheme 4).



Scheme 4. Reagents and conditions: (i) NaH, NMP, 205 °C, 81%.

In accordance with our expectations, product **33** was rather soluble, although being a linear heptacycle; for example, ^{1}H NMR could be recorded in deuterated chloroform without any problem. Surprisingly enough, extension of this protocol to the analogous dioxolo-derivative **35** was not successful (Scheme 5).

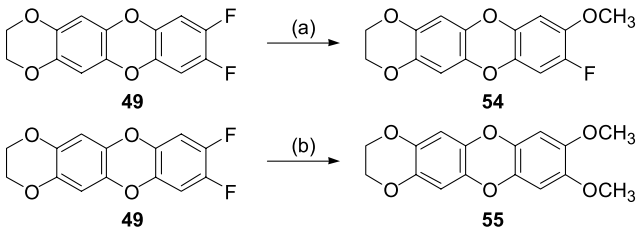


Scheme 5. Reagents and conditions: (i) NaH, NMP, 205 °C.

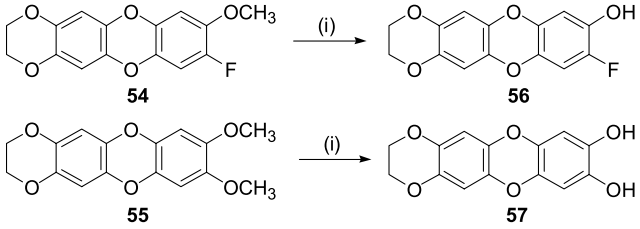
We then investigated the application of this methodology for the higher analogues of linear benzodioxins.

Selective methoxylation of the difluoro-derivative **49** to either the fluoromethoxy- or the dimethoxy-analogue (**54** and **55**) proceeded in useful yields, 81 and 63%, respectively (Scheme 6).

These could then be conveniently demethylated using the boron tribromide dimethylsulfide complex,[16] yielding the corresponding phenols (**56** and **57**) in 93 and 86% respectively (Scheme 7).



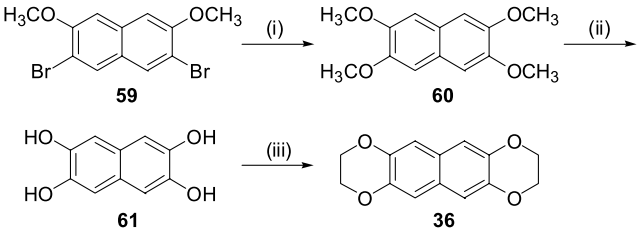
Scheme 6. Reagents and conditions: (a) NaOMe (1.1 equiv.), NMP, 90 °C, 83% (b) NaOMe (4 equiv.), NMP, 140 °C, 61%.



Scheme 7. Reagents and conditions: (i) $BBr_3(CH_3)_2S$, 1,2-dichloroethane, reflux. 93 and 86% respectively.

Our attempts to synthesize longer homologues of **33** have so far been unsuccessful. All attempts to dimerize **56** under basic conditions, or **57** under acidic conditions failed. Also, much to our disappointment, the dihydroxyderivative **58** seemed to be more or less useless as a nucleophile; all attempts to react this compound with 1,2-dibromo-4,5-difluorobenzene, or even iodomethane, failed.[17] Similarly, all attempts to substitute the dibromodibenzodioxin **47** were unsuccessful or, as in the case of methoxylation, less rewarding than the corresponding reactions for the fluoro-derivative **49**.

Bis(dihydrodioxino)naphthalene **36** could be synthesized from commercially available 2,7-dihydroxynaphthalene via 2,7-dibromo-3,6-dimethoxynaphthalene (**59**) (Scheme 8). Methoxylation of 2,7-dibromo-3,6-dimethoxynaphthalene[18] (**59**) with sodium methoxide in the presence of copper(I) iodide in DMF gave 2,3,6,7-tetramethoxynaphthalene[19] (**60**) in up to 80% yield. By refluxing 2,3,6,7-tetramethoxy-naphthalene in concentrated hydrobromic acid in the presence of a catalytical amount of tetra-*n*-butylammonium bromide,[20] a fourfold demethylation occured to give 2,3,6,7-tetrahydroxynaphthalene (**61**) in quantitative yield. 2,3,6,7-tetrahydroxynaphthalene was used immediately in the next step without further purification. 2,3,6,7-Tetra-hydroxynaphthalene **61** seemed to be quite unstable, since the primary off-white material turned green and then

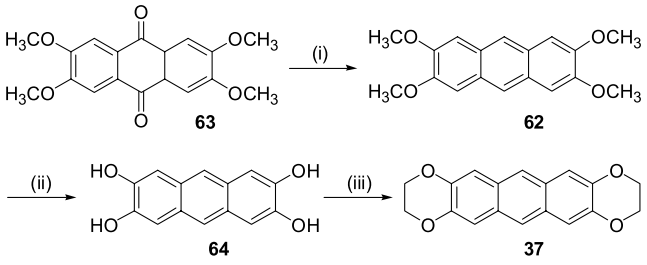


Scheme 8. Reagents and conditions: (i) NaOMe, Cu(I)I, DMF, 64% (ii) conc. HBr, n-Bu_4NBr, reflux, quant (iii) 1-chloro-2-bromoethane, K_2CO_3, DMSO, 100 °C 23%.

darkened further within minutes when exposed to ambient laboratory atmosphere.

Treatment of 2,3,6,7-tetrahydroxynaphthalene **61** with 1-chloro-2-bromoethane in DMSO in the presence of potassium carbonate gave the desired 2,3,6,7-bis(ethylenedioxy)-naphthalene **36** in 23% yield.

The 2,3,6,7-bis(ethylenedioxy)-anthracene **37** was prepared from 2,3,6,7-tetramethoxyanthracene **62**, which was synthesized from the corresponding anthraquinone **63**[21] by reduction with tetra-*n*-butylammonium borohydride/iodomethane (Scheme 9). Demethylation of 2,3,6,7-tetramethoxyanthracene **62** yielded 2,3,6,7-tetrahydroxy-anthracene **64** in 85% and subsequent fourfold alkylation then gave the desired compound **37**.[22]



Scheme 9. Reagents and conditions: (i) *n*-Bu_4NBH_4, CH_3I; (ii) conc. HBr, *n*-Bu_4NBr, reflux; (iii) 1-chloro-2-bromo-ethane, K_2CO_3, DMSO, 100 °C.

2.1. Cyclic voltammetry

All compounds except **9** and **36** showed one quasi-reversible oxidation–reduction couple (Table 4).

Table 4. Cyclic voltammetric results from synthesized dibenzodioxins[a]

Compound	$E^{1/2}$	Compound	$E^{1/2}$
8	1.12	**22**	1.02
9	>1.6	**27**	0.93
10	1.24	**33**	1.03
11	1.24	**34**	0.93
12	1.46	**36**	1.35
19	1.14	**37**[b]	1.08
20	1.05	**60**	1.08
21	1.04	**62**	0.83

[a] 1 mM in $TBAPF_6$ (0.15 M) CH_2Cl_2, scan rate 100 mV/s, E versus SCE.
[b] 1 mM in $TBABF_4$ (0.15 M) CH_2Cl_2, scan rate 100 mV/s, E versus SCE.

Several features are noteworthy. The bis-alkoxysubstituted dibenzodioxins **27** and **34** have the lowest oxidation potentials, as could be expected but the mono-annulated (**8**, **20**, **21**, **22**) derivatives were only roughly 100 mV higher.

Also apparent is the inefficiency of more than two methoxy substituents in lowering the oxidation potential; donor **11** has an oxidation potential 200 mV higher than **22**.

The addition of one more benzodioxin unit is not lowering the oxidation potential, as seen by the comparison between **27** and **33**. The interpretation of the cyclic voltammetry of **33** is not trivial since the rather low solubility makes comparison difficult, so we cannot rule out that the oxidation potential at 1.03 V is a two-electron process, but we have no reasons to believe this. Furthermore, it is also evident that the dibenzodioxin core is a better donor than the corresponding anthracene (**27** and **37**). The hypothesis that longer π-systems should give lower electron–electron repulsion is however not supported by the current CV-data.

2.2. Electrocrystallization

Some of the target dioxins were tested as donors to cation radical salts in a constant current electrolysis in a divided cell.

Donors **9**, **10**, **11**, **12**, and **19** did not yield any cation radical salts under these conditions. This is perhaps not surprising in the case of **9**, since it is either very insoluble or very hard to oxidize. In the case of **10**, **11** and **12**, they are substituted with steric demanding substituents that should make precipitation less favorable. In these cases we did observe a strongly colored solution under electrolysis, which supports the hypothesis that the cation radicals of these donors are too soluble under these conditions. Electrolysis in a freezer did not improve the situation for donor **10**.

Donors **33** and **36** gave to our disappointment only polycrystalline materials that were difficult to analyze.

More rewarding was the electrolysis of donors **8**, **21**, **22** and **27**. Well-formed crystals with the composition $(\mathbf{8})_2AsF_6$ (2:1-salt), $(\mathbf{21})AsF_6$ (1:1-salt), and $(\mathbf{27})_2AsF_6$, $(\mathbf{27})_2PF_6$, $(\mathbf{27})_2ClO_4$, (2:1-salts), could be harvested after approximately one week of electrolysis. The dimethoxy-substituted donor **22** formed a non-stoicheometric salt with AsF_6, with a donor equivalent of 1.1–1.2.

The salt $(\mathbf{8})_2AsF_6$ is a semiconductor with a room temperature conductivity of $\approx 6\times10^{-3}$ S/cm and a very high number of spins as measured by ESR (0.25 spins/molecular unit). Details of the solid-state properties of these salts will be published elsewhere.

The results from the cyclovoltammetry and electrolysis experiments clearly show the superiority of the ethylenedioxy substituent as a good compromise between donor strength and good crystallinity through low steric demands.

2.3. Other applications

An unforeseen application for the symmetric dioxins **27** and **33** as substrates in matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS) has also been investigated. The dioxins combination of robust MS-properties (low fragmentation) and electroactivity render them with interesting properties, and make them useful as substrates for sensitizing other low molecular weight compounds, which are otherwise impossible to analyze with standard techniques.[23]

Linear acenes like pentacene have been demonstrated to work as an active component in field-effect transistors.[24] We are now pursuing experiments to establish whether our longer dioxins could work in these applications as well,

albeit being more soluble. Results of this work will be published in due course.

3. Conclusion

We have synthesized a series of new alkoxylated dibenzodioxin donors. Several of these are the first representatives of entirely new heterocyclic systems. The more alkoxy-substituted donors have half-wave potential in the range 0.9–1.0 V versus SCE which characterizes them as good to fair electron donors. The dioxins are more soluble than the corresponding all-carbon acenes. We have also demonstrated that good quality cation radical salts can be synthesized from dibenzodioxins, especially those with ethylenedioxy-substitution. However, the longer derivatives do not show any promising properties in terms of the results achieved from cyclovoltammetry and electrocrystallization.

4. Experimental

4.1. General

All operations except where indicated were performed in ambient atmosphere, without any special care taken for the exclusion of air or moisture. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AM 400 and at 500 and 125 MHz, respectively, on a Bruker AM 500. Mass spectra were recorded on a Finnegan SSQ 7000 (electron impact). Elemental analyses were performed by Analytische Laboratorien GmbH, Germany. THF was freshly distilled from sodium benzophenone ketyl, and NMP and DMPU were dried over CaH_2. All other commercial reagents and solvents were used as received, without further purification. Melting points are uncorrected. Commercial compounds: **2**, **15**, **18**, **24**, **46**, **48**, **50** and **52**. Substances **4**,[25] **17**,[26] **23**,[27] **38** and **42**,[28] **59**[18] were prepared according to literature procedures. We have provided sufficient analytical data for all end-products to be unequivocally characterized, whereas some of the intermediates have in a few cases only been characterized by NMR.

4.1.1. 6,7-Diiodo-2,3-dihydrobenzo[1,4]dioxin 3. I_2 (17.74 g, 69.9 mmol) and H_5IO_6 (5.31 g, 23.3 mmol) were dissolved in a mixture of 100 mL HOAc, 10 mL H_2O and 5 mL conc. H_2SO_4. 1,4-benzodioxane (11.10 g, 81.5 mmol) was then added with stirring. The reaction flask was then sealed with a septum and heated to 50 °C overnight. After cooling to rt crystals were filtered off and dissolved in CH_2Cl_2. Addition of H_2O to the reaction mixture afforded more crystals. The aqueous phase was extracted with CH_2Cl_2 and the organic layers were combined, washed with H_2O, dried over $MgSO_4$ and the solvent was then evaporated yielding 27.78 g (82%) of sufficiently pure product **3**. Recrystallization from MeOH afforded 11.57 g (37%) analytically pure shiny crystals of **3**.

Mp=118.9–119.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.22 (s, 4H), 7.34 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=64.1, 96.1, 127.3, 144.2. MS (EI) *m/e* (%) 387.9 (M^+, 100).

4.1.2. Diodoprehnitene 5. I_2 (35.87 g, 141.3 mmol) and H_5IO_6 (10.73 g, 47.1 mmol) were dissolved in 500 mL of a mixture of HOAc, H_2O and conc. H_2SO_4 in the proportions of 100/20/3 respectively. 1,2,3,4-Tetramethylbenzene (22.13 g, 164.9 mmol) was then added under stirring. The flask was then sealed and heated to 50–55 °C overnight. After cooling to rt the crystals formed were collected by filtration, washed with hexane, and dried to give 51.10 g of NMR-pure crystalline material. An additional 7.35 g of semicrystalline material could be isolated from the reaction mixture by extractive methods, which could be recrystallized from EtOH to give 1.90 g of pure product as white crystals. The combined yield of **5** was 83%.

Mp=184–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.28 (s, 6H), 2.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=18.7, 31.7, 114.8, 135.7, 139.8. GC-MS (EI) *m/e* (%) 386 (M^+, 100).

4.1.3. Diiodo-1,2,3,4-tetramethoxybenzene 6. I_2 (7.61 g, 30.0 mmol) and H_5IO_6 (2.28 g, 10.0 mmol) were dissolved in 100 mL of a mixture of HOAc, H_2O and conc. H_2SO_4 in the proportions of 100/20/3 respectively. 1,2,3,4-Tetramethoxybenzene[29] (6.94 g, 35.0 mmol) was then added under stirring. The flask was then sealed and heated to 50–55 °C overnight. After cooling to rt the reaction mixture was separated between H_2O and CH_2Cl_2 the organic phase was then washed with additional H_2O, $NaHCO_3$ solution, $Na_2S_2O_3$ solution and finally brine. After drying over $MgSO_4$ and evaporation under reduced pressure, 12.86 g of **6** as a heavy oil could be isolated. Crystallization occurred after a few weeks, mp=29–30 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ=3.80, (s, 6H), 3.95, (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=60.7, 61.2, 99.5, 147.3, 151.0. GC-MS (EI) *m/e* (%) 450 (M^+, 100).

4.1.4. 3,4-Diiodo-2,5-dimethylthiophene 7. I_2 (19.39 g, 76.4 mmol) and H_5IO_6 (5.81 g, 25.5 mmol) were dissolved in 250 mL of a mixture of HOAc, H_2O and conc. H_2SO_4 in the proportions of 100/20/3 respectively. 2,5-dimethylthiophene (10.00 g, 89.1 mmol) was then added. The reaction was heated to 30 °C and stirred overnight. The reaction mixture was transferred to a separatory funnel and H_2O was added. The H_2O phase was extracted 4×300 mL with CH_2Cl_2. The organic phase was then washed with 500 mL H_2O, 4×500 mL $NaHCO_3$ solution and 500 mL $Na_2S_2O_3$ solution. After drying over $MgSO_4$ and evaporation under reduced pressure could the mayor part of the product be achieved by hot filtration from 200 mL EtOH. An additional amount of product was obtained from the filtrate of the hot filtration through crystallization overnight. The total yield was 15.70 g (48%) of slightly brown crystals.

R_f (hexane/CH_2Cl_2; 1:1)=0.55. Mp=77–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.50 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ=19.8, 93.4, 137.0. GC-MS (EI) *m/e* (%) 364 (M^+, 100).

4.1.5. 6,7-Dibromo-2,3-dihydrobenzo(1,4-dithiin) 13. 2,3-Dihyd-robenzo(1,4-dithiin)[30] (10.30 g, 61.2 mmol) was dissolved in 250 mL of CH_2Cl_2 and Br_2 (6.6 mL, 128.6 mmol) dissolved in 50 mL of CH_2Cl_2 was added

dropwise during 30 min. The mixture was allowed to stir for an additional 1 h, and then H_2O was added. The resulting mixture was transferred to a separatory funnel, the phases separated, and the organic phase was washed with an additional 200 mL of H_2O, 175 mL of $NaHCO_3$ solution, 200 mL of $Na_2S_2O_3$ solution, and finally with 200 mL of brine. The resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure, to yield 18.92 g (95%) of pink crystals with satisfactory NMR-purity. Further purification can be achieved by recrystallization from EtOH.

Mp = 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.25 (s, 4H, CH_2), 7.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 28.7, 120.4, 132.1, 132.4. GC-MS (EI) *m/e* (%) 326 (M^+ + 2, 100).

4.1.6. 5,8-Dimethyl-6,7-dibromo-2,3-dihydrobenzo(1,4-dithiin) 14. Commercially available 2,5-dimethylcyclohexanone (5.00 g, 39.6 mmol, isomeric mixture) was dissolved in 50 mL CH_2Cl_2 together with 1,2-ethanedithiol (3.32 mL, 39.6 mmol). Borontrifluoride etherate (0.73 mL, 5.9 mmol) was then cautiously added and the resulting solution was left on stirring at ambient temperature for 1 h, at which time TLC showed consumption of all starting ketone. The reaction was stopped by the addition of H_2O, the resulting phases were separated in a separatory funnel. The organic phase was washed with $NaHCO_3$ solution and with an additional portion of H_2O, dried over $MgSO_4$ and subsequently concentrated under reduced pressure to give 6.62 g (83%) of the corresponding ethylenedithioketal (6,9-dimethyl-1,4-dithiaspiro[4,5]-decane) as an oily material. Despite the complicated ^{1}H NMR due to the mixture of isomers, ^{13}C NMR showed no additional signals other than two sets of nine signals that could be attributed to two isomers of the desired product.

^{13}C NMR: major isomer: 18.07, 21.96, 32.50, 34.30, 34.50, 38.74, 39.87, 42.78, 54.30; minor isomer: 17.52, 22.14, 27.57, 31.90, 38.15, 39.17, 41.48, 45.76, 74.47.

We therefore decided to use these products directly in the following reaction. Thus the ethylenedithioketal (3.00 g, 9.9 mmol) was dissolved in 70 mL of CH_2Cl_2 and Br_2 (11.84 g, 74.1 mmol), dissolved in 20 mL of CH_2Cl_2 was added during 30 min. After addition the resulting dark solution was left under stirring for 1 h, brought to a brief reflux, and quenched with H_2O after cooling. The resulting mixture was transferred to a separatory funnel, phases separated, and the organic phase washed with an additional portion of H_2O, then $NaHCO_3$ solution, $Na_2S_2O_3$ solution, and finally with brine. The resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure, to yield 5.63 g of semicrystalline material. Recrystallization from EtOH yielded 5.00 g (95%) of slightly reddish crystals.

Mp = 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.58 (s, 6H), 3.24 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.8, 30.3, 124.7, 132.7, 135.5. GC-MS (EI) *m/e* (%) 354 (M^+ + 2, 100).

4.1.7. Dibromo-1,2,3,4-tetramethoxybenzene 16. 1,2,3,4-Tetra-methoxybenzene (5.71 g, 28.8 mmol) was dissolved in 50 mL of CH_2Cl_2 under stirring. Bromine (9.67 g, 60.5 mmol) in 50 mL CH_2Cl_2 was then added dropwise during 1 h. The resulting light brown mixture was transferred to a separatory funnel and washed with 200 mL of H_2O, 175 mL of $NaHCO_3$ solution, 200 mL of $Na_2S_2O_3$ solution, and finally with 200 mL of brine. The resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure, to give **16** in quantitative yield as a heavy oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.85 (s, 6H), 3.93 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 61.0, 61.4, 115.1, 147.2, 148.5. GC-MS (EI) *m/e* (%) 356 (M^+ + 2, 100).

Synthesis of dioxins **8**-**12** and **19**-**22**, general procedure: NaH (42.0 mmol, 60 or 80% oil dispersion) was cautiously added to 2,3-dihydroxynaphthalene, (**2**), (3.20 g, 20.0 mmol), dissolved in DMPU (200 mL) under nitrogen. After hydrogen evolution had ceased, Cu(I)I (7.62 g, 40.0 mmol) was added together with the appropriate dihaloaromatic electrophile (20.0 mmol). The resulting dark solution was warmed to 150 °C during 21 h and the bulk of the solvent was then distilled under pump vacuum. The tarry residue was treated with 2 M HCl, the precipitate filtered and dissolved in CH_2Cl_2 with the aid of an ultrasonic bath. This solution was once again filtered, the filtrate washed with 2 M NaOH, dried and evaporated. The crude product thus obtained was treated with EtOH from which the product precipitated. The product was submitted to gradient chromatography (hexane/CH_2Cl_2) which usually afforded NMR-pure material. An analytically pure sample was obtained after recrystallization from toluene:EtOH or sublimation (1.5×10^{-2} mbar).

4.1.8. Dioxin 8. Chromatography gave 505 mg (8%) of white crystals.

Mp > 260 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.23 (s, 4H, CH_2), 6.51 (s, 2H, CH), 7.21 (s, 2H, CH), 7.32 (m, 2H, CH), 7.63 (m, 2H, CH). ^{13}C NMR (DMSO-d_6) δ = 64.14 (OCH_2), 104.82 (C–H), 111.96 (C–H), 125.43 (C–H), 126.79 (C–H), 130.42 q, 134.54 q, 139.18 q, 140.90 q. MS (EI) *m/e* (%) 292.1 (M^+, 100).

Anal. Calcd for $C_{18}H_{12}O_4$: C, 73.96; H, 4.15. Found: C, 73.94; H, 4.20. Anal. Calcd for 2:1 salt of $(\mathbf{8})_2AsF_6$: C, 55.90; H, 3.13; F, 14.74. Found: C, 55.75; H, 3.07; F, 14.97.

4.1.9. Dioxin 9. The crude product was sublimed at 215 °C, which gave 1.40 g (25%) of grey crystals.

R_f (toluene) = 0.79. Mp > 230 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (s, 4H, CH), 7.36 (m, 4H, CH), 7.69 (m, 4H, CH). MS (EI) *m/e* (%) 284 (M^+, 100).

4.1.10. Dioxin 10. Chromatography yielded 1.23 g (21%) of white crystals.

R_f (hexane/CH_2Cl_2; 1:1) = 0.83. Mp = 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.16 (s, 6H,CH_3), 2.24 (s, 6H, CH_3), 7.27 (s, 2H, CH), 7.31 (m, 2H, CH), 7.63 (m, 2H,

CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=11.7, 15.7, 111.6, 121.1, 124.8, 126.6, 129.8, 130.7, 137.3, 142.4. MS (EI) *m/e* (%) 290 (M^+, 100). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.44; H, 6.34.

4.1.11. Dioxin 11. 106 mg (2%) of white crystals was achieved after chromatography.

R_f (CH_2Cl_2)=0.3. Mp=127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.91 (s, 6H, CH_3), 3.97 (s, 6H, CH_3), 7.34 (m, 2H, CH), 7.36 (s, 2H, CH), 7.66 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=61.8, 61.9, 112.4, 125.4, 126.8, 130.9, 132.4, 137.7, 141.0, 142.6. MS (EI) *m/e* (%) 354 (M^+, 53). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.78; H, 5.13. Found: C, 67.47; H, 5.25.

4.1.12. Dioxin 12. Chromatography yielded 463 mg (9%) of off-white crystals. This compound can also be recrystallized from EtOH to give beige needles.

R_f (hexane/CH_2Cl_2; 1:1)=0.54. Mp=159–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.30 (6H, s), 7.32–7.35 (4H, m), 7.66 (2H, dd, J=6.3, 3.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.6, 109.3, 112.4, 125.1, 126.7, 130.3, 134.3, 140.9. MS (EI) *m/e* (%) 268 (M^+, 100). Anal. Calcd for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.42; H, 4.50.

4.1.13. Dioxin 19. Chromatography yielded 2.21 g (34%) of white crystals.

R_f (hexane/CH_2Cl_2; 1:1)=0.43. Mp=233–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.24 (s, 4H, CH2), 6.82 (s, 2H, CH), 7.24 (s, 2H, CH), 7.33 (m, 2H, CH), 7.64 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=29.5, 112.2, 116.5, 125.3, 126.4, 126.8, 130.7, 139.5, 141.4. MS (EI) *m/e* (%) 324 (M^+, 100). Anal. Calcd for $C_{18}H_{12}O_2S_2$: C, 66.64; H, 3.74. Found: C, 66.45; H, 3.81.

4.1.14. Dioxin 20. Chromatography yielded 342 mg (8%) of white crystals.

Mp=195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.31 (s, 1H), 3.21 (s, 1H), 7.27 (s, 1H), 7.32 (dd, 2H, J=6.3, 3.3 Hz), 7.63 (dd, 2H, J=6.3, 3.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.0, 30.2, 111.9, 122.2, 125.1, 126.7, 127.0, 130.7, 137.5, 141.8. MS (EI) *m/e* (%) 352 (M^+, 100), 337 (10), 324 (20). Anal. Calcd for $C_{20}H_{16}O_2S_2$: C, 68.15; H, 4.58. Found: C, 67.96; H, 4.65.

4.1.15. Dioxin 21. Chromatography yielded 231 mg (4%) of off-white crystals.

R_f (hexane:CH_2Cl_2; 1:1)=0.51. Mp >240 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.92 (s, 2H, CH2), 6.52 (s, 2H, CH), 7.20 (s, 2H, CH), 7.32 (m, 2H, CH), 7.63 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=98.3, 101.5, 111.8, 126.7, 130.8, 135.6, 141.7, 143.0. MS (EI) *m/e* (%) 278 (M^+, 100). Anal. Calcd for $C_{17}H_{10}O_4$: C, 73.37; H, 3.63. Found: C, 73.60; H, 3.76. Anal. Calcd for (**21**)AsF_6: C, 43.70; H, 2.16. Found: C, 43.47; H, 2.06.

4.1.16. Dioxin 22. Chromatography yielded 2.54 g (43%) of white crystals.

R_f (hexane/CH_2Cl_2; 1:1)=0.53. Mp=156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.86 (s, 6H, CH_3), 6.56 (s, 2H, CH), 7.21 (s, 2H, CH), 7.33 (m, 2H, CH), 7.64 (m, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=56.3, 100.9, 111.8, 125.1, 126.6, 130.7, 134.3, 141.7, 144.8. MS (EI) *m/e* (%) 294 (M^+, 100). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.45; H, 4.80. Found: C, 73.43; H, 4.75.

4.1.17. 2,3-Dihydrobenzo[1,4]dioxin-6,7-diol 25. 1,4-Benzodioxane-6-carboxaldehyde (57.46 g, 0.35 mol) was dissolved in CH_2Cl_2 (1200 mL) and MCPBA (45.30 g, 0.525 mol, 50% in H_2O) was added to the solution, which was gently refluxed at 45 °C for 17 h and a yellow precipitate formed. The CH_2Cl_2 was evaporated and the residue was dissolved in EtOAc, washed with a saturated $NaHCO_3$ solution, followed by brine and then dried over $MgSO_4$. The solvent was evaporated yielding 55.3 g (88%) of formate as a red brown oil. This intermediate product was dissolved in MeOH and was hydrolyzed at rt for 45 min with a KOH solution (10% excess). The solution was neutralized with 2 M HCl and the aqueous phase was extracted with CH_2Cl_2, dried over $MgSO_4$ and evaporated to dryness yielding 39.7 g (85%) of 2,3-dihydrobenzo[1,4]dioxin-6-ol. 15 g of the crude product was submitted to chromatography on a silica gel column (hexane/EtOAc; 80:20), affording 10 g pure material as a brown oil and 4.5 g of material with some small impurities (overall yield of 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ=4.21 (m, 4H), 6.32 (dd, 1H, J=8.5, 2.7 Hz), 6.38 (d, 1H, J=2.7 Hz), 6.72 (d, 1H, J=8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ=64.1, 64.6, 104.3, 108.3, 117.6, 137.6, 143.8, 150.0.

To a solution of KH_2PO_4 (7.08 g, 52.0 mmol) in 450 mL H_2O, cooled on an ice-bath, $NO(KSO_3)_2$ (Fremy's salt) (50.00 g, 186.3 mmol) was added in portions under vigorous stirring. 2,3-dihydrobenzo[1,4]dioxin-6-ol (14.18 g, 93.2 mmol) was dissolved in 20 mL MeOH and added dropwise to the mixture during 25 min and was then left stirring on the ice-bath for a further 1 h. The red precipitate that formed was filtered, washed with H_2O and dried in a desiccator, yielding 2,3-dihydrobenzo[1,4]dioxin-6,7-dione in 10.99 g (71%) yield as orange crystals.

Mp=223–226 °C (lit. 232 °C[31]). ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.43 (s, 4H), 5.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=64.7, 108.6, 157.7, 179.2. MS (EI) *m/e* (%) 168.2 (M^++2,20) 166.2 (M^+, 10), 138.2 (100).

The 2,3-dihydrobenzo[1,4]dioxin-6,7-dione was suspended in 200 mL H_2O and reduced by addition of $Na_2S_2O_4$. The suspension was transferred to a separatory funnel and extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was evaporated yielding beige crystals of **25**, 9.23 g (75%).

Mp=173.5–174.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ=4.07 (s, 4H), 6.24 (s, 2H) 8.46 (s, 2H, −OH). ^{13}C NMR (100MHz, DMSO-d_6) δ=63.9, 104.2, 135.2, 139.2. MS (EI) *m/e* (%) 168.2 (M^+, 100).

4.1.18. 6,7-Dibromo-2,3-dihydrobenzo[1,4]dioxin 26. Br_2 (25.83 g, 161.6 mmol) dissolved in 50 mL CH_2Cl_2 was

added dropwise to 1,4-benzodioxane (10.00 g, 73.5 mmol) in 50 mL CH_2Cl_2. The reaction mixture was stirred at rt overnight. The precipitate that formed was dissolved in an additional amount of CH_2Cl_2 and extracted with H_2O, a $Na_2S_2O_3$ solution and finally brine. The organic phase was dried over $MgSO_4$ and the solvent evaporated, yielding white crystals of **26**, 19.42 g (90%).

Mp = 139.1–139.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.23 (s, 4H), 7.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 64.2, 115.1, 121.6, 143.5. MS (EI) *m/e* (%) 296.0 (50), 294.0 (M^+, 100), 292.0 (50).

4.1.19. Dibromoprehnitene 31. 1,2,3,4-Tetramethylbenzene (prehnitene, 53.66 g, 0.4 mol) was dissolved in 300 mL of CH_2Cl_2. Br_2 (41 mL, 0.8 mol) dissolved in 100 mL of CH_2Cl_2 was added under stirring during 1 h. The reaction mixture was then left stirring for an additional 1 h. Subsequently, H_2O was added to quench the reaction. The phases were separated in a separatory funnel, and the organic layer washed with a $NaHCO_3$ solution, H_2O, and finally brine. After drying over $MgSO_4$ the solution was concentrated under reduced pressure to give 84.90 g (73%) of NMR-pure **31** as white crystals.

Mp = 204–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.25 (s, 6H), 2.50 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 17.8, 22.7, 125.5, 135.4, 135.6. GC-MS (EI) *m/e* (%) 292 (M^+ + 2, 100).

4.1.20. Dihydroxyprehnitene 32. Sodium (4.72 g, 205.3 mmol) was added to 250 mL of dry MeOH. After completion of the reaction, anhydrous DMF (185 mL), Cu(I)I (6.50 g, 34.2 mmol), and dibromoprehnitene **31** (10.00 g, 34.2 mmol) was added. The temperature was raised to 120 °C and the reaction mixture was stirred under a reflux condenser during 14 h. The reaction mixture was then mixed with 250 mL 1 M HCl, and the resulting precipitate filtered off and washed with H_2O.

The resulting solids were dissolved in CH_2Cl_2, the resulting organic phase repeatedly washed with H_2O to remove remaining DMF, dried with $MgSO_4$ and concentrated under reduced pressure to give 6.02 g of crude dimethoxyprehnitene (1,2-dimethoxy-3,4,5,6-tetramethylbenzene) that could be used in the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.16 (s, 6H), 2.19 (s, 6H), 3.79 (s, 3H). MS (EI) *m/e* (%) 194 (M^+, 94).

1,2-Dimethoxy-3,4,5,6-tetramethylbenzene (5.80 g, 29.9 mmol) was dissolved in 60 mL of conc. HBr and tetra-*n*-butylammonium bromide (120 mg) was added. The resulting mixture was brought to reflux. After 3 h, the reaction mixture was poured onto an ice–H_2O mixture, and the resulting precipitate filtered off. The achieved solids were subjected to gradient chromatography (hexane/CH_2Cl_2/MeOH) to give 1.52 g of pure 1,2-dihydroxy-3,4,5,6-tetramethylbenzene **32** as off-white crystals.

Mp = 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.14 (s, 6H), 2.17 (s, 6H), 5.00 (broad s, 2H). MS (EI) *m/e* (%) 166 (M^+, 100).

4.1.21. Dibromodiarylether 39. Diaryl ether **38** (8.95 g, 31.2 mmol) was dissolved in 100 mL CH_2Cl_2 in a 250 mL three-necked round bottom flask. Br_2 (3.36 g, 65.6 mmol) dissolved in CH_2Cl_2 was added dropwise. The reaction was stirred at ambient temperature for 3.5 h and was then washed with 100 mL H_2O, 2×100 mL $NaHCO_3$, 100 mL brine and finally 100 mL $Na_2S_2O_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, to yield 12.90 g (94%) **39** as off-white crystals.

Mp = 151–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.22 (s, 8H, CH_2), 6.41 (s, 2H, CH), 7.11 (s, 2H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 64.1, 64.4, 104.5, 108.4, 121.2, 140.4, 143.3, 147.6. MS (EI) *m/e* (%) 445.9 (M^+ + 4, 45), 443.8 (M^+ + 2, 100), 441.9 (M^+, 45).

4.1.22. Monoaldehyde 40. Dibromodiarylether **39** (10.00 g, 22.6 mmol) was dissolved in 150 mL THF and cooled to −70 °C under nitrogen. *n*-Butyllithium (9 mL, 2.5 M) was added dropwise and the reaction mixture was left stirring for 1 h. DMF (1.9 mL, freshly distilled) was then added. After 10 min the cooling bath was removed and the temperature allowed to rise to ambient. The reaction mixture was heated for 1 h. The solvent was then removed by evaporation and the crude product dissolved in CH_2Cl_2 and washed with 2 M HCl. Subsequent drying over $MgSO_4$ and removal of solvent, yielded 9.40 g (quant.) crude product, which was submitted to gradient chromatography (hexane/CH_2Cl_2/MeOH). The pure fractions were collected and 4.36 g (49%) of **40** as off-white crystals, was achieved after evaporation of solvent.

R_f (CH_2Cl_2) = 0.23. Mp = 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.25 (s, 8H, CH_2), 6.24 (s, 1H, CH), 6.60 (s, 1H, CH), 7.14 (s, 1H, CH), 7.43 (s, 1H, CH), 10.36 (s, 1H, CHO).

4.1.23. Bromophenol 41. Monoaldehyde **40** (4.36 g, 11.1 mmol) was dissolved in 90 mL CH_2Cl_2. MCPBA (3.58 g, 16.6 mmol, 80% in H_2O) was added. The mixture was refluxed overnight. The solvent was evaporated and the residue was dissolved in EtOAc, which was extracted with 2×125 mL $NaHCO_3$ and 100 mL brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. 3.86 g (84%) formate was achieved and was immediately hydrolyzed.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.22 (s, 4H, CH_2), 4.23 (s, 4H, CH_2), 6.41 (s, 1H, CH), 6.52 (s, 1H, CH), 6.74 (s, 1H, CH), 7.09 (s, 1H, CH), 8.26 (s, 1H, OCHO).

The formate (3.86 g, 9.4 mmol) was suspended in MeOH, the material did not dissolve even during heating. The mixture was set under nitrogen atmosphere and KOH (0.58 g, 10.3 mmol) was added with subsequent darkening of the mixture. The hydrolysis was carried out in 1.5 h. The blend was neutralized with the addition of 2 M HCl and transferred to a separatory funnel. The H_2O phase was extracted with 4×100 mL CH_2Cl_2. The extracts were dried over $MgSO_4$ and rotary evaporated, affording **41** in

quantitative yield as brown crystals. The product was immediately used in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.65 (broad s, 1H, OH), 4.22 (s, 8H, CH_2), 6.35 (s, 1H, CH), 6.55 (s, 1H, CH), 6.57 (s, 1H, CH), 7.10 (s, 1H, CH).

4.1.24. Tri-dioxin 27. Bromophenol **41** (3.62 g, 9.5 mmol) was transferred to a 100 mL three-necked round bottom flask and 50 mL DMPU was added. NaH (0.42 g, 10.5 mmol, 60% oil dispersion) was added and then Cu(I)I (1.9 g, 10.0 mmol). The temperature was raised to 140 °C and the reaction was stirred for 65 h. The solvent was distilled off and the residue was succumbed to 2 M HCl. The precipitate that formed was filtered and extracted into CH_2Cl_2 (2 times) with sonification. The organic phase was extracted with 2 M NaOH and there after dried over $MgSO_4$. Subsequent evaporation of solvent yielded 3.06 g crude product, which was recrystallized from a mixture of EtOH and toluene to give 900 mg tri-dioxin (31%) The mother liquor was evaporated and then boiled with EtOH, yielding additional 300 mg of **27**. The recrystallized fraction was sublimed at 250 °C, to give an analytically pure sample as white crystals.

Mp >255 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.19 (s, 8H, CH_2), 6.38 (s, 4H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 64.3, 104.76, 135.7, 138.8. MS (EI) *m/e* (%) 300 (M^+, 100). Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.79; H, 4.08. Anal. Calcd for (**27**)$_2ClO_4$: C, 54.90; H, 3.46; Cl, 5.06. Found: C, 55.04; H, 3.57; Cl, 5.22. Anal. Calcd for (**27**)$_2AsF_6$: C, 48.68; H, 3.07; F, 14.44. Found: C, 48.68; H, 14.51. Anal. Calcd for (**27**)$_2PF_6$: C, 51.55; H, 3.25; F, 15.29. Found: C, 51.58; H, 3.26; F, 15.11.

4.1.25. Dibromo arylether 43. In a procedure similar to that used for preparing **39**, diarylether **42** (1.03 g, 4.0 mmol) was reacted with Br_2 (1.34 g, 8.4 mmol) to give a quantitative yield of **43** as off-white crystals.

Mp=119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.98 (s, 4H, CH_2), 6.42 (s, 2H, CH), 7.04 (s, 2H, CH). MS (EI) *m/e* (%) 416 (M^+, 38), 256 (M^+-2Br, 100).

4.1.26. Monoaldehyde 44. In a procedure similar to that used for preparing **40**, **42** (7.5 g) was converted to 3.1 g of pure **44** (47%) as brownish crystals.

Mp=156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.02 (s, 2H, CH_2), 6.03 (s, 2H, CH_2), 6.22 (s, 1H, CH), 6.61 (s, 1H, CH), 7.07 (s, 1H, CH), 7.32 (s, 1H, CH), 10.38 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ=98.11, 102.52, 102.84, 103.41, 105.69, 105.90, 112.70, 119.87, 144.00, 145.65, 146.68, 148.18, 154.04, 157.80, 187.54. MS (EI) *m/e* (%) 366 (M^++2), 364 (M^+, 16), 285 (M^+-Br, 100).

4.1.27. Bromophenol 45. In a procedure similar to that for preparing **41**, Monoaldehyde **44** (2.15 g) was reacted with MCPBA to give a quantitative yield (2.24 g) of formate.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.97 (s, 2H, CH_2), 5.98 (s, 2H, CH_2), 6.42 (s, 1H, CH), 6.52 (s, 1H, CH), 6.70 (s, 1H, CH), 7.01 (s, 1H, CH), 8.25 (s, 1H, OCHO).

The formate was subsequently hydrolyzed to give 1.70 g (86%) of brown crude phenol **45**, which was immediately used in the cyclization reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ=5.32 (bs, 1H, OH), 5.89 (s, 2H, CH_2), 5.98 (s, 2H, CH_2), 6.38 (s, 1H, CH), 6.52 (s, 1H, CH), 6.61 (s, 1H, CH), 7.03 (s, 1H, CH).

4.1.28. Bis(dioxolo)dibenzodioxin 34. In a procedure analogous to the one used for preparing **27**, **45** (1.8 g) could be transformed to 500 mg (36%) of pure **34** as white crystals.

Mp >210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.89 (4H, s), 6.40 (4H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ=98.1, 101.4, 136.0, 142.9. MS (EI) *m/e* (%) 272 (M^+, 100). Anal. Calcd for $C_{14}H_8O_6$: C, 61.77; H, 2.96. Found: C, 61.76; H, 3.09.

4.1.29. Dibromodibenzodioxin 47. 2,3-Dihydrobenzo[1,4]dioxin-6,7-diol **25** (5.23 g, 31.1 mmol) was dissolved in 400 mL of dry DMPU, hereafter sodium hydride (2.8 g 60% oil dispersion) was added in portions during 15 min. After evolution of hydrogen had ceased 1,2-dibromo-4,5-difluorobenzene **46** (8.46 g 31.1 mmol) was added in portions to the green solution. The flask was sealed and put under a slightly positive nitrogen pressure and heated to 150 °C overnight. The resulting mixture was concentrated under reduced pressure to yield a semisolid mass that was treated with 200 mL of EtOH. The resulting crystals could be collected by filtration, and was rinsed with MeOH, H_2O and then MeOH again. After drying, a quantitative (12.44 g) yield of **47** could be collected. An analytically pure sample could be achieved from sublimation at 230 °C (1.5×10^{-2} mbar), yielding light yellow crystals. Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 4.20 (s, 4H), 6.42 (s, 2H), 7.08 (s, 2H). **47** is too insoluble to give any ^{13}C NMR. MS (EI) *m/e* (%) 401.9 (50), 399.9 (M^+, 100), 397.9 (30). Anal. Calcd for $C_{14}H_8Br_2O_4$: C, 42.02; H, 2.02. Found: C, 41.86; H, 2.03.

4.1.30. Difluorodibenzodioxin 49. 2,3-Dihydrobenzo[1,4]-dioxin-6,7-diol **25** (53.4 mmol) was dissolved in 75 mL dry DMPU (nitrogen atmosphere). 1.1 equiv. of NaH (60% oil dispersion) were added. After 50 min 1,2,4,5-tetrafluorobenzene **48** (53.4 mmol) was added and the temperature was raised to 70 °C for 30 min, when an additional amount of 1.1 equiv. of NaH was added. The temperature was raised to 140 °C and the mixture was stirred for 8 h. Afterwards the solvent was removed by distillation and the residue was treated with 2 M HCl. The light brown precipitate that formed was filtered and recrystallized from EtOH and warm filtered, yielding 10.69 g (72%) beige crystals of product **49**. An analytically pure sample could be attained from sublimation at 230 °C (1.5×10^{-2} mbar), yielding light yellow crystals.

Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.20 (s, 4H), 6.41 (s, 2H), 6.68 (t, 2H, J=8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ=64.1, 104.8, 105.8 (q), 134.0, 137.2, 139.4, 144.1. MS (EI) *m/e* (%) 278.1 (M^+, 100). Anal. Calcd for $C_{14}H_8F_2O_4$: C, 60.44; H, 2.90. Found: C, 60.26; H, 3.03.

4.1.31. Bromodibenzodioxin 51. To a solution of **25**

(1.88 g, 11.2 mmol) in 15 mL of dry DMPU, under argon atmosphere, 1.1 equiv. of NaH were added. After stirring the reaction mixture for 25 min, 3,4-difluorobromobenzene **50** (1.28 g, 11.2 mmol) was added and the mixture was stirred at 70 °C for another 20 min. An additional amount of 1.1 equiv. of NaH was then added and the temperature was raised to 140 °C and the mixture left for 4 h. After cooling to rt, the reaction mixture was poured onto H_2O. The precipitate was filtered, washed with H_2O and recrystallized from EtOH yielding 1.42 g (39%) beige crystals of **51**.

Mp = 181.1–181.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.20 (s, 4H), 6.40 (s, 1H), 6.41 (s, 1H), 6.96 (dd, 1H, J = 8.3, 2.3 Hz), 6.98 (d, 1H, J = 2.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 64.3 (2C), 104.9, 105.0, 114.9, 117.5, 119.4, 126.3, 135.3, 135.5, 139.1, 139.2, 141.2, 142.6. MS (EI) *m/e* (%) 322.1 (90), 320.1 (M^+, 100). Anal. Calcd for $C_{14}H_9BrO_4$: C, 52.36; H, 2.82. Found: C, 52.48; H, 2.90.

4.1.32. Tetra-dioxin 33. 2,3-Dihydrobenzo[1,4]dioxin-6,7-diol **25** (1.84 g, 10.94 mmol) and 1,2,4,5-tetrafluorobenzene **48** (0.83 g, 5.53 mmol, 0.5 equiv.) were dissolved in NMP (50 mL) under nitrogen. NaH (0.5 g, 12.5 mmol, 1.14 equiv., 60% oil dispersion) was added cautiously. After gas evolution ceased the solution was heated to 95 °C. After 40 min the flask was removed from the heating bath and another 0.6 g of NaH was added cautiously. After gas evolution ceased the solution was heated to 205 °C and left to react overnight. The solution was poured onto a 2 M HCl/ice slurry (400 mL), whereby a precipitate was formed. The precipitate was filtered, rinsed generously with H_2O and then EtOH to give 1.79 g (81%) of grey tetra-dioxin **33** that is essentially NMR-pure. The product could be recrystallized from DMF. An analytically pure material could also be obtained from sublimation at 220 °C (1.5×10^{-2} mbar). We did not succeed in achieving good ^{13}C NMR of this compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.39, (s, 2H), 6.37 (s, 1H), 4.20 (s, 4H). MS (EI) *m/e* (%) 406.1 (M^+, 100). Anal. Calcd for $C_{22}H_{14}O_8$: C, 65.03; H, 3.47. Found: C, 64.87; H, 3.58.

4.1.33. Benzo[1,3]dioxole-5,6-diol 53. Sesamol (benzo[1,3]-dioxole-5-ol) was treated according to the procedure for 2,3-dihydrobenzo[1,4]dioxin-6-ol, yielding benzo[1,3]-dioxole-5,6-dione as thin orange crystals (71%).

Mp 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.03 (s, 2H), 6.10 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 101.3, 104.1, 160.8, 177.3. MS (EI) *m/e* (%) 152.2 (M^+, 100).

The benzo[1,3]dioxole-5,6-dione was then reduced by $Na_2S_2O_4$, as described for the preparation of **25**, yielding 0.95 g (68%) light brown crystals of **53**.

Mp 158–160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.78 (s, 2H), 6.40 (s, 2H) 8.47 (s, 2H, –OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 98.2, 100.0, 138.8, 139.0.MS (EI) *m/e* (%) 154.0 (M^+, 100).

4.1.34. Monomethoxylated dibenzodioxin 54. The difluorodibenzodioxin **49** (3.00 g, 10.8 mmol) was dissolved in 25 mL dry NMP (nitrogen atmosphere). Sodium methoxide (10.8 mmol, 1 equiv. 25% w/v in MeOH) was added and the temperature was raised to 90 °C. The dark brown reaction mixture was left on stirring overnight. After cooling to rt, the reaction mixture was poured on ice H_2O and a precipitate formed. Filtration by suction and washing with H_2O yielded 2.59 g (83%) beige crystals of **54**.

Mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 4.20 (s, 4H), 6.40 (s, 2H), 6.50 (d, 1H, J = 7.9 Hz), 6.64 (d, 1H, J = 11.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 56.6, 64.1, 102.7, 104.8 (q), 133.6, 133.6, 134.5, 137.0, 139.2, 139.2, 143.1, 143.2, 145.9, 147.8. MS (EI) *m/e* (%) 290.2 (M^+, 100). Anal. Calcd for $C_{15}H_{11}FO_5$: C, 62.07; H, 3.82. Found: C, 61.89; H, 3.98.

4.1.35. Dimethoxydibenzodioxin 55. Compound **49** (7.3 mmol) was dissolved in dry 40 mL dry NMP (nitrogen atmosphere). NaOMe (29.2 mmol, 4 equiv. 25% w/v in MeOH) was added and the temperature was raised to 130 °C. The dark brown reaction mixture was left stirring overnight. After cooling to rt, the reaction mixture was poured onto 200 mL ice/H_2O. The light brown precipitate formed was filtered by suction and washed with H_2O and yielded 1.33 g (61%) beige crystals of **55** after drying.

Mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.81 (s, 6H), 4.20 (s, 4H), 6.39 (s, 2H), 6.45 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 56.2, 64.3, 100.3, 104.7, 134.2, 135.6, 138.6, 144.2. MS (EI) *m/e* (%) 302.2 (M^+, 100). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.75; H, 4.84.

4.1.36. Fluorophenol 56. Compound **54** was dissolved in 40 mL dry 1,2-dichloroethane and the solution was purged with N_2. $BBr_3S(CH_3)_2$ (4 equiv.) was added and the mixture was refluxed overnight. When no starting material was left the mixture was cooled, H_2O and Et_2O were added and the layers were separated. The H_2O phase was extracted 2 times with Et_2O and the combined organic layers were extracted with brine and dried over $MgSO_4$. The solvent was evaporated in vacuum yielding 0.76 g (93%) of **56** as light brown crystals. An analytically pure sample could be obtained from sublimation at 210 °C (1.5×10^{-2} mbar) of 150 mg of material, yielding 120 mg light yellow crystals of pure **56**.

Mp > 200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.18 (s, 4H), 6.50 (s, 1H), 6.52 (d, 1H, J = 8.3 Hz), 6.53 (s, 1H), 6.88 (d, 1H, J = 11.1 Hz). MS (EI) *m/e* (%) 276.2 (M^+, 100). Anal. Calcd for $C_{14}H_9FO_5$: C, 60.88; H, 3.28. Found: C, 61.08; H, 3.38.

4.1.37. Dihydroxydibenzodioxin 57. *Compound* **55** was demethylated according to the procedure for compound **56**, yielding 0.94 g (86%) grey crystals of **57**.

Mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.20 (s, 4H), 6.39 (s, 2H), 6.43 (s, 2H). MS (EI) *m/e* (%) 274.2 (M^+, 100).

4.1.38. 2,3,6,7-Tetramethoxynaphthalene 60. Sodium (2.3 g) was added in portions to 700 mL of dry MeOH. After complete dissolution of the sodium, 100 mL of DMF, Cu(I)I (22.3 g) and 2,7-dibromo-3,6-dimethoxynaphthalene

(41.0 g, 118.4 mmol) **59** was added cautiously. The resulting reaction mixture was refluxed under nitrogen overnight. The reaction was quenched with 400 mL of 2 M HCl and diluted with 1.6 L of H_2O. The precipitate was filtered off and recrystallized to give 18.7 g (64%) of 2,3,6,7-tetramethoxy-naphthalene **60**.

Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.97 (s, 3H), 7.04 (s, 1H), MS (EI) *m/e* (%) 248 (M^+, 100).

4.1.39. 2,3,6,7-Tetrahydroxynaphthalene 61. 2,3,6,7-Tetrameth-oxynaphthalene (5.0 g, 20.1 mmol) and tetra-*n*-butyl-ammonium bromide (100 mg) was added to 50 mL of conc. HBr. The mixture was brought to reflux for 20 min, whereafter it was added to an ice/H_2O mixture, some Zinc dust was added and the mixture was filtered again. The filtrate is then evaporated under reduced pressure, the residue dried under vacuum, to give a quantitative yield of **61**, which was used immediately in the following reaction.

^{1}H NMR (400 MHz, DMSO-d_6) δ=6.80 (s, 1H), –OH protons could not be detected. ^{13}C NMR (100 MHz, DMSO-d_6) δ=108.4, 123.8, 144.4

4.1.40. 2,3,6,7-Bis(ethylenedioxy)naphthalene 36. The crude 2,3,6,7-tetrahydroxynaphthalene **61**, from the previous preparation was dissolved under nitrogen in dry DMSO (200 mL), where after K_2CO_3 (27.6 g, 0.2 mol) and 1-bromo-2-chloroethane (11.53 g, 80.4 mmol) was added. The resulting mixture was heated to 100 °C during 48 h. After cooling to rt the mixture was diluted with H_2O. The resulting precipitate was filtered off and purified by gradient chromatography (hexanes/EtOAc) to give 1.14 g (23%) of NMR-pure **36**.

Mp=231–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.30 (8H, s), 7.06 (4H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ=64.6, 111.0, 125.5, 142.8. MS (EI) *m/e* (%) 244 (M^+, 100%). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.59; H, 5.14.

4.1.41. 2,3,6,7-Tetramethoxyanthracene 62. 2,3,6,7-Tetramethoxy-9,10-anthraquinone **63**[32] (4.5 g, 13.7 mmol), and tetra-*n*-butylammonium borohydride (17 g) were added to 200 mL CH_2Cl_2. The resulting suspension was cooled to 0 °C, and iodomethane (4.5 mL) was added slowly during 20 min. The reaction was allowed to reach ambient temperature overnight, to give an almost clear solution, with just a tint of yellow. Since TLC showed presence of starting material, the mixture was once again cooled to 0 °C, and additional tetra-*n*-butylammonium borohydride (10 g) and iodomethane (3 mL) were added. The mixture was once again allowed to reach rt overnight, where after 5 mL of H_2O was added to quench the reaction. The mixture was concentrated under reduced pressure, and the resulting semisolid mass was treated with 200 mL of EtOH. The resulting crystals were collected by filtration and rinsed thoroughly to give 3.7 g of crude material. Purification by sublimation (1.5×10^{-2} mbar) gave 410 mg **63** of good purity, together with 2.0 g of impure material. The impure material was purified by gradient chromatography (1,2-dichloroethane/MeOH) to give an additional 455 mg. Combined yield: 865 mg (21%).

Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.90 (12H, s), 7.27 (4H, s), 8.10 (2H, s). MS (EI) *m/e* (%) 298.2 (M^+, 100%).

4.1.42. 2,3,6,7-Tetrahydroxyanthracene 64. 2,3,6,7-Tetramethoxy-anthracene **62** (470 mg, 1.6 mmol) and tetra-*n*-butyl-ammonium bromide (6 mg) was added to 30 mL of conc. HBr. The mixture was brought to reflux overnight. Afterwards it was added to an ice/H_2O mixture and then brown precipitate was filtered off. The residue was dried in desiccator overnight, to give 387 mg of crude **64**, which was treated with boiling MeOH. The solvent was evaporated yielding 323 mg (85%) of almost pure **64**, which was used rapidly in the following reaction.

^{1}H NMR (400 MHz, DMSO-d_6) δ=3.89 (4H, bs), 7.05 (4H, s), 7.77 (2H, s). MS (EI) *m/e* (%) 242.3 (M^+, 100%).

4.1.43. 2,3,6,7-Bis(ethylenedioxy)anthracene 37. The crude 2,3,6,7-tetrahydroxyanthracene **64** (300 mg, 1.2 mmol) from the previous preparation was dissolved under nitrogen in dry DMSO (10 mL), where after K_2CO_3 (1.712 g, 12 mol) and 1-bromo-2-chloroethane (0.4 ml, 5.0 mmol) was added. The resulting mixture was heated to 100 °C during 48 h. After cooling to rt the mixture was diluted with H_2O. The resulting precipitate was filtered off and purified by column chromatography (CH_2Cl_2) to give 91 mg (25%) pure bright fluorescent yellow crystals of **36**.

Mp >200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.36 (8H, s), 7.29 (4H, s), 8.00 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ=64.5, 110.8, 122.1, 127.9, 143.9. MS (EI) *m/e* (%) 294.3 (M^+, 100%). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.25; H, 4.87.

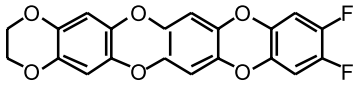
Acknowledgements

Financial support from the Swedish Research council as well as the Foundation for Strategic Research is gratefully acknowledged.

References and notes

1. Wurthner, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1037–1039.
2. Söderholm, S.; Werner, H. P.; Krzystek, J.; von Schütz, J. U.; Hellberg, J.; Ahlgren, G. *Synth. Met.* **1987**, *20*, 15–34.
3. (a) Krzystek, J.; von Schütz, J. U.; Ahlgren, G.; Hellberg, J.; Söderholm, S.; Olovsson, G. *J. Physique* **1986**, *47*, 1021–1027. (b) Söderholm, S.; von Schütz, J. U.; Hellberg, J. *Synth. Met.* **1986**, *19*, 403–408.
4. Tomita, M.; Ueda, S.; Nakai, Y.; Deguchi, Y.; Takaki, H. *Tetrahedron Lett.* **1963**, 1189–1194.
5. In contrast to example thianthrenes, dibenzodioxins are essentially planar; Meyers, E. A.; Zingaro, R. A.; Rainville, D.; Irgolic, K. J.; Dereu, N. L. M.; Chakcrudeorthy, R.; Pappalardo, G. C. In *Proceedings of the Fourth International Conference of the Organic Chemistry of Selenium and Tellurium 1983*, Barry, F. J., McWhinnie, W. R., Eds.; The University of Aston in Birmingham, 1983; p 391.

6. B3LYP/g-31G*-calculations gave a pronounce difference in stiffness between a linear all carbon acene and the corresponding dibenzodioxin towards bending.
7. (a) Czompa, A.; Dinya, Z.; Antus, S.; Varga, Z. *Arch. Pharm. (Weinheim, Ger.)* **2000**, *333*, 175–180. (b) Gu, W. X.; Jing, X. B.; Pan, X. F.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **2000**, *41*, 6079–6082. (c) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96. (d) Bolognesi, M. L.; Budriesi, R.; Cavalli, A.; Chiarini, A.; Gotti, R.; Leonardi, A.; Minarini, A.; Poggesi, E.; Recanatini, M.; Rosini, M.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **1999**, *42*, 4214–4224. (e) Hodgetts, K. J.; Kieltyka, A.; Brodbeck, R.; Tran, J. N.; Wasley, J. W. F.; Thurkauf, A. *Bioorg. Med. Chem.* **2001**, *9*, 3207–3213.
8. (a) Spicer, J. A.; Denny, W. A. *Anti-Cancer Drug Des.* **2000**, *15*, 453–458. (b) Mastrolorenzo, A.; Scossafava, A.; Supuran, C. T. *J. Enzym. Inhib.* **2000**, *15*, 557–569. (c) Booth, R. J.; Josyula, V. P. V. N.; Meyer, A. L.; Steinbaugh, B. A. WO Patent 2001-051479, *Chem. Abstr.* **2001**, *135*, 107243. (d) Coudert, G.; Khatib, S.; Moreau, P.; Caiganrd, D. -H.; Renard, P.; Atassi, G.; Pierre, A. EU Patent EP 841337, *Chem. Abstr.* **1998**, *129*, 4652
9. Hellberg, J.; Pelcman, M. *Tetrahedron Lett.* **1994**, *35*, 1769–1772.
10. (a) Gray, A. P.; Cepa, S. P.; Solomon, I. J.; Aniline, O. *J. Org. Chem.* **1976**, *41*, 2435–2437. (b) Singh, S. K.; Kumar, S. *J. Agric. Food Chem.* **1993**, *41*, 1511–1516. (c) Eastmond, G. C.; Paprotny, J.; Steiner, A.; Swanson, L. *New J. Chem.* **2001**, *25*, 379–384.
11. Lee, H. H.; Denny, W. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1071–1074.
12. (a) Ueda, S. *Yakugaku Zasshi* **1963**, *83*, 805. *Chem. Abstr.* **1964**, *59*, 15279g. (b) Cambie, R. C.; Janssen, S. J.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1991**, *420*, 387–418.
13. (a) Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829–2835. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. (c) Keegstra, M. A.; Peters, T. H. A.; Brandsma, L. *Tetrahedron* **1992**, *48*, 3633–3652. (d) Manchand, P. S.; Townsend, J. M.; Belica, P. S.; Wong, H. S. *Synthesis* **1980**, 409–410. (e) McKillop, A.; Howarth, B. D.; Kobylecki, R. *J. Synth. Commun.* **1974**, *4*, 35–43. (f) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565–5578.
14. Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn* **1966**, *39*, 128–131.
15. Hellberg, J.; Ahlgren, G.; Söderholm, S.; Olovsson, G.; von Schütz, J. U. *Mol. Cryst. Liq. Cryst.* **1985**, *120*, 273–276.
16. Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731–3734.
17. After prolonged reaction with 1,2,4,5-tetrafluorobenzene at elevated temperatures, an unknown substance could be isolated. To our confusion, mass spectrometry and NMR give contradictory result, the former suggesting the 'halfway' difluoro structure **58**, whereas NMR suggests a more symmetrical product. A higher 'pentadioxin' homologue would fit the NMR-data, but can probably be ruled out since the present compound is more soluble than the 'tetradioxin' **33**. Further analytical studies are in progress.



58

18. Cooke, R. G.; Johnson, B. L.; Owen, W. R. *Aust. J. Chem.* **1960**, *13*, 256–260.
19. Laundon, B.; Morrison, G. A. *J. Chem. Soc. C* **1971**, 1694–1704.
20. Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1978**, 771–773.
21. (a) Muller, A.; Raltschewa, M.; Papp, M. *Chem. Ber.* **1942**, *75*, 692–703. (b) Ostaszewski, R. *Tetrahedron* **1998**, *54*, 6897–6902.
22. 2,3,6,7-Tetramethoxyanthraquinone is prepared by the reaction of veratrole and acetaldehyde in slightly diluted sulfuric acid and subsequent oxidation. When this procedure is applied to benzo(1,4)dioxane, intractable material is the only product.
23. Woldegiorgis, A.; von Kieseritzky, F.; Hellberg, J.; Dahlstedt, E.; Brinck, T.; Roeraade, J. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 841–852.
24. (a) Meng, H.; Bendikov, M.; Mitchell, G.; Helgeson, R.; Wudl, F.; Bao, Z.; Siegrist, T.; Kloc, C.; Chen, C.-H. *Adv. Mater.* **2003**, *15*, 1090–1093. (b) Kraft, A. *ChemPhysChem* **2001**, *2*, 163–165.
25. Hellberg, J.; Pelcman, M.; Allared, F. *Synth. Commun.* **2003**, *33*, 2751–2756.
26. Cook, M. J.; Jafari-Fini, A. *Tetrahedron* **2000**, *56*, 4085–4094.
27. Mattern, D. L. *J. Org. Chem.* **1984**, *49*, 3051–3053.
28. Engman, L.; Hellberg, J.; Ishag, C.; Söderholm, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2095–2101.
29. (a) Syper, L.; Kloc, K.; Mlochowski, J. *Tetrahedron* **1980**, *36*, 123–129. (b) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2017–2022.
30. Caputo, R.; Ferreri, C.; Palumbo, G.; Russo, F. *Tetrahedron* **1991**, *47*, 4187–4194.
31. Eltsov, A. V. *Zh. Obsch. Khim.* **1963**, *33*, 2006. *Chem. Abstr.* **1964**, *59*, 11463d.
32. Prepared according to lit.,[21] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta =$ 4.07 (12H, s), 7.68 (4H, s).

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8913–8918
Tetrahedron

Squaraines based on 2-arylpyrroles

Raymond Bonnett,* Majid Motevalli and Jason Siu

Department of Chemistry, Queen Mary, University of London, Mile End Road, London E1 4NS, UK

Received 15 April 2004; revised 14 June 2004; accepted 8 July 2004

Available online 23 August 2004

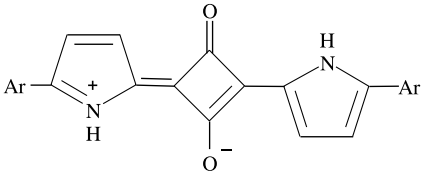
Abstract—Various derivatives of 2-phenylpyrrole were condensed with squaric acid to give the corresponding squaraines. The products are drawn with the *anti* geometry rather than the *syn* geometry generally shown in the past: the arguments for this formulation are given, including the analogy with 2,5-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)-1,4-benzoquinone, for which an X-ray structure is presented. Solutions of the new bis(5-arylpyrrol-2-yl)squaraines have intense, sharp absorption bands shifted to the red. Condensation of squaric acid with arylpyrroles possessing fused ring systems, and condensation with 2-styrylpyrrole, gave chromophores with high values for λ_{max} and ε_{max}. Certain of these chromophores appear to be suitable for further structural elaboration to give materials having potential in optoelectronic and photodynamic applications.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

The squaraines are a series of organic dyestuffs characterised by intense absorption in the red region of the spectrum. They have attracted considerable commercial interest because of their optoelectronic properties, finding applications in such areas as solar cells, xerographic sensitisers, near-IR dyes and optical recording.[1–4] There has also been some limited activity in applications as sensitisers in photodynamic therapy.[5–9] In both of these areas, two current interests are (i) to shift the absorption maximum to lower energies, and (ii) to alter the solution properties, since many of the squaraines have poor solubility in polar and in non-polar solvents. Here we address the first of these.

Our present aim has been to investigate the preparation and electronic absorption spectra of 2,4-bis(5-arylpyrrol-2-yl)squaraines **1**. Such molecules might be advantageous here since they would be expected to have red-shifted absorption maxima (with respect to the parent skeleton) because of the aryl conjugation; and the aryl ring would provide sites for substituents aimed at modulating solution and spectroscopic properties.

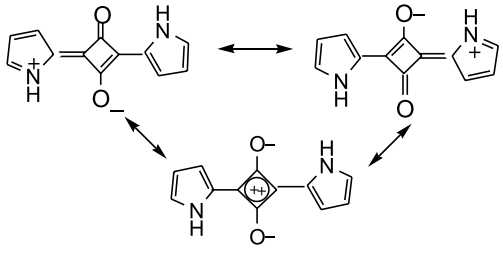
Although the bis(pyrrol-2-yl)squaraines were amongst the first of the squaraine dyes to be reported,[10,11] they have subsequently been relatively little studied, and the 5-arylpyrrol-2-yl derivatives are unknown. The photophysical properties of bis(4-acetyl-3,5-dimethylpyrrol-2-yl)-squaraine have been reported.[12] Recently there have been several reports on the non-linear optical properties,[13,14] electrical conductivities,[15–18] and lithium ion sequestration[19] of various polymeric (*N*-alkylpyrrol-2-yl)squaraines. Copolymers comprised of bis(pyrrol-2-yl)squaraine units based on *N*-substituted and *N*-unsubstituted pyrroles have also been prepared.[20]



1

Ar = Ph, substituted Ph, naphthyl, etc

The bis-pyrrolylsquaraines are highly π-delocalised systems which may be regarded as possessing 2πe aromaticity, as shown in Scheme 1. Thus the carbonyl stretching



Scheme 1. Delocalisation in the bis(pyrrol-2-yl)squaraine system.

Keywords: Oxocarbon acids and derivatives; Electronic spectra; Pyrroles, Aryl; Red-absorbing dyes.
* Corresponding author. Tel.: +44-020-7882-5024; fax: +44-020-7882-7794; e-mail: r.bonnett@qmul.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.023

frequency in the IR spectrum appears at about 1600 cm^{-1}, consistent with considerable single bond character.

For the various applications already mentioned, the squaraines have some distinct advantages, especially the sharp intense absorption in the red region. Thus the squaraine **2** has λ_{max} 560 nm (ε 200,000 M^{-1} cm^{-1}) in chloroform (Fig. 1) which is little affected by modest changes in the acidity of the medium (small hypsochromic shift in $CHCl_3$–HCl). Secondly, such compounds can be synthesised, usually in good yield, in one step from squaric acid and an α-free pyrrole. Thus in the original work of Treibs and Jacob[10,11] compound **2** was obtained in 90% isolated yield from kryptopyrrole as shown in Scheme 2. Such a one step preparation is a clear benefit with respect to cost and environmental considerations when a potentially commercial interest is in view, although the starting materials still have to be obtained. Thirdly, although most squaraines that have been described have symmetrical structures, it is possible to carry out the synthesis in two independent stages, and so attach two different π-excessive units, thus increasing the range of structural variation.[4,21–23]

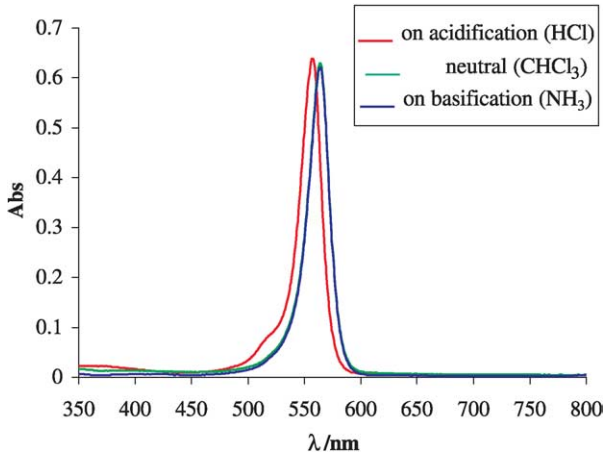
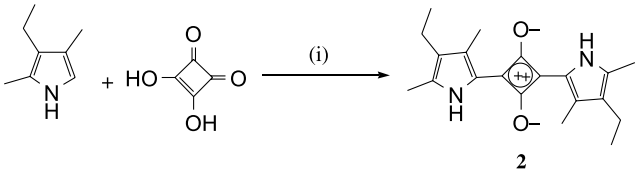


Figure 1. The electronic absorption spectrum of 2,4-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)cyclobutenediylium-1,3-diolate [2,4-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)squaraine] **2** in chloroform.

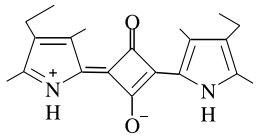


Scheme 2. Synthesis of 2,4-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)squaraine **2**. (i) *n*-BuOH/PhH = 1:1, reflux, 3 h.

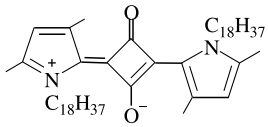
2. Results and discussion

2.1. Structure

It is necessary at the outset to address the question of the detailed structure of 2,4-bis(pyrrol-2-yl)squaraine [2,4-bis(pyrrol-2-yl)cyclobutenediylium-1,3-diolate]. When Treibs and Jacob first described **2**, the structure was drawn as shown at **3**, and the majority of subsequent authors of original papers and reviews have followed suit:[3,12,24] reference 25, where an *anti* structure is given without specific comment, appears to be the only exception. The matter has been given some attention for squaraines derived from *N*-substituted pyrroles. Thus the squaraine obtained from 2,4-dimethyl-1-octadecylpyrrole behaves as a single substance, and has been thought most likely to prefer the *anti* geometry **4** for steric reasons.[13] Polymeric systems derived from *N*-alkylpyrroles have also sometimes been represented with the *anti* stereochemistry.[19,26]



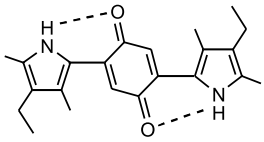
3



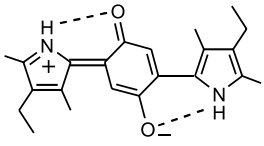
4

We believe that for the squaraines derived from *N*-unsubstituted pyrroles the *anti* stereochemistry shown in Scheme 1 will be preferred because it maximises intramolecular hydrogen bonding. Such intramolecular hydrogen bonding involving pyrrolic imino hydrogen has been encountered elsewhere, for example in bilirubin (where it is also thought to be associated with low solubility in polar solvents).[27]

Attempts to grow crystals of the new bis(2-arylpyrrol-2-yl)squaraines (below) suitable for X-ray analysis have not so far been successful, and we have found no closely related X-ray structure in the literature. However, we have carried out a crystal analysis of a structurally related compound, the 2,5-bis(pyrrol-2-yl)-1,4-benzoquinone **5**,[28] which is found to have the intramolecularly hydrogen bonded structure shown in Figure 2. Moreover, the observed bond lengths accord with contributions from canonicals such as **6**, again analogous to the situation shown in Scheme 1.



5



6

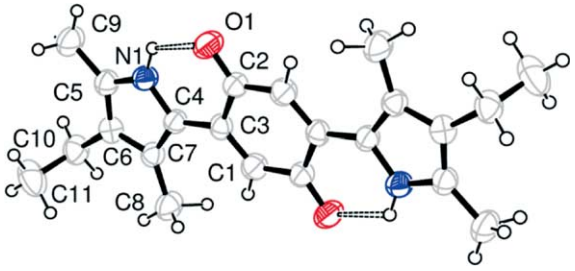


Figure 2. Molecular structure of 2,5-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)-1,4-benzoquinone [2,5-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)cyclohexadiene-1,4-dione] **5** (crystallographic numbering shown).

Thus, in **5** the C–O bond lengths are 1.242 Å (1.222 Å in 1,4-benzoquinone)[29] indicating increased single bond character, confirmed by the IR stretching frequency at 1602 cm^{-1}. These and other bond lengths selected for their relevance to this point are shown in Figure 3. Particularly

significant are the lengthening in the six membered ring of the C1–C2 and C2–C3 bonds, and the shortening of the C3–C4 bond (chemical numbering) with respect to the corresponding values in 1,4-benzoquinone.

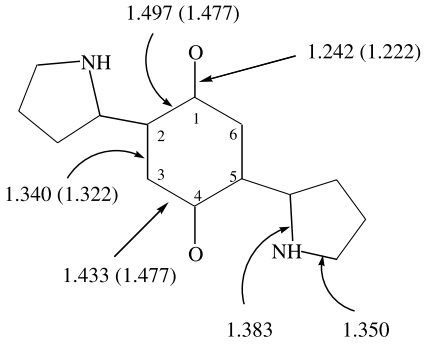


Figure 3. Selected bond lengths (Å) of compound **5** compared with corresponding bond lengths in 1,4-benzoquinone (in parenthesis).[29,30] (Chemical numbering shown).

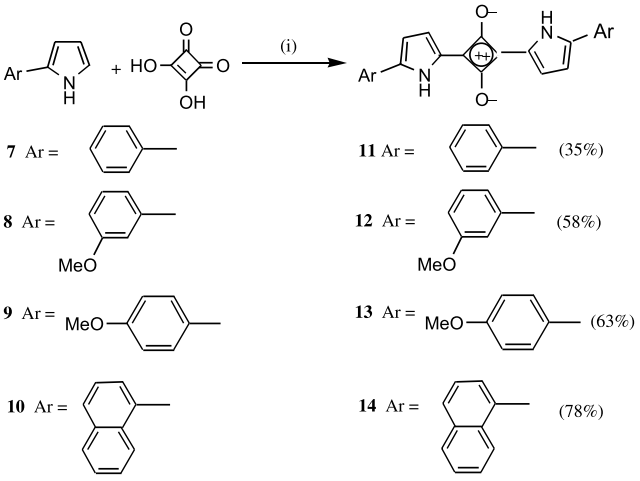
Thus in this paper we show the bispyrrol-2-ylsquaraines with the *anti* geometry (as in Scheme 1) throughout. This is not to imply that the alternative geometry may not be accessible in solution by overcoming the barrier to restricted rotation. Although ^{1}H NMR work has not led to its detection with the new compounds described here, such equilibration has been observed in this way with other systems (e.g. with dialkylaminohydroxyphenyl squaraines).[25] Recent studies in non-protic solvents on semisquaraines with *o*-diethylaminophenyl substitution have been interpreted in terms of intramolecular hydrogen bonding which is disrupted in protic solvents.[31]

2.2. 2,4-Bis(5-arylpyrrol-2-yl)squaraines

Our approach has thus been to push the absorption maximum of the bis-pyrrolylsquaraine system towards the red by introducing α-aryl substituents and by constraining such substituents more or less to the plane by non-conjugative ring formation. Such an approach has been used recently in modifying the chromophores of difluoroboron(III) pyrromethene derivatives used as fluorescent labels for DNA sequencing to increase the range of absorption and fluorescence.[32,33]

2-Phenylpyrrole **7** and its derivatives **8**–**10** were prepared by coupling *N*-Boc-2-bromopyrrole[34] with the appropriate arylboronic acid using the Suzuki reaction.[33] Condensation of these 2-arylpyrroles **7**–**10** with squaric acid in butanol–benzene in the presence of molecular sieve gave the corresponding squaraines **11**–**14** (Scheme 3) as crystalline or amorphous greenish solids. The squaraines were characterised by elemental analysis and/or HRMS and by spectroscopic methods.

Some minor problems were encountered: the crystals tended to retain water (observed also by others[11]): and in some cases it was not possible to obtain satisfactory ^{1}H NMR spectra, which is attributed to low solubility and/or to line broadening by radical impurities. The electronic spectra of compounds **11**–**14** are compared graphically in Figure 4, and refer to chloroform solution: treatment with traces of acid and base (cf. Fig. 1) caused little or no discernible change (data not shown).



Scheme 3. Condensation of squaric acid with 2-phenylpyrrole and analogues to give the corresponding squaraines. [(i)=*n*-BuOH–benzene, △, 4 h, molecular sieves].

It is apparent that the introduction of the 2-phenyl substituent into the pyrrole moiety causes a marked bathochromic shift (λ_{max} 564 nm for **2**, 621 nm for **11**). The peak is further shifted to lower energy by the *p*-methoxy group in **13** (λ_{max} 643 nm, cf. delocalisation pathway in **15**) but is essentially unaffected by the *m*-methoxy group in **12** (λ_{max} 624 nm, oxygen lone pair not delocalisable onto the squaraine system), except that the molecular absorbance decreases. The absorption bands are particularly sharp, with little absorption in the remaining part of the visible region, and the solutions are strikingly coloured (purple-blue shades) the brilliance of which we suppose to be associated with the narrowness of this absorption band.

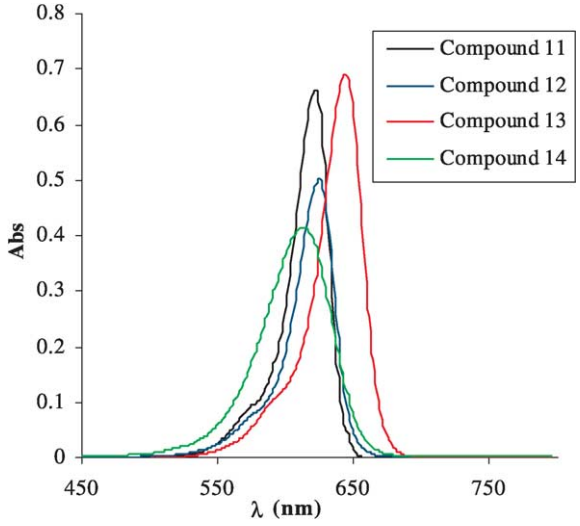
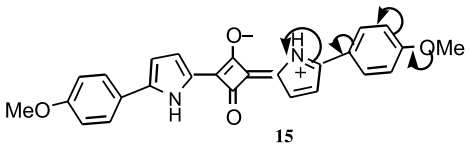
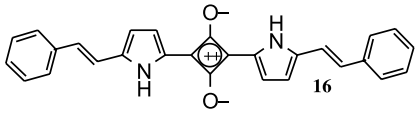


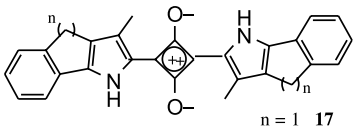
Figure 4. The electronic absorption spectra of squaraines **11**–**14** in chloroform.



However, the spectrum of the α-(1-naphthyl) derivative **14** showed quite different behaviour: the λ_{max} value had decreased (613 nm) and the peak had become broader and less intense (Fig. 4). This is attributed to a steric effect which causes the larger naphthyl substituent to rotate out-of-plane, leading to reduced conjugation.

The example of the α-(1-naphthyl) derivative **14** pointed to the need to facilitate conjugation by introducing features which enhance coplanarity of the benzenoid and squaraine chromophores. We sought to do this in two ways: (i) by using styryl rather than phenyl substitution, as in **16**; and (ii) by introducing an additional saturated ring to force the benzenoid substituent to lie more or less in the plane of the bispyrrolylsquaraine nucleus, as in **17** and **18**.





2-(*E*)-Styrylpyrrole **19**[35] was condensed with squaric acid as before to give 2,4-bis[5-(*E*)-styrylpyrrol-2-yl]cyclobutenediylium-1,3-diolate **16** as a dark green solid in 54% yield. The electronic spectrum in chloroform (Fig. 5) showed λ_{max} 673 nm (ε 146,000 M^{-1} cm^{-1}). Although the molecular absorbance is lower than might have been expected, the λ_{max} of the absorption band is shifted well into the red. Since this work was completed, a tetramethoxy derivative of 2,4-bis[5-(*E*)-styrylpyrrol-2-yl]squaraine has been reported to have λ_{max} 695 nm, showing the pronounced auxochromic effect of additional methoxy groups.[3]

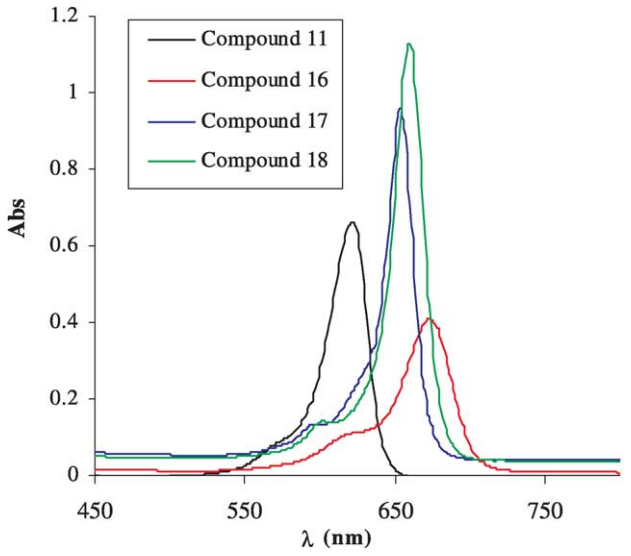
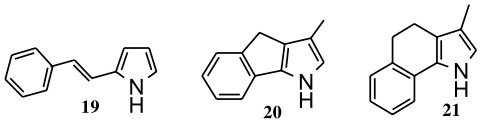


Figure 5. The electronic absorption spectra of squaraine compounds **11** and **16**–**18** in chloroform. The base line for **17** and **18** has been displaced for clarity.



3-Methyl-4*H*-indano[1,2-*b*]pyrrole **20**[32] was condensed with squaric acid to give the corresponding squaraine **17** as fine lustrous greenish needles in 42% yield. This substance was especially difficult to study because of its poor solubility: it was sparingly soluble in pyridine and in trifluoroacetic acid, which proved to be satisfactory solvents for several of the squaraines studied here. Squaraine **17** gave a satisfactory analysis, but it was not sufficiently soluble (DTFA–$CDCl_3$; pyridine-d_5) to give a ^1H NMR spectrum. The electronic spectrum (chloroform) is shown in Figure 5 (λ_{max} 654 nm, ε 347,000 M^{-1} cm^{-1}). In an analogous manner, 3-methyl-4,5-dihydro-1*H*-benz[1,2-*g*]indole **21**[32] condensed with squaric acid to give the squaraine **18** as fine green needles in 80% yield. It gave satisfactory elemental analysis and high resolution molecular ion measurements. Although in this case the substance did dissolve in pyridine–chloroform to give a bright green solution, a satisfactory ^1H NMR spectrum was not obtained. The electronic spectrum showed a sharp band at 660 nm with a high ε value (403,500 M^{-1} cm^{-1}).

Thus with respect to the 2-phenylpyrrole squaraine derivative **11**, both structural variations, i.e. the extended conjugation in **16**, and the constraints imposed in **17** and **18**, have led to significant shifts of the absorption band into the red region, with the additional advantage of marked hyperchromic effects for **17** and **18**.

3. Conclusions

(i) It is argued that the preferred geometry of the *N*-unsubstituted bis(pyrrol-2-yl)squaraine system is *anti* because this geometry allows greater intramolecular hydrogen bonding than the *syn* structure. This conclusion is supported by an X-ray crystal structure of a closely analogous compound, 2,5-bis(4-ethyl-3,5-dimethylpyrrol-2-yl)-1,4-benzoquinone **5**.

(ii) Squaraines derived from 2-arylpyrroles are prepared for the first time. They possess sharp strong absorption bands shifted to the red region of the spectrum when compared with the known alkylated analogues. Especially is this so for the molecules in which the aryl ring is constrained to be more or less in the plane of the pyrrole ring, as in **18** (λ_{max} 660 nm, ε 403,500 M^{-1} cm^{-1}).

(iii) The chromophores represented by **13**, **16**, **17** and **18** may have potential for optoelectronic and photodynamic therapeutical applications. Solubility in common solvents remains a problem with the present compounds, but the presence within these structures of benzenoid sites which can carry groups designed to modulate physical properties (particularly solubility

and photophysical parameters) offers a pathway for future development.

4. Experimental

4.1. General

Electronic spectra were measured on a Perkin–Elmer 552 spectrometer; ^{1}H NMR spectra were measured with tetramethylsilane as internal standard and were recorded either with a Brüker AM-250, a JEOL EX-270, a Brüker AMX-400 or a Brüker AMX-600 (ULIRS service) instrument. The coupling constants (J values) are given in Hz; peak assignments for **12–14** by COSY and NOESY spectroscopy. Mass spectra were recorded on a Micromass ZAB-2SE (ULIRS service): relative abundances and assignments are given in parentheses. Unless otherwise stated ionisation was by fast atomic bombardment (FAB): the matrix was *m*-nitrobenzyl alcohol (NOBA). Mps were measured on a hot-stage apparatus, and are uncorrected. Reactions were monitored using TLC on Merck Kieselgel 60 silica gel plastic sheets. Column chromatography was carried out on Merck Kieselgel 60 silica gel (0.040–0.063 mm). The 2-aryl pyrroles **7–10** were prepared by coupling *N*-*t*-butyloxycarbonyl-2-bromopyrrole with the appropriate arylboronic acid as described in the literature.[33]

4.2. General procedure for the synthesis of squaraine derivatives

4.2.1. 2,4-Bis[5-phenylpyrrol-2-yl]cyclobutenediylium-1,3-diolate (11). 2-Phenylpyrrole **7** (35 mg, 0.24 mmol), and squaric acid (11.5 mg, 0.10 mmol) were dissolved in butanol/benzene (1:1) (10 mL) and refluxed for 4 h with 4 Å molecular sieves (ca. 50 mg). The reaction mixture was cooled to room temperature; ethanol (4 mL) was added and the mixture was decanted from the molecular sieves and kept in the freezer overnight. The crystalline product was filtered off, washed with ethanol (20 mL), and dried to give the title squaraine (12.9 mg, 35%) as lustrous greenish needles, mp $>$ 300 °C; R_f=0.40 (EtOAc:CHCl$_3$=3:7). This substance did not give satisfactory NMR signals in DMSO-d_6, DTFA–CDCl$_3$, and pyridine-d_5, due to poor solubility. λ_{max} (CHCl$_3$)/nm 621 (ε 237,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3400, 1618, 1583, 1560, 945, 918, 758; *m*/*z* (FAB) 365 (100, M+H), 364 (50, M), 363 (35), 199 (75); HRMS M+H, $C_{24}H_{17}N_2O_2$ calcd 365.1290, found 365.1285. Anal. calcd for $C_{24}H_{16}N_2O_2\cdot 1.8H_2O$, C, 72.64; H, 4.98; N, 7.06. Found C, 72.53; H, 4.34; N, 6.82.

4.2.2. 2,4-Bis[5-(3-methoxy)phenylpyrrol-2-yl]cyclobutenediylium-1,3-diolate (12). Lustrous greenish needles (58%), mp $>$ 300 °C; R_f=0.35 (EtOAc/CHCl$_3$ =3:7); δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 7.73 (2H, bd, pyrrole 3-H), 7.46 (4H, m, benzenoid C5′ and C6′), 7.38 (2H, bs, benzenoid C2′), 7.10 (2H, m, benzenoid C4′), 7.06 (2H, d, J=4.8 Hz, 4-H of pyrrole), 4.00 (6H, s, OMe). λ_{max} (CHCl$_3$)/nm 625 (ε 177,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3393, 1635, 1603, 1558, 1508, 934, 822, 800; *m*/*z* (FAB) 425 (100, M+H), 346 (35); HRMS M+H, $C_{26}H_{21}N_2O_4$ calcd 425.1501, found 425.1516. Anal. calcd for $C_{26}H_{20}N_2O_4\cdot 0.5H_2O$, C, 72.04; H, 4.88; N, 6.46. Found C, 72.07; H, 4.78; N, 6.21.

4.2.3. 2,4-Bis[5-(4-methoxyphenyl)pyrrol-2-yl]cyclobutenediylium-1,3-diolate (13). Lustrous greenish crystals (63%), mp 230 °C; δ_H (400 MHz; d$_5$-pyridine–CDCl$_3$; Me$_4$Si) 7.99 (4H, d, J=8.8 Hz, AA′BB′ benzenoid C2′ and C6′ H), 7.95 (2H, d, J=3.8 Hz, 3-H of pyrrole), 7.02 (2H, d, J=3.8 Hz, 4-H of pyrrole), 6.94 (4H, d, J=8.8 Hz, AA′BB′ benzenoid C3′ and C5′ H), 3.70 (6H, s, OMe). λ_{max} (CHCl$_3$)/nm 643 (ε 248,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3393, 1603, 1583, 1560, 941, 916, 829, 797, 783; *m*/*z* (FAB) 425 (35, M+H), 424 (35, M), 336 (55); HRMS M+H, $C_{26}H_{21}N_2O_4$ calcd 425.1501, found 425.1516. Anal. calcd for $C_{26}H_{20}N_2O_4\cdot 0.1H_2O$ requires C, 73.26; H, 4.78; N, 6.57. Found C, 73.19; H, 4.83; N, 6.34.

4.2.4. 2,4-Bis[5-(1-naphthyl)pyrrol-2-yl]cyclobutenediylium-1,3-diolate (14). Greenish solid (78%), mp $>$ 300 °C; R_f=0.36 (EtOAc/CHCl$_3$=3:7); δ_H (400 MHz; DTFA–CDCl$_3$; Me$_4$Si) 8.20 (2H, m, naphthyl C-1′H), 8.05, 7.95 (each 2H, m, naphthyl C–H), 7.82 (2H, m, 3-H of pyrrole), 7.70 (2H, bs, naphthyl C–H), 7.61 (6H, m, naphthyl C-3′, 6′ and 7′ H), 7.15 (2H, m, 4-H of pyrrole). λ_{max} (CHCl$_3$)/nm 613 (ε 149,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3425, 3051, 1624, 1593, 1558, 1516, 945, 768 and 664; *m*/*z* (FAB) 487 (13, M+Na), 465 (90, M+H), 464 (100, M), 443 (25), 349 (33), 336 (57), 329 (87), 307 (48), 289 (40), 264 (28); HRMS M, $C_{32}H_{20}N_2O_2$ calcd 464.1525, found 464.1502. Anal. calcd for $C_{32}H_{20}N_2O_2$, C, 82.74; H, 4.34; N, 6.03. Found C, 81.91; H, 4.29; N, 5.75.

4.2.5. 2,4-Bis[(*E*)-5-styrylpyrrol-2-yl]cyclobutenediylium-1,3-diolate (16). Greenish solid (54%), mp $>$ 300 °C; R_f=0.40 (EtOAc/CHCl$_3$=3:7). This substance did not give a satisfactory ^{1}H NMR spectrum in CDCl$_3$/DTFA or in pyridine-d_5. λ_{max} (CHCl$_3$)/nm 673 (ε 146,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3421, 1593, 1551, 1501, 941, 847, 799, 745, 687 and 640; *m*/*z* (FAB) 417 (78, M+H), 416 (82, M), 338 (45); HRMS M, $C_{28}H_{20}N_2O_2$ calcd 416.1525, found 416.1505.

4.2.6. 2,4-Bis[5-(4-methyl)indano-4*H*-[1,2-*b*]pyrrol-2-yl]cyclobutenediylium-1,3-diolate (17). Lustrous greenish fine needles (42%), mp $>$ 300 °C. An ^{1}H NMR spectrum could not be obtained (low solubility in CDCl$_3$/DTFA and pyridine-d_5). λ_{max} (CHCl$_3$)/nm 654 (ε 347,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3450, 1612, 1535, 1447, 1408, 1045, 945, 814, 795, 768 and 714; *m*/*z* (FAB); HRMS M, $C_{28}H_{20}N_2O_2$ calcd 416.1525, found 416.1545. Anal. calcd for $C_{28}H_{20}N_2O_2$, C, 80.75; H, 4.84; N, 6.73. Found C, 80.92; H, 4.90; N, 6.49.

4.2.7. 2,4-Bis[5-(3-methyl-4,5-dihydro-1*H*)benz[*g*]-indolyl-2-yl]cyclobutenediylium-1,3-diolate (18). Fine greenish crystals (80%), mp 280 °C; R_f=0.72 (EtOAc/CHCl$_3$=3:7). ^{1}H NMR spectra could not be obtained (low solubility in CDCl$_3$/DTFA and pyridine-d_5). λ_{max} (CHCl$_3$)/nm 660 (ε 403,500 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3400, 1612, 1528, 1472, 1420, 1369, 1302, 1283, 1180, 1113, 1088, 1061, 972, 955, 885 and 764; *m*/*z* (FAB) 445 (33, M+H), 444 (50, M), 329 (40); HRMS M, $C_{30}H_{24}N_2O_2$ calcd 444.1838, found 444.1846. Anal. calcd for $C_{30}H_{24}N_2O_2$, C, 81.05; H, 5.44; N, 6.30. Found C, 81.25; H, 5.44; N, 6.27.

4.3. Model compound

4.3.1. 2,5-Bis[3,5-dimethyl-4-ethylpyrrol-2-yl]cyclohexadiene-1,4-dione (5). 3-Ethyl-2,4-dimethylpyrrole (30 mg, 0.24 mmol) in ethanol (3 ml) and 1,4-benzoquinone (36.3 mg, 0.34 mmol.) in chloroform/ethanol mixture (1:1) (3 ml) were mixed together and stirred at room temperature for 20 min. The solution became purple in colour, and then very dark. The reaction was diluted with ethanol (6 ml) and kept in the freezer overnight. The greenish purple solid was filtered off and washed with ethanol (10 ml) to give 12 mg (28% yield) of the title quinone as a dark purple solid with a greenish iridescence, mp 245–250 °C (lit[28] mp 250 °C); R_f=0.33 (light petroleum/$CHCl_3$ =1:4); δ_H (400 MHz; $CDCl_3$; Me_4Si) 10.90 (2H, bs, N–H), 6.60 (2H, s, quinone C–H), 2.40 (8H, quartet, J=7.4 Hz, CH_2CH_3), 2.30 (12H, bs, C-3, C-5 CH_3), 1.10 (6H, t, J=7.4 Hz, CH_2CH_3); ($CHCl_3$)/nm 569 (ε 30,000 M^{-1} cm^{-1}); ν_{max} (KBr)/cm^{-1} 3346, 1602, 1560, 1535, 991, 962, 864, 791; *m/z* (FAB) 353 (32), 352 (86), 351 (100, M+H), 350 (79, M) and 349 (42); HRMS calcd for M+H, $C_{22}H_{27}N_2O_2$ 351.2073, found 351.2080. It proved possible to obtain crystals of **5** suitable for X-ray analysis by slow evaporation of a chloroform solution at room temperature.[30]

Acknowledgements

We thank the Medical Research Council (MRC) and Scotia Pharmaceuticals Plc., Stirling for an industrial collaborative research award (to J.S.), Dr. H. Toms and Mr. P. Haycock for 600 and 400 MHz NMR spectroscopic studies (ULIRS service), and Mr. M. Cocksedge for mass spectrometric results (School of Pharmacy, ULIRS service).

References and notes

1. Seitz, G.; Imming, P. *Chem. Rev.* **1992**, *92*, 1227–1260.
2. Law, K.-Y. *Chem. Rev.* **1993**, *93*, 449–486.
3. Ajayaghosh, A. *Chem. Soc. Rev.* **2003**, *32*, 181–191.
4. Yagi, S.; Hyodo, Y.; Matsumoto, S.; Takahashi, N.; Kono, H.; Nakazumi, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 599–603.
5. Bonnett, R. *Chemical Aspects of Photodynamic Therapy*; Gordon & Breach: Amsterdam, 2000.
6. Ramaiah, D.; Joy, A.; Chandasekhar, N.; Eldho, N. V.; Das, S.; George, M. V. *Photochem. Photobiol.* **1997**, *65*, 783–790.
7. Ramaiah, D.; Eckert, I.; Arun, K. T.; Weidenfeller, L.; Epe, B. *Photochem. Photobiol.* **2002**, *76*, 672–677.
8. Reis, V.; Serrano, J. P. C.; Almeida, P.; Santos, P. F. *Synlett* **2002**, 1617–1620.
9. Morgan, A. R.; Menes, M. E.; Wang, R. PCT Int. Appl. WO 00 44,742, 3 Aug 2000, pp 1–37; *Chem. Abstr.* **2000**, *133*, 151988.
10. Treibs, A.; Jacob, K. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 694.
11. Treibs, A.; Jacob, K. *Liebig's Ann Chem.* **1966**, *699*, 153–167.
12. Patrick, B.; George, M. V.; Kamat, P. V.; Das, S.; Thomas, K. J. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 671–676.
13. Lynch, D. E.; Geisler, U.; Peterson, I. R.; Floersheimer, M.; Terbrack, R.; Chi, L. F.; Fuchs, H.; Calos, N. J.; Wood, B.; Kennard, C. H. L.; Langley, G. J. *J. Chem. Soc., Perkin Trans.* **1997**, *2*, 827–832.
14. Lynch, D. E.; Peterson, I. R.; Floersheimer, M.; Essing, D.; Chi, L. F.; Fuchs, H.; Calos, N. J.; Wood, B.; Kennard, C. H. L.; Langley, G. J. *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 779–784.
15. Ajayaghosh, A.; Chenthamarakshan, C. R.; George, M. V. *Chem. Mater.* **1997**, *9*, 644–646.
16. Chenthamarakshan, C. R.; Ajayaghosh, A. *Chem. Mater.* **1998**, *10*, 1657–1663.
17. Ajayaghosh, A.; Eldo, J. *Org. Lett.* **2001**, *3*, 2595–2598.
18. Eldo, J.; Ajayaghosh, A. *Chem. Mater.* **2002**, *14*, 410–418.
19. Chenthamarakshan, C. R.; Eldo, J.; Ajayaghosh, A. *Macromolecules* **1999**, *32*, 5846–5851.
20. Chenthamarakshan, C. R.; Eldo, J.; Ajayaghosh, A. *Macromolecules* **1999**, *32*, 251–257.
21. Treibs, A.; Jacob, K. *Liebig's Ann. Chem.* **1968**, *712*, 123–137.
22. Law, K.-Y.; Bailey, F. C. *J. Org. Chem.* **1992**, *57*, 3278–3286.
23. Terpetschnig, E.; Jakowicz, J. R. *Dyes Pigments* **1993**, *21*, 227–234.
24. Maahs, G.; Hegenberg, P. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 888–893. Sprenger, H.-E.; Ziegenbein, W. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 530–535. Schmidt, A. H. *Synthesis* **1980**, 961–994.
25. Kazmaier, P.; Hamer, G. K.; Burt, R. A. *Can. J. Chem.* **1990**, *68*, 530–536.
26. Chenthamarakshan, C. R.; Ajayaghosh, A. *Tetrahedron Lett.* **1998**, *39*, 1795–1798.
27. Bonnett, R.; Davies, J. E.; Hursthouse, M. B.; Sheldrick, G. M. *Proc. R. Soc. London* **1978**, *B202*, 249–268.
28. Fischer, H.; Treibs, A.; Zaucker, E. *Chem. Ber.* **1959**, *92*, 2026–2029.
29. Trotter, J. *Acta Crystallogr.* **1960**, *13*, 86–90.
30. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-210221. Copies of the data can be obtained, free of charge, on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336-033 or e-mail deposit@ccdc.cam.ac.uk]
31. Block, M. A. B.; Khan, A.; Hecht, S. *J. Org. Chem.* **2004**, *69*, 184–187.
32. Chen, J.; Burghart, A.; Derecskei-Kovacs, A.; Burgess, K. *J. Org. Chem.* **2000**, *65*, 2900–2906.
33. Burghart, A.; Kim, H.; Welch, M. B.; Thoresen, L. H.; Reibenspies, J.; Burgess, K. *J. Org. Chem.* **1999**, *64*, 7813–7819.
34. Chen, W.; Stephenson, E. K.; Cava, M. P.; Jackson, Y. A. *Org. Synth.* **1991**, *70*, 151–156.
35. Jones, R. A.; Lindner, J. A. *Aust. J. Chem.* **1954**, *18*, 875–885.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8919–8927

Synthesis of 3,3,3-trifluoroprop-1-enyl compounds from some enolizable aldehydes

Satomi Yamamoto,[a] Hiroshi Sugimoto,[a] Osamu Tamura,[a] Tatsuya Mori,[b] Noritada Matsuo[b] and Hiroyuki Ishibashi[a,*]

[a]*Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kanazawa, Ishikawa 920-1192, Japan*
[b]*Agricultural Chemicals Research Laboratory, Sumitomo Chemical Co. Ltd, Takarazuka, Hyogo 665-8555, Japan*

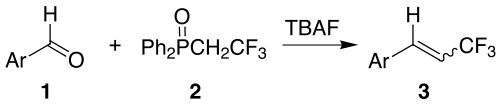
Received 30 April 2004; accepted 7 July 2004

Available online 23 August 2004

Abstract—2,2,2-Trifluoroethyldiphenylphosphine oxide [$Ph_2P(O)CH_2CF_3$] (**2**) is known to give no Horner reaction product with enolizable aldehydes. We found, however, that some enolizable aldehydes such as *N*-Boc-pyrrolidine-2-aldehyde (**9**) gave the expected 3,3,3-trifluoroprop-1-enyl compounds by reaction with **2**. The products could be further transformed to some 2,2,2-trifluoroethyl-substituted nitrogen-containing heterocycles by using radical cyclization or Heck reaction.
© 2004 Elsevier Ltd. All rights reserved.

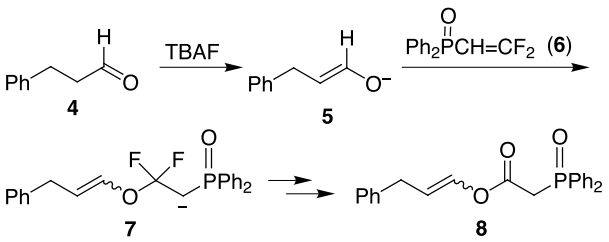
1. Introduction

The introduction of fluorine atoms into biologically active compounds often intensifies their activities.[1] A 3,3,3-trifluoroprop-1-enyl structure ($CF_3CH{=}CH–$) has been found in candidates for medicines[2] or agricultural chemicals.[3] Various methods have been developed for synthesizing 3,3,3-trifluoroprop-1-enyl compounds, but the methods have several disadvantages, such as the requirement of a multi-step sequence of reactions and the use of expensive and/or the low boiling point reagents.[4] One of the most direct routes to synthesize trifluoropropenyl structure seems to be the use of Wittig-type reaction of an aldehyde with a trifluoromethyl-containing reagent. We have recently reported a convenient method for the synthesis of 3,3,3-trifluoroprop-1-enyl compounds **3** by means of Horner reaction of aromatic aldehydes **1** with 2,2,2-tifluoroethyldiphenylphosphine oxide (**2**) using tetrabutylammonium fluoride (TBAF) as a base (Scheme 1).[5]



Scheme 1.

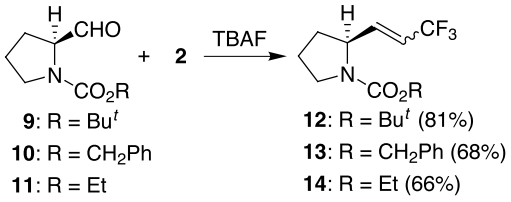
In the course of our studies, reaction of **2** with aliphatic aldehydes such as 3-phenylpropanal (**4**) was found to afford no desired 3,3,3-trifluoroprop-1-enyl compound and instead to give only ester **8** (Scheme 2). Formation of **8** may be explained by assuming that aldehyde **4** gives enolate **5** by action of the basic TBAF, and enolate **5** attacks vinylphosphine oxide **6**, which is formed from **2** by an elimination of HF under basic conditions, to give the adduct **7**. This compound is then transformed to ester **8** via steps. Therefore, the preparation of 3,3,3-trifluoroprop-1-enyl compounds with **2** appeared to be restricted to non-enolizable aldehydes. We soon found, however, that some enolizable aliphatic aldehydes such as *N*-Boc-pyrrolidine-2-aldehyde (**9**) gave the expected 3,3,3-trifluoroprop-1-enyl compounds by reaction with **2**. This paper describes the results of our work in this area, including the conversion of the products to some 2,2,2-trifluoroethyl-substituted nitrogen-containing heterocycles such as **34**.



Scheme 2.

Keywords: 3,3,3-Trifluoroprop-1-enyl compounds; 2,2,2-Trifluoroethyldiphenylphosphine oxide; Enolizable aldehydes.
* Corresponding author. Tel.: +51-76-234-4474; fax: +51-76-234-4476; e-mail: isibasi@p.kanazawa-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.030



Scheme 3.

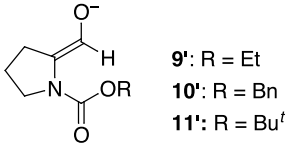
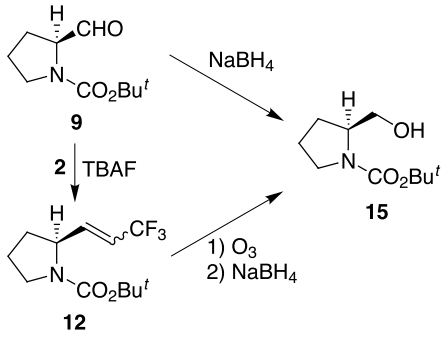


Figure 1.



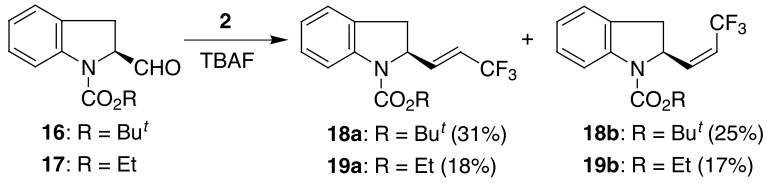
Scheme 4.

2. Results and discussion

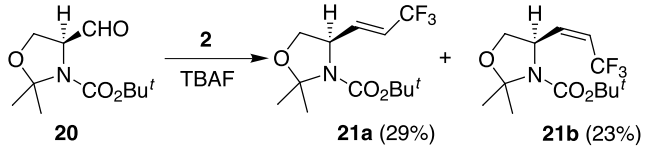
We initiated our investigation by examining the reaction of **2** with *N*-protected pyrrolidine-2-aldehydes **9–11** under previously reported[5] conditions. Treatment of a mixture of *N*-Boc-pyrrolidine-2-aldehyde (**9**) and 2 equiv. of **2** with 10 equiv. of TBAF in THF at room temperature gave trifluoropropenyl compound **12** in 19% yield as a mixture of *E*- and *Z*-olefins in a ratio of 4:1 along with several unidentified products (Scheme 3).

Encouraged by the success in obtaining **12** from **9**, we further examined a similar reaction at −40 °C using a 1:3 mixture of **9** and **2** in the presence of 9 equiv. of TBAF to give **12** in 81% yield as a mixture of *E* and *Z* olefins in a ratio of 1:1. Compounds **10** and **11** with **2** also gave the corresponding trifluoropropenyl compounds **13** and **14** in 68% (*E*/*Z*=1:1) and 66% (*E*/*Z*=3:2) yields, respectively.

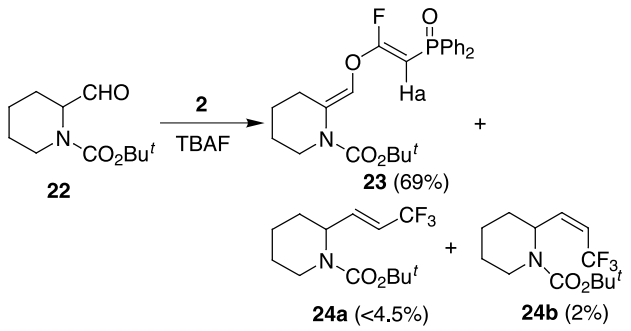
The higher yield of compound **12** (81%) compared to those of compounds **13** (68%) and **14** (66%) may be the result of the presence of a sterically more demanding *N*-Boc group in compound **9**. In the enolate forms **9′**, **10′** and **11′** derived from compounds **9–11**, the C2-position of the pyrroridine ring is an sp^2 hybridization as depicted in Figure 1, and, hence, the *N*-protecting group and the enolate would lie on the same plane. It can therefore be presumed that the presence of a large *N*-Boc group prevents the formation of the enolate **9′** and gives the desired Horner reaction product **12** in high yield.



Scheme 5.



Scheme 6.



Scheme 7.

The above assumption was supported by the following evidence. Reduction of aldehyde **9** with $NaBH_4$ gave alcohol **15** (Scheme 4). The specific rotation of **15** thus obtained was −47.7 (*c*=0.40, $CHCl_3$), which is virtually identical to that [−45.1 (*c*=0.40, $CHCl_3$] for compound **15** obtained by ozonolysis of the product **12**, prepared from **9**, followed by reduction of the resulting aldehyde with $NaBH_4$. These results clearly indicated that the starting compound **9** did not racemize under the basic conditions employed.

N-Boc-indoline-2-aldehyde (**16**) also gave the expected (*E*)-trifluoropropenyl compounds **18a** and its (*Z*)-isomer **18b** in 31 and 25% yields, respectively (Scheme 5). Similar reaction of the *N*-ethoxycarbonyl congener **17** gave **19a** and its isomer **19b**, though their yields were slightly lower (18 and 17%, respectively) than those of **18a**,**b**.

The reaction of Garner's aldehyde **20** with **2** gave the *E*-olefin **21a** and its *Z*-isomer **21b** in 9 and 17% yields at −40 °C, respectively (Scheme 6). When a similar reaction

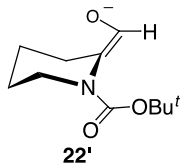
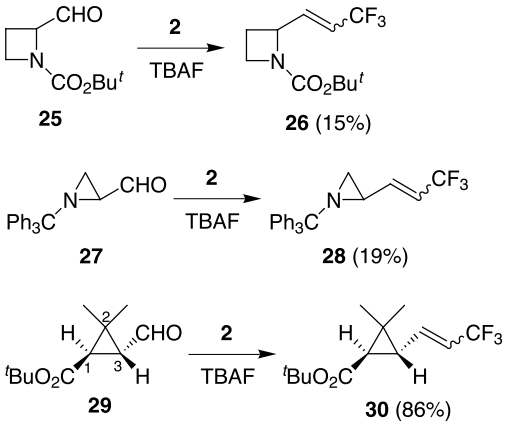
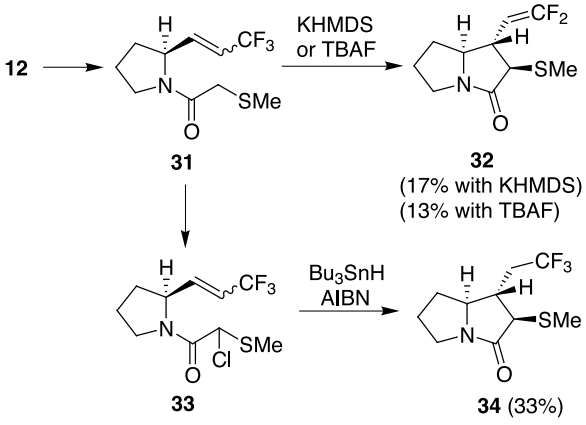


Figure 2.



Scheme 8.



Scheme 9.

was carried out at −60 °C, the yields of **21a** and **21b** were improved to 29 and 23%, respectively.

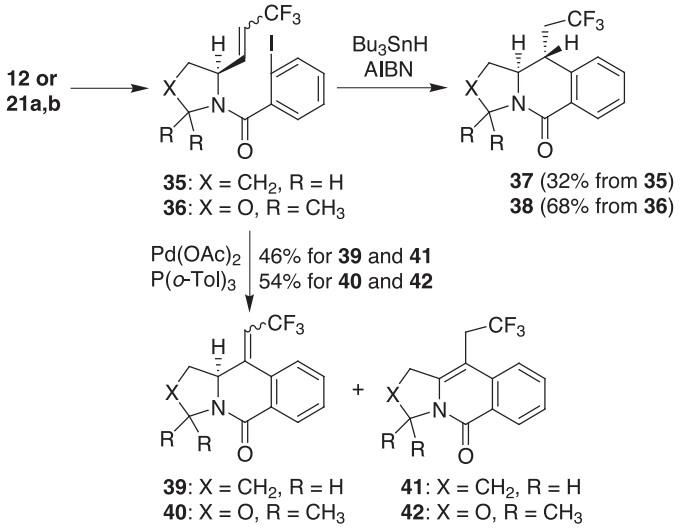
The reaction of piperidine derivative **22** with **2** gave **23** as the major product (69%), along with small amounts (<6.5%) of the desired products **24a**,**b** (Scheme 7). These results indicate that the compound **22** is easily enolizable, because enolate **22′** generated from **22** can be twisted in its chair form (Fig. 2). The stereochemistry of **23** as depicted in Scheme 7 was deduced by considering that the oxygen atom of the vinyl ether (O–CH=C–N) must be located so as to avoid the steric repulsion and the spin–spin coupling constant (J= 34.5 and 6.1 Hz) of the alkenic proton (H_a).

The azetidine-2-aldehyde **25** and aziridine-2-aldehyde **27** were expected to retard enolization due to the nature of their small ring, but, only 15% (E/Z=2:3) and 19% (E/Z=1:2) yields of the desired trifluoropropenyl compounds **26** and **28** were obtained (Scheme 8). The reasons for low yields of **26** and **28** are not known at present. However, cyclopropanealdehyde **29** gave the expected trifluoropropenyl compound **30** (E/Z=4:1) in very high yield (86%).

Finally, transformation of trifluoropropenyl compound **12** to several fluorine-containing heterocycles was examined. *N*-Deprotection of **12** with trifluoroacetic acid followed by acylation of the resulting amine with (methylthio)acetic acid gave (methylthio)acetamide **31**. Base-promoted cyclization of **31** using KHMDS or TBAF gave compound **32**, although the yields were low (17 and 13%, respectively) (Scheme 9).

On the other hand, chlorination of **31** with NCS followed by treatment of the resulting α-chlorosulfide **33** with Bu_3SnH in the presence of azobisisobutyronitrile (AIBN) gave the 5-*exo* radical cyclization product **34** in 33% yield along with several unidentified products, some of which might be stereoisomers of **34**.

Radical cyclization of compound **35**, prepared from **12**, afforded **37** in 32% yield (Scheme 10). The Heck reaction of **35** with $Pd(OAc)_2$ in the presence of $P(o\text{-Tol})_3$ and Et_3N gave a mixture of **39** and **41** in 46% overall yield in a ratio of



Scheme 10.

1:5. When this mixture was exposed to Et_3N, the ratio of **39** and **41** changed to 1:10.

Similarly, radical reaction of **36**, prepared from **21a**,**b**, gave **38** in 68% yield. The Heck reaction of **36** gave a mixture of **40** and **42** in 54% overall yield in a ratio of 1:2.

3. Conclusions

In conclusion, we have revealed that some enolizable aliphatic aldehydes such as prrolidine-2-aldehydes **9–11** give the desired 3,3,3-trifluoroprop-1-enyl compounds **12–14** by reaction with **2**. We assumed that the effectiveness of formation of **12–14** from **9–11** may be a result of the difficulty of enolization due to the presence of a sterically more demanding *N*-protecting group of compound **9–11**.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured with a HORIBA SEPA-300 polarimeter. IR spectra were recorded with a Shimadzu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were measured on JEOL JNM-EX 270 and JEOL JNM-GSX 500 spectrometers for solutions in $CDCl_3$ [except for ^1H NMR spectrum of compounds **37** and **38** and ^{13}C NMR spectrum of compounds **32**, 5,5,5-trifluoro-2-(*N*-2-iodobenzoyl)amino-3-penten-1-ol (an intermediate for the synthesis of **36**), **38**]. δ Values quoted are relative to TMS (tetramethylsilane). For ^{13}C NMR, diagnostic data are expressed. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102A instrument. Column chromatography was performed on Silica gel 60 PF_{254} under pressure. 1 M solution of TBAF was purchased from Tokyo Chemical Industry. Aldehydes **9**,[6] **10**,[7] **11**,[8] **16**,[9] **22**,[10] **25**[11] and **27**[12] were prepared from the corresponding alcohols according to the reported procedures. Aldehydes **20** and **29** were purchased from Tokyo Chemical Industry and Sumitomo Chemical Co., Ltd, respectively.

4.2. Physical data for compounds 9, 10, 11, 16, 22, 25 and 27

4.2.1. (*S*)-1-*tert*-Butoxycarbonyl-2-pyrrolidinecarboxaldehyde (9).[6] $[\alpha]_D^{24}$ −98.4 (*c* 0.66, $CHCl_3$); ^1H NMR δ 1.43 (s, *t*Bu), 1.48 (total 9H, s, *t*Bu), 1.82–2.21 (4H, m, H-3, 4), 3.41–3.63 (2H, m, H-5), 3.98–4.27 (1H, m, H-2), 9.47 (s, C*H*O), 9.56 (total 1H, s, C*H*O).

4.2.2. (*S*)-1-Benzyloxycarbonyl-2-pyrrolidinecarboxaldehyde (10).[7] $[\alpha]_D^{24}$ −62.2 (*c* 1.3, MeOH); ^1H NMR δ 1.75–2.18 (4H, m, H-3, 4), 3.51–3.62 (2H, m, H-5), 4.18–4.32 (1H, m, H-2), 5.13 (s, CH_2Ph), 5.17 (total 2H, s, CH_2Ph), 7.26–7.42 (5H, m, Ar-H), 9.49 (s, C*H*O), 9.59 (total 1H, s, C*H*O).

4.2.3. (*S*)-1-Ethoxycarbonyl-2-pyrrolidinecarboxaldehyde (11).[8] $[\alpha]_D^{24}$ −97.6 (*c* 0.31, EtOH); ^1H NMR δ 1.19–1.31 (3H, m, CH_2CH_3), 1.85–2.21 (4H, m, H-3,4), 3.49–3.65 (2H, m, H-5), 4.03–4.30 (3H, m, H-2, CH_2CH_3), 9.51 (s, C*H*O), 9.58 (total 1H, s, C*H*O).

4.2.4. 1-*tert*-Butoxycarbonyl-2-indolinecarboxaldehyde (16).[9] ^1H NMR δ 1.53–1.61 (9H, m, *t*Bu), 3.14 (1H, dd, J=16.7, 5.4 Hz, one of H-3), 3.29–3.52 (1H, br, one of H-3), 4.63–4.92 (1H, br, H-2), 6.92–7.28 (3H, m, Ar-H), 7.36–7.97 (1H, br, Ar-H), 9.65 (1H, s, C*H*O).

4.2.5. 1-*tert*-Butoxycarbonyl-2-piperidinecarboxaldehyde (22).[10] ^1H NMR δ 1.15–1.73 (5H, m), 1.47 (9H, s, *t*Bu), 2.14–2.21 (1H, m), 2.75–3.00 (1H, br), 3.80–4.09 (1H, br), 4.44–4.66 (1H, br), 9.59 (1H, s, C*H*O).

4.2.6. 1-*tert*-Butoxycarbonyl-2-azetidinecarboxaldehyde (25).[11] ^1H NMR δ 1.44 (9H, s, *t*Bu), 1.97–2.51 (2H, m, H-3), 3.73–4.04 (2H, m, H-4), 4.50–4.66 (1H, m, H-2), 9.78 (1H, s, C*H*O).

4.2.7. 1-Triphenylmethyl-2-aziridinecarboxaldehyde (27).[12] ^1H NMR δ 1.55 (1H, d, J=6.3 Hz, one of H-3), 1.98 (1H, td, J=6.3, 2.6 Hz, H-2), 2.31 (1H, d, J=1.7 Hz, one of H-3), 7.19–7.54 (15H, m, Ar-H), 9.32 (s, C*H*O), 9.34 (total 1H, s, C*H*O).

4.3. Horner reaction of 9–11

4.3.1. (*S*)-1-*tert*-Butoxycarbonyl-2-(3,3,3-trifluoroprop-1-enyl)pyrrolidine (12). General procedure. Molecular sieves 4A (MS 4A) (1.5 g) were added to a 1 M solution of TBAF in THF (1.8 mL), and the mixture was stirred at room temperature overnight. The mixture was cooled to −40 °C, and to the mixture was added a solution of aldehyde **9** (39.9 mg, 0.2 mmol) and phosphine oxide **2** (170.5 mg, 0.6 mmol) in THF (5 mL) at −40 °C. After the mixture was stirred for 15 min, water (3 mL) was added dropwise and the mixture was allowed to warm to room temperature. After removal of MS 4A by filtration, water was added to the filtrate, and the whole was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 4:1) to give **12** (42.9 mg, 81%, *E*/*Z*=1:1) as a colorless oil. Rotamers of **12** were observed by ^1H and ^{13}C NMR. IR ν 1690 cm^{-1}; ^1H NMR δ 1.43 (9H, s, *t*Bu), 1.66–2.28 (4H, m, H-3, 4), 3.34–3.60 (2H, m, H-5), 4.25–4.76 (1H, br, H-2), 5.47–5.71 (1H, m, CH=C*H*CF_3), 5.86–6.05 [1/2H, br t, J=10.3 Hz, (*Z*)-C*H*=$CHCF_3$], 6.17–6.35 [1/2H, br d, J=16.2 Hz, (*E*)-C*H*=$CHCF_3$]; ^{13}C NMR (for one rotamer) δ 23.3, 28.7, 32.1, 46.8, 55.4, 80.2, 118.4 (q, J=34.2 Hz), 123.5 (q, J=272.2 Hz), 141.1, 154.7; MS (EI) *m*/*z* (%) 265 (M^+, 9.9), 209 (63), 192 (48), 96 (39), 57 (100); HRMS (FAB) calcd for $C_{12}H_{19}F_3NO_2$ [$(M+H)^+$] 266.1368, found 266.1379.

4.3.2. (*S*)-1-Benzyloxycarbonyl-2-(3,3,3-trifluoroprop-1-enyl)pyrrolidine (13). According to the general procedure, aldehyde **10** (116.6 mg, 0.5 mmol) was treated with phosphine oxide **2** (426.3 mg, 1.5 mmol) in THF (10 mL) in the presence of a 1 M solution of TBAF in THF (4.5 mL, 4.5 mmol) and MS 4A (3.6 g) at −40 °C for 15 min. Workup and chromatography (hexane–AcOEt, 3:1) gave **13** (102.4 mg, 68%, *E*/*Z*=1:1) as a colorless oil. Rotamers of **13** were observed by ^1H and ^{13}C NMR. IR ν 1700 cm^{-1}; ^1H

NMR δ 1.64–2.30 (4H, m, H-3, 4), 3.38–3.65 (2H, m, H-5), 4.35–4.57 [1/2H, br d, (*E*)-H-2], 4.68–4.83 [1/2H, m, (*Z*)-H-2], 5.02–5.20 (2H, m, C*H*$_2$Ph), 5.41–5.77 (1H, m, CH=C*H*CF$_3$), 5.82–6.03 [1/2H, m, (*Z*)-C*H*=CHCF$_3$], 6.20–6.38 [1/2H, m, (*E*)-C*H*=CHCF$_3$], 7.18–7.42 (5H, m, Ar-H); ^{13}C NMR (for one rotamer) δ 24.3, 34.0, 47.5, 55.3, 67.4, 118.8 (q, J=34.2 Hz) [117.32 (q, J=34.2 Hz)], 121.1, 128.4, 128.5, 128.8, 128.9, 136.9, 140.7, 144.8 (the signals for CF$_3$ could not be identified due to the low intensity and high multiplicity); MS (FAB) *m*/*z* (%) 300 (M+1$^+$, 16), 192 (11), 149 (7.9), 91 (100); HRMS (FAB) calcd for $C_{15}H_{17}F_3NO_2$ [(M+H)$^+$] 300.1211, found 300.1215.

4.3.3. (*S*)-1-Ethoxycarbonyl-2-(3,3,3-trifluoroprop-1-enyl)pyrrolidine (14). According to the general procedure, aldehyde **11** (85.6 mg, 0.5 mmol) was treated with phosphine oxide **2** (426.3 mg, 1.5 mmol) in the presence of a 1 M solution of TBAF in THF (4.5 mL, 4.5 mmol) and MS 4A (3.6 g) in THF (10 mL) at −40 °C for 15 min. Workup and chromatography (hexane–AcOEt, 3:1) gave **14** (78.3 mg, 66%, *E*/*Z*=3:2) as a colorless oil. Rotamers of **14** were observed by ^{1}H and ^{13}C NMR. IR ν 1680 cm^{-1}; ^{1}H NMR δ 1.09–1.38 (3H, m, CH$_2$C*H*$_3$), 1.62–2.29 (4H, m, H-3,4), 3.32–3.65 (2H, m, H-5), 3.95–4.28 (2H, m, C*H*$_2$CH$_3$), 4.30–4.60 [3/5H, br, (*E*)-H-2], 4.65–4.81 [2/5H, m, (*Z*)-H-2], 5.44–5.79 (1H, m, CH=C*H*CF$_3$), 5.79–6.02 [2/5H, m, (*Z*)-C*H*=CHCF$_3$], 6.15–6.38 [3/5H, br d, J=15.3 Hz, (*E*)-C*H*=CHCF$_3$]; ^{13}C NMR (for one rotamer) δ 14.6, 22.8, 31.6, 46.5, 57.1, 61.2, 118.2 (q, J=34.7 Hz), 123.1 (q, J=268.1 Hz), 140.2, 155.2; HRMS (FAB) calcd for $C_{10}H_{15}F_3NO_2$ [(M+H)$^+$] 238.1055, found 238.1066.

4.4. Formation of 15 from 9 or 12

4.4.1. Reduction of 9. To a solution of aldehyde **9** (300 mg, 1.51 mmol) in MeOH (5 mL) was added NaBH$_4$ (178.7 mg, 4.72 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, from 2:1 to 1:1) to give (*S*)-1-*tert*-butoxycarbonyl-2-pyrrolidinemethanol (**15**) (241.7 mg, 80%) as a colorless oil: $[\alpha]_D^{26}$ −47.7 (*c*, 0.40, CHCl$_3$) [lit.[13] $[\alpha]_D^{24}$ −48.83 (*c* 1.2, CHCl$_3$)]; ^{1}H NMR δ 1.47 (9H, s, *t*Bu), 1.72–2.09 (4H, m, H-3, 4), 3.25–3.96 (4H, m, H-5, C*H*$_2$OH), 3.83–4.05 (1H, br, H-2), 4.67–4.82 (1H, br, O*H*).

4.4.2. Ozonolysis of 12 followed by reduction of 9. Ozone was introduced into a solution of compound **12** (400 mg, 1.51 mmol) in CH$_2$Cl$_2$–MeOH (10:1, 5 mL) at −78 °C for 50 min. To the mixture diluted with MeOH (5 mL) was added NaBH$_4$ (68.5 mg, 1.81 mmol), and the mixture was allowed to warm to 0 °C. After 3.5 h, the mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1) to give **15** (39.3 mg, 40%) as a colorless oil: $[\alpha]_D^{26}$ −45.1 (*c* 0.40, CHCl$_3$) [lit.[13] $[\alpha]_D^{24}$ −48.83 (*c* 1.2, CHCl$_3$)].

4.4.3. 1-Ethoxycarbonyl-2-indolinecarboxaldehyde (17). To a solution of (*S*)-indoline-2-carboxylic acid (500 mg, 3.06 mmol) in MeOH (5 mL) was added thionyl chloride (0.34 mL, 4.59 mmol), and the mixture was heated under reflux for 27 h. After cooling, the mixture was concentrated under reduced pressure to give crude methyl ester hydrochloride as a solid, which was dissolved in a mixture of CH$_2$Cl$_2$ and a saturated NaHCO$_3$ solution (1:1, 6 mL). Ethyl chloroformate (0.44 mL, 4.59 mmol) was added to the mixture at 0 °C, and the mixture was stirred vigorously at room temperature for 18.5 h. Water was added and the whole was extracted with CHCl$_3$, and the organic phase was washed with brine, dried (MgSO$_4$), and concentrated. The residue was dissolved in THF (10 mL), and this solution was added to a solution of LiBH$_4$ (286.8 mg, 13.2 mmol) in THF (5 mL) at 0 °C. After stirring at room temperature for 2 h, the mixture was diluted with water and the whole was extracted with AcOEt. The organic phase was washed with brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 3:1) to give (*S*)-1-ethoxycarbonyl-2-indolinemethanol (508.6 mg, 75%) as a colorless oil: $[\alpha]_D^{22}$ −56.6 (*c* 0.40, CHCl$_3$); IR ν 3420, 1690 cm^{-1}; ^{1}H NMR δ 1.39 (3H, t, J=7.3 Hz, CH$_2$C*H*$_3$), 2.74–3.00 (1H, br d, J=16.3 Hz, one of H-3), 3.36 (1H, dd, J=16.3, 10.1 Hz, one of H-3), 3.65–3.85 (2H, m, CH$_2$OH), 4.33 (2H, q, J=7.3 Hz, C*H*$_2$CH$_3$), 4.54–4.71 (1H, br, H-2), 6.95–7.26 (3H, m, Ar-H), 7.39–7.75 (1H, br, Ar-H); ^{13}C NMR δ 15.0, 31.6, 61.4, 62.6, 65.9, 116.0, 123.5, 125.3, 127.9, 130.6, 142.0, 187.6; HRMS (FAB$^+$) calcd for $C_{12}H_{16}NO_3$ (M+1) 222.1130, found 222.1123. To a solution of *o*-iodoxybenzoic acid (IBX) (965.2 mg, 3.45 mmol) in DMSO (8 mL) was added a solution of (*S*)-1-ethoxycarbonyl-2-indolinemethanol (508.6 mg, 2.3 mmol) in THF (5 mL) at room temperature and the mixture was allowed to stand for 7 days. White precipitates were removed by filtration, water was added to the filtrate, and the whole was extracted with AcOEt. The extract was washed with brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, from 7:1 to 5:1) to give **17** (144.9 mg, 29%) as a pale yellow oil: ^{1}H NMR δ 1.22–1.55 (3H, m, CH$_2$C*H*$_3$), 3.19 (1H, dd, J=16.8, 5.0 Hz, one of H-3), 3.37–3.48 (1H, dd, J=16.8, 11.5 Hz, one of H-3), 4.19–4.42 (2H, m, C*H*$_2$CH$_3$), 4.75–4.94 (1H, m, H-2), 6.97–7.26 (3H, m, Ar-H), 7.45–7.98 (1H, br, Ar-H), 9.67 (1H, s, C*H*O). This compound was used immediately in the next step.

4.5. Horner reactions of 16, 17, 20, 22, 25, 27 and 29

4.5.1. (*S*)-1-*tert*-Butoxycarbonyl-2-[(*E*)-3,3,3-trifluoroprop-1-enyl]indoline (18a) and its (*Z*)-isomer (18b). According to the general procedure, aldehyde **16** (78.2 mg, 0.316 mmol) was treated with phosphine oxide **2** (269.6 mg, 0.948 mmol) in the presence of a 1 M solution of TBAF in THF (2.8 mL, 2.8 mmol) and MS 4A (2.3 g) in THF (15 mL) at −20 °C for 15 min. The crude material was chromatographed on silica gel (hexane–AcOEt, 12:1). The first fraction gave **18b** (24.3 mg, 25%) as a pale yellow oil: $[\alpha]_D^{24}$ −34.2 (*c* 0.40, CHCl$_3$); IR ν 1795 cm^{-1}; ^{1}H NMR δ 1.53 (9H, s, *t*Bu), 2.83 (1H, dd, J=16.6, 4.1 Hz, one of H-3), 3.50–3.65 (1H, m, one of H-3), 5.29–5.44 (1H, br, H-2), 5.58 (1H, dqd, J=11.5, 8.9, 1.3 Hz, CH=C*H*CF$_3$), 6.12 (1H, dd, J=11.9, 8.6 Hz, C*H*=CHCF$_3$), 6.93–7.25 (3H, m, Ar-H), 7.65–7.85 (1H, br, Ar-H); ^{13}C NMR δ 28.3, 35.7, 56.8, 81.7, 115.2, 116.7 (q, J=34.7 Hz), 122.7, 124.1,

124.6, 127.8, 141.8, 144.4, 144.5, 152.2 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{16}H_{19}F_3NO_2$ [$(M+H)^+$] 314.1368, found 314.1363. The second fraction gave **18a** (31.0 mg, 31%) as a pale yellow oil: $[\alpha]_D^{24}$ −24.7 (*c* 0.40, $CHCl_3$); IR ν 1700 cm^{-1}; ^1H NMR δ 1.53 (s, *t*Bu), 1.56 (total 9H, s, *t*Bu), 2.83 (1H, dd, *J*=16.2, 3.0 Hz, one of H-3), 3.48 (1H, dd, *J*=16.2, 10.4 Hz, one of H-3), 4.90–5.14 (1H, br, H-2), 5.72 (1H, dqd, *J*=15.8, 6.3, 1.8 Hz, CH=C*H*CF_3), 6.36 (1H, ddq, *J*=15.8, 6.9, 2.0 Hz, C*H*=$CHCF_3$), 6.95–7.26 (3H, m, Ar-H), 7.55–7.85 (1H, br, Ar-H); ^{13}C NMR δ 28.2, 34.1, 59.1, 81.7, 115.3, 118.6 (q, *J*=34.7 Hz), 123.0, 124.1, 124.7, 125.0, 128.0, 128.1, 139.3, 152.0 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{16}H_{19}F_3NO_2$ [$(M+H)^+$] 314.1368, found 314.1374.

4.5.2. (*S*)-1-Ethoxycarbonyl-2-[3,3,3-trifluoroprop-1-(*E*)-enyl]indoline (19a) and its (*Z*)-isomer (19b). According to the general procedure, aldehyde **17** (144.9 mg, 0.66 mmol) was treated with phosphine oxide **2** (563.9 mg, 1.98 mmol) in the presence of a 1 M solution of TBAF in THF (5.9 mL, 5.9 mmol) and MS 4A (4.8 g) in THF (10 mL) at −20 °C for 15 min. The crude material was chromatographed on silica gel (hexane–AcOEt, 20:1). The first fraction gave **19b** (32.2 mg, 17%) as a white solid: mp 68–69 °C (hexane); $[\alpha]_D^{25}$ −9.6 (*c* 0.40, $CHCl_3$); IR ν 1700 cm^{-1}; ^1H NMR δ 1.31 (3H, t, *J*=6.9 Hz, CH_2CH_3), 2.85 (1H, dd, *J*=16.5, 4.0 Hz, one of H-3), 3.55 (1H, dd, *J*=16.5, 10.5 Hz, one of H-3), 4.26 (2H, q, *J*=6.9 Hz, CH_2CH_3), 5.27–5.38 (1H, m, H-2), 5.59 (1H, dqd, *J*=11.9, 8.5, 1.0 Hz, CH=C*H*CF_3), 6.06 (1H, dd, *J*=11.9, 9.2 Hz, C*H*=$CHCF_3$), 6.90–7.26 (3H, m, Ar-H), 7.65–7.88 (1H, br, Ar-H); ^{13}C NMR δ 14.8, 35.8, 57.0, 62.2, 115.7, 117.6 (q, *J*=34.2 Hz), 121.4, 123.5, 125.2, 128.4, 129.4, 141.8, 143.4, 153.5 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{14}H_{15}F_3NO_2$ (M+1) 286.1055, found 286.1057. The second fraction gave **19a** (34.2 mg, 18%) as a brown solid: mp 79–80 °C (hexane); $[\alpha]_D^{24}$ −44.3 (*c* 0.40, $CHCl_3$); IR ν 1700 cm^{-1}; ^1H NMR δ 1.33 (3H, t, *J*=6.9 Hz, CH_2CH_3), 2.86 (1H, dd, *J*=16.2, 3.0 Hz, one of H-3), 3.50 (1H, dd, *J*=16.2, 10.2 Hz, one of H-3), 4.15–4.39 (2H, m, CH_2CH_3), 4.92–5.11 (1H, m, H-2), 5.74 (1H, dq, *J*=15.5, 6.3 Hz, CH=C*H*CF_3), 6.36 (1H, ddq, *J*=15.8, 6.9, 2.0 Hz, C*H*=$CHCF_3$), 6.97–7.26 (3H, m, Ar-H), 7.57–7.92 (1H, m, Ar-H); ^{13}C NMR δ 14.9, 34.6, 59.3, 62.3, 115.8, 119.2 (q, *J*=34.2 Hz), 121.3, 123.7, 125.3, 128.4, 129.3, 139.2, 141.9, 153.4 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{14}H_{15}F_3NO_2$ [$(M+H)^+$] 286.1055, found 286.1056.

4.5.3. (*S*)-3-*tert*-Butoxycarbonyl-4-[(*E*)-3,3,3-trifluoroprop-1-enyl]-2,2-dimethyl-1,3-oxazolidine (21a) and its (*Z*)-isomer (21b). According to the general procedure, aldehyde **20** (200 mg, 0.87 mmol) was treated with phosphine oxide **2** (743.5 mg, 2.61 mmol) in the presence of a 1 M solution of TBAF in THF (7.85 mL, 7.85 mmol) and MS 4A (6.3 g) in THF (40 mL) at −60 °C for 45 min. The crude material was chromatographed on silica gel (hexane–AcOEt, 12:1). The first fraction gave **21b** (61.4 mg, 23%) as an oil: $[\alpha]_D^{27}$ +4.3 (*c* 0.60, $CHCl_3$); IR ν 1695 cm^{-1}; ^1H NMR δ 1.43 (9H, s, *t*Bu), 1.43–1.63 (6H, m, 2×Me), 3.75 (1H, dd, *J*=9.1, 3.5 Hz, one of H-5), 4.16 (1H, dd, *J*=9.1, 6.8 Hz, one of H-5), 4.72–4.92 (1H, br, H-4), 5.64 (1H, br quin, *J*=9.9 Hz, CH=C*H*CF_3), 6.03 (1H, br t, *J*=10.3 Hz, C*H*=$CHCF_3$); ^{13}C NMR δ 23.9, 26.4, 28.3, 55.0, 68.5, 80.6, 94.7, 118.0 (q, *J*=34.7 Hz), 122.9 (q, *J*=270.5 Hz), 143.7, 151.7; HRMS (FAB) calcd for $C_{13}H_{21}F_3NO_3$ [$(M+H)^+$] 296.1473, found 296.1477. The second fraction gave **21a** (74.0 mg, 29%) as an oil: $[\alpha]_D^{27}$ −8.2 (*c* 0.60, $CHCl_3$); IR ν 1695 cm^{-1}; ^1H NMR δ 1.43 (9H, s, *t*Bu), 1.44–1.63 (6H, m, 2×Me), 3.80 (1H, dd, *J*=8.2, 2.3 Hz, one of H-5), 4.10 (1H, dd, *J*=8.2, 6.0 Hz, one of H-5), 4.31–4.57 (1H, m, H-4), 5.64–5.86 (1H, m, CH=C*H*CF_3), 6.23–6.41 (1H, m, C*H*=$CHCF_3$); ^{13}C NMR δ 23.5, 26.4, 28.3, 57.5, 67.2, 80.4, 94.6, 119.8 (q, *J*=34.7 Hz), 122.8 (q, *J*=268.2 Hz), 138.5, 151.5; HRMS (FAB) calcd for $C_{13}H_{21}F_3NO_3$ [$(M+H)^+$] 296.1473, found 296.1464.

4.5.4. 1-*tert*-Butoxycarbonyl-2-{(*E*)-[(*Z*)-1-fluoro-2-(diphenylphosphinoyl)ethenyl]oxymethylene}piperidine (23), 1-*tert*-butoxycarbonyl-2-[(*E*)-3,3,3-trifluoroprop-1-enyl]piperidine (24a) and its (*Z*)-isomer (24b). According to the general procedure, aldehyde **22** (219.7 mg, 1.03 mmol) was treated with phosphine oxide **2** (878.3 mg, 3.09 mmol) in the presence of a 1 M solution of TBAF in THF (9.3 mL, 9.3 mmol) and MS 4A (7.5 g) in THF (20 mL) at −40 °C for 15 min. The crude material was chromatographed on silica gel (hexane–AcOEt, 7:1 then 3:1 then 2:1 then 1:1 then AcOEt). The first fraction gave **24a** (12.9 mg, <4%) as an oil: ^1H NMR δ 1.07–1.76 (6H, m, H-3,4,5), 1.46 (9H, s, *t*Bu), 2.72–2.85 (1H, m, one of H-6), 3.95–4.05 (1H, m, one of H-5), 4.88–4.94 (1H, br, H-2), 5.62 (1H, dqd, *J*=15.8, 6.3, 2.0 Hz, CH=C*H*CF_3), 6.31 (1H, ddq, *J*=15.8, 4.3, 2.3 Hz, C*H*=$CHCF_3$). This material contained small amounts of inseparable by-products. The second fraction gave **24b** (7.2 mg, 2.5%) as a colorless oil: IR ν 1685 cm^{-1}; ^1H NMR δ 1.39–1.71 (6H, m, H-3,4,5), 1.44 (9H, s, *t*Bu), 2.85–2.95 (1H, m, one of H-6), 4.02–4.07 (1H, m, one of H-6), 5.21–5.29 (1H, br, H-2), 5.51 (1H, dqd, *J*=12.0, 8.8, 2.0 Hz, CH=C*H*CF_3), 6.26 (1H, dd, *J*=12.0, 9.4 Hz, C*H*=$CHCF_3$), ^{13}C NMR δ 20.0, 25.5, 28.8, 31.1, 39.6, 49.3, 80.5, 118.2 (q, *J*=34.2 Hz), 140.2, 155.4 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{13}H_{21}F_3NO_2$ [$(M+H)^+$] 280.1525, found 280.1527. The third fraction gave **23** (326.9 mg, 69%) as a plate: mp 168.5–170 °C (from AcOEt–hexane); IR ν 1655 cm^{-1}; ^1H NMR δ 1.39 (9H, s), 1.55–1.74 (4H, m, H-4,5), 2.28 (2H, t, *J*=5.6 Hz, H-6), 3.51 (2H, t, *J*=5.6 Hz, H-3), 4.71 (1H, dd, *J*=34.5, 6.1 Hz, PCH=CF), 6.51 (1H, s, OCH=C), 7.43–7.81 (10H, m, ArH); ^{13}C NMR δ 24.6, 24.7, 25.4, 28.7, 47.0, 71.8 (dd, *J*=111, 22 Hz), 81.2, 127.9, 129.0 (d, *J*=12 Hz), 131.5 (d, *J*=11 Hz), 132.1, 133.4, 134.4 (d, *J*=93 Hz), 154.1, 164.2 (d, *J*=270 Hz). Anal. calcd for $C_{25}H_{29}F_3NO_4P$: C, 65.64; H, 6.39; N, 3.06. Found: C, 65.44; H, 6.38; N, 2.99.

4.5.5. (*S*)-1-*tert*-Butoxycarbonyl-2-(3,3,3-trifluoroprop-1-enyl)azetidine (26). According to the general procedure, aldehyde **25** (128.0 mg, 0.69 mmol) was treated with phosphine oxide **2** (589.2 mg, 2.1 mmol) in the presence

of a 1 M solution of TBAF in THF (6.2 mL, 6.2 mmol) and MS 4A (5.0 g) in THF (28 mL) at −40 °C for 15 min. Workup and chromatography (hexane–AcOEt, from 5:1 to 3:1) gave **26** (26.8 mg, 15%, *E*/*Z*=2:3) as a colorless oil: IR ν 1695 cm^{-1}; ^1H NMR δ 1.42 (9H, s, *t*Bu), 1.97–2.10 (1H, m, one of H-3), 2.39–2.55 (1H, m, one of H-3), 3.80–3.97 (2H, m, H-4), 4.69–4.80 [2/5H, m, (*E*)-H-2], 5.06–5.19 [3/5H, m, (*Z*)-H-2], 5.60 [3/5H, dqd, *J*=11.8, 8.8, 1.3 Hz, (*Z*)-CH=C*H*CF_3], 5.82 [2/5H, dqd, *J*=15.5, 6.5, 1.5 Hz, (*E*)-CH=C*H*CF_3], 6.28 [3/5H, dd, *J*=11.8, 7.9 Hz, (*Z*)-C*H*=$CHCF_3$], 6.47 [2/5H, ddq, *J*=15.5, 5.3, 2.0 Hz, (*E*)-C*H*=$CHCF_3$]; ^{13}C NMR δ: 22.5, 23.2, 28.3, 58.1, 80.0, 117.7 (q, *J*=34.7 Hz), 139.3, 143.6, 156.4 (the signals for CF_3 of (*E*)- and (*Z*)-isomers could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{11}H_{17}F_3NO_2$ [$(M+H)^+$] 252.1211, found 252.1210.

4.5.6. (*S*)-2-(3,3,3-Trifluoroprop-1-enyl)-1-triphenylmethylaziridine (28). According to the general procedure, aldehyde **27** (57.1 mg, 0.183 mmol) was treated with phosphine oxide **2** (155.8 mg, 0.55 mmol) in the presence of a 1 M solution of TBAF in THF (1.65 mL, 1.65 mmol) and MS 4A (1.3 g) in THF (20 mL) at −40 °C for 1 h. Workup and chromatography (hexane–AcOEt, 7:1) gave **28** (13.2 mg, 19%, *E*/*Z*=1/2) as a pale yellow oil: IR ν 1670 cm^{-1}; ^1H NMR δ 1.43–2.32 (3H, m, H-2,3), 5.72 [1/3H, dq, *J*=11.7, 8.9 Hz, (*Z*)-CH=C*H*CF_3], 5.87 [2/3H, dq, *J*=15.9, 6.3 Hz, (*E*)-CH=C*H*CF_3], 5.92 [1/3H, dd, *J*=11.7, 9.4 Hz, (*Z*)-C*H*=$CHCF_3$], 6.37 [2/3H, ddq, *J*=15.9, 7.5, 2.0 Hz, (*E*)-C*H*=$CHCF_3$], 7.22–7.48 (15H, m, Ar-H); ^{13}C NMR δ 14.1, 22.7, 29.7, 126.9, 127.5, 127.6, 129.4, 144.0 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{24}N_{21}F_3N$ [$(M+H)^+$] 380.1627, found 380.1642.

4.5.7. (*R*)-*trans*-3-(3,3,3-Trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid *tert*-butylester (30). According to the general procedure, aldehyde **29** (140.0 mg, 0.707 mmol) was treated with phosphine oxide **2** (400.0 mg, 1.41 mmol) in the presence of a 1 M solution of TBAF in THF (7.0 mL, 7.0 mmol) and MS 4A (3.5 g) in THF (5 mL) at room temperature for 2 h. Workup and chromatography (hexane–AcOEt, 1:1) gave **30** (160.0 mg, 86%, *E*/*Z*=4:1): ^1H NMR δ 1.18 (3H, s, Me), 1.26 (3H, s, Me), 1.46 (9H, s, *t*Bu), 1.5–1.8 (1H, m, H-1), 2.02 [4/5H, m, (*E*)-H-3], 2.35 [1/5H, m, (*Z*)-H-3], 5.5–6.2 (2H, m, C*H*=C*H*CF_3); MS (FAB) *m*/*z* 265 [$(M+H)^+$]. An analytical sample was not obtained, since this compound was very volatile.

4.5.8. (*S*)-2-(3,3,3-Trifluoroprop-1-enyl)-1-[(methylthio)acetyl]pyrrolidine (31). To a solution of compound **12** (269.7 mg, 1.017 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.78 mL, 10.17 mmol) at room temperature. After stirring for 20 min, the mixture was concentrated to give the residue, which was dissolved in CH_2Cl_2 (4 mL). To this solution were added (methylthio)-acetic acid (0.13 mL, 1.53 mmol), EDC (292.4 mg, 1.53 mmol), Et_3N (0.21 mL, 1.53 mmol) and DMAP (15 mg, 0.12 mmol) at room temperature, and the mixture was stirred for 2 days. Water was added to the mixture and the whole was extracted with $CHCl_3$, washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **31** (189.5 mg, 73%, *E*/*Z*=1:1) as an oil. Rotamers of **31** were observed by ^1H and ^{13}C NMR. IR ν 1635 cm^{-1}; ^1H NMR δ 1.71–2.08 (4H, m, H-3,4), 2.21 (3H, s, S*Me*), 3.12–3.21 (2H, m, CH_2SMe), 3.48–3.75 (2H, m, H-5), 4.69–4.82 (1/2H, br, H-2), 4.88–5.05 (1/2H, m, H-2), 5.50–5.78 (1H, m, CH=C*H*CF_3), 5.92 [dd, *J*=12.0, 8.4 Hz, (*Z*)-C*H*=$CHCF_3$], 6.05 [total 1/2H, dd, *J*=12.0, 8.4 Hz, (*Z*)-C*H*=$CHCF_3$], 6.27–6.45 [1/2H, m, (*E*)-C*H*=$CHCF_3$]; ^{13}C NMR (for one rotamer) δ 15.3, 23.7, 29.8, 36.0, 47.3, 56.4, 118.2 (q, *J*=34.7 Hz), 118.3 (q, *J*=34.7 Hz), 119.1 (q, *J*=34.7 Hz)], 121.9, 139.1, 167.7 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{10}H_{15}F_3NOS$ [$(M+H)^+$] 254.0827, found 254.0819.

4.5.9. (1*S*,2*R*,7a*S*)-Hexahydro-1-(2,2-difluorovinyl)-2-methylthio-3*H*-pyrrolizin-3-one (32). To a solution of **31** (89.7 mg, 0.354 mmol) in THF (1 mL) was added a 0.5 M solution of KHMDS in toluene (2.12 mL, 1.062 mmol) at −78 °C and the mixture was stirred at the same temperature for 30 min. The reaction mixture was allowed to warm to room temperature and the mixture was poured into water and extracted with AcOEt, washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 1:1) to give **32** (14.0 mg, 17%) as a pale yellow oil: $[\alpha]_D^{25}$ +15.9 (*c* 0.23, $CHCl_3$); IR ν 1695 cm^{-1}; ^1H NMR δ 1.43–1.54 (1H, m, one of H-6), 2.02–2.26 (3H, m, H-7, one of H-6), 2.18 (3H, s, S*Me*), 2.67 (1H, br q, *J*=9.9 Hz, H-1), 3.08–3.18 (1H, m, H-7a), 3.51 (1H, d, *J*=12.0 Hz, H-2), 3.58–3.65 (2H, m, H-5), 4.32 (ddd, *J*=24.0, 9.5, 1.5 Hz, C*H*=CF_2); ^{13}C NMR (C_6D_6) δ 13.2, 26.1, 30.5, 41.9, 43.8, 55.7, 63.2, 78.4 (t, *J*=18 Hz), 157.9 (t, *J*=288 Hz), 169.2; HRMS calcd for $C_{10}H_{13}F_2NOS$ 233.0686, found 233.0670.

4.5.10. (1*S*,2*R*,7a*S*)-Hexahydro-1-(2,2,2-trifluoroethyl)-2-methylthio-3*H*-pyrrolizin-3-one (34). NCS (158.2 mg, 1.19 mmol) was added to a solution of **31** (250 mg, 0.99 mmol) in CCl_4 (2 mL) at 0 °C, and the mixture was stirred at room temperature for 15 min. The precipitates were filtered off and the filtrate was concentrated to give crude α-chlorosulfide **33**. To a boiling solution of α-chlorosulfide **33** in benzene (50 mL) was added dropwise a solution of Bu_3SnH (0.4 mL, 1.19 mmol) and AIBN (24.2 mg, 0.15 mmol) in benzene (50 mL) over a period of 3 h. After concentration of the mixture, Et_2O (30 mL) and an 8% aqueous KF solution (30 mL) were added to the residue, and the mixture was vigorously stirred at room temperature overnight. After filtration of the mixture, the organic phase was separated, and the aqueous phase was further extracted with Et_2O. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel (hexane–AcOEt, 7:1) to give **34** (83.9 mg, 33%) as a pale yellow oil: $[\alpha]_D^{24}$ +43.0 (*c* 1.20, $CHCl_3$); IR ν 1690 cm^{-1}; ^1H NMR δ 1.37–1.51 (1H, m, one of H-6), 2.03–2.14 (4H, m, H-1, 7, one of H-6), 2.16 (3H, s, S*Me*), 2.19–2.42 (1H, m, one of CH_2CF_3), 2.73 (1H, dqd, *J*=14.5, 11.9, 2.6 Hz, one of CH_2CF_3), 3.13 (1H, td, *J*=11.5, 3.6 Hz, one of H-5), 3.41 (1H, d, *J*=11.5 Hz, H-2), 3.56 (1H, dt, *J*=11.5, 8.3 Hz, one of H-5), 3.64 (1H, td, *J*=8.3, 5.9 Hz, H-7a); ^{13}C NMR δ 12.7, 26.2, 31.3, 35.9 (q, *J*=29.3 Hz), 41.3, 42.2, 55.3, 64.1,

126.1 (q, J=277.1 Hz), 168.6; HRMS (FAB) calcd for $C_{10}H_{15}F_3NOS$ [$(M+H)^+$] 254.0827, found 254.0828.

4.5.11. (*S*)-1-(2-Iodobenzoyl)-2-(3,3,3-trifluoroprop-1-enyl)pyrrolidine (35). To a solution of **12** (265.26 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) was added trifluoroacetic acid (0.77 mL, 10.0 mmol) at room temperature. After stirring for 45 min, the mixture was concentrated to give the residue, which was dissolved in a mixture of CH_2Cl_2 and a saturated $NaHCO_3$ solution (1:1, 6 mL). To this mixture was added a solution of 2-iodobenzoyl chloride (799.4 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) at room temperature. After the mixture was vigorously stirred for 5 h, water was added and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel (hexane–AcOEt, 3:1) to give **35** (370.2 mg, 94%, E/Z=7:5) as a brown oil. ^1H and ^{13}C NMR showed **35** to be a mixture of rotamers. IR ν 1630 cm^{-1}; ^1H NMR δ 1.77–2.40 (4H, m, H-3,4), 3.16–3.38 (1H, m, one of H-5), 3.63–3.97 (1H, m, one of H-5), 4.18–4.25 [1/2×7/12H, m, (*E*)-H-2], 4.55–4.69 [1/2×5/12H, m, (*Z*)-H-2], 4.82–4.97 [1/2×7/12H, m, (*E*)-H-2], 5.05–5.15 [1/2×5/12H, m, (*Z*)-H-2+1/2×7/12H, m, (*E*)-CH=C*H*CF_3], 5.24 [1/2×5/12H, dqd, J=11.5, 8.9, 1.7 Hz, (*Z*)-CH=C*H*CF_3], 5.68 [1/2×5/12H, dqd, J=11.8, 9.0, 1.5 Hz, (*Z*)-CH=C*H*CF_3], 5.85–6.02 [1/2×5/12H, m, (*Z*)-C*H*=$CHCF_3$+1/2×7/12H, m, (*E*)-CH=C*H*CF_3], 6.09 [1/2×7/12H, ddq, J=15.5, 6.8, 2.0 Hz, (*E*)-C*H*=$CHCF_3$], 6.24 [1/2×5/12H, dd, J=11.8, 8.5 Hz, (*Z*)-C*H*=$CHCF_3$], 6.46 [1/2×7/12H, ddq, J=15.8, 6.3, 2.2 Hz, (*E*)-C*H*=$CHCF_3$], 7.01–7.44 (3H, m, Ar-H), 7.78–7.85 (1H, m, Ar-H); ^{13}C NMR (for one rotamer) δ 24.5, 34.6, 49.1, 57.1, 119.5 (q, J=34.2 Hz), 127.3, 128.0, 128.3, 128.9, 129.3, 130.8, 139.7, 143.6, 169.4 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{14}H_{14}F_3INO$ [$(M+H)^+$] 396.0072, found 396.0043.

4.5.12. (*S*)-4-(3,3,3-Trifluoroprop-1-enyl)-3-(2-iodobenzoyl)-2,2-dimethyl-1,3-oxazolidine (36). A mixture of compound **21a**,**b** (379.5 mg, 1.28 mmol) and TsOH (1.222 g, 6.42 mmol) in MeOH (25 mL) was heated under reflux for 8 h. After cooling, the mixture was concentrated, and the residue was dissolved in a mixture of $CHCl_3$ and a saturated $NaHCO_3$ solution (1:3, 20 mL). To this mixture was added a solution of 2-iodobenzoyl chloride (513.6 mg, 1.93 mmol) in $CHCl_3$ (3 mL) at room temperature, and the mixture was vigorously stirred for 2 h. Water was added and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel (hexane–AcOEt, 7:1) to give 5,5,5-trifluoro-2-(*N*-2-iodobenzoyl)-amino-3-penten-1-ol (435.0 mg, 89%, E/Z=1:1) as a pale yellow solid. IR ν 3420, 1670 cm^{-1}; ^1H NMR δ 3.79–3.91 (2H, m, CH_2OH), 4.74–4.88 (br, NHC*H*), 4.99–5.13 (total 1H, br, NHC*H*), 5.78 [1/2H, br dq, J=11.5, 8.2 Hz, (*Z*)-CH=C*H*CF_3], 6.00 [1/2H, dqd, J=15.9, 5.9, 1.4 Hz, (*E*)-CH=C*H*CF_3], 6.16 [1/2H, dd, J=11.9, 9.2 Hz, (*Z*)-C*H*=$CHCF_3$], 6.41–6.52 [1/2H, m, (*E*)-C*H*=$CHCF_3$], 6.71–6.85 (1H, m, NH), 7.05-7.40 (m, Ar-H), 7.78–8.04 (total 4H, m, Ar-H); ^{13}C NMR (CD_3OD) δ 54.6, 65.1, 94.2, 122.1 (q, J=34.1 Hz), 130.1, 130.2, 130.3, 130.4, 133.3, 140.1, 141.9, 142.0 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{12}H_{12}F_3NO_2I$ [$(M+H)^+$] 385.9865, found 385.9865. A mixture of 5,5,5-trifluoro-2-(*N*-2-iodobenzoyl)amino-3-penten-1-ol (154.9 mg, 0.403 mmol), 2,2-dimethoxypropane (0.496 mL, 4.03 mmol), and (+)-10-camphorsulfonic acid (18.72 mg, 0.081 mmol) in benzene (16 mL) was heated under reflux for 1 h. After cooling, water was added and the organic phase was separated. The aqueous phase was extracted with AcOEt, and the combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel (hexane–AcOEt, 7:1) to give **36** (115.6 mg, 68%) as a pale yellow oil: IR ν 1650 cm^{-1}; ^1H NMR δ 1.78 (s, Me), 1.82 (s, Me), 1.84 (total 6H, m, Me), 3.76–3.82 (1H, m, one of H-5), 4.09–4.17 (1H, m, one of H-5), 4.58–4.71 (br, H-4), 4.84–5.03 (total 1H, br, H-4), 5.33 (1H, dq, J=11.9, 8.9 Hz, CH=C*H*CF_3), 5.93–6.26 (1H, br, C*H*=$CHCF_3$), 7.01–7.14 (2H, m, Ar-H), 7.27–7.38 (1H, m, Ar-H), 7.77–7.82 (1H, m, Ar-H); ^{13}C NMR δ 23.2, 26.9, 57.1, 68.5, 70.0, 97.0, 118.4, 118.9, 128.6, 131.0, 131.1, 139.6, 141.2, 142.7, 167.7 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity); HRMS (FAB) calcd for $C_{15}H_{16}F_3INO_2$ [$(M+H)^+$] 426.0178, found 426.0176.

4.6. Bu_3SnH-mediated radical cyclization of 35 and 36

4.6.1. (10*S*,10a*S*)-10-(2,2,2-Trifluoroethyl)-2,3,10a-tetrahydro-1*H*-pyrrolo[1,2-*b*]isoquinolin-5-one (37). Using a procedure similar to that for **34**, a solution of **35** (75.2 mg, 0.19 mmol) in benzene (50 mL) was treated with a solution of Bu_3SnH (0.076 mL, 0.285 mmol) and AIBN (4.7 mg, 0.0285 mmol) in benzene (50 mL). After the workup, the residue was chromatographed on silica gel (hexane–AcOEt, from 5:1 to 1:1) to give **37** (16.3 mg, 32%) as a white solid: mp 106–107 °C (hexane); $[\alpha]_D^{28}$ +126.7 (*c* 0.56, $CHCl_3$); IR ν 1645 cm^{-1}; ^1H NMR (C_6D_6) δ 0.85–1.42 (4H, m, H-3,4), 1.59 (1H, dqd, J=16.1, 11.9, 2.3 Hz, one of CH_2CF_3), 2.17 (1H, dqd, J=16.1, 11.5, 6.3 Hz, one of CH_2CF_3), 2.43 (1H, ddd, J=12.5, 6.3, 2.3 Hz, H-10), 2.67–2.78 (1H, m, H-10a), 3.32–3.42 (1H, m, one of H-2), 3.57–3.66 (1H, m, one of H-2), 7.06–7.45 (3H, m, Ar-H), 8.41–8.51 (1H, m, Ar-H); ^{13}C NMR δ 22.5, 32.8, 34.4 (q, J=30.0 Hz), 38.4, 45.6, 61.1, 124.3, 126.8 (q, J=258.1 Hz), 127.5, 128.2, 130.3, 132.0, 139.0, 162.7; HRMS (FAB) calcd for $C_{14}H_{15}F_3NO$ [$(M+H)^+$] 270.1106, found 270.1109.

4.6.2. (10*R*,10a*R*)-10-(2,2,2-Trifluoroethyl)-3,3-dimethy-10,10a-dihydro-1*H*-oxazolo[3,4-b]isoquinolin-5-one (38). Using a procedure similar to that for **34**, a solution of **36** (110 mg, 0.259 mmol) in benzene (20 mL) was treated with a solution of Bu_3SnH (0.105 mL, 0.389 mmol) and AIBN (6.4 mg, 0.039 mmol) in benzene (20 mL). After the workup, the residue was chromatographed on silica gel (hexane–AcOEt, 7:1) to give **38** (52.8 mg, 68%) as a white solid: mp 143–145 °C (AcOEt–hexane); $[\alpha]_D^{28}$ +97.9 (*c* 0.60, $CHCl_3$); IR ν 1655 cm^{-1}; ^1H NMR (C_6D_6) δ 1.53 (1H, dqd, J=16.5, 11.6, 3.0 Hz, one of CH_2CF_3), 1.69 (3H, s, Me), 1.80 (3H, s, Me), 2.09 (1H, dqd, J=16.5, 11.2, 5.9 Hz, one of CH_2CF_3), 2.55 (1H, ddd, J=12.5, 5.9, 3.0 Hz, H-10), 3.13 (1H, ddd, J=12.5, 9.6, 5.3 Hz, H-10a), 3.32 (1H, dd,

J=9.6, 8.2 Hz, one of H-11), 3.72 (1H, dd, J=8.2, 5.3 Hz, one of H-11), 6.78–6.81 (1H, m, Ar-H), 7.01–7.15 (2H, m, Ar-H), 8.37–8.41 (1H, m, Ar-H); ^{13}C NMR (C_6D_6) δ 5.8, 27.0, 35.1 (q, J=29.3 Hz), 36.5, 60.1, 70.0, 96.7, 125.1, 128.2, 129.6, 129.7, 129.8, 129.9, 132.8, 160.9 (the signals for CF_3 could not be identified due to the low intensity and high multiplicity). Anal. calcd for $C_{15}H_{16}F_3NO_2$: C, 60.20; H, 5.39; N, 4.68. Found: C, 60.11; H, 5.34; N, 4.74.

4.7. Heck reaction of 35 and 36

4.7.1. (*S*)-10-(2,2,2-Trifluoroethylidene)-2,3,10,10a-tetrahydro-1*H*-pyrrolo[1,2-*b*]isoquinolin-5-one (39) and 10-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*b*]isoquinolin-5-one (41). To a solution of $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) and tris-*o*-tolylphosphine (3.04 mg, 0.01 mmol) in CH_3CN (0.1 mL) were added a solution of **35** (39.51 mg, 0.1 mmol) in CH_3CN (0.4 mL) and Et_3N (0.031 mL, 0.22 mmol) at room temperature, and then the mixture was stirred at 80 °C for 2 days. After concentration of the mixture, the residue was chromatographed on silica gel (hexane–AcOEt, 1:1) to give a mixture of **39** and **41** in a ratio of 1:5 (18.9 mg, 71%) as a brown oil: ^{1}H NMR δ 1.83–2.13 (1/6×4H, m, H-3, 4 for **39**), 2.24 (5/6×2H, quint, J=7.6 Hz, H-3 for **41**), 3.18 (5/6×2H, t, J=7.6 Hz, H-4 for **41**), 3.51 (5/6×2H, q, J=10.2 Hz, CH_2CF$_3$ for **41**), 3.85 (1/6×2H, dd, J=12.0, 8.8 Hz, H-2 for **39**), 4.25 (5/6×2H, t, J=7.3 Hz, H-2 for **41**), 4.38–4.56 (1/6×1H, m, H-10a for **39**), 5.76 (1/6×1H, qd, J=8.9, 2.3 Hz, C=CHCF$_3$ for **39**), 7.05–7.35 (1/6×3H, m, Ar-H for **39**), 7.41–7.72 (5/6×3H, m, Ar-H for **41**), 8.10–8.14 (1/6×1H, m, Ar-H for **39**), 8.45–8.48 (5/6×1H, m, Ar-H for **41**); HRMS (FAB) calcd for $C_{14}H_{13}F_3NO$ [$(M+H)^+$] 268.0949, found 268.0943.

4.7.2. (*R*)-3,3-Dimethyl-10-(2,2,2-trifluoroethylidene)-10,10a-dihydro-1*H*-oxazolo[3,4-*b*]isoquinolin-5-one (40) and 3,3-dimethyl-10-(2,2,2-trifluoroethyl)-1*H*-oxazolo[3,4-*b*]isoquinolin-5-one (42). Using a procedure similar to that for **39**, compound **36** (104.7 mg, 0.246 mmol) was treated with $Pd(OAc)_2$ (1.38 mg, 0.006 mmol), tris-*o*-tolylphophine (7.49 mg, 0.025 mmol) and Et_3N (72.0 μL, 0.517 mmol) in CH_3CN (8.2 mL) for 8 h. After concentration of the mixture, the residue was chromatographed on silica gel (hexane) to give a mixture of **40** and **42** in a ratio of 1:2 (39.1 mg, 54%) as a brown oil: ^{1}H NMR δ 1.72 (1/3×3H, s, Me for **40**), 1.76 (1/3×3H, s, Me for **40**), 1.86 (2/3×6H, s, 2×Me for **42**), 3.42 (2/3×2H, q, J=10.2 Hz, CH_2CF$_3$ for **42**), 4.09 (1/3×1H, dd, J=9.0, 8.3 Hz, one of H-11 for **40**), 4.40 (1/3×1H, dd, J=8.3, 5.6 Hz, one of H-11 for **40**), 4.60–4.71 (1/3×1H, m, H-10a for **40**), 5.09 (2/3×2H, s, H-11 for **42**), 5.49 (1/3×3/4H, qd, J=8.6, 2.3 Hz, C=CHCF$_3$ for **40**), 6.31 (1/3×1/4H, qd, J=9.8, 3.0 Hz, C=CHCF$_3$ for **40**), 7.45–7.78 (3H, m, Ar-H), 8.10–8.20 (2/3×1H, m, Ar-H for **42**), 8.45–8.48 (1/3×1H, m, Ar-H for **40**); HRMS calcd for $C_{15}H_{14}F_3NO_2$ 297.0976, found 297.0977.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. For reviews, see: (a) Schlosser, M. *Tetrahedron* **1978**, 34, 3. (b) Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, 11, 197. (c) Ishikawa, N. *Kagaku No Ryoiki* **1981**, 35, 441. (d) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha, Elsevier Biomedical: Tokyo, 1982. (e) Welch, J. T. *Tetrahedron* **1987**, 43, 3123. (f) Resnati, G. *Tetrahedron* **1993**, 49, 9385. (g) Hiyama, T. *Organofluorine Compounds—Chemistry and Applications*; Springer: Berlin, 2000.
2. (a) Wataya, Y.; Matsuda, A.; Santi, D. V.; Bergstrom, D. E.; Ruth, J. L. *J. Med. Chem.* **1979**, *22*, 339. (b) Bergstrom, D. E.; Ruth, J. L.; Reddy, P. A.; Clercq, E. D. *J. Med. Chem.* **1984**, *27*, 279. Noyori, R.; Morisawa, Y.; Maeda, T.; Yasuda, S.; Uchida, K. **1990**, JP-02056462.
3. (a) Bentley, P. D.; Cheetham, R.; Huff, R. K.; Pascoe, R.; Sayle, J. D. *Pestic. Sci.* **1980**, *11*, 156. (b) Mack, H.; Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 184. (c) Mack, H.; Hanack, M. *Liebigs Ann. Chem.* **1989**, 833. (d) Nägele, U. M.; Hanack, M. *Liebigs Ann. Chem.* **1989**, 847. Scheiblich, S.; Maier, T.; Baltruschat, H. S.; Hoellmueller, T. **2000**, US-6130188.
4. (a) Bentley, P. D.; Cheetham, R.; Huff, R. K.; Pascoe, R.; Sayle, J. D. *Pestic. Sci.* **1980**, *11*, 156. (b) Mack, H.; Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 184. (c) Mack, H.; Hanack, M. *Liebigs Ann. Chem.* **1989**, 833. (d) Nägele, U. M.; Hanack, M. *Liebigs Ann. Chem.* **1989**, 847. Scheiblich, S.; Maier, T.; Baltruschat, H. S.; Hoellmueller, T. **2000**, US-6130188. (f) Jiang, B.; Zhang, F.; Xiong, W. *Tetrahedron* **2002**, *58*, 265.
5. (a) Kobayashi, T.; Eda, T.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 3156. (b) More recently, Hanamoto et al. have reported Wittig reaction of a trifluoromethyl-substituted ylide with aromatic aldehydes, see: Hanamoto, T.; Morita, N.; Shindo, K. *Eur. J. Org. Chem.* **2003**, 4279.
6. Miles, N. J.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299.
7. St-Denis, Y.; Chan, T. *J. Org. Chem.* **1992**, *57*, 3078.
8. Sato, T.; Tsujimoto, K.; Matsubayashi, K.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1992**, *40*, 2308.
9. Zhao, H.; He, X.; Thurkauf, A.; Hoffman, D.; Kieltyka, A.; Brodbeck, R.; Primus, R.; Wasley, J. W. F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3111.
10. Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6043.
11. Balboni, G.; Marastoni, M.; Merighi, S.; Borea, P. A.; Tomatis, R. *Eur. J. Org. Chem.* **2000**, *35*, 979.
12. Utsunomiya, I.; Fuji, M.; Sato, T.; Natsume, M. *Chem. Pharm. Bull.* **1993**, *41*, 854.
13. Harris, B. D.; Bhat, K. L.; Jullie, M. M. *Heterocycles* **1986**, *24*, 1045.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8929–8936

Synthesis and conformational investigation of tetrapeptide analogues of the fragment B23-B26 of insulin

Lígia M. Rodrigues, José I. Fonseca and Hernâni L. S. Maia*

Centro de Química, IBQF, University of Minho, 4710-057 Braga, Portugal

Received 13 May 2004; revised 2 July 2004; accepted 6 July 2004

Available online 18 August 2004

Abstract—Tetrapeptides containing one of a set of four different α,α-dialkyl glycines at the C-terminus were synthesized by conventional methods in solution and their conformational behavior investigated by ^{1}H NMR spectroscopy in connection with molecular mechanics calculations. The results were consistent with conformations stabilized by a γ-turn in the case of compounds with alkyl groups larger than methyl, while the corresponding Aib derivative did not exhibit intramolecular hydrogen bonding.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Peptides containing one or more residues of an α,α-dialkyl glycine are conformationally constrained owing to restriction of their conformational freedom imparted by the α-alkyl substituents. This conformational rigidity is a requirement to increase potency and selectivity, to improve bioavailabitlity, and to enhance the resistance to peptidases.[1] In addition, the design of conformationally constrained sequences is one of the approaches for development of bioactive peptides with high activity and selectivity towards a specific receptor.[2] Deltorfin and Leu-enkephalin analogues containing α,α-dialkyl glycine residues are examples of this strategy.[3,4] Thus, α,α-dialkyl glycines are interesting building blocks for modification of peptides as probes to investigate biologically active conformations and as models for conformational analysis of the peptide backbone (formation of α- or 3_{10}-helices, or β-turns). It has been observed by X-ray crystallography that a residue of α-aminoisobutyric acid (Aib) stabilizes type II β-turn conformations in peptides having 2–4 residues;[5] it is also known[6–8] that when inserted in peptides Aib imparts a 3_{10}-helical conformation, and α,α-diethyl glycine and α,α-dipropyl glycine convey fully planar C_5 conformations. Bulkier substituents (diethyl, di-*n*-propyl) favor both fully extended structures and folded helical conformations in crystal structures.[9–11] However, it has been also reported that the local sequence may influence the conformation adopted at the disubstituted residue.[12]

It is part of our program concerning this class of amino acids to investigate the effect of incorporation of derivatives with side chains larger than methyl into biologically active compounds. Now, we present the synthesis and the results of an investigation by ^{1}H NMR spectroscopy in connection with molecular mechanics calculations of the conformational behavior of four tetrapeptide analogues of the sequence B23-B26 of insulin having α,α-dialkyl glycine residues at their C-terminus. A considerable number of insulin analogues has been designed by substituting amino acid residues within its B23-B30 sequence (GlyB23-Phe-Phe-Tyr-Thr-Pro-Lys-ThrB30). These studies revealed that B26-des-(B27-B30)-insulin-NH_2 exhibits full potency, and modification at its N-terminus, that is, at position B26, may cause dramatic changes in its binding activity. For example, replacement of B-26-tyrosine by D-Ala raised the receptor affinity to 1250%. In addition, it has been proposed that binding of insulin to its receptor needs a conformational change.[13]

Owing to steric hindrance related to the tetrasubstitution at their α-carbon atom, α,α-dialkyl glycines are problematic compounds with regard both to their synthesis and to insertion into peptide chains. Nevertheless, we have been engaged in developing an improved synthesis of these amino acids[14] and reports can be found in literature of incorporation of such compounds into peptides by taking advantage of various coupling reagents with different efficiencies.[15–19]

2. Results and discussion

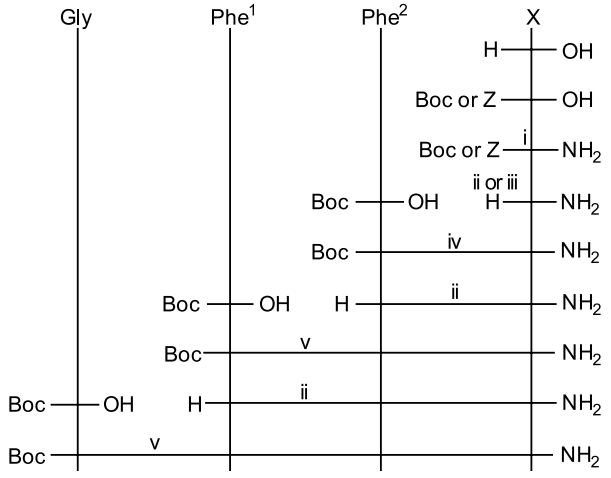
2.1. Synthesis

N-tert-Butyloxycarbonyl-dimethyl and diethyl glycine, and

Keywords: α,α-Dialkyl glycines; Peptide synthesis; Conformational analysis; NMR.
* Corresponding author. Tel.: +351-253-604-371; fax: +351-253-678-983; e-mail: hmaia@quimica.uminho.pt

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.014

N-benzyloxycarbonyl-dipropyl and di-isobutyl glycine were treated with DCC/HOBt followed by reaction with an aqueous solution of ammonium hydroxide[20] to give the corresponding *N*-acylamino acid amides in yields of 78, 54, 63 and 75%, respectively. Quantitative cleavage of the N-protecting groups and coupling to *N*-Boc-phenylalanine, using the DCC 'pre-mix' procedure with formation of the symmetrical anhydride in situ,[17] gave the fully protected dipeptides in yields of 83, 76, 83 and 50%, respectively. The fully protected tetrapeptides Boc-Gly-Phe^1-Phe^2-X-NH_2, with X = α,α-dimethyl glycine (Aib), α,α-diethyl glycine (Deg), α,α-dipropyl glycine (Dpg) and α,α-di-isobutyl glycine (Dbg), were then obtained by a stepwise procedure as shown in Scheme 1 in overall yields of 32, 22, 22 and 12%, respectively, from the N-protected amino acids. These were prepared in yields varying within the range 43–68%, with exception of diethyl glycine derivative, which was commercially available.



Scheme 1. i—DCC, HOBT, NH_4OH (method A); ii—TFA (method B); iii—HBr/HOAc (method C); iv—DCC (method D); v—DCC, HOBt (method E). Boc = *terc*-butyloxycarbonyl; Z = benzyloxycarbonyl. X = dimethyl (**1**); diethyl (**2**); dipropyl (**3**); di-isobutyl (**4**).

2.2. Conformational analysis

Diluted solutions (5 mM) of the fully protected tetrapeptides **1**–**4** (Scheme 1, Table 1) in DMSO-d_6 were prepared for conformational ^{1}H NMR spectroscopy experiments. The room temperature spectra exhibited the number of signals that would fit either a single dominant conformation or several conformations under fast exchange. Full proton assignment was obtained by double resonance, HMQC and HMBC techniques in addition to peak splitting patterns. By means of the Karplus equation,[21] $J_{\alpha H-NH} = 6.7\cos^2(\phi - 60) - 1.3\cos(\phi - 60) + 1.5$, the dihedral angles ϕ were calculated from the NH–CH coupling constants measured in the ^{1}H spectra (Fig. 1, Table 1).

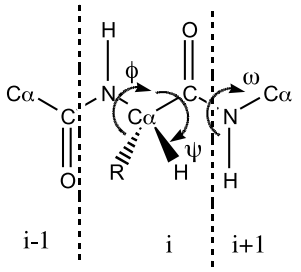


Figure 1. Definitions of the dihedral angles ϕ, ψ and ω.

Plots of chemical shifts versus temperature were obtained for all four compounds from spectra run at various temperatures within the range 298–333 K. These were linear and allowed to calculate the variation of the amide proton chemical shifts with temperature, $\Delta\delta/\Delta T$, which are shown in Table 1. Chemical exchange of the NH_2 amide protons at the C-terminal was observed on heating.

Larger NH temperature gradients were observed for Phe^2 ($\Delta\delta/\Delta T = -6.5$ to 8.2 ppb K^{-1}) as compared to those for the other residues. As in DMSO-d_6 solutions of peptides $\Delta\delta/\Delta T$ values greater than -4 ppb K^{-1} are indicative of NH participation in intermolecular hydrogen bonds with solvent,[22] we assume that the Phe^2 amide group has an external orientation. In contrast, the low temperature coefficient, $\Delta\delta/\Delta T$, observed for the α,α-dialkyl glycine NH proton in compounds **2**–**4** is in agreement with its participation in intramolecular hydrogen bonding; this effect is more pronounced in the case of compounds **3** and **4** ($\Delta\delta/\Delta T = -1.8$ ppb K^{-1}), which have the largest side chains at their C-terminal residue. Compound **1** behaves differently; the NH proton of its Aib residue is sensitive to temperature (Table 1, $\Delta\delta/\Delta T = -5.8$ ppb K^{-1}) and may be solvent exposed, and its glycine amide proton ($\Delta\delta/\Delta T = -3.8$ ppb K^{-1}) may be involved in a weak intramolecular hydrogen bond. Based on the NMR data presented above, we propose that peptides **2**–**4** assume a conformation stabilized by an intramolecular hydrogen bond involving the NH proton of the α,α-dialkyl glycine residue and the carbonyl oxygen atom of Phe^1 to give rise to a seven-membered ring structure (Fig. 2). This does not seem to apply to compound **1**, for which our NMR data is inconclusive.

Table 1. Temperature coefficients of NH protons, $J_{\alpha H-NH}$ coupling and calculated dihedral angles (ϕ) in DMSO-d_6 for compounds **1**–**4**

Compound	Residue									
	Gly	Phe^1	Phe^2	X	Gly		Phe^1		Phe^2	
	$-\Delta\delta/\Delta T$ (ppb/K)				$J_{\alpha H-NH}$ (Hz)	ϕ (°)	$J_{\alpha H-NH}$ (Hz)	ϕ (°)	$J_{\alpha H-NH}$ (Hz)	ϕ (°)
1	3.8	4.8	6.5	5.8	5.7	34; 87; −75; −166	8.1	−146; −154	6.9	60; −84; −156
2	5.0	6.2	8.2	2.4	6.0	83; 37; −77; −163	8.7	−101; −139	7.2	−86; −154
3	5.5	6.5	8.1	1.8	6.0	83; 37; −77; −163	8.4	−97; −143	7.5	−89; −151
4	6.0	6.7	8.0	1.8	6.3	42; 78; −79; −161	8.7	−101; −139	8.1	−146; −154

X = dimethyl (**1**); diethyl (**2**); dipropyl (**3**); di-isobutyl (**4**).

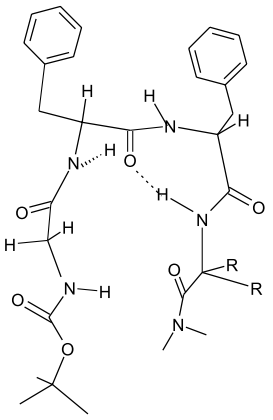


Figure 2. Representation of the conformation for compounds **2**–**4**.

A preference for a γ-turn has been reported for peptides containing an α,α-dialkylglycine, namely 1-aminocyclopropane carboxylic acid;[23] this has been related to the polarity of solvents,[22] namely DMSO as it is our case.

No information concerning the involvement of carbonyl groups in hydrogen bonds could be obtained from the ^{13}C NMR data. The chemical shifts of the carbonyl groups of glycine (ca. 169 ppm), Boc (ca. 156 ppm) and Phe^1 (ca. 171.5 ppm) were almost invariant in all four compounds. The corresponding chemical shifts for the α,α-dialkyl glycine residues varied within the range 174.4–176.2 ppm but do not show any coherent relationship with structure. The downfield shift observed for the carbonyl carbon atom of Phe^2 in compound **1** (0.8–1.1 ppm) as compared to compounds **2**–**4** suggests deshielding of this atom.

NOE difference spectra were run for the four tetrapeptides. In the case of compounds **2**–**4**, no NOE between N_iH and $N_{i+1}H$ was observed and only small NOEs between $C_i\alpha CH$ and $N_{i+1}H$ were detected. Compound **2** showed NOE values of 0.8 and 1% for $C\alpha HPhe^1$–$NHPhe^2$ and $C\alpha HPhe^2$–NHDeg, respectively. In the spectra for compounds **3** and **4**, values of 0.6 and 3% were observed for $C\alpha HPhe^2$–NHDpg/Dbg and CH_2Gly–$NHPhe^1$, respectively. The intra-residue NOEs ($C_i\alpha CH$–N_iH) were very weak or absent in the case of compound **2**. In the spectrum of compound **3**, values of 5 and 0.8% were observed for NH–CH_2Gly and $NHPhe^2$–$C\alpha HPhe^2$, respectively. Compound **4** showed values of 5 and 2% for NH–CH_2Gly and $NHPhe^1$–$C\alpha HPhe^1$, respectively. In the case of compound **1** the following NOEs were detected: NHGly–$NHPhe^1$, 2%; CH_2Gly–$NHPhe^1$, 2%; $C\alpha HPhe^1$–$NHPhe^2$, 1%; $C\alpha HPhe^2$–NHAib, 3%; NH–CH_2Gly, 1%; $NHPhe^1$–$C\alpha HPhe^1$, 4%; $NHPhe^2$–$C\alpha HPhe^2$, 0.7%. The NOE data confirms that our compounds do not adopt extended conformations. In fact, for extended structures small N_iH–$N_{i+1}H$ and large $C_i\alpha CH$–$N_{i+1}H$ NOEs are to be expected, with $C_i\alpha CH$–$N_{i+1}H$ NOEs larger than those for $C_i\alpha CH$–N_iH, which does not agree with the results reported above.[12]

A systematic conformational search of each of the tetrapeptides was performed using the Hyperchem 7.0 molecular modeling software and the AMBER force field by varying the dihedral angles of the glycine and phenylalanine residues; the set of minimum energy conformations obtained was then re-optimized with the same force field. The resulting conformations were examined and those consistent with $J_{\alpha H-NH}$ coupling constants and hydrogen bond patterns derived from NMR data were selected as the most probable conformations in solution (Fig. 3). In the case of compounds **2**–**4**, a hydrogen bond between NH proton of the α,α-dialkyl glycine residue and the carbonyl oxygen atom of Phe^1 was found, the dihedral angles calculated being close to the experimental values. The conformations

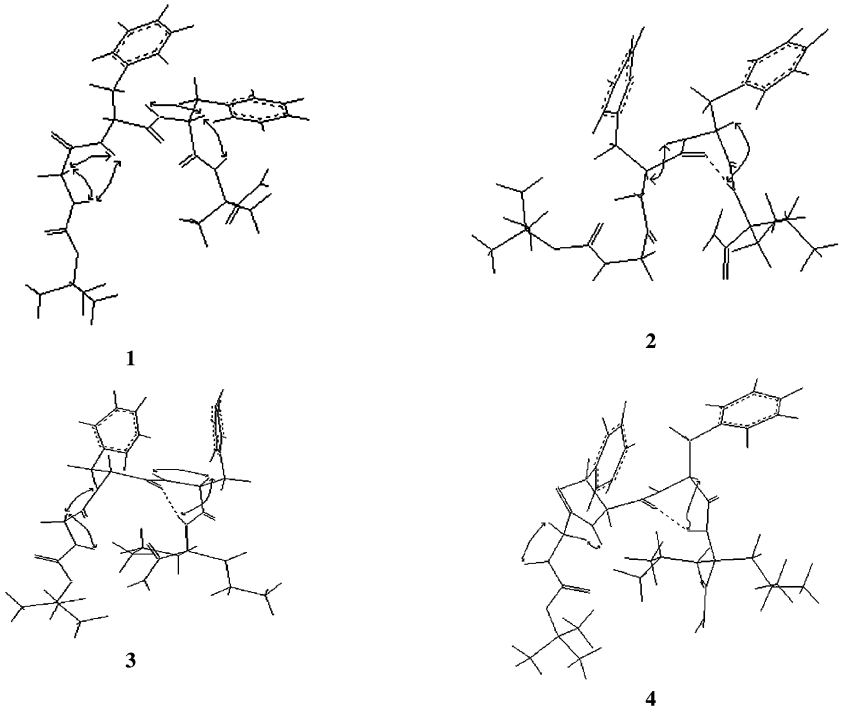


Figure 3. Conformations calculated for compounds **1**–**4**. Double tipped arrows indicate the observed NOE values.

calculated for these three compounds are similar and show a bend in agreement with the proposed structure that may be due to repulsive interaction of the two aromatic rings with each other. For compound **1** no intramolecular hydrogen bonding was found, but a bent conformation was also obtained. In this conformation, the values found for the dihedral angles were close to the experimental ones; in addition, the NOEs observed were consistent with the calculated structure, as the distances between the interacting atoms for which NOEs were observed varied from 2.1 to 2.9 Å.

3. Conclusion

The tetrapeptide analogues of the fragment B23-B26 of insulin having an α,α-dialkyl glycine residue at the C-terminus could be obtained by DCC promoted stepwise synthesis. The use of the DCC 'pre-mix' technique proved to be efficient in the problematic coupling of Boc-Phe to the α,α-dialkyl glycine amide.

Both NMR data and molecular mechanics calculations for all compounds but one were consistent with a folded γ-turn type conformation stabilized by an intramolecular hydrogen bond; this involves the NH proton of the α,α-dialkyl glycine residue and the carbonyl oxygen atom of the first phenylalanine residue. The exception was the peptide having the smallest side chains at the C-terminal residue, that is, the Aib derivative (**1**), which exhibited a different folded conformation without intramolecular hydrogen bonding. Our results indicate that substitution of methyl at the α,α-dialkyl C-terminal residue by larger groups changes the conformational preferences of these compounds. Little conformational change was observed on branching at the β-carbon.

4. Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography was carried out on pre-coated plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV-light and exposure to vaporized iodine and to ninhydrin reagent. ^{1}H and ^{13}C NMR data were recorded on a Varian Unity Plus 300 Spectrometer in DMSO-d_6; δ ppm were measured vs TMS and J values are given in Hz. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of proton and carbon signals in the NMR spectra. Elemental analyses were carried out on a Leco CHNS 932 instrument. Commercially available compounds, including Boc-Deg-OH, and solvents were used without previous purification; light petroleum refers to the fraction boiling at 40–60 °C; the hydrobromides of α,α-dipropyl and α,α-di-isobutyl glycine were synthesized by a Ugi-Passerini reaction as published elsewhere[14] and Boc-Phe-OH was synthesized by a literature method.[24]

4.1. General methods

Method A. General procedure for the synthesis of α,α-dialkyl glycine amides. The *N*-protected amino acid (10 mmol) was dissolved in a mixture of DCM (40 mL) and DMF (10 mL); HOBt (10.1 mmol) and DCC (10.05 mmol) were added and the mixture was stirred at room temperature for 30 min. An aqueous solution of 25% ammonium hydroxide (13 mmol) was then added and the reaction mixture was stirred overnight. The insoluble materials were filtered off and the resulting solution was diluted with DCM (50 mL). The organic layer was washed successively with 5% $NaHCO_3$, water, 5% citric acid and water. After drying over $MgSO_4$ and filtration, the solvent was removed under reduced pressure and the residue thus obtained was crystallized from an appropriate solvent as indicated below.

Method B. General procedure for deprotection of N-tert-butyloxycarbonylamino acid amides or peptide amides. The *N-tert*-butyloxycarbonyl amino acid amide or peptide amide (10 mmol) was treated with TFA (30 mL) at room temperature. The mixture was set aside under protection from moisture and stirred occasionally. After one to one and a half hours the excess reagent was removed under reduced pressure and the solid obtained was triturated with ether, filtered, washed with ethyl ether, dried and recrystallised from the appropriate solvent whenever indicated.

Method C. General procedure for deprotection of N-benzyl-oxycarbonylamino acid amides. The *N*-benzyloxycarbonyl amino acid amide (10 mmol) was treated with 40% HBr in acetic acid (20 mL) for 1 h at room temperature and under occasional stirring. Ethyl ether was added to precipitate the resulting hydrobromide, which was filtered, washed with ether, dried over KOH in a desiccator and used without further purification.

Method D. General procedure for peptide bond formation involving α,α-dialkyl glycine amides. The Boc- or Z-amino acid (10 mmol) was dissolved in dichloromethane (30 mL) containing DMF (3 mL) and treated with DCC (5 mmol) after cooling to 0 °C. The mixture was stirred for 30 min and the α,α-dialkyl glycine amide salt as obtained from N-deprotection (5 mmol) was added followed by triethylamine (5 mmol). After leaving the reaction mixture overnight under stirring at room temperature, the insoluble materials were filtered off, the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed successively with 5% $NaHCO_3$, water, 5% citric acid, water and brine. After drying over $MgSO_4$ and filtration, the solvent was removed under reduced pressure and the resulting product crystallized from the appropriate solvent.

Method E. General procedure for peptide bond formation. The required Boc-amino acid (10 mmol) was dissolved in dichloromethane (40 mL) containing DMF (5 mL) and treated with HOBt (10 mmol). After cooling to 0 °C, DCC (10 mmol) was added followed by the *N*-deprotected peptide amide (10 mmol) and triethylamine (10 mmol). After leaving the reaction mixture stirring overnight at room temperature, it was worked up as above.

4.1.1. Boc-Gly-Phe-Phe-Aib-NH_2 (1). *Boc-Aib*. 2-Amino-isobutyric acid (10 mmol, 1.03 g) was added to a mixture of water (20 mL), dioxane (20 mL) and NaOH solution (10 mmol, 10 mL 1 M) with vigorous stirring. The reaction

mixture was cooled to 0 °C and treated with Boc_2O (0.011 mol, 2.40 g). Stirring was continued at room temperature for three hours and the solution was concentrated under reduced pressure to remove the organic solvent. The remaining aqueous layer was then cooled to 0 °C, acidified to pH 2 with 1 M $KHSO_4$ and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue thus obtained was crystallized from ethyl acetate/light petroleum. The white solid was filtered and dried to yield 61% of the required product, mp 116–117 °C (lit.[25] mp 117–118 °C). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.28 (s, 6H, 2×CH_3), 1.35 (s, 9H, Boc), 7.05 (s, 1H, *N*H), 12.20 (br s, 1H, CO_2H). Anal. calcd for $C_9H_{17}NO_4$: C: 53.20, H: 8.43, N: 6.89; found: C: 53.38, H: 8.36, N: 6.93.

Boc-Aib-NH$_2$. General Method A was used to give the product in a yield of 78%, mp 168–170 °C (ethyl acetate/hexane). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.30 (6H, s, 2×CH_3), 1.40 (9H, s, Boc), 6.70 (1H, s, N*H* Aib), 6.80 and 7.00 (2H, 2s, NH_2). Anal. calcd for $C_9H_{18}N_2O_3$: C: 53.45, H: 8.91, N: 13.85; found: C: 53.36, H: 8.62, N: 13.83.

H-Aib-NH$_2$, TFA. Following Method B, one-hour after the reaction had been started ethyl ether was added and the mixture was cooled for 2 h; the precipitated solid was filtered off, washed with ethyl ether and dried; no further purification was required. Yield 96%, mp 206–207 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.40 (s, 6H, 2×CH_3), 7.50 and 7.70 (2s, 2H, NH_2), 8.10 (br s, 3H, NH_3^+).

Boc-Phe-Aib-NH$_2$. General Method D was used to prepare this compound as a crystalline material in a yield of 83%, mp 182–182.2 °C (from ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.24 (s, 6H, 2×CH_3), 1.28 (s, 9H, Boc), 2.70–2.90 (m, 2H, βCH_2 Phe), 4.10 (m, 1H, αC*H* Phe), 6.90 (br s, 2H, NH_2), 7.10 (d, 1H, J=8.2 Hz, N*H* Phe), 7.30 (m, 5H, Ar), 8.00 (s, 1H, N*H*Aib). Anal. calcd for $C_{18}H_{27}N_3O_4$: C: 61.87, H: 7.78, N: 12.02; found: C: 61.75, H: 8.09, N: 11.68.

H-Phe-Aib-NH$_2$, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was used without further purification. Yield 96%, mp 269–270 °C dec. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.24 (s, 6H, 2×CH_3), 3.00 (m, 2H, βCH_2 Phe), 4.00 (apparent t, 1H, J=7.5 Hz, αC*H*Phe), 6.90 and 7.00 (2s, 2H, NH_2), 7.30 (m, 5H, Ar), 8.10 (br s, 3H, NH_3^+), 8.30 (s, 1H, N*H* Aib). Anal. calcd for $C_{15}H_{20}N_3O_4F_3$: C: 49.59, H: 5.55 H, N: 11.56; found: C: 49.56, H: 5.50, N: 11.56.

Boc-Phe-Phe-Aib-NH$_2$. General Method E was used to obtain the required product in a yield of 77%, mp 187–188 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.20 (s, 6H, 2×CH_3), 1.30 (s, 9H, Boc), 2.85 (m, 2H, βCH_2 Phe), 3.00 (m, 2H, βCH_2 Phe), 4.10 (m, 1H, αC*H* Phe), 4.40 (m, 1H, αC*H* Phe), 6.80–6.90 (m, 3H, NH_2+N*H* Phe), 7.20 (m, 10H, Ar), 7.90 (s, 1H, N*H* Aib), 8.10 (d, 1H, J=8.3 Hz, N*H* Phe). Anal. calcd for $C_{27}H_{36}N_4O_5$: C: 65.30, H: 7.31 H, N: 11.28; found: C: 65.51, H: 7.33, N: 11.24.

H-Phe-Phe-Aib-NH$_2$, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was pure by tlc and used without further purification. Yield 90%, mp 229–230 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 1.30 (s, 6H, 2×CH_3), 2.90 (m, 2H, βCH_2 Phe), 3.10 (m, 2H, βCH_2 Phe), 4.00 (m, 1H, αC*H* Phe), 4.50 (m, 1H, αC*H* Phe), 6.80 and 6.90 (2s, 2H, NH_2), 7.20 (m, 10H, Ar), 8.00 (br s, 3H, NH_3^+), 8.10 (s, 1H, N*H* Aib), 8.80 (d, 1H, J=8.2 Hz, N*H* Phe).

Boc-Gly-Phe-Phe-Aib-NH$_2$. General Method E was used to obtain the required product in a yield of 77%, mp 116–118 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.20 (s, 6H, 2×CH_3), 1.30 (s, 9H, Boc), 2.80 (m, 2H, βCH_2 Phe), 3.00 (m, 2H, βCH_2 Phe), 3.40–3.60 (dABq, 2H, J=5.7, 16.0 Hz, CH_2Gly, partially under water signal), 4.30 (m, 1H, αC*H* Phe^2), 4.50 (m, 1H, αC*H* Phe^1), 6.80–6.90 (m, 3H, N*H* Gly+NH_2), 7.20 (m, 10H, Ar), 7.82 (s, 1H, N*H* Aib), 7.90 (d, 1H, J=8.1 Hz, N*H* Phe^1), 8.37 (d, 1H, J=6.9 Hz, N*H*Phe^2). ^{13}C NMR (DMSO-d_6) δ (ppm): 176.2 (*C*O Aib), 171.3 (*C*O Phe^1), 170.0 (*C*O Phe^2), 169.2 (*C*O Gly), 155.7 (*C*O Boc), 137.6 (2×*C* Ar), 136.43 (2×*C*H Ar), 129.2 (2×*C*H Ar), 128.1 (2×*C*H Ar), 128.0 (2×*C*H Ar), 126.3 (2×*C*H Ar), 78.0 (*C* Boc), 55.8 (*C* Aib), 54.6 (α*C*H Phe^2), 53.6 (α*C*H Phe^1), 43.0 (*C*H$_2$ Gly), 37.5 (β*C*H$_2$ Phe), 36.9 (β*C*H$_2$ Phe), 28.2 (3×*C*H$_3$ Boc), 25.3 (*C*H$_3$ Aib), 24.3 (*C*H$_3$ Aib). Anal. calcd for $C_{29}H_{39}N_5O_6$: C: 62.91, H: 7.10, N: 12.65; found: C 63.03, 7.09 H, 12.61.

4.1.2. Boc-Gly-Phe-Phe-Deg-NH2 (2). *Boc-Deg-NH$_2$*. General Method A was used to obtain the required product in a yield of 54%, mp 155–156 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d$_6$) δ (ppm): 0.64 (t, 6H, J=7.2 Hz, 2×CH_3), 1.36 (s, 9H, Boc), 1.64–2.07 (m, 4H, 2×CH_2), 6.09 (s, 1H, N*H* Deg), 7.29 and 7.45 (2s, 2H, NH_2). Anal. calcd for $C_{11}H_{22}N_2O_3$: C: 57.37, H: 9.63, N: 12.16; found: C: 57.51, H: 9.60, N: 12.11.

H-Deg-NH$_2$, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained in a quantitative yield, which was pure by tlc and used without further purification. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.86 (t, 6H, J=7.1 Hz, CH_3), 1.60–1.90 (m, 4H, 2×CH_2), 7.62 and 7.73 (2s, 2H, NH_2), 7.95 (s, 3H, NH_3^+).

Boc-Phe-Deg-NH$_2$. General Method D was used to obtain the required product in a yield of 76%, mp 218–219 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.56 (t, 3H, J=7.3 Hz, CH_3), 0.64 (t, 3H, J=7.3 Hz, CH_3), 1.29 (s, 9H, Boc), 1.63 (m, 2H, CH_2), 2.34 (m, 2H, CH_2), 2.74–3.00 (m, 2H, βCH_2 Phe), 3.90 (m, 1H, αC*H* Phe), 7.26 (m, 5H, Ar), 7.37 and 7.48 (2s, 2H, NH_2), 7.49 (d, 1H, J=7.8 Hz, N*H* Phe), 7.68 (s, 1H, N*H* Deg). Anal. calcd for $C_{20}H_{31}N_3O_4$: C: 63.63, H: 8.28, N: 11.13; found: C: 63.54, H: 8.40, N: 11.05.

H-Phe-Deg-NH$_2$, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained in a yield of 98%, which required no further purification, mp 230–231 °C dec. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.47 (t, 3H, J=7.3 Hz, CH_3), 0.61 (t, 3H, J=7.3 Hz, CH_3), 1.63 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 2.80 (dd, 1H, J=7.3, 13.8 Hz, βCH_2 Phe), 3.10 (dd, 1H, J=7.3, 13.9 Hz, βCH_2 Phe), 4.36 (m, 1H, αC*H* Phe), 7.36 (s, 1H, NH_2), 7.32

(m, 6H, Ar+NH_2), 7.89 (s, 1H, N*H* Deg), 8.15 (br s, 3H, NH_3^+). Anal. calcd for $C_{17}H_{24}N_3O_4F_3$: C: 52.17, H: 6.14, N: 10.74; found: C: 51.58, H: 6.11, N: 10.62.

Boc-Phe-Phe-Deg-NH_2. General Method E was used to obtain the required product in a yield of 83%, mp 113–115 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.51 (t, 3H, J=7.3 Hz, CH_3), 0.63 (t, 3H, J=7.3 Hz, CH_3), 1.25 (s, 9H, Boc), 1.65 (m, 2H, CH_2), 2.27 (m, 2H, CH_2), 2.86 (m, 2H, βCH_2 Phe), 3.07 (m, 2H, βCH_2 Phe), 4.17 (m, 1H, αC*H* Phe), 4.40 (m, 1H, αC*H* Phe), 6.87 (d, 1H, J=8.5 Hz, N*H* Phe), 7.30 and 7.40 (2s, 2H, NH_2), 7.27 (m, 10H, Ar), 7.60 (s, 1H, N*H* Deg), 8.60 (d, 1H, J=7.6 Hz, N*H* Phe). Anal. calcd for $C_{29}H_{40}N_4O_5$: C: 66.39, H: 7.68, N: 10.68; found: C: 66.00, H: 7.92, N: 10.37.

H-Phe-Phe-Deg-NH_2, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was pure by tlc and used without further purification. Yield 86%, mp 127–130 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.54 (t, 3H, J=7.3 Hz, CH_3), 0.65 (t, 3H, J=7.3 Hz, CH_3), 1.68 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.80 (m, 2H, βCH_2 Phe), 3.10 (m, 2H, βCH_2 Phe), 3.95 (m, 1H, αC*H* Phe), 4.50 (m, 1H, αC*H* Phe), 7.30 (m, 10H, Ar), 7.40 and 7.50 (2s, 2H, NH_2), 7.63 (s, 1H, N*H* Deg), 8.10 (br s, 3H, NH_3^+), 9.13 (d, 1H, J=7.6 Hz, N*H* Phe).

Boc-Gly-Phe-Phe-Deg-NH_2. General Method E was used to obtain the required product in a yield of 75%, mp 218–219 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.55 (t, 3H, J=7.3 Hz, CH_3), 0.64 (t, 3H, J=7.3 Hz, CH_3), 1.30 (s, 9H, Boc), 1.70 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.60–2.80 (m, 2H, βCH_2 Phe), 3.10 (m, 2H, βCH_2 Phe), 3.30–3.60 (dABq, 2H,, J=5.7, 16.8 Hz, CH_2 Gly, partially under the water signal), 4.35 (m, 1H, αC*H* Phe^2), 4.54 (m, 1H, αC*H* Phe^1), 6.78 (t, 1H, J=6.0 Hz, N*H* Gly), 7.22 (m, 10H, Ar), 7.37 and 7.44 (2s, 2H, NH_2), 7.57 (s, 1H, N*H* Deg), 7.92 (d, 1H, J=8.7 Hz, N*H* Phe^1), 8.75 (d, 1H, J=7.2 Hz, N*H* Phe^2). ^{13}C NMR (DMSO-d_6) δ (ppm): 174.4 (*C*O Deg), 171.6 (*C*O Phe^1), 169.2 (*C*O Phe^2), 168.8 (*C*O Gly), 155.6 (*C*O Boc), 138.0 (*C* Ar), 137.9 (*C* Ar), 129.2 (2×*C*H Ar), 129.0 (2×*C*H Ar), 128.2 (2×*C*H Ar), 127.9 (2×*C*H Ar), 126.3 (*C*H Ar), 126.2 (*C*H Ar), 78.0 (*C* Boc), 64.0 (*C* Deg), 55.5 (α*C*H Phe^2), 53.5 (α*C*H Phe^1), 42.9 (*C*H$_2$ Gly), 37.9 (β*C*H2 Phe), 37.0 (β*C*H2 Phe), 28.2 (3×*C*H$_3$ Boc), 27.2 (*C*H$_2$ Deg), 24.5 (*C*H$_2$ Deg), 8.1 (*C*H$_3$ Deg), 7.8 (*C*H$_3$ Deg). Anal. calcd for $C_{31}H_{43}N_5O_6$: C: 64.00, H: 7.45, N: 12.04; found: C: 63.84, H: 7.56, N: 11.86.

4.1.3. Boc-Gly-Phe-Phe-Dpg-NH_2 (3). *Z-Dpg-OH*. The amino acid hydrobromide (10.8 mmol, 2.12 g) was dissolved in 1 M NaOH (21.6 mL) and stirred with cooling in an ice bath. A solution of benzyl chloroformate was added dropwise with the pH kept at 11 by addition of 1 M NaOH under vigorous stirring; the temperature was then raised to 40 °C and maintained as such for 4 h, while the pH was kept at 11. The mixture was then extracted with four portions of ethyl ether, the aqueous layer cooled and the pH adjusted to 1.5 by addition of 6 M HCl. The oil thus formed was extracted into ethyl acetate and the solution dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oil that crystallized on standing. Yield 68%, mp 76–78 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (t, 6H, J=7.1 Hz, 2×CH_3), 1.10 (m, 4H, 2×CH_2), 1.65 (m, 4H, 2×CH_2), 5.00 (s, 2H, CH_2Ar), 7.00 (s, 1H, N*H* Dpg), 7.30 (m, 5H, Ar), 12.60 (br s, 1H, CO_2H). Anal. calcd for $C_{16}H_{23}NO_4$: C: 65.51, H: 7.90, N: 4.78; found: C: 65.24, H: 7.79, N: 5.08.

Z-Dpg-NH_2. General Method A was used to give the product in a yield of 62%, mp 155–156 °C (ethyl ether/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (t, 6H, J=7.2 Hz, 2×CH_3), 1.10 (m, 4H, 2×CH_2), 1.60 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 5.00 (s, 2H, CH_2Ar), 6.50 (s, 1H, N*H* Dpg), 7.30 (m, 6H, Ar+NH_2), 7.45 (s, 1H, NH_2). Anal. calcd for $C_{16}H_{24}N_2O_3$: C: 65.73, H: 8.27, N: 9.58; found: C: 66.02, H: 8.49, N: 9.63.

H-Dpg-NH_2, HBr. Following general Method C, a solid compound was obtained, which was pure by tlc and used without further purification. Yield 93%, mp 227–229 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (t, 6H, J=6.9 Hz, 2×CH_3), 1.10 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.70 (m, 4H, CH_2), 7.60 and 7.70 (2s, 2H, NH_2), 7.90 (s, 3H, NH_3^+).

Boc-Phe-Dpg-NH_2. General Method D was used to obtain the required product in a yield of 83%, mp 191–192 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80–0.90 (m, 8H, 2×CH_3+CH_2), 1.30 (s+m, 11H, Boc+CH_2), 1.55 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.70–2.90 (dd, 1H, J=10.8, 13.2 Hz, βCH_2 Phe), 3.00 (dd, 1H, J=4.8, 13.7 Hz, βCH_2 Phe), 3.90 (m, 1H, αC*H* Phe), 7.25 (m, 5H, Ar), 7.50 (d+s, 2H, N*H* Phe+NH_2), 7.40 (s, 1H, NH_2), 7.65 (s, 1H, N*H* Dpg). Anal. calcd for $C_{22}H_{35}N_3O_4$: C: 65.16, H: 8.70, N: 10.36; found: C: 65.15, H: 8.75, N: 10.24.

H-Phe-Dpg-NH_2, TFA. Following general Method B, a solid compound was obtained, which was pure by tlc and used without further purification. Yield 88%, mp 232–233 °C dec. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.60–0.90 (m, 8H, 2×CH_3+CH_2), 1.20 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.00–2.20 (m, 2H, CH_2), 2.90 (dd, 1H, J=7.3, 13.8 Hz, βCH_2 Phe), 3.00 (dd, 1H, J=7.3, 13.9 Hz, βCH_2 Phe), 4.30 (t, 1H, J=7.3 Hz, αC*H* Phe), 7.20–7.45 (m, 7H, Ar+NH_2), 7.85 (s, 1H, N*H* Dpg), 8.15 (br s, 3H, NH_3^+). Anal. calcd for $C_{19}H_{28}N_3O_4F_3$: C: 54.41, H: 6.68, N: 10.02; found: C: 54.06, H: 6.42, N: 9.97.

Boc-Phe-Phe-Dpg-NH_2. General Method E was used to obtain the required product in a yield of 69%, mp 106–108 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.75 (m, 6H, 2×CH_3), 0.90 (m, 2H, CH_2), 1.10 (m, 2H, CH_2), 1.30 (s, 9H, Boc), 1.60 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 2.55–2.90 (m, 2H, βCH_2 Phe), 2.90–3.10 (m, 2H, βCH_2 Phe), 4.20 (m, 1H, αC*H* Phe), 4.40 (m, 1H, αC*H* Phe), 6.85 (d, 1H, J=8.2 Hz, N*H* Phe), 7.20 (m, 11H, Ar+NH_2), 7.40 (s, 1H, NH_2), 7.55 (s, 1H, N*H* Dpg), 8.50 (d, 1H, J=7.5 Hz, N*H* Phe). Anal. calcd for $C_{31}H_{44}N_4O_5$: C: 67.34, H: 8.02, N: 10.14; found: C 67.08, H: 8.21, N: 9.86.

H-Phe-Phe-Dpg-NH_2, TFA. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was pure by tlc and used without further purification. Yield 89%, mp 126–128 °C. ^{1}H NMR

(DMSO-d_6) δ (ppm): 0.75 (m, H, 2×CH_3), 0.80–1.00 (m, 2H, CH_2), 1.00–1.10 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 2.70–2.90 (m, 2H, βCH_2 Phe), 3.10 (dd, 2H, J=5.6, 13.9 Hz, βCH_2 Phe), 3.95 (m, 1H, αC*H* Phe), 4.50 (m, 1H, αC*H* Phe), 7.20–7.40 (m, 11H, Ar+NH_2), 7.45 (1s, 1H, NH_2), 7.60 (s, 1H, N*H* Dpg), 8.00 (br s, 3H, NH_3^+), 9.10 (d, 1H, J=7.9 Hz, N*H* Phe).

Boc-Gly-Phe-Phe-Dpg-NH$_2$. General Method E was used to obtain the required product in a yield of 86%, mp 120–122 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.75 (m, 6H, 2×CH_3), 0.80–1.00 (m, 2H, CH_2), 1.00–1.10 (m, 2H, CH_2), 1.30 (s, 9H, Boc), 1.60 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 2.60– 2.90 (m, 2H, βCH_2 Phe), 3.10 (dd, 2H, J=5.7, 13.9 Hz, βCH_2 Phe), 3.30–3.50 (dABq, 2H, J=6.0, 16.2 Hz, CH_2Gly, partially under water signal), 4.30 (m, 1H, αC*H* Phe^2), 4.50 (m, 1H, αC*H* Phe^1), 6.80 (t, 1H, J=6.0 Hz, N*H* Gly), 7.00–7.20 (m, 10H, Ar), 7.30 and 7.40 (2s, 2H, NH_2), 7.50 (s, 1H, N*H* Dpg), 7.90 (d, 1H, J=8.6 Hz, N*H* Phe^1), 8.70 (d, 1H, J=7.6 Hz, N*H* Phe^2). ^{13}C NMR (DMSO-d_6) δ (ppm): 174.7 (*C*O Dpg), 171.5 (*C*O Phe^1), 168.9 (*C*O Phe^2), 168.8 (*C*O Gly), 155.6 (*C*O Boc), 137.9 (2×*C* Ar), 129.2 (2×*C*H Ar), 129.0 (2×*C*H Ar), 128.2 (2×*C*H Ar), 127.9 (2×*C*H Ar), 126.3 (*C*H Ar), 126.2 (*C*H Ar), 78.0 (*C* Boc), 62.9 (*C* Dpg), 55.4 (*C*α Phe^1), 53.4 (*C*α Phe^2), 42.8 (*C*H$_2$ Gly), 37.9 (β*C*H$_2$ Phe), 37.0 (β*C*H$_2$Phe), 36.9 (*C*H$_2$), 36.8 (*C*H$_2$), 28.2 (3×*C*H$_3$ Boc+*C*H$_2$), 16.6 (*C*H$_2$), 16.2 (*C*H$_2$), 14.1 (2×*C*H$_3$ Dpg). Anal. calcd for $C_{33}H_{47}N_5O_6$: C: 65.00, H: 7.77, N: 11.49; found: C: 65.11, H: 7.79, N: 11.21.

4.1.4. Boc-Gly-Phe-Phe-Dbg-NH$_2$ (4). *Z-Dbg-OH*. Following the procedure described for Z-Dpg-OH above, this compound was synthesized in a 15 mmol scale. The reaction was carried out at 50 °C for 4 h. After working up the reaction mixture an oil was obtained, which crystallized on standing. Yield 43%, mp 71–72 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (2d, 12H, J=4.9 Hz, 4×CH_3), 1.50 (m, 2H, 2×C*H*), 1.60 (dd, 2H, J=6.7, 13.8 Hz, CH_2), 2.00 (dd, 2H, J=5.5, 13.8 Hz, CH_2), 5.00 (s, 2H, CH_2Ar), 6.50 (s, 1H, N*H*), 7.30 (m, 5H, Ar). Anal. calcd for $C_{18}H_{27}NO_4$: C: 67.26, H: 8.47, N: 4.36; found: C: 67.34, H: 8.76, N: 4.49.

Z-Dbg-NH$_2$. General Method A was used to give the product in a yield of 75%, mp 129.5–130 °C (ethyl ether/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (2d, 12H, J=5.2 Hz, 4×CH_3), 1.40 (m, 2H, 2×C*H*), 1.58 (dd, 2H, J=5.9, 14.0 Hz, CH_2), 2.10 (dd, 2H, J=6.1, 14.3 Hz, CH_2), 5.00 (s, 2H, CH$_2$Ar), 6.50 (s, 1H, N*H*), 7.30 (m, 5H, Ar), 7.42 and 7.60 (2s, 2H, NH_2). Anal. calcd for $C_{18}H_{28}N_2O_3$: C: 67.47, H: 8.81, N: 8.74; found: C: 67.46, H: 8.85, N: 8.95.

H-Dbg-NH$_2$, *HBr*. Following general Method C, a solid compound was obtained, which was pure by tlc and used without further purification. Yield 98%, mp 205.7–206 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.80 (apparent t, 12H, J=6.4 Hz, 4×CH$_3$), 1.40–1.80 (m, 6H, 2×CH+2×CH$_2$), 7.60 and 7.80 (2s, 2H, NH$_2$), 7.9 (br s, 3H, NH$_3^+$).

Boc-Phe-Dbg-NH$_2$. General Method D was used to obtain the required product in a yield of 50%, mp 169.8–171 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.70–0.80 (m, 12H, 4×CH_3), 1.30 (s, 9H, Boc), 1.50 (m, 4H, 2×CH_2), 2.30 (m, 2H, 2×C*H*), 2.70 (dd, 1H, J=3.4, 14.0 Hz, βCH_2 Phe), 2.80–3.00 (m, 1H, βCH_2 Phe), 3.90 (m, 1H, αC*H* Phe), 7.30 (m, 5H, Ar), 7.40 and 7.60 (2s, 2H, NH_2), 7.50 (d, 1H, J=8.1 Hz, N*H* Phe), 7.90 (s, 1H, N*H* Dbg). Anal. calcd for $C_{24}H_{39}N_3O_4$: C: 66.48, H: 9.09, N: 9.69; found: C: 66.11, H: 9.02, N: 9.68.

H-Phe-Dbg-NH$_2$, *TFA*. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was pure by tlc and used without further purification. Yield 90%, mp 264 °C dec. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.70–0.80 (m, 12H, 4×CH_3), 1.20 (m, 1H, C*H*), 1.55 (m, 3H, C*H*+CH_2), 2.24 (m, 2H, CH_2), 2.85 (dd, 1H, J=6.0, 13.9 Hz, βCH_2 Phe), 3.10 (m, 1H, βCH_2 Phe), 4.40 (apparent t, 1H, J=6.0 Hz, αC*H* Phe), 7.30 (m, 6H, Ar+NH_2), 7.55 (s, 1H, NH_2), 8.00 (br s, 3H, NH_3^+), 8.10 (s, 1H, N*H* Dbg). Anal. calcd for $C_{21}H_{32}N_3O_4F_3$: C: 56.38, H: 7.16, N: 9.40; found: C: 56.55, H: 7.13, N: 9.50.

Boc-Phe-Phe-Dbg-NH$_2$. General Method E was used to obtain the required product in a yield of 67%, mp 93.2–95.4 °C (ethyl acetate/light petroleum). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.70–0.80 (m, 12H, 4×CH_3), 1.25 (s, 9H, Boc), 1.50 (m, 4H, 2×C*H*+CH_2), 2.30 (m, 2H, CH_2), 2.60–2.90 (m, 2H, βCH_2 Phe), 3.00–3.20 (m, 2H, βCH_2 Phe), 4.20 (m, 1H, αC*H* Phe1), 4.40 (m, 1H, αC*H* Phe), 6.85 (d, 1H, J=8.8 Hz, N*H* Phe), 7.20 (m, 10H, Ar), 7.40 and 7.55 (2s, 2H, NH_2), 7.80 (s, 1H, N*H* Dbg), 8.60 (d, 1H, J=8.2 Hz, N*H* Phe). Anal. calcd for $C_{33}H_{48}N_4O_5$: C: 68.24, H: 8.33, N: 9.65; found: C: 68.14, H: 8.25, N: 9.64.

H-Phe-Phe-Dbg-NH$_2$, *TFA*. Following general Method B, 90 min after the reaction had been started a solid compound was obtained, which was pure by tlc and used without further purification. Yield 53%, mp 119–121 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.70–0.80 (m, 12H, 4×CH_3), 1.30 (m, 1H, C*H*), 1.50 (m, 3H, C*H*+CH_2), 2.30 (m, 2H, CH_2), 2.80 (m, 2H, βCH_2 Phe), 3.15 (m, 2H, βCH_2 Phe), 3.95 (m, 1H, αC*H* Phe), 4.50 (m, 1H, αC*H* Phe), 7.30 (m, 10H, Ar), 7.45 and 7.60 (2s, 2H, NH_2), 7.80 (s, 1H, N*H* Dbg), 8.00 (br s, 3H, NH_3^+), 9.20 (d, 1H, J=8.2 Hz, N*H* Phe).

Boc-Gly-Phe-Phe-Dbg-NH$_2$. General Method E was used to obtain the final product, requiring no further purification, in a yield of 98%, mp 144–146 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 0.70–0.80 (m, 12H, 4×CH_3), 1.30 (m, 10H, Boc+C*H*), 1.50 (m, 3H, C*H*+CH_2), 2.30 (m, 2H, CH_2), 2.60–2.80 (m, 2H, βCH_2 Phe), 3.10 (m, 2H, βCH_2 Phe), 3.30–3.50 (m, 2H, CH_2 Gly), 4.40 (m, 1H, αC*H* Phe^2), 4.50 (m, 1H, αC*H* Phe^1), 6.78 (t, 1H, J=6.3 Hz, N*H* Gly), 7.20 (m, 10H, Ar), 7.48 and 7.62 (2s, 2H, NH_2), 7.85 (s, 1H, N*H* Dbg), 7.99 (d, 1H, J=8.7 Hz, N*H* Phe^1), 8.86 (d, 1H, J=8.1 Hz, N*H* Phe^2). ^{13}C NMR (DMSO-d_6) δ (ppm): 175.6 (*C*O Dbg), 171.5 (*C*O Phe^1), 168.9 (*C*O Phe^2), 168.7 (*C*O Gly), 155.6 (*C*O Boc), 138.1 (*C* Ar), 138.0 (*C* Ar), 129.2 (2×*C*H Ar), 128.9 (2×*C*H Ar), 128.2 (2×*C*H Ar), 127.9 (2×*C*H Ar), 126.2 (2×CH Ar), 77.9 (*C* Boc), 61.9 (*C* Dbg), 55.3 (*C*α Phe^1), 53.4 (*C*α Phe^2), 43.9 (2*C*H$_2$ Dbg) 42.8 (*C*H$_2$ Gly), 38.1 (β*C*H$_2$ Phe), 36.8 (β*C*H$_2$ Phe), 28.2 (3×*C*H$_3$ Boc+*C*H), 24.1 (*C*H$_3$ Dbg), 24.0 (*C*H$_3$ Dbg), 23.9 (*C*H Dbg), 23.1 (*C*H$_3$ Dbg), 22.7 (*C*H$_3$ Dbg). Anal. calcd for $C_{35}H_{51}N_5O_6$: C: 65.91, H: 8.06, N: 10.98; found: C: 65.86, H: 8.29, N: 10.75.

Acknowledgements

We wish to acknowledge Dr. Sílvia M. A. Pereira-Lima for the preparation of amino acids H-Dpg-OH and H-Dbg-OH, Miss Elisa Pinto for running the NMR experiments and for the elemental analyses, and Mr. Nuno Cerqueira for help with molecular modeling. We also wish to acknowledge the Fundação para a Ciência e a Tecnologia for financial support to the Instituto de Biotecnologia e Química Fina (University of Minho).

References and notes

1. Lombard, A.; Simone, G.; Galdiero, S.; Nastri, F.; Costanzo, L.; Makihira, K.; Yamada, T.; Pavone, V. *Biopolymers* **2000**, *53*, 150–160 and references cited therein.
2. Lombardi, A.; De Simone, G.; Galdiero, S.; Lombard, A.; Simone, G.; Galdiero, S.; Nastri, F.; Costanzo, L.; Makihira, L.; Yamada, T.; Pavone, V. *Biopolymers* **2000**, *53*, 182–188 and references cited therein.
3. Benedetti, E.; Isernia, C.; Nastri, F.; Pedone, C.; Saviano, M.; Mierke, D.; Melchiorri, P.; Negri, L.; Potenza, R.; Severini, C.; Erspamer, V. *Eur. J. Org. Chem.* **1998**, 2279–2287.
4. Horikawa, M.; Shigeri, Y.; Yumoto, N.; Yoshikawa, S.; Nakajima, T.; Ohfune, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2027–2032 and references cited therein.
5. Halab, L.; Bélec, L.; Lubell, W. *Tetrahedron* **2001**, *57*, 6439–6446 and references cited therein.
6. Karle, I.; Balaram, P. *Biochemistry* **1990**, *29*, 6747–6756.
7. Benedetti, E.; Toniolo, C.; Hardy, P.; Barone, V.; Bavoso, A.; Grimaldi, P.; Lelj, F.; Pavone, V.; Pedone, C.; Bonora, G.; Lingham, I. *J. Am. Chem. Soc.* **1984**, *106*, 8146–8152.
8. Benedetti, E. *Biopolymers* **1996**, *40*, 3–44.
9. Blasio, B.; Pavone, V.; Saviano, M.; Lombardi, A.; Nastri, F.; Pedone, C.; Benedetti, E.; Crisma, M.; Anzolin, M.; Toniolo, C. *J. Am. Chem. Soc.* **1992**, *114(16)*, 6273–6278.
10. Crisma, M.; Valle, J.; Toniolo, C.; Rao, R.; Prasad, S.; Balaram, P. *Biopolymers* **1995**, *35*, 1–9.
11. Benedetti, E.; Barone, V.; Bavoso, A.; Di Blasio, B.; Lelj, F.; Pavone, V.; Pedone, C.; Bonora, G.; Toniolo, C.; Leplawy, M.; Kaczmarek, K.; Redlinski, A. *Biopolymers* **1988**, *27*, 357–371.
12. Kaul, R.; Banumathi, S.; Velmuragan, D.; Ravikumar, K.; Balaji, R.; Balaram, P. *J. Peptide Res.* **2000**, *55*, 271–278.
13. Brandenburg, D. *Exp. Clin. Endocrinol. Diabetes* **1999**, *107*(Suppl. 2), S6–S11.
14. Costa, S.; Maia, H.; Pereira-Lima, S. *Org. Biomol. Chem.* **2003**, *1*, 1475–1479.
15. Spencer, J.; Antonenko, V.; Delaet, N.; Goodman, M. *Int. J. Peptide Protein Res.* **1992**, *40*, 282–293.
16. Coste, J.; Frérot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437–2446.
17. Gross, E.; Meinhofer, J.; *The Peptides, Synthesis, Analysis, Biology*, Vol. 1; Academic: London, 1979 pp 256–58.
18. Akaji, K.; Kuriyama, N.; Kiso, Y. *Tetrahedron Lett.* **1994**, *35*(20), 3315–3318.
19. Fu, Y.; Hammer, R. *Org. Lett.* **2002**, *4*(2), 237–240 and references cited therein.
20. Chen, S.-T.; Wu, S.-H.; Wang, K.-T. *Synth. Commun.* **1989**, 37–38.
21. Ludvigsen, S.; Andersen, K.; Poulsen, F. *J. Mol. Biol.* **1991**, 731–736.
22. Stachel, S.; Hu, H.; Van, Q.; Shaka, A.; Van Vranken, D. *Bioorg. Med. Chem.* **1998**, *6*, 1439–1446.
23. Paradisi, M.; Torrini, I.; Zecchini, G.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G. *Tetrahedron* **1995**, *51*, 2379–2386 and references cited therein.
24. Bodansky, M.; Bodansky, A. *The Practice of Peptide Synthesis*; Springer: Berlin, 1984 p 20.
25. Pettit, G.; *Synthetic Peptides*, Vol. 3; Academic: London, 1975.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8937–8947
Tetrahedron

Regioselective synthesis of 4- and 5-oxazole-phosphine oxides and -phosphonates from 2*H*-azirines and acyl chlorides

Francisco Palacios,* Ana M. Ochoa de Retana, José I. Gil and José M. Alonso

Departamento de Química Orgánica I, Facultad de Farmacia, Universidad del País Vasco. Apartado 450, 01080 Vitoria, Spain

Received 11 May 2004; revised 2 July 2004; accepted 6 July 2004

Available online 18 August 2004

Abstract—A simple and efficient regioselective synthesis of 4-oxazole-phosphine oxides **11** and -phosphonates **12** from 2*H*-azirine-phosphine oxides **1** and -phosphonates **6** is described. The key step for the synthesis of oxazoles **11** is a base-mediated ring closure of vinylogous α-aminophosphorus compounds derived from phosphine oxides **4** and from phosphonates **8**. These derivatives **4** and **8** are obtained by reaction of functionalized azirines **1** and **6** with acyl chlorides **2** and subsequent acid-catalyzed ring opening of *N*-acylaziridine-phosphine oxides **3** and -phosphonates **7**. Regioselective thermal ring cleavage of *N*-acylaziridine-phosphine oxides **3** leads α-chloro-β-(*N*-acylamido)-phosphine oxides **13** and their treatment with bases gives 5-oxazole-phosphine oxides **16**.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

2*H*-Azirine ring systems represent an important class of compounds because of their high reactivity[1] in the preparation of acyclic functionalized amino derivatives[2a–c] and heterocycles.[2d–h] In particular, 2*H*-azirines containing a carboxylic ester group are constituents of naturally occurring antibiotics[1a] and are excellent reagents for the preparation of functionalized aziridines[1,3] and α-[3b,4a–e] and β-amino acid derivatives,[3b,4f–h] while molecular modifications involving the introduction of organophosphorus functionalities, replacing the carboxylic ester for an isosteric phosphorus group, could increase the use of these substrates as intermediates not only in organic synthesis but also in medicinal chemistry.[1,5] For this reason, we have previously reported the preparation of 2*H*-azirine-phosphine oxides[6] and -phosphonates by a base-mediated Neber reaction of tosyl oximes.[7]

In this context, we have also described new methods for the preparation of five,[8] and six[9] membered phosphorus substituted nitrogen heterocycles from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of acyclic compounds[10] and phosphorus-containing heterocycles.[11] Recently, we described the use of phosphorylated 2*H*-azirines for the synthesis of α- and β-amino phosphorus derivatives[12] as well as their dimerization to phosphorylated pyrazines[13] and the ring opening of these azirines **I** with carboxylic acids followed by the cyclization of the corresponding adducts **II** to oxazoles containing phosphorus substituents in position 4 **III** through the azirine-oxozolone methodology[14] (Fig. 1). Furthermore, the reaction of acyl halides with simple azirines to give *N*-acylaziridines,[15] oxazoles,[16] or unsaturated *N*-acylimines[17] has been described. However, the behaviour of phosphorylated azirines with acyl halides has not been reported. For this reason and continuing with our interest in the synthesis of new phosphorus substituted heterocycles, we here report an easy and high yielding synthesis of 4- (**III**, Fig. 1) and

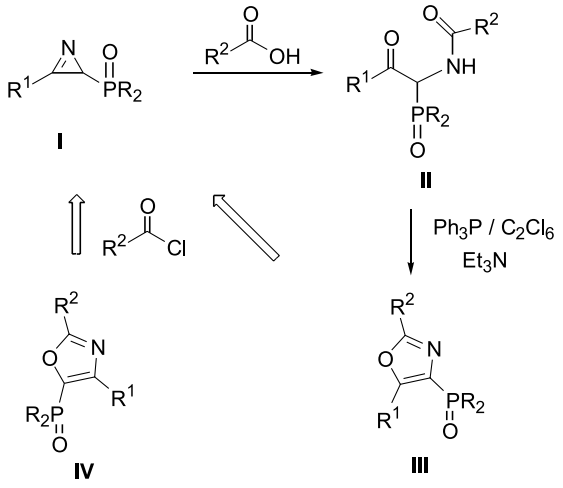


Figure 1.

Keywords: Azirine phosphine oxide and phosphonate; Oxazole; Acyl chloride.

* Corresponding author. Tel.: +34-945-013103; fax: +34-945-013049; e-mail: qoppagaf@vf.ehu.es

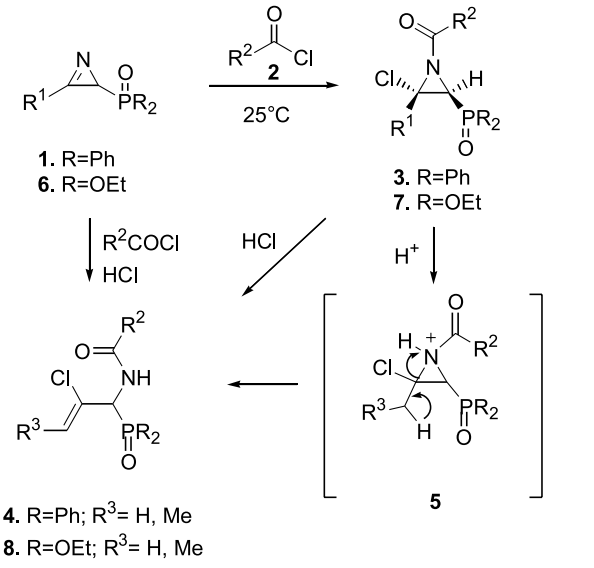
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.013

5-(oxazolyl)-phosphorus derivatives (**IV**, Fig. 1) from easily available azirines and acyl chlorides, as well as the formation and isolation of their *N*-acyl-aziridine precursors. Simple oxazoles are common units in a wide variety of polyoxazole marine natural products possessing biological activity,[18] and oxazoles are also widely used intermediates for functional transformations.[19]

2. Results and discussion

2.1. Reaction of azirines 1 and 6 with acyl chlorides

2*H*-Azirines are ambident reagents and are capable of acting in organic reactions not only as nucleophiles (N-1), but also as electrophiles (C-3).[1] Carboxylic acids can ring open these strained three membered heterocycles **I** to give amides **II** by means of acid-catalyzed addition of carboxylate nucleophile and these amides **II** can be used for the preparation of oxazoles **III** (Fig. 1). However, a different behaviour could be expected in the case of other carboxylic derivatives such as acyl chlorides, because in this case the acyl group could act as electrophile. So, we initially explored the reaction of acyl chlorides with phosphorylated azirines. Reaction of azirine-phosphine oxide **1a** (R=Ph, $R^1=CH_3$) with acetyl chloride **2a** ($R^2=CH_3$) at room temperature led exclusively to the formation of *trans*-(*N*-acyl-3-chloro-3-methyl-aziridinyl-phosphine oxide) **3aa** (R=Ph, $R^1=R^2=CH_3$) (Scheme 1, Table 1, entry 1). No trace of the *cis*-aziridine could be observed by ^{31}P NMR. Spectroscopic data were in agreement with the assigned structure of compound **3aa**. In the ^{31}P NMR spectrum the phosphine oxide group of this aziridine **3aa** resonated at $\delta_P=23.2$ ppm, while well resolved doublets at $\delta=3.32$ ppm ($^2J_{PH}=23.0$ Hz) for H-2 in the ^1H NMR spectrum as well as at $\delta_C=44.7$ ppm ($^1J_{PC}=96.2$ Hz) and at $\delta_C=59.8$ ppm ($^2J_{PC}=5.5$ Hz) for C-2 and C-3 in the ^{13}C NMR spectrum were observed. The stereochemical assignment was based on NOE experiments. The exclusive formation of *trans*-aziridine **3aa** suggests that the approach of the chloride to the cyclic compound from the opposite position to the phosphine oxide group is more favourable, due to the high exocyclic dihedral angle of the saturated carbon and to the presence of the bulky phosphorus group. The scope of the reaction was not limited to acetyl chloride **2a** ($R^2=CH_3$), given that not only benzoyl chloride **2b** ($R^2=Ph$), but also functionalized acyl chlorides containing olefine groups **2c** ($R^2=(CH_2)_4CH=CH_2$), and **2d** ($R^2=CH=CH_2$) also reacted with azirine **1a** to give functionalized *trans*-(*N*-acylaziridines) **3ab**-**3ad** (Scheme 1, Table 1, entries 2–4) in a regioselective fashion. Likewise, 3-ethyl- **1b** ($R^1=C_2H_5$) and 3-phenyl-azirines **1c** ($R^1=Ph$) also reacted with acetyl chloride **2a** ($R^2=CH_3$) to afford only *trans*-aziridinyl-phosphine oxides **3ba** and **3ca** (Scheme 1, Table 1, entries 5,6).



Scheme 1.

Table 1. *N*-Acylaziridine-phosphine oxides **3** obtained

Entry	Compound	R^1	R^2	Yield (%)[a]
1	**3aa**	CH_3	CH_3	76
2	**3ab**	CH_3	Ph	81
3	**3ac**	CH_3	$(CH_2)_4CH=CH_2$	43
4	**3ad**	CH_3	$CH=CH_2$	96
5	**3ba**	C_2H_5	CH_3	85
6	**3ca**	Ph	CH_3	80

[a] Yield of isolated purified compounds **3**.

Ring expansion of *N*-acylaziridines to five membered heterocycles can be achieved by thermal treatment or in the presence of acids,[20] while no ring opening reaction of *N*-acylaziridines containing phosphorus substituents has been reported. We explored the reaction of azirine-phosphine oxides because this reaction can be used as a model of the influence of phosphorus substituents by the ring opening reaction of these substrates and functionalized amides generated could then be used for the preparation of phosphorylated oxazoles. Treatment of functionalized *N*-acylaziridines **3aa**-**ac** with hydrogen chloride in THF at room temperature led to the formation of vinylogous α-amido-phosphine oxides **4aa**-**ac** (Scheme 1, Table 2, entries 1–3). Both conjugative addition of HCl to the acryloyl group of *N*-acylaziridine **3ad** ($R^2=CH=CH_2$) and the ring opening was observed when this aziridine **3ad** was treated with HCl to give α-amido-phosphine oxides **4ad** ($R^2=CH_2$–CH_2Cl) (Scheme 1, Table 2, entry 4). Spectroscopic data were in agreement with the assigned structure of compounds **4**. The formation of α-amido-phosphine oxides **4** could be explained by protonation of the nitrogen atom of the *N*-acylaziridine followed by formation of the carbon–carbon double bond and ring opening of activated aziridinium ion **5**. From a synthetic point of view, it is noteworthy that the preparation of these α-amido-phosphine oxides **4** can also be directly prepared from azirines **1** without the isolation of *N*-acylaziridines **3**, when these heterocycles **1** were treated with acyl chlorides **2** in a THF solution containing hydrogen chloride (Scheme 1, Table 2, entries 1–3). The use of azirines containing an ethyl group at 3-position **1b** ($R^1=C_2H_5$) gave **4ba** ($R^3=CH_3$) (Scheme 1, Table 2, entry 5) and allowed us to assign the *Z*-configuration of the carbon–carbon double bond based on NOE experiments.

These processes can be extended to azirines derived from phosphonates **6**. Treatment of 3-alkyl azirines **6a** (R=OEt, $R^1=Me$) and **6b** (R=OEt, $R^1=C_2H_5$), with acetyl chloride

Table 2. Vinylogous amides **4** and **8** obtained

Entry	Compound	R	R^2	R^3	Yield (%)[a]
1	**4aa**	Ph	CH_3	H	96 (96)[b]
2	**4ab**	Ph	Ph	H	33 (42)[b]
3	**4ac**	Ph	$(CH_2)_4CH{=}CH_2$	H	22 (40)[b]
4	**4ad**	Ph	$CH_2{-}CH_2Cl$	H	48
5	**4ba**	Ph	CH_3	CH_3	58[b]
6	**8aa**	OEt	CH_3	H	91
7	**8ad**	OEt	$CH{=}CH_2$	H	78
8	**8ba**	OEt	CH_3	CH_3	87

[a] Yield of isolated purified compounds **4** and **8**.
[b] Yield of isolated compounds **4** obtained one pot from azirines **1**.

2a ($R^2{=}CH_3$) and acryloyl chloride **2d** ($R^2{=}CH{=}CH_2$) gave vinylogous amides containing a diethoxyphosphoryl group in the α-position **8aa** (R=OEt, $R^2{=}CH_3$, $R^3{=}H$), **8ad** (R=OEt, $R^2{=}CH{=}CH_2$, $R^3{=}H$) and **8ba** (R=OEt, $R^2{=}CH_3$, $R^3{=}CH_3$) (Scheme 1, Table 2, entries 6–8), without the isolation of the *N*-acylaziridine precursors **7**. This strategy describes, as far as we know, the first synthesis of vinylogous α-amido-phosphine oxides and -phosphonates. α-Aminophosphonates[21] can be considered as surrogates for α-aminoacids,[22a] and have been used as haptens for the generation of catalytic antibodies,[10b,c] as antibacterial agents,[22d,e] and as nucleoside,[22f] or as phosphapeptide enzyme inhibitors.[22g–k]

2.2. Formation of oxazoles 11, 12 and 16

Oxazoles are common heterocycles in a wide variety of natural products possessing biological activity and also are widely used intermediates for functional transformations.[18,19] Given that phosphorus substituents regulate important biological functions,[5] we thought that *N*-acylaziridines **3** or α-amido-phosphine oxides **4** could be used for the preparation of oxazoles. Vinylogous amides **4** (R=Ph, $R^3{=}$ H, CH_3) were treated with 2 N aqueous NaOH solution in dichloromethane to give 3-alkyl-oxazole phosphine oxides **11** (R=Ph, $R^1{=}CH_3$, C_2H_5) in good yields and in a regioselective fashion (Scheme 2, Table 3, entries 1–5). Formation of oxazoles **11** could be explained by cyclization of intermediate **9** and subsequent loss of HCl from dihydrooxazol **10**. However, in the case of oxazoles containing an aryl substituent, this 5-phenyl oxazole **11ca** (R=Ph, $R^1{=}$Ph) was directly obtained from 3-phenyl azirine **1c** by ring expansion with acetyl chloride and HCl via an aziridinium cation (Scheme 2, Table 3, entry 6).

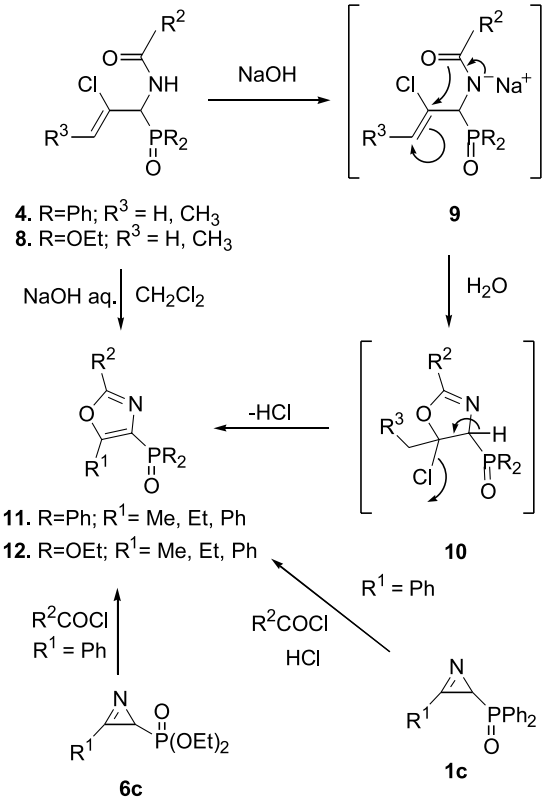
Table 3. 4-Oxazolyl-phosphine oxides **11** and -phosphonates **12** obtained

Entry	Compound	R	R^1	R^2	Yield (%)[a]
1	**11aa**	Ph	CH_3	CH_3	87
2	**11ab**	Ph	CH_3	Ph	82
3	**11ac**	Ph	CH_3	$(CH_2)_4CH{=}CH_2$	71
4	**11ad**	Ph	CH_3	$CH{=}CH_2$	52
5	**11ba**	Ph	C_2H_5	CH_3	67
6	**11ca**	Ph	Ph	CH_3	58
7	**12aa**	OEt	CH_3	CH_3	59
8	**12ad**	OEt	CH_3	$CH{=}CH_2$	63
9	**12ba**	OEt	C_2H_5	CH_3	65
10	**12ca**	OEt	Ph	CH_3	92

[a] Yield of isolated purified compounds **11** and **12**.

Ring closure of α-amido-phosphonates **8** with 2 N aqueous NaOH solution gave oxazole phosphonates **12** (Scheme 1, Table 3, entries 7–9), and ring expansion of 3-phenyl azirine **6c** (R=OEt, $R^1{=}$Ph) with acetyl chloride **2a** ($R^2{=}CH_3$) gave directly 5-phenyl oxazole phosphonate **12ca** (R=OEt, $R^1{=}$Ph, $R^2{=}CH_3$) (Scheme 2, Table 3, entry 10).

Next, we also explored the behaviour of *N*-acylaziridines **3** when they were heated in the presence of a base, in order to test whether these substrates could be opened in a different regioselective fashion than before, with presence of acid. Thermal treatment of *N*-acylaziridines **3aa** (R=Ph, $R^1{=}R^2{=}CH_3$), **3ab** (R=Ph, $R^1{=}CH_3$, $R^2{=}$Ph), **3ad** (R=Ph, $R^1{=}CH_3$, $R^2{=}CH{=}CH_2$), **3ba** (R=Ph, $R^1{=}C_2H_5$, $R^2{=}CH_3$), in refluxing chlorobenzene and in the presence of tributylamine led to the formation of vinylamides **13aa**, **13ab**, **13ad** and **13ba** in moderate yields (Scheme 3, Table 4, entries 1–4) and a small proportion of oxazoles **11**. The formation of oxazoles **11** (minor components) can be explained as before (Scheme 2) by regioselective ring opening of the N–C2 bond followed by cyclization to the five membered ring, while formation of major compounds **13** could be explained by regioselective ring opening of the

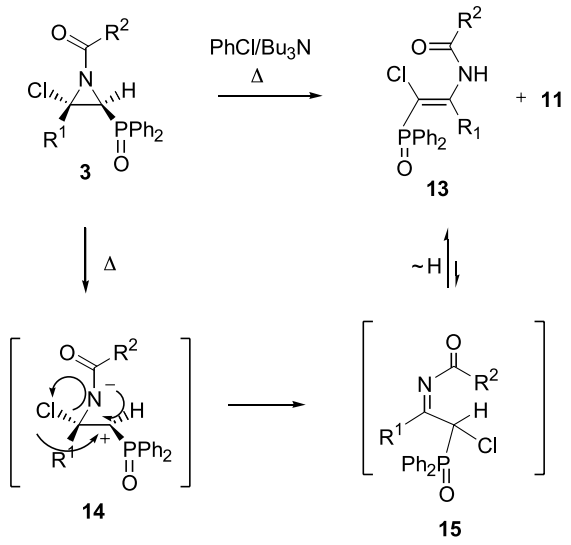


Scheme 2.

Table 4. Enamides **13** and 5-oxazolyl-phosphine oxides **16**

Entry	Compound	R^1	R^2	Yield (%)[a]
1	**13aa**	CH_3	CH_3	41
2	**13ab**	CH_3	Ph	60
3	**13ad**	CH_3	$CH{=}CH_2$	15
4	**13ba**	C_2H_5	CH_3	54
5	**16aa**	CH_3	CH_3	65
6	**16ab**	CH_3	Ph	72
7	**16ba**	C_2H_5	CH_3	57

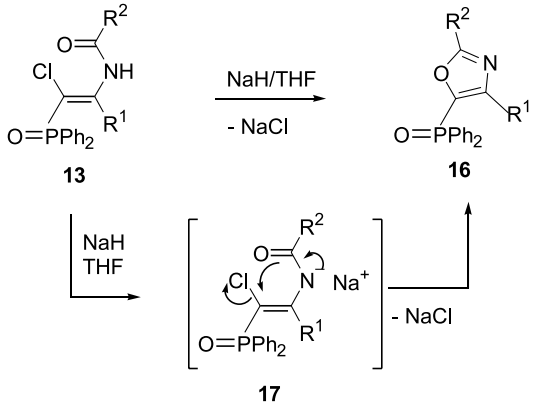
[a] Yield of isolated purified compounds **13** and **16**.



Scheme 3.

N–C1 single bond of the ring through an intermediate **14**, chloride rearrangement and formation of functionalized acylimine **15** containing chloro and phosphine oxide groups in the α position, followed by tautomerization.

Finally, base-mediated (NaH) ring closure of enamides **13** in THF reflux gave only 5-oxazolyl-phosphine oxides **16** (Scheme 4, Table 4, entries 5–7) in good yields and in a regioselective fashion. The formation of oxazoles **16** can be explained by deprotonation, sodium amidure salt formation and intramolecular nucleophilic cyclization of intermediate **17** with the loss of NaCl. As far as we know, this process describes the first synthesis of oxazole derivatives containing phosphorus substituent in position 5.



Scheme 4.

3. Conclusion

In conclusion, this account describes a simple, mild, and convenient strategy for the preparation of oxazoles containing phosphorus substituents in position 4 and 5 from easily available azirine-phosphine oxides **1** and -phosphonates **6** and acyl chlorides. *N*-Acylaziridines **3** can be isolated and these strained heterocycles can be used for the preparation of vinylogous α-amido-phosphine oxides **3** and phosphonates **8** when azirines were treated with acyl chlorides in the presence of HCl, while functionalised enamides **13** were obtained by thermal treatment of *N*-acylaziridines **3**. Ring closure of vinylogous α-amides **4**, **8** gives 4-oxazolyl-phosphine oxides **11** and -phosphonates **12** while intramolecular cyclization of enamides **13** affords 5-oxazolyl-phosphine oxides **16**. Oxazoles[18] are common compounds in a wide variety of natural products possessing biological activity and both oxazoles and α-aminophosphonates[21] are widely used intermediates in organic and medicinal chemistry.[18,19,21,22]

4. Experimental

4.1. General

Chemicals were purchased from Aldrich Chemical Company. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (400, 300, 250 MHz), ^{13}C (100, 75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Bruker Avance 400 MHZ and a Varian Unity 300 MHz Plus spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ= 0.00 ppm) for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) (δ=0.0 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 spectrometer or by chemical ionization (CI) on a Hewlett Packard 1100 MSD spectrometer. Data are reported in the form m/z (intensity relative to base=100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Azirines **1** and **6** were prepared according to literature procedures.[6,7]

4.2. General procedure for the preparation of *N*-acylaziridine-phosphine oxides 3

The corresponding acyl chloride **2** (5 mmol) was added to a solution of 2*H*-azirine-2-diphenylphosphine oxide **1** (5 mmol) in benzene (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature until TLC indicated the disappearance of azirine (1–38 h). Evaporation of solvent under reduced pressure and chromatographic purification by flash column chromatography with hexane/ethyl acetate or crystallization afforded the corresponding derivatives **3**.

4.2.1. *trans*-*N*-Acetyl-3-chloro-3-methyl-aziridin-2-yl diphenyl phosphine oxide (3aa). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) and acetyl chloride **2a** (0.38 mL, 5 mmol). Chromatographic purification and crystallization

from hexane/ethyl acetate gave 1.27 g (76%) of compound **3aa**; mp 197–198 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.23 (s, 3H), 3.32 (d, $^2J_{PH}$=23.0 Hz, 1H), 7.39–7.54 (m, 6H), 7.73–7.81 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.0, 44.7 (d, $^1J_{PC}$=96.2 Hz), 59.8 (d, $^2J_{PC}$=5.5 Hz), 128.6–132.6 (m), 178.2 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 23.2 ppm; IR (KBr) ν_{max} 3065, 1720, 1388, 1366, 1210 cm^{-1}; *MS* (EI): *m/z* 335 (M^++2, 21), 333 (M^+, 62). Anal. Calcd for $C_{17}H_{17}ClNO_2P$: C, 61.18; H, 5.13; N, 4.20. Found: C, 61.35; H, 5.11; N, 4.21.

4.2.2. *trans*-*N*-Benzoyl-3-chloro-3-methyl-aziridin-2-yl diphenyl phosphine oxide (3ab). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) and benzoyl chloride **2b** (0.58 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.60 g (81%) of compound **3ab**; mp 144–145 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.57 (d, $^2J_{PH}$= 22.7 Hz, 1H), 7.40–7.58 (m, 9H), 7.79–7.97 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 44.2 (d, $^1J_{PC}$= 96.7 Hz), 61.6 (d, $^2J_{PC}$=5.0 Hz), 128.1–134.0 (m), 175.0 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 23.5 ppm; IR (KBr) ν_{max} 3065, 1697, 1384, 1201 cm^{-1}; *MS* (EI): *m/z* 397 (M^++2, 18), 395 (M^+, 55). Anal. Calcd for $C_{22}H_{19}ClNO_2P$: C, 66.76; H, 4.84; N, 3.54. Found: C, 66.56; H, 4.81; N, 3.54.

4.2.3. *trans*-3-Chloro-3-methyl-*N*-(6-heptenoyl)-aziridin-2-yl diphenyl phosphine oxide (3ac). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) and 6-heptenoyl chloride **2c** (0.73 g, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 0.85 g (43%) of compound **3ac**; mp 153–154 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (m, 2H), 1.69 (m, 2H), 2.06 (m, 2H), 2.11 (m, 3H), 2.58 (m, 2H), 3.40 (d, $^3J_{PH}$= 24.0 Hz, 1H), 4.97 (m, 2H), 5.78 (m, 1H), 7.45–7.63 (m, 6H), 7.81–7.88 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 25.1, 28.1, 33.3, 37.8, 44.2 (d, $^1J_{PC}$=97.0 Hz), 60.1 (d, $^2J_{PC}$=5.6 Hz), 114.7, 128.5–132.5 (m), 138.2, 181.1 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 23.3 ppm; IR (KBr) ν_{max} 3060, 1700, 1200 cm^{-1}; *MS* (EI): *m/z* 403 (M^++2, 21), 401 (M^+, 68). Anal. Calcd for $C_{22}H_{25}ClNO_2P$: C, 65.75; H, 6.27; N, 3.49. Found: C, 65.60; H, 6.29; N, 3.48.

4.2.4. *trans*-*N*-Acryloyl-3-chloro-3-methyl-aziridin-2-yl diphenyl phosphine oxide (3ad). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) and acryloyl chloride **2d** (0.41 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.66 g (96%) of compound **3ad**; mp 113–114 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (m, 3H), 3.40 (d, $^2J_{PH}$= 22.6 Hz, 1H), 5.89 (dd, $^3J_{HHcis}$=9.5 Hz, $^2J_{HHgem}$=3.8 Hz, 1H), 6.35 (m, $^3J_{HHcis}$=9.5 Hz, $^2J_{HHgem}$=3.8 Hz, $^3J_{HHtrans}$= 1.7 Hz, 2H), 7.40–7.56 (m, 6H), 7.76–7.83 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 44.3 (d, $^1J_{PC}$=96.2 Hz), 60.5 (d, $^2J_{PC}$=5.5 Hz), 128.6–132.6 (m), 131.1, 131.4, 173.3 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 23.4 ppm; IR (KBr) ν_{max} 3060, 1705, 1187 cm^{-1}; *MS* (EI): *m/z* 347 (M^++2, 11), 345 (M^+, 33). Anal. Calcd for $C_{18}H_{17}ClNO_2P$: C, 62.53; H, 4.96; N, 4.05. Found: C, 62.44; H, 4.98; N, 4.07.

4.2.5. *trans*-*N*-Acetyl-3-chloro-3-ethyl-aziridin-2-yl diphenyl phosphine oxide (3ba). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1b** (1.34 g, 5 mmol) and acetyl chloride **2a** (0.38 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.47 g (85%) of compound **3ba**; mp 120–121 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, $^3J_{HH}$=7.3 Hz, 3H), 2.22 (m, $^3J_{HH}$=7.2 Hz, $^3J_{HHgem}$=7.2 Hz, 1H), 2.29 (d, $^5J_{PH}$= 1.4 Hz, 3H), 2.47 (m, $^3J_{HH}$=7.2 Hz, $^3J_{HHgem}$=7.2 Hz, 1H), 3.43 (d, $^2J_{PH}$=23.2 Hz, 1H), 7.25–7.61 (m, 6H), 7.81–7.89 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.2, 25.0, 30.8, 45.4 (d, $^1J_{PC}$=96,7 Hz), 65.4 (d, $^2J_{PC}$= 4.5 Hz), 127.3–132.5 (m), 178.5 (d, $^3J_{PC}$=2.5 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 22.7 ppm; IR (KBr) ν_{max} 3058, 1666, 1434, 1374, 1199 cm^{-1}; *MS* (CI): *m/z* 348 (M^++1, 90). Anal. Calcd for $C_{18}H_{19}ClNO_2P$: C, 62.16; H, 5.51; N, 4.03. Found: C, 62.28; H, 5.50; N, 4.01.

4.2.6. *trans*-*N*-Acetyl-3-chloro-3-phenyl-aziridin-2-yl diphenyl phosphine oxide (3ca). The general procedure was followed using 2*H*-azirine-2-diphenylphosphine oxide **1c** (1.59 g, 5 mmol) and acetyl chloride **2a** (0.38 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.58 g (80%) of compound **3ca**; mp 97–98 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.86 (d, $^2J_{PH}$= 18.5 Hz, 1H), 7.12–7.58 (m, 13H), 7.79–7.86 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 47.6 (d, $^1J_{PC}$=98.2 Hz), 61.3 (d, $^2J_{PC}$=5.5 Hz), 127.8–134.3 (m), 179.3 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 22.6 ppm; IR (KBr) ν_{max} 3065, 1699, 1434, 1381, 1242 cm^{-1}; *MS* (CI): *m/z* 335 (M^++1, 40). Anal. Calcd for $C_{22}H_{19}ClNO_2P$: C, 66.76; H, 4.84; N, 3.54. Found: C, 66.62; H, 4.85; N, 3.55.

4.3. General procedure for the preparation of α-amidophosphine oxides 4

A solution of the corresponding *N*-acylaziridine-phosphine oxide **3** (5 mmol) in THF (10 mL) was saturated with hydrogen chloride and the mixture was stirred at room temperature under a nitrogen atmosphere until the formation of a precipitate (4 h). Evaporation of solvent under reduced pressure and crystallization from ethyl acetate afforded compounds **4**.

4.3.1. *N*-[2-Chloro-1-(diphenylphosphinyl)-allyl]-acetamide (4aa). The general procedure was followed using *N*-acylaziridinephosphine oxide **3aa** (1.67 g, 5 mmol). Crystallization from ethyl acetate gave 1.60 g (96%) of compound **4aa**; mp 228–229 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 5.29 (d, $^2J_{HHgem}$= 2.1 Hz, 1H), 5.48 (dd, $^2J_{HHgem}$=2.1 Hz, $^4J_{PH}$=2.2 Hz, 1H), 5.77 (dd, $^2J_{PH}$=7.4 Hz, $^3J_{HH}$=9.8 Hz, 1H), 7.47–7.56 (m, 6H), 7.65 (d, $^3J_{HH}$=9.8 Hz, 1H), 7.74–7.86 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 53.9 (d, $^1J_{PC}$= 76.0 Hz), 118.1 (d, $^3J_{PC}$=6.5 Hz), 128.5–132.5 (m), 135.5, 169.7 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.7 ppm; IR (KBr) ν_{max} 3227, 3180, 3060, 1670, 1205 cm^{-1}; *MS* (EI): *m/z* 335 (M^++2, 15), 333 (M^+, 42). Anal. Calcd for

$C_{17}H_{17}ClNO_2P$: C, 61.18; H, 5.13; N, 4.20. Found: C, 61.39; H, 5.12; N, 4.21.

The compound **4aa** was obtained directly (1.60 g, 96%) when 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) was added to a solution of acetyl chloride **2a** (0.38 mL, 5 mmol) in benzene (10 mL) saturated of hydrogen chloride and the mixture was stirred at room temperature for 2 h.

4.3.2. *N*-[2-Chloro-1-(diphenylphosphinyl)-allyl]-benzamide (4ab). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ab** (1.98 g, 5 mmol). Crystallization from ethyl acetate gave 0.65 g (33%) of compound **4ab**; mp 223–224 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (d, $^2J_{HHgem}$=2.1 Hz, 1H), 5.50 (d, $^2J_{HHgem}$=2.1 Hz, 1H), 5.91 (dd, $^2J_{PH}$=9.3 Hz, $^3J_{HH}$=8.1 Hz, 1H), 7.37–7.57 (m, 11H), 7.69 (d, $^3J_{HH}$=7.5 Hz, 1H), 7.81–7.90 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.4 (d, $^1J_{PC}$=75.0 Hz), 118.2 (d, $^3J_{PC}$=6.6 Hz), 127.2–133.3 (m), 135.5, 166.8 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.8 ppm; IR (KBr) ν_{max} 3204, 3065, 1646, 1200 cm^{-1}; *MS* (EI): *m/z* 398 (M^++3, 15), 396 (M^++1, 73). Anal. Calcd for $C_{22}H_{19}ClNO_2P$: C, 66.76; H, 4.84; N, 3.54. Found: C, 66.98; H, 4.78; N, 3.55.

The compound **4ab** was obtained directly (1.60 g, 96%) when 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) was added to a solution of benzoyl chloride **2b** (0.58 mL, 5 mmol) in benzene (10 mL) saturated of hydrogen chloride and the mixture was stirred at room temperature for 2 h.

4.3.3. *N*-[2-Chloro-1-(diphenylphosphinyl)-allyl]-heptenamide (4ac). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ac** (2.01 g, 5 mmol). Crystallization from ethyl acetate gave 0.44 g (22%) of compound **4ac**; mp 187–188 °C (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16–1.26 (m, 2H), 1.31–1.51 (m, 2H), 1.91–1.98 (m, 2H), 2.09–2.29 (m, 2H), 4.90–4.98 (m, 2H), 5.30 (d, $^4J_{PH}$=0.5 Hz, 1H), 5.45 (d, $^4J_{PH}$=0.5 Hz, 1H), 5.68 (m, 1H), 5.77 (dd, $^2J_{PH}$=9.9 Hz, $^3J_{HH}$=7.5 Hz, 1H), 7.35 (d, $^3J_{HH}$=7.5 Hz, 1H), 7.44–7.58 (m, 6H), 7.75–7.87 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0, 28.1, 33.3, 36.1, 53.6 (d, $^1J_{PC}$=76.0 Hz), 114.6, 118.1 (d, $^3J_{PC}$=6.6 Hz), 128.5–132.5 (m), 135.5, 138.3, 172.6 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.7 ppm; IR (KBr) ν_{max} 3220, 3065, 1660, 1195 cm^{-1}; *MS* (EI): *m/z* 404 (M^++3, 1), 402 (M^++1, 3). Anal. Calcd for $C_{22}H_{25}ClNO_2P$: C, 65.75; H, 6.27; N, 3.49. Found: C, 65.82; H, 6.23; N, 3.46.

The compound **4ac** was obtained directly (0.80 g, 40%) when 2*H*-azirine-2-diphenylphosphine oxide **1a** (1.28 g, 5 mmol) was added to a solution of 6-heptenoyl chloride **2c** (0.73 g, 5 mmol) in benzene (10 mL) saturated of hydrogen chloride and the mixture was stirred at room temperature for 2 h.

4.3.4. 3-Chloro-*N*-[2-chloro-1-(diphenylphosphinyl)-allyl]-propionamide (4ad). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ad** (1.75 g, 5 mmol). Crystallization from ethyl acetate gave 0.92 g (48%) of compound **4ad**; mp 236–237 °C (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (t, $^3J_{HH}$=6.6 Hz, 2H), 3.62 (t, $^3J_{HH}$=6.6 Hz, 2H), 5.29 (d, $^2J_{HHgem}$=2.1 Hz, 1H), 5.47 (d, $^2J_{HHgem}$=2.1 Hz, 1H), 5.74 (dd, $^2J_{PH}$=9.5 Hz, $^3J_{HH}$=7.1 Hz, 1H), 7.46–7.53 (m, 6H), 7.73–7.83 (m, 4H), 7.91 (d, $^3J_{HH}$=7.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2, 39.0, 54.3 (d, $^1J_{PC}$=76.0 Hz), 119.7 (d, $^3J_{PC}$=7.5 Hz), 129.0–133.7 (m), 131.4 (d, $^2J_{PC}$=10.0 Hz), 172.3 (d, $^3J_{PC}$=5.5 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 31.7 ppm; IR (KBr) ν_{max} 3231, 3065, 1672, 1189 cm^{-1}; *MS* (EI): *m/z* 384 (M^++3, 16), 382 (M^++1, 18). Anal. Calcd for $C_{18}H_{18}Cl_2NO_2P$: C, 56.56; H, 4.75; N, 3.66. Found: C, 56.76; H, 4.76; N, 3.67.

4.3.5. *N*-[2-Chloro-1-(diphenylphosphinyl)-buten-2-enyl]-acetamide (4ba). This compound **4ba** was obtained directly when 2*H*-azirine-2-diphenylphosphine oxide **1b** (1.34 g, 5 mmol) was added to a solution of acetyl chloride **2a** (0.38 mL, 5 mmol) in benzene (10 mL) saturated of hydrogen chloride and the mixture was stirred at room temperature for 5 h. Crystallization from ethyl acetate gave 1.01 g (58%) of compound **4ba**; mp 231–232 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (m, $^5J_{PH}$=6.4 Hz, $^3J_{HH}$=3.0 Hz, 3H), 1.92 (s, 3H), 5.71 (dd, $^2J_{PH}$=9.9 Hz, $^3J_{HH}$=7.0 Hz, 1H), 5.82 (m, $^4J_{PH}$=6.6 Hz, $^3J_{HH}$=3.2 Hz, 1H), 7.21–7.80 (m, 10H), 8.00 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6 (d, $^4J_{PC}$=3.0 Hz), 54.0 (d, $^1J_{PC}$=78.1 Hz), 127.3–132.6 (m), 170.0 (d, $^3J_{PC}$=6.4 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 32.6 ppm; IR (KBr) ν_{max} 3230, 3184, 3051, 1660, 1182 cm^{-1}; *MS* (CI): *m/z* 348 (M^++1, 100). Anal. Calcd for $C_{18}H_{19}ClNO_2P$: C, 62.16; H, 5.51; N, 4.03. Found: C, 62.30; H, 5.52; N, 4.02.

4.4. General procedure for the preparation of diethyl α-amidophosphonate 8

The corresponding acyl chloride **2** (5 mmol) was added to a solution of the corresponding 2*H*-azirine-phosphonate **6** (5 mmol) in benzene (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature until TLC indicated the disappearance of azirine (1–36 h). Evaporation of solvent under reduced pressure and chromatographic purification by flash column chromatography with hexane/ethyl acetate afforded the corresponding derivatives **8**.

4.4.1. Diethyl (1-acetylamino-2-chloro-allyl)-phosphonate (8aa). The general procedure was followed 2*H*-azirine-phosphonate **6a** (0.96 g, 5 mmol) and acetyl chloride **2a** (0.38 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.35 g (91%) of compound **8aa** as an oil; R_f 0.65 (ethyl acetate/methanol 5%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (m, 6H), 2.01 (s, 3H), 4.15 (m, 4H), 5.15 (dd, $^2J_{PH}$=21.4 Hz, $^3J_{HH}$=9.3 Hz, 1H), 5.41 (m, 1H), 5.53 (m, 1H), 6.70 (d, $^3J_{HH}$=9.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1, 22.5, 51.8 (d, $^1J_{PC}$=159.3 Hz), 63.3, 63.6, 117.1 (d, $^3J_{PC}$=9.1 Hz), 135.3 (d, $^2J_{PC}$=4.0 Hz), 169.7 (d, $^3J_{PC}$=7.5 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.1 ppm; IR (NaCl) ν_{max} 3258, 1666, 1186, 1097 cm^{-1}; *MS* (EI): *m/z* 271 (M^++2, 27), 269 (M^+, 42). Anal. Calcd for $C_9H_{17}ClNO_4P$: C, 40.09; H, 6.35; N, 5.19. Found: C, 40.28; H, 6.33; N, 5.20.

4.4.2. Diethyl (1-acryloylamino-2-chloro-allyl)-phosphonate (8ad). The general procedure was followed

2*H*-azirine-phosphonate **6a** (0.96 g, 5 mmol) and acryloyl chloride **2d** (0.41 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.10 g (78%) of compound **8ad** as an oil; R_f 0.51 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (m, $^3J_{HH}$= 7.3 Hz, 6H), 4.11 (m, 4H), 5.25 (dd, $^2J_{PH}$=21.5 Hz, $^3J_{HH}$= 9.5 Hz, 1H), 5.41 (m, 1H), 5.59 (m, 1H), 5.65 (dd, $^5J_{PH}$= 2.4 Hz, $^3J_{HHcis}$=9.3 Hz), 6.27 (m, 2H), 7.28 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 (d, $^3J_{PC}$=5.5 Hz), 16.3 (d, $^3J_{PC}$=3.5 Hz), 51.9 (d, $^1J_{PC}$=159.1 Hz), 63.5 (d, $^2J_{PC}$= 7.0 Hz), 63.7 (d, $^2J_{PC}$=7.0 Hz), 117.4 (d, $^3J_{PC}$=8.6 Hz), 127.8, 129.9, 135.2, 165.0 (d, $^3J_{PC}$=8.1 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.3 ppm; IR (NaCl) ν_{max} 3257, 1679, 1533, 1241, 1029 cm^{-1}; *MS* (EI): *m/z* 281 (M^+, 70). Anal. Calcd for $C_{10}H_{17}ClNO_4P$: C, 42.64; H, 6.08; N, 4.97. Found: C, 42.50; H, 6.10; N, 4.95.

4.4.3. Diethyl (1-acetylamino-2-chloro-but-2-enyl)-phosphonate (8ba). The general procedure was followed 2*H*-azirine-phosphonate **6b** (1.03 g, 5 mmol) and acetyl chloride **2a** (0.38 mL, 5 mmol). Chromatographic purification and crystallization from hexane/ethyl acetate gave 1.23 g (87%) of compound **8ba** as an oil; R_f 0.45 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (m, 6H), 1.72 (dd, $^5J_{PH}$=6.7 Hz, $^3J_{HH}$=4.4 Hz, 3H), 2.01 (s, 3H), 4.09 (m, 4H), 5.17 (dd, $^2J_{PH}$=21.7 Hz, $^3J_{HH}$=9.5 Hz, 1H), 5.97 (m, $^4J_{PH}$=6.7 Hz, $^3J_{HH}$=3.5 Hz, 1H), 6.94 (d, $^3J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.3 (d, $^3J_{PC}$=5.0 Hz), 23.0, 52.3 (d, $^1J_{PC}$=160.6 Hz), 63.3 (d, $^2J_{PC}$=7.0 Hz), 126.7 (d, $^3J_{PC}$=10.1 Hz), 128.2 (d, $^2J_{PC}$=1.5 Hz), 169.3 (d, $^3J_{PC}$=7.5 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.8 ppm; IR (NaCl) ν_{max} 3482, 2979, 1712, 1454, 1261, 1016 cm^{-1}; *MS* (CI): *m/z* 284 (M^++1, 40). Anal. Calcd for $C_{10}H_{19}ClNO_4P$: C, 42.34; H, 6.75; N, 4.94. Found: C, 42.48; H, 6.77; N, 4.93.

4.5. General procedure for the preparation of 4-oxazolyl-phosphine oxides 11 and -phosphonates 12

To a solution of the corresponding vinylogous amide **4** (5 mmol) in dichloromethane (20 mL) a 2 N aqueous NaOH solution (0.95 mL, 25 mmol) was added and the heterogeneous mixture was stirred at room temperature for 2 days. The crude was extracted with dichloromethane and the organic layer was dried with anhidrous magnesium sulfate. Evaporation of solvent under reduced pressure afforded a mixture that was chromatographied on silica gel to give compounds **11** and **12**.

4.5.1. 2,5-Dimethyl-oxazol-4-yl diphenylphosphine oxide (11aa). The general procedure was followed using α-amidophosphine oxide **4aa** (1.67 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.29 g (87%) of compound **11aa** as a white solid; mp 117–118 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.59 (d, $^4J_{PH}$=1.8 Hz, 3H), 7.41–7.88 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 13.8, 126.5 (d, $^1J_{PC}$=145.0 Hz), 128.3–133.8 (m), 158.9 (d, $^2J_{PC}$= 26.1 Hz), 160.4 (d, $^3J_{PC}$=19.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.8 ppm; IR (KBr) ν_{max} 3070, 1590, 1447, 1195 cm^{-1}; *MS* (EI): *m/z* 297 (M^+, 89). Anal. Calcd for $C_{17}H_{16}NO_2P$: C, 68.68; H, 5.42; N, 4.71. Found: C, 68.88; H, 5.40; N, 4.69.

4.5.2. 5-Methyl-2-phenyl-oxazol-4-yl diphenylphosphine oxide (11ab). The general procedure was followed using α-amidophosphine oxide **4ab** (1.98 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.47 g (82%) of compound **11ab** as a white solid; mp 134–135 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (d, $^4J_{PH}$=1.9 Hz, 3H), 7.35–7.96 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 126.5–133.8 (m), 159.0 (d, $^2J_{PC}$=27.0 Hz), 160.7 (d, $^3J_{PC}$=18.29 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.9 ppm; IR (KBr) ν_{max} 3070, 1780, 1585, 1442, 1187 cm^{-1}; *MS* (EI): *m/z* 359 (M^+, 56). Anal. Calcd for $C_{22}H_{18}NO_2P$: C, 73.53; H, 5.05; N, 3.90. Found: C, 73.43; H, 5.06; N, 3.91.

4.5.3. 2-(Hex-5-enyl)-5-methyl-oxazol-4-yl diphenylphosphine oxide (11ac). The general procedure was followed using α-amidophosphine oxide **4ac** (2.01 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.30 g (71%) of compound **11ac** as a white solid; mp 77–78 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (tt, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2H), 1.75 (tt, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2H), 2.12 (dt, $^3J_{HH}$=7.5 Hz, $^3J_{HH}$=7.5 Hz, 2H), 2.58 (d, $^4J_{PH}$=2.1 Hz, 3H), 2.73 (t, $^3J_{HH}$=7.5 Hz, 2H), 4.98 (m, 2H), 5.78 (m, 1H), 7.41–7.89 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 26.3, 27.7, 28.2, 29.6, 114.7, 126.0 (d, $^1J_{PC}$=145.0 Hz), 128.2–133.9 (m), 138.3, 158.6 (d, $^2J_{PC}$=26.7 Hz), 163.8 (d, $^3J_{PC}$= 17.6 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.3 ppm; IR (KBr) ν_{max} 3070, 1686, 1600, 1434, 1195 cm^{-1}; *MS* (EI): *m/z* 365 (M^+, 100). Anal. Calcd for $C_{22}H_{24}NO_2P$: C, 72.31; H, 6.62; N, 3.83. Found: C, 72.41; H, 6.60; N, 3.83.

4.5.4. 5-Methyl-2-vinyl-oxazol-4-yl diphenylphosphine oxide (11ad). The general procedure was followed using α-amidophosphine oxide **4ad** (1.91 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.80 g (52%) of compound **11ad** as a white solid; mp 100–101 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 (d, $^4J_{PH}$=2.1 Hz, 3H), 5.58 (dd, $^2J_{HHgem}$=0.9 Hz, $^3J_{HHcis}$=11.1 Hz, 1H), 6.10 (dd, $^2J_{HHgem}$=0.9 Hz, $^3J_{HHtrans}$=17.7 Hz, 1H), 6.50 (dd, $^3J_{HHcis}$=11.1 Hz, $^3J_{HHtrans}$=17.7 Hz, 1H), 7.38–7.86 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11,7, 122.4, 123.0, 126.4 (d, $^1J_{PC}$=145.0 Hz), 128.3–133.4 (m), 158.9 (d, $^2J_{PC}$= 26.7 Hz), 159.9 (d, $^3J_{PC}$=18.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 18.9 ppm; IR (KBr) ν_{max} 3065, 1750, 1600, 1180 cm^{-1}; *MS* (EI): *m/z* 310(M^++1, 26). Anal. Calcd for $C_{18}H_{16}NO_2P$: C, 69.90; H, 5.21; N, 4.53. Found: C, 69.75; H, 5.19; N, 4.55.

4.5.5. 5-Ethyl-2-methyl- oxazol-4-yl diphenylphosphine oxide (11ba). The general procedure was followed using α-amidophosphine oxide **4ba** (1.73 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.04 g (67%) of compound **11ba** as a white solid; mp 78–79 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $^3J_{HH}$=7.5 Hz, 3H), 2.43 (s, 3H), 3.04 (q, $^4J_{PH}$=1.2 Hz, $^3J_{HH}$=7.5 Hz, 2H), 7.41–7.87 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8, 13.8, 19.2, 125.4 (d, $^1J_{PC}$= 142.5 Hz), 128.2–133.8 (m), 160.4 (d, $^3J_{PC}$=18.1 Hz); 163.7 (d, $^2J_{PC}$=27.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.0 ppm; IR (KBr) ν_{max} 3059, 1586, 1440, 1196 cm^{-1}; *MS* (EI): *m/z* 311 (M^+, 100). Anal. Calcd for

$C_{18}H_{18}NO_2P$: C, 69.45; H, 5.83; N, 4.50. Found: C, 69.48; H, 5.84; N, 4.48.

4.5.6. 2-Methyl-5-phenyl-oxazol-4-yl diphenylphosphine oxide (11ca). The compound **11ca** was obtained directly when 2*H*-azirine-2-diphenylphosphine oxide **1c** (1.58 g, 5 mmol) was added to a solution of acetyl chloride **2a** (0.38 mL, 5 mmol) in benzene (10 mL) saturated of hydrogen chloride and the mixture was stirred at room temperature for 24 h. Chromatographic separation (hexane/ethyl acetate) gave 1.04 g (58%)of compound **11ca** as a white solid; mp 134–135 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.51 (t, $^3J_{HH}$=7.5 Hz, 3H), 7.32–8.09 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 128.3–132.2 (m), 159.0 (d, $^2J_{PC}$=25.2 Hz), 160.5 (d, $^3J_{PC}$=20.0 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.6 ppm; IR (KBr) ν_{max} 3051, 1580, 1481, 1202 cm^{-1}; *MS* (CI): *m*/*z* 360 (M^++1, 100). Anal. Calcd for $C_{22}H_{18}NO_2P$: C, 73.53; H, 5.05; N, 3.90. Found: C, 73.68; H, 5.04; N, 3.91.

4.5.7. Diethyl 2,5-(dimethyl-oxazol-4-yl) phosphonate (12aa). The general procedure was followed using diethyl α-amidophosphonate **8aa** (1.35 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.69 g (59%) of compound **12aa** as a colorless oil; R_f 0.34 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, $^3J_{HH}$=7.1 Hz, 6H), 2.44 (s, 3H), 2.54 (d, $^4J_{PH}$=2.4 Hz, 3H), 4.16 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 16.4 (d, $^3J_{PC}$=6.6 Hz), 62.5 (d, $^2J_{PC}$=5.5 Hz), 127.0 (d, $^1J_{PC}$=243.7 Hz), 158.5 (d, $^2J_{PC}$=39.8 Hz), 160.9 (d, $^3J_{PC}$=22.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.0 ppm; IR (NaCl) ν_{max} 2985, 1730, 1600, 1440, 1029 cm^{-1}; *MS* (EI): *m*/*z* 233 (M^+, 28). Anal. Calcd for $C_9H_{16}NO_4P$: C, 46.35; H, 6.92; N, 6.01. Found: C, 46.50; H, 6.94; N, 5.99.

4.5.8. Diethyl (5-methyl-2-vinyl-oxazol-4-yl)-phosphonate (12ad). The general procedure was followed using diethyl α-amidophosphonate **8ad**, (1.40 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.77 g (63%) of compound **12ad** as a colorless oil; R_f 0.51 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $^3J_{HH}$=6.4 Hz, 6H), 2.53 (d, $^4J_{PH}$=2.3 Hz, 3H), 4.10 (m, 4H), 5.59 (d, $^3J_{HHcis}$=11.1 Hz, 1H), 6.04 (t, $^2J_{HHgem}$=0.8 Hz, $^3J_{HHtrans}$=17.6 Hz, 1H), 6.50 (dd, $^3J_{HHcis}$=11.3 Hz, $^3J_{HHtrans}$=17.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 16.3 (d, $^3J_{PC}$=6.6 Hz), 62.6 (d, $^2J_{PC}$=5.5 Hz), 122.6, 122.9, 158.5 (d, $^2J_{PC}$=39.8 Hz), 160.2 (d, $^3J_{PC}$=22.2 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.6 ppm; IR (NaCl) ν_{max} 2979, 1739, 1593, 1023 cm^{-1}; *MS* (EI): *m*/*z* 245 (M^+, 42). Anal. Calcd for $C_{10}H_{16}NO_4P$: C, 48.98; H, 6.58; N, 5.71. Found: C, 49.10; H, 6.56; N, 5.72.

4.5.9. Diethyl (5-ethyl-2-methyl-oxazol-4-yl)-phosphonate (12ba). The general procedure was followed diethyl α-amidophosphonate **8ba**, (1.41 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.76 g (65%) of compound **12ba** as a colorless oil; R_f 0.44 (ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD): δ 1.08 (m, $^3J_{HH}$=7.0 Hz, 9H) Hz, 2.24 (s, 3H), 2.78 (dq, $^4J_{PH}$=1.5 Hz, $^3J_{HH}$=7.5 Hz, 2H), 3.71 (m, $^3J_{HH}$=7.8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 13.3 (d, $^3J_{PC}$=4.1 Hz), 17.0 (d, $^4J_{PC}$=7.0 Hz), 20.0, 61.5, 129.8 (d, $^1J_{PC}$=221.1 Hz), 160.4 (d, $^2J_{PC}$=33.2 Hz), 161.7 (d, $^3J_{PC}$=19.1 Hz) ppm; ^{31}P NMR (120 MHz, CD_3OD): δ 5.0 ppm; IR (NaCl) ν_{max} 2985, 2925, 1666, 1586, 1434, 1049 cm^{-1}; *MS* (EI): *m*/*z* 247 (M^+, 34). Anal. Calcd for $C_{10}H_{18}NO_4P$: C, 48.58; H, 7.34; N, 5.67. Found: C, 48.71; H, 7.32; N, 5.69.

4.5.10. Diethyl (2-methyl-5-phenyl-oxazol-4-yl)-phosphonate (12ca). The compound **12ca** was obtained directly when 2*H*-azirinephosphonate **6c** (1.27 g, 5 mmol) was added to a solution of acetyl chloride **2a** (0.38 mL, 5 mmol) in benzene (10 mL) and the mixture was stirred at room temperature for 24 h. Chromatographic separation (hexane/ethyl acetate) gave 1.36 g (92%) of compound **12ca** as a colorless oil; R_f 0.51 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, $^3J_{HH}$=7.1 Hz, 6H), 2.55 (d, $^5J_{PH}$=0.5 Hz, 3H), 4.18 (m, 4H), 7.43 (m, 3H), 8.0 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 15.9 (d, $^4J_{PC}$=6.6 Hz), 62.4 (d, $^2J_{PC}$=5.5 Hz), 123.9 (d, $^1J_{PC}$=226.8 Hz), 126.0–129.5 (m), 157.1 (d, $^2J_{PC}$=37.8 Hz), 160.4 (d, $^3J_{PC}$=22.7 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.0 ppm; IR (NaCl) ν_{max} 3065, 2979, 1580, 1487, 1023 cm^{-1}; *MS* (EI): *m*/*z* 295 (M^+, 24). Anal. Calcd for $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.14; N, 4.74. Found: C, 57.10; H, 6.16; N, 4.73.

4.6. General procedure for the preparation of *N*-vinylamides 13

A solution of the corresponding *N*-acylaziridine-phosphine oxide **3** (5 mmol) and tributylamine (1.15 mL, 5 mmol) in chlorobenzene (10 mL) was refluxing in an atmosphere of nitrogen until TLC indicated the disappearance of *N*-acylaziridine. The crude was washed with HCl 2 N watery solution. The organic layer was dried with anhidrous magnesium sulfate. Evaporation of solvent under reduced pressure afforded a mixture that was chromatographied on silica gel to give compounds **13**.

4.6.1. *cis*-*N*-[2-Chloro-1-methyl-2-(diphenylphosphinyl)-vinyl)-acetamide (13aa). The general procedure was followed using *N*-acylaziridinephosphine oxide **3aa** (1.67 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.68 g (41%) of compound **13aa** as a white solid; mp 130–131 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (d, $^4J_{PH}$=2.4 Hz, 3H), 2.63 (d, $^6J_{PH}$=0.9 Hz, 3H), 7.49–7.85 (m, 10H), 11.64 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (d, $^3J_{PC}$=6.0 Hz), 25.3, 100.4 (d, $^1J_{PC}$=114.0 Hz), 125.0–132.9 (m), 155.0 (d, $^2J_{PC}$=7.5 Hz), 168.7 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 35.6 ppm; IR (KBr) ν_{max} 3158, 3065, 1706, 1630, 1328, 1175 cm^{-1}; *MS* (EI): *m*/*z* 335 (M^++2, 10), 333 (M^+, 30). Anal. Calcd for $C_{17}H_{17}ClNO_2P$: C, 61.18; H, 5.13; N, 4.20. Found: C, 61.39; H, 5.10; N, 4.25.

4.6.2. *cis*-*N*-[2-Chloro-1-methyl-2-(diphenylphosphinyl)-vinyl]-benzamide (13ab). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ab** (1.98 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.19 g (60%) of compound **13ab** as a white solid; mp 136–137 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (d, $^4J_{PH}$=1.5 Hz, 3H), 7.38–8.04 (m, 15H), 12.53 (s, 1H) ppm; ^{13}C NMR (75 MHz,

$CDCl_3$): δ 19.0 (d, $^3J_{PC}=6.5$ Hz), 101.1 (d, $^1J_{PC}=115.0$ Hz), 127.0–134.1 (m), 155.0 (d, $^2J_{PC}=7.5$ Hz), 165.1 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 35.8 ppm; IR (KBr) ν_{max} 3120, 1689, 1310, 1154 cm^{-1}; *MS* (EI): *m/z* 397 ($M^+ +2$, 7), 395 (M^+, 17). Anal. Calcd for $C_{22}H_{19}ClNO_2P$: C, 66.76; H, 4.84; N, 3.54. Found: C, 66.80; H, 4.85; N, 3.50.

4.6.3. *cis*-*N*-[2-Chloro-1-methyl-2-(diphenylphosphinyl)-vinyl]-acrylamide (13ad). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ad** (1.75 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.26 g (15%) of compound **13ad** as a white solid; mp 97–98 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (d, $^4J_{PH}=1.8$ Hz, 3H), 5.75 (dd, $^3J_{HHcis}=10.2$ Hz, $^2J_{HHgem}=1.2$ Hz, 1H), 6.20 (dd, $^3J_{HHcis}=10.2$ Hz, $^3J_{HHtrans}=17.1$ Hz, 1H), 6.39 (dd, $^3J_{HHtrans}=17.1$ Hz, $^2J_{HHgem}=1.2$ Hz, 1H), 7.49–7.83 (m, 10H), 11.96 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (d, $^3J_{PC}=6.0$ Hz), 101.1 (d, $^1J_{PC}=114.0$ Hz), 127.8, 128.5–132.7 (m), 155.0 (d, $^2J_{PC}=8.0$ Hz), 163.6 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 35.6 ppm; IR (KBr) ν_{max} 3140, 1700, 1515, 1333, 1192 cm^{-1}; *MS* (EI): *m/z* 347 ($M^+ +2$, 17), 345 (M^+, 54). Anal. Calcd for $C_{18}H_{17}ClNO_2P$: C, 62.53; H, 4.96; N, 4.05. Found: C, 62.36; H, 5.00; N, 4.06.

4.6.4. *cis*-*N*-[2-Chloro-2-(diphenylphosphinyl)-1-ethyl-vinyl)-acetamide (13ba). The general procedure was followed using *N*-acylaziridinephosphine oxide **3ba** (1.73 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.94 g (54%) of compound **13ba** as a white solid; mp 73–74 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (m, 3H), 1.97 (s, 3H), 3.02 (q, $^3J_{HH}=7.32$ Hz, 2H), 7.33–7.65 (m, 10H), 11.42 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8, 24.1 (d, $^3J_{PC}=5.5$ Hz), 25.4, 100.2 (d, $^1J_{PC}=113.8$ Hz), 128.2–132.9 (m), 160.4 (d, $^2J_{PC}=6.6$ Hz), 168.1 ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 35.7 ppm; IR (KBr) ν_{max} 3124, 3032, 1706, 1606, 1374, 1248 cm^{-1}; *MS* (CI): *m/z* 348 ($M^+ +1$, 53). Anal. Calcd for $C_{18}H_{19}ClNO_2P$: C, 62.16; H, 5.51; N, 4.03. Found: C, 62.30; H, 5.52; N, 4.04.

4.7. General procedure for the preparation of 5-oxazolyl-phosphine oxides 16

A solution of the corresponding *N*-vinylamide **13** (5 mmol) in THF (20 mL) was added to a 0 °C suspension of NaH (0.24 g, 6 mmol) in THF (15 mL). The mixture was refluxed in nitrogen atmosphere until TLC indicated the disappearance of *N*-vinylamide. Ice was added and the mixture was extracted with dichlorometane. The organic layer was dried with anhidrous magnesium sulfate. Evaporation of solvent under reduced pressure afforded a mixture that was chromatographied on silica gel to give compounds **16**.

4.7.1. 2,4-Dimethyloxazol-5-yl diphenylphosphine oxide (16aa). The general procedure was followed using *N*-vinylamide **13aa** (1.67 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 0.97 g (65%) of compound **16aa** as a white solid; mp 111–112 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (d, $^4J_{PH}=1.8$ Hz, 3H), 2.45 (s, 3H), 7.46–7.77 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 14.0, 128.3–133.8, 137.9 (d, $^1J_{PC}=134.4$ Hz), 149.5 (d, $^2J_{PC}=18.1$ Hz), 164.9 (d, $^3J_{PC}=10.1$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.6 ppm; IR (KBr) ν_{max} 3065, 1593, 1441, 1315, 1202 cm^{-1}; *MS* (EI): *m/z* 297 (M^+, 100). Anal. Calcd for $C_{17}H_{16}NO_2P$: C, 68.68; H, 5.42; N, 4.71. Found: C, 68.88; H, 5.40; N, 4.73.

4.7.2. 4-Methyl-2-phenyl-oxazol-5-yl diphenylphosphine oxide (16ab). The general procedure was followed using *N*-vinylamide **13ab** (1.98 g, 5 mmol). Chromatographic separation (hexane/ethyl acetate) gave 1.29 g (72%) of compound **16ab** as a white solid; mp 158–159 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (d, $^4J_{PH}=1.8$ Hz, 3H), 7.48–8.04 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.9, 126.5–132.5, 138.1 (d, $^1J_{PC}=133.0$ Hz), 150.7 (d, $^2J_{PC}=18.0$ Hz), 164.2 (d, $^3J_{PC}=10.1$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.6 ppm; IR (KBr) ν_{max} 3070, 3020, 1699, 1205 cm^{-1}; *MS* (EI): *m/z* 359 (M^+, 60). Anal. Calcd for $C_{22}H_{18}NO_2P$: C, 73.53; H, 5.05; N, 3.90. Found: C, 73.36; H, 5.03; N, 3.91.

4.7.3. 4-Ethyl-2-methyl-oxazol-5-yl diphenylphosphine oxide (16ba). The general procedure was followed using *N*-vinylamide **13ba**. Chromatographic separation (hexane/ethyl acetate) gave 0.89 g (57%) of compound **16ba** as a white solid; mp 75–76 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, $^3J_{HH}=7.5$ Hz, 3H), 2.39 (d, $^5J_{PH}=0.8$ Hz, 3H), 2.55 (q, $^3J_{HH}=7.6$ Hz, 2H), 7.40–7.70 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 14.1, 19.9, 128.5–132.4, 137.2 (d, $^1J_{PC}=134.5$ Hz), 155.0 (d, $^2J_{PC}=18.1$ Hz), 165.1 (d, $^3J_{PC}=10.6$ Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 16.3 ppm; IR (KBr) ν_{max} 3058, 1719, 1585, 1427, 1202 cm^{-1}; *MS* (EI): *m/z* 311 (M^+, 100). Anal. Calcd for $C_{18}H_{18}NO_2P$: C, 69.45; H, 5.83; N, 4.50. Found: C, 69.57; H, 5.84; N, 4.51.

Acknowledgements

The authors thank the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, PPQ2003-00910) and the Universidad del País Vasco (UPV, GC/ 2002) for supporting this work. J. M. Alonso thanks the Ministerio de Educación y Cultura (Madrid) for a predoctoral fellowship and J. I. Gil thanks the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid) for postdoctoral support.

References and notes

1. For recent reviews on azirines see: (a) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219–269. (b) Gilchrist, T. L. *Aldrichim. Acta* **2001**, *34*, 51–55. (c) Zwanenburg, B.; ten Holte, P. *Top. Cur. Chem.* **2001**, *216*, 93–124. (d) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401–2414.
2. (a) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238–264. (b) Bucher, C. B.; Heimgartner, H. *Helv. Chim. Acta* **1996**, *79*, 1903–1915. (c) Lehmann, J.; Linden, A.;

Heimgartner, H. *Tetrahedron* **1999**, *55*, 5359–5376. (d) Hong, B. C.; Gupta, A. K.; Wu, M. F.; Liao, J. H. *Tetrahedron Lett.* **2004**, *45*, 1663–1666. (e) Timen, S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958–9963. (f) Pinho e Melo, T. M. V. D.; Cardoso, A. L.; d'A Rocha Gonzalves, A. *Tetrahedron* **2003**, *59*, 2345–2351. (g) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; d'A Rocha Gonzalves, A.; Beja, J. A.; Paixao, A. M.; Silva, M. R.; Alte da Veiga, L. *J. Org. Chem.* **2002**, *67*, 66–71. (h) Banert, K.; Höhler, F. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 174–177.

3. (a) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
4. (a) Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 1399–1402. (b) Filigheddu, S. N.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3857–3860. (c) Zwanenburg, B.; Thijs, L. *Pure Appl. Chem.* **1996**, *68*, 735–738. (d) Davis, F. A.; Liu, H.; Reddy, C. V. *Tetrahedron Lett.* **1996**, *37*, 5473–5476. (e) Ploux, O.; Caruso, M.; Chassaing, G.; Marquet, A. *J. Org. Chem.* **1988**, *53*, 3154–3158. (f) Righi, G.; D'Achielle, R. *Tetrahedron Lett.* **1996**, *37*, 6893–6896. (g) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431–8434. (h) Tanner, D.; Bergsson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903–1906.
5. For reviews see: (a) Engel, R. *Handbook of organophosphorus Chemistry*, M. Dekker, Inc: New York, 1992. (b) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur* **1991**, *63*, 193–215. (c) Hoagland, R. E.; *Biologically Active natural Products* Culter, H. G., Ed., ACS Symposium Series 380 American Chemical Society: Washington DC; 1988, 182. (d) Toy, A. D. F.; Walsh, E. N. *Phosphorus Chemistry in Everyday Living*, American Chemical Society: Washington DC, 1987 p 333.
6. Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213–3217.
7. Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363–5366.
8. (a) Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J. *Eur. J. Org. Chem.* **2003**, 913–919. (b) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961–1972. (c) Palacios, F.; Ochoa de Retana, A. M.; Pagalday, J. *Tetrahedron* **1999**, *55*, 14451–14458. (d) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1999**, *55*, 13767–13778.
9. (a) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; Rodríguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617–2623. (b) Palacios, F.; Aparicio, D.; Vicario, J. *Eur. J. Org. Chem.* **2002**, 4131–4136. (c) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 5947–5964. (d) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; García, J.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 3105–3116.
10. (a) Palacios, F.; Oyarzabal, J.; Pascual, S.; Ochoa de Retana, A. M. *Org. Lett.* **2002**, *4*, 769–772. (b) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941–1946. (c) Palacios, F.; Aparicio, D.; García, J.; Rodríguez, E.; Fernández, A. *Tetrahedron* **2001**, *57*, 3131–3141. (d) Palacios, F.; Herrán, E.; Rubiales, G. *J. Org. Chem.* **1999**, *64*, 6239–6246.
11. (a) Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; López de Munain, R. *Tetrahedron Lett.* **2002**, *43*, 5917–5920. (b) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 3091–3104. (c) Barluenga, J.; López, F.; Palacios, F. *Tetrahedron Lett.* **1987**, *28*, 2875–2876.
12. Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; López de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689–700.
13. Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; López de Munain, R. *Org. Lett.* **2002**, *4*, 2405–2408.
14. (a) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002**, *67*, 7283–7288. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 2525–2541.
15. (a) Fowler, F. W.; Hassner, A. *J. Am. Chem. Soc.* **1968**, *90*, 2875–2881. (b) Hassner, A.; Burke, S. S.; Jesse, C. *J. Am. Chem. Soc.* **1975**, *97*, 4670–4692.
16. (a) Schmid, H.; Gilgen, P.; Heimgartner, H. *Helv. Chim. Acta* **1974**, *57*, 1393–1403. (b) Sato, S.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn* **1967**, *40*, 2938–2942.
17. (a) Widmer, U.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 815–821. (b) Schaumamn, E.; Kausch, E.; Walter, W. *Chem. Ber.* **1975**, *108*, 2500–2509.
18. For recent contributions see: (a) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935–938. (b) Berger, R.; Shoop, W. L.; Pivnichny, J. V.; Warmke, L. M.; Zakson-Aiken, M.; Owens, K. A.; de Montigny, P.; Schamatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Coletti, S. L. *Org. Lett.* **2001**, *3*, 3715–3718. (c) Wipf, P.; Methot, J. L. *Org. Lett.* **2001**, *3*, 1261–1264. (d) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459–3466. (e) Yokokawa, F.; Asano, T.; Shiori, T. *Tetrahedron* **2001**, *57*, 6311–6327. (f) Radspieler, A.; Liebscher, J. *Tetrahedron* **2001**, *57*, 4867–4871. (g) Yokokawa, F.; Asano, T.; Shiori, T. *Org. Lett.* **2000**, *2*, 4169–4172. (h) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897–6900.
19. For recent reviews on oxazoles see: (a) Lewis, J. R. *Nat. Prod. Rep.***2001**, *18*, 95–128. (b) Boyd, G. V. *Prog. Heterocycl. Chem.* **1999**, *11*, 213–229. (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *115*, 417–437. (d) *Comprehensive Heterocyclic Chemistry II*; Hartner, F. W.; Katritzky, A. R.; Rees, C. W., Eds.; Elsevier: Oxford; 1996, Vol. 3, p. 261–318.
20. For recent reviews see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743. (b) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39–50. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.
21. For reviews see: (a) *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*. Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, 2000. (b) Fields, S. F. *Tetrahedron* **1999**, *55*, 12237–12273. (c) Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211–218.
22. (a) Smith, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888. (b) Smithrud, D. B.; Benkovic, P. A.; Benkovic, S. J.; Taylor, C. M.; Yager, K. M.; Witherington, J.; Phillips, B. W.; Sprengler, P. A.; Smith, A. B.; Hirschmann, R. *J. Am. Chem. Soc.* **1997**, *119*, 278–282. (c) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Spengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237. (d) Meyer, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4600–4609. (e) Chackalamannil, S.; Chung, S.; Atamford, A. W.; McKittrick, B. A.; Wang, Y.; Tsai, H.; Cleven, R.; Fawzi, A.; Czarniecki, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1257–1260. (f) Steere, J. A.; Sampson, P. B.; Honek, J. F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 457–460. (g) Cristau, H. J.; Cooulombeau, A.; Genevis-Borella, A.; Pirat, J. L. *Tetrahedron Lett.* **2001**, *42*,

4491–4494. (h) Georgiadis, D.; Dive, V.; Yiotakis, A. *J. Org. Chem.* **2001**, *66*, 6604–6610. (i) Wallace, E. M.; Moliterni, J. A.; Moskal, M. A.; Neubart, A. D.; Marcopulos, N.; Stamford, L. B.; Trapani, A. J.; Savage, P.; Chou, M.; Jeng, A. Y. *J. Med. Chem.* **1998**, *41*, 1513–1523. (j) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502–509. (k) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8949–8956

Enantioselective synthesis of functionalized γ-butyrolactones

Ali Samarat,[a] Hassen Amri[a,*] and Yannick Landais[b,*]

[a]*Laboratoire de Chimie Organique and Organométallique, Faculté des Sciences, Campus Universitaire, 1060-Tunis, Tunisia*
[b]*Laboratoire de Chimie Organique and Organométallique, Université Bordeaux-I, 351 cours de la Libération, 33405 Talence, Cedex, France*

Received 1 April 2004; revised 1 July 2004; accepted 6 July 2004

Available online 14 August 2004

Abstract—Sharpless asymmetric dihydroxylation and aminohydroxylation of (*E*)-dimethyl-2-alkylidene glutarates **2** were shown to afford enantio-enriched or enantiopure highly functionalized γ-butyrolactones **3** and **7**.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Functionalized γ-lactones have attracted considerable attention in recent years due to their importance as building blocks in the synthesis of a number of natural products and biologically relevant compounds,[1], for example, precursors of inhibitors of HIV-1 protease.[2,3] We wish to propose here a rapid access to these attractive intermediates using a straightforward approach based on the utilization of Sharpless asymmetric dihydroxylation (AD) and amino-hydroxylation (AA) of diesters **2**(**a**-**e**).[4,5]

2. Stereoselective synthesis of dimethyl (*E*)-2-alkylidene glutarates 2

We have previously described a highly stereoselective synthesis of dialkyl 2-alkylidene glutarates by nucleophilic substitution of the vinylic bromine atom in **1** by magnesium dialkyl cuprates generated in situ at low temperature.[6] The dimethyl (*E*)-2-bromomethylene glutarate **1** was prepared through a simple tandem-process: bromination–dehydro-bromination of dimethyl-2-methylene glutarate **2a** according to the Ref. 7.

We report herein, our results on the conjugated addition of dialkyl organocuprates to the dimethyl (*E*)-2-bromomethyl-ene glutarate **1**, leading to the corresponding dimethyl-2-alkylidene glutarates **2** in excellent yields with total *E*-stereoselectivity (Scheme 1, Table 1).

Keywords: (*E*)-2-Alkylidene glutarates; Asymmetric dihydroxylation; Asymmetric amino-hydroxylation; γ-Butyrolactones.
* Corresponding authors. Tel.: +216-71-872-600; fax: +216-71-885-008 (H.A.); fax: +33-5-40006286 (Y.L.); e-mail: hassen.amri@fst.rnu.tn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.012

3. Results and discussion

The catalytic asymmetric dihydroxylation of these olefins was then examined. The intermediate diols were not detected but spontaneously lactonized to give the corresponding functionalized γ-butyrolactones **3**(**a**-**e**), possessing a quaternary centre in modest to good yields. It is interesting to notice that spontaneous cyclization of the resulting diols under the AD reaction conditions was completely regioselective in the examined cases, only γ-butyrolactones being obtained. Prediction of the absolute configuration of the major enantiomer for chiral γ-lactones **3**(**a**-**e**) was based on Sharpless'mnemonic device[5a,b] (Scheme 2).

As shown in Table 2, several commercially available Sharpless ligands were tested as chiral ligands and the best results were obtained using $(DHQ)_2AQN$. In each case, the reaction was also carried out in racemic series using quinuclidine as ligand.

The absence of a suitable chromophore on the lactone **3**(**a**-**c**) and **3e** prevented us to determine the enantiomeric excesses of these compounds through HPLC on chiral column. We thus protected first the hydroxyl function of alcohols **3**(**a**-**c**) as their benzoate **4**(**a**-**c**). However, all attempts to convert sterically hindered **3e** into the corresponding benzoate failed. The silylated ether **4e** was prepared instead but finally proved to be unsuitable for the determination of the enantiomeric excess through HPLC (Scheme 3).

The ee values of **4**(**a**-**c**) were eventually determined through HPLC using Chiracel OD® column. Enantiomeric excesses are moderate to excellent depending on the nature of the R group on the olefin. Sharpless ligands used in this study are usually known to provide moderate enantioselectivities with

Table 1. Synthesis of dimethyl 2-alkylidene glutarates **2**(**a**-**e**)

Entry	RMgX (equiv.)	Yield (%)[a]
2a	—	65[b]
2b	CH_3MgI (2.3)	84
2c	*i*-PrMgBr (2.3)	70
2d	$PhCH_2MgBr$ (2.2)	88
2e	*t*-BuMgCl (2.1)	96

[a] Yields referred to isolated pure products characterized by IR, ^1H, ^{13}C NMR and mass spectrometry.
[b] Dimethyl-2-methylene glutarate **2a** was prepared by dimerisation of methyl acrylate in the presence of HMPT according to Ref. 8.

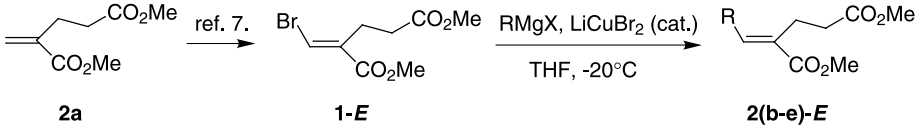
Z-olefins.[5b,9] In the other hand, catalytic dihydroxylation of diethyl α-methylene adipate **5**[10] using achiral quinuclidine as ligand, led to the resulting diol **6** which did not lactonize in the reaction medium (Scheme 4).

Such encouraging results, obtained during the dihydroxylation of (*E*)-dimethyl-2-alkylidene glutarates **2**, prompted us to investigate the analogous aminohydroxylation, which would give rise to useful amino alcohol intermediates for organic synthesis. The regioselectivity of the Sharpless Asymmetric Aminohydroxylation reaction (AA) is controlled by several factors, including alkene substitution, alkene polarisation and ligand-substrate interactions.[11] It is well established that the nitrogen group is generally introduced at the β-position in α,β-unsaturated esters.[12]

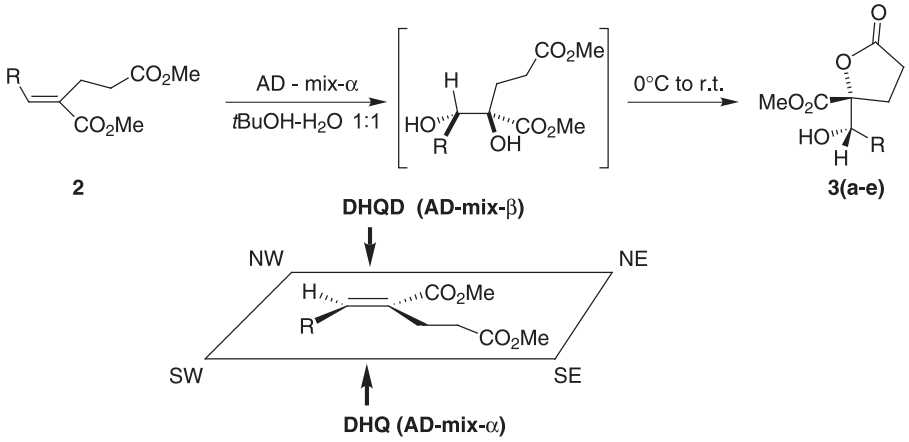
As summarized in Scheme 5, we observed that when dimethyl-2-methylene glutarate **2a** was subjected to the AA process, using commercially available chloramine-T as a nitrogen source, the resulting α-hydroxy isomer was obtained as the major compound and lactonized spontaneously to give the corresponding functionalized γ-butyrolactone **7a** in good isolated yield, but with poor to moderate enantioselectivity (19–63% ee). As above, the absolute configuration of $\mathbf{7a}_1$ and $\mathbf{7a}_2$ was predicted based on Sharpless mnemonic device, assuming a similar mode of action of DHQ and DHQD ligands in asymmetric dihydroxylation (AD) and amino-hydroxylation processes (AA) (Scheme 5).

The amino-hydroxylation of olefins **2**(**b**-**e**) in racemic series using quinuclidine as ligand was then examined, but a low regioselectivity was obtained in all cases. Moreover, the degree of conversion of the starting olefin is generally moderate and an important amount of diol was formed through competing dihydroxylation. In order to improve the selectivity of the process, we varied reaction conditions (source of nitrogen, solvent) but unfortunately, all our attempts met with failure. For instance, amino-hydroxylation reaction of **2b** using quinuclidine as ligand gave the γ-butyrolactone **7b** in 30% isolated yield along with the β-hydroxy regioisomer **8** in 6%, the dihydroxylation product **3b** (26%) and recovered starting materials (25%) (Scheme 6).

In order to increase the selectivity we then tried as a nitrogen source, chloramine-M which is less sterically hindered than chloramine-T. Interestingly, it was found that catalytic amino-hydroxylation reaction of **2d** led mainly to the α-hydroxy regioisomer **9** (54% isolated yield) along with the corresponding lactonized product **7d** (22%), the lactone **3d** (18%) formed through competitive dihydroxylation as well as some recovered starting material (5%) (Scheme 7). Although these preliminary investigations on amino-hydroxylation reaction led to modest results, isolation of regioisomer **9** is noteworthy as it provides an entry towards substituted piperidines through cyclisation involving the amino group and one of the ester functions.

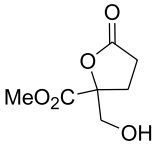
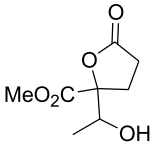
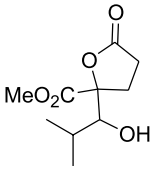
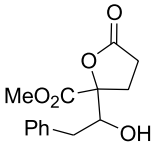
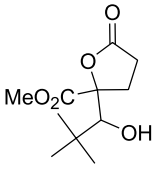


Scheme 1.

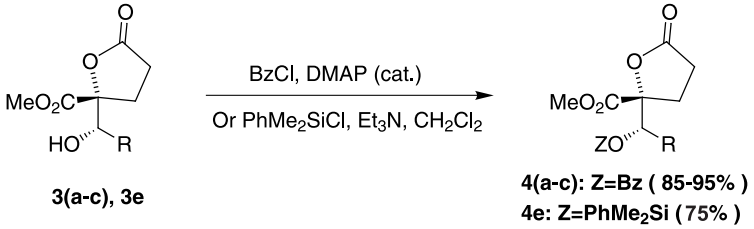


Scheme 2.

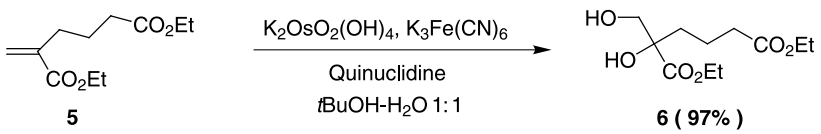
Table 2. Isolated γ-butyrolactones from asymmetric dihydroxylation of olefins **2**(**a**-**e**)

Entry	Product	Ligand	Conditions	ee[a]	Yield (%)[b]
3a		Quinuclidine	0 °C to rt, 6 h	—	61
		$(DHQ)_2PHAL$	0 °C to rt, 6 h	17	62
		$(DHQ)_2AQN$	0 °C to rt, 8 h	51	66
3b		Quinuclidine	0 °C to rt, 12 h	—	69
		$(DHQ)_2PHAL$	0 °C to rt, 10 h	68	66
		$(DHQ)_2AQN$	0 °C to rt, 12 h	77	63
3c		Quinuclidine	0 °C to rt, 18 h	—	61
		$(DHQ)_2PHAL$	0 °C to rt, 18 h	87	58
		$(DHQ)_2AQN$	0 °C to rt, 20 h	90	56
3d		Quinuclidine	0 °C to rt, 6 h	—	76
		$(DHQ)_2PYR$	0 °C to rt, 16 h	9	62
		$(DHQ)_2PHAL$	0 °C to rt, 12 h	72	66
		$(DHQ)_2AQN$	0 °C to rt, 16 h	98	68
3e		Quinuclidine	0 °C to rt, 14 h	—	68
		$(DHQ)_2PHAL$	0 °C to rt, 16 h	—	67
		$(DHQ)_2AQN$	0 °C to rt, 18 h	—	61

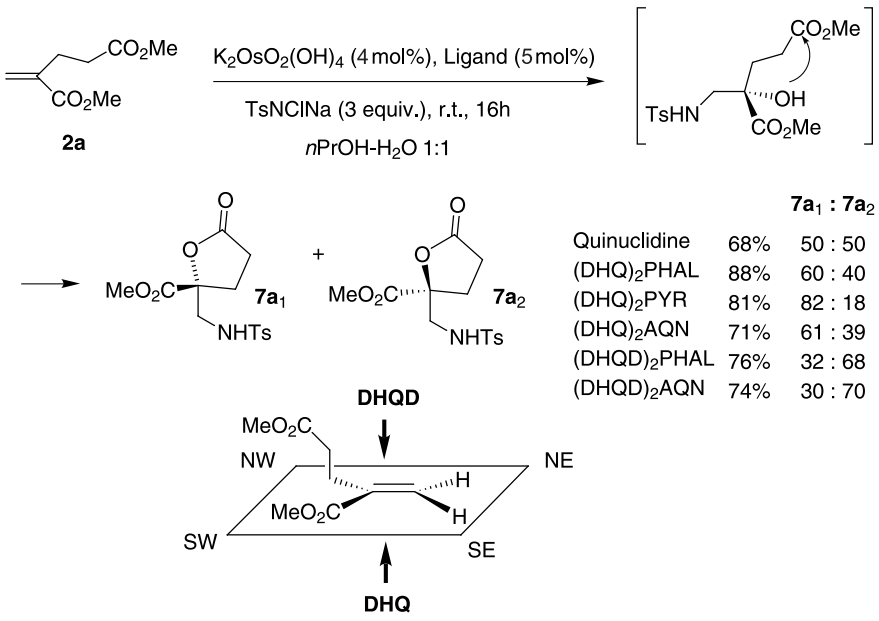
[a] Determined by HPLC analysis on a Chiracel OD® column (hexane/*i*PrOH, see Section 5 for details).
[b] Isolated yield after purification by column chromatography.



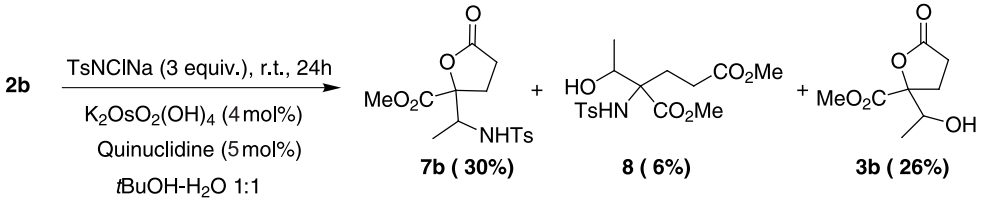
Scheme 3.



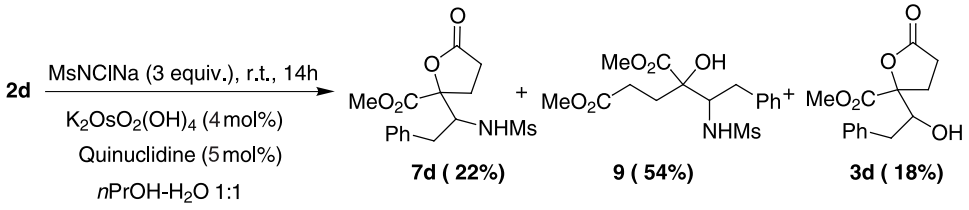
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

4. Conclusion

In conclusion, we have demonstrated that (*E*)-dimethyl 2-alkylidene glutarates **2** represent useful building blocks for the enantioselective synthesis of highly functionalized γ-butyrolactones through application of the Sharpless AD and AA processes. Two chiral centres, one of which is quaternary, have been generated with good enantioselectivities. While good to excellent enantiomeric excesses are observed upon dihydroxylation process, aminohydroxylation led to a modest level of enantioselectivity along with various amount of diol issued from a competitive dihydroxylation. However, by changing the nature of the nitrogen source it was possible to obtain useful building block such as **9** which should be elaborated further en route to biologically relevant piperidine targets. Work along these lines in currently under investigation in our laboratories.

5. Experimental

5.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 250 and on Bruker AC-300 FT (^{1}H: 300 MHz, ^{13}C: 75 MHz) with $CDCl_3$ as internal reference. The chemical shifts (δ) and coupling constants (J) are respectively expressed in ppm and Hz. IR spectra were recorded with a Perkin–Elmer paragon 1000 Ft-IR spectrophometer. High- and low-resolution mass spectra were recorded with a Micromass autospec-Q mass spectrophometer (EI, 70 eV, LSIMS with a 3-nitrobenzyl alcohol matrix). Elemental analyses, expressed in percentage, were performed by the CNRS laboratory at Vernaison (France). Melting points were not corrected and determined by using a Büchi Totolli apparatus. Merck silica gel 60 (70–230 mesh) and (0.063–0.200 mm) were used for flash chromatography.

Enantiomeric excess were established by HPLC on a Waters 600 apparatus equipped with a 996 photodiode array detector and Chiracel OD® chiral column using hexane and isopropanol as eluent.

5.2. Synthesis of (*E*)-dimethyl 2-alkylidene glutarates 2(a-d)

All reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. Solvents were distilled under nitrogen immediately prior to use. Grignard reagents were prepared by the known methods and stored under inert atmosphere. They were titrated prior to use,[13] that is, with 1 M solution of benzyl alcohol in anhydrous toluene and in presence of 2,2′-bipyridil as indicator.

General procedure. An ether or THF solution of alkylmagnesium halide RMgX was added dropwise over a period of 20–30 min to a mixture of dimethyl (*E*)-2-bromomethylene glutarate **1** (1.25 g, 5 mmol) and 1 M solution of $LiCuBr_2$ (0.15 mL, 3 mol%) diluted in dry THF (20 mL) at −20 °C under nitrogen atmosphere and magnetic stirring. After a few minutes (TLC), the reaction mixture was quenched with a saturated NH_4Cl solution (10 mL) then extracted with ether (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt/hexane, 1:9) to afford (*E*)-dimethyl-2-alkylidene glutarates **2**(**b**-**e**).

5.2.1. Spectral data of products 2(b-e). *(E)-2-Ethylidene pentanedioic acid dimethyl ester* **2b**. IR (film): ν= 1704 cm^{-1}, 1697, 1642. ^1H NMR (300 MHz, $CDCl_3$): δ=6.91 (q, J=7.0 Hz, 1H, CH), 3.70 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 2.58 (m, 2H, CH_2), 2,41 (m, 2H, CH_2), 1.81 (d, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 173.4 (C=O), 167.7 (C=O), 139.2 (CH), 131.2 (C), 51.7 (OCH_3), 51.5 (OCH_3), 33.1 (CH_2), 21.9 (CH_2), 14.2 (CH_3). MS (EI, 70 eV); *m*/*z* (%): 186 (M^+, 2), 171 (48), 154 (100), 127 (72), 113 (64), 99 (30).

(E)-2-(2-Methylpropylidene) pentanedioic acid dimethyl ester **2c**. IR (film): ν=1738 cm^{-1}, 1713, 1644. ^1H NMR (300 MHz, $CDCl_3$): δ=6.64 (d, J=10.0 Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 2.73 (m, 1H, CH), 2.65 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 1.03 (d, J=7.7 Hz, 6H, $(CH_3)_2$) ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.1 (C=O), 167.9 (C=O), 150.7 (CH), 127.8 (C), 51.5 (OCH_3), 51.4 (OCH_3), 33.6 (CH_2), 27.7 (CH), 22.4 (CH_2), 22.2 (CH_3), 22.1 (CH_3). MS (EI, 70 eV); *m*/*z* (%): 214 (M^+, 1), 182 (100), 154 (48), 122 (38), 108 (31), 95 (71), 81 (56), 41 (29).

(E)-2-Phenylethylidene pentanedioic acid dimethyl ester **2d**. IR (film): ν=1731 cm^{-1}, 1710, 1644. ^1H NMR (300 MHz, $CDCl_3$): δ=7.31–7.19 (m, 5H, aromatic H), 6.98 (t, J=7.9 Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.58 (d, J=7.9 Hz, 2H, CH_2), 2.72 (m, 2H, CH_2), 2.53 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 173.3 (C=O), 167.6 (C=O), 142.2 (aromatic C), 139.8 (CH), 135.4 (aromatic CH), 134.5 (aromatic CH), 133.6 (aromatic CH), 128.6 (C), 51.8 (OCH_3), 51.7 (OCH_3), 34.6 (CH_2), 33.2 (CH_2), 22.2 (CH_2). MS (EI, 70 eV); *m*/*z* (%): 262 (M^+, 1), 230 (46), 189 (55), 170 (100), 91 (32).

(E)-2-(2,2-Dimethylpropylidene) pentanedioic acid dimethyl ester **2e**. IR (film): ν=1726 cm^{-1}, 1713, 1650. ^1H NMR (300 MHz, $CDCl_3$): δ=6.85 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.78 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 1.19 (s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.2 (C=O), 168.6 (C=O), 152.8 (CH), 129.2 (C), 51.7 (OCH_3), 51.4 (OCH_3), 33.7 (CH_2), 30.3 (C), 29.1 ($(CH_3)_3$), 22.6 (CH_2). MS (EI, 70 eV); *m*/*z* (%): 228 (M^+, 1), 213 (83), 196 (100), 169 (62), 155 (48), 141 (55).

5.3. General procedure for the Sharpless asymmetric dihydroxylation of olefins 2(a-e)

In a 50 mL flask, were placed AD-mix-α [$K_3Fe(CN)_6$ (990 mg, 3 mmol), K_2CO_3 (415 mg, 3 mmol), $K_2OsO_2(OH)_4$ (3.7 mg, 0.01 mmol), ligand (0.01 mmol)], H_2O (5 mL) and *t*-BuOH (5 mL). The solution was stirred for 5 min at room temperature and methanesulfonamide (95 mg, 1 mmol) was added. No $CH_3SO_2NH_2$ should be added for terminal olefin (Table 2, entry 1). The orange solution was cooled down to 0 °C and olefin **2** (1 mmol) was introduced. The mixture was vigorously stirred at 0 °C then allowed to warm to room temperature for 6–20 h. The solution was then cooled to 0 °C, and solid sodium sulfite (1.5 g, 12 mmol) was added and the mixture was allowed to stir at room temperature for 45 min. Ethyl acetate (10 mL) was added and the aqueous layer was further extracted with ethyl acetate (4×5 mL). If $CH_3SO_2NH_2$ was used, the combined organic layers were washed with (10%) aqueous NaOH (10 mL), dried over $MgSO_4$ then concentrated. The crude product was purified by column chromatography on silica gel to afford the γ-butyrolactones **3** in yields ranging between 56 and 76%.

5.3.1. Spectral data of γ-butyrolactones 3(a-e). *2-Hydroxymethyl-5-oxotetrahydrofuran-2-carboxylic acid methyl ester* **3a**. Colorless oil, R_f=0.31 (CH_2Cl_2/AcOEt 3:2); IR (film): ν=3416 cm^{-1}, 1787, 1744. ^1H NMR (250 MHz, $CDCl_3$): δ=4.03–3.86 (AB, J_{AB}=13.7 Hz, 2H, CH_2OH), 3.79 (s, 3H, OCH_3), 3.11 (br. s, 1H, OH), 2.62 (m, 2H, CH_2), 2.35 (m, 2H, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=176.2 (C=O), 170.8 (C=O), 86.6 (C), 64.9 (CH_2OH), 53.0 (OCH_3), 27.9 (CH_2), 27.1 (CH_2). MS (EI, 70 eV); *m*/*z* (%): 174 (M^+, 2), 143 (9), 115 (100), 59 (32), 31 (84). $C_7H_{10}O_5$ (174.15): Calcd C 48.28, H 5.79; found: C 48.19, H 5.82.

2-(1-Hydroxyethyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **3b**. Yellow oil, R_f=0.23 (CH_2Cl_2/AcOEt 7:3); IR (film): ν=3477 cm^{-1}, 1782, 1741. ^1H NMR (250 MHz, $CDCl_3$): δ=4.13 (q, J=6.4 Hz, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 2.94 (br. s, 1H, OH), 2.62–2.58 (m, 2H, CH_2), 2.54–2.44 (m, 2H, CH_2), 1.21 (d, J=6.4 Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.9 (C=O), 170.9 (C=O), 88.9 (C), 69.5 (CH), 52.9 (OCH_3), 27.9 (CH_2), 25.6 (CH_2), 16.8 (CH_3). MS (EI, 70 eV); *m*/*z* (%): 188 (M^+, 1), 143 (26), 129 (28), 88 (95), 45 (62), 43 (100). $C_8H_{12}O_5$ (188.18): Calcd C 51.06, H 6.43; found: C 51.37, H 6.47.

2-(1-Hydroxy-2-methylpropyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **3c**. Colorless crystal, mp 74–75 °C,

R_f=0.44 (AcOEt/pentane 2:3); IR (film): ν=3500 cm^{-1}, 1783, 1741. ^1H NMR (300 MHz, $CDCl_3$): δ=3.80 (s, 3H, OCH_3); 3.67 (dd, J=7.9, 9.0 Hz, 1H, C*H*OH); 2.64 (d, J=9.0 Hz, 1H, OH); 2.56–2.53 (m, 4H, $2CH_2$); 1.81 (m, 1H, CH); 0.97 (d, J=7.1 Hz, 3H, CH_3), 0.93 (d, J=6.7 Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.6 (C=O), 171.5 (C=O), 88.3 (C), 78.3 (CH), 53.0 (OCH_3), 30.1 (CH), 27.8 (CH_2), 27.6 (CH_2), 20.4 (CH_3), 17.3 (CH_3). MS (LSIMS); *m/z* (%): 239 $[M+Na]^+$ (100), 217 $[M+H]^+$(55), 199 (64), 154 (24), 147 (33), 137 (42). HRMS [M+Na] $C_{10}H_{16}O_5Na$: Calcd 239.0895; found: 239.1223.

2-(1-Hydroxy-2-phenylethyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **3d**. White solid, mp 121–122 °C, R_f=0.30 (hexane/AcOEt 7:3); IR (film): ν=3582 cm^{-1}, 1788, 1740. ^1H NMR (250 MHz, $CDCl_3$): δ=7.29 (m, 5H, aromatic H), 4.16 (ddd, J=7.0, 9.7, 14.0 Hz, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 2.95 (dd, J=14.0, 2.7 Hz, 1H, OH), 2.67–2.61 (2m, 4H, CH_2+CH_2Ph), 2.62–2.49 (m, 2H, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.6 (C=O), 171.0 (C=O), 137.2 (aromatic C), 129.4 (aromatic CH), 128.6 (aromatic CH), 126.8 (aromatic CH), 87.8 (C), 74.9 (CH), 53.2 (OCH_3), 37.7 (CH_2), 28.0 (CH_2), 26.6 (CH_2). MS (EI, 70 eV); *m/z* (%): 264 (M^+, 1), 246 (12), 205 (6), 187 (76), 173 (18), 91 (100). $C_{14}H_{16}O_5$ (264.27): Calcd C 63.63, H 6.10; found: C 63.66, H 6.22. HPLC 0.7 mL min^{-1}, Hex/*i*-PrOH (90:10), 259.2 nm, R_T (min)=20.6, 31.2.

2-(1-Hydroxy-2,2-dimethylpropyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **3e**. White solid, mp 82–83 °C, R_f=0.42 (petroleum ether/AcOEt 3: 2); IR (film): ν=3582 cm^{-1}, 1784, 1737. ^1H NMR (250 MHz, $CDCl_3$): δ=3.80 (s, 3H, OCH_3), 3.63 (d, J=8.5 Hz, 1H, C*H*OH), 2.89 (d, J=8.5 Hz, 1H, OH), 2.61–2.52 (m, 4H, $2CH_2$), 0.96 (s, 9H, $(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.5 (C=O), 172.0 (C=O), 87.6 (C), 81.3 (CH), 52.9 (OCH_3), 35.4 (C), 29.6 ($(CH_3)_3$), 27.6 (CH_2), 26.9 (CH_2). MS (EI, 70 eV); *m/z* (%): 230 (M^+, 1), 173 (11), 156 (19), 144 (80), 88 (100), 57 (73). $C_{11}H_{18}O_5$ (230.26): Calcd C 57.38, H 7.88; found: C 57.19, H 7.76.

5.4. Synthesis of the protected alcohols 4(a-c)

General procedure. To a stirred solution of alcohol **3** (1 mmol) and a catalytic amount of DMAP (9.8 mg, 8 mol%) in pyridine (3 mL) was added freshly distilled benzoyl chloride (0.23 mL, 2 equiv.) at 0 °C under argon. The reaction was allowed to stir at room temperature for 6 h then brine (15 mL) and ether (15 mL) were added. The organic layer was decanted, washed with 1 M aqueous HCl, brine, saturated aqueous $NaHCO_3$ then with brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a residue, which was purified over silica gel to give **4**(**a**-**c**).

5.4.1. Spectral data of γ-butyrolactones 4(a-c). *2-Benzoyloxymethyl-5-oxotetrahydrofuran-2-carboxylic acid methyl ester* **4a**. Colorless oil (264 mg, 95%), R_f=0.16 (pent/AcOEt 4:1); IR (film): ν=1772 cm^{-1}, 1738, 1732. ^1H NMR (250 MHz, $CDCl_3$): δ=7.97 (m, 2H, aromatic H), 7.47 (m, 3H, aromatic H), 4.70 (AB, J_{AB}=14.7 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 2.66 (m, 2H, CH_2), 2.46 (m, 2H, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=175.1 (C=O), 169.8 (C=O), 165.7 (C=O), 133.6 (aromatic CH), 129.7 (aromatic CH), 129.1 (aromatic C), 128.6 (aromatic CH), 84.1 (C), 66.0 (CH_2O), 53.4 (OCH_3), 28.1 (CH_2), 27.7 (CH_2). HPLC 1 mL min^{-1}, Hex/*i*-PrOH (90:10), 227.4 nm, R_T (min)=30.9, 34.4.

2-(1-Benzoyloxyethyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **4b**. Yellow oil (272 mg, 93%), R_f=0.24 (pent/AcOEt 7:3); IR (film): ν=1776 cm^{-1}, 1733, 1731. ^1H NMR (300 MHz, $CDCl_3$): δ=7.99 (m, 2H, aromatic H), 7.49 (m, 3H, aromatic H), 5.60 (q, J=6.4 Hz, 1H, CH), 3.74 (s, 3H, OCH_3), 2.64 (m, 2H, CH_2), 2.39 (m, 2H, CH_2), 1.41 (d, J=6.4 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.0 (C=O), 170.0 (C=O), 165.1 (C=O), 133.3 (aromatic CH), 129.6 (aromatic CH), 129.3 (aromatic C), 128.4 (aromatic CH), 87.3 (C), 71.8 (CH), 53.1 (OCH_3), 27.4 (CH_2), 27.2 (CH_2), 13.8 (CH_3). HPLC 1 mL min^{-1}, Hex/*i*-PrOH (90:10), 227.4 nm, R_T (min)=26.2, 55.1.

2-(1-Benzoyloxy-2-methylpropyl)-5-oxotetrahydrofuran-2-carboxylic acid methyl ester **4c**. White solid (272 mg, 85%), mp 79–80 °C, R_f=0.13 (petroleum ether/AcOEt 7:3); IR (film): ν=1778 cm^{-1}, 1742, 1737. ^1H NMR (300 MHz, $CDCl_3$): δ=8.04 (m, 2H, aromatic H), 7.52 (m, 3H, aromatic H), 5.47 (d, J=4.8 Hz, 1H, CH), 3.77 (s, 3H, OCH_3), 2.59 (m, 2H, CH_2), 2.47 (m, 2H, CH_2), 2.14 (m, 1H, CH), 1.05 (d, J=6.8 Hz, 3H, CH_3), 0.99 (d, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.8 (C=O), 170.0 (C=O), 165.5 (C=O), 133.4 (aromatic CH), 129.7 (aromatic CH), 129.1 (aromatic C), 128.5 (aromatic CH), 87.6 (C), 78.0 (OCH), 53.0 (OCH_3), 29.2 (CH), 28.1 (CH_2), 27.3 (CH_2), 20.8 (CH_3), 17.9 (CH_3). HPLC 1 mL min^{-1}, Hex/*i*-PrOH (90:10), 227.4 nm, R_T (min)=20.1, 43.8.

5.5. Synthesis of the protected alcohol 4e

To a stirred solution of alcohol **3e** (230 mg, 1 mmol), triethylamine (0.27 mL, 2 equiv.) and a catalytic amount of DMAP (4.9 mg, 4 mol%) in dry CH_2Cl_2 (5 mL) was added freshly distilled $PhMe_2SiCl$ (0.34 mL, 2 equiv.) at 0 °C under argon. The reaction mixture was allowed to stir overnight at room temperature then diluted with CH_2Cl_2 (10 mL) then brine (10 mL). The organic layer was separated and the aqueous solution was extracted with ethyl acetate (2x10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified over silica gel to afford the silylated ether **4e**.

5.5.1. 2-[1-(Dimethylphenylsilyloxy)-2,2-dimethylpropyl]-5-oxotetrahydrofuran-2-carboxylic acid methyl ester 4e. White solid (273 mg, 75%), mp 101–102 °C, R_f=0.58 (petroleum ether/AcOEt 4:1); IR (film): ν=1789 cm^{-1}, 1739, 1117, 1252. ^1H NMR (250 MHz, $CDCl_3$): δ=7.60 (m, 2H, aromatic H), 7.38 (m, 3H, aromatic H), 4.02 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 2.59 (m, 2H, CH_2), 2.33 (m, 2H, CH_2), 0.85 (s, 9H, $(CH_3)_3$), 0.44 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.1 (C=O), 170.4 (C=O), 137.6 (aromatic C), 133.5 (aromatic CH), 129.4 (aromatic CH), 127.7 (aromatic CH), 90.7 (C), 80.4 (CH), 52.5 (OCH_3), 35.5 (C), 28.6 (CH_2), 27.1 ($(CH_3)_3$), 24.3 (CH_2), −0.8 ($SiCH_3$), −1.0 ($SiCH_3$). ^{29}Si NMR (59.6 MHz, $CDCl_3$): δ=9.4.

5.6. Synthesis of the diol 6

In a 50 mL flask charged with $K_3Fe(CN)_6$ (2 g, 6 mmol), K_2CO_3 (0.83 g, 6 mmol), $K_2OsO_2(OH)_4$ (7.2 mg, 0.02 mmol) and quinuclidine (2.3 mg, 0.02 mmol) was added the diester **5** (428 mg, 2 mmol) adjusted to 0.1 M in *t*-BuOH:H_2O (1:1 v/v). The reaction mixture was stirred at 0 °C for 5 h then warmed at room temperature until TLC indicates complete consumption of the olefin (10 h). The solution was cooled at 0 °C and sodium sulfite (3 g, 24 mmol) was added. After stirring for 1 h, the reaction mixture was extracted with ethyl acetate (3x15 mL) and the organic extracts were combined, washed with brine then dried over $MgSO_4$. The resulting organic layer was filtered and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography over silica gel to afford the diol **6**.

5.6.1. 2-Hydroxy-2-hydroxymethylhexanedioic acid diethyl ester 6. Colorless oil (481 mg, 97%), R_f=0.34 (pent/AcOEt 1:1); IR (film): ν=3443 cm^{-1}, 2981, 1733, 1731. ^1H NMR (250 MHz, $CDCl_3$): δ=4.29 (q, J=7.0 Hz, 2H, OCH_2), 4.12 (q, J=7.6 Hz, 2H, OCH_2), 3.78 (AB, J_{AB}=12.5 Hz, 2H, CH_2OH), 3.60 (br. s, 1H, OH), 2.38 (br s, 1H, OH), 2.26 (t, J=6.7 Hz, 2H, CH_2), 1.77–1.71 (m, 2H, CH_2), 1.67–1.55 (m, 2H, CH_2), 1.33 (t, J=7.0 Hz, 3H, CH_3), 1.20 (t, J=7.6 Hz, 3H, CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=174.9 (C=O), 173.1 (C=O), 78.3 (C), 67.8 (CH_2OH), 62.4 (OCH_2), 60.4 (OCH_2), 34.2 (CH_2), 34.0 (CH_2), 18.7 (CH_2), 14.3 (CH_3), 14.2 (CH_3).

5.7. Asymmetric aminohydroxylation of glutarates 2

Typical procedure. To a stirred solution of ligand (5 mol%) in *n*-PrOH (12 mL) and water (12 mL), were added dimethyl-2-methylene glutarate **2a** (344 mg, 2 mmol), chloramine-T trihydrate (1.47 g, 6 mmol, 3 equiv.) and $K_2OsO_2(OH)_4$ (29.8 mg, 0.08 mmol, 4 mol%). The reaction flask was immersed in a water bath at room temperature and the slurry was stirred overnight. A saturated aqueous sodium sulfite solution (10 mL) was added and the reaction mixture was stirred for 45 min then extracted with ethyl acetate (3× 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give a crude product which was chromatographed on silica gel column.

5.7.1. Spectral data of amino-hydroxylation products. *5-Oxo-2-[(toluene-4-sulfonylamino)methyl] tetrahydrofuran-2-carboxylic acid methyl ester* **7a**. White solid, mp 94–96 °C, R_f=0.19 (petroleum ether/AcOEt 3:2); IR (film): ν= 3054 cm^{-1}, 1732, 1725. ^1H NMR (300 MHz, $CDCl_3$): δ= 7.72 (d, J=7.9 Hz, 2H, aromatic H), 7.29 (d, J=8.3 Hz, 2H, aromatic H), 5.60 (t, J=7.2 Hz, 1H, NH), 3.72 (s, 3H, OCH_3), 3.36 (d, J=7.2 Hz, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.51–2.36 (m, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.6 (C=O), 170.3 (C=O), 143.6 (aromatic C), 136.5 (aromatic C), 129.7 (aromatic CH), 126.8 (aromatic CH), 84.6 (C), 53.1 (OCH_3), 46.9 (CH_2N), 27.8 (CH_2), 27.7 (CH_2), 21.3 (CH_3). MS (LSIMS); *m/z* (%): 350 $[M+Na]^+$ (95), 328 $[M+H]^+$(95), 174 (21), 155 (100), 139 (46), 132 (64). $C_{14}H_{17}NO_6S$ (327.35): Calcd C 51.37, H 5.23, N 4.28, S 9.80; found: C 51.18, H 5.80, N 4.05, S 9.84. HPLC 1 mL min^{-1}, Hex/*i*-PrOH (70:30), 227.4 nm, R_T (min)=16.8, 23.6.

5-Oxo-2-[1-(toluene-4-sulfonyamino)ethyl] tetrahydrofuran-2-carboxylic acid methyl ester **7b**. White solid (204 mg, 30%), mp 164–165 °C, R_f=0.41 (petroleum ether/AcOEt 1:1); IR (film): ν=3278 cm^{-1}, 1790, 1744. ^1H NMR (300 MHz, $CDCl_3$): δ=7.75 (d, J=8.3 Hz, 2H, aromatic H), 7.33 (d, J=7.9 Hz, 2H, aromatic H), 5.23 (d, J=10.9 Hz, 1H, NH), 3.74 (s, 3H, OCH_3), 3.62 (q, J= 6.8 Hz, 1H, CH), 2.60 (m, 2H, CH_2), 2.51–2.40 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 0.99 (d, J=6.8 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.2 (C=O), 170.9 (C=O), 143.8 (aromatic C), 137.9 (aromatic C), 129.8 (aromatic CH), 126.9 (aromatic CH), 86.8 (C), 54.7 (CHN), 53.0 (OCH_3), 29.8 (CH_2), 27.6 (CH_2), 21.5 (CH_3), 16.3 (CH_3). MS (LSIMS); *m/z* (%): 364 $[M+Na]^+$ (100), 342 $[M+H]^+$ (73), 198 (21), 155 (30). HRMS $C_{15}H_{19}NO_6SNa$ Calcd 364.0831; found: 364.0093. $C_{15}H_{19}NO_6S$ (341.38): Calcd C 52.77, H 5.61, N 4.10, S 9.39; found: C 52.81, H 5.61, N 4.15, S 9.96.

2-(1-Hydroxyethyl-2-toluene-4-sulfonylamino) pentanedioic acid dimethyl ester **8**. White solid (45 mg, 6%), mp 132–134 °C, R_f=0.43 (petroleum ether/AcOEt 1:1); IR (film): ν=3502 cm^{-1}, 3274, 1737, 1732. ^1H NMR (300 MHz, $CDCl_3$): δ=7.73 (d, J=7.2 Hz, 2H, aromatic H), 7.33 (d, J=7.9 Hz, 2H, aromatic H), 4.70 (d, J=10.2 Hz, 1H, OH), 3.66 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.63 (br s, 1H, NH), 2.44 (s, 3H, CH_3), 2.41 (q, J=6.7 Hz, 1H, CH), 2.12 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 1.02 (d, J=6.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.8 (C=O), 173.2 (C=O), 143.4 (aromatic C), 138.7 (aromatic C), 129.6 (aromatic CH), 126.9 (aromatic CH), 79.2 (C), 54.4 (CH), 53.3 (OCH_3), 51.8 (OCH_3), 30.4 (CH_2), 28.5 (CH_2), 21.4 (CH_3), 15.5 (CH_3).

Preparation of $CH_3SONClNa$. Solid NaOH (2 g, 0.05 mol) was added to a solution of methanesulfonamide (4.81 g, 0.05 mol) in water (40 mL), followed by a freshly prepared solution of *tert*-butyl hypochlorite. The mixture was stirred overnight at room temperature. Water and *t*-BuOH were then evaporated under reduced pressure to afford the chloramines salt as a white solid (7.5 g, 98%), used in the next step without further purification.

In a 50 mL flask equipped with a magnetic stirrer, a solution of quinuclidine (2.3 mg, 0.02 mmol, 5 mol%) in *n*-PrOH (15 mL) was added to a solution of CH_3SO_2NClNa (0.91 g, 6 mmol, 3 equiv.) in water (15 mL). After homogenisation, $K_2OsO_2(OH)_4$ (29.8 mg, 0.08 mmol, 4 mol%) then glutarate **2d** (524 mg, 2 mmol) were added at room temperature. The reaction mixture was stirred for 14 h then cooled at 0 °C and solid sodium sulfite (3 g, 24 mmol) was added. The resulting mixture was warmed to room temperature then stirred for 1 h. The aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford a residue, which was purified by chromatography on silica gel.

2-(1-Methanesulfonylamino-2-phenylethyl)-5-oxotetrahydrofuran-2-carboxtlic acid methyl ester **7d**. Colorless oil

(150 mg, 22%), R_f=0.38 (pentane/AcOEt 1:1); IR (film): ν=3237 cm^{-1}, 1747, 1729. ^1H NMR (300 MHz, $CDCl_3$): δ=7.33–7.24 (m, 5H, aromatic H), 5.36 (d, J=9.8 Hz, 1H, NH), 3.87 (s, 3H, OCH_3), 3.24 (dd, J=13.5, 13.9 Hz, 1H, CH), 2.78–2.70 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.46 (m, 2H, CH_2), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.3 (C=O), 171.5 (C=O), 137.4 (aromatic C), 130.0 (aromatic CH), 128.9 (aromatic CH), 127.4 (aromatic CH), 86.1 (C), 61.9 (CH), 53.3 (OCH_3), 41.2 (CH_3), 37.4 (CH_2), 30.9 (CH_2), 27.6 (CH_2).

2-Hydroxy-2-(1-methanesulfonylamino-2-phenylethyl) pentanedioic acid dimethyl ester **9**. Colorless oil (403 mg, 54%), R_f=0.24 (pentane/AcOEt 1:1); IR (film): ν=3545 cm^{-1} (OH), 3243 (NH), 1776 (C=O), 1742 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ=7.31–7.23 (m, 5H, aromatic H), 4.96 (d, J=9.7 Hz, 1H, NH), 3.95 (br. s, 1H, OH), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.23 (dd, J=13.6, 13.7 Hz, 1H, CH), 2.56–2.52 (m, 2H, CH_2), 2.23 (m, 4H, $2CH_2$), 1.88 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.6 (C=O), 173.5 (C=O), 138.0 (aromatic C), 130.1 (aromatic CH), 128.8 (aromatic CH), 127.1 (aromatic CH), 79.6 (C), 61.8 (CH), 53.6 (OCH_3), 51.9 (OCH_3), 40.9 (CH_3), 35.8 (CH_2), 30.6 (CH_2), 28.9 (CH_2).

Acknowledgements

This work was supported by the CNRS and the Institut Universitaire de France. A.S. thanks the DGRST and CMCU for a grant.

References and notes

1. (a) Yokomatsu, T.; Yuasa, Y.; Kano, S.; Shibuya, S. *Heterocycles* **1991**, *32*, 2315. (b) Gasey, M.; Manoge, A. C.; Murphy, P. J. *Tetrahedron Lett.* **1992**, *33*, 965. (c) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891.
2. (a) Ghosh, A. K.; Mckee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500. (b) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795. (c) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.
3. (a) Cooper, R. D.; Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1984**, *25*, 5215. (b) Wright, A. E.; Schafer, M.; Midland, S.; Munnecke, D. E.; Sims, J. J. *Tetrahedron Lett.* **1989**, *30*, 5699. (c) Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137.
4. (a) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11461. (b) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11471. (c) Harcken, C.; Brückner, R. *Tetrahedron Lett.* **2001**, *42*, 3967. (d) Harcken, C.; Brückner, R.; Rank, E. *Chem. Eur. J.* **1998**, *4*, 2342.
5. (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Barta, N. S.; Sidler, D. R.; Somerville, K. B.; Weissman, S. A.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2821.
6. Samarat, A.; Lebreton, J.; Amri, H. *Synth. Commun.* **2001**, *31*, 1675.
7. Ben Ayed, T.; Elgaïed, M. M.; Amri, H. *Synth. Commun.* **1995**, *25*, 2981.
8. (a) Amri, H.; Rambaud, M.; Villiéras, J. *Tetrahedron Lett.* **1989**, *30*, 7381. (b) Nemec, J. W.; Wuchter, R. B. US Patent, 1979, 4, 145, 559, *Chem. Abst.* **1979**, *91*, 49609 (c) Cookson, R. C.; Smith, S. A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2447.
9. Landais, Y.; Zekri, E. *Eur. J. Org. Chem.* **2002**, 4037.
10. Samarat, A.; Fargeas, V.; Villiéras, J.; Lebreton, J.; Amri, H. *Tetrahedron Lett.* **2001**, *42*, 1273.
11. Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.
12. (a) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2810. (c) Li, G.; Chang, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451. (d) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326.
13. Waston, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 8957–8966

Reaction of silyl ketene acetals with epoxides: a new method for the synthesis of γ-butanolides

Veselin Maslak,[a,b] Radomir Matović[b] and Radomir N. Saičić[a,b,*]

[a]*Faculty of Chemistry, University of Belgrade, Studentski trg 16, PO Box 158, 11000 Belgrade, Serbia and Montenegro*
[b]*I. C. T. M. Center for Chemistry, Njegoševa 12, 11000 Belgrade, Serbia and Montenegro*

Received 10 March 2004; revised 9 June 2004; accepted 1 July 2004

Available online 23 August 2004

Abstract—Titanium tetrachloride promoted reaction of silyl ketene acetals with epoxides, followed by acidic work-up, affords butanolides in moderate/good yields. With epihalohydrins the reaction is regioselective and occurs at the less substituted end of the epoxide; the γ-haloalkyl-γ-butanolides thus obtained can be further transformed into various products.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Epoxide ring opening with carbon nucleophiles is one of the most useful reactions in organic synthesis.[1] However, the role of nucleophile is usually conferred to organometallics, while the analogous reactions of ketone and ester enolates are generally less efficient. While the group I and II ketone enolates do not react with epoxides at all, γ-hydroxyketones can be obtained when the reaction is performed in the presence of boron trifluoride etherate,[2] scandium triflate,[3] in 5 M etheral solution of lithium perchlorate[4] or, indirectly, with the enolate of the corresponding imine[5] or *N*,*N*-dimethylhydrazone.[6] Similarly, although sporadic examples of epoxide ring opening with lithium mono- and dianions of carboxylic acids and derivatives have been reported,[7] these species are essentially unreactive towards epoxides and their reactions have not found broad synthetic application. Aluminum ester enolates, which can be obtained by transmetallation of their lithium counterperts with chloroalanes are much more reactive and their reactions with epoxides offer an efficient approach to γ-hydroxy carboxylic acid derivatives and butanolides.[8] Reactions of epoxides with enolates have been recently reviewed.[9] Indirect methods for butanolide synthesis have also been devised, relying on reactions of alkoxyalkynilalanes[8a] or, more recently, silylynamines as the reactive intermediates.[10]

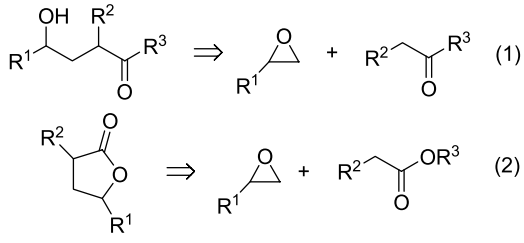
Keywords: Epoxides; Ketene acetals; Lactones; Titanium and compounds; Alkylation.

* Corresponding author. Address: Faculty of Chemistry, University of Belgrade, Studentski trg 16, PO Box 158, 11000 Belgrade, Serbia and Montenegro. Tel.: +381 113282537; fax: +381 11636061; e-mail: rsaicic@chem.bg.ac.yu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.07.007

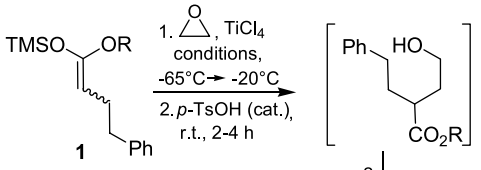
2. Results and discussion

Some time ago, we found that silyl enol ethers react with epoxides under the conditions of the Mukaiyama reaction, to give the homoaldol type products.[11] The reaction, initially suspected to proceed via the titanium enolate, was subsequently shown to involve the catalysis by $TiCl_4$ as a Lewis acid.[12] In this way, the scope of the homoaldol transform, represented by the Eq. (1) in Scheme 1, was enlarged by a new synthetic transformation, complementary to the existing ones. We now wish to report the extension of this method to silyl ketene acetals, which offers an alternative synthetic approach to γ-butanolides (Eq. (2)).



Scheme 1. Homoaldol transforms for γ-hydroxyketones and butanolides.

When a dichloromethane solution of silyl ketene acetal (SKA) **1**, prepared from isopropyl phenylbutanoate,[14] and ethylene oxide was submitted to the action of $TiCl_4$ at −60 °C, the TLC of the reaction mixture indicated the formation of two products which, upon acidic work-up, converged to a single compound—α-(2-phenylethyl)-γ-butanolide **2**—which was isolated in 19% yield (Scheme 2). Other Lewis acids ($BF_3 \cdot Et_2O$, $ZnCl_2$, $Ti(O^iPr)_4$, $SnCl_4$,



Conditions:

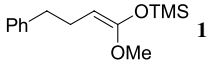
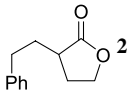
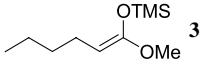
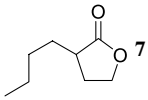
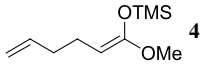
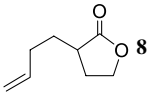
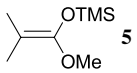
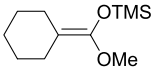
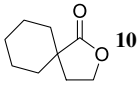
R	Solvent	Yield (%)
^{i}Pr	CH_2Cl_2	19
Me	CH_2Cl_2	38
Me	CH_2Cl_2/ *n*-hexane (1 : 2)	62

Scheme 2. The first experiments with ethylene oxide.

TMSOTf) were ineffective catalysts for this transformation. Reducing the size of the ester alkyl group proved beneficial, as substituting the smaller methyl group for isopropyl in **1** increased the yield to 38%. Further improvements were achieved by performing the reaction in the mixed solvent: *n*-hexane/dichloromethane = 2/1, which resulted in the yield enhancement to 62% (97%, based on the recovered methyl 4-phenylbutanoate). The best results were obtained when the reagents were used in the molar ratio: SKA/ethylene oxide/$TiCl_4$ = 1/2/3; change in the molar ratio, or the alternative order of addition, decreased the yield.

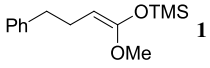
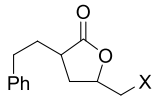
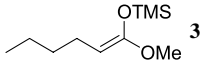
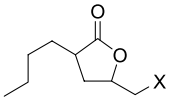
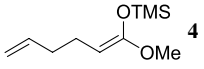
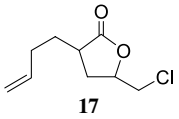
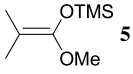
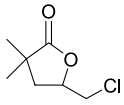
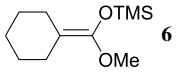
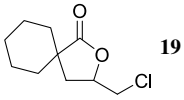
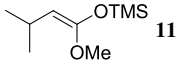
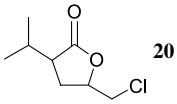
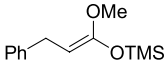
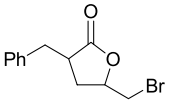
Several other SKA were submitted to these reaction conditions. In all cases the desired γ-butyrolactones were obtained in 53–69% yields, as shown in Table 1. The reaction proved suitable for the preparation of lactones possessing a saturated (entry 2), unsaturated (entry 3) or a side chain with an aromatic unit (entry 1), as well as those possessing a quaternary center in the α-position (entry 4), including spirolactones (entry 5).

Table 1. Reactions of SKA with ethylene oxide

Entry	Reactant	Product	Yield (%)[a]
1.	 **1**	 **2**	62 (97)[b]
2.	 **3**	 **7**	69
3.	 **4**	 **8**	64
4.	 **5**	 **9**	53
5.	 **6**	 **10**	66

[a] Isolated yields of pure products.
[b] Yield calculated on the basis of recovered methyl 4-phenylbutanoate.

Table 2. Reactions with epichloro- and epibromohydrin

Entry	Reactant	Product	Yield (%)[a]
1.	 **1**	 **13** X = Cl	49
2.		**14** X = Br	50
3.	 **3**	 **15** X = Cl	64
4.		**16** X = Br	64
5.	 **4**	 **17**	83
6.	 **5**	 **18**	44
7.	 **6**	 **19**	69
8.	 **11**	 **20**	59
9.	 **12**	 **21**	54

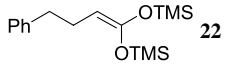
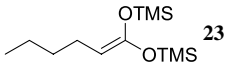
[a] Isolated yields of pure products.

A higher level of product functionalization was obtained when performing the reaction with epihalohydrins. Thus, both epichloro- and epibromohydrin reacted with a range of SKA to afford the corresponding γ-halomethylbutanolides in 44–83% yield (Table 2). Owing to a negative inductive effect of the halide substituent, the epoxide ring opening is regioselective, with the nucleophilic attack occurring exclusively at the less substituted epoxide end. The reaction is not stereoselective, however, as the products were obtained as equimolar mixtures of *cis* and *trans* isomers.

Bis-trimethylsilyl ketene acetals, which can be obtained from carboxylic acids, are also efficient reaction partners. As can be seen from Table 3, the yields in their reactions with ethylene oxide and epihalohydrins compare favourably with those of SKA.

We also examined the reaction of SKA with substituted epibromohydrins of type **24**. These compounds can be

Table 3. Reactions of bis-SKA

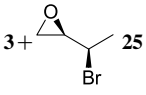
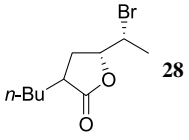
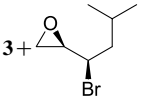
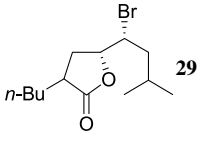
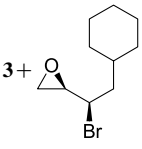
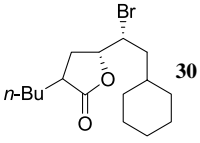
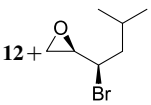
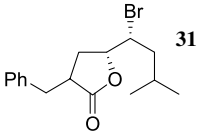
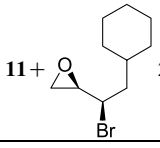
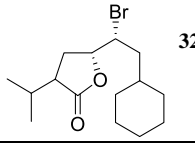
Entry	Reactants	Product	Yield (%)[a]
	 **22**		
1.	**22** + 	**2**	66
2.	**22** + 	**13**	59
3.	**22** + 	**14**	53 (73%[b])
	 **23**		
4.	**23** + 	**7**	80
5.	**23** + 	**15**	67

[a] Isolated yields of pure products.
[b] Yield determined.

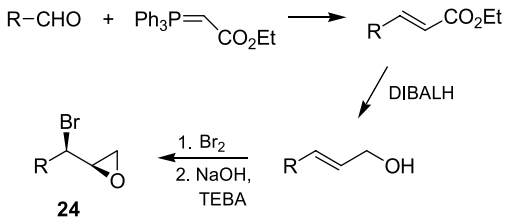
stereoselectively obtained by a four-step sequence displayed in Scheme 3.

The results of SKA alkylation with substituted epibromohydrins of type **24** are displayed in Table 4. No isomerization occurs under the reaction conditions and all the products were obtained as *syn*-isomers, with the retention

Table 4. Alkylations of SKA with substituted epibromohydrins

Entry	Reactants	Product	Yield (%)[a]
1.	**3** +  **25**	 **28**	73
2.	**3** +  **26**	 **29**	66
3.	**3** +  **27**	 **30**	54
4.	**12** +  **26**	 **31**	21
5.	**11** +  **27**	 **32**	69

[a] Isolated yields of pure products.

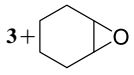
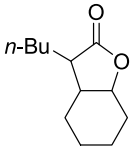
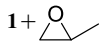
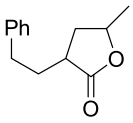
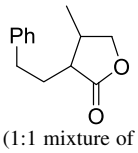
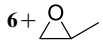
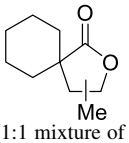
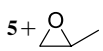
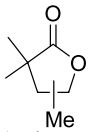
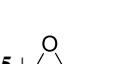
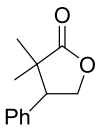


Scheme 3. Synthesis of substituted epibromohydrins.

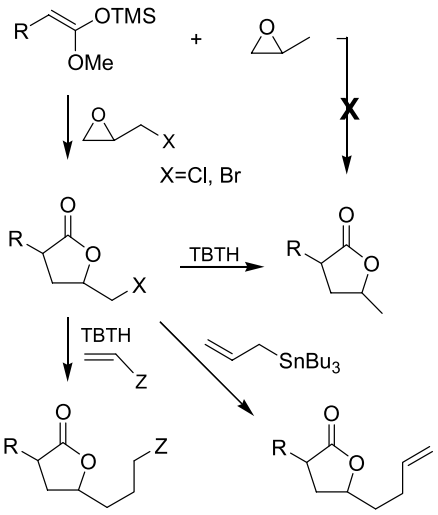
of configuration of the stereocenters originating from the bromohydrin.

Reactions with epoxides that do not possess a halide substituent in the vicinal position were less successful (Table 5). Alkylation of **3** with cyclohexene oxide furnished the condensed bicyclic lactone **33** in an acceptable 48% yield (entry 1), but with the structurally similar SKA **1** and **23** lower yields were obtained. The reactions with propene oxide gave rise to mixtures of regioisomers which were isolated in modest yields (entries 2–4). In the case of styrene oxide, the reaction could be performed in the presence of $BF_3 \cdot Et_2O$, and gave the 3-phenylbutanolide derivative **40** regioselectively (entry 5; this is the only case where the

Table 5. Reactions of SKA with epoxides other than epihalohydrins

Entry	Reactants	Product	Yield (%)[a]
1.	**3** + 	 **33**	48
2.	**1** + 	 **34** +  **35** (1:1 mixture of regioisomers)	29
3.	**6** + 	 **36**+**37** (1:1 mixture of regioisomers)	35
4.	**5** + 	 **38**+**39** (1:1 mixture of regioisomers)	38
5.	**5** + 	 **40**	15, 32[b]

[a] Isolated yields of pure products.
[b] BF_3Et_2O was used instead of $TiCl_4$.



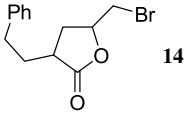
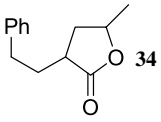
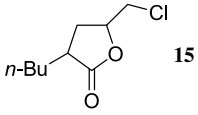
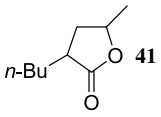
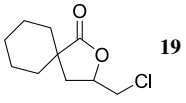
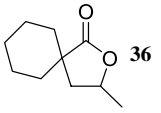
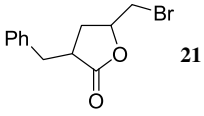
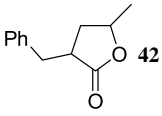
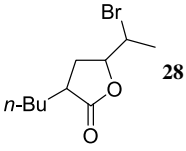
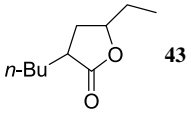
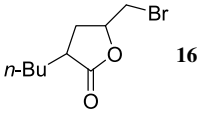
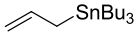
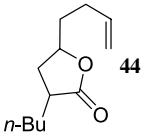
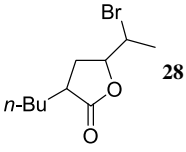
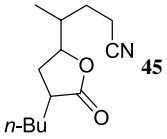
Scheme 4. Transformations of products.

coupling could be achieved with a Lewis acid other than $TiCl_4$).

However, the poor performance of unsymmetrical, non-halogen-containing epoxides, does not necessarily restrict the scope of the reaction to the synthesis of quite simple derivatives, as the products of the coupling with epihalohydrins are amenable to further synthetic transformations (Scheme 4). Thus, the combination of the alkylation with epihalohydrin and the reduction with tributyltinhydride affords regioselectively γ-alkyl substituted butanolides, which are not directly obtainable by the reaction with the corresponding unsymmetrical epoxides (Table 6, entries 1, 3–6). This transformation can also be carried out with hypophosphorous acid as a non-toxic and environmentally-friendly reagent (entry 2).[15] Carbon–carbon bond forming reactions are also possible, and the examples of allylation and of the Giese addition are given in entries 7 and 8, respectively. Radical reactions are particularly well suited for these type of transformations as, in contrast to β-alkoxy organometallics, β-alkoxy radical intermediates are not susceptible to β-elimination. These combinations of reactions are the synthetic equivalents of the alkylation with structurally more complex epoxides.

In conclusion, a new reaction of silyl ketene acetals with epoxides is described, which complements the existing methods for the synthesis of γ-butanolides.

Table 6. Transformations of 4-haloalkylbutanolides

Entry	Reactants		Products	Yield (%)[a]
1.	 **14**	Bu_3SnH	 **34**	73
2.		H_3PO_2		76
3.	 **15**	Bu_3SnH	 **41**	74
4.	 **19**	Bu_3SnH	 **36**	78
5.	 **21**	Bu_3SnH	 **42**	80
6.	 **28**	Bu_3SnH	 **43**	82
7.	 **16**		 **44**	83
8.	 **28**	Bu_3SnH  AIBN	 **45**	76

[a] Yield of the isolated pure compound.

3. Experimental

3.1. General

All chromatographic separations were performed on Silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Varian Genmini 200, ^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard, coupling constants (J) are in Hz. IR spectra were recorded on a Perkin–Elmer 457 grating FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on a Finnigan ITDS 700 instrument. Microanalyses were performed at the Vario EL III instrument CHNOS Elementar Analyzer, Elemantar Analysensysteme GmbH, Hanau-Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. GC analyses were performed on a Varian 3400 instrument, equipped with Varian 4270 integrator, VOCOL™ column (105 m, ID: 0.53 mm, film thickness 3.0 μm, carrier gas H_2, 10 mL/min), FI detector. Preparative gas chromatography was performed on a Varian P-90 instrument, using 2 m long stainless steel column packed with 10% OV-101 on Chromosorb 80, (carrier gas H_2, 10 mL/min).

3.2. General procedure for the synthesis of silyl ketene acetals.[14]

To a cold (−78 °C) solution of LDA (13 mmol) in THF (13 mL) was added a solution of the corresponding ester (10 mmol) in THF (10 mL), dropwise, with stirring. After 30 min, TMSCl (2.16 g; 20 mmol) was added, the mixture was stirred for additional 30 min at −78 °C, then allowed to reach rt. The solvent was removed at the rotary evaporator, the product was extracted from the residue with *n*-hexane, the organic extract was concentrated at the rotavapor and the residue was distilled under reduced pressure.

3.2.1. 4-Phenyl-1-methoxy-1-trimethylsilyloxy-1-butene (1). 82%. Colorless oil, bp 95 °C/0.4 mmHg. Spectroscopic data for this compound have not been reported in the literature.[16] ^{1}H NMR δ: 7.82–7.60 (m, 5H); 4.20–3.90 (m, 4H); 3.20–3.05 (m, 2H); 2.85–2.75 (m, 2H); 0.18 (s, 9H).

3.2.2. 1-Methoxy-1-trimethylsilyloxy-1-hexene (3). 60%. Colorless oil, bp 55–8 °C/2 mmHg; spectroscopic data identical to that reported in the literature.[17]

3.2.3. 1-Methoxy-1-trimethylsilyloxy-1,5-hexadiene (4). 79%. Colorless oil, bp 40 °C/1 mmHg. Spectroscopic data for this compound have not been reported in the literature.[18] ^{1}H NMR δ: 5.90–5.70 (m, 1H); 5.05–4.90 (m, 2H). 3.90–3.80 (m, 1H); 3.50 (s, 3H, major isomer); 3.45 (s, 3H, minor isomer); 2.07–2.04 (m, 4H); 0.22 (s, 9H).

3.2.4. 2-Methyl-1-methoxy-1-trimethylsilyloxy-1-propene (5). 52%. Colorless oil, bp 63 °C/25 mmHg; spectroscopic data identical to that reported in the literature.[14]

3.2.5. (Cyclohexylidene(methoxy)methoxy)trimethylsilane (6). 74%. Colorless oil, bp 80 °C/25 mmHg; spectroscopic data identical to that reported in the literature.[14]

3.2.6. 3-Methyl-1-methoxy-1-trimethylsilyloxy-1-butene (11). 40%. Colorless oil, bp 45 °C/1 mmHg. Spectroscopic data for this compound have not been reported in the literature.[13b] ^{1}H NMR δ: 3.66–3.45 (m, 4H); 2.56–2.45 (m, 1H); 0.93 (d, J=6.8 Hz, 6H); 0.22 (s, 9H).

3.2.7. 3-Phenyl-1-methoxy-1-trimethylsilyloxy-1-propene (12). 53%. Colorless oil, bp 85 °C/1 mmHg; spectroscopic data identical to that reported in the literature.[19]

3.2.8. 4-Phenyl-1,1-bis(trimethylsilyloxy)-1-butene (22). 72%. Colorless oil, bp 130 °C/0.2 mmHg. Due to its lability, compound **22** has not been fully characterized, but was identified only by ^{1}H NMR spectrum. ^{1}H NMR δ: 7.30–7.11 (m, 5H); 3.55 (t, J=7.2 Hz, 1H); 2.64–2.51 (m, 2H); 2.28–2.11 (m, 2H); 0.19 (s, 9H); 0.17 (s, 9H).

3.2.9. 1,1-Bis(trimethylsilyloxy)-1-hexene (23). 95%. Colorless oil, bp 80 °C/1 mmHg. Due to its lability, compound **23** has not been fully characterized, but was identified only by ^{1}H NMR spectrum. ^{1}H NMR δ: 3.55 (t, J=7.2 Hz, 1H); 1.96–1.86 (m, 2H); 1.33–1.22 (m, 4H); 0.92–0.85 (m, 3H); 0.21 (s, 9H); 0.17 (s, 9H).

3.3. Synthesis of γ-butanolides. General procedure for the alkylation of silyl ketene acetals with epoxydes

To a cold (−60 °C) solution of silyl ketene acetal (1 mmol) and epoxide (2 mmol) in a solvent mixture dichloromethane–*n*-hexane=1:2 (3 mL) was added dropwise a solution of $TiCl_4$ in dichloromethane (0.82 mL of the 3.65 M solution; 3 mmol), with stirring under an argon atmosphere. The reaction mixture was allowed to reach −20 °C, then cooled to −30 °C and quenched by the addition of conc. aq NH_4Cl (5 mL). The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). To a combined extract was added *p*-TsOH (20 mg; 0.1 mmol) and the reaction mixture was stirred 3 h at rt. The solution was washed with water, dried over anh. Na_2SO_4 and concentrated under reduced pressure. Purification by dry-flash chromatography afforded the corresponding γ-butanolides.

3.3.1. 2-(2-Phenylethyl)-4-butanolide (2). Purification by dry-flash chromatography was performed using 20% acetone in petroleum–ether as an eluent, to give the title compound in 66% yield when the reaction is performed with 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22**, (when 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1** was used as the starting compound the yield was 62%). Colorless oil, bp 135–145 °C/0.3 mmHg (Kugelrohr). IR_{film}: 3063, 3029, 2922, 2861, 1769, 1495, 1454, 1376, 1184, 1150, 1026, ^{1}H NMR δ: 7.40–7.10 (m, 5H); 4.34 (ddd, J_1=J_2=9.0 Hz, J_3=2.7 Hz, 1H); 4.16 (ddd, J_1=J_2=9.0 Hz, J_3=6.6 Hz, 1H); 2.85–2.60 (m, 2H); 2.60–2.10 (m, 3H); 2.10–1.60 (m, 2H); ^{13}C NMR δ: 179.3; 140.7; 128.4; 128.3; 126.1; 66.3; 38.2; 33.1; 31.8; 28.6; HRMS (EI): M^+, found 190.0997; $C_{12}H_{14}O_2$ requires 190.0994. MS (EI) *m/z*: 190 (M^+, 17%); 105 (15%); 91 (25%); 85 (100%).

3.3.2. 2-Butyl-4-butanolide (7). Colorless oil, 80% from 1,1-bis(trimetilsilyloxy)-1-hexene, (69% from 1-methoxy-1-trimethylsilyloxy-1-hexene). Spectroscopic data for this compound have not been reported in the literature.[20] IR_{film}: 3053, 2959, 2931, 1773, 1462, 1376, 1168, 1026; ^1H NMR δ: 4.35 (ddd, $J_1=J_2=9.0$ Hz, $J_3=3.0$ Hz, 1H); 4.20 (ddd $J_1=J_2=9.0$ Hz, $J_3=6.4$ Hz, 1H); 2.60–2.30 (m, 2H); 2.10–1.80 (m, 2H); 1.60–1.25 (m, 5H); 1.00–0.80 (m, 3H); ^{13}C NMR δ: 179.6; 66.4; 39.0; 29.8; 29.3; 28.4; 22.2; 13.7.

3.3.3. 2-(3-Butenyl)-4-butanolide (8). Colorless oil, 64%, spectroscopic data identical to that reported in the literature.[21] ^{13}C NMR spectra for this compound have not been reported; ^{13}C NMR δ: 179.2 (C); 136.9 (CH); 115.2 (CH_2); 66.1 (CH_2); 38.1 (CH); 30.9 (CH_2); 29.0 (CH_2); 28.2 (CH_2).

3.3.4. 2,2-Dimethyl-4-butanolide (9). Colorless oil, 53%, spectroscopic data identical to that reported in the literature.[21] ^{13}C NMR spectra for this compound have not been reported; ^{13}C NMR δ: 182.0; 64.4; 38.1; 36.4; 23.6.

3.3.5. 2-Oxa-spiro[4.5]decan-1-one (10). Colorless oil, 66%. ^1H NMR δ: 4.26 (t, $J=7.1$ Hz, 2H); 2.16 (t, $J=7.1$ Hz, 2H); 1.80–1.20 (m, 10H); ^{13}C NMR δ: 181.9; 65.1; 43.0; 32.9; 32.2; 25.2; 22.0; HRMS (EI): M^+, found 154.0976; $C_{12}H_{20}O_2$ requires 154.0994; MS (EI) *m/z*: 154 (M^+, 32%); 99 (100%); 86 (82%); 81 (56%); 67 (32%).

3.3.6. 2-(2-Phenylethyl)-4-chloromethyl-4-butanolide (13). Colorless oil, 60% from 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22** (49% from 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1**), obtained as a 1:1 mixture of stereoisomers. The isomers were preparatively separated by a second dry-flash chromatography, using 5% acetone in petroleum–ether as an eluent. Anal. Calcd for $C_{13}H_{15}ClO_2$: C 65.41, H 6.33; Found: C 65.88, H 6.34. Isomer **A**: IR_{film}: 3028, 2950, 1773, 1603, 1496, 1453, 1167, 1033; ^1H NMR δ: 7.40–7.10 (m, 5H); 4.74 (ddt, $J_1=J_2=8.6$ Hz, $J_3=4.7$ Hz, 1H); 3.65 (d, $J=4.7$ Hz, 2H); 2.90–2.60 (m, 3H); 2.45–2.25 (m, 1H); 2.25–2.00 (m, 2H); 1.90–1.70 (m, 1H); ^{13}C NMR δ: 178.3 (C); 140.5 (C); 128.5 (CH); 128.3 (CH); 126.2 (CH); 76.1 (CH); 45.9 (CH_2); 38.1 (CH); 33.1 (CH_2); 32.8 (CH_2); 30.9 (CH_2). Isomer **B**: IR_{film}: 3027, 2925, 1775, 1603, 1496, 1453, 1165, 1035; ^1H NMR δ: 7.40–7.20 (m, 5H); 4.57 (ddt, $J_1=J_2=10.2$ Hz, $J_3=5.0$ Hz, 1H); 3.69 (d, $J=5.0$ Hz, 2H); 2.90–2.40 (m, 4H); 2.40–2.20 (m, 1H); 1.90–1.70 (m, 2H); ^{13}C NMR δ: 177.7 (C); 140.5 (C); 128.5 (CH); 128.4 (CH); 126.3 (CH); 76.3 (CH); 45.3 (CH_2); 39.5 (CH); 33.1 (CH_2); 32.2 (CH_2); 31.9 (CH_2).

3.3.7. 2-(2-Phenylethyl)-4-bromomethyl-4-butanolide (14). Colorless oil, 53% from 4-phenyl-1,1-bis(trimethylsilyloxy)-1-butene **22**, (50% from 4-phenyl-1-methoxy-1-trimethylsilyloxy-1-butene **1**), obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_{13}H_{15}BrO_2$: C 55.14, H 5.34; found: C 55.16, H 5.58; IR_{film}: 3020, 2949, 2861, 1768, 1602, 1494, 1454, 1160; ^1H NMR δ: 7.35–7.18 (m, 5H); 4.74 (ddt, $J_1=8.1$ Hz, $J_2=5.7$ Hz, $J_3=4.4$ Hz, 1H, isomer **A**); 4.54 (ddt, $J_1=10.3$ Hz, $J_2=J_3=4.0$ Hz, 1H, isomer **B**); 3.62–3.42 (m, 2H); 2.89–2.48 (m, 3H); 2.41–2.06 (m, 2H); 1.88–1.66 (m, 2H); ^{13}C NMR δ: 178.3; 177.6; 140.5; 128.5; 128.4; 126.3; 76.0; 75.9; 39.7; 38.2; 34.0; 33.6; 33.4; 33.2; 33.1; 32.8; 32.0; 31.8.

3.3.8. 2-Butyl-4-chloromethyl-4-butanolide (15). Colorless oil, 67% from 1,1-bis(trimetilsilyloxy)-1-hexene, (64% from 1-methoxy-1-trimethylsilyloxy-1-hexene), obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_9H_{15}ClO_2$: C 56.69, H 7.93; found: C 56.84, H 7.78; HRMS (EI): M^+, found 190.07821; $C_{12}H_{14}O_2$ requires 190.07606; IR_{film}: 3055, 2959, 2934, 1775, 1461, 1345, 1175; ^1H NMR δ: 4.76 (ddt, $J_1=8.6$ Hz, $J_2=J_3=4.4$ Hz, 1H, diastereoisomer **A**); 4.64 (ddt, $J_1=10.0$ Hz, $J_2=5.6$ Hz, $J_3=5.1$ Hz, 1H, diastereoisomer **B**); 3.80–3.65 (m, 2H); 2.80–2.40 (m, 2H); 2.40–2.00 (m, 1H); 2.00–1.30 (m, 6H); 1.00–0.80 (m, 3H); ^{13}C NMR δ: 178.5; 177.8; 76.3; 76.1; 48.5; 46.1; 45.3; 40.3; 38.8; 31.9; 30.7; 29.8; 29.2; 29.1; 22.2; 13.7.

3.3.9. 2-Butyl-4-bromomethyl-4-butanolide (16). Colorless oil, 64%, obtained as a 1:1 mixture of stereoisomers. Anal. Calcd for $C_9H_{15}BrO_2$: C 45.98, H 6.43; found: C 45.74, H 6.55; IR_{film}: 2958, 2933, 2864, 1777, 1461, 1343, 1174. Isomer **A**: ^1H NMR δ: 4.75 (ddt, $J_1=8.2$ Hz, $J_2=J_3=5.0$ Hz, 1H); 3.55 (d, $J=5.0$ Hz, 2H); 2.82–2.66 (m, 1H); 2.39 (ddd, $J_1=13.4$ Hz, $J_2=9.6$ Hz, $J_3=4.6$ Hz, 1H); 2.17 (ddd, $J_1=13.4$ Hz, $J_2=J_3=7.9$ Hz, 1H); 1.92–1.79 (m, 1H); 1.58–1.27 (m, 5H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 178.4 (C); 75.9 (CH); 38.8 (CH); 34.3 (CH_2); 31.6 (CH_2); 30.5 (CH_2); 29.0 (CH_2); 22.1 (CH_2); 13.6 (CH_3). Isomer **B**: ^1H NMR δ: 4.60 (ddt, $J_1=10.4$ Hz, $J_2=J_3=5.6$ Hz, 1H); 3.57 (d, $J=5.6$ Hz, 2H); 2.75–2.51 (m, 2H); 1.95–1.65 (m, 2H); 1.52–1.27 (m, 5H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 177.7 (C); 75.9 (CH); 40.4 (CH); 33.5 (CH_2); 33.1 (CH_2); 29.6 (CH_2); 29.0 (CH_2); 22.1 (CH_2); 13.5 (CH_3).

3.3.10. 2-(3-Butenyl)-4-chloromethyl-4-butanolide (17). Colorless oil, 83%, obtained as a 1:1 mixture of diastereoisomers, which could not be separated by column chromatography, but were separated by preparative gas chromatography. Bp 100–105 °C/0.3 mmHg (Kugelrohr, for the mixture of isomers). Anal. Calcd for $C_9H_{13}O_2$: C 57.30; H 6.95; Found: C 56.98; H 6.98. Isomer **A**: IR_{film}: 3074, 2919, 2862, 1774, 1641, 1347, 1170, 1038; ^1H NMR δ: 5.90–5.70 (m, 1H); 5.15–4.95 (m, 2H); 4.76 (app. hex., $J=4.6$ Hz, 1H); 3.71 (dd, $J_1=J_2=5.4$ Hz, 2H); 2.85–2.65 (m, 1H); 2.60–2.30 (m, 2H); 2.30–1.90 (m, 2H); 1.70–1.50 (m, 2H); ^{13}C NMR δ: 178.6; 136.9; 115.9; 76.2; 46.0; 38.2; 31.2; 30.8; 30.3. Isomer **B**: 3074, 2939, 2864, 1775, 1641, 1345, 1172, 1037; ^1H NMR δ: 5.89–5.69 (m, 1H); 5.15–4.95 (m, 2H); 4.60 (m, 1H); 3.71 (dd, $J_1=5.2$ Hz, $J_2=1.1$ Hz, 2H); 2.80–2.40 (m, 2H); 2.30–2.00 (m, 3H); 1.95–1.50 (m, 2H); ^{13}C NMR δ: 177.8; 137.0; 115.9; 76.3; 45.3; 39.6; 32.2; 31.2; 29.4.

3.3.11. 2,2-Dimethyl-4-chloromethyl-4-butanolide (18). Colorless oil, 44%. Spectroscopic data for this compound have not been reported in the literature.[8c] IR_{film}: 2968, 2933, 1775, 1461, 1385, 1207, 1117; ^1H NMR δ: 4.69 (ddt, $J_1=9.4$ Hz, $J_2=6.5$ Hz, $J_3=5.2$ Hz, 1H); 3.70 (d, $J=5.2$ Hz, 2H); 2.24 (dd, $J_1=12.9$ Hz, $J_2=6.5$ Hz, 1H); 2.00 (dd, $J_1=12.9$ Hz, $J_2=9.4$ Hz, 1H); 1.32 (s. 3H); 1.30 (s. 3H); ^{13}C NMR δ: 180.9; 74.9; 45.5; 40.5; 40.2; 24.9; 24.8.

3.3.12. 3-Chloromethyl-2-oxa-spiro[4.5]decan-1-one (19). Colorless oil, 69%. IR_{film}: 2933, 2859, 1768, 1450, 1344, 1269, 1193, 1162, 1099, 1031; ^1H NMR δ: 4.68 (ddt, $J_1=9.2$ Hz, $J_2=6.9$ Hz, $J_3=4.7$ Hz, 1H); 3.74 (d, $J=4.7$ Hz, 2H); 2.43 (dd, $J_1=13.0$ Hz, $J_2=6.9$ Hz, 1H); 1.90 (dd, $J_1=13.0$ Hz, $J_2=9.2$ Hz, 1H); 1.85–1.20 (m, 10H); ^{13}C NMR δ: 180.4 (C); 75.1 (CH); 45.7 (CH_2); 44.4 (C); 36.0 (CH_2); 33.6 (CH_2); 31.8 (CH_2); 24.8 (CH_2); 21.8 (CH_2); 21.6 (CH_2); HRMS (EI): M^+, found 202.0760; $C_{12}H_{15}ClO_2$ requires 202.0782; MS (EI) *m/z*: 202 (M^+, 44%); 153 (35%); 147 (56%); 134 (82%); 81 (100%); 67 (58%).

3.3.13. 2-Isopropyl-4-chloromethyl-4-butanolide (20). Colorless oil, 59%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers, bp 95 °C/0.8 mmHg. IR_{film}: 2964, 2880, 1774, 1465, 1342, 1173, 1035; HRMS (EI): $[M-CH_3]^+$, found 161.0355; $C_7H_{10}ClO_2$ requires 161.0369 (the intensity of M^+ ion was too low for a high resolution signal). Isomer **A**: ^1H NMR δ: 4.77–4.61 (m, 1H); 3.71–3.68 (m, 2H); 2.71 (ddd, $J_1=9.5$ Hz, $J_2=8.4$ Hz, $J_3=5.0$ Hz, 1H); 2.29–2.06 (m, 3H); 1.04 (d, $J=6.8$ Hz, 3H); 0.95 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 177.8 (C); 76.2 (CH); 46.4 (CH_2); 45.0 (CH); 28.7 (CH); 26.5 (CH_2); 20.1 (CH_3); 18.1 (CH_3). Isomer **B**: ^1H NMR δ: 4.59 (ddd, $J_1=11.2$ Hz, $J_2=6.1$ Hz, $J_3=5.1$ Hz, 1H)m, 1H); 3.72 (d, $J=5.0$ Hz, 2H); 2.67 (ddd, $J_1=12.1$ Hz, $J_2=9.1$ Hz, $J_3=5.0$ Hz, 1H); 2.35 (ddd, $J_1=12.1$ Hz, $J_2=9.1$ Hz, $J_3=6.2$ Hz, 1H); 2.26–2.13 (m, 1H); 2.00–1.83 (m, 1H); 1.06 (d, $J=6.4$ Hz, 3H); 0.94 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 176.9 (C); 75.9 (CH); 46.4 (CH_2); 45.3 (CH); 27.5 (CH_2); 27.4 (CH); 20.3 (CH_3); 18.0 (CH_3).

3.3.14. 2-(2-Phenylmethyl)-4-bromomethyl-4-butanolide (21). Colorless oil, 54%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers, which were separated by column chromatography. Spectroscopic data for this compound have not been reported in the literature.[22] IR_{film}: 2923, 2862, 1777, 1604, 1496, 1341, 1161; HRMS (EI): M^+, found 268.0091; $C_{13}H_{13}BrO_2$ requires 268.0099. Isomer **A**: ^1H NMR δ: 7.37–7.17 (m, 5H); 4.54 (ddt, $J_1=10.7$ Hz, $J_2=J_3=5.2$ Hz, 1H); 3.46 (d, $J=5.2$ Hz, 2H); 3.23–3.02 (m, 1H); 2.92–2.72 (m, 2H); 2.26–2.14 (m, 2H); ^{13}C NMR δ: 178.2 (C); 138.1 (C); 128.8 (CH); 128.7 (CH); 126.8 (CH); 126.7 (CH); 76.1 (CH); 40.7 (CH); 36.4 (CH_2); 34.0 (CH_2); 30.7 (CH_2). Isomer **B**: ^1H NMR δ: 7.37–7.18 (m, 5H); 4.54 (dddd, $J_1=9.5$ Hz, $J_2=J_3=6.2$ Hz, $J_4=4.5$ Hz, 1H); 3.49 (dd, $J_1=12.1$ Hz, $J_2=4.2$ Hz, 1H); 3.38 (dd, $J_1=12.1$ Hz, $J_2=6.2$ Hz, 1H); 3.28 (dd, $J_1=12.0$ Hz, $J_2=4.6$ Hz, 1H); 3.00 (dddd, $J_1=11.4$ Hz, $J_2=J_3=9.0$ Hz, $J_4=4.2$ Hz, 1H); 3.23–3.02 (m, 1H); 2.79 (dd, $J_1=12.1$ Hz, $J_2=9.0$ Hz, 1H); 2.42 (ddd, $J_1=13.1$ Hz, $J_2=9.0$ Hz, $J_3=6.2$ Hz, 1H); 1.76 (ddd, $J_1=13.1$ Hz, $J_2=11.4$ Hz, $J_3=9.5$ Hz, 1H); ^{13}C NMR δ: 177.1 (C); 138.1 (C); 128.8 (CH); 128.7 (CH); 126.8 (CH); 76.2 (CH); 42.5 (CH); 36.0 (CH_2); 33.1 (CH_2); 32.8 (CH_2).

3.3.15. 2-Butyl-4-(1-bromoethyl)-4-butanolide (28). Colorless oil, 73%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers. Anal. Calcd for $C_{10}H_{17}BrO_2$: C 48.21, H 6.88; found: C 47.71, H 6.98; IR_{film}: 2958, 2931, 2865, 1779, 1452, 1355, 1220, 1171; Isomer **A**: ^1H NMR δ: 4.57 (ddd, $J_1=8.5$ Hz, $J_2=4.8$ Hz, $J_3=3.5$ Hz, 1H); 4.20 (dq, $J_1=6.9$ Hz, $J_2=3.5$ Hz, 1H); 2.83–2.70 (m, 1H); 2.34 (ddd, $J_1=13.5$ Hz, $J_2=10.0$, $J_3=4.1$ Hz, 1H); 2.09 (ddd, $J_1=13.5$ Hz, $J_2=8.5$ Hz, $J_3=7.3$ Hz, 1H); 1.93–1.70 (m, 1H); 1.75 (d, $J=6.9$ Hz, 3H); 1.50–1.32 (m, 5H); 0.95–0.85 (m, 3H); ^{13}C NMR δ: 179.0 (C); 80.0 (CH); 50.8 (CH); 39.3 (CH); 31.2 (CH_2); 31.1 (CH_2); 29.3 (CH_2); 22.3 (CH_2); 21.2 (CH_3); 13.8 (CH_3). Isomer **B**: ^1H NMR δ: 4.50–4.39 (m, 1H); 4.28–4.12 (m, 1H); 2.75–2.43 (m, 2H); 1.96–1.81 (m, 1H); 1.75 (d, $J=6.9$ Hz, 3H); 1.53–1.27 (m, 6H); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 178.0 (C); 80.2 (CH); 49.0 (CH); 40.4 (CH); 31.8 (CH_2); 29.6 (CH_2); 29.1 (CH_2); 22.1 (CH_2); 21.0 (CH_3); 13.6 (CH_3).

3.3.16. 2-Butyl-4-(1-bromo-3-methylbutyl)-4-butanolide (29). Colorless oil, 66%, obtained as a 1:1 mixture of *cis*- and *trans*-isomers. Anal. Calcd for $C_{13}H_{23}BrO_2$: C 53.61, H 7.96; found: C 53.32, H 7.84; IR_{film}: 2958, 2868, 1773, 1462, 1362, 1267, 1173; HRMS (EI): M^+, found 324.0736; $C_{16}H_{21}O_2Br$ requires 324.0725. Isomer **A**: ^1H NMR δ: 4.61 (ddd, $J_1=8.7$ Hz, $J_2=4.7$ Hz, $J_3=3.2$ Hz, 1H); 4.12 (dt, $J_1=6.8$ Hz, $J_2=3.2$ Hz, 1H); 2.89–2.73 (m, 1H); 2.38 (ddd, $J_1=13.0$ Hz, $J_2=10.0$ Hz, $J_3=4.6$ Hz, 1H); 2.17–2.06 (m, 1H); 2.02–1.81 (m, 3H); 1.63–1.32 (m, 6H); 0.98–0.88 (m, 9H); ^{13}C NMR δ: 179.2 (C); 79.3 (CH); 56.6 (CH); 43.0 (CH_2); 39.3 (CH); 31.5 (CH_2); 31.3 (CH_2); 29.3 (CH_2); 25.9 (CH); 23.0 (CH_3); 22.4 (CH_2); 20.8 (CH_3); 13.8 (CH_3). Isomer **B**: ^1H NMR δ: 4.47 (ddd, $J_1=10.0$ Hz, $J_2=6.0$ Hz, $J_3=4.0$ Hz, 1H); 4.12 (dt, $J_1=10.4$ Hz, $J_2=3.8$ Hz, 1H); 2.74–2.41 (m, 2H); 2.02–1.78 (m, 4H); 1.63–1.34 (m, 6H); 0.99–0.89 (m, 9H); ^{13}C NMR δ: 178.0 (C); 79.4 (CH); 54.4 (CH); 42.6 (CH_2); 40.4 (CH); 32.1 (CH_2); 29.8 (CH_2); 29.5 (CH_2); 25.9 (CH); 23.1 (CH_3); 22.4 (CH_2); 20.7 (CH_3); 13.8 (CH_3).

3.3.17. 2-Butyl-4-(1-bromo-2-cyclohexylethyl)-4-butanolide (30). Colorless oil, 54%, obtained as a 1:1 mixture of diastereoisomers. IR_{film}: 2923, 2858, 1751, 1449, 1351, 1272, 1181, 1117, 1064, 1032. Isomer **A**: ^1H NMR δ: 4.53–4.41 (m, 1H); 4.16 (ddd, $J_1=10.7$ Hz, $J_2=J_3=3.6$ Hz, 1H); 2.73–2.29 (m, 3H); 2.00–1.50 (m, 12H); 1.47–1.12 (m, 7H); 0.96–0.89 (m, 3H); ^{13}C NMR δ: 178.0 (C); 79.5 (CH); 57.7 (CH); 46.6 (CH_2); 40.5 (CH); 35.1 (CH); 33.7 (CH_2); 32.1 (CH_2); 31.6 (CH_2); 29.8 (CH_2); 29.5 (CH_2); 26.4 (CH_2); 26.1 (CH_2); 25.8 (CH_2); 22.4 (CH_2); 13.8 (CH_3). Isomer **B**: mp 82 °C. Anal. calcd. for $C_{16}H_{27}BrO_2$: C 58.01, H 8.21; found: C 57.65, H 8.18; ^1H NMR δ: 4.60 (ddd, $J_1=8.6$ Hz, $J_2=4.7$ Hz, $J_3=3.1$ Hz, 1H); 4.21–4.11 (m, 1H); 2.88–2.73 (m, 1H); 2.39 (ddd, $J_1=13.3$ Hz, $J_2=10.1$ Hz, $J_3=4.6$ Hz, 1H); 2.09 (ddd, $J_1=13.3$ Hz, $J_2=8.6$ Hz, $J_3=7.4$ Hz, 1H); 1.95–1.51 (m, 10H), 1.45–1.11 (m, 9H); 0.95–0.85 (m, 3H); ^{13}C NMR δ: 179.1 (C); 79.3 (CH); 56.0 (CH); 41.7 (CH_2); 39.3 (CH); 35.2 (CH); 33.6 (CH_2); 31.7 (CH_2); 31.5 (CH_2); 31.3 (CH_2); 29.3 (CH_2); 26.4 (CH_2); 26.1 (CH_2); 25.9 (CH_2); 22.5 (CH_2); 13.8 (CH_3).

3.3.18. 2-(2-Phenylmethyl)-4-(1-bromo-3-methylbutyl)-4-butanolide (31). Colorless oil, 21%, single isomer. IR_{film}: 3032, 2958, 2874, 1774, 1603, 1496, 1459, 1362, 1172, 1038; ^1H NMR δ: 7.37–7.10 (m, 5H); 4.39 (ddd, $J_1=8.2$ Hz, $J_2=5.2$ Hz, $J_3=3.2$ Hz, 1H); 4.03 (ddd, $J_1=J_2=7.0$ Hz, $J_3=3.2$ Hz, 1H); 3.26–3.10 (m, 2H); 2.82 (dd, $J_1=15.0$ Hz, $J_2=10.0$ Hz, 1H); 2.33–2.07 (m, 2H); 1.97–1.77 (m, 2H); 1.58–1.44 (m, 1H); 0.94 (d, $J=6.6$ Hz, 3H); 0.87 (d, $J=6.6$ Hz, 3H); ^{13}C NMR δ: 178.4 (C); 139.0 (C); 129.0 (CH); 128.8 (CH); 126.9 (CH); 79.3 (CH); 56.6 (CH); 43.1

(CH_2); 41.0 (CH); 37.0 (CH_2); 30.6 (CH_2); 25.9 (CH); 22.9 (CH_3); 20.8 (CH_3).

3.3.19. 4-(1-Bromo-2-cyclohexylethyl)-2-isopropyl-4-butanolide (32). Colorless oil, 69%, obtained as a 1:1 mixture of diastereoisomers, which were separated by dry-flash chromatography. IR_{film}: 2926, 2846, 1758, 1448, 1377, 1238, 1160, 1039. Isomer **A**: ^1H NMR δ: 4.55 (ddd, $J_1=7.6$ Hz, $J_2=6.0$ Hz, $J_3=3.0$ Hz, 1H); 4.16 (ddd, $J_1=J_2=6.6$ Hz, $J_3=3.5$ Hz, 1H); 2.77 (ddd, $J_1=J_2=9.0$ Hz, $J_3=5.0$ Hz, 1H); 2.29–2.17 (m, 3H); 1.81–1.51 (m, 8H); 1.35–1.12 (m, 3H); 1.02 (d, $J=6.9$ Hz, 3H); 0.95 (d, $J=6.9$ Hz, 3H); 0.91–0.75 (m, 2H); ^{13}C NMR δ: 178.3 (C); 79.4 (CH); 56.5 (CH); 45.4 (CH); 41.7 (CH_2); 35.2 (CH); 33.6 (CH_2); 31.7 (CH_2); 29.2 (CH); 27.4 (CH_2); 26.3 (CH_2); 26.0 (CH_2); 25.8 (CH_2); 20.2 (CH_3); 18.1 (CH_3); HRMS (EI): M^+, found 316.1043; $C_{15}H_{25}BrO_2$ requires 316.1038. Isomer **B**: ^1H NMR δ: 4.44 (ddd, $J_1=10.1$ Hz, $J_2=6.1$ Hz, $J_3=4.0$ Hz, 1H); 4.18 (ddd, $J_1=J_2=7.4$ Hz, $J_3=3.5$ Hz, 1H); 2.64 (ddd, $J_1=12.2$ Hz, $J_2=9.0$ Hz, $J_3=5.0$ Hz, 1H); 2.40–2.15 (m, 2H); 2.10–1.53 (m, 9H); 1.42–1.11 (m, 3H); 1.05 (d, $J=7.0$ Hz, 3H); 0.95 (d, $J=7.0$ Hz, 3H); 0.89–0.72 (m, 2H); ^{13}C NMR: 176.9 (C); 79.1 (CH); 53.7 (CH); 46.6 (CH); 41.4 (CH_2); 35.1 (CH); 33.7 (CH_2); 31.6 (CH_2); 27.7 (CH_2); 27.6 (CH); 26.4 (CH_2); 26.1 (CH_2); 25.8 (CH_2); 20.5 (CH_3); 18.3 (CH_3); HRMS (EI): M^+, found 316.1053; $C_{15}H_{25}BrO_2$ requires 316.1038.

3.3.20. 3-Butylhexahydrobenzofuran-2-one (33). Colorless oil, 48%, obtained as a 1:1 mixture of stereoisomers which were separated by preparative gas chromatography. HRMS (EI): M^+, found 196.1463; $C_{12}H_{20}O_2$ requires 196.1482; MS (EI) *m/z*: 196 (M^+; 8%); 140 (100%); 95 (8%); 82 (6%); 67 (9%); IR_{film}: 2937, 2864, 1777, 1457, 1389, 1206, 1175, 1124, 1080, 1024. Isomer **A**: ^1H NMR δ: 3.70 (ddd, $J_1=J_2=10.8$ Hz, $J_3=3.8$ Hz, 1H); 2.30–2.15 (m, 2H); 2.10–1.70 (m, 4H); 1.65–1.20 (m, 10H); 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 178.6; 82.6; 49.9; 46.2; 30.1; 29.2; 28.2; 28.1; 25.3; 24.0; 22.8; 13.9. Isomer **B**: ^1H NMR δ: 3.97 (ddd, $J_1=J_2=10.8$ Hz, $J_3=4.0$ Hz, 1H); 2.50–2.40 (m, 1H); 2.30–2.10 (m, 1H); 2.00–1.80 (m, 4H); 1.60–1.20 (m, 10H) 0.91 (t, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 175.0; 82.0; 47.7; 44.0; 30.7; 29.6; 25.4; 25.0; 24.7; 23.9; 22.6; 13.9.

3.3.21. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34) and 2-(2-phenylethyl)-3-methyl-4-butanolide (35). Colorless oil, 30% (41% yield calculated on the basis of the recovered starting compound), obtained as a mixture of regioisomers in a 7:3 ratio (regioisomer **34** as 1:1 mixture of diastereoisomers; regioisomer **35** as 3:1 mixture of diastereoisomers). Anal. Calcd for $C_{13}H_{16}O_2$: C 76.44, H, 7.90; found: C 76.26; H 8.09; IR_{film}: 3028, 2975, 2932, 1769, 1603, 1496, 1454, 1185; ^{1}HNMR δ: 7.47–7.16 (m, 5H); 4.67 (ddq, $J_1=12.7$ Hz, $J_2=J_3=6.3$ Hz, 1H, **34**, isomer **A**); 4.45 (ddq, $J_1=11$ Hz, $J_2=6.2$ Hz, $J_3=5.5$ Hz, 1H, **34**, isomer **B**); 4.36 (dd, $J_1=8.8$ Hz, $J_2=7.0$ Hz, 1H, **35**, isomer **A**); 3.69 (dd, $J_1=J_2=6.4$ Hz, 1H, **35**, isomer **B**); 2.85–2.40 (m, 4H); 2.30–1.90 (m, 2H); 1.85–1.58 (m, 1H); 1.41 (d, $J=6.3$ Hz, 3H, **34**, isomer **A**); 1.35 (d, $J=6.2$ Hz, 3H, **34**, isomer **B**); 1.13 (d, $J=6.4$ Hz, 3H, **35**, isomer **B**); 1.04 (d, $J=7.0$ Hz, 3H, **35**, isomer **A**); ^{13}C NMR δ: 179.1; 178.8; 140.7; 128.5; 128.4; 126.1; 75.0; 74.8; 73.0; 72.4; 45.8; 40.5; 38.3; 37.0; 36.3; 35.0; 33.2; 33.1; 32.6; 32.3; 31.8; 30.5; 26.5; 21.1; 20.8; 16.4; 13.4.

3.3.22. 3-Methyl-2-oxaspiro[4.5]decane-1-one (36) and 4-methyl-2-oxaspiro[4.5]decane-1-one (37). Mixture of regioisomers in 2:1 ratio, obtained as a colorless oil in 35% yield. The regioisomers were separated by preparative gas chromatography. Physical data for 3-methyl-2-oxaspiro(4.5(decane-1-one (**36**):[23] White crystals, mp 70 °C; IR: 2930, 2859, 1756, 1452, 1391, 1212, 1135, 1086, 1015; ^1H NMR spectra identical to that reported in the literature;[23] ^{13}C NMR δ: 182.0 (C); 73.6 (CH); 45.3 (C); 41.1 (CH_2); 34.3 (CH_2); 31.5 (CH_2); 25.3 (CH_2); 22.1 (CH_2); 22.0 (CH_2); 21.4 (CH_3). Physical data for 4-methyl-2-oxaspiro (4.5(decane-1-one (**37**):[24] Colorless oil; IR and ^1H NMR spectra identical to that reported in the literature;[24] ^{13}C NMR spectra for this compound have not been reported in the literature;^{13}C NMR δ: 181.2 (C); 71.5 (CH_2); 45.1 (C); 38.3 (CH); 31.9 (CH_2); 27.2 (CH_2); 25.4 (CH_2); 21.9 (CH_2); 21.6 (CH_2); 13.5 (CH_3).

3.3.23. 2,2,4-Trimethyl-4-butanolide (38) and 2,2,3-trimethyl-4-butanolide (39). Mixture of regioisomers in 3:2 ratio, obtained as a colorless oil in 38% yield. The regioisomers were separated by preparative gas chromatography. Physical data for 2,2,4-trimethyl-4-butanolide (**38**):[25] White crystals, mp 53 °C; IR: 2975, 2938, 2878, 1766, 1459, 1387, 1186, 1112; ^1H NMR spectra identical to that reported in the literature;[25] ^{13}C NMR δ: 182.1; 73.3; 45.2; 40.8; 25.0; 24.3; 21.1. Physical data for 2,2,3-trimethyl-4-butanolide (**39**):[26] Colorless oil; Spectroscopic data for this compound have not been reported in the literature;[26]IR_{film}: 2971, 2923, 1775, 1462, 1393, 1220, 1109; ^1H NMR δ: 4.37 (dd $J_1=9.0$ Hz, $J_2=7.5$ Hz, 1H); 3.80 (dd, $J_1=J_2=9.0$ Hz, 1H); 2.33 (ddq, $J_1=9.5$ Hz, $J_2=J_3=7.0$ Hz, 1H); 1.25 (s, 3H); 1.09 (s, 3H); 1.05 (d, $J=7.0$ Hz, 3H); ^{13}C NMR δ: 182.6; 71.1; 41.4; 40.6; 23.2; 17.9; 11.1.

3.3.24. 2,2-Dimethyl-3-phenyl-4-butanolide (40). Colorless oil, 15% yield. When the reaction was performed by substituting $BF_3\cdot Et_2O$ for $TiCl_4$, the title compound was isolated in 32% yield. Spectroscopic data for this compound have not been reported in the literature.[27] IR_{film}: 3032, 2977, 2915, 2876, 1774, 1595, 1492, 1457, 1393, 1207, 1108, 1029; ^1H NMR δ: 7.40–7.15 (m, 5H); 4.56 (dd, $J_1=J_2=8.0$ Hz, 1H); 4.50 (dd, $J_1=J_2=8.0$ Hz, 1H); 3.42 (dd, $J_1=J_2=8.0$ Hz, 1H); 1.35 (s, 3H); 0.90 (s, 3H); ^{13}C NMR δ: 181.5 (C); 136.0 (C); 128.7 (CH); 128.0 (CH); 127.4(CH); 68.6 (CH_2); 52.1 (CH); 24.1 (CH_3); 19.6 (CH_3).

3.4. General procedure for the reduction of 4-(1-haloalkyl)-4-butanolides with tributyltin hydride

A solution of the corresponding 4-(1-haloalkyl)-4-butanolide (1 mmol), tributyltin hydride (1.5 mmol) and a catalytic amount of azobis(isobutyronitrile) in benzene (5 mL) was heated to reflux, with stirring, under an argon atmosphere. The course of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure, dissolved in diethyl ether (20 mL), a saturated aqueous solution of sodium fluoride (10 mL) was added and the mixture was vigorously stirred for 24 h at rt. The organic layer was separated, dried over anh. Na_2SO_4,

filtered, concentrated under reduced pressure and the product was purified by dry-flash chromatography.

3.4.1. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34). Colorless oil, 73%, obtained from **14** as a 1:1 mixture of diastereoisomers. Spectroscopic data for this compound have not been reported in the literature.[28] IR_{film}: 3059, 3028, 2978, 2931, 1769, 1604, 1453, 1350, 1186, 1113; ^1H NMR δ: 7.32–7.13 (m, 5H); 4.63 (ddq, $J_1=12.7$ Hz, $J_2=J_3=6.3$ Hz, 1H, isomer **A**); 4.41 (ddq, $J_1=11.0$ Hz, $J_2=6.2$ Hz, $J_3=5.5$ Hz, 1H isomer **B**); 2.75–2.36 (m, 4H); 2.31–1.90 (m, 2H); 1.83–1.61 (m, 1H); 1.38 (d, $J=6.2$ Hz, 3H isomer **A**); 1.35 (d, $J=6.3$ Hz, 3H, isomer **B**); ^{13}C NMR δ: 178.9 (C); 178.6 (C); 140.6 (C); 128.2 (CH); 128.1 (CH); 125.9 (CH); 74.8 (CH); 74.7 (CH); 40.3 (CH); 38.2 (CH); 36.8 (CH_2); 34.7 (CH_2); 33.1 (CH_2); 33.0 (CH_2); 32.1 (CH_2); 31.7 (CH_2); 20.9 (CH_3); 20.6 (CH_3).

3.4.2. 2-Butyl-4-methyl-4-butanolide (41). Colorless oil, 74%, obtained from **15** as a 1:1 mixture of diastereoisomers. Spectroscopic data for this compound have not been reported in the literature.[28] IR_{film}: 2961, 2933, 2865, 1772, 1460, 1346, 1179. ^1H NMR δ: 4.67 (ddq, $J_1=J_2=J_3=6.4$ Hz, 1H, isomer **A**); 4.49 (ddq, $J_1=11.0$ Hz, $J_2=J_3=6.0$ Hz, 1H isomer **B**); 2.70–2.43 (m, 1.5H); 2.11–1.76 (m, 2H); 1.56–1.27 (m, 5.5H); 1.42 (d, $J=6.0$ Hz, 3H isomer **B**); 1.37 (d, $J=6.4$ Hz, 3H, isomer **A**); 0.95–0.88 (m, 3H); ^{13}C NMR δ: 179.3 (C); 179.0 (C); 74.9 (CH); 74.8 (CH); 41.2 (CH); 39.1 (CH); 36.8 (CH_2); 34.8 (CH_2); 30.2 (CH_2); 29.8 (CH_2); 29.3 (CH_2); 22.2 (CH_2); 21.0 (CH_3); 20.7 (CH_3); 13.6 (CH_3).

3.4.3. 3-Methyl-2-oxa-spiro[4.5]decane-1-one (36). White crystals, mp 70 °C, 78%. The spectra of **36** are given in Section 3.3.22.

3.4.4. 2-(2-Phenylmethyl)-4-methyl-4-butanolide (42). From **21A**. Colorless oil, 80%. Spectroscopic data identical to that reported in the literature.[20,29]

3.4.5. 2-Butyl-4-ethyl-4-butanolide (43). From **28A**. Colorless oil, 82%. Spectroscopic data for this compound have not been reported in the literature.[30] IR_{film}: 3050, 2960, 2928, 1770, 1461, 1357, 1180. ^1H NMR δ: 4.50–4.21 (m, 1H); 2.67–2.37 (m, 1H); 2.12–2.01 (m, 2H); 1.93–1.27 (m, 8H); 1.04–0.89 (m, 6H); ^{13}C NMR δ: 178.0 (C); 80.0 (CH); 39.3 (CH); 33.0 (CH_2); 30.6 (CH_2); 29.5 (CH_2); 28.5 (CH_2); 22.4 (CH_2); 13.9 (CH_3); 9.6 (CH_3).

3.5. Reduction of 4-bromoalkyl-4-butanolides with hypophosphorous acid. 2-(2-Phenylethyl)-4-methyl-4-butanolide (34)

To a refluxing solution of **14** (150 mg; 0.53 mmol), hypophosphorous acid (289 μL of the 50% aqueous solution; 2.65 mmol) and triethylamine (295 mg; 2.92 mmol) in dioxane (4.8 mL) was added AIBN (113 mg; 0.7 mmol) in four portions, at 30 min intervals. Upon completion, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water. The organic extract was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. Purification by dry-flash chromatography afforded 82 mg (76%) of the title compound **34**, whose physical data are given in Section 3.4.1.

3.6. Allylation of 4-bromomethyl-2-butyl-4-butanolide (16) with allyl tributyltin. 4-(3-Butenyl)-2-butyl-4-butanolide (44)

A solution of 4-bromomethyl-2-butyl-4-butanolide (116 mg; 0.49 mmol), allyl tributyltin (326 mg; 0.99 mmol) and azobis(isobutyronitrile) (catalytic amount) in benzene (1 mL) was heated to reflux, with stirring, under an argon atmosphere. The reaction was monitored by TLC. Work-up of the reaction mixture as described in Section 3.4., followed by purification by dry-flash chromatography, afforded 80 mg (83%) of the title compound **44**, as a colorless oil. Anal. calcd. for $C_{12}H_{20}O_2$: C 73.43, H 10.27; found: C 73.63, H 10.61; IR_{film}: 2933, 2866, 1771, 1458, 1357, 1287, 1178; ^1H NMR δ: 5.81 (ddt, $J_1=17.0$ Hz, $J_2=10.3$ Hz, $J_3=6.6$ Hz, 1H); 5.12–4.99 (m, 2H); 4.51 (ddt, $J_1=7.9$ Hz, $J_2=J_3=6.2$ Hz, 1H); 2.67–2.52 (m, 1H); 2.31–1.98 (m, 4H); 1.92–1.55 (m, 4H); 1.49–1.27 (m, 6H); 0.92 (t, $J=7.6$ Hz, 3H); ^{13}C NMR δ: 172.4 (C); 137.1 (CH); 115.6 (CH_2); 78.0 (CH); 39.2 (CH); 34.8 (CH_2); 33.4 (CH_2); 30.5 (CH_2); 29.5 (CH_2); 29.4 (CH_2); 22.4 (CH_2); 13.9 (CH_3).

3.7. Tributyltin hydride mediated free radical addition of 4-bromomethyl-2-butyl-4-butanolide (28) to acrylonitrile. 4-(4-Cyano-2-butyl)-2-butyl-4-butanolide (45)

To a refluxing solution of 4-bromomethyl-2-butyl-4-butanolide **28A** (120 mg; 0.48 mmol), acrylonitrile (510 mg; 9.6 mmol) and azobis(isobutyronitrile) (catalytic amount) in benzene (24 mL), tributyltin hydride (9 mL of 0.07 M solution in benzene; 0.63 mmol) was added in 4 portions, in 30 min intervals, with stirring, under an argon atmosphere. The reaction was monitored by TLC. Work-up of the reaction mixture as described in Section 3.4, followed by purification by dry-flash chromatography, afforded 82 mg (76%) of the title compound **45**, as a colorless oil (obtained as 1:1 mixture of diastereoisomers). IR_{film}: 2961, 2935, 2870, 2247, 1769, 1463, 1183, 1001; ^1H NMR: 4.46–4.36 (m, 1H, isomer **A**); 4.22 (dd, $J_1=15.3$ Hz, $J_2=6.9$ Hz, 1H, isomer **B**); 2.70–2.55 (m, 1H); 2.53–2.36 (m, 2H); 2.24–1.97 (m, 3H); 1.92–1.75 (m, 3H); 1.67–1.27 (m, 5H); 1.00 (t, $J=6.3$ Hz, 3H); 0.95–0.88 (m, 3H); ^{13}C NMR: 179.2 (C); 179.0 (C); 119.4 (C); 119.2 (C); 82.0 (CH); 80.8 (CH); 39.5 (CH); 39.4 (CH); 37.3 (CH); 36.6 (CH); 31.6 (CH_2); 30.8 (CH_2); 30.7 (CH_2); 30.6 (CH_2); 29.3 (CH_2); 28.6 (CH_2); 28.0 (CH_2); 22.3 (CH_2); 14.9 (CH_2); 14.8 (CH_2); 14.4 (CH_3); 13.7 (CH_3); 13.2 (CH_3); HRMS (EI): M^+, found 223.1564; $C_{13}H_{21}NO_2$ requires 223.1572.

Acknowledgements

We dedicate this work to Professor Živorad Čeković, with the sentiments of gratitude and respect, on the occasion of his 70th birthday. This work was financially supported by the Ministry of science, technology and development (Project N° 1719). Part of the research was performed at the Free University of Berlin. One of us (V. M.) is grateful

to Professor Hans-Ulrich Reissig for helpful discussions and his interest in this work, and to Mrs. Ivana Veljkovic for recording HRM spectra of several samples. The authors gratefully acknowledge the support of Professor Ernst-Walter Knapp and the D. A. A. D. foundation.

References and notes

1. Reviews on the reactions of epoxides with carbon nucleophiles: (a) with non-stabilized carbanions: Klunder, J. M.; Posner, G. H.; Trost, B. M., Fleming, I., Eds.; *Comprehensive Organic Synthesis*; Vol. 3. Pergamon: Oxford; 1991, p 223–226. (b) With vinyl carbanions: Knight, D. W.; Trost, B. M., Fleming, I., Eds.; *Comprehensive Organic Synthesis*; Vol. 3. Pergamon: Oxford; 1991, p 262–266. (c) With alkynyl carbanions: Garratt, P. J.; Trost, B. M., Fleming, I., Eds.; *Comprehensive Organic Synthesis*; Vol. 3. Pergamon: Oxford; 1991, p 277–280.
2. Posner, G. H.; Maxwell, J. P.; Kahraman, M. *J. Org. Chem.* **2003**, *68*, 3049–3054.
3. Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M. *J. Org. Chem.* **1996**, *61*, 9548–9552.
4. Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, 7583–7586.
5. Larcheveque, M.; Valette, G.; Cuvigny, T.; Normant, H. *Synthesis* **1975**, 256–259.
6. Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362–1383.
7. (a) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907. For examples of synthetic applications of this reaction, see: (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028–3030. (c) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Org. Chem.* **1979**, *44*, 3092–3093. Phenylthioacetic acid dianion reacts with epoxides under mild conditions: (d) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn* **1977**, *50*, 242–247. (e) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991. (f) Caille, J.-C.; Miel, H.; Armstrong, P.; McKervey, M. A. *Tetrahedron Lett.* **2004**, *45*, 863–865.
8. (a) Danishefsky, S.; Kitahara, T.; Tsai, M.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1669–1671. (b) Sturm, T.-J.; Marolewski, A. E.; Rezenka, D. S.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039–2040. In the presence of alanes chromium enolates also react with epoxides: (c) Hojo, M.; Sakata, K.; Maimaiti, X.; Ueno, J.; Nishikori, H.; Hosomi, A. *Chem. Lett.* **2002**, 142–143.
9. (a) Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1163. (b) Gorzynski-Smith, J. *Synthesis* **1984**, 629–656.
10. Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456–2457.
11. (a) Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *41*, 763–766. Under the similar reaction conditions bis(trimethylsilyloxy)-butadienes, derived from 1,3-dicarbonyl compounds, yield 2-alkylidenetetrahydrofurans: (b) Langer, P.; Eckardt, T. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4343–4346.
12. Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583–591.
13. (a) Preliminary communication: Maslak, V.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2002**, *43*, 5411–5413. (b) For a single example of $LiClO_4$ promoted reaction of pivalic acid derived silyl ketene acetal with epoxide, see: Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1993**, *126*, 1905–1912.
14. All silyl ketene acetals in this work were prepared according to: Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59–71.
15. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838–6842.
16. Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991**, 281–284.
17. Slougui, N.; Rousseau, G.; Conia, J.-M. *Synthesis* **1982**, 58–60.
18. Rousseau, G.; Slougui, B. *J. Am. Chem. Soc.* **1984**, *106*, 7283–7285 no spectroscopic data have been reported for this compound.
19. Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645.
20. Jedlinski, Z.; Kowalczuk, M.; Kurock, P.; Grzegorzek, M.; Ermel, J. *J. Org. Chem.* **1987**, *52*, 4601–4602.
21. Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696–4705.
22. Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 6843–6846.
23. Larcheveque, M.; Debal, A. *Synth. Commun.* **1980**, *10*, 49–57.
24. Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 3908–3918.
25. Sucrow, W.; Slopianka, M.; Winkler, D. *Chem. Ber.* **1972**, *105*, 1621–1633.
26. Jaime, C.; Segura, C.; Dinares, I.; Font, J. *J. Org. Chem.* **1993**, *58*, 154–158.
27. Scheeren, J. W.; Dahmen, F. J. M.; Bakker, C. G. *Tetrahedron Lett.* **1979**, *31*, 2925–2928.
28. Wang, J.-X.; Alper, H. *J. Org. Chem.* **1986**, *51*, 273–275.
29. Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428–2440.
30. Fujita, T.; Watanabe, S.; Suga, K. *Aust. J. Chem.* **1974**, *27*, 2205–2208.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 8967–8973

Simple and efficient per-*O*-acetylation of carbohydrates by lithium perchlorate catalyst

Kuo-Cheng Lu,[a] Shu-Yi Hsieh,[a,b] Laxmikant N. Patkar,[a] Chien-Tien Chen[b] and Chun-Cheng Lin[a,c,*]

[a]*Institute of Chemistry, Academia Sinica, 128, Sec. 2, Yen-Chiu-Yuan Rd, Nankang, Taipei 115, Taiwan*
[b]*Department of Chemistry, National Taiwan Normal University, Taipei 106, Taiwan*
[c]*Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300, Taiwan*

Received 23 March 2004; revised 24 June 2004; accepted 29 June 2004

Available online 21 August 2004

Abstract—Lithium perchlorate is demonstrated to be a highly efficient and convenient catalyst for the per-*O*-acetylation of various saccharides with excellent yields.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Acetylation of alcohols is a basic and widely used transformation in organic chemistry,[1] primarily to synthetically protect hydroxyl groups, and as an aid to structurally elucidate polyhydroxyl containing natural products such as oligosaccharides. In the context of carbohydrate chemistry, fully acetylated monosaccharides are widely used as starting materials to synthesize oligosaccharides and glycoconjugates. Among the reagents available for alcohol acetylation, acetic anhydride or acetyl chloride is frequently used as an acetyl source under basic media[1c,2] or with Lewis base[1,3] or acid catalysts.[1,4] In preparing per-*O*-acetylated saccharides, the most widespread reaction condition is pyridine as solvent with a catalytic amount of 4-dimethylaminopyridine (DMAP).[5] Recently, various reagents have been designed for catalyzing saccharide per-*O*-acetylation, including: sodium acetate,[6] Lewis acids ($ZnCl_2$,[6] $FeCl_3$,[7] $V(O)(OTf)_2$,[8] Cu $(OTf)_2$ and $Sc(OTf)_3$[9]), Bronsted acids ($HClO_4$,[6] H_2SO_4[10]), heterogeneous catalysts (montmorillonite K-10,[11] H-beta zeolite,[12] zirconium sulfophenyl phosphonate[13]), iodine,[14] and ionic liquid.[15] Although the previously mentioned catalysts perform acetylation efficiently, some are incompatible with the sensitive functional groups contained in alcohols. Additionally, most reaction conditions using a significant excess of acetic anhydride result in difficulties in large-scale handling and the disposal of spent catalyst and reagent. Furthermore, acetylation of carbohydrates or its intermediates is challenging despite the impressive array of acetylation catalyst owing to its easy isomerization from pyranose to furanose form, as well as the presence of other sensitive functional groups which may be transformed with the catalyst. Therefore, the search in carbohydrate chemistry for a new mild, efficient and selective peracetylation catalyst that minimizes isomerization and loss of sensitive functional groups is continuing.

2. Results and discussion

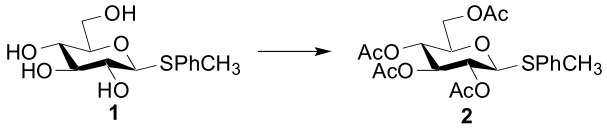
Lithium perchlorate ($LiClO_4$) is well known as a mild and efficient Lewis acid catalyst for various organic reactions.[16,17] Prompted by a recent report of alcohol acetylation using litium perchlorate[4b] as a mild catalyst, we explored $LiClO_4$ for carbohydrate acetylation. The findings of this work are outlined below. Initially, to optimize reaction conditions using lithium perchlorate catalyst, various proportions of catalyst and acetic anhydride and commonly used solvents were tried (Table 1) with **1** as a substrate.

The amount of catalyst used and reaction temperature influence reaction rate. When a large excess of acetic anhydride (20 equiv, 5 equiv of Ac_2O per OH) and 0.4 equiv of lithium perchlorate were used at ambient temperature, acetylation was very slow, whereas when the temperature was raised to 40 °C, peracetylation was completed within 1 h (Table 1, entries 1 and 2). When the amount of catalyst was reduced to 0.1 equiv, the reaction took four days under the same reaction conditions (entry 3).

Keywords: Acetylation; Sialic acid; Lithium perchlorate.
* Corresponding author.; e-mail: cclin@chem.sinica.edu.tw

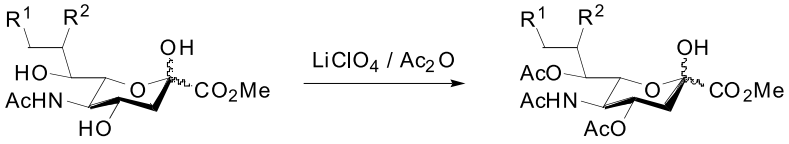
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.138

Table 1. Acetylation of **1** by using $LiClO_4$ as catalyst



Entry	Ac_2O	$LiClO_4$	Temperature (°C)	Solvent	Time (h)
1	20	0.4	rt	—	Slow
2	20	0.4	40	—	1
3	20	0.1	40	—	4 days
4	4.4	0.4	40	—	1
5	4.4	0.4	40	CH_2Cl_2	1
6	4.4	0.4	40	CH_3CN	1
7	—	0.4	40	AcOH	—

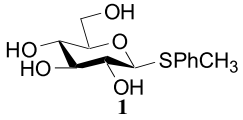
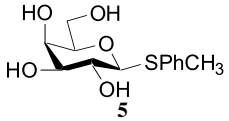
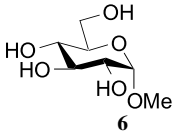
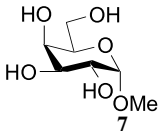
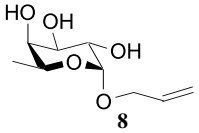
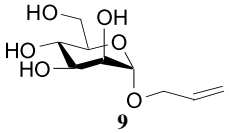
Table 2. Acetylation of sialic acid derivatives catalyzed by $LiClO_4$



Entry	Substrate	R^1	R^2	Time h	Product	β:α	Yield %
1[a]	**3a**	OH	OH	12	**4a**[19b]	1:0	98
2	**3b**[20]	OTBDPS	OH	18	**4b**	10:1	85
3	**3c**	OBz	OH	28	**4c**	5:1	85
4	**3d**[21]	*O*-4-Pentenoyl	OH	22	**4d**	4:1	81
5	**3e**[22]	SAc	OAc	16	**4e**	7:1	90

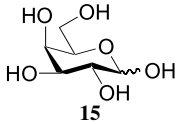
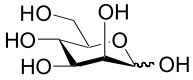
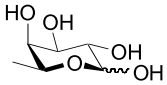
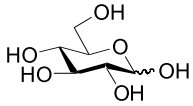
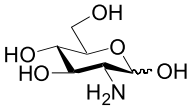
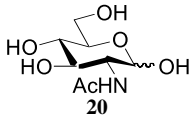
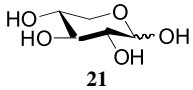
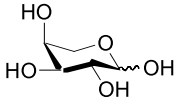
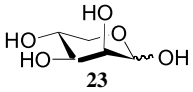
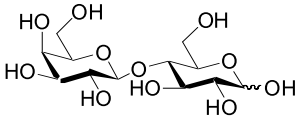
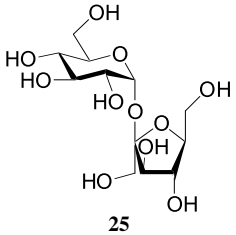
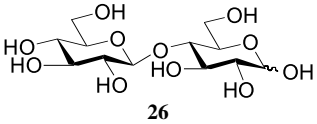
[a] In the presence of CH_2Cl_2 as cosolvent, two days were needed to complete the reaction.
[b] For this compound $R^1=R^2=OAc$.

Table 3. Peracetylation of anomeric protected sugars by using $LiClO_4$

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1**	1	**2**	99
2	 **5**	20	**10**[18]	99
3	 **6**	18	**11**[23]	99
4	 **7**	30	**12**[24]	99
5	 **8**	15	**13**[25]	99
6	 **9**	12	**14**[26]	99

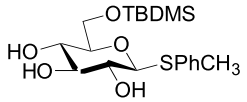
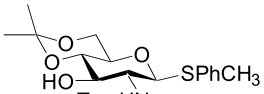
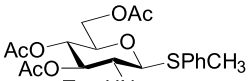
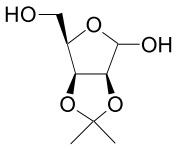
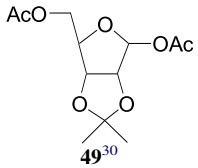
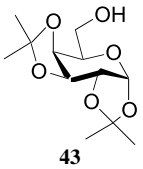
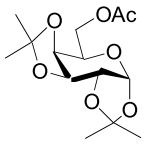
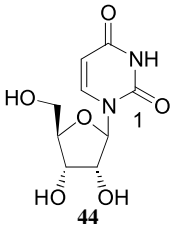
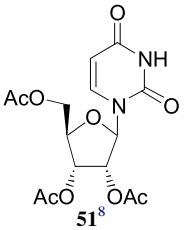
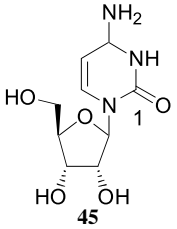
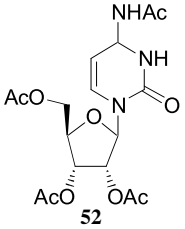
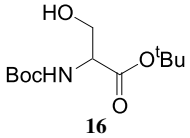
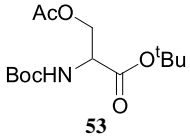
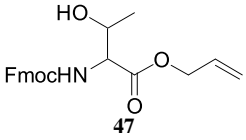
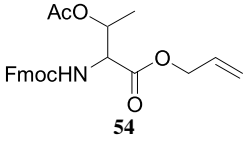
[a] Yield of crude product with purity higher then 97% according to ^1H NMR spectroscopy.

Table 4. Acetylation of sugars by using $LiClO_4$ as catalyst

Entry	Substrate	Time (h)	Product	Total[a] (%)	Pyranose (α/β)/Furanose
1	 **15**	10	**28**[14]	98	45/55
2	 **16**	5	**29**[14]	99	(1.1/1)[b]
3	 **17**	2	**30**[11]	99	50(1/5)[b]/50
4	 **18**	5.5	**31**[14]	99	(1.1/1[b])
5	 **19**	13[c]	**32**[14]	98	—
6	 **20**	13[c]	**32**	98	—
7	 **21**	10	**33**[27]	99	80(1/1.1)[b]/20
8	 **22**	15	**34**[27]	98	63(1/1.4)[b]/37
9	 **23**	9	**35**[27]	99	79(1/4.2)[b]/21
10	 **24**	12	**36**[8]	99	(1/1)[b]
11	 **25**	5	**37**[15]	98	—
12	 **26**	72	**38**[11]	96	—
13	β-Cyclodextrin **27**	50	**39**[28]	93	—

[a] Yield of crude product with purity higher than 97% according to ^1H NMR spectrosopy.
[b] Ratio of α/β.
[c] Reaction temperature is 60 °C.

Table 5. Acetylation of substrates with acid-labile-protecting groups by using $LiClO_4$

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1[b]	 **40**	30	2	91[c]
2[b]	 **41**	30	 **48**[29]	99[c]
3[b]	 **42**	24	 **49**[30]	90
4	 **43**	48	 **50**	96
5	 **44**	10	 **51**[8]	94
6	 **45**	10	 **52**	99
7[b]	 **16**	8	 **53**	90[c]
8	 **47**	2	 **54**	95

[a] Yield of crude product with purity higher than 97% according to ^1H NMR spectroscopy.
[b] CH_2Cl_2 was used as co-solvent.
[c] Yield after silica gel column chromatography.

Using 4.4 equiv of acetic anhydride (1.1 equiv of Ac_2O per OH) as solvent and reagent at 40 °C with 0.4 equiv of catalyst (0.1 equiv of $LiClO_4$ per OH) obtained product **2**[18] in 1 h (entry 4). To increase the solubility of starting material and partial acetylated product and enhance the reaction rate, dichloromethane and acetonitrile were used, but the reaction rate was unchanged (entries 5 and 6). Using acetic acid as both an acetylation reagent and solvent, did not produce any peracetylated product **2** (entry 7). Notably, the use of catalytic amount of LiOAc and $HClO_4$ (0.1 equiv per OH) with 4.4 equiv of acetic acid as solvent, resulted in

a very slow reaction. Catalytic amount of $HClO_4$ combined with acetic anhydride gave good yield of peracetylated product. Although these results indicate the possible role of $HClO_4$ as an active catalyst, it should be noted that the acetylation of compound **3a** (Table 2) catalyzed by $HClO_4$ (0.1 equiv per OH)[19] gave full peracetylated product while with use of $LiClO_4$ only **4a** was obtained. Thus, the peracetylation mechanism by $LiClO_4$ needs to be further investigated. In this report, the optimum reaction conditions for the acetylation were determined to be 1.1 equiv of acetic anhydride with 0.1 equiv of lithium perchlorate for each OH at 40 °C.

The above reaction conditions were then applied to numerous other peracetylations of anomeric center protected monosaccharides, obtaining very high yields, as listed in Tables 2 and 3. Particularly interesting is the acetylation of **3a** (Table 3) to the corresponding product **4a** in which the hydroxyl at C-2 position is not acetylated. Compound **4a** is an important precursor for the synthesis of sialic acid phosphite donor. The preparation of **4a** is usually preformed by acetic anhydride with $HClO_4$. However, high yield is not always reproducible because full acetylation is a serious competing side reaction, especially in large-scale synthesis. Many sialic acid derivatives were peracetylated by the present conditions and gave desired products as shown in Table 2. Thus, our method provides an easy access to prepare sialic acid derivatives with 2-hydroxyl group unprotected.

More examples of the per-*O*-acetylations of free saccharides are listed in Table 4. The anomeric configurations and the ratio between pyranose and furanose were determined based on 400 MHz ^{1}H NMR spectral analyses. Generally, the peracetylation of hexoses with 'galactosyl type' configuration (entries 1 and 3) and pentoses (entries 7–9) produced a mixture of pyranose and furanose. Notably, the long reaction time in entries 12 and 13 may be caused by the low substrate solubility under the reaction conditions. Also, β-cyclodextrin, which contains 21 hydroxyl groups, was peracetylated efficiently under the same conditions. The peracetylation conditions employed here were also applied to the saccharides with acid-labile-protecting groups, as listed in Table 5. Although the TBDMS and terminal acetonide protecting groups were cleaved (Table 5, entries 1 and 2) under $LiClO_4/Ac_2O$ reaction conditions, internal acetonide, Boc, and *t*-butyl protecting groups survived.

3. Conclusion

In summary, this study has demonstrated the utility of lithium perchlorate as a peracetylation catalyst in carbohydrate chemistry. The conditions used are very mild, yields are high, and only simple workup procedures are required. Thus, the method presented here displays potential for large-scale preparation of per-*O*-acetylated intermediates of carbohydrates.

4. Experimental

4.1. General per-*O*-acetylation procedure

A mixture of sugar (1 mmol), Ac_2O (1.1 equiv per OH), and $LiClO_4$ (0.1 equiv per OH) was stirred at 40 °C (oil bath temperature). The reaction progress was followed with TLC. Once the reaction was completed, it was quenched with water and extracted with ethyl acetate. The resulting organic layer was successively washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. Solvent evaporation yielded almost pure per-*O*-acetylated saccharide.

Compounds **2**,[18] **4a**,[19] **10-14**,[18,23–26] **28-39**,[8,11,14,15,27,28] **48**,[29] **49**[30] and **51**[8] have previously been reported and the NMR spectral data are in good agreement with the literature data.

4.1.1. Methyl (5-acetamido-9-*O*-*tert*-butyldiphenylsilyl-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4b). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 (s, 9H), 1.90 (s, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.10–2.12 (m, 1H), 2.12 (s, 3H), 2.58 (dd, 1H, *J*=13.6, 4.8 Hz), 3.70 (s, 3H), 3.70–3.82 (m, 1H), 3.93 (q, 1H, *J*=10.4 Hz), 4.01 (dd, 1H, *J*=2.8, 11.2 Hz), 4.24 (dd, 1H, *J*=2.0, 10.4 Hz), 5.05–5.09 (m, 1H), 5.30–5.37 (m, 1H), 5.48 (dd, 1H, *J*=2.0, 6.0 Hz), 5.61 (d, 1H, *J*=10.4 Hz), 7.36–7.45 (m, 6H), 7.61–7.66 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.18, 20.66, 20.79, 23.11, 26.63, 26.79, 35.69, 49.74, 52.95, 61.74, 67.72, 69.09, 69.45, 72.26, 73, 97.60, 127.55, 127.67, 129.59, 133.31, 135.50, 135.52, 166.30, 168.17, 170.06, 170.12, 170.74. HRMS (EI) Calcd for $C_{34}H_{45}O_{12}NSiNa$ $[M+Na]^+$: 710.2609. Found: 710.2621.

4.1.2. Methyl (5-acetamido-9-*O*-benzoyl-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4c). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90 (s, 3H), 1.99 (s, 3H), 2.01–2.06 (m, 1H), 2.08 (s, 3H), 2.15–2.20 (m, 1H), 2.17 (s, 3H), 3.84 (s, 3H), 4.15 (q, 1H, *J*=10.0 Hz), 4.22–4.29 (m, 1H), 4.30 (dd, 1H, *J*=2.4, 10.8 Hz), 4.85 (dd, 1H, *J*=2.4, 12.8 Hz), 5.19–5.25 (m, 1H), 5.38–5.49 (m, 2H), 6.00 (d, 1H, *J*=10.0 Hz) 7.39–7.49 (m, 2H), 7.52–7.57 (m, 1H), 7.98–8.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.75, 20.80, 23.08, 29.23, 29.66, 36.03, 36.13, 49.48, 53.51, 63.16, 68.30, 69.19, 71.20, 71.68, 94.93, 128.27, 128.44, 132.97, 166.35, 166.09, 170.31, 170.40, 170.88, 171.20. HRMS (EI) Calcd for $C_{25}H_{32}O_{13}N$ $[M+H]^+$: 554.1874. Found: 554.1867.

4.1.3. Methyl (5-acetamido-9-*O*-(4-pentenoyl)-4,7,8-tri-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4d). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.91 (s, 3H), 2.03 (s, 3H), 2.04–2.15 (m, 2H), 2.10 (s, 3H), 2.15 (s, 3H), 2.34–2.49 (m, 4H), 3.74–3.89 (m, 1H), 3.87 (s, 3H), 4.03 (dd, 1H, *J*=7.2, 12.4 Hz), 4.12–4.18 (m, 2H), 4.49 (dd, 1H, *J*=2.4, 12.4 Hz), 4.98–5.13 (m, 2H), 5.21–5.38 (m, 3H), 5.77–5.85 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.99, 23.08, 28.47, 33.17, 36.09, 49.33, 53.38, 62.51, 67.99, 68.26, 70.96, 71.34, 71.44, 94.84, 115.38, 136.61, 166.31, 169.01, 170.23, 170.27, 171.02, 172.88. HRMS (EI) Calcd for $C_{21}H_{27}O_{11}S$ $[M+H]^+$: 487.1196. Found: 487.1194.

4.1.4. Methyl (5-acetamido-9-thioacetyl-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranoside)onate (4e). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.16 (s, 3H), 2.20–2.25 (m, 2H), 2.31 (s, 3H), 2.72 (dd, 1H, J=10.0, 14.4 Hz), 3.73 (dd, 1H, J=2.8, 14.4 Hz), 3.84 (s, 3H), 4.13–4.20 (m, 1H), 4.22 (dd, 1H, J=2.0, 10.0 Hz), 5.01 (ddd, 1H, J=2.8, 4.4, 10.0 Hz), 5.19–5.26 (m, 1H)), 5.34 (dd, 1H, J=2.0, 4.4 Hz), 5.82 (d, 1H, J=10.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.89, 23.13, 29.47, 30.47, 49.73, 53.35, 68.78, 69.40, 71.09, 73.11, 94.94, 169.02, 170.33, 170.44, 170.76, 171.09, 195.94. HRMS (EI) Calcd for $C_{20}H_{30}O_{12}NS$ $[M+H]^+$: 508.2489. Found: 508.1479.

4.1.5. 1,2,3,4-Diisopropylidene-6-acetyl-D-galactopyranose (50). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 2.09 (s, 3H), 4.01–4.04 (m, 1H), 4.19 (dd, 1H, J=7.6, 11.6 Hz), 4.24 (dd, 1H, J=8.0, 2.0 Hz), 4.29 (dd, 1H, J=4.8, 11.6 Hz), 4.25 (dd, 1H, J=5.2, 2.4 Hz), 4.62 (dd, 1H, J=2.4, 8.0 Hz), 5.54 (d, 1H, J=5.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.71, 24.36, 24.82, 24.83, 25.83, 25.85, 63.36, 63.84, 70.32, 70.58, 70.95, 96.17, 108.61, 109.46, 170.79. HRMS (FAB) Calcd for $C_{14}H_{23}O_7$ $[M+H]^+$: 303.1439. Found: 303.1444.

4.1.6. 2,3,5-*O*-Acetyl-*N*-acetyl-cytidine (52). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (s, 3H), 2.05–2.07 (m, 1H), 2.07 (s, 3H), 2.11 (s, 3H), 2.24 (s, 3H), 4.36–4.39 (m, 3H), 5.30 (t, 1H, J=5.6 Hz), 5.44 (dd, 1H, J=3.6, 5.6 Hz), 6.01 (d, 1H, J=3.6 Hz), 7.47 (d, 1H, J=7.6 Hz), 7.91 (d, 1H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.54, 20.89, 24.95, 40.85, 62.72, 69.65, 73.84, 79.87, 89.64, 97.37, 144.24, 155.02, 163.33, 169.56, 169.64, 170.33, 131.37. HRMS (FAB) Calcd for $C_{17}H_{22}O_9N_3$ $[M+H]^+$: 412.1350. Found: 412.1356.

4.1.7. *O*-Acetyl-*N*-carbo-*tert*-butyloxy-serine-*tert*-butyl-ester (53). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46 (s, 9H), 1.46 (s, 9H), 2.05 (s, 3H), 4.28 (dd, 1H, J=4.4, 12.0 Hz), 4.44–4.46 (m, 2H), 5.29 (d, 1H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.62, 27.90, 28.28, 53.42, 64.73, 80.07, 82.70, 155.19, 168.70, 170.45. HRMS (FAB) Calcd for $C_{14}H_{26}O_6N$ $[M+H]^+$: 304.1760. Found: 304.1755.

4.1.8. 2-(9*H*-Fluoren-9-ylmeyhoxycarbonylamino)-3-acetyl-butyric acid allyl ester (54). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (d, 3H, J=6.4 Hz), 2.04 (s, 3H), 4.27 (t, 1H, J=6.8 Hz), 4.47 (d, 2H, J=6.8 Hz), 4.54 (dd, 1H, J=2.6, 9.8 Hz), 4.60–4.70 (m, 2H), 5.28 (dd, 1H, J=1.2, 10.4 Hz), 5.35 (dd, 1H, J=1.2, 16.6 Hz), 5.45–5.52 (m, 2H), 5.86–5.95 (m, 1H), 7.30–7.35 (m, 2H), 7.40–7.44 (m, 2H), 7.62–7.65 (m, 2H), 7.79 (d, 2H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.06, 21.03, 40.97, 42.74, 47.28, 57.78, 66.51, 67.40, 70.48, 119.36, 120.13, 120.14, 125.19, 127.23, 127.89, 129.62, 131.44, 141.44, 143.76, 143.95, 156.66, 169.73, 169.84. HRMS (FAB) Calcd for $C_{24}H_{26}O_6N$ $[M+H]^+$: 424.1766. Found: 424.1760.

Acknowledgements

The authors would like to thank Academia Sinica (AS92IC6), National Taiwan Normal University, and National Science Council of Taiwan (NSC91-3112-P-001-041-Y and 91-2113-M-001-013) for financial support.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 17–245. (b) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994; pp 21–94. (c) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1999; pp 1955–1957.
2. Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358–3359.
3. (a) Verkade, J. G.; Ilankumaran, P. *J. Org. Chem.* **1999**, *64*, 9063–9066. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, J. M. *J. Org. Chem.* **1993**, *58*, 7286–7288.
4. (a) Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896–1897. (b) Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, *10*, 1584–1586. (c) Pansare, S. V.; Malusare, M. G.; Rai, A. N. *Synth. Commun.* **2000**, *30*, 2587–2592. (d) Orita, A.; Nagano, Y.; Nakazawa, K.; Otera, J. *Synlett* **2000**, 599–602. (e) Sabitha, G.; Reddy, B. V. S.; Srividya, R.; Yadav, J. S. *Synth. Commun.* **1999**, *29*, 2311–2315. (f) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743–1744. (g) Orita, A.; Ito, T.; Yasui, Y.; Otera, J. *Synlett* **1999**, 1927–1929. (h) Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263–3266. (i) Damen, E. W. P.; Braamer, L.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 6081–6082. (j) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702–5703. (k) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413–4414.
5. Höfle, G.; Steglich, W.; Vorüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583.
6. Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, 1989; pp 644–651.
7. Dasguta, F.; Singh, P. P.; Srivastava, H. C. *Carbohydr. Res.* **1980**, *80*, 346–349.
8. Chen, C.-T.; Kuo, J.-H.; Li, C.-H.; Barhate, N. B.; Hon, S.-W.; Li, T.-W.; Chao, S.-D.; Liu, C.-C.; Li, Y.-C.; Chang, I.-H.; Lin, J.-S.; Liu, C.-J.; Chou, Y-C. *Org. Lett.* **2001**, *3*, 3729–3732.
9. Lee, J.-C.; Tai, C.-A.; Hung, S.-C. *Tetrahedron Lett.* **2002**, *43*, 851–855.
10. Hyatt, J. A.; Tindall, G. W. *Heterocycles* **1993**, *35*, 227–234.
11. Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215–2218.
12. Bhaskar, P. M.; Loganathan, D. *Synlett* **1999**, 129–131.
13. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Rossi, M. *Synth. Commun.* **2000**, *30*, 1319–1329.
14. Kartha, K. P. R.; Field, R. A. *Tetrahedron* **1997**, *53*, 11753–11766.
15. (a) Murugesan, S.; Karst, N.; Islam, T.; Wiencek, J. M.; Linhardt, R. J. *Synlett* **2003**, 1283–1286. (b) Forsyth, S. A.; MacFarlane, D. R.; Thomson, R. J.; von Itzstein, M. *Chem. Commun.* **2002**, 714–715.
16. Although the decomposition of $LiClO_4$ starts at ca 400 °C, a violent explosion by using $LiClO_4$ in Et_2O under reflux has been reported: Silva, R. A. *Chem. Eng. News* **1992**.

17. Saito, S. *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley: New York, 2000; pp 9–58.
18. Goran, M. *J. Org. Chem.* **1977**, *42*, 913–914.
19. Marra, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *190*, 317–322.
20. Brandstetter, H. H.; Zbiral, E.; Schulz, G. *Liebig Ann. Chem.* **1982**, 1–13.
21. Kiefel, M. J.; Wilson, J. C.; Bennett, S.; Gredley, M.; von Itzstein, M. *Bioorg. Med. Chem.* **2000**, *8*, 657–664.
22. Martin, R.; Witte, K. L.; Wong, C.-H. *Bioorg. Med. Chem.* **1998**, *6*, 1283–1292.
23. Derek, H.; John, H. L. *J. Org. Chem.* **1969**, *34*, 86–92.
24. Vesna, P.; Srdaka, T.; Maja, M. *Cabohydr. Res.* **2002**, *337*, 863–867.
25. Van Seeventer, P. B.; van Dorst, A. L. M.; Siemerink, J. F.; Kamerling, J. P.; Vliegenthart, J. F. G. *Cabohydr. Res.* **1997**, *300*, 369–373.
26. RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759–1769.
27. Durette, P. L.; Horton, D. *J. Org. Chem.* **1971**, *36*, 2658–2669.
28. Takeo, K.; Kuge, T. *Agric. Bio. Chem.* **1970**, *34*, 1416–1419.
29. Lin, C.-C.; Hsu, T.-S.; Lu, K.-C.; Huang, I.-T. *J. Chin. Chem. Soc.* **2000**, *47*, 921–928.
30. Joelle, B.; Jacques, G.; Derek, H. *Cabohydr. Res.* **1991**, *219*, 115–121.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 60 (2004) 8975–8979
Tetrahedron

Briaexcavatolides X–Z, three new briarane-related derivatives from the gorgonian coral *Briareum excavatum*

Ping-Jyun Sung,[a,b] Wan-Ping Hu,[c] Shwu-Li Wu,[a,d] Jui-Hsin Su,[a] Lee-Shing Fang,[b] Jeh-Jeng Wang[c] and Jyh-Horng Sheu[a,*]

[a]*Department of Marine Resources, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC*
[b]*National Museum of Marine Biology and Aquarium, 2 Houwan Road, Checheng, Pingtung 944, Taiwan, ROC*
[c]*Faculty of Biotechnology, Kaohsiung Medical University, Kaohsiung 807, Taiwan, ROC*
[d]*The Center for General Education, National Kaohsiung Marine University, Kaohsiung 811, Taiwan, ROC*

Received 6 May 2004; accepted 21 June 2004

Available online 18 August 2004

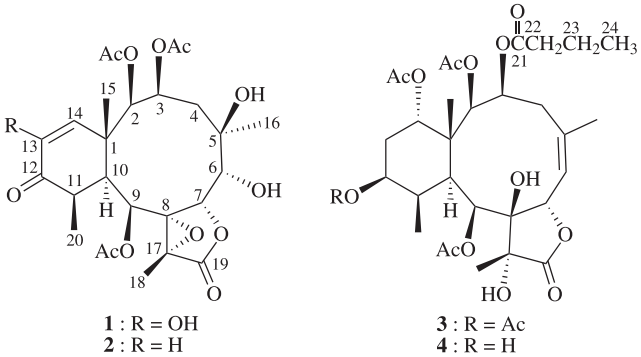
Abstract—Three new polyoxygenated briarane-type diterpenoids, briaexcavatolides X–Z (**1**-**3**), have been isolated from the gorgonian coral *Briareum excavatum*. The structures, including the relative configurations of briaranes **1**-**3**, were elucidated by spectroscopic methods, particularly in 1D and 2D NMR experiments. The configuration of briarane **1** was further supported by molecular mechanics calculations.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Previous investigations on the secondary metabolites of the Indo-Pacific Ocean gorgonian coral *Briareum excavatum* (Nutting) (phylum Cnidaria, class Anthozoa, subclass Octocorallia, order Gorgonacea, family Briareidae)[1] have resulted in the isolation of 52 new diterpenoids with briarane carbon skeleton. These metabolites are excavatolides A–Z,[2–5] briaexcavatolides A–W[6–10] and briantheins A–C.[11] In addition, a number of briaranes have been isolated from various marine organisms, including Gorgonacea, Pennatulacea, Alcyonacea, Stolonifera, Nudibranch and Porifera.[12] Furthermore, there is a growing interest in highly functionalized briarane-related metabolites because of their biological and pharmacological activities.[12] Our continuing research on the chemical constituents of the gorgonian coral *B. excavatum*, collected off the southern Taiwan coast, have yielded three new briarane derivatives, briaexcavatolides X–Z (**1**-**3**) (Fig. 1). The structures of these three minor components were elucidated by spectroscopic and chemical methods and the configuration of a novel briarane **1** was further supported by molecular mechanics calculations.

2. Results and discussion

Briaexcavatolide X (**1**), $[\alpha]_D^{25} = -39°$ (*c* 0.2, $CHCl_3$), had a molecular formula of $C_{26}H_{34}O_{13}$ as derived from EIMS and NMR data. Thus, 10 degrees of unsaturation were determined for **1**. Strong IR absorptions were observed at 3472, 1792, 1748 and 1703 cm^{-1}, suggesting the presence of hydroxy, γ-lactone, ester and conjugated ketone groups in **1**. The conjugated ketone moiety was further confirmed by an UV absorption at 241 nm and the ^{13}C NMR signals at δ 193.1 (s), 150.2 (d) and 130.0 (s) (Table 1). The EI-MS of **1** exhibited peaks at *m/z* 555 $(M+H)^+$, 537 $(M+H-H_2O)^+$, 495 $(M+H-AcOH)^+$, 477 $(M+H-AcOH-H_2O)^+$, 441 $(M+H-AcOH-3H_2O)^+$, 435 $(M+H-2AcOH)^+$, 417 $(M+H-2AcOH-H_2O)$, 399 $(M+H-2AcOH-2H_2O)^+$, 381 $(M+H-2AcOH-3H_2O)^+$, 375 $(M+H-3AcOH)^+$, 357



1 : R = OH
2 : R = H

3 : R = Ac
4 : R = H

Figure 1. The structures of briaranes **1**-**4**.

Keywords: *Briareum excavatum*; Gorgonian; Briarane; Diterpenoid; Briaexcavatolide.
* Corresponding author. Tel.: +886-7-5252000x5030; fax: +886-7-5255020; e-mail: sheu@mail.nsysu.edu.tw

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.06.132

Table 1. The full assignments of proton and carbon signals of compounds **1** and **2**

C/H	**1**		**2**	
	^{1}H	^{13}C	^{1}H	^{13}C
1		45.6 (s)		43.2 (s)
2	5.27 s	80.0 (d)	5.28 s	80.6 (d)
3	5.04 d (5.5)	70.6 (d)	5.08 d (6.5)	70.7 (d)
4α/β	2.14 d (16.5); 2.45 dd (16.5, 5.5)	38.2 (t)	2.11 d (16.5); 2.47 dd (16.5, 6.5)	33.2 (t)
5		59.3 (s)		59.4 (s)
6	3.05 d (8.5)	62.7 (d)	3.06 d (8.5)	62.7 (d)
7	4.42 d (8.5)	76.4 (d)	4.43 d (8.5)	76.4 (d)
8		68.7 (s)		68.8 (s)
9	5.21 d (10.0)	65.8 (d)	5.24 d (9.5)	66.2 (d)
10	2.95 dd (10.0, 4.5)	39.7 (d)	2.93 dd (9.5, 5.0)	41.8 (d)
11	3.16 m	42.6 (d)	2.91 m	40.0 (d)
12		193.1 (s)		200.7 (s)
13		130.0 (s)	6.18 d (10.5)	126.4 (d)
14	6.82 s	150.2 (d)	6.61 d (10.5)	154.5 (d)
15	1.13 s	17.5 (q)	1.08 s	17.5 (q)
16	1.33 s	21.6 (q)	1.34 s	21.0 (q)
17		60.1 (s)		59.8 (s)
18	1.61 s	10.4 (q)	1.61 s	10.4 (q)
19		170.1 (s)		170.3 (s)
20	1.32 d (7.5)	14.5 (q)	1.27 d (7.0)	14.5 (q)
acetate	2.26 s	21.7 (q)	2.03 s	21.5 (q)
		168.8 (s)		169.8 (s)
	2.24 s	21.4 (q)	2.24 s	21.7 (q)
		170.2 (s)		170.3 (s)
	2.05 s	20.9 (q)	2.25 s	21.8 (q)
		170.1 (s)		168.9 (s)

$(M+H-3AcOH-H_2O)^+$ and 339 $(M+H-3AcOH-2H_2O)^+$, indicating the presence of three hydroxy and three acetoxy groups in **1**. Resonances in the ^{13}C NMR of **1** at δ 193.1 (s), 170.2 (s), 170.1 (s), 170.1 (s) and 168.8 (s) supported the presence of a ketone, a γ-lactone and three additional esters. The esters were identified as acetates by the presence of three methyl resonances in the ^{1}H NMR spectrum at δ 2.26 (3H, s), 2.24 (3H, s) and 2.05 (3H, s) (Table 1). On the basis of the above data, briarane **1** was found to be a tetracyclic compound. An epoxide containing a methyl substituent was confirmed from the signals of two quaternary oxygen-bearing carbons at δ 68.7 (C-8) and 60.1 (C-17) and from the proton signal of a methyl singlet resonating at δ 1.61 (3H, s, H_3-18). Moreover, a methyl doublet (δ 1.32, 3H, d, J= 7.5 Hz, H_3-20), two methyl singlets (δ 1.33, 3H, s, H_3-16; 1.13, 3H, s, H_3-15), a trisubstituted olefin proton (δ 6.82, 1H, s, H-14), two aliphatic methine protons (δ 3.16, 1H, m, H-11; 2.95, 1H, dd, J=10.0, 4.5 Hz, H-10), a pair of methylene protons (δ 2.45, 1H, dd, J=16.5, 5.5 Hz, H-4β; 2.14, 1H, d, J=16.5 Hz, H-4α) and five oxygenated methine protons (δ 5.27, 1H, s, H-2; 5.21, 1H, d, J=10.0 Hz, H-9; 5.04, 1H, d, J=5.5 Hz, H-3; 4.42, 1H, d, J=8.5 Hz, H-7; 3.05, 1H, d, J=8.5 Hz, H-6), were observed in the ^{1}H NMR spectrum of **1**.

The gross structure of briarane **1** was further established by the 2D NMR studies, particularly in ^{1}H–^{1}H COSY, HMQC and HMBC experiments (Fig. 2). To establish the proton relationships of **1**, the ^{1}H–^{1}H COSY spectrum was used to reveal the connectivity of H-2/H-3; H-3/H-4α/β; H-6/H-7; H-9/H-10; H-10/H-11; and H-11/H_3-20. These data, together with the ^{1}H–^{13}C long-range correlations observed in the HMBC experiment, established the carbon skeleton of **1**. The methyl groups attached at C-5 and C-11 were confirmed by the HMBC correlations between H_3-16/, C-4, C-5, C-6 and H_3-20/C-10, C-11, C-12, respectively. The C-15 methyl group was positioned at C-1 from the HMBC correlations between H_3-15/C-1, C-2, C-10 and C-14. Furthermore, the acetoxy groups positioned at C-2, C-3 and C-9 were confirmed from the HMBC correlations between δ 5.27 (H-2), 5.04 (H-3), 5.21 (H-9) and the ester carbonyl carbons appeared at δ 170.1 (s), 170.2 (s), 168.8 (s), respectively. In addition, the proton of the hydroxy-bearing methine showed the signal at δ 3.05 (1H, d, J= 8.5 Hz) was assigned to H-6. The 5-hydroxy group was confirmed from the signal of a quaternary oxygen-bearing carbon at δ 59.3 (s) and from the chemical shift of the tertiary methyl H_3-16 (δ 1.33, 3H, s). Thus, the remaining hydroxy groups had to be positioned at C-13, an oxygen-bearing olefinic quaternary carbon resonating at δ 130.0. The latter was further confirmed from the HMBC correlations observed between H-11/C-13 and H-14/C-13. These data, together with the HMBC correlations between H_3-18/C-8, C-17 and C-19, unambiguously established the molecular framework of **1**.

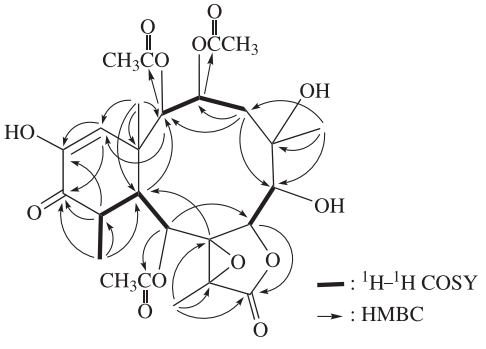


Figure 2. The selective ^{1}H–^{1}H COSY and HMBC correlations of **1**.

The relative stereochemistry of **1** was elucidated from the NOE interactions observed in a NOESY experiment (Fig. 3) and by the vicinal ^1H–^1H coupling constants. In the NOESY experiment of **1**, H-10 gives NOE correlations to H-3 and H-11, but not to H_3-15, and H-3 was found to show NOE responses with H-2 and one proton of the C-4 methylene (δ 2.14, d, $J=16.5$ Hz), indicating that these protons (H-2, H-3, H-4α, H-10 and H-11) are located on the same face of the molecule and assigned as α-protons, since the C-15 and C-20 methyls are the β-substituents at C-1 and C-11, respectively. The signal of H_3-18 showed NOE correlations with H_3-20, indicating the β-orientation of H_3-18. The configuration of C-9 is worthy of comment. H-9 was found to show NOE responses with H-10, H-11, H_3-18 and H_3-20. From the consideration of molecular models, H-9 was found to be reasonably close to H-10, H-11, H_3-18 and H_3-20, while H-9 should be placed on the α face in **1**. In addition, H-7 showed NOE interactions with H-4β (δ 2.45, dd, $J=$ 16.5, 5.5 Hz) and H-6, suggesting that the hydroxy group attached at C-6 was α-oriented. Furthermore, the NOE responses between H_3-16 and H-4α, indicated that the 5-hydroxy group was β-oreinted. From the above results, the structure, including the relative configuration of **1**, was established.

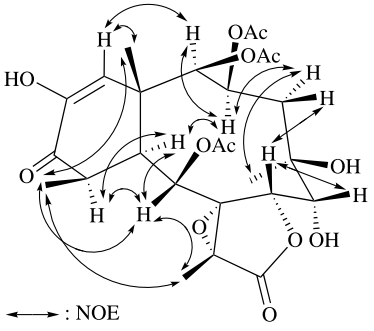


Figure 3. Selective NOESY correlations of **1**.

Geometry optimization was performed using DISCOVER utilizing the consistent valence force field (CVFF) calculations for energy minimization. The results were visualized using INSIGHT II running on a Silicon Graphics IRIS (SGI) INDIGO XS24/R4000 workstation. The conformational search suggested the most stable conformation as shown in Figure 4.

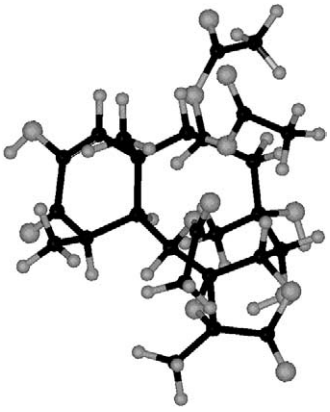


Figure 4. Stereoview of **1** generated from computer modeling.

Our present study has also led to the isolation of the new briarane, briaexcavatolide Y (**2**), $[\alpha]_D^{25}=-15°$ (c 0.7, $CHCl_3$). The molecular formula of $C_{26}H_{34}O_{12}$ was deduced from FABMS and NMR data. This showed that briarane **2** also contained 10 degrees of unsaturation. From detailed analysis, the spectral data [IR, ^1H and ^{13}C NMR (Table 1)] of **2** were found to be close to those of **1** and showed the presence of an α,β-unsaturated ketone, a γ-lactone, two hydroxy and three acetoxy groups. Comparison of the ^1H and ^{13}C NMR spectral data of **2** with those of **1**, showed that the hydroxy group attached to C-13 in **1** was replaced by an olefinic proton in **2**. These observations could be further confirmed by the correlations observed in the 2D NMR experiments of **2** including ^1H–^1H COSY, HMQC and HMBC spectra. The relative configuration of **2** was deduced from a NOESY experiment and the ^1H–^1H coupling constants data analysis. The *cis* geometry of the C-13/C-14 double bond was indicated by a 10.5 Hz coupling constant between H-13 (δ 6.18) and H-14 (δ 6.41). Moreover, the configurations of the eleven chiral centers, including C-1, C-2, C-3, C-5, C-6, C-7, C-8, C-9, C-10, C-11 and C-17 in **2**, were found to be very similar to those of **1**, as the chemical shifts and proton coupling constants were essentially identical and NOE correlations observed for **2** were comparable to those of **1**. Thus, from the above findings, compound **2** was found to be the 13-dehydroxy derivative of **1** with the structure as described by formula **2**.

It has to be noted here that a briarane containing a six-membered ring with an α-hydroxy-α,β-unsaturated ketone functional group, as presented in **1**, is unprecedential. Moreover, although briarane possessing a hydroxy group at C-6 has been discovered by our group,[13] the 5,6-dihydroxy-briaranes such as **1** and **2** were discovered for the first time.

The new briarane **3**, named briaexcavatolide Z, $[\alpha]_D^{25}=-41°$ (c 0.8, $CHCl_3$), had the composition $C_{32}H_{46}O_{14}$ as determined by HRFABMS, with 10 degrees of unsaturation thereby being determined for the molecule. The IR absorptions of **3** showed the presence of hydroxy (3466 cm^{-1}), γ-lactone (1782 cm^{-1}) and ester carbonyl (1738 cm^{-1}) groups. Carbonyl resonances in the ^{13}C NMR spectrum of **3** at δ 175.8 (s), 173.2 (s), 170.7 (s), 170.1 (s), 169.2 (s) and 168.6 (s) (Table 2), confirmed the presence of a γ-lactone and five other esters in the molecule. In the ^1H NMR spectrum of **3** (Table 2), four acetate methyls (δ 2.28, 3H, s; 2.12, 3H, s; 2.08, 3H, s; 1.95, 3H, s) and a *n*-butyryloxy group (δ 2.24, 2H, t, $J=7.5$ Hz; 1.64, 2H, m; 0.96, 3H, t, $J=7.5$ Hz) were observed. According to detailed analysis, the spectral data (IR, ^1H and ^{13}C NMR) of **3** were similar to those of a known briarane diterpenoid, briaexcavatolide L (**4**),[7] except that **3** showed signals corresponding to an additional acetoxy substituent. In addition, the ^1H and ^{13}C NMR spectra revealed that the signals corresponding to the hydroxy-bearing C-12 methine group in **4** (δ_H 3.88, br s; δ_C 69.6, d) were shifted downfield in **3** (δ_H 5.23, br s; δ_C 71.1, d), indicating that briaexcavatolide Z (**3**) is the 12-acetyl derivative of **4**. Acetylation of briaexcavatolide L (**4**) gave a less polar product that was found to be identical with diterpenoid **3** by comparison of the physical (mp and optical rotation value) and NMR (^1H and ^{13}C) data. Thus, the structure of diterpenoid **3** was established.

Table 2. ^{1}H and ^{13}C NMR data and HMBC and ^{1}H–^{1}H COSY correlations for compound **3**

C/H	^{1}H	^{13}C	HMBC (H→C)	^{1}H–^{1}H COSY
1		42.7 (s)	H-2, H-9, H-10, H-14, H_3-15, H_3-20	
2	5.83 d (3.0)	72.5 (d)	H-10, H-4α/β, H-14, H_3-15	H-3
3	4.87 br s	73.1 (d)	H-2, H-4α/β, H_3-15	H-2, H-4α/β
4α	2.04 d (15.0)	33.0 (t)	H-2, H_3-16	H-3, H-4β
β	3.20 dd (15.0, 4.5)			H-3, H-4α
5		142.1 (s)	H-4β, H-7, H_3-16	
6	5.54 d (10.0)	125.0 (d)	H-4β, H-7, H_3-16	H-7
7	5.39 d (10.0)	85.6 (d)	H-6, H_3-16, OH-8	H-6
8		81.7 (s)	H-7, H-9, H-10, H_3-18, OH-8, OH-17	
9	6.12 s	65.0 (d)	H-10, OH-8	H-10
10	3.07 d (7.0)	43.2 (d)	H-9, H_3-15, H_3-20	H-9, H-11
11	2.32 m	34.8 (d)	H-9, H-10, H_3-20	H-10, H-12, H_3-20
12	5.23 br s	71.1 (d)	H-10, H_3-20	H-11, H-13α/β
13α	1.85 m	31.9 (t)	H-14	H-13β, H-14
β	2.03 m			H-13α, H-14
14	5.18 dd (12.0, 5.0)	73.8 (d)	H-2, H-10, H_3-15	H-13α/β
15	1.54 s	19.6 (q)	H-2, H-14	
16	1.79 s	22.8 (q)	H-6	
17		76.9 (s)	H-7, H-9, H_3-18, OH-17	
18	1.38 s	16.7 (q)		
19		175.8 (s)	H-7, H_3-18	
20	1.03 d (7.0)	15.0 (q)		H-11
OH-8	2.87 s			
OH-17	2.62 s			
Acetate	2.28 s	22.0 (q)		
		168.6 (s)	H-9, acetate methyl	
	2.12 s	20.9 (q)		
		169.2 (s)	H-2, acetate methyl	
	2.08 s	20.6 (q)		
		170.7 (s)	H-14, acetate methyl	
	1.95 s	20.9 (q)		
		170.1 (s)	H-12, acetate methyl	
n-Butyrate		173.2 (s)	H_2-22	
	2.24 t (7.5)	35.8 (t)	H_2-23, H_3-24	
	1.64 m	17.9 (t)	H_2-22, H_3-24	
	0.96 t (7.5)	13.6 (q)	H_2-22, H_2-23	

Cytotoxcity of metabolites **1**-**3** toward a limited panel of tumor cell lines has been evaluated. The panel includes P-388D1 (mouse lymphoid neoplasm), DLD-1 (human colon adenocarcinoma), IMR-32 (human neuroblastoma), RPMI 7951 (human malignant melanoma) and CCRF-CEM (human T-cell acute lymphoblastic leukemia) cells. Although many briarane-related diterpenoids have been reported to possess interesting biological activities,[12] however, compounds **1**-**3** were found to be not cytotoxic toward above tumor cell lines.

3. Experimental

3.1. General experimental procedures

Melting points were determined on a FARGO apparatus and were uncorrected. Optical rotation values were measured in $CHCl_3$ with a JASCO D-370 digital polarimeter at 25 °C. Infrared spectra were obtained on a JASCO 5300 FT-IR spectrometer. Low-resolution mass spectral data were obtained by EI or by FAB with a VG QUATTRO GC/MS spectrometer. HRMS were recorded by ESI FT-MS on a BRUKER APEX II mass spectrometer or by FAB on a VG 70-250S GC/MS spectrometer. NMR spectra were recorded on a VARIAN UNITY INOVA 500 FT-NMR at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, in $CDCl_3$ using TMS as an internal standard. Column chromatography was performed on Si 60 (230–400 mesh) (Merck, Darmstadt, Germany). TLC spots (Si gel 60 F_{254}, Merck) were detected with an UV_{254} lamp and by 10% H_2SO_4 followed by heating at 120 °C for 5 min. All solvents used were either freshly distilled or of analytical grade.

3.2. Animal material

Specimen of *B. excavatum* was collected by hand using scuba at the southern Taiwan coast in July 1995, at depths of 4–5 m. The voucher specimen was deposited in the Department of Marine Resources, National Sun Yat-Sen University (specimen no. KTSC-103).

3.3. Extraction and isolation

The organism (3.6 kg) was collected and freeze-dried. The freeze-dried material (1.9 kg) was minced and extracted with EtOAc. The residue was dissolved in EtOAc, and the solution was stored at 0 °C to give a solid (5.5 g) that was found to be a mixture of long-chain esters arising from saturated fatty acids and alcohols and was discarded. The remaining mixture was separated by silica gel column chromatography, using *n*-hexane and *n*-hexane–EtOAc mixtures of increased polarity. Briarane **3** was eluted with *n*-hexane–EtOAc (5:2), **2** with *n*-hexane–EtOAc (3:2) and **1** with *n*-hexane–EtOAc (1:1).

3.3.1. Briaexcavatolide X (1). White powder (1.5 mg); mp 220–221 °C; $[\alpha]_D^{25} = -39°$ (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 241 nm (3.39); IR (neat) ν_{max} 3472, 1792, 1748, 1703 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR data, see Table 1; EIMS (70 eV) *m/z* 555 ($M^+ + H$), 537, 495, 477, 441, 435, 417, 399, 381, 375, 357, 339; ESI FT-MS *m/z* 441.1549 (Calcd for $M^+ + H–AcOH–3H_2O$, 441.1544).

3.3.2. Briaexcavatolide Y (2). White powder (2.7 mg); mp 119–121 °C; $[\alpha]_D^{25} = -15°$ (*c* 0.7, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 226 nm (3.62); IR (neat) ν_{max} 3460, 1792, 1744, 1686 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR data, see Table 1; FABMS *m/z* 521 ($M^+ + H–H_2O$), 479, 461, 419, 401, 383, 365, 359, 341, 323; ESI FT-MS *m/z* 521.2022 (Calcd for $M^+ + H–H_2O$, 521.2017).

3.3.3. Briaexcavatolide Z (3). White powder (2.5 mg); mp 147–148 °C; $[\alpha]_D^{25} = -41°$ (*c* 0.8, $CHCl_3$); IR (neat) ν_{max} 3466, 1782, 1738 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR data, see Table 2; FABMS *m/z* 655 ($M^+ + H$), 637, 595, 535, 507, 475, 465, 447, 405, 391, 387, 345, 327; HRFABMS *m/z* 655.2971 (Calcd for $M^+ +$ H, 655.2966).

3.4. Acetylation of briaexcavatolide L (4)

Briaexcavatolide L (**4**) (3.0 mg) was stirred with 1 mL of acetic anhydride in 1 mL of pyridine for 72 h at room temperature. After evaporation of excess reagent, the residue was separated by column chromatography on silica gel to give pure briaexcavatolide Z (**3**) (*n*-hexane–EtOAc, 5:2, 2.5 mg, 78%); physical and spectral data were in full agreement with those of the natural product **3**.

3.5. Molecular mechanics calculations

The minimum energy conformation of briaexcavatolide X (**1**) was determined using the MSI Insight II/DISCOVER version 95 molecular modeling package incorporating an empirical force field, the consistent valence force field (CVFF),[14] on a Silicon Graphics IRIS Indigo XS24/R4000 workstation. All the force field calculations were carried out in vacuo (dielectric constant = 1). The conformational space of briarane **1** was scanned using the high-temperature molecular dynamics simulation technique followed by energy minimization. A 100 ps molecular dynamics simulation at 1000 K provided a set of 500 conformations of **1**. Each of them was used as starting structure for the subsequent energy minimization (1000 steps, conjugated gradient algorithm). In the subsequent analysis, only 10 conformations with a reasonably low energy (at most 5 kcal/mol higher with respect to the lowest energy conformer) were used. The conformer shown in Figure 4 is the lowest energy conformation of briarane **1**.

3.6. Cytotoxicity testing

The cytotoxicity of tested compounds **1**-**3** was assayed with a modification of the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method. Cytotoxicity assays were carried out according to the procedures described previously.[15]

Acknowledgements

This research work was supported by a grant from the National Science Council of the Republic of China awarded to J.-H. Sheu (contract no. NSC 91-2113-M-110-009).

References and notes

1. Bayer, F. M. *Proc. Biol. Soc. Wash.* **1981**, *94*, 902–947.
2. Sheu, J.-H.; Sung, P.-J.; Cheng, M.-C.; Liu, H.-Y.; Fang, L.-S.; Duh, C.-Y.; Chiang, M. Y. *J. Nat. Prod.* **1998**, *61*, 602–608.
3. Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Lin, S.-F.; Duh, C.-Y.; Sheu, J.-H. *J. Nat. Prod.* **1999**, *62*, 457–463.
4. Neve, J. E.; McCool, B. J.; Bowden, B. F. *Aust. J. Chem.* **1999**, *52*, 359–366.
5. Sheu, J.-H.; Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Duh, C.-Y.; Shen, Y.-C.; Chiang, M. Y.; Chen, I-T. *J. Nat. Prod.* **1999**, *62*, 1415–1420.
6. Sheu, J.-H.; Sung, P.-J.; Su, J.-H.; Liu, H.-Y.; Duh, C.-Y.; Chiang, M. Y. *Tetrahedron* **1999**, *55*, 14555–14564.
7. Sung, P.-J.; Su, J.-H.; Duh, C.-Y.; Chiang, M. Y.; Sheu, J.-H. *J. Nat. Prod.* **2001**, *64*, 318–323.
8. Wu, S.-L.; Sung, P.-J.; Chiang, M. Y.; Wu, J.-Y.; Sheu, J.-H. *J. Nat. Prod.* **2001**, *64*, 1415–1420.
9. Wu, S.-L.; Sung, P.-J.; Su, J.-H.; Sheu, J.-H. *J. Nat. Prod.* **2003**, *66*, 1252–1256.
10. Wu, S.-L.; Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Sheu, J.-H. *Heterocycles* **2004**, *63*, 895–898.
11. Aoki, S.; Okano, M.; Matsui, K.; Itoh, T.; Satari, R.; Akiyama, S.; Kobayashi, M. *Tetrahedron* **2001**, *57*, 8951–8957.
12. Sung, P.-J.; Sheu, J.-H.; Xu, J.-P. *Heterocycles* **2002**, *57*, 535–579.
13. Sung, P.-J.; Lin, M.-R.; Chen, W.-C.; Fang, L.-S.; Lu, C.-K.; Sheu, J.-H. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1229–1230.
14. MSI INSIGHT II/DISCOVER (version 95.0/2.97) is a molecular modeling software package of MSI Technologies Inc., Barnes Canyon Rd., San Diego, CA, 92121, USA.
15. Alley, M. C.; Acudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemark, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589–601.