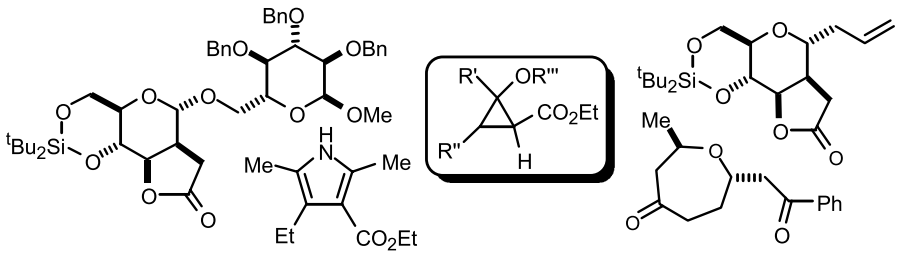
ELSEVIER

Tetrahedron

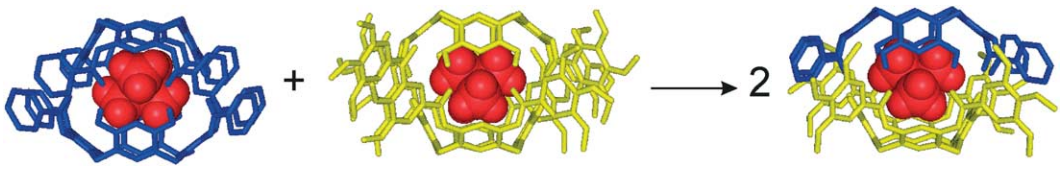
Tetrahedron Vol. 61, No. 2, 2005

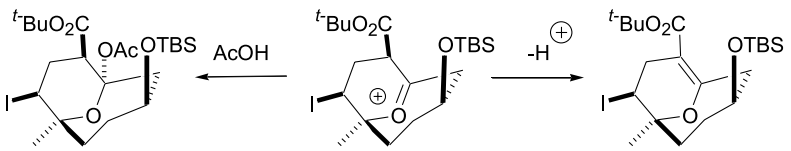
Contents

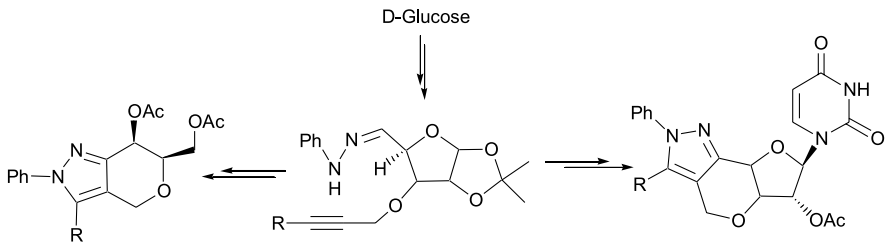
REPORT

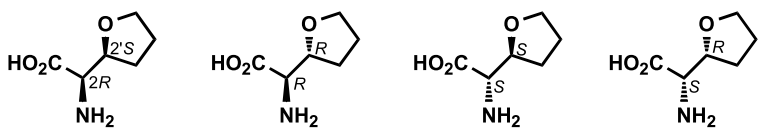


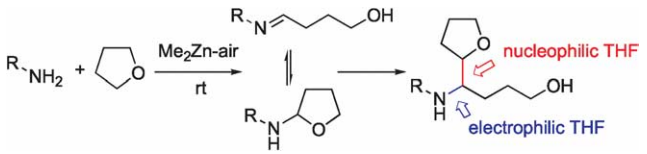
ARTICLES

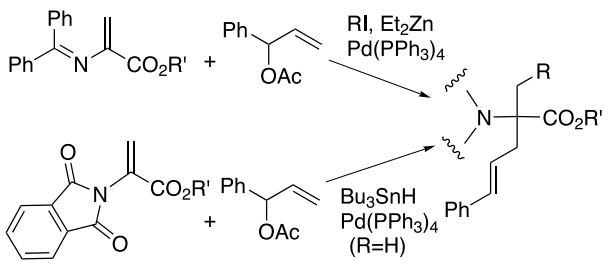


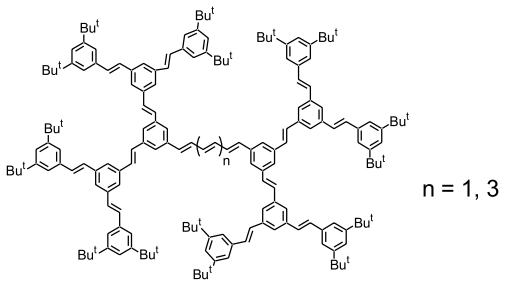


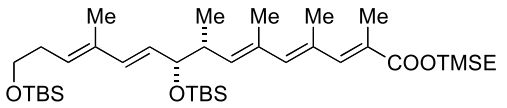


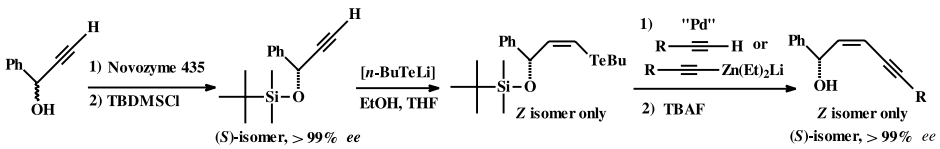


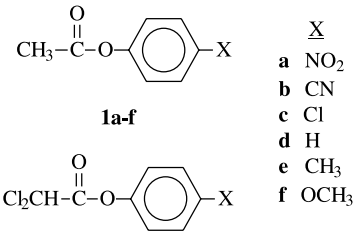






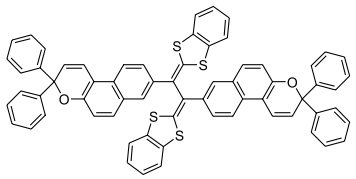


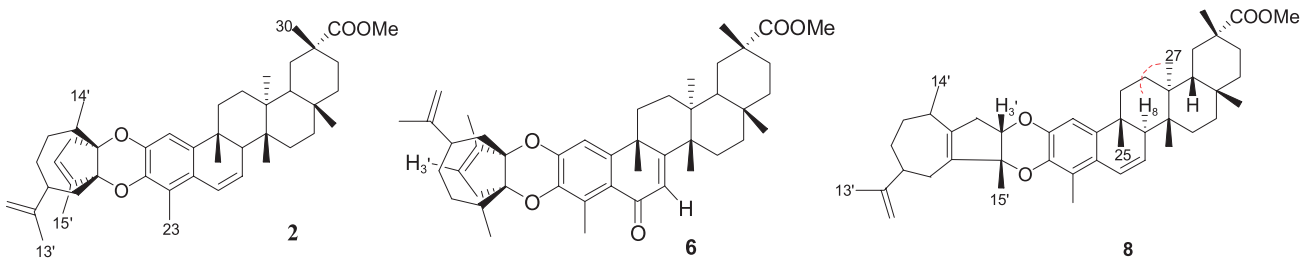


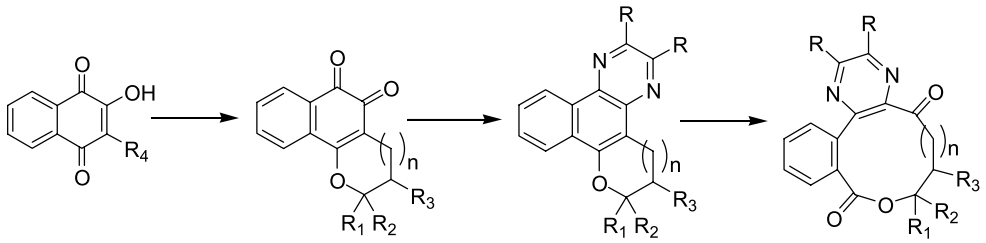


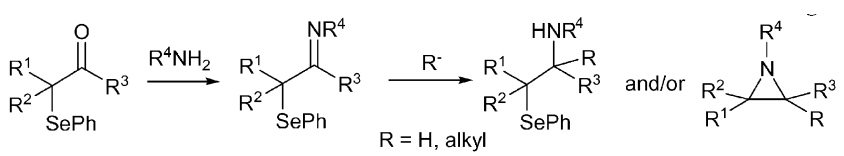
1a-f

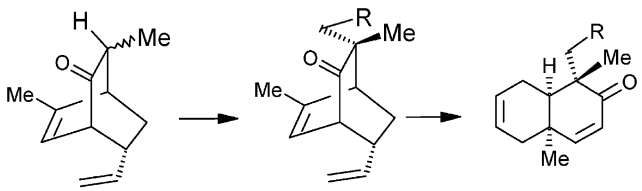
2a-f

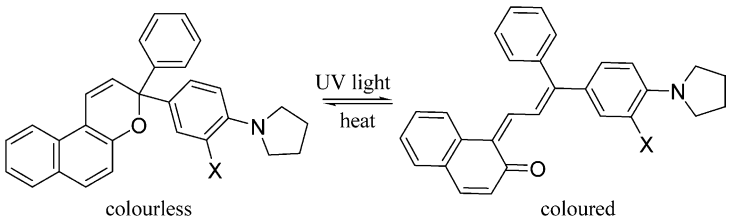


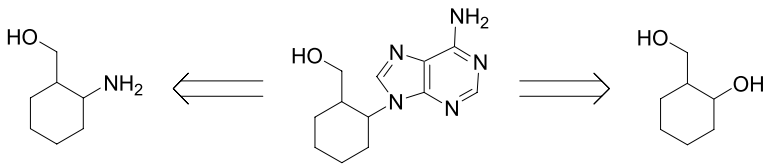


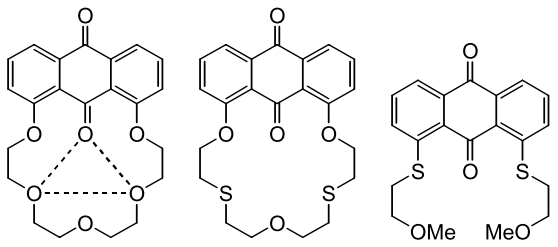


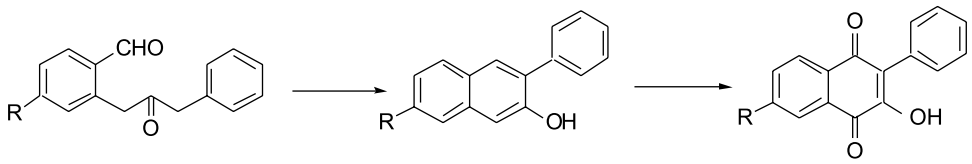


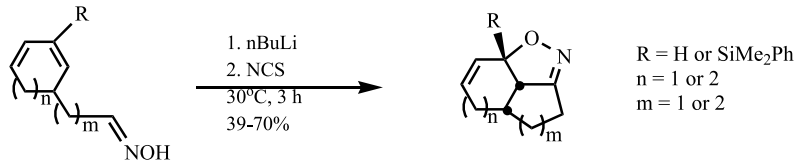


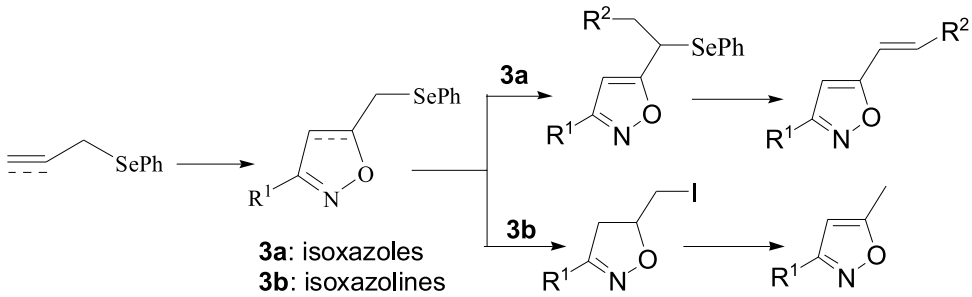


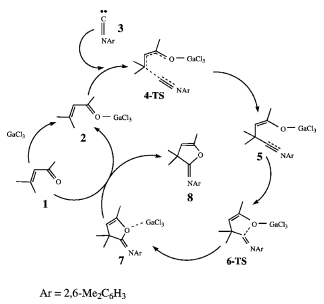


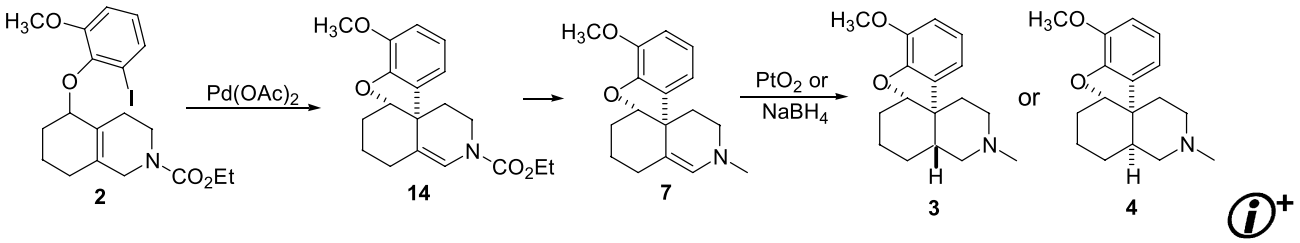












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 321–347

Tetrahedron report number 700

Recent advances in donor–acceptor (DA) cyclopropanes

Ming Yu and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, 1 University Station A5300, Austin, TX 78712, USA

Received 12 October 2004

Available online 18 November 2004

Contents

* Corresponding author. Tel.: +1 512 232 5896; e-mail: pagenkopf@mail.utexas.edu

doi:10.1016/j.tet.2004.10.077

1. History of donor–acceptor (DA) cyclopropanes

1.1. General DA cyclopropanes

Synthetic preparation methods and reactivity of donor–acceptor (DA) cyclopropanes have been widely documented and thoroughly reviewed.[1] This review focuses on recent advances and synthetic applications of donor–acceptor cyclopropanes principally involving 1,3-dipole intermediates revealed by reaction with Lewis acids. Particular emphasis is placed on reactions involving sugar-derived substrates.

The high degree of reactivity present in cyclopropanes makes them versatile building blocks in modern organic synthesis.[2] While unactivated cyclopropanes have been directly employed for certain useful chemical transformations,[3] most of the cyclopropane based synthetic methodologies have relied on activation from additional functional groups. Cyclopropanes substituted with electron accepting groups can react as homo Michael acceptors in nucleophilic ring openings (Fig. 1, Eq. i). On the other hand, donor substituted cyclopropanes can be cleaved by electrophiles to afford cation equivalents for further transformations (Fig. 1, Eq. ii).[4]

Vicinal donor–acceptor (DA) cyclopropanes are particularly useful synthetic building blocks because the reactivity imparted to the cyclopropane by the substituents is amplified by a synergistic electron 'push–pull' relationship.[1] Under Lewis acidic conditions, the doubly activated cyclopropanes undergo formal retro-aldol rearrangement to 1,3-zwitterionic intermediates that can be considered as 1,3-dipole equivalents (Fig. 1, Eq. iii).

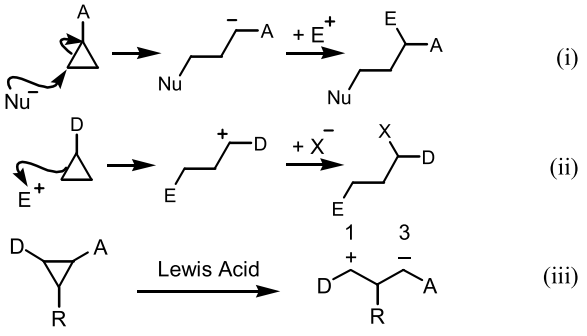
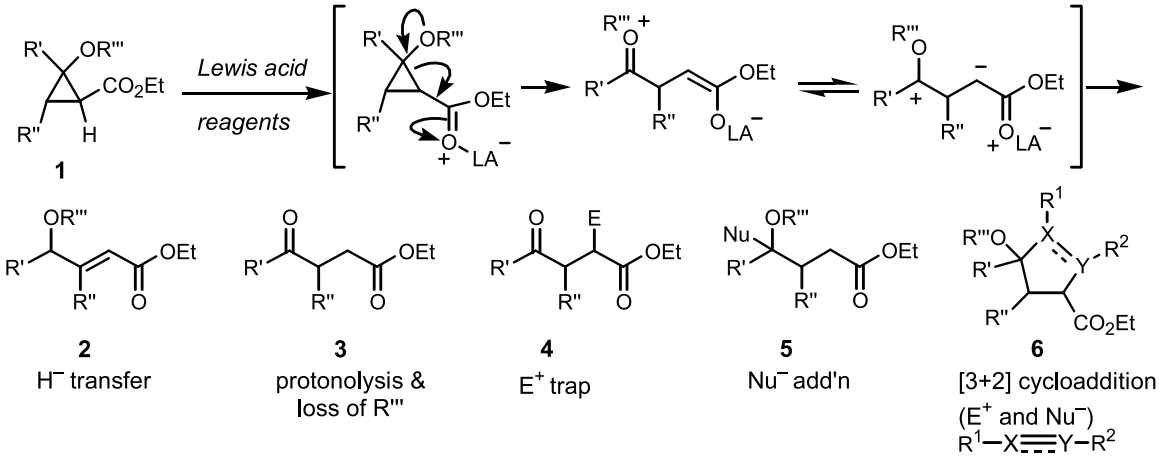


Figure 1.

The ultimate fate of the 1,3-zwitterion is highly dependent on the nature of the reaction conditions, and the intermediates can react in an intramolecular fashion by hydride[5] or proton transfers to give γ-alkoxy α,β-unsaturated esters **2** or saturated γ-oxoesters **3** (Scheme 1). Siloloxy substituted DA cyclopropanes are particularly susceptible to give the simple protonolysis products **3**.[6] Intermolecular reactions can occur at just one or at both sites of the dipole.[1] Examples of α addition from electrophilic trapping of enolates to afford **4**,[7] and nucleophilic addition to the intermediate oxocarbenium ions to give **5** are both known.[8] Combining the dual reactivity of the 1,3-dipole results in formal [3+2] cycloadditions to furnish highly functionalized carbon or heterocyclopentane derivatives **6**.[9] These latter transformations involving DA cyclopropanes are synthetically powerful methods for accessing products often not readily available through traditional routes.

1.2. Carbohydrate-derived donor cyclopropanes

One of the most important advances in cyclopropane chemistry over the last decade has been the integration of cyclopropanes and carbohydrates.[10] Carbohydrates have an exciting history in organic and medicinal chemistry.[11] Not only are they ubiquitous natural products occurring throughout the biosphere, but they provide key functional subunits for rational drug designs.[12] They are inexpensive yet powerful members of the chiral pool, which makes them irresistible platforms for asymmetric synthesis.[13–15] The cyclopropanation of glycals affords unique bicyclic structures combining the high reactivity of cyclopropanes together with the extreme optical purity and functional density associated with sugars.[10] The electron donating effect from the pyran ring oxygen conveniently helps one predict cyclopropane reactivity for accessing C(2) carbon branched glycosides as well as the C(1) functionalized carbohydrate scaffolds.



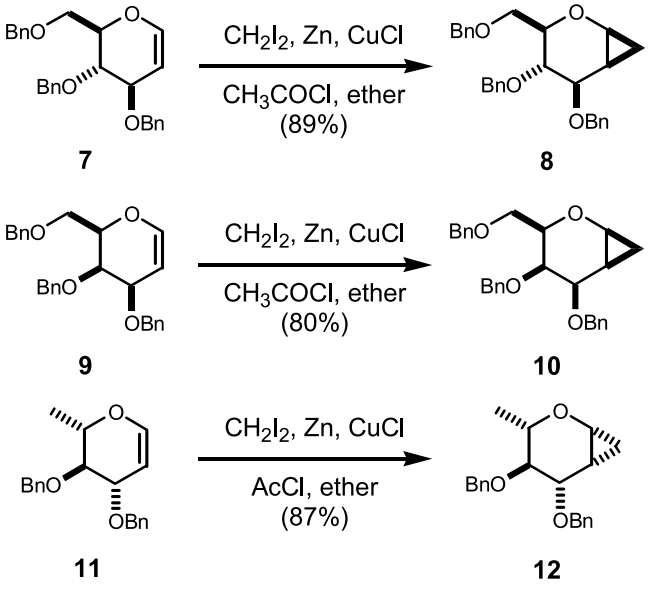
Scheme 1.

1.2.1. Preparation of carbohydrate-derived donor cyclopropanes. Despite the strong synthetic potential of cyclopropanated carbohydrates, the area remained dormant until recent decades, in which time efficient and reliable procedures for carbohydrate cyclopropanation were established. Vasella has pioneered this area with an effective synthetic approach toward monosaccharide-derived spirocyclic cyclopropylamines through diazo ester cyclopropanation of C(1) exocyclic methene glycals or cycloaddition of glycal-derived C(1) diazirine with acrylates.[16] The spirocyclopropanes from this method display activity as glycosidase inhibitors. Most of the work in carbohydrate cyclopropanation has, however, been focused on cyclopropanation of the C(1)–C(2) enol ether component of glycal scaffolds. These methods can be classified into three main categories according to the cyclopropanation method: Simmons–Smith reaction (Section 1.2.1.1), dihalocarbene cycloaddition (Section 1.2.1.2) and diazo ester cyclopropanation (Section 1.2.1.3).

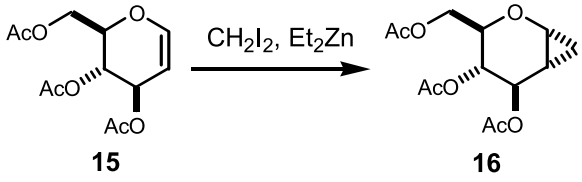
1.2.1.1. Simmons–Smith cyclopropanation. The classic Simmons–Smith reaction is an efficient method for facially selective conversion of alkenes to cyclopropanes. The reaction is believed to proceed through a 'butterfly-type' transition state that involves partial delivery of methylene group between $IZnCH_2I_2$ and the double bond.[17] When faced with allylic alcohols/ethers, the organozinc species stereoselectively adds to the double bond on the face *syn* to the allylic hydroxyl/alkoxyl group, presumably due to the strong chelating effect of the allylic oxygen to the dimeric organozinc reagents.

An early example of Simmons–Smith glycal cyclopropanation was reported by Nagarajan and co-workers in 1995.[18] In that study, the cyclopropanation of benzyl protected glycals **7**, **9** and **11** was achieved by treatment with CH_2I_2/Zn/CuCl activated by acetyl chloride (Scheme 2). This process proved efficient both in terms of reaction yield (>80%) and facial selectivity. In the examples reported, the C(3) substituent appeared responsible for complete control over facial selectivity to provide exclusively the *syn* diastereoisomer. The directing effect of the allylic oxygen overrode potential steric discouragement from the C(4) and/or C(6) substituents.

The Furukawa modification[19] of the Simmons–Smith reaction employs diethyl zinc instead of Zn(Cu), which results in more reproducible results under milder reaction conditions. This reagent combination displayed high compatibility with different protecting groups (Table 1), and demonstrated the same level of facial selectivity even on substrates essentially flattened by the cyclic 4,6-di-*tert*-butylsilylene ether (entry 4).[20] The cyclopropanated glycals were mostly received in 88–96% yield, but when faced with steric challenges, the reaction provided only moderate 33% yield (entry 5). When the steric effect became extreme such as in tri-*tert*-butyldimethylsilyl glycal (entry 6), the cyclopropane formation process was completely shut down.[20a] Unusual *trans* selectivity was reported by Lorica and co-workers on 3,4,6-triacetyl glycal under classic Simmons–Smith conditions (Scheme 3).

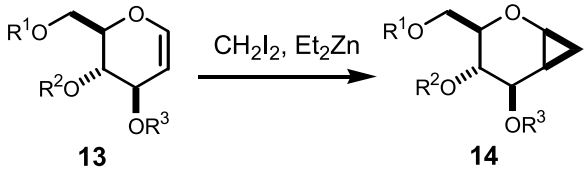


Scheme 2.



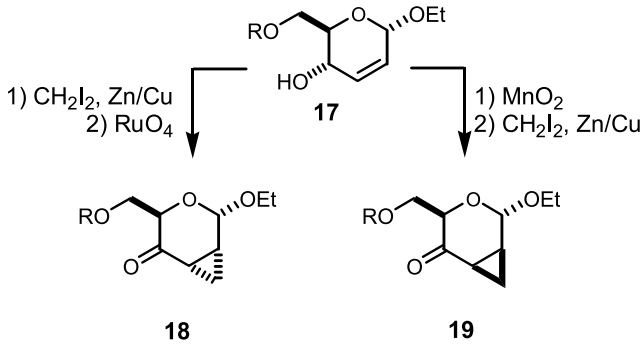
Scheme 3.

Table 1.



Entry	R^1	R^2	R^3	Yield (%)
1	Bn	Bn	Bn	92
2	Me	Me	Me	94
3	TBS	H	H	88
4		$-Si(^tBu)_2-$	H	96
5		$-C(Me)_2-$	H	33
6	TBS	TBS	TBS	0

In addition to glycal substrates, allylic alcohol directed cyclopropanations were investigated with 2,3- and 4,5-unsaturated carbohydrate derivatives (Scheme 4).[21] Fraser-Reid and co-workers developed a strategy to access both facial diastereomers in the cyclopropanation of Ferrier rearrangement products **17**.[22] Reaction with **17** provided the expected directed addition product **18**, but the directing effect of the C(4) hydroxyl group was circumvented by prior oxidation. Note that the acetal ethoxy group does not direct the cyclopropanation.



Scheme 4.

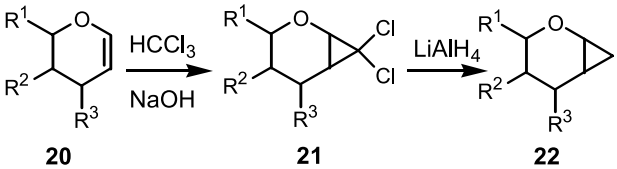
1.2.1.2. Dihalocarbene cyclopropanation. Another strategy for *trans* cyclopropanation of allylic hydroxyl/alkoxyl substituted carbohydrates was realized through dihalocarbene cycloaddition. In 1967, Brimacombe and co-workers reported the first carbohydrate cyclopropanation of a trimethyl glycal (Table 2, entry 1) through dichlorocarbene-glycal cycloaddition.[23] However, only recently was a general methodology developed by Nagarajan for *trans* cyclopropanation, as illustrated by reaction with a series of protected glycal substrates: galactal, rhamnal and xylal (entries 2–5).[24] The glycals **20** were converted to the corresponding dichlorocyclopropanes generally in >80% yield by treatment with $CHCl_3$ in the presence of sodium hydroxide. Similar selectivity has been observed with furanose substrates.[25]

Like other olefin-dihalocarbene cycloadditions, the stereochemistry in this process is governed by steric approach control, with the substituent at C(3) being of primary importance. An important aspect of this chemistry is the ease with which reductive dehalogenation can be achieved to afford products with stereochemistry complementary to that obtained by Simmons–Smith and related processes.

1.2.1.3. Diazo ester cyclopropanation methods for carbohydrate DA cyclopropanes. Transition metal catalyzed diazo ester cyclopropanation has also been investigated on carbohydrate substrates.[26–28] The lack of cyclopropane functionality of the products prepared through Simmons–Smith or diahalocarbene cycloadditions limits opportunities for subsequent synthetic elaboration. In this regard, the products from reaction with diazo esters are doubly activated DA cyclopropanes, and the ester provides a well-situated functional handle suitable for further modification. The first literature example of carbohydrate-diazo ester cyclopropanation was reported in 1981,[26] but detailed studies of transition metal catalyzed diazoester carbohydrate cyclopropanations were not reported until over a decade later by Henry and Fraser-Reid.[27] They found that the cyclopropanation of tri-*O*-*tert*-butyldimethylsilyl-D-glucal with copper powder provided exclusive β facial selectivity giving the cyclopropane **23b** in 92% yield (Table 3, entry 1). The cyclopropanation of the tri-benzyl protected analog was also selective, but the stereochemistry was unassigned and the yield was only 34%. When applied to galactal **24** and L-rhamnal **26** derivatives (Scheme 5), the cyclopropanation products **25** and **27** were obtained with α facial selectivity predominating. While yields were consistently excellent with these substrates (>85%), the diastereoselectivities were modest 3–5:1 (α:β).

Shortly thereafter, Hoberg and Claffey reported their results from an independent investigation of this reaction using other carbohydrate substrates and transition metal catalysts.[28] As illustrated in Table 3 (entries 2–7), many commonly used protecting groups such as TBS, TIPS, benzyl ether, acetyl and acetonide were found compatible with the cyclopropanation conditions. However, unlike Fraser-Reid's results in which β-facial selectivity predominated (Table 3, entry 1), in Hoberg's examples the α diastereomers were obtained (in good to excellent yield). α-Facial selectivity was also observed in the cyclopropanation of tri-acetyl galactal **28** and L-rhamnal **30** (Scheme 6), but these reactions were less selective. Hoberg attributed the observed facial selectivity to a steric control process,[10] and the blocking effect from larger protecting groups (especially

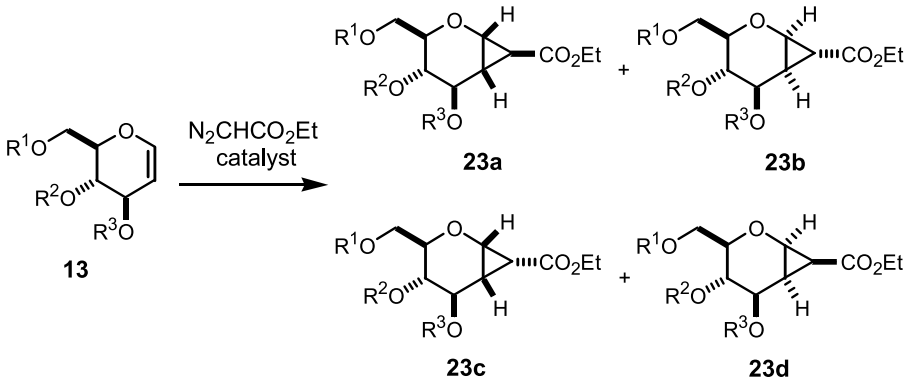
Table 2.



Entry	R^1	R^2	R^3	**21** (%)
1[a]	$MeOCH_2$ (β)	MeO (α)	MeO (β)	82
2[b]	$BnOCH_2$ (β)	BnO (α)	BnO (β)	84
3[b]	$BnOCH_2$ (β)	BnO (β)	BnO (β)	92
4[b]	Me (α)	BnO (β)	BnO (α)	95
5[b]	H	BnO (α)	BnO (β)	55

[a] See Ref. 23.
[b] See Ref. 24.

Table 3.



Entry	Protecting Groups			Catalyst	Yield (%)	Product Ratio			
	R^1	R^2	R^3			**23a**	**23b**	**23c**	**23d**
1[a]	TBS	TBS	TBS	Cu^0	92	0	100	0	0
2[b]	TBS	TBS	TBS	$Rh_2(OAc)_4$	81	97	3	0	0
3[b]	TBS	Ac	Ac	$Rh_2(OAc)_4$	93	94	2	2	3
4[b]	TIPS	TIPS	TIPS	$Rh_2(OAc)_4$	66	91	3	3	3
5[b]	Bn	Bn	Bn	$Rh_2(OAc)_4$	44	76	8	8	8
6[b]	Ac	Ac	Ac	$Rh_2(OAc)_4$	73	81	6	4	9
7[b]	Ac	Ac	Ac	$Cu(acac)_2$	4	70	12	6	12

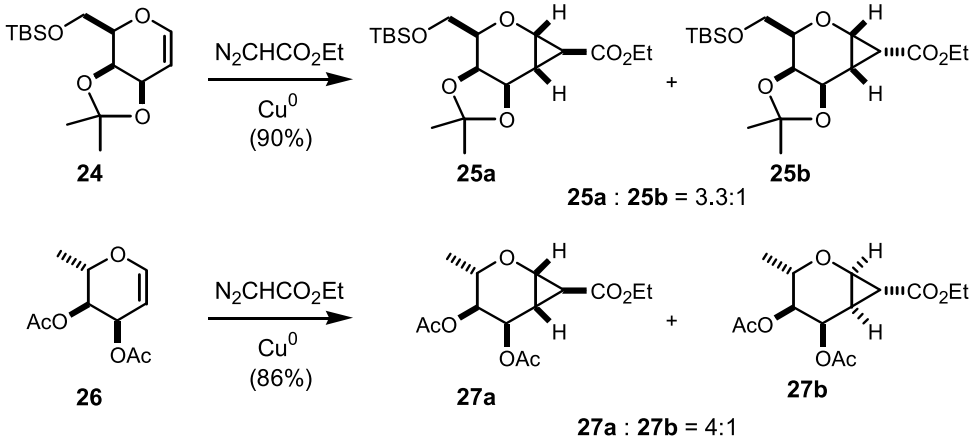
[a] See Ref. 27.
[b] See Ref. 28.

the C(3) protection) was believed to enforce *trans* addition (e.g., entries 2, 3, 4 versus entries 5, 6).

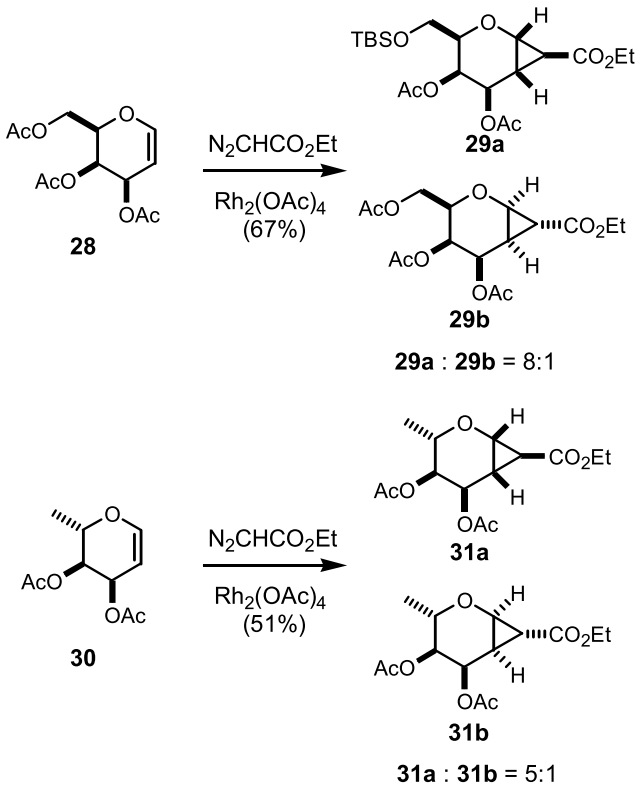
These studies and the work by van Boon[29] and co-workers on the cyclopropanation of furanose and pyranose ring systems (**32**, **34**, Scheme 7) revealed that among the homogeneous catalysts examined $Rh_2(OAc)_4$ resulted in the highest efficiency. Judicious employment of either $Rh_2(OAc)_4$ or Cu(0) catalysts in the cyclopropanation of glycals with ethyl diazoacetate provides convenient access to products with complementary stereochemistry.

1.2.2. Important reactions of carbohydrate-derived cyclopropanes and related compounds. The potential reactivity and high optical purity of carbohydrate-derived cyclopropanes makes this class of compounds stand out as attractive and economical materials for developing new asymmetric synthetic methodologies. In pioneering efforts, several groups have persistently sought strategies to exploit 1,2-cyclopropanated carbohydrates, and a consistent theme emerging from those works is the need for general and predictable cyclopropane ring opening processes. The primary synthetic strategies thus far have invoked two types of cyclopropane ruptures (Scheme 8): electrophilic cyclopropane ring opening at the C(1)–C(7) position (pathway A) or Lewis acid assisted pyran ring expansion (a process that has been called a σ-Ferrier rearrangement), (pathway B).

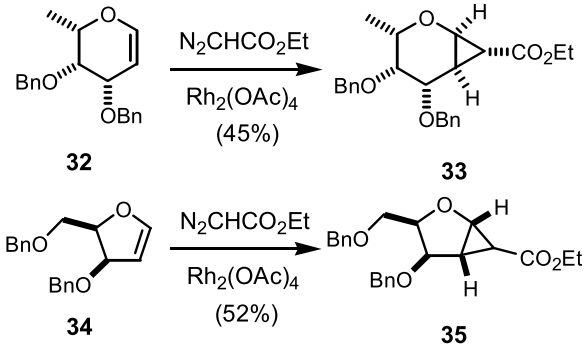
1.2.2.1. Electrophilic C(1)–C(7) cyclopropane ring cleavage. The ring opening of carbohydrate derived cyclopropanes along pathway A provides C(2) branched glycosides (Scheme 8). The reaction normally proceeds through electrophilic cyclopropane methylene activation by an electron deficient species that leads directly to formation of the oxonium ion intermediate. An example of



Scheme 5.



Scheme 6.

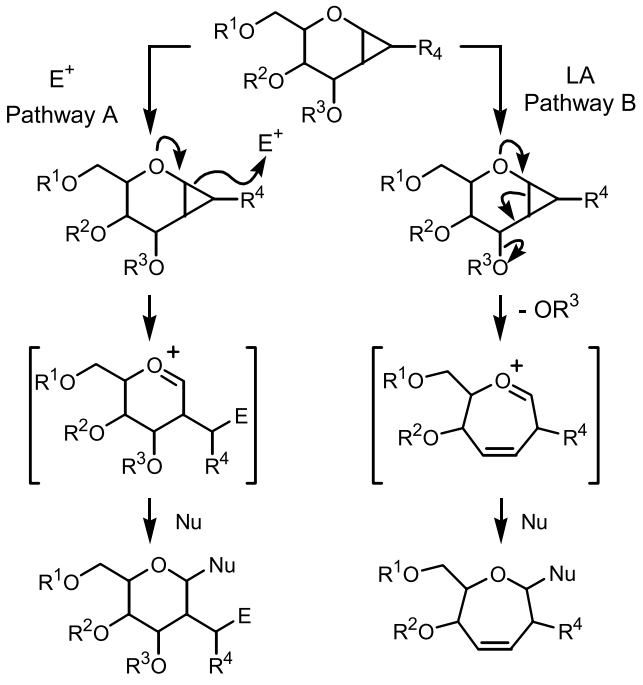


Scheme 7.

electrophilic cyclopropane ring-opening was achieved on the pyran derived substrate **36** via mercury(II) salt activation (Scheme 9).[30] This regioselectivity was thought to originate from partial cation charge stabilization by the pyran oxygen.

This strategy was later adapted by Heathcock to access C(2) methyl glucal **40** (Scheme 10).[31] Treatment of **8** with mercury(II) trifluoroacetate in the presence of water afforded hemiacetal **39**, which after subsequent Bu_3SnH reduction and elimination provided glucal **40**.

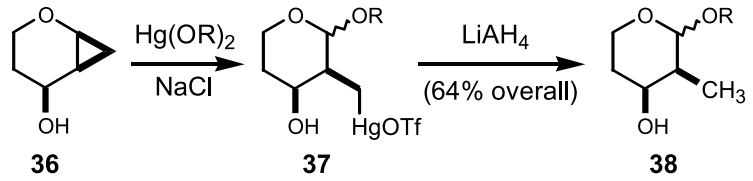
A conceptually equivalent transformation has been recently developed by Danishefsky and co-workers using *N*-iodosuccinimide (NIS) to access the geminal methyl groups in the synthesis of cytotoxic agents epothilone A and B (Scheme 11).[32,33] Importantly, the high efficiency observed in the preparation of the intermediate **42** using NIS activation eradicated the need for highly toxic mercury salts.



Scheme 8.

Several applications of, and modifications to, the facinating NIS strategy have been reported.[34–36] Compared with the organomercury intermediate **37**, the iodomethylene appendage obtained directly from the NIS protocol opened a window for more environmentally responsible C(2) elaboration. Nagarajan and co-workers[35] discovered sharply different cyclopropane reactivity between diastereomers **44** and **8** (Scheme 12). Reaction of α-cyclopropane **44** with either NIS or NBS occurred rapidly and provided an anomeric mixture of **45** in ~90% yield. In contrast, reaction under otherwise identical conditions with β-cyclopropane **8** results in slower formation of **46** with pronounced anomeric selectivity. The same trend in reactivity was also observed on diastereomeric substrates **47** and **49** in which the free C(6) hydroxyl is available to participate in an intramolecular nucleophilic attack. The differences in reactivity were accredited to steric hindrance on the β-cyclopropanes **8** and **49** *toward the approaching electrophilic activator*. The most reactive α-cyclopropane **47** not only has the advantage of the least C(3) steric hindrance, but is equipped with a free hydroxyl ideally positioned for S_N2-like participation. The β-cyclopropane **49** is not disposed for direct substitution and is blocked from the electrophilic activators.

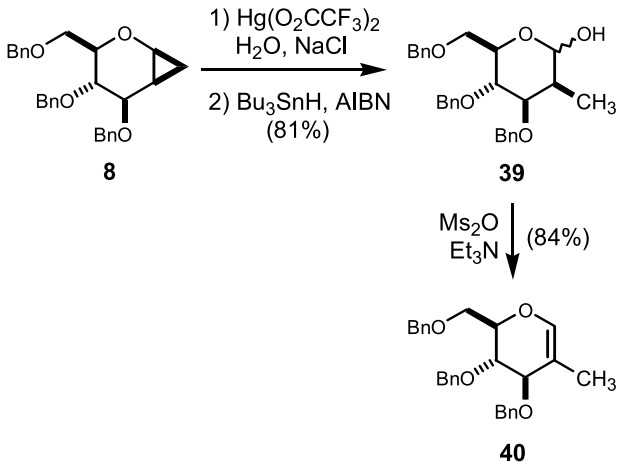
In addition to investigations on 1,2-disubstituted cyclopropanes (e.g., Scheme 12), the electrophilic ring cleavage strategy was applied to substrates prepared through diazo ester cyclopropanation. In an early example reported by Hoberg,[28] the 1-bromopyran derivative **52** was prepared in moderate yield (38%) by treating **51** with 30% HBr in acetic acid, but the reaction was inevitably accompanied with C(3) 'S_N2-like' substitution by bromide (Scheme 13). In a similar example by Fraser-Reid, the carboxylate substitution on **53** was used to adventageously in a highly selective cyclopropylcarbinyl-homoallyl rearrangement (Scheme 14).[26] Ester reduction by lithium aluminum hydride ($LiAlH_4$) followed by standard Mitsunobu manipulation employing benzoic



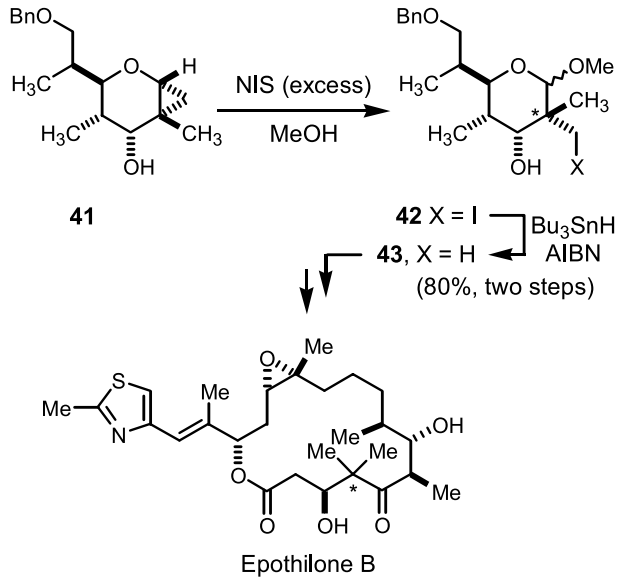
Scheme 9.

acid as the nucleophile gave 66–90% yield of 2-deoxy-2-vinyl glycals **55** as anomeric mixtures. Very recently, an efficient method for the synthesis of C(2) branched glycol-amino acids **58** has been developed by Chandrasekaran through direct NIS mediated ring opening in methanol (Scheme 15).[37]

Although electrophilic ring opening reactions of carbohydrate-derived cyclopropanes provide access to C(2) branched glycosides, literature examples have unfortunately been restricted mainly to simple Brønstead nucleophiles (alcohol/water) as glycosyl acceptors. The resulting acetals or hemiacetals offer a transitional intermediate for further C(1) transformations, but direct formation of C(1) *C*-branched glycosides remained elusive. Moreover, due to the limited assortment of electrophilic activators (i.e., Hg(II), or NIS/NBS), the resultant C(2) moieties were limited to few synthetic transformations.



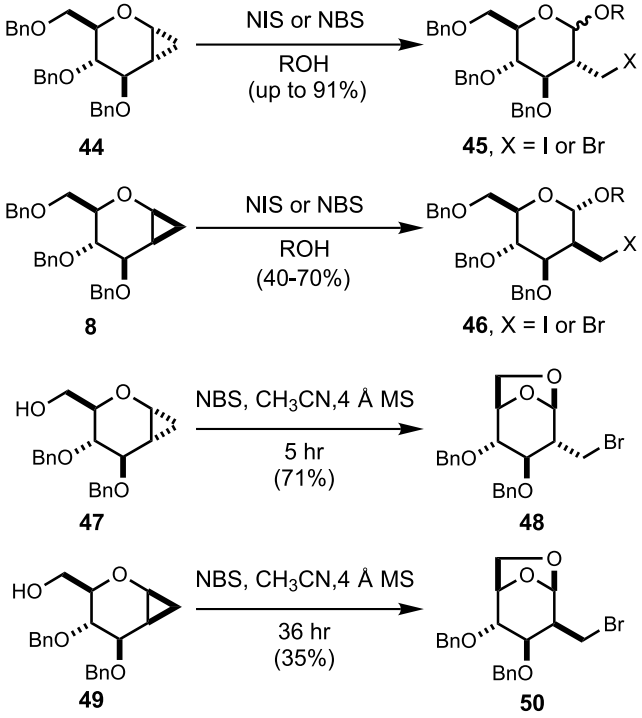
Scheme 10.



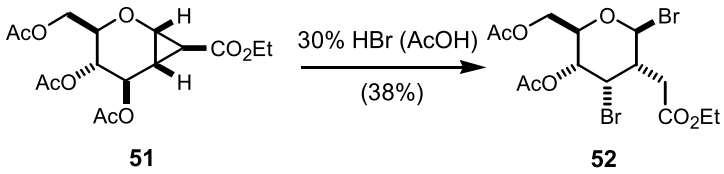
Scheme 11.

1.2.2.2. Pyran ring expansion. Another transformation of 1,2-cyclopropanated carbohydrates that has been actively investigated is pyran to oxepane ring expansion, which is driven primarily by release of cyclopropyl ring strain. The logistics of this rearrangement can be rationalized based on conformation models (Scheme 16). In the glucal-derived bicyclic substrate **14**, the fused cyclopropane distorts the pyran skeleton and prevents it from adapting an ideal chair conformation. The pseudo equatorial C(3) substituent will retain an orientation reasonably anti-parallel to the C(1)–C(2) bond. This bonding alignment therefore accommodates a manifold for smooth elimination facilitated by Lewis acid activation of the C(3) oxygen.

Hoberg has carried out detailed investigations on this ring expansion (Scheme 17).[20] Upon treatment with TMSOTf, the cyclopropanes **14** were cleaved exclusively at the C(1)–C(2) bond as a result of collaboration between the 'donating' pyran oxygen and the quasi 'accepting' effect from the departing C(3) substituent. Depending on substrate protective groups and reaction conditions, the intermediate



Scheme 12.



51 52

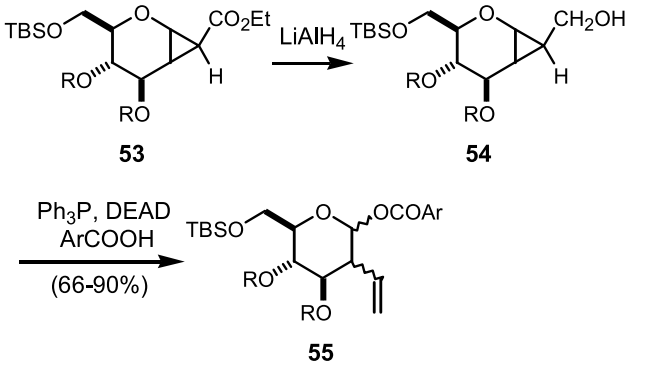
Scheme 13.

oxonium ion can be converted preferentially into one of three oxapenes: **59**, **60** or **61**. In examples where labile C(6) silyloxy protecting groups were present, intramolecular ring closure occurred faster than external nucleophilic substitution to provide anhydro-sugars **59** in up to 78% yield. To facilitate intermolecular attack at the C(1) oxonium ion, C(6) deoxygenation or slightly more robust hydroxyl protection (e.g., $R^1=R^2={}^tBu_2Si$) was required. Successful exogenous nucleophiles capable of C(1) functionalization include allylsilanes, silyl ketene acetals and silylthiazole, but the products **60** were formed with only moderate facial selectivity (2:1) and elimination to **61** was competitive. The poor diastereoselectivity was recently reported to be significantly improved by using the corresponding cyclopropane derived from galactal.[38] In the examples with sufficient suppression of intramolecular nucleophilic addition, the absence of external nucleophiles lured the oxocarbenium ion intermediate preferentially into a C(2) deprotonation pathway, which led to the oxacycloheptadiene **61** ($R^1=R^2={}^tBu_2Si$, 81% yield).

Similar ring expansion-nucleophilic addition sequences have been reported,[39] and Sugita and co-workers described an interesting reaction of cyclopropanated pyranones **62** with a variety of silyl enol ethers and silyl ketene acetals (Scheme 18).[40] Compared with the conformationally restricted rigidly planar 4,6-di-*tert*-butylsilylene ether on substrate **14** ($R^1=R^2={}^tBu_2Si$), the unfettered C(6) substituent induced excellent *trans* stereochemistry.

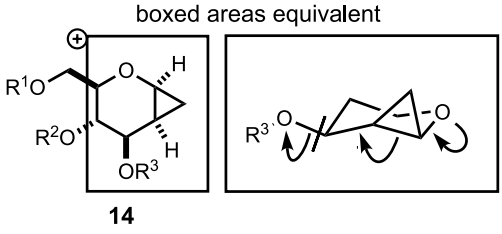
A mechanistically distinct transformation has been explored by Nagarajan for solvolytic ring-expansion of dihalocyclopropanated sugars to prepare the corresponding halogen substituted anomeric oxepane products **65** (Scheme 19).[24b] A significant difference in this process is that conversion to the 2-halo allylic cationic intermediate is initiated by base. The addition regiochemistry was attributed to the preferential delocalization of the allylic cation adjacent to the stabilizing pyran oxygen.

Glucal-derived DA cyclopropanes prepared through diazo ester cyclopropanation are reluctant participants in ring opening reactions (cf., Scheme 13).[28] The different reactivity of those cyclopropanes was believed to originate from deactivation of the cyclopropane by the ester group,[28] a postulate that is entirely consistent with Sugita's observation on 2,3-methanochromanones **66** (Scheme 20).[41] Those studies elegantly compared the electron withdrawing ability of a ketone vs a geminal ester substituent under different Lewis acidic conditions: $BF_3\cdot OEt_2$, TMSOTf or $SnCl_4$. The unsubstituted cyclopropane expanded to the 6,7



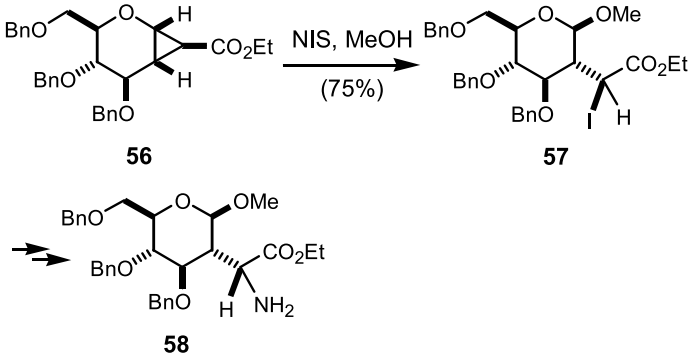
53 54 55

Scheme 14.



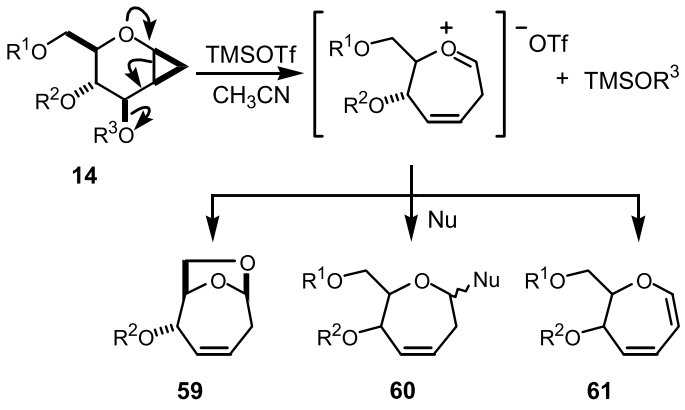
14

Scheme 16.



56 57 58

Scheme 15.



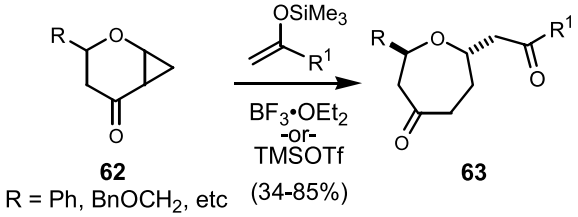
Scheme 17.

bicyclic intermediate **A**, which after formal dipolar cycloaddition with silyl enol ethers afforded the oxepanone derivatives **67** in 40–95% yield. In contrast, the dicarboxylate substituted cyclopropane maintained the methanochromanone core and underwent exo ring cleavage to a zwitterionic intermediate **B**. A subsequent cyclization with carbonyl compounds provided mainly the *trans* fused tricyclic products **68** in 67–99% yield.

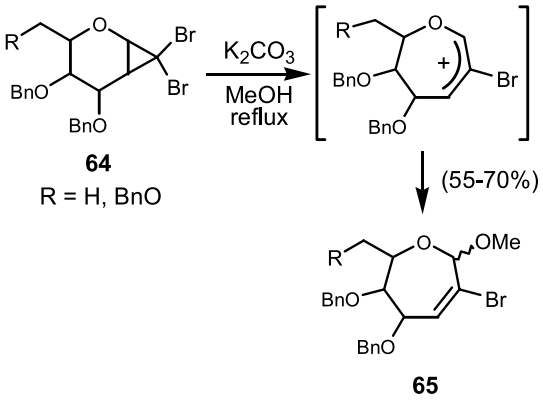
2. Intramolecular glycal cyclopropanation

2.1. Reaction design

A recurring objective of carbohydrate cyclopropanation investigations has been development of new ways to access highly functionalized C(1) and C(2) branched glycosides. Cyclopropanes bearing an ester electron withdrawing group are poised for more elaborate transformations (e.g., Scheme 15) compared to their unsubstituted counterparts. In this regard, the reported ability to control the facial and endo/exo selectivity of diazoester glycal cyclopropanations through catalyst selection (e.g., Section 1.2.1.3) is an important accomplishment. However, in the authors' experience, achieving stereo-complementary results with a variety of protected glucal substrates proved elusive.[42]



Scheme 18.

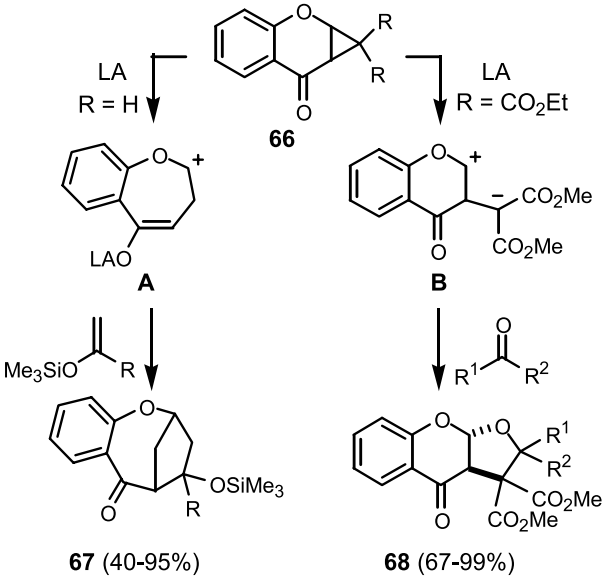


Scheme 19.

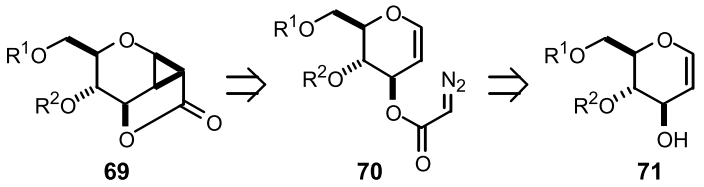
Yu and Pagenkopf recently reported an intramolecular tactic that circumvents potential difficulties in stereochemical control endemic to glycal cyclopropanations (Scheme 21).[43] The strategy takes advantage of a molecular tether for obtaining absolute control over cyclopropanation facial selectivity, and the unique conformation and strain inherent to the products results in new cyclopropane reactivity, which will be described in subsequent sections.

2.2. Substrate preparation

The hallmarks of standard intramolecular diazo ester cyclopropanations are efficiency and a remarkable increase in molecular complexity.[44–46] Generally, excellent stereocontrol is observed in the intramolecular cyclopropanation of allylic alcohols. In pioneering investigations, Corey and



Scheme 20.



Scheme 21.

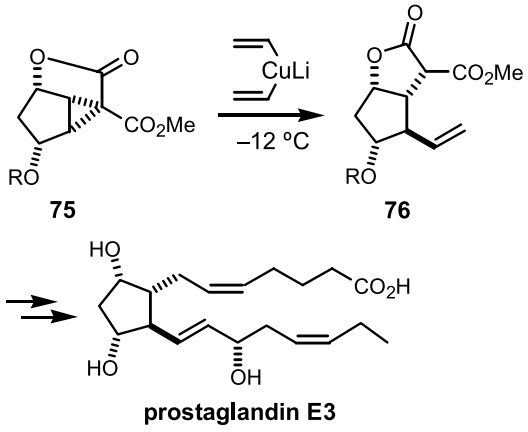
Myers[45] developed glyoxylic acid chloride *p*-toluenesulfonylhydrazone **73**[47] as a versatile and practical reagent for efficient preparation of diazoacetic esters from allylic alcohols. However, despite ample precedence, there were surprisingly no reports of intramolecular glycal cyclopropanation in the literature.

As representative examples (Scheme 22), the glucals **72** were converted to their diazoacetates **70** in excellent yield using a slightly modified version of the Corey–Myers procedure. Specifically, the use of DMF proved critical for this transformation, and in its absence less than 10% of the product could be isolated. The best (pre)catalyst identified for cyclopropanation was bis(*N-tert*-butylsalicylaldiminato) copper(II) [$Cu(TBS)_2$].[48] It is noteworthy that cyclopropanation was not accompanied by C–H insertion, even with rhodium(II) catalysts.[49] Presumably, the limited conformational freedom of the intermediate carbenoid precluded the necessary perpendicular orientation at either C(2) or C(4).[50] The product stereochemistry is complementary to that obtained by intermolecular cyclopropanation methods.[26,28] Alternative diazoacetic esterification methods, such as Doyle's diketene approach,[51] were unsuccessful with **72**.

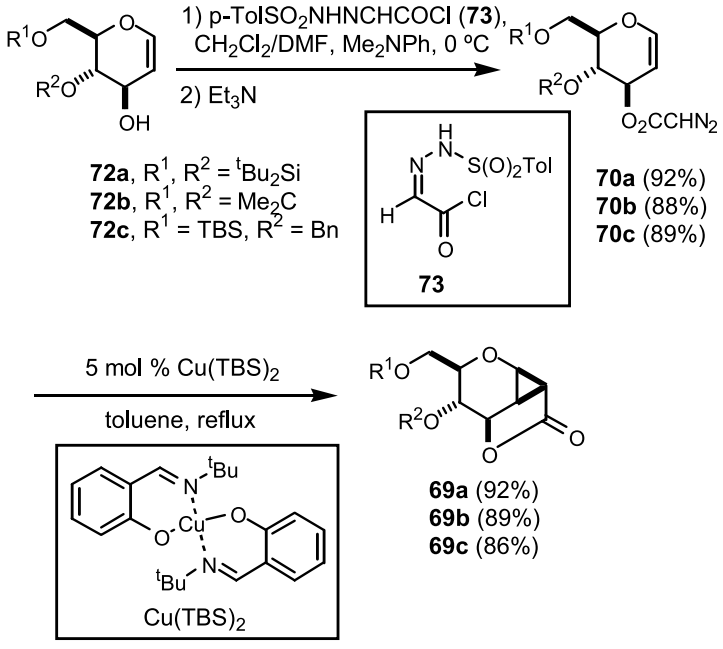
2.3. Transformations under mild conditions

Although DA cyclopropanes enjoy dual activation, reaction conditions to fragment these species are often quite harsh. However, the lactonized substrates undergo reaction under milder conditions, and this has opened the door to new reaction pathways.

2.3.1. Reactions attempted with organocopper reagents. Acceptor substituted cyclopropanes **75** are opened by vinyl cuprates through what is generally perceived as an S_N2 type reaction (Scheme 23).[52] The *trans* addition established the requisite stereochemistry for prostaglandin E3 synthesis.[45,53]

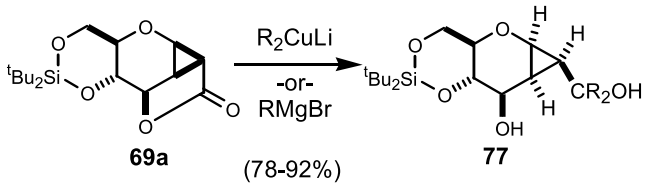


Scheme 23.



Scheme 22.

However, the lactonized cyclopropanes **69** failed to react in an analogous fashion, and eventually addition to the lactone carbonyl was observed (Scheme 24). The ring strain appears to make these lactones more electrophilic than normal, and coupled with cyclopropane deactivation (toward nucleophiles) from the pyran oxygen, reaction at the cyclopropane under nucleophilic conditions has not been observed.



Scheme 24.

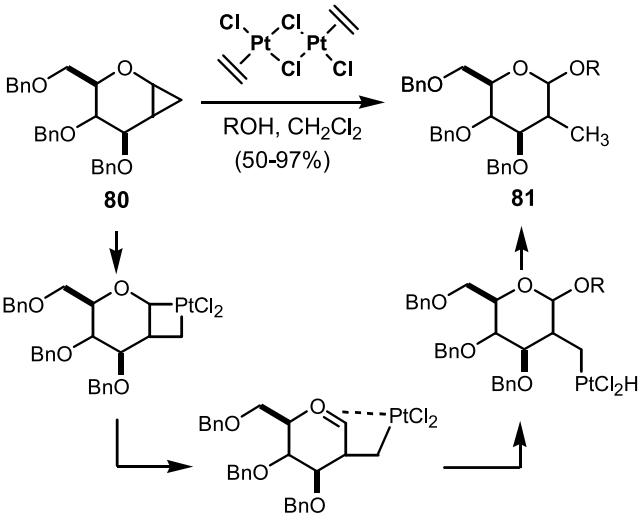
2.3.2. Transition metal mediated DA cyclopropane ring opening. Transition metal catalyzed rearrangements of DA cyclopropanes to give (or regenerate) enol ether products are well established (Scheme 25).[54–56] A broad range of transitional metals such as rhodium(I) ($[Rh(CO)_2Cl]_2$), ruthenium(II) ($[Ru(CO)_3Cl_2]_2$), platinum(II) ($PtCl_2 \cdot 2PhCN$), copper bronze and CuCl were reported to be efficient catalysts for this transformation, which is thought to proceed by a regioselective oxidative addition to generate a metallacyclobutane intermediate. Subsequent β-elimination and reductive elimination affords the vinyl ether products, which have shown little tendency for C=C bond migration.

Using Ziese's dimer in alcoholic solvent, Madsen recently extended this transformation to glycal-derived cyclopropane substrates **80** as a means to access C(2) branched glycosides (Scheme 26).[57] Interestingly, the platinacyclobutane intermediate gained sufficient lifetime for competitive C(1)–Pt bond dissociation before β-elimination to afford the glycoside products **81**. Even when challenged with substrates bearing a carboxylate group, the same reaction pathway was observed (Scheme 27).

Reaction of the lactonized cyclopropane **69a** in the presence of transition metal catalysts (vide infra) gave the vinyl ether product **84** in 79% yield (Scheme 28).[58]

3. Lewis acid mediated reactions of DA cyclopropanes

Lewis acid (LA) mediated ring opening reactions are among the most important synthetic transformations for DA cyclopropanes.[1] Reaction of DA-cyclopropanes prepared by intermolecular cyclopropanation of glycals provides substrates that offer an efficient method for oxepane



Scheme 26.

synthesis.[10] While useful for accessing 7-membered rings, the transformation fails to exploit the difficult-to-establish cyclopropane stereochemistry.

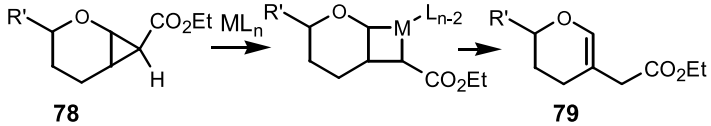
In this regard, the unique bond angles of the lactonized DA cyclopropanes **69** offered an excellent opportunity to circumvent the pyran expansion side reaction (Scheme 29). Singe crystal X-ray crystallographic analysis of **69a** (Fig. 2) revealed a twisted boat conformation of the pyran and a C(1)–C(2)–C(3)–O(8) dihedral angle of 70.6°, which disfavors the C(3)–O(8) elimination pathway as observed on the intermolecular counterparts. Additionally, alignment is now suitable for C(1)–C(7) bond cleavage.

Three Lewis acids in particular have been identified that initiate the particularly useful C(1)–C(7) bond cleavage: $BF_3 \cdot OEt_2$ (Section 3.1), TMSOTF (Section 3.2), $TiCl_4$ (Section 3.3). Several of these discoveries have been expanded to encompass general DA cyclopropanes (and not just those derived from sugars).

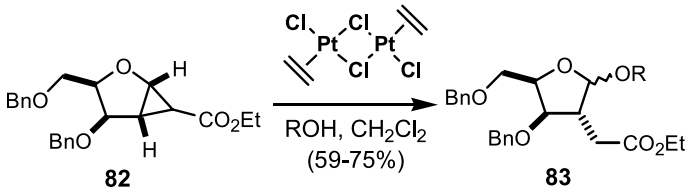
3.1. Reactions mediated by $BF_3 \cdot OEt_2$

Compared with TMSOTf and $TiCl_4$, the use of $BF_3 \cdot OEt_2$ as an activator of DA cyclopropanes has received less attention. Generally, DA cyclopropanes are quite resilient to this promoter, and application of $BF_3 \cdot OEt_2$ has been mostly restricted to initiating cascade sequences consisting of pyran expansion and nucleophilic addition (Section 1.2.2.2).[40,41,43]

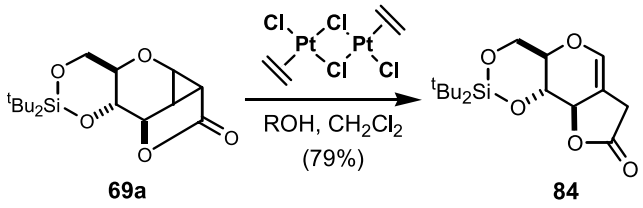
The lactonized DA cyclopropanes were found to be essentially unreactive toward $BF_3 \cdot OEt_2$. When forcing conditions were applied (e.g., 80 °C, toluene), the



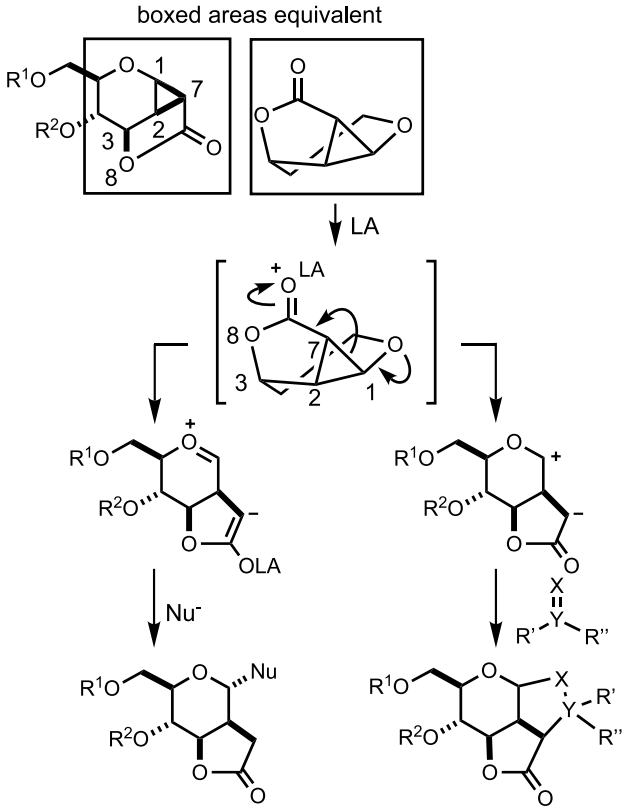
Scheme 25.



Scheme 27.



Scheme 28.



Scheme 29.

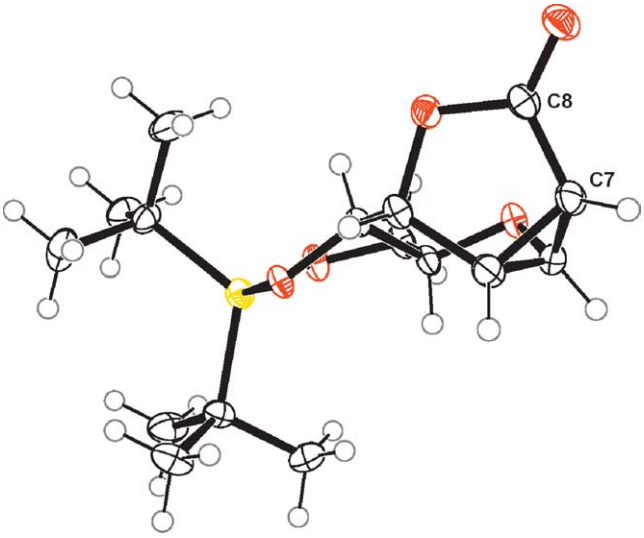
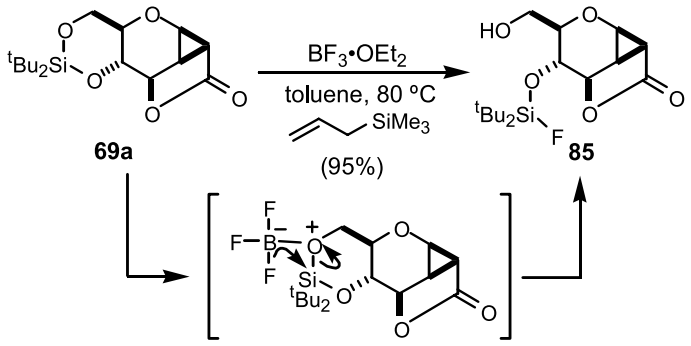


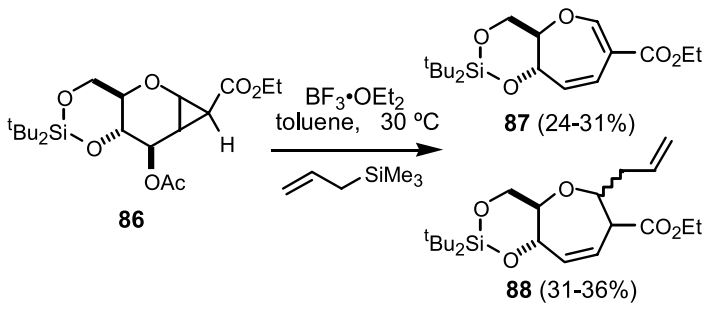
Figure 2.

cyclopropane nucleus remained intact, but the di-*tert*-butylsilylene ether succumbed to ring cleavage (Scheme 30), giving the primary alcohol **85** in nearly quantitative yield.[43] The general reactivity and selectivity of the deprotection and the stability of the fluorosilane protective group have been systematically explored and described.[59] A useful observation from those studies is that the stability of the di-*tert*-butylsilylene ether was shown to fall between that of the *tert*-butyl-dimethylsilyl and triisopropylsilyl protective groups.

The reactivity (or stability) of **69a** afforded the opportunity for an important comparison between similar cyclopropanes. Specifically, the cyclopropane **86** underwent rapid ring expansion at temperatures as low as −30 °C, giving oxacycloheptene products **87**, **88** (Scheme 31).[42] The distinctly different reactivity displayed by the structurally similar substrates in Scheme 30 and Scheme 31 appears to



Scheme 30.

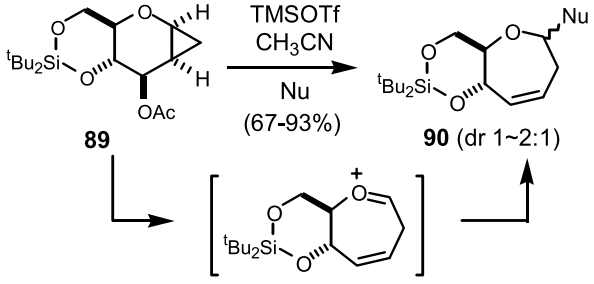


Scheme 31.

support the hypothesis that a lactone linkage is a viable strategy for suppressing the ring expansion process.

3.2. Reactions mediated by TMSOTf

The use of TMSOTf to activate cyclopropanes has seen more frequent success. For example, Hoberg showed that catalytic TMSOTf generated an oxocarbenium ion intermediate sufficiently long lived that it could be intercepted with a variety of nucleophiles, including allylsilanes, propargylsilanes, sily enol ethers and disulfides (Scheme 32).[20b]



Scheme 32.

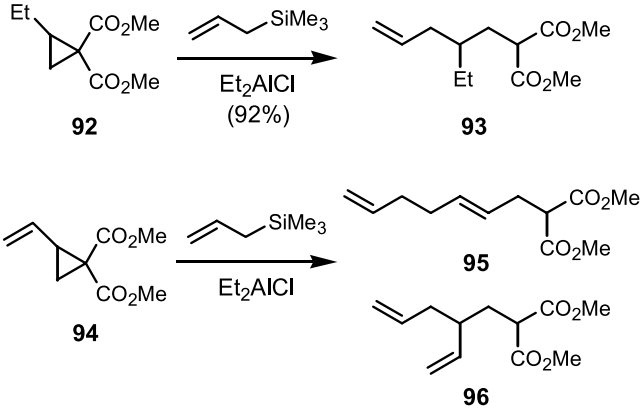
In contrast, under similar conditions employing catalytic TMSOTf the lactonized DA cyclopropane **69a** remained intact even in refluxing CH_2Cl_2 (Scheme 33). Cyclopropane cleavage at the C(1)–C(7) bond was eventually realized when 1.5 equiv of TMSOTf was deployed, but these conditions also led to destruction of the silylene ether. Formation of anhydro-sugar **91** appears very favorable, having out-competed nucleophilic allyl trimethylsilane.

Attempts to intercept the oxocarbenium generated from reaction of the lactonized DA cyclopropanes with TMSOTf using other nucleophiles eventually met success, and these results will be described in Section 4.2.

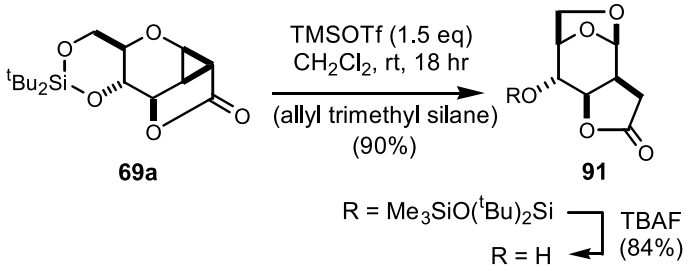
3.3. Reactions mediated by $TiCl_4$

3.3.1. Stereoselective allylation. The allylation of activated cyclopropanes is an attractive strategy for increasing molecular diversity. Kemmitt pioneered homoconjugate allyl additions to geminally activated cyclopropanes (Scheme 34).[60] The allylation of **92** occurred regioselectively at the substituted position, but in the case of **94**, addition to the vinyl group was also observed. Hoberg reported the direct allylation of donor activated glycal-derived cyclopropane **14** ($R^1=R^2={}^tBu_2Si$, $R^3=Ac$, Section 3.2), but the flattened bicycle oxonium intermediate did not show high facial selectivity toward allylsilane attack (Scheme 32).

Direct Lewis acid mediated allylation of DA cyclopropane might be anticipated to be a straightforward process,

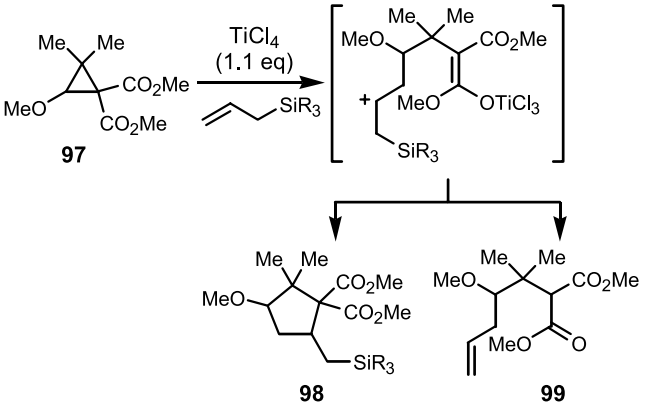


Scheme 34.



Scheme 33.

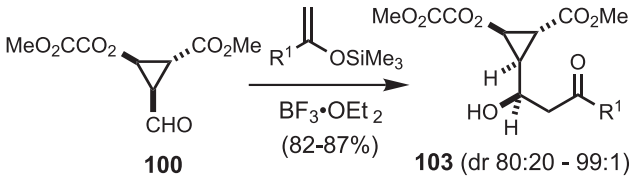
but throughout the literature there are few examples. Because allylsilanes can also function as both 1,2 and 1,3 dipoles, the allylation of DA cyclopropanes **97** is often accompanied, or even dominated, by [3+2] cycloaddition (Scheme 35).[61]



Scheme 35.

Products derived from the formal allylation of DA cyclopropanes were recently reported by Reiser,[62,63] but that process does not involve authentic allylation of the cyclopropane core (Scheme 36). Instead, reaction of cyclopropane **100** with allyltrimethyl silane in the presence of $BF_3 \cdot OEt_2$ resulted in Sakurai reaction with the pendant aldehyde. The alcohol **101** was converted into the lactone **102** through treatment with acid or base. Even with two electron withdrawing groups, the remarkable stability of the cyclopropane ring was further demonstrated by its noninvolvement during a Mukaiyama aldol reaction (Scheme 37).

A wealth of information is known about allylation of glycosyl donors,[64] but only very recently was the direct allylation of DA cyclopropanes reported (Scheme 38).[65] The authors noted that order of addition was important, and treating a mixture of the cyclopropane and allylsilane with Lewis acid, which is a typical protocol for Sakurai reactions,[66] resulted in substrate decomposition. Instead, treatment of the cyclopropane with $TiCl_4$ for 2 hours at room temperature resulted in formation of a polar intermediate, speculated to be the α-chloropyran



Scheme 37.

intermediate **104**,[67] which then cleanly converted to the allylation product upon addition of allylsilane or stannane. The moderate 4:1 selectivity was improved to 8:1 by bulking up the lactone sterics through transient silylation (Scheme 39). The stereochemistry of the major β-product was determined by single crystal X-ray analysis (Fig. 3). Attempts to reverse the selectivity through an intramolecular allylation were unsuccessful (Scheme 40).

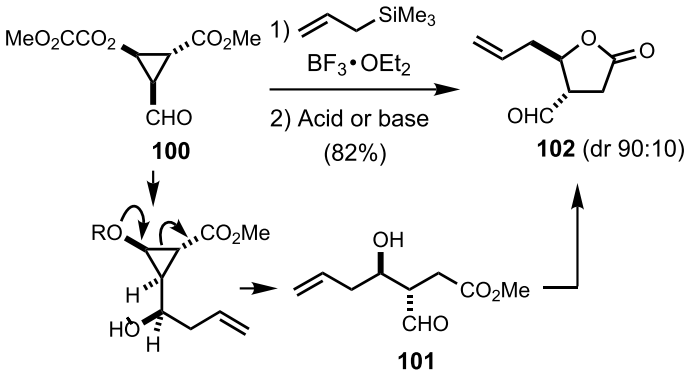
3.3.2. Stereoselective glycosylation. In addition to direct allylation, Lewis acid ($TiCl_4$) also proved efficient in mediating alcohol solvolysis of lactonized glucal-derived cyclopropanes, which provides C(2) branched glycoside products **108** (Scheme 41).[58] To access oligosaccharides or other structures where the use of excess alcohol is not feasible, practical glycosylation can be achieved through a two-step sequence that involves traditional *S*,*O*-acetals **109** (Scheme 42).

4. Formal [3+2] dipolar cycloaddition of DA cyclopropanes

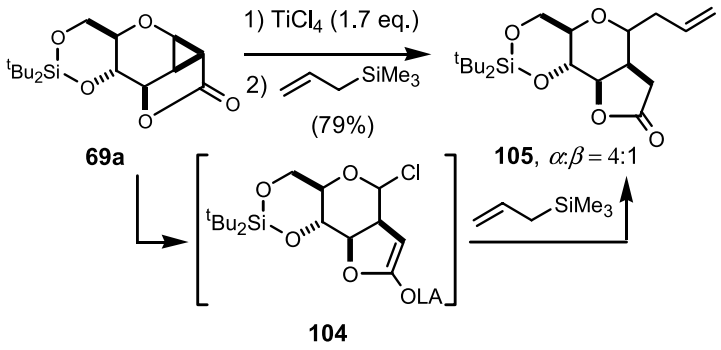
One of the most important synthetic applications of DA cyclopropanes has been in the area of (formal) [3+2] dipolar cycloadditions to generate five-membered carbocyclic and heterocyclic structures.[1] Because of the dual electrostatic character of the intermediate 1,3-zwitterion (Scheme 1), the cyclization can begin with either an electrophilic or nucleophilic reaction with the intermediate 1,3-dipole.

4.1. Reactions with general DA cyclopropanes

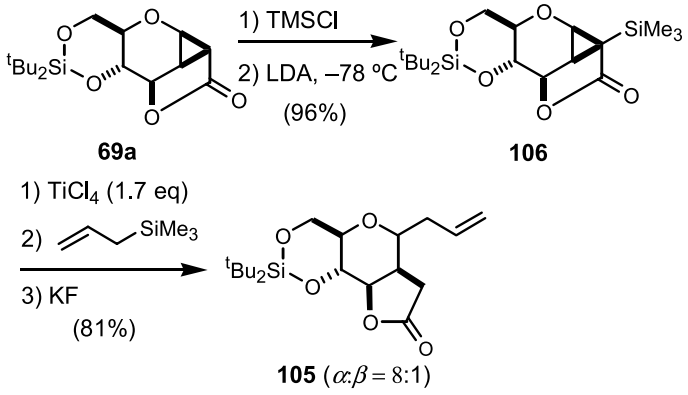
A wide variety of π-electron systems are efficient dipolarophiles for cyclization with DA cyclopropanes, and aldehydes and ketones were among the first successful dipolarophiles to be identified. However, the majority of



Scheme 36.



Scheme 38.



Scheme 39.

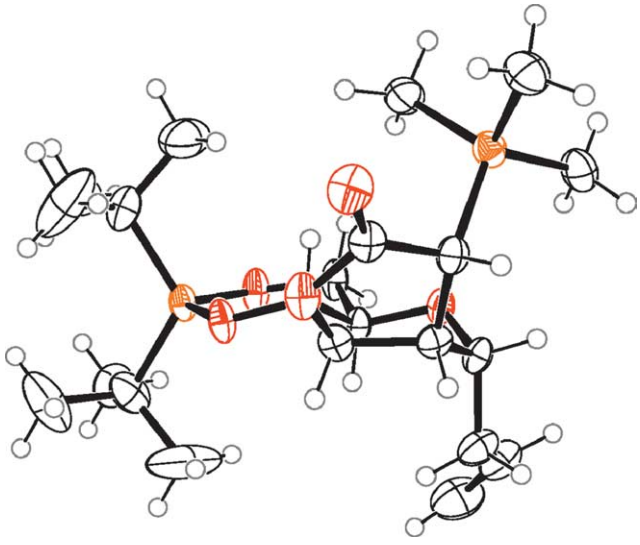
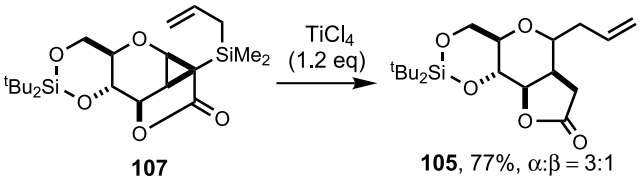


Figure 3.

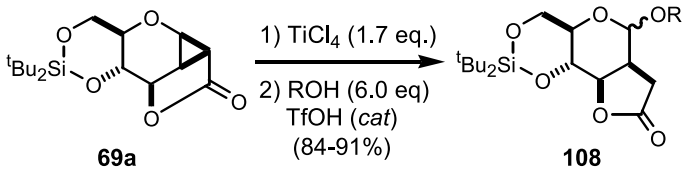


Scheme 40.

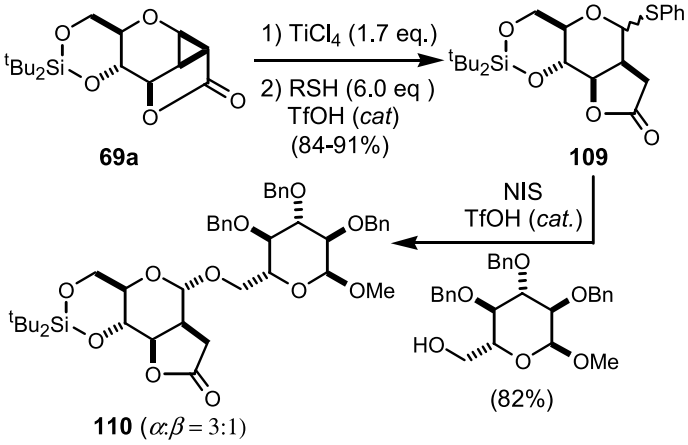
successful examples employed cyclopropanes featuring 'extra' activation by additional electron donor or acceptor groups. For example, reaction of **111** with aldehydes followed by an acidic workup provided γ-lactone products **112** (Scheme 43).[68] The reaction was selective for the diastereomer with a *cis* relationship between the carboxylate and R^2, but a subsequent basic epimerization provided access to the *trans* epimer **113**. A similar reaction with a less substituted cyclopropane such as **114** resulted in the formation of four diastereomers (Scheme 44), but a single isomer **116** was available by base catalyzed equilibration.[69] Excellent stereocontrol was observed in the reaction with symmetric ketones (Scheme 45),[70] and similar aldehyde and ketone cyclizations have also been reported on 2,3-carboxylate substituted methanochromanone derived DA cyclopropane **66** (Section 1.2.2.2).[41b,c]

Carbon-nitrogen double bonds in the form of imines,[71] isocyanates,[72] and isothiocyanates[73] react with DA cyclopropanes to provide lactams **119**, **121** and thiolactams **122** (Scheme 46 and Scheme 47). Unlike the corresponding lactones (vide supra), attempts at basic epimerization of **119** with NaOEt were plagued with lactam ring opening.

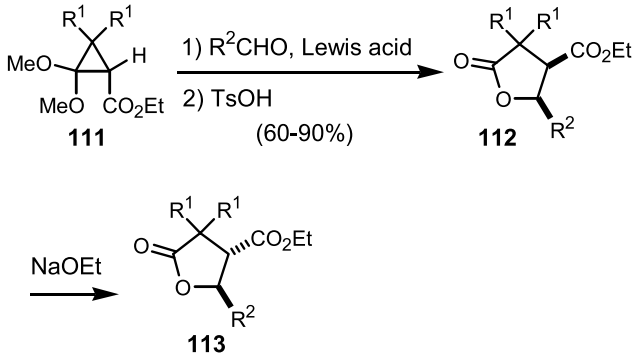
DA cyclopropanes have also been reported to undergo thermal cyclization with azodicarbonyl compounds in 70–80% yields (Scheme 48).[74] The diastereoselectivity of these reactions is highly dependent on the conformation of **120** as well as the polarity of the solvents. In other examples, the cyclization of **120** with electron deficient acetylene **124**[75] or alkene **126**[76] provided the cyclic products **125** and **127**



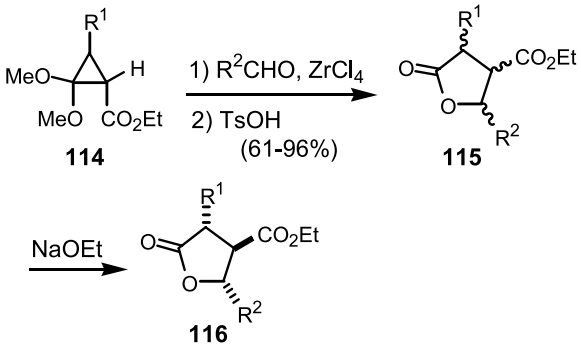
Scheme 41.



Scheme 42.



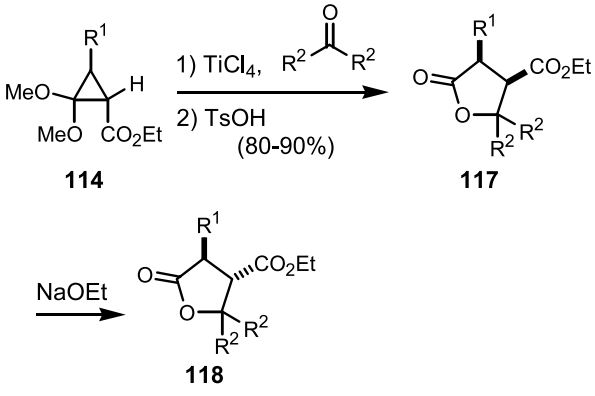
Scheme 43.



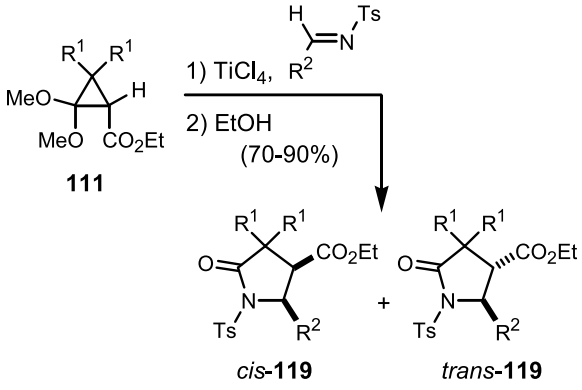
Scheme 44.

(Scheme 49). Both the reactions have very good diastereoselectivity, but the former was accompanied with considerable formation of acyclic addition product.

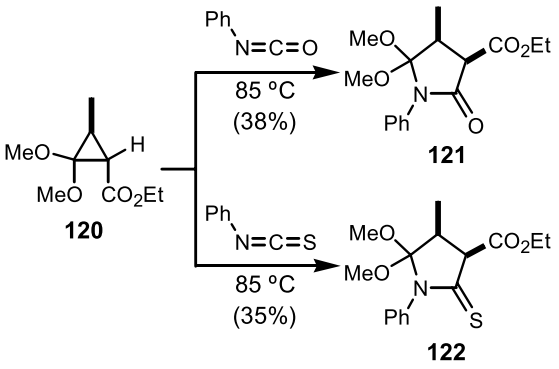
Compared with the large diversity of electron deficient dipolarophiles, fewer electron rich dipolarophilic components have been reported to participate with DA cyclopropanes. The reaction with electron rich dipolarophiles normally requires catalytic Lewis acid activation. The reaction of cyclopropyl carboxylate or ketone **128** with



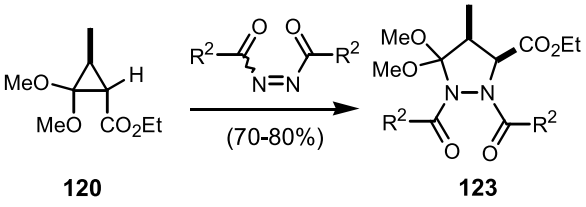
Scheme 45.



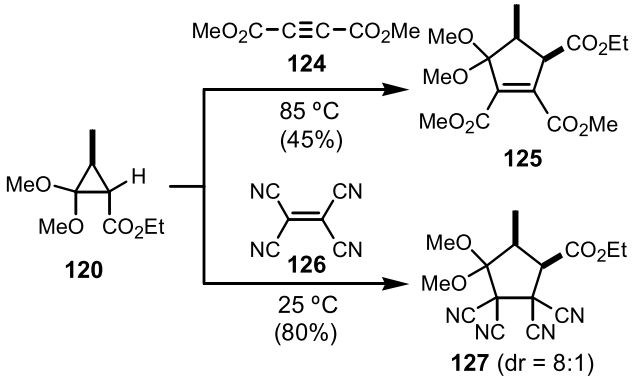
Scheme 46.



Scheme 47.

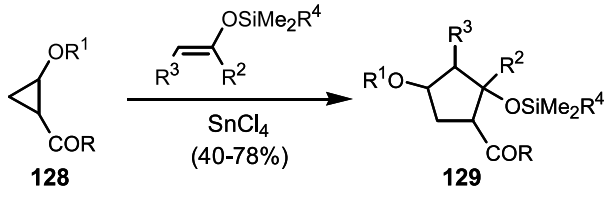


Scheme 48.



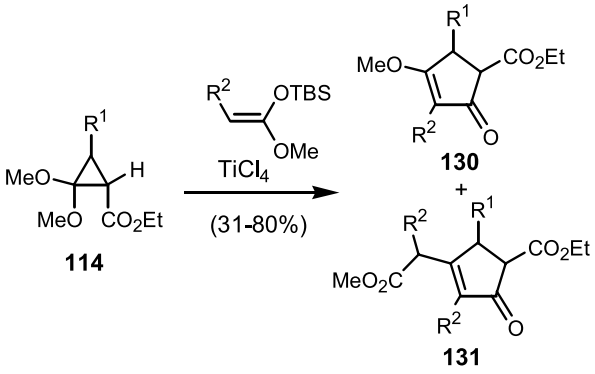
Scheme 49.

silyl enol ethers under $SnCl_4$ activation afforded the cyclopentane products **129** in good yields, but without stereoselectivity (Scheme 50).[77] The reaction of cyclopropane **114** and silyl ketene acetals, however, did not stop at the cyclopentanes, and spontaneous elimination of MeOH gave the cyclopentenone products **130** and **131** (Scheme 51).[78]

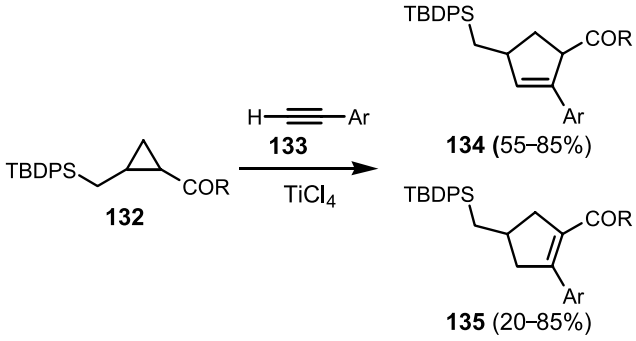


Scheme 50.

Recently, Yadav and co-workers have reported formal [3+2] cyclizations between DA cyclopropanes and aryl acetylenes (Scheme 52).[79] These reactions demonstrated



Scheme 51.



Scheme 52.

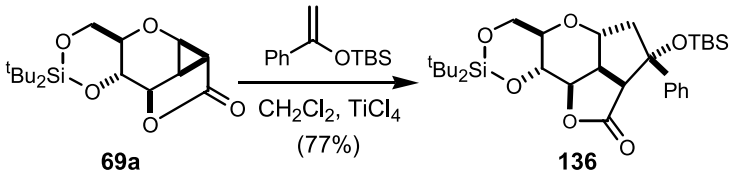
both high regio- and stereocontrol, and provided convenient access to highly functionalized cyclopentene derivatives.

4.2. Cyclization with glycal-derived DA cyclopropanes

Despite the diverse reactivity observed with general DA cyclopropanes, a formal [3+2] dipolar cycloaddition with a carbohydrate-derived cyclopropane was reported only recently.[80,81] An important reason behind the lack of development in this area again rests in the divergent reactivity of glycal-derived cyclopropanes prepared by either intra- or intermolecular carbene addition. This section is intended to summarize those new formal [3+2] dipolar cyclization reactions that have been recently discovered in this area.

4.2.1. Cyclization with silyl enol ethers. With the assistance of 1.5 equiv of $TiCl_4$ the lactonized cyclopropane **69a** cyclizes with silyl enol ethers to provide the cycloadduct **136** as the only isolable product in 77% yield (Scheme 53).[42] The stereochemistry of the product **139** was determined by single crystal X-ray analysis (Fig. 4).

The product stereochemistry is consistent with a steric control process during which the nucleophilic silyl ether approaches the oxocarbenium ion intermediate from the sterically more accessible α-face (Scheme 54). The subsequent intramolecular ring closure places the larger substituent (TBS) preferentially in a pseudo-equatorial position. Cyclization with silyl enol ethers occurred with promotion by $TiCl_4$, but other Lewis acids (e.g., $ZrCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf) were unsuccessful.



Scheme 53.

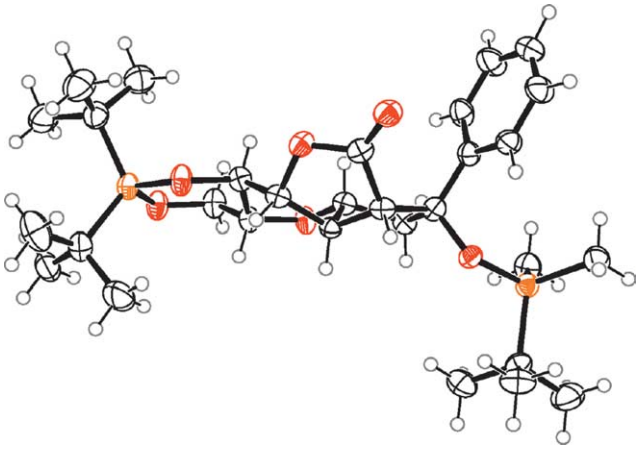
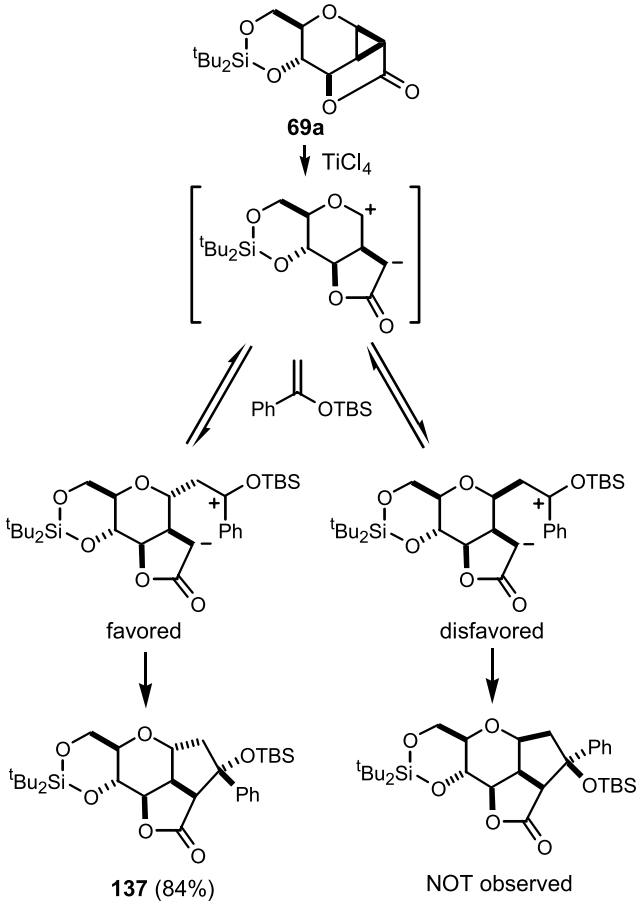


Figure 4.



Scheme 54.

4.2.2. Cyclization with imines and carbonyl compounds. Electron deficient dipolarophiles also participate in cyclizations with lactonized DA cyclopropanes. The TMSOTf mediated cycloaddition of imines with **69a** furnishes the aminal product **138** in 82% yield (Scheme 55). The reaction displayed excellent stereoselectivity and dependence upon a single Lewis acid (vide supra).

Reactions with aldehydes and ketones required activation by $TiCl_4$ (Scheme 56). The cyclic acetal product **139** is highly susceptible to hydrolysis, which complicated isolation, and they were therefore fully characterized as their anomeric acetals **140**.

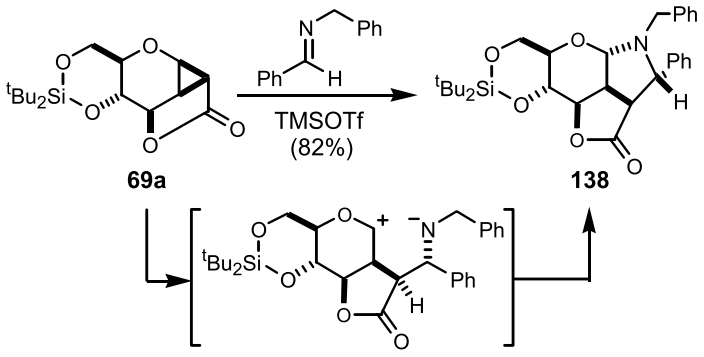
4.2.3. Cyclization with nitriles.

4.2.3.1. Formal [3+2] cyclization with nitriles. Acetonitrile is a common solvent for reactions involving charged intermediates, and often it becomes incorporated into reaction products, as in the classic Ritter reaction.[82] Acetonitrile is a useful and unreactive solvent for ring opening reactions of DA cyclopropanes, even when highly electrophilic oxocarbenium ion intermediates are present (e.g., Scheme 17, Scheme 32). In marked contrast, treating the lactonized DA cyclopropanes **69a** under similar reaction conditions using TMSOTf as Lewis acid resulted in clean formation of 2*H*−3,4-dihydropyrrole products **141** in good to excellent yields, even in the presence of excess allyltrimethylsilane (Scheme 57).[80] This formal dipolar cycloaddition demonstrated broad reagent compatibility with aliphatic, aromatic and α,β-unsaturated nitriles (Table 4). At its current state of development, electron deficient nitriles have failed to participate. Once again, conformational control of reactivity appears to be an indispensable strategy for harnessing new DA cyclopropane reactivity.

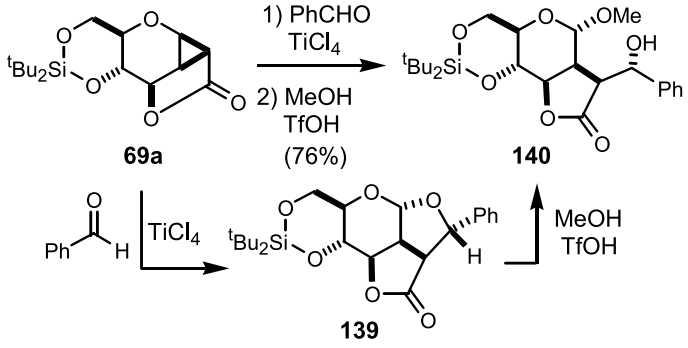
The stereochemical course of the reaction was unambiguously established by single crystal X-ray analysis of the benzonitrile cyclization product (Table 4, entry 2; Fig. 5).

Curiously, the *cis*-like stereochemistry of this cyclization is *opposite of that observed in the cycloaddition with silyl enol ethers* (Scheme 53, Fig. 4). A mechanistic hypothesis consistent with a Rittter-like transformation starts with nucleophilic nitrile addition onto an intermediate oxonium ion (Scheme 57). Steric approach control would favor attack at the α-face, but presumably the electrophilic linear nitrilium ion is too distant for enolate attack. In contrast, the sterically less favourable *cis*-like intermediate can be trapped by the enolate giving the observed product.

4.2.3.2. Pyrrole synthesis through DA cyclopropane-nitrile cycloaddition. Recently, Yu and Pagenkopf developed a novel pyrrole synthesis based on the nitrile cycloaddition methodology.[81] When extended to general



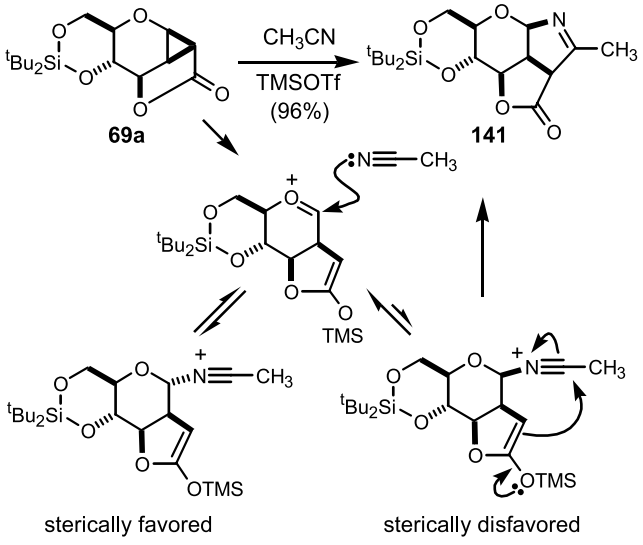
Scheme 55.



Scheme 56.

non-lactonized DA cyclopropane substrates **143**, the nitrile cycloadditions failed to stop at the dihydropyrroles, but continued to the aromatic pyrroles **144** after elimination and tautomerization (Scheme 58).

Extension of the nitrile [3+2] cyclization required extensive reaction optimization, including the use specific solvents. For example, the cyclizations of lactonized cyclopropanes with nitriles other than MeCN or EtCN (Table 4) were performed in CH_2Cl_2. However, the same conditions with general DA cyclopropanes resulted in cyclopropane rearrangement to the γ-keto ester (Table 5, entry 1; Scheme 1) before incorporation of the nitrile component. Reaction in $MeNO_2$ or $EtNO_2$ solvent apparently prolonged the lifetime of the oxocarbenium sufficiently that even with a stoichiometric amount of nitrile successful cycloadditions were observed.



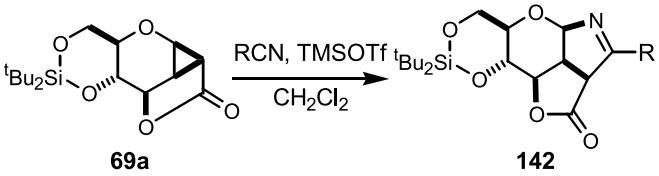
Scheme 57.

This pyrrole synthesis offers several advantages over other classic methods, including absolute regiochemical control (which is seldom possible by condensation procedures), high yields, simple purification, use of commercially available nitriles (Table 5) and diverse substitution patterns around the pyrrole (Table 6). This method can install alkyl groups selectively around the pyrrole product at either, both, or neither of the C(4) and C(5) positions without formation of constitutional isomers (Table 6). The method can also be used to prepare indoles by catalytic dehydrogenation (entries 17 and 18).[42] It is worth noting that identical yields were obtained from **145** regardless of cyclopropane stereochemistry.

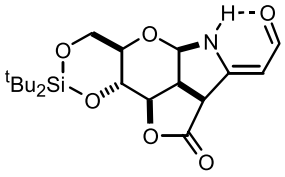
4.2.3.3. Bipyrrole and thienylpyrrole synthesis. Extension of the pyrrole synthesis to 2-cyanopyrroles **148** and 2-cyanothiophenes **150** has lead to convenient access toward unsymmetrical bipyrroles **149** and thienylpyrroles **151**.[83] Compared with general nitriles, the electron donating ability of the pyrrole ring proved to make these nitriles good dipolarophiles for this reaction (Table 7). When electron donating alkyl groups were introduced to the parent pyrrole ring (3,4-diethyl-1*H*-pyrrole-2-carbonitrile), reaction efficiency improved. Remarkably, protection of the pyrrole was unnecessary.

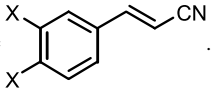
The identical reaction conditions were less effective when

Table 4.



69a 142

Entry	Nitrile	Product	Yield (%)
1	MeCN	R=Me	96
2	PhCN	R=Ph	81
3	PrCN	R=Pr	95
4	^{t}BuCN	R=^{t}Bu	79
5	$Cl(CH_2)_3CN$	R=$(CH_2)_3Cl$	87
6[a,b]	Ar–CH=CH–CN	R=CHCHAr	60
7[a,c]	Ar–CH=CH–CN	R=CHCHAr	75
8	MeO–CH=CH–CN		78

[a] Nitrile =  .
[b] X=H.
[c] X=OMe.

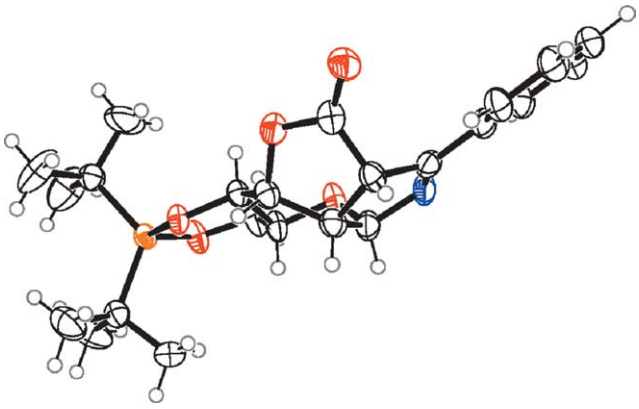
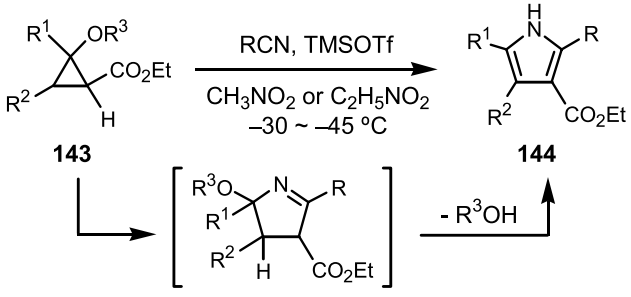


Figure 5.



Scheme 58.

applied to the cyclization of thiophene-2-carbonitrile and various DA cyclopropanes (Table 8), but the method remains an attractive option for its operational simplicity and brevity.

A structural constancy and potential limitation of this pyrrole method is the C(3) β-ethyl carboxylate, but this remnant can be removed efficiently by decarboxylation (Scheme 59).

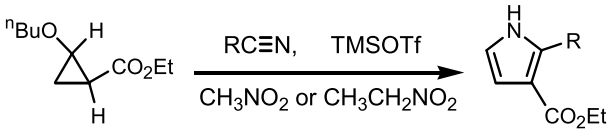
5. Conclusion

The diverse functionality and reactivity provided by donor–acceptor cyclopropane makes them attractive substrates for chemical development. This review focused primarily on carbohydrates-derived cyclopropanes and summarized advances in this area from the last decade. The preparation of chiral donor–acceptor cyclopropanes remains a hot area of research, and the utilization of carbohydrate scaffolds has proven to be one effective strategy to prepare enantiomerically pure variants of these reactive species. Continued advances in the area can surely be expected.

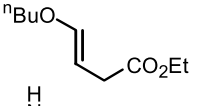
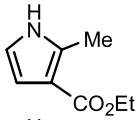
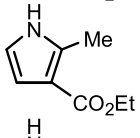
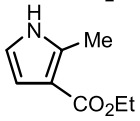
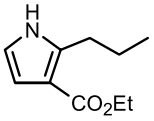
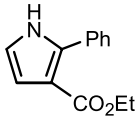
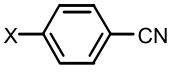
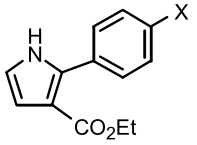
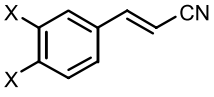
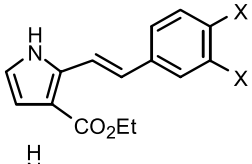
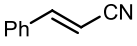
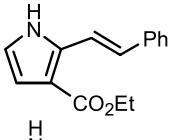
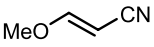
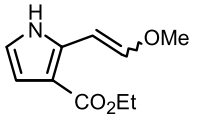
Acknowledgements

We thank the Robert A. Welch foundation for support, and Prof. John Hoberg for helpful discussions.

Table 5.



145 **146**

Entry	Nitrile	Product	Yield (%)
1[a]	MeCN		51
2[b]	MeCN		9
3[c]	MeCN		80
4[d]	MeCN		73
5	PrCN		77
6	PhCN		35
7[e]			55
8[e]			85
9			39
10			91

[a] Room temperature, solvent = CH_2Cl_2.
[b] Room temperature, solvent = MeCN.
[c] −40 °C, solvent = MeCN.
[d] −25 °C, solvent = $MeNO_2$.
[e] X = OMe.

Table 6

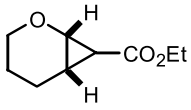
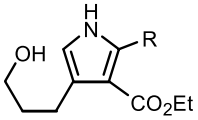
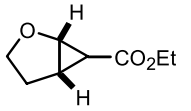
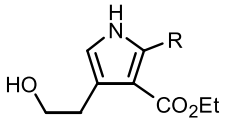
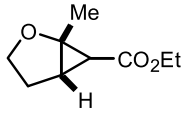
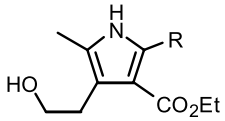
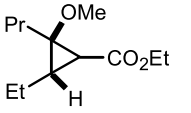
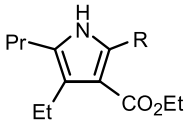
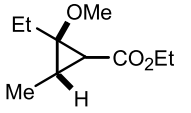
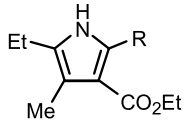
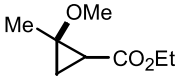
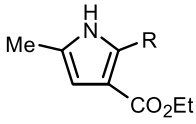
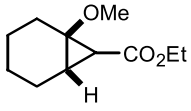
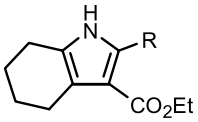
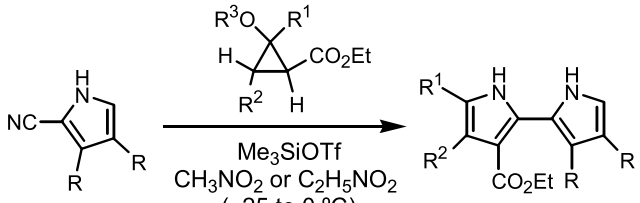
Entry	Substrate	Nitrile	Pyrrole	Yield (%)
1		MeCN		72
2		PrCN		78
3		PhCN		58
4		$Cl(CH_2)_3CN$		61
5		MeCN		52
6		PrCN		58
7		$MeOC_2H_2CN$		81
8		MeCN		31
9		PrCN		25
10		MeCN		93
11		PrCN		82
12		PhCN		76
13		MeCN		98
14		PrCN		85
15		MeCN		62
16		PrCN		55
17		MeCN		72
18		PrCN		75

Table 7.



148

149a, R = H
149b, R = Et

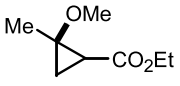
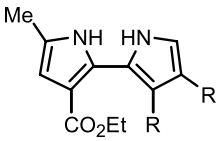
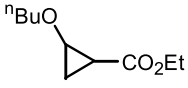
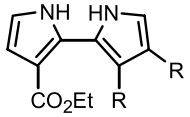
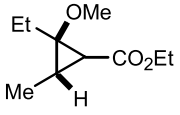
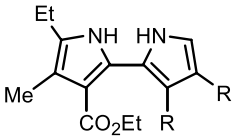
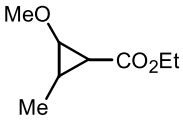
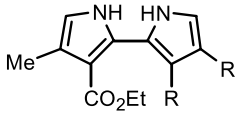
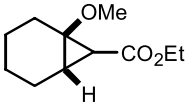
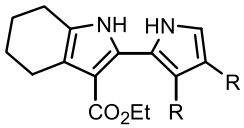
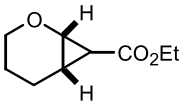
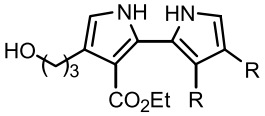
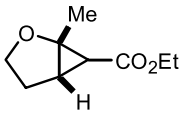
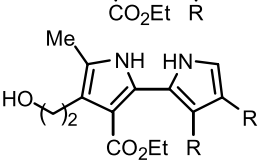
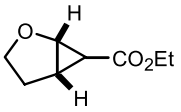
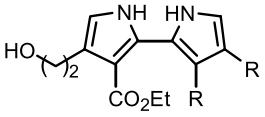
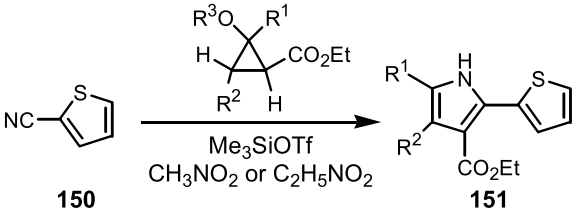
Entry	Substrate	Product	Yield (%)
1			78[a]
2			82[b]
3			41[a]
4			45[b]
5			82[a]
6			85[a]
7			48[a]

Table 7 (*continued*)

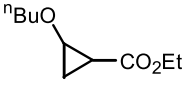
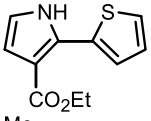
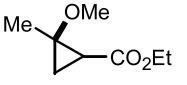
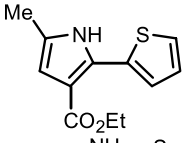
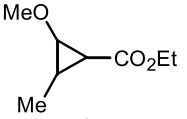
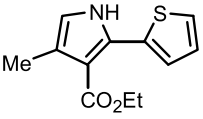
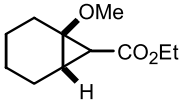
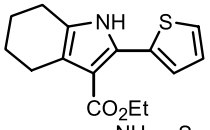
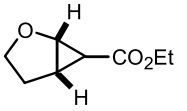
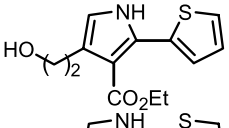
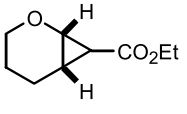
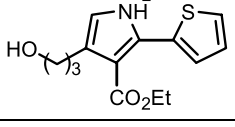
Entry	Substrate	Product	Yield (%)
8			62[a]
9			82[b]
10			46[a]
11			54[b]
12			84[b]
13			42[b]

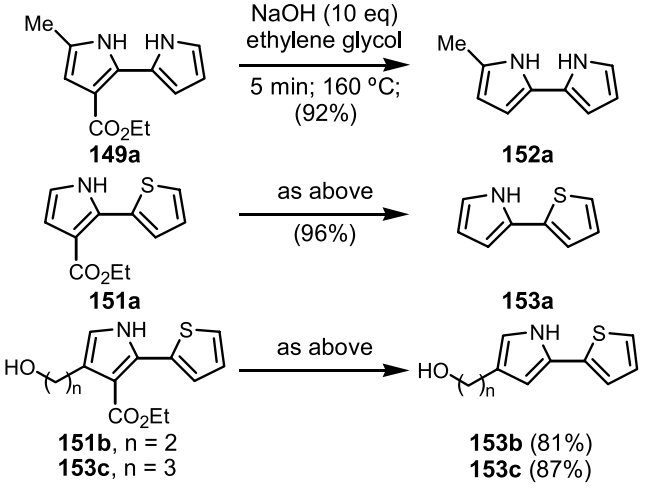
[a] R=H.
[b] R=Et.

Table 8.



150 **151**

Entry	Substrate	Product	Yield (%)
1			47
2			69
3			63
4			37
5			41
6			73



Scheme 59.

References and notes

1. For leading reviews, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (b) von Angerer, S. In de Meijere, A., Ed.; Carbocyclic Three- and Four-membered Ring Compounds. Methods of Organic Chemistry (Houben–Weyl); Verlag: New York, 1997; Vol. E17c, pp 2121–2153. (c) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73–135. (d) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31.
2. (a) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733–750. (b) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1987; Chapter 8, pp 375–443. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C. W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (d) Kulinkovich, O. G. *Pol. J. Chem.* **1997**, 849–882. (e) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1–67. (f) de Meijere, A.; Kozhushkov, S. I.; Khlebnikow, A. F. *Top. Curr. Chem.* **2000**, *207*, 89–147. (g) de Meijere, A.; Kozhushkov, S. I.; Hadjiarapoglou, L. P. *Top. Curr. Chem.* **2000**, *207*, 149–227.
3. For reviews, see: (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley: New York, 1987. (b) Houben–Weyl Methods of Organic Chemistry. Thieme: Stuttgart, 1997; Vol. E17c. (c) de Meijere, A. Small Ring Compounds in Organic Synthesis VI; Springer: Berlin, 2000; Vol 207. (d) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charetter, A. *Chem. Rev.* **2003**, *103*, 977–1050.
4. Salaün, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 4–71.
5. For selected examples, see: (a) Reissig, H. U. *Tetrahedron Lett.* **1985**, *26*, 3943–3946. (b) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53–61.
6. For selected examples, see: (a) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31. (b) Wenkert, E. *Heterocycles* **1980**, *14*, 1703–1708. (c) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802–819. (d) Adams, J.; Frenette, R.; Belley, M.; Chibante, F.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5432–5437. (e) Brückner, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440–2450. (f) Brückner, C.; Holzinger, H.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2450–2456. (g) Kanemasa, S.; Otsuka, T.; Doi, K.; Tsuge, O.; Wada, E. *Synthesis* **1990**, 1167–1169. (h) Angert, H.; Kunz, T.; Reissig, H.-U. *Tetrahedron* **1992**, *48*, 5681–5690. (i) Reissig, H.-U.; Reichelt, I.; Kunz, T. *Org. Synth.* **1993**, *71*, 189–199. (j) Reissig, H.-U.; Angert, H.; Kunz, T.; Janowitz, A.; Handke, G.; Bruce-Adjei, E. *J. Org. Chem.* **1993**, *58*, 6280–6285. (k) Angert, H.; Schumacher, R.; Reissig, H.-U. *Chem. Ber.* **1996**, *129*, 227–232. (l) Angert, H.; Czerwonka, R.; Reissig, H.-U. *Liebigs Ann.* **1996**, 259–263. (m) Angert, H.; Czerwonka, R.; Reissig, H.-U. *J. Prakt. Chem.* **1997**, *339*, 453–455. (n) Angert, H.; Czerwonka, R.; Reissig, H.-U. *Liebigs Ann.* **1997**, 2215–2220.
7. For selected examples, see: (a) Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139–3150. (b) Zimmer, R.; Reissig, H.-U. *Synthesis* **1989**, 908–911.
8. For selected examples, see: (a) Shimada, S.; Saigo, K.; Hashimoto, Y.; Maekawa, Y.; Yamashita, T.; Yamamoto, T.; Hasegawa, M. *Chem. Lett.* **1991**, 1475–1478. (b) Sugita, Y.; Kawai, K.; Hosoya, H.; Yokoe, I. *Heterocycles* **1999**, *51*, 2029–2033. (c) Sugita, Y.; Kimura, C.; Hosoya, H.; Yamadoi, S.; Yokoe, I. *Tetrahedron Lett.* **2001**, *42*, 1095–1098. (d) Sugita, Y.; Kimura, C.; Yokoe, I. *Heterocycles* **2001**, *55*, 855–859. (e) Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657–658.
9. (a) Graziano, M. L.; Iesce, M. R. *J. Chem. Res. (S)* **1987**, 362–363. (b) Graziano, M. L.; Chiosi, S. *J. Chem. Res. (S)* **1989**, 44–45. (c) Graziano, M. L.; Cimminiello, G. *J. Chem. Res. (M)* **1989**, 446–447. (d) Saigo, K.; Shimada, S.; Hasegawa, M. *Chem. Lett.* **1990**, 905–908. (e) Graziano, M. L.; Iesce, M. R.; Cermola, F.; Cimminiello, G. *J. Chem. Res. (M)* **1992**, 157–172. (f) Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 5226–5234. (g) Graziano, M. L.; Iesce, M. R.; Cermola, F. *J. Chem. Res. (M)* **1996**, 622–629. (h) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2001**, *55*, 135–144.
10. For a recent review, see: Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174.
11. Bols, M. *Carbohydrate Building Blocks*; Wiley: Toronto, 1996.
12. For recent reviews, see: (a) Boas, U.; Heegaard Peter, M. H. *Chem. Soc. Rev.* **2004**, *33*, 43–63. (b) Horstkorte, R.; Keppler, O. T.; Reutter, W. *Carbohydrate-based Drug Discovery* **2003**, *2*, 863–873. (c) Macmillan, D.; Daines, A. M. *Curr. Med. Chem.* **2003**, *10*, 2733–2773. (d) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 231–253.
13. For recent reviews: (a) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779–884. (b) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465–4494. (c) Hollingsworth, R. I.; Wang, G. *J. Chem. Rev.* **2000**, *100*, 4267–4282.
14. For selected examples, see: (a) Kim, J. Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303–306. (b) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709–1712. (c) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917–1920. (d) Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601–9604. (e) DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179–3180. (f) Linker, T.; Sommermann, T.; Kahlenberg, G. *J. Am. Chem. Soc.* **1997**, *119*, 9377–9384. (g) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419. (h) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.
15. Chapleur, T.; Chetein, F. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 207–264.
16. For selected examples: (a) Briner, K.; Vasella, A. *Helv. Chim. Acta* **1989**, *72*, 1371–1382. (b) Huber, R.; Molleyres, L. P.;

Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 1329–1337. (c) Vasella, A. *Pure Appl. Chem.* **1993**, *65*, 731–752. (d) Remen, L.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 1118–1127. (e) Bluechel, C.; Ramana, C. V.; Chepuri, V.; Vasella, A. *Helv. Chim. Acta* **2003**, *86*, 2998–3036.
17. For reviews, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (b) Marsh, J. *Adv. Org. Chem.*, 4th ed.; Wiley: New York, 1992.
18. Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995**, 217–218.
19. For selected examples, see: (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353–3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.
20. Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831–6834. (b) Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615–6618.
21. For selected examples, see: (a) Boeckman, R. K.; Charette, A. B.; Asberson, T.; Johnson, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553–7555. (b) Boyer, F.-D.; Lallemand, J.-Y. *Synlett* **1992**, 969–971. (c) Gurjar, M. K.; Chakrabarti, A.; Venkateswara Rao, B.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885–6888.
22. Fraser-Reid, B.; Carthy, B. J. *Can. J. Chem.* **1972**, *50*, 2928–2934.
23. Brimacombe, J. S.; Evans, M. E.; Forbes, E. J.; Foster, A. B.; Webber, J. M. *Carbohydr. Res.* **1967**, *4*, 239–243.
24. Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995**, 217–218. (b) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703.
25. Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 447–449.
26. Baidzhigitova, E. A.; Afanas'ev, V. A.; Dolgii, I. E. *Izv. Akad. Nauk Kirg. SSR* **1981**, 50–56.
27. Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901–8904.
28. Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533–2536.
29. Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C.; Vandermarel, G. A.; van Boom, J. H. *Tetrahedron: Asymmetry* **1996**, *7*, 49–52.
30. Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882–6889. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094–2096.
31. Scott, R. W.; Heathcock, C. M. *Carbohydr. Res.* **1996**, *291*, 205–208.
32. Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.
33. Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000–8001.
34. Fernandez-Megia, E.; Gourlaouen, S.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991–994.
35. Ramana, C.; Nagarajan, M. *Synlett* **1997**, 763–764. (b) Ramana, C.; Nagarajan, M. *Carbohydr. Lett.* **1998**, *3*, 117–119.
36. Boechman, R.; Charette, A.; Asberom, T.; Johnston, B. *J. Am. Chem. Soc.* **1991**, *113*, 5337–5353.
37. Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran, S. *Org. Lett.* **2004**, *6*, 1777–1779.
38. Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043–9045.
39. For selected examples, see: (a) Gurjar, M. K.; Charkrabarti, A.; Venkateswara Rao, B.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885–6888. (b) Takemoto, Y.; Ibuka, T. *Tetrahedron Lett.* **1998**, *39*, 7545–7548. (c) Takemoto, Y.; Furuse, S.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, C.; Ibuka, T. *Chem. Commun.* **1999**, 2525–2526.
40. Sugita, Y.; Kimura, C.; Hosoya, H.; Yamadoi, S.; Yokoe, I. *Tetrahedron Lett.* **2001**, *42*, 1095–1098.
41. Sugita, Y.; Kawai, K.; Hosoya, H.; Yokoe, I. *Heterocycles* **1999**, *51*, 2029–2033. (b) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2000**, *53*, 657–664. (c) Sugita, Y.; Kawai, K.; Yokoe, I. *Heterocycles* **2001**, *55*, 135–144.
42. Yu, M.; Pagenkopf, B. L. Unpublished results.
43. Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563–2566.
44. (a) Adams, J.; Belley, M. *Tetrahedron Lett.* **1986**, *27*, 2075–2078. (b) Adams, J.; Belley, M. *J. Org. Chem.* **1986**, *51*, 3878–3881.
45. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559–3562.
46. Ziegler, F. E.; Martino, A. F.; Petroff, O. A. C.; Studt, W. L. *Tetrahedron Lett.* **1974**, *15*, 2035–2038.
47. Blankley, C. J.; Suture, F. J.; House, H. O. *Org. Synth.* **1970**, 259–262.
48. Charles, R. G. *J. Org. Chem.* **1957**, *22*, 677–679.
49. For recent reviews, see: (a) Doyle, M. P. In *Advances in Chemistry Series, Homogeneous Transition Metal Catalyzed Reaction*, 1992; Vol. 230, pp 443–461. (b) Yakura, T. *J. Pharm. Soc. Jpn* **2000**, *120*, 1309–1322.
50. For selected examples, see: (a) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773–1776. (b) Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org. Lett.* **2001**, *3*, 2261–2264.
51. For selected examples: see (a) Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 1906–1912. (b) Doyle, M. P.; Van, O.; Arjan, W.; Larry, J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982–8984. (c) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964. (d) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J. *J. Am. Chem. Soc.* **1995**, *117*, 5763–5775. (e) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N. M. A. B.; Parker, D. L., Jr.; Ene, D. G.; Lynch, V. *J. Am. Chem. Soc.* **1997**, *119*, 8826–8837. (f) Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839–8847. (g) Doyle, M. P.; Catino, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 925–928.
52. For selected examples, see: (a) Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014–4015. (b) Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* **1972**, *13*, 997–1000. (c) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1975**, *16*, 529–532. (d) Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1980**, *21*, 1433–1436. (e) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M.; Bell Lab, M. H. *J. Am. Chem. Soc.* **1982**, *104*, 5824–5826. (f) Prowotorow, I.; Wicha, J.; Mikami, K. *Synthesis* **2001**, 145–149.
53. Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490–1491.
54. For selected examples, see: (a) Hall, P. W.; Puddephatt, R. J.; Tipper, C. F. H. *J. Organomet. Chem.* **1974**, *71*, 145–151. (b) Al-Essa, R. J.; Ling, S. S. M.; Puddephatt, R. J. *Organometallics* **1987**, *6*, 951–959. (c) Al-Essa, R. J.; Puddephatt, R. J.; Thompson, P. J.; Tipper, C. F. H. *J. Am. Chem. Soc.* **1980**, *102*, 7546–7553.
55. For reviews, see: (a) Puddephatt, R. J. *Coord. Chem. Rev.*

1980, *33*, 149–194. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245–269. (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241–2290.
56. For selected examples, see: (a) Doyle, M. P.; Van Leusen, D. *J. Am. Chem. Soc.* **1981**, *103*, 5917–5919. (b) Doyle, M. P.; Van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326–5338. (c) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (d) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27–31.
57. Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137–12138.
58. Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765–2771.
59. Yu, M.; Pagenkopf, B. L. *J. Org. Chem.* **2002**, *67*, 4553–4558.
60. Bambal, R.; Kemmett, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734–735.
61. Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657–658.
62. Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955–2965.
63. Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260–270.
64. For selected examples, see: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209. (c) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169. (d) Yadav, J. S.; Subba, B. V.; Chand, P. K. *Tetrahedron Lett.* **2001**, *42*, 4057–4059.
65. Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 4639–4640.
66. For selected reviews, see: (a) Yamamoto, Y.; Sasaki, N. *Stereochem. Org. Inorg. Compd.* **1989**, *3*, 363–441. (b) Dai, L.-X.; Lin, Y.-R.; Hou, X.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 1033–1040. (c) Fürstner, A.; Voigtländer, D. *Synthesis* **2000**, 959–969.
67. For selected examples, see: (a) Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. J. *Chem. Soc., Chem. Commun.* **1984**, *6*, 6355–6356. (b) Adams, N.; Blake, C.; Broadhurst, M. J.; Bushnell, D. J.; Hassall, C. H. *J. Med. Chem.* **1990**, *33*, 2375–2379. (c) Thiem, J.; Koepper, S. *Tetrahedron* **1990**, *46*, 113–138. (d) Niggemann, J.; Lindhorst, T. K.; Walfort, M.; Laupichler, L.; Sajus, H.; Thiem, J. *Carbohydr. Res.* **1993**, *246*, 73–184. (e) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295–1297. (f) Skrydstrup, T.; Jarreton, O.; Mazeas, D. L.; Urban, D.; Beau, J.-M. *Chem. Eur. J.* **1998**, *4*, 655–671.
68. Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126–7133.
69. Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 5226–5234.
70. Shimada, S.; Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Tetrahedron* **1993**, *49*, 1589–1604.
71. Saigo, K.; Shimada, S.; Hasegawa, M. *Chem. Lett.* **1990**, 905–908.
72. Graziano, M. L.; Iesce, M. R. *J. Chem. Res. (S)* **1987**, 362–363.
73. Graziano, M. L.; Cimminiello, G. *J. Chem. Res. (S)* **1989**, 42–43.
74. Graziano, M. L.; Cimminiello, G. *J. Chem. Res. (M)* **1989**, 446–447.
75. Graziano, M. L.; Iesce, M. R.; Cermola, F.; Cimminiello, G. *J. Chem. Res. (S)* **1992**, *1992*, 157–172.
76. Graziano, M. L.; Chiosi, S. *J. Chem. Res. (S)* **1989**, 44–45.
77. Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771–773.
78. Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093–1096.
79. Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669–2671.
80. Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122–8123.
81. Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099–5101.
82. Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *7*, 213–325.
83. Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057–1059.

Biographical sketch

Ming Yu was born and grew up in Centre China, Hubei Province. In 1991, after finishing Middle school at his hometown, he went to Shanghai and attended East China University of Science and Technology, where he earned his BS in Pharmaceutical Technology in 1995 and MS in Medicinal Chemistry in 1998. He then joined the graduate school at The University of Texas at Austin in the Department of Chemistry and Biochemistry and received his chemistry PhD in 2004. During his PhD research, he made several significant discoveries in the area of donor–acceptor cyclopropanes. Dr. Yu is currently employed in California in the pharmaceutical industry.

Brian Pagenkopf earned his BS degree from the University of Minnesota, Twin Cities, in 1991, and his PhD from Montana State University, Bozeman, in 1996 under the supervision of Prof. Tom Livinghouse. He was a NIH postdoctoral fellow at Caltech and the ETH in Zürich under the supervision of Prof. Erick Carreira. He started his independent career at the University of Texas at Austin in 1999, and has published in areas that include methods development, asymmetric catalysis, organic materials for electronic devices and natural product synthesis.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 349–352

Selective formation of heterodimeric resorcinarene capsules

Alexander Shivanyuk*

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02094 Kyiv 94, Murmanska str. 5, Ukraine

Received 6 September 2004; revised 15 October 2004; accepted 29 October 2004

Available online 19 November 2004

Abstract—C_{2V}-symmetrical resorcinarene tetraesters **1** form in $CDCl_3$ dimeric capsules encapsulating one Me_4N^+ cation. The homodimeric capsules of the tetra(3,4,5-trimethoxybenzoate) **1d** and tetrabenzoate **1b** or tetrafuroylate **1c** disproportionate in solution to give quantitatively the heterodimers. The higher stability of the heterodimer is, most probably, caused by π–π attractions between the π-basic trimethoxyphenyl rings of **1d** and relatively more π-accepting phenyl or furyl fragments of **1b** or **1c**.

1. Introduction

Hydrogen bonded molecular capsules[1] are excellent hosts for neutral and ionic guests. These assemblies are usually centrosymmetrical because they are composed by two or more identical self-complementary molecules and include symmetrical guests. Non-centrosymmetrical dimeric heterocapsules provide an opportunity to study supramolecular isomerism (carcerism)[2] and allow to build capsular polymers[3] and multiple catenanes.[4] The simplest approach towards *exclusive formation* of heterodimeric molecular capsules is the interaction of two complementary hemispherical molecules.[5] In the literature there is one example of selective formation of the heterodimeric capsules through the aggregation of different self-complementary subunits. Namely, two homodimeric capsules of calix[4]arene tetraurea derivatives[6] disproportionate to give non-centrosymmetrical heterodimers which, normally, co-exist with the original homodimers in a statistical 2:1:1 ratio.[7] However, when the tetratosyl- and tetraarylureas are mixed only the

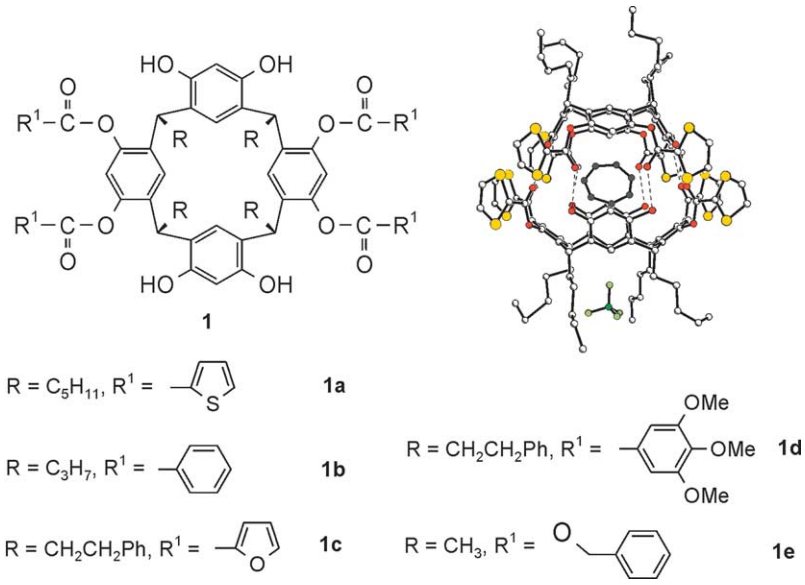


Figure 1. Line drawing of resorcinarene tetraesters **1** (left) and the crystal structure of $C_7H_7^+$ @**1a**$_2$ BF_4^- (right). Disordered sulfur atoms are shown as yellow circles.

Keywords: Supramolecular chemistry; Hydrogen bonds; Self-assembly; Molecular capsules.
* Corresponding author. Tel.: +038 044 551 06 16; fax: +038 044 573 26 43; e-mail: shivan@bpci.kiev.ua

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.089

heterocapsules are formed.[8] This selectivity was explained by stronger hydrogen bonding in the heterodimer compared to the homodimers.

C_{2V}-symmetrical resorcinarene tetrastersters **1** form dimeric hydrogen bonded capsules in the presence of tropylium cation[9] (Fig. 1). The mixing of two different homocapsules in $CDCl_3$ results in the statistical formation of the heterocapsules which co-exist with the homocapsules. The present research has been undertaken in order to find conditions for the selective formation of heterodimeric capsules of resorcinarene tetraesters **1**.

2. Results and discussion

Molecular mechanics calculations[10] have been performed on the basis of the crystallographic coordinates of $C_7H_7^+$ @**1a₂** BF_4^- (Fig. 1)[11] and showed that Me_4N^+ can be readily accommodated in the cavity of $\mathbf{1}_2$ (Fig. 2). These capsules were predicted to be stabilized by eight intermolecular C═O···H–O hydrogen bonds and multiple C–H···π host–guest interactions similarly to the original crystal structure. The shortest distances between the parallel aryl rings of the ester fragments are 3.6 Å, which indicate four π–π attractions in the parallel displaced configurations. Recent theoretical ab initio studies[12] showed that for the dimer of benzene the energy of such an interaction is 2.7 kcal/mol. On the basis of these considerations it was predicted that a heterocapsule formed by the resorcinarene tetraesters containing π-donating and π-accepting aryl fragments[13] should be more stable than the corresponding homocapsules.[14]

Compounds **1** were prepared in 20–30% yield according to the known procedures.[15] Their structure was established by ^1H and ^{13}C NMR spectroscopy and by single crystal X-ray analysis.[16]

The ^1H NMR spectrum of tetraester **1b** in $CDCl_3$ (Fig. 3(a)) contains four sharp singlets for the protons of the resorcinol rings and one triplet for the methine protons of the bridges according to the C_{2V}-symmetrical structure. The protons of the hydroxy groups emerge as a broad singlet at 6.78 ppm.[17] The addition of $Me_4N^+BF_4^-$ to the solution of **1b** gives rise to the new set of the resorcinarene signals which increase at the expense of the original set as the salt concentration increases (Fig. 3(b)). The up-field window of the spectrum contains one singlet at 0.28 ppm corresponding to the protons of the encapsulated Me_4N^+. Integration reveals that two resorcinarene molecules bind one cation (Fig. 2 (top)). The strong shielding of the guest protons ($\Delta\delta = -2.82$ ppm) indicates a close proximity to the diamagnetic currents of the host, which is typical for self-assembled *dimeric* capsules.[18] The ^1H NMR spectrum of the capsular complex (Fig. 3(c)) contains doublet of doublets for the methine protons of the bridges while the protons of the OH groups

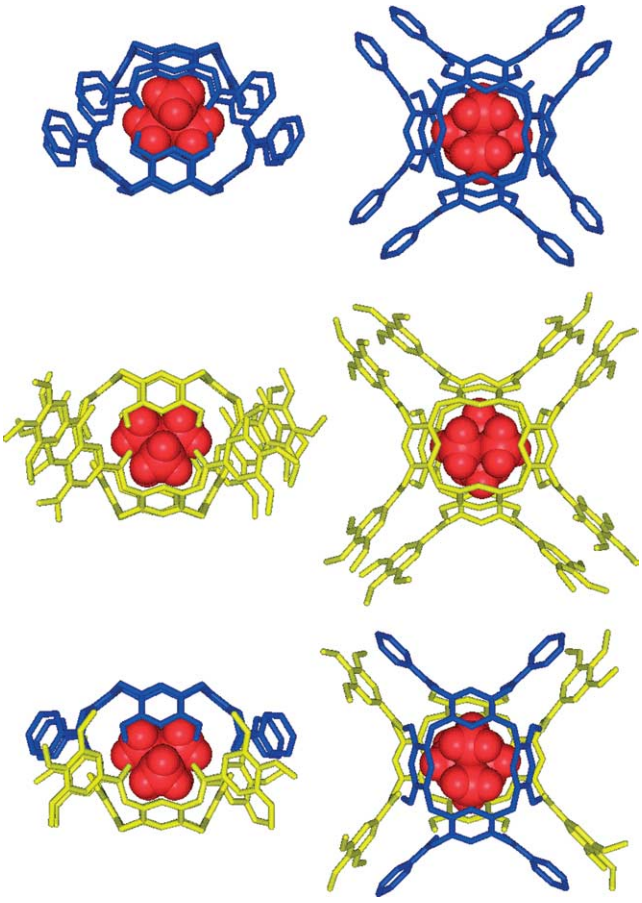


Figure 2. Energy minimized structure of Me_4N^+ @ $\mathbf{1b_2}$ (top), Me_4N^+ @ $\mathbf{1d_2}$ (middle), Me_4N^+ @ **1b**·**1d** (bottom). Encapsulated cation is shown in the space filling presentation. Pendant alkyl chains and CH hydrogen atoms of resorcinarenes are omitted for clarity. **1b**—blue, **1d**—yellow.

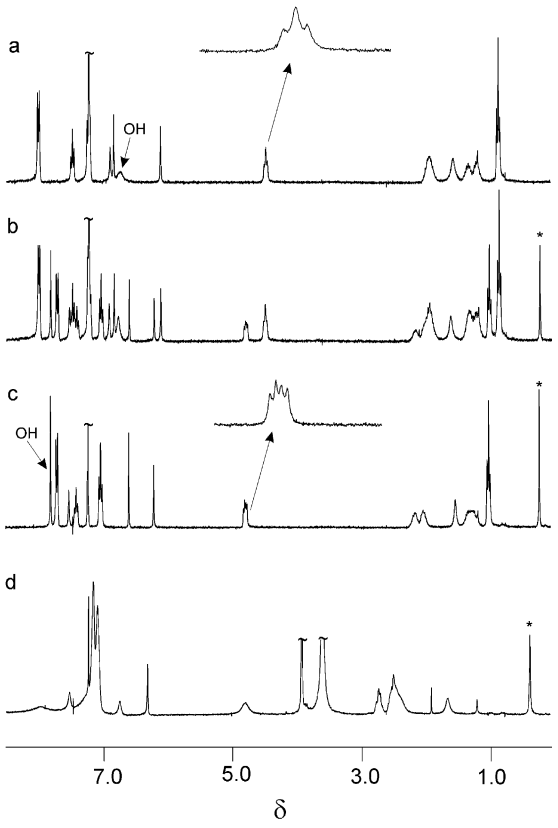


Figure 3. ^1H NMR spectra (300 MHz, $CDCl_3$, 298 K) of: (a) **1b**; (b) 4 **1b** + Me_4N^+ BF_4^-; (c) 2 **1b** + Me_4N^+ BF_4^-; (d) 2 **1d** + Me_4N^+ BF_4^-. The signal of the encapsulated cation is indicated by *. Signals for the methine protons of the bridges in free **1b** (a) and in Me_4N^+ @ $\mathbf{1b_2}$ (c) are enlarged.

appear as a sharp singlet at 7.83 ppm ($\Delta\delta = 1.05$ ppm) apparently due to the hydrogen bonding. The ^{19}F NMR spectrum of the capsule contains one signal for the unbound BF_4^- anion ($\delta = -148.5$ ppm) which does not change upon the addition of Bu_4N^+ BF_4^-. This proves that only the cation is encapsulated.[19] The complexation is size selective since tri- and tetraethylammonium cations are not encapsulated.

Tetrafuroylate **1c** has the same binding properties as tetrabenzoate **1b**. In contrast, tetrabenzylcarbonate **1e** does not form dimeric capsules in the presence of Me_4N^+ or tropylium cation, neither the heterocapsules are formed when Me_4N^+ @ **1b₂**BF_4^- or Me_4N^+ @ **1c₂**BF_4^- are mixed with **1e** in the presence of the free guest. This can be explained by weaker hydrogen bonding affinity of carbonate fragments and by flexibility of the benzyl residues that disfavours the additional arene–arene interactions.

The ^1H NMR spectrum of Me_4N^+ @ **1d₂** BF_4^- is broad at 298 K (Fig. 3(d)), apparently due to the lower kinetic stability of Me_4N^+ @**1d₂** BF_4^- compared to Me_4N^+ @ **1b₂** BF_4^- and Me_4N^+ @ **1c₂** BF_4^-. It seems likely that high electron density on the face to face aligned trimethoxyphenyl rings[13] (Fig. 2 (middle)) could cause some electrostatic repulsions, destabilizing the dimeric capsule. The addition of methanol (ca. 20%) to the solution of Me_4N^+ @ **1b₂** BF_4^- and Me_4N^+ @ **1c₂** BF_4^- decreases their kinetic stability so that the ^1H NMR signals become broad.

The mixing of Me_4N^+ @ **1b₂** BF_4^- and Me_4N^+ @ **1c₂** BF_4^- in a 1:1 molar ratio gives rise to the additional set of signals for **1b** and **1c** in keeping with the formation of heterodimeric capsule Me_4N^+ @ **1b·1c** BF_4^- (Fig. 4(a)). A statistical ratio between the heterodimer and the homodimers (2:1:1) indicates comparable stabilities of all three capsules. The mixing of Me_4N^+ @ **1b₂** BF_4^- and Me_4N^+ @ **1d₂** BF_4^- in a 1:1 molar ratio leads to the quantitative formation of the heterodimer, which is, apparently, much more stable than the homodimers. The ^1H NMR spectrum of Me_4N^+ @ **1b·1d** BF_4^- (Fig. 4(b)) contains one set of signals for each resorcinarene and one singlet for the protons of the encapsulated cation at

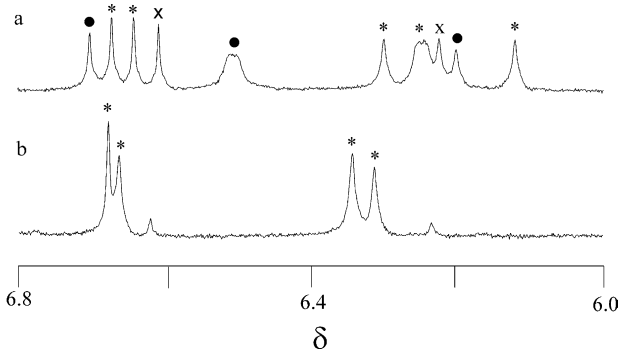


Figure 4. Section of the ^1H NMR spectrum (300 MHz, $CDCl_3$, 298 K) of: (a) Me_4N^+ @ **1b₂** BF_4^- + Me_4N^+ @ **1c₂** BF_4^-. (b) Me_4N^+ @ **1b₂** BF_4^- + Me_4N^+ @ **1d₂** BF_4^-. Singlets—aromatic protons of the resorcinol rings. Broadened multiplets-protons of the furoyl fragments of **1c**. *—signals of the heterodimer; x—signals of Me_4N^+ @ **1b₂** BF_4^-; ●—signals of Me_4N^+ @ **1c₂** BF_4^- The signals were assigned by variation of the ratio between the homodimers.

0.35 ppm ($\Delta\delta = -2.79$ ppm). The addition of Me_4N^+ @ **1b₂** BF_4^-or Me_4N^+ @ **1d₂** BF_4^- to the solution of Me_4N^+ @ **1b·1d** BF_4^- revealed that the equilibrium between the heterodimer and the excess of the homodimer is slow on the ^1H NMR timescale at 298 K. It was found that Me_4N^+ @ **1d₂** BF_4^- and Me_4N^+ @ **1c₂** BF_4^- also disproportionate to give quantitatively heterodimer Me_4N^+ @ **1c·1d** BF_4^-.

3. Conclusions

In conclusion, resorcinarene tetraesters **1b–d** form dimeric capsules around Me_4N^+. Intermolecular C═O···H–O hydrogen bonds, multiple C–H···π host–guest attractions and π–π interactions between the aroyl aromatic rings contribute to the stability of these assemblies. Selective formation of non-centrosymmetrical heterocapsules Me_4N^+@**1b·1d** and Me_4N^+@**1c·1d** in $CDCl_3$ is the result of their much higher stability compared to the homodimers. It seems likely that the π–π interactions of highly π-basic trimethoxyphenyl rings of **1d** with the phenyl or furoyl rings of **1b** or **1c** cause an additional stabilization of the heterodimers. High kinetic stability of the heterocapsules and availability of resorcinarenes **1** with different aroyl fragments make them promising systems for the evaluation of aryl–aryl interactions.[13]

References and notes

1. For a review see: (a) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508. (b) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991–2005. (c) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647–1668. (d) Mac Gillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018–1033.
2. (a) Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 12074–12075. (b) Scarso, A.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 13981–13983. (c) Timmerman, P.; Verboom, W.; Van Veggel, F. C. J. M.; Van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1994**, *33*, 2345–2347.
3. Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 7132–7137.
4. Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312–1314.
5. (a) Kobayashi, K.; Ishii, K.; Sakamoto, S.; Shirasaka, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 10615–10624. (b) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764–766. (c) Corbellini, F.; Di Costanzo, L.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946–9947.
6. (a) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403–12407. (b) Rebek, J., Jr. *Chem. Commun.* **2000**, 637–643. (c) Hamman, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1996**, *35*, 1326–1329.
7. Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489–8496.
8. Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12671–12672.

9. Shivanyuk, A.; Paulus, E. F.; Böhmer, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 2906–2909.
10. MMX force field was used as implemented in the PC Model program: PCMODEL for Windows V. 7.50.00, 2000, Serena Software.
11. Tropylium cation was removed from the cavity and the thiophene rings were replaced by the phenyl or 3,4,5-trimethoxyphenyl fragments. Only the capsular cations were optimized.
12. Sinokrot, M. O.; Valeev, E. F.; Sherrill, D. C. *J. Am. Chem. Soc.* **2002**, *124*, 10887–10893.
13. About repulsive and attractive π–π interactions in supramolecular systems see: Adams, H.; Hunter, C. A.; Lawson, K. R.; Perkins, J.; Spey, S. E.; Urch, C. J.; Sanderson, J. M. *Chem. Eur. J.* **2001**, *7*, 4863–4877.
14. Unfortunately, molecular mechanics calculations do not allow to evaluate the relative stabilities of the capsules.
15. Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63*, 6448–6449.
16. (a) Shivanyuk, A.; Paulus, E. F.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Chem. Eur. J.* **2001**, *7*, 1944–1951. (b) Shivanyuk, A.; Rafai Far, A.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 1555–1558.
17. The OH resonance was assigned by H–D exchange experiment with methanol-d_4.
18. For a recent example see: Shivanyuk, A.; Friesse, J.; Döring, S.; Rebek, J., Jr. *J. Org. Chem.* **2003**, *68*, 6489–6496.
19. Compare to: Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662–7665.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 353–363

Synthetic studies on the DEF-rings of FR182877 and hexacyclinic acid☆

Paul A. Clarke,[a,*] Matthew Grist,[a] Mark Ebden,[b] Claire Wilson[a] and Alexander J. Blake[a]

[a]*School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[b]*Medicinal Chemistry, AstraZeneca Charnwood, Bakewell Road, Loughborough, Leics LE11 5RH, UK*

Received 1 September 2004; revised 11 October 2004; accepted 29 October 2004

Abstract—A synthesis of model DEF-rings of the polyketide anti tumor natural products FR182877 and hexacyclinic acid has been achieved. The key steps in the synthesis are an intramolecular Pd(0) catalyzed allylic substitution reaction, which was used to generate a 9-membered carbocycle, and a novel transannular iodocyclization reaction which furnished the DF-rings of both natural products.

1. Introduction

As part of a screening program searching for new antimitotic compounds the Fujisawa Pharmaceutical Company isolated FR182877 **1**, from the culture broth of *Streptomyces* sp. no. 9885.[1] This compound has an unprecedented hexacyclic ring system, with a bridgehead double bond as part of a vinylogous carbonate unit, and has been shown to have potent anti-tumor activity. In biological assays FR182877 was shown to have IC_{50} values of between 73 and 21 ng/ml depending on the cell line, and it has been shown to prolong the life of tumor bearing mice. The mode of action of FR182877 has been shown to be that of an antimitotic agent as HT-29 cells treated with FR182877 were determined to be in the G2/M phase and microtubule assembly was detected.[2,3] These findings are consistent with other known antimitotic agents such as taxol and the epothilones. Originally the structure was assigned as the enantiomer of **1**.[4] This error was realized by the efforts of Sorensen when he achieved the first total synthesis of the unnatural enantiomer.[5] Total synthesis of the natural enantiomer, by the group of Evans, followed closely behind.[6] Both of these elegant total syntheses utilized a similar approach, which involved the synthesis of a macrocyclic precursor followed by spontaneous tandem transannular Diels–Alder/hetero Diels–Alder reactions to install five of the six rings. The final E-ring was installed by lactonization.

Several other groups have also targeted FR182877 for synthesis, with Prunet,[7] Nakada[8] and Roush[9] reporting syntheses of the A-, AB- and ABC-rings, respectively. Prunet adopted a ring closing metathesis approach to the A-ring. Nakada utilized an intramolecular Diels–Alder reaction to furnish an AB-ring system, while Roush employed a Morita–Baylis–Hilman reaction to construct the ABC-rings of FR182877. The DEF-rings of FR182877 have also been the subject of synthetic study, with Armstrong reporting a procedure for the synthesis of a number of DE-ring analogues.[10]

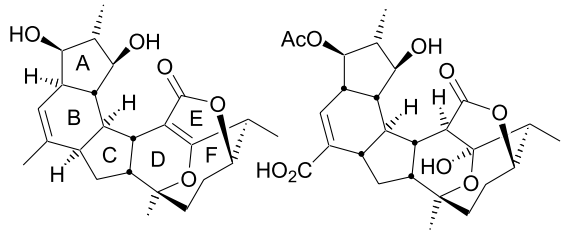
Another new natural product, hexacyclinic acid **2**, which bears remarkable similarity to FR182877, was isolated contemporaneously from the culture broth of *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013) following an OSMAC (one strain/many compounds) cultivation program.[11] The structure of hexacyclinic acid was determined by NMR studies and X-ray crystallography. Hexacyclinic acid shows weak cytotoxic activity when tested against HM02, HEPG2 and MCF7 cell lines with GI_{50} values up to 14.0 $\mu mol\,L^{-1}$. The structural similarity between FR182877 and hexacyclinic acid suggests that these two molecules may have a similar biogenetic origin. Comparison of both structures show that they differ only in the oxidation state of C13, the stereochemistry of the AB- and BC-ring junctions, acylation of the C9 hydroxyl and the level of hydration of the DE-ring junction. This similarity was noted by Evans, who proposed that the different stereochemistry around the B-ring could result from

☆ Taken in part from the Ph.D. Thesis of Matthew Grist, University of Nottingham, 2004.

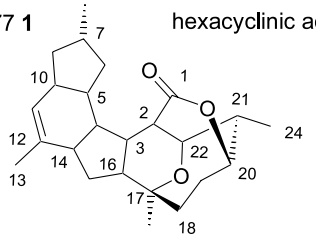
Keywords: Transannular; Iodocyclisation; Natural products; Medium sized rings.
* Corresponding author. Tel.: +44 115 9513566; fax: +44 115 9513564; e-mail: paul.clarke@nottingham.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.095

differing modes of intramolecular Diels–Alder cyclization. However, extensive studies by Evans yielded only the diasteroisomer which led to FR182877.[6] We too were intrigued by the prospect of developing a common strategy for the synthesis of both FR182877 and hexacyclinic acid, however, we decided to focus our initial endeavors on the challenging DEF-ring systems of these natural products.[12,13]



FR182877 **1** hexacyclinic acid **2**

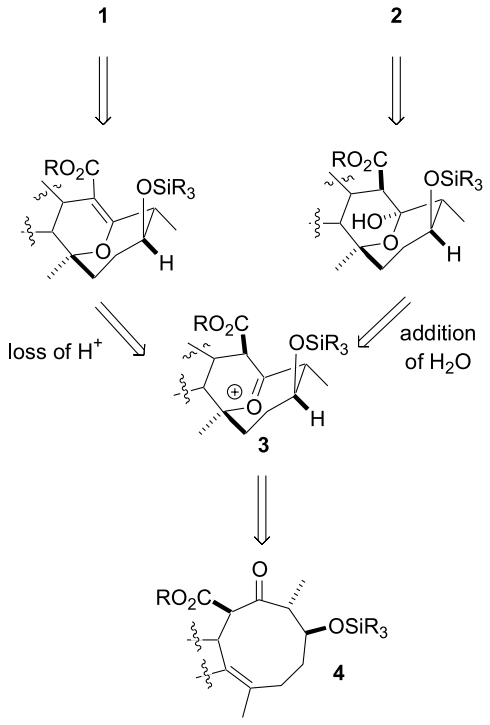


2. Results and discussion

Our alternative strategy for the synthesis of the DEF-rings does not involve their formation through an intramolecular hetero Diels–Alder reaction. Instead we proposed an approach in which the DEF-rings are constructed from a common carbocyclic precursor by means of a transannular cationic cyclization event. As such cationic cyclisations are known in the biosynthesis of other natural products, this approach provides an alternative biosynthetic hypothesis for the construction of the DEF-ring cores of these natural products.

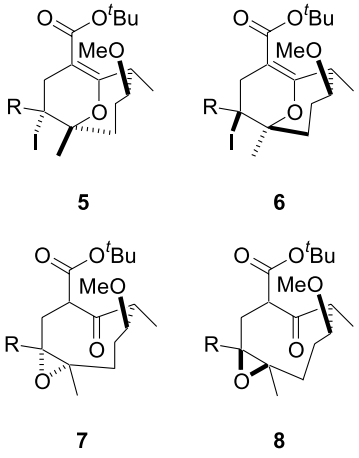
Retrosynthetic analysis of the DEF-rings of both FR182877 and hexacyclinic acid is outlined in Scheme 1. We reasoned that both the FR182877 and the hexacyclinic acid DEF-ring systems could be accessed from the same oxocarbenium ion **3**. In the synthetic direction the FR182877 DEF-rings would arise from the loss of a proton from **3**, while the hexacyclinic acid DEF-ring system would result from the addition of water to **3**. In turn, **3** would be formed from the transannular intramolecular cationic cyclization of the ketone carbonyl of a β-ketoester on to an appropriately positioned double bond. This disconnection reveals 9-membered carbocycle **4** as the immediate precursor to **3**.

There are a number of key stereochemical concerns arising from this strategy. The primary one being whether the transannular cationic cyclization event would occur on the desired α-face or undesired β-face of the carbon–carbon double bond. In order to generate confidence that the correct mode of cyclization would ensue molecular modelling studies were conducted. We initially modelled the two possible diastereomers resulting from iodocyclization on to both an α- and β-iodonium ion, **5** and **6**, respectively.[14]



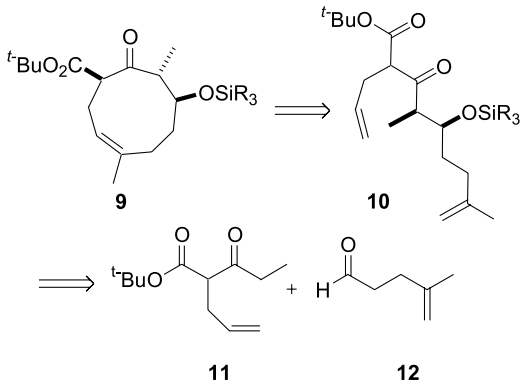
Scheme 1.

Molecular modelling studies on these ring systems indicated that the desired diastereomer **6** was some 4.5 kcal mol^{-1} lower in energy than **5**. Since the intermediate iodonium ions were not parameterized for in our version of Macromodel the corresponding epoxides **7** and **8** were modelled. The results of this study suggested that the energy difference between the two epoxides were minimal, at only 0.35 kcal mol^{-1}. If the difference in energy between the cyclized products is reflected in the energies of their respective transition states, and the difference in the epoxides is carried through to the corresponding iodonium ions then, given the reversibility of iodonium ion formation we anticipated that conditions could be found to favor formation of the desired thermodynamic product **6**.



Encouraged by the results of the molecular modelling studies, we embarked upon the synthesis of a model 9-membered carbocycle to test the synthetic utility of our

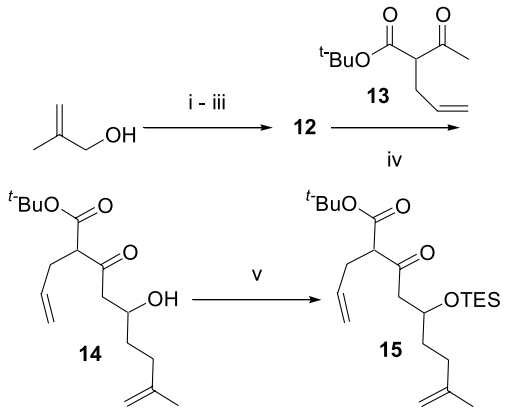
transannular cationic cyclization approach to the DEF-rings of FR182877 and hexacyclinic acid. Our initial retrosynthetic plan is given in Scheme 2. Scission of the trisubstituted double bond in **9** reveals diene **10**, which can be constructed from the aldol reaction of β-ketoester **11** with aldehyde **12**. However, due to the general lack of diastereoselectivity in the aldol reactions of γ-substituted β-ketoesters,[15] and the desire to test our key transannular cationic cyclization strategy, we opted to synthesize a 9-membered ring without the α-methyl group.



Scheme 2.

2.1. Synthesis of the cationic cyclization precursor 17

Aldehyde **12** was synthesized in 3 steps in 91% yield from methallyl alcohol by Johnson orthoester Claisen rearrangement and lithium aluminium hydride reduction, followed by a Swern oxidation. *tert*-Butyl acetoacetate was allylated with NaH and allyl bromide with the reaction being quenched after 6 min to avoid formation of the *bis*-allylated product. Diene **14** was formed in 78% yield as an inseparable mixture of diastereomers by the slow addition of aldehyde **12** to a solution of the dianion of **13**. The free hydroxyl was protected as the TES ether by the action of TESCl and DMAP in pyridine to provide **15** in 90% yield (Scheme 3).



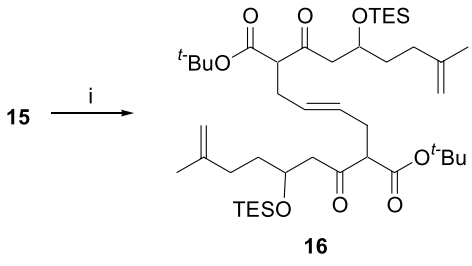
Scheme 3. Reagents and conditions: (i) propionic acid, triethyl orthoacetate, 120 °C, 98%; (ii) $LiAlH_4$, Et_2O, 0 °C, 99%; (iii) DMSO, oxalyl chloride, triethylamine, CH_2Cl_2, −78 °C, 94%; (iv) NaH, 0 °C, THF then *n*BuLi, 0 °C, THF; −78 °C, addition of **12**, 78%; (v) TESCl, DMAP, pyridine, 90%.

Given the recent advances in ring closing olefin metathesis (RCM) we investigated the possibility of closing the 9-membered carbocycle by this reaction. Fürstner has reported the use of Grubbs' second generation catalyst to achieve the formation of 5 and 6 membered rings containing either a tri- or tetra-substituted double bond.[16] Contemporaneously with our studies Clark reported the use of the RCM reaction for the formation of a 9-membered carbocycle in his synthesis of the cornexistin core.[17] In addition to these studies, Granja used Grubbs' second generation catalyst to form a tri-substituted double bond in an 8-membered carbocyle.[18]

When our metathesis precursor **15** was subjected to typical metathesis conditions of 1 mol% Grubbs' second generation catalyst, 0.32 M concentration in toluene at 80 °C it resulted in removal of the TES group (Table 1, entry 1). With 10 mol% catalyst and higher dilution no reaction was observed. Upon extending the reaction time to 5–10 days, dimerization at the least substituted double bond to give **16** was seen (Table 1, entry 2), (Scheme 4). Although this was not the desired result it did show that the metathesis reaction was occurring. In order to promote cyclization over dimerization the reaction concentration was reduced (Table 1, entries 3 and 4), however, this led to the formation of reduced quantities of dimer **16** over a longer time. Further dilution resulted in no reaction (Table 1, entries 5–8).

Table 1. Results of concentration studies on the metathesis reaction

Entry	Concn. (M)	Catalyst (mol%)	Result
1	0.32	1	Loss of TES
2	0.036	10	Dimer **16**
3	0.0036	10	Dimer **16**
4	0.0030	10	Trace dimer **16**
5	0.0024	10	No reaction
6	0.0016	10	No reaction
7	0.0008	10	No reaction
8	0.0004	10	No reaction

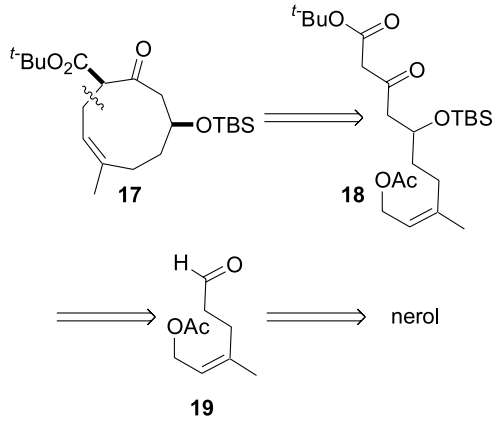


Scheme 4. Reagents and conditions: (i) Grubbs' second generation catalyst, toluene, 80 °C, 5–10 days.

Following the failure of the metathesis strategy to deliver the 9-membered carbocycle a recent hypothesis came to light.[19] This hypothesis suggested that substrates with an oxygen atom five or six atoms away from the alkylidene carbene are more susceptible to the problem of chelation rendering the catalyst unreactive. Since chelation is possible in our substrate regardless of which double bond reacts first,

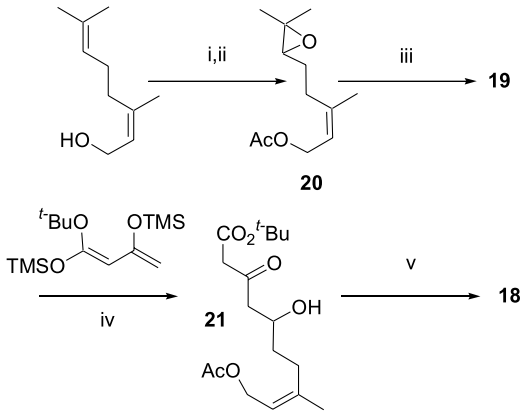
the need for vastly extended reaction times may not be surprising.

Due to the failure of the RCM approach to yield any of the desired 9-membered carbocycle an alternative approach to its synthesis was developed. Scission of the indicated bond in **17** reveals acyclic precursor **18**. In the synthetic direction it was envisaged that an intramolecular allylation reaction would close the ring and furnish **17**. Cyclization precursor **18** would arise from the aldol reaction of *tert*-butyl acetoacetate on aldehyde **19**, which is derived from nerol (Scheme 5).



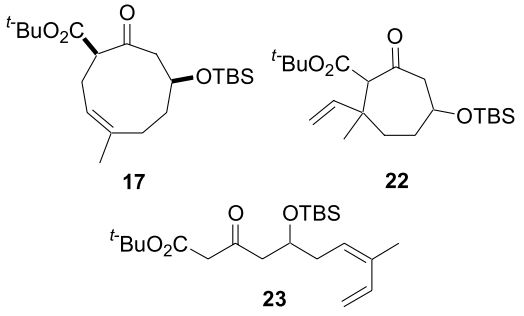
Scheme 5.

Aldehyde **19** was prepared from nerol by acylation with acetic anhydride in pyridine in 100% yield, followed by epoxidation of the terminal double bond with *m*CPBA in 85% yield, and periodic acid oxidative cleavage to generate the desired aldehyde **19** in 81% yield.[20] Mukaiyama aldol reaction of the *bis*-silyl enolether of *tert*-butyl acetoacetate and aldehyde **19** in the presence of $TiCl_4$ gave the desired aldol product **21** in 79% yield. The free hydroxyl group of **21** was further protected in 98% yield as the TBS ether with TBSOTf in pyridine at −30 °C to provide **18** (Scheme 6).



Scheme 6. Reagents and conditions: (i) DMAP, acetic anhydride, pyridine, 18 h, 100%; (ii) *m*CPBA, 2 h, CH_2Cl_2, 0 °C, 85%; (iii) periodic acid, THF/water, 2 h, 0 °C, 81%; (iv) $TiCl_4$, CH_2Cl_2, −78 °C, 3 h, 79%; (v) TBSOTf, py, −35 °C, 8 h, 97%.

As the formation of 9-membered carbocyclic rings via S_N^2 displacement is notoriously troublesome, we decided to investigate the use of an intramolecular Pd(0) catalyzed allylic substitution reaction. Trost has shown that cyclisations wherein 9- and 7-membered ring formation compete, the reaction is finely balanced, with bulkier nucleophiles favoring attack at the terminus of the π-allyl system generating the 9-membered ring.[21] In cases where the nucleophile is a β-ketoester problems of competing *O*-alkylation arise.[22] Theoretically the product of *O*-alkylation may be converted to the desired carbocycle by a sigmatropic rearrangement. Initial trials of the Pd(0) catalyzed allylic substitution reaction using the conditions reported by Trost led to a complex mixture of products, from which 3 compounds were isolated in poor yields. These were later identified as 9-membered ring **17** (trace amounts), 7-membered ring **22** (18%) and diene **23** (72%). While **17** and **22** arise from attack of the nucleophile on the opposite ends of the π-allyl system, **23** arises from its elimination. Although elimination was not unexpected, the extent to which it occurred was. Indeed, only two examples of this process could be found in the literature and then elimination occurred because no nucleophile was present.[23] Performing the reaction without first pre-forming the anion did not result in diene formation, demonstrating that deprotonation of the π-allyl system by the pre-formed anion was responsible for the elimination. Syringe pump addition of the anion to a solution of the catalyst significantly reduced the amount of diene **23** formed. To favor the formation of **17** over **22**, a number of different diphosphine ligands and stoichiometries were screened. The most significant of these results are displayed in Table 2.



As can be seen in Table 2, entry 3 the formation of **17** peaked with the use of dppe as a ligand. This could be attributed to the diphosphine ligand affecting the rate of formation of the π-allyl complex. Slowing the formation of

Table 2. Optimization of the Pd(0) catalyzed π-allyl substitution reaction

Entry[a]	Ligand	Yield (%)[b]	Ratio **17**:**22**:**23**[c]
1	Ph_3P	91	trace:1:4
2	dppm	97	trace:1:8
3	dppe	93[d]	2:trace:1
4	dppp	94	1:1:2
5	dppf	90	3:2:8

[a] Reagents and conditions: (i) **18**, NaH, $Pd(PPh_3)_4$ (5 mol%), ligand (10 mol%), THF, reflux.
[b] Combined yield. All compounds co-ran and exhaustive flash column chromatography provided only small amounts of purified products.
[c] By ^1H NMR (400 MHz).
[d] Isolation of **17** (61%) and **23** (32%) proved possible by flash column chromatography on $AgNO_3$ impregrated silica gel.[24,25]

the complex due either to the rates of diphosphine chelation (entries 2 and 4), or to sterics (entry 5) would result in an increase in pre-formed anion concentration, and hence subsequent increase in diene production. Despite optimization of the reaction, the three major products proved difficult to separate; with exhaustive chromatography furnishing only milligram quantities of each product. However, silver nitrate absorbed onto silica gel could be used to aid chromatographic separation.[24] Trials of this method successfully separated the 9-membered ring **17** from the mixture but the 7-membered ring **22** and diene **23** remained mixed. Small quantities of **23** were eventually purified by extensive chromatography.[26] Optimization of the Pd(0) catalyzed allylic substitution reaction resulted in the desired 9-membered ring product **17** being isolated in 61% yield as a single diastereomer. To our knowledge this is the first report of this type of Pd(0) catalyzed allylic substitution reaction where the β-ketoester nucleophile is internal to the ring being formed. ^{1}H NMR and gradient NOE experiments determined that the relative stereochemistry of the substituents on the 9-membered ring were *cis*. Interestingly, this also highlighted that the 9-membered ring existed in a chair–boat conformation (Fig. 1).[27]

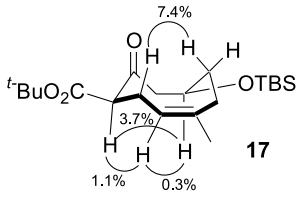


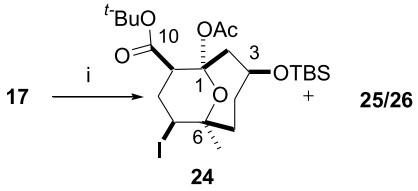
Figure 1. Key NOEs indicating the chair–boat conformation of **17**.

2.2. Synthesis of a model DEF-ring core of hexacyclinic acid

With quantities of **17** now available we could study the crucial transannular cationic cyclization reaction. We were initially attracted to the work of Gopalan[28] who showed that internal nucleophiles, such as carbonyl groups of esters, can trap the cation generated by the addition of $Hg(OTf)_2$ to a proximal double bond in an acyclic polyene. Gopalan also showed that when the nucleophile was a β-ketoester, cyclization occurred through the oxygen of the ketone carbonyl rather than through the ester carbonyl. In this case loss of a proton generated a double bond to give a cyclic enol ether. This is applicable to the formation of the DEF-rings of FR182877, but examples of the addition of an external nucleophile required to generate the hexacyclinic acid system were not reported.

Attempts at cyclizing **17** with $Hg(OTf)_2$ using the procedures of either Gopalan[28] or Nishizawa[29] resulted in a complex mixture of products. It was thought that the TfOH formed was causing decomposition of the desired product, however, when the cyclizations were performed in the presence of an amine base no reaction resulted. Disappointed at this lack of success, we turned our attention to halocyclization reactions. The use of iodine reagents, such as I_2,[30] NIS,[31] NIP[32] and AcOI,[33] for iodolactonization and iodoetherification have been widely reported in the literature, but these have usually involved cyclization of a carboxylic acid or of a free hydroxyl group onto an iodonium ion. At the time of these studies we could find no examples of a transannular iodocyclisation of a ketone carbonyl group. The most relevant conditions were reported for the use of AcOI by Cambie and co-workers, who perform a transannular iodoetherification across an 8-membered ring.[33]

Trial reactions with AcOI in AcOH gave our first promising cyclization results. When **17** was treated with AcOI in glacial acetic acid a new product was formed, which was assigned as the DF-ring system **24**, similar to that in hexacyclinic acid. The formation of this product implies the intermediacy of an oxocarbenium ion, which is quenched by the addition of the AcOH solvent (Scheme 7).[27]



Scheme 7. Reagents and conditions: (i) iodine, silver acetate, AcOH, rt, 1 h, **24** (61%), **25/26** (30%).

Two additional side products which proved inseparable from each other were also isolated from the reaction. The structures of these were determined by X-ray crystallography as a 1:1 co-crystal of iodolactones **25** and **26** (Fig. 2), resulting from a 5-*exo* and 6-*endo* cyclization, respectively of the ester carbonyl group.

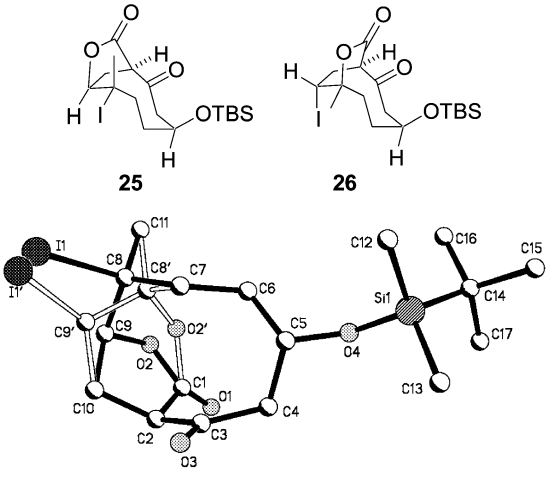
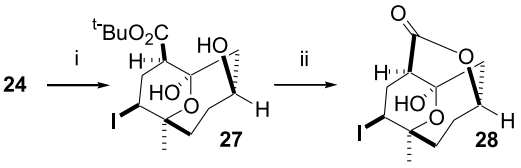
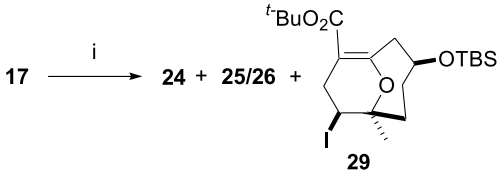


Figure 2. Structure of the 1:1 co-crystal of the 5-*exo* **25** and 6-*endo* **26** products arising from cyclization through the ester carbonyl. The open bonds and primed atom labels represent where the 6-*endo* product **26** deviates from the structure of the 5-*exo* product **25**.

With the DF ring system **24** available, removal of the protecting groups was necessary (Scheme 8). Treatment of **24** with two equivalents of HF in MeCN gave the hemi-ketal **27** as a white crystalline solid in 97% yield. A single crystal X-ray structure of **27** (Fig. 3) showed the desired relative stereochemistry and confirmed our earlier NMR assignment of **24**. No unusual features were observed in the crystal.



Scheme 8. Reagents and conditions: (i) HF, MeCN, rt, 18 h, 97%; (iv) TFA, CH_2Cl_2, rt, 4 days 100%.



Scheme 9. Reagents and conditions: (i) iodine, silver acetate, AcOH, rt, 1 h, **24** (61%), **25/26** (30%) and **29** (5%).

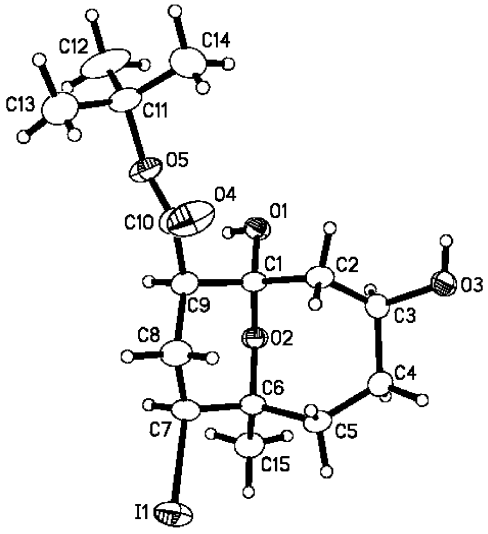


Figure 3. Crystal structure of the hexacyclinic acid DF ring intermediate **27**.

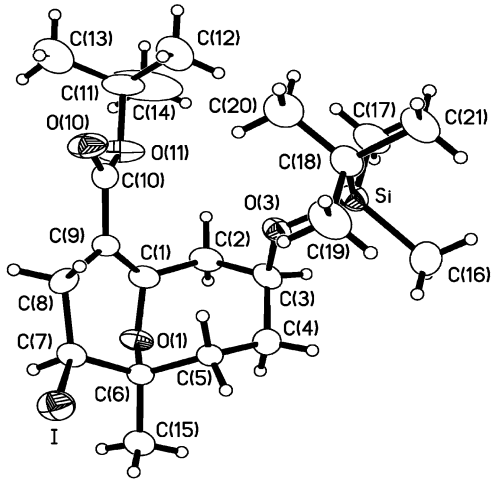


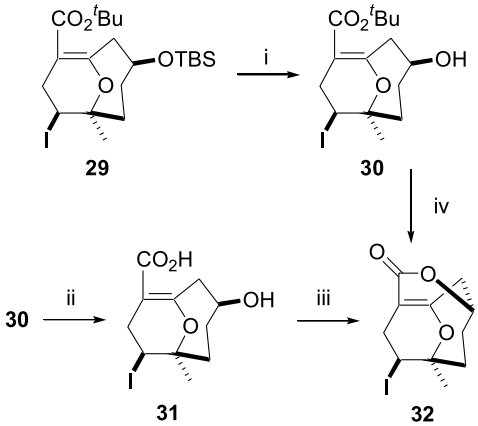
Figure 4. Crystal structure of the FR182877 DF ring intermediate **29**.

Removal of the *tert*-butyl ester proved troublesome. Exposure of hemi-ketal **27** to TFA in CH_2Cl_2 could be seen, by TLC, to remove the *tert*-butyl group but isolation of the resulting acid proved to be difficult. Isolation of a product was finally achieved by exposure of the hemi-ketal **27** to TFA in CH_2Cl_2 for an extended time period. This resulted in removal of the ester and subsequent lactonization in one reaction. Isolation of the model DEF system of hexacyclinic acid **28** was achieved quantitatively from hemi-ketal **27** (Scheme 8). The ^{1}H NMR spectrum of the model DEF-ring system **28**, as well as showing that the protecting groups had been removed, gave key evidence for the lactonization, in the form of the carbinol resonance H-3, which had shifted to a higher frequency (δ 5.52) as is expected by lactonisation.[27]

2.3. Synthesis of a model DEF-ring core of FR182877

When performed on quantities greater than 0.5 g, the reaction of **17** with AcOI in AcOH delivered around 5% of a previously undetected white crystalline solid. The ^{1}H NMR spectrum of this solid showed retention of the TBS group, the *tert*-butyl ester and the methyl group although, it did not show incorporation of an acetate group. Ten other distinct resonances with relative integrals of one were also present. The spectrum was assigned as the FR182877 model DF-ring system **29**[27] (Scheme 9). This assignment was confirmed by a single crystal X-ray analysis of **29** (Fig. 4). The crystal structure showed no unusual features or strain in the bridgehead double bond. Obtaining both **27** and **29** from the same reaction proved that our concept of generating both ring systems from a common oxocarbenium ion intermediate was a valid one.

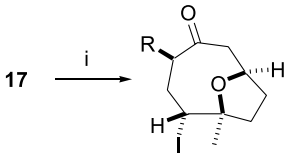
In a similar manner to the hexacyclinic acid route, removal of the TBS group from **29** was achieved using HF in MeCN to give the free alcohol **30**. Treatment of the alcohol **30** with TFA in CH_2Cl_2 resulted in removal of the *tert*-butyl ester and isolation of the acid **31** in 96% yield. Closure of the lactone was possible by either resubmitting **31** to TFA or by using Mukaiyama's reagent as the group of Evans had done.[6] It was later found that the DEF ring system **32** was formed in the initial TFA promoted removal of the *tert*-butyl



Scheme 10. Reagents and conditions: (i) HF, MeCN, rt, 6 h, 100%; (ii) TFA, CH_2Cl_2, rt, 8 h, 96%; (iii) TFA, CH_2Cl_2, rt, 4 h, 96%; or Mukaiyama's reagent, Et_3N, MeCN, CH_2Cl_2, 75%; (iv) TFA, CH_2Cl_2, rt, 8 h, 100%.

ester, but chromatography resulted in opening the lactone ring. By careful purification of the reagents and solvents used in the reaction,[34] the DEF-ring system **32** could be isolated from the TFA mediated reaction in quantitative yield (Scheme 10). Interestingly, this DEF-ring unit is stable in air unlike the natural product. Solutions of **32** of varying concentrations have been stored, open to the air, for periods of up to four weeks without decomposition or epoxidation.

Although we had proved our initial concept that both DEF-ring systems are available via the same method, the yield of the FR182877 system was not particularly pleasing. In an attempt to induce loss of a proton we carried out the reaction in a non-nucleophilic solvent. When $CHCl_3$ was used as a solvent iodolactones **25** and **26** were formed exclusively. Treatment of **17** with AcOI in Et_2O proceeded smoothly to give a single product. Unfortunately, this product was identified as the [5.2.1]bicycloiodoketone **33** (Scheme 11). The related compound **34** was isolated when THF, MeCN or MeOH were used as solvents. The use of benzene, hexane, CCl_4, EtOAc, DMF, DMSO, pyridine, TFA or 1,1,1,3,3,3-hexafluoro-*iso*-propanol all resulted in re-isolation of **17**. In the case where **33** was formed it was believed that the desired iodonium ion was being generated but since the reaction was not anhydrous an equivalent of HI was formed. We believed that this HI promoted the removal of the TBS group with subsequent cyclization through the free alcohol. The TBSI generated cleaved the *tert*-butyl ester with subsequent decarboxylation. We, therefore, performed the reaction under anhydrous conditions and in the presence of a variety of bases with the intention of sequestering any HI formed and hence leaving the TBS group intact. The presence of base only served to inhibit all cyclization reactions.



33 R=H, **34** R=$CO_2{}^t$Bu

Scheme 11. Reagents and conditions: (i) AcOI, Et_2O, 100%.

These solvent studies showed that cyclization was possible through each of the oxygen containing functionalities in 9-membered carbocycle **17**. We were understandably interested in this range of reactivity and in how each of these products was formed. A number of possible explanations are feasible; (1) keto–enol tautomers of the 9-membered carbocycle **17** could react in different manners; (2) epimerization at C2 of **17** would result in diastereomers, each of which could react differently; or (3) different solvents may lead to population of different conformations of **17**, which could result in different reactivity. These possibilities were investigated by the use of ^{1}H NMR spectroscopy, in both $CDCl_3$ and d_3-acetic acid which showed; (1) no detectable enol tautomer; (2) no detectable epimerization of **17**; and (3) no conformational change of **17** on changing solvent from $CDCl_3$ to d_3-acetic acid. The NOE data in both $CDCl_3$ and d_3-acetic acid showed the same ground state chair–boat conformation (Fig. 1) discussed earlier.

It is obvious that a change in conformation of **17** was required to satisfy any of the observed modes of reactivity. In the ground state chair–boat conformation, none of the oxygen containing functionalities are in sufficiently close proximity to the double bond to react on formation of an iodonium ion. As such none of the observed reaction pathways can occur via the observed chair–boat conformation. The observed reactivity can be rationalized as arising from conformational differences of the two possible iodonium ions (either α- or β-). As such the formation of each of the observed products can be rationalized through an appropriate conformation of either the α- or β-iodonium ion. The formation of the iodolactones **25** and **26** arise from an α-iodonium ion reacting through a chair–chair conformation **35** (Fig. 5). This conformation of the α-iodonium ion results in the ester carbonyl group being in a suitable position to attack the iodonium ion resulting in the products **25** and **26** shown.

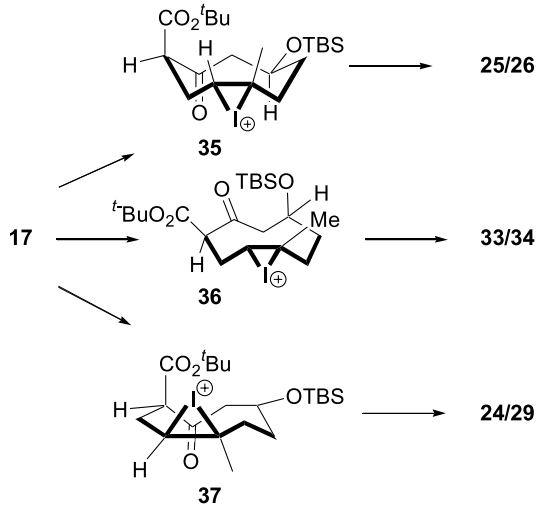


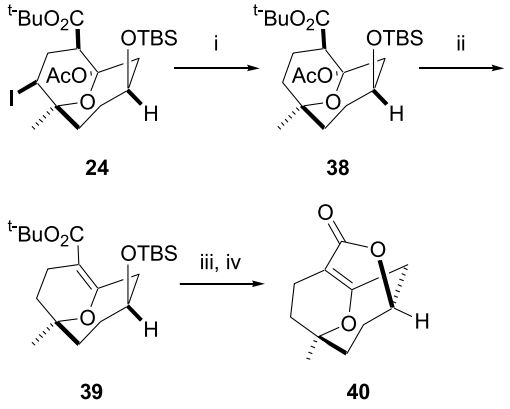
Figure 5. Proposed reacting conformations of **17**.

The bicyclic ethers **33** and **34** also arise from the reaction of an α-iodonium ion, this time through a boat–boat reacting conformation **36** (Fig. 5), placing the OTBS oxygen in a suitable position for attack on the iodonium ion. The hexacyclinic acid and FR182877 DF-ring systems arise from a β-iodonium ion reacting via a boat–boat conformation **37** (Fig. 5) with cyclization occurring through the ketone carbonyl. Conformations **35**, **36** and **37** of the 9-membered ring **17** are all presumably within about 2 kcal mol^{-1} of the ground state chair–boat conformation.

Since the products **25/26**, **33/34** and **24/29** arise from the cyclization of the different functionalities, onto the two diastereotopic iodonium ions (either α- or β-), through different conformations, we conclude that the solvent in some way stabilizes one of these iodonium ion conformations to a greater extent than the others. This increased stability of one iodonium ion conformation could lead to an increase in the population of this conformation and that this

population distribution governs which of the products is the major one formed.

As we were unable to influence the course of the iodocyclisation reaction to favor the formation of **29**, we sought to convert **24** into a FR182877 DEF-ring system. This was achieved by the reductive removal of the iodine, either via Bu_3SnH and catalytic AIBN or via catalytic transfer hydrogenation in a disappointing, although unoptimized 23% yield. The dehalogenated DF-ring **38** was treated with DBU[35] which provided 93% yield of **39**. The DF-ring **39** now contained the vinylogous carbonate unit required for the construction of the DEF-rings of FR182877. The synthesis of a FR182877 DEF-ring **40** was achieved by deprotection and lactonization by sequential treatment of **39** with aq HF in MeCN followed by TFA in CH_2Cl_2 in 100% yield over the two steps (Scheme 12).



Scheme 12. Reagents and conditions: (i) $Pd(PPh_3)_4$, Bu_3N, HCO_2H, DMF, 23%; (ii) DBU, MeCN, reflux, 93%; (iii) 40% aq HF, MeCN, 100%; (iv) TFA, CH_2Cl_2, 100%.

3. Conclusions

We have developed a novel intramolecular Pd(0) allylic substitution, transannular iodocyclization approach to the DEF-ring cores of both hexacyclinic acid and FR182877, utilizing the formation of a common oxocarbenium ion intermediate. We believe that this transannular cationic cyclization provides support for a possible alternative biosynthetic hypothesis to the one previously advanced.[5,6] Interestingly, the nature of the transannular cyclization is highly solvent dependant, and conditions were discovered that allowed for cyclization through any of the oxygen functionalities in the 9-membered ring precursor. We believe that this is due to the solvent subtly affecting the population of different conformations of similar energy of the 9-membered ring. Work is ongoing in an attempt to apply this transannular iodocyclisation reaction to the total synthesis of both hexacyclinic acid and FR182877.

4. Experimental

4.1. General

All melting points are uncorrected. Reaction progress was monitored using glass-backed TLC plates pre-coated with silica UV_{254} and visualized by using either UV radiation (254 nm), ceric ammonium molybdate or anisaldehyde stains. Column chromatography was performed using silica gel 60 (220–240 mesh), with the solvent systems indicated in the relevant experimental procedures. Silver nitrate impregnated silica gel and TLC plates were prepared according to standard procedures.[24] Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, dimethyl formamide was stirred with calcium hydride and distilled prior to use. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other reagents were used as received from commercial suppliers unless stated otherwise in the appropriate text. For the sake of journal space experimental and characterization data for key compounds only is presented here. Full details of other procedures and compounds can be found in the accompanying supporting information.

4.2. Pd(0) Catalyzed cyclization reaction of 18. Synthesis of 17, 22 and 23

A solution of *tert*-butyl-10-acetoxy-8-methyl-5-(*tert*-butyl, dimethylsilanyloxy)-3-oxo-dec-8-enoate **18** (240 mg, 0.550 mmol) in THF (6 ml) was added to a flask containing sodium hydride (22 mg, 0.56 mmol) and the solution was stirred for 15 min. The yellow solution was drawn into a syringe and the syringe was equipped with a needle fitted with a small glass wool plug. The solution was added to a solution of *tetrakis*triphenylphosphine palladium (32 mg, 0.027 mmol) and dppe (10 mol%) in THF (5 ml) under reflux, at a rate of 4.76 ml/h via syringe pump. The resulting mixture was maintained under reflux for a further 1 h before being allowed to cool to room temperature. The mixture was filtered through a plug of silica with ether (75 ml) and concentrated in vacuo. The resulting oil was subjected to chromatography on silver nitrate impregnated silica (9:1 hexane–ether elution) to give the 9-membered carbocycle **17** (61%), the 7-membered carbocycle **22** and diene **23**.

4.2.1. 1-Oxo-8-(*tert*-butyl dimethylsilanyloxy)-5-methyl-2-(carbo-*tert*-butoxy)-cyclonon-4-ene (17). ν_{max} (solution; $CHCl_3$) 2956 (CH stretch), 2931 (CH stretch), 1738 (C=O stretch), 1705 (C=O stretch), 1472 (CH bend), 1277 (C–O stretch), 1257 (C–O stretch), 1070 (Si–O stretch) and 837 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.33 (1H, t, $J=8.0$ Hz, H4), 4.09 (1H, tt, $J=9.1$, 3.1 Hz, H8), 3.39 (1H, dd, $J=10.8$, 3.1 Hz, H2), 2.92 (1H, dd, $J=14.3$, 9.1 Hz, H9), 2.73 (1H, m, H3), 2.59 (1H, dd, $J=14.3$, 3.0 Hz, H9), 2.46 (1H, ddd, $J=14.3$, 8.0, 3.1 Hz, H3), 2.28 (1H, ddd, $J=14.0$, 12.0, 4.5 Hz, H7), 1.89 (1H, app tt, $J=14.0$, 4.5 Hz, H6), 1.79 (1H, dt, $J=14.0$, 4.5 Hz, H7), 1.70 (1H, m, H6), 1.69 (3H, s, 5Me), 1.57 (9H, s, ^{t}Bu), 0.89 (9H, s, TBS), 0.11 (3H, s, TBS) and 0.9 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 207.8 (s, C10), 168.5 (s, C1), 139.2 (s, C5), 121.4 (d, C4), 82.0 (s, ^{t}Bu), 68.2 (d, C8) 59.9 (d, C2), 50.3 (t, C9), 35.6 (t, C7), 28.1 (q, ^{t}Bu), 27.2 (t, C3), 26.9 (t, C6), 25.9 (q, TBS), 22.8 (q, 4Me), 18.1 (s, TBS), −4.7 (q, TBS) and −4.7 (q, TBS) ppm. MS (CI NH_3) *m/z* 400 $(M+NH_4)^+$, 383 $(M+H)^+$ and 344 $(M+NH_4, -{}^tBu)^+$; found M+H 383.2622, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.2. 1-Oxo-6-(*tert*-butyl dimethylsilanyloxy)-3-methyl-3-(eth-2-enyl)-2-(carbo-*tert*-butoxy)-cycloheptane (22). ν_{max} (solution; $CHCl_3$) 2955 (CH stretch), 2930 (CH stretch), 1738 (C=O stretch), 1694 (C=O stretch), 1258 (C–O stretch), 1145 (C–O stretch), 1075 (Si–O stretch) and 835.3 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.87 (1H, dd, $J=17.5$, 10.8 Hz, 3 vinyl), 5.04 (1H, dd, $J=17.5$, 0.6 Hz, 3 vinyl), 5.02 (1H, dd, $J=10.8$, 0.6 Hz, 3 vinyl), 4.16 (1H, m, H6), 3.95 (1H, s, H2), 2.75 (1H, ddd, $J=17.6$, 5.9, 1.3 Hz, H7), 2.63 (1H, dd, $J=17.6$, 3.2 Hz, H7), 2.11 (1H, ddd, $J=11.6$, 3.2, 3.2 Hz, H5), 1.90 (1H, m, H5), 1.77 (1H, m, H4), 1.55 (1H, m, H4), 1.43 (9H, s, ^{t}Bu), 1.24 (3H, s, 3Me), 0.92 (9H, s, TBS) and 0.08 (6H, t, $J=1.6$ Hz, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 206.3, 168.2, 146.2, 112.0, 80.9, 68.0, 66.0, 52.3, 40.1, 36.6, 32.2, 27.9, 25.7, 20.4, 18.0, 1.0, −4.9 and −5.1 ppm. MS (CI NH_3) *m/z* 383 $(M+H)^+$; found M+H 383.2627, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.3. *tert*-Butyl-8-methyl-5-(*tert*-butyl dimethylsilanyloxy)-3-oxo-dec-7,9-dienoate (23). ν_{max} (solution; $CHCl_3$) 2930 (CH stretch), 2884 (CH stretch), 1713 (C=O stretch), 1607 (C=O stretch), 1411 (CH bend), 1256 (C–O stretch), 1224 (C–O stretch), 1060 (Si–O stretch) and 830 (=CH oop bend) cm^{-1}. δ_H (400 MHz; DMSO) 6.34 (1H, dd, $J=10.7$, 17.4 Hz, H9), 5.51 (1H, t, $J=7.0$ Hz, H7), 5.10 (1H, d, $J=$ 17.4 Hz, H10 *cis*), 4.95 (1H, d, $J=10.7$ Hz, H10 *trans*), 4.17 (1H, app pentet, $J=5.6$ Hz, H5), 3.44 (2H, s, H2), 2.66 (1H, dd, $J=16.2$, 6.5 Hz, H4), 2.58 (1H, dd, $J=16.2$, 4.0 Hz, H4), 2.28 (2H, dd, $J=7.0$, 6.5 Hz, H6), 1.68 (3H, s, 8Me), 1.40 (9H, s, ^{t}Bu), 0.82 (9H, d, $J=1.6$ Hz, TBS), 0.03 (3H, d, $J=1.3$ Hz, TBS) and 0.00 (3H, d, $J=1.3$ Hz, TBS) ppm. δ_C (100 MHz; DMSO) 202.1 (s, C3), 166.1 (s, C1), 141.2 (s, C8), 135.4 (d, C7), 128.4 (d, C9), 111.4 (t, C10), 80.7 (s, ^{t}Bu), 68.1 (d, C5), 51.2 (t, C2), 49.4 (t, C4), 35.8 (t, C6), 27.7 (q, ^{t}Bu), 25.7 (q, TBS), 17.6 (s, TBS), 11.7 (q, 8Me), −4.8 (q, TBS) and −5.0 (q, TBS) ppm. MS (ES+) *m/z* 383 $(M+H)^+$, 327 $(M+H, -{}^tBu)^+$ and 309 $(M+H, -TBS)^+$; found M+H 383.2620, $C_{21}H_{39}O_4Si$ requires M+H 383.2618.

4.2.4. Iodocyclization of 17. Synthesis of 24 and 29. To a mixture of iodine (1.92 g, 7.6 mmol) and silver acetate (1.26 g, 7.6 mmol) was added acetic acid (54 ml). The mixture was stirred for 30 min before being transferred via syringe to a solution of **17** (1.00 g, 2.5 mmol) in acetic acid (21 ml). The mixture was stirred for 1 h before being diluted with water (500 ml) and CH_2Cl_2 (100 ml), and neutralized with solid $NaHCO_3$. The resulting solution was saturated with solid sodium chloride and extracted with CH_2Cl_2 (5× 200 ml). The organic phase was washed with saturated aqueous sodium thiosulfate solution (500 ml), saturated aqueous $NaHCO_3$ solution (3×200 ml), water (3×200 ml) and brine (250 ml) before being dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was subjected to column chromatography (98:2 petrol–ether) to give **24** (816 mg, 4.6 mmol, 61%) as a colorless oil, **29** (73 mg, 0.13 mmol, 5%) as a white crystalline solid.

4.2.5. 9-(Carbo-*tert*-butoxy)-7-iodo-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-1-acetoxy-oxabicyclo[4.3.1]-nonane (24). ν_{max} (solution; $CHCl_3$) 2990 (CH stretch), 2857 (CH stretch), 1747 (C=O stretch), 1721 (C=O stretch), 1294 (C–O stretch), 1257 (C–O stretch), 1075 (Si–O stretch) and 837 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.33 (1H, m, H3), 4.15 (1H, dd, $J=14.0$, 4.7 Hz, H7), 4.04 (1H, dd, $J=13.1$, 4.7 Hz, H9), 2.70 (1H, ddd, $J=$ 14.5, 14.0, 13.1 Hz, H8), 2.52–2.45 (2H, m, H2, H8), 2.25–2.18 (2H, m, H4, H5), 2.04 (3H, s, Ac), 1.76–1.68 (2H, m, H2, H4), 1.57 (1H, m, H5), 1.44 (9H, s, ^{t}Bu), 1.38 (3H, s, 6Me), 0.90 (9H, s, TBS), 0.07 (3H, s, TBS) and 0.07 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 168.8 (s, C10), 168.6 (s, Ac), 101.8 (s, C1), 81.3 (s, ^{t}Bu), 78.6 (s, C6), 65.1 (d, C3), 48.0 (d, C9), 39.9 (t, C2), 34.5 (t, C8), 33.0 (d, C7), 31.5 (t, C5), 29.6 (t, C4), 28.0 (q, ^{t}Bu), 28.0 (q, 6Me), 26.0 (q, TBS), 22.7 (q, Ac), 18.3 (s, TBS), −4.7 (q, TBS) and −4.8 (q, TBS) ppm. MS (CI NH_3) *m/z* 586 $(M+NH_4)^+$, 526 $(M-OAc, +NH_4)^+$, 509 $(M-OAc)^+$, 460 $(M-I, +NH_4)^+$, 327 $(M-TBS, -I)^+$, 284 $(M-TBS, -Ac)^+$; found $M+NH_4$ 586.2060, $C_{23}H_{45}IO_6SiN$ requires $M+NH_4$ 586.2061. Anal. Calcd for $C_{23}H_{41}IO_6Si$: C, 48.59, H, 7.27. Found C, 48.98, H, 7.17.

4.2.6. 9-(Carbo-*tert*-butoxy)-7-iodo-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-oxabicyclo[4.3.1]non-9-ene (29). Mp 89–90 °C. ν_{max} (solution; $CHCl_3$) 2955 (CH stretch), 2857 (CH stretch), 1698 (C=O stretch), 1432 (CH bend), 1258 (C–O stretch), 1146 (C–O stretch), 1059 (Si–O stretch) and 836 (=CH oop bend) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.41 (1H, t, $J=8.4$ Hz, H7), 4.21 (1H, m, H3), 3.58 (1H, dt, $J=12.5$, 1.8 Hz, H2), 3.17 (1H, dd, $J=18.8$, 7.6 Hz, H8), 3.04 (1H, ddd, $J=18.8$, 8.4, 1.8 Hz, H8), 2.30 (1H, dd, $J=14.6$, 11.0 Hz, H5), 2.23 (1H, ddd, $J=12.5$, 4.7, 1.8 Hz, H2), 1.78 (1H, ddt, $J=13.0$, 12.4, 1.5 Hz, H4), 1.72 (1H, m, H4), 1.49 (1H, m, H5), 1.46 (9H, s, ^{t}Bu), 1.44 (3H, s, 6Me), 0.88 (9H, s, TBS) and 0.57 (6H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 166.6 (s, C10), 161.9 (s, C9), 128.4 (s, C1), 116.9 (s, C6), 80.2 (s, ^{t}Bu), 78.1 (d, C3), 67.4 (t, C2), 42.4 (t, C8), 36.0 (d, C7), 33.6 (t, C4), 31.9 (t, C5), 28.5 (q, ^{t}Bu), 26.2 (q, TBS),26.1 (q, 6Me), 18.4 (s, TBS), −4.7 (q, TBS) and −5.0 (q, TBS) ppm. MS (ES+) *m/z* 509 $(M+H)^+$, 453 $(M+H, -{}^tBu)^+$, 395 $(M+H, -TBS)^+$; found M+H 509.1580, $C_{21}H_{38}IO_4Si$ requires M+H 509.1579. Anal. Calcd for $C_{21}H_{37}IO_4Si$: C, 49.60, H, 7.33. Found C, 49.25, H, 7.21.

4.2.7. 7-Hydroxy-5-methyl-4-iodo-10,6-dioxatricyclo-[5.3.2.0]dodecan-1-one (28). To a solution of **27** (37 mg, 0.087 mmol) in CH_2Cl_2 (2 ml) was added TFA (0.01 ml, 0.1 mmol) and the mixture stirred for 4 days. Further portions (0.01 ml, 0.1 mmol) of TFA were added after 1, 2 and 3 days. The mixture was concentrated in vacuo to give the product (29 mg, 0.087 mmol, 100%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 3573 (br, OH stretch), 3186 (CH stretch), 2932 (CH stretch), 1780 (C=O stretch), 1453 (CH bend), 1152 (C–O stretch) and 1118 (C–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.52 (1H, dddd, $J=12.3$, 6.5, 6.5, 3.3 Hz, H9), 4.06 (1H, m, H4), 2.74–2.62 (4H, m, H8, H8, H3, H3), 2.46 (1H, m, H11), 2.29 (1H, m, H12), 2.09 (1H, dd, $J=14.3$, 3.1 Hz, H2), 1.85 (1H, ddd, $J=15.2$, 4.2, 2.8 Hz, H12), 1.68 (1H, ddd, $J=15.2$, 7.1, 3.3 Hz, H11) 1.44 (1H, s, OH) and 1.42 (3H, s, 5Me) ppm. δ_C (100 MHz; $CDCl_3$) 172.7 (s, C1), 95.9 (s, C5), 78.1 (s, C7), 72.8 (d, C9), 54.7 (d, C4), 35.7 (t, C3 or C8), 34.5 (t, C3 or C8), 31.3 (d, C2), 29.2 (t, C12), 28.0 (q, 5Me) and 27.4 (t, C11) ppm. MS

(CI NH_3) *m/z* 356 $(M+NH_4)^+$; found $M+NH_4$ 356.0353, $C_{11}H_{19}IO_4N$ requires $M+NH_4$ 356.0353.

4.2.8. 5-Methyl-4-iodo-10,6-dioxatricyclo[5.3.2.0]dodec-2(7)-en-1-one (32). To a solution of **30** (15 mg, 0.04 mmol) in CH_2Cl_2 (5 ml) was added TFA (0.1 ml, 0.40 mmol) and the mixture stirred for 24 h. The mixture was concentrated in vacuo to give the product (14 mg, 0.04 mmol, 100%) as a white crystalline solid. Mp 190–193 °C (darkens significantly at 173 °C). ν_{max} (solution; $CHCl_3$) 2928 (CH stretch), 2856 (CH stretch), 1688 (C=O stretch), 1423 (CH bend), 1285 (C–O stretch) and 1260 (C–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 5.40 (1H, m, H9), 4.43 (1H, dd, $J=9.0$, 7.5 Hz, H4), 3.97 (1H, dt, $J=13.7$, 1.7 Hz, H8), 3.23 (1H, dd, $J=19.1$, 7.5 Hz, H3), 3.16 (1H, ddd, $J=19.1$, 9.0, 1.7 Hz, H3), 2.39 (1H, ddd, $J=13.7$, 4.3, 1.7 Hz, H8), 2.22 (1H, dd, $J=15.2$, 6.7 Hz, H12), 2.02–1.95 (2H, m, H11, H11), 1.68 (1H, ddd, $J=15.2$, 6.7, 1.6 Hz, H12) and 1.53 (3H, s, 5Me) ppm. δ_C (100 MHz; $CDCl_3$) 171.1 (s), 163.0 (s), 115.3 (s), 79.0 (s), 73.7 (d), 38.7 (t), 34.8 (t), 28.5 (d), 28.0 (t), 26.8 (t) and 25.5 (q) ppm. MS (EI+) *m/z* 321 $(M+H)^+$, 193 $(M-I)^+$, 165 $(M-I, -CO)^+$; found M 320.9985, $C_{11}H_{14}IO_3$ requires M 320.9988. Anal. Calcd for $C_{11}H_{13}IO_3$: C, 41.27, H, 4.09. Found C, 41.66, H, 3.89.

4.2.9. 9-(Carbo-*tert*-butoxy)-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-1-acetoxy-oxabicyclo[4.3.1]nonane (38). A mixture of **24** (10 mg, 0.02 mmol), $Pd(PPh_3)_4$ (4 mg, 0.003 mmol), Bu_3N (10 mg, 0.05 mmol) and formic acid (2 mg, 0.03 mmol) in DMF (2 ml) was stirred together for 18 h at 60 °C. The mixture was heated under reflux for 24 h before being cooled to room temperature. The mixture was filtered through celite with ether (75 ml) and the resulting solution concentrated in vacuo. The resulting oil was subjected to column chromatography (9:1 hexane–ether elution) to give the product (2 mg, 0.005 mmol, 23%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2981 (CH stretch), 2850 (CH stretch), 1744 (C=O stretch), 1729 (C=O stretch), 1266 (C–O stretch), 1221 (C–O stretch) and 1054 (Si–O stretch) cm^{-1}. δ_H (400 MHz; $CDCl_3$) 4.35 (1H, m, H3), 3.79 (1H, dd, $J=12.7$, 4.7 Hz, H9), 2.50 (1H, dd, $J=15.0$, 11.7 Hz, H2), 2.26 (1H, ddd, $J=14.1$, 8.3, 2.8 Hz, H4), 2.17 (1H, dd, $J=14.1$, 2.8 Hz, H4), 2.12 (1H, m, H8), 2.04 (3H, s, Ac), 1.87 (1H, m, H5), 1.74 (1H, dd, $J=15.0$, 3.2 Hz, H2), 1.62 (1H, m, H8), 1.51 (1H, m, H5), 1.45 (9H, s, ^{t}Bu), 1.31 (1H, m, H7), 1.19 (3H, s, 6Me), 1.08 (1H, d, $J=5.5$ Hz, H7), 0.90 (9H, s, TBS), 0.08 (3H, s, TBS) and 0.07 (3H, s, TBS) ppm. δ_C (100 MHz; $CDCl_3$) 171.0 (s), 168.9 (s), 102.5 (s), 80.7 (s), 76.1 (s), 65.9 (d), 45.1 (d), 40.5 (t), 34.1 (t), 31.5 (t), 31.4 (t), 29.2 (q), 28.1 (q), 26.0 (q), 22.9 (q), 21.3 (t), 18.4 (s), −4.7 (q) and −4.8 (q) ppm. MS (CI NH_3) *m/z* 460 $(M+NH_4)^+$, 386 $(M+H, -{}^tBu)^+$, 328 $(M+H, -TBS)^+$, 271 $(M+H, -{}^tBu, -TBS)^+$; found $M+NH_4$ 460.3097, $C_{23}H_{46}NO_6Si$ requires $M+NH_4$ 460.3094.

4.2.10. 9-(Carbo-*tert*-butoxy)-6-methyl-3-(*tert*-butyl dimethylsilanyloxy)-oxabicyclo[4.3.1]non-9(1)-ene (39). To a solution of **38** (6 mg, 0.013 mmol) in MeCN (4 ml) was added DBU (3 mg, 0.020 mmol) and the mixture heated under reflux for 8 days. An additional portion of DBU (3 mg, 0.020 mmol) was added after 1 day. The mixture was cooled to room temperature and diluted with ether (50 ml). The resulting solution was washed successively with saturated aqueous $NaHCO_3$ solution (2×20 ml), water (2×20 ml) and brine (20 ml). The aqueous washes were extracted with ether (3×20 ml) and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was subjected to column chromatography (9:1 hexane–ether elution) to give the product (5 mg, 0.013 mmol, 93%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2930 (CH stretch), 2856 (CH stretch), 1640 (C=O stretch), 1451 (CH bend), 1262 (C–O stretch), 1134 (C–O stretch) and 1089 (Si–O stretch) cm^{-1}. δ_H (500 MHz; $CDCl_3$) 4.16 (1H, m, H3), 3.40 (1H, dd, $J=14.0$, 4.6 Hz, H2), 2.63 (1H, ddd, $J=14.9$, 6.6, 2.1 Hz, H8), 2.60 (1H, ddd, $J=14.9$, 6.6, 2.1 Hz, H8), 1.99 (1H, m, H5 or H7), 1.92 (1H, m, H5 or H7), 1.86 (1H, ddd, $J=14.0$, 8.0, 2.1 Hz, H2), 1.75–1.64 (2H, m, H4, H4), 1.58–1.52 (2H, m, H5, H7), 1.50 (9H, s, ^{t}Bu), 1.34 (3H, s, 6Me), 0.88 (9H, s, TBS), 0.07 (3H, s, TBS) and 0.06 (3H, s, TBS) ppm. δ_C (125 MHz; $CDCl_3$) 166.5 (s), 165.3 (s), 121.3 (s), 80.4 (s), 80.1 (s), 70.2 (d), 41.3 (t), 37.4 (t), 32.3 (t), 28.5 (q), 28.2 (t), 26.0 (q), 21.3 (t), 18.2 (s), 14.2 (q), −4.5 (q) and −4.6 (q) ppm. MS (CI NH_3) *m/z* 383 $(M+H)^+$, 327 $(M+H, -{}^tBu)^+$ and 269 $(M+H, -TBS)^+$; found M+H 383.2609, $C_{21}H_{39}O_4Si$ requires M+H 383.2612.

4.2.11. 5-Methyl-10,6-dioxatricyclo[5.3.2.0]dodec-2(7)-en-1-one (40). To a solution of 9-(carbo-*tert*-butoxy)-7-iodo-6-methyl-3-hydroxy-oxabicyclo[4.3.1]non-9-ene (7 mg, 0.02 mmol) in CH_2Cl_2 (1 ml) was added TFA (0.02 ml, 0.30 mmol) and the mixture stirred for 7 h. The mixture was concentrated in vacuo to give the crude product as a white solid. The solid was subjected to column chromatography (4:1 hexane–ether elution) to give the product (2 mg, 0.01 mmol, 50%) as a colorless oil. ν_{max} (solution; $CHCl_3$) 2929 (CH stretch), 2855 (CH stretch), 1644 (C=O stretch), 1261 (C–O stretch) and 1224 (C–O stretch) cm^{-1}. δ_H (500 MHz; $CDCl_3$) 5.35 (1H, m, H9), 3.93 (1H, dd, $J=14.2$, 1.9 Hz, H8), 2.71 (1H, ddd, $J=15.9$, 8.4, 2.4 Hz, H3), 2.52 (1H, ddd, $J=14.2$, 5.0, 1.9 Hz, H8), 2.36 (1H, t, $J=7.7$ Hz, H12), 2.20 (1H, m, H3), 2.08 (1H, ddd, $J=13.0$, 9.2, 2.4 Hz, H4), 2.05–1.91 (2H, m, H11, H11), 1.73 (1H, dt, $J=13.0$, 8.4 Hz, H4), 1.65 (1H, m, H12) and 1.40 (3H, s, 5Me) ppm. δ_C (125 MHz; $CDCl_3$) 171.1, 165.3, 117.5, 79.2, 77.6, 74.8, 37.9, 36.2, 28.0, 27.2 and 19.7 ppm. MS (EI+) *m/z* 194 $(M)^+$, 176 $(M, -H_2O)^+$ and 131 $(M, -H_2O, -CO_2)^+$.

5. Supporting information available

Experimental procedures and spectroscopic data for compounds **12**, **14**, **15**, **16**, **18**, **19**, **20**, **21**, **27**, **30**, **31** and **33**.

Discussion of spectroscopic data for compounds **17**, **24**, **28** and **29**.

Copies of NMR spectra for compounds **15**, **18**, **17**, **21**, **22**, **23**, **24**, **28**, **29**, **33**, **28**, **39** and **40**.

Supplementary crystallographic data in CIF format for compounds **25/26**, **27** and **29**.

Acknowledgements

We thank the EPSRC and AstraZeneca for funding under the CASE award for New Academics scheme (M.G.), AstraZeneca for an unrestricted research support grant (P.A.C.), the EPSRC National Mass Spectrometry service, Swansea for accurate mass determination and the EPSRC for the award of a diffractometer. We also thank Dr. Adrienne Davis (Nottingham) for NMR technical advice and support and Dr. Hitesh Sanganee (AstraZeneca) for helpful discussions and William Martin for preliminary work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.095

References and notes

1. Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123.
2. Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204.
3. Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.
4. Yoshimura, S.; Sato, B.; Kiroshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2002**, *55*, C1.
5. Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.
6. Starr, J. T.; Evans, D. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787. Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531.
7. Funel, J.-A.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555.
8. Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263.
9. Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223.
10. Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585.
11. Hofs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258.
12. Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560.
13. Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron Lett.* **2004**, *45*, 927.
14. Using MM2 forcefield implemented in Macromodel 5.1.
15. Formation of the *syn* or *anti* aldol product is controlled by the geometry of the enolate. At present there are no reliable methods for the exclusive formation of the desired Z-enolate. Some advances have been made with the use of silyl enolethers. However, even here mixtures of E- and Z-silyl enolethers are obtained. SeeChan, T. H.; Brownbridge, P. *Tetrahedron* **1981**, *37*, 387. Therefore, while this strategy may be employed for the synthesis of the actual DEF-ring system, separation of the *syn* and *anti* aldol product diastereomers would be required.
16. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787. Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.
17. Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89.
18. Codesido, E. M.; Castedo, L.; Granja, J. R. *Org. Lett.* **2001**, 1483.
19. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3941. Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
20. For use of this route in the synthesis of a geraniol based aldehyde see: Tago, K.; Arai, M.; Kogen, H. *J. Chem. Soc., Perkin. Trans 1* **2000**, 2073.
21. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
22. Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550.
23. Domhöver, B.; Kläui, W. *J. Organomet. Chem.* **1996**, *522*, 207. Harayama, H.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 8475.
24. For a review of the use of $AgNO_3$ in chromatography see: Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.
25. For full details refer to the experimental section and the supporting information.
26. Silica gel chromatography was performed multiple times. Eluent was 5% ether in hexane increasing in polarity to 20% ether in hexane. Crude reaction mixture (200 mg) yielded pure diene **23** (10 mg).
27. A full discussion of the spectroscopic data can be found in the supporting information.
28. Gopalan, A.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* **1992**, *33*, 1679.
29. Nishizawa, M.; Taltenska, H.; Hanashi, Y. *J. Org. Chem.* **1986**, *51*, 806. Nishizawa, M.; Takao, H.; Iwamoto, H.; Imagawa, H. *Synlett* **1998**, 79.
30. For a recent example see: Knight, D. W.; Shaw, D. E.; Staples, E. R. *Eur. J. Org. Chem.* **2004**, 1973.
31. Hart, D. J.; Leroy, V.; Merriman, G. H.; Young, D. G. J. *J. Org. Chem.* **1992**, *57*, 5670.
32. Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.
33. Cambie, R. C.; Rutledge, P. S.; Stewart, G. M.; Woodgate, P. D.; Woodgate, S. D. *Aust. J. Chem.* **1984**, *37*, 1689.
34. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Butterworth-Heinemann: Oxford, 1988.
35. Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Chem. Commun.* **2002**, 2436.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 365–371

Cyclization in situ of enose-/ynose-nitrilimines: an expedient approach to the synthesis of chiral glycopyrazoles and pyrazolonucleosides

Ashim Roy, Sk. Sahabuddin, Basudeb Achari and Sukhendu B. Mandal*

Division of Medicinal Chemistry, Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Kolkata 700 032, India

Received 25 August 2004; revised 7 October 2004; accepted 29 October 2004

Abstract—Intramolecular [3+2] nitrilimine cycloaddition reactions on carbohydrate-derived substrates proceed in a regioselective fashion, affording structurally novel chiral glycopyrazoles (**4–6** and **10a–c**) in good yields. The products can be subsequently transformed to bicyclic pyrazoles (viz. **11** from **4**) or nucleoside analogues (viz. **12** from **4**).

1. Introduction

The pyrazole moiety is present in a large number of biologically active compounds,[1] which find wide application in the pharmaceutical[2] and agrochemical industries.[3] Numerous synthetic routes to pyrazole heterocycles have been developed based on (i) the condensation of hydrazines with β-dicarbonyl compounds[4] or with α, β-unsaturated carbonyl compounds followed by appropriate transformations,[5] and (ii) inter-, intra-, or sequential inter-intramolecular [3+2] cycloaddition reaction of diazo compounds[6] or nitrilimines[7] to alkynes or alkenes followed by oxidation. The 1,3-dipolar cycloaddition reactions of nitrilimines to obtain pyrazoles appears to have tremendous potential for the development of structurally novel synthetic entities, particularly when the nitrilimine is generated[8,9] through oxidation of aldehyde hydrazones with chloramine T or lead tetraacetate; judicious manipulation of the aldehyde and the olefin moieties allows a lot of flexibility in achieving the target structure. Although the synthesis of enantiomerically pure pyrazole derivatives employing chiral dipolarophiles and homochiral nitrilimines has been reported,[10] reports on the intramolecular version of this methodology on a carbohydrate backbone are rare.[11] For our research programme directed towards the synthesis of enantiomerically pure pyrazole derivatives, we opted to use this reaction on appropriately designed carbohydrate-derived precursors. We realized that introduction of a *C*-/*O*-allyl or propargyl group at C-3 of the glucose ring and generation of an aldehyde group at C-5 through simple functional group manipulations followed by conversion of the aldehyde to nitrilimine could lead to spontaneous [3+2] cycloaddition, furnishing optically active and structurally unique pyrazoles or pyrazolines (Fig. 1). Opening of the furanose ring in the addition products was expected to furnish fused pyrazoles/pyrazolines. Besides, introduction of various nucleobases directly onto the anomeric center of the furanose ring could lead to nucleoside analogues with

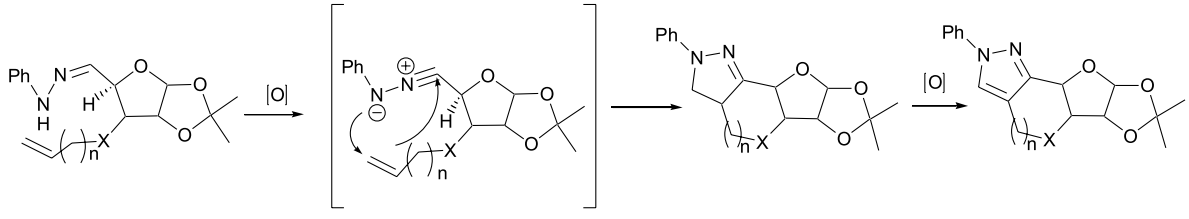
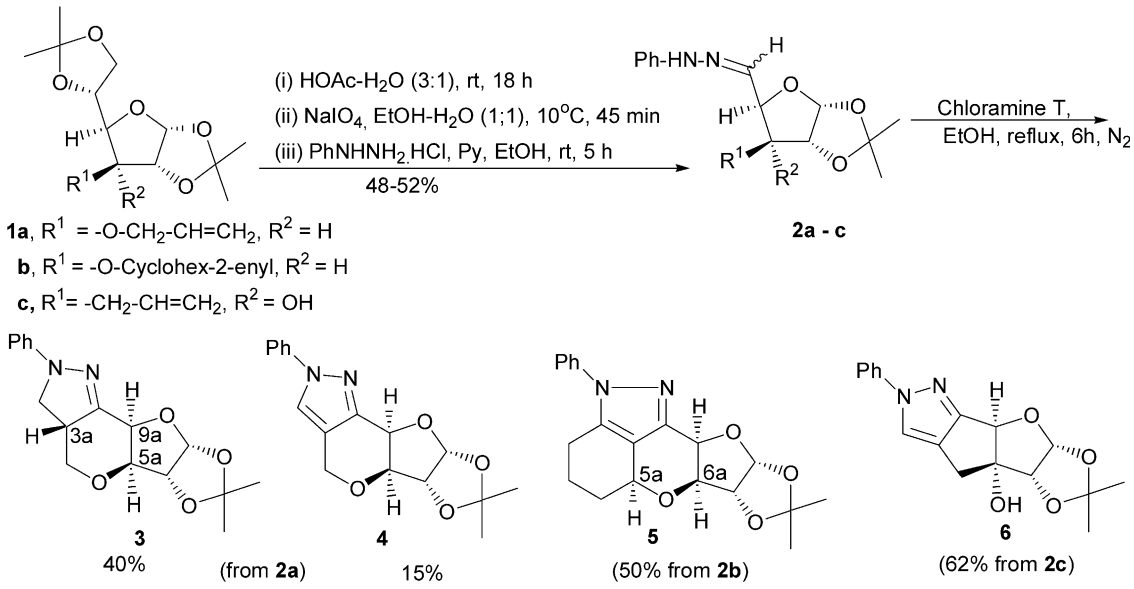


Figure 1. A general method for the synthesis of glycopyrazoles.

Keywords: Nitrilimine cycloaddition reaction; Synthesis; Glycopyrazoles; Pyrazolonucleosides; D-Glucose.
* Corresponding author. Tel.: +91 332473 3491; fax: +91 3324735197; e-mail: sbmandal@iicb.res.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.096



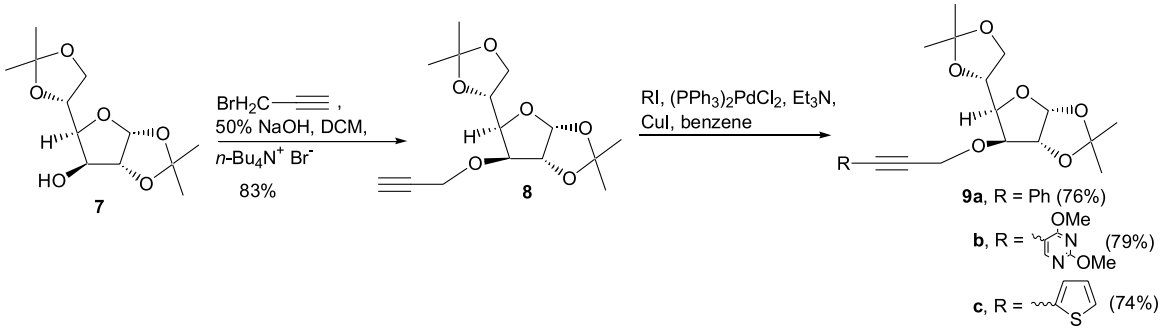
Scheme 1. Synthesis of pyrazoline **3** and pyrazoles **4–6** through INIC reaction.

pyrazole/pyrazoline ring in the structures. The present communication deals with the scope of this reaction for developing functionalized chiral glycopyrazoles and pyrazolonucleosides.

2. Results and discussion

Selective opening of the 5,6-*O*-isopropylidene group of the D-glucose-derived precursors **1a–c**[12] by acid treatment followed by vicinal diol cleavage with sodium periodate and reaction with phenyl hydrazine furnished the corresponding hydrazones **2a–c** (as a mixture of *cis* and *trans* isomers as evident from the duplicity of peaks in the ^{1}H NMR). Oxidation with chloramine T thereafter was expected to furnish the respective pyrazolines as the intramolecular nitrilimine cycloaddition (INIC) products. However, the initially formed pyrazolines appear to have undergone in situ oxidation to form the pyrazoles (Scheme 1); only **2a** yielded the pyrazoline **3** (40%) as the major product along with the pyrazole **4** (15%), while **2b** and **2c** gave **5** and **6**, respectively. Formation of **3** was indicated by the disappearance of vinylic proton signals of **1a** in the δ 5.20–5.30 and 5.80–6.00 regions along with appearance of peaks for methylene protons at δ 3.25–3.34 (m, 2H) and for a methine proton at δ 3.55–3.62 (m, 1H) in the ^{1}H NMR spectrum. This was confirmed by the presence of three quaternary (δ 112.6, 145.6 and 147.0) and two methylene (δ 49.9 and 71.5) carbon signals in its ^{13}C NMR spectrum. The absence of similar proton signals in the NMR of **4** and the appearance instead of a 1H singlet at δ 7.63 confirmed its formation through the oxidation of **3**. Regarding the identification of the other products, the appearance of a double doublet for H-5a at δ 4.54 (J=5.3, 10.2 Hz) in the ^{1}H NMR spectrum of **5** and of five quaternary carbon signals in its ^{13}C NMR spectrum indicated its formation. Similarly, the absence of signals in the olefinic proton region (δ 5.18–6.03) coupled with the presence of two singlets at δ 5.09 and 7.63 in the ^{1}H NMR spectrum and of five quaternary carbons in the ^{13}C NMR spectrum of **6** indicated the structure shown. The *trans* relationship of H-3a (δ 3.59) with H-9a (δ 4.98) (and hence with H-5a at δ 4.02) in **3** was borne out by the absence of correlation in the NOESY spectrum. However, the presence of distinct cross-peaks between the signals for the H-6a (δ 4.36) and the H-5a (δ 4.54) in the NOESY spectrum of **5** signified their *cis* relationship.

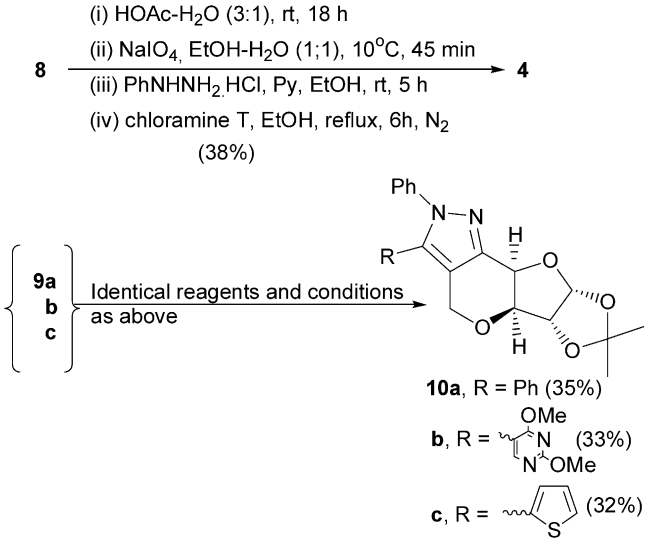
The INIC reaction was also attempted on the substrates carrying an *O*-propargyl or substituted propargyl group at *C*-3 of the carbohydrate precursor. Starting with **7** (Scheme 2), the 3-*O*-propargyl-α-D-glucofuranose



Scheme 2. Preparation of 3-*O*-alkynyl-1,2:5,6-diacetone-D-glucose derivatives **8**, **9a–c**.

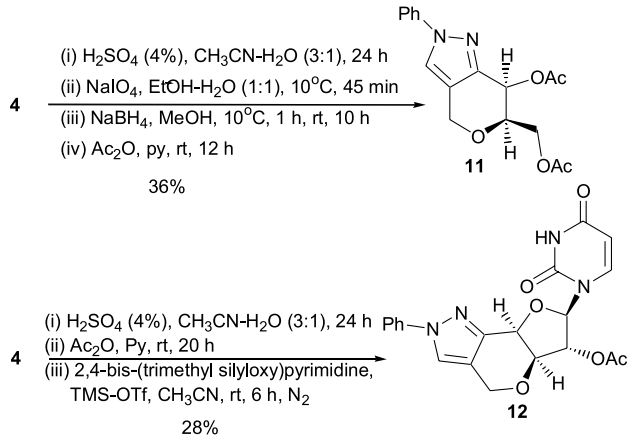
derivative **8** was prepared through propargylation (propargyl bromide, CH_2Cl_2, 50% aq NaOH, n-$Bu_4N^+Br^-$, rt, 12 h) of C-3–OH group. Compounds **9a–c** were, however, synthesized by incorporating phenyl, 2,4-dimethoxyuracil-5-yl and thiophen-2-yl groups at the terminal carbon of the triple bond of **8** though Sonogashira coupling[13] with the corresponding iodides in the presence of a catalytic amount of bis(triphenylphosphine)dichloro palladium(II) and copper (I) iodide. The formation of the desired product in each case was tested by NMR spectroscopy. Thus, the acetylenic proton signal at δ 2.48 in the ^{1}H NMR of **8** was found absent in those of the products **9a–c**. Instead the characteristic signals for protons of the substituent were observed.

When the acetylenic compounds **8** and **9a–c** were subjected to dil acetic acid treatment, they afforded the respective 5,6-dihydroxy derivatives. The products were subjected to vicinal diol cleavage with $NaIO_4$ and reaction with phenyl hydrazine to furnish the corresponding hydrazones. Oxidation of these hydrazones with chloramine T followed by cycloaddition reactions of the generated nitrilimines furnished the corresponding pyrazoles **4** and **10a–c** in 32–38% overall yields (Scheme 3). The structures of the products were deduced from spectral analyses.



Scheme 3. Conversion of **8** and **9a–c** to pyrazoles **4** and **10a–c**.

The derived INIC products could be further transformed into new varieties of bicyclic pyrazoles and nucleoside analogues (Scheme 4). Thus, **4** was converted to pyranopyrazole **11** through a sequence of reactions involving removal of the 1,2-*O*-isopropylidene group with 4% H_2SO_4 in CH_3CN–H_2O (3:1), $NaIO_4$ cleavage of the masked aldehyde, $NaBH_4$ reduction, and acetylation of the diol with acetic anhydride in pyridine. Besides, nucleobases could be successfully installed on **4** by cleavage of the acetonide group, acetylation to form a mixture of the diacetates and reaction with 2,4-bis-(trimethylsilyloxy)pyramidine in presence of TMS–OTf in CH_3CN at room temperature to furnish the nucleoside derivative **12**. Anchimeric assistance



Scheme 4. Conversion of **4** to bicyclic pyrazole **11** and modified nucleoside **12**.

by the neighbouring acetoxy group directs the incoming nucleobase to the β-face.

The formation of **11** was deduced from the appearance of an acetoxy peak at δ 2.11 (s, 6H) and of two methylene carbon signals at δ 62.8 and 63.1 in its ^{1}H and ^{13}C NMR spectra. The presence of a 3H singlet at δ 2.19 (OAc) and two doublets at δ 5.63 and 7.70 (olefin protons of uracil) in the ^{1}H NMR of **12** confirmed the presence of the nucleoside base at the anomeric carbon of the ribose ring.

In summary, it appears that intramolecular [3+2] nitrilimine cycloaddition reaction could be applied to D-glucose derived substrates to synthesize chiral pyrazoles of diverse structures and also pyrazolonucleoside analogues. The method is very simple and capable of extension to many other carbohydrate based precursors.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 L spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained using either JEOL AX-500 or Micromass Q-Tof micro™ spectrometers. IR spectra were measured on a JASCO 700 spectrophotometer. Elemental analyses were carried out with a C, H, N-analyzer. Specific rotations were measured at 589 nm on a JASCO P-1020 polarimeter. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}).

3.1.1. 1,2-*O*-Isopropylidene-3-*O*-allyl-5-aldoglucofuranose phenylhydrazones (2a *cis/trans* mixture). *Typical procedure*. Compound **1a** (3.0 g, 10.0 mmol) was dissolved in dil HOAc (75%, 50 mL) and stirred at rt for 18 h. The solvent was evaporated in vacuo and the last trace of HOAc was removed through coevaporation with toluene (3× 50 mL) to afford a crude residue, which was purified by column chromatography over silica gel using $CHCl_3$–MeOH (49:1) to afford the corresponding 5,6-dihydroxy glucose derivative (2.08 g). The material was dissolved in EtOH (40 mL); the solution was cooled to 10 °C and treated

with an aqueous solution (40 mL) of $NaIO_4$ (2.05 g, 9.6 mmol) dropwise while stirring (45 min). The reaction mixture was filtered, the filtrate was concentrated and the product was extracted with $CHCl_3$ (2×40 mL). The $CHCl_3$ solution was washed with H_2O (2×50 mL), dried (Na_2SO_4) and evaporated to give a crude aldehyde (1.37 g). Without further purification, it was treated with phenylhydrazine hydrochloride (900 mg, 6.18 mmol) and pyridine (1.0 mL), and the mixture was stirred at rt for 5 h. The solvent was evaporated and the product was extracted with $CHCl_3$ (3×25 mL). The $CHCl_3$ solution was washed with H_2O (2×25 mL), dried (Na_2SO_4) and the solvent was evaporated to yield the hydrazone mixture **2a** (1.62 g, 51%) as a sticky mass; [found: C, 64.02; H, 6.82; N, 8.58. $C_{17}H_{22}N_2O_4$ requires C, 64.13; H, 6.97; N, 8.80]; IR (KBr): ν_{max} 3305, 1648, 1601, 1585, 1318, 1257, 1100, 1004, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s), 1.49 (s), 1.51 (s), 1.55 (s), 3.97–4.14 (m), 4.30 (br s), 4.59 (m), 4.85 (br s), 5.18–5.30 (m), 5.97–6.07 (m), 6.87 (m), 7.01 (d), 7.06 (d), 7.23 (m), 7.46 (br s); ESIMS, *m/z*: 319 (M^++H), 341 (M^++Na).

3.1.2. 1,2-*O*-Isopropylidene-3-*O*-cyclohex-2-enyl-5-aldo-glucofuranose phenylhydrazone (2b *cis/trans* mixture). Sticky mass; [found: C, 66.88; H, 7.08; N, 7.59. $C_{20}H_{26}N_2O_4$ requires C, 67.02; H, 7.31; N, 7.82]; IR (KBr): ν_{max} 3330, 1645, 1601, 1321, 1262, 1072, 998, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s), 1.50 (s), 1.55 (s), 1.63-2.10 (m), 3.96–4.39 (m), 4.58 (d), 4.85 (t-like), 5.70–6.06 (m, merged with a d at δ 5.97), 6.82–6.91 (m), 6.99–7.11 (m), 7.21 (t-like), 7.61 (br s); ESIMS, *m/z*: 359 (M^++H), 381 (M^++Na).

3.1.3. 1,2-*O*-Isopropylidene-3-*C*-allyl-5-aldoallofuran-ose-phenylhydrazone (2c *cis/trans* mixture). Gum; [found: C, 63.90; H, 6.77; N, 8.60. $C_{17}H_{22}N_2O_4$ requires C, 64.13; H, 6.97; N, 8.80]; IR (neat): ν_{max} 3472, 3312, 1640, 1600, 1256, 1079, 1007, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s), 1.40 (s), 1.63 (s), 2.14–2.29 (m), 2.39–2.48 (m), 3.60 (br s), 4.36 (d), 4.39 (d), 4.48 (d), 4.75 (d), 5.12–5.21 (m), 5.78–5.93 (m), 6.47 (d), 6.86 (t), 6.94 (d), 7.03 (t-like), 7.22 (d), 7.27 (d), 7.65 (s), 9.12 (s); ESIMS, *m/z*: 319 (M^++H), 341 (M^++Na).

3.1.4. (3a*R*,5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2-phenyl-2,3,3a,4,5a,5b,8a,9a-octahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (3); (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-dimethyl-2-phenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (4). *Typical procedure*. To the hydrazone **2a** (636 mg, 2.0 mmol) dissolved in ethanol (40 mL) was added chloramine T (843 mg, 3.0 mmol) and the mixture was heated at reflux under N_2 for 6 h. The solvent was evaporated in vacuo and the residual mass was extracted with $CHCl_3$ (2×30 mL). The $CHCl_3$ solution was washed successively with water (2×25 mL), 1 M NaOH (20 mL), and brine (2×20 mL), and then dried (Na_2SO_4). Evaporation of the solvent furnished a reddish gummy material, which was purified by chromatography on silica gel using $CHCl_3$ as eluent to afford **3** (253 mg, 40%) and **4** (94 mg, 15%).

3.1.5. Compound 3. Gummy mass; [found: C, 64.34; H, 6.18; N, 8.58. $C_{17}H_{20}N_2O_4$ requires C, 64.54; H, 6.37; N, 8.86]; $[\alpha]_D^{25} = +117.4$ (*c* 0.56, $CHCl_3$); IR (neat): ν_{max} 1598, 1500, 1377, 1214, 1161, 1093, 1013, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.56 (s, 3H), 3.25–3.34 (m, 2H), 3.54–3.66 (m, 1H), 3.98 (dd, 1H, J=10.1, 11.5 Hz), 4.02 (d, 1H, J=1.9 Hz), 4.21 (dd, 1H, J=6.3, 10.5 Hz), 4.58 (d, 1H, J=3.5 Hz), 4.98 (d, 1H, J=1.9 Hz), 6.01 (d, 1H, J=3.5 Hz), 6.85 (dt, 1H, J=0.6, 7.3 Hz), 6.99 (dd, 2H, J=0.6, 7.8 Hz), 7.25–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7 (CH_3), 27.2 (CH_3), 41.7 (CH), 49.9 (CH_2), 71.5 (CH_2), 74.1 (CH), 83.6 (CH), 84.0 (CH), 106.4 (CH), 112.6 (C), 113.2 (2×CH), 120.0 (CH), 129.6 (2×CH), 145.6 (C), 147.0 (C); EIMS, *m/z*: 316 (M^+).

3.1.6. Compound 4. Sticky material; [found: C, 64.95; H, 5.73; N, 8.72. $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91]; $[\alpha]_D^{25} = +23.1$ (*c* 0.4, $CHCl_3$); IR (neat): ν_{max} 1597, 1503, 1389, 1213, 1162, 1084, 1015, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.59 (s, 3H), 4.17 (d, 1H, J=2.0 Hz), 4.65 (d, 1H, J=13.9 Hz), 4.71 (d, 1H, J=3.6 Hz), 4.92 (d, 1H, J=13.9 Hz), 5.20 (d, 1H, J=2.1 Hz), 6.05 (d, 1H, J=3.6 Hz), 7.30 (t, 1H, J=7.3 Hz), 7.43 (t, 2H, J=8.1 Hz), 7.67 (d, 2H, J=7.2 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 (CH_3), 27.3 (CH_3), 62.7 (CH_2), 70.8 (CH), 81.2 (CH), 84.3 (CH), 106.4 (CH), 112.5 (C), 117.1 (C), 119.8 (2×CH), 121.6 (CH), 127.2 (CH), 129.8 (2×CH), 140.4 (C), 145.1 (C); FABMS, *m/z*: 315 (M^++1).

3.1.7. (5a*S*,6a*S*,7*R*,8*R*,9a*R*)-7,8-Isopropylidene-dioxy-3,4,5,5a,6a,7,8,9a-octahydro-2*H*-6,9-dioxa-1,2-diaza-cyclopenta[*d*]acenaphthalene (5). Foam; [found: C, 67.69; H, 6.18; N, 7.63. $C_{20}H_{22}N_2O_4$ requires C, 67.78; H, 6.26; N, 7.90]; $[\alpha]_D^{25} = -7.1$ (*c* 0.33, $CHCl_3$); IR (KBr): ν_{max} 1597, 1503, 1380, 1217, 1162, 1077, 1017, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.58 (s, 3H), 1.81–1.90 (m, 2H), 2.15–2.24 (m, 2H), 2.68 (m, 1H), 3.00 (dd, 1H, J=6.0, 16.8 Hz), 4.36 (d, 1H, J=2.2 Hz), 4.54 (dd, 1H, J=5.3, 10.2 Hz), 4.69 (d, 1H, J=3.6 Hz), 5.28 (d, 1H, J=2.2 Hz), 6.02 (d, 1H, J=3.6 Hz), 7.30 (t, 1H, J=7.4 Hz), 7.42 (t, 2H, J=7.9 Hz), 7.62 (d, 2H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7 (CH_2), 24.2 (CH_2), 26.8 (CH_3), 27.4 (CH_3), 29.2 (CH_2), 71.4 (CH), 72.3 (CH), 82.7 (CH), 84.1 (CH), 106.5 (CH), 112.2 (C), 120.7 (C), 122.3 (2×CH), 127.1 (CH), 129.5 (2×CH), 136.9 (C), 140.7 (C), 143.8 (C); FABMS, *m/z*: 355 (M^++H).

3.1.8. (3a*R*,3b*R*,4a*R*,7b*R*)-2,2-Dimethyl-6-phenyl-3a,6,7b,8a-tetrahydro-4*H*-1,3,8-trioxa-6,7-diaza-dicyclo-penta[*a*,*e*]pentalen-3b-ol (6). Foamy mass; [found: C, 64.79; H, 5.65; N, 8.87. $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91]; $[\alpha]_D^{25} = +112.7$ (*c* 0.25, $CHCl_3$); IR (neat): ν_{max} 3449, 1598, 1504, 1380, 1218, 1162, 1080, 1030, 999, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 3H), 1.67 (s, 3H), 2.93 (d, 1H, J=16.2 Hz), 3.01 (d, 1H, J=16.2 Hz), 4.51 (d, 1H, J=3.6 Hz), 5.09 (s, 1H), 6.01 (d, 1H, J=3.6 Hz), 7.29 (1H merged signal), 7.42 (t, 2H, J=7.8 Hz), 7.63 (s, 1H), 7.64 (d, 2H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.4 (CH_3), 27.8 (CH_3), 34.7 (CH_2), 82.6 (CH), 83.5 (CH), 94.6 (C), 107.2 (CH), 113.7 (C), 119.9 (2×CH), 122.4 (CH), 125.9 (C), 126.9 (CH), 129.8 (2×CH), 141.1 (C), 158.6 (C); EIMS, *m/z*: 314 (M^+).

3.1.9. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-6-prop-2-ynyloxy-tetrahydro-furo[2,3-*d*][1,3]dioxole (8). To a stirred heterogeneous

solution of **7** (1.30 g, 5.0 mmol) in dichloromethane (70 mL) and 50% NaOH (70 mL) containing *n*-tetrabutylammonium bromide (160 mg), was added propargyl bromide (893 mg, 7.5 mmol) and the mixture was stirred at rt for 12 h. The organic layer was taken out, washed with H_2O until neutral and then dried (Na_2SO_4). The solvent was evaporated and the resulting product was purified by silica gel column chromatography using $CHCl_3$–pet. ether (1:9) as the eluent to obtain **8** (1.25 g, 83%) as a thick liquid; [found: C, 60.37; H, 7.28. $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43]; IR (neat): ν_{max} 3275, 2117, 1378, 1216, 1076, 1022, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 2.48 (t, 1H, $J=2.3$ Hz), 3.99 (dd, 1H, $J=5.4$, 8.6 Hz), 4.07–4.11 (m, 2H), 4.14 (dd, 1H, $J=3.0$, 7.6 Hz), 4.25–4.31 (m, 3H), 4.63 (d, 1H, $J=3.6$ Hz), 5.88 (d, 1H, $J=3.6$ Hz); EIMS, *m/z*: 298 (M^+).

3.1.10. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-6-(3-phenyl-prop-2-ynyloxy)-tetrahydro-furo[2,3-*d*][1,3]dioxole (9a). *Typical procedure*. To a solution of **8** (2.00 g, 6.71 mmol) in dry benzene (50 mL) was added bis(triphenylphosphine)palladium dichloride (93 mg, 0.13 mmol), cuprous iodide (13 mg, 0.06 mmol), triethyl amine (4.6 mL) and iodobenzene (1.63 g, 0.9 mL), and the mixture was stirred under N_2 for 20 h at rt. After removal of the solvent under reduced pressure, the residue obtained was extracted with $CHCl_3$ (3×30 mL). The $CHCl_3$ solution was washed with water (2×20 mL), dried (Na_2SO_4) and evaporated to give a crude product, which was purified by column chromatography on silica gel. Elution with pet. ether–$CHCl_3$ (1:1) furnished **9a** (1.91 g, 76%) as a light yellowish oil; [found: C, 67.15; H, 6.90. $C_{21}H_{26}O_6$ requires C, 67.36; H, 7.00]; $[\alpha]_D^{25}=-10.5$ (*c* 0.43, $CHCl_3$); IR (neat): ν_{max} 2237, 1498, 1448, 1375, 1254, 1215, 1163, 1077, 1026, 847, 758, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H). 1.42 (s, 3H), 1.51 (s, 3H), 4.02 (dd, 1H, $J=5.6$, 8.4 Hz), 4.11 (dd, 1H, $J=6.1$, 8.4 Hz), 4.18 (m, 2H), 4.34 (dd, 1H, $J=5.8$, 11.8 Hz), 4.50 (s, 2H), 4.69 (d, 1H, $J=3.4$ Hz), 5.90 (d, 1H, $J=3.4$ Hz), 7.32 (m, 3H), 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.2 (CH_3), 26.1 (CH_3), 26.7 ($2\times CH_3$), 58.6 (CH_2), 67.0 (CH_2), 72.4 (CH), 80.9 (CH), 81.2 (CH), 82.6 (CH), 84.4 (C), 86.4 (C), 105.1 (CH), 108.9 (C), 111.7 (C), 128.1 ($2\times$CH), 128.4 (CH), 130.1 (C), 131.6 ($2\times$CH); FABMS, *m/z*: 375 ($M^+ +H$).

3.1.11. (3a*R*,4*S*,5*R*,6a*R*)-5-{3-[5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-yloxy]-prop-1-ynyl}-2,4-dimethoxy-pyrimidine (9b). Gummy material; [found: C, 57.68; H, 6.33; N, 6.19. $C_{21}H_{28}N_2O_8$ requires C, 57.79; H, 6.47; N, 6.42]; $[\alpha]_D^{25}=-5.5$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 2226, 1594, 1551, 1472, 1388, 1077, 1017, 848, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.51 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 4.09–4.18 (m, 4H), 4.32 (m, 1H), 4.53 (s, 2H), 4.70 (d, 1H, $J=3.6$ Hz), 5.90 (d, 1H, $J=3.6$ Hz), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 27.2 ($2\times CH_3$), 54.9 (CH_3), 55.5 (CH_3), 59.3 (CH_2), 67.6 (CH_2), 73.0 (CH), 78.5 (C), 81.4 (CH), 82.0 (CH), 83.2 (CH), 91.5 (C), 105.6 (CH), 109.4 (C), 112.2 (C), 162.0 (CH), 164.7 (C), 2 quaternary C signals not observed; FABMS, *m/z*: 437 ($M^+ +H$), 459 ($M^+ +Na$).

3.1.12. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3] dioxolan-4*R*-yl)-2,2-dimethyl-6-(3-thiophen-2-yl-prop-2-ynyloxy)-tetrahydro-furo[2,3-*d*][1,3]dioxole (9c). Gum; [found: C, 59.67; H, 6.38. $C_{19}H_{24}O_6S$ requires C, 59.98; H, 6.36]; $[\alpha]_D^{25}=-5.53$ (*c* 0.75, $CHCl_3$); IR (neat): ν_{max} 2222, 1375, 1253, 1214, 1163, 1077, 1024, 847, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 4.01 (dd, 1H, $J=5.4$, 8.5 Hz), 4.10 (dd, 1H, $J=6.1$, 8.4 Hz), 4.15 (m, 2H), 4.29–4.35 (m, 1H), 4.51 (s, 2H), 4.67 (d, 1H, $J=3.6$ Hz), 5.90 (d, 1H, $J=3.6$ Hz), 6.98 (dd, 1H, $J=3.7$, 4.9 Hz), 7.23 (d,1H, $J=3.4$ Hz), 7.27 (d, 1H, $J=4.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 27.2 ($2\times CH_3$), 59.3 (CH_2), 67.6 (CH_2), 72.9 (CH), 80.2 (C), 81.5 (CH), 81.9 (CH), 83.2 (CH), 89.0 (C), 105.6 (CH), 109.4 (C), 112.2 (C), 122.7 (C), 127.3 (CH), 127.9 (CH), 132.9 (CH). FABMS, *m/z*: 381 ($M^+ +H$), 403 ($M^+ +Na$).

3.1.13. (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2,3-diphenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10a). The reaction was carried out according to the method adopted for **3**. Thus, the hydrazone (392 mg, 1.0 mmol) derived from **9a** as described was dissolved in ethanol (40 mL), treated with chloramine T (418 mg, 1.5 mmol) and heated at reflux for 6 h under N_2. Usual work-up followed by purification using silica gel column chromatography and $CHCl_3$–MeOH (99.5:0.5) as eluent afforded **10a** (273 mg, 70%) as a thick gum; [found: C, 70.69; H, 5.55; N, 6.91. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.68; N, 7.17]; $[\alpha]_D^{25}=-4.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 1596, 1498, 1448, 1373, 1216, 1162, 1081, 1015, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.59 (s, 3H), 4.24 (d, 1H, $J=1.8$ Hz), 4.72 (d, 1H, $J=3.6$ Hz), 4.77 (s, 2H), 5.24 (d, 1H, $J=1.9$ Hz), 6.08 (d, 1H, $J=3.6$ Hz), 7.07 (m, 2H), 7.31 (br s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.9 (CH_3), 27.3 (CH_3), 63.1 (CH_2), 71.1 (CH), 81.3 (CH), 84.3 (CH), 106.5 (CH), 112.5 (C), 115.7 (C), 125.5 ($2\times$CH), 127.9 (CH), 128.9 (CH), 129.1 ($2\times$CH), 129.3 ($4\times$CH), 129.9 (C), 137.2 (C), 140.1 (C), 144.2 (C); ESIMS, *m/z*: 413 ($M^+ +Na$), 803 ($2M^+ +Na$).

3.1.14. (5a*S*,5b*R*,8a*R*,9a*R*)-3-(2,4-Dimethoxypyrimidin-5-yl)-7,7-dimethyl-2-phenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10b). Foamy solid; [found: C, 60.88; H, 5.32; N, 12.19. $C_{23}H_{24}N_4O_6$ requires C, 61.05; H, 5.35; N, 12.38]; $[\alpha]_D^{25}=+3.5$ (*c* 1.38, $CHCl_3$); IR (KBr): ν_{max} 1735, 1613, 1572, 1552, 1480, 1455, 1391, 1082, 1015, 758, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.58 (s, 3H), 3.78 (s, 3H), 3.99 (s, 3H), 4.23 (d, 1H, $J=2.0$ Hz), 4.66–4.72 (m, 3H), 5.23 (d, 1H, $J=2.1$ Hz), 6.07 (d, 1H, $J=3.5$ Hz), 7.28–7.36 (m, 5H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 (CH_3), 27.3 (CH_3), 54.4 (CH_3), 55.5 (CH_3), 62.9 (CH_2), 70.9 (CH), 81.3 (CH), 84.3 (CH), 105.6 (C), 106.5 (CH), 112.5 (C), 117.2 (C), 124.7 ($2\times$CH), 128.2 (CH), 129.2 (C), 129.4 ($2\times$CH), 140.3 (C), 144.2 (C), 159.4 (CH), 165.9 (C), 168.3 (C); ESIMS, *m/z*: 475 ($M^+ +Na$).

3.1.15. (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2-phenyl-3-thiophen-2-yl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10c). Foamy solid; [found: C, 63.68; H, 5.05; N, 6.94. $C_{21}H_{20}N_2O_4S$ requires C, 63.62; H, 5.08; N, 7.07]; $[\alpha]_D^{25}=+5.27$ (*c* 0.56,

$CHCl_3$); IR (KBr): ν_{max} 1736, 1596, 1498, 1455, 1376, 1219, 1162, 1085, 1016, 759, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.58 (s, 3H), 4.22 (d, 1H, J= 1.6 Hz), 4.72 (d, 1H, J=3.8 Hz), 4.73 (d, 1H, J=13.4 Hz), 4.90 (d, 1H, J=14.1 Hz), 5.21 (d, 1H, J=1.9 Hz), 6.07 (d, 1H, J=3.5 Hz), 6.72 (dd, 1H, J=0.9, 3.5 Hz), 6.97 (dd, 1H, J=3.7, 5.0 Hz), 7.31–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.9 (CH_3), 27.3 (CH_3), 63.1 (CH_2), 70.9 (CH), 81.1 (CH), 84.2 (CH), 106.5 (CH), 112.5 (C), 115.9 (C), 126.3 (2×CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.3 (CH), 129.5 (CH), 130.4 (C), 131.5 (C), 140.0 (C), 144.1 (C); ESIMS, *m/z*: 419 (M^++Na), 815 ($2M^+$+Na).

3.1.16. (6*R*,7*R*)-Acetic acid-6-acetoxymethyl-2-phenyl-2,4,6,7-tetrahydro-pyrano [4,3-*c*] pyrazol-7-yl ester (11). Compound **4** (314 mg, 1.0 mmol) was dissolved in 4% H_2SO_4 in CH_3CN–H_2O (3:1) (25 mL) and kept at rt for 24 h. The acidic solution was neutralized with solid $CaCO_3$, filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in EtOH (20 mL) and treated dropwise at 10 °C with an aqueous solution (20 mL) of $NaIO_4$ (314 mg, 1.0 mmol) with stirring for 45 min. Usual work-up followed by $NaBH_4$ reduction in MeOH (30 mL) afforded an alcohol, which was acetylated with Ac_2O (0.5 mL) in pyridine (1.5 mL) at rt for 12 h to furnish a crude product. The product was purified by silica gel column chromatography using pure $CHCl_3$ as an eluent to afford **11** (119 mg, 36%) as a thick gum; [found: C, 61.68; H, 5.28; N, 8.30. $C_{17}H_{18}N_2O_5$ requires C, 61.81; H, 5.49; N, 8.48]; $[\alpha]_D^{25}=-74.5$ (*c* 0.52, $CHCl_3$); IR (neat): ν_{max} 1743, 1598, 1503, 1371, 1225, 1049, 958, 758, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 6H), 4.01–4.06 (m, 1H), 4.27 (dd, 1H, J=7.2, 11.5 Hz), 4.36 (dd, 1H, J=5.3, 11.5 Hz), 4.75 (d, 1H, J=14.0 Hz), 5.05 (d, 1H, J= 14.0 Hz), 6.16 (d, 1H, J=1.9 Hz), 7.29 (t, 1H, J=7.6 Hz), 7.44 (t, 2H, J=8.1 Hz), 7.66 (d, 2H, J=7.9 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6 (CH_3), 20.8 (CH_3), 62.6 (CH), 62.8 (CH_2), 63.1 (CH_2), 75.6 (CH), 116.9 (C), 119.3 (2×CH), 121.2 (CH), 126.8 (CH), 129.3 (2×CH), 139.8 (C), 145.5 (C), 169.9 (C), 170.5 (C); ESIMS, *m/z*: 353 (M^++Na).

3.1.17. (5a*S*,6*R*,7*R*,8a*R*)-Acetic acid-7-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-phenyl-2,4,5a,6,7,8a-hexahydro-5,8-dioxa-1,2-diaza-*as*-indacen-6-yl ester (12). 2,4-Bis-(trimethyl silyloxy)pyramidine was prepared by refluxing a mixture of uracil (336 mg, 3.0 mmol) and trimethylsilyl chloride (2 drops) dissolved in hexamethyl disilazane (7 mL) under N_2 for 10 h. The residue obtained after evaporation of the solvent in vacuo was dissolved in acetonitrile (5 mL) and added to a solution of the diacetate mixture (358 mg, 1.0 mmol) in acetonitrile (5 mL) [generated from **4** through opening of 1,2-*O*-isopropylidene group followed by acetylation] and TMS–OTf (0.5 mL). The mixture was stirred for 6 h at rt under N_2. TLC showed complete disappearance of the starting material. The solution was neutralized with solid $NaHCO_3$, treated with water (3 drops), and the solvent was evaporated in rotary evaporator. The gummy material was extracted with $CHCl_3$ (2×25 mL), the $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography eluting with $CHCl_3$–MeOH mixture (49.5:0.5) to afford **12** (193 mg, 47%) as a foamy solid; [found C, 58.60; H, 4.38; N, 13.40. $C_{20}H_{18}N_4O_6$ requires C, 58.53; H, 4.42; N, 13.65]; $[\alpha]_D^{25}=+73.7$ (*c* 0.95, $CHCl_3$); IR (KBr): ν_{max} 3408, 1747, 1688, 1503, 1459, 1391, 1221, 1060, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 4.20 (d, 1H, J= 2.2 Hz), 4.71 (d, 1H, J=14.1 Hz), 4.98 (d, 1H, J=14.1 Hz), 5.18 (d, 1H, J=2.2 Hz), 5.27 (br s, 1H), 5.63 (d, 1H, J= 8.0 Hz), 6.21 (d, 1H, J=1.1 Hz), 7.33 (t, 1H, J=7.4 Hz), 7.44–7.49 (m, 3H), 7.70 (d, 2H, J=7.8 Hz), 7.77 (s, 1H), 8.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2 (CH_3), 62.9 (CH_2), 72.9 (CH), 79.9 (CH), 81.5 (CH), 90.5 (CH), 102.7 (CH), 116.7 (C), 119.8 (2×CH), 121.9 (CH), 127.6 (CH), 129.9 (2×CH), 140.2 (C), 141.0 (CH), 143.5 (C), 150.3 (C), 163.2 (C), 169.7 (C); ESIMS, *m/z*: 433 (M^++Na), 843 ($2M^+$+Na).

Acknowledgements

The work was supported by a grant from the Department of Science and Technology (Govt. of India). One of the authors (A. R.) gratefully acknowledges the Council of Scientific and Industrial Research for providing him a Senior Research Fellowship.

References and notes

1. (a) Elguero, J. In Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1996; Vol. 3, pp 1–75. (b) Wang, X.-J.; Tan, J.; Grozinger, K.; Betageri, R.; Kirrane, T.; Proudfoot, J. R. *Tetrahedron Lett.* **2000**, *41*, 5321. (c) Genim, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J. Med. Chem.* **2000**, *43*, 1034. (d) Stauffer, S. R.; Coletta, C. J.; Tedesco, R.; Nishiguchi, G.; Carlson, K.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2000**, *43*, 4934. (e) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833. (f) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555. (g) Yuan, J.; Gulianello, M.; De Lambaert, S.; Brodbeck, R.; Kieltyka, A.; Hodgetts, K. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2133. (h) Kopp, M.; Lancelot, J.-C.; Dallemagne, P.; Rault, S. *J. Heterocycl. Chem.* **2001**, *38*, 1045. (i) Commeiras, L.; Woodcock, S. C.; Baldwin, J. E.; Adlington, R. M.; Cowley, A. R.; Wilkinson, P. J. *Tetrahedron* **2004**, *60*, 933. (j) Dodd, D. S.; Martinez, R. L. *Tetrahedron Lett.* **2004**, *45*, 4265. (k) Majid, T.; Hopkins, C. R.; Pedgrift, B.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 2137.
2. Tang, J.; Shewchuk, L. M.; Sato, H.; Sasegawa, M.; Washio, Y.; Nishigaki, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2985.
3. Ancel, J. E.; Elkam, L.; Gadras, A.; Grimaud, L.; Jana, N. K. *Tetrahedron Lett.* **2002**, *43*, 8319.
4. Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015.
5. (a) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 6787. (b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (c) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, M.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2004**, *45*, 6033.
6. Aggarwal, V. K.; De Vincente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381.

7. (a) Molteni, G.; Broggini, G.; Pilati, T. *Tetrahedron: Asymmetry* **2002**, *13*, 2491. (b) Broggini, G.; Molteni, G.; Pilati, T.; Zecchi, G. *Synth. Commun.* **2001**, *31*, 3799. (c) Broggini, G.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1975.
8. (a) Gladstone, W. A. F.; Aylward, J. B.; Norman, R. O. C. *J. Chem. Soc. (C)* **1969**, 2587. (b) Lokanatha Rai, K. M.; Hassner, A. *Synth. Commun.* **1989**, *19*, 2799.
9. Other methods for generating nitrilimines involve the thermolysis or photolysis of tetrazoles,[14] photolysis of sydnones[15] and treatment of hydrazonoyl halides with triethyl amine.[16]
10. (a) Benasutti, L. D.; Garanti, L.; Molteni, G. *Tetrahedron* **2004**, *60*, 4627. (b) Benasutti, L. D.; Garanti, L.; Molteni, G. *Tetrahedron: Asymmetry* **2004**, *15*, 1127.
11. Agócs, A.; Gunda, T. E.; Batta, G.; Kovács.-Kulyassa, À.; Herczegh, P. *Tetrahedron: Asymmetry* **2001**, *12*, 469.
12. (a) Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Ghoshal, N.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265. (b) Tripathi, S.; Singha, K.; Achari, B.; Mandal, S. B. *Tetrahedron* **2004**, *60*, 4965. (c) Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1996**, *37*, 7635.
13. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
14. Huisgen, R.; Seidel, M.; Wallbillich, G.; Knupfer, H. *Tetrahedron* **1962**, *17*, 3.
15. Marky, M.; Meimer, H.; Wunderli, A.; Heimgartner, H.; Schmidt, H.; Hansen, H. J. *Helv. Chim. Acta* **1978**, *61*, 1477.
16. Baruah, A. K.; Prajapati, D.; Sandhu, J. *Tetrahedron* **1988**, *44*, 6137.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 373–377

Conformationally constrained amino acids: enantiodivergent synthesis of all four stereoisomers of 2-(tetrahydrofuran-2-yl)glycine

Aigars Jirgensons,† Maura Marinozzi and Roberto Pellicciari*

Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 1-06123 Perugia, Italy

Received 19 July 2004; revised 6 October 2004; accepted 29 October 2004

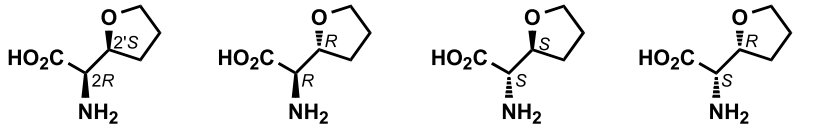
Abstract—The first enantiodivergent synthesis of all four possible 2-(tetrahydrofuran-2-yl)glycine stereoisomers is described. The key step of the route is the highly stereocontrolled allylboration of the (*S*)- or (*R*)-Garner's aldehydes to give four chiral homoallylalcohols. Starting from them, the title compounds are obtained in five steps.

1. Introduction

There is an ever increasing interest in the synthesis and bioorganic applications of conformationally constrained amino acids.[1] Indeed, this approach has led to the discovery of highly active analogs of important amino acidic neurotransmitters.[2] The incorporation of constrained amino acids into biologically active peptides, moreover, is a commonly followed strategy in the search for peptidomimetics endowed with specific conformational and topographical features as well as with improved properties such as potency, stability, bioavailability and selectivity.[3]

As a part of our continuing interest in the synthesis and biological applications of conformationally constrained amino acids,[4] we become interested in the preparation of 2-(tetrahydrofuran-2-yl)glycine isomers (2-THFGs, **1a**–**d**) and utilization as new peptidomimetic units. This is a class of compounds characterized by a cyclically constrained oxygen able to donate its lone pair in a directed way and therefore they are useful constrained mimics of side chain oxygen-functionalized amino acids such as serine or threonine. The aim of the work herein reported has been the development of a new, efficient synthetic route to all four possible 2-THFG stereoisomers (**1a**–**d**) (Fig. 1).

The few reported syntheses give access only to diastereoisomeric or racemic mixtures of 2-THFGs. In particular, 2-THFG mixtures have been obtained by hydrogenation of 2-(furan-2-yl)glycine derivatives,[5] by reductive cleavage of 7-oxabicyclo[2.2.1]heptane derivatives[6] and, more recently, by an aldol reaction/ring closing metathesis protocol.[7] There has been only one enantioselective approach towards the synthesis of 2-THFGs based on an asymmetric aldol coupling and subsequent cyclization of the β-hydroxy-α-amino acid derivative, thus obtained.[8] The absolute configuration of the two enantiomers thus prepared, however, was not unambiguously determined.

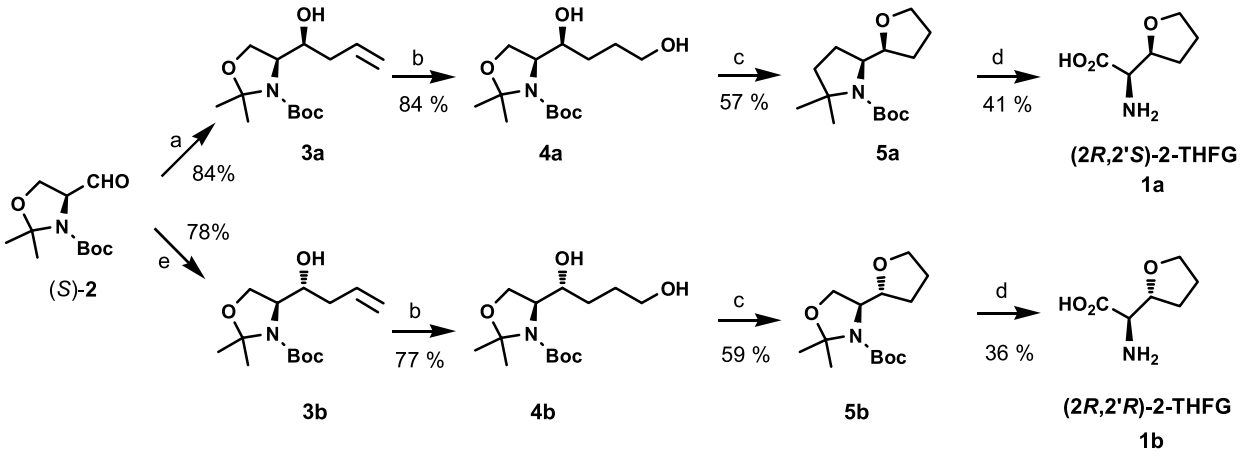


(2*R*,2'*S*)-2-THFG **1a** (2*R*,2'*R*)-2-THFG **1b** (2*S*,2'*S*)-2-THFG **1c** (2*S*,2'*R*)-2-THFG **1d**

Figure 1.

Keywords: Conformationally constrained amino acids; Unnatural amino acids; Garner's aldehyde; Allylboration.
* Corresponding author. Tel.: +39 0755855120; fax: +39 0755855124; e-mail: rp@unipg.it
† Present address: Institute of Organic Synthesis, 21 Aizkraukles str., 1006 Riga, Latvia.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.091

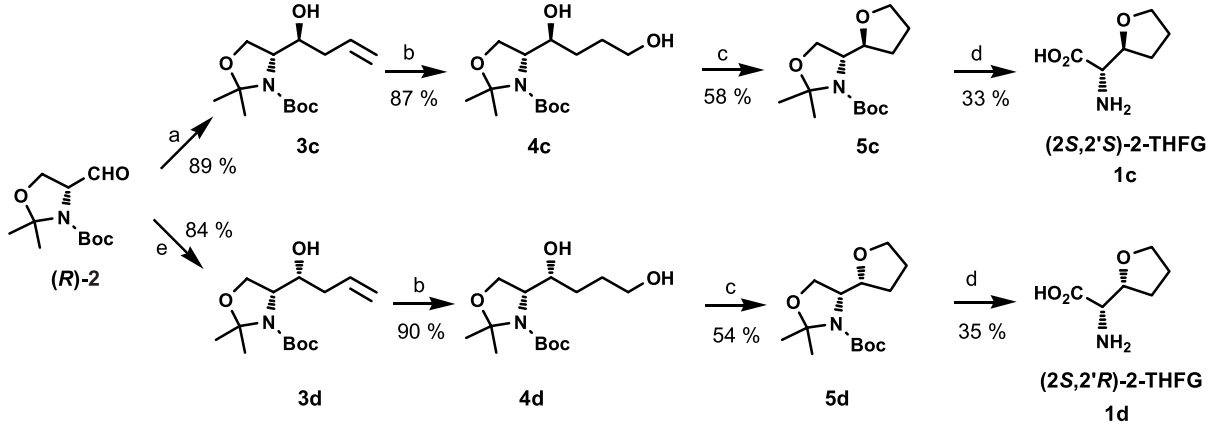


Scheme 1. Reagents and conditions: (a) (4*R*,5*R*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester, toluene, −78 °C, 3 h; (b) BH_3–THF, THF, 0–5 °C, 1 h then 30% H_2O_2, 2 M NaOH; 0–5 °C, 30 min; (c) (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 48 h, (ii) MPLC; (d) (i) 0.01 N *p*TsOH in MeOH, 5–7 h, then $NaHCO_3$, 30 min, (ii) PDC, DMF, rt, 15 h, (iii) 4.5 N HCl in dioxane, rt, 2 h, (iv) Dowex 50WX2-200, 10% NH_4OH; (e) (4*S*,5*S*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester toluene, −78 °C, 3 h.

2. Results and discussion

The chiral homoallylalcohols[9] **3a–d** are the starting materials for our synthetic route, depicted in Schemes 1 and 2. The alcohol **3a** (Scheme 1) was obtained as the major component of an inseparable mixture of **3a** and **3b** (**3a/3b**= 83:17 by GC analysis) by treatment of isopropylidene-*N*-Boc-(*S*)-serinal[10] (Garner's aldehyde, (*S*)-**2**) with distilled (4*R*,5*R*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester.[9] The reaction of the same aldehyde (*S*)-**2** with the tartrate derived allylboronate (4*S*,5*S*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester[9] provided the (4*S*,1′*R*)-diastereoisomer **3b** together with a minor amount of the diastereoisomer **3a** (**3b/3a**= 82:18 by GC analysis). Hydroboration of the unresolved mixture of **3a** and **3b** (83:17) with borane–THF complex followed by oxidation with hydrogen peroxide under basic conditions at 0–5 °C afforded the corresponding diols (4*S*,1′*S*)-**4a** and (4*S*,1′*R*)-**4b** which could not be separated by silica gel chromatography. Treatment of the mixture of **4a** and **4b** with *p*-toluenesulfonyl chloride and triethylamine in the presence of DMAP provided the tetrahydrofuranyl derivatives **5a** and **5b**.[11] At this point, the major component **5a** was separated from the minor isomer **5b** by medium pressure liquid chromatography (MPLC) on silica gel. By following an analogous procedure, the hydroboration–oxidation of the diastereoisomeric mixture of **3b** and **3a** (82:18) gave a mixture of the corresponding diols **4b** and **4a**, which was converted into the tetrahydrofuranyl derivatives **5b** and **5a**, then resolved by MPLC to give the pure (4*S*,2′*R*) *tert*-butyl 2,2-dimethyl-4-(tetrahydrofuran-2′-yl)oxazolidine-3-carboxylate (**5b**). The acetonide protecting group was cleaved in the single isomers **5a** and **5b** under mild acidic conditions. The resulting *N*-*tert*-butoxycarbonyl protected amino alcohols were oxidized with excess of pyridinium dichromate (PDC). The intermediate protected amino acids were deprotected under standard conditions to give, after ion-exchange chromatography, the desired (2*R*,2′*S*)- and (2*R*,2′*R*)-2-THFGs (**1a**) and (**1b**) in 13 and 12% overall yield, respectively.

The preparation of the other pair of diastereoisomers **1c** and **1d**, endowed with the *S*-configuration at amino acidic center, was achieved in the same fashion by using isopropylidene-*N*-Boc-(*R*)-serinal [(*R*)-**2**] as the starting material (Scheme 2). The above described synthetic protocol involving asymmetric



Scheme 2. Reagents and conditions: (a) (4*R*,5*R*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester, toluene, −78 °C, 3 h; (b) BH_3–THF, THF, 0–5 °C, 1 h then 30% H_2O_2, 2 M NaOH; 0–5 °C, 30 min; (c) (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 48 h, (ii) MPLC; (d) (i) 0.01 N *p*TsOH in MeOH, 5–7 h, then $NaHCO_3$, 30 min, (ii) PDC, DMF, rt, 15 h, (iii) 4.5 N HCl in dioxane, rt, 2 h, (iv) Dowex 50WX2-200, 10% NH_4OH; (e) (4*S*,5*S*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester, toluene, −78 °C, 3 h.

allylboration with both (4*R*,5*R*)- and (4*S*,5*S*)-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic acid bis-isopropyl ester, hydroboration–oxidation, cyclization of the diols, cleavage of acetonide, oxidation of the primary alcohol and final hydrolysis, provided (2*S*,2′*S*)- and (2*S*,2′*R*)-2-THFG (**1c**) and (**1d**) in 15 and 12% overall yield, respectively.

The absolute configuration of the THFGs (**1a–d**) thus obtained, was established according to the stereochemical characterization of the corresponding homoallylic alcohol precursors **3a–d**, previously reported by Roush.[9] In addition, the relative stereochemistries of the (2*S*,2′*S*)-2-THFG (**1c**) [or (2*R*,2′*R*)-2-THFG (**1a**)] and (2*S*,2′*R*)-2-THFG (**1d**) [or (2*R*,2′*S*)-2-THFG (**1b**)] was determined by spectroscopic analysis. A proof of the relative configuration of C-2 and C-2′ follows from the H–H coupling constants ($J_{2-2'}$) which are 4.0 and 6.0 Hz for the diastereoisomers **1c** and **1d**, respectively. According to the Karplus equation, these H–C(2)–C(2′)–H proton vicinal coupling constants are compatible with torsional angles around the H–C(2)–C(2′)–H rotatable bond of 49° for **1c** and 135° for **1d**. Assuming that for both diastereoisomers the preferred conformations in solution (Fig. 2) derive from the electrostatic interaction between the positive charged amino group and the partially negative charged ring-oxygen, the diastereoisomer **1c**, whose coupling constant value is 4.0 Hz, is endowed with 2*S*,2′*S* configuration (or 2*R*,2′*R* configuration). On the contrary, **1d** has the 2*S*,2′*R*

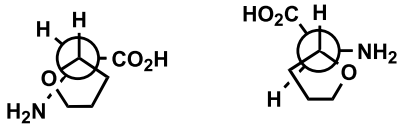


Figure 2. Preferred conformations of (2*S*,2′*S*)-2-THFG (**1c**) and (2*S*,2′*R*)-2-THFG (**1d**).

configuration (or 2*R*,2′*S* configuration), compatible with a larger torsional angle.

A further confirmation of the spatial disposition between H-2 and H-2′ is given by chemical shift values of the amino acidic proton which is more deshielded in the diastereoisomer **1c** (3.9 ppm as against 3.6 ppm for **1d**) due to the proximity with the oxygen of the tetrahydrofuranyl ring. The stereochemical assignments were supported by NOESY experiments (Fig. 3): in the case of (2*S*,2′*S*)-2-THFG (**1c**), strong NOE occurs between H-2 and H-2′, whereas NOEs were observed between H-2 and both H_a-3′ and H_a-4′ in the spectrum of (2*S*,2′*R*)-2-THFG (**1d**).

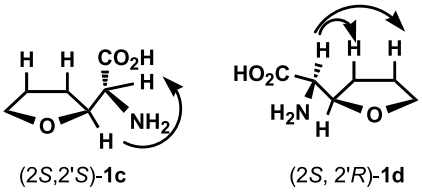


Figure 3. NOESY correlations of (2*S*,2′*S*)-2-THFG (**1c**) and (2*S*,2′*R*)-2-THFG (**1d**).

Since the stereochemistry at C-2 is unambiguously defined from the starting Garner's aldehyde, the assignment of the relative stereochemistry is indirectly a confirmation of the absolute configuration of each 2-THFG.

In conclusion, we have developed the first efficient synthetic route giving access to all four individual stereoisomers of the conformationally constrained unnatural amino acid, 2-(tetrahydrofuran-2-yl)glycine. The availability of these enantiomerically pure amino acids allows the preparation of novel constrained peptide surrogates. The results of our investigations in this area will be published in due time.

3. Experimental

3.1. General methods

Flash chromatography was performed on Merck silica gel (0.040–0.063 mm). Medium pressure chromatography (MPLC) was performed on Merck LiChroprep Si 60 Lobar columns. Melting points were determined in open capillary tubes on a Büchi 535 electrothermal apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were registered on a Bruker AC 200 or Bruker AC 400 using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported in ppm. Optical rotations were recorded on a Jasco Dip-360 digital polarimeter. HPLC analyses were carried out on a Shimadzu (Kyoto, Japan) LC-Workstation Class LC-10 equipped with a CBM-10A system controller, two LC-10AD high pressure binary gradient delivery systems, a SPD-10A variable-wavelength UV–Vis detector and a Rheodyne 7725i injector (Rheodyne, Inc., Cotati, CA, USA) with a 20 μL stainless steel loop. Microanalyses were carried out on a Carlo Erba 1106 elemental analyzer. IR spectra were recorded on a Jasco FT-IR-410 spectrometer.

3.2. General procedure for the preparation of *tert*-butyl 2,2-dimethyl-4-(1′,4′-dihydroxybut-1′-yl)oxazolidine-3-carboxylates (4a–d)

1 M BH_3 in THF (16 mL) was added dropwise to a 0 °C cooled solution of **3**[9] (1.09 g, 4 mmol) in dry THF (16 mL) magnetically stirred under argon. After 1 h, 2 N aqueous NaOH (16 mL) was added dropwise to maintain gentle H_2 evolution. 30% H_2O_2 (16 mL) was then added and the mixture was stirred at rt for 30 min. The reaction mixture was diluted with H_2O (50 mL) and extracted with $CHCl_3$ (2×30 mL). Combined organic phases were washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography. Elution with light petroleum/EtOAc (1:1) gave **4**.

3.2.1. (4*S*,1′*S*)-4a. The title compound was prepared from **3a** in 84% yield (976 mg) as a waxy solid; mp 61–63 °C; ^{1}H NMR (200 MHz) δ 1.52 (12H, s, *t*-Bu and 2-CH_3), 1.61 (3H, s, 2-CH_3), 1.42–1.80 (4H, m, 2′-CH_2 and 3′-CH_2), 3.00 (1H, brs, OH), 3.66–4.00 (6H, m, 1′-CH, 4′-CH_2, 4-CH, and 5-CH_2), 4.70 (1H, brs, OH); ^{13}C NMR (50 MHz) δ 24.2, 26.9, 28.3, 29.1, 31.4, 62.2, 62.7, 64.8, 74.0, 81.4. 94.1, 155.2; IR (neat) 3412, 2977, 2934, 2878, 1673, 1366, 1255,

1170, 1058 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.40; N, 4.84. Found: C, 58.27; H, 9.49; N, 4.82.

3.2.2. (4*S*,1′*R*)-4b. The title compound was prepared from **3b** in 77% yield (895 mg) as a waxy solid; mp 54–56 °C; ^{1}H NMR (200 MHz) δ 1.52 (12H, s, *t*-Bu and 2-CH_3), 1.61 (3H, s, 2-CH_3), 1.30–1.81 (4H, m, 2′-CH_2 and 3′-CH_2), 3.60–4.09 (6H, m, 1′-CH, 4′-CH_2, 4-CH and 5-CH_2); ^{13}C NMR (50 MHz) δ 24.0, 26.4, 28.3, 29.8, 62.2, 62.7, 64.8, 73.3, 81.2. 94.3, 154.3; IR (neat) 3415, 2977, 2938, 2878, 1675, 1360, 1249, 1171, 1062 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.40; N, 4.84. Found: C, 58.25; H, 9.51; N, 4.82.

3.2.3. (4*R*,1′*S*)-4c. The title compound was prepared from **3c** in 87% yield (1.01 g) as a waxy solid; mp 59–61 °C.

3.2.4. (4*R*,1′*R*)-4d. The title compound was prepared from **3d** in 90% yield (1.05 g) as a waxy solid; mp 54–61 °C.

3.3. General procedure for the preparation of *tert*-butyl 2,2-dimethyl-4-(tetrahydrofuran-2′-yl)oxazolidine-3-carboxylates (5a–d)

Distilled Et_3N (1.00 g, 9.9 mmol), *p*-toluenesulfonyl chloride (0.69 g, 3.6 mmol) and DMAP (95 mg) were added to a magnetically stirred solution of **4** (0.95 g, 3.3 mmol) in dry CH_2Cl_2 (33 mL). The reaction mixture was stirred under argon for 48 h at rt and filtered trough short SiO_2 column. The solvent was removed in vacuo and the residue was purified by flash chromatography eluting with light petroleum/EtOAc (8:2). Partial separation of isomers was achieved. The partially separated fractions were submitted to MPLC eluting with light petroleum/EtOAc (8:2) to give **5** as a pure isomer.

3.3.1. (4*S*,2′*S*)-5a. The title compound was prepared from **4a** in 57% yield (508 mg) as an oil; ^{1}H NMR (200 MHz) δ 1.51 (12H, s, *t*-Bu an 2-CH_3), 1.63 (3H, s, 2-CH_3), 1.82–2.10 (4H, m, 3′-CH_2 and 4′-CH_2), 3.70–4.00 and 4.00–4.32 (4H and 2H, both m, 2′-CH, 5′-CH_2, 4-CH and 5-CH_2); ^{13}C NMR (50 MHz) δ 22.8, 24.2, 26.0, 26.4, 26.7, 27.0, 28.4, 58.5, 64.0, 68.4, 78.1, 78.5, 78.8, 80.0, 93.9, 94.3, 152.3, 152.6; IR (neat) 2976, 2873, 1694, 1365, 1254, 1171, 1053 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.75; H, 9.42; N, 5.10.

3.3.2. (4*S*,2′*R*)-5b. The title compound was prepared from **4b** in 59% yield (525 mg) as a waxy solid; mp 45–47 °C; ^{1}H NMR (200 MHz) δ 1.51 (12H, s, *t*-Bu and 2-CH_3), 1.59 (3H, s, 2-CH_3), 1.80–2.10 (4H, m, 3′-CH_2 and 4′-CH_2), 3.75–4.00 and 4.00–4.35 (6H, both m, 2′-CH, 5′-CH_2, 4-CH and 5-CH_2); ^{13}C NMR (50 MHz) δ 23.0, 24.5, 27.1, 27.5, 28.4, 28.8, 59.8, 65.0, 65.5, 68.1, 79.4, 80.0, 93.6, 94.1, 152.1, 153.1; IR (neat) 2978, 2872, 1694, 1365, 1255, 1170, 1053 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.40; N, 5.10.

3.3.3. (4*R*,2′*S*)-5c. The title compound was prepared from **4c** in 58% yield (517 mg) as a waxy solid; mp 41–43 °C.

3.3.4. (4*R*,2′*R*)-5d. The title compound was prepared from **4d** in 54% yield (481 mg) as an oil.

3.4. General procedure for the preparation of 2-(tetrahydrofuran-2′-yl)glycines (1a–d)

A solution of **5** (0.43 g, 1.6 mmol) in 0.01 N methanolic *p*-toluenesulfonic acid (16 mL) was stirred for 7 h at rt and $NaHCO_3$ (0.27 g, 3.2 mmol) was then added. The resulting suspension was stirred for an additional 40 min and the solvent was removed in vacuo. The residue was purified by flash chromatography. Elution with light petroleum/EtOAc (1:1) gave the corresponding alcohol which was dissolved in DMF (7 mL) and treated with PDC (4.9 g, 13 mmol). The reaction mixture was stirred for 15 h at rt and then diluted with H_2O (15 mL) and 5% $NaHSO_4$ (35 mL). The suspension was extracted with EtOAc (2×30 mL). The combined organic phases were washed with brine (2×20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was passed through a short silica gel column to give the corresponding N-protected amino acid which was dissolved in 4.6 N HCl/dioxane and the resulting solution stirred at rt for 2 h. The excess of HCl and dioxane were removed in vacuo. The residue was made basic with 30% NH_4OH and again evaporated. The residue was dissolved in H_2O and submitted to resin exchange chromatography (Dowex 50WX2-200). Elution with H_2O followed by 10% NH_4OH gave **1**, which was treated with CH_3CN (5 mL) overnight. The crystals thus obtained were collected on a filter and dried in vacuo over P_2O_5 to give pure **1**.

3.4.1. (2*S*,2′*S*)-2-(Tetrahydrofuran-2′-yl)glycine (1c). The title compound was prepared from **5c** in 41% overall yield (94 mg) as colourless crystals: mp 203–205 °C (dec.); $[\alpha]_D^{22} = -16.4$ ($c=0.53$, H_2O); purity 98% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μm), MeCN–H_2O 1:9, 1 mL/min]; ee 96% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μM), (1 mM $Cu(AcO)_2$+2 mM *N*,*N*-Me_2-*S*-Phe), pH=4];[12] ^{1}H NMR (400 MHz, D_2O) δ 1.69–1.75 (1H, m, 3-CH_a), 1.86–1.93 (3H, m, 3′-CH_b and 4′-CH_2), 3.72–3.76 (1H, m, 5′-CH_a), 3.82–3.87 (1H, m, 5′-CH_b), 3.93 (1H, d, J=4 Hz, 2-CH), 4.25–4.35 (1H, m, 2′-CH); ^{13}C NMR (100 MHz, D_2O) δ 25.1, 25.1, 56.3, 68.9, 76.5, 171.5. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.48; H, 7.52; N, 9.54.

3.4.2. (2*S*,2′*R*)-2-(Tetrahydrofuran-2′-yl)glycine (1d). The title compound was prepared from **5d** in 36% overall yield (83 mg) as colourless crystals: mp 213–215 °C (dec.); $[\alpha]_D^{22} = -36.7$ ($c=0.53$, H_2O); purity 97% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μm), MeCN–H_2O 1:9, 1 mL/min]; ee 98% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μM), (1 mM $Cu(AcO)_2$+2 mM *N*,*N*-Me_2-*S*-Phe), pH=4];[12] ^{1}H NMR (400 MHz, D_2O) δ 1.75–1.95 (3H, m, 3′-CH_a and 4′-CH_2), 2.05–2.15 (1H, m, 3′-CH_b), 3.62 (1H, d, J=6 Hz, 2-CH), 3.71–3.82 (2H, m, 5′-CH_2), 4.19 (1H, q, J=6.5 Hz, 2′-CH); ^{13}C NMR (100 MHz, D_2O) δ 25.0, 28.2, 57.5, 68.5, 77.0, 172.2. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.74; H, 7.72; N, 9.56.

3.4.3. (2*R*,2′*S*)-2-(Tetrahydrofuran-2′-yl)glycine (1a). The title compound was prepared from **5a** in 33% overall yield (76 mg) as colourless crystals; mp 208–210 °C (dec.); $[\alpha]_D^{22} = +16.2$ ($c=0.52$, H_2O); purity 98% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μm), MeCN–H_2O 1:9,

1 mL/min]; ee >99% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μM), (1 mM $Cu(AcO)_2$+2 mM *N*,*N*-Me_2-*S*-Phe), pH=4].[12]

3.4.4. (2*R*,2′*R*)-2-(Tetrahydrofuran-2′-yl)glycine (1b). The title compound was prepared from **5b** in 35% overall yield (81 mg) as colourless crystals: mp 214–216 °C (dec.); $[\alpha]_D^{22}=+33.6$ ($c=0.51$, H_2O); purity 97% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μm), MeCN–H_2O 1:9, 1 mL/min]; ee >99% [HPLC: Lichospher 100 RP18 (250×4.0 mm i.d., 5 μM), (1 mM $Cu(AcO)_2$+2 mM *N*,*N*-Me_2-*S*-Phe), pH=4].[12]

Acknowledgements

A.J. thanks Merz Pharmaceuticals GmbH for a post-doctoral fellowship.

References and notes

1. *Asymmetric Synthesis of Novel Sterically Constrained Amino Acids; Symposium-in Print*; Hruby, V. J., Soloshonok, V. A., Eds.; Tetrahedron; **2001**, 6329–6650.
2. (a) Pellicciari, R.; Curini, M.; Natalini, B.; Ceccherelli, P. IX International Symposium on Medicinal Chemistry, Berlin, **1986**, p 118. (b) Shimamoto, K.; Ohfune, Y. *J. Med. Chem.* **1996**, *39*, 407–423. (c) Pellicciari, R.; Luneia, R.; Costantino, G.; Marinozzi, M.; Natalini, B.; Jakobsen, P.; Kanstrup, A.; Lombardi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1995**, *38*, 3717–3719. (d) Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G. G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2874–2876.
3. (a) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300–2310. (b) Rajesh, S.; Ami, E.; Kotake, T.; Kimura, T.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3615–3617. (c) Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C.; Van Gunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904–7915. (d) Dubuisson, C.; Kukumoto, Y.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3697–3704.
4. (a) Pellicciari, R.; Natalini, B.; Luneia, R.; Marinozzi, M.; Roberti, M.; Rosato, G.; Sadeghpour, B. M.; Snyder, J. P.; Monahan, J. B.; Moroni, F. *Med. Chem. Res.* **1992**, *2*, 491–494. (b) Marinozzi, M.; Pellicciari, R. *Tetrahedron Lett.* **2000**, *41*, 9125–9128. (c) Del Carmen Teran Moldes, M.; Costantino, G.; Marinozzi, M.; Pellicciari, R. *Il Farmaco* **2001**, *56*, 609–613.
5. (a) Ben-Ishal, D.; Sataty, I.; Bernstein, Z. *Tetrahedron* **1976**, *32*, 1571–1573. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547–1557. (c) Janusz, J. M.; Young, P. A.; Blum, R. B.; Riley, C. M. *J. Med. Chem.* **1990**, *33*, 1676–1682.
6. Viti, G.; Perrotta, E.; Giannotti, D.; Nannicini, R. *Tetrahedron* **1999**, *53*, 8519–8530.
7. Kazmaier, U.; Pähler, S.; Endermann, R.; Häbich, D.; Kroll, H.-P.; Riedl, B. *Bioorg. Med. Chem.* **2002**, *10*, 3905–3913.
8. Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843–3846.
9. Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798–806.
10. Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18–28.
11. Paquette, L. A.; Ohmuri, N.; Lowinger, T. B.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 4303–4308.
12. Natalini, B.; Marinozzi, M.; Sardella, R.; Macchiarulo, A.; Pellicciari, R. *J. Chromatogr. A* **2004**, *1033*, 363–367.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 379–384

Dimethylzinc-initiated radical reaction of cyclic ethers with arylamines, alkoxyamines, and dialkylhydrazines

Yasutomo Yamamoto, Masaru Maekawa, Tito Akindele, Ken-ichi Yamada and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received 14 October 2004; revised 27 October 2004; accepted 28 October 2004

Available online 18 November 2004

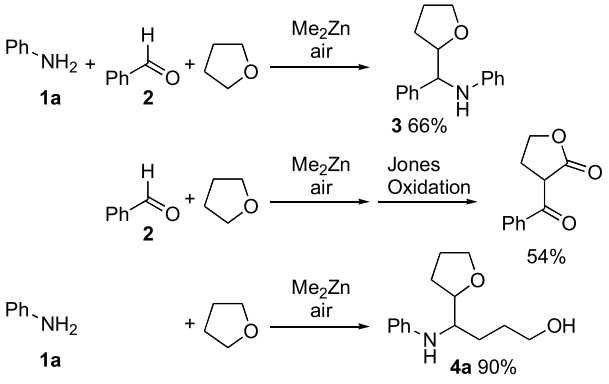
Abstract—Dimethylzinc-initiated radical reaction of THF with arylamines afforded aminoalcohols which were derived from the two molecules of THF and one molecule of an arylamine. The reaction seems to proceed via two-consecutive processes, electrophilic and then nucleophilic reactions of THF-derived species. Alkoxyamines and dialkylhydrazines reacted with electrophilic cyclic ether species to give the corresponding oximes and hydrazones of ω-hydroxyalkanal.

1. Introduction

It is well recognized that one-pot, consecutive reactions are powerful and green methodologies for multi-bonds forming reactions. A highly valued example of these processes is the tandem conjugate addition–alkylation reaction of metallated nucleophiles with α,β-unsaturated carbonyl compounds and their equivalents which play a dual role as an electrophile in the first step and as a nucleophile in the alkylation step.[1] We describe herein a dual role of THF as an electrophile and as a nucleophile in the dimethylzinc-initiated radical reaction with arylamines. Two THF molecules reacted with one molecule of arylamines to afford amino alcohols through the consecutive electrophilic amination to give aminals and then a nucleophilic radical addition to the resulting imines. Alkoxyamines and dialkylhydrazines reacted with cyclic ethers to afford the corresponding oximes and hydrazones.

2. Results and discussion

These reactions were discovered during our studies on the reaction of ether radicals generated from dimethylzinc–air.[2] We have already reported that THF radical chemoselectively reacted with the imine generated in situ in the three-component reaction of THF, aniline **1a** and benzaldehyde **2** (Scheme 1).[3] Further studies revealed that two-component reaction of benzaldehyde **2** and THF gave



Scheme 1. The reaction of THF with aniline **1a** and/or benzaldehyde **2**.

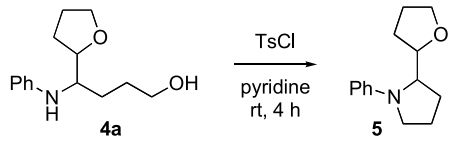
unexpected THF β-adduct.[4] This interesting result led us to investigate the reaction of aniline **1a** with THF. The reaction of **1a** (1 mmol) in THF (22 mL) was conducted at room temperature (rt) for 13 h with dimethylzinc (12 mmol) under continuous air stream (0.5 mL/h) to give **4a** in 90% yield.[5]

A ca 1:1 mixture of diastereomeric alcohols **4a** was separated by silica gel column chromatography to give each diastereomer. The diastereomers were then separately converted to pyrrolidines **5** in high yields through treatment with tosyl chloride in pyridine (Scheme 2).

Various arylamines **1** bearing electron-donating and withdrawing substituents on the aryl ring were compatible with **1a**. 4-Toluidine **1b**, *p*-anisidine **1c**, and 4-chloroaniline **1e** gave **4b**, **4c**, and **4e** in 90, 73, and 87% yields, respectively

Keywords: Radical reaction; Cyclic ethers; Amines; Oximes; Hydrazones.
* Corresponding author. Tel.: +81 757534553; fax: +81 757534604; e-mail: tomioka@pharm.kyoto-u.ac.jp

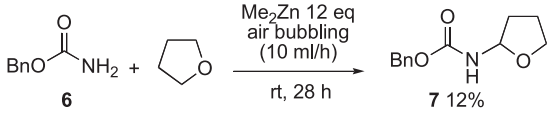
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.080



Scheme 2. Conversion of **4a** to bicyclic pyrrolidine **5**.

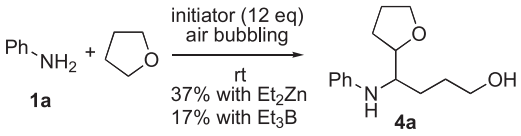
(Table 1, entries 2, 3, and 5). *o*-Anisidine **1d** reacted more slowly, probably due to the *ortho*-substitution, to give **4d** in 58% yield (entry 4). Amine **1f** with the much more electron-withdrawing 4-trifluoromethyl group reacted sluggishly to give **4f** in 36% yield (entry 6). Diphenylamine **1g** failed to react with THF, resulting in the recovery of **1g** (entry 7).[6]

The dependency of the reaction on the electronic nature of arylamines suggested the nucleophilic attack of arylamines to electrophilic THF species as the first step of the reaction. Thus, the reaction of benzyl carbamate **6** did not give the expected two-THF adduct, instead one-THF adduct **7**[7] was produced in 12% yield, apparently indicating that the nucleophilicity of nitrogen is critical in the first step and its electron donating nature to generate C=N double bond in the second step (Scheme 3).



Scheme 3. The reaction of benzyl carbamate **6** with THF giving **7**.

Radical initiator, dimethylzinc, is also critical to the reaction. For example, the reaction with diethylzinc,[2] in place of dimethylzinc, gave aminoalcohol **4a** in 37% yield after 75 h reaction time at rt. Triethylborane[8] gave **4a** in 17% yield after 48 h (Scheme 4).

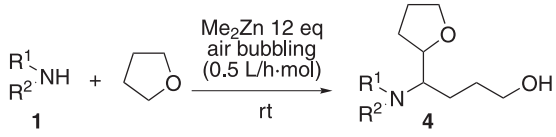


Scheme 4. Diethylzinc and triethylborane-initiated reaction of **1a** giving **4a**.

The reaction of cyclic ethers with alkoxyamines **8** and dialkylhydrazines **9** gave *O*-alkyloximes **10** and hydrazones **11** by the one-THF reaction (Table 2). The reaction of methoxyamine **8a** and benzyloxyamine **8b** with THF gave **10a** and **10b** in 77 and 90% yields, respectively (entries 1 and 2). Cyclic ethers of 4-, 6- and 7-membered rings are also good partners of the reaction with **8b** to give **10c**, **10d**, and **10e** in 45, 80, and 72% yields, respectively (entries 3–5). The reaction of *N*,*N*-diphenyl- and *N*,*N*-dimethylhydrazines **9a** and **9b** with THF gave the corresponding hydrazones **11a** and **11b** in moderate yields also by the one-THF reaction (entries 6 and 7). Treatment of *O*-benzyl-oxime **10b** with THF under the radical reaction conditions recovered **10b** unchanged, indicating poorer reactivity of oxime C=N double bond in the present conditions.

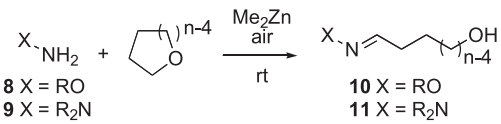
The reaction of **1a** with tetrahydropyran (THP) provided a

Table 1. Dimethylzinc-mediated reaction of **1** with THF



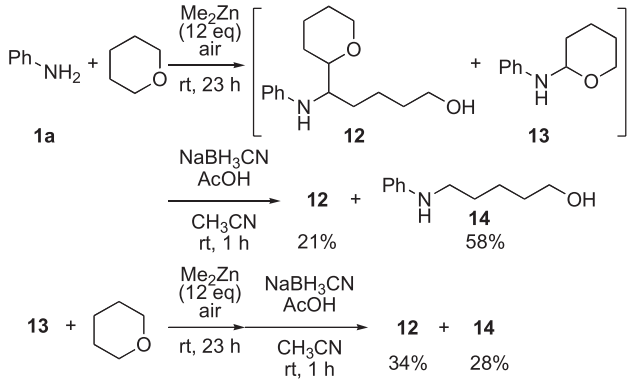
Entry	1	R^1	R^2	Time (h)	4	Yield (%)
1	**1a**	Ph	H	13	**4a**	90
2	**1b**	4-MeC_6H_4	H	20	**4b**	90
3	**1c**	4-$MeOC_6H_4$	H	26	**4c**	73
4	**1d**	2-$MeOC_6H_4$	H	24	**4d**	58
5	**1e**	4-ClC_6H_4	H	20	**4e**	87
6	**1f**	4-$CF_3C_6H_4$	H	15	**4f**	36
7	**1g**	Ph	Ph	72	**4g**	0

Table 2. The reaction of alkoxyamines **8** and hydrazines **9** with cyclic ethers



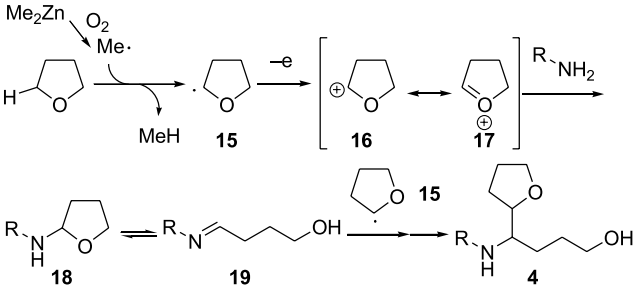
Entry	8/9	X	*n*	Me_2Zn (equiv)	Time (h)	10/11	Yield (%)
1	**8a**	MeO	5	12	120	**10a**	77
2	**8b**	BnO	5	12	18	**10b**	90
3	**8b**	BnO	4	12	20	**10c**	45
4	**8b**	BnO	6	18	70	**10d**	80
5	**8b**	BnO	7	12	22	**10e**	72
6	**9a**	Ph_2N	5	24	120	**11a**	33
7	**9b**	Me_2N	5	12	24	**11b**	42

clue to a mechanistic aspect. The reaction mixture containing aminoalcohol **12** and aminal **13** was treated with sodium cyanoborohydride to give **12** in 21% yield along with **14** in 58% yield (Scheme 5). The reaction of **13**[9] with THP under the same radical conditions as the reaction of **1a** with THP gave, after reduction, **12** in 34% yield and **14** in 28% yield. These results indicated that aminal intermediate **13** is involved in the reaction of arylamines **1** with cyclic ethers.



Scheme 5. Reaction of **1a** with THP giving **12**–**14**.

Based on the results above, a plausible mechanism is shown in Scheme 6. In the first step of the THF reaction, α-alkoxyalkyl radical **15**, generated by α-hydrogen atom abstraction by a methyl radical, undergoes further oxidation to an electrophilic α-alkoxyalkyl cation[10,11] **16** and **17** which is nucleophilically attacked by an amine nitrogen **1**, **6**, **8**, and **9** to give aminal **18**.[12] If the electron-donating power of the nitrogen atom of **18** is high enough, imine **19** is formed, which in turn accepts nucleophilic attack by **15** to complete the second step.[13] The reaction of benzyl carbamate **6** stops at the first step to produce **7** due to the delocalization of nitrogen lone pair electron with a carbonyl group. The reactions of alkoxyamines **8** and hydrazines **9** also stop at the first step due to the poor reactivity of C=N double bonds of oximes **10** and hydrazones **11** in the present conditions.[14]



Scheme 6. Plausible mechanism of the reaction of amines with ethers.

3. Conclusion

We have found one-pot, two-consecutive reaction of arylamines with dimethylzinc-generated cyclic ether radicals.[15] It is highly probable that the polarity reversal of α-alkoxyalkyl radicals by one electron oxidation is involved.

4. Experimental

4.1. General

^{1}H- and ^{13}C NMR spectra were taken in $CDCl_3$. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Coupling constants *J* values are presented in Hz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectroscopy of oil sample was measured as neat liquid film. The wave-numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. MS (EI) is presented in *m/z*. Extracts were washed with brine and then dried over sodium sulfate. Silica gel column chromatography was used for purification.

4.2. Typical procedure for the reaction of an amine with THF

To a solution of an amine (1 mmol) in THF (22 mL, 0.27 mol) was added the indicated amount of dimethylzinc (1.0 M solution in hexane) at rt. The reaction mixture was stirred at rt with continuous air bubbling (flow rate; 0.5 mL/h). After the indicated period, saturated aqueous $NaHCO_3$ was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate three times. After concentration the crude mixture was purified by column chromatography.

4.2.1. 4-(Oxolan-2-yl)-4-(phenylamino)butan-1-ol (4a) (Table 1, entry 1). A 1:1 diastereomer mixture was separated by chromatography ($CHCl_3$/EtOAc=2/1). The less polar isomer (**4a-1**) as a pale yellow oil. ^{1}H NMR: 1.60–1.85 (m, 8H), 3.40–3.50 (m, 1H), 3.57–3.59 (m, 2H), 3.72–3.76 (m, 1H), 3.86–3.89 (m, 1H), 3.98–3.99 (m, 1H), 6.58 (d, *J*=7.7 Hz, 2H), 6.63 (t, *J*=7.4 Hz, 1H), 7.11–7.13 (m, 2H). ^{13}C NMR: 26.0, 28.0, 29.3, 29.4, 55.0, 62.6, 68.6, 80.7, 112.7, 116.7, 129.2, 148.3. IR: 3390, 1600, 1500, 1060. MS: 235 (M^+), 164 ($M^+-C_4H_7O$), 71 (C_4H_7O). HRMS: calcd for $C_{14}H_{21}NO_2$, 235.1572; found, 235.1569. The more polar isomer (**4a-2**) as a pale yellow oil. ^{1}H NMR: 1.40–1.95 (m, 8H), 3.07 (brs, 2H), 3.39–3.43 (m, 1H), 3.56–3.59 (m, 2H), 3.68–3.72 (m, 1H), 3.79–3.89 (m, 2H), 6.61–6.67 (m, 3H), 7.11–7.14 (m, 2H). ^{13}C NMR: 25.7, 28.0, 28.1, 29.2, 56.6, 62.5, 68.2, 81.5, 113.3, 117.0, 129.1, 148.0. IR: 3360, 1600, 1500, 1060. MS: 235 (M^+), 164 ($M^+-C_4H_7O$), 71 (C_4H_7O). HRMS: calcd for $C_{14}H_{21}NO_2$, 235.1572; found, 235.1573.

4.2.2. Cyclization of aminoalcohol 4a (Scheme 2). To a solution of **4a-2** (7.1 mg, 0.03 mmol) in pyridine (0.03 mL) was added TsCl (10.3 mg, 0.054 mmol) at rt. After the reaction mixture was stirred at rt for 4 h, 10% aqueous NaOH (0.5 mL) was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with diethyl ether three times. After concentration the crude mixture was purified by chromatography (hexane/Et_2O=5/1) to afford **5-2** as a pale yellow oil (6.6 mg, quant). ^{1}H NMR: 1.60–1.70 (m, 1H), 1.80–2.05 (m, 6H), 2.10–2.20 (m, 1H), 3.13–3.18 (m, 1H), 3.54 (ddd, *J*=1.8, 8.9, 8.9 Hz, 1H), 3.70–3.74 (m, 1H), 3.82–3.86 (m, 1H), 3.91–3.93 (m, 1H), 4.09 (ddd, *J*=3.0, 6.7, 8.8 Hz, 1H), 6.65–6.70 (m, 3H), 7.19–7.22 (m, 2H). ^{13}C NMR: 24.0, 25.9, 27.1, 28.5, 49.6, 61.1, 68.3, 80.8, 112.4, 115.7, 129.0, 148.1. IR: 1600, 1500,

1070. MS: 217 (M^+), 146 ($M^+-C_4H_7O$), 77 (Ph). HRMS: calcd for $C_{14}H_{19}NO$, 217.1467; found, 217.1462.

The other isomer **4a-1** was converted to **5-1** as a pale yellow oil in 89% yield. ^{1}H NMR: 1.56–1.64 (m, 1H), 1.82–2.10 (m, 7H), 3.13–3.18 (m, 1H), 3.52–3.56 (m, 1H), 3.72–3.77 (m, 1H), 3.89–3.93 (m, 2H), 4.02 (ddd, J=5.9, 5.9, 8.5 Hz, 1H), 6.67–6.77 (m, 3H), 7.19–7.22 (m, 2H). ^{13}C NMR: 24.2, 26.0, 27.7, 28.1, 49.7, 61.6, 68.1, 81.3, 112.7, 116.0, 128.8, 148.7. IR: 1600, 1500, 1070. MS: 217 (M^+), 146 ($M^+-C_4H_7O$), 77 (Ph). HRMS: calcd for $C_{14}H_{19}NO$, 217.1467; found, 217.1472.

4.2.3. 4-(4-Methylphenylamino)-4-(oxolan-2-yl)butan-1-ol (4b) (Table 1, entry 2). A 1:1 diastereomer mixture was separated by chromatography ($CHCl_3$/EtOAc=2/1). The less polar isomer as a pale yellow oil. ^{1}H NMR: 1.60–1.89 (m, 8H), 2.21 (s, 3H), 2.80 (brs, 2H), 3.41–3.44 (m, 1H), 3.59–3.62 (m, 2H), 3.73–3.77 (m, 1H), 3.86–3.91 (m, 1H), 3.98–4.01 (m, 1H), 6.52 (d, J=8.3 Hz, 2H), 6.95 (d, J=8.3 Hz, 2H). ^{13}C NMR: 20.2, 26.0, 27.8, 29.45, 29.51, 55.5, 62.8, 68.6, 80.7, 113.1, 126.1, 129.8, 146.1. IR: 3391, 1616, 1520, 1057. MS: 249 (M^+), 178 ($M^+-C_4H_7O$), 91 (tolyl), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{23}NO_2$, 249.1729; found, 249.1735. The more polar isomer as a pale yellow oil. ^{1}H NMR: 1.41–1.49 (m, 1H), 1.59–1.96 (m, 7H), 2.22 (s, 3H), 2.77 (brs, 2H), 3.36–3.39 (m, 1H), 3.58–3.65 (m, 2H), 3.69–3.73 (m, 1H), 3.81–3.90 (m, 2H), 6.57 (d, J=8.3 Hz, 2H), 6.96 (d, J=8.3 Hz, 2H). ^{13}C NMR: 20.2, 25.8, 28.1, 28.2, 29.4, 57.2, 62.8, 68.3, 81.5, 113.8, 126.7, 129.8, 145.7. IR: 3387, 1616, 1520, 1061. MS: 249 (M^+), 178 ($M^+-C_4H_7O$), 91 (tolyl), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{23}NO_2$, 249.1729; found, 249.1724.

4.2.4. 4-(4-Methoxyphenylamino)-4-(oxolan-2-yl)butan-1-ol (4c) (Table 1, entry 3). A 1:1 mixture of diastereomers as a pale brown oil. ^{1}H NMR: 1.42–1.96 (m, 8H), 3.29–3.37 (m, 1H), 3.59–3.77 (m, 3H), 3.74 (s, 3H), 3.81–4.00 (m, 2H), 6.56–6.65 (m, 2H), 6.74–6.76 (m, 2H). ^{13}C NMR: 25.9, 26.1, 28.0, 28.1, 28.2, 29.4, 29.56, 29.60, 55.75, 55.78, 56.5, 58.4, 62.9 (overlap), 68.3, 68.6, 80.8, 81.2, 114.6, 114.9, 115.0, 115.6, 142.0, 142.5, 151.9, 152.4. IR: 3380, 1510, 1040. MS: 265 (M^+), 194 ($M^+-C_4H_7O$), 107 ($C_6H_4OCH_3$), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{23}NO_3$, 265.1678; found, 265.1671.

4.2.5. 4-(2-Methoxyphenylamino)-4-(oxolan-2-yl)butan-1-ol (4d) (Table 1, entry 4). A 56:44 mixture of diastereomers as a yellow oil. ^{1}H NMR: 1.47–1.99 (m, 8H), 3.42–3.50 (m, 1H), 3.61–3.64 (m, 2H), 3.71–3.93 (m, major 3H and minor 2H), 3.83 (s, 3H), 4.02–4.06 (m, minor 1H), 6.59–6.65 (m, major 1H and minor 2H), 6.69–6.71 (m, major 1H), 6.75–6.76 (m, 1H), 6.81–6.85 (m, 1H). ^{13}C NMR: 25.8, 26.1, 27.9, 28.3, 28.4, 29.2, 29.3, 29.6, 55.1, 55.4, 56.7, 62.9, 63.0, 68.3, 68.7, 80.8, 81.9, 109.66, 109.73, 109.8, 110.6, 115.8, 116.1, 121.23, 121.27, 138.0, 138.3, 146.7, 146.8. IR: 3422, 1601, 1516, 1460, 1246, 1223, 1053, 1030. MS: 265 (M^+), 194 ($M^+-C_4H_7O$), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{23}NO_3$, 265.1678; found, 265.1672.

4.2.6. 4-(4-Chlorophenylamino)-4-(oxolan-2-yl)butan-1-ol (4e) (Table 1, entry 5). A 1:1 diastereomer mixture was separated by chromatography ($CHCl_3$/EtOAc=1/1). The less polar isomer as a pale yellow oil. ^{1}H NMR: 1.60–1.75 (m, 5H), 1.84–1.92 (m, 3H), 3.40–3.43 (m, 1H), 3.63–3.65 (m, 2H), 3.74–3.78 (m, 1H), 3.87–3.91 (m, 1H), 3.96–4.00 (m, 1H), 6.52 (d, J=8.9 Hz, 2H), 7.08 (d, J=8.9 Hz, 2H). ^{13}C NMR: 26.0, 28.1, 29.3, 29.4, 55.4, 62.7, 68.7, 80.7, 113.9, 121.2, 129.1, 147.1. IR: 3371, 1601, 1504, 1057. MS: 269 (M^+), 198 ($M^+-C_4H_7O$), 111 (C_6H_4Cl), 71 (C_4H_7O). HRMS: calcd for $C_{14}H_{20}ClNO_2$, 269.1183; found, 269.1185. The more polar isomer as a pale yellow oil. ^{1}H NMR: 1.42–1.49 (m, 1H), 1.58–1.97 (m, 7H), 3.38–3.42 (m, 1H), 3.62–3.64 (m, 2H), 3.70–3.74 (m, 1H), 3.80–3.84 (m, 1H), 3.87–3.91 (m, 1H), 6.57 (d, J=8.9 Hz, 2H), 7.08 (d, J=8.9 Hz, 2H). ^{13}C NMR: 25.8, 27.95, 27.98, 29.2, 57.0, 62.7, 68.3, 81.5, 114.5, 121.7, 129.1, 146.8. IR: 3352, 1601, 1497, 1057. MS: 269 (M^+), 198 ($M^+-C_4H_7O$), 111 (C_6H_4Cl), 71 (C_4H_7O). HRMS: calcd for $C_{14}H_{20}ClNO_2$, 269.1183; found, 269.1179.

4.2.7. 4-(4-Trifluoromethylphenylamino)-4-(oxolan-2-yl)-butan-1-ol (4f) (Table 1, entry 6). A 3:2 diastereomer mixture was separated by chromatography. The major isomer as a yellow oil. ^{1}H NMR: 1.60–2.00 (m, 8H), 3.45–3.55 (m, 1H), 3.64 (t, J=5.6 Hz, 2H), 3.70–3.80 (m, 1H), 3.85–4.05 (m, 2H), 6.59 (d, J=8.6 Hz, 2H), 7.36 (d, J=8.6 Hz, 2H). ^{13}C NMR: 26.0, 28.3, 29.3, 29.7, 54.8, 62.8, 68.7, 80.7, 111.8, 116.8 (q, $^3J_{CF}$=34.0), 125.0 (q, $^1J_{CF}$=208), 126.7 (q, $^3J_{CF}$=3.0), 150.9. The minor isomer as a yellow oil. ^{1}H NMR: 1.40–2.00 (m, 8H), 3.45–3.55 (m, 1H), 3.63 (t, J=5.8 Hz, 2H), 3.70–4.00 (m, 3H), 6.64 (d, J=8.6 Hz, 2H), 7.36 (d, J=8.6 Hz, 2H). ^{13}C NMR: 25.8, 27.9, 28.0, 29.1, 56.1, 62.6, 68.3, 81.6, 112.2, 116.8 (q, $^3J_{CF}$=34.0), 125.0 (q, $^1J_{CF}$=208), 126.6 (q, $^3J_{CF}$=3.0), 150.7. IR and MS were measured as a mixture of diastereomers. IR: 3380, 1620, 1060. MS: 303 (M^+), 232 ($M^+-C_4H_7O$), 71 (C_4H_7O). HRMS: calcd for $C_{15}H_{20}F_3NO_2$, 303.1446; found, 303.1457.

4.2.8. 4-Hydroxybutanal *O*-methyloxime (10a) (Table 2, entry 1). A 3:2 mixture of *E*- and *Z*-isomer as a colorless oil. ^{1}H NMR *E*-isomer: 1.71–1.81 (m, 2H), 2.31 (dt, J=5.8 Hz, 7.3, 2H), 3.70 (t, J=6.1 Hz, 2H), 3.82 (s, 3H), 7.42 (t, J=5.8 Hz, 1H). *Z*-isomer: 1.71–1.81 (m, 2H), 2.43 (dt, J=6.1 Hz, 7.3, 2H), 3.65 (t, J=6.1 Hz, 2H), 3.88 (s, 3H), 6.70 (t, J=6.1 Hz, 1H). ^{13}C NMR: 21.9, 26.0, 28.8, 29.2, 61.1, 61.50, 61.53, 61.6, 150.5, 151.2. IR: 3391, 1636, 1053. MS: 117 (M^+). HRMS: calcd for $C_5H_{11}NO_2$, 117.0790; found, 117.0793.

4.2.9. 4-Hydroxybutanal *O*-benzyloxime (10b) (Table 2, entry 2). A 3:2 mixture of *E*- and *Z*-isomer as a colorless oil. ^{1}H NMR *E*-isomer: 1.55–1.65 (m, 1H), 1.71–1.80 (m, 2H), 2.31 (dt, J=6.1 Hz, 7.2, 2H), 3.61–3.68 (m, 2H), 5.05 (s, 2H), 7.27–7.36 (m, 5H), 7.50 (t, J=6.1 Hz, 1H). *Z*-isomer: 1.55–1.65 (m, 1H), 1.71–1.80 (m, 2H), 2.47 (dt, J=5.8 Hz, 7.3, 2H), 3.61–3.68 (m, 2H), 5.11 (s, 2H), 6.74 (t, J=5.8 Hz, 1H), 7.27–7.36 (m, 5H). ^{13}C NMR: 22.2, 26.2, 28.9, 29.1, 61.7, 61.8, 75.6, 75.8, 127.9, 128.1, 128.3, 128.42, 128.44, 137.6, 137.7, 151.1, 151.7. IR: 3391, 1632, 1454, 1369, 1042. MS: 193 (M^+), 149, 91 (benzyl), 77 (phenyl). HRMS: calcd for $C_{11}H_{15}NO_2$, 193.1103; found, 193.1107.

4.2.10. 3-Hydroxypropanal *O*-benzyloxime (10c) (Table 2, entry 3). A 4:1 mixture of *E*- and *Z*-isomer as a

colorless oil. ^{1}H NMR *E*-isomer: 2.40–2.43 (m, 2H), 3.74–3.90 (m, 2H), 5.06 (s, 2H), 7.25–7.36 (m, 5H), 7.52 (t, J=5.2 Hz, 1H). *Z*-isomer: 2.60–2.63 (m, 2H), 3.74–3.90 (m, 2H), 5.12 (s, 2H), 6.83 (t, J=5.5 Hz, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR: 29.4, 32.6, 59.4, 75.77, 75.83, 127.86, 127.96, 128.00, 128.3, 128.41, 128.44, 137.4, 137.8, 149.2. IR: 3379, 1632, 1454, 1369, 1049. MS: 179 (M^+), 162 (M^+-OH), 91 (benzyl), 77 (phenyl). HRMS: calcd for $C_{10}H_{13}NO_2$, 179.0946; found, 179.0943.

4.2.11. 5-Hydroxypentanal *O*-benzyloxime (10d) (Table 2, entry 4). A 16:9 mixture of *E*- and *Z*-isomer as a colorless oil. ^{1}H NMR *E*-isomer: 1.50–1.61 (m, 4H), 2.21–2.25 (m, 2H), 3.61–3.65 (m, 2H), 5.05 (s, 2H), 7.29–7.37 (m, 5H), 7.46 (t, J=6.1 Hz, 1H). *Z*-isomer: 1.50–1.61 (m, 4H), 2.40 (dt, J=5.5 Hz, 7.2, 2H), 3.61–3.65 (m, 2H), 5.10 (s, 2H), 6.69 (t, J=5.5 Hz, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR: 22.4, 22.6, 25.4, 29.1, 31.9, 32.1, 62.25, 62.30, 75.5, 75.7, 127.78, 127.85, 128.0, 128.3, 128.4, 137.6, 138.0, 151.3, 152.2. IR: 3379, 1632, 1454, 1369, 1049. MS: 207 (M^+), 190 (M^+-OH), 149, 91 (benzyl), 77 (phenyl). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.25; H, 8.30; N, 6.67.

4.2.12. 6-Hydroxyhexanal *O*-benzyloxime (10e) (Table 2, entry 5). A 3:1 mixture of *E*- and *Z*-isomer as a colorless oil. ^{1}H NMR *E*-isomer: 1.35–1.60 (m, 7H), 2.18–2.23 (m, 2H), 3.62 (t, J=6.6 Hz, 2H), 5.05 (s, 2H), 7.28–7.37 (m, 5H), 7.45 (t, J=6.1 Hz, 1H). *Z*-isomer: 1.35–1.60 (m, 7H), 2.38 (dt, J=5.5 Hz, 7.5, 2H), 3.62 (t, J=6.6 Hz, 2H), 5.10 (s, 2H), 6.68 (t, J=5.5 Hz, 1H), 7.28–7.37 (m, 5H). ^{13}C NMR: 25.1, 25.4, 25.7, 25.9, 26.3, 29.3, 32.3, 62.6, 75.5, 127.75, 127.82, 127.9, 128.2, 128.4, 137.7, 151.4, 152.3. IR: 3368, 1454, 1366, 1053, 1018. MS: 221 (M^+), 204 (M^+-OH), 149, 91 (benzyl), 77 (phenyl). HRMS: calcd for $C_{13}H_{19}NO_2$, 221.1416; found, 221.1411.

4.2.13. 4-Hydroxybutanal *N*,*N*-diphenylhydrazone (11a). *Z*-Isomer was obtained as a pale yellow oil. Spectral data were identical to those reported.[16]

4.2.14. 4-Hydroxybutanal *N*,*N*-dimethylhydrazone (11b) (Table 2, entry 7). *Z*-Isomer was obtained as a pale yellow oil. ^{1}H NMR: 1.77–1.82 (m, 2H), 2.36–2.40 (m, 2H), 2.73 (s, 6H), 3.68 (t, J=6.1 Hz, 2H), 6.72 (t, J=4.9 Hz, 1H). ^{13}C NMR: 29.8, 29.9, 43.2 (overlap), 62.1, 138.7. IR: 3375, 1610, 1470, 1447, 1254, 1142, 1038. MS: 130 (M^+). HRMS: calcd for $C_6H_{14}N_2O$, 130.1106; found, 130.1110.

4.2.15. 5-(Phenylamino)-5-(tetrahydro-2*H*-pyran-2-yl)pentan-1-ol (12) (Scheme 5). A 2:3 diastereomer mixture was separated by chromatography (benzen/EtOAc=4/1). The less polar isomer as a pale yellow oil. ^{1}H NMR: 1.35–1.75 (m, 11H), 1.75–1.90 (m, 1H), 3.28 (ddd, J=2.3, 6.5, 6.5 Hz, 1H), 3.35–3.50 (m, 2H), 3.62 (t, J=7.3 Hz, 2H), 3.90–4.10 (m, 1H), 6.57 (d, J=7.6 Hz, 2H), 6.62 (t, J=7.3 Hz, 1H), 7.10–7.20 (m, 2H). ^{13}C NMR: 22.8, 23.4, 26.1, 28.1, 31.7, 32.8, 56.6, 62.8, 68.8, 78.6, 112.6, 116.4, 129.3, 148.4. IR: 3400, 1500, 1080, 1050. MS: 263 (M^+), 178 ($M^+-C_5H_9O$), 85 (C_5H_9O). HRMS: calcd for $C_{16}H_{25}NO_2$, 263.1885; found, 263.1893. The more polar isomer as a pale yellow oil. ^{1}H NMR: 1.00–1.20 (m, 12H), 3.25–3.40 (m, 3H), 3.55–3.65 (m, 2H), 3.95–4.05 (m, 1H), 6.59 (d, J=7.9 Hz, 2H), 6.65 (t, J=7.3 Hz, 1H), 7.10–7.20 (m, 2H). ^{13}C NMR: 22.6, 23.6, 26.2, 28.7, 30.4, 32.8, 57.1, 62.8, 68.8, 80.1, 113.2, 116.9, 129.2, 148.2. IR: 3400, 1600, 1500, 1080, 1050. MS: 263 (M^+), 178 ($M^+-C_5H_9O$), 85 (C_5H_9O). HRMS: calcd for $C_{16}H_{25}NO_2$, 263.1885; found, 263.1888.

4.3. Reduction of aminal 12

To the mixture, obtained by the reaction of aniline (93.1 mg, 1.0 mmol) and THP (26 mL, 270 mmol), in CH_3CN (3.0 mL) was added sodium cyano-borohydride (94.3 mg, 1.5 mmol). After stirring for 15 min, acetic acid (0.06 mL) was added and the mixture was stirred for 1 h, and concentrated. The residue was dissolved in CH_2Cl_2, and was successively washed with 5% KOH and brine, dried over Na_2SO_4. Concentration and purification by column chromatography (hexane/EtOAC=4/3) afford **12** (55.5 mg, 21%) and **14**[17] (104.1 mg, 58%).

Acknowledgements

This research was partially supported by the 21st Century COE (Center of excellence) Program 'Knowledge Information Infrastructure for Genome Science', a Grant-in-Aid for Young Scientists (B) and a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. Examples from our laboratories: (a) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199–8203. (b) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 6979–6982. (c) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303–1312.
2. (a) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Chen, J.-b.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595–6597. (b) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531–1534. (c) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509–3511.
3. Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797–1799.
4. Yamamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 797–799.
5. The three-component reaction[3] of aniline **1a**, benzaldehyde **2** and THF gave **4a** in 26% yield.
6. The reaction of *n*-butylamine or 2-phenylethylamine gave complex mixture, and **4** was not obtained.
7. Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477–480.
8. (a) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 7548–7550. (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625–627. (c) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745–1746.
9. Prepared by the reported procedure: Cheng, X.; Hii, K. K. *Tetrahedron* **2001**, *57*, 5445–5450.

10. Generation of α-alkoxyalkyl cation from α-alkoxyalkyl radicals and reaction with alcohols: (a) Ochiai, M.; Tsuchimoto, Y.; Hayashi, T. *Tetrahedron Lett.* **2003**, *44*, 5381–5384. (b) Barks, J. M.; Gilbert, B. C.; Parsons, A. F.; Upeandran, B. *Tetrahedron Lett.* **2000**, *41*, 6249–6252. (c) Eikawa, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1999**, *64*, 4676–4679.
11. Reaction of α-alkoxyalkyl cation with water: Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron* **2001**, *57*, 10319–10328.
12. Formation of aminals through anodic oxidation of THF and aminyl anions: Fuchigami, T.; Sato, T.; Nonaka, T. *J. Org. Chem.* **1986**, *51*, 366–369.
13. Formation of zinc alkoxide and amide of **18** and **19** is possible event.
14. Generally, oximes and hydrazones are known to be good radical acceptors: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461–5496.
15. Recently reported impressive α-alkoxyalkyl radical reactions: (a) Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461–2464. (b) Tsujimoto, S.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 5601–5604. (c) Hirano, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2002**, *43*, 3617–3620. (d) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985–1987. (e) Kim, S.; Kim, N.; Chung, W.-J.; Cho, C. H. *Synlett* **2001**, 937–940. (f) Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2457–2458. (g) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 613–615.
16. Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580–3581.
17. Abbenhuis, R. A. T. M.; Boersma, J.; Van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282–4290.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 385–393

Synthesis of α,α-disubstituted amino acids based on tandem reaction of dehydroamino acid derivatives

Hideto Miyabe, Ryuta Asada and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Received 24 September 2004; accepted 28 October 2004

Abstract—The formation of all-substituted sp^3-hybridized carbon-center was investigated via tandem reaction of dehydroamino acid derivatives. The diethylzinc-promoted reaction of dehydroamino acid derivatives with acid anhydride or π-allyl palladium complex proceeded smoothly to afford α,α-disubstituted amino acids via a radical and anionic carbon–carbon bond-forming processes. The tandem reductive reaction of *N*-phthaloyl dehydroalanine also proceeded effectively by using Bu_3SnH and $Pd(PPh_3)_4$.

1. Introduction

Non-proteinogenic α,α-disubstituted amino acids, which restrict the conformational flexibility of the peptide, have been attracting considerable attention in view of their biological and medicinal properties.[1] Therefore, the development of efficient methods for preparing all-substituted sp^3-hybridized carbon-center has become a great importance.[1] Diphenylimino glycinate **1** is an useful anionic synthon for the synthesis of α-monosubstituted amino acids, and extensive synthetic studies on the α-alkylation of **1** have been conducted (Fig. 1).[2] In contrast, the difficulty of achieving the α-alkylation of α-substituted diphenylimino esters **2** has remained unsolved due to poor acidic property of α-hydrogen atom of **2**.[3] As an alternative approach to α-substituted enolate anion **A**, we have studied the tandem reaction of dehydroamino acid derivative **3**, providing a new and efficient method for the synthesis of α,α-disubstituted amino acids.[4]

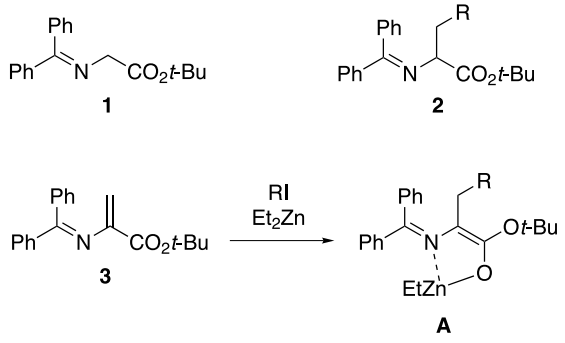


Figure 1. Anionic synthon for the synthesis of amino acids.

Multiple carbon–carbon bond formation based on tandem radical reaction is of great significance from economical and ecological points of view. In recent years, numerous radical methodologies have been reported.[5,6] However, tandem radical and anionic reactions are not well explored. Oshima's group has demonstrated that tandem radical addition-aldol condensations of enones or enals could be performed by Et_3B as a radical initiator.[7] Recently, some tandem radical and anionic reactions have been achieved.[8] Dehydroamino acid derivatives are well known to be excellent radical acceptors.[9] We report here in detail the synthesis of α,α-disubstituted amino acids based on the tandem radical and anionic reactions of dehydroamino acid derivative **3**.[4] We also report the reductive reaction of *N*-phthaloyl dehydroalanine using Bu_3SnH and $Pd(PPh_3)_4$.

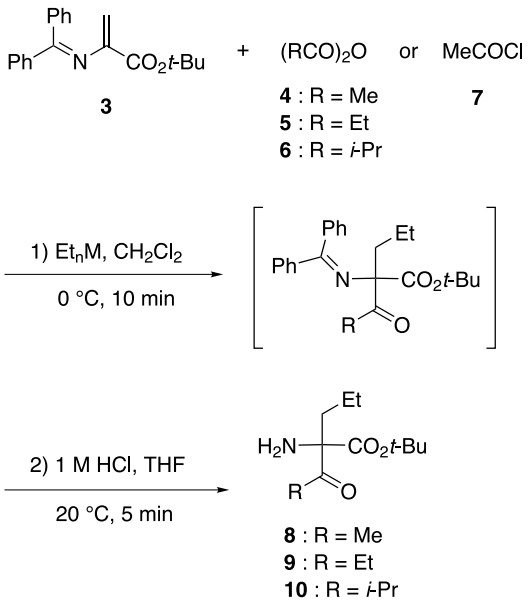
2. Results and discussion

2.1. Free radical-mediated tandem reaction of dehydroamino acid derivative 3

At first, we investigated the formation of α-substituted enolate anion **A** from dehydroamino acid derivative **3** by using acid anhydrides as electrophiles (Scheme 1). The radical initiators of choice were Et_2Zn and Et_2B because of the exceptional tolerance of other functional groups.[5,6] To a

Keywords: Radical; Palladium; Tandem; Dehydroamino acids; Amino acids.
* Corresponding author. Tel.: +81 075 753 4610; fax: +81 075 753 4569; e-mail: takemoto@pharm.kyoto-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.104



Scheme 1.

not proceed when Et_3B was employed as an ethyl radical source (entry 2). The failure of reaction with Et_3B may be attributed due to the low reactivity of Et_3B toward the radical α to an ester group.[12] Therefore, the reaction of **3** having an α,β-unsaturated ester moiety did not proceed when Et_3B was employed as an ethyl radical source. The tandem reaction with acid anhydrides **5** and **6** gave the products **9** and **10** by using Et_2Zn (entries 3 and 4). In addition, acetyl chloride **7** also worked well under the similar reaction conditions (entry 5).

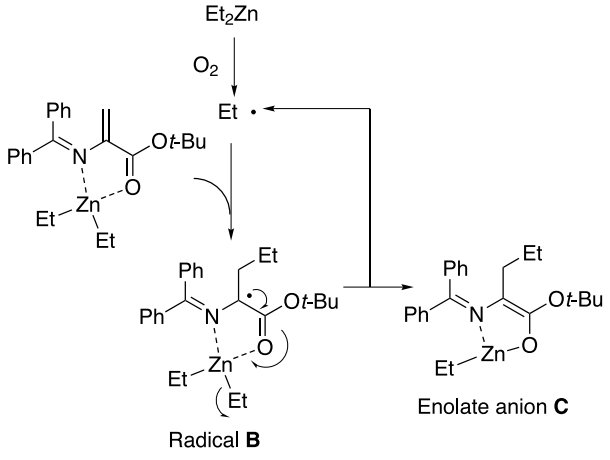
As a major reaction pathway, the α-substituted zinc-enolate anion **C** would be generated via the oxgen-initiated radical mechanism as shown in Scheme 2.[13] Initially, an ethyl radical was generated from Et_2Zn and O_2, and then, the ethyl radical added to dehydroamino acid **3** to give the intermediate radical **B**. In this reaction, Et_2Zn acted as an effective reagent for trapping the intermediate radical **B** to give the zinc-enolate anion **C** and an ethyl radical. Recently, the formation of zinc enolates from α,β-unsaturated esters in diethylzinc-mediated radical reactions was reported by Bertrand's group.[8b]

Table 1. Tandem reaction of dehydroamino acid derivative **3**[a]

Entry	Et_nM	Reagent	Product	Yield (%)[b]
1	Et_2Zn	**4**	**8**	63
2	Et_3B	**4**		No detection
3	Et_2Zn	**5**	**9**	43
4	Et_2Zn	**6**	**10**	41
5	Et_2Zn	**7**	**8**	56

[a] Reactions were carried out with **3** (1 equiv), **4**–**7** (1.2 equiv) and Et_2Zn (1.5 equiv) in CH_2Cl_2.
[b] Isolated yields after hydrolysis of diphenylimino group.

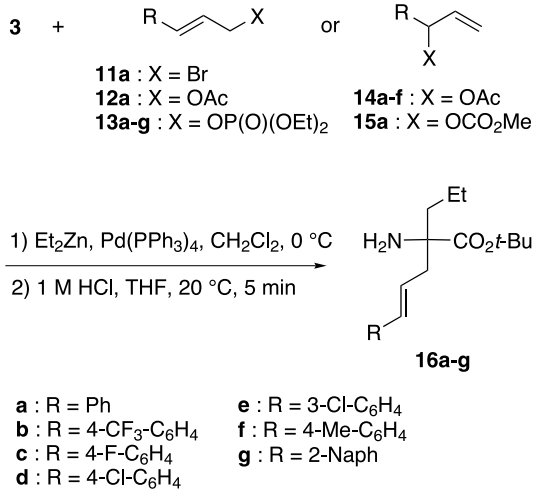
solution of dehydroamino acid derivative **3** and acetic anhydride **4** (1.2 equiv) in CH_2Cl_2 was added a 1.0 M solution of Et_2Zn in hexane (1.5 equiv) at 0 °C (Table 1, entry 1). As expected, dehydroamino acid derivative **3** exhibited a good reactivity toward Et_2Zn to give the desired α,α-disubstituted amino acid **8** in 63% yield, after hydrolysis of diphenylimino moiety. A trace amount of O_2 was an essential source for successful reaction.[10,11] Thus, the reaction was carried out by using undegassed dry solvent under Ar. In marked contrast, the tandem reaction of **3** did



Scheme 2.

2.2. Combination of radical reaction and transition metal-catalyzed reaction

On the basis of tandem acylation reaction, we next investigated the tandem allylation reaction of **3** by using different types of electrophiles **11a**–**15a** (Scheme 3). In the absence of palladium catalyst, the diethylzinc-promoted reaction of **3** with cinnamyl bromide **11a** did not give the allylated product **16a** (Table 2, entry 1). The electrophilic



Scheme 3.

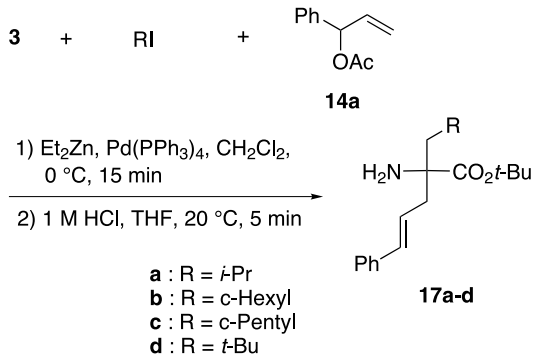
Table 2. Tandem palladium-catalyzed reaction of **3** with **11a–15a**[a]

Entry	Et_nM	Catalyst	Reagent	Time (min)	Product	Yield (%)[b]
1	Et_2Zn	None	**11a**	60	**16a**	No detection
2	Et_2Zn	$Pd(PPh_3)_4$	**11a**	60	**16a**	29
3	Et_2Zn	$Pd(PPh_3)_4$	**12a**	20	**16a**	54
4	Et_2Zn	$Pd(PPh_3)_4$	**13a**	20	**16a**	61
5	Et_2Zn	$Pd(PPh_3)_4$	**14a**	20	**16a**	59
6	Et_2Zn	$Pd(PPh_3)_4$	**15a**	20	**16a**	45
7	Et_3B	$Pd(PPh_3)$	**13a**	60		No detection
8	Et_3B	$Pd(PPh_3)_4$	**14a**	60		No detection
9	Et_2Zn	$Pd(PPh_3)_4$	**13b**	20	**16b**	40
10	Et_2Zn	$Pd(PPh_3)_4$	**13c**	20	**16c**	51
11	Et_2Zn	$Pd(PPh_3)_4$	**13d**	20	**16d**	61
12	Et_2Zn	$Pd(PPh_3)_4$	**13e**	20	**16e**	56
13	Et_2Zn	$Pd(PPh_3)_4$	**13f**	20	**16f**	47
14	Et_2Zn	$Pd(PPh_3)_4$	**13g**	20	**16g**	46
15	Et_2Zn	$Pd(PPh_3)_4$	**14d**	20	**16d**	68
16	Et_2Zn	$Pd(PPh_3)_4$	**14e**	20	**16e**	46
17	Et_2Zn	$Pd(PPh_3)_4$	**14f**	20	**16f**	41

[a] Reactions were carried out with **3** (1 equiv), **11a–15a** (1.5 equiv), and Et_2Zn (1.5 equiv) in the presence of $Pd(PPh_3)_4$ (0.15 equiv).
[b] Isolated yields after hydrolysis of diphenylimino group.

π-allyl palladium complex has shown excellent reactivity toward soft carbanions. Thus, we next studied the diethylzinc-promoted reaction of **3** with π-allyl palladium complex.[14] To a solution of dehydroamino acid derivative **3**, cinnamyl bromide **11a**, and $Pd(PPh_3)_4$ (0.15 equiv) in CH_2Cl_2 was added Et_2Zn at 0 °C, and then the reaction mixture was stirred for 60 min (entry 2). As expected, the formation of the allylated product **16a** was observed in the presence of $Pd(PPh_3)_4$, after hydrolysis of diphenylimino moiety. To see the effect of allylic reagents, we investigated the reactions with precursors **12a–15a**. Among them, phosphate **13a** and branched acetate **14a** were found to be effective for tandem allylation reaction of **3** (entries 3–6). The reaction of **3** with phosphate **13a** proceeded smoothly in the presence of $Pd(PPh_3)_4$ to give the allylated product **16a** in 61% yield, after being stirred at 0 °C for only 20 min (entry 4). The reaction with the branched acetate **14a** also gave the product **16a** in 59% yield, after hydrolysis of diphenylimino moiety (entry 5). The tandem allylation reaction of **3** did not proceed when Et_3B was employed as an ethyl radical source (entries 7 and 8). The tandem reaction of **3** was performed with other π-allyl palladium complexes (entries 9–17). The reactions of **3** with aromatic allylic phosphates **13b–g** and branched acetates **14d–f** were carried out in the presence of $Pd(PPh_3)_4$ (0.15 equiv). As expected, the tandem allylation reaction proceeded smoothly to give the α,α-disubstituted amino acids **16b–g**, allowing facile incorporation of structural variety. The present reaction is the first example of a combination of radical reaction and transition metal-catalyzed allylation in tandem carbon–carbon bond-forming process.

With the optimal allylic reagent **14a**, three-component reaction using several radical precursors (RI) was examined (Scheme 4). The isopropylated amino acid derivative **17a** was obtained in 56% yield by using *i*-PrI (Table 3, entry 1). Other secondary alkyl radical precursors such as *c*-pentyl-I and *c*-hexyl-I worked well to give the desired products **17b–c** (Table 3, entries 2 and 3). The reaction with a bulky *tert*-butyl radical also gave the allylated amino acid **17d** in 30% yield (entry 4). These results supported the radical mechanism. A favorable experimental feature of this radical method is that the reaction proceeded smoothly even in the absence of toxic tin hydride or heavy metals via the iodine atom-transfer radical process as shown in Scheme 5.



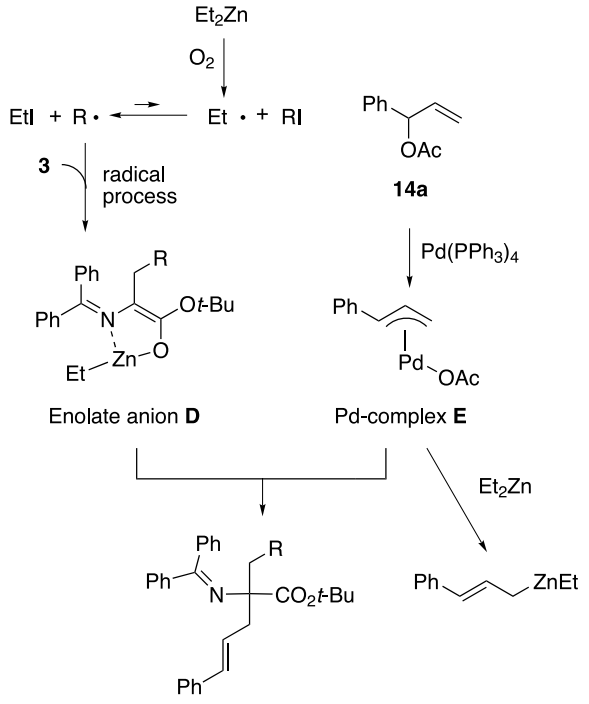
Scheme 4.

Table 3. Tandem palladium-catalyzed reaction of **3** with **14a** and RI[a]

Entry	RI	Product	Yield (%)[b]
1	*i*-PrI	**17a**	56
2	c-Hexyl I	**17b**	56
3	c-Pentyl I	**17c**	58
4	*t*-Bu I	**17d**	30

[a] Reactions were carried out with **3** (1 equiv), **14a** (2.0 equiv), RI (30 equiv), and Et_2Zn (3.0 equiv) in the presence of $Pd(PPh_3)_4$ (0.3 equiv).
[b] Isolated yields after hydrolysis of diphenylimino group.

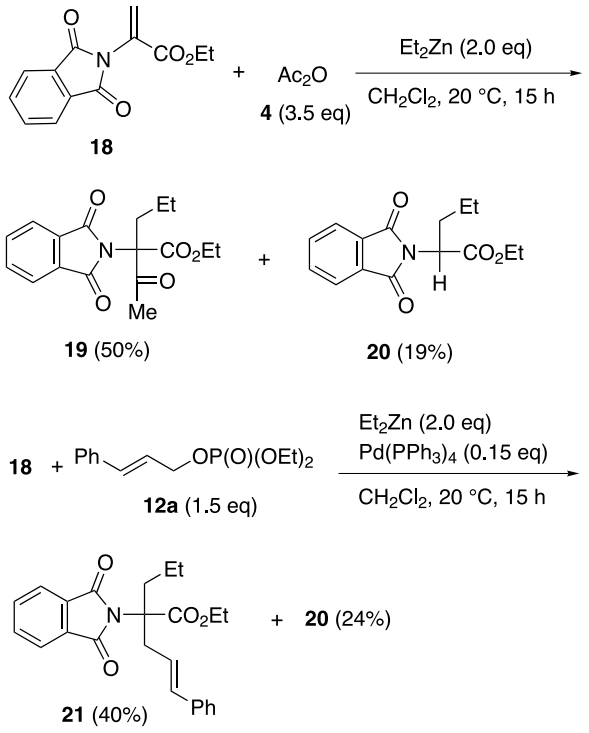
The following points should be noted for the success of the present tandem allylation: (I) a high reactivity of Et_2Zn as a radical initiator, (II) an excellent intermolecular reactivity of dehydroamino acid derivative **3** as a radical acceptor, and (III) a high reactivity of Et_2Zn as a trapping reagent toward the alkoxycarbonyl-stabilized α-radical **B** (Scheme 2). The reactivity of dehydroamino acid derivative **3** toward Et_2Zn is also important, because the reaction of electrophilic π-allyl palladium complex **E** with Et_2Zn could give the allyl zinc reagent as a by-product (Scheme 5).[15]



Scheme 5.

2.3. Reaction of *N*-phthaloyl dehydroalanine and its application to tandem reductive reaction

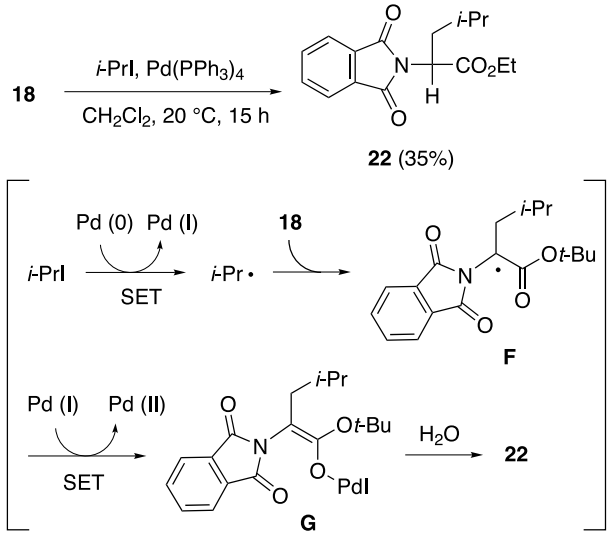
In the case of dehydroamino acid derivative **3**, it was assumed that a stable 5-membered zinc-enolate anion **D** is formed as a result of the coordination with nitrogen atom of diphenylimino group. We next investigated the reaction of *N*-phthaloyl dehydroalanine **18**,[9b,d] which would not give the stable coordinating zinc-enolate anion (Scheme 6). We expected that the direct comparison of **3** with **18** would lead to informative and instructive suggestions regarding the combination of radical reaction and transition metal-catalyzed allylation.



Scheme 6.

The diethylzinc-promoted reaction of *N*-phthaloyl dehydroalanine **18** was investigated by using acetic anhydride as an electrophile. In marked contrast to the excellent reactivity of dehydroamino acid derivative **3**, the tandem acylation reaction of **18** proceeded slowly to give the desired product **19** in 50% yield, accompanied with a 19% yield of the protonated product **20**, after being stirred at 20 °C for 15 h. The tandem allylation reaction of **18** with **12a** was investigated in the presence of $Pd(PPh_3)_4$ (0.15 equiv). Although the desired allylated product **21** was obtained in 40% yield, the tandem allylation of **18** also proceeded with a low chemical efficiency.

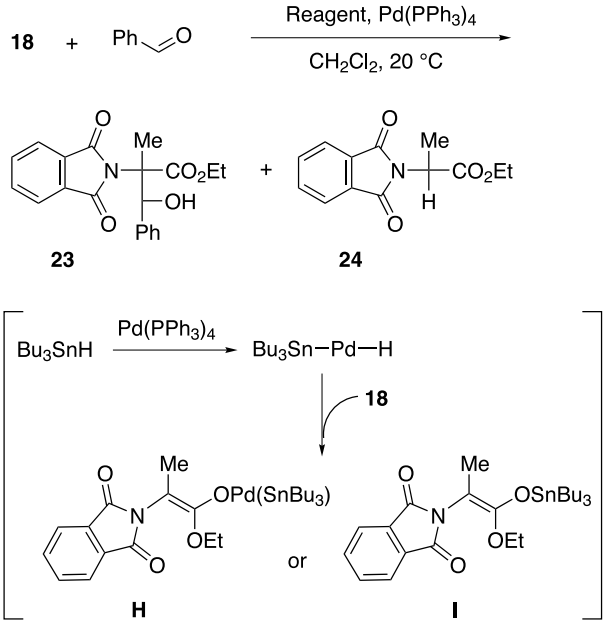
We also investigated the tandem allylation of **18** by using radical precursors such as *i*-PrI or *tert*-BuI. However, the palladium-catalyzed allylation of less reactive *N*-phthaloyl dehydroalanine **18** did not proceed effectively in the presence of alkyl iodides. The formation of the desired products was not observed, probably due to deactivation of $Pd(PPh_3)_4$ by alkyl iodides. As an important effect of palladium catalyst, D. P. Curran reported the palladium (0)-promoted radical cyclization of unsaturated α-iodocarbonyl compounds.[16] These results indicated that $Pd(PPh_3)_4$ serves as a radical initiator, and thus, the deactivation of $Pd(PPh_3)_4$ would proceed via the single-electron transfer (SET) process from palladium (0) to alkyl iodides. In order to test the viability of $Pd(PPh_3)_4$ as a radical initiator, the simple isopropyl radical addition to **18** was investigated (Scheme 7). As expected, $Pd(PPh_3)_4$ served as a single-electron transfer radical initiator to afford the isopropylated product **22** in 35% yield. These results indicate that the success of tandem allylation of **3** using radical precursors reflects the excellent reactivity of **3**.



Scheme 7.

The reductive aldol reactions are attractive reaction, since a reductive method does not require preformation of metal enolates or silyl enol ethers.[17] Therefore, construction

of all-substituted sp^3-hybridized carbon-center via a reductive process is a challenging problem. As an alternative approach to α-substituted enolate anion, we finally investigated the reductive aldol reaction of **18** (Scheme 8). In the presence of $Pd(PPh_3)_4$, the reductive aldol reaction of **18** with benzaldehydride was studied (Table 4). Among several reducing reagents evaluated, Bu_3SnH was found to be the most effective for the reductive aldol reaction of **18** to afford the desired product **23** in 65% yield, accompanied with 16% yield of the protonated product **24** (entry 1). The reaction would proceed via enolate anion **H** or **I** generated from $Pd(PPh_3)_4$ and Bu_3SnH.



Scheme 8.

Table 4. Reductive tandem reaction of **18** with benzaldehyde[a]

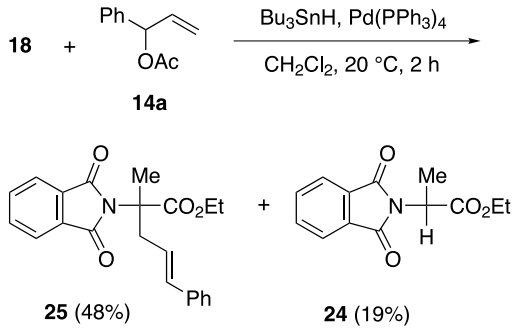
Entry	Reagent	Time (h)	Product (% yield)[b]
1	Bu_3SnH	2	**23** (65%), **24** (16%)
2	Et_3SiH	24	No reaction
3	$Cl(i\text{-}Pr)_2SiH$	24	No reaction
4	$(TMS)_3SiH$	24	**24** (72%)

[a] Reactions were carried out with **18** (1 equiv), reagent (1.2 equiv), and benzaldehyde in the presence of $Pd(PPh_3)_4$ (0.1 equiv).
[b] Isolated yields.

To survey the scope of the present method, the reductive allylation reaction of **18** was studied by using the branched acetate **14a** (Scheme 9). The allylation proceeded smoothly to give the desired product **25** in 48% yield. In addition to the diethylzinc-promoted tandem reactions, the reductive reactions disclosed a broader aspect of the utility of dehydroamino acids for the synthesis of α,α-disubstituted amino acids.

3. Conclusion

We have demonstrated the formation of α-substituted



Scheme 9.

enolate anions from dehydroamino acid derivative **3** or *N*-phthaloyl dehydroalanine **18**. The diethylzinc-promoted tandem reaction of **3** gave the α,α-disubstituted amino acids by using acid anhydrides or π-allyl palladium complexes as electrophiles. A remarkable feature of this reaction is the construction of all-substituted sp^3-hybridized carbon-center via a tandem process, which involves the sequential two steps of carbon–carbon bond forming reactions. The reductive reaction of **18** proceeded smoothly in the presence of Bu_3SnH and $Pd(PPh_3)_4$ to give α,α-disubstituted amino acid derivatives.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz and at 125 MHz, respectively; chemical shifts are measured in ppm. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI, CI, or FAB methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$).

4.2. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with acid anhydride 4–6 or acetyl chloride 7

To a solution of **3** (1.00 g, 3.26 mmol) and acid anhydride **4–6** or acetyl chloride **7** (3.91 mmol) in CH_2Cl_2 (50 mL) was added Et_2Zn (1.0 M in hexane, 4.89 mL, 4.89 mmol) at 0 °C. After being stirred at the same temperature for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (30 mL), and then 1 M HCl (20 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane–AcOEt=5:1) afforded **8–10**.

4.2.1. *tert*-Butyl 2-acetyl-2-aminopentanoate (8). A colorless oil. IR ($CHCl_3$) 3399, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.23 (3H, s), 1.96 (1H, m), 1.86 (2H, br s), 1.77 (1H, m), 1.47 (9H, s), 1.27 (2H, br sex, J=7.6 Hz), 0.95 (3H, t, J=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 205.6, 171.0, 82.6, 71.3, 37.8, 27.7, 25.1, 16.8, 14.3.

4.2.2. *tert*-Butyl 2-amino-3-oxo-2-propylpentanoate (9). A colorless oil. IR ($CHCl_3$) 3400, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.64 (1H, m), 2.51 (1H, m), 1.93 (1H, m), 1.88 (2H, br s), 1.78 (1H, m), 1.46 (9H, s), 1.25 (2H, m), 1.08 (3H, t, J=7.7 Hz), 0.95 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 208.2, 171.0, 82.2, 70.9, 37.5, 30.3, 27.5, 16.6, 14.0, 7.9. MS (CI^+) *m/z*: 230 ($M+H^+$, 1.1), 116 (100). HRMS calcd for $C_{12}H_{24}NO_3$ ($M+H^+$) 230.1756, found 230.1761.

4.2.3. *tert*-Butyl 2-amino-4-methyl-3-oxo-2-propylpentanoate (10). A colorless oil. IR ($CHCl_3$) 3432, 1724, 1668 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.96 (1H, br m), 4.49 (1H, br m), 2.40 (1H, m), 1.79 (1H, m), 1.61 (1H, m), 1.47 (9H, s), 1.34 (2H, m), 1.17 (3H, d, J=6.7 Hz), 1.16 (3H, t, J=6.7 Hz), 0.93 (3H, t, J=7.3 Hz). MS (CI^+) *m/z*: 244 ($M+H^+$, 0.6), 72 (100). HRMS calcd for $C_{13}H_{25}NO_3$ ($M+H^+$) 244.1913, found 244.1908.

4.3. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with allyic reagent 11–15

To a solution of **3** (100 mg, 0.32 mmol), allylic reagent **11–15** (0.48 mmol), and $Pd(PPh_3)_4$ (56 mg, 0.048 mmol) in CH_2Cl_2 (4 mL) was added Et_2Zn (1.0 M in hexane, 0.48 mL, 0.48 mmol) at 0 °C. After being stirred at the same temperature for 20–60 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (4 mL), and then 1 M HCl (2 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **16a–g**.

4.3.1. (*E*)-*tert*-Butyl 2-amino-5-phenyl-2-propylpent-4-enoate (16a). A colorless oil. IR ($CHCl_3$) 3366, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.21 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.11 (1H, m), 2.67 (1H, dd, J=13.4, 6.4 Hz), 2.36 (1H, dd, J=13.4, 8.5 Hz), 1.74 (1H, m), 1.68 (2H, br s), 1.52 (1H, m), 1.48 (9H, s), 1.45–1.25 (2H, m), 0.93 (3H, t, J=7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 137.2, 134.1, 128.5, 127.3, 126.2, 124.6, 81.0, 61.2, 43.7, 42.5, 28.0, 17.2, 14.4. MS (FAB^+) *m/z*: 290 ($M+H^+$, 43), 234 (100). HRMS calcd for $C_{18}H_{28}NO_2$ ($M+H^+$) 290.2120, found 290.2123.

4.3.2. (*E*)-*tert*-Butyl 2-amino-5-(4-(trifluoromethyl)-phenyl)-2-propylpent-4-enoate (16b). A colorless oil. IR ($CHCl_3$) 3395, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.54 (2H, d, J=8.2 Hz), 7.41 (2H, d, J=8.2 Hz), 6.51 (1H, d, J=15.9 Hz), 6.25 (1H, m), 2.68 (1H, dd, J=13.7, 6.7 Hz), 2.40 (1H, dd, J=13.7, 8.4 Hz), 1.75 (1H, m), 1.70 (2H, br s), 1.54 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.24 (1H, m), 0.94 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 140.6, 132.6, 129.2 (q, J=32 Hz), 127.7, 126.3, 125.5, 124.2 (q, J=271 Hz), 81.1, 61.2, 43.7, 42.4, 28.0, 17.1, 14.4. MS (CI^+) *m/z*: 358 ($M+H^+$, 0.8), 116 (100). HRMS calcd for $C_{19}H_{27}F_3NO_2$ ($M+H^+$) 358.1994, found 358.1989.

4.3.3. (*E*)-*tert*-Butyl 2-amino-5-(4-fluorophenyl)-2-propylpent-4-enoate (16c). A colorless oil. IR ($CHCl_3$) 3395, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.22 (2H, m), 6.99 (2H, br t, J=8.6 Hz), 6.44 (1H, d, J=15.9 Hz), 6.02 (1H, m), 2.64 (1H, dt, J=13.4, 6.7 Hz), 2.35 (1H, dt, J=13.4, 8.2 Hz), 1.77 (1H, m), 1.73 (2H, br s), 1.52 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.23 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.3, 162.5 (d, J=246 Hz), 133.6, 133.1, 127.9 (d, J=7.2 Hz), 124.6, 115.7 (d, J=22 Hz), 81.3, 61.4, 43.9, 42.7, 28.3, 17.4, 14.7. MS (CI^+) *m/z*: 308 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{18}H_{27}FNO_2$ ($M+H^+$) 308.2026, found 308.2030.

4.3.4. (*E*)-*tert*-Butyl 2-amino-5-(4-chlorophenyl)-2-propylpent-4-enoate (16d). A colorless oil. IR ($CHCl_3$) 3413, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31–7.20 (4H, m), 6.43 (1H, d, J=15.9 Hz), 6.10 (1H, m), 2.65 (1H, dd, J=13.7, 6.7 Hz), 2.36 (1H, dd, J=13.7, 8.2 Hz), 1.75 (1H, m), 1.70 (2H, br s), 1.52 (1H, m), 1.47 (9H, s), 1.41 (1H, m), 1.23 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 135.7, 132.9, 132.8, 128.7, 127.4, 125.4, 81.0, 61.2, 43.7, 42.4, 28.0, 17.1, 14.4. MS (CI^+) *m/z*: 324 ($M+H^+$, 0.5), 116 (100). HRMS calcd for $C_{18}H_{27}ClNO_2$ ($M+H^+$) 324.1730, found 324.1729.

4.3.5. (*E*)-*tert*-Butyl 2-amino-5-(3-chlorophenyl)-2-propylpent-4-enoate (16e). A colorless oil. IR ($CHCl_3$) 3394, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.31 (1H, s), 7.25–7.14 (3H, m), 6.41 (1H, d, J=15.9 Hz), 6.15 (1H, m), 2.65 (1H, dd, J=13.7, 6.7 Hz), 2.37 (1H, dd, J=13.7, 8.4 Hz), 1.76 (1H, m), 1.73 (2H, br s), 1.51 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.22 (1H, m), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 139.3, 134.7, 132.9, 130.0, 127.5, 126.6, 126.4, 124.6, 81.3, 61.4, 43.9, 42.6, 28.3, 17.4, 14.6. MS (CI^+) *m/z*: 324 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{18}H_{27}ClNO_2$ ($M+H^+$) 324.1730, found 324.1729.

4.3.6. (*E*)-*tert*-Butyl 2-amino-2-propyl-5-*p*-tolylpent-4-enoate (16f). A colorless oil. IR ($CHCl_3$) 3427, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.21 (2H, d, J=7.6 Hz), 7.09 (2H, d, J=7.6 Hz), 6.45 (1H, d, J=15.6 Hz), 6.05 (1H, m), 2.66 (1H, dd, J=13.6, 6.6 Hz), 2.34 (1H, dd, J=13.6, 8.4 Hz), 2.32 (3H, s), 1.74 (1H, m), 1.69 (2H, br s), 1.51 (1H, m), 1.47 (9H, s), 1.42 (1H, m), 1.22 (1H, m), 0.93 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 175.9, 136.9, 134.2, 133.7, 129.0, 125.8, 123.2, 80.7, 60.9, 43.5, 42.2, 27.8, 20.8, 16.9, 14.2. MS (CI^+) *m/z*: 304 ($M+H^+$, 0.6), 116 (100). HRMS calcd for $C_{19}H_{30}lNO_2$ ($M+H^+$) 304.2276, found 304.2281.

4.3.7. (*E*)-*tert*-Butyl 2-amino-5-(naphthalen-2-yl)-2-propylpent-4-enoate (16g). A colorless oil. IR ($CHCl_3$) 3410, 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.82–7.73 (3H, m), 7.67 (1H, s), 7.56 (1H, d, J=8.6 Hz), 7.43 (2H, m), 6.65 (1H, d, J=15.6 Hz), 6.25 (1H, m), 2.73 (1H, dd, J=13.7, 7.0 Hz), 2.44 (1H, dd, J=13.7, 8.9 Hz), 1.78 (1H, m), 1.71 (2H, br s), 1.57 (1H, m), 1.49 (9H, s), 1.42 (1H, m), 1.25 (1H, m), 0.95 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 175.8, 134.4, 133.9, 133.4, 132.6, 127.9, 127.7, 127.5, 126.0, 125.7, 125.5, 124.8, 123.2, 80.8, 61.0, 43.6, 42.2, 27.8, 16.9, 14.2. MS (CI^+) *m/z*: 340 ($M+H^+$, 1.5), 116 (100). HRMS calcd for $C_{22}H_{30}lNO_2$ ($M+H^+$) 340.2276, found 340.2281.

4.4. Typical experimental procedure for tandem reaction of dehydroamino acid derivative 3 with allylic reagent 14a and radical precurser

To a solution of **3** (60 mg, 0.20 mmol), allylic reagent **14a** (69 mg, 0.39 mmol), RI (5.9 mmol), and $Pd(PPh_3)_4$ (68 mg, 0.059 mmol) in CH_2Cl_2 (2 mL) was added Et_2Zn (1.0 M in hexane, 0.59 mL, 0.59 mmol) at 0 °C. After being stirred at the same temperature for 15 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (4 mL), and then 1 M HCl (1 mL) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **17a–d** and **18**.

4.4.1. (*E*)-*tert*-Butyl 2-amino-2-isobutyl-5-phenylpent-4-enoate (17a). A colorless oil. IR ($CHCl_3$) 3391, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.18 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.09 (1H, m), 2.66 (1H, dd, J=13.0, 6.3 Hz), 2.33 (1H, dd, J=13.0, 8.7 Hz), 1.76 (2H, m), 1.66 (2H, br s), 1.53 (1H, m), 1.48 (9H, s), 0.97 (3H, d, J=5.2 Hz), 0.90 (3H, d, J=5.2 Hz). ^{13}C NMR ($CDCl_3$) δ 176.6, 137.2, 134.3, 128.6, 127.4, 126.2, 124.3, 81.1, 60.9, 48.3, 45.3, 28.0, 24.6, 24.4, 23.3. MS (FAB^+) *m/z*: 304 ($M+H^+$, 38), 248 (100). HRMS calcd for $C_{19}H_{30}NO_2$ ($M+H^+$) 304.2276, found 304.2276.

4.4.2. (*E*)-*tert*-Butyl 2-amino-2-(cyclohexylmethyl)-5-phenylpent-4-enoate (17b). A colorless oil. IR ($CHCl_3$) 3390, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.17 (5H, m), 6.47 (1H, d, J=15.9 Hz), 6.08 (1H, m), 2.65 (1H, dd, J=13.4, 6.7 Hz), 2.33 (1H, dd, J=13.4, 8.6 Hz), 1.76 (1H, m), 1.65 (2H, br s), 1.50 (1H, m), 1.48 (9H, s), 1.45–0.88 (11H, m). ^{13}C NMR ($CDCl_3$) δ 176.3, 136.9, 134.0, 128.3, 127.1, 125.9, 124.1, 80.8, 60.6, 46.7, 44.9, 34.9, 33.8, 33.7, 27.7, 26.0 (2C), 25.9. MS (FAB^+) *m/z*: 344 ($M+H^+$, 28), 288 (100). HRMS calcd for $C_{22}H_{34}NO_2$ ($M+H^+$) 344.2589, found 344.2582.

4.4.3. (*E*)-*tert*-Butyl 2-amino-2-(cyclopentylmethyl)-5-phenylpent-4-enoate (17c). A colorless oil. IR ($CHCl_3$) 3410, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36–7.20 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.10 (1H, m), 2.68 (1H, dd, J=13.5, 6.4 Hz), 2.34 (1H, dd, J=13.5, 8.5 Hz), 1.94–1.72 (5H, m), 1.69 (2H, br s), 1.67–1.51 (4H, m), 1.48 (9H, s), 1.17 (1H, m), 1.09 (1H, m). ^{13}C NMR ($CDCl_3$) δ 176.8, 137.4, 134.5, 128.8, 127.6, 126.4, 124.7, 81.3, 61.6, 46.1, 45.0, 36.6, 34.4, 33.9, 28.3, 25.1, 25.0. MS (FAB^+) *m/z*: 330 ($M+H^+$, 57), 274 (100). HRMS calcd for $C_{21}H_{32}NO_2$ ($M+H^+$) 330.2433, found 330.2437.

4.4.4. (*E*)-*tert*-Butyl 2-amino-2-neopentyl-5-phenylpent-4-enoate (17d). A colorless oil. IR ($CHCl_3$) 2956, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34–7.20 (5H, m), 6.48 (1H, d, J=15.6 Hz), 6.05 (1H, m), 2.65 (1H, dd, J=13.4, 6.4 Hz), 2.32 (1H, dd, J=13.4, 8.9 Hz), 2.00 (1H, d, J=14.3 Hz), 1.74 (2H, br s), 1.56 (1H, d, J=14.3 Hz), 1.49 (9H, s), 1.01 (9H, s). ^{13}C NMR ($CDCl_3$) δ 176.7, 137.2, 134.6, 128.6, 127.4, 126.2, 123.9, 81.3, 61.5, 52.0, 47.4, 31.5, 31.2, 28.0. MS (FAB^+) *m/z*: 318 ($M+H^+$, 45), 262 (100). HRMS calcd for $C_{20}H_{32}NO_2$ ($M+H^+$) 318.2433, found 318.2428.

4.4.5. Ethyl 2-acetyl-2-(1,3-dioxoisoindolin-2-yl)pentanoate (19). To a solution of **18** (50 mg, 0.2 mmol) and acetic anhydride (0.07 mL, 0.71 mmol) in CH_2Cl_2 (1 mL) was added Et_2Zn (1.0 M in hexane, 0.41 mL, 0.41 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **19** (32 mg, 50%) and **20** (10 mg, 19%). A colorless oil. IR ($CHCl_3$) 1782, 1719 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.00 (2H, q, J=7.0 Hz), 2.48 (2H, t, J=7.6 Hz), 2.01 (3H, s), 1.42–1.28 (2H, m), 1.36 (3H, t, J=7.0 Hz), 0.93 (3H, t, J=7.0 Hz). MS (EI^+) *m/z*: 317 (M^+, 0.8), 229 (100). HRMS calcd for $C_{17}H_{19}NO_5$ (M^+) 317.1263, found 317.1258.

4.4.6. Ethyl 2-(1,3-dioxoisoindolin-2-yl)pentanoate (20). A colorless oil. IR ($CHCl_3$) 1739, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.86 (1H, dd, J=11.0, 4.6 Hz), 4.21 (2H, m), 2.27 (1H, m), 2.18 (1H, m), 1.34 (2H, m), 1.23 (3H, t, J=7.0 Hz), 0.94 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 169.5, 167.8, 134.1, 131.9, 123.5, 61.7, 52.0, 30.5, 19.5, 14.0, 13.3. MS (EI^+) *m/z*: 275 (M^+, 2.2), 202 (100). HRMS calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1157, found 275.1155.

4.5.7. (*E*)-Ethyl 2-(1,3-dioxoisoindolin-2-yl)-5-phenyl-2-propylpent-4-enoate (21). To a solution of **18** (50 mg, 0.20 mmol), allylic reagent **12a** (83 mg, 0.31 mmol), and $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added Et_2Zn (1.0 M in hexane, 0.41 mL, 0.41 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$) afforded **21** (31 mg, 40%) and **20** (16 mg, 24%). A colorless oil. IR ($CHCl_3$) 1720, 1713 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.69 (2H, m), 7.26–7.12 (5H, m), 6.36 (1H, d, J=15.6 Hz), 6.14 (1H, m), 4.24 (2H, q, J=7.0 Hz), 3.31 (1H, dd, J=13.7, 6.4 Hz), 3.07 (1H, dd, J=13.7, 7.3 Hz), 2.45 (1H, m), 2.30 (1H, m), 1.35 (2H, m), 1.24 (3H, t, J=7.0 Hz), 0.96 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 171.0, 168.8, 137.2, 134.1, 131.5, 128.4, 127.3, 126.2, 124.4, 123.5, 123.2, 123.1, 67.1, 61.4, 38.0, 36.1, 30.5, 17.6, 14.2. MS (EI^+) *m/z*: 391 (M^+, 1.0), 244 (100). HRMS calcd for $C_{24}H_{25}NO_4$ (M^+) 291.1783, found 291.1779.

4.5.8. Ethyl 4-methyl-2-(1,3-dioxoisoindolin-2-yl)pentanoate (22). To a solution of **18** (100 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (471 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) was added isopropyl iodide (0.40 mL, 4.1 mmol) at 20 °C. After being stirred at the same temperature for 15 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **22** (42 mg, 35%). A colorless oil. IR ($CHCl_3$) 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.74 (2H, m), 4.94 (1H, dd, J=11.6, 4.6 Hz), 4.20 (2H, m), 2.33 (1H, m), 1.97 (1H, m), 1.50 (1H, m), 1.23 (3H, t, J=7.0 Hz), 0.96 (3H, d, J=6.4 Hz), 0.93 (3H, d, J=6.7 Hz). ^{13}C NMR ($CDCl_3$) δ 169.8, 167.9, 134.2, 131.9, 123.5, 61.8, 50.8, 37.2, 25.1, 23.1, 21.0, 14.0. MS (FAB^+) m/z: 290 ($M+H^+$, 48), 216 (100). HRMS calcd for $C_{16}H_{19}NO_4$ ($M+H^+$) 290.1393, found 290.1395.

4.5.9. Ethyl 3-hydroxy-2-methyl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (23). To a solution of **18** (50 mg, 0.20 mmol), benzaldehyde (0.04 mL, 0.41 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was added Bu_3SnH (0.07 mL, 0.25 mmol) at 20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. After being roughly removed the tin residue by flash chromatography (hexane–AcOEt=5:1), purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded diastereomixture of **23** (46 mg, 65%) in 9:1 ratio and **24** (8 mg, 16%). Major isomer: a colorless oil. IR ($CHCl_3$) 3526, 1718 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.83–7.71 (4H, m), 7.32–7.15 (5H, m), 5.60 (1H, br s), 4.36 (1H, br s), 4.26 (2H, q, J=7.0 Hz), 1.94 (3H, s), 1.23 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 174.4, 168.3, 137.8, 134.5, 131.6, 128.5, 128.1, 127.7, 123.5, 73.8, 65.9, 62.3, 15.7, 14.1. MS (FAB^+) m/z: 354 ($M+H^+$, 21), 336 (100). HRMS calcd for $C_{20}H_{20}NO_5$ ($M+H^+$) 354.1341, found 354.1347.

4.5.10. Ethyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (24). A colorless oil. IR ($CHCl_3$) 1720, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.87 (2H, m), 7.75 (2H, m), 4.97 (1H, q, J=7.3 Hz), 4.21 (2H, m), 1.70 (3H, d, J=7.3 Hz), 1.24 (3H, t, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 169.7, 167.5, 134.1, 131.9, 123.5, 61.8, 47.5, 15.2, 14.0. MS (FAB^+) m/z: 348 ($M+H^+$, 72), 174 (100). HRMS calcd for $C_{13}H_{14}NO_4$ ($M+H^+$) 248.0923, found 248.0918.

4.5.11. (*E*)-Ethyl 2-methyl-2-(1,3-dioxoisoindolin-2-yl)-5-phenylpent-4-enoate (25). To a solution of **18** (32 mg, 0.13 mmol), allylic reagent **14a** (27 mg, 0.16 mmol), and $Pd(PPh_3)_4$ (15 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) was added Bu_3SnH (0.04 mL, 0.16 mmol) at 20 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. After being roughly removed the tin residue by flash chromatography (hexane–AcOEt=5:1), purification of the residue by preparative TLC (hexane–AcOEt=5:1) afforded **25** (15 mg, 48%) and **24** (9 mg, 19%). A colorless oil. IR ($CHCl_3$) 1723, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.70 (2H, m), 7.26–7.15 (5H, m), 6.40 (1H, d, J=15.6 Hz), 6.18 (1H, m), 4.24 (2H, m), 3.28 (1H, dd, J=14.0, 7.3 Hz), 3.00 (1H, dd, J=14.0, 7.3 Hz), 1.92 (3H, s), 1.25 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 172.1, 168.6, 137.2, 134.3, 134.1, 131.7, 128.5, 127.3, 126.2, 124.2, 123.5, 123.2, 63.4, 61.6, 40.0, 22.3, 14.0. MS (FAB^+) m/z: 364 ($M+H^+$, 51), 216 (100). HRMS calcd for $C_{22}H_{22}NO_4$ ($M+H^+$) 364.1549, found 364.1544.

Acknowledgements

This work was supported in part by The Japan Health Sciences Foundation and Grant-in-Aid for Scientific Research (B) (Y.T.) and for Young Scientists (B) (H.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and for Reseach Grants, 21st Century COE Program 'Knowledge Information Infrastructure for Genome Science'. We thank Mitsubishi Chemical Corporation Fund (H.M.).

References and notes

1. For recent review: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. And also see: (b) Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704.
2. For some reviews: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3018. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
3. López, A.; Moreno-Manas, M.; Pleixats, R.; Roglans, A.; Ezquerra, J.; Pedregai, C. *Tetrahedron* **1996**, *52*, 8365.
4. Miyabe, H.; Asada, R.; Yoshida, K.; Takemoto, Y. *Synlett* **2004**, 540.
5. For a recent review, see: (a) Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2. For some examples, see: (b) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 941. (c) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (d) Marco-Contelles, J. *Chem. Commun.* **1996**, 2629. (e) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831. (f) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709. (g) Sibi, M. P.; Miyabe, H. *Org. Lett.* **2002**, *4*, 3435. (h) Kitagawa, O.; Yamada, Y.; Sugawara, A.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1011. (i) Takasu, K.; Ohsato, H.; Kuroyanagi, J.; Ihara, M. *J. Org. Chem.* **2002**, *67*, 6001. (j) Demircan, A.; Parsons, P. J. *Eur. J. Org. Chem.* **2003**, 1729.
6. For our studies, see: (a) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835. (b) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618. (c) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831. (d) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071.
7. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041. (b) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1991**, *64*, 403. (c) Chandrasekhar, S.; Narsihmulu, C.; Reddy, N. R.; Reddy, M. S. *Tetrahedron Lett.* **2003**, *44*, 2583.
8. (a) Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 152. (b) Bazin, S.; Feray, L.; Siri, D.; Naubron, J.-V.; Bertrand, M. P. *Chem. Commun.* **2002**, 2506.
9. The simple radical addition to dehydroamino acid derivatives, see: (a) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293. (b) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron: Asymmetry* **2002**, *13*, 503. (c) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535. (d) Renaud, P.; Stojanovic,

A. *Tetrahedron Lett.* **1996**, *37*, 2569. (e) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem, Commun.* **1990**, 1087. (f) Crich, D.; Davies, J. W.; Negrón, G.; Quintero, L. *J. Chem. Research (S)* **1988**, 140.

10. Ryu and Komatsu reported that Et_2Zn can serve as a radical initiator in the absence of O_2. See: Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.
11. O_2-Effect on 1,4-addition of Et_2Zn to enone, see: Van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593.
12. (a) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925. (b) Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195.
13. For studies on Et_2Zn-induced radical reactions, see: (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (b) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951. (c) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (d) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443.
14. For our studies, see: (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418.
15. Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
16. Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933.
17. Several selected examples, see: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156. (b) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (c) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (d) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (e) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237. (f) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (g) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 395–400

Synthesis, characterization and optical response of polyene-cored stilbenoid dendrimers

Antonio R. Cano-Marín, Enrique Díez-Barra and Julián Rodríguez-López*

Área de Química Orgánica, Facultad de Química, Universidad de Castilla-La Mancha, 13071 Ciudad Real, Spain

Received 8 September 2004; revised 26 October 2004; accepted 28 October 2004

Available online 13 November 2004

Dedicated to Dr. Juan Carlos del Amo, deceased on 11 March 2004 in Madrid attacks.

Abstract—The synthesis of first- and second-generation dendrimers bearing phenylenevinylene chromophores within the dendritic branches (stilbenoid dendrimers) and polyenes (3 and 5 double bonds) as cores is described. A preliminary study of the optical properties of the resulting compounds was conducted by UV/vis and fluorescence spectroscopy.

1. Introduction

In recent years organic molecules with high photoluminescence efficiencies have been the focus of intensive research effort. Such compounds have been considered as advanced materials for electronic and photonic applications.[1] For this reason, it is important to devise efficient methods for the synthesis of novel fluorophores that are amenable to further chemical functionalization or modification, which in turn can be elaborated to obtain materials with tuneable optoelectronic properties.

Monodisperse dendritic materials have emerged as attractive candidates for photonic applications. There has been a substantial body of work published over the past decade regarding the synthesis of new dendrimeric structures and the study of such systems in the development of new applications.[2] Dendrimers with polyconjugated branches represent an important group within this class of material. These compounds are interesting because of their electrical, optical, nonlinear optical, electroluminescent and photophysical properties. For example, such compounds have been used successfully both as charge transporting[3] and light-emitting materials.[4] Moreover, dendritic structures have been shown to be efficient synthetic light-harvesting antenna molecules.[5]

Herein we describe the synthesis and characterization of new first- and second-generation polyene-cored dendrimer architectures containing phenylenevinylene chromophores within the dendritic branches (stilbenoid dendrimers). We also present the preliminary studies on the photophysical properties (UV/vis and fluorescence measurements) of these luminescent compounds.

2. Results and discussion

Figure 1 shows the structures of the synthesized first- (**1**, **2**) and second-generation (**3**, **4**) dendrimers. The dendritic branches are known polyphenylenevinylene (stilbenoid) chromophores while polyenes are used as dendrimer cores for the first time. We chose the 3,5-di-*tert*-butylphenyl group as the surface functionality in order to impart solubility and to achieve short wavelength absorption and emission. Indeed, THF, chloroform and dichloromethane were found to be very good solvents for all the dendrons and dendrimers prepared.

On the other hand, polyene systems of different lengths allow control of the absorption as well as the colour of the light emission, although it is known that after six double bonds the red shift trend in polyenes shows a decrease.

2.1. Synthesis

The preparation of branches (in this case the phenylenevinylene chromophores) with a wide variety of peripheral groups is well established.[6] We therefore focused our efforts on developing a versatile methodology to build the cores from the appropriate focal points. An aldehyde group at the focus of the dendron was used to achieve this goal by

Keywords: Dendrimers; Stilbenoid dendrimers; Polyphenylenevinylene chromophores; Polyenes.
* Corresponding author. Tel.: +34 926295300; fax: +34 926295318; e-mail: julian.rodriguez@uclm.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.083

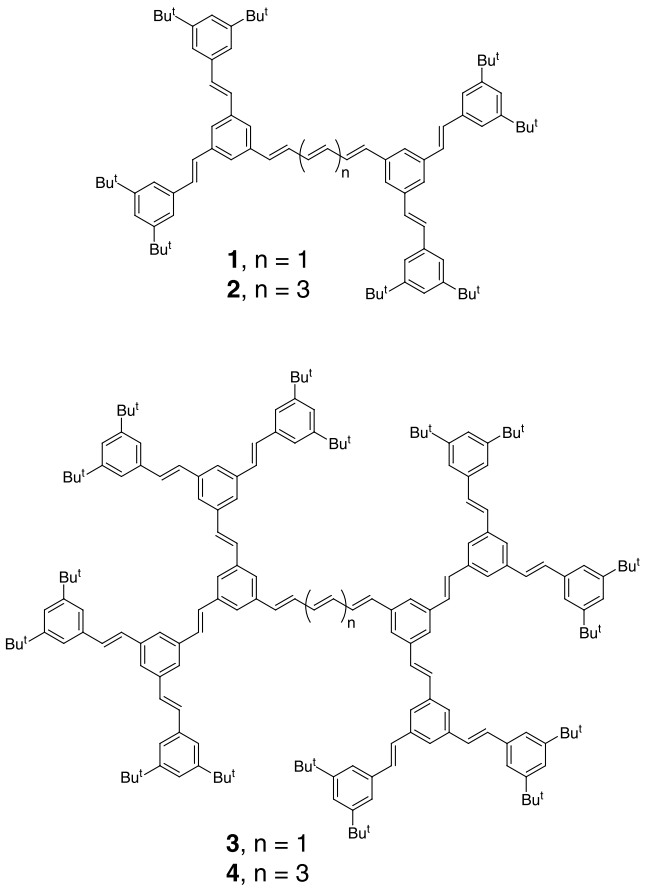
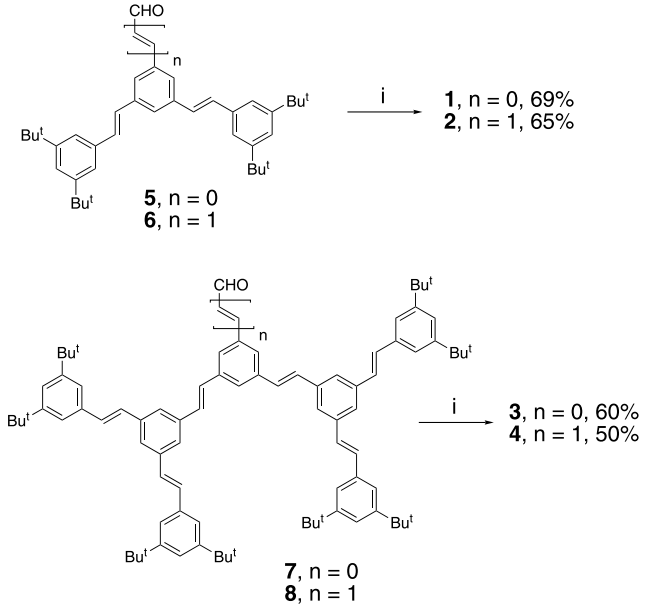


Figure 1. Structure of the prepared polyene-cored stilbenoid dendrimers.

reaction with the diphosphonate derivative **9** to form the polyene-cored dendrimers by a Horner–Wadsworth–Emmons (HWE) reaction (Scheme 1).[7] The synthesis of aldehyde-focused dendrons has been reported previously by Burn and Samuel.[4a] Initially, it was expected that a number of polyenals could be prepared from these dendrons (and their extended counterparts) by successive chain extensions. The efficient use of Wittig[8] and HWE[9] reactions for this purpose has been widely reported.



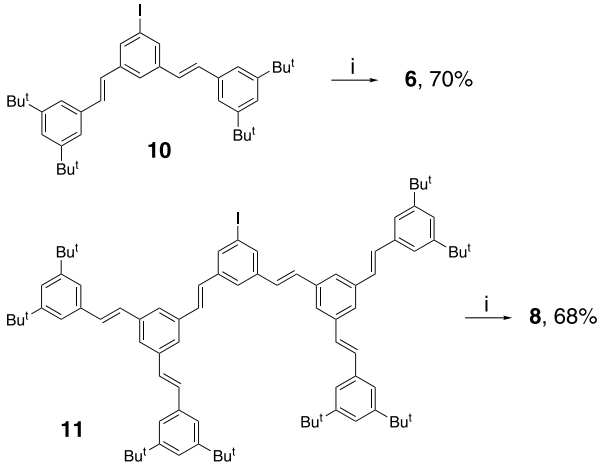
Scheme 1. Synthesis of polyene-cored dendrimers **1**–**4**. Reagents and conditions: (i) $(EtO)_2(O)P–CH_2–CH{=}CH–CH_2–P(O)(OEt)_2$ (**9**), K^{t}BuO/THF, rt.

However, in our case, the use of reagents such as the commercially available triphenylphosphoranylideneacetaldehyde and diethyl phosphonoacetaldehyde diethyl acetal, as well as 1,3-dioxan-2-ylmethyltributyl phosphorane, proved unsuccessful.

All other attempts based on these reagents failed. In an effort to overcome this drawback we decided to perform a Heck coupling reaction with acrolein on the first and second generation iodo-focused dendrons **10** and **11**, which were easily prepared by HWE reactions of 1-iodo-3,5-bis (diethoxyphosphorylmethyl)benzene with 3,5-di-*tert*-butylbenzaldehyde and dendron **5**, respectively. In this way, the corresponding vinylogous compounds **6** and **8** were obtained in 70 and 68% yield, respectively. In all cases the *E*-isomers were the only products (Scheme 2).

With dendrons **5**–**8** in hand, we embarked on building the desired dendrimers by a new HWE reaction at room temperature with diphosphonate **9** in KBu^{t}O/THF. The ^{1}H NMR spectra of the crude products showed some impurities that arose, at least in part, from geometrical isomers. However, after careful chromatography over silica, the desired dendrimers were isolated in good yields.

All new compounds were characterized using various analytical techniques. MS and NMR experiments proved very useful to confirm the structures of the compounds (see Section 4). With their high degree of symmetry, the assignment of the dendrimer structures by ^{1}H and ^{13}C NMR was relatively straightforward. The *trans* stereochemistry for the double bonds was unequivocally established on the basis of the coupling constant of the vinylic protons in the ^{1}H NMR spectra ($J = 15$–16 Hz).[10] HRMS analyses of first-generation dendrimers gave the expected molecular ions. The MALDI-TOF technique proved to be very useful for the identification of the higher structures. All



Scheme 2. Synthesis of vinylogous compounds **6** and **8**. Reagents and conditions: (i) acrolein, *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium (II), 2,6-di-*tert*-butylcresol, anhydrous *N*,*N*-dimethylacetamide, sodium bicarbonate, 130 °C.

the spectra registered for the higher generations showed peaks matching the calculated molecular weights.

2.2. Optical properties of dendrimers 1–4

The optical properties of the dendrimers were investigated by UV/vis and PL spectroscopy on CH_2Cl_2 solutions of the compounds at room temperature. Figure 2 shows the UV/vis spectra of compounds **1–4** and the main data obtained are listed in Table 1.

Owing to the *meta* arrangement through which the dendrons

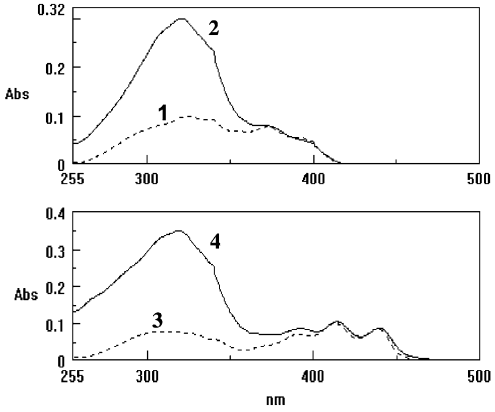


Figure 2. Absorption spectra of **1–4** in CH_2Cl_2 ($c=10^{-6}$ M).

Table 1. UV/vis and photoluminescence (PL) data for dendrimers **1–4**

Compound	UV/vis $\lambda_{max.}$ (nm)	ε (M^{-1} cm^{-1})	PL $\lambda_{max.}$ (nm)
1	324.0, 372.5	99,100, 77,700	421, 444
2	320.5, 373.0	300,100, 80,100	423, 445
3	313.5, 391.0, 412.5, 438.5	82,400, 75,900, 105,900, 91,100	424, 447, 513, 550, 589
4	319.5, 392.0, 414.5, 439.5	351,300, 87,700, 106,100, 88,600	422, 513, 550, 587

are linked, in all cases the observed absorption spectra consist of a superposition of the absorptions due to the different chromophores, stilbenoid branches and polyene cores. The strength of the absorption due to the core (above 370 nm) relative to the peak at 320 nm (associated with stilbene units) decreases for higher generations because of the increase in the number of stilbene units from 4 to 12. The main difference between the spectra of the dendrimers is the bathochromic shift observed for the bands due to the core when five double bonds are present. This shift allows the absorptions due to each chromophore to be clearly differentiated and will be useful to analyse the fluorescence behaviour when branches and cores are irradiated.

Figure 3 shows the fluorescence spectra of compounds **1** and **2**. In both cases the spectra are similar. Excitation at 320–4 nm, that is, at the absorption maxima of the stilbene units, resulted in emission bands at 422 and 444 nm, which are typical of stilbenoid compounds.[11] It has been reported[4c] for similar stilbenoid dendrimers that the absence of emission below 400 nm indicates an efficient energy transfer from the branches to the core (a light-harvesting

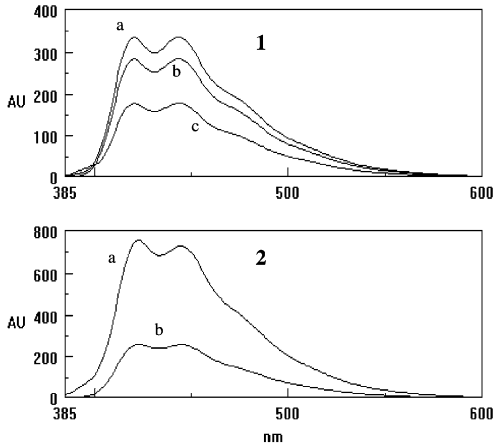


Figure 3. PL spectra of **1** and **2** in CH_2Cl_2 ($c=10^{-7}$ M). **1**; λ_{exc}: (a) 324.0, (b) 372.5 and (c) 393.0 nm. **2**; λ_{exc}: (a) 320.5 and (b) 373.5 nm.

process). However, it is not possible to affirm this phenomenon in this case. The spectra also contain a shoulder at 470 nm, indicating that some energy transfer could have taken place from the stilbene units to the polyene core. Excitation at higher wavelengths (372–393 nm) resulted in a decay in the intensity of the bands in the range 400–450 nm.

The fluorescence spectra of compounds **3** and **4** (Fig. 4) are even more illustrative. As indicated above, in these dendrimers it is possible to irradiate selectively the branches and the core because of their well-resolved absorption bands. In both cases, excitation at 313–9, that is, at the absorption maxima of the stilbene units, again resulted in fluorescence in the region 400–450 nm together with small peaks at 513, 550 and 589 nm (emission from the core).[12] This can be indicative of some energy transfer, however, these data give only a qualitative idea on the behaviour of these dendrimers, while more quantitative information is necessary in order to discuss the occurrence (or lack of occurrence) of energy transfer between the different chromophoric groups. Excitation at higher wavelengths resulted, as expected, in a decay in the intensity of the emission due to the stilbene units. When the samples were

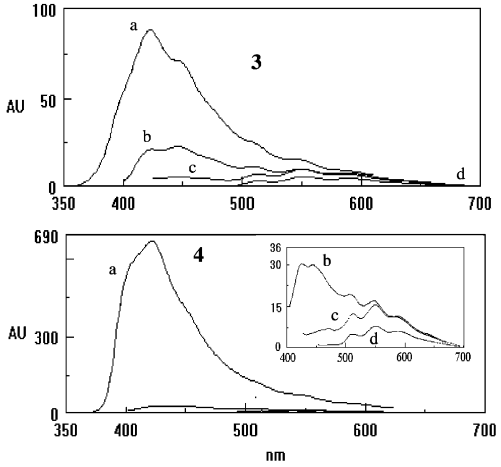


Figure 4. PL spectra of **3** and **4** in CH_2Cl_2 ($c=10^{-6}$ M). **3**; λ_{exc}: (a) 313.5, (b) 391.0, (c) 412.5 and (d) 438.5 nm. **4**; λ_{exc}: (a) 319.5, (b) 392.0, (c) 414.5 and (d) 439.5 nm.

irradiated at 439 nm, only fluorescence from the core was observed.

3. Conclusions

A Heck reaction with acrolein followed by a HWE reaction with diphosphonate **9** allowed the synthesis of first- and second-generation dendrimers having phenylenevinylene (stilbenoid) chromophores as the branches and polyenes (3 and 5 double bonds) as the cores.

The *meta*-substitution pattern causes all chromophores to be independent. The PL spectra of the resulting materials show that excitation of the branches results in fluorescence in the region 400–450 nm, which is typical of stilbenoid compounds, together with emission from the core. More quantitative information is necessary in order to discuss the occurrence (or lack of occurrence) of energy transfer between the different chromophoric groups. Complementary experiments probing this effect are now in progress in our laboratories.

4. Experimental

4.1. General

In air- and moisture-sensitive reactions all glassware was oven-dried and cooled under Ar. All reagents were used as received and without further purification—except acrolein, which was distilled prior to use. THF was refluxed over sodium/benzophenone ketyl and distilled under a positive pressure of dry argon immediately prior to use. CCl_4 was distilled and stored over molecular sieves (4 Å). Column chromatography was carried out with Merck silica gel for flash columns (230–400 mesh). NMR spectra were recorded in $CDCl_3$ on a Varian Inova-500 instrument with TMS or the solvent carbon signal as the standards. IR spectra were recorded on a Nicolet 550 spectrophotometer (FT-IR). UV/vis spectra were recorded in CH_2Cl_2 on a Jasco V-530 spectrophotometer using standard 1 cm quartz UV cells. Fluorescence spectra were recorded on a Jasco FP-750 spectrofluorimeter. Mass spectrometry and elemental analyses were performed at the Universidad Autónoma de Madrid (Servicio Interdepartamental de Investigación, S. I. D. I.). Spectra matrices: 3-nitrobenzyl alcohol (HRMS, LSIMS) and dithranol, α-cyano-4-hydroxycinnamic acid (compound **10**) and 2,5-dihydroxybenzoic acid (compound **6**) (MALDI-TOF). Poly(ethylene glycol) was used for internal calibration. 3,5-Di-*tert*-butylbenzaldehyde,[13] *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)[14] and dendrons **5** and **7**[4a] were prepared according to literature procedures. 1-Iodo-3,5-bis-(diethoxyphosphorylmethyl)-benzene and diphosphonate **9** were prepared by Arbuzov reaction of 1,3-bis(bromomethyl)-5-iodobenzene[15] and *trans*-1,4-dibromo-2-butene, respectively, with triethyl phosphite following a standard methodology.

4.1.1. Compound 10. To a stirred solution of 1-iodo-3,5-bis(diethoxyphosphorylmethyl)benzene (1.3 g, 2.58 mmol) and 3,5-di-*tert*-butylbenzaldehyde (1.13 g, 5.16 mmol) in anhydrous THF (20 mL) under argon was added potassium *tert*-butoxide (1.74 g, 15.48 mmol) in small portions. The coloured mixture was stirred at room temperature for 4 h. After hydrolysis with water, the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were successively washed with water and brine, and then dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product was triturated thoroughly with hot EtOH to give 1.26 g (77%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.37 (s, 36H, 12×CH_3), 7.01 (A of ABq, 2H, J=16.5 Hz, 2×CH=), 7.19 (B of ABq, 2H, J=16.5 Hz, 2×CH=), 7.38 (s, 6H, arom.), 7.61 (br s, 1H, arom.), 7.77 (d, 2H, J=1.5 Hz, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 139.9 (C), 136.0 (C), 133.8 (CH), 131.2 (CH), 126.2 (CH), 124.0 (CH), 122.5 (CH), 121.0 (CH), 95.2 (C–I), 34.9 (C), 31.4 (CH_3). MS (MALDI) m/z 632.3 (M^+). HRMS Calcd for $C_{38}H_{49}I$ 632.2879. Found: 632.2878.

4.1.2. Compound 11. The synthetic procedure used was similar to that described for **10**. Starting from 1-iodo-3,5-bis(diethoxyphosphorylmethyl)benzene (471 mg, 0.93 mmol) and dendron **5** (995 mg, 1.86 mmol) the desired compound was obtained as a white solid (871 mg, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 72H, 24×CH_3), 7.16 (A of ABq, 2H, J=16.5 Hz, 2×CH=), 7.17 (A of ABq, 4H, J=16.5 Hz, 4×CH=), 7.23 (B of ABq, 2H, J=16.5 Hz, 2×CH=), 7.28 (B of ABq, 4H, J=16.5 Hz, 4×CH=), 7.39 (t, 4H, J=1.5 Hz, arom.), 7.43 (d, 8H, J=1.5 Hz, arom.), 7.61 (br s, 4H, arom.), 7.64 (br s, 2H, arom.), 7.68 (br s, 1H, arom.), 7.82 (br s, 2H, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 139.7 (C), 138.4 (C), 137.4 (C), 136.4 (C), 134.4 (CH), 130.4 (CH), 130.1 (CH), 127.5 (CH), 127.3 (CH), 124.4 (CH), 124.1 (CH), 123.8 (CH), 122.3 (CH), 120.9 (CH), 95.2 (C), 34.9 (C), 31.5 (CH_3). MS (MALDI) m/z 1265.9 (M^+). HRMS Calcd for $C_{86}H_{105}I$ 1264.7261. Found: 1264.7260.

4.1.3. Compound 6. A mixture of dendron **10** (600 mg, 0.95 mmol), acrolein (70 mg, 1.2 mmol), anhydrous sodium carbonate (127 mg, 1.20 mmol), *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolyl-phosphino)benzyl]dipalladium(II) (catalytic amount), 2,6-di-*tert*-butylcresol (105 mg, 0.47 mmol) and anhydrous *N*,*N*-dimethylacetamide (6 mL) was deoxygenated thoroughly by stirring under oil-pump vacuum followed by purging with argon several times. The mixture was then heated under argon at 130 °C for 8 h. After cooling, ether and hydrochloric acid (1.5 M) were added carefully. The organic layer was washed with water (×5) and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product was triturated thoroughly with hexanes. Recrystallization from $CHCl_3$/hexanes gave 375 mg (70%) of the desired compound as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.38 (s, 36H, 12×CH_3), 6.84 (dd, 1H, J=7.5, 16.0 Hz, CH=), 7.14 (A of ABq, 2H, J=16.0 Hz, 2×CH=), 7.27 (B of ABq, 2H, J=16.0 Hz, 2×CH=), 7.40 (t, 2H, J=1.5 Hz, arom.), 7.41 (d, 4H, J=1.5 Hz, arom.), 7.54 (d, 1H, J=16.0 Hz, CH=), 7.62 (d, 2H, J=1.0 Hz, arom.), 7.77 (br s, 1H, arom.), 9.76 (d, 1H, J=7.5 Hz, CH=O). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 193.7 (CHO), 152.7 (CH), 151.2 (C), 138.8 (C), 136.0 (C), 134.7 (C), 131.2 (CH), 129.0 (CH), 127.0 (CH), 126.7 (CH), 125.2 (CH), 122.6 (CH), 121.0 (CH), 34.9 (C), 31.5 (CH_3). IR (KBr): ν 1683 (C=O) cm^{-1}. MS

(MALDI) *m/z* 560.4 (M^+). HRMS Calcd for $C_{41}H_{52}O$ 560.4018. Found: 560.4006.

4.1.4. Compound 8. The synthetic procedure used was similar to that described for **6**. Starting from dendron **11** (300 mg, 0.24 mmol) and acrolein (20 mg, 0.36 mmol) the desired compound was obtained as a pale yellow solid (195 mg, 68%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 72H, 24×CH_3), 6.86 (dd, 1H, J=7.5, 16.0 Hz, CH═), 7.18 (A of ABq, 4H, J=16.5 Hz, 4×CH═), 7.30 (s, 4H, 4×CH═), 7.30 (B of ABq, 4H, J=16.5 Hz, 4×CH═), 7.39 (t, 4H, J=1.5 Hz, arom.), 7.44 (d, 8H, J=1.5 Hz, arom.), 7.57 (d, 1H, J=16.0 Hz, CH═), 7.65 (s, 4H, arom.), 7.66 (br s, 4H, arom.), 7.84 (br s, 1H, arom.), 9.79 (d, 1H, J=7.5 Hz, CH═O). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 193.6 (CHO), 152.4 (CH), 151.1 (C), 138.7 (C), 138.4 (C), 137.4 (C), 136.3 (C), 134.9 (C), 130.4 (CH), 130.2 (CH), 129.2 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 125.7 (CH), 124.4 (CH), 123.8 (CH), 122.3 (CH), 120.9 (CH), 34.9 (C), 31.5 (CH_3). IR (KBr): ν 1681 (C═O) cm^{-1}. MS (MALDI) *m/z* 1193.9 (M^+). HRMS Calcd for $C_{89}H_{108}O$ 1192.8400. Found: 1192.8435.

4.1.5. Compound 1. To a stirred solution of diphosphonate **9** (154 mg, 0.47 mmol) and dendritic aldehyde **5** (503 mg, 0.94 mmol) in anhydrous THF (20 mL) under argon was added potassium *tert*-butoxide (316 mg, 2.82 mmol) in small portions. The coloured mixture was stirred at room temperature for 4 h. After hydrolysis with water, the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were successively washed with water and brine, and then dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product was purified by column chromatography (silica gel, hexanes/EtAcO, 9.5:0.5) and recrystallization from $CHCl_3$/EtOH to give the desired compound as a pale yellow solid (352 mg, 69%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 72H, 24×CH_3), 6.63 (dd, 2H, J=7.0, 3.0 Hz, 2×CH═), 6.68 (d, 2H, J=15.5 Hz, 2×CH═), 7.03 (ddd, 2H, J=15.5, 7.0, 3.0 Hz, 2×CH═), 7.14 (A of ABq, 4H, J=16.0 Hz, 4×CH═), 7.25 (B of ABq, 4H, J=16.0 Hz, 4×CH═), 7.38 (t, 4H, J=1.5 Hz, arom.), 7.42 (d, 8H, J=1.5 Hz, arom.), 7.50 (d, 4H, J=1.5 Hz, arom.), 7.60 (t, 2H, J=1.5 Hz, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 138.2 (C), 138.0 (C), 136.4 (C), 133.8 (CH), 132.6 (CH), 130.2 (CH), 129.6 (CH), 127.6 (CH), 123.8 (CH), 123.6 (CH), 122.2 (CH), 120.9 (CH), 34.9 (C), 31.5 (CH_3). MS (LSIMS) *m/z* 1088.5 (M^+). HRMS Calcd for $C_{82}H_{104}$ 1088.8138. Found: 1088.8140. Anal. Calcd for $C_{82}H_{104}$: C, 90.38; H, 9.62. Found: C, 89.98; H, 9.79.

The synthetic procedure used for **2**, **3** and **4** was similar to that described for **1**.

4.1.6. Compound 2. Yellow solid. Yield: 65%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.38 (s, 72H, 24×CH_3), 6.42–6.52 (m, 6H, 6×CH═), 6.64 (d, 2H, J=15.5 Hz, 2×CH═), 6.96–7.02 (m, 2H, J=15.5 Hz, 2×CH═), 7.13 (A of ABq, 4H, J=16.5 Hz, 4×CH═), 7.24 (B of ABq, 4H, J=16.5 Hz, 4×CH═), 7.38 (t, 4H, J=2.0 Hz, arom.), 7.41 (d, 8H, J=2.0 Hz, arom.), 7.47 (br s, 4H, arom.), 7.58 (br s, 2H, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 138.2 (C), 138.1 (C), 136.4 (C), 133.8 (CH), 133.6 (CH), 132.5 (CH), 130.2 (CH), 129.7 (CH), 127.7 (CH), 123.7 (CH), 123.6 (CH), 122.2 (CH), 120.9 (CH), 34.9 (C), 31.5 (CH_3). MS (LSIMS) *m/z* 1141.7 (M^+). HRMS Calcd for $C_{86}H_{108}$ 1140.8451. Found: 1140.8474.

4.1.7. Compound 3. Pale yellow solid. Yield: 60%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (s, 144H, 48×CH_3), 6.68 (dd, 2H, J=7.0, 3.0 Hz, 2×CH═), 6.73 (d, 2H, J=15.0 Hz, 2×CH═), 7.05–7.12 (m, 2H, 2×CH═), 7.19 (A of ABq, 8H, J=16.0 Hz, 8×CH═), 7.30 (s, 8H, 8×CH═), 7.31 (B of ABq, 8H, J=16.0 Hz, 8×CH═), 7.36 (br s, 2H, arom.), 7.40 (t, 8H, J=1.5 Hz, arom.), 7.45 (d, 16H, J=1.5 Hz, arom.) 7.57 (br s, 4H, arom.), 7.66 (br s, 8H, arom.), 7.67 (br s, 4H, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 138.3 (C), 138.2 (C), 138.1 (C), 137.8 (C), 136.4 (C), 133.9 (CH), 132.6 (CH), 130.3 (CH), 129.8 (CH), 129.1 (CH), 128.7 (CH), 127.7 (CH), 124.1 (CH), 124.1 (CH), 123.9 (CH), 123.7 (CH), 122.3 (CH), 120.9 (CH), 34.9 (C), 31.5 (CH_3). MS (MALDI) *m/z* 2355.5 (M^+). Anal. Calcd for $C_{178}H_{216}$ C, 90.76; H, 9.62. Found: C, 90.41; H, 9.75.

4.1.8. Compound 4. Yellow solid. Yield: 50%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (s, 144H, 48×CH_3), 6.46–6.56 (m, 6H, 6×CH═), 6.67 (d, 2H, J=16.0 Hz, 2×CH═), 6.99–7.05 (m, 2H, J=15.5 Hz, 2×CH═), 7.18 (A of ABq, 8H, J=16.5 Hz, 8×CH═), 7.28 (s, 8H, 8×CH═), 7.30 (B of ABq, 8H, J=16.5 Hz, 8×CH═), 7.36 (br s, 2H, arom.), 7.39 (t, 8H, J=1.5 Hz, arom.), 7.44 (d, 16H, J=1.5 Hz, arom.), 7.53 (br s, 4H, arom.), 7.64 (br s, 8H, arom.), 7.65 (br s, 4H, arom.). ^{13}C NMR and DEPT ($CDCl_3$, 125 MHz): δ 151.1 (C), 138.3 (C), 138.2 (C), 138.1 (C), 137.8 (C), 136.4 (C), 134.0 (CH), 133.7 (CH), 133.6 (CH), 132.3 (CH), 130.3 (CH), 129.9 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 124.1 (CH), 124.0 (CH), 123.8 (CH), 123.7 (CH), 122.3 (CH), 120.9 (CH), 34.9 (C), 31.5 (CH_3). MS (MALDI) *m/z* 2407.7 (M^+).

Acknowledgements

Financial support from the Spanish DGI (BQU2002-01327) and the Junta de Comunidades de Castilla-La Mancha (GC-02-013) is gratefully acknowledged.

References and notes

1. (a) Seminario, J. M.; Tour, J. M. In *Molecular Electronics-Science and Technology*; Aviran, A., Ratner, M., Eds.; New York Academy of Science: New York, 1998. (b) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: New York, 1998.
2. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. Dendrimers and Dendrons; Wiley-VCH: Weinheim, 2001. (b) *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001. (c) Hawker, C. J.; Wooley, K. L. In Newkome, G. R., Ed.; Advances in Dendritic Macromolecules; Jai: Greenwich, 1995; Vol. 2. (d) Vögtle, F., Ed.; Dendrimers in Top. Curr. Chem.; Springer: Berlin, 1998; Vol. 197. (e) Bosman, A. W.; Janssen, H. M.; Meijer, E. W.

Chem. Rev. **1999**, *99*, 1665–1688. (f) Majoral, J. P.; Caminade, A. M. *Chem. Rev.* **1999**, *99*, 845–880. (g) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681–1712. (h) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353–1361. (i) Vögtle, F.; Gestermann, S.; Hesse, R.; Schwierz, H.; Windisch, B. *Prog. Polym. Sci.* **2000**, *25*, 987–1041. (j) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819–3867.

3. (a) Bettenhausen, J.; Strohriegl, P. *Adv. Mater.* **1996**, *8*, 507–510. (b) Miller, L. L.; Duan, R. G.; Tully, D. C.; Tomalia, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 1005–1010. (c) Shirota, Y.; Kuwabara, Y.; Inada, H.; Wakimoto, T.; Nakada, H.; Yonemoto, Y.; Kawami, S.; Imai, K. *Appl. Phys. Lett.* **1994**, *65*, 807–809. (d) Lupton, J. M.; Samuel, I. D. W.; Beavington, R.; Burn, P. L.; Bässler, H. *Adv. Mater.* **2001**, *13*, 258–261.
4. (a) Pillow, J. N. G.; Halim, M.; Lupton, J. M.; Burn, P. L.; Samuel, I. D. W. *Macromolecules* **1999**, *32*, 5985–5993. (b) Wang, P. W.; Liu, Y. J.; Devadoss, C.; Bharathi, P.; Moore, J. S. *Adv. Mater.* **1996**, *8*, 237–241. (c) Halim, M.; Pillow, J. N. G.; Samuel, I. D. W.; Burn, P. L. *Adv. Mater.* **1999**, *11*, 371–374.
5. (a) Choi, M.-S.; Yamazaki, T.; Yamazaki, I.; Aida, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 150–158. (b) Balzani, V.; Juris, A. *Coord. Chem. Rev.* **2001**, *211*, 97–115. (c) Adronov, A.; Fréchet, J. M. J. *Chem. Commun.* **2000**, 1701–1710. (d) Balzani, V.; Campagna, S.; Denti, G.; Juris, A.; Serroni, S.; Venturi, M. *Acc. Chem. Res.* **1998**, *31*, 26–34. (e) Jiang, D.-L.; Aida, T. *Nature* **1997**, *388*, 454–456. (f) Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354–4360.
6. (a) Meier, H.; Lehmann, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 643–645. (b) Meier, H.; Lehmann, M.; Kolb, U. *Chem. Eur. J.* **2000**, *6*, 2462–2469. (c) Díez-Barra, E.; García-Martínez, J. C.; Rodríguez-López, J. *Tetrahedron Lett.* **1999**, *40*, 8181–8184. (d) Díez-Barra, E.; García-Martínez, J. C.; Merino, S.; del Rey, R.; Rodríguez-López, J.; Sánchez-Verdú, P.; Tejeda, J. *J. Org. Chem.* **2001**, *66*, 5664–5670. (e) Meier, H.; Lehmann, M. In Nalwa, H. S., Ed.; Encyclopedia of Nanoscience and Nanotechnology; American Scientific: Stevensons Ranch, 2004; Vol. 10, pp 95–106.
7. See Section 4.
8. Spangler, C. W.; McCoy, R. K. *Synth. Commun.* **1988**, *18*, 51–59.
9. Mladenova, M.; Ventelon, L.; Blanchard-Desce, M. *Tetrahedron Lett.* **1999**, *40*, 6923–6926.
10. Assessment of the overall purity of these molecules proved difficult. The ^{1}H NMR spectra of these dendrimers are well-resolved and do not reveal impurities, but the high number of lines in the 7–8 ppm zone could obscure the presence of small amounts of other compounds.
11. This result is in agreement with the previous report showing the fluorescence spectrum of tris-1,3,5-(*p*-tolylvinyl)benzene, a good model for the stilbenoid branches, where two maxima at 396 and 414 nm were observed. See Ref. 6d.
12. Low concentration of the compounds (10^{-6}–10^{-7}) is favorable to minimize the possibility of intermolecular interactions ocurring as a result of aggregation.
13. Deb, S. K.; Maddux, T. D.; Yu, L. *J. Am. Chem. Soc.* **1997**, *119*, 9079–9080.
14. Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357–1364.
15. (a) Duchêne, K.-H.; Vögtle, F. *Synthesis* **1986**, 659–661. (b) Díez-Barra, E.; García-Martínez, J. C.; Guerra, J.; Hornillos, V.; Merino, S.; del Rey, R.; Rodríguez-Curiel, I. R.; Rodríguez-López, J.; Sánchez-Verdú, P.; Tejeda, J.; Tolosa, J. *Arkivoc* **2002**, *V*, 17–26.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 401–408

Development of an end-game strategy towards apoptolidin: a sequential Suzuki coupling approach

Bohan Jin, Qingsong Liu and Gary A. Sulikowski*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, TX 77842-3012, USA

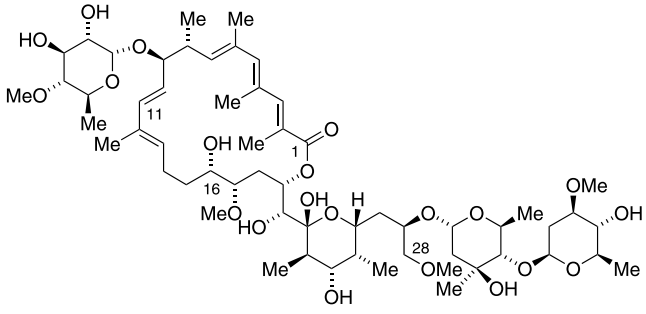
Received 30 April 2004; revised 26 October 2004; accepted 28 October 2004

Available online 18 November 2004

Abstract—An end-game strategy towards the synthesis of apoptolidin has been demonstrated in a model study, in which the C(1)–C(15) fragment was successfully assembled using three consecutive Suzuki coupling reactions.

1. Introduction and discussion

In the mid-1980's Seto and co-workers in Japan developed several immortalized cell lines transfected with oncogenes in order to screen natural product isolates for genotype selective anticancer agents.[1] In 1997, these investigations led to the isolation of apoptolidin from the *Nocardiopsis* sp. soil bacteria, a macrolide natural product that selectively induces apoptosis in cells transformed with the E1A oncogene.[2a] One year later the complete structure of apoptolidin was assigned based on NMR analysis and featured two sugar units located at C(9) and C(27) and an aglycone consisting of a 20-membered macrolactone (**1**).[2b] Apoptolidin was determined to induce apoptosis in cells transformed with the E1A oncogene while exhibiting cytostatic activity against normal cells. This unique pattern of cytotoxicity was later shown by workers at Stanford University to correlate with apoptolidin's ability to inhibit mitochondrial F_0F_1-ATPase.[3] Apoptolidin's remarkably selective cytotoxicity profile could prove useful in the development of new strategies for cancer treatment, as well as further the understanding of cellular events leading to apoptosis in cells.[4] Owing to its biological attributes and complex molecular architecture, apoptolidin has been the subject of extensive synthetic studies.[5–7] Previously, we reported a synthesis of the C(16)–C(28) fragment **2** (Scheme 2).[4f] In this paper we describe the successful development of an end-game strategy resulting in the completion of the C(1)–C(15) fragment of **1**.[5e,g]



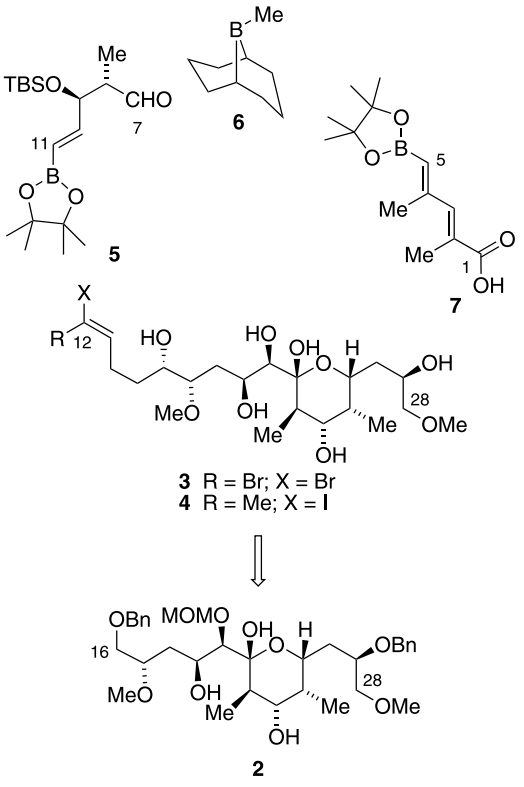
1

2. Synthetic design

The goal of our synthetic design was to develop a convergent route that integrates a novel synthesis of the polyene fragment imbedded in the 20-membered macrolactone, particularly the unique C(1)–C(7) highly substituted trienoate moiety. To that end, we propose strategic bond disconnections of apoptolidin leading to three major components: the lower portion as either a 1,1-geminal dibromide **3** or vinyliodide **4**; the C(7)–(11) boronate **5**; and the C(1)–C(5) dienoate boronate **7** (Scheme 1). Our plan was to form the C(11)–C(12) bond first via a Suzuki cross-coupling reaction between 1,1-dibromo olefin **3** (or vinyliodide **4**) and boronate **5**. Subsequently the aldehyde functionality at C(7) of the coupled product would be homologated to a 1,1-geminal dibromide, which would then be used in a second Suzuki cross-coupling reaction with the C(1)–C(5) boronate **7**. In the end, we would convert the remaining vinylbromides at C(6) and C(12), or the mono bromide at C(6) if vinyliodide **4** would have been used in the

Keywords: Natural product synthesis; Trienoate; Cross-coupling.
* Corresponding author. Tel.: +1 979 845 5746; fax: +1 979 862 7963; e-mail: g-sulikowski@tamu.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.088

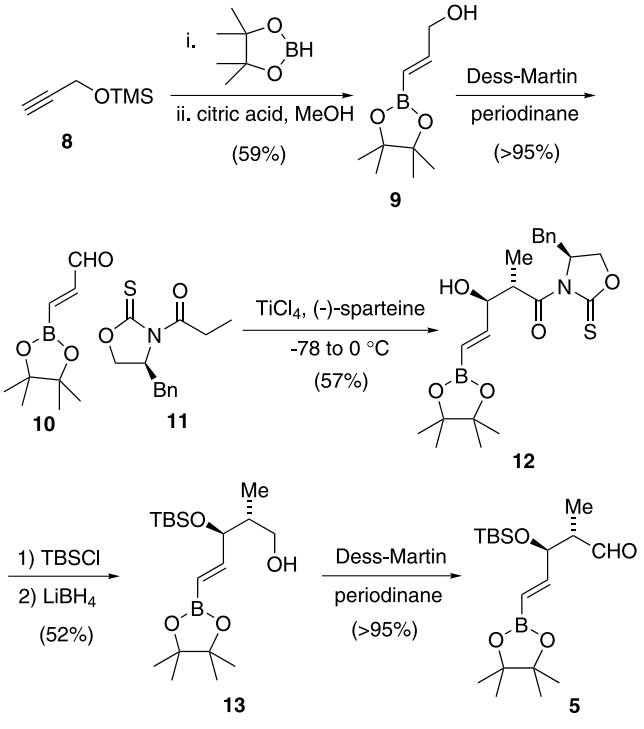


Scheme 1.

first Suzuki coupling reaction, to the requisite methyl groups via a final cross-coupling reaction using Me-9-B-BBN **6**.[8]

3. Results and discussion

The preparation of boronate **5** started with trimethylsilyl ether **8**[9a] (Scheme 2). Following a procedure developed by Vaultier,[9b] hydroboration of **8** using pinacolborane was followed by acidic methanolysis to afford allylic alcohol **9** in 59% yield for two steps. The oxidation of **9** to aldehyde **10** was then accomplished in near quantitative yield by Dess–Martin periodinane oxidation[10] following a modified work up protocol.[11] Aldol reaction between **10** and thioxazolidinone **11** furnished *syn* aldol product **12** in 57% yield (>99:1 diastereoselectivity determined by HPLC). The relatively low yield was presumably a reflection of the instability of aldehyde **10** under the reaction conditions.[12] The structure of adduct **12** was unambiguously confirmed by single crystal X-ray analysis.[13] The resulting hydroxyl group was protected as a TBS silylether (84%), and the auxiliary was reductively removed to furnish alcohol **13** in 61% yield. Finally, Dess–Martin oxidation gave rise to the C(7)–C(11) aldehyde **5**.

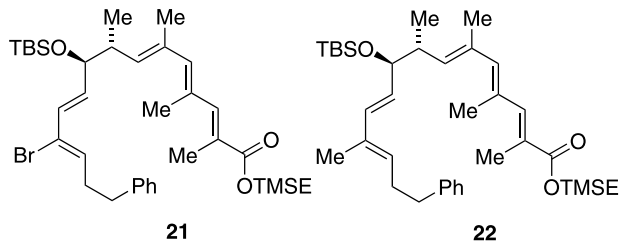


Scheme 2.

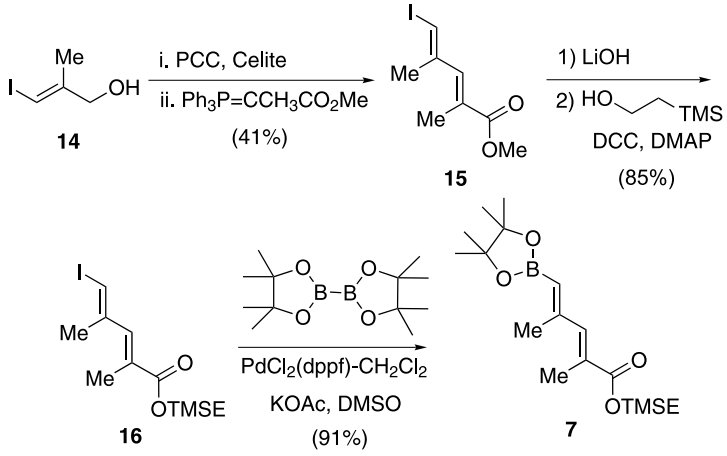
The synthesis of the C(1)–C(5) dienoate boronate **7** started with the known alcohol **14** (Scheme 4).[14] PCC oxidation, followed by Wittig olefination gave dienoate **15** in 41% yield for the two steps. The methyl ester was then exchanged for a trimethylsilylethyl ester (**16**) which was subsequently cross coupled with bis(pinacolato)diborane to give boronate **7** in 91% yield (Scheme 3).[15]

With the requisite C(7)–C(11) (**5**) and C(1)–C(5) (**7**) fragments in hand, we first set out to examine the possibility of using 1,1-dibromide **3** (Scheme 1) in the first Suzuki coupling reaction in order to form the C(11)–C(12) bond. To this end, dibromide **17** was used in a model study depicted in Scheme 4. Boronate **5** underwent Suzuki coupling with 1,1-geminal dibromide **17** in the presence of $Pd(PPh_3)_4$ and TlOEt[16] to give diene **18** in 70% yield. The aldehyde group was subsequently homologated to dibromide **19** using the ylide derived from Ramirez salt (PPh_3CHBr_3, *t*-BuOK).[17] Attempted Corey–Fuchs olefination[18] of **18** resulted in β-elimination of the OTBS group. A second Suzuki coupling reaction was then carried out between **19** and dienoate boronate **7** to afford the complete trienoate **20**.

What needed to be done at this stage was the conversion of the remaining C(6) and C(12) vinylbromides to the required methyl groups. After screening a variety of palladium mediated processes to no avail, using Me_4Sn,[19] MeMgBr,[20a] and $AlMe_3$[20b] as the methyl sources, we turned our attention again to Suzuki coupling reactions using Me-9-B-BBN, $CH_3B(OH)_2$,[21] and methyl pinacolborate[22] as the methyl sources.



Under standard reaction conditions [$Pd(PPh_3)_4$,TlOEt, THF–H_2O], the C(6) bromide underwent facile cross-



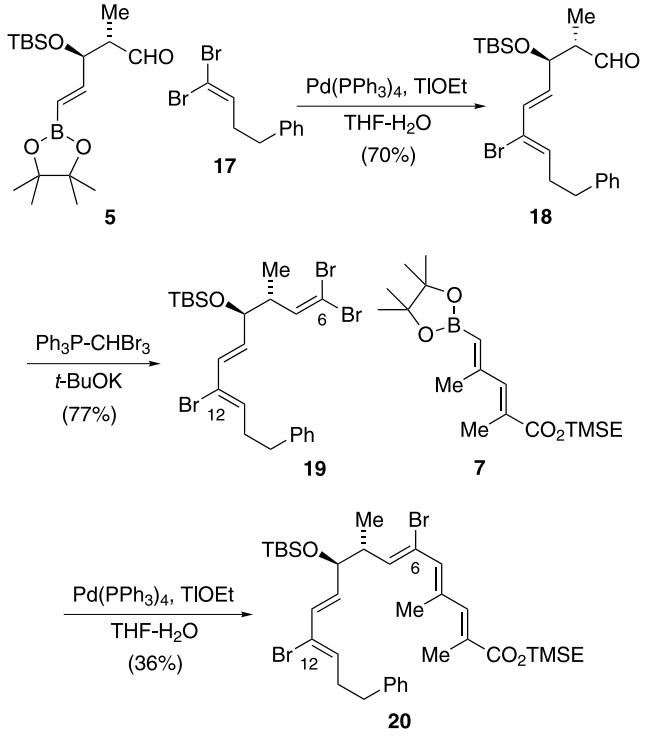
Scheme 3.

coupling, however, the more electron-rich but less sterically demanding C(12) bromide was found to be surprisingly resistant towards methylation, despite prolonged reaction times and heating. For example, when Me-9-B-BBN was used, **21** was isolated as the only product in 78% yield. With $CH_3B(OH)_2$, again only **21** was obtained in a comparable 74% yield. The only case where the bis-methylated product **22** was obtained was when methyl pinacolborate was used, however, as a 1:2 inseparable mixture with **21** (major product).

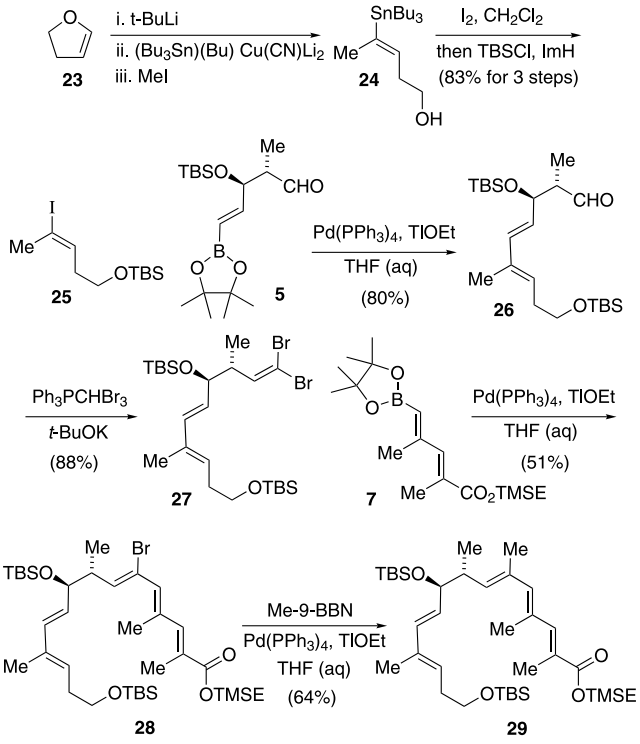
In light of the difficulty in effecting a cross-coupling reaction at the C(12) bromide, we elected to examine the possibility of using vinyliodide **4** (Scheme 1) in the first Suzuki coupling reaction to form the C(11)–C(12) bond, in which case the C(12) methyl group was already in place. Vinyliodide **25**, synthesized from dihydrofuran **23**,[23] was used in the model study described in Scheme 5. Boronate **5** underwent Suzuki coupling reaction with vinyliodide **25** in the presence of $Pd(PPh_3)_4$ and TlOEt to afford diene **26** in 80% yield. The aldehyde functionality was subsequently homologated to 1,1-geminal dibromide **27**. A second Suzuki coupling reaction was subsequently carried out between **27** and dienoate boronate **7** to furnish trienoate **28**. Finally, the C(6) bromide was uneventfully methylated using Me-9-B-BBN to afford the complete trienoate fragment **29** in high purity and good yield (64%).

4. Conclusion

In summary, the C(1)–C(15) polyene portion of apoptolidin has been synthesized, successfully demonstrating a tandem Suzuki coupling reaction based end-game strategy. The



Scheme 4.



Scheme 5.

application of this strategy to the synthesis of apoptolidin will be reported in due course.

5. Experimental

5.1. General

Unless indicated, all commercial reagents were used as received without further purification. All reactions were carried out under a nitrogen or argon atmosphere using dry glassware that had been flame-dried under a stream of nitrogen, unless otherwise noted. All reaction solvents were dried and/or purified before use. Reagent grade tetrahydrofuran was dried over 4 Å molecular sieves; dichloromethane and benzene were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 230–400 mesh) with the indicated solvent system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were taken on a micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon-13 (^{13}C NMR) spectra were recorded on a 300 or 500 MHz spectrometer at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane (δ 0 ppm, $CDCl_3$) or residual non-deuterated solvent δ 7.26 ppm from $CHCl_3$, δ 7.16 ppm for C_6D_5H). For ^{13}C spectra, chemical shifts are reported relative to the δ 77.23 ppm resonance of $CDCl_3$ or the δ 128.39 resonance of C_6D_6. Infrared (IR) spectra were recorded as thin films or solutions in the indicated solvent. Mass spectra were obtained at the Laboratory for Biological Mass Spectrometry (Texas A&M University).

5.1.1. Trimethyl-prop-2-ynyloxy-silane 8.[9a] To a solution of propargyl alcohol (20 mL, 344 mmol) in ether (150 mL, reagent grade) at 0 °C was added TMSCl (66 mL, 516 mmol, reagent grade) and pyridine (50 mL, 619 mmol, reagent grade). The white slurry was stirred at ambient temperature for 43 h, diluted with petroleum ether (300 mL), and filtered through a bed of silica gel and rinsed with petroleum ether–ether (1 L, 10:1). Solvent was removed to give 34 g (77%) of **8** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, J=1.2 Hz, 2H), 2.38 (t, J=1.5 Hz, 1H), 0.19 (s, 9H).

5.1.2. 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-prop-2-en-1-ol 9. To a solution of **8** (20 g, 169 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added $BH_3\cdot SMe_2$ (16.9 mL, 169 mmol). The colorless solution was stirred at 0 °C for 1 h and then at ambient temperature for 3 h before a solution of 179 (10.8 g, 84.5 mmol) in CH_2Cl_2 (10 mL) was introduced via cannula. The reaction mixture was then heated to 50 °C and stirred sealed for 4 d. Solvent was removed and MeOH (60 mL) was added, followed by citric acid (17.7 g, 84.5 mmol). After 5 min, solvent was removed in vacuo and the residue was diluted with ether (700 mL) and washed with $NaHCO_3$ (4×60 mL, sat.). The aqueous layers were back extracted with ether (3×100 mL). The organic layers were combined and solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 2:1) gave 9.2 g (59%, 2 steps) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dt, J=18.0, 4.5 Hz, 1H), 5.68 (dt, J=18.0, 1.8 Hz, 1H), 4.22 (m, 2H), 1.25 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 83.2, 64.4, 24.7; HRMS (ESI) m/z 191.1462 [(M+Li)$^+$, calcd for $C_9H_{17}BO_3$ 191.1431].

5.1.3. 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-propenal 10. To a solution of **9** (4.3 g, 23.3 mmol) in CH_2Cl_2 (7 mL) was added Dess–Martin periodinane (11.9 g, 28 mmol). The white slurry was stirred for 1.5 h. Solvent was removed in vacuo and the residue was filtered through a fine fritted funnel and rinsed with petroleum ether–ether (330 mL, 10:1). Removal of solvent gave 4.2 g (>95%) of **10** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, J=7.5 Hz, 1H), 6.77 (dd, J=18.5, 8.0 Hz, 1H), 6.64 (d, J=18.5 Hz, 1H), 1.28 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 147.0, 84.4, 24.7; HRMS (ESI) m/z 189.1272 [(M+Li)$^+$, calcd for $C_9H_{15}BO_3$ 189.1274]

5.1.4. 1-(4-Benzyl-2-thioxo-oxazolidin-3-yl)-3-hydroxy-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-en-1-one 12. To a solution of 1-(4-benzyl-2-thioxo-oxazolidin-3-yl)-propan-1-one (2.4 g, 9.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C was slowly added titanium tetrachloride (9.7 mL, 9.7 mmol, 1.0 M in CH_2Cl_2). The resulting yellow slurry was stirred at 0 °C for 5 min, before (−)-sparteine (2.95 mL, 12.8 mmol) was introduced neat. The homogeneous solution was stirred at 0 °C for 20 min before being cooled to −78 °C. A solution of **10** (1.8 g, 9.9 mmol) in CH_2Cl_2 (20 mL) was added via cannula over 10 min. The reaction mixture was stirred at −78 °C for 1.5 h and then at 0 °C for another 30 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and filtered through a bed of Celite and rinsed with CH_2Cl_2. HPLC analysis of the crude product showed a diastereomeric ratio of >99:1. Flash chromatography of the residue (petroleum ether–ether: 4:1→1:1) gave 5.8 g (57%) of **12** as a white solid. Recrystallization from EtOAc gave a colorless needle crystalline suited for X-ray analysis. Mp 138–139 °C. $[\alpha]_D$=+62.3° (c 3.7, CH_2Cl_2); IR (CH_2Cl_2) 3595, 2986, 1696, 1358, 963 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.33 (m, 5H), 6.55 (dd, J=18.0, 4.5 Hz, 1H), 5.76 (dd, J=18.0, 2.0 Hz, 1H), 4.92 (m, 1H), 4.78 (dq, J=7.0, 3.0 Hz, 1H), 4.63 (m, 1H), 4.30 (m, 2H), 3.24 (dd, J=13.5, 3.5 Hz, 1H), 2.74 (dd, J=13.5, 10.0 Hz, 1H), 1.25 (s, 12H), 1.24 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 177.3, 151.1, 135.1, 129.4, 129.0, 127.5, 83.4, 72.9, 70.2, 60.1, 42.1, 37.5, 24.8, 24.7, 10.5; HRMS (ESI) m/z 432.2016 [(M)$^+$, cald for $C_{22}H_{31}BNO_5S$ 432.2044].

5.1.5. 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-en-1-ol 13. To a solution of **12** (1.6 g, 3.8 mmol) in CH_2Cl_2 (6 mL) at 0 °C was imidazole (772 mg, 11.3 mmol) and TBSCl (1.7 g, 11.3 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 17 h. The mixture was quenched with water (10 mL). The aqueous

layer was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 10:1) gave 2.5 g (84%) of the corresponding TBS ether as a colorless oil. $[\alpha]_D=+35.4°$ (*c* 0.48, CH_2Cl_2); IR (CH_2Cl_2) 2996, 1716, 1153 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.34 (m, 5H), 6.58 (dd, *J*= 18.0, 5.1 Hz, 1H), 5.63 (dd, *J*=18.0, 1.2 Hz, 1H), 4.76 (m, 2H), 4.56 (dt, *J*=4.8, 1.2 Hz, 1H), 4.27 (dd, *J*=9.3, 1.8 Hz, 1H), 4.18 (m, 1H), 3.28 (dd, *J*=12.9, 3.0 Hz, 1H), 2.73 (dd, *J*=13.2, 10.2 Hz, 1H), 1.23 (s, 12H), 1.18 (d, *J*=6.6 Hz, 3H), 0.87 (s, 9H), −0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 175.0, 152.8, 135.3, 129.4, 128.9, 127.3, 83.1, 74.9, 69.8, 60.7, 43.8, 37.2, 25.7, 24.7, 24.6, 18.0, 11.0, −4.4, −5.4; HRMS (ESI) *m/z* 546.2881 $[(M+H)^+$, calcd for $C_{28}H_{45}BNO_5SSi$ 546.2792]. To a solution of thus obtained TBS ether (4.6 g, 8.4 mmol) in ether–MeOH (20 mL–155 μL) at 0 °C was added $LiBH_4$ (7.9 mL, 15.6 mmol, 2.0 M in ether). The reaction mixture was stirred at ambient temperature for 4.5 h, diluted with petroleum ether (100 mL), and filtered through a bed of silica gel and rinsed with petroleum ether–ether (600 mL, 1:2). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 5:1→2:1) gave 1.86 g (61%) of **13** as a colorless oil. $[\alpha]_D=-20.8°$ (*c* 0.48, CH_2Cl_2); IR (CH_2Cl_2) 3490, 2960, 1639, 856 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (dd, *J*=17.5, 5.0 Hz, 1H), 5.64 (dd, *J*=17.5, 2.0 Hz, 1H), 4.30 (m, 1H), 3.60 (dd, *J*=11.0, 9.0 Hz, 1H), 3.44 (dd, *J*=10.5, 4.5 Hz, 1H), 1.98 (m, 1H), 1.25 (s, 12H), 0.88 (s, 9H), 0.80 (d, *J*=7.0 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 83.2, 77.4, 65.7, 40.8, 25.8, 24.8, 24.7, 18.1, 12.1, −4.5, −5.2; HRMS (ESI) *m/z* 357.2636 $[(M)^+$, calcd for $C_{18}H_{37}BO_4Si$ 357.2646].

5.1.6. 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-enal 5. To a solution of **13** (890 mg, 2.49 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (1.16 g, 2.75 mmol). The white slurry was stirred for 1.5 h. Solvent was removed in vacuo and the residue was filtered through a fine fritted funnel and rinsed with petroleum ether–ether (330 mL, 10:1). Removal of solvent gave 885 mg (>95%) of **5** as a colorless oil. $[\alpha]_D=+12.8°$ (*c* 5.08, CH_2Cl_2); IR (CH_2Cl_2) 2960, 1737, 1639, 1148 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, *J*=1.0 Hz, 1H), 6.55 (dd, *J*=17.5, 5.0 Hz, 1H), 5.68 (dd, *J*=17.5, 1.5 Hz, 1H), 4.64 (m, 1H), 2.40 (m, 1H), 1.21 (s, 12H), 1.00 (d, *J*=2.0 Hz, 3H), 0.82 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 152.2, 83.3, 73.5, 51.9, 25.8, 24.8, 24.7, 18.1, 7.9, −4.2, −5.2; HRMS (ESI) *m/z* 355.2476 $[(M)^+$, calcd for $C_{18}H_{35}BO_4Si$ 355.2476].

5.1.7. 5-Iodo-2,4-dimethyl-penta-2,4-dienoic acid methyl ester 15. To a solution of **14**[14] (9.3 g, 47 mmol) in CH_2Cl_2 (350 mL) at 0 °C was added Celite (21 g) and pyridinium chlorochromate (15 g, 70 mmol). The mixture was stirred at 0 °C for 3.5 h and filtered through a bed of silica gel and rinsed with ether (500 mL). Solvent was removed in vacuo to give a volatile brown crude oil. To a solution of the above-generated oil in CH_2Cl_2 (50 mL) at 0 °C was added $Ph_3P{=}C(CH_3)COOMe$ (10.6 g, 30 mmol). The solution was stirred at ambient temperature for 1.5 h. Solvent was removed and the residue was filtered through a bed of silica gel and rinsed with ether (500 mL). Solvent was removed to give a crude oil. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 5.1 g (41%) of **15** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (m, 1H), 6.39 (t, *J*=1.2 Hz, 1H), 3.74 (s, 3H), 1.98 (dd, *J*=1.2, 0.6 Hz, 3H), 1.93 (d, *J*=1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 143.6, 138.9, 128.0, 85.4, 52.1, 24.5, 14.2; HRMS (ESI) *m/z* 272.9937 $[(M+Li)^+$, calcd for $C_8H_{11}IO_2$ 272.9964].

5.1.8. 5-Iodo-2,4-dimethyl-penta-2,4-dienoic acid 2-trimethylsilanyl-ethyl ester 16. To a solution of **15** (2.55 g, 9.6 mmol) in MeOH–H_2O (9–3 mL) was added lithium hydroxide (1.2 g, 48 mmol). The clear solution was stirred at ambient temperature for 6.5 h. Solvent was removed in vacuo and the residue was diluted with CH_2Cl_2 (20 mL) and water (10 mL). The biphasic mixture was then acidified with concentrated aqueous HCl to pH=3. The aqueous layer was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 4:1) gave 2.4 g (99%) of the corresponding carboxylic acid as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.49 (s, 1H), 2.01 (d, *J*= 1.2 Hz, 3H), 1.94 (d, *J*=1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 143.6, 140.9, 86.9, 24.4, 13.8. To a solution of the above carboxylic acid (470 mg, 1.86 mmol) in CH_2Cl_2 (4 mL) was added DMAP (cat.) and trimethylsilyl-ethyl alcohol (281 μL, 1.96 mmol). The mixture was cooled to 0 °C and DCC (404 mg, 1.96 mmol) was added. The reaction mixture was stirred at 0 °C for 80 min then at ambient temperature for 30 min. The white slurry was filtered and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 562 mg (86%) of **16** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.37 (s, 1H), 4.22 (m, 2H), 1.97 (s, 3H), 1.91 (d, *J*=1.5 Hz, 3H), 1.01 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 143.7, 138.5, 128.4, 85.2, 63.2, 24.5, 17.3, 14.2, −1.5; HRMS (ESI) *m/z* 359.0515 $[(M+Li)^+$, calcd for $C_{12}H_{21}IO_2Si$ 359.0516].

5.1.9. 2,4-Dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-penta-2,4-dienoic acid 2-trimethylsilanyl-ethyl ester 7. To a mixture of $PdCl_2$(dppf)–CH_2Cl_2 (34 mg, 0.04 mmol), KOAc (409 mg, 4.2 mmol), and bis(pinacolato)diboron (1 g, 4.2 mmol) flushed with argon was added a solution of **16** (490 mg, 1.4 mmol) in DMSO (5 mL) via cannula. The resulting dark reddish solution was heated to 80 °C and stirred in the dark under Ar for 10 min. It was cooled to ambient temperature, diluted with ether (250 mL), washed with water (30 mL), and dried over Na_2SO_4. Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 15:1) gave 444 mg (91%) of **7** as a pale yellow solid; IR (CH_2Cl_2) 2991, 2249, 1706, 1265, 907 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.36 (s, 1H), 4.22 (m, 2H), 2.09 (s, 3H), 1.96 (d, *J*=1.5 Hz, 3H), 1.26 (s, 12H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 154.8, 142.9, 128.3, 83.0, 62.9, 24.8, 21.3, 17.3, 14.1, −1.5; ^{11}BNMR (96 MHz, $CDCl_3$, $BF_3\cdot OEt_2$ as reference) δ 95.9; HRMS (FAB) *m/z*

375.2139 [$(M+Na)^+$, calcd for $C_{18}H_{33}BO_4SiNa$ 375.2146].

5.1.10. 6-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-9-phenyl-nona-4,6-dienal 18. To a solution of **5** (400 mg, 1.13 mmol) and **17** (109 mg, 0.376 mmol) in THF–H_2O (9–3 mL, degassed) was added $Pd(PPh_3)_4$ (44 mg, 0.0376 mmol). After 5 min, TlOEt (48 μL, 0.67 mmol) was introduced and the mixture was stirred in the dark for 90 min. A second batch of $Pd(PPh_3)_4$ (44 mg, 0.0376 mmol) was added and the mixture was stirred for another 1 h. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (300 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 100:0→30:1→20:1) gave 115 mg (70%) of **18** as a colorless oil. $[\alpha]_D=-3.5°$ (*c* 0.57, CH_2Cl_2); IR (CH_2Cl_2) 2971, 2858, 1747, 840 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, $J=1.5$ Hz, 1H), 7.89–7.30 (m, 5H), 6.19 (d, $J=15.0$ Hz, 1H), 6.01 (dd, $J=15.0$, 5.5 Hz, 1H), 5.96 (t, $J=7.0$ Hz, 1H), 4.68 (m, 1H), 2.74 (m, 2H), 2.59 (q, $J=7.0$ Hz, 2H), 2.46 (m, 1H), 1.07 (d, $J=7.0$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 141.1, 133.8, 133.6, 130.2, 128.4, 128.3, 126.1, 124.8, 72.1, 52.6, 34.4, 33.3, 25.7, 18.1, 8.2, −4.2, −5.0; HRMS (ESI) *m/z* 437.1508 [$(M+H)^+$, calcd for $C_{22}H_{33}BrO_2Si$ 437.1511].

5.1.11. [4-Bromo-1-(3,3-dibromo-1-methyl-allyl)-7-phenyl-hepta-2,4-dienyloxy]-*tert*-butyl-dimethyl-silane 19. To a slurry of Ph_3P–$CHBr_3$ (1.47 g, 2.86 mmol) in THF (3 mL) at 0 °C was added *t*-BuOK (291 mg, 1.6 mmol). The bright yellow slurry was stirred at ambient temperature for 20 min and cooled to 0 °C. A solution of **18** (115 mg, 0.26 mmol) in THF (12 mL) was then introduced via cannula. The reaction mixture was stirred at 0 °C for 15 h and quenched with brine (10 mL). The aqueous layer was separated and extracted with ether (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 30:1→1:1) gave 134 mg (77%) of **19** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.29 (m, 5H), 6.28 (d, $J=9.5$ Hz, 1H), 6.15 (d, $J=15.0$ Hz, 1H), 5.96 (dd, $J=14.5$, 5.5 Hz, 1H), 5.94 (t, $J=7.0$ Hz, 1H), 4.23 (t, $J=5.0$ Hz, 1H), 2.75 (m, 2H), 2.61 (q, $J=7.5$ Hz, 2H), 2.56 (m, 1H), 0.97 (d, $J=7.0$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 141.2, 134.4, 133.1, 129.8, 128.4, 128.4 (overlapping signal), 126.0, 125.2, 88.3, 74.1, 65.4, 44.9, 34.4, 33.4, 25.8, 18.2, 13.3, −4.4, −5.0; HRMS (ESI) *m/z* 597.0004 [$(M+Li)^+$, calcd for $C_{23}H_{33}Br_3OSi$ 597.0011].

5.1.12. 6,12-Dibromo-9-(*tert*-butyl-dimethyl-silanyloxy)-2,4,8-trimethyl-15-phenyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 20. To a solution of **19** (19 mg, 0.032 mmol) and **7** (58 mg, 0.163 mmol) in THF–H_2O (1.5–0.5 mL, degassed) was added $Pd(PPh_3)_4$ (4 mg, 0.00327 mmol). After 5 min, TlOEt (4.2 μL, 0.0589 mmol) was introduced and the mixture was stirred in the dark for 30 min. The resulting dark yellow slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 50:1→10:1→1:1) gave 8.4 mg (36%) of **20** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H), 7.08 (s, 1H), 6.15 (d, $J=14.5$ Hz, 1H), 6.05 (s, 1H), 6.03 (dd, $J=14.5$, 6.0 Hz, 1H), 5.92 (t, $J=7.0$ Hz, 1H), 5.65 (dd, $J=9.0$, 1.0 Hz, 1H), 4.23 (m, 2H), 2.82 (m, 1H), 2.74 (m, 2H), 2.60 (q, $J=8.0$ Hz, 2H), 2.00 (s, 3H), 1.93 (d, $J=1.5$ Hz, 3H), 1.03 (d, $J=7.0$ Hz, 3H), 1.02 (m, 2H), 0.88 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.2, 141.0, 135.9, 135.6, 134.9, 133.6, 132.9, 129.7, 128.4, 128.4 (overlapping signal), 126.1, 125.2, 120.1, 75.1, 63.1, 43.9, 34.5, 33.3, 25.8, 18.2, 18.1, 17.4, 14.5, 14.2, −1.4, −4.3, −4.9; HRMS (ESI) *m/z* 743.2177 [$(M+Li)^+$, calcd for $C_{35}H_{54}Br_2O_3Si_2$ 743.2138].

5.1.13. 12-Bromo-9-(*tert*-butyl-dimethyl-silanyloxy)-2,4,6,8-tetramethyl-15-phenyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 21. To a solution of **20** (12.6 mg, 0.017 mmol) in THF (1.5 mL, degassed) was sequentially added $Pd(PPh_3)_4$ (4 mg, 0.0034 mmol), Me-9-B-BBN (204 μL, 0.51 mmol, 2.5 M in THF), TlOEt (18 μL, 0.255 mmol), and H_2O (0.3 mL, degassed). The yellow-brownish slurry was stirred in the dark for 19 h. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 9 mg (78%) of **21** as a colorless oil. It was further purification by HPLC (silica gel, 4 mL/min, 269 nm detection, 1% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H), 7.13 (s, 1H), 6.06 (d, $J=14.5$ Hz, 1H), 6.03 (s, 1H), 5.94 (dd, $J=14.5$, 5.5 Hz, 1H), 5.88 (t, $J=7.0$ Hz, 1H), 5.19 (d, $J=10.0$ Hz, 1H), 4.23 (m, 2H), 3.99 (t, $J=5.5$ Hz, 1H), 2.73 (m, 2H), 2.60 (m, 2H), 2.31 (m, 1H), 2.01 (d, $J=1.0$ Hz, 3H), 1.81 (d, $J=1.0$ Hz, 3H), 1.77 (s, 3H), 1.03 (m, 2H), 0.91 (d, $J=6.5$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 9H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 142.6, 141.3, 136.3, 134.8, 133.2, 132.4, 132.2, 132.1, 128.7, 128.4, 128.3, 126.2, 126.0, 125.5, 76.1, 62.9, 40.6, 34.5, 33.3, 25.9, 23.6, 18.3, 18.0, 17.4, 15.5, 14.2, −1.4, −4.3, −4.9; HRMS (ESI) *m/z* 695.2927 [$(M+Na)^+$, calcd for $C_{36}H_{57}BrO_3Si_2Na$ 695.2922].

5.1.14. *tert*-Butyl-(4-iodo-pent-3-enyloxy)-dimethyl-silane 25. To a solution of CuCN (448 mg, 5 mmol) in THF–ether (6–10 mL) at −40 °C was added *n*-BuLi (4.85 mL, 10 mmol, 2.06 M in hexanes). After 5 min, cooling bath was removed and the mixture was stirred at ambient temperature for 15 min and cooled to −40 °C. Bu_3SnH (2.7 mL, 10 mmol) was then introduced and the mixture was stirred at −40 °C for 70 min. Separately, to a solution of dihydrofuran (378 μL, 5 mmol) in THF (5 mL) at −60 °C was added *t*-BuLi (3.5 mL, 6 mmol, 1.7 M in pentane). The mixture was stirred at −60 °C for 10 min and at 0 °C for 55 min before it was transferred to the above-generated mixture via cannula. The resulting orange solution was then stirred at 0 °C for 1.5 h. MeI (2.2 mL, 35 mmol) was added and the mixture was allowed to warm to ambient temperature in 1 h and stirred at ambient temperature for another 3 h. The resulting mixture was poured into a mixture of NH_4Cl (100 mL, sat.) and NH_3–H_2O (25 mL) at 0 °C and stirred for 30 min. The aqueous layer was separated and extracted with ether (3×100 mL). The combined organic layers were dried briefly over Na_2SO_4 and concentrated in vacuo. Removal of solvent

gave 196 as a colorless crude oil, which was used in the next step without further purification. To a solution of the above-generated alcohol **24** in CH_2Cl_2 (5 mL) at 0 °C was added a solution of I_2 (1.4 g, 5.4 mmol) in CH_2Cl_2 (45 mL) until brown color persisted. Imidazole (1 g, 14.8 mmol) was then added followed by TBSCl (2.23 g, 14.8 mmol). The resulting slurry was stirred at 0 °C for 20 min and quenched with $Na_2S_2O_3$ (25 mL) and stirred for 5 min. The aqueous layer was separated and extracted with ether (3×100 mL). The combined organic layers were dried briefly over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 100:0→20:1) gave 1.35 g (83%, 3 steps) of **25** as a colorless oil. Observed physical properties were identical with those previously reported.[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (tq, J=8.0, 1.0 Hz, 1H), 3.59 (t, J=6.5 Hz, 2H), 2.35 (s, 3H), 2.22 (q, J=6.5 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 95.3, 61.8, 34.2, 27.7, 25.9, 18.3, −5.3; HRMS (ESI) m/z 333.0731 [$(M+Li)^+$, calcd for $C_{11}H_{23}IOSi$ 333.0723].

5.1.15. 3,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,6-dimethyl-nona-4,6-dienal 26. To a solution of **25** (87 mg, 0.246 mmol) and **7** (53 mg, 0.164 mmol) in THF–H_2O (3–1 mL, degassed) was added $Pd(PPh_3)_4$ (19 mg, 0.0164 mmol). After 5 min, TlOEt (17 μL, 0.246 mmol) was introduced and the mixture was stirred in the dark for 35 min. The resulting reddish-brown slurry was filtered through a bed of Celite and rinsed with ether (200 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 56.3 mg (80%) of **26** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (d, J=1.5 Hz, 1H), 6.18 (d, J=15.5 Hz, 1H), 5.48 (dd, J=15.5, 7.0 Hz, 1H), 5.45 (t, J=7.7 Hz, 1H), 4.54 (dd, J=6.5, 5.0 Hz, 1H), 3.62 (t, J=7.0 Hz, 2H), 2.46 (m, 1H), 2.34 (q, J=6.5 Hz, 2H), 1.71 (s, 3H), 1.04 (d, J=7.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 136.1, 134.3, 129.5, 126.6, 73.8, 62.6, 53.2, 32.1, 25.9, 25.8, 18.3, 18.1, 12.6, 8.5, −4.1, −5.0, −5.3, −5.3; HRMS (ESI) m/z 433.3149 [$(M+Li)^+$, calcd for $C_{23}H_{46}O_3Si_2$ 433.3146].

5.1.16. 1,1-Dibromo-4,10-bis-(*tert*-butyl-dimethyl-silanyloxy)-3,7-dimethyl-deca-1,5,7-triene 27. To a slurry of Ph_3P–$CHBr_3$ (579 g, 1.12 mmol) in THF (2 mL) at 0 °C was added *t*-BuOK (67 mg, 0.6 mmol). The bright yellow slurry was stirred at ambient temperature for 20 min and cooled to 0 °C. A solution of **26** (32 mg, 0.075 mmol) in THF (4 mL) was then introduced via cannula. The reaction mixture was stirred at 0 °C for 1 h and quenched with brine (10 mL). The aqueous layer was separated and extracted with ether (3× 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 30:1) gave 38.2 mg (88%) of **27**as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (d, J=9.5 Hz, 1H), 6.13 (d, J=15.5 Hz, 1H), 5.46 (dd, J=15.5, 7.0 Hz, 1H), 5.44 (t, J=7.0 Hz, 1H), 4.11 (t, J=5.5 Hz, 1H), 3.63 (t, J=6.5 Hz, 2H), 2.53 (m, 1H), 2.35 (q, J=7.0 Hz, 2H), 1.72 (s, 3H), 0.96 (d, J=6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H), 0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 135.5, 134.5, 128.8, 127.5, 87.8, 75.6, 62.7, 45.3, 32.1, 25.9, 25.8, 18.4, 18.2, 13.6, 12.7, −4.2, −4.9, −5.2, −5.3; HRMS (ESI) m/z 587.1530 [$(M+Li)^+$, calcd for $C_{24}H_{46}Br_2O_2Si_2$ 587.1563].

5.1.17. 6-Bromo-9,15-bis-(*tert*-butyl-dimethyl-silanyloxy)-2,4,8,12-tetramethyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 28. To a solution of **27** (38 mg, 0.0656 mmol) and **7** (115 mg, 0.32 mmol) in THF–H_2O (3–1 mL, degassed) was added $Pd(PPh_3)_4$ (7.6 mg, 0.00656 mmol). After 5 min, TlOEt (8 μL, 0.118 mmol) was introduced and the mixture was stirred in the dark for 30 min. The resulting yellow slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 50:1) gave 8.4 mg (36%) of **28** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.13 (d, J=15.5 Hz, 1H), 6.04 (d, J=1.0 Hz, 1H), 5.65 (dd, J=9.0, 1.0 Hz, 1H), 5.53 (dd, J=15.5, 7.0 Hz, 1H), 5.42 (t, J=7.5 Hz, 1H), 4.23 (m, 2H), 4.10 (t, J=6.0 Hz, 1H), 3.62 (t, J=7.0 Hz, 2H), 2.78 (m, 1H), 2.34 (q, J=7.0 Hz, 2H), 2.00 (d, J=1.5 Hz, 3H), 1.92 (d, J=1.5 Hz, 3H), 1.72 (s, 3H), 1.02 (d, J=6.5 Hz, 3H), 1.01 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 9H), 0.02 (s, 6H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.1, 136.4, 135.5, 135.4, 134.6, 133.8, 128.5, 128.3, 128.1, 119.7, 76.6, 63.0, 62.7, 44.3, 32.0, 25.9, 25.8, 18.4, 18.2, 18.1, 17.3, 14.8, 14.2, 12.6, −1.5, −4.1, −4.9, −5.3, −5.3; HRMS (ESI) m/z 733.3690 [$(M+Li)^+$, calcd for $C_{36}H_{67}BrO_4Si_3Li$ 733.3691].

5.1.18. 9,15-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,4,6,8,12-pentamethyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 29. To a solution of **28** (50 mg, 0.068 mmol) in THF (3 mL, degassed) was sequentially added $Pd(PPh_3)_4$ (8 mg, 0.0068 mmol), Me-9-B-BBN 189 (378 μL, 0.68 mmol, 1.8 M in THF), TlOEt (9 μL, 0.12 mmol), and H_2O (0.6 mL, degassed). The yellow slurry was stirred in the dark for 23 h. HPLC analysis of the reaction mixture showed complete consumption of starting material 200. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 36.6 mg (81%) of 201 as a colorless oil. Further purification by HPLC (silica gel, 4 mL/min, 269 nm detection, 0→3% gradient EtOAc/hexanes) gave 29 mg (64%) of analytically pure **29** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.05 (d, J=16.0 Hz, 1H), 6.04 (s, 1H), 5.43 (dd, J=16.0, 7.0 Hz, 1H), 5.38 (t, J=7.0 Hz, 1H), 5.20 (dt, J=10.0, 1.5 Hz, 1H), 4.23 (m, 2H), 3.91 (t, J=6.0 Hz, 1H), 3.61 (t, J=7.0 Hz, 2H), 2.33 (q, J=7.0 Hz, 2H), 2.29 (m, 1H), 2.01 (d, J=1.5 Hz, 3H), 1.82 (d, J=1.0 Hz, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.03 (m, 2H), 0.89 (d, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 9H), 0.02 (s, 6H), 0.00 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 142.8, 134.9, 134.7, 134.6, 133.2, 133.1, 131.5, 129.2, 127.9, 126.2, 77.5, 62.8, 62.7, 40.8, 32.1, 25.9, 23.6, 18.3, 18.2, 18.0, 17.4, 15.4, 14.1, 12.6, −1.4, −4.1, −4.8, −5.2, −5.3; HRMS (ESI) m/z 685.4479 [$(M+Na)^+$, calcd for $C_{37}H_{70}O_4Si_3Na$ 685.4480].

Acknowledgements

Support by the National Institutes of Health (CA-59515-08) and the Robert A. Welch foundation (A-1230) is gratefully acknowledged. The National Science Foundation (CHE-0077917) is acknowledged for providing funds for the purchase of NMR instrumentation. We also thank Joseph Reibenspies for determining the X-ray crystal structure of aldol adduct and Shane E. Tichy for high resolution mass spectrum analysis.

References and notes

1. Hayakawa, Y.; Sohda, K.; Shin-ya, K.; Hidaka, T.; Seto, H. *J. Antibiot.* **1995**, *48*, 954–961. (b) Hayakawa, Y.; Sohda, K.; Furihata, K.; Kuzuyama, T.; Shin-ya, K.; Seto, H. *J. Antibiot.* **1996**, *49*, 974–979. (c) Hayakawa, Y.; Adachi, H.; Kim, J. W.; Shin-ya, K.; Seto, H. *Tetrahedron* **1998**, *54*, 15871–15878.
2. Kim, J. W.; Adachi, H.; Shin-ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 628–630. (b) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524–3525.
3. Salomon, A. R.; Woehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71–80. (b) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14766–14771.
4. Salomon, A. R.; Zhang, Y.; Seto, H.; Khosla, C. *Org. Lett.* **2001**, *3*, 57–59. (b) Wender, P. A.; Gulledge, A.; Jankowski, O. D.; Seto, H. *Org. Lett.* **2002**, *4*, 3819–3822. (c) Pennington, J. D.; Williams, H. J.; Salomon, A. R.; Sulikowski, G. A. *Org. Lett.* **2002**, *4*, 3823–3825. (d) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 487–490. (e) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 2299–2302.
5. Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H. *Chem. Commun.* **2000**, 307–308. (b) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett.* **2000**, *41*, 621–624. (c) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439–1442. (d) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873–8876. (e) Chng, S.; Xu, J.; Loh, T. *Tetrahedron Lett.* **2003**, *44*, 4997–5000. (f) Chen, Y.; Evarts, J. B. Jr.; Torres, E.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 3571–3574. (g) Paquette, W. D.; Taylor, R. E. *Org. Lett.* **2004**, *6*, 103–106.
6. Total synthesis of apoptolidin: (a) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H.; Weyershausen, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3849–3854. Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3854–3857. (c) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433–15442. (d) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443–15454.
7. (a) Total synthesis of apoptolidinone: Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem. Int. Ed.* **2001**, *40*, 2063–2066. (b) Total synthesis of apoptolidin: Wehlan, H.; Dauber, M.; Fernaud, M.-T.M.; Schuppan, J.; Mahrwald, R.; Ziemer, B.; Garcia, M-E. J. ; Koert, U. *Angew. Chem. Int. Ed.* **2004**, *43*, 4597–4601.
8. For the synthesis of Me-9-BBN, see: Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281–293. For related work, see: Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5541–5542.
9. Demina, M.; Velikanov, A.; Medvedeva, A.; Larina, L.; Voronkov, M. *J. Organomet. Chem.* **1998**, *553*, 129–133. (b) Jehanno, E.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 4439–4442.
10. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
11. The reaction solvent CH_2Cl_2 was removed in vacuo, and the residue was triturated with petroleum ether–ether (10:1) to give the aldehyde in quantitative yield and $>95\%$ purity. The normal basic (1.3 M NaOH) or reductive (aqueous $NaHCO_3$–$Na_2S_2O_3$) work-ups only resulted in decomposition of product.
12. Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902.
13. The atomic coordinates have been submitted to the Cambridge Crystallographic Data Centre.
14. Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65.
15. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126–127. (c) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813–9816.
16. Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691–2694 and references within.
17. Ramirez, F.; Mckelvie, N. *J. Am. Chem. Soc.* **1957**, *79*, 5829–5830. (b) Wolkoff, P. *Can. J. Chem.* **1975**, *53*, 1333–1335. (c) Dolhem, F.; Lievre, C.; Demailly, G. *Tetrahedron Lett.* **2002**, *43*, 1847–1849.
18. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
19. Biagetti, M.; Bellina, F.; Carpita, A.; Viel, S.; Mannina, L.; Rossi, R. *Eur. J. Org. Chem.* **2002**, *6*, 1063–1076. (b) Villar, L.; Bullock, J. P.; Khan, M. M.; Nagarajan, A.; Bates, R. W. *J. Organomet. Chem.* **1996**, *517*, 9–18. (c) Rossi, R.; Bellina, F.; Carpita, A.; Raffaele, G. *Gazz. Chim. Ital.* **1995**, *9*, 381–392.
20. Miller, M.; Hegedus, L. S. *J. Org.Chem.* **1993**, *24*, 6779–6785. (b) Hirota, K.; Kitada, Y.; Kanbe, Y.; Maki, Y. *J. Org. Chem.* **1992**, *57*, 5268–5270.
21. Brown, H. C.; Cole, T. E. *Organometallics* **1985**, *4*, 816–821.
22. Brown, H. C.; Park, W. S.; Cha, J. S.; Cho, B. T.; Brown, C. A. *J. Org. Chem.* **1986**, *5*, 337–342.
23. Fargeas, V.; Menez, P. L.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613–6634.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 409–415
Tetrahedron

Regio- and stereoselective synthesis of *Z*-vinylic tellurides from propargylic alcohols: a route to chiral *Z*-enynes

Cristiano Raminelli, Nathalia C. da Silva, Alcindo A. Dos Santos, André L. M. Porto, Leandro H. Andrade and João V. Comasseto*

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-900 São Paulo, SP, Brazil

Received 23 September 2004; revised 25 October 2004; accepted 28 October 2004

Available online 13 November 2004

Abstract—*tert*-Butyldimethylsilyl ethers of propargylic alcohols are hydrotellurated regioselectively to give 1,2-*Z*-vinylic tellurides. Enantiomerically pure propargylic alcohols give enantiomerically pure vinylic tellurides, which are coupled with alkynes under Pd catalysis to give enantiomerically pure allylic enynols.

1. Introduction

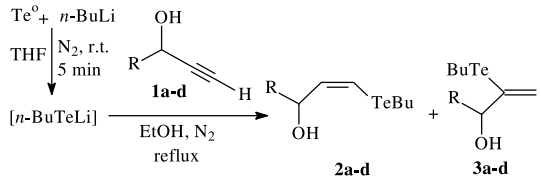
Hydrotelluration of alkynes gives *Z*-vinylic tellurides exclusively,[1] whereas other hydrometallation reactions give the *E*-vinyl organometallics preferentially.[2] The transformation of *Z*-vinylic tellurides into *Z*-organometallics is well established[1] and recently it was used in the first step of the synthesis of Macrolactin A, an antiviral macrolactone.[3] Although the hydrotelluration of conjugated alkynes gives only the 1,2-regioisomer, the hydrotelluration of propargylic alcohols **1** leads to the formation of 1,2- and 2,2-substituted allylic alcohols **2** and **3**, respectively[4] (Scheme 1). Another limitation of the hydrotelluration reaction consists in the traditional use of dibutylditelluride as starting material, which is a bad smelling compound and is not commercially available. Recently, we solved this problem by substituting the classically used methodology[1] by a different one, consisting in the reaction of commercially available elemental tellurium and *n*-butyllithium, which generates lithium butyltellurolate.[1] In the presence of water or ethanol, this intermediate reacts with alkynes[5] leading to *Z*-vinylic tellurides in yields similar to the ones obtained by the dibutylditelluride/sodium borohydride method (Scheme 1).[1,5] In view of the occurrence of allylic alcohols in the structure of many natural products[6] or synthetic intermediates,[7] we decided to investigate the hydrotelluration of propargylic alcohols in order to control its regiochemistry. In this work the lithium *n*-butyltellurolate/EtOH methodology was employed throughout.

2. Results and discussion

Initially, the propargylic alcohols **1a–d** were hydrotellurated by reacting them with the system *n*-BuTeLi/EtOH in order to verify the influence of their structures in the isomeric ratios of the formed vinylic tellurides. The results are presented in Table 1.

As can be observed, isomeric mixtures of **2** and **3** were obtained. The isomeric ratios suggest that the nature of the R group has a deep influence in the regioselectivity of the hydrotelluration reaction. As the steric demand of the R group increases, the amount of the desired 1,2-regioisomer increases. In view of these results, we decided to increase the steric demand at C_3 by protecting the OH function with bulky protecting groups. Three commonly used protecting groups were chosen for this purpose (Scheme 2, Table 2). Initially alcohol **1b** was protected with the three bulky protecting groups, leading to the propargylic ethers **4a–c**, which were submitted to hydrotelluration (Scheme 2, Table 2).

As can be observed the hydrotelluration of **4a**,**b** occurred in good yields and with high regioselectivity. The *tert*-butyldimethylsilyl (TBDMS) protected product presented



Scheme 1.

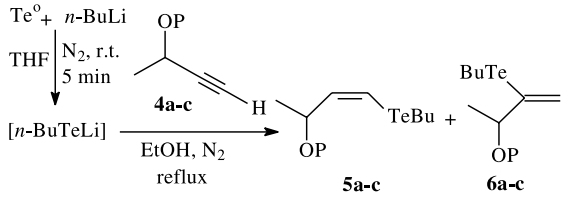
Keywords: *Z*-Vinylic tellurides; Propargylic alcohols; Chiral *Z*-enynes.
* Corresponding author. Tel.: +55 11 3091 2176; fax: +55 11 3815 5579; e-mail: jvcomass@iq.usp.br

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.087

Table 1. Hydrotelluration of propargylic alcohols **1a–d** produced according to Scheme 1

Entry	R	Time (h)	Yield (%)[a]	Isomeric ratio (2:3)[b]
1	H (**a**)	4	80	1:3
2	CH_3 (**b**)	6	74	2:3
3	$(CH_3)_2CH$ (**c**)	6	60	2:1
4	Ph (**d**)	6	60	2:1

[a] Isolated yields after column chromatography on silica gel.
[b] The isomeric ratio was determined by ^1H NMR data and confirmed by GC analysis.



Scheme 2.

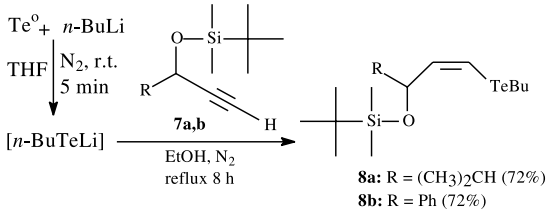
a 10:1 regioisomeric ratio in favor of the 1,2-isomer **5a**, confirming the steric control of the reaction. The tetrahydropyranyl group conferred a moderate selectivity leading to a 6:1 ratio (entry 2, Table 2). The propargylic alcohol protected by the trityl group did not react with the hydrotellurating agent (entry 3, Table 3). In view of the good results obtained by using the TBDMS group, the propargylic ethers **7a**,**b** were prepared and submitted to the hydrotelluration conditions. In this case, it was observed the exclusive formation of the 1,2-substituted vinylic tellurides **8a**,**b** in 72% isolated yield (Scheme 3).

Recently, we obtained chiral propargylic alcohols by a kinetic resolution of the racemic mixture using Novozyme 435.[8] In order to prepare enantiomerically enriched vinylic tellurides, we prepared (*S*)-(+)-**11a** and (*R*)-(−)-**11a** (Scheme 4) using our kinetic resolution conditions and submitted them to the hydrotelluration conditions, obtaining the chiral vinylic tellurides (*S*)-(+)-**8b** and (*R*)-(−)-**8b** (Scheme 4). Vinylic tellurides are precursors of enynes and enediynes by Te-Sonogashira reactions with alkynes[9,10] or alkynoates[9] promoted by Pd. In order to obtain chiral allylic enynols, we submitted compound **8b** to the coupling reaction with 1-heptyne promoted by $PdCl_2$/CuI[9,10] and then deprotected the TBDMS-ether **13** with tetrabutylammonium fluoride (TBAF). Initially racemic **14** was prepared and then the whole sequence was repeated to obtain (*S*)-(+)-**14** and (*R*)-(−)-**14** (Scheme 5).

Table 3. Coupling of chiral *Z*-vinylic tellurides with zincates using palladium and copper as catalysts produced according to Scheme 6

Entry	R	Compound	Yield (%)[a]
1	n-C_5H_{11}	(*S*)-(+)-**13a**	77
2	n-C_5H_{11}	(*R*)-(−)-**13a**	71
3	Ph	(*S*)-(+)-**13b**	87
4	Ph	(*R*)-(−)-**13b**	87

[a] Isolated yields after column chromatography on silica gel.



Scheme 3. Regioselective synthesis of *Z*-vinylic tellurides **8a**,**b** from propargylic ethers **7a**,**b**.

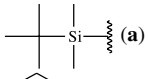
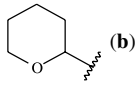
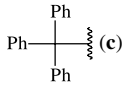
In order to use catalytic amounts of Pd, we then performed the coupling reaction of (*S*)-(+)-**8b** and (*R*)-(−)-**8b** with the zinc alkynoate as described recently.[9b] In this case 10 mol% of $Pd(PPh_3)_4$ was used as catalyst, leading to the coupled products **13a**,**b** in good yields (Scheme 6, Table 3).

To demonstrate that the enantiomeric excesses of the starting materials (*S*)-(+)-**11a** and (*R*)-(+)-**12** are kept unchanged throughout the transformations described in Schemes 4–6, compound (*R*)-(−)-**13a** was deprotected with TBAF to give alcohol (*R*)-(−)-**14** with an enantiomeric excess similar to the one of (*R*)-(+)-**12** (Fig. 1).

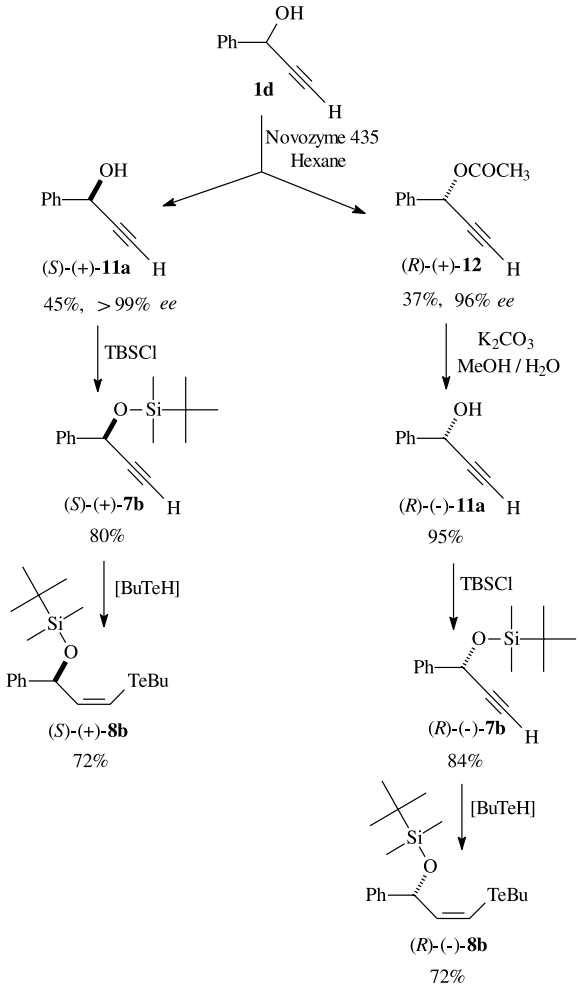
3. Conclusions

In conclusion, the hydrotelluration of propargylic alcohols

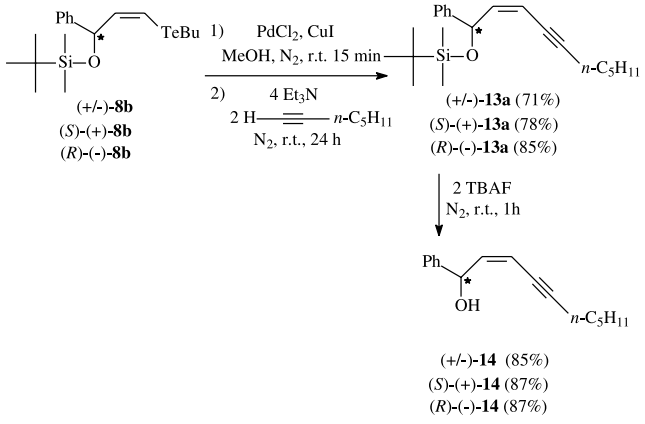
Table 2. Hydrotelluration of propargylic ethers **4a–c** produced according to Scheme 2

Entry	P	Time (h)	Yield (%)[a]	Isomeric ratio (5:6)[b]
1	 (**a**)	8	74	10:1
2	 (**b**)	8	73	6:1
3	 (**c**)	24	N.R.[c]	—

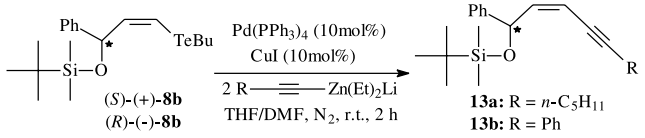
[a] Isolated yields after column chromatography on silica gel.
[b] The isomeric ratio was determined by ^1H NMR data and confirmed by GC analysis.
[c] The product was not formed.



Scheme 4. Regioselective synthesis of chiral *Z*-vinylic tellurides (*S*)-(+)-**8b** and (*R*)-(−)-**8b**.



Scheme 5. Synthesis of racemic and chiral *Z*-enynes **13a** and **14**.



Scheme 6.

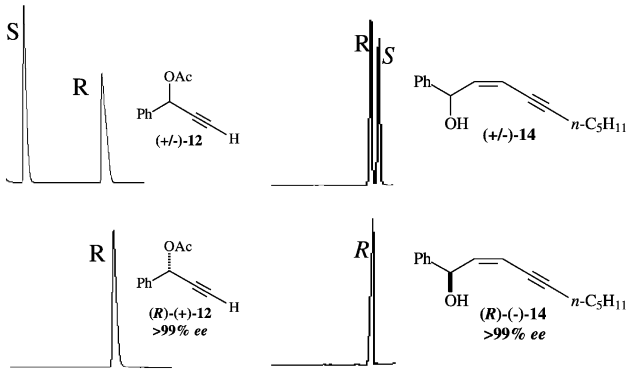


Figure 1. Chiral chromatography of (+/−)-**12**, (+/−)-**14**, (*R*)-(+)-**12** and (*R*)-(−)-**14**.

can be controlled to give the 1,2-regioisomer by transforming them into the bulky *tert*-butyldimethylsilyl ether. By using an enantiomerically enriched starting propargylic alcohol, enantiomerically enriched vinylic tellurides are obtained, which are chiral building blocks to the synthesis of chiral allylic enynols.

4. Experimental

4.1. Materials

All reagents and solvents used were previously purified and dried in agreement with the literature.[11] THF was distilled from sodium/benzophenone under N_2 immediately before use.[11] *n*-BuLi was titrated using 1,10-phenanthroline as indicator prior to use.[12] N_2 gas used in the reactions was deoxygenated and dried as described in the literature.[11,13] All operations were carried out in flame-dried glassware. Column chromatography separations were carried out with Vetec silicagel 60 (0.063–0.200 mm, 70–230 mesh) or Acros Organics silicagel (0.035–0.075 mm, pore diameter ca 6 nm). Tellurium metal (−200 mesh) was obtained from Aldrich Chemical Co. and dried overnight in an oven at 100 °C. Palladium dichloride and copper (I) iodide were purchased from Aldrich Chemical Co. and dried in a desiccator containing $CaCl_2$ and P_2O_5 under vacuum. *Tetrakis*(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) was prepared as described in the literature[14] and maintained in amber flask under nitrogen atmosphere. The following reagents were prepared according to literature procedures: 4-methyl-pent-1-yn-3-ol (**1c**);[15] 1-phenyl-2-propyn-1-ol (**1d**);[15] *tert*-butyl (but-3-yn-2-yloxy) dimethylsilane (**4a**);[16] 2-(but-3-yn-2-yloxy)-tetrahydro-2*H*-pyran (**4b**);[17] (but-3-yn-2-yloxy) triphenylmethane (**4c**);[18] (4-methyl-pent-1-yn-3-yloxy) (*tert*-butyl) dimethylsilane (**7a**)[16] and (1-phenyl-prop-2-ynyloxy) (*tert*-butyl) dimethylsilane (**7b**).[16] These last compounds presented analytical data which agree with the proposed structures. Novozyme 435 (immobilized lipase from *Candida antartica*) was obtained as a gift from Novozymes Brasil (Paraná-Brazil). The remaining chemicals were obtained from commercial sources.

4.2. Instrumentation

^1H and ^{13}C NMR spectra were obtained on a Bruker AC-200 (200 MHz, ^1H; 50 MHz, ^{13}C) or DRX-500 (500 MHz, ^1H;

125 MHz, ^{13}C) or on a Varian INOVA 300 (300 MHz, ^{1}H; 75 MHz, ^{13}C) spectrometers. All spectra were taken in $CDCl_3$ and the chemical shifts are given in ppm with respect to tetramethylsilane (TMS) used as internal standard. ^{125}Te NMR spectra were obtained on a Bruker DRX-500 (157 MHz, ^{125}Te) spectrometer using $CDCl_3$ as solvent. The chemical shifts refer to diphenyl ditelluride $(PhTe)_2$ in $CDCl_3$ (1 mol L^{-1}) ($\delta=420$ ppm at 25 °C) as external standard. Enantiomeric excesses of the enzyme-catalyzed reactions were determined using a Shimadzu GC-17A gas chromatograph equipped with a chiral capillary column Chirasil-Dex CB β-cyclodextrin (25 m×0.25 mm) or with a chiral capillary column Gamma Dex 120 Supelco (30 m×0.25 mm×0.25 μm film thickness). Optical rotation values were measured in a Jasco DIP-378 polarimeter and the reported data refer to the Na-line value using a 0.1 dm cuvette. Low resolution mass spectra were obtained on a Shimadzu CG-17A/CGMS-QP5050A instrument. Near IR spectra were obtained on a Bomem MB-100 spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Chemistry, Universidade de São Paulo. The IUPAC names were obtained using the software ChemDraw Ultra, version 8.0.

4.3. Typical procedures

4.3.1. Preparation of *Z*-vinylic tellurides.[5b] To a 50 mL two-necked round-bottomed flask equipped with magnetic stirring, heating and reflux condenser under nitrogen atmosphere were added elemental tellurium (0.254 g, 2 mmol) and THF (10 mL). To the suspension obtained, *n*-BuLi (1.3 mL, 2 mmol of a 1.5 mol L^{-1} solution in hexane) was added dropwise at room temperature. A clear solution was formed after 5 min of stirring. After that, the appropriate alkyne (2.4 mmol) in deoxygenated ethanol (20 mL) was added and the resulting mixture was refluxed by the time indicated in the Tables 1 and 2 and Scheme 3. The reaction was quenched with brine (50 mL) followed by extraction with ethyl acetate (3×50 mL). The extracts were dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using appropriate eluent.

4.3.2. (*Z*)-3-(Butyltellanyl)prop-2-en-1-ol (2a)/2-(butyltellanyl) prop-2-en-1-ol (3a).[4a] Eluent: hexane/ethyl acetate (9:1); yield: 0.386 g (80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.77 (ddd, $J=9.6$, 1.2, 1.5 Hz, 0.4H), 6.40 (ddd, $J=9.6$, 5.2, 5.4 Hz, 0.4H), 6.16 (dd, $J=1.6$, 1.5 Hz, 1H), 5.52 (dd, $J=1.3$, 1.2 Hz, 1H), 4.19 (s, 1H), 4.11 (dd, $J=3.6$, 3.3 Hz, 0.4H), 2.72 (t, $J=7.5$ Hz, 2H), 2.60 (t, $J=4.8$ Hz, 0.8H), 1.74 (m, 2.8H), 1.36 (m, 2.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 137.4, 127.1, 122.7, 104.6, 70.1, 64.9, 34.0, 33.7, 25.0, 24.8, 13.3, 7.1, 6.1.

4.3.3. (+/−)-(*Z*)-4-(Butyltellanyl)but-3-en-2-ol (2b)/(+/−)-3-(butyltellanyl) but-3-en-2-ol (3b). Eluent: hexane/ethyl acetate (9:1); yield: 0.379 g (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.69 (dd, $J=9.6$, 0.9 Hz, 1H), 6.28 (dd, $J=9.6$, 6.9 Hz, 1H), 6.12 (d, $J=0.9$ Hz, 1.5H), 5.40 (s, 1.5H), 4.33 (quint, $J=6.3$ Hz, 1H), 4.22 (q, $J=5.7$ Hz, 1.5H), 2.73 (t, $J=7.9$ Hz, 3H), 2.65 (t, $J=7.5$ Hz, 2H), 1.77 (m, 5H), 1.39 (m, 5H), 1.33 (d, $J=6.3$ Hz, 4.5H), 1.27 (d, $J=6.6$ Hz, 3H), 0.92 (t, $J=7.2$ Hz, 7.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.0, 135.6, 120.7, 103.2, 74.1, 70.5, 34.0, 33.4, 25.1, 24.9, 23.8, 22.4, 13.3, 7.1, 6.4; Near IR (film) ν (cm^{-1}) 3387, 2959, 2926, 2866, 1597, 1455, 1370, 1177; LRMS *m/z* (relative intensity) 258 (13%, M^+), 184 (21%), 71 (30%), 57 (100%)/258 (13%, M^+), 184 (7%), 71 (100%), 57 (60%). Anal. Calcd for $C_8H_{16}OTe$ C 37.56, H 6.30. Found C 37.75, H 6.12.

4.3.4. (+/−)-(*Z*)-1-(Butyltellanyl)-4-methyl-pent-1-en-3-ol (2c)/(+/−)-2-(butyltellanyl)-4-methyl-pent-1-en-3-ol (3c). Eluent: hexane/ethyl acetate (9:1); yield: 0.341 g (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.82 (dd, $J=9.8$, 0.8 Hz, 1H), 6.28 (dd, $J=9.8$, 7.1 Hz, 1H), 6.11 (d, $J=0.9$ Hz, 1H), 5.48 (s, 1H), 3.90 (dd, $J=6.5$, 6.48 Hz, 1H), 3.53 (d, $J=7.1$ Hz, 1H), 2.75 (dt, $J=7.5$, 3.0 Hz, 2H), 2.65 (dt, $J=7.5$, 1.9 Hz, 2H), 1.78 (m, 6H), 1.40 (m, 4H), 1.00 (d, $J=6.6$ Hz; 3H), 0.96 (d, $J=6.7$ Hz, 6H), 0.92 (m, 9H), 0.86 (d, $J=6.7$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 139.3, 133.9, 122.2, 105.7, 84.1, 79.2, 34.1, 33.8, 33.5, 33.4, 25.2, 24.5, 19.5, 18.1, 17.8, 17.7, 13.3, 7.1, 6.4; Near IR (film) ν (cm^{-1}) 3429, 3060, 2958, 2927, 2870, 1598, 1463, 1380, 1030, 1009; LRMS *m/z* (relative intensity) 284 (11%, M^+), 282 (7%), 185 (13%), 183 (9%), 99 (10%), 81 (87%), 57 (100%), 284 (7%, M^+), 282 (4%), 185 (11%), 183 (7%), 99 (6%), 81 (16%), 57 (100%). Anal. Calcd for $C_{10}H_{20}OTe$ C 42.31, H 7.10. Found C 42.59, H 6.61.

4.3.5. (+/−)-(*Z*)-3-(Butyltellanyl)-1-phenyl-prop-2-en-1-ol (2d)/(+/−)-2-(butyltellanyl)-1-phenyl-prop-2-en-1-ol (3d). Eluent: hexane/ethyl acetate (9:1); yield: 0.382 g (60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 7.5H), 6.86 (dd, $J=9.9$, 1.5 Hz, 1H), 6.48 (dd, $J=9.9$, 6.6 Hz, 1H), 6.29 (d, $J=1.2$ Hz, 0.5H), 5.62 (d, $J=1.2$ Hz, 0.5H), 5.26 (d, $J=6.3$ Hz, 1H), 5.20 (d, $J=3.6$ Hz, 0.5H), 2.67 (t, $J=7.2$ Hz; 3H), 2.57 (t, $J=7.5$ Hz, 1.5H), 2.46 (d, $J=5.1$ Hz, 0.5H), 2.16 (d, $J=2.7$ Hz, 1H), 1.79 (m, 4H), 1.66 (m, 2H), 1.40 (m, 5H), 0.93 (t, $J=7.5$ Hz, 4H), 0.87 (t, $J=7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 142.5, 140.1, 132.7, 128.6, 128.3, 127.8, 127.7, 126.4, 126.2, 123.6, 105.0, 79.8, 76.4, 34.3, 33.6, 25.3, 25.2, 13.5, 7.7, 7.3; Near IR (film) ν (cm^{-1}) 3397, 3084, 3061, 3025, 2957, 2925, 2870, 2857, 1596, 1491, 1454, 1377, 1035, 761, 699; LRMS *m/z* (relative intensity) 320 (18%, M^+), 318 (17%), 204 (28%), 115 (100%), 89 (8%), 77 (47%), 57 (62%), 320 (13%, M^+), 318 (13%), 261 (25%), 149 (20%), 131 (88%), 115 (100%), 91 (7%), 77 (88%), 57 (72%). Anal. Calcd for $C_{13}H_{18}OTe$ C 49.12, H 5.71. Found C 49.36, H 5.46.

4.3.6. (+/−)-((*Z*)-4-(Butyltellanyl) but-3-en-2-yloxy) (*tert*-butyl) dimethylsilane (5a)/(+/−)-(3-(butyltellanyl) but-3-en-2-yloxy) (*tert*-butyl)dimethylsilane (6a). Eluent: hexane; yield: 0.548 g (74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.54 (dd, $J=9.9$, 0.6 Hz, 1H), 6.23 (dd, $J=9.9$, 7.2 Hz, 1H), 4.28 (dt, $J=6.7$, 0.9 Hz, 1H), 2.63 (dt, $J=7.8$, 3.6 Hz, 2H), 1.75 (quint, $J=7.2$ Hz, 2H), 1.38 (sext, $J=7.5$ Hz, 2H), 1.18 (d, $J=6.6$ Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 143.9, 100.2, 72.0, 34.1, 26.0, 24.9, 23.4, 18.2, 13.3, 6.8, −4.3, −4.6; ^{125}Te NMR (157 MHz, $CDCl_3$) δ (ppm) 265; Near IR (film) ν (cm^{-1}) 2958, 2929, 2886, 2857, 1640, 1463, 1200, 1117, 1092; LRMS *m/z* (relative intensity) 372 (6%, M^+), 370 (5%), 315 (13%), 241 (12%), 185 (22%),

183 (15%), 181 (11%), 127 (100%), 75 (47%), 73 (59%), 57 (18%), 55 (20%). Anal. Calcd for $C_{14}H_{30}OSiTe$ C 45.44, H 8.17. Found C 45.38, H 8.05.

4.3.7. (+/−)-2-((*Z*)-4-(Butyltellanyl) but-3-en-2-yloxy)-tetrahydro-2*H*-pyran (5b)/(+/−)-2-(3-(butyltellanyl) but-3-en-2-yloxy)-tetrahydro-2*H*-pyran (6b). Eluent: hexane; yield: 0.496 g (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.79 (dd, J=9.7, 0.6 Hz, 1H), 6.67 (dd, J=9.8, 0.9 Hz, 0.2H), 6.31 (dd, J=9.8, 7.1 Hz, 0.2H), 6.13 (dd, J=9.7, 7.9 Hz, 1H), 6.09 (d, J=1.0 Hz, 0.2H), 6.08 (d, J=1.0 Hz, 0.2H), 4.71 (dd, J=4.4, 3.1 Hz, 0.2H), 4.61 (dd, J=4.5, 3.0 Hz, 0.2H), 4.59 (dd, J=6.5, 0.6 Hz, 1H), 4.34 (ddt, J=7.8, 6.5, 0.6 Hz, 1H), 4.30–4.26 (m, 0.4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 145.0, 140.1, 134.3, 120.2, 105.5, 102.4, 96.7, 96.5, 96.1, 74.5, 73.7, 63.1, 62.6, 62.6, 34.1, 33.4, 30.9, 30.9, 30.6, 26.0, 25.5, 25.4, 25.3, 22.9, 20.5, 20.0, 19.7, 19.6, 19.4, 13.4, 6.9, 6.8, 5.2; Near IR (film) ν (cm^{-1}) 2954, 2929, 2870, 1598, 1462, 1454, 1368, 1201, 1121, 1077, 1034, 1021, 986; LRMS *m/z* (relative intensity) 340 (6%, M^+), 256 (3%), 242 (10%), 184 (17%), 85 (70%), 67 (25%), 57 (100%), 340 (5%), 256 (8%), 201 (10%), 182 (6%), 85 (87%). Anal. Calcd for $C_{13}H_{24}O_2Te$ C 45.93, H 7.12. Found C 45.91, H 6.83.

4.3.8. (+/−)-((*Z*)-1-(Butyltellanyl)-4-methyl-pent-1-en-3-yloxy) (*tert*-butyl)dimethylsilane (8a). Eluent: hexane; yield: 0.573 g (72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.67 (dd, J=9.6, 0.6 Hz, 1H), 6.17 (dd, J=9.6, 8.1 Hz, 1H), 3.78 (dd, J=7.9, 5.7 Hz, 1H), 2.65 (m, 2H), 1.76 (quint, J=7.5 Hz, 2H), 1.70 (m, 1H), 1.39 (dq, J=7.2, 7.5 Hz, 2H), 0.92 (t, J=7.2 Hz, 3H), 0.86 (d, J=6.9 Hz, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 142.0, 103.0, 80.6, 34.9, 34.1, 25.9, 24.9, 18.4, 18.1, 17.9, 13.3, 6.9, −4.0, −4.8; ^{125}Te NMR (157 MHz, $CDCl_3$) δ (ppm) 267; Near IR (film) ν (cm^{-1}) 2957, 2929, 2886, 2857, 1598, 1465, 1125, 1069; LRMS *m/z* (relative intensity) 398 (2%, M^+), 357 (28%), 355 (24%), 155 (23%), 115 (5%), 81 (15%), 75 (36%), 73 (100%), 57 (19%), 55 (11%). Anal. Calcd for $C_{16}H_{34}OSiTe$ C 48.27, H 8.61. Found C 48.45, H 8.21.

4.3.9. (+/−)-((*Z*)-3-(Butyltellanyl)-1-phenyl-allyloxy) (*tert*-butyl)dimethylsilane (8b). Eluent: hexane; yield: 0.622 g (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.38–7.37 (m, 2H), 7.33–7.29 (m, 2H), 7.21–7.24 (m, 1H), 6.68 (dd, J=9.6, 0.6 Hz, 1H), 6.33 (dd, J=9.6, 7.6 Hz, 1H), 5.21 (d, J=7.6 Hz, 1H), 2.64–2.74 (m, 2H), 1.79 (dt, J=7.5, 7.4 Hz, 2H), 1.40 (dq, J=7.5, 7.4 Hz, 2H), 0.92 (t, J=4.1 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 143.5, 142.5, 128.3, 127.1, 125.8, 102.2, 34.1, 26.0, 24.9, 18.3, 13.4, 7.4, −4.2, −4.6; ^{125}Te NMR (157 MHz, $CDCl_3$) δ (ppm) 278; Near IR (film) ν (cm^{-1}) 3062, 3025, 2956, 2929, 2888, 2857, 1597, 1463, 1254, 1089, 1066, 868, 838; LRMS *m/z* (relative intensity) 432 (3%, M^+), 377 (7%), 303 (3%), 247 (20%), 189 (23%), 115 (100%), 73 (82%), 57 (17%). Anal. Calcd for $C_{19}H_{32}OSiTe$ C 52.81, H 7.46. Found C 53.15, H 7.27.

4.3.10. Kinetic resolution of compound 1d using Novozyme 435.[8] To a 125 mL Erlenmeyer flask were added hexane (HPLC grade) (20 mL), vinyl acetate (1 mL), Novozyme 435 (0.300 g) and 1-phenyl-prop-2-yn-1-ol (**1d**) (0.560 g, 4 mmol). The reaction mixture was stirred on a rotary shaker (32 °C, 170 rpm) for 40 min. After that, the mixture was filtered and the solvent evaporated. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent. The enatiomeric rate (*E*) for the kinetic resolution of 1-phenyl-prop-2-yn-1-ol (**1d**) was > 200 and the convertion (*c*) was 50%.

4.3.11. (*S*)-(+)-1-Phenyl-prop-2-yn-1-ol (11a). Yield: 0.218 g (39%); enantiomeric excess (*ee*): >99%; $[\alpha]_D^{25}$ = +16.3 (*c* 4.34, $CHCl_3$), 99% *ee* {Lit. $[\alpha]_D^{25}$ = +20.0 (*c* 1.13, $CHCl_3$), 72% *ee*}[19] ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.56–7.51 (m, 2H), 7.50–7.28 (m, 3H), 5.43 (d, J=2.2 Hz, 1H), 2.65 (d, J=2.0 Hz, 1H), 2.49 (s_{broad}, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 140.0, 128.6, 128.4, 126.5, 83.5, 74.7, 64.3; Near IR (film) ν (cm^{-1}) 3371, 3293, 3088, 3065, 3033, 2880, 2118, 1454, 1276, 1022, 739, 699, 651; LRMS *m/z* (relative intensity) 132 (86%, M^+), 131 (100%), 115 (26%), 103 (42%), 89 (12%), 77 (75%), 63 (20%), 53 (84%).

4.3.12. (*R*)-(+)-1-Phenyl-prop-2-ynyl acetate (12). Yield: 0.339 g (46%); enantiomeric excesses (*ee*): 96–99%; $[\alpha]_D^{25}$ = +4.4 (*c* 4.33, $CHCl_3$), 98% *ee*; {Lit. $[\alpha]_D^{25}$ = +3.4 (*c* 1.07, $CHCl_3$), 85% *ee*}[19] ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.59–7.52 (m, 2H), 7.47–7.39 (m, 3H), 6.48 (d, J=2.2 Hz, 1H), 2.68 (d, J=2.0 Hz, 1H), 2.13 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 169.6, 136.5, 129.0, 128.6, 127.6, 80.2, 75.3, 65.2, 20.9; Near IR (film) ν (cm^{-1}) 3289, 3066, 3036, 2940, 2126, 1742, 1456, 1371, 1228, 760, 698, 653; LRMS *m/z* (relative intensity) 174 (M^+, 9.6%), 132 (37.2%), 114 (100.0%), 103 (8.0%), 89 (11.8%), 77 (11.2%), 63 (13.5%), 43 (44.6%).

4.3.13. Preparation of compound (*R*)-(−)-11a.[20] To a 25 mL two-necked round-bottomed flask equipped with magnetic stirring were added (*R*)-(+)-**12** (0.330 g, 1.9 mmol), methanol (3 mL), water (3 mL) and K_2CO_3 (0.262 g, 1.9 mmol). The mixture was stirred at room temperature for 12 h. After that, the reaction was quenched with brine (15 mL) followed by extraction with ethyl acetate (4 x 15 mL). The extracts were dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure.

(R)-(−)-1-Phenyl-prop-2-yn-1-ol (**11a**). Yield: 0.238 g (95%); $[\alpha]_D^{25}$ = −24.7 (*c* 2.20, $CHCl_3$). (The spectral data agreed with those obtained for compound (*S*)-(+)-**11a**.)

4.3.14. Preparation of (*S*)-(+)-7b and (*R*)-(−)-7b.[16] To a 25 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere were added (*S*)-(+)-**11a** or (*R*)-(−)-**11a** (0.210 g, 1.6 mmol), $CHCl_3$ (2.5 mL), *tert*-butyldimethylsilyl chloride (0.271 g, 1.8 mmol) and imidazole (0.238 g, 3.5 mmol). The mixture was stirred at room temperature for 12 h. After that, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with water (3×100 mL). The organic phase was dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure.

*(R)-(−)-1-Phenyl-prop-2-ynyloxy) (*tert*-butyl) dimethyl silane* (**7b**).[16b] Yield: 0.331 g (84%); $[\alpha]_D^{25}$ = −16.62 (*c* 2.10, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.51–

7.47 (m, 2H), 7.38–7.28 (m, 3H), 5.48 (d, $J=2.2$ Hz, 1H), 2.53 (d, $J=2.2$ Hz, 1H), 0.94 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); LRMS *m/z* (relative intensity) 231 (1%), 189 (100%), 179 (46%), 159 (1%), 145 (2%), 135 (18%), 115 (78%), 105 (28%), 89 (9%), 83 (45%), 75 (21%), 57 (8%).

*(S)-(+)-1-Phenyl-prop-2-ynyloxy) (*tert*-butyl) dimethyl silane* (**7b**). Yield: 0.315 g (80%); $[\alpha]_D^{25}=+9.35$ (*c* 2.00, $CHCl_3$). (The spectral data agreed with those obtained for compound (*R*)-(−)-**7b**).

4.3.15. Preparation of compounds (*S*)-(+)-8b and (*R*)-(−)-8b. The reactions were performed as described in Section 4.3.1. in a 1.2 mmol scale.

*((S,Z)-(+)-3-(Butyltellanyl)-1-phenylallyloxy) (*tert*-butyl)-dimethylsilane* (**8b**). Yield: 0.373 g (72%); $[\alpha]_D^{25}=+137.39$ (*c* 2.30, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**8b**).

*((R,Z)-(−)-3-(Butyltellanyl)-1-phenylallyloxy) (*tert*-butyl)-dimethylsilane* (**8b**). Yield: 0.373 g (72%); $[\alpha]_D^{25}=-144.50$ (*c* 2.00, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**8b**).

4.3.16. Preparation of compounds (+/−)-13, (*S*)-(+)-13a and (*R*)-(−)-13a: cross-coupling reaction using $PdCl_2$/CuI.[9a,10] To a 25 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere were added $PdCl_2$ (0.124 g, 0.7 mmol), CuI (0.133 g, 0.7 mmol), methanol (7 mL) and the telluride **8b** (0.300 g, 0.7 mmol). The mixture was stirred at room temperature for 15 min under nitrogen atmosphere. After that, 1-heptyne (0.135 g, 1.4 mmol) and triethylamine (0.4 mL, 0.283 g, 2.8 mmol) were added to the reaction mixture which was stirred under nitrogen atmosphere at room temperature for 24 h. Then, the solids were filtered off over celite®, washing several times with methanol. The solvent was evaporated under reduced pressure. To the residue was added brine (30 mL), and the mixture was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried over $MgSO_4$ and then filtered. The organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using hexane as eluent. The analytical data of products were obtained after purification by preparative thin layer chromatography using hexane as eluent.

4.3.17. (+/−)-(*Z*)-*tert*-Butyl-dimethyl-(1-phenyl-dec-2-en-4-ynyloxy)-silane (13). Yield: 0.170 g (71%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.46–7.41 (m, 2H), 7.35–7.18 (m, 3H), 5.90–5.78 (m, 2H), 5.55–5.42 (m, 1H), 2.39 (td, $J=6.8$, 2.2 Hz, 2H), 1.59 (quint, $J=7.0$ Hz, 2H), 1.47–1.24 (m, 4H), 0.93 (s, 9H), 0.90 (t, $J=7.0$ Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 144.6, 143.9, 128.2, 127.0, 125.4, 108.7, 95.6, 77.1, 72.2, 31.2, 28.5, 25.9, 22.2, 19.5, 18.3, 13.4, −4.4, −4.9; Near IR (film) ν (cm^{-1}) 3063, 3029, 2956, 2931, 2859, 2216, 1603, 1492, 1464, 1390, 1254, 1091, 1068, 874, 837, 744, 698; LRMS *m/z* (relative intensity) 342 (1%, M^+), 327 (1%), 285 (91%), 267 (1%), 229 (4%), 211 (26%), 203 (7%), 189 (8%), 169 (4%), 153 (18%), 141 (18%), 129 (9%), 115 (17%), 105 (5%), 91 (25%), 75 (100%), 55 (2%). Anal. Calcd for $C_{22}H_{34}OSi$ C 77.13, H 10.00. Found C 77.39, H 10.05.

*((S,Z)-(+)-1-Phenyl-dec-2-en-4-ynyloxy) (*tert*-butyl) dimethyl-silane* (**13a**). Yield: 0.187 g (78%); $[\alpha]_D^{25}=+192.50$ (*c* 2.30, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**13**).

*((R,Z)-(−)-1-Phenyl-dec-2-en-4-ynyloxy) (*tert*-butyl) dimethylsilane* (**13a**). Yield: 0.204 g (85%); $[\alpha]_D^{25}=-254.35$ (*c* 2.30, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**13**).

4.3.18. Preparation of compounds (+/−)-14, (*S*)-(+)-14 and (*R*)-(−)-14.[21] To a 15 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere were added the appropriate *Z* enyne (+/−)-**13** (0.150 g, 0.4 mmol) and tetrabutylammonium fluoride (1.0 mol L^{-1} solution in THF) (0.8 mL, 0.8 mmol). The reaction mixture was stirred under nitrogen atmosphere at room temperature for 1 h. The reaction was quenched with brine (50 mL) followed by extraction with ethyl acetate (3×50 mL). The extracts were dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) as eluent. The analytical data of the products were obtained after purification by preparative thin layer chromatography using hexane/ethyl acetate (9:1) as eluent.

4.3.19. (+/−)-(*Z*)-1-Phenyl-dec-2-en-4-yn-1-ol 14. Yield: 0.077 g (85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.47–7.23 (m, 5H), 5.99 (dd, $J=10.5$, 8.3 Hz, 1H), 5.79 (d, $J=8.3$ Hz, 1H), 5.60 (dt, $J=10.5$, 2.0 Hz, 1H), 2.37 (td, $J=7.0$, 2.2 Hz, 2H), 2.22 (s_{broad}, 1H), 1.58 (quint, $J=6.9$ Hz, 2H), 1.48–1.25 (m, 4H), 0.91 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 142.8, 142.8, 128.5, 127.6, 125.8, 110.7, 96.8, 76.6, 72.0, 31.1, 28.41, 22.2, 19.6, 14.0; Near IR (film) ν (cm^{-1}) 3386, 3085, 3062, 3029, 2957, 2931, 2860, 2214, 1602, 1493, 1453, 1378, 1046, 746, 699; LRMS *m/z* (relative intensity) 228 (3%, M^+), 213 (0.5%), 199 (2%), 185 (6%), 171 (34%), 157 (44%), 143 (14%), 128 (29%), 115 (20%), 105 (100%), 91 (36%), 77 (65%), 65 (16%), 55 (31%); Anal. Calcd for $C_{16}H_{20}O$ C 84.16, H 8.83. Found C 83.98, H 8.66.

(S,Z)-(+)-1-Phenyl-dec-2-en-4-yn-1-ol (**14**). Yield: 0.079 g (87%); $[\alpha]_D^{25}=+350.50$ (*c* 2.00, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**14**).

(R,Z)-(−)-1-Phenyl-dec-2-en-4-yn-1-ol (**14**). Yield: 0.079 g (87%); $[\alpha]_D^{25}=-308.33$ (*c* 1.20, $CHCl_3$). (The spectral data agreed with those obtained for compound (+/−)-**14**).

4.3.20. Cross-coupling reaction using $Pd(PPh_3)_4$ and CuI as catalysts.[9b] *Preparation of the zinc reagent*. To a 15 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere were added the appropriate alkyne (1 mmol) and THF (4 mL). Then, *n*-BuLi (0.77 mL, 1 mmol of a 1.3 mol L^{-1} solution in hexane) was added dropwise at −70 °C, and the mixture was stirred for 10 min. After that, Et_2Zn (1 mL, 1 mmol of a 1.0 mol L^{-1} solution in THF) was added to the reaction mixture which was

then warmed to room temperature. The zinc reagent became ready for use.

Cross-coupling reaction. To a 25 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere were added the telluride **8b** (0.216 g, 0.5 mmol), THF (4 mL), $Pd(PPh_3)_4$ (0.027 g, 0.05 mmol), CuI (0.095 g, 0.05 mmol), DMF (4 mL) and the appropriate zinc reagent (1 mmol of the solution prepared above) via syringe. The reaction mixture was stirred under inert atmosphere at room temperature for 2 h. The reaction was quenched with brine (50 mL) followed by extraction with ethyl acetate (3× 50 mL). The extracts were dried over $MgSO_4$ and then filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using hexane as eluent. The analytical data of the products were obtained after purification by preparative thin layer chromatography using hexane as eluente.

*((*S,Z*)-(+)-1-Phenyl-dec-2-en-4-ynyloxy) (*tert*-butyl) dimethylsilane* (**13a**). Yield: 0.133 g (78%). (For spectral data see Section 4.3.16.)

*((*R,Z*)-(−)-1-Phenyl-dec-2-en-4-ynyloxy) (*tert*-butyl) dimethylsilane* (**13a**). Yield: 0.145 g (85%). (For spectral data see Section 4.3.16.)

*((*S,Z*)-(+)-1,5-Diphenyl-pent-2-en-4-ynyloxy) (*tert*-butyl) dimethylsilane* (**13b**). Yield: 0.151 g (87%); $[\alpha]_D^{25} = +266.67$ (*c* 0.37, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.50–7.23 (m, 10H), 6.01 (d, $J=10.5$ Hz, 1H), 5.97 (dd, $J=9.9$, 9.0 Hz, 1H), 5.72 (d, $J=9.9$ Hz, 1H), 0.94 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); 50 MHz RMN ^{13}C ($CDCl_3$) (ppm) 145.9, 143.5, 131.5, 128.4, 128.3, 128.3, 127.1, 125.5, 108.1, 94.2, 85.9, 72.3, 25.8, 25.8, 18.3, −4.4, −4.9; Near IR (film) ν (cm^{-1}) 2955, 2930, 2857, 1948, 1877, 1805, 1740, 1597, 1490, 1467, 1254, 1092, 1064, 1027, 1005, 954, 939; LRMS *m/z* (relative intensity) 348 (3%, M^+), 293 (7%), 292 (28%), 291 (100%), 218 (16%), 217 (78%), 216 (17%), 215 (51%), 213 (31%), 202 (39%), 115 (40%), 91 (18%), 75 (47%), 73 (34%), 57 (14%); Anal. Calcd for $C_{23}H_{28}OSi$ C 79.26, H 8.10. Found C 79.38, H 8.10.

*((*R,Z*)-(−)-1,5-Diphenyl-pent-2-en-4-ynyloxy) (*tert*-butyl) dimethylsilane* (**13b**). Yield: 0.151 g (87%); $[\alpha]_D^{25} = -308.33$ (*c* 0.37, $CHCl_3$). (The spectral data agreed with those obtained for compound (*S*)-(+)-**13b**).

Acknowledgements

The authors acknowledge Novozymes Brasil (Paraná-Brazil) for a gift of Novozyme 435 and CNPq and FAPESP for financial support.

References and notes

1. (a) Irgolic, K. J. In *Houben Weyl: Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1990; Vol. E12b. (b) Petragnani, N. *Tellurium in Organic Synthesis*; Academic: New York, 1994. For recent reviews see: (c) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373. (d) Comasseto, J. V.; Barrientos-Astigarraga, R. E. *Aldrichim. Acta* **2000**, *33*, 66. (e) Vieira, M. L.; Zinn, F. K.; Comasseto, J. V. *J. Braz. Chem. Soc.* **2001**, *12*, 586.
2. Casson, S.; Kocienski, P. In *Organometallic Reagents in Organic Synthesis*; Batesson, J. H., Mitchel, M. B., Eds.; Academic: London, 1994; Chapter 7, pp 129–159.
3. Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664.
4. (a) Takahashi, H.; Ohe, K.; Uemura, S.; Sugita, N. *Nippon Kagaku Kaishi* **1987**, 1508. (b) Ohe, K.; Takahashi, H.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1987**, *326*, 35. (c) Barros, S. M.; Dabdoub, M. J.; Dabdoub, V. M. B.; Comasseto, J. V. *Organometallics* **1989**, *8*, 1661.
5. (a) Sashida, H. *Rev. Heteroatom Chem.* **2000**, *22*, 59 and references cited therein. (b) Zeni, G.; Formiga, H. B.; Comasseto, J. V. *Tetrahedron Lett.* **2000**, *41*, 1311.
6. See Commemorative issue of Natural Product Reports in honor of Professor John Falkner, D. *Nat. Prod. Rep.* **2004**, *21*, 1–210.
7. Corey, E. J.; Cheng, X.-M. In *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
8. Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117.
9. (a) Zeni, G.; Comasseto, J. V. *Tetrahedron Lett.* **1999**, *40*, 4619. (b) Dabdoub, M. J.; Dabdoub, V. B.; Marino, J. P. *Tetrahedron Lett.* **2000**, *41*, 437. For a review see: Zeni, G.; Braga, A. L.; Stefani, H. A. *Acc. Chem. Res.* **2003**, *36*, 731.
10. Raminelli, C.; Prechtl, M. H. G.; Santos, L. S.; Eberlin, M. N.; Comasseto, J. V. *Organometallics* **2004**, *23*, 3990.
11. Perrin, D. D.; Armarego, W. L. F. In *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1980.
12. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
13. Tucci, F. C.; Chieffi, A.; Comasseto, J. V. *J. Org. Chem.* **1996**, *61*, 4975.
14. Komiya, S. In Komiya, S., Ed.; Synthesis of Organometallic Compounds—A Practical Guide; Wiley: Chichester, 1997; Vol. 1, p 286.
15. Mortier, J.; Vaultier, M.; Carreaux, F.; Douin, J.-M. *J. Org. Chem.* **1998**, *63*, 3515.
16. (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*(17), 6190. (b) Horsham, M. A.; Class, T. J.; Johnston, J. J.; Casida, J. E. *J. Agric. Food Chem.* **1989**, *37*, 777.
17. Bongini, A.; Cardilho, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.
18. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 95.
19. Waldinger, C.; Schneider, M.; Botta, M.; Corelli, F.; Summa, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1485.
20. Danda, H.; Nagatomi, T.; Maehara, A.; Umemura, T. *Tetrahedron* **1991**, *47*, 8701.
21. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; pp 127–141.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 417–422

Effect of electron-withdrawing substituents on the electrophilicity of carbonyl carbons

R. Contreras,[a,b,†,*] J. Andrés,[b,*] L. R. Domingo,[c,*] R. Castillo[b] and P. Pérez[d]

[a]*Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile*
[b]*Departament de Cienciès Experimentals, Universitat Jaume I, Box 224, 12080 Castelló, Spain*
[c]*Instituto de Ciencia Molecular, Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain*
[d]*Departamento de Ciencias Químicas, Facultad de Ecología y Recursos Naturales, Universidad Andrés Bello, República 275, Santiago, Chile*

Received 8 June 2004; revised 25 October 2004; accepted 28 October 2004

Available online 13 November 2004

Abstract—The substituent effects on the carbonyl carbon atom for a series of twelve substituted phenyl acetates have been rationalized using a global electrophilicity index. This index is linearly correlated with the experimental reaction rate coefficients. We found that, in contrast to the proposed interpretation based on experimental ^{13}C NMR chemical shifts and ground state destabilization calculations, the electrophilicity of carbonyl compounds increases due to the effect promoted by electron-withdrawing groups in these systems.

1. Introduction

It is well established that nucleophilic attack on the carbonyl carbon of RCOX compounds depends mainly on the electron-withdrawing (EW) ability of both R and X substituents. The presence of an EW substituent in the leaving group, X, or in the remaining acyl group, R, increases the reaction rate coefficient.[1–3] This result has been confirmed by a Hammett analysis of the substituent constants, showing positive slopes when plotted against the reaction rate coefficients k.[2,3] This behavior has been currently interpreted as an increase in electrophilicity at the reaction center due to the presence of EW substituent in the carbonyl substrate.

The electrophilicity of the carbonyl carbon is one of the determining factors of the chemical reactivity exhibited by fundamental compounds, such as aldehydes, ketones or carboxylic acid derivatives. The substituent effects on nucleophilic reactions of acyl-substituted phenyl acetates and phenyl-substituted phenyl acetates have been studied recently by Neuvonen et al.[4,5] Good correlations with negative slopes for the plots of log k versus the ^{13}C NMR chemical shift δ_C (C═O) have been found. The upfield shift of the carbonyl carbon signal in the ^{13}C NMR spectra was related with the EW ability of the phenyl substituent of phenyl dichloroacetates or benzoyl substituent in methyl benzoates.[4,5] Since an upfield chemical shift is usually associated with an increase of the electron density at the site, Neuvonen et al. interpreted this positive variation of the electron density at the carbonyl carbon as a decrease of the electrophilicity at this site.

Murray et al.[6] studied the reactivity of a series of cyclic ureides toward nucleophilic attacks, using the molecular electrostatic potential surface (MEPS) at the carbonyl carbon. For a series of substituted 2-imidazolidinones they found that the MEPS at the carbonyl carbon provided a basis for predicting the relative hydrolytic tendency. Susceptibility toward hydrolysis is expected to increase roughly as the MEPS becomes more positive. They also found that the calculated atomic charges at the carbonyl carbon bear little or no relationship to the electrostatic potential values.

Recently, we have shown[7–12] that the electrophilicity of a molecule may be conveniently described by the global index, ω, proposed by Parr et al.[13] This index, which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment, is defined by the following simple

Keywords: Carbonyl reactivity; Electron-withdrawing effects; Electrophilicity; DFT calculations.
* Corresponding authors. Tel.: +56 2 6787272; fax: +56 2 2713888 (R.C.); e-mail: rcontrer@argon.ciencias.uchile.cl
† Departamento de Química, Facultad de Ciencias, Universidad de Chile, Las Palmeras, Casilla 653, Santiago, Chile.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.085

expression:[13]

$$\omega = \frac{\mu^2}{2\eta}, \tag{1}$$

in terms of the electronic chemical potential, μ (the negative of electronegativity), and the chemical hardness, η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbitals, HOMO and LUMO, ε_H and ε_L, as $\mu=(\varepsilon_H+\varepsilon_L)/2$ and $\eta\approx\varepsilon_L-\varepsilon_H$, respectively.[14]

Electrophilicity, as ranked in terms of reaction rates becomes a kinetic concept.[15] However, although there is no rigorous procedure to establish the kinetic character of the theoretical ω index, yet the comparison between both the experimental and theoretical electrophilicity scales[7,8] seems to confirm the ω index as a reliable quantitative representation of electrophilicity. According to Eq. 1, this index contains information about the propensity of the electrophile to acquire an additional electronic charge represented by the square of the electronegativity, and the resistance of the system to exchange electronic charge with the environment described by η. The atomic electron population, is in this sense, just a piece of information encompassed in the electrophilicity concept.

Substituent effects on electrophilicity evaluated from ω for Diels–Alder[9] and 1,3-dipolar cycloaddition[10] reactions have been found to be in good agreement with the experimental relative rates. Furthermore, it was found that the difference in electrophilicity for the diene/dienophile pair determined the nature of the reaction mechanism (non-polar or polar character of the process),[9] thereby reinforcing the reliability of the ω index as a kinetic descriptor of reactivity. More recently we have shown that the global electrophilicity index and its local counterpart may be used to characterize the reactivity pattern of the C=C double bond towards nucleophilic addition reactions. A wide family of molecules including ketones, esters, anhydrides, nitriles and nitrocompounds containing appropriate substitution on the C=C double bond have been classified within an unique scale of reactivity.[16] This index has been found to be almost insensitive to solvent effects for neutral electrophiles.[11] Thus, gas phase calculations suffice to establish the electrophilic power of molecules. Finally, we have shown that the intrinsic electronic contribution to the σ_p Hammett substituent constants, $\sigma_e(\omega)$, can be estimated from the ω index calculated for a series of substituted ethylenes.[12] EW substitution on ethylene increases the electrophilicity of molecules, and the corresponding $\sigma_e(\omega)$ values were consistently predicted as positive numbers.[12]

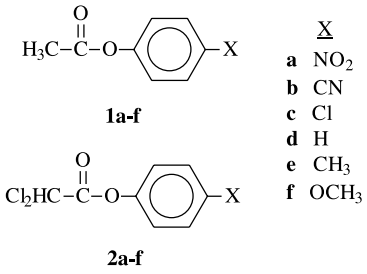
The aim of this paper is to show that despite the electron density accumulation observed in the ^{13}C NMR spectra,[4,5] the electrophilicity of these compounds does increase by substitution with EW groups.

2. Computational details

DFT calculations have been carried out using the B3LYP[17] exchange-correlation functionals, together with the standard 6-31G* basis set.[18] The optimizations were performed using the Berny analytical gradient optimization method.[19] The stationary points were characterized by frequency calculations in order to verify that minima and transition structures (TSs) have zero and one imaginary frequency, respectively. The intrinsic reaction coordinate (IRC)[20] path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism, by using the second order González–Schlegel integration method.[21] The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[22] The solvent effects have been evaluated at B3LYP/6-31+G* level, as single point calculations performed on the gas-phase geometries. The method used was the self-consistent reaction field (SCRF)[23] based on the polarizable continuum model (PCM) of Tomasi's group.[24] All calculations were carried out with the Gaussian 98 suite of programs.[25]

3. Results and discussion

In order to evaluate the effects of EW substituents on the reactivity of the carbonyl compounds experimentally studied by Neuvonen et al.[4,5] the global electrophilicity of the substituted phenyl acetates **1a–f** and substituted phenyl dichloroacetates **2a–f** were studied (see Scheme 1). The ω indices for the whole series of molecules considered in this work together with the experimental rate coefficients for the alkaline hydrolysis of substituted phenyl acetates **1a–f**[26] and for the neutral hydrolysis of substituted phenyl dichloroacetates **2a–f**[4] are listed in Table 1. In Figure 1(a) we report a comparison between rate coefficients for the alkaline hydrolysis of substituted phenyl acetates **1a–f** and their corresponding global electrophilicity values. It may be seen that both quantities display a linear relationship ($R^2=0.98$) with a positive slope, thereby indicating that the increase in the reaction rates is correlated with an enhanced electrophilicity induced by EW substitution on the phenyl ring.



Scheme 1. Series of substituted phenyl acetates and phenyldichloro acetates.

In order to further test the quality of the regression equation (Eq. 2) to predict the experimental rate coefficients, we evaluated the electrophilicity index for the *p*-COMe, **1g**, and *p*-F, **1h**, phenyl derivatives not included in the Neuvonen's subseries **1a–f**. For **1g**, which has a $\omega=1.64$ eV (see Table 1), the Eq. 2 predicts a value of $k=17.30\ s^{-1}$ that is in a reasonably agreement with the experimental value of $k=10.00\ s^{-1}$.[26] For **1h**, which has a $\omega=0.98$ eV (see Table 1),

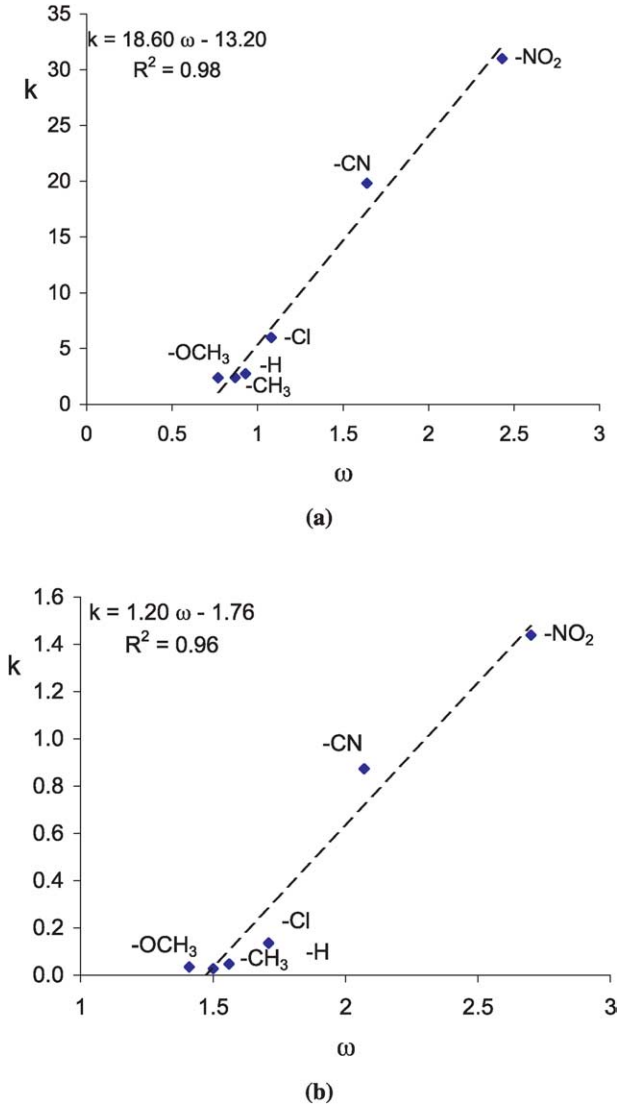


Figure 1. Comparison between rate coefficients and the electrophilicity index for (a) the alkaline hydrolysis of substituted phenyl acetates **1a–f** and (b) for the neutral hydrolysis of substituted phenyl dichloroacetates **2a–f**.

the predicted value of $k=5.03\ s^{-1}$ is also in good agreement with the experimental value of $k=4.20\ s^{-1}$.[26] Note that the predictive capability of Eq. 2 means in this context, that the estimated k values for the *p*-F and *p*-COMe derivatives are correctly lower and upper bounded by derivatives by weaker and stronger EW groups, respectively: phenyl acetate $<$ *p*-F-phenyl acetate $<$ *p*-Cl-phenyl acetate and *p*-Cl-phenyl acetate $<$ *p*-COMe-phenyl acetate-$\approx$*p*-CN-phenyl acetate (see Table 1). This result is useful if one consider that the variations in the rate coefficients fall within a narrow range. The second subseries **2a–f** is shown in Figure 1(b). In both cases the increase of the rate coefficients induced by increasing EW ability of the X substituent group is correlated with an enhanced electrophilicity.

$$k = 18.60\,\omega - 13.20 \tag{2}$$

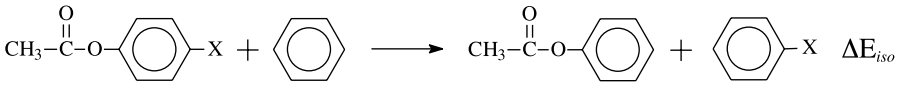
Neuvonen et al.[4,5] proposed that the destabilization of the ground state (GS) induced by EW substitution could account for the increase of the reaction rate by means of a decrease in the activation energy: $\Delta E^{\neq}=E_{TS}-E_{GS}$. Isodesmic reactions were used to evaluate the GS destabilization for a series of X-substituted phenyl trifluoroacetates, phenyl dichloroacetates and phenyl acetates. In their study the energies were computed at the PM3 semiempirical level.

For the sake of simplicity, we evaluated the effects of the EW substitution on both GS stabilization and activation energy for the series of the X-substituted phenyl acetates **1a–f**. The GS destabilization energies were evaluated using the isodesmic model reaction shown in Scheme 2, and computing the total energies at the B3LYP/6-31G* level. The results are displayed in Table 2. An analysis of ΔE_{iso} values shows that substitution on the phenyl group destabilizes the GS relative to **1d** (X=H) by a small amount, ranging from 0.1 to 0.6 kcal/mol (see Table 2). In addition, substitution on the phenyl ring by π-electron-releasing groups, –Cl or –OMe, produces a larger destabilization of the GS than the π-electron-withdrawing ones, $-NO_2$ or –CN.

Table 1. Global properties[a] of the series for the substituents X for the substituted phenyl acetates **1a–f** and phenyl dichloroacetates **2a–f** and rate coefficients of the alkaline hydrolysis for the substituted phenyl acetates **1a–f**[b] and the neutral hydrolysis for the phenyl dichloroacetates **2a–f**[c]

	HOMO	LUMO	μ	η	ω	k
1a	−0.2698	−0.0892	−0.1795	0.1806	2.43	31.0
1b	−0.2576	−0.0547	−0.1561	0.2028	1.64	19.8
1c	−0.2407	−0.0225	−0.1316	0.2181	1.08	6.0
1d	−0.2402	−0.0105	−0.1254	0.2297	0.93	2.8
1e	−0.2308	−0.0082	−0.1195	0.2226	0.87	2.4
1f	−0.2139	−0.0036	−0.1087	0.2102	0.77	2.4
1g	−0.2479	−0.0562	−0.1521	0.1917	1.64	10.0
1h	−0.2381	−0.0149	−0.1265	0.2232	0.98	4.2
2a	−0.2824	−0.099	−0.1907	0.1833	2.70	1.440
2b	−0.2699	−0.0746	−0.1722	0.1953	2.07	0.874
2c	−0.2523	−0.0592	−0.1557	0.1932	1.71	0.136
2d	−0.2539	−0.0513	−0.1526	0.2026	1.56	0.048
2e	−0.2436	−0.0493	−0.1464	0.1943	1.50	0.027
2f	−0.2251	−0.0470	−0.1360	0.1781	1.41	0.035

[a] HOMO and LUMO energies, μ and η in a.u.; ω in eV.
[b] Rate coefficients (in s^{-1}) for the alkaline hydrolysis of compounds **1a–h** from Ref. 26.
[c] Rate coefficients (in s^{-1}) for the neutral hydrolysis of compounds **2a–f** from Ref. 4.



Scheme 2. Isodesmic model reaction used to evaluate the ground state destabilization energies ΔE_{iso} for substituted phenyl acetates **1a–f**.

Table 2. B3LYP/6-31G* total energies[a] (in a.u., including ZPE) and energies for the isodesmic reaction given in Scheme 2 (ΔE_{iso}, in kcal/mol)

	–X	X-Ph-OCOCH$_3$	Ph-X	ΔE_{iso}
1a	–NO$_2$	−664.481932	−436.647001	−0.13
1b	–CN	−552.227663	−324.392769	−0.16
1c	–Cl	−919.587983	−691.75375	−0.57
1e	–CH$_3$	−499.273428	−271.438396	−0.07
1f	–OCH$_3$	−574.471957	−346.637685	−0.55

[a] The total energies for benzene and methyl benzoate are −232.147878 and −459.983022 a.u., respectively.

The effects of the EW substitution on the activation energies were studied by computing the barriers for nucleophilic attack by the hydroxide ion on the subseries of substituted phenyl acetates **1a–f**. The gas-phase potential energy surfaces for these substitution reactions were explored by B3LYP/6-31G* calculations. One TS corresponding to a concerted process was found and characterized, in each case. The geometries of the TSs are given in Figure 2. An analysis of the geometries indicates that there is not an appreciable structural change induced by substitution on the phenyl acetate. The lengths of O–C forming bond, between 2.54–2.60 Å, and C–C breaking bonds, between 1.40–1.41 Å, indicate that these TSs correspond to early processes. Although the unique imaginary frequency characteristic of these TSs is associated to the atomic motion of the hydroxyl oxygen toward the carbonyl carbon, the IRC analysis from the TS to products asserts the concerted nature of these processes.

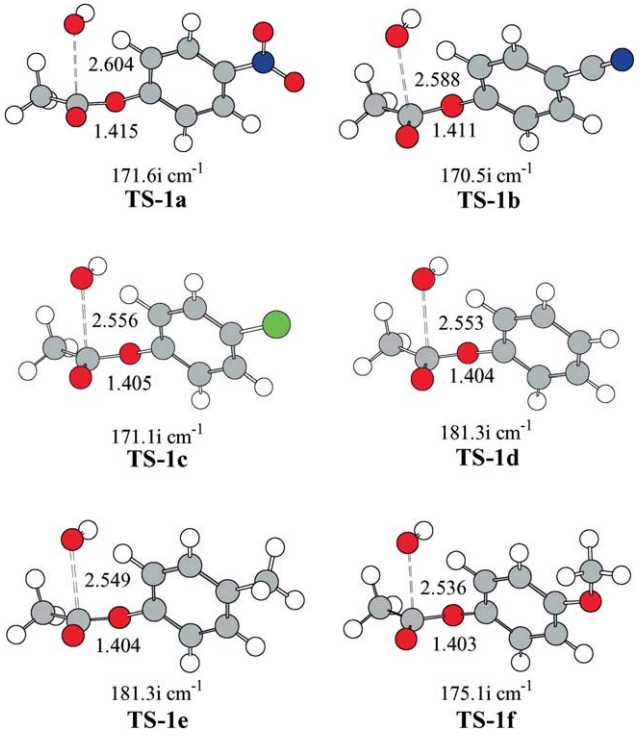


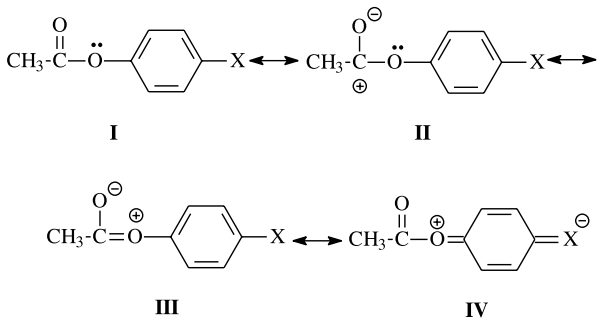
Figure 2. Transition structures corresponding to the nucleophilic attack of hydroxyl anion the substituted phenyl acetates **1a–f**. The bond lengths directly involved in the reaction are given in angstroms.

The barriers for nucleophilic attack of the hydroxyl anion to the whole subseries **1a–f** acetates were obtained at the B3LYP/6-31+G*(PCM)//B3LYP/6-31G* level. The predicted values of the activation energy, $\Delta E^{\neq}$, are comprised between 14.5 kcal/mol (ω=2.43 eV) and 17.2 kcal/mol (ω=0.77 eV) for the strong EW NO_2 and the electron releasing OCH_3 groups, respectively (see Table 2). This result stresses the linear relationship between increasing rate coefficient and enhanced electrophilicity of the substrate. The predicted barriers at this level of theory are reliable. For instance, for phenyl acetate **1d**, we obtain a value of $\Delta E^{\neq}$ = 16.1 kcal/mol, which is in acceptable agreement with the experimental activation energy of 12.6 kcal/mol measured for hydrolysis in aqueous acetone. This result is also in agreement with previous work of Tantillo and Houk for the case of *p*-nitrophenyl acetate (**1a**).[27] The SCI-PCM solvation calculations predict a barrier for the concerted process associated with the *p*-nitrophenyl derivative **1a** 1.6 kcal/mol[27] lower than that for the reference phenyl acetate **1d** (a barrier lowering of 1.6 kcal/mol has been experimentally measured for this system[28]) (Table 3).

The energy analysis allows to draw up two main conclusions: (i) the GS destabilization with EW NO_2 substitution, 0.13 kcal/mol, is smaller than the reduction of the barrier, 1.64 kcal/mol, and as a result, the increase of the reaction rate is driven by a TS stabilization with the EW substitution, and (ii) the increase of the global electrophilicity by increasing the EW character of the substituent in the order H<Cl<CN<NO_2 causes a reduction of the barrier for the nucleophilic attack on the carbonyl group.

Table 3. B3LYP/6-31G* Total energies (*E*, in a.u., including ZPE) and B3LYP/6-31+G*(PCM)//B3LYP/6-31G* barriers ($\Delta E^{\neq}=(E_{TS}-E_{GS})$, in kcal/mol, including ZPE) in water for the nucleophilic attack of the hydroxyl anion on the phenyl acetates **1a–f**

	E	$\Delta E^{\neq}_{water}$
TS-1a	−740.2857732	14.50
TS-1b	−628.0293878	15.51
TS-1c	−995.3819359	17.49
TS-1d	−535.7679834	16.14
TS-1e	−575.0575821	16.07
TS-1f	−575.0522171	17.15



Scheme 3. Possible resonant structures for EW substituted phenyl acetates.

Note that this result is consistent with the global electrophilicity index evaluated for the whole series of phenyl esters **1a–f** and **2a–f** (see Fig. 1(a) and (b)).

For molecules of general type RC(=O)Z:, the susceptibility to nucleophilic attack has been found to correlate with the reactivity of the acyl group, reflecting the resonance structures **I–III** in Scheme 3.[29] Neuvonen et al. proposed an increase of the π-electron density on the carbonyl carbon through a destabilization of structure **III**.[4,5] For phenyl-substituted esters an additional resonant structure **IV** can be draw which has only significance for EW groups. It provides double bond character of the carbonyl C–O bond, thereby allowing an additional explanation for the increase of the stretching frequencies in the IR spectrum. In addition, structure **IV** also provides an explanation for the upfield shift of the ^{13}C NMR chemical shift of the carbonyl carbon through a displacement of the π-electron density of the C–O double bond toward the carbonyl carbon.

4. Concluding remarks

In summary, the present study shows that the electrophilicity concept is better represented by the electrophilicity index proposed by Parr et al. than the population analysis-based quantities. The results obtained for the GSs of carbonyl compounds show that the electrophilicity increases with the EW substituent effects in these systems, and that inspite of the observed electron density accumulation at the carbonyl group, the enhanced electrophilicity induced by the EW groups in the substrates drives the nucleophilic attack at the carbonyl carbon. The analysis based on thermodynamic, ΔE_{iso}, and kinetic, $\Delta E^{\neq}$, energetic aspects shows that the effect of the EW substitution on the corresponding TS largely outweighs the energy destabilization in the GS. The present interpretation of the EW substitution effect on the carbonyl compounds is completely consistent with the kinetic data reported for these systems.

Acknowledgements

R.C. and P.P. acknowledge financial support from Fondecyt grants 1030548 and 1020069; and Millennium Nucleus for Applied Quantum Mechanics and Computational Chemistry, grant P02-004-F. L.R.D. thanks the Ministerio de Ciencia y Tecnología of the Spanish Government by DGICYT (project BQU2002-01032) and the Agencia Valenciana de Ciencia y Tecnología of the Generalitat Valenciana (reference GRUPOS03/176). J.A. acknowledges financial support from the Ministerio de Ciencia y Tecnología Project BQU2003-04168-C03-03.

References and notes

1. Williams, A. *Concerted Organic and Bio-Organic Mechanism*; CRC: Boca Raton, 2000; Chapter 4 and references therein.
2. Kirby, A. J. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1980; p 161.
3. Connors, K. A. *Structure Reactivity Relationships: the Study of Reaction Rates in Solution*; VCH: New York, 1990; p 311.
4. Neuvonen, H.; Neuvonen, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1497.
5. Neuvonen, H.; Neuvonen, K.; Koch, A.; Kleinpeter, E.; Pasanen, P. *J. Org. Chem.* **2002**, *67*, 6995.
6. Murray, J. S.; Lane, P.; Brinck, T.; Politzer, P.; Sjoberg, P. *J. Phys. Chem.* **1991**, *95*, 844.
7. Pérez, P.; Toro-Labbé, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* **2002**, *67*, 4747.
8. Pérez, P. *J. Phys. Chem. A* **2003**, *107*, 522.
9. Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417.
10. Pérez, P.; Domingo, L. R.; Aurell, M. J.; Contreras, R. *Tetrahedron* **2003**, *59*, 3117.
11. Pérez, P.; Toro-Labbé, A.; Contreras, R. *J. Am. Chem. Soc.* **2001**, *123*, 5527.
12. Domingo, L. R.; Pérez, P.; Contreras, R. *J. Org. Chem.* **2003**, *68*, 6060.
13. Parr, R. G.; Szentpály, L. v.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
14. Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford Science: New York, 1994.
15. Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.
16. Domingo, L. R.; Pérez, P.; Contreras, R. *Tetrahedron* **2004**, *60*, 6585.
17. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
18. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.
19. (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214. (b) Schlegel, H. B. Geometry Optimization on Potential Energy Surface. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific: Singapore, 1994.
20. Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.
21. (a) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523. (b) González, C.; Schlegel, H. B. *J. Chem. Phys.* **1991**, *95*, 5853.
22. (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
23. (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Simkin, B. Y.; Sheikhet, I. *Quantum Chemical and Statistical Theory of Solutions-A Computational Approach*; Ellis Horwood: London, 1995.
24. (a) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys.*

Lett. **1996**, *255*, 327. (b) Cances, M. T.; Mennunci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.

25. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; W. Gill, P. M.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.6, Gaussian, Inc.: Pittsburgh PA, 1998.
26. Nishioka, T.; Fujita, T.; Kitamura, K.; Nakajima, M. *J. Org. Chem.* **1975**, *40*, 2520.
27. Tantillo, D. J.; Houk, K. N. *J. Org. Chem.* **1999**, *6*, 3066. These authors recently studied the TSs for the addition-elimination reaction of phenyl acetate (**1d**) and hydroxide ion at the RHF/6-31+G* level. In the gas phase the reaction is concerted, but when aqueous solvation is considered through PCM and SCI-PCM calculations, the barrier to addition dramatically increases, and a stepwise addition-elimination pathway was predicted.
28. Tommila, E.; Hinshelwood, C. N. *J. Chem. Soc.* **1938**, 1801.
29. Sjoberg, P.; Politzer, P. *J. Phys. Chem.* **1990**, *94*, 3959.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 423–428

Synthesis, electrochemical and photochromic behaviour of a series of (1,4-dithiafulven-6-yl)substituted 3*H*-naphtho[2,1-*b*]pyran derivatives

Aude-Emmanuelle Navarro,[a] Fabrice Moggia,[a] Corinne Moustrou,[a] Arnault Heynderickx,[a] Frédéric Fages,[a] Philippe Leriche[b] and Hugues Brisset[a,*]

[a]*Groupe de Chimie Organique Matériaux Moléculaires, UMR CNRS 6114, Faculté des Sciences de Luminy, 163 avenue de Luminy, 13288 Marseille Cedex 9, France*
[b]*Groupe Systèmes Conjugués Linéaires, CIMMA UMR CNRS 6200, UFR Sciences d'Angers, 2 Boulevard Lavoisier, 49045 ANGERS Cedex 01, France*

Received 21 July 2004; revised 22 October 2004; accepted 28 October 2004

Available online 18 November 2004

Abstract—The synthesis and electrochemical and photochromic properties of new 3,3-diphenyl-8-(1,4-dithiafulven-6-yl)-[3*H*]-naphtho[2,1-*b*]pyran derivatives containing differently substituted dithiafulvenyl units are described. An example of electrochemical dimerization is shown which gives access to electroactive bichromophoric systems. Such systems could allow the study of the interplay of photochromic and electrochemical properties.

1. Introduction

Tetrathiafulvalene (TTF) and naphthopyrans have been widely investigated during the three last decades for the generation of superconductive charge-transfer salts[1] and photochromic materials,[2] respectively.

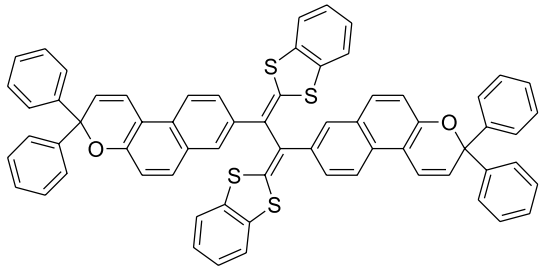
Naphthopyrans belong to an important class of organic photochromic compounds which exhibit reversible changes between colorless and colored isomers. The colored isomer is obtained by UV irradiation while the reverse reaction is thermally controlled. To obtain the bistability of the two different forms with the possibility of a binary on/off control of the interconversion, most of the investigations have focused on naphthopyrans bearing different pendant groups.[3]

In this context, we have designed a new molecule (**1c**) including naphthopyran and TTF vinylogue units, that possess both electrochromic and photochromic properties (Chart 1).

Indeed, the TTF vinylogue unit can be reversibly oxidized to the dication. Then, it was anticipated that such system could represent a new class of molecular switches in which a reversible redox change could alter the photochromic response of the naphthopyran unit (Scheme 1).

In this work, the synthesis and the characterizations of new organic photochromic compounds (**2a–d**) which combine 3,3-diphenylnaphthopyrans and substituted 1,4-dithiafulvenes units are presented (Chart 2).

The synthesis of **1c** by the electrochemical dimerization of **2c** was investigated and the preliminary photochromic results presented.

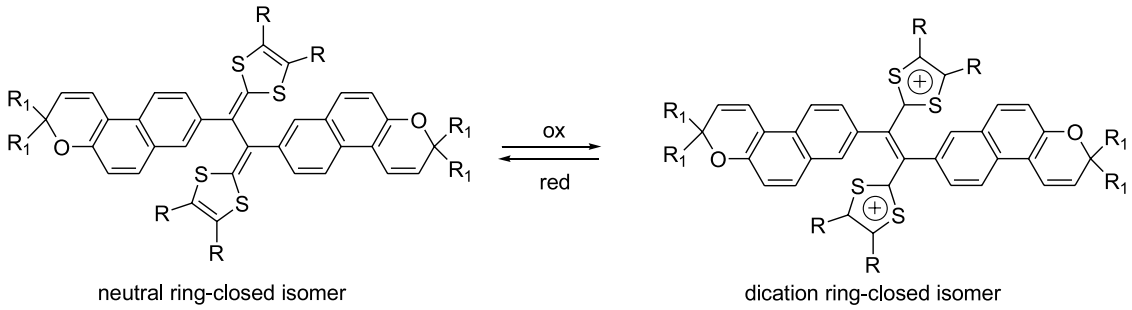


1c

Chart 1.

Keywords: Tetrathiafulvalene; Naphthopyran.
* Corresponding author. Tel.: +33 49 182 9587; fax: +33 49 182 9580; e-mail: brisset@luminy.univ-mrs.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.084



Scheme 1.

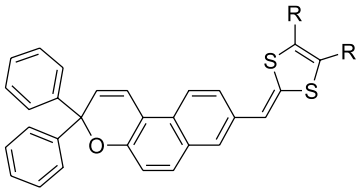


Chart 2.

2. Results and discussion

2.1. Synthesis of compounds 2a–d

The synthesis of compounds **2a**–**d** is depicted in Scheme 2.

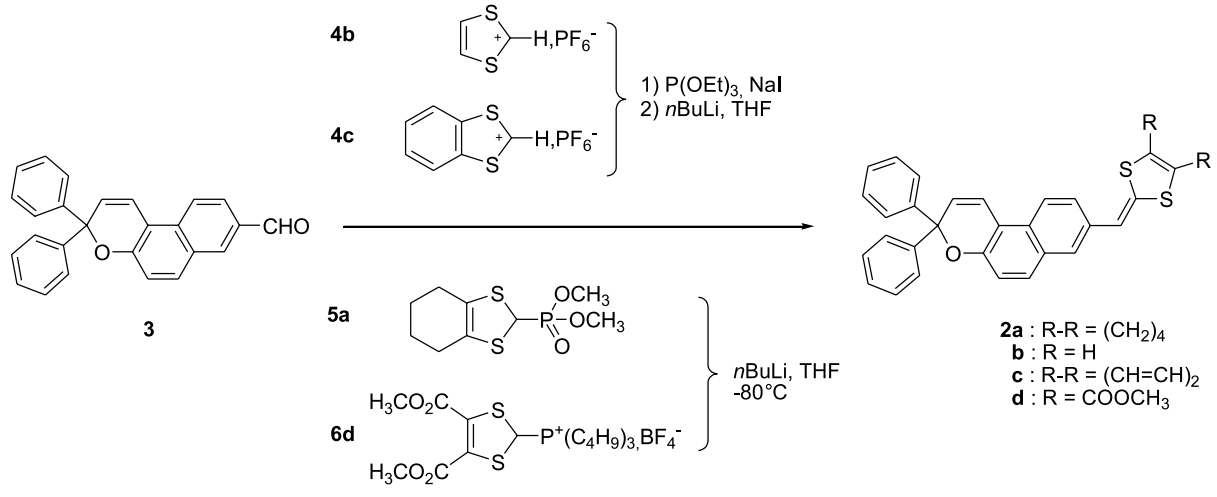
The target compounds **2a**–**d** were then obtained in 45–50% yield from the Wittig–Horner olefination of 3,3-diphenyl-8-formyl-[3*H*]-naphtho[2,1-*b*]pyran **3** prepared as described in the literature[4] using an appropriately substituted dithiolium salts **4b**,**c** or phosphonate anion **5a** or phosphonium salt **6d**.

2.2. Electrochemistry of compounds 2a–d and electrosynthesis of 1

Electrochemical studies of compounds **2a**–**d** were performed by cyclic voltammetry with a platinum disk electrode ($A=2\ mm^2$) in a 10^{-3} M acetonitrile solution containing 0.1 M tetrabutylammonium hexafluorophosphate as the supporting electrolyte and an Ag/AgCl reference electrode. The electrochemical data are collected in Table 1.

In all cases the cyclic voltammograms (CV) of compounds **2a**–**d** exhibit one irreversible oxidation wave (Fig. 1).

As expected the replacement of the electron-withdrawing methylcarboxylate group in **2d** by an electron-donating group, such as the cyclohexyl substituent, leads to a 0.34 V



Scheme 2.

Table 1. Electrochemical data for compounds **2a**–**d** vs Ag/AgCl at 25 °C. Ferrocene used as internal standard

Compound	R	E_{pa}/V	E_{pa}new/V	E_{pc}new/V
2a	$(CH_2)_4$	0.61	0.38	0.34
2b	H	0.68	0.44	0.39
2c	$(CH{=}CH)_2$	0.82	0.64	0.60
2d	$COOCH_3$	0.95	0.80	0.71

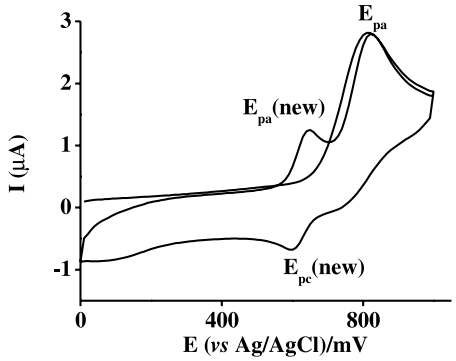


Figure 1. Cyclic voltammogram of **2c** in $CH_3CN/n\text{-}Bu_4NPF_6$ 0.1 M at a scan rate of 100 mV s^{-1}.

negative shift of E_{pa}. In all cases the appearance of a new reversible redox system at lower potentials, is observed after the first scan (Fig. 1). Previous works on phenyl substituted 1,4-dithiafulvenes which can be reversibility oxidized in cation radical have shown that these compounds lead to the formation of tetrathiafulvalene vinylogues by electrochemical dimerization.[5]

By analogy the new redox system can be attributed to the dimer formation in the solution. In order to confirm this hypothesis the electrosynthesis of the dimer of **2c**, **1c**, was performed on a preparative scale using a reticulated vitreous carbon working electrode and 2 mol of electron per mol of substrate as described in the literature. After reduction the target dimer was purified classically by chromatography on silica gel column. The CV of **1c** was recorded under the same experimental conditions as those used for compound **2c** and displayed a reversible two-electron oxidation wave with an anodic peak at 0.63 V and the corresponding cathodic wave at 0.60 V (Fig. 2) in good accordance with the electrochemical response observed for TTF vinylogue substituted derivatives on the vinylogue bonds by phenyl groups.

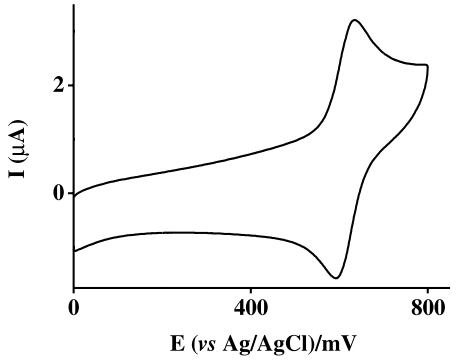


Figure 2. Cyclic voltammogram of **1c** in $CH_3CN/n\text{-}Bu_4NPF_6$ 0.1 M at a scan rate of 100 mV s^{-1}.

2.3. Optical properties

Upon UV irradiation, the compounds **2a–d** were shown to undergo a thermally reversible color change due to an electrocyclic rearrangement of the pyrane moiety. The photochromic behaviour of these new TTF naphthopyrans have been evaluated under continuous irradiation with a xenon lamp at room temperature using toluene as solvent (Fig. 3).

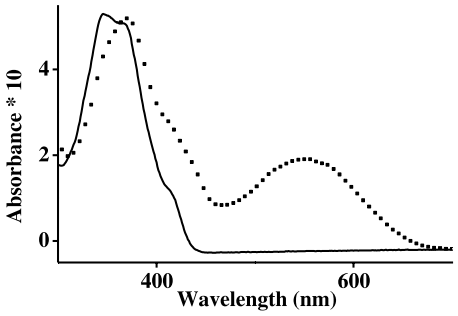


Figure 3. Electronic absorption spectra of the closed (solid line) and opened (dotted line) forms of compound **2c** (toluene, $c=10^{-3}$ mol L^{-1}, 20 °C).

Spectrokinetic data are summarized in Table 2 and compared with those obtained with the unsubstituted naphthopyran taken as a reference. Three parameters were considered in order to characterize the colored form: the maximum wavelength of absorption; the thermal decoloration rate (k_Δ) and the colorability ($A\infty$), e.g. the absorbance measured under steady-state irradiation.

When compared to the unsubstituted naphthopyran the absorption maxima wavelength of the closed form (λ_{max}CF) shift bathochromically in the case of **2a** and hypsochromically for **2b–d** in accordance with the electro-donating and the electron-withdrawing groups. This behaviour is again more pronounced in the opened form. Thus, the absorption maxima wavelength of the colored opened forms (λ_{max}OF) of **2a–c** undergo important bathochromic shifts, from 92 to 117 nm when compared to the unsubstituted naphthopyran. These results reveal that the effect of substituted 1,4-dithiafulvenes groups on the naphthopyran core is more important in the opened forms. Moreover, compounds **2a–c** display the same colorability $A\infty$ as that of the unsubstituted chromene and present a faster thermal decoloration. The thermal decoloration rate for **2a–c** increase from 0.038 to 0.051 s^{-1} in accordance with the electron-withdrawing effect of the substituent grafting on the 1,4-dithiafulvenes moiety. On other hand compound **2d** was observed not to display any photochromic properties under our conditions due to the very strong electron-withdrawing effect of the ester groups.

The dimer compound, **1c**, was observed to display a weak photochromic behaviour (Fig. 4).

Very little absorbance was observed for the opened form of compound **1c** which indicate a quasi disappearance of the photochromic properties due to a very stable closed form or a faster thermally reverse reaction. On the basis of the literature the neutral compound **1c** is probably non planar.[5] In this context the stability of the closed or/and opened forms could be altered by steric hindrances. Moreover, the absorption maximum wavelength of the closed and opened

Table 2. Photochromic parameters obtained under continuous irradiation in toluene solutions (150 W xenon lamp, 25 °C) for compounds **2a–d**

Compound	R	λ_{max}CF	λ_{max}OF	$A\infty$	K_Δ (s^{-1})
Naphthopyran	—	345	432	0.17	0.060
2a	$(CH_2)_4$	369	549	0.17	0.038
2b	H	342	532	0.17	0.042
2c	$(CH{=}CH)_2$	336	524	0.17	0.051
2d	$COOCH_3$	327	—	—	—

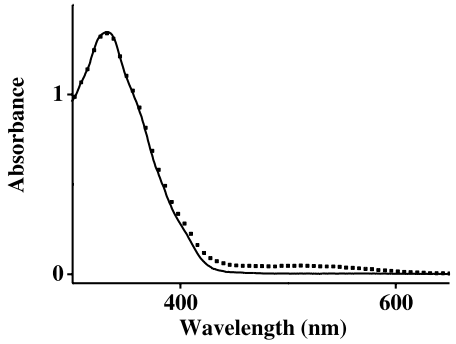


Figure 4. Electronic absorption spectra of the closed (solid line) and opened (dotted line) forms of compound **1c** (tetrahydrofurane, $c = 10^{-5}$ mol L^{-1}, 20 °C).

forms were recorded at 333 and about 511 nm, respectively, corresponding to hypsochromic shifts relative to the naphthopyran precursor **2c**. More detailed investigations are currently underway especially to determine the influence of the TTF vinylogue moiety redox state on the photochromic properties of **1c**.

3. Conclusion

The synthesis of new substituted 3,3-diphenyl-8-(1,4-dithiafulven-6-yl)-[3*H*]-naphtho[2,1-*b*]pyrans has been performed. These compounds display interesting photochromic properties. The spectroscopic data show that the shift of the absorption maximum and the thermal decoloration rate correlate with the electro-donating or electron-withdrawing effect of the substituent groups. Future work is directed of the improvement of the photochromic properties of naphthopyran derivatives incorporating a TTF vinylogue unit and the investigation of synergistical coupling between optical and electrochemical properties.

4. Experimental

4.1. General

Materials. Cyclohexane, methylenechloride, diethylether, tetrahydrofurane (THF), chloroform, hexane, ethylacetate were purchased from CarloErba. Anhydrous acetonitrile (analytical grade) was purchased from CarloErba and used as received. Tetrabutylammonium hexafluorophosphate was purchased from Fluka. Silica gel (240–400 mesh) from Merck. Triethylphosphite, butyllithium in hexane, were purchased from Sigma-Aldrich.

Instrumentation. Melting points are uncorrected and were obtained from an Electrothermal 9100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 250 at, respectively, 250 MHz and 62.5 MHz. UV spectra were obtained on Varian Cary 50. FAB mass spectra were obtained with a JEOL FX 102 Mass spectrometer (Laboratoire de Mesures Physiques, USTL, Montpellier, France). The bulk electrolysis and the cyclic voltammetry (CV) were performed with computer-based Bioanalytical instrument (BAS 100) electrochemical workstation. The bulk electrolysis was made in a divided cell with reticulated vitreous carbon working electrode, platinium counter electrode and reference electrode, Ag/AgCl. The CV data were acquired using a with 1.6 mm diameter platinium working electrode; platinium counter electrode; reference electrode, Ag/AgCl.

For compounds **2a–d** the photochromic measurements were performed in toluene solutions of spectrometric grade at 20 °C (0.2°), at a concentration of 5×10^{-3} mol L^{-1}. For compound **1c** the photochromic measurements were performed in tetrahydrofurane solution of spectrometric grade at 20 °C (0.2°), at a concentration of 5×10^{-5} mol L^{-1}. The irradiation flux in each case was 4 W m^{-2}. The analysis cell (optical pathlength 10 mm) was placed in a thermostated copper block inside the sample chamber of a Varian Cary 50 spectrometer. An Oriel 150 W high pressure Xe lamp was used for irradiation.

4.1.1. 8-(4,5-Cyclohexeno-1,3-benzodithiol-2-ylidene)-3,3-diphenyl-[3*H*]-naphtho[2,1-*b*]pyrane 2a. Into a flask of 50 mL, 181 mg (0.68 mmol) of phosphonate **5a** prepared as describe in literature,[6] and 7 mL of anhydrous THF were cooling to −78 °C under argon. 0.27 mL (0.68 mmol) of *n*BuLi (solution 2.5 M in hexane) are added drop by drop and 120 mg (0.45 mmol) of chromene carbaldehyde **3** was added. The mixture is let return at ambient temperature. Water was added and the mixture is extracted with methylene chloride. The combined organic phases were washed with water, dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified on a silica gel column and eluting with ethyl acetate–cyclohexane mixture (5/95). The desired fractions were pooled and concentrated to afford 0.10 g (44%) of pale yellow solid: Mp 192–194 °C; ^{1}H NMR (400 MHz, pyridine-d_5) δ: 1.74–1.82 (m, 4H); 2.22–2.32 (m, 4H); 6.24 (d, J=9.9 Hz, 1H); 6.54 (s, 1H); 7.16 (d, J=8.8 Hz, 1H); 7.20–7.33 (m, 7H); 7.36 (dd, J=1.7, 8.9 Hz, 1H); 7.44–7.50 (m, 4H); 7.55 (br s, 1H); 7.62 (d, J=8.8 Hz, 1H); 7.86 (d, J=8.9 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ: 82.64 (C); 22.63 (–CH_2–); 22.67 (–CH_2–); 25.06 (–CH_2–); 25.68 (–CH_2–); 112.08 (–CH=); 114.09 (C); 118.67 (–CH=); 119.63 (–CH=); 121.44 (–CH=); 123.98 (C); 124.30 (C); 125.08 (–CH=);

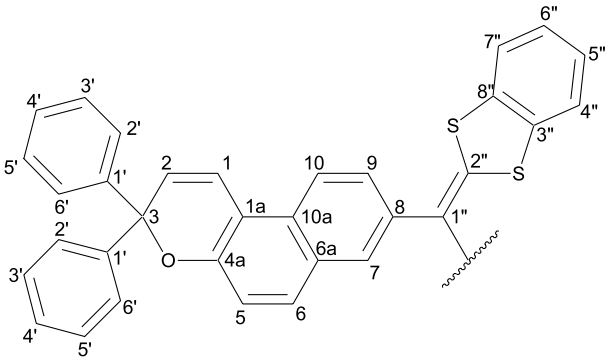
126.85 (–CH═); 127.11 (4×–CH═); 127.60 (2×–CH═); 127.87 (–CH═); 128.18 (4×–CH═ and C); 129.63 (C); 129.85 (–CH═); 132.72 (C); 134.32 (C); 144.97 (2×C); 150.40 (C). IR (KBr) 3059, 3019, 2935, 2925, 2857, 1634, 1587, 1579, 1543, 1492, 1469, 1447, 1372, 1246, 1210, 1094, 1083, 1010, 954, 857, 837, 806, 764, 729, 701, 636, 606. MS (EI) 502 (M^+, 5), 307 (30); HRMS for $C_{33}H_{26}OS_2$ calcd 502.1425, found 502.1432.

4.1.2. 8-(Bis(1,3-dithiol-2-ylidene)-3,3-diphenyl-[3*H*]-naphtho[2,1-*b*]pyrane 2b. In a round-bottomed flask equipped with a dropping funnel and argon inlet were introduced dithiolium salt **4b**[7] (0.20 g, 0.8 mmol), triethyl phosphite (0.14 mL, 0.8 mmol) and NaI (0.12 g, 0.8 mmol) in 4 mL of acetonitrile. After 2 h stirring at room temp., evaporation of the solvent and excess of triethyl phosphite left the phosphonate as an oil. Dry THF (4 mL) and chromene carbaldehyde **3** (0.29 g, 0.8 mmol) were then added and the mixture cooled to 0 °C. *n*-Butyllithium (0.5 mL, 0.8 mmol) (1.6 M in hexanes) was added dropwise, and the mixture stirred for 2 h at room temp. Upon addition of methanol a red precipitate and was formed which is filtered, washed with methanol–diethyl ether and dried. Yield 0.19 g (54%): Mp ^{1}H NMR (400 MHz, pyridine-d_5) δ: 6.26 (dd, J=1.2, 6.7 Hz, 1H); 6.35 (d, J=6.7 Hz, 1H); 6.63 (br s, 1H); 7.18 (d, J=8.8 Hz, 1H); 7.22–7.34 (m, 6H); 7.26 (superimposed d, J=9.9 Hz, 1H); 7.37 (dd, J=1.8, 8.8 Hz, 1H); 7.44–7.50 (m, 4H); 7.57 (d, J=1.8 Hz, 1H); 7.63 (d, J=8.8 Hz, 1H); 7.89 (d, J=8.8 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ: 82.65 (C); 112.73 (–CH═); 114.09 (C); 117.42 (–CH═); 117.50 (–CH═); 118.76 (–CH═); 119.56 (–CH═); 121.54 (–CH═); 124.99 (–CH═); 126.61 (–CH═); 127.09 (4×–CH═); 127.61 (2×–CH═); 127.78 (C); 127.92 (–CH═); 128.18 (4×–CH═); 129.54 (C); 129.85 (–CH═); 132.46 (C); 136.01 (–C═); 144.92 (2×C); 150 50 (C). IR (neat) 3062, 3027, 1688, 1633, 1600, 1566, 1508, 1493, 1447, 1264, 1245, 1222, 1160, 1092, 1007, 879, 809, 762, 737, 700, 646.

4.1.3. 8-(1,3-benzodithiol-2-ylidene)-3,3-diphenyl-[3*H*]-naphtho[2,1-*b*]pyrane 2c. Into a flask of 50 mL, 302 mg (1 mmol) of 4,5,6,7-tetrahydro-benzo[1,3]dithiol-1-ylium hexafluorophosphate **4c**[8] 0.171 mg (1 mmol) of triethylphosphite, 149 mg (1 mmol) of sodium iodide and 3 mL of acetonitrile are successively introduced. The reaction carried out under inert argon. After 2 h of agitation at ambient temperature the solvent were remove under vaccuo. The resulting oil is taken again with 3 mL of anhydrous THF and the reactional mixture is brought to 0 °C under argon. 362 mg (1 mmol) of carboxaldehyde chromene **3** and 0.625 mL (1 mmol) of *n*BuLi (solution 1.6 M in hexane) are added drop by drop without the temperature exceeding 5 °C. The mixture is let return at ambient temperature. The reaction is controlled by CCM with a pentane/diethylic mixture (50:50). The addition of methanol leads to the precipitation of the compound **2c**. After filtration, 408 mg (0.441 mmol, 44%) of product are obtained in the form of a yellow powder: Mp 227–228 °C; ^{1}H NMR (400 MHz, pyridine-d_5) δ: 6.30 (d, J=9.9, 1H); 6.67 (s, 1H); 7.09–7.20 (m, 2H); 7.23 (d, J=8.8 Hz, 1H); 7.25–7.40 (m; 9H); 7.47 (br s, J=8.7 Hz, 1H); 7.52 (d, J=7.6 Hz, 4H); 7.68 (br s, 1H); 7.69 (d, J=8.8 Hz, 1H); 7.95 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ: 82.70 (C); 114.08 (C); 114, 65 (–CH═); 118.84 (–CH═); 119.49 (–CH═); 121.01 (–CH═); 121.61 (–CH═); 121.78 (–CH═); 125.66 (–CH═); 125.95 (–CH═); 126.02 (–CH═); 126.69 (–CH═); 127.08 (4×–CH═); 127.60 (2×–CH═); 127.95 (–CH═); 128.10 (C); 128.17 (4×–CH═); 129.47 (C); 129.93 (–CH═); 132.17 (2×C); 134.87 (C); 136.41 (C); 144.90 (2×C); 150.71 (C). UV (toluene) (log ε): 346 (4.33); 369 (4.30);415 (3.64). IR (KBr) 3059, 3032, 2925, 2852, 1632, 1587, 1572, 1556, 1510, 1491, 1460, 1448, 1381, 1245, 1221, 1091, 1009, 841, 809, 765, 753, 743, 734, 699, 614. MS (EI) 498 ($M^{\cdot +}$, 22), 421 (12), 347 (8); HRMS for $C_{33}H_{22}OS_2$ calcd 498.1112, found 498.1152.

4.1.4. 8-(4,5-Bis(methoxycarbonyl)-1,3-dithiol-2-ylidene)-3,3-diphenyl-[3*H*]-naphtho[2,1-*b*]pyrane 2d. Into a flask of 50 mL, 421 mg (0.8 mmol) of [4,5-Bis(methoxycarbonyl)-1,3-dithiol-2-yl]tributyl-phosphonium tetrafluoroborate **6d**[9] are introduced in 5 mL of THF. The reactional mixture is brought to 0 °C under argon. 200 mg (0.55 mmol) of carboxaldehyde chromene **3** and 0.38 mL (0.61 mmol) of *n*BuLi (solution 1.6 M in hexane) are added drop by drop without the temperature exceeding 5 °C. The addition of methanol leads to the precipitation of the compound **2d**. After filtration, 204 mg (66%) of product are obtained in the form of a orange solid: Mp 196–197 °C; ^{1}H NMR (400 MHz, pyridine-d_5) δ: 3.87 (s, 3H); 3.89 (s, 3H); 6.31 (d, J=9.9 Hz, 1H); 6.56 (br s, 1H); 7.23 (d, J=8.8 Hz, 1H); 7.25–7.40 (m, 8H); 7.51 (d, J=7.5 Hz, 4H); 7.53 (br s, 1H); 7.67 (d, J=8.9 Hz, 1H); 7.93 (d, J=8.8 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ: 53.30 (CH_3–); 53.46 (CH_3–); 82.76 (C); 114.09 (C); 115.68 (–CH═); 119.01 (–CH═); 119.37 (–CH═); 121.81 (–CH═); 125.95 (–CH═); 126.31 (–CH═); 127.06 (4×–CH═); 127.64 (2×–CH═); 128.06 (–CH═); 128.18 (4×–CH═); 128.31 (C); 129.32 (2×C); 129.68 (C); 129.97 (–CH═); 131.30 (C); 131.49 (C); 144.75 (2×C); 150.94 (C); 159.91 (OC═O); 160.35 (OC═O). IR (KBr) 3060, 3028, 2949, 2928, 1741, 1732, 1701, 1631, 1584, 1553, 1491, 1470, 1448, 1431, 1376, 1247, 1093, 1086, 1054, 1010, 868, 836, 807, 769, 756, 738, 700, 637. HRMS for $C_{33}H_{26}OS_2$ calcd 564.1065, found 564.1057.

4.1.5. 3,3-diphenyl-8-8-[Benzo[1,3]dithiol-2-ylidene-methyl]-[3*H*]-naphto-[2,1-*b*]pyrane 1c. 68.3 mg (0.14 mmol) of **2c** was dissolved in 75 mL of acetonitrile containing 19.35 g (50 mmol) of tetrabutylammonium hexafluorophosphate The solution is then oxidized under controlled potential (0.80 V vs Ag/AgCl). The colored solution is reduced at −0.2 V vs Ag/AgCl without any treatment (1 mol of electron per mol of substrate). The solvent was removed under reduce pressure and diethyl-ether was added to the residue. Tetrabutylammonium hexafluorophosphate precipitated and was filtered off. The solvent was evaporated in vacuo and the crude product was purified on a silica gel column and eluting with methylene chloride–cyclohexane mixture (1/1). Concentration under reduced pressure affords 57 mg (0.06 mmol, 83%) of yellow powder corresponding to title compound: Mp 304–305 °C.



^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.23 (d, $J=9.9$ Hz, 2H, H_2), 7.05 (m, 2H, $H_{6''}$), 7.08 (m, 2H, $H_{5''}$), 7.15 (d, $J=8.9$ Hz, 2H, H_5), 7.16 (m, 2H, $H_{4''}$), 7.21 (m, 2H, $H_{7''}$), 7.23 (d, $J=9.9$ Hz, 2H, H_1), 7.23 (m, 4H, $H_{4'}$), 7.30 (m, 8H, $H_{3'}$, $H_{5'}$), 7.46 (m, 8H, $H_{2'}$, $H_{6'}$), 7.61 (d, $J=8.9$ Hz, 2H, H_6), 7.63 (dd, $J=8.9;1.8$ Hz, 2H, H_9), 7.86 (d, $J=9.0$ Hz, 2H, H_{10}), 7.91 (d, $J=1.6$ Hz, 2H, H_7), ^{13}C NMR (270 MHz, $CDCl_3$) δ: 82.65 (C_3), 114.16 (C_{1a}), 118.70 (C_5), 119.60 (C_1), 121.39 ($C_{4''}$), 121.63 ($C_{7''}$), 121.87 (C_{10}), 125.50 ($C_{1''}$), 125.57 ($C_{5''}$), 125.75 ($C_{6''}$), 125.93 (C_9), 126.77 (C_7), 127.08 ($C_{2'}$), 127.60 ($C_{4'}$), 127.92 (C_2), 128.17 ($C_{3'}$), 128.79 (C_{10a}), 129.41 (C_{6a}), 130.12 (C_6), 133.35 (C_8), 136.33 ($C_{2''}$), 136.47 ($C_{3''}$), 136.56 ($C_{8''}$), 144.85 ($C_{1'}$), 150.88 (C_{4a}); UV–Vis (CH_2Cl_2) λ_{max} nm (log ε); MS (EI) 994 ($M^{\cdot +}$, 100), 55 (15), 22 (31); HRMS for $C_{66}H_{42}O_2S_4$ calcd 994.2068, found 994.2060.

References and notes

1. (a) Bryce, M. R. *Chem. Soc. Rev.* **1991**, *20*, 355–390. (b) Khodorkovsky, V.; Becker, J. Y. In *Organic Conductors*; Farges, J.-P., Ed.; Dekker: New York, 1994. (c) Bryce, M. R. *J. Mater. Chem.* **1995**, *5*, 1481–1496.
2. Crano, J. C.; Guglielmetti, R. J. In *Organic Photochromic and Thermochromic Compounds*, *Vols. 1 and 2*; Kluwer Academic/ Plenum: New York, 1998.
3. Samat, A.; Lokshin, V.; Chamontin, K.; Levi, D.; Pepe, G.; Guglielmetti, R. *Tetrahedron* **2001**, *57*, 7349–7359 and references therein.
4. Chamontin, K.; Lokshin, V.; Rossolin, V.; Samat, A.; Guglielmetti, R. *Tetrahedron* **1999**, *55*, 5821–5830.
5. (a) Mayer, R.; Kröber, H. *J. Prakt. Chem.* **1974**, *6*, 907–912. (b) Frère, P.; Behamed-Gasmi, A.; Roncali, J.; Jubault, M.; Gorgues, A. *J. Chim. Phys.* **1995**, *92*, 863–866. (c) Shöberl, U.; Salbeck, J.; Daub, J. *Adv. Mater.* **1992**, *4*, 41–44. (d) Lorcy, D.; Carlier, R.; Robert, A.; Tallec, A.; le Maguerès, P.; Ouahab, L. *J. Org. Chem.* **1995**, *60*, 2443–2447. (e) Ohta, A.; Yamashita, Y. *Heterocycles* **1995**, *40*, 123–126. (f) Fourmigué, M.; Johansen, I.; Boubekeur, K.; Nelson, C.; Batail, P. *J. Am. Chem. Soc.* **1993**, *115*, 3752–3759. (g) Yamashita, Y.; Tomura, M.; Badruz Zaman, M.; Imaeda, K. *Chem. Commun.* **1998**, 1657–1658.
6. Mora, H.; Fabre, J. M.; Giral, L.; Montginoul, C. *Bull. Soc. Chim. Belg.* **1992**, *101*, 137–146.
7. Schukat, G.; Fanghanel, E. *Sulfur Reports* **2003**, *24*(1–2), 1–190.
8. (a) Nakayama, J.; Fujiyama, K.; Oshino, M. *Chem. Lett.* **1975**, 1099–1102. (b) Nakayama, J. *Synthesis* **1975**, 38.
9. Sato, M.; Gonella, M. C.; Cava, M. P. *J. Org. Chem.* **1979**, *44*, 930–934.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 429–436

Cheiloclines A–I. First examples of octacyclic sesquiterpene-triterpene hetero-Diels–Alder adducts

Dulce Mesa-Siverio,[a,b] Haydee Chávez,[c] Ana Estévez-Braun[a,b,*] and Ángel G. Ravelo[a,b,*]

[a]*Instituto Universitario de Bio-Orgánica 'Antonio González', Universidad de La Laguna, Avda. Astrofísico Fco. Sánchez 2, La Laguna, 38206 Tenerife, Spain*
[b]*Instituto Canario de Investigación del Cáncer, Hospital Universitario de La Candelaria, 38010, Tenerife, Spain*
[c]*Facultad de Farmacia y Bioquímica, Universidad San Luis Gonzaga de Ica, Peru*

Received 16 August 2004; revised 20 October 2004; accepted 21 October 2004

Abstract—Cheiloclines A–I (**1–9**) have been isolated from the root bark of *Cheiloclinium hippocratioides* (Celastraceae). They represent the first examples of hetero-Diels–Alder adducts between a *nor*-triterpenequinone and a sesquiterpene. Their structures were elucidated on the basis of spectral analysis, including homonuclear and heteronuclear correlation NMR experiments (COSY, ROESY, HSQC and HMBC). These compounds were tested for antitumoral, antibacterial and aldose reductase inhibitory activities.

1. Introduction

Among the most powerful of all synthetic organic transformations is the Diels–Alder cycloaddition, which is very useful for construction of cyclic products with high regio- and stereoselectivity under mild conditions.[1] It has been applied to the preparation of complex pharmaceutical and biologically active compounds.[2] Although evidence[3–7] on natural Diels–Alderases has been accumulated in the biosynthesis of secondary metabolites, there is not enough information on the structural details of the natural Diels–Alderases, being of particular interest its function and catalytic mechanism owing to the diversity of molecular skeletons in natural Diels–Alder adducts.[8] In this sense, it has been recently reported the 1.70 Å resolution crystal structure of the natural Diels–Alderase, fungal macrophomate synthase (MPS), in complex with pyruvate.[9]

Itokawa and collaborators and our group have isolated triterpene dimers[10–16] and triterpene trimers[17] from Celastraceae plants. It has been postulated that this type of compounds is biosynthesized by hetero-Diels–Alder reactions, which was supported by the synthesis of one triterpene dimer carried out in our laboratory.[11] In this paper we report the isolation from *Cheiloclinium hippocratioides* (Celastraceae) of nine octacyclic hetero Diels–Alder adducts (**1–9**) with a novel structure based on two monomer units from guaiane and D:A-friedo-*nor*-oleanane sesqui/triterpene skeletons. All adducts were found to be composed of one aromatic triterpene unit derived from pristimerin and one sesquiterpene unit derived from guaia-1(5),3(4),11(13)-triene, being the first examples of this kind of adducts isolated from natural sources. The isolation of octacyclic adducts implying different stereo- and regioisomeric relationships and derived by hypothetical hetero-Diels–Alder reactions, leads to the possibility of studying potential enzymatic systems in Celastraceae species with Diels–Alderase activity.

Together with the new adducts, we also isolated nine triterpenes and four triterpene dimers. The known compounds were identified as 6-epibarudione,[18] 3-oxo-29-hydroxyfriedelane,[19] 28-hydroxyfriedelane-1,3-dione,[20] dis-pernmoquinone,[21] pristimerin,[22] blepharodol,[23] 6-oxo-pristimerol,[24] 7α-hydroxy-blepharodol,[23] 7-oxo-blepharodol,[18] isoblepharodol,[18] cangaronsin αA,[14] isocangaronsin αA,[14] scutionin[11] and 7,8-dihydro-scutionin-αA.[11]

2. Results and discussion

Our interest for the chemical constituents of South American medicinal plants, and particularly those with antitumoral activity,[25] led us to investigate the root bark of *C. hippocratioides*[26–28] (Celastraceae). The roots of species belonging to the Celastraceae family are characterized by

Keywords: Terpenoids; Metabolites; Plants; NMR; Diels–Alder reaction.
* Corresponding authors. Tel.: +34 92 231 8576; fax: +34 92 231 8575 (A.E.-B.); e-mail addresses: aestebra@ull.es; agravelo@ull.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.074

the presence of cytotoxic triterpenoid quinonemethides. These pigments are considered as chemotaxonomic indicators in the plant family.[29,30] The (*n*-hexane/Et_2O; 1:1) extract of the root bark of *C. hippocratioides* was repeatedly chromatographed on Sephadex LH-20 and silica gel to give compounds **1**–**9**, which were named cheiloclines A–I (Fig. 1).

Compound **1** was isolated as an amorphous white solid with $[\alpha]_D = -94.5$ (*c* 0.6, $CHCl_3$). The molecular formula was shown to be $C_{45}H_{62}O_4$ by HRMS and ^{13}C NMR data. Its ^1H NMR spectrum showed two double doublets at δ 6.62 (J= 2.9, 9.9 Hz) and δ 5.87 (J=2.7, 9.9 Hz), a singlet at δ 6.48, a methoxy group, and signals for six angular methyls (δ 2.15, 1.19, 1.10, 1.04, 0.93 and 0.85). These signals are characteristic of the hydrogens H-1, H-6, H-7 and the corresponding methyls (Me-23, Me-30, Me-28, Me-26, Me-25 and Me-27) in triterpene skeleton type pristimerol, which is present as aromatic-triterpene unit in some triterpene dimers isolated from Celastraceae (Fig. 2).[11,16]

The ^1H NMR of **1** also showed the presence of one vynilic proton (δ 5.45, 1H, bs), two singlets at δ 4.70 and 4.65 (characteristic of the hydrogens of a terminal methylene group), a secondary methyl at δ 1.25 (J=6.2 Hz), and two methyls on double bond at δ 1.65 (d, J=1.3 Hz) and δ 1.74 (s). From the analysis of the ^{13}C NMR, DEPT, HRMS and MS spectra, it was possible to establish the sesquiterpenic

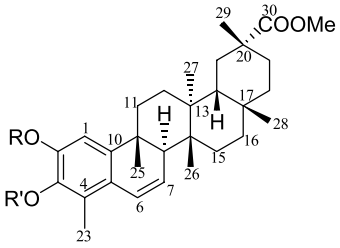


Figure 2. Structure of the triterpene unit.

nature of the second unit with a formula $C_{15}H_{22}$. The molecule presents 15 degrees of unsaturation, and the triterpenic unit accounts for ten of them. Two additional degrees could correspond to two C=C double bonds present in the second unit [151.03 (C), 140.52 (C), 128.75 (CH), 108.69 (CH_2)], and the remaining three unsaturations could be the result of rings. The multiple correlations observed in the HMBC spectra for the signals at δ 92.72 and 97.13 suggest the existence of a bridged bicyclic system, with these quaternary carbons being in the bridgehead positions. The thoroughly analysis of COSY, HSQC, HMBC spectra showed that the sesquiterpene unit belongs to the guaiane series (Fig. 3), and the sesquiterpene and triterpene units are linked together by two ether linkages between the A ring of the pristimerine unit and the corresponding fused carbons of the bicyclic sesquiterpene.

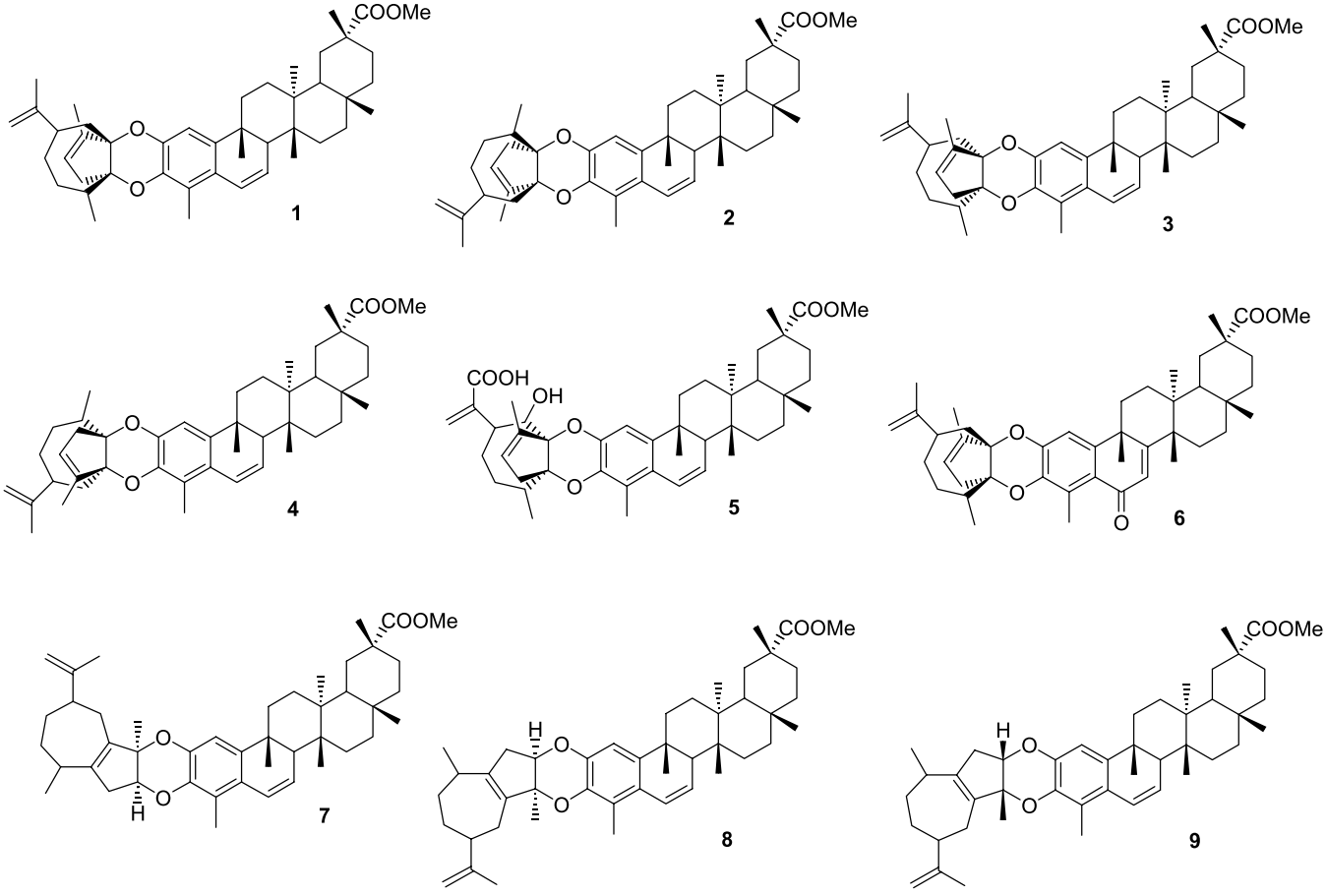


Figure 1. Structures of cheiloclines A–I (**1**–**9**).

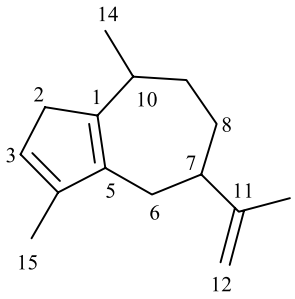


Figure 3. Structure of the sesquiterpene unit.

The most representative HMBC correlations are shown in Figure 4.

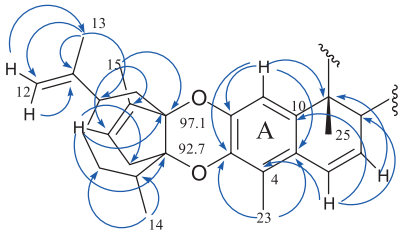


Figure 4. Selected HMBC correlations.

There may be two different regioisomers (**A** or **B**) depending on the linkages between the two units, and for each regioisomer two different stereoisomers in which the cyclopentene ring can be in β or α arrangement. In the case of compound **1**, the NOE effect between Me-23 and Me-14, and the correlations between H-1 and the methyls Me-13′ and Me-15′, favors option **A**, with linkages between the units [2-O-1′][3-O-5′]. The β-disposition of the cyclopentane ring was also established by the NOE effect between the Me-15′ and Me-25 (Fig. 5).

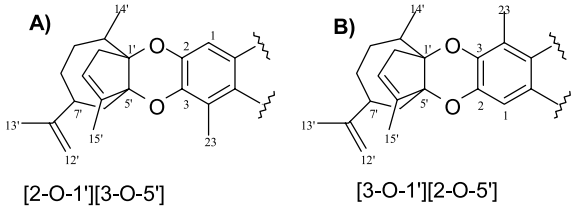


Figure 5. Possible regioisomers.

With respect to the biosynthesis of this type of compound, we propose that the 1,4-dioxane ring, is formed by a hetero Diels–Alder reaction between the triterpenic unit in form of *o*-quinone and the tetrasubstituted double bond of the sesquiterpene (Fig. 6). A similar mechanism has been

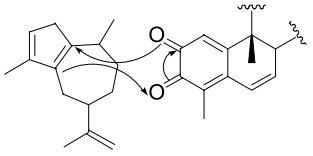


Figure 6. Possible biogenetic formation.

Table 1. ^{1}H NMR ($CDCl_3$) of compounds **1–9**

Proton	1	2	3	4	5	6	7	8	9
1	6.48 s	6.50 s	6.55 s	6.53 s	6.60 s	6.82 s	6.49 s	6.49 s	6.53 s
6	6.62 dd (2.9, 9.9)	6.64 dd (2.9, 9.9)	6.65 dd (2.9, 9.9)	6.62 dd (2.9, 9.9)	6.65 dd (2.9,10.1)	—	6.64 dd (2.9, 9.9)	6.64 dd (2.7, 9.8)	6.64 dd (2.9, 9.9)
7	5.87 dd (2.7, 9.9)	5.86 dd (2.7, 9.9)	5.87 dd (2.7, 9.9)	5.88 dd (2.6, 9.9)	5.90 dd (2.5, 9.8)	6.22 s	5.87 dd (2.8, 9.9)	5.86 dd (2.4, 9.9)	5.87 dd (2.7, 9.9)
8	2.51 sa	2.48 sa	2.49 sa	1.59 s	2.48 s	—	2.47 s	2.49 s	2.48 s
18	1.58 s	1.58 s	1.60 s	1.75 s	1.58 s	1.59 s	1.57 bs	1.58 s	1.58 s
23	2.15 s	2.15 s	2.16 s	2.16 s	2.16 s	2.57 s	2.14 s	2.15 s	2.17 s
25	0.93 s	0.98 s	0.99 s	0.99 s	1.00 s	1.53 s	1.00 s	0.98 s	0.99 s
26	1.04 s	1.05 s	1.06 s	1.06 s	1.06 s	1.28 s	1.04 s	1.05 s	1.04 s
27	0.85 s	0.84 s	0.83 s	0.83 s	0.82 s	0.55 s	0.82 s	0.83 s	0.83 s
28	1.10 s	1.10 s	1.11 s	1.11 s	1.11 s	1.09 s	1.09 s	1.10 s	1.10 s
30	1.19 s	1.19 s	1.19 s	1.19 s	1.19 s	1.17 s	1.18 s	1.19 s	1.19 s
OMe	3.65 s	3.63 s	3.64 s	3.63 s	3.62 s	3.53 s	3.62 s	3.63 s	3.62 s
3′	5.45 bs	5.58 d (1.62)	5.39 bs	5.53 s	5.60 s	5.53 s	4.76 t (7.6)	4.84 t (7.7)	4.24 m
12′a	4.70 s	4.64 s	4.78 s	4.70 s	6.22 d (3.53)	4.69 s	4.72 s	4.72 s	4.68 s
12′b	4.65 s	4.57 s	4.72 s	4.65 s	5.48 d (2.33)	4.65 s	4.69 s	4.69 s	4.65 s
13′	1.74 s	1.69 s	1.79 s	1.74 s	—	1.74 s	1.76 s	1.75 s	1.73 s
14′	1.25 d (6.2)	1.11 d (6.8)	1.15 d (6.9)	1.20 d (6.8)	1.20 d (7.56)	1.21 d (6.76)	1.08 d (7.3)	1.11 d (6.9)	1.06 d (2.4)
15′	1.65 d (1.3)	1.46 s	1.46 bs	1.69 d (1.5)	1.70 s	1.68 bs	1.62 s	1.63 s	1.37 s

Table 2. ^{13}C NMR ($CDCl_3$) of compounds **1–9**

Carbon	1	2	3	4	5	6	7	8	9
1	108.62 d	107.77 d	107.65 d	109.12 d	108.8 d	111.4 d	108.88 d	107.6 d	108.2 d
2	146.47 s	141.96 s	141.40 s	144.95 s	141.1 s	149.6 s	137.91 s	145.8 s	142.4 s
3	141.70 s	137.74 s	141.37 s	142.69 s	141.7 s	143.2 s	142.23 s	136.2 s	138.6 s
4	123.05 s	121.36 s	120.80 s	122.30 s	121.3 s	126.0 s	121.06 s	122.7 s	121.6 s
5	125.45 s	124.30 s	124.42 s	125.68 s	126.0 s	124.1 s	124.98 s	124.0 s	124.6 s
6	124.28 d	124.44 d	123.57 d	124.30 d	124.2 d	187.7 s	124.30 d	124.2 d	124.2 d
7	128.62 d	128.40 d	127.69 d	128.67 d	129.2 d	126.1 d	128.79 d	128.3 d	128.6 d
8	45.39 d	45.59 d	44.79 d	44.42 d	45.61 d	171.2 s	45.53 d	45.63 d	45.65 d
9	37.52 s	37.24 s	36.31 s	37.20 s	37.21 s	40.05 s	37.02 s	37.30 s	37.28 t
10	143.60 s	142.18 s	141.35 s	143.27 s	142.8 s	151.7 s	141.82 s	143.0 s	142.7 s
11	31.02 t	31.12 t	30.36 t	30.54 t	31.16 t	34.12 t	31.91 t	31.10 t	31.15 t
12	29.96 t	30.36 t	29.17 t	38.17 t	30.55 t	28.50 t	30.55 t	30.08 t	29.97 t
13	38.95 s	39.35 s	38.07 s	38.85 s	38.91 s	38.99 s	38.85 s	39.02 s	38.89 s
14	38.96 s	39.24 s	38.18 s	45.37 s	39.02 s	44.60 s	38.96 s	38.94 s	38.99 s
15	28.13 t	28.14 t	27.35 t	28.10 t	28.24 t	29.82 t	28.10 t	28.21 t	28.24 t
16	35.48 t	35.97 t	35.59 t	35.38 t	35.99 t	35.38 t	36.22 t	36.42 t	35.98 t
17	30.35 s	30.56 s	29.56 s	30.33 s	30.42 s	30.50 s	30.36 s	30.41 s	30 39 s
18	44.41 d	44.46 d	43.66 d	43.61 d	44.47 d	44.29 d	44.44 d	44.51 d	44.47 d
19	30.59 t	30.02 t	29.22 t	29.96 t	30.06 t	30.85 t	30.99 t	30.57 t	30.57 t
20	40.56 s	40.50 s	39.70 s	40.47 s	40.52 s	40.41 s	40.49 s	40.54 s	40.51 s
21	29.66 t	29.94 t	29.78 t	29.90 t	29.95 t	29.87 t	29.38 t	30.02 t	29.76 t
22	36.50 t	36.38 t	36.13 t	35.93 t	36.42 t	36.39 t	36.35 t	36.03 t	36.40 t
23	10.85 c	10.79 c	9.95 c	10.73 c	10.72 c	13.10 c	10.89 c	11.03 c	10.93 c
25	22.23 c	16.84 c	21.57 c	22.07 c	22.29 c	37.70 c	22.31 c	22.28 c	22.17 c
26	16.96 c	22.18 c	16.04 c	16.81 c	16.92 c	20.78 c	16.81 c	16.89 c	16.90 c
27	17.49 c	17.42 c	16.64 c	17.35 c	17.44 c	18.27 c	17.39 c	17.47 c	17.41 c
28	31.77 c	31.77 c	30.98 c	31.73 c	31.79 c	31.57 c	31.76 c	31.79 c	31.78 c
29	179.30 s	179.11 s	178.28 s	179.08 s	179.1 s	178.8 s	179.10 s	179.1 s	179.1 s
30	32.17 c	32.15 c	31.33 c	32.10 c	32.08 c	32.74 c	32.14 c	32.13 c	32.09 c
OMe	51.59 c	51.54 c	50.73 c	51.57 c	51.50 c	51.49 c	51.54 c	51.55 c	51.49 c
1′	92.72 s	87.13 s	90.35 s	92.25 s	90.50 s	92.70 s	139.95 s	135.40 s	142.7 s
2′	38.65 t	41.77 t	44.63 t	36.34 t	45.82 t	38.38 t	35.96 t	36.52 t	34.48 t
3′	128.75 d	124.22 d	124.42 d	128.24 d	128.2 d	128.1 d	74.23 d	74.20 d	78.80 d
4′	140.52 s	151.17 s	141.20 s	140.63 s	140.6 s	140.6 s	90.10 s	89.90 s	86.10 s
5′	97.13 s	84.35 s	89.40 s	96.82 s	89.70 s	96.80 s	134.62 s	137.7 s	138.00 s
6′	38.13 t	35.20 t	35.18 t	38.91 t	84.60 d	39.13 t	30.02 t	32.11 t	34.97 t
7′	43.66 d	45.34 d	39.87 d	45.47 d	41.44 d	43.28 d	49.36 d	49.65 d	46.28 d
8′	35.98 t	38.89 t	35.81 t	32.75 t	29.68 t	34.80 t	29.93 t	29.71 t	30.04 t
9′	32.71 t	38.97 t	29.68 t	31.11 t	29.61 t	32.97 t	39.84 t	39.56 t	38.53 t
10′	40.10 d	32.88 d	43.03 d	39.45 d	43.24 d	39.35 d	42.61 d	42.56 d	34.72 d
11′	151.03 s	151.93 s	150.58 s	151.12 s	140.1 s	150.8 s	150.71 s	150.7 s	151.20 s
12′	108.69 t	108.45 t	108.01 t	108.59 t	119.1 t	108.8 t	108.63 t	108.7 t	108.5 t
13′	19.88 c	19.36 c	20.06 c	19.89 c	169.7 s	19.97 c	20.48 c	20.38 c	20.37 c
14′	19.09 c	20.35 c	17.84 c	19.07 c	18.97 c	19.08 c	17.09 c	17.10 c	19.29 c
15′	12.57 c	22.87 c	10.69 c	12.51 c	14.36 c	12.40 c	13.93 c	14.02 c	22.28 c

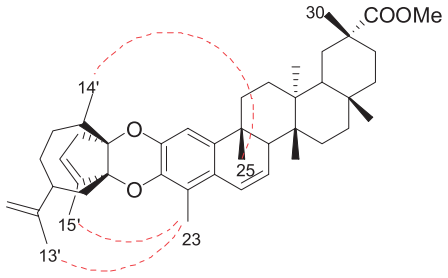


Figure 7. Selected ROESY correlations for compound **2**.

Compound **5** is an amorphous white solid with the molecular formula $C_{45}H_{60}O_7$. It presented spectroscopic data for the triterpenic unit similar to those in compounds **1**–**4**. The differences were the signals corresponding to the C_{15}-unit. In this sense, the ^{1}H NMR spectrum pointed out the presence of a multiplet at δ 3.80 (1H), one geminal proton to a secondary alcohol at δ 4.42 (J=9.7 Hz, 1H) and the lack of the singlet assignable to Me-13′. The analysis of the ^{13}C NMR spectrum revealed the existence of a carboxylic carbon (δ 169.7) and corroborated the presence of an oxygenated methine carbon at δ 84.60. The ^{1}H–^{13}C long-range correlations detected in the HMBC spectra

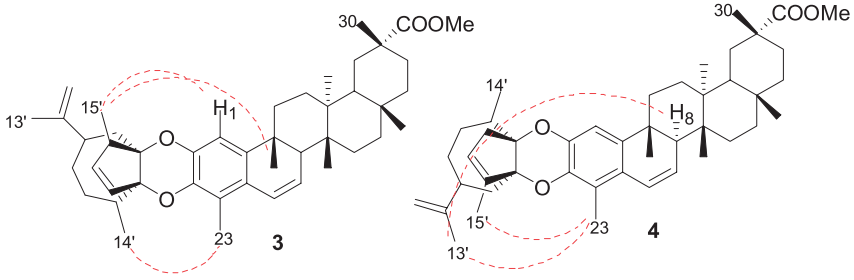


Figure 8. Selected ROESY correlations for compound **3** and **4**.

proposed in the formation of triterpene dimers and triterpene trimers also isolated from other species of Celastraceae.[11,17]

All of these data allow us to establish the structure of **1** depicted in Figure 1, which we have named cheilocline A. Dihydro-β-agarofuran sesquiterpenes are the usual sesquiterpenes present in the Celastraceae family, and there are not reports on the isolation of guaiane sesquiterpenes in this family, in spite of the fact that both series of sesquiterpenes have the same biogenetic precursor (*EE*-farnesyl cation).[29] Furthermore the sesquiterpene monomer has never been isolated from a natural source.

Compound **2** was also isolated as an optically active solid. It presented the formula $C_{45}H_{62}O_4$ in HRMS and spectroscopic data very similar to those of compound **1**. The main differences were the shift of H-3′, which appeared 65 Hz downfield, and the signals of Me-13′, Me-14′ and Me-15′, which appeared 25, 70 and 95 Hz upfield from those in compound **1** (Table 1). Its ^{13}C NMR spectrum (Table 2) also presented significant differences in the shifts of C-2, C-3, C-1′ and C-15′ with respect to the same signals in **1**. The thoroughly analysis of the HMBC, HSQC and ROESY spectra indicate that compound **2** is an isomer of compound **1**, with the structure shown in Figure 7. Thus the NOEs observed from Me-23 to Me-13′ and Me-15′, and from Me-14′ to Me-25, are consistent with both the disposition α of the cyclopentene ring, and the corresponding regiosubstitution pattern shown in Figure 7.

Compounds **3** and **4** were identified as the two remaining isomers of **1**. The NOEs effects depicted in Figure 8 agree with the proposed structures for these compounds. Compounds **1**–**4** represent the four possible hetero Diels–Alder adducts between the triterpene and sesquiterpene monomers described above.

determined the positions of these groups. Thus, the position of the C-6-OH group and the carboxylic group at C-13′ were established from the following correlations: H-6′/C-11′, H-6′/C-1′, H-6′/C-8′, H-12′/C-13′, H-12′/C-7′and H-7′/C-13′. Finally, the NOEs effects shown in Figure 9 were consistent with the structure assigned to this adduct.

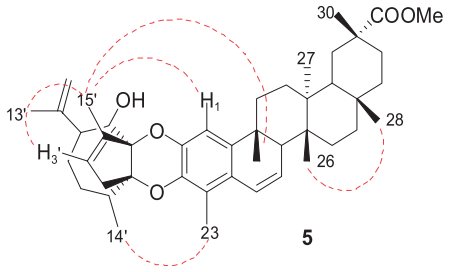


Figure 9. Selected ROESY correlations for compound **5**.

Compound **6** was isolated as an amorphous yellow solid with negative optical activity ($[\alpha]_D^{20}=-72.9$, c=0.2, $CHCl_3$) and molecular formula $C_{45}H_{60}O_5$. Its IR spectrum showed the existence of carbonyl groups (1731 and 1648 cm^{-1}), aromatic nucleus (1590, 1476 and 1433 cm^{-1}) and a terminal methylene (891 cm^{-1}). Its ^{1}H NMR spectrum showed signals similar to **1** for the protons assignable to the sesquiterpenic unit, but not for the hydrogens corresponding to the triterpenic unit. The main differences were the lack of the double doblets assignable to H-6 and H-7, the presence of a singlet at δ 6.22, and the downfield shift of Me-23. The ^{13}C NMR spectrum of **6** confirmed the existence of a carbonyl group at δ 187.7 and the presence of a trisubstituted double bond. The location of these functional groups through C-6, C-7 and C-8 was established by the correlations detected in the HMBC spectra, which are shown in the Figure 10, and it leads to a structure type 6-oxo-pristimerol for the triterpene moiety.

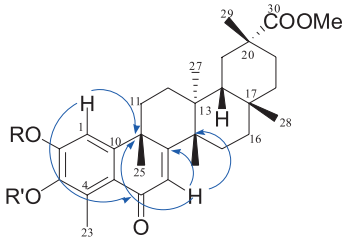


Figure 10. Selected HMBC correlations for compound **6**.

The NOEs observed in the ROESY spectrum agree with the stereochemistry represented in Figure 11.

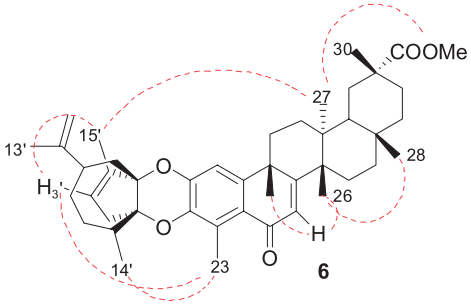


Figure 11. Selected ROESY correlations for compound **6**.

Compounds **7** and **8** presented the same formula $C_{45}H_{62}O_4$ and similar spectroscopic data. They also showed be composed by the same triterpenic unit that compounds **1**–**5**. Their NMR spectra mainly differ from those of **1**–**5** in the shift and multiplicity of H-3 (see Table 1); and the presence of a tetrasubstituted double bond. After studying the COSY, ROESY, HSQC and HMBC spectra, we concluded that compounds **7** and **8** do not have the bridged cyclopentane ring present in all above compounds. Consequently, the corresponding linkage between the triterpene and the sesquiterpene occurs through the trisubstituted double bond instead of the tetrasubstituted double bond. The selected HMBC correlations shown in Figure 12 corroborated this views. The *cis* orientation of H-3′ and Me-15′ and its α or β disposition were established on the basis of the NOEs effect found in the ROESY spectrum. Thus the following connectivities:

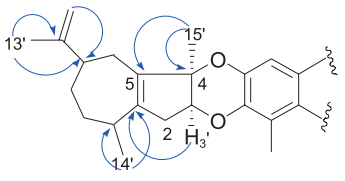


Figure 12. Selected HMBC correlations for compound **7** and **8**.

Me-15′/H-3′; Me-15′/H-6′; Me-15′/Me-27; Me-13′/H-1 determined the stereochemistry of compound **7** shown in Figure 13. The relative stereochemistry of compound **8** was also established by the following NOEs effects: Me-15′/H-3′; Me-15′/H-6′; Me-15′/Me-27; Me-14′/H-3′; Me-13′/Me-23. Therefore, the structures of these adducts (7 and 8) were clearly defined as shown in Figure 13.

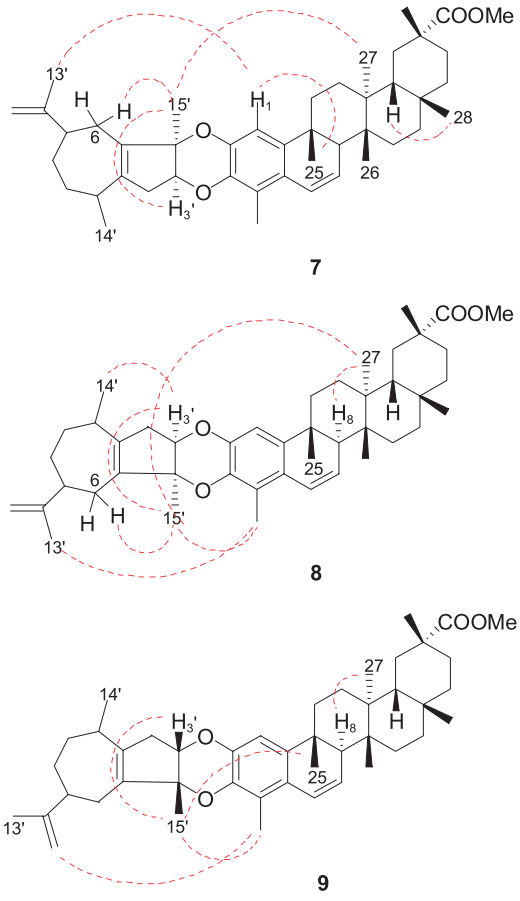


Figure 13. Selected ROESY correlations for compound **7**, **8** and **9**.

Compound **9** showed spectroscopic data very close to those of **8**. Its ^{1}H NMR spectrum featured signals for H-3′ 24 Hz downfield from those of H-3′ in **8**. The analysis of the NOEs detected in the ROESY spectrum determined that **8** is a stereoisomer of **9**.

The complete assignments of the ^{1}H and ^{13}C NMR signals of all cheiloclines are shown in Tables 1 and 2, respectively. These unequivocal assignments were made on the basis of the COSY, HSQC and HMBC spectra.

None of the cheiloclines showed significant antibacterial, antitumor and aldose reductase inhibitory activities when they were tested in the corresponding assays.[31] Because the triterpene subunits in monomer compounds tend to be bioactive,[25] the size of the molecule plays an important role in the bioactivity.

Unfortunally all our attempts to obtain suitable crystals for X-ray diffraction, and consequently the determination of the absolute configuration of cheiloclines, failed. As natural triterpenes are found as chiral products in only one enantiomeric series, we can establish the absolute stereochemistry of the carbons 1′ and 5′ of cheiloclines A–F, and the absolute configuration of the carbons 3′ and 4′of cheiloclines G–I, on the basis of the detected NOEs effects. Thus, compounds **1**, **4** and **5** present the configuration (1′S, 5′S); compounds **2**, **3** and **6** have the configuration (1′R, 5′R), compounds **7**, **8** (3′S, 4′R) and **9** present the configuration (3′R, 4′S). The absolute configuration of

C-7′, C-10′ in all cheiloclines and also of the C-6′ in cheilocline E remains to be determined.

The isolation of these novel C-15/C-30 octacyclic adducts suggests, once again, that Celastraceae species possess enzymatic systems catalyzing hetero Diels–Alder reactions.

3. Experimental

3.1. General methods

UV spectra were collected in absolute EtOH on a JASCO V-560 spectrophothometer. IR spectra were obtained using a Bruker IFS28/55 spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, repectively, with TMS as the internal reference. The 2D NMR experiments were conducted on a Bruker WP-400 SY NMR spectrometer in $CDCl_3$ at 400 MHz. High- and low-resolution mass spectra were obtained on a VG Autospec spectrometer. Macherey–Nagel polygram Sil G/UV254 and preparative TLC Sil G-100UV254 foils were used for TLC. Silica gel (0.2–0.63 mm) and Sephadex LH-20 were used for column chromatography. TLC plates were visualised by spraying with H_2SO_4/H_2O/AcOH (1:4:20) and heating.

3.2. Plant material

Roots of *C. hippocratioides* were collected in San Martin Region (Perú), in November 2001, and it was identified by the botanist G. Yarupaitan. A voucher specimen is on file (No. 3020) with the Herbarium of the Museo de Historia Natural, Lima, Perú.

3.3. Extraction and isolation

Root bark of *Cheiloclinium* hippocratioides (0.4 Kg) was extracted with *n*-hexane/Et_2O (1:1) (2 L) in a Soxhlet apparatus for 48 h. Evaporation of the solvent under reduced pressure provided 70 g of a dark extract. This residue was chromatographed on Sephadex LH-20 eluting with *n*-hexanes/$CHCl_3$/MeOH (2:1:1) to afford 41 fractions. Fractions with similar TLC profile were combined and reduced to 6 fractions (A–F). Each was rechromatographed on silica gel column, using mixtures of *n*-hexane/EtOAc of increasing polarity as eluent. Some of the eluted products were separated by TLC preparative. Cheilocline E (54 mg), cheilocline F (3 mg), 7α-hydroxy-blepharodol (14.4 mg) and 7-oxo-blepharodol (4.6 mg) were isolated from fraction A. Fraction B yielded cheilocline A (6.4 mg), cheilocline B (2.7 mg), cheilocline C (5.8 mg), cheilocline D (17.4 mg), 29-hydroxy-friedolean-1,3-dione (5.4 mg), 29-hydroxy-friedolean-3-one (6.0 mg). Fraction C afforded cheilocline G (22 mg), cheilocline H (14.3 mg), cheilocline I (22.5 mg.), pristimerine (0.7 g) and dispermoquinone (20.0 mg). Isoblepharodol (24.3 mg), 6-oxo-pristimerol (34.7 mg), 6-epibarudiona (8.0 mg) and blepharodol (17.4 mg) were separated from fraction D. Fraction E yielded escutionin αA (6.3 mg) and 7,8-dihidro-escutionin αA (5.2 mg). Cangaronsin αA (4.3 mg) and isocangaronsin αA (8 mg) were isolated from fraction F.

3.3.1. Cheilocline A (1). Amorphous white solid; $[\alpha]_D^{20} = -94.5$ (*c* 0.64, $CHCl_3$); UV (EtOH) λ_{max} 278, 233, 201 nm; IR (film) λ_{max} 2928, 1728, 1644, 1599, 1580, 1475, 1378, 1317, 1214, 1145, 1096, 1068, 1028, 977, 922, 890, 864, 814, 758 cm^{-1}; EM *m/z* (rel. int.) 666 (M^+, 45), 466 (20), 217 (6), 202 (100), 188 (41), 173 (11), 159 (82), 145 (54), 131 (23), 119 (28), 105 (29); HRMS 666.4648 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^{1}H NMR ($CDCl_3$, 500 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 125 MHz) (see Table 2).

3.3.2. Cheilocline B (2). Amorphous white solid; $[\alpha]_D^{20} = +53.3$ (*c* 0.27, $CHCl_3$); UV (EtOH) λ_{max} 278, 233, 202 nm; IR (film) λ_{max}: 2924, 2854, 1732, 1645, 1600, 1578, 1463, 1376, 1322, 1215, 1144, 1077, 986, 889, 758 cm^{-1}; MS *m/z* (rel. int.): 666 (M^+, 45), 466 (10), 202 (70), 188 (45), 173 (16), 159 (100), 145 (94), 131 (49), 119 (53), 105 (68); HRMS: 666.4667 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^{1}H NMR ($CDCl_3$, 500 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 125 MHz) (see Table 2).

3.3.3. Cheilocline C (3). Amorphous white solid; $[\alpha]_D^{20} = -31.4$ (*c* 0.58, $CHCl_3$); UV (EtOH) λ_{max} 307, 278, 233, 211, 202 nm; IR (film) λ_{max} 2935, 1728, 1644, 1582, 1472, 1377, 1321, 1254, 1215, 1143, 1111, 1092, 1066, 1046, 987, 916, 889 cm^{-1}; MS *m/z* (rel. int.) 666 (M^+, 92), 466 (26), 217 (11), 202 (100), 188 (50), 173 (15), 159 (96), 145 (82), 131 (27), 119 (37), 105 (37); HRMS: 666.4666 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^{1}H NMR ($CDCl_3$, 500 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 125 MHz) (see Table 2).

3.3.4. Cheilocline D (4). Amorphous white solid; $[\alpha]_D^{20} = -3.0$ (*c* 1.74, $CHCl_3$); UV (EtOH) λ_{max} 278, 233, 202 nm; IR (film) λ_{max}: 2934, 1727, 1645, 1599, 1583, 1475, 1378, 1317, 1215, 1145, 1095, 1065, 1014, 980, 956, 924, 891, 817, 758 cm^{-1}; MS *m/z* (rel. int.): 666 (M^+, 38), 466 (22), 269 (12), 217 (7), 202 (100), 188 (60), 173 (13), 159 (90), 145 (55), 131 (26), 105 (34); HRMS 666.4648 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^{1}H NMR ($CDCl_3$, 500 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 125 MHz) (see Table 2).

3.3.5. Cheilocline E (5). Amorphous white solid; $[\alpha]_D^{20} = -9.0$ (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 276 (2.82), 206 (3.35), 202 (3.38) nm; IR (film) λ_{max} 2925 2854, 1775, 1730, 1600, 1584, 1463, 1378, 1308, 1255, 1213, 1188, 1143, 1116, 1092, 1068, 1045, 1013, 992, 757 cm^{-1}; MS *m/z* (rel. int.): 694 ($M^+ - H_2O$, 100), 466 (2), 429 (21), 322 (28), 229 (26), 201 (16), 149 (84), 107 (30); HRMS 694.4219 (Calcd 694.4233, $C_{45}H_{58}O_6$) ($M^+ - H_2O$); ^{1}H NMR ($CDCl_3$, 300 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2).

3.3.6. Cheilocline F (6). Amorphous yellow solid; $[\alpha]_D^{20} = -72.9$ (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log () 299 (3.88), 251 (4.06), 205 (4.42), 203 (4.41) nm; IR (film) λ_{max} 2934, 2360, 2333, 1731, 1648, 1590, 1476, 1433, 1378, 1310, 1218, 1159, 1101, 979, 891, 755, 688 cm^{-1}; MS *m/z* (rel. int.): 680 (M^+, 81), 480 (31), 218 (14), 202 (100), 187 (21), 173 (12), 159 (92), 145 (77), 131 (23), 119 (33), 105 (28); HRMS 680.4491 (Calcd 680.4441, $C_{45}H_{60}O_5$); ^{1}H NMR ($CDCl_3$, 300 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2).

3.3.7. Cheilocline G (7). Amorphous white solid; $[\alpha]_D^{20} = -91.3$ (*c* 0.53, $CHCl_3$); UV (EtOH) λ_{max} 279, 237, 203 nm; IR (film) λ_{max} 2926, 1728, 1634, 1599, 1576, 1460, 1378, 1307, 1215, 1144, 1076, 1014, 985, 923, 888, 816, 758 cm^{-1}; MS *m/z* (rel. int): 666 (M^+, 100), 466 (8), 401 (18), 201 (54), 159 (34), 145 (48), 136 (17), 107 (26); HRMS 666.4651 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^1H NMR ($CDCl_3$, 300 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2).

3.3.8. Cheilocline H (8). Amorphous white solid; $[\alpha]_D^{20} = -24.8$ (*c* 2.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 288 (4.03), 235 (4.4), 202 (4.41) nm; IR (film) λ_{max} 2928, 2870, 1731, 1600, 1575, 1462, 1380, 1319, 1263, 1243, 1216, 1186, 1173, 1144, 1094, 1077, 1048, 984, 889, 757 cm^{-1}; MS *m/z* (rel. int.) 666 (55), 466 (23), 202 (100), 187 (29), 159 (88), 145 (63), 119 (38), 105 (28); HRMS 666.4679 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^1H NMR ($CDCl_3$, 300 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2).

3.3.9. Cheilocline I (9). Amorphous white solid; $[\alpha]_D^{20} = +27.1$ (*c* 1.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 278 (3.7), 231 (4.1), 202 (4.2) nm; IR (film) λ_{max} 2927, 1732, 1462, 1377, 1321, 1247, 1214, 1185, 1143, 1121, 1093, 1048, 1014, 994, 927, 887, 858, 814, 796, 757 cm^{-1}; MS *m/z* (rel. int.): 666 (M^+, 100), 401 (7), 201 (49), 159 (45), 145 (57), 119 (25), 107 (21); HRMS 666.4631 (Calcd 666.4648, $C_{45}H_{62}O_4$); ^1H NMR ($CDCl_3$, 300 MHz) (see Table 1); ^{13}C NMR ($CDCl_3$, 75 MHz) (see Table 2).

Acknowledgements

This work has been funded by the Spanish MCYT (SAF2003-04200-C02-02) and by the ICIC (Instituto Canario de Investigación del Cáncer). D.M.S. thanks Caja Canarias-ULL for a predoctoral fellowship.

References and notes

1. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.
2. Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Products Synthesis through Percyclic Reactions*; American Chemical Society: Washington, DC, 1983.
3. Watanabe, K.; Mie, T.; Ichihara, A.; Oikawa, H.; Honma, H. *J. Biol. Chem.* **2000**, *275*, 38393–38401.
4. Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1321–1322.
5. Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, H.; Ichihara, A. *Biochim. Biophys. Acta* **1998**, *1384*, 387–395.
6. Oikawa, H.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748–8756.
7. Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D.; Van den Heever, J.; Hutchinson, C.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519–11520.
8. Ichihara, A.; Oikawa, H. In Barton, D., Nakanishi, K., Meth-Cohn, O., Eds.; Comprehensive Natural Products Chemistry; 1999, 367–408.
9. Ose, T.; Watanabe, K.; Mie, T.; Honma, M.; Watanabe, H.; Yao, M.; Oikawa, H.; Tanaka, I. *Nature* **2003**, *422*, 185–189.
10. González, A. G.; Jiménez, J. S.; Moujir, L. M.; Ravelo, A. G.; Luis, J. G.; Bazzocchi, I. L.; Gutiérrez, A. M. *Tetrahedron* **1992**, *48*, 769–774.
11. González, A. G.; Alvarenga, N. L.; Estévez-Braun, A.; Ravelo, A. G.; Bazzocchi, I. L.; Moujir, M. L. *Tetrahedron* **1996**, *52*, 9597–9608.
12. González, A. G.; Kennedy, M. L.; Rodríguez, F. M.; Bazzocchi, I. L.; Jiménez, I. A.; Ravelo, A. G.; Moujir, L. *Tetrahedron* **2001**, *57*, 1283–1287.
13. Shirota, O.; Morita, H.; Takeya, K.; Itokawa, H. *Tetrahedron* **1995**, *51*, 1107–1120.
14. Shirota, O.; Morita, H.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1997**, *60*, 1100–1104.
15. Shirota, O.; Morita, H.; Takeya, K.; Itokawa, H. *Chem. Pharm. Bull.* **1998**, *46*, 102–106.
16. Shirota, O.; Morita, H.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1997**, *60*, 111–115.
17. González, A. G.; Alvarenga, N. L.; Bazzocchi, I. L.; Ravelo, A. G.; Moujir, M. L. *J. Nat. Prod.* **1999**, *62*, 1185–1187.
18. Rodríguez, F. M. Estudio fotoquímico de especies de la familia Celastraceae: Maytenus blepharodes y Crossopetalum lobatum. Tesis Doctoral, Universidad de la Laguna, 2000.
19. Betancor, C.; Freire, R.; González, A. G.; Pascard, C.; Pringue, T. *Phytochemistry* **1980**, *19*, 1989.
20. Chávez, H.; Estévez-Braun, A.; Ravelo, A. G.; González, A. G. *J. Nat. Prod.* **1998**, *61*, 82–85.
21. Martin, J. D. *Tetrahedron* **1973**, *29*, 2997–3000.
22. Jonson, A.; Juby, P.; King, T.; Tam, S. *J. Chem. Soc.* **1963**, 2884.
23. González, A. G.; Alvarenga, N. L.; Rodríguez, F. M.; Ravelo, A. G.; Bazzocchi, I. L.; Gupta, M. P. *Nat. Prod. Lett.* **1995**, *7*, 209–218.
24. Shirota, O.; Morita, H.; Takeya, K.; Itokawa, H. *J. Nat. Prod.* **1994**, *57*, 1675–1681.
25. Ravelo, A. G.; Estévez-Braun, A.; Chávez, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Top. Med. Chem.* **2004**, *4*, 241–265.
26. Soukup, J. *Nombres Vulgares de la Flora Peruana*; Editorial Salesianos: Lima, 1997.
27. Gupta, M. P. *270 Plantas Medicinales Iberoamerica*; Convenio Andrés Bello: Colombia, 1995.
28. Duke, J. A.; Vasquez, R. *Amazonian Ethnobotanical Dictionary*; CRC: Boca Raton, Florida, 1994.
29. Dewick, P. M. *Medicinal Natural Products, a Biosynthetic Approach*, 2nd. ed.; Wiley: New York, 2002.
30. Brüning, R.; Wagner, H. *Phytochemistry* **1978**, *17*, 1821.
31. The biological assays are the same described in references 12, 20.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 437–445

Synthesis of 9- and 10-membered macrolactones by selective ozonolysis of 1,4-diazaphenanthrene derivatives

Elisa Pérez-Sacau,[a,b] Jorge Soto-Delgado,[a,b] Ana Estévez-Braun[a,b,*] and Ángel G. Ravelo[a,b,*]

[a]*Instituto Universitario de Bio-Orgánica 'Antonio González', Avda. Astrofísico Fco. Sánchez 2, 38206, La Laguna, Tenerife, Spain*
[b]*Instituto Canario de Investigación del Cáncer, Hospital Universitario de La Candelaria, 38010, Tenerife, Spain*

Received 9 August 2004; revised 18 October 2004; accepted 21 October 2004

Abstract—9- and 10-membered macrolactones bearing benzo and diazine rings were obtained by chemoselective ozonolysis of dihydrofuran and pyran 1,4-diazaphenathrene derivatives. This is the first example of preparation of macrolactones by chemoselective ozonolysis of an enol double bond shared by aromatic and heterocyclic rings.

1. Introduction

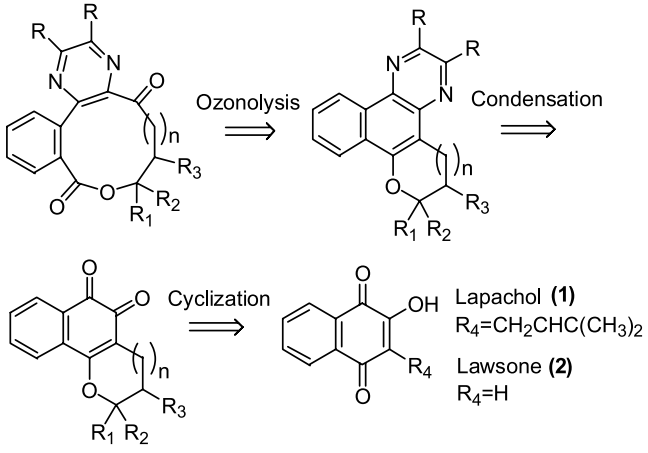
Macrolides are an attractive class of compounds that have shown a wide variety of interesting bioactivities.[1] Some representative examples are leucascandrolide,[2] epothilone,[3] erythromycin,[4] or salicylihalamide.[5] Among the 9- and 10-membered macrolactones, the antibiotic activity of lustromycin,[6] the anti-proliferative properties of apicularen,[7] or the bacterial DNA primase inhibitory activity of Sch 642305,[8] stand out. This variety of activities may be due to the fact that macrolides often show multiple low-energy conformations. Changes in the position and nature of the substituents can alter the free energy penalty for distortion of one of these small molecules upon binding to a protein target.[9] Consequently, the ability of these host molecules to bind guests is often very specific, enabling the host to recognize just one molecule or ion in a mixture.

On the other hand, there are many examples of natural and synthetic phenazines which exhibit diverse activities like antimalarial,[10] trypanocidal,[11] fungicidal,[12] or antiplatelet.[13] These heterocyclic compounds fulfill the fundamental physicochemical requirements for DNA intercalation, exhibiting antitumor activity in leukaemia and solid tumours. Some benzophenazines are dual inhibitors of topoisomerase I and II, two key enzymes that affect the topology of DNA at different points in the cell cycle.[14]

This paper describes the preparation of macrocyclic compounds with fused benzo and diazine moieties. The presence of diaza heterocyclic rings close to the ion-binding macrolactone moiety opens attractive possibilities, offering the potential of coupling DNA-damage with ion-binding properties.

2. Results and discussion

Scheme 1 shows the retrosynthetic pathway toward the macrolactones. It involves ozonolysis, condensation and cyclization processes.

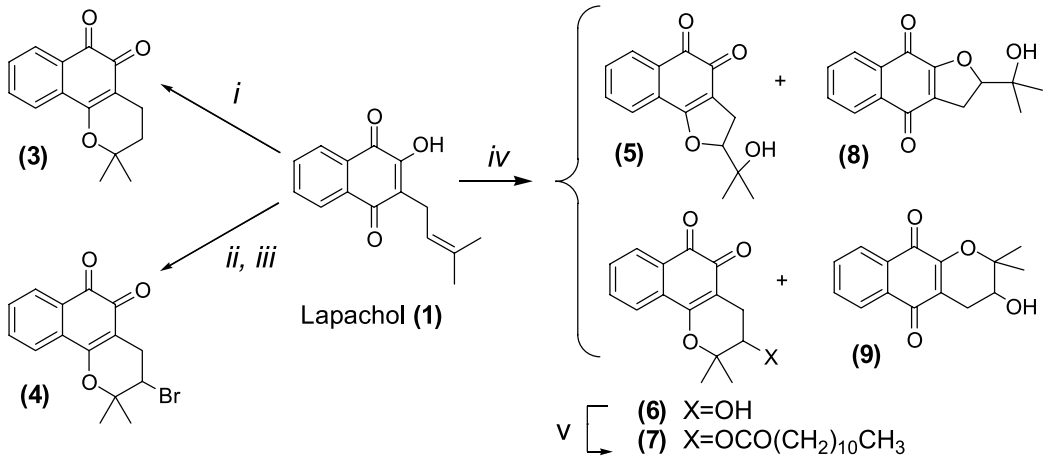


Scheme 1.

The initial precursors, lapachol **1** and lawsone **2**, are bioactive naphthoquinones isolated from plants of the

Keywords: 1,4-Diazaphenanthrene derivatives; Ozonolysis; 9- and 10-membered macrolactones.
* Corresponding authors. Tel.: +34 922 318576; fax: +34 922 318571; e-mail addresses: aestebra@ull.es; agravelo@ull.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.075

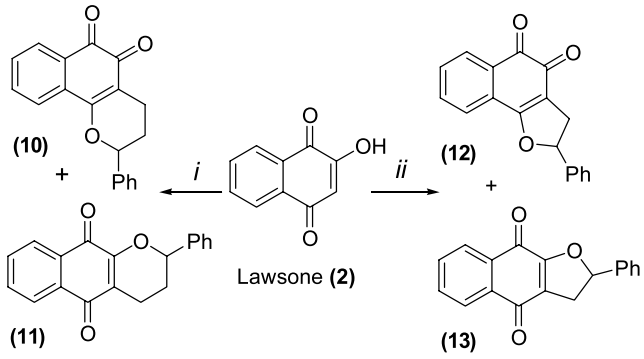


Scheme 2. Reagents and conditions: (i) H_2SO_4, 0 °C; (ii) Lutidine, $ClCOCH_3$, dry CH_2Cl_2, 0 °C; (iii) Br_2, dry CH_2Cl_2; (iv) *m*-CPBA, CH_2Cl_2, 0 °C; (v) Py, $ClCO(CH_2)_{10}CH_3$, dry CH_2Cl_2, 0 °C.

Bignoniaceae family.[15] They are also commercial products easily available. The furan ($n=0$) and pyran ($n=1$) *ortho*-1,2-naphthoquinones were synthesized from **1** and **2**. Lapachol was converted into *ortho*-naphthoquinones by intra-cyclization in different conditions[15,16] (H_2SO_4, Br_2, *m*-CPBA). The treatment of **1** with *m*-CPBA also afforded *para*-1,4-naphthoquinone analogues (α-isomers **8** and **9**) (see Scheme 2).

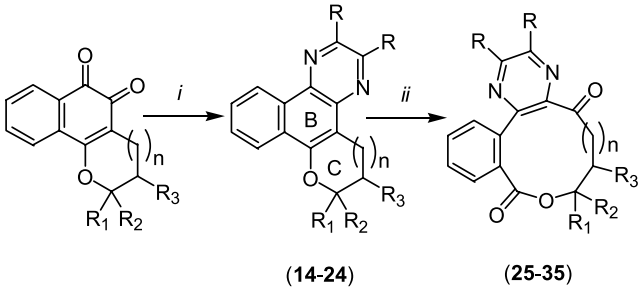
The non-prenyl *ortho*-naphthoquinones **10** and **12** were obtained from lawsone **2** following the reactions shown in Scheme 3. The Knoevenagel condensation of **2** and paraformaldehyde $(CH_2O)_n$ leads to a quinone methide intermediate, which undergoes hetero Diels–Alder reaction with styrene as dienophile[17] yielding, in one-pot reaction, the pyran-naphthoquinone derivatives **10** and **11**. The treatment of **2** with CAN and styrene[18] also yielded in one-pot reaction the dihydrofuran-naphthoquinone derivatives **12** and **13** via [3+2] type cycloaddition.

1,4-Diazaphenanthrene derivatives were synthesized by condensation of the *ortho*-quinones with 1,2-ethylendiamine or *trans*-1,2-diaminecyclohexane.[19]



Scheme 3. Reagents and conditions: (i) Dioxane, 7 equiv $(CH_2O)_n$, reflux, 3 equiv styrene; (ii) CH_3CN/H_2O (3/1), 2 equiv CAN, 0 °C-rt, 10 equiv styrene.

The dihydrofuran or pyran 1,4-diazaphenanthrene compounds were treated with ozone, which produced a selective oxidative cleavage of the enol double bond shared by rings B and C, leading to the corresponding macrolactones (Scheme 4).



Scheme 4. Reagents and conditions: (i) 1,2-ethylenediamine or *trans*-1,2-diamine cyclohexane, molecular sieves 4 Å toluene, Δ, 24 h–2 days; (ii) (a) O_3, −78 °C, dry CH_2Cl_2, 10–20 min. (b) Me_2S.

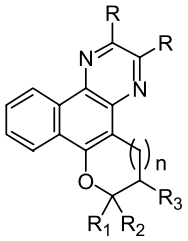
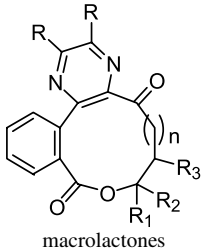
This enol double bond shows a behaviour similar to the 9,10-double bond in polyaromatic phenanthrene systems, which is the most labile in terms of its chemical reactivity, and readily broken under oxidative conditions to yield dialdehydes or acid derivatives.[20]

By far, the most general route to macrolactones is by intramolecular ring closure.[21] Other strategies are ring contraction and ring expansion. Ring contractions leading to macrolactones are relatively rare because of the problem of finding suitable large ring precursors for reactions.[22] The ring expansion can be achieved by cleavage of a C–C bond of suitable starting materials,[23] by C=C double bond cleavage of bicyclic vinyl ethers,[24] and sometimes also by a Baeyer-Villiger oxidation reaction.[25]

To the best of our knowledge, this letter presents the first example of macrolide formation by ozonolysis of an aromatic double bond at the site of fusion of the pyran or dihydrofuran moiety.

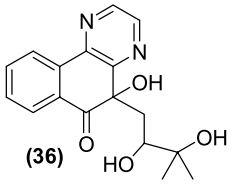
Table 1 summarizes the results obtained in the formation of 1,4-diazaphenanthrene derivatives and macrocyclic compounds. The reactivity seemed quite substrate dependent. The diazines from 1,2-ethylenediamine were obtained in yields higher than those from *trans*-1,2-

Table 1. Yields of 1,4-diazaphenanthrenes (**14**–**24**) and macrolactones (**25**–**35**)

Entry	*n*	R	R_1	R_2	R_3	 1,4-diazaphenanthrenes	 macrolactones
1	0	$-(CH_2)_4-$	$-C(OH)(CH_3)_2$	H	H	**14** 70%	**25** 68%
2	0	$-(CH_2)_4-$	Ph	H	H	**15** 49%	**26** 22%
3	1	$-(CH_2)_4-$	Me	Me	H	**16** 71%	**27** 68%
4	1	$-(CH_2)_4-$	Me	Me	OH	**17** 47%	**28** 47%
5	1	$-(CH_2)_4-$	Me	Me	Br	**18** 51%	**29** 46%
6	1	$-(CH_2)_4-$	Me	Me	$-OCO(CH_2)_{10}CH_3$	**19** 78%	**30** 22%
7	0	H	$-C(OH)(CH_3)_2$	H	H	**20** 70%	**31** 70%
8	1	H	Me	Me	H	**21** 68%	**32** 61%
9	1	H	Me	Me	OH	**22** 89%	**33** 68%
10	1	H	Me	Me	Br	**23** 80%	**34** 37%
11	1	H	Ph	H	H	**24** 51%	**35** 53%

diaminecyclohexane. The best results in the ozonolysis were found for 1,4-diazaphenanthrene derivatives bearing non-voluminous substituents at the pyran or dihydrofuran ring (compounds **25**, **27**, **31** and **32**).

We also tried an oxidative cleavage using *m*-CPBA as oxidative agent, but mixtures of several N-oxide derivatives and polyalcohols were obtained. However, the ozonolysis process provides cleaner and more selective reactions, only in one case (Entry 9), was the polyalcohol **36** (21%) produced together with the desired macrolactone **33**.



(36)

The NMR spectra of the 10-membered macrolactones ($n=1$) with $R_3=$Br, –OH or $-OCO(CH_2)_{10}CH_3$ (compounds **28**, **29**, **30**, **33** and **34**), showed the existence of two thermodynamically interchangeable conformers in a ratio 3:1. When $R_3=$Br (**27** and **32**), the two conformers are easy to distinguish in their ^{1}H and ^{13}C NMR spectra. In order to obtain an approximate idea on the geometry and energy of these molecules, an analysis was made using GMMX calculations.[26] After multiple minimizations of **32**, two main lower-energy conformers I and II were found (see Fig. 1). According to the studies on C_7–C_{10} cycloalkanes conformers recently carried out by Wiberg,[27] the structures of conformers I and II are similar to the geometries defined as S_5 and S_9 respectively, with slight distortions due to the presence of aromatics rings.

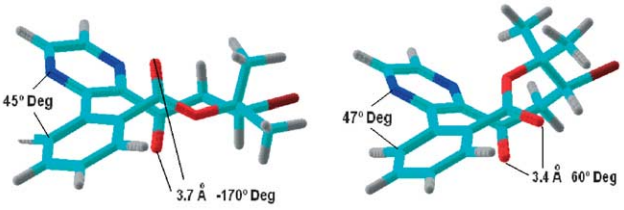


Figure 1. Lower-energy Conformers I and II.

The values of coupling constants between the proton geminal to the bromine group and the contiguous hydrogens were estimated, and the results agree with the experimental data.

Macrolides are very important target molecules in synthetic studies because of their biological and medicinal activities. Our work describes a new pathway to form highly functionalized 9- and 10-membered lactone rings from phenanthrenic aromatic systems linked face-to-face in a heterocyclic system.

Studies concerning the evaluation of biological activities, and the extended application of this methodology to other phenanthrenic systems, are in progress.

3. Experimental

3.1. General methods

All condensation reactions of the *ortho*-quinones with 1,2-diamine were carried out in toluene using activated molecular sieves 4 Å. Ozonolysis reactions were carried out on anhydrous conditions using glassware dried overnight at 100 °C and flamed just before using it. CH_2Cl_2 was dried on CaH_2 and distilled before use. Me_2S was dried on CaH_2 and distilled over molecular sieves. Ozon-Generator OZIV Fisher Labortechnik was used to generate O_3 flow. Reactions were monitored by TLC (on silica gel POLYGRAM® SIL G/UV_{254} foils). Purification by column flash-chromatography used Merck Kiesel 60-H (0.063–0.2 mm) as adsorbent and different mixtures of hexanes–ethylacetate as eluent. Pre-coated TLC plates SIL G-100 UV_{254} (Macherey-Nagel) were used for preparative-TLC purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 using a Bruker AMX-300 MHz. Chemical

shifts are given in parts per million (ppm) and J values are given in Hertz (Hz). Complete ^{1}H and ^{13}C assignments were achieved by 2D NMR spectroscopy (COSY, HMBC and HSQC). Bidimensional spectra were recorded in $CDCl_3$ or C_6D_6 using a Bruker AMX-400 MHz. MS and HRMS were recorded at VG Micromass ZAB-2F. All compounds were named using ACD40 Name-Pro program, which is based on IUPAC rules.

3.2. General procedure for the preparation of 1,4-diazaphenantrenes (14–24)

A solution of *ortho*-naphthoquinone and *trans*-1,2-diaminecyclohexane or 1,2-ethylendiamine (1.2–2 equiv) in dry toluene was stirred under reflux for 24 h in the presence of molecular sieves 4 Å. The reaction mixture was cooled to room temperature, filtered and the solvent removed under vacuum. The crude product was chromatographed using mixtures of hexanes/EtOAc as eluent.

3.2.1. 2-(1,2,9,10,11,12-Hexahydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)-2-propanol (14). Following the general procedure described above, 30 mg (0.12 mmol) of **5** were treated with 17 μL (0.14 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica gel with 9:1 to 1:1 Hex/EtOAc, to obtain 27 mg (70%) of **14**. ^{1}H NMR ($CDCl_3$) δ: 9.15 (1H, m, H-7), 8.04 (1H, m, H-4), 7.71 (2H, m, H-5+H-6), 4.99 (1H, m, H-2), 3.66 (1H, dd, J=15.8, 9.9 Hz, H-1a), 3.58 (1H, dd, J=15.8, 8.8 Hz, H-1b), 3.17 (4H, m, H-9+H-12), 2.04 (4H, m, H-10+H-11), 1.46 (3H, s, H-2′), 1.31 (3H, s, H-3′). ^{13}C NMR ($CDCl_3$) δ: 155.8 (s, C-3a), 152.9 (s, C-8a), 148.7 (s, C-12a), 139.2 (s, C-13a), 136.6 (s, C-7b), 131.3 (s, C-7a), 128.0 (d, C-5), 127.2 (d, C-6), 124.8 (d, C-7), 122.5 (s, C-3b), 121.4 (d, C-4), 114.3 (s, C-13b), 91.1 (d, C-2), 72.2 (s, C-1′), 32.9 (t, C-12), 32.8 (t, C-9), 29.9 (t, C-1), 26.0 (q, C-2′), 23.8 (q, C-3′), 23.0×2 (t, C-10, 11). MS *m*/*z* (rel. int): 334 (M^+, 100), 275 (M^+ − C(OH)$(CH_3)_2$, 78), 263 (M^+ −71, 97). HRMS: 334.1674 (calcd for $C_{21}H_{22}N_2O_2$ (M^+) 334.1681).

3.2.2. 2-Phenyl-1,2,9,10,11,12-hexahydrobenzo[*a*]furo[2,3-*c*]phenazines (15). Following the general procedure described above, 108 mg (0.39 mmol) of **12** were treated with 88 μL (0.73 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica with 19:1 to 4:1 Hex/EtOAc, to yield 67 mg (49%) of **15**. ^{1}H NMR ($CDCl_3$) δ: 9.18 (1H, m, H-7), 8.13 (1H, m, H-4), 7.71 (2H, m, H-5+H-6), 7.50 (2H, m, H-2′+H-6′), 7.34 (3H, m, H-3′+H-4′+H-5′), 6.15 (1H, m, H-2), 4.15 (1H, dd, J=15.6, 10.1 Hz, H-1a), 3.69 (1H, dd, J=15.6, 7.4 Hz, H-1b), 3.19 (2H, bs, H-9), 3.14 (2H, bs, H-12), 2.03 (4H, bs, H-10+H-11). ^{13}C NMR ($CDCl_3$) δ: 156.0 (s, C-3a), 152.9 (s, C-8a), 148.6 (s, C-12a), 142.1 (s, C-1′), 139.3 (s, C-13a), 136.7 (s, C-7b), 131.5 (s, C-7a), 128.7×2 (d, C-3′, 5′), 128.1×2 (d, C-5, 4′), 127.2 (d, C-6), 125.7×2 (d, C-2′, 6′), 124.8 (d, C-7), 122.7 (s, C-3b), 121.8 (d, C-4), 113.3 (s, C-13b), 85.6 (d, C-2), 37.3 (t, C-1), 32.9 (t, C-12), 32.8 (t, C-9), 23.1 (t, C-11), 23.0 (t, C-10). MS *m*/*z* (rel. int): 352 (M^+, 100), 275 (M^+ − Ph, 69). HRMS: 352.1596 (calcd for $C_{24}H_{20}N_2O$ (M^+) 352.1576).

3.2.3. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines (16). Following the general procedure described above, 219 mg (0.90 mmol) of **3** were treated with 230 μL (1.92 mmol) of *trans*-1,2-diaminecyclohexane. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 204 mg (71%) of **16**. ^{1}H NMR (C_6D_6) δ: 9.57 (1H, m, H-8), 8.55 (1H, m, H-5), 7.53 (2H, m, H-6+H-7), 3.32 (2H, t, J=6.7 Hz, H-1), 3.06 (4H, m, H-10+H-13), 1.66 (2H, t, J=6.7 Hz, H-2), 1.61 (4H, m, H-11+H-12), 1.26 (6H, s, H-1′+H-2′). ^{13}C NMR (C_6D_6) δ: 151.9 (s, C-9a), 149.7 (s, C-4a), 148.4 (s, C-13a), 141.3 (s, C-14a), 135.9 (s, C-8b), 131.0 (s, C-8a), 128.1 (s, C-4b), 127.9 (d, C-6), 126.9 (d, C-7), 124.5 (d, C-8), 122.0 (d, C-5), 110.3 (s, C-14b), 74.9 (s, C-3), 33.0 (t, C-2), 32.6 (t, C-10 or 13), 32.3 (t, C-13 or 10), 26.4×2 (q, C-1′+C-2′), 23.0×2 (t, C-11, 12), 18.3 (t, C-1). MS *m*/*z* (rel. int): 318 (M^+, 83), 303 (M^+ − Me, 6), 275 (M^+ − C_3H_7, 100). HRMS: 318.1723 (calcd for $C_{21}H_{22}N_2O$ (M^+) 318.1732).

3.2.4. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-2-ol (17). Following the general procedure described above, 180 mg (0.70 mmol) of **6** were treated with 100 μL (0.83 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica gel with 9:1 to 1:1 Hex/EtOAc, to obtain 108 mg (49%) of **17**. ^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, m, H-8), 8.21 (1H, m, H-5), 7.66 (2H, m, H-6+H-7), 4.02 (1H, bs, H-2), 3.32 (2H, m, H-1), 3.27–3.10 (2H, m, H-13), 3.04 (2H, m, H-10), 2.46 (1H, bs, OH), 2.03 (4H, m, H-11+H-12), 1.58 (3H, s, H-1′), 1.39 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 152.2 (s, C-9a), 149.0 (s, C-13a), 148.4 (s, C-4a), 140.7 (s, C-14a), 135.5 (s, C-8b), 130.1 (s, C-8a), 127.7 (d, C-7), 127.1 (d, C-6), 126.9 (s, C-4b), 123.9 (d, C-8), 121.6 (d, C-5), 107.6 (s, C-14b), 78.0 (s, C-3), 69.5 (d, C-2), 32.9 (t, C-13), 32.6 (t, C-10), 27.5 (t, C-1), 24.4 (q, C-1′), 23.0×2 (t, C-11+C-12), 22.6 (q, C-2′). MS *m*/*z* (rel. int): 334 (M^+, 36), 263 (M^+ − $C(CH_3)_2CHOH$, 100). HRMS: 334.1674 (calcd for $C_{21}H_{22}N_2O_2$ (M^+) 334.1681).

3.2.5. 2-Bromo-3,3-dimethyl-2, 3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines (18). Following the general procedure described above, 97 mg (0.30 mmol) of **4** were treated with 43 μL (0.36 mmol) of *trans*-1,2-diaminecyclohexane. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (19:1) as eluent, to obtain 61 mg (51%) of **18**. ^{1}H NMR ($CDCl_3$) δ: 9.11 (1H, m, H-8), 8.25 (1H, m, H-5), 7.68 (2H, m, H-6+H-7), 4.47 (1H, dd, J=8.5, 5.6 Hz, H-2), 3.92 (1H, dd, J=18.0, 5.6 Hz, H-1a), 3.61 (1H, dd, J=18.0, 8.5 Hz, H-1b), 3.16 (4H, m, H-13+H-10), 2.03 (4H, m, H-11+H-12), 1.70 (3H, s, H-1′), 1.58 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 152.4 (s, C-9a), 149.2 (s, C-13a), 148.4 (s, C-4a), 140.1 (s, C-14a), 135.8 (s, C-8b), 130.4 (s, C-8a), 128.0 (d, C-6), 127.2 (d, C-7), 127.0 (s, C-4b), 124.0 (d, C-8), 121.7 (d, C-5), 108.9 (s, C-14b), 77.9 (s, C-3), 53.0 (d, C-2), 32.9 (t, C-13), 32.7 (t, C-10), 30.3 (t, C-1), 26.8 (q, C-1′), 23.1 (t, C-11), 23.0 (t, C-12), 22.0 (q, C-2′). MS *m*/*z* (rel. int): 398 (M^++2, 46), 396 (M^+, 46), 317 (M^+ − Br, 100). HRMS: 396.0860 (calcd for $C_{21}H_{21}N_2O\,Br^{79}$ (M^+) 396.0837).

3.2.6. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-2-yl laurate (19). Following the general procedure described above, 98 mg (0.22 mmol) of **7** were treated with 52 μL (0.43 mmol) of *trans*-1,2-

diaminecyclohexane. The crude was chromatographed on silica gel with 19:1 to 4:1 Hex/EtOAc, to obtain 88 mg (78%) of **19**. ^{1}H NMR ($CDCl_3$) δ: 9.12 (1H, m, H-8), 8.30 (1H, m, H-5), 7.68 (2H, m, H-6+H-7), 5.28 (1H, t, J= 5.2 Hz, H-2), 3.51 (1H, dd, J=18.1, 5.3 Hz, H-1a), 3.27 (dd, 1H, J=18.1, 5.2 Hz, H-1b), 3.18 (2H, bs, H-13), 3.13 (2H, bs, H-10), 2.30 (2H, m, H-4′), 2.02 (4H, m, H-11+H-12), 1.57 (4H, m, H-5′+H-6′), 1.48 (3H, s, H-2′), 1.46 (3H, s, H-1′), 1.21 (14H, bs, H-7′+H-8′+H-9′+H-10′+H-11′+ H-12′+H-13′), 0.87 (3H, m, H-14′). ^{13}C NMR ($CDCl_3$) δ: 173.3 (s, C-3′), 152.3 (s, C-9a), 149.0 (s, C-13a), 148.5 (s, C-4a), 140.7 (s, C-14a), 135.8 (s, C-8b), 130.4 (s, C-8a), 127.9 (d, C-7), 127.2 (d, C-6), 127.1 (s, C-4b), 124.0 (d, C-8), 121.8 (d, C-5), 107.7 (s, C-14b), 76.2 (s, C-3), 70.7 (d, C-2), 34.5 (t), 32.9 (t), 32.7 (t), 31.9 (t), 29.5×2 (t), 29.4 (t), 29.3 (t), 29.2 (t), 29.1 (t), 25.1 (t), 24.8 (q, C-1′), 24.7 (t), 23.1 (t, C-12), 23.0 (t, C-11), 22.6 (t), 22.6 (q, C-2′), 14.1 (q, C-14′). MS *m/z* (rel. int): 516 (M^+, 8), 316 (M^+ − $OCO(CH_2)_{10}CH_3$, 61), 301 (316-Me, 100). HRMS: 516.3351 (calcd for $C_{33}H_{44}N_2O_3$ (M^+) 516.3352).

3.2.7. 2-(2,3-Dihydrobenzo[*f*]furo[2,3-*h*]quinoxalin-2-yl)-2-propanol (20). Following the general procedure described above, 101 mg (0.39 mmol) of **5** were treated with 52 μL (0.78 mmol) of 1,2-ethylendiamine. The crude was chromatographed on silica gel with 4:1 to 2:3 Hex/EtOAc, to obtain 79 mg (70%) of **20**. ^{1}H NMR ($CDCl_3$) δ: 9.09 (1H, m, H-8), 8.72 (1H, d, J=2.1 Hz, H-5), 8.67 (1H, d, J=2.1 Hz, H-6), 7.98 (1H, m, H-11), 7.67 (2H, m, H-9+ H-10), 4.98 (1H, t, J=9.3 Hz, H-2), 3.60 (2H, d, J=9.3 Hz, H-3), 1.47 (3H, s, H-2′), 1.31 (3H, s, H-3′). ^{13}C NMR ($CDCl_3$) δ: 157.0 (s, C-11b), 143.9 (d, C-5), 141.4 (s, C-3b), 139.7 (d, C-6), 138.9 (s, C-8b), 131.3 (s, C-8a), 128.7 (d, C-10), 127.6 (d, C-9), 125.0 (d, C-8), 122.8 (s, C-11a), 121.5 (d, C-11), 114.5 (s, C-4b), 91.5 (d, C-2), 72.0 (s, C-1′), 29.5 (t, C-3), 26.0 (q, C-2′), 24.0 (q, C-3′). MS *m/z* (%): 280 (M^+, 41), 221 (M^+ −71, 100). HRMS: 280.1210 (calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212).

3.2.8. 7,7-Dimethyl-6,7-dihydro-5*H*-benzo[*f*]pyrano [2,3-*h*]quinoxaline (21). Following the general procedure described above, 110 mg (0.45 mmol) of **3** were treated with 60 μL (0.90 mmol) of 1,2-ethylendiamine. The crude was chromatographed on silica gel with 19:1 to 4:1 Hex/EtOAc, to obtain 81 mg (68%) of **21**. ^{1}H NMR ($CDCl_3$) δ: 9.13 (1H, m, H-12), 8.80 (1H, d, J=2.0 Hz, H-3), 8.71 (1H, d, J=2.0 Hz, H-2), 8.33 (1H, m, H-9), 7.73 (2H, m, H-10+ H-11), 3.23 (2H, t, J=6.7 Hz, H-5), 2.03 (2H, t, J=6.7 Hz, H-6), 1.50 (6H, s, H-1′+H-2′). ^{13}C NMR ($CDCl_3$) δ: 150.8 (s, C-8a), 143.4 (s, C-4a), 143.4 (d, C-3), 139.9 (d, C-2), 138.1 (s, C-12b), 130.3 (s, C-12a), 128.6 (d, C-10), 128.2 (s, C-8b), 127.3 (d, C-11), 124.2 (d, C-12), 121.9 (d, C-9), 110.0 (s, C-4b), 75.7 (s, C-7), 32.4 (t, C-6), 26.7×2 (q, C-1′+C-2′), 18.2 (t, C-5). MS *m/z* (rel. int): 264 (M^+, 65), 249 (M^+ −Me, 16), 221 (M^+ −Me–CO, 100). HRMS: 264.1249 (calcd for $C_{17}H_{16}N_2O$ (M^+) 264.1263).

3.2.9. 7,7-Dimethyl-6,7-dihydro-5*H*-benzo[*f*]pyrano [2,3-*h*]quinoxalin-6-ol (22). Following the general procedure described above, 152 mg (0.59 mmol) of **6** were treated with 80 μL (1.20 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (3:2) as eluent, to obtain 147 mg (89%) of **22**. ^{1}H NMR ($CDCl_3$) δ: 9.12 (1H, m, H-12), 8.76 (1H, bs, H-3), 8.72 (1H, bs, H-2), 8.33 (1H, m, H-9), 7.73 (2H, m, H-10+ H-11), 5.11 (1H, m, H-6), 3.46 (1H, dd, J=17.7, 5.0 Hz, H-5a), 3.31 (1H, dd, J=17.7, 4.5 Hz, H-5b), 1.57 (3H, s, H-1′), 1.47 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 149.8 (s, C-8a), 143.5 (d, C-3), 140.3 (d, C-2), 138.7 (s, C-4a), 134.7 (s, C-12b), 130.4 (s, C-12a), 128.8 (d, C-10), 127.6 (d, C-11), 127.5 (s, C-8b), 124.2 (d, C-12), 122.0 (d, C-9), 108.0 (s, C-4b), 78.3 (s, C-7), 69,4 (d, C-6), 27.5 (t, C-5), 24.7 (q, C-1′), 22.2 (q, C-2′). MS *m/z* (rel. int): 280 (M^+, 41), 209 (M^+ −71, 100). HRMS: 280.1197 (calcd for $C_{17}H_{16}N_2O$ (M^+) 280.1212).

3.2.10. 6-Bromo-7,7-dimethyl-6,7-dihydro-5*H*-benzo[*f*] pyrano[2,3-*h*]quinoxaline (23). Following the general procedure described above, 108 mg (0.33 mmol) of **4** were treated with 45 μL (0.67 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 88 mg (80%) of **23**. ^{1}H RMN ($CDCl_3$) δ: 9.15 (1H, m, H-12), 8.81 (1H, d, J=1.9 Hz, H-3), 8.76 (1H, d, J=1.9 Hz, H-2), 8.32 (1H, m, H-9), 7.76 (2H, m, H-10+H-11), 4.49 (1H, dd, J=8.4, 5.6 Hz, H-6), 3.94 (1H, dd, J=17.9, 5.6 Hz, H-5a), 3.65 (1H, dd, J=17.9, 8.4 Hz, H-5b), 1.71 (3H, s, H-1′), 1.60 (3H, s, H-2′). ^{13}C RMN ($CDCl_3$) δ: 149.7 (s, C-8a), 143.6 (d, C-3), 142.5 (s, C-4a), 140.5 (d, C-2), 138.4 (s, C-12b), 130.5 (s, C-12a), 128.9 (d, C-10), 127.8 (d, C-11), 127.5 (s, C-8a), 124.3 (d, C-12), 121.9 (d, C-9), 109.0 (s, C-4b), 78.3 (s, C-7), 52.4 (d, C-6), 30.3 (t, C-5), 26.7 (q, C-1′), 22.3 (q, C-2′). MS *m/z* (rel. int): 398 (M^+ +2, 46), 396 (M^+, 46), 317 (M^+ −Br, 100). HRMS: 396.0860 (calcd for $C_{21}H_{21}N_2O\,Br^{79}$ (M^+) 396.0837).

3.2.11. 7-(1-Hydroxy-1-methylethyl)-6,7-dihydro[2] benzoxonino[6,7-*b*]pyrazine-5,9-dione (24). Following the general procedure described above, 43 mg (0.15 mmol) of **4** were treated with 20 μL (0.30 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 22 mg (51%) of **24**. ^{1}H RMN ($CDCl_3$) δ: 9.16 (1H, m, H-12), 8.81 (1H, d, J=2.0 Hz, H-3), 8.75 (1H, d, J=2.0 Hz, H-2), 8.37 (1H, m, H-9), 7.74 (2H, m, H-10+H-11), 7.55 (2H, m, H-2′+H-6′), 7.44 (3H, m, H-3′+H-4′+H-5′), 5.34 (1H, d, J=10.1 Hz, H-7), 3.43 (1H, m, H-6a), 3.24 (1H, m, H-6b), 2.52 (1H, m, H-5a), 2.25 (1H, m, H-5b). ^{13}C NMR ($CDCl_3$) δ: 151.8 (s, C-8a), 143.5 (d, C-3), 143.2 (d, C-4a), 141.1 (s, C-1′), 140.3 (d, C-2), 138.3 (s, C-12b), 130.3 (s, C-12a), 128.8 (d, C-10), 128.6×2 (d, C-3′+C-5′), 127.9 (d, C-4′), 127.6 (s, C-8b), 127.5 (d, C-11), 125.9×2 (d, C-2′+ C-6′), 124.3 (d, C-12), 121.8 (d, C-9), 111.5 (s, C-4b), 78.3 (s, C-7), 29.5 (t, C-6), 20.5 (t, C-5). MS *m/z* (rel. int): 312 (M^+, 62), 221 (M^+ −N–Ph, 100). HRMS: 312.1282 (calcd for $C_{21}H_{16}N_2O$ (M^+) 312.1263).

3.3. General procedure for the preparation of the macrolactones (25–35)

A solution of diazine in dry CH_2Cl_2 cooled to −78 °C, was ozonized until the colour of the solution changed to dark blue-grey. The reaction mixture was then quenched with dry Me_2S (2 equiv), concentrated under vacuum and chromatographed by preparative-TLC using mixtures of hexanes/

EtOAc as eluent, to afford the corresponding macrolactones **25**–**35**.

3.3.1. 7-(1-Hydroxy-1-methylethyl)-7,8,11,12,13,14-hexahydro[2]benzoxonino[6,7-*b*]quinoxaline-5,9-dione (25). 16 mg (0.05 mmol) of **14** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 6 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 12 mg (68%) of **25**. ^{1}H RMN ($CDCl_3$) δ: 8.03 (1H, m, H-4), 7.92 (1H, m, H-1), 7.72 (1H, m, H-3), 7.52 (1H, m, H-2), 5.49 (1H, bs, H-7), 4.12 (2H, m, H-8), 3.05 (4H, bs, H-11+H-14), 2.00 (4H, bs, H-12+H-13), 1.19 (3H, s, H-2′), 1.16 (3H, s, H-3′). MS *m*/*z* (rel. int): 366 (M^+, 2), 348 (M^+-H_2O, 3), 289 (348-C(OH)$(CH_3)_2$, 100). HRMS: 366.1548 (calcd for $C_{21}H_{22}N_2O_4$ (M^+) 366.1579).

3.3.2. 7-Phenyl-7,8,11,12,13,14-hexahydro[2] benzoxonino[6,7-*b*]quinoxaline-5,9-dione (26). 48 mg (0.13 mmol) of **15** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 15 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 11 mg (22%) of **26**. ^{1}H RMN ($CDCl_3$) δ: 8.02 (1H, bs, H-1), 7.90 (1H, d, J=7.8 Hz, H-4), 7.67 (1H, t, J=7.5 Hz, H-2), 7.49 (1H, t, J=7.5 Hz, H-3), 7.25 (3H, m, H-3′+H-4′+H-5′), 7.06 (2H, bs, H-2′+H-6′), 6.49 (1H, bs, H-7), 3.95 (1H, bs, H-8a), 3.52 (1H, bs, H-8b), 3.01 (4H, m, H-11+H-14), 1.92 (4H, s, H-12+H-13). MS *m*/*z* (rel. int): 384 (M^+, 1), 340 (M^+-CO_2, 9), 252 (M^+-COCH_2CHPh, 100). HRMS: 384.1466 (calcd for $C_{24}H_{20}N_2O_3$ (M^+) 384.1474).

3.3.3. 7,7-Dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10(7*H*)-dione (27). 97 mg (0.30 mmol) of **16** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 40 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 71 mg (68%) of **27**. ^{1}H NMR (C_6D_6) δ: 8.22 (1H, d, J=7.8 Hz, H-4), 7.68 (1H, d, J=7.8 Hz, H-1), 7.23 (1H, m, H-2), 7.02 (1H, m, H-3), 3.78 (1H, ddd, J=13.8, 6.3, 4.2 Hz, H-9a), 2.74 (4H, m, H-12+H-15), 2.59 (1H, ddd, J=15.1, 11.2, 3.9 Hz, H-9b), 2.16 (1H, ddd, J=14.8, 11.2, 4.2 Hz, H-8b), 1.66 (1H, ddd, J=18.7, 16.5, 5.8 Hz, H-7a), 1.44 (3H, s, H-1′), 1.42 (m, 4H, H-13+H-14), 1.16 (3H, s, H-2′). ^{13}C NMR (C_6D_6) δ: 201.6 (s, C-10), 165.5 (s, C-5), 152.9 (s, C-15a), 150.4 (s, C-16b), 149.1 (s, C-11a), 148.4 (s, C-10a), 139.0 (s, C-16a), 133.4 (d, C-3), 132.0 (d, C-2), 130.6 (d, C-4), 129.2 (s, C-4a), 128.6 (d, C-1), 83.8 (s, C-7), 37.9 (t, C-8), 36.1 (t, C-9), 31.9 (t, C-12 or C-15), 31.4 (t, C-15 or C-12), 26.6 (q, C-1′), 23.8 (q, C-2′), 22.4 (t, C-13 or C-14), 22.3 (t, C-14 or C-13). MS *m*/*z* (rel. int): 350 (M^+, 4), 335 (M^+-Me, 2), 253 ($M^+-CO(CH_2)C(Me)_2$, 100). HRMS: 350.1657 (calcd for $C_{21}H_{22}N_2O_3$ (M^+) 350.1630).

3.3.4. 8-Hydroxy-7,7-dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10 (7*H*)-dione (28). 33 mg (0.10 mmol) of **17** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 12 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 17 mg (47%) of **28**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, m, H-4), 7.64 (1H, m, H-1), 7.47 (2H, m, H-2+H-3), 4.02–3.96 (2H, m, H-8+H-9a), 3.02 (4H, bs, H-12+H-15), 2.73 (1H, m, H-9b), 2.30 (1H, bd, J=5.6 Hz, OH), 2.00 (4H, bs, H-13+H-14), 1.61 (3H, s, H-1′), 1.52 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 197.0 (s, C-10), 171.4 (s, C-5), 154.6 (s, C-15a), 153.4 (s, C-16b), 152.5 (s, C-11a), 149.5 (s, C-10a), 135.4 (s, C-16a), 132.8 (d, C-3), 132.0 (d, C-2), 130.9 (s, C-4a), 128.6 (d, C-4), 124.8 (d, C-1), 78.6 (s, C-7), 70.2 (d, C-8), 44.5 (t, C-9), 32.1 (t, C-12 or C-15), 31.4 (t, C-15 or C-12), 27.4 (q, C-1′), 24.4 (q, C-2′), 22.5 (t, C-13 or C-14), 22.4 (t, C-14 or C-13). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, m, H-4), 7.64 (1H, m, H-1), 7.47 (2H, m, H-2+H-3), 4.34 (1H, bs, H-9a), 3.92 (1H, m, H-8), 3.02 (4H, bs, H-12+H-15), 2.88 (1H, m, H-9b), 2.61 (1H, bd, J=4.8 Hz, OH), 2.00 (4H, bs, H-13+H-14), 1.67 (3H, s, H-1′), 1.31 (3H, s, H-2′). MS *m*/*z* (rel. int): 366 (M^+, 4), 350 (M^+-Me, 2), 295 (M^+-71, 100). HRMS: 366.7127 (calcd for $C_{21}H_{22}N_2O_4$ (M^+) 350.7101).

3.3.5. 8-Bromo-7,7-dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10(7*H*)-dione (29). 20 mg (0.05 mmol) of **18** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 6 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 10 mg (46%) of **29**. Major conformer: ^{1}H RMN ($CDCl_3$) δ: 8.07 (1H, d, J=7.5 Hz, H-4), 7.66 (1H, m, H-1), 7.50 (2H, m, H-2+H-3), 4.32 (1H, dd, J=12.5, 4.1 Hz, H-8), 4.10 (1H, dd, J=14.4, 4.2 Hz, H-9a), 3.10 (1H, m, H-9b), 3.03 (4H, m, H-12+H-15), 2.02 (4H, m, H-13+H-14), 1.74 (3H, s, H-1′), 1.69 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 197.6 (s, C-10), 164.3 (s, C-5), 153.7 (s, C-15a), 149.9 (s, C-16b), 149.8 (s, C-11a), 148.0 (s, C-10a), 138.1 (s, C-16a), 133.1 (d, C-2 or C-3), 132.9 (d, C-2 or C-3), 131.3 (d, C-4), 130.9 (s, C-4a), 128.7 (d, C-1), 87.1 (s, C-7), 52.6 (d, C-8), 47.2 (t, C-9), 32.1 (t, C-12 or C-15), 31.5 (t, C-12 or C-15), 25.4 (q, C-1′), 22.5×2 (t, C-13+C-14), 18.3 (q, C-2′). Minor conformer. ^{1}H RMN ($CDCl_3$) δ: 7.91 (1H, d, J=7.8 Hz, H-4), 7.70 (1H, m, H-1), 7.53 (2H, m, H-2+H-3), 5.22 (1H, dd, J=12.6, 4.6 Hz, H-8), 4.71 (1H, m, H-9a), 3.03 (5H, m, H-9b+H-12+H-15), 2.00 (4H, m, H-13+H-14), 1.86 (3H, s, H-1′), 1.16 (3H, s, H-2′). MS *m*/*z* (rel. int): 430 (M^++2, 3), 428 (M^+, 3), 349 (M^+-Br, 4), 253 ($M^+-CO(CH_2)CH(Br)C(Me)_2$, 100). HRMS: 428.0722 (calcd for $C_{21}H_{21}N_2O_3Br^{79}$ (M^+) 428.0736).

3.3.6. 7,7-Dimethyl-5,10-dioxo-7,8,9,10,12,13,14,15-octahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxalin-8-yl laurate (30). 54 mg (0.10 mmol) of **19** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 13 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 18 mg (22%) of **30**. Major conformer: ^{1}H NMR (C_6D_6) δ: 8.44 (1H, d, J=7.9 Hz, H-4), 7.72 (1H, d, J=7.9 Hz, H-1), 7.34 (1H, m, H-2), 7.13 (1H, m, H-3), 5.74 (1H, dd, J=11.4, 4.6 Hz, H-8), 4.29 (1H, dd, J=13.4, 4.6 Hz, H-9a), 2.93 (1H, dd, J=13.4, 11.4 Hz, H-9b), 2.78 (4H, m, H-12+H-15), 2.10 (2H, m, H-13+H-14), 1.77 (3H, s, H-1′), 1.60 (3H, s, H-2′), 1.49 (3H, s,

H-14′), 1.37 (18H, m, H-5′+H-6′+H-7′+H-8′+H-9′+H-10′+H-11′+H-12′+H-13′), 1.01 (s, 3H, H-2′). ^{13}C NMR (C_6D_6) δ: 196.9 (s, C-10), 171.5 (s, C-5), 164.3 (s, C-1′), 153.5 (s, C-15a), 150.2 (s, C-16b), 149.5 (s, C-11a), 148.9 (s, C-10a), 139.4 (s, C-16a), 133.8 (d, C-3), 132.6 (d, C-2), 132.4 (s, C-4a), 131.2 (d, C-4), 128.5 (d, C-1), 84.8 (s, C-7), 72.8 (d, C-8), 42.5 (t, C-4′), 34.0 (t), 32.0×2 (t), 31.9 (t), 31.3 (t), 29.9 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.3×2 (t), 24.9 (t), 23.8 (q, C-1′), 22.5 (t), 22.2 (t), 18.6 (q, C-2′), 14.1 (q, C-14′). MS *m/z* (rel. int): 549 (M^++1, 41), 349 (M^++1-OCO$(CH_2)_{10}CH_3$, 23), 253 (349-CO$(CH_2)_2C(Me)_2$, 7), 69 (100). HRMS: 549.3341 (calcd for $C_{33}H_{45}N_2O_5$ (M^++1) 549.3328).

3.3.7. 7-(1-Hydroxy-1-methylethyl)-6, 7-dihydro[2] benzoxonino[6,7-*b*]pyrazine-5,9-dione (31). 37 mg (0.13 mmol) of **20** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 20 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (1:4) as eluent, to obtain 28 mg (70%) of **31**. ^{1}H NMR ($CDCl_3$) δ: 8.74 (1H, d, J=2.4 Hz, H-2), 8.50 (1H, d, J=2.4 Hz, H-3), 8.19 (1H, bs, H-13), 7.92 (1H, d, J=7.8 Hz, H-10), 7.72 (1H, m, H-12), 7.56 (1H, m, H-11), 5.53 (1H, bs, H-7), 2.86 (1H, bs, H-6a), 1.87 (1H, bs, H-6b), 1.15 (3H, s, H-1′), 1.13 (3H, s, H-2′). MS *m/z* (rel. int): 312 (M^+, 1), 297 (M^+−Me, 5), 254 (M^+−Me–CO_2, 54), 183 (254-CHCOH$(CH_3)_2$, 100). HRMS: 297.0863 (calcd for $C_{16}H_{13}N_2O_4$ (M^+−Me) 297.0875).

3.3.8. 8,8-Dimethyl-7,8-dihydro-6*H*-[2]benzoxecino [7,8-*b*]pyrazine-5,10-dione (32). 58 mg (0.21 mmol) of **21** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 27 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (3:2) as eluent, to obtain 38 mg (61%) of **32**. ^{1}H NMR ($CDCl_3$) δ: 8.70 (1H, m, H-2), 8.49 (1H, m, H-3), 8.04 (1H, m, H-11), 7.65 (1H, m, H-14), 7.51 (2H, m, H-12+H-13), 3.65 (1H, ddd, J=14.5, 5.8, 4.1 Hz, H-6a), 2.67 (1H, ddd, J=16.5, 14.5, 3.9 Hz, H-6b), 2.18 (1H, ddd, J=18.7, 4.1, 3.9 Hz, H-7b), 1.99 (1H, ddd, J=18.7, 16.5, 5.8 Hz, H-7a), 1.63 (3H, s, H-1′), 1.39 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 201.9 (s, C-5), 164.9 (s, C-10), 153.4 (s, C-14b), 151.6 (s, C-4a), 144.4 (d, C-2), 140.5 (d, C-3), 137.9 (s, C-14a), 132.7×2 (d, C-12, 13), 130.8 (d, C-11), 129.0 (d, C-14), 128.2 (s, C-10a), 84.4 (s, C-8), 38.3 (t, C-7), 36.3 (t, C-6), 26.9 (q, C-1′), 23.7 (q, C-2′). MS *m/z* (rel. int): 296 (M^+, 17), 268 (M^+−CO, 9), 199 (M^+−CO–Me–NCH=CHN, 100). HRMS: 296.1164 (calcd for $C_{17}H_{16}N_2O_3$ (M^+) 296.1161).

3.3.9. 7-Hydroxy-8,8-dimethyl-7,8-dihydro-6*H*-[2] benzoxecino[7,8-*b*]pyrazine-5, 10-dione (33). 21 mg (0.08 mmol) of **22** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 10 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 16 mg (68%) of **33** and 5 mg (21%) of **36**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.77 (1H, d, J=2.3 Hz, H-2), 8.51 (1H, d, J=2.3 Hz, H-3), 8.05 (1H, d, J=7.8 Hz, H-11), 7.67 (1H, m, H-14), 7.52 (2H, m, H-12+H-13), 4.12 (1H, m, H-7), 3.90 (1H, dd, J=13.9, 4.4 Hz, H-6a), 2.79 (1H, dd, J=13.9, 10.3 Hz, H-6b), 2.26 (1H, bd, J=5.8 Hz, OH), 1.62 (3H, s, H-1′), 1.51 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 196.7 (s, C-10), 175.4 (s, C-5), 150.6 (s, C-14a), 150.6 (s, C-4a), 144.7 (d, C-3), 140.9 (d, C-2), 134.6 (s, C-14b), 132.9×2 (d, C-12+C-13), 131.0 (d, C-11), 129.3 (s, C-10a), 129.1 (d, C-14), 86.6 (s, C-8), 74.1 (d, C-7), 44.6 (t, C-6), 24.4 (q, C-1′), 24.1 (q, C-2′). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.77 (d, J=2.3 Hz, 1H, H-2), 8.51 (m, 1H, H-3), 8.03 (m, 1H, H-11), 7.67 (m, 1H, H-14), 7.52 (m, 2H, H-12, 13), 4.50 (m, 1H, H-7), 4.04 (m, 1H, H-6a), 2.89 (dd, J=12.9, 4.6 Hz, 1H, H-6b), 2.36 (bd, J=4.1 Hz, 1H, OH), 1.70 (s, 3H, H-1′), 1.16 (s, 3H, H-2′). MS *m/z* (rel. int): 312 (M^+, 1), 297 (M^+−Me, 2), 199 (M^+−$COCH_2CH(OH)C(CH_3)_2$, 65), 183 (199-16, 100). HRMS: 312.1128 (calcd for $C_{17}H_{16}N_2O_4$ (M^+) 312.1110).

3.3.10. 5-(2, 3-Dihydroxy-3-methylbutyl)-5-hydroxy benzo[*f*]quinoxalin-6(5*H*)-one (36). ^{1}H NMR ($CDCl_3$) δ: 8.57 (1H, d, J=2.3 Hz, H-3), 8.52 (1H, d, J=2.3 Hz, H-2), 8.46 (1H, d, J=7.5 Hz, H-10), 8.00 (1H, m, H-7), 7.60 (2H, m, H-8+H-9), 4.44 (1H, d, J=5.5 Hz, H-2′), 3.35 (1H, dd, J=14.2, 5.5 Hz, H-1a′), 2.94 (1H, d, J=14.2 Hz, H-1b′), 1.51 (6H, s, H-1″+H-4′). ^{13}C NMR ($CDCl_3$) δ: 199.8 (s, C-6), 152.7 (s, C-10b), 151.0 (s, C-4a), 144.0 (d, C-3), 143.5 (d, C-2), 132.1 (s, C-10a), 131.1 (d, C-8 or 9), 130.9 (d, C-8 or 9), 129.0 (s, C-6a), 127.5 (d, C-10), 125.6 (d, C-7), 84.0 (d, C-2′), 82.2 (s, C-5), 69.9 (s, C-3′), 38.8 (t, C-1′), 27.3 (q, C-4′), 22.7 (q, C-1″). MS *m/z* (rel. int): 314 (M^+, 15), 299 (M^+−Me, 21), 221 (M^+−93, 100). HRMS: 314.1285 (calcd for $C_{17}H_{18}N_2O_4$ (M^+) 314.1267).

3.3.11. 7-Bromo-8,8-dimethyl-7,8-dihydro-6*H*-[2] benzoxecino[7,8-*b*]pyrazine-5,10-dione (34). 57 mg (0.17 mmol) of **23** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 20 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 23 mg (37%) of **34**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.74 (1H, m, H-2), 8.55 (1H, m, H-3), 8.10 (1H, d, J=7.9 Hz, H-11), 7.73 (1H, m, H-14), 7.51 (2H, m, H-12+H-13), 4.30 (1H, dd, J=12.5, 4.0 Hz, H-7), 4.08 (1H, dd, J=14.3, 4.0 Hz, H-6b), 3.13 (1H, dd, J=14.3, 12.5 Hz, H-6b), 1.76 (3H, s, H-1′), 1.66 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 196.8 (s, C-5), 163.9 (s, C-10), 153.5 (s, C-14b), 151.1 (s, C-4a), 144.8 (d, C-2), 141.0 (d, C-3), 137.7 (s, C-14a), 133.1 (d, C-12), 132.9 (d, C-13), 131.4 (d, C-11), 129.1 (d, C-14), 127.6 (s, C-10a), 87.3 (d, C-8), 52.3 (d, C-7), 47.1 (t, C-6), 25.3 (q, C-1′), 18.3 (q, C-2′). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.79 (m, 1H, H-2), 8.56 (m, 1H, H-3), 7.97 (d, J=7.8 Hz, 1H, H-11), 7.73 (m, 1H, H-14), 7.51 (m, 2H, H-12+H-13), 5.25 (dd, J=12.6, 4.6 Hz, 1H, H-7), 4.47 (dd, J=12.6, 12.1 Hz, 1H, H-6a), 3.06 (dd, J=12.1, 4.6 Hz, 1H, H-6b), 1.87 (s, 3H, H-1′), 1.13 (s, 3H, H-1′). ^{13}C NMR ($CDCl_3$) δ: 197.7 (s, C-5), 163.8 (s, C-10), 153.5 (s, C-14b), 151.1 (s, C-4a), 145.5 (d, C-2), 140.7 (d, C-3), 137.7 (s, C-14a), 133.0 (d, C-12), 132.9 (d, C-13), 131.1 (d, C-11), 129.5 (d, C-14), 119.9 (s, C-10a), 86.4 (d, C-8), 51.4 (d, C-7), 44.5 (t, C-6), 26.8 (q, C-1′), 21.6 (q, C-2′). MS *m/z* (rel. int): 376 (M^++2, 0.4), 374 (M^+, 0.4), 295 (M^+−Br, 7), 199 (M^+−CO(CH_2)-CH(Br)C$(Me)_2$, 100). HRMS: 374.0350 (calcd for $C_{17}H_{15}N_2O_3Br^{79}$ (M^+) 374.0266).

3.3.12. 8-Phenyl-7,8-dihydro-6*H*-[2]benzoxecino[7,8-*b*] pyrazine-5,10-dione (35). 19 mg (0.06 mmol) of **24** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 10 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 11 mg (53%) of **35**. ^{1}H NMR ($CDCl_3$) δ: 8.82 (1H, d, $J=2.5$ Hz, H-2), 8.54 (1H, d, $J=2.5$ Hz, H-3), 8.20 (1H, d, $J=7.8$ Hz, H-11), 7.74 (2H, m, H-12+H-13), 7.56 (1H, m, H-14), 7.25 (3H, m, H-3′+H-4′+H-5′), 7.03 (2H, m, H-2′+H-6′), 6.15 (1H, dd, $J=11.3$, 2.8 Hz, H-8), 3.67 (1H, ddd, $J=15.0$, 5.0, 3.6 Hz, H-6a), 2.72 (1H, ddd, $J=15.0$, 12.4, 3.5 Hz, H-6b), 2.50 (1H, ddd, $J=12.3$, 6.1, 3.5 Hz, H-7a), 2.22 (1H, m, H-7b). ^{13}C NMR ($CDCl_3$) δ: 202.2 (s, C-5), 165.3 (s, C-10), 153.1 (s, C-14b), 151.1 (s, C-4a), 144.8 (d, C-2), 140.4 (d, C-3), 138.7 (s, C-15), 137.8 (s, C-14a), 133.6 (d, C-13), 133.4 (d, C-12), 132.2 (d, C-11), 129.4 (d, C-14), 128.5×2 (d, C-3′+C-5′), 128.3 (d, C-18), 126.3 (s, C-10a), 125.8×2 (s, C-2′+C-6′), 77.2 (d, C-8), 39.2 (t, C-6), 32.9 (t, C-7). MS *m/z* (rel. int): 344 (M^+, 93), 316 (M^+-CO, 43), 238 (M^+-CO–Ph, 18), 183 ($M^+-OCH(Ph)(CH_2)_2CO$, 95), 104 (PhCO, 100). HRMS: 344.1158 (calcd for $C_{21}H_{16}N_2O_3$ (M^+) 344.1161).

Acknowledgements

This work has been funded by Spanish MCYT (SAF2003-04200-C02-02) and by ICIC (Instituto Canario de Investigaciones del Cáncer). E.P.S. thanks the ICIC for a postdoctoral fellowship. The authors thank Dr. J. Platas for valuable discussions regarding the structures of lower-energy conformers.

References and notes

1. Stratmann, K.; Burgoyne, D.; Moore, R.; Patterson, G. *J. Org. Chem.* **1994**, *59*, 7219–7226. (b) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535–5538. (c) Mulzer, J.; Öhler, E. *Chem. Rev.* **2003**, *103*, 3753–3786. (d) Labro, M. In *Macrolide Antibiotics*; Schoenfeld, W., Kirst, H., Eds.; Birkhaeuser: Basel, Switzerland, 2002; pp 37–52. (e) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93.
2. D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–60.
3. Nicolaou, K.; Sasmal, P.; Rassias, G.; Reddy, M.; Altmann, K.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3515–3520.
4. Kudoh, S.; Azuma, A.; Tamaoki, J.; Nakata, K.; Takizawa, H.; Goto, H. In *Macrolide Antibiotics*, 2nd ed.; Omura, S., Ed.; Academic: San Diego, CA, 2002; pp 533–569.
5. Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306.
6. Handa, M.; Ui, H.; Yamamoto, D.; Monma, S.; Iwai, Y.; Sunazuka, T.; Omura, S. *Heterocycles* **2003**, *59*, 497–500.
7. Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075–1080. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2000**, 913–919.
8. Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.; McPhail, A. *J. Nat. Prod.* **2003**, *66*, 1527–1530.
9. Keller, T.; Neeland, E.; Retting, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858–7868. (b) Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255. (c) Andrew, D.; Kenneth, P. *Chem. Rev.* **1997**, *97*, 1251–1268.
10. Makgatho, M.; Anderson, R.; O'Sullivan, J.; Egan, T.; Freese, J.; Cornelius, N.; Van Rensburg, C. *Drug Dev. Res.* **2000**, *50*, 195–202. (b) Andrade-Nieto, V.; Goulart, M.; da Silva, J. F.; da Silva, M. J.; Pinto, M.; Pinto, A.; Zalis, M.; Carvalho, L.; Krettli, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1145–1149.
11. Neves-Pinto, C.; Malta, V.; Pinto, M.; Santos, R.; Castro, S.; Pinto, A. *J. Med. Chem.* **2002**, *45*, 740–743.
12. Cartwright, D.; Chilton, W.; Benson, D. *Appl. Microbiol. Biotechnol.* **1995**, *43*, 211–216. (b) Ligon, J.; Dwight, S.; Hammer, P.; Torkewitz, N.; Hofmann, D.; Kempf, H.; Pée, K. *Pest. Manag. Sci.* **2000**, *56*, 688–695.
13. Muller, M.; Sorrell, T. *Prostaglandins Other Lipid Mediat.* **1995**, *50*, 301–311.
14. Rewcastle, G.; Denny, W.; Baguley, B. *J. Med. Chem.* **1987**, *30*, 843–851. (b) Funayama, S.; Eda, S.; Komiyama, K.; Omura, S. *Tetrahedron Lett.* **1989**, *30*, 3151–3154. (c) Wang, S.; Miller, W.; Milton, J.; Vicker, N.; Stewart, A.; Charlton, P.; Mistry, P.; Hardick, D.; Denny, W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 415–418. (d) Vicker, N.; Burgess, L.; Chuckowree, I.; Dodd, R.; Folkes, A.; Hardick, D.; Hancox, T.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S.; Charlton, P.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A.; Denny, W. *J. Med. Chem.* **2002**, *45*, 721–739. (e) Gamage, S.; Spicer, J.; Rewcastle, G.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P.; Denny, W. *J. Med. Chem.* **2002**, *45*, 740–743.
15. (a) Ravelo, A.; Estévez-Braun, A.; Pérez-Sacau, E. In Atta-Ur-Rahman, Ed.; Studies in Natural Products Chemistry; Elsevier Science: Amsterdam, 2003; Vol. 29 (part J), pp 719–760; and references cited therein. (b) Ravelo, A.; Estévez-Braun, A.; Chávez, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Top. Med. Chem.* **2004**, *4*, 241–265.
16. Pérez-Sacau, E.; Estévez-Braun, A.; Ravelo, A.; Ferro, E.; Tokuda, H.; Mukainaka, T.; Nishino, H. *Bioorg. Med. Chem.* **2003**, *11*, 483–488.
17. Nair, V.; Treesa, P. *Tetrahedron Lett.* **2001**, *42*, 4549–4551.
18. Kobayashi, K.; Mori, M.; Uneda, T.; Morikawa, O.; Konishi, K. *Chem. Lett.* **1996**, 451–452. (b) Sun, J.; Geiser, A.; Frydman, B. *Tetrahedron Lett.* **1998**, *39*, 8221–8224.
19. Woo, G.; Snyder, J.; Wan, Z. *Prog. Heterocyclic Chem.* **2002**, *14*, 279–309.
20. Burton, S.; Kaye, P.; Wellington, K. *Synth. Commun.* **2000**, *30*, 511–522. (b) Huh, T. *Bull. Korean Chem. Soc.* **2000**, *21*, 369–370. (c) Huang, W.; Chen, C.; Lee, S. *Heterocycles* **2003**, *60*, 1573–1588.
21. Nazaré, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1125–1128. (b) Ohara, T.; Kume, M.; Narukawa, Y.; Motokawa, K.; Uotani, K.; Nakai, H. *J. Org. Chem.* **2002**, *67*, 9146–9152. (c) Nicolaou, K.; Kim, D.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704. (d) Pilli, R.; Victor, M. *Tetrahedron Lett.* **2002**, *43*, 2815–2818. (e) Williams, D.; Patnaik, S.; Plummer, S. *Org. Lett.* **2003**, *5*, 5035–5038. (f) Colby, E.; O'Brien, K.; Jamison, T. *J. Am. Chem. Soc.* **2004**, *126*, 998–999. (g) Bulusu, M.; Waldstätten, P.; Tricotett, T.; Schulz, G. *Tetrahedron Lett.* **2004**, *45*, 2527–2530. (h) Schmidt, D.; Kwon, O.; Schreiber, S. *J. Comb. Chem.* **2004**, *6*, 286–292.
22. Garcia-Rubio, S.; Meinwald, J. *J. Org. Chem.* **2001**, *66*,

1082–1096. (b) Lazarova, T.; Binet, S.; Vo, N.; Chen, J. *Org. Lett.* **2003**, *5*, 443–445.
23. Borowitz, I.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. *J. Org. Chem.* **1966**, *31*, 3032–3037.
24. Goulart, M.; Cioletti, A.; de Souza, J.; de Simone, C.; Castellano, E.; Emery, F.; de Moura, K.; Pinto, M.; Pinto, A. *Tetrahedron Lett.* **2003**, *44*, 3581–3585. (b) Baskaran, S.; Islam, I.; Raghavan, M.; Chandrasekaran, S. *Chem. Lett*. **1987**, *6*, 1175–1178. (c) Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, *50*, 4980–4982. (d) Grant, P.; Hanton, L.; Tsai, S. *Aust. J. Chem.* **1985**, *38*, 1461–1470. (e) Moricz, A.; Gassman, E.; Bienz, S.; Hesse, M. *Helv. Chim. Acta* **1995**, *78*, 663–669.
25. Hunt, K.; Gireco, P. *Org. Lett.* **2000**, *2*, 1717–1719.
26. PC-Model version 7.0 was used to carry out the GMMX calculations.
27. Wiberg, K. *J. Org. Chem.* **2003**, *68*, 9322–9329.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 447–456

α-Phenylselanyl imines: preparation of β-phenylselanyl amines and original synthesis of allylaziridines

Catherine Miniejew, Francis Outurquin* and Xavier Pannecoucke*

Université et INSA de Rouen-IRCOF, UMR 6014 CNRS, 1 rue Tesnière, 76821 Mont Saint Aignan, France

Received 9 July 2004; revised 15 October 2004; accepted 21 October 2004

Available online 5 November 2004

Abstract—Resorting to suitable methods, a wide variety of α-phenylselanyl imines **2–5** were prepared from α-phenylselanyl aldehydes and α-phenylselanyl ketones **1**. These compounds were reduced to afford β-phenylselanyl amines **6–9**. Our experimental conditions have limited the well known deselenenylation side-reaction occurring with most hydrides. On the other hand, the reaction of α-phenylselanyl imines **2** with organometallics led to the expected addition products only in the case of allylated derivatives. Depending on the temperature, either β-phenylselanyl amines **11** or unexpected allylaziridines **12** were recovered.

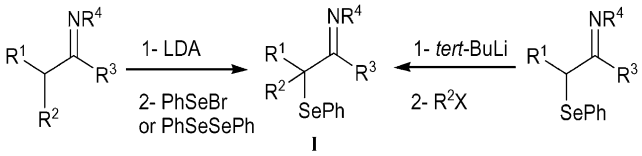
1. Introduction

As illustrated by the large number of organoselenium intermediates involved in natural product synthesis, the selenium methodology offers useful synthetic tools to organic chemists.[1] Our laboratory is especially interested in the applications of α-phenylselanyl carbonyl compounds as valuable bifunctional synthons. During the course of our work, a simple multigram-scale preparation of α-phenylselanyl aldehydes and α-phenylselanyl ketones has been developed.[2a] Obtention and applications of β-phenylselanyl silyl enol ethers have next been reported.[3] α-Phenylselanyl imines are other pivotal targets which give access to interesting nitrogen-containing compounds. However, they seem to have been little studied.[4]

Preliminary studies on the various routes to access α-phenylselanyl imines **I** have been performed, based on the work on α-sulfanyl imines.[5] By analogy with the sulfur series, three methods were assayed to prepare selenenylated imines **I**. Two of them were based on a metallation process (Scheme 1), selenenylation of imines or alkylation of α-phenylselanyl imines. Therefore, using LDA as base, followed by addition of PhSeBr or PhSeSePh, imines deriving from aldehydes or ketones could be transformed into α-phenylselanyl imines **I** but in poor yields varying from 20 (R^4=Bn) to 60% (R^4=*tert*-Bu). The second metallation procedure, based on the alkylation of α-phephenylselanyl imines, revealed to be even more difficult. Indeed, using different bases (best one: *tert*-BuLi), we could not avoid the formation of dialkylated products or diselenenylated imines together with the desired imines **I**. As the selenenylated imines **I** are difficult to purify, these two methods yielded the desired products in rather low yields were abandoned. We then focused our efforts on a third pathway which consists in the synthesis of imines **I** from α-phenylselanyl carbonyl compounds. In this paper, we reported a study on the preparation of selenenylated imines **I** from α-phenylselanyl aldehydes or ketones and their direct transformations via reduction and organometallic additions (Scheme 2), which comes to complete our preliminary observations.[4a]

2. Synthesis of α-phenylselanyl imines

The reactivity of α-phenylselanyl carbonyl compounds is highly variable and depends particularly on the steric hindrance at the α carbon. Thus, in each case, the best and simplest experimental conditions were selected to convert α-phenylselanyl aldehydes or ketones into imines. The condensation of α-phenylselanyl ethanal **1a**[2a] with benzylamine was achieved in ether at −30 °C in the presence of potassium hydroxide. Starting from aldehydes **1b–f**,[2a] better

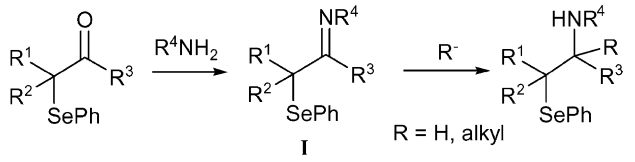


I

Scheme 1.

Keywords: Selenium; Aziridine; Imine.
* Corresponding authors. Tel.: +33 2 3552 2402; fax: +33 2 3553 2959; e-mail addresses: francis.outurquin@univ-rouen.fr; xavier.pannecoucke@insa-rouen.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.065

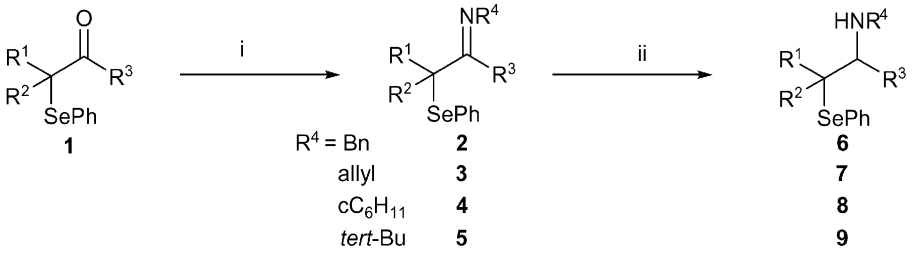


Scheme 2.

results were obtained in dichloromethane at room temperature in the presence of magnesium sulfate. The more hindered aldehydes **1g–i**,[2b] bearing a tertiary α carbon, could also be converted into α-phenylselanyl imines **2g–i** either at reflux of toluene with a Dean–Stark apparatus or in the presence of titanium tetrachloride and 4 equiv of amine.[4] These latter conditions were the sole allowing access to imines **2j–o** from α-phenylselanyl ketones **1j–o**.[2a] The use of benzylamine allows further easy debenzylation to access to primary amines. Nevertheless, our developed methodology can also be transposed to other amines as shown with α-phenylselanyl imines **3c**, **4c** and **5c** resulting from the condensation of α-phenylselanyl butanal **1c** with allylamine, cyclohexylamine or *tert*-butylamine. The stability of the imines increases with the hindrance of the amine or the carbonyl substituents. Thus, α-phenylselanyl imines can be kept at 0 °C under inert atmosphere (a few days for **2g–i**, one day for enolisable imines, while compound **2a** should be prepared just before use), but no purification (distillation, chromatography) could be achieved due to decomposition. However, the crude imines are pure enough for further transformations. The α-phenylselanyl imines **2h–i** are solids which, after rinsing with hexane, gave satisfactory elemental analysis. Only one set of signal in ^{1}H NMR was observed for imines **2a–i** issued from aldehydes. According to literature data,[6] we assumed that the α-phenylselanyl aldimines adopt the *anti* configuration. No tautomery was observed. Nevertheless, the enaminic form of the *N*-*tert*-butyl imine **5c** could be obtained after a prolonged heating in dichloromethane.

3. Reduction of α-phenylselanyl imines

The most important problem known to occur during the reduction of imines **2–5**, is the substrate's deselenenylation leading to the formation of deselenenylated amines. This side-reaction results from a selenophilic attack of the hydride as observed during the reduction of α-phenylselanyl ketones.[7] Indeed, treatment of α-phenylselanyl imines with $LiAlH_4$ led to a complete deselenenylation, even at low temperatures. Among less reactive reducing agents ($NaBH_4$, $Zn(BH_4)_2$, BH_3–THF, BH_3–SMe_2), only $NaBH_4$ afforded the desired β-phenylselanyl amines, but together with the deselenenylated amines (15–20%) (Scheme 3, Table 1).

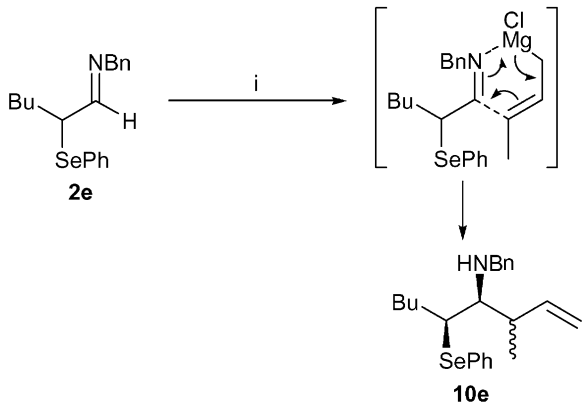


Scheme 3. (i) Method A: R^4NH_2 (1 equiv), KOH, Et_2O, −30 °C, 2 h; Method B: R^4NH_2 (1 equiv), $MgSO_4$, CH_2Cl_2, 20 °C, 4 h; Method C: R^4NH_2 (1 equiv), toluene, reflux, 12 h; Method D, R^4NH_2 (4 equiv), $TiCl_4$, Et_2O, 20 °C, 4 h. (ii) $NaBH_3CN$ (0.5 equiv), AcOH, EtOH, −78 °C, 1 h.

Table 1. Synthesis of β-phenylselanyl amines **6–9** via imines **2–5** (Scheme 3)

Substrates	R^1	R^2	R^3	R^4	Method for imine preparation	Products	Yield[a] (%) (*syn*/*anti*)
1a	H	H	H	Bn	A	**6a**	54
1b	Me	H	H	Bn	B	**6b**	41
1c	Et	H	H	Bn	B	**6c**	72
				Allyl	B	**7c**	64
				cC_6H_{11}	B	**8c**	57
				tert-Bu	B[b]	**9c**	56
1d	*i*Pr	H	H	Bn	B	**6d**	69
1e	Bu	H	H	Bn	B	**6e**	65
1f	Bn	H	H	Bn	B	**6f**	67
1g	Me	Me	H	Bn	C or D	**6g**	64
1h	Ph	Me	H	Bn	C or D	**6h**	59
1i	$-(CH_2)_5-$		H	Bn	C[c] or D	**6i**	51
1j	H	H	Me	Bn	D	**6j**	50
1k	H	H	*tert*-Bu	Bn	D	**6k**	71
1l	H	H	Ph	Bn	D	**6l**	68
1m	Me	H	Et	Bn	D	**6m**	57 (80/20)
1n	Me	H	Ph	Bn	D	**6n**	53 (100/0)
1o	H	$-(CH_2)_4-$		Bn	D	**6o**	57 (80/20)

[a] Estimated from **1**.
[b] 12 h at reflux of CH_2Cl_2.
[c] 48 h at reflux of toluene.



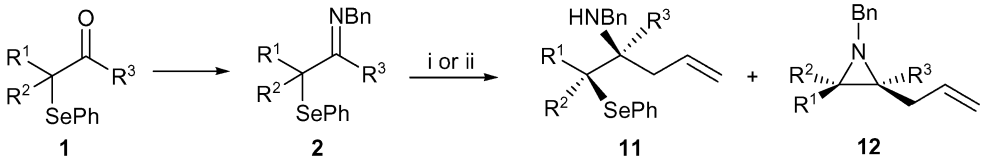
Scheme 4. (i) CrotylMgCl (1.1 equiv), THF, −40→0 °C, 2 h.

The best results were obtained with $NaBH_3CN$ at −78 °C in the presence of acetic acid. These experimental conditions avoided the formation of the deselenenylated amines and afforded the β-phenylselanyl amines **6**–**9** in 41–72% yield. It should be underlined that ketone **1m** led to the β-phenylselanyl amine **6m** in 60% de while substrate **1n** afforded the sole *syn* diastereomer **6n**. The stereochemistry of products **6m**,**n** was assigned after analysis of the corresponding aziridines obtained after an internal S_N2 displacement of the selanyl group.[4a] Such *syn* selectivity has already been observed during the reduction of α-phenylselanyl ketones.[8] It can be rationalized by a Felkin–Ahn-type model with a stereoelectronic controle by the selanyl group.

4. Organometallic additions to α-phenylselanyl imines

In order to access to various other β-phenylselanyl amines, we next studied organometallic additions on imines **2**. After numerous assays with lithium derivatives (MeLi, BuLi), zinc derivatives (Et_2Zn, BuZnCl), a copper derivative (MeCu) and arylated or alkylated grignard reagents (BnMgBr, VinylMgBr, PropylMgBr), only allylated magnesium derivatives led to the expected addition products. The use of crotyl magnesium showed that, in these cases, the reaction proceed through a six-membered cyclic transition state (Scheme 4). The addition of allylmagnesium chloride to imines **2** was first achieved in mild experimental conditions to avoid the substrate's deselenenylation (Scheme 5, Table 2).

At −40 °C, the reaction proceeded cleanly and led to β-phenylselanyl amines **11** in 47–78% yield. However with **2h**, the desired amine **11h** was obtained as a mixture with the unexpected allylaziridine **12h**. Starting from **1m**, the aza-heterocycle **12m** was even the sole product of the reaction, along with diphenyldiselenide, coming from the hydrolysis of PhSeMgBr. Such in situ cyclization has already been observed during reduction or organometallic additions to α-chloro imines.[9] After considering different reaction parameters, we realized that we could favor either one or the other product by controlling the temperature. Indeed, when the allylmagnesium additions were carried out at reflux of THF, the allylaziridines **12** became the sole or the major products of the reaction. Probably because of the substrate's hindrance, no addition product was observed with the pinacolone derivative **1k**. No allylaziridine has been obtained from **1j** even at higher temperature.

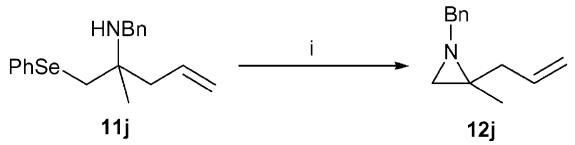


Scheme 5. (i) allylMgCl (1.1 equiv), THF, −40→0 °C, 2 h. (ii) allylMgCl (1.1 equiv), THF, reflux, 2 h.

Table 2. Synthesis of homoallylic β-phenylselanyl amines **11** and allylaziridines **12** via imines **2** (Scheme 5)

Substrates	R^1	R^2	R^3	*T* (°C)	**11** Yield[a] (%) (*syn*/*anti*)	**12** Yield[a] (%) (*cis*/*trans*)
1d	*i*Pr	H	H	−40→0	78 (55/45)	—
				65	—	73 (55/45)
1e	Bu	H	H	−40→0	69 (100/0)	—
				65	—	53 (100/0)
1g	Me	Me	H	−40→0	74	—
				65	11	57
1h	Me	Ph	H	−40→0	47 (100/0)	20 (0/100)
				65	18 (100/0)	41 (0/100)
1j	H	H	Me	−40→0	58	—
				65	52	—
1k	H	H	*t*Bu	−40→0	—[b]	
				65	—[b]	
1l	H	H	Ph	−40→0	65	—
				65	—	61
1m	Me	H	Et	−40→0	—	61 (100/0)
				65	—	57 (100/0)
1n	Me	H	Ph	−40→0	64 (100/0)	—
				65	—	59 (0/100)

[a] Estimated from **1**.
[b] Starting material recovered.



Scheme 6. (i) NBS (1.1 equiv), CH_3CN, 20 °C, 5 min.

Nevertheless, the allylaziridine **12j** could be synthesized after activation of the selanyl group of **11j** with *N*-bromosuccinimide (Scheme 6).[10] When the reaction product exhibits two stereogenic centers, only one diastereomer was obtained either for the β-phenylselanyl amines **11** or for the allylaziridines **12** except for compounds **11d** and **12d** derived from isovaleraldehyde. NOE experiments on allylaziridines **12h**, **12n** and **12m** allowed to assign the *cis* stereochemistry to allylaziridines **12**. We then deduced a *syn* relationship between the amino and the selanyl group of the corresponding β-phenylselanyl amines **11**.

In summary, we report convenient methods to convert α-phenylselanyl aldehydes and ketones into the corresponding α-phenylselanyl imines **2–5**. The reduction of these latter with $NaBH_3CN$ led to β-phenylselanyl amines **6–9** without deselenenylation of the substrates. On the other hand, depending on the temperature, addition of allyl magnesium chloride provided either β-phenylselanyl amines **11** or allylaziridines **12**. To our knowledge, this constitutes the first synthesis of allylaziridines.

5. Experimental

THF was distilled over sodium/benzophenone and dichloromethane over P_2O_5. Ether was dried over sodium.

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Brucker DPX 300 instrument and carried out in $CDCl_3$. ^{77}Se NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 76.29 MHz for ^{77}Se, using as pulsed length 19 μs (90° pulse = 19 μs) and an optimized relaxation delay of 2 s. An average of 1500 scans for ^{77}Se NMR was necessary to have reliable information. Chemical shifts (δ) are expressed in ppm relative to TMS for ^1H and ^{13}C nuclei and to Me_2Se for ^{77}Se nuclei; coupling constants (J) are given in Hertz; coupling multiplicities are reported using conventional abbreviations. Elemental analysis were obtained on a Carlo-Erba 1106 analysor and Mass Spectra on a HP5890 (electronic impact 70 eV) using GC–MS coupling with a Jeol AX 500.

5.1. Preparation of α-phenylselanyl imines 2–5

Procedure A: A solution of α-phenylselanyl ethanal **1a** (995 mg, 5 mmol) in ether (5 ml) was added dropwise at −30 °C to the amine (5.5 mmol) in the same solvent (30 ml). The mixture was stirred for 2 h at −30 °C before adding KOH (1 g) and then stirred for 15 h at −5 °C. The solution was filtered and concentrated. This α-phenylselanyl aldimine should be used immediately after its preparation.

Procedure B: Magnesium sulfate (3 g) was added to a solution of α-phenylselanyl aldehydes **1b–f** (5 mmol) in dichloromethane (50 ml). The mixture was stirred for 10 min at −5 °C and the amine (5 mmol) was added dropwise. The whole was then stirred for 3 h at room temperature. The magnesium sulfate was filtered, rinsed with dichloromethane and the organic phase was concentrated. These α-phenylselanyl aldimines could be stored one day at 0 °C under argon.

Procedure C: A solution of α-phenylselanyl aldehydes **1g–i** (5 mmol) and amine (5.25 mmol) in toluene (50 ml) was heated for 12 h under reflux with elimination of water (Dean–Stark). For **2i**, the heating should be continued for 48 h. The solvent was eliminated under vacuo. The imines **2h** and **2i** crystallized slowly and were rinsed with hexane. These α-phenylselanyl aldimines could be stored a few days at 0 °C under argon.

Procedure D: Amine (20 mmol) was added to the α-phenylselanyl carbonyl compounds **1g–n** (5 mmol) in ether (50 ml) at 0 °C, under argon. A solution of titanium tetrachloride (708 mg, 3.75 mmol) in heptane (2 ml) was then slowly introduced. The mixture was stirred for 30 min at 0 °C and then for 3 h at room temperature. The titanium salts were filtered and rinsed with ether.

All the α-phenylselanyl imines **2–5** were isolated but not purified because of decomposition. That is why for most of them we just reported the ^1H NMR spectra. For **2a–g** IR $\nu_{C=N} = 1640–1650\ cm^{-1}$.

5.1.1. Phenyl-*N*-(2-(phenylselanyl)ethylidene)methanamine 2a. ^1H NMR δ: 3.68 (d, 2H, J = 5.7 Hz, H-2), 4.54 (s, 2H, CH_2Ph), 7.05–7.35 (m, 8H, Ph), 7.50–7.55 (m, 2H, Ph), 7.78 (t, 1H, J = 5.7 Hz, H-1).

5.1.2. Phenyl-*N*-(2-(phenylselanyl)propylidene)methanamine 2b. ^1H NMR δ: 1.55 (d, 3H, J = 7.0 Hz, H-3), 3.71–4.20 (m, 1H, H-2), 4.44 (d, 1H, J = 14.0 Hz, CH_2Ph), 4.54 (d, 1H, J = 14.0 Hz, CH_2Ph), 7.0–7.10 (m, 2H, Ph), 7.15–7.35 (m, 6H, Ph), 7.45–7.60 (m, 2H, Ph), 7.71 (d, 1H, J = 6.1 Hz, H-1).

5.1.3. Phenyl-*N*-(2-(phenylselanyl)butylidene)methanamine 2c. ^1H NMR δ: 1.06 (t, 3H, J = 7.3 Hz, H-4), 1.63–2.10 (m, 2H, H-3), 3.84 (dt, 1H, J = 7.1, 7.1 Hz, H-2), 4.42 (d, 1H, J = 14.0 Hz, CH_2Ph), 4.55 (d, 1H, J = 14.0 Hz, CH_2Ph), 7.00–7.05 (m, 2H, Ph), 7.10–7.30 (m, 6H, Ph), 7.45–7.52 (m, 2H, Ph), 7.64 (d, 1H, J = 7.1 Hz, H-1).

5.1.4. Phenyl-*N*-(3-methyl-2-(phenylselanyl)butylidene) methanamine 2d.[4a] ^1H NMR δ: 1.11 (d, 3H, J = 6.7 Hz, H-4), 1.18 (d, 3H, J = 6.7 Hz, H-4), 1.96–2.39 (m, 1H, H-3), 3.82 (dd, 1H, J = 7.8, 8.2 Hz, H-2), 4.40 (d, 1H, J = 13.9 Hz, CH_2Ph), 4.57 (d, 1H, J = 13.9 Hz, CH_2Ph), 7.00–7.06 (m, 2H, Ph), 7.15–7.37 (m, 6H, Ph), 7.48–7.53 (m, 2H, Ph), 7.70 (d, 1H, J = 8.2 Hz, H-1).

5.1.5. Phenyl-*N*-(2-(phenylselanyl)hexylidene)methanamine 2e. ^1H NMR δ: 0.82 (d, 3H, J = 7.2 Hz, H-6), 1.15–1.48 (m, 4H, H-5, H-4), 1.67–1.82 (m, 2H, H-3), 3.80–3.85 (m, 1H, H-2), 4.34 (d, 1H, J = 14.1 Hz, CH_2Ph), 4.47 (d, 1H, J = 14.1 Hz, CH_2Ph), 6.93–7.42 (m, 10H, Ph), 7.54 (d, 1H, J = 7.7 Hz, H-1).

5.1.6. Phenyl-*N*-(3-phenyl-2-(phenylselanyl)propylidene) methanamine 2f. ^{1}H NMR δ: 3.22–3.30 (m, 2H, H-3), 4.24–4.35 (m, 1H, H-2), 4.50 (s, 2H, CH_2Ph), 6.95–7.05 (m, 2H, Ph), 7.20–7.40 (m, 11H, Ph), 7.55–7.60 (m, 2H, Ph), 7.75 (d, 1H, J=6.8 Hz, H-1).

5.1.7. Phenyl-*N*-(2-methyl-2-(phenylselanyl)propylidene) methanamine 2g.[4a] ^{1}H NMR δ: 1.47 (s, 6H, H-3), 4.46 (s, 2H, CH_2Ph), 7.04–7.38 (m, 10H, Ph), 7.69 (s, 1H, H-1).

5.1.8. Phenyl-*N*-(2-phenyl-2-(phenylselanyl)propylidene) methanamine 2h. Mp=35 °C. IR $\nu_{C=N}$=1630 cm^{-1}. ^{1}H NMR δ: 1.87 (s, 3H, H-3), 4.56 (d, 2H, J=14.1 Hz, CH_2Ph), 4.66 (d, 2H, J=14.1 Hz, CH_2Ph), 7.07–7.42 (m, 15H, Ph), 8.16 (s, 1H, H-1). ^{13}C NMR δ: 24.9 (C-3), 55.1 (C-2), 63.8 (*C*H_2Ph), 126.8, 127.1, 127.4, 127.8, 128.4, 128.6, 128.9, 129.1, 138.0, 139.1, 142.2 (Ph), 166.3 (C-1). Anal. Calcd for $C_{22}H_{21}$NSe: C, 69.83; H, 5.59; N, 3.70. Found: C, 69.71; H, 5.39; N, 3.61.

5.1.9. Phenyl-*N*-((1-(phenylselanyl)cyclohexyl)methylidene) methanamine 2i. Mp=43 °C. IR $\nu_{C=N}$= 1625 cm^{-1}. ^{1}H NMR δ: 1.25–2.05 (m, 10H, Cy), 4.53 (s, 2H, CH_2Ph), 7.10–7.50 (m, 10H, Ph), 7.66 (s, 1H, H-1). ^{13}C NMR δ: 23.4, 25.7, 29.4, 34.0 (Cy), 54.8 (*C*-Se), 63.9 (*C*H_2Ph), 126.4, 126.6, 127.7, 128.2, 128.3, 128.4, 128.5, 137.9 (Ph), 166.7 (C-1). Anal. Calcd for $C_{20}H_{23}$NSe: C, 67.40; H, 6.51; N, 3.93. Found: C, 67.34; H, 6.57; N, 3.85.

5.1.10. Phenyl-*N*-(1-(phenylselanyl)propan-2-ylidene)-methan amine 2j.[4a] ^{1}H NMR δ: 1.98 (s, 3H, H-3), 3.69 (s, 2H, H-1), 4.33 (s, 2H, CH_2Ph), 7.04–7.52 (m, 10H, Ph).

5.1.11. Phenyl-*N*-(3,3-dimethyl-1-(phenylselanyl)butan-2-ylidene)methanamine 2k.[4a] *Z*/*E*: 85/15 (non assigned). Major configuration: ^{1}H NMR δ: 1.16 (s, 9H, H-4), 3.64 (s, 2H, H-1), 4.52 (s, 2H, CH_2Ph), 7.14–7.47 (m, 10H, Ph). Minor configuration: ^{1}H NMR δ: 1.17 (s, 9H, H-4), 3.80 (s, 2H, H-1), 4.76 (s, 2H, CH_2Ph), 7.14–7.47 (m, 10H, Ph).

5.1.12. Phenyl-*N*-(1-phenyl-2-(phenylselanyl)ethylidene) methanamine 2l. *Z*/*E*: 60/40 (non assigned). Major configuration: ^{1}H NMR δ: 4.01 (s, 2H, H-2), 4.33 (s, 2H, CH_2Ph), 6.99–7.50 (m, 15H, Ph). Minor configuration: ^{1}H NMR δ: 4.03 (s, 2H, H-2), 4.48 (s, 2H, CH_2Ph), 7.08–7.78 (m, 15H, Ph).

5.1.13. Phenyl-*N*-(2-(phenylselanyl)pentan-3-ylidene) methanamine 2m.[4a] ^{1}H NMR δ: 1.04 (t, 3H, J=7.7 Hz, H-5), 1.56 (d, 3H, J=7.1 Hz, H-1), 2.36–2.50 (m, 2H, H-4), 4.01 (q, 1H, J=7.1 Hz, H-2), 4.44 (s, 2H, CH_2Ph), 7.06–7.47 (m, 10H, Ph).

5.1.14. Phenyl-*N*-(1-phenyl-2-(phenylselanyl)propylidene) methanamine 2n.[4a] ^{1}H NMR δ: 1.54 (d, 3H, J= 7.2 Hz, H-3), 4.22–4.38 (m, 1H, H-2), 4.29 (s, 2H, CH_2Ph), 7.11–7.45 (m, 15H, Ph).

5.1.15. Phenyl-*N*-(2-(phenylselanyl)cyclohexylidene) methanamine 2o.[4a]

^{1}H NMR δ: 1.40–2.40 (m, 8H, Cy), 4.07–4.20 (m, 1H, H-2), 4.43 (s, 2H, CH_2Ph), 7.04–7.24 (m, 8H, Ph) 7.45–7.52 (m, 2H, Ph). ^{13}C NMR δ: 23.2, 26.9, 34.7, 52.2 (C-2), 54.1 (*C*H_2Ph), 126.5, 127.0, 128.4, 129.1, 129.6, 129.8, 134.8.

5.1.16. *N*-(2-(Phenylselanyl)butylidene)allylamine 3c. ^{1}H NMR δ: 1.03 (t, 3H, J=7.3 Hz, H-4), 1.60–2.03 (m, 2H, H-3), 3.76 (dt, 1H, J=7.2, 7.2 Hz, H-2), 3.85–3.95 (m, 2H, CH_2CH=CH$_2$), 4.90–5.05 (m, 2H, CH$_2$CH=CH_2), 5.67–5.75 (m, 1H, CH$_2$C*H*=CH$_2$), 7.20–7.30 (m, 2H, Ph), 7.45–7.65 (m, 4H, Ph, H-1).

5.1.17. *N*-(2-(Phenylselanyl)butylidene)cyclohexylamine 4c. ^{1}H NMR δ: 1.04 (t, 3H, J=7.4 Hz, H-4), 1.05–1.87 (m, 12H, Cy, H-3), 2.79–2.87 (m, 1H, Cy), 3.78 (dt, 1H, J=7.4, 7.4 Hz, H-2), 7.15–7.60 (m, 6H, Ph, H-1).

5.1.18. *N*-(2-(Phenylselanyl)butylidene)*tert*-butylamine 5c. ^{1}H NMR δ: 1.04 (s, 9H, C(CH_3)$_3$), 1.08 (t, 3H, J= 7.4 Hz, H-4), 1.54–2.02 (m, 2H, H-3), 3.85 (dt, 1H, J=7.4, 7.4 Hz, H-2), 7.10–7.55 (m, 6H, Ph, H-1).

5.2. Reduction of α-phenylselanyl imines 2–5

To the α-phenylselanyl imines **2**–**5** (5 mmol) in ethanol (60 ml) at −78 °C, under argon, were added successivelly sodium cyanoborohydride (162 mg, 2.5 mmol) and acetic acid (300 mg, 5 mmol). The reaction mixture was stirred for 1 h at −78 °C and quenched with water (70 ml). After dichloromethane (100 ml) addition, the aqueous phase was separated and washed with dichloromethane (2×80 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/Et_2O: 90/10).

5.2.1. *N*-Benzyl-2-(phenylselanyl)ethan-1-amine 6a. Yield: 54%. ^{1}H NMR δ: 1.80 (sl, 1H, N*H*), 2.88–2.95 (m, 2H, H-2), 3.05–3.12 (m, 2H, H-1), 3.80 (s, 2H, CH_2Ph), 7.22–7.36 (m, 8H, Ph), 7.47–7.55 (m, 2H, Ph). ^{13}C NMR δ: 28.5 (C-2), 48.2 (C-1), 53.3 (*C*H_2Ph), 127.0, 127.7, 128.0, 128.4, 129.0, 131.4, 132.9, 140.1 (Ph). Anal. Calcd for $C_{15}H_{17}$NSe: C, 62.06; H, 5.90; N, 4.82. Found: C, 62.33; H, 6.21; N, 4.59.

5.2.2. *N*-Benzyl-2-(phenylselanyl)propan-1-amine 6b. Yield: 41%. $Bp_{0.05}$: 121–122 °C. ^{1}H NMR δ: 1.52 (d, 3H, J=6.7 Hz, H-3), 1.95 (sl, 1H, N*H*), 2.71–2.97 (m, 2H, H-1), 3.42–3.59 (m, 1H, H-2), 3.90 (s, 2H, CH_2Ph), 7.25–7.45(m, 8H, Ph), 7.60–7.65(m, 2H, Ph). ^{13}C NMR δ: 20.3 (C-3), 40.0 (C-2), 53.3, 54.6 (C-1, *C*H_2Ph), 126.7, 126.9, 127.4, 127.9, 128.2, 128.7, 135.2, 140.1 (Ph). Anal. Calcd for $C_{16}H_{19}$NSe: C, 63.15; H, 6.29; N, 4.60. Found: C, 63.45; H, 6.35; N, 4.34.

5.2.3. *N*-Benzyl-2-(phenylselanyl)butan-1-amine 6c. Yield: 72%. ^{1}H NMR δ: 1.03 (t, 3H, J=7.3 Hz, H-4), 1.60–1.74 (m, 2H, H-3), 1.80 (sl, 1H, N*H*), 2.65–2.82 (m, 2H, H-1), 3.17–3.25 (m, 1H, H-2), 3.75 (d, 1H, J=13.6 Hz, CH$_2$Ph), 3.82 (d, 1H, J=13.6 Hz, CH_2Ph), 7.17–7.32 (m, 8H, Ph), 7.47–7.51 (m, 2H, Ph). ^{13}C NMR δ: 12.6 (C-4), 27.0 (C-3), 49.4 (C-2), 52.8 (C-1), 53.8 (*C*H_2Ph), 126.9, 127.3, 127.7, 128.2, 128.5, 129.0, 135.4, 140.4 (Ph). Anal. Calcd for $C_{17}H_{21}$NSe: C, 64.14; H, 6.65; N, 4.40. Found: C, 64.35; H, 6.72; N, 4.29.

5.2.4. *N*-Benzyl-3-methyl-2-(phenylselanyl)butan-1-amine 6d.[4a] Yield: 69%. ^{1}H NMR δ: 1.01 (d, 3H, J= 6.7 Hz, H-4), 1.05 (d, 3H, J=6.7 Hz, H-4), 2.00–2.06 (m, 1H, H-3), 2.20 (sl, 1H, N*H*), 2.81 (dd, 1H, J=8.4, 12.5 Hz, H-1), 2.91 (dd, 1H, J=5.1, 12.5 Hz, H-1), 3.24–3.29 (m, 1H, H-2), 3.70 (d, 1H, J=13.4 Hz, CH_2Ph), 3.75 (d, 1H, J= 13.4 Hz, CH_2Ph), 7.17–7.33 (m, 8H, Ph), 7.52–7.59 (m, 2H, Ph). ^{13}C NMR δ: 20.1 (C-4), 21.0 (C-4), 31.2 (C-3), 51.7 (C-1), 53.6 (*C*H$_2$Ph), 56.7 (C-2), 126.8, 127.1, 127.4, 128.0, 128.3, 128.9, 134.3, 140.2 (Ph). Anal. Calcd for $C_{18}H_{23}NSe$: C, 65.05; H, 6.98; N, 4.21. Found: C, 64.86; H, 6.71, N, 4.49.

5.2.5. *N*-Benzyl-2-(phenylselanyl)hexan-1-amine 6e. Yield: 65%. ^{1}H NMR δ: 0.87 (t, 3H, J=7.2 Hz, H-6), 1.22–1.55 (m, 4H, H5, H-4), 1.56–1.60 (m, 2H, H-3), 1.80 (sl, 1H, N*H*), 2.67 (dd, 1H, J=7.9, 12.3 Hz, H-1), 2.77 (dd, 1H, J=4.8, 12.3 Hz, H-1), 3.21–3.31(m, 1H, H-2), 3.74 (d, 1H, J=13.4 Hz, CH_2Ph), 3.81 (d, 1H, J=13.4 Hz, CH_2Ph), 7.21–7.34 (m, 8H, Ph), 7.47–7.51 (m, éH, Ph). ^{13}C NMR δ: 14.1 (C-6), 22.6 (C-5), 30.1 (C-4), 33.6 (C-3), 47.5 (C-2), 53.0 (C-1), 53.7 (*C*H$_2$Ph), 127.0, 127.7, 128.2, 128.3, 128.5, 129.0, 135.4, 140.4 (Ph). Anal. Calcd for $C_{19}H_{25}NSe$: C, 65.88; H, 7.27; N, 4.04. Found: C, 66.14; H, 6.95; N, 4.27.

5.2.6. *N*-Benzyl-3-phenyl-2-(phenylselanyl)propan-1-amine 6f. Yield: 67%. ^{1}H NMR δ: 2.67–2.87 (m, 2H, H-1), 2.94–3.14 (m, 2H, H-3), 3.50–3.65 (m, 1H, H-2), 3.71 (d, 1H, J=13.5 Hz, CH_2Ph), 3.81 (d, 1H, J=13.5 Hz, CH_2Ph), 7.15–7.40 (m, 13H, Ph), 7.47–7.53 (m, 2H, Ph). ^{13}C NMR δ: 40.3 (C-3), 47.5 (C-2), 51.7, 53.5 (C-1, *C*H$_2$Ph), 126.9, 127.7, 128.2, 128.4, 129.0, 129.1, 135.3, 139.6 (Ph). Anal. Calcd for $C_{22}H_{23}NSe$: C, 69.46; H, 6.09; N, 3.68. Found: C, 69.30; H, 6.12; N, 3.55.

5.2.7. *N*-Benzyl-2-methyl-2-(phenylselanyl)propan-1-amine 6g.[4a] Yield: 64%. ^{1}H NMR δ: 1.40 (s, 6H, H-3), 1.84 (sl, 1H, N*H*), 2.50 (s, 2H, H-1), 3.86 (s, 2H, CH_2Ph), 7.25–7.40 (m, 8H, Ph), 7.47–7.53 (m, 2H, Ph). ^{13}C NMR δ: 28.4 (C-3), 48.4 (C-2), 54.0 (*C*H$_2$Ph), 59.2 (C-1), 126.8, 127.0, 127.6, 128.1, 128.3, 128.9, 134.2, 141.1 (Ph). Anal. Calcd for $C_{17}H_{21}NSe$: C, 64.14; H, 6.65; N, 4.40. Found: C, 64.45; H, 6.79; N, 4.19.

5.2.8. *N*-Benzyl-2-phenyl-2-(phenylselanyl)propan-1-amine 6h. Yield: 59%. ^{77}Se NMR δ: 564.8. ^{1}H NMR δ: 1.50 (sl, 1H, N*H*), 1.84 (s, 3H, H-3), 3.00 (d, 1H, J= 12.0 Hz, H-1), 3.25 (d, 1H, J=12.0 Hz, H-1), 3.79 (s, 2H, CH_2Ph), 7.10–7.35 (m, 15H, Ph). ^{13}C NMR δ: 26.0 (C-3), 52.7 (C-2), 54.2 (*C*H$_2$Ph), 58.7 (C-1), 126.8, 127.0, 127.4, 127.8, 128.2, 128.3, 128.5, 128.6, 128.7, 137.9, 140.5, 144.1 (Ph). Anal. Calcd for $C_{22}H_{23}NSe$: C, 69.46; H, 6.09; N, 3.68. Found: C, 69.26; H, 5.86; N, 3.98.

5.2.9. Phenyl-*N*-((1-(phenylselanyl)cyclohexyl)methyl) methanamine 6i. Yield: 51%. ^{1}H NMR δ: 0.90–1.90 (m, 11H, Cy, N*H*), 2.47–2.52 (m, 2H, H-1), 3.81 (s, 2H, CH_2Ph), 7.20–7.45 (m, 8H, Ph), 7.57–7.64 (m, 2H, Ph). ^{13}C NMR δ: 26.1, 31.4, 35.5, 53.2, 54.0 56.1 (C-1, *C*H$_2$Ph), 126.7, 128.0, 128.2, 128.5, 129.0, 131.3, 137.9, 140.4 (Ph). Anal. Calcd for $C_{20}H_{25}NSe$: C, 67.02; H, 7.03; N, 3.91. Found: C, 66.73; H, 6.86; N, 3.78.

5.2.10. *N*-Benzyl-1-(phenylselanyl)propan-2-amine 6j.[4a] Yield: 50%. ^{1}H NMR δ: 1.18 (d, 3H, J=6.1 Hz, CH_3), 1.80 (sl, 1H, N*H*), 2.85–3.09 (m, 3H, H-1, H-2), 3.70 (d, 1H, J= 13.1 Hz, CH_2Ph), 3.80 (d, 1H, J=13.1 Hz, CH_2Ph), 7.20–7.35 (m, 8H, Ph), 7.45–7.49(m, 2H, Ph). ^{13}C NMR δ: 20.8 (C-3), 36.3 (C-1), 51.3 (*C*H$_2$Ph), 51.7 (C-2), 127.0, 127.3, 128.2, 128.5, 129.2, 130.4, 133.0, 140.4 (Ph). Anal. Calcd for $C_{16}H_{19}NSe$: C, 63.15; H, 6.30; N, 4.60. Found: C, 63.47; H, 6.39; N, 4.27.

5.2.11. *N*-Benzyl-3,3-dimethyl-1-(phenylselanyl)butan-2-amine 6k.[4a] Yield: 71%. ^{1}H NMR δ: 1.06 (s, 9H, C(CH_3)$_3$), 1.37 (sl, 1H, N*H*), 2.59 (dd, 1H, J=9.0, 3.4 Hz, H-1), 3.00 (dd, 1H, J=12.1, 9.0 Hz, H-2), 3.39 (dd, 1H, J=12.1, 3.4 Hz, H-2), 3.85 (d, J=12.4 Hz, CH_2Ph), 4.06 (d, J= 12.4 Hz, CH_2Ph), 7.28–7.45 (m, 8H, Ph), 7.58–7.62 (m, 2H, Ph). ^{13}C NMR δ: 27.1 (C-4), 32.3 (C-1), 36.4 (C-3), 55.4 (*C*H$_2$Ph), 66.6 (C-2), 126.8, 127.3, 128.0, 128.4, 129.1, 130.0, 133.6, 141.1 (Ph). Anal. Calcd for $C_{19}H_{25}NSe$: C, 65.88; H, 7.28; N, 4.04. Found: C, 66.10; H, 7.31; N, 4.29.

5.2.12. *N*-Benzyl-1-phenyl-2-(phenylselanyl)ethan-1-amine 6l. Yield: 68%. ^{77}Se NMR δ: 268.5. ^{1}H NMR δ: 2.25(sl, 1H, N*H*), 3.06 (dd, 1H, J=9.7, 12.3 Hz, H-2), 3.22 (dd, 1H, J=4.3, 12.3 Hz, H-2), 3.49 (d, 1H, J=13.4 Hz, CH_2Ph), 3.70 (d, 1H, J=13.4 Hz, CH_2Ph), 3.75 (dd, 1H, J=4.3, 9.7 Hz, H-1), 7.20–7.32 (m, 13H, Ph), 7.40–7.44 (m, 2H, Ph). ^{13}C NMR δ: 37.0 (C-2), 51.6 (*C*H$_2$Ph), 61.1 (C-1), 127.0, 127.2, 127.3, 127.7, 128.3, 128.5, 128.8, 129.2, 129.8, 133.2, 140.4, 143.0 (Ph). Anal. Calcd for $C_{21}H_{21}NSe$: C, 68.84; H, 5.78; N, 3.82. Found: C, 68.86; H, 5.96; N, 4.19.

5.2.13. *N*-Benzyl-2-(phenylselanyl)pentan-3-amine 6m.[4a] Yield: 57%, *syn*/*anti*: 80/20. Diastereomer *syn*; ^{1}H NMR δ: 0.89 (t, 3H, J=7.4 Hz, H-5), 1.41 (d, 3H, J=7.1 Hz, H-1), 1.42–1.51 (m, 1H, H-4), 1.66–1.77 (m, 1H, H-4), 2.00 (sl, 1H, N*H*), 2.57 (dt, 1H, J=4.9, 6.6 Hz, H-3), 3.46 (qd, 1H, J=4.9, 7.1 Hz, H-2), 3.74 (d, 1H, J=13.3 Hz, CH_2Ph), 3.79 (d, 1H, J=13.3 Hz, CH_2Ph), 7.15–7.32 (m, 8H, Ph), 7.50–7.54 (m, 2H, Ph). ^{13}C NMR δ: 10.4 (C-5), 18.8 (C-1), 23.9 (C-4), 44.7 (C-2), 51.9 (*C*H$_2$Ph), 62.7 (C-3), 127.0, 127.4 128.3, 128.5, 129.0, 129.4, 134.9, 140.2 (Ph). Diastereomer *anti*; ^{1}H NMR δ: 0.88 (t, 3H, J=7.4 Hz, H-5), 1.39 (d, 3H, J=7.1 Hz, H-1), 1.50–1.60 (m, 1H, H-4), 1.66–1.76 (m, 1H, H-4), 2.00 (sl, 1H, N*H*), 2.52–2.59 (m, 1H, H-3), 3.60–3.65 (m, 1H, H-2), 3.88 (m, 2H, CH_2Ph), 7.15–7.32 (m, 8H, Ph), 7.48–7.52 (m, 2H, Ph). ^{13}C NMR δ: 11.2 (C-5), 17.6 (C-1), 24.7 (C-4), 45.3 (C-2), 51.9 (*C*H$_2$Ph), 62.7 (C-3), 127.8, 128.8, 129.0, 129.9, 130.2, 134.9, 135.3, 139.8 (Ph). Anal. Calcd for $C_{18}H_{23}NSe$: C, 65.05; H, 6.98; N, 4.21. Found: C, 65.36; H, 6.81; N, 4.59.

5.2.14. *syn*-*N*-Benzyl-1-phenyl-2-(phenylselanyl)propan-1-amine 6n.[4a] Yield: 53%. ^{1}H NMR δ: 1.30 (d, 3H, J= 7.1 Hz, H-3), 2.20 (sl, 1H, N*H*), 3.47 (d, 1H, J=13.3 Hz, CH_2Ph), 3.61 (qd, 1H, J=3.5, 7.1 Hz, H-2), 3.76 (d, 1H, J= 13.3 Hz, CH_2Ph), 3.83 (d, 1H, J=3.4 Hz, H-1), 7.20–7.40 (m, 13H, Ph), 7.46–7.50 (m, 2H, Ph). ^{13}C NMR δ: 15.7 (C-3), 47.3 (C-2), 51.7 (*C*H$_2$Ph), 64.3 (C-1), 127.0, 127.4, 127.7, 128.0, 128.3, 128.4, 129.2, 129.4, 129.6, 135.0, 140.5, 141.0 (Ph). Anal. Calcd for $C_{22}H_{23}NSe$: C, 69.47; H, 6.09; N, 3.68. Found: C, 69.82; H, 6.31; N, 3.49.

5.2.15. *N*-Benzyl-2-(phenylselanyl)cyclohexanamine 6o.[4a] Yield: 57%, *syn*/*anti*: 80/20. Diastereomer *syn*; ^{1}H NMR δ: 1.20–2.20 (m, 9H), 2.76 (m, 1H, H-1), 3.74 (s, 2H, CH_2Ph), 3.81 (m, 1H, H-2), 7.20–7.40 (m, 8H, Ph) 7.45–7.49 (m, 2H, Ph). ^{13}C NMR δ: 23.5, 23.8, 30.3, 31.2, 50.7 (*C*H_2Ph), 52.2 (C-2), 57.5 (C-1), 126.9, 127.0, 128.4, 129.1, 129.6, 129.8, 134.9, 141.0 Diastereomer *anti*; ^{1}H NMR δ: 1.20–2.20 (m, 9H), 2.45 (m, 1H, H-1), 3.08 (m, 1H, H-2), 3.71 (d, 1H, J=13.1 Hz, CH_2Ph), 3.93 (d, 1H, J=13.1 Hz, CH_2Ph), 7.15–7.35 (m, 8H, Ph), 7.40–7.43 (m, 2H, Ph). ^{13}C NMR δ: 24.7, 27.4, 32.5, 34.4, 50.9 (C-2), 51.0 (*C*H_2Ph), 59.6 (C-1), 127.0, 128.3, 128.5, 129.1, 129.6, 129.8, 135.1, 140.5 (Ph). Anal. Calcd for $C_{19}H_{23}NSe$: C, 66.27; H, 6.73; N, 4.07. Found: C, 66.17; H, 6.67; N, 4.12.

5.2.16. *N*-Allyl-2-(phenylselanyl)butan-1-amine 7c. Yield: 64%. $bp_{0.05}$: 93 °C. ^{1}H NMR δ: 1.03 (t, 3H, J= 7.2 Hz, H-4), 1.58–1.81 (m, 2H, H-3), 2.10 (sl, 1H, N*H*), 2.63–2.83 (m, 2H, H-1), 3.14–3.28 (m, 3H, H-2, CH_2CH=CH$_2$), 5.02–5.20 (m, 2H, CH$_2$CH=CH_2), 5.77–5.97 (m, 1H, CH$_2$C*H*=CH$_2$), 7.18–7.28 (m, 3H, Ph), 7.50–7.63 (m, 2H, Ph). ^{13}C NMR δ 12.4 (C-4), 26.8 (C-3), 49.2 (C-2), 52.0 (*C*H_2CH=CH$_2$), 52.7 (C-1), 115.9 (CH$_2$CH=H$_2$), 127.5, 127.6, 128.9, 129.1, 131.4, 135.1, 136.7 (Ph, CH$_2$*C*H=CH$_2$). Anal. Calcd for $C_{13}H_{19}NSe$: C, 58.20; H, 7.14; N, 5.22. Found: C, 58.02; H, 7.30; N, 4.94.

5.2.17. *N*-Cyclohexyl-2-(phenylselanyl)butan-1-amine 8c. Yield: 57%. ^{77}Se NMR δ: 332.9. ^{1}H NMR δ: 1.07 (t, 3H, J=7.2 Hz, H-4), 1.10–1.31 (m, 6H, Cy), 1.57–1.85 (m, 7H, Cy, H-3, N*H*), 2.38 (m, 1H, Cy), 2.69 (dd, 1H, J=8.9, 12.5 Hz, H-1), 2.85 (dd, 1H, J=4.8, 12.5 Hz, H-1), 3.16–3.25 (m, 1H, H-2), 7.25–7.40 (m, 3H, Ph), 7.55–7.60 (m, 2H, Ph). ^{13}C NMR δ: 12.5 (C-4), 25.1, 26.2, 27.0 (Cy), 33.8 (C-3), 49.7 (C-2), 50.6 (C-1), 56.6 (Cy), 127.6, 129.0, 128.9, 135.4 (Ph). Anal. Calcd for $C_{16}H_{25}NSe$: C, 61.92; H, 8.12; N, 4.51. Found: C, 61.58; H, 7.87; N, 4.71.

5.2.18. *N*-*tert*-Butyl-2-(phenylselanyl)butan-1-amine 9c. Yield: 56%. ^{1}H NMR δ: 1.07 (t, 3H, J=7.4 Hz, H-4), 1.10 (s, 9H, C(CH_3)$_3$), 1.65–1.81 (m, 2H, H-3), 2.67–2.80 (dd, 1H, J=7.9, 11.8 Hz, H-1), 2.66 (dd, 1H, J=5.1, 11.8 Hz, H-1), 3.11–3.22 (m, 1H, H-2), 7.25–7.30 (m, 3H, Ph), 7.55–7.60 (m, 2H, Ph). ^{13}C NMR δ: 12.5 (C-4), 27.2 (C-3), 29.3 (C(*C*H$_3$)$_3$), 46.4 (C-1), 50.1 (C-2), 50.3 (*C*(CH$_3$)$_3$), 127.6, 128.6, 129.0, 135.3 (Ph). Anal. Calcd for $C_{14}H_{23}NSe$: C, 59.14; H, 8.15; N, 4.93. Found: C, 58.86; H, 7.92; N, 4.65.

5.3. Preparation of β-phenylselanyl amines 10e and 11

A solution of alkylmagnesium chloride 2M in THF (1.1 ml, 2.2 mmol) was slowly added to α-phenylselanyl imines **2** (2 mmol) in THF (30 ml), at −40 °C, under argon. The whole was stirred for 30 min at −40 °C and allowed to reach 0 °C in 2 h. A saturated aqueous solution of ammonium chloride (5 ml) was added, followed by a mixture of water/ether: 1/1 (40 ml). After separation, the aqueous phase was washed with ether (2×50 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane/Et_2O: 95/5).

5.3.1. *N*-Benzyl-3-methyl-5-(phenylselanyl)non-1-en-4-amine 10e. Yield: 56%, two diastereomers: 70/30. Major diastereomer; ^{1}H NMR δ: 0.86 (t, 3H, J=7.2 Hz, H-9), 1.06 (d, 3H, J=6.6 Hz, CH_3), 1.20–1.50 (m, 4H, H-8, H-7), 1.51 (sl, 1H, N*H*), 1.80–1.98 (m, 2H, H-6), 2.55 (dd, 1H, J=2.4, 7.4 Hz, H-4), 2.58–2.72 (m, 1H, H-3), 3.32 (td, 1H, J=2.4, 7.2 Hz, H-5), 3.83 (s, 2H, CH_2Ph), 5.06–5.16 (m, 2H, H-1), 5.76–5.88 (m, 1H, H-2), 7.25–7.40 (m, 8H, Ph), 7.55–7.58 (m, 2H, Ph). ^{13}C NMR δ: 14.1 (C-9), 18.8 (*C*H$_3$), 22.6 (C-8), 30.6 (C-7), 35.4 (C-6), 42.9 (C-3), 53.4 (C-5), 54.7 (*C*H_2Ph), 64.4 (C-4), 115.6 (C-1), 140.9 (C-2), 126.9, 127.0, 128.4, 128.9, 129.0, 131.7, 134.4, 142.1 (Ph). Minor diastereomer; ^{1}H NMR δ: 0.89 (t, 3H, J=7.0 Hz, H-9), 1.06 (d, 3H, J= 6.7 Hz, CH_3), 1.19–1.99 (m, 7H, H-8, H-7, H-6, N*H*), 2.49–2.61 (m, 1H, H-3), 2.71–2.76 (m, 1H, H-4), 3.43–3.52 (m, 1H, H-5), 3.81 (d, 1H, J=12.3 Hz, CH_2Ph), 3.88 (d, 1H, J= 12.3 Hz, CH_2Ph), 5.00–5.06 (m, 2H, H-1), 5.70–5.83 (m, 1H, H-2), 7.25–7.40 (m, 8H, Ph), 7.55–7.58 (m, 2H, Ph). ^{13}C NMR δ: 14.4 (C-9), 17.6 (*C*H$_3$), 22.9 (C-8), 31.2 (C-7), 31.4 (C-6), 42.2 (C-3), 52.6 (C-5), 54.8 (*C*H_2Ph), 65.7 (C-4), 114.5 (C-1), 142.9 (C-2), 127.3, 127.5, 128.6, 128.7, 129.4, 131.5, 134.5, 143.0 (Ph). Anal. Calcd for $C_{23}H_{31}NSe$: C, 68.98; H, 7.80; N, 3.50. Found: C, 68.62; H, 7.91; N, 3.36.

5.3.2. *N*-Benzyl-6-methyl-5-(phenylselanyl)hept-1-en-4-amine 11d. Yield: 78%, *syn*/*anti*: 55/45. Diastereomer *syn*; ^{1}H NMR δ: 1.02 (d, 3H, J=6.6 Hz, H-7), 1.06 (d, 3H, J=6.6 Hz, H-7), 1.68 (sl, 1H, N*H*), 2.16 (m, 1H, H-6), 2.48 (m, 2H, H-3), 2.88 (m, 1H, H-4), 3.10–3.14 (m, 1H, H-5), 3.74 (d, 1H, J=13.1 Hz, CH_2Ph), 3.89 (d, 1H, J=13.1 Hz, CH_2Ph), 4.93–5.05 (m, 2H, H-1), 5.69–5.79 (m, 1H, H-2), 7.22–7.34 (m, 8H, Ph), 7.55–7.58 (m, 2H, Ph). ^{13}C NMR δ: 21.5 (C-7), 22.1 (C-7), 31.5 (C-6), 37.3 (C-3), 52.0 (*C*H_2Ph), 59.0 (C-4), 62.4 (C-5), 117.4 (C-1), 135.9 (C-2), 126.8, 127.0, 128.3, 128.4, 129.0, 132.1, 133.8, 140.7 (Ph). Diastereomer *anti*; ^{1}H NMR δ: 1.07 (d, 3H, J=6.6 Hz, H-7), 1.15 (d, 3H, J=6.6 Hz, H-7), 1.66 (sl, 1H, N*H*), 2.12–2.20 (m, 1H, H-6), 2.26–2.34 (m, 1H, H-3), 2.44–2.54 (m, 1H, H-3), 2.85–2.95 (m, 1H, H-4), 3.23–3.27 (m, 1H, H-5), 3.68 (s, 2H, CH_2Ph), 4.99–5.10 (m, 2H, H-1), 5.70–5.90 (m, 1H, H-2), 7.22–7.35 (m, 8H, Ph), 7.55–7.60 (m, 2H, Ph). ^{13}C NMR δ: 21.5 (C-7), 22.1 (C-7), 31.0 (C-6), 36.8 (C-3), 51.6 (*C*H_2Ph), 59.2 (C-4), 62.8 (C-5), 116.9 (C-1), 136.3 (C-2), 126.8, 127.0, 128.3, 128.4, 129.0, 132.1, 133.8, 140.7 (Ph). Anal. Calcd for $C_{21}H_{27}NSe$: C, 67.73; H, 7.31; N, 3.76. Found: C, 67.61; H, 7.56; N, 3.59.

5.3.3. *syn*-*N*-Benzyl-5-(phenylselanyl)non-1-en-4-amine 11e. Yield: 69%. ^{1}H NMR δ: 0.87 (t, 3H, J=7.2 Hz, H-9), 1.22–1.35 (m, 3H, H-8, H-7), 1.42–1.63 (m, 3H, H-7, H-6 N*H*), 1.84–1.95 (m, 1H, H-6), 2.20–2.31 (m, 1H, H-3), 2.51–2.62 (m, 1H, H-3), 2.76–2.82 (m, 1H, H-4), 3.24–3.32 (m, 1H, H-5), 3.74 (d, 1H, J=13.4 Hz, CH_2Ph), 3.80 (d, 1H, J=13.4 Hz, CH_2Ph), 4.99–5.07 (m, 2H, H-1), 5.64–5.78 (m, 1H, H-2), 7.22–7.35 (m, 8H, Ph), 7.55–7.60 (m, 2H, Ph). ^{13}C NMR δ: 14.1 (C-9), 22.6 (C-8), 30.7 (C-7), 31.9 (C-6), 36.5 (C-3), 52.0 (*C*H_2Ph), 52.2 (C-5), 59.8 (C-4), 117.5 (C-1), 136.2 (C-2), 127.0, 127.2, 128.3, 128.4, 129.0, 130.8, 134.4, 140.8 (Ph). Anal. Calcd for $C_{22}H_{29}NSe$: C, 68.38; H, 7.56; N, 3.62. Found: C, 68.52; H, 7.91; N, 3.86.

5.3.4. *N*-Benzyl-2-methyl-2-(phenylselanyl)hex-5-en-3-amine 11g. Yield: 74%. ^{1}H NMR δ: 1.38 (s, 3H, H-1),

1.44 (s, 3H, H-1), 1.55 (sl, 1H, N*H*), 2.14–2.25 (m, 1H, H-4), 2.63–2.77 (m, 2H, H-4, H-3), 3.78 (d, 1H, $J=12.6$ Hz, CH_2Ph), 3.92 (d, 1H, $J=12.6$ Hz, CH_2Ph), 5.06–5,16 (m, 2H, H-6), 5.83–5.98 (m, 1H, H-5), 7.25–7.40 (m, 8H, Ph), 7.62–7.65 (m, 2H, Ph). ^{13}C NMR δ: 27.0 (C-1), 27.7 (C-1), 37,0 (C-4), 54.6 (*C*H_2Ph), 65.6 (C-3), 77.36 (C-2), 116.8 (C-6), 137.1 (C-5), 127.0, 127.4, 128.3, 128.4, 128.5, 128.7, 138.5, 140.8 (Ph). Anal. Calcd for $C_{20}H_{25}NSe$: C, 67.03; H, 7.03; N, 3.91. Found: C, 67.31; H, 7.27; N, 3.79.

5.3.5. *syn*-*N*-Benzyl-2-phenyl-2-(phenylselanyl)hex-5-en-3-amine 11h. Yield: 47%. ^{1}H NMR δ: 1.57 (sl, 1H, N*H*), 1.86 (s, 3H, H-1), 1.96–2.06 (m, 1H, H-4), 2.18–2.25 (m, 1H, H-4), 3.62 (dd, 1H, $J=3.2$, 8.3 Hz, H-3), 4.06 (d, 1H, $J=12.3$ Hz, CH_2Ph), 4.13 (d, 1H, $J=12.3$ Hz, CH_2Ph), 4.93–4.99 (m, 2H, H-6), 5.70–5.84 (m, 1H, H-5), 6.99–7.52 (m, 15H, Ph). ^{13}C NMR δ: 21.5 (C-1), 37.7 (C-4), 55.0 (*C*H_2Ph), 61.4 (C-2), 65.7 (C-3), 116.7 (C-6), 136.7 (C-5), 126.3, 127.1, 127.6, 127.8, 128.0, 128.3, 128.5, 128.7, 129.4, 137.6, 140.7, 144.1 (Ph). Anal. Calcd for $C_{25}H_{27}NSe$: C, 71.41; H, 6.47; N, 3.33. Found: C, 71.02; H, 6.19; N, 3.03.

5.3.6. *N*-Benzyl-2-methyl-1-(phenylselanyl)pent-4-en-2-amine 11j. Yield: 58%. ^{1}H NMR δ: 1.26 (s, 3H, CH_3), 1.57 (sl, 1H, N*H*), 2.30–2.51 (m, 2H, H-3), 3.16 (d, 1H, $J=$ 11.8 Hz, H-1), 3.26 (d, 1H, $J=11.8$ Hz, H-1), 3.69 (s, 2H, CH_2Ph), 5.11–5.18 (m, 2H, H-5), 5.81–5.93 (m, 1H, H-4), 7.25–7.38 (m, 8H, Ph), 7.55–7.59 (m, 2H, Ph). ^{13}C NMR δ: 25.0 (*C*H_3), 40.2 (C-1), 43.7 (C-3), 46.5 (*C*H_2Ph), 55.9 (C-2), 118.6 (C-5), 134.2 (C-4), 126.8, 127.0, 128.2, 128.4, 129.2, 131.5, 132.9, 140.9 (Ph). Anal. Calcd for $C_{20}H_{25}NSe$: C, 67.03; H, 7.03; N, 3.91. Found: C, 66.96; H, 6.75; N, 4.02.

5.3.7. *N*-Benzyl-2-phenyl-1-(phenylselanyl)pent-4-en-2-amine 11l. Yield: 65%. ^{1}H NMR δ: 1.88 (sl, 1H, N*H*), 2.65–2.80 (m, 2H, H-3), 3.45 (d, 1H, $J=12.0$ Hz, CH_2Ph), 3.55 (d, 1H, $J=12.0$ Hz, CH_2Ph), 3.62 (s, 2H, H-1), 4.99–5.07 (m, 2H, H-5), 5.43–5.58 (m, 1H, H-4), 7.20–7.60 (m, 15H, Ph). ^{13}C NMR δ: 38.9 (C-1), 44.2 (C-3), 46.7 (*C*H_2Ph), 61.5 (C-2), 118.8 (C-5), 133.5 (C-4), 126.8, 126.9, 127.0, 128.3, 128.4, 128.5, 129.1, 131.2, 133.3, 140.7, 144.0 (Ph). Anal. Calcd for $C_{24}H_{25}NSe$: C, 70.92; H, 6.20; N, 3.44. Found: C, 70.55; H, 6.15; N, 3.22.

5.3.8. *syn*-*N*-Benzyl-3-phenyl-2-(phenylselanyl)hex-5-en-3-amine 11n. Yield: 64%. ^{77}Se NMR δ: 364.0. ^{1}H NMR δ: 1.31 (d, 3H, $J=6.9$ Hz, H-1), 2.33 (sl, 1H, N*H*), 2.88 (dd, 1H, $J=5.3$, 14.8 Hz, H-4), 3.08 (dd, 1H, $J=8.3$, 14.8 Hz, H-4), 3.65 (d, 1H, $J=12.5$ Hz, CH_2Ph), 3.74 (q, 1H, $J=$ 6.9 Hz, H-2), 3.82 (d, 1H, $J=12.5$ Hz, CH_2Ph), 5.15–5.22 (m, 2H, H-6), 5.90–5.98 (m, 1H, H-5), 7.20–7.60 (m, 15H, Ph). ^{13}C NMR δ: 19.0 (C-1), 38.2 (C-4), 46.8 (*C*H_2Ph), 51.6 (C-2), 64.1 (C-3), 118.5 (C-6), 134.0 (C-5), 126.9, 127.1, 127.2, 127.8, 128.0, 128.2, 128,5, 129.0, 130.8, 134.7, 140.9, 141,5 (Ph). Anal. Calcd for $C_{25}H_{27}NSe$: C, 71.41; H, 6.47; N, 3.33. Found: C, 71.12; H, 6.39; N, 3.15.

5.4. Preparation of allylaziridines 12

A solution of allylmagnesium chloride 2M in THF (1.1 ml, 2.2 mmol) was slowly added to α-phenylselanyl imine **2** (2 mmol) in refluxing THF (30 ml), under argon. The whole was stirred for 2 h under reflux. A saturated aqueous solution of ammonium chloride (5 ml) was added, followed by a mixture of water/ether: 1/1 (40 ml). After separation, the aqueous phase was washed with ether (2×50 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane/Et_2O: 80/20).

5.4.1. 2-Allyl-1-benzyl-3-isopropylaziridine 12d. Yield: 73%, *cis*/*trans*: 55/45. Diastereomer *cis*; ^{1}H NMR δ: 0.84 (d, 3H, $J=6.1$ Hz, CH(CH_3)$_2$), 0.90 (d, 3H, $J=6.7$ Hz, CH(CH_3)$_2$), 1.23 (dd, 1H, $J=6.5$, 9.6 Hz H-3), 1.28–1.38 (m, 1H, C*H*(CH$_3$)$_2$), 1.55–1.63 (m, 1H, H-2), 2.13–2.25 (m, 2H, CH_2CH=CH$_2$), 3.37 (d, 1H, $J=12.6$ Hz, CH_2Ph), 3.49 (d, 1H, $J=12.6$ Hz, CH_2Ph), 4.97–5.11 (m, 2H, CH$_2$CH=CH_2), 5.70–5.87 (m, 1H, CH$_2$C*H*=CH$_2$), 7.26–7.36 (m, 5H, Ph). ^{13}C NMR δ: 20.4 (CH(*C*H$_3$)$_2$), 21.4 (CH(*C*H$_3$)$_2$), 27.7 (*C*H(CH$_3$)$_2$), 32.9 (*C*H$_2$CH=CH$_2$), 44.3 (C-2), 51.5 (C-3), 65.8 (*C*H$_2$Ph), 115.8 (CH$_2$CH=H$_2$), 139.3 (CH$_2$*C*H=CH$_2$), 126.9, 127.2, 128.3, 139.7 (Ph). MS m/z: 215 (M$^+$, 2), 172 (27), 124 (4), 91 (39), 55 (100). Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.50. Found: C, 83.40; H, 9.82; N, 6.61. Diastereomer *trans*; ^{1}H NMR δ: 0.74 (d, 3H, $J=6.4$ Hz, CH(CH_3)$_2$), 0.88 (d, 3H, $J=6.7$ Hz, CH(CH_3)$_2$), 1.14 (dd, 1H, $J=2.3$, 9.2 Hz H-3), 1.19–1.27 (m, 1H, C*H*(CH$_3$)$_2$), 1.87–1.97 (m, 1H, H-2), 2.19–2.36 (m, 1H, CH_2CH=CH$_2$), 2.42–2.54 (m, 1H, CH_2CH=CH$_2$), 3.39 (d, 1H, $J=13.3$ Hz, CH_2Ph), 3.86 (d, 1H, $J=13.3$ Hz, CH_2Ph), 4.97–5.20 (m, 2H, CH$_2$CH=CH_2), 5.82–5.97 (m, 1H, CH$_2$C*H*=CH$_2$), 7.19–7.37 (m, 5H, Ph). ^{13}C NMR δ: 19.9 (CH(*C*H$_3$)$_2$), 20.6 (CH(*C*H$_3$)$_2$), 31.0 (*C*H$_2$CH=CH$_2$), 31.8 (*C*H(CH$_3$)$_2$), 42.0 (C-2), 52.8 (C-3), 56.5 (*C*H$_2$Ph), 116.3 (CH$_2$CH=*C*H$_2$), 136.1 (CH$_2$*C*H=CH$_2$), 126.9, 128.2, 128.4, 140.2 (Ph). MS *m*/*z*: 215 (M$^+$, 2), 172 (27), 124 (4), 91 (38), 55 (100).

5.4.2. *cis*-2-Allyl-1-benzyl-3-butylaziridine 12e. Yield: 53%. ^{1}H NMR δ: 0.85 (t, 3H, $J=6.6$ Hz, CH$_2$CH$_2$CH$_2$CH_3), 1.22–1.43 (m, 6H, CH_2CH_2CH_2CH$_3$), 1.46–1.58 (m, 2H, H-2, H-3), 2.07–2.18 (m, 1H, CH_2CH=CH$_2$), 2.19–2.29 (m, 1H, CH_2CH=CH$_2$), 3.44 (d, 1H, $J=13.3$ Hz, CH_2Ph), 3.50 (d, 1H, $J=13.3$ Hz, CH_2Ph), 4.96–5.10 (m, 2H, CH$_2$CH=CH_2), 5.71–5.83 (m, 1H, CH$_2$C*H*=CH$_2$), 7.22–7.35 (m, 5H, Ph). ^{13}C NMR δ: 14.1 (CH$_2$CH$_2$CH$_2$*C*H$_3$), 22.7 (CH$_2$CH$_2$*C*H$_2$CH$_3$), 27.9 (CH$_2$*C*H$_2$CH$_2$CH$_3$), 30.2 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 32.8 (*C*H$_2$CH=CH$_2$), 43.6 (C-2), 44.2 (C-3), 65.3 (*C*H$_2$Ph), 115.7 (CH$_2$CH=H$_2$), 136.2 (CH$_2$*C*H=CH$_2$), 127.0, 128.2, 128.4, 139.4 (Ph). MS m/z: 229 (M$^+$, 1), 186 (9), 172 (20), 91 (65), 69 (72), 55 (80), 44 (90), 41 (100). Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.62; H, 10.33; N, 6.05.

5.4.3. 3-Allyl-1-benzyl-2,2-dimethylaziridine 12g. Yield: 57%. ^{1}H NMR δ: 1.20 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.39–1.43 (m, 1H, H-3), 2.06–2.17 (m, 1H, CH_2CH=CH$_2$), 2.27–2.37 (m, 1H, CH_2CH=CH$_2$), 3.67 (s, 2H, CH_2Ph), 4.95–5.08 (m, 2H, CH$_2$CH=CH_2), 5.73–5.83 (m, 1H, CH$_2$C*H*=CH$_2$), 7.18–7.36 (m, 5H, Ph). ^{13}C NMR δ: 18.6 (*C*H$_3$), 22.1 (*C*H$_3$), 34.1 (*C*H$_2$CH=CH$_2$), 40.0 (C-2), 49.9 (C-3), 56.9 (*C*H$_2$Ph), 115.5 (CH$_2$CH=H$_2$), 136.3 (CH$_2$*C*H=CH$_2$), 126.5, 127.6, 128.3, 140.6 (Ph). MS m/z: 201 (M$^+$, 12), 186 (34), 160 (16), 110 (24), 91 (68), 55 (75).

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.34; H, 9.61; N, 7.05.

5.4.4. *trans*-3-Allyl-1-benzyl-2-methyl-2-phenylaziridine 12h. Yield: 41%. ^{1}H NMR δ: 1.54 (s, 3H, CH_3), 2.04–2.09 (m, 1H, H-3), 2.22–2.34 (m, 1H, CH_2CH=CH$_2$), 2.39–2.51 (m, 1H, CH_2CH=CH$_2$), 2.78 (d, 1H, J=14.1 Hz, CH_2Ph), 3.54 (d, 1H, J=14.1 Hz, CH_2Ph), 5.01–5.18 (m, 2H, CH$_2$CH=CH_2), 5.75–5.86 (m, 1H, CH$_2$CH=CH$_2$), 7.22–7.37 (m, 10H, Ph). ^{13}C NMR δ: 22.8 (*C*H$_3$), 33.9 (*C*H$_2$CH=CH$_2$), 47.9 (C-3), 48.7 (C-2), 59.0 (*C*H$_2$Ph), 116.2 (CH$_2$CH=H$_2$), 135.9 (CH$_2$*C*H=CH$_2$), 126.7, 127.5, 128.0, 128.2, 128.3, 129.8, 140.1, 140.6 (Ph). Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.40; H, 8.17; N, 5.42.

5.4.5. 2-Allyl-1-benzyl-2-phenylaziridine 12l. Yield: 61%. ^{1}H NMR δ: 1.88 (s, 1H, H-3), 2.12 (s, 1H, H-3), 2.27 (dd, 1H, J=7.2, 14.1 Hz, CH_2CH=CH$_2$), 2.85 (d, 1H, J=14.1 Hz, CH_2Ph), 2.90 (dd, 1H, J=7.2, 14.1 Hz, CH_2CH=CH$_2$), 3.45 (d, 1H, J=14.1 Hz, CH_2Ph), 4.91–4.99 (m, 2H, CH$_2$CH=CH_2), 5.62–5.76 (m, 1H, CH$_2$CH=CH$_2$), 7.19–7.37 (m, 10H, Ph). ^{13}C NMR δ: 38.0 (C-3), 45.2 (*C*H$_2$CH=CH$_2$), 48.9 (C-2), 58.7 (*C*H$_2$Ph), 117.1 (CH$_2$CH=H$_2$), 134.6 (CH$_2$*C*H=CH$_2$), 126.8, 127.0, 127.2, 127.4, 127.7, 128.2, 137.5, 140.1 (Ph). MS m/z: 249 (M$^+$, 24), 208 (10), 172 (5), 158 (30), 91 (100), 77 (20), 55 (75). Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.32; H, 7.56; N, 5.32.

5.4.6. *cis*-2-Allyl-1-benzyl-2-ethyl-3-methylaziridine 12m. Yield: 57%. ^{1}H NMR δ: 0.98 (t, 3H, J=7.2 Hz, CH$_2$CH_3), 1.20 (d, J=5.6 Hz, 3H, CH_3), 1.47 (q, 1H, J=5.6 Hz, H-3), 1.52–1.63 (m, 2H, CH_2CH$_3$), 2.16 (dd, 1H, J=7.3, 14.6 Hz, CH_2CH=CH$_2$), 2.28 (dd, 1H, J=7.3, 14.6 Hz, CH_2CH=CH$_2$), 3.59 (d, 1H, J=14.1 Hz, CH_2Ph), 3.83 (d, 1H, J=14.1 Hz, CH_2Ph), 5.02–5,15 (m, 2H, CH$_2$CH=CH_2), 5.70–5.85 (m, 1H, CH$_2$CH=CH$_2$), 7.22–7.39 (m, 5H, Ph). ^{13}C NMR δ: 10.9 (CH$_2$*C*H$_3$), 14.6 (*C*H$_3$), 22.4 (*C*H$_2$CH$_3$), 36.8 (*C*H$_2$CH=CH$_2$), 45.3 (C-3), 47.0 (C-2), 56.5 (*C*H$_2$Ph), 116.7 (CH$_2$CH=H$_2$), 135.8 (CH$_2$*C*H=CH$_2$), 126.7, 127.9, 128.5, 140.7 (Ph). MS m/z: 215 (M$^+$, 1), 200 (25), 186 (13), 124 (15), 91 (72), 69 (85), 56 (40), 41 (100). Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.77; H, 9.72; N, 6.51.

5.4.7. *trans*-2-Allyl-1-benzyl-3-methyl-2-phenylaziridine 12n. Yield: 41%. ^{1}H NMR δ: 1.38 (d, J=5.6 Hz, 3H, CH_3), 2.12 (q, 1H, J=5.6 Hz, H-3), 2.38 (dd, 1H, J=6.9, 14.6 Hz, CH_2CH=CH$_2$), 2.79 (d, 1H, J=14.3 Hz, CH_2Ph), 2.91 (dd, 1H, J=6.9, 14.6 Hz, CH_2CH=CH$_2$), 3.56 (d, 1H, J=14.3 Hz, CH_2Ph), 4.87–4.93 (m, 2H, CH$_2$CH=CH_2), 5.52–5.66 (m, 1H, CH$_2$CH=CH$_2$), 7.17–7.31 (m, 10H, Ph). ^{13}C NMR δ: 14.6 (*C*H$_3$), 41.1 (*C*H$_2$CH=CH$_2$), 43.9 (C-3), 51.9 (C-2), 58.9 (*C*H$_2$Ph), 116.9 (CH$_2$CH=H$_2$), 134.7 (CH$_2$*C*H=CH$_2$), 126.6, 127.5, 127.7, 128.1, 128.3, 130.6, 138.9, 140.3 (Ph). MS m/z: 263 (M$^+$, 31), 248 (14), 220 (2), 172 (38), 91 (69), 69 (100), 41 (59). Anal. Calcd for $C_{19}H_{21}N$: C, 86.65; H, 8.04; N, 5.32. Found: C, 86.30; H, 8.31; N, 5.37.

5.5. Cyclisation of 11j

To the β-phenylselanyl amine **11j** (1 mmol) in acetonitrile (10 ml) was added NBS (195 mg, 1.1 mmol) at room temperature. After 5 min of stirring, the mixture became red-brown and sodium bicarbonate (212 mg, 2 mmol) was introduced. The mixture turned rapidly yellow. Water (10 ml) was added and the aqueous phase was extracted with dichloromethane (2×10 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane/Et$_2$O: 80/20) to afford the aziridine **12j**.

5.5.1. 2-Allyl-1-benzyl-2-methylaziridine 12j. Yield: 72%. ^{1}H NMR δ: 1.24 (s, 1H, CH_3), 1.26 (s, 1H, H-3), 1.87 (s, 1H, H-3), 2.04–2.30 (m, 1H, CH_2CH=CH$_2$), 3.65 (s, 2H, CH_2Ph), 5.02–5.13 (m, 2H, CH$_2$CH=CH_2), 5.74–5.88 (m, 1H, CH$_2$CH=CH$_2$), 7.20–7.39 (m, 5H, Ph). ^{13}C NMR δ: 14.9 (*C*H$_3$), 39.9 (C-3), 45.0 (C-2), 45.2 (*C*H$_2$CH=CH$_2$), 57.1 (*C*H$_2$Ph), 117.0 (CH$_2$CH=H$_2$), 135.4 (CH$_2$*C*H=CH$_2$), 126.8, 127.7, 128.5, 140.5 (Ph). MS m/z: 187 (M$^+$, 19), 146 (21), 96 (32), 91 (100), 55 (93). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.07; H, 8.94; N, 7.28.

Acknowledgements

The authors want to thank the region Haute-Normandie for their financial support (PhD fellowship to C. M.). A special thank to Claudette Martin who prepared a lot of the starting materials.

References and notes

1. Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1984. Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley: New York, 1986. Liotta, D. *Organoselenium Chemistry*; Wiley: New York, 1987. Krief, A.; Hevesi, L. *Organoselenium Chemistry*; Springer: Berlin, 1988. Back, T. G. *Organoselenium Chemistry: A Practical Approach*; Oxford University Press: Oxford, 1999. Wirth, T. *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Springer: Berlin, 2000. Mugesh, G.; du Mont, W.-W. *Chem. Rev.* **2001**, *101*, 2125.
2. (a) Houllemare, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C. *Synthesis* **1997**, 10. (b) Paulmier, C.; Lerouge, P. *Tetrahedron Lett.* **1982**, *23*, 1557. Lerouge, P.; Paulmier, C. *Tetrahedron Lett.* **1984**, *25*, 1983.
3. Ponthieux, S.; Outurquin, F.; Paulmier, C. *Tetrahedron* **1995**, *51*, 9569. Ponthieux, S.; Outurquin, F.; Paulmier, C. *Tetrahedron* **1997**, *53*, 6365. Ponthieux, S.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1998**, *39*, 4017.
4. (a) Boivin, S.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **2000**, *41*, 663. (b) Besev, M.; Engman, L. *Organic Lett.* **2000**, *2*, 1589.
5. Coates, R. B.; Pigott, H. D.; Ollinger, J. *Tetrahedron Lett.*

1974, 3955. Bates, G. S.; Ramaswamy, S. *Can. J. Chem.* **1983**, *61*, 2466. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synthesis* **1983**, 632. Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159.

6. Ahlbrecht, H. *Tetrahedron Lett.* **1972**, *44*, 4491. De Kimpe, N.; Verhé, R.; De Buyck, L.; Moëns, L.; Schamp, N. *Synthesis* **1982**, 43. Moss, N.; Gauthier, J.; Ferland, J.-M. *Synlett* **1994**, 142. Concellon, J. M.; Bernard, P. L.; Riego, E. J. *J. Org. Chem.* **2001**, *66*, 2764.
7. Uemura, S.; Ohe, K. *J. Chem. Soc, Perkin Trans. 1* **1990**, 907.
8. Houllemare, D. Thesis, Rouen, 1997.
9. De Kimpe, N.; Verhé, R.; De Buyck, L.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 2457. De Kimpe, N.; De Corte, B.; Verhé, R.; De Buyck, L.; Schamp, N. *Tetrahedron Lett.* **1984**, *25*, 1095.
10. Miniejew, C.; Outurquin, F.; Pannecoucke, X. *Org. Biomol. Chem.* **2004**, *2*, 1575.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 457–462

Studies on alkylation of bicyclo[2.2.2]octenones and 3,3-sigmatropic shift: synthesis of advanced *cis*-decalins

Vishwakarma Singh* and Sridhar R. Iyer

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400 076, India

Received 14 August 2004; revised 28 September 2004; accepted 21 October 2004

Available online 5 November 2004

Abstract—A stereoselective method for alkylation of bicyclo[2.2.2]octenones and their 3,3-sigmatropic shift leading to *cis*-decalins containing various types of appendages is described. A simple and convenient method for the introduction of a butenyl chain onto the bicyclooctenones employing 1,4-dibromobutane as an equivalent of 4-bromobutene, was developed.

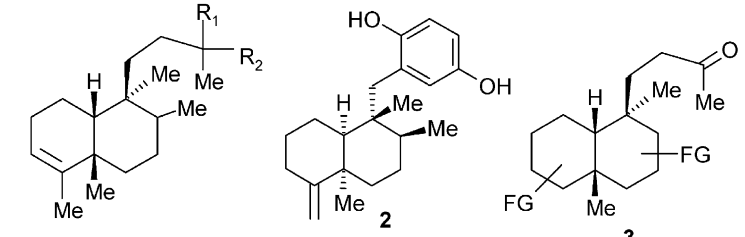
1. Introduction

There has been a considerable interest[1,2] in the development of stereoselective methods for the synthesis of functionalised *cis*-decalin ring systems due to the occurrence and isolation[3] of many natural products such as plathyterpol[4] **1a**, the clerodane diterpene **1b**[5] and arenarol **2**[6] that contain a *cis*-decalin framework. In addition to a *cis*-decalin core with contiguous stereocentres, many clerodanes contain a five-carbon side chain having a methyl group at C-13 whose introduction poses considerable synthetic problems. While, the syntheses of plathyterpol **1a** and the acid **1b** have not been reported yet, in general, the introduction of such type of side chains in a decalin framework is done via extension in a multi-step sequence.[7] In this context, it was envisioned that the side chains present in **1a**,**b** and other related compounds may be prepared in a more efficient manner if a four carbon unit containing an oxo group at C-13 such as in **3**, is present on the *cis*-decalin scaffold.

In view of the above and to expand the scope of our recently reported method for the synthesis of *cis*-decalins,[8] we decided to develop a stereoselective route to *cis*-decalins such as **4** and **5** having a four-carbon chain at C-9, and **6** containing a benzyl side chain as model systems (Scheme 1). It was further thought that such *cis*-decalins would be obtained via a 3,3-shift in bicyclo[2.2.2]octenones of type **7** and **8** followed by further manipulation. The precursors **7** and **8** were thought to be derived from the readily available ketone **9**.[8] We wish to report herein a stereoselective method for the synthesis of bicyclo[2.2.2]octenones **7** and **8** and their transformation to advanced *cis*-decalins **4–6** from a common precursor.

2. Results and discussion

Towards the aforementioned objective, alkylation of the ketone **9**[8] with 4-bromobutene was attempted. Thus, the



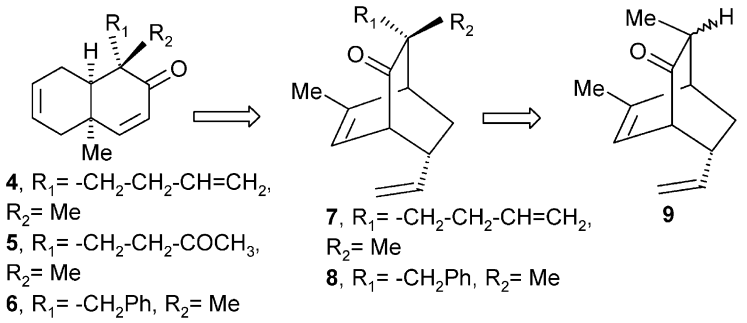
2 **3**

1a, R_1 = OH, R_2 = CH=CH_2
b, R_1, R_2 = =COOH

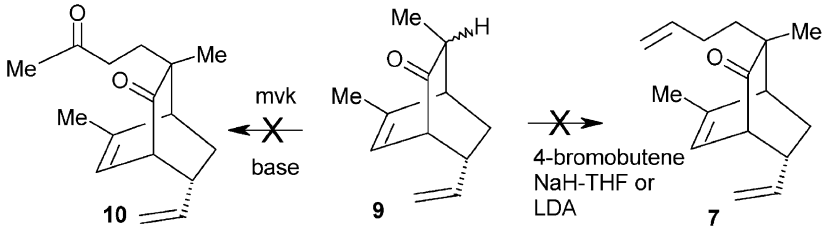
ketone **9** was treated with 4-bromobutene in the presence of sodium hydride–THF. However, no alkylation was observed and the unreacted starting material was recovered. Moreover, the aforementioned alkylation in the presence of

Keywords: Bicyclo[2.2.2]octenones; *cis*-Decalin; [3,3]-Sigmatropic shift; Alkylation.
* Corresponding author. Tel.: +91 2225767168; fax: +91 2225723480; e-mail: vks@chem.iitb.ac.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.066



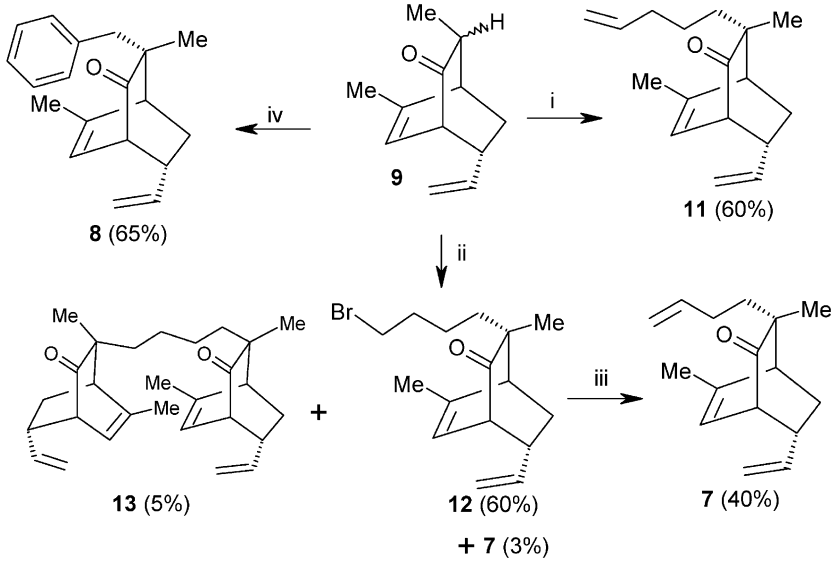
Scheme 1.



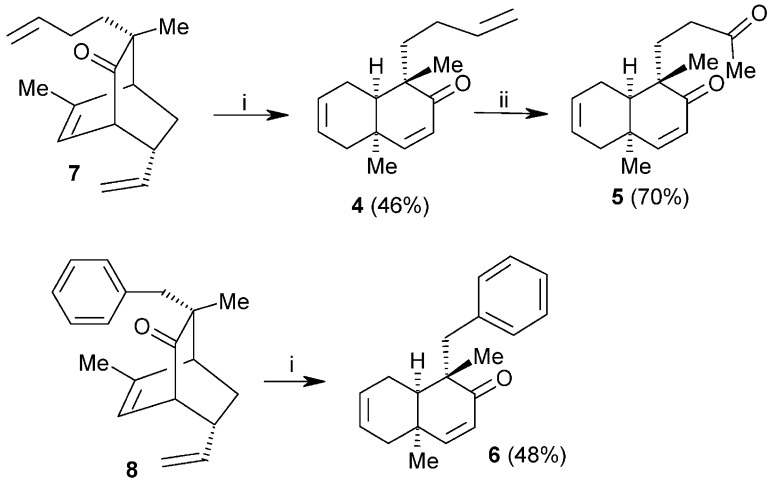
Scheme 2.

various bases such as LDA and KO^{t}Bu under a variety of experimental conditions, also proved to be futile. Furthermore, attempts towards the Michael addition of the ketone **9** with methyl vinyl ketone were also unsuccessful (Scheme 2).

It was very difficult to rationalize the aforementioned failure since a few instances of alkylation with 4-bromobutene, especially with more stabilized carbanions, have been reported.[9] It was not clear as to whether the failure was due to the unreactivity of 4-bromobutene or the steric bulk of the electrophile, or some other problem. In order to gain some insight into this, alkylation of **9** with an unactivated electrophile such as 5-bromopentene was examined. It was interesting to observe that the treatment of **9** with NaH–THF followed by addition of 5-bromopentene led to a smooth and clean reaction (TLC). Chromatography of the product mixture on silver nitrate impregnated silica gel, furnished the compound **11** in good yield having the alkyl chain in *syn* orientation as a result of stereoselective alkylation (Scheme 3). The structure and stereochemistry of the alkylated product was deduced from it's spectroscopic data and comparison with analogous compounds. The orientation of the alkyl chain is revealed from the chemical shift of the methyl group α-to the ketone. In general the methyl group in *syn* isomer appears at relatively down field compared to the *anti* isomer in such type of bicyclo[2.2.2]octenones.[8] The *syn* orientation of pentenyl group in **11** was suggested from the chemical shift of the methyl group α- to the ketone which exhibited a signal at δ 1.05 (s, 3H). This chemical



Scheme 3. Reagents/conditions: (i) NaH–THF, 5-bromopentene, $\triangle$; (ii) NaH–THF, 1,4-dibromobutane; (iii) KO^{t}Bu–^{t}BuOH, $\triangle$; (iv) NaH–THF, benzyl bromide, $\triangle$.



Scheme 4. Reagents/conditions: (i) diphenyl ether, 195 °C; (ii) $PdCl_2$, aq. DMF, CuCl, O_2, rt.

shift compares well with other *syn* isomers of this series such as **7** and **12** (vide infra).

This result clearly indicated that neither the steric bulk nor the reactivity of the electrophile could be the reason for the failure of alkylation with 4-bromobutene; perhaps the propensity of 4-bromobutene to undergo base promoted decomposition[10] during the alkylation might be responsible.

The aforementioned observation led us to think that the desired compound **7** might be obtained via alkylation of the ketone **9** with 1,4-dibromobutane and subsequent dehydrohalogenation. At the outset, we were aware that the formation of product **13** as a result of *bis*-alkylation might pose a considerable problem. Keeping this in mind, a mixture of the ketone **9** and sodium hydride in tetrahydrofuran was treated with an excess of 1,4-dibromobutane at 80 °C. Indeed, it was gratifying to obtain the compound **12** (60%) [mixture of *syn–anti* (85:15), ^{1}H NMR] as a major product along with minor amounts of **7** (3%) and the *bis*-alkylated product **13** (~5%). The treatment of **12** with KO^{t}Bu in ^{t}butanol, followed by chromatography on the silver nitrate impregnated silica gel gave the desired compound **7** in reasonable yield (40%). Thus, 1,4-dibromobutane proved to be a good electrophile that is devoid of the problems during alkylation (encountered with 4-bromobutene) as well as an inexpensive equivalent of 4-bromobutene. Similarly, the ketone **9** was also alkylated with benzyl bromide to furnish the benzyl derivative **8** as a major product (Scheme 3). Such type of π-facial selectivity during alkylation of bicyclooctenones has also been observed earlier.[11,12a]

It may be worth mentioning that while the alkylation of bridged bicyclic ketones with allyl- and propargyl halides have been reported from our own as well as other groups,[12] the introduction of a four carbon chain via alkylation is relatively less documented.

After having developed a simple method for the synthesis of bicyclic systems **7** and **8**, we examined their Cope rearrangement. It may be noted that reversibility in the Cope rearrangement often limits its synthetic potential.[13] In general, this difficulty is overcome by employing its oxyanion version,[14] whereas the corresponding Cope rearrangement in bridged bicyclic systems is not so well known. We contemplated that the presence of a carbonyl group in the bicyclo[2.2.2]octenones **7** and **8** might help in driving the equilibrium towards *cis*-decalins because of generation of a conjugated system.

In view of the above, a solution of **7** in diphenyl ether was heated at 195 °C for about 12 h to give the compound **4**. Wacker oxidation of **4** furnished the desired *cis*-decalin **5** (Scheme 4) whose structure was clearly revealed from spectroscopic data. Similarly, the Cope rearrangement of **8** gave the compound **6** having a *cis*-decalin core with a benzyl side chain related to natural products such as arenarol **3**.

3. Conclusion

In summary, a general and stereoselective route to a variety of bicyclo[2.2.2]octenones and *cis*-decalins from a common precursor is described. Our methodology provides, a simple method for the introduction of a four- or five- carbon chain onto a bicyclo[2.2.2]octenone. 1,4-Dibromobutane has been shown to be a good equivalent of 4-bromobutene, an expensive reagent that is reluctant to undergo alkylation.

4. Experimental

4.1. General remarks

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on Varian VXR 300 instrument. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on Bruker 400 MHz instrument. The high resolution mass spectra were recorded on Bruker Daltonics APEX 3 Telsa Fourier Transform Mass Spectrophotometer and Q-Tof micro (YA-105) Mass Spectrometer. Melting points were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored

with thin layer chromatography and spots were visualized with iodine vapor. Column chromatography was performed using SRL/Thomas Baker silica gel (60–120 and 100–200 mesh) and silver nitrate impregnated silica gel. The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixture.

4.1.1. 3-*syn*-Pent-4-enyl-3,5-dimethyl-7-*endo*-vinyl-bicyclo[2.2.2]oct-5-en-2-one (11). Sodium hydride (250 mg of 60 w/w% suspension in oil, excess) was placed in a dry two necked flask and washed with dry petroleum ether, and tetrahydrofuran (1 mL) was added to it. A solution of ketone **9**[8] (80 mg, 0.45 mmol) in tetrahydrofuran (3 mL) was added slowly to the reaction mixture and the reaction mixture was refluxed for 1 h. 5-Bromopentene (0.4 mL, excess) was then added to the reaction mixture and the reaction mixture was further refluxed for 6 h. The reaction mixture was then cooled and quenched by careful addition of water and it was filtered on a celite pad. The filtrate was then concentrated under vacuum. The residue was diluted with water (6 mL) and extracted with ether (3× 5 mL). The combined extract was washed with water (5 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Removal of solvent and column chromatography [petroleum ether–ethyl acetate, (99:1)] of the residue on silver nitrate impregnated silica gel first gave a small amount of mixture (*syn–anti*) of alkylated products. Further elution with the same solvent gave the *syn* isomer **11** (66 mg, 60%) as a colorless liquid.

IR (neat) ν_{max}: 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 5.78–5.47 (d merged with clusters of m, $J=6$ Hz, 3H, olefinic protons), 4.96 (d, $J=16.8$ Hz, 2H, olefinic protons), 4.89 (d, $J=9.3$ Hz, 2H, olefinic protons), 2.93 (d, $J=4.8$ Hz, 1H), 2.64 (m, 1H), 2.47 (d, $J=2.4$ Hz, 1H), 2.19–2.12 (m, 1H), 2.00–1.96 (m, 2H), 1.88 (d, $J=1.5$ Hz, 3H, CH_3), 1.50–1.06 (clusters of m, 5H), 1.05 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 215.47 (CO), 147.24, 141.10, 138.19, 116.81, 114.93, 113.95 (six olefinic carbons), 54.56, 46.32, 45.55, 39.61, 37.34, 34.10, 28.16, 23.36, 21.30, 20.77. Mass (*m/z*): 244 (M^+). ES-MS: *m/z* Found 244.1839 (M^+); Calcd for $C_{17}H_{24}O$: 244.1827 (M^+).

4.1.2. 3-(4-Bromo-butyl)-3,5-dimethyl-7-*endo*-vinyl-bicyclo[2.2.2]oct-5-en-2-one (12). Sodium hydride (1.5 g of 60 w/w% suspension in oil, excess) was placed in a dry two necked flask and washed with dry petroleum ether, and tetrahydrofuran (5 mL) was added to it. A solution of ketone **9** (320 mg, 1.81 mmol) in tetrahydrofuran (10 mL) was added slowly to the reaction mixture and refluxed for 1 h. 1,4-Dibromobutane (0.8 mL, excess) was then added to the reaction mixture and it was further refluxed for 6 h. The reaction mixture was then cooled and quenched by careful addition of water and it was filtered on a celite pad. The filtrate was then concentrated under vacuum. The residue was diluted with water and extracted with ether (3×10 mL). The combined extract was washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Removal of solvent and column chromatography [petroleum ether–ethyl acetate, (99:1)] of the residue on silica gel first gave compound **7** as a *syn–anti* mixture (12 mg, 3%). Elution with petroleum ether–ethyl acetate (97:3) gave the alkylated adduct **12** [as a *syn–anti* mixture] (338 mg, 60%) as a colorless liquid. Further elution with petroleum ether–ethyl acetate (93:7) furnished the *bis* alkylated compound **13** (36 mg, 5%) as a colorless solid.

Data for **12**. IR (neat) ν_{max}: 1713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (d, $J=6$ Hz, 1H, olefinic proton), 5.60–5.52 (m, 1H, olefinic proton), 4.98 (d, $J=17.2$ Hz, 1H, olefinic proton), 4.92 (d, $J=9.6$ Hz, 1H, olefinic proton), 3.4 (t, $J=6.2$ Hz, 2H, $-CH_2Br$), 2.98 (d, $J=6$ Hz, 1H), 2.68 (m, 1H), 2.50 (broad s, 1H), 2.17 (t, $J=11$ Hz, 1H), 1.90 (s, 3H, CH_3), 1.86–1.72 (m, 3H), 1.48 (m, 2H), 1.34–1.12 (clusters of multiplet, 2H), 1.08 (s, 3H, CH_3) (data for major *syn* isomer). HRMS (EI): Found 310.0931 and 312.0919 (M^+); Calcd for $C_{16}H_{23}OBr$: 310.0932 and 312.0932 (M^+).

Data for **13**. Mp 128–130 °C. IR (film) ν_{max}: 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.61 (d, $J=7.5$ Hz, 1H, β proton of the β,γ-enone moiety), 5.58–5.51 (m, 1H, olefinic proton), 4.96 (d, $J=17.2$ Hz, 1H, olefinic proton), 4.90 (d, $J=10$ Hz, 1H, olefinic proton), 2.96 (dd, $J_1=6.2$ Hz, $J_2=1.8$ Hz, 1H), 2.65 (m, 1H), 2.46 (m, 1H), 2.14 (m, 1H), 1.86 (d, $J=2$ Hz, 3H, CH_3), 1.42 (m, 1H), 1.28–1.1 (clusters of multiplet, 4H), 1.04 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.94 (CO), 147.74, 141.38, 116.76, 114.07 (olefinic carbons), 54.89, 46.45, 45.93, 39.82, 38.05, 28.29, 24.58, 21.47, 20.90. Mass (*m/z*): 406 (M^+). ES-MS: *m/z* Found 407.2988 [$M^+ + H$]; Calcd for $C_{28}H_{38}O_2$: 407.2950 [$M^+ + H$].

4.1.3. 3-*syn*-But-3-enyl-3,5-dimethyl-7-*endo*-vinyl-bicyclo[2.2.2]oct-5-en-2-one (7). To a solution of the compound **12** (150 mg, 0.48 mmol) in tertiary butanol (6 mL) was added potassium tertiary butoxide (162 mg, 1.45 mmol) and the reaction mixture was heated at 85 °C for 6 h. The reaction mixture was brought to room temperature and a saturated solution of NH_4Cl was added and extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous sodium sulphate. Removal of solvent and chromatography [petroleum ether–ethyl acetate, (98:2)] of the residue on silver nitrate impregnated silica gel furnished the compound **7** (44 mg, 40%) as a colorless liquid.

IR (neat) ν_{max}: 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 5.72–5.47 (m, 3H, olefinic protons), 4.99–4.87 (m, 4H, olefinic protons), 2.93 (dd, $J_1=6.1$ Hz, $J_2=1.6$ Hz, 1H), 2.63 (m, 1H), 2.47 (d, $J=2.1$ Hz, 1H), 2.20–2.06 (m, 3H), 1.90 (d, $J=1.5$ Hz, 3H, CH_3), 1.55 (d of t, $J_1=12.8$ Hz, $J_2=5.1$ Hz, 1H), 1.33–1.29 (m, 1H), 1.14 (ddd, $J_1=13.5$ Hz, $J_2=6.1$ Hz, $J_3=2.4$ Hz, 1H), 1.06 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 214.72 (CO), 147.21, 141.22, 138.29, 117.12, 114.80, 114.19 (six olefinic carbons), 54.68, 46.67, 45.56, 39.77, 37.21, 28.59, 28.34, 21.51, 20.82. HRMS (EI): Found 230.1666 (M^+); Calcd for $C_{16}H_{22}O$: 230.1670 (M^+).

4.1.4. 3-*syn*-Benzyl-3,5-dimethyl-7-*endo*-vinyl-bicyclo-[2.2.2]oct-5-en-2-one (8). Sodium hydride (150 mg of 60 w/w% suspension in oil, excess) was placed in a dry two necked flask and washed with dry petroleum ether, and tetrahydrofuran (1 mL) was added to it. A solution of ketone **9** (100 mg, 0.56 mmol) in tetrahydrofuran (3 mL) was

added slowly to the reaction mixture and the reaction mixture was refluxed for 1 h. Benzyl bromide (0.8 mL, excess) was then added to the reaction mixture and the reaction mixture was further refluxed for 8 h. The reaction mixture was then cooled and quenched by careful addition of water and it was filtered on a celite pad. The filtrate was then concentrated under vacuum. The residue was diluted with water and extracted with ether (3×5 mL). The combined extract was washed with water (5 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Removal of solvent and column chromatography [petroleum ether–ethyl acetate, (99:1)] of the residue on silica gel first gave a mixture (*syn–anti*) of alkylated products (120 mg, 80%). The *syn–anti* mixture was subjected to further chromatography on silver nitrate impregnated silica gel. Elution with petroleum ether–ethyl acetate (99:1) first gave the mixture of the *syn–anti* isomers followed by the *syn* isomer **8** (98 mg, 65%) as a colorless liquid.

IR (neat) ν_{max}: 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.23 (m, 3H, aromatic protons), 7.21–7.15 (m, 2H, aromatic protons), 5.74 (d, $J=6.2$ Hz, 1H, β proton of the β,γ-enone moiety), 5.63–5.50 (m, 1H, olefinic proton), 4.98 (d with structure, $J=17$ Hz, 1H, olefinic proton), 4.92 (d with structure, $J=9.8$ Hz, 1H, olefinic proton), 3.08 (dd, $J_1=6.4$ Hz, $J_2=1.6$ Hz, 1H), 2.84 (part of AB system, $J_{AB}=13.5$ Hz, 1H, benzylic methylene proton), 2.78–2.67 (m, 1H), 2.56 (m, 1H), 2.52 (part of an AB system partially merged with another multiplet, $J_{AB}=13.5$ Hz, 1H, benzylic methylene proton), 2.08 (d merged with m, $J=1.8$ Hz, 4H), 1.12 (ddd, $J_1=13.5$ Hz, $J_2=6.2$ Hz, $J_3=2.5$ Hz, 1H), 0.92 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.37 (CO), 147.86, 141.18, 137.43, 131.01, 128.02, 126.45, 117.63, 114.07 (aromatic and olefinic carbons), 54.98, 46.88, 45.67, 43.30, 39.58, 28.41, 21.68, 21.50. HRMS (EI): Found 266.1663 (M^+); Calcd for $C_{19}H_{22}O$: 266.1666 (M^+).

4.1.5. 1-But-3-enyl-1,4a-dimethyl-4a,5,8,8a-tetrahydro-1*H*-naphthalen-2-one (4). A solution of the compound **7** (100 mg, 0.43 mmol) in diphenyl ether (5 mL) was heated at 195 °C in a sealed tube for 12 h, after which it was brought to room temperature. The reaction mixture was chromatographed on silica gel. Elution with petroleum ether first gave diphenyl ether. Further elution with petroleum ether–ethyl acetate (98:2) furnished the Cope rearranged product **4** (46 mg, 46%) as a colorless liquid.

IR (neat) ν_{max}: 1668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, $J=10.2$ Hz, 1H, β proton of the α,β-enone moiety), 5.88 (d, $J=10.2$ Hz, 1H, α proton of the α,β-enone moiety), 5.81–5.72 (m, 2H, olefinic protons), 5.69–5.63 (m, 1H, olefinic proton), 5.02–4.88 (m, 2H, olefinic protons), 2.31–2.26 (m, 1H), 2.19–1.73 (m, 7H), 1.49–1.39 (m, 1H), 1.18 (s, 3H, CH_3), 1.0 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2 (CO), 158.6, 138.7, 126.04, 126.01, 123.3, 114 (six olefinic carbons), 48.4, 38.5, 36.2, 34.8, 34.2, 29.3, 29.1, 22.4, 21.2. Mass (*m/z*): 230 (M^+). ES-MS: *m/z* Found 231.1756 [$M^+ + H$]; Calcd for $C_{16}H_{22}O$: 231.1749 [$M^+ + H$].

4.1.6. 1,4a-Dimethyl-1-(3-oxo-butyl)-4a,5,8,8a-tetrahydro-1*H*-naphthalen-2-one (5). $PdCl_2$ (3 mg), cuprous chloride (7 mg) and water (0.1 mL) were taken in DMF (0.1 mL) and oxygen was bubbled into the reaction mixture for 20 min. A solution of the compound **4** (8 mg, 0.034 mmol) in DMF (0.2 mL) was added to the reaction mixture and the contents were stirred at room temperature in an oxygen atmosphere. After 14 h the reaction mixture was quenched with 10% HCl and it was extracted with ether (3×4 mL). The combined organic layer was washed with brine (3 mL) and dried over anhydrous sodium sulphate. Removal of solvent followed by chromatography [petroleum ether–ethyl acetate (90:10)] of the residue furnished the diketone **5** (6 mg, 70%) as a colorless liquid.

IR (neat) ν_{max}: 1714, 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, $J=10$ Hz, 1H, β proton of α,β-enone moiety), 5.88 (d, $J=10$ Hz, 1H, α proton of the α,β-enone moiety), 5.75 (m, 1H, olefinic proton), 5.66 (m, 1H, olefinic proton), 2.31–2.22 (m, 3H), 2.18–2.06 (s merged with m, total 6H), 1.98–1.93 (m, 1H), 1.88 (d, $J=8$ Hz, 1H), 1.74–1.64 (m merged with signal due to H_2O present in $CDCl_3$, 1H), 1.18 (s, 3H, CH_3), 1.03 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.71 (CO), 204.00 (CO), 159.05, 125.90, 125.74, 123.17 (four olefinic carbons), 47.98, 39.34, 39.28, 34.76, 34.32, 30.64, 29.87, 29.18, 22.52 and 20.80. Mass (*m/z*): 246 (M^+). ES-MS: *m/z* Found 247.1690 [$M^+ + H$]; Calcd for $C_{16}H_{22}O_2$: 247.1698 [$M^+ + H$].

4.1.7. 1-Benzyl-1,4a-dimethyl-4a,5,8,8a-tetrahydro-1*H*-naphthalen-2-one (6). A solution of the compound **8** (75 mg, 0.28 mmol) in diphenyl ether (4 mL) was heated at 195 °C in a sealed tube for 10 h, after which it was brought to room temperature. The reaction mixture was chromatographed on silica gel. Elution with petroleum ether first gave diphenyl ether. Further elution with petroleum ether–ethyl acetate (98:2) furnished the Cope rearranged product **6** (36 mg, 48%) as a solid.

Mp 90–92 °C. IR (film) ν_{max}: 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.11 (m, 3H, aromatic protons), 7.06–7.03 (m, 2H, aromatic protons), 6.63 (d, $J=10$ Hz, 1H, β proton of α,β-enone moiety), 5.82 (d merged with multiplet, $J=10$ Hz, 2H, olefinic protons), 5.70–5.63 (m, 1H, olefinic proton), 3.52 (part of an AB system, $J_{AB}=13.5$ Hz, 1H,), 2.55 (part of an AB system, $J_{AB}=13.5$ Hz, 1H), 2.29–2.24 (m, 2H), 2.11 (part of an AB system, $J_{AB}=18$ Hz, 1H), 1.95–1.84 (multiplet of part of an AB system, $J_{AB}=18$ Hz, 2H), 1.11 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.94 (CO), 159.41, 138.80, 130.36, 128.18, 126.29, 126.22, 126.14, 123.50 (aromatic and olefinic carbons), 50.83, 43.05, 37.87, 35.20, 34.30, 28.75, 23.14, 21.61. HRMS (EI): Found 266.1670 (M^+); Calcd for $C_{19}H_{22}O$: 266.1666 (M^+).

Acknowledgements

We thank the DST, New Delhi for continued financial support. Thanks are due to RSIC, IIT Bombay for spectral data. One of us (SRI) is grateful to CSIR, New Delhi for a fellowship.

References and notes

1. (a) Anderson, J. C.; Blake, A. J.; Graham, J. P.; Wilson, C. *Org. Bioorg. Chem.* **2003**, *1*, 2877. (b) Diaz, S.; Cuesta, J.; Gonzalez, A.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400. (c) Toro, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847. (d) Jung, M. E.; Piizzi, G. *J. Org. Chem.* **2003**, *68*, 2572. (e) Kim, K.; Maharoof, U. S. M.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777. (f) Tokoroyama, T. *Synthesis* **2000**, *5*, 611 and references cited therein.
2. (a) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Org. Lett.* **1999**, *1*, 1547. (b) Banwell, M. G.; Dupuche, J. R. *J. Chem. Soc., Chem. Commun.* **1996**, 869. (c) Piers, E.; Breau, L. M.; Han, Y.; Plourde, G. L.; Yeh, W. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 963. (d) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (e) Sammes, P. G.; Street, L. J.; Whitby, R. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 281. (f) Jackson, W. P.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1516.
3. Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243.
4. (a) King, T. J.; Rodrigo, S.; Wallwork, S. C. *J. Chem. Soc., D* **1969**, 683. (b) King, T. J.; Rodrigo, S. *J. Chem. Soc., Chem. Commun.* **1967**, 575.
5. Lopes, L. M. X.; Bolzani, V. Da. S.; Trevisan, L. M. V. *Phytochemistry* **1987**, *26*, 2781.
6. Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241.
7. (a) Liu, H.-J.; Shia, K.-S. *Tetrahedron* **1998**, *54*, 13449. (b) Liu, W.-C.; Liao, C.-C. *Synlett* **1998**, 912.
8. Singh, V.; Iyer, S. *J. Chem. Soc., Chem. Commun.* **2001**, 2578.
9. (a) Toyota, M.; Majo, V. J.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 1555. (b) Taber, D. F.; Wang, Y.; Stachel, S. J. *Tetrahedron Lett.* **1993**, *34*, 6209.
10. (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4547.
11. Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324.
12. (a) Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927. (b) Zhang, W.; Dowd, P. *Tetrahedron* **1993**, *49*, 1965.
13. Hill, R. K. In Comprehensive Organic Synthesis, Vol. 5; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; p 785.
14. Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 463–471

Synthesis and photochromic properties of substituted 3*H*-naphtho[2,1-*b*]pyrans

Christopher D. Gabbutt,[a] B. Mark Heron,[a,*] Alicia C. Instone,[a] Peter N. Horton[b] and Michael B. Hursthouse[b]

[a]*Department of Colour and Polymer Chemistry, The University of Leeds, Leeds LS2 9JT, UK*
[b]*Department of Chemistry, The University of Southampton, Highfield, Southampton SO17 1BJ, UK*

Received 30 July 2004; revised 24 September 2004; accepted 21 October 2004

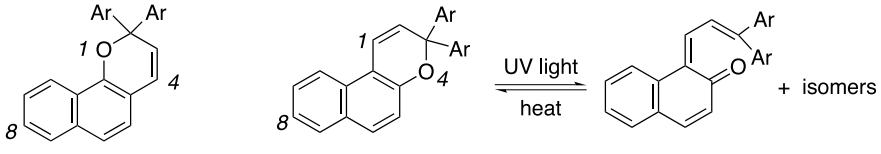
Abstract—The synthesis and spectroscopic properties of novel 3*H*-naphtho[2,1-*b*]pyrans are described. Subtle variation of the colour of the photo-generated merocyanine dyes derived from these naphthopyrans can be accomplished by controlling the steric interactions between a terminal pyrrolidine donor group and a proximal substituent.

1. Introduction

The isomeric naphthopyrans **1** and **2** are presently the systems of choice to impart a photochromic response into a host matrix. The ophthalmic sun lens industry makes extensive use of these isomers[1] and related fused carbocyclic[2] and heterocyclic[3] analogues in commercial lens formulations. Furthermore, the application of these isomers in other light induced colour change applications, e.g. fuel markers[4] and security markers,[5] continues to grow.

The mechanism of the reversible colour generation operates through a facile electrocyclic ring-opening of the 2*H*-pyran moiety to afford an equilibrium mixture of coloured geometrical isomers that gradually electrocyclise to the colourless pyran ring on cessation of irradiation (type T photochromism) (Scheme 1).[6] Recently, the formation of an additional photo-generated species, an allenylnaphthol, has been detected by NMR spectroscopy in this equilibrium mixture.[7]

The photochromic response of the 3*H*-naphtho[2,1-*b*]pyran system **2** is typified by the generation of vibrant yellow to purple colours that fade relatively rapidly on removal of the source of irradiation.[8] Unfortunately, this rapid fade of the photo-generated colour gives the overall impression to an observer of weak colour generation and may be perceived as an undesirable property of this naphthopyran isomer. The intensification of the photo-generated colour of **2** has been accomplished through the incorporation of an amino or methoxy group at the 6-position, e.g. **3**,[9] or alternatively, by introduction of a group into at least one of the *ortho* positions of one of the aryl groups attached to 3-C, e.g. **4**[10] and **5a**.[11] In the former compounds **3** the intensification of colour, termed hyperchromism, has been rationalised by a contribution from an additional resonance form that



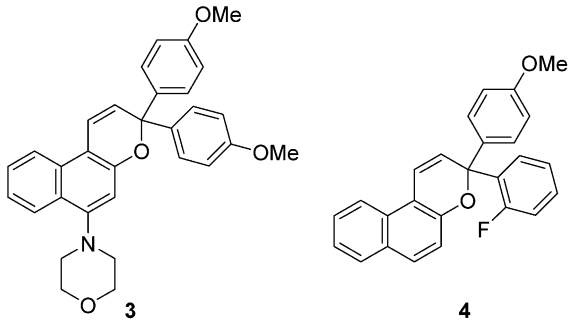
1 2*H*-naphtho[1,2-*b*]pyran — **2** 3*H*-naphtho[2,1-*b*]pyran

Scheme 1.

Keywords: Naphthopyrans; Photochromism; Steric effects; X-ray crystallography; Synthesis.
* Corresponding author. Tel.: +44 113 3432925; fax: +44 113 3432947; e-mail: b.m.heron@leeds.ac.uk

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.069

stabilises the ring-opened form (merocyanine dye). In the latter compounds **4** and **5a** the *ortho* substituent hinders the ring closure to the colourless pyran form. The net result of these electronic and steric effects is a photostationary state in which there is an appreciable concentration of the merocyanine valence tautomer, which results in intensification of the developed colour.



5a X = H, Y = halogen, Me, MeO
5b Y = H, X = halogen

We were interested in exploring photochromic naphthopyrans of type **5b** in which the influence of replacing an H atom with a bulky substituent adjacent to the terminal pyrrolidine unit could be investigated.

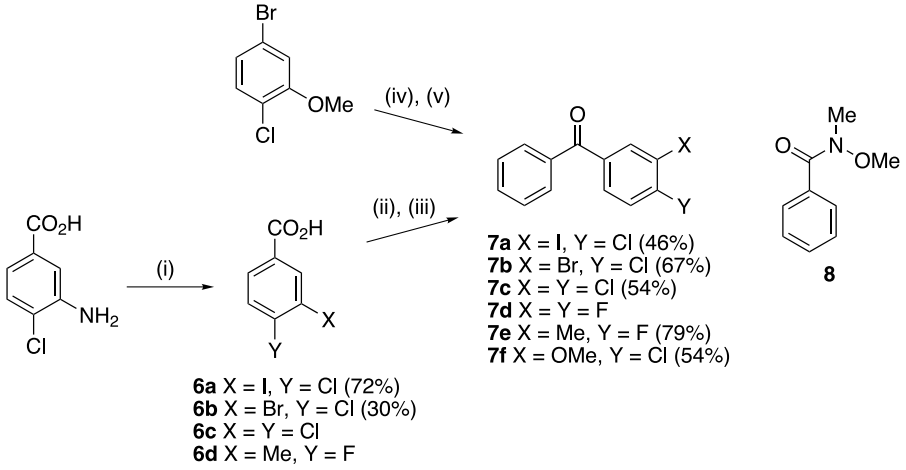
2. Results and discussion

The most versatile and efficient route to 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans relies upon the one pot, acid-catalysed reaction of a 2-naphthol with a 1,1-diarylprop-2-yn-1-ol;[12] a transformation that was developed from an original naphthopyran synthesis reported by Iwae and Ide in 1962.[13]

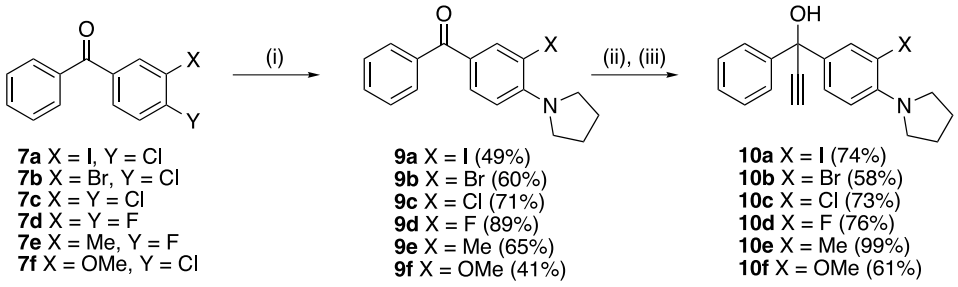
The 1,1-diarylprop-2-yn-1-ols can be conveniently accessed by addition of lithium trimethylsilylacetylide (LiTMSA) to a benzophenone with subsequent removal of the TMS group.[14] In this present work we required access to several new benzophenones each with a pyrrolidine ring at 4-C and a substituent at 3-C. Traditional Friedel–Crafts chemistry[15] was employed to construct the benzophenone from benzene and an appropriately substituted 4-halogenobenzoyl chloride. Nucleophilic displacement of the activated halogen with pyrrolidine was then investigated. Chlorobenzoic acids **6a**,**b** were readily obtained from 3-amino-4-chlorobenzoic acid using diazonium salt methodology.[16] Treatment of **6a**,**b** with thionyl chloride gave the requisite acid chlorides which were used directly to obtain the benzophenones **7a**,**b**, respectively. The acid chlorides derived from commercial benzoic acids **6c**,**d** were similarly converted into the respective benzophenones **7c**,**e** (Scheme 2). 4-Chloro-3-methoxybenzophenone **7f** was accessed by a different strategy involving addition of the Grignard reagent derived from 2-chloro-5-bromoanisole to the Weinreb amide **8**.[17]

The nucleophilic displacement of the activated halogen in the benzophenones **7** was investigated. Pyrrolidine (bp 88 °C) was the amine of choice used in this study since it is an excellent donor group[18] that provides a large bathochromic shift in λ_{max} of the photogenerated isomers.[11] Furthermore, pyrrolidine is highly nucleophilic and less volatile than other secondary amines with similar donor properties, e.g. diethylamine (bp 55 °C); a feature which facilitates the nucleophilic displacement reaction. Heating the benzophenones **7** in an excess of pyrrolidine effected the smooth formation of the 4-pyrrolidinobenzophenones **9a–f** in 41–89% yield after purification (Scheme 3). The reaction time was markedly influenced by the nature of the 3-substituent: with the difluorobenzophenone **7d** showing high conversion to **9d** in ca. 2 h whilst the 3-methoxy analogue **7f** required 4 days to afford **9f** in only 41% yield. Clearly the efficiency of the S_NAr reaction is decreased by the electron donating effect of the *ortho* methoxy group in **7f**.

The benzophenones **9** were efficiently transformed into the



Scheme 2. Reagents: (i) concd HCl, $NaNO_2$, H_2O, 0 °C then either CuBr or KI and heat; (ii) $SOCl_2$, heat; (iii) $AlCl_3$, PhH, heat; (iv) Mg, anhyd. Et_2O, heat; (v) amide **8**, anhyd. Et_2O, heat then aqueous HCl.



7a X = I, Y = Cl
7b X = Br, Y = Cl
7c X = Y = Cl
7d X = Y = F
7e X = Me, Y = F
7f X = OMe, Y = Cl

9a X = I (49%)
9b X = Br (60%)
9c X = Cl (71%)
9d X = F (89%)
9e X = Me (65%)
9f X = OMe (41%)

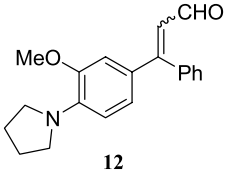
10a X = I (74%)
10b X = Br (58%)
10c X = Cl (73%)
10d X = F (76%)
10e X = Me (99%)
10f X = OMe (61%)

Scheme 3. Reagents: (i) pyrrolidine, heat; (ii) LiTMSA, anhyd. THF, 0 °C—RT; (iii) KOH, MeOH then AcOH.

prop-2-yn-1-ols **10** on reaction with an excess of LiTMSA which was derived from *n*-butyllithium and trimethylsilylacetylene. Removal of the TMS group from the initial adduct was accomplished in the same flask by addition of methanolic KOH (2 equiv). Yields for this conversion are typically high (58–99%); though the alkynol can be markedly sensitive to over acidification with AcOH during work-up resulting in the formation of intractable multi-component tars.

The naphthopyrans **11a–f** were obtained on heating the propynols **10** with 2-naphthol in toluene in the presence of acidic alumina (Scheme 4). The ^{1}H NMR spectra of **11** displayed a doublet at $\sim\delta$ 6.2 with a coupling constant of 10 Hz characteristic of 2-H in 3*H*-naphtho[2,1-*b*]pyrans.[12,19] The doublet for 1-H was obscured by the aromatic protons, however, 2D ^{1}H–^{1}H COSY experiments on a range of **11** (e.g., Fig. 1 for **11d**) revealed that 3-H resonated at δ 7.3.

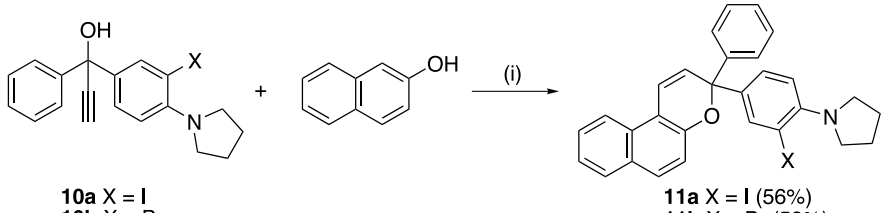
Naphthopyrans **11e** (24%) and **11f** (16%) were isolated in significantly lower yields compared with those recorded for **11a–d** (ca. 60%). Interestingly, a significant amount of a by-product was isolated from the reaction between 2-naphthol and **10f**. This material, which darkened on standing in air, was characterised as a mixture of geometrical isomers of the α,β-unsaturated aldehyde **12**. The ^{1}H NMR spectrum of this compound displayed a doublet at δ 9.60 (minor isomer) and at δ 9.36 (major isomer) with coupling constants of 8.0 and 8.2 Hz, respectively, which are assigned to the aldehyde proton of each isomer. From the signals for the methoxy groups at δ 3.82 (minor) and δ 3.73 (major), the isomer ratio is 1.0:4.2.



12

We have previously observed the formation of such aldehydes[12] as by-products from the acid-catalysed reaction between naphthols and prop-2-yn-1-ols and have rationalised their formation by either a Meyer–Schuster[20] or Rupe rearrangement.[21]

The spectroscopic data (Table 1) obtained for the naphthopyrans (**11a–h**) merit some comment. It is apparent from these data that as the size of the substituent X increases λ_{max} gradually decreases until a limit where X=Br (**11b**). Replacement of the bromine atom with the larger iodine atom (**11a**) has a negligible influence on λ_{max}. We have attributed this gradual hypsochromic shift to decreasing conjugation between the pyrrolidine donor unit and the remaining chromophore. This diminished conjugation arises as a consequence of torsion of the pyrrolidine unit about the C_{phenyl}–N bond to alleviate steric pressure exerted by the proximal X group on the *N*-methylene units of the pyrrolidine ring. These results compare favourably with literature data for a series of 4-aminophenylazo dyes (e.g., **13a**,**b**) where similar hypsochromic shifts in λ_{max} are noted when a terminal dimethylamino function is crowded by adjacent methyl group.[22] A theoretical account of these steric effects in azo dyes has been presented.[23] Interestingly, the effect of congestion about a terminal donor group in triarylmethine dyes is complex with both bathochromic and



10a X = I
10b X = Br
10c X = Cl
10d X = F
10e X = Me
10f X = OMe

11a X = I (56%)
11b X = Br (58%)
11c X = Cl (64%)
11d X = F (68%)
11e X = Me (24%)
11f X = OMe (16%)
11g X = H

Scheme 4. Reagents: (i) acidic alumina, PhMe, heat.

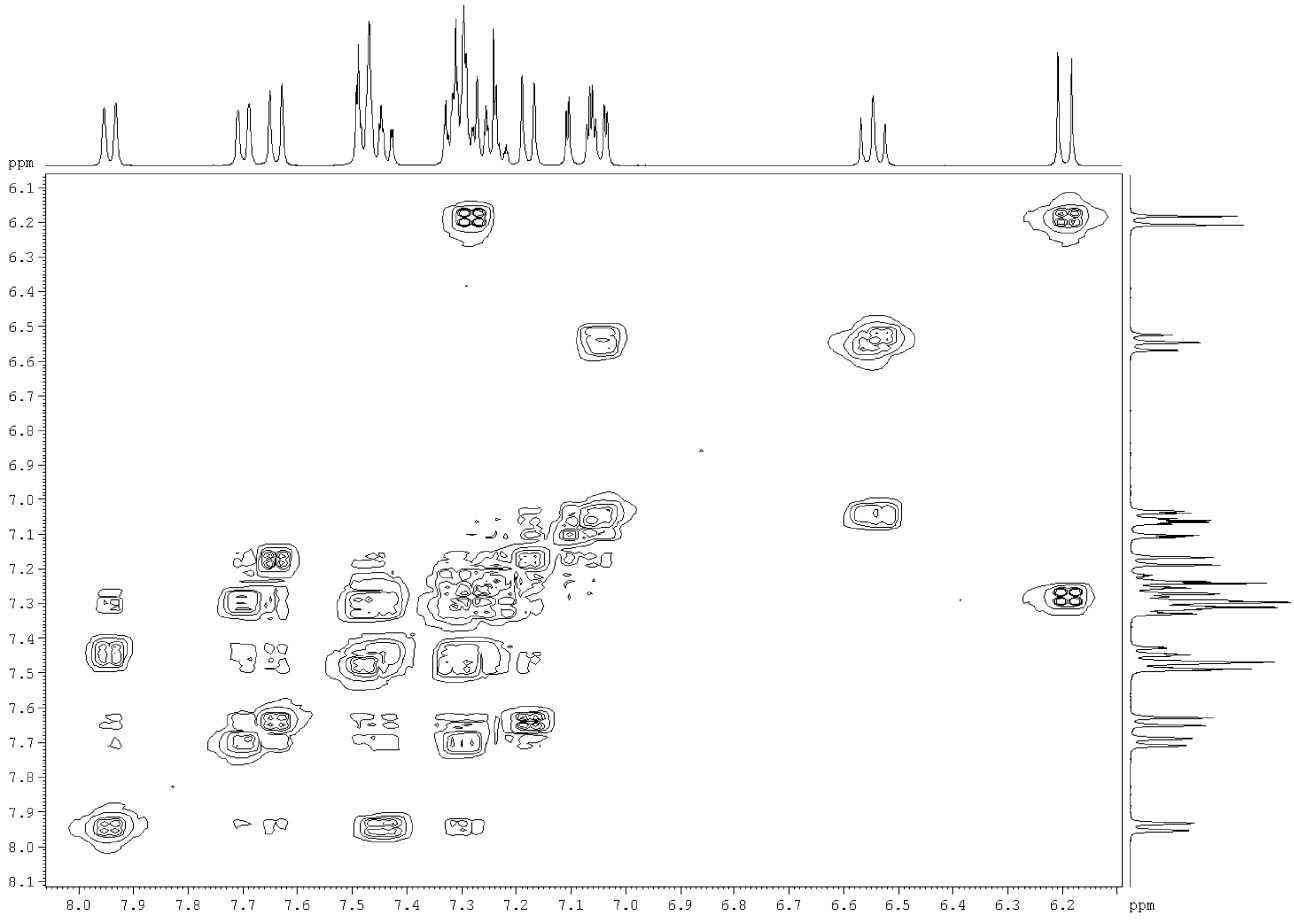
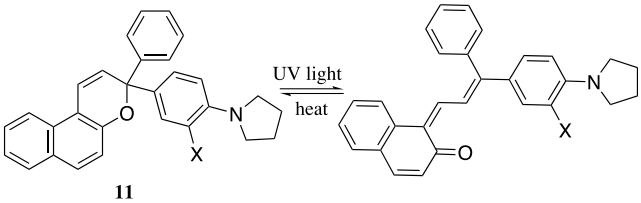


Figure 1. ^{1}H–^{1}H COSY NMR spectrum of **11d**.

hypsochromic shifts in λ_{max} noted.[24] We believe that the twist of the pyrrolidine unit is maximised when X=Br and that no further reduction in steric congestion by twisting can be achieved. It is noteworthy that the position of λ_{max} for **11e**, where X=Me, is comparable with that for **11c**; this feature is in accord with observations that a chlorine atom and a methyl group have similar spatial requirements.[25] λ_{max} for **11f**, with an *ortho* methoxy substituent, is apparently at odds with the observed trend. However, previous results would suggest that a methoxy group is not as spatially demanding as a methyl group,[11] but is significantly more electron donating. In this instance we suggest that the reduced conjugation of the pyrrolidine unit induced by twisting to minimise crowding with the adjacent methoxy group is countered by the donating power of the methoxy unit which, although located in a non conjugating site, is

Table 1. Spectroscopic data for naphthopyrans **11**



11

Entry	X	λ_{max} (nm)	$t_{½}$ (s)
11a	I	494	5
11b	Br	493	4
11c	Cl	513	4
11d	F	529	4
11e	Me	517	3
11f	OMe	557	5
11h	H	538	5

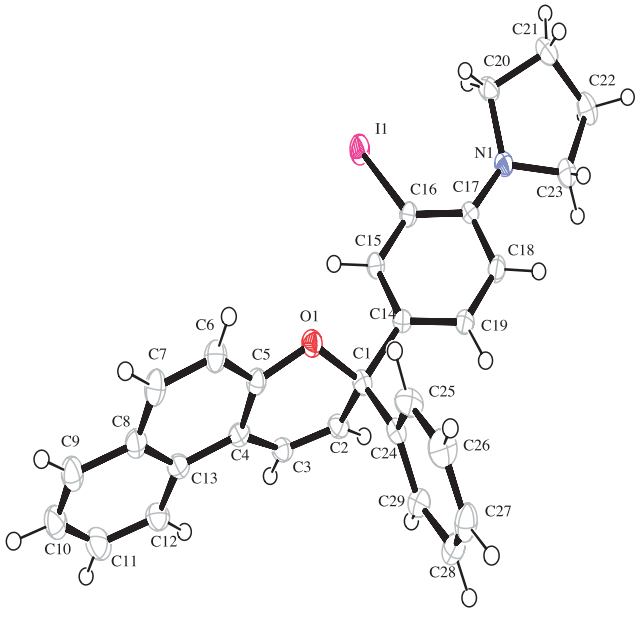


Figure 2. X-ray crystallographic structure of compound **11a**.

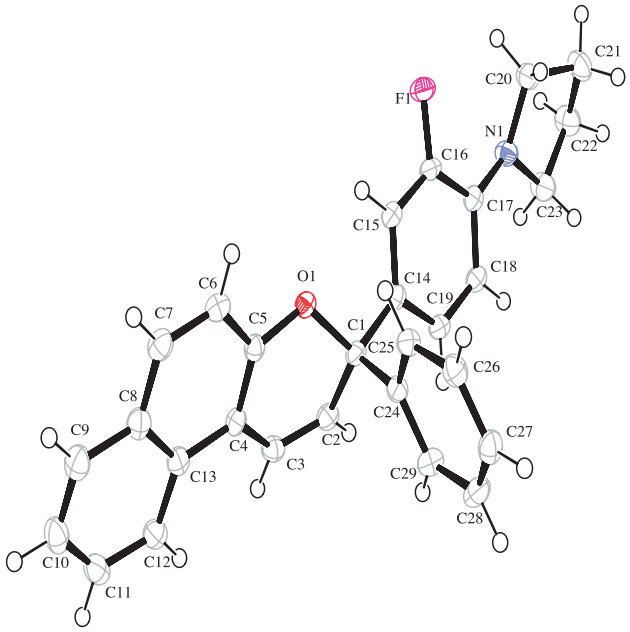
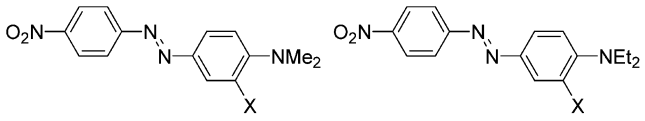


Figure 3. X-ray crystallographic structure of compound **11d**.

significant. This balance of properties has been observed for azo dye **14a** which has λ_{max} virtually identical with its methoxy substituted analogue **14b**.[26]



13a X = H, λ_{max} = 480 nm
13b X = Me, λ_{max} = 422 nm

14a X = H, λ_{max} = 490 nm
14b X = MeO, λ_{max} = 492 nm

X-ray crystal structures of naphthopyrans **11a** (X=I)[27] and **11d** (X=F)[28] are presented in Figures 2 and 3, respectively.

Comparative space filling model representations of **11a** and **11d** showing the steric interactions between the halogen substituent and the pyrrolidine units are provided in Figure 4. These representations confirm an increasing steric interaction between the halogen and pyrrolidine ring as the size of the halogen increases. If we consider the situation in the coloured ring-opened form, where there is appreciable N–C_{aryl} double bond character in the excited state, then such steric interactions are more pronounced and significant twisting about the N–C_{aryl} bond must occur resulting in diminished conjugation and a hypsochromic shift in λ_{max}. Hallas has discussed the influence of cyclic terminal groups and associated steric interactions on λ_{max} of aminoazobenzene dyes.[18]

The half-life, $t_{½}$, is the time taken for the intensity of the absorbance to fade to half its original value recorded under steady state conditions. It is interesting to note that whilst variation of the X group changes λ_{max}, only minor variations in the $t_{½}$ values are noted. This is somewhat surprising since it has been established that the electronic properties of the group located at the *para* position of the geminal aryl rings influence the persistence of the ring-opened form, with powerful electron donor groups resulting in decreased $t_{½}$ values.[6] Presumably, $t_{½}$ is less sensitive than λ_{max} to the subtle variations in the electron donating properties of the terminal pyrrolidine ring induced by steric interactions.

In summary, a series of novel substituted photochromic 3*H*-naphtho[2,1-*b*]pyrans **11** have been accessed from the reaction between 2-naphthol and a prop-2-yn-1-ol **10**. The colour of the reversibly photo-generated merocyanine dyes has been manipulated through control of steric interactions between a terminal pyrrolidine donor function and neighbouring substituents. As the magnitude of these steric interactions increase λ_{max} is shifted hypsochromically until a maximum interaction is observed between the pyrrolidine

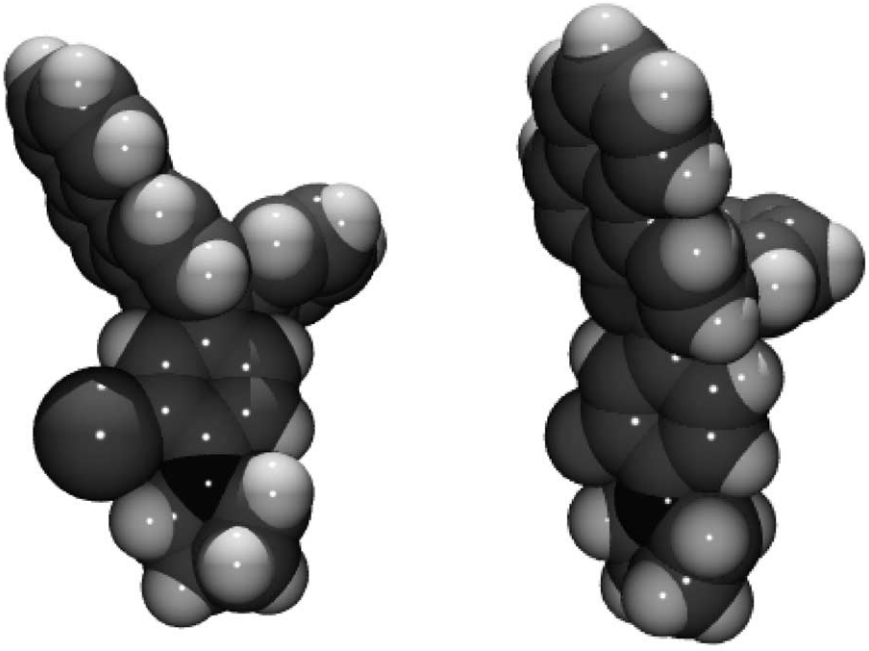


Figure 4. Space filling representations of **11a** (left) and **11d** (right).

methylene and a bromine atom. The data recorded for the electron donating methoxy group is at odds with the observed trend indicating that its electronic effect is significant despite it being located in a non-conjugating position. The rate of fade of the photo-generated colour is relatively insensitive to the subtle changes in electron donor group strength induced by steric interactions with an adjacent substituent.

3. Experimental

3.1. General

Melting points were determined in capillary tubes and are uncorrected. Visible spectra were recorded for ca. 1×10^{-5} mol dm^{-3} solutions in spectroscopic grade toluene in 10 mm quartz cells at 20 °C using an Analytik Jena Specord S100 diode array spectrophotometer. Samples were irradiated to a steady state of absorbance using a Spectroline 8 W lamp (365 nm). Infrared spectra were recorded on a Perkin-Elmer 882 spectrophotometer in KBr discs unless otherwise specified. NMR spectra were recorded on a Bruker Avance 400 MHz instrument for solutions in $CDCl_3$ unless otherwise stated; J values are given in Hz. Flash chromatography separations were performed on chromatography silica (40–60 μm particle size distribution) as supplied by Fluorochem Ltd.

3.2. Preparation of 3-substituted-4-chlorobenzoic acids (6)

A solution sodium nitrite (102 mmol) in water (15 ml) was added slowly to a cold (0 °C) stirred solution of 3-amino-4-chlorobenzoic acid (100 mmol) in water (250 ml) and conc. HCl (75 ml). On completion of the addition the solution was stirred for 5 min and then a solution of the appropriate halide (102 mmol) in water (25 ml) was added. The cooling bath was removed and the mixture stirred for a further 5 min before carefully heating the suspension to 90 °C for 10 min. The mixture was cooled to room temperature and the precipitated solid collected and washed with water ($3\times$ 50 ml). The crude product was recrystallised from ethanol and water. The following acids were prepared in this way:

3.2.1. 4-Chloro-3-iodobenzoic acid, (6a). From potassium iodide as an off-white powder (72%), mp 215–217 °C (Lit. mp 216–217 °C[29]); δ_H($CDCl_3$, d_6-DMSO) 3.67 (1H, bs, OH), 7.69 (1H, d, $J=8.3$ Hz, 5-H), 7.91 (1H, dd, $J=8.3$, 2.0 Hz, 6-H), 8.00 (1H, d, $J=2.0$ Hz, 2-H).

3.2.2. 3-Bromo-4-chlorobenzoic acid, (6b). From copper(I) bromide as an off-white powder (30%), mp 214–216 °C (Lit. mp 215–216 °C[29]); δ_H($CDCl_3$, d_6-DMSO) 3.55 (1H, bs, OH), 7.71 (1H, d, $J=8.3$ Hz, 5-H), 7.82 (1H, dd, $J=8.3$, 1.6 Hz, 6-H), 8.00 (1H, d, $J=1.6$ Hz, 2-H).

3.3. Preparation of 3-substituted-4-halogenobenzophenones (7)

The 3-substituted-4-halogenobenzoic acid (26 mmol), thionyl chloride (40 mmol) and one drop of *N*,*N*-dimethylformamide were refluxed for 2 h. The excess thionyl chloride was removed from the cooled reaction mixture and the remaining acid chloride was dissolved in benzene (130 mmol). Aluminium chloride (29 mmol) was added portion-wise over ca. 10 min to this solution and the resulting suspension was refluxed for ca. 1 h. The reaction mixture was poured onto ice (300 g) and conc. HCl (50 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 ml). The combined organic phases were washed with 5% aqueous NaOH solution (50 ml), water (3×50 ml) and dried (anhyd. Na_2SO_4). Removal of the solvent gave the crude benzophenones that were recrystallised from hexane and ethyl acetate. The following benzophenones were obtained by this protocol:

3.3.1. 4-Chloro-3-iodobenzophenone, (7a). From 4-chloro-3-iodobenzoic acid as pale brown microcrystals, (46%), mp 96–98 °C, ν_{max} 1651 cm^{-1}; δ_H 7.50 (2H, m, Ar-H), 7.55 (1H, d, $J=8.3$ Hz, 5-H), 7.62 (1H, m, Ar-H), 7.70 (1H, dd, $J=8.3$, 2.0 Hz, 6-H), 7.76 (2H, m, Ar-H), 8.28 (1H, d, $J=$ 2.0 Hz, 2-H). (Found: C, 45.93; H, 2.39 $C_{13}H_8ClIO$ requires C, 45.58; H, 2.35%).

3.3.2. 3-Bromo-4-chlorobenzophenone, (7b). From 3-bromo-4-chlorobenzoic acid as pale brown microcrystals, (67%), mp 89–91 °C (lit. mp 109 °C[30]); δ_H 7.52 (2H, m, Ar-H), 7.57 (1H, m, Ar-H), 7.63 (2H, m, Ar-H), 7.78 (2H, m, Ar-H), 7.90 (1H, d, $J=1.9$ Hz, 2-H).

3.3.3. 3,4-Dichlorobenzophenone, (7c). From 3,4-dichlorobenzoyl chloride as off-white microcrystals, (54%), mp 102–104 °C (lit. mp 101.5–102.0 °C[31]); δ_H 7.51 (2H, m, Ar-H), 7.57 (1H, d, $J=8.3$ Hz, 5-H), 7.63 (2H, m, Ar-H), 7.77 (2H, m, Ar-H), 7.89 (1H, d, $J=1.9$ Hz, 2-H).

3.3.4. 4-Fluoro-3-methylbenzophenone, (7e). From 4-fluoro-3-methylbenzoyl chloride as cream microcrystals, (79%), mp 50–52 °C (lit. mp 52–54 °C[32]); δ_H 2.34 (3H, s, CH_3), 7.09 (1H, m, Ar-H), 7.49 (2H, m, Ar-H), 7.58 (2H, m, Ar-H), 7.63 (1H, m, Ar-H), 7.77 (2H, m, Ar-H).

3.4. Preparation of 4-chloro-3-methoxybenzophenone (7f)

A solution of 4-bromo-2-chloroanisole (23 mmol) in anhyd. diethyl ether (20 ml) was added dropwise to magnesium turnings (23 mmol) in anhyd. diethyl ether (20 ml). After ca. 1/3 of the solution of 4-bromo-2-chloroanisole had been added one crystal of iodine was added and the mixture stirred. Upon initiation of the reaction mixture the remaining solution of 4-bromo-2-chloroanisole was added at such a rate so as to maintain a steady reflux. On completion of the addition the suspension was refluxed for a further 1 h and then cooled to room temperature. A solution of *N*-methoxy-*N*-methylbenzamide (18 mmol) in anhyd. diethyl ether (20 ml) was added dropwise via syringe to this solution of the Grignard reagent so as to maintain a constant reflux. On completion of the addition the mixture was refluxed for a further 2 h and then left to stand overnight at room temperature. The mixture was poured onto ice ($\sim$200 g) and aqueous HCl ($\sim$100 ml, 2 M) and the organic layers separated. The aqueous layer was extracted

with ethyl acetate (3×100 ml) and the combined organic phases were washed with water (3×50 ml), dried (anhyd. Na_2SO_4) and evaporated to afford a sticky gum. Elution of this crude product from silica using 40% ethyl acetate/hexane gave the title compound, **7f**, as cream microcrystals, (54%), mp 52–54 °C, ν_{max} 1650, 1574 cm^{-1}; δ_H 3.97 (3H, s, OCH_3), 7.27 (1H, dd, J=8.1, 1.9 Hz, 6-H), 7.46 (2H, m, Ar-H), 7.50 (2H, m, Ar-H), 7.61 (1H, m, Ar-H), 7.79 (2H, m, Ar-H). (Found: C, 67.91; H, 4.40; $C_{14}H_{11}O_2Cl$ requires C, 68.16; H, 4.49%).

3.5. Preparation of 3-substituted-4-pyrrolidinobenzophenones (9)

The halogenobenzophenone (23 mmol) was dissolved in pyrrolidine (140 mmol) and stirred at room temperature for 10 min and then refluxed until TLC examination of the reaction mixture indicated that no further changes were apparent (2 h–4 days). The cooled mixture was poured into water (300 ml) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 ml) and the combined organic phases were washed with water (6×50 ml), dried (anhyd. Na_2SO_4) and evaporated to afford the crude product. Purification was effected by either flash chromatography or by repeated recrystallisation from hexane and ethyl acetate. The following benzophenones were prepared in this manner:

3.5.1. 3-Iodo-4-pyrrolidinobenzophenone, (9a). From 4-chloro-3-iodobenzophenone as yellow microcrystals, (49%), mp 43–45 °C, ν_{max} 1640, 1573 cm^{-1}; δ_H 1.98 (4H, m, $(CH_2)_2$), 3.56 (4H, m, $N(CH_2)_2$), 6.73 (1H, d, J=8.7 Hz, 5-H), 7.47 (2H, m, Ar-H), 7.54 (1H, m, Ar-H), 7.70 (3H, m, Ar-H), 8.35 (1H, d, J=2.1 Hz, 2-H). (Found: $[M+H]^+$ 378.0353, $C_{17}H_{16}INO$ requires $[M+H]^+$ 378.0349).

3.5.2. 3-Bromo-4-pyrrolidinobenzophenone, (9b). From 3-bromo-4-chlorobenzophenone as yellow microcrystals, (60%), mp 59–60 °C, ν_{max} 1644, 1589 cm^{-1}; δ_H 1.97 (4H, m, $(CH_2)_2$), 3.60 (4H, m, $N(CH_2)_2$), 6.75 (1H, d, J=8.8 Hz, 5-H), 7.47 (2H, m, Ar-H), 7.53 (1H, m, Ar-H) 7.64 (1H, m, Ar-H), 7.72 (2H, m, Ar-H), 7.82 (1H, d, J=2.1 Hz, 2-H). (Found: C, 61.51; H, 4.69; N, 4.06; $C_{17}H_{16}NOBr$ requires C, 61.83; H, 4.88; N, 4.24%).

3.5.3. 3-Chloro-4-pyrrolidinobenzophenone, (9c). From 3,4-dichlorobenzophenone as yellow microcrystals, (71%), mp 54–56 °C, ν_{max} 1635, 1589 cm^{-1}; δ_H 1.99 (4H, m, $(CH_2)_2$), 3.60 (4H, m, $N(CH_2)_2$), 6.75 (1H, d, J=8.7 Hz, 5-H), 7.47 (2H, m, Ar-H), 7.55 (1H, m, Ar-H) 7.64 (1H, dd, J=8.7, 2.0 Hz, 6-H), 7.72 (2H, m, Ar-H), 7.82 (1H, d, J=2.1 Hz, 2-H). (Found: C, 71.04; H, 5.68; N, 4.90; $C_{17}H_{16}NOCl$ requires C, 71.45; H, 5.64; N, 4.90%).

3.5.4. 3-Fluoro-4-pyrrolidinobenzophenone, (9d). From 3,4-difluorobenzophenone as yellow microcrystals, (89%), mp 127–129 °C, ν_{max} 1632, 1595 cm^{-1}; δ_H 1.99 (4H, m, $(CH_2)_2$), 3.54 (4H, m, $N(CH_2)_2$), 6.57 (1H, m, 5-H), 7.45 (2H, m, Ar-H), 7.54 (3H, m, Ar-H) 7.70 (2H, m, Ar-H). (Found: C, 75.64; H, 6.07; N, 5.19; $C_{17}H_{16}NOF$ requires C, 75.82; H, 5.99; N, 5.20%).

3.5.5. 3-Methyl-4-pyrrolidinobenzophenone, (9e). From 4-fluoro-3-methylbenzophenone as yellow microcrystals, (65%), mp 78–81 °C, ν_{max} 1635, 1597, 1589 cm^{-1}; δ_H 1.97 (4H, m, $(CH_2)_2$), 2.16 (3H, s, CH_3), 3.43 (4H, m, $N(CH_2)_2$), 6.71 (1H, d, J=8.6 Hz, 5-H), 7.45 (2H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.59 (1H, dd, J=8.6, 2.0 Hz, 6-H), 7.66 (1H, m, Ar-H), 7.73 (2H, m, Ar-H). (Found: C, 81.45; H, 7.21; N, 5.27; $C_{18}H_{19}NO$ requires C, 81.48; H, 7.22; N, 5.28%).

3.5.6. 3-Methoxy-4-pyrrolidinobenzophenone, (9f). From 4-chloro-3-methoxybenzophenone as a viscous orange oil, (41%), bp 278 °C at 0.4 mmHg; ν_{max} 1634, 1584 cm^{-1}; δ_H 1.94 (4H, m, $(CH_2)_2$), 3.52 (4H, m, $N(CH_2)_2$), 3.85 (3H, s, OCH_3), 6.54 (1H, d, J=8.4 Hz, 5-H), 7.32 (1H, dd, J=8.4, 2.0 Hz, 6-H), 7.45 (2H, m, Ar-H), 7.51 (2H, m, Ar-H), 7.73 (2H, m, Ar-H). (Found: $[M+H]^+$ 282.1485; $C_{18}H_{19}NO_2$ requires $[M+H]^+$ 282.1489).

3.6. Preparation of prop-2-yn-1-ols (10)

n-Butyllithium (1.6 M in hexanes) (15 mmol) was added slowly via syringe to a cold (−10 °C), stirred solution of trimethylsilylacetylene (15 mmol) in anhyd. tetrahydrofuran (60 ml) under nitrogen atmosphere. On completion of the addition (ca. 5 min) the cold solution was allowed to stir for 1 h. The benzophenone (12 mmol) was added in a single portion and the mixture stirred until TLC examination of the reaction mixture indicated that none of the benzophenone remained (ca. 3 h). The reaction mixture was re-cooled to 0 °C and a solution of methanolic potassium hydroxide (from potassium hydroxide (31 mmol) in methanol (20 ml) was added in a single portion. The cooling bath was then removed and the mixture warmed to room temperature, after ca. 15 min TLC examination indicated that deprotection was complete. The mixture was acidified to pH ~7 using glacial acetic acid and then poured into water (500 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 ml). The organic phases were combined, washed with water (3×50 ml) and dried (anhyd. Na_2SO_4). Removal of the solvent gave the prop-2-yn-1-ol that was sufficiently pure for subsequent use. Analytically pure samples were obtained by recrystallisation from hexane and ethyl acetate. The following alkynols were obtained in this way:

3.6.1. 1-(3-Iodo-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10a). From 3-iodo-4-pyrrolidinobenzophenone as pale brown microcrystals, (74%), mp 86–89 °C, ν_{max} 3285, 1602 cm^{-1}; δ_H 1.77 (4H, m, $(CH_2)_2$), 2.73 (1H, s, alkynic-H), 2.77 (1H, bs, OH), 3.14 (4H, m, $N(CH_2)_2$), 6.68 (1H, d, J=8.6 Hz, 5-H), 7.18 (4H, m, Ar-H), 7.44 (2H, m, Ar-H), 7.93 (1H, d, J=2.2 Hz, 2-H). (Found: C, 56.41; H, 4.10; N, 3.17; $C_{19}H_{18}NOI$ requires C, 56.59; H, 4.50; N, 3.47%).

3.6.2. 1-(3-Bromo-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10b). From 3-bromo-4-pyrrolidinobenzophenone as pale brown microcrystals, (58%), mp 86–89 °C, ν_{max} 3286, 1595 cm^{-1}; δ_H 1.77 (4H, m, $(CH_2)_2$), 2.72 (1H, s, alkynic-H), 2.77 (1H, bs, OH), 3.22 (4H, m, $N(CH_2)_2$), 6.66 (1H, d, J=8.6 Hz, 5-H), 7.15 (4H, m, Ar-H), 7.39 (1H, d, J=2.2 Hz, 2-H), 7.44 (2H, m, Ar-H). (Found: C, 63.64; H, 4.85; N, 3.91; $C_{19}H_{18}NOBr$ requires C, 64.06; H, 5.09; N, 3.93%).

3.6.3. 1-(3-Chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10c). From 3-chloro-4-pyrrolidinobenzophenone as an off-white powder, (73%), mp 93–95 °C, ν_{max} 3285, 1604 cm^{-1}; δ_H 1.91 (4H, m, $(CH_2)_2$), 2.82 (1H, bs, OH), 2.86 (1H, s, alkynic-H), 3.36 (4H, m, $N(CH_2)_2$), 6.79 (1H, d, $J=8.6$ Hz, 5-H), 7.30 (4H, m, Ar-H), 7.53 (1H, d, $J=2.3$ Hz, 2-H), 7.59 (2H, m, Ar-H). (Found: C, 72.85; H, 6.01; N, 4.47; $C_{19}H_{18}NOCl$ requires C, 73.19; H, 5.82; N, 4.49%).

3.6.4. 1-(3-Fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10d). From 3-fluoro-4-pyrrolidinobenzophenone as colourless microcrystals, (76%), mp 118–120 °C, ν_{max} 3281, 1571 cm^{-1}; δ_H 1.91 (4H, m, $(CH_2)_2$), 2.78 (1H, bs, OH), 2.84 (1H, s, alkynic-H), 3.35 (4H, m, $N(CH_2)_2$), 6.57 (1H, m, 2-H), 7.18 (2H, m, Ar-H), 7.27 (1H, m, Ar-H), 7.32 (2H, m, Ar-H), 7.58 (2H, m, Ar-H). (Found: C, 77.05; H, 6.22; N, 4.67; $C_{19}H_{18}NOF$ requires C, 77.27; H, 6.14; N, 4.74%).

3.6.5. 1-(3-Methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10e). From 3-methyl-4-pyrrolidinobenzophenone as pale brown microcrystals, (99%), mp 71–74 °C, ν_{max} 3285, 1600 cm^{-1}; δ_H 1.78 (4H, m, $(CH_2)_2$), 1.93 (1H, s, OH), 2.16 (3H, s, CH_3), 2.70 (1H, s, alkynic-H), 3.04 (4H, m, $N(CH_2)_2$), 6.64 (1H, d, $J=8.4$ Hz, 5-H), 7.15 (5H, m, Ar-H), 7.47 (2H, m, Ar-H). (Found: C, 82.41; H, 7.07; N, 4.59; $C_{20}H_{21}NO$ requires C, 82.44; H, 7.26; N, 4.81%).

3.6.6. 1-(3-Methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol, (10f). From 3-methoxy-4-pyrrolidinobenzophenone as a dark brown gum (61%) which decomposed on attempted purification, δ_H (crude) 1.89 (4H, m, $(CH_2)_2$), 2.07 (1H, bs, OH), 2.85 (1H, s, alkynic-H), 3.27 (4H, m, $N(CH_2)_2$), 3.79 (3H, s, OMe), 6.67 (1H, d, $J=8.2$ Hz, 5-H), 7.08 (2H, m, Ar-H), 7.34 (3H, m, Ar-H), 7.59 (2H, m, Ar-H).

3.7. Preparation of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans (11)

A stirred solution of 2-naphthol (3.3 mmol) and the prop-2-yn-1-ol (3.3 mmol) in toluene (40 ml) was warmed to 50 °C. Acidic alumina (2.5 g) was added and the mixture was refluxed until TLC examination indicated that none of the prop-2-yn-1-ol remained (ca. 1.5 h). The mixture was cooled to ~50 °C, filtered and the alumina was washed with hot toluene (2×20 ml). Removal of the toluene from the combined washings and filtrate gave a gum that was eluted from silica (40% ethyl acetate/hexane) to afford the naphthopyran. The following naphthopyrans were obtained using this protocol:

3.7.1. 3-(3-Iodo-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11a). From 1-(3-iodo-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale brown microcrystals, (56%), mp 123–126 °C, ν_{max} 1591 cm^{-1}; δ_H 1.86 (4H, m, $(CH_2)_2$), 3.23 (4H, m, $N(CH_2)_2$), 6.18 (1H, d, $J=9.9$ Hz, 2-H), 6.79 (1H, d, $J=8.5$ Hz, Ar-H), 7.23 (7H, m, Ar-H, 1-H), 7.46 (3H, m, Ar-H), 7.63 (1H, d, $J=8.8$ Hz, Ar-H), 7.69 (1H, d, $J=8.8$ Hz, Ar-H), 7.94 (2H, m, Ar-H, 10-H). (Found: M^+ 529.0906; C, 65.87; H, 4.79; N, 2.63; $C_{29}H_{24}INO$ requires M^+ 529.0897; C, 65.79; H, 4.57; N, 2.65%).

3.7.2. 3-(3-Bromo-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11b). From 1-(3-bromo-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as off-white microcrystals, (58%), mp 126–129 °C, ν_{max} 1605 cm^{-1}; δ_H 1.88 (4H, m, $(CH_2)_2$), 3.33 (4H, m, $N(CH_2)_2$), 6.19 (1H, d, $J=9.9$ Hz, 2-H), 6.75 (1H, d, $J=8.6$ Hz, Ar-H), 7.17 (2H, m, Ar-H, 1-H), 7.25 (5H, m, Ar-H), 7.43 (4H, m, Ar-H), 7.64 (1H, d, $J=8.8$ Hz, Ar-H), 7.69 (1H, d, $J=8.8$ Hz, Ar-H), 7.93 (1H, d, $J=8.5$ Hz, 10-H). (Found: M^+ 481.1028; C, 71.96; H, 5.41; N, 3.12; $C_{29}H_{24}^{79}BrNO$ requires M^+ 481.1036; C, 72.20; H, 5.01; N, 2.90%).

3.7.3. 3-(3-Chloro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11c). From 1-(3-chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals, (64%), mp 138–140 °C, ν_{max} 1605 cm^{-1}; δ_H 1.86 (4H, m, $(CH_2)_2$), 3.31 (4H, m, $N(CH_2)_2$), 6.18 (1H, d, $J=10.0$ Hz, 2-H), 6.74 (1H, d, $J=8.6$ Hz, Ar-H), 7.17 (2H, m, Ar-H, 1-H), 7.24 (5H, m, Ar-H), 7.43 (4H, m, Ar-H), 7.63 (1H, d, $J=8.8$ Hz, Ar-H), 7.69 (1H, d, $J=8.8$ Hz, Ar-H), 7.93 (1H, d, $J=8.4$ Hz, 10-H). (Found: $[M+H]^+$ 438.1623; C, 79.50; H, 5.60; N, 3.20; $C_{29}H_{24}^{35}ClNO$ requires $[M+H]^+$ 438.1624; C, 79.53; H, 5.52; N, 3.20%).

3.7.4. 3-(3-Fluoro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11d). From 1-(3-fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals, (68%), mp 167–169 °C, ν_{max} 1625 cm^{-1}; δ_H 1.88 (4H, m, $(CH_2)_2$), 3.32 (4H, m, $N(CH_2)_2$), 6.19 (1H, d, $J=10.0$ Hz, 2-H), 6.54 (1H, m, Ar-H), 7.07 (2H, m, Ar-H), 7.17 (1H, m, Ar-H), 7.24 (5H, m, Ar-H, 1-H), 7.47 (3H, m, Ar-H), 7.63 (1H, d, $J=8.8$ Hz, Ar-H), 7.69 (1H, d, $J=8.8$ Hz, Ar-H), 7.94 (1H, d, $J=8.4$ Hz, 10-H). (Found: $[M+H]^+$ 422.1922; C, 82.29; H, 5.84; N, 3.33; $C_{29}H_{24}NOF$ requires $[M+H]^+$ 422.1920; C, 82.64; H, 5.74; N, 3.32%).

3.7.5. 3-(3-Methyl-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11e). From 1-(3-methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as cream microcrystals, (24%), mp 111–114 °C, ν_{max} 1606, 1590 cm^{-1}; δ_H 1.89 (4H, m, $(CH_2)_2$), 2.27 (3H, s, CH_3), 3.16 (4H, m, $N(CH_2)_2$), 6.25 (1H, d, $J=10.0$ Hz, 2-H), 6.75 (1H, d, $J=8.4$ Hz, Ar-H), 7.11 (1H, m, Ar-H), 7.21 (2H, m, Ar-H, 1-H), 7.24 (2H, m, Ar-H), 7.30 (3H, m, Ar-H), 7.44 (1H, m, Ar-H), 7.49 (2H, m, Ar-H), 7.63 (1H, d, $J=8.8$ Hz, Ar-H), 7.69 (1H, d, $J=8.8$ Hz, Ar-H), 7.94 (1H, d, $J=8.5$ Hz, 10-H). (Found: M^+ 417.2088; C, 86.38; H, 6.50; N, 3.32; $C_{30}H_{27}NO$ requires M^+ 417.2087; C, 86.30; H, 6.52; N, 3.35%).

Two fractions were isolated from 1-(3-methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol and 2-naphthol.

3.7.6. Fraction 1. 3-(3-Methoxy-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran, (11f). As dark green microcrystals, (16%), mp 117–119 °C; δ_H 1.88 (4H, m, $(CH_2)_2$), 3.25 (4H, m, $N(CH_2)_2$), 3.74 (3H, s, OCH_3), 6.25 (1H, d, $J=10.0$ Hz, 2-H), 6.64 (1H, d, $J=8.3$ Hz, Ar-H), 6.86 (1H, dd, $J=8.3$ Hz, 1.8, Ar-H), 6.98 (1H, d, $J=1.6$ Hz, Ar-H), 7.19 (1H, d, $J=8.8$ Hz, Ar-H), 7.28 (5H, m, Ar-H, 1-H), 7.48 (3H, m, Ar-H), 7.64 (1H, d, $J=8.8$ Hz, Ar-H),

7.70 (1H, d, $J=8.0$ Hz, Ar-H), 7.95 (1H, d, $J=8.5$ Hz, 10-H). (Found: $[M+H]^+$ 434.2115; $C_{30}H_{27}NO_2$ requires $[M+H]^+$ 434.2114).

3.7.7. Fraction 2. 3-(3-Methoxy-4-pyrrolidinophenyl)-3-phenylprop-2-enal, (12). As an inseparable mixture of geometrical isomers (ratio 1.0:4.2), δ_H mixture 1.95 (8H, m, $(CH_2)_2$), 3.43 (8H, m, $N(CH_2)_2$), 3.73 (3H, s, OCH_3 (major)), 3.82 (3H, s, OCH_3 (minor)), 6.5–7.7 (18H, m, Ar-H and alkene-H), 9.36 (1H, d, $J=8.2$ Hz, aldehyde-H (major)) 9.60 (1H, d, $J=8.0$ Hz, aldehyde-H (minor)). (Found for mixture: $[M+H]^+$ 308.1646; $C_{20}H_{21}NO_2$ requires $[M+H]^+$ 308.1645).

Acknowledgements

We thank the EPSRC for the provision of a mass spectrometry service, University of Wales (Swansea) and an X-ray crystallographic service, University of Southampton. James Robinson Ltd, (Huddersfield) and the University of Leeds are thanked for financial support to A.C.I.

References and notes

1. Mann, C.; Melzig, M.; Weigand, U. PCT WO 03/080595 A1, 2003. Chan, Y. -P.; Breyne, O.; Jean, P. PCT WO 01/36424 A2 2001. Lin, J.; Van Gemert, B. PCT WO 99/31082, 1999. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 00/18755 A1, 2000.
2. Breyne, O.; Chan, Y. -P.; Jean, P. PCT WO 02/30916 A1 2002. Izumi, S.; Nagoh, H. PCT WO 02/090342 A1, 2002. Kumar, A. PCT WO 98/32037, 1998.
3. Melzig, M.; Weigand, U. PCT WO 02/22594 A1, 2002. Breyne, O.; Chan, Y. -P.; Jean, P. PCT WO 00/77007 A1, 2000. Qin, X. PCT WO 03/025638 A1, 2003.
4. McCallien, D. W. J.; Bezer, M. GB Pat. No. 2344599, 2000.
5. Camus, M. Eur. Pat. No. 488902, 1992.
6. (a) Delbaere, S.; Luccioni-Houze, B.; Bochu, C.; Teral, Y.; Campredon, M.; Vermeersch, G. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1153. (b) Görner, H.; Chibisov, A. K. *J. Photochem. Photobiol. A: Chem.* **2002**, *149*, 83. (c) Jockusch, S.; Turro, N. J.; Blackburn, F. R. *J. Phys. Chem. A* **2002**, *106*, 9236.
7. Delbaere, S.; Vermeersch, G. *Tetrahedron Lett.* **2003**, *44*, 259.
8. (a) Van Gemert, B. In *Organic Photochromic and Thermochromic Compounds, Volume 1: Main Photochromic Families*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum: New York, 1998; p 113. (b) Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Colour Science '98, Volume 1: Dye and Pigment Chemistry*; Griffiths, J., Ed.; University of Leeds: Leeds, 1999; p 161.
9. Rickwood, M.; Smith, K. E.; Gabbutt, C. D.; Hepworth, J. D. PCT WO 94/22850, 1994.
10. Van Gemert, B.; Bergomi, M. P. US Pat. No. 5066818, 1991.
11. Gabbutt, C. D.; Heron, B. M.; Instone, A. C. *Heterocycles* **2003**, *60*, 843.
12. Gabbutt, C. D.; Heron, B. M.; Instone, A. C.; Thomas, D. A.; Partington, S. M.; Hursthouse, M. B.; Gelbrich, T. *Eur. J. Org. Chem.* **2003**, 1220.
13. Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1962**, *10*, 926.
14. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Partington, S. M.; Thomas, D. A. *Dyes Pigments* **2001**, *49*, 65.
15. In *Friedel–Crafts and Related Reactions*, Olah, G. A., Ed.; Wiley-Interscience: New York, Vols. I–IV, 1963.
16. (a) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. (b) Zollinger, H. *Angew. Chem.* **1978**, *90*, 151. (c) Nonhebel, D. C. *Chem. Soc. Special Publ.* **1970**, 409.
17. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
18. Hallas, G. *J. Soc. Dyers Colourists* **1994**, *110*, 342.
19. Gabbutt, C. D.; Gelbrich, T.; Hepworth, J. D.; Heron, B. M.; Hursthouse, M. B.; Partington, S. M. *Dyes Pigments* **2002**, *54*, 79.
20. Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.
21. Rupe, H. *Helv. Chim. Acta* **1920**, *9*, 672.
22. Griffiths, J.; Roozpeikar, B.; Thomasson, J. *J. Chem. Res. (S)* **1981**, 302.
23. Gordon, P. F.; Gregory, P. *Organic Chemistry in Colour*; Springer: Berlin, 1983; p. 157.
24. (a) Barker, C. C.; Hallas, G.; Stamp, A. *J. Chem. Soc.* **1960**, 3790. (b) Castelino, R. W.; Hallas, G. *J. Chem. Soc. (B)* **1971**, 1471. (c) Hallas, G.; Paskins, K. N.; Waring, D. R.; Humpston, J. R.; Jones, A. M. *J. Chem. Soc. Perkin Trans. 2* **1977**, 450. (d) Brindle, I.; Jones, A. M. *Dyes Pigments* **2000**, *47*, 117.
25. Collings, P. J.; Hird, M. *Introduction to Liquid Crystals: Chemistry and Physics*; Taylor Francis: London, 1997; p 70.
26. Mustroph, H.; Gussmann, F. *J. Prakt. Chem.* **1990**, *332*, 93.
27. Crystal data for **11a**: $C_{29}H_{24}INO$, $M=529.39$, monoclinic, space group $P2_1$, $a=8.575(5)$ Å, $b=22.507(5)$ Å, $c=11.773(5)$ Å, $\beta=93.701(5)$ Å, $U=2267.4(17)$ Å^3, $D_{calcd}=1.551$ Mg m^{-3}, $Z=4$, Mo Kα radiation ($\gamma=0.71073$ Å), $\mu=1.434$ mm^{-1}, $T=120(2)$ K, 31,310 measured reflections, 10,150 observed reflections ($R_{int}=0.0623$), $R_1=0.0578$ [$F^2>2\sigma(F^2)$], $wR_2=0.0809$ (all data). The structure was solved and refined using the SHELXL-97 suite of programs.[33] Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC243892.
28. Crystal data for **11d**: $C_{29}H_{24}FNO$, $M=421.49$, monoclinic, space group $P2_1/n$, $a=15.1016(3)$ Å, $b=8.3820(2)$ Å, $c=17.3016(4)$ Å, $\beta=105.9620(10)$, $U=2105.62(8)$ Å^3, $D_{calcd}=1.330$ Mg m^{-3}, $Z=4$, Mo Kα radiation ($\lambda=0.71073$ Å), $\mu=0.086$ mm^{-1}, $T=120(2)$ K, 27,595 measured reflections, 4807 observed reflections ($R_{int}=0.0617$), $R_1=0.0581$ [$F^2>2\sigma(F^2)$], $wR_2=0.1157$ (all data). The structure was solved and refined using the SHELXL-97 suite of programs.[33] Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC243891.
29. Hodgson, H. H.; Beard, H. G. *J. Chem. Soc.* **1927**, 20.
30. Cam-Van, N. T.; Diep, B. K.; Buu-Hoi, N. P. *Tetrahedron* **1964**, *20*, 2195.
31. Wagner, P. J.; Truman, R. J.; Puchalski, A. E.; Wake, R. *J. Am. Chem. Soc.* **1986**, *108*, 7727.
32. Bomben, A.; Marques, C. A.; Selva, M.; Tundo, P. *Synthesis* **1996**, 1109.
33. Sheldrick, G. M. *SHELXL-97 Program System*; University of Göttingen: Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 473–478

1,2-Disubstituted cyclohexane nucleosides: comparative study for the synthesis of *cis* and *trans* adenosine analogues

Dolores Viña,[a,*] Lourdes Santana,[a] Eugenio Uriarte[a] and Carmen Terán[b]

[a]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*
[b]*Departamento de Química Orgánica, Universidad de Vigo, E-36200 Vigo, Spain*

Received 19 February 2004; revised 21 September 2004; accepted 21 October 2004

Available online 11 November 2004

Abstract—A new class of adenosine analogues with 1,2-disubstituted carbocycles (with *cis* and *trans* stereochemistry) have been synthesized. Construction of the base on the amino group of (±)-*cis*-(2-aminocyclohexyl)methanol was more efficient than the Mitsunobu condensation between the purine base and protected (±)-*trans*-(2-hydroxymethyl)cyclohexanol. The latter strategy gave the final compound with *cis* stereochemistry in a short number of steps with the overall yield depending on the nature of the protecting group on the hydroxymethyl group of the diol. However, Mitsunobu condensation between a purine base and the protected (±)-*cis*-(2-hydroxymethyl)cyclohexanol is not an ideal method to obtain *trans* purine derivatives because the elimination reaction is faster than the substitution reaction.

1. Introduction

Carbanucleosides are compounds in which the endocyclic oxygen of the nucleoside sugar ring has been replaced by a methylene group. Such compounds have recently been the focus of a great deal of attention in the development of new antiviral and antitumoral therapeutic agents.[1] This modification reduces phosphorylase- and hydrolase-catalyzed reactivity (thereby increasing the in vivo half life)[2] and increases lipophilicity (thus favouring absorption and penetration of the cell membrane).

On the other hand, removal of the hydroxyl groups in the 2′- and 3′-positions of the carbocycle has generated drugs of choice for treatment of certain viral infections, including human immunodeficiency virus (HIV) infection, which works by blocking viral reproduction, thus inhibiting reverse transcriptase.[3]

Additionally, transposition of the base or the 5′-hydroxymethyl group from their normal 1′- or 4′-position to non-natural or isomeric positions has generated significant interest in the synthesis of non-natural nucleosides.[4,5] For some year, we have been examining a group of 2′,3′-dideoxy-cyclopentyl analogues which have the hydoxymethyl group and the heterocyclic base attached to contiguous positions of the carbocycle, being the pseudo-sugar a cyclopentane or cyclopentene ring. Some of them have shown an interesting profile of activity against the proliferation of murine leukaemia cells (L1210/0) and human T-lymphocyte cells (Molt4/C8 and CEM/0).[6–8]

Despite the fact that carbocyclic nucleosides have been extensively studied, little effort has been directed toward the synthesis of six-membered carbocyclic analogues. However, recent publications have described the potent antiviral activity of such compounds.[9,10]

In view of the success obtained on carrying out these modifications, we became interested in exploring the potential of 1,2-disubstituted cyclohexane nucleoside analogues. In the target compounds the usual 1,3-substitution pattern of the heterocyclic base and hydroxymethyl group on the carbocycle is replaced by a 1,2-pattern.

2. Results and discussion

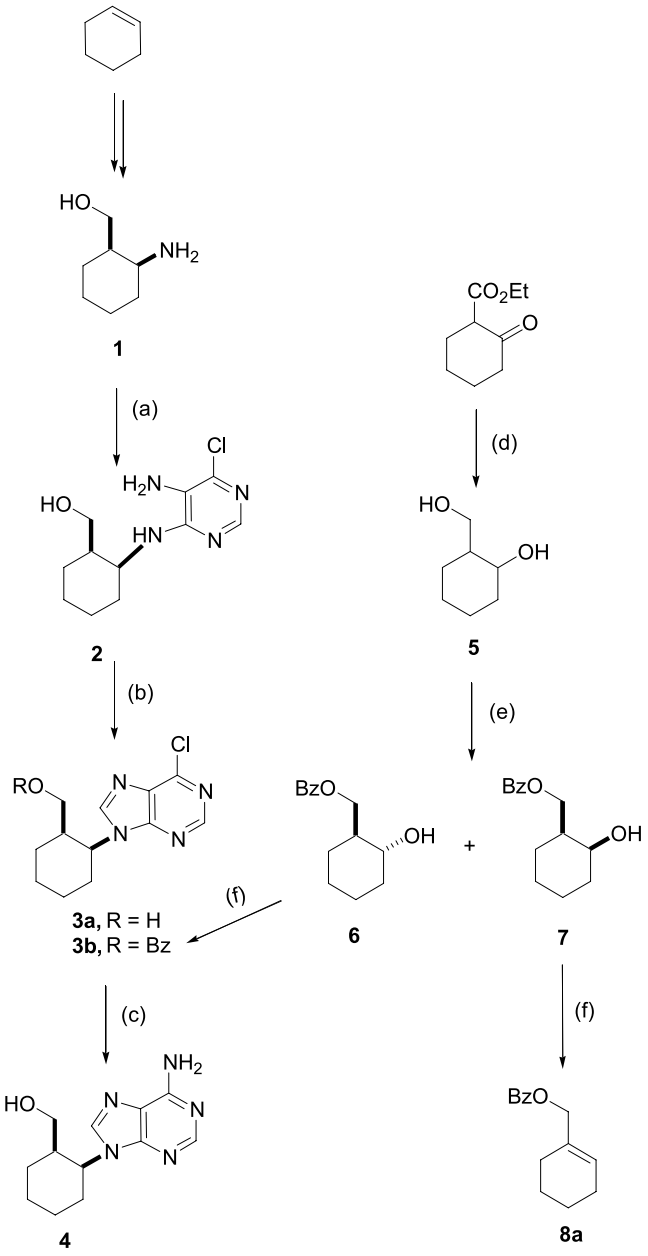
As a preliminary study to the synthesis of a large series of this kind of compound, we investigated the efficiency with it was possible to prepare a representative purine (adenosine analogue) as a racemic mixture, with either the *cis* or *trans* stereochemistry, using the two routes that have been most widely employed in this field.[11] These two routes are (i)

Keywords: Carbanucleosides; Aminocyclohexanemethanol; Hydroxycyclohexanemethanol; Adenine; Mitsunobu reaction.
* Corresponding author. Fax: +34 981 594912; e-mail: qovina@usc.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.076

construction of the heterocyclic base on the primary amino group of an appropriate aminoalcohol[12,13] and (ii) direct condensation between the heterocyclic base and an appropriately functionalized carbocyclic moiety, in this case Mitsunobu condensation of 6-chloropurine with the corresponding protected diol and subsequent nucleophilic substitution of the 6-chloro atom to afford the adenosine analogue.[14–16]

Route (i), starting from the aminoalcohol **1**, involved a sequence of three steps: condensation of **1** with 5-amino-4,6-dichloropyrimidine to give the substituted diaminopyrimidine **2**, reaction of the product with ethyl orthoformate in an acidic medium and, finally, nucleophilic exchange of the 6-chloro atom to give an amino group. This route afforded compound **4** in 50% overall yield (Scheme 1).



Scheme 1. Reagents and conditions: (a) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux, 24 h, 71%; (b) $CH(OEt)_3$, 12 M HCl, reflux, 12 h, 71%; (c) from **3a**: NH_4OH, reflux, 4 h, 99%; from **3b**: NH_3/MeOH, 80 °C, 20 h, 75%; (d) $NaBH_4$, EtOH, rt, 3 h, 71%; (e) BzCl, Et_3N, CH_2Cl_2, rt, 3 h, **6**: 32%, **7**: 27%; (f) 6-chloropurine, Ph_3P, $N_2(CO_2Et)$, THF, rt, 60 h, **3b**: 30%, **8a**: 80%.

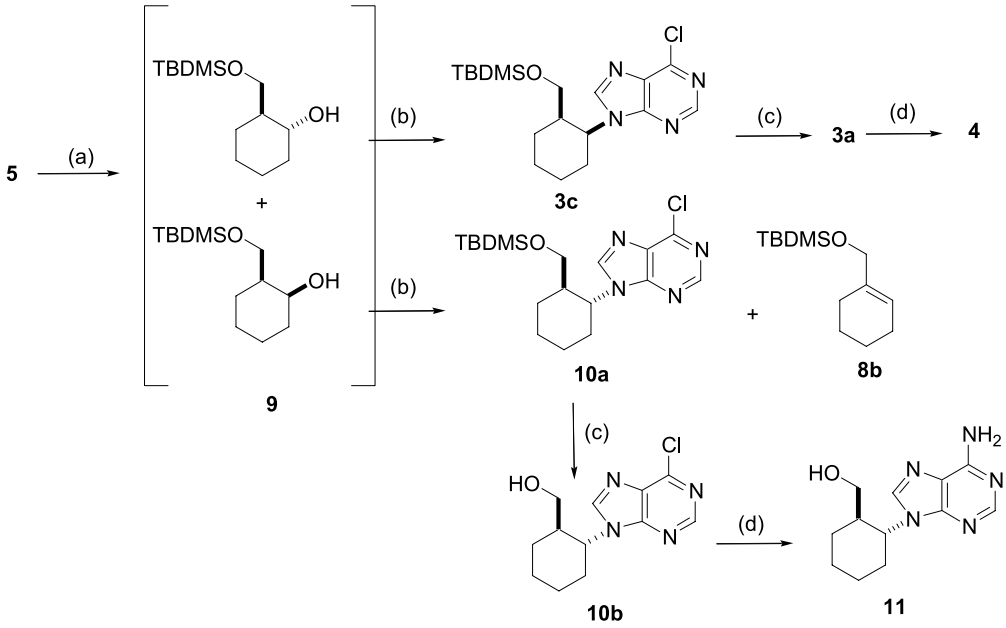
Alternatively, compound **4** was obtained from the alcohol **6** in two steps in 23% overall yield by following route (ii): direct condensation of 6-chloropurine and (±)-*trans*-(2-hydroxy)cyclohexylmethyl benzoate (**6**) in the presence of triphenylphosphine and diethyl azodicarboxylate gave **3b**, which was converted into **4** by treatment with saturated methanolic ammonia (Scheme 1).

Furthermore, whereas aminoalcohol **1** was prepared in 20% overall yield from cyclohexene, the starting compound for the Mitsunobu reaction (compound **6**) was prepared from ethyl 2-oxocyclohexanecarboxylate in 23% overall yield using an easier and more direct procedure. Aminoalcohol **1** was obtained by a (2+2) cycloaddition between cyclohexene and chlorosulphonylisocyanate followed by hydrolysis of the resulting lactam, esterification of the amino acid and subsequent reduction with $LiAlH_4$.[17] Compound **6** was obtained by reduction of ethyl 2-oxocyclohexanecarboxylate with $NaBH_4$ to give a mixture of (±)-*cis*/*trans* diols **5**. Subsequent benzoylation of the primary hydroxyl group using benzoyl chloride gave a mixture of (±)-*cis*/*trans*-(2-hydroxy)cyclohexylmethyl benzoate, which could be separated by silica gel column chromatography (1.2:1 ratio of compounds **6** and **7**).

Treatment of (±)-*cis*-(2-hydroxy)cyclohexylmethyl benzoate (**7**) with 6-chloro-purine under Mitsunobu conditions afforded the dehydratation compound **8a**, a reaction that proceeds by anti E2 elimination.[18]

The use of *tert*-butyldimethylsilyl as a protecting group was necessary to obtaining the *trans* purine derivative **11** through a Mitsunobu reaction (Scheme 2). Silyl derivative **9**[19] was obtained in 77% yield, starting from compound **5**, by treatment with *tert*-butyldimethylsilyl chloride and imidazole in anhydrous THF. The *cis* and *trans* isomers of **9** could not be separated and the mixture was used in the reaction with 6-chloropurine under Mitsunobu conditions giving the (±)-*cis*-derivative **3c** (41% yield), the (±)-*trans*-derivative **10a** (10% yield) and the dehydratation compound **8b** (30% yield) which could be separated by silica gel column chromatography. Compounds **3c** and **10a** must arise from the *trans* and *cis* isomers of **9** respectively, whereas the compound **8b** must arise from the *cis* isomer of **9** by dehydratation reaction, such as compound **7** had yielded **8a**.

Deprotection of silyl derivatives **3c** and **10a** was performed by treatment with an acidic medium[20] (CH_3COOH, H_2O, THF) to afford (±)-*cis*- and (±)-*trans*-6-chloropurine derivatives **3a** and **10b**, respectively in quantitative yield. *cis*/*trans* Assignment was made in an unequivocal way (by comparison) because compound **3a** had been also obtained following the stereoespecific route (i). Moreover, when NOE experiments were performed, NOE effects were more intensive between the protons 1′ and 6′ for the compound **3a** (*cis*) than for compound **10b** (*trans*). Finally, substitution of the 6-chloro atom by an amino group in both compounds, **3a** and **10b**, was performed by treatment with NH_4OH to give



Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, THF, rt, 4.5 h, 77%; (b) 6-chloropurine, Ph_3P, $N_2(CO_2Et)_2$, THF, rt, 24 h, **3c**: 41%, **10a**: 10%, **8b**: 30%; (c) CH_3COOH/H_2O/THF, rt, 5 h, **3a**: 99%, **10b**: 95%; (d) NH_4OH, reflux, 4 h, 99%.

in almost quantitative yield the final compounds **4** and **11**, respectively.

In summary, novel cyclohexyl nucleosides, in which the base and the hydroxymethyl group have a 1,2-relationship, have been synthesized using two different methodologies. The first route (i) gave the final carbanucleoside compounds in an acceptable overall yield, although numerous steps are required. The other route (ii) involved the Mitsunobu reaction and is a more direct procedure. However, the common use of benzoate as a protecting group for the primary hydroxyl group of **5** only allowed the *cis*-derivative to be obtained (in a low yield) and not the *trans* derivative. This drawback arises because the protected diol *cis* **7** afforded only the dehydration product. Nevertheless, when *tert*-butyldimethylsilyl is used as the protecting group for the hydroxymethyl group of the diol, both *cis* and *trans* derivatives (**4** and **11**) could be synthesized. In this case, the *cis* derivative was obtained with a higher yield whereas the yield of the *trans* derivative was low due to the persistence in the formation of the elimination compound from the protected *cis* diol.

Preliminary assays of antiviral activity showed that compound **4** presenting moderate activity against respiratory syncytial virus at concentrations of 3.2 μg/mL (1.92 μg/mL for Rivabirin). An extensive series of these compounds is currently being synthesized for pharmacological evaluation.

3. Experimental

3.1. General

Melting points were determined using a Stuart Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1640 FT spectrophotometer (υ in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX (250 MHz) and Bruker AMX (500 MHz) spectrometers, using TMS as internal standard (chemical shifts as δ in ppm, J in Hz). The complete assignment of the signals was performed by DEPT, HMQC or HMBC experiments and comparison with analogues of these compounds previously synthesized in our group. Mass spectra and HRMS (EI) were obtained using a Hewlett Packard 5988A spectrometer and Micromass Autospec spectrometer, respectively. Elemental analyses were performed on a Perkin–Elmer 240B microanalyser. UV/Vis spectra were measured by means of a Kontron UVICON-810P spectrophotometer. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical thin layer chromatography (TLC) was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

3.1.1. (±)-*cis*-5-Amino-6-chloro-4-[2-(hydroxymethyl)-cyclohexylamino]pyrimidine (2). A mixture of amino-alcohol **1** (320 mg, 2.48 mmol), 5-amino-4,6-dichloropyrimidine (426 mg, 2.60 mmol), Et_3N (1.43 mL) and *n*-BuOH (8.55 mL) was heated under reflux for 24 h under Ar. The solvent was evaporated under vacuum and the solid residue was redissolved in ethyl acetate by stirring with IRA-420 (OH) until all turbidity had disappeared. The resin was filtered off, the solvent was evaporated under vacuum and the residue was purified by FC using CH_2Cl_2/MeOH (98:2) as eluent, which gave pure **2** (450 mg, 71%). Mp: 177–179 °C (acetonitrile). IR (KBr): 3246, 2932, 1654, 1576, 1472, 1364, 1015. ^1H NMR (DMSO-d_6) δ: 1.24–1.90 (m, 9H, $(-CH_2-)_4+-CH-C-O$), 3.30 (m, 2H, $-CH_2-O$), 4.93 (m, 2H, –CH–N– and –OH), 5.24 (s, 2H, $-NH_2$), 6.10 (d, 1H, –NH–, $J=7.7$ Hz), 7.70 (s, 1H, H-2). ^{13}C NMR (DMSO-d_6) δ: 22.0, 23.7, 24.0, 29.6, 41.6, 48.2, 61.7, 123.8, 137.2, 145.9, 151.9. MS m/z (%): 258 ($(M+2)^+$, 3), 256 (M^+, 9), 146 ($(M+2)^+-C_7H_{12}O$, 33), 144 ($M^+-C_7H_{12}O$, 100), 117 (100). HRMS (EI): (M^+) calcd for $C_{11}H_{17}ClN_4O$: 256.1090, found 256.1092.

3.1.2. (±)-*cis*-6-Chloro-9*H*-9-[2-(hydroxymethyl)cyclohexyl]purine (3a). A mixture of compound **2** (450 mg, 1.75 mmol), $CH(OEt)_3$ (9.6 mL) and 12 M HCl (0.11 mL) was stirred for 12 h at room temperature. The solvent was evaporated under vacuum and the solid residue was redissolved in tetrahydrofuran (THF) (28 mL) and 0.5 M HCl (36.7 mL). The mixture was stirred for 2 h at room temperature and neutralized with 0.5 M NaOH. The solvent was evaporated under vacuum (forming an azeotropic mixture with ethanol/toluene) and the solid residue was purified by FC using CH_2Cl_2/MeOH (98:2) as eluent, which gave pure **3a** (330 mg, 71%). Mp: 160–162 °C (hexane/$CHCl_3$). IR (KBr): 3285, 3092, 2930, 1594, 1568, 1397, 1340. ^{1}H NMR ($CDCl_3$) (δ): 1.50–2.40 (m, 9H, $(-CH_2-)_4$ +–CH–C–O), 2.90 (bs, 1H, –OH), 3.14 (m, 1H, –*H*CH–O), 3.50 (m, 1H, –HC*H*–O), 5.10 (m, 1H, –CH–N), 8.37 (s, 1H, H-8), 8.73 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$) (δ): 23.3 (4′), 24.5 (3′), 25.6 (5′), 28.9 (6′), 42.6 (2′), 54.2 (1′), 62.5 (7′), 131.8 (5), 144.9 (8), 151.8 (4), 152.0 (2), 152.6 (6). UV/Vis (CH_3OH): λ_{max}=270 nm. MS *m*/*z* (%): 268 ($(M+2)^+$, 4), 266 (M^+, 12), 157 ($(M+2)^+-C_7H_{11}O$, 33), 155 ($M^+-C_7H_{13}O$, 100), 119 (14). Anal. calcd for $C_{12}H_{15}ClN_4O$: C, 54.0; H, 5.7; N, 21.0. Found: C, 54.0; H, 5.7, N, 20.9. Compound **3a** was also obtained in 99% yield by hydrolysis of the *tert*-butyldimethylsilyloxymethyl derivative **3c** with CH_3COOH/H_2O/THF (1.8:0.6:0.6 mL) at room temperature for 5 h.

3.1.3. (±)-*cis*-9-[2-(Hydroxymethyl)cyclohexyl]adenine (4). A mixture of compound **3a** (120 mg, 0.45 mmol), NH_4OH (16 mL) and a few drops of dioxane (sufficient to obtain a solution of **3a**) was heated under reflux for 6 h. The solvent was evaporated under vacuum and the solid residue was purified by FC using CH_2Cl_2/MeOH (95:5) as eluent, which gave pure **4** (110 mg, 99%). Mp: 278–280 °C ($CHCl_3$). IR (KBr): 3344, 3199, 2928, 2868, 1667, 1606, 1586, 1480, 1322, 1052, 653. ^{1}H NMR (DMSO-d_6) (δ): 1.55–2.25 (m, 9H, $(-CH_2-)_4$+–CH–CO), 2.97 (m, 1H, –*H*CH–O), 3.42 (m, 1H, –HC*H*–O), 4.29 (t, 1H, –OH, J= 5.1 Hz), 4.65 (m, 1H, –CH–N), 7.15 (s, 2H, $-NH_2$), 8.11, 8.14 (2s, 2H, H-2 and H-8). ^{13}C NMR (DMSO-d_6) (δ): 20.8 (4′), 24.9 (3′), 25.7 (5′), 27.0 (6′), 40.6 (2′), 54.5 (1′), 58.6 (7′), 118.7 (5), 139.8 (8), 149.8 (4), 152.5 (2), 156.4 (6). UV/Vis (CH_3OH): λ_{max}=261 nm. MS *m*/*z* (%): 247 (M^+, 30), 230 (M^+-OH, 15), 217 (M^+-CH_2O, 12), 162 (35), 135 ($M^+-C_7H_{12}O$, 100), 108 (32), 66 (34). Anal. calcd for $C_{12}H_{17}N_5O$: C, 58.3; H, 6.9; N, 28.3. Found: C, 58.1; H, 6.9; N, 28.1. Compound **4** was also obtained in 75% yield from **3b** (130 mg, 0.35 mmol) by heating a solution in saturated methanolic ammonia (15 mL) at 80 °C for 20 h.

3.1.4. (±)-*trans*-(2-Hydroxy)cyclohexylmethyl benzoate (6) and (±)-*cis*-(2-hydroxy)cyclohexylmethyl benzoate (7). Benzoyl chloride (0.5 mL) was added to a solution of diol **5** (500 mg, 3.84 mmol) and Et_3N (1.8 mL) in anhydrous CH_2Cl_2 (10 mL) under Ar. The mixture was stirred at room temperature for 3 h. The organic layer was washed with $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated under vacuum. The residue was purified by FC using hexane/EtOAc (85:15) to give firstly compound **7** (240 mg, 27%) and then compound **6** (290 mg, 32%) as colourless oils. Compound **7**: IR (KBr): 3477, 2932, 2857, 1718, 1702, 1275, 1114, 708. ^{1}H NMR ($CDCl_3$) (δ): 1.18–1.90 (m, 8H, $(-CH_2-)_4$), 2.15 (m, 1H, –C*H*–CH_2–OBz), 3.99 (m, 1H, C*H*–OH), 4.12 (dd, 1H, –*H*CH–OBz, J=11.1, 5.7 Hz), 4.53 (dd, 1H, HC*H*–OBz, J=11.1, 9.1 Hz), 7.45 (m, 2 Ar-H.), 7.56 (m, 1 Ar-H), 8.05 (m, 2 Ar-H). ^{13}C NMR (Cl_3CD) (δ): 20.4, 23.4, 25.5, 32.9, 41.7, 66.2, 66.8, 128.8, 130.0, 130.5, 133.5, 167.6. MS *m*/*z* (%): 235 ($(M+1)^+$, 82), 217 ($(M+1)^+-H_2O$, 100), 123 (34), 95 (C_7H_5O, 84). Compound **6**: IR (KBr): 3434, 2921, 2846, 1713, 1446, 1275, 1114, 708. ^{1}H NMR ($CDCl_3$) (δ): 1.31 (m, 2H, $-CH_2-$), 1.75 (m, 5H, $(-CH_2-)_2$+–*H*CH–), 2.03 (m, 1H, –HC*H*–), 2.65 (m, 1H, –C*H*–CH_2–OBz), 3.38 (m, 1H, –CH–OH), 4.27 (dd, 1H, –*H*CH–OBz, J=11.2, 4.3 Hz), 4.70 (dd, 1H, –HC*H*–OBz, J=11.2, 4.7 Hz), 7.43 (m, 2 Ar-H), 7.58 (m, 1 Ar-H), 8.05 (m, 2 Ar-H). ^{13}C NMR ($CDCl_3$) (δ): 25.2, 25.7, 28.7, 35.3, 45.9, 67.1, 71.5, 128.8, 130.0, 130.4, 133.5, 166.8. MS *m*/*z* (%): 235 ($(M+1)^+$, 100), 217 ($(M+1)^+-H_2O$, 92), 123 (45), 105 (86), 95 (C_7H_5O, 64).

3.1.5. (±)-*cis*-6-Chloro-9*H*-9-[2-(benzoyloxymethyl)-cyclohexyl]purine (3b). 6-Chloropurine (299 mg, 1.94 mmol) was added at 0 °C to a solution of Ph_3P (515 mg, 1.94 mmol) and diethyl azodicarboxylate (0.30 mL, 1.94 mmol) in anhydrous THF (10 mL) and the mixture was stirred for 10 min. Alcohol **6** (278 mg, 1.19 mmol) in anhydrous THF (5 mL) was added and the mixture was stirred at room temperature for 60 h. The solvent was evaporated under vacuum and the residue purified by FC using CH_2Cl_2/MeOH (95:5) as eluent, which gave pure **3b** (132 mg, 30%) as a colourless oil. IR (KBr): 3409, 3123, 3058, 2931, 2856, 1712, 1589, 1557, 1269. ^{1}H NMR ($CDCl_3$) (δ): 1.22–2.19 (m, 8H, $(-CH_2-)_4$), 2.38 (m, 1H, –CH–C–O), 4.30 (m, 2H, $-CH_2-O$), 4.98 (m, 1H, –CH–N), 7.32 (m, 2 Ar-H), 7.48 (m, 3 Ar-H), 8.23, 8.67 (2s, 2H, H-2 and H-8). ^{13}C NMR ($CDCl_3$) (δ): 23.45, 24.87, 27.92, 28.65, 29.63, 58.23, 67.65, 109.36, 122.87, 124.18, 125.66, 128.42, 129.22, 132.11, 143.37, 151.06, 165.93. HRMS (EI): (M^+) calcd for $C_{19}H_{19}ClN_4O_2$: 370.1197, found 370.1196.

3.1.6. (Cyclohexen-1-yl)methyl benzoyl ester (8a). Reaction of (±)-*cis*-(2-hydroxy)cyclohexylmethyl benzoate (**7**, 398 mg, 1.70 mmol) with 6-chloropurine under Mitsunobu conditions, in an analogous way to the procedure described for **3b**, gave a residue that was purified by FC using hexane/*i*prOH (95:5) as eluent to afford **8a** as a colourless oil (294 mg, 80%). IR (KBr): 2931, 2835, 1718, 1269, 1109. ^{1}H NMR ($CDCl_3$) (δ): 1.66 (m, 4H, $(-CH_2-)_2$), 2.06 (m, 4H, $(-CH_2-)_2$), 4.69 (s, 2H, $-CH_2-O$), 5.84 (s, 1H, –CH=), 7.43 (t, 2 Ar-H, J=7.4 Hz), 7.55 (t, 1 Ar-H, J=7.4 Hz), 8.05 (dd, 2 Ar-H, J=1.4, 7.4 Hz). ^{13}C NMR ($CDCl_3$) (δ): 21.1, 21.3, 25.4, 26.2, 69.7, 125.9, 126.6, 128.7, 129.4, 130.0, 133.3, 165.5. MS *m*/*z* (%): 105 (C_7H_5O, 100), 94 (53), 79 (40), 77 (35).

3.1.7. (±)-*cis*/*trans*-2-(*tert*-Butyldimethylsilyloxymethyl)cyclohexanol (9). TBDMSCl (2.2 g, 15.12 mmol) was slowly added to a solution of diol **5** (1.30 g, 9.98 mmol) and imidazole (1.68 g, 23.95 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was stirred at room temperature for 4.5 h and the solvent was evaporated under vacuum. The residue was redissolved in Et_2O and washed with water (3×30 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under vacuum.

The residue was distilled under vacuum (0.15 mbar, 138–140 °C) to give **9**[19] (1.87 g, 77%) as a colourless oil.

3.1.8. Mitsunobu reaction of 9 with 6-chloropurine. 6-Chloropurine (1.06 g, 8.47 mmol) was added at 0 °C to a solution of Ph_3P (2.25 g, 8.47 mmol) and diethyl azodicarboxylate (1.32 mL, 8.47 mmol) in anhydrous THF (10 mL) and the mixture was stirred for 10 min. Alcohol **9** (1.26 g, 5.16 mmol) in anhydrous THF (5 mL) was added and the mixture was stirred for 24 h at room temperature. The solvent was evaporated under vacuum and the residue purified by FC using hexane/EtOAc (85:15) as eluent to give compound **8b** (350 mg, 30%), compound **10a** (197 mg, 10%) and finally compound **3c** (800 mg, 41%), all of them as colourless oils.

3.1.9. (Cyclohexen-1-yl)methyl-*tert*-butyldimethylsilyl ether (8b). ^{1}H NMR ($CDCl_3$) (δ): −0.02 (s, 6H, $(-CH_3-)_2$–Si), 0.84 (s, 9H, $(-CH_3-)_3$–C), 1.10–2.20 (m, 8H, $(-CH_2-)_4$), 3.92 (s, 2H, $-CH_2-O$), 5.52 (m, 1H, –CH═).

3.1.10. (±)-*trans*-6-Chloro-9*H*-9-[2-(*tert*-butyldimethylsilyloxymethyl) cyclohexyl]purine (10a). IR (KBr): 2932, 2852, 1580, 1545, 1318, 1244, 1188, 1097, 784. ^{1}H NMR ($CDCl_3$) (δ): 0.00 (s, 6H, $(-CH_3)_2$), 0.99 (s, 9H, $(-CH_3)_3$), 1.46–2.58 (m, 9H, $(-CH_2-)_4$+CH–C–O), 3.30 (m, 1H, –*H*CH–O), 3.47 (m, 1H, –HC*H*–O), 4.63 (m, 1H, CH–N), 8.28, 8.89 (2s, 2H, H-2 and H-8). ^{13}C NMR ($CDCl_3$) (δ): 18.5, 25.5, 26.0, 26.2, 26.2, 29.5, 32.9, 43.9, 57.9, 64.4, 132.4, 145.5, 151.3, 151.7, 152.1. HRMS (EI): (M^+) calcd for $C_{18}H_{29}ClN_4OSi$: 380.1799, found 380.1801.

3.1.11. (±)-*cis*-6-Chloro-9*H*-9-[2-(*tert*-butyldimethylsilyloxymethyl) cyclohexyl]purine (3c). IR (KBr): 2966, 2864, 1585, 1551, 1335, 1250, 1193, 1102, 943, 841, 773. ^{1}H NMR ($CDCl_3$) (δ): 0.00 (s, 6H, $(-CH_3)_2$), 0.89 (s, 9H, $(-CH_3)_3$), 1.81–2.20 (m, 8H, $(-CH_2-)_4$), 2.55 (m, 1H, –CH–C–O), 3.69 (d, 2H, $-CH_2-O$, J=5.7 Hz), 5.20 (m, 1H, –CH–N), 8.44, 8.92 (2s, 2H, H-2 and H-8). ^{13}C NMR ($CDCl_3$) (δ): 18.4, 22.3, 24.9, 26.1, 27.8, 28.4, 40.7, 55.6, 63.0, 126.3, 131.9, 144.6, 151.2, 151.9, 152.4. HRMS (EI): (M^+) calcd for $C_{18}H_{29}ClN_4OSi$: 380.1799, found 380.1795.

3.1.12. (±)-*trans*-6-Chloro-9*H*-9-[2-(hydroxymethyl)-cyclohexyl]purine (10b). This compound was prepared from **10a** (70 mg, 0.184 mmol) in an analogous way to **3a** from **3c**. The crude product was purified by FC using CH_2Cl_2/MeOH (98:2) as eluent to give pure **10b** (46 mg, 95%). Mp: 148–150 °C (hexane/$CHCl_3$). IR (KBr): 3341, 2943, 2868, 1597, 1557, 1330. ^{1}H NMR ($CDCl_3$) (δ): 1.47–2.17 (m, 9H, $(-CH_2-)_4$+–CH–C–O), 2.88 (s, 1H, OH), 3.13 (dd, 1H, –*H*CH–O, J=1.8, 9.3 Hz), 3.33 (dd, 1H, –HC*H*–O, J=1.8, 11.2 Hz), 4.55 (m, 1H, CH–N), 8.22, 8.75 (2s, 2H, H-8 and H-2). ^{13}C NMR ($CDCl_3$) (δ): 26.7 (4′), 27.1 (3′), 30.6 (5′), 34.0 (6′), 45.3 (2′), 59.3 (1′), 64.8 (7′), 131.3 (5), 148.1 (8), 151.5 (2), 153.0 (4), 153.6 (6). UV/Vis (CH_3OH): λ_{max}=270 nm. MS *m/z* (%): 268 ($(M+2)^+$, 2), 266 (M^+, 6), 235 (4), 181 (9), 155 ($M^+-C_7H_{13}O$, 100), 119 (16). Anal. calcd for $C_{12}H_{15}ClN_4O$: C, 54.0; H, 5.7; N, 21.0. Found: C, 53.8; H, 5.7, N, 21.1.

3.1.13. (±)-*trans*-9-[2-(Hydroxymethyl)cyclohexyl]adenine (11). This compound was prepared from **10b** (60 mg, 0.22 mmol) in an analogous way to **4** from **3a**. The crude product was purified by FC using CH_2Cl_2/MeOH (95:5) as eluent to give pure **11** (55 mg, 99%). Mp: 266–268 °C (Hexane/$CHCl_3$). IR (KBr): 3300, 2950, 2871, 1687, 1610, 1567, 1477, 1419, 1303, 651. ^{1}H NMR ($CDCl_3$) (δ): 1.48–2.13 (m, 8H, $(-CH_2-)_4$), 2.50 (m, 1H, –CH–C–O), 3.36 (m, 2H, $-CH_2-O$), 4.58 (m, 2H, –CH–N, –OH), 7.14 (bs, 2H, $-NH_2$), 8.11, 8.17 (2s, 2H, H-2, H-8). ^{13}C NMR ($CDCl_3$) (δ): 23.45 (4′), 24.87 (3′), 26.76 (5′), 27.06 (6′), 34.54 (2′), 56.67 (1′), 60.14 (7′), 118.20 (5), 140.98 (8), 152.10 (2), 152.77 (6), 155.85 (4). UV/Vis (CH_3OH): λ_{max}=261 nm. MS *m/z* (%): 247 (M^+, 25), 230 (M^+-NH_3, 15), 217 (M^+-CH_2O, 9), 162 (13), 135 ($M^+-C_7H_{12}O$, 100), 108 (22), 66 (14). Anal. calcd for $C_{12}H_{17}N_5O$: C, 58.3; H, 6.9; N, 28.3. Found: C, 58.2; H, 6.9; N, 28.4.

Acknowledgements

We thank the Spanish Ministry of Science and Technology (SAF 2003-02222) and the Xunta de Galicia (PGIDT00PXI20317PR) for financial support. D.V. is grateful to the Spanish Ministry of Science and Technology for a predoctoral grant (FPU). We also thank Professor Eric De Clercq for the biological assays.

References and notes

1. Marquez, V. E. *Adv. Antivir. Drug Des.* **1996**, *2*, 89–146.
2. Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885–3887.
3. Balzarini, J.; De Clercq, E. Nucleoside and non nuclease reverse transcriptase inhibitors active against HIV. In *Textbook of AIDS Medicine*; Merigan, T. C., Bartlett, J. G., Bolognesi, D., Eds.; Williams and Wilkings: Baltimore, 1999; pp 815–847.
4. Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953.
5. Nair, V.; St Clair, M. H.; Reardon, J.; Krasny, H. C.; Hazen, R. C.; Paff, M. T.; Boone, L. R.; Tisdale, M.; Najera, I.; Dornsife, R. E.; Averett, D. R.; Borroto-Esoda, K.; Yale, J. L. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993–1999.
6. Santana, L.; Uriarte, E.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1349–1352.
7. Estrada, E.; Uriarte, E.; Montero, A.; Teijeira, M.; Santana, L.; De Clercq, E. *J. Med. Chem.* **2000**, *43*, 1975–1985.
8. Besada, P.; González-Moa, M. J.; Terán, C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, *16*, 2445–2449.
9. Wang, J.; Herdewijn, P. *J. Org. Chem.* **1999**, *64*, 7820–7827.
10. Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736–745.
11. Santana, L.; Teijeira, M.; Terán, C.; Uriarte, E.; Viña, D. *Synthesis* **2001**, *10*, 1532–1538.
12. Szakonyi, Z.; Martinek, T.; Hetenyi, A.; Fulop, F. *Tetrahedron: Asymmetry* **2000**, *11*, 4571–4579.
13. Katagiri, N.; Nomura, N.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuro, T. *J. Med. Chem.* **1992**, *35*, 1882–1886.
14. Kinast, G.; Tietze, L.-F. *Chem. Ber.* **1976**, *109*, 3626–3639.
15. (a) Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*,

5252–5253. (b) Theil, F.; Ballschuh, S. *Tetrahedron: Asymmetry* **1996**, *7*, 3565–3572.
16. Girard, F.; Lee, M.-G.; Agrofoglio, L. A. *J. Heterocycl. Chem.* **1998**, *35*, 911–913.
17. Viña, D.; Santana, L.; Uriarte, E.; Quezada, E.; Valencia, L. *Synthesis* **2004**, 2517–2522.
18. Takamasa, I.; Yasuo, O.; Takeshi, O. *Tetrahedron Lett.* **1991**, *32*, 1209–1212.
19. Osamu, K.; Isao, K. *Tetrahedron* **2000**, *56*, 5639–5648.
20. Theil, F.; Ballschuh, S.; Flatan, S.; von Janta-Lipinski, M.; Matthes, E. *Bioorg. Med. Chem.* **1998**, *6*, 701–706.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 479–484

Structural and electronic features important to $n\pi^*$–$\pi\pi^*$ inversion sensors: synthesis, luminescence, and electrochemical properties of sulfur and chlorine-containing macrocycles. Part 3

Mariappan Kadarkaraisamy, Eric Dufek, Desire Lone Elk and Andrew G. Sykes*

Department of Chemistry, University of South Dakota, Vermillion, SD 57069, USA

Received 6 August 2004; revised 15 October 2004; accepted 15 October 2004

Abstract—The synthesis and structural characterization of anthraquinone-based luminescence macrocycles containing sulfur and chlorine is reported. Luminescence is dependent on both electronic contributions of the substituted quinone and structural features of the binding site, which effect the inversion of $n\pi^*$ and $\pi\pi^*$ states. X-ray crystallographic results of different 1,8-oxybis(ethyleneoxyethyleneoxy)-anthracene-9,10-dione structures is also compared.

1. Introduction

The carbonyl groups in the 9 and 10 positions of anthraquinone (AQ) activate the 1,8 (or 4,5) positions towards aromatic nucleophilic substitution, making anthraquinone a versatile scaffold for substituting a large variety of organic directing groups. We have previously reported a new type of anthraquinone-based luminescence sensor that is responsive to common oxoacids; where the two most common motifs are the closed ring structure as in **2** and the open-ringed structure (bipodands) as in **8**.[1–3] Single-crystal structural analysis of the perchloric acid adduct of **2** has also shown that hydronium ion becomes complexed within the polyether ring and strong hydrogen bonds are formed between the carbonyl oxygen of the anthraquinone lumophore and two of the polyether oxygens.[1] This coordination geometry is represented by the dashed line in **2**.

Hydrogen bonding to the carbonyl results in inversion of $n\pi^*$ and $\pi\pi^*$ excited states of the anthraquinone lumophore, producing a broad, intense emission band, centered at ~570 nm (Fig. 1).[4] In a non-polar environment, the $n\pi^*$ transition relaxes by a non-radiative process, that is, the sensor is switched off. Coordination of hydronium ion to the carbonyl oxygen raises the energy of the $n\pi^*$ transition above the $\pi\pi^*$ transition, switching on the luminescence. Previous work has established that luminescence efficiency decreases in the following order: closed rings > bipodands > monopodands, and that luminescence efficiency is also acid dependent.[2] The present study investigates the relationship between electronic contributions of the anthraquinone substitutents and the identity of the hydronium ion binding sites. For this study, the 1 and 8 positions of the anthraquinone are defined is the proximal positions in the macrocycle, and the ether or sulfide binding sites (base of the triangle in **2**) are the distal positions.

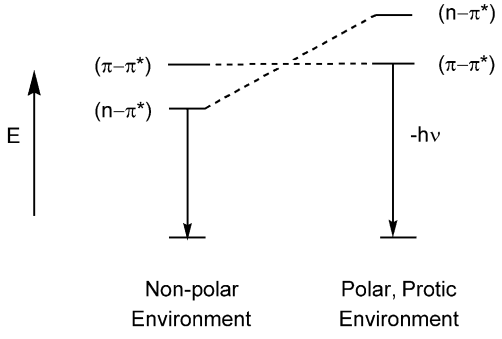


Figure 1. Inversion of $n\pi^*$ and $\pi\pi^*$ excited states depending upon hydrogen-bonding environment.

2. Results

We have successfully synthesized a series of sulfur and chlorine-containing macrocycles that luminesce in the presence of strong oxoacids in solution. Our initial attempt

Keywords: Anthraquinone; Luminescence; Sensors.
* Corresponding author. Tel.: +1 605 677 5487; fax: +1 605 677 6397; e-mail: asykes@usd.edu

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.047

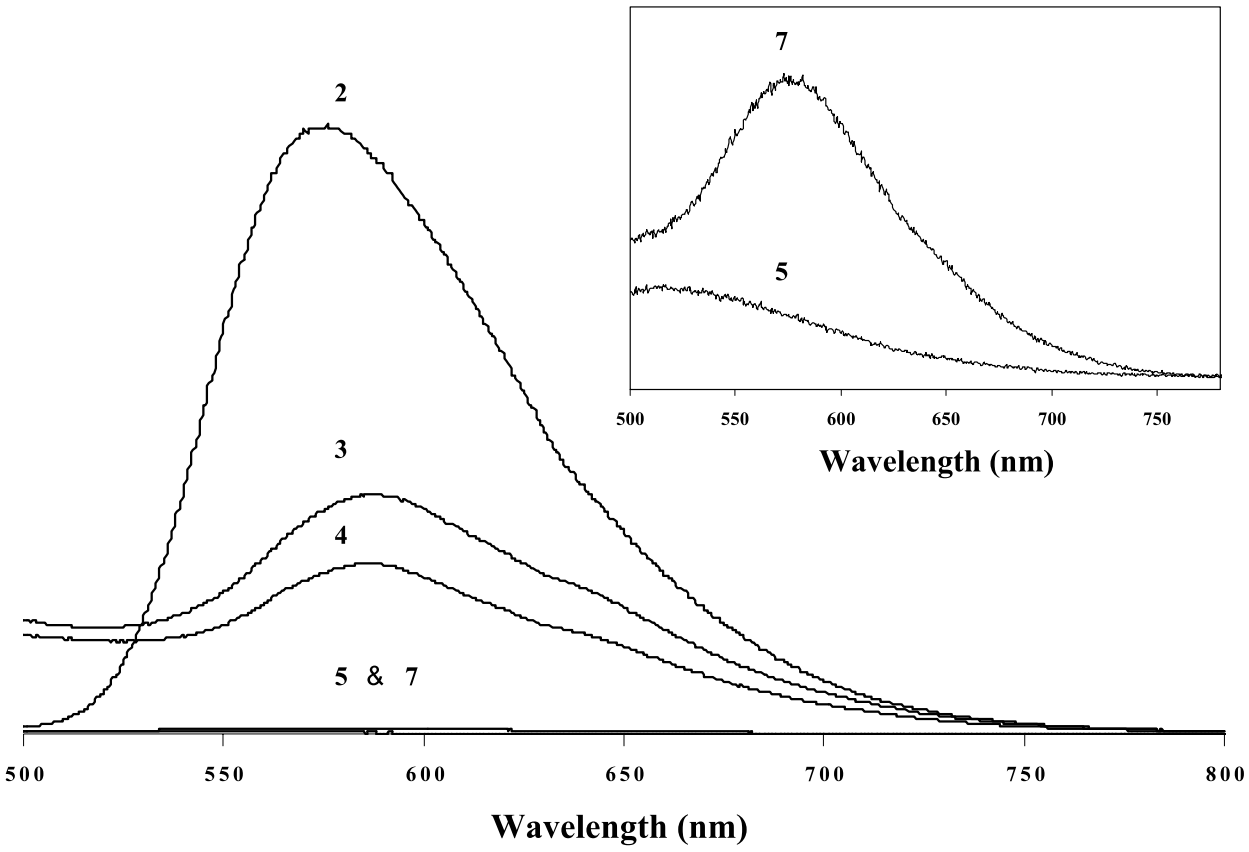


Figure 2. Emission spectra of compounds **2–5**, and **7** (6.5×10^{-5} M) in CH_3CN/1.0 M $HClO_4$.

to generate compound **3** in one step, starting from 1,8-dichloroanthraquinone and 6-oxa-3,9-dithiaundecane-1,11-diol, proved unsuccessful. Using an alternate route beginning with the dibromo derivative **1**, both ring structures **3** and **4** were made in significant yield. These two compounds are less soluble than the oxygen analog **2**. Refluxing 1,8-dichloroanthraquinone with 2-methoxyethanethiol, followed by chromatographic separation, yielded both the bipodand, **5**, and the monopodand, **6**, which was used as the starting material to make the asymmetric heteroatom product **7**. Compound **9**, an analog of **2**, contains two chlorine atoms; however the yield for this reaction is extremely small, probably due to the unfavorable electronic effect of the *para* substituted chlorines.

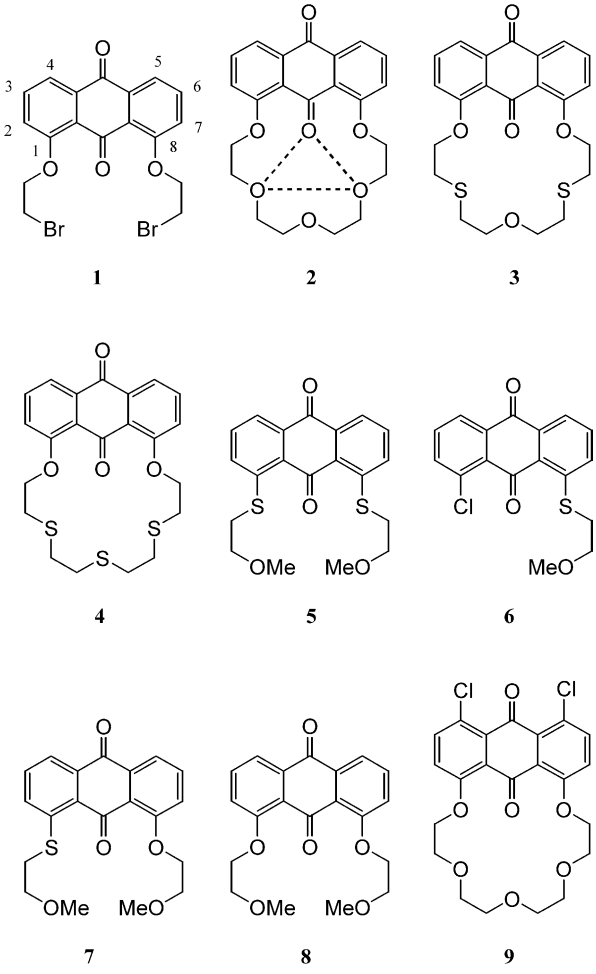
Emission spectra of **2** and the sulfur analogs **3–5** and **7** in the presence of 1.0 M $HClO_4$ in acetonitrile are shown in Figure 2. Compounds **3** and **4** which have the same cyclic structure as **2** ($\lambda_{max}=574$ nm) produce a yellow-orange emission with a small shift to longer wavelength ($\lambda_{max}=588$ nm). In the presence of $HClO_4$, the emission intensities (Fig. 2) and the quantum yields for **3** and **4** ($\Phi=0.013$ and 0.008, respectively) decrease as compared to **2** ($\Phi=0.015$).[2] Sulfur-substituted compounds **5** and **7**, which have the same open structural motif as **8**, are considerably less luminescent (inset, Fig. 2) than either **8** ($\Phi=0.013$)[2] or the cyclic structures.

Electrochemical potentials for the two, reversible one-electron reductions of the anthraquinone in each compound are listed in Table 1. Comparing reduction potentials for compounds **5** thru **8**, where the heteroatoms of the anthraquinone substituents change, the first one-electron reduction for **8** (E^{o1}) has the most negative potential (hardest to reduce). Consecutive replacement of the oxygens by sulfur in the 1 and 8 positions of the quinone shift the reduction potentials to less negative values, that is, E^{o1} potentials increase (become less negative) in the order

Table 1. One-electron reductions potentials for compounds **2–9** versus SCE. Potentials for **2** are from Ref. 5

Compound	$E^2_{p(c)}$	$E^2_{p(a)}$	E^{o2}	$E^1_{p(c)}$	$E^1_{p(a)}$	E^{o1}	λ_{max}	ε at 420 nm
2	−1.43	−1.28	−1.36	−1.01	−0.95	−0.98	378	2300
3	−1.36	−1.23	−1.30	−0.98	−0.89	−0.93	378	2100
4	−1.35	−1.22	−1.29	−0.95	−0.86	−0.95	380	2900
5	−1.42	−1.34	−1.38	−0.85	−0.77	−0.81	448	7100
6	−1.39	−1.30	−1.34	−0.80	−0.73	−0.76	430	4500
7	−1.39	−1.29	−1.34	−0.87	−0.78	−0.83	418	7300
8	−1.45	−1.30	−1.37	−0.98	−0.90	−0.94	378	2000
9	−1.51	−1.21	−1.36	−1.05	−0.93	−0.99	384	2400

8<**7**<**5**. E^{o1} for the monopodand, **6**, which contains one chlorine and one sulfur heteroatom, is comparable to the disulfur derivative, **5**. When sulfur is substituted in the distal ring positions in compounds **3** and **4**, there is only a small shift in E^{o1} as compared to **2**. Compounds **2**, **3**, **4**, **8** and **9** all have two oxygen substituents in the 1,8 positions of the quinone and have very similar reduction potentials.



X-ray crystallography of compound **9**, crystallized by slow evaporation from ethyl acetate containing a drop of concentrated perchloric acid, yields [**9**·H_3O]ClO_4 (Fig. 3). Hydronium ion is found encapsulated by the crown portion of the molecule and is hydrogen bonded to the intraannular carbonyl oxygen and the two distal ether oxygens: O1h–O1 = 2.572 (4); O1h–O3 = 2.497 (4); O1h–O5 = 2.508 (4) Å. This structure is quite similar to the structure of [**2**·H_3O]ClO_4, reported previously.[1] The hydrogen bond distances in the structure of [**9**·H_3O]ClO_4 are on average approximately 0.04 Å shorter than in [**2**·H_3O]ClO_4.

A second crystal structure of the macrocycle without hydronium ion present was also completed. Compound **2**, crystallized by slow evaporation from ethyl acetate, forms single-crystals of composition **2**·H_2O (Fig. 4). Here a single water molecule bridges the two distal oxygen atoms. The hydrogen bond distances found in this structure (O3–O1s = 3.142 (4); O5–O1s = 3.083 (4) Å) are significantly longer than in the structure of [**9**·H_3O]ClO_4 which contains the electropositive hydronium ion guest molecule. Other bond

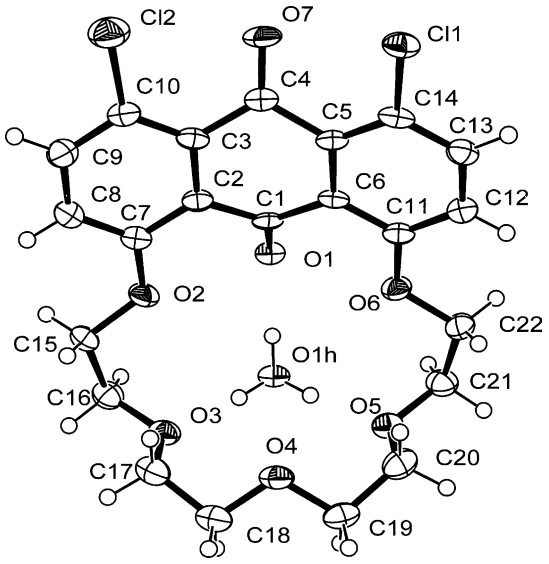


Figure 3. Thermal ellipsoid diagram (50%) of [1,8-dichloro-4,5-oxybis-(ethyleneoxy-ethyleneoxy)anthracene-9,10-dione·H_3O](ClO_4) (**9**). The perchlorate counterion has been omitted for clarity. O1–C1 = 1.227 (4); O7–C4 = 1.201 (5); Cl1–C14 = 1.730 (4): and Cl2–C10 = 1.741 (4) Å.

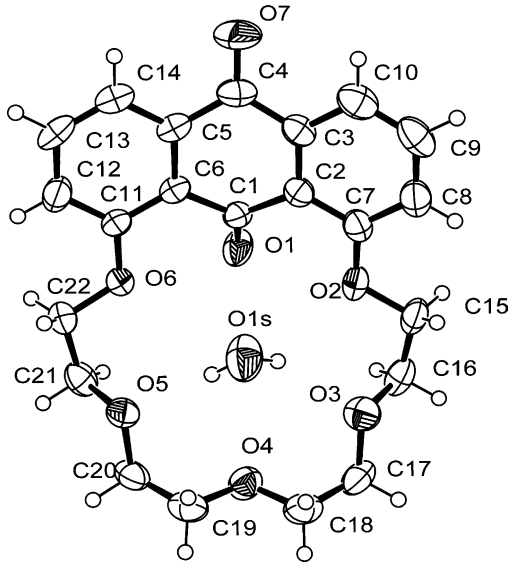


Figure 4. Thermal ellipsoid diagram (50%) of **2**·H_2O. O7–C4 = 1.221 (4), and O1–C1 = 1.213 (4) Å.

distances of interest in these structures have been listed in the figure captions.

3. Discussion

The factors that control luminescence efficiency in these systems can be divided into two effects: (A) electronic influences of the proximal substituents acting on the lumophore, and (B) electronegativity and structural influences of the distal coordination sites.

Substitution by sulfur in the 1 and 8 proximal positions of anthraquinone shifts the lowest energy n–π^* transition to

longer wavelengths. This progression is observed best in the analogous series **8**, **7** and **5** where only the proximal atoms of the anthraquinone change. Bathochromic shifts in anthroquinines when substituted by strong electron donor groups are commonly observed.[5] The shift to longer wavelength is also accompanied by a corresponding reduction (less negative potential) in the first one-electron reduction potential (Table 1), which corresponds to the π^* LUMO energy level. If luminescence in this system occurs due to a benzenoid-centered π–π^* transition that is relatively insensitive to substitution, the disulfur adduct cannot undergo inversion in a polar, protic environment due to its significantly reduced n–π^* transition energy. Compound **7** in Figure 2 has relatively the same emission maximum as **8**; however, **5** has almost no emission, indicating an oxygen-substituted benzene is important for luminescence. A red-colored 1,8-substituted aryl-selenium-anthraquinone has also been recently reported in the literature.[6] The authors postulate a through-space five-centered, four-electron bond to account for the seleno-anthraquinone's planar geometry. The disulfur derivative **8** may also be influenced by this interaction. All the anthraquinones substituted by oxygen in the 1,8 positions that we have investigated maintain significant bending of the anthraquinone plane even without hydronium ion present, vida infra Figure 5.

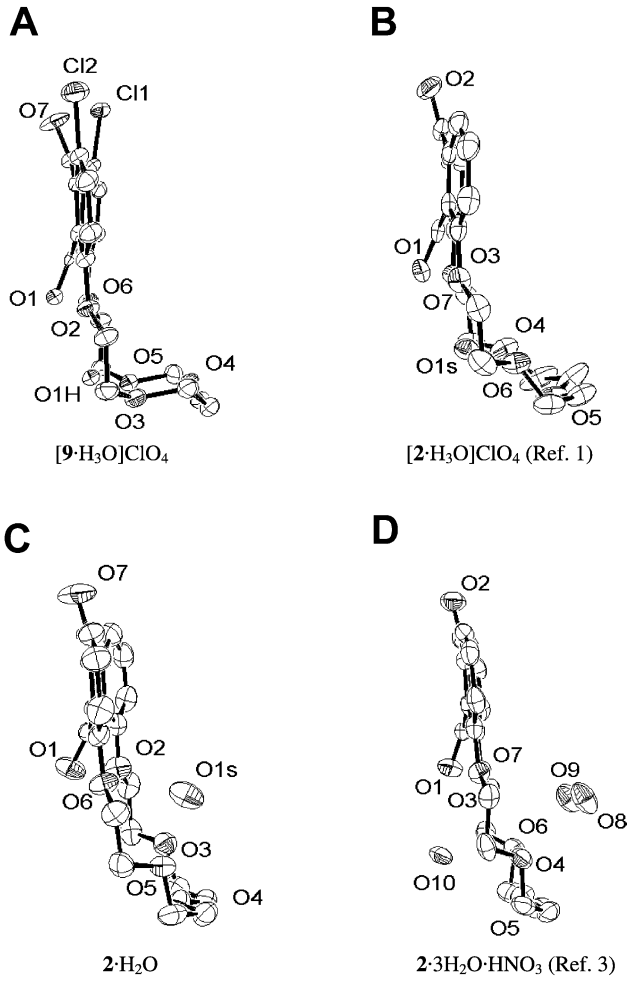


Figure 5. Thermal ellipsoid diagrams (50%) showing side views of anthraquinone-polyether structure.

Regarding issue B above, Figure 5 shows the side-view of four related anthraquinone-polyether structures of the same ring size. The structures of $[\mathbf{2}\cdot H_3O]ClO_4$ (**B**) and the unique ternary structure $\mathbf{2}\cdot 3H_2O\cdot HNO_3$ (**D**) have been previously reported.[1,3] Also, **B** is identical in composition to **A**; however the two chlorine atoms are not present. For **D**, three water molecules surround the macrocycle and nitric acid (not shown) is hydrogen bonded to O8. O1h and O1s are the hydronium ions in **A** and **B** and are centered in the middle of an equilateral triangle represented by the carbonyl oxygen (O1) and the two distal oxygens. In these structures, the polyether ring has been bent to accommodate the formation of the hydronium ion complex and draws the two distal oxygens together. In **A**, which has the shortest hydrogen bonds, this distance is 4.33 Å (03–05). In **B**, this distance is slightly longer, O4–O6 = 4.40 Å. The base of the ring in these two structures have reversed conformations in fact, producing a larger apparent bend in $[\mathbf{9}\cdot H_3O]ClO_4$. The structures of **C** and **D** do not contain hydronium ion and the distal oxygen distances are much larger: O3–O5 in **C** = 4.95 Å and O4–O6 in **D** = 5.09 Å. The long, external hydrogen bonds in **C** and **D** result in structures of more planar geometry; this is quite evident in the structure in **D** where two water molecules, not just one, bridge the distal oxygens.

We have shown that replacing the distal oxygens by sulfur decreases luminescence efficiency. We attribute part of this decrease in efficiency to the formation of weaker hydrogen bonds between the hydronium ion and the distal sulfurs of the polythioether rings of **3** and **4**. In this case, the energy gained by hydronium ion complexation and the formation of S···H–O hydrogen bonds is not sufficient to compensate for the strain placed on the ring in its required bent conformation. Another contributing factor may also be that sulfide C–S–C bond angles, (~97°) which are smaller than ether C–O–C bond angles (~105°), have different steric constraints than their ether counterparts. Unfortunately we were unable to grow suitable X-ray quality crystals of either proximal or distal-substituted sulfur anthraquinones.

4. Experimental

4.1. General

1,8-Bis(2-bromoethoxy)anthracene-9,10-dione (**1**)[7], 1,8-oxybis(ethyleneoxyethylene-oxy)anthracene-9,10-dione (**2**)[8] and 1,8-bis(2-methoxyethoxy)anthracene-9,10-dione (**8**)[2] were synthesized according to existing literature procedures. 1,4,5,8-Tetrachloroanthracene-9,10-dione was purchased from City Chemical, West Haven, CT. The synthesis of 2-methoxyethanethiol is described in Ref. 9. 300 MHz ^1H and 75 MHz ^{13}C NMR spectra were obtained at room temperature in $CDCl_3$.

4.1.1. 1,8-Oxybis(ethylenethioethyleoxy)anthracene-9,10-dione (3). 0.3045 g (2.2 mmol) of 2-mercaptoethyl ether in 10 mL of THF was slowly added to a warm solution of 0.16 g (6.6 mmol) of NaH and 25 mL of dry THF under inert atmosphere. The mixture was allowed to stir for 10 min and a solution of **1** (1 g, 2.2 mmol) in 25 mL of THF

was added dropwise. The mixture was refluxed for 3 h and cooled to room temperature and concentrated under reduced pressure. The residue was added to 100 mL of distilled water and extracted with dichloromethane. The organic phase were washed with brine, dried (anhydrous Na_2SO_4), concentrated under reduced pressure and mixed with an excess of *n*-hexane. A fibrous pale yellow color compound was obtained, recrystallized from ethanol-ethyl acetate (2:1) mixture, yielding 0.86 g (90%) of **3**. Mp = 158–160 °C. Elemental analyses calculated for $C_{22}H_{22}O_5S_2$: C, 61.37; H, 5.15; S, 14.89%. Found: C, 61.36; H, 5.29; S, 14.66%. ^{1}H NMR: δ 7.85 (*d*, 2H, 4 and 5-H); 7.61 (*t*, 2H, 3 and 6-H); 7.27 (*d*, 2H, 2 and 7-H); 4.35 (*t*, 4H, Ar-O–CH_2); 3.85 (*t*, 4H, O–CH_2); 3.16 (*t*, 4H, S–CH_2); 3.08 (*t*, 4H, S–CH_2). ^{13}C NMR: δ 31.3 (S–CH_2); 31.7 (S–CH_2); 71.1 (O–CH_2); 71.8 (O–CH_2); 119.7 (C2); 120.2 (C4); 124.9 (C11); 133.9 (C3); 134.9 (C12); 158.6 (C1); 182.2 (C9); 184.1 (C10).

4.1.2. 1,8-Oxybis(ethylenethioethylthio)anthracene-9,10-dione (4). The synthesis is identical to the synthesis of **3**. One gram of **1** (2.2 mmol) and 2-mercaptoethyl sulfide (0.32 g, 2.2 mmol) were combined. A lemon yellow solid was obtained. Yield 0.5 g (51%). Mp = 161–163 °C. Elemental Analyses calculated for $C_{22}H_{22}O_4S_3$: C, 59.17; H, 4.97; S, 21.54%. Found: C, 59.30; H, 5.03; S, 21.31%. ^{1}H NMR: δ 7.87 (*d*, 2H, 4 and 5-H); 7.63 (*t*, 2H, 3 and 6-H); 7.30 (*d*, 2H, 2 and 7-H); 4.38 (*t*, 4H, Ar-O–CH_2); 3.23 (*t*, 4H, S–CH_2); 3.13 (*t*, 4H, S–CH_2); 3.03 (*t*, 4H, S–CH_2). ^{13}C NMR: δ 31.2 (S–CH_2); 32.9 (S–CH_2); 33.3 (S–CH_2); 72.5 (O–CH_2); 119.9 (C2); 120.2 (C4); 124.4 (11); 134.1 (C3); 134.9 (12); 158.6 (C1); 181.9 (C9); 184.1 (C10).

4.1.3. 1,8-Bis((2-methoxyethyl)thio)anthracene-9,10-dione (5). In 10 mL of THF, 1.0 g (10.86 mmol) of 2-methoxyethanethiol was slowly added to a warm solution of 0.29 g (12.8 mmol) of NaH and 50 mL of dry THF under inert atmosphere. The mixture was allowed to stir for 10 min and a solution of 1,8-dichloroanthraquinone (1.5 g, 5.42 mmol) in 30 mL of THF was added dropwise. After refluxing for 3 h, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was added to 100 mL of distilled water and extracted with dichloromethane. The organic phases were washed with brine, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. TLC analysis indicated the presence of two products. After elution down a silica gel column using dichloromethane and ethyl acetate (1.8:0.2), a red orange fibrous product was obtained (compound **5** is the second band) in 10% (0.21 g) yield. Mp is 147–148 °C. Elemental analyses calculated for $C_{20}H_{20}O_4S_2$: C, 61.83; H, 5.19; S, 16.51%. Found: C, 61.66; H, 5.30; S, 16.75%. ^{1}H NMR: δ 8.05 (*d*, 2H, 4 and 5-H); 7.57–7.72 (*m*, 4H, 2, 3, 6 and 7-H); 3.72 (*t*, 4H, O–CH_2); 3.40 (*s*, 6H, O–CH_3); 3.20 (*t*, 4H, S–CH_2). ^{13}C NMR: δ 31.8 (S–CH_2); 59.1 (O–CH_3); 70.4 (O–CH_2); 123.3 (C2); 129.7 (C1); 130.1 (C4); 132.7 (C3); 134.6 (C11); 144.7 (C12); 183.2 (C9); 184.1 (C10).

4.1.4. 1-Chloro-8-((2-methoxyethyl)thio)anthracene-9,10-dione (6). This compound was eluted by CH_2Cl_2 as the first product (first band) in the previous synthesis. An orange colored solid was obtained in 39% (0.7 g) yield. Mp = 156–157 °C. Elemental analyses calculated for $C_{17}H_{13}O_3SCl$: C, 61.35; H, 3.94; S, 9.63%. Found: C, 61.12; H, 3.87; S, 9.80%. ^{1}H NMR: δ 8.19 (*d*, 1H, 3-H); 8.02 (*d*, 1H, 6-H); 7.58–7.79 (*m*, 4H, 2, 4, 5 and 7-H); 3.71 (*t*, 2H, O–CH_2); 3.40 (*s*, 3H, O–CH_3); 3.20 (*t*, 2H, S–CH_2). ^{13}C NMR: δ 32.1 (S–CH_2); 59.1 (O–CH_3); 70.4 (O–CH_2); 123.3 (C2); 126.5 (C4); 130.3 (C8); 130.6 (C5); 132.9 (C6); 133.5 (C3); 134.4 (C1); 135.1 (C11, C13); 135.3 (C14); 138.1 (C7); 144.6 (C12); 182.5 (C9, C10).

4.1.5. 1-Oxy-8-thio(2-methoxyethyl)anthracene-9,10-dione (7). 0.071 g (0.94 mmol) of 2-methoxyethanol in 10 mL of THF was slowly added to a warm solution of 0.03 g (1.25 mmol) of NaH and 20 mL of dry THF under inert atmosphere. The mixture was stirred for 10 min and a solution of **6** (0.31 g, 0.93 mmol) in 10 mL of THF was added dropwise. After refluxing for 3.5 h, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was added to 100 mL of distilled water and extracted with dichloromethane. The organic phases were washed with brine, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The required product was obtained by elution through a silica gel column using dichloromethane and ethyl acetate (1.6:0.4) as solvent. The dried residue was dissolved in 10 mL of dichloromethane and mixed with 30 mL of *n*-hexane. Red needle-shaped crystals were obtained in 50% (0.17 g) yield. Mp = 102–104 °C. Elemental analyses calculated for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41; S, 8.61%. Found: C, 64.37; H, 5.21; S, 8.71%. ^{1}H NMR: δ 8.01 (*d*, 1H, 3-H); 7.87 (*d*, 1H, 6-H); 7.57–7.69 (*m*, 4H, 2, 4, 5-H); 7.38 (*d*, 1H, 7-H); 4.32 (*t*, 2H, Ar-O–CH_2); 3.91 (*t*, 2H, O–CH_2–C–O); 3.72 (*t*, 2H, O–CH_2–C–S); 3.52 (*s*, 3H, CH_3–O–C–C–O); 3.41 (*s*, 3H, CH_3–O–C–C–S); 3.18 (*t*, 2H, S–CH_2). ^{13}C NMR: δ 31.8 (S–CH_2); 58.9 (O–CH_3); 59.6 (O–CH_3); 69.7 (O–CH_2); 70.4 (O–CH_2); 71.0 (O–CH_2); 119.8 (C2); 120.7 (C4); 122.8 (C11, 13); 122.9 (C7); 130.1 (C5); 131.1 (C8); 132.2 (C6); 134.4 (C3); 134.6 (14); 143.43 (C12); 159.61 (C1); 182.7 (C9); 183.5 (C10).

4.1.6. 1,8-Dichloro-4,5-oxybis(ethyleneoxyethyleneoxy)-anthracene-9,10-dione (9). 1.24 g (6.4 mmol) tetraethyleneglycol were added to 60 mL DMF under argon. To this solution, 12.1 g of Cs_2CO_3 (37 mmol) was added and the solution was stirred for an additional 30 min. A slurry of 2.19 g (6.3 mmol) 1,4,5,8-tetrachloroanthracene-9,10-dione in 160 mL DMF and was slowly added over the course of 25 min and the final mixture was heated to reflux overnight. After cooling, the Cs_2CO_3 was filtered off and the DMF was evaporated resulting in a sticky, red mixture. The mixture was purified on a silica column using CH_2Cl_2 and ethyl acetate. The third band after slow evaporation yielded 0.062 g of small red crystals of **9** ($\sim$2% yield). Melting point is 170–173 °C. Analyses calculated for $C_{22}H_{20}Cl_2O_2$: C, 56.55; H, 4.31. Found: C, 56.70; H, 4.54. ^{1}H NMR: δ 7.54 (*d*, 2H, 2 and 7-H), δ 7.02 (*d*, 2H, 3 and 6-H), δ 4.22 (*t*, 4H, and –OCH_2), δ 4.00 (*t*, 4H, and –OCH_2), δ 3.80 (*m*, 8H, and –OCH_2). ^{13}C NMR: δ 68.6, 69.6, 70.2, 70.9 (O–CH_2); 117.9 (C2); 123.7 (C4); 125.7 (C11); 133.2 (C12); 136.2 (C3); 156.9 (C1); 180.7 (C9); 182.5 (C10).

Emission quantum yields were determined according to Refs. 2 and 10. The electrochemical data were collected at room temperature under argon atmosphere in 0.1 M TBAP/

acetonitrile. Glassy carbon was used as the working electrode and electrochemical potentials are reported versus SCE. The first and second redox potentials for compounds **2–8** are tabulated in Table 1.

Crystallographic data for $\mathbf{2}\cdot H_2O$ was collected at room temperature using a Nonius CAD4 diffractometer equipped with a FR590 generator using Mo K_α radiation. Refinement was completed using the WinGX suite of crystallographic software.[11] Psi-scan data were used to apply an absorption correction. A crystal of $[\mathbf{9}\cdot H_3O]ClO_4$ was mounted on a Bruker SMART Platform CCD diffractometer for a data collection at 173 (2) K. The intensity data were corrected for absorption and decay (SADABS).[12] Final cell constants were calculated from the xyz centroids of ~2000 reflections from the actual data collection after integration (SAINT).[13] The structure was solved and refined using SHELXTL.[14] Refs. 15 and 16 list additional crystal and refinement information. This data can also be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors thank the American Chemical Society-Petroleum Research Fund (34076-B1) and the National Science Foundation (CHE-0082978) for financial support. E.D. wishes to thank NSF EPSCoR (EPS-0091948) for summer support and D.L.E. was supported by NSF REU (CHE-0138951). The authors also thank Dr. Victor Young and the University of Minnesota X-ray Crystallographic Laboratory for data collection and solution refinement of $[\mathbf{9}\cdot H_3O]ClO_4$.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.047

References and notes

1. Young, V. G. Jr.; Quiring, H. L.; Sykes, A. G. *J. Am. Chem. Soc.* **1997**, *119*, 12477.
2. Kampmann, B.; Lian, Y.; Klinkel, K. L.; Vecchi, P. A.; Quiring, H. L.; Soh, C. C.; Sykes, A. G. *J. Org. Chem.* **2002**, *67*, 3878.
3. Young, V. G. Jr.; Sykes, A. G. *Inorg. Chem.* **1998**, *37*, 376.
4. (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515 and references within. (b) Kalyanasundaram, K.; Thomas, J. K. *J. Phys. Chem.* **1977**, *81*, 2176. (c) Lianos, P.; Lux, B.; Gerald, D. J. *Chim. Phys.* **1988**, *77*, 907.
5. *Color Chemistry*; Zollinger, H., Ed.; VCH, 1991; p 209.
6. Nakanishi, W.; Hayashi, S.; Itoh, N. *Chem. Commun.* **2003**, 124.
7. (a) Chen, Z.; Schall, O.; Alcala, M.; Li, Y.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1992**, *114*, 444. (b) Kim, H.; Schall, O. F.; Fang, J.; Trafton, J. E.; Lu, T.; Atwood, J. L.; Gokel, G. W. *J. Phys. Org. Chem.* **1992**, *5*, 482.
8. Delgado, M.; Gustowski, D. A.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1988**, *110*, 119.
9. Tisato, F.; Maina, T.; Shao, L.; Heeg, M. J.; Deutsch, E. *J. Med. Chem.* **1996**, *39*, 1253.
10. Meyer, T. J.; Crosby, G. *J. Am. Chem. Soc.* **1975**, *97*, 7031.
11. WinGX: an integrated system of windows programs for the solution, refinement, and analysis of single crystal X-ray diffraction data, Ver. 1.63 Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.
12. An empirical correction for absorption anisotropy, Blessing, R. *Acta Cryst.* **1995**, *A51*, 33.
13. *SAINT V6.2, Bruker Analytical X-ray Systems*, Madison, WI, 2001.
14. *SHELXTL V6.10, Bruker Analytical X-ray Systems*, Madison, WI, 2000.
15. Crystallographic data for $[\mathbf{9}\cdot H_3O]ClO_4$: MW=585.8; monoclinic; space group, *P*2(1)/*c*; a=14.968 (4) Å, b=17.347 (5) Å, c=12.131 (3) Å, β=107.385 (4)°; V=3006.0 (15) Å^3; Z=4; density (calc.)=1.56 g cm^{-3}; Mo K_α radiation, (=0.71073; Siemens CCD area detector diffractometer; R=0.08140, wR2=0.2328. Additional crystallographic data is also provided in the supplemental material (Table S1). CCDC # 246678.
16. Crystallographic data for $\mathbf{2}\cdot H_2O$: MW=416.4; triclinic; space group, *P*-1; a=7.441 (×), b=11.499 (×), c=12.480 (4) Å, a=98.60 (×), β=105.75 (×), g=98.60 (×)°; V=1005.5 (×) Å^3; Z=2; density (calc.)=1.32 g cm^{-3}; Mo K_α radiation, λ=0.71073; Nonius CAD4 diffractometer; R=0.0620, wR2=0.1074. Additional crystallographic data is also provided in the supplemental material (Table S1). CCDC # 246677.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 485–492

Studies on the chemistry of 2-(2-oxo-3-phenylpropyl)-benzaldehydes: novel total synthesis of 3-phenylnaphthalen-2-ols and 2-hydroxy-3-phenyl-1,4-naphthoquinones

Ana Martínez, Marcos Fernández, Juan C. Estévez, Ramón J. Estévez* and Luis Castedo

Departamento de Química Orgánica and Unidade Asociada (C.S.I.C.), Universidade de Santiago, 15782 Santiago de Compostela, Spain

Received 10 September 2003; revised 11 October 2004; accepted 14 October 2004

Abstract—We describe the first studies on the chemistry of 2-(2-oxo-3-phenylpropyl)benzaldehydes, which were converted into 3-benzylisochromen-1-ones via the corresponding 2-(2-oxo-3-phenylpropyl)benzoic acid. The 2-(2-oxo-3-phenylpropyl)benzaldehydes proved to be convenient starting materials for the synthesis of 3-phenyl-2-naphthols. Oxidation of the latter compounds resulted in a novel, efficient synthesis of 3-phenyl-1,2-naphthoquinones, which were efficiently transformed into 2-hydroxy-3-phenyl-1,4-naphthoquinones.

Molecules with the quinoid structure constitute one of the most interesting classes of compounds in organic chemistry. Their syntheses as well as their diverse chemical and physical properties have been compiled into two volumes of Patai's series 'The Chemistry of Functional Groups'.[1] The perennial chemical interest in naphthoquinones is due to their biological properties, their industrial applications and their potential as intermediates in the synthesis of heterocycles.[2]

Although a large number of 1,2-naphthoquinones have been described, 1,4-naphthoquinones are more abundant—particularly those that have one hydroxy group attached directly to the quinone moiety, a wide variety of which are found in nature. Most of these compounds exhibit interesting biological activity and this is reflected in the ever increasing number of publications concerning their isolation, characterization and synthesis in the laboratory.[3] Natural hydroxyquinones vary in structural complexity from the simple hydroxynaphthoquinones such as lawsone, the main component of a natural dye,[4] to hydroxyphenylnaphthoquinones[5] or complex structures such as the trimeric hydroxynaphthoquinone conocurvone, a potential anti-HIV agent.[6]

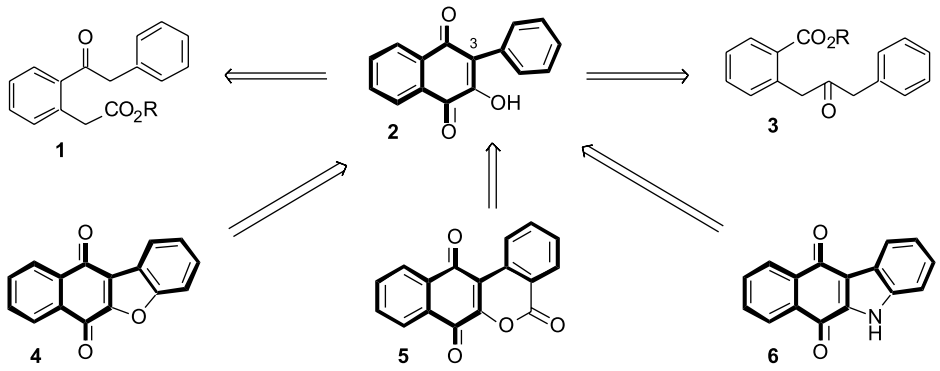
The common method for the synthesis of simple *o*-naphthoquinones consists of the oxidation of 2-naphthols,[6g,7] which are difficult to access, or the more problematic oxidation of the more readily available 1-naphthols.[8] Both approaches have been efficiently used in the synthesis of complex *o*-naphthoquinones.[9] Moreover, oxidation of simple *o*-naphthoquinones is a common method for the preparation of 2-hydroxy-1,4-naphthoquinones.[10] By contrast, similar chemistry for 3-phenyl-1,2-naphthoquinones **15** (Scheme 2) is very limited and, although some methods have been described for the preparation of such targets from 3-phenyl-1-naphthols,[11] to the best of our knowledge the preparation of quinones **15** from 3-phenyl-2-naphthols **14** (Scheme 2) has not been described.[12] On the other hand, only one example has been reported involving the oxidation of 3-phenyl-1,2-naphthoquinones **15** to 3-phenyl-2-hydroxy-1,4-naphthoquinones **2** (Scheme 1).[12a]

This paper represents a novel contribution to the chemistry of 3-phenyl-2-hydroxynaphthoquinones **2** and includes the first general method for the synthesis of 3-phenyl-2-naphthols **14**. A novel oxidation is described for the conversion of compounds **14** to the corresponding *o*-naphthoquinones **15**, which were further oxidized to 3-phenyl-2-hydroxy-1,4-naphthoquinones **2**.

The starting point for this work was the observation that a 2-phenyl-1,4-naphthoquinone subunit is present in the polycyclic ring system of a wide range of quinonoid compounds, including benzofuronaphthoquinones **4**,[13] benzopyronaphthoquinones **5**[14] and indolonaphthoquinones

Keywords: Quinones; Cyclization; Oxidation; Aldol reaction.
* Corresponding author. Tel.: +34 981 563100x14242; fax: +34 981 591014; e-mail: qorjec@usc.es

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.043

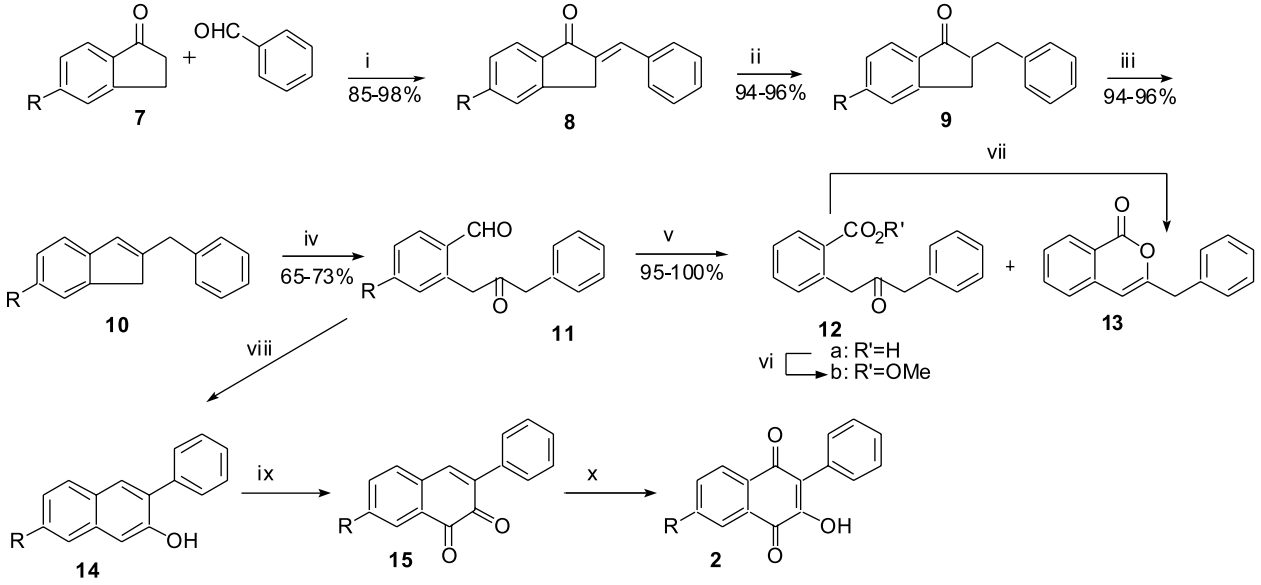


Scheme 1.

6[15] (Scheme 1). This structural relationship was the basis for the development of a practical synthesis of these naphthoquinone targets from 2-hydroxy-3-phenyl-1,4-naphthoquinones (**2**), which were in turn prepared by attachment of a phenyl substituent to the C_3 position of 2-hydroxy-1,4-naphthoquinones and/or, more directly and efficiently, by mixed Claisen condensation of alkyl *o*-phenylethylphenylacetates **1**. However, this interesting methodology has not yet been fully exploited, probably due to the limited scope in terms of the availability of the necessary starting materials.

In the search for new routes for the preparation of 3-phenyl-2-hydroxy-1,4-naphthoquinones **2** without the above limitations, we reasoned that alkyl 3-phenyl-2-ketopropyl benzoates **3** should undergo a mixed Claisen condensation in a similar way to ketoacid esters **1** to give the naphthoquinones **2** on the basis that compounds **3** also have the necessary carbon skeleton and functionality for this transformation (Scheme 1). In order to confirm this hypothesis, we decided to explore the preparation of the practically unknown ketoacids **3** by the novel route outlined in Scheme 2, starting from 1-indanones.[16]

2-Benzylidene-1-indanone **8a**,[17] formed by the aldol condensation of 1-indanone **7a** and benzaldehyde, was subjected to controlled catalytic hydrogenation. The only process observed was the desired selective reduction of the double bond and this gave a quantitative yield of the previously obtained benzylindanone **9a**.[18] The IR spectrum of **9a** showed a band at 1708 cm^{-1} corresponding to the carbonyl group. The ^1H NMR spectrum included four doublet of doublets at 2.67, 2.86, 3.17 and 3.42 ppm, which are due to the two methylene groups, together with a multiplet at 3.01 ppm due to the proton in the α-position to the carbonyl. Subsequent treatment of compound **9a** with $NaBH_4$ in methanol led to complete transformation of this compound into a mixture of 2-benzyl-1-indanols,[19] which was heated under reflux with concentrated sulfuric acid in order to promote its dehydration.[20] The expected 2-benzylindene **10a** was obtained in 93% yield. The ^1H NMR spectrum of **10a** contained signals between 7.12 and 7.40 ppm for a total of nine aromatic protons, a singlet at 6.57 ppm corresponding to the proton of the double bond, and two singlets at 3.33 and 3.86 ppm, each due to two protons, which were assigned to the two methylene groups. The next step involved cleavage of the double bond in



Scheme 2. 2, **7**, **8**, **9**, **10**, **11**, **14**, **15**: (a) R=H; (b) R=OMe. Conditions. (i) NaMeO/MeOH, rt, 15–27 h. (ii) H_2, Pd/C, AcOEt, 1 atm, 1.5–3.5 h. (iii) (a) $NaBH_4$, MeOH, rt, 1–1.5 h; (b) H_2SO_4, reflux, 1–2 h. (iv) (a) O_3, −78 °C, 3–6 min; (b) Me_2S, −78 °C (4–7 h), rt (13 h). (v) CrO_3, H_2SO_4, H_2O, rt, 45 min. (vi) H_2SO_4, MeOH, reflux, 75 min. (vii) NaMeO, MeOH, reflux, 3 h. (viii) NaOH aq, rt, 1.5–2 h. (ix) Fremy's salt, K_2HPO_4, acetone, rt, 1–4 h. (x) H_2SO_4, MeOH, reflux, 29 h.

indene **10a**, which was achieved by ozonolysis in dichloromethane at −78 °C, and subsequent reduction of the resulting ozonide with methylene sulfide.[21] In this way, ketoaldehyde **11a** was obtained in 71% yield and was easily identified from its analytical and spectroscopic data. The ^{1}H NMR spectrum showed a singlet at 9.98 ppm—corresponding to the aldehyde proton—and the ^{13}C NMR spectrum contained signals at 193.5 and 204.9 ppm corresponding to ketone and aldehyde carbonyls, respectively. Finally, oxidation of this ketoaldehyde under Jones conditions[22] (CrO_3, H_2O, H_2SO_4) led to a mixture of compounds. The major component (82% yield) was the expected ketoacid **12a**,[23] which showed in its IR spectrum an OH band at 2931–2856 cm^{-1} and carbonyl bands at 1714 and 1693 cm^{-1} corresponding to the carboxyl and the ketone functionalities, respectively. The ^{1}H NMR and ^{13}C NMR spectra of **12a** were very similar to those of the precursor **11a**, with the ^{13}C spectrum containing signals at 168.4 and 205 ppm due to the carboxyl and ketone carbonyls, respectively. The minor compound, isolated in 18% yield, was identified as lactone **13**[23] on the basis of its spectroscopic properties. For example, the IR spectrum contained a lactone carbonyl band at 1727 cm^{-1} and the ^{1}H NMR showed a singlet at 6.16 ppm due to the proton of the double bond and another singlet at 3.85 due to the methylene group. Additional confirmation of the structure of compound **13** was obtained from its ^{13}C NMR spectrum, which contained a highly deshielded signal at 162.8 ppm due to the lactone carbonyl together with a signal at 157 ppm, assigned to a carbon linked to oxygen, and a third signal at 39.8 ppm, corresponding to the methylene group.

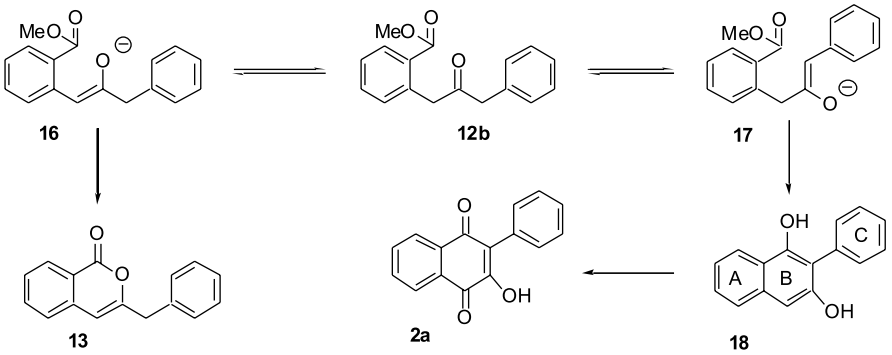
Benzylisochromanone **13** should result from the dehydration of ketoacid **12a** under the reaction conditions employed; in a separate experiment ketoacid **12a** was heated under reflux for 2 h in toluene containing H_2SO_4 to give isochromanone **13** in 92% yield.[24] Unfortunately, when ketoacid **12a** was esterified and a methanolic solution of the resulting ketoester **12b**[23] containing sodium methoxide was stirred at room temperature for 3 h, the expected naphthoquinone **2a** was not obtained. The only product in this reaction was the previously obtained benzylisochromanone **13**.[23]

The easy transformation of ketoester **12b** into benzylisochromanone **13** can be explained in terms of a competition between two irreversible processes (Scheme 3): cyclization of enolate **16** to compound **13** and transformation of enolate **17** into naphthol **18**, a possible precursor of naphthoquinone **2a**, would involve a mixed Claisen cyclization followed by aromatization of ring B. Formation of **13** as the only reaction product can be explained by assuming that enolate **16** is kinetically and thermodynamically more favoured than enolate **17**, due to interaction of the enolate moiety with the methoxycarbonyl group.

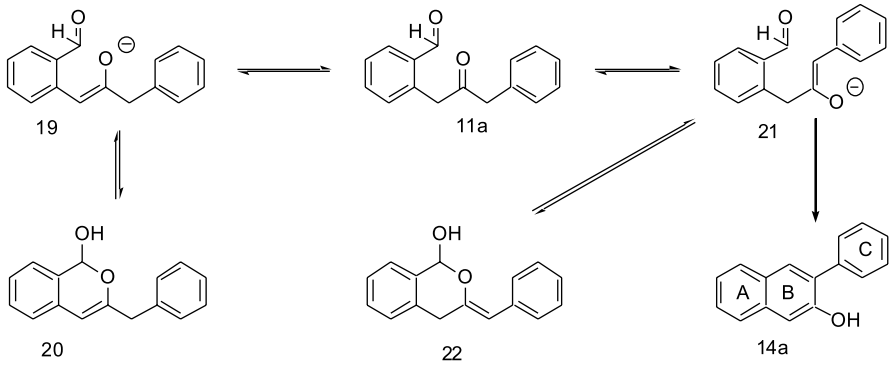
Although our initial route to prepare hydroxyphenylnaphthoquinone **2a** from ketoacid ester **12b** failed, satisfactory results were obtained on using its precursor, ketoaldehyde **11a**. Thus, when **11a** was subjected to basic conditions, a quantitative yield of 2-naphthol **14a** was obtained as a result of an intramolecular aldol condensation (Scheme 2). The IR spectrum of the product contained a typical band for a phenolic hydroxy group at 3457 cm^{-1}; the ^{1}H NMR spectrum showed a broad signal at 5.44 ppm, due to the hydroxy proton, and the ^{13}C NMR include a deshielded signal at 150.9 ppm, which was assigned to the carbon bearing the hydroxy group.

The different behaviour of ketoaldehyde **11a** with respect to its ketoester derivative **12b** can be explained in terms of a competition between three different processes (Scheme 4). The formation of hemiacetals **20** or **22** from ketoaldehyde **11a** via their respective enolates **19** and **21** should be reversible processes, but enolate **21** can also give naphthol **14a** by an intramolecular aldol reaction followed by enolization and dehydration to allow the aromatization of the B ring. The irreversible nature of this last transformation is the reason for the displacement of all the equilibria to the formation of compound **14a**.

Our synthetic plan continued with the transformation of naphthol **14a** into hydroxyphenylnaphthoquinone **2a** and this was achieved easily in two steps. Treatment of **14a** with Fremy's salt and potassium biphosphate in an aqueous acetone solution gave a 68% yield of *o*-naphthoquinone **15a**.[8f] The ^{1}H NMR spectrum of this compound showed a doublet for an aromatic proton at 8.03 ppm, a multiplet for an aromatic protons at 7.58 ppm and a multiplet due to seven aromatic protons and the proton of the double bond at 7.31–7.47 ppm. The ^{13}C NMR spectrum showed two very close signals at 180 and 179.1 ppm due to the carbonyl groups. Finally, aqueous sodium hydroxide was added to a methanolic solution of naphthoquinone **15a** and the mixture was stirred at room temperature for 15 min.[12a] This reaction gave 93% yield of the desired hydroxynaphthoquinone **2a**,[5a]



Scheme 3.



Scheme 4.

which was identified by direct comparison with an authentic sample of this compound.

The potential of this new synthetic route was confirmed by the successful preparation of hydroxyphenylnaphthoquinone **2b** from ketoaldehyde **11b** (Scheme 2). Compound **11b** was easily and efficiently obtained by aldol condensation of 1-indanone **7b** and benzaldehyde, followed by the regioselective hydrogenation of benzylideneindanone **8b**,[24] reduction of **9b** and dehydration of the resulting mixture of indanols and ozonolysis of benzylindene **10b**. As expected, the intramolecular aldol condensation of **11b** provided naphthol **14b**, which was easily oxidized to *o*-naphthoquinone **15b**. Finally, treatment of this compound with H_2SO_4 afforded the desired 2-hydroxynaphthoquinone **2b**.

In summary, we describe here the first total synthesis of phenylketopropylbenzaldehydes in a process that allowed us to develop novel chemistry in the field of quinones. Oxidation of these aldehydes constitutes a new and efficient method for the preparation of ketoacids **12**. Dehydration of the latter compounds constitutes a new and efficient method to obtain 3-benzylisochromanones **13**. Furthermore, the intramolecular aldol condensation of ketoaldehydes **11** constitutes the first general, efficient synthesis of 3-phenylnaphthalen-2-ols (**14**), which were oxidized to 3-phenyl-1,2-naphthoquinones (**15**) for the first time. Further oxidation of the latter compounds is the last step of a new, simple and efficient synthesis of 3-phenyl-2-hydroxy-1,4-naphthoquinones (**2**).

Work is now in progress to apply this synthetic route for naphthoquinones to the synthesis of complex naphthoquinones, including benzofuronaphthoquinones **4**, benzopyronaphthoquinones **5** and indolonaphthoquinones **6**.

1. Experimental

1.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, on a Bruker WM-250 apparatus, using deuterochloroform solutions containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol mixtures as eluant; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 25. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate. Compounds **2a**, **8a**, **8b**, **9a**, **10a** and **12a**, **12b**, **13**, **15a** and **2a** have been previously prepared.

1.1.1. (*E*)-2-Benzylideneindan-1-one (8a). To a solution of benzaldehyde (2.44 mL, 24.06 mmol) in dry methanol was added a solution of sodium methoxide (prepared by addition of 66 mL of dry methanol to 157 mg of sodium) and a solution of 1-indanone (3 g, 22.70 mmol) in dry methanol (54 mL) dropwise at 0 °C under argon. The resulting mixture was stirred at rt for 13 h. The reaction mixture was then poured into water (100 mL) and the resulting suspension was acidified by the addition of 2 M HCl. The product was extracted into dichloromethane (3×100 mL). The combined organic extracts were dried with anhydrous sodium sulfate and concentrated to dryness in vacuo. Crystallisation of the solid residue with MeOH yielded the title compound (4.735 g, 95%) as white crystals. Mp 109–111 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1697 (C=O). ^1H NMR (δ, ppm): 4.01 (s, 2H, $-CH_2-$), 7.38–7.67 (m, 9H, 8× Ar–H and CH=C), 7.90 (d, 1H, $J=7.5$ Hz, Ar–H). ^{13}C NMR (δ, ppm): 32.4 (CH_2), 124.5 (CH), 126.2 (CH), 127.7 (CH), 129.0 (2×CH), 129.7 (CH), 130.8 (2×CH), 134.0 (CH), 134.7 (CH), 134.8 (C), 135.5 (C), 138.1 (C), 149.7 (C), 194.4 (C=O). MS (*m*/*z*, %): 220 (M^+, 58), 219 [$(M-1)^+$, 100].

1.1.2. 2-Benzylindan-1-one (9a). 10% Pd/C (32.5 mg) was added to a deoxygenated solution of benzylideneindanone **8a** (4.802 g, 21.80 mmol) in ethyl acetate (480 mL) and the mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 75 min. After removal of the excess of hydrogen in vacuo, the reaction mixture was filtered though celite, which was eluted with ethyl acetate. The filtrate was concentrated to dryness in vacuo to give a quantitative yield of the title compound (4.62 g) as a transparent oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 1708 (C=O). ^1H NMR (δ, ppm): 2.67 (dd, 1H, $J=13.8$, 10.4 Hz, $-CH_2-$), 2.86 (dd, 1H, $J=16.9$, 3.3 Hz, $-CH_2-$), 3.01 (m, 1H, –CH–), 3.17 (dd, 1H, $J=16.9$, 7.5 Hz, $-CH_2-$), 3.42 (dd, 1H, $J=13.8$, 3.8 Hz, $-CH_2-$), 7.26–7.42 (m, 7H, 7×Ar–H), 7.58 (t, 1H, $J=7.4$ Hz, Ar–H), 7.80 (d, 1H, $J=$

7.4 Hz, Ar–H). ^{13}C NMR (δ, ppm): 32.2 (CH_2), 37.0 (CH_2), 48.9 (CH), 124.1 (CH), 126.4 (CH), 126.7 (CH), 127.5 (CH), 128.6 (2×CH), 129.0 (2×CH), 134.9 (CH), 136.7 (C), 139.7 (C), 153.7 (C), 207.9 (C=O). MS (*m/z*, %): 222 (M^+, 51), 131 (100).

1.1.3. 2-Benzyl-1*H*-indene (10a). Small portions of $NaBH_4$ (1.607 g, 42.50 mmol) were added every 15 min during 1 h to a solution of benzylindanone **9a** (1.18 g, 5.31 mmol) in methanol (80 mL). The mixture was stirred at rt for 30 min and poured into water (50 mL). The methanol was evaporated in vacuo and the remaining suspension was extracted with dichloromethane (3×100 mL). The combined organic extracts were dried and concentrated to dryness in vacuo. The resulting solid was immediately mixed with 9 M H_2SO_4 (100 mL) and the stirred suspension was heated under reflux in a dry atmosphere for 30 min. 20% aqueous NaOH was added to give a basic pH and the suspension was extracted with dichloromethane (3× 100 mL). The combined organic extracts were dried and concentrated to dryness in vacuo to give a 93% yield of the title compound (4.13 g) as a transparent oil ^{1}H NMR (δ, ppm): 3.33 (s, 2H, CH_2), 3.86 (s, 2H, CH_2), 6.57 (s, 1H, HC=C), 7.12–7.40 (m, 9H, 9×Ar–H). ^{13}C NMR (δ, ppm): 38.1 (CH_2), 40.9 (CH_2), 120.4 (CH), 123.7 (CH), 124.1 (CH), 126.4 (CH), 126.5 (CH), 128.0 (CH), 128.7 (2×CH), 129.1 (2×CH), 140.2 (C), 143.6 (C), 145.5 (C), 149.5 (C). MS (*m/z*, %): 206 (M^+, 30), 91 (100).

1.1.4. 2-(2-Oxo-3-phenylpropyl)benzaldehyde (11a). N_2, O_2 and O_3 were bubbled consecutively for 10, 10 and 2 min, respectively, through a solution of indene **10a** (200 mg, 0.97 mmol) in dichloromethane (30 mL) at −78 °C until the persistent presence of a blue color due to the ozonide was detected. O_2 was then bubbled through for a further 10 min to destroy excess O_3 and finally N_2 was bubbled for 5 min. Dimethyl sulfide was added and the mixture was stirred at −78 °C under argon for 4 h 30 min and at rt for 25 h. The solvent was removed in vacuo and the solid residue was submitted to column chromatography (eluent: AcOEt/hexane, 1:9) to yield 71% of the target compound (164 mg) as a yellow oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 1706 (CHO, C=O). ^{1}H NMR (δ, ppm): 3.95 (s, 2H, $-CH_2-$), 4.14 (s, 2H, $-CH_2-$), 7.14 (d, 1H, J=6.9 Hz, Ar–H), 7.30–7.55 (m, 7H, 7×Ar–H), 7.79 (m, 1H, Ar–H), 9.98 (s, 1H, –CHO). ^{13}C NMR (δ, ppm): 46.9 (CH_2), 50.1 (CH_2), 127.1 (CH), 127.8 (CH), 128.8 (2×CH), 129.9 (2×CH), 132.8 (CH), 133.8 (CH), 134.3 (C), 134.5 (C), 135.2 (CH), 136.0 (C), 193.5 (C=O), 204.9 (CHO). MS (*m/z*, %): 238 (M^+, 1), 91 (100). HRMS: $C_{16}H_{14}O_2$ (M^+), calcd 238.0994; found 238.0989.

1.1.5. 2-(2-Oxo-3-phenylpropyl)benzoic acid (12a) and 3-benzylisochromen-1-one (13). 1.5 mL of the Jones reagent (500 mg of CrO_3, 1 mL H_2O, 0.5 mL H_2SO_4) was added to solution of ketoaldehyde **11a** in acetone (12 mL) under a dry atmosphere. The mixture was stirred at rt for 45 min, isopropyl alcohol (1 mL) was added and the acetone was evaporated in vacuo. The resulting suspension was extracted with dichloromethane (3×75 mL) and the combined organic layers were washed with 10% aq NaOH (3× 75 mL) and concentrated to dryness in vacuo. Isochromanone **13** was obtained in 18% yield as a yellow liquid. IR ($\bar{\nu}$, cm^{-1}, NaCl): 1727 (C=O). ^{1}H NMR (δ, ppm): 3.85 (s, 2H, $-CH_2-$), 6.16 (s, 1H, –CH=C–), 7.29–7.48 (m, 6H, 6×Ar–H), 7.45 (m, 1H, Ar–H), 7.65 (m, 1H, Ar–H), 8.24 (m, 1H, Ar–H). ^{13}C NMR (δ, ppm): 39.8 ($-CH_2-$), 103.9 (–CH–), 120.1 (C), 125.2 (CH), 127.2 (CH), 127.8 (CH), 128.7 (2×CH), 129.3 (2×CH), 129.5 (CH), 134.7 (CH), 135.7 (C), 137.3 (C), 157.0 (C–O), 162.8 (C=O). MS (*m/z*, %): 236 (M^+, 44), 89 (11).

The basic organic extracts were neutralized with concentrated HCl and the resulting suspension was extracted with dichloromethane (3×100 mL). The combined organic extracts were washed with water (2×100 mL), dried and concentrated to dryness in vacuo to give 82% yield of the ketoacid **12a** (108 mg) as white crystals. Mp 133–135 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 2931–2856 (OH), 1714 (COOH) 1693 (C=O). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.83 (s, 2H, CH_2), 4.14 (s, 2H, CH_2), 7.20–7.38 (m, 7H, 7×Ar–H), 7.49 (t, 1H, J=7.1 Hz, Ar–H), 7.92 (dd, 1H, J=7.6, 1.1 Hz, Ar–H). ^{13}C NMR (δ, ppm, DMSO): 48.2 (CH_2), 48.8 (CH_2), 126.7 (CH), 127.2 (2×CH), 128.4 (2×CH), 130.1 (CH), 130.6 (CH), 132.3 (CH), 132.7 (CH), 135.2 (C), 136.1 (C), 137.2 (C), 168.4 ($-CO_2H$), 205.0 (C=O). MS (*m/z*, %): 236 [$(M-18)^+$, 19], 135 (100).

1.1.6. 2-(2-Oxo-3-phenylpropyl)benzoic acid methyl ester (12b). A solution of ketoacid **12a** (160 mg, 0.63 mmol) and concentrated sulfuric acid (1 mL) in methanol (20 mL) was heated under reflux in a dry atmosphere for 75 min. The methanol was evaporated in vacuo and the residue was poured into saturated sodium bicarbonate (50 mL). The suspension was extracted with dichloromethane (3×50 mL). The combined organic layers were dried and concentrated to dryness in vacuo. The solid residue was submitted to column chromatography (eluent AcOEt/hexane, 1:9) to give isochormanone **13** (0.09 mmol, 14% yield) and ketoester **12b** (0.43 mmol, 68% yield) as a yellow oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 1726 (C=O), 1655 (C=O). ^{1}H NMR (δ, ppm): 3.83 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 4.11 (s, 2H, CH_2), 7.11 (d, 1H, J=7.5 Hz, Ar–H), 7.25–7.37 (m, 6H, 6×Ar–H), 7.45 (m, 1H, Ar–H), 8.03 (dd, 1H, J= 7.8, 1.4 Hz, Ar–H). ^{13}C NMR (δ, ppm): 48.2 (CH_2), 49.8 (CH_2), 51.9 (OCH_3), 126.9 (CH), 127.2 (CH), 128.6 (2×CH), 129.2 (C), 129.7 (2×CH), 131.0 (CH), 132.3 (CH), 132.5 (CH), 134.4 (C), 136.7 (C), 167.4 (C=O), 205.2 (C=O). MS (*m/z*, %): 268 (M^+, 1), 91 (100).

1.1.7. 3-Benzyl-isochromen-1-one (13). A mixture of sodium methoxide (10.8 mg, 0.2 mmol) and ketoester **12b** (300 mg, 1.12 mmol) in dry methanol (10 mL) was heated under reflux during 3 h. The reaction mixture was acidified by adding 10% aq HCl and the resulting suspension was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with water (25 mL), dried and concentrated to dryness in vacuo to give quantitative yield of the title compound as a yellow oil.

1.1.8. 3-Phenylnaphthalen-2-ol (14a). A solution of ketoaldehyde **11a** (86 mg, 0.36 mmol) in 5% aq NaOH (5 mL) was stirred under a dry atmosphere at rt for 2 h. The reaction mixture was acidified by adding 10% aq HCl and the resulting suspension was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with water (25 mL), dried and concentrated to

dryness in vacuo to give a quantitative yield of the target compound as a white solid. Mp 87–89 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 3457 (–OH). ^1H NMR (δ, ppm): 5.44 (br s, 1H, –OH), 7.35–7.68 (m, 8H, 8×Ar–H), 7.74–7.83 (m, 3H, 3×Ar–H). ^{13}C NMR (δ, ppm): 110.3 (CH), 124.0 (CH), 126.3 (CH), 126.6 (CH), 127.9 (CH), 128.2 (CH), 129.3 (CH), 129.4 (2×CH), 129.7 (2×CH), 130.6 (C), 134.4 (C), 137.0 (C), 150.9 (C–OH). MS (*m/z*, %): 220 (M^+, 100). Anal. Calcd for $C_{16}H_{12}O$, C: 87.25; H: 5.49. Found C: 87.14; H: 5.51.

1.1.9. 3-Phenyl-1,2-naphthoquinone (15a). A solution of Fremy's salt (682 mg, 2.54 mmol) and potassium biphosphate (120 mg, 0.88 mmol) in water (18 mL) was added to a solution of naphthol **14a** (80 mg, 0.34 mmol) in acetone (10 mL). The suspension was stirred in a dry atmosphere at rt for 1 h and the acetone was evaporated in vacuo. The pink suspension was extracted with dichloromethane (3× 25 mL) and the combined organic layers were washed with water (25 mL), dried and concentrated to dryness in vacuo. The remaining solid residue was submitted to flash column chromatography (eluent: AcOEt/hexane, 1:9) and the target compound **15a** was isolated (57 mg, 68% yield) as a pink solid. Mp 125–127 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1663 (C=O). ^1H NMR (δ, ppm): 7.31–7.47 (m, 8H, 7×Ar–H and –CH=C–), 7.58 (m, 1H, Ar–H), 8.03 (d, 1H, J= 7.6 Hz, Ar–H). ^{13}C NMR (δ, ppm): 128.4 (2×CH), 128.5 (2×CH), 128.9 (CH), 130.0 (CH), 130.1 (CH), 130.4 (CH), 130.8 (C), 134.1 (C), 135.3 (C), 136.0 (CH), 138.8 (C), 141.9 (CH), 179.1 (C=O), 180.0 (C=O). MS (*m/z*, %): 234 (M^+, 4), 206 (100).

1.1.10. 2-Hydroxy-3-phenyl-[1,4]naphthoquinone (2a). A suspension of quinone **14a** (27 mg, 0.12 mmol), MeOH (2 mL) and 20% aq NaOH (2 mL) was stirred under a dry atmosphere at rt for 15 min. The mixture was acidified with 2 M HCl and extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with water (25 mL), dried and concentrated to dryness in vacuo to yield the target quinone **2a** (0.11 g, 93% yield) as a red solid. Mp 47–49 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 3425 (–OH), 1710 (C=O), 1650 (C=O). ^1H NMR (δ ppm): 7.40–7.54 (m, 5H, 5×Ar–H), 7.72–7.85 (m, 2H, 2×Ar–H), 8.15–8.23 (m, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm): 126.2 (CH), 127.3 (CH), 128.0 (2×CH), 128.7 (CH), 129.3 (C), 129.9 (C), 130.6 (2×CH), 133.0 (C), 133.2 (CH), 135.3 (CH), 152.2 (C–OH), 181.9 (C=O), 183.1 (C=O). MS (*m/z*, %): 250 (M^+, 5), 149 (100).

1.1.11. (*E*)-2-Benzylidene-5-methoxy-indan-1-one (8b). In a similar way to **8a**, reaction of methoxyindanone **7b** (4.0 g, 24.66 mmol) and benzaldehyde (2.7 mL, 26.17 mmol) gave 81% yield of the title compound as white crystals. Mp 171–173 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1686 (C=O). ^1H NMR (δ, ppm): 3.90 (s, 3H, OMe), 3.98 (d, J=1.0 Hz, 2H, CH_2), 6.92–6.97 (m, 2H, HC=C and ArH), 7.38–7.48 (m, 3H, 3×ArH), 7.59–7.66 (m, 3H, 3×ArH), 7.84 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (δ, ppm): 32.4 (CH_2), 55.6 (OMe), 109.6 (CH), 115.2 (CH), 126.1 (CH), 128.8 (2×CH), 129.3 (C), 130.5 (2×CH), 131.4 (C), 132.6 (CH), 135.2 (C), 135.5 (C), 152.5 (C), 165.2 (C), 192.7 (C=O). MS (*m/z*, %, CI): (251 [(M^++1), 100].

1.1.12. 2-Benzyl-5-methoxyindan-1-one (9b). Benzylydeneindanone **8b** was submitted to catalytic hydrogenation under the same conditions as for **8a** to give a quantitative yield of the title compound as white crystals. Mp 102–104 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1689 (C=O). ^1H NMR (δ, ppm): 2.61–2.83 (m, 2H, –CH_2–), 2.94–3.14 (m, 2H, –CH_2–), 3.38 (dd, J=4.1, 13.9 Hz, 1H, –CH–), 3.85 (s, 3H, –OMe), 6.82–6.91 (m, 2H, 2×ArH), 7.19–7.32 (m, 5H, 5×ArH), 7.71 (d, J=8.5 Hz, 1H, ArH). ^{13}C NMR (δ, ppm): 32.1 (CH_2), 37.1 (CH_2), 49.0 (CH), 55.5 (OMe), 109.6 (CH), 115.3 (CH), 125.6 (CH), 126.2 (CH), 128.4 (2×CH), 128.9 (2×CH), 129.7 (C), 139.7 (C), 156.5 (C), 165.4 (C), 205.9 (C=O). MS (*m/z*, %): 252 (M^+, 33), 161 (100). Anal. Calcd for $C_{17}H_{16}O_2$, C: 80.93; H: 6.39. Found C: 81.09; H: 6.12.

1.1.13. 2-Benzyl-5-methoxy-1*H*-indene (10b). Reaction of benzylmethoxyindanone **9b** (2.84 g, 11.27 mmol) with $NaBH_4$ and then with H_2SO_4, in a similar way to **10a**, gave 76% yield of the title compound (1.39 g) as a white solid. Mp 64–66 °C (MeOH/Et_2O). ^1H NMR (δ, ppm): 3.27 (s, 2H, CH_2), 3.81 (s, 2H, CH_2), 3.82 (s, 3H, OMe), 6.47 (s, 1H, =CH), 6.81 (dd, J=8.2 Hz, J'=2.3 Hz, 1H, ArH), 6.98 (d, J=1.3 Hz, 1H, ArH), 7.17–7.36 (m, 6H, 6×ArH). ^{13}C NMR (δ, ppm): 37.9 (CH_2), 40.8 (CH_2), 55.5 (OMe), 110.4 (CH), 111.6 (CH), 120.3 (CH), 126.1 (CH), 127.1 (CH), 128.4 (2×CH), 128.8 (2×CH), 138.4 (C), 140.2 (C), 145.2 (C), 146.9 (C), 157.3 (C). MS (*m/z*, %): 236 (M^+, 38), 145 (100). Anal. Calcd for $C_{17}H_{16}O$, C: 86.40; H: 6.82. Found C: 86.67; H: 6.69.

1.1.14. 2-(4-Methoxy-2-oxo-3-phenylpropyl)benzaldehyde (11b). Ozonolysis of compound **10b** under the same conditions as for **10a** gave a 72% yield of the title compound as a white solid. Mp 164–166 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1705 (C=O), 1718 (–CHO). ^1H NMR (δ, ppm): 3.83 (s, 3H, –OMe), 3.93 (s, 2H, CH_2), 4.09 (s, 2H, CH_2), 6.64 (d, J=2.5 Hz, 1H, ArH), 6.92 (m, 1H, ArH), 7.26–7.36 (m, 5H, 5×ArH), 7.71 (d, J=8.5 Hz, 1H, ArH), 9.84 (s, 1H, CHO). ^{13}C NMR (δ, ppm): 47.0 (CH_2), 50.0 (CH_2), 55.4 (OMe), 112.1 (CH), 118.7 (CH), 126.9 (–CH), 127.6 (C), 128.5 (2×CH), 129.7 (2×CH), 134.3 (C), 137.9 (CH), 138.3 (C), 163.5 (C), 191.6 (CHO), 204.6 (C=O). MS (*m/z*, %): 268 (M^+, 5), 91 (100). Anal. Calcd for $C_{17}H_{16}O_3$, C: 76.10; H: 6.01. Found C: 69.91; H: 6.27.

1.1.15. 7-Methoxy-3-phenyl-naphthalen-2-ol (14b). In a similar way to **14a**, reaction of the ketoaldehyde **11b** (559 mg, 2.08 mmol) with 5% aq NaOH provided the title compound (502 mg, 97%) as a white solid. Mp 164–166 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 3405 (OH). ^1H NMR (δ, ppm): 3.94 (s, 3H, –OMe), 5.67 (s, 1H, OH), 7.05–7.10 (m, 2H, 2×ArH), 7.45–7.73 (m, 7H, 8×ArH). ^{13}C NMR (δ, ppm): 55.2 (OMe), 104.2 (CH), 109.4 (CH), 116.5 (CH), 124.2 (C), 127.6 (CH), 127.8 (C), 128.9 (2×CH), 129.1 (2×CH), 129.2 (CH), 129.2 (CH), 135.4 (C), 136.9 (C), 151.2 (C), 157.9 (C). MS (*m/z*, %): 250 (M^+, 100). Anal. Calcd for $C_{17}H_{14}O_2$, C: 81.58; H: 5.64. Found C: 81.29; H: 6.47.

1.1.16. 7-Metoxy-3-phenyl-1,2-naphthoquinone (15b). Reaction of naphthol **14b** (194 mg, 0.78 mmol) with Fremy's salt (1.46 mg, 5.43 mmol) and potassium biphosphate (256 mg, 1.88 mmol) under the same conditions as for

the oxidation of **14a**, gave 63% yield of the title compound (123 mg) as a pink solid. Mp 167–169 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1662 (C=O), 1648 (C=O). ^1H NMR (δ, ppm): 3.88 (s, 3H, OMe), 7.11 (m, 2H, =CH and ArH), 7.29–7.55 (m, 7H, 7×ArH). ^{13}C NMR (δ, ppm): 55.8 (OMe), 114.3 (CH), 121.9 (CH), 128.2 (C), 128.2 (4×CH), 128.4 (CH), 131.7 (CH), 132.0 (C), 134.2 (C), 135.7 (C), 142.1 (CH), 161.3 (C), 178.7 (C=O), 179.6 (C=O). MS (*m*/*z*, %): 264 (M^+, 19), 236 (100). Anal. Calcd for $C_{17}H_{12}O_3$, C: 77.26; H: 4.58. Found C: 76.91; H: 4.60.

1.1.17. 2-Hydroxy-7-methoxy-3-phenyl-[1,4]naphthoquinone (2b). Reaction of *o*-naphthoquinone **14b** with 20% aq NaOH under the same conditions as for the preparation of **14a** gave 90% yield of the title compound as a red solid. Mp 164–166 °C (MeOH/Benzene). IR ($\bar{\nu}$, cm^{-1}, KBr): 3327 (OH), 1660 (C=O), 1596 (C=O). ^1H NMR (δ, ppm): 3.94 (s, 3H, –OMe), 7.21–7.25 (m, 1H, ArH), 7.37–7.55 (m, 6H, 6×ArH), 8.10 (d, J=8.8 Hz, 1H, ArH). ^{13}C NMR (δ, ppm): 56.0 (OMe), 109.6 (CH), 121.2 (CH), 121.7 (C), 125.9 (C), 127.7 (2×CH), 128.5 (CH), 129.4 (CH), 129.9 (C), 130.6 (2×CH), 130.8 (C), 151.8 (C), 163.3 (C), 181.8 (C=O), 182.9 (C=O). MS (*m*/*z*, %): 280 (M^+, 100). Anal. Calcd for $C_{17}H_{12}O_3$, C: 72.85; H: 4.32. Found C: 73.12; H: 3.97.

Acknowledgements

We thank the Spanish Ministry of Science and Technology and the Xunta de Galicia for financial support, and the latter for grants to Ana Martínez and to Marcos Fernández.

References and notes

1. *The Chemistry of the Quinoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1988.
2. (a) Tisler, M. In *Heterocyclic Quinones*; Katritzky, A. R., Ed.; Advances in Heterocyclic Chemistry; Academic: London, 1989; Vol. 45, p 37. (b) Thomson, R. H. *Naturally Occurring Quinones*, 4th ed.; Chapman & Hall: London, 1997.
3. For a recent review, see: Spyroudis, S. *Molecules* **2002**, *5*, 1291.
4. Mehendale, A. R.; Thomson, R. H. Binaphthoquinones in *Lomatia ferruginea*. *Phytochemistry* **1975**, *14*, 801–802.
5. (a) Barcia, J. C.; Cruces, J.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **2002**, *43*, 5141. (b) Yin, J.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 5726–5727. (c) Mackenzie, N. E.; Surendrakumar, S.; Thomson, R. H.; Cowe, H. J.; Cox, P. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2233.
6. (a) Emadi, A.; Harwood, J. S.; Kohanim, S.; Stagliano, K. W. *Org. Lett.* **2002**, *4*, 521. (b) Krohn, K.; Rieger, H.; Khanbabaee, K. *Chem. Ber.* **1989**, *122*, 2323. (c) Barton, D. H. R.; Finet, J. P.; Thomas, M. *Tetrahedron* **1988**, *44*, 6397. (d) Murali, D.; Rao, G. S. K. *Indian J. Chem., Sect. B* **1987**, *26B*, 668. (e) Duchstein, H. s. J. *Arch. Pharm.* **1987**, *320*, 460. (f) Laatsch, H. *Liebigs Ann. Chem.* **1985**, 1847. (g) Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1473. (h) Sukumaran, K. B.; Harvey, R. G. B. *J. Org. Chem.* **1980**, *45*, 4407. (i) Ishii, H.; Hanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron* **1976**, *32*, 2693.
7. (a) Chauhan, S. M. S.; Kalra, B.; Mohapatra, P. P. *J. Mol. Catal.* **1999**, *137*, 85. (b) Suresh, S.; Skaria, S.; Ponrathnam, S. *Synth. Commun.* **1996**, *26*, 2113. (c) Krohn, K.; Rieger, H.; Brueggmann, K. *Synthesis* **1990**, 1141. (d) Suzuki, J.; Watanabe, T.; Suzuki, S. *Chem. Pharm. Bull.* **1988**, *36*, 2204. (e) Lemaire, M.; Guy, A.; Roussel, J.; Guette, J. P. *Tetrahedron* **1987**, *43*, 835. (f) Pinto, A. V.; Ferreira, V. F.; Pinto, M. C. F. R. *Synth. Commun.* **1985**, *15*, 1177. (g) Arzeno, H.; Barton, D. H. R.; Berge-Lurion, R. M.; Lusinchi, X.; Pinto, B. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2069. (h) Horner, L.; Weber, K. H. *Chem. Ber.* **1965**, 1246.
8. For recent examples on the oxidation of naphthols to naphthoquinones, see: (a) Chen, X.; Zhang, J. S.; Zhao, M. *Chin. Chem. Lett.* **2001**, *12*, 297. (b) Ray, J. K.; Gupta, S.; Kar, G. K.; Roy, B. C.; Lin, J.-M.; Amin, S. *J. Org. Chem.* **2000**, *65*, 8134. (c) Kumar, S.; Kim, T.-Y. *J. Org. Chem.* **2000**, *65*, 3883. (d) Couladouros, E. A.; Strongilos, A. T. *Tetrahedron Lett.* **2000**, *41*, 535. (e) Buttery, J. H.; Wege, D. *Aust. J. Chem.* **1998**, *51*, 409. (f) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928.
9. (a) Croux, S.; Maurette, M.-T.; Hocquaux, M.; Ananides, A.; Braun, A. M.; Oliveros, E. *New J. Chem.* **1990**, *14*, 161–167. (b) Min, D. M.; Croux, S.; Tournair, C.; Hocquaux, M.; Jacquet, B.; Oliveros, E.; Maurette, M.-T. *Tetrahedron* **1990**, *48*, 1869–1882. (c) Bekaert, A.; Andrieux, J.; Plat, M.; Brion, J.-D. *Tetrahedron Lett.* **1997**, *38*, 4219–4220.
10. (a) Lipshutz, B. H.; Shin, Y.-J. *Tetrahedron Lett.* **1998**, *39*, 7017. (b) Kost, A. N.; Terenin, V. I.; Yudin, L. G.; Sagitullin, R. S. *Khim. Geterotsiklich. Soedin.* **1980**, 1272. (c) Fields, D. L. *J. Org. Chem.* **1971**, *36*, 3002.
11. For previous, low yielding methods for the synthesis of 3-phenyl-1,2-naphthoquinones, see: (a) Mackenzie, N. E.; Surendrakumar, S.; Thomson, R. H.; Cowe, H. J.; Cox, P. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2233. (b) Asselin, J.; Brassard, P.; L'Ecuyer, P. *Can. J. Chem.* **1966**, *44*, 2563.
12. (a) Martinez, E.; Martinez, L.; Treus, M.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **2000**, *56*, 6023. (b) Martínez, E.; Martínez, L.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **1998**, *39*, 2175–2176. (c) Cheng, C. C.; Dong, Q.; Liu, D. F.; Luo, Y. L.; Liu, L. F.; Chen, A. Y.; Yu, C.; Savaraj, N.; Chou, T. C. *J. Med. Chem.* **1993**, *36*, 4108.
13. (a) Gabaja, C.; Perchelet, E. M.; Perchellet, J.-P.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 3007–3010. (b) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. (c) Echavarren, A. M.; Tamayo, N.; Cardenas, D. J. *J. Org. Chem.* **1994**, *59*, 6075. (d) Watanabe, M.; Date, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 292.
14. (a) Kobayashi, K.; Taki, T.; Kawakita, M.; Uchida, M.; Morikawa, O.; Konishi, H. *Heterocycles* **1999**, *51*, 349–354. (b) Echavarren, A. M.; Tamayo, N.; De Frutos, O.; Garcia, A. *Tetrahedron* **1997**, *53*, 16835. (c) Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **1993**, *34*, 6479.
15. Martínez, A.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **2000**, *41*, 2365–2367.
16. For a previous lower yielding preparation of benzylydeneindanone **8a**, see: Titouani, S.; Soufiaoui, M.; Toupet, L.; Carrie, R. *Tetrahedron* **1990**, *46*, 3869. For a lower yielding preparation of **8a** in acidic conditions, see: Berthelette, C.;

McCooye, C.; Leblanc, Y.; Trimble, L. A.; Tsou, N. N. *J. Org. Chem.* **1997**, *62*, 4339.
17. (a) Basavaiah, D.; Reddy, R. M. *Tetrahedron Lett.* **2001**, *42*, 3025. (b) Buttery, J. H.; Wege, D. *Aust. J. Chem.* **1998**, *51*, 409.
18. Chatterjee, A.; Dutta, L. N.; Chatterjee, S. K. *Indian J. Chem., Sect. B* **1980**, *19B*, 955.
19. Campbell, N.; Davison, P. S.; Heller, H. G. *J. Chem. Soc.* **1963**, 993.
20. Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, 5353.
21. Rangarajan, R.; Eisenbraun, E. J. *J. Org. Chem.* **1985**, *50*, 2435.
22. For a previous less efficient synthesis of ketoacid **12a**, see: Schnekenburger, J. *Arch. Pharm.* **1964**, *279*, 734.
23. Rama, N. H.; Iqbal, R.; Zamani, K.; Malik, A. *Indian J. Chem., Sect. B* **1998**, *37B*, 1021.
24. Tewari, S. C.; Rastogi, S. N.; Anand, N. *Indian J. Chem., Sect. B* **1980**, *19B*, 139.
25. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 493–500

Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides

Ming-Chang P. Yeh,* Chi-Fen Jou, Wei-Tzou Yeh, Da-Yu Chiu and N. Ravi Kumar Reddy

Department of Chemistry, National Taiwan Normal University, 88 Ding-Jou Road, Section 4, Taipei 117, Taiwan, ROC

Received 3 September 2004; accepted 12 October 2004

Abstract—Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and -1,3,5-triene-tethered nitrile oxides gave tricyclic isoxazolines as a single stereoisomer in most cases. The relative stereochemistry of tricycle-fused isoxazolines resulting from 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides is *cis–cis*, whereas from cyclohepta-1,3,5-triene-tethered nitrile oxides the *cis–trans* isomer predominates.

1. Introduction

Cycloaddition of nitrile oxide and olefin produces isoxazoline derivatives, which has played an important role for the construction of five-membered heterocycles. The isoxazoline ring has been revealed to be a latent precursor for a variety of difunctional compounds like γ-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles and unsaturated oximes,[1] therefore the heterocycles has been utilized for construction of natural products having such functionalities.[2] On the other hand, the intramolecular cycloaddition is useful synthetic strategy to yield bicyclic compounds, which often proceeds with high regio- and stereoselectivity. When nitrile oxides were used as the intramolecular 1,3-dipole, bicyclic isoxazolines were produced.[3–5] For example, norbonadiene-tethered nitrile oxides underwent intramolecular cycloaddition to afford good yields of highly regio- and stereoselective tetracyclic compounds.[6] Recently, we are interested in the intramolecular cycloaddition of conjugated dienes with nitrile oxides because of highly stereoselective polycyclic products as new building blocks for synthesis of naturally occurring materials. Surprisingly, reports on the intramolecular cycloaddition of conjugated dienes and nitrile oxides are rare.[7] This report describes synthesis of cyclo-1,3-diene- and 1,3,5-triene-tethered nitrile oxides by treatment of the corresponding aldoximes with *n*-BuLi and *N*-chlorosuccinimide (NCS), and the intramolecular 1,3-dipolar cycloaddition.

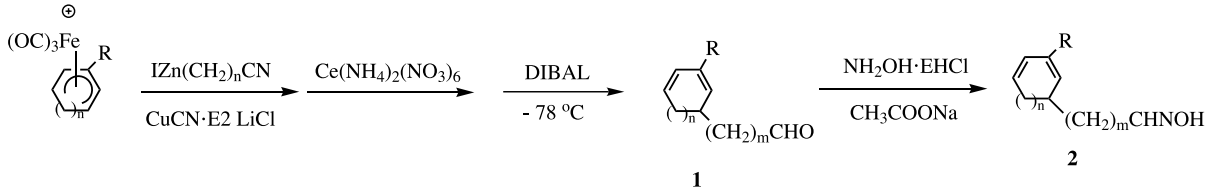
Keywords: Aldoximes; Isoxazolines; Cyclohexa- and cyclohepta-1,3-dienes; Cyclohepta-1,3,5-trienes.
* Corresponding author. Tel.: +886 2 29350750; fax: +886 2 29324249; e-mail: cheyeh@scc.ntnu.edu.tw

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.078

2. Results and discussion

Cyclo-1,3-dienaldoximes were synthesized according to the literature procedures.[8–11] As shown in Scheme 1, the starting cyclohexa-1,3-dienaldoximes **2a–f** were prepared starting from addition of functionalized zinc–copper reagents to (η^5-cyclohexadienyl)tricarbonyliron cation salt. Treating cyclohexa-1,3-dienals **1a–f**[8,9] with NH_2-OH·HCl and CH_3COONa in MeOH at 30 °C afforded **2a–f** (entries 1–6, Table 1). Cyclohepta-1,3-dienaldoximes **2g–h** (entries 7–8, Table 1) were synthesized in the similar fashion starting from (η^5-cycloheptadienyl)tricarbonyliron cation salt.[8,10] Cyclohepta-1,3,5-triene derivatives **3a–c** (entries 10–12, Table 1) were synthesized starting from the corresponding zinc–copper reagents and (η^7-cycloheptatrienyl)tricarbonylchromium cation salt (Scheme 2).[8,11]

Dienaldoxime **2a** in CH_2Cl_2 solution (0.03 M) was treated with NCS (1.3 mol equiv) at 30 °C for 2 h followed by slow addition of triethylamine (1.5 mol equiv) at 0 °C. The reaction was stirred at 30 °C for 24 h and led in 45% yield to tricyclic isoxazoline **4** (entry 1, Table 1). The other method was employed to produce the corresponding nitrile oxide using *n*-BuLi as base. Reaction of *n*-BuLi (1.1 mol equiv) with **2a** at 0 °C for 30 min followed by addition of NCS (1.3 mol equiv, 0.03 M in THF) gave a light yellow solution. The yellow solution was stirred at 30 °C for 3 h under nitrogen to give compound **4** as the only diastereomer isolated in 64% (entry 1, Table 1) after chromatographic purification. Thus, the use of the C-5 tethered cyclohexa-1,3-dienaldoxime allowed controlling the stereochemistry of three contiguous asymmetric centers of the tricycle-fused isoxazolines in a single step. Moreover, the current reaction



a : R = H, m = 2, n = 1

b : R = H, m = 3, n = 1

d : R = $SiMe_2Ph$, m = 3, n = 1
e : R = $SiMe_2Ph$, m = 4, n = 1
g : R = H, m = 2, n = 2

h : R = H, m = 3 , n = 2

Scheme 1.

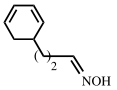
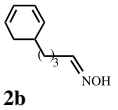
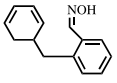
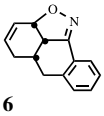
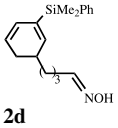
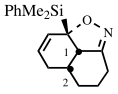
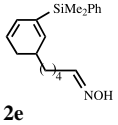
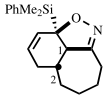
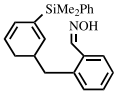
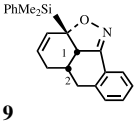
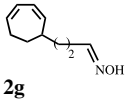
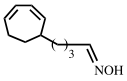
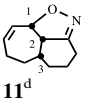
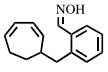
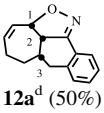
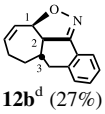
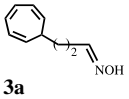
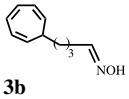
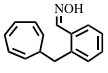
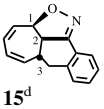
condition (*n*-BuLi, NCS, and cyclo-1,3-dienaldoxime, 30 °C, 3 h) for 1,3-dipolar cycloaddition is easier than those of alkene analogs, which normally required higher temperatures (80–110 °C) and longer hours (15–48 h).[6] NMR studies provided the initial evidence for support of the structural assignments. The ^{1}H NMR spectrum of compound **4** exhibited a multiplet at δ 5.96 assigned to the vinyl H at C-7 (Scheme 3); a broad doublet at δ 5.76 assigned to the vinyl H at C-6; a doublet of doublets, centered at δ 4.92 assigned to the methine H at C-7a; a doublet of doublets at δ 3.83 assigned to the methine H at C-7b. The C-13 NMR spectrum exhibited a signal at δ 170.1 assigned to C-2a (iminyl); two signals at δ 130.7 and 125.2 assigned to two vinyl carbons (C-6 and C-7); and a signal at δ 74.6 assigned to C-7a. The relative stereochemistry for **4** was assigned by NOESY (nuclear Overhauser enhancement spectroscopy) measurements. For example, cross peaks for **7a** and **7b** and **7b** and **4a** in the NOSEY spectrum indicated that *cis–cis* relative stereochemistry for the three fused methine protons. The stereochemical outcome suggested that the dipole is aligned to the face of the cyclohexadiene in which the tethering chain resides (Scheme 3). This stereoselectivity is consistent to those of 1,3-dipolar cycloaddition of cyclohexene-tethered nitrile oxides.[4c] Under the same reaction condition, tricyclic isoxazolines **5** (70%) and **6** (66%) were produced from intramolecular 1,3-dipolar cycloadditions of **2b** (entry 2, Table 1) and **2c** (entry 3, Table 1), respectively. The *cis–cis* relative stereochemistry assigned for both **5** and **6** was based on NOSEY measurements and comparison of their coupling constants of fused methine protons with the corresponding data of **4**.

Several entries in Table 1 deserve special mention. Substrates with a bulky dimethylphenylsilyl group at the C-3 position of the cyclohexa-1,3-diene ring, **2d–f** (entries 4–6, Table 1), also underwent intramolecular dipolar cycloaddition to produce **7** (39%), **8** (25%), and **9** (48%), respectively, as the only diastereomeric product in each case. Since norbornadiene derivative, **16**, with a trimethylsilyl group at the olefinic carbon failed to give cycloadducts after stirring in toluene at 90 °C for 96 h (Eq. 1),[11] it is reasonable to state that cyclo-1,3-diene-tethered nitrile oxides are more reactive substrates than unconjugated norbornadiene analogs. The *cis* relationship for the dimethylphenylsilyl group and H_1 of **7** is fixed by syn cycloaddition of the olefin with the tethered nitrile oxide. The relative stereochemistry for H_1 and H_2 assigned as *cis* came from the coupling constant of 5.2 Hz for H_1–H_2, which is close to those of the same methine protons of **5** (6.5 Hz) and **6** (5.2 Hz). The *cis–cis* stereochemistry was secured by X-ray diffraction analysis of **7**. Similarly, the relative configuration for the two fused methine protons of **9** determined to be *cis* was based on the coupling constant of 4.7 Hz for H_1–H_2. However, a coupling constant of 10.4 Hz for H_1–H_2 of **8** suggested a *trans* relationship between H_1 and H_2. This assignment was further confirmed by comparison of the coupling constant with those of *trans* methine fused protons of **12b** and **13–15** (see below). The stereochemical course of formation of tricyclic isoxazoline **8** indicated that the tether with four methylene carbons may be long enough for the dipole to align to the dipolarophile on the opposite face of the cyclohexadiene ring (Scheme 4).

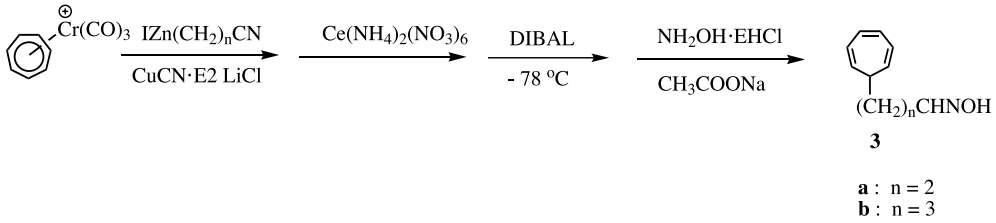
Increasing the ring size by one with the cyclohepta-1,3-diene derivatives **2g** (entry 7, Table 1) and **2h** (entry 8, Table 1) also underwent 1,3-dipolar cycloaddition to provide tricyclic isoxazolines **10** (70%) and **11** (60%), respectively, as the only stereoisomer in each case. The *cis–cis* configurations of **10** and **11** were secured by X-ray diffraction analysis. Surprisingly, 1,3-dipolar cycloaddition of cyclohepta-1,3-diene containing an aromatic nitrile oxide, **2i**, generated a mixture of diastereomers **12a** (50%) and **12b** (20%) (entry 9, Table 1). The structure for **12a** was established using coupling constants of H_1–H_2 and H_2–H_3. The centered H_2 of **12a** exhibited as a doublet of doublets with coupling constants of 11.2 and 4.4 Hz which are close to those of **10** (11.0, 7.5 Hz) and **11** (10.8, 5.3 Hz). However, the ^{1}H NMR spectrum of **12b** revealed a triplet for H_2 at δ 3.25, with a coupling constant of 12.1 Hz. The large coupling constant indicated a *cis* relationship between H_1 and H_2 and a *trans* relationship between H_2 and H_3 in the tricycle-fused isoxazoline **12b**. Rigorous proof of the structures were accomplished by X-ray diffraction analysis of **12a** and **12b**. The generation of both diasteroisomers **12a** and **12b** suggested that 1,3-dipolar cycloaddition of **2i** occurred on both faces of the cycloheptadiene ring.

Under the same reaction condition, cyclohepta-1,3,5-triene-tethered nitrile oxides **3a–3c** (entries 10–12, Table 1) afforded tricyclic isoxazolines **13** (15%), **14** (80%), and **15** (68%), respectively, as a single stereoisomer in each case. The structures for **13–15** were established as *cis–trans* by

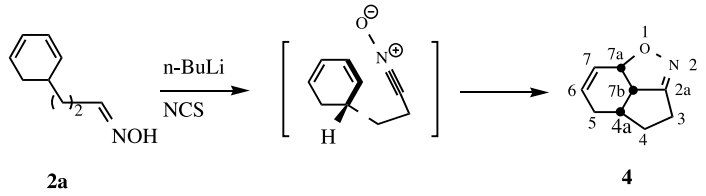
Table 1. Intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene-tethered nitrile oxides

Entry[a]	Dienaldoximes	Cycloadducts		Yield[b]
1	 **2a**	 **4**		64%[a]
2	 **2b**	 **5**		70%[a]
3	 **2c**	 **6**		66%[a]
4	 **2d**	 **7**[d]		39%[c]
5	 **2e**	 **8**		25%[c]
6	 **2f**	 **9**		48%[c]
7	 **2g**	 **10**[d]		70%[a]
8	 **2h**	 **11**[d]		60%[a]
9	 **2i**	 **12a**[d] (50%)	 **12b**[d] (27%)	77%[a]
10	 **3a**	 **13**[d]		15%[c]
11	 **3b**	 **14**[d]		80%[a]
12	 **3c**	 **15**[d]		68%[a]

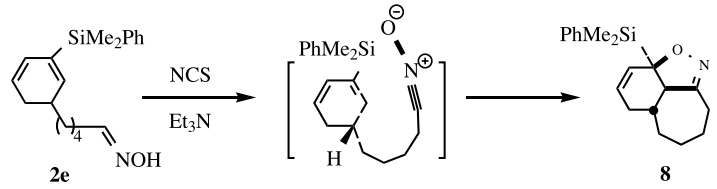
[a] Cyclizations were carried out in THF using *n*-BuLi (1.2 equiv) and NCS at 30 °C for 3 h.
[b] Isolated yields after column chromatography.
[c] Cyclizations were carried out in THF using Et_3N (1.2 equiv) and NCS at 30 °C for 24 h.
[d] The structure is confimed by X-ray diffraction analysis.



Scheme 2.

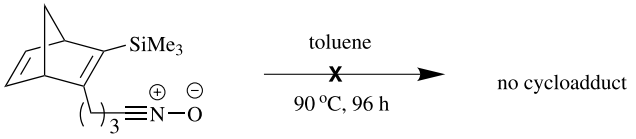


Scheme 3.



Scheme 4.

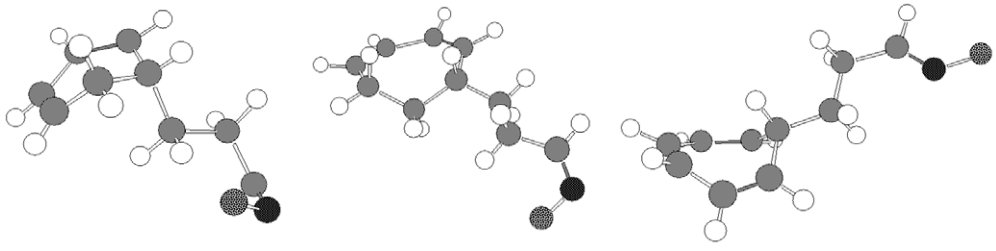
comparison of their ^{1}H NMR spectral data with the corresponding data of **12b**. Rigorous proof of the structures was accomplished by X-ray diffraction analysis of **13**–**15**. The result suggested that 1,3-dipolar cycloaddition of cyclohepta-1,3,5-triene-tethered nitrile oxides occurred on the β-face of the ring. The different stereochemical outcome between cyclic diene and triene analogs may be explained by computer-based modeling methods. Molecular modeling of the cyclohepta-1,3,5-triene derivative **3a** reveals that all six sp^2 carbons of the ring are nearly on the same plane and the C-7 carbon locates above the plane. Thus, the tethered dipole could add to the dipolarophile on the β-face of the ring to give the *cis–trans* diastereomer (Fig. 1). While tethered nitrile oxides of cyclic diene analogs (**2a** and **2g**) locating at the α-face of the ring would approach to the olefine from α-face (Fig. 1).



(1)

3. Conclusion

The reactions outlined herein demonstrate that intramolecular 1,3-dipolar cycloaddition of cyclo-1,3-diene- and 1,3,5-triene-tethered nitrile oxides can be an effective method for synthesis of tricycle-fused isoxazolines in



2a **2g** **3a**

Figure 1.

diastereoselective fashion. Specially, it is a synthetic advantage that the tricycle-fused isoxazolines contain a masked allyl alcohol. In the particular reaction cases demonstrated in this work, products having an α-silyl allyl alcohol functionality masked in the fused isoxazolines are generated. Moreover, tricyclic isoxazolines containing a conjugated diene in a seven-membered ring would be expected to demonstrate still higher levels of synthetic utility.

4. Experimental

4.1. General

All reactions were run under a nitrogen atmosphere in oven-dried glassware unless otherwise indicated. Anhydrous solvents or reaction mixtures were transferred via an oven-dried syringe or cannula. Tetrahydrofuran (THF) was dried by passing through two sequential columns of activated alumina.[12] Aldehydes **1a–b**[8,11] were prepared according to literature procedures. Flash column chromatography, following the method of Still, was carried out with silica gel (230–400 mesh) using the indicated solvents.[13] ^{1}H nuclear magnetic resonance (NMR) spectra were obtained with 400 and 500 MHz spectrometers. The chemical shifts are reported in parts per million with either tetramethylsilane (0.00 ppm) or $CHCl_3$ (7.26 ppm) as internal standard. ^{13}C NMR spectra were recorded frequency of 100 and 125 MHz with $CDCl_3$ (77.0 ppm) as the internal standard. Mass spectra were acquired at an ionization potential of 70 eV and are reported as mass/charge (*m*/*e*) with percent relative abundance. High-resolution mass spectra (HRMS) were obtained with a double-focusing mass spectrometer.

4.2. Typical procedures for intramolecular 1,3-dipolar cycloaddition via sequential additions of hydroxylamine hydrochloride, *N*-chlorosuccinimide, and *n*-BuLi to cyclo-1,3-diene-tethered aldehydes

In a typical procedure, to a 100 mL round bottom flask under nitrogen was added NaOAc (0.63 g, 7.71 mmol), $NH_2OH\cdot HCl$ (0.54 g, 7.71 mmol) and MeOH (10 mL). To the reaction mixture at 30 °C, aldehyde **1a** (0.70 g, 5.14 mmol in 10 mL of MeOH) was added via syringe and was stirred at 30 °C for 2 h. The reaction mixture was concentrated. The resulting mixture was diluted with 50 mL of CH_2Cl_2 and 50 mL of water. The reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The resultant solution was washed with water (3×50 mL) and brine (2×100 mL), dried over anhydrous magnesium sulfate (5.0 g), and concentrated to give the crude mixture (0.70 g, 4.63 mmol, 90%). Flash column chromatography of the crude mixture produced aldoximes as a mixture of Z and E isomers and was used without further separation. To a 100 mL Shlenk flask under nitrogen was added aldoxime **2a** (0.10 g, 0.66 mmol) in 22 mL of THF. To the reaction mixture at −78 °C, *n*-BuLi (0.34 mL, 2.5 M, 0.86 mmol) was added slowly and was stirred at 30 °C for 30 min.[14] To the reaction mixture at 0 °C, NCS (0.11 g, 0.86 mmol) in 15 mL of THF was added slowly via syringe to give a light yellow solution. The reaction mixture was quenched with 30 mL of saturated aqueous ammonium chloride after aldoxime **2a** was no longer appeared on TLC (ca. 3 h). The reaction mixture was extracted with EtOAc (3× 30 mL). The resultant solution was washed with water (3× 50 mL) and brine (2×100 mL), dried over anhydrous magnesium sulfate (5.0 g), and concentrated to give the crude mixture.

4.2.1. Cycloadduct 4. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2a** (0.10 g, 0.66 mmol) using *n*-BuLi (0.34 mL, 2.5 M, 0.86 mmol) and NCS (0.11 g, 0.86 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **4** (0.062 g, 0.42 mmol, 64%) as a yellow oil: IR (CH_2Cl_2) 3052, 2944, 2872, 1652, 1439, 1422, 1391, 1282, 1267, 1256, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.76 (br d, J=10.0 Hz, 1H), 4.92 (dd, J=9.9, 3.7 Hz, 1H), 3.83 (dd, J=9.5, 8.0 Hz, 1H), 2.37 (m, 4H), 2.19 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 130.7, 125.2, 74.6, 54.5, 35.4, 29.2, 24.5, 19.8; MS (EI) *m*/*z* 149.1 (M^+, 30), 132.1 (14), 117.1 (16), 95.0 (11), 91.0 (100), 79.1 (22), 77.0 (19), HRMS (EI) *m*/*z* calcd for $C_9H_{11}NO$ 149.0841, found 149.0842. The relative stereochemistry for **4** was determined by NOESY (nuclear Overhauser enhancement spectroscopy) measurements. Cross peaks for **7a** and **7b** and **7b** and **4a** in the NOSEY spectrum showed a *cis–cis* relationship among these protons.

4.2.2. Cycloadduct 5. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2b** (0.20 g, 1.21 mmol) using *n*-BuLi (0.58 mL, 2.5 M, 1.45 mmol) and NCS (0.21 g, 1.57 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **5** (0.14 g, 0.85 mmol, 70%) as a yellow oil: IR (CH_2Cl_2) 3060, 2942, 2855, 1732, 1657, 1434, 1422, 1394, 1282, 1267, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (ddd, J=10.0, 6.4, 2.1 Hz, 1H), 5.76 (dt, J=11.0, 4.4 Hz, 1H), 5.04 (dd, J=11.0, 4.4 Hz, 1H), 3.33 (dd, J=10.9, 6.5 Hz, 1H), 2.75 (dd, J=11.1, 3.6 Hz, 1H), 2.38 (m, 1H), 2.08 (m, 2H), 1.74 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 132.5, 124.7, 74.4, 48.8, 31.0, 28.6, 24.6, 24.3, 18.7; MS (EI) *m*/*z* 163.1 (M^+, 75), 146.1 (26), 131.1 (21), 117.0 (20), 109.0 (21), 105.1 (36), 91.0 (100), 79.0 (46); 77.0 (30); HRMS (EI) *m*/*z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0996. The relative stereochemistry for **5** was determined by NOESY measurements.

4.2.3. Cycloadduct 6. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2c** (0.30 g, 1.40 mmol) using *n*-BuLi (0.67 mL, 2.5 M, 1.68 mmol) and NCS (0.23 g, 1.68 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **6** (0.20 g, 0.86 mmol, 66%) as a yellow solid: mp 108–110 °C; IR (CH_2Cl_2) 3061, 2986, 2927, 1732, 1610, 1483, 1462, 1438, 1424, 1375, 1282, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=7.9 Hz, 1H), 7.34 (dt, J=7.4, 1.3 Hz, 1H), 7.25 (m, 2H), 6.01 (ddd, J=10.2, 5.9, 1.9 Hz, 1H), 5.72 (dt, J=10.2, 4.2 Hz, 1H), 5.20 (br d, J= 9.5 Hz, 1H), 3.64 (dd, J=9.6, 5.2 Hz, 1H), 3.16 (dd, J= 16.9, 5.6 Hz, 1H), 2.83 (dd, J=16.9, 1.9 Hz, 1H), 2.69 (m,

1H), 2.04 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 136.3, 132.0, 130.5, 129.8, 126.8, 126.0, 125.2, 123.9, 76.3, 47.4, 35.3, 28.5, 25.2; MS (EI) *m/z* 211.1 (M^+, 100), 194.1 (43), 165.1 (41), 116.1 (83), 79.1 (48), 77.0 (32); HRMS (EI) *m/z* calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0998. The relative stereochemistry for **6** was determined by NOESY measurements.

4.2.4. Cycloadduct 7. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2d** (0.26 g, 0.87 mmol) using NCS (0.20 g, 1.46 mmol) and triethylamine (0.15 mL, 1.07 mmol) in CH_2Cl_2 for 24 h was purified by flash-column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **7** (0.10 g, 0.34 mmol, 39%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **7**: mp 89–90 °C; IR (CH_2Cl_2) 3627, 2944, 2854, 1684, 1635, 1428, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.31 (m, 3H), 5.91 (ddd, J=10.1, 5.8, 2.3 Hz, 1H), 5.62 (ddd, J=10.1, 2.9, 1.5 Hz, 1H), 3.03 (d, J=5.2 Hz, 1H), 2.76 (m, 1H), 2.02 (m, 2H), 1.96 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.65 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 0.40 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 135.2, 134.4, 129.6, 129.4, 127.7, 126.2, 76.5, 51.4, 30.4, 29.0, 24.6, 24.2, 18.1, −5.6, −6.1; MS (EI) *m/z* 297.2 (M^+, 8), 255.2 (5), 229.2 (10), 213.1 (4), 153.1 (5), 152.1 (13), 151.1 (100), 137.1 (11), 135.1 (36); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NOSi$ 297.1549, found 297.1550. Anal. Calcd for $C_{18}H_{23}NOSi$: C, 72.68; H, 7.79; N, 4.71. Found: C, 72.98; H, 7.84; N, 4.78. The relative stereochemistry for **7** was confirmed by X-ray diffraction analysis.

4.2.5. Cycloadduct 8. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2e** (0.60 g, 1.91 mmol) using NCS (0.38 g, 2.87 mmol) and triethylamine (0.29 mL, 2.09 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **8** (0.15 g, 0.48 mmol, 25%) as a yellow oil: IR (CH_2Cl_2) 3629, 2927, 2862, 1830, 1636, 1602, 1427 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.40 (m, 3H), 5.91 (br s, 2H), 2.83 (d, J=10.4 Hz, 1H), 2.48 (ddd, J=16.8, 12.2, 4.3 Hz, 1H), 2.15 (dt, J=17.0, 4.3 Hz, 1H), 1.94–1.78 (m, 4H), 1.40 (m, 2H), 1.30 (m, 1H), 1.25 (m, 1H), 1.24 (m, 1H), 0.36 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 134.9, 134.5, 129.4, 127.7, 127.5, 125.9, 81.0, 54.6, 36.8, 35.3, 30.9, 27.9, 26.9, 24.8, −6.3, −6.9; MS (EI) *m/z* 311.2 (M^+, 0), 213.1 (5), 152.1 (10), 151.1 (100), 137.0 (4), 136.1 (4), 135.1 (31), 107.0 (4), 91.0 (9); HRMS (EI) *m/z* calcd for $C_{19}H_{25}NOSi$ 311.1705, found 311.1700. The relative stereochemistry for **8** was determined by the coupling constant between the centered and the adjacent fused methine protons.

4.2.6. Cycloadduct 9. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2f** (0.43 g, 1.25 mmol) using triethylamine (0.20 mL, 1.37 mmol) and NCS (0.20 g, 1.50 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **9** (0.21 g, 0.60 mmol, 48%) as a yellow oil: IR (CH_2Cl_2) 3684, 3070, 3025, 2921, 2838, 1768, 1609, 1460, 1428, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=7.6 Hz, 1H), 7.67 (m, 2H), 7.40 (m, 3H), 7.31 (dt, J=7.5, 1.3 Hz, 1H), 7.23 (m, 2H), 5.89 (ddd, J=10.1, 5.48, 2.12 Hz, 1H), 5.65 (dd, J=10.2, 2.1 Hz, 1H), 3.40 (d, J=4.7 Hz, 1H), 3.03 (dd, J=16.7, 4.6 Hz, 1H), 2.73 (dd, J=16.8, 1.9 Hz, 1H), 2.21 (m, 1H), 1.96 (dt, J=18.0, 5.9 Hz, 1H), 1.76 (ddt, J=18.0, 11.3, 2.5 Hz, 1H), 0.52 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.2, 134.9, 134.4, 134.1, 130.2, 129.8, 129.5, 127.8, 126.6, 126.1, 125.4, 125.3, 78.4, 50.4, 35.7, 28.6, 25.2, −5.4, −5.7; MS (EI) *m/z* 345.1 (M^+, 0), 255.2 (1), 299.0 (3), 213.0 (1), 153.0 (3), 152.0 (10), 151.0 (100), 137.0 (5), 135.0 (20), 85.9 (7), 83.9 (11); HRMS (EI) *m/z* calcd for $C_{22}H_{23}NOSi$ 345.1549, found 345.1542. The relative stereochemistry for **9** was determined by the coupling constant between the centered and the adjacent fused methine protons.

4.2.7. Cycloadduct 10. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2g** (0.20 g, 1.21 mmol) using *n*-BuLi (0.58 mL, 2.5 M, 1.45 mmol) and NCS (0.19 g, 1.45 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **10** (0.14 g, 0.85 mmol, 70%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **10**: mp 82–84 °C; IR (CH_2Cl_2) 3053, 2928, 2873, 1739, 1654, 1422, 1286, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J=11.2, 6.8, 3.1 Hz, 1H), 5.53 (ddd, J=11.2, 3.6, 1.8 Hz, 1H), 5.08 (dd, J=11.2, 4.5 Hz, 1H), 3.93 (dd, J=11.0, 7.5 Hz, 1H), 2.37 (m, 6H), 1.89 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 132.9, 126.5, 80.1, 60.9, 39.1, 35.7, 30.6, 28.8, 20.1; MS (EI) *m/z* 163.1 (M^+, 9), 146.1 (11), 117.1 (18), 105.1 (19), 91.0 (100), 88.0 (21), 79.1 (26), 70.0 (53), 61.0 (69); HRMS (EI) *m/z* calcd for $C_{10}H_{13}NO$ 163.0997, found 163.0999. The relative stereochemistry for **10** was confirmed by X-ray diffraction analysis.

4.2.8. Cycloadduct 11. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **2h** (0.18 g, 1.0 mmol) using *n*-BuLi (0.50 mL, 2.5 M, 1.2 mmol) and NCS (0.16 g, 1.2 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **11** (0.12 g, 0.67 mmol, 60%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **11**: mp 66–68 °C; IR (CH_2Cl_2) 3052, 2939, 2896, 1605, 1438, 1422, 1280, 1266, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dt, J=12.0, 3.6 Hz, 1H), 5.78 (ddt, J=12.0, 5.8, 2.0 Hz, 1H), 4.80 (dd, J=11.0, 7.5 Hz, 1H), 3.30 (dd, J=10.8, 5.3 Hz, 1H), 2.75 (dd, J=11.5, 4.2 Hz, 1H), 2.43 (br d, J=11.5 Hz, 1H), 2.22 (m, 2H), 2.12 (m, 1H), 1.81 (m, 2H), 1.60 (m, 3H), 1.39 (d, J=11.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 137.5, 122.2, 57.7, 37.7, 32.3, 31.7, 26.3, 25.9, 22.1; MS (EI) *m/z* 177.1 (M^+, 30), 148.1 (21), 134.1 (20), 117.1 (25), 105.1 (37), 91.0 (100), 79.1 (54), 67.1 (54); HRMS (EI) *m/z* calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1148. The relative stereochemistry for **11** was confirmed by X-ray diffraction analysis.

4.2.9. Cycloadduct 12a. The crude mixture obtained from

intramolecular 1,3-dipolar cycloaddition starting from oxime **2i** (0.30 g, 143 mmol) using *n*-BuLi (0.69 mL, 2.5 M, 1.7 mmol) and NCS (0.23 g, 1.7 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **12a** (0.15 g, 0.66 mmol, 50%) and **12b** (0.08 g, 0.36 mmol, 27%) both as white solids. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **12a**: mp 119–121 °C; IR (CH_2Cl_2) 3052, 2928, 2858, 1720, 1613, 1484, 1460, 1436, 1422, 1364, 1282, 1266, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J=7.6$ Hz, 1H), 7.30 (m, 1H), 7.40 (m, 1H), 7.31 (td, $J=7.4$, 1.3 Hz, 1H), 5.80 (m, 1H), 5.58 (ddd, $J=11.6$, 4.2, 2.5 Hz, 1H), 5.30 (br d, $J=11.3$ Hz, 1H), 3.83 (dd, $J=11.2$, 4.4 Hz, 1H), 3.20 (dd, $J=16.0$, 4.5 Hz, 1H), 2.76 (dd, $J=16.0$, 2.5 Hz, 1H), 2.56 (m, 1H), 2.23 (m, 1H), 2.17 (m, 1H), 1.67 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 136.4, 132.4, 130.2, 129.3, 127.0, 126.7, 125.8, 125.0, 80.8, 52.4, 39.1, 35.3, 29.7, 29.1; MS (EI) *m/z* 225.1 (M^+, 53), 195.1 (30), 167.1 (31), 165.1 (30), 115.0 (29), 91.0 (100), 77.0 (28), 65.0 (17), HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1154. The relative stereochemistry for **12a** was confirmed by X-ray diffraction analysis.

4.2.10. Cycloadduct 12b. Mp 120–122 °C; IR (CH_2Cl_2) 3051, 2928, 2858, 1721, 1613, 1484, 1462, 1436, 1424, 1364, 1278, 1266, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J=6.2$ Hz, 1H), 7.22 (m, 3H), 5.63 (m, 3H), 3.25 (t, $J=12.1$ Hz, 1H), 2.86 (dd, $J=12.3$, 4.3 Hz, 1H), 2.70 (dd, $J=12.3$, 9.8 Hz, 1H), 2.21 (m, 3H), 1.77 (m, 1H), 1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.7, 131.8, 129.9, 128.5, 126.5, 126.2, 125.8, 125.3, 80.3, 52.8, 37.1, 35.4, 28.0, 25.2; MS (EI) *m/z* 225.1 (M^+, 100), 194.1 (19), 183.1 (23), 170.0 (73.67), 165.1 (37), 115.0 (61), 91.0 (83), 81.1 (67), 77.0 (63), 65.0 (25), HRMS (EI) *m/z* calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1151. The relative stereochemistry for **12b** was confirmed by X-ray diffraction analysis.

4.2.11. Cycloadduct 13. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3a** (0.20 g, 1.23 mmol) using NCS (0.20 g, 1.47 mmol) and triethylamine (0.19 mL, 1.35 mmol) in CH_2Cl_2 for 24 h was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **13** (0.03 g, 0.70 mmol, 15%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **13**: mp 84–86 °C; IR (CH_2Cl_2) 3683, 3065, 2988, 1739, 1640, 1422, 1270 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, $J=12.0$, 2.2 Hz, 1H), 6.10 (dd, $J=10.0$, 3.9 Hz, 1H), 5.95 (m, 2H), 4.97 (d, $J=10.6$ Hz, 1H), 3.45 (t, $J=11.0$ Hz, 1H), 2.59 (m, 2H), 2.28 (m, 2H), 2.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 134.3, 133.0, 126.4, 79.0, 66.6, 41.3, 30.9, 29.2, 21.4; MS (EI) *m/z* 161.1 (M^+, 21), 144.1 (47), 143.1 (19), 117.1 (22), 116.1 (36), 115.1 (30), 105.1 (18), 104.1 (19), 91.1 (100), 79.1 (24), 77.0 (37); HRMS (EI) *m/z* calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0840; Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.44; H, 5.73; N, 8.59. The relative stereochemistry for **13** was confirmed by X-ray diffraction analysis.

4.2.12. Cycloadduct 14. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3b** (0.30 g, 1.69 mmol) using *n*-BuLi (0.88 mL, 2.5 M, 2.20 mmol) and NCS (0.27 g, 2.03 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **14** (0.24 g, 1.36 mmol, 80%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **14**: mp 66–68 °C; IR (CH_2Cl_2) 3683, 3471, 3056, 2936, 2855, 1605, 1421, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (dd, $J=11.7$, 2.08 Hz, 1H), 5.93 (m, 2H), 5.81 (dd, $J=10.2$, 4.4 Hz, 1H), 4.98 (d, $J=11.1$ Hz, 1H), 3.07 (t, $J=11.5$ Hz, 1H), 2.74 (dd, $J=10.2$, 4.3 Hz, 1H), 2.26 (m, 1H), 2.16 (td, $J=12.8$, 5.4 Hz, 1H), 2.04 (m, 2H), 1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 137.7, 132.3, 126.3, 125.2, 79.8, 62.4, 40.7, 30.3, 26.4, 25.0; MS (EI) *m/z* 175.1 (M^+, 16), 147.1 (36), 146.1 (36), 129.0 (20), 119.1 (30), 117.1 (30), 115.0 (30), 107.0 (59), 91.0 (97), 79.0 (100), 77.0 (48); HRMS (EI) *m/z* calcd for $C_{11}H_{13}NO$ 175.0997, found 175.0996; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.42; H, 7.55; N, 7.96. The relative stereochemistry for **14** was confirmed by X-ray diffraction analysis.

4.2.13. Cycloadduct 15. The crude mixture obtained from intramolecular 1,3-dipolar cycloaddition starting from oxime **3c** (0.30 g, 1.33 mmol) using *n*-BuLi (0.70 mL, 2.5 M, 1.73 mmol) and NCS (0.21 g, 1.60 mmol) was purified by flash column chromatography (silica gel, gradient elution: 10–30% ethyl acetate in hexanes) to give **15** (0.20 g, 0.91 mmol, 68%) as a white solid. Crystals suitable for X-ray diffraction were grown from ethyl acetate and hexanes. Compound **15**: mp 104–106 °C; IR (CH_2Cl_2) 3057, 2990, 2893, 1614, 1462, 1438, 1355, 1277, 1269, 1260, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, $J=7.6$ Hz, 1H), 7.31 (td, $J=7.4$, 1.5 Hz, 1H), 7.23 (m, 2H), 6.26 (dd, $J=11.8$, 1.6 Hz, 1H), 6.01 (m, 2H), 5.93 (m, 1H), 5.28 (d, $J=12.0$ Hz, 1H), 3.87 (t, $J=12.6$ Hz, 1H), 3.04 (m, 2H), 2.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 138.1, 136.5, 136.4, 130.0, 128.8, 128.2, 126.6, 125.7, 125.6, 125.3, 80.0, 65.6, 37.4, 35.0; MS (EI) *m/z* 223.1 (M^+, 100), 194.1 (51), 180.1 (30), 178.1 (46), 169.0 (45), 165.0 (40), 115.0 (45), 107.0 (93), 91.0 (58), 79.0 (80), 77.0 (41); HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0999; Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.67; H, 5.68; N, 6.24. The relative stereochemistry for **15** was confirmed by X-ray diffraction analysis.

Crystallographic data crystallographic data (excluding structure factors) for the structures **7**, **10**, **11**, **12a**, **12b**, **13**–**15** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 248696-248703, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was supported by grants from National Taiwan Normal University (ORD 92-2) and National Science Council (NSC 92-2113-M-003-009).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.078

References and notes

1. Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
2. (a) Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575. (b) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719. (c) *Nitriles, Nitrones, and Nitronates in Organic Synthesis*; Torssell, K. B. G., Ed.; VCH: New York, 1988. (d) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
3. Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.
4. (a) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1986**, *27*, 1407. (b) Hassner, A.; Murthy, K. S. K.; Maurya, R.; Dehaen, W.; Friedman, O. *J. Heterocycl. Chem.* **1994**, *31*, 687. (c) Fernández-Mateos, A.; Coca, G. P.; González, R. R.; Hernández, C. T. *J. Org. Chem.* **1996**, *61*, 9097.
5. (a) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277. (b) Dahaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896. (c) Kozikowski, A. P.; Park, P. U. *J. Org. Chem.* **1990**, *55*, 4668.
6. (a) Yip, C.; Handerson, S.; Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 276. (b) Bock, K.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1181. (c) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757.
7. Only one example of intermolecular 1,3-dipolar cycloaddition of an acyclic 1,3-diene with a nitrile oxide to give an isoxazoline was reportedTabrizi, M. A.; Baraldi, P. G.; Guarneri, M.; Manfredini, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1991**, *34*, 683. Two examples of intramolecular nitrile oxide cycloaddition in the dihydrotropone series were studiedRigby, J. H.; McGuire, T. W. *Tetrahedron Lett.* **1993**, *34*, 3017.
8. (a) Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941. (b) Yeh, M. C. P.; Sun, M. L.; Lin, S. K. *Tetrahedron Lett.* **1991**, *32*, 113. (c) Yeh, M. C. P.; Liang, J. H.; Jiang, Y. L.; Tsai, M. S. *Tetrahedron* **2003**, *59*, 3409.
9. Yeh, M. C. P.; Chuang, S. C.; Lai, M. L.; Chou, C. C. *Organometallics* **1997**, *16*, 4435.
10. Blankenfeldt, W.; Liao, J. W.; Lo, L. C.; Yeh, M. C. P. *Tetrahedron Lett.* **1996**, *37*, 7361.
11. Yeh, M. C. P.; Chuang, C. N. *J. Chem. Soc., Chem. Commun.* **1994**, 703.
12. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
13. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
14. In some cases, triethylamine was added at 0 °C and the reaction was allowed to stir at 25 °C for 18 h.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 501–506

Preparation of isoxazol(in)yl substituted selenides and their further deselenenylation reaction to synthesize 3,5-disubstituted isoxazoles

Wei Ming Xu,[a,b] E. Tang[a] and Xian Huang[a,c,*]

[a]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, People's Republic of China*
[b]*Center of Analysis and Measurement, Zhejiang University, Hangzhou 310028, People's Republic of China*
[c]*Laboratory of Organometallic Chemistry, Chinese Academy of Sciences Shanghai 200032, People's Republic of China*

Received 7 May 2004; revised 6 October 2004; accepted 12 October 2004

Available online 11 November 2004

Abstract—We report a mild 1,3-dipolar cycloaddition protocol for the preparation of 3-aryl-5-phenylselenomethyl isoxazoles and isoxazolines regioselectively. The former was further reacted with LDA and electrophilic substrates followed by selenoxide *syn*-elimination to afford 3-aryl-5-*E*-substituted-ethenyl isoxazoles stereoselectively and the latter was subjected to a 'two-step' elimination to afford 3-aryl-5-methyl isoxazoles.

1. Introduction

1,3-Dipolar cycloaddition reactions are of the most important synthetic manipulations allowing the construction of five-membered carbocycles and heterocycles.[1] Among them, nitrile oxides have been shown to be effective 1,3-dipoles and they undergo smooth reactions with substituted alkynes or alkenes to give substituted isoxazoles or isoxazolines, respectively. Both classes of heterocycles are versatile intermediates for the synthesis of complex natural products and biologically active compounds[2] that are observed in many therapeutic agents.

Diorganic selenides have attracted considerable interest because of their potential as anticancer and antioxidant agents.[3] They are also key intermediates[4] for they can be efficiently introduced, manipulated, and removed under mild conditions and usually in good yields. But to date, there are very rare reports on the 1,3-dipolar cycloaddition of phenylseleno-substituted alkynes and alkenes.[5] Our research group[6] has been interested in the application of selenium in organic synthesis for several years. Here we reported a mild, regioselective protocol to prepare 3-aryl-5-phenylselenomethyl isoxazoles and isoxazolines **3** and their further applications to prepare 3-aryl-5-methyl isoxazoles **7** and 3-aryl-5-*E*-substituted ethenyl isoxazoles **5**, which cannot be obtained via the reaction of Wittig reagents with the corresponding aldehydes when the unstable Wittig reagents are used.[7]

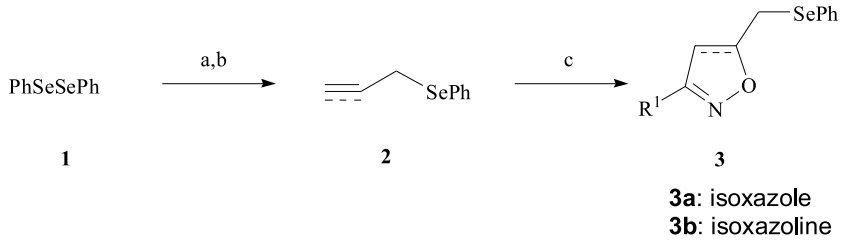
2. Results and discussion

We began our experiment from diphenyl diselenide, which was treated with $NaBH_4$ and propargyl bromide (or allyl bromide) to get phenylpropargyl selenide **2a** (or phenylallyl selenide **2b**).[8] Without any further purification, phenylpropargyl selenide was then reacted with hydroximoyl halide and Et_3N. In this process Et_3N was slowly added dropwise in 6 h in order to avoid the dimerization of the nitrile oxides. 3-Aryl-5-phenylselenomethyl isoxazoles **3a** were obtained in moderate to good yields. The use of phenylallyl selenide in place of phenylpropargyl selenide gave 3-aryl-5-phenylselenomethyl isoxazolines **3b** using the same procedure (Scheme 1). The results are summarized in Table 1.

A useful feature of organoselenium is its ability to stabilize adjacent carbanions. Although the direct deprotonation of phenylselenomethyl isoxazolines **3b** (aryl alkyl selenide) is difficult,[9] the co-stabilization of isoxazolyl- and phenylseleno- made phenylselenomethyl isoxazoles **3a** react with LDA smoothly to form α-seleno alkyllithium (Scheme 2, step 1). Because of its easy availability and high nucleophilicity, α-seleno alkyllithium plays an important

Keywords: 1,3-Dipolar cycloaddition; Isoxazoles; Isoxazolines; Selenoxide *syn*-elimination.
* Corresponding author. Fax: +86 571 88807077;
e-mail: huangx@mail.hz.zj.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.071



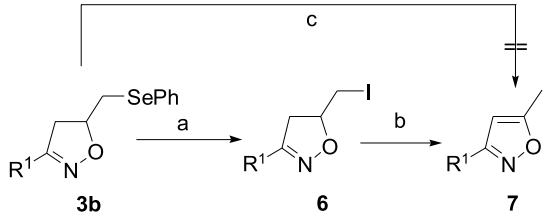
Scheme 1. Reagents and conditions: (a) $NaBH_4$, THF, EtOH, rt, 1 h; (b) propargyl bromide(allyl bromide), THF, rt, 2 h; (c) $R^1C(Cl)=NOH$, CH_2Cl_2, Et_3N, rt, 6 h.

Table 1. Synthesis of 3-aryl-5-phenylselenomethyl isoxazoles and isoxazolines

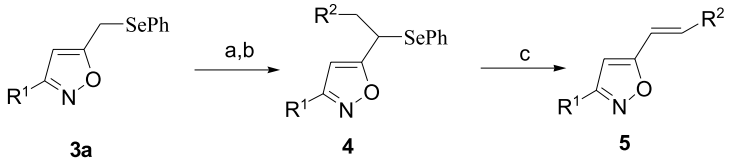
Product[a]	R^1	Yield (%)[b]
3aa	4-BrC_6H_4	79
3ab	4-$CH_3C_6H_4$	78
3ac	4-ClC_6H_4	76
3ad	4-FC_6H_4	67
3ae	C_6H_5	78
3ba	4-$CH_3OC_6H_4$	86
3bb	4-BrC_6H_4	83
3bc	4-$CH_3C_6H_4$	84
3bd	4-$NO_2C_6H_4$	56
3be	4-FC_6H_4	73

[a] All the products were characterized by IR, ^1H NMR, ^{13}C NMR and MS spectroscopy.
[b] Isolated yield.

Although a β-H exists in the molecule, 3-aryl-5-phenylselenomethyl isoxazolines **3b** did not undergo selenoxide *syn*-elimination even we mixed them with H_2O_2 in THF and stirred at 50 °C for 1 h (Scheme 3, step c). To solve this



Scheme 3. Reagents and conditions: (a) CH_3I, NaI, DMF, 80 °C, 20 h; (b) DBU or NaCN, THF, reflux, 12 h; (c) H_2O_2, THF, 50 °C, 1 h.



Scheme 2. Reagents and conditions: (a) LDA (1.0 equiv), THF, −78 °C, 1.5 h; (b) R^2CH_2X (1.0 equiv), THF, −78 to −50 °C, 1 h; (c) H_2O_2, THF, 0 °C, 1 h, then rt, 20 min.

role in organic synthesis, which allows the formation of new functionalized carbon–carbon bonds when it is used to react with carbon electrophiles. Alkyl halides are used here as carbon electrophiles to perform the α-alkylation reaction to afford alkylated product **4**, which followed by selenoxide *syn*-elimination to obtain 3-aryl-5-*E*-substituted ethenyl isoxazoles **5** stereoselectively (Scheme 2). The results are summarized in Table 2.

Table 2. Synthesis of 3-aryl-5-*E*-substituted-ethenyl isoxazoles

Product[a]	R^1	R^2	Yield (%)[b]
5a	4-$CH_3OC_6H_4$	CH_2=CH	82
5b	4-$CH_3C_6H_4$	CH_3	78
5c	4-ClC_6H_4	CH_2=CH	76
5d	4-$CH_3C_6H_4$		80
5e	4-$CH_3C_6H_4$	C_6H_5	83
5f	4-$CH_3C_6H_4$	CH_3OOC	77
5g	4-FC_6H_4	CH_2=C(CH_3)	74
5h	4-BrC_6H_4	CH_3	71
5i	4-$CH_3C_6H_4$	CH_2=CH	76

[a] All the products were characterized by IR, ^1H NMR, ^{13}C NMR and MS spectroscopy.
[b] Isolated yield.

problem, we used a mild 'two-step' deselenium protocol in which 3-aryl-5-phenylselenomethyl isoxazolines first reacted with NaI and CH_3I in DMF to afford 3-aryl-5-iodomethyl isoxazoline,[10] which was then treated with DBU to afford 3-aryl-5-methyl isoxazoles almost quantitatively (Scheme 3). It should be pointed out that NaCN could take the place of DBU as a base to perform the reaction. The results are summarized in Table 3.

Table 3. Synthesis of 3-aryl-5-methyl isoxazoles

Product	R^1	Yield (%)[a]
7a	4-$CH_3OC_6H_4$	82
7b	4-FC_6H_4	79
7c	4-$CH_3C_6H_4$	86
7d	4-$NO_2C_6H_4$	87
7e	C_6H_5	83
7e[b]	C_6H_5	85

[a] Isolated yield.
[b] NaCN was used otherwise DBU was used as a base.

3. Conclusion

We have developed a mild 1,3-dipolar cycloaddition protocol to prepare 3-aryl-5-phenylselenomethyl isoxazoles

and isoxazolines regioselectively. The former was further reacted with LDA and electrophilic substrates followed by selenoxide *syn*-elimination to afford 3-aryl-5-*E*-substituted-ethenyl isoxazoles, and the synthesis was general with excellent control of *E* geometry.[7] The latter underwent a 'two-step' elimination to afford 3-aryl-5-methyl isoxazoles.

4. Experimental

The melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard; chemical shifts were quoted in ppm and *J* values were given in Hz. IR spectra recorded on a IR-408 spectrometer. EIMS was run on a HP 5989B mass spectrometer. Elemental analysis was run on Thermo-finnigan Flash EA 1112.

4.1. General procedure of 3-aryl-5-phenylselenomethyl isoxazoles 3a and isoxazolines 3b

Phenylpropargyl selenide (or phenylallyl selenide) (1 mmol) was added to a mixture of hydroximoyl chloride (1.1 mmol) in 10 mL CH_2Cl_2 (prepared from 1.1 mmol of aldoxime and 1.1 mmol of NCS stirring at rt for about 3 h before use). A mixture of Et_3N (1.2 mmol) in 10 mL CH_2Cl_2 was slowly dropwised in 6 h. After the reaction, the mixture was washed with 15 mL saturated $NaHCO_3$ aq solution and 15 mL water then dried over $MgSO_4$. Dryness followed by purification via flash chromatography with *n*-hexanes–EtOAc (9:1, v/v) as the eluent to give **3a** (or **3b**).

4.1.1. Compound 3aa. 3-(4-Bromo-phenyl)-5-phenyl-selenomethyl isoxazole; pale yellow solid; mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 7.61–7.54 (6H, m), 7.32–7.30 (3H, m), 6.21 (1H, s), 4.13 (2H, s); ^{13}C NMR ($CDCl_3$) δ 171.3, 162.0, 134.6, 132.5, 129.7, 129.2, 128.7, 128.6, 128.4, 124.7, 100.6, 20.7; MS *m/z* 157 (100), 393 (M^+); IR ν_{max} (cm^{-1}) 3442, 3113, 1632, 1430, 1074, 733. Elemental analysis calcd for $C_{16}H_{12}BrNOSe$: C, 48.88; H, 3.08; N, 3.56. Found: C, 48.99; H, 2.96; N, 3.47.

4.1.2. Compound 3ab. 3-(4-Methyl-phenyl)-5-phenyl-selenomethyl isoxazole; pale yellow solid, mp 40–41 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (2H, d, J=7.6 Hz), 7.56 (2H, d, J=7.6 Hz), 7.31–7.25 (5H, m), 6.22 (1H, s), 4.13 (2H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.7, 162.8, 140.5, 134.6, 129.9, 129.7, 129.3, 128.6, 127.0, 126.6, 100.7, 21.8, 20.8; MS *m/z* 172 (100), 329 (M^++1); IR ν_{max} (cm^{-1}) 3441, 3127, 1615, 1600, 1431, 739, 671. Elemental analysis calcd for $C_{17}H_{15}NOSe$: C, 62.20; H, 4.61; N, 4.27. Found: C, 62.08; H, 4.71; N, 4.15.

4.1.3. Compound 3ac. 3-(4-Chloro-phenyl)-5-phenyl-selenomethyl isoxazole; pale yellow solid, mp 70–71 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (2H, d, J=8.4 Hz), 7.56–7.54 (2H, m),7.42 (2H, d, J=8.4 Hz), 7.32–7.28 (3H, m), 6.21 (1H, s), 4.13 (2H, s); ^{13}C NMR ($CDCl_3$) δ 171.3, 161.9, 136.4, 134.6, 129.7, 129.5, 129.2, 128.6, 128.4, 127.9, 100.6, 20.7; MS *m/z* 192 (100), 348 (M^++1); IR ν_{max} (cm^{-1}) 3112, 3054, 1633, 1602, 1430, 736. Elemental analysis calcd for $C_{16}H_{12}ClNOSe$: C, 55.11; H, 3.47; N, 4.02. Found: C, 55.24; H, 3.37; N, 4.11.

4.1.4. Compound 3ad. 3-(4-Fluoro-phenyl)-5-phenyl-selenomethyl isoxazole; pale yellow solid, mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.75–7.72 (2H, m), 7.57–7.55 (2H, m), 7.33–7.31 (3H, m), 7.14 (2H, t, J=8.8 Hz), 6.21 (1H, s), 4.13 (2H, s); ^{13}C NMR ($CDCl_3$) δ 171.2, 164.2 (J=248.6 Hz), 162.0, 134.6, 129.7, 129.2, 129.0 (J=8.3 Hz), 128.6, 125.6 (J=3.3 Hz), 116.4 (J=21.9 Hz), 100.6, 20.7; MS *m/z* 176 (100), 333 (M^++1); IR ν_{max} (cm^{-1}) 3113, 3024, 1607, 1591, 1435, 735, 690. Elemental analysis calcd for $C_{16}H_{12}FNOSe$: C, 57.84; H, 3.64; N, 4.22. Found: C, 57.98; H, 3.71; N, 4.10.

4.1.5. Compound 3ae. 3-Phenyl-5-phenylselenomethyl isoxazole; pale yellow solid, mp 54–56 °C; ^{1}H NMR ($CDCl_3$) δ 7.74–7.72 (2H, m), 7.55–7.53 (2H, m), 7.44–7.42 (3H, m), 7.30–7.28 (3H, m), 6.23 (1H, s), 4.12 (2H, s); ^{13}C NMR ($CDCl_3$) δ 170.9, 162.9, 134.6, 130.4, 129.7, 129.5, 129.3, 128.6, 127.2, 100.8. 20.8; MS *m/z* 77 (100), 315 (M^++1); IR ν_{max} (cm^{-1}) 3119, 3050, 1600, 1577, 1469, 1439, 768, 691. Elemental analysis calcd for $C_{16}H_{13}NOSe$: C, 61.15; H, 4.17; N, 4.46. Found: C, 61.30; H, 4.09; N, 4.34.

4.1.6. Compound 3ba. 3-(4-Methoxyl-phenyl)-5-phenyl-selenomethyl isoxazoline; pale yellow solid, mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 7.64–7.56 (4H, m), 7.31–7.28 (3H, m), 6.92 (2H, d, J=8.8 Hz), 4.89–4.87 (1H, m), 3.44 (1H, dd, J_1=10.0 Hz, J_2=16.8 Hz), 3.85 (3H, s), 3.34 (1H, dd, J_1=4.4 Hz, J_2=12.0 Hz), 3.19 (1H, dd, J_1=6.8 Hz, J_2=16.8 Hz), 3.03 (1H, dd, J_1=9.2 Hz, J_2=12.8 Hz); ^{13}C NMR ($CDCl_3$) δ 161.5, 156.2, 133.6, 129.7, 129.2, 128.7, 127.9, 122.4, 114.5, 80.5, 55.7, 40.7, 31.8; MS *m/z* 176 (100), 346 (M^++1); IR ν_{max} (cm^{-1}) 2960, 1609, 1517, 1253, 835, 728, 689. Elemental analysis calcd for $C_{17}H_{17}NO_2Se$: C, 58.96; H, 4.95; N, 4.04. Found: C, 59.10; H, 4.89; N, 4.14.

4.1.7. Compound 3bb. 3-(4-Bromo-phenyl)-5-phenyl-selenomethyl isoxazoline; pale yellow solid, mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.59–7.50 (6H, m), 7.32–7.28 (3H, m), 4.95–4.92 (1H, m), 3.43 (1H, dd, J_1=10.4 Hz, J_2=16.8 Hz), 3.34 (1H, dd, J_1=4.4 Hz, J_2=12.4 Hz), 3.18 (1H, dd, J_1=6.8 Hz, J_2=16.8 Hz), 3.02 (1H, dd, J_1=9.2 Hz, J_2=12.8 Hz); ^{13}C NMR ($CDCl_3$) δ 155.8, 133.7, 132.3, 129.7, 129.0, 128.8, 128.5, 128.0, 124.8, 81.1, 40.2, 31.7; MS *m/z* 91 (100), 395 (M^++2); IR ν_{max} (cm^{-1}) 1634, 1589, 1436, 1118, 823, 734, 690. Elemental analysis calcd for $C_{16}H_{14}BrNOSe$: C, 48.63; H, 3.57; N, 3.54. Found: C, 48.52; H, 3.66; N, 3.63.

4.1.8. Compound 3bc. 3-(4-Methyl-phenyl)-5-phenyl-selenomethyl isoxazoline; pale yellow solid, mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.59–7.54 (4H, m), 7.31–7.28 (3H, m), 7.22 (2H, d, J=7.2 Hz), 4.92–4.89 (1H, m), 3.43 (1H, dd, J_1=10.0 Hz, J_2=16.8 Hz), 3.32 (1H, dd, J_1=4.4 Hz, J_2=12.0 Hz), 3.19 (1H, dd, J_1=6.8 Hz, J_2=16.8 Hz), 3.02 (1H, dd, J_1=9.2 Hz, J_2=12.8 Hz), 2.40 (3H, s); ^{13}C NMR ($CDCl_3$) δ 156.6, 140.7, 133.6, 129.8, 129.7, 129.2, 127.9, 127.1, 127.0, 80.6, 40.6, 31.9, 21.8; MS *m/z* 91 (100), 330 (M^+); IR ν_{max} (cm^{-1}) 2924, 2854, 1579, 1436, 1376, 895,

817, 727, 688. Elemental analysis calcd for $C_{17}H_{17}NOSe$: C, 61.82; H, 5.19; N, 4.24. Found: C, 61.96; H, 5.11; N, 4.17.

4.1.9. Compound 3bd. 3-(4-Nitro-phenyl)-5-phenylselenomethyl isoxazoline; pale yellow solid, mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (2H, d, J=7.2 Hz), 7.79 (2H, d, J=7.2 Hz), 7.60–7.56 (2H, m), 7.33–7.28 (3H, m), 5.04–4.99 (1H, m), 3.47 (1H, dd, J_1=10.4 Hz, J_2=16.8 Hz), 3.34 (1H, dd, J_1=4.4 Hz, J_2=12.4 Hz), 3.23 (1H, dd, J_1=6.8 Hz, J_2=16.8 Hz), 3.04 (1H, dd, J_1=9.2 Hz, J_2=12.8 Hz); ^{13}C NMR ($CDCl_3$) δ 155.1, 148.9, 135.9, 133.7, 129.8, 128.9, 128.1, 127.8, 124.4, 81.9, 39.8, 31.6; MS *m/z* 91 (100), 362 (M^++1); IR ν_{max} (cm^{-1}) 1634, 1589, 1436, 1118, 823, 734, 690. Elemental analysis calcd for $C_{16}H_{14}N_2O_3Se$: C, 53.20; H, 3.91; N, 7.75. Found: C, 53.04; H, 3.80; N, 7.64.

4.1.10. Compound 3be. 3-(4-Fluoro-phenyl)-5-phenylselenomethyl isoxazoline; pale yellow solid, mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.66–7.61 (2H, m), 7.60–7.57 (2H, m), 7.32–7.28 (3H, m), 7.08 (2H, t, J=8.8 Hz), 5.95–4.90 (1H, m), 3.43 (1H, dd, J_1=10.4 Hz, J_2=16.8 Hz), 3.32 (1H, dd, J_1=4.4 Hz, J_2=12.8 Hz), 3.19 (1H, dd, J_1=6.8 Hz, J_2=16.8 Hz), 3.02 (1H, dd, J_1=9.2 Hz, J_2=12.8 Hz); ^{13}C NMR ($CDCl_3$) δ 164.2 (J=248.6 Hz), 155.6, 133.6, 129.7, 129.1, 129.0 (J=8.3 Hz), 128.0, 126.1 (J=3.0 Hz), 116.2 (J=21.4 Hz), 80.9, 40.5, 31.8; MS *m/z* 164 (100), 335 (M^++1); IR ν_{max} (cm^{-1}) 3071, 1601, 1512, 1228, 834, 733, 690. Elemental analysis calcd for $C_{16}H_{14}FNOSe$: C, 57.49; H, 4.22; N, 4.19. Found: C, 57.42; H, 4.15; N, 4.28.

4.2. General procedure of 3-aryl-5-substituted ethenyl isoxazoles 5

3-Aryl-5-phenylselenomethyl isoxazole **3a** (0.5 mmol) was solved in 10 mL dry THF, cooled to −78 °C, and added dropwise LDA (2 M in THF/hexane, 0.3 mL) under nitrogen. After stirring at −78 °C for 0.5 h, a solution of alkyl halide (0.6 mmol) in 1 mL of dry THF was added. The suspension was stirred at −78 °C for another 0.5 h. Slowly warm up to −50 °C in 0.5 h then quenched with 0.1 mL H_2O. To the mixture was added 30% (aq) H_2O_2 (0.5 mL) and stirred at 0 °C for 1 h followed by 20 min at room temperature. After the reaction, 20 mL CH_2Cl_2 was added. The mixture was washed with 15 mL saturated $NaHCO_3$ aq solution and 15 mL water and dried over $MgSO_4$. Dryness followed by purification via flash chromatography with *n*-hexanes–EtOAc (9:1, v/v) as the eluent to give **5**.

4.2.1. Compound 5a. 3-(4-Methoxyl-phenyl)-5-(*E*-1,3-butdienyl) isoxazole; pale yellow solid, mp 47–49 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, J=8.2 Hz), 7.04–6.97 (3H, m), 6.52–6.45 (3H, m), 5.53 (1H, d, J=16.8 Hz), 5.41 (1H, d, J=10.4 Hz), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.8, 162.6, 161.4, 136.2, 135.7, 128.5, 122.4, 122.0, 117.4, 114.7, 99.7, 56.7; MS *m/z* 227 (M^+, 100); IR ν_{max} (cm^{-1}) 3405, 3027, 1623, 1495, 1449, 967, 759, 690. Elemental analysis calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.10; H, 5.66; N, 6.10.

4.2.2. Compound 5b. 3-(4-Methyl-phenyl)-5-(1-*E*-propenyl) isoxazole; pale yellow solid, mp 74–76 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (2H, d, J=8.4 Hz), 7.27 (2H, d, J=8.4 Hz), 6.64–6.56 (1H, m), 6.41 (1H, d, J=16.0 Hz), 6.36 (1H, s), 2.42 (3H, s), 1.97 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 162.9, 140.3, 134.0, 129.9, 127.0, 126.8, 117.6, 98.1, 21.8, 19.0; MS *m/z* 69 (100), 199 (M^+); IR ν_{max} (cm^{-1}) 1666, 1563, 1525, 1427, 965, 819, 788. Elemental analysis calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.30; H, 6.49; N, 6.95.

4.2.3. Compound 5c. 3-(4-Chloro-phenyl)-5-(*E*-1,3-butdienyl) isoxazole; pale yellow solid, mp 75–76 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, J=8.0 Hz), 7.45 (2H, d, J=8.0 Hz), 7.03 (1H, dd, J_1=7.2 Hz, J_2=16.0 Hz), 6.53–6.47 (3H, m), 5.55 (1H, d, J=8.8 Hz), 5.42 (1H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 169.4, 162.1, 136.4, 136.2, 136.1, 129.6, 128.4, 128.0, 122.8, 117.1, 99.6; MS *m/z* 66 (100), 231 (M^+); IR ν_{max} (cm^{-1}) 3403, 3025, 1627, 1424, 965, 819, 692. Elemental analysis calcd for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.05. Found: C, 67.50; H, 4.28; N, 5.98.

4.2.4. Compound 5d. 3-(4-Methyl-phenyl)-5-(epoxy-*E*-ethenyl) isoxazole; pale yellow solid, mp 70–72 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (2H, d, J=7.6 Hz), 7.28 (2H, d, J=7.6 Hz), 6.74 (1H, d, J=16.0 Hz), 6.49 (1H, s), 6.31 (1H, dd, J_1=7.6 Hz, J_2=16.4 Hz), 3.56–3.54 (1H, m), 3.13–3.10 (1H, m), 2.81–2.79 (1H, m), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.7, 163.0, 140.6, 134.3, 130.0, 127.0, 126.4, 119.0, 100.2, 51.8, 49.9, 21.8; MS *m/z* 158 (100), 227 (M^+); IR ν_{max} (cm^{-1}) 1608, 1515, 1414, 895, 817, 727, 670. Elemental analysis calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.87; H, 5.87; N, 6.08.

4.2.5. Compound 5e. 3-(4-Methyl-phenyl)-5-(*E*-phenylethenyl) isoxazole; pale yellow solid, mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J=7.6 Hz), 7.54–7.52 (2H, m), 7.42–7.34 (4H, m), 7.27 (2H, d, J=7.6 Hz), 6.99 (1H, d, J=16.4 Hz), 6.54 (1H, s), 2.41 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.2, 163.1, 140.5, 136.0, 135.2, 130.0, 129.5, 129.3, 127.5, 127.1, 126.7, 113.6, 99.8, 21.8; MS *m/z* 261 (M^+, 100); IR ν_{max} (cm^{-1}) 1642, 1582, 1426, 993, 829, 747, 697. Elemental analysis calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.66; H, 5.88; N, 5.44.

4.2.6. Compound 5f. 3-(4-Methyl-phenyl)-5-(methoxycarbonyl-*E*-ethenyl) isoxazole; pale yellow solid, mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J=7.6 Hz), 7.55 (1H, d, J=16.0 Hz), 7.30 (2H, d, J=7.6 Hz), 6.76 (1H, s), 6.68 (1H, d, J=16.0 Hz), 3.86 (3H, s), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 166.6, 166.3, 163.3, 141.0, 130.1, 128.1, 127.1, 125.9, 123.7, 104.5, 52.5, 21.8; MS *m/z* 158 (100), 243 (M^+); IR ν_{max} (cm^{-1}) 1711, 1651, 1560, 1528, 1429, 1385, 1312, 1262, 1173, 972, 816. Elemental analysis calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.98; H, 5.52; N, 5.89.

4.2.7. Compound 5g. 3-(4-Fluoro-phenyl)-5-(2-methyl-*E*-1,3-butdienyl) isoxazole; yellow low pointing solid; ^{1}H NMR ($CDCl_3$) δ 7.82–7.79 (2H, m), 7.18–7.10 (3H, m), 6.48 (1H, s), 6.44 (1H, d, J=16.4 Hz), 5.30 (2H, d, J=12.4 Hz), 1.97 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.3, 163.8 (J=248.6 Hz), 161.7, 140.9, 137.9, 128.6 (J=8.1 Hz), 125.3 (J=4.3 Hz), 121.6, 116.0 (J=21.7 Hz), 113.3, 98.9, 18.0; MS *m/z* 229 (100, M^+); IR ν_{max} (cm^{-1}) 3062, 3028, 1624, 1435, 975, 735, 692. Elemental analysis calcd for

$C_{14}H_{12}FNO$: C, 73.35; H, 5.28; N, 6.11. Found: C, 73.22; H, 5.39; N, 6.01.

4.2.8. Compound 5h. 3-(4-Bromo-phenyl)-5-(1-*E*-propenyl) isoxazole; pale yellow solid, mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (2H, d, J=6.8 Hz), 7.30 (2H, d, J=6.8 Hz), 6.65–6.59 (1H, m), 6.38 (1H, d, J=16.0 Hz), 6.36 (1H, s), 1.97 (3H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.8, 162.0, 134.5, 132.5, 128.7, 128.6, 124.5, 117.4, 97.9, 19.1; MS *m/z* 69 (100), 264 (97, M^+), 266 (94, M^++2); IR ν_{max} (cm^{-1}) 1666, 1593, 1559, 1501, 1424, 1376, 961, 846, 813, 774, 505. Elemental analysis calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.70; H, 3.70; N, 5.42.

4.2.9. Compound 5I. 3-(4-Methyl-phenyl)-5-(*E*-1,3-butdienyl) isoxazole; yellow low pointing solid; ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J=8.2 Hz), 7.28 (2H, d, J=8.2 Hz), 7.02 (1H, dd, J_1=10.4 Hz, J_2=15.6 Hz), 6.53–6.47 (3H, m), 5.53 (1H, d, J=16.8 Hz), 5.17 (1H, d, J=10.4 Hz), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 168.9, 163.0, 140.5, 136.2, 135.8, 130.0, 127.1, 126.6, 122.4, 117.4, 99.9, 21.8; MS *m/z* 158 (100), 211 (M^+); IR ν_{max} (cm^{-1}) 3405, 3027, 1624, 1493, 1449, 967, 753, 692. Elemental analysis calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.38; H, 6.29; N, 6.72.

4.3. General procedure of 3-aryl-5-methyl isoxazoles 7

3-Aryl-5-phenylselenomethyl isoxazoline **3b** (0.5 mmol), NaI (0.5 g), CH_3I (0.5 mL) and 5 mL DMF were mixed together and the mixture was stirred at 80 °C for 20 h. After the reaction, 20 mL CH_2Cl_2 was added. The mixture was washed with 15 mL saturated $NaHCO_3$ aq solution and water (15 mL×2) and dried over $MgSO_4$. Dryness followed by purification via flash chromatography with *n*-hexanes–EtOAc (9:1, v/v) as the eluent to give **6**. The obtained **6** was dissolved in 5 mL DMF–THF (2:3, v/v), to the mixture DBU (0.8 mmol) was added. The mixture was stirred at 90 °C for 10 h. After the reaction, 20 mL CH_2Cl_2 was added. The mixture was washed with 20 mL saturated $NaHCO_3$ aq solution and water (15 mL×3) and dried over $MgSO_4$. Dryness without further purification gave **7** as single products.

4.3.1. Compound 7a. 3-(4-Methoxyl-phenyl)-5-methyl isoxazole; white solid; mp 92–93 °C (lit.[11] 92–93 °C); ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J=8.4 Hz), 6.96 (2H, d, J=8.4 Hz), 6.24 (1H, s), 3.85 (3H, s), 2.46 (3H, s).

4.3.2. Compound 7b. 3-(4-Fluoro-phenyl)-5-methyl isoxazole; white solid, mp 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 7.79–7.75 (2H, m), 7.14 (2H, d, J=8.4 Hz), 6.26 (1H, s), 2.48 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.1, 163.7 (J=249.1 Hz), 161.6, 126.6 (J=8.2 Hz), 125.5 (J=3.8 Hz), 115.9 (J=21.6 Hz), 99.6, 12.4; MS *m/z* 177 (M^+, 100); IR ν_{max} (cm^{-1}) 3139, 1614, 1596, 1525, 1432, 1226, 844, 795. Elemental analysis calcd for $C_{10}H_8FNO$: C, 67.79; H, 4.55; N, 7.91. Found: C, 67.88; H, 3.46; N, 7.79.

4.3.3. Compound 7c. 3-(4-Methyl-phenyl)-5-methyl isoxazole; white solid, mp 57–59 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (2H, d, J=8.0 Hz), 7.21 (2H, d, J=8.0 Hz), 6.26 (1H, s), 2.41 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.6, 162.5, 140.0, 129.5, 126.6, 126.5, 99.6, 21.3, 12.3; MS *m/z* 173 (100, M^+); IR ν_{max} (cm^{-1}) 3058, 1622, 1599, 1378, 1222, 829. Elemental analysis calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.39; H, 6.49; N, 7.97.

4.3.4. Compound 7d. 3-(4-Nitro-phenyl)-5-methyl isoxazole; white solid; mp 153–155 °C (lit.[11] 154–155 °C); ^{1}H NMR ($CDCl_3$) δ 8.22 (2H, d, J=7.6 Hz), 7.80 (2H, d, J=7.6 Hz), 6.55 (1H, s), 2.61 (3H, s).

4.3.5. Compound 7e. 3-Phenyl-5-methyl isoxazole; white solid; mp 40–42 °C (lit.[11] 41–42 °C); ^{1}H NMR ($CDCl_3$) δ 7.79–7.77 (2H, m), 7.45–7.43 (3H, m), 6.29 (1H, s), 2.48 (3H, s).

Acknowledgements

We are grateful to the Natural Science Foundation of China (Project No.20332060) and the CAS Academician Foundation of Zhejiang Province.

References and notes

1. For reviews, see the following. (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984. (b) Torsell, K. G. B. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (c) Padwa, A.; Pearson, W. H. *The Chemistry of Heterocyclic Compounds, Volume 59: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: New York, 2002.
2. (a) Talley, J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, L.; Perkins, W. E.; Rogers, S.; Shaffer, A. F.; Zhang, Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775–777. (b) Simoni, D.; Roberti, M.; Invidiata, F. P.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Capone, F.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; Landino, M.; D'Allesandro, N.; Tolomeo, M.; Arindam, D.; Lu, S.; Benbrook, D. M. *J. Med. Chem.* **2001**, *44*, 2308–2318. (c) Koiowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416.
3. (a) El-Bayoumy, K. *Nutr. Cancer* **2001**, *40*, 4–5. (b) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2003**, *125*, 13455–13460. (c) Back, T. G.; Moussa, Z.; Parvez, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1268–1270.
4. (a) Krief, A. *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1991. (b) Liotta, D. *Organoselenium Chemistry*; Wiley: New York, 1987. (c) Wirth, T. *Organoselenium Chemistry*; Springer: Berlin, 2000. (d) Back, T. G. *Organoselenium Chemistry*; Oxford University Press: Oxford, 1999.
5. Sheng, S. R.; Liu, X. L.; Xu, Q.; Song, C. S. *Synthesis* **2003**, 2763–2764.
6. (a) Huang, X.; Xu, W. M. *Tetrahedron Lett.* **2002**, *43*, 5495–5497. (b) Huang, X.; Xie, M. H. *Org. Lett.* **2002**, *4*, 1331–1334. (c) Huang, X.; Sun, A. M. *J. Org. Chem.* **2000**, *65*, 6561–6565. (d) Huang, X.; Xu, W. M. *Org. Lett.* **2003**, *5*, 4649–4652.
7. The stereochemistry of obtained olefin is high with excellent control of Z geometry when unstable Wittig reagent was used,

see: (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823–2831. (b) Huang, Y. Z.; Shi, L. L.; Yang, J. H.; Cai, Z. W. *J. Org. Chem.* **1987**, *52*, 3558–3560.

8. The preparation of phenylpropargyl selenide is described as follows: diphenyl diselenide (5 mmol) was dissolved in 10 mL dry THF. To the solution, a mixture of $NaBH_4$ (11 mmol) in 10 mL dry EtOH was slowly added. After stirring at rt for 1 h, propargyl bromide (12 mmol) was added and stirred at rt for another 2 h. Extractive workup followed by dryness and evaporation. Without further purification, phenylpropargyl selenide (1.93 g) was obtained as a single product. Yield was up to 98%.
9. (a) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049–1095. (b) Reich, H. J. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987.
10. Corey, E. J.; Jautelat, M. *Tetrahedron Lett.* **1968**, *55*, 5787–5788.
11. Shvekhgeimer, G. A.; Baranski, A.; Grzegozek, M. *Synthesis* **1976**, 612–614.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 507–512

A computational study on the mechanism for the $GaCl_3$-catalyzed [4+1] cycloaddition of α,β-unsaturated ketone and 2,6-dimethylphenyl isocyanide

Yong Wu,[a] Kailai Xu[a] and Daiqian Xie[a,b,*]

[a]*Department of Chemistry, Sichuan University, Chengdu 610064, China*
[b]*Laboratory of Mesoscopic Chemistry, Department of Chemistry, Institute of Theoretical and Computational Chemistry, Nanjing University, Nanjing 210093, China*

Received 7 May 2004; revised 1 October 2004; accepted 11 October 2004

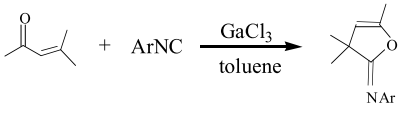
Available online 5 November 2004

Abstract—The reaction of the $GaCl_3$-catalyzed [4+1] cycloaddition of α,β-unsaturated ketone with 2,6-dimethylphenyl isocyanide leading to unsaturated γ-lactone derivative has been investigated using the density functional theory with the B3LYP hybrid functional. According to our calculations we found that the reaction is stepwise and exothermic. The reaction proceeds via three steps. The first step is the coordination of $GaCl_3$ to the oxygen atom in mesityloxide leading to a more electrophilic C3 atom. At the second step, 2,6-dimethylphenyl isocyanide attacks mesityloxide to form the C3–C6 bond with $GaCl_3$ activator, which is the rate-limiting step. Finally, the C6–O bond is formed to give the five-member cycle product due to the attack of the C6 atom to the O atom. In addition, our calculations also suggest that $GaCl_3$ activator can be easily detached from the product. The theoretical results are in good agreement with the recent experimental observations.

1. Introduction

Isocyanides are stable organic compounds with an extraordinary functional group and a formally divalent carbon atom. This unusual valence structure and reactivity have been discussed for over one and a half centuries. One of the classic themes in the chemistry of isocyanides is related to the heterocycle synthesis. The synthetically most important property of isocyanides is the reaction with nucleopiles and electrophiles at the isocyanide carbon atom. Most of other functional groups in organic chemistry could react with nucleophiles and electrophiles at different centers. Therefore, isocyanides are usually recognized as useful building blocks in organic synthesis[1,2] and in polymer science.[3] Isocyanides were widely used in cycloaddition reactions in the presence of promoters such as acids, Lewis acids, or transition metal complex. Ito and Saegusa[4] reported that Et_2AlCl can promote 1,4-cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides to afford unsaturated *N*-substituted iminolactones, which are stereoselectively converted to γ-butyrolactones via hydrogenation on Pd/C and then acid hydrolysis. Recently, $GaCl_3$ was used as a good activator in many organic reactions.[5–11] Chatani and co-workers[12] reported that $GaCl_3$ can promote the cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides leading to unsaturated γ-lactone derivatives.

To our best knowledge, there are rare theoretical studies on the mechanisms of the $GaCl_3$-catalyzed reactions.[13,14] In our previous calculations,[13] we have showed that the $GaCl_3$ activator has high catalytic activity for the skeletal reorganization of enynes to 1-vinylcycloalkenes and the reaction undergoes a stereoselective reorganization. The motive of the present study is to clarify the mechanism of the $GaCl_3$-catalyzed [4+1] cycloaddition of α,β-unsaturated ketone with 2,6-dimethylphenyl isocyanide leading to unsaturated γ-lactone derivative (Eq. 1) and to make clear that $GaCl_3$ is desirable for the detachment from the product. To this end, we have performed detailed calculations using the B3LYP hybrid functional method to study the title reaction mechanism. In addition, we have carried out the natural bond orbital (NBO) analysis to observe the bond order changes in the process of the reaction.



(1)

Ar = 2,6-$Me_2C_6H_3$

Keywords: $GaCl_3$; DFT; Cycloaddition; α,β-Unsaturated ketone; Isocyanides.
* Corresponding author. Fax: +86 25 83686467;
e-mail: dqxie@nju.edu.cn

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.068

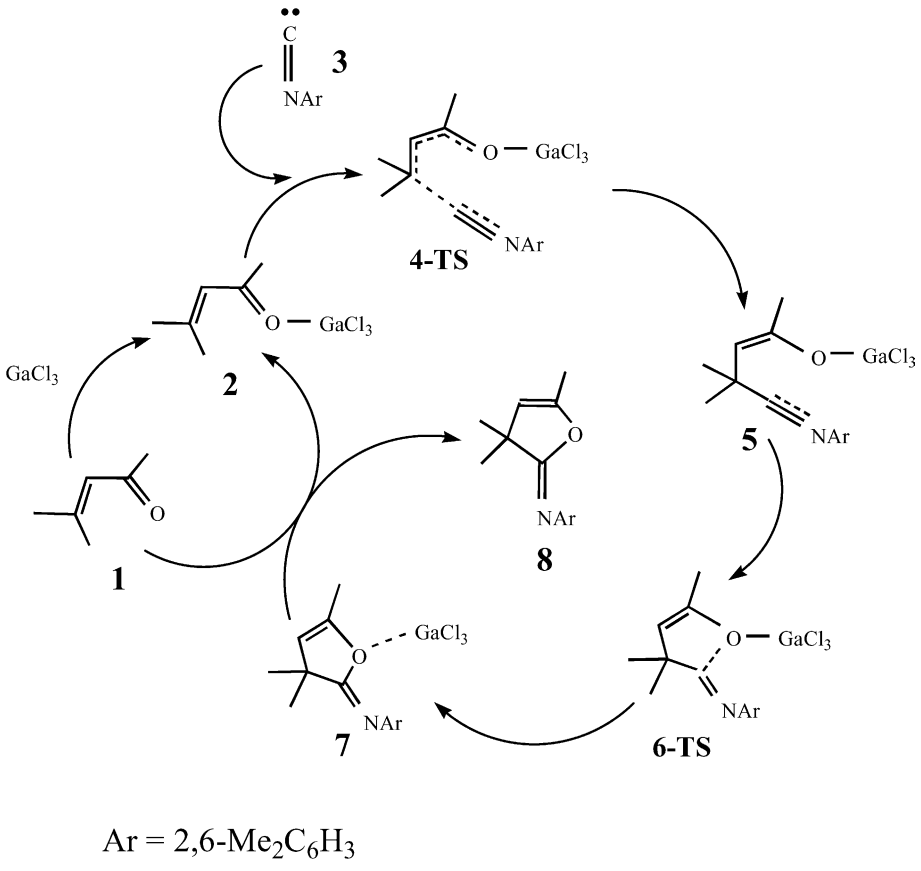


Figure 1. Catalytic cycle for the title reaction.

2. Computational details

All calculations were carried out with the Gaussian 98 program.[15] The structures of all the reactants, transition states, intermediates, and products were located and characterized with the DFT calculations using the B3LYP hybrid functional.[16,17] The 6-31G* basis set for all atoms were used to optimize this series of relevant structures. For all stationary points, vibrational frequencies were also calculated to investigate the nature of the stationary points and to provide the thermodynamic quantities such as the zero-point vibrational energies (ZPVE), thermal corrections, enthalpies, Gibbs free energies and entropies at the temperature of 298.15 K and the pressure of 1 atm. Each stationary point was characterized as a minimum with all positive frequencies and a transition state with only one imaginary frequency. Single-point energies were further calculated at the B3LYP/6-311++G** level. In order to take into account the solvent effect, we also adopt the self-consistent reaction field (SCRF) method based on the polarized continuum model (PCM)[18] for the title reaction. In addition, the electronic structures of all stationary points were analyzed by the natural bond orbital (NBO) method.[19]

3. Results and discussions

In this work, as shown in Figure 1, we have explored the catalytic cycle for the title reaction. The corresponding geometries and parameters are listed in Figure 2 and Table 1, respectively.

3.1. The process of the title reaction with $GaCl_3$ activator

As shown in Figure 2 and Table 1, there exist two transition states in the title reaction. According to the calculational results, the whole reaction process is found to be proceeded via three steps as follows.

3.1.1. First step—formation of the complex 2. The first step is the coordination of $GaCl_3$ to the lone pair electrons of the O atom in mesityloxide **1**. At the B3LYP/6-31G* level, the C1═O and C2═C3 bond lengths were found to be 1.2634 and 1.3650 Å in **2**, which are about 0.04 and 0.015 Å longer than those in **1**, while the C1–C2 bond length is 1.4425 Å in **2**, which is about 0.04 Å shorter than that in **1**. Wiberg bond indices given in Table 3 show that the bond orders of the C1═O and C2═C3 bonds change from 1.7506 and 1.7718 in **1** to 1.4451 and 1.6561 in **2**, respectively, while the bond order of the C1–C2 bond changes from 1.0722 in **1** to 1.1912 in **2**. The natural charge of C3 atom changes from 0.096 in **1** to 0.176 in **2** with natural population analysis (NPA). Therefore, the coordination of $GaCl_3$ to the oxygen atom in **1** results in the weakness of the C1═O and C2═C3 bonds and the enhancement of the C1–C2 bond, leading to a more electrophilic C3 atom. As shown in Table 2, the binding energy is 32.98 kcal/mol (including ZPVE) at 25 °C at the B3LYP/6-31G* level and 25.53 kcal/mol without ZPVE at the B3LYP/6-311++G**

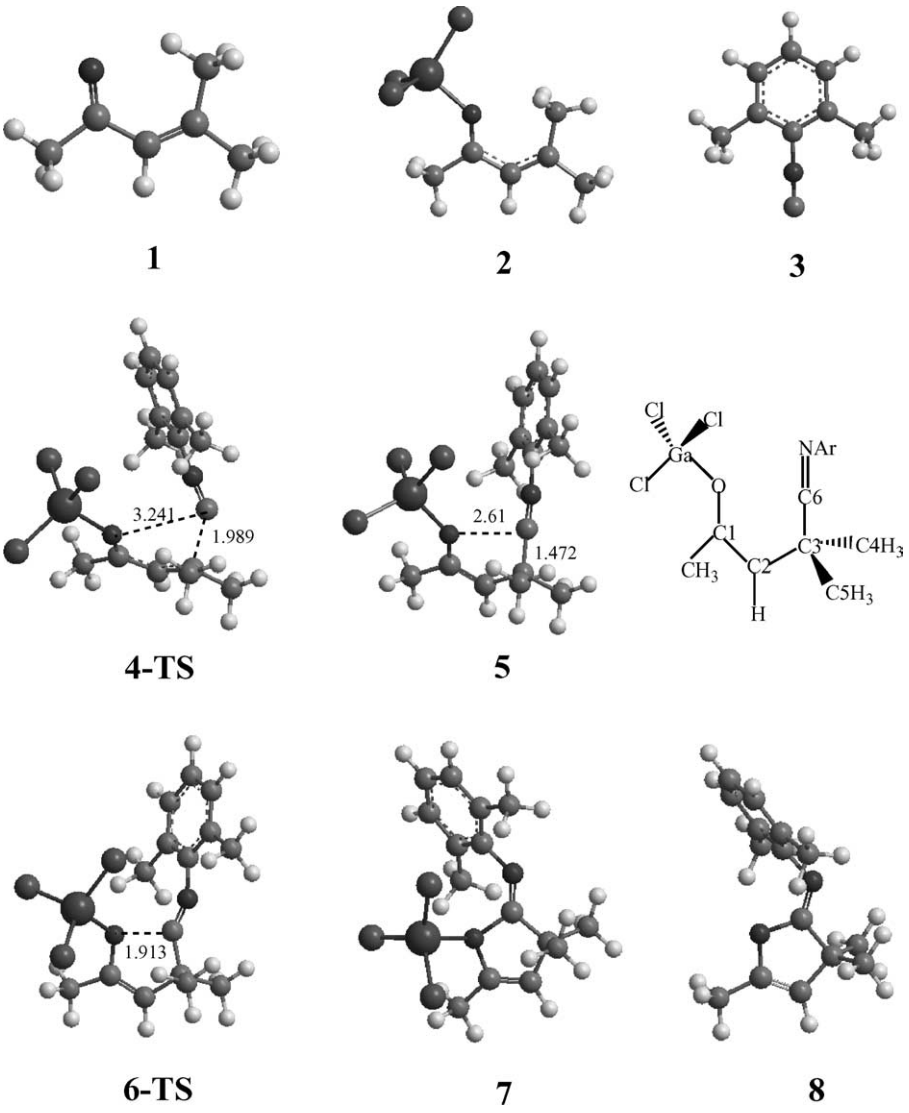


Figure 2. Optimized geometries for the stationary points in the title reaction.

Table 1. Optimized geometry parameters for stationary points at the B3LYP/6-31G* level[a]

	1	2	4-TS	5	6-TS	7	8
Bond lengths (Å)							
Ga–O	—	1.9805	1.9249	1.8912	1.9593	2.0734	—
C1–O	1.2253	1.2634	1.2934	1.3297	1.3802	1.4439	1.4016
C1–C2	1.4842	1.4425	1.3962	1.3581	1.3375	1.3283	1.3337
C2–C3	1.3517	1.3650	1.4227	1.5234	1.5117	1.5119	1.5124
C3–C6	—	—	1.9889	1.4724	1.4989	1.5209	1.5320
C6–O	—	—	3.2408	2.6100	1.9126	1.4893	1.3849
C6–N	—	—	1.1724	1.1580	1.1852	1.2400	1.2622
Bond angles (°)							
O–C1–C2	124.86	120.07	120.46	118.03	114.68	110.60	112.52
C1–C2–C3	127.97	126.13	126.43	120.82	115.89	112.27	109.82
C2–C3–C6	—	—	104.18	105.08	105.48	100.60	100.21
C3–C6–N	—	—	142.68	176.61	144.35	128.63	125.79
C6–N–C7	—	—	176.44	176.31	156.01	133.04	123.48
Dihedral angles (°)							
C1–C2–C3–C4	0.00	0.00	37.01	66.93	96.61	103.47	117.64
C1–C2–C3–C5	180.00	180.00	179.52	−167.89	−138.47	−131.26	−116.75
C1–C2–C3–C6	—	—	−69.40	−51.38	−20.55	−13.21	0.41

[a] For the reactant **3**, the bond length of C6–N is 1.1816 Å.

Table 2. Calculated energies (hartree) and relative energies (kcal/mol) at the B3LYP/6-31G* level for the stationary points[a]

	E	ΔE_{ZPE}	ΔE_{298}	ΔH_{298}	ΔE^{b}
$GaCl_3$+1+3		0.00	0.00	0.00	0.00
2+3		−33.62	−32.98	−33.57	−25.53
4-TS	−4016.696168	−24.52	−23.62	−24.80	−12.87
5	−4016.716734	−36.29	−35.37	−36.56	−26.47
6-TS	−4016.713315	−34.28	−33.95	−35.14	−23.21
7	−4016.718565	−36.76	−36.44	−37.63	−25.32
8[c]	−713.013657	−56.22	−56.23	−57.42	−46.40
9[d]	−4326.593763	−37.23	−35.48	−37.28	
10-TS[d]	−4326.592895	−36.83	−35.02	−36.88	

[a] The energies for **$GaCl_3$**, **1**, **2**, and **3** are −3303.682327, −309.875092, −3613.612422, and −403.096294 hartree, respectively.
[b] At B3LYP/6-311++G** level.
[c] The difference between **8+2** and **$GaCl_3$+1+1+3**.
[d] Relative to **$GaCl_3$+1+1+3**.

level. The results indicate that the coordination of $GaCl_3$ to the oxygen atom is favorable to proceed.

3.1.2. Second step—an attack of 3 to 2. Due to an electrophilic C3 atom in **2** and 2,6-dimethylphenyl isocyanide with an extraordinary functional group and a formally divalent carbon, it is possible that 2,6-dimethylphenyl isocyanide attacks **2** at the β-position (C3 atom). In our study, we have located the transition state **4-TS**, which is formed in the process that **3** attacks **2** at the C3 position. For the **4-TS** structure, the imaginary frequency is 311.09i cm^{-1}. Analysis of the vibrational modes indicates that this imaginary frequency is associated with the C3–C6 stretching motion. The C1–C2–C3–C4 dihedral angle is deviated from the plane by 37.01°, while the C1–C2–C3–C5 dihedral angle is 179.5°. In addition, the C1═O and C2═C3 bond lengths are 1.2934 and 1.4227 Å, which are 0.03 and 0.06 Å longer than those in **2**, whereas the C1–C2 bond length is 1.3962 Å, which is 0.0463 Å shorter than that in **2**. Wiberg bond indices of the C1═O, C2═C3 and C2–C3 bonds change from 1.4451, 1.6561 and 1.1912 in **2** to 1.2701, 1.2891 and 1.4020 in **4-TS**, respectively, which indicate that the C1═O and C2═C3 double bonds are partly broken and the C1═C2 double bond is partly formed in **4-TS**. After the reaction has surpassed the transition state **4-TS**, the intermediate **5** is formed. Wiberg bond indices of the C1–O, C2–C3, C1═C2 and C3–C6 bonds for **5** are 1.1075, 0.9603, 1.6702, and 1.0380, respectively. Both bond lengths and bond orders show that the C1═O and C2═C3 double bonds in **2** evolve to the single bonds, while the C1–C2 single bond in **2** evolves to the double bond, and the C3–C6 bond has been formed. In addition, the C1–C2–C3–C4 and C1–C2–C3–C5 dihedral angles are deviated from the plane in **2** to 66.93° and −167.89° in **5**. In the view of hybridization, the hybridization of the C3 atom changes from sp^2 to sp^3 in the process of **3** attacking **2**.

One can see from Table 2 that the energy barrier, calculated at the B3LYP/6-31G* level, is 9.36 kcal/mol (including ZPVE) at 25 °C in the process of an attack of **3** to **2**, while the energy barrier increases to 12.66 kcal/mol without ZPVE at the B3LYP/6-311++G** level.

3.1.3. Third step—an attack of the C6 atom to the O atom and the formation of the product 8. For the intermediate **5**, the distance between the O and C6 atoms is 2.61 Å and the natural charges of the O and C6 atom are −0.846 and 0.665, respectively. Due to the short distance and the strong electrostatic interaction between the C6 and O atom, it should be easy for the C6 atom to attack the O atom in the intermediate **5**. Actually, we have located the transition state **6-TS** in the process of the C6 atom attacking the O atom to form a five-member cycle structure. For the transition state **6-TS**, the imaginary frequency is 157.95i cm^{-1}. Analysis of the vibrational modes indicates that this imaginary frequency is associated with the C6–O stretching motion, which leads to the formation of the C6–O bond. The distance between the O and C6 atoms is 1.9126 Å, which is 0.6874 Å shorter than that in **5**. In order to form the five-member cycle structure, the C1–C2–C3–C6 and O–C1–C2–C3 dihedral angles change from −51.38 and 2.15° in **5** to −20.55 and 3.09° in **6-TS**, which imply that the C1–C2–C3–C6 dihedral angle rotates about 30° from **5** to form the transition state **6-TS**. The intermediate **7** is formed after the reaction has overcome the barrier of **6-TS**. For **7**, the C6–O bond length is 1.4893 Å, which is 1.1207 Å and 0.4233 Å shorter than that in **5** and **6-TS**, respectively. The Wiberg bond index of the C6–O bond is 0.7566. Both bond length and bond order indicates that the C6–O bond is formed.

Compound **8** is the product detached $GaCl_3$ from **7**. Compared with **7**, the product **8** has some significant

Table 3. Selected Wiberg bond indices for stationary points at the B3LYP/6-31G* level

	Ga–O	C1–O	C1–C2	C2–C3	C3–C6	C6–O	C6–N
1	—	1.7506	1.0722	1.7718	—	—	—
2	0.2948	1.4451	1.1912	1.6561	—	—	—
3	—	—	—	—	—	—	2.3289
4-TS	0.3470	1.2701	1.4020	1.2891	0.4912	0.0263	2.3949
5	0.3854	1.1075	1.6702	0.9603	1.0380	0.0304	2.4243
6-TS	0.3067	0.9648	1.8014	0.9812	1.0089	0.3366	2.2513
7	0.2193	0.8402	1.8616	0.9865	0.9713	0.7566	1.9485
8	—	0.9253	1.8291	0.9938	0.9602	0.9639	1.8183

differences without the hindrance of $GaCl_3$. The C1–C2–C3–C6, O–C1–C2–C3, C1–C2–C3–C4, and C1–C2–C3–C5 dihedral angles are 0.4, −0.06, −117.64, and −116.75° in **8**, respectively, which indicate that the five-member cycle is almost in a plane and that two CH_3 groups, which are attached at the C3 position, are deviated from the plane to almost the same degrees in the opposite direction. The C6–O bond length is 1.3849 Å in **8**, which is 0.014 Å shorter than that in **7**. The Wiberg bond index of the C6–O bond is 0.9639 in **8**, which is 0.207 larger than that in **7**. As shown in Table 3, for the five-member cycle product **8**, one can see that the C1–O, C2–C3, C3–C6, C6–O bonds are single bonds and that the C1–C2 bond is a double bond.

The corresponding energies for this step are also shown in Table 2. One can see that the barrier height is only 1.42 kcal/mol (including ZPVE) and 3.26 kcal/mol (without ZPVE) at 25 °C at the B3LYP/6-31G* and B3LYP/6-311++G** levels, respectively. It is clear that the second step is the rate-limiting step in the whole reaction.

3.2. Solvent effect on the title reaction with $GaCl_3$ activator

Chatani et al.[12] used toluene as the solvent for the title reaction in their experimental study. Accordingly, in order to take into account the solvent effect, we performed the single-point energy calculations using the SCRF/PCM method at the B3LYP/6-31G* level. Compared with the results calculated in gas phase, the solvent effects do not change the trend of the title reaction significantly in toluene. For the first step, the binding energy is 35.41 kcal/mol without ZPVE, which is close to 32.98 kcal/mol in gas phase. For the second step, the energy barrier was found to be 14.32 kcal/mol, about 5.0 kcal/mol higher than that in gas phase. For the final step, the energy barrier is 3.38 kcal/mol, which is only about 1.0 kcal/mol higher than that in gas phase. It turned out that the solvent effect has little influence on the reaction process.

3.3. Effect of the reactant 1

From Tables 1 and 3, one can see that the Ga–O bond is 2.0734 Å and its Wiberg bond index is 0.2193 in the intermediate **7**, which shows that $GaCl_3$ could bind with the oxygen atom in **7** although the Ga–O interaction is weak. In order to investigate the process of the detachment of $GaCl_3$ from **7**, we have tried to locate a minimum like **7** under the effect of the reactant **1**. But such minimum was not found. Instead, our calculations showed that $GaCl_3$ can be easily detached from **7** and then binds with the oxygen atom in the reactant **1** to form **2** without an energy barrier. In the view of binding energies, the binding energy of $GaCl_3$ to **1** was found to be 32.98 kcal/mol, while the binding energy of $GaCl_3$ to **8** is 13.19 kcal/mol. Therefore, the intermediate **7** can be transformed into the product **8** under the effect of the reactant **1** in the catalytic cycle.

In order to further take into account the effect of reactant **1** on the reactions, we have recalculated the third step under the existence of the reactant **1**. The corresponding calculated results are shown in Table 2 and Figures 3 and 4. In our calculations, we have located a transition state **10-TS**, which

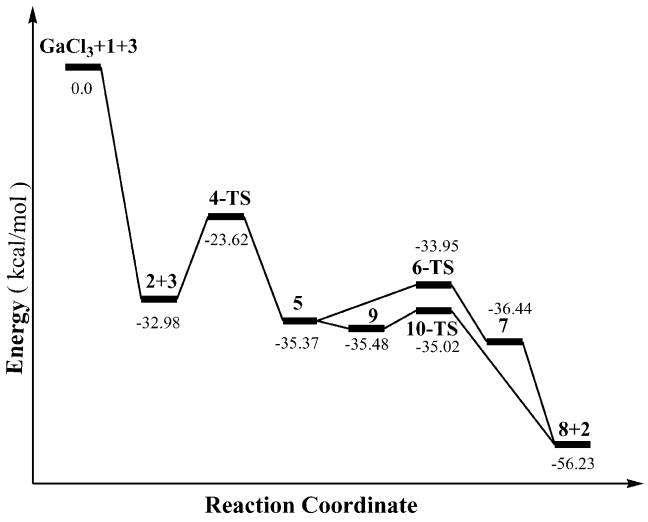


Figure 3. Relative energy profile (at 25 °C) at the B3LYP/6-31G* level.

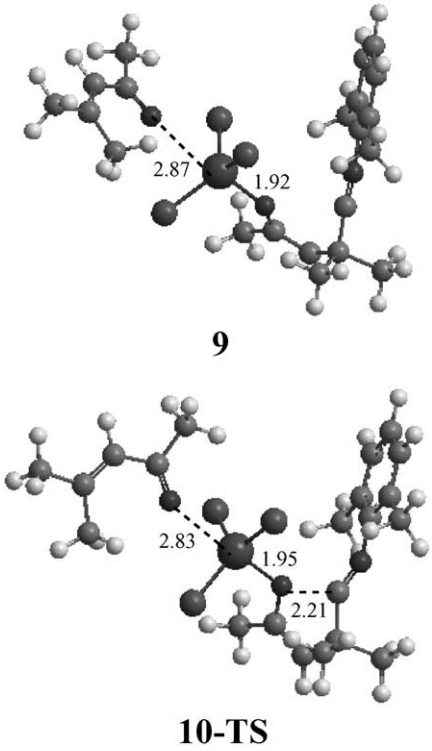


Figure 4. Optimized geometries for the intermediate **9** and transition state **10-TS**.

directly connects **9** and the products **8** and **2**. For the transition state **10-TS**, the imaginary frequency is 25.74i cm^{-1} at the B3LYP/6-31G* level. Analysis of the vibrational modes indicates that this imaginary frequency is associated with the C6–O stretching motion, leading to the formation of the C6–O bond and the five-member cycle product. At the B3LYP/6-31G* level, the C6–O bond length is 2.2119 Å, which is 0.3569 Å shorter than that in **9**, while the Ga–O bond length is 1.9486 Å, which is 0.03 Å longer than that in **9**. The corresponding energy barrier (including ZPVE) is 0.46 kcal/mol at 25 °C at the B3LYP/6-31G* level, which is significantly lower than that calculated without the effect of reactant **1**. It is clear that $GaCl_3$ can be

easily detached in the reaction process at the existence of reactant **1** and then binds with the reactant **1** to take part in the next catalytic cycle in the title reaction. Therefore, a catalytic amount of $GaCl_3$ can promote the title reaction to give the product in high yield, just as observed by Chatani et al.[12]

3.4. The reaction process without $GaCl_3$ activator

In order to illuminate the activation of $GaCl_3$, we further studied the title reaction without $GaCl_3$. In this process, as shown in Figure 5, we can only find a transition state **TS-1**. For the **TS-1** structure, the C3–C6 bond length is 1.7433 Å, which is 0.2456 Å shorter than that in **4-TS**. The imaginary frequency is 332.83i cm^{-1}, which is close to that in **4-TS**. Analysis of the vibrational modes indicates that this imaginary frequency is associated with the C3–C6 stretching motion. At the B3LYP/6-31G* level, the energy barrier is 22.8 kcal/mol (including ZPVE) at 298.15 K, which is 13.44 kcal/mol higher than that in the title reaction with $GaCl_3$ activator. We also performed the single-point energy calculation at the B3LYP/6-311++G** level. The results show that the energy barrier is 23.95 kcal/mol without ZPVE, which is 11.29 kcal/mol higher than that in the title reaction. It is clear from our calculations that the activator $GaCl_3$ can significantly lower the energy barrier and promote the title reaction.

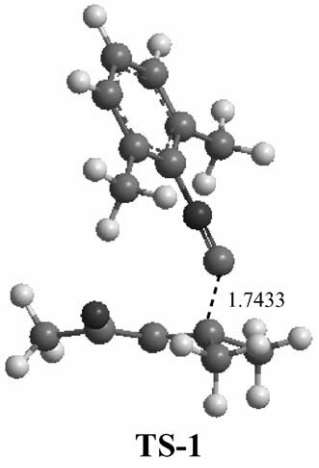


Figure 5. Optimized geometry for the transition state **TS-1**.

4. Conclusion

The mechanism of the $GaCl_3$-catalyzed [4+1] cycloaddition of α,β-unsaturated ketone with 2,6-dimethylphenyl isocyanide leading to unsaturated γ-lactone derivative has been studied with DFT/B3LYP method. In this reaction, $GaCl_3$ at first binds with mesityloxide **1** to form **2**, then 2,6-dimethylphenyl isocyanid **3** attacks **2** at the C3 position to form the C3–C6 bond, then the C6–O bond is formed due to an attack of the C6 atom to the O atom and the five-member heterocycle product **8** is formed. According to the calculated results, the title reaction is an exothermic process and the rate-limiting step is to overcome the barrier of the transition state **4-TS** at the second step. Taken into account the effect of the reactant **1**, $GaCl_3$ can be easily detached from the product and then involved in the next catalytic cycle to promote the reaction.

Acknowledgements

This project has been supported by the National Natural Science Foundation of China (Grant No. 30370337), and by the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, China.

References and notes

1. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
2. Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67–83.
3. Cornelissen, J. J. L. M.; Rowan, A. E.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. *Chem. Rev.* **2001**, *101*, 4039–4070.
4. Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741–743.
5. Yonehara, F.; Kido, Y.; Morita, S.; Yamaguchi, M. *J. Am. Chem. Soc.* **2001**, *123*, 11310–11311.
6. Kido, Y.; Yonehara, F.; Yamaguchi, M. *Tetrahedron* **2001**, *57*, 827–833.
7. Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789–790.
8. Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2001**, *67*, 1414–1417.
9. Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528–8529.
10. Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2002**, *4*, 2209–2211.
11. Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295.
12. Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812–7813.
13. Xu, K. L.; Wu, Y.; Xie, D. Q. *Chin. Sci. Bull.* **2004**, *49*, 535–537.
14. Yamabe, S.; Minato, T. *J. Org. Chem.* **2000**, *65*, 1830–1841.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Munnucci, B.; Pomelli, C.; Adamo, C.; Clliford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Pikorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nakayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., GAUSSIAN98, Revision A.11.3; Gaussian, Inc.: Pittsburgh, PA, 1998.
16. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
17. Parr, R. G.; Yang, W. *Density-functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, 1989.
18. Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253–260.
19. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 513–520

Stereoselective synthesis of morphine fragments *trans*- and *cis*-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolines

Ling-Wei Hsin,* Li-Te Chang, Chien-Wei Chen, Chia-Huei Hsu and Hung-Wei Chen

Institute of Pharmaceutical Sciences, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Room 1336, Taipei 10018, Taiwan, ROC

Received 31 May 2004; revised 17 August 2004; accepted 11 October 2004

Abstract—A stereoselective synthesis of the ACNO partial structures of morphine has been developed. Palladium-catalyzed cyclization of carbamate **2** provided the tetracyclic (ACNO) 3-ethoxycarbonyl-9-methoxy-2,3,5,6,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**14**); while treatment of 5-(2-bromo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**8**) under the same reaction condition gave 8a-(2-hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**11**) via an unusual Claisen rearrangement. 9-Methoxy-3-methyl-2,3,5,6,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**7**) was successfully transformed to *trans*-octahydroisoquinoline **3** and *cis*-octahydroisoquinoline **4** via catalytical hydrogenation over PtO_2 and chemical reduction with acidic $NaBH_4$, respectively.

1. Introduction

The rigid structure of morphine, a potent analgesic alkaloid, consists of five rings (ABCNO, Chart 1). Although narcotic analgesics display excellent antinociceptive activity, the numerous adverse effects of opiate narcotics continue to stimulate the discovery and development of better analgesics with no abuse-liability and milder side effects.[1] Approaches based on simplification of the morphine skeleton for the development of potent and nonaddictive analgesics have been adopted by generations of medicinal chemists and have resulted in the discovery of many potent analgesics, such as meperidine, pentazocine, and levorphanol.[1–3]

Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ols, which contain the ACNO partial structure of morphine, have been found to retain potent analgesic activity.[4,5] The *N*-cyclopropylmethyl analog **1** (J-6549) displayed potent oral analgesic and narcotic-antagonism activity and therefore, is likely to have a low potential for addiction.[5] Since the first synthesis of the ACNO skeleton of morphine by Schultz et al.,[6] several synthetic strategies have been published for the construction of the ACNO fragment of morphine.[4,7–12] Nevertheless, either due to inefficiency in these synthesis or inadequate structure-activity relationship (SAR) study, these ACNO compounds have not been developed for clinical use yet.

Researches in this laboratory have been focused on the development of novel synthetic strategies for stereoselective construction of the ACNO ring system of morphine and investigation of pharmacological activities of new ACNO compounds.[11–13] Previously, we reported a convergent approach towards the construction of the ACNO fragment of morphine via an intramolecular radical cyclization.[13]

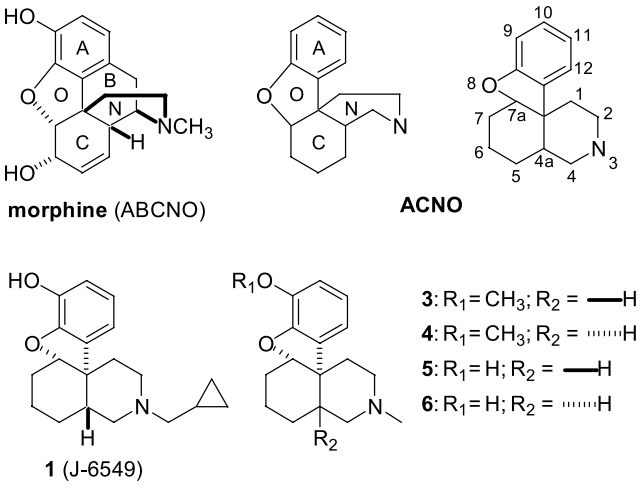


Chart 1.

Keywords: Stereoselective; Morphine; Intramolecular cyclization; Heck reaction; Claisen rearrangement.
* Corresponding author. Tel: +886 2 2395 2310; fax: +886 2 2351 2086; e-mail: lwh@ntumc.org

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.067

However, the difficulty in control of stereoselectivity prohibited further application.

Another attractive pathway towards the construction of the ACNO partial structure of morphine was demonstrated by Liou et al., in which a palladium-catalyzed cyclization was adopted as the key step (Chart 2).[14] However, the chirality of C-4a has not been established yet, and the stereoisomers may possess significantly different pharmacological profiles.[15–17] Therefore, to further study the SAR and the therapeutic potential of ACNO derivatives, an efficient and stereoselective synthetic route is highly desired. As a continued effort in this area, we have developed a novel synthetic approach, in which the O ring and the crucial quaternary carbon center were formed simultaneously by an intramolecular cyclization of carbamate **2** and the *trans*- and *cis*-C/N ring junctions were constructed via stereoselective catalytic hydrogenation and acidic $NaBH_4$ reduction, respectively. Here, we report this concise and stereoselective approach towards the construction of ACNO fragments of morphine, as exemplified by the synthesis of compounds **3**–**6**.

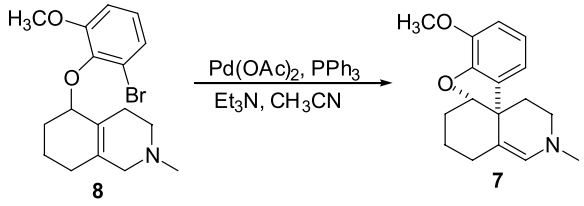


Chart 2. Intramolecular palladium-catalyzed cyclization.[14]

2. Results and discussion

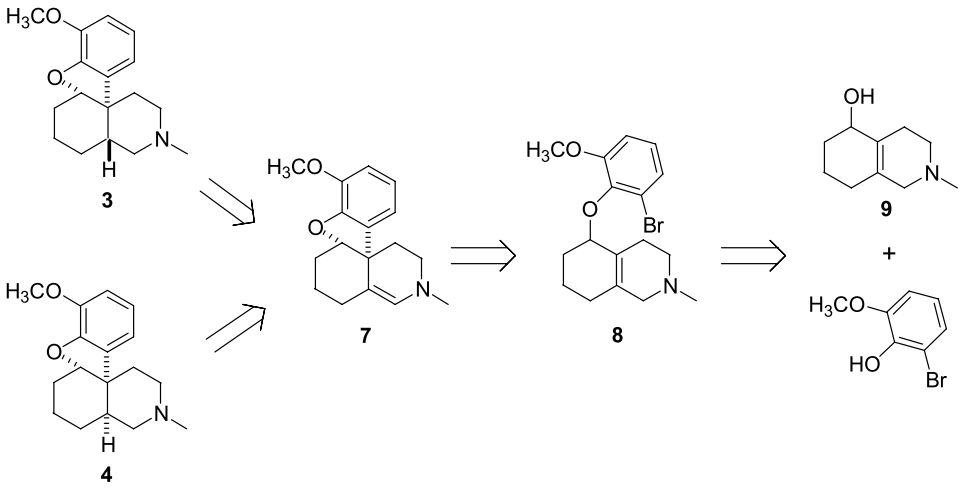
Initially, palladium-catalyzed cyclization reaction was considered as one of the key reactions in our retrosynthetic route as shown in Scheme 1. The *trans*- and *cis*-C/N ring junctions in compounds **3** and **4** could be established by stereoselective reductions of enamine **7**, which is prepared from aryl bromide **8** via the Heck reaction. Compound **8** is synthesized by coupling of compound **9** with 2-bromo-6-methoxyphenol under Mitsunobu reaction condition as previously described.[13]

Aminoalcohol **9** was prepared from 5,6,7,8-tetrahydroisoquinoline in five steps according to the previous procedures.[13] Coupling of **9** with 2-bromo-6-methoxyphenol and 2-iodo-6-methoxyphenol[18] under Mitsunobu reaction conditions provided aryl halides **8** and **10**, respectively (Scheme 2). Then the tetracyclic enamine **7** was supposed to be prepared from either bromide **8** or iodide **10** using the cyclization condition in the literature.[14] However, all attempts to convert aryl bromide **8** to enamine **7** using different Heck reaction conditions failed and afforded only one identifiable product **11**.

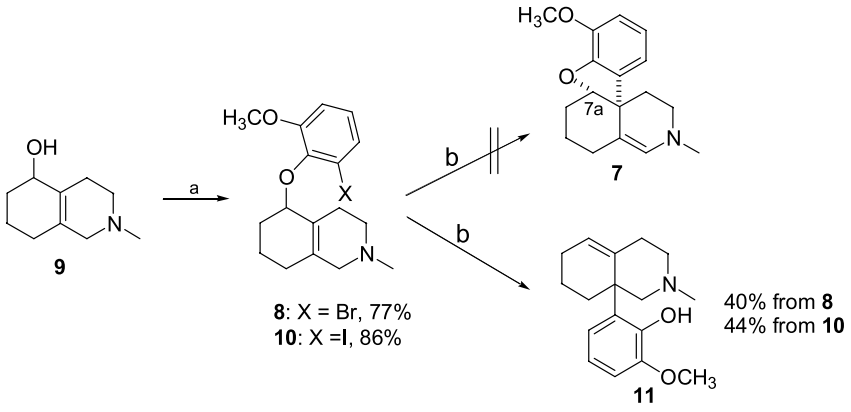
Initially, compound **11** was misinterpreted as the desired compound **7** since compound **11** and the reference compound, which was prepared and assigned as **7** in the literature,[14] showed almost identical ^{1}H and ^{13}C NMR spectra as shown in Tables 1 and 2. However, to our knowledge, the H-7a and C-7a of ACNO compounds usually display signals in the characteristic regions in the NMR spectra (i.e. δ 4.0–4.5 and 85–95, respectively). The disappearance of these typical signals prompted us to reinterpret the structure of **11**. The high-resolution mass (HRMS) data suggested that compound **11** contained two more hydrogen atoms than compound **7**. 2D NMR experiments, including COSY, NOESY, HMBC, and HMQC, were conducted and the structure of compound **11** was determined as 8a-(2-hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline. The X-ray diffraction analysis of the HCl salt of compound **11** confirmed the assigned structure (Fig. 1). Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 251042.

In general, the aryl iodides are more active than the aryl bromides in palladium-catalyzed cyclization. Therefore, iodide **10** was subjected to the same Heck reaction conditions as above. Again, the rearrangement product **11** was the only product isolated in a yield similar to that of using bromide **8** as Heck reaction substrate.

A [3,3]-sigmatropic-rearrangement and a reduction reaction were involved in this reaction. To study the mechanism of this unusual rearrangement, the debrominated derivative **12**



Scheme 1.



Scheme 2. Reagents and conditions: (a) 2-bromo-6-methoxyphenol or 2-iodo-6-methoxyphenol, DEAD, Bu_3P, THF, rt; (b) $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 125 °C.

Table 1. The ^1H NMR spectral data (δ, ppm) of compounds **11**, '**7**',[14] and **7**

11	'**7**'[14]	**7**
1.44–1.54 (m, 3H)	1.44–1.54 (m, 3H)	1.10–1.26 (m, 1H), 1.35–1.45 (m, 1H), 1.55–1.62 (m, 1H)
1.96–2.10 (m, 5H)	1.96–2.10 (m, 4H)	1.78–1.89 (m, 3H), 1.91–1.96 (m, 1H)
2.12–2.21 (m, 1H)	2.12–2.21 (m, 1H)	2.03–2.07 (m, 1H)
2.26 (s, 3H)	2.26 (s, 3H)	2.60 (s, 3H)
2.30–2.34 (m, 1H)	2.30–2.34 (m, 1H)	2.68–2.74 (m, 1H)
2.87–2.90 (m, 1H)	2.87–2.90 (m, 1H)	2.76–2.82 (m, 1H)
3.84 (s, 3H)	3.84 (s, 3H)	3.86 (s, 3H)
3.86–3.87 (m, 1H)	3.86–3.87 (m, 1H)	4.43 (dd, J=9.2, 6.1 Hz, 1H)
5.62 (s, 1H)	5.62 (s, 1H)	5.88 (s, 1H)
6.68–6.76 (m, 3H)	6.68–6.76 (m, 3H)	6.73–6.94 (m, 3H)

was prepared by coupling of **9** with phenol under Mitsunobu reaction condition and then subjected to the same palladium-catalyzed reaction condition. Only starting material was recovered after heating for 72 h as shown in Chart 3. Furthermore, treatment of **8** under the same reaction condition except in the absence of $Pd(OAc)_2$ only afforded the starting material from the resulting reaction mixture. Thus, both the palladium and bromo-substituent are essential for this unusual rearrangement. Shown in Scheme 3 is the proposed mechanism for the palladium-induced rearrangement of compound **8**. Oxidative addition of **8** to the Pd(0) in the presence of ligands, such as PPh_3 and bromide anion, gave Pd(II) species **I**. Coordination of the long electron pair of basic nitrogen atom to Pd provided species **II**. Then an unusual Claisen rearrangement of **II** including a [3,3]-sigmatropic-rearrangement and a rearomatization of the unstable intermediate **III** gave species **IV**. Hydrolysis of **IV** provided product **11**.

The failure of the Heck reaction and the undesired rearrangement may be due to the basic amino group in compounds **8** and **10**. Therefore, a modified synthetic pathway using carbamate **2** as key intermediate for the palladium-catalyzed cyclization reaction was developed (Scheme 4). Treatment of compound **13**[18] with 2-iodo-6-methoxyphenol[14] under Mitsunobu conditions provided

Table 2. The ^{13}C NMR spectral data (δ, ppm) of compounds **11**, '**7**',[14] and **7**

11	'**7**'[14]	**7**
19.8	19.7	22.6
25.4	25.5	29.2
33.0	29.6, 33.1	29.6
35.9	35.8	37.0
45.3	45.4	42.9
55.8	55.8	45.8
57.2	57.3	46.6
64.7	64.8	55.8
77.2	—	90.6
108.4	108.5	106.6
118.2	118.2	111.3
122.4	122.5	116.7
123.6	123.7	120.5
131.0	131.0	134.2
140.0	140.0	138.1
145.1	145.0	145.1
148.5	148.5	146.0

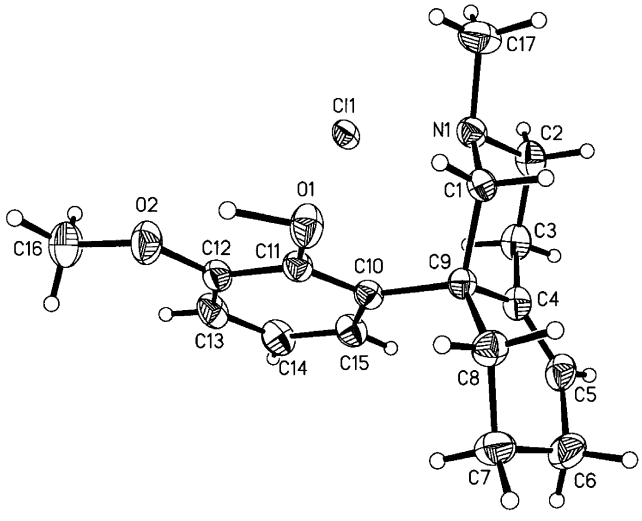


Figure 1.

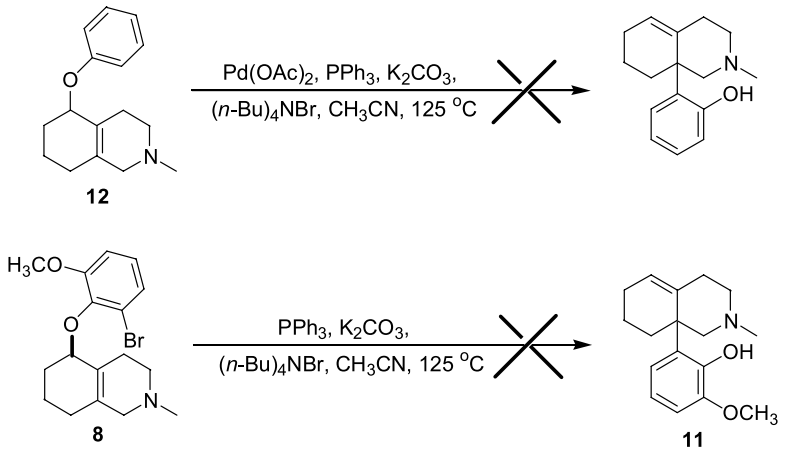
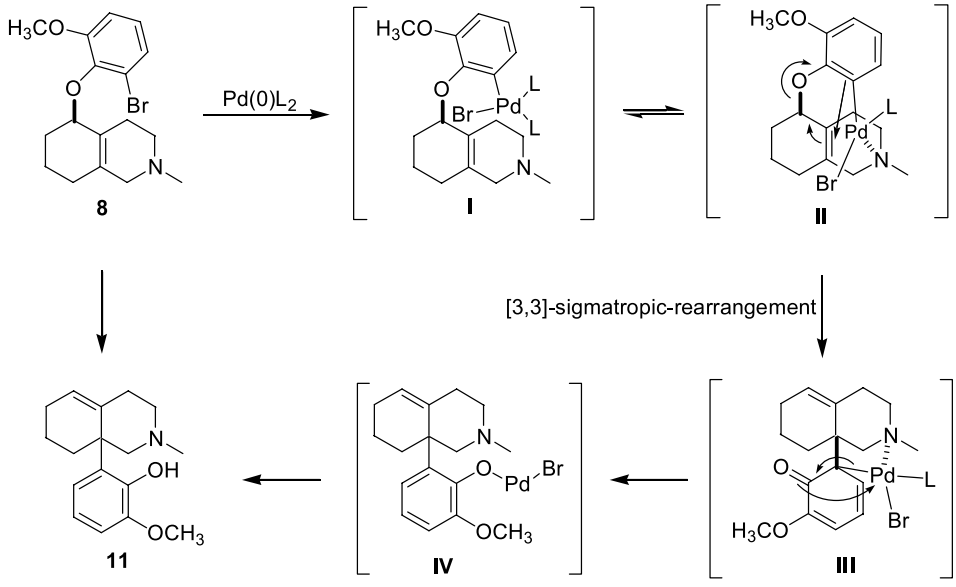
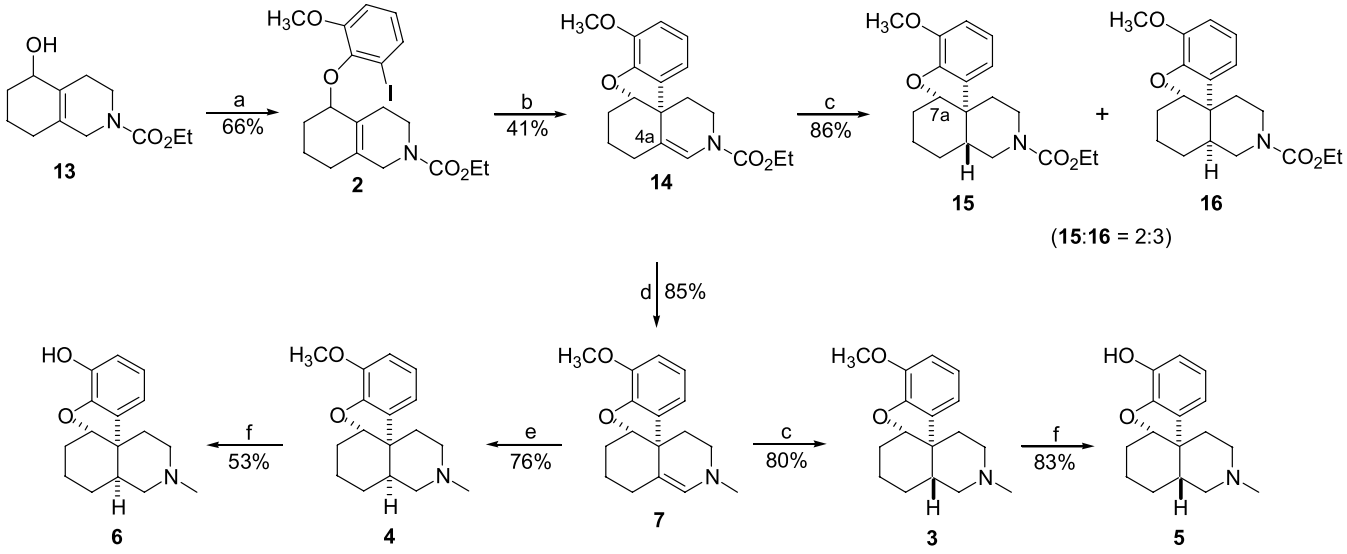


Chart 3.



Scheme 3.



Scheme 4. Reagents and conditions: (a) 2-iodo-6-methoxyphenol, DEAD, Bu_3P, THF, rt; (b) $Pd(OAc)_2$, PPh_3, K_2CO_3, $(n\text{-}Bu)_4NBr$, CH_3CN, 125 °C; (c) H_2, PtO_2, EtOH, rt; (d) $LiAlH_4$, ether, rt; (e) CH_3SO_3H, $NaBH_4$, MeOH, rt; (f) BBr_3–$(CH_3)_2S$, $ClCH_2CH_2Cl$, reflux.

carbamate **2**. Compound **2** was subjected to Heck reaction condition using $Pd(OAc)_2$, PPh_3, $(n\text{-}Bu)_4NBr$, and K_2CO_3 in acetonitrile at 125 °C in a sealed bottle and the tetracyclic (ACNO) carbamate **14** was successfully afforded in 41% yield. Furthermore, there was no rearrangement product observed in the crude reaction mixture. This result offered another evidence to support that the basic nitrogen atom is essential for the rearrangement.

Another task in this paper is the stereoselective establishment of the chirality of C-4a. Previously, catalytic hydrogenation was used to stereoselectively introduce H-4a into the 7-oxygenated ACNO derivatives.[11] Therefore, compound **14** was hydrogenated over platinum oxide (PtO_2). However, a mixture of the *trans*-carbamate **15** and *cis*-carbamate **16** in a ratio of 2:3 (the ratio was determined based on the H-7a signals in the ^1H NMR spectrum) was afforded. Thus, the carbamate group of **14** was removed using $LiAlH_4$ in THF to provide enamine **7**.

As mentioned above, the disappearance of the characteristic H-7a and C-7a signals in the NMR spectra of compound **11** led us to discover the unusual rearrangement and the correct structure of **11**. Therefore, the NMR spectra of enamine **7** are compared with those of compound **11**: (i) compound **7** shows a characteristic double doublet at δ 4.43 for H-7a and a tertiary carbon peak at δ 90.6 for C-7a, whereas compound **11** does not show any corresponding signals; (ii) the *N*-methyl proton signal of enamine **7** is significantly more downfield than that of amine **11** (δ 2.60 and 2.26, respectively); (iii) in DEPT spectra, enamine **7** displays five CH_2 and five CH carbon signals, whereas compound **11** possesses six CH_2 and four CH carbon signals.

Catalytic hydrogenation of enamine **7** over PtO_2 in ethanol provided *trans*-decahydroisoquinoline **3** as the major product (i.e. *trans*/*cis*=8:1). Stereoselective synthesis of *cis*-decahydroisoquinoline **4** was achieved by acidic $NaBH_4$ reduction[7] of **7**, which provided *cis*-**4** as the major product (i.e. *trans*/*cis*=1:12). *O*-Demethylation of compounds **3** and **4** using BBr_3–$(CH_3)_2S$ in 1,2-dichloroethane gave phenols *trans*-**5** and *cis*-**6**, respectively.

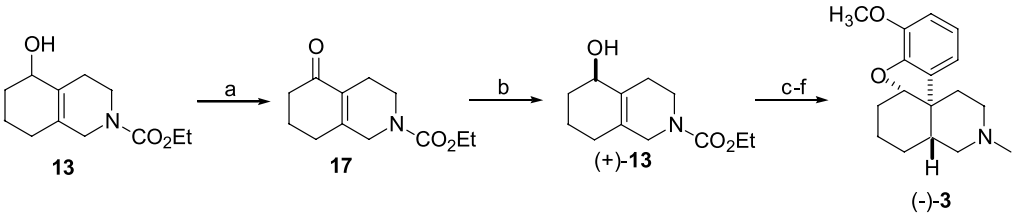
Another attractive advantage of this synthetic strategy is the feasibility of asymmetric synthesis of chiral ACNO derivatives. In our preliminary results, oxidation of racemic carbamate **13** with activated MnO_2 afforded ketone **17**. Asymmetric reduction of **17** with (*S*)-2-methyl-CBS-oxazaborolidine[19,20] gave optically active carbamate (+)-**13** in a moderate yield and in 64% ee as shown in Scheme 5. The chirality in (+)-**13** was then used to control the chirality of other chiral centers formed in the following steps by its directing effects. Thus, optically active (−)-**3** was successfully prepared starting from (+)-**13** via the same reaction sequence for the synthesis of racemic **3**. The hydrochloride salt of optically active (−)-**3** was recrystallized to afford optically pure (−)-**3** (ee=100%).

In summary, we have established an efficient and stereoselective synthesis for construction of the ACNO partial structure of morphine. Compounds **3** and **4** with the *trans* and *cis*-C/N ring junctions could be afforded selectively from enamine **7** via catalytical hydrogenation over PtO_2 and chemical reduction with acidic $NaBH_4$, respectively. Palladium-catalyzed (Heck) cyclization of carbamate **2** successfully formed the quaternary carbon center and the O ring, and provided compound **14** containing the tetracyclic ACNO skeleton. Treatment of amines **8** or **10** under the same Heck reaction conditions gave compound **11** via an unusual Claisen rearrangement. The detailed mechanism and application of this reaction in organic synthesis are currently under investigation.

3. Experimental

3.1. General procedures

Melting points were determined on a MEL-TEMP II apparatus by Laboratory Devices and are uncorrected. NMR spectra were recorded on Bruker DPX-200 and AMX-400 FT-NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a tetramethylsilane (TMS) internal standard. Mass spectra were recorded on a Jeol JMS-D300 mass spectrometer. High-resolution mass spectroscopy (HRMS) measurements were obtained using a Jeol-HX110 mass spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400-CHN instrument, and were within $\pm$0.4% for the elements indicated. The enantiomeric excess (ee) values were determined by HPLC based on the UV absorption areas of the two enantiomers using a chiral column (Daicel chiralcel OD, 0.46 cm×25 cm), a flow rate of 1 mL/min, and 1∼10% 2-propanol in *n*-hexane with 0.2% diethylamine as the mobile phase. Thin-layer chromatography (TLC) was performed on Merck (art. 5554) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor, or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (art. 9385) 40–63 μm silical gel 60. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone prior to use. No attempt was made to optimize yields.



Scheme 5. Reagents and conditions: (a) MnO_2, CH_2Cl_2, reflux; (b) BH_3, (*S*)-MeCBS, THF, rt; (c) 2-iodo-6-methoxyphenol, DEAD, Bu_3P, THF, rt; (d) $Pd(OAc)_2$, PPh_3, K_2CO_3, $(n\text{-}Bu)_4NBr$, CH_3CN, 125 °C; (e) $LiAlH_4$, ether, rt; (f) H_2, PtO_2, EtOH, rt.

3.1.1. 5-(2-Iodo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (10). To a stirred solution of **9** (429 mg, 2.56 mmol), tributylphosphine (1.9 mL, 5.13 mmol), and 2-iodo-6-methoxyphenol[14] (1.92 g, 5.13 mmol) in dry THF (10 mL) was added diethyl azodicarboxylate (DEAD, 5.13 mmol) dropwise at rt. After 40 min, the solvent was evaporated and the residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.6:5.4:94) to afford **10** (886 mg, 86%) as a pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39–1.62 (m, 2H), 1.89–1.91 (m, 2H), 1.96–2.20 (m, 2H), 2.25–2.32 (m, 1H), 2.31 (s, 3H), 2.35–2.39 (m, 1H), 2.60–2.73 (m, 3H), 2.91 (d, J=15.7 Hz, 1H), 3.76 (s, 3H), 4.66 (s, 1H), 6.69 (t, J=8.0 Hz, 1H), 6.82 (dd, J=8.2, 1.5 Hz, 1H), 7.31 (dd, J=7.8, 1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.4, 27.80, 27.84, 28.3, 45.6, 52.5, 55.3, 58.4, 77.5, 93.5, 112.4, 124.9, 126.4, 130.9, 132.6, 147.4, 152.5; HRMS (FAB) Calcd for $C_{17}H_{23}INO_2$ $[M+H]^+$ 400.0774, found 400.0783.

3.1.2. 8a-(2-Hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline (11). A solution of **8** (130 mg, 0.37 mmol) and a catalytic amount of $Pb(OAc)_2$ (8.3 mg, 0.037 mmol), triphenylphosphine (29.1 mg, 0.11 mmol) and triethylamine (0.15 mL, 1.11 mmol) in dry acetonitrile (11 mL) was heated in a sealed bottle at 125 °C for 38 h. The solvent was evaporated and the residue was treated with EtOAc. The EtOAc solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (silica gel; CH_3OH/CH_2Cl_2 1:15) to afford **11** (40 mg, 40%) as a pale yellow solid; mp 126–128 °C (HCl salt, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.54 (m, 3H), 1.96–2.10 (m, 5H), 2.12–2.21 (m, 1H), 2.26 (s, 3H), 2.30–2.34 (m, 1H), 2.87–2.90 (m, 1H), 3.84 (s, 3H), 3.85–3.87 (m, 1H), 5.62 (s, 1H), 6.68–6.76 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 25.4, 33.0, 35.9, 45.3, 55.8, 57.2, 64.7, 77.2, 108.4, 118.2, 122.4, 123.6, 131.0, 140.0, 145.1, 148.5; HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1721. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl \cdot H_2O$: C, 62.28; H, 7.99; N, 4.27. Found: C, 62.20; H, 7.83; N, 4.06.

3.1.3. 2-Methyl-5-phenoxy-1,2,3,4,5,6,7,8-octahydroisoquinoline (12). To a stirred solution of alcohol **9** (207 mg, 1.24 mmol), tributylphosphine (0.6 mL, 2.48 mmol) and phenol (233 mg, 2.48 mmol) in THF (6 mL) was added dropwise DEAD (1.0 mL, 2.48 mmol) at rt. After 1 h, the mixture was evaporated and the residue was chromatographed (silica gel; 6% CH_3OH in CH_2Cl_2) to afford **12** (187 mg, 62%) as a yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57–1.79 (m, 3H), 1.81–2.06 (m, 3H), 2.08–2.24 (m, 1H), 2.27–2.43 (m, 2H), 2.36 (s, 3H), 2.52–2.77 (m, 2H), 2.96 (d, J=15.8 Hz, 1H), 4.50 (s, 1H), 6.85–6.96 (m, 3H), 7.20–7.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 27.5, 27.6, 27.7, 45.6, 52.3, 58.3, 73.2, 116.0, 120.6, 125.8, 129.4, 132.9, 158.6; HRMS (EI) Calcd for $C_{16}H_{21}NO$ $[M]^+$ 243.1623, found 243.1628.

3.1.4. 5-(2-Iodo-6-methoxy-phenoxy)-3,4,5,6,7,8-hexahydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester (2). To a stirred solution of alcohol **13** (1.85 g, 8.2 mmol), tributylphosphine (6.1 mL, 24.6 mmol) and 2-iodo-6-methoxyphenol (6.15 g, 24.6 mmol) in dry THF (60 mL) was added dropwise DEAD (24.6 mmol) at rt and stirred for 1 h. The solvent was evaporated and the residue was chromatographed (silica gel; 25% EtOAc in *n*-hexane) to afford **2** (2.47 g, 66%) as a pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 1.37–1.62 (m, 2H), 1.95–2.13 (m, 5H), 2.56–2.64 (m, 1H), 3.43–3.75 (m, 1H), 3.75–3.90 (m, 3H), 3.80 (s, 3H), 4.13 (q, J=7.1 Hz, 2H), 4.67 (s, 1H), 6.72 (t, J=7.9 Hz, 1H), 6.84 (dd, J=7.9, 1.3 Hz, 1H), 7.33 (dd, J=7.9, 1.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 18.4, 26.8, 27.5, 28.3, 40.9, 46.7, 55.5, 61.1, 77.2, 93.6, 112.5, 125.2, 127.3, 131.1, 132.1, 147.3, 152.6, 155.5; HRMS (FAB) Calcd for $C_{19}H_{25}INO_4$ $[M+H]^+$ 458.0828, found 458.0826.

3.1.5. 9-Methoxy-2,3,5,6,7,7a-hexahydro-1*H*-benzo[4,5]-furo[3,2-*e*]isoquinoline-3-carboxylic acid ethyl ester (14). A solution of **2** (450 mg, 0.98 mmol) and a catalytic amount of $Pb(OAc)_2$ (22 mg, 0.098 mmol), triphenylphosphine (77 mg, 0.29 mmol), K_2CO_3 (813 mg, 5.88 mmol) and $(n\text{-}Bu)_4NBr$ (630 mg, 1.96 mmol) in dry acetonitrile (40 mL) was heated in a sealed bottle at 125 °C for 36 h. The solvent was evaporated and the residue was treated with EtOAc. The EtOAc solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; 17% EtOAc in *n*-hexane) to afford **14** (132 mg, 41%) as a colorless oil; R_f 0.41 (40% EtOAc in *n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22–1.34 (q, J=7.3 Hz, 3H), 1.40–1.53 (m, 1H), 1.61–1.73 (m, 2H), 1.80 (dd, J=13.1, 4.0 Hz, 1H), 1.89–1.95 (m, 2H), 2.05 (m, 2H), 3.11–3.24 (m, 1H), 3.85 (s, 3H), 3.95–4.02 (m, 1H), 4.16–4.26 (m, 2H), 4.46 (dd, J=9.5, 6.3 Hz, 1H), 6.66 (dd, J=5.9, 2.5 Hz, 1H), 6.76–6.81 (m, 2H), (6.87, 6.98) (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 22.0, 29.3, 29.7, 35.3, (38.3, 38.5), (46.8, 46.9), 55.9, (61.8, 61.9), 90.1, 111.8, (114.9, 115.3), 116.5, 120.9, (121.6, 122.1), 135.6, 145.4, 146.1, (153.1, 153.5); HRMS (EI) Calcd for $C_{19}H_{23}NO_4$ $[M]^+$ 329.1627, found 329.1620 (since the carbamate group in compound **14** could adopt either a *cis* or *trans* configuration, some of the ^{1}H and ^{13}C signals appear as pairs).

3.1.6. 9-Methoxy-3-methyl-2,3,5,6,7,7a-hexahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (7). To a stirred solution of $LiAlH_4$ in diethyl ether (0.53 M, 1.5 mL) was added a solution of **14** (127 mg, 0.39 mmol) in diethyl ether (2 mL). The mixture was stirred at rt for 1 h, and then a solution of 20% H_2O in THF was added and stirred for 10 min. To the solution was added 40% aqueous NaOH, and then the resulting mixture was stirred for another 10 min, dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; 30% EtOAc in *n*-hexane) to afford **7** (90 mg, 85%) as a pale yellow oil; R_f 0.33 (40% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.26 (m, 1H), 1.35–1.45 (m, 1H), 1.55–1.62 (m, 1H), 1.78–1.89 (m, 3H), 1.91–1.96 (m, 1H), 2.03–2.07 (m, 1H), 2.60 (s, 3H), 2.68–2.74 (m, 1H), 2.76–2.82 (m, 1H), 3.86 (s, 3H), 4.43 (dd, J=9.2, 6.1 Hz, 1H), 5.88 (s, 1H), 6.73–6.94 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 29.2, 29.6, 37.0, 42.9, 45.8, 46.6, 55.8, 90.6, 106.6, 111.3, 116.7, 120.5, 134.2, 138.1, 145.1, 146.0; HRMS (EI) Calcd for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1572, found 271.1568.

3.1.7. *trans*-9-Methoxy-3-methyl-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (3). A

mixture of **7** (49 mg, 0.18 mmol) and PtO_2 (5 mg) in EtOH (3 mL) was shaken in a Parr hydrogenator under 10 bar of H_2 at rt for 18 h. The catalyst was removed via filtration through Celite and the filtrate was evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.8:8:92) to afford **3** as a pale yellow solid; mp 189–191 °C (HCl salt, 2-propanol/EtOAc); R_f 0.18 ($NH_4OH/CH_3OH/CH_2Cl_2$ 0.1:1:15); ^1H NMR (200 MHz, $CDCl_3$) δ 1.10–1.24 (m, 1H), 1.32–1.60 (m, 4H), 1.76–1.83 (m, 2H), 1.93–2.09 (m, 2H), 2.30–2.44 (m, 1H), 2.40 (s, 3H), 2.54 (t, J=11.6 Hz, 1H), 2.65–2.77 (m, 2H), 3.87 (s, 3H), 4.48 (t, J=5.6 Hz, 1H), 6.78–6.81 (m, 2H), 7.12 (t, J=4.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 24.5, 28.1, 39.3, 39.4, 46.1, 48.0, 50.9, 55.7, 57.3, 89.4, 111.0, 119.5, 119.6, 133.0, 145.2, 148.4; HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1724. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.90; H, 7.81; N, 4.52. Found: C, 65.76; H, 8.02; N, 4.26. Optically active (−)-**3** was dissolved in a solution of HCl in CH_2Cl_2, and then evaporated to provide (−)-**3**·HCl. Recrystallization of the hydrochloride salt of (−)-**3** afforded optically pure (−)-**3**·HCl (ee=100.0%): $[\alpha]_D = -35.6°$ (c=0.58, MeOH).

3.1.8. *cis*-9-Methoxy-3-methyl-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (4). To a stirred solution of compound **7** (170 mg, 0.626 mmol) in MeOH (10 mL) cooled in an ice bath was added methanesulfonic acid (66 mg, 0.689 mmol) and the ice bath was removed after 5 min. Ten minutes later the mixture was again cooled in an ice bath, and $NaBH_4$ (284 mg, 7.51 mmol) was then added in portions over 1 min. The reaction mixture was stirred for 13 h at rt, and then brine (20 mL) was added to the resulting solution followed by 2 M aqueous HCl (9 mL), 3 M aqueous NaOH (20 mL), and H_2O (20 mL). The mixture was extracted with $CHCl_3$ (50 mL×2). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.5:5.5:94) to afford **4** (130 mg, 76%) as a colorless oil; mp 246 °C (HCl salt, 2-propanol/EtOAc); R_f 0.38 ($NH_4OH/CH_3OH/CH_2Cl_2$ 0.1:1:15); ^1H NMR (200 MHz, $CDCl_3$) δ 1.46–1.50 (m, 1H), 1.63–1.80 (m, 7H), 1.95–2.17 (m, 2H), 2.32 (s, 3H), 2.39–2.47 (m, 1H), 2.54–2.75 (m, 2H), 3.87 (s, 3H), 4.30 (s, 1H), 6.75–6.90 (m, 2H), 7.08–7.12 (m, 1H); HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1727.

3.1.9. *trans*-9-Hydroxy-3-methyl-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (5).[4,10] A solution of **3** (51 mg, 0.19 mmol) and BBr_3–$(CH_3)_2S$ (0.9 mmol) in $ClCH_2CH_2Cl$ (18 mL) was brought to reflux for 3 h, and then cooled to rt. The reaction mixture was treated with H_2O and basified to pH=9 with saturated aqueous Na_2CO_3. The solution was extracted with a solution of 2-propanol and CH_2Cl_2 (1:4, 75 mL×3). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 1.4:12.6:86) to afford **5** (40 mg, 83%) as a colorless oil; mp 268 °C (HCl salt, 2-propanol/EtOAc); ^1H NMR (200 MHz, $CDCl_3$) δ 1.17–1.23 (m, 2H), 1.40–1.53 (m, 4H), 1.80–1.85 (m, 2H), 1.95–2.01 (m, 2H), 2.41 (s, 3H), 2.35–2.49 (m, 1H), 2.58 (t, J=11.8 Hz, 1H), 2.77–2.83 (m, 2H), 4.43 (t, J=5.3 Hz, 1H), 6.71–6.76 (m, 2H), 7.00 (dd, J=5.3, 3.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 24.7, 28.3, 38.8, 39.1, 45.8, 48.4, 50.8, 57.1, 89.3, 115.5, 118.5, 120.1, 132.8, 142.2, 147.3; HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1562. Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.84; H, 7.47; N, 4.73.

3.1.10. *cis*-9-Hydroxy-3-methyl-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (6). A solution of **4** (52 mg, 0.19 mmol) and BBr_3–$(CH_3)_2S$ (0.9 mmol) in $ClCH_2CH_2Cl$ (18 mL) was heated to reflux for 3 h, and then cooled to rt. The reaction mixture was treated with H_2O and basified to pH=9 with $NH_4OH_{(conc.)}$. The solution was extracted with a solution of 2-propanol and CH_2Cl_2 (1:4, 75 mL×3). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 1.4:12.6:86) to afford **6** (26 mg, 53%) as a colorless oil; mp 276–278 °C (HCl salt, 2-propanol/EtOAc); ^1H NMR (200 MHz, $CDCl_3$) δ 1.49–1.82 (m, 8H), 1.98–2.06 (m, 2H), 2.33 (s, 3H), 2.40–2.44 (m, 1H), 2.52–2.70 (m, 3H), 4.30 (s, 1H), 6.71–6.76 (m, 2H), 7.00 (t, J=4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 26.4, 26.5, 30.6, 38.6, 44.8, 46.7, 53.4, 57.6, 87.7, 115.0, 116.2, 120.9, 138.6, 141.3, 145.6; HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1571.

3.1.11. 5-Oxo-3,4,5,6,7,8-hexahydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester (17). To a stirred solution of **13** (4.00 g, 17.8 mmol) in CH_2Cl_2 (250 mL) was added activated MnO_2 (46.0 g, 450 mmol) by portions. The mixture was stirred at rt for 48 h, filtered through Celite and the filtrate was evaporated. The residue was chromatographed (silica gel; CH_3OH/CH_2Cl_2 1:20) to afford **17** (2.88 g, 43%) as a yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, J=7.1 Hz, 3H), 2.01–2.05 (m, 2H), 2.29–2.34 (m, 4H), 2.45 (t, J=6.1 Hz, 2H), 3.54 (t, J=5.7 Hz, 2H), 4.05 (s, 2H), 4.17 (q, J=7.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 21.6, 22.0, 27.7, 37.4, 40.2, 46.6, 61.2, 130.2, 152.2, 155.1, 197.4; HRMS (EI) Calcd for $C_{12}H_{17}NO_3$ $[M]^+$ 223.1208, found 223.1209.

Acknowledgements

We acknowledge the National Science Council of the Republic of China (Grant No. NSC 91-2320-B-002-205) for partial financial support of this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.067.

References and notes

1. Willette, R. E. Analgesic Agents. In *Wilson and Gisvold's*

Textbook of Organic Medicinal and Pharmaceutical Chemistry, 10th ed.; Delgado, J. N., Remers, W. A. Eds.; Lippincott-Raven: Philadelphia, 1998; pp 687–708.
2. Fries, D. S. Opioid Analgesics. In *Foye's Principles of Medicinal Chemistry*, 5th ed.; Lemke, T. L., Williams, D. A., Eds.; Lippincott Williams & Wilkins, 2002; pp 453–479.
3. Michne, W. F. Chemistry of Opiate Analgesics and Antagonists. In *Analgesics: Neurochemical, Behavioral, and Clinical Perspectives*; Kuhar, M., Pasternak, G., Eds.; Raven: New York, 1984; pp 125–148.
4. Ciganek, E. *J. Am. Chem. Soc.* **1981**, *102*, 6261–6262.
5. Ciganek, E. U.S. Patent 4,243,668, 1981; *Chem. Abstr.* **1981**, *95*, 809241.
6. Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925.
7. Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064–5074.
8. Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239–5242.
9. Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597–4605.
10. Shenvi, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942–2947.
11. Cheng, C. Y.; Hsin, L.-W.; Tsai, M. C.; Schmidt, W. K.; Smith, C.; Tam, S. W. *J. Med. Chem.* **1994**, *37*, 3121–3127.
12. Hsin, L.-W. Synthesis and Pharmacology of Novel Non-peptide Opioids. Ph.D. Dissertation, June 1995.
13. Cheng, C.-Y.; Hsin, L.-W.; Liou, J.-P. *Tetrahedron* **1996**, *52*, 10935–10944.
14. Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. *Tetrahedron Lett.* **1997**, *38*, 4571–4574.
15. Srinivas, N. R.; Barbhaiya, R. H.; Midha, K. K. *J. Pharm. Sci.* **2001**, *90*, 1205–1215.
16. Hsin, L.-W.; Dersch, C. M.; Baumann, M. H.; Horel, R.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321–1329.
17. Hsin, L.-W.; Prisinzano, T.; Wilkerson, C. R.; Dersch, C. M.; Horel, R.; Jacobson, A. E.; Rothman, R. B.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 553–556.
18. Liou, J.-P.; Cheng, C.-Y. *Tetrahedron Lett.* **2000**, *41*, 915–918.
19. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
20. Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970–2976.