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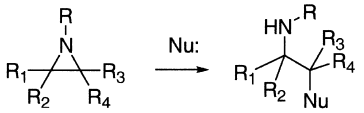
Contents

REPORT

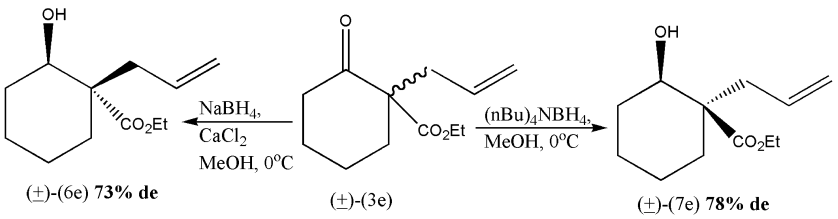
Nucleophilic ring opening of aziridines **pp 2701–2743**
X. Eric Hu



This review presents recent progress in nucleophilic ring opening aziridines. There are 165 references included in this article.

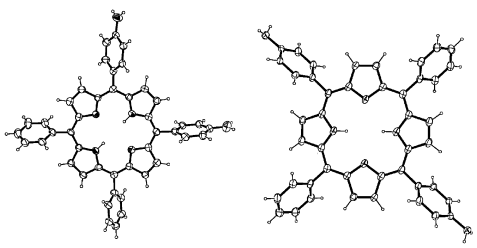
ARTICLES

Studies on diastereoselective reduction of cyclic β-ketoesters with boron hydrides. Part 4: The reductive profile of functionalized cyclohexanone derivatives **pp 2745–2755**
Carlos A. M. Fraga,* Lis Helena P. Teixeira, Carla Maria de S. Menezes, Carlos Mauricio R. Sant'Anna, Maria da Conceição K. V. Ramos, Francisco R. de Aquino Neto and Eliezer J. Barreiro



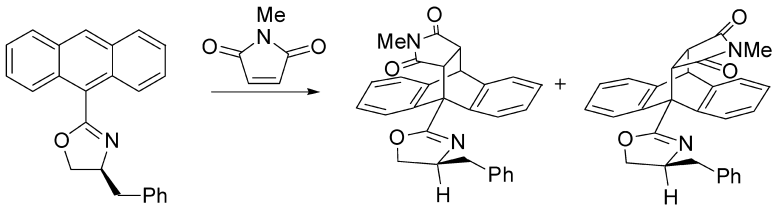
Synthesis and reactions of *meso*-(*p*-nitrophenyl)porphyrins **pp 2757–2763**
Raymond Luguya, Laurent Jaquinod, Frank R. Fronczek, M. Graça H. Vicente* and Kevin M. Smith*

New mild methods for regioselective *para*-nitration of 5,10,15,20-tetraarylporphyrins are reported; use of variable amounts of $NaNO_2$/TFA permits the isolation of mono-, di-, and tri-nitrophenyl derivatives. Reduction affords the corresponding aminoporphyrins, for example, bis-(4-aminophenyl)porphyrins **7** and **8**.

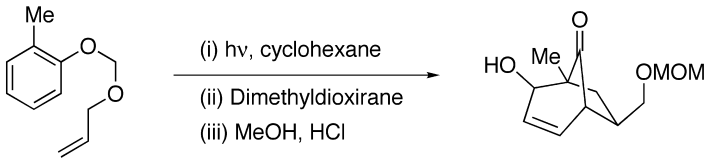


7 **8**

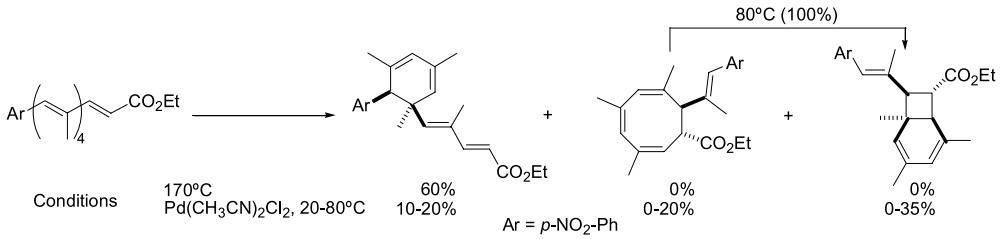
Synthesis and Diels–Alder reactions of 9-(4-benzyloxazolin-2-yl) anthracene **pp 2765–2770**
Ramadan A. Bawa and Simon Jones*



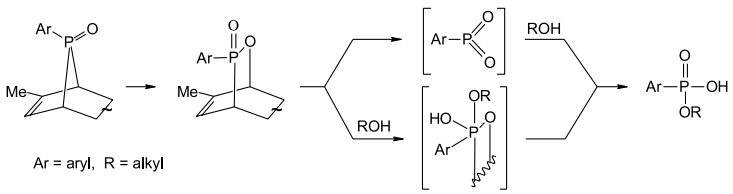
The use of temporary tethers in the *meta* photocycloaddition reaction **pp 2771–2784**
Clive S. Penkett,* Paul W. Byrne, Barry J. Teobald, Benedicte Rola, Aurelie Ozanne and Peter B. Hitchcock



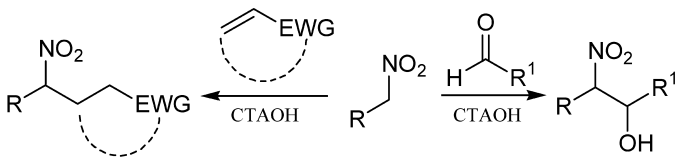
Thermal and palladium catalyzed pericyclic rearrangements of a pentaene ester **pp 2785–2788**
Sébastien Brückner, Jack E. Baldwin,* Robert M. Adlington, Tim D. W. Claridge and Barbara Odell



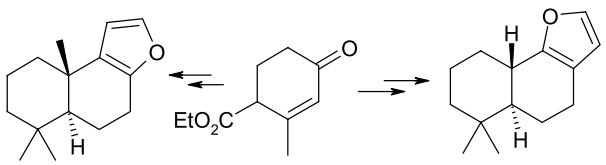
Aryl-2,3-oxaphosphabicyclo[2.2.2]octene derivatives—the precursors of oxoarylphosphine oxides (aryl metaphosphonates) **pp 2789–2797**
Stefan Jankowski,* György Keglevich,* Tomasz Nonas, Henrietta Forintos, Marek Główka and Juliusz Rudziński



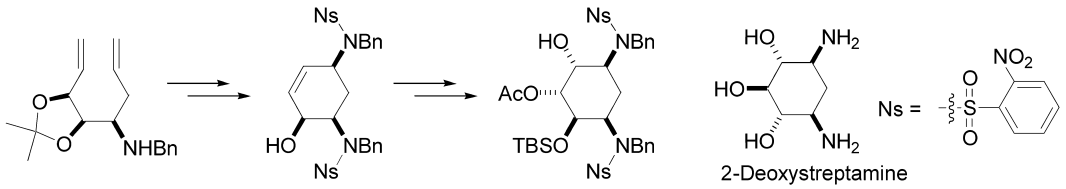
Cetyltrimethylammonium hydroxide (CTAOH) as a general, ecofriendly catalyst for the formation of carbon–carbon bond through nitroalkanes **pp 2799–2804**
Roberto Ballini,* Dennis Fiorini, Maria Victoria Gil and Alessandro Palmieri



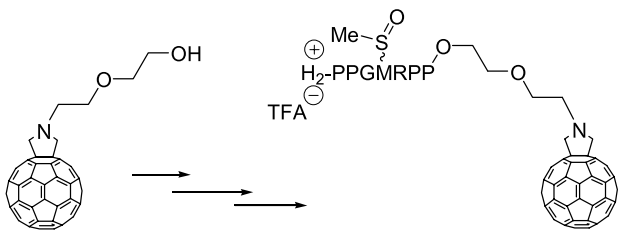
Synthetic studies towards furosesquiterpenoids: total synthesis of (±) desmethylpallescensin-A, (±) isopallescensin-A and (±) isopallescensin-1 **pp 2805–2811**
Sajal Kanti Mal, Gandhi K. Kar and Jayanta K. Ray*



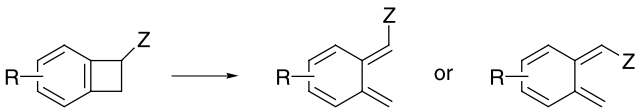
Synthesis of orthogonally protected 2-deoxystreptamine stereoisomers **pp 2813–2822**
Steven H. L. Verhelst, Tom Wennekes, Gijsbert A. van der Marel, Herman S. Overkleeft, Constant A. A. van Boeckel and Jacques H. van Boom*



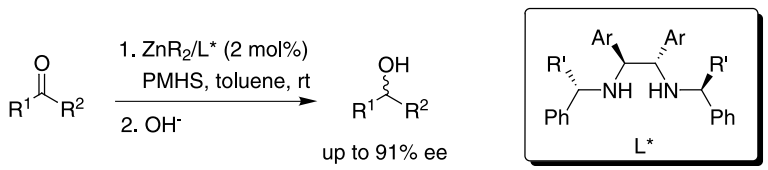
Synthesis of a proline-rich [60]fullerene peptide with potential biological activity **pp 2823–2828**
Panagiota Sofou, Yiannis Elemes,* Eugenia Panou-Pomonis, Athanassios Stavrakoudis, Vassilios Tsikaris, Constantinos Sakarellos, Maria Sakarellos-Daitsiotis, Michele Maggini, Fernando Formaggio and Claudio Toniolo



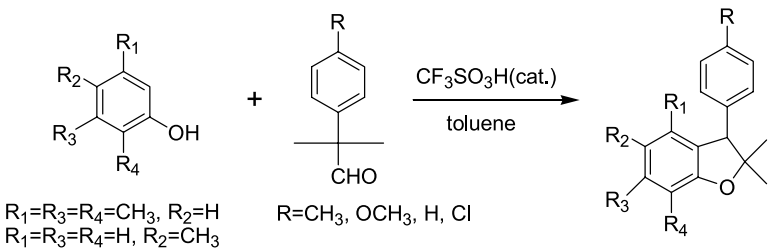
A computational study of the thermal opening of benzocyclobutenes to (*E*)- and (*Z*)-xylylenes **pp 2829–2835**
Natacha Mariet, Hélène Pellissier, Jean-Luc Parrain and Maurice Santelli*



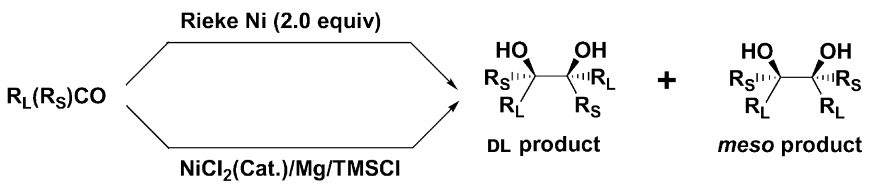
New developments in zinc-catalyzed asymmetric hydrosilylation of ketones with PMHS **pp 2837–2842**
Virginie Bette, André Mortreux, Diego Savoia and Jean-François Carpentier*



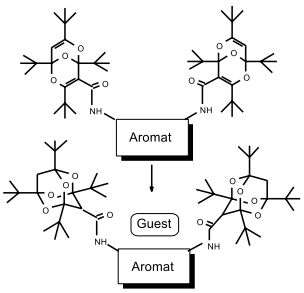
A convenient ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols and 2-aryl-2,2-dialkylacetaldehydes **pp 2843–2849**
Makoto Yamashita,* Yujirou Ono and Hiroyuki Tawada



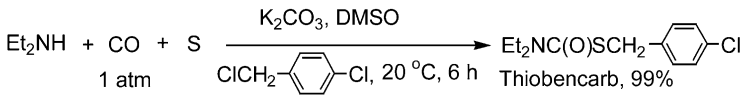
Novel and efficient Ni-mediated pinacol coupling of carbonyl compounds **pp 2851–2855**
Lei Shi, Chun-An Fan, Yong-Qiang Tu,* Min Wang and Fu-Min Zhang



2,6,9-Trioxabicyclo[3.3.1]nona-3,7-dien-4-oyl and tetraoxaadamantan-9-oyl functionalized aromatic di- and triamines: synthesis, stereochemistry and complexation **pp 2857–2867**
Werner Heilmayer, Ralf Smounig, Karl Gruber, Walter M. F. Fabian, Claudia Reidlinger, C. Oliver Kappe, Curt Wentrup and Gert Kollenz*

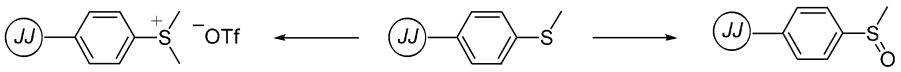


Practical synthesis of *S*-alkyl thiocarbamate herbicides by carbonylation of amines with carbon monoxide and sulfur **pp 2869–2873**
Takumi Mizuno,* Toshiyuki Iwai and Takatoshi Ito

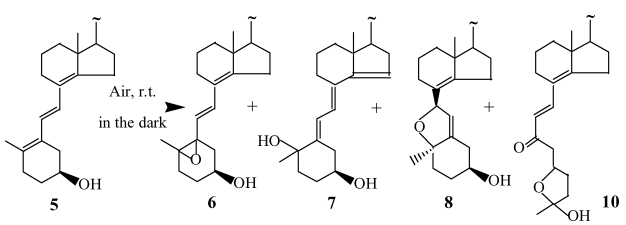


An industrially synthetic method of *S*-alkyl thiocarbamate herbicides was developed.

Polymer-supported thioanisole: a versatile platform for organic synthesis reagents **pp 2875–2879**
Matthew Kwok Wai Choi and Patrick H. Toy*

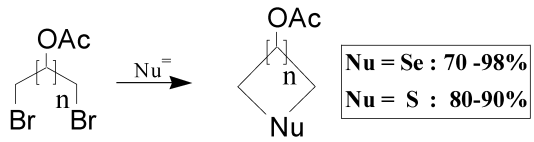


Autoxidation of isotachysterol **pp 2881–2888**
Xiaoling Jin, Xinping Yang, Li Yang,* Zhong-Li Liu* and Fa Zhang

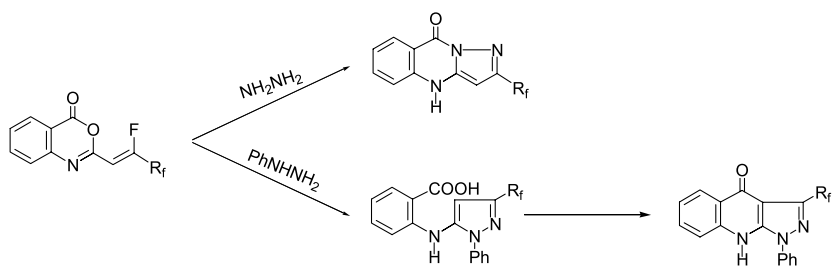


Isotachysterol, the acid-catalyzed isomerization product of vitamin in D_3, produces seven previously unknown oxygenation products in a self-initiated autoxidation reaction under atmospheric oxygen in the dark at ambient temperature. The formation of these products is explained in terms of free radical peroxidation chemistry.

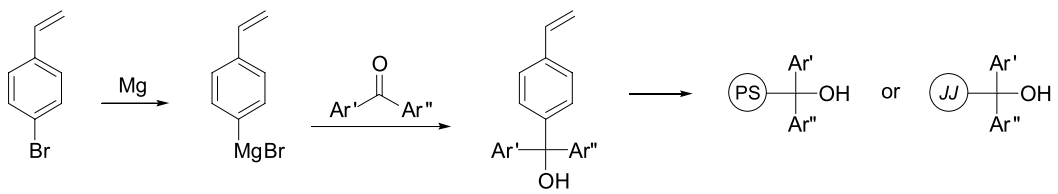
Expedious synthesis of polyhydroxylated selena and thia-heterocycles via Se and S-ring closure of α,ω-dibromoalditols **pp 2889–2895**
Mohammed Benazza,* Sami Halila, Camille Viot, Alain Danquigny, Christèle Pierru and Gilles Demailly



The reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with dinucleophilic reagents: a convenient route to fluoroalkylated nitrogen-containing tricyclic compounds **pp 2897–2902**
Xian-Jin Yang, Jin-Tao Liu* and He-Jun Lu



An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports **pp 2903–2907**
Matthew Kwok Wai Choi and Patrick H. Toy*



OTHER CONTENTS

Contributors to this issue **p I**
Instructions to contributors **pp III–VI**

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Nucleophilic ring opening of aziridines

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Contents

1. Introduction 2702
2. Carbon nucleophilic addition 2702
   2.1. Alkyl and aryl carbanions 2702
   2.2. Enamines, enolates and olefins 2705
   2.3. Rearrangement of aziridines 2708
   2.4. Cyanide 2709
3. Oxygen nucleophilic addition 2710
   3.1. Alkyl and aryl alcohols 2710
   3.2. Hydroxyl anion 2712
   3.3. Carboxylate anion 2715
   3.4. Miscellaneous 2718
4. Sulfur nucleophilic addition 2718
   4.1. Alkyl and arylsulfide anion 2718
   4.2. Thioacyl acids 2719
   4.3. Miscellaneous 2719
5. Nitrogen nucleophilic addition 2720
   5.1. Amines 2720
   5.2. Amides 2725
   5.3. Azides 2725
   5.4. Miscellaneous 2727
6. Halogen nucleophilic addition 2727
   6.1. Chloride 2727
   6.2. Bromide 2730
   6.3. Fluoride 2730
   6.4. Iodide 2731
7. Hydrogen nucleophilic addition 2732
   7.1. Hydrogen from hydrogenation 2733
   7.2. Hydride 2734
   7.3. Miscellaneous 2734
8. Cycloaddition 2735
9. Miscellaneous: other heteroatom nucleophilic addition 2737
   9.1. Phosphorus nucleophilic addition 2737
   9.2. Silanes 2737
   9.3. Selenols 2737
   9.4. Cobalt 2738
   9.5. Conversion of 2-iodomethyl aziridines to allylic amines 2739
10. Concluding remarks 2739

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1. Introduction

The aziridine functionality, or alternatively named the azaethylene or ethylenimine unit, represents one of the most valuable three membered ring systems in modern synthetic chemistry, because of its widely recognized versatility as a significant building block for chemical bond elaborations and functional group transformations. Its powerful synthetic utility has been extensively demonstrated by overwhelmingly documented methodologies in aziridine preparation, especially those including asymmetric approaches, and its broad applications to other syntheses.[1–5] The synthetic scope has quickly blossomed in recent years, which is evident in a literature search by a term of 'aziridine reviews', resulting in more than 125 hits of review articles in the last four decades. Among them, 23 reviews were published since year 2000, averaging 5 reviews per year. Because of the emerging interests in nitrogen containing organic compounds and the potential utility of aziridine ring opening chemistry, the intensity in aziridine research is anticipated to increase in the future.

In this review, it is by no means intended to seek a comprehensive overview of aziridine chemistry including chiral aziridines,[6] nor to cover examples of broad applications for the synthesis of amino acids,[7] azasugars,[8–10] chiral ligands,[11,12] biologically active compounds,[13] natural products[8,14] and other synthesis. Instead, the focus of this review is designed to remain in a landscape of presenting only recent noteworthy advances in the development of new methodologies, particularly in nucleophilic ring opening of aziridines, since the review by McCoull and Davis in 2000.[15] Examples of new procedures are presented to highlight reaction conditions, stereo and regio-selectivity, reagent advantages and limitations, so to provide a useful reference tool set of methods handy to satisfy particular reaction needs. The reports of preparative procedures of aziridines and reapplication of existing protocols with little methodological values are excluded from this review to minimize redundancy and exhaustiveness.

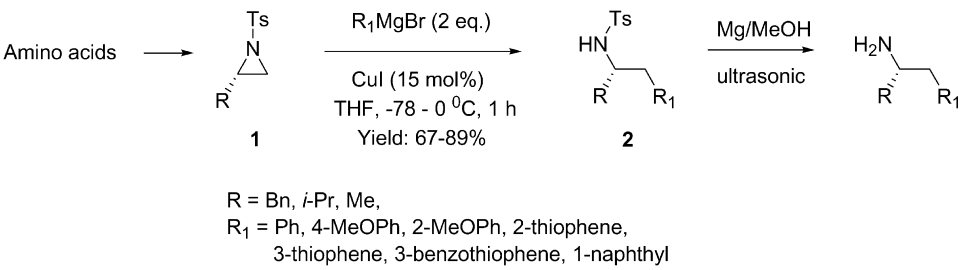
2. Carbon nucleophilic addition

Nucleophilic ring opening of aziridines by organometallic reagents has been known for over three decades.[16] However, the application of the carbanion addition was not significantly accelerated until a more efficient method developed by Eis and Ganem in the opening of non-activated aziridines by organocuprates catalyzed by Lewis acid BF_3 was reported.[17] A subsequent report by Baldwin et al. in the ring opening of N-sulfonated aziridines with requirement of no catalysis further enhanced its broad use.[18] Since then, carbanion nucleophilic addition to aziridines has found its significantly appreciable position in organic synthesis for carbon–carbon bond formation as one of the very prominent methods for organic functional group transformation.

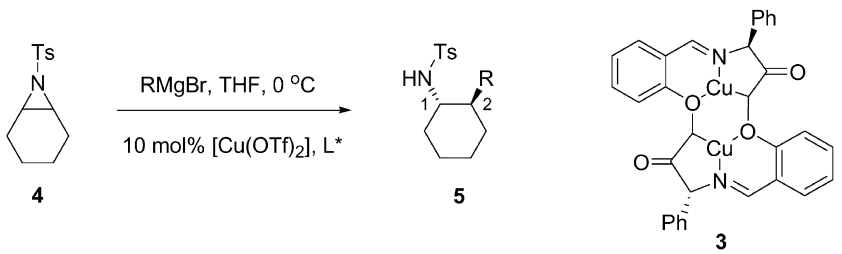
2.1. Alkyl and aryl carbanions

Increasing interest in β-aryl- and β-heteroarylamines due to their pharmacological effects in recent years has triggered considerable attention in asymmetric synthesis of these amines. One representative procedure is outlined in Scheme 1 using *N*-tosyl aziridines **1** derived from optically active amino acids as effective templates to undergo nucleophilic ring opening by aryl and heteroaryl Grignard reagents.[19] The reaction took place in THF in the presence of catalytic CuI premixed with Grignard reagents, and consistent good to high yields of amine derivatives **2** were obtained throughout the cases studied. Regio-chemistry appeared to be specific at the unsubstituted ring carbon in most examples. The tosyl group could be easily removed using magnesium in methanol under ultrasonic conditions, which makes the methodology a very attractive approach to effectively synthesize β-aryl- and β-heteroarylamines.

Recent advances in asymmetric synthesis, especially the development of chiral ligands, led to desymmetrization of *meso*-*N*-sulfonyl aziridines by nucleophilic Grignard addition. Muller and Nury examined a set of chiral ligands



Scheme 1.



Scheme 2.

in ring opening of symmetric aziridines derived from cyclic olefins with Grignard reagents as depicted in Scheme 2 and found Cu complex **3** resulted in the most appreciable asymmetric induction.[20] As shown in the representative examples in Table 1, high asymmetric induction could be achieved in 91% ee with 30 mol% of the chiral ligand under an optimized conditions. Although MeMgBr ring opening gave 55% ee with 10 mol% of the ligand, PhMgBr addition did not provide enantio-selectivity. Increased steric hindrance at the benzene ring as exemplified with (mesityl)MgBr resulted in increased enantio-selectivity, which culminated in 72% ee with **5**. However, acyclic aziridines did not produce desymmetrization products.

Table 1. Cu-catalyzed ring opening of *N*-tosyl aziridine with Grignard reagents

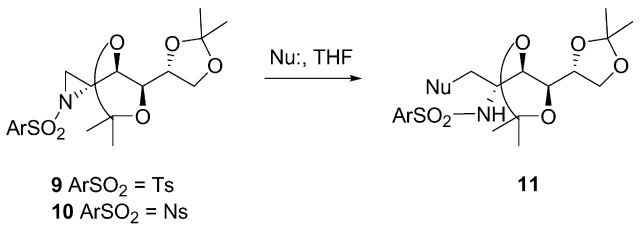
RMgBr	Ligand **3** (mol%)	Time (h)	Yield (%)	ee (%)	Abs. Config.
Me	10	2.0	89	55	(1*S*, 2*S*)
Me	30	1.5	52	91	(1*S*, 2*S*)
I-Pr	10	1.5	71	21	—
Ph	10	2.0	80	0	—
Mes	10	3.0	45	72	—

One of the most useful applications of nucleophilic ring opening of aziridines with carbanions was demonstrated in stereo and regio-controlled synthesis of 3-amino-4-substituted piperidines in our laboratory recently.[21] As shown in Scheme 3, piperidinyl aziridine **6** bearing an *N*-phosphonate activating group was treated with various Grignard reagents/CuI giving the ring opening products (**7** and **8**) mainly derived from C4 addition *trans* to the aziridine ring. The reaction proceeded smoothly with alkyl Grignard reagents in high yields, but hindered *t*-BuMgBr did not add to the aziridine. This was also true for those having sp^2 carbon nucleophiles. In addition, other organometallic reagents such as *n*-BuLi and *n*-BuZnBr gave only complex mixtures (Table 2). The surprising high regio-selectivity in such a simple system was rationalized based on conformational and steric analyses by a computer-assisted modeling approach. The *trans*-3-amino-4-alkyl piperidine derivatives are useful side chains of quinolone antibiotics.

Appropriately activated aziridines could undergo nucleophilic ring opening by various carbanions. The electronic accessibility of the aziridines was demonstrated by Compernolle et al.[22] as shown in Scheme 4 and Table 3. For example, less nucleophilic malonate and sulfonylacetonitrile anions readily attacked either tosyl aziridine **9** or nosyl aziridine **10** to give ring opening products **11** in good to high yields. Stronger carbon nucleophiles of phenyl and 1,3-dithian-2-yl anions reacted with tosyl aziridine in relatively shorter time. Although the nosyl group has been

Table 2. Regio-selective ring opening of aziridine **6** with Grignard reagents

R	Time (h)	Yield (%)	**7**:**8**
MeMgBr	3	86	13:1
EtMgBr	3	78	15:1
n-BuMgBr	5	87	13:1
i-PrMgBr	5	92	22:1
c-PrMgBr	3	78	14:1
c-HexylMgBr	5	82	12:1
t-BuMgBr	5	0	—
CH_2=CHMgBr	24	0	—
PhMgBr	24	0	—
n-BuLi	3	0	—
n-BuZnBr	24	0	—



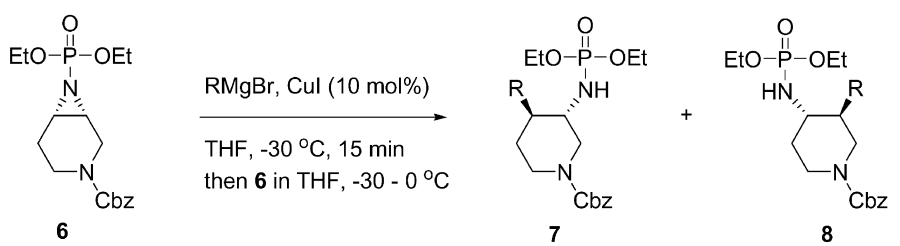
Scheme 4.

Table 3. Nucleophilic ring opening of aziridines

Nu:	Base	Time (h)		Yield (%)	
		Tosyl	Nosyl	Tosyl	Nosyl
$CH(CO_2Me)_2$	NaH	48	4	65	78
$CH(CN)SO_2Ph$	NaH	24	24	87	Mixt.
Ph	PhMgBr/CuI	1	1	75	Mixt.
1,3-Dithian-2-yl	*n*-BuLi	4	—	90	—

widely accepted as an excellent activating group, which can be more readily removed than the tosyl group, it might not be compatible with strong nucleophiles, which may contribute to the complex mixtures of some reactions as illustrated in Table 3.

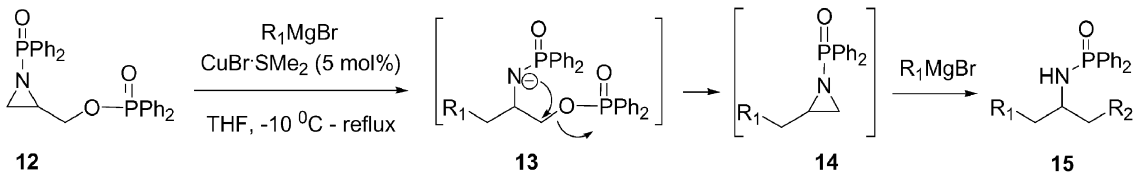
One interesting aziridine containing *N*,*O*-bis(diphenylphsphinyl) (DiDpp) functionality was prepared by Sweeney and Cantrill,[23] which could undergo double nucleophilic addition to give either dialkylated symmetric amines or unsymmetrical amines. The opening of DiDpp aziridine **12** with 5 equiv. of Grignard reagents was facilitated by $CuBr{\cdot}SMe_2$ in reflux THF to produce **15** in good yields. On the other hand, when 1 equiv. of the Grignard reagents was used, mono-alkylated aziridine products **14** were isolated in acceptable yields. Due to two electrophilic carbons present in **12**, the authors attempted to rationalize the addition process by the following assumption. The first



Scheme 3.

Table 4. Reaction of diphenylphosphinyl aziridine with copper(I)-modified Grignard reagents

12→15 R_1=R_2		**12→14**		**14→15** R_1=*i*-Bu	
R_1	Yield (%)	R_1	Yield (%)	R_2	Yield (%)
i-Bu	78	Et	70	Homoallylic	60
Homoallylic	75	*n*-Bu	52	Cyclohexyl	66
Ph	75	*i*-Bu	63	$Ph(CH_2)_3$	72

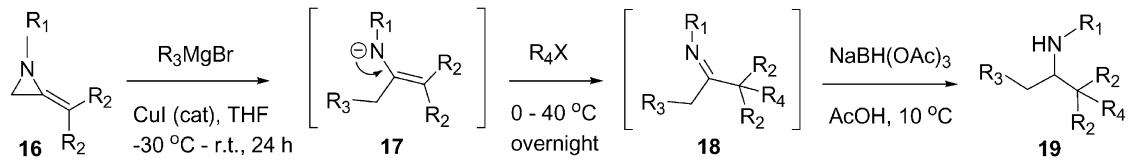


Scheme 5.

addition occurred at the aziridine to give phosphinamide anion **13**, which formed a new aziridine **14**. The second aziridine then underwent the subsequent attack by the Grignard reagents to give the final dialkyl methylamines **15**. The proposed mechanism was experimentally assured by carrying out the addition with the chiral (*R*)-aziridine of **12** and the determination of the reversed chiral center in **14** supported the initial carbanion attack at the aziridine ring carbon, followed by the second addition at the newly formed aziridine intermediate **14** (Table 4, Scheme 5).

Most reported ring opening of aziridines with carbanion nucleophiles required activation of the aziridine ring by incorporating an electron-withdrawing group on the ring nitrogen to facilitate the ring cleavage. However, one example was found in the literature describing the ring opening of aziridines without activation under Grignard nucleophilic addition conditions.[24] As shown in Scheme 6, 2-methylene- and 2-isopropylidene-aziridines **16** having alkyl groups attached to the ring nitrogen reacted with Et or *n*-BuMgBr to give ring cleaved intermediate imines **18** presumably via enamine anion **17**, after being quenched with either MeI or BnBr. Then sequential reduction with $NaBH(OAc)_3$ resulted in secondary amines **19**. This one-pot/three sequential step/multi-component procedure effectively converted aziridines to amines with three new chemical bonds formed in high overall yield (56–73%) shown in Table 5. In addition, when the chiral aziridines bearing *N*-(*S*)-CHMePh chirality were used, optically active amines **19** could be synthesized in excellent diastereoselectivity in the case of 2-isopropylidene **16**. The application of this multi-component method was demonstrated in asymmetric synthesis of 2-substituted piperidines leading to (*S*)-coniine in high enantio-selectivity.[25]

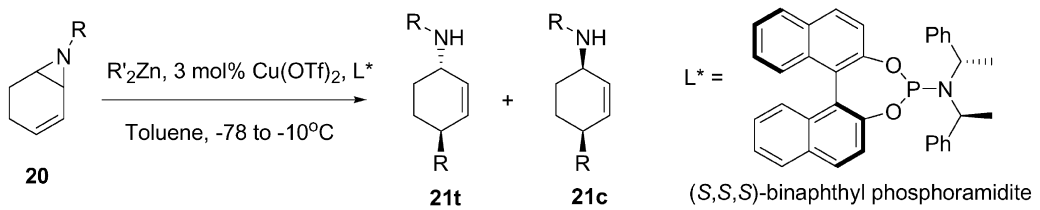
When aziridines possessed a vinyl functionality, the nucleophilic ring opening reaction proceeded with products derived from an alternative pathway involving Sn2′ addition. An effective method was recently developed by Pineschi and co-workers for controlled regio-, stereo- and enantio-selectivity in ring opening of aziridines.[26] The addition of Et_2Zn to *N*-Cbz aziridine **20** in the presence of $Cu(OTf)_2$ occurred smoothly to afford nearly 1:1 ratio of *trans*:*cis* products (**21t** and **21c**, respectively) in 95% conversion. However, a kinetic resolution controlled reaction protocol was used with only 0.55 equiv. of Et_2Zn in the presence of 6 mol% of a chiral ligand, binaphthyl phosphoramidite shown in Scheme 7. Results of 42% conversion of the starting aziridine to the products in 91:9 ratio of the *trans* isomer as a major component was observed with 78% enantio-selectivity. Methyl addition from Me_2Zn proved to be optimal in terms of stereo- and enantio-selectivity. When 1.5 equiv. of Et_2Zn were used in the



Scheme 6.

Table 5. Ring opening of 2-isopropylidene and 2-methylele-aziridines with Grignard reagents

R_1	R_2	R_3	R_4X	Yield (%)	de (%)
(*S*)-CHMePh	Me	Et	MeI	73	≥98
(*S*)-CHMePh	Me	Et	BnBr	56	~100
(*S*)-CHMePh	H	Et	MeI	63	≤25
Cyclohexyl	H	*n*-Bu	BnCl	63	—



Scheme 7.

presence of the chiral ligand, quantitative conversion was obtained with a combined yield of 75% for both stereoisomers, but with diminished enantio-selectivity (8% ee). The presence of the chiral phosphoramidite not only enhanced *anti* stereo-selectivity significantly, but provided a method for kinetic resolution of racemic cyclic 2-alkynyl aziridines. Non-activated *N*-Bn aziridine essentially did not react with organozinc agents under these conditions (Table 6).

Table 6. Regio, stereo and enantio-selective addition of R_2Zn to vinyl aziridines

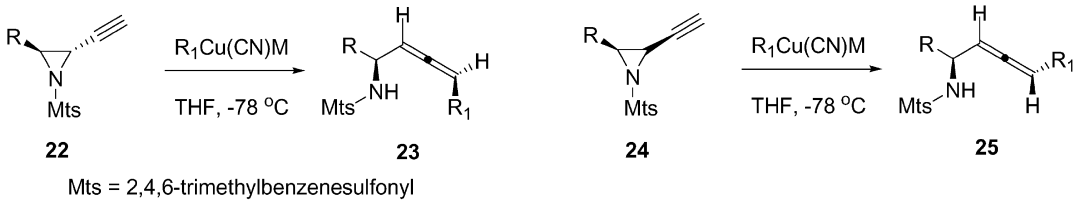
R	R'_2Zn (equiv.)	L* (mol%)	Time (h)	Conv. (%)	**21t**:**21c**	ee (%)
Cbz	Et (1.50)	None	3	>95	48:52	—
Cbz	Et (0.55)	6	2	42	91:9	78
Cbz	Me (0.40)	6	2	48	>95:<5	83
Cbz	Et (1.50)	6	18	100	80:20	8
Bn	Et (1.50)	6	18	<5	—	—

In light of organocopper-mediated ring opening of propargylic epoxides leading to the corresponding hydroxy allenes in a highly regio- and *anti*-Sn2′ selective manner, Ohno et al. also developed regio- and stereo-selective ring opening of chiral ethynylaziridines giving amino allenes.[27] As illustrated in Scheme 8, the *trans* propargylic aziridines **22** could be converted to allene adducts **23** by organocopper reagents in excellent regio- and stereo-specificity under selected reaction conditions in the representative examples in Table 7. In contrast, the *cis* propargylic aziridines **24** resulted in allenes **25** with opposite stereochemistry. The stereochemistry outcome was deduced from the well-established organocyanocuprate-mediated *anti*-Sn2′ pathway, which was further supported by the unambiguous structure assignment of one of the adducts by X-ray analysis.

2.2. Enamines, enolates and olefins

Indoles have been found to be good substrates for ring opening of aziridines under appropriate Lewis acid catalysis conditions. 2-Substituted indole **26** having enamine functionality embedded in the heteroaryl ring readily underwent nucleophilic addition to activated aziridines **27**, when facilitated by $Sc(ClO_4)_3$, to give 2-substituted tryptophan **28** in good yield.[28] This method provided only the adduct derived from the attack at the less hindered aziridine carbon, whereas a mixture of regio-isomers were obtained when catalyzed by $Sc(OTf)_3$. This intermediate was then converted to a fully deprotected α-*C*-mannosyltryptophan, a compound having interesting biological activity. Other Lewis acids such as $BF_3{\cdot}Et_2O$, $Zn(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$ and $InCl_3$ were studied, but only $Sc(ClO_4)_3$ was found as a superior catalyst for the ring opening of the aziridine with respect to regio-selectivity and reproducibility (Scheme 9).[29]

N-Tosyl aziridines also reacted with heteroaromatics under catalytic indium(III) chloride ($InCl_3$) conditions.[30] The heteroaromatics including indole, pyrrole, thiophene and furan readily underwent nucleophilic attacks to either

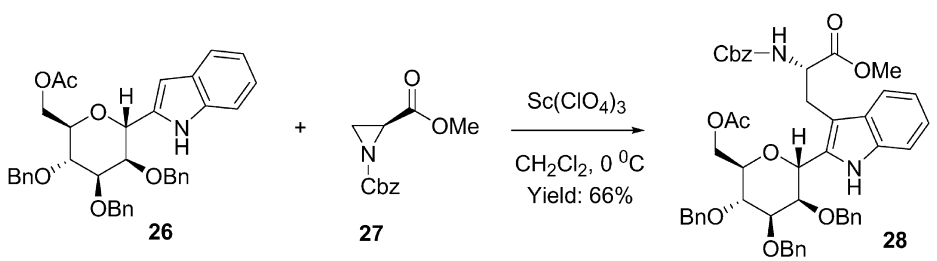


Scheme 8.

Table 7. Ring opening of 2-ethylylaziridines with organocopper reagents

Aziridine	R	$R_1Cu(CN)M$	Time (h)	Yield (%)	Product
22	*i*-Pr	MeCu(CN)Li	3.0	93	**23**
22	*i*-Pr	*i*-PrCu(CN)MgCl	0.5	99	**23**
22	*i*-Pr	*n*-BuCu(CN)Li	0.5	97	**23**
22	*i*-Pr	$Bu_3SnCu(CN)Li$	0.5	90	**23**
24	*i*-Pr	MeCu(CN)Li	0.5	98	**25**
22	Bn	MeCu(CN)Li	2	96	**23**
24	$TBSOCH_2$	MeCu(CN)Li	0.5	98	**25**

symmetric or unsymmetrical aziridines to give the corresponding ring opening products in high yields (Table 8). Indole reacted with cyclopentene and styrene *N*-tosyl aziridines to afford 3-alkylated indole derivatives **29** and **30**, whereas pyrrole gave 2-alkylated derivative **31** as a major isomer along with 3-alkylated isomer **32**. Thiophene and furan added similarly to the aziridines to yield internal adducts. Although this method was claimed to be mild and efficient, low to moderate regio-selectivity was consistently reproduced in unsymmetrical aziridines.



Scheme 9.

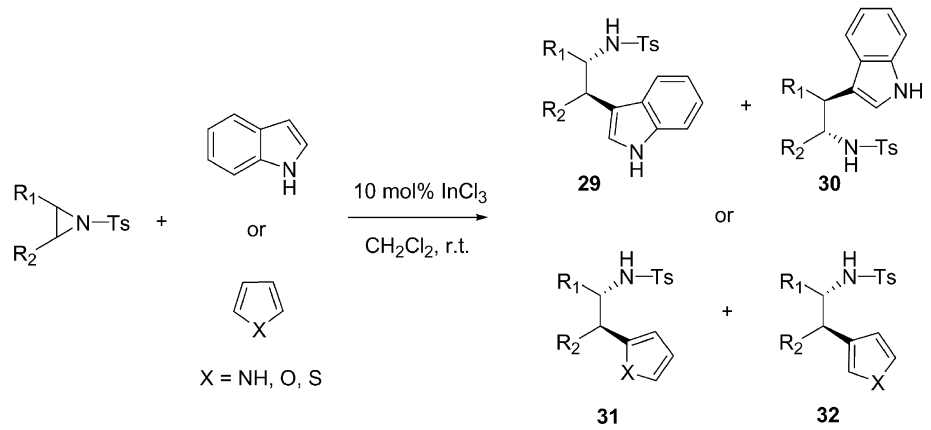
Table 8. $InCl_3$-catalyzed ring opening of aziridines with heteroaromatics

R_1	R_2	Nucleophile	Time (h)	Yield (%)	Isomer ratio
$-(CH_2)_4-$		Indole	12	75	—
$-(CH_2)_4-$		Pyrrole	5.5	72	—
Ph	H	Indole	5.5	85	60:40[a]
Ph	H	Pyrrole	2.5	90	87:13[b]
Ph	H	Thiophene	5.0	87	90:10[a]
Ph	H	Furan	4.0	80	70:30[a]
4-MeO-Bn	H	Pyrrole	4.5	85	75:25[b]
n-C_4H_9	H	Pyrrole	2.5	85	70:30[b]

[a] Ratio of products resulting from internal attack versus external attack of a nucleophile.
[b] Ratio of 2 versus 3-alkylated pyrrole products.

Table 9. Diastereo-selective ring opening of aziridines with lithium enolate

R in aziridine	Yield (%)	(2*R*)/(2*S*)
(*S*)-Ph	88	96/4
(*S*)-Me	89	89/11
(*S*)-*i*-Pr	87	93/7
(*S*)-Bn	93	95/5
(*R*)-Ph	91	75/25
(*R*)-Me	86	85/15
(*R*)-*i*-Pr	90	77/23
(*R*)-Bn	85	70/30



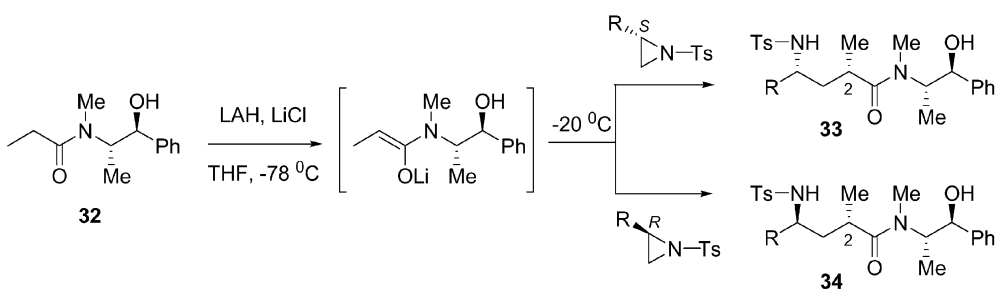
Scheme 10.

Indium(III) tribromide ($InBr_3$) also effectively catalyzed ring opening of aziridines with pyrrole to give products in good yields, but moderate regio-selectivity (Scheme 10).[31]

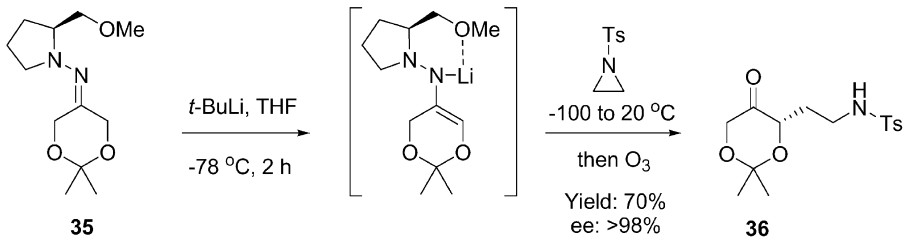
Enolates derived from ketones, esters and amides have been used as effective nucleophiles to undergo addition to aziridines. The application of the enolate addition to aziridines has largely occurred in stereo-selective ring opening to form γ-amino carbonyl difunctionalized derivatives. In a recent report, γ-amino amides were prepared via stereo-controlled addition of a chiral amide enolate to activated optically active aziridines.[32] As shown in Scheme 11, the reaction of amide **32** proceeded at low temperature in THF to give addition products **33** and **34** in high yields and diastereo-selectivity. The diastereo-induction was largely governed by the chiral auxiliary (*S*,*S*)-pseudoephedrine to give (2*R*)-stereoisomers as predominant products. However, the configuration of the starting aziridines had a striking influence on the diastereo-selectivity, in which the (*S*)-aziridines produced high ratio of diastereomers (2*R*)/(2*S*), whereas reduced diastereo-selectivity was the result in the (*R*)-aziridines. The γ-amino amides were readily converted to chiral γ-amino acids and pyrrolidin-2-ones as useful reagents and building blocks for other syntheses (Table 9).

The SAMP-hydrazone of 2,2-dimethyl-1,3-dioxan-5-one represented a valuable chiral equivalent of ketone functionality for asymmetric alkylation with aziridines.[33] The nucleophilic addition of *N*-tosyl aziridine was achieved with the SAMP-hydrazone aza-enolate, generated by deprotonation of **35** with *tert*-BuLi, leading to **36** in good yield (70%) and excellent enantio-selectivity (ee >98%) after the removal of the hydrazone by ozonolysis (Scheme 12).

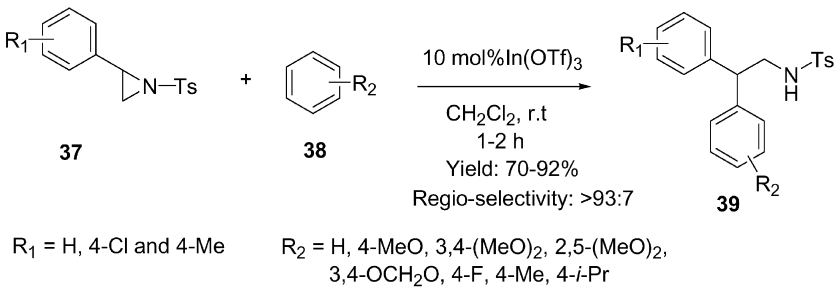
Excellent results were reported by Yadav et al. in their aziridine chemistry research of electron-rich aryl addition to *N*-Ts aziridines.[34] This was the first report regarding arenes **38** to undergo effective nucleophilic ring opening of aziridines in the presence of indium triflate $In(OTf)_3$



Scheme 11.



Scheme 12.

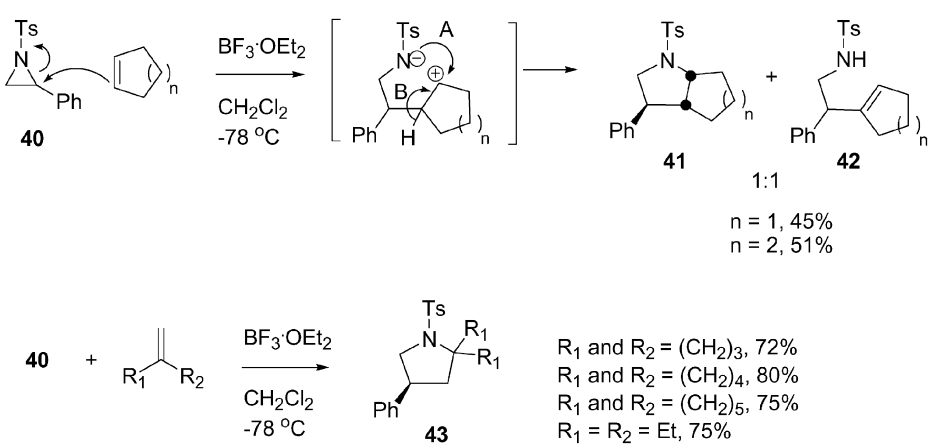


Scheme 13.

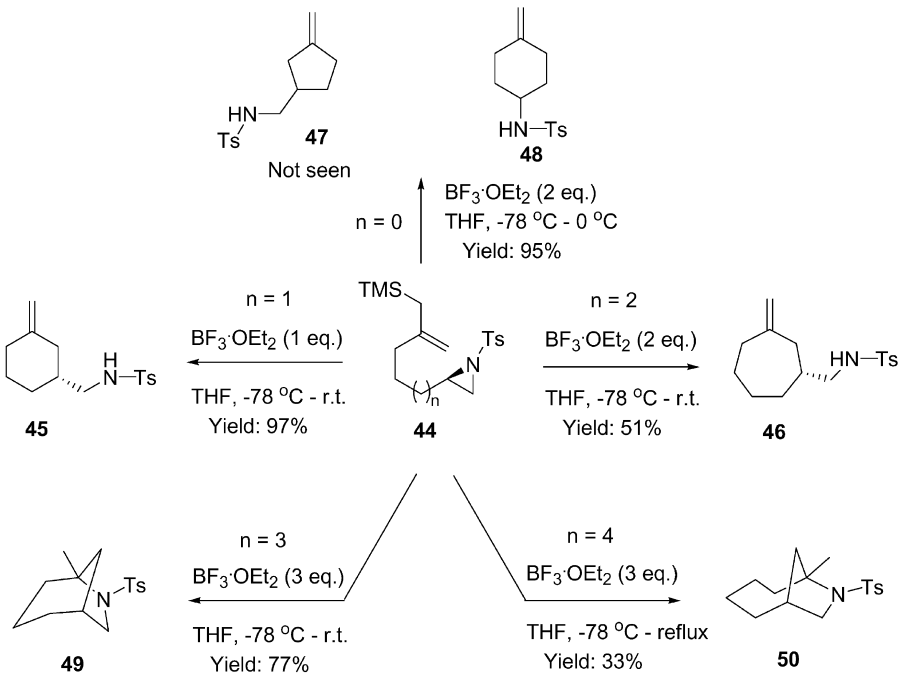
(Scheme 13). Among Lewis acids investigated, $In(OTf)_3$ and $Sc(OTf)_3$ were found to be the most effective catalysts to facilitate the ring cleavage with activated arenes. However, $In(OTf)_3$ was the only catalyst found to trigger C-arylation with non-activated aromatics such as benzene and naphthalene. The arene addition consistently proceeded at the benzylic position of the aziridines **37** leading to 1,2-bisaryl ethylamines **39** in very high regio-selectivity and high chemical yields.

Aziridines have been known for regio-selective ring opening reactions with carbanion nucleophiles, so being considered as useful building blocks for other syntheses. However, aziridines have also been found to undergo ring opening with non-anionic olefin functionality with its potential utility in robust construction of substituted pyrrolidines. This was reported by Mann and co-workers in [3+2] cycloaddition of phenyl aziridine **40** with olefins.[35] As depicted in Scheme 14, cyclopentene reacted with *N*-Ts phenyl aziridine catalyzed by $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at low temperature to give a mixture of bicyclic pyrrolidine **41** and substituted cyclopentene by-product **42** in 1:1 ratio. The designed product was presumably derived from the ring closure of a zwitterionic intermediate via path A, whereas the by-product formed via path B by loss of a β-proton from the intermediate carbocation. Similar results were also observed in the reaction with cyclohexene, which were consistent with those of dihydropyran in their earlier report.[36] The utility of the procedure was further extended to other olefins having methylenecycloalkanes of 4–6 membered rings and 1,1-diethylethylene. The cycloaddition products from these olefins were 2-spiropyrrolidines and 2,2-dialkylpyrrolidine in high yields (72–80%). These non-trivial molecules could be easily built using the cyclo-addition method.

Aziridine-allylsilanes were useful precursors for the synthesis of γ-amino olefin containing C-cycles of various ring sizes. Bergmeier and co-workers[37] found that when requisite aziridine-allylsilane **44** (n=1) was treated with 1 equiv. of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, *exo*-6-membered cyclic olefin **45** was obtained in nearly quantitative yield (Scheme 15). The Lewis acid mediated addition occurred at the C2 position of the aziridine. The consistent addition pattern was

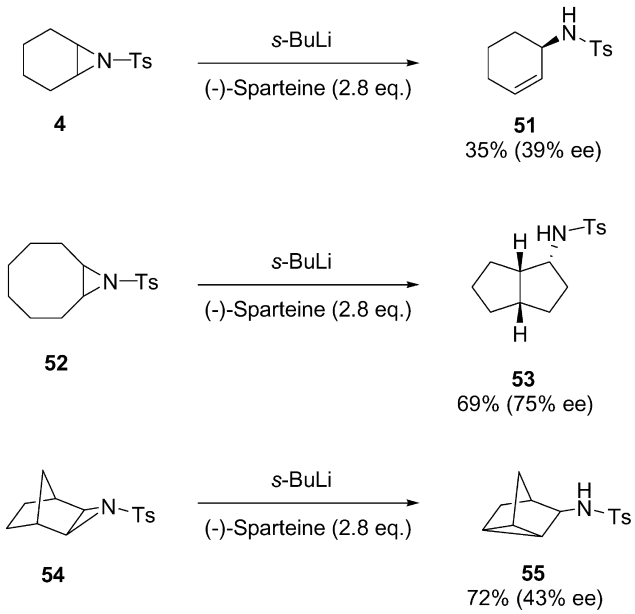


Scheme 14.



Scheme 15.

seen in the case of n=2, but with 2 equiv. of the Lewis acid needed to form *exo*-7-membered cyclic olefin **46** in 51% yield. In contrast, cyclization of aziridine-allylsilane (n=0) did not give C2 addition product **47**, but C1 adduct **48**. Small amount of desilylated azabicyclo[3.2.1]octane **49** was isolated, which was generated from intramolecular cyclo-addition of the sulfonamide to the olefin catalyzed by the Lewis acid. This observation inspired the researchers to convert aziridine-allylsilane precursors directly to an azabicyclic system in one pot. To achieve this sequential cyclization, 3 equiv. of $BF_3{\cdot}OEt_2$ were required and both azabicyclo[3.2.1]octane **49** and azabicyclo[4.2.1]nonane **50** were formed in 77 and 33% yields, respectively.

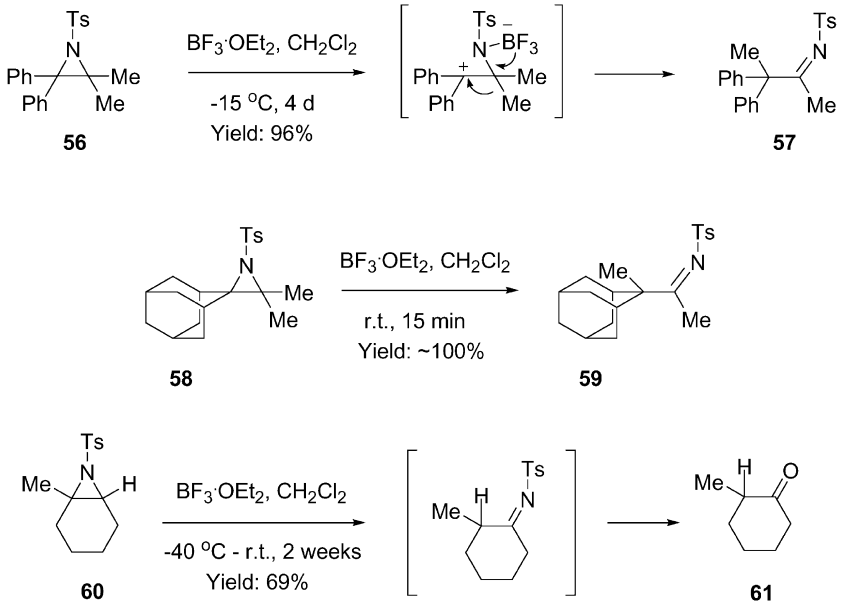


Scheme 16.

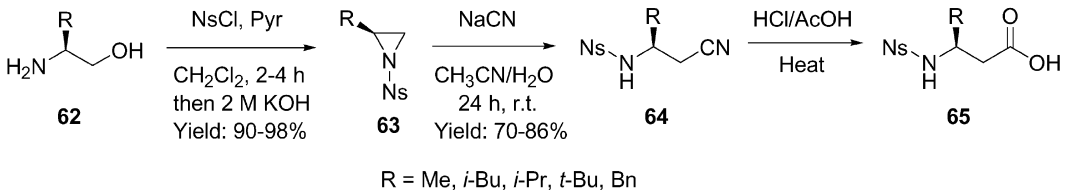
2.3. Rearrangement of aziridines

Muller and Nury further extended their desymmetrization chemistry to rearrangement of *meso*-*N*-tosyl aziridines leading to optically active carbocyclic amines.[20] As exhibited in Scheme 16, when the symmetric aziridine was exposed to *s*-BuLi in the presence of (−)-sparteine, the cyclohexene derived aziridine **4** gave an allylic amine **51** in low yield and low ee. On the other hand, appreciable yield (69%) and enantio-selectivity (75% ee) were seen in the rearrangement of cyclooctene aziridine **52** generating a *cis*-fused bicyclic amine **53**. In addition, bicyclic bridge-headed aziridine **54** underwent rearrangement under the same reaction conditions to afford product **55**. Although the researchers claimed these ring-opening amines were products of intramolecular carbenoid insertion analogous to that in epoxide lithiation, no sufficient experimental data were offered to support the argument. O'Brien et al. disclosed their work quite identical to the work mentioned above.[38] Results of more extensive aziridine rearrangement were captured in another report by Mordini and co-workers. Superbases were used to promote the rearrangement with cyclic and acyclic aziridines[39] and exemplified in the synthesis of α- and β-amino acids.[40]

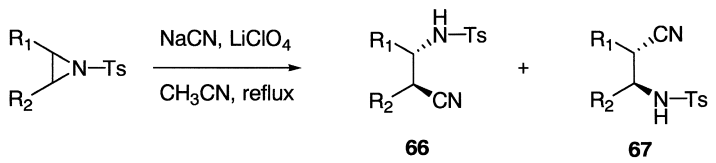
Substituted *N*-tosyl aziridines could undergo another type of rearrangement, namely aza-pinacol rearrangement. Similar to epoxide pinacol rearrangement, $BF_3{\cdot}OEt_2$ was a choice of a robust catalyst to facilitate such a transformation.[41] As exhibited in Scheme 17, tetra-substituted aziridine **56** was treated with the catalyst in CH_2Cl_2 to form *N*-tosyl imine **57**, which was hypothetically derived form a phenyl stabilized carbocation with coordination of the boron reagent to the ring nitrogen, followed by subsequent migration of a methyl group. The same results were obtained in aziridine **58** in quantitative yield. However, tri-substituted aziridine **60** was rearranged to give ketone product **61**, as a result of a



Scheme 17.



Scheme 18.



Scheme 19.

hydrolysed derivative from an imine intermediate. The migration evidently illustrated the preference of a hydrogen atom over an alkyl group.

2.4. Cyanide

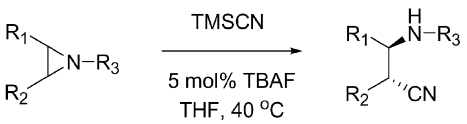
In general, ring opening of non-activated aziridines with a cyanide anion does not proceed without the assistance of Lewis acids, due to low nucleophilicity. However, when appropriate activating groups (such as carbonyl, carboxylate or sulfonamide) are attached to the aziridine nitrogen, the reaction becomes so useful that β-amino acids can be generated as one of its most useful applications. As shown in Scheme 18, aziridines **63** containing *p*-nitrobenzenesulfonyl (Ns) activating element could be derived from 1,2-aminols **62** and readily underwent nucleophilic attack with NaCN to give nitriles **64** in high yields.[42] High regioselectivity was consistently derived from the nitrile addition at the less hindered methylene carbon, except for phenyl aziridine showing a complex mixture. Acid mediated hydrolysis of addition products led to the synthesis of β-amino acids **65**. Because the starting amino alcohols were reduction products of α-amino acids, this method furnishes a complementary procedure for converting α-amino acids to β-amino acids in a straightforward manner.

In a separate report by Yadav and co-workers, no reaction was determined when NaCN was used to open the *N*-Ts aziridine ring.[43] However, they found the reaction took place effectively in the presence of 10 mol% $LiClO_4$ in hot acetonitrile (Scheme 19). Table 10 illustrated nucleophilic addition could be accomplished in less than 10 h to give nitrile products **66** and **67** in high yields. The reaction procedure remained to be simple with clean product profiles, but the regio-selectivity only appeared moderate.

Table 10. $LiClO_4$ catalyzed synthesis of β-azidoamines

R_1	R_2	Time (h)	Yield (%)	**66**:**67**
$-(CH_2)_3-$		7	90	—
$-(CH_2)_4-$		6.5	85	—
Ph	H	5.5	90	92:8
n-C_4H_9	H	8	87	15:85
n-C_8H_{17}	H	9.5	83	10:90

Trimethylsilylcyanide was found to be an efficient nucleophile for ring opening of aziridines under tetrabutylammonium fluoride (TBAF) catalytic conditions as shown in Scheme 20.[44] TBAF was used to release the cyanide anion, which then attacked the activated aziridines at the less hindered site. β-Amino nitrile derivatives **68** were obtained in excellent yields and regio-selectivity. It is noticeable that both phenyl and alkyl aziridines gave the external nitrile regio-isomers, which is in contrast to the regio-selectivity outcome of many other nucleophilic additions resulting in opposite selectivity. The activating group at the aziridine nitrogen seemed to be important to facilitate the addition, in which strong electron-withdrawing groups (Ts and COPh) were needed, except for the *t*-Boc aziridine giving complicated results. Non-activated aziridines did not react with TMSCN. Similar results were also reported by others, when catalysed by lanthanide cyanides [$(Yb(CN)_3$, $Y(CN)_3$ and $Ce(CN)_3$)] (Table 11).[45]



68

Scheme 20.

Table 11. Ring opening of aziridines with TMSCN mediated by TBAF

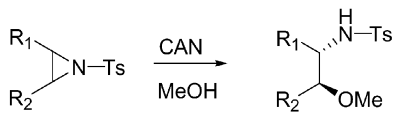
R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Ts	0.5	95
$-(CH_2)_3-$		Ts	5	>99
$-(CH_2)_6-$		Ts	24	0
H	H	Ts	10	91
Ph	H	Ts	0.6	>99
n-C_4H_9	H	Ts	0.3	>99
n-C_6H_{13}	H	Ts	2	82
$-(CH_2)_4-$		COPh	12	88
$-(CH_2)_4-$		H	24	0
$-(CH_2)_4-$		Bn	24	0
$-(CH_2)_4-$		Boc	24	0

3. Oxygen nucleophilic addition

Although structurally identical to epoxides, aziridines, in general, show lower reactivity toward oxygen containing nucleophiles. Therefore, the ring opening of aziridines is largely dependent on the activation at the ring nitrogen either by attaching electron-withdrawing groups and/or on the use of appropriate Lewis acids in oxygen nucleophilic addition. Due to appealing use of bi-functionalized amines in organic synthesis and pharmaceutical research, dramatic progress has been made in recent years in searching for efficient, convenient, low cost and environmentally friendly reagents, as well as simple conditions for ring opening of aziridines.

3.1. Alkyl and aryl alcohols

A powerful aziridine ring opening reagent, ceric ammonium nitrate (CAN) was identified by Chandrasekhar et al. recently to catalyze aziridine ring cleavage to form vicinal amino methyl ethers.[46] The nucleophilic addition of methanol to various tosyl activated aziridines catalyzed by CAN presents a general method for the preparation of amino ethers **69** due to a robust procedure and high yields (Scheme 21). However, the limit remains in the regio-chemistry, when less sterically biased aziridines were used for the ring opening reaction (Table 12).



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Scheme 21.

Table 12. Ring opening of *N*-tosylaziridines with MeOH

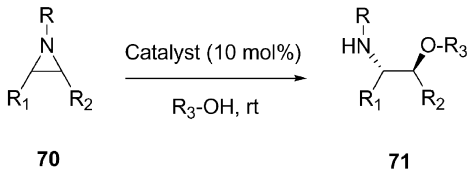
R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_4-$		93	—
$-(CH_2)_3-$		94	—
$-(CH_2)_5-$		77	—
H	Ph	90	Internal
n-C_4H_9	H	87	23:77
$MeO_2C(CH_2)_8$	H	85	28:72

A variety of N-substituted aziridines **70** underwent the ring opening reaction with primary alcohols to give vicinal *trans* amino ether **71** in excellent yields, when catalytic amount of $Sn(OTf)_2$ and $BF_3{\cdot}OEt_2$ were used.[47] The tosyl activated aziridine was a good substrate for the ring opening, whereas a non-activated phenyl aziridine worked almost equally well, but with much shorter reaction time needed to complete the addition. On the other hand, the $BF_3{\cdot}OEt_2$ catalyst accelerated the ring opening significantly, particularly in the cases of MeOH and BnOH. This is one of most robust methods reported in the literature for the alcoholysis ring opening of aziridines. It is noticed that regio-selectivity appeared to be poor as reported in mono-substituted aziridines. Similar results were reported using the same catalysts under the microwave conditions.[48] The pronounced advantage for this procedure includes the addition with hindered alcohols that was achieved in microwave in less than 15 min instead of 2 days without microwave irradiation (Table 13, Scheme 22).

Another very interesting regio-selective ring opening of a piperidinyl aziridine with alcohols was disclosed recently from our laboratory.[49] This nucleophilic addition took place with piperidinyl aziridine **6** in the presence of $BF_3{\cdot}OEt_2$ in alcoholic solvents. We found the size of the alcohols played

Table 13. Cleavage of aziridines with alcohols catalyzed by $Sn(OTf)_2$ and $BF_3{\cdot}OEt_2$

R	R_1	R_2	R_3	$Sn(OTf)_2$		$BF_3{\cdot}OEt_2$	
				Time	Yield (%)	Time	Yield (%)
Ts	$-(CH_2)_4-$		Me	1 h	99	20 min	99
	$-(CH_2)_4-$		Allyl	1 h	99	1 h	92
	$-(CH_2)_4-$		Bn	20 h	90	2 h	94
	H	Ph	MeOH	30 min	98	15 min	99
	C_5H_{11}	H	MeOH	30 h	76	4 h	96
Ph	$-(CH_2)_4-$		Me	10 min	76	10 min	92
	$-(CH_2)_4-$		Allyl	15 min	86	5 min	91
	$-(CH_2)_4-$		Bn	24 h	66	2 h	86



Scheme 22.

a role in the rate of the addition: longer reaction time for hindered *t*-BuOH to complete the conversion. In all the cases studied, the nucleophilic addition occurred at the *para* position to the piperidine nitrogen in >20:1 ratio in favor of the designed products **72** (Table 14). The consistent high yields with remarkably high regio-selectivity in such a simple system were a gift to our research program. The regio-selectivity was rationalized based on a plausible argument in which a nucleophile accessed the C4 carbon more readily than the C3 carbon, due to the bottom face shielding by the carboxylate-boron complex (Scheme 23). The more pronounced selectivity in the Lewis acid catalyzed ring open of the aziridine is consistent with that in carbanion addition discussed in Section 2.1.

Table 14. Ring opening of aziridine with alcohols catalyzed by $BF_3{\cdot}OEt_2$

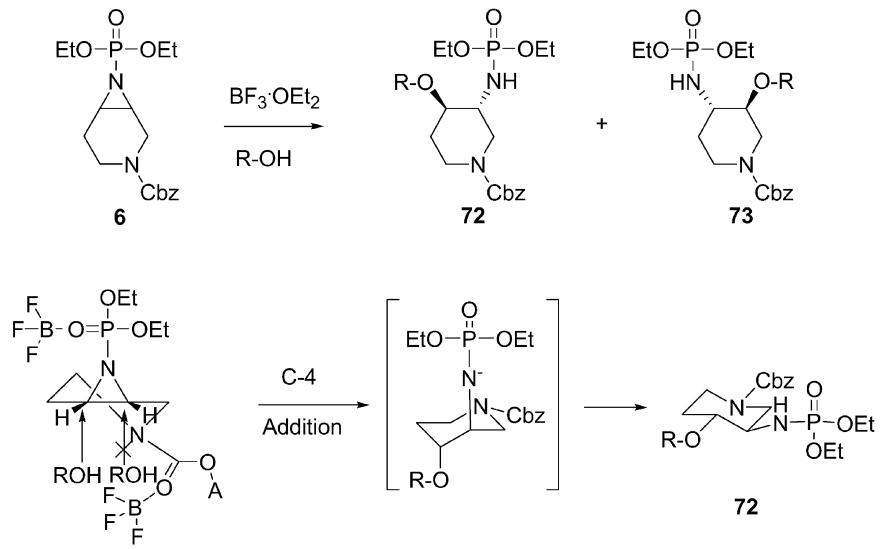
R-OH	Temperature	Time (h)	Yield (%) of **72** (%)	**72**:**73**
MeOH	0 °C	2	72	>20/1
EtOH	0 °C	2	83	>20/1
i-PrOH	0 °C–rt	5	84	>20/1
t-BuOH	rt	16	87	>20/1
BnOH (CH_2Cl_2)	rt	6	81	>20/1
PhOH(CH_2Cl_2)	rt	6	78	>20/1

Table 15. KSF clay catalyzed ring opening of aziridines with alcohols

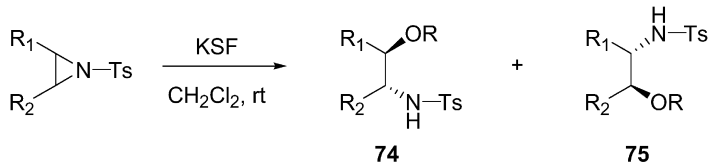
R_1	R_2	R	Time (h)	Yield (%)	**74**:**75**
$-(CH_2)_4-$		Allyl	5.0	89	—
$-(CH_2)_4-$		Propargyl	6.5	90	—
$-(CH_2)_3-$		Allyl	6.0	85	—
Ph	H	Et	3.5	90	96:4
p-Tolyl	H	Allyl	3.0	88	97:3
p-Tolyl	H	Benzyl	4.0	89	92:8
Cyclohexyl	H	Et	6.0	81	7:93
n-Bu	H	Allyl	8.5	87	12:88

The advances in organic chemistry in searching for effective solid acidic catalysts such as clays, ion-exchange resins and zeolites have led to discovery of montmorillonite KSF catalysis for the cleavage of aziridines with alcohols.[50] The low cost and environmentally compatible catalyst triggered the ring opening of tosyl aziridines with various alcohols (Scheme 24). The procedure not only presented a convenient method in operation, but gave the products in high yields as seen in Table 15. More significantly, the clay catalysis resulted in the nucleophilic addition to alkyl substituted aziridines with higher regio-selectivity than that in other protic or Lewis acid catalytic conditions.

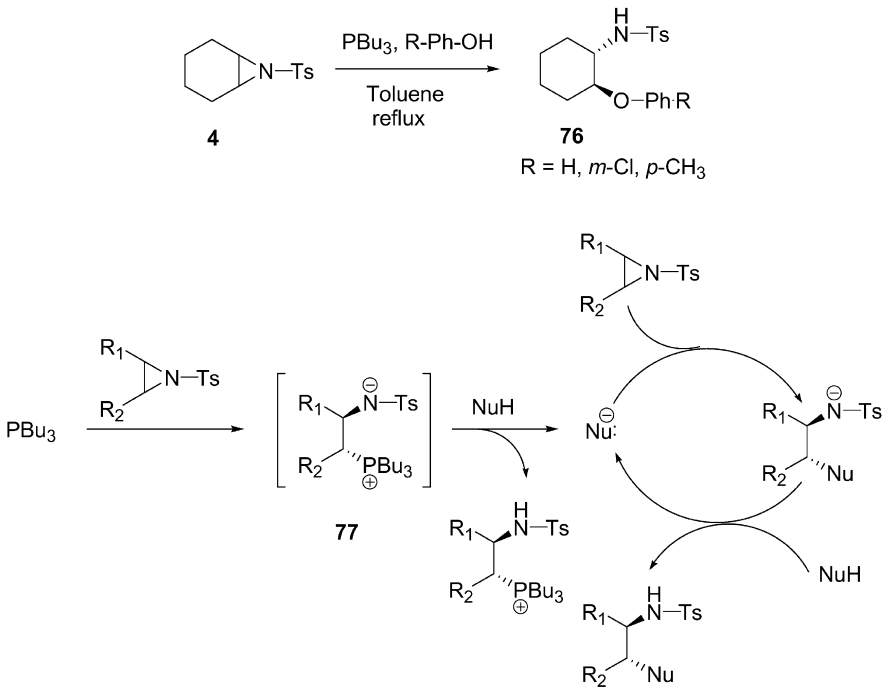
It has been noticed that phosphine reagents are weaker bases, but stronger nucleophiles than amines. This unique feature was captured by Dai and co-workers in ring opening of aziridines promoted by tributylphosphines.[51] When *N*-tosyl cyclohexyl aziridine **4** and phenol was treated with 10 mol% of PBu_3 in refluxing toluene, good to excellent yields of aziridine ring opening products were obtained with *trans* stereochemistry. Under the same conditions, no ring opening products were obtained in the



Scheme 23.



Scheme 24.



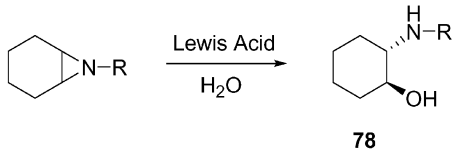
Scheme 25.

absence of PBu_3, which suggested that the phosphine reagent was involved in the catalysis. This was further supported by a mechanistic study of the ring opening reaction, in which a crystalline perchlorate salt of phosphonium **77** was isolated and characterized by ^1H and ^{31}P NMR spectroscopies. A possible pathway was proposed as shown in Scheme 25, where the organophosphine acts as a nucleophilic trigger to produce **77**, which then serves as a base to deprotonate the nucleophile. The aryloxy anion then attacks the aziridine to complete the catalytic cycle. However, the application of this procedure remains limited only to aryl alcohols and regio-selectivity was not discussed.

3.2. Hydroxyl anion

The ring opening of both activated and non-activated aziridines with a water molecule can be achieved similarly to that with alcohols. Reaction conditions have been developed mainly under protic or Lewis acid catalyzed conditions. The stereochemical outcome of the addition is controlled by an *anti* attack in general and the regio-chemistry is largely dependent on the reaction conditions chosen. Steric effects and effects from the functional group present in substrates also play roles in governing the site of the addition.

The ring opening of activated aziridines with the water nucleophile has long been recognized under the conditions of mineral acids[52] and recently Lewis acids, such as $BF_3{\cdot}OEt_2$ and $Sn(OTf)_2$, were reported in the literature to promote the ring opening reaction.[53] As shown in Scheme 26, the water molecule attacked the cyclohexyl ring *anti* to the aziridine nitrogen to give *trans* aminols **78**. Both activated and non-activated aziridines proved substrates for the opening reaction. Although other Lewis acids, such as $Cu(OTf)_2$, $CuCl_2$, $SnCl_2$, $AlCl_3$, $FeCl_3$ and $LiClO_4$, were also explored to catalyze the ring opening reaction, only inefficient functional group transformation was observed with essentially impractical chemical yields (Table 16).



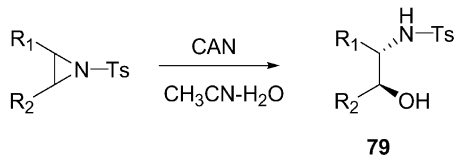
Scheme 26.

Table 16. Ring opening of cyclohexylimines with water catalyzed by $BF_3{\cdot}OEt_2$ and $Sn(OTf)_2$

R, Lewis acid	*p*-Tosyl			Ph		
	Solvent	Time (h)	Yield (%)	Solvent	Time (min)	Yield (%)
$BF_3{\cdot}OEt_2$	CH_3CN	5	90	THF	20	90
$Sn(OTf)_2$	CH_3CN	15	89	THF	20	92

Ceric ammonium nitrate (CAN) again demonstrated high utility in catalyzing ring opening of aziridines leading to the synthesis of vicinal amino alcohols as seen in vicinal amino ether formation.[46] Tosyl activated aziridines underwent the ring opening smoothly and consistent high chemical yields for aminols **79** were obtained in all cases reported. Again, the same limitation for the poor regio-chemistry was seen in water addition as that in alcohol addition mentioned above (Scheme 27), except for that in aryl aziridines (Table 17).[54]

High regio-selective aziridine ring opening was demonstrated by Concellon and Riego[55] in the case of non-activated amino aziridines. The water molecule attacked the amino aziridines at either C3 or C2 depending on the reaction conditions employed. When the dibenzylamino



79

Scheme 27.

Table 17. Ring opening of *N*-tosylaziridines

R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_4-$		95	—
$-(CH_2)_3-$		90	—
$-(CH_2)_5-$		75	—
H	Ph	92	Internal
C_4H_9	H	90	70:30
$MeO_2C(CH_2)_8$	H	75	68:32

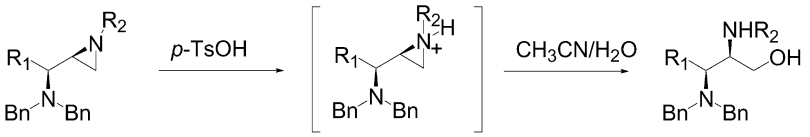
aziridines **80** was treated with 1 equiv. of *p*-TsOH in a mixed solvent CH_3CN/H_2O (Scheme 28), the addition occurred at the less hindered methylene via a protonated aziridinium intermediate, leading to 2,3-diaminoalkan-1-ols **81** as a result of the C3 addition in good to high yields, as shown in Table 18. This is consistent with the observation reported earlier by Davis and co-worker[56] with regio- and stereo-selectivity of the addition to an arylaziridine under protic conditions. The reaction proceeded faster at higher temperature (80 °C) with limited effects on the reaction yield and purity. However, higher regio-selectivity (19:1 ratio) was observed at 20 °C.

Alternatively, the same group developed another set of reaction conditions, which allowed the C3 addition as a predominant ring opening site.[55] $BF_3{\cdot}OEt_2$ was used to promote the addition at the more hindered carbon. In this case, the reaction was carried out in CH_3CN on heating and amino alcohols **82** were obtained in low to good yields. Total regio- and stereo-selective ring opening was characterized by NMR spectroscopy. Addition at the C2 position was rationalized by neighboring group participation of the dibenzylamine resulting in a highly activated aziridinium salt form as shown in Scheme 29, which underwent water attack to give the C2 addition products. The double inversion at the C2 center led to the retained stereochemistry (Table 19).

Table 19. C-2 Ring opening of aziridine **80**

R_1	Me	Me	*i*-Bu	Bn	$TBSOCH_2$
R_2	Bn	Pr	Bn	Bn	Bn
Yield (%)	40	38	81	74	76

Aziridinyl carboxylates are of particular interests in nucleophilic addition, due to the importance of addition products as useful amino acid congeners. Under protic conditions, the ring opening preferentially proceeded at the β-position to give serine-type amino acid analogs. In connection with work on pyrrolidine-containing HIV protease inhibitors, Iqbal's group developed an efficient synthetic pathway to construct tripeptide derivatives by using regio- and stereo-selective ring opening of aziridine peptide (Scheme 30).[57] *p*-TsOH promoted addition of water



80 81

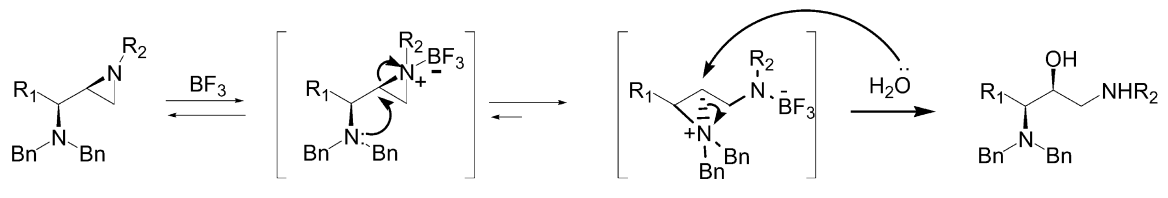
Scheme 28.

Table 18. C-3 Ring opening of aziridine **80**

R_1	R_2	Temperature (°C)	Time (h)	Yield (%)
Me	Bn	80	1	72
Me	Bn	20	24	90
Me	Pr	80	1	76
i-Bu	Bn	80	0.5	78
Bn	Bn	80	0.5	74

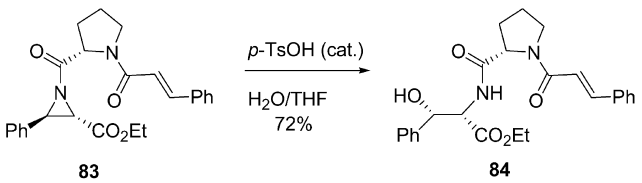
to the aziridine **83** occurred at the β-position in an *anti* attack fashion to give β-hydroxy phenylanaline analog **84** in 72% yield as a single stereo-isomer.

Alternatively, an indirect α-addition to an aziridine to result in an α-ring opening product was presented by Cardillo and co-workers[58–60] An acyl activated aziridinyl amide **85** was catalyzed by $BF_3{\cdot}OEt_2$ to initially produce a rearrangement oxazoline **86**, which was then hydrolyzed to give an isoserine product **87**, an equivalent of β-adduct. The stereo center at the α-position was inverted during this



80 82

Scheme 29.



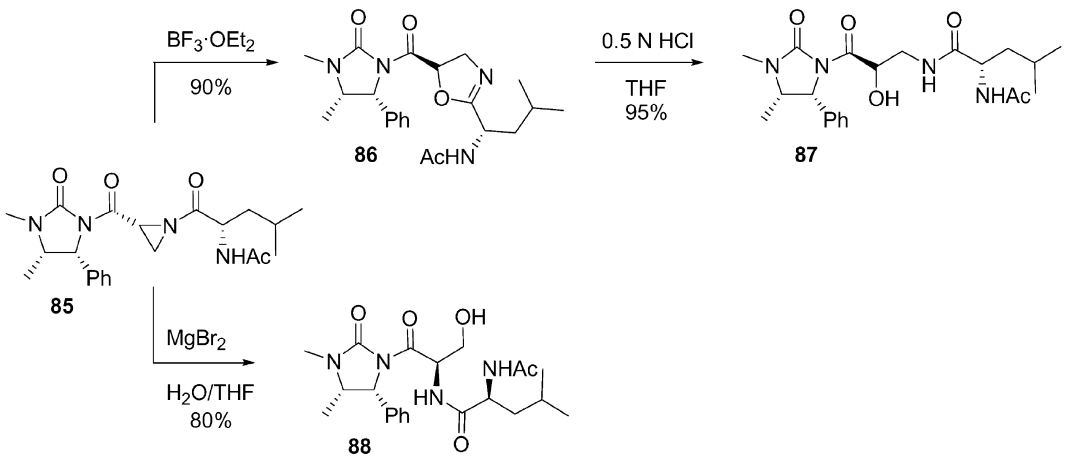
Scheme 30.

transformation by *anti* attack. In addition, the β-attack could also be achieved using a different set of ring opening conditions involving Lewis acid $MgBr_2$ and only 1.1 equiv. of the water molecule needed to give D-serine product **88** (Scheme 31).

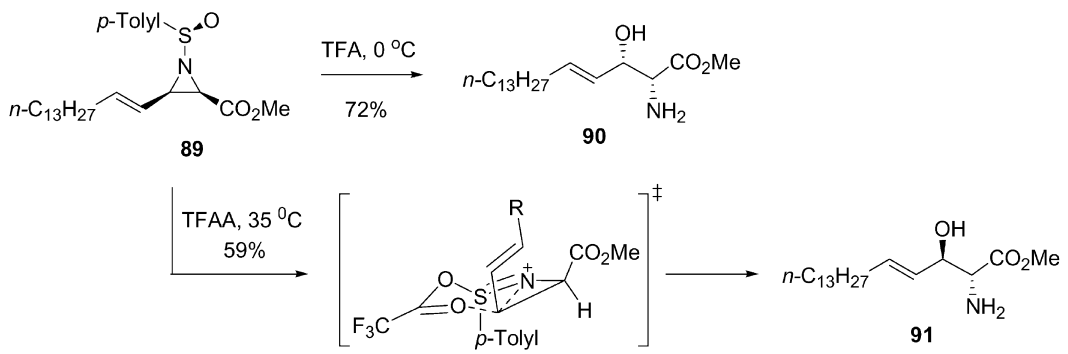
Other reaction conditions were also explored in the aziridine ring opening to form a hydroxy amine difunctionality, including trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA).[61] In both cases, the same regio-chemistry, β to the carboxylate of aziridine **89**, was observed. One notable difference was observed with opposite chirality between adducts **90** and **91**. This was rationalized via an intramolecular transition state as shown in Scheme 32. A complementary procedure was also reported using an acyl or a carbamate as an activating group, which was involved in the ring opening reaction to form an oxazolidinone.[62,63] After hydrolysis, a hydroxy amine was obtained for further functionalization (Scheme 33).

Most of aziridine ring openings to form amino alcohols were achieved under either protic or Lewis acid conditions. However, Besbes[64] reported the ring opening could also be achieved using a neutral protocol, but the addition occurred specifically at the more substituted carbon of acyl aziridines **92**. The formation of a tertiary carbocation for the confirmed regio-specificity was excluded by the author, whereas a mechanism involving the formation of a hydrogen bond with the acyl group at the aziridine nitrogen was proposed to support the observation. The second water molecule came to break the weakened bond in the transition state to yield the tertiary alcohols **93** in 76–91%.

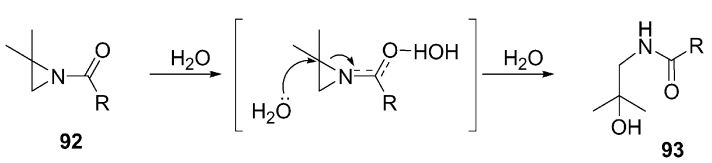
Scarce examples were found in the literature describing



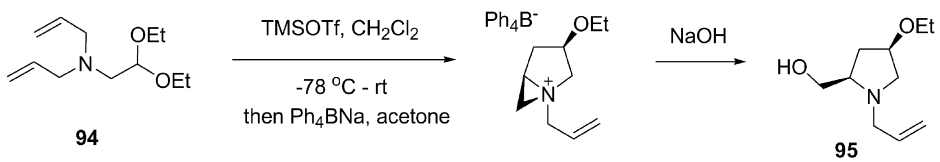
Scheme 31.



Scheme 32.

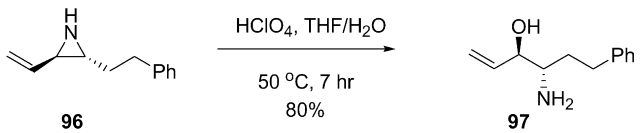


Scheme 33.

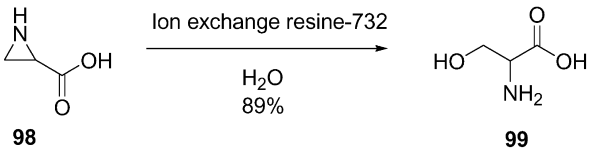


Scheme 34.

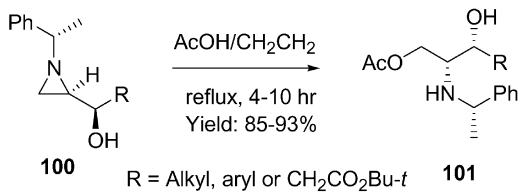
nucleophilic aziridine ring opening to form aminols under basic conditions, which has been believed largely due to insufficient activation of the aziridine ring. Exceptions were found in a report by Rayner and co-workers[65] in which a highly activated aziridinium intermediate was generated from diallylamine **94** and underwent attack by a hydroxy group to give pyrrolidinyl methanol **95** in 67%. Steric control governed the site of the addition at the less hindered carbon leading to the primary alcohol (Scheme 34). This tandem cationic cyclization-aziridinium ion formation-nucleophilic ring opening procedure provided a useful methodology for the stereo-controlled synthesis of substituted pyrrolidines from an acyclic precursor.



Scheme 35.



Scheme 36.



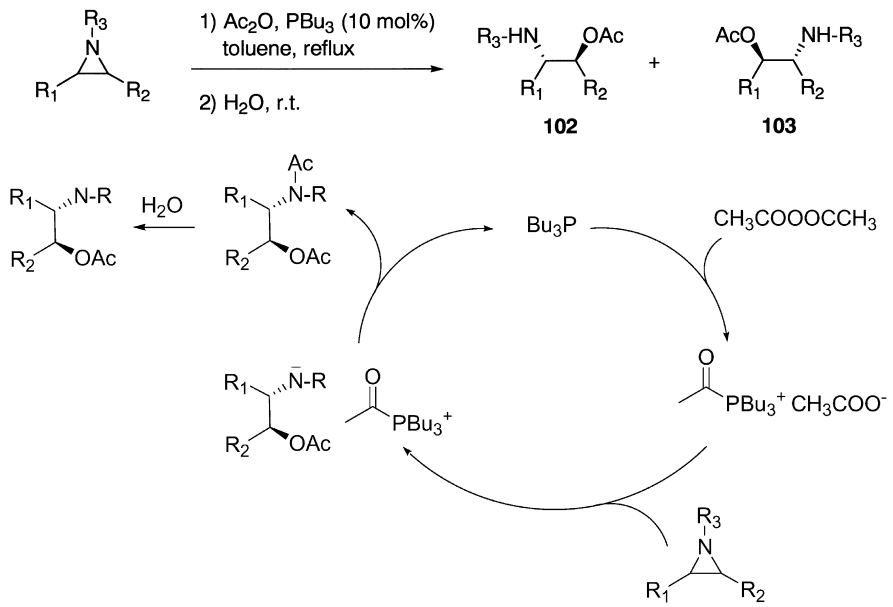
Scheme 37.

The majority of aziridine hydrolysis leading to amino alcohol derivatives took place with fully substituted aziridine ring nitrogen for sufficient activation to undergo nucleophilic attacks. However, it should be noted that hydrolysis of *N*-H aziridines can also be achieved under protic conditions, such as $HClO_4$ (Scheme 35)[66] ion exchange resin (Scheme 36)[67] with high regio-selectivity and stereo-selectivity.

3.3. Carboxylate anion

Regio-selective ring opening of activated or non-activated aziridines in the presence of carboxylic acids proceeds in a similar steric controlled fashion to that of the alcohols and the water molecule. The carboxylates of the addition products usually resided at the less congested carbons. The work reported by Ha and co-workers[68,69] is a recent example of the regio-selective ring opening of aziridines **100** with carboxylic acids to give amino alcohol **101**. It is widely believed that the acid used catalyzes the addition by activating the ring nitrogen and then the second acid molecule attacks the less hindered ring carbon to give amino carboxylates (Scheme 37).[70]

The ring opening of aziridines catalyzed by tributylphophine with acetic anhydride is a complementary procedure to prepare amino esters. Based on previous observation of

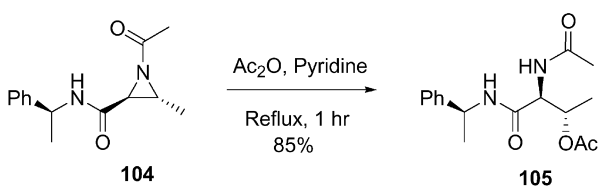


Scheme 38.

an organophosphine promoted ring opening reaction of aziridines and epoxides, Fan and Hou[71] found that activation of anhydrides with a catalytic amount of the organophosphine facilitated the aziridine ring opening under neutral conditions with high chemical yields (Scheme 38). In general, the reaction products (**102** and **103**) were obtained in good yields with excellent regio-selectivity, but regio-chemistry suffered in the phenyl aziridine case (Table 20). The steric argument may explain the results due to the increasing bulkiness of the activated tributylphosphine-anhydride complex, leading to the attack at the less crowded ring carbon. A plausible mechanism was proposed based on ^{31}P NMR spectral evidence. Tributylphosphine activated the anhydride by forming $Bu_3P^+OAc{\cdot}AcO^-$, which underwent attack to the aziridine to yield the ring opening product with recycling of the phosphine catalyst.

Table 20. The tributylphosphine catalyzed ring opening of aziridines with acetic anhydride

R_1	R_2	R_3	Time (h)	Yield (%)	**102**:**103**
$-(CH_2)_4-$		Tosyl	24	85	—
Ph	H	Tosyl	12	76	65:35
$-(CH_2)_4-$		-COPh	24	72	—
$-(CH_2)_4-$		Boc	48	81	—
n-Bu	H	Tosyl	24	89	>95:5



Scheme 39.

Table 21. $In(OTf)_3$-catalyzed ring opening of aziridines with carboxylic acids

R_1	R_2	Acid	Time (h)	Yield (%)	**107**:**108**
$-(CH_2)_3-$		Acetic acid	3.5	89	—
$-(CH_2)_3-$		Crotonic acid	2.5	92	—
Ph	H	Phenylacetic acid	3.0	90	92:8
Ph	H	Acetic acid	2.5	92	96:4
c-Hex	H	Acetic acid	4.0	89	7:93
n-Bu	H	Acetic acid	4.5	87	12:88

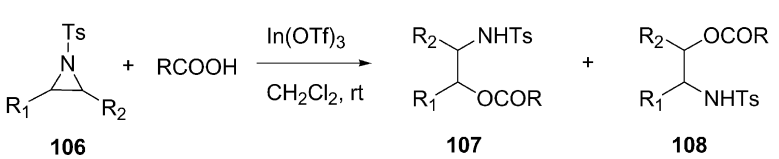
This method is equally applicable to epoxide ring opening with even higher chemical yields.

A similar procedure was used by Cardillo and co-workers to convert acyl aziridines to enantio-pure L-allo-threonine analogs.[72] The activated aziridine ester **104** was treated with acetic anhydride in the presence of pyridine. The ring opening reaction was conducted in refluxing pyridine with high regio- and stereo-selectivity in product **105** as shown in Scheme 39. It was believed that the catalytic cycle for the aziridine ring opening with Ac_2O-Pyr should likely proceed in an identical fashion to that with Ac_2O-PBu_3 as mentioned previously.

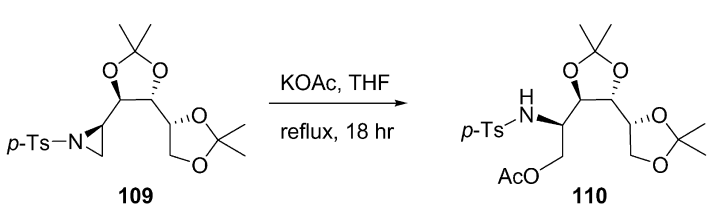
A general procedure was recently developed in the laboratory of Yadav,[73] in which indium triflate was found to effectively catalyze the ring opening of aziridine **106** under mild reaction conditions leading to β-amino acetates and benzoates in high yields and high regio-selectivity. Both phenyl-and alkyl-*N*-tosyl aziridines underwent cleavage by acids to form the products **107** and **108** in decent, but opposite, regio-selectivity as seen in other nucleophilic addition to aziridines. However, the authors did not mention potential application of this method for alcohol nucleophiles, which could be indicative of the limitation of the method only to the acids, not general to other types of nucleophiles (Table 21, Scheme 40).

An alternative method for the ring opening of an *N*-tosyl aziridine was reported by the laboratory of Compernolle[74] describing conversion of aziridine **109** to the corresponding amino acetate **110** using potassium acetate as a nucleophile. The tosyl aziridine was heated with KOAc in THF for 18 h to afford the product in 90% (Scheme 41). Excess nucleophile must be used to prevent dimeric by-product formation. The product generated was a precursor to an aminoglucital leading to the synthesis of analogs of 1-deoxymannojirimycin, inhibitors of mannosidases. The experiment represented an example of the aziridine ring opening under neutral conditions without a catalyst (Scheme 41).

Rearrangement of acyl aziridines into oxazolines has been well documented in the literature. The most widely used method would be the ring opening of aziridine catalyzed by $BF_3{\cdot}OEt_2$. One very recent representative sample included



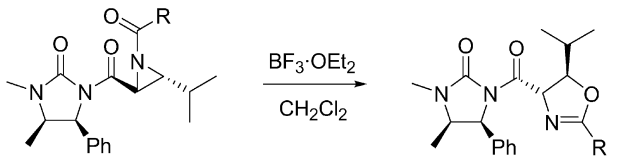
Scheme 40.



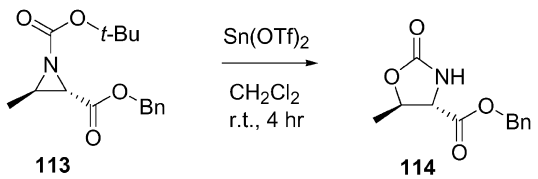
Scheme 41.

the report from Cardillo's group in an effort toward synthesis of 5-isopropyl-oxazoline-4-imide as *syn*-hydroxyleucine precursor.[75] The ring expansion to the corresponding *trans*-oxazolines occurred under complete regio- and stereo-control, by treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Scheme 42). The reaction of both alkyl and aryl amides **111** provided high chemical yields. The mechanistic aspects of this reaction were discussed by Hori[76] and Lectka,[77] in which an S_N1 pathway was suggested to explain the observed stereochemistry. A number of isomerization methods have been developed to facilitate this transformation, including mineral acid H_2SO_4,[78] azaphilic metal salts $Cu(OTf)_2$, $Sn(OTf)_2$, $Zn(OTf)_2$,[79,80] $MgBr_2$, $Zn(O_2CCF_3)_2$,[81] and halide salt NaI.[82] These methods are complementary to that by $BF_3{\cdot}OEt_2$ catalysis for the improvement of reaction conditions, regio- and stereo-selectivity. The formed oxazolines **112** can be hydrolyzed to vicinal amino alcohols, useful functionalized intermediates as building blocks for other syntheses (see Section 3.2).

Aziridine ring expansion has been further extended to another subclass of oxazolidines under Lewis acid conditions. One recent report by Lucarini and Tomasini[83] showed that the optically active aziridine ester **113** containing a *t*-Boc group was converted to the corresponding oxazolidin-2-one **114** in quantitative yield with complete regio- and stereo-selectivity (Scheme 43). The retention of the stereochemistry at the carbon of the bonding breaking and forming process can be rationalized in the same fashion as that discussed earlier.



Scheme 42.



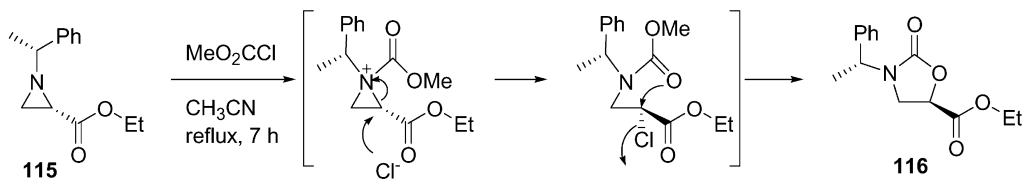
Scheme 43.

Due to sufficient nucleophilicity of the aziridine nitrogen, the ring opening could be initiated by the formation of the aziridinium ion intermediates when treated with chloroformates, which then underwent double nucleophilic addition to form oxazolidines. This work was reported by Lee and co-workers[84] in the enantio-selective synthesis of 5-functionalized oxazolidin-2-ones **116**. Because of double nucleophilic additions at the chiral center of aziridines **115**, retention of the configuration was the result with high chemical yields. In contrast to other Lewis acid catalysed aziridine ring expansion to form oxazolidin-2-ones, the regio-chemistry occurred at the α-position of the aziridine carboxylates, with the chloride attacking the chiral carbon to give a ring opening intermediate followed by ring closure to form an oxazolidinone ring as depicted in Scheme 44. Methyl and allyl chloroformates were good substrates for the ring expansion, whereas benzyl chloroformate caused a dramatic decrease in the reaction rate.

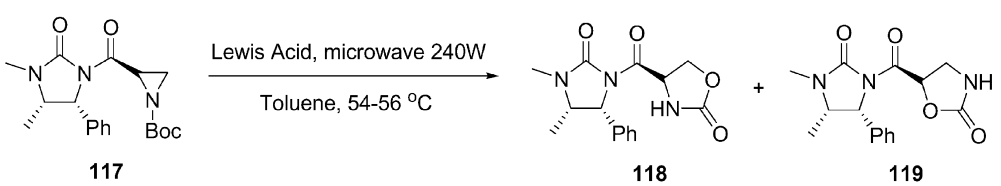
Microwave-assisted rearrangement of *N*-Boc-chiral aziridine-2-imides and esters to oxazolidin-2-ones in the presence of different Lewis acids was reported by Cardillo's laboratory.[85] The regio-selectivity of the reaction strongly depends upon the Lewis acids selected and the reaction conditions. As shown in Scheme 45 and Table 22, the treatment of aziridine **117** with 1 equiv. of the Lewis acid, $Cu(OTf)_2$, gave nearly 100% yield, but low ratio of regio-isomers, in favor of 4-substituted oxazolin-2-one **118** over isomer **119**, whereas $Zn(OTf)_2$ resulted in lower yield, but excellent regio-selectivity. In contrast, $BF_3{\cdot}OEt_2$ catalyzed the ring expansion with both excellent yield and

Table 22. Lewis acid assisted aziridine ring opening

Lewis acid	Reagent concentration (M)	Yield (%)	**118**:**119**
$Cu(OTf)_2$	0.028	>99%	64:36
$Zn(OTf)_2$	0.028	65	>99:1
$BF_3{\cdot}OEt_2$	0.056	>99	72:28
$BF_3{\cdot}OEt_2$	0.028	>99	>99:1
$MgBr_2{\cdot}OEt_2$	0.028	0	—
$BF_3{\cdot}OEt_2$	0	65	85:15



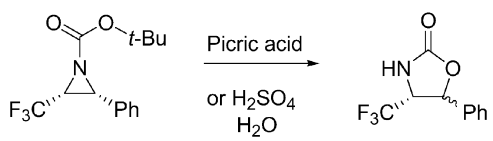
Scheme 44.



Scheme 45.

regio-selectivity at only 0.028 M concentration, but reduced ratio of regio-isomers at a higher concentration. $MgBr_2 \cdot OEt_2$ was found ineffective to the ring expansion under the microwave conditions with only recovered starting aziridine. The same reaction conditions were used to initiate the rearrangement catalyzed by $BF_3 \cdot OEt_2$ in 0.028 M concentration without microwave assistance, the products were observed in 65% yield, but 85:15 ratio of regio-isomers. This suggested that the ring expansion is activated by microwave irradiation (Table 22).

In contrast, a racemization outcome of stereochemistry is a result of selection of protic acids as catalysts in the ring expansion of aziridines to oxazolidin-2-ones. Two representative examples were found in the literature using H_2SO_4 and picric acid (Scheme 46),[86] in which stereo-selectivity suffered so much that the synthetic potential is greatly diminished in comparison to the aforementioned mild and selective methods.



picric acid: 2,4,6-trinitrophenol

Scheme 46.

3.4. Miscellaneous

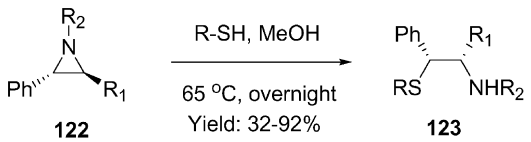
Other oxygen containing acids such as *p*-tolyl solfonic acid[87] and phosphoric acid[88] were also reported as effective nucleophiles to undergo ring opening of aziridines. A particular notion should be made to Sommerdijk's[89] work on autocatalytic ring opening of *N*-acylaziridines with complete control of regio-selectivity (Scheme 47). The researchers deliberately incorporated fatty acid chains and phenoxy groups to the aziridine **120** to increase their lipophilicity, which then acted as an interface orientation pointer under the reaction conditions of an organic-aqueous medium. Therefore, the unsubstituted aziridine carbon atom was exposed to the aqueous layer leading to the attack by phosphoric acid, which resulted in exclusive regio-selectivity (**121**).

4. Sulfur nucleophilic addition

The ring opening reaction of aziridines by thiols can readily proceed in either an activated or a non-activated form. The aziridine ring nitrogen in the non-activated form can served as a base to abstract a proton from the thiophinols or alkyl thiols to form an aziridinium intermediate, which is a very labile species. The nucleophiles of the deprotonated thiol anion then attack the aziridine ring carbon. The orientation of the attack generally occurs at a less hindered site to provide 2-amino sulfide products. On the other hand, activated aziridines, lacking basic nitrogen, often require a Lewis acid for further activation; thiol nucleophiles approach the less hindered site to open the ring. Consistently high chemical yields and high regio-selectivity have been observed in many reports.

4.1. Alkyl and arylsulfide anion

Thiophenols and aliphatic mercaptans are nucleophiles sufficient to induce ring opening of aziridines without assistance of catalysts or bases. A recent report by Leeuwen and co-workers[90] described such conditions in regio-selective addition of various sulfur nucleophiles to aziridines **122** derived from norephedrine. The reaction required heating in methanol overnight to complete the addition (Scheme 48). The optically active vicinal amino disulfide products **123** were efficient catalytic ligands for asymmetrical transfer hydrogenation of unsymmetrical ketones. Similar results were also reported by others in thiophenol addition to non-activated aziridines to give regio-selective β-amino sulfides in good yield.[91,92]



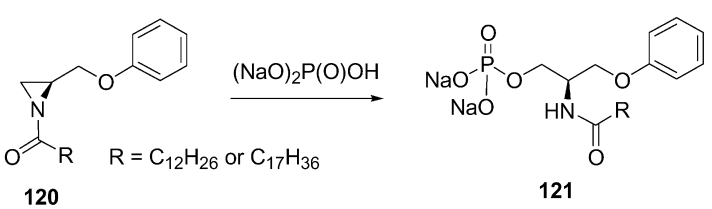
122 123

R = Ph, Bn, *i*-Pr; R_1 = Me or Ph; R_2 = H or Me;

Scheme 48.

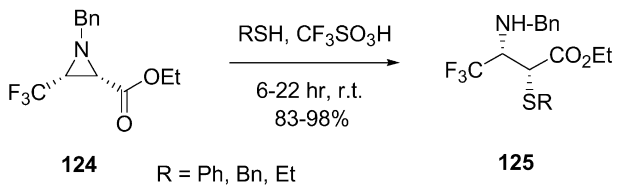
Alternatively, the ring opening reaction proceeded more readily with thiols in the presence of a strong acid (CF_3SO_3H).[93] In this case, the reaction was carried out at room temperature and completed in less than 16 h with alkyl thiols, but 22 h with thiophenol. The ring opening of **124** was highly regio-selective with the thiol addition at the α-carbon of the carboxylate and stereo-selective with the *anti* attack to the ring to give the corresponding adducts **125** in high chemical yields (Scheme 49).

It was found that the use of Lewis acids significantly accelerated the ring opening of aziridines when attacked by thiophenols and other thiols.[94] For example, (2*S*,3*S*)-*N*-benzyl-2,3-diphenylaziridine **126** underwent nucleophilic addition with thiophenol to give only 8% of the corresponding adduct **127** in 24 h at room temperature. However, in the presence of $ZnCl_2$ (10 mol%), the same ring opening reaction was complete within 5 min at room temperature in 85% yield (Scheme 50). The Lewis acid could catalyze

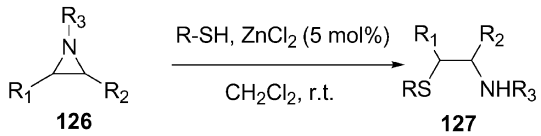


120 121

Scheme 47.



Scheme 49.



Scheme 50.

the ring opening of the activated and non-activated aziridines in good to excellent yields (Table 23). The addition occurred at the less hindered ring carbon with high regio-selectivity. Other Lewis acid catalysts were also found to effectively promoted the ring opening of aziridines, including $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$.

Table 23. Ring opening of aziridines with thiols catalyzed by $ZnCl_2$

R_1	R_2	R_3	R	Yield (%)
H	Ph	H	*p*-Cl-Ph	61
H	Ph	Bn	Ph	81
H	Ph	Bn	Bn	71
H	Ph	Bn	*n*-Bu	79
$-(CH_2)_4-$		PhCO	Ph	72
$-(CH_2)_4-$		Boc	Ph	81
$-(CH_2)_4-$		Ts	Ph	67
H	*n*-Bu	Bn	*p*-*t*-Bu-Ph	95

Boron trifluoride-diethyl etherate has been widely used in catalytic ring opening of aziridines under nucleophilic conditions using thiophenols and other thiols. However, at least a stoichiometric amount of $BF_3{\cdot}OEt_2$ and excess thiol were needed to achieve practical chemical results. As shown below, phenyl aziridine carboxylate **128** underwent the ring opening with 3 equiv. of *p*-$MeOPhCH_2SH$ under catalytic conditions of 1.5 equiv. of $BF_3{\cdot}OEt_2$ to provide (2*R*,3*S*)-Boc protected β-phenylcysteine derivative **129** in 67% yield (Scheme 51).[95]

Aqueous organophosphine-mediated ring opening of aziridines was developed by Fan and Hou.[96] In the presence of catalytic amount of tributylphosphine, the ring opening proceeded smoothly with various nucleophiles including thiophenols and aliphatic mercaptans in water as a solvent as shown in Scheme 52. In a control reaction, it was found no reaction took place in the absence of the organophosphine agent. The screening of several organophosphines resulted in the identification of tributylphosphine as the best catalyst to promote the ring opening reaction. A plausible mechanism was proposed: the phosphine attacked the aziridine **130** to form a salt, which acted as a base to abstract a proton from the nucleophile to generate the sulfur anion. Then the anion attacked the activated aziridine as depicted in Section 3.1. This method exhibits potential of being both economical and environmentally benign (Table 24).

Table 24. Ring-opening reaction of aziridines in water catalyzed by PBu_3

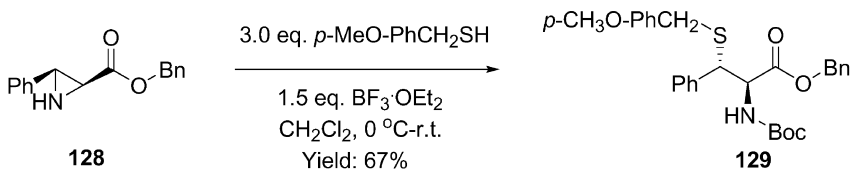
R_1	R_2	R_3	R	Yield (%)	**131**:**132**
$-(CH_2)_4-$		Tosyl	Ph	98	—
$-(CH_2)_4-$		Tosyl	4-Me-$PhCH_2$	99	—
$-(CH_2)_4-$		Bn	Ph	62	—
$-(CH_2)_4-$		Tosyl	*t*-Bu	88	—
Ph	H	Tosyl	Ph	98	50:50

4.2. Thioacyl acids

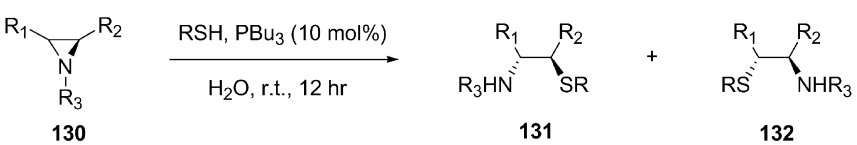
Only limited reports were found in the literature describing addition of thioacyl acids to aziridines in recent years. It was believed that the proton transfer from thio acids to aziridines to form aziridinium cation was the rate determining step. Therefore, in a study of the acidity influence of thio acids to aziridines was carried out by Lee and co-workers,[92] and found that the aziridine ring opening (**133**) was significantly fast with thioacetic acid: at −78 °C, the reaction finished within 3 min and gave the corresponding product **134** in 87% yield (Scheme 53), whereas thiophenols and other thiols took longer time at room temperature to complete the reaction as discussed earlier.

4.3. Miscellaneous

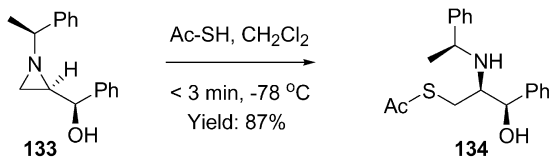
A recent report described a new and expeditious asymmetric



Scheme 51.



Scheme 52.



Scheme 53.

synthesis of 2-amino alkanesulfonic acids from chiral aziridines.[97] As shown in Scheme 54, the unsubstituted aziridines **135** could undergo ring opening with sodium bisulfite ($NaHSO_3$). The reaction proceeded in high regio-selectivity, in which the bisulfite anion attacked the aziridines at the less hindered site. 2-Amino alkanesulfonic acids **136** are mimics of amino acids and potentially useful for the study of the physiological processes of some compounds found in many mammalian tissues.

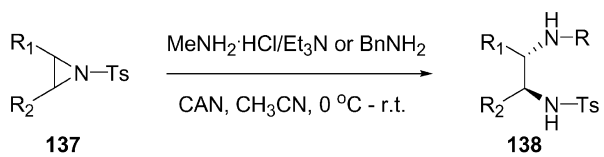
Scheme 54.

5. Nitrogen nucleophilic addition

Ring opening of aziridines with nitrogen nucleophiles including amines and azides still attracts significant attention of organic community due to increasing interests in diamine compounds in synthetic and medicinal chemistry. Amines are strong nucleophilic agents attacking either activated or non-activated aziridines without assistance of catalysts. However, recent advances in aziridine chemistry have led to the development of a number of efficient and useful methods under catalytic conditions representing high yields, high regio-selectivity and ease of experimental operation, complementary to those already reported in the literature.

5.1. Amines

Activated aziridines could be converted to ring opening products when alkylamines were used to attack the aziridines in the absence of assistance of Lewis acids to yield the corresponding 1,2-diamino derivatives.[98] As shown in Scheme 55, both $MeNH_2{\cdot}HCl$ salt/Et_3N or $BnNH_2$ could open the aziridine ring in **137** containing a tosyl group at the ring nitrogen. As shown in Table 25, both methyl- and benzylamines attacked the phenyl substituted aziridines at the benzylic carbon, whereas no reaction was seen with $BnNH_2$ in the case of mono-substituted phenyl aziridine at room temperature. In contrast, methylamine did not react with cyclohexyl- and cylcopentylaziridines, but



Scheme 55.

Table 25. Ring opening of *N*-tosylaziridines with amines in CH_3CN

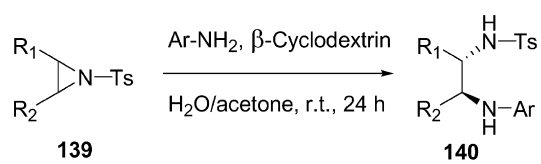
R_1	R_2	R	Time (h)	Yield (%)
Ph	H	Me	12	81
Ph	H	Bn	12	No reaction
Ph	CH_2OBn	Me	10	82
Ph	CH_2OBn	Bn	8	94
	$-(CH_2)_3-$	Me	12	No reaction
	$-(CH_2)_3-$	Bn	7	87
	$-(CH_2)_4-$	Me	12	No reaction
	$-(CH_2)_4-$	Bn	3 (at 55 °C)	93

benzylamine did. In general, the reaction occurred at room temperature with complete regio- and stereo-selectivity for **138**. However, heating could potentially compromise regio-selectivity. Similar results with amine nucleophilic addition to aziridines were also reported by others with regio- and stereo-selectivity (Table 26).[99]

Table 26. β-Cyclodextrin catalyzed aziridine opening with aniline nucleophiles

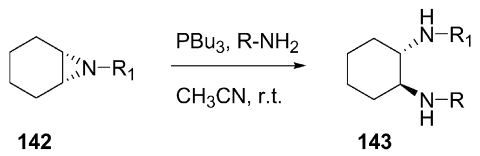
R_1	R_2	Ar	Yield (%)
	$-(CH_2)_4-$	Ph	89
	$-(CH_2)_4-$	*p*-MeOPh	92
n-C_4H_9	H	*o*-MeOPh	89
H	Ph	*o*-MeOPh	79

In contrast to ring opening of aziridines with azides catalyzed by Lewis acids (Section 5.3), there have been fewer methods developed for Lewis acid catalysis of amine addition to aziridines. This is largely due to incompatibility of many Lewis acids with basic amines under reaction conditions. One elegant procedure was recently developed using non-Lewis acid catalytic conditions, β-cyclodextrin, to facilitate ring opening of aziridines.[100] The reaction was carried out by dissolving β-cyclodextrin, a cyclic oligo-saccharide, in water followed by addition of various aziridines **139** and nucleophiles. The optimum ratio of the catalyst was found to be 0.25 mol% of the substrate and it could be recovered for recycling. The alkyl aziridine gave the adducts **140** from the attack at the less hindered carbon; in contrast, the phenyl aziridine afforded the products from attack at the benzylic carbon, all with high regio-selectivity (Scheme 56).



Scheme 56.

Similar to the examples discussed earlier in Section 3.1, tributylphosphine also demonstrated its potential in promoting the nucleophilic addition of free amines to aziridines. As shown in Scheme 57, the conversion of aziridines **142** to diamines was carried out smoothly with aniline and alkylamines in the presence of catalytic tributylphosphine (10 mol%) at room temperature to give good to high yields of addition products **143**. This method not only allowed the ring opening of activated aziridines,



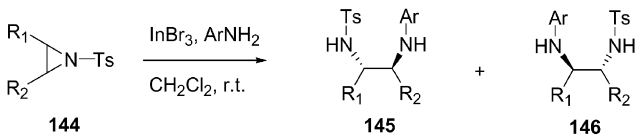
Scheme 57.

but non-activated ones as well in good yields. It was found that only low yields of products were obtained in the absence of the catalyst in the *N*-tosyl aziridine, whereas traces of products were detected in *N*-Boc and *N*-Bn aziridines. Regio-selectivity was not discussed in this case, but assumed to be less pronounced, similar to that in the ring opening of aziridines with alcohols (Table 27).

Table 27. Ring opening of aziridines with amines catalyzed by *n*-Bu_3P

R_1	R	Yield (%) (10 mol% catalyst)	Yield (%) (no catalyst)
Ts	Ph	89	55
Ts	Bn	85	50
Ts	*i*-Pr	80	50
Boc	Ph	70	Trace
Bn	Ph	62	Trace

Among Lewis acids studied for catalytic ring opening of aziridines, indium tribromide ($InBr_3$) has recently been identified as an alternative Lewis acid catalyst to effectively activate the aziridine ring for nucleophilic addition.[101] A mild reaction procedure was developed which required only 10 mol% of the $InBr_3$ catalyst to facilitate the addition of aziridines **144** (Scheme 58). This catalyst was compared with $YbCl_3$ and higher chemical yields were obtained throughout the cases examined (Table 28). In addition, good to high regio-selectivity was seen, especially in the case of the alkyl substituted aziridine (up to 95:5). The limitation of this procedure remains in the use of aryl amines as nucleophiles, and no examples of alkylamine nucleophiles were reported in the publication.



Scheme 58.

In recent years, the laboratory of Yadav has been actively involved in the development of effective catalysts facilitating ring opening of aziridines with various nucleophiles. One of his new findings included lithium perchlorate-catalyzed analine addition to aziridines as depicted in Scheme 59 below.[102] When aziridines were treated with aromatic amines in the presence of catalytic $LiClO_4$ in acetonitrile, 1,2-diamine derivatives **147** and **148** were formed in high yields (82–95%). Styrene-*N*-tosyl imine underwent cleavage in a regio-selective manner with preferential attack at the benzylic carbon as shown in Table 29, whereas external attack was seen in the alkyl aziridine. Higher regio-selectivity was seen in the latter case. However, a limitation existed in the choice of nucleophiles, in which only aromatic amines produced the ring opening to give the diamine products, but aliphatic amines failed to react with aziridines under the conditions described.

Table 29. $LiClO_4$ catalyzed ring opening of aziridines with arylamines

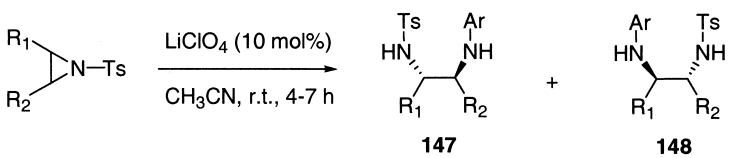
R_1	R_2	Ar	Time (h)	Yield (%)	**147**:**148**
$-(CH_2)_4-$		Ph	5.5	90	—
$-(CH_2)_4-$		4-MeO-Ph	5.0	95	—
H	Ph	Ph	4.0	90	78:22
H	Ph	4-MeO-Ph	4.0	91	87:13
Vinyl	Ph	Ph	6.5	82	75:25
n-C_5H_{11}	H	Ph	5.0	90	95:5
n-C_5H_{11}	H	4-MeO-Ph	7.5	85	92:8

A method using $LiClO_4$ to facilitate the ring opening of aziridines was described by another group as a complimentary procedure to that of Yadav's demonstrated above.[103] As shown in Scheme 60, the reaction took place with non-activated aziridines in refluxing acetonitrile in the presence of $LiClO_4$ and resulted in ring opening products **149** in good to high yields. In this case, aliphatic amines were used as nucleophiles to attack the aziridines. However, the chiral amine addition led to a mixture of diastereomers with no diastereo-selectivity, although *trans* addition was consistent throughout the study.

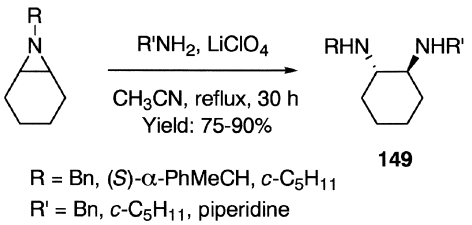
Bismuth trichloride represented one of the mildest and most efficient methods for ring opening of aziridines with amines.[104] The addition reaction of either activated or non-activated aziridines was carried out with anilines in the

Table 28. Indium tribromide catalyzed aminolysis of aziridines with aryl amines

R_1	R_2	Ar	10% $InBr_3$ time (h)	Yield (%)	Ratio (**145**:**146**)	10% $YbCl_3$ time (h)	Yield (%)
$-(CH_2)_3-$		Ph	6	92	—	7.5	81
$-(CH_2)_4-$		Ph	5.5	90	—	7.0	82
$-(CH_2)_4-$		2,5-$(MeO)_2$Ph	7.5	78	—	9.0	69
H	Ph	Ph	4	90	78:22	6.0	83
H	*n*-Bu	Ph	7	85	95:5	9.0	71

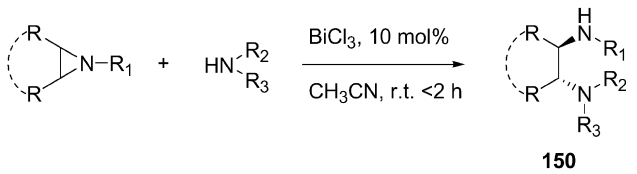


Scheme 59.



Scheme 60.

presence of $BiCl_3$ to give nearly quantitative yields of 1,2-diamines **150** (Scheme 61 and Table 30). Although the convenient procedure was attractive, neither regio-selectivity was discussed in the report, nor the generality of amine nucleophiles for aliphatic amines. In addition, the nucleophiles were limited to only aniline type amines.



Scheme 61.

Table 30. $BiCl_3$ catalyzed aziridines opening with amines

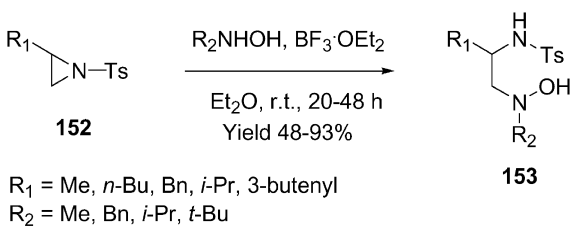
R–R	R_1	Amine	Time (h)	Yield (%)
$-(CH_2)_4-$	Ts	$PhNH_2$	1.5	96
$-(CH_2)_4-$	4-MeOPh	$PhNH_2$	2	94
$-(CH_2)_4-$	Ph	4-$MeOPhNH_2$	2	93
$-(CH_2)_3-$	Ph	$PhNH_2$	1.5	95
Me, Me	Bn	PhNHMe	2	93

Although BF_3 Lewis acid has been widely used in catalytic ring opening of aziridines with a number of nucleophiles, including alcohols, thiols, azides, nitrile, there has been limited success in ring opening of aziridines with amines. This is suspected to be largely due to deactivation of the amine nucleophile by the catalyst toward reaction with the aziridine. To circumvent this detrimental effect, Yudin and Watson recently developed a method using tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] as an effective Lewis acid to promote the ring opening successfully with amines.[105] The addition reaction to non-activated aziridine took place with amines in the presence of 10 mol% $B(C_6F_5)_3$ in refluxing CH_3CN to give diamine products **151** in nearly quantitative yields (Table 31). It was found that at least 2 equiv. of water were needed to facilitate the opening reaction, which was proven by elucidation of ^1H, ^{19}F NMR spectra and X-ray crystal structure. As shown in Scheme 62, an intermediate was proposed, in which a water molecule was involved in the catalytic process leading to the ring opening product. Although (*S*)-methyl benzylamine amine added to the aziridine in excellent yield, it failed to provide diastereoselectivity. This method also worked for the *N*-tosyl activated aziridines as effective as non-activated ones. The diamine product formed an adduct complex with $B(C_6F_5)_3$, which was inseparable by chromatography and basic extraction. However, the diamine product could be separated by the solid resin Amberlyst A-21.

Table 31. Ring opening of non-activated aziridines catalyzed by $B(C_6F_5)_3$

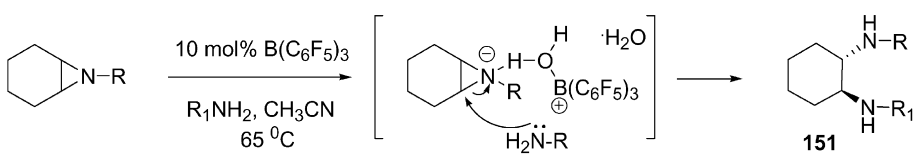
R	R_1	Equiv. of amine	Time (h)	Yield (%)
Bn	Bn	1.0	16	98
Bn	Ph	1.2	24	99
Bn	(*S*)-MeCHPh	1.2	24	98 (1:1)
$(CH_2)_3OH$	Bn	2.0	48	97
Ts	Bn	1.2	12	99

BF_3, in general, was not an effective catalyst for ring opening of aziridines as mentioned above, but proved to be the mediator of choice to facilitate hydroxylamine addition to aziridines. O'Neil et al. demonstrated that BF_3 smoothly catalyzed ring cleavage of mono-substituted *N*-tosylated aziridines **152** with hydroxylamines at the less hindered site to afford the hydroxylamine adduct **153** in reasonable to high yields (Scheme 63).[106] The β-*N*-tosylaminohydroxylamine products are differentially functionalized 1,2-diamine precursors, useful for other synthesis.

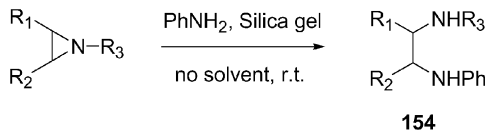


Scheme 63.

In distinction to other methods reported for catalytic ring opening of aziridines, Singh et al. took a different approach by opening non-activated aziridine rings with aryl amines without Lewis acids.[107] The reaction took place on the surface of silica gel resulting in diamines **154**. The great feature of this procedure included a solvent free condition, and addition products were easily obtained by eluting the silica gel on a column with solvents (Scheme 64). Reaction yields varied depending on the substituents of the aziridines and aniline nucleophiles as shown in Table 32. Aliphatic amines were found inactive under these conditions and the finding can be potentially useful for selective ring opening.



Scheme 62.

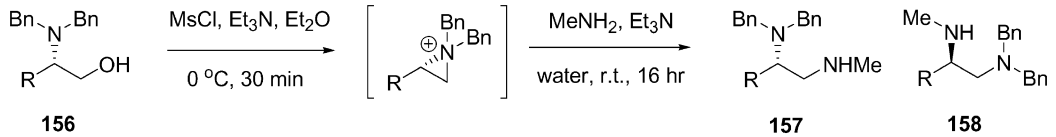


Scheme 64.

Table 32. Silica gel assisted ring opening of aziridines with amines

R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Ph	1	91
$-(CH_2)_4-$		Bn	2	91
Me	Me	Bn	24	45
H	Ph	*n*-Bu	48	89
n-$C_{10}H_{21}$	H	*t*-Bu	10	35

1,2-Diamines, especially chiral 1,2-diamines, are of considerable synthetic interests due to their synthetic and pharmaceutical value. One recent approach involved intermediate aziridinium ions as activated species to undergo nucleophilic ring opening by amines.[108] This intermediate could be directly derived from chiral amino alcohols as shown in Scheme 65. The study on the regio-selectivity of methylamine addition to the aziridinium ions indicated that methyl substituted aziridinium ion gave low regio-selectivity. However, benzyl and isopropyl substituted amino alcohols gave excellent selectivity. In contrast, phenyl aziridinium salt produced the corresponding diamine in nearly exclusive opposite regio-selectivity. In this case, no Lewis acids or bases were needed to facilitate the ring opening reaction. An identical work was reported by Lowden and Mendoza in parallel synthesis of 1,2-phenethyldiamines from ring opening of aziridines via an aziridinium ion (Table 33).[109]



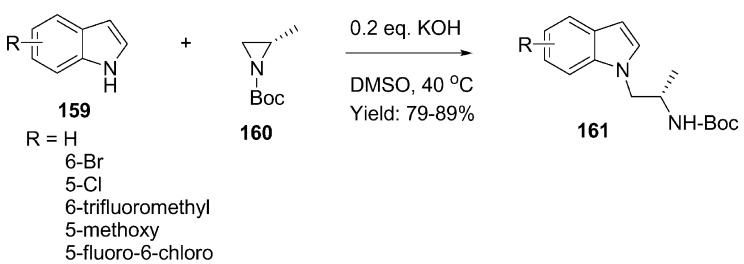
Scheme 65.

Table 33. Study of regio-selectivity of ring opening of aziridinium ions

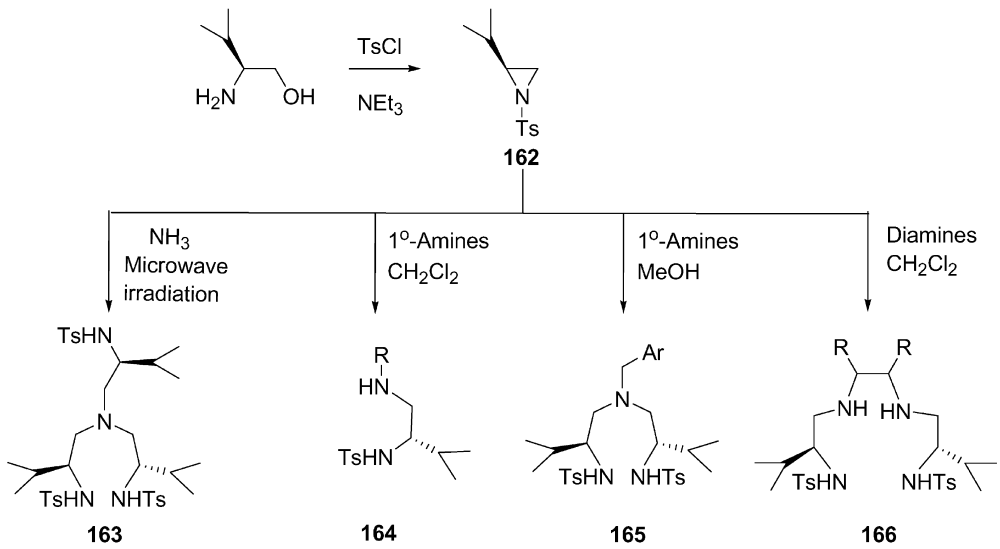
R	Yield (%) (isolated)	**157**:**158**
Me	98 (78)	70:30
Bn	94 (70)	94:6
i-Pr	81 (62)	93:7
Ph	78 (—)	2:98

As discussed earlier in Section 2.2, indoles can undergo nucleophilic addition to aziridines to give ring opening products derived from the C3 attack of the indoles. However, the indole nitrogen cac also conduct the ring opening of aziridines under a different set of reaction conditions. A method published very recently as an improved process for the N-alkylation of indoles **159** using chiral 2-methylaziridine **160** with activation.[110] The reaction was carried out in a catalytic KOH solution in DMSO as an optimal procedure with a high degree of conversion to products **161** (79–89% yield) and simple precipitation for purification as shown in Scheme 66.

The development and application of new monochiral ligands in asymmetric catalysis continues to be an area of enormous interests and activity, since the approach represents one of the most efficient means of obtaining enantiopure chiral compounds. Ring opening of aziridines by nucleophilic addition of amines represented an attractive method for synthesis of monochiral ligands. Moberg and co-workers[111] presented their results by altering the mole amount of aziridines relative to amines used to optimize the formation of desired products. As shown in Scheme 67, the *N*-Ts aziridine **162** was prepared from (*S*)-alaninol and then underwent alkylation with various amine nucleophiles. Under microwave conditions with ammonia, a C3-symmetric tripodal tris(sulfonamide) **163** was obtained in 88% yield. It was found that a ratio of 4.5:1 of the aziridine:NH_3 was optimal with no detectable mono- and di-adducts (Table 34). Alkylation could be stopped at mono-addition (**164**) with a large access of amines (3.0 equiv.). On the other hand, when 3.0 equiv. of the aziridine was used, di-alkylation products **165** were the predominant adducts as C2-symmetric dipodal bis(sulfonamide). Alternatively, when C2-symmetric primary diamines were taken as nucleophiles to add to 2.1 equiv. of the aziridine, tetradentate ligands **166** were obtained in good to high yields. The important aspect of these symmetric ligands was their potential utility in asymmetric induction, such as diethylzinc addition to benzaldehyde mediated by Ti(O*i*-Pr)$_4$. Solvent effects of single and double ring opening of *N*-tosyl chiral aziridines with $BnNH_2$ was also reported by others,[112] in which chemo-selectivity favored the single ring opening



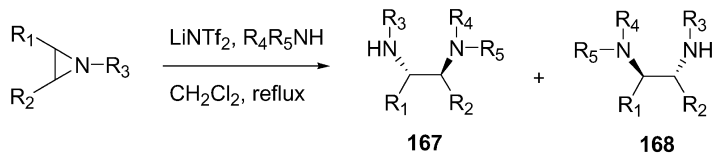
Scheme 66.



Scheme 67.

Table 34. Ring opening of aziridine **162** with ammonia, benzylamines and diamines

Amine	**162** (equiv.)	Solvent	Time	Temperature	Yield (%)	Product
NH_3	4.5	MeOH	45 min (MW)	160 °C	88	**163**
$BnNH_2$	0.33	CH_2Cl_2	21 h	0 °C –rt	75	**164**
Ph_3CNH_2	0.33	CH_2Cl_2	21 h	0 °C–rt	100	**164**
t-$BuNH_2$	0.33	CH_2Cl_2	21 h	0 °C–rt	66	**164**
$BnNH_2$	3.0	MeOH	35 h	45–55 °C	63	**165**
$Ph(CH_3)CHNH_2$ (*R*)	3.0	CH_2Cl_2	2–3 d	rt	83	**165**
Ph_2CHNH_2	3.0	CH_2Cl_2	2–3 d	rt	82	**165**
R=Ph (*R,R*)	2.1	CH_2Cl_2	2–3 d	rt	84	**166**
R=$(CH_2)_4$ (*R,R*)	2.1	CH_2Cl_2	2–3 days	rt	64	**166**
R=binaphthyl (*R*)	2.1	CH_2Cl_2	2–3 days	rt	58	**166**



Scheme 68.

in acetonitrile exclusively, whilst the double ring opening took place in methanol. In a similar fashion, double adduct bis(sulfonamide) **165** was converted to chiral 1,4,7-triazacyclononanes, useful metal-chelating agents (Table 34).[113]

Table 35. Reaction of amines with aziridines

R_1	R_2	R_3	R_4	R_5	Time (h)	Yield (%)	**167**:**168**
$-(CH_2)_4-$		Bn	Bn	H	48	83	—
$-(CH_2)_4-$		Bn	Et	Et	48	45	—
$-(CH_2)_4-$		Ts	$Ph(CH_2)_2$	H	72	87	—
$-(CH_2)_4-$		Ts	Et	Et	48	0[a]	—
$-(CH_2)_4-$		Ts	Et	Et	48	60	—
$-(CH_2)_4-$		Boc	$Ph(CH_2)_2$	H	48	73	—
H	Ph	Ts	$Ph(CH_2)_2$	H	72	73	70:30

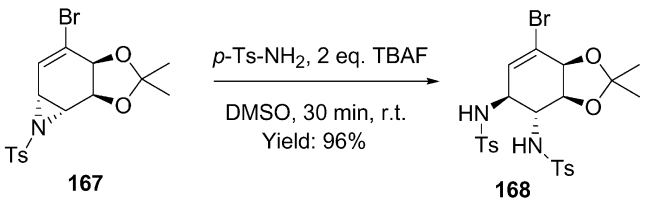
[a] In the absence of $LiNTf_2$.

When lithium bistrifluoromethanesulfonimide ($LiNTf_2$) was used as a promoter, either activated or non-activated aziridines could be converted to the corresponding ring opening diamine products.[114] As shown in Scheme 68 and Table 35, 0.2 equiv. of the catalyst was used to accelerate the ring opening reaction at reflux CH_2Cl_2. $LiNTf_2$ not only catalyzed the *N*-tosyl aziridines to open the ring by amine attack, but so did *N*-benzyl aziridine as well. Primary amine nucleophiles resulted in high yield of products **167** (or **168**), whereas diethylamine and diallylamine gave the products with only reduced yields. A Boc group was also a suitable activating substituent for the aziridines, when catalyzed by $LiNTf_2$. However, regio-selectivity is less appealing when

unsymmetrical aziridines were studied, in comparison to other alternatives.

5.2. Amides

There have been only sparse reports describing amide nucleophilic addition to aziridines in recently years. One related work was found in the literature by Hudlicky and co-workers[115] showing that vinyl aziridine **169** opening could be accomplished with *p*-toluenesulfonamide as the nucleophile by employing TBAF as a catalyst. 1,2-*trans*-Diamino relationship for the synthesis of 3,4-diamino-3,4-dideoxyl-L-*chiro*-inositol was established. The addition occurred under such mild reaction conditions (Scheme 69) that excellent chemical yield (95%) for **170** was achieved coupled with high regio- and stereo-selectivity.



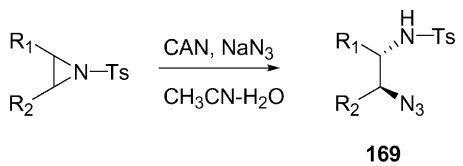
Scheme 69.

5.3. Azides

There have been tremendously increasing activities in method development for ring opening of aziridines with azides in recent years. Most of these activities have remained in searching for catalysts, which promote the nucleophilic addition with either metal azide salts or trimethylsilylazide. Most of the reported methodologies are practically useful, but complementary in various perspectives including high chemical yield, high regio-selectivity, easy operation (mild reaction condition, short reaction time, quick work up and non-anhydrous conditions), low cost of reagents and non-hazardous chemicals. All these provide multiple options of methods with consideration of substrate and product criteria.

Ceric ammonium nitrate (CAN) has demonstrated its utility in hydrolysis and alcoholysis of aziridines to form vicinal amino alcohols and amino ethers (see Section 2.1 and 2.2). In addition, its application has been extended to synthesis of vicinal azidoamines by azide addition to aziridines.[46] Due to the mild reaction conditions used, high chemical yields were obtained in most of cases reported. But moderate regio-selectivity was observed when alkyl substituted aziridines were subjected to the ring opening reaction conditions (Scheme 70 and Table 36).

Although activated aziridines were commonly used as electrophiles to undergo ring opening by the azide attack,

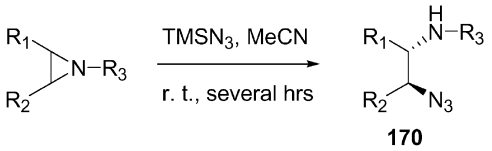


Scheme 70.

Table 36. Ring opening of *N*-tosylaziridines

R_1	R_2	Yield (%)	Ratio (internal:external)
$-(CH_2)_3-$		92	—
$-(CH_2)_4-$		95	—
$-(CH_2)_5-$		70	—
H	Ph	93	internal
C_4H_9	H	83	25:75
$MeO_2C(CH_2)_8$	H	82	18:82

non-activated aziridines were also precursors to produce the ring opening smoothly with trimethylsilylazide.[116] When *N*-benzyl cyclohexylaziridine was treated with $TMSN_3$ in CH_2Cl_2, a quantitative yield of the azido adduct **170** was obtained (Scheme 71). The optimal solvents were found to be CH_2Cl_2 and MeCN, but high tolerance to various solvents was observed when $Sn(OTf)_2$ was added as a catalyst. The addition appeared to be regio-selective when unsymmetrical aziridines were used (Table 37). It was assumed that the non-activated aziridines formed an aziridinium complex with TMS, and then the activated species underwent nucleophilic addition by the azide to give the ring opening products.[117] This assumption was supported by the evidence that *N*-Ts aziridine reacted slowly with $TMSN_3$ in 20 days to complete the reaction.

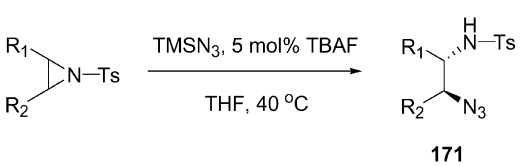


Scheme 71.

Table 37. Cleavage of N-substituted aziridines with TMS azide in MeCN at room temperature

R_1	R_2	R_3	Time (h)	Yield (%)
$-(CH_2)_4-$		Bn	2.5	99
$-(CH_2)_4-$		Ph	4	98
H	Ph	Bn	2	83
n-C_7H_{15}	H	Bn	1	93
n-C_9H_{19}	H	*t*-Bu	1	82
$-(CH_2)_4-$		Ts	20 d	70

Although activated aziridines were not good substrates for the ring opening with $TMSN_3$ alone, the reaction could be facilitated in the presence of tetrabutylammonium fluoride in excellent yields.[44] The reaction occurred under mild conditions and was complete within several hours dependent on the substrates (Scheme 72). However, poor regio-selectivity was seen in the case of a phenyl substituted aziridine, excellent regio-selectivity was obtained in the alkyl substituted aziridines as shown in Table 38. Activating groups were sensitive to the reaction conditions and *N*-tosyl



Scheme 72.

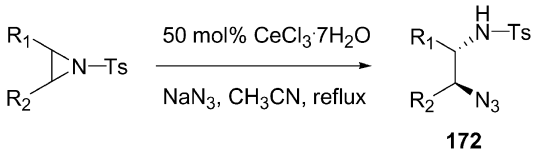
Table 38. Ring opening of *N*-tosylaziridines with $TMSN_3$

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_3-$		12	83
$-(CH_2)_4-$		4	99
H	Ph	4	90 (36:64)[a]
n-C_4H_9	H	6	97
n-C_6H_{13}	H	4	99

[a] Ratio of internal adduct versus external adduct.

was identified to be the most suitable group for the ring opening reaction.

With *N*-sulfonamide activation, aziridines could also be attacked by sodium azide in the presence of Lewis acid cerium(III) chloride to give ring opening products. This was a convenient and efficient method developed by Yavad and co-workers for the synthesis of 1,2-azidoamines.[118] Various *N*-Ts aziridines were treated with NaN_3 and 50 mol% $CeCl_3{\cdot}7H_2O$ in acetonitrile and water mixed solvent at reflux temperature for 3–6 h to give the corresponding azidoamines derivatives **172** in high yields. The regio-selectivity was very high in all examples studied in which the addition proceeded at the internal site with aryl aziridines and at the external site with alkyl aziridines as shown in Scheme 73 and Table 39. Identical results were also reported by the same group using $TMSN_3$ catalyzed by a different Lewis acid to promote the ring opening of aziridines.[119]



Scheme 73.

Table 39. Regio-selective ring opening of aziridines using $CeCl_3{\cdot}7H_2O/NaN_3$

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_4-$		3	97
H	Ph	3	94 (3)[a]
H	4-Me-Ph	3	90 (5)[a]
n-C_4H_9	H	6	90
n-C_8H_{17}	H	6	95

[a] Yield for the other regio-isomer.

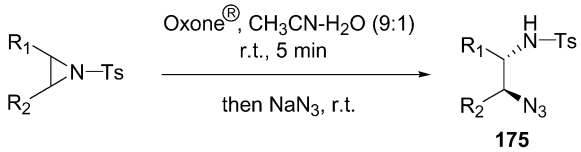
Along with emerging application of lithium perchlorate as an effective promoter for various organic transformations, this mild Lewis acid also found its utility in catalyzing ring opening of aziridines with sodium azide.[120] As shown in Scheme 74 and Table 40, the nucleophilic addition of the azide to aziridines containing an *N*-Tosyl group resulted in

Table 40. $LiClO_4$ catalyzed synthesis of β-azidoamines

R_1	R_2	Time (h)	Yield (%)	**173**:**174**
$-(CH_2)_3-$		6	90	—
$-(CH_2)_4-$		5.5	85	—
Ph	H	4	90	8:92
4-Me-Ph	H	3.5	92	5:95
n-C_4H_9	H	6	90	13:87
n-C_8H_{17}	H	6	85	12:88

the ring opening products **173** and **174** in high chemical yields and acceptable regio-selectivity. The efficacy of other Lewis acids, such as $InCl_3$, Ycl_3 and $YbCl_3$, was also studied for this transformation and $LiClO_4$ was found to be the most effective catalyst. These conditions were claimed to display mild and clean reaction profiles, simplicity in operation and low cost in the catalyst.

Analogous to ring opening of epoxides, Oxone® ($2KHSO_5$, $KHSO_4$, K_2SO_4) could also convert the aziridines to 1,2-azidoamine derivatives under very mild reaction conditions.[121] This inexpensive, safe and readily available oxidizing agent appeared to be more powerful than many other Lewis acid catalysts in ring opening of aziridines, due to its extraordinarily mild conditions and high yields coupled with high regio-selectivity (Scheme 75 and Table 41).



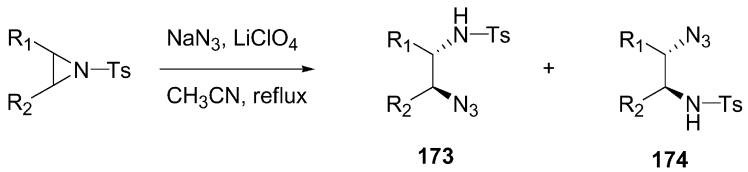
Scheme 75.

Table 41. Regio-selective ring opening of aziridines with NaN_3 in the presence of Oxone®

R_1	R_2	Time (h)	Yield (%)
$-(CH_2)_3-$		1	94
$-(CH_2)_4-$		1	98
$-(CH_2)_6-$		1	96
H	Ph	1.5	93 (5)[a]
H	4-Me-Ph	1.5	89 (6)[a]
Cyclohexyl	H	1.5	96
n-C_4H_9	H	3	89 (2)[a]
n-C_8H_{17}	H	3	94 (3)[a]

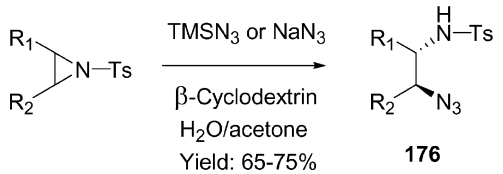
[a] Yield for the other regio-isomer.

Like ring opening of aziridines with amines, β-cyclodextrin equivalently catalyzed the ring opening of aziridines with either sodium azide or trimethylsilylazide to form azido-amines.[100] Unlike many other ring opening reactions mentioned previously, this reaction required aqueous conditions in a mixed solvent of water and acetone. The



Scheme 74.

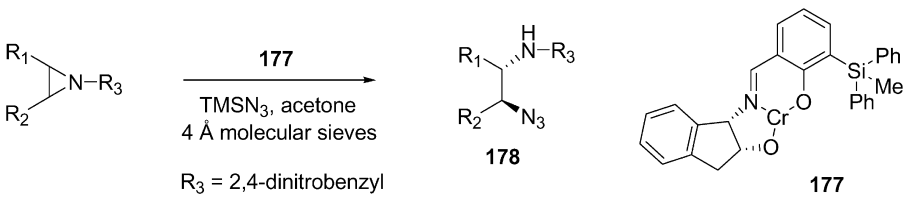
reaction took place at room temperature and good chemical yields were commonly obtained with various substituted *N*-Ts aziridine substrates (Scheme 76). With unsymmetrical aziridines, the reaction was highly regio-selective with the formation of only one product **176**, which was due to attack of the nucleophile at the less hindered terminal carbon atom.



R_1, R_2 = $(CH_2)_4$; R_1 = *n*-Bu, R_2 = H; R_1 = H, R_2 = Ph

Scheme 76.

Asymmetric nucleophilic ring opening of aziridines with azides has been of significant interest, but only limited success had been achieved with regard to scope and efficacy, although asymmetric ring opening of epoxides with $TMSN_3$ has demonstrated great success with the emergence of (salen)Cr(III) complexes. Recently, Jacobsen and co-workers discovered new and effective chromium(III) complexes containing tridentate Schiff bases to catalyze the ring opening of *meso* aziridines.[122] After examining a number of complexes of metals and chiral ligands, Cr(III) tridentate complex **177** as shown in Scheme 77 was identified to be one of the most optimal catalysts resulting in nucleophilic addition of the azide to symmetric aziridines. The reaction was carried out in acetone in the presence of 4 Å molecular sieves at −15 or −30 °C with only 5–10 mol% of the catalyst required. A high degree of conversion of the aziridines to azidoamines **178** and a high level of enantio-selectivity were obtained as summarized in Table 42. However, the ring opening reaction appeared to be very slow, and the application of this method for kinetic ring opening of other aziridines remains to be explored for its potential utility.



Scheme 77.

Table 42. Enantio-selective ring opening of *meso* aziridines catalyzed by chiral chromium(III) complexes

R_1	R_2	Time (h)	Temperature (°C)	Yield (%)	ee (%)
$-(CH_2)_4-$		48	−30	95	94
$CH_2CH{=}CHCH_2$		100	−30	75	88
$-(CH_2)_3-$		72	−30	87	87
CH_2OCH_2		90	−15	73	90
Me	Me	96	−30	80	83

5.4. Miscellaneous

Imidazolines could also be derived from aziridines as a ring expansion reaction. This was reported by Moretti and collegues in aziridine ring expansion reaction.[123] When an acyl activated aziridine **179** was treated with $BF_3{\cdot}OEt_2$ in CH_3CN, the solvent attacked the less substituted ring carbon to give an intermediate shown in Scheme 78, which underwent ring closure to form *N*-acetyl-imidazole **180** with complete stereo retention. The imidazoline then could be hydrolyzed in 10% HCl to afford optically active 2,3-diaminopropanoic acid **181**, a recognized useful building block for other synthesis.

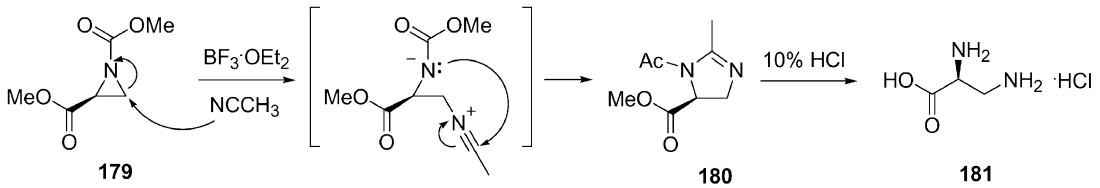
6. Halogen nucleophilic addition

Since a review describing metal halide opening of aziridine rings by Tighi and Bonini,[124] development of new methods for halogen nucleophilic ring opening of aziridines continues to occur in recent years, concerning improving reaction conditions, chemical yields and selectivity by applying more efficient catalysts. As results, the new procedures are either complementary or superior to other known methods in the literature.

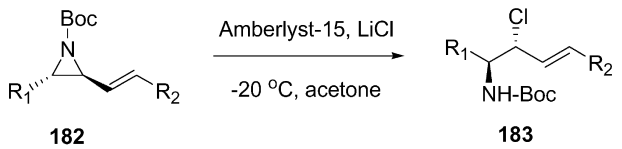
6.1. Chloride

Amberlyst-15 catalyzes aziridine alcoholysis (see Section 3.1). It is also an effective catalyst in halogen addition to aziridine rings. Righi and co-workers found that the reaction of *N*-Boc-alkenyl aziridines **182** with lithium chloride in the presence of Amberlyst 15 afforded the regio- and stereo-selective ring opening products in high yields (Scheme 79).[125] The regio-selectivity was examined with various substituents (R_1) and only single regio-isomers **183** were detected in the reaction and assigned to be anti addition allylic chloro derivatives (Table 43). However, regio-selectivity suffered when the carboxylate group was replaced with a methyl group.

Hydrogen chloride itself is a source of a proton for activation and of a chloride anion for the ring opening of aziridines. One representative example demonstrated that a non-activated aziridine **184** could undergo halogenolysis in dry HCl-ether solution to give a chloro amine product **185** in excellent yield and exclusive regio-selectivity (Scheme 80).[93] Another example illustrated the use of an aqueous HCl solution in the ring opening reaction of non-activated aziridines. Regio-isomer **186** was isolated with quantitative yields (Scheme 81).[126] A similar result was found in the literature in the case of bicyclic aziridine **187** with regio-selective formation of product **188** (Scheme 82).[127] Under



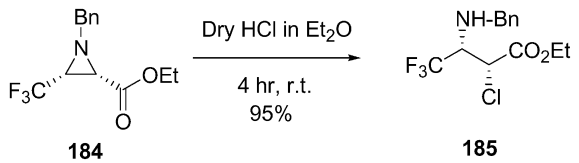
Scheme 78.



Scheme 79.

Table 43. Ring opening of alkenyl aziridines by Amberlyst-15/LiCl

R_1	R_2	Yield (%)
n-Propyl	CO_2Et	84
Cyclohexyl	CO_2Et	86
t-butyl	CO_2Et	82
R	Methyl	Mixture of regio-isomers



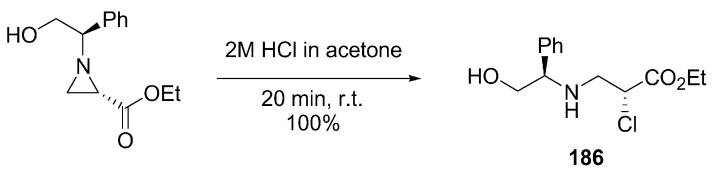
Scheme 80.

Table 44. Regio-selective ring opening of aziridines using cerium(III) chloride

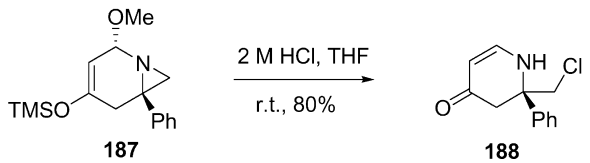
R_1	R_2	Product	Yield (%)
Ph	H	**190**	92
4-Chloro-Ph	H	**190**	91
$-(CH_2)_4-$		—	92
$-(CH_2)_6-$		—	90
Et	H	**191**	95
n-Octyl	H	**191**	90

aqueous HCl conditions, the β-methoxy TMS vinyl either was decomposed to give a substituted 2,3-di-hydro-1*H*-pyridin-4-one **189** in 80% yield. The common feature in the examples demonstrated that non-activated aziridines can undergo highly regio-selective ring opening halogenolysis to give vicinal chloroamines in high yields.

Cerium(III) chloride, an inexpensive, non-toxic and ready available inorganic salt, has found its application in the ring opening reaction of aziridines to form β-chloroamines.[128] The reaction was performed under very mild conditions with short reaction time and excellent chemical yield. In addition, very high regio-selectivity was observed with aryl aziridines giving internal adducts **190**, and with alkyl



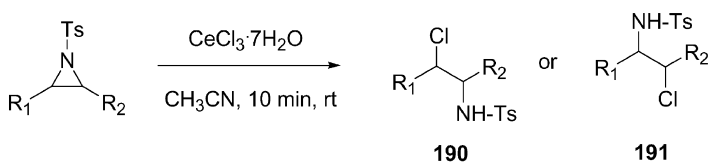
Scheme 81.



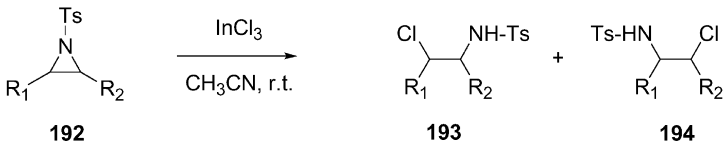
Scheme 82.

aziridines giving only external adducts **191** (Scheme 83 and Table 44). This procedure represents one of the most efficient conversions of aziridines to chloroamines to date.

Indium trichloride also demonstrated its utility in the ring opening of aziridines with high conversion and selectivity (Scheme 84).[129] The reaction results of the substituted aziridines **192** having tosyl activation with indium tricholide



Scheme 83.

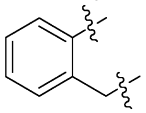


192 193 194

Scheme 84.

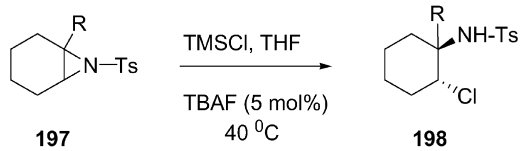
in acetonitrile were summarized in Table 45 below. In the cases of cyclohexyl and cyclopentyl aziridines, *trans* stereoisomers were obtained in 98:2 ratio. In aryl substituted aziridines, the internal addition products **192** were isolated as major regio-isomers. However, the external regio-isomers **193** were obtained predominantly in alkyl substituted aziridines. Although regio-selectivity in the ring opening of unsymmetrical aziridines is not as compatible as in the methods aforementioned, the method itself represents a useful procedure of simple operation, high chemical yield and use of non-toxic and water-tolerant indium reagent.

Table 45. Regio-selective ring opening of aziridines with indium trichloride

R_1	R_2	Time (h)	Yield (%)	**193**:**194**
$-(CH_2)_4-$		8.5	78	—
$-(CH_2)_3-$		9.0	80	—
		7.0	83	92:8 (internal:external)
Ph	H	5.0	90	80:20
i-butyl	H	7.5	77	10:90
n-Butyl	H	9.0	75	17:83
n-Octyl	H	8.5	80	5:95

Another source of the chloride anion is generated from phosgene, with which oxazolidin-2-ones were formed from enantiomerically pure aziridine 2(*R*)-methanol.[130] The other important feature of phosgene is the activation of the aziridine by forming an oxazolidinonium salt, which underwent rapid ring opening at low temperature (Scheme 85). The conversion of the aziridines **195** to oxazolidinone rings **196** was achieved in the presence of a base (NaH) to facilitate oxazolidinone ring closure. A bicyclic aziridinium salt was proposed as a reaction intermediate, which then underwent nucleophilic chloride addition at the less hindered aziridine carbon. Consistent high chemical yields were obtained in all cases (Table 46), even those with sterically hindered alcohols. This method appears to be general for the direct conversion of aziridinyl alcohols to oxazolidinonyl methylchlorides.

The ring opening of aziridines with a chloride nucleophile can also be achieved by trimethylsilyl chloride. The reaction proceeded with TMSCl in THF in the presence of a tetrabutylammonium fluoride (TBAF) trigger.[131] The addition occurred *anti* to the aziridine ring in cyclohexyl aziridines **197** with the regio-selectivity at the less hindered ring carbon. The ring opening took place very fast (<10 min) with unsubstituted bicyclic aziridines, but much more slowly with a methyl substituent (6 h). High yields and high regio-selectivity for **198** were observed in TMSCl/TBAF addition to the aziridines (Scheme 86 and Table 47). The TBAF was proposed to release the chloride anion, which underwent nucleophilic attack to the aziridines to give the chloro adducts.

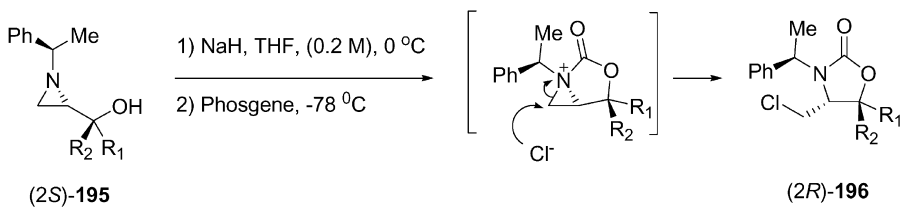


197 198

Scheme 86.

Table 47. Ring opening of *N*-tosylaziridines

n	R	Time (h)	Yield (%)
1	H	0.1	97
0	H	0.1	94
1	Me	12	99



(2*S*)-**195** (2*R*)-**196**

Scheme 85.

Table 46. Conversion of aziridines to oxazolidinones

	196										
	a	b	c	d	e	f	g	h	i	j	k
R_1	H	Me	Ph	H	H	H	H	H	H	H	Vinyl
R_2	H	Ph	Ph	Me	*n*-Bu	*t*-Bu	Ph	*p*-F-Ph	*m*-totyl	Vinyl	H
Yield (%)	89	92	83	91	84	90	88	85	90	89	80

6.2. Bromide

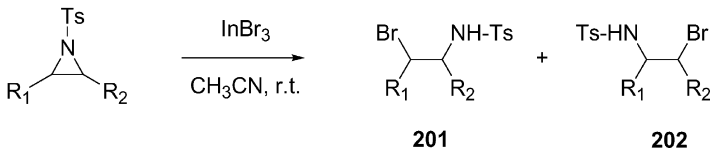
Highly regio-selective ring opening of *N*-Boc-2,3-aziridino alcohol derivatives **199** with $MgBr_2$ was successfully achieved by Righi and co-workers.[132] Instead of a commonly used tosyl amide as an activating functionality for the ring opening, interestingly, they found *N*-Boc amide could serve the same purpose in activating and directing the nucleophilic addition (Scheme 87). In addition, this reaction gave excellent regio-selectivity with great ease of deprotection at the nitrogen. In all examples presented in the ring opening reaction, a bulky *t*-butyldimethyl silyl (TBDMS) group might also play role in directing the site of the addition by the halide (Table 48). Because of the excellent regio-selectivity in the ring opening with $MgBr_2$, the bromoamine products **200** could be reduced to give the corresponding amino alcohols with high chemo-selectivity and high chemical yields.

Scheme 87.

Table 48. Regio-selective ring opening of *N*-Boc-aziridines with $MgBr_2$

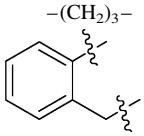
R	Methyl	*n*-Propyl	Cyclohexyl	Ph
Ratio (C3/C2)	>99:1	>99:1	>99:1	>99:1

Indium tribromide was also used as a nucleophile to undergo the ring opening of aziridines similarly to that of indium trichloride as discussed in Section 6.1. In the same report, Yadav and co-workers[129] found that the bromide reagent effectively converted tosyl aziridines to β-bromo amino adducts **201** and **202** in high chemical yields (Scheme 88), but reduced regio-selectivity as seen in Table 49, when compared to indium trichloride. However, the orientation of the addition remained the same.

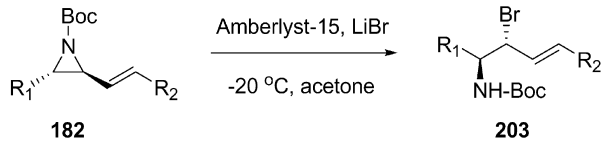


Scheme 88.

Table 49. Regio-selective ring opening of aziridines with indium tribromide

R_1	R_2	Time (h)	Yield (%)	**201**:**202**
$-(CH_2)_4-$		6.5	83	—
$-(CH_2)_3-$		7.5	84	—
		5.5	85	88:12 (internal:external)
Ph	H	4.5	87	76:24
i-butyl	H	6.0	85	15:85
n-Butyl	H	8.0	83	12:88
n-Octyl	H	6.0	85	8:92

Another ring opening reaction of aziridines with bromide was reported using Amberlyst-15/LiBr conditions.[125] The reaction took place in acetone at low temperature to give vicinal bromo amine derivatives **203** in high chemical yields and excellent regio-selectivity (Scheme 89 and Table 50). These results were identical to those seen in the Amerlyst-15/LiCl conditions in Section 6.1.



Scheme 89.

Table 50. Ring opening of alkenyl aziridines by Amberlyst-15/LiBr

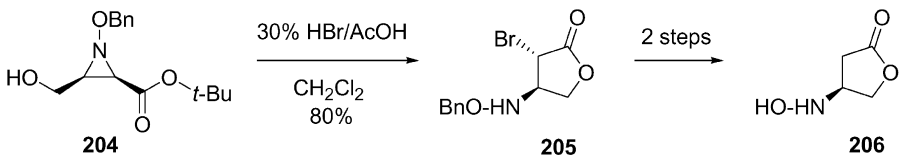
R_1	R_2	Yield (%)
n-Propyl	CO_2Et	94
Cyclohexyl	CO_2Et	94
t-butyl	CO_2Et	87

Hydrogen bromide has been a widely used agent for ring opening of aziridines to form vicinal bromo amines for a long time. The advantages of HBr conditions include no need for activation on the aziridine nitrogen to promote the ring opening and high regio- and stereo-selectivity. Recently, Hanessian et al. successfully applied the HBr nucleophilic addition to aziridine **204** in the synthesis of enantiomerically pure hydroxylamino lactone derivatives **206** as a useful building block (Scheme 90).[133]

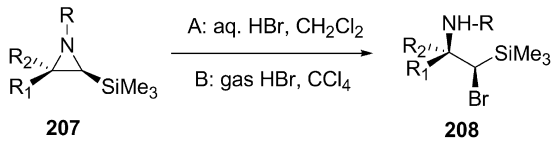
Trialkylsilyl groups played an important role in strongly directing the site of the nucleophilic ring opening of aziridines (Scheme 91). Such results were reported by Taylor and co-workers[134] in the ring opening reaction of 2-trialkylsilylaziridines **207**. Activation or non-activation at the aziridine nitrogen did not seem to affect the addition reaction (Table 51). Apparently, the protic acid served as an activating factor and the bromide attacked the weakened N–C bond adjacent to the silyl group. The addition gave bromoamines in moderate to good yields with regio-specificity, using either gaseous or aqeous HBr.

6.3. Fluoride

In contrast to other halide nucleophilic addition to aziridines, there have been fewer reports documented in



Scheme 90.

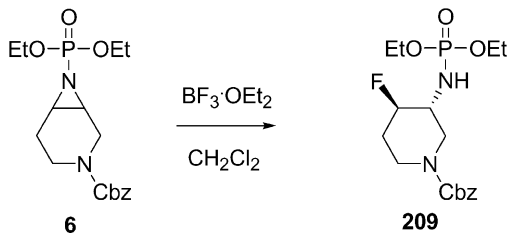


Scheme 91.

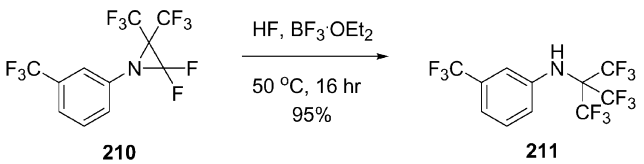
Table 51. Addition of HBr to a range of trimethylsilyl aziridines

R	R_1	R_2	Method	Yield (%)
n-Propyl	Ph	H	A	83
n-Propyl	Ph	H	B	72
Ph	Ph	H	B	76
H	Ph	*n*-Butyl	B	65
CO_2Et	H	H	B	52

the literature recently describing methods for the ring opening of aziridine with a fluoride anion. In our recent effort toward the $BF_3{\cdot}OEt_2$ catalyzed ring opening of a piperidine aziridine with various alcohols (see Section 2.2.1), an intriguing finding of a by-product containing fluoro atom led to a regio- and stereo-selective conversion of the aziridine **6** to 3-amino-4-substituted piperidine derivative **209**.[49] The reaction was carried out in dry CH_2Cl_2 in the presence of 2 equiv. of $BF_3{\cdot}OEt_2$, and the fluoro adduct was isolated in 66% yield (Scheme 92). This is one of the most convenient methods reported for the conversion of aziridines to vicinal fluoro amine adducts.



Scheme 92.



Scheme 93.

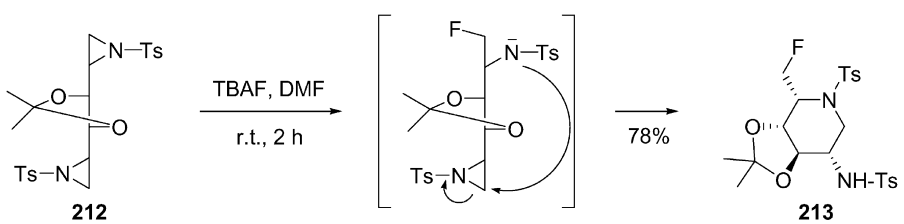
Due to the weak acidity of hydrogen fluoride, the ring opening of aziridines required a Lewis acid to facilitate the nucleophilic addition. This work was demonstrated by Petrov[135] in the synthesis of poly-fluoronated amines **211** from aziridine **210** as shown in Scheme 93. Excellent yield and regio-selectivity were seen in this particular case in the presence of $BF_3{\cdot}OEt_2$. When other halogen substituted aryl aziridines were used to undergo the ring opening reaction, complicated results were obtained.

Other fluorinating agents include tetrabutylammonium fluoride (TBAF) in the ring opening of bis-aziridines **212** in the synthesis of enantiomerically pure piperidine derivatives.[136] The bis-aziridine derived from D-mannitol was treated with this highly nucleophilic fluorinating agent in DMF to give mono-addition aziridine ring opening intermediate, which then underwent rapid ring closure to form piperidine **213** (Scheme 94). The regio-selectivity was derived from the addition at the less hindered terminal aziridine carbon. In the same report, it was found that $LiBF_4$ was much less effective in the ring opening reaction.

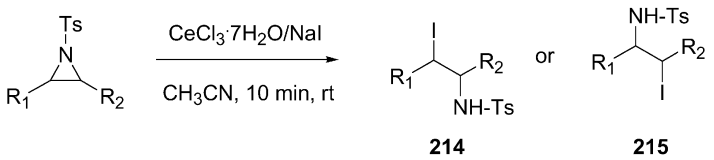
6.4. Iodide

As reviewed in Section 2.5.1, cerium(III) chloride reacted with the tosyl aziridines to give highly regio-selective chloro amine derivatives. Interestingly, when the same conditions were used to undergo the ring opening of aziridines in the presence of 1 equiv. of sodium iodide, the products isolated were β-iodo sulfonamides with complete iodo-chloro exchange (Scheme 95).[128] As shown in Table 52, the reaction gave excellent yields and excellent regio-selectivity in all cases. The orientation of the iodo addition proceeded in the same fashion as that of the chloro addition: internal addition with the aryl aziridines to give **214**, and external addition with the alkyl aziridines to give **215**.

Similar results were obtained in the ring opening of aziridines with indium(III) iodide as those with $InCl_3$ and $InBr_3$ as discussed in Section 5.1.[129] In this reaction β-iodo amino adducts were synthesized in high chemical yields (Scheme 96), but reduced regio-selectivity as seen in



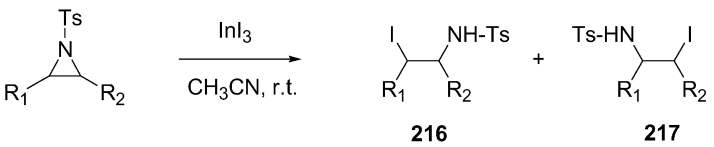
Scheme 94.



Scheme 95.

Table 52. Regio-selective ring opening of aziridines using cerium (III) iodide

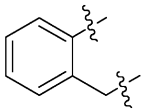
R_1	R_2	Product	Yield (%)
Ph	H	A	99
4-Chloro-Ph	H	A	95
$-(CH_2)_4-$		—	96
$-(CH_2)_6-$		—	92
Et	H	B	97
n-Octyl	H	B	91



Scheme 96.

$InBr_3$ when compared with indium trichloride as seen in Table 53. Again, the orientation of the addition remained to be the same: internal addition for the aryl aziridines to give **216**, but external for the alkyl aziridine to give **217**.

Table 53. Regio-selective ring opening of aziridines with indium triiodide

R_1	R_2	Time (h)	Yield (%)	**216**:**217**
$-(CH_2)_4-$		5.5	87	—
$-(CH_2)_3-$		5.5	88	—
		4.0	88	85:15 (internal:external)
Ph	H	3.5	92	70:30
n-Butyl	H	5.0	90	17:83

Amberlyst-15 can not only catalyze the ring opening of aziridines by nucleophilic attacks of chloride and bromide from lithium halides, but also can catalyze the same reaction with LiI.[125] The reaction proceeded at very mild conditions as described before, but somehow reduced chemical yields were seen with iodo adduct **218** (Scheme 97 and Table 54). These results were identical to those seen in the Amerlyst-15/LiCl conditions in Section 6.1. The low yields were due to the activity of the iodide anion as a leaving group to form oxazolidinones **219**.

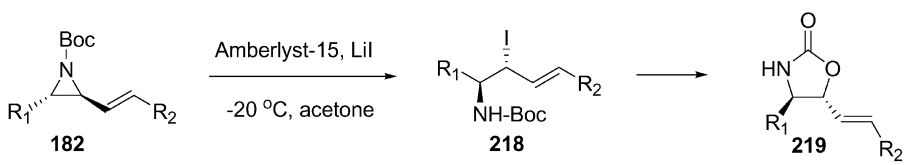
Table 54. Ring opening of alkenyl aziridines by Amberlyst-15/LiBr

R_1	R_2	Yield (%)
n-Propyl	CO_2Et	70
Cyclohexyl	CO_2Et	72
t-butyl	CO_2Et	67

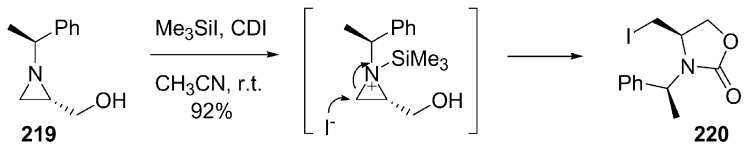
The ring opening of aziridines when treated with trimethylsilyl iodide (TMSI) led to iodo amine compounds, which were a useful building block for tryptophanol synthesis.[137] TMSI nucleophilic addition could take place on non-activated aziridine **219**. The silyl reagent was assumed to initially activate the ring nitrogen and then the released iodo anion acted as a nucleophile to attack the less hindered ring carbon to give an iodo imide anion (Scheme 98). In the presence of carbodiimidazole, an iodomethyl-2-oxazolidinone **220** was obtained in high yield and high regio-selectivity.

7. Hydrogen nucleophilic addition

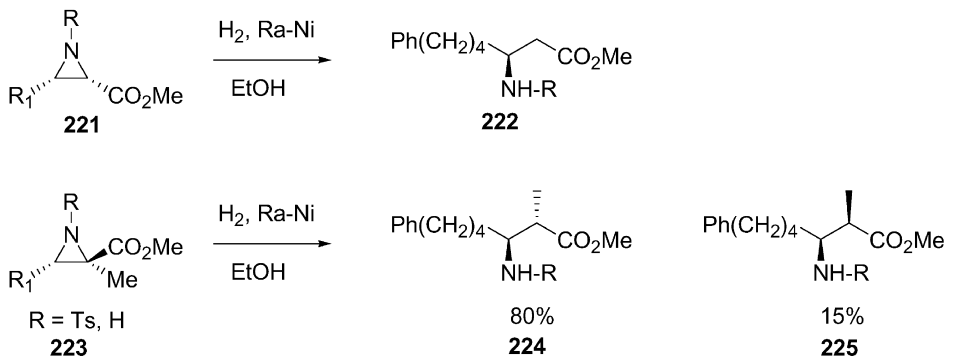
Although hydrogen is not characterized as a nucleophile, it serves the purpose of cleaving the aziridine ring. Catalytic hydrogenation of both activated and non-activated aziridines produces amines as useful building blocks for other synthesis and synthon for the synthesis of biologically active products. Hydrides are common nucleophiles analogous to those mentioned above to undergo ring opening of aziridines. However, hydride reduction requires activation of aziridines to lead to ring opening products. In addition, hydrogenation of aziridines provides the corresponding amine products with highly controlled regio-selectivity, whereas hydride reduction is less appreciable in terms of site of the ring cleavage.



Scheme 97.



Scheme 98.

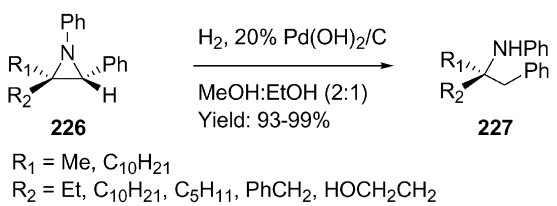


Scheme 99.

7.1. Hydrogen from hydrogenation

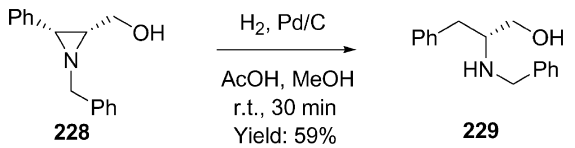
Davis et al. examined the catalyst and solvent effects on hydrogenation ring opening of aziridine-2-carboxylates.[138,139] It was found that Raney-Ni/EtOH conditions provided the optimum results (**222**) with nearly quantitative yield in the case of **221**, whereas two diastereomers **224** and **225** were obtained in the case of 2-methylaziridine **223**, and the major isomer was derived from the ring opening with retention of configuration (Scheme 99).

Hydrogenation ring opening of aziridines catalyzed by Pearson's palladium reagent appears to be a widely used method to cleave the C–N bond. A recent study by Satoh and co-workers described an effective method to convert aziridines **226** to amines **227** bearing a quaternary chiral center.[140] The reaction was catalyzed by 20% $Pd(OH)_2/C$ in 100–300 wt% in excellent chemical yields and low catalyst loading resulting in incomplete ring opening (Scheme 100). It should be noticed that all aziridines reported in the study involved benzylic type amine functionality, which was the site of the cleavage. Optically active quaternary amines can also be synthesized from this method.



Scheme 100.

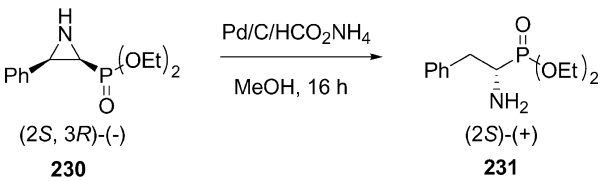
Less frequent reports were also found in the literature in hydrogenation ring opening of aziridines with palladium on carbon. One recent example is shown below in Scheme 101, in which a non-activated (2*S*,3*R*)-(−)-*cis*-aziridine derivative **228** underwent ring opening under hydrogenation conditions in the presence of acetic acid for protonation.[141] The reaction proceeded with selective ring opening at the benzylic carbon, whereas the benzyl group was not cleaved.



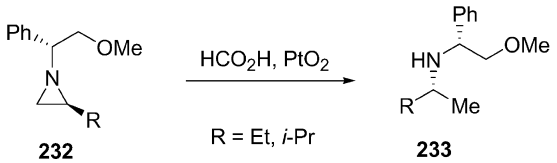
Scheme 101.

This result may be related to the release of the aziridine ring strain in the cleavage. However, the chiral amine product **229** was obtained in only moderate chemical yield (59%).

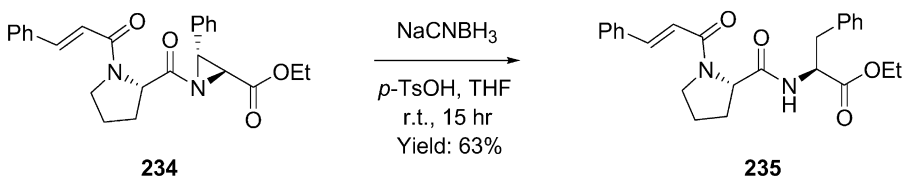
In general, N-activation of the aziridine ring was required to facilitate ring opening by hydrogenation. However, cases without activation were also found in the literature, in which the ring opening occurred at the benzylic position as an exceptional example of benzylamine type reduction.[142] As shown in Scheme 102, hydrogenation was carried out by the hydrogen transfer agent ammonium formate. Because of the benzylic amine type reduction of **230**, the ring opening proceeded specifically at the benzyl carbon to give the corresponding amino acid mimic **231** with good to excellent yields (67–98%). On the other hand, aziridines **232** could also be cleaved with Adam's catalyst[143] as presented in



Scheme 102.



Scheme 103.



Scheme 104.

Scheme 103, in which cleavage occurred at the sterically preferred carbon to give amines **233**.

7.2. Hydride

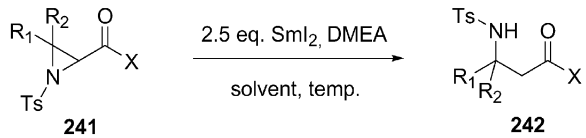
In comparison to the reports of the ring opening of aziridines by reductive hydrogenation, much less occurrence of ring opening methods of aziridines by hydride reduction has appeared in recent years. One application involved the reductive cleavage of aziridine containing peptidomimetics using $NaCNBH_3$ under acidic conditions.[144] As shown in Scheme 104, a dipeptide analog **234** underwent hydride nucleophilic ring opening regio-selectively at the benzylic ring carbon to give a corresponding L-Pro-L-PheOEt derivative **235** in 63% yield.

A second method was recently described in the literature using $NaBH_4$ to cleave aziridine rings.[145] The researchers intended to demonstrate methods of asymmetric synthesis of α or β-aminophosphonates from enantiomerically enriched aziridines. However, the $NaBH_4$ reductive ring opening of aziridine **236** resulted in only a nearly 1:1 ratio mixture of α or β-aminophosphonates (**237** and **238**) (Scheme 105), which proved the method was much less attractive for preparative synthesis. Identical lack of regio-selectivity results were also seen in other reports in the ring opening of aziridines with $NaBH_4$.[146]

Regio-selectivity of reductive ring opening of aziridines with hydrides has posed a considerable challenge. In order to improve the regio-selectivity, Davis and co-workers[147] found a hydroxyl group directing effect of the hydride addition by taking advantage of those studying the ring opening of aziridines with other nucleophiles in the presence of neighboring group effect. When 2,3-disubstituted aziridine-2-carboxylate **239** was treated with LAH, the initial intermediate alcohol from carboxylate reduction chelated the reducing agent. Then, the hydride was delivered via a five membered-ring transition state to give the exclusive C2 addition products **240** in very high yields (Scheme 106). The hydroxyl group was then oxidized to the corresponding carboxylic acids, which led to the synthesis of α-alkyl-β-amino acids, compounds relatively hard to synthesize via reductive ring opening of aziridines.

7.3. Miscellaneous

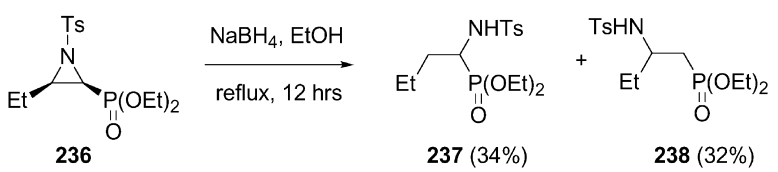
Samarium(II) iodide (SmI_2) has a wide range of application in reducing a number of functional groups due to its single-electron transfer capability. Similar to a process of SmI_2 cleavage of α-heterosubstituted carbonyl substrates, ring opening of aziridines can also be achieved by SmI_2 reductive method developed by Molander and co-workers.[148] A number of aziridine carbonyl functional groups (**241**) were examined for the ring opening including ketones, esters and amides. The reaction provided β-amino carbonyl derivatives **242** not only in high yields, but also in



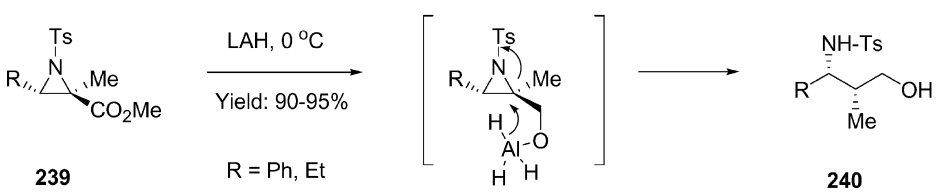
Scheme 107.

Table 55. Reduction of *N*-Ts aziridine-2-carboxamides with SmI_2

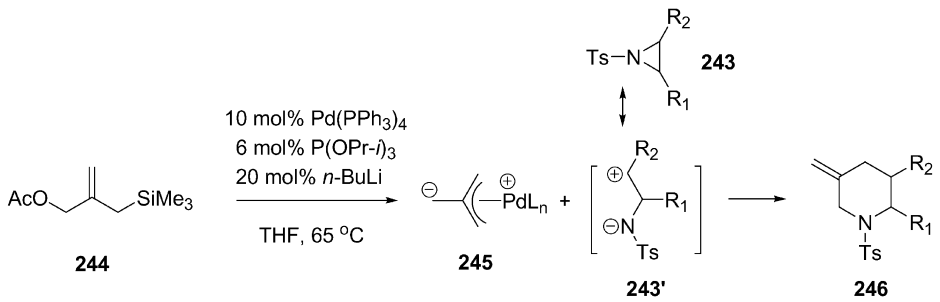
R_1	R_2	X	DMEA	Solvent	Temperature (°C)	Yield (%)
H	Ph	Me	0	MeOH	0	82
H	H	Me	0	MeOH	0	79
Me	Me	Me	0	MeOH	0	88
H	Ph	OEt	5.0	THF	0	87
H	H	OEt	5.0	THF	0	98
Me	Me	OMe	5.0	THF	0	87
H	H	NMe_2	5.0	THF	−25	86
Me	H	NEt_2	5.0	THF	−25	70



Scheme 105.



Scheme 106.



Scheme 108.

excellent regio-selectivity, due to initial formation of a ketyl or a radical species, which cleaved the adjacent N-C bond (Scheme 107 and Table 55). Reduction of the 2-keto-aziridine required no additive *N*,*N*-dimethylethanolamine (DMEA), whereas reduction of the 2-ester-aziridines and 2-amide-aziridines involved the DMEA additive serving as an effective proton source, a possible chelator to the Sm(II) reductant for the reactivity and rectifier for regio-selectivity. This method was also useful in the presence of other *N*-activating groups, such as Ac, Boc, Fmoc, CO_2Et, trityl and phenyl, thereby demonstrating generality of the procedure.

8. Cycloaddition

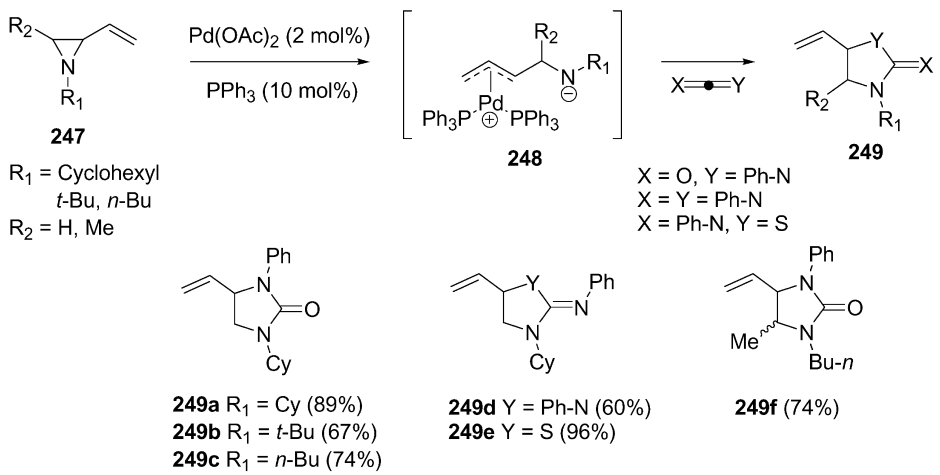
Aziridines are also known to undergo cycloaddition reaction, although their addition by various nucleophiles has been well established as summarized in this review above. The cycloaddition reaction of aziridines involves either the formation of double charged 1,3-dipole species or azahomoallyl radical species as reacting intermediates to react with a double bond and then generate a five- or six-membered ring skeleton from simple substrates. From this single step transformation, the cycloaddition can provide some complex heterocyclic scaffolds to demonstrate a powerful tool in organic synthesis.

Table 56. [3+3] Cycloadditon of aziridines with Pd-TMM complex

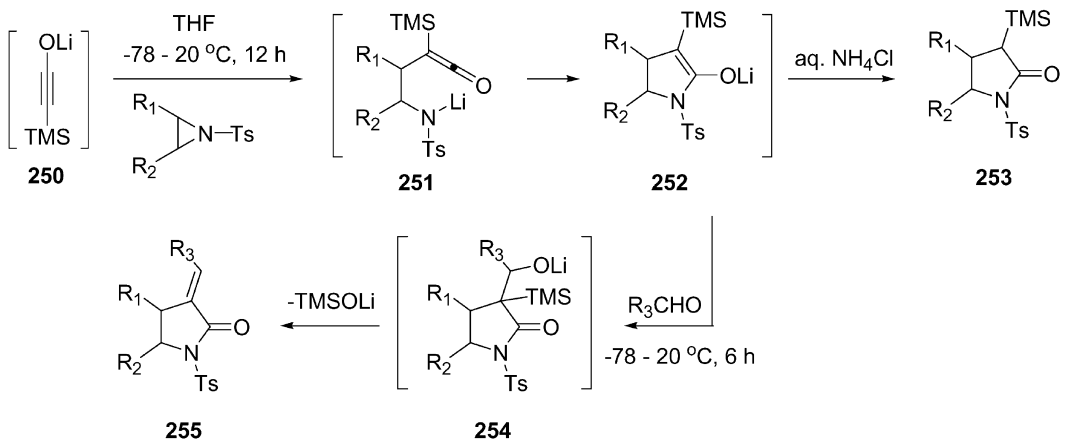
R_1	R_2	Yield (%)	Configuration
(*S*)-Me	H	82	(*S*)-
(*S*)-*i*-Pr	H	72	(*S*)-
(*R*)-*n*-Pr	H	44	(*R*)-
Ph	H	68 (1:1.6)	—
(*S*)-Bn	H	79	(*S*)-
$-(CH_2)_4-$		31	—

Recent work presented by Harrity et al.[149] illustrated the method via a [3+3] cycloaddition of aziridines with a complex of Pd-trimethylenemethane (Pd-TMM) **245** to build functionalized piperidines. Pd-TMM was generated by mixing commercially available 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **244** with $Pd(PPh_3)_4$ in the presence of $P(OPr\text{-}i)_3$ and reductant *n*-BuLi in THF. This complex was in turn treated with the requisite aziridine substrates **243** in situ as shown in Scheme 108. The reactive species, a known double charged 1,3-dipole **243′**, can be proposed,[35] which readily formed the ring with the Pd-TMM complex to afford piperidine product **246**. Notably, the aziridines underwent regio-selective addition with the Pd-TMM complex at the less hindered site and furnished the products in enantiomerically pure form. In contrast, 2-phenyl aziridine resulted in almost non-regio-selective cycloaddition with a nearly equal mixture of regio-isomers (Table 56). In addition, the cycloaddition required activation by an aryl sulfonyl group at the aziridine nitrogen, whereas carbamate (Boc or Cbz) and diphenyl phosphinoyl moieties failed to provide the corresponding piperidines.

2-Vinyl aziridines **247** could be catalyzed by Pd(0) to undergo [3+2] cycloaddition with a number of hetero-cumulenes in a regio-selective manner to afford five-membered heterocyclic products.[150] This reaction required



Scheme 109.



Scheme 110.

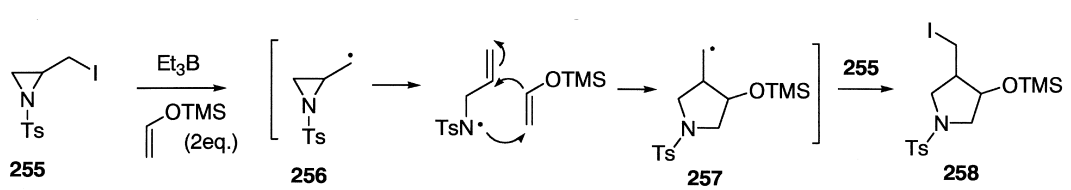
Table 57. Reaction of silylynolate with aziridines and olefination with aldehydes

Cyclization of ynolate with aziridines				Cyclization and olefination				
R_1	R_2	Yield (%)	Diast. ratio	R_1	R_2	R_3	Yield (%)	*E*/*Z*
H	H	61	—	H	H	*t*-Bu	71	100:0
H	Me	65	68:32	H	H	Pr	49	96:4
H	*i*-Pr	72	60:40	H	H	2-furan	64	96:4
$-(CH_2)_4-$		77	77:23	H	Me	*t*-Bu	80	100:0
Et	Et (*cis*)	39	52:48	$-(CH_2)_4-$		*t*-Bu	70	60:40
Et	Et (*trans*)	36	100:0					

only 2 mol% of $Pd(OAc)_2$ with 10 mol% of PPh_3 to complete the conversion of the aziridines to cycloaddition products. The heterocumulenes used in this study include isocyanates, carbodiimides and isothiocyanates. The cycloaddition, in general, provided imidazolidin-2-ones **249a**, imidazolidin-2-ylideneamine **249b** and thiazolidin-2-ylideneamine **249c** in high yield and high regio-selectivity (Scheme 109). A plausible mechanism was proposed for this transformation via an intermediate **248** by forming a (π-allyl)palladium complex. However, the process was less stereo-selective in the case of *cis*-aziridine to give a mixture of *cis* and *trans* product **249f** in 2:1 ratio, when R_2=Me. Trost et al. took the advantage of cycloaddition of vinyl aziridines with heterocumulenes and performed dynamic kinetic asymmetric cycloaddition with isocyanates using chiral ligands.[151] High yields and enantio-selectivity were obtained. The cyclized imidazolidinones were precursors to chiral diamines useful for the synthesis of SALEN ligands.

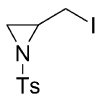
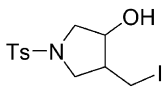
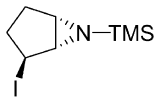
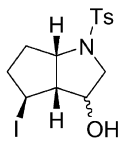
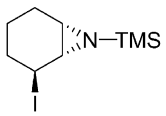
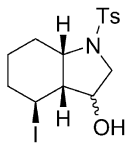
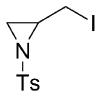
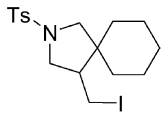
A silylynolate, generated from the carbonylation of lithium silyldiazomethane, was reacted with *N*-tosyl aziridines to produce various γ-lactams in respectable yields.[152] As outlined in Scheme 110, the ynolate **250** initially added to the aziridine to produce ring opening ketenylation of **251**. This intermediate readily underwent lactam ring formation leading to the lithium enolate **252**. Upon hydrolysis, five-membered lactam **253** was obtained. The ketenylation took place at the less hindered carbon of the aziridine (R_2=Me and *i*-Pr) to give highly regio-selective products. However, the stereo-selectivity was rather disappointing with only limited selectivity of unidentified preference as shown in Table 57. A *trans*-bicyclic γ-lactam of high ring constraint was synthesized from a cyclohexane aziridine precursor through this ketenylation-cyclization process. The lactam enolate could also be trapped by aldehydes to give Peterson olefination product **255** after elimination of siloxy anion from primary adduct **254**. Thermodynamically stable *E*-olefins were obtained as major products from less hindered aziridines, whereas poor selectivity was seen from the hindered cyclohexane aziridine.

Taguchi and co-workers recently disclosed their results of [3+2] cycloaddition reaction via azahomoallyl radical precursors.[153] The azahomoally radical precursors, reactive radical species, were derived from *N*-tosyl aziridines, and then underwent ring formation with electro-rich alkenes such as enol ethers and ketene acetals. As illustrated in Scheme 111, radical species **256** originated from iodomethyl aziridine **255** by radical initiator Et_3B in CH_2Cl_2 at room temperature. Isomerization of **256** led to the azahomoallyl radical intermediate, which readily cyclized with alkene to form pyrrolidinyl methyl radical **257**. The iodo-transformation completed the radical reaction cycle to give the corresponding iodomethylated pyrrolidine **258**. Representative examples are shown in Table 58 with monocyclic, bicyclic- and spiro-pyrrolidine products in respective yields. The stereo-selectivity, however, was less impressive with only marginal bias in favor of *cis*



Scheme 111.

Table 58. Radial [3+2] cycloaddition of various iodoaziridines with vinyloxytrimethylsilane

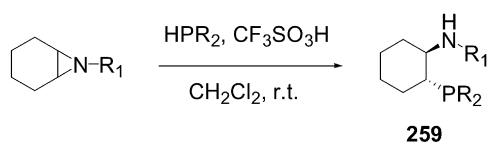
Aziridine	Olefin	Product	Yield (%)	*cis/trans*
			66	1.3/1
			60	1.5/1
			62	1/1.4
			56	—

isomers. Enantio-selectivity was also demonstrated by the researchers, when an optically active aziridine was used to carry out the cycloaddition with essentially complete reservation of the chirality as introduced.

9. Miscellaneous: other heteroatom nucleophilic addition

9.1. Phosphorus nucleophilic addition

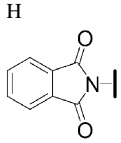
Only limited reports were found in the literature using phosphines as nucleophiles in ring opening of aziridines. The most practical preparative method was developed by Yudin's group in the synthesis of cyclohexane-based P,N-ligands in recent years, which were used as effective ligands for transition metal catalysis.[154] Acid catalyzed ring opening of 7-azabicyclo[4.1.0]heptane with diphenylphsphine resulted in a moderate yield of *trans*-1-amino-2-diphenylphosphino cyclohexane **259**. Dicyclohexylphosphine led to the formation of *trans*-1-amino-2-dihexylphosphino cyclohexane in only 30% yield. However, the aziridine activated by a phthalimide group under the same reaction conditions gave the ring opening product in 65% yield (Scheme 112 and Table 59). The new P,N-ligand was used to successfully catalyze the Suzuki coupling between sterically hindered substrates.



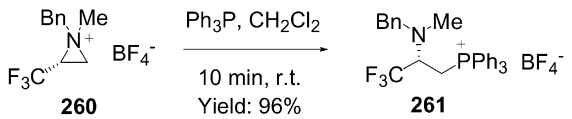
259

Scheme 112.

Table 59. Ring opening with diphenyl- and dicyclohexylphospines

R_1	R_2	Yield (%)
H	Ph	50
H	Cyclohexyl	30
	Ph	65

A highly activated aziridinium salt could undergo nucleophilic ring opening with triphenylphosphine to give an α-amino phosphonium salt adduct in 96% yield. Phosphine and other nucleophiles attacked exclusively at the unsubstituted ring carbon.[155] Although organophosphines are sufficiently nucleophilic to open the aziridinium ring of **260**, the formed phosphonium salt product **261** has not been shown to be useful in organic chemistry and other fields. Such phosphonium salts were only used as catalytic bases in nucleophilic addition to catalyze ring opening of aziridines (see Section 3.1, 3.3, 4.1 and 5.1) (Scheme 113).



260 **261**

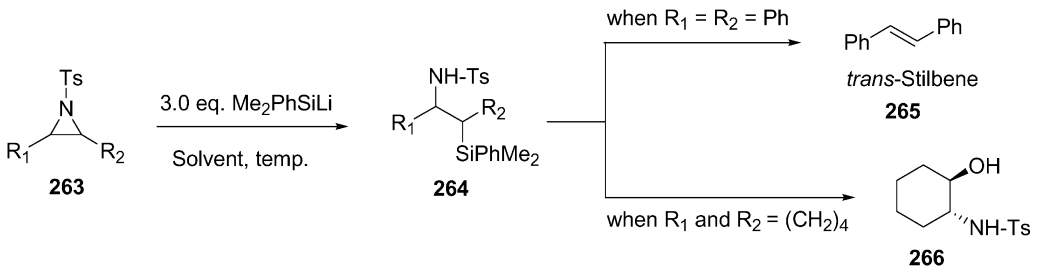
Scheme 113.

9.2. Silanes

Organosilane anions are well known to have wide application as organosilane bases for deprotonation of carbonyls and esters to form enolates, and also as nucleophiles to undergo additions to a number of electrophiles, including esters, carbonyls, imines and α,β-unsaturated carbonyls. However, rare reports were seen in the literature regarding organosilane anion addition to aziridines, and the latest ring opening of aziridines was published by Fleming and co-workers[156] describing nucleophilic attack of dimethylphenylsilyllithium to aziridines **262**. The ring opening reaction proceeded with 3.0 equiv. of the organosilyllithium reagent to give regio- and stereoselective β-silylethyl sulfonamides **263** as shown in Scheme 114. The *trans*- and *cis*-2,3-diphenyl aziridines gave *anti* addition products as diastereomers. The optimal solvent was found to be toluene, as presented in Table 60. The applications outlined in their publication include β-elimination of either threo- or erythro-β-silylethyl sulfonamides to give *trans*-stilbene **264** in good yields and oxidation with peroxide to afford β-hydroxyl sulfonamides **265**.

9.3. Selenols

Similar to alcohols and thiols, selenols are also nucleophiles attacking aziridines to give corresponding ring opening products. Non-activated aziridines **267** reacted with phenylselenol to give ring opening products **268** in high yields and regio-selectivity[157] as shown in Scheme 115. Presumably, the organoselenol was sufficiently acidic to protonate the non-activated aziridines so as to catalyze the ring opening process. The organoselenides are precursors for radical ring closure under tributyltinhydride/AIBN conditions to form pyrrolidines **269** in high stereoselectivity. Further extension of this methodology was reported recently for the formation of pyrrolidin-3-ones.[158]



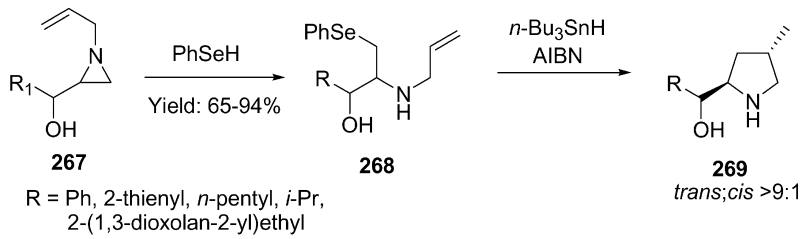
Scheme 114.

Table 60. Ring opening of aziridines with dimethylphenylsilyllithium

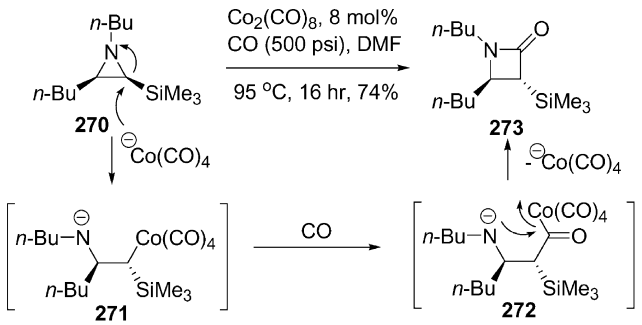
R_1	R_2	Solvent	Temperature (°C)	Yield (%)
trans-Ph	Ph	THF	0	56 (*erythro*)
cis-Ph	Ph	THF	−78	43 (*threo*)
Ph	H	Toluene	0	73
n-C_6H_{13}	H	THF	0	44
$-(CH_2)_4-$		THF	0	48 (*trans*)

9.4. Cobalt

Single step conversion of aziridines to β-lactams, or so called carbonylation of aziridines, was realized under transition metal cobalt catalyzed carbonylation conditions. Aggarwal and et al. found that the ring expansion took place with non-activated aziridines **270** catalyzed by $Co(CO)_8$, whereas activated aziridines gave only recovered starting material.[159] As shown in Scheme 116, the cobalt attacked

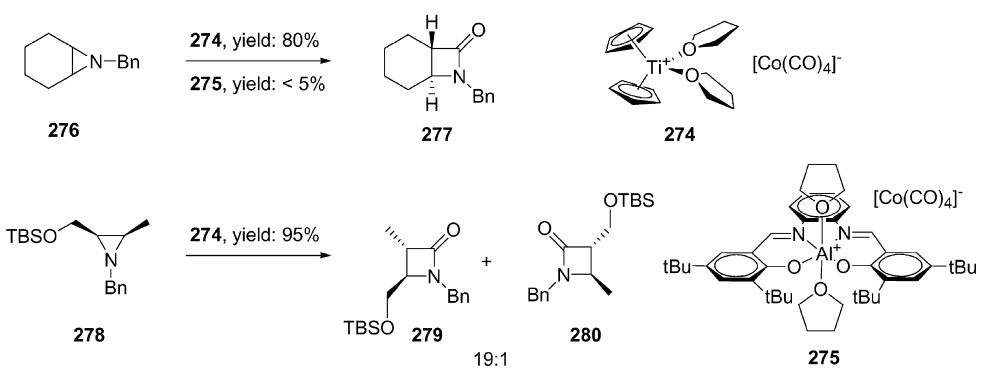


Scheme 115.



Scheme 116.

the aziridine from the backside at the $SiMe_3$ attached carbon to give intermediate **271** with inversion of the stereochemistry. The carbonyl insertion took place with retention of the chiral center in **272**. Then, the ring closure provided the β-lactam ring formation (**273**) in 74% yield. Although a single electron transfer mechanism was proposed for the ring opening reaction by others,[160] the nucleophilic addition approach seems to provide a more convincing way to rationalize the stereochemical outcome.[161,162] The ring expansion of aziridines to β-lactams provides a versatile tool for stereo-selective construction of diverse β-lactams, which was further exemplified by Coates et al. using new catalysts $[Cp_2Ti(THF)_2][Co(CO)_2]$ (**274**) and

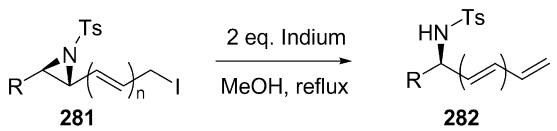


Scheme 117.

[(salph)Al(THF)$_2$][Co(CO)$_2$] (**275**)[163] and generating more complex β-lactam systems (**277** and **279**) with improved chemical yields and regio-selectivity as shown in Scheme 117.

9.5. Conversion of 2-iodomethyl aziridines to allylic amines

Indium mediated transformation of functional groups has recently attracted much interest of organic chemistry due largely to its water and air stability, and readily reacting with electrophiles. Indium initiated efficient conversion of 2-iodomethyl aziridines to ring opening products of allylic amines is an example of recent advances in indium chemistry.[164] When 2-iodomethyl aziridines **281** or conjugated iodomethy aziridines containing a vinyl group were treated with indium in refluxing methanol, the conversion proceeded smoothly to give allylic amines in excellent yields (90–96%). The ring opening products **282** were the result of the double bond migration (Scheme 118). This useful method provides potential for the synthesis of chiral allylic amines (Table 61).



281 **282**

Scheme 118.

Table 61. Indium mediated conversion of 2-iodomethyl *N*-Ts aziridines to chiral allylic amines

R	*n*	Time (h)	Yield (%)
n-C_5H_{11}	0	4	96
n-C_8H_{17}	0	4	96
BnO$(CH_2)_2$	0	4.5	92
PMBO$(CH_2)_4$	0	5	90
n-C_5H_{11}	1	4.5	91
BnO$(CH_2)_2$	1	5	93

A much less known tellurium agent in organic chemistry found application in ring opening of aziridines as reported by Dittmer et al.[165] Te^{2-}, generated from reduction of Te(0) by $NaBH_4$ in water, initially displaced tosylate of **283** under phase transfer conditions (Adogen-464), which then underwent aziridine ring opening with concurrent tellurium containing ring formation (Scheme 119). Subsequent reductive elimination led to allylic amines **284** along with a black powder precipitate of Tellurium metal. However, a phenyl aziridine did not react under the conditions, probably due to attack of telluride ion at the benzylic carbon favored by benzyl stabilization (Table 62). This procedure was applied to asymmetric synthesis of amines, when optically active aziridinemethanol tosylates were used.

Table 62. *N*-Tosylallylic amines from *N*-tosylaziridinemethyanol tosylates

R_1	R_2	R_3	Yield (%)
n-Pr	H	H	74[a]
H	Me	H	81[a]
Me	Me	H	85
$BnOCH_2$	H	H	88
H	$-(CH_2)_3-$		95
Ph	H	H	0

[a] Optically active amines.

10. Concluding remarks

Aziridines have proven to be versatile building blocks toward a number of nucleophiles for ring opening reactions. The development of new methodologies has provided choices for improvement of reaction conditions, chemical yields, regio-selectivity and ease of operation. Some of the procedures have been intended to address issues of cost efficiency and environment friendliness for potential manufacture needs. Moreover, [3+2] cycloadditon of aziridines has expanded its application to the construction of sophisticated cyclic and bicyclic scaffolds in a simple operation. The increasing interests in amine containing molecules both by organic and in pharmaceutical researches have further strengthened the important position of nucleophilic ring opening of aziridines in contemporary synthetic chemistry. Furthermore, aziridine chemistry has found its broad utility in organic and medicinal chemistry in particular, which is anticipated to increase in the future.

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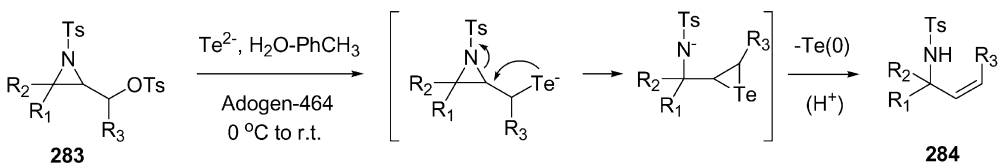

283 **284**

Scheme 119.

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Biographical sketch

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Studies on diastereoselective reduction of cyclic β-ketoesters with boron hydrides. Part 4: The reductive profile of functionalized cyclohexanone derivatives

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Abstract—Reduction of 2-allyl-2-carboalkoxycyclohexanones (**3d-f**), 2-propyl-2-carboethoxycyclohexanone (**3g**) and 2-benzyl-2-carboethoxycyclohexanone (**3h**) with boron hydrides in the presence and absence of several chelating agents were studied. Molecular modeling studies using semiempirical PM3 method were performed in order to find a suitable explanation of the diastereoselection of ketone carbonyl faces during the reductive process, which yielded *trans*-2-allyl-2-carboethoxycyclohexanol (**6e**) and *cis*-2-allyl-2-carboethoxy-cyclohexanol (**7e**) in good diastereomeric excess by using inexpensive sodium and tetrabutylammonium borohydrides.

1. Introduction

Cyclic β-ketoesters and its corresponding β-hydroxyester derivatives are important building blocks for the synthesis of natural products and many bioactive substances.[1,2] Several previous papers of our laboratory described the enantio-[3,4] and diastereoselective[5–8] preparation of cyclic β-hydroxyester derivatives, exploring the chemoselective reduction of the carbonyl group of 2-alkyl-2-carboalkoxy-cyclopentanone (**1**) and 2-acetyl-2-alkyl-butyrolactone derivatives (**2**) and their application in the synthesis of carbocyclic and heterocyclic building blocks[9–12] useful for construction of new drug candidates[13,14] (Fig. 1).

Now, we describe in this paper our studies about the reduction of 2-alkyl-2-carboalkoxycyclohexanone derivatives (**3d-m**) using boron hydrides and the investigation of its diastereoselection profile in comparison with those present by corresponding cyclopentanone derivatives (**1**). Additionally, molecular modeling studies were performed in derivatives of both series (**1**) and (**3**) in order to elucidate the structural reasons of their reductive profile (Fig. 1).

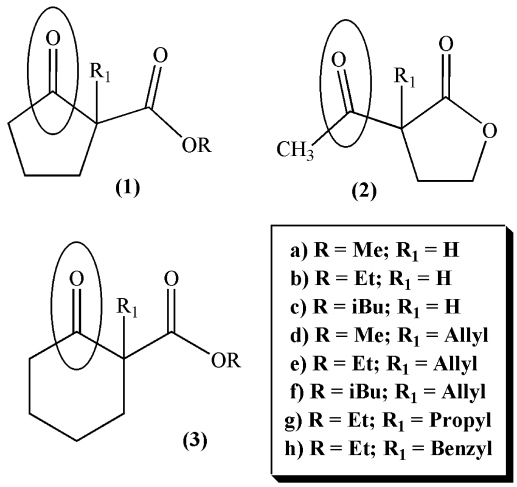

Figure 1. Cyclic β-ketoester derivatives.

2. Results and discussion

The 2-carboalkoxcyclohexanone derivatives (**3a**), (**3b**) and (**3c**) were synthesized in 90, 71 and 95% yield, respectively,

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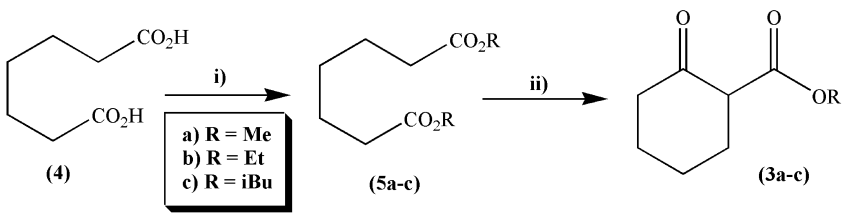


Scheme 1. (i) ROH, H_2SO_4 (cat.), reflux, 4–8 h, 98% (**5a**), 82% (**5c**); (ii) $AlCl_3$, Et_3N, rt, 2.5–4 h, 90% (**3a**), 71% (**3b**), 95% (**3c**).

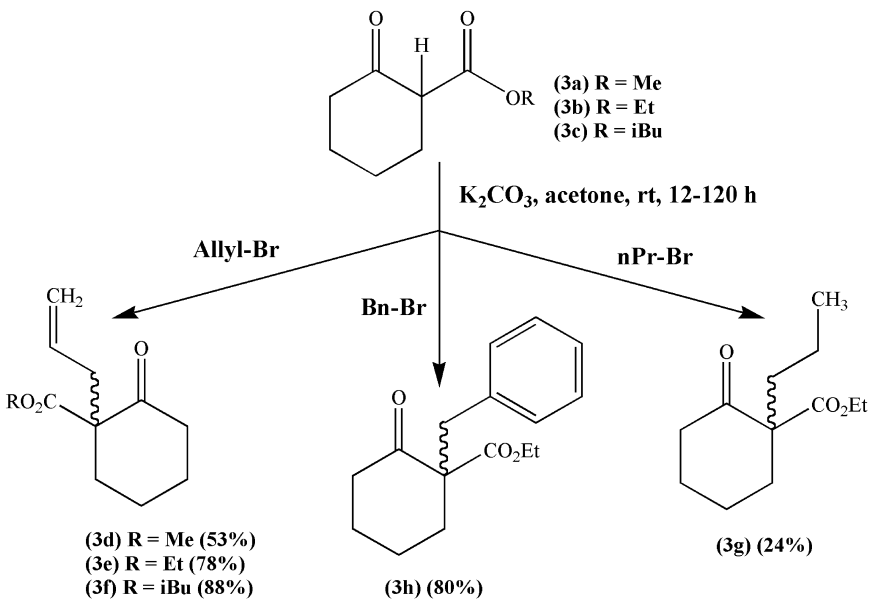
exploiting the Dieckmann condensation of the corresponding pimelic esters (**5a-c**) (Scheme 1) by treatment with $AlCl_3$ and triethylamine.[15] In spite of ethyl pimelate (**5b**) having been obtained commercially,[16] the corresponding methyl and isobutyl esters were obtained in 98 and 82% yield respectively from Fisher esterification of pimelic acid (**4**).[17]

When we employed reactive halides like allyl bromide and benzyl bromide, C-2 alkylated derivatives (**3d-f**) and (**3h**) were regioselectively obtained in yields ranging from 53 to 88%, by using a modification[18] of the classical Barco's conditions[19] which avoids the formation of the corresponding O-alkylated derivatives. Additionally, the alkylation of 2-carboethoxycyclohexanone (**3b**) with less reactive propyl bromide furnished the desired C-alkylated derivative (**3g**) in only 24% yield (Scheme 2).

Next, the 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) were submitted to the chemoselective reduction with sodium borohydride in methanol, in the presence or absence of calcium chloride, in order to compare its reductive profile with that previously described for the corresponding 2-allyl-2-carboalkoxycyclopentanone derivatives[5] (**1d-f**), as showed in Table 1. The composition of the diastereomeric alcohols mixture (**6** and **7**) was elucidated by NMR spectroscopy using growing concentrations of $Eu(thd)_3$[5,7] and the relative diastereomeric ratio was determined by HRGC using a β-cyclodextrin derivative as stationary phase,[20,21] as illustrated in Figure 2. The chiral HRGC method was elected instead of normal phase GC due to the better resolution profile previously evidenced for the diastereomeric separation of functionalized β-ketoesters.[20,21]

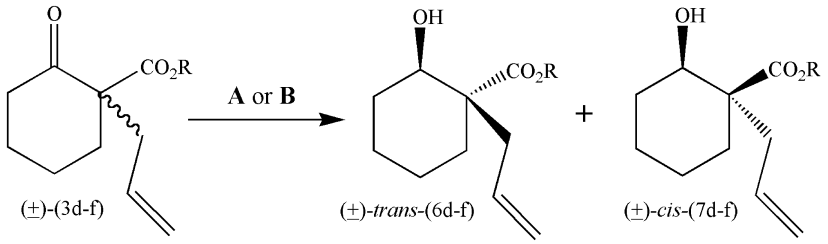
In spite of Frater[22] having described that the reduction of 2-allyl-2-carboethoxycyclohexanone (**3e**) with sodium borohydride in ethanol furnished the *cis*-cyclohexanol derivative (**7e**) in 33% de, we found that the use of methanol as solvent (entry 3, Table 1) produces a slight improvement of this diastereoselectivity profile, resulting also in the major formation of (**7e**), but in 43% de. The previous addition of 2 equiv. of $CaCl_2$ (entry 4, Table 1) resulted in the inversion of the relative configuration of the major isomer produced, that is, *cis*-cyclohexanol derivative (**6e**).

Next, we investigated the contribution of the size of ester-attached alkoxy group in the diastereoselective reductive profile of the 2-allyl-2-carboalkoxy-cyclohexanone derivatives (**3d-f**) with sodium borohydride (Table 1), following an experimental evidence related in a previous paper from our laboratory,[5] which indicated that the diastereoselectivity of the 2-allyl-2-carboalkoxycyclopentanone (**1d-f**) reduction was inversely proportional to the bulky of the alkoxy group. In fact, in that work the best diastereoselectivity index was achieved in the reduction of



Scheme 2.

Table 1. Reduction of (±)-2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) with sodium borohydride



Entry	Compound	R	Conditions[a]	Product **6**:**7**	Yield (%)	Diastereomeric ratio[b,c] *trans*/*cis*
1	**3d**	Me	A	**6d**:**7d**	74	1:1.6
2	**3d**	Me	B	**6d**:**7d**	85	4.3:1
3	**3e**	Et	A	**6e**:**7e**	90	1:2.5
4	**3e**	Et	B	**6e**:**7e**	96	6.5:1
5	**3f**	*i*Bu	A	**6f**:**7f**	92	1:2.4
6	**3f**	*i*Bu	B	**6f**:**7f**	96	2.2:1

[a] Conditions: (A) $NaBH_4$ (1.2 equiv.), MeOH, 0 °C, 30 min; (B) (i) $CaCl_2$ (2 equiv.), MeOH, rt, (ii) $NaBH_4$ (1.2 equiv.), 0 °C, 30 min.
[b] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).
[c] The qualitative determination of diastereomeric alcohols was made by analysis of ^1H NMR at 200 MHz, in presence of $Eu(thd)_3$.

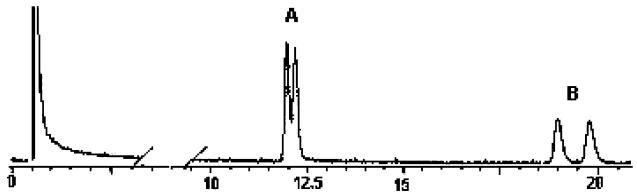


Figure 2. Chiral-HRGC of stereoisomers of the 2-allyl-2-carbomethoxycyclohexanol derivatives (**6d**) and (**7d**), at 100 °C, in a capillary glass column (20 m×0.3 mm×0.3 μm) covered with 10% of 2,3-dimetil-6-*O*-terc-butildimetilsilil-β-cyclodextrina/SE-54. A=(±)-*cis*-2-allyl-2-carbomethoxycyclohexanols (**7d**); B=(±)-*trans*-2-allyl-2-carbomethoxycyclohexanols (**6d**).

2-allyl-2-carbomethoxycyclopentanone (**1d**) with sodium borohydride in the absence or in the presence of calcium chloride[5,6] (Fig. 2). However, in the present work the diastereoselection of the ketone carbonyl faces of 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d-f**) by hydride anion have no relationship with the size of the alkoxy group (Table 1) since the diastereomeric excess followed the order (**3e**)>(**3d**)>(**3f**). As showed previously, the best diastereoselective control was achieved during the reduction of the ethyl ester (**3e**) with $NaBH_4/CaCl_2$, which produced the *cis*-(±)-2-allyl-2-carboethoxycyclohexanol (**7e**) in 73% de. Intriguingly, despite applying the same experimental conditions, the diastereocourse of the reduction of the cyclohexanone derivatives with sodium borohydride in the absence or in the presence of $CaCl_2$ was opposite to that of the corresponding cyclopentanone derivatives (**1d-f**), as illustrated in Figure 3 for the reduction of methyl ester (**1d**).

In order to elucidate the possible reasons for the inversion of the diastereoselective reductive profile as consequence of the ring homologation, we made a comparison of the structural and electronic properties of the substrate molecules using the semiempirical PM3 method.[23] All optimized PM3 structures obtained in the group of 2-allyl-2-carboalkoxycyclohexanones (**3d-f**) had similar geometries, independently of the size of the ester-attached alkoxy group (OR). Similar geometries were also observed for each group of the respective complexes with the calcium ion. The optimized structures of (**3d**) and of its calcium complex (**3d**)+Ca^{2+} are presented in Figure 4. The comparison of these structures, especially the van der Waals radius representation, indicates a change in the conformation of the keto, alkoxy ester, and allyl groups in (**3d**) that allows the molecule to act as a tridentate ligand, in order to stabilize the positive charge of the calcium ion. This geometry is in accordance with the calculated geometry previously reported for the complex of (**1d**) with a Zn^{2+} ion.[6]

Electronic surfaces as MEP and frontier orbitals maps are useful theoretical tools to evaluate the 3D electronic properties of a compound, and with its associated molecular size and shape, may be of great value to interpret, elucidate and predict experimental results of stereoselective organic reactions.[24,25] The MEP illustrates the most (red) and less (blue) electron-rich regions, throughout an energetic gradient illustrated by a red–orange–yellow–green–blue scale. Also considering a similar color scale, the LUMO (Lowest Unoccupied Molecular Orbital) map shows the absolute value of the LUMO onto the total electron density surface.

The MEPs observed onto the *Re* and *Si* faces of (**3d**) (Fig. 5(A)) allow the recognition of an electron-poorer region (a more intense blue color) near the *Re* face of the ketone carbonyl group (see Fig. 5(D)) than on the corresponding region on the *Si* face (a green colored region). The LUMO maps (Fig. 5(B)) also indicate the *Re* face of the ketone carbonyl (a much more intense blue color) as the most favorable to suffer the attack of a nucleophile[26,27] (hydride anion). In addition, an electron-rich region can be seen on the *Si* face (a yellow–orange colored region in the MEP and a red–orange colored region in the LUMO map), corresponding to the oxygen atom of the alcoxy ester group, which may render unfavorable the approximation of a nucleophile due to electrostatic repulsion. Moreover, the orientation of the alkoxy ester group may also interfere with the borohydride approximation on the *Si* face by steric hindrance over the ketone carbonyl. In

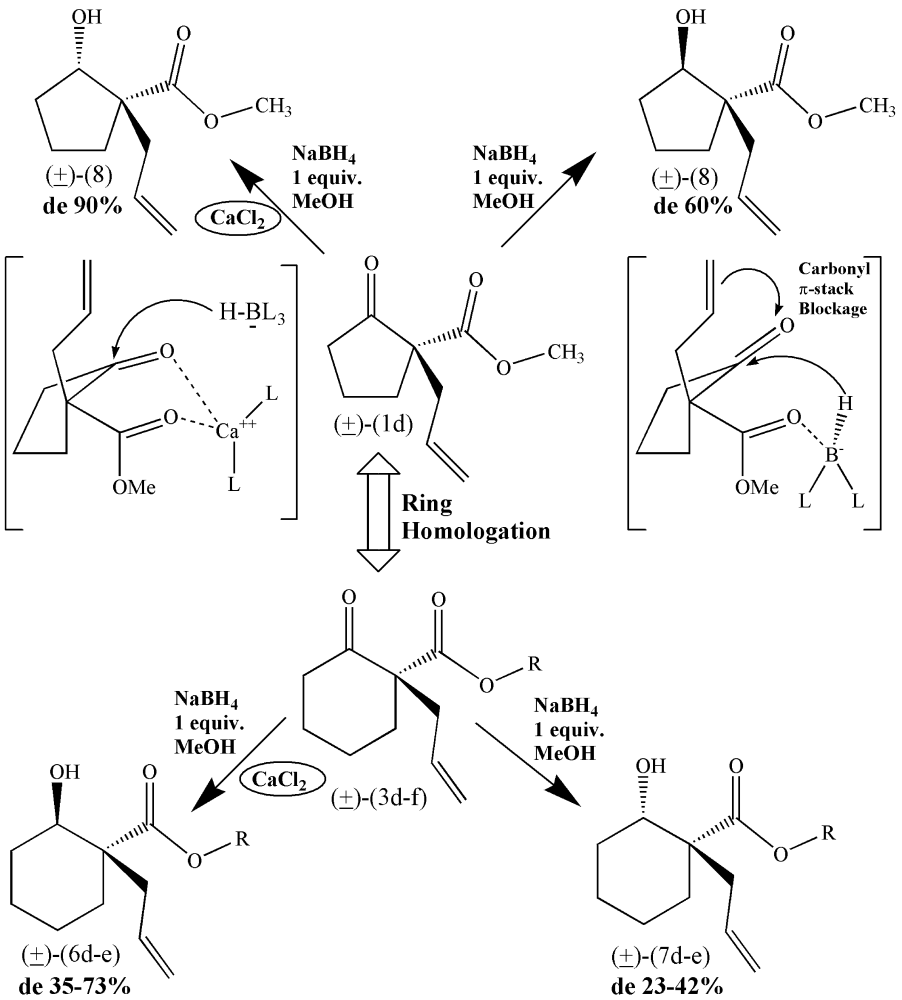


Figure 3. Inversion of the diastereoselective profile of the cyclic β-hydroxyesters (**6**-**8**) obtained from reduction of 2-allyl-2-carbomethoxycyclopentanone derivative (**1d**) or 2-allyl-2-carboalkoxycyclohexanone derivatives (**3d**-**f**) with sodium borohydride in the presence or absence of calcium chloride.

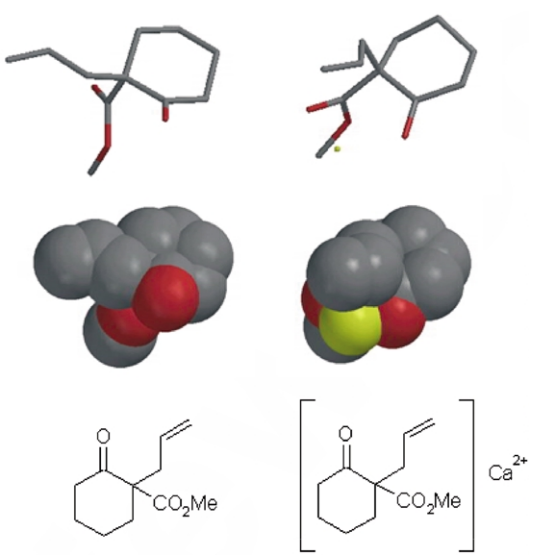


Figure 4. Tube and space-filling representations showing the conformational changes in the keto, alcoxy ester, and allyl groups of (**3d**) that allows it to interact with the calcium ion as a tridentate ligand in the (**3d**+Ca^{2+}) complex. Color code for the atoms is: carbon, gray; oxygen, red; and calcium, yellow. The hydrogen atoms were omitted for clarity.

contrast, the electronic effect of the allyl group on the *Re* face should not greatly influence the nucleophilic attack because it results in a less intense electron-rich region than the alkoxy ester group and it is oriented in the opposite direction in relation to the ketone carbonyl group.

The MEP and LUMO maps of the compounds complexed with the calcium ion, exemplified in the Figure 5 by (**3d**)+Ca^{2+}, show the region corresponding to the *Si* face on the ketone carbonyl group (Fig. 5(A.1) and (B.1)) as a relatively electron-poor region (orange–green color). On the other hand, the *Re* face of the ketone group is now almost completely hindered by the allyl group because of its conformational change towards the Ca^{2+} ion, which is better illustrated by the space-filling model representation (Fig. 5(C.1)). This steric hindrance would probably have a stronger effect on the nucleophilic attack than the electrostatic repulsion created by the oxygen atoms of the alkoxy ester group (red and red–orange regions on the MEP and LUMO maps, respectively) observed on the *Si* face. As a result, in opposition to uncomplexed (**3d**), the *Re* face of its complex with Ca^{2+} is much less susceptible to approximation and, consequently, to nucleophilic attack. Therefore, the (±)-*trans*-cyclohexanol derivatives (**6**) must be obtained

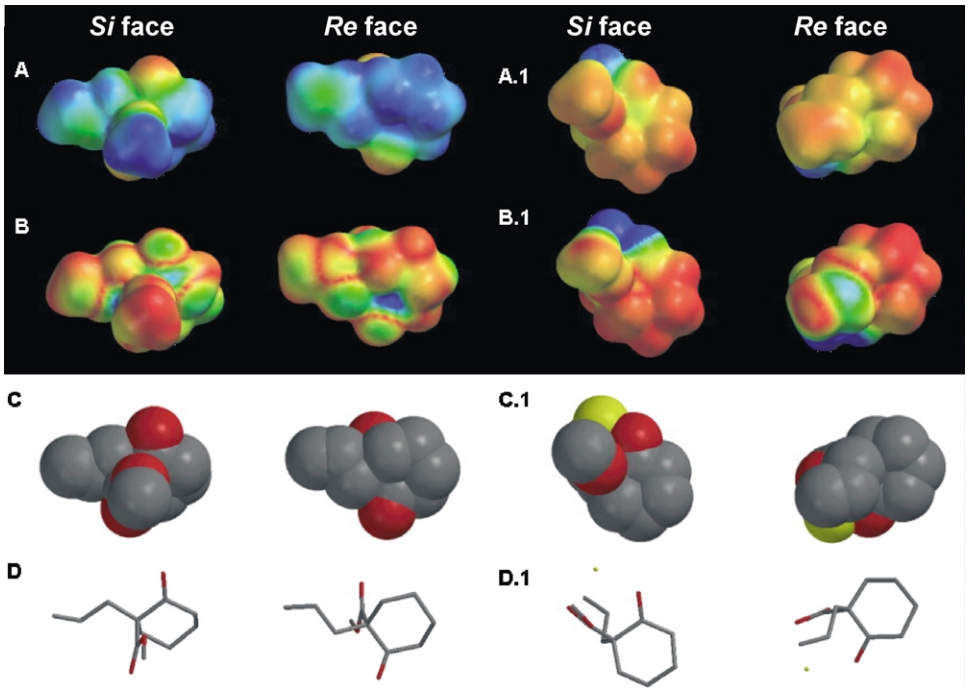


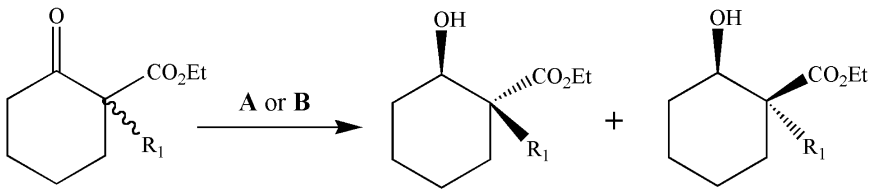
Figure 5. Representations of (**3d**) and (**3d**)+Ca^{2+}. (A) MEPs are in the range of −54 (red) to +20 (blue) kcal/mol; (B) LUMO maps in the range of 1.10^{-7} (red) to 0.030 (blue) kcal/mol; (C) space-filling model representation; (D) tube model representation; (A.1) MEPs in the range of +115 (red) to +380 (blue) kcal/mol; (B.1) LUMO maps in the range of 7.10^{-8} (red) to 0.0090 (blue) kcal/mol; (C.1) space-filling representation; (D.1) tube model representation. Color code for the atoms is: carbon, gray; oxygen, red; and calcium, yellow. The hydrogen atoms were omitted for clarity.

in greater proportion than the corresponding (±)-*cis*-cyclohexanol derivatives (**7**), which is in agreement with the experimental results (Table 1).

In order to evaluate the effect of the allyl group in the diastereoselectivity of the ethyl ester derivative (**3e**) (Table 1, entries 3 and 4) we studied the reductive profile of the corresponding saturated propyl derivative (**3g**) and the benzyl analogue (**3h**) with sodium borohydride in the presence or absence of calcium chloride. As depicted in Table 2, the reduction of saturated derivative (**3g**) resulted in the formation of a mixture of the cyclohexanol derivatives (**6g**) and (**7g**) with a decrease of the diastereomeric excess in comparison to that obtained from the reduction of the respective allyl derivatives (**6d**) and (**7d**) (Table 1), that is, 26% (entry 7, Table 2) versus 42% (entry 3, Table 1) without the use of $CaCl_2$ and 62% de (entry 8, Table 2) versus 73% (entry 4, Table 1) when $CaCl_2$ was used as a complexing agent (entry 8). These results indicated to us that the change of the allyl to propyl group in the derivative (**3g**) influenced directly of the diastereocourse of this reaction, by adopting a particular conformation that could partially block the less hindered *Re* face of the keto-carbonyl group or by the absence of formation of a ternary complex with calcium ion, as anticipated by molecular modeling studies.

The reduction of benzyl derivative (**3h**) with sodium

Table 2. Reduction of (±)-2-propyl-2-carboethoxycyclohexanone (**3g**) and (±)-2-benzyl-2-carboethoxycyclohexanone derivatives (**3h**) with sodium borohydride



(±)-(3g-h) (±)-*trans*-(6g-h) (±)-*cis*-(7g-h)

Entry	Compound	R_1	Conditions[a]	Product **6**:**7**	Yield (%)	Diastereomeric ratio[b,c] *trans*/*cis*
7	**3g**	*n*Pr	A	**6g**:**7g**	91	1:1.7
8	**3g**	*n*Pr	B	**6g**:**7g**	98	4.3:1
9	3h	Bn	A	**6h**:**7h**	98	1:2.4
10	**3h**	Bn	B	**6h**:**7h**	90	2.9:1

[a] Conditions: (A) $NaBH_4$ (1.2 equiv.), MeOH, 0 °C, 30 min; (B) (i) $CaCl_2$ (2 equiv.), MeOH, rt, (ii) $NaBH_4$ (1.2 equiv.), 0 °C, 30 min.
[b] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).
[c] The qualitative determination of diastereomeric alcohols was made by analysis of ^1H NMR at 200 MHz, in presence of $Eu(thd)_3$.

borohydride without $CaCl_2$ (Table 2, entry 9) did not result in any change of the diastereoselectivity in comparison with that showed by the corresponding allyl derivative (**3e**) (Table 1, entry 3). On the other hand, the use of calcium chloride as Lewis acid (Table 2, entry 10) resulted in a expressive drop of the comparative diastereoselection (see Table 1, entry 4), indicating that possibly for steric reasons benzyl group is not so able to adopt the adequate orientation which permits the formation of the ternary complex between the allyl group of compound (**3e**) and calcium ion, reducing selective blockage on the *Si* face of the ketone carbonyl group.

Considering the results described herein, we elected the 2-allyl-2-carboethoxy-cyclohexanone derivative (**3e**) for further studies varying the conditions of the reductive step as well as the nature and the size of the hydride transferring reagent, in order to optimize the diastereoselective formation of *cis*-2-allyl-2-carboethoxycyclohexanol (**7e**), obtained only in very poor de.

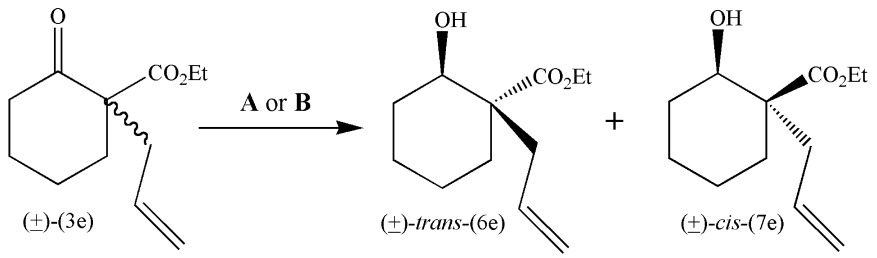
The initial modification, which consisted in the change of methanol used as solvent to isopropanol (Table 3, entries 11 and 12) or aprotic tetrahydrofuran (Table 3, entry 3), led to the loss of the diastereoselectivity evidenced before. This distinct profile may be explained by the presence of different reducing species in the media, since sodium borohydride reacts with methanol to give sterically demanding trimethoxyborohydride, whereas solutions of sodium borohydride in isopropanol or tetrahydrofuran are very stable.[28]

Once that we obtained the best diastereoselective excess by using $CaCl_2$ as complexing agent, we decide next investigate the profile of the reductive process with sodium borohydride employing four other Lewis acids presenting a variation of the atomic radius of the divalent metal from Mg^{+2} to Zn^{+2} (Table 3, entries 14–17). However, besides the reductions of the allyl derivative (**3e**) using these other metallic chlorides have not been able to improve the diastereoselectivity, the diastereofacial discrimination of the nucleophilic hydride attack to the ketone group was abolished, resulting in the equal formation of the isomers *trans*-(**6e**) and *cis*-(**7e**) (Table 3, entries 14–17). The evidenced profile indicated that, contrarily to the results previously described by Taniguchi et al.,[29] the reduction of derivative (**3e**) in the presence of Lewis acids did not show a direct correlation between the ionic radius of the metal and the diastereoselectivity of the reductive process.

Finally, the last variation in the reductant conditions consisted in the employment of other boron hydrides with different reactivity, size and solubility in the aprotic solvent THF, represented by the use of zinc borohydride,[30] lithium tri-*sec*-butylborohydride[31] (L-Selectride) and tetrabutylammonium borohydride[32] (Table 3, entries 18–20, respectively). In spite of being well-known that the use of bulky boron hydrides led to an improvement of the diastereofacial discrimination of carbonyl ketone group, the treatment of allyl functionalized derivative (**3e**) either with zinc borohydride or L-Selectride in THF resulted in an almost complete absence of the diastereoselectivity between the cyclohexanol derivatives (**6e**) and (**7e**) (Table 3, entries 18 and 19), indicating to us that bulky hydride-containing species are not able to discriminate the faces of the ketone carbonyl group.

On the other hand, the reduction of derivative (**3e**) with tetrabutylammonium borohydride in THF, furnished the *cis*-cyclohexanol derivative (**7e**) with the desired improvement of the diastereoselectivity from 42% (Table 1, entry 3) to 68% de (Table 3, entry 20). The preferential formation of the diastereomer (**7e**) by the usage of a $(n\text{Bu})_4\text{NBH}_4$ in THF (Table 3, entry 20) can be explained by the better solubility of the non-bulky hydride species in the aprotic media, which

Table 3. Reduction of 2-allyl-2-carboethoxycyclohexanone derivative (**3e**)



Entry	Redutor	Lewis acid	Solvent and temperature (°C)	Product **6**:**7**	Yield (%)	Diastereomeric ratio[a,b] *trans*/*cis*
11	$NaBH_4$	—	iPrOH, 0 °C	**6e**:**7e**	85	1:1.2
12	$NaBH_4$	$CaCl_2$	iPrOH, 0 °C	**6e**:**7e**	90	1:1.1
13	$NaBH_4$	—	THF, 0 °C	**6e**:**7e**	77	1:1
14	$NaBH_4$	$MgCl_2$	MeOH, 0 °C	**6e**:**7e**	98	1.6:1
15	$NaBH_4$	$MnCl_2$	MeOH, 0 °C	**6e**:**7e**	96	1:1.3
16	$NaBH_4$	$CeCl_3$	MeOH, 0 °C	**6e**:**7e**	91	1.2:1
17	$NaBH_4$	$ZnCl_2$	MeOH, 0 °C	**6e**:**7e**	98	1:1
18	$Zn(BH_4)_2$	—	THF, 0 °C	**6e**:**7e**	91	1.2:1
19	L-Selectride	—	THF, −78 °C	**6e**:**7e**	95	1:1.1
20	$(n\text{Bu})_4\text{NBH}_4$	—	THF, 0 °C	**6e**:**7e**	86	1:5.3
21	$(n\text{Bu})_4\text{NBH}_4$	—	MeOH, 0 °C	**6e**:**7e**	89	1:8.2

[a] The relative diastereomeric ratio was determined by HRGC in a 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 capillary column (20 m×0.3 mm×0.3 μm).

[b] The qualitative determination of diastereomeric alcohols was made by analysis of ^{1}H NMR at 200 MHz, in presence of $Eu(thd)_3$.

raised the speed of the reaction favoring the attack on the less hindered *Si* face of ketone carbonyl group (Fig. 5). Nevertheless, the change of the solvent from aprotic THF to protic methanol (Table 3, entry 21) curiously increased the diastereoselective formation of alcohol (**7e**) to 78% de. In fact, in spite of there are not many works in the literature describing the use of $(n\text{Bu})_4\text{NBH}_4$ in protic to solvents for the reduction of carbonyl compounds[29,33] is well-known that its application in the reduction of β-ketoesters[29] followed the Felkin–Ahn's model[34] with the attack of the hydride anion at the less hindered face of ketone carbonyl group (Fig. 6), in agreement with the molecular modeling and chemical results obtained in the present work.

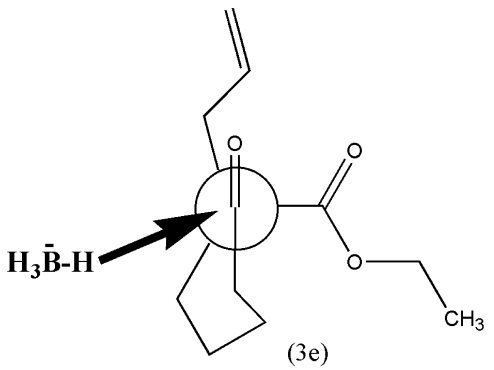


Figure 6. Felkin–Ahn's attack of hydride anion to less hindered face of cyclohexanone derivative (**3e**).

3. Conclusion

In summary, the results obtained from this research work furnished a nice approach to the diastereoselective synthesis of (±)-*trans*-cyclohexanol derivative (**6e**) and (±)-*cis*-cyclohexanol derivative (**7e**) respectively in 73 and 78% de, using available and inexpensive sodium or tetrabutylammonium borohydrides. The developed synthetic methodologies showed to be extremely dependent of the solvent and the Lewis acid employed, being the best results obtained when the reductions were carried out in methanol and, for the preparation of (**6e**), calcium chloride was used as Lewis acid.

4. Experimental

4.1. Molecular modeling

The molecular modeling analysis was performed using the SPARTAN 1.0.5 program (Wavefunction Inc., Irvine, CA, 2000) on a Pentium III 900 MHz computer. The structure of the compounds (**3d-f**) and (**1d**) and of their respective complexes with calcium ion, (**3d-f**)+Ca^{2+} and (**1d**)+Ca^{2+}, were optimized with the PM3 method.[23] This semiempirical method is parameterized for calcium, present in the Lewis acid $CaCl_2$ used in the experimental methodology, and was previously used to analyze diastereoselective experimental data.[12,35]

The optimized structures of the compounds were submitted to Hessian matrix analysis to unequivocally characterize them as true minima of the potential energy surface. A Monte Carlo conformational analysis with the PM3 method was employed. The minimal energy conformers were selected and submitted to single-point energy calculations with the ab initio 3-21G* basis set in order to better evaluate their electronic properties. In this study, the map of the electrostatic potential (MEP), and the map of the absolute value of the lowest-unoccupied molecular orbital (LUMO map), both onto an electron density surface of 0.002 e/au^3, were considered for the analysis of the stereoselectivity results obtained in the Section 4.

4.2. Chemistry

^{1}H and ^{13}C NMR spectra were determined in deuterochloroform containing ca. 1% tetramethylsilane as an internal standard with Brucker AC 200 and Varian VxR 300 spectrometers. Splitting patterns were as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; dd, double doublet; ddt, double double triplet; m, multiplet. Infrared spectra (IR) spectra were obtained with a Nicolet 505 Magna spectrophotometer as neat films on sodium chloride plates. The mass spectra (MS) were obtained on a GC/VG Micromass 12 at 70 eV. Gas chromatography (HRGC) was recorded in a Hewlett Packard model 5890 series II using injection in the split mode. The HRGC analyses were performed in 10% 2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl-β-cyclodextrin in SE-54 (1% vinyl; 5% phenyl; 94% methylpolysiloxane) house made capillary column (20 m×0.3 mm×0.3 μm) at 100 °C/2 °C/min/130 °C. Microanalysis data were obtained with a Perkin–Elmer 240 analyzer, using Perkin–Elmer AD-4 balance.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm×6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were visualized with molybdatophosphoric acid in ethanol. For column chromatography Merck silica gel (70–230 mesh) was used. Solvents used in the reactions were redistilled prior use and stored over 3–4 Å molecular sieves. Reactions were generally carried out under nitrogen atmosphere and magnetic stirring. The 'usual workup' means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and filtered.

4.3. General procedure for the esterification of pimelic acid (4)

To a solution of pimelic acid[15] (**4**) (1 g; 6.25 mmol) in 12 mL of methyl or isobutyl alcohol was slowly added 0.73 mL of concentrated sulfuric acid. The resulting mixture was stirred at reflux until that tlc analysis indicated the total consumption of the starting material (eluent: hexanes/AcOEt 70:30). Next, the mixture was poured into crushed ice and then, extracted with dichloromethane (5×50 mL). The organic layers were washed with 5% aq. $NaHCO_3$ solution and submitted to the 'usual workup' to furnish the corresponding pimelate ester (**5a**) or (**5c**) as described above.

4.3.1. Dimethyl pimelate (5a). The spectroscopic data

of this compound, which was obtained in 99% yield, are in agreement with those previously related in literature.[36]

4.3.2. Diisobutyl pimelate (5c). This compound was obtained in 82% yield, after 8 h, as a yellow oil; IR (film): ν C–H 2875 and 2961, ν C=O 1737, ν C–O 1175 cm^{-1}; ^1H NMR (200 MHz): 0.92 (d, 12H, J=6.7 Hz, $OCH_2CH(CH_3)_2$), 1.38 (m, 2H, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 1.64 (qt, 4H, J=7.5 Hz, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 1.89 (sp, 2H, J=6.7 Hz, $OCH_2CH(CH_3)_2$), 2.31 (t, 4H, J=7.5 Hz, $O{=}CCH_2CH_2CH_2CH_2CH_2C{=}O$), 3.85 (d, 4H, J=6.7 Hz, $OCH_2CH(CH_3)_2$) ppm; ^{13}C NMR (75 MHz): 19.2 ($OCH_2CH(CH_3)_2$), 24.8 (CH_2-4), 27.8 ($OCH_2CH(CH_3)_2$), 28.8 (CH_2-3 and CH_2-5), 34.3 (CH_2-2 and CH_2-6), 70.6 ($OCH_2CH(CH_3)_2$), 173.8 ($C{=}O$) ppm. Anal. calcd for $C_{15}H_{28}O_4$: C 66.14; H 10.36. Found: C 66.21; H 10.44.

4.4. General procedure for Dieckmann cyclization[16] of the esters (5a-c)

To a suspension of anhydrous aluminum chloride (16 g, 120 mmol) in 50 mL of dichloromethane was added a solution of the corresponding pimelate ester derivative (**5a-c**) (46 mmol) in 50 mL dichloromethane. After cooling the obtained mixture at 0 °C, 16 mL of triethylamine (120 mmol) was carefully added and reaction was stirred at room temperature until that tlc analysis indicated the total consumption of the starting material. Next, a 1:1 mixture of 10% aq. HCl and crushed ice (100 mL) was added and the reaction was extracted with dichloromethane (4×40 mL). The organic layers were washed with a saturated aq. oxalic acid solution and submitted to the usual workup to furnish the corresponding 2-carboalkoxycyclohexanone derivative (**3a-c**) as described next.

4.4.1. 2-Carbomethoxycyclohexanone (3a). The spectroscopic data of this compound, which was obtained in 90% yield, are in agreement with those previously related in literature.[37]

4.4.2. 2-Carboethoxycyclohexanone (3b). The spectroscopic data of this compound, which was obtained in 71% yield, are in agreement with that previously related in literature.[38,39]

4.4.3. 2-Carboisobutoxycyclohexanone (3c). The spectroscopic data of this compound, which was obtained in 95% yield, are in agreement with that previously related in literature.[38]

4.5. General procedure for the C-alkylation of the β-ketoesters (5a-c)[17,18]

To a suspension of anhydrous potassium carbonate (2.44 g; 17.6 mmol) in anhydrous acetone (6 mL) was added a solution of 2-carboalkoxycyclohexanone derivative (**5a-c**) (5.8 mmol) in anhydrous acetone (2 mL). The reaction mixture displays a characteristic yellow color after stirring at room temperature for 30 min due to the formation of the corresponding enolate intermediate. Then, respective alkyl bromide (7.6 mmol) was added slowly and the mixture was stirred at room temperature until that tlc analyses (Hex/AcOEt, 9:1) indicated the total consumption of the starting material. The suspension was filtered, the filtrate concentrated at reduced pressure (80 mm Hg) and the residue diluted with ether (50 mL). The 'usual workup' gives the respective 2-alkyl-2-carboalkoxycyclohexanone derivative (**3d-g**).

4.5.1. 2-Allyl-2-carbomethoxycyclohexanone (3d). The spectroscopic data of this compound, which was obtained in 53% yield, are in agreement with that previously related in literature.[40]

4.5.2. 2-Allyl-2-carboethoxycyclohexanone (3e). The spectroscopic data of this compound, which was obtained in 53% yield, are in agreement with that previously related in literature.[22,40]

4.5.3. 2-Allyl-2-carboisobutoxycyclohexanone (3f). From alkylation of (**3c**) with allyl bromide (0.66 mL), this compound was obtained in 88% yield,[41] after 24 h, as a yellow oil; IR (film): ν C=C–H 3078, ν C–H 2960 and 2873, ν C=O 1737 and 1716, ν C–O 1219 and 1203 cm^{-1}; ^1H NMR (200 MHz): 0.86 (d, 6H, J=6.7 Hz, $COOCH_2CH(CH_3)_2$), 1.30–2.00 (m, 6H, $O{=}CCH_2CH_2CH_2CH_2$; $COOCH_2CH(CH_3)_2$ and $CHHCH{=}CH_2$), 2.33–2.51 (m, 5H, $O{=}CCH_2CH_2CH_2CH_2$ and $CHHCH{=}CH_2$), 3.83 (d, 2H, J=6.6 Hz, 1H, $COOCH_2CH(CH_3)_2$), 4.93–5.01 (m, 2H, $CH_2CH{=}CH_2$), 5.62–5.76 (m, 1H, $CH_2CH{=}CH_2$) ppm; ^{13}C NMR (50 MHz): 207.3 ($C{=}O$), 171.5 ($COOCH_2CH(CH_3)_2$), 133.4 ($CH_2CH{=}CH_2$), 118.1 ($CH_2CH{=}CH_2$), 71.3 ($COOCH_2CH(CH_3)_2$), 61.0 (C-2), 41.1 ($CH_2CH{=}CH_2$), 39.4 (CH_2-6), 35.7 (CH_2-3), 27.7 ($COOCH_2CH(CH_3)_2$), 27.5 (CH_2-5), 22.4 (CH_2-4), 19.1 ($COOCH_2CH(CH_3)_2$) ppm. Anal. calcd for $C_{14}H_{22}O_3$: C 70.56; H 9.30. Found: C 70.67; H 9.35.

4.5.4. 2-Benzyl-2-carboethoxy-cyclohexanone (3h). From alkylation of (**3b**) with benzyl bromide (0.83 mL), this compound was obtained in 80% yield, after 12 h, as a yellow oil; IR (film): ν –C=C–H 3085, 3062 and 3029, ν C–H 2942 and 2867, ν C=O 1740 and 1714, ν C–O 1188 cm^{-1}; ^1H NMR (200 MHz): 1.16 (t, 3H, J=7.1 Hz, $COOCH_2CH_3$), 1.65–1.71 (m, 4H $O{=}CCH_2CH_2CH_2CH_2$), 1.80–2.00 (m, 3H, $O{=}CCH_2CH_2CHCHH$-*syn* to benzyl group), 2.37–2.47 (m, 3H, $O{=}CCH_2CH_2CH_2CHH$-*anti* to benzyl group), 2.86 (d, 2H, J=13.7 Hz, PhC*H*H), 3.30 (d, 2H, J=13.7 Hz, PhCH*H*), 4.08 (q, 2H, J=7.1 Hz, $COOCH_2CH_3$), 7.08–7.12 (m, 2H, *meta*Ar-*H*), 7.18–7.26 (m, 3H, *ortho*Ar-*H* and *para*Ar-*H*) ppm; ^{13}C NMR (50 MHz): 207.3 ($C{=}O$), 171.1 ($COOCH_2CH_3$), 136.7 (*ipso*Ar), 130.4 (*ortho*Ar), 128.0 (*meta*Ar), 126.7 (*para*Ar), 62.2 (C-2), 61.3 ($COOCH_2CH_3$), 41.4 ($-CH_2Ph$), 40.5 (CH_2-6), 36.0 (CH_2-3), 27.7 (CH_2-5), 22.6 (CH_2-4), 14.0 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{16}H_{20}O_3$: C 73.82; H 7.74. Found: C 73.77; H 7.81.

4.5.5. 2-Propyl-2-carboethoxycyclohexanone (3g). From alkylation of (**3b**) with *n*-propyl bromide (0.65 mL), this compound was obtained in 24% yield, after 120 h, as a yellow oil; IR (film): ν C–H 2961, 2939 and 2372, ν C=O 1732 and 1715, ν C–O 1204 cm^{-1}; ^1H NMR (200 MHz): 0.90 (m, 5H, $CH_2CH_2CH_3$), 1.22–1.29 (m, 5H, $COOCH_2CH_3$

and $CH_2CH_2CH_3$), 1.39–1.68 (m, 6H, O=CCH$_2$CH_2-CH_2CH_2), 2.26–2.33 (m, 2H, O=CCH_2CH$_2$CH$_2$CH$_2$), 3.99–4.21 (m, 2H, COOCH_2CH$_3$) ppm; ^{13}C NMR (50 MHz): 205.3 (C=O), 173.7 (COOCH$_2$CH$_3$), 61.2 (C-2), 60.3 (COOCH_2CH$_3$), 41.3 (CH$_2$-6), 34.3 (CH$_2$-3), 27.8 (CH$_2$-5), 24.7 (CH_2CH$_2$CH$_3$), 22.7 (CH$_2$-4), 17.7 (CH$_2$$CH_2CH_3$), 14.4 (COOCH$_2$$CH_3$ and CH$_2$CH$_2$$CH_3$) ppm. Anal. calcd for $C_{12}H_{20}O_3$: C 67.89; H 9.50. Found: C 67.93; H 9.43.

4.6. General procedure for reduction of 2-alkyl-2-carboalkoxy-cyclohexanone derivatives (3d-g) with sodium borohydride, in the presence or in the absence of metallic halides

A solution of β-ketoester derivative (**3d**-**g**) (1 mmol) in solvent (methanol, isopropanol or THF) (6 mL), in the presence or absence of the anhydrous metallic halide (2 mmol), was stirred at room temperature for 30 min. The reaction mixture was cooled at 0 °C (or −78 °C), and 0.045 g (1.2 mmol) of sodium borohydride was slowly added. A clear solution was obtained, which was stirred at 0 °C (or −78 °C) for 30 min. The solvent was concentrated at reduced pressure (80 mm Hg). The white doughy residue was diluted with methylene chloride (30 mL). The resulting solution was washed with saturated aqueous ammonium chloride solution (30 mL). Usual workup of the organic layer afforded the mixture of diastereomeric alcohols as described in Tables 1–3.

4.7. Reduction of the 2-allyl-2-carboethoxy-cyclohexanone (3e) with zinc borohydride

To a solution of β-ketoester derivative (**3e**) (1 mmol) in anhydrous THF (6 mL), cooled at 0 °C under nitrogen atmosphere, was slowly added 2.3 mL (1.2 mmol) of 0.12 M solution[42] of zinc borohydride in anhydrous THF. The reaction mixture was stirred for 30 min at 0 °C, and afterwards the solvent was concentrated at reduced pressure (80 mm Hg). for 15 min at 0 °C, 5 mL of 1 M solution of H_2O_2 and 7 mL of 0.2 N aq. solution of NaOH were added). The white doughy residue was diluted with methylene chloride (30 mL) and the resulting solution was washed with saturated aqueous ammonium chloride solution (30 mL). Usual workup of the organic layer afforded the diastereomeric mixture of cyclohexanols (**6e**) and (**7e**) as described in Table 3.

4.8. Reduction of the 2-allyl-2-carboethoxy-cyclohexanone (3e) with lithium-tri-*sec*-butyl-borohydride (L-Selectride)

To a solution of β-ketoester derivative (**3e**) (1 mmol) in anhydrous THF (6 mL), cooled at −78 °C under nitrogen atmosphere, was slowly added 1.2 mL (1.2 mmol) of 1 M solution of lithium-tri-*sec*-butyl-borohydride in anhydrous THF. The reaction mixture was stirred for 30 min at −78 °C, then for 15 min at 0 °C, and afterwards 5 mL of 1 M solution of H_2O_2 and 7 mL of 0.2 N aq. solution of NaOH were added. After 15 min, the system was diluted with ethyl ether (10 mL) and the organic layer was separated, washed with a saturated aqueous solution of sodium bissulfite (5 mL) and submitted to the usual workup affording the mixture of diastereomeric alcohols (**6e**) and (**7e**) as described Table 3.

4.9. General procedure for reduction of 2-allyl-2-carboethoxy-cyclohexanone (3e) with tetrabutylammonium borohydride

To a solution of β-ketoester derivative (**3e**) (1 mmol) in solvent (methanol or anhydrous THF) (6 mL), cooled at 0°, was slowly added 0.325 g (1.2 mmol) of tetrabutylammonium borohydride. The mixture was stirred at 0 °C (or −78 °C) for 30 min, when the solvent was concentrated at reduced pressure (80 mm Hg). The white doughy residue was diluted with methylene chloride (30 mL). The resulting solution was washed with 1 N aq. HCl solution (30 mL). Usual workup of the organic layer afforded the mixture of diastereomeric alcohols as described in Table 3.

4.9.1. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carbomethoxy-cyclohexanols (6d) and (7d). Prepared from reduction of (**3d**); IR (film): ν O–H 3457, ν C=C–H 3077, ν C–H 2940 and 2863, ν C=O 1727, ν C–O 1223 cm^{-1}; ^{1}H NMR (200 MHz): 1.15–1.95 (m, 8H, CH_2 in cyclohexane ring), 2.40 (dd, 1H, *J*=7.1, 14.2 Hz, C*H*HCH=CH$_2$), 2.55 (dd, 1H, *J*=7.1, 14.2 Hz, C*H*HCH=CH$_2$), 3.45 (dd, 0.7H, *J*=3.5, 9.8 Hz, C*H*(OH), *cis* diastereomer), 3.69 (s, 1H, COOCH_3), 3.71 (s, 2H, COOCH_3), 4.93 (dd, 0.3H, *J*=3.5, 8.4 Hz, C*H*(OH), *trans* diastereomer), 5.00–5.15 (m, 2H, CH$_2$CH=CH_2), 5.65–5.90 (m. 1H, CH$_2$C*H*=CH$_2$) ppm; ^{13}C NMR (50 MHz): 177.2 and 177.3 (*C*OOCH$_3$), 134.1 (CH$_2$*C*H=CH$_2$, *trans* diastereomer), 133.3 (CH$_2$*C*H=CH$_2$, *cis* diastereomer), 118.4 (CH$_2$CH=*C*H$_2$, *cis* diastereomer), 117.7 (CH$_2$-CH=*C*H$_2$, *trans* diastereomer), 74.3 (*C*HOH, *cis* diastereomer), 71.5 (*C*HOH, *trans* diastereomer), 51.7 (COO*C*H$_3$), 52.2 and 51.3 (C-2), 41.2 and 35.5 (*C*H$_2$-CH=CH$_2$), 32.3 and 31.5 (CH$_2$-6), 29.1 and 28.9 (CH$_2$-3), 23.9 and 22.6 (CH$_2$-5), 22.6 and 20.1 (CH$_2$-4) ppm. Anal. calcd for $C_{11}H_{18}O_3$: C 66.64; H 9.15. Found: C 66.51; H 9.21.

4.9.2. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carboethoxy-cyclohexanols (6e) and (7e). Prepared from reduction of (**3e**); IR (film): ν O–H 3490, ν C=C–H 3077, ν C–H 2979, 2937 and 2863, ν C=O 1723, ν C–O 1221 and 1201 cm^{-1}; ^{1}H NMR (200 MHz): 1.27 (t, 3H, *J*=7.1 Hz, COOCH$_2$CH_3), 1.38–1.77 (m, 8H, CH_2 in cyclohexane ring), 2.35 (dd, 1H, *J*=7.5, 14.2 Hz, C*H*HCH=CH$_2$), 2.60 (dd, 1H, *J*=7.5, 14.2 Hz, C*H*HCH=CH$_2$), 3.90–4.02 (m, 1H, C*H*(OH)), 4.16 (q, 2H, *J*=7.1 Hz, COOCH_2CH$_3$), 5.02–5.10 (m, 2H, CH$_2$-CH=CH_2), 5.70–5.79 (m. 1H, CH$_2$C*H*=CH$_2$) ppm; ^{13}C NMR (50 MHz): 176.7 and 177.3 (*C*OOCH$_2$CH$_3$), 134.1 (CH$_2$*C*H=CH$_2$, *trans* diastereomer), 133.3 (CH$_2$*C*H=CH$_2$, *cis* diastereomer), 118.2 (CH$_2$CH=*C*H$_2$, *cis* diastereomer), 117.5 (CH$_2$CH=*C*H$_2$, *trans* diastereomer), 74.3 (*C*HOH, *cis* diastereomer), 71.2 (*C*HOH, *trans* diastereomer), 60.5 (COO*C*H$_2$CH$_3$), 51.7 (C-2), 41.2 (*C*H$_2$CH=CH$_2$, *cis* diastereomer), 35.7 (*C*H$_2$CH=CH$_2$, *trans* diastereomer), 32.2 (CH$_2$-6, *cis* diastereomer), 31.5 (CH$_2$-3, *cis* diastereomer), 29.6 (CH$_2$-6, *trans* diastereomer), 29.4 (CH$_2$-3, *trans* diastereomer), 23.9 (CH$_2$-5, *cis* diastereomer), 22.5 (CH$_2$-4, *cis* diastereomer), 22.3 (CH$_2$-5, *trans*

diastereomer), 21.4 (CH_2-4, *trans* diastereomer), 14.2 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{12}H_{20}O_3$: C 67.89; H 9.50. Found: C 67.74; H 9.60.

4.9.3. Diastereomeric mixture of *trans*- and *cis*-(±)-2-allyl-2-carboisobutoxy-cyclohexanols (6f) and (7f). Prepared from reduction of (**3f**); IR (film): ν O–H 3497, ν C=C–H 3077, ν C–H 2938 and 2872, ν C=O 1723, ν C–O 1222 and 1200 cm^{-1}; ^1H NMR (200 MHz): 0.95 (d, 6H, J=6.6 Hz, $COOCH_2CH(CH_3)_2$), 1.25–1.96 (m, 9H, CH_2 in cyclohexane ring and $COOCH_2CH(CH_3)_2$), 2.35 (dd, 1H, J=7.1, 14.2 Hz, $CHHCH{=}CH_2$), 2.60 (dd, 1H, J=7.1, 14.2 Hz, $CHHCH{=}CH_2$), 2.90 (s, D_2O exchangeable, 1H, CH(OH)), 3.44 (dt, 0.7H, J=9.9, 3.3 Hz, CH(OH), *cis* diastereomer), 3.57 (d, 0.3H, J=10.1 Hz, *trans* diastereomer), 3.82–3.97 (m, 2H, $COOCH_2CH(CH_3)$), 5.05 (d, 2H, J=12.8 Hz, $CH_2CH{=}CH_2$), 5.79 (qt, 1H, J=9.5 Hz, $CH_2CH{=}CH_2$) ppm; ^{13}C NMR (50 MHz): 176.9 and 176.7 ($COOCH_2CH(CH_3)_2$), 134.1 and 133.3 ($CH_2CH{=}CH_2$), 118.3 and 117.6 ($CH_2CH{=}CH_2$), 77.8 and 74.3 (CHOH), 70.9 ($COOCH_2CH(CH_3)_2$), 52.1 and 51.1 (C-2), 42.0 ($CH_2CH{=}CH_2$), 33.0 and 32.0 (CH_2-6), 29.7 (CH_2-3), 27.7 ($COOCH_2CH(CH_3)_2$), 24.4 and 23.0 (CH_2-5), 23.0 and 22.0 (CH_2-4), 19.2 and 19.1 ($COOCH_2CH(CH_3)_2$) ppm. Anal. calcd for $C_{14}H_{24}O_3$: C 69.96; H 10.07. Found: C 70.09; H 10.12.

4.9.4. Diastereomeric mixture of *trans*- and *cis*-(±)-2-propyl-2-carboethoxy-cyclohexanols (6g) and (7g). Prepared from reduction of (**3g**); IR (film): ν O–H 3477, ν C=C–H 3077, ν C–H 2955 and 2865, ν C=O 1724, ν C–O 1218 cm^{-1}; ^1H NMR (200 MHz): 0.86 (m, 3H, $CH_2CH_2CH_3$), 1.23–2.10 (m, 15H, CH_2 in cyclohexane ring, $CH_2CH_2CH_3$ and $COOCH_2CH_3$), 3.40 (m, 1H, CHOH, *trans* diastereomer), 3.90 (m, 1H, CHOH, *cis* diastereomer), 4.16 (q, 2H, J=7.0 Hz, $COOCH_2CH_3$) ppm; ^{13}C NMR (50 MHz): 175.8 ($COOCH_2CH_3$), 74.9 (CHOH, *cis* diastereomer), 72.0 (CHOH, *trans* diastereomer), 60.6 and 60.5 ($COOCH_2CH_3$), 50.6 (C-2), 32.8 ($CH_2CH_2CH_3$), 32.5 (CH_2-6, *cis* diastereomer), 31.7 (CH_2-6, *trans* diastereomer), 29.8 (CH_2-3, *cis* diastereomer), 29.5 (CH_2-3, *trans* diastereomer), 24.0 (CH_2-5, *cis* diastereomer), 22.8 (CH_2-5, *trans* diastereomer), 21.4 (CH_2-4), 17.6 and 17.5 ($CH_2CH_2CH_3$), 14.9 and 14.8 ($COOCH_2CH_3$), 14.4 ($CH_2CH_2CH_3$) ppm. Anal. calcd for $C_{12}H_{12}O_3$: C 67.26; H 10.35. Found: C 67.33; H 10.29.

4.9.5. Diastereomeric mixture of *trans*- and *cis*-(±)-2-benzyl-2-carboethoxy-cyclohexanols (6h) and (7h). Prepared from reduction of (**3h**); IR (film): ν O–H 3479, ν C=C–H 3063 and 3028, ν C–H 2979 and 2918, ν C=O 1747, ν C–O 1180 cm^{-1}; ^1H NMR (200 MHz): 1.07 (t, 0.9H, J=7.1 Hz, $COOCH_2CH_3$), 1.21 (t, 2.1H, J=7.1 Hz, $COOCH_2CH_3$), 1.27–2.20 (m, 5H $O{=}CCHHCH_2CH_2CH_2$), 2.37–2.47 (m, 3H, $O{=}CCHHCH_2CHCH_2$), 2.85 (d, 0.5H, J=14.4 Hz, PhCHH), 3.06 (s, 1.5H, PhCHH), 3.96–4.19 (m, 2H, $COOCH_2CH_3$), 7.08–7.12 (m, 2H, *meta*Ar-H), 7.10–7.30 (m, 5H, C_6H_5) ppm; ^{13}C NMR (50 MHz): 177.3 ($COOCH_2CH_3$), 130.8 (*ipso*Ar), 130.1 (*ortho*Ar), 128.1 (*meta*Ar), 126.7 and 126.5 (*para*Ar), 73.7 and 71.4 (CHOH), 60.7 and 60.6 ($COOCH_2CH_3$), 53.0 (C-2), 42.4 ($-CH_2Ph$), 32.9 and 31.8 (CH_2-6), 29.8 and 28.7 (CH_2-3), 24.5 and 22.9 (CH_2-5), 22.4 and 21.8 (CH_2-4), 14.1 and 14.0 ($COOCH_2CH_3$) ppm. Anal. calcd for $C_{16}H_{22}O_3$: C 73.25; H 8.45. Found: C 73.18; H 8.37.

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Synthesis and reactions of *meso*-(*p*-nitrophenyl)porphyrins

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Abstract—An improved methodology is reported for the regioselective nitration of the phenyl groups of *meso*-tetraphenylporphyrin **1**, using $NaNO_2$ and TFA. The degree of nitration is easily controlled by the equivalent amount of $NaNO_2$ used and the reaction time. The nitroporphyrins are reduced to the corresponding aminoporphyrins under standard $SnCl_2$/HCl conditions. Reaction of tri-aminoporphyrin **9** with 1-formyl-*o*-carborane followed by reduction using $NaBH_4$ gave a novel tri-carboranylporphyrin bearing amine linkages between the porphyrin and the carborane groups.

1. Introduction

Porphyrin-type compounds have been actively investigated as sensitizing drugs for application in cancer diagnosis and treatment using photodynamic therapy (PDT)[1] and also using boron neutron capture therapy (BNCT).[2] PDT and BNCT are binary therapies that involve activation of a tumor-localized sensitizer with light (in PDT) or low-energy neutrons (in BNCT). The main cytotoxic species generated in PDT is believed to be singlet oxygen, which causes effective photo-oxidative damage to tumor tissue.[3] On the other hand in BNCT, the high linear energy transfer particles $^4He^{2+}$ and $^7Li^{3+}$ are produced, which cause cell damage via ionization processes.[2,4] In the last decade, two porphyrin derivatives were approved by the Food and Drug Administration for the PDT treatment of various conditions and many other promising derivatives are currently being evaluated in preclinical and clinical studies.[5] From these investigations it is known that certain porphyrin derivatives have the ability to selectively localize in tumor tissues, possibly as a result of their affinity for carrier biomolecules and/or biological membranes.[6] In particular, positively-charged porphyrins, such as *meso*-tetra(methylpyridyl)- and tetra-(trimethylaminophenyl)-porphyrins, have been shown to strongly interact with the negatively charged groups of potential biological targets, such as certain proteins,[5] DNA[7] and RNA,[8] and to be effective photosensitizers for PDT.[5,9] It has been shown that the number and distribution of positive charge about the porphyrin macrocycle plays a very important role in photodynamic efficacy.[5] Amphiphilic porphyrin derivatives bearing one, two or three water-solubilizing groups, such as $-NMe_3^+$, have demonstrated increased photodynamic efficacy compared with more hydrophilic, symmetric macrocyles.[5,10,11] On the other hand, nitro-substituted aromatic compounds have been found to be effective electron-affinity radiosensitizers.[12] Therefore, nitro- and amino-substituted amphiphilic porphyrins are useful synthetic precursors to biologically active molecules. Furthermore, nitro and amino groups can be easily functionalized,[11,13,14] and conjugated with bioactive molecules, such as monoclonal antibodies,[15] oligomeric carboranyl phosphate diesters,[16] polymer backbones,[17] and cyclodextrins.[18]

Current synthetic routes to mono-, di- and tri-nitro functionalized *meso*-tetraphenylporphyrins involve total synthesis via a crossed Rothemund approach,[17] or by electrophilic nitration of the *p*-phenyl groups of *meso*-tetraphenylporphyrin (TPP, **1**).[19,20] In the first method co-condensation of pyrrole, benzaldehyde and nitrobenzaldehyde, results in low to moderate yields of the targeted porphyrins, which can be tedious to purify from the resulting reaction mixtures. Whereas this is the methodology of choice for the synthesis of *o*- and *m*-nitrophenylporphyrins, higher yields of *p*-nitrophenylporphyrins can be obtained by direct nitration of the *p*-positions of the *meso*-phenyl groups. Using fuming nitric acid Kruper et al.[19] obtained mono-nitroporphyrin **2** in moderate yields (46–56%) by direct nitration of TPP **1** in chloroform solution. Under these conditions further nitration of **2** gave up to 28% yield of the di-nitroporphyrins and about 20% of the tri-nitroporphyrin. Macrocyclic degradation products were also observed. Higher yields were reported by Meng et al.[20] using a combination of nitric acid and acetic or sulfuric acids (namely up to 74% yield for mono-nitroporphyrin **2**), and

Keywords: Aminoporphyrins; Carboranylporphyrins; Nitration; Porphyrins; Reductive amination.
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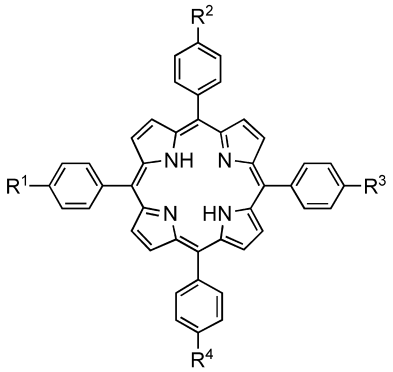
reaction times ranging from 1 h to 7 days. These somewhat milder reaction conditions produced better yields of the targeted nitroporphyrins; we rationalized that even milder conditions should lead to higher yields and regioselectivity of mono-, di- and tri-nitroporphyrins, with minimum macrocyclic degradation. These resulting nitroporphyrins can then be easily reduced to the corresponding aminoporphyrins and/or further derivatized.[19–21]



1: R^1, R^2, R^3, R^4 = H
2: R^1 = NO_2: R^2, R^3, R^4 = H
3: R^1, R^3 = NO_2; R^2, R^4 = H
4: R^1, R^2 = NO_2; R^3, R^4 = H
5: R^1, R^2, R^3 = NO_2; R^4 = H
6: R^1 = NH_2: R^2, R^3, R^4 = H
7: R^1, R^3 = NH_2; R^2, R^4 = H
8: R^1, R^2 = NH_2; R^3, R^4 = H
9: R^1, R^2, R^3 = NH_2; R^4 = H

2. Results and discussion

We have developed an alternative route to nitro-substituted porphyrins via regioselective *para*-phenyl nitration of TPP **1**, using sodium nitrite in TFA.[22,23] High yields of nitrated benzene and substituted benzenes have been reported under these conditions, and both NO_2^+ and N_2O_3 were proposed as the electrophiles in these reactions.[23] By varying the amount of sodium nitrite and the reaction time, selective nitration of one or more of the phenyl groups of TPP can be achieved, leading to the ready preparation of porphyrins **2**, **3**, **4** and **5** in high yields. Reduction of the nitro groups with excess tin(II) chloride gives the corresponding aminoporphyrins (**6**, **7**, **8** and **9**).

When a concentrated solution of TPP **1** in TFA was treated with 1.8 equiv. of $NaNO_2$ for 3 min, the mono-nitroporphyrin **2** was obtained as the major product in 80–90% yield. Increasing the amount of $NaNO_2$ to 8.1 equiv. resulted in the formation of a mixture of the two isomeric di-nitrophenylporphyrins **3** and **4** as the major products, after only 1.5 min. Thin layer chromatography (TLC) of the reaction mixture showed two spots of similar rf in the ratio of about 1:2, and trace amounts of a more polar fraction, the trinitroporphyrin **5**.

Based on statistics, the fastest running band was identified as the *opp*-isomer **3**, and the main second band as the *adj*-isomer **4**. After mono-nitration, there are two phenyl rings that can be nitrated to give the *adj*-isomer whereas there is only one that can be nitrated to produce the *opp*-isomer. To obtain the tri-nitrophenylporphyrin **5** as the major product a large excess of sodium nitrite was used and the reaction time was increased to 1 h. Longer reaction times resulted in the formation of the tetra-nitro derivative, which was identified by comparison with a sample of *meso*-tetra(4-nitrophenyl)-porphyrin obtained from the condensation of 4-nitrobenzaldehyde with pyrrole.

Due to the poor solubility of the nitro-substituted porphyrins, these were converted into the corresponding aminoporphyrins by reduction with tin(II) chloride and HCl in yields of about 50%, as previously reported in the literature.[19–21] The resulting aminoporphyrins **6**, **7**, **8** and **9** were easily separated by flash column chromatography on silica gel, using a gradient elution (dichloromethane/petroleum ether). The two di-aminoporphyrin regioisomers **7** and **8** were isolated in a 1:2 ratio and showed similar electronic and NMR spectra. However, there were characteristic differences in the shifts of the β-hydrogens in their ^{1}H NMR spectra and the resonances observed in the ^{13}C NMR, which allowed us to distinguish between the two regioisomers. The β-hydrogens of **8** appear as two singlets at 8.92 and 8.81 ppm, whereas those of **7** were two doublets with a coupling constant J=4.5 Hz, characteristic of β-H/β-H proton coupling of highly symmetrical di-substituted porphyrins. The larger number of signals in the ^{13}C NMR spectrum of the *adj*-isomer **8** further confirmed its lower symmetry compared with the *opp*-isomer **7**. The structures of mono-aminoporphyrin **6** and di-aminoporphyrins **7** and **8** were further confirmed by X-ray crystallography (Figs. 1–3). Figure 1 shows one of the three crystallographically independent, centrosymmetric porphyrin molecules for **6**. For this molecule, the porphyrin N atoms are symmetry-constrained to be coplanar, and the 24-atom porphyrin ring system is nearly so, exhibiting mean and maximum deviations of 0.042 and 0.081(3) Å, respectively. This porphyrin plane forms a dihedral angle of 82.3(1)° with the unsubstituted phenyl ring, and a smaller angle, 66.37(4)° with the phenyl ring carrying the NH_2 group. Figure 2 shows one of the three crystallographically independent, centrosymmetric porphyrin molecules for **7**. For this molecule, the 24-atom porphyrin ring system is slightly less coplanar than in **6**, exhibiting mean and maximum deviations of 0.081 and 0.168(2) Å, respectively. The phenyl rings are twisted out of the porphyrin plane by about 60°, forming dihedral angles of 58.22(6)° (phenyl) and 63.23(9)° (aminophenyl) with it. The structure of porphyrin **8** is shown in Figure 3. Its 24-atom porphyrin ring system is also nearly planar, exhibiting a mean deviation of 0.055 Å and a maximum of 0.131(7) Å, as a result of the internal hydrogen bonds, with N···N distances of 2.905(7)–2.954(7) Å. The phenyl rings are twisted out of the porphyrin plane by about 60° (torsion angle magnitudes 58.2(8)–77.0(8)°).

Aminoporphyrins **6**, **7**, **8** and **9** are readily converted into amphiphilic water-soluble molecules, for example by alkylation or by condensation with carboxylic acid-containing molecules.[13–18,24] We recently reported the condensation of porphyrin **6** with a dimeric carboranyl phosphate diester via an amide linkage, to give a negatively-charged conjugate, which is currently being evaluated in our

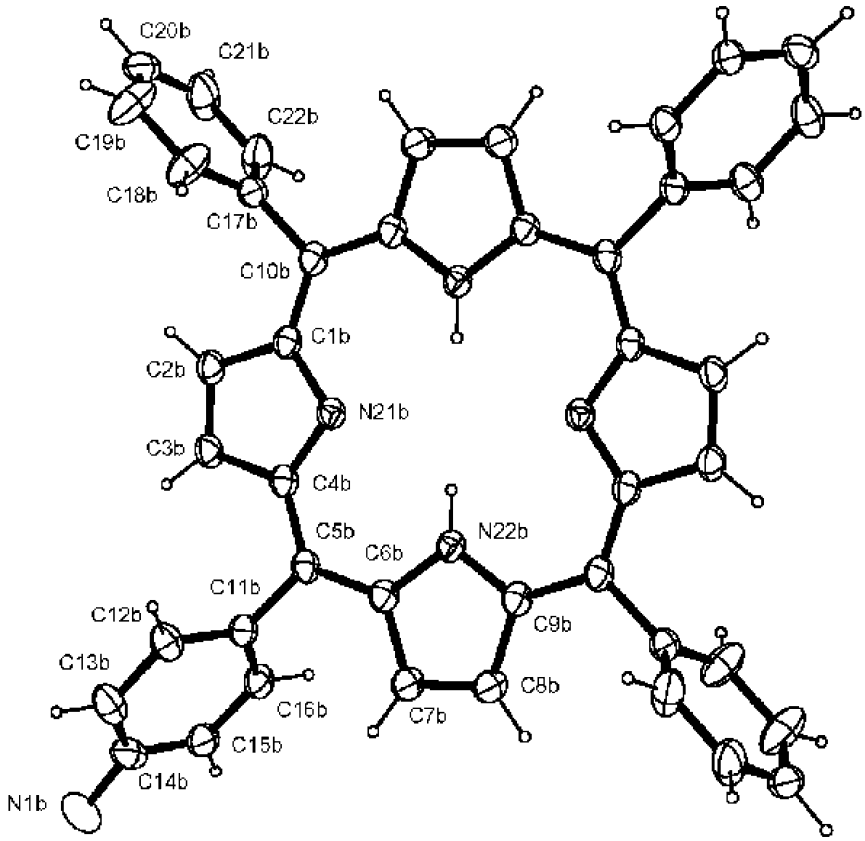


Figure 1. ORTEP diagram, showing the molecular structure of **6**. The molecule packs in the crystal such that there is 50% population of the amino group on the two diametrically opposed phenyl rings; only one form is shown.

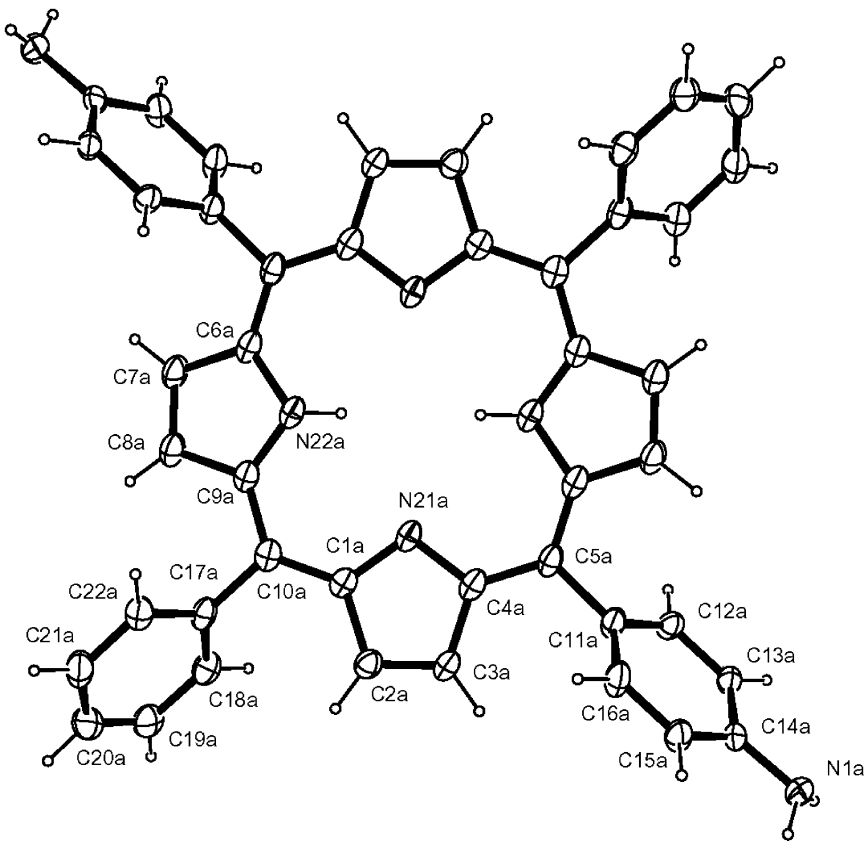


Figure 2. ORTEP diagram showing the molecular structure of **7**.

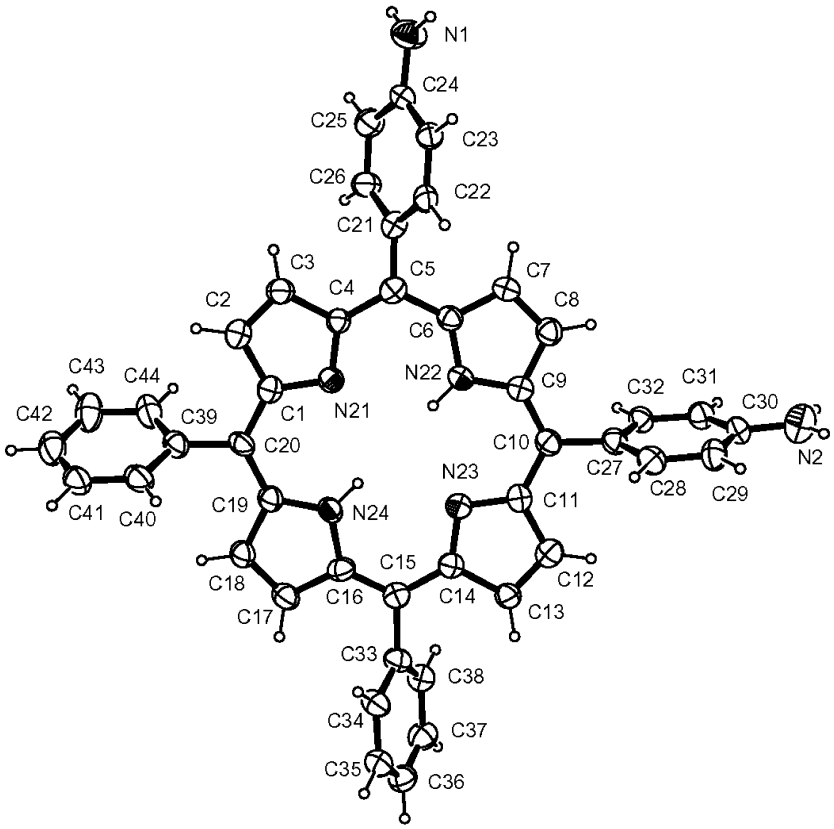


Figure 3. ORTEP diagram showing the molecular structure of **8**.

laboratories as a boron delivery agent for BNCT.[16] Alkylation of aminoporphyrins **7** and **8** with methyl iodide in the presence of a bulky base produced two positively charged porphyrins, DADP-o and DADP-a, with potential application in PDT.[11] Reductive amination[25] of 1-formyl-*o*-carborane using tri-aminoporphyrin **9**, leads to a tri-carboranylporphyrin with potential application in BNCT (Scheme 1).

Reaction of porphyrin **9** with 1-formyl-*o*-carborane **10**[26] produced the imineporphyrin **11**, which upon reduction with sodium borohydride afforded porphyrin **12** in 47% overall yield. In order to increase the solubility of this porphyrin in water, the *closo*-carboranyl cages were degraded to the corresponding *nido*-cages using a mixture of pyridine and piperidine (3:1) as reported previously,[27,28] to afford the negatively-charged water-soluble porphyrin **13**. The biological evaluation of porphyrin **13** is currently underway in our laboratories.

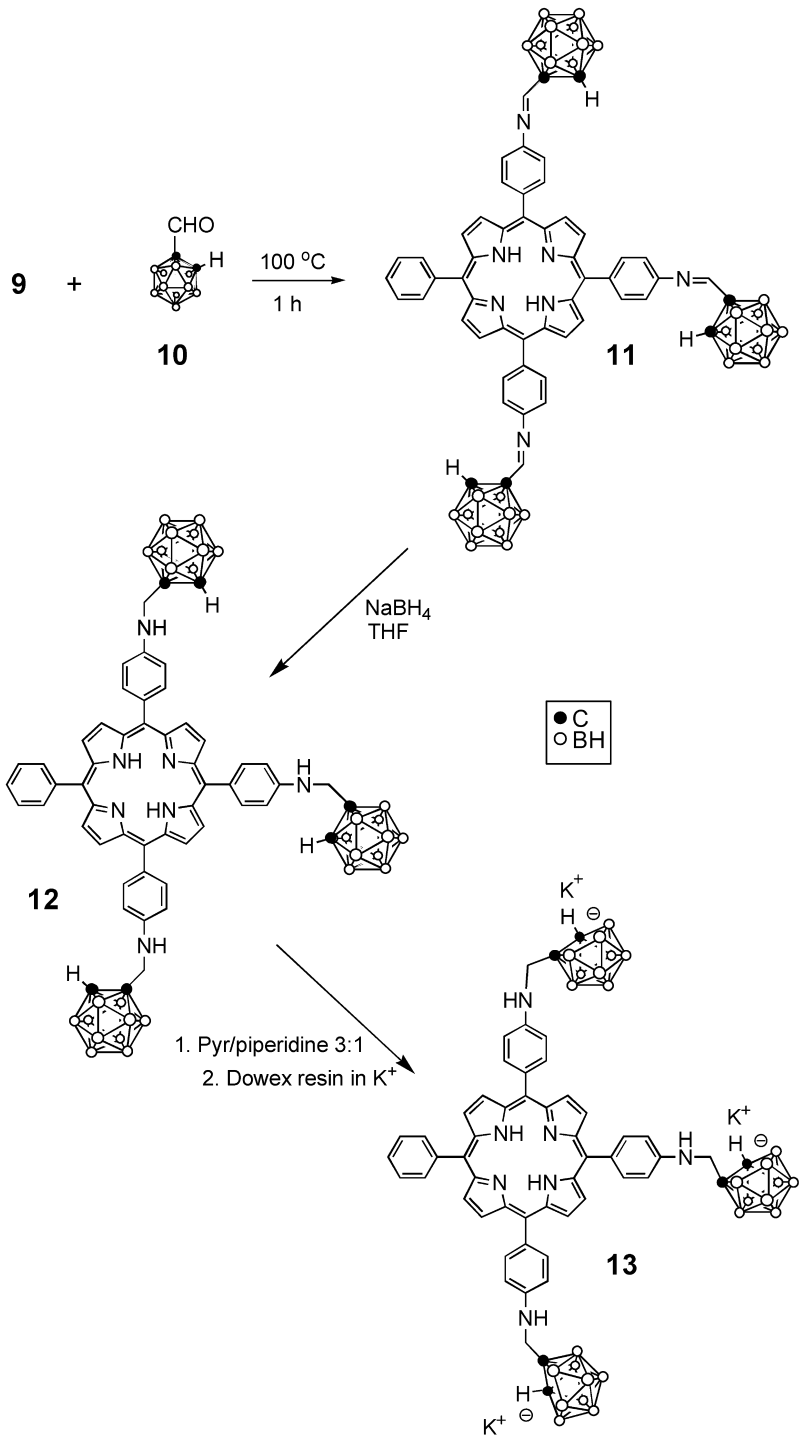
3. Conclusions

We have developed a mild method for electrophilic nitration of the phenyl groups of TPP, by using sodium nitrite in the presence of TFA. This approach is highly regiospecific allowing only nitration at the *para* position of the phenyl groups in TPP and provides selective control in the number of phenyl groups nitrated by varying the amount of sodium nitrite and the duration of the reaction. The nitroporphyrins are easily reduced to their corresponding aminoporphyrins, which are valuable intermediates in the synthesis of water-soluble, amphiphilic porphyrins for application as sensitizers in the PDT and/or the BNCT of cancers. As an example of their versatility, a tri-aminoporphyrin was condensed with 1-formyl-*o*-carborane to produce a tri-carboranyl-imineporphyrin, which was reduced to the corresponding amine and converted into a water-soluble tri-carboranylporphyrin, bearing amine linkages between the porphyrin and the carborane groups.

4. Experimental

4.1. General

Silica gel 60 (70–230 and 230–400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III) were used for column chromatography. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (pre-coated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry. ^{1}H NMR spectra were obtained in deuterochloroform or acetone-d_6 solution, using a Brucker 250 or 400 MHz spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.26 ppm) and/or TMS (0 ppm). Unless otherwise stated, electronic absorption spectra were measured in dichloromethane solution using a Hewlett–Packard 8450A spectrophotometer. Mass spectra were obtained at the Mass Spectrometry Facility at Louisiana State University, or at the University of California, San Francisco. Sodium nitrite, sodium borohydride, tin(II) chloride and trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich and used without further purification. Anhydrous sodium sulfate,



Scheme 1. Syntheses of tri-carboranylporphyrins **11**–**13**.

sodium bicarbonate and all solvents were purchased from Fisher Scientific. Dried solvents were obtained according to literature procedures.[29]

4.1.1. 5,10,15-Tris(4-nitrophenyl)-20-phenylporphyrin (5). To a solution of **1** (160 mg, 0.261 mmol) in TFA (10 mL) was added sodium nitrite (660 mg, 9.57 mmol). After 55 min stirring at room temperature, the reaction was quenched with water (100 mL) and the mixture extracted with dichloromethane (6×25 mL). The organic layers were washed once with saturated aqueous $NaHCO_3$ and once with water before being dried over anhydrous Na_2SO_4. Recrystalization from dichloromethane gave 120 mg (62%) of porphyrin **5**. MS (MALDI) *m*/*z* 749.8 (M^+); ^1H NMR ($CDCl_3$) δ ppm: −2.80 (br, 2H), 7.80 (m, 3H), 8.20 (m, 2H), 8.40 (d, *J*=7.50 Hz, 6H), 8.65 (d, *J*=7.50 Hz, 6H), 8.80 (m, 6H), 8.93 (d, *J*=5.0 Hz, 2H). UV–Vis ($CHCl_3$) λ_{max}: 420 nm (ε 368,500), 514 (28,400), 549 (14,100), 589 (9800) and 645 (5600). Anal. Calcd for $C_{44}H_{27}N_7O_6 \cdot 1.5H_2O$: C, 68.03; H, 3.89; N, 12.66. Found: C, 67.82; H, 3.71; N, 12.75.

4.1.2. 5-(4-Aminophenyl)-10,15,20-triphenylporphyrin

(6). To a solution of **1** (100 mg, 0.163 mmol) in TFA (10 mL) was added sodium nitrite (20 mg, 0.29 mmol). After 3 min stirring at room temperature, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (6×25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and water as described above and then the solvent was removed under vacuum. The residue was purified on a plug of silica gel, eluting with dichloromethane. After evaporation of the solvent, the residue was dissolved in concentrated hydrochloric acid (10 mL) and, while stirring, tin(II) chloride (220 mg, 0.975 mmol) was carefully added. The final mixture was heated to 65 °C for 1 h under argon before being poured into cold water (100 mL). The aqueous solution was neutralized with ammonium hydroxide until pH 8. The aqueous solution was extracted with dichloromethane until colorless. The organic layer was then concentrated under vacuum and the residue was purified on a plug of alumina using dichloromethane for elution. The final residue was recrystallized from methanol, yielding 55.3 mg (54%) of porphyrin **6**. The spectroscopic data obtained for the title compound are in agreement with those in the literature;[19] MS (MALDI) *m/z* 629.8 (M^+); ^{1}H NMR ($CDCl_3$) δ ppm: −2.75 (br, 2H), 4.02 (s, 2H), 7.07 (d, *J*=9.0 Hz, 2H), 7.75 (m, 9H), 7.98 (d, *J*=9.0 Hz, 2H), 8.20 (m, 6H), 8.84 (s, 6H), 8.96 (s, 2H). UV–Vis ($CHCl_3$) λ_{max}: 417.5 nm (ε 315,800), 514 (28,900), 551 (20,600), 589 (15,600) and 645.5 (12,800). Anal. Calcd for $C_{44}H_{31}N_5{\cdot}0.5H_20$: C, 82.79; H, 4.98; N, 10.98. Found: C, 82.55; H, 5.11; N, 10.95.

4.1.3. 5,15-Bis(4-aminophenyl)-10,20-diphenylporphyrin (7) and 5,10-bis(4-aminophenyl)-15,20-diphenylporphyrin (8). To a solution of TPP (200 mg, 0.326 mmol) in TFA (10 mL) was added sodium nitrite (183 mg, 2.65 mmol). After 90 seconds stirring at room temperature, the reaction was poured into water (100 mL) and extracted with dichloromethane (6×25 mL). The residue obtained was purified as described above and then reduced using 0.8 g (3.55 mmol) of tin(II) chloride and 50 mL of HCl. The two regioisomers were eluted with dichloromethane (the 5,10-isomer eluted first) and were recrystallized from methanol, yielding 52 mg (43%) of the 5,10-isomer and 13 mg (21%) of the 5,15-isomer. The spectroscopic data obtained for the title compounds are in agreement with those in the literature.[20] For the *opp*-isomer **7**: MS (MALDI) *m/z* 644.38 (M^+), MS (ESI) 645.77 (M^++1); ^{1}H NMR^{1}H NMR ($CDCl_3$) δ ppm: −2.74 (br, 2H), 4.04 (s, 4H), 7.06 (d, *J*=9.0 Hz, 4H), 7.74 (m, 6H), 7.99 (d, *J*=9.0 Hz, 4H), 8.21 (m, 4H), 8.81 (d, *J*=4.5 Hz, 4H), 8.92 (d, *J*=4.5 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ ppm: 113.7, 122.5, 126.8, 127.8, 134.7, 135.8, 142.5, 146.1. UV–Vis ($CHCl_3$) λ_{max}: 420 nm (ε 278,000), 517 (13,500), 555 (9570), 591 (4300) and 649 (4600). Anal. Calcd for $C_{44}H_{32}N_6{\cdot}1.5H_2O$: C, 78.66; H, 5.25; N, 12.52. Found: C, 78.25; H, 5.00; N, 12.22. For the *adj*-isomer **8**: MS (MALDI) *m/z* 644.38 (M^+); ^{1}H NMR ($CDCl_3$) δ ppm: −2.74 (br, 2H), 4.03 (s, 4H), 7.06 (d, *J*=8.0 Hz, 4H), 7.76 (m, 6H), 7.99 (d, *J*=8.0 Hz, 4H), 8.21 (m, 4H), 8.81 (s, 4H), 8.92 (s, 4H). ^{13}C NMR ($CDCl_3$) δ ppm: 113.7, 120.5, 126.8, 127.8, 132.7, 134.7, 135.9, 142.5, 146.1. UV–Vis ($CHCl_3$) λ_{max}: 420 nm (ε 181,100), 517 (14,700), 554 (11,400), 590 (6000) and 647 (5200). Anal. Calcd for $C_{44}H_{32}N_6{\cdot}0.5H_2O$: C, 80.89; H, 5.02; N, 12.87. Found: C, 80.73; H, 5.14; N, 12.76.

4.1.4. 5,10,15-Tris(4-aminophenyl)-20-phenylporphyrin (9). *meso*-Tris(4-nitrophenyl)phenylporphyrin **5** (100 mg, 0.163 mmol) was dissolved in hydrochloric acid (40 mL) and, while stirring, tin(II) chloride (540 mg, 2.39 mmol) was carefully added. The final mixture was heated to 65 °C for 1 h under argon before being poured into cold water (100 mL). The aqueous solution was neutralized with ammonium hydroxide until pH 8. The aqueous solution was extracted with dichloromethane until colorless. The organic layer was then concentrated under vacuum and the residue purified on a plug of alumina using dichloromethane for elution. The final residue obtained was recrystallized from petroleum ether, yielding 47 mg (54%) of the title compound. MS (MALDI) *m/z* 658.5 (M^+); ^{1}H NMR ($CDCl_3$) δ ppm: −2.72 (br, 2H), 4.05 (s, 6H), 7.08 (d, *J*=7.82 Hz, 6H), 7.76 (m, 3H), 7.99 (d, *J*=7.82 Hz, 6H), 8.22 (m, 2H), 8.81 (d, *J*=4.69 Hz, 2H), 8.92 (m, 6H). UV–Vis ($CHCl_3$) λ_{max}: 423 nm (ε 256,000), 518 (10,400), 558 (9500), 593 (3600) and 652 (4480). Anal. Calcd for $C_{44}H_{33}N_7{\cdot}H_2O$: C, 78.07; H, 5.70; N, 14.49. Found: C, 78.12; H, 5.20; N, 14.26.

4.1.5. 5,10,15-Tris(4-carboranyliminophenyl)-20-phenylporphyrin (11). *meso*-Tris-(4-aminophenyl)phenylporphyrin **9** (50 mg, 0.076 mmol) and 1-formyl-*o*-carborane (180 mg, 1.05 mmol) were dissolved in THF (15 mL) at room temperature under argon. The mixture was heated at 100 °C for 1 h until all the porphyrin was consumed (TLC), and then poured into water and extracted with dichloromethane. The dichloromethane extract was dried over $NaSO_4$ anhydrous and then concentrated under vacuum. The residue was purified on alumina column using dichloromethane for elution. The final residue obtained was recrystallized from hexane, yielding 40 mg (48%) of the title product. HRMS (MALDI-QTOF) for $C_{53}H_{63}N_7B_{30}$+H: calculated *m/z* 1123.8230, found 1123.8210; ^{1}H NMR ($CDCl_3$) δ ppm: −2.80 (br, 2H), 1.6–3.0 (br, 30H), 4.70 (s, 3H), 7.49 (d, *J*=9.3 Hz, 6H), 7.77(m, 3H), 8.18 (m, 5H), 8.22 (d, *J*=9.3 Hz, 6H), 8.85(m, 8H). UV–Vis ($CHCl_3$) λ_{max}: 421 (364,000), 516 (17,700), 552 (10,800), 590 (6330) and 646 (5460).

4.1.6. 5,10,15-Tris[(4-carboranylaminomethyl)phenyl]-20-phenylporphyrin (12). To a solution of porphyrin **11** (40 mg, 0.036 mmol) in THF (10 mL) was added excess sodium borohydride (22 mg, 0.582 mmol) and the final mixture was stirred at room temperature for 1 h, under argon. Water was slowly added and the final mixture extracted with dichloromethane (4×20 mL). The dichloromethane extracts was dried over $NaSO_4$ anhydrous and evaporated to dryness. The residue was recrystallized from dichloromethane and methanol to give 39 mg (98%) of the title product. HRMS (MALDI-QTOF) for $C_{53}H_{69}N_7B_{30}$+H: calculated *m/z* 1129.8700, found 1129.8687; ^{1}H NMR ($CDCl_3$) δ ppm: −2.77 (br, 2H), 1.0–3.0 (br, 30H), 3.96 (s, 3H), 4.12 (d, *J*=7.4 Hz, 6H), 4.37 (t, 3H), 6.95 (d, *J*=8 Hz, 6H), 7.74 (m, 3H), 8.01(d, *J*=8 Hz, 6H), 8.19 (m, 2H), 8.82 (m, 8H). UV–Vis ($CHCl_3$) λ_{max}: 424 (ε 334,000), 519 (16,000), 558 (13,500), 592 (6140) and 651 (7040).

4.1.7. 5,10,15-Tris[(4-*nido*-carboranylaminomethyl)phenyl]-20-phenylporphyrin (13). Porphyrin **12** (20 mg,

0.018 mmol) was dissolved in pyridine/piperidine 3:1 (3 mL) and allowed to stir at room temperature for 36 h under argon. After removing the pyridine and piperidine under vacuum the residue was dissolved in 40% aqueous acetone and passed slowly through a Dowex 50WX2–100 resin in the potassium form. The porphyrin fraction was collected, dried under vacuum, redissolved in 70% aqueous acetone and again passed through the ion-exchange resin. After removal of the solvent under vacuum the title *nido*-carboranylporphyrin **13** was obtained in quantitative yield. HRMS (MALDI-QTOF) for $C_{53}H_{69}N_7B_{27}$; calculated *m/z* 365.2787; Found 365.2806. ^{1}H NMR (acetone-d_6) δ ppm: −2.40 (br, 5H), 1.6–3.0 (br, 27H), 3.50 (m, 6H), 5.10 (br, 3H), 7.07 (m, 6H), 7.79 (m, 3H), 7.96 (m, 6H), 8.22 (m, 3H), 8.76 (m, 2H), 8.99 (m, 6H). UV–Vis (ethanol) λ_{max}: 427 (ε 165,000), 520 (10,000), 567 (13,400) and 658 (6600).

4.2. Molecular structures

The crystal structures of solvates of **6**, **7** and **8** were determined, using data collected at T=100 K to =25.7° with Mo K radiation on a Nonius KappaCCD diffractometer. Compounds **6** and **7** were crystallized as the 2/3 dichloromethane solvates, and are essentially isostructural, both having three independent porphyrin molecules, all lying on inversion centers. Thus, for monoamino compound **6**, all three molecules have the NH_2 group disordered into two half-populated sites related by inversion. In **7**, two of the three independent molecules have ordered NH_2 groups, while third has its NH_2 groups disordered onto the alternate phenyl groups approximately 60% of the time. For **6**, R=0.091 for 7049 observed data of 9510 unique data. For **7**, R=0.065 for 6570 observed data of 9971 unique data. For **8**, the disordered solvent region was modeled as $0.6CH_2Cl_2$, $0.4H_2O$. R=0.106 for 3598 observed data of 5698 unique data. The X-ray crystallographic data for **6**, **7** and **8** can be found in supplementary publications CCDC-229546, CCDC-223888 and CCDC-220719 respectively, available from the Cambridge Crystallographic Data Centre.

Acknowledgements

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Synthesis and Diels–Alder reactions of 9-(4-benzyloxazolin-2-yl) anthracene

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Abstract—The synthesis of 9-(4-benzyloxazolin-2-yl)anthracene is described employing a new approach for the cyclisation of β-hydroxy amides to oxazolines. Thermal Diels–Alder reactions with *N*-methyl maleimide were found to be considerably slower than those previously observed. Essentially no diastereoselectivity was observed in these reactions as the benzyl stereodirecting group is remote from the reactive site. Minor rate enhancements were noticeable in the presence of some added Lewis acids, but with no diastereoselection.

1. Introduction

Chiral auxiliaries now form part of the routine set of tools available to the synthetic chemist and can be used in a great variety of stereoselective transformations.[1] As part of an ongoing research programme we have been developing chiral anthracene derived auxiliaries such as the methyl ether **1** (Fig. 1) that make use of a highly diastereoselective Diels–Alder reaction with alkenes in the addition step.[2–5]

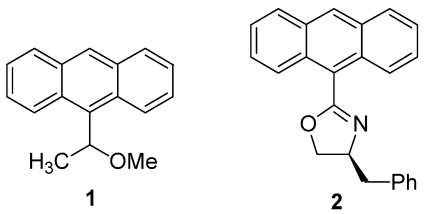

Figure 1.

Although the synthesis of ether **1** in enantiomerically pure form is relatively straightforward, this still requires use of catalytic asymmetric reduction to introduce the chirality. In contrast, more classical auxiliaries, such as Evans' oxazolidinone, employ stereogenic elements installed directly from the chiral pool. We have been working towards the goal of introducing stereogenic elements from the chiral pool directly into the anthracene framework. This work details our approach to the synthesis and evaluation of Diels–Alder reactions of 9-(4-benzyloxazolin-2-yl)-anthracene **2** (Fig. 1). This target was chosen since oxazolines can easily be prepared from naturally occurring α-amino acids and have been successfully employed in many asymmetric transformations.[6]

2. Results and discussion

2.1. Synthesis of oxazoline 2

Synthesis of the target oxazoline **2** started from commercially available anthracene 9-carboxylic acid **3**. Heating in an excess of thionyl chloride gave the acid chloride **4** in excellent yield (98%), followed by treatment with (*S*)-phenylalaninol[7] to give the key β-hydroxy amide **5**. Cyclisation of this amide to the oxazoline proved to be troublesome. Classical reaction with thionyl chloride[8] surprisingly returned starting material, as did direct treatment with the more reactive $TiCl_4$. Use of triethylorthoformate as a dehydrating agent also returned starting material (Scheme 1).

However, using diethylaminosulfur trifluoride (DAST) the reaction was more successful.[9] Addition of 1.1 equiv. of DAST at low temperature gave the desired oxazoline **2** cleanly. Although this reagent gave the desired product, its high cost is prohibitive of performing this reaction on a larger scale. Research from this group has recently reported a titanium catalysed phosphorylation procedure[10] that could be used to prepare the phosphate **6** which could then be induced to cyclise upon treatment with a suitable base. However, using the standard conditions for this reaction only the chloride **7** was obtained in excellent isolated yield. This is surprising, since in the phosphorylation of all primary alcohols previously studied, no trace of the corresponding chloride was ever observed. In any event, reaction of the chloride **7** with *t*-BuOK led to deprotonation

Keywords: Oxazoline; Anthracene; Diels–Alder.
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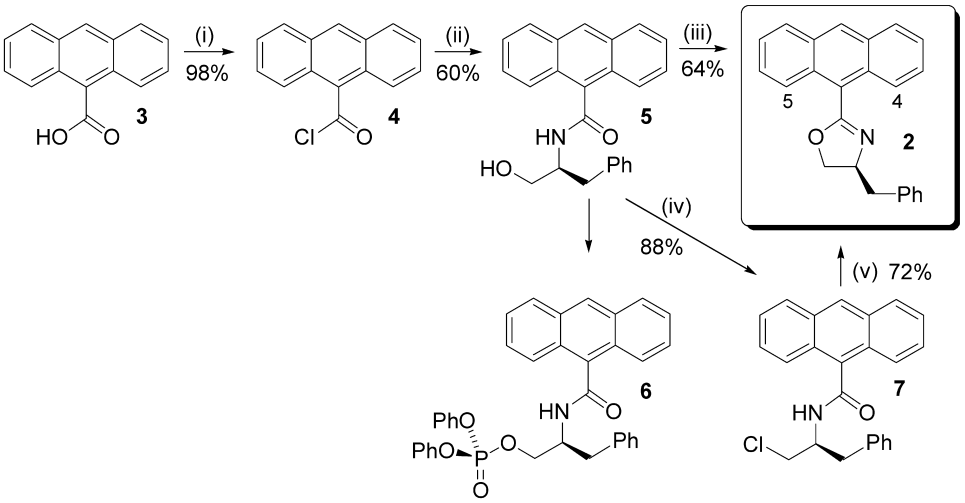


Scheme 1. Reagents and conditions: (i) $SOCl_2$ (excess), △; (ii) (*S*)-phenylalaninol, Et_3N, THF, 0 °C; (iii) DAST, CH_2Cl_2, −78 °C; (iv) 5 mol. % $TiCl_4$, $(PhO)_2P(O)Cl$, Et_3N, CH_2Cl_2, rt; (v) *t*-BuOK, THF.

of the N–H proton of the amide and subsequent ring closure to give the target oxazoline **2**. Although this route comprises two steps, the overall yield of 63% is comparable to that of the DAST reaction, but at a fraction of the cost of the reagents. Efforts are ongoing to further elaborate this method as an effective alternative route for the synthesis of oxazolines.

It is interesting to note that if the oxazoline **2** was left for prolonged periods of time during the crystallization process, the dimer **8** was formed (Fig. 2). Attempts to replicate this using photochemical dimerisation in acetonitrile returned starting material. Thermal dimerisation by heating at reflux in toluene returned starting material even after 5 days, although changing solvent to dichloromethane gave a small quantity of dimer (15%). The dimer could be cleaved back to the anthracene adduct by heating at reflux in toluene for 24 h.

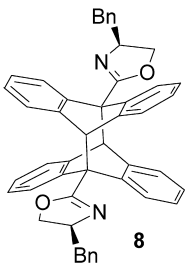


Figure 2.

The ^{1}H NMR spectrum of the oxazoline **2** is interesting compared to the methyl ether **1**. Many 9-substituted anthracenes suffer from restricted rotation around the C-9 bond due to steric interactions with the proximal *peri* hydrogen atoms (H-4 and H-5). For the ether **1** this manifests itself as broad signals for the *peri* protons at δ 8.71 ppm leading to a rotational barrier of approximately 12.2 kcal mol^{-1} at 281 K.[4] However the H-4 and H-5 protons of the oxazoline **2** appear as sharp signals in the aromatic region of the ^{1}H NMR spectrum implying free rotation about the C-9 bond. This is a consequence of a change in hybridisation from sp^3 to sp^2 adjacent to C-9 leading to a reduction of allylic strain. This was confirmed by calculation of the rotational barrier of oxazoline **2** using molecular modeling[11] giving an estimated energy barrier to rotation of 3.43 kcal mol^{-1}. Such a small value would permit free rotation at room temperature. The minimum energy conformer was found to be that with the oxazoline lying perpendicular to the anthracene ring system (Fig. 3).

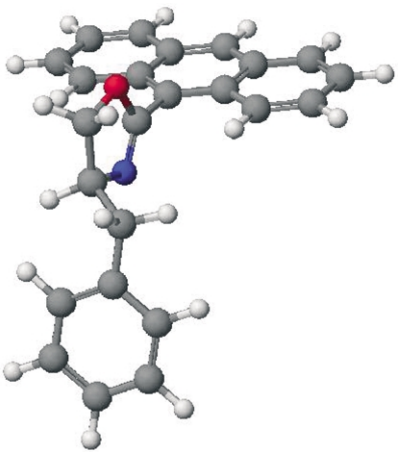
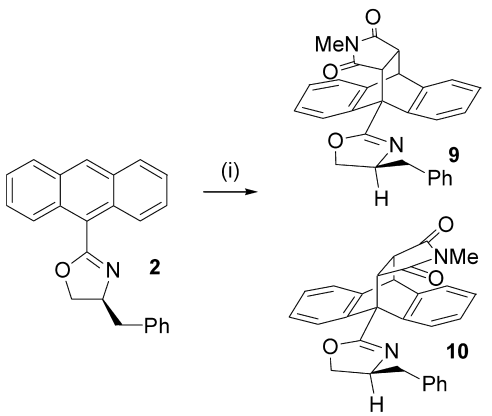


Figure 3. Minimum energy conformer of oxazoline **2**.

2.2. Thermal Diels–Alder reactions

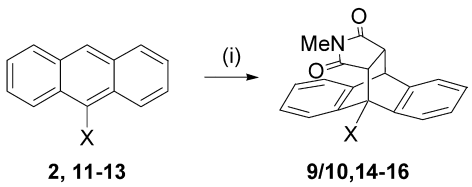
Trial Diels–Alder reactions were performed by heating oxazoline **2** in toluene at reflux for 2 h with maleic anhydride and *N*-methylmaleimide. Surprisingly, no reaction was observed with maleic anhydride, however some product (73%) was observed with *N*-methyl maleimide giving the addition adduct as a 50:50 mixture of diastereoisomers **9** and **10** as observed from the signals in the ^{1}H NMR spectrum (Scheme 2). Partial separation of these two diastereoisomers allowed the relative assignment of a number of signals in the ^{1}H and ^{13}C NMR spectrum, although absolute assignment was not possible.

The yield observed in this reaction is significantly lower



Scheme 2. Reagents and conditions: (i) *N*-methyl maleimide, $C_6H_5CH_3$, △, 2 h.

when compared to the ether **1** (73% for **2** vs 96% for **1** under otherwise identical reaction conditions). This was attributed to the electron withdrawing nature of the oxazoline group and to confirm this, the Diels–Alder reaction with *N*-methyl maleimide was performed with a series of electron rich and poor 9-substituted anthracene derivatives (Scheme 3, Table 1). These results predictably indicate that electron withdrawing groups do retard the rate of the Diels–Alder reaction and that the oxazoline, as suspected, is a good electron withdrawing group.



Scheme 3. Reagents and conditions: (i) *N*-methyl maleimide, $C_6H_5CH_3$, △, 2 h.

Table 1. Diels–Alder additions of anthracene derivatives **2**, **11**–**13** with *N*-methyl maleimide in toluene at reflux for 2 h

Starting material	X	Product	Conversion (%)[a]
11	Me	**14**	98
12	H	**15**	81
13	Br	**16**	82
2	2-Oxazolinyl	**9/10**	73

[a] Calculated from the ratio of integrals of the signals corresponding to starting material and addition product in the ^{1}H NMR spectrum.

The absence of diastereoselectivity observed in this reaction is in retrospect perhaps not so surprising. Using a rationale based upon kinetic arguments,[12,13] the approach of a dienophile will occur where electrostatic interactions can be minimized. The minimum energy conformation of the oxazoline is likely to have the oxazoline ring orientated orthogonally to the anthracene ring system to minimize *peri* interactions, a premise supported by the modeling studies discussed earlier. However in this conformation, the stereogenic centre of the oxazoline ring is located remote from the reactive centre, resulting in no interaction with the carbonyl group of the dienophile on either face of the anthracene ring and hence no discrimination (Fig. 4). Invoking a rationale based upon thermodynamic stability of the diastereoisomeric products, the predicted heats of formation of **9** and **10** are −8.66 and −8.50 kcal mol^{-1}, respectively, leading to a calculated K_{eq} of 1.23 at 110 °C.[14] This equates to a 55:45 ratio of diastereisomers which is in good agreement with the observed selectivity.

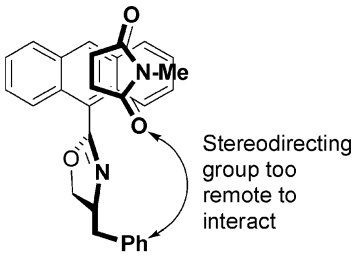


Figure 4.

2.3. Diels–Alder reactions in the presence of Lewis acidic metal triflates

Lewis acids, especially metal triflates, have been used to successfully catalyse the room temperature Diels–Alder reaction of anthracene derivatives with dienophiles.[15] Oxazolines have also been shown to act as efficient templates for cation co-ordination. Thus, oxazoline **2** was treated with *N*-methyl maleimide at room temperature in the presence of the metal triflates $Mg(OTf)_2$, $Cu(OTf)_2$, $Y(OTf)_3$ and $Sc(OTf)_3$. Unfortunately, essentially no rate enhancement was observed, with any improvement in the diastereomeric ratio. The latter is not surprising since addition of a Lewis acid is unlikely to bring the benzyl stereodirecting group into closer proximity to the reactive site.

3. Conclusions

Synthesis of 9-(4-benzyloxazolin-2-yl) anthracene has been achieved and a new synthetic route to such compounds disclosed. All attempted stereoselective Diels–Alder reactions proved to be unsuccessful resulting from poor reaction rates and no selectivity. However this work does indicate the need for an electron-rich auxiliary to increase reaction rates, in addition to ensuring the close proximity of the stereodirecting group to the reaction centre for high selectivity.

4. Experimental

4.1. General

THF and toluene were freshly dried over sodium, while CH_2Cl_2 was dried over lithium aluminium hydride. Anhydrous DMSO was obtained by distillation in vacuuo. Glassware was flame dried and cooled under vacuum before use and all reactions were carried out under nitrogen unless otherwise stated. TLC was carried out using Merck aluminium TLC sheets (silica gel 60 F_{254}). Visualisation of the TLC plates was carried out using a UV lamp or by dipping in $KMnO_4$ then exposure by heating. Flash column

chromatography was carried out with Fluorochem Limited Silica Gel 40-63u 60A. Melting points were measured on a Gallenkamp apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC-250 or a Bruker Avance 300 spectrometer or AMX-400 spectrometer or JEOL 500 MHz spectrometer. Residual proton signals from the deuteriated solvents were used as references [chloroform (^{1}H, 7.25 ppm; ^{13}C, 77 ppm) and DMSO (^{1}H, 2.50 ppm; ^{13}C, 39.7 ppm)]. Coupling constants were measured in Hz. All infrared spectra were recorded on Perkin–Elmer Spectrum RX/FT-IR system with a Dura-Sampl*IR* II ATR accessory. Optical rotations were recorded on a Perkin–Elmer 241 automatic polarimeter at 589 nm (Na D line) with a path length of 1 dm with concentrations quoted in gm 100 mL^{-1}. Mass spectra were recorded on a Micromass Autospec M spectrometer.

4.1.1. 9-Anthranoyl chloride 4.[16] 9-Anthracene carboxylic acid **3** (0.455 g, 2.05 mmol) and thionyl chloride (3.5 cm^3) were stirred at reflux for 3 h under nitrogen, then allowed to cool to room temperature. The excess thionyl chloride was removed under reduced pressure, the residue washed with diethyl ether (2×2 cm^3), and the diethyl ether evaporated to afford a dull yellow solid of 9-anthranoyl chloride **4** (0.489 g, 98%) that required no further purification, mp 94–96 °C (lit.[15] 96–97 °C); δ_H (300 MHz; $CDCl_3$) 8.62 (1H, s, 10H), 8.14 (2H, d, *J*=8.7 Hz, ArC*H*), 8.08 (2H, d, *J*=8.4 Hz, ArC*H*), 7.67 (2H, dd, *J*=8.7, 6.6 Hz, ArCH), 7.56 (2H, dd, *J*=8.4, 6.6 Hz, ArCH). Spectroscopic data was in agreement to that in the literature.

4.1.2. Anthracene-9-carboxylic acid (1-benzyl-2*S*-hydroxy-ethyl)-amide 5. 9-Anthranoyl chloride **4** (1.73 g, 7.17 mmol) was dissolved in THF (30 cm^3) in the presence of triethylamine (2.60 cm^3, 18.68 mmol). A solution of (*S*)-3-phenyl-2-amino-1-propanol (1.09 g, 7.19 mmol) in THF (35 cm^3) was then added dropwise to the reaction mixture at 0 °C. The reaction was stirred at 0 °C for 1 h, warmed to room temperature followed by filtration. The solvent was removed to afford a yellow solid, which was dissolved in CH_2Cl_2 (20 cm^3), washed with water (3×10 cm^3), and the organic phase dried over Na_2SO_4. The solvent was removed to obtain a yellow solid of the hydroxyl-amide **5** (1.54 g, 60%) that was used without purification in subsequent steps. A sample was purified for analytical purposes by two recrystallizations from EtOAc/petrol) giving the title compound as yellow needles, mp 190–194 °C (EtOAc/petrol); $[\alpha]_D$=+13.3 (*c* 1, $CHCl_3$); (Found: C, 80.95; H, 5.97; N, 3.87. $C_{24}H_{21}NO_2$ requires C, 81.10; H, 5.96; N, 3.94%); ν_{max} (film)/cm^{-1} 1634, 1519, 1455; δ_H [300 MHz; $(CD_3)_2SO$] 8.65 (1H, d, *J*=9.0 Hz, ArC*H*), 8.59 (1H, s, 10H), 8.11–8.03 (3H, m, ArC*H*), 7.57–7.35 (8H, m, ArC*H*), 7.22 (1H, dd, *J*=8.3, 6.7 Hz, ArC*H*), 7.02 (1H, d, *J*=8.7 Hz, N*H*), 5.07 (1H, t, *J*=5.6 Hz, O*H*), 4.65 (1H, m, C*H*), 3.56 (1H, ddd, *J*=11.6, 10.5, 5.6 Hz, C*H*HOH), 3.59 (1H, ddd, *J*=11.6, 10.5, 5.6 Hz, C*H*HOH), 3.11 (1H, dd, *J*=13.7, 4.0 Hz, PhC*H*H), 2.63 (1H, dd, *J*=13.7, 11.0 Hz, PhC*H*H); δ_C [75 MHz; $(CD_3)_2SO$] 168.0 (*C*=O), 139.7 (Ar*C*), 134.1 (Ar*C*), 131.0 (Ar*C*), 130.9 (Ar*C*H), 129.7 (Ar*C*H), 128.6 (Ar*C*H), 128.3 (Ar*C*H), 127.5 (Ar*C*H), 127.1 (Ar*C*H), 126.6 (Ar*C*H), 126.4 (2×Ar*C*H), 126.2 (Ar*C*H), 126.0 (Ar*C*H), 125.8 (Ar*C*H), 64.4 (CH_2OH), 53.5 (*C*HNH), 37.0 (PhCH_2); *m*/*z* (EI^+) 355.1576 (33%, $C_{24}H_{21}NO_2$ requires 355.1572), 221 (31), 205 (100, $C_{15}H_9O^+$), 177 (38), 151 (5), 91 (6).

4.1.3. 9-(4*S*-Benzyloxazolin-2-yl)anthracene 2 (DAST method). The hydroxy-amide **5** (2.534 g, 7.140 mmol) was dissolved in dry CH_2Cl_2 (140 cm^3) and then cooled to −78 °C. DAST (2 cm^3, 16.33 mmol) was added to the cooled mixture and stirred for 2 h at −78 °C. The resulting solution was quenched with NH_4OH (25 cm^3, 10% by vol.) and the reaction mixture warmed to room temperature. EtOAc (20 cm^3) was added, followed by $NaHCO_3$ (25 cm^3) and the organic layer separated. The aqueous layer was extracted with EtOAc (2×20 cm^3) and the combined organic layers washed with brine (25 cm^3) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford a dull yellow solid (2.348 g). The crude material was purified using column chromatography (EtOAc/petrol 10:90) to afford the title compound **2** as a thick yellow oil (1.532 g, 64%); $[\alpha]_D$=−12.7 (*c* 1, $CHCl_3$); (Found: C, 85.80; H, 5.44; N, 4.18. $C_{24}H_{19}NO$ requires C, 85.43; H, 5.68; N, 4.15%); ν_{max} (film)/cm^{-1} 3056, 3028, 1659; δ_H (300 MHz; $CDCl_3$) 8.56 (1H, s, 10H), 8.04–7.97 (4H, m, ArC*H*), 7.53–7.43 (4H, m, ArC*H*), 7.38–7.29 (5H, m, ArC*H*), 5.04 (1H, dtd, *J*=9.6, 7.8, 4.9 Hz, C*H*), 4.66 (1H, dd, *J*=8.6, 7.8 Hz, CH*H*O), 4.48 (1H, dd, *J*=8.6, 9.6 Hz, C*H*HO), 3.46 (1H, dd, *J*=13.8, 4.9 Hz, PhC*H*H), 3.21 (1H, dd, *J*=13.8, 7.8 Hz, PhC*H*H); δ_C (75 MHz; $CDCl_3$) 163.8 (*C*=N), 138.0, (Ar*C*), 131.4 (Ar*C*H), 130.5 (Ar*C*H), 130.2 (Ar*C*H), 129.9 (Ar*C*H), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 127.1 (Ar*C*H), 125.8 (Ar*C*H), 123.1 (Ar*C*), 72.0 (*C*H_2O), 69.0 (*C*HN), 42.1 (PhCH_2); *m*/*z* (EI^+) 337.1461 (35%, $C_{24}H_{19}NO$ requires 337.1467), 246 (100, M^+-C_7H_7), 218 (21), 203 (52), 191 (8), 177 (12), 91 (11).

4.1.4. Anthracene-9-carboxylic acid (1*S*-benzyl-2-chloro-ethyl)-amide 7. $TiCl_4$ (0.01 cm^3, 0.07 mmol, 2 mol %) was dissolved in THF (5 cm^3) and the hydroxyl amide (1.18 gm, 3.33 mmol) was added as a solution in THF (15 cm^3) via a dropping funnel followed by Et_3N (0.71 cm^3, 5.00 mmol), THF (5 cm^3), diphenylphosphorochloridate (1.04 cm^3, 5.00 mmol) and THF (10 cm^3). The resulting mixture was stirred at room temperature for 1 h before quenching with water (15 cm^3). The organic layer was extracted with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4 and filtered. Removal solvent afforded the crude material (1.72 gm, 2.93 mmol, 88% yield) that was used without purification in subsequent steps. A sample was purified for analytical purposes by column chromatography (10% EtOAc/petrol) followed by recrystallization from toluene to give white crystals, mp 198–203 °C (toluene); $[\alpha]_D$=−14 (*c* 0.5, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 1673, 1488, 1424; δ_H (250 MHz; $CDCl_3$) 8.51 (1H, s, ArC*H*), 8.32 (1H, d, *J*=8.4 Hz, ArC*H*), 8.08–7.95 (3H, m, ArC*H*), 7.61–7.30 (9H, m, ArC*H*), 6.27 (1H, d, *J*=7.9 Hz, N*H*), 5.14 (1H, m, C*H*), 4.09 (1H, dd, *J*=11.5, 4.2 Hz, CH*H*Cl), 3.82 (1H, dd, *J*=11.5, 3.5 Hz, C*H*HCl), 3.21–3.10 (2H, m, PhCH_2); δ_C (100 MHz; $CDCl_3$) 172.3 (*C*O), 131.4 (Ar*C*), 130.6 (Ar*C*), 129.7 (Ar*C*H), 129.4 (Ar*C*H), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.4 (Ar*C*H), 127.7 (Ar*C*H), 127.5 (Ar*C*H), 127.2 (2×Ar*C*H), 125.9 (Ar*C*H), 125.6 (Ar*C*H), 125.3 (Ar*C*H), 51.8 (*C*H), 47.7 (*C*H_2Cl), 38.3 (*C*H_2Ph); *m*/*z* (ES) 374.1314 (42% $C_{24}H_{21}NOCl$ requires 374.1312), 205 (100); (EI^+) 374 (32), 373 (22), 307 (21), 289 (12), 222 (87), 205 (44), 177 (13), 154 (100), 136 (74).

4.1.5. 9-(4*S*-Benzyloxazolin-2-yl)anthracene 2 (from 7). Potassium *t*-butoxide (1.2 gm, 10.66 mmol) was added as a solid to a stirred solution of chloride **7** (3.12 gm, 5.31 mmol) in THF (20 cm^3). The reaction mixture was stirred for 1 h at room temperature, filtered through short pad of silica, eluting with EtOAc (5 cm^3). Removal of solvent gave the title compound **2** (1.28 g, 3.80 mmol, 72%).

4.1.6. 9-(4*S*-Benzyloxazolin-2-yl)-10-hydro-9,10-ethanoanthracene-11*R*,12*R*-dicarbonyl *N*-methylamide 9 and 9-(4*S*-benzyloxazolin-2-yl)-10-hydro-9,10-ethanoanthracene-11*S*,12*S*-dicarbonyl *N*-methylamide 10. 9-(4-Benzyloxazolin-2-yl)anthracene **2** (0.500 g, 1.48 mmol) was dissolved in dry toluene (10 cm^3), the resulting solution heated to 90–95 °C and *N*-methylmaleimide (0.442 g, 3.98 mmol) added. This was left at this temperature for 4 and 1/2 h, then cooled to room temperature, and the solvent was removed under reduced pressure to afford a pale yellow solid of the two diastereisomers **9** and **10** (50/50 by ^{1}H NMR spectroscopy). This mixture was purified using column chromatography (EtOAc/petrol, 30:70) to give a 60/40 mixture of two diastereoisomers (0.279 g, 42%) as a yellow solid; ν_{max} (ATR)/cm^{-1} 1776, 1697, 1456, 1433, mp 101–104 °C; $[\alpha]_D$=−8.0 (*c* 0.5, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) Diastereoisomer A, 8.28 (1H, d, *J*=7.3 Hz, ArC*H*), 7.32–7.26 (4H, m, ArC*H*), 7.23–7.02 (7H, m, ArC*H*), 6.84 (1H, d, *J*=7.3 Hz, ArC*H*), 4.81 (1H, m, C*H*), 4.68 (1H, m, C*H*), 4.47 (1H, m, CH*H*O), 4.26 (1H, m, CH*H*O), 3.76 (1H, d, *J*=8.6 Hz, C*H*), 3.32 (1H, dd, *J*=13.8, 5.0 Hz, C*H*), 3.21–3.15 (1H, m, PhC*H*H), 2.99–2.91 (1H, m, PhC*H*H), 2.40 (3H, s, CH_3); Diastereoisomer B, 8.22 (1H, d, *J*=7.1 Hz, ArC*H*), 7.32–7.26 (4H, m, ArC*H*), 7.23–7.02 (7H, m, ArC*H*), 6.95 (1H, d, *J*=7.2 Hz, ArC*H*), 4.81 (1H, m, C*H*), 4.68 (1H, m, C*H*), 4.47 (1H, m, CH*H*O), 4.26 (1H, m, CH*H*O), 3.82 (1H, d, *J*=8.6 Hz, C*H*), 3.41 (1H, dd, *J*=13.7, 5.5 Hz, C*H*), 3.21–3.15 (1H, m, PhC*H*H), 2.99–2.91 (1H, m, PhC*H*H), 2.42 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 176.9 (*C*=O), 175.9 (*C*=O), 141.2 (*C*=N), 138.6, 138.0, 137.2, 130.1 (Ar*C*H), 129.8 (Ar*C*H), 129.1 (Ar*C*H), 127.6 (Ar*C*H), 127.5 (Ar*C*H), 127.1 (Ar*C*H), 127.0 (Ar*C*H), 126.1 (Ar*C*H), 125.1 (Ar*C*H), 124.3 (Ar*C*H), 123.7 (Ar*C*H), 71.7 (Diastereomer A, *C*H_2O), 71.3 (Diastereomer B, *C*H_2O), 69.1, 68.7, 51.3, 49.4, 49.1, 47.7, 46.4, 42.4, 42.2, 24.7 (N*C*H_3); *m*/*z* (ES) 449.1881 (100%, $C_{29}H_{25}N_2O_3$ requires 449.1865).

4.1.7. 9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarbonyl *N*-methylamide 15.[17] Anthracene **12** (0.178 g, 1.00 mmol) was dissolved in toluene (10 cm^3), the resulting solution heated to 90–95 °C, and *N*-methylmaleimide (0.111 g, 1.00 mmol) was added in one portion. The reaction mixture was stirred at 90–95 °C for 2 h, cooled to room temperature and the solvent was removed under reduced pressure to afford the title product **15** as a grey solid, which was recrystallized from toluene (0.169 g, 59%), mp 278–279 °C (lit.[17] 262–264 °C); δ_H (300 MHz; $CDCl_3$) 7.40 (2H, m, ArC*H*), 7.27 (2H, m, ArC*H*), 7.20–7.12 (4H, m, ArC*H*), 4.80 (2H, s, ArC*H*), 3.22 (2H, s, COC*H*), 2.52 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 177.3 (*C*=O), 141.8 (Ar*C*), 138.9 (Ar*C*), 127.4 (Ar*C*H), 127.1 (Ar*C*H), 125.3 (Ar*C*H), 125.7 (Ar*C*H), 47.4 (*C*H), 45.9 (*C*H), 24.7 (*C*H_3). Spectroscopic data was in agreement to that in the literature.

4.1.8. 9,10-Dihydro-9-bromo-9,10-ethanoanthracene-11,12-dicarbonyl *N*-methylamide 16. *N*-Methylmaleimide (0.611 g, 5.51 mmol) was added in one portion as a solid at 90–95 °C to a stirred solution of 9-bromoanthracene **13** (0.500 g, 1.95 mmol) in toluene (12 cm^3). The resulting mixture was left stirring for further 7 h at 90–95 °C, cooled to room temperature and the solvent removed under reduced pressure to give the target compound, which was recrystallized from toluene to afford a white solid of the title compound **16** (0.554 g, 77%), mp 228–232 °C; (Found: C, 62.0; H, 3.8; N, 3.8; Br, 21.9. $C_{19}H_{14}BrNO_2$ requires C, 62.0; H, 3.8; N, 3.80; Br, 21.70%); ν_{max} (ATR)/cm^{-1} 1776, 1690, 1456, 1426; δ_H (300 MHz; $CDCl_3$) 7.82 (1H, m, ArC*H*), 7.63 (1H, m, ArC*H*), 7.32 (1H, m, ArC*H*), 7.25–7.12 (5H, m, ArC*H*), 4.74 (1H, d, *J*=3.3 Hz, C*H*), 3.37 (1H, d, *J*=8.6 Hz, COC*H*CHCO), 3.25 (1H, dd, *J*=8.6, 3.3 Hz, COC*H*CH), 2.48 (3H, s, NCH_3); δ_C (100 MHz; $CDCl_3$) 175.3 (*C*=O), 173.4 (*C*=O), 141.0 (Ar*C*), 140.0 (Ar*C*), 138.1 (Ar*C*), 136.6 (Ar*C*), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.5 (Ar*C*H), 127.1 (Ar*C*H), 125.8 (Ar*C*H), 125.3 (Ar*C*H), 124.5 (Ar*C*H), 123.5 (Ar*C*H), 64.6 (*C*Br), 53.4 (*C*H), 49.0 (*C*H), 45.1 (*C*H), 24.5 (N*C*H_3); *m*/*z* (ES) 390.0117 (100%, M^++Na; $C_{19}H_{14}NO_2Na^{79}Br$ requires 390.0106); *m*/*z* (EI^+) 370 (6%), 369 [14, M^+ (^{81}Br)], 367 [21, M^+ (^{79}Br)], 259 (15), 258 (97, $C_{14}H_8{}^{81}Br^+$), 256 (100, $C_{14}H_8{}^{79}Br^+$), 202 (11), 177 (13), 176 (16), 101 (8).

4.1.9. 9,10-Dihydro-9-methyl-9,10-ethanoanthracene 11,12-dicarbonyl *N*-methylamide 14.[18] 9-Methylanthracene **11** (0.192 g, 1.00 mmol) was dissolved in toluene (10 cm^3) then the resulting solution was heated to 90–95 °C and *N*-methylmaleimide (0.111 g, 1.00 mmol) was added in one portion as a solid. The reaction mixture was stirred at 90–95 °C for 2 h, cooled to room temperature and finally the solvent was removed under reduced pressure to afford the title product **14** as a white solid in 98% conversion as calculated from the ^{1}H NMR spectrum, which was recrystallized from toluene (0.247 g, 82%), mp 146–150 °C (lit.[18] 267–168 °C);† δ_H (300 MHz; $CDCl_3$) 7.44–7.39 (2H, m, ArC*H*), 7.30–7.11 (6H, m, ArC*H*), 4.78 (1H, d, *J*=3.3 Hz, COCHC*H*), 3.28 (1H, dd, *J*=3.3, 8.4 Hz, COC*H*CH), 2.86 (1H, d, *J*=8.4 Hz, COC*H*CHCO), 2.53 (3H, s, NCH_3), 2.31 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 177.2 (*C*=O), 176.6 (*C*=O), 144.9 (Ar*C*), 142.2 (Ar*C*), 141.4 (Ar*C*), 139.0 (Ar*C*), 127.3 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (2×Ar*C*H), 125.2 (Ar*C*H), 124.2 (Ar*C*H), 122.5 (Ar*C*H), 122.4 (Ar*C*H), 51.0 (*C*H), 48.9 (*C*H), 45.9 (*C*H), 45.4 (*C*), 24.7 (N*C*H_3), 15.7 (*C*H_3).

4.1.10. 9-(3-Benzyloxazolinoyl)anthracene dimer 8. The title compound was obtained as a yellow solid on leaving a toluene solution of oxazoline **2** to slowly evaporate over the period of several weeks, mp 219–221 °C; $[\alpha]_D$=−6.0 (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 1651, 1476, 1454; δ_H (250 MHz; $CDCl_3$) 7.46–7.29 (11H, m, ArC*H*), 7.06 (4H, m, ArC*H*), 6.75 (5H, m, ArC*H*), 6.61 (4H, m, ArC*H*), 5.98 (2H, t, *J*=3.5 Hz, PhC*H*), 4.87 (2H, m, C*H*), 4.46 (2H, t, *J*=9.0 Hz, CH*H*O), 4.26 (2H, dd, *J*=9.0, 7.6 Hz, 2×C*H*HOH), 3.25 (4H, m, PhCH_2); δ_C (100 MHz; $CDCl_3$) 169.3 (*C*=N), 142.6 (Ar*C*), 142.1 (Ar*C*), 142.0 (Ar*C*), 141.9 (Ar*C*H),

† The reported melting point for this compound is as stated but probably refers to 167–168 °C. No other spectroscopic data is reported for this compound.

137.1 (Ar*C*H), 130.3 (Ar*C*H), 128.6 (Ar*C*H), 128.1 (Ar*C*H), 127.9 (Ar*C*H), 126.8 (Ar*C*H), 126.2 (Ar*C*H), 125.9 (Ar*C*H), 125.6 (Ar*C*H), 125.5 (Ar*C*H), 125.4 (Ar*C*H), 71.6 (*C*H_2O), 66.7 (N*C*H), 59.8 (Ph*C*), 55.8 (Ph*C*H), 41.3 (Ph*C*H_2); *m/z* (ES^+) 675.2988 (7% $C_{48}H_{39}N_2O_2$ requires 675.3012); (FAB^+) 675 (12%, MH^+), 613 (19), 461 (20), 460 (71), 443 (13), 392 (27), 391 (100), 354 (14), 339 (27), 338 (96), 337 (41).

4.2. General procedure for metal triflate-catalysed Diels–Alder reaction

9-(3-Benzyloxazolinoyl)anthracene **2** (0.100 g, 0.297 mmol) was dissolved in CH_2Cl_2 and *N*-methylmaleimide (0.033 g, 0.297 mmol) was added as a solid followed by the addition of metal triflate (0.0003 mmol, 10 mol %) in CH_2Cl_2. The reaction mixture was stirred overnight at room temperature, brine (5 cm^3) added and the organic layer separated and dried over Na_2SO_4. The solution was filtered and the solvent removed to give crude material that was analyzed by ^1H NMR spectroscopy.

Acknowledgements

We would like to thank the Committee of Higher Education in Libya and The Libyan Arab People's Bureau for a scholarship (R.A.B.).

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The use of temporary tethers in the *meta* photocycloaddition reaction

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Abstract—The use of temporary tethers in facilitating *meta* photocycloaddition reactions between phenol and allyl alcohol derivatives has been investigated. The merits of silicon, carbonate and methylene acetal tethers were assessed, whilst considering strategies for the preparation of the natural products gymnomitrol and gelsemine. The photoadducts were epoxidised, and then subjected to acid catalysed fragmentation with concomitant cleavage of the tether. Depending on whether water or methanol was used during the fragmentation stage of the methylene tethers, the methylene group was either removed altogether or transformed into a MOM group.

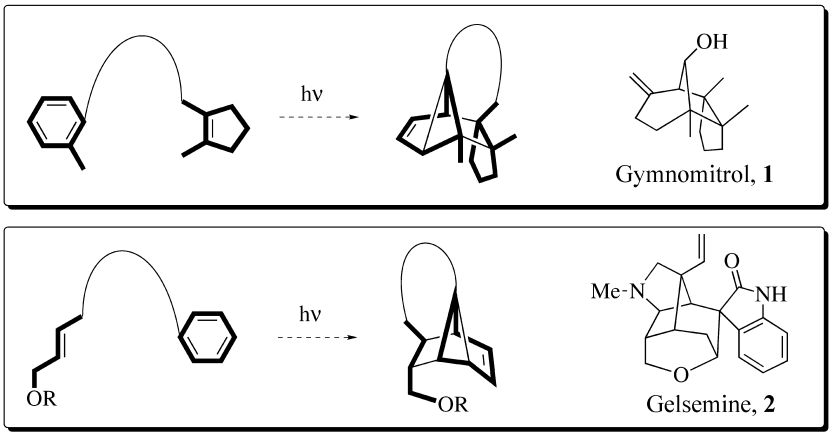
1. Introduction

The use of temporary tethers[1] to improve the efficiency of *meta* photocycloaddition reactions[2] has been investigated for the assembly of the core skeletons of the natural products gymnomitrol **1**[3] and gelsemine **2**[4] (Scheme 1).

1.1. Temporary tethers

Stork[5] originally introduced the concept of using a 'temporary tether' to convert an intermolecular reaction into an intramolecular one. The decreased entropic demands on such a system increased the likelihood of two reacting sites colliding with each other and thereby increased the rate of a particular reaction. The lower degrees of freedom of the unimolecular transition-state will also give rise to increased levels of regio- and stereoselectivity between the two reacting partners.

The three main considerations when selecting a suitable tether are that it is easily coupled to the two reacting partners via straightforward chemical transformation; that it is stable to a variety of chemical conditions; and, when it has served its purpose, that it be selectively cleaved from the final product, leaving no trace of its original existence.



Scheme 1.

Keywords: Temporary tethers; Photochemistry; Cycloaddition; Epoxidation; Fragmentation.
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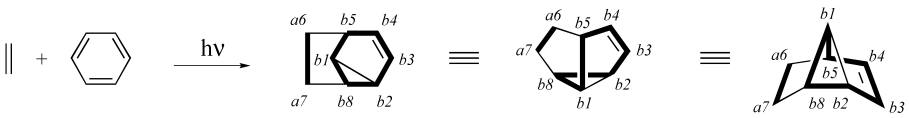


Figure 1. The *meta* photocycloaddition product between ethene and benzene is represented in three different forms. The numbering system of the basic *meta* photocycloadduct shown above is used throughout this publication, with the letters *a* and *b* signifying whether the atoms are derived from the former alkene and benzene portions, respectively.

Temporary tethers have found extensive use in radical and thermal cycloaddition reactions, because of the advantages these types of reaction have when carried out in an intramolecular sense.[1] They have also been applied in [2+2] photocycloaddition reactions,[6] although their usage has been somewhat limited.

1.2. The *meta* photocycloaddition reaction

The *meta* photocycloaddition reaction was initially reported in 1966[2a,b] and involves the 1,3-addition of an alkene across the excited state of a benzene derivative. The simplest version of this reaction between ethene and benzene is shown in Figure 1, with the former ethene and benzene ring portions being highlighted in bold.

The regiochemistry of the photocycloaddition reaction is strongly dependent on the electronic nature of the substituent on the aromatic ring of the photosubstrate. Electron-donating groups tend to favour position *b1* in the photoadduct, whilst electron-withdrawing groups favour positions *b2* or *b4* (Fig. 2).

The intramolecular variant of the *meta* photocycloaddition reaction was discovered almost by accident,[7] whilst investigating light induced *cis*/*trans* isomerism of 6-phenyl-hex-2-ene. So far the majority of such reactions have involved a three-atom chain linking the benzene and alkene portions, for which three modes of *meta* cycloaddition tend to occur. Two photoadducts are derived from alkene addition across the 1,3-positions of the aromatic ring, whilst the other is derived from alkene addition across the aromatic 2,6-positions (Fig. 3).

Most of the photoadducts reported in this publication have a four-atom tether between the benzene and alkene portions and, because the tethers were electron donating, only the 2,6-mode of cycloaddition across the aromatic ring was observed. The additional flexibility associated with this longer tether allowed it to link from the *b1* position of the photoadduct to either the *a6* or the *a7* positions (Fig. 4).

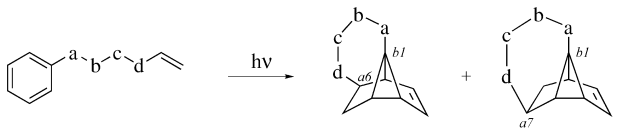


Figure 4. The two modes of intramolecular *meta* photocycloaddition for benzene linked to an alkene by a four-atom tether involving 2,6 addition of the olefin across the aromatic ring.

2. Results and discussion

2.1. Gymnomitrol studies

Whilst investigating the steric effects associated with the *meta* photocycloaddition reaction between cyclopentene and anisole derivatives, Hoye[8] attempted to assemble the

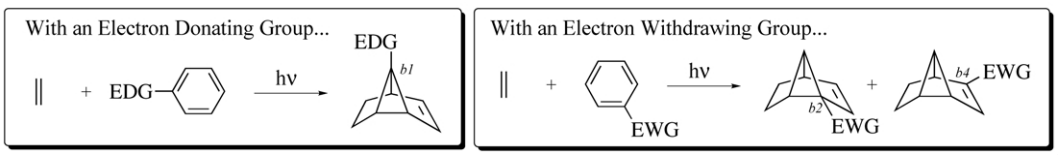


Figure 2. Regioselectivity of *meta* photocycloaddition reactions.

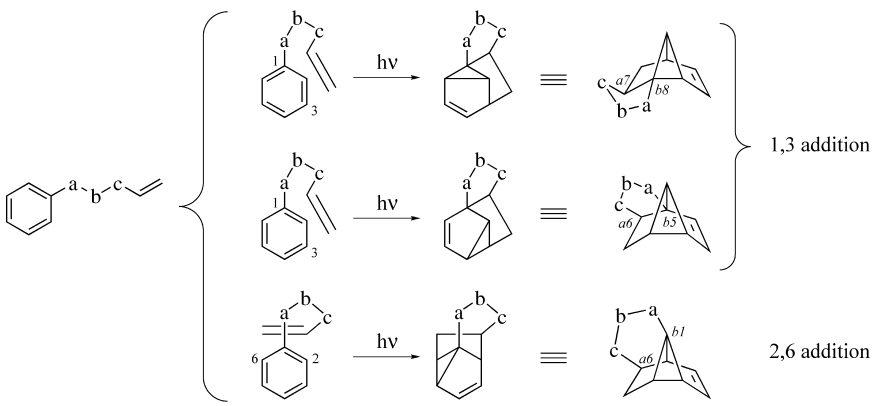
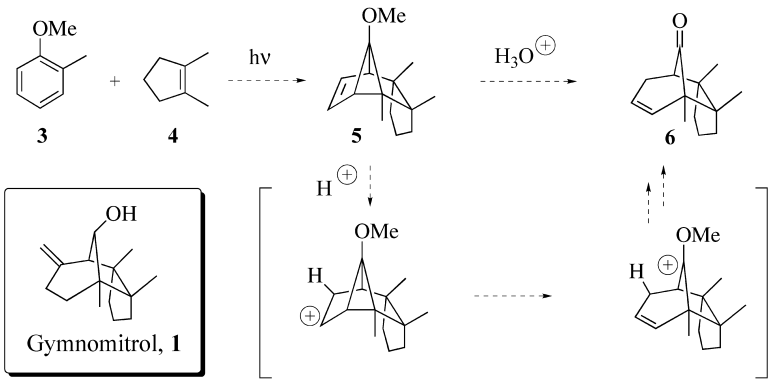


Figure 3. The three possible modes of intramolecular *meta* photocycloaddition for benzene linked to an alkene by a three-atom tether.



Scheme 2.

core structure of the sesquiterpene gymnomitrol **1** by irradiating 1-methoxy-2-methylbenzene **3** in the presence of 1,2-dimethylcyclopentene **4** and then fragmenting the *meta* photoadduct **5** using aqueous acid (Scheme 2). Unfortunately, the desired *meta* photocycloaddition between **3** and **4** failed to provide any of the desired photoadduct **5**, leading the authors to conclude that an intermolecular photoaddition reaction between a di-substituted aromatic and a tetra-substituted alkene was disfavoured on the grounds of steric hindrance.

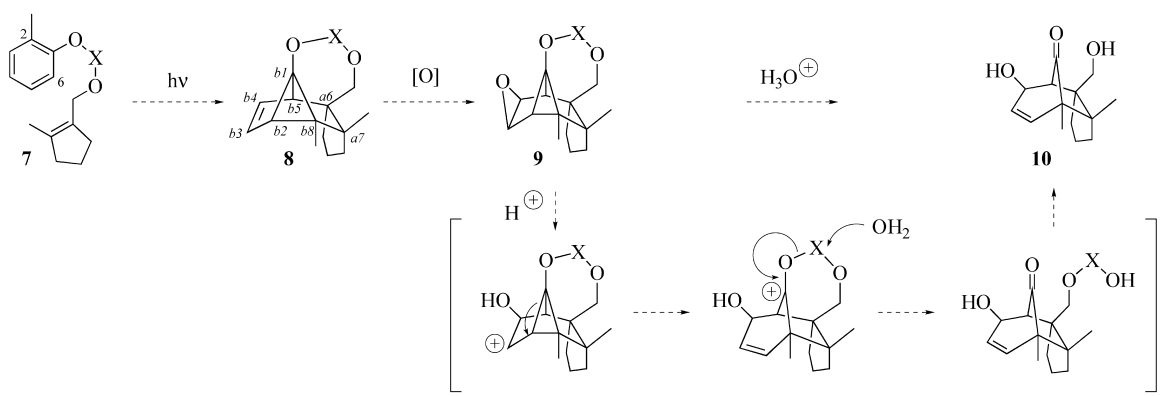
We considered that the inherent advantages of carrying out an intramolecular version of this reaction might overcome these steric obstacles and proposed using a temporary tether, X, to assemble the core skeleton of gymnomitrol. Our strategy was to couple appropriate aromatic and olefin groups together via a tether to provide the photosubstrate **7** and then initiate an intramolecular *meta* photocycloaddition reaction. The predicted photoadduct **8** would be epoxidised to **9** and hydrolysed under acidic conditions to afford the keto-diol **10**, which would subsequently be converted to gymnomitrol **1** (Scheme 3).

The electron-donating oxygen atom on the phenolic ring of **7** should direct the addition of the alkene across the 2,6 positions of the aromatic ring of the photosubstrate during the *meta* photocycloaddition reaction[2c] to give **8**. Other regioisomers could also be formed, which would be related by the ultimate position of the methyl group derived from the aromatic ring (at either position *b5* or *b8* in compound **8**) and the attachment points of the tether (between *b1* and either the *a6* or *a7* positions). The potential photoadduct **8** represented in Scheme 3 shows the methyl group at position *b8* and the tether attached between the *b1* and *a6* positions. Quite which regioisomer would be generated would be resolved as a result of experimentation. (Note that the same numbering system in Figure 1 is used, when referring to *meta* photocycloadducts).

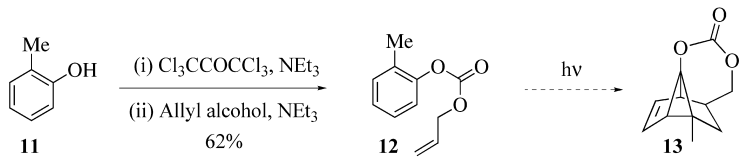
We prepared a series of simplified model substrates using 2-methylphenol **11** to determine what would be the most appropriate tether. One priority in considering a suitable tether was its stability towards silica-based chromatography since earlier work had shown some silicon-based tethers to be very labile under these conditions.

The first type of tether we chose was the carbonate. The mixed carbonate **12** was prepared using the procedure of Larock and Lee[9] by sequential reaction of triphosgene with 2-methylphenol and allyl alcohol in the presence of triethylamine. Unfortunately, irradiation of **12** failed to yield any of the desired photoadduct **13** (Scheme 4). This may have been due to internal quenching of the excited state in the aromatic ring by the adjacent carbonyl group. Alternatively, the restricted conformation of the various rotomeric forms associated with the ester-like carbonate may have prevented close association of the alkene with its aromatic partner.

Next, we turned our attention to the preparation of a methylene acetal tether. To achieve this we required a source of aryl chloromethyl ether, which could be

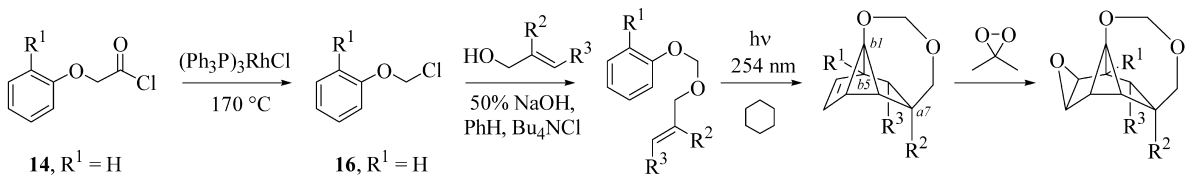


Scheme 3.



Scheme 4.

Table 1. The preparation, irradiation and oxidation of methylene acetal tethered *meta* photocycloadducts



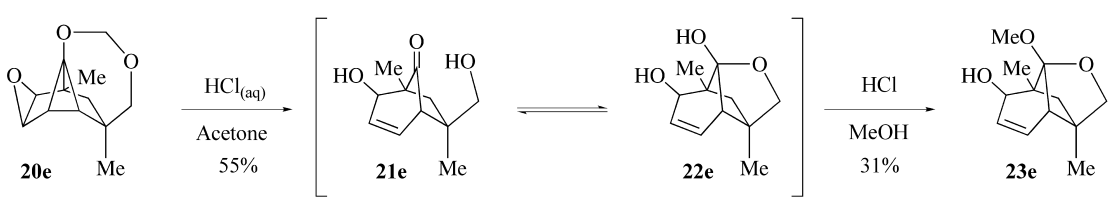
Entry	R^1	R^2	R^3	Yield of **18** (%)	Yield of **19** (%)	Yield of **20** (%)
a	H	H	H	77	0	—
b	H	Me	H	71	0	—
c	H	H	Me	72[a]	0	—
d	Me	H	H	79	13	100
e	Me	Me	H	86	17	100
f	Me	H	Me	78[a]	7[b]	100

[a] Obtained as a 4:1 mixture of *E*/*Z* isomers.
[b] Only *E* isomer underwent *meta* photocycloaddition.

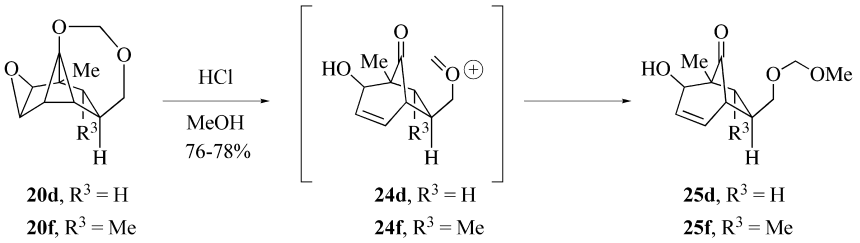
subsequently coupled to various allylic alcohols. The highly efficient procedure of Benneche and Undheim[10] was employed, which involved decarbonylation of a phenoxyacetyl chloride by heating with Wilkinson's catalyst at 170 °C. 2-Methylphenyl chloromethyl ether **17** was prepared as gymnomitrol required the aromatic ring to be substituted with a methyl group. We also prepared phenyl chloromethyl ether **16**, to assess the effect of removing the 2-methyl group on the photoreaction. Both aryl chloromethyl ethers were then coupled to three allylic alcohols to give six potential methylene acetal photosubstrates **18a–f**. Each were separately dissolved in cyclohexane (0.1 M) and irradiated in a quartz immersion-well photoreactor for 7 days using a 6 W low-pressure mercury vapour lamp. We found that only the photosubstrates **18d–f** derived from 2-methylphenol underwent *meta* photocycloaddition. Irradiation of the photosubstrates **18a–c** derived from phenol led to unreacted starting material and the formation of a complex polymeric mixture. At this point, we resolved the regiochemical issues spoken of earlier and found that the former aromatic methyl group was incorporated at the *b5* position of the photoadducts **19d–f** with the tether attached between the *b1* and *a7* positions (see Fig. 1 for photoadduct numbering system). In the case of **18f**, which was a 4:1 mixture of *E* and *Z* alkenes, only the *E* isomer underwent *meta* photocycloaddition. After chromatographic purification, the 1,3-cycloadducts **19d–f** were oxidised to their corresponding *exo*-epoxides using dimethyl dioxirane.[11] The results of these experiments are summarised in Table 1.

Alternative methods for fragmentating the epoxides **20d–f** was next investigated. Epoxide **20e** was fragmented using aqueous acid to produce the hydroxy-ketone **21e**, which existed in equilibrium with its hemi-acetal **22e**. This mixture was converted to the methoxyacetal **23e** by stirring in acidified methanol for a few days, which had the effect of protecting the primary hydroxyl group and the bridgehead ketone and leaving the allylic alcohol free for further chemical manipulation (Scheme 5).

Whilst trying to convert epoxides **20d** and **20f** directly to **23d** and **23f** using only acidified methanol, a different transformation was observed. The methylene oxonium ion **24**, which must have formed initially, was trapped with methanol rather than water. This had the effect of protecting the primary hydroxyl as a MOM group, whilst the bridgehead position remained as an unprotected ketone (Scheme 6). Extended exposure of either **25d** or **25f** to acidified methanol led only to significant decomposition.



Scheme 5.



Scheme 6.

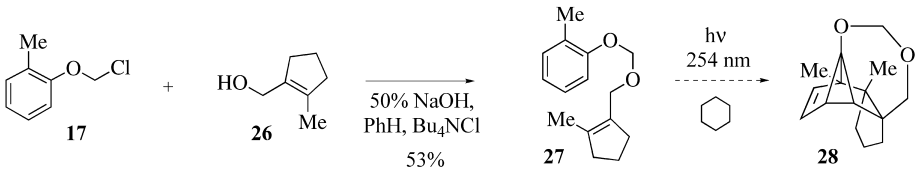
Having established these encouraging results with a methylene acetal tether, (2-methylcyclopent-1-enyl)methanol **26** was prepared according to the procedure of Inouye et al.[12] and reacted with 2-methylphenyl chloromethyl ether **17** using phase transfer conditions again. Unfortunately, irradiation of **27** led to none of the desired *meta* photocycloadduct **28** being isolated (Scheme 7). This indicated that even the inherent steric advantages of an intramolecular reaction were insufficient to overcome the steric encumbrance involved with a tetra-substituted olefin reacting with a di-substituted aromatic ring.

2.2. Gelsemine studies

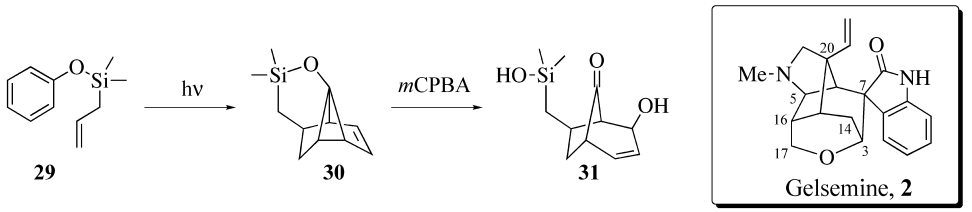
We have already shown how the core skeleton of gelsemine **2** might be assembled with a silicon tethered *meta* photocycloaddition protocol[13] (Scheme 8).

The hydroxyketone **31**, which formed as a result of an epoxidation-fragmentation reaction on photoadduct **30**, contained suitable functionality at all positions to complete a possible gelsemine synthesis, except at what would become C16 (gelsemine numbering, Scheme 8). The carbonyl group could be used to create the quarternary centre at C20, the allylic alcohol group could be used to introduce the oxindole unit at C7 and the silicon group could be oxidatively cleaved and replaced by nitrogen at C5 using a Curtius rearrangement. The shortcoming of this approach was that it would not allow the incorporation of the *endo* oxymethylene group at C17, as the appropriate *E* disubstituted olefin photosubstrate would be extremely unstable due to elimination (Scheme 9).

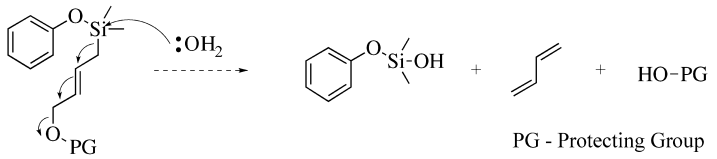
The obvious solution to this problem was to introduce an additional oxygen atom between the removable tether and the allyl group. We could not use a methylene acetal tether, as we had already discovered allyloxymethoxybenzene **18a** would not undergo the desired *meta* photocycloaddition reaction, so we chose the more labile silicon tether instead. Preliminary studies were performed with allyloxydimethylphenoxysilane **35**, which was prepared by the reaction of chlorodimethylphenoxysilane[14] **33** with the lithium salt of allyl alcohol **34**. A solution of the silicon-tethered photosubstrate **35** in cyclohexane was irradiated in a quartz immersion-well photoreactor using a 16 W low-pressure mercury vapour lamp. The silicon tether was very prone to hydrolysis during silica-based chromatography, although we managed to isolate both the *b1–a6* and *b1–a7* tethered



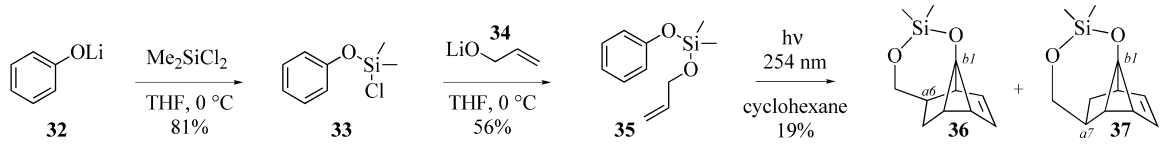
Scheme 7.



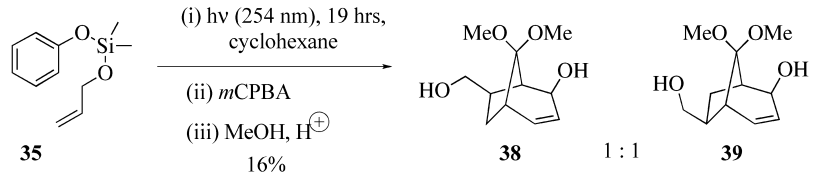
Scheme 8.



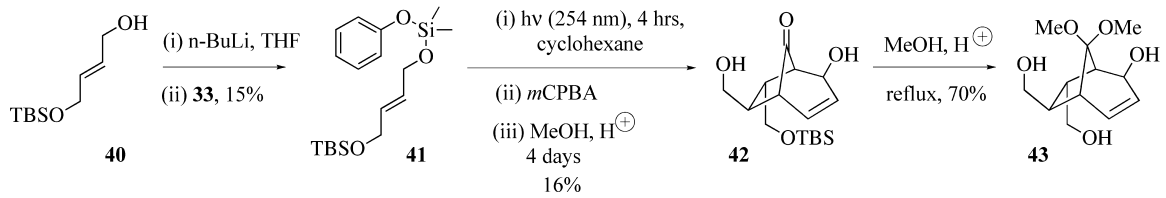
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

meta photocycloadducts **36** and **37** together as a 1:2 inseparable mixture (Scheme 10).

The losses we encountered whilst attempting to isolate **36** and **37**, caused us to irradiate **35**, oxidise and then fragment in one pot. A 1:1 mixture of the ketodiols **38** and **39** was obtained in 16% overall yield (Scheme 11) and the diastereomeric pair could be separated at this stage. In each case the primary hydroxyl group did not cyclise onto the bridgehead position, which was protected as a dimethyl acetal. Interestingly, the diols **38** and **39** were isolated as a 1:1 mixture in contrast to the 1:2 mixture of photoadducts **36** and **37** after irradiation.

Diol **38** provided strong encouragement for the preparation of the gelsemine skeleton, because if a *trans* oxymethylene group could be introduced onto the terminus of the olefin of **35**, the resulting *endo* oxymethylene group would be incorporated at what would become C16 of the gelsemine structure after the photochemical stage. *E*-4-(ᵗButyl-dimethylsilanyloxy)-but-2-en-1-ol **40**, prepared by mono-silylation[15] of the corresponding diol,[16] was chosen as the alkene partner to accomplish this, and was coupled to chlorodimethylphenoxysilane **33**. The resulting silicon tethered photosubstrate **41** was irradiated, epoxidised and hydrolysed to afford the single keto-diol **42** in 16% overall yield from **41** (Scheme 12).

There were significant differences between the preparation of **42** from **41** compared with the corresponding reaction using **35** (Scheme 11). Only one diol product **42** was formed, which indicated that one mode of photocyclo-addition had occurred. During the photoaddition step, the tether was attached at the *a7 exo* position (see Fig. 1) in a manner similar to **39** and none of the *a6 exo* regioisomer was formed. Unlike compounds **38** and **39**, the diol **42** was isolated with the bridgehead ketone intact and not protected as a dimethyl acetal. Further exposure to acidic methanol at elevated temperatures led to the formation of dimethyl acetal **43**, however, the silyl-protecting group was hydrolysed as a consequence.

3. Conclusion

This methodology allows the formation of unique tetra-cyclic compounds, which would otherwise be inaccessible through conventional means. We have shown that temporary tethers can play an important role in promoting certain *meta* photocycloaddition reactions, although they require an additional degree of complexity in their formation. It has also been demonstrated that methylene acetal tethers can act as alternatives to silicon tethers. Their increased stability has advantages in their purification and they can also be converted into useful protecting groups (e.g., a MOM group) after they have served their initial purpose.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Bruker DPX300, Varian unityINOVA-300, Varian unityINOVA-400 or Bruker AMX500 Fourier transform spectrometers at 300, 400 or 500 MHz, respectively. Chemical shifts (δ) are quoted in ppm using tetramethylsilane or residual chloroform as internal reference (δ=0.00 ppm), and coupling constants (J) are quoted in Hz. ^{13}C NMR spectra were recorded using the same instruments, and chemical shifts (δ) are quoted in ppm using $CDCl_3$ as internal reference ((δ)=77.0 ppm).

IR spectra were recorded on Perkin–Elmer Spectrum One Fourier transform instruments, either using a liquid film between sodium chloride plates (LF) or by the method of attenuated total reflectance (ATR). Frequencies (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Low- and high-resolution electron impact (EI) and chemical impact (CI) mass spectra were recorded using a Fisons Autospec instrument. High-resolution electrospray ionisation (ESI) mass spectra were recorded using a Bruker Daltonics APEXIII instrument.

The starting materials for the synthesis of the compounds were obtained from the usual suppliers (Sigma-Aldrich-Fluka, Lancaster, Fisher etc.) unless otherwise stated. The anhydrous solvents, tetrahydrofuran and diethyl ether (ether), were obtained from Aldrich Chemicals in Sure/Seal™ bottles and were used without further purification. Petrol refers to petroleum ether with a boiling range of 40–60 °C. Flash column chromatography was performed using Fisher Matrex 60 (35–70 μm) silica, and the same silica was used for silver nitrate impregnation by the method of Li et al.[17] Analytical thin layer chromatography (TLC) was performed using Whatman K6F silica gel plates (60 Å porosity) developed with UV light or an alkaline solution of potassium permanganate followed by heating to give yellow spots. Analytical silver nitrate impregnated plates were also prepared from these and developed simply by heating to give black spots.

Irradiations were carried out in 75 ml and 150 ml quartz immersion well reactors fitted with 6- or 125-watt mercury vapour lamps as supplied by Photochemical Reactors Ltd, Reading, UK. Oxygen free solvent for the irradiation experiments was simply obtained by passing a vigorous stream of nitrogen gas through a sintered glass tube into the solvent for 15 min at rt. Experiments were conducted with gentle stirring of the reaction solution under an atmosphere of nitrogen and with cold-water cooling of the lamp and vessel contents throughout.

4.1.1. 2-Methylphenyl 2-propenyl carbonate 12. Following the procedure of Larock and Lee[9] a solution of triethylamine (6.44 ml, 46.2 mmol) in ether (20 ml) was added dropwise over 45 min to an ice-cold solution of 2-methylphenol **11** (5.00 g, 46.6 mmol) and triphosgene (4.59 g, 15.5 mmol) in ether (50 ml) to form a dense white suspension. More ether (50 ml) was added to aid stirring, followed by triethylamine (6.44 ml, 46.2 mmol) in one portion. A solution of 2-propen-1-ol (3.14 ml, 46.2 mmol) in ether (20 ml) was added dropwise over 20 min to the ice-cold suspension, which was then slowly allowed to warm to rt by stirring overnight. The dense suspension was filtered and the filtrate was concentrated in vacuo to afford an orange oil (8.17 g). Distillation afforded the pure product **12** (5.53 g, 62%) as a colourless liquid (bp 90–94 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.26 (4H, m, Ar-*H*), 5.94–6.07 (1H, m, $(CH_2)CH{=}C$), 5.32–5.46 (2H, m, $=CH_2$), 4.74 (2H, d, J=5.8 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 149.6, 131.2, 131.1, 130.0, 127.0, 126.3, 121.4, 119.4, 69.1, 15.9; IR (film) 3085, 3029, 2985, 2954, 1762, 1720, 1649, 1585, 1492, 1461 cm^{-1}; MS (EI) *m/z* 192 (2, M^+), 148 (23), 133 (29), 107 (25), 91 (20), 77 (23), 41 (100). Sample decomposed prior to accurate mass measurement.

4.1.2. [(2-Propenyloxy)methoxy]benzene 18a. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.834 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.29 g, 30 mmol) and 2-propen-1-ol (2.0 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 4 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a colourless liquid (4.94 g). Distillation afforded the pure product **18a** (3.72 g, 77%) as a colourless liquid (bp 52–54 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.32 (2H, m, Ar-*H*), 6.98–7.07 (3H, m, Ar-*H*), 5.85–5.98 (1H, m, $(CH_2)CH{=}$), 5.19–5.34 (2H, m, $=CH_2$), 5.25 (2H, s, OCH_2O), 4.21 (2H, d, J=5.5 Hz, OCH_2C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 133.8, 129.4, 121.8, 117.6, 116.2, 92.4, 69.1; IR (film) 3074, 3042, 3020, 2958, 2896, 1648, 1598, 1589 cm^{-1}; MS (EI) *m/z* 164 (30, M^+), 134 (69), 119 (25), 107 (25), 94 (33), 77 (43), 65 (21), 41 (100); HRMS (ESI) *m/z* calcd for $C_{10}H_{12}NaO_2$ ($[M+Na]^+$) 187.0730, found 187.0733.

4.1.3. [[(2-Methyl-2-propenyl)oxy]methoxy]benzene 18b. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.840 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.30 g, 30 mmol) and 2-methyl-2-propen-1-ol (2.52 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a colourless liquid (6.11 g). Distillation afforded the pure product **18b** (3.79 g, 71%) as a colourless liquid (bp 65–67 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.32 (2H, m, Ar-*H*), 6.98–7.08 (3H, m, Ar-*H*), 5.24 (2H, s, OCH_2O), 5.00 (1H, s, $=C(H)H$), 4.91 (1H, s, $=C(H)H$), 4.10 (2H, s, OCH_2C), 1.73 (3H, s, *Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 141.3, 129.4, 121.8, 116.2, 112.7, 92.3, 72.0, 19.5; IR (film) 3075, 3042, 3041, 2973, 2946, 2909, 1659, 1599, 1589 cm^{-1}; MS (EI) *m/z* 178 (12, M^+), 148 (22), 133 (58), 94 (31), 77 (27), 55 (100); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}NaO_2$ ($[M+Na]^+$) 201.0886, found 210.0886.

4.1.4. [(2-Butenyloxy)methoxy]benzene 18c. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.830 g, 3.0 mmol) were added to a solution of (chloromethoxy)benzene[8] **16** (4.32 g, 30 mmol) and 2-buten-1-ol (2.55 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 4 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.01 g). Distillation afforded **18c** (3.86 g, 72%) as a colourless liquid (bp 70–74 °C at 1 mm Hg), which was a 4:1 mixture of (*E*)/(*Z*) alkenes.

^{1}H NMR (300 MHz, $CDCl_3$) δ [(*E*)-major isomer] 7.25–7.32 (2H, m, Ar-*H*), 6.97–7.08 (3H, m, Ar-*H*), 5.66–5.81

(1H, m, =C*H*(Me)), 5.51–5.62 (1H, m, –(H_2C)*H*C=), 5.23 (2H, s, OCH_2O), 4.13 (2H, d, *J*=6.2 Hz, OCH_2C), 1.71 (3H, d, *J*=6.2 Hz, =C(H)*Me*); δ [(*Z*)-minor isomer] 7.25–7.32 (2H, m, Ar-*H*), 6.97–7.08 (3H, m, Ar-*H*), 5.66–5.81 (1H, m, =C*H*(Me)), 5.51–5.62 (1H, m, –(H_2C)*H*C=), 5.24 (2H, s, OCH_2O), 4.27 (2H, d, *J*=6.7 Hz, OCH_2C), 1.66 (3H, d, *J*=6.7 Hz, =C(H)*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) [(*E*)/(*Z*) mixture ~4:1] δ [(*E*)-major isomer] 157.3, 130.6, 129.4, 126.5, 121.7, 116.2, 92.1, 68.8, 17.8; δ [(*Z*)-minor isomer] 157.3, 129.4, 129.0, 125.7, 121.7, 116.2, 92.2, 63.3, 13.1; IR (film) 3064, 3027, 2963, 2943, 2916, 2859, 1674, 1599 cm^{-1}; MS (EI) *m/z* 178 (36, M^+), 148 (60), 107 (54), 94 (94); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}NaO_2$ ([M+Na]$^+$) 201.0886, found 210.0886.

4.1.5. 1-Methyl-2-[(2-propenyloxy)methoxy]benzene 18d. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.832 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-propen-1-ol (2.0 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 75 min and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.59 g). Distillation afforded the pure product **18d** (4.10 g, 79%) as a colourless liquid (bp 62–66 °C at 1 mm Hg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.16 (3H, m, Ar-*H*), 6.89–6.93 (1H, m, Ar-*H*), 5.86–5.99 (1H, m, (CH_2)C*H*=), 5.27 (2H, s, OCH_2O), 5.26 (2H, m, =CH_2), 4.21 (2H, d, *J*=5.6 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.9, 130.7, 127.3, 126.8, 121.5, 117.5, 113.9, 92.4, 69.1, 16.3; IR (film) 3080, 3024, 2951, 2908, 1648, 1602, 1591, 1495, 1463 cm^{-1}; MS (EI) *m/z* 178 (41, M^+), 148 (57), 133 (32), 107 (42), 91 (35), 77 (27), 41 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{14}O_2$ (M^+) 178.0993, found 178.1007.

4.1.6. 1-Methyl-2-[[(2-methyl-2-propenyl)oxy]methoxy]-benzene 18e. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.836 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-methyl-2-propen-1-ol (2.53 ml, 30 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (8.16 g). Distillation afforded the pure product **18e** (4.97 g, 86%) as a colourless liquid (bp 74–76 °C at 1 mm Hg).

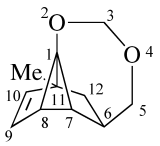
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.15 (3H, m, Ar-*H*), 6.89–6.92 (1H, m, Ar-*H*), 5.26 (2H, s, OCH_2O), 5.00 (1H, s, =C(H)*H*), 4.91 (1H, s, =C(*H*)H), 4.11 (2H, s, OCH_2C), 2.24 (3H, s, Ar-*Me*), 1.73 (3H, s, *Me*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 141.5, 130.7, 127.3, 126.8, 121.5, 113.9, 112.6, 92.5, 72.1, 19.5, 16.3; IR (film) 3077, 3026, 2973, 2948, 2915, 2862, 1656, 1603, 1591, 1495, 1461 cm^{-1}; MS (EI) *m/z* 192 (52, M^+), 162 (80), 147 (100), 121 (43), 107 (79), 91 (67), 79 (83), 55 (37), 41 (54); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1143.

4.1.7. 1-[(2-Butenyloxy)methoxy]-2-methylbenzene 18f. Fifty percent aqueous sodium hydroxide (60 ml) and tetrabutylammonium chloride (0.835 g, 3.0 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (4.70 g, 30 mmol) and 2-buten-1-ol (2.5 ml, 29 mmol) in benzene (60 ml). The resulting two-phase mixture was stirred vigorously at rt for 1 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a yellow liquid (6.42 g). Distillation afforded **18f** (4.37 g, 78%) as a colourless liquid (bp 64–74 °C at 1 mm Hg), which was a 4:1 mixture of (*E*)/(*Z*) alkenes.

^{1}H NMR (400 MHz, $CDCl_3$) δ [(*E*)-major isomer] 7.12–7.15 (2H, Ar-*H*), 7.05–7.09 (1H, m, Ar-*H*), 6.88–6.92 (1H, m, Ar-*H*), 5.67–5.79 (1H, m, =C*H*(Me)), 5.53–5.62 (1H, m, –(H_2C)*H*C=), 5.25 (2H, s, OCH_2O), 4.13 (2H, d, *J*=6.4 Hz, OCH_2C), 2.24 (3H, s, Ar-*Me*), 1.71 (3H, d, *J*=6.4 Hz, =C(H)*Me*); δ [(*Z*)-minor isomer] 7.12–7.15 (2H, m, Ar-*H*), 7.05–7.09 (1H, m, Ar-*H*), 6.88–6.92 (1H, m, Ar-*H*), 5.67–5.79 (1H, m, =C*H*(Me)), 5.53–5.62 (1H, m, –(H_2C)*H*C=), 5.26 (2H, s, OCH_2O), 4.27 (2H, d, *J*=6.9 Hz, =CH(Me)), 2.25 (3H, s, Ar-*Me*), 1.66 (3H, d, *J*=6.9 Hz, =C(H)*Me*); ^{13}C NMR (75 MHz, $CDCl_3$) δ [(*E*)-major isomer] 155.4, 130.7, 130.4, 127.3, 126.8, 126.6, 121.4, 113.8, 92.1, 68.9, 17.8, 16.3; δ [(*Z*)-minor isomer] 155.4, 130.7, 129.0, 127.3, 126.8, 125.8, 121.4, 113.8, 92.1, 63.2, 16.3, 13.1; IR (film) 3024, 2946, 2917, 2859, 1602, 1591, 1495, 1463 cm^{-1}; MS (EI) *m/z* 192 (12, M^+), 162 (24), 108 (100), 55 (84), 39 (96); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1163.

4.1.8. 2,4-Dioxa-11-methyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]-dodec-9-ene 19d. Under an atmosphere of nitrogen, a solution of **18d** (1.34 g, 7.5 mmol) in oxygen free cyclohexane (75 ml) was irradiated with a 6-watt low-pressure mercury vapour lamp for 7 days using a 75 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (1.30 g). The oil was purified by flash chromatography on silica (65 g) eluted with increasing concentrations of dichloromethane in petrol (30, 50 and 100%). Five components were isolated: (in order of increasing polarity) unchanged starting material (0.78 g, 58%); possible intermolecular by-product (0.013 g, 1%); impure uncharacterised by-product (0.008 g, 0.6%); impure *meta*-addition product (0.324 g, 24%); and possible unstable *ortho*-addition product (0.069 g, 5%).

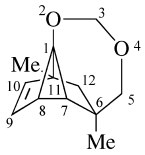
The impure *meta*-addition product was purified further by flash chromatography on silver nitrate impregnated silica[17] (30 g) and eluted with methanol/dichloromethane/petrol (5:20:75) to afford another uncharacterised by-product (0.049 g, 4%) and the pure *meta*-addition product **19d** as a pale yellow oil (0.178 g, 13%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, d, *J*=5.6 Hz, H-10), 5.46 (1H, dd, *J*=5.6, 2.6 Hz, H-9), 5.31 (1H, d,

J=6.1 Hz, H-3$_{endo}$), 4.68 (1H, d, J=6.1 Hz, H-3$_{exo}$), 3.80 (1H, dd, J=11.2, 1.9 Hz, H-5$_{endo}$), 3.42 (1H, d, J=11.2 Hz, H-5$_{exo}$), 2.87 (1H, d, J=7.0 Hz, H-6), 2.73 (1H, ddd, J=8.2, 2.6, 1.4 Hz, H-8), 1.87 (1H, dd, J=12.7, 7.0 Hz, H-12$_{endo}$), 1.59 (1H, d, J=2.7 Hz, H-12$_{exo}$), 1.47 (1H, d, J=8.2 Hz, H-7), 1.30 (3H, s, 11-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 121.3, 98.7, 85.3, 83.0, 57.9, 48.1, 46.9, 42.4, 37.8, 17.6; IR (film) 3059, 3039, 2949, 2927, 2869, 1604, 1456, 1449 cm^{-1}; MS (EI) m/z 178 (18, M$^+$), 97 (28), 81 (49), 69 (100), 57 (56), 41 (64). Sample decomposed prior to accurate mass measurement.

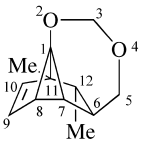
4.1.9. 2,4-Dioxa-6$_{endo}$,11-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 19e. Under an atmosphere of nitrogen, a solution of **18e** (1.45 g, 7.5 mmol) in oxygen free cyclohexane (75 ml) was irradiated with a 6-watt low-pressure mercury vapour lamp for 16 days using a 75 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (1.37 g). The oil was purified by flash chromatography (dichloromethane/petrol 1:1) then neat dichloromethane. Four components were isolated: (in order of increasing polarity) unchanged starting material (0.882 g, 61%); possible intermolecular by-product (0.013 g, 0.9%); possible *ortho*-addition product (0.012 g, 0.8%); and pure *meta*-addition product **19e** as a pale yellow oil (0.250 g, 17%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (1H, d, J=5.6 Hz, H-10), 5.49 (1H, dd, J=5.6, 2.6 Hz, H-9), 5.29 (1H, d, J=5.9 Hz, H-3$_{endo}$), 4.69 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.53 (1H, d, J=11.0 Hz, H-5$_{endo}$), 3.23 (1H, d, J=11.0 Hz, H-5$_{exo}$), 2.66 (1H, ddd, J=8.2, 2.6, 1.3 Hz, H-8), 1.79 (1H, d, J=12.6 Hz, H-12$_{exo}$), 1.60 (1H, dd, J=12.6, 1.3 Hz, H-12$_{endo}$), 1.29 (3H, s, 11-Me), 1.28 (1H, m, H-7), 1.18 (3H, s, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 121.4, 98.1, 88.7, 85.2, 58.3, 53.7, 49.5, 47.7, 40.6, 19.0, 17.9; IR (ATR) 2927, 2866, 1605 cm^{-1}; MS (EI) m/z 192 (1, M$^+$), 132 (100), 117 (84), 91 (31). Sample decomposed prior to accurate mass measurement.

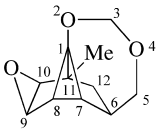
4.1.10. 2,4-Dioxa-11,12$_{endo}$-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 19f. Under an atmosphere of nitrogen, a solution of **18f** (2.88 g, 15.0 mmol) in oxygen free cyclohexane (150 ml) was irradiated with a 125-watt low-pressure mercury vapour lamp for 13 days using a 150 ml quartz immersion-well photo reactor. The solution was removed from the reactor and concentrated in vacuo to leave a pale yellow oil (2.72 g). The oil was purified by flash chromatography using increasing concentrations of dichloromethane with petrol (30, 50 and 100%). Four components were isolated: (in order of increasing polarity) unchanged starting material (1.31 g, 45%); impure uncharacterised by-product (0.014 g, 0.5%); impure *meta*-addition product (0.422 g, 15%); and possible unstable *ortho*-addition product (0.104 g, 4%).

The impure *meta*-addition product was purified further by flash chromatography on silver nitrate impregnated silica[17] (42 g) eluted with methanol/dichloromethane/petrol (5:20:175) to afford the still impure *meta*-addition product (0.343 g, 12%). Another purification by flash chromatography on silica (100 g) eluted with 7.5% 2-methoxy-2-methylpropane in petrol gave an uncharacterised by-product (0.063 g, 2%) and the pure *meta*-addition product **19f** (0.194 g, 7%) as a pale yellow low-melting solid mp <20 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, dd, J=5.5, 2.4 Hz, H-9), 5.52 (1H, d, J=5.5 Hz, H-10), 5.28 (1H, d, J=6.0 Hz, H-3$_{endo}$), 4.65 (1H, d, J=6.0 Hz, H-3$_{exo}$), 3.89 (1H, dd, J=11.3, 1.8 Hz, H-5$_{endo}$), 3.42 (1H, d, J=11.3 Hz, H-5$_{exo}$), 2.73 (1H, ddd, J=8.2, 2.4, 1.5 Hz, H-8), 2.43 (1H, m, H-6), 2.06 (1H, q, J=7.4 Hz, H-12), 1.34 (1H, d, J=8.2 Hz, H-7), 1.21 (3H, s, 11-Me), 0.85 (3H, d, J=7.4 Hz, 12-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 122.6, 98.1, 87.5, 82.2, 60.6, 54.7, 48.9, 47.5, 35.2, 17.4, 17.1; IR (ATR) 3062, 2957, 2915, 2861, 1609 cm^{-1}; MS (EI) m/z 192 (1, M$^+$), 162 (27), 147 (21), 119 (44), 108 (100), 91 (47), 77 (23), 55 (47); HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_2$ ([M+Na]$^+$) 215.1043, found 215.1035.

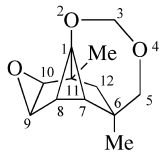
4.1.11. 2,4-Dioxa-11-methyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]-dodec-9-ene oxide 20d. A 0.1 M solution of ice cold dimethyldioxirane[9] in acetone (27 ml, 2.7 mmol) was added to the *meta* photoadduct **19d** (53 mg, 0.30 mmol) and allowed to warm to rt overnight. The remaining solvent was removed in vacuo and any residual water was removed by addition of ethyl acetate (20 ml), drying ($MgSO_4$), filtering and concentrating in vacuo to give the product **20d** (57 mg, 100%) as a pale yellow crystalline solid mp 79–80 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (1H, dd, J=5.9, 0.5 Hz, H-3$_{endo}$), 4.47 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.92 (1H, dd, J=11.4, 1.8 Hz, H-5$_{endo}$), 3.45 (1H, br d, J=11.3 Hz, H-5$_{exo}$), 3.35 (1H, dd, J=3.3, 1.3 Hz, H-9), 2.95 (1H, dd, J=3.3, 1.3 Hz, H-10), 2.88 (1H, ddd, J=8.9, 1.3, 1.2 Hz, H-8), 2.65 (1H, br d, J=6.7 Hz, H-6), 1.65 (1H, ddd, J=13.4, 6.7, 1.2 Hz, H-12$_{endo}$), 1.57 (1H, br d, J=13.4 Hz, H-12$_{exo}$), 1.33 (3H, s, 11-Me), 1.31 (1H, dd, J=8.9, 1.8 Hz, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.1, 81.6, 74.3, 62.5, 53.7, 52.2, 49.3, 42.0, 40.2, 35.2, 16.0; IR (ATR) 2981, 2928, 2869, 1485, 1457, 1383 cm^{-1}; MS (EI) m/z 194 (25, M$^+$), 169 (35); HRMS (ESI) m/z calcd $C_{22}H_{28}Na\ O_6$ ([2M+Na]$^+$) 411.1778, found 411.1774.

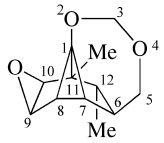
4.1.12. 2,4-Dioxa-6$_{endo}$,11-dimethyl-tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene oxide 20e. An ice-cold solution of the *meta* photoadduct **19e** (0.100 g, 0.52 mmol) in dichloromethane (10 ml) was treated with small aliquots of a ~0.1 M solution of dimethyldioxirane[9] in acetone, over 1 h,

until TLC indicated that all of the starting material had been consumed (total volume added: 9.3 ml, ~0.93 mmol). After stirring at ice temperature for 1 h, the solution was concentrated in vacuo to give the product **20e** (0.108 g, 100%) as a colourless waxy solid mp 79–80 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, d, J=5.9 Hz, H-3$_{endo}$), 4.49 (1H, d, J=5.9 Hz, H-3$_{exo}$), 3.68 (1H, d, J=11.2 Hz, H-5$_{endo}$), 3.37 (1H, dd, J=3.3, 1.3 Hz, H-9), 3.28 (1H, dd, J=11.2, 1.1 Hz, H-5$_{exo}$), 2.96 (1H, dd, J=3.3, 1.2 Hz, H-10), 2.80 (1H, ddd, J=8.8, 1.3, 1.2 Hz, H-8), 1.73 (1H, dd, J=13.3, 1.2 Hz, H-12$_{exo}$), 1.37 (1H, dd, J=13.3, 1.1 Hz, H-12$_{endo}$), 1.31 (3H, s, 11-Me), 1.13 (1H, dd, J=8.8, 1.2 Hz, H-7), 1.06 (3H, s, 6-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.5, 87.2, 74.5, 62.7, 54.0, 52.2, 49.0, 48.4, 47.4, 38.7, 18.6, 16.3; IR (ATR) 2999, 2956, 2932, 2861 cm^{-1}; MS (EI) m/z 208 (5, M$^+$), 178 (17), 133 (22), 119 (72), 105 (100), 97 (24), 91 (89), 83 (38), 65 (20), 55 (25), 41 (36). Sample decomposed prior to accurate mass measurement.

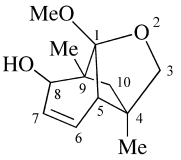
4.1.13. 2,4-Dioxa-11,12$_{endo}$-dimethyl-tetracyclo-[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene oxide 20f. A 0.1 M solution of ice cold dimethyldioxirane[9] in acetone (27 ml, 2.7 mmol) was added to the *meta* photoadduct **19f** (62 mg, 0.32 mmol) and allowed to warm to rt overnight. The remaining solvent was removed in vacuo and any residual water was removed by addition of ethyl acetate (20 ml), drying ($MgSO_4$), filtering and concentrating in vacuo to give the product **20f** (67 mg, 100%) as a pale yellow crystalline solid mp 81–82 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (1H, dd, J=6.0, 0.5 Hz, H-3$_{endo}$), 4.47 (1H, d, J=6.0 Hz, H-3$_{exo}$), 3.98 (1H, dd, J=11.3, 1.9 Hz, H-5$_{endo}$), 3.43 (1H, dd, J=3.2, 1.4 Hz, H-9), 3.39 (1H, ddd, J=11.3, 0.8, 0.8 Hz, H-5$_{exo}$), 3.14 (1H, dd, J=3.2, 1.3 Hz, H-10), 2.84 (1H, ddd, J=8.8, 1.4, 1.4 Hz, H-8), 2.33 (1H, m, H-6), 2.10 (1H, br q, J=7.7 Hz, H-12$_{exo}$), 1.27 (3H, s, 11-Me), 1.22 (1H, br d, J=8.9 Hz, H-7), 1.02 (1H, d, J=7.7 Hz, 12$_{endo}$-Me); ^{13}C NMR (125 MHz) δ 98.7, 81.2, 76.0, 59.7, 55.0, 53.2, 52.0, 50.4, 46.9, 34.9, 15.3, 15.0; HRMS (ESI) m/z calcd $C_{12}H_{16}NaO_3$ ([M+Na]$^+$) 231.0992, found 231.0983. Structure also confirmed by single crystal X-ray analysis.[18]

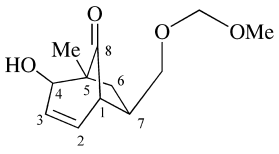
4.1.14. 2-Oxa-8$_{exo}$-hydroxy-1-methoxy-4,9-dimethyl-tricyclo[4.4.0.0^{4,5}.0.^{9,10}]dec-6-ene 23e. A single drop of 2.0 M aqueous hydrochloric acid was added to an ice-cold solution of epoxide **20e** (60 mg, 0.29 mmol) in acetone (12 ml). The solution was stirred for 1 h and allowed to warm to rt, after which flash silica (0.75 g) was added and the resulting mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica (6 g) eluted with 3% methanol in dichloromethane to afford the major product as a pale yellow oil (31 mg, 55%). ^{1}H NMR spectrum indicated that this was a mixture of ketone **21e** and hemiacetal **22e**.

This mixture (31 mg, 0.16 mmol) was dissolved in a 0.01 M solution of HCl in anhydrous methanol (2 ml) and stirred at rt for 4 days. Flash silica (0.25 g) was then added and the mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica (3 g) eluted with 2% methanol in dichloromethane to afford the product **23e** (10 mg, 30%) as a white crystalline solid mp 71.5–73.5 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, dd, J=9.5, 4.3 Hz, H-7), 5.72 (1H, dd, J=9.5, 6.3 Hz, H-6), 3.66 (2H, m, H-3), 3.53 (1H, dd, J=11.5, 4.3 Hz, H-8), 3.37 (3H, s, 1-OMe), 2.88 (1H, d, J=11.5 Hz, 8-OH), 2.42 (1H, dd, J=6.3, 0.9 Hz, H-5), 1.35 (1H, dd, J=12.7, 0.9 Hz, H-10$_{exo}$), 1.28 (1H, dd, J=12.7, 2.7 Hz, H-10$_{endo}$), 1.20 (3H, s, 9-Me), 0.98 (3H, s, 4-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 124.3, 111.6, 77.9, 76.6, 52.3, 47.7, 46.5, 45.8, 45.5, 16.0, 15.5; IR (ATR) 3536, 3034, 2971, 2960, 2932, 2871, 1645 cm^{-1}; MS (EI) m/z 210 (2, M$^+$), 121 (25), 110 (26), 105 (29), 95 (100); HRMS (ESI) m/z calcd $C_{12}H_{18}NaO_3$ ([M+Na]$^+$) 233.1148, found 233.1156.

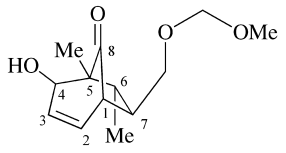
4.1.15. 4$_{exo}$-Hydroxy-7$_{exo}$-methoxymethoxymethyl-5-methyl-bicyclo[3.2.1]oct-2-en-8 one 25d. Epoxide **20d** (17 mg, 0.087 mmol) was stirred in a 0.01 M solution of HCl in methanol (5 ml) for 1 h. The residue was isolated by concentration in vacuo and then passed through a small plug of silica eluting with petrol/ethyl acetate (1:2) to yield the product **25d** as a yellow oil (15 mg, 76%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (1H, dd, J=8.9, 7.1 Hz, H-2), 5.76 (1H, dd, J=9.0, 3.8 Hz, H-3), 4.57 (2H, s, OCH_2OMe), 4.30 (1H, m, H-4), 3.42 (1H, dd, J=9.6, 5.0 Hz, 7-CH(H)O), 3.34 (3H, s, OMe), 3.32 (1H, dd, J=9.6, 6.8 Hz, 7-CH(H)O), 2.70 (1H, dd, J=11.0, 7.0 Hz, H-1), 2.35 (1H, m, H-7), 2.08 (1H, dd, J=14.0, 9.5 Hz, H-6$_{endo}$), 1.63 (1H, dd, J=14.0, 2.0 Hz, H-6$_{exo}$), 1.56 (1H, br s, 4-OH), 1.19 (3H, s, 5-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 135.0, 128.4, 96.5, 85.0, 70.4, 55.4, 50.6, 39.3, 34.4, 30.9, 15.8; IR (film) 3430, 2930, 1749, 1635 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{18}O_4$ (M$^+$) 226.1205, found 226.1223.

4.1.16. 4$_{exo}$-Hydroxy-7$_{exo}$-methoxymethoxymethyl-5,6$_{endo}$-dimethyl-bicyclo[3.2.1]oct-2-en-8-one 25f. Epoxide

20f (11 mg, 0.053 mmol) was stirred in a 0.01 M solution of HCl in methanol (5 ml) for 1 h. The residue was isolated by concentration in vacuo and then passed through a small plug of silica eluting with petrol/ethyl acetate (1:2) to yield the product **25f** as a yellow oil (10 mg, 78%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (1H, dd, J=9.0, 7.2 Hz, H-2), 5.78 (1H, dd, J=9.0, 3.9 Hz, H-3), 4.57 (2H, s, OCH_2OMe), 4.47 (1H, m, H-4), 3.41 (1H, dd, J=9.6, 5.0 Hz, 7-CH(H)O), 3.35 (3H, s, OMe), 3.27 (1H, dd, J=9.6, 7.0 Hz, 7-CH(H)O), 2.63 (1H, d, J=7.2 Hz, H-1), 1.91 (1H, ddd, J=7.0, 5.1, 4.2 Hz, H-7), 1.82 (1H, m, H-6$_{exo}$), 1.38 (1H, br d, J=10 Hz, 4-OH), 1.20 (3H, s, 5-Me), 1.82 (1H, d, J=11.0 Hz, 6$_{exo}$-Me); ^{13}C NMR (1 MHz, $CDCl_3$) δ 216.3, 136.2, 128.7, 96.5, 87.2, 70.1, 55.4, 54.0, 50.1, 47.6, 40.0, 16.1, 15.2; IR (film) 3418, 2962, 2929, 1747, 1640 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{20}O_4$ (M^+) 240.1362, found 240.1379.

4.1.17. 1-Methyl-2-[[(2-methyl-1-cyclopenten-1-yl)methoxy]methoxy]benzene 27. Fifty percent aqueous sodium hydroxide (33 ml) and tetrabutylammonium chloride (0.460 g, 1.7 mmol) were added to a solution of 1-(chloromethoxy)-2-methylbenzene[8] **17** (2.58 g, 16 mmol) and 2-methyl-1-cyclopentene-1-methanol[10] **26** (1.85 g, 16 mmol) in benzene (33 ml). The resulting two-phase mixture was stirred vigorously at rt for 5 h and then separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow liquid (5.10 g). Distillation afforded a colourless liquid (bp 94–96 °C at 1 mm Hg) (2.62 g), which was still impure. Further purification by flash chromatography on silica (130 g) eluted with 10% dichloromethane in petrol afforded the product **27** as a colourless liquid (2.04 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.15 (2H, m, Ar-H), 7.07–7.09 (1H, m, Ar-H), 6.88–6.92 (1H, m, Ar-H), 5.22 (2H, s, OCH_2O), 4.23 (2H, s, OCH_2C), 2.31–2.39 (4H, m), 2.25 (3H, s, Ar-Me), 1.75–1.83 (2H, m), 1.69 (3H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 138.3, 130.9, 130.7, 127.2, 126.8, 121.3, 113.9, 92.0, 64.0, 38.8, 34.7, 21.6, 16.3, 13.9; IR (ATR) 2949, 2843, 1603, 1591, 1494 cm^{-1}; MS (EI) m/z 232 (10, M^+), 202 (18), 163 (7), 141 (55), 121 (70); HRMS (EI) m/z calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1478.

4.1.18. Chlorodimethylphenoxysilane 33. To a stirred solution of phenol (11.75 g, 125 mmol) in dry tetrahydrofuran (90 ml) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of n-butyllithium (50 ml, 2.5 M in hexanes). After addition, the phenoxide solution was allowed to warm to rt and added dropwise to a stirred solution of freshly distilled dichlorodimethylsilane (113.7 ml, 938 mmol) in dry tetrahydrofuran (100 ml) at −78 °C. The reaction mixture was left to stir overnight allowing it to warm to rt whereby it was concentrated in vacuo, washed with petrol and filtered to remove the white salts. The orange solution was then concentrated in vacuo and distilled under high vacuum to yield **33** a colourless oil (18.85 g, 81%)

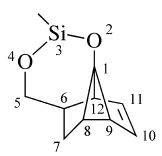
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, dd, J=7.5, 8.5 Hz, Ar-H), 7.07 (1H, t, J=7.4 Hz, Ar-H), 7.00 (2H, d, J=8.5 Hz, Ar-H), 0.63 (6H, s, Si–Me$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 129.6, 122.7, 120.0, 2.4; IR (film) 3065, 3041, 2970, 1596 cm^{-1}; MS (EI) m/z 186 (70%, $[M]^+$), 171 (78), 151 (50), 93 (98), 77 (100); HRMS (EI) m/z calcd for $C_8H_{11}OSiCl$ (M^+) 186.0268, found 186.0284.

4.1.19. Allyloxydimethylphenoxysilane 35. To a stirred solution of allyl alcohol (2.2 ml, 32.2 mmol) in dry tetrahydrofuran (60 ml) at 0 °C was added a solution of n-butyllithium (12.9 ml, 2.5 M, 32.2 mmol) dropwise. This was then added dropwise to a solution of chlorodimethylphenoxysilane **33** (6.00 g, 32.2 mmol) in dry tetrahydrofuran (125 ml) and allowed to stir at rt for 2 days. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (50 ml), filtered and concentrated in vacuo leaving a yellow liquid, which was distilled under high vacuum to give **35** as a colourless oil (3.75 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, m, Ar-H), 6.99 (3H, m, Ar-H), 5.97 (1H, ddt, J=17.1, 10.4, 4.9 Hz, (H_2C)HC=), 5.31 (1H, dt, J=17.1, 1.7 Hz, =C(H)H), 5.14 (1H, dt, J=10.4, 1.5 Hz, =C(H)H), 4.34 (2H, dd, J=4.9, 1.6 Hz, OCH_2), 0.30 (6H, s, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 136.3, 129.4, 121.7, 119.7, 114.9, 63.6, −2.8; IR (film) 2965, 1597 cm^{-1}; MS (EI) m/z 208 (100, $[M^+]$), 193 (60), 175 (61), 151 (94); HRMS (EI) m/z calcd for $C_{11}H_{16}O_2Si$ (M^+) 208.0919, found 208.0899.

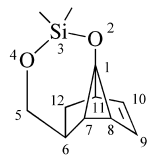
4.1.20. 2,4-dioxa-3-(dimethylsilyl)tetracyclo-[6.4.0.0^{1,9}.0^{6,12}]dodec-10-ene 36 and 2,4-dioxa-3-(dimethylsilyl)tetracyclo[6.4.0.0^{1,8}.0^{6,7}]dodec-9-ene 37. A stirred solution of allyloxydimethylphenoxysilane **35** (650 mg) in cyclohexane (180 ml) was irradiated for 19 h with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solvent was removed in vacuo and the residue was subjected to column chromatography (silica gel, petrol/ethyl acetate 20:1) to yield a mixture of **36** and **37** in a 1:2 ratio as a colourless oil (123 mg, 19%).

Minor isomer **36**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (1H, dd, J=5.8, 2.5 Hz, H-11), 5.51 (1H, dddd, J=5.8, 2.7, 1.5, 0.9 Hz, H-10), 4.03 (1H, ddd, J=11.5, 1.7, 0.9 Hz, H-5), 3.96 (1H, dd, J=11.5, 2.3 Hz, H-5), 2.97 (1H, dd, J=2.5, 2.5 Hz, H-12), 2.37 (1H, ddddd, J=8.0, 1.1, 1.1, 1.1, 1.1 Hz, H-9), 1.97 (1H, ddd, J=13.6, 6.5, 2.3 Hz, H-7), 2.11 (1H, m, H-6), 1.74 (1H, ddd, J=8.1, 6.5, 1.7 Hz, H-8), 1.69 (1H, dddd, J=13.7, 5.9, 1.9, 0.9 Hz, H-7), 0.27 (3H, s, Si–Me), 0.18 (3H, s, Si–Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.4, 127.5, 83.8, 70.5, 59.7, 52.3, 38.8, 33.4, 27.3, −1.5.

Major isomer **37**

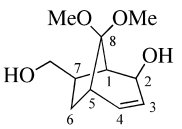


^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (1H, dddd, J=5.8, 2.8, 0.8, 0.8 Hz, H-10), 5.53 (1H, dd, J=5.8, 2.5 Hz, H-9), 3.82 (1H, dd, J=10.4, 1.1 Hz, H-5), 3.72 (1H, dd, J=10.4, 2.1 Hz, H-5), 3.18 (1H, dddd, J=8.3, 2.8, 1.5, 0.9 Hz, H-11), 2.79 (1H, dddd, J=7.7, 2.1, 2.1, 1.1 Hz, H-6), 2.44 (1H, dd, J=8.4, 2.5 Hz, H-8), 2.22 (1H, ddd, J=12.9, 8.3, 2.1 Hz, H-12$_{exo}$), 1.56 (1H, ddd, J=12.9, 7.7, 1.5 Hz, H-12$_{endo}$), 1.44 (1H, br d, J=8.4 Hz, H-7), 0.26 (3H, s, Si–Me), 0.17 (3H, s, Si–Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 123.9, 83.6, 73.9, 56.6, 46.4, 41.7, 40.7, 35.5, −0.5.

For the mixture: MS (EI) m/z 208 (98, [M$^+$]), 193 (71), 176 (76), 151 (89), 75 (100); HRMS (EI) m/z calcd for $C_{11}H_{16}O_2Si$ (M$^+$) 208.0919, found 208.0901.

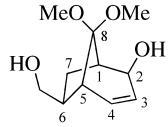
4.1.21. 7-Hydroxymethyl-8,8-dimethoxy-bicyclo-[3.2.1]oct-3-en-2-ol 38 and 6-hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol 39. A stirred solution of allyloxydimethylphenoxysilane 35 (1.00 g, 4.8 mmol) in cyclohexane (180 ml) was irradiated for 19 h with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solution was filtered and concentrated in vacuo, whereby the resultant oil was dissolved in CH_2Cl_2 (20 ml). With stirring, a solution of basewashed m-CPBA (4.8 mmol) in CH_2Cl_2 (10 ml) was added slowly at rt. After 2 h 2-methyl-2-butene (1.5 ml) was added and the solution was allowed to stir for a further 0.5 h, before adding a saturated solution of $NaHCO_3$.The organic phase was separated and washed with saturated brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The resultant oil was dissolved in a solution of PTSA (0.100 g) in methanol (20 ml) and stirred under an atmosphere of nitrogen for 3 days at rt. Ethyl acetate (20 ml) was added and the solution was concentrated in vacuo until approximately 5 ml remained, this process was repeated a further 3 times. After a further addition of ethyl acetate (20 ml) the organic material was washed with saturated $NaHCO_3$ solution, then saturated brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica chromatography (Et_2O/acetone 9:1) to yield 38 (80 mg, 8%) and 39 (80 mg, 8%) as colourless oils.

7-Hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol **38**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, dd, J=9.4, 6.8 Hz, H-4), 5.65 (1H, ddd, J=9.4, 3.9, 1.5 Hz, H-3), 3.92 (1H, m, H-2), 3.62 (1H, br d, J=11.5 Hz, 2-O*H*), 3.54 (1H, dd, J=10.3, 6.6 Hz, 7-C(*H*)H), 3.48 (1H, dd, J=10.3, 7.7 Hz, 7-C(H)*H*), 3.17 (3H, s, 8-OMe), 3.13 (3H, s, 8-OMe), 2.48 (1H, ddd, J=6.8, 2.0, 6.0 Hz, H-5), 2.38 (1H, m, H-1), 1.86 (1H, br s, CH_2O*H*), 1.73 (1H, m, H-7$_{endo}$), 1.64 (1H, dd, J=12.1, 9.0 Hz, H-6$_{exo}$), 1.47 (1H, ddd, J=12.1, 6.2, 6.0 Hz, H-6$_{endo}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 128.4, 109.2, 75.0, 65.9, 50.1, 48.0, 43.7, 40.9, 40.5, 32.0; IR (film) 3433, 2952 cm^{-1}; MS (EI) m/z 213 (1, [M−H]$^+$), 197 (4, [M−OH]$^+$), 183 (5), 101 (100); HRMS (EI) m/z calcd for $C_{11}H_{17}O_3$ ([M−OH]$^+$) 197.1178, found 197.1182.

6-Hydroxymethyl-8,8-dimethoxy-bicyclo[3.2.1]oct-3-en-2-ol **39**



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (1H, ddd, J=9.4, 7.1, 0.5 Hz, H-4), 5.65 (1H, ddd, J=9.4, 3.6, 1.4 Hz, H-3), 3.92 (1H, br d, J=9.9 Hz, H-2), 3.54 (2H, d, J=6.2 Hz, 7-CH_2O), 3.39 (1H, br d, J=10.6 Hz, 2-O*H*), 3.20 (3H, s, 8-OMe), 3.13 (3H, s, 8-OMe), 2.51 (1H, br s, O*H*), 2.50 (1H, dd, J=7.5, 1.6 Hz, H-1), 2.39 (1H, dd, J=7.1, 2.0 Hz, H-5), 2.08 (1H, m, H-6$_{endo}$), 1.58 (1H, ddd, J=13.8, 7.5, 5.3 Hz, H-7$_{exo}$), 1.45 (1H, dd, J=13.8, 9.7 Hz, H-7$_{endo}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 128.7, 109.7, 74.5, 65.9, 50.3, 47.5, 47.0, 43.2, 42.7, 26.1; IR (film) 3412, 2948 cm^{-1}; MS (EI) m/z 197 (9, [M−OH]$^+$), 183 (22), 149 (16), 131 (100); HRMS (EI) m/z calcd for ([M−OH]$^+$) 197.1178, found 197.1187.

4.1.22. 4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-en-1-ol 40. This preparation followed the procedure of McDougal et al.[15] for the monosilylation of symmetrical diols. To a stirred solution of NaH (4.54 g, 114 mmol, 60% dispersion in oil) in dry tetrahydrofuran (100 ml) was added dropwise *E*-but-2-ene-1,4-diol[16] (10.0 g, 114 mmol) in dry tetrahydrofuran (60 ml) at rt. This was stirred for 45 min after which *tert*butyldimethylsilylchloride (17.1 g, 114 mmol) in tetrahydrofuran (15 ml) was added in one portion and allowed to stir for a further 45 min. Ether (450 ml) was added and the solution washed with 10% K_2CO_3 (300 ml) and then brine. The aqueous layers were washed with Et_2O and the organic layers combined, dried ($MgSO_4$), filtered and concentrated in vacuo to leave a yellow liquid, which was subjected to silica chromatography (petrol/ethyl acetate 4:1) to yield **40** (20.4 g, 89%)

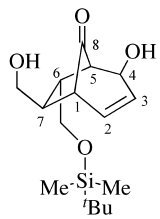
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (2H, m), 4.13 (4H, m), 1.62 (1H, brs, O*H*), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 128.9, 63.2, 63.1, 25.9, 18.4, −5.3; IR (film) 3367, 2955, 2930, 2857 cm^{-1}; MS (EI) m/z 171 (5, [M−CH_2OH]$^+$), 145 (63), 127 (41), 75 (100); HRMS (EI) m/z calcd for $C_9H_{19}OSi$ ([M−CH_2OH]$^+$) 171.1205, found 171.1206

4.1.23. {[4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-enyl-oxy]-dimethyl-silanyloxy}-benzene 41. To a stirred solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-but-2-en-1-ol **40** (7.44 g, 36.8 mmol) in dry tetrahydrofuran (60 ml) at 0 °C under an atmosphere of nitrogen was added dropwise a solution of *n*-butyllithium (14.7 ml, 2.5 M in hexanes). The solution had turned yellow and after stirring for a

further 1 h the solution was allowed to reach rt before it was added dropwise to a solution of chlorodimethylphenoxysilane **33** (6.87 g, 36.82 mmol) in dry tetrahydrofuran (90 ml) at −78 °C under an atmosphere of nitrogen. After addition the solution was allowed to warm to rt over a period of 14 h and then concentrated in vacuo, washed with petrol, filtered and again concentrated in vacuo. The brown oil was then distilled under high vacuum and the highest boiling fraction was further subjected to silica chromatography (petrol/CH_2Cl_2 1:1) to yield **41** (1.99 g, 15%).

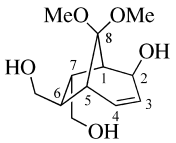
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (5H, m, Ar-H), 5.82 (2H, s, HC═CH), 4.33 (2H, s, OCH_2), 4.18 (2H, s, OCH_2), 0.93 (9H, s, SiC(*Me*)$_3$), 0.29 (6H, s, Si*Me*$_2$), 0.08 (6H, s, Si*Me*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 130.5, 129.5, 128.0, 121.7, 119.8, 63.1, 62.9, 25.9, 18.4, −2.6, −5.3; IR (film) 2956, 2929, 2857, 1597 cm^{-1}; MS (CI) *m*/*z* 370 (100, $[M+NH_4]^+$), 308 (22), 242 (16), 221 (16), 185 (11); HRMS (CI) *m*/*z* calcd for $C_{18}H_{36}NO_3Si_2$ ($[M+NH_4]^+$) 370.2234, found 370.2231.

4.1.24. 6-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxy-7-hydroxymethyl-bicyclo[3.2.1]oct-en-8-one 42. A stirred solution of **41** (520 mg, 1.48 mmol) in cyclohexane (180 ml) was irradiated for 4hrs with a 6 W low-pressure mercury vapour lamp in a quartz immersion-well photo reactor. The solvent was removed in vacuo, the crude material taken up in CH_2Cl_2 (5 ml) and then a solution of base-washed *m*-CPBA (2.5 mmol, 7.5 ml, 0.33 M) in CH_2Cl_2 was added. After 1 h 2-methyl-2-butene (0.3 ml, 2.83 mmol) was added to ensure removal of excess *m*-CPBA and the resultant solution was washed and extracted from $NaHCO_3$ solution, then brine and the organic phase dried ($MgSO_4$), filtered and concentrated in vacuo. The yellow oil was then dissolved in methanol (10 ml) and PPTS (0.05 g) added. This was allowed to stir for 4 days before ethyl acetate (30 ml) was added and the solution was partially concentrated in vacuo until 10 ml remained. Ethyl acetate (30 ml) was again added and the process repeated 2 more times. The solution was then washed with $NaHCO_3$, then brine and dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then subjected to silica chromatography (petrol/ethyl acetate 1:2) to provide **42** as a colourless oil (49 mg, 11%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, dd, *J* 8.9, 0.4 Hz, H-2), 5.81 (1H, ddd, *J* 9.0, 3.7, 1.0 Hz, H-3), 4.85 (1H, dd, *J* 3.4, 3.2 Hz, H-4), 3.82 (1H, dd, *J*=9.6, 7.6 Hz, 6$_{endo}$-C*H*(H)), 3.63 (1H, dd, *J*=9.4, 8.3 Hz, 6$_{endo}$-CH(*H*)), 3.48 (1H, dd, *J*=10.3, 6.3 Hz, 7$_{exo}$-C*H*(H)), 3.44 (1H, dd, *J*=10.6, 7.0 Hz, 7$_{exo}$-CH(*H*)), 2.73 (1H, br d, *J*=7.6 Hz, H-5), 2.55 (1H, dd, *J*=7.2, 1.2 Hz, H-1), 2.28 (1H, dddd, *J*=7.8, 7.8, 7.7, 4.3 Hz, H-6$_{exo}$), 1.96 (1H, ddd, *J*=6.6, 6.6, 4.5 Hz, H-7$_{endo}$), 0.90 (9H, s, H-11), 0.83 (6H, s, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 135.9, 128.6, 75.1, 65.2, 64.0, 54.0, 48.7, 45.4, 39.4, 25.6, 18.0, −5.2; IR (film) 3400, 2954, 2929, 2857, 1754, 1471 cm^{-1}; MS (CI) *m*/*z* 330 (4, $[M+NH_4]^+$), 298 (100); HRMS (CI) *m*/*z* calcd for $C_{16}H_{32}NSiO_4$ ($[M+NH_4]^+$) 330.2101, found 330.2101.

4.1.25. 6,7-Bis-hydroxymethyl-8,8-dimethoxy-bicyclo-[3.2.1]-oct-3-en-2-ol 43. A stirred solution of **42** (11 mg, 35 mmol) and PPTS (48 mg) in methanol (5 ml) was heated to reflux for 4 h. After cooling to rt, ethyl acetate (25 ml) was added and the solution was partially concentrated in vacuo until ca. 5 ml remained and a white solid formed. Ethyl acetate (10 ml) was added and the solution was washed with $NaHCO_3$ then brine and the organic layer was separated and dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was then subjected to silica chromatography (petrol/ethyl acetate 1:4) to yield **43** as a colourless oil (6 mg, 70% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J*=7.3, 9.2 Hz, H-4), 5.62 (1H, dd, *J*=3.7, 9.2 Hz, H-3), 4.73 (1H, dd, *J*=3.8, 6.6 Hz, H-2), 4.14 (1H, dd, *J*=7.6, 8.5 Hz, −CH_2O), 3.65 (2H, m, −CH_2O), 3.62 (1H, dd, *J*=2.6, 8.7 Hz, −CH_2O), 3.26 (3H, s, 8-OMe), 3.14 (3H, s, 8-OMe), 2.91 (1H, ddd, *J*=1.5, 6.6, 7.1 Hz, H-1), 2.50 (2H, m), 2.35 (1H, brs, O*H*, absent with CD_3OD), 1.93 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 126.9, 79.5, 74.9, 65.8, 58.3, 53.4, 51.1, 49.4, 48.1, 42.4, 41.8; IR (film) 3402, 2952 cm^{-1}; MS (CI) *m*/*z* 262 (3, $[M+NH_4]^+$), 231 (100); HRMS (CI) *m*/*z* calcd for $C_{12}H_{24}NO_5$ ($[M+NH_4]^+$) 262.1654, found 262.1654.

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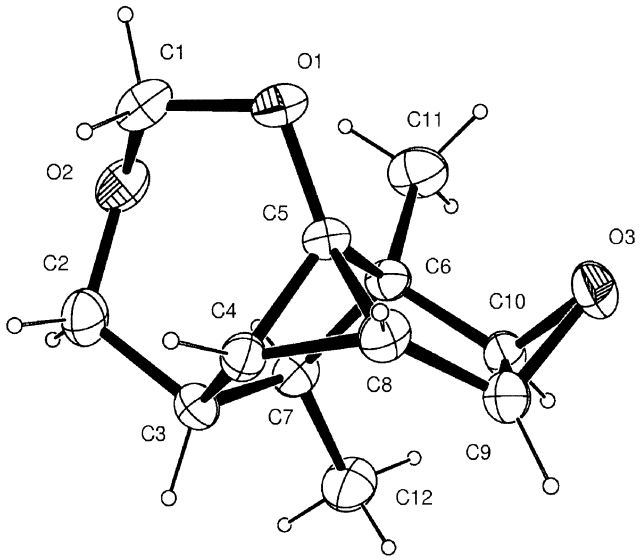

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Tetrahedron

Thermal and palladium catalyzed pericyclic rearrangements of a pentaene ester

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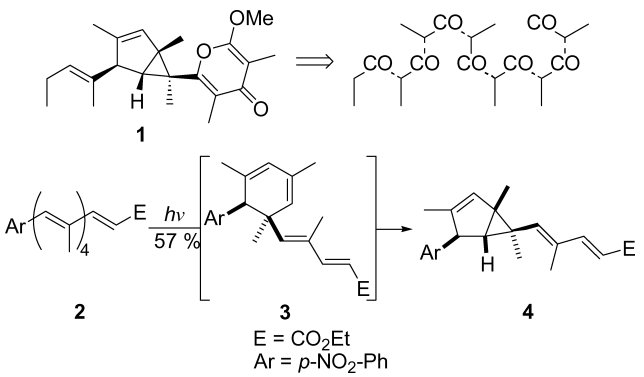
Abstract—This paper describes thermal and/or palladium promoted pericyclic rearrangements of a pentaene ester. These transformations involve selective double bond isomerizations followed by electrocyclizations, affording a cyclohexadiene and a bicyclic[4.2.0] core resulting from a cyclic triene.

1. Introduction

During continuing efforts towards the biomimetic synthesis of the propionate derived natural photodeoxytridachione **1**,[1] we have become interested in the development of pentaene **2** as a flexible synthon (Scheme 1).[2]

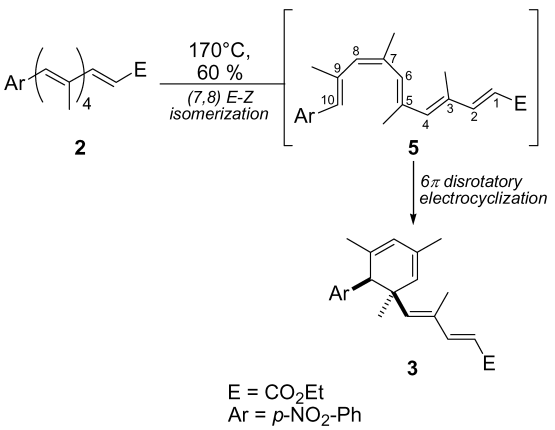


Scheme 1.

As previously reported,[2] polyene ester **2** gives, under photochemical conditions, bicyclo[3.1.0] derivative **4** via cyclohexadiene **3** (Scheme 1). This prompted us to investigate further rearrangements of ester **2**.

2. Results and discussion

Heating **2** to 170 °C[3] afforded cyclohexadiene **3** in 60% yield via a selective (7,8) *E*–*Z* isomerization to give **5**, followed by a 6π disrotatory electrocyclization, thermally allowed by the Woodward–Hoffman rules[4] (Scheme 2).



Scheme 2.

Attempts to increase the yield of **3** by heating at lower temperature failed.[5] Palladium(II) salts are well known to induce double bond isomerization under milder conditions.[6,7a] Thus compound **2** was treated with dichlorobis(acetonitrile)palladium(II) at room temperature (RT).[3] This gave the same cyclization as described above, but generating the diene **3** in only up to 20% yield.[2b] The only other isolated product was cyclooctatriene **7** in up to 20% yield (Scheme 3). The structure of **7** was determined by a

Keywords: Palladium; Electrocyclization; Cyclohexadiene.
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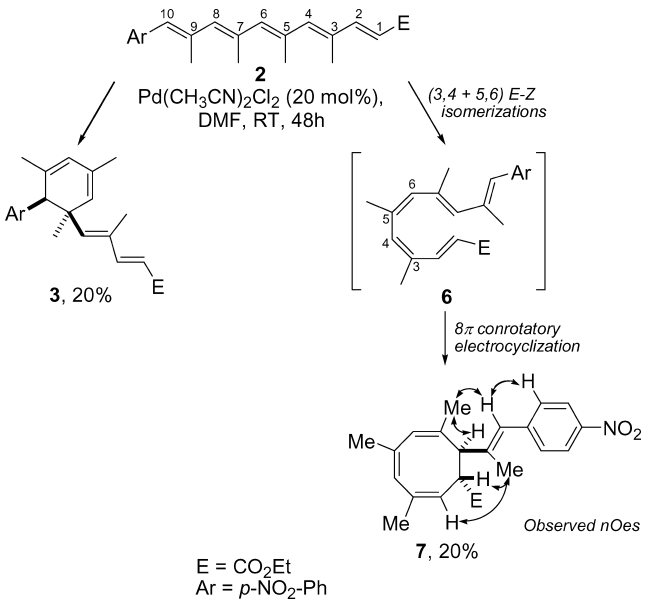
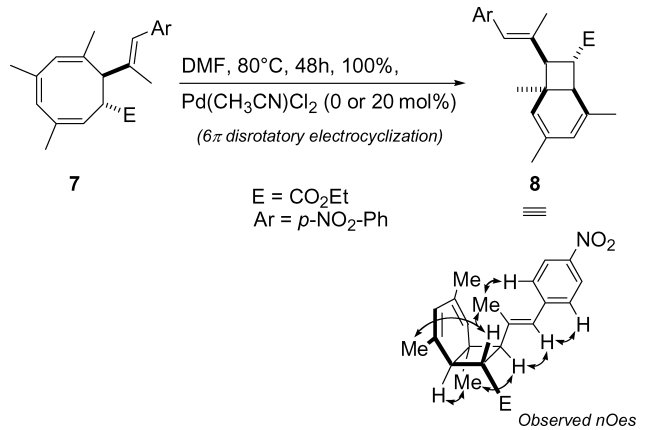


Scheme 3.

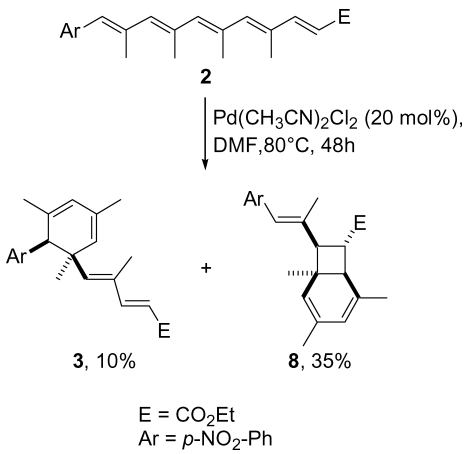
combination of NMR methods, including nOe and 2-D NMR analyses. Mechanistically, we propose that the metal induces selective (3,4+5,6) *E*–*Z* isomerizations to give intermediate **6**. The (*E*,*E*,*Z*,*Z*,*E*)-pentaene **6** then undergoes a thermally allowed 8π conrotatory electrocyclization[4] to generate the cyclic triene **7**. This process might be promoted by a chelation of the electrophilic palladium nucleus to the ester function.

As **7** is, potentially, able to undergo an intramolecular 6π disrotatory electrocyclization,[4,7] it was heated (Scheme 4).



Scheme 4.

Contrary to analogous cyclic trienes which spontaneously cyclize at or below 25 °C,[7] a minimum temperature of 80 °C was required to obtain the expected bicyclic[4.2.0] compound **8** in quantitative yield. The same transformation occurred in the presence of palladium(II) at 80 °C. Efforts to obtain the bicyclic core **8** at a lower temperature by treating **7** with neutral palladium complexes were unsuccessful. This indicates that the 6π disrotatory electrocyclization seems to be a purely thermal reaction.[8] Indeed, as expected, when the palladium catalyzed reaction of **2** was directly carried out at 80 °C,[3] dienes **3** and **8**[9] are obtained in 10 and 35% yield, respectively (Scheme 5).



Scheme 5.

3. Conclusion

In conclusion, we have demonstrated that cyclohexadienes **3** and **8** can be obtained by treating pentaene ester **2** under thermal or palladium promoted conditions. Heating to 170 °C allowed a selective single *E*–*Z* isomerization of pentaene **2** giving intermediate **5**, which then cyclized to form diene **3**, whereas palladium induced a selective double *E*–*Z* isomerization of **2**. This generated intermediate **6**, allowing the formation of cyclooctatriene **7** via an 8π conrotatory electrocyclization. Moreover, compound **7** can be converted quantitatively into the bicyclic[4.2.0] core **8** through a thermally allowed 6π disrotatory electrocyclization. Finally, dienes **3** and **8** can be obtained in a one-pot reaction by heating pentaene **2** in the presence of a catalytic amount of palladium(II) salt. This work demonstrates the feasibility of selective double bond isomerizations of pentaene ester **2** and the efficiency of the subsequent electrocyclizations.

4. Experimental

4.1. General procedure

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 2 mm Hg. All experiments were carried out under a positive atmosphere of argon and in glassware protected from sunlight. ^{1}H NMR spectra were recorded at 400 MHz using Bruker DPX400 instrument or at 500 MHz using Bruker DRX500 instrument. For ^{1}H spectra recorded in C_6D_6, chemical shifts are quoted in parts per million

(ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; b, broad. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 100 MHz using Bruker DPX400 instrument or at 125 MHz using Bruker DRX500 instrument. Carbon spectra assignments are supported by DEPT-135 spectra, $^{13}C-^{1}H$ (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak. Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel. Thin-layer chromatography was carried out on pre-coated aluminium plates (silica gel 60 F_{254} from Merck), visualized with UV light, stained with a solution of *p*-anisaldehyde (9.2 mL), H_2SO_4 (12.5 mL), CH_3CO_2H (3.75 mL) in C_2H_5OH (338 mL) followed by charring. Infrared spectra were recorded as a thin film between NaCl plates on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionization mass spectrometer and on a VG autospec chemical ionization mass spectrometer.

4.2. Ethyl (2*E*,4*E*)-4-methyl-5-[(1*R* *,6*R* *)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (3)

In a sealed tube purged with argon, a solution of pentaene ester **2** (100 mg, 262 μmol) in xylene (15 mL) was heated at 170 °C during 2 days. The solution was allowed to cool to RT and the solvent evaporated under reduced pressure. Purification by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) gave title compound **3** as a yellow oil (60 mg, 60%).

4.2.1. Data for 3. R_F 0.5 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2964, 2927, 2858, 1713, 1618, 1521, 1453, 1330, 1165; δ_H (400 MHz, C_6D_6) 0.85 (3H, s), 0.99 (3H, t, *J*=8.0 Hz), 1.18 (3H, s), 1.42 (3H, s), 1.64 (3H, s), 2.63 (1H, s), 4.06 (2H, q, *J*=8.0 Hz), 5.12 (1H, s), 5.37 (1H, s), 5.58 (1H, s), 5.68 (1H, d, *J*=16.0 Hz), 6.71 (2H, d, *J*=8.0 Hz), 7.42 (1H, d, *J*=16.0 Hz), 7.72 (2H, d, *J*=8.0 Hz); δ_C (100 MHz, C_6D_6) 13.6, 14.8, 21.6, 22.9, 29.7, 44.4, 56.5, 60.5, 117.4, 123.0, 124.3, 127.8, 129.6, 131.1, 135.5, 136.3, 146.5, 146.8, 147.6, 150.3, 167.3; *m*/*z*(CI) 399 (MNH_4^+, 8%), 382 (MH^+, 100), 352 (11), 336 (43), 308 (40); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2026.

4.3. Ethyl (2*E*,4*E*)-4-methyl-5-[(1*R* *,6*R* *)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (3) and ethyl (1*R* *,8*S* *)-3,5,7-trimethyl-8-[(*E*)-1-methyl-2-(4-nitrophenyl)ethenyl]cycloocta-2,4,6-triene-1-carboxylate (7)

Ester **2** (300 mg, 786 μmol) and $Pd(MeCN)_2Cl_2$ (41 mg, 157 μmol) were placed in a dry flask, which was purged with argon. DMF (8 mL) was added, and the solution was stirred for 2 days at RT, and then water (8 mL) was added. The mixture was extracted with DCM (3×3 mL) and the combined organic fractions were washed with water (3×2 mL), brine (3 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the mixture concentrated under reduced pressure. The crude yellow residue was purified by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) to give tetraene **3** as a yellow oil (60 mg, 20%) and cyclooctatriene **7** as a yellow oil (60 mg, 20%).

4.3.1. Data for 7. R_F 0.5 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3020, 2933, 2855, 1718, 1595, 1517, 1477, 1425, 1345, 1215, 1015, 929, 759; δ_H (500 MHz, C_6D_6) 0.93 (3H, t, *J*=7.0 Hz), 1.62 (3H, s), 1.75 (3H, s), 1.77 (3H, s), 1.77 (3H, s), 3.89 (1H, bs), 3.94 (2H, q, *J*=7.0 Hz), 4.25 (1H, bd, *J*=7.5 Hz), 5.46 (1H, bs), 5.68 (1H, bs), 6.08 (1H, bd, *J*=7.5 Hz), 6.23 (1H, bs), 6.87 (2H, d, *J*=10.0 Hz), 7.87 (2H, d, *J*=10.0 Hz); δ_C (125 MHz, C_6D_6) 14.7, 23.1, 23.1, 27.0, 27.1, 46.4, 56.6, 60.9, 123.9, 126.5, 126.7, 128.9, 129.2, 129.6, 129.7, 129.8, 136.5, 137.6, 144.6, 146.9, 173.2; *m*/*z*(CI) 382 (MH^+, 48%), 352 (18), 325 (95), 279 (100), 262 (77), 232 (83), 212 (64); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2007.

4.4. Ethyl (1*R* *,6*S* *,7*R* *,8*R* *)-1,3,5-trimethyl-8-[(*E*)-1-methyl-2-(4-nitrophenyl)ethenyl]bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (8)

4.4.1. Thermal conditions. In a sealed tube purged with argon, a solution of cyclooctatriene **7** (50 mg, 131 μmol) in DMF (15 mL) was heated at 80 °C during 2 days. The solution was allowed to cool to RT and the solvent evaporated under reduced pressure to afford title compound **8** as a yellow oil (50 mg, 100%).

4.4.2. Palladium conditions. Same procedure as described above for compounds **3** and **7** but by heating the reaction mixture at 80 °C during 2 days. A purification by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) gave title compound **8** as a yellow oil (105 mg, 35%) and cyclodiene **3** as a yellow oil (29 mg, 10%).

4.4.3. Data for 8. R_F 0.4 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3019, 2924, 2855, 1718, 1594, 1517, 1444, 1344, 1216, 1110, 1027, 858, 757; δ_H (500 MHz, C_6D_6) 0.98 (3H, t, *J*=7.0 Hz), 1.18 (3H, s), 1.60 (3H, s), 1.79 (3H, s), 1.86 (3H, s), 2.69 (1H, d, *J*=10.0 Hz), 3.27 (1H, d, *J*=10.0 Hz), 3.40 (1H, t, *J*=10.0 Hz), 3.96 (2H, q, *J*=7.0 Hz), 4.90 (1H, bs), 5.39 (1H, bs), 6.19 (1H, bs), 6.79 (2H, d, *J*=10.0 Hz), 7.85 (2H, d, *J*=10.0 Hz); δ_C (125 MHz, C_6D_6) 14.7, 18.5, 22.0, 22.5, 29.1, 44.0, 45.7, 46.2, 60.4, 60.6, 121.9, 122.6, 123.4, 123.7, 129.7, 131.3, 134.5, 140.2, 144.4, 146.3, 173.6; *m*/*z*(CI) 382 (MH^+, 45%), 352 (45), 340 (24), 310 (23), 279 (15), 262 (18), 232 (100), 205 (29); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2031.

Acknowledgements

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3. The reaction was conducted for a 2 day period.
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8. In order to elucidate this mechanism further modifications will be studied and reported.
9. Compound **8** results from the thermal cyclization of **7**, since the formation and disappearance of **7** is observed during the reaction.

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Aryl-2,3-oxaphosphabicyclo[2.2.2]octene derivatives—the precursors of oxoarylphosphine oxides (aryl metaphosphonates)

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We would like to dedicate our paper in memory of Late Professor William E. McEven, distinguished chemist and founder editor of Heteroatom Chemistry

Abstract—The Baeyer–Villiger oxidation of 7-phosphanorbornene 7-oxides with sterically demanding substituents on the phosphorus atom (**4a–d**) by *m*-chloroperbenzoic acid afforded the title products (**5a–d**) as a mixture of two regioisomers (**A** and **B**). Isomer **A**, the result of thermodynamic control, was stable, while isomer **B**, the product of kinetic control, underwent decomposition and/or epoxidation. Single crystal X-ray analysis of *P*-(2,4,6-triisopropylphenyl) oxaphosphabicyclooctene (**5Ac**) was not only useful in the evaluation of its structure, but, for the first time in the literature, a low-coordinated arylmetaphosphonate (**15c**) formed by fragmentation on X-ray irradiation could also be detected. The precursors (**5Aa-c**) were utilized in the thermoinduced and UV light-mediated fragmentation-related phosphorylations of alcohols. Beside the well-known elimination-addition mechanism via the metaphosphonate intermediate (**15**), a novel addition-elimination route involving a species with a pentavalent pentacoordinated phosphorus atom (**16**) was also substantiated.

1. Introduction

The first synthesis of oxophenylphosphine oxide (phenyl metaphosphonate) Ph-PO_2 and its methyl derivatives $Me_nC_6H_{5-n}$-PO_2, (n=1–3) in the reaction of aryl phosphonic acids with aryl phosphonic dichloride was reported by Michaelis over hundred years ago.[1] Almost eighty years later it was shown that the trimers of oxoarylphosphine oxides were formed rather than monomers.[2] The intermediacy of metaphosphonate Ph-PO_2 was proposed in several reactions on the basis of the resulting oligometaphoshonates and the trapping products formed by reaction with the added nucleophiles,[3,4] as well as from kinetic experiments.[5]

Attempts to decrease the reactivity of phenyl metaphosphonate by the introduction of *t*-butyl groups in *ortho* positions of the phenyl ring were unsuccessful. Oxidation of diphosphene Ar-P=P-Ar (Ar=2,4,6-^{t}Bu$_3$C$_6$H$_2$–) led to a polymer that was presumably (Ar-PO_2)$_n$.[6] The metaphosphonate Ar-PO_2 was formed as an intermediate during the flash vacuum pyrolysis of a cyclic phosphonite. Subsequent insertion of the PO_2 moiety into the neighboring methyl group led to a stable cyclic phosphinic acid.[7] *N*-*t*-Butyl-*P*-(2,4,6-tri-*t*-butylphenyl)phosphonamidic acid was reported to be an unstable precursor of 2,4,6-tri-*t*-butylphenylmetaphosphonate.[8]

Since 1985, the thermal or photochemical fragmentation of 2,3-oxaphosphabicyclo[2.2.2]octene ring systems has been widely used as a source of metaphosphoric (RO-PO_2) or metaphosphonic (R-PO_2) acid anhydride.[4] The intermediacy of *meta*(thio)phosphates Y-P(X)O (Y=RO, R′R′R″N; X=O, S) in the fragmentation of oxa(thia)phosphabicyclooctenes was confirmed by mechanistic studies.[9,10]

In this paper, we present the synthesis of *P*-aryl oxaphosphabicyclooctenes that are the precursors of metaphosphonates ArPO_2 with sterically demanding substituents on the phosphorus atom (Ar=2,4,6-^{i}Pr$_3$C$_6$H$_2$, 2,4,6-Me$_3$C$_6$H$_2$, 4-MeC$_6$H$_4$).

Keywords: Phosphorus heterocycles; Baeyer–Villiger reactions; Fragmentation reactions; Metaphosphonate; Mechanisms; Phosphonylation.
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2. Results and discussion

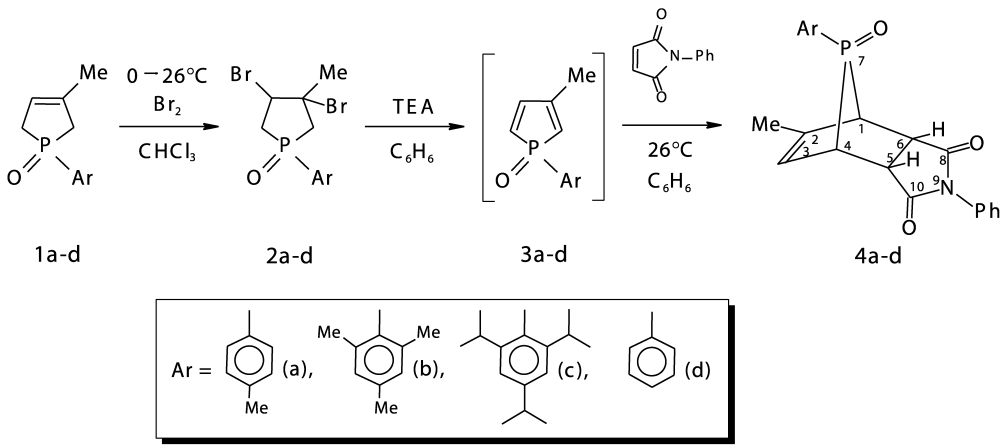
2.1. *O*-insertion into the 7-PNB framework

To investigate the effect of the P-substituent on the synthesis and fragmentation of 2,3-oxaphoshabicyclo[2.2.2]octenes, we utilized compounds **4a–c** that were prepared according to an earlier protocol (Scheme 1).[11]

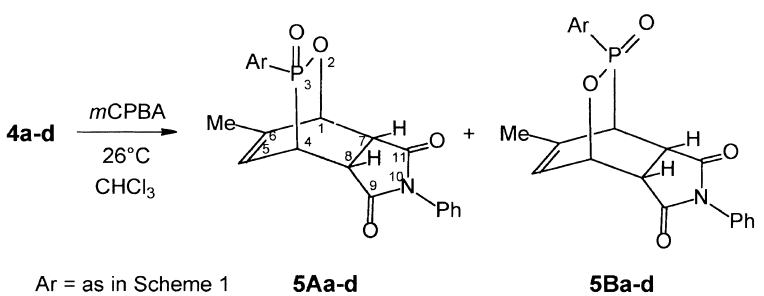
The *O*-insertion realized by *m*CPBA led to two regioisomers **5A** and **5B** (Scheme 2). Additional products were observed after a certain period of time, which depended on the substrate. As compared to phenyl derivative **4d**, the reaction was slower when electron donating 4-methylphenyl (**4a**) or bulky trialkylphenyl substituents (**4b** and **4c**) were present on the phosphorus atom. This is consistent with the associative $S_N2(P)$ or addition–elimination (AE) mechanisms. The formation of regioisomer **5A** (shifted downfield in the ^{31}P NMR spectrum at δ_P 41–37) was faster than that of **5B** (δ_P of 35–39). The ratio of regioisomers **5A** and **5B** also depended on the space requirement of the substituent and was constant up to the time shown in Scheme 2; then it was increasing. Simultaneously, new upfield signals at δ_P 20–26 appeared.

It is known from earlier work that regioisomers of type **5A** and **5B** have different stability, and usually the minor isomers were lost during the isolation procedures.[12,13] However, in the case of the *P*-ethoxy[12] and the *P*-mesitylamino[14] derivatives both regioisomers were isolated and characterized. The regioisomers could be distinguished by the ^{31}P NMR chemical shift and coupling constant between the carbon atom of the vinyl methyl group and the phosphorus atom. For the regioisomer of type **5B**, a coupling of 4–4.4 Hz with phosphorus was observed, while a value of 0–2.7 Hz was detected for regioisomers of type **5A**.[12–14] From the above data it was concluded that the isolated products of *O*-insertion into *P*-Aryl 7-PNB system were regioisomers **5Aa-d**. To prove this conclusion, the X-ray analysis of a **5Ac** crystal obtained by vapor diffusion was carried out. A sample dissolved in dichloromethane was equilibrated against hexane at 10 °C for several days. Due to the small size of the crystals obtained, a synchrotron source had to be used for data collection. Routine solution and refinement procedures[15,16] confirmed unambiguously the structure of the product from the *O*-insertion as **5Ac** (Fig. 1).

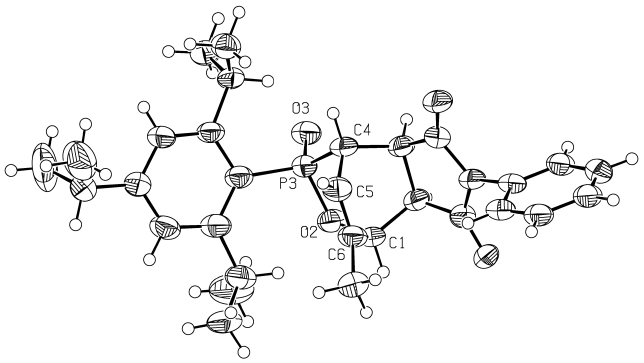
Though the geometry of **5Ac** is consistent with that of analogous derivatives[17,18] and anisotropic thermal parameters do not show any unusual features (Fig. 1), the *R* factor remained high (R_1=0.167) and several unexpected peaks (the highest one of 2.57 e A^{-3} was 1.2 Å from phosphorus) appeared on the final electron density map (Fig. 2(A)). A detailed analysis of the map suggested, however, the presence of a metaphosphonate group built of the two highest differential peaks, (Q_1 at 1.22 Å from P1 and Q_2 at 1.17 Å from O2) and the original atom O3. These two new P–O distances are 1.46 Å and the O–P–O angle is 114° (Fig. 2(B)). The three atoms Q_1, Q_2 and O3 lie in a plane parallel to that of *P*-aryl with a separation of 1.2 Å on the opposite side of the phosphonate group in



Scheme 1.



Scheme 2.



Selected bond lengths (Å)		Selected bond angles (deg)	
P3 –O2	1.608(2)	O2 –P3 –O3	109.7(2)
P3 –O3	1.476(3)	O2 –P3 –C4	98.4(2)
P3 –C4	1.853(3)	O2 –P3 –C01	109.7(2)
P3 –C01	1.816(3)	O3 –P3 –C4	117.7(2)
		O3 –P3 –C01	113.2(2)
		C4 –P3 –C01	107.1(2)

Figure 1. The view of molecular structure and selected geometric parameters of **5Ac** in solid state.

5Ac than the vinyl bridge. Hence, there is space for the planar diene system (**14**) emerging after the fragmentation (Scheme 5). It explains the shift of the *P*-aryl fragment, allowed by the loose packing in the crystal (Fig. 2(A)). The distance between the neighboring 2,4,6-isopropylphenyl groups equals 6.044 Å, that is the *b* dimension of the unit cell.

We suppose that powerful synchrotron X-rays could initiate the extrusion of metaphosphonate. Both products were observable in the same crystal by diffraction method due to their moderate amounts and fairly loose packing, which enabled the measured monocrystal to remain intact after the fragmentation. A decomposition degree of 10–15% was estimated from absolute electron densities of residual peaks corresponding to new P and O positions.

This is the first example of metaphosphonate Ar-PO_2 structure in the solid state. The X-ray structure was determined only for a more stable sulphur analogue.[19] Dithioxo(tri-*tert*-butylphenyl)phosphorane Ar-PS_2 (Ar=2,4,6-$^tBu_3C_6H_2$–) was obtained by reaction of bis-(trimethylsilyl)(tri-*tert*-butylphenyl)phosphane with sulfur dichloride. The CPS_2 moiety was planar and the torsion angle of the aryl group to the PS_2 plane was ca. 80°.

The reaction of 7-phosphanorbornenes (7-PNB) with *m*-chloroperbenzoic acid (*m*CPBA) proceeds with retention of phosphorus configuration.[13] *m*CPBA attacks the phosphorus atom with the formation of P(V) intermediates **7-1** and **7-2**, possessing one of the P–C bonds in an apical, while the other in the equatorial position (Scheme 3). The pseudorotation places the peroxy group into the equatorial position necessary for the migration of the P–C bond (**8-1** and **8-2**). According to this mechanism, the phosphoryl oxygen should remain intact.

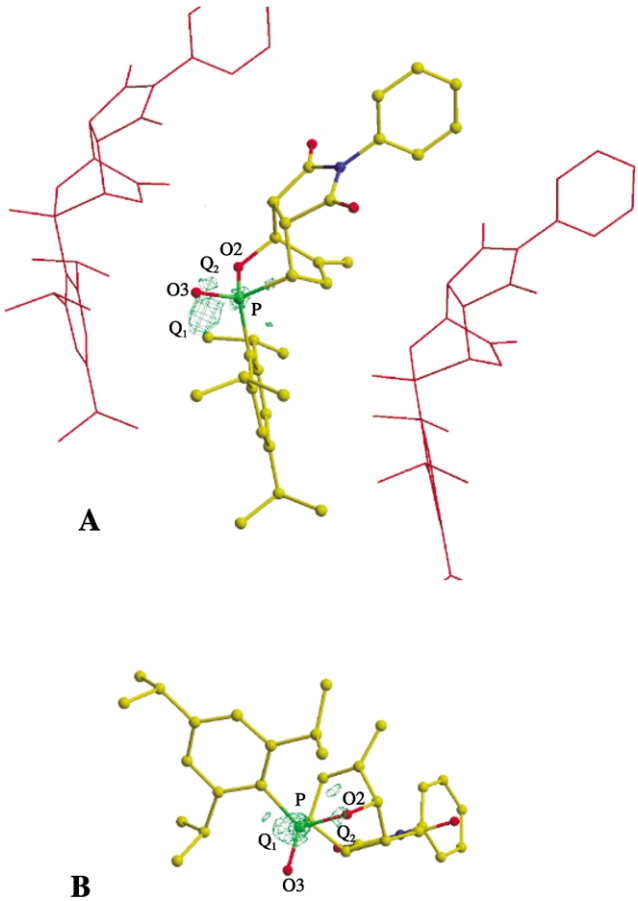
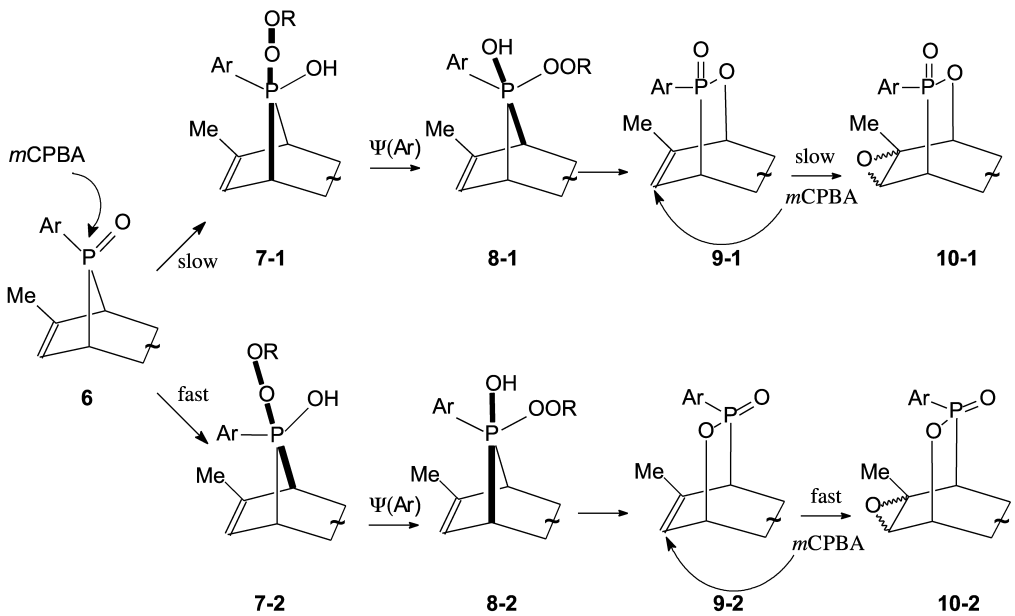


Figure 2. Residual peaks comprising metaphosphonate **15c** formed by fragmentation of **5Ac** on X-ray irradiation in the crystalline phase. (A) Viewed parallelly to the 2,4,6-triisopropylphenyl groups and showing their packing. (B) Viewed perpendicularly to the newly formed metaphosphonate moiety.

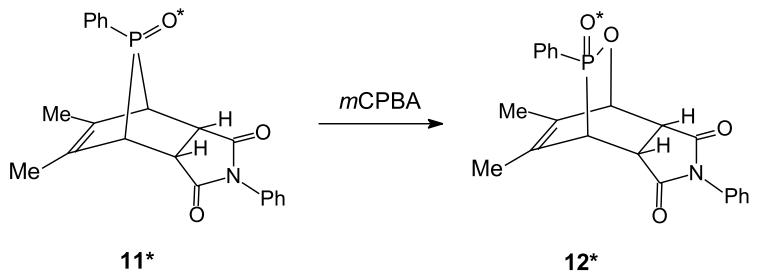
To investigate this problem, 7-phosphanorbornene **11*** labeled with O-18 in the phosphoryl group was treated with *m*CPBA. The product **12*** contained the same amount of heavy oxygen and its ^{31}P NMR spectrum showed the same $^{16}O/^{18}O$ splitting as in the substrate. This is an additional proof that reaction of 7-phosphanorbornenes with *m*CPBA follows a similar mechanism as the oxidation of ketones (Scheme 4).[20]

After the substrate **4a–c** was consumed, the excess of *m*CPBA and its reduction product *m*-chlorobenzoic acid were removed from the solution by complexation on the surface of anhydrous potassium fluoride. Phosphorus containing by-products were also adsorbed. We were successful in isolating the by-product from the synthesis of **5Ac** using the preparative TLC for the reaction mixture obtained without KF treatment. The major by-product was probably a product of double *O*-insertion **13**. The epoxidation of the double-bond for the phosphabicyclooctene system by *m*CPBA was observed previously by Kashman[21] and for 3,4-dimethyl-1-phenylphosphole oxide by Quin.[22]

The steric hindrance due to the substituents in 7-PNB system (**6**, Scheme 3) decreases the rate of *O*-insertion and prolongs the time of exposure to *m*CPBA. The oxygen is



Scheme 3.



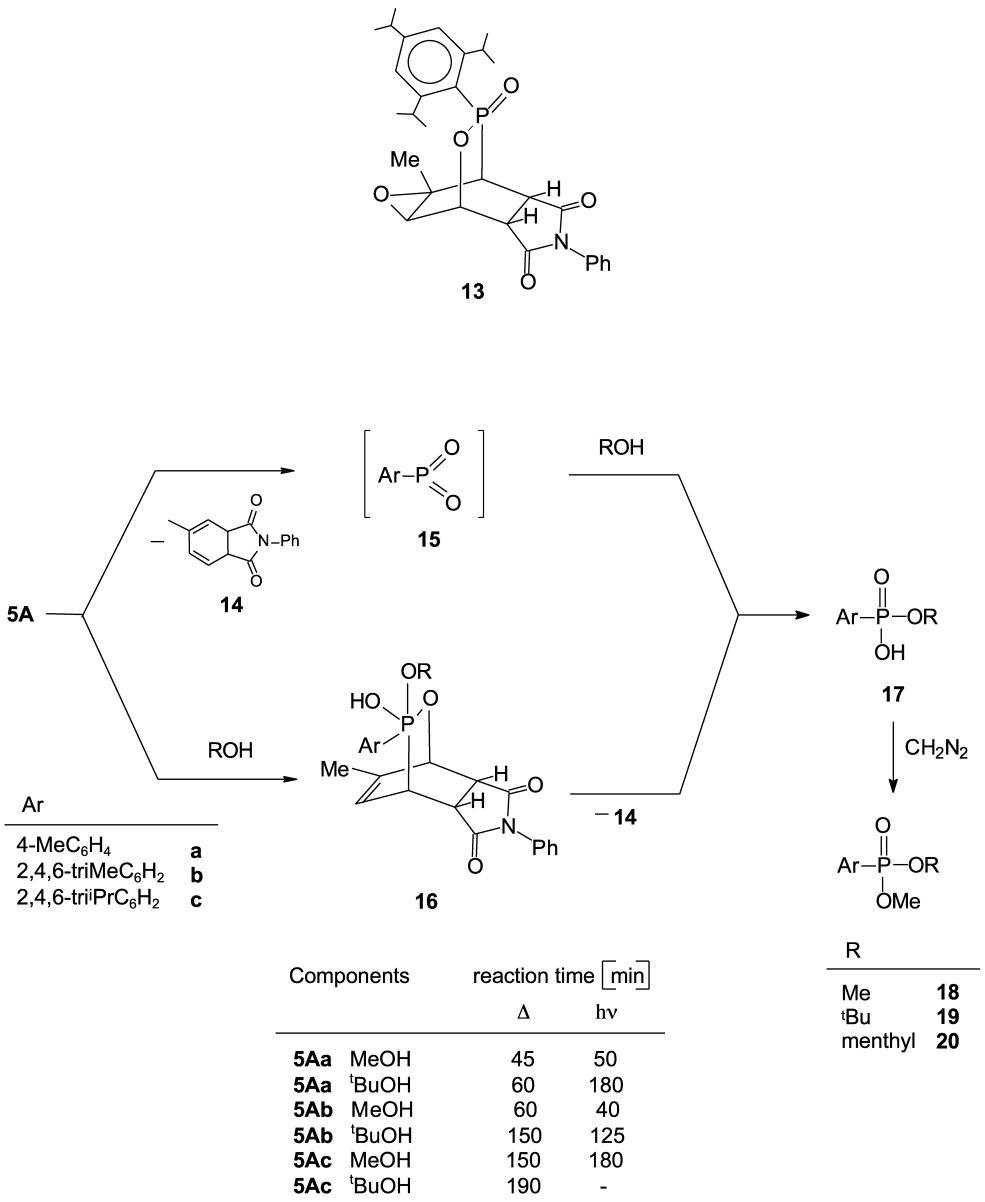
Scheme 4.

inserted easier into the P–C bond placed farther from the vinyl methyl group, than in the other case (**8-2** vs. **8-1**). The epoxidation of the double-bond is facilitated when the vinyl methyl group and the phosphorus atom are on the same side (**9-2** vs. **9-1**). The standard ab initio LCAO-SCF calculations[23] (STO-2G and STO-4G) evidenced that the unsymmetrical transition state is energetically favorable in the reaction of peroxy acids with olefins–the peroxyacid oxygen attacks one of the vinyl carbons.[24] Thus, the steric effect of the substituents at phosphorus is responsible for the kinetic control of the *O*-insertion and the consecutive epoxidation of the double bond.

2.2. Fragmentation reaction of 2,3-oxaphosphabicyclo[2.2.2]octenes 5A in the presence of alcohols

The fragmentation of 2,3-oxaphosphabicyclo[2.2.2]octenes can be achieved by thermolysis or photolysis.[4] The thermolysis of compounds **5Aa-c** in toluene at 110 °C in the presence of methanol or *tert*-butyl alcohol or irradiation at 254 nm in 1,2-dichloroethane in the presence of an alcohol, followed by reaction with diazomethane led to the corresponding phosphonates **18a–c** and **19a–c**, respectively (Scheme 5).

The necessary time for the consumption of the substrate increases with the steric hindrance of the *P*-aryl substituent (Scheme 5). Reaction with methanol is much faster than that with *tert*-butyl alcohol. For the thermal or photochemical fragmentation of 2,3-oxaphosphabicyclo[2.2.2]octene derivatives, a pure retrocycloaddition process was postulated.[9,10] The sensitivity to steric effects suggests the mixture of EA and $S_N(2)P$ (or AE) mechanisms, as for the EA mechanism no significant effect of the alcohol on the rate should be observed.[25] The pure $S_N(2)P$ or AE mechanism can also be excluded, as the phosphonylation of the sterically hindered and low nucleophilic *tert*-butyl alcohol evidences the intermediacy of **14a–c**.[26] The participation of $S_N2(P)$ or AE is reduced by the increase of steric hindrance of the reactants, or even eliminated in the case of reaction of **5Ac** with *tert*-butyl alcohol. The participation of **15c** was additionally proved by the result of the reaction with menthol or with a mixture of alcohols. When menthol was used, the (1:1) mixture of diastereoisomers of **20c** was found in the reaction mixture after the methylation of menthol phosphonate (**17**, R=menthyl) with diazomethane. The lack of stereoselectivity evidences the presence of planar 3-coordinated intermediate.[27] Competition experiment with different alcohols was also performed in order to check the selectivity. We found that **5Ac** reacts three times faster with methanol than with *tert*-butyl alcohol in toluene at 110 °C. A somewhat lower selectivity (2.1) was observed for the reaction of Et-P(S)O with ethanol and *tert*-butyl alcohol in chloroform.[9] The



Components		reaction time [min] Δ	hν
5Aa	MeOH	45	50
5Aa	^{t}BuOH	60	180
5Ab	MeOH	60	40
5Ab	^{t}BuOH	150	125
5Ac	MeOH	150	180
5Ac	^{t}BuOH	190	-

Scheme 5.

systematic kinetic studies to establish the ratio of EA and $S_N2(P)$ or AE mechanisms will be continued.

3. Experimental

3.1. General

NMR spectra were recorded on Bruker Avance DPX 250 spectrometer at 250.13 MHz (^{1}H), 101.20 MHz (^{31}P) and 62.86 MHz (^{13}C) in $CDCl_3$, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. FAB/MS were recorded on a APO Electron (Ukraine) model MI 12001E mass spectrometer equipped with a FAB ion source (3-nitrobenzyl alcohol matrix). HRMS spectra were recorded on a Finnigan MAT 95 (Finnigan MAT GmbH, Germany) mass spectrometer. Column chromatography was performed with glass column packed with silica gel (0.063–0.2 mm) (Fluka). Eluents: $CHCl_3$ and $CHCl_3$/MeOH (95/5). Melting point was determined using Boetius apparatus. Alcohols (Aldrich, Fluka, P. O. Ch. Poland) were dried over CaH_2. L-Menthol (Fluka, pure) was used without additional purification. Chloroform and dichloromethane (P. O. Ch., Poland, analytical grade) were dried over P_2O_5. KF (Bruxelles-r.c.b. 85078 Belgium) was dried in a dryer at 100–110 °C. Diazomethane in ethyl ether was generated from Diazald (Aldrich) directly before use. Water with 79.3% enrichment of ^{18}O was supplied by Techsnabeksport (USSR).

3.2. 7-Phosphanorbornenes 4a–c and 11

Compounds **4a–d** and **11** were prepared following literature procedures.[11,22]

3.2.1. 2-Methyl-7-oxo-9-phenyl-7-*p*-tolyl-9-aza-7-phosphabicyclo[5.2.1.0^{2,6}]dec-2-ene-8,10-dione (4a). Colorless

solid, mp 230–232 °C (ethyl acetate); ν_{max} (CCl_4) 1704, 1496, 1392, 1192, 1136, 784 cm^{-1}; δ_P (101.3 MHz, $CDCl_3$) 84.2; δ_H (250.1 MHz, $CDCl_3$) 7.42–7.58 (5H, m, Ph), 7.26–7.29 (2H, m, H_{Ar}), 7.12–7.16 (2H, m, H_{Ar}), 5.86 (1H, ddq, *J*=11.2 Hz, C_3H), 4.15 (2H, bd, *J*=1.8 Hz, C_5H, C_6H), 3.72–3.80 (m, 1H, C_4H), 3.57–3.63 (1H, m, C_1H), 2.40 (3H, s, $C_{4'}CH_3$), 1.81 (3H, dd, *J*=1.56 Hz, C_2CH_3); δ_C (125.7 MHz, $CDCl_3$) 174.4 (d, *J*=13.4 Hz), 174.1 (d, *J*=13.0 Hz), 142.1, 139.8 (d, *J*=10.3 Hz), 130.7, 128.5 (d, *J*=11.3 Hz), 128.2, 127.8, 125.5, 121.9 (d, *J*=97.0 Hz), 121.4 (d, *J*=7.9 Hz), 45.9 (d, *J*=64.1 Hz), 44.0 (d, *J*=13.3 Hz), 42.8 (d, *J*=11.5 Hz), 42.8 (d, *J*=64.7 Hz), 20.6, 18.3; *m/z* (FAB/NBA) 378 (100, MH^+), 286 (11), 240 (22); HRMS (FAB/NBA): MH^+, found 378.1254. $C_{22}H_{21}NO_3P$ requires 378.1259.

3.2.2. 2-Methyl-7-oxo-9-phenyl-7-(2,4,6-trimethylphenyl)-9-aza-7-phosphabicyclo[5.2.1.0^{2,6}]dec-2-ene-8,10-dione (4b). Colorless solid, mp 246–248 °C (ethyl acetate); ν_{max} (CCl_4) 2960, 1712, 1596, 1496, 1448, 1380, 1184, 1040, 880, 660; δ_P (101.3 MHz, $CDCl_3$) 84.2; δ_H (250.1 MHz, $CDCl_3$) 7.45–7.38 (3H, m, H_{Ar}), 7.15–7.11 (m, 2H, H_{Ar}), 6.88 (2H, d, H_{Ar}), 5.85 (ddtq, 1H, *J*=10.4, 3.1, 1.6 Hz, C_3H), 4.11–4.15 (2H, bd, *J*=1.7 Hz, C_5H, C_6H), 3.94–4.02 (1H, m, C_4H), 3.83–3.90 (1H, m, C_1H), 2.61 (3H, s, $C_{6'}CH_3$), 2.51 (3H, s, $C_{4'}CH_3$), 2.28 (3H, s, $C_{2'}CH_3$), 1.72 (3H, t, *J*=1.6 Hz, C_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 18.2, 20.1, 21.9 (d, *J*=6.4 Hz), 22.2 (d, *J*=4.7 Hz), 42.3 (d, *J*=13.8 Hz), 43.7 (d, *J*=15.4 Hz), 46.3 (d, *J*=63.2 Hz), 48.8 (d, *J*=62.9 Hz), 119.6 (d, *J*=9.4 Hz), 122.0 (d, *J*=94.6 Hz), 125.0, 125.5, 128.0, 128.2, 130.7, 139.6 (d, *J*=8.9 Hz), 140.1 (d, *J*=9.4 Hz), 140.2 (d, *J*=11.5 Hz), 140.7 (d, *J*=2.2 Hz), 174.5 (d, *J*=14.0 Hz), 174.7 (d, *J*=15.9 Hz); *m/z* (FAB/NBA) 406 (100, MH^+), 167 (86, ArPOH); HRMS (FAB/NBA): MH^+, found 406.1561. $C_{24}H_{25}NO_3P$ requires 406.1572.

3.2.3. 2-Methyl-7-oxo-9-phenyl-7-phenyl-9-aza-7-phosphabicyclo[5.2.1.0^{2,6}]dec-2-ene-8,10-dione (4d). Colorless solid, mp 239–241 °C (ethyl acetate); δ_P (101.3 MHz, $CDCl_3$); ν_{max} (KBr) 1776, 1712, 1496, 1384, 1200, 752, 704 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 7.76–7.55 (3H, m, H_{Ar}), 7.55–7.40 (5H, m, Ph), 7.22–7.13 (2H, m, H_{Ar}), 5.89 (1H, dddq, *J*=11.3, 5.0, 1.8, 1.7 Hz, C_3H), 4.20 (2H, ddd, *J*=2.3, 1.7, 04 Hz, C_5H, C_6H), 3.88–3.80 (1H, m, C_4H), 3.70–3.64 (1H, m, C_1H), 1.84 (t, 3H, *J*=1.8 Hz, C_2CH_3), δ_C (62.9 MHz, CDCl3) 175.2, (d, *J*=13.8 Hz), 175.0 (d, *J*=13.6 Hz), 140.9; 140.7, 132.4 (d, *J*=2.8 Hz), 131.4 (d, *J*=8.7 Hz), 129.2, 128.9, 128.3 (d, *J*=11.8 Hz), 126.5 (d, *J*=91.4 Hz), 126.4, 122.4 (d, *J*=8.8 Hz), 46.8 (d, *J*=64.0 Hz), 44.9 (d, *J*=14.2 Hz), 43.6 (d, *J*=64.2 Hz), 43.7 (d, *J*=12.6 Hz), 19.3 (d, *J*=3.3 Hz); HRMS (FAB/NBA): MH^+, found 364.1086. $C_{21}H_{19}NPO_3$ requires 364.1103.

3.3. Synthesis of 2,3-oxaphosphabicyclo[2.2.2]octenes (5Aa-c)

A solution of 0.20 mmol of 7-phosphanorbornene derivative **4a–c** in dry $CHCl_3$ (1 mL) was added to a solution of *m*CPBA/15% *m*CBA (202 mg, 1.02 mmol) in dry $CHCl_3$ (4 mL). The solution was stirred at room temperature and monitored by ^{31}P NMR. After the completion of reaction, the ^{31}P NMR spectra were complex (**4a**: δ (rel. int.)=36.6 (54), 34.8 (27), 21.2 (9), 12.8 (3), 12.4 (7); **4b**: 40.5 (29), 24.6 (65), −3.7 (6); **4c**: 40.3 (16), 27.3 (23), 26.2 (14), 23.1 (6), 21.6 (3), 18.9 (6), 14.5 (27), −2.4 (5). Then KF (202 mg, 3.5 mmol) was added and the mixture was stirred for 3 h at room temp. The suspension was filtered off (Celite 500) and the solvent evaporated. The crude product was subjected to column chromatography ($CHCl_3$/MeOH) and then crystallized from AcOEt to give analytically pure product in about 15–20% yield.

The reaction of **4d** with *m*CPBA was carried out in an NMR tube (10 mg of substrate) and monitored by ^{31}P NMR to examine the kinetics of *O*-insertion only, without isolation of the product. Attempts to isolate the by-products of *O*-insertion by column chromatography were unsuccessful. However, when preparative TLC chromatography (2 mm silica gel plates, Merck) was applied to the reaction mixture after the synthesis of **5Ac**, the component at R_F=0.88 (chloroform/methanol 5% as an eluent) was extracted with acetone to give **13**; δ_P (101.3 MHz, $CDCl_3$) 21.1; HRMS (ESI): MH^+, found 521.2326. $C_{30}H_{36}NO_5P$ requires 521.2322.

3.3.1. 5-Methyl-8-(4-methylphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epoxyphosphano)isoindole-1,3-dione 8-oxide (5Aa). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 35.2; ν_{max} (neat) 2984, 1716, 1648, 1496, 1448, 1400, 1208, 1144, 792 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 7.56–7.43 (5H, m, Ph) 7.31–7.26 (2H, m, H_{Ar}), 7.17–7.13 (2H, m, H_{Ar}), 5.95–5.85 (1H, m, C_5H), 5.36 (1H, ddd, *J*=21.9, 4.2, 2.0 Hz, C_4H), 4.18 (1H, dt, *J*=7.5, 4.2 Hz, C_8H), 4.02 (1H, dt, *J*=7.5, 2.6 Hz, C_7H), 3.67 (1H, dt, *J*=7.5, 7.3, 2.6 Hz, C_1H), 2.42 (3H, s, $C_{4'}CH_3$), 1.99 (3H, dd, *J*=5.2, 1.75 Hz C_6CH_3); δ_C (62.9 MHz, $CDCl_3$) 175.6 (d, *J*=15.1 Hz), 173.0, 143.9, 142.0 (d, *J*=10.7 Hz), 132.7 (d, *J*=10.7 Hz), 131.3, 129.2, 129.0, 126.1, 125.4 (d, *J*=90.0 Hz), 123.5 (d, *J*=8.2 Hz), 76.7 (d, *J*=9.4 Hz), 46.1 (d, *J*=12.0 Hz), 36.5 (d, *J*=79.6 Hz), 36.8 (d, *J*=6.8 Hz), 21.6, 19.8 (d, *J*=2.5 Hz); *m/z* (FAB/NBA) 394 (30, MH]$^+$), 240 (75, $[MH-ArPO_2]^+$,), 154 (15); HRMS (FAB/NBA): MH^+, found 394.1214. $C_{22}H_{21}NO_4P$ requires 394.1208.

3.3.2. 8-Mesityl-5-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epoxyphosphano) isoindole-1,3-dione 8-oxide (5Ab). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 38.97; ν_{max} (neat) 2976, 1716, 1604, 1380, 1188, 984, 760 cm^{-1}; δ_H (250.1 MHz $CDCl_3$) 7.47–7.42 (3H, m, H_{Ar}), 7.16–7.12 (2H, m, H_{Ar}), 6.88 (2H, d, *J*=5.0 Hz, $C_{3'}H$, $C_{5'}H$), 5.85–5.70 (1H, m, C_5H), 5.31 (1H, ddd, *J*=20.1, 4.0, 2.0 Hz, C_4H), 4.15 (1H, dt, *J*=7.9, 4.0 Hz, C_8H), 3.97 (1H, dt, *J*=2.5, 7.9 Hz, C_7H), 3.94 (1H, dt, *J*=7.5, 2.5 Hz, C_1H), 2.58 (6H, s, $C_{2'}CH_3$, $C_{6'}CH_3$), 2.28 (3H, s, $C_{4'}CH_3$), 1.90 (3H, dd, *J*=5.15, 1.75 Hz, C_6CH_3); *m/z* (FAB/NBA) 422 (60, MH^+), 240 (57, $[MH-ArPO_2]^+$,), 154 (100), 136 (82); HRMS (FAB/NBA): MH^+, found 422.1514. $C_{24}H_{25}NO_4P$ requires 422.1521.

3.3.3. 6-Methyl-2-phenyl-9-(2,4,6-triisopropylphenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7 (phosphanomethano)isoindole-1,3-dione 9-oxide (5Ac). Colorless solid, mp 162–164 °C; δ_P (101.3 MHz $CDCl_3$) 39.0; ν_{max} (KBr) 2960, 1712, 1396, 1212, 1184, 1128, 984 cm^{-1}; δ_H (250.1 MHz,

$CDCl_3$) 7.39–7.35 (3H, m, H_{Ar}); 7.09–7.05 (2H, m, H_{Ar}), 7.00 (2H, d, J=5.0 Hz, $C_{3'}H$, $C_{5'}H$), 5.70 (1H, dddd, J=7.50, 7.25, 2.0, 1.50 Hz, C_5H), 5.21 (1H, ddd, J=22.0, 4.50, 2.00 Hz, C_4H), 1.17 (d, 12H, $^3J_{HH}$=6.75 Hz, $(CH_3)_2CH-C_{2'}$, $(CH_3)_2CH-C_{6'}$), 4.07 (1H, ddd, J=8.25, 7.25, 4.5 Hz, C_8H), 3.94 (1H, dt, J=2.5, 8.25 Hz, C_7H), 3.80 (1H, dt, J=7.25, 2.5 Hz, C_1H), 3.62 (2H, ht, J=6.75 Hz, $(CH_3)_2CHC_{2'}$, $CH_3)_2CHC_{6'}$), 2.80 (1H, ht, J=6.5 Hz, $(CH_3)_2CHC_{4'}$), 1.78 (3H, dd, J=6.75, 1.50 Hz, CH_3C_6), 1.19 (6H, d, 6.5, $(CH_3)_2CHC_{4'}$), δ_C (62.9 MHz, $CDCl_3$) 176.0 (d, J=15.1 Hz), 173.2, 152.9, 152.6 (d, J=12.6 Hz), 141.4 (d, J=11.7 Hz), 131.4, 129.3, 129.0, 126.2, 125.5 (d, 93.7 Hz), 122.8 (d, J=8.2 Hz), 76.1 (d, J=10.1 Hz), 46.3 (d, J=10.2 Hz), 38.9 (d, J=77.9 Hz), 36.7 (d, J=5.2 Hz), 34.3, 31.6 (d, J=4.2 Hz), 26.6, 24.9 (d, J=25.4 Hz), 20.0; m/z (FAB/NBA) 506 (22, MH^+), 240 (22, $[MH-ArPO_2]^+$), 154 (100), 136 (71); HRMS (FAB/NBA): MH^+, found 506.2466. $C_{30}H_{37}NO_4P$ requires 506.2460.

3.3.4. 5-Methyl-8-phenyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epoxyphosphano)isoindole-1,3-dione 8-oxide (5Ad). Colorless solid, mp 132–134 °C; δ_P (101.3 MHz, $CDCl_3$) 34.7; ν_{max} (CCl_4) 2928, 1712, 1388, 1232, 1192, 984, 936, 784 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 7.75–7.46 (8H, m, H_{Ar}) 7.17–7.13 (2H, m, H_{Ar}), 5.95–5.84 (1H, m, C_5H), 5.37 (1H, ddd, J=21.3, 4.3, 2.0 Hz, C_4H), 4.18 (1H, dd, J=7.3, 4.3 Hz, C_8H), 4.02 (1H, dt, J=7.3, 2.5 Hz, C_7H), 4.02 (1H, dt, J=7.3, 7.3, 2.5 Hz, C_1H), 2.00 (3H, dd, J=5.0, 1.75 Hz, C_6CH_3); δ_C (62.9 MHz, $CDCl_3$) 175.5 (d, J= 15.6 Hz), 173.0, 142.1 (d, J=10.6 Hz), 133.1 (d, J=2.5 Hz), 132.7 (d, J=9.4 Hz), 131.3, 129.3, 128.6 (d, J=10.9 Hz), 126.1, 123.5 (d, J=7.9 Hz), 46.2 (d, J=11.3 Hz), 36.8 (d, J=6.9 Hz), 36.5 (d, J=80.5 Hz), 19.8 (d, J=2.8 Hz); m/z (FAB/NBA) 380 (30, MH^+), 240 (40, $[MH-ArPO_2]^+$), 154 (75), 137 (90), 109 (100); HRMS (FAB/NBA): MH^+, found 380. 1044, $C_{21}H_{19}NO_4P$ requires 380. 1052.

3.4. Thermolysis of bicyclooctenes 5Aa-c

A solution (1 mL) of **5Aa-c** (0.02 mmol) and an alcohol (2 mmol) in dry toluene were placed into 5 mm NMR tube and sealed under argon. Sample was placed in thermostat at 110 °C and the reaction was monitored by ^{31}P NMR. When the signal of substrate diminished the solvent was evaporated and the excess of diazomethane in diethyl ether was added. The solution was again evaporated to dryness and phosphonate methyl esters **15** were purified by column chromatography ($CHCl_3$) with 90% yield.

3.5. Photolysis of bicyclooctenes 5Aa-c

A solution (1 mL) of **5Aa-c** (0.02 mmol) and an alcohol (2 mmol) in dry 1,2-dichloroethane in 5 mm quartz NMR tube was placed in the centre of Rayonet reactor fitted with 8 low-pressure mercury lamps (253.7 nm). The reaction was monitored by ^{31}P NMR. After the completion of reaction the same protocol as in case of thermolytic reaction was applied. The reaction of **5Aa** and **5Ab** with alcohols proceeded quantitatively and the corresponding methyl esters **17a** and **17b** obtained after treatment with diazomethane were isolated in about 90% yield. In case of reaction of **5Ac** with methanol the yield was only 29% and by-products were observed at 53.7, 36.3 and 35.0 ppm. When **5Ac** was irradiated in the presence of *tert*-butyl alcohol, the product of phosphonylation could not be detected.

3.5.1. Dimethyl 4-methylphenylphosphonate (18a). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 22.7; ν_{max} (neat, NaCl) 2952, 1248, 1188, 1032 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 2.41 (s, 3H, $CH_3-C_{4'}$), 3.75 (d, 6H, $^3J_{HP}$=11.0 Hz, CH_3O), 7.26–7.31 (m, 4H, Ar);); δ_C (62.9 MHz, $CDCl_3$) 132.0 (d, J=10.3 Hz), 129.3 (d, J=15.1 Hz), 129.2, 124.3 (d, J=94.4 Hz), 52.6 (d, J=5.4 Hz), 21.7; m/z (FAB/NBA) 201 (MH^+, 100), 91 (24), 77 (20); HRMS (EI): M^+, found 200.0595. $C_9H_{13}O_3P$ requires 200.0602.

3.5.2. *tert*-Butyl methyl 4-methylphenylphosphonate (19a). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 16.8; ν_{max} (neat, NaCl) 2952, 1192, 1128, 1048 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 1.51 (s, 9H, $(CH_3)3-C$), 2.40 (s, 3H, $CH_3-C_{4'}$), 3.65 (d, 3H, $^3J_{HP}$=10.0 Hz, CH_3O), 7.23–7.28 (m, 4H, Ar); δ_C (62.9 MHz, $CDCl_3$) 131.6 (d, J=10.1 Hz), 129.2, 129.0 (d, J=15.1 Hz), 124.4 (d, J=95.0 Hz), 83.2, 52.0, (d, J=5.4 Hz), 30.4 (d, J=3.8 Hz), 21.7; m/z (FAB/NBA) 243 (5, MH^+), 187 ([100), 173 (13), 91 (11), 57 (17); HRMS (EI): M^+, found 242.1077.$C_{12}H_{19}O_3P$ requires 242.1072.

3.5.3. Dimethyl mesitylphosphonate (18b). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 23.9; ν_{max} (neat, NaCl) 2952, 1232, 1208, 1184, 1032 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 2.27 (s, 3H, $CH_3-C_{4'}$), 2.58 (s, 6H, $CH_3-C_{2'}$, $CH_3-C_{6'}$), 3.73 (d, 6H, $^3J_{HP}$=11.5 Hz, CH_3O), 6.91 (d, 2H, $^4J_{HP}$=5.0 Hz, $H-C_{3'}$, $H-C_{5'}$); δ_C (62.9 MHz, CDCl3) 142.2, 129.2 (d, J=10.7 Hz), 130.4 (d, J=16.4 Hz), 120.9 (d, J=98.4 Hz) 51.7 (d, J=5.0 Hz), 23.0; m/z (FAB/NBA) 229 (100, MH^+), 197 (8), 119 (18), 91 (15), 77 (14); HRMS (EI): M^+, found 228.0919.$C_{11}H_{17}O_3P$ requires 228.0915.

3.5.4. *tert*-Butyl methyl mesitylphosphonate (19b). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 17.7; ν_{max} (film, NaCl) 2976, 1256, 1212, 1168, 1040 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 1.49 (s, 9H, $(CH_3)3-C$), 2.34 (s, 3H, CH_3-C4'), 2.59 (s, 6H, $CH_3-C_{2'}$, $CH_3-C_{6'}$), 3.62 (d, 3H, $^3J_{HP}$=11.5, CH_3O), 6.89 (d, 2H, $^4J_{HP}$=4.5, $H-C_{3'}$, $H-C_{5'}$); δ_C (62.9 MHz, $CDCl_3$) 142.0, 130.4 (d, J=15.7 Hz), 129.2 (d, J=9.4 Hz); 120.6 (d, J=97.0 Hz), 77.2 (d, J=1.8 Hz), 22.7, 21.1; m/z (FAB/NBA) 271 (5, MH^+), 215 (100), 197 (10), 119 (9); HRMS (EI): M^+, found 270.1389.$C_{14}H_{23}O_3P$ requires 270.1385.

3.5.5. Dimethyl 2,4,6-triisopropylphenylphosphonate (18c). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 24.3; ν_{max} (film, NaCl) 2960, 1240, 1212, 1188, 1024 cm^{-1}; δ_H (250.1 MHz, $CDCl_3$) 1.24 (d, 12H, $^3J_{H-H4}$=5.50 Hz), 1.26 (d, 6H, $^3J_{H-H}$=5.75 Hz), 2.83 (ht, 1H, $^3J_{H-H}$=5.75 Hz), 3.75 (d, 6H, $^3J_{HP}$=11.26 Hz), 4.11 (ht, 2H, $^3J_{H-H}$=5.50 Hz), 7.14 (d, $2H_{ar}$, $^4J_{Har-P}$=5.28 Hz); δ_C (62.9 MHz, $CDCl_3$) 152.8, 155.2 (d, J=13.8 Hz), 121.6 (d, J=15.7 Hz), 52.0 (d, J=5.6 Hz), 34.3, 30.5 (d, J=2.5 Hz), 24.9, 23.6; HRMS (CI, isobutane): MH^+, found 313.1925. $C_{17}H_{30}O_3P$ requires 313.1933.

3.5.6. *tert*-Butyl methyl 2,4,6-triisopropylphenylphosphonate (19c). Thick oil; δ_P (101.3 MHz, $CDCl_3$) 18.4; ν_{max} (film, NaCl) 2960, 1256, 1240, 1168, 1044 cm^{-1};

δ_H (250.1 MHz, $CDCl_3$) 1.22 (d, 12H, $^3J_{H-H}$=6.75 Hz), 1.25 (d, 6H, $^3J_{H-H}$=6.75 Hz), 1.56 (s, 9H), 2.88 (ht, 1H, $^3J_{H-H}$=6.75 Hz), 3.64 (d, 3H, $^3J_{H-P}$=11.51 Hz), 4.24 (ht, 2H, $^3J_{H-H}$=6.75 Hz), 7.10 (d, 2H_{ar}, $^4J_{H-P}$=5.00 Hz);); δ_C (62.9 MHz, $CDCl_3$) 151.9, 151.5 (d, J=13.8 Hz), 122.4 (d, J=15.7 Hz), 77.2 (d, J=1.8 Hz), 51.5 (d, J=5.7 Hz), 34.3, 30.5 (d, J=3.8 Hz), 30.1, 25.1; HRMS (CI, isobutane): MH^+, found 355.2399. $C_{20}H_{35}O_3P$ requires 355.2402.

3.6. Synthesis of 12* labeled with O-18

The solution of **11** (30 mg, 0.0796 mmol) and $H_2^{18}O$ (15 mg, 0.85 mmol) in dry acetonitrile was sealed in glass ampule under argon and kept at 100 °C for 45 h. Then the solution was evaporated to dryness under reduced pressure (0.5 mm Hg), dissolved in $CHCl_3$ and filtered through the silica gel layer. ^{31}P NMR spectrum showed broad resonances of **11** at 77.86 ppm and of **11*** at 77.82 ppm. The ^{18}O shift of 0.04 ppm is characteristic for the P=O group.[28] The isotopic ratios $[M^+ +3]/[M^+ +3]$ were determined by FAB/MS analysis and equal to 1.982±0.020 and 0.049±0.002 for **11*** and **11**, respectively. *m*CPBA (27 mg, 0.135 mmol) was added to the solution of **11*** (17 mg, 0.045 mmol) in chloroform (1 mL) and left with stirring for 3 h. Then KF (27 mg) was added and stirring was continued for next 90 min. After filtration and solvent evaporation the residue was crystallized from ethyl acetate. Yield of **12***: 10 mg (0.025 mmol) (55.6%). The product showed a pair of well resolved peaks at 34.66 and 34.62 (1:1.9) and mass spectrometric analysis gave the isotopic ratios 1.987±0.022 and 0.048±0.005 for **12*** and **12**, respectively.

3.7. Crystal data of 5Ac

Colorless prisms. Crystal size 0.10×0.05×0.03 mm, $C_{30}H_{36}NO_4P$, M=505.57, monoclinic, a=42.105(8) Å, b=6.044(1) Å, c=20.930(4) Å, $\alpha=\gamma=90°$, β=93.36(3)°, V=5317.17 Å^3, T=100 K, space group $C2/c$, Z=8, μ=0.14 mm^{-1}, λ=0.7 Å, D(cal)=1.263 Mg/m^3, F(000)=2160, $R1$=0.167, for 4442 observed, $wR2$=0.559 for all 4594 reflections. Diffraction data were collected on the 5-ID beam line of the DND-CAT at the Advanced Photon Source, Argonne, IL, using a MARCCD detector.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-226060. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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Authors are thankful to Dr. Zdzislaw Wawrzak for X-ray data collection at the DuPont-Northwestern-Dow Collaborative Access Team (DND-CAT) Synchrotron Research Center located at Sector 5 of the Advanced Photon Source. DND-CAT is supported by the E. I. DuPont de Nemours and Co., the Dow Chemical Company, the U.S. National Science Foundation through Grant DMR-9304725 and the State of Illinois through the Department of Commerce and the Board of Higher Education Grant IBHE HECA NWU 96. Use of the Advanced Photon Source was also supported by the U. S. Department of Energy, Basic Energy Sciences, Office of Energy Research under Contract No. W-31-102-Eng-38.

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Cetyltrimethylammonium hydroxide (CTAOH) as a general, ecofriendly catalyst for the formation of carbon–carbon bond through nitroalkanes

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Abstract—Nitroalkanes have been found to give good yields in Michael and nitroaldol (Henry) reactions by the use of a catalytic amount (10 mol%) of CTAOH, at room temperature and under solvent free conditions and in very short reaction times. The methods do not need a large excess of the nitroalkanes and show good chemoselectivity toward further functionalities.

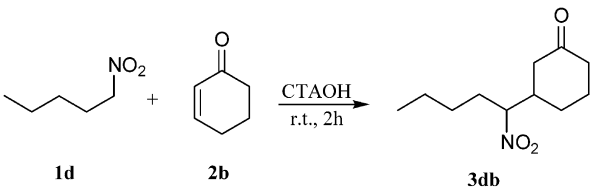
1. Introduction

Carbon–carbon bond formation is the essence of organic synthesis and nitroalkanes are very important starting materials in this context.[1,3] This is mainly due to their easy conversion into the corresponding nitronate anions because the high electron-withdrawing power of the nitro group that provides an outstanding enhancement of the acidity of α-hydrogens atoms. Therefore, nitronate salts can act as carbon nucleophiles with a range of electrophiles such as aldehydes, giving the nitroaldol (Henry reaction),[4,5] or with electron poor alkenes, giving the conjugate addition (Michael) reaction.[6] As routine procedures the Henry and Michael reactions are performed in the presence of different bases in homogeneous solutions of organic solvent or water or, alternatively, under heterogeneous catalysis[6,7] and, for these purposes, even the help of sonication[8] or high pressure[9,10] have been proposed. Although each of the above procedures have been widely studied, very often these suffer from different drawbacks such as: (i) for the nitroaldol reaction, low yields, retroaldol reaction, the formation of side products due to the aldol condensation and/or Cannizzaro reaction of aldehydes or olefin formation, and (ii), for the Michael reaction, low yields, efficiency restricted to a class of electrophilic olefins, the need of ultrasound, and/or a large excess of the nitroalkane that, for valuable nitro derivatives, is a serious economic drawback.

Thus, considering that over the past few years, a significant amount of research has been directed towards the development of new technologies for environmentally benign processes (green chemistry). An important area of the green chemistry deals with solvent minimization,[11–13] and new efficient, economical and environmentally friendly catalytic processes for both Henry and Michael reactions, are desirable.

2. Results and discussion

In this context, we report herein a new catalytic approach developed in our laboratory, and carried out with cetyltrimethylammonium hydroxide (CTAOH, 10% water solution) as ecofriendly catalyst. First, we investigated the Michael reaction and, in order to verify the best substrates/catalyst ratio, the method was tested (Scheme 1) through the reaction of 1-nitropentane **1d** with an hindered electrophilic alkene such as 2-cyclohexen-1-one **2b**.



1d **2b** **3db**

Scheme 1.

The choice of this model reaction is due to the well known behaviour of the conjugate additions of nitroalkanes to **2b** that, generally, need long reaction times and the Michael adducts are generally obtained in low to satisfactory yields, probably due to the steric hindrance of the acceptor.[2,6] The reaction was performed by adding the Michael acceptor **2b**

Keywords: Henry reaction; Michael reaction; Nitroalkanes; β-Nitroalcohol; CTAOH.
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Table 1. Study of Michael addition of 1-nitropentane **1d** to 2-cyclohexen-2-one **2b** with different amount of CTAOH (reaction time 2 h)

% of CTAOH	Yield (%) of **3db**
2.5	30
5	65
10	90
15	91
20	90

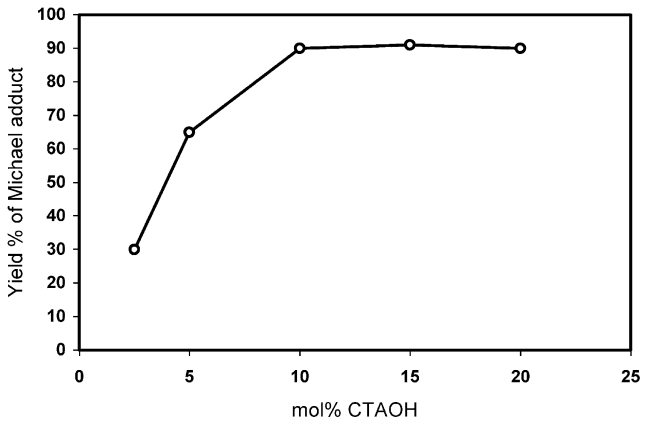
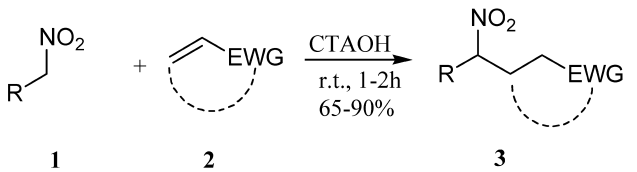


Figure 1. Trend of Michael adduct **3db** with different amount of CTAOH.

to an equimolar amount of a stirred mixture of **1d** and in the presence of different quantities of CTAOH (Table 1, Fig. 1).

As reported in Figure 1, 10 mol% of the catalyst was found to be most appropriate and the Michael adduct **3db** was obtained in excellent yield (90%) and in a very short reaction time (2 h, Table 1).

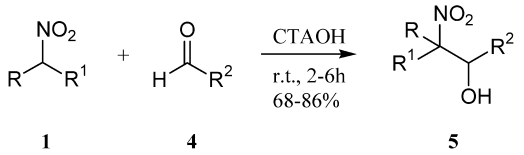
Thus, a number of different nitroalkanes **1** and electron poor alkenes **2** were chosen to assess the scope of the reaction (Scheme 2).



Scheme 2.

All the reactions were carried out in the presence of a minimum amount of water (due to the use of 10% water solution of the catalyst) and involved simple mixing stoichiometric amounts of **1** (1 mmol) and **2** (mmol) with 10% mol% of CTAOH (10% water solution), at room temperature, and leaving the mixture for further 1–2 h.

The synthetic results of the reactions are presented in Table 2. Under this method simple and functionalized nitroalkanes easily react with a variety of electrophilic alkenes, and the yields seem to be fairly independent of the degree of electron-deficiency of the alkene and of steric hindrance (**3bb**,**db**). It is worthy of note that this procedure affords compounds **3** in good yields (65–90%). Encouraged by these excellent results, we applied the same reaction



Scheme 3.

conditions to the nitroaldol reaction investigating the reactivity of a series of linear and cyclic nitroalkanes **1** with an array of both aliphatic and aromatic aldehydes **4** (Scheme 3).

Although these reactions are slower than the conjugate additions (2–6 h vs 1–2 h), we found that the β-nitro-alcohols **5** are produced in good yields (68–86%, Table 3) and contrary to other methods, the very mild reaction conditions needed prevent the typical side reactions such as retro-aldol reaction or dehydration of the 2-nitro alcohol into nitroalkenes, even if aromatic aldehydes are used.[14,15]

3. Conclusion

In summary, we have reported general catalytic method for the formation of carbon–carbon bond using nitroalkanes with several electrophilic alkenes (such as α,β-unsaturated ketones, α,β-unsaturated esters, α,β-unsaturated suphones, and α,β-unsaturated nitriles) and both aromatic and aliphatic aldehydes. All the reactions work well with short reaction times, mild reaction conditions (room temperature and 10% of the catalyst), in the presence of a minimum amount of water. High chemoselectivity is observed since further functionalities are preserved under these conditions. It is noteworthy that our method avoids the need for a large excess of the nitroalkanes and uses organic solvents during the work up only. Thus, because an important area of green chemistry deals with solvents[16,17] and by products minimization our results represent an improved, inexpensive and ecological process.

4. Experimental

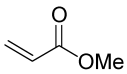
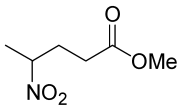
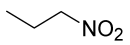
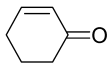
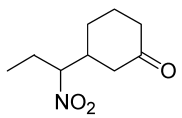
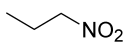
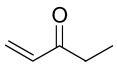
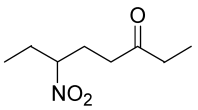
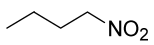
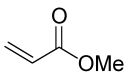
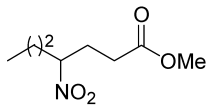
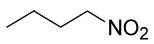
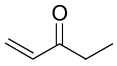
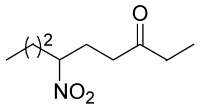
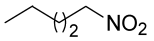
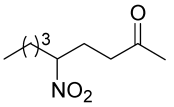
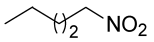
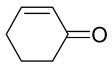
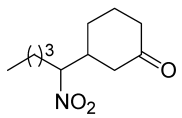
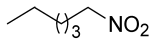
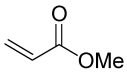
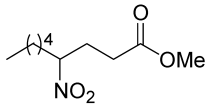
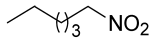
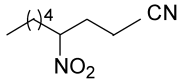
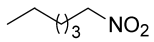
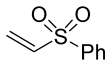
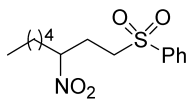
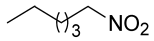
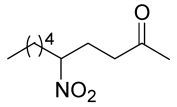
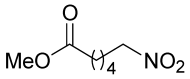
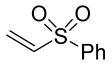
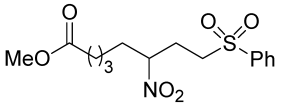
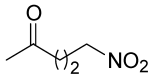
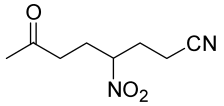
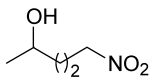
4.1. General

^{1}H NMR were recorded at 300 MHz on a Varian VXR300 in $CDCl_3$ as solvent. ^{13}C NMR were recorded at 75 MHz in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyser MODEL EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin–Elmer Paragon 500 FT-IR. GLC analyses were performed on a fised silica (0.32 mm×25 m), stationary phase SE54. Mass spectra were performed on a Hewlett–Packard GC/MS 5970 by means of the EI technique (70 eV). CTAOH was supplied by Fluka as a 10% water solution.

4.2. General procedure for the Michael reaction

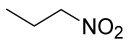
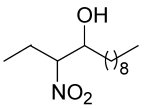
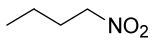
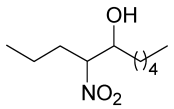
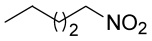
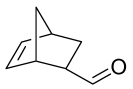
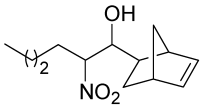
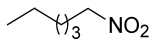
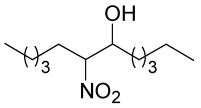
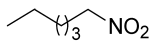
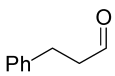
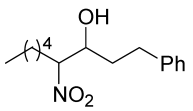
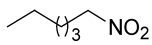
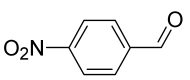
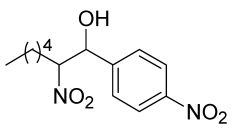
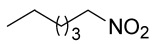
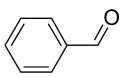
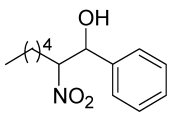
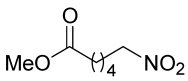
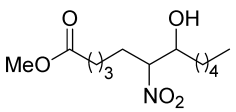
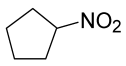
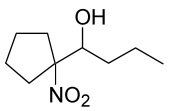
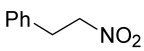
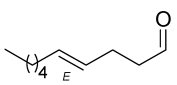
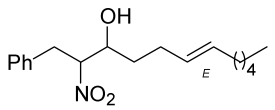
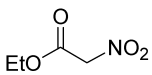
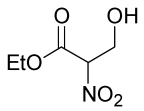
The Michael acceptor **2** (1 mmol) was added to a stirred mixture of nitrocompound **1** (1 mmol; when the nitro-alkanes **1a** and **1b** were employed 1.2 mmol were utilised) in a 10% water solution of hexadecyltrimethyl ammonium

Table 2. Michael addition of nitro compounds **1** to α,β-unsaturated systems **2**

Nitro compound **1**		α,β-Unsaturated compound **2**		Michael adduct **3**		Time (h)	Yield (%)[a]
1a		**2a**		**3aa**		1	78
1b		**2b**		**3bb**		1	80
1b		**2c**		**3bc**		1	83
1c		**2a**		**3ca**		1	77
1c		**2c**		**3cc**		1	75
1d		**2d**		**3dd**		1	74
1d		**2b**		**3db**		2	90
1e		**2a**		**3ea**		1	87
1e		**2e**		**3ee**		1	70
1e		**2f**		**3ef**		1	70
1e		**2d**		**3ed**		1	77
1f		**2f**		**3ff**		2	73
1g		**2e**		**3ge**		2	65
1h		**2e**		**3he**		1	72

[a] Yields of pure, isolated compounds.

Table 3. Addition of nitro compounds **1** to aldehydes **4**

Nitro compound **1**		Aldehyde **4**		Nitroalcohol **5**		Time (h)	Yield (%)[a]
1b		**4a**		**5ba**		3	82
1c		**4b**		**5cb**		2	83
1d		**4c**		**5dc**		3	85
1e		**4b**		**5eb**		3	81
1e		**4d**		**5ed**		4	75
1e		**4e**		**5ee**		4	76
1e		**4f**		**5ef**		6	68
1f		**4b**		**5fb**		3	77
1i		**4g**		**5ig**		4	83
1j		**4i**		**5ji**		3	86
1k		**4h**		**5kh**		4	75

[a] Yields of pure, isolated compounds.

hydroxide (CTAOH, 0.300 mL). The reaction progress was monitored by withdrawing aliquots which were analyzed by GC and TLC. Then the solution was treated with brine (10 mL) and extracted by CH_2Cl_2 (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum to afford the crude product **3**, that was purified on flash cromatography (cyclohexane–ethyl acetate).

4.2.1. Methyl-4-nitropentanoate (3aa). Yield 78% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[18]

4.2.2. 3-(1-Nitropropyl)-1-cyclohexanone (3bb). (Diastereomeric mixture, 1:1). Yield 80% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[19]

4.2.3. 6-Nitro-3-octanone (3bc). Yield 83% of colourless oil. Spectroscopic data corresponds to that reported in the literature.[20]

4.2.4. Methyl-4-nitroheptanoate (3ca). Yield 77% of yellow oil; IR (cm^{-1}, neat) 1364, 1560, 1740; ^1H NMR δ (ppm) 0.95 (t, 3H, J=7.3 Hz), 1.28–1.47 (m, 2H), 1.61–1.81 (m, 1H), 1.90–2.42 (m, 5H), 3.70 (s, 3H), 4.52–4.65 (m, 1H); ^{13}C NMR δ (ppm) 13.5, 19.1, 28.7, 30.0, 35.9, 52.0, 87.6, 172.5; EI-MS: m/z=190, 172, 158, 143, 127, 111, 83, 69, 55 (100), 41. Anal. calcd for $C_8H_{15}NO_4$

(189.21) C, 50.78; H, 7.99; N, 7.40. Found: C, 50.93; H, 8.12; N, 7.29.

4.2.5. 6-Nitro-3-nonanone (3cc). Yield 75% of colourless oil; IR (cm^{-1}, neat) 1363, 1548, 1717; ^1H NMR δ (ppm) 0.95 (t, 3H, J=7.3 Hz), 1.07 (t, 3H, J=6.4 Hz), 1.22–1.43 (m, 2H), 1.60–1.79 (m, 1H), 1.89–2.18 (m, 3H), 2.38–2.52 (m, 4H), 4.42–4.60 (m, 1H); ^{13}C NMR δ (ppm) 7.7, 13.1, 18.9, 29.4, 34.5, 36.0, 40.1, 83.0, 208.5; EI-MS: m/z=188, 157, 141, 127, 110, 83, 69, 57 (100), 41. Anal. calcd for $C_9H_{17}NO_3$ (187.24) C, 57.73; H, 9.15; N, 7.48. Found: C, 57.88; H, 9.06; N, 7.39.

4.2.6. 5-Nitro-2-nonanone (3dd). Yield 74% of colourless oil. Spectroscopic data corresponds to that reported in the literature.[20]

4.2.7. 3-(1-Nitropentyl)-1-cyclohexanone (3db). (Diastereomeric mixture, 1:1). Yield 90% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[20]

4.2.8. Methyl-4-nitrononanoate (3ea). Yield 87% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[18]

4.2.9. 4-Nitrononanenitrile (3ee). Yield 70% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[21]

4.2.10. 3-Nitro-1-(phenylsulfonyl)octane (3ef). Yield 70% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[21]

4.2.11. 5-Nitro-2-decanone (3ed). Yield 77% of colourless oil. Spectroscopic data corresponds to that reported in the literature.[22]

4.2.12. Methyl-6-nitro-8-(phenylsulfonyl)octanoate (3ff). Yield 73% of yellow oil; IR (cm^{-1}, neat) 1308, 1556, 1732; ^1H NMR δ (ppm) 1.22–1.41 (m, 2H), 1.58–1.82 (m, 3H), 1.90–2.09 (m, 1H), 2.21–2.39 (m, 4H), 3.11 (t, 2H, J=7.4 Hz), 3.67 (s, 3H), 4.58–4.67 (m, 1H), 7.58–7.93 (m, 5H); ^{13}C NMR δ (ppm) 24.2, 25.2, 26.6, 33.5, 33.6, 51.8, 52.5, 86.5, 128.2, 129.8, 134.4, 138.8, 173.7; EI-MS: m/z=265, 171, 143, 123, 95, 77 (100), 67, 55, 41. Anal. calcd for $C_{15}H_{21}NO_6S$ (343.39) C, 52.47; H, 6.16; N, 4.08. Found: C, 52.59; H, 6.30; N, 3.99.

4.2.13. 4-Nitro-7-oxooctanenitrile (3ge). Yield 65% of yellow oil; IR (cm^{-1}, neat) 1363, 1560, 1729, 2249; ^1H NMR δ (ppm) 2.02–2.25 (m, 6H), 2.33–2.60 (m, 5H), 4.57–4.70 (m, 1H); ^{13}C NMR δ (ppm) 14.4, 27.2, 29.4, 30.2, 38.8, 85.9, 117.9, 206.2; EI-MS: m/z=185, 155, 113, 95, 71, 55, 43 (100). Anal. calcd for $C_8H_{12}N_2O_3$ (184.24) C, 52.17; H, 6.57; N, 15.21. Found: C, 52.31; H, 6.66; N, 15.08.

4.2.14. 7-Hydroxy-4-nitrooctanenitrile (3he). (Diastereomeric mixture 1:1). Yield 72% of yellow oil; IR (cm^{-1}, neat) 1376, 1552, 2250, 3422; ^1H NMR δ (ppm) 1.21 (d, 3H, J=6.2 Hz), 1.41–1.55 (m, 2H), 1.71–1.82 (bs, 1H), 1.95–2.49 (m, 6H), 3.71–3.92 (m, 1H), 4.58–4.76 (m, 1H); ^{13}C NMR δ (ppm) 14.5, 24.0, 24.1, 29.2, 29.4, 29.8, 30.3, 34.5, 34.9, 66.8, 67.4, 86.6, 87.2, 118.1; EI-MS: m/z=171, 122, 96, 82, 67, 55, 45 (100), 39. Anal. calcd for $C_8H_{14}N_2O_3$ (186.21) C, 51.60; H, 7.58; N, 15.04. Found: C, 51.77; H, 7.66; N, 14.95.

4.3. General procedure for the Henry reaction

The aldehyde **4** (1 mmol) was added to a stirred mixture of nitrocompound **1** (1 mmol) in a 10% water solution of hexadecyltrimethyl ammonium hydroxide (0.300 mL). The reaction progress was monitored by withdrawing aliquots which were analyzed by TLC. Then the solution was treated with brine (10 mL) and extracted by CH_2Cl_2 (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum to afford the crude product **5**, that was purified on flash cromatography (cyclohexane–ethyl acetate).

4.3.1. 3-Nitro-4-tridecanol (5ba). Yield 82% of yellow oil; IR (cm^{-1}, neat) 1377, 1559, 3435; ^1H NMR δ (ppm) 0.83–0.90 (m, 3H), 0.93–1.02 (m, 3H), 1.18–1.56 (m, 16H), 1.78–2.19 (m, 2H), 2.46–2.52 (m, 0.5H), 2.58–2.62 (m, 0.5H), 3.82–3.92 (m, 0.5H), 3.94–4.02 (m, 0.5H), 4.30–4.41 (m, 1H); ^{13}C NMR δ (ppm) 10.4, 10.7, 14.3, 21.8, 22.9, 24.1, 25.5, 25.8, 29.4, 29.5, 29.6, 29.7, 29.8, 32.1, 33.5, 33.7, 72.0, 72.4, 94.2, 94.7. Anal. calcd for $C_{13}H_{27}NO_3$ (245.36) C, 63.64; H, 11.09; N, 5.71. Found: C, 63.75; H, 11.20; N, 5.58.

4.3.2. 4-Nitro-5-decanol (5cb). Yield 83% of colourless oil; IR (cm^{-1}, neat) 1380, 1560, 3436; ^1H NMR δ (ppm) 0.82–1.01 (m, 6H), 1.22–1.57 (m, 10H), 1.62–1.85 (m, 1H), 1.95–2.15 (m, 1H), 2.20–2.38 (m, 0.5H), 2.35–2.40 (m, 0.5H), 3.80–3.90 (m, 0.5H), 3.93–4.05 (m, 0.5H), 4.41–4.55 (m, 1H); ^{13}C NMR δ (ppm) 13.6, 13.7, 14.2, 19.3, 19.5, 22.7, 25.2, 25.5, 30.1, 31.7, 31.8, 32.7, 33.4, 33.8, 72.3, 72.6, 92.3, 92.9. Anal. calcd for $C_{10}H_{21}NO_3$ (203.28) C, 59.09; H, 10.41; N, 6.89. Found: C, 59.23; H, 10.55; N, 6.77.

4.3.3. 1-Bicyclo[2.2.1]hept-5-en-2-yl-nitrohexan-1-ol (5dc). Yield 85% of white solid, mp 43–45 °C; IR (cm^{-1}, neat) 1365, 1543, 1625, 3040, 3420; ^1H NMR δ (ppm) 0.83–1.05 (m, 3H), 1.22–1.57 (m, 7H), 1.70–2.38 (m, 5H), 2.82–2.94 (m, 1H), 3.02–3.12 (m, 1H), 4.38–4.76 (m, 2H), 5.82–6.27 (m, 2H); ^{13}C NMR δ (ppm) 13.9, 22.3, 28.0, 28.1, 28.4, 29.6, 29.8, 30.7, 42.6, 44.4, 49.1, 49.2, 50.1, 50.2, 75.8, 76.0, 91.3, 91.4, 132.5, 132.6, 138.3, 138.5. Anal. calcd for $C_{13}H_{21}NO_3$ (239.31) C, 65.25; H, 8.84; N, 5.85. Found: C, 65.39; H, 8.99; N, 5.77.

4.3.4. 7-Nitro-6-dodecanol (5eb). Yield 81% of colourless oil; IR (cm^{-1}, neat) 1379, 1561, 3447; ^1H NMR δ (ppm) 0.82–1.05 (m, 6H), 1.19–1.90 (m, 15H), 2.01–2.42 (m, 2H) 3.80–3.91 (m, 0.5H), 3.93–4.12 (m, 0.5H), 4.38–4.59 (m, 1H); ^{13}C NMR δ (ppm) 13.7, 14.3, 21.9, 23.0, 24.3, 28.4, 28.5, 30.1, 31.0, 31.2, 33.8, 33.9, 72.9, 73.1, 92.9, 93.0. Anal. calcd for $C_{12}H_{25}NO_3$ (231.33) C, 62.30; H, 10.89; N, 6.05. Found: C, 62.15; H, 11.00; N, 5.98.

4.3.5. 4-Nitro-1-phenyl-3-nonanol (5ed). Yield 75% yellow oil; IR (cm^{-1}, neat) 1376, 1560, 1603, 3027, 3448; ^1H NMR δ (ppm) 0.83–0.99 (m, 3H), 1.21–1.40 (m, 6H), 1.68–2.17 (m, 4H) 2.38–2.45 (m, 0.5H), 2.51–2.56 (m, 0.5H), 2.62–3.01 (m, 2H), 3.82–4.11 (m, 1H), 4.41–4.57

(m, 1H), 7.18–7.37 (m, 5H); ^{13}C NMR δ (ppm) 14.0, 14.1, 22.5, 25.5, 25.8, 28.2, 30.6, 31.3, 31.4, 31.8, 32.0, 35.0, 35.5, 71.5, 71.8, 92.6, 93.2, 126.5, 128.7, 128.8, 141.0, 141.1. Anal. calcd for $C_{15}H_{23}NO_3$ (265.35) C, 67.90; H, 8.74; N, 5.28. Found: C, 68.03; H, 8.86; N, 5.19.

4.3.6. 2-Nitro-1-(4-nitrophenyl)-1-heptanol (5ee). Yield 76% of yellow oil; IR (cm^{-1}, neat) 1349, 1520, 1556, 1607, 3082, 3522; ^{1}H NMR δ (ppm) 0.81–0.97 (m, 3H), 1.09–1.40 (m, 6H), 1.62–2.13 (m, 2H), 3.03 (bs, 1H), 4.61–4.77 (m, 1H), 5.05–5.10 (m, 0.5H), 5.13–5.18 (m, 0.5H), 7.60 (d, 2H, J=8.3 Hz), 8.22 (d, 2H, J=8.3 Hz); ^{13}C NMR δ (ppm) 13.9, 22.4, 25.4, 25.6, 27.5, 27.7, 30.4, 31.0, 31.1, 73.6, 74.7, 92.9, 93.3, 124.1, 124.3, 128.0, 145.9, 148.5. Anal. calcd for $C_{13}H_{18}N_2O_5$ (282.29) C, 55.31; H, 6.43; N, 9.92. Found: C, 55.44; H, 6.24; N, 9.85.

4.3.7. 2-Nitro-1-phenyl-1-heptanol (5ef). Yield 68% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[23]

4.3.8. Methyl-7-hydroxy-6-nitrododecanoate (5fb). Yield 77% of yellow oil; IR (cm^{-1}, neat) 1371, 1556, 1731, 3497; ^{1}H NMR δ (ppm) 0.83–0.97 (m, 3H), 1.22–1.91 (m, 12H), 1.92–2.21 (m, 2H), 2.27–2.39 (m, 2H), 2.44–2.51 (m, 0.5H), 2.58–2.62, (m, 0.5H), 3.65 (s, 3H), 3.77–3.91 (m, 0.5H), 3.92–4.02 (m, 0.5H), 4.32–4.49 (m, 1H); ^{13}C NMR δ (ppm) 14.1, 22.7, 24.4, 25.1, 25.4, 25.7, 27.9, 30.2, 33.4, 33.7, 33.8, 51.8, 72.2, 72.5, 92.3, 92.9, 173.9, 174.0. Anal. calcd for $C_{13}H_{25}NO_5$ (275.34) C, 56.71; H, 9.15; N, 5.09. Found: C, 56.84; H, 9.03; N, 4.98.

4.3.9. 1-(1-Nitrocyclopentyl)-1-butanol (5ig). Yield 83% of colourless oil; IR (cm^{-1}, neat) 1357, 1537, 3445; ^{1}H NMR δ (ppm) 0.92 (t, 3H, J=7.0 Hz), 1.22–1.91 (m, 9H), 2.03–2.20 (m, 1H), 2.37–2.62 (m, 3H), 3.79–3.91 (m, 1H); ^{13}C NMR δ (ppm) 14.0, 19.7, 24.8, 25.0, 33.8, 34.7, 35.6, 75.7, 103.8. Anal. calcd for $C_9H_{17}NO_3$ (187.24) C, 57.73; H, 9.15; N, 7.48. Found: C, 57.89; H, 9.27; N, 7.33.

4.3.10. (*E*)-2-Nitro-1-phenyl-6-dodecen-3-ol (5ji). Yield 86% of yellow oil; IR (cm^{-1}, neat) 1377, 1560, 1605, 3031, 3066, 3544; ^{1}H NMR δ (ppm) 0.9 (t, 3H, J=6.9 Hz), 1.21–1.39 (m, 6H), 1.57–1.71 (m, 2H), 1.93–2.05 (m, 2H), 2.09–2.30 (m, 2H), 2.38–2.42 (m, 0.5H), 2.48–2.53, (m, 0.5H), 3.13–3.38 (m, 2H), 3.83–3.94 (m, 0.5H), 4.08–4.17 (m, 0.5H), 4.68–4.77 (m, 1H), 5.30–5.59 (m, 2H), 7.16–7.37 (m, 5H); ^{13}C NMR δ (ppm) 14.3, 22.7, 28.7, 28.9, 29.3, 31.6, 32.7, 33.1, 33.8, 34.6, 36.8, 71.1, 72.1, 93.6, 93.7, 127.6, 127.7, 129.0, 129.1, 132.6, 132.8, 135.3, 136.0. Anal. calcd for $C_{18}H_{27}NO_3$ (305.42) C, 70.79; H, 8.91; N, 4.59. Found: C, 70.91; H, 9.01; N, 4.47.

4.3.11. Ethyl-3-hydroxy-2-nitropropanoate (5kh). Yield 75% of yellow oil. Spectroscopic data corresponds to that reported in the literature.[24]

Acknowledgements

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Synthetic studies towards furosesquiterpenoids: total synthesis of (±) desmethylpallescensin-A, (±) isopallescensin-A and (±) isopallescensin-1

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Abstract—A new approach for a short and efficient synthesis of common cyclohexenone intermediate towards the total synthesis of some furosesquiterpenes and their analogues are described. Regioselective alkylation of Hagemann's ester with 2/3-furyl-2-ethyl bromide followed by hydrolysis cum in situ decarboxylation and 1,4-addition with Gilman's reagent produced the cyclohexanone derivatives which have been utilized for total synthesis of (±) isopallescensin-A, (±) 10-desmethylpallescensin-A, (±) 5-desmethyl-4,5-dehydromicrocionin-1 and (±) isopallescensin-1.

1. Introduction

Furoterpenes have been found to occur abundantly in nature particularly in higher plants and marine organism. The biological activity associated with a number of drimane metabolites[1] specially furosesquiterpenes has stimulated considerable interest in their synthesis.[2] Among the broad structural variety of these natural furosesquiterpenes occupy a special place.[3] Most of these natural products have attracted much interest due to their inherent biological properties.[4] Synthesis of such furoterpenes are a challenging problem for many research laboratories even today. These includes compounds like Pallescensin A-G,[5] Pallescensin 1-3,[5] Microcionin,[5] Spiniferin[5] and several other furanosesquiterpenes. A large number of syntheses[6a–m] of several furoterpenes with complex structures have come out in last few decades and many more are still coming out. This attracted us to study the synthesis of various furoterpenes and our aim is to achieve the synthesis of such compounds via a common intermediate. One such common intermediate for the synthesis of compound **2**-**9** may be suitably substituted cyclohexenone derivatives (**1**), which in turn can easily be obtained from Hagemann's ester (Fig. 1).

The construction of a carbocyclic framework, especially one with a quaternary center, is key to the rapid and efficient synthesis of many natural products.[7] As part of our current research programme towards the synthesis of potentially bioactive furosesquiterpenes, we have developed a method for constructing a tricyclic framework using acid catalysed cyclisation reactions leading to tricyclic sesquiterpenoids and we sought to prepare a range of model compounds. These are shown in Figure 1.

In earlier synthesis of tricyclic furanosesquiterpenoids, most of the synthesis describes the linear approaches that sequentially build the tricyclic skeleton from C ring precursor or AB ring precursor to ABC tricyclic framework. In our present approach we have utilized a common AC ring precursor 2-(2-furyn-3-yl-ethyl)-3-methyl cyclohex-2-enone (**1**) (X=H) for constructing ABC tricyclic framework (Fig. 2).

2. Results and discussion

The model study in this connection was performed with 2-furyl analogue as in Scheme 1 to achieve the synthesis of (±) isopallaescensin-A and (±) isopallescensin-1.

Employing our experience[8] in the synthesis of regiospecifically substituted furan we targeted to expand our protocol towards the synthesis of furosesquiterpenes through a common intermediate (**1**). In this connection we wish to report our approach towards the synthesis of such furoterpenes and their analogues via common intermediate 2-(2-furan-3-yl-ethyl)-3-methyl-cyclohex-2-enone (**1**) (X=H) and its 2-furyl analogues (**12**) respectively. Thus the Hagemann's ester (**10**) on regioselective alkylation with 2-(2-furyl-ethyl bromide)/^{t}BuOK in ^{t}BuOH under reflux

Keywords: Hagemann's ester; Alkylation; Furoterpenes; Conjugate addition; Cyclisation; Isopallescensis-A; Desmethyl pallescensin-A.
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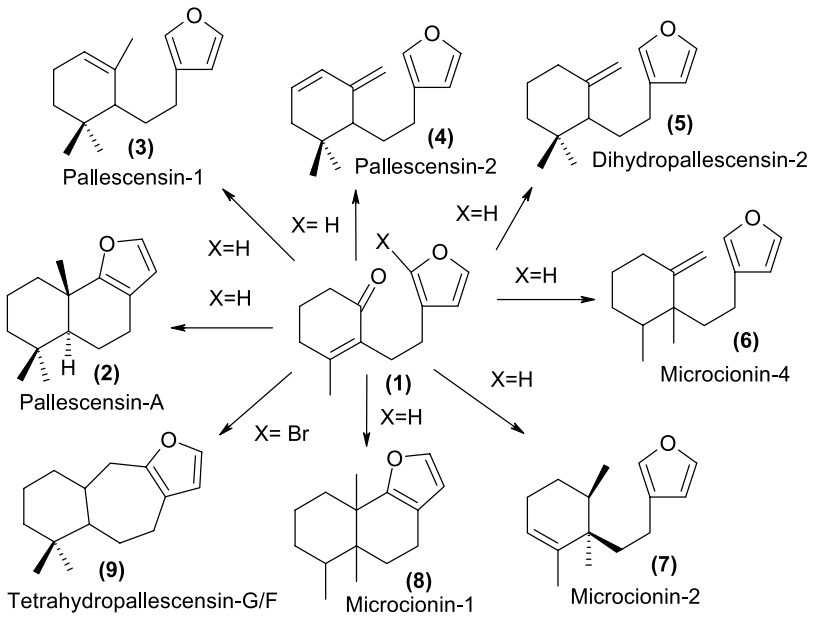


Figure 1.

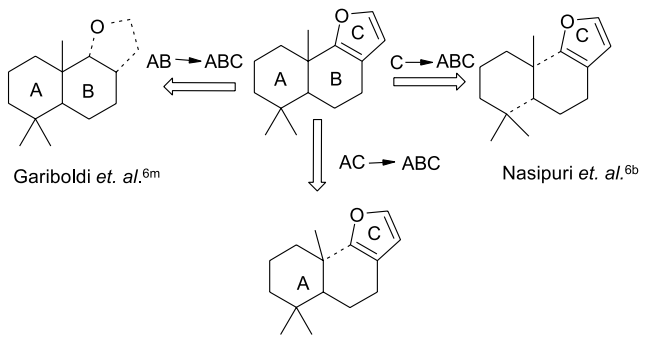
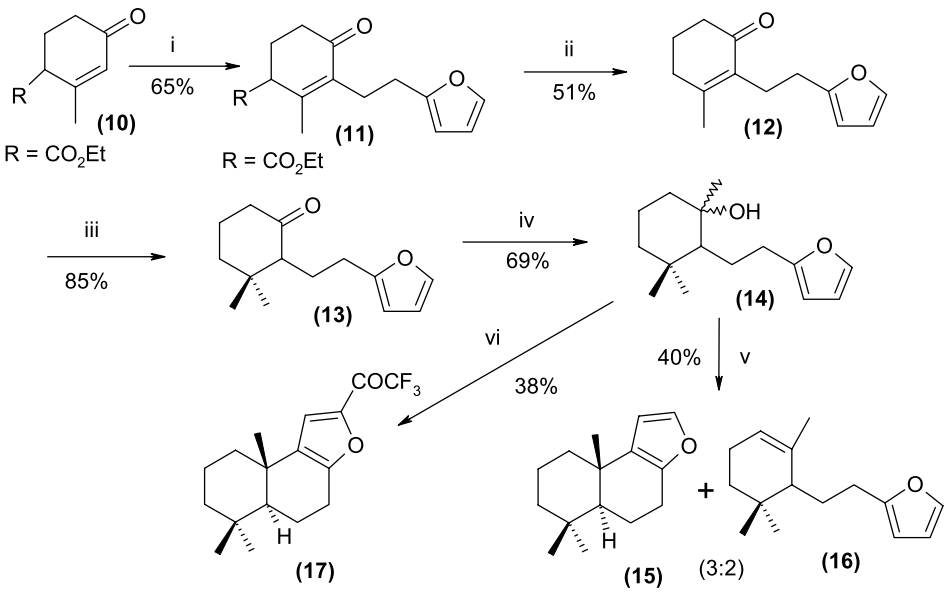
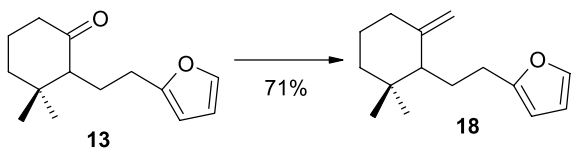


Figure 2.

afforded compound (**11**) as viscous yellow oil in 65% yield. Hydrolysis of (**11**) with KOH/EtOH–H_2O furnished 2-(2-furan-2-yl-ethyl)-3-methyl cyclohex-2-enone (**12**) in 51% yield in inert atmosphere. Conjugate addition to the α,β unsaturated ketone (**12**) with CH_3MgI/CuI met with failure. However, compound (**13**) was successfully synthesized in good yield from the cyclohexenone derivative (**12**) using Gilman's reagent (Me_2CuLi) in combination with BF_3:Et_2O.[9] The ketone (**13**) when treated with MeLi/or MeMgI in ether at −30 °C furnished the desired cyclohexanol derivative. Attempts to cyclise the cyclohexanol derivatives with BF_3:Et_2O or Poly Phosphoric Acid (PPA) met with failure. However, this compound was successfully cyclised with the help of a mixture of anhydrous HCO_2H and cyclohexane to produce a mixture of (±) isopallescensin-A



Scheme 1. Reagents and conditions: (All the reactions were carried out under argon atm) (i) ^{t}BuOK, 2-(2-furyl-ethyl bromide), reflux, 12 h (ii) KOH, EtOH–H_2O, reflux for 8 h (iii) Me_2CuLi, BF_3:Et_2O, ether, −50 °C (15 min), then −30 °C (1 h) (iv) MeLi, ether, −30 °C (1 h) (v) Anh. HCOOH, cyclohexane, rt, 30 min (vi) $(CF_3CO)_2O$, CF_3COOH, rt, 8 h.



Scheme 2. Reagents and conditions: Ph_3PCH_3I/*n*-BuLi; THF, −30 °C to rt, 3 h (N_2 atmosphere).

(**15**) and (±) isopallescensin-1 (**16**) (in the ratio 3:2) as colourless oil and the structures were confirmed from their ^1H and ^{13}C NMR spectra. The *trans*-stereochemistry of the A/B ring junction of compound (**15**) was assigned from the chemical shift value for the *gem*-dimethyl at C-4 and angular methyl group at C-10 (which appeared at δ 0.91, 0.94 and 1.14 ppm, respectively) as well as by analogy.[10] Attempt to cyclise with the help of a mixture of trifluoroacetic anhydride in trifluoroacetic acid led to the formation of the trifluoroacetyl derivatives (**17**) of isopallescensin-A (**15**) in 38% yield.

Wittig olefination of the ketone (**13**) with the ylide $Ph_3P{=}CH_2$ resulted in the formation of 1,2-dihydro isopallescensin-2 (**18**) in 71% yield Scheme 2.

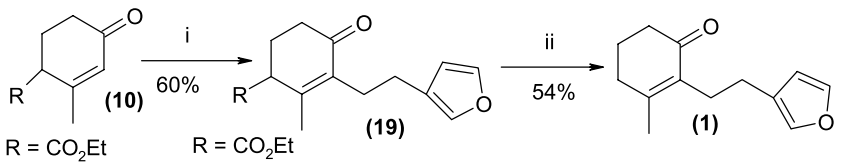
Thus the method showed the potential for the entry to the synthesis of many sesquiterpenoids via suitable furyl-ethyl cyclohexenone derivatives as common intermediates.

Being inspired with these results we then directed our efforts to apply this methodology for the synthesis of various natural pallescensins from the cyclohexenone derivative (**1**) (X=H). Compound **1** was prepared from Hagemann's ester (**10**) and 2-(3-furyl) ethyl bromide following a two steps procedure as used for the synthesis of compound **19** Scheme 3.

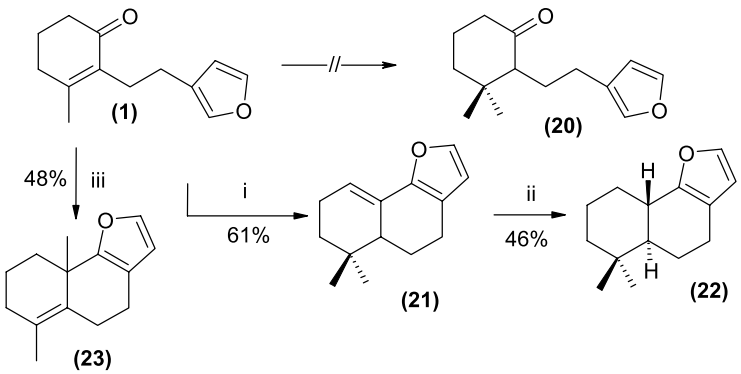
However, when this cyclohexenone derivative (**1**) (X=H) was treated with the $Me_2CuLi/BF_3{:}Et_2O$ furnished no 2-(2-furan-3-yl-ethyl)-3,3-dimethyl cyclohexanone (**20**) as expected but disappointingly it directly formed the tricyclic product (**21**) (61%), possibly through nucleophilic attack on the intermediate ketone (**20**) formed, by the activated furan moiety, followed by Lewis acid catalysed dehydration of the resulting *tert*-alcohol. We next surveyed the possibility of transforming **21** into compound **22** by hydrogenation over 5% palladium on carbon in different solvent systems. The most suitable solvent systems composed of ethyl acetate, ethanol, diethyl amine (1:1:0.2). In order to stop over reduction, the progress of the reaction was arrested before full conversion, furnished (±) 10-desmethylpallescensin-A (**22**) as a major isolable product in 46% yield. The *trans*-geometry was confirmed by 2D ^1H spectra and as well as by analogy Scheme 4.[6i]

1,2-Addition reaction of the cyclohexenone derivative (**1**) with MeLi in ether also furnished no isolable cyclohexanol derivative. In this case also the cyclohexanol derivative undergoes rapid cyclisation to produce (±) 5-desmethyl-4,5-dehydromicrocionin-1 (**23**) as the only isolable product from the reaction mixture. The crude product was identical with the product obtained after column purification. All these compounds have been characterized by the usual spectroscopic method (IR, ^1H NMR, ^{13}C NMR, Mass spectra) as well as elemental analysis.

In summary, the present study has established the feasibility of preparing the common intermediates by a very convenient method based on alkylation of Hagemann's ester with furyl-ethyl bromide to generate 2-(2/3-furan-2-yl-ethyl)-3-methylcyclohex-2-enone derivative as a common intermediate which can be exploited as a gateway to several tricyclic furoterpenes and their analogues.



Scheme 3. Reagents and conditions: (All the reactions were carried under argon atm) (i) ^{t}BuOK, 2-(3-furyl-ethyl bromide), reflux, 12 h (ii) KOH, EtOH–H_2O, reflux for 8 h.



Scheme 4. Reagents and conditions: (i) $Me_2CuLi–BF_3{:}Et_2O$, ether, −50 °C (15 min), then −30 °C (1 h) (ii) H_2/5% Pd–C (iii) MeLi, ether, −30 °C to rt.

3. Experimental

3.1. General information

The compounds described are all racemates. All reagents and solvents were reagent grade. Further purification and drying by standard methods were employed in each step. All organic solvents were evaporated under reduced pressure with a rotary evaporator. The plates used for thin-layer chromatography (TLC) were E. Merck silicagel $60F_{254}$ (0.25 mm thickness) precoated on aluminum plates, and they were visualized under short (254 nm) UV light. Column chromatography was performed using silica gel (60–120 mesh and 230–400 mesh for flash chromatography, SRL) and neutral alumina. NMR spectra were recorded on a Bruker spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C). All NMR measurements were carried out at 300 K in deuterated chloroform solution (dried with 4 Å molecular sieves) unless otherwise stated. Chemical shifts are reported as parts per million (ppm) in δ unit in the scale relative to the resonance of $CDCl_3$ (7.26 ppm in the ^1H, 77.00 ppm for the central line of the triplet in the ^{13}C modes, respectively). Coupling constants (J) are reported in Hz. Splitting patterns are described by using the following abbreviation: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet; brd, broad doublet. ^1H NMR data are reported in this order: chemical shift; multiplicity, number of proton, coupling constant(s). IR spectra were recorded on a Parkin–Elmer 830 machine. Mass spectra were obtained from IICB, Kolkata and determined at an ionized voltage of 70 eV. Relevant data were tabulated as m/z. Elemental analyses were performed at CDRI, Lucknow.

3.1.1. 3-(2-Furan-2-yl-ethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (11). Potassium (1.07 g, 27.44 mmol) was dissolved in dry *tert*-butyl alcohol (20 mL) and then the latter was distilled off until a white solid appeared. This was cooled to room temperature (rt) and 2-methyl-4-oxocyclohex-2-ene carboxylate (Hagemann's ester) (**10**) (5 g, 27.47 mmol) was added in one portion with stirring under N_2 atmosphere. The red solution so formed turned into straw-yellow solid a few minutes after the addition. 2-Furyl ethyl bromide (4.8 g, 27.43 mmol) was then added and the resultant solution refluxed with stirring for 12 h. The cooled reaction mixture was then poured onto crushed ice, acidified with cold HCl (6 N) and extracted with ether (3×100 mL). The ether solution was washed thoroughly with water and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow liquid which was purified by reduced pressure distillation.

Faint yellow oil (4.9 g, 65%) (bp 140–142 °C/1 mm Hg); IR ($CHCl_3$): ν 1662 (–CO_2Et), 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H, J=7.1 Hz, methyl protons), 1.8 (s, 3H, methyl protons), 2.00–2.61 (m, 4H), 2.66 (brs, 4H), 3.24 (brt, 1H, J=4.8 Hz), 4.18 (q, 2H, J=7.1 Hz, methylene protons), 5.93 (d, 1H, J=2.9 Hz, furan β proton), 6.24 (dd, 1H, J=2.9, 1.9 Hz, furan β proton), 7.27 (d, 1H, J=1.9 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.01 (CH_3), 19.97 (CH_3), 24.41 (CH_2), 25.44 (CH_2), 26.74 (CH_2), 34.17 (CH_2), 47.59 (–CH), 61.13 (CH_2), 105.37 (–CH), 110.15 (–CH), 135.97, 140.74 (–CH), 151.26, 155.19, 172.13, 197.35; MS (EI, 70 eV) m/z 276 (M^+), 203, 182, 123, 67. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.74; H, 7.23.

3.1.2. 2-(2-Furan-2-yl-ethyl)-3-methyl-cyclohex-2-enone (12). A solution of KOH (3.25 g, 58.03 mmol) in 12 mL water and 12 mL ethanol was added to the ketoester (**11**) (4 g, 14.49 mmol). The reaction mixture was refluxed with stirring under N_2 atmosphere for 8 h. Excess alcohol was then removed by distillation under reduced pressure and the residue was diluted with ice water, acidified with 6 N HCl, and extracted with ether (4×50 mL). The ether extract was washed successively with brine solution, 5% $NaHCO_3$ solution, and water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether–ethyl acetate; 7:3).

Yellow oil (1.5 g, 51%); IR ($CHCl_3$): ν 1661 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (s, 3H, methyl protons), 1.86–1.96 (m, 2H), 2.25–2.39 (m, 4H), 2.58–2.63 (m, 4H), 5.90 (d, 1H, J=3.16 Hz, furan β proton), 6.23–6.25 (m, 1H, furan β proton), 7.27 (d, 1H, J=1.8 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.77 (CH_3), 22.17 (CH_2), 25.47 (CH_2), 27.73 (CH_2), 32.79 (CH_2), 38.12 (CH_2), 105.17 (–CH), 110.12 (–CH), 134.09, 140.65 (–CH), 155.62, 156.47, 198.55; MS (EI, 70 eV) m/z 204 (M^+), 136, 123, 104, 89, 67. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.32; H, 7.72.

3.1.3. 2-(2-Furan-2-yl-ethyl)-3,3-dimethyl-cyclohexanone (13). To a stirred suspension of CuI (1.40 g, 7.35 mmol) in dry ether (5 mL) under N_2 at −25 °C (bath temperature) was added MeLi in ether (1.3 M) (11.2 mL, 14.55 mmol). The resulting yellow suspension was cooled to −50 °C and BF_3:Et_2O (0.93 mL, 7.33 mmol) was added. After 20 min the cyclohexanone (0.5 g, 2.45 mmol) in Et_2O (5 mL) was added dropwise (15 min) and the mixture was stirred at −30 °C for 15 min. An additional lot of BF_3:Et_2O (0.93 mL, 7.33 mmol) was added and stirring was continued at −30 °C for 1 h and then allowed to 0 °C. Quench it with aqueous NH_4Cl and extracted with ether (3×50 mL). The ether extract was washed successively with ice water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether–ethyl acetate 8:2).

Sweet smelling yellow oil (0.46 g, 85%); IR ($CHCl_3$): ν 1708 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75 (s, 3H), 1.01 (s, 3H), 1.59–2.5 (m, 8H), 2.6–2.65 (m, 3H), 5.95 (d, 1H, J=3.04 Hz), 6.25 (brs, 1H), 7.28 (d, 1H, J=1.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.44 (CH_3), 22.11 (CH_2), 22.89 (CH_2), 25.27, 26.70 (CH_2), 29.20 (CH_3), 39.22 (CH_2), 41.19 (CH_2), 59.48 (–CH), 104.78 (–CH), 109.77 (–CH), 140.54 (–CH), 155.64, 212.97; MS (EI, 70 eV) m/z 220 (M^+), 126, 106, 88, 67. Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.21; H, 8.95.

3.1.4. 2-(2-Furan-2-yl-ethyl)-1,3,3-trimethyl-cyclohexanol (14). To a stirred solution of ketone (**13**) (0.3 g, 1.36 mmol) at −30 °C in dry ether (5 mL), an ethereal solution of MeMgI [prepared from Mg turnings (0.035 g, 1.46 mmol), MeI (0.1 mL) in dry ether (5 mL)] or MeLi

(1.3 M, 1.1 mL, 1.36 mmol) was added dropwise for 30 min. The mixture was stirred for an additional 1 h at 0–5 °C. After workup with ether, the cyclohexanol (**14**) was obtained as yellow oil, which was purified by column chromatography (silica gel, pet ether–ethyl acetate 1:1).

Yellow oil (0.22 g, 69%); IR ($CHCl_3$): ν 3380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 0.96 (s, 3H), 1.16 (s, 3H), 1.44–1.69 (m, 8H), 2.62–2.75 (m, 4H), 5.99 (d, 1H, J=2.9 Hz), 6.27 (brs, 1H), 7.29 (d, 1H, J=1.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.23, 21.36, 24.37, 29.67, 30.25, 31.84, 34.70, 41.16, 41.73, 53.34, 65.80, 104.63, 110.01, 140.68, 156.20. MS (EI, 70 eV) m/z 236 (M^+), 221, 219, 81, 67. Anal. calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.34; H, 10.11.

3.1.5. 6,6,9a-Trimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[2,1-*b*]furan (15). Alcohol (**14**) (0.1 g, 0.42 mmol) was dissolved in cyclohexane (1.5 mL), and formic acid (100%) (0.1 mL) was added. The mixture was stirred vigorously for 1 h at rt under inert atmosphere. The upper layer of the two phase system was yellow to brown in colour, the bottom layer was dark purple. Ice water (5 mL) was added, the aqueous layer was extracted with ether (2×25 mL). The combined extracts were washed with 5% $NaHCO_3$ solution and brine. Solvent removed and the crude products were purified by flash chromatography (200–400 mesh, pet ether).

Colourless oil (36 mg, 40% [this is mixture of two isomers which was separated using preparative thin-layer chromatographic technique, elution with hexane]); IR ($CHCl_3$): 2928, 1496, 1435, 1295, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.94 (s, 3H), 1.14 (s, 3H), 1.38–1.90 (m, 8H), 2.54–2.69 (m, 3H), 6.15 (d, 1H, J=1.9 Hz), 7.17 (d, 1H, J=1.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.89, 21.16, 22.63, 23.26, 24.33, 27.39, 34.19, 38.22, 41.97, 48.49, 53.43, 109.92, 120.25, 140.56, 156.61. Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.76; H, 9.96.

3.1.6. 2-[2-(2,6,6-Trimethyl-cyclohex-2-enyl)-ethyl]-furan (16). Colourless oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s, 3H), 1.02 (s, 3H), 1.47 (s, 3H), 1.6–1.7 (m, 4H), 1.93–1.97 (m, 2H), 2.36–2.7 (m, 4H), 5.96 (brs, 1H, vinylic proton), 6.26 (brs, 1H), 7.28 (brs, 1H). Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.84; H, 9.98.

3.1.7. 2,2,2-Trifluoro-1-(6,6,9a-trimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[2,1-*b*] furan-2-yl)-ethanone (17). A mixture of cyclohexanol (**14**) (50 mg, 0.21 mmol), trifluoroacetic anhydride (2 mL), and trifluoroacetic acid (0.5 mL) was stirred for 8 h at rt under argon atmosphere. The brown mixture was then poured onto crushed ice and extracted with ether (3×25 mL). The ether extract was then washed successively with ice-cold 5% $NaHCO_3$ solution and brine and then dried (Na_2SO_4) and concentrated. The crude compound thus obtained was purified by column chromatography (Silica gel/benzene–pet ether, 1:9)

Colourless oil (25 mg, 38%); IR ($CHCl_3$): ν 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 3H, *gem*-dimethyl protons), 0.92 (s, 3H, *gem*-dimethyl protons), 1.17 (s, 3H, angular methyl protons), 1.22–2.15 (m, 9H), 2.69–2.85 (m, 2H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.39, 18.74, 21.28, 23.64, 25.02, 27.10, 33.18, 33.38, 34.66, 38.10, 41.78, 51.79, 113.81, 129.4, 152.5, 160.56, 192.5; MS (EI, 70 eV) m/z 314 (M^+), 299 ($M-15$, B^+), 271, 257, 245, 243, 231, 217, 178, 137, 121, 103, 89, 67. Anal. calcd for $C_{17}H_{21}F_3O_2$: C, 64.96; H, 6.73. Found: C, 65.14; H, 6.65.

3.1.8. 2-[2-(2,2-Dimethyl-6-methylene-cyclohexyl)-ethyl]furan (18). A 1.6 M solution of *n*-butyllithium (1.0 mL, 1.6 mmol) was injected slowly to a cold (−30 °C) stirred suspension of methyltriphenylphosphonium iodide (0.65 g, 1.60 mmol) in dry THF (2.5 mL), under argon atmosphere. After 2.5 h a THF solution of (0.5 mL) of the cyclohexanone (**13**) (0.1 g, 0.46 mmol) was injected dropwise. The stirring was continued at −30 °C for about 30 min and then allowed to attain rt. It was further stirred at rt (3–3.5 h) before quenching with ice water. The THF was removed in rotary evaporator under reduced pressure. Extraction with ether (3×25 mL) followed by the usual work up afforded the crude product which was purified by column chromatography (Neutral alumina/benzene–pet ether, 1:5).

Colourless oil (70 mg, 71%); IR ($CHCl_3$): ν 1635, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.94 (s, 3H), 1.4–2.2 (m, 8H), 2.41–2.65 (m, 3H), 4.56 (brs, 1H), 4.8 (brs, 1H), 5.95 (d, 1H, J=3.0 Hz), 6.28 (dd, 1H, J=3.0, 1.8 Hz), 7.27 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.56, 24.76, 26.28, 26.57, 28.29, 32.22, 36.01, 39.20, 53.43, 104.41, 107.61, 109.30, 140.57, 155.32, 156.14; MS (EI, 70 eV) m/z 218 (M^+), 203, 121, 67. Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.62; H, 10.10.

3.1.9. 3-(2-Furan-3-yl-ethyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylic acid ethyl ester (19). Potassium (0.64 g, 16.41 mmol) was dissolved in dry *tert* butyl alcohol (12 mL) and then the latter was distilled off until a white solid appeared. This was cooled to rt and 2-methyl-4-oxocyclohex-2-ene carboxylate (Hagemann's ester) (**10**) (3 g, 16.48 mmol) was added in one portion with stirring under N_2 atmosphere. The red solution so formed turned into straw-yellow solid a few minutes after the addition. 3-furyl ethyl bromide (2.9 g, 16.57 mmol) was then added and the resultant solution refluxed with stirring for 12 h. The cooled reaction mixture was then poured onto crushed ice, acidified with cold HCl (6 N) and extracted with ether (3×100 mL). The ether solution was washed thoroughly with water and dried (Na_2SO_4). Evaporation of the solvent afforded a yellow liquid which was purified by reduced pressure distillation.

Yellow oil (2.7 g, 60%); (bp 148–150 °C/1 mm Hg); IR ($CHCl_3$): ν 1666, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, 3H, J=7.0 Hz, methyl protons), 1.86 (s, 3H, methyl protons), 2.20–2.57 (m, 8H), 3.24 (brt, 1H, J=4.7 Hz), 4.24 (q, 2H, J=7.0 Hz, methylene protons), 6.27 (d, 1H, J=1.1 Hz, furan β proton), 7.21(brs, 1H, furan α proton), 7.33 (brs, 1H, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.27, 18.14, 23.35, 25.49, 25.98, 34.25, 47.60, 61.27, 111.13, 124.38, 137.60, 139.20, 142.47, 150.67, 172.06, 197.25; MS (EI, 70 eV) m/z 276 (M^+), 261($M-15$), 203 ($M-CO_2Et$), 135, 95, 81. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.78; H, 7.18.

3.1.10. 2-(2-Furan-3-yl-ethyl)-3-methyl-cyclohex-2-enone (1). A solution of KOH (1.62 g, 28.92 mmol) in 8 mL water and 8 mL ethanol was added to the ketoester (**11**) (2 g, 7.25 mmol). The reaction mixture was refluxed with stirring under N_2 atmosphere for 8 h. Excess alcohol was then removed by distillation under reduced pressure and the residue was diluted with ice water, acidified with 6 N HCl, and extracted with ether (4×50 mL). The ether extract was washed successively with brine solution, 5% $NaHCO_3$ solution, and water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography.

Light orange oil (0.79 g, 54%); IR ($CHCl_3$): ν 1662 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz) δ 1.84 (s, 3H), 1.88–2.03 (m, 2H), 2.29–2.54 (m, 8H), 6.28 (brs, 1H), 7.18 (brs, 1H), 7.32 (brs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.19, 22.22, 23.98, 26.05, 32.82, 37.83, 111.18, 126.29, 134.77, 138.85, 142.49, 156.04, 198.63; MS (EI, 70 eV) *m/z* 204 (M^+), 161, 110, 108, 95, 81. Anal. calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.79; H, 7.75.

3.1.11. 6,6-Dimethyl-4,5,5a,6,7,8-hexahydro-naphtho[1,2-*b*]furan (21). To a stirred suspension of CuI (1.12 g, 5.87 mmol) in dry ether (5 mL) under N_2 at −25 °C (bath temperature) was added MeLi in ether (1.3 M) (8.95 mL, 11.81 mmol). The resulting yellow suspension was cooled to −50 °C and BF_3:Et_2O (0.74 mL, 5.86 mmol) was added. After 20 min the cyclohexanone (0.4 g, 1.96 mmol) in Et_2O (2 mL) was added dropwise (15 min) and the mixture was stirred at −30 °C for 15 min. An additional lot of BF_3:Et_2O (0.74 mL, 5.86 mmol) was added and stirring was continued at −30 °C for 1 h and then allowed to 0 °C. Quench it with aqueous NH_4Cl and extracted with ether (4×50 mL). The ether extract was washed successively with ice water and then dried (Na_2SO_4). Removal of the solvent gave the title compound, which was purified by column chromatography (silica gel, pet ether).

Sweet smelling yellow oil (0.24 g, 61%); IR ($CHCl_3$): 1475, 1380, 1372, 1273, 1135, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 1.03 (s, 3H), 1.38–1.45 (m, 2H), 1.97–2.17 (m, 3H), 2.53–2.56 (m, 4H), 5.97 (brs, 1H vinylic proton, not exchangeable with D_2O), 6.22 (d, 1H, *J*=1.7 Hz) 7.23 (d, 1H, *J*=1.7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.23, 22.37, 22.42, 24.53, 28.00, 29.68, 31.26, 37.65, 45.27, 110.82, 115.17, 127.58, 140.35, 140.85; MS (EI, 70 eV) *m/z* 202 (M^+), 187, 172, 131, 119, 105, 91, 81. Anal. calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.42; H, 8.76.

3.1.12. 6,6-Dimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[1,2-*b*]furan (22). To a solution of **21** (30 mg, 0.15 mmol) in ethyl acetate (1 mL), ethanol (1 mL), and diethyl amine (0.2 mL) was added 20 mg 5% Palladium on carbon. This stirred mixture was blanked with hydrogen. After 12 h stirring at rt the catalyst was removed by filtration through celite, and the filtrate concentrated. The residue was chromatographed on silica gel (elution with hexane).

Colourless oil (14 mg, 46%); IR ($CHCl_3$): 2925, 1598, 1453, 1220, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3H), 1.04 (s, 3H), 1.15–1.41 (m, 4H), 1.45–2.12 (m, 6H), 2.41–2.44 (m, 2H), 6.14 (brs,1H), 7.22 (brs, 1H); MS (EI, 70 eV) *m/z* 204 (M^+). Anal. calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.56; H, 10.13.

3.1.13. 6,9a-Dimethyl-4,5,7,8,9,9a-hexahydro-naphtho[1,2-*b*]furan (23). To a stirred solution of **1** (0.1 g, 0.49 mmol) in ether at −30 °C in N_2 atmosphere add MeLi in ether (1.3 M) (0.35 mL, 0.45 mmol) solution into the reaction mixture. Stirring was continued for 2 h at that temperature, and then allowed reaching the rt. Quench with ice cold NH_4Cl solution and extracting with ether (3×25 mL), washed with ice water and dried (Na_2SO_4). Solvent was removed and chromatographed on silica gel (elution with pet ether).

Light yellow oil (48 mg, 48%); IR ($CHCl_3$): 1540, 1497, 1367, 1263, 1110, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H, methyl protons), 1.72 (s, 3H, methyl protons), 1.98–2.12 (m, 4H), 2.25–2.45 (m, 4H), 2.70–2.73 (m, 2H), 6.14 (d, 1H, *J*=1.7 Hz, furan β proton), 7.22 (d, 1H, *J*=1.7 Hz, furan α proton); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.32 (CH_2), 19.18 (CH_3), 22.96 (CH_2), 23.91 (CH_2), 25.71 (CH_3), 32.13 (CH_2), 34.08 (CH_2), 36.71, 109.87, 114.77, 126.60, 132.83, 140.45, 158.27; MS (EI, 70 eV) *m/z* 202 (M^+), 187, 172, 159, 131, 119, 105, 91, 81. Anal. calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.13; H, 8.82.

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Synthesis of orthogonally protected 2-deoxystreptamine stereoisomers

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Abstract—Enantiomerically pure 4,6-diaminocyclohexenols are obtained from carbohydrate derived 1,7-dienes by ring-closing metathesis and palladium catalyzed allylic amination using *o*-nitrobenzenesulfonylamides as nucleophiles. In the latter reaction the use of a cyclic carbonate as a leaving group proved to be essential to facilitate a smooth substitution. The obtained compounds were converted into orthogonally protected diaminocyclitols, which are stereoisomers of the naturally occurring 2-deoxystreptamine, a constituent of aminoglycoside antibiotics.

1. Introduction

RNA is involved in several important biological processes including protein synthesis and regulation of transcription and translation. Small molecules that are able to modulate RNA functions are interesting compounds for the development of drugs.[1] For example, aminoglycoside antibiotics, such as neomycin B and kanamycin B (Fig. 1), form a major lead in RNA targeting drug research. The current clinical use of aminoglycoside antibiotics is based on the binding to the A-site of 16S rRNA[2] and its ability to induce misreading of the genetic code.[3] In the last decade aminoglycosides have been shown to target a variety of other RNA structures including hepatitis delta virus ribozyme,[4] HIV *trans*-activating region (TAR),[5] and HIV rev responsive element (RRE).[6] It may be expected that the development of aminoglycosides that can selectively target RNA structures will broaden the application of aminoglycoside antibiotics.

The preparation of aminoglycoside analogs has attracted the

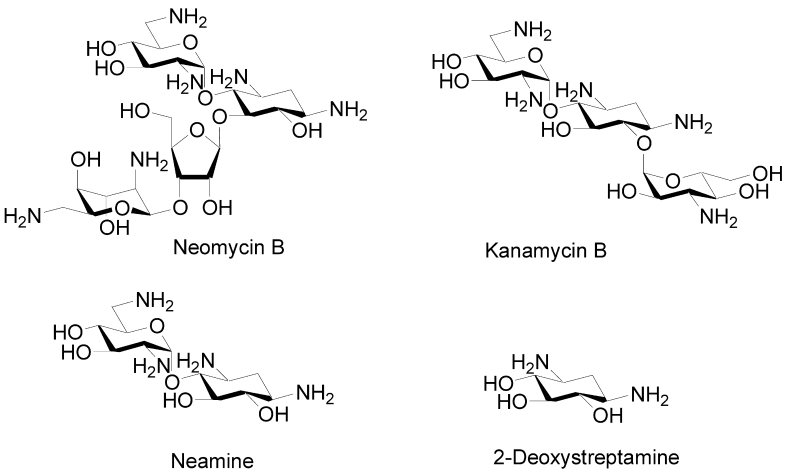

Figure 1. Examples of aminoglycoside antibiotics.

Keywords: Aminoglycoside antibiotics; 2-Deoxystreptamine; Cyclitols; Allylic substitution.
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attention of synthetic chemists. Most recent studies are based on the derivatization of natural aminoglycosides or substructures thereof, such as neamine and 2-deoxystreptamine (2-DOS; Fig. 1). For example, 2-DOS has been functionalized with polyamines[7] and aryl substituents.[8] Another promising approach towards the construction of aminoglycoside analogs is based on the glycosylation of cyclitol building blocks. The naturally occurring 2-DOS can be effectively obtained in its *meso* form by hydrolysis of neomycin B,[9] while protected and enantiomerically pure 2-DOS can be prepared by chemical transformation of neamine[10] or enzymatic desymmetrization of 2-DOS.[11] Both 2-DOS and its 2,5-dideoxy congener[12] have recently been used in glycosylations to obtain analogs of aminoglycoside antibiotics that closely resemble the natural products.[11,13,14]

The functionalization of synthetic, unnatural diaminocyclitols represents an attractive alternative strategy towards selective RNA binding molecules. The stereochemically more diverse aminoglycosides resulting from this approach can be an important extension of the aminoglycoside antibiotic research, since the three-dimensional positioning of the amino groups in the aminoglycoside core may well be decisive for selective interaction with the negatively charged binding pockets in RNA.[15]

We here report the synthesis, starting from carbohydrate derivatives, of chiral diaminocyclohexene derivatives **A** (Fig. 2) and their conversion into orthogonally protected stereoisomers of 2-deoxystreptamine (**B**), which are valuable compounds in the design of novel aminoglycoside antibiotics having unnatural stereochemistry.

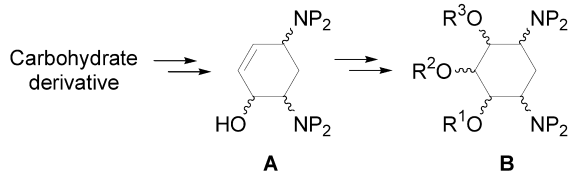
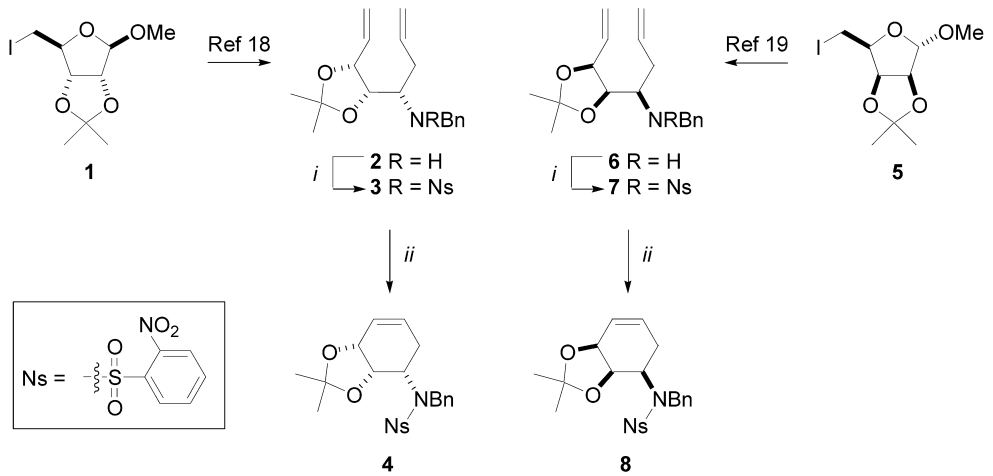


Figure 2. Strategy towards stereoisomers of 2-DOS.

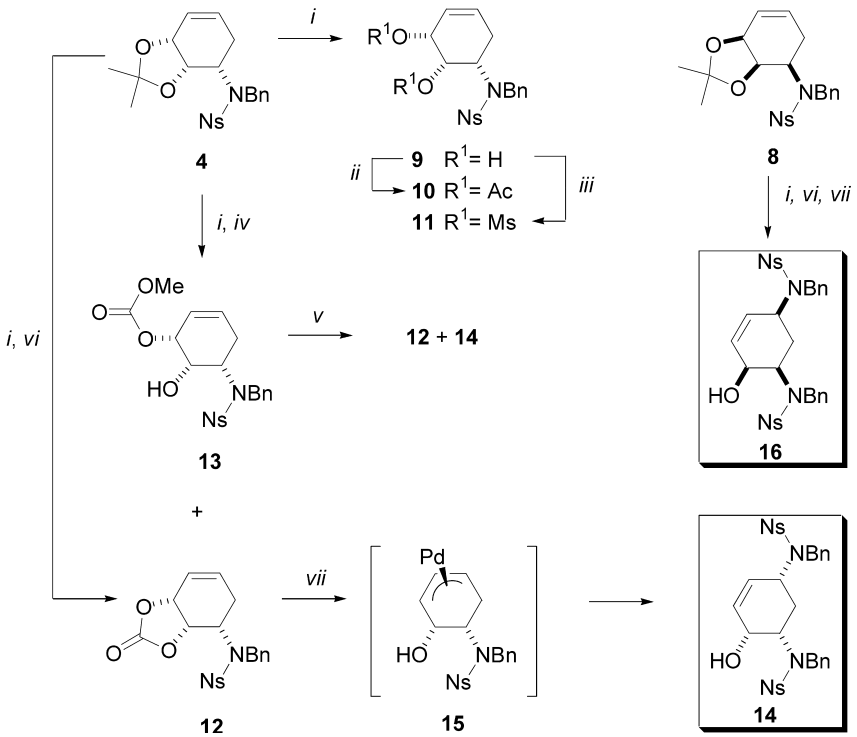
2. Results and discussion

The first objective in our approach comprises the transformation of a carbohydrate derivative into a six-membered carbocycle. A revolution in the synthesis of carbocycles was caused by the development of powerful metathesis catalysts.[16] Specifically, cyclization of 1,7-dienes by ring-closing metathesis proved to be an attractive method to synthesize cyclitols.[17,18] In the first instance, we used 1,7-dienes, prepared by the Vasella–Barbier reaction[18] of easily accessible 5-iodopentafuranosides, in the synthesis of diaminocyclohexenols **14** and **16**.[19] 1,7-Diene **2** was synthesized from methyl 5-deoxy-5-iodo-2,3-isopropylidene-β-D-ribofuranoside **1** in a one-pot process including Vasella fragmentation, entrapment of the intermediate aldehyde by an amine and subsequent Barbier type imine allylation (Scheme 1).[18] Similarly, the enantiomeric 1,7-diene **6** was obtained starting from methyl 5-deoxy-5-iodo-2,3-isopropylidene-β-D-lyxofuranoside (**5**).[19] The secondary amino functions in compounds **2** and **6** were protected with the *o*-nitrobenzenesulfonyl[20] (nosyl, Ns) group to give **3** and **7** in 92 and 89% yield, respectively. Both protected dienes smoothly underwent ring-closing metathesis using 0.5 mol% Grubbs' catalyst ($Cl_2(PPh_3)_2Ru{=}CHPh$)[16a] to give the fully protected cyclohexene derivatives **4** and **8**.

It was envisaged that a palladium catalyzed allylic amination using nitrobenzenesulfonamides as nucleophiles[21] could be employed to introduce the second amine functionality on the carbocyclic ring. In order to enable substitution, the protected allylic hydroxyl in compounds **4** and **8** had to be converted into a suitable leaving group. To this end, several leaving groups were installed on ribose-derived scaffold **4**. 1,2-Diacetate **10** and 1,2-dimesylate **11**, were obtained by cleavage of the isopropylidene and subsequent acetylation or mesylation of diol **9** (Scheme 2). Unfortunately, both compounds were unreactive, which is rather surprising, taken into consideration that especially allylic acetates are often used in Pd(0)-catalyzed allylic substitutions. It was expected that productive Pd(0) catalyzed allylic substitution could be effected when the hydroxyl functions of diol **9** were converted into methylcarbonates. This functionality has been described in the literature to be favorable compared with acetates, as CO_2 is



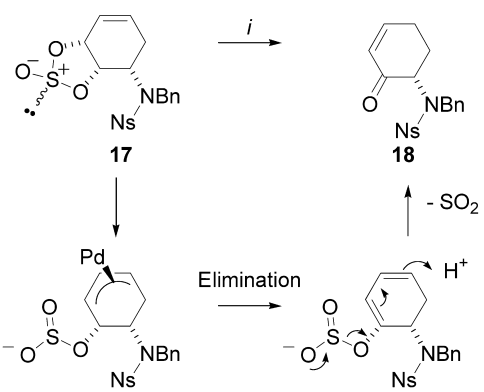
Scheme 1. Reagents and conditions: (i) *o*-Nitrobenzenesulfonylchloride (NsCl), DCM/sat. Na_2CO_3, **3**: 92%, **7**:89%. *(ii)* Grubbs' catalyst (0.5 mol%), quant.



Scheme 2. Reagents and conditions: (i) AcOH/H_2O 8:2, reflux. (ii) Ac_2O, pyridine, 94% (2 streps from **4**). (iii) MsCl (5 equiv.), pyridine, 69% (2 steps from **4**). (iv) Methyl chloroformate (5 equiv.), pyridine (6 equiv.), DCM. (v) NsNHBn (2.2 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF. (vi) Phosgene (1.1 equiv.), pyridine, DCM, **12**: 98%. (vii) NsNHBn (1.3 equiv.), $Pd_2(dba)_3{-}CHCl_3$ (0.25 mol%), PPh_3 (2.5 mol%), Et_3N (3 equiv.), THF, **14**: 87%. **16**: 76% (three steps).

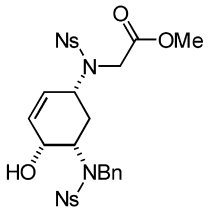
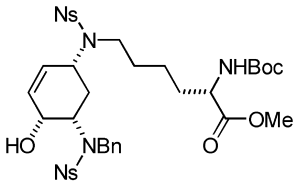
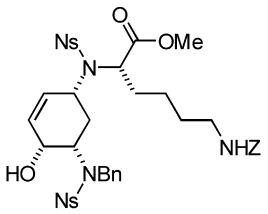
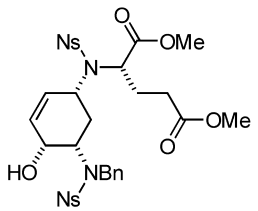
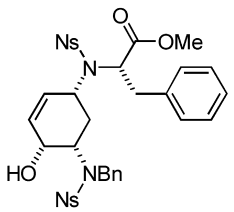
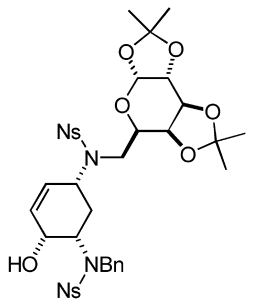
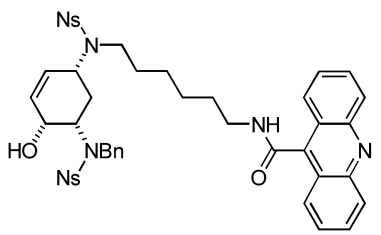
liberated upon substitution, leading to a favorable entropic contribution.[22] However, the installation of methylcarbonate functionalities on the hydroxyls of compound **9** did not proceed efficiently. Reaction of **9** with an excess of methylchloroformate led to the formation of a mixture of cyclic carbonate **12** and monosubstituted compound **13**. Subjection of **13** to the Pd(0)-catalyzed allylic amination using *N*-benzyl-nosylamide as a nucleophile, led to the sluggish formation of cyclic carbonate **12**, presumably via intramolecular attack of the free hydroxyl group on the carbonyl function (Scheme 2). Apart from this, a small amount of target molecule **14** was detected, probably originating from substitution of the in situ formed cyclic carbonate **12**. The latter reaction did not go to completion due to degradation of the palladium catalyst, as judged by the color of the reaction mixture, which turned from bright yellow to dark brown. However, cyclic carbonate **12** could be prepared on a large scale by hydrolysis of acetonide **4** under standard conditions and subsequent reaction of the diol with a slight excess of phosgene (98%; Scheme 2). Pd(0) catalyzed allylic amination of **12** gave the diaminocyclohexene derivative **14** in 87% yield. The regio- and stereoselectivity of this reaction originates from the formation of the π-allyl complex **15** and subsequent attack of the nucleophile at the less hindered carbon atom. Subjection of the enantiomeric carbocycle **8** to the same reaction conditions gave the diaminocyclohexene derivative **16**, which was isolated in 76% yield over 3 steps (Scheme 2).

The observation that cyclic carbonate **12**, but not its acyclic counterpart **13**, was a useful substrate indicates that the release of carbon dioxide and possibly the relief of strain in the five-six fused ring system of compound **12** upon formation of the π-allyl complex provides a favorable energetic contribution resulting in a smooth and high yielding reaction. We expected that cyclic sulfite **17**, accessible after reaction of diol **9** with thionylchloride, would follow a similar course to give compound **14**. However, subjection of **17** to the paladium catalyzed allylic amination gave the unexpected cyclohexenone derivative **18** in a non-optimized yield of 30%. The formation of **18** may be explained by the mechanism proposed in Scheme 3. Instead of substitution of the π-allyl complex by the nitrosulfonamide nucleophile, elimination of palladium takes place followed by liberation of sulfur dioxide to form the α,β-unsaturated ketone **18**. The observation that performing the reaction in the absence of catalyst did not result in the formation of **18** illustrates that the Pd(0) species plays a crucial role.[23]



Scheme 3. Reagents and conditions: (i) NsNHBn (2.2 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF.

Table 1. Transformation of **5** into 4,6-diaminocyclohexene derivatives[a]

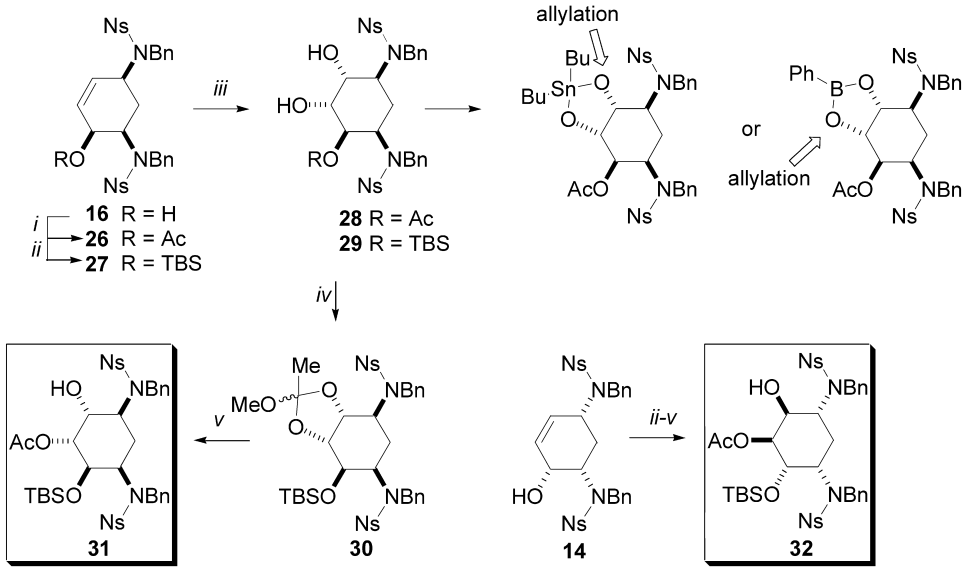
Entry	Product		Yield (%)
1		**19**	85
2		**20**	71
3		**21**	36
4		**22**	37
5		**23**	44 (51)[b]
6		**24**	80
7		**25**	58

[a] General conditions: NsNHR (1.5 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF.
[b] 10% Pd(0) catalyst was used.

The scope of the allylic amination of cyclic carbonate **12** was broadened by the use of other nosylamides as nucleophiles, leading to highly functionalized diaminocyclohexene derivatives (Table 1). Application of Ns-glycine methyl ester and ε-Ns-α-Boc-L-lysine methyl ester as nucleophiles led to the formation of peptide derivatives **19** and **20** in 85 and 71%, respectively. Lysine, glutamic acid and phenylalanine derivatives **21**–**23** were synthesized using the respective amino acids with a Ns-group at the α-amino functions. However, yields were lower compared to those in entry 1 and 2, probably due to steric hindrance around the nucleophilic center. A double amount of palladium catalyst only led to a slight increase in yield (see entry 5). In an attempt to improve the yield of the substitution by α-amino acids, several additional experiments were conducted using phenylalanine derivatives. However, the use of the less sterically demanding *p*-nitrobenzenesulfonyl group and the more electron withdrawing di-nitrobenzenesulfonyl group did not have a beneficial effect on the outcome of the reaction.

Besides nosyl-protected amino acids, acridine and galactose derivatives featuring a terminal nosylated amine were reacted with cyclic carbonate **12** to give compounds **24** and **25** in satisfactory yields (entry 6 and 7). The latter two compounds are of particular interest in the synthesis of aminoglycoside analogs. Acridine conjugate **24** can combine the RNA binding properties of positively charged amino functions on the aminocyclitol with the intercalating properties of acridine. Compound **25** illustrates that the cyclitol moiety can be easily appended to carbohydrates via an amine bond instead of a more difficult to introduce glycosidic linkage.

At this stage, we focused our attention on the conversion (Scheme 4) of the 4,6-diaminocyclohexene derivatives **14** and **16** into orthogonally protected 2-deoxystreptamine stereoisomers **31** and **32**. The first step entails protection of the allylic alcohol function in **16**. It was anticipated that the difference in reactivity of the equatorial and axial hydroxyl function, resulting from dihydroxylation of the double bond, could be utilized for selective introduction of a protective group. For example, the use of organotin derivatives in alkylations is a well-established method to discriminate between equatorial and axial hydroxyl functions.[24] With the purpose to regioselectively introduce an allyl protecting group, we first acetylated the alcohol function in compound **16**. Dihydroxylation of **26** using *N*-methylmorpholine-*N*-oxide (NMO) and a catalytic amount of osmium tetroxide yielded **28** in 92% yield (Scheme 4). Several attempts to allylate the equatorial hydroxyl in **28** via the tin-ketal procedure were abortive. Exploration of a recently reported regioselective alkylation of cyclic phenylboronate derivatives[25] on our substrates was also not successful. It may therefore be concluded that the hydroxyl functions in **28** are not reactive enough due to the electron withdrawing protecting groups on the nitrogen and oxygen functionalities. On the other hand, it is well documented that the opening of an orthoester of pyranose derivatives proceeds to give the axial acetate. Therefore, we decided to use this method in our route. The synthesis of the required orthoester **31** was accomplished by the following steps. The free hydroxyl in compound **16** was protected with a TBS group



Scheme 4. Reagents and conditions: (i) Ac_2O, pyridine, quant. (ii) TBSCl (3 equiv.), imidazole (4 equiv.), DMF, 59% or TBSOTf (1.2 equiv.), pyridine (5 equiv.), DCM, 89%. (iii) NMO (2.2 equiv.), $K_2OsO_4{\cdot}2H_2O$ (1 mol%); **28**: 92%, **29**: 94%. (iv) $(MeO)_3CHMe$, *p*-TsOH, DCM; (v) AcOH/H_2O (v/v); **31**: 95%. **32** 71% (4 steps).

under standard conditions (TBSCl, imidazole, DMF) to give compound **27** in a yield of 59%. The more reactive silylating agent TBS triflate yielded **27** in 89%. Dihydroxylation of **27** using a catalytic amount of osmium tetroxide and NMO as a co-oxidant provided 2-DOS stereoisomer **29** in 94% yield. Treatment of *cis*-diol **29** with trimethyl orthoacetate and subsequent acid mediated cleavage of the resulting orthoester yielded the desired orthogonally protected derivative **31** in 95%. Similarly, enantiomer **14** gave the second 2-deoxystreptamine stereoisomer **32** in 71% yield over the four last steps.

3. Conclusion

In this paper, we presented a route towards chiral, 4,6-diaminocyclohexene derivatives starting from carbohydrate derived 1,7-dienes. The versatility of our approach was demonstrated by the use of structurally diverse nucleophiles including amino acid, carbohydrate and intercalator derived nosyl amides. Two of the thus obtained diaminocyclohexene derivatives were converted into orthogonally protected diaminocyclitols via a four-step procedure. The use of 2-deoxystreptamine stereoisomers **31** and **32** in the construction of novel, stereochemically diverse aminoglycoside antibiotics, is currently under investigation.

4. Experimental

4.1. General methods and materials

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker AC-200 (200 MHz, 50.1 MHz, respectively), a Bruker DPX-300 (300 MHz, 75.1 MHz respectively), a Bruker AV-400 (400 MHz, 100 MHz respectively) or a DMX-600 (600 MHz, 150 MHz respectively). ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to tetramethyl silane (0.0) or $CDCl_3$ (77.0) as internal standards. Mass spectra were recorded on a Perkin–Elmer Sciex API 165 equipped with a custom made electrospray interface (ESI). Column chromatography was performed on silica gel 60 (230–400 mesh, Fluka). TLC-analysis was conducted on TLC-plastic sheets 60 F_{254} (Merck) with detection by UV absorption (254 nm) where applicable and/or by spraying with 20% H_2SO_4 in EtOH or a solution of molybdate (ammonium molybdate 25 g/L) and ceric ammonium sulfate (10 g/L in 10% aq. H_2SO_4) followed by charring at ~150 °C. Olefins were visualized by spraying with a permanganate solution (2% $KMnO_4$ and 1% K_2CO_3 in water).

4.2. Experimental procedures

Before performing reactions that require anhydrous conditions, traces of water were removed from the starting material by coevaporation with 1,2-dichloroethane, 1,4-dioxane or toluene. Reactions were run at ambient temperature unless stated otherwise.

4.3. General procedure for the Pd(0) catalyzed allylic aminations

THF was freshly distilled from $LiAlH_4$ under argon. Triethylamine was distilled from $LiAlH_4$ and stored on KOH. To a solution of the carbocycle and the appropriate nosylamide (1.5 equiv.) in THF (final concentration of carbocycle: 0.1 M) under argon was added 3 equiv. of Et_3N, 2.5 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 25 mol% of triphenylphosphine. The red mixture turned into a bright yellow solution within 1 min. After TLC analysis indicated no change in the composition of the reaction mixture, the solvent was evaporated and the reaction mixture was purified by column chromatography. Reactions were performed on a 50–100 mg scale. Note that on a large scale (see compounds **14** and **16**) the amount of catalyst was reduced to 0.25 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 2.5 mol% PPh_3.

4.4. *o*-Nitrobenzenesulfonyl-*N*-benzylamine

Benzylamine (8.7 mL, 80 mmol) was added to a mixture of $NaHCO_3$ (13.44 g, 160 mmol), dioxane (200 mL) and water (200 mL). To the white suspension, NsCl (19.5 g, 88 mmol, 1.1 equiv.) was added in portions. The reaction mixture was stirred for 2 h followed by evaporation of the solvents. The light yellow residue was dissolved in water (150 mL) and extracted EtOAc (4×150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The solid material was recrystallized from toluene/PE, affording the title compound (21.93 g, 75 mmol, 94%) as white crystals, mp 97 °C. ν_{max} (neat): 3294, 1541, 1367, 1340, 1171 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 8.03–7.98 (m, 1H, H_{arom}), 7.85–7.81 (m, 1H, H_{arom}), 7.72–7.60 (m, 2H, H_{arom}), 7.22 (s, 5H, H_{arom}), 5.72 (m, 1H, NH), 4.32 (d, 2H, CH_2 Bn, J=6.6 Hz). ESI-MS: *m/z*: 315.0 $[M+Na]^+$, 607.2 $[2M+Na]^+$. HRMS: MNH_4^+, found 310.0849, $C_{13}H_{16}N_3O_4S$ requires 310.0862.

4.4.1. (3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-(*N*-benzyl)-*o*-nitro-benzenesulfon-amino-octa-1,7-dien-3,4-diol (3). Aminodiene **2** (16.2 g, 56.5 mmol) was dissolved in DCM/sat Na_2CO_3 (1:1 v/v, 250 mL) and NsCl (18.8 g, 84.8 mmol, 1.5 equiv.) was added. The reaction mixture was stirred vigorously overnight. Pyridine was added to destroy the excess of NsCl and, after stirring for 15 min, the solvent was removed under reduced pressure. Water was added to the residue and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Silicagel column chromatography (elution 10%→20% EtOAc in light petroleum) yielded **3** (24.7 g, 52.2 mmol, 92%) as a white, crystalline solid, mp 90–91 °C. $[\alpha]_D^{20}$=+86 (c=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1371, 1340, 1159, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.54–7.15 (m, 9H, H_{arom}), 6.07–5.89 (m, 1H, H2 or H7), 5.73–5.65 (m, 1H, H2 or H7), 5.54–5.35 (m, 4H, H1, H8), 5.00–4.79 (m, 2H, H3, H4), 4.75 (d, 1H, C*H*H Bn, J=15.4 Hz), 4.56 (d, 1H, CH*H* Bn, J=15.4 Hz), 4.21–4.07 (m, 1H, H5), 2.47–2.34 (m, 1H, C*H*H H6), 2.22–2.11 (m, 1H, CH*H* H6), 1.47 (s, 3H, Me isoprop), 1.26 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 136.7, 134.1 ($C_{q,\ arom}$), 134.3, 132.9, 131.1, 130.9, 128.8, 127.9, 127.1, 123.5 (CH_{arom}, H2, H7), 118.3, 117.0 (C1, C8), 108.3 (C_q isoprop), 81.1, 78.2 (C3, C4), 59.0 (C5), 48.5 (CH_2 Bn), 32.1 (C6), 26.1, 24.1 (Me isoprop). HRMS: MNH_4^+, found 490.2058, $C_{24}H_{32}N_3O_6S$ requires 490.2012.

4.4.2. (1*S*,2*R*,6*S*)-3-(*N*-Benzyl)-*o*-nitrobenzenesulfon-amino-1,2-*O*-isopropylidene-cyclohex-3-en-1,2-diol (4). Oxygen was removed from a solution of compound **3** (24.7 g, 52.2 mmol) in DCM (500 mL) by purging with argon for 15 min. Grubbs' catalyst $Cl_2(PPh_3)_2Ru$=CHPh (210 mg, 0.5 mol%) was added and the solution was stirred overnight under argon. The solvent was evaporated under reduced pressure affording crude **4** as a light brown foam. Crude RCM-product was applied in the next step without purification. A small purified sample was used for characterization. $[\alpha]_D^{20}$=−50.0 (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.60–7.12 (m, 9H, H_{arom}), 5.75–5.68 (m, 1H, H_{olef}), 5.56–5.50 (m, 1H, H_{olef}), 4.94 (d, 1H, C*H*H Bn, J=16.1 Hz), 4.77–4.69, 4.49–4.39 (2m, 4H, CH*H* Bn, H1, H2, H6), 2.55–2.40 (m, 1H, C*H*H H5), 2.19–2.04 (m, 1H, CH*H* H5), 1.33 (s, 3H, Me isoprop), 1.26 (s, 3H, Me isoprop). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 137.3, 134.0 ($C_{q,\ arom}$), 133.0, 131.2, 130.5, 127.8, 127.7, 126.9, 126.7, 125.9, 123.6 (CH_{arom}, C3, C4), 109.7 (C_q isoprop), 76.1, 74.8 (C1, C2), 55.1 (C6), 49.0 (CH_2 Bn), 27.5, 26.5 (Me isoprop), 25.1 (C5). ESI-MS: *m/z* 467.2 $[M+Na]^+$, 911.4 $[2M+Na]^+$.

4.4.3. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-cyclohex-3-ene-1,2-diol (9). Crude product **4** was refluxed in AcOH/H_2O (8:2, v/v, 0.2 M final concentration) for 2 h. After TLC analysis had showed complete conversion to a lower running product, the mixture was concentrated with coevaporation from toluene to remove traces of water and acetic acid. The crude diol was immediately used for protection of the hydroxyl functions.

4.4.4. (1*S*,2*R*,6*S*)-1,2-Di-*O*-acetyl-6-(*N*-benzyl)-*o*-nitrobenzenesulfonamino-cyclohex-3-ene-1,2-diol (10). A solution of compound **9** (888 mg, 2.0 mmol, 0.2 M in pyridine/Ac_2O) and dimethylaminopyridine (cat.) was stirred overnight. Solvents were removed under reduced pressure. 1 M HCl was added and the mixture was extracted two times with EtOAc. Combined organic layers were washed with sat. $NaHCO_3$ and brine. Water phases were backextracted. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography yielded title compound **10** (914 mg, 1.87 mmol, 94%) as a white solid, mp 132 °C. $[\alpha]_D^{20}$=−55 (c=0.50, $CHCl_3$). ν_{max} (neat): 1740, 1539, 1373, 1219, 1165, 1034, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.16 (m, 9H, H_{arom}), 5.86–5.81 (m, 1H, H_{olef}), 5.65–5.58 (m, 2H, H1, H2), 5.42–5.39 (m, 1H, H_{olef}), 4.75 (d, 1H, C*H*H Bn, J=16.6 Hz), 4.59 (d, 1H, CH*H* Bn, J=16.6 Hz), 4.51 (dd, 1H, H6, J=5.6, 11.2 Hz), 2.65–2.56 (m, 1H, C*H*H H5), 2.26 (dt, 1H, CH*H* H5, J=5.4, 17.0 Hz), 1.94 (s, 3H, Me Ac), 1.90 (s, 3H, Me Ac). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 169.7 (CO), 137.0, 134.0 ($C_{q,\ arom}$), 133.5, 131.7, 131.2, 128.5, 127.4, 127.2, 124.3, 124.0 (C3, C4, CH_{arom}), 70.6, 69.6 (C1, C2), 53.8 (C6), 49.0 (CH_2Bn), 26.8 (C5), 20.9, 20.7 (Me Ac). ESI-MS: *m/z*=511.2 $[M+Na]^+$, 977.4 $[M+M+H]^+$, 999.3 $[M+M+Na]^+$. HRMS: MNH_4^+, found 506.1605, $C_{23}H_{28}N_3O_8S$ requires 506.1597.

4.4.5. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfon-amino-1,2-di-*O*-methanesulfonyl-cyclohex-3-ene-1,2-diol (11). Methanesulfonylchloride (131 μL, 1.69 mmol, 10 equiv.) was added to a solution of compound **9** (150 mg, 0.338 mmol) in pyridine (3 mL). The solution was stirred overnight and concentrated under reduced pressure. EtOAc was added and the solution was washed with 1 M HCl, sat. $NaHCO_3$ and brine. Water phases were separately back-extracted with EtOAc and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography yielded compound **11** (131 mg, 0.234 mmol, 69%) as a yellowish oil. ν_{max} (neat): 1539, 1340, 1159 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ_H 7.59–7.13 (m, 9H, H_{arom}), 5.99–5.89, 5.63–5.36 (m, 4H, H1, H2, H3, H4), 5.02 (d, 1H, C*H*H Bn, J=16.8 Hz), 4.75 (d, 1H, CH*H* Bn, J=16.8 Hz), 4.69–4.61 (m, 1H, H6), 3.17 (s, 3H, Ms), 3.12 (s, 3H, Ms), 2.61–2.26 (m, 2H, H5). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ_C 147.0, 136.4, 133.8 ($C_{q,\ arom}$),

133.8, 133.5, 131.9, 131.1, 130.0, 128.2, 127.6, 127.4, 123.8, 122.3 (C3, C4, CH_{arom}), 79.9, 76.2 (C1, C2), 53.7 (C6), 48.9 (CH_2 Bn), 39.5, 38.0 (2× Ms), 26.7 (C5).

4.4.6. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-1,2-*O*-carbonyl-cyclo-hex-3-ene-1,2-diol (12). Compound **9** (52.2 mmol) was dissolved in pyridine (19 mL) and DCM (40 mL), placed under argon and cooled to 0 °C. Next, phosgene (30 mL, 1.93 M in toluene, 58 mmol, 1.1 equiv.) was carefully added over a period of approximately 2 min. The reaction mixture was stirred for 2 h, after which the excess phosgene was quenched with water. The resulting mixture was poured into 1 M HCl. After separation of the organic layer, the water layer was extracted twice with DCM. Combined organic layers were washed with diluted $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silicagel column chromatography (elution 0%→16% EtOAc in toluene) furnished **12** (21.99 g, 51.1 mmol, 98%) as a white foam. $[\alpha]_D^{20}=-76.4$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1798, 1539, 1369, 1344, 1153, 1126, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ_H 7.52–7.47 (m, 2H, H_{arom}), 7.40–7.39 (d, 1H, H_{arom}, J=8.0, 1.4 Hz), 7.27–7.24 (m, 1H, H_{arom}), 7.19–7.13 (m, 2H, H_{arom}), 7.07–7.04 (m, 3H, H_{arom}), 6.04 (ddd, 1H, H_{olef}, J=10.2, 6.2, 1.9 Hz), 5.64–5.61 (m, 1H, H_{olef}), 5.25–5.22 (m, 1H, H2), 5.09–5.07 (m, 1H, H1), 4.80 (d, 1H, C*H*H Bn, J=15.9 Hz), 4.55–4.52 (m, 2H, H6, CH*H* Bn), 2.47–2.42 (m, 1H, C*H*H H5), 2.32–2.28 (m, 1H, CH*H* H5). ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C 154.1 (CO), 147.0, 135.7, 134.2 ($C_{q,\ arom}$), 133.4, 132.7, 131.7, 131.2, 128.3, 128.1, 127.7, 124.0, 121.1 (C1, C2, CH_{arom}), 79.0, 75.1 (C1, C2), 54.4 (C6), 49.3 (CH_2 Bn), 25.2 (C5). ESI-MS: m/z=431.2 $(M+H)^+$. HRMS: MNa^+, found 453.0672, $C_{20}H_{18}N_2O_7SNa$ requires 453.0732.

4.4.7. (1*R*,4*R*,6*S*)-4,6-Bis[(*N*-benzyl)-*o*-nitrobenzenesulfon-amino]-cyclohex-2-enol (14). To a solution of cyclic carbonate **12** (14.63 g, 34 mmol) and *o*-nitrobenzenesulfonyl-*N*-benzylamine (12.9 g, 44.2 mmol, 1.3 equiv.) in THF under argon, was added Et_3N (14.2 mL, 102 mmol, 3 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (87 mg, 0.25 mol%) and triphenylphosphine (223 mg, 2.5 mol%). The initial dark red solution turned bright yellow, and the solution was stirred for 3 h, followed by concentration under reduced pressure. Silica column chromatography (elution 0%→12.5% EtOAc in toluene) yielded the title compound (20.10 g, 29.6 mmol, 87%) as a white foam. $[\alpha]_D^{20}=-17.8$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1539, 1340, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz): δ_H 7.79–7.70 (m, 1H, H_{arom}), 7.56–7.51 (m, 5H, H_{arom}), 7.43–7.40 (m, 1H, H_{arom}), 7.39–7.36 (m, 1H, H_{arom}), 7.19–7.04 (m, 10H, H_{arom}), 5.80 (ddd, 1H, H_{olef}, J=10.0, 5.7, 2.6 Hz), 5.56–5.54 (m, 1H, H_{olef}), 4.69–4.65 (m, 1H, H4), 4.58 (d, 1H, C*H*H Bn, J=16.4 Hz), 4.50 (d, 1H, C*H*H Bn, J=15.8 Hz), 4.41 (d, 1H, CH*H* Bn, J=16.4 Hz), 4.27 (d, 1H, CH*H* Bn, J=15.8 Hz), 4.14 (bs, 1H, H1), 3.96 (dt, 1H, H6, J=13.1, 2.9 Hz), 2.04–1.97 (m, 1H, C*H*H H5), 1.80–1.74 (m, 1H, CH*H* H5), 1.53 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ_C 147.49, 147.46, 137.28, 133.84 ($C_{q,\ arom}$), 133.78, 133.52, 133.39, 131.68, 131.65, 131.37, 131.32, 130.95, 130.92, 128.51, 128.38, 127.73, 127.68, 127.45, 124.12, 124.08 (C2, C3, CH_{arom}), 66.72 (C1), 56.97, 56.75 (C4, C6), 49.29, 48.79 (CH_2 Bn), 27.44 (C5). ESI-MS: m/z=701.4 $[M+Na]^+$.

4.4.8. (1*S*,2*R*,6*S*)-6-(*N*-Benzyl)-*o*-nitrobenzenesulfonamino-1,2-*O*-sulfonyl-cyclohex-3-ene-1,2-diol (17). A solution of pyridine (170 μL, 2.1 mmol, 2.1 equiv.) in EtOAc (1 mL) was added to a solution of compound **9** (444 mg, 1.0 mmol) and $SOCl_2$ (77 μL, 1.05 mmol) in EtOAc (4 mL) cooled in the waterbath. After TLC analysis indicated complete conversion to a higher running product (±1 h), the reaction was diluted with 1 M HCl and extracted twice with EtOAc. Organic phase was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (elution 0%→12.5% EtOAc in toluene) afforded cyclic sulfite **17** (350 mg, 0.77 mmol, 77%) as a white foam, being a mixture of two diastereoisomers of the sulfur ylide. ν_{max} (neat): 1541, 1369, 1346, 1209, 1161, 1124 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.59–7.10 (m, 9H, H_{arom}), 5.97–5.81, 5.60–5.56, 5.40–5.37 (3× m, 4H, H1, H2, H3, H4), 5.02–4.89 (m, 1H, benzylic H), 4.80–4.63 (m, 2H, H6, benzylic H), 2.69–2.61, 2.48–2.22 (2× m, 2H, H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 136.1, 136.0 ($C_{q,\ arom}$), 133.4, 133.2, 131.7, 131.6, 131.3, 131.5, 129.9, 129.8, 128.4, 128.3, 128.2, 127.7, 127.5, 124.1, 124.0, 123.7, 122.4 (C3, C4, CH_{arom}), 85.0, 81.3, 80.2, 79.0 (C1, C2), 55.2, 53.8 (C6), 49.4, 49.3 (CH_2 Bn), 25.6, 25.2 (C5). ESI-MS: m/z=450.9 $[M+H]^+$, 468.2 $[M+NH_4]^+$, 473.0 $[M+Na]^+$. HRMS: MNH_4^+, found 468.0889, $C_{19}H_{22}N_3O_7S_2$ requires 468.0899.

4.4.9. (6*S*)-6-[(*N*-Benyzl)-*o*-nitrobenzenesulfonamino]-cyclo-hex-2-enone (18). Pd(0) catalyzed allylic amination on cyclic sulfite **17** was performed according to the general procedure. After column chromatography (elution 0%→15% EtOAc in toluene) compound **18** was isolated as a light brown oil in an unoptimized yield of 13 mg (30%). ν_{max} (neat): 1688, 1539, 1346, 1159, 1122 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99–7.17 (m, 9H, H_{arom}), 6.97–6.91 (m, 1H, H3), 6.04 (dd, 1H, H2, J=2.5, 10.0 Hz), 4.96–4.86 (m, 2H, H6, C*H*H Bn), 4.14 (d, 1H, CH*H* Bn, J=16.1 Hz), 2.67–2.55 (m, 1H, C*H*H H4), 2.48–2.35 (m, 1H, CH*H* H4), 2.26–2.18 (m, 1H, C*H*H H5), 1.95–1.81 (m, 1H, CH*H* H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ195.0 (CO), 150.4 (C3), 137.0, 133.0 ($C_{q,\ arom}$), 132.7, 131.4, 130.9, 129.4, 128.7, 128.4, 128.2, 127.8, 127.6, 123.9 (CH_{arom}, C2), 64.1 (C6), 50.0 (CH_2 Bn), 30.4, 26.9 (C4, C5). ESI-MS: m/z 387.0 $[M+H]^+$, 409.1 $[M+Na]^+$, 795.2 $[M+M+Na]^+$. HRMS: MNH_4^+, found 404.1297, $C_{19}H_{22}N_3O_5S$ requires 404.1280.

4.4.10. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzene-sulfonamino-cyclohex-2-enol-4-yl]-glycine methyl ester (19). The title compound was isolated as an off-white foam (67 mg, 85%). $[\alpha]_D^{20}=-56$ (c=1.0, $CHCl_3$). ν_{max} (neat): 1749, 1541, 1346, 1159, 1124 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.18–8.15 (m, 1H, H_{arom}), 7.72–7.56 (m, 6H, H_{arom}), 7.45–7.39 (m, 1H, H_{arom}), 7.26–7.12, m, 5H, H_{arom}), 5.93 (ddd, 1H, H_{olef}, J=2.4, 5.7, 9.9 Hz), 5.63 (bd, 1H, H_{olef}, J=10.1 Hz), 4.79 (d, 1H, C*H*H Bn, J=16.5 Hz), 4.73–4.67 (m, 1H, H4), 4.61 (d, 1H, CH*H* Bn, J=16.5 Hz), 4.26 (bs, 1H, H1), 4.10–4.01 (m, 3H, H6, 2Hα), 3.62 (s, 3H, OMe), 2.13–2.03 (m, 1H, C*H*H H5), 1.95–1.93 (m, 1H, CH*H* H5). ^{13}C NMR (50.1 MHz): δ_C 170.1 (CO), 147.7, 147.3, 137.1 ($C_{q,\ arom}$), 133.9 (CH_{arom}), 133.4 ($C_{q,\ arom}$), 133.1 (CH_{arom}), 132.6 ($C_{q,\ arom}$), 132.0, 131.6, 131.4, 130.9, 129.8, 128.5, 127.7, 127.5, 124.3, 124.0 (C2, C3, CH_{arom}), 66.7 (C1), 56.6, 56.5 (C4,

C6), 52.3 (OMe), 49.4, 45.0 (Cα, CH2 Bn), 26.9 (C5). ESI-MS: *m/z* 683.3 $[M+Na]^+$. HRMS: MNH_4^+, found 678.1587, $C_{28}H_{32}N_5O_{11}S_2$ requires 678.1540.

4.4.11. N^{α}-*t*-Butyloxycarbonyl-N^{ε}-*o*-nitrobenzenesulfonyl-N^{ε}-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]-L-lysine methyl ester (20). The title compound was isolated as an off-white foam (68 mg, 71%). $[\alpha]_D^{20}=-40$ (*c*=1.0, $CHCl_3$). ν_{max} (neat): 2972, 2901, 1740, 1699, 1541, 1369, 1344, 1159, 1057 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.09–8.00 (m, 1H, H_{arom}), 7.74–7.09 (m, 12H, H_{arom}), 5.99–5.94 (m, 1H, H_{olef}), 5.72 (d, 1H, H_{olef}, *J*=10.0 Hz), 5.10 (d, 1H, NH, *J*=8.7 Hz), 4.82 (d, 1H, C*H*H Bn, *J*=16.6 Hz), 4.76 (d, 1H, CH*H* Bn, *J*=16.6 Hz), 6.64 (bs, 1H, H4), 4.29–4.22 (m, 2H, H1, Hα), 4.19–4.08 (m, 1H, H6), 3.72 (s, 3H, OMe), 3.33–3.24 (m, 1H, *CH*H, Hε), 3.19–3.09 (m, 1H, CH*H* Hε), 2.07–2.00 (m, 1H, C*H*H H5), 1.79–1.678 (m, 3H, CH*H* H5, C*H*H Hδ, C*H*H Hβ), 1.63–1.51 (m, 2H, CH*H* Hβ, CH*H* Hδ), 1.38 (s, 9H, Boc), 1.33–1.16 (m, 2H, Hγ). ^{13}C NMR (50.1 MHz): δ_C 173.0 (CO ester), 155.5 (CO carbamate), 147.8, 147.5, 137.1, 133.6 ($C_{q,\ arom}$), 133.1 (CH_{arom}), 131.9 ($C_{q,\ arom}$), 131.5, 131.1, 130.9, 128.3, 127.9, 127.3, 124.2, 123.9 (CH_{arom}, C2, C3), 80.0 (C_q Boc), 67.0 (C1), 56.7, 56.3 (C4, C6), 52.3 (OMe+Cα), 49.7, 44.7 (CH_2 Bn, Cε), 32.3, 29.9, 27.0, 22.0 (C5, Cβ, Cγ, Cδ), 28.1 (Me Boc). ESI-MS: *m/z* 732.4 $[M\text{-Boc}+H]^+$ 854.3 $[M+Na]^+$. HRMS: MNH_4^+, found 849.2762, $C_{37}H_{49}N_6O_{13}S_2$ requires 849.2799.

4.4.12. N^{ε}-Benzyloxycarbonyl-N^{α}-*o*-nitrobenzenesulfonyl-N^{α}-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]-L-lysine methyl ester (21). The title compound was isolated as an off-white foam (37 mg, 36%). $[\alpha]_D^{20}=-72$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 1740, 1705, 1541, 1369, 1344, 1157, 1124 cm^{-1}. ^1H NMR (300 MHz): δ_H 7.96–7.93 (m, 1H, H_{arom}), 7.72–7.12 (m, 17H, H_{arom}), 5.95–5.89 (m, 1H, H_{olef}), 5.67 (bd, 1H, H_{olef}, *J*=10.2 Hz), 5.07 (s, 2H, CH_2 Z), 4.91–4.82 (m, 2H, C*H*H Bn, NH Z), 4.75 (d, 1H, CH*H* bn, *J*=16.6 Hz), 4.59 (bs, 1H, H4), 4.25 (bs, 1H, H1), 4.18–4.07 (m, 2H, H6, Hα), 3.70 (s, 3H, OMe), 3.11 (q, 2H, Hε, *J*=6.4 Hz), 2.56–2.44 (m, 1H, C*H*H H5), 2.37 (bs, 1H, OH), 2.18–2.04 (m, 1H, CH*H* H5), 1.76–1.64 (m, 2H, Hβ), 1.50–1.28 (m, 4H, Hγ, Hδ).^{13}C NMR (50.1 MHz): δ_C 171.0 (CO ester), 156.5 (CO carbamate), 148.3, 147.5, 137.6, 131.2, 133.8 ($C_{q,\ arom}$), 133.3, 131.7, 131.0, 130.8, 130.6, 128.5, 128.4, 128.1, 127.7, 127.3, 124.1, 124.0 (C2, C3, CH_{arom}), 66.9 (C1), 66.6 (CH_2 Z), 59.3, 57.3, 56.8, 52.5 (C4, C6, Cα, OMe), 49.4 (CH_2 Bn), 40.5, 31.0, 29.3, 28.0, 23.8 (C5, Cβ, Cγ, Cδ, Cε). ESI-MS: *m/z* 866.6 $[M+H]^+$ 888.3 $[M+Na]^+$.

4.4.13. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitro-benzenesulfonamino-cyclohex-2-enol-4-yl]-L-glutamic acid methyl ester (22). The title compound was isolated as an slightly yellow foam (31 mg, 37%). $[\alpha]_D^{20}=-66$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 2957, 2901, 1736, 1541, 1371, 1346, 1161, 1124, 1065 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.01 (d, 1H, H_{arom}, *J*=1.4 Hz), 7.69–7.10 (m, 12H, H_{arom}), 5.96 (ddd, 1H, H_{olef}, *J*=2.5, 5.8, 9.8 Hz), 5.70 (bd, 1H, H_{olef}, *J*=10.0 Hz), 4.89 (d, 1H, C*H*H Bn, *J*=16.6 Hz), 4.77 (d, 1H, CH*H* Bn, *J*=16.6 Hz), 4.61–4.59 (m, 1H, H4), 4.35–4.27 (m, 2H, H1, Hα), 4.11–4.07 (m, 1H, H6), 3.65 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.55–2.37 (m, 4H, C*H*H H5, C*H*H Hβ, 2Hγ), 2.10–1.98 (m, 2H, CH*H* H5, CH*H* Hβ). ^{13}C NMR (50.1 MHz): δ_C 173.0, 170.5 (2 CO), 147.5, 137.6 ($C_{q,\ arom}$), 133.9 (CH_{arom}), 133.7 ($C_{q,\ arom}$), 133.3, 132.1, 132.0, 131.7, 131.6, 131.1, 130.8, 130.5, 128.6, 128.4, 127.9, 127.8, 127.3, 124.1, 124.0 (CH_{arom}), 66.8 (C1), 58.0, 57.3, 56.7 (C4, C6, Cα), 52.6, 51.8 (2 OMe), 49.4 (CH_2 Bn), 30.8, 27.8, 26.9 (C5, Cβ, Cγ). ESI-MS: *m/z* 769.3 $[M+Na]^+$. HRMS: MNH_4^+, found 764.1862, $C_{32}H_{38}N_4O_{13}S_2$ requires 764.1908.

4.4.14. *N*-*o*-Nitrobenzenesulfonyl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenz-enesulfonamino-cyclohex-2-enol-4-yl]-L-phenylalanine methyl ester (23). The title compound was isolated as a slightly yellow foam (38 mg, 44%). $[\alpha]_D^{20}=-35$ (*c*=0.5, $CHCl_3$). ν_{max} (neat): 1742, 1541, 1369, 1344, 1159, 1124, 1061 cm^{-1}. ^1H NMR (300 MHz): δ_H 7.86–7.11 (m, 18H, H_{arom}), 5.88 (ddd, 1H, H_{olef}, *J*=2.5, 5.8, 9.9 Hz), 5.35 (bd, 1H, H_{olef}, *J*=10.7 Hz), 4.90 (d, 1H, CH*H* Bn, *J*=16.5 Hz), 4.74 (d, 1H, CH*H* Bn, *J*=16.5 Hz), 4.69–4.34 (m, 1H, H4), 4.45 (dd, 1H, Hα, *J*=5.9, 8.6 Hz), 4.23 (bs, 1H, H1), 4.15–4.05 (m, 1H, H6), 3.55 (s, 3H, OMe), 3.42 (dd, 1H, C*H*H Hβ, *J*=8.8, 13.9 Hz), 3.04 (dd, 1H, CH*H* Hβ, *J*=5.9, 13.9 Hz), 2.50 (q, 1H, C*H*H H5, *J*=12.0 Hz), 2.09–2.03 (m, 1H, CH*H* H5). ^{13}C NMR (50.1 MHz): δ_C 170.5 (CO), 148.6, 147.3, 137.7, 136.7, 133.9 ($C_{q,\ arom}$), 133.3 (CH_{arom}), 131.7 ($C_{q,\ arom}$), 130.9, 130.7, 129.5, 128.5, 127.7, 127.4, 127.0, 124.1 (C2, C3, CH_{arom}), 66.9 (C1), 60.9, 57.1, 56.8 (C4, C5, Cα), 52.5 (OMe), 49.4 (CH2 Bn), 38.0 (Cβ), 28.0 (C5). ESI-MS: *m/z* 773.3 $[M+Na]^+$. HRMS: MNH_4^+, found 768.1989, $C_{35}H_{38}N_5O_{11}S_2$ requires 768.2009.

4.4.15. Acridine-9-carboxylic acid-(6-{*N*-*o*-nitrobenzenesulfon-yl-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitrobenzenesulfon-amino-cyclohex-2-enol-4-yl]}-aminohexyl) amide (24). The title compound was isolated as a yellow foam (60 mg, 58%). ν_{max} (neat): 2928, 1639, 1541, 1439, 1369, 1342, 1159, 1121 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.03–7.96 (m, 2H, H_{arom}), 7.86–7.83 (m, 1H, H_{arom}), 7.69–7.03 (m, 18H, H_{arom}), 5.79–5.74 (m, 1H, H2′), 5.54 (bd, 1H, H3′, *J*=10.3 Hz), 4.73 (d, 1H, C*H*H Bn, *J*=16.3 Hz), 4.64–4.59 (m, 2H, H4′, CH*H* Bn), 4.18 (bs, 1H, H1′), 4.04–4.00 (m, 1H, H6′), 3.58 (q, 2H, H1, *J*=6.5 Hz), 3.22 (t, 2H, H6, *J*=7.8 Hz), 2.30–2.19 (m, 1H, C*H*H H5′), 1.82–1.79 (m, 1H, CH*H* H5), 1.67–1.60 (m, 4H, H2, H5), 1.42–1.22 (m, 4H, H3, H4). ^{13}C NMR (50.1 MHz): δ_C 166.9 (CO), 147.72, 147.66, 147.1, 141.4, 137.1, 134.1, 133.6 ($C_{q,\ arom}$), 133.3 (CH_{arom}), 133.1 ($C_{q,\ arom}$), 132.0, 131.8, 131.6, 131.4, 131.0, 130.8, 130.5, 128.7, 128.6, 128.3, 128.2, 127.8, 127.2, 126.6, 125.1, 124.1 123.8 (C2, C3, CH_{arom}), 121.9 ($C_{q,\ arom}$), 66.6 (C1), 56.5 (br; C4, C6) 53.4, 49.9, 44.9, 39.8, 30.5, 29.0, 27.5, 25.8 (CH_2 Bn, C5, CH_2 hexyl) ESI-MS: *m/z* 893.4 $[M+H]^+$, 915.2 $[M+Na]^+$.

4.4.16. 1,2,3,4-Di-*O*-isopropylidene-6-*N*-*o*-nitrobenzenesulfonyl-6-*N*-[(1*R*,4*R*,6*S*)-6-(*N*-benzyl)-6-*o*-nitro-benzenesulfonamino-cyclohex-2-enol-4-yl]-amino-D-galactose (25). The title compound was isolated as a white foam (77 mg, 80%). $[\alpha]_D^{20}=-94$ (*c*=1.0, $CHCl_3$). ν_{max} (neat): 1541, 1371, 1342, 1211, 1161, 1065 cm^{-1}. ^1H NMR (300 MHz): δ_H 8.05–8.02 (m, 1H, H_{arom}), 7.76–7.05 (m, 12H, H_{arom}), 6.18–6.12 (ddd, 1H, H2, *J*=2.4, 6.1, 9.8 Hz), 5.51 (dd, 1H, H3, *J*=2.2, 10.0 Hz), 5.41 (d, 1H, H1′,

J=5.0 Hz), 5.02 (d, 1H, C*H*H Bn, *J*=16.4 Hz), 4.82 (d, 1H, CH*H* Bn, *J*=16.4 Hz), 4.76–4.70 (m, 1H, H4), 4.54 (dd, 1H, H3′), *J*=2.5, 7.8 Hz), 4.32–4.29 (m, 2H, H1, H4′), 4.23–4.08 (m, 3H, H2′, H5′, H6), 3.61 (d, 1H, C*H*H H6′, *J*=16.4 Hz), 3.25 (dd, 1H, CH*H* H6′, *J*=7.5, 16.4 Hz), 2.92–2.80 (m, 1H, C*H*H H5), 2.35–2.22 (m, 1H, CH*H* H5), 1.38 (s, 3H, Me isoprop), 1.30 (s, 3H, Me isoprop), 1.22 (s, 3H, Me isoprop), 1.03 (s, 3H, Me isoprop). ^{13}C NMR (50.1 MHz): δ_C 148.2, 127.1, 137.4, 134.7 ($C_{q,\ arom}$), 133.8, 133.0, 132.8, 132.0, 131.1, 130.9, 129.4, 128.0, 127.0, 124.3, 123.7 (C2, C3, CH_{arom}), 109.4, 109.3 (C_q isoprop), 96.4 (C1′), 72.3, 70.5, 70.1 (br), 67.8 (1, 2′, 3′, 4′, 5′), 56.6, 56.5 (C4, C6), 49.5, 46.5 (C6′, CH_2 Bn), 29.1 (C6), 25.9, 25.5, 24.7, 24.3 (Me isoprop). ESI-MS: *m*/*z* 845.5 $[M+NH_4]^+$. HRMS: MNH_4^+, found 848.2440, $C_{37}H_{46}N_5O_{14}S_2$ requires 848.2483.

4.4.17. (1*S*,4*S*,6*R*)-4,6-bis[(*N*-benzyl)-*o*-nitrobenzenesulfon-amino]-1-*O*-(*tert*-butyldimethylsilyl)-cyclohex-2-enol (27). Pyridine (0.20 mL, 2.5 mmol, 5 equiv.) and *tert*-butyldimethylsilyl triflate (0.138 mL, 0.6 mmol, 1.2 equiv.) were added to a solution of compound **16** (339 mg, 0.5 mmol) in DCM (2 mL). After stirring for 2.5 h sat. $NaHCO_3$ was added and the mixture was extracted three times with EtOAc. Combined organic layers were dried ($MgSO_4$), and evaporated under reduced pressure. Silica column chromatography (elution 0%→20% EtOAc in toluene) afforded the title compound (353 mg, 0.446 mmol, 89%) as a white foam. $[\alpha]_D^{20}$=+60.8 (*c*=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1367, 1344, 1157, 1124, 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.96 (d, 1H, H_{arom}, *J*=8.3 Hz), 7.67–6.97 (m, 15H, H_{arom}), 6.87 (d, 2H, H_{arom}, *J*=7.3 Hz), 5.86 (ddd, 1H, H_{olef}, *J*=2.3, 5.5, 9.9 Hz), 5.52 (d, 1H, H_{olef}, *J*=10.1 Hz), 4.91–4.84 (m, 1H, H4), 4.70–4.65 (m, 2H, 2× C*H*H benzyl), 4.45 (d, 1H, CH*H* benzyl, *J*=16.2 Hz), 4.39–4.33 (m, 2H, H1, CH*H* benzyl), 4.03 (bd, 1H, H6, *J*=12.9 Hz), 2.24–2.15 (m, 1H, C*H*H H5), 1.99–1.91 (m, 1H, CH*H* H5), 0.91 (s, 9H, *t*-Bu), 0.19 (s, 3H, Me), 0.11 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 147.7, 147.3, 137.7, 136.2, 135.2, 134.0 ($C_{q,\ arom}$), 133.4, 132.8, 132.6, 131.8, 131.7, 131.1, 130.7, 129.8, 127.5, 127.3, 124.2, 123.7 (CH_{arom}, C2, C3), 68.9 (C1), 57.3, 57.1 (C4, C6), 50.1, 48.7 (CH_2 Bn), 28.3 (C5), 25.9 (Me *t*-Bu), 17.9 (C_q *t*-Bu), −4.0, −4.6 (2× Me TBS). ESI-MS: *m*/*z*=815.5 $[M+Na]^+$. HRMS: MNH_4^+, found 810.2603, $C_{38}H_{48}N_5O_9S_2Si$ requires 810.2663.

4.4.18. 1L-(1,4,6/2,3)-4,6-Bis[(*N*-benzyl)-nitrobenzenesulfon-amino]-1-*O*-(*tert*-butyldimethylsilyl)-cyclohexane-1, 2, 3-triol (29).[26] *N*-Methyl-morpholine-*N*-oxide (107 mg, 0.91 mmol, 2.2 equiv.) and $K_2Os_2O_4{\cdot}2H_2O$ (1.2 mg, 0.75 mol%) were added to a solution of alkene **27** (328 mg, 0.414 mmol) in acetone/water (2 mL, 3:1 v/v). After 72 h the reaction was quenched with aqueous $NaHSO_3$ and extracted three times with EtOAc. Combined organic layers were dried on $MgSO_4$ and evaporated under reduced pressure. Column chromatography (elution 10%→50% EtOAc in toluene) yielded compound **29** (314 mg, 0.38 mmol, 92%) as a slightly yellow foam. $[\alpha]_D^{20}$=+72.4 (*c*=0.50, $CHCl_3$). ν_{max} (neat): 1541, 1340, 1159, 1123, 1087, 1059, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.14–8.11 (m, 1H, H_{arom}), 7.73–7.01 (m, 15H, H_{arom}), 6.88–6.86 (m, 1H, H_{arom}), 4.68 (d, 1H, C*H*H benzyl, *J*=16.5 Hz), 4.56 (d, 1H, C*H*H benzyl, *J*=16.1 Hz), 4.48 (d, 1H, CH*H* benzyl, *J*=16.1 Hz), 4.41–4.36 (m, 2H, H6, CH*H* benzyl), 4.21–4.14 (m, 1H, H4), 4.00 (bs, 1H, H1), 3.77 (bs, 1H, H2), 3.73–3.68 (m, 1H, H3), 2.76 (d, 1H, OH, *J*=1.9 Hz), 2.61 (d, 1H, OH, *J*=5.4 Hz), 1.91–1.81 (m, 1H, C*H*H H5), 1.68–1.63 (m, 1H, CH*H* H5), 0.87 (s, 9H, *t*-Bu), 0.13 (s, 3H, Me), 0.03 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 147.5, 147.2, 137.5, 136.6, 134.6 ($C_{q,\ arom}$), 133.8. 132.9 (CH_{arom}), 132.8 ($C_{q,\ arom}$), 132.2, 131.7, 131.4, 130.9, 128.7, 128.1, 137.9, 127.8, 127.2, 124.3, 123.8 (CH_{arom}), 75.4, 72.4, 66.9 (C1, C2, C3), 57.1, 54.7 (C4, C6), 49.6, 48.2 (CH_2 Bn), 29.0 (C5), 25.9 (Me *t*-Bu), 17.7 (C_q *t*-Bu), −4.6, −5.0 (2× Me TBS). ESI-MS: *m*/*z*=827.3 $[M+H]^+$, 849.3 $[M+Na]^+$. HRMS: MNH_4^+, found 844.2657, $C_{38}H_{50}N_5O_{11}S_2Si$ requires 844.2718.

4.4.19. 1L-(1,4,6/2,3)-4,6-Bis[(*N*-benzyl)-nitrobenzenesulfon-amino]-2-*O*-acetyl-1-*O*-(*tert*-butyldimethylsilyl)-cyclo-hexane-1, 2, 3-triol (31). A solution of diol **29** (165 mg, 0.20 mmol), trimethylorthoacetate (0.25 mL, 2 mmol, 10 equiv.) and *p*-TsOH (4 mg, 0.1 equiv.) in DCM (1 mL) was stirred for 1 h. TLC analysis (eluens: toluene/EtOAc 2:1) indicated complete conversion to two higher running products, being the two stereoisomers of orthoester **30**. The reaction was neutralized with triethylamine and the solvents were removed under reduced pressure. Sat. $NaHCO_3$ was added and the mixture was extracted three times with EtOAc. Combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Crude orthoester **30** (ESI-MS: *m*/*z*=905.5 $[M+Na]^+$) was immediately used in the next step. It was dissolved in AcOH/H_2O (4:1 v/v) and stirred for 2 h, when TLC analysis indicated complete disappearance of the orthoester. The reaction mixture was diluted with toluene and concentrated under reduced pressure. During evaporation of the solvents, toluene was added several times to remove acetic acid traces. Silica column chromatography (elution 10%→40% EtOAc in toluene) provided orthogonally protected 2-deoxystreptamine epimer **31** (165 mg, 0.190 mmol, 95%) as a white foam. $[\alpha]_D^{20}$=+88.4 (*c*=1.0, $CHCl_3$). ν_{max} (neat): 1747, 1541, 1369, 1348, 1226, 1161, 1124, 1090, 1059, 1045, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.10–8.07 (m, 1H, H_{arom}), 7.72–7.02 (m, 15H, H_{arom}), 6.81 (d, 2H, H_{arom}, *J*=7.1 Hz), 4.94 (t, 1H, H2, *J*=4.6 Hz), 4.76 (d, 1H, C*H*H Bn, *J*=16.0 Hz), 4.60 (d, 1H, C*H*H Bn, *J*=16.3 Hz), 4.37–4.21 (m, 4H, H4, H6, 2× CH*H* Bn), 4.11–4.09 (m, 1H, H1), 3.99–3.94 (m, 1H, H3), 2.42 (d, 1H, OH, *J*=7.8 Hz), 2.15 (s, 3H, Me Ac), 1.83–1.71 (m, 2H, H5), 0.89 (s, 9H, Me *t*-Bu), 0.18 (s, 3H, Me TBS), 0.15 (s, 3H, Me TBS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 170.1 (CO), 147.6, 147.3, 137.1, 136.0, 134.5 ($C_{q,\ arom}$), 133.6 (CH_{arom}), 133.1 ($C_{q,\ arom}$), 132.9, 131.7, 131.5, 131.1, 130.5, 128.7, 128.09, 128.05, 128.0, 127.3, 124.2, 123.6 (CH_{arom}), 73.9 (C2), 73.3 (C1), 65.4 (C3), 57.6, 55.0 (C4, C6), 49.5, 48.0 (CH_2 Bn), 30.0 (C5), 25.9 (Me *t*-Bu), 20.7 (Me Ac), 17.7 (C_q *t*-Bu), −4.6, −5.2 (Me TBS). ESI-MS: *m*/*z*=869.5 $[M+H]^+$, 891.4 $[M+Na]^+$. HRMS: MNH_4^+, found 886.2781, $C_{40}H_{52}N_5O_{12}S_2Si$ requires 886.2823.

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Synthesis of a proline-rich [60]fullerene peptide with potential biological activity

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Dedicated to Dr. Ulf Ragnarsson, from the Department of Biochemistry, University of Uppsala, Biomedical Center, Uppsala, Sweden, on the occasion of his retirement

Abstract—A proline-rich [60]fullerene peptide was synthesized by use of (i) a 1,3-dipolar cycloaddition of an N-substituted glycine derivative to [60]fullerene, (ii) esterification of the isolated alcohol with the C-terminal amino acid of the desired peptide sequence, and finally (iii) coupling of the remaining hexapeptide to give the final product **8** as a TFA salt, with oxidized methionine. Product **8** was found to be biologically active against sera from MCTD and SLE patients (ELISA experiment).

1. Introduction

Considerable effort in fullerene chemistry has been directed to establish this novel form of carbon as a standard building block in organic synthesis.[1–3] Especially, the most abundand member of the fullerene family, C_{60}, has received the highest attention as C_{60}-based molecules display a wide range of interesting features, which include nonlinear optical properties and superconductivity.[4] The exceptionally hydrophobic nature and spheroidal shape of C_{60} make it very interesting for its potential use in medicinal chemistry.[5] A series of [60]fullerene derivatives displays a wide range of biological properties, including neuroprotective, enzymatic, antiapoptotic, antibacterial, DNA photocleaving, nitric oxide synthase inhibiting, and chemotactic activities.[5] Among the different classes of derivatives, fullerene-based amino acids and peptides are particularly interesting, both for structural studies and biological applications.[5a] For example, C_{60}-based 3,4-fullero-proline (Fpr), which is the fullerene homologue of the natural proline residue, has been inserted into small peptides for studying its propensity to induce β-turn conformations and to influence the *cis–trans* equilibrium around the tertiary amide bond.[5a,6] Fulleroproline amino acid derivatives are also shown to interact with different hydrolytic enzymes in model transesterification reactions, and to form supramolecular complexes with, and selectively discriminate between, different size calix-[*n*]arenes, cyclodextrines, and other rationally designed peptides forming cavities.[7] Incorporation of the C_{60} moiety into biologically active peptides is thus desirable to possibly alter both the structure and the biological activity of the parent peptide.

The synthesis of the first [60]fullerene peptide was reported in 1993,[8] where a methanofullerene was linked to the terminal part of a pentapeptide with an alternating-Aib (α-amino isobutyric acid)-Ala- sequence. This model fullero-peptide was able to adopt a 3_{10}-helical structure.[9] Today a few examples of fullero-peptides are known, prepared under solution chemistry conditions.[10] More recently, the first example of solid-state fullero-peptide synthesis has been reported.[11] Here we wish to report the synthesis of a new proline-rich [60]fullerene peptide, which contains a solubilizing appendage (ethyleneglycol chain), covalently attached between the fullerene moiety and a heptapeptide, namely H-PPGMRPP-OH, which has antigenic properties.[12] The above proline-rich heptapeptide, found to be present in several copies in Sm and U1RNP autoantigens, is the main target of the *anti*-Sm and *anti*-U1RNP autoantibodies in sera of patients with autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and

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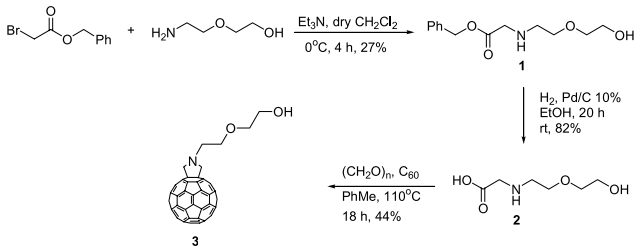
Mixed Connective Tissue Disease (MCTD). It was also found that the H-PPGMRPP-OH epitope is recognized by *anti*-Ro/La positive sera, although they are negative for *anti*-Sm and *anti*-U1RNP.[13] More recently, it has been demonstrated that conversion of the C-terminal carboxylate group of the parent peptide into the amide form resulted in a substantial decrease of the *anti*-Ro/La recognition, probably due to the predominance of one unfavorable conformer.[14,15]

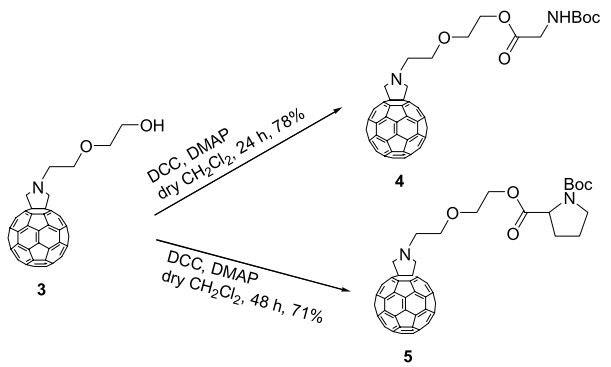
2. Results and discussion

2.1. Chemistry and spectroscopy

The synthesis of compound **8**, was performed according to Schemes 1 and 2. Accordingly, aminolysis of benzyl 2-bromo-acetate by 2-(2-aminoethoxy)ethanol in dry CH_2Cl_2 in the presence of Et_3N, afforded **1**, which upon catalytic hydrogenolysis with Pd/C 10% in ethanol, gave the N-substituted glycine **2**. 1,3-Dipolar cycloaddition of the azomethine ylide generated by condensation of **2** with formaldehyde to C_{60} led to good yields (~44%) of fulleropyrrolidine **3**, N-substituted with an ethyleneglycol chain (Scheme 1). This product gave correct ^{1}H NMR and ESI MS spectra. In particular, ^{1}H NMR spectra showed five signals for the five different types of protons in **3**.



Scheme 1. Synthesis of derivative **3**.

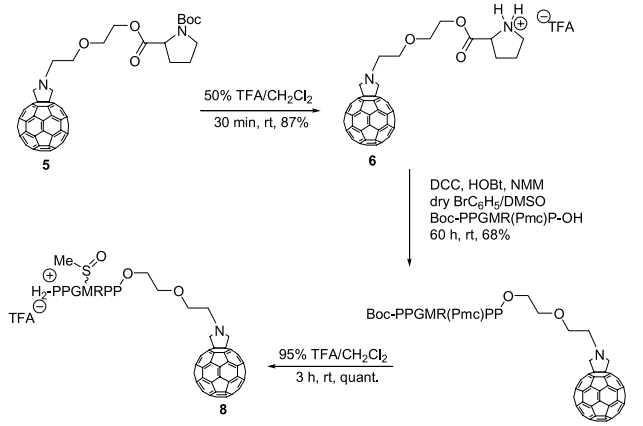


Scheme 2. Esterification of derivative **3** with Boc-protected amino acids.

At this stage it should be mentioned that attempts to couple derivative **3** with the protected Fmoc-PPGMR(Mtr)P-OH hexapeptide in one step were unsuccessful, (Fmoc-: 9-Fluorenylmethoxycarbonyl-, Mtr-: 4-methoxy-2,3,6-trimethylbenzenesulfonyl-). Therefore, we turned our efforts to introduce first a Boc-protected amino acid (Boc-: *tert*-butoxycarbonyl-) via an esterification reaction at the terminal hydroxyl group of derivative **3**. This was done successfully with both Boc-glycine and Boc-proline, affording as products synthetic intermediates **4**, and **5**, respectively, in relatively high yields (Scheme 2).

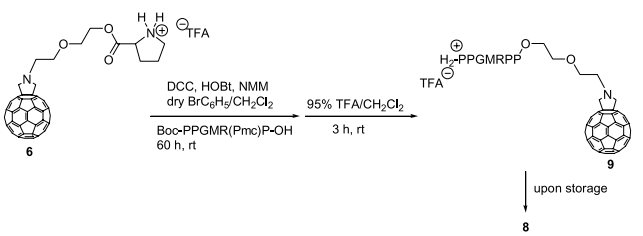
Both of the above amino acid-containing [60]fullero derivatives, were characterized by ^{1}H NMR and ESI MS spectroscopies, gave the correct spectra with regard to their chemical structure. Because we were interested in a covalent connection of derivative **3** to the known peptide H-PPGMRPP-OH, we decided to proceed with the proline connected fullero-derivative **5**, in that it contains the C-terminal amino acid of the parent heptapeptide sequence.

To this end, derivative **5** was first deprotected with a 50% solution of 2,2,2-trifluoroacetic acid (TFA) in CH_2Cl_2 and the resulted TFA salt was subjected to coupling with the protected hexapeptide Boc-PPGMR(Pmc)P-OH[10a] (Pmc-: 2,2,5,7,8-pentamethylchroman-6-sulfonyl-) (Scheme 3). Periodically the reaction progress was checked by TLC (PhMe/MeOH). After 60 h stirring at room temperature (rt), the reaction was stopped and product **7** was isolated by column chromatography on SiO_2, with PhMe/MeOH 6:1 v/v solvent mixture as eluant. The final step was the simultaneous removal of the protecting groups in **7** with a 95% solution of TFA in CH_2Cl_2. The TFA salt of the fullero-peptide derivative **8** was isolated, as a dark brown powder in 42% overall yield starting from **3**.



Scheme 3. Synthesis of [60]fullero-peptide **8**.

The ESI MS spectra of **8** showed a $[M+2H]^{2+}$=801.7 signal which corresponds to the compound with the oxidized methionine thioether group (i.e., containing a sulfoxide group). When the coupling reaction of the protected hexapeptide was performed in dry BrC_6H_5/CH_2Cl_2 the final deprotected [60]fullero peptide **9**, after chromatographic purification and deprotection steps as above,



Scheme 4. Synthesis of compound **9**, that gradually oxidized to **8**.

showed a correct ESI MS molecular ion signal of $[M+2H]^{2+}=792.98$ (Scheme 4).

This second sample **9**, gradually oxidized to compound **8** while in the solid state, even under an Ar atmosphere. After a month of storage it gave almost a complete oxidation of methionine –SMe group to –S(=O)Me (the final product showed an ion signal of $[M+2H]^{2+}=800.81$). From our experience we know that DMSO causes methionine oxidation to a small percentage after a long period of time.[16] Also, C_{60} itself or fullerene-containing derivatives are known to be effective photosensitizers for singlet oxygen, $^1O_2$, production.[17] We are of the opinion that the combination of both the above factors are the reason for the pronounced oxidation of methionine in derivative **8** (due to O_2 traces contained in the reagents/solvents). To further verify the above reasoning we stirred a solution of the protected peptide PPGMR(Pmc)P-OH in DMSO for 24 h. The ESI MS spectra showed only a small peak corresponding to the oxidized product, $[M-H]^{-1}=1034.71$, whereas the major peak, $[M-H]^{-1}=1018.75$, corresponded to the normal protected peptide. When the same conditions were applied in CH_2Cl_2 in the presence of a catalytic quantity of C_{60}, after 24 h the ESI-MS spectra showed two peaks, $[M+H]^{+}=1036.66$ and $[M+Na^{+}]^{+}=1058.59$, both of them corresponding to the protected peptide with oxidized methionine.

All of the proton resonances and the amino acid sequence of the oxidized TFA salt **8** were identified by combining COSY, TOCSY and NOESY 2D NMR experiments in DMSO-d_6. In agreement with our previously reported results,[12,13] two *cis–trans*-conformers out of the eight theoretically possible, due to the presence of four proline residues, were detected. All of the X-Pro peptide bonds of the major conformer were identified in the *trans* form. The assignment was based on either the presence of the X-$C^{\alpha}H$/P-$C^{\alpha}H$ and/or the absence of the X-$C^{\alpha}H$/P-$C^{\alpha}H$ NOE effects. However, the localization of the *cis* X-Pro peptide bonds was not possible in the minor conformer due to its low percentage (<10%). Table 1 summarizes the proton chemical shift values for the major conformer of **8**.

Table 1. Proton chemical shifts (ppm) of **8** in DMSO-d_6 at 303 K

Amino acid	NH	$C^{\alpha}H$	$C^{\beta}H$	$C^{\gamma}H$	$C^{\delta}H$	Other protons
Pro[1]	Nd[a]	4.19	2.50	Nd[a]	3.79	
Pro[2]	—	4.38	2.13	1.91	3.62	
					3.46	
Gly[3]	8.27	3.68	—	—	—	
Met[4]	7.89	4.43	1.94	2.68	—	
			1.84			
Arg[5]	8.28	4.43	1.68	1.52	3.07	7.50 ($N^{\varepsilon}H$)
						7.28 ($N^{\eta}H$)
						6.87 ($N^{\eta}H$)
Pro[6]	—	4.58	2.18	1.95	3.71	
					3.51	
Pro[7]	—	4.32	1.91	2.17	3.82	
					3.62	

[a] Not detected.

2.2. Biological activity

[60]Fullerene peptide **8**, with oxidized methionine, was evaluated for its ability to recognize *anti*-Sm and *anti*-U1RNP autoantibodies in SLE and MCTD patients' sera, (ELISA experiment). In Table 2, the reactivities of derivative **8**, as tested against *anti*-Sm/U1RNP sera from SLE and MCTD patients with Sjogren's syndrome, are listed in comparison with the parent peptide in its free and C-terminal amide form.

Table 2. Reactivity of sera containing various auto-antibodies against [60]fullerene derivatives **8** and **3**

Derivative	*Anti*-Sm/U1RNP (+) *anti*-Ro/La (−) (%)	*Anti*-Ro/La (+) *anti*-Sm/U1RNP (−) (%)
H-PPGMRPP-OH[a]	75	40
H-PPGMRPP-NH_2[a]	75	17
[60]Fullerene derivative **8**	92	100
[60]Fullerene derivative **3**	0	0

[a] From Refs. 13,14.

As can be seen from Table 2, derivative **8** strongly recognizes *anti*-Sm/U1RNP specificities. Surprisingly, derivative **8** is fully recognized by *anti*-Ro/La positive sera, which are negative to *anti*-Sm/U1RNP sera. Derivative **3**, showing no recognition at all, was taken as a control. Taking into account that derivative **3** is not reactive at all, one could hypothesize that conversion of the carboxylic end of the parent peptide to an ester functionality in derivative **8** would be responsible for the decrease in disease specificity. This effect could be attributed to the predominance of a different conformer with respect to that prevailing in H-PPGMRPP-NH_2. In addition, the oxidized form of the thioether group of methionine may also affect the specificity of the compound.

3. Conclusions

The present work describes the synthesis of a [60]fullero-peptide which contains an ethyleneglycol chain between the fullerene and biologically active peptide moieties. The fullero-peptide was characterized with NMR, ESI MS, and MALDI-TOF MS spectroscopies. In addition, it showed strong recognition against *anti*-Sm/U1RNP sera from SLE and MCTD patients. This encouraging result could be of help for the design and synthesis of new derivatives that could be more potent and more disease selective. More detailed conformational studies of derivative **8** by 2D NMR spectroscopy are currently underway.

4. Experimental

4.1. General

All NMR spectra were taken in $CDCl_3$ 98% D, unless otherwise noted, on a Bruker 400 MHz AMX instrument. ESI MS spectra were taken on a quadrapole Micromass Platform LC, model MassLynx v3.3. MALDI-TOF MS spectra were taken on a Voyager DE-STR (Applied Biosystems, Foster City, CA) Spectrometer, with DHB (2,5-dihydroxybenzoic acid) as matrix. Spectra were aquired at 20 kV acceleration voltage, in the reflector mode.

[C_{60}]Fullerene was purchased from Materials and Electronical Research Corporation (Tucson, AZ, USA). All reagents and solvents were obtained from commercial suppliers and used without further purification. Dry quality solvents were obtained according to literature procedures,[18] and kept in MS 4A under Ar atmosphere. Thus, CH_2Cl_2 distilled from P_2O_5; PhMe, distilled from Na with benzophenone as an indicator; DMSO, stirred with NaOH for 24 h and then distilled at 2–3 mm Hg under continuous flow of N_2; pyridine, pre-dried with $MgSO_4$, and then distilled from BaO; *N*-methyl-morpholine distilled from Na; bromo-benzene distilled in vacuo; DMF pre-dried with KOH, refluxed for 1 h in the presence of ninhydrin and then distilled from BaO.

4.2. Peptide synthesis

Peptides were synthesized on a 2-chlorotrityl chloride resin following the Fmoc SPPS procedure.[19] Arginine was introduced as Fmoc-Arg(Mtr)-OH and Fmoc-Arg(Pmc)-OH, the N-terminal proline as Fmoc-Pro-OH and Boc-Pro-OH for the synthesis of Fmoc-PPGMR(Mtr)P-OH and Boc-PPGMR(Pmc)P-OH respectively, methionine as Fmoc-Met-OH, and glycine as Fmoc-Gly-OH. Fmoc groups were removed using 20% piperidine in DMF. Couplings were performed using an amino acid/TBTU/HOBt/DIEA/resin molar ratio of 3:2.9:3:3:1 (TBTU: *O*-benzotriazol-1-yl-*N*,*N*,*N*′, *N*′-tetra-methyluronium tetrafluoroborate, HOBt: 1-hydroxybenzotriazole, DIEA: *N*,*N*-diisopropylethyl-amine). DMF, used for couplings, was previously distilled in the presence of ninhydrin to remove traces of amines. The crude peptides were obtained by treatment of the peptidyl resin for 2 h with a mixture of acetic acid/2,2,2-trifluoro-ethanol/dichloromethane (2:2:6, v/v/v). The resin was removed by filtration, the filtrate was evaporated under reduced pressure, and the product precipitated with cold diethyl ether. The yields were 64 and 86% for Fmoc-PPGMR(Mtr)P-OH (ESI MS calculated molecular ion $[M-H]^{-1}$: 1087.30, found: 1087.17) and Boc-PPGMR(Pmc)P-OH (ESI MS calculated molecular ion $[M-H]^{-1}$: 1019.30, found: 1018.97) respectively. The purity of the peptides, assessed by analytical HPLC, ranged between 80 and 90%. They were used for covalent attachment to fullero-proline derivatives without further purification.

4.2.1. Synthesis of *N*-2-(2-aminoethoxy-ethanol-)glycine (2). The synthesis of **2** was performed in two steps. In the first step aminolysis of benzyl 2-bromoacetate with 2-(2-amino-ethoxy)-ethanol afforded ester **1**, which upon catalytic hydrogenolysis led to the N-substituted glycine (**2**).

4.2.1.1. Aminolysis of benzyl 2-bromoacetate. In a 250 mL, flame dried, two necked round-bottomed flask, equipped with a dropping funnel, and a magnetic stirring bar, under N_2, were placed 2.5 mL (25 mmol) of 2-(2-amino-ethoxy)-ethanol, and 2.5 mL of dry triethylamine diluted with 90 mL of dry CH_2Cl_2. The mixture was cooled at 0 °C, and 2.5 mL (15.9 mmol) of benzyl 2-bromoacetate (as a solution in 10 mL of dry CH_2Cl_2) were added over a period of 1 h. The reaction mixture was left at rt with stirring for 4 h. Then, the organic phase was washed with H_2O (three times) and then with brine (two times), and dried over Na_2SO_4. The solvent was removed with a rotary evaporator and the remaining material was chromatographed on a silica gel column (SiO_2) with an EtOAc/MeOH mixture, 99:1 v/v, as eluant. By this procedure 1.1 g (4.34 mmol) of the benzyl ester of N-substituted glycine **1** were isolated in 27% yield, as a pale yellow viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.82 (t, 2H, J=5.0 Hz), 3.49 (s, 2H), 3.58 (m, 4H), 3.70 (t, 2H, J=4.5 Hz), 5.17 (s, 2H). ^{13}C NMR (62 MHz, $CDCl_3$) δ 48.8, 50.7, 61.8, 66.6, 70.4, 72.3, 128.3, 128.6, 135.5, 172.2. FT IR (KBr) ν_{max}: 700.72, 747.57, 1071.23, 1123.45, 1191.18, 1354.71, 1384.55, 1457.34, 1740.46, 2870.53, 3338.50 cm^{-1}. ESI MS calculated molecular ion $[M+H]^+$: 254.30, found: 254.75.

4.2.1.2. Catalytic hydrogenolysis of 1 to give 2. In a 250 mL, one-necked round-bottomed flask equipped with a magnetic stirring bar, were placed 1.1 g (4.34 mmol) of **1**, dissolved in 124 mL of EtOH. The solution was degassed with an N_2 stream and then 62 mg of Pd/C 10% were added. Hydrogen was passed through the reaction mixture for 20 h at rt. Then, the catalyst was removed by filtration and the solvent was removed in a rotary evaporator, leaving 0.58 g (3.55 mmol) of **2**, (82% yield), as a yellow viscous oil, which was used in the next step without further purification. ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.00 (t, 2H, J=5.2 Hz), 3.20 (s, 2H), 3.49 (m, 4H), 3.62 (t, 2H, J=5.2 Hz). ^{13}C NMR (62 MHz, $CDCl_3$) δ 168.8, 73.1, 67.0, 61.1, 50.8, 47.4. FT IR (KBr) ν_{max}: 481.89, 593.62, 692.76, 892.44, 1070.40, 1127.18 (C–O), 1324.87, 1400.78, 1632.29 (C=O), 2358.20, 2940.29, 3401.26 cm^{-1}. MALDI-TOF MS (matrix: DHB): calculated molecular ion $[M+H]^+$: 164.17, found $[M+H]^+$: 164.16, $[M+Na]^+$: 186.15.

4.2.2. Synthesis of N-substituted 3,4-fullero pyrrolidine (3). In a two-necked, 500 mL round-bottomed flask, were placed 250 mg (0.347 mmol) of C_{60} dissolved in 300 mL of PhMe. Then, to this solution 113 mg (0.692 mmol) of 2 (dissolved in a small amount of EtOH) were added at once followed by the addition of 52 mg (0.577 mmol) of $(CH_2O)_n$ with the help of a small quantity of PhMe. The resulting mixture was refluxed (~120 °C) with stirring for 18 h. After column chromatography on silica gel (SiO_2) with PhMe/EtOAc, 4:1 v/v, as eluant, 129.3 mg (0.152 mmol) of **3** were isolated in 44% yield, as a black powder. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.40 (t, 2H, J=5.5 Hz), 3.83 (m, 4H), 4.09 (t, 2H, J=5.6 Hz), 4.58 (s, 4H). ^{13}C NMR (62 MHz, $CDCl_3$) δ 54.2, 62.1, 68.2, 70.1, 70.3, 136–156 (C_{60} skeletal carbon signals). FT IR (KBr) ν_{max}: 526.62 (C_{60}), 1115.42 (C–O), 1183.12 (C_{60}), 1425.41 (C_{60}), 1629.45, 2776.11, 2865.67, 2926.00, 3447.83 (OH) cm^{-1}. ESI MS calculated molecular ion $[M+H]^+$: 852.82, found: 852.73. MALDI-TOF MS (matrix: DHB) found: 852.64. Elemental analysis calculated for $C_{66}H_{13}O_2N$: C, 93.07; H 1.54; N 1.64%, found: C 93.42, H 1.49, N 1.60%.

4.2.3. Synthesis of glycine [60]fullerene derivative 4. In a flame dried, 100 mL two-necked, round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, under N_2 atmosphere, were placed 16.45 mg (0.094 mmol) of Boc-Gly-OH and 19.4 mg (0.094 mmol) of DCC (*N*,*N*′-dicyclohexylcarbodiimide), dissolved in dry CH_2Cl_2. The resulted mixture was stirred at rt for 30 min. Then, 20 mg (0.023 mmol) of **3** were added, followed by the addition of 1.15 mg (0.009 mmol) of 4-(dimethylamino)-pyridine (DMAP), both of them dissolved in dry CH_2Cl_2.

The reaction mixture was left with stirring at rt under N_2 for 24 h. Column chromatography on silica gel (SiO_2), eluant: PhMe/EtOAc, 4:1 v/v, afforded 18 mg (0.018 mmol) of derivative **4**, (78% yield), as a dark brown powder. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.37 (t, 2H, J=5.4 Hz), 3.90 (t, 2H, J=4.7 Hz), 3.97 (d, 2H, J=5.5 Hz), 4.06 (t, 2H, J=5.4 Hz), 4.44 (t, 2H, J=4.7 Hz), 4.51 (s, 4H), 4.99 (s, 1H). ^{13}C NMR (62 MHz, $CDCl_3$) δ 170.4, 169.9, 155.0, 147.3, 146.2, 146.0, 145.7, 145.4, 145.3, 144.5, 143.1, 142.6, 142.2, 142.1, 141.9, 140.2, 136.2, 80.0, 70.8, 70.5, 68.9, 68.5, 64.4, 54.2, 42.5, 28.3. FT IR (KBr) ν_{max}: 527.30, 567.68, 597.52, 769.10, 1052.58, 1119.72, 1163.81, 1242.81, 1364.96, 1637.29, 1716.55, 1746.36, 2776.11, 2924.70, 3432.63 cm^{-1}. ESI MS calculated molecular ion $[M+H]^+$: 1009.99, found: 1009.68. FT IR (as a TFA salt after removal of −Boc group, KBr) ν_{max}: 527.03 (C_{60}), 1060.04, 1130.42 (C−O), 1201.37, 1427.12 (C_{60}), 1632.41, 1678.77, 1751.84, 2924.16, 3430.34 cm^{-1}. MALDI-TOF (of the TFA salt after removal of −Boc group), (matrix: DHB): calculated molecular ion $[M+H]^+$: 909.87, found: 909.59.

4.2.4. Synthesis of proline [60]fullerene derivative 5. In a flame dried, 100 mL two-necked round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, under N_2 atmosphere, were placed 75.8 mg (0.35 mmol) of Boc-Pro-OH and 72.7 mg (0.35 mmol) of DCC, dissolved in dry CH_2Cl_2. The resulted mixture was stirred at rt for 30 min. Then, 30 mg (0.035 mmol) of 3 were added, followed by the addition of 4.28 mg (0.014 mmol) of DMAP, both of them dissolved in dry CH_2Cl_2. The reaction mixture was left with stirring at rt, under N_2, for 48 h. Column chromatography on silica gel (SiO_2), eluant: PhMe/EtOAc, 9:1 v/v, afforded 26.2 mg (0.025 mmol) of derivative **5**, (71% yield), as a dark brown powder. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 and 1.46 (two s, 9H trans/cis -Boc, 60/40), 2.00 (m, 2H), 2.17 (m, 2H), 3.36 (t, 2H, J=5.3 Hz), 3.52 (m, 2H), 3.88 (t, 2H, J=4.7 Hz), 4.05 (t, 2H, J=5.4 Hz), 4.27 (q, 1H, J=4.2 Hz), 4.40 (m, 2H), 4.51 (s, 4H). ^{13}C NMR (62 MHz, $CDCl_3$) δ 173.2, 172.9, 155.1, 155.0, 154.4, 153.7, 147.3, 146.2, 146.1, 145.7, 145.4, 145.3, 144.6, 143.1, 142.6, 142.2, 142.1, 141.9, 140.1, 136.2, 79.9, 79.7, 70.8, 70.6, 70.5, 69.1, 68.6, 68.5, 64.0, 59.1, 58.8, 54.3, 46.6, 46.4, 31.0, 30.1, 28.5, 28.4, 24.4, 23.7. FT IR (KBr) ν_{max}: 527.35, 720.61. 769.10, 1082.42, 1124.00, 1185.76, 1268.92, 1397.36, 1455.42, 1630.73, 1699.90, 1738.90, 2917.91, 2970.14, 3434.44 cm^{-1}. ESI MS calculated molecular ion $[M+H]^+$: 1050.08, found: 1049.80. MALDI-TOF MS (matrix: DHB) found: 1049.91.

4.2.5. Deprotection of 5 to give salt 6. In a 50 mL round-bottomed flask equipped with a magnetic stirring bar were placed 26.2 mg (0.025 mmol) of **5**, dissolved in 4 mL of CH_2Cl_2. Then 4 mL of TFA were added and the mixture stirred at rt for 30 min. Removal of the solvent (and the remaining TFA) with a rotary evaporator afforded 23 mg (0.022 mmol) of **6**, (yield 87%), as a brown powder. ESI MS calculated molecular ion $[M+H]^+$: 949.96, found: 950.03. MALDI-TOF MS (matrix: DHB) found: 950.01.

4.2.6. Synthesis of the [60]fullerene heptapeptide 8

4.2.6.1. Coupling of the protected hexapeptide Boc-PPGMR(Pmc)P-OH with the [60]fullerene derivative 6 (isolation of 7). In a 100 mL flame dried, two-necked, round-bottomed flask, equipped with a reflux condenser and a magnetic stirring bar, under N_2 atmosphere, were placed 38.8 mg (0.038 mmol) of the protected hexapeptide Boc-PPGMR(Pmc)P-OH, 10.2 mg (0.05 mmol) of DCC, and 7.6 mg (0.05 mmol) of HOBt, dissolved in 1 mL of dry DMSO. The reaction mixture was stirred at rt for 30 min. Then, 20 mg (0.019 mmol) of derivative **6**, after being dissolved in 3 mL of dry BrC_6H_5/DMSO 6:1 v/v, and neutralized with 4.18 μL (0.038 mmol) of *N*-methyl morpholine, were added to the solution. The reaction mixture was left with stirring at rt for 60 h. After column chromatography on silica gel, PhMe/MeOH 6:1 v/v as eluant, protected product **7** was isolated (25 mg, 0.013 mmol) in fairly good yield (68%), as a brown powder.

4.2.6.2. Deprotection of 7 to give 8. 14.5 mg (0.007 mmol) of the above isolated, protected fullerene peptide, dissolved in 5 mL of CH_2Cl_2, was placed in a 50 mL round-bottomed flask equipped with a magnetic stirring bar. Then, to the above solution 5 mL (65.34 mmol) of TFA were added, and the reaction mixture was left on stirring at rt for 3 h. The solvent and excess TFA were removed on rotary evaporator followed by high vacuum pump. By this procedure 12.5 mg (0.007 mmol) of **8** were isolated quantitatively, (42% overall yield starting from **3**). ESI MS calculated molecular ion for **9**, with non-oxidized methionine $[M+2H]^{2+}$: 793.35, found: 792.98. ESI MS calculated molecular ion for **8**, with oxidized methionine $[M+2H]^{2+}$: 801.25, found: 801.07. MALDI-TOF (matrix: DHB): calculated molecular ion $[M+H]^+$: 1601.71, found: 1602.04. FT IR (KBr) ν_{max}: 527.41 (C_{60}), 1124.77 (C−O), 1184.77 (C_{60}), 1449.01 (C_{60}), 1641.05, 1738.90, 2955.22, 3430.98 cm^{-1}.

4.3. ELISA test

All sera were initially tested for ANA (Antinuclear Antibodies) using Hep-2 cells as substrate. Antigen, 10 μg/mL in carbonate buffer pH 9.6, was coated to 96-well polystyrene cuvettes (NUNC, Denmark), 50 μL/well, and was incubated at 4°C overnight. The non-specific binding sites were blocked with 5% bovine serum albumin (BSA) in Tris (50 mM)−NaCl (0.9%)−NaN_3 (0.01%) pH 7.4 (100 μL/well), overnight at 4 °C. After washing with PBS, sera were incubated (50 μL/well) at rt for 1 h in 1:100 dilution in PBS/BSA (2%)/Tween 20 (0.05%). After washing with PBS, the antibodies bound to the peptide were detected with alkaline phosphatase conjugated to *anti*-human IgG (Seralas), which was incubated for 30 min at rt (1/2500 dilution, in PBS/BSA (2%)/Tween 20 (0.005%), 50 μL/well. Finally, the plates were washed with PBS and a solution of OPD (*o*-phenyl diamine in 10 mL of citrate buffer 0.05 M, pH 5, 5 μL H_2O_2, was added to the wells (50 μL/well). The enzymatic reaction was stopped after 5 min with the addition of 2 N HCl solution (50 μL/well), and the absorbance (A) was read at 405 nm. Positive values were considered those which were above the mean optical density of normals increased by three standard deviations.

4.4. NMR spectroscopy

Identification of amino acid spin systems and sequential assignment in **8**, was made using a combination of TOCSY

and NOESY experiments. One- and two-dimensional NMR spectra were recorded on a Bruker model AMX 400 MHz spectrometer, with DMSO-d_6 as the deuterated solvent and also as a reference.

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A computational study of the thermal opening of benzocyclobutenes to (*E*)- and (*Z*)-xylylenes☆

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Abstract—The structures of eleven 1-substituted benzocyclobutenes and corresponding (*E*)-*o*-xylylenes and (*Z*)-*o*-xylylenes have been calculated at the Becke3LYP/6-311G(d,p) level. Some *o*-xylylenes are plane and even some (*Z*)-isomers. In three cases (substituent: methoxy, amino and formamido groups), *the* (*Z*)*-isomer is more stable than the* (*E*)*-isomer*. The regioselectivity of the Diels–Alder reaction between (*o*)-xylylenes and propene or ethylvinylether is discussed according to the frontier OM coefficients.

1. Introduction

In the course of a program directed towards the development of new steroids which could exhibit improved therapeutic actions over existing drugs,[1] we reported a convergent steroid synthesis[2] based on the approach A+D→AD→ABCD. This latter involved the use of an intramolecular cycloaddition of *o*-xylylenes developed first by Oppolzer[3] and Kametani[4] for the generation of the BC ring system of steroids.[5]

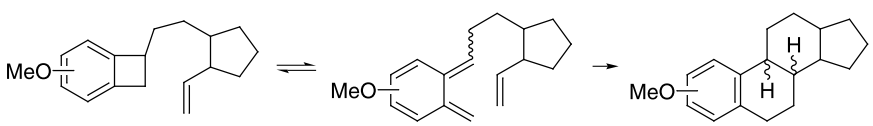
On heating, conveniently substituted benzocyclobutenes undergo reversible conrotatory ring opening to the corresponding *o*-xylylenes. Then, these species can readily participate to an intramolecular Diels–Alder type cycloaddition reaction. Consequently, the stereochemistry of the B/C ring system depends on the steric control of the opening of the benzocyclobutenes and the intramolecular xylylene-cycloaddition (Scheme 1).

Generally, the cycloaddition reaction exhibits a high degree of regio- and stereoselectivities. The four possible approaches are summarized in Scheme 2.

They provide either a *trans* B/C ring junction (for the two first cases) (the *endo* transition state from the *Z*-xylylene seems to be too constraint) or a *cis* B/C ring junction (for the two other cases).

2. Structure of benzocyclobutenes and (*E*)- or (*Z*)-*o*-xylylenes

To the best of our knowledge, no study has been devoted to determine the relative stability of substituted *o*-xylylenes. However, Jefford and Houk reported experimental findings on the thermolytic behavior of several benzocyclobutene derivatives.[6] They studied the torquoselectivity of the ring opening of 1-substituted benzocyclobutenes by means of ab initio molecular orbital calculations (3-21G). The ring opening of substituted benzocyclobutene can involve either an outward or an inward rotation of the substituent. As for 3-substituted cyclobutenes,[7] ab initio calculations on the transition states indicate that the tendency for outward rotation of substituents leading to (*E*)-xylylenes, increases with the donor character of the substituent.[8]



Scheme 1.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.01.049

Keywords: Benzocyclobutenes; *o*-Xylylenes; Diels–Alder reaction.
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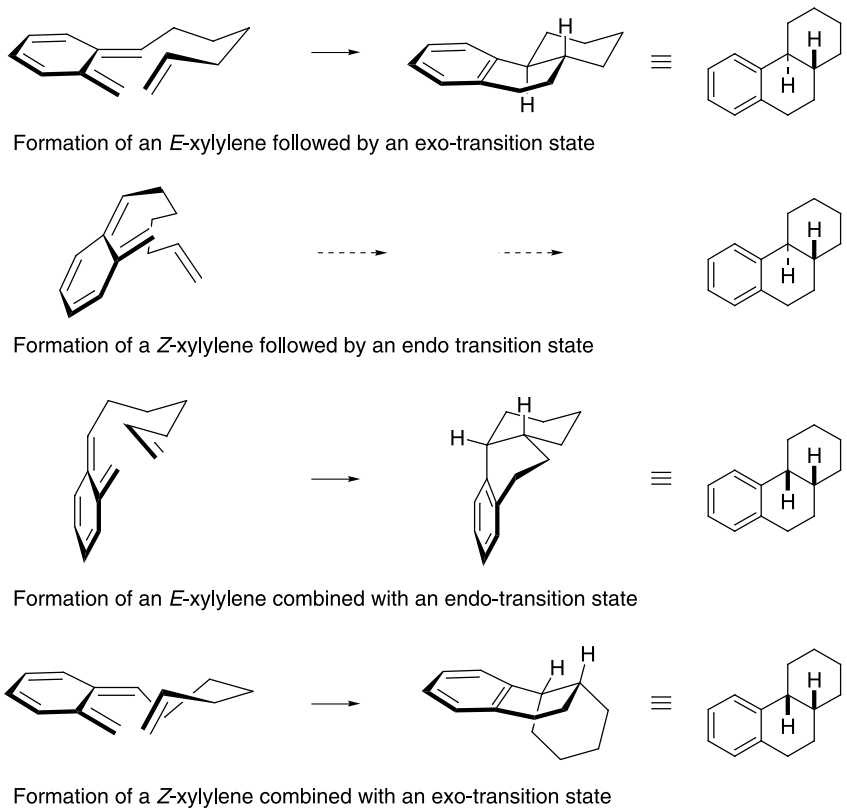


Scheme 2.

In the present work, we have calculated the structures of benzocyclobutenes **1a**–**11a** and corresponding (*E*)-*o*-xylylenes **1b***E*–**11b***E* and (*Z*)-*o*-xylylenes **1b***Z*–**8b***Z* (Scheme 3). The geometry was first optimized with the semi-empirical PM3 method followed by calculations at the HF/6-31G(d,p) level. Then, the geometries were optimized with density functional theory (DFT) using the Becke3LYP functionals[9] and 6-311G(d,p) basis set. For all optimized structures, harmonic vibrational frequencies have been calculated at the same level allowing the correction for the zero-point energies (ZPE).[10]

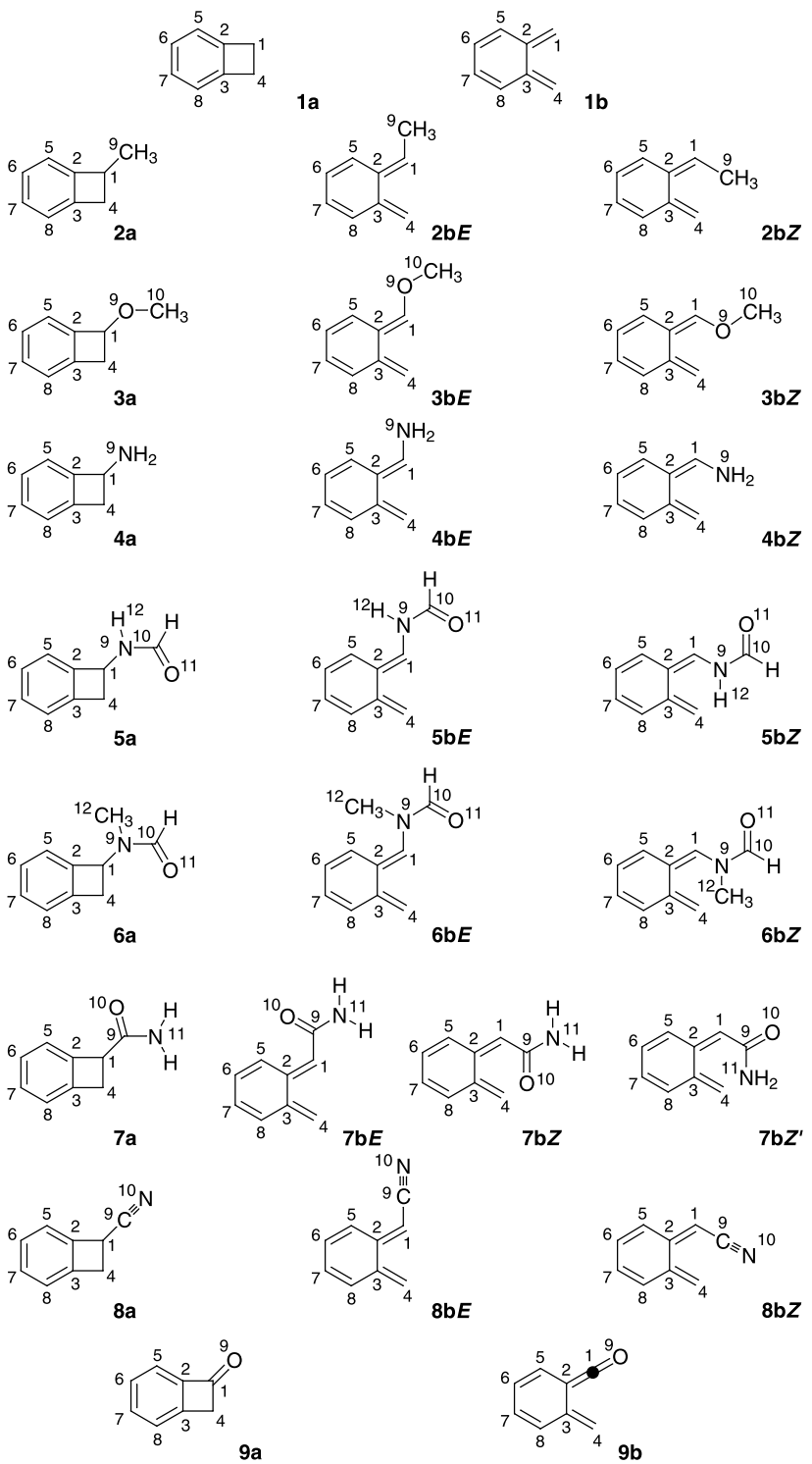
In order to compare their geometries, energies of molecular orbitals and energies, we have calculated the structure of *cis* and *trans*-*o*-xylylenes bearing either electron donating groups (methyl, methoxy, amino, formamido) or electron-withdrawing groups (carboxamido, cyano, oxo) (Scheme 3). Moreover, the structures of 1-methyl-4-methoxybenzocyclobutene and 1-methyl-5-methoxybenzocyclobutene and those of corresponding (*E*)-xylylenes have been calculated in order to modelize the formation of the B-cycle of steroids (Scheme 4). The results concerning the geometries of benzocyclobutenes are collected in Tables 1SI and 2SI and those of *o*-xylylenes are collected in Tables 3SI–5SI (Supplementary Information, SI).

Compound **1a** is the sole benzocyclobutene whose bond lengths have been determined by X-ray crystallographic analysis at −170 °C.[11] The differences between these latter and the calculated bond lengths (after correction considering the rigid-body motion of molecules in crystals)[12] are in ±0.2% range. As expected, the bonds in the benzene ring adjacent to the annelated bond, are shortened [C(2)–C(5) or C(3)–C(8)]. Moreover, optimized angles values are identical to those determined by X-ray analysis. Calculations at the MP2/6-311G(d,p) show more discrepancies (Table 1SI).

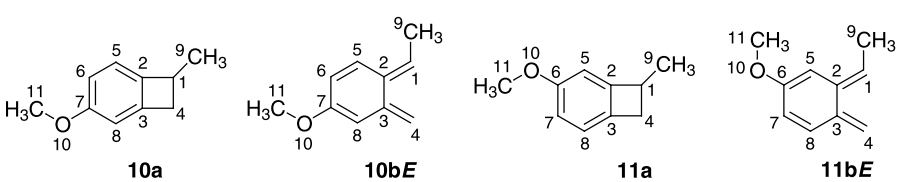
The geometries of *o*-xylylenes present some interesting features (Table 3SI). The expected bond alternation is quite marked since we note, for instance, that in the case of **10b***E*, the lengthening of the C(2)C(3) bond (1.503 Å)[C(2)C(3) bond, means for (*E*)-isomers: 1.493 Å; means for (*Z*)-isomers: 1.487 Å]. There is much more conjugation throughout the (*Z*)-amino-substituted xylylene **4b***Z* (**4b***Z* presents the shortest C(2)C(3), C(2)(C5), C(6)C(7) bonds and the longest C(1)C(2), C(3)C(4), C(7)C(8) bonds). Curiously, the C(1)X(9) bonds in (*E*)-isomers are longer than in corresponding (*Z*)-isomers, even in the case of **6b***Z* bearing a sterically hindered substituent (Δ=0.008 Å). Consequently, for (*Z*)-isomers, the (X)–C(4) distance is short (2.88 Å for the distance O–C(4) in **3b***Z*, 3.02 and 3.04 Å for the distance N–C(4) in **4b***Z* and **5b***Z*, respectively, 2.88 Å for the distance O–C(4) in **7b***Z*).

In the same way, we note that the C(2)(C1)X(9) angle is little modified by the change of geometry (**2b***E*, 128.0°, **2b***Z*, 129.5°, Δ=1.5°; **3b**, Δ=2°; **4b**, Δ=0.6°; **5b**, Δ=−0.5°; **6b**, Δ=6.9°; **7b**, Δ=4.4°) (Table 4, SI).

Amazingly, at the Becke3LYP/6-311G(d,p) level, some *o*-xylylenes are plane and even some (*Z*)-isomers (Table 5SI).[13] Even though **1b** and nine others *o*-xylylenes are nonplanar, it is astonishing that **2b***Z*, **3b***Z*, **8b***E*, **8b***Z*, **9b** and **10b***E* are plane molecules. The tendency of the planarity for the (*Z*)-isomers is underlined by the decreasing of the C(1)C(2)C(3)C(4) dihedral angle from **7b***E* (26.1°) to **7b***Z*



Scheme 3.



Scheme 4.

Table 1. Calculated energies of the xylylene formation **1b**–**11b** from corresponding substituted benzocyclobutenes at the Becke3LYP/6-311G(d,p) level

	Total energy (hartree)	ZPE	ZPE[a]	Corrected total energy (hartree)	Formation energy (hartree)	Formation energy (kcal/mol)
1a	−309.70865	0.13382	0.13235	−309.57630		
1b	−309.68871	0.13148	0.13003	−309.55868	0.01762	11.057
2a	−349.03546	0.16164	0.15986	−348.87560		
2b*E*	−349.01565	0.15929	0.15754	−348.85811	0.01749	10.97
2b*Z*	−349.01486	0.15985	0.15809	−348.85677	0.01883	11.81
3a	−424.26066	0.16603	0.16420	−424.09646		
3b*E*	−424.24725	0.16413	0.16232	−424.08493	0.01153	7.23
3b*Z*	−424.24961	0.16448	0.16267	−424.08694	0.00952	5.97
4a	−365.07728	0.15104	0.14938	−364.92790		
4b*E*	−365.06929	0.14865	0.14701	−364.92228	0.00562	3.53
4b*Z*	−365.07346	0.14950	0.14785	−364.92561	0.00229	1.44
5a	−478.45438	0.16085	0.15908	−478.29530		
5b*E*	−478.44084	0.15894	0.15719	−478.28365	0.01165	7.31
5b*Z*	−478.44274	0.15941	0.15770	−478.28504	0.01026	6.44
6a	−517.76999	0.18886	0.18678	−517.58321		
6b*E*	−517.75150	0.18719	0.18513	−517.56637	0.01684	10.57
6b*Z*	−517.75090	0.18704	0.18498	517.56592	0.01729	10.85
7a	−478.46690	0.16071	0.15894	−478.30796		
7b*E*	−478.45014	0.15872	0.15697	−478.29316	0.01479	9.28
7b*Z*	−478.44563	0.15910	0.15734	−478.28828	0.01968	12.35
8a	−401.97213	0.13268	0.13122	−401.84091		
8b*E*	−401.96011	0.13068	0.12924	−401.83087	0.01004	6.30
8b*Z*	−401.95978	0.13103	0.12959	−401.83019	0.01072	6.73
9a	−383.74880	0.11525	0.11398	−383.63482		
9b	−383.72089	0.11299	0.11175	−383.60914	0.02568	16.11
10a	−463.59075	0.19380	0.19167	−463.39908		
10b*E*	−463.57443	0.19151	0.18940	−463.38503	0.01405	8.82
11a	−463.59072	0.19381	0.19168	−463.39904		
11b*E*	−463.57505	0.19170	0.18959	−463.38546	0.01358	8.52

[a] ZPEs (zero point energies) are scaled by a factor of 0.989, as recommended in Ref. 10.

(12.9°). In fact, the conformational change induces only a very weak difference of the total energy for the *o*-xylylenes. For example, at the B3LYP/6-311G(d,p) level, the total energy of **1b** with a planar structure is 0.23 kcal/mol less stable than **1b** with a nonplanar structure! In other part, for the (*Z*)-*o*-xylylene substituted by a formamido group, the *s-cis* conformation **7b***Z* is 1.52 kcal/mol more stable than the *s-trans* conformation **7b***Z*′.

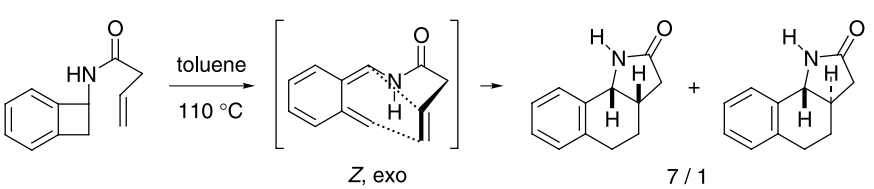
The above remarks are confirmed by results concerning the calculated formation energies (Table 1). First, it is gratifying to note that for **1b** the energy formation (11.06 kcal/mol) is in very good agreement with the experimental value (11.1 kcal/mol) determined by Roth.[14,15c] Except for **9b**, the presence of substituents induces a decreasing of the energy formation in particular in the case of donor groups, such as methoxy, amino or formamido groups. Actually, the opening of 7-aminobenzocyclobutene **4a** occurs at room temperature giving mainly (*Z*)-aminoxylylene **4b***Z*. For a long time, it has been known that the presence of electron-rich substituents favored the opening of the benzocyclobutenes (the required temperature varies from 25 to 200 °C).[16] Moreover, in these three later cases, the (*Z*)-isomer was found to be more stable than the (*E*)-isomer.

By this way, the concept of steric control governing the course of the conrotatory opening of 1-benzocyclobutene derivatives appears to be no relevant. Rather, the ratio of (*E*)- and (*Z*)-xylylenes is dictated by electronic factors which finally determines the stereochemical outcome.

Some experimental results are in accordance with an inward rotation and the easy formation of *Z*-xylylenes. Thus, in the course of the synthesis of alkaloid skeletons, Oppolzer has observed the formation of the following tricyclic lactames by heating a benzocyclobutene amide at 110 °C. The structure of the major isomer could result of the formation of the *Z*-xylylene which cyclized according to an *exo* transition state, rather than the postulated very strained *endo* transition state with the corresponding *E*-xylylene (Scheme 5).[17]

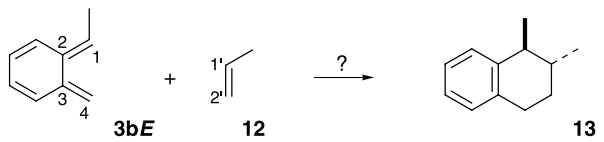
3. Diels–Alder reactions of *o*-xylylenes with propene

In order to explain the selectivity observed during the formation of B-ring of steroids, we next decided to examine the cycloaddition step. The cycloaddition of the methylxylylene **2b***E* with propene **12** providing the *trans*-dimethyltetraline **13** (Scheme 6) can be an interesting model for the



Z, exo 7 / 1

Scheme 5.



Scheme 6.

induces a decreasing of the electrophilic properties of xylylene.

The C(4)/C(1) coefficient ratios for HOMO and LUMO are given in Table 2. From the examination of these results, we would predict the formation of the '*ortho*' products for the

Table 2. Calculated HOMO and LUMO energies, coefficients of the HOMO and the LUMO, relative weights of coefficients of *o*-xylylenes **1b**–**11b***E* and **12** at the Becke 3LYP/6-311G(d,p) level[a]

	HOMO energy (eV) (n°)	HOMO coeff.	C(4)/C(1) coeff. ratio[b]	LUMO energy (eV) (n°)	LUMO coeff.	C(4)/C(1) coeff. ratio[c]
1b	−5.547 (28)	C(1): 0.164 C(4): −0.164	1	−2.250 (29)	C(1): −0.168 C(4): −0.168	1
2b*E*	−5.358 (32)	C(1): 0.178 C(4): −0.191	1.073	−2.048 (33)	C(1): 0.195 C(4): 0.185	0.949
2b*Z*	−5.349 (32)	C(1): 0.129 C(4): −0.131	1.015	−2.041 (33)	C(1): −0.143 C(4): −0.134	0.937
3b*E*	−5.066 (36)	C(1): 0.158 C(4): −0.203	1.285	−1.905 (37)	C(1): 0.193 C(4): 0.178	0.922
3b*Z*	−4.952 (36)	C(1): 0.121 C(4): −0.136	1.124	−1.737 (37)	C(1): −0.143 C(4): −0.127	0.888
4b*E*	−4.787 (32)	C(1): 0.149 C(4): −0.205	1.376	−1.721 (33)	C(1): 0.199 C(4): 0.160	0.804
4b*Z*	−4.852 (32)	C(1): 0.133 C(4): −0.187	1.406	−1.615 (33)	C(1): −0.182 C(4): −0.150	0.824
5b*E*	−5.397 (39)	C(1): 0.157 C(4): −0.201	1.280	−2.373 (40)	C(1): 0.178 C(4): 0.180	1.011
5b*Z*	−5.462 (39)	C(1): 0.146 C(4): −0.197	1.349	−2.391 (40)	C(1): −0.180 C(4): −0.176	0.978
6b*E*	−5.294 (43)	C(1): 0.148 C(4): −0.218	1.473	−2.200 (44)	C(1): 0.175 C(4): 0.198	1.131
6b*Z*	−5.407 (43)	C(1): 0.150 C(4): −0.219	1.460	−2.205 (44)	C(1): −0.176 C(4): −0.213	1.210
7b*E*	−5.826 (39)	C(1): 0.171 C(4): −0.175	1.023	−2.764 (40)	C(1): 0.158 C(4): 0.205	1.297
7b*Z*	−5.727 (39)	C(1): 0.160 C(4): −0.142	0.891	−2.653 (40)	C(1): −0.131 C(4): −0.179	1.364
8b*E*	−6.122 (34)	C(1): 0.134 C(4): −0.122	0.910	−3.231 (35)	C(1): 0.121 C(4): 0.139	1.149
8b*Z*	−6.097 (34)	C(1): 0.134 C(4): −0.118	0.880	−3.138 (35)	C(1): 0.119 C(4): 0.141	1.185
9b	−5.276 (31)	C(1): 0.094 C(4): −0.151	1.596	−1.938 (32)	C(1): 0.129 C(4): 0.107	0.829
10b*E*	−5.094 (40)	C(1): 0.115 C(4): −0.146	1.269	−1.929 (41)	C(1): −0.144 C(4): −0.113	0.785
11b*E*	−5.168 (40)	C(1): 0.179 C(4): −0.161	0.899	−1.849 (41)	C(1): 0.161 C(4): 0.195	1.211
12	−7.154 (12)	C(1′): 0.169 C(2′): 0.185	1.095	0.021 (14)	C(1′): 0.188 C(2′): −0.155	0.824

[a] Atom numbering is as in Schemes 3 and 4.
[b] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **12**) of the HOMO.
[c] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **12**) of the LUMO.

intramolecular addition (Scheme 1).[18] At the B3LYP/6-311G(d,p) level, the *trans*-dimethyltetraline **13** is 56.7 kcal/mol more stable than the reactants.[19]

According to the frontier-orbital theory applied to the Diels–Alder reactions, the main contributor to the rate determining step is the transfer of electrons from the diene to the dienophile. Thus, the stereodirecting orbitals are the HOMO of the diene (donor) and the LUMO of the dienophile (acceptor).[20] The regioselectivity of the reactions can be predicted from the HOMO and LUMO polarization (match up the larger coefficient on one component with the larger on the other).

Propene is a dienophile without activating electron withdrawing substituent. Consequently, two interactions between either the LUMO of the xylylene **2b***E* and the HOMO of the propene (ΔE xylylene/propene: $E_{LUMO}-E_{HOMO}$=5.106 eV) (Type II according to the classification of Sustmann)[21] or the HOMO of **2b***E* and the LUMO of the propene (ΔE xylylene/propene: $E_{HOMO}-E_{LUMO}$=5.379 eV) can occur (Table 2). However, this last case presents a more favorable configuration concerning the orbital overlap (Type I). The frontier MO energies imply that the methylxylylene **2b***E* should be slightly more electrophilic than propene. The reverse situation should be noted for methoxyxylylenes **10b***E* and **11b***E* (ΔE (eV) xylylene/propene: **10b***E*, $E_{HOMO}-E_{LUMO}$=5.12; $E_{LUMO}-E_{HOMO}$=5.23. **11b***E*, $E_{HOMO}-E_{LUMO}$=5.19; $E_{LUMO}-E_{HOMO}$=5.31). The donor character of the methoxy group reaction of propene with **7b***Z*, **8b***E*, **8b***Z* and **11b***E* and the '*meta*' products in the other cases. It is interesting to note that the addition reaction of **11b***E* with propene is the sole case where the regioselectivity is in accordance with the intramolecular reaction used in the synthesis of steroids (Fig. 1).

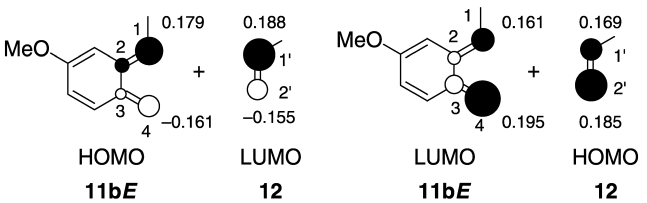
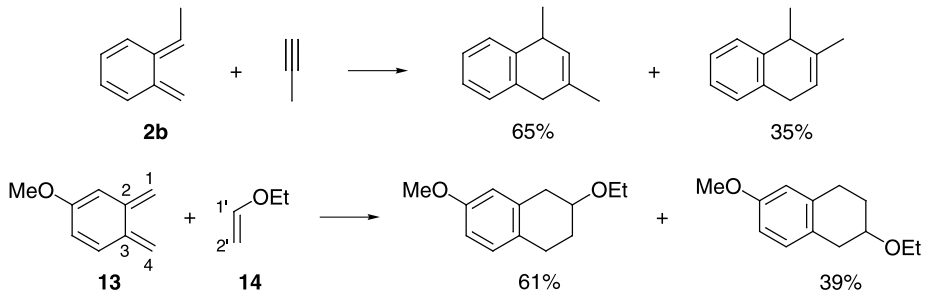


Figure 1.

To the best of our knowledge, only one experimental result concerns the Diels–Alder reaction of methylxylylene **2b**. Indeed, Fleming et al. have studied the regiochemistry of the reaction of **2b** with propyne and as expected the major product was the '*meta*' isomer (Scheme 7).[22]

The same authors have studied the cycloaddition of methoxyxylylene **13** to the ethylvinylether **14**. The adducts are obtained in poor regioselectivity which is plainly not steric in origin. We have calculated at the Becke3LYP/6-311G(d,p) level the structure of **13** and **14** (Table 3). The Diels–Alder reaction is of Type II according to the classification of Sustmann, since the separation between the LUMO of the xylylene **13** and the HOMO of **14** (ΔE **13**/



Scheme 7.

Table 3. Calculated HOMO and LUMO energies, coefficients of the HOMO and the LUMO, relative weights of coefficients of *o*-xylylene **13** and ethylvinylether **14** at the Becke 3LYP/6-311G(d,p) level[a]

	HOMO energy (eV) (n°)	HOMO coeff.	C(4)/C(1) coeff. ratio[b]	LUMO energy (eV) (n°)	LUMO coeff.	C(4)/C(1) coeff. ratio[c]
13	−5.15 (36)	C(1): 0.141 C(4): −0.109	0.77	−2.21 (37)	C(1): 0.119 C(4): 0.137	1.150
14	−6.29 (20)	C(1′): 0.123 C(2′): 0.180	0.68	0.17 (22)	C(1′): 0.163 C(2′): −0.140	1.16

[a] Atom numbering is as in Scheme 7.
[b] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **14**) of the HOMO.
[c] Relative weights of coefficients (2s, $2p_x$, $2p_y$, $2p_z$) at C(1) and C(4) (or C(1′) and C(2′) for **14**) of the LUMO.

14: $E_{LUMO}-E_{HOMO}=4.08$ eV) is smaller than the separation between the HOMO of **13** and the LUMO of **14** (ΔE **13/14**: $E_{HOMO}-E_{LUMO}=5.32$ eV). Interestingly, the observed regioselectivity is in accordance with the orbital coefficients.

4. Conclusion

In conclusion, this study show that the formation of (*Z*)-xylylenes is unexpectedly possible. Indeed, in the case of xylylenes **3b**, **4b** and **5b**, calculations have proven that the (*Z*)-isomers were the most stable in each case. Amazingly, even the presence of a sterically hindered substituent such as a *N*-methylformamido group is in agreement with the formation of a (*Z*)-xylylene.

Thus, the favored formation of (*Z*)-xylylene seems to be dictated by electronic factors rather than steric control. Moreover, most of the time, the regioselectivity of the Diels–Alder reaction is imposed by the intramolecular reaction character whereas the frontier MO coefficients are rather in favor of the opposite regioselectivity.

Acknowledgements

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New developments in zinc-catalyzed asymmetric hydrosilylation of ketones with PMHS

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Abstract—The influence of structural modifications of the diamine ligand and the ZnR_2 precursor in the [ZnR_2–diamine]-catalyzed asymmetric hydrosilylation of prochiral ketones with PMHS in aprotic medium is reported. A new diamine ligand giving up to 91% ee in the reduction of acetophenone is described. The scope of this reduction system has been investigated using variously functionalized ketones and some deactivation pathways have been identified.

1. Introduction

Enantiomerically pure chiral alcohols are key intermediates in the synthesis of numerous biologically active molecules.[1] For this reason, much effort has been paid in the last 30 years to develop efficient techniques for asymmetric reduction of prochiral ketones. In particular, asymmetric catalysis provides organic chemists with a whole tool of efficient methods,[2] none of them being yet optimal.[3] Among others, asymmetric hydrosilylation leads to very high enantiomeric excesses on a large range of substrates, the best results being usually obtained with Rh- and Ti-based catalysts.[4] Nevertheless, the toxicity, price and low stability of the reagents (molecular hydrosilanes and hydrosiloxanes) and/or catalysts limit its industrial applications. The recent rediscovery of polymethylhydrosiloxane (PMHS), a stable inexpensive and non-toxic hydrosilane, has opened new perspectives to asymmetric hydrosilylation.[5] In this context, we got particularly interested in an original Zn–diamine catalytic system reported by Mimoun et al. for chemoselective hydrosilylation/reduction of aldehydes, ketones and esters.[6] An asymmetric version was also described, limited to the enantioselective reduction of acetophenone.[7]

We report here complementary studies on this zinc-based catalytic system. Our goals were (i) to further explore the influence of reaction parameters, for example, structural modifications of the diamine ligand and the ZnR_2 precursor, to improve eventually on the enantioselectivity in the hydrosilylation of simple alkyl aryl ketones; and (ii) to investigate the scope of this reduction system for variously functionalized ketones.

2. Results and discussion

2.1. Influence of ligand structure

In the results disclosed by Mimoun et al.,[7] the best ees for the reduction of acetophenone (**K1**) were reached with (*R*,*R*)-*N*,*N*′-ethylene-bis(1-phenylethylamine) (ebpe, **1a**, Scheme 1) (76% ee, Table 1, entry 1) and (*S*,*S*)-*N*,*N*′-dibenzyl-1,2-diphenyl-1,2-ethanediamine (*N*-Bn-dpen, **3a**) (88% ee, entry 6). Alternatively, we first modified the substituents on the skeleton of ebpe with the series of ligands **1b–d** (Scheme 1). It appears that replacing the phenyl ring by a bulkier aromatic substituent does not affect the catalyst activity (**1b**, entry 2). On the other hand, a significant decrease in activity is observed with a *p*-chlorophenyl substituted ligand (**1c**, entry 3); the latter decrease is tentatively ascribed to competitive reversible coordination of chlorine to the zinc center, leading to a catalytically less active or inactive species. Nevertheless, the level of enantioselectivity for the reduction of **K1** is equivalent irrespective of the aryl-derivative used within this series (**1a–c**). In sharp contrast, a dramatic loss of enantioselectivity is observed with the cyclohexyl-ebpe derivative (**1d**, entry 4), which likely accounts for the influence of electronic factors (vide infra). Moreover, the rigidity provided by a propylene bridge in ligand **2** seems

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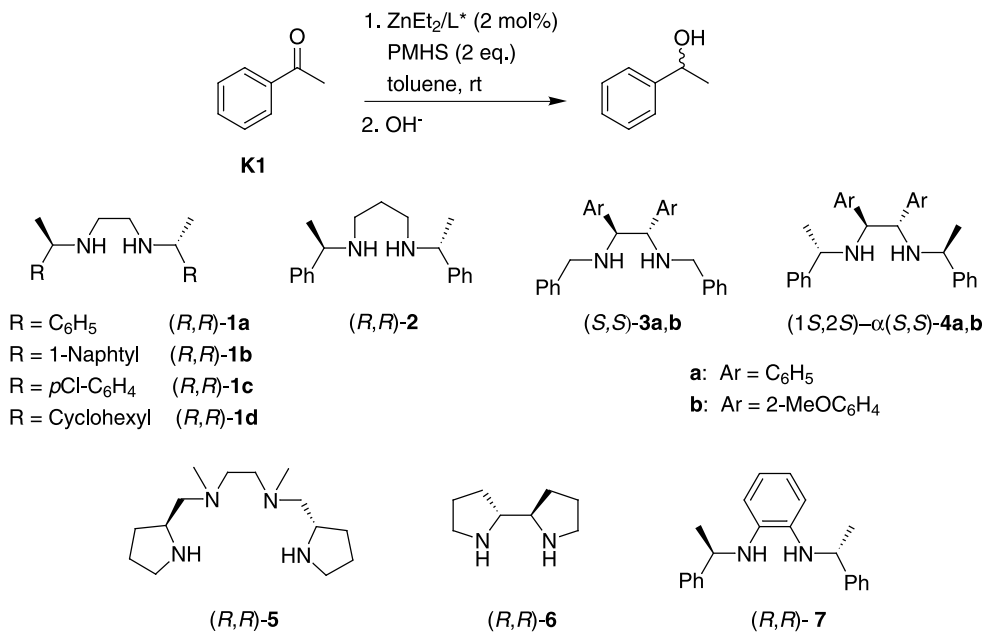


Scheme 1.

Table 1. Zinc-catalyzed reduction of acetophenone (**K1**) with PMHS using ligands **1**–**7**[a]

Entry	Ligand	Time[b] (h)	Yield (mol%)	ee (conf.) (%)
1[c]	(*R*,*R*)-**1a**	18	>99	76 (*S*)
2	(*R*,*R*)-**1b**	6	94	78 (*S*)
3	(*R*,*R*)-**1c**	6	14	76 (*S*)
4	(*R*,*R*)-**1d**	6	68	22 (*S*)
5	(*R*,*R*)-**2**	4	15	0
6[c]	(*S*,*S*)-**3a**	18	>99	88 (*R*)
7	(*S*,*S*)-**3b**	72	>99	83 (*R*)
8	(1*S*,2*S*)-α(*S*,*S*)-**4a**	170	56	84 (*R*)
9	(1*S*,2*S*)-α(*S*,*S*)-**4b**	288	66	91 (*R*)
10	(*R*,*R*)-**5**	16	91	0
11	(*R*,*R*)-**6**	18	>99	22 (*R*)
12	(*R*,*R*)-**7**	2	2	<5

[a] PMHS/**K1**/$ZnEt_2$/diamine=60:50:1:1 [**K1**]=0.89 M in toluene.
[b] Reaction time not optimized.
[c] Results from Ref. 7.

insufficient to enable effective activation and enantiodifferentiation for the reduction, as reflected by the limited racemic conversion (entry 5). C_2-symmetric secondary diamine ligands **5** and **6** that bear no aromatic substituents proved also inefficient in terms of enantioselectivity, and bis-aniline-type diamine **7** showed only poor activity (entries 10–12). In light of these results, it appears thus important to keep both a C_2-symmetric 1,2-ethylenediamine ligand backbone as well as a *N*-benzyl group, either α to the nitrogen or on the 1,2 positions of the ethylene bridge.

The 2-methoxyphenyl-substituted diamine **3b** was synthesized in order to assess the effect of a restricted rotation of the aryl ring on the catalyst performance. As somewhat lower activity is obtained, the enantioselectivity remains slightly below that promoted by *N*-Bn-dpen (**3a**, entries 6 and 7). The association of the aforementioned two types of chiral centers (α and 1,2) was realized through the new diamines **4a**,**b**. $ZnEt_2$-catalyst systems based on these bulky ligands promote hydrosilylation/reduction of **K1**, but only with modest rates (entries 8 and 9). On an enantioselective point of view, the results show that no cooperative effect of the α and (1,2) chiral centers takes place within ligand **4a**. Indeed, although both (*S*,*S*)-dpen (**3a**) and (*S*,*S*)-ebpe (**1a**) lead to the same major product of absolute configuration (*R*), the performance of the 'matched' ligand **4a** (84% ee, entry 8) is only in between that of each individual ebpe **1a** and dpen **3a**. Thus, with respect to **3a**, the introduction of a α-methyl substituent on the *N*-benzyl arm only lowers the catalyst performances. Nevertheless, further improvement of enantioselectivity in the hydrosilylation/reduction of **K1** was obtained with the 2-methoxyphenyl-substituted diamine **4b**, which delivers the best ee with the so-called matched-pair of this ligand (91% ee, entry 9). This improvement is possibly due to the hindered rotation of the phenyl moiety, assisted in this case by the α-methyl arms.

2.2. Other reaction parameters: zinc precursor, hydrosilane

The influence of the catalyst precursor ZnR_2 was investigated by varying the bulkiness and electronic properties of the R residues (R=Et, *i*Pr, Ph). While the use of $Zn(iPr)_2$ in place of $ZnEt_2$ was not so sensitive in the case of **K1**, the use of $ZnPh_2$ greatly affected the reaction rate (Table 2, entries 13 and 14; compare with Table 1, entry 1). A similar trend was observed in the reduction of methyl phenylglyoxylate (**K2**, entries 15–17). For both **K1** and **K2**, the impact of the R residue on the enantioselectivity is noticeable although rather limited. Mechanistically, this evidences that at least one R residue remains coordinated onto the Zn center throughout catalysis (vide infra).[†] Though the $ZnPh_2$/(*R*,*R*)-ebpe system leads to 82% ee in the case of **K1**, i.e., an increase in $\Delta\Delta G^{\#}$ of ca. 0.2 kcal mol^{-1} as compared to $ZnEt_2$, this parameter can not be, however, advantageously exploited from a synthetic point of view, due to the poor

[†] The enantioselectivity of all the systems reported in this paper is constant over the whole reaction time, as probed by GLC monitoring.

Table 2. Zinc–(*R*,*R*)-ebpe (**1a**)-catalyzed reduction of acetophenone (**K1**) and methyl phenylglyoxylate (**K2**): influence of the zinc precursor and silane[a]

Entry	Ketone	ZnR_2 (R)	Silane	Time[b] (h)	Yield (mol%)	ee (conf.) (%)
13	**K1**	*i*Pr	PMHS	48	>99	76 (*S*)
14	**K1**	Ph	PMHS	18	31	82 (*S*)
15	**K2**	Et	PMHS	6	>99	28 (*R*)
16	**K2**	*i*Pr	PMHS	6	>99	33 (*R*)
17	**K2**	Ph	PMHS	4	31	48 (*R*)
18	**K1**	Et[c]	PMHS	44	19	82 (*S*)
19	**K1**	Et	Et_3SiH	48	0	—
20	**K1**	Et	Ph_2SiH_2	5	>99	79 (*S*)
21	**K1**	Et	$PhSiH_3$	18	>99	76 (*S*)

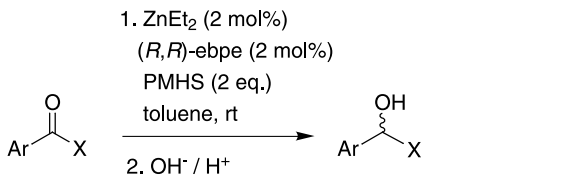
[a] SiH/**K**/ZnR_2/(*R*,*R*)-**1a**=60:50:1:1 [**K**]=0.89 M in toluene.
[b] Reaction time not optimized.
[c] *T*=−20 °C.

reduction rate associated. Therefore, no further preparation of $Zn(Ar)_2$ precursor was attempted. Similarly, only a slight improvement of the enantioselectivity was noticed when the reduction was carried out at −20 °C, along a neat decrease of the reaction rate (entry 18). Pre-activation of the catalyst, through brief heating (50 °C) of $ZnEt_2$, diamine and 1 equiv. of substrate together, proved useless.

Except trialkylsilanes (entry 19), various molecular monoalkyl- and dialkylsilanes lead to as effective systems as PMHS for the reduction of **K1**, with ees in the same range (entries 20 and 21). No specific rate acceleration was detected with PMHS as compared to other silanes.[8] Nevertheless, the intrinsic characteristics of this polymeric siloxane (low price, low toxicity, stability to air and moisture) largely justify its use as reducing agent in current efforts to access inexpensive and efficient reducing systems.

2.3. Scope of the catalytic reaction—deactivation pathways

Another point of interest was to assess the reductive abilities of this Zn/diamine catalyst system in toluene towards functionalized ketones, since only the reduction of simple alkyl aryl ketones has been reported so far. Using $ZnEt_2$–(*R*,*R*)-**1a** as the model catalyst, a variety of ketones were reduced with moderate to good activities, total chemoselectivity for the corresponding alcohol, and interesting levels of enantioselectivities for some of them (Scheme 2, Table 3). For instance, reduction of 2-acetylthiophene (**K6**) provides



Ar = Ph, X = Me **K1**
$COCH_3$ **K2**
CF_3 **K3**
CH_2Cl **K4**
$CH_2CO_2CH_3$ **K5**
Ar = 2-Thienyl, X = Me **K6**
$CH_2CH_2NMe_2$ **K7**
Ar = 2-Pyridyl, X = Me **K8**

Scheme 2.

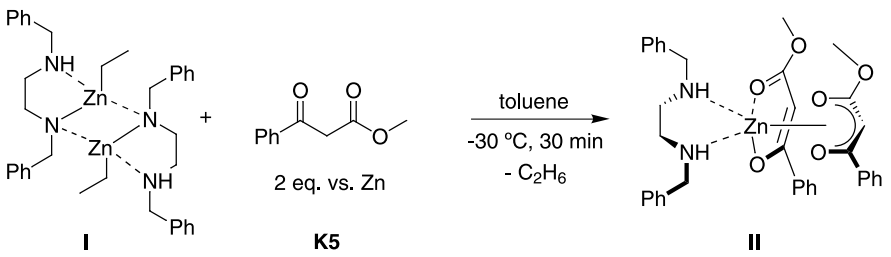
Table 3. Zinc–(*R*,*R*)-ebpe (**1a**)-catalyzed reduction of carbonyl compounds **K3**–**K8**[a]

Entry	Ketone	Time[b] (h)	Yield (mol%)	ee (conf.) (%)
22	**K3**	1	>99	27 (*R*)
23	**K4**	18	43	62 (*R*)
24	**K5**	18	0	—
25	**K6**	48	>99	78 (*R*)
26	**K7**	48	80	35 (*R*)
27	**K8**	4	69	17 (*R*)

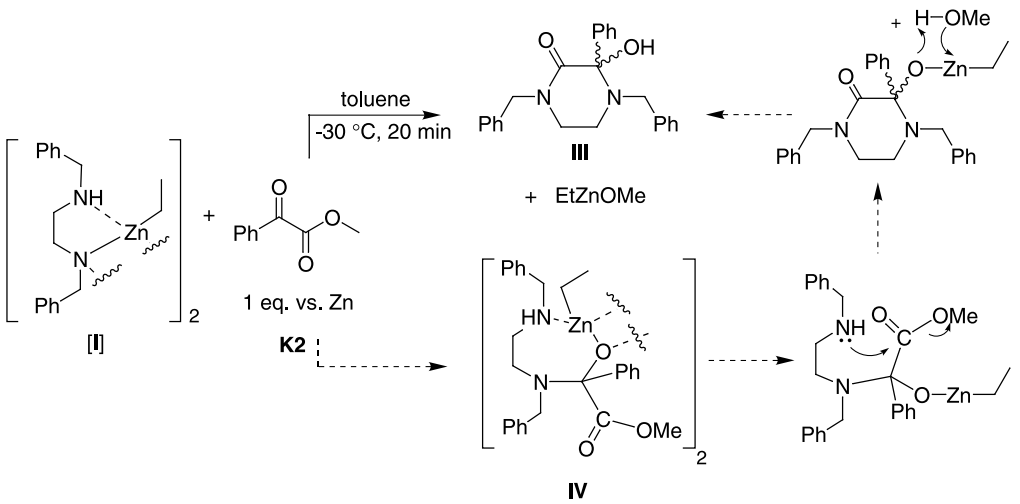
[a] PMHS/**K**/$ZnEt_2$/(*R*,*R*)-**1a**=60:50:1:1, [**K**]=0.89 M in toluene.
[b] Reaction time not optimized.

2-(1-thienyl)ethanol with excellent chemoselectivity and 78% ee (entry 25). The presence of a strongly electron-withdrawing group α to the carbonyl function, such as in α,α,α-trifluoroacetophenone (**K3**), activates greatly the reaction, however ending with quite a low enantioselectivity in this case (entry 22). Also, as already mentioned, higher α-ketoesters such as methyl phenylglyoxylate (**K2**) are quantitatively reduced to the corresponding α-hydroxy-esters, which can be readily recovered in high yields after careful hydrolysis (Table 2, entry 15). This result is noteworthy if one takes into account the excellent activity of this Zn–diamine system in the chemoselective reduction of esters and lactones under harsher conditions.[6] In spite of these encouraging results, limitations of this system appeared. For instance, the final hydrolysis step proved somehow troublesome, particularly in the case of lower α-ketoesters such as ethyl and methyl pyruvate, though initial reduction appeared quantitative and chemoselective (^{1}H NMR). More problematic is the presence of potentially coordinating functionalities, such as chlorine (**K4**) and amino groups (**K7**, **K8**), either on the alkyl or aryl moieties of the ketones, which lower the activity of the system (entries 23, 26 and 27). This observation is consistent with the detrimental effect of a chloro group on the ligand backbone (vide supra, entry 3) and suggests also poisoning of the catalytically active zinc species by competitive coordination of the chloro/amino group onto the metal center. Moreover, substrates prone to the formation of enols, for example, β-ketoesters such as **K5**, cannot be reduced with this catalyst system in toluene (entry 24). ^{1}H NMR analysis of the reaction mixture (before hydrolysis) indicated that the substrate (**K5**) remains intact under those conditions; no silyl ether nor silylated enol was detected. Also, cross-experiments showed that β-ketoester **K5** inhibits the catalytic reduction of **K1** and **K2**. The formation of a [Zn–acetylacetonate] species was suspected to account for this inhibition. Indeed, in a separate reaction, the addition of 2 equiv. (vs Zn) of benzoylacetoacetate **K5** on the dimeric amine–amido Zn precursor **I**[9] was found to give the zinc–bis(acac) complex **II**, which was isolated in high yield and identified by elemental analysis and ^{1}H, ^{13}C and 2D NMR (Scheme 3).[10] Complex **II** proved totally inefficient in promoting the reduction of **K1** under standard conditions in toluene, in contrast to **I** which is a highly effective catalyst.

In a parallel experiment, the addition of 1 equiv. (vs Zn) of methyl phenylglyoxylate (**K2**) on amine–amido Zn complex **I** enabled us to isolate, as the major product (50% yield), the 3-hydroxypiperazin-2-one **III**, identified by ^{1}H,



Scheme 3.



Scheme 4.

^{13}C and 2D NMR, and X-ray diffraction.‡ The formation of **III**[11] can be explained on the basis of Mimoun's mechanism,[7] by degradation of a transient (not observed) intermediate complex of type **IV**, that would initially arise from insertion of the carbonyl function of the substrate into the Zn–*N*(amido) bond of complex **I** (Scheme 4). Interestingly, this stoichiometric reaction does not seem to take place under catalytic conditions with ZnR_2–(*R*,*R*)-ebpe systems, since **K2** is quantitatively reduced to methyl mandelate with constant enantioselectivity (Table 2, entries 15 and 16). We assume that the higher bulkiness of ebpe (**1a**) (as compared to that of *N*,*N*-dibenzylethylenediamine) may prevent this side reaction.§ Also, the hydrosilane present under catalytic conditions may likely convert the [$ZnEt_2$–diamine] precursor into another (hydrido) species, which has its own reactivity towards **K2**.

3. Conclusion

Although the ZnR_2–diamine–PMHS hydrosilylation system in aprotic solvents proved relatively limited in scope, its activity and enantioselectivity in the reduction of simple alkyl aryl ketones are noteworthy for such an unusual catalyst system. The enantioselectivity (91% ee) reached with the new 2-methoxyphenyl derivative **4b** compares favorably with recent [Rh]–diphosphine catalysts, such as those based on EtTRAP-H,[12] MiniPHOS[13] or BMPF[14] leading to 85–94% ee on alkyl aryl ketones. Its reactivity and chemoselectivity towards α-ketoesters is also remarkable, though modest enantioselectivity could be achieved so far. As previously reported,[9] the use of similar Zn–diamine systems in protic solvents (alcohol) is an interesting alternative to avoid the final hydrolysis step, which turns out sometimes problematic, and to broaden the scope of this hydrosilylation reaction. Further results obtained under these conditions will be reported soon.

4. Experimental

4.1. General

GLC analyses were performed on Chrompack CP 9001 apparatuses equipped with a flame ionization detector and, respectively, a BPX5 (25 m×0.32 mm, SGE) and a chiral Chirasil-DEX CB (25 m×0.25 mm, Chrompack) column. ^{1}H NMR spectra were recorded on AC-200 and AC-300 Bruker spectrometers at 23 °C in $CDCl_3$; chemical shifts are reported in ppm downfield from TMS and were determined by reference to the residual ^{1}H (δ 7.25) solvent peak; all coupling constants are reported in Hz. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 25 °C in a 1 dm cell. IR spectra were recorded on a Nicolet 510

‡ Poor final *R* values (*R*=0.1066; wR_2=0.2704) were obtained in this X-ray diffraction analysis due to poor quality crystals and disorder problems associated to solvent molecules. However, the data confirmed unambiguously the atom connectivity of **III**.

§ Note that ebpe (**1a**) reacts with $ZnEt_2$ at room temperature to form the diamine complex $ZnEt_2$(ebpe),[7] while *N*,*N*-dibenzylethylenediamine reacts rapidly with $ZnEt_2$ to form the amine–amido complex **I**.[9]

FTIR spectrophotometer in a KBr cell and are expressed by wave number (cm^{-1}). Melting points are uncorrected.

Diamines **1a–d** and **2**,[7] *N*-Bn-Dpen (**3a**),[15] **5**,[16] and **7**[17] were prepared following slightly modified reported procedures and strictly purified by distillation or column chromatography and subsequent recrystallization. The new diamines **3b** and **4a**,**b** were prepared according to known procedures and their synthesis will be described elsewhere. Diamine **6**[18] was kindly provided by Pr. A. Alexakis (University Geneva). $ZnEt_2$ (1.1 M solution in toluene) was purchased from Aldrich and used as received. Complex **I** was prepared as described previously.[9] Ketones were distilled over CaH_2 and degassed before use. PMHS (Aldrich) was degassed before use. Toluene was freshly distilled from Na/K amalgam and degassed before use.

4.1.1. Complex II. Methyl benzoylacetoacetate (**K5**, 0.19 mL, 1.20 mmol, 2.0 equiv. vs Zn) was added dropwise under nitrogen to a solution of complex **I** (0.200 g, 0.30 mmol of dimer, 0.60 mmol of Zn) in toluene (5 mL) cooled at −20 °C. The resulting solution was stirred with a magnetic stir bar for 20 min at −20 °C, and then for 30 min at 25 °C. Volatiles were removed under vacuum to give a yellow oil which was triturated with pentane (5 mL). The resulting precipitate was separated off from the liquid phase, washed with pentane (2×5 mL), and dried under vacuum to give **II** as a white powder (0.260 g, 70%). ^{1}H NMR ($C_6D_5CD_3$): δ 8.13 (d, J=6.4 Hz, 4H, *o*-Ph), 7.70–6.85 (m, 16H, arom.), 6.00 (s, 2H, C*H* acac), 4.09 (s, 4H, NHCH_2Ph), 3.50 (s, 6H, OCH_3), 2.25 (s, 4H, CH_2NHBn). ^{13}C{^{1}H} NMR ($C_6D_5CD_3$): δ 183.4 (ZnO*C*(Ph)=), 175.4 (*C*OOMe), 143.1, 139.1, 133.6, 130.0, 129.3, 129.2, 129.0, 128.6, 127.5 (all *C* arom.), 82.2 (*C*H), 53.2 (NH*C*H_2Ph), 50.6 (O*C*H_3), 45.7 (*C*H_2NHBn). Anal. calcd for $C_{36}H_{38}N_2O_6Zn$ (660.09): C 65.44, H 5.75, N 4.24; found C 65.79, H 5.88, N 3.89.

4.1.2. 3-Hydroxy-1,4-dibenzyl-piperazin-2-one (III). Methyl phenylglyoxylate (**K2**, 0.13 mL, 0.92 mmol, 1.03 equiv. vs Zn) was added dropwise under nitrogen to a solution of complex **I** (0.296 g, 0.445 mmol of dimer, 0.890 mmol of Zn) in toluene (10 mL) cooled at −30 °C. The solution was stirred for 30 min at −30 °C, then for 1 h at 25 °C. Volatiles were removed under vacuum to give a white solid which was triturated with pentane (5 mL). The resulting precipitate was separated off from the liquid phase, washed with pentane (2×5 mL), and dried under vacuum to give a small amount of **III** (0.020 g). The residue was dried under vacuum (0.206 g) and extracted with pentane (5×5 mL). The solution was filtered and volatiles were removed under vacuum to afford **III** as a white powder (total: 0.164 g, 50%). Crystals for X-ray diffraction were grown from toluene/pentane (2:1) at −30 °C. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J=7.0 Hz, 2H, arom.), 7.40–7.10 (m, 13H, arom.), 4.69 (d, J=14.3 Hz, 1H, CONC*H*HPh), 4.56 (d, J=14.3 Hz, 1H, CONCH*H*Ph), 3.74 (d, J=14.6 Hz, 1H, C(OH)NC*H*HPh), 3.54 (d, J=14.3 Hz, 1H, C(OH)NCH*H*Ph), 3.55 (m, 1H, C*H*HN(Bn)CO), 3.15 (m, 2H, CH*H*N(Bn)CO+C*H*HN(Bn)C(OH)), 2.83 (s, 1H, O*H*), 2.70 (m, 1H, CH*H*N(Bn)C(OH)). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 170.4 (*C*O), 142.5, 138.9, 136.3, 129.9, 128.8, 128.3, 128.2, 128.10, 128.0, 127.7, 126.9, 126.6 (all *C* arom.), 89.7 (*C*OH), 52.2 (C(OH)N*C*H_2Ph), 50.7 (CON*C*H_2Ph), 47.0 (*C*H_2N(Bn)CO), 41.1 (*C*H_2N(Bn)C(OH)).

4.1.3. Zn–diamine-catalyzed asymmetric hydrosilylation of acetophenone by PMHS. *General procedure*. Catalytic reactions were performed under nitrogen using standard Schlenk techniques. In a typical experiment (Table 1, entry 1), to a solution of (*S*,*S*)-**1a** (14.7 mg, 0.055 mmol) in freshly distilled toluene (2.5 mL), were added $ZnEt_2$ (50 μL of a 1.1 M solution in toluene, 0.055 mmol), then acetophenone (0.32 mL, 2.75 mmol) and finally PMHS (0.21 mL, 3.30 mmol). The solution was stirred at room temperature and the reaction was monitored by GLC as follows: aliquot samples (ca. 0.1 mL) from the reaction mixture were hydrolyzed by aqueous KOH (45 wt%), the organic products (**K1** and 1-phenylethanol) were extracted in diethyl ether, and this organic phase was analyzed by quantitative GLC. The enantiomeric purity of 1-phenylethanol was assessed by GLC on a Chirasil-DEX CB column (110 °C, 0.7 bar). When the same reaction was carried out on a preparative scale, no aliquots were sampled and the final mixture was hydrolyzed after 3 days and extracted as described above, yielding spectroscopically pure 1-phenylethanol in more than 95% isolated yield.

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A convenient ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols and 2-aryl-2,2-dialkylacetaldehydes

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Abstract—A new and simple route for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols is described. In the presence of an acid catalyst phenols react with 2-aryl-2,2-dialkylacetaldehydes, prepared in good yield from 2-arylacetonitriles in 2 steps, to give 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans. Electron-donating substituents were required on the phenols in order to give 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans in good yield.

1. Introduction

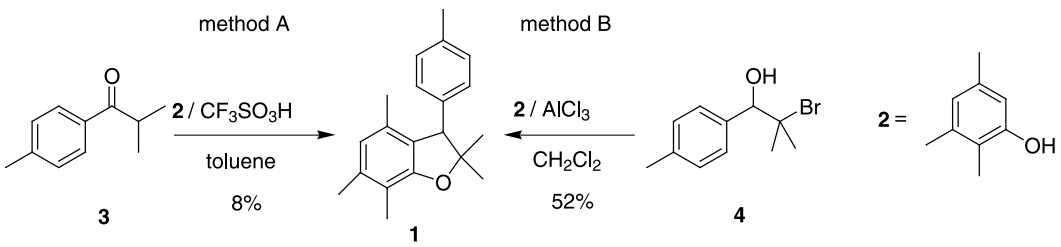
2,3-Dihydrobenzofuran derivatives are useful as key intermediates in the synthesis of a variety of biologically active compounds.[1] For example, 2,3-dihydrobenzofurans were developed for the treatment of traumatic and ischchemic central nervous system (CNS) injury,[1a] and 2,3-dihydro-5-benzofuranamines are said to be useful in treating arteriosclerosis, hepatopathy, and cerebrovascular disease.[1c]

In our laboratories, we have required a facile and efficient synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans to support one of our drug development programs. Although various methods for the preparation of 3-unsubstituted-2,2-dialkyl-2,3-dihydrobenzofurans have been reported,[2] there are only a few reports of the synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans,[1a,3] and none of them are suitable for large scale manufacture. In this paper we wish to describe a new simple, economical, and practical process for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans.

2. Results and discussion

2.1. Preliminary studies for the preparation of 2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1)

Two synthetic methods[2c,e] were investigated for the preparation of dihydrobenzofuran **1**, as shown in Scheme 1. In method A, the propiophenone derivative **3**[4] was reacted with 2,3,5-trimethylphenol (**2**) in the presence of CF_3SO_3H to afford the desired dihydrobenzofuran in low yield. Method B, involving the reaction of phenol **2** with the alcohol derivative **4**, prepared from 2-bromo-4′-methylisobutyrophenone (**5**)[5] (see Section 4), in the presence of $AlCl_3$ gave the desired dihydrobenzofuran **1** in moderate yield.



Scheme 1.

Keywords: 2,3-Dihydrobenzofurans; Phenols; Aldehydes; Wagner–Meerwein rearrangement.
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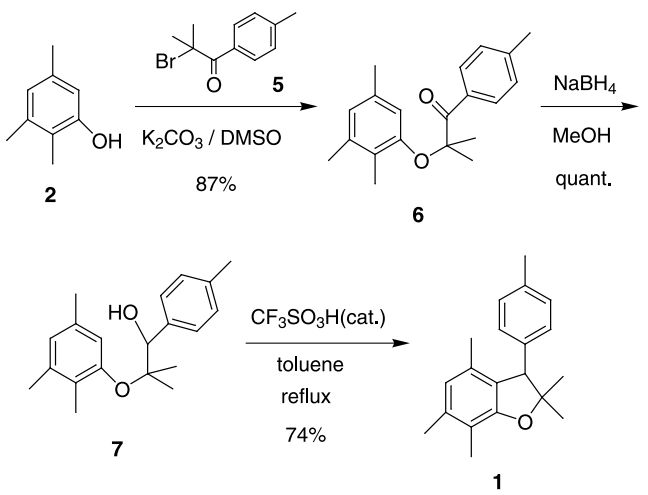
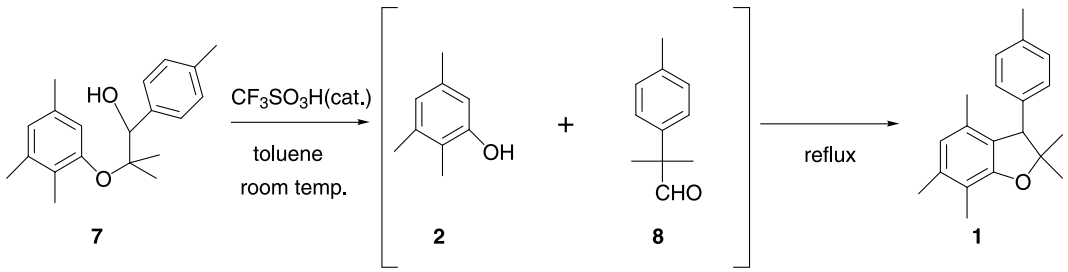
However, as neither of these processes were sufficiently high yielding for our purpose, we decided to investigate a new approach, using an intramolecular cyclization reaction of alcohol derivative **7**, to synthesize dihydrobenzofuran **1** (Scheme 2). Intermediate **7** was prepared from phenol **2** by alkylation with **5**[5] in the presence of potassium carbonate to give 2-methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-one (**6**) in 87% yield. Subsequent reduction of **6** with $NaBH_4$ in MeOH gave 2-methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-ol (**7**) in quantitative yield. The cyclization reaction of **7** was then performed using 0.1 equiv. of CF_3SO_3H in refluxing toluene for 1 h to afford the dihydrobenzofuran **1** in 74% yield.



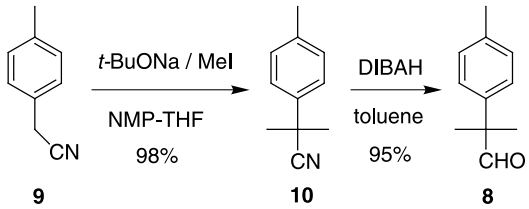
Scheme 2.



Scheme 3.

When the cyclization reaction was carried out at room temperature, **1** was only obtained in low yield and two unknown products were formed. When the reaction mixture was refluxed for a further hour the dihydrobenzofuran **1** was obtained. Isolated the two unknown products by silica gel column chromatography suggested their structures to be phenol **2** and 2-methyl-2-(4-methylphenyl)propanal (**8**), from ^{1}H NMR and Mass spectrometry {^{1}H NMR ($CDCl_3$); C*H*O for 9.47 ppm, MS (EI); *m*/*e*=162 (M^+)} (Scheme 3).

The aldehyde structure was confirmed by comparison with the spectral data of an authentic sample, which was prepared by Schaffner's method.[6] Aldehyde **8** was obtained by oxidation of the corresponding alcohol prepared in two steps, and we also synthesized aldehyde **8** by an alternative synthetic method, as shown in Scheme 4. Treatment of 4-methylbenzylcyanide (**9**) with MeI[7] (4 equiv.) in the presence of *t*-BuONa (4 equiv.) gave 2-methyl-2-(4-methylphenyl)propionitrile (**10**) in 98% yield, and subsequent reduction[8] of **10** with DIBAH (1.3 equiv.) gave aldehyde **8** in 95% yield.

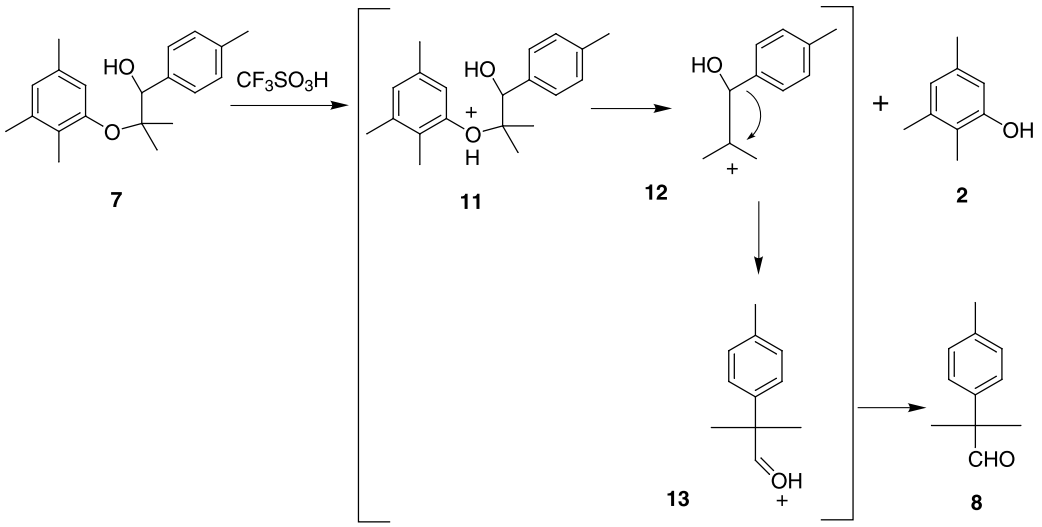


Scheme 4.

We considered that the reaction mechanism for the formation of phenol **2** and aldehyde **8** from **7** is similar to the Wagner–Meerwein rearrangement[9] shown in Scheme 5. Treatment of **7** with CF_3SO_3H in toluene at room temperature initially cleaves the ether bond and leads to the formation of **2** and cation **12**, which then undergoes Wagner–Meerwein type rearrangement to form aldehyde **8**.

2.2. Exploration of a new convenient ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans from phenols and 2-aryl-2,2-dialkylacetaldehydes

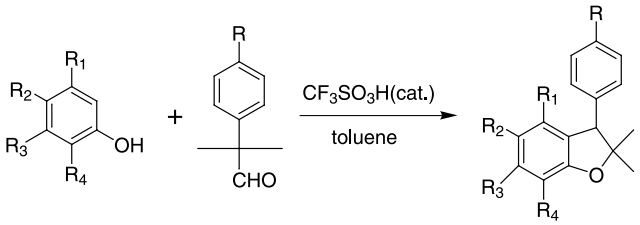
The identification of phenol **2** and aldehyde **8** as intermediates in the cyclization reaction prompted us to explore a new ring formation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans. According to this result, it should be possible to obtain dihydrobenzofuran **1** by reaction of phenol **2** with aldehyde **8** in the presence of an acid catalyst. When phenol **2** was reacted with aldehyde **8** in the presence of a catalytic amount of CF_3SO_3H in refluxing toluene, dihydrobenzofuran **1** was obtained in 75% yield. Various acids were evaluated in this reaction (eg. $AlCl_3$, BF_3/Et_2O, $TiCl_4$, $SnCl_4$, $ZnCl_2$, H_2SO_4, $MeSO_3H$, PPA, *p*-TsOH, CF_3SO_3H), but CF_3SO_3H was found to be superior to the others in terms of yield. The reaction was carried out with other phenols and aldehydes to investigate the scope of this new method for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans, and phenols **2**, **14a–c** and aldehydes **8**, **15a–c** were examined (Scheme 6, Table 1). Reaction of 2,3,5-trimethylphenol (**2**) and *p*-cresol (**14a**) with aldehydes **8**, **15a–c** afforded dihydrobenzofurans **1**, **16–22** in good yield (entry 1–8). However, reaction of phenol (**14b**) and



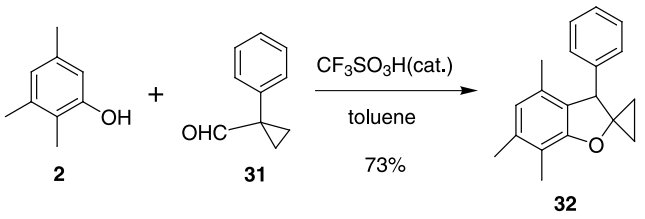
Scheme 5.

p-chlorophenol (**14c**) with aldehydes **8**, **15a–c** gave dihydrobenzofurans **23–30** in low yield (entry 9–16).

These results indicate that although electron-donating substituents are required on the phenols for good conversion, the substituents on the aldehydes have little effect on the reaction, and therefore a variety of 2-aryl-2,2-dialkylacetaldehydes may be used. For example, reaction of phenol **2** with 1-phenylcyclopropanecarbaldehyde (**31**) afforded 4,6,7-trimethyl-3-phenyl-3*H*-spiro-[1-benzofuran-2,1′-cyclopropane] (**32**) in good yield (Scheme 7).



Scheme 6.



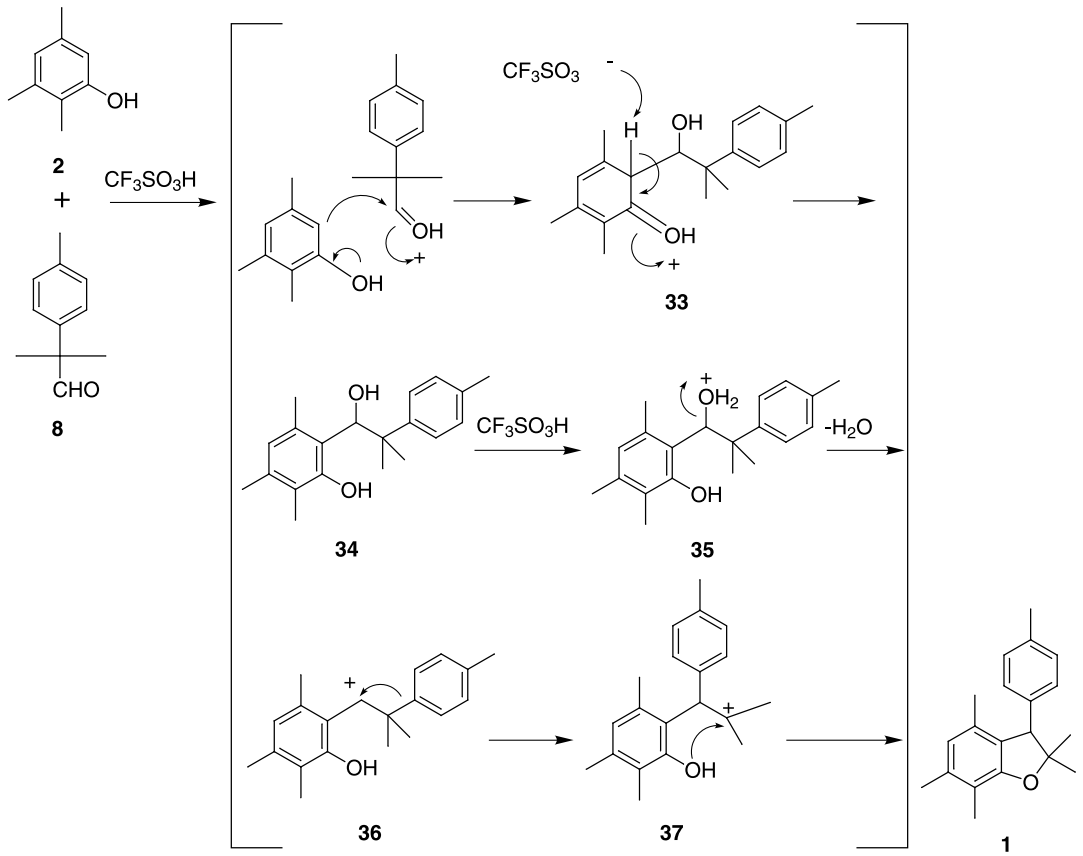
Scheme 7.

The proposed reaction mechanism for this process is shown in Scheme 8. In the presence of CF_3SO_3H, phenol **2** and aldehyde **8** initially form **34**, which after protonation followed by dehydration, leads to cation **36**, which then

Table 1. Reaction[a] of phenols and 2-aryl-2,2-dialkylacetaldehydes

Entry	Phenols					Aldehydes		Temperature	Time	Products	
		R1	R2	R3	R4		(R)	(°C)	(h)		(yield %)
1	**2**	CH_3	H	CH_3	CH_3	**8**	CH_3	110	1	**1**	75[b]
2	**2**	CH_3	H	CH_3	CH_3	**15a**	OCH_3	110	1	**16**	77[b]
3	**2**	CH_3	H	CH_3	CH_3	**15b**	H	110	1	**17**	90[b]
4	**2**	CH_3	H	CH_3	CH_3	**15c**	Cl	110	1	**18**	85[b]
5	**14a**	H	CH_3	H	H	**8**	CH_3	110	2	**19**	52[b]
6	**14a**	H	CH_3	H	H	**15a**	OCH_3	25	17	**20**	60[b]
7	**14a**	H	CH_3	H	H	**15b**	H	25	15	**21**	62[b]
8	**14a**	H	CH_3	H	H	**15c**	Cl	25	17	**22**	65[b]
9	**14b**	H	H	H	H	**8**	CH_3	110	1	**23**	11[c]
10	**14b**	H	H	H	H	**15a**	OCH_3	25	15	**24**	6[c]
11	**14b**	H	H	H	H	**15b**	H	25	15	**25**	8[c]
12	**14b**	H	H	H	H	**15c**	Cl	25	17	**26**	32[c]
13	**14c**	H	Cl	H	H	**8**	CH_3	110	2	**27**	8[c]
14	**14c**	H	Cl	H	H	**15a**	OCH_3	110	2	**28**	11[c]
15	**14c**	H	Cl	H	H	**15b**	H	25	15	**29**	7[c]
16	**14c**	H	Cl	H	H	**15c**	Cl	25	17	**30**	13[c]

[a] Reaction conditions: 1.0 equiv. of phenols, 1.0 equiv. of aldehydes, 0.1 equiv. (entry 1–5) or 0.5 equiv. (entry 6–16) of CF_3SO_3H, toluene was used as solvent.
[b] Isolated yield.
[c] Not isolated yield but HPLC analyses. The structure of **23–30** was just assigned by LC-Ms.



Scheme 8.

undergoes Wagner–Meerwein type rearrangement and cyclization to form the desired product **1**.

3. Conclusions

We have developed a new and convenient ring formation reaction for the synthesis of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans using phenols and 2-aryl-2,2-dialkylacetaldehydes, and its reaction mechanism was elucidated. The ease and utility of this method indicates that it may be applicable to the industrial manufacture of 3-aryl-2,2-dialkyl-2,3-dihydrobenzohurans, and investigations are in progress.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. NMR spectra were run at 300 MHz on a Bruker DPX-300 spectrometer. Chemical shifts are reported as δ values using tetramethylsilane as an internal standard and the coupling constants (J) are given in Hz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. All column chromatography was performed on Merck Silica gel 60 (0.063–0.200 mm). The HPLC data in Table 1 was obtained under the following conditions: detector, ultraviolet absorption photometer (wavelength 230 nm); column, YMC-Pack ODS-A302 (4.6 mm i.d.×150 mm); mobile phase, 0.02 M KH_2PO_4 aqueous solution/MeCN (20/80); flow rate, 1.0 ml/min; column temperature, 25 °C. All compounds were judged to be of greater than 95% purity based upon ^{1}H NMR and HPLC analysis. Elemental analysis and mass spectra were carried out by Takeda Analytical Research Laboratories, Ltd.

4.1.1. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 1, Method A). A solution of phenol **2** (1.36 g, 10 mmol), 4′,2-dimethylpropiophenone (**3**)[4] (1.62 g, 10 mmol) and CF_3SO_3H (3.73 g, 25 mmol) in toluene (13.6 ml) was refluxed for 3 h. The reaction mixture was cooled to room temperature, and aqueous NaOH (6 M, 10 ml) was added. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **1** (0.21 g, 8%) as a white crystalline powder. Mp 119–120 °C. IR (cm^{-1}, KBr) 1457, 1511, 1589, 3436; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.49 (3H, s), 1.83 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 2.30 (3H, s), 4.09 (1H, s), 6.48 (1H, s), 6.5–7.1 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.1, 19.3, 20.9, 24.8, 29.8, 57.5, 88.5, 115.4, 123.0, 126.2, 128.4, 128.8, 132.0, 136.0, 136.7, 137.3, 157.3. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.67, H, 8.74.

4.1.2. 2-Bromo-2-methyl-1-(4-methylphenyl)propan-1-ol (4). A solution of 2-bromo-4′-methylisobutyrophenone (**5**)[5] (5.0 g, 20.7 mmol) in MeOH (50 ml) was cooled to 10 °C,

and $NaBH_4$ (0.24 g, 6.3 mmol) was added and stirred for 4 h. To the reaction mixture was added aqueous HCl (1 M, 8 ml) and the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate and water, the organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **4** (4.2 g, 84%) as a colorless oil. IR (cm^{-1}, neat) 1101, 1384, 3540; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (3H, s), 1.73 (3H, s), 2.33 (3H, s), 2.77 (1H, bs), 4.77 (1H, s), 7.14 (2H, d, J=8.0 Hz), 7.27 (2H, d, J=8.1 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.0, 27.3, 31.6, 74.8, 81.9, 127.7, 128.4, 134.9, 137.8; MS (EI): m/z 242 (M^+); HRMS (EI) calcd for $C_{11}H_{15}BrO$ (M^+) 242.0306. Found: 242.0281.

4.1.3. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 1, Method B). A solution of **2** (0.28 g, 2 mmol) and **4** (0.5 g, 2 mmol) in dichloromethane (5 ml) was cooled to 5 °C, and $AlCl_3$ (0.27 g, 2 mmol) was added. The mixture was stirred at room temperature for 20 h and diluted with toluene and aqueous HCl (6 M). The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **1** (0.3 g, 52%) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 118–119 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.84, H, 8.65.

4.1.4. 2-Methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-one (6). A suspension of phenol **2** (13.6 g, 100 mmol) and K_2CO_3 (27.6 g, 200 mmol) in DMSO (68 ml) was warmed to 35 °C, and **5**[5] (42.2 g in 68 ml of DMSO, 175 mmol) was added and stirred for 24 h. MeOH (95 ml) and water (95 ml) were added to the reaction mixture, which was stirred at 40 °C for 1 h. The precipitate was filtered, washed with MeOH/H_2O (1:1) twice to give the crude product. The crude cake was dissolved in refluxing MeOH (204 ml), and then water (68 ml) was added and it was cooled to 40 °C. After stirring at 40 °C for 1 h, the precipitate was collected by filtration, washed with MeOH/H_2O (3:1) and water, and dried in vacuo at 50 °C to afford **6** (25.8 g, 87.0% based on **2**) as a white crystalline powder. Mp 115–117 °C. IR (cm^{-1}, KBr) 1141, 1604, 1664, 2985; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (6H, s), 2.05 (3H, s), 2.18 (3H, s), 2.20 (3H, s), 2.34 (3H, s), 6.18 (1H, s), 6.54 (1H, s), 7.18 (2H, d, J=8.3 Hz), 8.23 (2H, d, J=8.3 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 12.0, 20.0, 20.9, 21.5, 25.9, 84.7, 115.3, 124.2, 124.4, 129.0, 130.1, 132.1, 134.9, 137.7, 143.4, 153.2, 202.4. Anal. calcd for $C_{20}H_{24}O_2$ (296.40): C, 81.04, H, 8.16. Found: C, 80.74, H, 7.90.

4.1.5. 2-Methyl-1-(4-methylphenyl)-2-(2,3,5-trimethylphenoxy)propan-1-ol (7). To a suspension of **6** (25.2 g, 85 mmol) in MeOH (252 ml) was added $NaBH_4$ (2.6 g, 69 mmol), and the mixture was stirred at 35 °C for 3 h under nitrogen gas purge. The reaction mixture was cooled to 15 °C and adjusted to pH 7 at 20 °C with aqueous HCl (1 M), and the whole was concentrated in vacuo. The residue was diluted with toluene and water, the organic layer was separated, washed with water, dried over sodium sulfate and concentrated in vacuo to afford **7** (25.4 g) quantitatively as a colorless oil. The product was subsequently used without further purification. IR (cm^{-1}, neat) 1128, 1298, 2981, 3558; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, s), 1.22 (3H, s), 2.13 (3H, s), 2.22 (3H, s), 2.25 (3H, s), 2.34 (3H, s), 3.38 (1H, bs), 4.87 (1H, s), 6.72 (1H, s), 6.74 (1H, s), 7.13 (2H, d, J=8.3 Hz), 7.34 (2H, d, J=8.3 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.2, 20.3, 20.7, 21.0, 21.1, 22.8, 80.5, 84.2, 121.6, 126.0, 127.8, 128.4, 134.9, 136.7, 137.2, 137.9, 152.7. Anal. calcd for $C_{20}H_{26}O_2$ (298.42): C, 80.50, H, 8.78. Found: C, 80.71, H, 8.65; MS (CI): m/z 299 $(M+H)^+$.

4.1.6. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 2). A solution of **7** (25.4 g, 85 mmol) and CF_3SO_3H (1.28 g, 8.5 mmol) in toluene (127 ml) was refluxed for 1 h. The reaction mixture was cooled to 50 °C before aqueous NaOH (1 M, 76 ml) was added and then the mixture was stirred at 35 °C for 30 min. The organic layer was separated and washed with water and concentrated in vacuo. The residue was diluted with 2-propanol (76 ml) and heated to 60 °C, and water (76 ml) was added dropwise at the same temperature. The mixture was cooled to room temperature and stirred for 1 h. The precipitate was filtered, washed with 2-propanol/H_2O (1:1) twice and dried in vacuo at 50 °C to afford **1** (17.6 g, 74.0% based on **6**) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 119–120 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.54, H, 8.79.

4.1.7. Reaction of (7) with CF_3SO_3H at room temperature. A solution of **7** (1.0 g) and CF_3SO_3H (0.05 g) in toluene (6 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with aqueous $NaHCO_3$ and separated. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford phenol **2** (305 mg) as a white crystalline powder, aldehyde **8** (353 mg) as a colorless oil, and benzofuran **1** (169 mg) as a white crystalline powder.

4.2. General procedure for the preparation of 2-aryl-2,2-dialkylacetaldehydes

4.2.1. 2-Methyl-2-(4-methylphenyl)propanal (8). A solution of *t*-BuONa (19.9 g, 207 mmol) in 1-methyl-2-pyrrolidone/THF (1:1, 68 ml) was cooled to 5 °C, and a solution of 4-methylbenzylcyanide (**9**) (6.8 g, 52 mmol) and methyl iodide (12.9 ml, 207 mmol) was added maintaining the reaction temperature below 10 °C. After the mixture was stirred for 1 h, diluted with aqueous HCl (3 M) and toluene, the organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried over sodium sulfate and concentrated in vacuo to afford 2-methyl-2-(4-methylphenyl)propionitrile (**10**) (8.1 g, 98%) as a red-brown oil, which was used in the next reaction without further purification. IR (cm^{-1}, neat) 815, 1513, 2235, 2981; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (6H, s), 2.35 (3H, s), 7.17–7.22 (2H, m), 7.33–7.37 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 29.0, 36.6, 124.5, 124.8, 129.4, 137.4, 138.4; MS (EI): m/z 159 (M^+). A solution of **10** (8.1 g, 51 mmol) in toluene (81 ml) was cooled to −50 °C, and DIBAH (1.5 M

in toluene, 42 ml, 63 mmol) was added dropwise maintaining the reaction temperature below −40 °C and stirred for 1 h. Aqueous HCl (6 M) was added to the reaction mixture, which was stirred at room temperature for 30 min. The organic layer was separated, washed with aqueous HCl (2 M), aqueous $NaHCO_3$ and brine successively, dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/19) to afford **8** (7.8 g, 93% based on **9**) as a colorless oil. IR (cm^{-1}, neat) 1514, 1728, 2973; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (6H, s), 2.33 (3H, s), 7.14–7.24 (4H, m), 9.47 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.8, 22.3, 49.9, 126.5, 129.4, 136.8, 138.0, 202.1; MS (EI): *m/z* 162 (M^+); HRMS (EI) calcd for $C_{11}H_{14}O$ (M^+) 162.1045. Found: 162.1034.

The following compounds were obtained according to the general procedure.

4.2.2. 2-Methyl-2-(4-methoxyphenyl)propanal (15a). Yield 72%, colorless oil. IR (cm^{-1}, neat) 1254, 1514, 1724, 2971; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (6H, s), 3.80 (3H, s), 6.88–6.93 (2H, m), 7.17–7.22 (2H, m), 9.44 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.4, 49.6, 55.1, 114.1, 127.7, 132.9, 158.6, 202.0. Anal. calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13, H, 7.92. Found: C, 73.77, H, 7.99; MS (EI): *m/z* 178 (M^+).

4.2.3. 2-Methyl-2-phenylpropanal (15b). Yield 70%, colorless oil. IR (cm^{-1}, neat) 1448, 1496, 1722, 2981; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (6H, s), 7.25–7.30 (3H, m), 7.35–7.40 (2H, m), 9.49 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.3, 50.3, 125.2, 126.5, 127.1, 128.4, 128.7, 141.1, 202.0; MS (EI): *m/z* 148 (M^+); HRMS (EI) calcd for $C_{10}H_{12}O$ (M^+) 148.0888. Found: 148.0878.

4.2.4. 2-Methyl-2-(4-chlorophenyl)propanal (15c). Yield 87%, colorless oil. IR (cm^{-1}, neat) 1105, 1495, 1724, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (6H, s), 7.18–7.23 (2H, m), 7.32–7.36 (2H, m), 9.47 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 22.4, 49.9, 128.0, 128.8, 133.1, 139.6, 201.4; MS (EI): *m/z* 182 (M^+); HRMS (EI) calcd for $C_{10}H_{11}ClO$ (M^+) 182.0499. Found: 182.0481.

4.2.5. 1-Phenylcyclopropanecarbaldehyde (31). Yield 90%, colorless oil. IR (cm^{-1}, neat) 1446, 1498, 1711, 2823; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.41 (2H, m), 1.54–1.58 (2H, m), 7.29–7.36 (5H, m), 9.28 (1H, s). ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.0, 37.3, 127.5, 128.5, 129.9, 137.4, 200.8; MS (EI): *m/z* 146 (M^+); HRMS (EI) calcd for $C_{10}H_{10}O$ (M^+) 146.0732. Found: 146.0726.

4.3. General procedure for the preparation of 3-aryl-2,2-dialkyl-2,3-dihydrobenzofurans using phenols and 2-aryl-2,2-dialkylacetaldehydes

4.3.1. 2,2,4,6,7-Pentamethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (1). (Scheme 6). A suspension of phenol **2** (0.84 g, 6.2 mmol), aldehyde **8** (1.0 g, 6.2 mmol) and CF_3SO_3H (0.09 g, 0.62 mmol) in toluene (6.2 ml) was refluxed for 1 h. The reaction mixture was cooled to room temperature, and aqueous NaOH (1 M) was added before it was stirred for 30 min. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane=1/39) to afford **1** (1.3 g, 75%) as a white crystalline powder. The spectral data (IR, NMR) were identical with these of the sample that was prepared by using method A (Scheme 1). Mp 118–120 °C. Anal. calcd for $C_{20}H_{24}O$ (280.40): C, 85.67, H, 8.63. Found: C, 85.67, H, 8.72; MS (EI): *m/z* 280 (M^+).

The following compounds were obtained according to the general procedure.

4.3.2. 2,2,4,6,7-Pentamethyl-3-(4-methoxylphenyl)-2,3-dihydrobenzofuran (16). Yield 77%, white crystalline powder. Mp 105–106 °C. IR (cm^{-1}, KBr) 825, 1088, 1248, 1510, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.48 (3H, s), 1.84 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 3.76 (3H, s), 4.07 (1H, s), 6.48 (1H, s), 6.5–7.2 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.0, 19.3, 24.8, 29.7, 55.0, 57.1, 88.5, 113.4, 115.4, 123.0, 126.3, 129.5, 131.9, 132.5, 136.7, 157.2, 158.2. Anal. calcd for $C_{20}H_{24}O_2$ (296.40): C, 81.04, H, 8.16. Found: C, 80.81, H, 7.92; MS (EI): *m/z* 296 (M^+).

4.3.3. 2,2,4,6,7-Pentamethyl-3-phenyl-2,3-dihydrobenzofuran (17). Yield 90%, white crystalline powder. Mp 89–91 °C. IR (cm^{-1}, KBr) 698, 1090, 1456, 2979; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.50 (3H, s), 1.83 (3H, s), 2.14 (3H, s), 2.23 (3H, s), 4.12 (1H, s), 6.48 (1H, s), 6.5–7.3 (5H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.6, 18.0, 19.3, 24.8, 29.8, 57.9, 88.5, 115.5, 123.0, 126.1, 126.5, 128.1, 128.6, 132.0, 136.9, 140.4, 157.4. Anal. calcd for $C_{19}H_{22}O$ (266.38): C, 85.67, H, 8.32. Found: C, 85.52, H, 8.19; MS (EI): *m/z* 266 (M^+).

4.3.4. 2,2,4,6,7-Pentamethyl-3-(4-chlorophenyl)-2,3-dihydrobenzofuran (18). Yield 85%, white crystalline powder. Mp 110–112 °C. IR (cm^{-1}, KBr) 831, 1084, 1489, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.49 (3H, s), 1.83 (3H, s), 2.13 (3H, s), 2.23 (3H, s), 4.08 (1H, s), 6.48 (1H, s), 6.5–7.3 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.5, 18.0, 19.3, 24.8, 29.7, 57.2, 88.3, 115.6, 123.1, 125.7, 128.3, 129.9, 131.8, 132.3, 137.2, 139.0, 157.3. Anal. calcd for $C_{19}H_{21}OCl$ (300.82): C, 75.86, H, 7.04, Cl, 11.79. Found: C, 75.82, H, 6.99, Cl, 11.66; MS (EI): *m/z* 300 (M^+).

4.3.5. 2,2,5-Trimethyl-3-(4-methylphenyl)-2,3-dihydrobenzofuran (19). Yield 52%, colorless oil. IR (cm^{-1}, neat) 1251, 1491, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.56 (3H, s), 2.24 (3H, s), 2.33 (3H, s), 4.26 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.83 (1H, s), 6.95–6.99 (3H, m), 7.07–7.15 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 20.9, 24.0, 28.8, 58.1, 89.7, 109.2, 126.3, 128.7, 128.8, 128.9, 129.5, 130.3, 130.6, 136.5, 136.7, 156.8; MS (EI): *m/z* 252 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O$ (M^+) 252.1514. Found: 252.1511.

4.3.6. 2,2,5-Trimethyl-3-(4-methoxyphenyl)-2,3-dihydrobenzofuran (20). Yield 60%, pale yellow oil. IR (cm^{-1}, neat) 1250, 1491, 1512, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.55 (3H, s), 2.25 (3H, s), 3.79 (3H, s), 4.25 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.82–6.86 (3H, m), 6.95–7.02 (3H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.7, 55.1, 57.7, 89.8, 109.2, 113.6, 126.2, 128.7,

129.5, 129.8, 130.7, 131.8, 156.7, 158.6; MS (EI): *m/z* 268 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O_2$ (M^+) 268.1463. Found: 268.1443.

4.3.7. 2,2,5-Trimethyl-3-phenyl-2,3-dihydrobenzofuran (21). Yield 62%, pale yellow oil. IR (cm^{-1}, neat) 1252, 1491, 2974; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.57 (3H, s), 2.24 (3H, s), 4.29 (1H, s), 6.71 (1H, d, *J*=8.1 Hz), 6.84 (1H, s), 7.07–7.10 (2H, m), 7.24–7.30 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.8, 58.5, 89.7, 109.3, 126.3, 126.9, 128.2, 128.8, 128.9, 129.5, 130.3, 130.4, 139.8, 156.8; MS (EI): *m/z* 238 (M^+); HRMS (EI) calcd for $C_{17}H_{18}O$ (M^+) 238.1358. Found: 238.1353.

4.3.8. 2,2,5-Trimethyl-3-(4-chlorophenyl)-2,3-dihydrobenzofuran (22). Yield 65%, colorless oil. IR (cm^{-1}, neat) 1093, 1252, 1491, 2976; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.55 (3H, s), 2.24 (3H, s), 4.25 (1H, s), 6.72 (1H, d, *J*=8.1 Hz), 6.81 (1H, s), 6.96–7.03 (3H, m), 7.25–7.28 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.7, 24.0, 28.8, 57.9, 89.5, 109.4, 126.1, 128.4, 129.1, 129.6, 129.7, 129.9, 130.2, 132.8, 138.4, 156.8; MS (EI): *m/z* 272 (M^+); HRMS (EI) calcd for $C_{17}H_{17}ClO$ (M^+) 272.0968. Found: 272.0944.

4.3.9. 4,6,7-Trimethyl-3-phenyl-3*H*-spiro[1-benzofuran-2,1′-cyclopropane] (32). Yield 73%, pale yellow oil. IR (cm^{-1}, neat) 698, 1084, 1296, 1450, 2939; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01–2.05 (1H, m), 2.15 (3H, s), 2.18 (3H, s), 2.24 (3H, s), 2.46–2.53 (1H, m), 2.76–2.85 (2H, m), 3.92–3.95 (1H, m), 6.55 (1H, s), 7.17–7.42 (3H, m), 7.57–7.60 (2H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.7, 17.9, 19.2, 23.2, 35.1, 49.0, 90.9, 116.1, 123.0, 124.7, 127.3, 127.4, 128.1, 128.3, 128.9, 131.2, 137.1, 142.4, 158.7. Anal. calcd for $C_{19}H_{20}O$ (264.36): C, 86.32, H, 7.63. Found: C, 86.18, H, 7.86; MS (EI): *m/z* 264 (M^+).

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Novel and efficient Ni-mediated pinacol coupling of carbonyl compounds

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Abstract—It was firstly found that the Rieke Ni generated in situ was able to promote the pinacol coupling of various carbonyls efficiently. Based on this information, another catalytically effective, cheaper and more convenient $NiCl_2$(Cat.)/Mg/TMSCl system was designed and developed further successfully. The interesting single-electron transfer (SET) mechanisms for the coupling reactions were proposed. Additionally, the DL/*meso* diastereoselectivity and some additive effects were also explained in terms of the proposed mechanisms.

1. Introduction

One of the significant structure units in nature is the pinacols, which have wide occurrence in many biologically active molecules, such as Taxol,[1a] (−)-grayanotoxin III[1b] and so on. Recently, pinacols have been also used as the chiral ligands, auxiliaries[2] as well as versatile synthetic intermediates.[3] Generally, the pinacol units could be constructed through several approaches.[4] Among them, the particularly important and most widely used is the coupling of carbonyl compounds, which can be induced photochemically[5] and electrochemically,[6] or by use of various metals or their salts.[7] For the latter, the currently used metals included Sm, Ti and so on, however some limitations are still present. For example, some systems (e.g., $TiCl_4$/Li(Hg)[7r]) were only able to give low yield of corresponding pinacol products because of their strong reducing abilities; some metal coupling agents (e.g., Nb,[7l] Yb,[7n] Bi,[7p] U[7q]) were too expensive due to their rare deposits; and the experimental conditions in some systems (e.g., Na[7a]) were too rigorous to operate conveniently. In particular, the reported low-valent Ni coupling agents,[8] $Ni(COD)_2$ and $NiCl_2$/Li/Arene(Cat.), either was only limited to an intramolecular pinacol coupling or merely gave the pinacols as minor by-product. In general, these couplings mentioned above were only applicable to a relatively narrow scope of substrates.[9] Therefore, it is still of major importance to develop a mild, extensive and effective pinacol coupling sequence. In our efforts to this subject, we discovered two interesting pinacol coupling protocols for carbonyls, which were promoted by Ni generated in situ through the reaction of stoichiometric or catalytic amount of $NiCl_2$ with Li or Mg/TMSCl, respectively. Although increasing number of applications with organonickel agents have been reported in organic synthesis,[8c,10] to our knowledge, the two Ni-mediated coupling systems we developed have not been reported before. The major valuable features of both two coupling systems involved the broader application scope of substrates, the more convenient experiment operation and the low-cost of the Ni-mediated coupling reagents. Herein, we would like to report our results on the two systems.

2. Results and discussions

The Rieke Ni we examined was simply prepared by stirring a mixture of $NiCl_2$ (1.0 equiv.), Li (small cuts, 2.1 equiv.) and the naphthalene (0.3 equiv.) in THF under Ar at room temperature for 1 h.[11] The pinacol coupling was performed with various substrates and the Rieke Ni generated in situ following a general procedure (see Section 4.3). The results were listed in Table 1, from which we can see that the Rieke Ni-mediated pinacol coupling was effective, in good to excellent yields as well as with the preferential DL-diastereoselectivity, to a wide range of substrates including aromatic aldehydes (entries 1–7), aliphatic aldehydes (entries 10 and 11), aromatic ketones (entries 12–14) and aliphatic ketone (entry 15). It was notable that the Rieke Ni system exhibited the tolerance for some heteroatomic substituents (entries 3, 5 and 6) on substituted benzaldehydes.[11b] In addition the property and position of the substituents (entries 2–6) showed no significant effect on this coupling. However, when the substrate bears $-NO_2$ or −OH group (entries 8 and 9), no expected pinacol products,

Keywords: Pinacol; Coupling; Carbonyl compounds.
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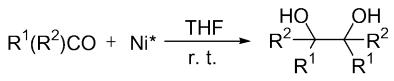
Table 1. Rieke Ni-mediated pinacol coupling reaction

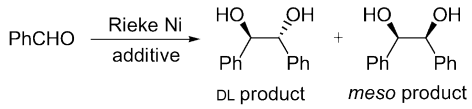


1 2

Entry	Substrate	R^1	R^2	Product[a]	Yield (%)	DL/*meso*[b]
1	**1a**	Ph	H	**2a**	82	67:33
2	**1b**	2-MeC_6H_4	H	**2b**	92	74:26
3	**1c**	2-ClC_6H_4	H	**2c**	76	59:41
4	**1d**	3-MeC_6H_4	H	**2d**	94	73:27
5	**1e**	3-$MeOC_6H_4$	H	**2e**	88	72:28
6	**1f**	4-$(Me_2N)C_6H_4$	H	**2f**	76	73:27
7	**1g**	1-Naphthyl	H	**2g**	72	74:26
8	**1h**	4-$NO_2C_6H_4$	H	[c]	72	
9	**1i**	3-MeO,4-HOC_6H_4	H	[c]	54	
10	**1j**	*n*-C_3H_7	H	**2j**	66	65:35
11	**1k**	Cyclohexyl	H	**2k**	62	75:25
12	**1l**	Ph	Me	**2l**	96	79:21
13	**1m**	Ph	*n*-Bu	**2m**	99	73:27
14	**1n**	Ph	Ph	**2n**	70	
15	**1o**	$PhCH_2CH_2$	Me	**2o**	64	79:21

[a] All analytical data of the diols are identical with those literature reported.
[b] Measured by ^1H NMR spectroscopy.
[c] Only the reduction product $R^1(R^2)CHOH$ was obtained.

Table 2. Additive effects on the Rieke Ni-mediated pinacol coupling reaction



Entry	Additive	Ratio[a]	Yield (%)	DL/*meso*[b]
1	TMEDA	2	40	73:27
2	HMPA	2	45	78:22
3	$ZnCl_2$	0.2	86	76:24
4	$AlCl_3$	0.2	80	74:26
5	$TiCl_4$	0.2	85	73:27
6	H_2O	0.1[c]	73[d]	
7	18-crown-6	2	86[d]	
8	1,3-Dinitrobenzene	2	92[d]	

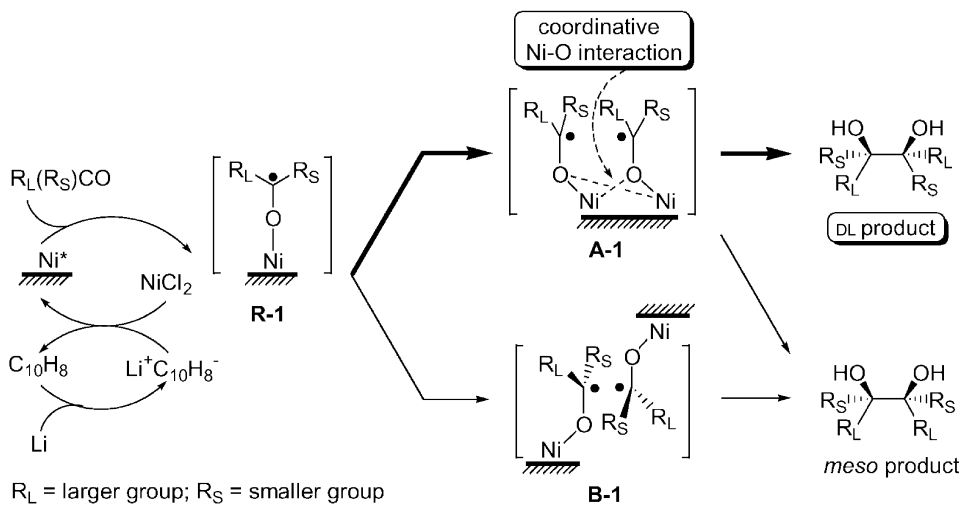
[a] The mole ratio between the additive and PhCHO **1a**.
[b] Measured by ^1H NMR spectroscopy.
[c] The volume ratio between H_2O and THF.
[d] The main products of entries 6–8 are $PhCH_2OH$.

but only simple reduction product $R^1(R^2)CHOH$ was formed.

To further examine the property of Rieke Ni-mediated pinacol coupling and also investigate the reaction mechanism, some additives, e.g. Lewis acid or base, or those with the –OH, $-NO_2$ or ether group were chosen to probe this reaction using PhCHO **1a** as a model substrate following a general procedure (see Section 4.4). From the results listed in Table 2, we found that when Lewis base (2.0 equiv.) was added in this reaction (entries 1 and 2), an improved distereoselectivity (DL/*meso*≈3/1) was observed in comparison with that of the corresponding entry 1 (DL/*meso*≈2/1) in Table 1 despite of their lower yields. Furthermore, when catalytic amount of Lewis acid was added (entries 3–5), both DL-selectivity (DL/*meso*≈3/1) and yield were improved. These results demonstrated that both Lewis acid and base were in favour of the DL-selectivity in this Rieke Ni-mediated coupling. However, if H_2O, 18-crown-6, or 1,3-dinitrobenzene was used as an additive (entries 6–8), only the simple reduction product $PhCH_2OH$ was given without the formation of desired pinacol product.

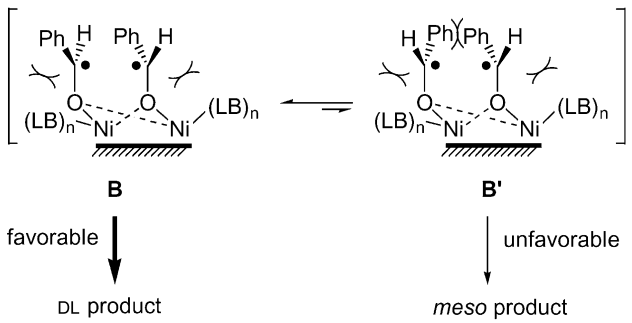
Based on the above experimental results together with corresponding literatures,[12] a plausible single-electron transfer (SET) mechanism was proposed as indicated in Scheme 1. The initial radical **R-1** was generated via a SET process between Rieke Ni and $R_L(R_S)CO$. Next two possible key coupling species **A-1** and **B-1** led to the formation of corresponding DL- and *meso*-products. Owing to the high oxyphilic ability and the high coordination number of the low-valent Ni, the formation of **A-1** with the coordinative Ni–O interaction was favoured than **B-1** without such interaction. Furthermore, two bulky R_L groups in **A-1** tended to display a favourable anticlinal conformation which resulted in the formation of DL-product, than the synperiplanar one which yielded the *meso*-product. Consequently, the Rieke Ni-mediated coupling could exhibit the more preferential DL-selectivity.

On the basis of the proposed reaction mechanism, some additives (entries 6–8 of Table 2) and substrates behavior (entries 8 and 9 of Table 1) in the coupling reaction could be

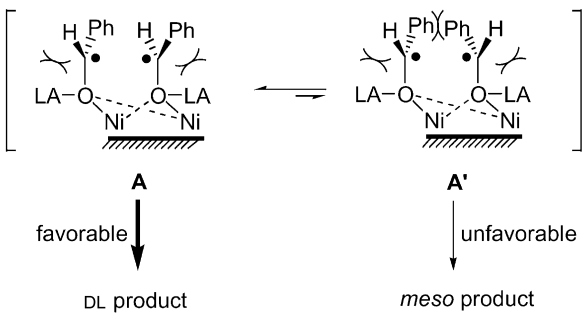


Scheme 1. Proposed mechanisms for Rieke Ni-promoted coupling pinacol reaction.

understood. Because the –OH, $-NO_2$ or ether group presented in the additives or substrates readily quench the radical **R-1**, the coupling process through **A-1** and **B-1** was inhibited to give the simple reduction product. Moreover, some properties of the coupling reaction in the presence of Lewis acid or base additives could be explained with the favourable **A-1**. Firstly, the improvement of the DL-selectivity caused by Lewis base (LB) additives (entries 1 and 2 of Table 2) could be understood from **B** and **B′** resulting from their coordination with the low-valent Ni (as shown in Scheme 2). Due to the steric encumbrance imposed by the coordinating LB additives on the nickel center, the rotation of C–O single bond in **B**, leading to the formation of more hindered **B′**, was restricted to some extent, so to improve DL-selectivity. Similarly, the additive effect of Lewis acid (LA) (entries 3–5 of Table 2) could also be explained in terms of the proposed Scheme 3. Because their coordination with the oxygen gave a more sterically crowded environment, the formation of **A** was favourable than that of **A′** and consequently improved DL-selectivity.



Scheme 2. The effect of Lewis base in Rieke Ni system.

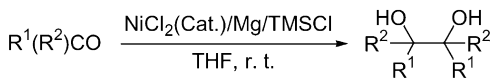


Scheme 3. The effect of Lewis acid in Rieke Ni system.

Encouraged by the above information that the Ni generated in situ can efficiently induce the pinacol coupling of carbonyl compounds via an interesting SET process, and also on considering that few reports on the Ni-mediated catalytic pinacol coupling were documented, we subsequently designed and developed another novel effective catalytical system, the $NiCl_2$(Cat.)/Mg/TMSCl, which has not been mentioned before to our knowledge.[13] Although a Mg/TMSCl system reported previously did not work at all for such kind of coupling,[7j] our experimental results below demonstrated the $NiCl_2$(Cat.)/Mg/TMSCl system we developed was effective to couple of aldehydes and ketone to the pinacol. The major values of this system involved the catalytic effectiveness, the use of cheap Mg metal and the convenient operation.

The preparation of $NiCl_2$(Cat.)/Mg/TMSCl system and the catalytic coupling experiment were performed in the following procedure: the catalytic amount of $NiCl_2$ (0.05 equiv.) was first mixed with Mg (2.0 equiv.) in THF to give a suspension, to which a solution of $R^1(R^2)CO$ (1.0 equiv.) and TMSCl (2.0 equiv.) was then added dropwise. The pinacol coupling took place readily (see Section 4.5). The results were tabulated in Table 3, which indicated that this catalytic system was effective, to a broad range of substrates including aromatic aldehydes (entries 1–9), aliphatic aldehyde (entry 10) and aromatic ketone (entry 11) to give pinacols in moderate to good yields. Further inspection of Table 3 showed some more important information. For example, in comparison with the corresponding Rieke Ni-mediated couplings in Table 1, the *meso*-selectivity for some substrates, such as **1e**, **1f**, **1j** and **1l**, was improved in different degree. In particularly, substrate **1f** (entry 8) gave exclusively the *meso*-product, which is of particular importance in organic synthesis.[14] It was also important that an intermolecular cross-pinacol coupling[15] was successfully conducted to produce the cross-coupling product **2al** in 52% yield (entry 12).

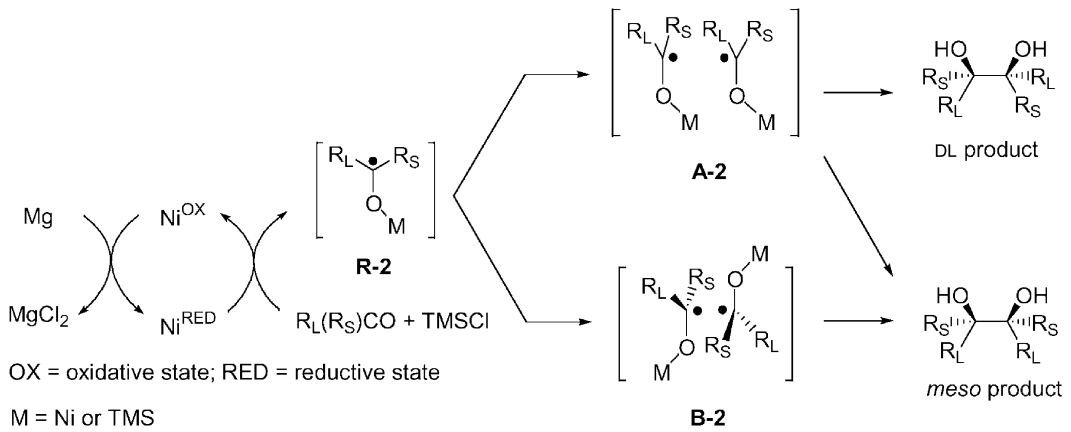
Table 3. $NiCl_2$(Cat.)/Mg/TMSCl-mediated pinacol coupling reaction



Entry	Substrate	R^1	R^2	Product[a]	Yield (%)	DL/*meso*[b]
1	**1a**	Ph	H	**2a**	70	78:22
2	**1p**	2-BrC_6H_4	H	**2p**	72	53:48
3	**1q**	2-$MeOC_6H_4$	H	**2q**	72	64:36
4	**1r**	3-ClC_6H_4	H	**2r**	77	57:43
5	**1e**	3-$MeOC_6H_4$	H	**2e**	79	52:48
6	**1s**	4-ClC_6H_4	H	**2s**	77	45:55
7	**1t**	4-$MeOC_6H_4$	H	**2t**	71	55:45
8	**1f**	4-$(Me)_2NC_6H_4$	H	**2f**	67	1:99
9	**1u**	2-Furyl	H	**2u**	66	69:31
10	**1j**	*n*-C_3H_7	H	**2j**	61	59:41
11	**1l**	Ph	Me	**2l**	51	50:50
12	**1a**+**1l**[c]			**2al**	52[d]	50:50

[a] The analytical data of the diols are all identical with those previously reported.
[b] Measured by ^{1}H NMR spectroscopy.
[c] Zn was co-reductant.
[d] A cross-pinacol coupling product **2al** (left R^2=right R^2=Ph, left R^1=Me, right R^1=H) was isolated, together with the minor diol **2a** (40%).

The Ni-catalyzed mechanism in this pinacol coupling was proposed in Scheme 4 on the basis of the above results and the related literatures.[13] The initial step would involve the reduction of oxidative state Ni (Ni^{OX}) by Mg to generate the active reductive state Ni (Ni^{RED}), which subsequently coordinated with the carbonyl of substrate $R_L(R_S)CO$ to form a radical **R-2** (M=Ni). Next two different coupling ways may be involved. If the Ni–O bond in the initially formed **R-2** (M=Ni) was cleaved by TMSCl before the pinacol coupling, the formation of **B-2** (M=TMS) would be favourable than that of **A-2** (M=TMS) because of the less hindrance in **B-2** (M=TMS) with the antiperiplanar conformation, and the subsequent coupling reaction would result in the formation of more *meso*-product. The other way



Scheme 4. Proposed mechanism for Ni-catalyzed pinacol coupling reaction.

may be that the initially formed **R-2** (M=Ni) directly underwent a pinacol coupling through **A-2** (M=Ni) and **B-2** (M=Ni), after which the Ni^{OX} was replaced by TMS for the next catalytic cycle This was just like the Rieke Ni system as shown in Scheme 1 resulted in the formation of more DL-product. In this catalytic system, we may determine the reaction type was the former, the latter or the combination of the two, according to the DL/*meso* selectivity which was highly dependent upon the substrate structure.

3. Conclusions

In conclusion, we have developed two novel and effective Ni-mediated pinacol coupling systems which were applicable to a broad substrate scope. Particularly we believe the optimized $NiCl_2$(Cat.)/Mg/TMSCl system would bring much application in practical organic synthesis. The further investigation is ongoing in our group.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon. THF was dried and freshly distilled over sodium/benzophenone before use. All reagents were commercial and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) on gel F_{254} plates. The silica gel (200–300 meshes) for column chromatography was from the Qingdao Marine Chemical Factory in China, and the distillation range of petroleum is 60–90 °C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on the Avance DRX-200 instruments, and spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard. High-resolution mass spectral analysis (HRMS) data were measured on the Bruker ApexII by means of ESI technique.

Spectroscopic data for these pinacol coupling adducts has been reported previously.[16]

4.2. General procedure for the preparation of Rieke Ni

In a typical process, Li (small cuts, 2.1 equiv.), naphthalene (0.3 equiv.) and anhydrous $NiCl_2$ (1.0 equiv.) were stirred in freshly distilled THF for 1–3 h at room temperature under argon atmosphere, then a black slurry was obtained and ready for use.

4.3. General procedure A: the Rieke Ni-mediated pinacol coupling

To a slurry of Rieke Ni (1.0 equiv.) prepared in situ was added the substrate **1** (0.5 equiv.) at room temperature under Ar. The reaction mixture was stirred and monitored by TLC until the substrate was consumed completely. Then the reaction was quenched with an aqueous solution (3 M) of $Na_2S_2O_3$ followed by the addition of CH_2Cl_2. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with the brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and column chromatography of the crude pinacol product on silica gel (petroleum/ethyl acetate 4/1→2/1) afforded the desired diol **2**.

4.4. General procedure B: the Rieke Ni-mediated pinacol coupling with the additives

To a stirred suspension of Rieke Ni (1.0 equiv.) and the additive (0.1 or 1.0 equiv.) in freshly distilled THF was added PhCHO (0.5 equiv.) at room temperature under Ar. The reaction mixture was further stirred efficiently. When TLC analysis indicated the PhCHO was consumed completely, the reaction was quenched. The following workup was similar to that of the general procedure A.

4.5. General procedure C: the $NiCl_2$(Cat.)/Mg/TMSCl-mediated pinacol coupling

A mixture of $NiCl_2$ (0.05 equiv.) and activated Mg powder (2.0 equiv.) in freshly distilled THF was stirred for 10 min at room temperature under Ar. Then a solution of substrate **1** (1.0 equiv.) and TMSCl (2.0 equiv.) was added dropwise to the above suspension, and the reaction mixture was stirred efficiently. After the substrate consumed by the check of TLC, Et_2O and an aqueous solution (1.5 M) of HCl were added to the resulting mixture. The organic layer was separated followed by the extraction of the aqueous layer with Et_2O. The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, and dried over

anhydrous Na_2SO_4. After removing the solvent the residue was purified by the column chromatography on silica gel (petroleum/ethyl acetate 4/1→2/1) to furnish the expected diol **2**.

Acknowledgements

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2,6,9-Trioxabicyclo[3.3.1]nona-3,7-dien-4-oyl and tetraoxaadamantan-9-oyl functionalized aromatic di- and triamines: synthesis, stereochemistry and complexation

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Abstract—Primary amino groups of di- or triaminoaryl compounds add a remarkably stable dioxinyl-α-oxoketene affording bis- or tris-[trioxabicyclo[3.3.1]nona-3,7-dienyl (bridged *bisdioxine*)] systems which can be converted into the corresponding bis- or tris-[2,4,6,8-tetraoxadamantanes] by acidic hydrolysis. Stereochemical peculiarities as well as preliminary host–guest abilities of these molecules are investigated with aid of NMR-spectroscopy, an X-ray analysis and ESI-mass spectrometry.

1. Introduction

Dimerization of dipivaloylketene, generated by flash vacuum pyrolysis of the corresponding furan-2,3-dione as suitable precursor,[1] affords the remarkably stable α-oxoketene **1** in quantitative yield. This oxoketene **1** smoothly adds primary aromatic amines bearing no or electron donating substituents under mild reaction conditions to furnish functionalized trioxabicyclo[3.3.1]nona-3,7-dienes **2** (bridged *bisdioxines*) in a one-step procedure.[2] From reactants having two amino- functionalities the corresponding bis- bridged bisdioxine derivatives (e.g. **3**) were obtained, which as a stereochemical peculiarity due to the concave nature of the *bisdioxine* system should be able to adopt a 'claw'-like conformation (see Chart 1),[2a] in particular in the presence of suitable guest molecules. In addition, the bridged bisdioxine unit in general may easily be converted into the 2,4,6,8-tetraoxaadamantyl scaffold (e.g. **4**) by acidic hydrolysis.[3] Furthermore, due to the axial chirality of the bridged *bisdioxine*—as well as of the tetraoxaadamantane ring system[2,3]—all compounds having two or more of those structural units should exist as a mixture of diastereomers (*R*,*R*; *S*,*S*; *S*,*R*; *R*,*S*) which might be observable by means of their NMR spectra.

Keywords: α-Oxoketene; Aromatic di- and triamines; Bridged *bisdioxines*; Tetraoxadamantanes; Complexation studies; X-ray analysis.
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2. Results and discussion

In order to determine the scope and limitations of the preparation of such potential claw-molecules several aromatic diamines as well as triamines with different molecular skeletons have been subjected to reactions with the dimeric α-oxoketene **1**. Besides the synthetic task we also wanted to investigate whether those molecules would adopt their *syn*- (claw-like) conformation when suitable guest-molecules are offered for complexation, since the unsubstituted trioxabicyclo[3.3.1]nona-3,7-diene system itself was found to coordinate transition metals (i.e. Rh^{+}, Pt^{2+}, or Pd^{2+}).[4]

2.1. 1,3-Diaminobenzene

Both amino groups of 1,4-diaminobenzene add the oxoketene **1** thus affording the bis-product **5**,[2a] while obviously due to steric hindrance only one amino group reacts, when 1,2-diaminobenzene is employed, giving **6**.[2b] On the other hand, 1,3-diaminobenzene, after a reaction time of 5 d again adds two molecules of **1** to give compound **7** in 83% yield (Scheme 1), since, as can be easily seen from molecule models, the distance between the two bulky bridged *bisdioxines* is now far enough to minimize steric interactions.

Furthermore, following the usual procedure,[3] H^{+}- catalyzed hydrolysis converts the bisdioxine-product **7** into the

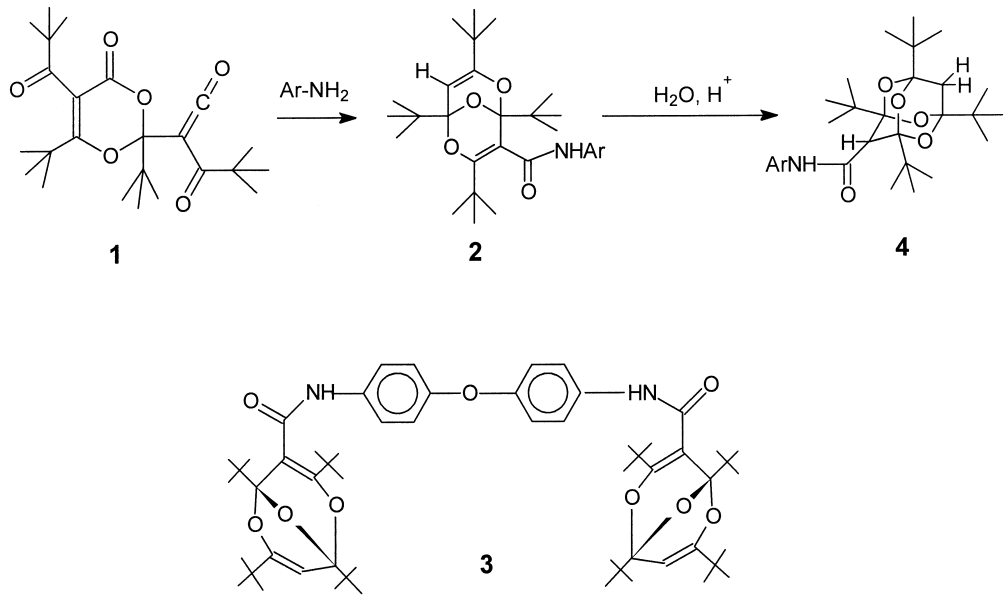
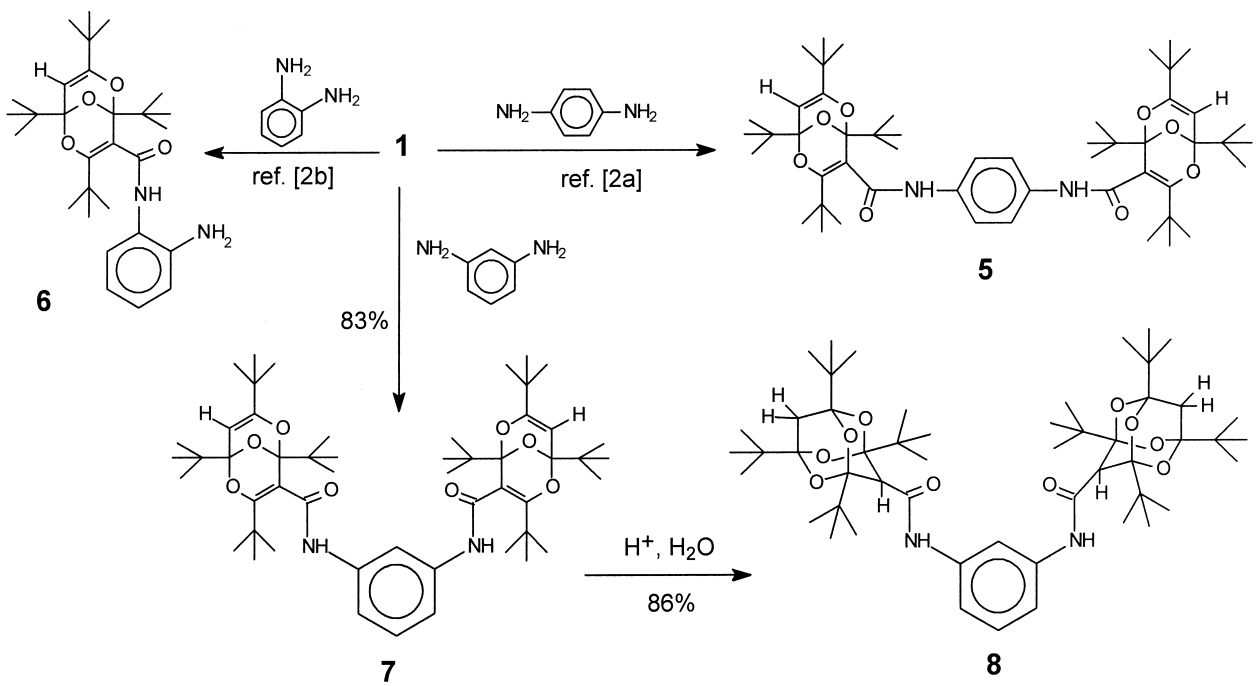


Chart 1.



Scheme 1. Reactions of diaminobenzenes with α-oxoketene **1**.

corresponding bis-tetraoxadamantanyl derivative **8**. The structural elucidation of **7** and **8** comes particularly from ^{1}H NMR data and their comparison with several analogues:[2,3] Signals at δ 4.83 (s, 2H, =CH) and at 1.05, 1.14, 1.20, 1.25 ppm (s, 18H each, rotamers, *t*-Bu) in **7**, as well as signals at δ 3.05 (s, 2CH), 1.78 (s, 2CH$_2$) and 0.98 (s, 18H, 2*t*-Bu), 1.05 (s, 36H, 4*t*-Bu), 1.28 ppm (s, 18H, 2*t*-Bu) for **8** are highly characteristic of the bridged *bisdioxine* and the tetraoxaadmantane skeletons.

There is no indication of any splitting of signals possibly coming from the presence of diastereomers. Obviously, the differences in the specific chemical shift values are too small to be detectable, at least at frequencies of 200, 360 or even 500 MHz.

2.2. Diamino-naphthalenes and -fluorenes

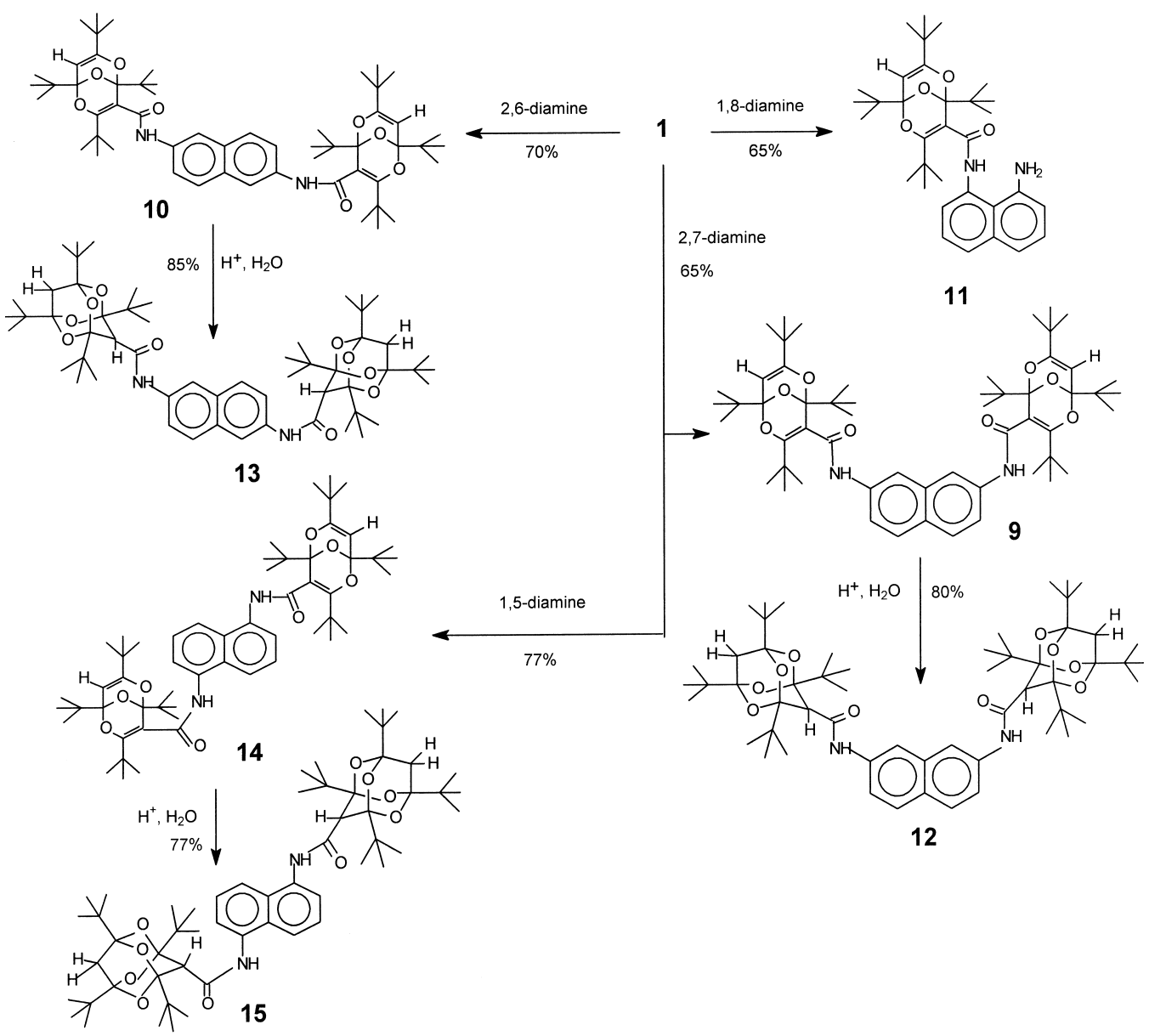
When 2,6- and 2,7-diaminonaphthalenes[5] were reacted with the dimeric oxoketene **1** the bis-bridged bisdioxine compounds **9** and **10** (2:1-ratio of reactants) were obtained as expected in yields of 65–70%. Since of all possible isomeric diaminonaphthalenes these two diamines exhibit the longest distance between the two amino functionalities, there is minimum or even no steric hindrance to be considered. On the other hand, 1,8-diaminonaphthalene

and **1** form the 1:1 adduct **11** only. Here, obviously, as in the case of 1,2-diaminobenzene (Scheme 1) the two amino groups are too close for them both to react with oxoketene **1** (Scheme 2).

The presence of the bridged *bisdioxine* unit in **9**–**11** as well as the 2,4,6,8-tetraoxaadamantane building block in **12** and **13** again is unambiguously established from characteristic NMR spectroscopic data (see discussion above).

Surprisingly, when 1,5-diaminonaphthalene was reacted with oxoketene **1**, the TLC-examination of the reaction product **14** revealed the presence of two compounds with slightly different R_f-values (0.31 and 0.28, eluent dichloromethane/*n*-hexane 3/2). With the aid of DCFC a separation was successfully achieved on a preparative scale, and the two compounds were obtained in a 2:1 (**14a** : **14b**) ratio. The results of the elemental analyses as well as the IR-spectra of **14a** and **14b** indicate the presence of isomers, most probably rotamers, since also the ^{1}H- as well as ^{13}C NMR spectra exhibited identical chemical shift values for the *t*-butyl groups (singlets at δ 1.06, 1.14, 1.24, 1.245 ppm), the olefinic protons (s, 4.92 ppm) and the carbons of the bisdioxine ring skeleton (C-1/C-5: 97.3/99.7; C-3/C-7: 162.2/162.3; C-4: 105.5; C-8: 92.0 ppm). There were only very minor differences ($\Delta\delta$=0.06–0.1 ppm) for three aromatic carbons in the ^{13}C NMR and a slightly different splitting pattern of the aromatic region in the ^{1}H NMR spectra to be observed.

In order to get some more insight into the three-dimensional structure of both isomers, NOE-experiments should be helpful: the signals at 1.06 (*t*-Bu at C-1) and 1.13 ppm (*t*-Bu at C-7) responded to the olefinic proton of the bisdioxine ring, while the signals at 1.24 (*t*-Bu at C-3) effected the CH-4 and CH-8, respectively, of the naphthalene ring. The correct assignment of all *t*-butyl groups was successfully achieved with the aid of HMBC-experiments.[6] The



Scheme 2. Reactions of diaminonaphthalenes with α-oxoketene **1**.

significant down-field shift of the *t*-butyl at C-5 (1.245 ppm) is obviously due to the anisotropic effect of nearby the amide carbonyl. The amazing result now was that all NOE's were found to be identical for both compounds. Therefore, one may conclude, that rotation around the CO–NH-bond is strongly restricted. As a consequence of that, the two isomers **14a** and **14b** could be regarded as *syn* or *anti* isomers with respect to the positions of the two bridged bisdioxines attached to the planar naphthalene ring (see Chart 2).

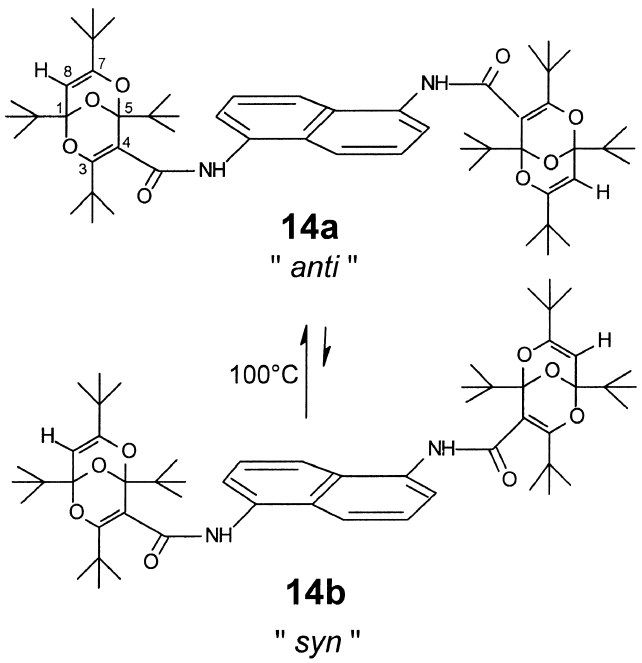


Chart 2.

Fortunately, an X-ray analysis provided unambiguous evidence that **14a** is the *anti*-isomer. In the crystal, **14a** is situated on a center of symmetry which relates the two halves of the molecule (Fig. 1). Furthermore, the structure makes evident the presence of a *R*,*S*-diastereomer. One of the four independent *tert*-butyl groups was found to be disordered over two orientations in each bisdioxine unit. The amide group is not coplanar with the naphthalene ring but is rotated out of the ring plane by approximately 50°. A packing analysis revealed a hydrogen bond between chloroform and the carbonyl oxygen of **14a** with a C···O distance of 3.0 Å.

It should further be noted, that **14b** could be quantitatively converted into the obviously more stable **14a** by heating in the solid state to 100 °C for 6 h.

2.3. Force field calculations

Since with compounds **9** and **10** no evidence was found for the formation of any kind of isomers like in case of **14**, it became highly desirable to obtain informations on the rotational barriers of the bridged *bisdioxine* moieties around the naphthalene axis in **9**, **10** and **14**.

Starting structures of isomeric diamides **9**, **10**, and **14** were generated by the Sybyl molecular modelling package[7] For the molecular mechanics calculations the MM3[8–15] as well as the Tripos[16] force fields were used. In the MM3 calculations, for the π-systems in **9**, **10** and **14** the variable electronegativity SCF (VESCF) correction[17] was applied. Gasteiger–Hückel charges[18] were used in combination with the Tripos force field. After initial minimization of these starting structures (see Fig. 2 for the lowest energy structure of **10**) a systematic conformational search was made for the two aryl –N torsional angels τ_1 and τ_2, defined by τ_1(**14**)=<(C1a–C1–N9–C10), τ_1(**9**, **10**)=<(C1–C2–N9–C10) and τ_2 (**14**)=<(C4a–C5–N9–C10), τ_2 (**10**)=<(C5–C6–N11–C12), τ_2 (**9**)=<(C8–C7–N11–C12) (for atom numbering, see Fig. 2).

2.3.1. Results. A typical conformational energy map (Tripos force field) is shown for **10** in Figure 3. As expected, these contours have an essentially symmetric appearance with potential energy minima at *s-cis* (τ_1, τ_2=±30°) and *s-trans* (τ_1, τ_2=±150°), respectively, orientations of either one of the two amide moieties in **10** and **9**. In contrast, for **14** only minima at *s-trans* (τ_1, τ_2=±150°) arrangements are calculated by both the Tripos and the MM3 force fields.

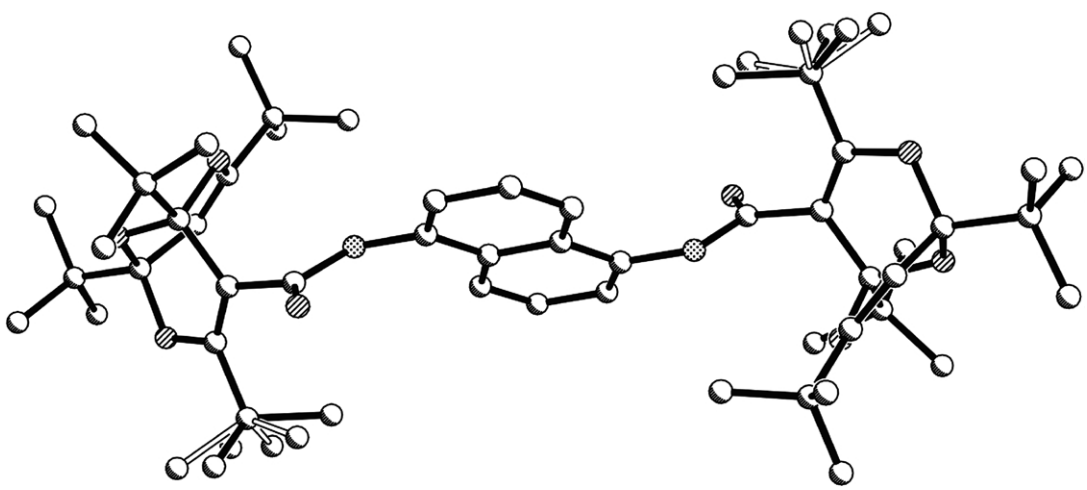


Figure 1. Perspective drawing of the molecule **14a**. Hatched circles represent oxygen atoms, dotted circles are nitrogen atoms (2*t*-butyl groups shown in two disordered orientations).

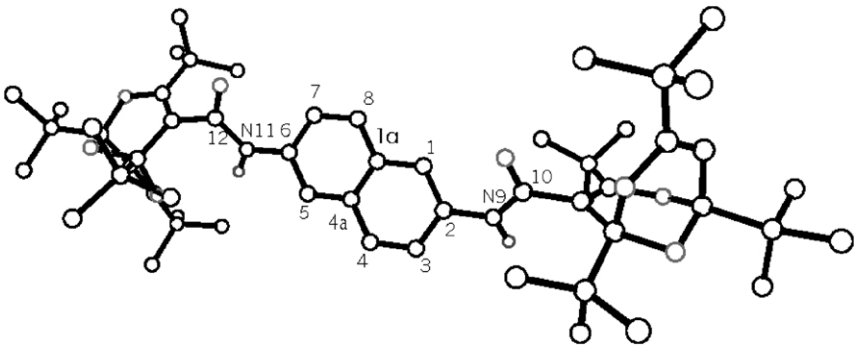


Figure 2. Calculated (Tripos force field) lowest energy structure of **10**.

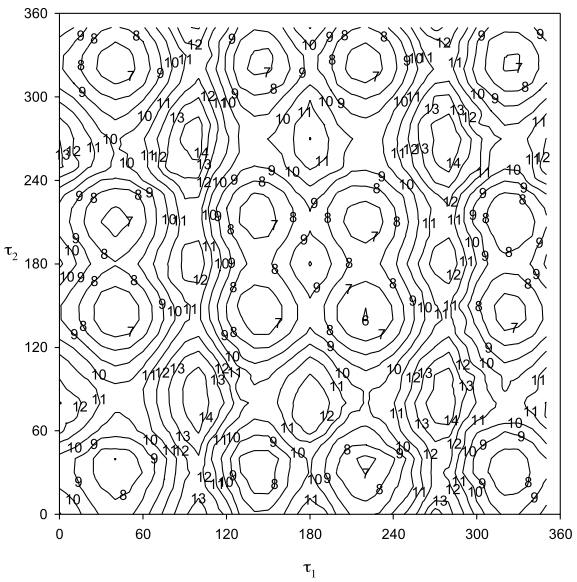


Figure 3. Contour plot (Tripos force field) for rotation of the amide groups (τ_1 and τ_2) in **10**.

Rotations around the two aryl –N bonds are more or less independent (Fig. 4) and, therefore, barriers can be estimated from potential energy curves obtained by varying τ_1 at approximately constant τ_2. For both **10** and **9** the barriers to planarity, i.e. those at 0 and 180° are considerably smaller than those at 90°. Not surprisingly, this result is especially pronounced in case of the MM3 force field with inclusion of π-conjugative effects via the VESCF procedure. For **14**, where no *cisoid* minima are calculated, the highest barrier is found at 0°. Most important, with both force fields the calculated barrier for **14** (10 kcal mol^{-1}) is twice that of either **10** and **9** (4–5 kcal mol^{-1}).

These results are in good agreement with the experimental findings and makes understandable that with compounds **9** and **10**, no rotamers could be detected. Similar results with chromatographic separation of *syn*–*anti*-rotamers of a large macrocyclic system were reported recently by Shimizu et al.[19] **14a**,**b** were also converted into the tetraoxa-adamanatane derivative **15**.

2,7-Diaminofluorene and the unsymmetrical 3,7-diamino-2-methoxyfluorene add the dimeric oxoketene **1** in the usual way to afford the bridged *bisdioxine* derivatives **16** and **17** in excellent yields (90–95%). Both again can be converted into the corresponding tetraoxaadamantanes **18** and **19**, respectively, by acidic hydrolysis. Obviously, the relatively small methoxy group in position 2 does not cause any steric hindrance on the addition of the ketene **1** to the amino group, affording **17** (Scheme 3).

As expected, due to the loss of symmetry caused by the methoxy-group, some signals in the ^{13}C NMR spectrum of **17** appear split compared to **16**, in particular those corresponding to the carbons of the bisdioxine moieties, e.g. the olefinic CH at 92.01 (**16**) and at 92.03, 91.45 ppm (**17**), the enolic C=*C*–O at 162.18, 161.75 (**16**) and at 162.49, 162.00, 161.88, 161.68 ppm (**17**) and the C=*C*–CO at 105.8 (**16**) and at 105.72, 107.01 ppm (**17**).

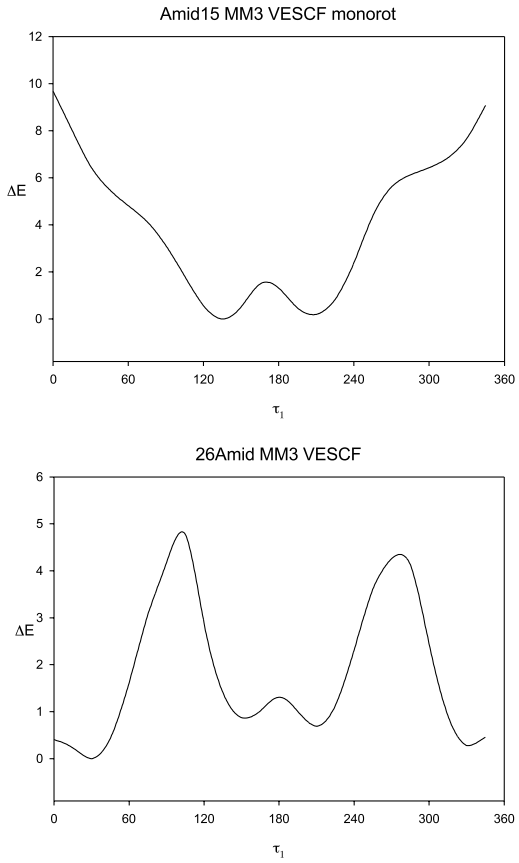
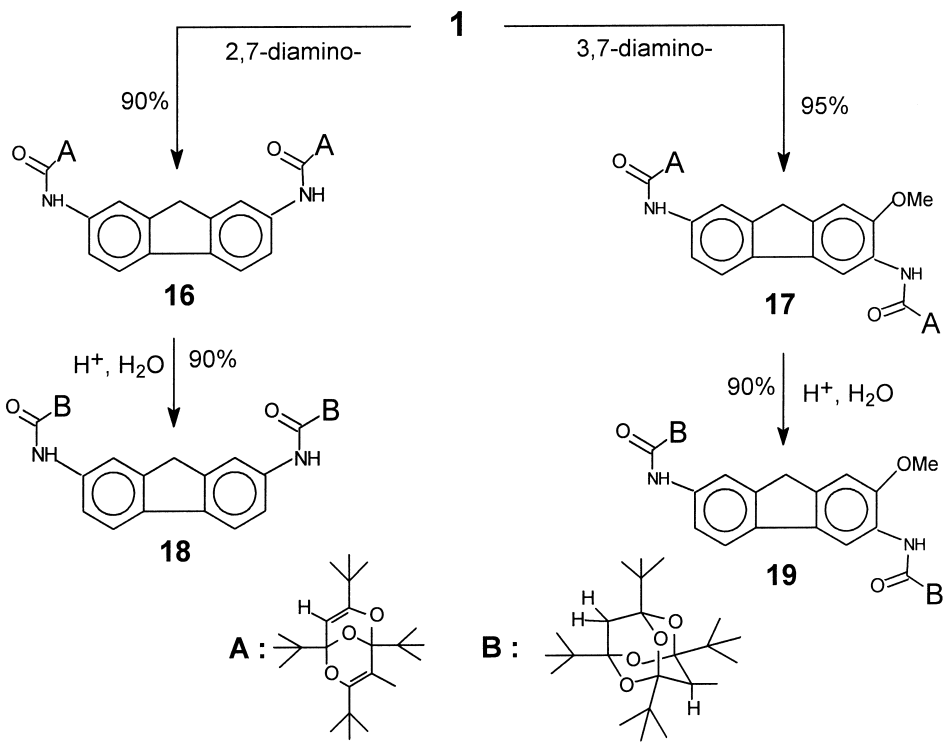
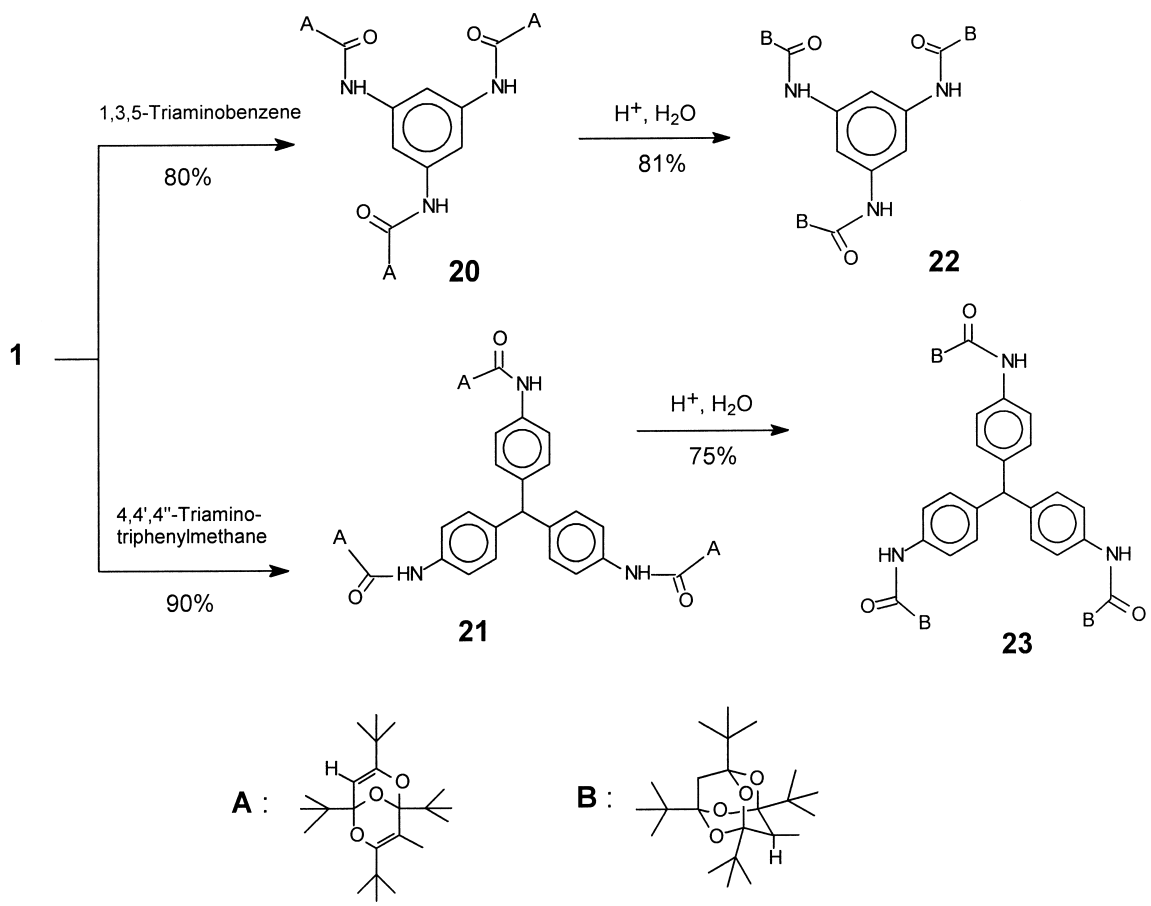


Figure 4. Rotational energy curve of **14** (upper) and **10** (lower) obtained by MM3 VESCF calculations.



Scheme 3. Reactions of diaminofluorenes with α-oxoketene **1**.



Scheme 4. Reactions of triamines with α-oxoketene **1**.

2.4. Triaminoaryl derivatives

In extension of our attempts to synthesize claw-like molecules from suitable diamines and oxoketene **1** we also tried to prepare 'bowl'-like compounds from reaction of corresponding triamines and **1** which could successfully be achieved with 1,3,5-triaminobenzene, prepared via catalytic hydrogenation of 3,5-dinitroaniline.[20] After a long reaction time (10 d) the desired 1 : 3-product **20** could be obtained in 80% yield. The size of the molecule was established by mass spectrometry (*m/z* 1252.9: $M+H^+$, FAB-mode) and elemental analysis (see Section 3 (Scheme 4)).

In a similar way the amino groups of 4,4′,4″-triaminotriphenylmethane[21] added **1** to afford compound **21** (90%, reaction time 3 d) now bearing three bridged *bisdioxines*, which again was established by FAB-mass spectrometry (*m/z*=1418.9, $M+H^+$), elemental analysis as well as by the correct ratio of aromatic to *t*-butyl protons in the ^1H NMR spectrum and correct ^{13}C NMR data, assigned with aid of H-coupling (for details, see the Section 3). Furthermore, both compounds **20** and **21** were converted into the corresponding tetraoxaadamantyl derivatives, **22** and **23** respectively, as evidenced by the presence of their characteristic CH and CH_2-signals of the tetraoxaadamantane moieties[3] at δ 3.03 and 1.75 ppm. Compounds of this type, in particular those with high molecular mass (**19**, **22**, **23**) show a strong tendency to retain water, even after a long period of drying over phosphorous pentoxide (see Section 3).

2.5. Host–guest experiments

Several samples of any type of compounds differing in size and kind of substituents (bridged *bisdioxine* or tetraoxaadamantane) were selected (**5**, **7**, **9**, **14**, **15**, **19**, **21**, and **23**) and their exact geometry was deduced from molecular (*Dreiding*) models. Organic guests were then adjusted considering their size, including estimated van der Waals radii, and their possible lipophilic affinity to the numerous bulky *t*-butyl groups present in the host system. From these considerations choline iodide, benzylammonium chloride and cholesterol were finally selected as promising guest candidates. Hosts and guests (excess) were then mixed in a 1:10 molar ratio in methanolic solution, and after stirring for 24 h at rt (for details see the Section 3) the solution as well as the residue formed were examined with aid of ESI-MS measurements. Electrospray ionization (ESI) has proven to be the method of choice for detection of supramolecular interactions by mass spectrometry in the gas phase.[22] The outcome of these experiments was, that benzylamine binds rather strongly to the host molecules **5**, **7**, **9**, **14**, **15**, **21** (intensity of the mass peaks 100%), somehow weaker to **23** (intensity 30%), choline interacts with **15**, **19** and **21** (peak intensities 20–50%), while cholesterol obviously is too big to show measurable interactions to any of the hosts. These results are summarized in Table 1.

In an attempt to gain insight into the stereochemical situation of the complexes determined by the ESI-MS, NMR-titration experiments were tried with selected

Table 1. ESI-MS data of hosts **5**, **7**, **9**, **14**, **15**, **19**, **21**, and **23** with choline iodide, benzylamine (Bzamine) hydrochloride and cholesterol as guest molecules in methanol or acetonitrile

Host	Mass (MW)	Guest	Mass (MW)	Solvent	Complexation	Mass (M+1)	Peak intensity (%)
5	861.5	Choline	104	MeOH	No		
	861.5	Bzamine	107	MeOH	Yes	968.5	100
7	861.5	Choline	104	MeOH	No		
	861.5	Bzamine	107	MeOH	Yes	968.5	100
9	911.5	Choline	104	MeCN	No		
	911.5	Bzamine	107	MeOH	Yes	1018.8	100
	911.5	Cholesterol	386.6	MeOH	No		
		Cholesterol	386.6	MeCN	No		
14	911.5	Choline	104	MeCN	No		
	911.5	Bzamine	107	MeOH	Yes	1018.5	100
	911.5	Cholesterol	386.6	MeOH	No		
	911.5	Cholesterol	386.6	MeCN	No		
15	947.5	Choline	104	MeOH	Yes	1051.5	20
	947.5	Bzamine	107	MeOH	Yes	1055.5	100
	947.5	Cholesterol	386.6	MeOH	No		
	947.5	Cholesterol	386.6	MeCN	No		
19	1014.5	Choline	104	MeOH	Yes	1119.8	50
	1014.5	Bzamine	107	MeOH	No		
	1014.5	Bzamine	107	MeCN	No		
	1014.5	Cholesterol	386.6	MeOH	No		
	1014.5	Cholesterol	386.6	MeCN	No		
21	1417.8	Choline	104	MeOH	Yes	1522.7	10
	1417.8	Bzamine	107	MeOH	Yes	1526.8	100
	1417.8	Cholesterol	386.6	MeOH	No		
23	1471.8	Choline	104	MeCN	No		
	1471.8	Bzamine	107	MeOH	Yes	1579.8	30
	1471.8	Cholesterol	386.6	MeOH	No		

examples (e.g. **7** with benzylamine hydrochloride, **19** with choline, both in d_4-methanol). No change in the chemical shift values was found when comparing the spectra of the host molecule **7** with those of a mixture of **7** and benzylamine hydrochloride (up to a molar ratio 1:20). Thus, obviously the host–guest interaction in solution here seems to be much weaker than in the gas phase. However, in case of **19** and choline iodide, the NMR titration exhibited a distinct down-field shift of the two NH-protons of 0.04 ppm ($\Delta\delta$ from 7.703 to 7.743 ppm). The aromatic protons H-1, H-4, H-5 and H-6 also move sligthly downfield (0.004–0.008 ppm), while H-8 of the fluorene ring after the final addition of choline is found slightly up-field shifted (0.007 ppm) Participation of both NH-functionalities gets understandable since complexation certainly must be regarded as a dynamic equilibrium with obviously no preference to one of the two opposite sites of the fluorene moiety. The significant deshielding of the NH-protons may be the result of a cation/π-electron complexation between the trimethylammonium part of the choline and the aromatic π-electrons of the fluorene moiety. Interactions of this type are well documented and found to be an important noncovalent binding force in host–guest chemistry in general.[23]

3. Experimental

3.1. General

All chemicals, in particular the diamino-compounds were purchased from Sigma-Aldrich Chemical Co. and used without further purification. 1,3,5-Triaminobenzene was prepared according to Ref. 20, and 4′,4″,4‴-triaminotriphenylmethane was obtained following Ref. 21. Solvents were dried according to standard protocols. α-Oxoketene **1** was prepared according to Ref. 1b. Melting points were determined on a Tottoli- or Gallenkamp Apparatus and are uncorrected. Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106; IR Spectra (KBr pellets) were recorded with a Perkin–Elmer 298. ^{1}H and ^{13}C NMR spectra were measured on a Varian XL 200 MHz, a Bruker AMX 360 MHz and a Bruker Avance 500 MHz spectrometer. Mass spectra were recorded on a HP-LC/MSD 1100 (ESI or APCI-mode) or a VG ZAB-2SEQ (FAB-mode).

3.2. Synthesis of the bridged bisdioxine bis-amides 7, 9–11, 14a,b, 16, 17. General procedure

0.24 mmol of the corresponding diamine is added to a stirred solution of 200 mg (0.48 mmol) of oxoketene **1** in dry acetonitrile (4 mL). The clear solution is kept at rt for 4–5 d with stirring and permanent TLC-monitoring of reactants and the new product formed. Then the solvent is partially evaporated until the product starts to precipitate. After suction filtration the crude products are recrystallized from methanol or ethylacetate/acetonitrile (**14**).

3.2.1. 1,3-Bis-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-benzene (7). Yield 170 mg (85%); mp: 100 °C; IR (KBr): 3440 (NH), 3000–2860 (CH), 1680, 1660 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.05 (s, 18H), 1.14, 1.15 (2s, 18H), 1.20, 1.21 (2s, 18H), 1.24, 1.25 (2s, 18H), 4.85 (s, 2H), 7.18–7.31 (m, 3H), 7.60 (sb, 1H). Anal. calcd for $C_{52}H_{80}N_2O_8$: C, 72.52; H, 9.36; N, 3.25. Found: C, 72.55; H, 9.44; N, 3.15.

3.2.2. 2,7-Bis-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-naphthalene (9). Yield 140 mg (65%); mp: 235 °C; IR (KBr): 3440 (NH), 3000–2860 (CH), 1680, 1660 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06 (s, 18H), 1.14 (s, 18H), 1.24 (s, 18H), 1.25 (s, 18H), 4.88 (s, 2H), 7.30 (d, 2H, *J*=8 Hz), 7.38 (s, 2H), 7.69 (d, 2H, *J*=8 Hz), 8.15 (s, 2H). Anal. calcd for $C_{56}H_{82}N_2O_8$: C, 73.81; H, 9.07; N, 3.07. Found: C, 73.43; H, 9.35; N, 3.03.

3.2.3. 2,6-Bis-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-naphthalene (10). Yield 150 mg (70%); mp: 245 °C; IR (KBr): 3440 (NH), 3100–2840 (CH), 1680, 1655 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06 (s, 18H), 1.14 (s, 18H), 1.22 (s, 18H), 1.28 (s, 18H), 4.89 (s, 2H), 7.22 (d, 2H; *J*=8 Hz), 7.35 (s, 2H), 7.72 (d, 2H, *J*=8 Hz), 8.29 (s, 2H). Anal. calcd for $C_{56}H_{82}N_2O_8$: C, 73.81; H, 9.07; N, 3.07. Found: C, 73.40; H, 9.21; N, 3.03.

3.2.4. 8-Amino-(-1-naphthyl-aminocarbonyl)-1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (11). Yield 130 mg (60%); mp: 160 °C; IR (KBr): 3440 (NH), 3350–3320 (NH_2), 3000–2860 (CH), 1660 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.05, 1.12, 1.20, 1.25 (4s, 9H each), 3.92 (b, 2H), 4.82 (s, 1H), 6.75 (d, 1H, *J*=7.5 Hz), 7.18–7.58 (m, 5H), 8.38 (b, 1H). Anal. calcd for $C_{33}H_{46}N_2O_4$: C, 74.12; H, 8.67; N, 5.24. Found: C, 73.81; H, 8.82; N, 5.20.

3.2.5. 1,5-Bis(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-aminocarbonyl)-naphthalene (14). Yield: 165 mg (77%); mp: 243 °C; separation of rotamers **14a/14b** was achieved by dry-column flash chromatography (silicagel 60H, eluent: dichloromethane/petrolether=3/2; R_f **14a**: 0.31; R_f **14b**: 0.23); IR (KBr): 3440 (NH), 3000–2860 (CH), 1685, 1660 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06, 1.14, 1.24, 1.245 (4s, 18H each), 4.92 (s, 2H), 7.45–7.67 (m, 4H, 2NH), 8.08 (d, 2H, *J*=8 Hz, **14a**), 8.10 (d, *J*=8 Hz, **14b**); ^{13}C NMR ($CDCl_3$): 24.20, 25.15, 28.43, 29.25 (C(CH_3)$_3$), 35.13, 37.90, 38.27, 40.17 (C(Me)$_3$)$_3$, 91.99 (C-8), 97.26, 99.70 (C-1, C-5), 105.44 (C-4), 117.28, 120.11 (**14a**), 120.02 (**14b**), 126.08 (**14a**), 126.03 (**14b**), 127.25 (**14a**), 127.18 (**14b**) (Ar-C), 132.82 (Ar-CN), 162.20, 162.25 (C-3, C-7), 167.38 (C═O). Anal. calcd for $C_{56}H_{82}N_2O_8$: C, 73.81; H, 9.07; N, 3.07. Found: C, 73.92; H, 9.35, N, 3.05 (**14a**); C, 73.99; H, 9.24; N, 2.81 (**14b**).

3.2.6. 2,7-Bis-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-fluorene (16). Yield: 225 mg (92%); mp: 212°C; IR (KBr): 3440 (NH), 3000–2860 (CH), 1680, 1660 (C═O), 1600 (C═C) cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.06 (s, 18H), 1.14 (s, 18H), 1.22 (s, 18H), 1.25 (s, 18H), 3.85 (s, 2H), 4.83 (s, 2H), 7.22 (s, 2H), 7.28 (d, 2H, *J*=8 Hz), 7.60 (d, 2H, *J*=8 Hz), 7.85 (sb, 2H); ^{13}C NMR ($CDCl_3$): 24.08, 24.94, 28.15, 28.95 (C(CH_3)$_3$), 37.74, 38.09, 40.09 (C(Me)$_3$), 40.90 (CH_2),

92.01 (C-8), 97.2, 99.51 (C-1, C-5), 105.8 (C-4), 116.62, 118.20, 118.81, 119.67 (Ar-CH), 136.60, 137.64 (Ar-C), 144.35 (Ar-CN), 161.76, 162.18 (C-3, C-7), 166.96 (C═O). Anal. calcd for $C_{59}H_{84}N_2O_8$: C, 74.65; H, 8.91; N, 2.95. Found: C, 74.38; H, 9.00; N, 2.94.

3.2.7. 3,7-Bis-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxabicyclo-[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-2-methoxy-fluorene (17). Yield: 210 mg (95%); mp: 242 °C; IR (KBr):3430 (NH), 3000–2870 (CH), 1680, 1655 (C═O), 1600 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$): 1.04, 1.14, 1.16, 1.20, 1.28 (5s, 72H), 3.83 (s, 2H), 3.85 (s, 3H), 4.84 (s, 1H), 4.88 (s, 1H), 7.28 (s, 1H); 7.40 (d, 1H, *J*=9.3 Hz), 7.30 (s, 1H); 7.63 (d, 1H, *J*=9.3 Hz), 7.79 (s, 1H), 8.0 (s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$): 24.16, 25.03, 28.26, 28.43, 28.94, 29.03 ($C(CH_3)_3$), 34.99, 35.07, 37.23, 37.81, 38.16 ($C(Me)_3$)$_3$, 40.06 (CH_2), 55.54 (CH_3), 91.45, 92.03 (C-8), 97.15, 99.50, 99.68 (C-1, C-5), 105.72, 107.01 (C-4), 111.75, 116.57, 118.04, 119.93, 125.83 (Ar-CH), 134.32, 136.11, 138.40, 138.93 (Ar-C), 144.07 (Ar-CN), 147.46 (Ar-CO), 161.88, 162.49 (C-3, C-7), 166.92 (C═O). Anal. calcd for $C_{60}H_{86}N_2O_9$: C, 73.59; H, 8.85; N, 2.86. Found: C, 73.30; H, 8.89; N, 2.80.

3.3. X-ray crystallographic analysis of 14a

Colorless crystals were grown by the slow vapor diffusion of acetonitrile into a chloroform solution of **14a**. The crystal was monoclinic, space group $P2_1/n$, with cell dimension a=9.708(4) Å, b=19.962(7) Å, c=16.587(6) Å, β=93.87(3)° and V=3207 Å^3. Z=2 molecules ($C_{56}H_{82}N_2O_8$·2$CHCl_3$, M_W=1150) in the unit cell (D_c=1.19 g cm^{-3}). Intensity data were measured for 4769 reflections (3646 unique, R_{int}=0.0386, $2\theta_{max}$=105°) at rt on a Siemens P4 diffractometer using a crystal with dimensions 0.3×0.3×0.2 mm [$F(000)$=1224, λ(Cu Kα)=1.54178 Å, μ=2.8 mm^{-1}]. The structure was solved by direct methods and refined by full-matrix least-squares analysis with SHELXL-97[24] minimizing the residuals for F^2. All hydrogen atoms were calculated at their theoretical position and were treated as 'riding' on the respective heavy atom. Convergence was reached at $R1$=0.0876 [for 1642 reflections with $I>2\sigma(I)$] and $wR2$=0.3010 (for all unique data). The Goodness-of-fit on F^2 was 0.975. The structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 228819).

3.4. Synthesis of the bridged *bisdioxine* tris-amides 20 and 21. General procedure

0.15 mmol of 1,3,5-triaminobenzene (or 4, 4′,4″-triamino-triphenylmethane), dissolved in dry THF (2 mL) are added dropwise to a solution of **1** (200 mg) in dry acetonitrile (4.5 mL) with stirring at rt. After 10d (**20**) or 3d (**21**), respectively, at rt, the solvent is evaporated to half of its volume. The precipitate formed over night is isolated by suction filtration and recrystallized from acetonitrile or ethanol.

3.4.1. 1,3,5-Tris-(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxa-bicyclo[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-benzene (20). Yield: 150 mg (80%); mp: 230 °C; IR (KBr): 3440 (NH), 3000–2860 (CH), 1680, 1660 (C═O), 1600 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$): 1.06, 1.14, 1.24, 1.25 (4s, 27H each), 4.83 (s, 3H), 7.20 (b, 3H), 7.60 (s, 3H); MS (FAB-mode, NOBA): *m/z* 1252.9 [M+H$^+$]. Anal. calcd for $C_{75}H_{117}N_3O_{12}$: C, 71.91; H, 9.41; N, 3.35. Found: C, 71.93; H, 9.57; N, 3.26.

3.4.2. 4,4′,4″-Tris(1,3,5,7-tetra-*t*-butyl-2,6,9-trioxa-bicyclo[3.3.1]nona-3,7-diene-4-yl-carbonylamino)-triphenylmethane (21). Yield: 190 mg (90%); mp: 350–352°C; IR (KBr): 3440 (NH), 3000–2860 (CH), 1680, 1660 (C═O), 1600 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$): 1.04, 1.14, 1.24, 1.26 (4s, 27H each), 4.86 (s, 3H), 5.40 (s, 1H), 7.05 (d, 6H, *J*=8.5 Hz), 7.20 (s, 3H), 7.38 (d, 6H, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$): 24.1, 25.0, 28.39, 28.98 ($C(CH_3)_3$), 35.02, 37.78, 38.13, 40.02 ($C(Me)_3$), 55.36 (CH, *J*=126 Hz), 92.07 (C-8, *J*=162 Hz), 97.11, 99.62 (C-1, C-5), 105.58 (C-4), 119.65, 129.94 (Ar-CH, *J*=156 Hz), 136.35, 139.70 (Ar-C), 161.79, 162.16 (C-3, C-7), 166.98 (C═O); MS (FAB, NOBA): *m/z* 1419.0 (M+H$^+$). Anal. calcd for $C_{88}H_{127}N_3O_{12}$: C, 74.49; H, 9.02; N, 2.96. Found: C, 74.03; H, 9.16; N, 2.82.

3.5. Synthesis of the 2,4,6,8-tetraoxaadamantanes 8, 12, 13, 15, 18, 19, 22 and 23. General procedure

200 mg of the corresponding bridged bisdioxine derivatives 7–21 are dissolved in a mixture of dichloromethane (2 mL) and acetic acid (2 mL). After addition of aqeuous HCl (150 μl) gaseous HCl is passed through the solution for 30 s and the reaction mixture is stirred for 12 h at rt. Whilst the dichloromethane is then allowed to slowly escape, a colorless residue precipitates, which after suction is recrystallized from acetonitrile.

3.5.1. 1,3-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-benzene (8). Yield: 180 mg (86%); mp: 300–302 °C; IR (KBr): 3410 (NH), 3005–2865 (CH), 1675 (C═O), 1625 cm^{-1}; ^1H NMR ($CDCl_3$): 0.98 (s, 18H), 1.05 (s, 36H), 1.28 (s, 18H), 1.78 (s, 4H, CH_2), 3.05 (s, 2H), 7.22–7.38 (m, 3H), 7.49 (s, 1H), 8.30 (s, 2H, NH). Anal. calcd for $C_{52}H_{84}N_2O_{10}$: C, 69.61; H, 9.43; N, 3.12. Found: C, 69.51; H, 9.74; N, 2.90.

3.5.2. 2,7-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-naphthalene (12). Yield: 165 mg (80%); mp: 210 °C; IR (KBr): 3410 (NH), 3010–2860 (CH), 1680 (C═O), 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 0.98 (s, 18H), 1.08 (s, 36H), 1.20 (s, 18H), 1.79 (s, 4H, CH_2), 3.10 (s, 2H), 7.38 (d, 2H, *J*=8.5 Hz), 7.68 (d, 2H, *J*=8.5 Hz), 8.08 (s, 2H), 8.42 (s, 2H). Anal. calcd for $C_{56}H_{86}N_2O_{10}$: C, 71.00; H, 9.15; N, 2.96. Found: 71.35; H, 9.26, N, 3.18.

3.5.3. 2,6-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-naphthalene (13). Yield: 175 mg (85%); mp: >350 °C; IR (KBr): 3400 (NH), 3100–2860 (CH), 1680 (C═O), 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 1.00 (s, 18H), 1.06 (s, 36H), 1.22 (s, 18H), 1.79 (s, 4H), 3.10 (s, 2H), 7.40 (d, 2H, *J*=9.5 Hz), 7.72 (d, 2H, *J*=9.5 Hz), 8.12 (s, 2H), 8.40 (s, 2H). Anal. calcd for $C_{56}H_{86}N_2O_{10}$: C, 71.00; H, 9.15; N, 2.96. Found: C, 69.69; H, 9.09; N, 2.99.

3.5.4. 1,5-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-naphthalene (15).

Yield: 160 mg (77%); mp: >350°C; IR (KBr): 3410 (NH), 3100–2860 (CH), 1675 (C═O), 1540 cm^{-1}; ^1H NMR ($CDCl_3$): 1.01 (s, 18H), 1.18 (sb, 54H), 1.81 (s, 4H), 3.23 (s, 2H), 7.50–8.05 (m, 6H), 8.45 (s, 2H). Anal. calcd for $C_{56}H_{86}N_2O_{10}$: C, 71.00; H, 9.15; N, 2.96. Found: C, 70.45; H, 9.19; N, 2.92.

3.5.5. 2,7-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-aminocarbonyl)-fluorene (18). Yield: 195 mg (90%); mp: 210 °C; ^1H NMR ($CDCl_3$): 0.95 (s, 18H), 1.08 (s, 36H), 1.21 (s, 18H), 1.79 (s, 4H), 3.10 (s, 2H), 3.85 (s, 2H), 7.25 (d, 2H, *J*=8.5 Hz), 7.60 (d, 2H, *J*=8.5 Hz), 7.85 (s, 2H), 8.37 (s, 2H). Anal. calcd for $C_{59}H_{88}N_2O_{10}$: C, 71.92; H, 8.99; N, 2.84. Found: C, 71.65; H, 9.20; N, 2.74.

3.5.6. 2,7-Bis(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-2-methoxy-fluorene (19). Yield: 190 mg (90%); mp: 310 °C (sublim.); IR (KBr): 3413, 3210 (NH, OH), 3100–2860 (CH), 1676 (C═O), 1530 cm^{-1}; ^1H NMR ($CDCl_3$): 0.98 (s, 18H), 1.10 (s, 36H), 1.18 (s, 9H), 1.20 (s, 9H), 1.79 (s, 2H), 1.80 (s, 2H), 3.09 (s, 1H), 3.18 (s, 1H), 3.82 (s, 2H), 3.85 (s, 3H), 7.03 (s, 1H), 7.11 (d, 1H, *J*=8.5 Hz), 7.63 (d, 1H, *J*=8.5 Hz), 7.91 (s, 1H), 8.32 (s, 2H), 8.5 (s, 1H); ^{13}C NMR ($CDCl_3$): 25.41, 25.71, 25.96, 26.15, 26.50, 26.76 ($C(CH_3)_3$), 28.39, 28.53 (CH_2-Ada), 39.12, 40.10, 40.43, 40.77 ($C(Me)_3$), 42.95 (CH_2), 52.92, 53.70 (CH), 56.94 (CH_3), 101.24, 101.40, 103.75 (O–C–O), 109.21, 116.26, 119.20, 120.48, 121.74, 127.40, 135.98, 137.30, 140.29, 141.63, 145.80, 150.67 (Ar-C), 170.18, 170.55 (C═O). Anal. calcd for $C_{60}H_{90}N_2O_{11}\cdot H_2O$: C, 69.76; H, 8.91; N, 2.71. Found: C, 70.16; H, 8.79; N, 2.78.

3.5.7. 1,3,5-Tris(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-benzene (22). Yield: 170 mg (81%); mp: >350 °C; IR (KBr): 3410, 3390 (NH, OH), 3000–2860 (CH), 1680 (C═O), 1600 cm^{-1}; ^1H NMR ($CDCl_3$): 0.95 (s, 27H), 1.05 (s, 54H), 1.16 (s, 27H), 1.75 (s, 6H), 3.02 (s, 3H), 7.52 (s, 3H), 8.29 (s, 3H). Anal. calcd for $C_{75}H_{123}N_3O_{15}\cdot H_2O$: C, 68.00; H, 9.50; N, 3.17. Found: C, 68.19; H, 9.38; N, 3.20.

3.5.8. 4,4′,4″-Tris(1,3,5,7-tetra-*t*-butyl-2,4,6,8-tetraoxa-adamantane-9-yl-carbonylamino)-triphenylmethane (23). Yield: 155 mg (75%); mp: >350 °C; IR (KBr): 3410, 3300 (NH, OH), 3100–2860 (CH), 1677 (C═O), 1600, 1522 cm^{-1}; ^1H NMR ($CDCl_3$): 0.95 (s, 27H), 1.05 (s, 54H), 1.15 (s, 27H), 1.75 (s, 6H), 3.05 (s, 3H), 7.05 (d, 6H, *J*=8.5 Hz), 7.35 (d, 6H, *J*=8.5 Hz), 8.25 (s, 3H); ^{13}C NMR ($CDCl_3$): 23.14, 23.89, 24.50 ($C(CH_3)_3$), 29.45 (t, *J*=126 Hz, CH_2-Ada), 37.85, 38.50, 40.66 ($C(Me_3)_3$), 50.64 (d, *J*=138 Hz, CH-Ada), 55.20 (d, *J*=124 Hz, CH), 99.21, 101.55 (O–C–O), 120.03, 129.61 (d, *J*=156.5 Hz, CH-Ar), 135.4, 139.45 (C-Ar), 167.9, 168.01 (C═O). Anal. calcd for $C_{88}H_{133}N_3O_{15}\cdot H_2O$: C, 70.93; H, 8.99; N, 2.81. Found: C, 70.93; H, 9.04; N, 2.68.

3.6. Host–guest experiments

(a) ESI-MS: 0.5–1 mg of the host molecules **5**–**23** together with a ten-fold excess of the corresponding guests (choline iodide, benzylamine hydrochloride and cholesterol) were mixed in methanol (1 mL) and stirred at rt for 24 h. Then, appropriate amounts of the solutions are injected into the mass spectrometer under ESI-conditions. In case a residue is formed during stirring, this solid is separated by decantation, dissolved in acetonitrile and again injected under identical conditions. The results obtained are listed in Table 1.

(b) NMR-titration: 0.5 mg of the host molecules (**7** or **19**) were dissolved in methanol-d_4 (800 μl) and a solution of the suitable guest molecules (benzylamine hydrochloride or choline iodide) in methanol-d_4 (100 μl, 100-fold excess) is added in portions of 20 μl and after each addition a ^1H NMR spectrum is recorded and the chemical shift values compared with those of the spectrum of the pure host compound.

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Practical synthesis of *S*-alkyl thiocarbamate herbicides by carbonylation of amines with carbon monoxide and sulfur

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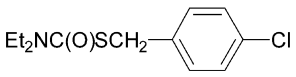
Dedicated to Professor Noboru Sonoda on the occasion of his 70th birthday

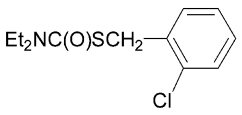
Abstract—An industrial and economic carbonylation of amines with carbon monoxide and sulfur has been developed for the synthesis of *S*-alkyl thiocarbamate herbicides. In the presence of potassium carbonate and solvent DMSO, *S*-alkyl thiocarbamates, such as thiobencarb and orbencarb (herbicides) are synthesized in excellent yields from amines, carbon monoxide, sulfur, and alkyl halides under mild conditions (1 atm, 20 °C).

1. Introduction

A series of *S*-alkyl thiocarbamates (**1**) is well known as useful herbicides, and these herbicides (**1**) (e.g., thiobencarb (**1a**) and orbencarb (**1b**)) have been produced in an industrial large-scale.[1–3] Therefore, development of synthetic methods of *S*-alkyl thiocarbamates (**1**) is of an importance.



Thiobencarb, **1a**



Orbencarb, **1b**

Many methods for the synthesis of *S*-alkyl thiocarbamates (**1**) have been reported. Among them, the reaction of amines (**2**) with thiols and phosgene or with carbonyl sulfide, followed by alkylation with alkyl halides has been known as the general routes.[4–6] Indeed, *S*-alkyl thiocarbamate herbicides (**1**) are industrially produced by a two-step reaction, which includes the generation of carbonyl sulfide from carbon monoxide and sulfur under high temperature, and the reaction of carbonyl sulfide with amines (**2**) and alkyl halides.[2]

Also, direct carbonylation of amines (**2**) with carbon monoxide and sulfur for the synthesis of *S*-alkyl thiocarbamate herbicides (**1**) has been developed. It seems to be a straightforward and useful method of herbicide synthesis.

Grisley and Stephens reported *S*-alkyl thiocarbamate (**1**) synthesis from secondary amines (**2**), carbon monoxide, sulfur, and alkyl halides.[8] However, this reaction requires high temperature and pressurized carbon monoxide.

In 1989, our research group found that selenium exhibits excellent catalytic activity toward the carbonylation of amines (**2**) with carbon monoxide and sulfur. This selenium-catalyzed carbonylation of amines (**2**) with carbon monoxide and sulfur smoothly proceeds under mild conditions to give thiocarbamate salts (**3**), the alkylation of which leads to the formation of *S*-alkyl thiocarbamates (**1**) in excellent yields.[9,10] Owing to the toxicity of selenium, however, use of this preparative method is considerably limited for industrial production of herbicides.

Next, we also found a high-yield synthesis of *S*-alkyl thiocarbamate (**1**) by the reaction of carbamoyl lithiums which were prepared in situ from lithium amides and carbon monoxide (1 atm) at low temperature (−78 °C), with elemental sulfur and alkyl halides, or disulfides.[11–13] However, this synthetic method may be not suitable for industrial production of *S*-alkyl thiocarbamate herbicides (**1**), because of the need for expensive lithium amides and low temperature reaction conditions (−78 °C).

Furthermore, we very recently reported the carbonylation of amines (**2**) with carbon monoxide and sulfur, assisted by

Keywords: *S*-Alkyl thiocarbamates; Herbicide; Carbon monoxide; Sulfur; Carbonylation.
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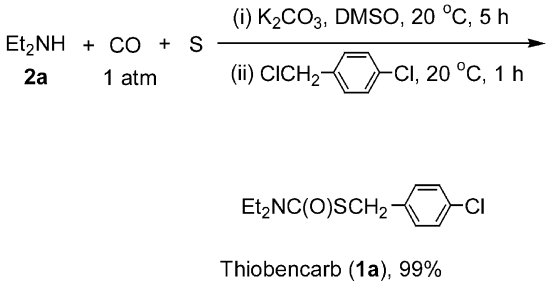
DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to provide *S*-alkyl thiocarbamates (**1**) in excellent yields under mild conditions (1 atm, 20 °C).[14] However, this method seems to be not attractive for industrial production of *S*-alkyl thiocarbamate herbicides (**1**), because of the price of DBU compared with inorganic bases.

Therefore, in our strategy, we explored an industrial and economic route to the *S*-alkyl thiocarbamates herbicides (**1**) under mild conditions (1 atm, 20 °C) using an inorganic base.

2. Results and discussion

Our trial employing K_2CO_3 as a base and DMSO as a solvent, which are cheap and commercially available, leads to successful carbonylation of diethylamine (**2a**) with carbon monoxide and sulfur. Diethylamine (2.07 mL, 20 mmol) (**2a**) easily reacted with carbon monoxide (1 atm) and sulfur (321 mg, 10 mmol) at 20 °C for 5 h in the presence of K_2CO_3 (2.07 g, 15 mmol) using DMSO (20 mL) as a solvent. The resulting thiocarbamate salt (**3a**) in DMSO was esterified by 4-chlorobenzyl chloride (1.39 mL, 11 mmol) under an ambient pressure, at 20 °C for 1 h to give *S*-4-chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] **1a**) in quantitative yield (Eq. 1).



(1)

The influence of bases and solvents on the synthesis of **1a** from diethylamine, carbon monoxide, sulfur, and 4-chlorobenzyl chloride was examined (Table 1).

Table 1. Influence of bases (15 mmol) and solvents (20 mL) on the synthesis of Thiobencarb (**1a**)

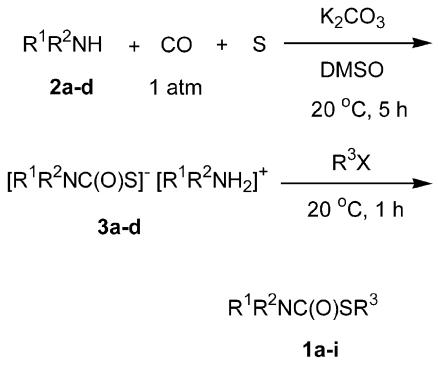
Entry	Base	Solvent	Yield (%)[a]
1	K_2CO_3	DMSO	99
2	K_2CO_3	DMSO	29[b]
3	K_2CO_3[c]	DMSO	69
4	K_2CO_3[d]	DMSO	66
5	K_2CO_3	DMF	68
6	K_2CO_3	NMP	48
7	K_2CO_3	Sulfolane	18
8	K_2CO_3	THF	10
9	Na_2CO_3	DMSO	60
10	$KHCO_3$	DMSO	50
11	$NaHCO_3$	DMSO	43
12	KOH	DMSO	54
13	NaOH	DMSO	47
14	AcONa	DMSO	70
15	none	DMSO	39

[a] Reaction conditions: diethylamine (2.07 mL, 20 mmol), sulfur (321 mg, 10 mmol), K_2CO_3 (2.07 g, 15 mmol), 4-chlorobenzyl chloride (1.39 mL, 11 mmol), DMSO (20 mL), CO (1 atm), 20 °C, 5 h for carbonylation and 1 h for alkylation.
[b] Et_2NH (10 mmol) was used.
[c] K_2CO_3 (10 mmol) was used.
[d] K_2CO_3 (5 mmol) was used.

S-4-Chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] **1a**) are prepared in excellent yields in the presence of 1.5 equiv. of K_2CO_3 and DMSO as a solvent under 1 atm of carbon monoxide at 20 °C for 6 h (entry 1). When using 10 mmol of Et_2NH (**2a**), yield of **1a** was much lowered (29%) (entry 2). Thus, the need of 2 equiv. of diethylamine (**2a**) may be suggested for the formation of *N*,*N*-diethyl-ammonium salt of *N*,*N*-diethylthiocarbamate (**3a**) as an intermediate.

Use of 1.0 or 0.5 equiv. of K_2CO_3 lowered the yields of *S*-4-chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] **1a**) (entries 3 and 4). Also, synthesis of **1a** in DMF resulted in moderate yield (entry 5). NMP, sulfolane, and THF as solvents were not effective for the preparation of **1a** (entries 6–8). The reaction in the presence of other bases (Na_2CO_3, $KHCO_3$, $NaHCO_3$, KOH, NaOH, AcONa) or in the absence of a base, resulted in the formation of the desired **1a** in moderate yields (43–70%) (entries 9–15).

In the presence of 1.5 equiv. of K_2CO_3 and DMSO as a solvent under 1 atm of carbon monoxide at 20 °C for 6 h, *S*-alkyl thiocarbamate herbicides (**1a-i**) were synthesized from the corresponding amines (**2a-d**) and alkyl halides (Eq. 2, Table 2).

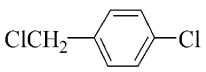
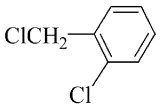
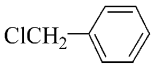
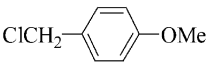
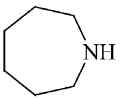
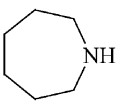
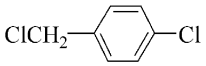


(2)

S-Alkyl thiocarbamates (**1a-i**) from secondary amines (**2a-d**) were prepared in excellent yields under mild conditions (1 atm, 20 °C) (entries 1–9). General names of herbicides are as follows: Thiobencarb: **1a**, Orbencarb: **1b**, Prosulfocarb: **1c**, Methiobencarb: **1d**, Molinate: **1e**, NTN-7072: **1f**, Ethiolate: **1g**, EPTC: **1h**, Cycloate: **1i**.[3] Even in considerably large scale, *S*-alkyl thiocarbamates (**1g**,**h**) were given in good yields (entries 7 and 8), although long reaction time was required (22 h for carbonylation and 2 h for alkylation).

Based on our finding on the smooth reaction of salts of thiolates **4** with carbon monoxide to convert into salts of thiocarbamates **3**,[15] we suggest a plausible pathway for this carbonylation of amines (**2**) with carbon monoxide and sulfur using K_2CO_3 and DMSO as follows (Scheme 1). Elemental sulfur is readily subjected to S–S bond fission by the reaction with secondary amines (**2**) strongly assisted by K_2CO_3 and DMSO as a solvent, to form ammonium salts of thiolate anions **4**.[16,17] The reaction of **4** with carbon

Table 2. Synthesis of *S*-alkyl thiocarbamate herbicides (**1a-i**)

Entry	R^1R^2NH		R^3X		Yield (%)[a]
1	Et_2NH	**2a**		**1a**[b]	99
2	Et_2NH	**2a**		**1b**[c]	98
3	*n*-Pr_2NH	**2b**		**1c**[d]	99
4	Et_2NH	**2a**		**1d**[e]	98
5		**2c**	EtI	**1e**[f]	94
6		**2c**		**1f**[g]	96
7	Et_2NH	**2a**	EtI	**1g**[h]	88(94)[i]
8	*n*-Pr_2NH	**2b**	EtI	**1h**[j]	94(85)[i]
9	*c*-HexEtNH	**2d**	EtI	**1i**[k]	98

[a] Reaction conditions: amine (20 mmol), sulfur (321 mg, 10 mmol), K_2CO_3 (2.07 g, 15 mmol), alkyl halide (11 mmol), DMSO (20 mL), CO (1 atm), 20 °C, 5 h for carbonylation and 1 h for alkylation.
[b] Thiobencarb.[3]
[c] Orbencarb.[3]
[d] Prosulfocarb.[3]
[e] Methiobencarb.[3]
[f] Molinate.[3]
[g] NTN-7072.[3]
[h] Ethiolate.
[i] Reaction conditions: amine (200 mmol), sulfur (3.21 g, 100 mmol), K_2CO_3 (20.7 g, 150 mmol), ethyl iodide (8.80 mL, 110 mmol), DMSO (50 mL), CO (1 atm), 20 °C, 22 h for carbonylation and 2 h for alkylation.
[j] EPTC.[3]
[k] Cycloate.[3]

monoxide gives the carbonylated species **5**. Through an elimination of carbonyl sulfide from **5**, ammonium salts of thiocarbamates **3** are generated.

It seems that the main role of K_2CO_3 and DMSO as a solvent in this carbonylation is the acceleration of the formation of thiolates **4**.

3. Conclusion

A practical synthetic method for *S*-alkyl thiocarbamate herbicides (**1**) has been developed under mild conditions (1 atm, 20 °C), in which the carbonylation of amines (**2**) with carbon monoxide and sulfur is powerfully assisted by K_2CO_3 and DMSO as a solvent.

From the viewpoint of application to actual industrial production of *S*-alkyl thiocarbamate herbicides (**1**), the present reaction is very significant, in terms of the use of easily available and cheap carbon monoxide, sulfur, K_2CO_3, and DMSO as a solvent, and mild reaction conditions (1 atm, 20 °C).

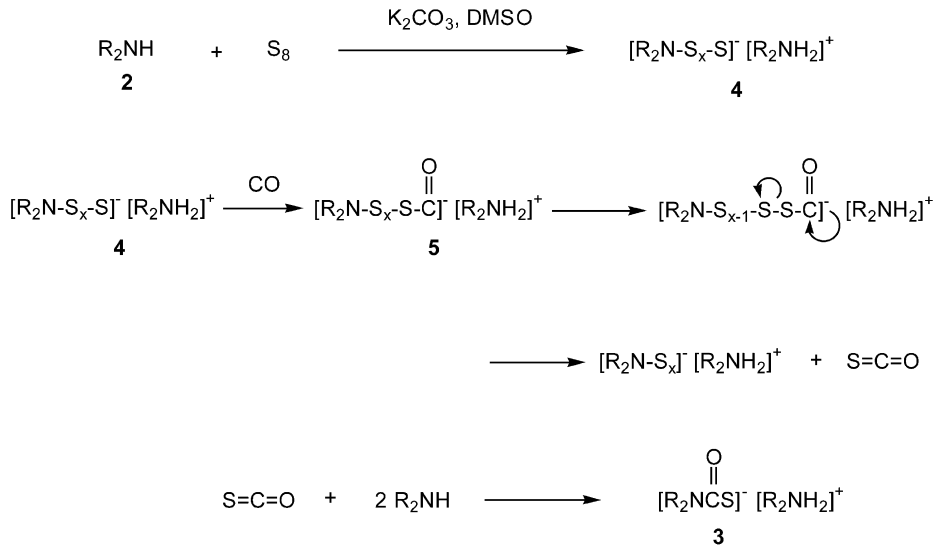
4. Experimental

4.1. General

Melting points were determined on a Mettler FP 5 instrument and were uncorrected. FT-IR spectra were recorded on a Nicolet Magna-IR 550 instrument. ^1H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300, 75 MHz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were recorded on a JEOL JMS-600 spectrometer. Amines (**2a-d**), alkyl halides, solvents, inorganic bases, sulfur (99.5%), and carbon monoxide (99.9%) were used as purchased.

4.2. Typical procedure for the synthesis of *S*-4-chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] 1a) from diethylamine (2a), 4-chlorobenzyl chloride, carbon monoxide, and sulfur

A DMSO (20 mL) solution containing diethylamine (**2a**) (2.07 mL, 20 mmol), powdered sulfur (321 mg, 10 mmol) and K_2CO_3 (2.07 g, 15 mmol) was vigorously stirred under carbon monoxide (1 atm) at 20 °C for 5 h. Into the DMSO



Scheme 1.

solution of thiocarbamate salt (**3a**), 4-chlorobenzyl chloride (1.39 mL, 11 mmol) was added slowly at 0 °C under argon atmosphere. The reaction mixture was stirred for additional 1 h at 20 °C. The resulting mixture was then poured into 1 N HCl (100 mL), and extracted with *t*-butyl methyl ether (100, 50 mL×2). After evaporation of solvents and purification by short-column chromatography (silica gel, toluene/AcOEt, 1:1), *S*-4-chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] **1a**) was obtained in a 99% yield (2.54 g) as a pure form. *S*-4-Chlorobenzyl *N*,*N*-diethylthiocarbamate (Thiobencarb,[3] **1a**): oil; IR (neat) 2975, 1650, 1410, 1250, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J*=7 Hz, 6H), 3.37 (br s, 4H), 4.11 (s, 2H), 7.23–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 33.8, 42.1, 128.6, 130.3, 132.8, 137.2, 166.3; MS (*m*/*z*, %) 257 (M^+, 45), 125 (28), 100 (100), 72 (38). Exact MS calcd for $C_{12}H_{16}ClNOS$: 257.0641. Found: 257.0630.

4.2.1. *S*-2-Chlorobenzyl *N*,*N*-diethylthiocarbamate (Orbencarb,[3] 1b). Oil; IR (neat) 2975, 1650, 1410, 1250, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J*=7 Hz, 6H), 3.37 (br s, 4H), 4.28 (s, 2H), 7.15–7.22 (m, 2H), 7.33–7.36 (m, 1H), 7.49–7.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 32.3, 42.1, 126.9, 128.5, 129.4, 131.3, 134.2, 136.3, 166.5; MS (*m*/*z*, %) 257 (M^+, 16), 222 (55), 125 (31), 100 (100), 89 (10), 72 (35). Exact MS calcd for $C_{12}H_{16}ClNOS$: 257.0641. Found: 257.0633.

4.2.2. *S*-Benzyl *N*,*N*-di-*n*-propylthiocarbamate (Prosulfocarb,[3] 1c). Oil; IR (neat) 2965, 1650, 1405, 1220, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=7 Hz, 6H), 1.60 (q, *J*=7 Hz, 4H), 3.22 (br s, 2H), 3.32 (br s, 2H), 4.15 (s, 2H), 7.22–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 21.6, 34.7, 49.3, 127.0, 128.5, 128.9, 138.3, 167.2; MS (*m*/*z*, %) 251 (M^+, 50), 128 (100), 92 (21), 91 (97), 86 (51). Exact MS calcd for $C_{14}H_{21}NOS$: 251.1344. Found: 251.1328.

4.2.3. *S*-4-Methoxybenzyl *N*,*N*-diethylthiocarbamate (Methiobencarb,[3] 1d). Oil; IR (neat) 2975, 1650, 1515, 1405, 1250, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, *J*=7 Hz, 6H), 3.37 (br s, 4H), 3.78 (s, 3H), 4.11 (s, 2H), 6.83 (d, *J*=8 Hz, 2H), 7.27 (d, *J*=8 Hz, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ 13.3, 34.0, 41.9, 55.2, 113.9, 130.0, 130.2, 158.6, 166.8; MS (*m*/*z*, %) 253 (M^+, 98), 121 (100), 100 (60), 72 (29). Exact MS calcd for $C_{13}H_{19}NO_2S$: 253.1137. Found: 253.1141.

4.2.4. *S*-Ethyl perhydroazepin-1-carbothioate (Molinate,[3] 1e). Oil; IR (neat) 2930, 1650, 1405, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, *J*=7 Hz, 3H), 1.54–1.60 (m, 4H), 1.73 (br s, 4H), 2.91 (q, *J*=7 Hz, 2H), 3.45 (t, *J*=6 Hz, 2H), 3.56 (t, *J*=6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 24.5, 26.9, 27.2, 27.9, 28.4, 47.3, 47.6, 167.8; MS (*m*/*z*, %) 187 (M^+, 73), 126 (100), 83 (24), 55 (36). Exact MS calcd for $C_9H_{17}NOS$: 187.1031. Found: 187.1021.

4.2.5. *S*-4-Chlorobenzyl perhydroazepin-1-carbothioate (NTN-7072,[3] 1f). Mp 58.0 °C (60–62 °C[4]); IR (melt) 2930, 1635, 1405, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54–1.57 (m, 4H), 1.73 (br s, 4H), 3.42 (q, *J*=6 Hz, 2H), 3.56 (t, *J*=6 Hz, 2H), 4.11 (s, 2H), 7.23–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 27.2, 27.8, 28.4, 33.9, 47.6, 47.7, 128.6, 130.3, 132.8, 137.2, 166.9; MS (*m*/*z*, %) 283 (M^+, 63), 126 (100), 125 (36), 55 (17). Exact MS calcd for $C_{14}H_{18}ClNOS$: 283.0798. Found: 283.0795.

4.2.6. *S*-Ethyl *N*,*N*-diethylthiocarbamate (Ethiolate,[3] 1g). Oil; IR (neat) 2975, 2935, 1650, 1405, 1250, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, *J*=7 Hz, 6H), 1.29 (t, *J*=7 Hz, 3H), 2.90 (q, *J*=7 Hz, 2H), 3.38 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 15.4, 24.5, 41.8, 167.2; MS (*m*/*z*, %) 161 (M^+, 26), 100 (100), 72 (83). Exact MS calcd for $C_7H_{15}NOS$: 161.0874. Found: 161.0859.

4.2.7. *S*-Ethyl *N*,*N*-di-*n*-propylthiocarbamate (EPTC,[3] 1h). Oil; IR (neat) 2965, 1650, 1405, 1220, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J*=7 Hz, 6H), 1.28 (t, *J*=7 Hz, 3H), 1.60 (br s, 4H), 2.90 (q, *J*=7 Hz, 2H), 3.27 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 15.3, 21.2, 24.6, 49.1, 167.7; MS (*m*/*z*, %) 189 (M^+, 28), 132 (24), 128 (100), 89 (20), 86 (80). Exact MS calcd for $C_9H_{19}NOS$: 189.1187. Found: 189.1185.

4.2.8. *S*-Ethyl *N*-cyclohexyl-*N*-ethylthiocarbamate (Cycloate,[3] 1i). Oil; IR (neat) 2935, 1650, 1405, 1230, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03–1.80 (m, 16H), 2.90 (q, J=7 Hz, 2H), 3.31 (q, J=7 Hz, 2H), 3.65 (br s, 0.5H), 4.17 (br s, 0.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2, 15.6, 24.3, 25.3, 25.7, 30.7, 38.2, 56.8, 167.1; MS (*m*/*z*, %) 215 (M^+, 38), 154 (100), 83 (98), 55 (31). Exact MS calcd for $C_{11}H_{21}NOS$: 215.1344. Found: 215.1331.

4.3. General procedure for the synthesis of ethyl *N*,*N*-diethylthiocarbamate (Ethiolate,[3] 1g) in large scale

A solution of diethylamine (**2a**) (20.7 mL, 200 mmol), powdered sulfur (3.21 g, 100 mmol) and K_2CO_3 (20.7 g, 150 mmol) in DMSO (50 mL) was very vigorously stirred under carbon monoxide (1 atm) at 20 °C for 22 h. Ethyl iodide (8.80 mL, 110 mmol) was added carefully at 0 °C under argon atmosphere into the DMSO solution of thiocarbamate salt (**3a**). The solution was stirred for additional 2 h at 20 °C. The resulting mixture was then poured slowly into 1 N HCl (100 mL), and extracted with *t*-butyl methyl ether (100, 50 mL×2). After evaporation of solvents and purification by vacuum distillation, *S*-ethyl *N*,*N*-diethylthiocarbamate (Ethiolate,[3] **1g**) was obtained in 94% yield (15.2 g).

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6. Very recently, *S*-alkyl thiocarbamtes (**1**) were synthesized by the reaction of trichloroacetyl chloride with amines (**2**) and thiols[7].
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Polymer-supported thioanisole: a versatile platform for organic synthesis reagents

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Abstract—A new cross-linked polystyrene-supported thioanisole reagent is reported. This reagent incorporates the flexible *J*anda*J*el™ cross-linker and can be treated with methyl trifluoromethanesulfonate to form the corresponding sulfonium salt. This salt can in turn be deprotonated to form a polymer-supported sulfur ylide that is able to react with aldehydes and ketones to form epoxides. The thioanisole reagent can also be oxidized to form an insoluble sulfoxide reagent that is useful in Swern oxidation reactions. In these reactions, the polymer-supported thioanisole-based reagents can be recovered, regenerated and reused.

1. Introduction

Recent years have seen polymer-supported reagents and catalysts become common tools for organic synthesis in what is known as polymer-assisted synthesis since they can simplify product isolation and purification.[1] In this context, both insoluble[2] and soluble[3] polymers may be used as the support. The utility and power of such reagents has been exquisitely demonstrated by Ley et al. in their syntheses of several complex natural products using these reagents exclusively.[4] In order to broaden the range of reactions capable of being performed using such polymer-assisted techniques, new polymer-supported reagents are continually being developed.

As part of our ongoing research into developing such reagents, we have recently reported some non-cross-linked polystyrene-based sulfoxide reagents that are useful in Swern oxidation reactions.[5] Due to the fact that these polymeric reagents require a precipitation operation prior to their removal from reaction mixtures by filtration, we sought to prepare an insoluble analogous cross-linked reagent so that filtration can be performed directly. We also sought to examine the utility of such a polymer in the sulfide oxidation state by converting it to other organic synthesis reagents. Herein we report our progress in developing an insoluble polymer-supported thioanisole that can be converted into reagents for oxidation and epoxide synthesis reactions.

2. Results and discussion

Previously, cross-linked polymer-supported thioanisole has been prepared by bromination of preformed polystyrene beads followed by lithiation and trapping of the resulting aryl lithium intermediate with dimethyl disulfide.[6,7] Since this procedure requires a sequence of three reactions that must proceed predictably in high yield with no side products being formed in order to obtain a homogeneous polymer-supported reagent, we chose to incorporate the sulfide moieties into our reagent by using a functional styrene monomer[8] in the polymerization process. Using this strategy allows for the direct preparation of a maximally loaded and homogeneous reagent in which all of the non-cross-linker aryl rings are derivatized with the desired methyl sulfide groups. This is the method that we previously employed in the development of the *J*anda*J*el™ polystyrene resins[9,10] incorporating a variety of functional monomers.[11]

Therefore, we prepared thioanisole monomer **1** according to the literature procedure from 4-bromostyrene (Scheme 1).[12] This was suspension co-polymerized[13] with 2 mol% of the flexible *J*anda*J*el™ cross-linker to afford polymer-supported thioanisole **2** (*J*anda*J*el™-SMe). By preparing reagent **2** in this manner, the loading level (5.9 mmol/g) could be maximized and thereby reducing the amounts of polymeric reagent and solvent necessary for performing the subsequent reactions.

In order to examine the versatility of **2** as a platform for sulfur-based organic synthesis reagents, it was treated separately with MeOTf and *tert*-butyl hydroperoxide (TBHP) in the presence of *p*-TSA to afford sulfonium salt **3** and sulfoxide **4**, respectively (Scheme 1). Reagent **3** was

Keywords: Thioanisole; *J*anda*J*el™; Epoxide.
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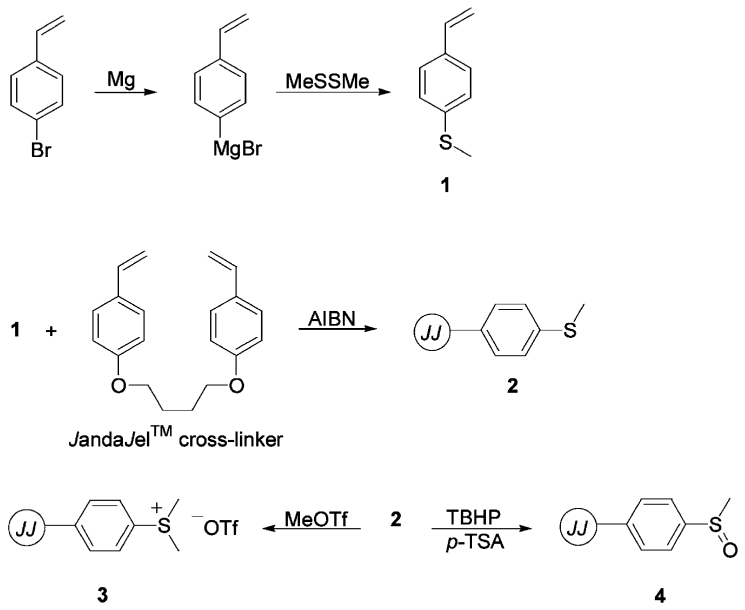


Scheme 1. Synthesis of monomer **1** and polymers **2**–**4**.

prepared in order to serve as a polymer-supported precursor to the Corey–Chaykovsky methylide reagent[14] which can be used to convert carbonyl groups into epoxide moieties.[7,15,16] Reagent **4** was prepared to serve as a polymer-supported analog of dimethyl sulfoxide for use in Swern oxidation reactions.[17]

Reagent **3** was deprotonated with sodium hydride under conditions similar to those reported by Fréchet et al.[7] for deprotonation of sulfonium salts using potassium *tert*-butoxide, and the resulting ylide was allowed to react with a range of aldehydes and ketones to afford the corresponding epoxides (Table 1). In all cases, the starting carbonyl compound was completely consumed and product was isolated in good to excellent yield. In the reaction of the ylide from **3** with *trans*-cinnamaldehyde, only 1,2-addition was observed (Table 1, entry 5). Furthermore, reactions with ketones afforded slightly higher yields (Table 1, entries 6–8) than did reactions with aldehydes (Table 1, entries 1–5).

In order to examine the recyclability of the polymer recovered from the epoxide synthesis reactions, the reaction represented in Table 1, entry 6 was performed five times using the same sample of **3**. Since **3** was used as the excess reagent in these reactions, the polymer recovered at the end of the reaction was a mixture of **2** and **3**. Therefore, at the end of each reaction cycle, the polymer was recovered, washed and reacted with MeOTf in order to convert it to pure **3**. This was then reused for epoxide formation in a total of 5 cycles (Table 2). As can be seen, essentially identical yields were observed for each reaction, clearly indicating that **3** can be regenerated and reused without any decrease in effectiveness.

Swern oxidation reactions using polymer **4** were examined next. A cross-linked polystyrene-based sulfoxide polymer related to **4** has been previously used in triphasic catalysis,[18] and in alcohol oxidation reactions involving chlorine activation.[6] Additionally, other polymer-supported sulfoxide reagents have been used previously in Swern oxidation reactions.[19,20] However, these reagents required multi-step synthesis to produce polymers that were not maximally functionalized with sulfoxide moieties, as is **4**.

Table 1. Epoxide synthesis reactions using **3**

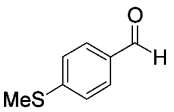
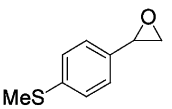
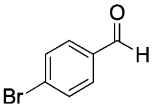
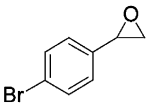
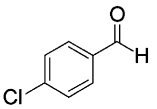
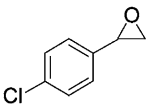
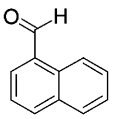
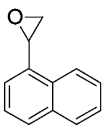
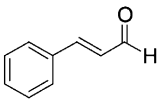
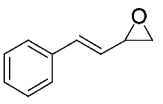
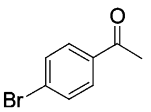
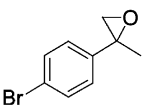
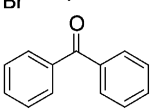
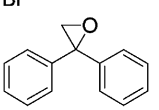
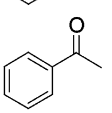
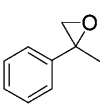
Entry	Substrate	Product	Yield (%)
1			69
2			85
3			80
4			70
5			65
6			97
7			98
8			97

Table 2. Yields of 2-(4-bromophenyl)-2-methyloxirane from 4′-bromoacetophenone using recycled **3**

Cycle number	Yield (%)
1	98
2	97
3	99
4	98
5	97

Therefore, **4** should be more efficient to use since the nature of its functionalization is known precisely and its relatively higher concentration of sulfoxide moieties means that less reagent and solvent are required for the oxidation reactions.

A variety of secondary alcohols were oxidized using excess **4** and oxalyl chloride. The results of these reactions are summarized in Table 3. In these reactions, the starting material was completely consumed and the yield reported represents isolated product. In all cases, the desired product could be isolated in essentially pure form from the reaction mixture in satisfactory yield after several filtration operations.

To assess the reusability of the polymer recovered from the oxidation reactions, the reaction represented in Table 3, entry 1 was performed five times using the same sample of **4**. Since the polymer recovered at the end of the reaction was a mixture of **2** and **4**, the sample was reoxidized with

Table 3. Swern oxidation reactions using reagent **4**

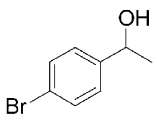
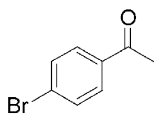
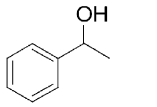
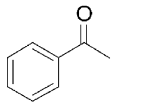
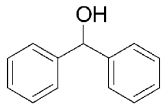
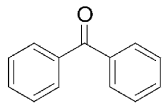
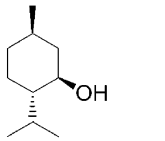
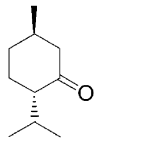
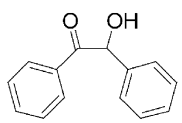
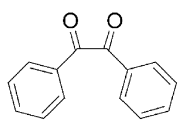
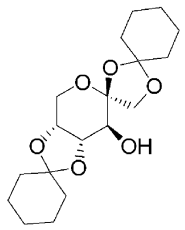
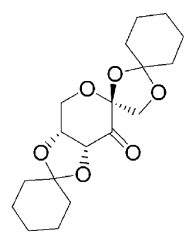
Entry	Alcohol	Product	Yield (%)
1			85
2			80
3			70
4			60
5			65
6			63

Table 4. Yields of 4′-bromoacetophenone from 1-(4-bromophenyl)ethanol oxidation using recycled **4**

Cycle number	Yield (%)
1	80
2	76
3	70
4	67
5	65

TBHP and *p*-TSA to regenerate homogeneous **4**. As can be seen in Table 4, only a modest decrease in product yield was observed in each subsequent cycle. Regardless of this, the results are acceptable because in each case the product was isolated in a pure state, and in polymer-assisted synthesis, generally product yield is of secondary importance to product purity.

3. Conclusions

In summary, we have developed a cross-linked polymer-supported thioanisole platform (**2**) that can serve as a foundation for the preparation various sulfur-based reagents for organic synthesis. We have used **2** to prepare a precursor of a sulfur ylide (**3**) and a sulfoxide (**4**) for oxidation reactions. These reagents can be used repeatedly with only modest decrease in their effectiveness. Furthermore, it is expected that **2** can serve as the starting material for additional polymer-supported reagents and studies directed at developing these are currently underway.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Tetrahydrofuran was distilled under a N_2 atmosphere over sodium and benzophenone. Dichloromethane and dimethyl sulfoxide were distilled under a N_2 atmosphere and in vacuo, respectively, over calcium hydride. Merck silica gel 60 (230–400 mesh) was used for chromatography. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. The NMR spectra were recorded using a Bruker DRX 400 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer. Elemental analyses were conducted at the Analytical and Testing Center of the Shanghai Institute of Organic Chemistry.

4.1.1. 4-Vinylphenyl methyl sulfide (1). Methyl disulfide (21.6 g, 229.0 mmol) was added slowly at 0 °C to a solution of the Grignard reagent prepared from 4-bromostyrene (28.0 g, 153.0 mmol) and Mg (7.4 g, 305.0 mmol) in dry THF (200 mL). The mixture was stirred at rt for 3 h. At this time, the reaction mixture was diluted with diethyl ether (500 mL), and then washed sequentially with water (250 mL), 10% aqueous HCl (250 mL), saturated aqueous

$NaHCO_3$ (250 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **1** as a clear, colorless liquid (16.0 g, 106.5 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 5.21 (dd, 1H, J=10.9, 0.9 Hz), 5.70 (dd, 1H, J=17.6, 0.9 Hz), 6.68 (dd, 1H, J=17.6, 10.9 Hz), 7.17–7.40 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 113.1, 126.6 (4C), 134.5, 136.2, 138.0. HR EI-MS: calcd for $C_9H_{10}S$, 150.0503; found, 150.0500.

4.1.2. *J*anda*J*el™-SMe (2). A solution of acacia gum (6.0 g) and NaCl (3.8 g) in warm deionized water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N_2 for 2 h.[21] A solution of **1** (10.0 g, 6.7 mmol), cross-linker (0.4 g, 1.5 mmol) and AIBN (0.2 g, 1.3 mmol) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. The mixture was heated at 85 °C for 20 h. The crude polymer was collected and washed with hot water (3×100 mL) and then placed in a Soxhlet extractor and washed with THF for 1 day. The beads were recovered, washed with methanol (250 mL), diethyl ether (250 mL), and hexanes (250 mL). The shrunken beads **2** (9.0 g, 90%) were dried in vacuo. Elemental analysis was used to determine the sulfur content (18.9%) and thus the loading level of 5.9 mmol S/g of **2**.

4.1.3. *J*anda*J*el™-S(Me)$_2$OTf (3). To a magnetically stirred suspension of **2** (3.0 g, 17.7 mmol) in CH_2Cl_2 (30 mL) at rt was added MeOTf (4.4 g, 27.0 mmol). Stirring was continued for 24 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, methanol, diethyl ether, and hexanes. The shrunken beads **3** (6.0 g) were dried in vacuo. Elemental analysis was used to determine the sulfur content (18.3%) and thus the loading level of 2.9 mmol S/g of **3**.

4.1.4. *J*anda*J*el™-S(O)Me (4). To a magnetically stirred suspension of **2** (5.0 g, 29.5 mmol) in CH_2Cl_2 (40 mL) at rt was added 70% TBHP (19.3 g, 150.0 mmol) and *p*-TSA (5.6 g, 30.0 mmol). Stirring was continued for 24 h at rt, at which time the resin was filtered off and washed sequentially with dichloromethane, methanol, diethyl ether, and hexanes. The shrunken beads **4** (5.5 g) were dried in vacuo. Elemental analysis was used to determine the sulfur content (15.4%) and thus the loading level of 4.8 mmol S/g of **4**. Previous reports using this oxidation system indicate that oxidation of the sulfide stops at the sulfoxide oxidation state and that no sulfone is formed.[5,18c]

4.2. General procedure for epoxide synthesis

A solution of the carbonyl compound (1.0 mmol) in anhydrous DMSO (4 mL) and anhydrous THF (1 mL) was added to a mixture of **3** (1.0 g, 2.9 mmol) and 60% NaH (0.12 g, 3.0 mmol) in anhydrous THF (2 mL) that was stirring at 0 °C. The mixture was slowly warmed to rt after the reaction was complete. The suspension was then filtered and the resin was washed with addition diethyl ether (3×10 mL). The combined filtrate was treated with water (40 mL) and extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was filtered through a plug of silica gel to provide the essentially pure epoxide product (Table 1).

4.3. Procedure for regeneration of polymer 3

The polymer mixture (**2** with **3**, ca. 1.0 g) recovered from the epoxide synthesis reaction was treated with MeOTf (1.5 g, 8.9 mmol) in CH_2Cl_2 (20 mL) and stirred for 24 h at rt. The resin was recovered and washed sequentially with dichloromethane, methanol, diethyl ether and hexanes. The shrunken beads **3** were dried in vacuo and reused in the epoxidation reaction. The same sample of **3** was used in all 5 cycles reported in Table 2 using this procedure.

4.4. General procedure for alcohol oxidation

A suspension of **4** (1.0 g, 4.8 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled to −70 °C and oxalyl chloride (0.6 g, 4.4 mmol) was added dropwise. After 30 min, a solution of the alcohol (1.2 mmol) in anhydrous CH_2Cl_2 was added. The mixture was stirred at low temperature for 1 h and then triethylamine (0.7 g, 7.2 mmol) was added. The solution is kept at −40 °C for 1 h more and then allowed to warm to rt. The suspension was then filtered and the resin was washed with addition CH_2Cl_2 (3×10 mL). The combined filtrate was concentrated in vacuo and the crude residue was filtered through a plug of silica gel to provide the essentially pure oxidation product (Table 3).

4.5. Procedure for regeneration of polymer 4

The polymer mixture (**2** with **4**, ca. 1.0 g) recovered from the oxidation reaction was treated with 70% TBHP (3.1 g, 24.0 mmol) and *p*-TSA (0.9 g, 4.8 mmol) in CH_2Cl_2 (20 mL) and stirred at rt for 24 h. The beads were recovered, and washed sequentially with dichloromethane, methanol, diethyl ether and hexanes. The shrunken beads **4** were dried in vacuo and reused in the oxidation reaction. The same sample of **4** was used in all 5 cycles reported in Table 4 using this procedure.

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Autoxidation of isotachysterol

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Abstract—Isotachysterol, the acid-catalyzed isomerization product of vitamin D_3, produces seven previously unknown oxygenation products in a self-initiated autoxidation reaction under atmospheric oxygen in the dark at ambient temperature. They are (5*R*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (**6a**), (5*S*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (**6b**), (10*R*)-9,10-secocholesta-5,7,14-trien-3β,10-diol (**7a**), (10*S*)-9,10-secocholesta-5,7,14-trien-3β,10-diol (**7b**), (7*R*,10*R*)-7,10-epoxy-9,10-secocholesta-5,8(14)-dien-3β-ol (**8**), 5,10-epidioxyisotachysterol (**9**) and 3,10-epoxy-5-oxo-5,10-*seco*-9,10-secocholesta-6,8(14)-dien-10-ol (**10**). The formation of these products is explained in terms of free radical peroxidation chemistry.

1. Introduction

The chemistry and biochemistry of cholecalciferol (vitamin D_3, **1**) have been extensively studied for over half a century due to the great diversity of its chemistry and, especially, its important roles in calcium regulation, immunological regulation and inducing cancer cell differentiation.[1] Over 30 natural metabolites of vitamin D_3 have been identified from human beings and animals[2] and much more synthetic analogues, especially those of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), have been made to explore their anticancer potentials and other biological activities.[3] Structural alterations of vitamin D_3 by metabolism mostly occur at the 1α-position and the side chain,[2] while the oxidation of the conjugated triene part has scarcely been reported.[4–6] The unique epoxide found in natural metabolites of vitamin D_3 is 7,8-epoxy-25-hydroxy-19-nor-10-oxovitamin D_3 (**2**).[4] Takayama and co-workers[5] found that **1** could be regio- and stereoselectively oxidized by *m*-chlorobenzoic acid and *tert*-butyl hydroperoxide catalyzed by $VO(acac)_2$, giving (7*R*)-7,8-epoxyvitamin D_3 (**3**) and (5*S*)-5,6-epoxyvitamin D_3 (**4**) respectively. Photosensitized oxidation of vitamin D_3 by singlet oxygen has also been reported.[6] However, autoxidation of vitamin D_3 and its isomers has not been reported previously. It is well-known that vitamin D_3 is relatively stable in the air at ambient temperature,[6a] while its acid-catalyzed isomerization product, isotachysterol (**5**), is very labile in the air even in the dark.[7,8] However, no effort has been made previously to identify the complex autoxidation products of isotachysterol. We report herein the isolation and identification of the principal autoxidation products of isotachysterol, including (5*R*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (**6a**), (5*S*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (**6b**), (10*R*)-9,10-secocholesta-5,7,14-trien-3β,10-diol (**7a**), (10*S*)-9,10-secocholesta-5,7,14-trien-3β,10-diol (**7b**), (7*R*,10*R*)-7,10-epoxy-9,10-secocholesta-5,8(14)-dien-3β-ol (**8**), 5,10-epidioxy-isotachysterol (**9**) and 3,10-epoxy-5-oxo-5,10-*seco*-9,10-secocholesta-6,8(14)-dien-10-ol (**10**). The formation of these products is discussed in terms of free radical peroxidation chemistry.

2. Results

Isotachysterol (**5**) was prepared by HCl-catalyzed isomerization of vitamin D_3 (**1**) in methanol.[8] The pale yellow oil of **5** was laid in a small beaker at ambient temperature in the dark. **5** was found oxidized rapidly to a very complex mixture as monitored by TLC and after 1–2 days only a little **5** was left. Oxidation by bubbling oxygen to a benzene solution of **5** at ambient temperature gave the similar result together with some polymeric/oligomeric materials which deposited out of the solution, particularly in the later stage of the oxidation. Addition of 2,2′-azobisisobutyronitrile (AIBN) to the benzene solution of **5** significantly accelerated the reaction, suggesting that the reaction proceeded by a free radical chain mechanism. The soluble materials were separated by reverse phase HPLC. Figure 1 shows the chromatogram of the reaction mixture obtained at the early stage (8 h) of the autoxidation of **5** at room temperature in benzene solution, corresponding to ca. 50% conversion of **5**. UV–Vis spectra in the range of 190–400 nm were obtained for all major products. The mixture was also examined at

Keywords: Vitamin D_3; Isotachysterol; Autoxidation; Epoxide; Dioxetane.
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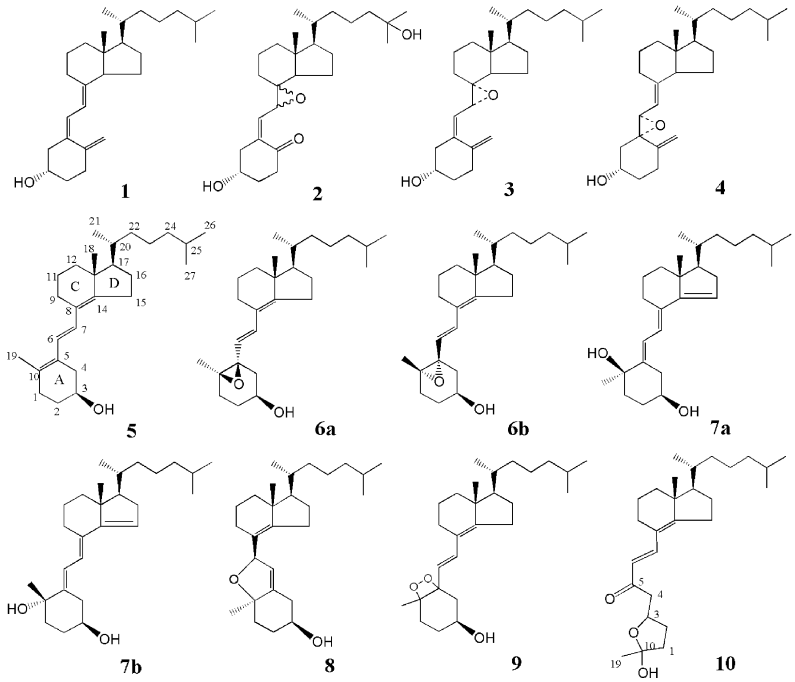


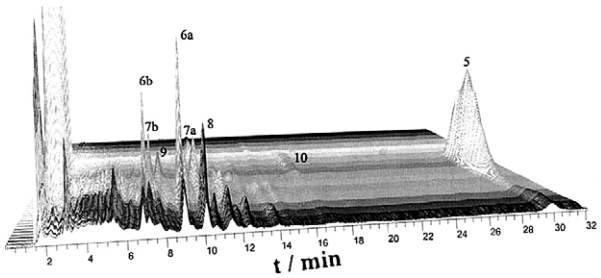


Figure 1. 3D HPLC diagram recorded from the reaction mixture of the autoxidation of isotachysterol in benzene at room temperature for 8 h on a Phenomenex Nucleosil C18 column (5 μm) eluted with MeOH–H_2O (88:12 v/v) at a flow rate of 1 ml/min. *x*-axis: retention time (min), *y*-axis: UV absorption; *z*-axis: intensity of the UV absorption. The peak numbers correspond to the numbers of compounds.

various stages of oxidation by coupled LC–MS using the same column and solvent system. The total ion current (TIC) chromatograms were similar to those obtained in the analytical HPLC, except of different peak intensities.

The peak 5 with the longest retention time (R_t) of 29.9 min and the molecular ion peak of 385.3463 ($C_{27}H_{44}O$+H requires 385.3470) was identified as unreacted isotachysterol (**5**) by comparing its R_t and UV spectrum with that of the authentic sample. The peaks 6a and 6b with R_t of 9.0 and 6.8 min respectively, gave molecular ion peaks of 401.3413 and 401.3422 respectively, corresponding to a same molecular formula with one more oxygen than **5** ($C_{27}H_{44}O_2$+H requires 401.3420). The UV spectra of **6a** and **6b** were almost identical, showing a band at 248 nm which is characteristic of conjugated double bonds. The comparison of their ^{1}H and ^{13}C NMR spectra (Table 1) with those of vitamin D_3 and its metabolites[9] and with that of isotachysterol[10] clearly demonstrates that **6a** and **6b** are 5,10-epoxides of **5** since the remarkable changes on ^{13}C chemical shifts are only observable for 5- and 10-Cs (from double bond carbons to epoxy carbons) and on ^{13}C and ^{1}H chemical shifts for 19-Me, and to a less extent, for 4-C. The coupling constants of 3-H are 8.0, 8.0, 4.5 and 4.5 Hz for **6a**, and 9.6, 9.6, 4.7 and 4.7 Hz for **6b**, respectively, demonstrating that the 3-H is axial in both **6a** and **6b**. The NOESY spectrum of **6a** showed clear cross peaks between 1α-H, 3α-H and 19-CH_3 and between 6-H, 1α-H and 19-CH_3 (Fig. 2), indicating that the epoxy ring and the 3-hydroxyl locate at the same side of the molecule. On the other hand, clear NOESY correlations between 6-, 4β-, 2β-, 1β-Hs and 19-CH_3 of **6b** (Fig. 2) demonstrates that the epoxy ring and the 3-hydroxyl are at the opposite sides of the molecule. In addition, epoxidation of isotachysterol (**5**) with anhydrous *tert*-butyl hydroperoxide (TBHP) in benzene in the presence of $VO(acac)_2$ (0.01 equiv.) at 0 °C gave **6a** as the sole epoxy product (yield 45%). It is well known that epoxidation of homoallylic alcohols with TBHP/$VO(acac)_2$ produces stereospecifically *syn*-epoxy alcohols.[11] Therefore, **6a** and **6b** are assigned as (5*R*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (5β,10-epoxy-isotachysterol) and (5*S*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol (5α,10-epoxy-isotachysterol) respectively.

The peaks 7a and 7b with R_t of 10.6 and 7.1 min respectively, gave molecular ion peak of 401.3416 and 401.3411 respectively, corresponding to a same molecular formula with one more oxygen than **5** ($C_{27}H_{44}O_2$+H requires 401.3420). Both of them exhibited an UV absorption maximum at 278 nm, suggesting the existence of a conjugated triene chromophore. The comparison of their ^{1}H and ^{13}C NMR spectra (Table 1) with those of isotachysterol (**5**)[10] showed remarkable differences on ^{13}C chemical shifts of 5-, 10- and 15-Cs, and to a less extent, on 16 and 19-Cs, which suggests that the 5(10), 6, 8(14)-triene structure in **5** might change to a 5,7,14-triene system in both **7a** and **7b**. The A-ring structure of **7a** and **7b** was confirmed by their gCOSY spectra which exhibited spin coupling network between the hydroxymethine proton 3-H and 4α-,

Table 1. ^{1}H and ^{13}C NMR chemical shifts of compounds **5**–**10** (acetone-d_6)[a]

Carbon	5	6a	6b	7a	7b	8	10	Proton	5	6a	6b	7a	7b	8	10
1	32.3	33.7	35.4	38.7	38.8	35.0	39.0	1α	1.82	1.42	1.87	1.42	1.51	2.13	1.68
								1β	2.17	1.86	1.46	1.89	1.79	1.53	1.98
2	32.1	30.4	32.7	31.5	32.1	31.2	31.7	2α	1.86	1.73	1.82	1.86	1.90	1.62	2.08
								2β	1.48	1.64	1.38	1.74	1.51	1.80	1.75
3	67.3	67.3	66.7	69.7	69.7	66.5	77.5	3α	3.81	3.81[b]	3.97[b]	3.62[b]	3.52[b]	4.06[b]	4.48
4	35.5	32.5	43.3	35.2	35.4	34.4	48.9	4α	2.53	1.76	1.95	2.65	3.01	2.28	2.95
								4β	2.04	1.88	1.60	2.55	2.04	2.51	2.69
5	127.1	77.6	77.1	144.2	143.8	142.9	198.7								
6	124.6	129.5	131.2	118.0	116.4	122.3	124.4	6	6.53	5.73	5.82	6.41	6.59	5.05	6.12
7	125.9	128.6	128.0	120.4	119.3	83.2	142.2	7	6.36	6.61	6.45	6.39	6.38	5.48	7.51
8	125.4	124.5	124.5	136.5	135.1	122.3	124.5								
9	26.3	26.1	26.1	28.2	27.7	25.3	26.2	9α	2.38	2.36	2.35	1.80	1.83	2.21	2.57
								9β	2.47	2.47	2.47	2.80	2.81	2.42	2.62
10	131.6	73.1	73.8	71.6	71.7	88.1	108.2								
11	27.6	27.6	27.6	22.8	21.9	28.1	27.3	11α	1.92	1.89	1.90	1.77	1.82	1.92	1.97
								11β	1.46	1.47	1.46	1.64	1.68	1.45	1.53
12	38.6	38.0	38.0	41.6	42.8	38.3	37.3	12α	1.18	1.19	1.18	1.64	1.45	1.20	1.23
								12β	2.01	2.01	1.98	2.02	2.00	1.98	2.07
13	44.6	44.4	44.4	47.9	47.0	44.9	45.5								
14	149.3	148.1	148.8	153.9	153.1	144.4	161.4								
15	24.8	25.0	25.0	119.9	118.9	23.2	24.4	15α	2.04	1.98	1.93	5.55	5.55	1.98	2.20
								15β	2.24	2.12	2.15			2.09	1.99
16	19.6	19.6	19.6	36.5	35.6	20.0	19.2	16α	1.90	2.01	2.01	2.16	2.20	1.96	1.80
								16β	1.74	1.75	1.73	1.90	1.97	1.65	2.03
17	57.2	57.1	57.2	59.5	58.8	56.7	56.8	17	1.18	1.19	1.20	1.65	1.64	1.17	1.25
18	18.4	18.4	18.4	17.6	16.7	18.8	18.3	18	0.90	0.90	0.90	0.90	0.88	0.86	0.95
19	18.9	23.9	23.8	27.3	27.3	23.4	22.1	19	1.75	1.08	1.18	1.33	1.33	1.25	1.33
20	35.3	35.3	35.3	39.7	38.8	35.4	35.2	20	1.50	1.48	1.51	1.50	1.48	1.50	1.58
21	19.4	19.3	19.4	21.4	20.4	19.4	19.3	21	0.97	0.97	0.97	1.04	0.94	0.97	0.98
22	36.6	36.6	36.6	36.6	36.6	36.7	36.5	22	1.10[c]	1.43	1.43	1.41	1.42	1.14[c]	1.42
									1.36[c]					1.44[c]	
23	24.4	24.3	24.3	24.3	24.3	24.4	24.4	23	1.10[c]	1.36	1.10[c]	1.08	1.10	1.10	1.12
									1.43[c]		1.36[c]				
24	40.1	40.2	40.1	43.6	42.8	40.2	40.2	24	1.17	1.15	1.11	1.16	1.17	1.18	1.19
25	28.6	28.6	28.6	28.6	28.6	28.8	28.6	25	1.50	1.48	1.52	1.50	1.52	1.53	1.54
26	22.8	23.0	23.0	23.2	23.0	23.0	23.0	26	0.86	0.87	0.86	0.87	0.87	0.87	0.86
27	23.0	22.8	22.8	22.8	23.0	22.8	22.8	27	0.86	0.87	0.86	0.87	0.87	0.87	0.86

[a] Data for compound **9** not included, see text.
[b] *J* values see text.
[c] α or β protons.

4β-, 2α-, 2-β, 1α- and 1β-Hs, and by their HMBC spectra which showed correlations between 19-CH_3 and 1-, 5- and 10-Cs. The structure of the C ring was confirmed by their gCOSY spectra which showed correlations between the allylic 9β-H and 9α-, 11α-, 11β-, 12α- and 12β-Hs, and by their HMBC spectra which show correlations between the olefinic 7-H and 8-, 9- and 14-Cs. The structure of the D ring was confirmed by their gCOSY spectra which showed correlations of the olefinic 15-H with 16α- and 16β-Hs, and 17-H with 16α-H, together with the HMBC correlation of 18-CH_3 with 13- and 14-Cs. The structure of the seco-B ring was confirmed by their HMBC spectra which showed correlations between the olefinic 6-H and 5-, 7-, 8- and 10-Cs. The coupling constants of 3-H (8.0, 8.0, 4.4 and 4.4 Hz for **7a**, and 9.2, 9.2, 4.6 and 4.6 Hz for **7b**, respectively) suggest that the 3-H is axial and the A-ring of **7a** and **7b** might be partitioned between a 30/70 and 24/76 equilibrium mixture of chair conformers favoring an α chair with the 3β-OH equatorially oriented.[9,12] The NOE enhancement was observed for the 7-H with 4α-H and 15-H, and for the 6-H with 9β-H and 19-CH_3 in both of **7a** and **7b**, indicating the triene configuration of the two compounds to be (5*E*, 7*E*, 14*E*), which were also supported by the coupling constant of the olefinic protons ($J_{6,7}$=12.0 Hz). The difference between **7a** and **7b** were observed only in their NOESY spectra which showed clear correlations between 3α-H and 4α-, 2α- and 1α-Hs, and between 19-CH_3 and 6-H in **7a**, while no such correlations occurred in **7b**. Instead, clear NOESY correlations were observed between 19-CH_3 and 4β-, 2β- and 1β-Hs in **7b** (Figure 2). This demonstrates that **7a** and **7b** are 10-epimers and the 19-CH_3 is equatorial and α-oriented in **7a**, while is axial and β-oriented in **7b**. The comparatively downfield shift of the chemical shifts of 2β-H and 4β-H(δ 1.74 and 2.55, respectively) in **7a** compared to those of **7b** (δ 1.51 and 2.04, respectively) also indicated that the 10-OH is axial and β-oriented in **7a** and equatorial and α-oriented in **7b**. Therefore, **7a** and **7b** were assigned as (10*R*)-9,10-secocholesta-5,7,14-trien-3β,10-diol and (10*S*)-9,10-secocholesta-5,7,14-trien-3β,10-diol, respectively.

The peak 8 with R_t of 10.1 min and the molecular ion peak of 401.3411 corresponds to a molecule with one more oxygen than **5**, same as **6** and **7** ($C_{27}H_{44}O_2$+H requires 401.3420). The UV absorption maximum of 206 nm indicates the absence of conjugated double bonds in the compound. The comparison of its ^{1}H and ^{13}C NMR spectra (Table 1) with those of isotachysterol (**5**)[10] showed remarkable differences on ^{13}C chemical shifts of 7- and 10-Cs, from olefinic carbons in **5** to oxygen-connecting

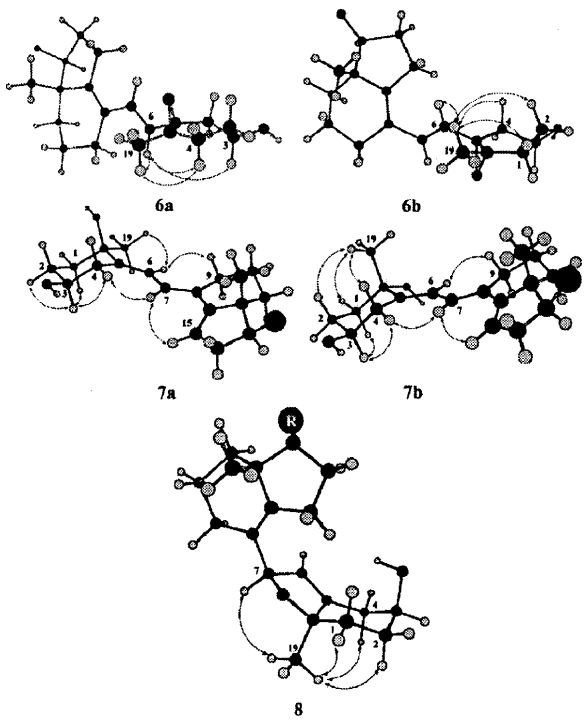


Figure 2. Principal NOE correlations of **6a**, **6b**,**7a**,**7b** and **8** presented with ball-and stick representations of the MM2-optimized structures.

quaternary carbons in **8**, suggesting that **8** is a 7,10 epoxide of **5** containing a dihydofuran ring. The structure of **8** was fully assigned by its 2D NMR spectroscopy. The structure of the A-ring was confirmed by its gCOSY spectrum (Fig. 3) in which the hydroxymethine proton 3α-H (δ 4.06) correlated with 2α-, 2β-, 4α- and 4β-Hs, and the 2β-H correlated with 1α- and 1β-Hs, and by its gHMBC spectrum (Fig. 4) which shows correlations between 19-CH_3 and 1-, 5- and 10-Cs. The dihydrofuran ring was supported by the HMBC correlations of the olefinic 6-H with 4-, 5-, 7- and 10-Cs. The structure of the C- and D-rings was confirmed by its H,H-COSY correlations of 9β-, 9α-, 11α-, 11β-, 12α- and 12β-Hs, of 15α-, 15β-, 16α-, 16β- and 17α-Hs, and by its HMBC correlations between 18-CH_3 and 12-, 13- and 14-Cs. The connection between the tetrahydrofuran ring and C-ring was supported by the HMBC correlations between the oxygen-connecting 7-H and 6-, 8- and 14-Cs. The NOESY 1D spectrum showed clear correlations between 19-CH_3 and 1α-, 2α- and 4α-Hs, indicating that the 19-CH_3 is axial and the 3-H is equatorial which is consistent with the coupling constant of 3-H (3.2, 3.2, 2.4 and 2.4 Hz). The NOESY 1D spectrum also exhibited a correlation between the 19-CH_3 and 7-H, demonstrating that they are located on the same side of the dihydrofuran ring. Thus **8** was assigned as (7*R*,10*R*)-7,10-epoxy-9,10-secocholesta-5,8(14)-dien-3β-ol.

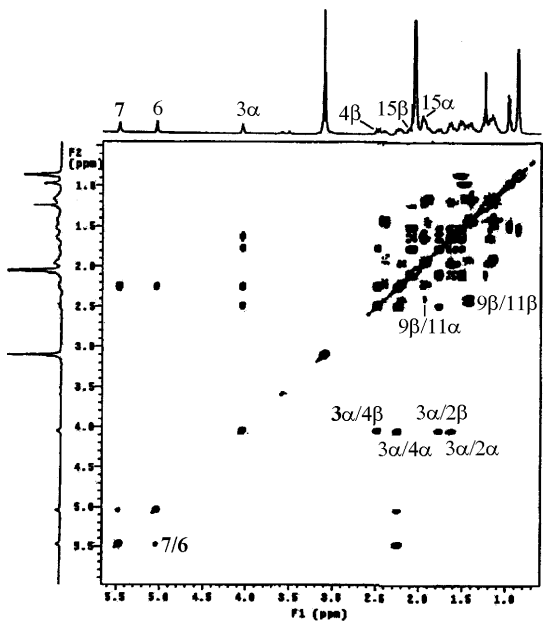


Figure 3. The gCOSY spectrum of **8**.

The peak 9 with R_t of 7.7 min and the molecular ion peak of 439.3211 corresponds to a molecule with two more oxygens than **5** ($C_{27}H_{44}O_3$+Na requires 439.3188). The UV absorption maximum at 296 nm suggested the presence of an extended conjugated system. However, this compound **9** was unstable and gradually converted to a new compound **10**, i.e., peak 10 with R_t of 17.0 min and λ_{max} at 305 nm, during the process of semipreparative HPLC separation of **9**. **10** gave the molecular ion peak of 417.3373 corresponding to a same molecular formula of **9** ($C_{27}H_{44}O_3$+H requires 417.3369). Its UV spectrum showed strong absorption maximum at 305 nm, suggesting the existence of an extended conjugated system. The ^{13}C NMR spectrum revealed the presence of a −C═O, a −OCH− and a −O−C−O− moieties. The comparison of its ^{13}C NMR chemical shifts with those of **5** demonstrated that, besides of the A-ring carbons as well as 7- and 14-Cs, other chemical shifts are almost identical. In the HMBC spectrum the olefinic 6- and 7-Hs and the methylenic 4-Hs correlated with the carbonyl carbon (δ 198.7), indicating that the −C═O is located at the 5-position, that also rationalizes the downfield shift of 4-, 7- and 14-Cs in comparison with those of **5**. The chemical shift of 10-C (δ 108.2) suggested it bonded to two oxygens. Its HMBC showed correlations between the 10-C and 19-CH_3 and 2-Hs, and between the oxygen-connecting 3-C (δ 77.5) with 2- and 4-Hs. Therefore, **10** was assigned as 3,10-epoxy-5-oxo-5,10-*seco*-9,10-secocholesta-6,8(14)-dien-10-ol and **9** was assigned as 5,10-epidioxy-isotachysterol. Total ^1H and ^{13}C NMR assignments are listed in Table 1.

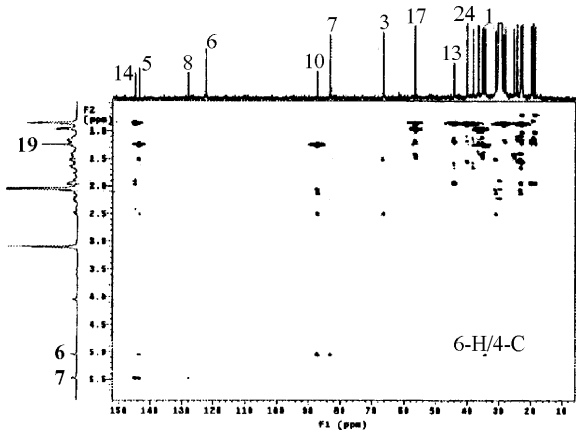
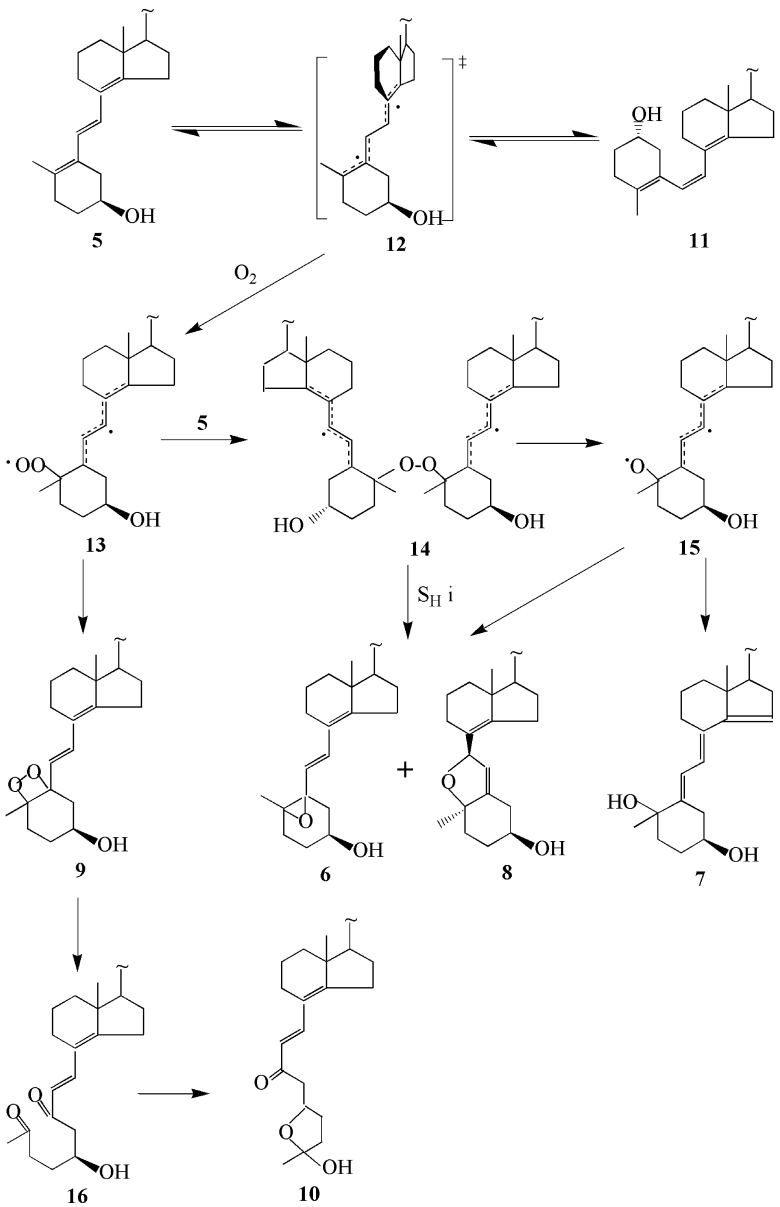


Figure 4. The gHMBC spectrum of **8**.

3. Discussion

Mordi and Walton[13] have studied in detail the autoxidation of β-carotene in the dark and proposed a self-initiated autocatalytic mechanism for the formation of the 5,6-epoxide of β-carotene and other oxidation products. Similar mechanism might also be applicable to this autoxidation of isotachysterol as shown in Scheme 1. That is, the *all-trans*-triene structure in **5** isomerizes to the corresponding 6,7-*cis*-isomer (**11**) *via* the singlet biradical transition state (**12**), similar to the case of β-carotene[13] which has been proved by Doering and co-workers to be able to take place at temperatures <40 °C.[14] As a matter of fact, a small peak close to the peak of **5** with absorption maximum at 253 nm corresponding to 6,7-*cis*-isotachysterol[15] (**11**) could be observed if a hexane solution of isotachysterol (**5**) was put in the dark and free of oxygen for 6 h as shown in Figure 5. This demonstrated the unambiguous formation of **11**, hence the occurrence of such *trans*/*cis*-isomerization process. It has been reported previously that isotachysterol (**5**) could isomerize to *cis*-isotachysterol (**11**) photochemically.[15a] The present work demonstrates clearly that the *trans*/*cis*-isomerization of isotachysterol can also take place thermally because the singlet biradical **12** is thermodynamically stabilized by delocalization of the two unpaired electrons to the two allylic moieties. This thermal *trans*/*cis*-isomerization of isotachysterol *via* the biradical (**12**) provides a ready explanation for the lability of isotachysterol and the self-initiated autoxidation of the substrate. That is, during twisting of the central carbon–carbon bond of isotachysterol the unpaired spin density would develop in each half of the molecule, reaching a maximum (one free spin in each half) in the perpendicular transition state (**12**). It is reasonably to assume that the unpaired spin can be 'captured' by oxygen to produce a carbon-peroxyl triplet biradical (**13**). Oxygen should preferably attack 10-C to enable the extensive delocalization of another unpaired electron. Being a triplet **13** would be relatively long-lived



Scheme 1. Proposed mechanism for the autoxidation of isotachysterol.

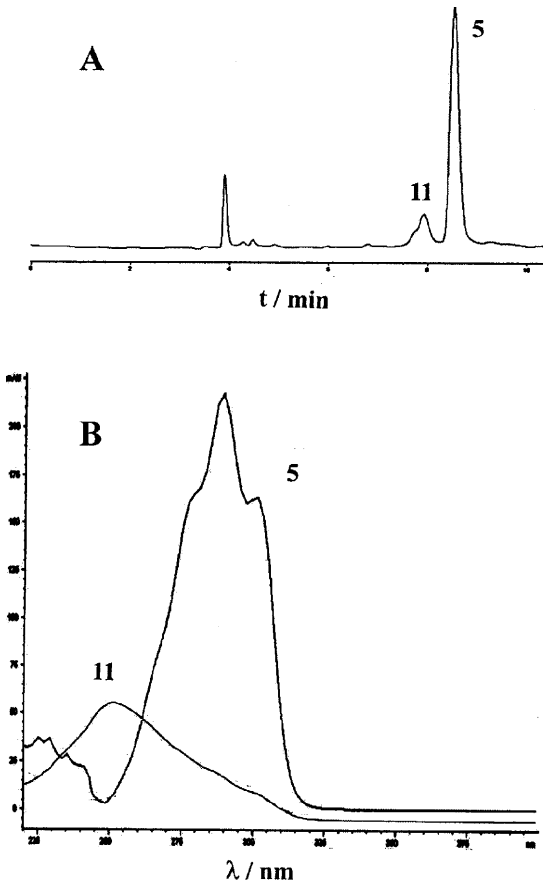
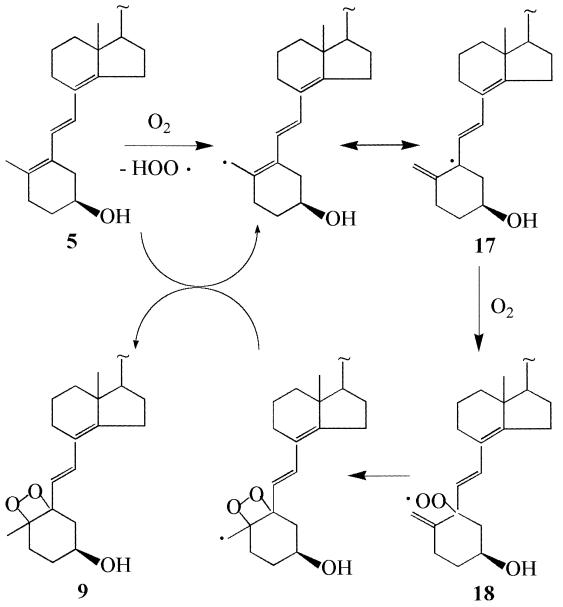


Figure 5. (A) HPLC diagram recorded from a hexane solution of isotachysterol which was stored free from oxygen in the dark for 6 h with a Zorbax Sil column (5 μm) eluted with hexane–AcOEt (85:15 v/v) at a flow rate of 1 ml/min. The UV detector was put at 260 nm. The peak numbers correspond to the numbers of the compounds. (B) The UV spectra of **5** and **11** recorded from the same solution. The intensity of **11** was magnified by 3 times.



Scheme 2. An alternative mechanism for the autoxidation of isotachysterol.

and be able to add to a second molecule of **5** to form a new biradical **14**, again at 10-C. Obviously, **14** can subject to the well-precedented intramolecular homolytic substitution (S_Hi)[16] producing the 5,10-epoxides **6** and the 7,10-epoxide **8** by 5,10- and 7,10-ring closure, respectively, of the intermediate alkoxyl biradical **15**. Compound **7** was also possibly derived from the alkoxyl biradical **15** by consecutive 1,5-sigmatropic rearrangement of the allylic 15-H to 6-C and 1,4-sigmatropic rearrangement of the 6-H to 10-O. On the other hand, the peroxyl biradical **13** may collapse to the thermally unstable dioxetane **9** which would easily subject to peroxide scission to produce the dicarbonyl intermediate **16** followed by acetalation, yielding the cyclic semiketal **10** (Scheme 1). Another possible initiation step might be the direct hydrogen abstraction by oxygen from allylic positions,[17] preferably at C-19 to form the allylic radical **17**, which reacts with oxygen to form the peroxy radical **18**. Being similar to **13** it can follow similar follow-up processes as mentioned above to give the products as exemplified in Scheme 2.

In conclusion, this work demonstrates that despite the relative stability of vitamin D_3 at ambient temperatures, its acid-catalyzed isomerization product, isotachysterol, is liable to autoxidation to form a variety of oxidation products. The formation of these oxidation products is interesting since they are formed in the dark and in the absence of any other oxidants and/or initiators apart from atmospheric oxygen. Other oxides of vitamin D_3 derivatives reported previously were all prepared by chemical and photochemical oxidations.[4–6] Since isotachysterol is the acid-catalyzed isomerization product of vitamin D_3 and also can be formed in the presence of acidic vitamins such as ascorbic acid and folic acid,[18] similar autoxidation reaction might also take place in living systems and have biological significance.

4. Experimental

4.1. General methods

HR-ESI-MS was determined on a Bruker APEX II FT-MS spectrometer. ^1H, ^{13}C and 2D NMR spectra were recorded on a Bruker AM 400 NMR spectrometer in acetone-d_6 with TMS as the internal standard. IR spectra were taken on a Nicolet 170SX IR spectrometer. UV spectra were recorded with a Hitachi 557 spectrophotometer in methanol. Optical rotation was measured on a Perkin–Elmer 341 polarimeter. HPLC was carried out with a Hewlett Packard 1100 system and a diode array detector. Best separations were achieved with a 250×4.6 mm^2 Phenomenex Nucleosil 5 μm C18 and 250×10 mm^2 Whatman Partisil 10 μm ODS-3 columns. Coupled LC–MS was carried out with the same HPLC system and the Bruker APEX II FT-MS spectrometer in the electrospray ionization mode.

4.1.1. Preparation of isotachysterol (5). To a solution of vitamin D_3 (**1**, 200 mg) in 30 ml methanol was added 0.1 ml HCl and the solution was refluxed for 0.5 h. The reaction mixture was neutralized with Na_2CO_3, extracted with AcOEt and dried over anhydrous Na_2SO_4. After removing

the solvent under reduced pressure using a rotavapor the residue was column chromatographed on silica gel (20 g) with AcOEt–PE (1:5) giving a pale yellow oil (150 mg, 75%) of isotachysterol (all-*trans*-9,10-secocholesta-5(10),6,8(14)-trien-3β-ol (**5**): HR-ESI-MS: 385.3463 ($C_{27}H_{44}O$+H requires 385.3470); $[\alpha]_D^{25}$=+4 (*c* 0.3 in acetone); ν_{max} (neat, cm^{-1}) 3403 (OH), 1671 and 1589 (conjugated triene), 957 (*trans*-CH=); λ_{max} (MeOH, nm) 288, indicative of an all-*trans*-triene system. For NMR data see Table 1.

4.2. Autoxidation of isotachysterol (5)

The pale yellow oil of **5** (150 mg) was laid in a small beaker at ambient temperature in the dark which was oxidized rapidly to a very complex mixture as monitored by TLC, and after 1–2 days little **5** was left. Oxidation by bubbling air to a benzene solution of **5** at 40 °C for 4 h gave the same result. The reaction mixture was separated by column chromatography (silica gel, AcOEt–PE, 1:1 v/v) followed by HPLC to give **6a** (10.6 mg), **6b** (6.3 mg), **7a** (4.0 mg), **7b** (5.8 mg), **8** (8.0 mg) and **10** (3.2 mg) respectively. Compound **9** could not be collected because it was unstable and changed to **10** during HPLC separation.

4.3. Stereospecific epoxidation of isotachysterol (5)

To a solution of **5** (100 mg, 0.31 mmol) and $VO(acac)_2$ (2 mg, 7.3 mmol) in dry benzene (2 ml) was added slowly anhydrous benzene solution of TBHP (0.21 ml, 0.62 mmol) at 5 °C. The solution was then stirred for 30 min at 5 °C. After addition of aqueous Na_2SO_3, the mixture was extracted with benzene, the extracts were washed with brine, dried over Na_2SO_4, and evaporated. The residue was chromatographed (silica gel, AcOEt–PE 1:1) to give **6a** (43 mg, 43%) as the predominant product.

4.3.1. (5*R*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol [5β,10-epoxy-isotac-hysterol] (6a). HR-ESI-MS: 401.3413 ($C_{27}H_{44}O_2$+H requires 401.3420; $[\alpha]_D^{25}$=+25.8 (*c* 1.0 in acetone); ν_{max} (neat, cm^{-1}) 3386 (OH), 1278, 859 and 800 (epoxide), 971 (*trans*-CH=); λ_{max} (MeOH, nm) 247. For NMR data see Table 1.

4.3.2. (5*S*)-5,10-epoxy-9,10-secocholesta-6,8(14)-dien-3β-ol [5α,10-epoxy-isotac-hysterol] (6b). HR-ESI-MS: 401.3422 ($C_{27}H_{44}O_2$+H requires 401.3420); $[\alpha]_D^{25}$=+29.1 (*c* 1.0 in acetone); ν_{max} (neat, cm^{-1}) 3388 (OH), 1275, 874 and 836 (epoxide), 970 (*trans*-CH=); λ_{max} (MeOH, nm) 247. For NMR data see Table 1.

4.3.3. (10*R*)-9,10-secocholesta-5,7,14-triene-3β,10-diol (7a). HR-ESI-MS: 401.3416 ($C_{27}H_{44}O_2$+H requires 401.3420); $[\alpha]_D^{25}$=−144 (*c* 0.7 in acetone); λ_{max} (MeOH, nm) 278. For NMR data see Table 1.

4.3.4. (10*S*)-9,10-secocholesta-5,7,14-triene-3β,10-ol (7b). HR-ESI-MS: 401.3411 ($C_{27}H_{44}O_2$+H requires 401.3420); $[\alpha]_D^{25}$=−112 (*c* 0.6 in acetone); λ_{max} (MeOH, nm) 278. For NMR data see Table 1.

4.3.5. (7*R*,10*R*)-7,10-epoxy-9,10-secocholesta-5,8(14)-dien-3β-ol [7,10-epoxy-isotac-hysterol] (8). HR-ESI-MS: 401.3411 ($C_{27}H_{44}O_2$+H requires 401.3420); $[\alpha]_D^{25}$=+134 (*c* 0.3 in acetone); λ_{max} (MeOH, nm) 206. For NMR data see Table 1.

4.3.6. 3,10-epoxy-5-oxo-5,10-*seco*-9,10-secocholesta-6,8(14)-dien-10-ol (10). HR-ESI-MS (417.3378 for $C_{27}H_{44}O_3$+H, requires 417.3369); λ_{max} (MeOH, nm) 305. For NMR data see Table 1.

Acknowledgements

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Expedious synthesis of polyhydroxylated selena and thia-heterocycles via Se and S-ring closure of α,ω-dibromoalditols

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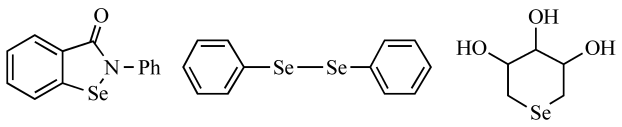
Abstract—The selena and thiaanhydro alditols (with *xylo*, *ribo*, D-*arabino*, *erythro*, D,L-*threo* and D-*manno* configuration) were easily and expeditiously synthesized in good to excellent yields by reaction of selenure and sulfur ions as binucleophiles with α,ω-dibromoalditols as bis-electrophilic substrates. With the 1,6-dibromo-D-glucitol derivative as substrate, only the corresponding thiepane derivative was obtained while the selenaheterocyclistation attempte led to complex mixture.

1. Introduction

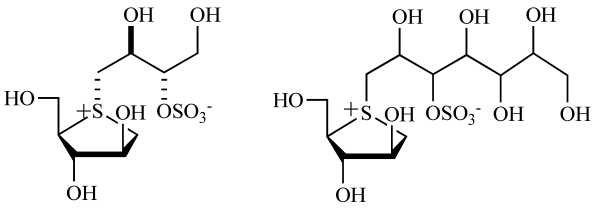
It is well recognised that some diseases such as cancer,[1] aids and the neurodegenerative diseases (e.g. Parkinson and Alzheimer)[2] emerging from abnormally high production of free radicals (oxydatif stress).[3] This is attributed to antioxydants deficiency (free radical scavengers) like vitamins[4] or of enzyme such selenodependent glutathione peroxydase where the sulfur atoms of it's cysteine moieties were replaced by selenium atoms.[5] This enzymatic antioxydant catalysed the hydroperoxyde reduction (reduced metabolite precursor of nossif HO free radical) with concomitante oxydation of a biologically important thiol, the glutathione which transformed in their disulfur.[6]

It was reported that a small organic molecules like Ebselen **A**[7] or the diphenyldiselenide **B**[8] play an important part as glutathione peroxydase mimics. More recently Schiesser and co-workers reported the ten steps synthesis of **C** (discribed in its perbenzylated *xylo*, *ribo* and D-*arabino* configurations) which is an hydrosoluble antioxydant.[9]

In the thiaheterosugars analogues series where the oxygen atom of the monosaccharide ring was replaced by sulfur atom, cyclic tetrahydro thiophene is an important building block of a large number of compounds that are very interesting from the point of view of biological activity. In particular it enters into the structures of nucleoside analogues[10] and certain compounds where the sulfur atom in the ring is in a trivalent state (spirocycle-like), such as the sulfimides,[11] salacinol **D** and kotalanol **E**,[12] which are excellent glycosidase inhibitors. Although analogues with more than six or seven membered rings (tetrahydrothiopyrane and thiepane) generally show weak glycosidase inhibition activity,[13] they are nevertheless excellent precursors for the thiacyclopentane ring through contraction of the ring[13,14] or for conduritol derivatives (from thiepane)[15] which are glycosidase inhibitor and much used as intermediates in the synthesis of inositol[16] and aminocyclitol derivatives.[17]



A **B** **C**



D **E**

The use of alditols as bielectrophilic substrates in heterocyclisation reactions has been reported in the literature. It has been shown, for instance, that the selenepane and thiepane ring are obtained mainly from bis-epoxyhexitol

Keywords: Alditols; Dibromoalditols; Thiaheterocycles; Selenaheterocycles; Antioxydants; Biselectrophiles.
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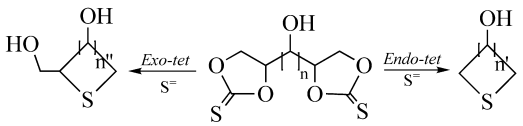
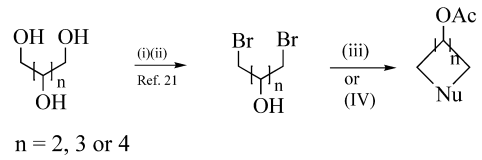
such as D-mannitol always protected in the 3,4 positions.[14b] However, this approach has limitations when applied to other alditols.[18] In our laboratory we have used alditols bis-cyclic-sulfates as bielectrophilic intermediates. Polyhydroxylated tetrahydrothiophene, tetrahydropyrane and thiepane derivatives have been isolated in good yields.[19] Unfortunately, this approach is only applicable to free tetritols and other partially protected alditols carrying only four free hydroxyl groups. Although the alditols cyclic bis-thionocarbonate derivatives formation take place efficiently and directly from umprotected alditols, their use as bis-electrophilic intermediates in thiaheterocyclisation often encountered the *endo-tet* and *exo-tet* competition (Scheme 1).[20] To avoid this competition, the α,ω-dibromoalditols seems to be a judicious alternative (Scheme 2).



Scheme 1. n=0 or 1; n'=2, 3 or 4; n''=2 or 3.



Scheme 2. (i) AcBr, 1,4-dioxane, rt, 16 h; (ii) Ac_2O, pyridine; (iii) Na_2S, DMSO; (iv) Se, $NaBH_4$, H_2O, DMSO, rt, 5 min.

Herein we report a general, short and efficient synthesis affording polyhydroxylated tetrahydroseleno/thiophene, tetrahydroseleno/thiopyrane and selene/thiepane rings from peracetylated α,ω-dibromo-α,ω-dideoxyalditols with *erythro*, D,L-*threo*, *xylo*, *ribo*, D-*arabino*, D-*manno* and D-*gluco* configurations. The latter are obtained directly by bromination of the corresponding alditols.[21]

2. Results and discussion

In the synthesis of thiaheterocycles from bis-electrophilic alditols derivatives, solvents such as EtOH,[13] MeOH[22] or a mixture of acetone–H_2O were used.[19] In the latter case, under mild conditions (rt, 15 min), we showed that cyclic tetritol bis-sulfates reacting with Na_2S, $9H_2O$ leads to corresponding thiacyclopentane derivatives in good yields. Initially, applying these conditions, 2,3,4-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxyxylitol (**8**) (Table 1, entry 3) lead, after flash chromatography, to the xylotetrahydrothiopyrane derivative **9** in only 37% yield. When this reaction is followed by acetylation of the reaction mixture, the yield of compound **9** reaches 90% (entry 3). This is explained by the concomitant deacetylation of the heterocyclisation product.

Under the same conditions, the *S*-cyclisation of α,ω-dibromoalditol derivatives **2**, **5**, **11**, **15**, **18** and **21** followed by acetylation leads to tetrahydrothiophene rings **3** and **6** (entries 1 and 2), tetrahydrothiopyrane **12** and **16** (entries 4 and 5) and thiepane **19** and **23** (entries 6 and 7) in yields from 70 to 95% for a reaction time of 18 h for complete disappearance of substrate.

It is interesting to emphasize that with brominated ribitol **11** and D-glucitol **21** (entries 4 and 7) non-negligible amount of anhydro compounds were isolated (**13** and **25**, respectively). In both cases the formation of these *O*-heterocyclic compounds could be explained by an initial attack at one of the primary sites by S=, followed by transesterification and *O*-heterocyclisation leading to those anhydro derivatives.

For compound **13**, ^{13}C NMR shows both an intra-cyclic secondary carbon atom at 70.82 ppm and another extra-cyclic at 30.9 ppm, plus a signal at 190 ppm shift for thioacetate group. In ^1H NMR, the coupling constant $J_{2,3}$=5.4 Hz is in agreement with a 1,4-anhydroribitol structure.[23]

In the case of the anhydro-D-glucitol derivative **25**, the sequence of coupling constantes $J_{2,3}$=3.48 Hz, $J_{3,4}$=10.96 Hz and $J_{4,5}$=0 Hz favours a 2,6-anhydro-D-glucitol structure. Mechanistically, this requires an initial regioselective attack on the primary C-1 site of disymetrique dibrominated D-glucitol derivative **21** (Scheme 3) followed by competition between *S*-cyclisation (path-a) leading to thiepane **23** and a 1,2-*trans*-esterification (path-b) leading to 2-hydroxy compound **24**. A subsequent *O*-heterocyclisation at 2,6 leads to 2,6-anhydro-D-glucitol derivatives **25**.[24]

To corroborate this higher reactivity of C-1 compared with C-6 in the derivative 1,6-dibromo-D-glucitol **21**, we attempted regioselective nucleophilic substitution using mononucleophiles such as acetate ion (AcO^-) and the alkylthiolate anions (n-$C_4H_9S^-$ and n-$C_8H_{17}S^-$) (Scheme 4).[24] In both cases we confirmed the high reactivity of C-1 leading respectively to 1,2,3,4,5-penta-*O*-acetyl-6-bromo-6-deoxy-D-glucitol (**26**), 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiobutyl-1-deoxy-D-glucitol (**28**) and 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiooctyl-1-deoxy-D-glucitol (**30**) in reasonable yields (50%). Derivatives **26**, **28** and **30** were respectively transformed into the derivatives 6-thiobutyl, 1-thiobutyl and 6-thiobutyl-1-thiooctyl-D-glucitol **27**, **29** and **31** in excellent yields. This regioselective functional transformation then enabled us to synthesise the derivative 1,6-dithioalkyl **31** with two alkyl chains of differing lengths. Note that with an excess of thiolate in the DMSO–THF mixture, the thioalkylation takes place indiscriminately at the two sites C-1 and C-6 to give the disubstituted compound **32**.[24]

Finally, while investigating the influence of the nature of the solvent on thioheterocyclisation, we were able, using DMSO as solvent, to isolate thioheterocyclic compounds in very good yields without subsequent acetylation and in particularly mild conditions (20–45 min, only 1.5 mmol of Na_2S–$9H_2O$ instead of 5 mmol in acetone–H_2O). Furthermore, in the case of ribitol (entry 4) and D-glucitol (entry 7) we noted any amounts of the corresponding anhydro derivatives **13** and **25**.

The above conditions in DMSO could not be applied

directly to selenaheterocyclisation since Na_2Se must be synthesized firstly from metallic selenium and $NaBH_4$ as reducing reagent in aqueous medium.[13] After some attempts, we showed that reaction of peracetylated α,ω-dibromoalditols derivatives in DMSO with a colorless solution obtained by addition of $NaBH_4$ to a suspension of Se in water, gave in less than 10 min the corresponding selenaheterocycles derivatives in good to excellent yields (Table, entries 1–6). Thus, the tetrahydroselenophene **33** (*erythro*, 93%) and **34** (D,L-*threo*, 98%), the tetrahydroselenopyrane **35** (*xylo*, 80%), **36** (*ribo*, 70%), **37** (D-*arabino*, 95%) and manoselenepane **38** (70%) were efficiently obtained. The high rate of *Se*-heterocyclisation could be attributed to both higher nucleophilicity of Se= (comparatively to S=) and to the temperature enhancement (approximately 40 °C) when $NaBH_4$ was added to Se. Farther more we had verify that the addition of the DMSO solution of α,ω-dibromoalditols substrates to the cooled solution of Se and $NaBH_4$ (to 14 °C) increased the reaction temperature of the mixture to 30 °C. Thus both Na_2Se formation and subsequente heterocyclisation were exothermal. We could note also that the peracetylated α,ω-dibromoalditols don't undertake any deacetylation reaction although the temperature enhancement and the basicity of the medium.

In conclusion, this work has led to the short and efficient synthesis in excellent yields of polyhydroxylated tetrahydrothio/selenophene, tetrahydrothio/selenopyrane and thie/selenepane derivatives in various configurations via dibrominated alditol derivatives that are readily prepared from the corresponding alditols. In addition we have shown a higher reaction rate at the primary C-1 compared with the C-6 site of the 2,3,4,5-tetra-*O*-acetyl-1,6-dibromo-D-glucitol (**21**). This opens the way to numerous derivatives of D-glucitol with various functional groups, as well as to a rare sugar, gulose.[25] Finally, it is of interest to emphasise that this strategie from pentitols led to high overal yields in selenaheterocyclic pentitols **35** (*xylo*), **36** (*ribo*) and **37** (D-*arabino*) comparatively to those obtained in the ten steps strategies reported in the literature.[9]

3. Experimental

3.1. General methods

Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 300 WB spectrometer; chemical shifts are reported in δ (ppm) relative to Me_4Si. Coupling constants, assigned by double irradiation, are in Hz. All ^{13}C NMR signals were assigned though C,H-correlated spectra with hsqc.grad experiment. TLC was performed on silica Gel 60 F_{254} 230 mesh (E. Merck) with hexane–EtOAc as eluent, and zones were detected by vanillin-H_2SO_4 reagent. The silica gel used in column chromatography was 35–70 m (Amicon). Optical rotations were determined with Jasco Dip 370 electronic micropolarimeter (10 cm cell) for compounds **37** and **38**, and Perkin–Elmer instruments, model 343 polarimeter (1 mL cell) for compounds **16** and, **19** and **23**. Elemental analyses were performed by the 'Service de Microanalyse du CNRS (Laboratoire de Bioorganique, Université de Reims Champagne Ardenne').

3.2. Synthesis of thiahetrocycles 3, 6, 9, 12, 16, 19 and 23

General procedure. To a solution of peracetylated α,ω-dibromoalditols (1 mmol)[21] in DMSO (5 mL), was added Na_2S, $9H_2O$ (1.5 mmol) and the mixture was stirred at rt for the time indicated in table. The extraction was realised with CH_2Cl_2 (30 mL) and H_2O (2×30 mL). The organic layer was concentrated and the products was purified by chromatography on silica gel and mixture of Hexan–EtOAc as eluent.

3.2.1. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-thioerythritol (3). 186.7 mg, 92% yield as colorless syrup; R_f 0.44 (6:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.77 (dd, 2H, $J_{1a,1b}$=$J_{4a,4b}$=11.1 Hz, $J_{1a,2}$=$J_{4a,3}$=5.4 Hz, $H_{1a,4a}$), 3.95 (dd, 2H, $J_{1b,2}$=$J_{4b,3}$=5.6 Hz, $H_{1b,4b}$), 5.21 (m, $H_{2,3}$); 1.98 (s, 6H, CH_3); ^{13}C NMR, δ 31 (C_1=C_4), 74.3 (C_2=C_3), 21.1 (CH_3), 170.2 (CO). Anal. calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; O, 31.33; S, 15.70. Found: C, 47.24; H, 6.11.

3.2.2. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-thio-D,L-threitol (6). 193 mg, 95% yield; white solid: mp 43–45 °C; R_f 0.47 (6:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.70 (dd, 2H, $J_{1a,1b}$=$J_{4a,4b}$=12.2 Hz, $J_{1a,2}$=$J_{4a,3}$=1.3 Hz, $H_{1a,4a}$), 3.17 (dd, 2H, $J_{1b,2}$=$J_{4b,3}$=4.0 Hz, $H_{1b,4b}$), 5.22 (m, 2H, $H_{2,3}$); 2.1 (s, 6H, CH_3); ^{13}C NMR, δ 34 (C_1=C_4), 77.9 (C_2=C_3), 21.2 (CH_3), 170.0 (CO). Anal. calcd for $C_8H_{12}O_4S$: C, 47.04; H, 5.92; O, 31.33; S, 15.70. Found: C, 47.32; H, 6.01.

3.2.3. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thioxylitol (9). 248.7 mg, 90% yield; white solid: mp 120–122 °C; R_f 0.39 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.53 (m, 2H, $J_{1a,1b}$=$J_{5a,5b}$=13.9 Hz, $J_{1a,2}$=$J_{5a,4}$=6.4 Hz, $H_{1a,5a}$), 2.74 (m, $J_{1b,2}$=$J_{5b,4}$=1.8 Hz, H_{1ab5b}), 4.93 (m, 3H, $H_{2,3,4}$), 1.96 (s, 6H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR, δ 30.6 ($C_{1,5}$), 72.7 ($C_{2,4}$), 73.7 (C3), 20.7 (CH_3), 169.7 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 47.93; H, 6.12.

3.2.4. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thioribitol (12). 215.3 mg, 78% yield; white solid: mp 89–91 °C; R_f 0.36 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.45 (dd, 2H, $J_{1a,1b}$=$J_{5a,5b}$=12.1 Hz, $J_{1a,2}$=$J_{5a,4}$=12.1 Hz, $H_{1a,5a}$), 2.80 (t, 2H, $J_{1b,2}$=$J_{5b,4}$=4.2 Hz, H_{1b5b}), 5.01 (m, 2H, $H_{2,4}$), 5.55 (s, 1H, H_3), 1.96 (s, 6H, CH_3), 2.15 (s, CH_3); ^{13}C NMR δ 25.1 ($C_{1,5}$), 70.9 ($C_{2,4}$), 69.2 (C_3), 20.8 (CH_3), 169.5, 169.7 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.01; H, 5.98.

3.2.5. 2,3-Di-*O*-acetyl-5-*S*-acetyl-1,4-anhydro-5-thio-D,L-ribitol (13). Obtained when the acetone/H_2O mixture was used solvent in the thiaheterocyclisation reaction (Table 1, entry 4). 55.3 mg, 20% yield; colorless syrup; R_f 0.28 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 3.76 (dd, 1H, $J_{1a,1b}$=10.4 Hz, $J_{1a,2}$=3.4 Hz, H_{1a}), 4.22 (dd, 1H, $J_{1b,2}$=5.1 Hz, H_{1b}), 5.13 (ddd, 1H, $J_{2,3}$=7.3 Hz, H_2), 4.06 (dd, 1H, $J_{3,4}$=5.4 Hz, H_3), 5.28 (dd, 1H, $J_{4,5a}$=6.0 Hz, $J_{4,5b}$=24.4 Hz, H_4), 5.01 (dd, 1H, $J_{5a,5b}$=14.1 Hz, H_{5a}), 3 (dd, 1H, H_{5b}), 2.02 (s, 3H, CH_3), 2.04 (s, 3H, CH_3 (Ac)),

Table 1. Regioselective thia and selenaheterocyclisation of peracetylated α,ω-dibromoalditols derivatives using sodium sulfide and sodium selenide

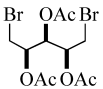
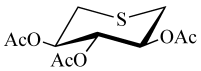
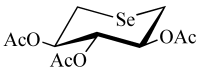
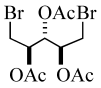
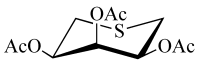
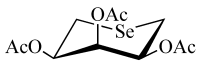
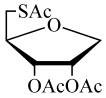
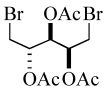
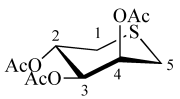
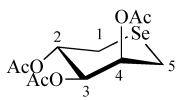
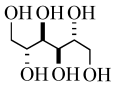
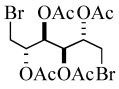
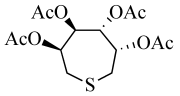
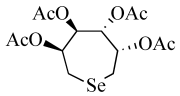
Entry	Substrates	α,ω-Dibromoalditols derivatives (yield (%))[a]	Isolated thiaheterocyclic products	Isolated yields (%) in conditions with acetone–H_2O as solvent[b]		Isolated yields (%) in conditions with DMSO as solvent[c]		Isolated selenahyeterocyclic products after 5 min of reaction time in DMSO/H_2O as solvent	
				Yield (%)[d]	Time (h)	Yield (%) Time (min)	Time (min)	Yield (%)	Time (min)
1				93	18	92	20		<10
	Erythritol (**1**)	**2** (85)	**3**					**33** (93)	
2				95	18	95	20		<10
	D,L-Threitol (**4**)	**5** (86)	**6**					**34** (98)	
3				90[e]	18	87	30		<10
	Xylitol (**7**)	**8** (70)	**9**					**35** (80)	
4				70	18	78	30		<10
	Ribitol (**10**)	**11** (68)	**12**						
				20	18	0	30	**36** (70)	<10
			13						
5				86	18	83	30		<10
	D-Arabinitol (**14**)	**15** (73)	**16**					**37** (95)	
6				82	18	88	45		<10
	D-Mannitol (**17**)	**18** (60)	**19**					**38** (70)	

Table 1 (*continued*)

Entry	Substrates	α,ω-Dibromoalditols derivatives (yield (%))[a]	Isolated thiaheterocyclic products	Isolated yields (%) in conditions with acetone–H_2O as solvent[b]		Isolated yields (%) in conditions with DMSO as solvent[c]		Isolated selenahyeterocyclic products after 5 min of reaction time in DMSO/H_2O as solvent	
				Yield (%)[d]	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)
7	D-Glucitol (**20**)	**21** (50)	**23**	75	18	85	45	Complex mixture	
			25 (2,6-Anhydro)	10		0			

[a] Isolated yields from the corresponding aditols.[21]
[b] 5 mmol of Na_2S, $9H_2O$.
[c] Isolated yields from α,ω-dibromoalditols derivatives and after acetylation of crude product.
[d] 1.5 mmol of Na_2S, $9H_2O$.
[e] 37% Yield if separation carryed out without previous acetylation.

Scheme 3. (i) Na_2S, $9H_2O$, Acetone–H_2O (15:1), rt, 18 h.

Scheme 4. R=OAc; (i) AcONa (3 equiv.), 60 °C, 5 h, DMSO; (ii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO, rt, 15 min; (iii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO-THF (1:1), rt, 15 min; (iv) AcONa (3 equiv.), 60 °C, 24 h, DMSO; (v) $C_8H_{17}SH$ (1.2 equiv.), NaH (1.1 equiv.), DMSO, TA, 15 min; (vi) C_4H_9SH (2.2 equiv.), NaH (2.4 equiv.) DMSO-THF (1:1), rt, 15 min.

2.33 (s, 3H, CH_3 (SAc)); ^{13}C NMR δ 70.8 (C_1), 78.0 (C_2), 73.5 (C_3), 71.2 (C_4), 30.9 (C_5), 20.5 (CH_3 (OAc)) 30.4 (CH_3 (SAc)), 169.8 (CO, (Ac)), 194.7 (CO (SAc)). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.07; H, 5.88.

3.2.6. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-thio-D-arabinitol (16). 229.1 mg, 83% yield; $[\alpha]_D=-20.4$ (*c* 3.3; $CHCl_3$); R_f 0.42 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.54 (dd, 1H, $J_{1a,1b}=14$ Hz, $J_{1a,2}=7.7$ Hz, H_{1a}), 2.83 (dd, 1H, $J_{1b,2}=2.2$ Hz, H_{1b}), 5.08 (ddd, 1H, $J_{2,3}=8.1$ Hz, H_2), 4.89 (dd, 1H, $J_{3,4}=2.6$ Hz, H_3), 5.28 (dd, 1H, $J_{4,5a}=7.2$ Hz, $J_{4,5b}=2.6$ Hz, H_4), 2.62 (dd, 1H, $J_{5a,5b}=14$ Hz, H_{5a}), 2.75 (dd, 1H, H_{5b}), 1.98 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.15 (s, CH_3); ^{13}C NMR δ 28.7 (C_1), 68.9 (C_2), 70.3 (C_3), 68.8 (C_4), 28.6 (C_5), 20.8 (CH_3), 169.5, 169.7, 169.9 (CO). Anal. calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84; O, 34.74; S, 11.61. Found: C, 48.18; H, 6.22.

3.2.7. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-thio-D-mannitol (19). 307.2 mg, 88% yield; white solid: mp 93–95 °C; $[\alpha]_D=-157$ (*c* 3.7; $CHCl_3$); R_f 0.42 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.79 (dd, 2H, $J_{1a,1b}=J_{6a,6b}=14.6$ Hz, $J_{1a,2}=J_{6a,5}=7.0$ Hz, $H_{1a,6a}$), 2.83 (dd, 2H, $J_{1b,2}=J_{6b,5}=4.5$ Hz, $H_{1b,6b}$), 5.28 (m, 2H, $J_{2,3}=J_{4,5}=0.8$ Hz, $H_{2,5}$), 5.28 (m, 2H, $H_{3,4}$),1.96 (s, 6H, CH_3), 1.99 (s, 6H, CH_3); ^{13}C NMR, δ 30.9 ($C_{1,6}$), 70.2 ($C_{2,5}$), 70.9 ($C_{3,4}$), 20.6 (CH_3), 169.3, 169.7 (CO). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.32; H, 6.05.

3.2.8. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-thio-D-glucitol (23). 296.7 mg; $[\alpha]_D=-0.2$ (*c* 1.6; $CHCl_3$); 85% yield; white solid: mp 76–78 °C; R_f 0.26 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$) (arbitrary numeration), δ 2.69 (dd, 1H, $J_{1a,1b}=14.6$ Hz, $J_{1a,2}=7.2$ Hz, H_{1a}), 2.84 (dd, 1H, $J_{1b,2}=3.9$ Hz, H_{1b}), 5.33 (ddd, 1H, $J_{2,3}=1.4$ Hz, H_2), 5.15 (dd, 1H, $J_{3,4}=8.1$ Hz, H_3), 5.49 (dd, 1H, $J_{4,5}=6$ Hz, H_4), 5.04 (ddd, 1H, $J_{5,6a}=7.4$ Hz, $J_{5,6b}=4.6$ Hz, H_5), 2.74 (dd, 1H, $J_{1a,1b}=15.4$ Hz, H_{6a}), 2.88 (dd, 1H, H_{6b}),1.95 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.02 (s,3H, CH_3); ^{13}C NMR δ 33.1 ($C_{1,6}$), 71.3 (C_2), 70.8 (C_3), 70.6 (C_4), 75.2 (C_5), 20.6, 20.8 (CH_3), 169.0, 169.1, 169.5, 169.8 (CO). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.63; H, 5.92.

3.2.9. 3,4,5-Tri-*O*-acetyl-1-*S*-acetyl-2,6-anhydro-1-thio-D-glucitol (25). Obtained when the acetone/H_2O mixture was used solvent in the thiaheterocyclisation reaction (Table 1, entry 7). 34.8 mg, 10% yield; Yelow syrup; R_f 0.38 (5:3, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 3 (dd, 1H, $J_{1a,1b}=14.5$ Hz, $J_{1a,2}=6.2$ Hz, H_{1a}), 3.52 (dd, 1H, $J_{1b,2}=3.3$ Hz, H_{1b}), 5.13 (ddd, 1H, $J_{2,3}=3.5$ Hz, H_2), 4.06 (dd, 1H, $J_{3,4}=11$ Hz, H_3), 5.38 (dd, 1H, $J_{4,5}=0$ Hz, H_4), 5.01 (ddd, 1H, $J_{5,6a}=1.8$ Hz, $J_{5,6b}=4.7$ Hz, H_5), 3.76 (dd, 1H, $J_{1a,1b}=10.7$ Hz, H_{6a}), 4.22 (dd, 1H, H_{6b}), 1.93 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.29 (s,3H, CH_3 (SAc)); ^{13}C NMR δ 72.3 (C_1), 67.8 (C_2), 79.4 (C_3), 74.5 (C_4), 77.3 (C_5), 30.8 (C_6), 20.7 (CH_3 (Ac)), 30.4 (CH_3 (SAc)), 169.3, 169.6 (CO (OAc)), 194.5 (CH3 (SAc)). Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; O, 36.74; S, 9.20. Found: C, 48.54; H, 5.83.

3.3. Synthesis of selenahetrocycles 33, 34, 35, 36, 37 and 38

General procedure. To a freshly colorless solution obtained from addition of $NaBH_4$ in H_2O to a suspension of Se in H_2O, was added a solution of peracetylated α,ω-dibromoalditols[21] in DMSO (Table 2). The mixture was stirred for <10 min. The extraction was realised with CH_2Cl_2 (20 mL) and H_2O (2×20 mL). The organic layer was concentrated and the products was purified by chromatography on silica gel and mixture of Hexan–EtOAc as eluant.

3.3.1. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-selenoerythritol (33). 70.5 mg, 93% yield as yellow syrup; R_f 0.52 (5:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.92 (dd, 2H, $J_{1a,1b}=J_{4a,4b}=10.3$ Hz, $J_{1a,2}=J_{4a,3}=5.9$ Hz, $H_{1a,4a}$), 3.11 (dd, 2H, $J_{1b,2}=J_{4b,3}=5.6$ Hz, $H_{1b,4b}$), 5.42 (m, $H_{2,3}$); 2.04 (s, 6H, CH_3); ^{13}C NMR, δ 21.9 (C_1=C_4), 75.9 (C_2=C_3), 21.4 (CH_3), 170.6 (CO). Anal. calcd for $C_8H_{12}O_4Se$: C, 38.26; H, 4.82; O, 25.48; Se, 31.44. Found: C, 38.43; H, 4.85.

3.3.2. 2,3-Di-*O*-acetyl-1,4-dideoxy-1,4-seleno-D,L-threitol (34). 74.3 mg, 98% yield; yellow syrup; R_f 0.55 (5:2, Hexan–EtOAc); ^1H NMR, ($CDCl_3$) δ 2.93 (dd, 2H, $J_{1a,1b}=J_{4a,4b}=11.0$ Hz, $J_{1a,2}=J_{4a,3}=2.4$ Hz, $H_{1a,4a}$), 3.20 (dd, 2H, $J_{1b,2}=J_{4b,3}=4.0$ Hz, $H_{1b,4b}$), 5.33 (m, 2H, $H_{2,3}$); 2.05 (s, 6H, CH_3); ^{13}C NMR, δ 24.80 (C_1=C_4), 78.5 (C_2=C_3), 21.4 (CH_3), 170.2 (CO). Anal. calcd for $C_8H_{12}O_4Se$: C, 38.26; H, 4.82; O, 25.48; Se, 31.44. Found: C, 38.75; H, 5.01.

3.3.3. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-selenoxylitol (35). 64 mg, 80% yield; red solid: mp 110–112 °C; R_f 0.46 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.64 (d, 2H, $J_{1a,1b}=J_{5a,5b}=12.1$ Hz, $J_{1a,2}=J_{5a,4}=0$ Hz, $H_{1a,5a}$), 2.72 (dd, $J_{1b,2}=J_{5b,4}=4.8$ Hz, H_{1ab5b}), 5.07 (m, 2H, $H_{2,4}$), 4.95 (d, H_3, 1.96 (s, 6H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR, δ 21.4 ($C_{1,5}$), 74.1 ($C_{2,4}$), 74.3 (C3), 20.9, 21.2 (CH_3), 169.9, 170.1 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 40.93; H, 5.12.

3.3.4. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-selenoribitol (36). 56 mg, 70% yield; pink solid: mp 128–130 °C; R_f 0.46 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.45 (dd, 2H, $J_{1a,1b}=J_{5a,5b}=11.7$ Hz, $J_{1a,2}=J_{5a,4}=4.1$ Hz, $H_{1a,5a}$), 2.97 (t, 2H, $J_{1b,2}=J_{5b,4}=11.7$ Hz, H_{1b5b}), 5.15 (m, 2H, $H_{2,4}$), 5.53 (s, 1H, H_3), 2.01 (s, 6H, CH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR δ 16.2 ($C_{1,5}$), 72.7 ($C_{2,4}$), 70.1 (C_3), 21.2 (CH_3), 170.2, 169.9 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 41.04; H, 5.23.

3.3.5. 2,3,4-Tri-*O*-acetyl-1,5-dideoxy-1,5-seleno-D-arabinitol (37). 76 mg, 95% yield; yellow syrup; $[\alpha]_D^{22}=-84.8$ (*c* 1.2, CH_2Cl_2); R_f 0.37 (5:2, Hexan–EtOAc); ^1H NMR ($CDCl_3$), δ 2.86–2.94 (m, 2H, $H_{1a,1b}$), 5.27 (ddd, 1H, $J_{2,3}=7.5$ Hz, H_2), 4.99 (dd, 1H, $J_{3,4}=2.8$ Hz, H_3), 5.43 (m, 1H, $J_{4,5a}=7.3$ Hz, $J_{4,5b}=3.1$ Hz, H_4), 2.67 (dd, 1H, $J_{5a,5b}=13.2$ Hz, H_{5a}), 2.70 (dd, 1H, H_{5b}), 1.98 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.11 (s, 9H, CH_3); ^{13}C NMR δ 19.2 (C_1), 69.7 (C_2), 71.0 (C_3), 69.8 (C_4), 19.5 (C_5), 20.4, 21.3, 21.2 (CH_3), 170.4, 170.2, 171.0 (CO). Anal. calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99; O, 29.70; Se, 24.43. Found: C, 40.73; H, 5.02.

3.3.6. 2,3,4,5-Tetra-*O*-acetyl-1,6-dideoxy-1,6-seleno-D-mannitol (38). 58 mg, 70% yield; white solid: mp 93–95 °C; $[\alpha]_D^{22}=-21.0$ (*c* 0.55, CH_2Cl_2); R_f 0.42 (5:3,

Table 2. Selenaheterocyclisation conditions of peracetylated α, ω-dibromoalditol derivatives

α,ω-Dibromoalditol	M (g mol^{-1})	m (g)	N (mol)	Se		$NaBH_4$		V_{H2O} (mL)	V_{DMSO} (mL)
				m (mg)	equiv.	m (mg)	equiv.		
Tetritol	332	0.100	0.3×10^{-3}	71	3	68	6	2×290 μL	1.10 mL
Pentitol	404	0.100	0.25×10^{-3}	59	3	56	6	2×230 μL	930 μL
Hexitol	476	0.100	0.2×10^{-3}	50	3	48	6	2×200 μL	790

Hexan–EtOAc); ^{1}H NMR ($CDCl_3$), δ 2.79 (dd, 2H, $J_{1a,1b}$=$J_{6a,6b}$=14.6 Hz, $J_{1a,2}$=$J_{6a,5}$=7.0 Hz, $H_{1a,6a}$), 2.83 (dd, 2H, $J_{1b,2}$=$J_{6b,5}$=4.5 Hz, $H_{1b,6b}$), 5.28 (m, 2H, $J_{2,3}$=$J_{4,5}$=0.8 Hz, $H_{2,5}$), 5.28 (m, 2H, $H_{3,4}$),1.96 (s, 6H, CH_3), 1.99 (s, 6H, CH_3); ^{13}C NMR, δ 30.9 ($C_{1,6}$), 70.2 ($C_{2,5}$), 70.9 ($C_{3,4}$), 20.6 (CH_3), 169.3, 169.7 (CO). Anal. calcd for $C_{14}H_{20}O_8Se$: C, 42.54; H, 5.10; O, 32.38; Se, 19.98. Found: C, 42.72; H, 5.55.

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The reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with dinucleophilic reagents: a convenient route to fluoroalkylated nitrogen-containing tricyclic compounds

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Abstract—The reactions of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (**2**) with hydrazine hydrate and phenyl hydrazine were investigated. The reaction of **2** with hydrazine hydrate in ethanol under reflux condition readily gave 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones (**3**) in high yields. The reaction of **2** with phenyl hydrazine, however, resulted in the formation of 2-(2-phenyl-5-fluoroalkyl-2*H*-pyrazol-3-yl) benzoic acids (**7**). Further treatment of **7** with PPA gave 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (**4**) in 65–80% overall yields.

1. Introduction

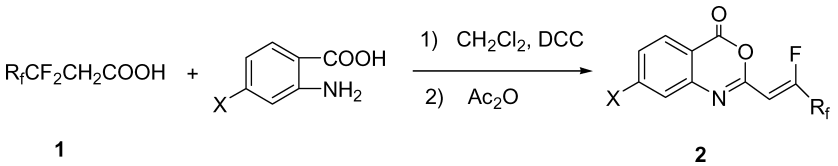
Many heterocyclic compounds containing fluorine or fluorocarbon groups showed potential biological activities and some of them had been employed in medicine and pesticides.[1] Thus to develop synthetic methods for fluorine-containing heterocyclic compounds has been a continuous subject of much research work in both organofluorine chemistry and organic synthesis. 4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones and 1-phenyl-4,9-dihydro-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones are important nitrogen-containing tricyclic compounds with unique biological properties, and their syntheses and properties have been studied in detail by Sircar and Catarzi respectively.[2,3] To our knowledge, little work was done on their fluorinated analogues due to the difficulty to synthesize these fluorine-containing heterocyclic compounds.

Recently, we developed a facile method for the preparation of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (**2**) from 2,2-dihydropolyfluoroalkanoic acids (Scheme 1).[4] Compound **2** is a reactive intermediate with both C-2 and the unsaturated carbon with a fluorine atom in the alkenyl group readily attacked by nucleophilic reagent.[5–12] It was found that **2** reacted with some dinucleophilic reagents readily, for instance, hydrazine hydrate or phenyl hydrazine. The subsequent cyclization gave tricyclic compound, 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones (**3**) and 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (**4**) respectively. The results are reported in this paper.

2. Results and discussion

2.1. Reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (2) with hydrazine hydrate

In the presence of Et_3N, compound **2** reacted readily with a little excess of hydrazine hydrate in ethanol under reflux to form a new compound as shown by TLC (Scheme 2). After workup, a white solid was obtained in high yield. The



1 2

Scheme 1.

Keywords: 2-(1-Hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones; Hydrazine hydrate; 2-Fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones; 3-Fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones; Phenyl hydrazine.
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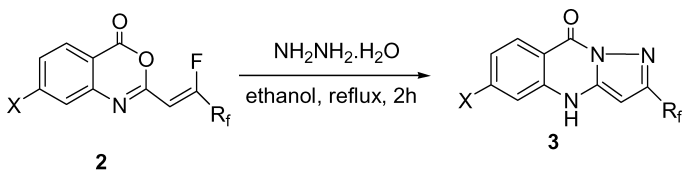


a : R_f = CF_2Cl, X = H; b : R_f = $(CF_2)_3F$, X = H; c : R_f = $(CF_2)_3Cl$, X = H;

d : R_f = $(CF_2)_5Cl$, X = H; e : R_f = $(CF_2)_3F$, X = Cl

Scheme 2.

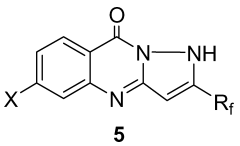


Figure 1.

in this reaction. The difference in spectra between the analogues of **3** and **5** are trivial in literature,[2,3,13–16] therefore it is difficult to determine the products' structures according to the above spectra. Fortunately a single crystal of compound **3e** was obtained and the X-ray crystallography assigned the structure as isomer **3** (Fig. 2). The results are summarized in Table 1.

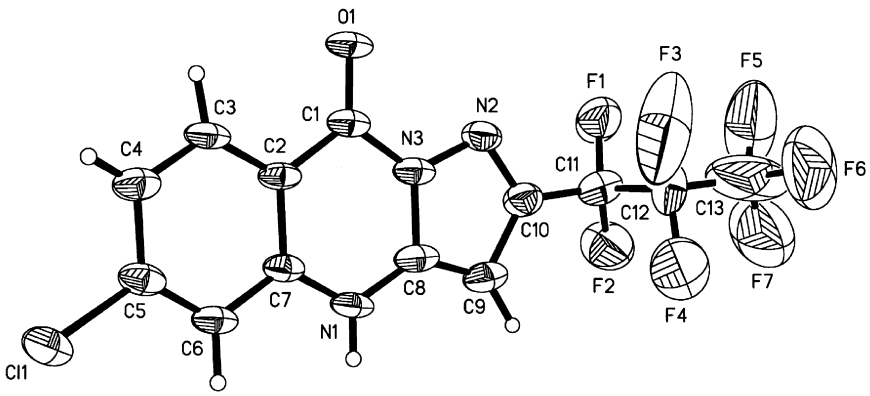


Figure 2. Molecular structure of compound **3e** (CCDC number: CCDC 219160).

Table 1. The Reaction of **2** with hydrazine hydrate

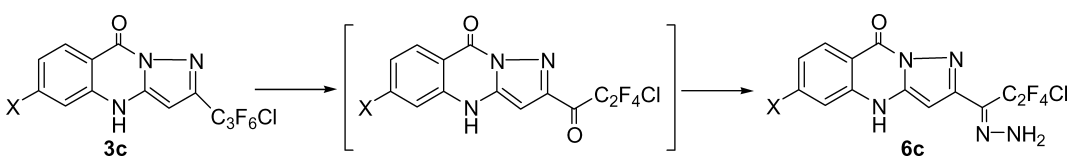
Entry	Substrate	R_f	X	Solvent	Product	Yield (%)
1	**2a**	CF_2Cl	H	EtOH	**3a**	96
2	**2a**	CF_2Cl	H	C_6H_6	**3a**	94
3	**2a**	CF_2Cl	H	DMF	**3a**	91
4	**2b**	$(CF_2)_2CF_3$	H	EtOH	**3b**	96
5	**2c**	$(CF_2)_3Cl$	H	EtOH	**3c**	96
6	**2d**	$(CF_2)_5Cl$	H	EtOH	**3d**	92
7	**2e**	$(CF_2)_2CF_3$	Cl	EtOH	**3e**	96

product is almost insoluble in chloroform, dichloromethane or benzene, but soluble in DMSO. Its ^{19}F NMR, ^{1}H NMR, HRMS and IR spectra indicated that it was a tricyclic compound with a fluoroalkyl substituent. According to the data, either 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-one (**3**) or its isomer, compound **5** (Fig. 1), might be formed

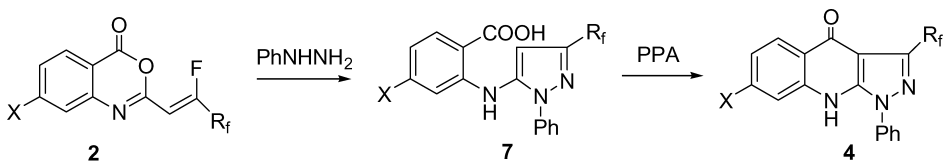
As shown in Table 1, both R_f and substituent X had little influence on the reaction result. Other solvents such as C_6H_6, MeCN and DMF may also be used. But for the reaction of **2c** compound **6c** was obtained as a by-product when longer time and excess hydrazine hydrate was used in the reaction of **2c** with hydrazine hydrate. This might be caused by the hydrolysis of the CF_2 group next to aromatic pyrazole ring[17,18] and the subsequent nucleophilic attack of hydrazine hydrate to the resulting carbonyl group (Scheme 3).

2.2. Reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones (2) with phenyl hydrazine

Under similar conditions the reaction of **2** with phenyl hydrazine, however, afforded the ring-opening product **7** as main product instead of the desired tricyclic compound as above (Scheme 4). As shown in Table 2, ethanol was the



Scheme 3.



b : R_f = (CF_2)$_3$F, X = H; c : R_f = (CF_2)$_3$Cl, X = H; e : R_f = (CF_2)$_3$F, X = Cl;

f : R_f = CF_3, X = H; g : R_f = CF_3, X = Cl; h : R_f = (CF_2)$_3$Cl, X = Cl

Scheme 4.

Table 2. The reaction of **2** with phenyl hydrazine

Entry	Substrate	R_f	X	Solvent	Product	Yield (%)
1	**2b**	$(CF_2)_2CF_3$	H	EtOH	**7b**	84
2	**2b**	$(CF_2)_2CF_3$	H	DMF	**7b**	43
3	**2b**	$(CF_2)_2CF_3$	H	PhH	**7b**	55
4	**2c**	$(CF_2)_3Cl$	H	EtOH	**7c**	82
5	**2e**	$(CF_2)_2CF_3$	Cl	EtOH	**7e**	76
6	**2f**	CF_3	H	EtOH	**7f**	75
7	**2g**	CF_3	Cl	EtOH	**7g**	72
8	**2h**	$(CF_2)_3Cl$	Cl	EtOH	**7h**	77

best solvent of all solvents tested. Usually better results were obtained when 1.2 equiv. of phenyl hydrazine was used and the yield of **7** decreased when more phenyl hydrazine was added. Treatment of compound **7** in polyphosphoric acid at 170 °C for about 4 h afforded the corresponding cyclization product, 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-one (**4**), in 91–95% yields. The reaction conditions must be controlled carefully for a good result. Higher temperature and longer reaction time would cause the reaction more complex and lower yields. The results are summarized in Table 3.

Table 3. Cyclization reaction of **7**

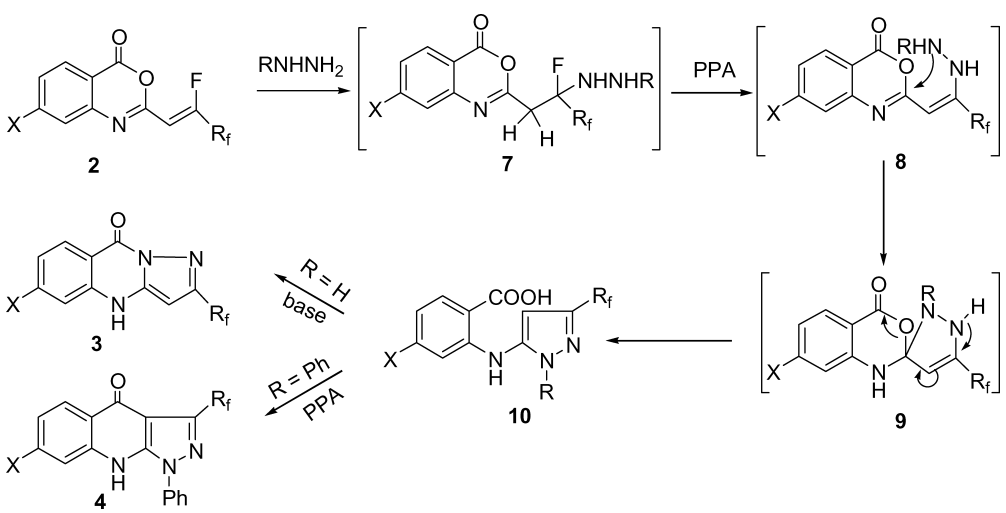
Entry	Substrate	R_f	X	Conditions	Product	Yield (%)
1	**7b**	$(CF_2)_3F$	H	PPA, 170 °C, 2 h	**4b**	95
2	**7f**	CF_3	H	PPA, 170 °C, 2 h	**4f**	92
3	**7f**	CF_3	H	PPA, 170 °C, 4 h	**4f**	85
4	**7f**	CF_3	H	PPA, 170 °C, 8 h	**4f**	77
5	**7g**	CF_3	Cl	PPA, 170 °C, 2 h	**4g**	91

2.3. Mechanism

A mechanism involving nucleophilic substitution and ring rearrangement was proposed for the formation of compound **3** and **4** as shown in Scheme 5. Nucleophilic attack of NH_2 to the unsaturated carbon with a fluorine atom in the alkenyl group of compound **2** followed by the elimination of a HF gave intermediate **8**. Next the carbon at 2-position in **8** was attacked by another nucleophilic nitrogen to give intermediate **9**, which underwent rearrangement to form the ring-opening intermediate **10**. For R=H, in the presence of Et_3N the condensation reaction between COOH and N–H in the pyrazole ring of intermediate **10** readily took place to give compound **3** as final product. In the case of phenyl hydrazine this condensation reaction did not occur since no N–H group in the pyrazole ring was present, and the condensation of COOH and C–H was difficult under the reaction conditions. Thus compound **7** was obtained in this step and underwent cyclization reaction under more vigorous conditions in PPA to give compound **4**.

3. Conclusions

In conclusion, the reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with hydrazine hydrate and phenyl hydrazine was achieved under mild conditions,



Scheme 5.

providing a convenient method for the synthesis of two kinds of fluoroalkylated nitrogen-containing tricyclic compounds, 2-fluoroalkyl-4*H*-pyrazolo[5,1-*b*]quinazolin-9-ones and 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones. Further investigation on the reaction of 2-(1-hydropolyfluoro-1-alkenyl)-4*H*-3,1-benzoxin-4-ones with other nucleophilic reagents is in progress.

4. Experimental

Melting points were uncorrected. IR spectra were taken on a Perkin–Elmer 983G IR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AM300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM300 (282 MHz) spectrometer, chemical shifts are reported as δ_{CFCl3} ($\delta_{CFCl3}=\delta_{TFA}-76.8$), negative for upfield shifts. Mass spectra were obtained on a Finnigan GC-MS 4021 spectrometer. X-ray data were measured at 293 K on a Bruker SMART CCD diffractomer with graphite monochromated Mo Kα radiation. Column chromatography was performed using silica gel H, particle size 10–40 μ.

4.1. Synthesis of 2-fluoroalkyl-*4H*-pyrazolo[5,1-*b*] quinazolin-9-ones (3)

Typical procedure. 1.0 mmol of **2**, 1.2 mmol of hydrazine hydrate and 1 mL of Et_3N in 10 mL of ethanol was stirred under reflux for about 2 h (monitored by TLC). After removal of the solvent, the solid residue obtained was purified by column chromatography (hexane/ethyl acetate=2:1) or by washing several times with chloroform and the subsequent recrystallization in ethanol to give **3**.

4.1.1. Compound 3a. White solid, mp 238–240 °C. IR (KBr, cm^{-1}): ν_{max} 3276, 3194, 3121, 2927, 2854, 1745, 1681, 1651, 1578, 1506, 1468, 1352, 1204, 1114, 990, 874, 748. ^{19}F NMR (acetone-d$_6$, δ, ppm): −67.8 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.21–8.16 (m, 1H), 7.72–7.64 (m, 1H), 7.40–7.34 (m, 1H), 7.26–7.21 (m, 1H), 6.27 (s, 1H), 2.70 (br, 1H). EI-MS *m*/*z*: 271 (M^++2, 22), 269 (M^+, 67), 234 (M^+-Cl, 72), 219 (M^+-CF_2, 24), 185 (M^+-CF_2Cl+1, 100). EI-HRMS calcd For $C_{11}H_6F_2N_3O$ (M^+-Cl): 234.0479. Found: 234.0457.

4.1.2. Compound 3b. White solid, mp 280–282 °C. IR (KBr, cm^{-1}): ν_{max} 3293, 3227, 3164, 1708, 1631, 1578, 1475, 1210, 1116, 989, 872, 751. ^{19}F NMR (acetone-d$_6$, δ, ppm): −81.1 (s, 3F), −112.8 (s, 2F), −127.1 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.21 (d, *J*=8.1 Hz, 1H), 7.73–7.68 (m, 1H), 7.40 (d, *J*=8.1 Hz, 1H), 7.27–7.22 (m, 1H), 6.33 (s, 1H), 2.70 (br, 1H). EI-MS *m*/*z*: 354 (M^++1, 100), 353 (M^+, 91), 335 (M^+-F, 14), 234 ($M^+-CF_2CF_3$, 30), 206 (61). EI-HRMS calcd for $C_{13}H_6F_7N_3O$: 353.0399. Found: 353.0417.

4.1.3. Compound 3c. White solid, mp 278–280 °C. IR (KBr, cm^{-1}): ν_{max} 3292, 3225, 3130, 1708, 1631, 1577, 1473, 1191, 1115, 756. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.4 (s, 2F), −110.8 (s, 2F), −122.1 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.28 (d, *J*=8.1 Hz, 1H), 7.80–7.74 (m, 1H), 7.49 (d, *J*=8.1 Hz, 1H), 7.34–7.29 (m, 1H), 6.18 (s, 1H), 3.20 (br, 1H). EI-MS *m*/*z*: 371 (M^++2, 32), 369 (M^+, 100), 334 (M^+-Cl, 20), 234 ($M^+-CF_2CF_2Cl$, 49), 206 (49). EI-HRMS calcd for $C_{13}H_6F_6N_3O$ (M^+-Cl): 334.0415. Found: 334.0431.

4.1.4. Compound 3d. White solid, mp 282–284 °C. IR (KBr, cm^{-1}): ν_{max} 3290, 3225, 1708, 1633, 1577, 1475, 1211, 1135, 1048, 973, 959, 752, 735. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.3 (s, 2F), −110.1 (s, 2F), −119.9 (s, 2F), −120.5 (s, 2F), −122.0 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 8.28 (d, *J*=8.1 Hz, 1H), 7.82–7.71 (m, 1H), 7.48 (d, *J*=8.1 Hz, 1H), 7.32–7.26 (m, 1H), 6.38 (s, 1H), 3.50 (br, 1H). EI-MS *m*/*z*: 471 (M^++2, 47), 469 (M^+, 100), 434 (M^+-Cl, 23), 234 ($M^+-CF_2CF_2CF_2CF_2Cl$, 62), 206 (37). Anal. calcd for $C_{15}H_6ClF_{10}N_3O$: C, 38.36; H, 1.29; N, 8.95. Found: C, 38.52; H, 1.53; N, 9.10.

4.1.5. Compound 3e. White solid, mp 288–290 °C. IR (KBr, cm^{-1}): ν_{max} 3280, 3196, 1645, 1347, 1272, 1224, 1110, 872, 756. ^{19}F NMR (acetone-d$_6$, δ, ppm): −80.2 (s, 3F), −107.3 (s, 2F), −126.8 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 7.09 (d, *J*=9.0 Hz, 1H), 6.35 (s, 1H), 6.21 (d, *J*=9.0 Hz, 1H), 5.45 (s, 1H). EI-MS *m*/*z*: 389 (M^++2, 41), 387 (M^+, 100), 268 (M^+-F, 34), 268 ($M^+-CF_2CF_3$). Anal. calcd for $C_{13}H_5ClF_7N_3O$: C, 40.28; H, 1.30; N, 10.84. Found: C, 40.20; H, 1.21; N, 10.81.

4.1.6. Compound 6c. White solid which decomposed at 280 °C. IR (KBr, cm^{-1}): ν_{max} 3498, 3406, 3294, 3104, 2966, 1668, 1641, 1562, 1117, 1091, 943, 753. ^{19}F NMR (acetone-d$_6$, δ, ppm): −68.6 (s, 2F), −106.2 (s, 2F). ^{1}H NMR (acetone-d$_6$, δ, ppm): 11.01 (br, 2H), 9.01 (br, 1H), 8.32–8.28 (m, 1H), 7.82–7.77 (m, 1H), 7.49–7.47 (m, 1H), 7.36–7.31 (m, 1H), 6.16 (s, 1H). EI-MS *m*/*z*: 363 (M^++2, 24), 361 (M^+, 72), 333 (59), 248 (100), 228 (26), 326 (M^+-Cl, 23), 228 ($M^+-C_2F_4Cl$). Anal. calcd for $C_{13}H_8ClF_4N_5O$: C, 43.17; H, 2.23; N, 19.36. Found: C, 43.25; H, 2.24; N, 19.56.

4.2. Synthesis of 2-(2-phenyl-5-fluoroalkyl-2*H*-pyrazol-3-yl) benzoic acids (7)

Typical procedure. A mixture of 1.0 mmol of compound **2** and 1.2 mmol of phenyl hydrazine in 10 mL of ethanol was stirred under reflux for 4–5 h. After removal of the solvent, the solid residue was subjected to column chromatography (light petroleum/ethyl acetate=1:2) to give compound **7**.

4.2.1. Compound 7b. Yellow solid, mp 241–243 °C. IR (KBr, cm^{-1}): ν_{max} 3250, 1663, 1594, 1563, 1236, 1109, 893, 866, 741. ^{19}F NMR ($CDCl_3$, δ, ppm): −79.1 (s, 3F), −110.7 (s, 2F), −126.3 (s, 2F). ^{1}H NMR ($CDCl_3$, δ, ppm): 9.68 (s, 1H), 8.05 (dd, *J*=8.2, 1.2 Hz, 1H), 7.41–7.59 (m, 6H), 7.19 (d, *J*=8.2 Hz, 1H), 6.94 (t, *J*=7.8 Hz, 1H), 6.59 (s, 1H). EI-MS *m*/*z*: 447 (M^+, 65), 429 (M^+-OH-1, 100), 310 ($M^+-OH-CF_3CF_2$, 29), 260 ($M^+-OH-C_3F_7$-1, 35). EI-HRMS calcd for $C_{19}H_{12}F_7N_3O_2$: 447.0818. Found: 447.0832.

4.2.2. Compound 7c. Yellow solid, mp 238–239 °C. IR (KBr, cm^{-1}): ν_{max} 3246, 1663, 1595, 1561, 1455, 1263, 1241, 1195. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.6 (s, 2F), −110.0 (s, 2F), −121.8 (s, 2F). ^{1}H NMR ($CDCl_3$, δ, ppm):

9.67 (s, 1H), 8.05 (dd, J=8.4, 1.2 Hz, 1H), 7.44–7.59 (m, 6H), 7.17 (d, J=8.4 Hz, 1H), 6.93 (t, J=7.7 Hz, 1H), 6.59 (s, 1H). EI-MS *m/z*: 465 (M^++2, 24), 463 (M^+, 69), 445 (M^+−OH-1, 100), 410 (M^+−OH−Cl-1, 7), 310 (M^+−OH−$ClCF_2CF_2$-1, 40), 260 (M^+−OH−$ClCF_3CF_2$-CF_2-1, 62). EI-HRMS calcd for: $C_{19}H_{12}ClF_6N_3O_2$: 463.0522. Found: 463.0486.

4.2.3. Compound 7e. Yellow solid, mp 251–254 °C. IR (KBr, cm^{-1}): ν_{max} 3255, 1665, 1587, 1234, 1186, 1112, 879, 764. ^{19}F NMR ($CDCl_3$, δ, ppm): −79.9 (s, 3F), −111.5 (s, 2F), −126.6 (s, 2F). ^1H NMR ($CDCl_3$, δ, ppm): 9.66 (s, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.34–7.56 (m, 5H), δ 7.07 (d, J=1.8 Hz, 1H), 6.88 (dd, J=8.6, 1.8 Hz, 1H), 6.61 (s, 1H). EI-MS *m/z*: 483 (M^++2, 23) 481 (M^+, 65), 463 (M^+−OH-1, 100), 344 (M^+−OH−CF_3CF_2-1, 33), 294 (M^+−OH−$CF_3CF_2CF_2$-1, 43). Anal. calcd for $C_{19}H_{11}ClF_7N_3O_2$: C, 47.37; H, 2.30; N, 8.72. Found: C, 47.25; H, 2.41; N, 8.40.

4.2.4. Compound 7f. Yellow solid, mp 255–257 °C. IR (KBr, cm^{-1}): ν_{max} 3274, 1668, 1589, 1269, 1247, 1122, 970, 751. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.6 (s, 3F). ^1H NMR ($CDCl_3$, δ, ppm): 9.69 (s, 1H), 8.04 (d, J=7.9 Hz, 1H), 7.42–7.58 (m, 6H), 7.20 (d, J=8.5 Hz, 1H), 6.93 (t, J=7.6 Hz, 1H), 6.57 (s, 1H). EI-MS *m/z*: 347 (M^+, 100), 329 (M^+−OH-1, 63), 260 (M^+−OH−CF_3-1, 15). EI-HRMS calcd for $C_{17}H_{12}F_3N_3O_2$: 347.0882. Found: 347.0858.

4.2.5. Compound 7g. Yellow solid, mp 263–264 °C. IR (KBr, cm^{-1}): ν_{max} 3285, 1663, 1603, 1585, 1241, 1149, 971, 759. ^{19}F NMR ($CDCl_3$, δ, ppm): −61.4 (s, 3F). ^1H NMR ($CDCl_3$, δ, ppm): 9.70 (s, 1H), 7.93 (d, J=7.5 Hz, 1H), 7.43–7.53 (m, 5H), 7.09 (s, 1H), 6.85 (d, J=7.5 Hz, 1H), 6.58 (s, 1H). EI-MS *m/z*: 383 (M^++2, 18), 381 (M^+, 52), 363 (M^+−OH-1, 100), 294 (M^+−OH−CF_3-1, 15). EI-HRMS calcd for $C_{17}H_9ClF_3N_3O$ (M^+−OH-1): 363.0386. Found: 363.0340.

4.2.6. Compound 7h. Yellow solid, mp 250–252 °C. IR (KBr, cm^{-1}): ν_{max} 3277, 1664, 1600, 1572, 1506, 1240, 1170, 1135, 821, 765. ^{19}F NMR ($CDCl_3$, δ, ppm): −65.5 (s, 2F), −108.8 (s, 2F), −120.1 (s, 2F). ^1H NMR ($CDCl_3$, δ, ppm): 9.67 (s, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.45–7.55 (m, 5H), 7.07 (s, 1H), 6.89 (d, J=8.6 Hz, 1H), 6.61 (s, 1H). EI-MS *m/z*: 497 (M^+, 55), 481 (M^+−OH+1, 66), 480 (M^+−OH, 47), 479 (M^+−OH-1, 100), 444 (M^+−OH−Cl-1, 8), 344 (M^+−OH−$ClCF_2CF_2$-1, 40). EI-HRMS calcd for $C_{19}H_{11}Cl_2F_6N_3O_2$: 497.0133. Found: 497.0131.

4.3. Synthesis of 1-phenyl-4,9-dihydro-3-fluoroalkyl-1*H*-pyrozolo[3,4-*b*]quinolin-4-ones (4)

Typical procedure. A mixture of 0.5 g of **7** and 10 g of PPA was stirred for 3–4 h at 170 °C. After cooling the reaction mixture was neutralized with aqueous 2 N NaOH to pH=7, extracted with ethyl ether (15 mL×3). The combined organic phase was washed with water and saturated NaCl solution twice respectively, dried over anhydrous Na_2SO_4. After removal of solvent, the solid residue was purified by column chromatography (hexane/ethyl acetate=3:1) to give compound **4**.

4.3.1. Compound 4b. Yellow solid, mp 250–253 °C. IR (KBr, cm^{-1}): ν_{max} 3198, 1627, 1593, 1233, 1117, 759. ^{19}F NMR (acetone-d_6, δ, ppm): −81.3 (s, 3F), −109.1 (s, 2F), −126.3 (s, 2F). ^1H NMR (acetone-d_6, δ, ppm): 8.42 (d, J=7.3 Hz, 1H), 7.88 (dd, J=8.8 Hz, 1.7 Hz, 1H), 7.68–7.78 (m, 6H), 7.38–7.42 (m, 1H), 3.10 (br, 1H). EI-MS *m/z*: 429 (M^+, 100), 310 (M^+−CF_2CF_3, 43). EI-HRMS calcd for $C_{19}H_{10}F_7N_3O$: 429.0712. Found: 429.0709.

4.3.2. Compound 4f. Yellow solid, mp 265–267 °C. IR (KBr, cm^{-1}): ν_{max} 3186, 1628, 1593, 1233, 758. ^{19}F NMR (acetone-d_6, δ, ppm): −63.4 (s, 3F). ^1H NMR (acetone-d_6, δ, ppm): 8.41 (d, J=8.0 Hz, 1H), 7.87 (dd, J=8.4, 1.4 Hz, 1H), 7.63–7.78 (m, 6H), 7.38–7.43 (m, 1H), 3.30 (br, 1H). EI-MS *m/z*: 329 (M^+, 100), 260 (M^+−CF_3, 8), 243 (45). EI-HRMS calcd for $C_{17}H_{10}F_3N_3O$: 329.0776. Found: 329.0766.

4.3.3. Compound 4g. Yellow solid, mp 271–272 °C. IR (KBr, cm^{-1}): ν_{max} 3168, 1631, 1596, 1139, 931. ^{19}F NMR (acetone-d_6, δ, ppm): −62.8 (s, 3F). ^1H NMR (acetone-d_6, δ, ppm): 8.33 (d, J=8.7 Hz, 1H), 7.62–7.85 (m, 6H), 7.35 (dd, J=8.7, 1.9 Hz, 1H), 3.15 (br, 1H). EI-MS *m/z*: 365 (M^++2, 37), 363 (M^+, 100), 328 (M^+−Cl, 17), 294 (M^+−CF_3, 8). EI-HRMS calcd for $C_{17}H_9ClF_3N_3O$: 363.0386. Found: 363.0382.

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An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

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Abstract—A straightforward synthesis of trityl alcohols in which one of the aryl rings is substituted with a vinyl group is presented. The synthesis of the alcohols involves the direct addition of the Grignard reagent prepared from 4-bromostyrene to substituted benzophenones. These compounds are used to incorporate trityl linker groups into polystyrene-based organic synthesis supports. Both non-cross-linked and cross-linked (*J*anda*J*el™) polystyrene have been prepared using these monomers.

1. Introduction

In polymer-supported synthesis, linker moieties are required for the attachment of the synthesis substrate to the polymer support. Commonly these linker groups are based on standard protecting groups used in traditional solution-phase synthesis.[1] Trityl groups[2] are often used in this context since they can be prepared with various substituents on the aryl rings that modulate their cleavage and because they can serve as protecting groups for alcohols,[3] acids,[4] amides,[5] amines,[6] amino acids,[7] hydroxamic acids,[8] imidazoles,[9] nucleotides,[10] thiols,[11] and thioureas.[12] The most common trityl group functionalized polymers used in this regard are cross-linked unsubstituted trityl resin[13] and 2-chlorotrityl resin.[14]

The polymer-bound trityl alcohol groups of such resins are usually introduced by one of three methods: (1) The sequence of lithiation of a halogentated phenyl group of a preformed polymer, followed by treatment with a benzophenone.[15] (2) The sequence of Friedal–Crafts acylation of a preformed polymer with a benzoyl chloride followed by the addition of an aryl Grignard reagent.[10,16] (3) Direct lithiation of cross-linked polystyrene using a 1:1 complex of *n*-BuLi and TMEDA, followed by reaction with a benzophenone.[17] However, a significant drawback of all of these methods is that since they derivatize preformed polymers, it is difficult to determine the final composition of the product polymer and to accurately control its homogeneity and loading level.[18]

Therefore, in order to prepare better defined polymers with easily controllable levels of trityl group incorporation, the functional monomer, (4-ethenylphenyl)diphenyl methanol (**1a**) (Scheme 1), has been prepared and co-polymerized with styrene and divinylbenzene under suspension polymerization conditions to afford polystyrene trityl resin by Kurth et al.[19] The first reported synthesis of **1a** involved the addition of *t*-BuLi to 4-bromostyrene followed by reaction of the thus formed aryl lithium species with benzophenone.[19a] The same authors also reported a procedure involving the use of potassium, potassium iodide and anhydrous magnesium chloride to activate 4-bromostyrene.[19b] Later, Rimmer et al. reported that the first synthesis of **1a** was not reproducible due to anionic polymerization of the starting material, and that an inverse addition procedure (4-bromostyrene added to *t*-BuLi) afforded acceptable and reproducible yields of **1a**.[20] Most recently, Janda et al. have reported the only other method for the preparation of **1a** which involves a four-step synthetic sequence starting with 4-vinylbenzyl alcohol.[21] While these reported syntheses do produce the desired product, they are less than optimal, especially when considering the reported difficulty in reproducing the results, the costs and hazards associated with using *t*-BuLi and potassium, and the length of the most recent synthesis. Furthermore, they have not been demonstrated to be general methods for the preparation of substituted trityl monomers, as they only report the synthesis of **1a**.

We are interested in the preparation and applications of polymers that incorporate monomers derivatized with various functional groups[22] and have successfully used the Grignard reagent formed from 4-bromostyrene to prepare monomers containing sulfide[23] and phosphine[24] groups.

Keywords: Trityl alcohols; Monomers; Peptide synthesis.
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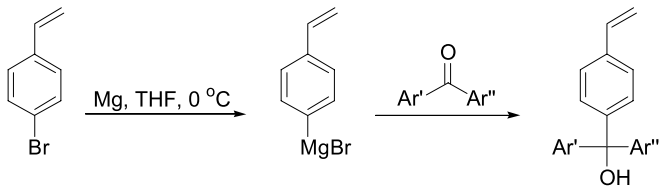


1a-1g

1a: Ar' = Ar" = Ph (65%)

1b: Ar' = Ph, Ar" = 4-Me-C_6H_4 (65%)

1c: Ar' = Ph, Ar" = 4-OMe-C_6H_4 (67%)

1d: Ar' = Ar" = 4-OMe-C_6H_4 (75%)

1e: Ar' = Ph, Ar" = 2-Cl-C_6H_4 (77%)

1f: Ar' = Ph, Ar" = 4-Cl-C_6H_4 (72%)

1g: Ar' = Ar" = 4-Cl-C_6H_4 (82%)

Scheme 1. Synthesis of monomers **1a**–**f**.

Herein we report our results using this reagent to prepare **1a** and derivatives of it and the incorporation of these into both cross-linked and, for the first time, non-cross-linked polystyrene polymers.

2. Results and discussion

Obviously, the most direct method for preparing compounds **1** is via the nucleophilic addition of a styrene equivalent to a substituted benzophenone. Hence this was the method used in the first reported synthesis of such compounds.[19a] However, the nucleophile used was an aryl lithium and the reagents used in the preparation of such a species can readily initiate anionic polymerization of styrene molecules and makes this method low yielding and unreliable.[20] Therefore we chose to examine the addition of the relatively less nucleophilic and more easily prepared styrene Grignard reagent, prepared simply from 4-bromostyrene and magnesium,[25] to a series of benzophenones (Scheme 1).

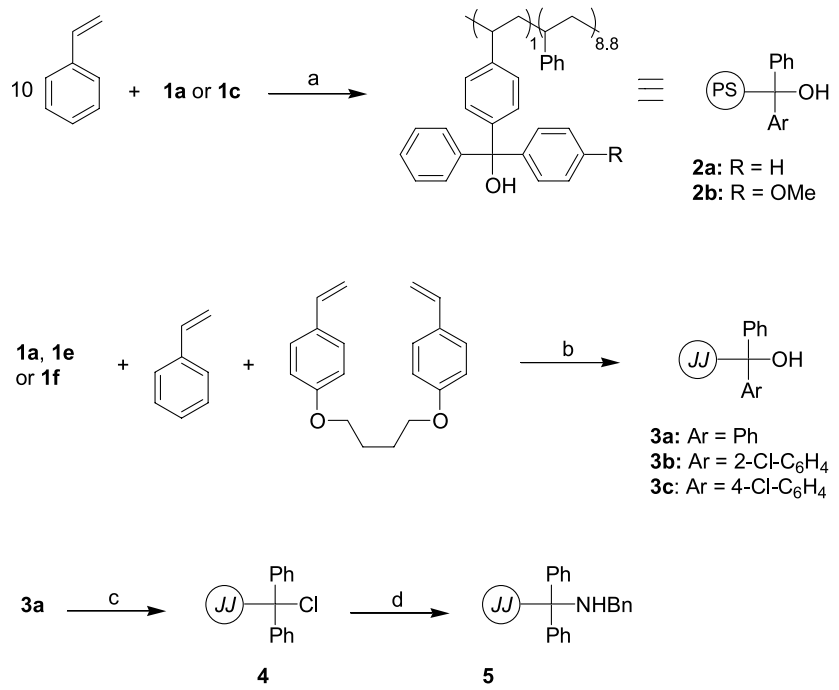
Gratifyingly, these reactions afforded good yields (65–82%) of the desired products (**1a**–**g**), even when the benzophenones were substituted with deactivating electron donating groups. As might be expected, the benzophenones substituted with electron withdrawing substituents afforded slightly higher yields (**1e**–**g**). In all of these reactions, 4-bromostyrene was used in excess of the benzophenone since any unreacted Grignard reagent was converted to easily removable styrene. When it was used as the limiting reagent, the excess benzophenone was more tedious to separate from the desired alcohol. It should be noted that the synthesis of only monomer **1a** has been previously reported and that monomer **1d** represents a new linker group. To our knowledge, no previously used trityl linker in solid-phase synthesis contained more than one electron donating group in addition to the alkyl group from the polystyrene backbone, to modulate the electron density at the incipient carbocation center.[26] Therefore the use of these types of more highly substituted linkers may allow for the synthesis substrates to be more selectively or mildly cleaved from the polymers.

We next examined the use of our monomers in the preparation of both non-cross-linked and cross-linked polystyrenes (Scheme 2). Co-polymerization of **1a** with styrene in the presence of AIBN afforded soluble polymer **2a**, which is reported here for the first time. In order to determine the efficiency of incorporation of the functional monomers in this polymerization process, monomer **1c** was co-polymerized with styrene to afford **2b**. Analysis of **2b** by ^{1}H NMR shows that reaction of a 10:1 ratio of styrene/**1c** results in the observed incorporation of these monomers in a ratio of 8.8:1. This indicates that the monomers with electron donating substituents are slightly more reactive than styrene in the polymerization process.

Suspension co-polymerization of **1a**, **1e** and **1f** with styrene and the *J*anda*J*el cross-linker, 1,4-bis(4-vinylphenoxy)-butane, afforded *JJ*-Tr-OH (**3a**), *JJ*-2-Cl-Tr-OH (**3b**), and *JJ*-4-Cl-Tr-OH (**3c**), respectively (Scheme 2).[27–29] It is important to note that the loading levels of **3b** and **3c**, based on elemental analysis of chlorine, are slightly lower than expected (theoretical 1.5 mmol/g loading each, observed 1.3 mmol/g (**3b**), and 1.1 mmol/g (**3c**)). This implies that, in contrast to **1c**, monomers **1e** and **1f** react more slowly than styrene during polymerization. These differences in reactivity must therefore be taken into account when preparing polymers with specific loading levels. In order to determine the rate of incorporation of **1a** into **3a**, we treated **3a** sequentially with TBDMSCl/DMSO[16c,30] and $BnNH_2$ to form **4** and **5**, respectively. Elemental analysis of both **4** (chlorine, 5.4%) and **5** (nitrogen, 2.1%) indicates that **3a** has a loading level close to the theoretical 1.5 mmol/g.

3. Conclusions

In summary, we have developed an improved, general and reproducible method for the synthesis of a variety of substituted triphenyl methanols that contain a vinyl group. These compounds can be used to directly introduce trityl linker groups into both soluble and insoluble polystyrene polymers. Given the wide range of substituted benzophenones that are commercially available or easily synthesized, our methodology allows access to a great number of



Scheme 2. Synthesis of polymers **2**–**5**. Reagents and conditions: (a) AIBN, toluene, 80 °C. (b) Chlorobenzene, benzoyl peroxide, water, acacia gum, NaCl, 85 °C. (c) TBDMSCl, DMSO, CH_2Cl_2, rt. (d) $BnNH_2$, THF, rt.

new trityl linkers having varying acid sensitivities, which should further enhance the applicability of such linkers. The utility of such linkers in the new non-cross-linked polymers **2a**–**b** in polymer-supported peptide/organic synthesis is currently being assessed.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Tetrahydrofuran was distilled under a N_2 atmosphere over sodium and benzophenone. Dichloromethane was distilled under a N_2 atmosphere over calcium hydride Merck silica gel 60 (230–400 mesh) was used for chromatography. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. The NMR spectra were recorded using a Bruker DRX 300 spectrometer. Chemical shift data are expressed in ppm with reference to TMS. EI-MS data were recorded on a Finnigan MAT 96 mass spectrometer.

4.1.1. (4-Ethenylphenyl)diphenyl methanol (1a). *Procedure A*. Benzophenone (12.4 g, 68 mmol) was added dropwise at 0 °C to a solution of the Grignard reagent prepared from 4-bromostyrene (14.0 g, 76 mmol) and Mg (2.2 g, 92 mmol) in dry THF (250 mL). After TLC analysis indicated electrophile consumption was complete, the reaction mixture was diluted with diethyl ether (1 L), and then washed sequentially with water (500 mL), 10% aqueous HCl (500 mL), saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **1a** as a white solid (12.6 g, 44 mmol, 65%). Mp 72–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77 (s, 1H, exchangeable with D_2O), 5.24 (dd, 1H, J=10.9, 0.9 Hz), 5.74 (dd, 1H, J=17.6, 0.9 Hz), 6.68 (dd, 1H, J=17.6, 10.9 Hz), 7.17–7.36 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.9, 114.1, 125.8, 127.3 (2C), 127.9 (4C), 128.0 (4C), 128.2 (2C), 128.7 (2C), 136.4, 144.3, 146.8 (2C). HR EI-MS: calcd for $C_{21}H_{18}O$, 286.1358; found 286.1356.

4.1.2. (4-Ethenylphenyl)-(4-methylphenyl)phenyl methanol (1b). This was prepared by procedure A using 4-methylbenzophenone (1.4 g, 6.9 mmol) to afford **1b** as a pale yellow solid (1.3 g, 4.5 mmol, 65%). Mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.73 (s, 1H, exchangeable with D_2O), 5.40 (dd, 1H, J=10.9, 0.9 Hz), 5.73 (dd, 1H, J=17.6, 0.9 Hz), 6.68 (dd, 1H, J=17.6, 10.9 Hz), 7.10–7.36 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 81.8, 114.0, 125.7 (2C), 127.2, 127.8 (2C), 127.90 (2C), 127.92 (2C), 128.1 (2C), 128.7 (2C), 136.38, 136.44, 137.0, 143.9, 146.6, 146.9. HR EI-MS: calcd for $C_{22}H_{20}O$, 300.1514; found 300.1512.

4.1.3. (4-Ethenylphenyl)-(4-methoxyphenyl)phenyl methanol (1c). This was prepared by procedure A using 4-methoxybenzophenone (6.5 g, 31 mmol) to afford **1c** as a pale yellow liquid (6.5 g, 21 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76 (s, 1H, exchangeable with D_2O), 3.78 (s, 3H), 5.23 (dd, 1H, J=10.9, 0.9 Hz), 5.73 (dd, 1H, J=17.6, 0.9 Hz), 6.68 (dd, 1H, J=17.6, 10.9 Hz), 6.81–7.35 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 81.6, 113.3 (2C), 114.0, 125.8 (2C), 127.2, 127.8 (2C),

127.9 (2C), 128.0 (2C), 129.2 (2C), 136.4, 136.5, 139.1, 146.7, 147.0, 158.8. HR EI-MS: calcd for $C_{22}H_{20}O_2$, 316.1463; found 316.1459.

4.1.4. Bis(4-methoxyphenyl)phenyl methanol (1d). This was prepared by procedure A using 4,4′-dimethoxybenzophenone (1.5 g, 6.1 mmol) to afford **1d** as a pale yellow liquid (1.6 g, 4.6 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 1H, exchangeable with D_2O), 3.79 (s, 6H), 5.23 (dd, 1H, J=10.9, 0.9 Hz), 5.73 (dd, 1H, J=17.6, 0.9 Hz), 6.67 (dd, 1H, J=17.6, 10.9 Hz), 6.81–7.36 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4 (2C), 81.4, 113.3 (4C), 114.1, 125.8 (2C), 128.1 (2C), 129.2 (4C), 136.47, 136.51, 139.5 (2C), 147.0, 158.8 (2C). HR EI-MS: calcd for $C_{23}H_{22}O_3$, 346.1569; found 346.1545.

4.1.5. (2-Chlorophenyl)-(4-ethenylphenyl)phenyl methanol (1e). This was prepared by procedure A using 2-chlorobenzophenone (7.5 g, 35 mmol) to afford **1e** as a colourless liquid. (8.5 g, 27 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 1H, exchangeable with D_2O), 5.20 (dd, 1H, J=10.9, 0.8 Hz), 5.71 (dd, 1H, J=17.6, 0.8 Hz), 6.69 (dd, 1H, J=17.6, 10.9 Hz), 6.74–7.34 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.4, 114.1, 125.9 (2C), 126.4, 127.4, 127.7 (2C), 127.96 (2C), 128.0 (2C), 129.1, 131.3, 131.4, 133.2, 136.4, 136.6, 143.6, 145.2, 145.5. HR EI-MS: calcd for $C_{21}H_{17}ClO$, 320.0968; found 320.0971.

4.1.6. (4-Chlorophenyl)-(4-ethenylphenyl)phenyl methanol (1f). This was prepared by procedure A using 4-chlorobenzophenone (7.5 g, 35 mmol) to afford **1f** as a pale yellow liquid (8.0 g, 25 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 1H, exchangeable with D_2O), 5.25 (dd, 1H, J=10.9, 0.7 Hz), 5.76 (dd, 1H, J=17.6, 0.7 Hz), 6.69 (dd, 1H, J=17.6, 10.9 Hz), 7.13–7.41 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.6, 114.4, 126.0 (2C), 127.6 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 129.4 (2C), 130.2, 133.3, 136.3, 136.8, 145.4, 146.1, 146.4. HR EI-MS: calcd for $C_{21}H_{17}ClO$, 320.0968; found 320.0960.

4.1.7. Bis(4-chlorophenyl)phenyl methanol (1g). This was prepared by procedure A using 4,4′-dichlorobenzophenone (1.7 g, 6.8 mmol) to afford **1g** as a pale yellow liquid (2.0 g, 5.6 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 1H, exchangeable with D_2O), 5.27 (dd, 1H, J=10.9, 0.7 Hz), 5.75 (dd, 1H, J=17.6, 0.7 Hz), 6.69 (dd, 1H, J=17.6, 10.9 Hz), 7.14–7.35 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.2, 114.6, 126.0 (2C), 127.9 (2C), 128.2 (4C), 129.2 (4C), 133.5 (2C), 136.1, 137.0, 144.8 (2C), 145.5. HR EI-MS: calcd for $C_{21}H_{16}Cl_2O$, 354.0578; found 354.0576.

4.1.8. Poly(styrene-*co*-[4-ethenylphenyl]diphenyl-methanol) (2a). *Procedure B*. To a solution of styrene (18.2 g, 175 mmol) and **1a** (5.0 g, 17 mmol) in toluene (100 mL) was added AIBN (0.3 g, 1.7 mmol). The mixture was purged with N_2 for 30 min and the solution was stirred at 90 °C for 24 h. The solution was concentrated in vacuo and then the residue was taken up in 10 mL of THF. This solution was added dropwise to vigorously stir cold methanol (200 mL). The white precipitate was filtered and dried to afford **2a** as a white powder (11.6 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–2.16 (bm, 33H), 6.47–7.48 (bm, 58H). Polymers **2** are soluble in THF, EtOAc, CH_2Cl_2, DMF. They are not soluble in methanol, ethanol, ether, and water.

4.1.9. Poly(styrene-*co*-[4-ethenylphenyl]-[4-methoxyphenyl]phenyl-methanol) (2b). This was prepared by procedure B using styrene (16.5 g, 158 mmol), **1c** (5.0 g, 16 mmol) and AIBN (0.3 g, 1.6 mmol) in toluene (100 mL) to afford **2b** as a white powder (8.8 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–2.16 (bm, 33H), 3.74 (bs, 3H), 6.47–7.48 (bm, 57H). The ratio of monomer incorporation into **2b** was determined by ^{1}H NMR to be 8.8:1 (styrene/**1c**). This corresponds to a loading level of 0.8 mmol/g of polymer.

4.1.10. Poly(styrene-*co*-[4-ethenylphenyl]diphenyl methanol-*co*-1,4-bis[4-vinylphenoxy]butane) (*J*anda*J*el-Tr-OH, 3a). *Procedure C*. A solution of acacia gum (6.0 g) and NaCl (2.75 g) in warm deionion water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N_2 for 2 h.[31] A solution of **1a** (4.3 g, 15.0 mmol), styrene (6.3 mL, 57 mmol), cross-linker (0.4 g, 1.5 mmol), AIBN (0.2 g) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. This mixture was heated at 85 °C for 20 h. The crude polymer was collected and washed with hot water (3×100 mL) and then placed in a Soxhlet extractor and washed with THF for one day. The beads were recovered, washed with methanol, diethyl ether and hexanes. The shrunken beads **3a** (8.0 g, 80%) were dried in vacuo. Polymers **3** were isolated as beads that mostly ranged in size between 100 and 200 mesh. They exhibit good swelling in solvents such as THF, benzene and CH_2Cl_2. They exhibit poor or no swelling in solvents such as acetonitrile, dimethyl formamide, ethanol and water.

4.1.11. Poly(styrene-*co*-[2-chlorophenyl]-[4-ethenylphenyl]phenyl methanol-*co*-1,4-bis[4-vinylphenoxy]butane) (*J*anda*J*el-2-Cl-Tr-OH, 3b). This was prepared by procedure C using of **1e** (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **3b** (7.3 g, 73%). Elemental analysis was used to determine the chlorine content (4.6%) and thus the loading level of 1.3 mmol Cl/g of **3b**.

4.1.12. Poly(styrene-*co*-[4-chlorophenyl]-[4-ethenylphenyl]phenyl methanol-*co*-1,4-bis[4-vinylphenoxy]butane) (*J*anda*J*el-4-Cl-Tr-OH, 3c). This was prepared by procedure C using of **1f** (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford **3c** (7.2 g, 72%). Elemental analysis was used to determine the chlorine content (3.7%) and thus the loading level of 1.1 mmol Cl/g of **3c**.

4.1.13. Poly(styrene-*co*-[4-ethenylphenyl]diphenyl chloride-*co*-1,4-bis[4-vinylphenoxy]butane) (*J*anda*J*el-Tr-Cl, 4). To a magnetically stirred suspension of **3a** (2.0 g) in anhydrous CH_2Cl_2 (20 mL) at rt and under a N_2 atmosphere was added *tert*-butyldimethylsilyl chloride (2.3 g, 15.0 mmol) and dimethyl sulfoxide (0.5 g, 6.0 mmol). Stirring was continued for 3 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, diethyl ether, and hexanes. The shrunken

beads **4** (2.2 g) were dried in vacuo. Elemental analysis was used to determine the chlorine content (5.4%) and thus the loading level of 1.5 mmol Cl/g of **4**.

4.1.14. Poly(styrene-*co*-[4-ethenylphenyl]diphenyl benzylamine-*co*-1,4-bis[4-vinylphenoxy]butane) (*J*anda*J*el-Tr-NHCH$_2$Ph, 5). To a magnetically stirred suspension of **4** (0.2 g, 0.3 mmol) in THF (5 mL) at rt was added benzylamine (0.2 g, 1.5 mmol). Stirring was continued for 24 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, methanol, diethyl ether, and hexanes. The shrunken beads **5** (0.2 g) were dried in vacuo. Elemental analysis was used to determine the nitrogen content (2.1%) and thus the loading level of 1.5 mmol N/g of **5**.

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