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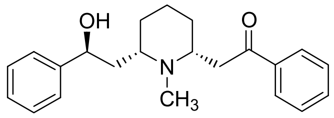
François-Xavier Felpin* and Jacques Lebreton*



(-)-lobeline

This review documents a brief history of the uses of *Lobelia inflata*, describing the fascinating saga of this plant from its original use by native Americans. Biosynthetic routes to *Lobelia* alkaloids are then discussed, followed by an overview of their chemistry, with particular emphasis on asymmetric syntheses. The last section of the review includes a discussion on the bioactivity of (−)-lobeline **1** and its application for the future.

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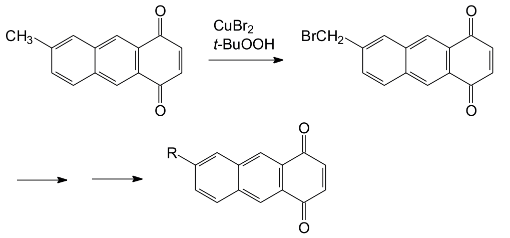

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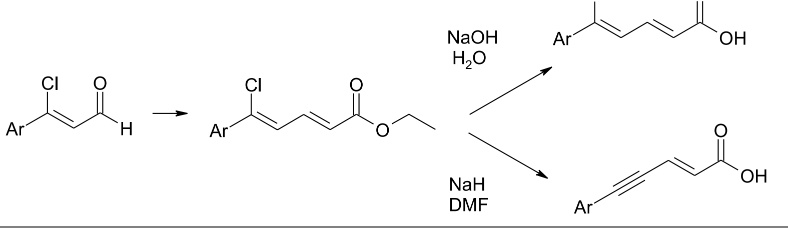

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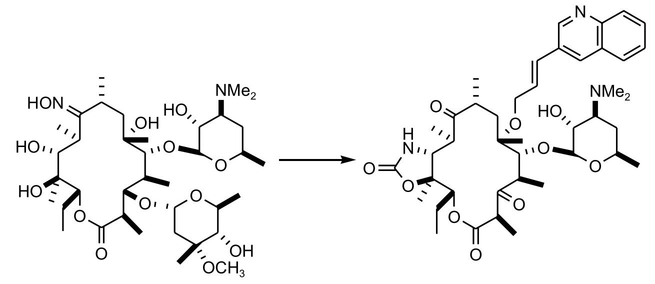

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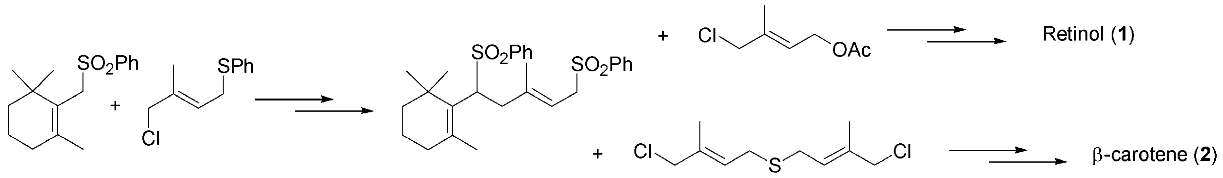

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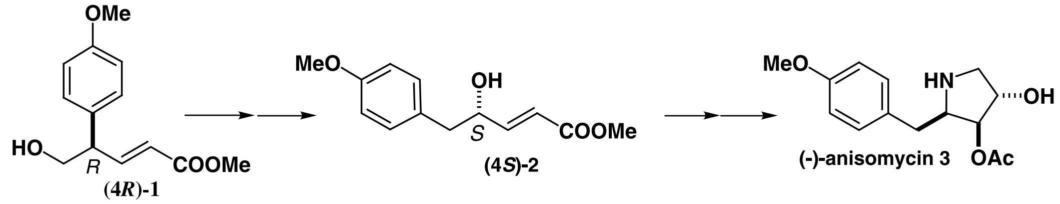

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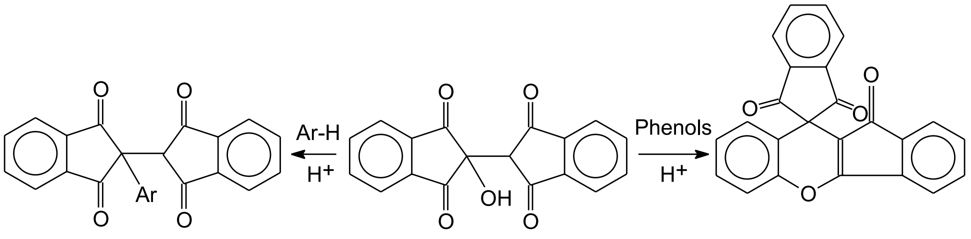

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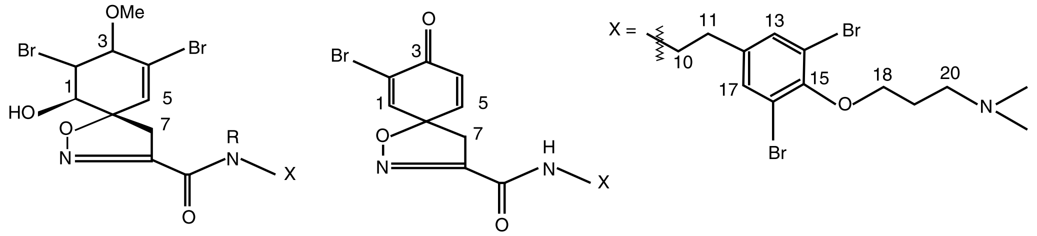

Purealidin Q (1) R=H
Purpurealidin A (2) R=Me

Purpurealidin B (3)

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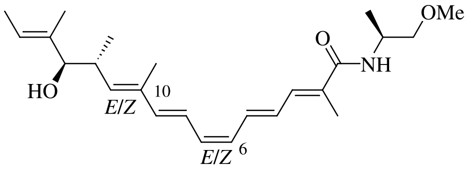

1: (6*E*,10*Z*)
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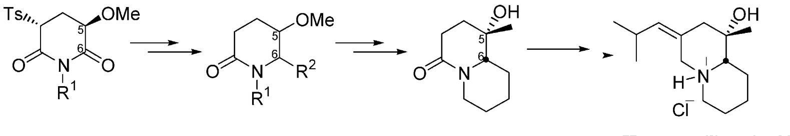

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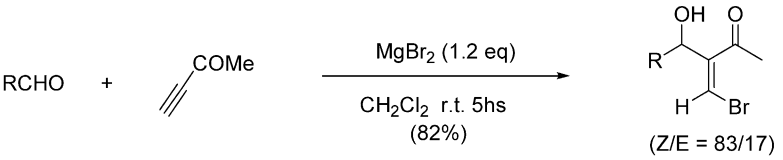
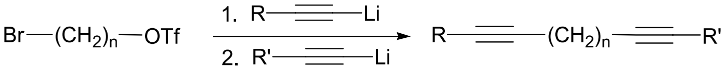
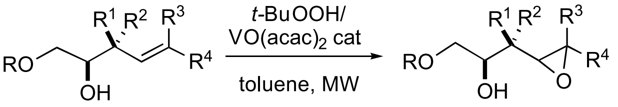
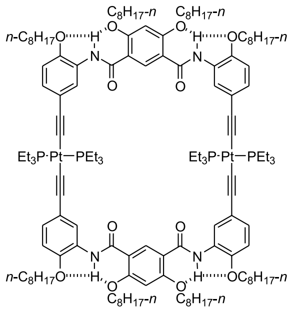
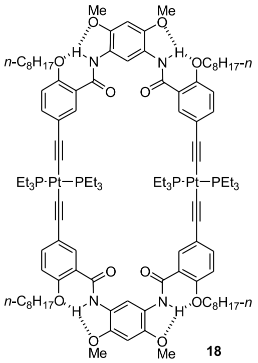


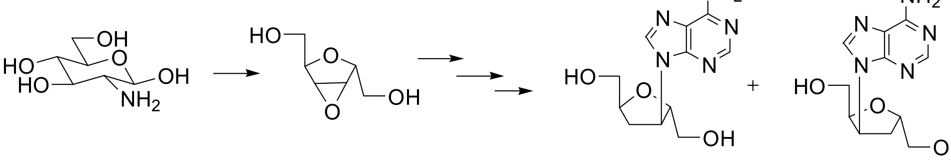

Br—(CH2)n—OTf
1. R—≡—Li
2. R'—≡—Li
R—≡—(CH2)n—≡—R'


R1 R2 R3
RO
OH
R4
t-BuOOH/
VO(acac)2 cat
toluene, MW
R1 R2 R3
RO
OH
R4
O


C8H17-n
n-C8H17O
OC8H17-n
Et3P·Pt—PEt3

17


Me
n-C8H17O
OC8H17-n
Et3P·Pt—PEt3
18


HO
OH
NH2
HO
OH
NH2
N
+

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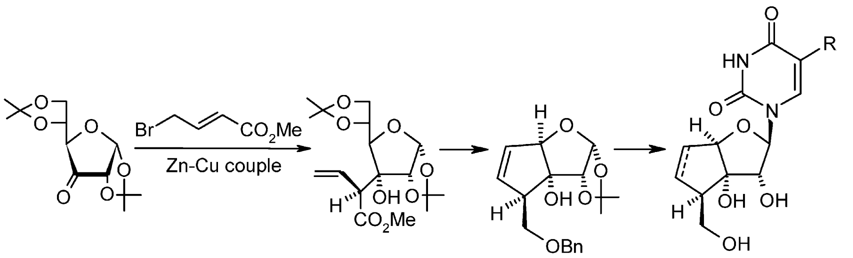

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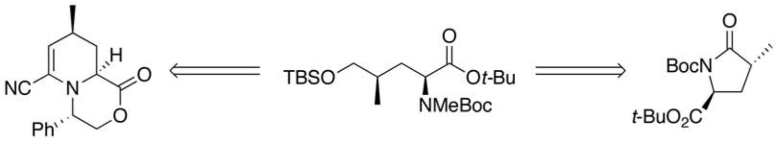

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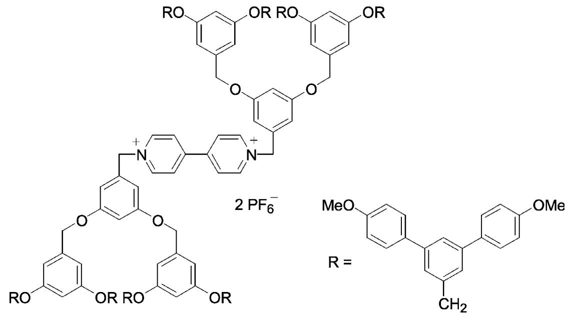

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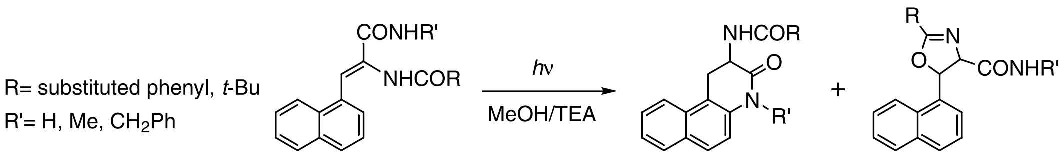

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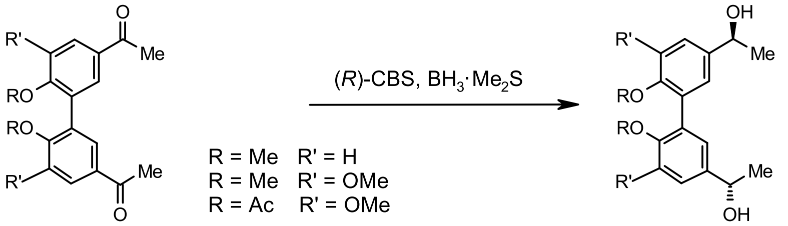

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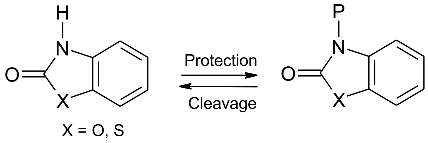

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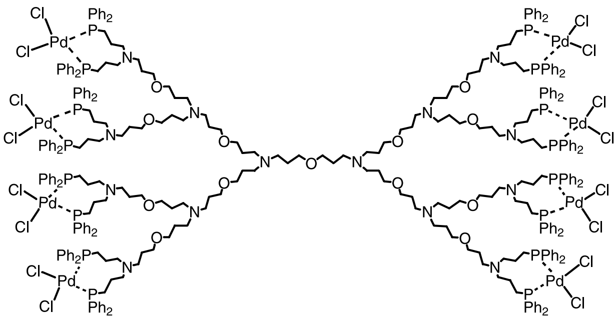

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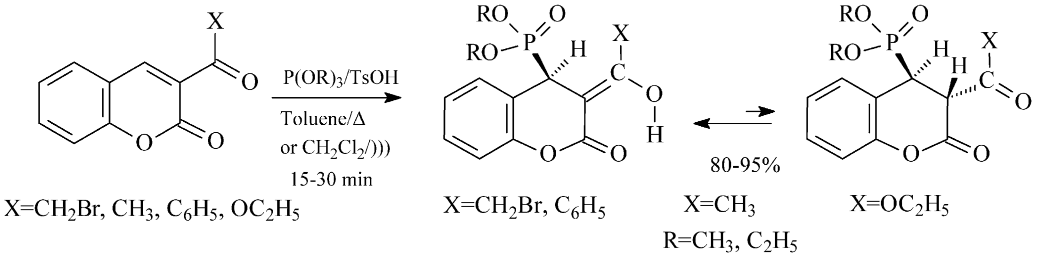

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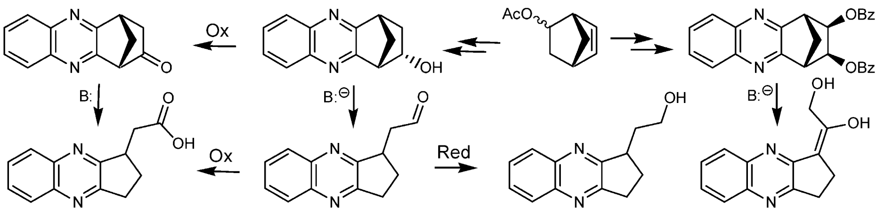

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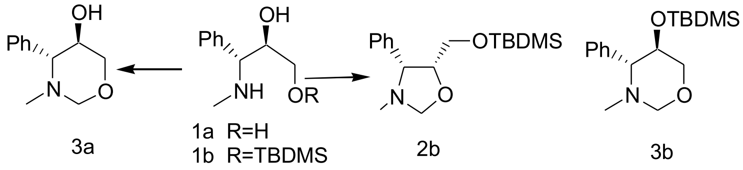

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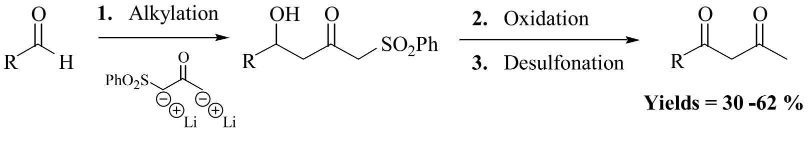
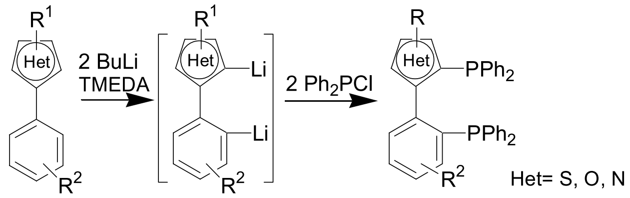


A three-step sequence was studied leading in good yields to 1,3-diketones from aldehydes.



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History, chemistry and biology of alkaloids from *Lobelia inflata*

François-Xavier Felpin*,† and Jacques Lebreton*

Laboratoire de Synthèse Organique, CNRS UMR 6513, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

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This review is dedicated to Professor Guillaume Le Baut on the occasion of his retirement

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Contents

1. Introduction

Piperidine alkaloids constitute a large family of compounds, many of which are of great interest for their various biological activities.[1] A search of the chemical and patent

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Keywords: Lobeline; *Lobelia inflata*; Alkaloids; Central nervous system.

* Corresponding authors. Tel.: +33-2-51-12-54-03; fax: +33-2-51-12-55-62; e-mail addresses: francois-xavier.felpin@icoo.u-bordeauxl.fr; lebreton@chimie.univ-nantes.fr

† Present address: Université Bordeaux-I, Laboratoire de Chimie Organique et Organométallique, 351, Cours de la Libération, 33405 Talence Cedex, France

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literature reveals thousands of references concerning this simple ring system, both in clinical and pre-clinical states.[2] Due to the extension of life expectancy in industrial countries, neurological disorders, like Alzheimer's or Parkinson's diseases, pose an important public health problem. Thus, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future.[3,4] In this context, *Lobelia inflata* alkaloids (Fig. 1) and, in particular, (−)-lobeline **1**, the most active of them, represent a new class of promising therapeutic agents acting on the central nervous system (CNS).

This review documents a brief history of the uses of *Lobelia inflata*, describing the fascinating saga of this plant from its original use by native Americans. Biosynthetic routes to *Lobelia* alkaloids are then discussed, followed by an overview of their chemistry, with particular emphasis on asymmetric syntheses. The last section of the review includes a discussion on the bioactivity of (−)-lobeline **1** and its application for the future.

2. History

There can be few plants with a history as rich as that of *Lobelia inflata*. It is a plant native to northern North America that grows in meadows, waste places, fields and open woods.[5] *Lobelia inflata* is medically the most important variety of the Lobelia family, which consists of more than 50 species including in particular *L. cardinalis*, *L. erinus*, *L. spitaca*, *L. siphilitica*, *L. puberula* and *L. appendiculata*.

Among this family, *Lobelia inflata* contains the greatest concentration of more than 20 piperidine alkaloids[6] (see Figure 1 for the identification of **1**–**20**). (−)-Lobeline **1** is the major and the most biologically active alkaloid of the plant. *Lobelia inflata* is an annual or biannual plant, which grows to 2 feet tall and blooms from June through October. The flowers are very small, white to pale blue, with three oval petals facing downward and two sharply-pointed petals pointing up. The fruit is an inflated pod, resembling a small balloon, which is easily compressible and contains an innumerable number of minute brown seeds.

The story of *Lobelia inflata* can be traced back over many centuries. The herb is actually named in honour of the famous French physician and botanist Matthias De Lobel (1570–1616), who was attached to the court of King James I. Its specific name, *inflata*, is due to its inflated seed pods. *Lobelia inflata* is also known as Indian tobacco, because the native Americans (the Penobscot tribes) smoked the dried leaves as a substitute for tobacco, to produce the effect of alkaloids on the central nervous system (CNS).

Lobelia inflata was extensively used by the people of New England, long before the time of Samuel Thomson (superintendent of Indian affairs in North America from 1756 to 1774), its assumed discoverer. The credit for the introduction of *Lobelia* into medical practice is due to Dr. Manasseh Cutler and Dr. Samuel Thomson. As early as 1773, Thomson became aware of its power to procure vomiting and, during 1791, he first became practically acquainted with its ability to afford relief in diseases like colic, rheumatism and fever. Thomson and Cutler claimed to have used *Lobelia* for the treatment of asthma in the period 1805–1809. Thus, during the 19th century, *Lobelia* was one of the most medically important plants, used as a valuable remedy for asthma. *Lobelia* can, however, be a deadly poison in sufficient quantities. Indeed, Thomson fatally poisoned one of his patients (Ezra Lovett) by the use of *Lobelia*. Nevertheless, *Lobelia*, in the ordinary sense of the term, is not a poison. Undoubtedly, its injudicious use has, and might, produce death, but the same is true for many other drugs that are not ordinarily considered as poisons.

Interest in this class of molecules, and, in particular, in lobeline **1**, the potent alkaloid of this family, has increased in recent years, due to their remarkable biological profile. Thus, lobeline **1**, the principal alkaloid of *Lobelia*, is currently the subject of renewed interest for the treatment of drug abuse and neurological disorders.[7]

3. Biosynthesis

The study of *Lobelia* alkaloid biosynthesis in the 1960s and 1970s principally concerned the most important of them, lobeline **1**. For this reason, we present in this review the biosynthetic pathway of lobeline **1** in more detail. An overview of the biosynthesis of other *Lobelia* alkaloids is also presented, with particular attention being paid to lobinaline **19**.

The extensive research into the explanation of the biosynthetic pathway of piperidinic alkaloids started with Robinson's hypothesis.[8] Robinson postulated that lysine **21** is the precursor of the piperidinic ring in many of the naturally occurring piperidine derivatives via the tetrahydropyridine **22**. Thus, it was shown that lysine **21** furnished the nucleus of various piperidine alkaloids like anabasine **23**,[9,10] and sedamine **24**,[11] a related structural analogue of lobeline **1** (Scheme 1).

Lobeline **1** presents an interesting biosynthetic problem due to the substitutions at the C2 and C6 positions of the piperidine ring by two related substituents. The two key precursors generally accepted are lysine **21** and phenylalanine **25**. It has also been suggested that piperidine alkaloids could be derived from benzoic acid and acetate or from acetate alone[12] like coniine[13,14] **26** (Scheme 2). Different tracer studies with sodium [1-^{14}C]-acetate, however, seem to reject this hypothesis for *Lobelia* alkaloids. Indeed, sodium [1-^{14}C]-acetate was fed to *Lobelia syphilita* and no labelled lobeline **1** was isolated, while in a separate experiment administration of [1-^{14}C]-lysine yielded active lobeline **1**.[15]

The possible pathway for the biosynthesis of the side chains is outlined in Scheme 3. Phenylalanine **25** is converted into *trans*-cinnamic acid **28** by the enzyme phenylalanine ammonia-lyase (PAL).[16] This enzyme has been isolated from a plant source.[17] The hydroxylation of **28** by the addition of a molecule of water gave 3-hydroxy-3-phenylpropanoic acid **29**, which has been isolated from

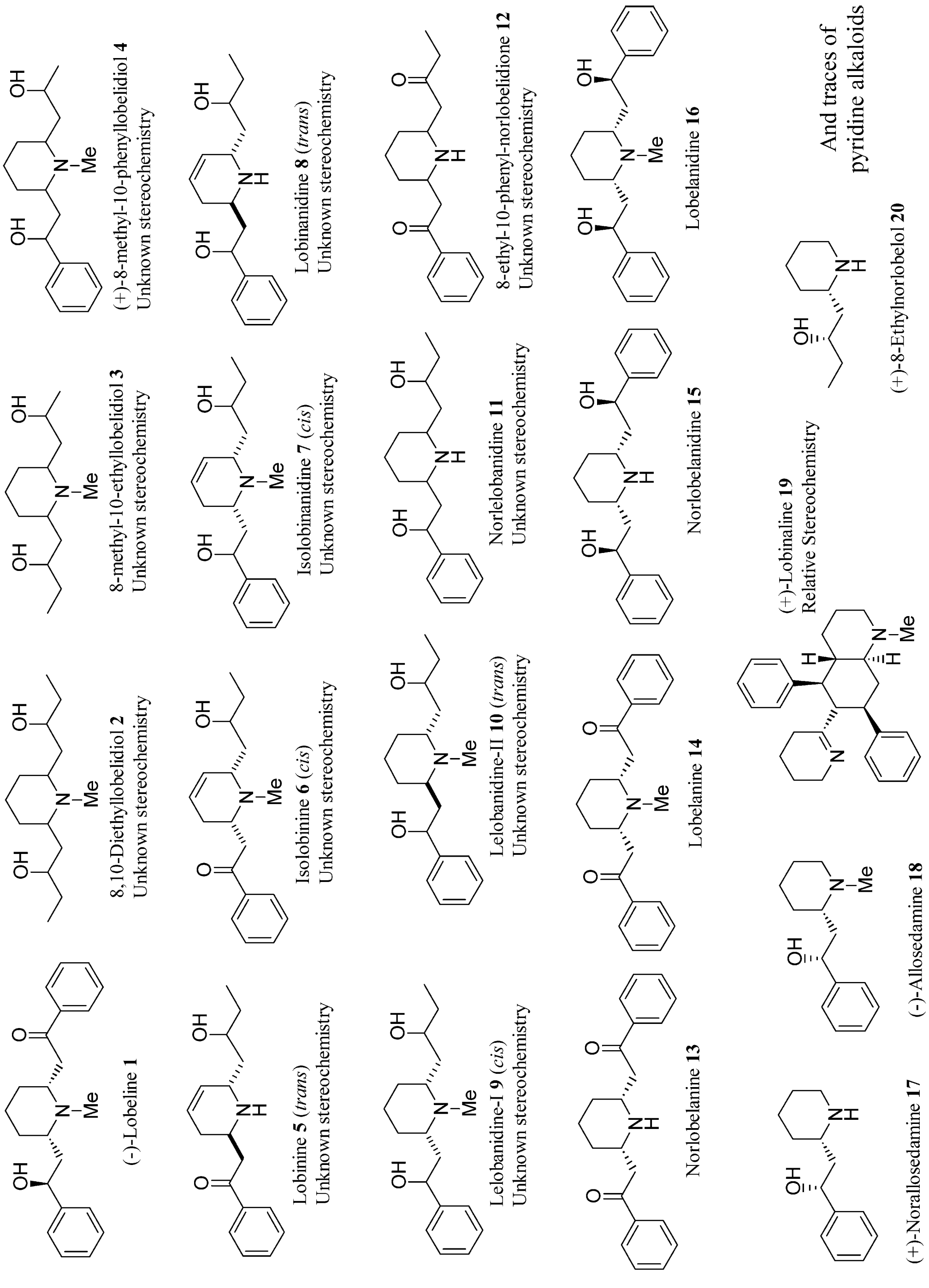
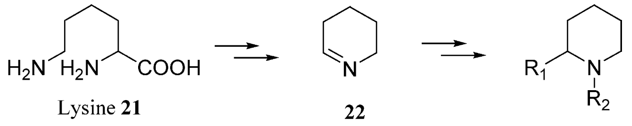
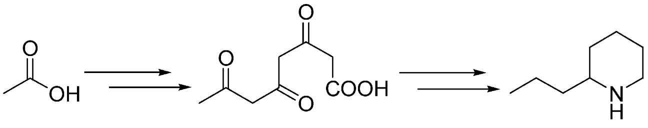


Figure 1. Alkaloids from *Lobelia inflata*.

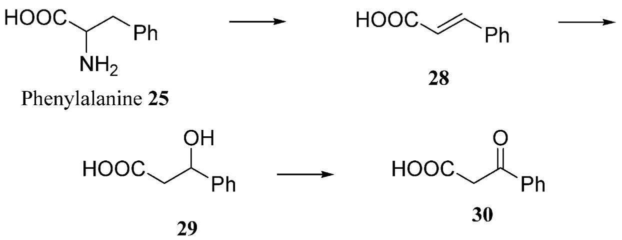

Lysine **21** **22**

R_1 = 3-furyl, R_2 = H : Anabasine **23**
R_1 = Ph-CHOH-CH_2, R_2 = Me : Sedamine **24**

Scheme 1.


27 Coniine **26**

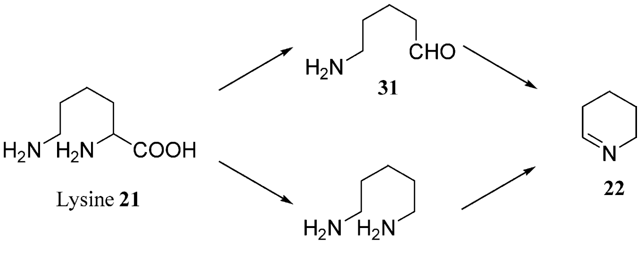
Scheme 2.


Phenylalanine **25** **28** **29** **30**

Scheme 3.

Lobelia inflata.[6] β-Oxidation gave benzoylacetic acid **30**, an important intermediate in the biosynthesis. Feeding experiments have been used to show that phenylalanine **25**, *trans*-cinnamic acid **28**, and 3-hydroxy-3-phenylpropanoic acid **29** are all intermediates in the biosynthetic route and have consequently validated this pathway.[18]

The formation of 2,3,4,5-tetrahydropyridine **22**, the potential intermediate in the biosynthesis of lobeline **1** or other piperidinic alkaloids, is unclear. Two possible pathways are the subject of some dispute (Scheme 4). In the first route, lysine furnished the 2,3,4,5-tetrahydropyridine **22** via 5-aminopentanal **31**.[19] The asymmetrical incorporation of substituents into the piperidine ring of a number of alkaloids favours this hypothesis.[20] It has been shown, however, that the substituents of lobeline **1** were symmetrically incorporated into lysine **21**.[16]

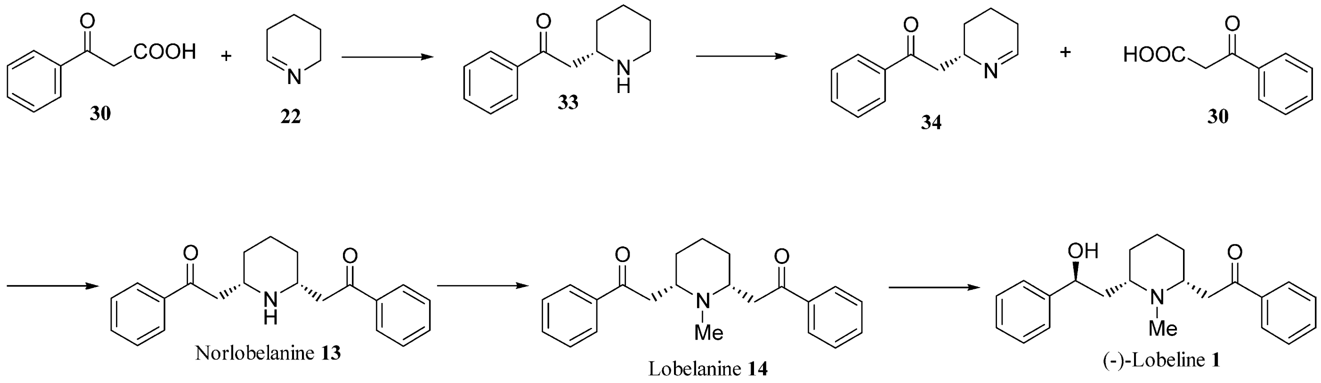

Lysine **21** **31** **32** **22**

Scheme 4.

The second pathway suggested the formation of 2,3,4,5-tetrahydropyridine **22** via cadaverine **32** (pentane-1,5-diamine). Although cadaverine **32** was incorporated into lobeline **1** and stimulated the production of alkaloids like anabasine **23**,[21,22] tracer studies have suggested that it was not a normal intermediate between lysine **21** and 2,3,4,5-tetrahydropyridine **22**. Indeed, [2-^{14}C]-lysine gave 2,3,4,5-tetrahydropyridine **22** with all the radioactivity at the C2 position.[23]

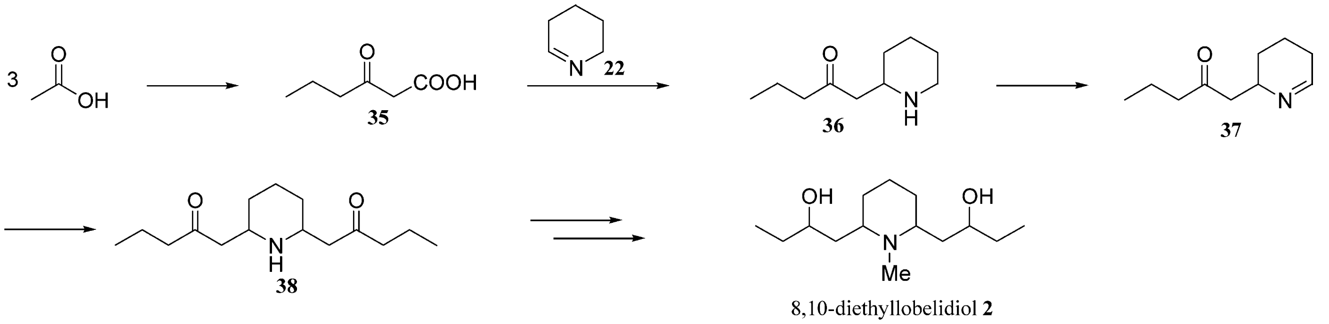
Condensation of 2,3,4,5-tetrahydropyridine **22** with benzoylacetic acid **30** furnished the amino ketone **33**, which on oxidation via **34** and reaction with another molecule of benzoylacetic acid **30**, gave norlobelanine **13** (Scheme 5). *N*-Methylation of **13** yielded lobelanine **14**. The role of lobelanine **14** in the biosynthesis of lobeline **1** has been shown in feeding experiments by incorporation of labelled lobelanine **14** into lobeline **1** in high yield.[24] Thus, the symmetrical the incorporation of lysine **21** into lobeline **1** (vide supra) could be explained by the intervention of the symmetrical intermediate lobelanine **14**. Consequently, a large volume of evidence has been gathered in favour of **31** as a possible intermediate in the formation of **22**. The last step in this process is the reduction of one of the carbonyl groups. Nevertheless, the biosynthesis of lobeline **1** has been poorly studied and the enzymes responsible for the final stages in the biosynthesis of lobeline **1** have not been characterised.

The biosynthetic pathways of other *Lobelia* alkaloids have been studied in less detail, but it seems that the side chains without phenyl groups are derived from acetate. Specific tracer studies with [1-^{14}C]-acetate are in total agreement with the foregoing hypothesis.[18] The 3-oxohexanoic acid **35**, derived from three units of acetate, reacted with 2,3,4,5-tetrahydropyridine **22** to yield **36**. Formation of the imine **37** and subsequent condensation of another molecule of **35** generated the dione **38**. Demethylation of the side chains, *N*-methylation and reduction of the carbonyl functions gave 8,10-diethyllobelidiol **2** (Scheme 6).


30 **22** **33** **34** **30**

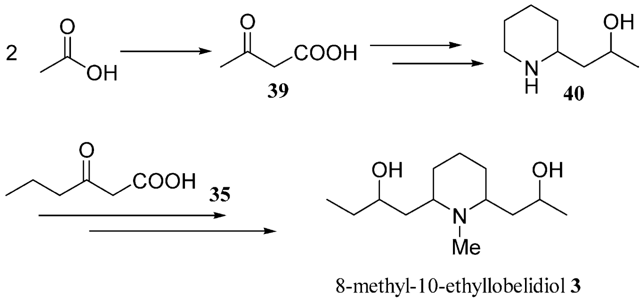
Norlobelanine **13** Lobelanine **14** (-)-Lobeline **1**

Scheme 5.



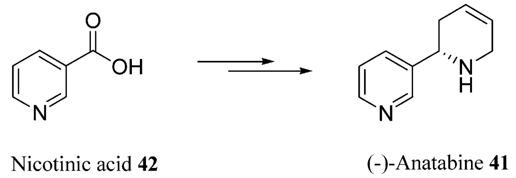
Scheme 6.

When the side chains are ethyl substituents, they are derived from two units of acetate to give 3-oxobutanoic acid **39** (Scheme 7). A similar biosynthetic cascade generated, for example, 8-methyl-10-ethyllobelidiol **3**.



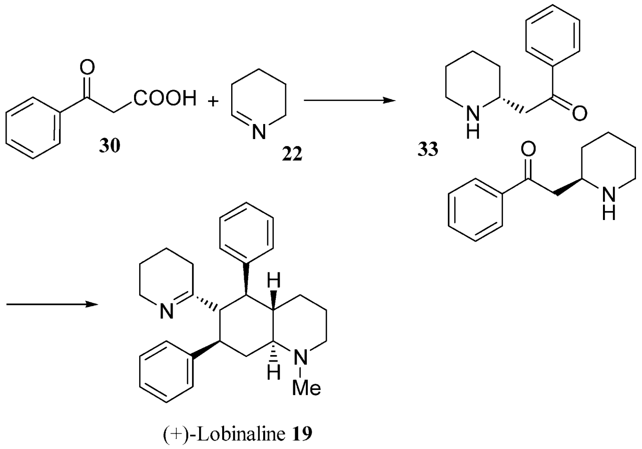
Scheme 7.

For **5** to **8**, in which the core is a tetrahydropyridine ring, the biosynthetic pathways have not been studied. In the case of anatabine **41**, however, an alkaloid of tobacco plants, the tetrahydropyridine ring is derived from nicotinic acid **42**[25] (Scheme 8). Moreover, pyridine alkaloids have been detected in *Lobelia inflata*.



Scheme 8.

The case of lobinaline **19** is an interesting problem, because of its particular structure in comparison with other *Lobelia* alkaloids. It should be noted that lobinaline **19** is the major alkaloid of *Lobelia cardinalis*. In spite of its original structure, it has been shown that lobinaline **19** derives from lysine **21** and phenylalanine **25**.[26] In fact, various tracer experiments, have shown that lobinaline **19** is formed simply by dimerisation[27] (Scheme 9) of phenacylpiperidine **33**, which is also an intermediate in the biosynthetic pathway of lobeline **1**.



Scheme 9.

Publications concerning the biosynthesis and isolation of lobeline-related alkaloids continue to appear at a steady rate. Studies in this area are presumably ongoing and we wait with anticipation for more detailed information about the latter stages of the biosynthetic route.

4. Chemistry of *Lobelia* alkaloids

Only a few of the *Lobelia* alkaloids have been synthesised. In this review, we will describe the synthesis of *Lobelia* alkaloids, paying particular attention to the stereoselective asymmetric strategy. Thus, we will present the total syntheses of allosedamine **18**, 8-ethylnorlobelol **20**, lobeline **1** and its related alkaloids lobelanine **14** and lobelanidine **16**. It should be noted that the syntheses of sedamine **24** (found in *Sedum acre*, but not in *Lobelia inflata*) where its diastereoisomer, allosedamine **18**, was a minor product, are not presented here (Fig. 2). Recently, *Sedum* alkaloids have been reviewed by Bates and Sa-Ei.[28]

4.1. Synthesis of (+)-8-ethylnorlobelol

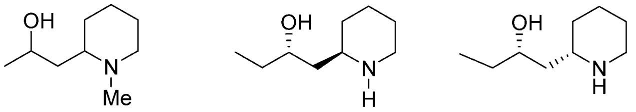
(+)-8-Ethylnorlobelol **20**, a minor alkaloid of *Lobelia inflata*, was first isolated by Wieland[6] et al. in 1939. These

Allosedamine **18** found in *Lobelia inflata*

Sedamine **24** found in *Sedum acre*

Figure 2.

workers described the molecular formula as $C_9H_{19}NO$ and postulated the structure as an *N*-methylpiperidine derivative **43**. This structural assignment was revised twenty years later, however, by Schöpf[29] who, at the same time, established the absolute configuration as (2*R*,8*S*), but without reporting experimental evidence (Fig. 3). Thus, for many years, the absolute configuration was accepted as that described by Schöpf. Recently, Hootelé et al.[30] questioned this assignment and correctly revised the absolute configuration to (2*S*,8*S*). This assertion of Hootelé was confirmed, a short time later, by Takahata's group,[31] with the first asymmetric total synthesis of (+)-**20**.



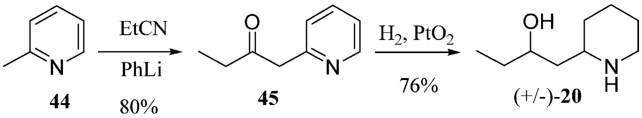
43 Structure proposed by Wieland *et al.*

20 Structure and absolute configuration (2*R*,8*S*) reported by Schölpf *et al.*

20 (2S,8S) corrected by Hootelé *et al.*

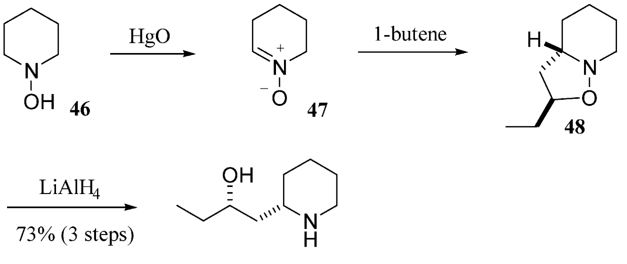
Figure 3.

4.1.1. Non-stereoselective racemic approach. Kracher[32] and co-workers described (Scheme 10) the first racemic synthesis of (+/−)-**20** by the reaction of α-picoline **44** with propionitrile to give, after acidic work-up, the ketopyridine **45** in good yield (80%). This short and efficient synthesis was achieved by catalytic hydrogenation over platinum oxide of the pyridine ring and the carbonyl group in one step to afford (+/−)-**20**. In these studies, the pharmacological profile of some related analogues was also investigated, but no results were disclosed for (+/−)-**20**.



Scheme 10.

4.1.2. Stereoselective racemic approach. More recently, Hootelé et al. have reported a very short diastereoselective synthesis of (+/−)-**20** (Scheme 11). Their approach exploited the advantageous properties of [2−3]-dipolar cycloaddition, which occurs with regio- and stereocontrol. Thus, the side chain was introduced by a regio- and stereoselective nitrone–alkene cycloaddition between 2,3,4,5-tetrahydropyridine-1-oxide **47** and 1-butene. The isoxazolidine **48** could easily be converted to (+/−)-**20** by cleavage of the N–O bond with $LiAlH_4$.



(+/-)-8-ethylnorlobelol **20**

Scheme 11.

In these studies, Hootelé also reported experimental evidence to assign the natural enantiomer as (2*S*,8*S*) (Fig. 3). Consequently, they correctly revised the absolute configuration previously established by Schöpf.

4.1.3. Asymmetric approach. To date, the synthesis of (+)-8-ethylnorlobelol reported by Takahata et al. constitutes an interesting challenge as the only asymmetric synthesis. Retrosynthetically, the Takahata synthesis was achieved using three key reactions (Fig. 4). The Sharpless dihydroxylation of 5-hexenylazide **52** followed by an intramolecular aminocyclisation and a second Sharpless dihydroxylation constitute the three crucial steps of this synthesis to provide (+)-8-ethylnorlobelol **20**. This strategy was also applied to the synthesis of numerous piperidine derivatives and some ant defence alkaloids.[33,34]

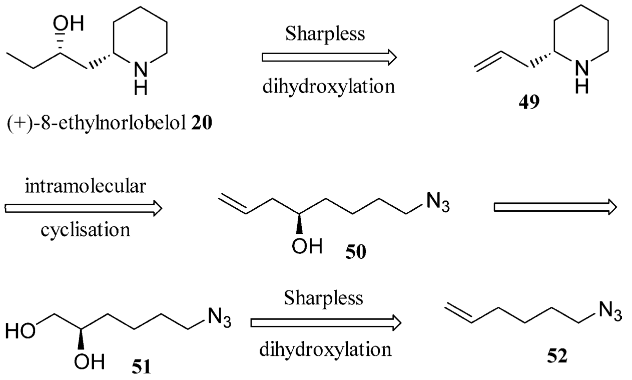
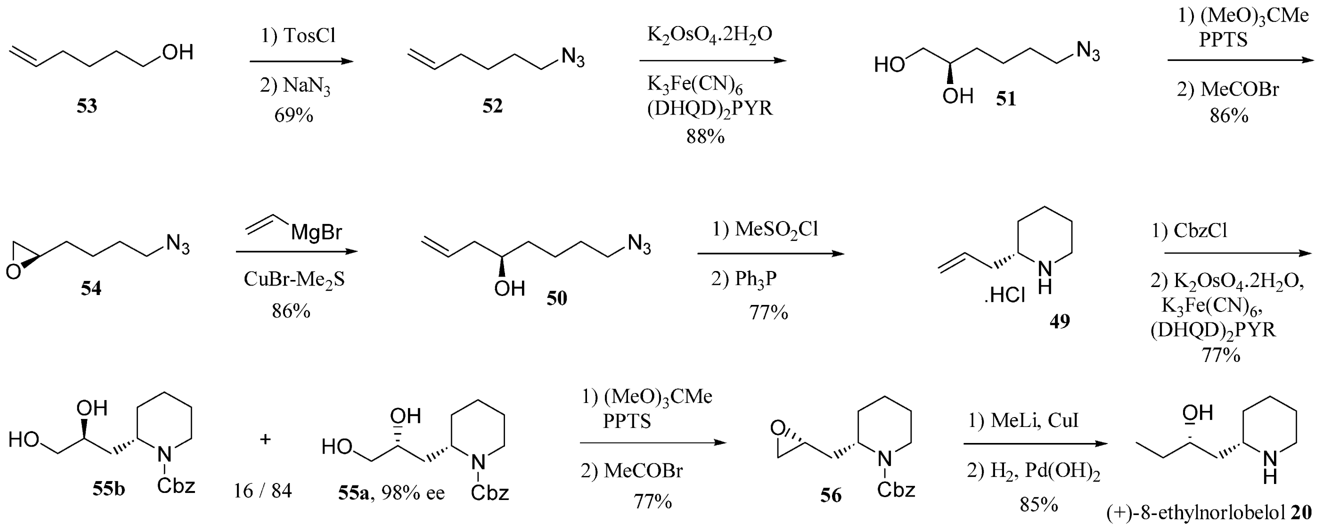


Figure 4.

The synthesis started from the commercially-available 5-hexenol **53** (Scheme 12). Tosylation of the hydroxyl group followed by substitution with sodium azide furnished **52** in 69% yield over two steps. The Sharpless asymmetric dihydroxylation of 5-hexenylazide **52** generated the diol **51** in 88% yield with 88% ee. The intermediate **51** was converted into the epoxide **54** by the Sharpless one-pot two-step protocol in 86% yield. Regioselective copper-mediated Grignard allylation of the epoxide **54** afforded the alcohol **50** in good yield (86%). Treatment of the free hydroxyl group of **50** with mesyl chloride and subsequent reduction of the azide by the Staudinger reaction led to an intramolecular cyclisation with total inversion of configuration to give the desired 2-propenylpiperidine **49** (77% yield) as its hydrochloride salt. Protection of the piperidine as a benzyl carbamate followed by a second asymmetric dihydroxylation reaction of the terminal olefin led to a mixture of two diastereoisomers **55a/55b** in an 84/16 mixture, separable by chromatography on silica gel. The major diastereoisomer **55a** was found to be >98% ee. The resulting diol **55a** was converted into the epoxide **56** by the Sharpless one-pot two-step protocol using the same conditions as before for the transformation of **51** into the epoxide **54**. Regioselective copper-mediated Grignard methylation of the epoxide **56** and subsequent hydrogenolysis of the benzyl carbamate completed the total synthesis of (+)-8-ethylnorlobelol **20**. The melting point and specific rotation are in total agreement with those reported for the natural product. This assignment confirmed that proposed a short time earlier by Hootelé et al.



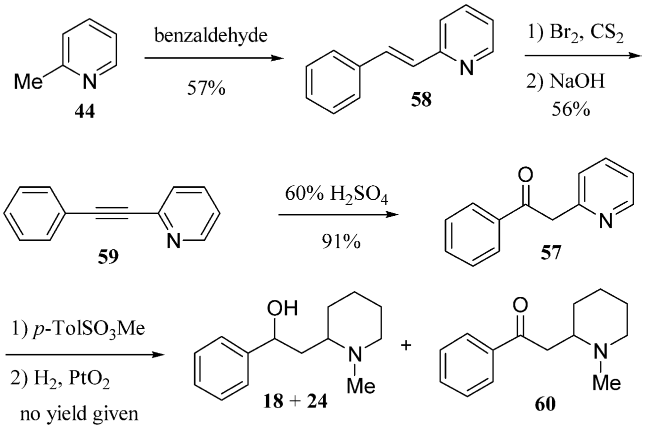
Scheme 12.

4.2. Synthesis of allosedamine

Although its biological properties are obsolete,[35] (−)-allosedamine has attracted attention as an interesting challenge and a valuable synthetic target for chemists.

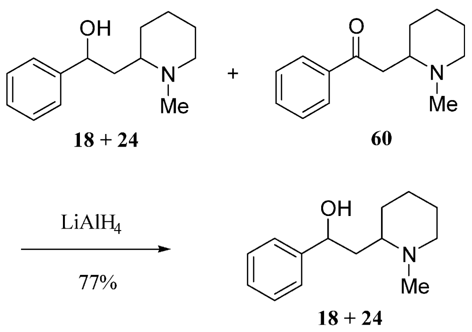
4.2.1. Non-stereoselective racemic approach. Before the 1960s, the piperidine core was often derived from a pyridine ring. The pyridine strategy provided an efficient and short route to piperidinic alkaloids, but yielded a mixture of diastereoisomers.

(−)-Allosedamine **18** was isolated from *Lobelia inflata*,[6,29] and the structural identification was reported by Marion[36] and co-workers on the basis of the first racemic synthesis (Scheme 13). It should be noted that these authors actually reported the structure of sedamine **24** (not found in *Lobelia* plants), which is a diastereoisomer of allosedamine **18**. These researchers envisaged the phenacylpyridine **57** as a key intermediate in their approach. The compound **57** was prepared by condensation of α-picoline **44** on benzaldehyde to give the alkene **58** after spontaneous elimination of a molecule of water. Bromination of the double bond and subsequent elimination in a basic medium furnished the acetylene **59** in 32% yield over the three steps. Hydration of the triple bond by treatment with concentrated sulphuric acid generated the expected key intermediate **57**. Methylation of the pyridine ring followed by catalytic hydrogenation gave a mixture of **18** and **60**. These products could be separated by the formation of the picrate salt derivatives, but with a rather low total yield.



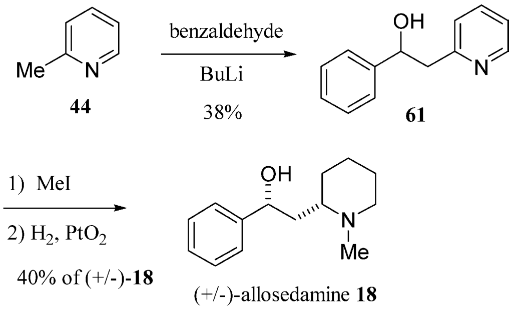
Scheme 13.

In order to avoid the formation of the picrate salt derivatives in the separation of **18** and **60**, Beyerman[37] and co-workers advocated treating the mixture with $LiAlH_4$ and, allosedamine **18** and sedamine **24** were then isolated as the single products (Scheme 14).



Scheme 14.

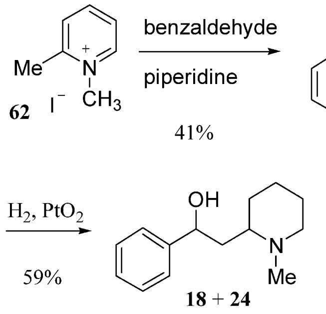
In their studies, however, the same workers also reported a simpler and shorter racemic synthesis starting from α-picoline **44** and benzaldehyde (Scheme 15). They found



Scheme 15.

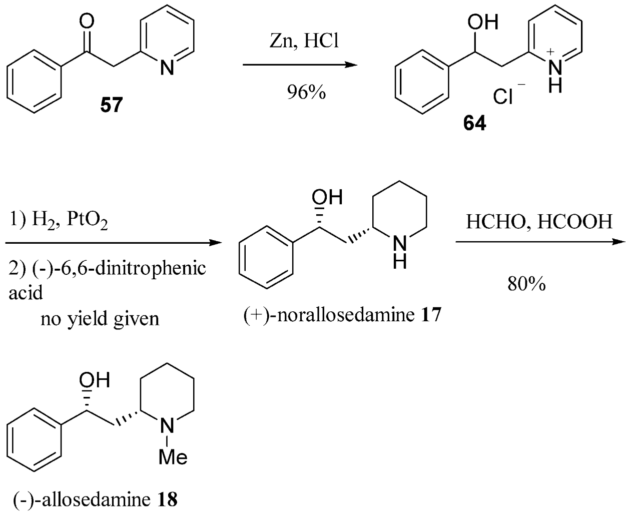
that the addition of α-picollyllithium to benzaldehyde furnished **61** without the elimination of a molecule of water, contrary to an acidic condensation. Subsequent *N*-methylation and catalytic hydrogenation gave a mixture of the two diastereoisomers, allosedamine **18** and sedamine **24**, which could be separated by fractional crystallisation.

Stanek[38] and co-workers observed the facile addition of 1,2-dimethylpyridinium iodide **62** to benzaldehyde to yield **63**, which on subsequent reduction furnished a mixture of **18** and **24** that were not separated (Scheme 16). In further studies, Beyerman[39] optimised the conditions described by Stanek to obtain the mixture of (+/−)-**18** and (+/−)-**24** in a better yield.



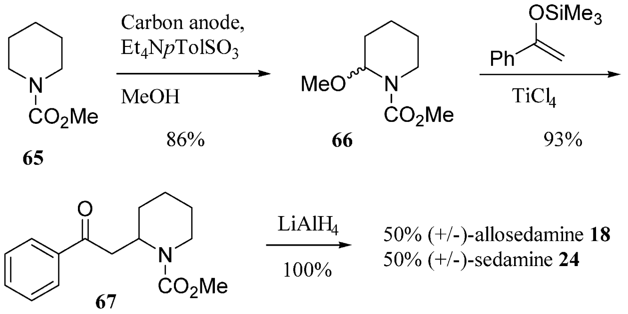
Scheme 16.

Starting from the phenacylpyridine **57**, Schöpf et al. isolated a mixture of norallosedamine **17** and its diastereoisomer by successive reduction of the carbonyl group with Zn and of the pyridine ring by catalytic hydrogenation over platinum oxide (Scheme 17). From this mixture, (+/−)-norallosedamine **17** was obtained in a pure form and was resolved by sequential crystallisations with (+)-6,6-dinitrophenic acid to give (+)-**17**. Compound (+/−)-**17** similarly treated with (−)-6,6-dinitrophenic acid gave (−)-**17**. Successive degradation of (+)-**17** led the authors to assign the absolute configuration as (2*S*,8*R*)-8-phenylnorlobelol **17**. Methylation of (+)-**17** under Eschweiler-Clarke conditions gave (−)-allosedamine **18**, the configuration of which is (2*S*,8*R*).



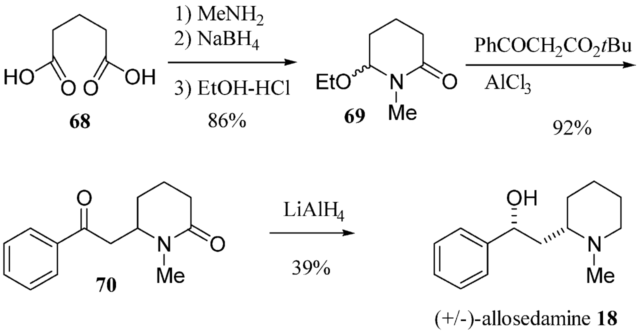
Scheme 17.

Introduction of the side chain via alkylation of an *N*-acyliminium precursor, formed in situ, also emerged as a suitable approach to achieve the synthesis of allosedamine **18** (Scheme 18). This strategy was advantageously used by Shono and co-workers.[40] The addition of 2-methoxypiperidine **66**, generated from **65** by anodic oxidation, to a silyl enol ether of acetophenone in the presence of $TiCl_4$, resulted in the isolation of **67** with high yield (93%). The non-stereoselective reduction of **67** with $LiAlH_4$ gave a mixture of (+/−)-sedamine **24** and (+/−)-allosedamine **18**, which were separated and identified by Schöpf's method.



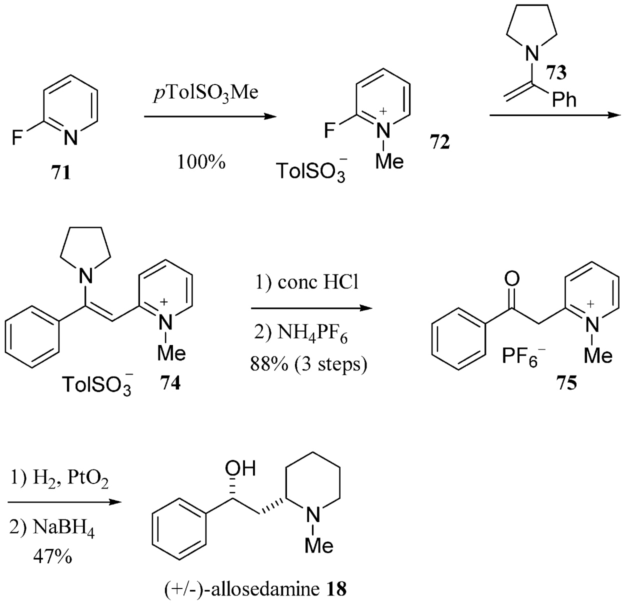
Scheme 18.

C–C bond formation between the piperidine precursor and the phenacyl side chain was also reported by Ozawa[41] in a similar approach (Scheme 19). 2-Ethoxy-6-piperidone **69**, readily prepared in two steps from glutaric acid **68**, was subjected to *C–C* bond formation with *tert*-butyl benzoylacetate and aluminum chloride to afford **70** after acidic hydrolysis. Reduction of the lactam and ketone functions with $LiAlH_4$ generated a mixture of sedamine **24** and (+/−)-allosedamine **18**, which were readily separated by column chromatography on silica gel.



Scheme 19.

More recently Meth-Cohn[42] and co-workers have developed a practical method for a short access to (+/−)-allosedamine **18** and related alkaloids via the pseudo Vilsmeier reagent **72**, which can easily be obtained by *N*-methylation of 2-fluoropyridine **71** (Scheme 20). The resulting iminium salt **72** was subjected to the enamine **73** to give **74**, which on acidic hydrolysis liberated the masked carbonyl group. Catalytic hydrogenation of the pyridinium ring of **75** followed by carbonyl reduction with $NaBH_4$ gave an equal mixture of diastereoisomers (+/−)-**18** and (+/−)-**24**, from which (+/−)-allosedamine **18** was isolated in a pure form after flash chromatography. It should be noted

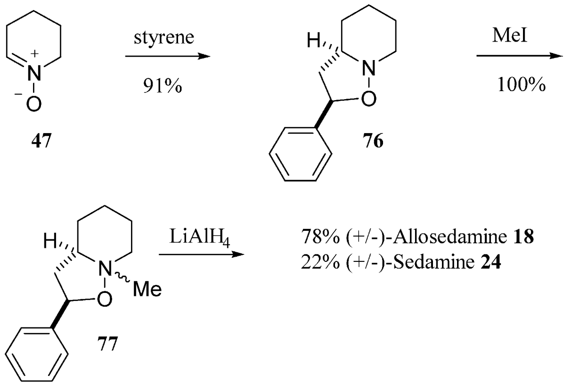


Scheme 20.

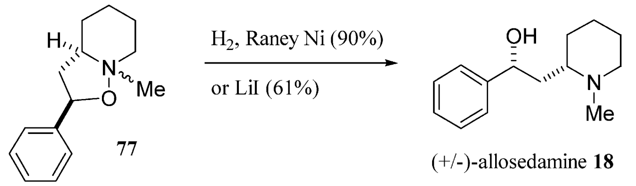
that the researchers developed an enzymatic resolution for some alkaloids to obtain chiral compounds. No experimental details were described, however, for (+/−)-allosedamine **18**. In addition, the application of this methodology to the synthesis of anti-Alzheimer agents was recently disclosed in a patent[43] by the same authors.

4.2.2. Stereoselective racemic approach. Tufariello[44] and, a few years later, Hootelé[45] developed a similar efficient route based on a regio- and stereoselective [2+3]-dipolar cycloaddition (Scheme 21). This strategy was widely used by Hootelé as an elegant route for various piperidinic derivatives including (+/−)-allosedamine **18** (vide supra).[46] Tufariello reported that the condensation of 2,3,4,5-tetrahydropyridine-1-oxide **47** with styrene afforded the isoxazolidine **76**, which upon *N*-methylation to **77** and subsequent treatment with $LiAlH_4$ furnished a mixture of (+/−)-allosedamine **18** (78%) and (+/−)-sedamine **24** (22%) with excellent overall yield. From this observation, the authors concluded that the cycloaddition step lacked stereoselectivity, to generate the isoxazolidine **76** in a 78/22 mixture of diastereoisomers.

In their studies, however, Hootelé et al. repeated the cycloaddition step in similar conditions and were surprised to note that analysis by gas–liquid chromatography of **76** revealed 97% of diastereoisomeric excess. This high diastereoselectivity resulted from an *exo* addition. Subsequent experiments showed that the reduction step with $LiAlH_4$ occurred with partial epimerisation. In order to overcome the critical step of the *N–O* bond cleavage without epimerisation, Hootelé et al. showed that hydrogenolysis of **77** with H_2/Raney nickel was the method of choice to generate (+/−)-allosedamine **18** as the sole product in high yield (Scheme 22). Liguori and co-workers[47] reported a valuable alternative to *N–O* bond cleavage in very mild experimental conditions by the use of LiI (Scheme 22). The yield was lower (61%) but the process was compatible with numerous functional groups.

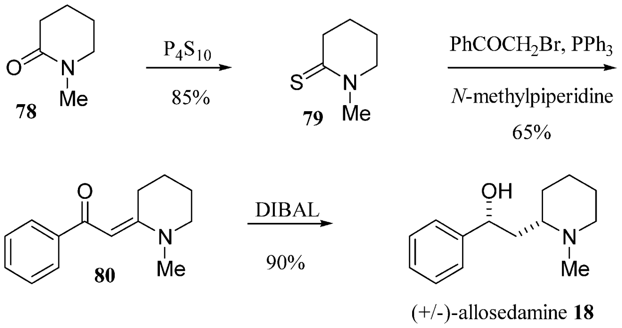


Scheme 21.



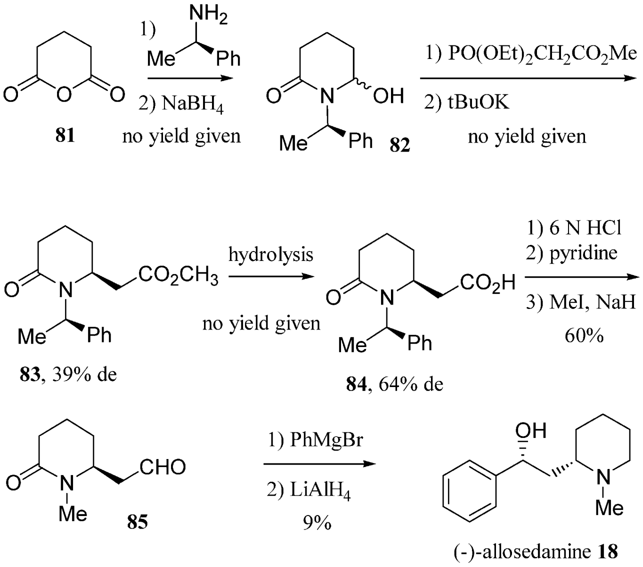
Scheme 22.

Ghiaci and Adibi[48] have reported more recently a straightforward synthesis of (+/−)-**18** by a judicious use of the Eschenmoser reaction (Scheme 23). The thiolactam **79**, easily prepared from the corresponding lactam **78**, reacted with phenacyl bromide to give the phenacylpiperidine **80** in good yield (65%). Reduction of **80** was conducted with a variety of reducing agents including $NaBH_4$, DIBAL-H, $LiAlH_4$ and H_2/Pt–C. DIBAL-H appeared to be the best reducing reagent and led exclusively to (+/−)-allosedamine **18**, probably via a chelated-type structure in the transition state.



Scheme 23.

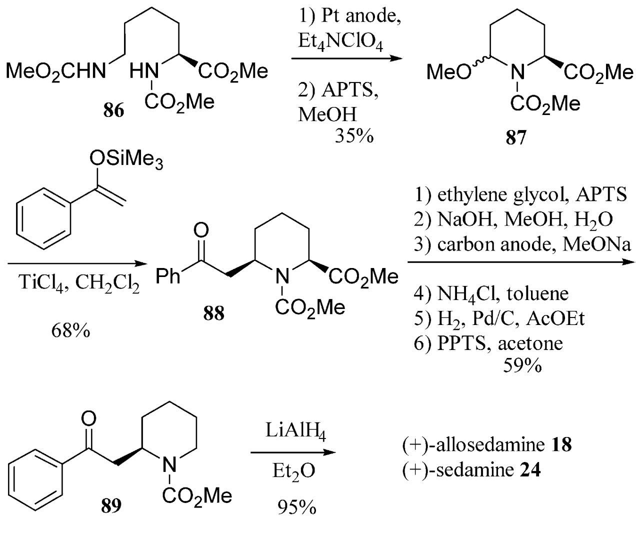
4.2.3. Asymmetric approach. The first asymmetric synthesis of **18** was described by the Wakabayashi[49] group and involved an asymmetric intramolecular Michal reaction (Scheme 24). Thus, treatment of glutaric anhydride **81** with (*R*)-(+)-α-phenylethylamine in harsh conditions followed by reduction with $NaBH_4$ generated the 6-hydroxy lactam **82**. A Wittig type condensation carried out on **82** and subsequent basic treatment gave **83** with modest selectivity (c.a. 39% de). Hydrolysis of the ester **83** to the acid **84**, however, and subsequent recrystallisation enhanced the de to 64%. The conversion of **84** into the aldehyde **85** was



Scheme 24.

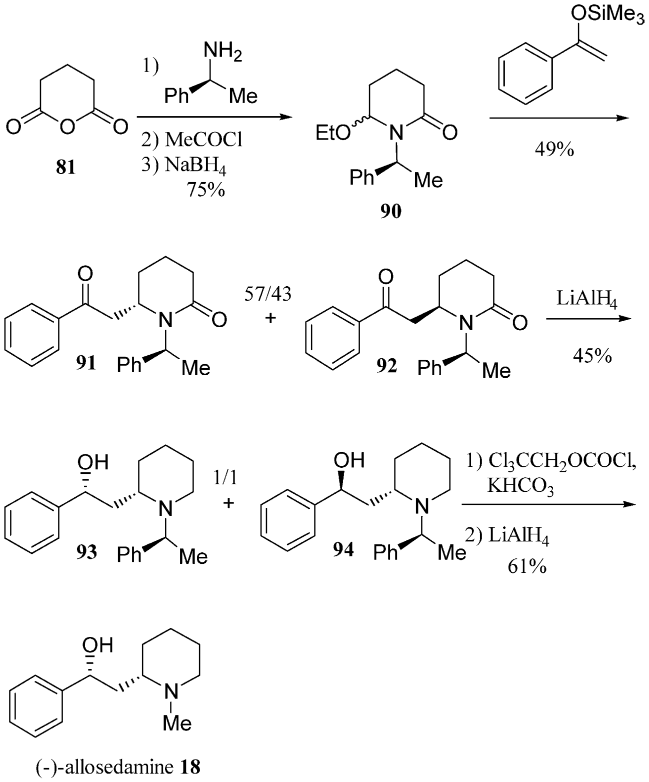
achieved by standard methods. Addition of Grignard reagent on the carbonyl group of **85** and reduction of the lactam function gave the expected mixture of **18** and **24** in an equal ratio with low yield. Pure (−)-allosedamine **18** was isolated after chromatography on alumina. Unfortunately, the authors failed to quote the yields of the first steps for the synthesis, so it is not possible to comment on the efficiency of their route.

Alkylation of an *N*-acyliminium precursor with the formation of a *C–C* bond has also been applied in an asymmetric approach. Tanaka[50] and co-workers reported the stereoselective alkylation (ca. 10:1) of **87**, easily prepared from the lysine derivative **86**, by a silyl enol ether (α-trimethylsiloxystyrene; APTS) in the presence of $TiCl_4$ (Scheme 25). The expected derivative **88** was then isolated in 68% yield. These workers considered it prudent to protect the ketone group to perform the decarbonylation in a four-step sequence. After removal of the acetal group, the ketocarbamate **89** was subjected to reductive non-stereoselective conditions to give an equal mixture of (+)-allosedamine **18** and (+)-sedamine **24**.



Scheme 25.

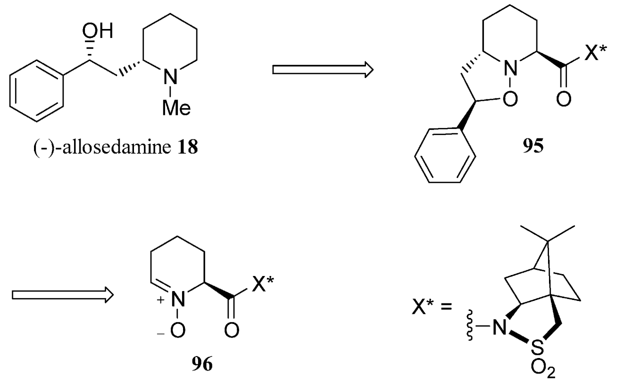
For their part, Naito[51] and co-workers opted for an *N*-phenylethyl chiral auxiliary to direct the stereoselectivity, but with low diastereoselectivity. The *N*-acyliminium precursor **90** was prepared by treatment of glutaric anhydride **81** with phenylethylamine followed by reduction of the imide and trapping of the resulting hydroxy-lactam by ethanolysis. Compound **90** was submitted to the silyl enol ether of acetophenone in the presence of $TiCl_4$ to give **91** and **92** with low diastereoselectivity (respectively in a 57/43 ratio) and modest yield (49%). The main diastereoisomer **91** was subjected to reduction with $LiAlH_4$ to give a 1:1 mixture of diastereoisomers, **93** and **94**, which were separated by medium-pressure column chromatography. Dealkylative carbamoylation and subsequent treatment with $LiAlH_4$ of **93** afforded (−)-allosedamine **18** in 61% yield (Scheme 26).



Scheme 26.

The first highly diastereo- and enantioselective synthesis of (−)-allosedamine **18** was achieved by Oppolzer.[52] The strategy involved an elegant chiral application of the widely used nitrone/styrene cycloaddition, followed by a reductive *N–O* cleavage (Fig. 5). It should be noted that this strategy was successfully applied to the synthesis of various pyrrolidine and piperidine alkaloids.[53–55]

The synthesis started from the known aldehyde[56] **97** (obtained in two steps from ε-caprolactone with 66% overall yield) which was acetalised with propane-1,3-diol (Scheme 27). A subsequent Me_3Al-mediated condensation of **98** with sultam (now known as Oppolzer's auxiliary)



(-)-allosedamine **18**

95

96

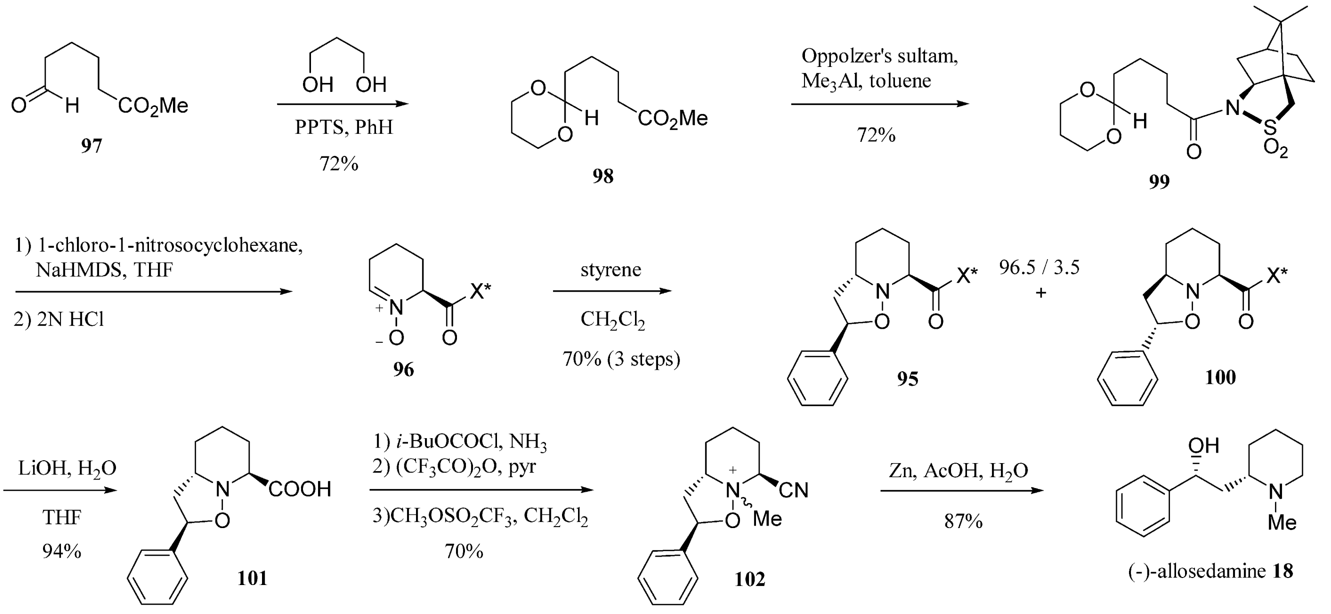
Figure 5.

afforded **99** in 72% yield. Compound **99** was deprotonated with NaHMDS and the resulting (*Z*)-enolate was trapped with 1-chloro-1-nitrosocyclohexane. Hydrolysis of the non-isolated acetal in acidic media gave the corresponding tetrahydropyridine *N*-oxide **96**, which was used without further purification in the next step. Thus, the crude dipole **96** reacted with styrene (dipolarophile) as a [3+2] cycloaddition with high stereoselectivity to give the cycloadduct **95**, contaminated by $<3.5\%$ of the diastereoisomeric cycloadduct **100**. The mixture was efficiently separated after flash chromatography and subsequent crystallisation. Cleavage of the chiral auxiliary with basic hydrolysis furnished the carboxylic acid **101** with recovery of the sultam auxiliary. The next step required the removal of the COOH group. Neither Barton's decarboxylation[57] nor Rapoport's decarbonylation,[58–60] however, afforded the desired product. An alternative method consisted of the transformation of the COOH group into a CN function, followed by a reductive α-aminonitrile decyanation. Thus, conversion of carboxylic acid **101** into the amide and subsequent dehydration of the resulting carboxamide generated the nitrile function. Unfortunately, the reductive decyanation failed again. In order to achieve the required transformation, the above results forced the researchers to plan an alternative strategy involving the methylation of nitrogen before the decyanation and *N–O*-cleavage. *N*-Methylation was performed with methyl triflate to give the ammonium triflate **102** as a 7/1 mixture of diastereoisomers. Treatment of the ammonium triflate **102** with activated Zn dust and HCl led not only to the *N–O*-cleavage, but also, in the meantime, removed the CN group in good yield (87%). Thus, the total synthesis of (−)-allosedamine **18** was achieved in nine steps and 21% overall yield from a known product (11 steps and 14% overall yield from a commercially available product).

Very recently, in connection with our programme towards the synthesis of natural products having biological activity on the central nervous system, we have reported an efficient and stereoselective synthesis of (−)-allosedamine **18**.

In our synthesis,[61] the chiral moiety at C2 was derived from a chiral homoallylic alcohol **105**. One of the key steps of this synthesis was to obtain the chiral homoallylic alcohol **105** with high enantiomeric excess. Previously, we have also used chiral homoallylic alcohols in the synthesis of various pyrrolidinic,[62,63] piperidinic,[64] and tetrahydropyridinic[65] alkaloids with high stereoselectivity. The second chiral centre was induced by the free hydroxyl group with a stereocontrolled epoxidation. Formation of the piperidine ring was achieved by an intramolecular cyclisation reaction (Fig. 6).

Thus, to obtain the chiral homoallylic alcohol **105** with high ee constituted the first challenge of this synthesis (Scheme 28). Numerous methods to synthesise homoallylic alcohols have been described in the literature.[66] We, however, have developed a new access to these intermediates that is applicable on a multigramme scale.[67] Thus, the chiral homoallylic alcohol **105** was obtained by a 2-step procedure which involved a condensation of allylmagnesium bromide on the commercial Weinreb amide **106** followed by an enantioselective reduction of the prochiral ketone[68–70] **107** with (+)-DIP-chloride™.[71] Thus, the



97 **98** **99** **96** **95** **100** **101** **102** (-)-allosedamine **18**

Scheme 27.

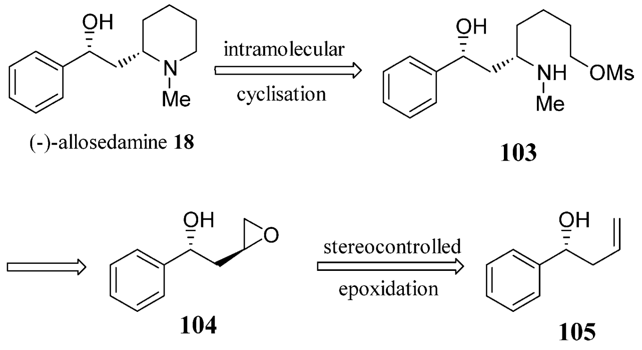


Figure 6.

alcohol **105** was isolated in good yield (84% in two steps) with high ee (>99%). For example, the direct allylboration of benzaldehyde with *B*-allyldiisopinocamphenylborane (^{l}Ipc$_2$Ball) gave **105** in similar yields, but resulted in a decrease in optical purity (95% ee).

A stereocontrolled epoxidation of the double bond by the Cardillo[72,73] procedure generated the second chiral centre of allosedamine with total diastereoselectivity to give the *syn* epoxy alcohol **104**. This procedure, which involved passage via the iodocarbonate **109**, was found to be better than the Sharpless protocol[74,75] using VO(acac)$_2$ and *t*BuOOH (*cis*/*trans*: 4/1). Protection of the benzylic hydroxyl function, followed by a regioselective opening of epoxide with allyl cuprate, generated **110**. The new hydroxyl function was converted into an amine. This step was found to be problematic when the conversion of the hydroxyl function into the amine occurred via an azide, according to the Mitsunobu protocol.[76] Indeed, the instability of the azide, which can spontaneously cyclise with the double bond as a [3+2] cycloaddition,[77,78] led to a complete decomposition of the product. Fortunately, persistent experimentation was rewarded when conversion into the amine **111** was found to occur in good yield (73% in two steps) by displacement of the corresponding mesylate with methylamine. The protection of the secondary amine into *tert*-butyl carbamate followed by hydroboration–oxidation of the double bond furnished the primary alcohol **112**. Activation of the hydroxyl group into the corresponding mesylate and subsequent treatment in methanolic acidic conditions led not only to the Boc cleavage, but also to the removal of the TBS protection to give a product which spontaneously cyclised during the basic treatment.

Thus, (−)-allosedamine **18** was efficiently obtained in 13 steps with an overall yield of 29%.

Riva, Passarella and co workers[79] reported a straightforward synthesis of (−)-allosedamine **18** based on three successive enzymatic resolutions of *N*-Boc-piperidine-2-ethanol **113** (Fig. 7).

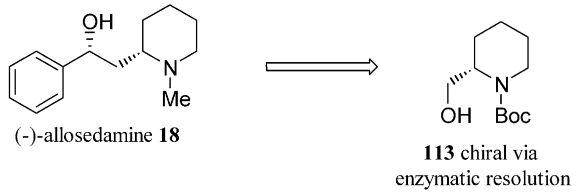
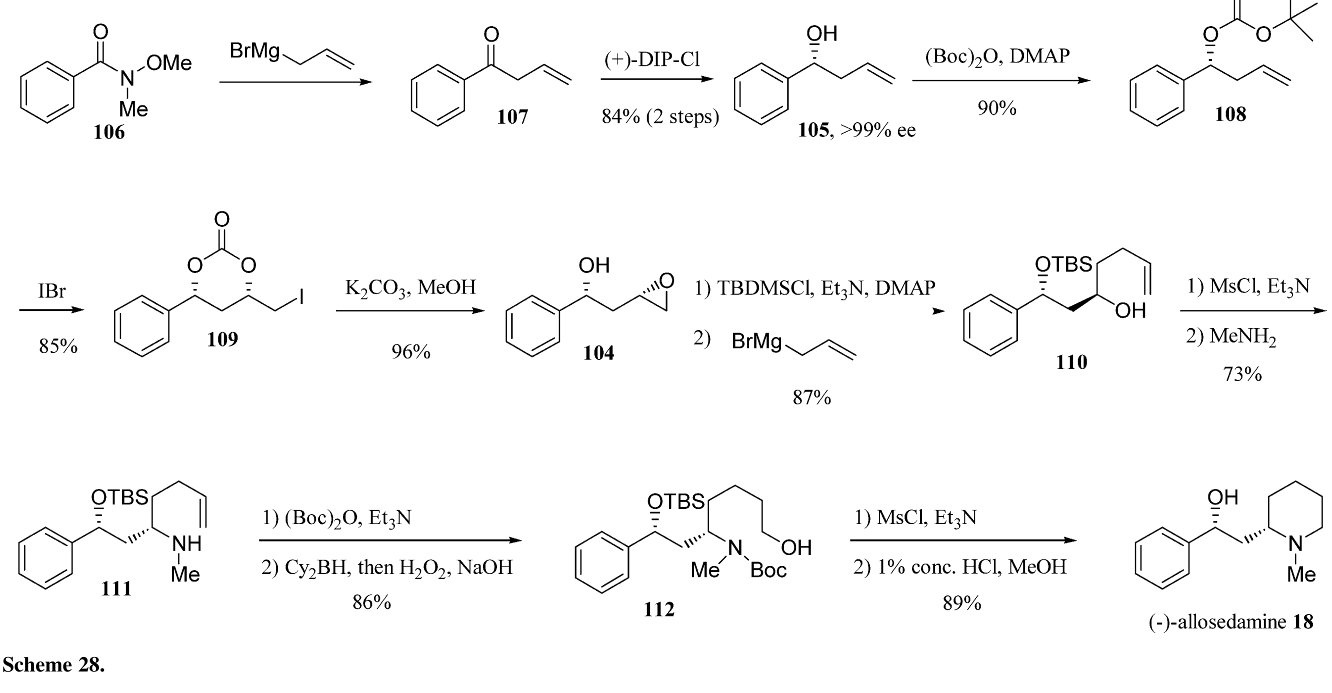
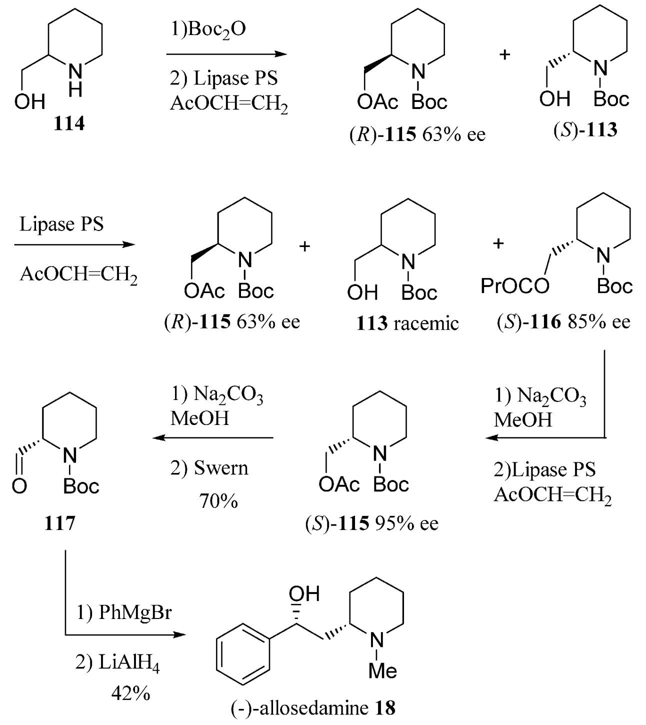


Figure 7.

Racemic commercially available piperidine-2-ethanol **114** was first protected as the corresponding *tert*-butyl carbamate and then submitted to the first enzymatic resolution with Lipase PS to give the acetate (*R*)-**115** with 63% ee and the alcohol (*S*)-**113** at 45% conversion (Scheme 29). After work-up, the crude mixture was then submitted to pancreatic lipase to give a separable mixture of the unreacted acetate (*R*)-**115**, the unreacted almost racemic alcohol **113** and the ester (*S*)-**116** with 85% ee. Compound **116** was chemically hydrolysed and was then again



Scheme 28.



Scheme 29.

submitted to a third enzymatic resolution with pancreatic lipase to give the acetate (*S*)-**115** with 95% ee. It should be noted that this sequence can be carried on multigramme scale, but the authors failed to quote a yield for this four-step process. The acetate protecting group of (*S*)-**115** was hydrolysed under basic condition and the resulting primary alcohol was oxidised by the Swern protocol to give the aldehyde **117** in 70% yields over two steps. The remaining steps, addition of phenylmagnesium bromide with low diastereoselectivity (3:2 dr) followed by the reduction of the *tert*-butyl carbamate with $LiAlH_4$ furnished (−)-allosedamine **18** in nine steps from the commercially available racemic piperidine-2-ethanol **114**.

Very recently, Raghavan and Rajender[80] have reported the total synthesis of (−)-allosedamine **18** via a diastereoselective addition of the sulphinyl anion **118** to the imine **119** followed by a bromohydration of the olefin **120** using the sulphinyl function as an internal nucleophile (Fig. 8).

Their synthesis began with the condensation of the sulphinyl anion **118** with the imine **119** in favour of the desired isomer **120** (3/1 dr) with 61% yield after separation of the diastereoisomers by column chromatography (Scheme 30). The next step involved a high-yielding stereo- and regioselective bromohydration of **120** using the sulphinyl group as an internal nucleophile via the transition state **A** to furnish **121**. After removal of the bromine atom, the free hydroxyl group was protected as the acetate derivative **122** and the nitrogen was alkylated with butenyl nosylate to give **123**. Subsequent treatment of **123** with trifluoroacetic anhydride in the presence of Et_3N (Pummerer rearrangement) followed by Wittig olefination generated the diethylenic substrate **124** in good yield (75%). In order to construct the piperidine core of (−)-allosedamine **18**, compound **124** was subjected to a first-generation Grubbs' catalyst **125** to give **126** in 80% yield via a ring-closing metathesis reaction. Concomitant deprotection of the tosylate and acetate protecting groups and subsequent reduction of the double bond gave (+)-norallosedamine **17**. Finally, reductive methylation of the secondary nitrogen using HCHO and $NaBH_3CN$ gave (−)-allosedamine **18** in 12 steps and 11% overall yield.

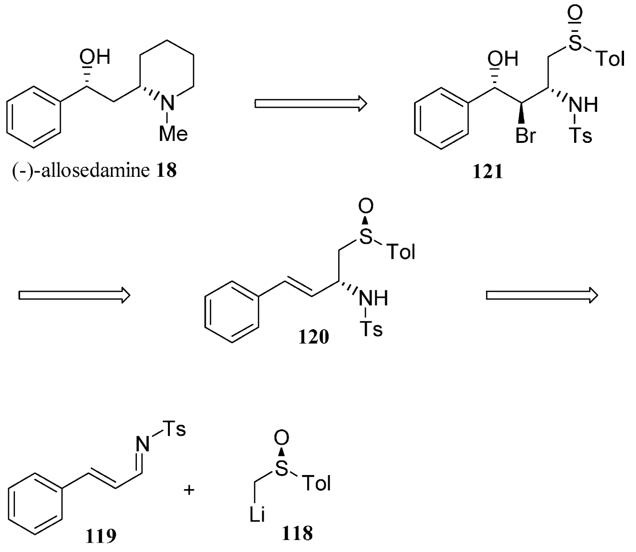


Figure 8.

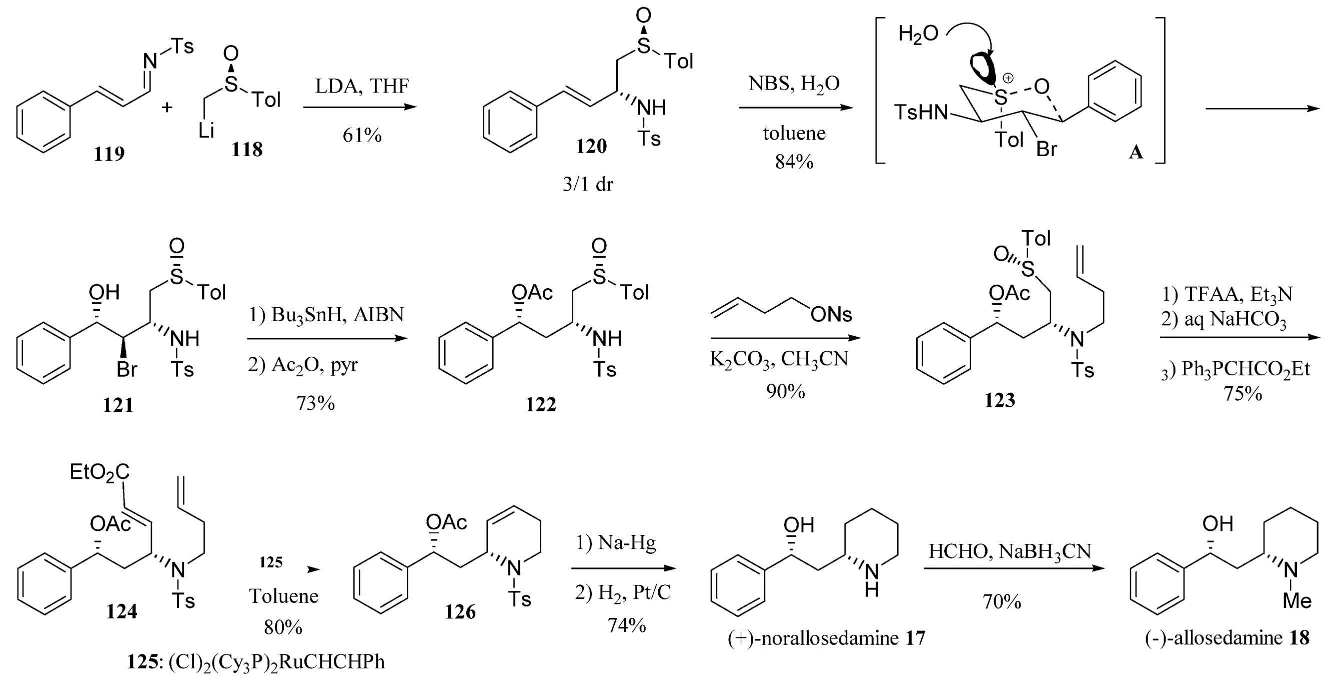
4.3. Synthesis of lobeline and related alkaloids

4.3.1. Chemical properties. Before discussing the chemistry of lobeline **1** and the related alkaloids, lobelanine **14** and lobelanidine **16**, it will be of interest to first consider some of their chemical properties.

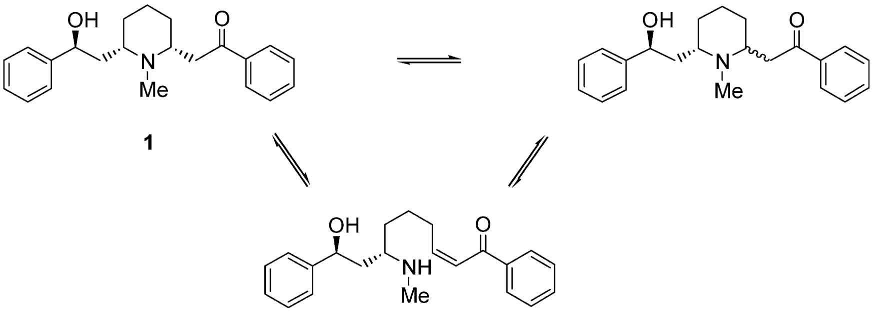
A problem occurred with lobeline, as with other ketopiperidine alkaloids. It was known that ketopiperidines are configurationally unstable and epimerise readily (Scheme 31). The mutarotation of (−)-lobeline is an interesting phenomenon, probably due to a retro Michael reaction that was studied during the 1960s. The rate of mutarotation of *cis*-(−)-lobeline **1** to a mixture of *cis* and *trans*-(−)-lobeline **1** is increased in hydrophilic solvents and in the presence of hydroxyl ions.[81] More recently, Marazano et al. noted that (−)-lobeline hydrochloride exists in solution as a single stereoisomer (vide infra). This shows that ketopiperidines are configurationally stable when the nitrogen lone pair is not available as its hydrochloride form. In our laboratory, we have paid particular attention to the mutarotation and it should be noted that, in its crystalline form, without solvent, no mutarotation occurred for *cis*-(−)-lobeline **1**.

Lobeline was first isolated by W. M. Procter Jr. in 1838.[1] Several incorrect characterisations of lobeline were proposed before Wieland[82] reported the correct chemical structure in 1929. This work was the starting point of extensive research into a better understanding of its complex pharmacological properties (vide infra).

To date, five total syntheses of lobeline **1** have been



Scheme 30.



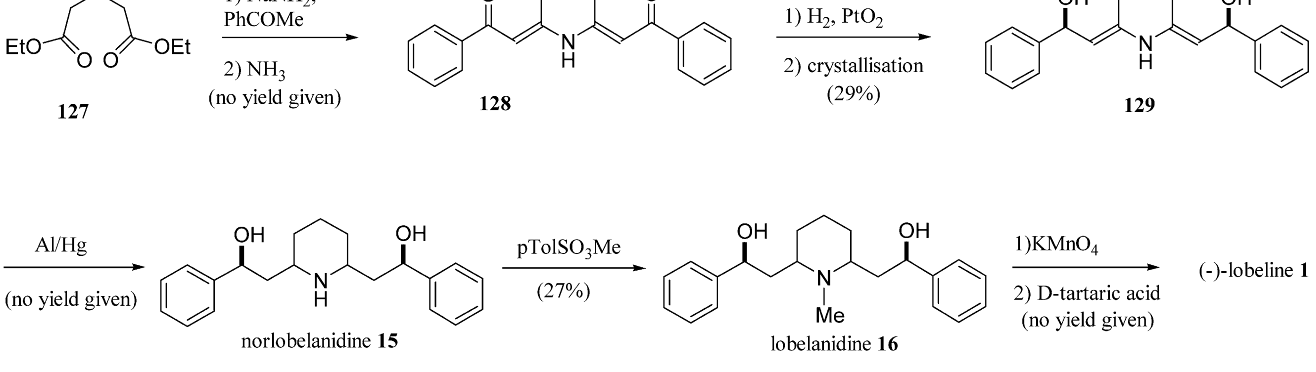
Scheme 31.

reported, among which, two involve the racemic form and three use asymmetric strategies. Wieland, Scheuing and Winterhalder, however, showed that lobelanidine **16** could be converted into lobeline **1** by a mild oxidation of a hydroxyl group. Moreover, lobelanine **14** could be reduced to lobelanidine **16** by catalytic hydrogenation over platinum oxide. Thus, a synthesis of lobelanine **14** and lobelanidine **16** constituted a formal synthesis of lobeline **1**.

4.3.2. Racemic approach to lobeline and related alkaloids.

The work concerning the racemic approach was published before the 1950s and the yield of each step was not always given. For this reason, it is difficult to comment on the efficiency of the different routes, although it is important to report the intellectual design.

The first synthesis of lobeline **1** was described by Wieland et al.[83] (Scheme 32). The synthesis started with an ingenious



Scheme 32.

double Claisen condensation between ethyl glutarate **127** and acetophenone, followed by treatment with ammonia to build the piperidine ring in **128**. The carbonyl groups were reduced by catalytic hydrogenation over platinum oxide to give a mixture of two diastereoisomers that were separated by crystallisation. The corresponding β-norlobelanidiene **129** was treated with an aluminum amalgam to yield norlobelanidine **15**, which was converted into its methylated derivative by treatment with *p*TolSO$_3$Me. The lobelanidine **16** produced was converted into lobeline **1** by treatment with an oxidising agent such as permanganate. The lobeline **1** obtained as the reaction product was separated from the unchanged starting material. (+/−)-Lobeline **1** was then resolved by D-tartaric acid giving (−)-lobeline **1**, which was found to be identical in every respect with the naturally occurring base. The value of the optical rotation indicated the presence of the two epimers (*cis* vs *trans*) in an approximate 1/1 ratio.

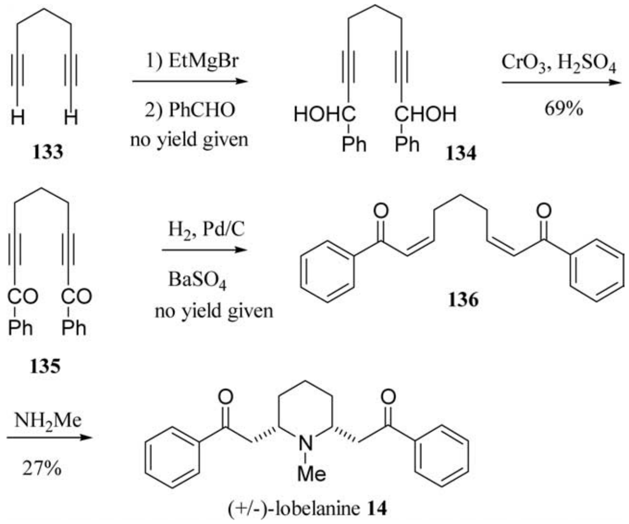
Simultaneously with Wieland, Scheuing and Winterhalder[84] disclosed their work on the total synthesis of lobeline **1** (Scheme 33). Their strategy involved the synthesis of the diphenylethynylpyridine **131** that could be obtained by a known method[85] from 2,6-lutidine **130**. Hydration of **131** with concentrated sulphuric acid furnished the diphenacylpyridine **132**. Alkylation of the pyridine ring with *p*TolSO$_3$Me gave a quaternary salt that could easily be reduced to lobelanidine **16** with 5 mol of H$_2$. A mild oxidation of **16** by potassium permanganate gave a mixture of the (+/−)-lobeline **1** and the unreacted starting material, which were separated by crystallisation.

By an exceptional one-pot multistep process, the synthesis of lobelanine **14** was achieved by Schöpf and Lehmann[86] in 1935 (Scheme 34). This elegant strategy involved a Mannich condensation and a Robinson type biomimetic reaction. Thus, a mixture of glutaric dialdehyde, benzoylacetic acid and methylamine hydrochloride was stirred for several days to give lobelanine **14** in one step, in 90% yield.

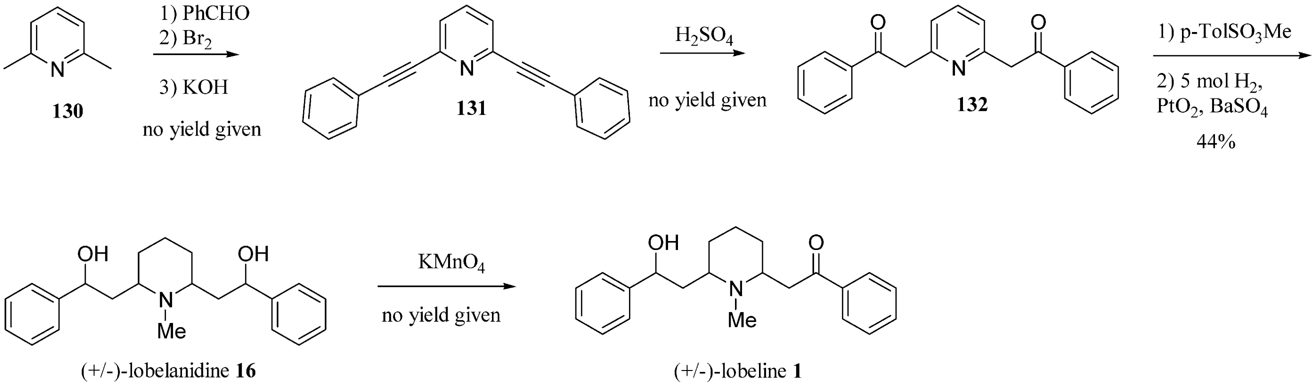
Parker advantageously exploited a double aza-Michael addition to build the piperidine core (Scheme 35). Hepta-1,6-diyne **133**, treated with 2 equiv of EtMgBr, reacted with benzaldehyde to give the diols **134** as a mixture of two diastereoisomers. Oxidation by chromium trioxide in an acidic medium, however, gave the symmetrical diketone **135**. The next stage, involving catalytic hydrogenation, produced the expected Michael acceptor **136** as a symmetrical *Z*,*Z*-dienone. The addition of methylamine to **136** proceeded stereospecifically to furnish *cis*-lobelanine **14**.

4.3.3. Asymmetric approach.

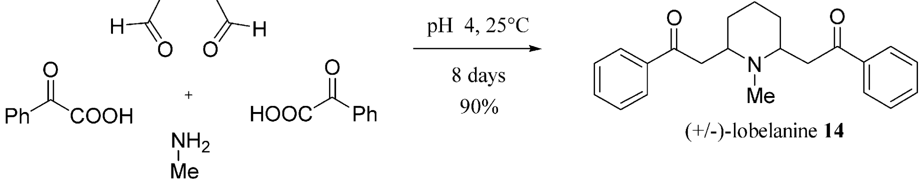
In the course of designing a synthesis for a natural product, it can be profitable to



Scheme 35.



Scheme 33.



Scheme 34.

consider how its structure may have arisen in nature. Inspired by a biogenetic process, Schöpf and Müller in the mid-1960s described the first asymmetric total synthesis of (−)-lobeline.[87] It was anticipated that (−)-sedamine **24** would provide (−)-lobeline **1** by alkylation at C6 (Fig. 9). Moreover, it was reasoned that the phenacylpyridine[88] **57** should be an ideal starting material to access (−)-sedamine **24**.

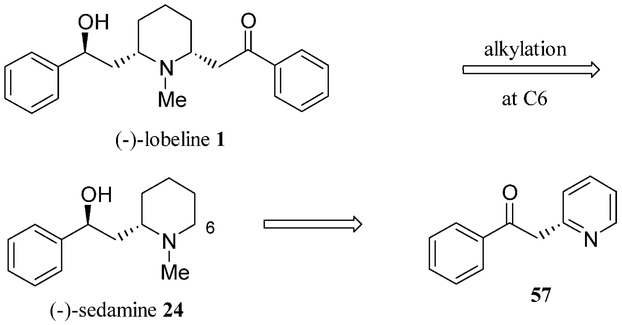
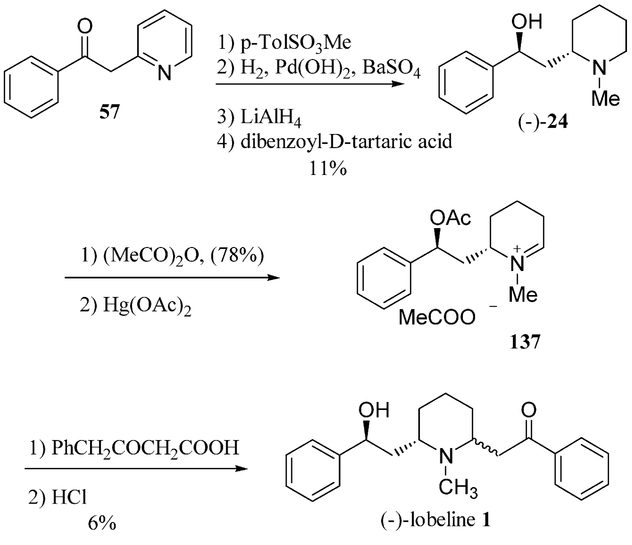


Figure 9.

The first aim was to synthesise (−)-**24** by using phenacylpyridine **57** as the readily available starting material (Scheme 36). With compound **57** in hand, (−)-**24** was obtained by the classical chemical transformation and resolution of (+/−)-**24** with dibenzoyl-D-tartric acid. Compound (−)-**24** was acetylated to give the corresponding *O*-acetyl derivative (78%), which was treated with mercuric acetate in acetic acid according to the procedure of Leonard et al.[89] Guided by the presumed biosynthetic pathway, the resulting iminium salt **137** was reacted with benzoyl acetic acid to yield the expected *O*-acetyl lobeline. A last hydrolysis of the acetate group enabled (−)-lobeline **1** to be isolated in an elegant fashion as a mixture of two epimers, even though the yield was low.



Scheme 36.

In the Marazano[90] synthesis, the piperidine ring of (−)-lobeline **1** was derived from a chiral pyridinium salt that was alkylated twice on the C2 and C6 positions by the Reformatsky reagent (Fig. 10). Alkylation of pyridinium salts has been extensively studied by Marazano to synthesise various piperidinic or tetrahydropyridinic alkaloids.[91] Thus, this methodology was successfully applied to the total synthesis of (−)-lobeline **1**.

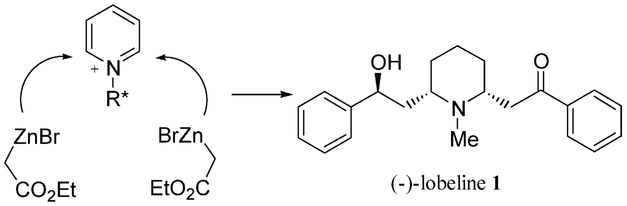
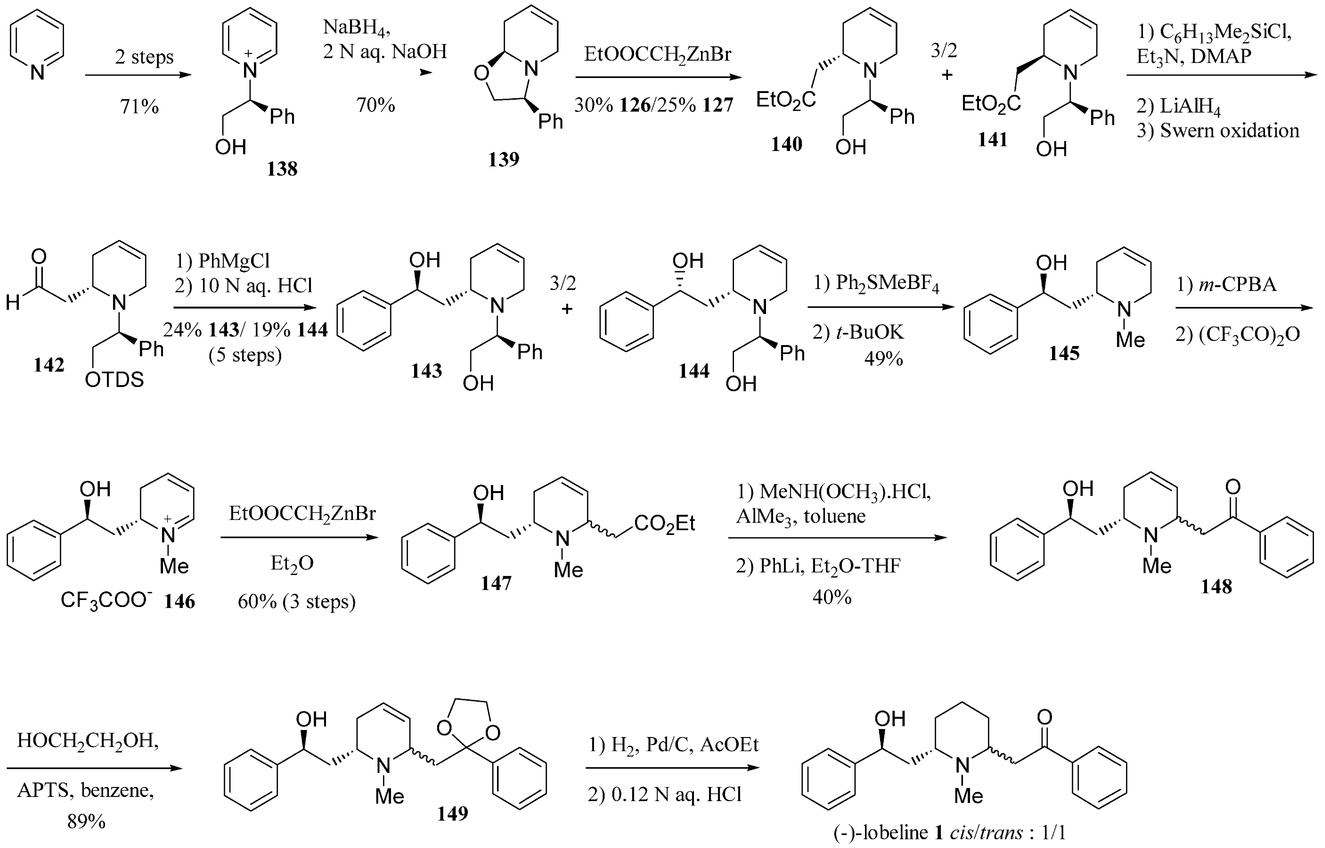


Figure 10.

The Marazano synthesis involved the formation of the chiral pyridinium salt **138** obtained in two steps from commercial products[92] (71% overall yield) (Scheme 37). The chiral pyridinium salt **138** was reduced to the oxazolidine **139**, which was opened by the Reformatsky reagent to give two diastereoisomers **140** and **141** with low selectivity (3/2 ratio, respectively) in 30% yield. Nevertheless, the diastereoisomers **140** and **141** were easily separated by chromatography on silica gel, which permitted the preparation of **140** on a large scale. The primary hydroxyl group was protected as a silyl derivative and the ester function was transformed into the unstable aldehyde **142** in two steps involving a reduction by $LiAlH_4$ followed by an oxidation with the Swern protocol. Addition of Grignard reagent to **142** and subsequent deprotection of the hydroxyl function in acidic conditions gave a mixture of two diastereoisomers **143** and **144** in a 3/2 ratio that were easily separated by chromatography on silica gel. The next step required the removal of the phenylethanol auxiliary and the methylation of nitrogen. The researchers used a quaternisation–elimination strategy in a two-step sequence. Thus, quaternisation with the powerful alkylating reagent diphenylmethylsulphonium tetrafluoroborate and subsequent removal of the chiral auxiliary by treatment with *t*BuOK provided 4,5-dihydrosedamine **145**. It should be noted that this route also allowed an access to (−)-sedamine **24** or (−)-allosedamine **18** by reduction of the double bond. The formation of the unstable iminium salt **146** in two steps by a modified Polonowski protocol followed by the addition of Reformatsky reagent gave **147** as an unseparable mixture of diastereoisomers. The next step was performed on the mixture of epimers. It is interesting to note that this alkylation step is similar to the formation of norlobelanine **13** in the biosynthetic pathway (vide supra). Thus, Marazano elegantly drew inspiration from a natural process.

Transformation of the ester function into a Weinreb amide followed by the addition of PhLi furnished the dehydrolobeline **148** as two epimers *cis*/*trans* in a 15/85 ratio. All attempts to selectively reduce the double bond in the presence of the free carbonyl group failed. The authors therefore used a protection of the carbonyl group to give the dioxalane **149**. Hydrogenation of the double bond followed by hydrolysis of the resulting dioxalane gave (−)-lobeline **1** in an equilibrium mixture of two epimers *cis*/*trans* in a 1/1 ratio.

Retrosynthetically, we used a similar strategy for the



Scheme 37.

synthesis of (−)-allosedamine **18** in the construction of (−)-lobeline **1** (vide supra) (Fig. 11). The synthesis involved the use of the *syn* epoxyalcohol **104**, which was a common chiral intermediate in the synthesis of (−)-allosedamine **18**. Formation of the piperidine ring was achieved by an intramolecular Michael reaction.

The synthesis began with the *syn* epoxyalcohol **104** previously described in the synthesis of (−)-allosedamine **18** (vide supra), (Scheme 38). Conversion into the *trans* isomer by the Mitsunobu protocol furnished the diastereoisomer **151** with total inversion of configuration. The key intermediate **152** was essentially obtained using the same cascade of reactions previously described (vide supra). A Dess–Martin oxidation into the aldehyde **153** followed by a Wittig olefination led to the enone **154**. Finally, removal of the TBS and the Boc groups in acidic media generated the enone **155**, which spontaneously cyclized during the basic treatment. Thus, (−)-lobeline **1** was obtained in an equilibrium mixture of two epimers *cis*/*trans* in a 1/1 ratio.

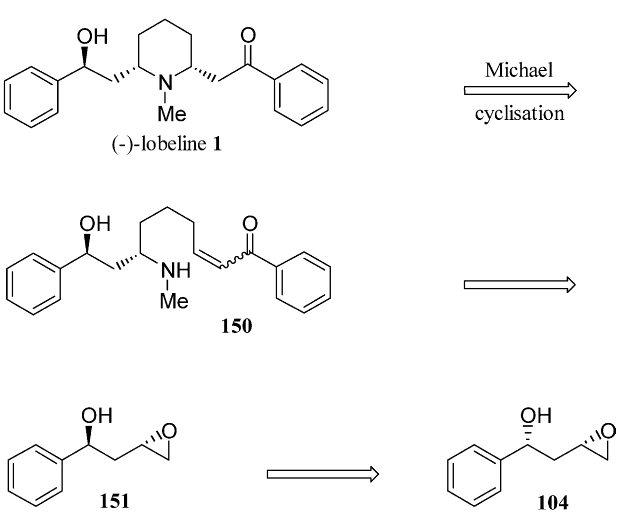
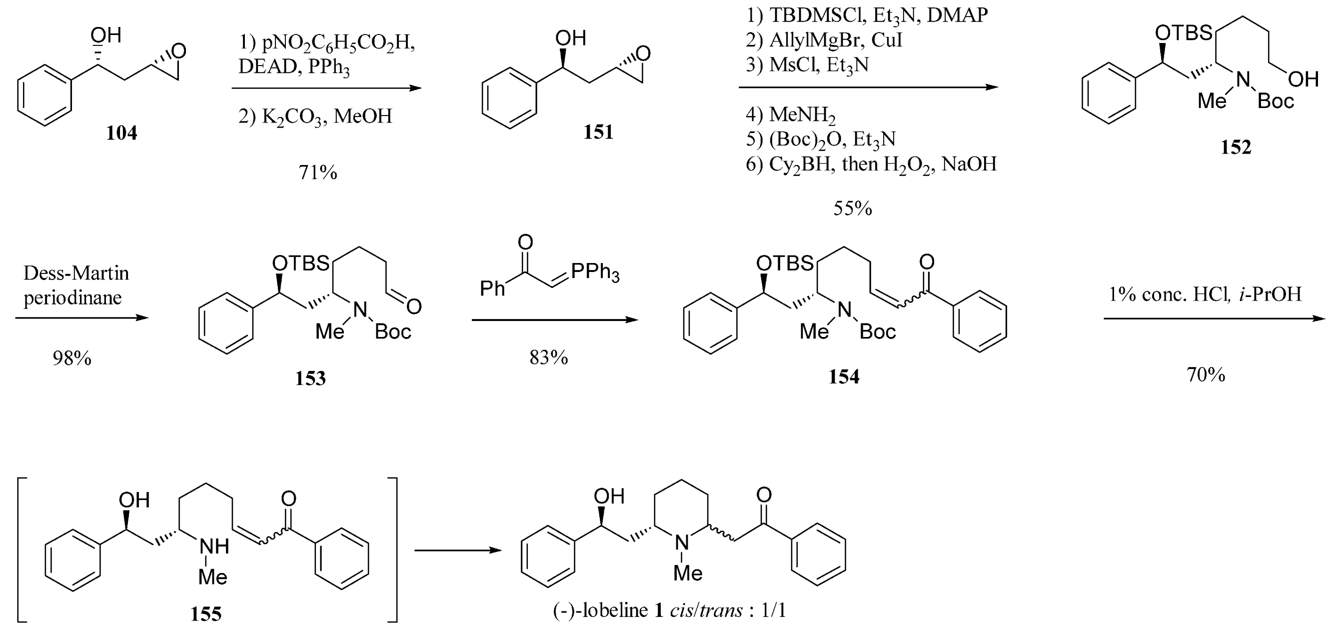


Figure 11.

Thus, the highly enantioselective synthesis of (−)-lobeline requires 16 steps from benzaldehyde and gives 14% overall yields. This efficient route could be applied to the preparation of interesting analogues for biological screening.[93]

5. Biology

(−)-Lobeline **1** appears to be the most biologically active alkaloid of *Lobelia* plants and consequently has been the subject of several pharmacological studies. Biological investigations over the last 25 years have shown that many of the medicinal properties empirically discovered by native Americans have a scientific basis. Each of the major effects, namely respiratory stimulant, drug deterrent, cognition enhancement in neurological disorders, as well as other minor biological properties reported for lobeline **1**, will be considered in turn, followed by its mode of action and the structure–activity relationship studies.



Scheme 38.

5.1. Biological activity of lobeline

5.1.1. Respiratory stimulant. For a very long time, the most important use for this drug has been in the treatment of respiratory problems. For this class of disease, no remedy was more highly valued by physicians in the late 19th century. Indeed, lobeline **1** was known as a powerful respiratory stimulant.[94] This important property has been explained by the activation of the carotid and aortic body chemoreceptors[95] at therapeutic doses. Larger doses may induce a cough. Lobeline **1** relaxes the tissues and favours expectoration when a large quantity of mucus is secreted. The potent action of this alkaloid on the respiratory system has therefore been used with success in numerous applications. Chronic pneumonia, asthma, bronchitis and laryngitis are all conditions in which lobeline **1** has been of great service.[5] It seems that the treatment of asthma reported by Thomson and Culter (see Section 2) constitutes the first modern therapeutic application.

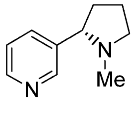
Lobeline **1** has also been advantageous for the treatment of victims who have been electrocuted or asphyxiated by toxic gases.[96] Moreover, it was useful in the case of the paralysis of respiratory centres after drug poisoning with alcohol, soporifics or morphine or after narcosis.[97] Lastly, **1** has also been used to treat asphyxia in newborn infants.[98]

Due to its unpredictable effects and the development of more effective agents, however, its use has become obsolete. Nevertheless, lobeline **1** is still officially listed in several pharmacopoeias.

5.1.2. Drug abuse. Lobeline **1** has been reported as a useful agent to treat dependency on drugs such as cocaine, amphetamine, caffeine, phenylcycline, opiates, barbiturates, benzodiazepines, cannabinoids, hallucinogens, alcohol and, especially, nicotine **156** (Fig. 12).[99] The most promising area in this field is the ability of **1** to be a substitute of nicotine **156**. Lobeline **1** produces several physiological effects similar to those produced by nicotine **156**. The use of **1** as a smoking deterrent was reported in 1936,[100] but several later studies led to a dispute between positive[101] and negative[102] reports. Numerous countries have sold drugs containing lobeline **1** such as: Nicoban™, Bantron™, CigArest™, NicFit™ and Smoker's Choice™. In 1993, however, the FDA claimed the inefficacy of these products and removed them from the market.

Nevertheless, a renewed interest in the treatment of smoking cessation with drugs containing **1** has resurfaced with the clinical experiments of Schneider and co-workers.[103] Their studies have shown that its inability to be an effective agent for smoking cessation was essentially due to its weak bioavailability. In a recent patent,[104] studies on a new formulation of drugs to deliver an effective amount of **1** to sublingual mucosa have been reported. In addition, the remarkable studies of Dwoskin and Crooks[105] reported the potential of **1** as a pharmacotherapy for the abuse of psychostimulants (e.g., amphetamine and methamphetamine). Thus, the development of new drugs providing lobeline **1** or its analogues with better availability is under investigation.

5.1.3. Lobeline as a treatment for CNS disorders. The most promising bioactivity of lobeline **1** concerns its use as an agent in the treatment of CNS diseases and pathologies. The effect of **1** on the CNS was extensively exploited by the native Americans, who smoked the dried leaves of *Lobelia* plants. Several studies have shown that **1** improves memory[106] in rodents, probably due to its involvement in cholinergic mechanisms of neurotransmission (vide infra).



(-)-nicotine **156**

Figure 12.

This pharmacological profile may be of great importance in the treatment of learning disorders like Alzheimer's disease (AD), the most common cause of dementia in the elderly. Indeed, two years ago, the cholinergic hypothesis was claimed to explain the cognitive symptoms of AD.[107] Thus, the development of new agents that selectively interact with cholinergic receptors could offer a new opportunity for AD therapy. AD is characterised by a gradual and progressive decline in intellectual function and behavioural abnormalities.

Lobeline **1** also appears to improve the performance of rats in sustained attention tasks,[108] and it could, therefore, be useful for the treatment of attention deficit hyperactivity disorder. This disorder afflicts children as well as adults and is characterised by inattention, restlessness, impulsiveness and hyperactivity. The agents acting via nicotinic acetylcholine receptors (nAChR) have not been extensively investigated as anxiolytic agents. Lobeline **1** has, however, been examined for its ability to decrease anxiety without cognitive impairment and without contributing to a depressive state.[109]

5.1.4. Other biological activities. In the 19th century, physicians used the emetic properties of lobeline **1** in cases of alimentary intoxication. Indeed, **1** causes direct central stimulation of the vomiting centre in the CNS and irritation of the gastrointestinal system. Lobeline **1** has many physiological effects often similar to those produced by nicotine **156** and, by stimulation of the autonomic ganglia, **1** produces sympathetic and parasympathetic effects.[110]

Sympathetic effects result in an increase in blood pressure (hypertension) and tachycardia. Bradycardia and hypotension have also been reported, however, in rats anesthetised with urethane and pentobarbital.[111] Parasympathetic effects, manifested in the gastrointestinal system, result in an increase in salivation and diarrhea.

After treatment with lobeline **1**, a slight suppression of appetite has been reported and its use of has therefore been suggested for the treatment of eating disorders such as obesity.[112]

In a recent patent, Yerka described a method for increasing hydration and lubrication of lacrimal,[113] vaginal[114] and cervical tissues by the administration of lobeline **1**. The invention is useful for treating dry eye disease and corneal injury, as well as vaginal dryness and vulvar pain.

5.2. Mode of action

The neurotransmitter[115] acetylcholine **157** acts on acetylcholine receptors (AChR), which can be divided into muscarinic (mAChR) and nicotinic (nAChR) receptors based, on the agonist activities of the alkaloids, muscarine **158** and nicotine **156** (Fig. 13). nAChR are members of the superfamily of ligand-gated ion channels including γ-aminobutyric acid ($\mathrm{GABA_A}$), *N*-methyl-D-aspartate (NMDA), serotonin (5-HT$_3$) and glycine receptors.[116] The nAChR have been the focus of intense research in recent years,[117] due to their involvement in cognitive, motor and behavioural systems.[118] Thus, modulation of cholinergic transmissions could be useful for the therapy of several CNS disorders, like Parkinson's disease and AD. nAChR are found on skeletal muscles at the neuromuscular junction and at numerous sites in the central and peripheral nervous system. Neuronal nAChR have a pentameric structure composed of α (α_2–α_9) and β (β_2–β_4) subunits with a considerable array of combinations.[119] Each of which displays specific physiological processes when a ligand acts on it. Thus, multiple populations of nAChR exist, but, in the brain, the $\alpha_4\beta_2$ and α_7 subunits are prevalent. Lobeline **1** displays a very low affinity for the α_7 subtype ($K_i >$ 10,000 nM) but a high affinity for $\alpha_4\beta_2$ ($K_i = 1$–5 nM).[120] A similar profile is observed for nicotine **156**.


acetylcholine **157**

L-muscarine **158**

Figure 13.

Although the determination of the nAChR pharmacophore is an exceedingly difficult task, some of the pharmacophoric elements are generally accepted[121,122]:

- A donor of hydrogen bonds, like a quaternised nitrogen atom or a tertiary amine protonated at physiological pH.
- An acceptor of hydrogen bonds, like a pyridine or a carbonyl function.
- A distance between the donor and acceptor elements of 4.6–6.3 Å, according to the binding models studied.

In their pioneering work, Beers and Reich[123] considered that the structure of **1** could adopt a conformation that is in agreement with the nAChR pharmacophore. According to Barlow and Johnson's[124] observations, however, **1** possesses two potential hydrogen bond acceptors. Indeed, the phenyl-2-ketoethyl and phenyl-2-hydroxyethyl groups could bind through hydrogen bonds to the receptors, even though the keto moiety has been reported to be a better hydrogen bond acceptor.[125]

Many similar effects for nicotine **156** and lobeline **1**, like tachycardia and hypertension,[126] anxiolytic activity[127] and improvement of learning and memory,[128] have been recorded. Contrary to **156**, however, lobeline **1** does not increase locomotor activity[129] or produce conditioned place preference.[130] In addition, and again in contrast with nicotine **156**, chronic treatment with lobeline **1** does not increase the number of nicotinic receptors in mouse brain regions.[131]

Thus, **1** possesses no obvious structural resemblance to nicotine and is currently considered as an agonist,[115] an antagonist,[132] as well as a mixed agonist/antagonist,[133] at nicotinic receptors. These properties have been attributed to its particular structure, which could possess an agonist part (the keto portion) and an antagonist part (the hydroxyl portion).[124]

Nicotine **156** and lobeline **1** evoked dopamine (DA) release from rat striatial slices.[134] Unlike **156**, however, lobeline-induced DA release was calcium-independent and was insensitive to mecamylamine, a non-competitive nicotinic receptor antagonist that blocks the ion channel of the receptor.[115] In addition, at weak concentrations that had no effect alone, lobeline **1** blocked nicotine-evoked DA release, indicating, in this case, that it acted as an antagonist at nAChR.[135] All of this work suggests that **156** and **1** act on nAChR via a non-common CNS mechanism. Thus, the pharmacological effect of **1** can either be mediated by minor subset populations of nAChR or through a non-nicotinic mechanism. It is also possible that **1** causes an allosteric effect at the nAChR, leading to a modification of its properties. In a recent paper, Dwoskin and Crooks[132] have proposed a novel mechanism of action for **1**, namely that it inhibited DA uptake into rat striatial synaptic vesicles by acting at the tetrabenzine binding site on vesicular monoamine transporter-2 (VMAT2). The induced inhibition of synaptic vesicular DA transport modified the concentration of DA in the cytosol and vesicles and, consequently, altered dopaminergic neurotransmission. The concentration of dopamine in the synaptic cleft and the activation of postsynaptic dopamine receptors diminished. Thus, by acting as an indirect antagonist of DA receptors, lobeline **1** antagonises the effect of psychostimulants (amphetamine and methamphetamine) which produce their effects, in part, by activation of the dopaminergic system. In this context, **1** and its analogues could represent a novel class of therapeutic agents with a great potential for the treatment of psychostimulant abuse. Thus, these recent studies suggest that **1** acts as an antagonist at the nAChR on the pre-synaptic dopaminergic nerve terminal and/or as an inhibitor at the tetrabenzine site on VMAT2 on synaptic vesicle membranes.

5.3. Structure–affinity relationships

In order to assess the contribution of the different structural components of the natural molecule **1** in binding to nAChR receptors, a wide range of lobeline-like structures **14**, **16**, **60**, **159–190** have been screened (Table 1).[136] Some structurally simplified analogues of lobeline with single arms have been synthesised to determine the usefulness of the phenyl-2-ketoethyl and phenyl-2-hydroxyethyl part. In every case, removal of one of the side chains resulted in a dramatic decrease in affinity, for nAChR. In addition, the absence of the piperidine ring in **175** resulted in a marked reduction in affinity in comparison with **60**. These data suggest the important contribution of both arms and the piperidine ring in the interaction with the receptors. Total deoxygenation of either side chain in **176**, **179**, **180** abolished affinity, suggesting an interaction of at least one oxygen with the receptor. Indeed, compounds **181** to **186**, where only one oxygen function (ketone or hydroxyl) was present, showed an enhanced affinity, in comparison with the totally deoxygenated compounds **177**, **179**, **180**. All of these affinity values are, however, modest in relation to those of lobeline **1**.

Thus, if the presence of one oxygen function is sufficient for binding, the asymmetrical derivatives **1**, **188** and **189** seem to be optimal. Surprisingly, lobelanine **14** and lobelanidine **16** display modest affinity for nAChR, although both oxygen functions are present. These results suggest that the presence of both oxygens is not a sufficient condition for high affinity binding. Each of the ketone and hydroxyl functions seemed to play an important role in receptor recognition. Protection of the hydroxyl group as its tosylate derivative **188** resulted in the conservation of affinity, but this result is unclear at the moment. Replacement of the hydroxyl group by a chloro function (**189**) retained the affinity of lobeline **1**. The potential of halogen atoms (Cl or F) is now well established in medicinal chemistry, due to their ability to participate in hydrogen bonding. Researchers have also envisaged the formation of the quaternary amine by intramolecular cyclisation, however, under the conditions of the binding assay. In order to study this possibility, the *N*-methylammonium salt **190** was prepared, but it displayed a 500-fold drop in affinity binding relative to lobeline **1**.

In their studies, Glennon and co-workers[136a] measured the analgesic activity of **180**, **183**, **187** and **1**, which displayed a broad range of affinities (Table 2). The analgesic effect produced was comparable for the four compounds. In the light of these results, it appears that the oxygen atoms are not required for the activity and that there was no relationship between the binding affinity for the $\alpha_4\beta_2$ receptor and the analgesic potency.

Terry's group[136b] also evaluated **1**, **159** and **161** for their mAChR affinity and for their ability to inhibit acetylcholinesterase (AChE) (Table 3). Although **1**, **159** and **161** display a lower affinity for mAChR, in comparison with nAChR, they are not inactive.

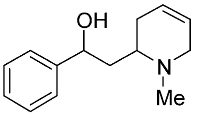
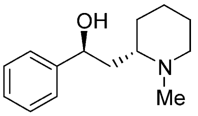
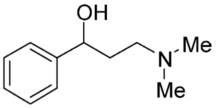
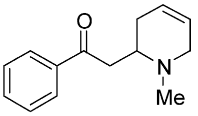
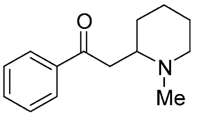
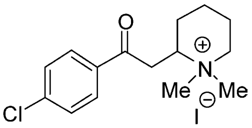
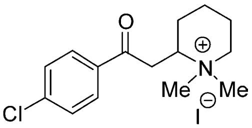
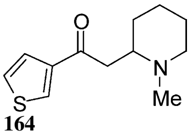
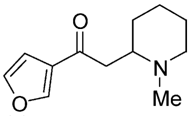
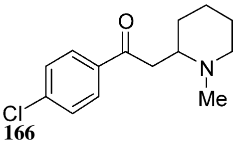
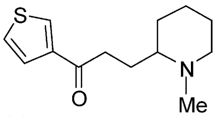
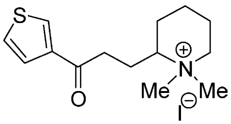
In the study of AChEI activity, lobeline **1** was found to be the more potent, although the standard for comparison (physostigmine, $IC_{50} = 0.25\ \mu M$) was 300-fold more potent. The authors concluded that the complex pharmacological activities of **1** could be mediated via nAChR, mAChR or other ion channel receptors and by inhibition of the enzyme AChE.

The inhibition of [^{3}H] DA uptake into the dopaminergic presynaptic terminal (inhibition of dopamine transporter 'DAT' activity) by several compounds was also evaluated by Crooks and Dwoskin[136c] (Table 4). Surprisingly, the inhibition of DAT was inversely proportional to the affinity value at nAChR. Deoxygenated compounds that displayed low affinity for nAChR interacted selectively with DAT, suggesting that oxygen atoms are not required for an optimal inhibition. This high selectivity for DAT interaction might be useful for the development of a novel class of therapeutic agents for the treatment of psychostimulant abuse.

6. Conclusion

Due to the extension of life expectancy in industrial countries and the prevalence of neurological disorders like Alzheimer's disease or Parkinson's disease, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future. Biological and chemical studies of *Lobelia inflata* alkaloids and, in particular, (−)-lobeline **1**, have increased over the last few years. Lobeline **1** might serve as a useful lead for

Table 1. nAChR receptor affinity of various lobeline analogues

Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **159**	15 000, [^{3}H]cytisine	136b
 **24**	>10 000, [^{3}H]nicotine	136a
 **160**	>10 000, [^{3}H]nicotine	136a
 **161**	5400, [^{3}H]cytisine	136b
 **60**	2200, [^{3}H]nicotine >100 000, [^{3}H]cytisine	136a 136d
 **162**	>100 000, [^{3}H]cytisine	136d
 **163**	>100 000, [^{3}H]cytisine	136d
 **164**	10 400, [^{3}H]cytisine	136d
 **165**	5990, [^{3}H]cytisine	136d
 **166**	>100 000, [^{3}H]cytisine	136d
 **167**	24 600, [^{3}H]cytisine	136d
 **168**	29 000, [^{3}H]cytisine	136d

(*continued on next page*)

Table 1 (*continued*)

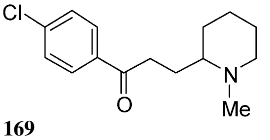
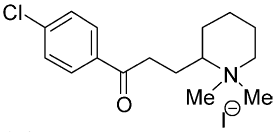
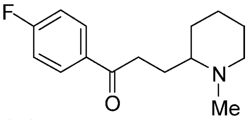
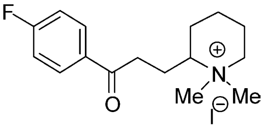
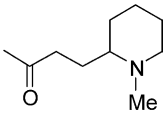
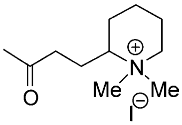
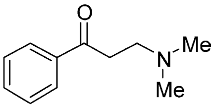
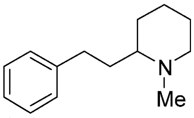
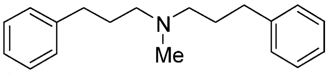
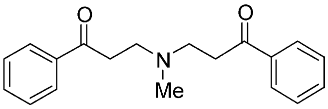
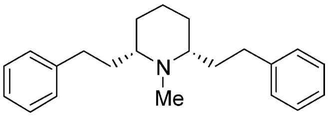
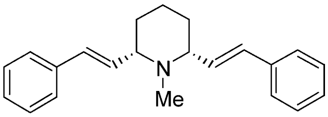
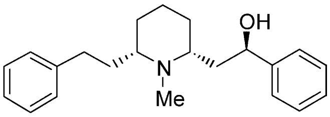
Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **169**	>100 000, [^{3}H]cytisine	136d
 **170**	62 600, [^{3}H]cytisine	136d
 **171**	23 400, [^{3}H]cytisine	136d
 **172**	>100 000, [^{3}H]cytisine	136d
 **173**	3700, [^{3}H]cytisine	136d
 **174**	1800, [^{3}H]cytisine	136d
 **175**	5900, [^{3}H]nicotine	136a
 **176**	2490, [^{3}H]nicotine	136a
 **177**	>10 000, [^{3}H]nicotine	136a
 **178**	>10 000, [^{3}H]nicotine	136a
 **179**	>10 000, [^{3}H]nicotine 14 300, [^{3}H]nicotine	136a 136c
 **180**	>10 000, [^{3}H]nicotine	136c
 **181**	160, [^{3}H]nicotine 340, [^{3}H]nicotine	136c 136a

Table 1 (*continued*)

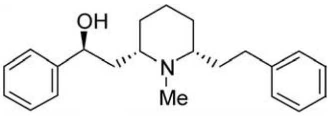
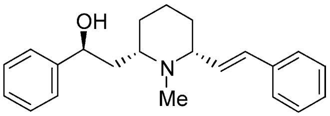
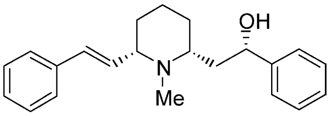
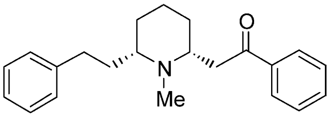
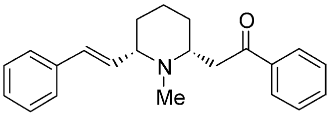
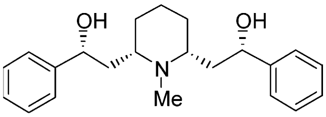
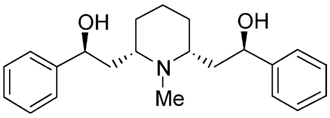
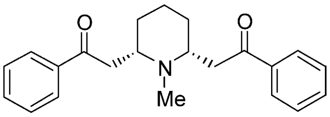
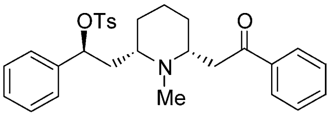
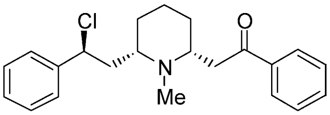
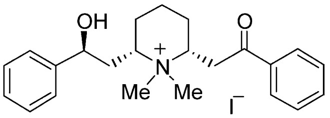
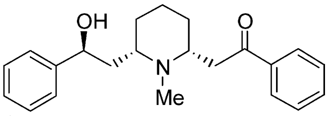
Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **182**	235, [^{3}H]nicotine	136a
 **183**	1315, [^{3}H]nicotine	136a
 **184**	4200, [^{3}H]nicotine	136c
 **185**	110, [^{3}H]nicotine	136a
 **186**	1085, [^{3}H]nicotine 130, [^{3}H]nicotine	136a 136c
 **187**	930, [^{3}H]nicotine	136c
 **16**	300, [^{3}H]nicotine	136a
 **14**	7800, [^{3}H]nicotine 11 000, [^{3}H]nicotine	136a 136c
 **188**	4.1, [^{3}H]nicotine	136c
 **189**	5, [^{3}H]nicotine	136a
 **190**	2035, [^{3}H]nicotine	136a
 **1**	4.3, [^{3}H]nicotine 4, [^{3}H]nicotine 16, [^{3}H]nicotine	136c 136a 136b

Table 2. Analgesic activity of **180**, **183**, **187** and **1**

Compound	Analgesic effect ED_{50} (μmol)/animal
1	23
180	27
183	32
187	38

Table 3. mAChR receptor affinity and inhibition of acetylcholinesterase for **1**, **159** and **161**

Compound	mAChR receptor affinity K_i, μmol, radioligand	AChRI activity IC_{50} (μmol)
1	37	76
159	55	5000
161	16	230

Table 4. Inhibition of DAT activity

Compound	Inhibition of DAT activity [^{3}H]-dopamine uptake, K_i (μmol)
1	45
14	25
179	3
180	0.8
181	8.9
184	1.3
186	3
187	54
188	39

the developement of new therapeutic agents that act on nAChR in a novel fashion. In addition, the non-nAChR-mediated pharmacological effects of lobeline **1** might provide new opportunities for a better understanding of neuronal disorders. Chemical studies in this area are probably at this prebiotic state.

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References and notes

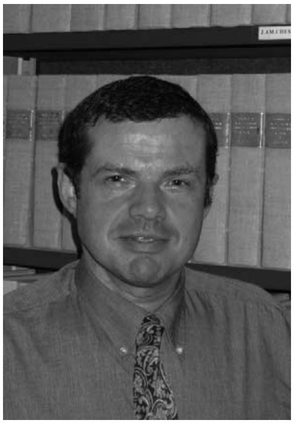
1. Elbein, A. D.; Molyeux, R. Chemical and Biological Perspectives. In *Alkaloids*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 57, p 1.
2. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.
3. Holladay, M. W.; Dart, M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169–4194.
4. Lloyd, G. K.; Williams, M. *J. Pharm. Exp. Ther.* **2000**, *292*, 461–467.
5. Millspaugh, C. F.; *Lobelia inflata In: American Medicinal Plants: an illustrated and descriptive guide to plants indigenous to and naturalized in the United States which are used in medicine*; Dover: New York, 1974 pp 385–388.
6. Wieland, H.; Koschara, E. D.; Renz, J.; Schwarze, W.; Linde, W. *Liebigs Ann. Chem.* **1939**, *540*, 103–156.
7. Damaj, M. I.; Patrick, G. S.; Creasy, K. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 410–419.
8. Robinson, R. *J. Chem. Soc.* **1917**, 876–899.
9. Leete, E.; Gros, E. G.; Gilbertson, T. J. *J. Am. Chem. Soc.* **1964**, *86*, 3907–3908.
10. Leete, E. *J. Am. Chem. Soc.* **1969**, *91*, 1697–1700.
11. Gupta, R. N.; Spenser, I. D. *Can. J. Chem.* **1967**, *45*, 1275–1285.
12. Leete, E. *Biosynthesis of Natural Products*; Bernfield, P., Ed.; Pergamon: Oxford, 1963; p 752.
13. Leete, E. *J. Am. Chem. Soc.* **1963**, *85*, 3523–3525.
14. Leete, E. *J. Am. Chem. Soc.* **1964**, *86*, 2509–2513.
15. O’ Donovan, D. G.; Keogh, M. F. *Tetrahedron Lett.* **1968**, 265–267.
16. Keogh, M. F.; O’ Donovan, D. G. *J. Chem. Soc. (C)* **1970**, 2470–2472.
17. Koukol, J.; Conn, E. E. *J. Biol. Chem.* **1961**, *236*, 2672–2698.
18. O’ Donovan, D. G.; Long, D. J.; Forde, E.; Geary, P. *J. Chem. Soc., Perkin Trans. 1* **1975**, 415–419.
19. Leete, E.; Chedekal, M. R. *Phytochemistry* **1972**, *11*, 2751–2756.
20. Gupta, R. N.; Spenser, I. D. *J. Biol. Chem.* **1969**, *244*, 88–94.
21. Walton, N. J.; Belshaw, N. J. *Plant Cell Rep.* **1988**, *7*, 115–118.
22. Walton, N. J.; Robins, R. J.; Rhodes, M. J. C. *Plant Sci.* **1988**, *54*, 125–131.
23. Leete, E. *J. Am. Chem. Soc.* **1956**, *78*, 3520–3523.
24. O’ Donovan, D. G.; Forde, T. *J. Chem. Soc. (C)* **1971**, 2889–2890.
25. Leete, E. Biosynthesis and Metabolism of the Tobacco Alkaloids. In *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, pp 85–152.
26. Gupta, R. N.; Spenser, I. D. *J. Chem. Soc., Chem. Commun.* **1966**, 893–894.
27. Gupta, R. N.; Spenser, I. D. *Can. J. Chem.* **1971**, *49*, 384–397.
28. Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978.
29. Schöpf, C.; Kauffmann, T.; Berth, P.; Bundschuh, W.; Dummer, G.; Fett, H.; Habermehl, G.; Wieters, E.; Wust, W. *Liebigs Ann. Chem.* **1957**, *608*, 88–127.
30. Mill, S.; Durant, A.; Hootelé, C. *Liebigs Ann.* **1996**, 2083–2086.
31. Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 3451–3454.
32. Büchi, J.; Kracher, F.; Schmidt, G. *Helv. Chim. Acta* **1962**, *45*, 729–737.
33. Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047–3054.
34. Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594–8601.

35. See structure–affinity relationships.
36. Marion, L.; Lavigne, R.; Lemay, L. *Can. J. Chem.* **1951**, *29*, 347–351.
37. Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Recl. Trav. Chim.* **1956**, *75*, 63–75.
38. Stanek, J.; Hebky, J.; Zverina, V. *Chem. Listy* **1952**, *46*, 735–736.
39. Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim.* **1959**, *78*, 43–58.
40. Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176.
41. Ozawa, N.; Nakajima, S.; Zaoya, K.; Hamaguchi, F.; Nagasaka, T. *Heterocycles* **1991**, *32*, 889–894.
42. (a) Yu, C.-Y.; Taylor, D. L.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6661–6664. (b) Yu, C.-Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6665–6668. (c) Meth-Cohn, O.; Yau, C. C.; Yu, C.-Y. *J. Heterocycl. Chem.* **1999**, *36*, 1549–1553.
43. Meth-Cohn, O. Patent EP 1050531, 2000.
44. Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1978**, *47*, 4647–4650.
45. Hootelé, C.; Ibebeke-Bomangwa, W.; Driessens, F.; Sabil, S. *Bull. Soc. Chim. Belg.* **1987**, *96*, 57–61.
46. (a) Ibebeke-Bomangawa, W.; Hootelé, C. *Tetrahedron* **1987**, *43*, 935–945. (b) Hootelé, C.; Ibebeke-Bomangawa, W.; Driessens, F.; Sabil, S. *Bull. Soc. Chim. Belg.* **1987**, *96*, 57–61.
47. Liguori, A.; Ottanà, R.; Romeo, G.; Sindona, G.; Uccella, N. *Chem. Ber.* **1989**, *122*, 2019–2020.
48. Ghiaci, M.; Adibi, M. *Org. Prep. Proced. Int.* **1996**, *28*, 474–477.
49. Wakabayashi, T.; Watanabe, K.; Kato, Y.; Saito, M. *Chem. Lett.* **1977**, 223–228.
50. Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633–635.
51. Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525–1535.
52. Oppolzer, W.; Deeberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554–560.
53. Oppolzer, W.; Merifield, E. *Helv. Chim. Acta* **1993**, *76*, 957–962.
54. Oppolzer, W. *Pure Appl. Chem.* **1994**, *94*, 2127–2130.
55. Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015–7018.
56. Bosone, E.; Farina, P.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942–944.
57. Barton, D. R. H.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479–5486.
58. Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448–7449.
59. Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259–1265.
60. Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4173–4178.
61. Felpin, F.-X.; Lebreton, J. *Tetrahedron Lett.* **2002**, *43*, 225–227.
62. Girard, S.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Tetrahedron Lett.* **2000**, *41*, 9245–9249.
63. Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121–1124.
64. Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312.
65. Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646–1648.
66. For review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
67. Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381–7389.
68. Singh, V. K. *Synthesis* **1992**, 605–617.
69. Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504.
70. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012.
71. DIP-Chloride™ is a trademark of Aldrich Chemicals Co.
72. Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626–4633.
73. Duan, J. J.-W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703–3711.
74. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.
75. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692.
76. Mitsunobu, O. *Synthesis* **1981**, 1–28.
77. Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571–7574.
78. Taber, D. F.; Rahimizadeh, M.; You, K. K. *J. Org. Chem.* **1995**, *60*, 529–531.
79. Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danieli, B. *J. Org. Chem.* **2003**, *68*, 9525–9527.
80. Raghavan, S.; Rajender, A. *Tetrahedron Lett.* **2004**, *45*, 1912–1919.
81. Ebnöther, A. *Helv. Chim. Acta* **1958**, *41*, 386–396.
82. Wieland, H.; Dragendorffs, O. *Justus Liebigs Ann. Chem.* **1929**, *473*, 83–101.
83. (a) Wieland, H.; Drishaus, I. *Justus Liebigs Ann. Chem.* **1929**, *473*, 102–118. (b) Wieland, H.; Koschara, W.; Dane, E. *Justus Liebigs Ann. Chem.* **1929**, *473*, 118–126.
84. Scheuing, G.; Winterhalder, L. *Justus Liebigs Ann. Chem.* **1929**, *473*, 126–136.
85. Shaw, B. D. *J. Chem. Soc.* **1924**, *125*, 2363–2365.
86. Schöpf, C.; Lehmann, G. *Justus Liebigs Ann. Chem.* **1935**, *518*, 1–37.
87. Schöpf, C.; Mueller, E. *Justus Liebigs Ann. Chem.* **1965**, *687*, 241–250.
88. The synthesis of **57** was mentioned in the description of allosedamine.
89. Leonard, N. J.; Hay, A. S.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439–444.
90. Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528–4532.
91. (a) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185–1187. (b) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625–626. (c) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052–2057. (d) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811–818. (e) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Génisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733.
92. Génisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431–434.
93. Unpublished work.
94. King, M. J.; Hosmer, H. R.; Dresbach, M. *J. Pharmacol. Exp. Ther.* **1928**, *32*, 241–272.
95. Aviado, D. M. Ganglionic stimulants and blocking drugs. In

Drill's Pharmacology in Medicine, 3rd ed.; Drill, V. A., DiPalma, J. R., Eds.; McGraw Hill: New York, 1971; pp 708–731.

96. Leybold, W. *Gas u. Wasserfach* **1927**, *70*, 652–653.
97. Wieland, H.; Mayer, R. *Arch. Exptl. Path. Pharm.* **1922**, *92*, 195–230.
98. Schumacher, P. *Z. Geburtshülfe Gynecol.* **1924**, *88*, 151–158.
99. Dwoskin, L. P.; Xu, R.; Ayers, J. T.; Crooks, P. A. *Exp. Opin. Ther. Patents* **2000**, *10*, 1561–1581.
100. Dorsey, J. L. *Ann. Int. Med.* **1936**, *10*, 628–631.
101. (a) Kalyuzhnyy, V. V. *J. Neural. Psychiat.* **1968**, *68*, 1864–1870. (b) Baum, L. Patent GB 1056214, 1967. (c) Reynolds, M. Patent US 6409991, 2002.
102. (a) Davison, G. C.; Rosen, R. C. *Psychol. Rep.* **1972**, *31*, 443–456. (b) Stead, L. F.; Hughes, J. R. Lobeline for smoking cessation (Cochrane Review). In *The Cochrane Library*; Oxford: Update Software Ltd, (4), 2002.
103. (a) Schneider, F. H.; Olsson, T. A. *Med. Chem. Res.* **1996**, *6*, 562–570. (b) Schneider, F. H.; Mione, P. J.; Raheman, F. S.; Phillips, B. M.; Quiring, J. N. *Am. J. Health Behav.* **1996**, *20*, 346–363.
104. Schneider, F. H.; Muni, I. A.; Murty, B. R.; Pandya, M. K.; Matharu, R. P. S. Patent WO 95/11678, 1995.
105. Dwoskin, L. P.; Crooks, P. A. Patent US, 5830904, 1998.
106. Decker, M. W.; Majchzark, M. J.; Anderson, D. J. *Brain Res.* **1992**, *572*, 281–285.
107. Newhouse, P. A.; Potter, A.; Kelton, M.; Corwin, J. *Biol. Psychiatry* **2001**, *49*, 268–278.
108. Terry, A. V.; Buccafusco, J. J.; Jackson, W. J.; Zagrodnick, S.; Evans-Martin, F. F.; Decker, M. W. *Psychopharmacology* **1996**, *123*, 172–181.
109. Decker, M. W.; Buckley, M. J.; Brioni, J. D. *Drug Dev. Res.* **1994**, *31*, 52–58.
110. Muhtadi, F. J. *Anal. Profiles Drug Subst.* **1990**, *19*, 261–313.
111. Sloan, J. W.; Martin, W. R.; Bostwick, M.; Hook, R.; Wala, E. *Pharmacol. Biochem. Behav.* **1988**, *30*, 255–267.
112. London, S. J. *Curr. Ther. Res.* **1963**, *5*, 167.
113. Yerka, B.; Peterson, W. M.; Cowlen, M. Patent WO 01/80844, 2001.
114. Yerka, B. Patent WO 01/87288, 2001.
115. Decker, M. W.; Brioni, J. D.; Bannon, A. W.; Arneric, S. P. *Life Sci.* **1995**, *56*, 545–570.
116. Sargent, P. B. *Annu. Rev. Neurosci.* **1993**, *16*, 403–443.
117. Changeux, J.-P.; Devillers-Thiery, A.; Chemouilli, P. *Science* **1984**, *225*, 1335–1345.
118. Rusted, J. M.; Newhouse, P. A.; Levin, E. D. *Behav. Brain Res.* **2000**, *113*, 121–129.
119. Dart, M. J.; Wasicak, J. T.; Ryther, K. B.; Schrimpf, M. R.; Kim, K. H.; Anderson, D. J.; Sullivan, J. P.; Meyer, M. D. *Pharm. Acta Helv.* **2000**, *74*, 115–123.
120. Brioni, J. D.; Decker, M. W.; Sullivan, J. P.; Arneric, S. P. *Adv. Pharmacol.* **1997**, *37*, 153–214.
121. Sheridan, R. P.; Nilakantan, R.; Dixon, J. S.; Venkataraghavan, R. *J. Med. Chem.* **1986**, *29*, 899–906.
122. Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, *6*, 465–486.
123. Beers, W. H.; Reich, E. *Nature* **1970**, *228*, 917–922.
124. Barlow, R. B.; Johnson, O. *Br. J. Pharmacol.* **1989**, *98*, 799–808.
125. Glaser, R.; Hug, P.; Drouin, M.; Michel, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1071–1079.
126. Olin, B. R.; Hebel, S. K.; Gremp, J. L.; Hulbertt, M. K. Smoking deterrents. In *Drug Facts and Comparisons*; Olin, B. R., Hebel, S. K., Gremp, J. L., Hulbertt, M. K., Eds.; Lippincott Co.: St. Louis, MO, 1995; pp 3087–3095.
127. Brioni, J. D.; O'Neill, A. B.; Kim, D. J. B.; Decker, M. W. *Eur. J. Pharmacol.* **1993**, *238*, 1–8.
128. Decker, M. W.; Majchzark, M. J.; Arneric, S. P. *Pharmacol. Biochem. Behav.* **1993**, *45*, 571–576.
129. Stolerman, I. P.; Garcha, H. S.; Mirza, N. R. *Psychopharmacology* **1995**, *117*, 430–437.
130. Fudala, P. J.; Iwamoto, E. T. *Pharmacol. Biochem. Behav.* **1986**, *25*, 1041–1049.
131. (a) Collins, A. C.; Romm, E.; Wehner, J. M. *Brain Res. Bull.* **1990**, *25*, 373–379. (b) Bhat, R. V.; Turner, S. L.; Selvaag, S. R.; Marks, M. J.; Collins, A. C. *J. Neurochem.* **1991**, *56*, 1932–1939.
132. Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharmacol.* **2002**, *63*, 89–98.
133. Abood, L. G.; Shahid Salles, K.; Maiti, A. *Pharmacol. Biochem. Behav.* **1988**, *30*, 403–408.
134. Teng, L.; Crooks, P. A.; Sonsalla, P. K.; Dwoskin, L. P. *J. Pharm. Exp. Ther.* **1997**, *280*, 1432–1444.
135. Dwoskin, L. P.; Crooks, P. A. Patent US, 6087376, 2000.
136. (a) Flammia, D.; Dukat, M.; Damaj, M. I.; Martin, B.; Glennon, R. A. *J. Med. Chem.* **1999**, *42*, 3726–3731. (b) Terry, A. V.; Williamson, R.; Gattu, M.; Beach, J. W.; McCurdy, C. R.; Sparks, J. A.; Pauly, J. R. *Neuropharmacology* **1998**, *37*, 93–102.Dwoskin, L. P.; Crooks, P. A.; Jones, M. D. Patent WO 01/08678, 2001. (d) Villeneuve, G.; Cécyre, D.; Lejeune, H.; Drouin, M.; Lan, R.; Quirion, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3847–3851.

Biographical sketch



Jacques Lebreton was born in Guérande (France) in 1960. He received his PhD degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor D-homosteroids. In 1986, he started his first post-doctoral fellowship with Professor James A. Marshall at the University of South Carolina working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second post-doctoral fellowship with Professor Robert E. Ireland at the University of Virginia working on the total synthesis of monensine, he joined in 1990 the laboratories of CIBA-GEIGY (Novartis) in Basle, where he worked in Dr. Alain De Mesmaeker's group in the area of antisense oligonucleotides. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villéras (UMR-CNRS 6513, Nantes) exposed to organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry, synthesis of bioactive molecules (HIV, cancer and central nervous system diseases) and synthesis of labelled molecules to study biological processes.

François-Xavier Felpin was born in Villefranche-sur-Saône (France) in 1977. During his undergraduate education he worked in the laboratory of Dr. Charles Mioskowski (CEA Saclay, France) under the direction of Dr. Eric Doris on the synthesis of labeled amino acids by rearrangement of cyclopropanone hydrate. He receives his PhD degree (2003) from the University of Nantes under the supervision of Professor Jacques Lebreton working on total synthesis of alkaloids (anabasine, anatabine, sedamine, lobeline, deoxoprosopinine…). After his PhD, he was engaged in a post-doctoral position with Professor Robert S. Coleman at The Ohio State University working on total synthesis of Mitomycin. In 2004 he joined the University of Bordeaux I as an Assistant Professor working in the group of Professor Yannick Landais.

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Synthesis and in vitro antitumor activity of substituted anthracene-1,4-diones

Duy H. Hua,[a,*] Kaiyan Lou,[a] Josh Havens,[a] Elisabeth M. Perchellet,[b] Yang Wang,[b] Jean-Pierre Perchellet[b] and Takeo Iwamoto[c]

[a]*Department of Chemistry, Kansas State University, Willard Hall, Manhattan, KS 66506, USA*
[b]*Department of Biology, Kansas State University, Manhattan, KS 66506, USA*
[c]*Department of Biochemistry, Kansas State University, Manhattan, KS 66506, USA*

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Abstract—Based on a rational approach, 6-substituted 1,4-anthracenediones were synthesized and found to exhibit potent cytotoxic activity against murine and human leukemic cells. The synthetic sequence includes a double Friedel–Crafts reaction, reductive quinone formation, and selective bromination of the alkyl side chain. A key intermediate, 6-bromomethyl-1,4-anthracenedione (**10**), was synthesized and converted to various active antitumor agents, including a water-soluble phosphate ester pro-drug. The interconversion reactions include displacement of the bromide with various nucleophiles and basic hydrolysis to the alcohol and subsequent oxidation to provide the aldehyde. Based on their ability to decrease L1210 and HL-60 tumor cell viability, 1,4-dihydroxyanthraquinones are inactive but 1,4-anthracenediones have interesting antitumor activity, which may be abolished by modification of the A-ring and improved by substitution of the C-ring. The cytostatic and cytotoxic activity of the representative compound **10** was verified at the National Cancer Institute in studies on the 60-human tumor cell line panel in the in vitro antitumor screening. A wide spectrum of tumor cells are sensitive to **10** inhibition, and concentrations required to inhibit tumor cell growth by 50% (GI_{50}) at 48 h are <10 nM in HL-60 and MOLT-4 and 37.1 nM in SR leukemia. Preliminary studies suggest that the molecular targets and mechanisms of action of **10** may be different from those of daunomycin.

1. Introduction

Since the discovery of the anticancer drugs daunomycin, adriamycin, and mitoxantrone (Fig. 1),[1] many anthraquinones have been investigated for their biological activities, especially their anticancer potential.[2] In almost all cases, 9,10-anthraquinones were studied;[1,2] only a limited number of 1,4-anthracenediones was known.[3] Our initial discovery of the antitumor activity of 1,4-anthracenedione (**1**)[4] prompted us to synthesize various substituted 1,4-anthracenediones in our search for new anticancer agents. Since the 1,4-quinone function of substituted 1,4-anthracenediones is highly reactive, a selective functionalization of a side chain of substituted 1,4-anthracenediones was a challenging problem. Herein, we report a rational design and synthesis of substituted 1,4-anthracendiones via functionalization of the methyl side chain of 6-methyl-1,4-anthracenedione (**2**),[3b] and their anticancer activities. Several analogs of **2** are nearly equipotent to adriamycin against L1210 leukemic cells.

2. Results and discussion

2.1. Synthesis of substituted 1,4-anthracenediones

Quinizarine(1,4-dihydroxyanthraquinone) contains a partial functionality of daunomycin; we therefore compared the anticancer activities of quinizarine and **1**.[3a] Using murine L1210 leukemia and human HL-60 tumor cells, we found that the IC_{50} values (inhibition concentration by 50%) of **1** are 42 ± 2 nM and 140 ± 7 nM (Table 1), respectively, while quinizarine is inactive in both cell lines when tested up to 1.6 μM. The inactivities of quinizarine toward cancer cells show that the central quinone ring of anthraquinones is an un-preferred location.[2a] To determine whether other substituted 1,4-dihydroxyanthraquinones would also be inactive, we then synthesized 6,7-dichloro-1,4-dihydroxyanthraquinone (**3**) and 6,7-dichloro-1,4-anthracenedione (**4**) and studied their anticancer activities.

Several methods have been reported for the synthesis of 1,4-anthracenediones.[2,3] We used a double Friedel–Crafts

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Keywords: Antitumor activity; Substituted anthracene-1,4-diones; Phosphate ester pro-drug; L1210 leukemic cell; Human HL-60 tumor cell; 6-Bromomethylanthracene-1,4-dione.

* Corresponding author. Tel.: +1 785-532-6699; fax: +1 785-532-6666; e-mail: duy@ksu.edu

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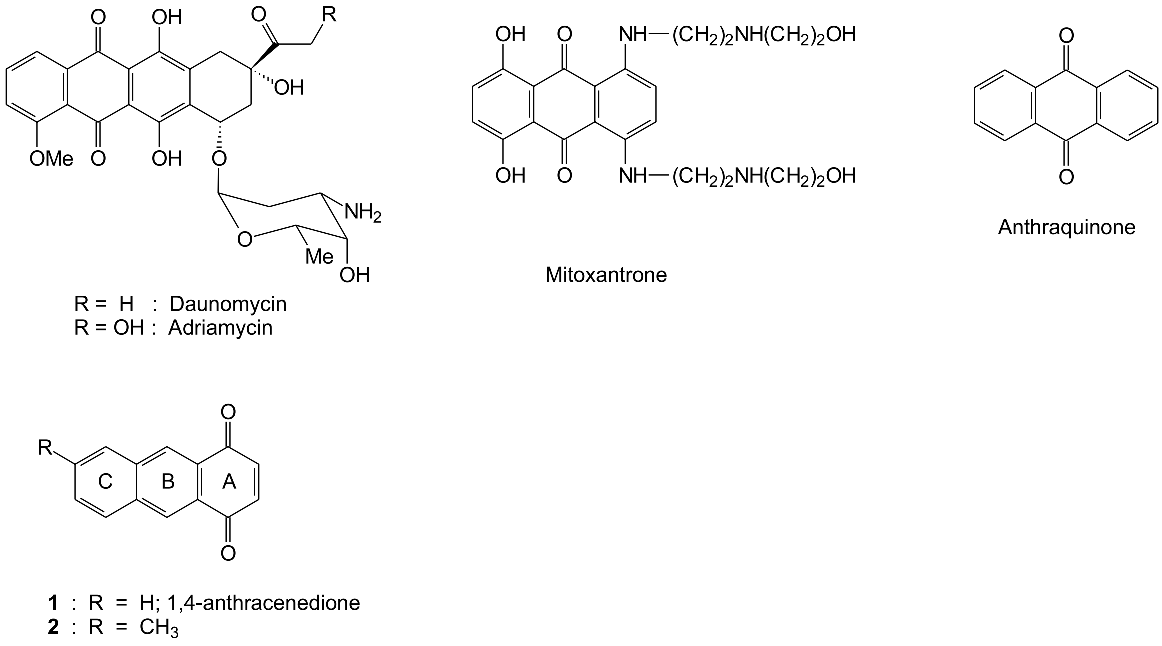


R = H : Daunomycin
R = OH : Adriamycin

Mitoxantrone

Anthraquinone

1 : R = H; 1,4-anthracenedione
2 : R = CH_3

Figure 1.

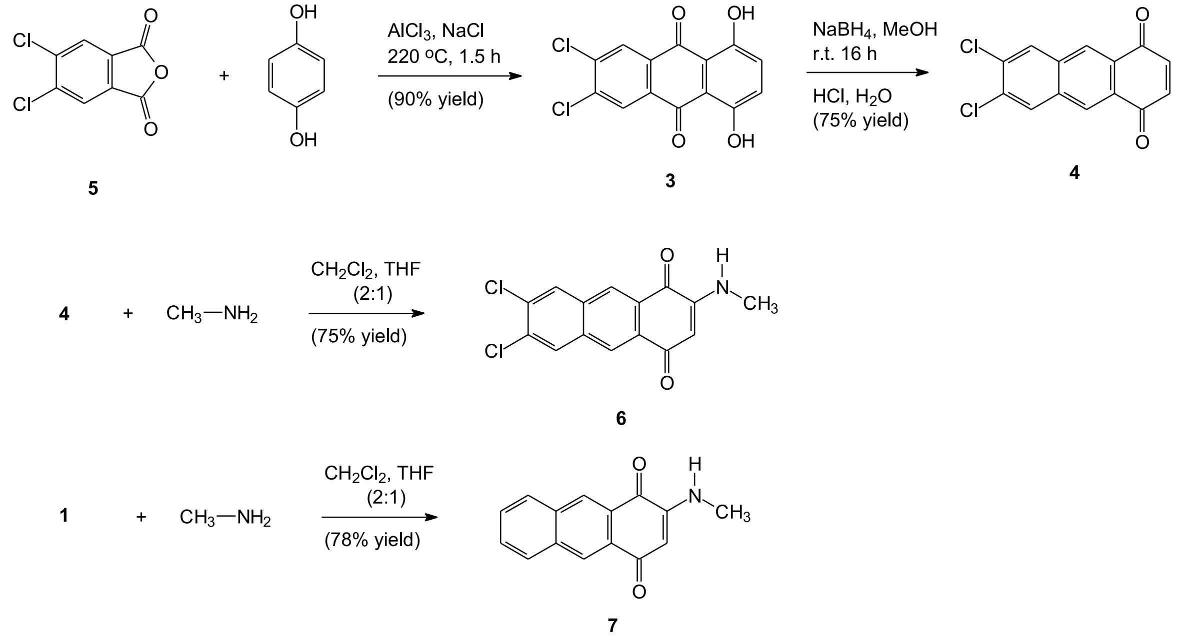
reaction[5] because 1,4-dihydroxyanthraquinones are produced as the intermediates, which can be reduced to give 1,4-anthracenediones.[3a] Hence, condensation of 4,5-dichlorophthalic anhydride (**5**) with hydroquinone in the presence of $AlCl_3$ and NaCl at 220 °C[5a] gave **3** (90% yield) which, upon reduction with $NaBH_4$ in MeOH followed by acidic work-up, afforded **4** (75% yield) (Scheme 1). As predicted,[6] the addition reaction of **4** with methylamine gave amine adduct **6**. 1,4-Dihydroanthraquinone **3** and A-ring substituted 1,4-anthracenequinone **6** show no significant anticancer activities (Table 1); while compound **4** possesses a potent antitumor activity with an IC_{50} value of 84 nM (against L1210). To verify that the substitution on the A ring decreases the antitumor activity, amine **7**, derived from **1** and methylamine, was prepared. Like **6**, amine quinone **7** exhibited no appreciable anticancer activity at a concentration of 640 nM (Table 1).

These antitumor data suggest that 9,10-anthraquinones that contain 1,4-dihydroxyl groups are inactive and that substitution on the A ring may reduce the antitumor activity of 1,4-anthracenediones. On the other hand, 1,4-anthracenediones with substitution on ring C, such as **4**, retain their antitumor activity. Therefore, we investigated anthracenedione **2** and its analogs containing a side chain at C6. Quinone **2** was then synthesized by following a similar double Friedel–Crafts reaction and reduction procedure as described above. 6-Methyl-1,4-dihydroxyanthraquinone (**9**) was obtained in 80% yield from 4-methylphthalic anhydride (**8**) and hydroquinone (Scheme 2), and reduction of **9** followed by acidic work-up furnished quinone **2** (98% yield). To our delight, quinone **2** and its analogs were found to be active against murine and human leukemic cells (vide infra).

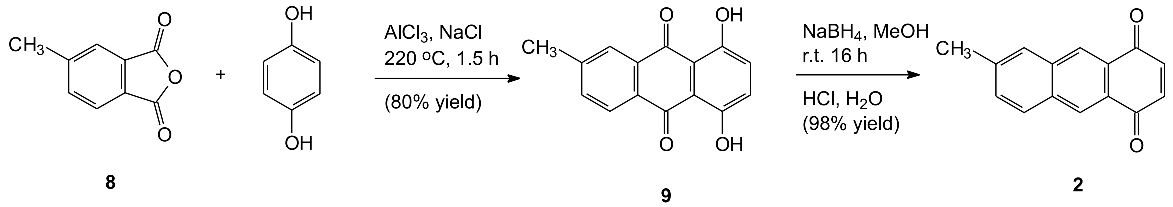
Table 1. Cytotoxicities of 1,4-anthracenediones in the L1210 and HL-60 tumor cell systems in vitro

Compound	L1210, IC_{50} (nM)	HL-60, IC_{50} (nM)
1	42±2	140±7
Quinizarine	Not active at 1.6 μM	Not active at 1.6 μM
2	29±1	87±4
3	Not active at 256 nM	Not active at 256 nM
4	84±6	243±16
6	Not active at 640 nM	Not active at 640 nM
7	Not active at 640 nM	Not active at 640 nM
9	Not tested	Not active at 10 μM
10	26±1	79±3
11	462±43	1260±104
12 and **13**	110±9	327±29
15	37±2	125±7
16	Not active at 4.0 μM	Not active at 4.0 μM
18	Not tested	919±78
21	Not tested	254±23
22	Not tested	1980±176
24	Not tested	133±9

We have attempted a number of functional group interconversions of **2**, such as benzylic oxidation with $RuCl_3$ and NaOCl[7] and free-radical benzylic halogenation with NBS-benzoyl peroxide, but no desired products were detected. Fortuitously, treatment of **2** with $CuBr_2$ and *t*-butyl hydroperoxide in acetic anhydride[8] at 80 °C gave a 75% yield of bromide **10**, 10% of aldehyde **11**, and a small amount of ring bromination products **12** and **13** (<5% yield; a ratio of 1:1; inseparable). The amount of **12** and **13** varies with reaction conditions and the purity of acetic anhydride. When dried acetic anhydride was used, **12** and **13** were not detected. Aldehyde **11** was likely produced from the hydrolysis of dibromide **14**, which may derive from the further bromination of **10**. Dibromide **14** was not isolable under our reaction conditions. Although compound **10** decomposed under basic conditions and strong acidic conditions, it was used to synthesize various anthracenedione analogs, and they exhibited potent anticancer activities. Treatment of **10** with silver trifluoroacetate in dioxane and water gave an excellent yield of alcohol **15**, which was oxidized with IBX (*o*-iodoxybenzoic acid) in DMSO[9] to aldehyde **11** (62% yield). The displacement product, 6-trifluoroacetoxy-1,4-anthracenedione, from **10** and silver trifluoroacetate, likely was hydrolyzed to **15**



Scheme 1.



Scheme 2.

under the reaction conditions. No desired product was obtained when **10** was treated with potassium acetate in ethanol (Scheme 3).

2.2. Synthesis of water-soluble analogs

Since all the above 6-substituted 1,4-anthracenediones exhibited potent anticancer activities (vide infra), water-soluble analogs were synthesized for anticancer evaluation in animal models. Syntheses of various water-soluble analogs containing a carboxylic acid group, (−)-quinic acid ester, and amino sugar moiety are described in Scheme 4. Oxidation of alcohol **15** with Jones reagent in acetone gave a good yield of carboxylic acid **16**. As described above, bromide **10** can be converted to various esters (containing a water-solubilized group) by reactions with silver salts of carboxylic acids. Hence, displacement of bromide **10** with the silver salt of (−)-quinic acid (**17**) in dioxane afforded ester **18** (46% yield). Amination of aldehyde **11** with 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**19**)[10] in pyridine and dichloromethane followed by sodium cyanoborohydride in acetic acid and methanol produced amine **21**. Attempts to remove the acetoxy protecting groups of **21** under basic or acidic conditions were unsuccessful; unidentifiable materials were formed. However, the hydrochloric acid salt of amine **21**, **22**, is soluble in water.

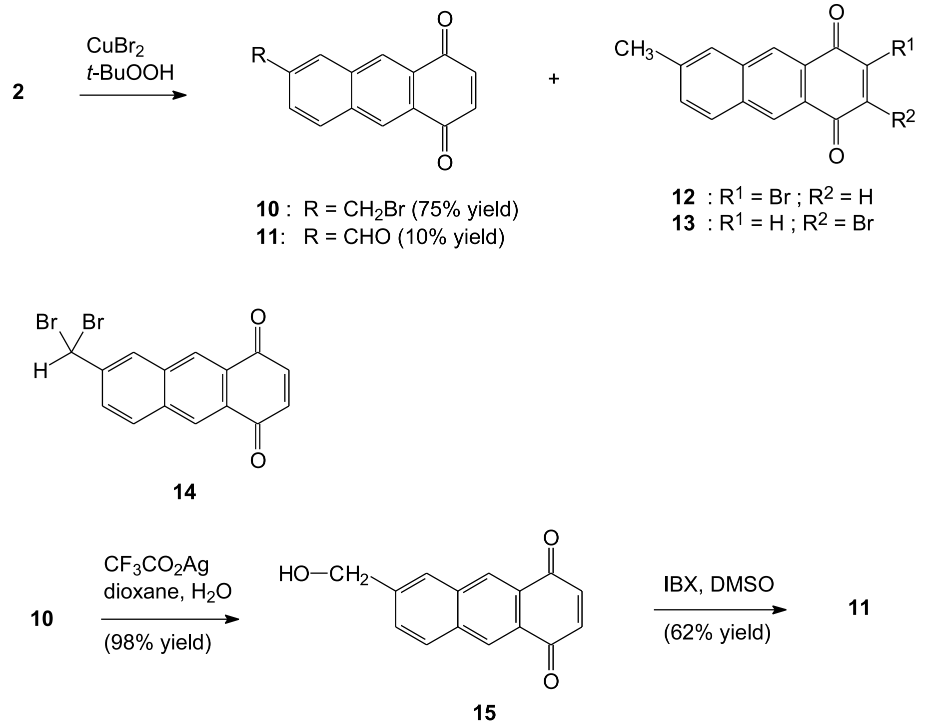
Among the above water-soluble analogs, **16** was inactive when tested up to 4 μM, and **18** and **22** inhibited HL-60 cell viability with disappointing IC_{50} values in the micromolar range (Table 1). However, water-insoluble intermediate amine **21** is much more potent with an IC_{50} value of 200 nM in the HL-60 system. The decreased antitumor activity of these water-soluble molecules may be due to their inability to readily cross-hydrophobic cell membranes. A water-soluble phosphate ester pro-drug was therefore investigated.

2.3. Synthesis of a phosphate ester pro-drug

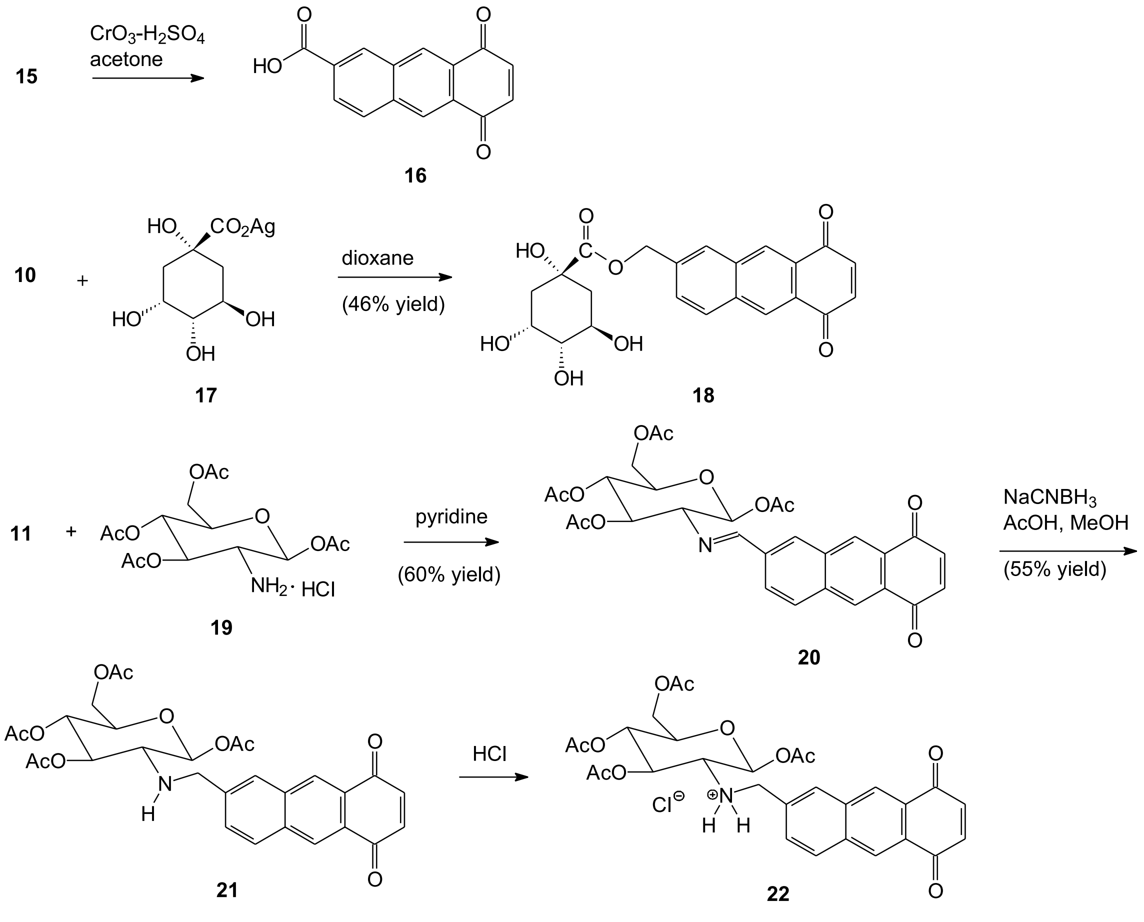
Since alcohol **15** exhibited potent anticancer activities (Table 1), a pro-drug of it, such as phosphate **23**, would be water soluble for administration to animals and release active quinone **15** upon reaction with basic or acidic phosphatases.[11] Treatment of bromide **10** with silver di-*t*-butyl phosphate[12] in chloroform under reflux gave a 48% yield of di-*t*-butyl phosphate **24** (Scheme 5). Removal of the *t*-butyl phosphate groups with trifluoroacetic acid in dichloromethane followed by neutralization with sodium carbonate furnished pro-drug phosphate salt **23**, which is soluble in water.

2.4. Anticancer activities

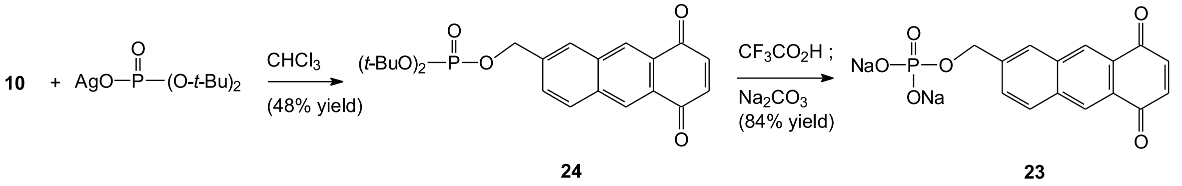
Table 1 summarizes IC_{50} values of L1210 and HL-60 leukemic cells at day 4 of various 1,4-anthraquinones and 1,4-dihydroxyanthraquinones. In general, the IC_{50} values of 1,4-anthraquinones are in the 26–462 nM range for L1210 and 79–1260 nM range for HL-60 cells, with the exception



Scheme 3.



Scheme 4.



Scheme 5.

of **6**, **7**, carboxylic acid **16**, and acetyl glucosamine HCl salt **22**. Because the ability of the latter compounds to cross-cellular membranes might decrease as their water solubility increases, they would be less likely to interact with intracellular molecular targets and organelles to trigger apoptosis. Under similar treatment conditions, the IC_{50} value of daunomycin, a known anticancer drug, is 30 nM against L1210 cells.[13] Based on the mitochondrial ability of these cells to metabolize the MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium]: PMS (phenazine methosulfate) reagent at day 4, compounds **2**, **10** and **15** are significantly more cytotoxic than the parental **1** structure in the L1210 and HL-60 tumor cell systems in vitro (Table 1).

Synthetic analogs of 1,4-anthracenedione (**1**) mimic the antitumor effects of the anthracycline quinone antibiotic daunomycin in the nanomolar range in vitro but have the additional advantage of blocking the cellular transport of purine and pyrimidine nucleosides and retaining their efficacy in multidrug-resistant (MDR) tumor cells.[4,14] Compounds **2**, **10**, and **15** induce cytochrome *c* release, caspase-9, -3 and -8 activities, poly(ADP-ribose) polymerase-1 cleavage and internucleosomal DNA fragmentation in wild-type and MDR HL-60 cells by a mechanism which is partially mediated by caspase-2 activation but does not involve Fas signaling.[15] Interestingly, these 1,4-anthracenedione analogs, which can also trigger cytochrome *c* release without caspase activation, might directly target mitochondria in cell and cell-free systems to induce a rapid loss of mitochondrial membrane potential under experimental conditions where daunomycin fails to do so.[16] This wider spectrum of molecular targets might make such anthracenedione analogs valuable in developing a novel synthetic class of quinone antitumor drugs effective in polychemotherapy.

The ability of **10** to inhibit L1210 (IC_{50}: 26 nM) and HL-60 (IC_{50}: 79 nM) tumor cell viability in our system at day 4 of this study has been verified in the 60 human tumor cell line panel of the National Cancer Institute's in vitro antitumor screen, in which a sulforhodamine B protein assay is used to estimate cell viability and growth after 2 days of continuous drug exposure. With this well-established methodology, the cytostatic/cytotoxic activity of **10** can be demonstrated in all 60 human tumor cell lines. Moreover, although this drug is generally more potent against ascetic than solid tumors, the selectivity pattern indicates that a wide spectrum of tumor cells is sensitive to **10** inhibition. Interestingly, the concentrations of **10** required to inhibit tumor cell growth by 50% (GI_{50}) at 48 h are <10 nM in HL-60 and MOLT-4 and 37.1 nM in SR leukemia. For solid tumors, **10** is the most effective against SN12C renal cancer (GI_{50}: 379 nM), HCT-116 colon cancer (GI_{50}: 606 nM) and MDA-MB-231/ATCC breast cancer (GI_{50}: 735 nM). Other solid tumor systems responding well to **10** inhibition include the LOX IMVI melanoma (GI_{50}: 1.28 μM), the A549/ATCC non-small cell lung cancer (GI_{50}: 1.62 μM), the DU-145 (GI_{50}: 1.63 μM) and PC-3 (GI_{50}: 1.64 μM) prostate cancers, and the OVCAR-3 ovarian cancer (GI_{50}: 2.16 μM). Naturally, the concentrations of **10** required for total growth inhibition (TGI) and to induce a net loss of 50% of the initial cell concentration (LC_{50}) are somewhat higher than the respective GI_{50} values in this NCI's in vitro cell line screen (data not shown).

3. Conclusion

A number of potent antitumor 1,4-anthracenediones were synthesized from a double Friedel–Crafts reaction of substituted phthalic anhydride with hydroquinone, regioselective benzylic bromination, and subsequent functional group interconversions. Compound **10**, for instance, inhibits the proliferation and viability of various ascetic and solid tumors in the 60 human tumor cell line panel of the National Cancer Institute. Compounds **2**, **10**, and **15** are nearly equipotent to daunomycin against L1210 and HL-60 tumor cell viability and have the advantage of blocking nucleoside transport, inducing mitochrondrial depolarization, and retaining their efficacy in multidrug-resistant sublines. These activities suggest that the molecular targets and mechanism of action of these quinone antitumor drugs may be different from that of daunomycin. From a limited structure-activity relationship, it appears that 1,4-dihydroxyanthraquinones are inactive, and modification of the A-ring of 1,4-anthracenediones decreases antitumor activity. Anticancer evaluation in animal models and a selective targeting of tumor cells[19] by a conjugation of 1,4-anthracenedione with folic acid are being investigated.

4. Experimental

4.1. General methods

NMR spectra were obtained at 400 MHz for ^1H and 100 MHz for ^{13}C in deuteriochloroform unless otherwise indicated. Infrared spectra are reported in wavenumbers (cm^{-1}). FAB spectra were taken by using Xe beam (8 kV) and *m*-nitrobenzyl alcohol as matrix. Quinizarine, methylamine in THF (2 M solution), 4,5-dichlorophthalic anhydride (**5**), 4-methylphthalic anhydride (**8**), aluminum trichloride, and *t*-butyl hydroperoxide were commercially available. 1,4-Anthracenedione (**1**) was prepared as described.[3a,17] Davisil silica gel, grade 643 (200–425 mesh), was used for the flash column chromatographic separation.

4.1.1. 6,7-Dichloro-1,4-dihydroxy-9,10-anthraquinone (3).[5a,c] A mixture of 12.0 g (90 mmol) of aluminum trichloride and 2.60 g (44 mmol) of sodium chloride was heated under argon at 180 °C for 3 min. To it, a mixture of 2.39 g (11 mmol) of 4,5-dichlorophthalic anhydride (**5**), 1.29 g (11.9 mmol) of *p*-dihydroquinone, and 5.00 g (38 mmol) of aluminum trichloride was added at once under argon. The mixture was stirred vigorously and heated at 220 °C for 1.5 h, cooled to 25 °C, and poured into 100 mL of ice and water. The mixture was neutralized with 6 N HCl, and the suspended red solids were collected by filtration. The solids were dried under vacuum, crystallized from ethanol to give 3.06 g (90% yield) of **3**.[5a,c] Mp 290–291 °C; ^{1}H NMR δ 8.42 (s, 2H), 7.36 (s, 2H). The solubility of the compound is too low to obtain ^{13}C NMR spectrum in $CDCl_3$, DMSO-d_6, or CD_3OD.

4.1.2. 6,7-Dichloro-1,4-anthracenedione (4). To a solution of 3.72 g (12 mmol) of **3** in 200 mL of methanol at 0 °C under argon, was added 4.60 g (0.12 mol) of sodium borohydride. The mixture was stirred at 25 °C for 12 h. To the reaction mixture, another 2.30 g (60 mmol) of sodium borohydride was added, and the reaction mixture was stirred for additional 3 h. The mixture was poured into a cold (0 °C) 120 mL of 6 N HCl, and yellow solids were collected by filtration. The solids were crystallized from ether to give 2.72 g (82% yield) of **4**. Mp > 300 °C; ^{1}H NMR δ 8.54 (s, 2H), 8.19 (s, 2H), 7.10 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 184.0, 140.1, 133.4, 132.4, 131.2, 129.3, 127.3. HRMS calcd for $C_{14}H_7Cl_2O_2$ (M+H) 276.9824, found 277.0170.

4.1.3. 2-(Methylamino)-6,7-dichloro-1,4-anthracenedione (6). To a cold (0 °C) solution of 0.10 g (0.36 mmol) of **4** in 4 mL of dichloromethane and 2 mL of THF under argon, was added methylamine by inserting a needle connected from a methylamine gas cylinder for 10 min. The introduction of methylamine gas was disconnected, and the mixture was concentrated to dryness. The crude product was column chromatographed on silica gel using a gradient mixture of hexane and methylene chloride as an eluent to give 82.6 mg (75% yield) of **6**. Mp > 300 °C; ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 1H), 8.60 (s, 1H), 8.57 (s, 1H), 8.49 (s, 1H), 7.81 (q, $J=5$ Hz, 1H, NH), 5.73 (s, 1H, C3-H), 2.81 (d, $J=5$ Hz, 3H, NMe); ^{13}C NMR δ 185.3 (2 C), 163.6, 156.2, 136.3 (4 C), 134.3, 128.2, 126.0, 125.6, 114.9, 101.4, 32.9. HRMS calcd for $C_{15}H_{10}Cl_2NO_2$ (M+H) 306.0085, found 306.0229.

4.1.4. 2-(Methylamino)-1,4-anthracenedione (7). To a solution of 0.10 g (0.48 mmol) of **1** in 5 mL of THF under argon at 0 °C, 0.24 mL (0.48 mmol) of methylamine (2 M in THF) was added via syringe. The solution was stirred at 0 °C for 1 h, concentrated to dryness under vacuum, and column chromatographed on silica gel using a gradient mixture of hexane, methylene chloride and ether as an eluent to give 91 mg (80% yield) of **7**. Mp 240–241 °C; IR (nujol) ν 3350 (m, NH), 1680, 1600; ^{1}H NMR δ 8.62 (s, 2H), 8.02 (m, 2H), 7.66 (m, 2H), 6.22 (q, $J=6.5$ Hz, 1H, NH), 6.00 (s, 1H), 3.01 (d, $J=6.5$ Hz, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 180.9, 180.7, 150.4, 135.0, 133.5, 130.1, 129.7 (2 C), 129.6, 128.7, 128.3, 127.6, 126.5, 101.2, 28.9. HRMS calcd for $C_{15}H_{12}NO_2$ (M+H) 238.0869, found 238.0655.

4.1.5. 6-Methyl-1,4-dihydroxyanthraquinone (9). To a hot (180 °C) mixture of 37.1 g (0.28 mol) of $AlCl_3$ and 7.25 g (0.12 mol) of NaCl under argon was added a mixture of 5.00 g (31 mmol) of 4-methylphthalic anhydride (**8**), 3.74 g (34 mmol) of hydroquinone, and 15.0 g (0.11 mol) of $AlCl_3$ in one portion. The mixture was stirred and heated at 220 °C for 2 h, cooled to 25 °C, poured into 300 mL of ice-water, and acidified with 12 N HCl. The precipitated solids were collected by filtration, washed with water, and dried under vacuo to give 6.28 g (80% yield) of **9**.[20] ^{1}H NMR δ 12.94 (s, 1H, OH), 12.90 (s, 1H, OH), 8.22 (d, $J=8$ Hz, 1H, C8-H), 8.12 (s, 1H, C5-H), 7.63 (d, $J=8$ Hz, 1H, C7-H), 7.29 (s, 2H, C2, 3-H), 2.55 (s, 3H); ^{13}C NMR δ 187.4, 187.1, 158.0, 157.9, 146.1, 135.6, 133.6, 131.4, 129.5, 129.3, 127.5, 127.4, 113.1, 113.0, 22.2.

4.1.6. 6-Methyl-1,4-anthracenedione (2). To a solution of 3.00 g (12 mmol) of **9** in 50 mL of methanol at 0 °C under argon, was added 1.80 g (47 mmol) of sodium borohydride. The mixture was stirred at 25 °C for 12 h and acidified with 6 N HCl. The resulting yellow solids were collected by filtration, dried, and column chromatographed on silica gel using a mixture of hexane–ether–CH_2Cl_2 (60:5:1) as an eluent to give 2.57 g (98% yield) of **2**.[21] ^{1}H NMR δ 8.58 (s, 1H), 8.53 (s, 1H), 7.97 (d, $J=8$ Hz, 1H), 7.83 (s, 1H), 7.53 (d, $J=8$ Hz, 1H), 7.05 (s, 2H), 2.58 (s, 3H); ^{13}C NMR δ 185.0, 184.9, 140.4, 140.3, 140.1, 135.3, 133.3, 132.2, 130.2, 129.4, 128.9, 128.7, 128.4, 128.0, 22.2.

4.1.7. 6-Bromomethyl-1,4-anthracenedione (10), 6-formyl-1,4-anthracenedione (11), 2-bromo-6-methyl-1,4-anthracenedione (12), and 2-bromo-7-methyl-1,4-anthracenedione (13). To a solution of 0.70 g (3.2 mmol) of **2** and 1.00 g (4.5 mmol) of $CuBr_2$ in 14 mL of acetic anhydride at 60 °C under argon, was added 1.1 mL (9.5 mmol) of *t*-BuOOH (90%) dropwise through a dropping funnel. The solution was stirred at 80 °C for 2 h, cooled to 25 °C, diluted with 200 mL of water, and extracted with dichloromethane three times. The combined extract was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as an eluent to give 0.72 g (75% yield) of **10**, 0.12 g (10% yield) of **11**, and 48 mg (5% yield) of a mixture of **12** and **13** (1:1). Compound **10**. Mp 183–184 °C; ^{1}H NMR δ 8.59 (s, 1H), 8.58 (s, 1H), 8.06 (d, $J=8.4$ Hz, 1H), 8.04 (d, $J=1.8$ Hz, 1H), 7.72 (dd, $J=8.4$, 1.8 Hz, 1H), 7.08 (s, 2H), 4.67 (s, 2H); ^{13}C NMR δ 184.7 (2 C, C=O), 140.3, 140.2, 139.4, 135.0, 134.6, 131.2, 130.7, 129.9, 129.1 (2 C), 128.9, 128.7, 32.8. Anal. Calcd for $C_{15}H_9BrO_2\cdot 0.025H_2O$: C, 58.37; H, 3.21. Found: C, 58.28; H, 2.92. Compounds **12** and **13** (inseparable). ^{1}H NMR δ 8.65 (s, 1H), 8.61 (s, 1H), 8.56 (s, 1H), 8.51 (s, 1H), 7.97 (d, $J=8$ Hz, 2H), 7.83 (bs, 2H), 7.59 (s, 2H), 7.55 (d, $J=8$ Hz, 2H), 2.59 (s, 6H); ^{13}C NMR δ 185.3 (2 C, C=O), 155.6, 142.2, 142.0, 132.6, 130.7, 130.2, 129.5 (2 C), 129.0, 107.8, 98.9, 22.2. Anal. Calcd for $C_{15}H_9BrO_2$: C, 59.83; H, 3.01. Found: C, 59.73; H, 2.86.

4.1.8. 6-Hydroxymethyl-1,4-anthracenedione (15). A mixture of 0.14 g (0.47 mmol) of bromide **10** and 0.12 g (0.70 mmol) of silver trifluoroacetate in 4 mL of 1,4-dioxane–water (4:1) was stirred under argon at 25 °C for 2 h, diluted with 10 mL of acetone, and filtered through

Celite. The filtrate was concentrated and column chromatographed on silica gel using a mixture of hexane–ethyl acetate (1:1) as an eluent to give 0.108 g (98% yield) of alcohol **15**. Mp 178–179 °C (crystallized from toluene); ^{1}H NMR δ 8.58 (s, 1H), 8.56 (s, 1H), 8.03 (d, J=8.4 Hz, 1H), 8.02 (d, J=1.4 Hz, 1H), 7.68 (dd, J =8.4, 1.4 Hz, 1H), 7.06 (s, 2H), 4.94 (s, 2H); ^{13}C NMR (DMSO-d$_6$) δ 184.3 (2 C, C=O), 144.6, 140.0, 139.9, 134.3, 133.4, 130.0, 128.8, 128.2, 127.9, 127.7 (2 C), 126.3, 62.6. Anal. Calcd For $C_{15}H_{10}O_3\cdot 0.02H_2O$: C, 74.14; H, 4.37. Found: C, 74.33; H, 4.50.

4.1.9. 6-Formyl-1,4-anthracenedione (11). A solution of 0.25 g (1.1 mmol) of alcohol **15** and 1.32 g (5 mmol) of IBX[9] in 5 mL of DMSO was stirred under argon at 25 °C for 12 h. The mixture was diluted with water and dichloromethane, filtered through Celite, and the filtrate was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (MgSO$_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (2:1) as an eluent to give 0.15 g (62% yield) of aldehyde **11**. Mp 185–186 °C; ^{1}H NMR δ 10.25 (s, 1H, CHO), 8.81 (s, 1H), 8.69 (s, 1H), 8.56 (d, J=1.6 Hz, 1H), 8.19 (d, J=8.0 Hz, 1H), 8.17 (dd, J=8.0, 1.6 Hz, 1H), 7.14 (s, 2H); ^{13}C NMR δ 191.5 (CHO), 184.5 (2 C, C=O), 140.3 (2 C), 138.0, 136.7, 135.7, 134.6, 131.5, 130.7, 130.3, 129.5, 128.8, 126.5. Anal. Calcd For $C_{15}H_8O_3$: C, 76.27; H, 3.41. Found: C, 75.87; H, 3.74.

4.1.10. 5,8-Dioxo-5,8-dihydroanthracene-2-carboxylic acid (16). To a solution of 0.12 g (0.5 mmol) of alcohol **15** in 10 mL of acetone under argon, was added a solution of 0.5 mL (1.35 mmol) of Jones reagent (prepared from 27 g of chromium trioxide and 23 mL of concentrated H$_2$SO$_4$ in 77 mL of water). The mixture was stirred at 25 °C for 3 h, filtered through Celite, concentrated to dryness, and column chromatographed on silica gel using a mixture of diethyl ether and ethanol (9:1) as an eluent to give 0.10 g (82% yield) of carboxylic acid **16**. ^{1}H NMR (DMSO-d$_6$) δ 8.91 (s, 1H), 8.81 (s, 1H), 8.69 (s, 1H), 8.37 (d, J=8.4 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 7.20 (s, 2H); ^{13}C NMR (DMSO-d$_6$) δ 184.3, 184.1, 166.8, 140.1, 140.0, 136.1, 133.6, 132.3, 131.3, 130.5, 129.7, 129.5, 128.8, 128.5, 127.7. Anal. Calcd For $C_{15}H_8O_4\cdot 0.03H_2O$: C, 69.35; H, 3.43. Found: C, 69.13; H, 3.75.

4.1.11. 5,8-Dioxo-5,8-dihydro-2-anthracenylmethyl (1*R*,3*R*,4*R*,5*R*)-1,3,4,5-tetrahydroxycyclohexanecarboxylate (18). A mixture of 50 mg (0.17 mmol) of bromide **10** and 90 mg (0.30 mmol) of silver (−)-quinate (**17**) [prepared from 0.10 g of (−)-quinic acid and 60 mg of Ag$_2$O in 3 mL of ethanol] in 1 mL of 1,4-dioxane was stirred under argon for 24 h. The mixture was filtered through Celite, concentrated, and column chromatographed on silica gel using a gradient mixture of hexane, ethyl acetate, methanol, and water as an eluent to give 32 mg (46% yield) of ester **18**: $[\alpha]^{22}_{D}=-41.7°$ (c 0.005, MeOH); ^{1}H NMR (DMSO-d$_6$) δ 8.62 (s, 1H), 8.58 (s, 1H), 8.28 (d, J=8.8 Hz, 1H), 8.26 (d, J=1.6 Hz, 1H), 7.77 (dd, J=8.8, 1.6 Hz, 1H), 7.16 (s, 2H), 5.61 (s, 1H, OH), 5.29 (d, J=13.2 Hz, 1H), 5.32 (d, J=13.2 Hz, 1H), 4.72 (d, J=3.6 Hz, 1H OH), 4.56 (d, J=4.4 Hz, 1H, OH), 4.51 (d, J=6.4 Hz, 1H, OH), 3.93 (m, 1H), 3.81 (m, 1H), 3.40 (m, 1H), 2.10–1.70 (m, 4H); ^{13}C NMR (DMSO-d$_6$) δ 184.4 (2 C, C=O), 173.4 (CO$_2$), 140.1 (2 C), 138.3, 134.1, 133.7, 130.3, 129.0, 128.5, 128.2, 128.0 (2 C), 127.9, 73.8, 72.9, 67.5, 67.3, 65.0, 37.6 ((2 C). Anal. Calcd For $C_{22}H_{20}O_8\cdot 0.02H_2O$: C, 62.81; H, 5.01. Found: C, 62.78; H, 4.84.

4.1.12. *N*-[(1,4-Dioxo-1,4-dihydroanthracenyl)methylidene]-2-amino-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (20). A mixture of 21 mg (89 μmol) of aldehyde **11**, 33 mg (95 μmol) of 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine hydrochloride (**19**),[10] 50 μL of pyridine, and 0.20 g of 4 Å molecular sieves in 3 mL of dichloromethane was stirred under argon at 25 °C for 24 h, filtered through Celite, and column chromatographed on silica gel using a mixture of hexane and diethyl ether (1:1) as an eluent to give 30 mg (60% yield) of **20**. Mp 192–193 °C; $[\alpha]^{22}_{D}=+125°$ (c 0.007, MeOH); ^{1}H NMR δ 8.68 (s, 1H), 8.63 (s, 1H), 8.45 (s, 1H), 8.23 (s, 1H, N=CH), 8.17 (d, J=8.4 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.10 (s, 2H), 6.02 (d, J=8 Hz, 1H), 5.51 (t, J=9.6 Hz, 1H), 5.19 (t, J=9.6 Hz, 1H), 4.40 (dd, J=12, 4.4 Hz, 1H), 4.16 (dd, J=12, 2 Hz, 1H), 4.02 (m, 1H), 3.61 (dd, J=9.6, 8.4 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.89 (s, 3H); ^{13}C NMR δ 184.3, 184.2, 170.6, 169.8, 169.5, 168.6, 163.9, 140.0, 139.9, 136.3, 136.1, 134.5, 132.3, 130.8, 129.4, 129.2, 128.9, 128.5, 127.3, 92.9, 73.0 (2 C), 72.8, 67.9, 61.7, 20.7, 20.6, 20.5, 20.4. HRMS calcd for $C_{29}H_{28}NO_{11}$ (M+H) 566.1657, found 566.1430.

4.1.13. *N*-[(1,4-Dioxo-1,4-dihydroanthracenyl)methyl]-2-amino-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (21). To a solution of 25 mg (44 μmol) of imine **20** in 0.1 mL of acetic acid and 1 mL of methanol under argon, was added 11 mg (0.17 mmol) of sodium cyanoborohydride. The solution was stirred at 25 °C for 3 h, diluted with water, and extracted twice with dichloromethane. The combined organic layers were washed with brine, dried (MgSO$_4$), concentrated, and column chromatographed on silica gel using a mixture of hexane and ethyl acetate (1:1) as an eluent to give 14 mg (55% yield) of amine **21**. Mp 120 °C (dec.); $[\alpha]^{22}_{D}=+175°$ (c 0.004, MeOH); ^{1}H NMR δ 8.54 (s, 1H), 8.52 (s, 1H), 7.99 (d, J=8 Hz, 1H), 7.89 (s, 1H), 7.59 (d, J=8 Hz, 1H), 7.05 (s, 2H), 5.69 (d, J=8.8 Hz, 1H), 5.06 (t, J=9.6 Hz, 1H), 4.31 (dd, J=12.4, 4 Hz, 1H), 4.13 (m, 1H), 4.10 (d, J=14.4 Hz, 1H, CH$_2$N), 4.04 (d, J=14.4 Hz, 1H, CH$_2$N), 3.83 (m, 1H), 3.00 (t, J=8.8 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H); ^{13}C NMR δ 184.6, 184.5, 170.8, 170.5, 169.5, 169.0, 141.9, 139.9, 139.8, 134.7, 134.0, 130.3, 130.0, 129.2, 128.5, 128.4, 128.3, 128.2, 94.8, 73.8, 72.4, 68.1, 61.6, 60.3, 51.7, 21.0, 20.8, 20.6, 20.5. HRMS calcd for $C_{29}H_{30}NO_{11}$ (M+H) 568.1819, found 568.1831.

To a solution of 5.0 mg (8.8 μmol) of amine **21** in 1 mL of methanol, was added 35 μL (0.14 mmol) of HCl (4 M in dioxane). The solution was stirred for 10 min. and concentrated to dryness to give 5.3 mg (100% yield) of hydrochloric salt **22**.

4.1.14. (1,4-Dioxo-1,4-dihydroanthracenyl)methyl di-*t*-butyl phosphate (24). A mixture of 0.10 g (0.33 mmol) of bromide **10** and 0.33 g (0.59 mmol) of silver di-*t*-butyl phosphate[12] in 15 mL of chloroform was reflux under argon for 6 h, filtered through Celite, concentrated, and column chromatographed on silica gel using a gradient mixture of hexane, ethyl acetate, and methanol as an eluent to give 68 mg (48% yield) of **24**. Mp 126–128 °C; ^{1}H NMR δ 8.61 (s, 2H), 8.07 (d, $J=8.6$ Hz, 1H), 8.05 (s, 1H), 7.71 (d, $J=8.6$ Hz, 1H), 7.08 (s, 2H), 5.22 (d, $J_{HP}=7.4$ Hz, 2H, OCH$_2$), 1.51 (s, 18H); ^{13}C NMR δ 184.8 (2C), 140.2 (2C), 138.9, 138.7, 134.9, 134.6, 130.6, 129.0 (2C), 128.8 (2C), 128.2, 83.1 (d, $J_{CP}=7.2$ Hz, 2C), 67.8 (d, $J_{CP}=5.7$ Hz, OCH$_2$), 30.1 (d, $J_{CP}=4.2$ Hz, 6C). Anal. Calcd For $C_{23}H_{27}O_6P\cdot 0.03H_2O$: C, 62.31; H, 6.46. Found: C, 62.49; 6,06.

4.1.15. Disodium (1,4-dioxo-1,4-dihydroanthracenyl)-methyl phosphate (23). A solution of 20 mg (47 μmol) of phosphate **24** and 0.12 mL (0.47 mmol) of 4 M HCl (in 1,4-dioxane) in 1 mL of 1,4-dioxane was stirred at 25 °C for 1 h, 78 mg (0.93 mmol) of NaHCO$_3$ was added, and the mixture was concentrated to dryness. To the solids, 2 mL of ethanol was added, and resulting mixture was stirred for 5 min, filtered, and the filtrate was concentrated to give 14 mg (84% yield) of **23**. ^{1}H NMR (D$_2$O) δ 8.63 (s, 1H), 8.57 (s, 1H), 8.25 (d, $J=10$ Hz, 1H), 8.19 (s, 1H), 7.78 (d, $J=10$ Hz, 1H), 7.16 (s, 2H), 4.92 (d, $J_{HP}=6.8$ Hz, 2H, CH$_2$P); ^{13}C NMR (D$_2$O) δ 182.3 (2 C), 152.3, 143.9, 139.4, 139.3, 138.0, 129.4, 128.0, 127.9 (2 C), 127.5, 117.7 (2 C), 88.5.

4.2. Cell viability assay

Suspension cultures of murine L1210 lymphocytic leukemia or human HL-60 promyelocytic leukemia cells (ATCC, Manassas, VA) were maintained in RPMI 1640 medium supplemented with 8.25% fetal bovine calf serum (Atlanta Biologicals, Norcross, GA) and penicillin (100 IU/ml)-streptomycin (100 μg/ml), incubated at 37 °C in a humidified atmosphere containing 5% CO$_2$, and grown in 48-well Costar cell culture plates for 4 days in the presence or absence (control) of drugs.[4,14,15] The viability of drug-treated tumor cells was assessed from their mitochondrial ability to bioreduce the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) reagent (Promega, Madison, WI) in the presence of phenazine methosulfate (PMS; Sigma, St. Louis, MO) into a water-soluble formazan product which absorbs at 490 nm.[18] After 4 days in culture, cell samples (about 10^6/0.5 ml/well for controls) were further incubated at 37 °C for 3 h in the dark in the presence of 0.1 ml of MTS–PMS (2:0.1) reagent and their relative metabolic activity was estimated by recording the absorbance at 490 nm, using a Cambridge model 750 automatic microplate reader (Packard, Downers Grove, IL). Blank values for culture medium supplemented with MTS–PMS reagent in the absence of cells were substracted from the results.[4,15,18] Cell viability results were expressed as % of the net absorbance of MTS/formazan after bioreduction by vehicle-treated control tumor cells after 4 days in culture, and IC$_{50}$ values were calculated from linear regression of the slopes of the log-transformed concentration-dependent survival curves.

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References and notes

1. Daunomycin: (a) Di Marco, A.; Gaetani, M.; Orezzi, P.; Scarpinato, B. M.; Silvestrini, R.; Soldati, M.; Dasdia, T.; Valentini, L. *Nature* **1964**, *201*, 706–707. Mitoxantrone: (b) White, R. J.; Durr, F. E. *Invest. New Drugs* **1985**, *3*, 85–93.
2. For reviews, see: (a) Anthracycline Antibiotics, New Analogues, Methods of Delivery, and Mechanisms of Action. Priebe, W., Ed.; American Chemical Society Symposium Series 574; 1993. (b) Driscoll, J. S.; Hazard, G. F. Jr.; Wood, H. B.; Goldin, A. *Cancer Chemother. Rep.* **1974**, *2*, 1–362. (c) Huang, H.-S.; Chiou, J.-F.; Fong, Y.; Hou, C.-C.; Lu, Y.-C.; Wang, J.-Y.; Shih, J.-W.; Pan, Y.-R.; Lin, J.-J. *J. Med. Chem.* **2003**, *46*, 3300–3307. (d) Cairns, D.; Michalitsi, E.; Jenkins, T. C.; Mackay, S. P. *Bioorg. Med. Chem.* **2002**, *10*, 803–807. For recent reviews: (e) Krapcho, A. P.; Maresch, M. J.; Hacker, M. P.; Hazelhurst, L.; Menta, E.; Oliva, A.; Spinelli, S.; Beggiolin, G.; Giuliani, F. C.; Pezzoni, G.; Tognella, S. *Curr. Med. Chem.* **1995**, *2*, 803–824. (f) Lown, J. W. *Pharmacol. Ther.* **1993**, *60*, 185–214. (g) Cheng, C. C.; Zee-Cheng, R. K. Y. *Prog. Med. Chem.* **1983**, *20*, 83–118 and references cited therein. The toxicity of quinones: (h) Schultz, T. W.; Sinks, G. D.; Cronin, M. T. D. *Aquat. Toxicol.* **1997**, *39*, 267–278.
3. (a) Bedworth, P. V.; Perry, J. W.; Marder, S. R. *Chem. Commun.* **1997**, 1353–1354. (b) Gready, J. E.; Hata, K.; Sternhell, S.; Tansey, C. W. *Aust. J. Chem.* **1990**, *43*, 593–600. (c) Martin, N.; Segura, J.; Seoane, C.; de la Cruz, P.; Langa, F.; Orti, E.; Viruela, P. M.; Viruela, R. *J. Org. Chem.* **1995**, *60*, 4077–4084. (d) Barranco, E.; Martin, N.; Segura, J. L.; Seoane, C.; de la Cruz, P.; Langa, F.; Gonzalez, A.; Pingarron, J. M. *Tetrahedron* **1993**, *49*, 4881–4892. (e) Anastasia, M.; Allevi, P.; Bettini, C.; Fiecchi, A.; Sanvito, A. M. *Synthesis* **1990**, 1083–1084. (f) Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458–6460. (g) Etienne, A.; Lepage, Y. *Academie des Sciences Séance* **1955**, 1233–1235. (h) Deschamps, J.; Cohen, A. *Academie des Sciences Séance* **1962**, 4048–4050.
4. Perchellet, E. M.; Magill, M. J.; Huang, X.; Dalke, D. M.; Hua, D. H.; Perchellet, J.-P. *Anti-Cancer Drugs* **2000**, *11*, 339–352.

5. (a) Pfister, J.; Schiessl, M.; Nachtrab, R. Eur Pat Appl EP 90-119283, 1991.(b) Sartori, G.; Bigi, F.; Tao, X.; Porta, C.; Maggi, R.; Predieri, G.; Lanfranchi, M.; Pellinghelli, M. A. *J. Org. Chem.* **1995**, *60*, 6588–6591. (c) Bansho, Y.; Suzuki, S.; Saito, I. *Tokyo Kogyo Shikensho Hokoku* **1961**, *56*, 158–164.
6. (a) Chu, K.-Y.; Griffiths, J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1083–1087. (b) Kutyrev, A. A. *Tetrahedron* **1991**, *47*, 8043–8065.
7. Sasson, Y.; Zappi, G. D.; Neumann, R. *J. Org. Chem.* **1986**, *51*, 2880–2883.
8. Chaintreau, A.; Adrian, G.; Couturier, D. *Synth. Commun.* **1981**, *11*, 669–672.
9. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
10. (a) Roeper, H.; Heyns, K.; Roeper, S.; Meyer, B. *Liebigs Ana. der. Chem.* **1982**, *4*, 780–793. (b) Kim, T. Y.; Davidson, E. A. *J. Org. Chem.* **1963**, *28*, 2475–2476. (c) Adam, M. J.; Hall, L. D. *Can. J. Chem.* **1982**, *60*, 2229–2237.
11. (a) Dasgupta, A.; Schlette, E. *J. Clin. Lab. Anal.* **2001**, *15*, 244–250. (b) Cirla, A.; Mann, J. *Nat. Prod. Rep.* **2003**, *20*, 558–564.
12. Bonsen, P. P. M.; De Haas, G. H. *Chem. Phys. Lipids* **1967**, *1*, 100–109.
13. Perchellet, E. M.; Magill, M. J.; Huang, X.; Brantis, C. E.; Hua, D. H.; Perchellet, J.-P. *Anti-cancer Drugs* **1999**, *10*, 749–766.
14. Wu, M.; Wang, B.; Perchellet, E. M.; Sperfslage, B. J.; Stephany, H. A.; Hua, D. H.; Perchellet, J. P. *Anti-Cancer Drugs* **2001**, *12*, 807–819.
15. Perchellet, E. M.; Wang, Y.; Weber, R. L.; Sperfslage, B. J.; Lou, K.; Crossland, J.; Hua, D. H.; Perchellet, J. P. *Biochem. Pharmacol.* **2004**, *67*, 523–537.
16. Wang, Y.; Ward, M. M.; Perchellet, E. M.; Lou, K.; Crossland, J.; Hua, D. H.; Perchellet, J. P. 226th American Chemical Society National Meeting, Sept 7–11, 2003; New York, NY: ACS Division of Medicinal Chemistry, Abstract 272.
17. Hua, D. H.; Tamura, M.; Huang, X.; Stephany, H.; Helfrich, B. A.; Perchellet, E. M.; Sperfslage, B. J.; Perchellet, J.-P.; Jiang, S.; Kyle, D. E.; Chiang, P. K. *J. Org. Chem.* **2002**, *67*, 2907–2912.
18. Cory, A. H.; Owen, J. C.; Barltrop, J. A.; Cory, J. G. *Cancer Commun.* **1991**, *3*, 207–212.
19. Lu, Y.; Low, P. S. *Adv. Drug Deliv. Rev.* **2002**, *54*, 675–693.
20. Murdock, K. C.; Child, R. G.; Fabio, P. F.; Angier, R. V. *J. Med. Chem.* **1979**, *22*, 1024–1030.
21. Gready, J. E.; Hata, K.; Sternhell, S.; Tansey, C. W. *Aust. J. Chem.* **1990**, *43*, 593–600.

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Tetrahedron

Extension of β-chloroenals to ethyl 5-chloro-2,4-pentadienoates using Wadsworth–Emmons reactions: subsequent conversions to 5-aryl-5-chloro-2,4-pentadienoic acids and 5-aryl-2-penten-4-ynoic acids

Stuart C. Clough,* John T. Gupton, David R. Driscoll, Katherine A. Griffin, Alisa M. Hewitt, Matthew S. Hudson, S. Adepeju Ligali, Seann P. Mulcahy, Matthew N. Roberts, Robert B. Miller, Tsegahiwot T. Belachew, Ivanka D. Kamenova, René P. F. Kanters and Bradley K. Norwood

Department of Chemistry, University of Richmond, VA 23173, USA

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Abstract—Convenient routes from (*Z*)-3-aryl-3-chloroenals to (2*E*,4*Z*)-5-aryl-5-chloro-2,4-pentadienoates and (2*E*)-5-aryl-2-penten-4-ynoates are described. The stereochemical assignments are based on NMR spectral data.

1. Introduction

Vinamidinium salts, chloropropenium salts, and β-chloroenals have served effectively as three carbon synthons[1] in the synthesis of a wide variety of heterocyclic systems including pyrroles,[2] pyrazoles,[3] pyrimidines,[4] and pyridines.[5] This resulting chemistry has been successfully applied to the synthesis of a number of natural products including Ningalin B[6] and Lukianol A[7] as well as compounds of pharmaceutical interest.[8] This paper explores the extension of the three carbon β-chloroenal synthons to analogous five carbon synthons.

Over the years there has been interest in polyenes and enynes as a consequence of the physiological behavior exhibited by representatives of these systems.[9–15] They have also been shown in many cases to serve as effective synthons in the construction of a wide variety of interesting molecules.[16–19] Welker has recently reported transition metal-mediated Diels–Alder reactions involving the zinc-mediated hydrocobaltation of enynes.[20] As a result, a number of synthetic approaches to the synthesis of conjugated dienes and enynes have been reported. For example, Wiley described the stereochemistry of several of these unsaturated systems including 3-methyl-5-arylpent-2-en-4-ynoic acids.[21] A highly stereoselective method for the synthesis of (*Z*)-2-en-4-ynoic acid derivatives involving cross coupling of propiolic acid derivatives with terminal alkynes in the presence of a palladium (0) catalyst has been describe by Lu, Huang, and Ma.[22]

2. Results and discussion

We report here convenient syntheses of (2*E*,4*Z*)-5-aryl-5-chloro-2,4-pentadienoic acid derivatives and (*E*)-5-aryl-2-penten-4-ynoic acids that were discovered in the course of our exploration of the chemistry of 5-aryl-5-halo-2,4-pentadienoates. We have found that the Wadsworth–Emmons[23] reactions with triethyl phosphonoacetate (TEPA) and (*Z*)-3-aryl-3-chloropropenals (**1a–f**),[24] using procedures patterned after those reported by Villieras and Rambaud,[25] yield alkyl (2*E*,4*Z*)-5-aryl-5-halo-2,4-pentadienoates (**2a–f**) with a high degree of stereoselectivity (Scheme 1) The stereochemistry of the β-chloroenals has been well established as the (*Z*) isomer in all cases,[10] and the stereochemistry is unchanged in the course of the reaction. The stereochemistry of the Wadsworth–Emmons product is shown to be (2*E*,4*Z*) based on the coupling constants observed (see Table 1) and NOESY experiments which indicated the proton at the 2′-position on the aromatic ring and the vinyl hydrogen at C-3 were in close proximity.

Hydrolysis of the esters under basic conditions (room temperature with 1.1 equiv of aqueous sodium hydroxide)

Keywords: Chloroenals; Chlorodienoates; Enynoic acids.

* Corresponding author. Tel.: +1 804 289-8247: fax: +1 804 287 1897; e-mail: sclough@richmond.edu

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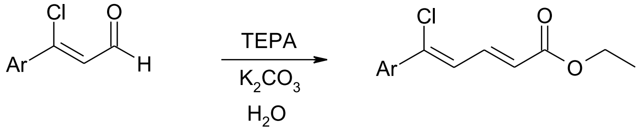


1 a-f **2 a-f**

a Ar = phenyl

b. Ar = p-methylphenyl

c. Ar = p-methoxyphenyl

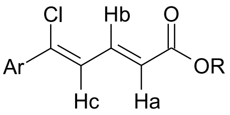
d. Ar = p-chlorophenyl

e. Ar = p-fluorophenyl

f. Ar = 3’4’-methylenedioxyphenyl

Scheme 1.

Table 1. Coupling constants of vinyl hydrogens (Hz)



2 R = ethyl
3 R = H

Compound	Ar	J_{ab} (Hz)	J_{bc} (Hz)	% Yield
2a	Phenyl	15.5	10.9	86
2b	*p*-Methylphenyl	15.5	10.7	87
2c	*p*-Methoxyphenyl	15.3	11.3	83
2d	*p*-Chlorophenyl	15.6	10.8	91
2e	*p*-Fluorophenyl	15.4	10.7	74
2f	3′,4′-Methylenedioxyphenyl	15.5	10.9	96
3a	Phenyl	15.9	10.9	57
3b	*p*-Tolyl	15.5	10.9	60
3c	*p*-Methoxy	15.5	10.9	63
3d	*p*-Chlorophenyl	15.4	10.9	52
3e	*p*-Fluoro	15.2	10.8	76

followed by protonation provides a route to the (2*E*,4*Z*)-5-aryl-5-halo-2,4-pentadienoic acids (**3a**–**e**) with no change in the stereochemistry of the conjugated system (Scheme 2).The stereochemical assignments were clearly indicated by the coupling constants (Table 1) which are very much in accord with coupling constants reported for similar systems[26] and from NOESY experiments.

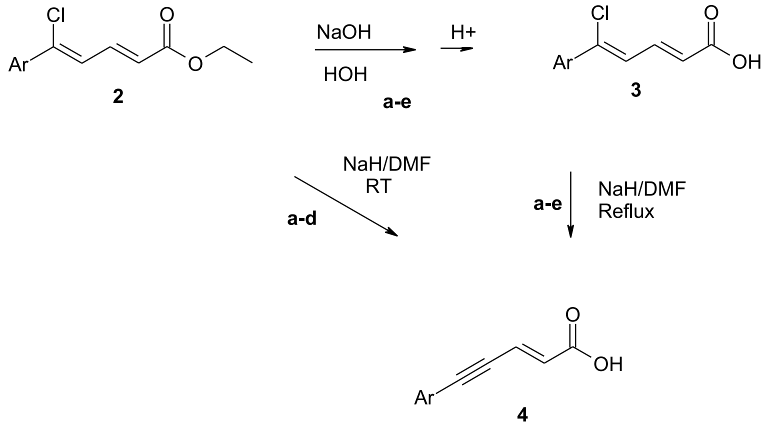
When harsher hydrolysis conditions were employed we observed some dehydrohalogenation occurring resulting in the formation of small amounts of 5-aryl-2-penten-4-ynoic acids. This suggested to us that perhaps use of a stronger base might provide a clean route to these compounds.

Treatment of the halo esters **2a**–**e** with 6 equiv of sodium hydride in DMF at room temperature followed by protonation resulted in a smooth and rapid dehydrohalogenation and dealkylation to (*E*)-5-aryl-2-penten-4-ynoic acid (**4**) in every case explored with the exception of the 5-(*p*-fluorophenyl)-derivative which yielded clean **3e** (Scheme 2). The geometry was again clear from the coupling constants of the vinyl hydrogens (Table 2).

This suggested to us that in aqueous base at room temperature the hydroxide was acting as a nucleophile to saponify the ester but was not a strong enough base to promote the dehydrohalogenation of the resulting carboxylates. Sodium hydride in DMF was a strong enough base such that the dehydrohalogenation reactions of **2a**–**d** proceeded rapidly at room temperature to give the enynoic esters, which then underwent a subsequent dealkylation to form the sodium salt of the carboxylic acid in every case except the *p*-fluorophenyl derivative (**2e**). In this case formation of the carboxylate anion **3e** is apparently faster than dehydrohalogenation. Dehydrohalogenation of the carboxylate anion is more difficult, and thus the enynoic acid is not formed under such reaction conditions. Although the chlorodienoic acids do not dehydrohalogenate when treated with NaH in DMF at room temperature, the enynoic acids (**4a**–**e**) are formed when the chlorodienoic acids (**3a**–**e**) are refluxed with sodium hydride in DMF.

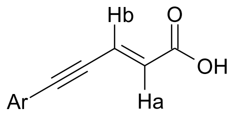
3. Conclusions

We have shown that the versatile β-chloroenals can be converted in high yield using Wadsworth–Emmons chemistry to ethyl 5-aryl-5-chloro-2,4-pentadieoates with a high degree of stereochemical control. These esters can subsequently be converted to the corresponding 5-aryl-5-chlorodienoic acids with aqueous base under mild conditions. Furthermore, they can be dehydrohalogenated and dealkylated under remarkably mild conditions to form



Scheme 2.

Table 2. Coupling constants of vinyl hydrogens (Hz)



4

Compound	Ar	J_{ab} (Hz)	% Yield
4a	Phenyl	15.9	87
4b	*p*-Methylphenyl	15.9	87
4c	*p*-Methoxyphenyl	15.8	98
4d	*p*-Chlorophenyl	15.4	82
4e	*p*-Fluorophenyl	16.1	67

5-aryl-2-penten-4-ynoic acids, thus providing convenient new routes to these important classes of compounds.

4. Experimental

4.1. General

The 300 MHz NMR data was collected with a GE Omega 300 MHz instrument. The 500 MHz NMR data was collected on a Bruker 500. The IR data was collected using a Nicolet Avatar fitted with a HATR accessory. The low resolution mass spectral data was obtained using a Shimadzu Model QP 5050 GC–MS equipped with a direct insert sampling device. HRMS data was provided by the Nebraska Center for Mass Spectrometry at the University of Nebraska-Lincoln. The purity of the esters was estimated at better than 95% based on gas chromatographic analysis. The purity of the acids was estimated at better than 95% based on the ^{13}C NMR data. Solvents and reagents were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific).

4.1.1. Ethyl (2*E*,4*Z*)-5-chloro-5-phenyl-2,4-pentadienoate (2a). A mixture of triethyl phosphonoacetate (5.93 g, 0.027 mol), (*Z*)-3-chloro-3-phenyl-2-propenal **1a** (3.69 g, 0.022 mol), potassium carbonate (8.0 g, 0.058 mol), and 6 mL of water was stirred at room temperature for 46 h. Water (10 mL) was added and the mixture was washed twice with ethyl acetate (25 mL). After drying ($MgSO_4$), the organic solvent was evaporated using a rotary evaporator yielding 4.46 g (86%) of **2a** as an oil. A Kugelrohr distillation provided an analytical sample: bp 140–145 °C at 0.25 mm Hg; mp 22–26 °C; IR (HATR) 2975, 1703, and 1137 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 ($J=7.2$ Hz, 3), 4.23 (q, $J=7.2$ Hz, 2), 6.07 (d, $J=15.5$ Hz, 1), 6.84 (d, $J=10.9$ Hz, 1), and 7.83 ppm (dd, $J=15.5$, 10.9 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 60.4, 123.2, 124.2, 126.7, 128.5, 129.9, 136.8, 139.4, 140.3, and 166.4 ppm; MS *m*/*z* 238 (4), 236 (12), 203 (11), 201 (74), 191 (19), 173 (100), 155 (14), 145 (7), 127 (52), 117 (20), and 102 (15); HRMS (EI, M$+$) calcd for $C_{13}H_{13}O_2Cl$ 236.0604, found 236.0607.

4.1.2. Ethyl (2*E*,4*Z*)-5-chloro-5-(*p*-methylphenyl)-2,4-pentadienoate (2b). This compound was prepared from **1b** in 87% yield using the procedure described above for the synthesis of **2a**: bp 155–160 °C at 0.25 mm Hg; mp 41–43 °C; IR (HATR) 2974, 1697, 1615, 1130 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, $J=7.2$ Hz, 3), 2.40 (s, 3), 4.27 (q, $J=7.2$ Hz, 2), 6.09 (d, $J=15.5$ Hz, 1), 6.85 (d, $J=10.7$ Hz, 1), 7.22 (d, $J=7.2$ Hz, 2), 7.60 (d, $J=7.2$ Hz, 2), and 7.86 ppm (dd, $J=15.5$, 10.7 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 21.3, 60.5, 122.4, 123.6, 126.7, 129.3, 134.1, 139.7, 140.3, 140.6, and 166.7; MS *m*/*z* 250 (13), 252 (4), 215 (100), 205 (15), 187 (87), 141 (33), 119 (50). HRMS (EI, M$+$) calcd for $C_{14}H_{15}O_2Cl$ 250.0761, found 250.0764.

4.1.3. Ethyl (2*E*,4*Z*)-5-chloro-5-(*p*-methoxyphenyl)-2,4-pentadienoate (2c). This compound was prepared from **1c** in 84% yield using the procedure described above for the synthesis of **2a**: bp 205 °C at 2.25 mm Hg; mp 52–55 °C; IR (HATR) 2983, 2839, and 1701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, $J=7.2$ Hz, 3), 3.87 (s,3), 4.28 (q, $J=7.2$ Hz, 2), 6.08 (d, $J=15.3$ Hz, 1), 6.80 (d, $J=11.3$ Hz, 1), 6.93 (d, $J=8.2$ Hz, 2), 7.66 (d, $J=8.2$ Hz, 2), and 7.85 ppm (dd, $J=15.3$, 11.3 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2, 55.4, 60.5, 113.9, 121.4, 123.1, 128.2, 129.4, 139.9, 140.3, 161.0, and 166.8 ppm; MS *m*/*z* 266 (8), 232 (15), 231 (100), 203 (63), 158 (24), 135 (85), and 115 (31); HRMS (EI, M$+$) calcd for $C_{14}H_{15}O_3Cl$ 266.0710, found 266.0704.

4.1.4. Ethyl (2*E*,4*Z*)-5-chloro-5-(*p*-chlorophenyl)-2,4-pentadienoate (2d). This compound was prepared from **1d** in 92% yield using the procedure described above for the synthesis of **2a**: bp 160–165 °C at 0.45 mm Hg; mp 65–68 °C; IR (HATR) 3060, 2975, 2897, and 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3), 4.28 (q, $J=7.1$ Hz, 2), 6.13 (d, $J=15.6$ Hz, 1), 6.86 (d, $J=10.8$ Hz, 1), 7.39 (d, $J=7.2$ Hz, 2), 7.64 (d, $J=7.2$ Hz, 2), and 7.82 ppm (dd, $J=15.6$, 10.8 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 60.6, 123.6, 124.6, 128.0, 128.8, 135.0, 136.0, 139.0, 139.2, and 166.5 ppm; MS *m*/*z* 270 (10), 235 (79), 225 (18), 207 (100), 189 (11), 162 (32), 139 (19), 126 (26), and 115 (11); HRMS (EI, M$+$) calcd for $C_{13}H_{12}O_2Cl_2$ 270.0214, found 270.0214.

4.1.5. Ethyl (2*E*,4*Z*)-5-chloro-5-(*p*-fluorophenyl)-2,4-pentadienoate (2e). This compound was prepared from **1e** in 74% yield using the procedure described above for the synthesis of **2a**: bp 139 °C at 1.25 mm Hg; IR (HATR) 2981, 1708, 1598 and 1235 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, $J=7.2$ Hz, 3), 4.27 (q, $J=7.2$ Hz, 2), 6.11 (d, $J=15.4$ Hz, 1),6.81 (d, $J=10.7$ Hz, 1), 7.10 (m, 3), 7.68 (m, 2), and 7.82 ppm (dd, $J=15.4$, 10.7 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 60.6, 115.6 (d, $J=22.0$ Hz), 123.2 (d, $J=0.7$ Hz), 124.2, 128.7 (d, $J=8.2$ Hz), 133.2 (d, $J=3.5$ Hz), 139.2, 139.4, 163.6 (d, $J=251.5$ Hz), and 166.6 ppm; MS *m*/*z* 256 (4), 254 (12), 219 (79), 209 (19), 191 (100), 173 (13), 146 (46), 135 (16), 123 (29), 99 (5), 87 (7), and 73 (29); HRMS (EI, M$+$) calcd for $C_{13}H_{12}O_2ClF$ 254.0510, found 254.0511.

4.1.6. Ethyl (2*E*,4*Z*)-5-chloro-5-(3′,4′-methylenedioxyphenyl)-2,4-pentadienoate (2f). This compound was prepared from **1f** in 96% yield using the procedure described above for the synthesis of **2a**: bp 164 °C at 0.8 mm Hg; IR (HATR) 2899, 1706, 1614, and 1486 cm^{-1}; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.1 Hz, 3), 4.26 (q, *J*=7.2 Hz, 2), 6.03 (s, 2), 6.07 (dd, *J*=0.8, 15.5 Hz, 1), 6.75 (dd, *J*=0.8, 10.9 Hz, 1), 6.83 (d, *J*=8.3 Hz, 1), 7.16 (d, *J*=1.9 Hz, 1), 7.25 (dd, *J*=1.9, 8.3 Hz, 1), and 7.82 ppm (dd, *J*=15.5, 10.9 Hz, 1); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 60.5, 101.7, 107.0, 108.2, 121.6, 122.1, 123.4, 131.2, 139.7, 1390.0, 148.1, 149.2, and 166.7 ppm; MS *m/z* 282 (6), 280(18), 245 (100), 235 (15), 217 (59), 207 (17), 172 (20), 149 (74), 131 (6), 117 (17), and 85 (14); HRMS (EI, M+) calcd for $C_{14}H_{13}O_4Cl$ 280.0502, found 280.0494.

4.1.7. (2*E*,4*Z*)-5-Chloro-5-phenyl-2,4-pentadienoic acid (3a). A solution of ethyl (2*E*,4*Z*)-5-chloro-5-phenyl-2,4-pentadienoate **2a** (0.5 g, 2.12 mmol) in a 1:1 mixture of H_2O/EtOH (100 mL) was treated with NaOH (0.093 mL, 2.23 mmol) and stirred at room temperature. After 48 h, the reaction mixture was made slightly acidic with 5% HCl (10 mL), extracted into ethyl acetate (2×75 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was recrystallized in chloroform (10 mL) and filtered to give 0.25 g (57%) of **3a** as a yellow powder: mp 161–163 °C; IR (HATR) 3200–2500 (broad), 3390, 2350, 2334, 1678, and 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (d, *J*=15.9 Hz, 1), 7.29 (d, *J*=10.9 Hz, 1), 7.49 (m, 3), and 7.82 ppm (m, 3); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 123.2, 124.4, 126.2, 128.2, 129.5, 136.2, 138.6, 138.7, and 166.1 ppm; MS *m/z* 208 (39), 191 (30), 173 (100), 162 (31), 127 (80), 115 (57), 105 (60), 86 (21), and 77 (64); HRMS (EI, M+) calcd for $C_{11}H_9ClO_2$ 208.0291,, found 208.0288.

4.1.8. (2*E*,4*Z*)-5-Chloro-5-(*p*-methylphenyl)-2,4-pentadienoic acid (3b). This compound was prepared from **2b** in 60% yield using the procedure described above for the synthesis of **3a**: mp 177–180 °C; IR (HATR) 3479, 3390, 3025, 2904, 1619, and 1541 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.414 (s, 3H), (6.110 (d, *J*=15.6 Hz, 1), 6.896 (d, 1H, *J*=10.7 Hz, 1), 7.236 (d, 2H), 7.622 (d, 2H), 7.958 (dd,, *J*=15.6, 10.7 Hz, 1); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 21.2, 123.6, 125.3, 127.5, 130.2, 134.9, 140.2, 140.3, 141.3, and 167.5 ppm; MS *m/z* 222(29), 187 (100), 141 (73), 131 (37), 119 (77), 115 (75), 91 (38) and 10 (50); HRMS (EI, M+) calcd for $C_{12}H_{11}ClO_2$ 222.0448,, found 222.0446.

4.1.9. (2*E*,4*Z*)-5-Chloro-5-(*p*-methoxyphenyl)-2,4-pentadienoic acid (3c). This compound was prepared from **2c** in 63% yield using the procedure described above for the synthesis of **3a**. The crude solid was recrystallized from hexane: mp 163–165 °C; IR (HATR) 2951 (broad), 2838, 2528, 1669, 1588 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.09 (d, *J*=15.5 Hz, 1), 6.755 (d, *J*=10.9 Hz, 1), 6.86 (d, 2H), 7.58 (d, 2H), 7.87 (dd, *J*=15.3, 15.4 Hz, 1H); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 55.9, 115.0, 122.5, 124.7, 129.1, 129.8, 140.1, 140.4, 162.3, and 167.5 ppm; MS *m/z* 238 (16), 203 (100), 158 (27), 135 (67), 115 (30), 89 (14), 77 (11), and 63 (19); HRMS (EI, M+) calcd for $C_{12}H_{11}ClO_3$ 238.0397,, found 238.0404.

4.1.10. (2*E*,4*Z*)-5-Chloro-5-(*p*-chlorophenyl)-2,4-pentandienoic acid (3d). This compound was prepared from **2d** in 52% yield using the procedure described above for the synthesis of **3a**: mp 218–222 °C; IR (HATR) 3321–1947 (broad), 1674, 1600, 1577, and 1491 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 1), 6.11 (d, *J*=15.4 Hz, 1), 6.90 (d, *J*=10.9 Hz, 1), 7.24 (d, *J*=8.0 Hz, 2), 7.62 (d, *J*=8.0 Hz, 2) and 7.96 ppm (dd, *J*=15.4, 10.9 Hz, 1); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 123.9, 125.0, 127.3, 128.4, 133.0, 135.0, 137.3, 138.5, and 166.0 ppm; MS *m/z* 242 (13), 207 (100), 196 (6), 189 (7), 162 (20), 139 (18), and 115 (28); HRMS (EI, M+) calcd for $C_{11}H_8O_2Cl_2$ 241.9901, found 241.9896.

4.1.11. (2*E*,4*Z*)-5-Chloro-5-(*p*-fluorophenyl)-2,4-pentadienoic acid (3e). This compound was prepared from **2e** in 76% yield using the procedure described above for the synthesis of **3a**: mp 223–225°; IR (HATR) 3370–2180 (broad), 1674, 1600, and 1425 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (s, 1), 6.14 (d, *J*=15.2 Hz, 1), 6.86 (d, *J*=10.8 Hz, 1), 7.13 (m, 2), 7.71 (m, 3), and 7.93 ppm (dd, *J*=10.8, 15.2 Hz, 1); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 115.4 (d, *J*=23.9 Hz), 124.5, 130.7, 132.3 (d, *J*=8.3 Hz), 134.1, 134.2, 165.6 (d, *J*=165.6 Hz), and 165.7 ppm; MS *m/z* 226 (18), 191(100), 173 (11), 145 (40), 135 (24), 123 (33), 95 (10), and 73 (23); HRMS (EI, M+) calcd for $C_{11}H_8O_2ClF$ 266.0197, found 266.0194.

4.1.12. (*E*)-5-Phenyl-pent-2-en-4-ynoic acid (4a) from 2a. A slurry of sodium hydride (0.63 g, 0.026 mol) in dry *N*,*N*-dimethylformamide (30 mL) was added to ethyl (2*E*,4*Z*)-5-chloro-5-phenyl-2,4-pentadienoate (1.0 g, 0.00425 mol). The resulting slurry was stirred at room temperature for 72 h. Water (200 mL) was carefully added followed by 50 mL of 18% HCl. The aqueous layer was extracted three times with 30 mL of ethyl acetate. The organic layers were combined and washed twice with water (25 mL), and dried ($MgSO_4$). Removal of solvent using a rotary evaporator afforded 0.64 g (87%) of a crude solid. Recrystallization from hexane yielded an analytical sample of (*E*)-5-phenyl-pent-2-en-4-ynoic acid: mp 129–132°; IR (HATR) 3700–2200 (broad), 2197, 1665, 1614, and 1414 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, *J*=15.9 Hz, 1), 7.11 (d, *J*=15.9 Hz, 1), 7.40 (m, 3), and 7.52 ppm (m, 2); ^{13}C NMR (125.8 MHz, acetone-d_6) δ86.7, 98.5, 123.0, 125.5, 129.6, 130.4, 131.5, 132.7, and 166.5 ppm; MS *m/z* 172 (100), 146 (20), 144 (13), 127 (30), 122 (24), 115 (64), 105 (68), 97 (17), and 77 (75); HRMS (EI, M+) calcd for $C_{11}H_8O_2$ 172.0524, found 172.0522.

4.1.13. (*E*)-5-(*p*-Methylphenyl)-2-penten-4-ynoic acid (4b) from 2b. This compound was prepared from **2b** in 87% yield using the procedure described above for the synthesis of **4a**: mp 173–179 °C; IR (HATR) 3700–2200 (broad), 2182, 1680, 1593, and 1424 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4 (s, 3), 3.72 (s, 1), 6.31 (d, *J*=15.9 Hz, 1), 7.09 (d, *J*=15.9 Hz, 1), 7.19 (d, *J*=7.5 Hz, 2), and 7.41 ppm (d, *J*=7.5 Hz, 2); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 21.5, 86.5, 92.9, 119.9, 125.8, 130.3, 131.0, 132.7, 140.8, and 166.5 ppm; MS *m/z* 187 (15), 186 (100), 171 (80), 157 (9), 139 (25), 129 (34), 115 (61), 90 (8), 75 (5), and 70(18); HRMS (EI, M+) calcd for $C_{12}H_{10}O_2$ 186.0677, found 186.0681.

4.1.14. (*E*)-5-(*p*-Methoxyphenyl)-2-penten-4-ynoic acid (4c) from 2c. This compound was prepared from **2c** in 98% yield using the procedure described above for the synthesis of **4a**: mp 164–165 °C; IR (HATR) 3200–2300 (broad), 2187, 1675, 1588, and 1414 cm^{-1}; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 3.86 (s, 3), 6.28 (d, $J=15.8$ Hz, 1), 6.90 (d, $J=9.1$ Hz, 2), 7.09 (d, $J=15.8$ Hz, 1), and 7.46 ppm (d, $J=9.1$ Hz, 2); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 55.9, 115.0, 122.5, 124.7, 129.1, 129.8, 140.1, 140.4, 162.3, and 167.6 ppm; MS *m/z* 202 (100), 187 (10), 185 (7), 159 (28), 136 (25), 131 (28), 113 (15), 103 (17), 77 (24), and 45 (89); HRMS (EI, M+) calcd for $C_{12}H_{10}O_3$ 202.0630, found 202.0630.

4.1.15. (*E*)-5-(*p*-Chlorophenyl)-pent-2-en-4-ynoic acid (4d) from 2d. This compound was prepared from **2d** in 82% yield using the procedure described above for the synthesis of **4a**: mp 196–201 °C; IR (HATR) 3400–2200 (broad), 2197, and 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (d, $J=15.4$ Hz, 1), 7.07 (d, $J=15.4$ Hz, 1), 7.36 (d, $J=8.7$ Hz, 2), and 7.45 ppm (d, $J=8.7$ Hz, 2); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 87.9, 97.0, 121.8, 125.2, 129.9, 132.0, 134.3, 136.0, and 166.4 ppm; MS *m/z* 208 (29), 206 (88), 189 (6), 171 (46), 160 (12), 149 (16), 136 (9), 126 (44) 115 (100), 99 (18), and 81 (20); HRMS (EI, M+) calcd for $C_{11}H_7O_2Cl$ 206.0129, found 206.0135.

4.1.16. (*E*)-5-(*p*-Fluorophenyl)-pent-2-en-4-ynoic acid (4e) from 2e. This compound was prepared from **2e** in 67% yield using the procedure described above for the synthesis of **4a**: mp 148–153 °C; IR (HATR) 2912, 2194, 1669, 1615, and 1588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, $J=16.5$ Hz, 1), 6.97 (d, $J=15.8$ Hz, 1), 7.24 (m, 3), and 7.62 ppm (m, 2); ^{13}C NMR (125.8 MHz, acetone-d_6) δ 85.8, 96.4, 115.9 (d, $J=22.4$ Hz), 118.5 (d, $J=3.4$ Hz), 124.4, 130.7, 134.2 (d, $J=8.8$ Hz), 163.1 (d, $J=250.6$ Hz), and 165.6 ppm; MS *m/z* 190 (100), 173 (10), 162 (18), 144 (38), 134 (53), 133 (100), 125 (44), and 99 (19); HRMS (EI, M+) calcd for $C_{11}H_7O_2F$ 190.0403, found 190.0427.

4.1.17. Dehydrohalogenation of 3 to form 4. A mixture resulting from adding a solution of the 5-aryl-5-chloro-2,4-pentadienoic acid (0.22 mmol) in 40 mL DMF to sodium hydride (0.90 mmol) was refluxed for 20 min. The reaction mixture was cooled to room temperature, diluted with water, made acidic with 10% HCl and extracted three times with 50 mL of ethyl acetate. The organic layer was then washed once with water and dried over $MgSO_4$. Removal of the solvent afforded the crude acid which was purified by recrystallization from hexane (**4a**, 88%; **4b**, 95%, **4c**, 54%; **4d**, 92%; **4e**, 93%).

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References and notes

1. Marson, C. M.; Giles, P. R. *Synthesis using Vilsmeier Reagents*; CRC: Boca Raton, FL, 1994; Chapter 2.
2. Gupton, J. T.; Krumpe, E. K.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, K. X.; Bruce, M. A.; Phong, V.; Vargas, M.; Kartik, M. K.; Hosein, K. N.; Jones, R. J.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075–5088.
3. Gupton, J. T.; Clough, S. C.; Miller, R. B.; Norwood, B. K.; Hickenboth, C. R.; Chertudi, I. B.; Cutro, S. R.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Sikorski, J. A. *Tetrahedron* **2002**, *58*, 5467–5474.
4. Gupton, J. T.; Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Vargas, M.; Hosein, K. N.; Sikorski, J. A. *Heterocycles* **1998**, *47*, 689–702.
5. Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Tarrant, J. G.; Bruno, S. M.; Vargas, M.; Hosein, K. N.; Gupton, J. T.; Sikorski, J. A. *Tetrahedron* **1995**, *51*(6), 1575–1584.
6. Gupton, J. T.; Clough, S. C.; Miller, R. B.; Lukens, J. R.; Henry, C. A.; Kanters, R. P. F.; Sikorski, J. A. *Tetrahedron* **2003**, *59*, 207–215.
7. Gupton, J. T.; Krumpe, E. K.; Burnham, B. S.; Webb, T. M.; Shuford, J. S.; Sikorski, J. A. *Tetrahedron* **1999**, *55*, 14515–14522.
8. Coverdale, H. A.; Hsung, R. P. *Chemtracts—Org. Chem.* **2003**, *16*, 238–248.
9. Jacobs, T. L.; Dankner, D.; Dankner, A. R. *J. Am. Chem. Soc.* **1958**, *80*, 864–866.
10. Prim, D.; Fuss, A.; Kirsch, G.; Silva, A. M. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1175–1180.
11. Trost, B. M.; Nanninga, T. N.; Chan, D. M. T. *Organometallics* **1982**, *1*, 1543.
12. Samuelsson, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 805.
13. Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *4*(11), 2587–2599.
14. Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 743.
15. Baeckstrom, P.; Jacobsson, U.; Norin, T.; Unelius, C. R. *Tetrahedron* **1988**, *44*, 2541–2548.
16. Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673–5676.
17. Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*(14), 2857–2870.
18. Wiley, R. H.; Crawford, T. H.; Staples, C. E. *J. Am. Chem. Soc.* **1962**, *27*, 1535–1539.
19. Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.*41**2000**, 5281–5286.
20. Pickin, K. A.; Kindy, J. M.; Day, C. S.; Welker, M. E. *J. Organomet. Chem.* **2003**, *681*(1–2), 120–133.
21. Wiley, R. H.; Staples, C. E. *J. Org. Chem.* **1963**, *28*, 3408–3412.
22. Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*(18), 2535–2538.
23. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
24. The 3-chloropropenals were easily prepared from commercially available acetophenones using standard methods: Liebscher, J.; Hartmann, H. *Synthesis* **1979**, 241.
25. Villieras, J.; Rambaud, M. *Synthesis* **1983**, 300–303.
26. For 1,3-butadiene $J_{trans}=16.8$ Hz, $J_{cis}=10.13$ Hz and $J_{2,3}=10.3$ Hz: Segre, A.; Zetta, L.; Di Corato, A. *J. Mol. Spectrosc.* **1969**, *32*, 296.

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Tetrahedron

The synthesis of ketolide antibiotic ABT-773 (cethromycin)

Daniel J. Plata,[a,*] M. Robert Leanna,[a,*] Michael Rasmussen,[a] Maureen A. McLaughlin,[a] Steven L. Condon,[a] Francis A. J. Kerdesky,[a] Steven A. King,[a] Matthew J. Peterson,[b] Eric J. Stoner[a] and Steven J. Wittenberger[a]

[a] *Global Pharmaceutical Research and Development, Abbott Laboratories, 1401 Sheridan Road, North Chicago, IL 60064-6285, USA*
[b] *Theravance, Inc., 901 Gateway Blvd, S. San Francisco, CA 94080, USA*

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Abstract—A practical and efficient synthesis of ketolide antibiotic cethromycin (ABT-773) (**1**) is described. An effective protection strategy allows high yielding, regioselective C6-O-alkylation and subsequent stereoselective modification of the erythromycin nucleus. ABT-773 was prepared in 10 steps from commercially available erythromycin A oxime.

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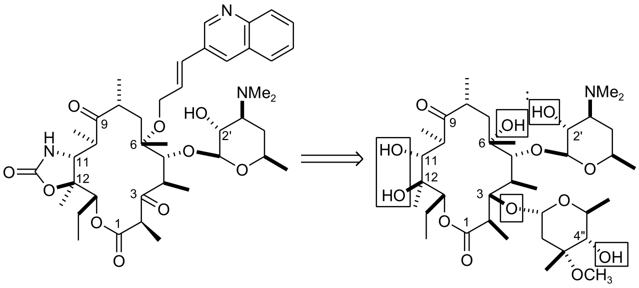
1. Introduction

Erythromycin A has been utilized as a safe and effective treatment for bacterial infections of the upper and lower respiratory tract for nearly half a century. However, erythromycin A undergoes acid-mediated degradation in the stomach, which results in diminished bioavailability and the formation of by-products that cause undesirable gastrointestinal side-effects.[1] The pursuit of semi-synthetic analogs of erythromycin A that reduce or eliminate these unwanted consequences while maintaining or enhancing anti-microbial activity led to the identification of macrolide antibiotics such as clarithromycin and azithromycin in the late 1980s.

More recently, research has focused upon the discovery of anti-microbials which possess activity toward macrolide-resistant pathogens.[2] In the 1990s, a new class of macrolide derivatives evolved, which overcome the resistance mechanisms of various bacterial organisms.[3] These compounds, known as ketolides, exhibit improved potency and longer post-antibiotic effects over their therapeutic precursors.[4] Structurally, the ketolides are most notably differentiated from the macrolide family by the exchange of the glycosidic cladinose moiety with a ketone function at C-3.

Structure–activity relationship studies have established that modification of the C-6, C-11 and C-12 carbinol centers (Scheme 1) have a profound effect on the activity of the agent.[5] With these key structural features recognized, a series of ketolides was prepared at Abbott, from which ABT-773 emerged as having superior potency against macrolide-resistant respiratory tract pathogens, while maintaining enhanced gastric stability and broad spectrum activity.[5c,6]



ABT-773, Cethromycin, **1**

Erythromycin A

Scheme 1. Retrosynthesis of ABT-773.

2. Hydroxyl protection strategy

After the discovery of ABT-773, studies were directed toward the development of an enabling synthetic route. The challenge inherent in the design and implementation of an efficient semi-synthetic route to ABT-773 centered upon the selective manipulation of the hydroxyl groups of the erythromycin nucleus. Specifically, the C-3 hydroxyl must be liberated and oxidized, the C-6 hydroxyl alkylated and the C-11,12 diol converted stereoselectively to a cyclic

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Keywords: Macrolides; ABT-773; Cethromycin.

* Corresponding authors. Tel.: +1 847 938 6602; fax: +1 847 938 2258; e-mail addresses: dan.j.plata@abbott.com; rob.r.leanna@abbott.com

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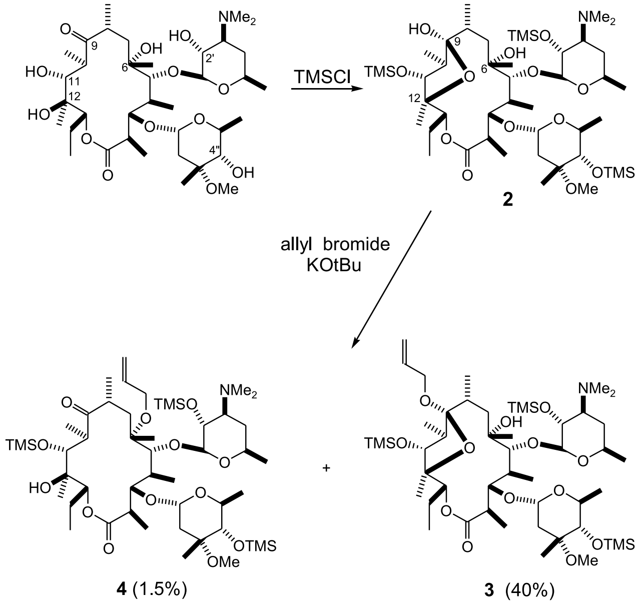
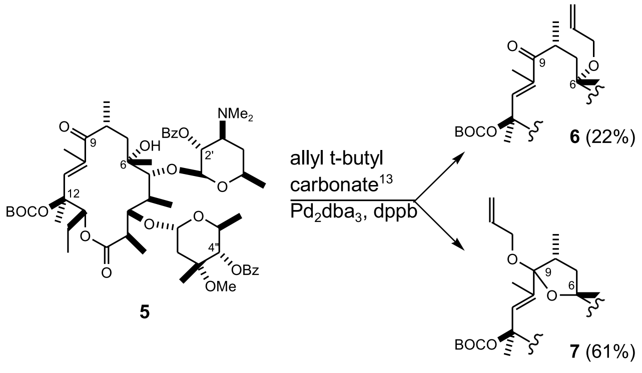
carbamate moiety. Furthermore, while it was desirable to minimize protection/deprotection sequences, it was clear that the reactive C-9 ketone and the C-2′ and C-4″ hydroxyls must be blocked in order to achieve these transformations (Scheme 1).

Selective chemical modification of the multiple alcohol functions of erythromycin A is complicated by the propensity of its conformationally constrained 14-membered ring to form intramolecular hemiketals with the electrophilic C-9 ketone.[7] Our initial, most direct routes to ABT-773 were hampered by this phenomenon. For example, as shown in Scheme 2, attempted silylation of the C-2′, C-4″ and C-11 hydroxyls of erythromycin A afforded a quantitative yield of tri-silylated 9,12-hemiketal **2**. Attempted alkylation of the C-6 hydroxyl of this molecule with allyl bromide resulted in the formation of a ∼25:1 mixture of C-9 and C-6 O-alkylation products **3** and **4**. In a second example (Scheme 3), a C-12-*O*-BOC-protected γ-hydroxy enone derivative (**5**) was treated under alkylating conditions (*vide infra*) to afford an intractable mixture of C-6 and C-9 ethers, **6** and **7**.



Scheme 2. Attempted silylation/alkylation of erythromycin A.



Scheme 3. Attempted alkylation of C-6 hydroxyl.

Strategically, early-stage alkylation of the C-6 hydroxyl would effectively circumvent the formation of deleterious hemiketal by-products throughout the synthesis.[8] However, as illustrated above, selective O-alkylation of the C-6 tertiary hydroxyl group is impossible without deactivation of the electrophilic C-9 ketone and proper protection of the more reactive hydroxyl functions.[9] Therefore, the identification of a strategic blocking regime for the C-9 ketone and the C-2′ and C-4″ sugar hydroxyls was paramount to the evolution of an efficient synthetic route to ABT-773.

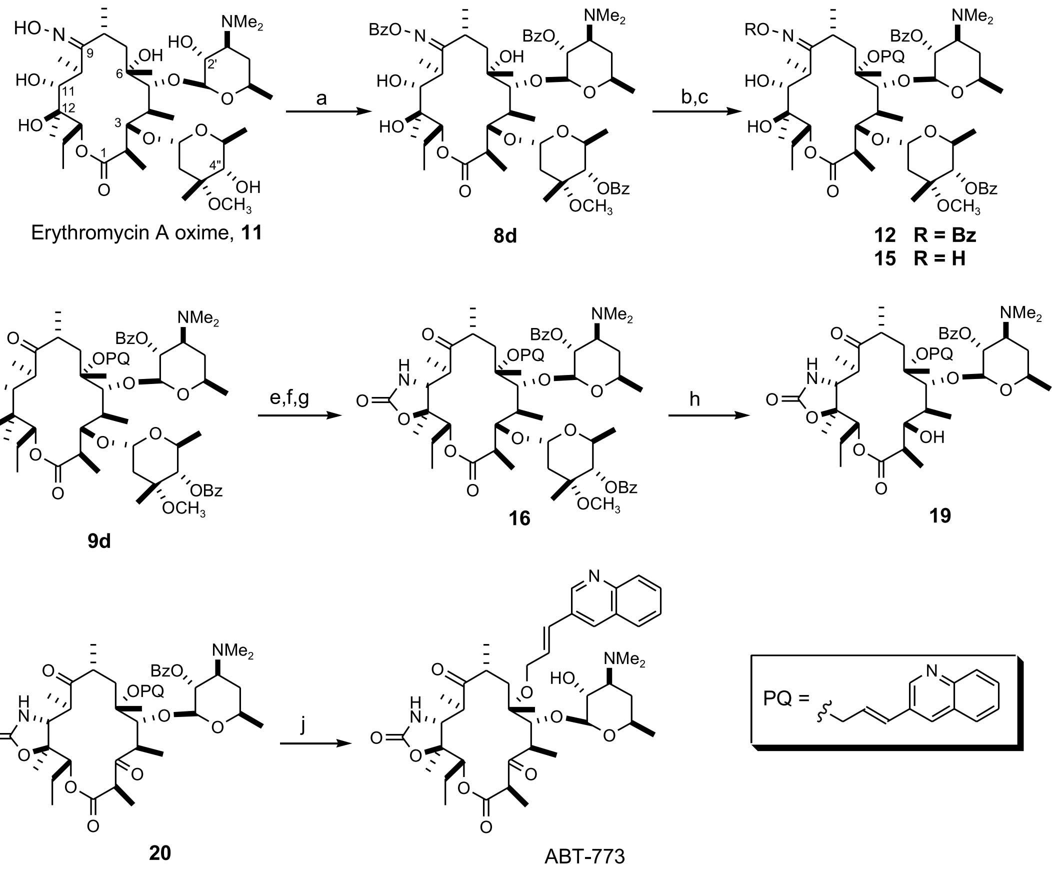
3. Results and discussion

Suitably protected erythromycin A, 9-oximino ethers have been utilized for selective C-6 O-methylation in the synthesis of clarithromycin.[10] Erythromycin A, 9-oxime **11** was chosen as a readily available starting material, which conveniently possesses the desired C-9 carbonyl protection required for our synthesis of ABT-773 (Scheme 4).[10a] A variety of fully protected 9-oximino erythromycin derivatives **8** were prepared, alkylated and subjected to deoximation conditions for the purpose of determining the most effective protective group system to accommodate these transformations.

The known derivative **8a**[10] could be alkylated [3-(3-quinolyl)-2-propenyl-1-*tert*-butyl carbonate **10**, Pd(0), THF, vide infra] in good yield using an excess of reagent, but the silyl-protecting groups fared poorly in the subsequent acidic deoximation step ($NaHSO_3$, L-tartaric acid, THF), affording the desired intermediate **9a** in only 55% yield (Table 1). 2′,4″-Dibenzoyl-protection of **8b** was superior to the disilyl-protection of **8a**, affording **9b** in 64% yield after deoximation, illustrating the subtle importance of the nature of the C-4″ hydroxyl protective group. Encouraged by this result, alternate benzoate protection arrays were studied. Not surprisingly, the unprotected cladinose moiety of dibenzoate **8c** complicated the alkylation, which was reflected in the 45% yield of product **9c**. The tribenzoate-protection scheme of **8d** proved to be optimum, affording intermediate **9d** in superior overall yield (70%). A notable trend in this series was the presence of varying amounts of numerous impurities, which were efficiently removed by recrystallization. However, the identification of individual components of these complex reaction mixtures was not pursued.

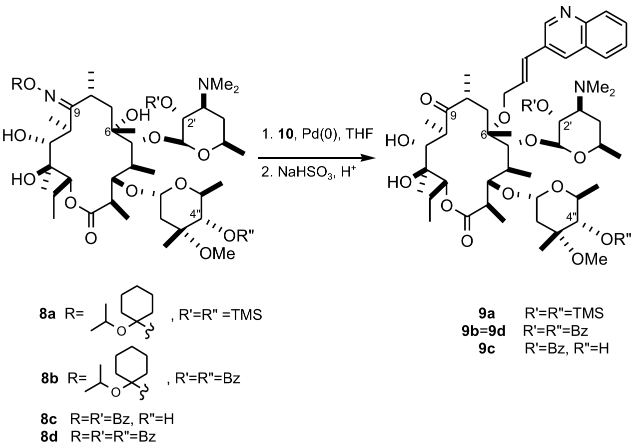
A distinct advantage of the benzoate derivatives was their ease of preparation and tendency to be crystalline. Protection of erythromycin A sugar hydroxyls as acetates were also briefly investigated, but over-acylation was a major drawback. In addition, the non-crystalline C-4″ acetates were more labile to hydrolytic conditions. Based on these observations, the tribenzoate protecting group scheme was pursued for the preparation of ABT-773.

Universal benzoate protection was achieved for the two sugar hydroxyls and the oxime hydroxyl by treatment of **11** with excess benzoic anhydride, triethlyamine and DMAP, which afforded tribenzoate **8d** in 82% yield after crystallization (Scheme 4). The oximino- and C-2′-hydroxyls reacted rapidly and completely in the absence of DMAP, but



Scheme 4. Total synthesis of ABT-773. Reagents and conditions: (a) Bz_2O, NEt_3, DMAP, THF, 82% (b) **10**, $Pd_2(dba)_3$, dppb, THF (c) 1 M NaOH, *i*PrOH, 0 °C, 94% (steps (b)–(c)) (d) L-TTA, $NaHSO_3$, THF, H_2O, 90 °C, 76% (e) 1,1′ carbonyldiimidazole, NaHMDS, THF, DMF (f) NH_3 (g) KO*t*Bu, 87% (steps (e)–(g)) (h) 2 N HCl, EtOH, 100% (i) Me_2S, *N*-chlorosuccinimide, NEt_3, CH_2Cl_2, 97% (j) MeOH, reflux, 92%.

Table 1. Study of alkylation/deoximation sequence

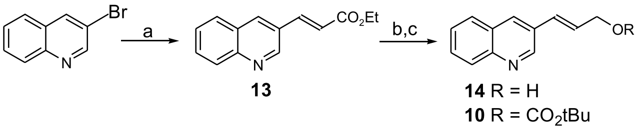


Sequence	**10** (equiv)	Yield alkylation (%)	Yield deoximation (%)	Overall yield (%)
8a→**9a**	2.5	92	60	55
8b→**9b**	2.5	92	70	64
8c→**9c**	1.5	80	56	45
8d→**9d**	1.15	99	71	70

benzoylation of the C-4″ hydroxyl was extremely sluggish, requiring addition of 1.0 equiv of DMAP for complete reaction. Formation of tetrabenzoylated product was minimally competitive. The crude reaction mixture typically contained 2–3% of tetrabenzoate, which was efficiently removed by crystallization. NMR studies determined that the fourth benzoylation occurred exclusively at the C-11 position; benzoylation at the C-6 or C-12 hydroxyls was not detected. Unreacted benzoic anhydride was difficult to remove either by extractive workup or by crystallization of the final product. However, it could be completely scavenged by treatment of the reaction mixture with *N*,*N*-dimethylethylenediamine. The resulting benzamide was easily removed during the extractive workup. Undesired reaction of *N*,*N*-dimethylethylenediamine with the C-9-oxime benzoate was avoided by careful temperature control and by monitoring the disappearance of benzoic anhydride by HPLC.

With a suitably protected erythromycin intermediate in hand, our investigations focused on C-6 O-alkylation with the fully elaborated 3-(*E*-propenyl)quinoline (PQ) side-chain. Alkylation of the C-6 hydroxyl of suitably protected erythromycin A derivatives has historically been accomplished by treatment with alkyl halides in the presence of strong base.[4,11] However, in the present context, this procedure was complicated by over-alkylation, variable yields and formation of by-products resulting from protective group cleavage. It was recently discovered in our laboratories that C-6 O-alkylation could be effected via a modified procedure originally demonstrated in carbohydrate chemistry.[12] Thus, treatment of tribenzoate **8d** with 1.15 equiv of *E*-3(3-quinolyl)-2-propenyl-1-*tert*-butyl carbonate (**10**), 0.5–1.0 mol% of tris(dibenzylideneacetone)-dipalladium (Pd_2dba_3) and 1.0–2.0 mol% 1,4-bis diphenylphosphinobutane (dppb) in refluxing anhydrous THF for 30 min afforded **12** exclusively, in nearly quantitative conversion. As little as 0.1 mol% of Pd_2dba_3 consumed starting materials and provided the desired product in satisfactory yield, although the rate of reaction decreased dramatically at this catalyst load.

Carbonate **10** was conveniently prepared in a three-step sequence (Scheme 5). Heck coupling of 3-bromoquinoline with ethyl acrylate afforded quinoline α,β-unsaturated ester **13** in high yield. Reduction of **13** with DIBAL provided quinolinepropenol **14**, which was transformed into the *t*-butyl carbonate **10**.[13]



Scheme 5. Synthesis of carbonate **10**. Reagents and conditions: (a) ethyl acrylate, $Pd(OAc)_2$, $(n\text{-Bu})_4NBr$, $NaHCO_3$, DMF (b) DIBAL, CH_2Cl_2 (c) BOC_2O, $(n\text{-Bu})_4N\cdot HSO_4$.

The oxime-benzoate group of **12** was selectively cleaved by treatment of the cooled alkylation reaction mixture with NaOH in *i*PrOH/water, affording **15** in high yield. Conditions for this transformation were carefully chosen and optimized to minimize the formation of over-hydrolysis by-products; utilization of isopropanol as a co-solvent greatly diminished cleavage of the 2′- and 4″-benzoates during the reaction. Following workup, oxime **15** was obtained in 94% assay yield from the one-pot alkylation/monodebenzoylation of erythromycin A oxime tribenzoate **8d**.

While the C-9 oxime may represent an effective and convenient means for the prevention of intramolecular hemiketal formation, this benefit may be offset by the requirement of a difficult unmasking protocol. In consideration of the sensitive functionality present in the erythromycin A nucleus, we acknowledged the challenge of the deoximation of intermediate **15** to the corresponding ketone and undertook a detailed investigation of the transformation. Although many methods for the hydrolysis of oximes exist in the literature,[10d–f,14] most utilize harsh acidic conditions, which are potentially incompatible with the functionality in our specific example. Since no single method stood out as an obvious starting point, we began the evaluation of a matrix of reagents and conditions. As a result, we discovered an effective protocol that afforded the desired product reproducibly and in high yield. Thus, heating oxime **15** in a THF/H_2O solution of $NaHSO_3$ (3.3 equiv) and L-tartaric acid (L-TTA, 3.6 equiv) to 90 °C afforded crystalline ketone **9d** in 76% yield and >95% purity. Minor variations in stoichiometry, solvent or temperature resulted in variable isolated yields primarily due to the formation of unidentified polar and non-impurities.

Oxime **15** existed as a mixture of geometric isomers, typically in greater than 95:5 *E*:*Z* ratio. In order to gain an understanding of the relative reactivity of each isomer, the major and minor oximes were isolated and independently examined under the reaction conditions. In a reaction mixture devoid of $NaHSO_3$, either oxime isomer afforded an equilibrium mixture of *E* and *Z*-isomers in a 6:1 ratio. A key finding was that the major oxime isomer hydrolyzed more rapidly than the minor oxime isomer and afforded a cleaner reaction to the desired ketone. Consequently, the optimal reaction conditions allow isomer interconversion and provide a productive pathway for the minor oxime isomer, ultimately resulting in an efficient, high-yielding route to key intermediate **9d**.

Stereoselective transformation of the C-11, C-12 diol moiety to the cyclic carbamate **16** was accomplished by modification of a known method[15] which ultimately led to a very efficient three-reaction, one-pot sequence. Installation of the cyclic carbamate commenced with conversion of **9d** to the 10,11-dehydro, 12-acyl imidazolide **17** in 98% HPLC assay yield by treatment with excess carbonyldiimidazole (CDI) and NaHMDS in a mixture of THF/DMF. This transformation proceeds through two transient intermediates, identified as shown in Figure 1.

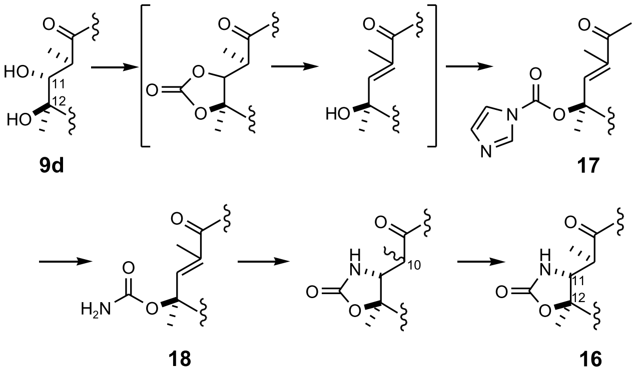


Figure 1. Mechanism for the formation of cyclic carbamate **16**.

Formation of the cyclic carbonate occurs rapidly with the first equivalent of CDI. The cyclic carbonate slowly decomposes to the hydroxy enone with loss of carbon dioxide and is quickly consumed by a second equivalent of CDI to give the acyl imidazolide **17**. Ammonolysis of the acylimidazolide was achieved by cooling the reaction mixture to −15 °C and treatment with gaseous NH_3. Reaction temperatures below −5 °C allowed sufficient solubility of ammonia to promote ammonolysis at a reasonable rate. The presence of DMF increases the solubility of CDI in the initial step and of ammonia in the second step, thus enhancing the reaction rate and yield for both steps. HPLC assay yield of the acyclic carbamate **18** was 90–95% for the two steps. When the ammonolysis reached completion, the mixture was warmed to ambient temperature and treated with 1.4 equiv of KO*t*Bu/THF solution, which mediated the cyclization of **18** to a variable mixture of C-10 epimeric cyclic carbamates. This mixture smoothly equilibrated under the reaction conditions to a 98:2 mixture in favor of desired C-10 stereoisomer **16**, which was isolated in 87% yield from diol **9d** after crystallization.

Selective cleavage of the cladinose sugar was accomplished by treating an ethanolic suspension of **16** with 2 N HCl for 12 h at 45 °C. Higher reaction temperatures resulted in lower yields. The cladinose-related by-products were removed in the aqueous workup. Carbinol **19** may be isolated by crystallization, but was routinely advanced into the next step without purification.

Oxidation of C-3 carbinol **19** by the Corey–Kim procedure[16] afforded ketolide **20** in 97% yield from **16** after crystallization (2 steps). Due to the sensitivity of the Corey–Kim reagent to water, efficient drying of the starting carbinol solution was critical. Alternative reaction solvents to CH_2Cl_2 were investigated, however the solubility of alcohol **19** greatly limited the options. THF was identified as a practical replacement solvent for CH_2Cl_2, although more reagents were required and afforded product in lower yield. Moreover, the use of THF in the reaction led to formation of unacceptable amounts of N-demethylation (0.5%) and was thus abandoned. Alternative oxidation methods were investigated in order to avoid the use of dimethyl sulfide, but the Corey–Kim method proved superior. For instance, oxidation was attempted using the TPAP reagent,[17] but the reaction inexplicably stalled at approximately 50% completion, even after rigorous exclusion of water and using stoichiometric quantities of TPAP.

The final step in the synthesis of ABT-773 was removal of the 2′-*O*-benzoate. It was observed during our investigations that the 2′-benzoate group was surprisingly stable to a variety of hydrolytic conditions. For example, minimal benzoate hydrolysis was detected in the deoximation step (acidic/aqueous), the cladinose removal (acidic/ethanol) and oxime-benzoyl hydrolysis (basic/isopropanol). Inspection of the literature reveals that the removal of a C-2′-*O*-acetyl protecting group from the desosamine hydroxyl of erythromycin A by simple treatment with methanol is precedented.[15,18] This method was extended to the removal of the C-2′ benzoyl of intermediate **20**. Thus, overnight treatment of monobenzoate **20** in refluxing MeOH afforded ABT-773 (**1**) in 92% yield. Separation of the methyl benzoate by-product was accomplished by acidification of the reaction mixture with dilute acid and extraction with ethyl acetate. The product was isolated in >98% purity by neutralization of the aqueous product-containing layer, followed by extraction into ethyl acetate and crystallization from ethyl acetate/heptane.

In summary, a practical route for the preparation of ABT-773 (**1**) has been developed. The key to the success of this synthetic route was the use of a highly effective and novel tribenzoate protection protocol, which allowed regiospecific alkylation of the sterically hindered C-6 hydroxyl group in high yield. Complications arising from the formation of intramolecular self-condensation by-products were avoided which resulted in an efficient and robust process. ABT-773 was prepared in ten reaction steps (seven isolations) from commercially available erythromycin A oxime.

4. Experimental

4.1. General

Melting points were measured with a capillary apparatus and are uncorrected. Unless otherwise specified, characterization data was taken as follows. IR spectra were measured from KBr pellets. ^1H NMR spectra were taken in $CDCl_3$ (300 MHz) with $CHCl_3$ (7.27 ppm) and/or tetramethylsilane (0.0 ppm) used as an internal standard. ^{13}C NMR spectra were taken in $CDCl_3$ (75 MHz) with $CDCl_3$ (77.0 ppm) used as an internal standard. Microanalyses were performed by Robertson Microlit Laboratories. HPLC analyses were performed on a Zorbax SB-C8 column, eluting with a gradient of acetonitrile and water (0.1% H_3PO_4). All reactions were performed under a positive pressure of nitrogen. Solvent concentration was accomplished by rotary evaporation ca. 20 mmHg with the bath temperature never exceeding 50 °C. Commercial grade anhydrous solvents and reagents were used without further purification unless otherwise specified. KF measurements were performed on Metrohm 728 instrument. Column chromatographies were performed on EM Science grade 60 silica gel.

4.1.1. Erythromycin A oxime tribenzoate (8d). Solid erythromycin A oxime (2.00 kg, 2.677 mol) was azeotropically dried by distillation of isopropyl acetate to a water content of 5–10 mol% as measured by Karl-Fischer titration. Isopropyl acetate was removed by distillation and THF (22 L), DMAP (0.3282 kg, 2.67 mol), triethylamine (1.198 kg, 11.84 mol) and benzoic anhydride (2.5 kg, 11.3 mol) were added and the mixture was stirred at 25 °C for 40 h. The reaction was monitored by HPLC. Retention times: DMAP: 1.8 min, benzoic acid: 4.4 min, dibenzoate: 9.9 min, regioisomeric dibenzoate: 10.7 min, tribenzoate: 13.0 min, benzoic anhydride: 13.7 min, tetrabenzoate: 14.3 min. At reaction completion, a 4.3:92:2.7 ratio of di- to tri- to tetrabenzoates were present. The reaction mixture was chilled to 0–5 °C and *N*,*N*-dimethylethylenediamine (0.427 kg, 4.9 mol) was added at a rate to maintain an internal temperature of <10 °C. After addition was complete, the mixture was stirred for 1 h at +5 °C until no benzoic anhydride remained. The reaction mixture was diluted with MTBE (20 L) and washed with 5% aq KH_2PO_4 solution (2×20 L), satd aq $NaHCO_3$ solution (20 L), and satd aq NaCl solution (10 L). The organic layer was concentrated and diluted with 12 L of isopropanol causing the product to crystallize. The mixture was cooled to −5 °C and stirred for 1.5 h. The product was filtered and dried in a vacuum oven at 50 °C to yield 2.32 kg (82%) of **8d** as a white crystalline solid: mp = 149–152 °C; IR (film, cm^{-1}) 1722, 1450, 1379, 1339, 1262; ^1H NMR ($CDCl_3$) δ 8.00 (m, 6H), 7.62–7.56 (m, 3H), 7.50–7.45 (m, 6H), 5.15 (dd, 2.4, 10.7 Hz, 1H), 5.10 (dd, $J = 3.6$, 10.4 Hz, 1H), 5.02 (d, $J = 4.9$ Hz, 1H), 4.93 (d, $J = 7.6$ Hz, 1H), 4.91 (d, $J = 9.8$ Hz, 1H), 4.44–4.39 (m, 2H), 3.87 (dd, $J = 1.3$, 9.2 Hz, 1H), 3.86–3.79 (m, 3H), 3.52 (s, 3H), 3.46 (d, $J = 6.7$ Hz, 1H), 3.22 (bs, 1H), 2.97 (bs, 1H), 2.81–2.76 (m, 2H), 2.46 (d, $J = 15.3$ Hz, 1H), 2.34 (s, 6H), 1.96–1.92 (m, 1H), 1.87 (m, 1H), 1.76 (m, 1H), 1.73 (dd, $J = 5.2$, 15.3 Hz, 1H), 1.55 (m, 2H), 1.41 (m, 1H), 1.38 (s, 3H), 1.37 (m, 1H), 1.31 (d, $J = 7.0$ Hz, 3H), 1.21 (s, 3H), 1.18 (d, $J = 6.9$ Hz, 3H), 1.17 (m, 3H), 1.10 (s, 6H), 0.90 (d, $J = 5.1$ Hz, 3H), 0.82 (t, $J = 7.3$ Hz, 3H), 0.75 (d, $J = 7.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.4, 175.1, 166.1, 165.4, 163.8, 133.3, 133.2, 132.7, 130.7, 129.9, 129.6 (4C), 129.5 (2C), 129.0, 128.5 (2C), 128.4 (2C), 128.2 (2C), 100.2, 95.7, 83.6, 79.2, 78.8, 77.0, 74.7, 74.3, 73.0, 72.3, 69.8, 67.7, 63.7, 63.5, 49.6, 44.5, 40.9 (2C), 39.0, 37.3, 35.3, 34.6, 31.8, 28.6, 26.4, 21.3, 21.2, 21.1, 18.5, 18.2, 16.5, 15.7, 14.9, 10.6, 9.3. MS (ESI) *m/z* 1061 (MH+). Anal. Calcd for $C_{58}H_{80}N_2O_{16}$: C, 65.64; H, 7.60; N, 2.64; O, 24.12; Found: C,65.37; H, 7.42; N, 2.52; O, 24.38.

4.1.2. Quinoline-3-propenoic acid, ethyl ester (13). 3-Bromoquinoline (300 g, 1.44 mol), ethyl acrylate (173 g, 1.73 mol), palladium (II) acetate (32.3 g, 144 mmol), *t*-butylammonium bromide (478 g, 1.44 mol), sodium bicarbonate (483.9 g, 5.76 mol), and DMF (anhydrous, 3 L) were combined and heated to 90 °C for approximately 30 min, when 3-bromoquinoline was no longer detected by HPLC analysis. The reaction mixture was cooled to ambient temperature, and ethyl acetate (2.65 L) was added. The resulting mixture was washed with H_2O (2×1500 mL). The combined aqueous layers were then back extracted with 1:1 toluene/EtOAc (4×1 L). The organic layers were combined and washed with satd NaCl solution (3×6 L) then evaporated to give 217.4 g (65%) of **13**: mp = 87–88 °C; IR (KBr, cm^{-1}) 3053, 2976, 1716, 1635, 1312, 1297, 1263, 1175, 1165; ^1H NMR($CDCl_3$) δ 9.06 (d, $J = 2.2$ Hz, 1H), 8.19 (d, $J = 2.2$ Hz, 1H), 8.08 (dd, $J = 8.5$, 1.1 Hz, 1H),7.81 (d, $J = 15.8$ Hz, 1H), 7.82 (dd, $J = 8.5$, 1.5 Hz, 1H), 7.72 (ddd, $J = 8.5$, 7.0, 1.5 Hz, 1H),7.55 (ddd, $J = 8.5$, 7.0, 1.1 Hz, 1H), 6.63 (d, $J = 15.8$ Hz, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$), δ 166.4, 149.2, 148.5, 141.1, 135.4, 130.5, 129.4, 128.2, 127.6, 127.4, 127.4, 120.2, 60.7, 14.3. MS $C_{14}H_{13}NO_2$ *m/z* ESI^+ [M + H] 228. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 73.97; H, 5.70; N, 6.05.

4.1.3. 3-(3-Quinolyl)-2-propen-1-ol (14). Quinoline-3-propenoic acid, ethyl ester (**13**, 141 g, 0.621 mol) was dissolved in anhydrous methylene chloride (2.0 L) and cooled to −57 °C. Diisobutylaluminum hydride (1.55 L, 1.55 mol, 1.0 M in methylene chloride) was added in a slow stream, keeping the temperature below −40 °C. The mixture was stirred for 30 min, until starting ester was consumed by HPLC. The reaction mixture was cooled to −78 °C, and methanol (434 mL) was added dropwise, maintaining the temperature below −40 °C. The mixture was then warmed to ambient temperature, 10% sodium potassium tartrate solution (2 L) was added portionwise and the stirred 1 h. The layers were separated, the organic layer was washed with aq saturated NaCl (2 L) solution and dried over $MgSO_4$. Evaporation gave 71 g (62%) of **14** as a pinkish solid: mp = 112–114 °C; IR (KBr, cm^{-1}) 3230, 2908, 2837, 1575, 1498, 1417, 1339, 1227, 1099, 990, 965, 927, 792, 747; ^1H NMR ($CDCl_3$) δ 8.94 (d, $J = 2$ Hz, 1H), 8.05 (d, $J = 8$, 1 Hz, 1H), 7.97 (d, $J = 2$ Hz, 1H), 7.72 (d, $J = 2$ Hz, 1H), 7.65 (m, 1H), 7.48 (m, 1H), 6.72 (appt dd, 1H), 6.55 (dt, $J = 16$, 6, 1 Hz, 1H,), 4.39 (dd, $J = 6$, 1 Hz, 2H), 3.36 (brs, 1H); ^{13}C NMR ($CDCl_3$), δ 149.0, 146.9, 132.5, 131.8, 129.7, 129.2, 128.7, 127.9, 127.7, 126.9, 126.6, 62.9. MS $C_{12}H_{11}NO$ *m/z* ESI^+ [M + H] 186. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.91; H, 5.99; N, 7.56; Found: C, 77.55; H, 5.96; N, 7.40.

4.1.4. 3-(3-Quinolyl)-2-propenyl-1-*tert*-butyl carbonate (10). 3-(3-Quinolyl)-2-propen-1-ol (**14**, 115.4 g, 623 mmol), di-*tert*-butyl dicarbonate (163.2 g, 748 mmol), and *t*-butylammonium hydrogen sulfate (6.35 g, 18.7 mmol) were dissolved in methylene chloride (721 mL), cooled to 0–5 °C and sodium hydroxide (92.7 g, 2.32 mol) in H_2O (293 mL) was added. The reaction was warmed to ambient temperature and was stirred for 17 h until starting alcohol was consumed by HPLC. The reaction mixture was diluted with methylene chloride (300 mL) and water (300 mL) and agitated. The aqueous layer was extracted with an additional 200 mL methylene chloride. The combined organic layers were washed with saturated aq NaCl solution (1 L), dried with Na_2SO_4, filtered and evaporated to give 285.8 g of crude material which was purified by silica gel chromatography (20:80 ethyl acetate/hexanes) to give 136.7 g (81%) of **10** as a beige solid; IR (KBr, cm^{-1}) 2978, 1737, 1367, 1277, 1256, 1161, 970, 860; ^1H NMR ($CDCl_3$) δ 8.93 (d, $J = 2.2$ Hz, 1H), 8.02 (d, $J = 8.5$ Hz, 1H), 7.97 (s, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.61 (ddd, $J = 8.5$, 6.6, 1.5 Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 6.80 (d, $J = 16$ Hz, 1H), 6.46 (ddd, $J = 16$, 6.3, 6.3 Hz, 1H), 4.73 (dd, $J = 6.3$, 1.5 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 153.1, 149.0, 147.5, 132.8, 130.5, 129.4, 129.2, 128.9, 127.7 (2C), 126.8, 125.3, 82.3, 66.9, 27.6 (3C). MS $C_{17}H_{19}NO_3$ *m/z* 285 $APCI^+$[M + H] 286, $DCI/NH3^+$ [M + H] 286, ESI^+[M + H] 286. Anal Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; Found: C, 71.36; H, 6.64; N, 4.72.

4.1.5. 6-*O*-3-(3-Quinolyl) propenyl erythromycin A oxime 2′,4″-dibenzoate (15). Erythromycin A oxime tribenzoate (**8d**, 1000 g, 0.942 mol) was dissolved in THF (5 L). The mixture was azeotropically dried by two successive distillations of THF until a water content of <2 mol% was obtained as measured by Karl–Fischer titration. The resulting foam was redissolved in THF (4 L) and deoxygenated. Solid 3-(3-quinolyl)-2-propen-1-ol (PQ), *tert*-butyl carbonate (309 g, 1.08 mol), $Pd_2(dba)_3$ (8.61 g, 0.0094 mol), and dppb (8.02 g, 0.018 mol) were added. The reaction mixture was heated to reflux (65 °C) for approximately 30 min until starting material was consumed as measured by HPLC analysis. Retention times: PQ carbonate: 11.6 min, starting macrolide: 12.1 min, product: 13.7 min. The reaction mixture containing intermediate **12** was chilled to +15 °C. Isopropyl alcohol (4 L) was added followed by 1 N NaOH (234 mL). The reaction mixture was stirred for 2 h until cleavage of the oxime benzoate was complete by HPLC analysis. The reaction mixture was poured into MTBE (12 L) and satd aq $NaHCO_3$ solution (8 L) and the layers were separated. The organics were washed with satd aq NaCl solution (8 L), the layers were separated and the solvents were removed to yield 1292 g of **15** as a crude foam. This material was assayed by HPLC at 997 g (94% yield) and carried on without further purification. For intermediate **12**; IR (film, cm^{-1}) 1728, 1453, 1339, 1265; ^{1}H NMR ($CDCl_3$) δ 8.98 (d, J=2.1 Hz, 1H), 8.18 (d, J=1.8 Hz, 1H), 8.07–8.01 (m, 7H), 7.80 (dd, J=1.0, 8.0 Hz, 1H), 7.63–7.58 (m, 4H), 7.55–7.45 (m, 7H), 6.51 (ddd, J=4.5, 8.2, 15.7 Hz, 1H), 6.20 (d, J=15.7 Hz, 1H), 5.31 (dd, J=2.4, 10.7 Hz, 1H), 5.11 (dd, J=7.6, 10.4 Hz, 1H), 5.05–5.01 (m, 2H), 4.93 (d, J=9.5 Hz, 1H), 4.53–4.47 (m, 1H), 4.36–4.30 (m, 1H), 4.14 (dd, J=3.0, 8.9 Hz, 1H), 3.97–3.91 (m, 1H), 3.86–3.77 (m, 3H), 3.76 (dd, J=1.5, 9.8 Hz, 1H), 3.70 (m, 1H), 3.56 (s, 3H), 3.24 (bs, 1H), 3.01–2.90 (m, 2H), 2.74 (q, J=7.3 Hz, 1H), 2.50 (d, J=15.3 Hz, 1H), 2.35 (s, 6H), 2.04–1.91 (m, 2H), 1.78–1.71 (m, 2H), 1.63–1.57 (m, 2H), 1.56 (s, 3H), 1.45–1.35 (m, 2H), 1.24 (d, J=7.0 Hz, 3H), 1.22 (s, 3H), 1.21 (d, J=4.3 Hz, 3H), 1.20 (s, 3H), 1.15 (d, J=7.0 Hz, 3H), 1.10 (s, 3H), 0.95 (d, J=7.1 Hz, 3H), 0.85 (t, J=7.6 Hz, 3H), 0.80 (d, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.2, 174.8, 166.1, 165.5, 162.8, 150.4, 147.4, 133.4, 133.1, 132.7, 132.6, 130.9, 130.1, 129.9, 129.6 (4C), 129.4, 129.3 (2C), 129.1, 128.8, 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.3, 128.2 (2C), 128.1, 126.2, 99.8, 96.3, 79.2, 79.1, 78.8, 78.7, 76.9, 74.1, 73.0, 72.7, 69.7, 67.4, 65.0, 63.8, 63.7, 49.5, 44.4, 40.9 (2C), 37.9, 36.8, 35.4, 34.4, 31.7, 28.7, 21.5, 21.4 (2C), 21.2, 18.9, 18.6, 16.5, 16.0, 15.3, 10.7, 9.5. MS (ESI) *m/z* 1228 (MH+). Anal. Calcd for $C_{70}H_{89}N_3O_{16}$: C, 68.44; H, 7.30; N, 3.42; O, 20.84; Found: C,68.64; H, 7.56; N, 3.28; O, 20.45. For intermediate **15**; IR (film, cm^{-1}) 1725, 1598, 1487, 1379, 1342, 1264; ^{1}H NMR ($CDCl_3$) δ 10.59 (bs, 1H), 8.80 (d, J=2.0 Hz, 1H), 8.05 –8.01 (m, 5H), 7.72 (d, J=1.8 Hz, 1H), 7.63–7.55 (m, 3H), 7.50–7.42 (m, 5H), 7.40 (t, J=8.2 Hz, 1H), 6.36 (ddd, J=4.9, 7.0, 16.1 Hz, 1H), 6.17 (d, J=16.1 Hz, 1H), 5.25 (dd, J=2.1, 10.7 Hz, 1H), 5.12 (dd, J=8.3, 10.7 Hz, 1H), 5.01 (d, J=6.6 Hz, 1H), 4.98 (d, J=4.9 Hz, 1H), 4.93 (d, J=9.8 Hz, 1H), 4.69 (s, 1H), 4.58–4.53 (m, 1H), 4.12 (dd, J=3.8, 11.3 Hz, 1H), 4.02 (dd, J=7.0, 11.3 Hz, 1H), 3.98 –3.92 (m, 1H), 3.89–3.84 (m, 1H), 3.78 (d, J=5.8 Hz, 1H), 3.71, (m, 1H), 3.67 (dd, J=1.2, 9.8 Hz, 1H), 3.55 (bs, 4H), 3.02– 2.96 (m, 1H), 2.85 (m, 1H), 2.60 (q, J=7.0 Hz, 1H), 2.47 (d, J=15.0 Hz, 1H), 2.35 (s, 6H), 2.04–1.99 (m,1H), 1.94–1.89 (m, 1H), 1.78–1.74 (m, 1H), 1.71 (dd, J=5.2, 15.2 Hz, 1H), 1.56 (s, 3H), 1.54–1.50 (m, 1H), 1.43–1.37 (m, 3H), 1.24 (d, J=6.1 Hz, 3H), 1.21 (s, 3H), 1.16 (d, J=7.0 Hz, 3H), 1.14 (d, J=7.0 Hz, 3H), 1.06 (s, 3H), 1.05 (d, J=7.0 Hz, 3H), 0.99 (d, J=5.8 Hz, 3H), 0.79 (t, J=7.3 Hz, 3H), 0.77 (d, J=7.3 Hz, 3H); ^{13}C ($CDCl_3$) δ 174.7, 169.0, 166.2, 165.5, 149.4, 146.3, 133.3, 132.6, 132.5, 131.1, 131.0, 130.6, 130.0, 129.7 (4C), 128.5, 128.4 (2C), 128.3, 128.2 (2C), 128.1, 127.8, 126.3, 126.2, 100.0, 96.2, 79.5, 79.4, 78.9 (2C), 76.8, 74.0, 73.0, 72.7, 70.6, 67.3, 64.7, 63.8, 63.7, 49.5, 44.4, 40.9 (2C), 38.2, 36.6, 35.4, 32.8, 31.8, 25.5 (2C), 21.4 (2C), 21.2, 19.0, 18.6, 16.5, 16.0, 15.2, 10.7, 9.5. MS (ESI) *m/z* 1124 (MH+). Anal. Calcd for $C_{63}H_{85}N_3O_{15}$: C, 67.30; H, 7.62; N, 3.74; O, 21.34; Found: C,67.02; H, 7.61; N, 3.59; O, 20.99.

4.1.6. 6-*O*-3-(3-Quinolyl)propenyl erythromycin A 2′,4″-dibenzoate (9d). Crude 6-*O*-3-(3-quinolyl) propenyl erythromycin A oxime dibenzoate (**15**, 800 g at 78% potency, 628 g, 0.559 mol), L-tartaric acid (280 g, 1.87 mol), $NaHSO_3$ (212 g, 2.04 mol), H_2O (3.4 L) and THF (1.2 L) were charged to a pressure vessel. The mixture was heated to 90 °C over 30 min and held at 85–90 °C for an additional 90 min with good agitation. The reaction was monitored by HPLC analysis until complete. Retention times: minor oxime: 11.5 min; major oxime: 12.4 min; 9-ketone: 12.9 min. The reaction mixture was diluted with EtOAc (4 L)/MTBE (2 L) and washed with 25% aq K_2CO_3 solution (3.6 L). The product layer was concentrated and absolute EtOH (8 L) was added. The resulting slurry was cooled to 5 °C, filtered, and dried in a vacuum oven at 40 °C to give 485 g (76%) of **9d** as a white crystalline solid: mp = 214–216 °C; IR (film, cm^{-1}) 1722, 1694, 1265, 1126, 1070; ^{1}H NMR ($CDCl_3$) δ 9.13 (d, J=2.1 Hz, 1H), 8.27 (d, J=1.8 Hz, 1H), 8.06–8.02 (m, 5H), 7.79 (dd, J=1.0, 8.6 Hz, 1H), 7.63–7.58 (m, 3H), 7.52–7.44 (m, 5H), 6.63 (d, J=16.2 Hz, 1H), 6.59–6.52 (m, 1H), 5.16 (dd, J=2.4, 11.0 Hz, 1H), 5.12–5.08 (m, 1H), 5.05 (d, J=4.9 Hz, 1H), 5.02 (d, J=7.6 Hz, 1H), 4.95 (d, J=9.4 Hz, 1H), 4.52–4.47 (m, 1H), 4.19 (dd, J=4.0, 10.8 Hz, 1H), 4.02 (dd, J=7.6, 11.0 Hz, 1H), 3.98–3.92 (m, 1H), 3.81 (d, J=5.7 Hz, 1H), 3.77 (dd, J=1.9, 9.7 Hz, 1H), 3.67 (s, 1H), 3.56 (s, 3H), 3.54 (bs, 1H), 3.05–3.00 (m, 2H), 2.99 (q, J=6.4 Hz, 1H), 2.91–2.85 (m, 1H), 2.64–2.659 (m, 1H), 2.50 (d, J=15.0 Hz, 1H), 2.36 (s, 6H), 2.02–1.96 (m, 1H), 1.92–1.87 (m, 1H), 1.79–1.75 (m, 3H), 1.57 (d, J=14.0 Hz, 1H), 1.49 (s, 3H), 1.43–1.37 (m, 2H), 1.24 (d, J=4.0 Hz, 3H), 1.23 (s, 3H), 1.22 (d, J=4.3 Hz, 3H), 1.14 (d, J=7.0 Hz, 3H), 1.04 (s, 3H), 1.03 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.1 Hz, 3H), 0.84 (t, J=7.4 Hz, 3H), 0.79 (d, J=7.6 Hz, 3H);^{13}C ($CDCl_3$) δ 220.2, 175.1, 166.1, 165.4, 150.2, 147.4, 133.4, 132.8, 132.7, 130.8, 130.2, 129.8, 129.6 (5C), 129.1, 128.8, 128.7, 128.4 (2C), 128.3 (2C), 128.2, 127.9, 126.4, 99.9, 96.2, 80.0, 79.2, 78.8, 78.7, 76.5, 74.2, 73.0, 72.5, 68.7, 67.4, 64.9, 63.8, 63.7, 49.5, 45.5, 44.4, 40.9 (2C), 38.1, 37.7, 37.4, 35.4, 31.8, 21.3 (2C), 21.2, 21.1, 18.6, 18.3, 16.3, 16.0, 12.2, 10.7, 9.5. MS (ESI) *m/z* 1109 (MH+). Anal. Calcd for $C_{63}H_{84}N_2O_{15}$: C, 68.21; H, 7.63; N, 2.53; O, 21.63; Found: C,67.98; H, 7.50; N, 2.39; O, 21.88.

4.1.7. 6-*O*-3-(3-Quinolyl)propenyl-11,12-carbamoyl erythromycin A 2′,4″-dibenzoate (16). Ketone **9d** (892 g, 0.778 mol) was suspended in a mixture of THF (3.5 L) and DMF (1.25 L). Solid 1,1′-carbonyldiimidazole (496 g, 3.05 mol) was added, followed by a solution of NaHMDS (1.0 M in THF, 1071 mL, 1.071 mol, 1.3 equiv) over 65 min. The reaction was stirred at ambient temperature for 18 h until HPLC analysis shows complete consumption of the intermediate 11,12 cyclic carbonate. Retention times: starting diol **9d**: 9.8 min, 11,12 cyclic carbonate: 9.9 min, 12-acyl imidazolide **17**: 11.5 min. The stirring 12-acylimidazolide solution was cooled to −15 °C and ammonia gas (927 g) was added *via* a sub-surface inlet. The reaction temperature was kept below −5 °C for 1.5 h until HPLC showed less than 1 PA% of 12-acylimidazolide by HPLC. Retention times: hydroxyenone: 10.8 min, acyclic carbamate: 9.5 min. The temperature of the reaction mixture was increased to room temperature. A solution of potassium tert-butoxide (1 M in THF, 918 mL, 0.918 mol) was added and stirred for 1.5 h. Retention times: desired product: 8.9 min, C-10 methyl epimer: 9.8 min. The reaction mixture was poured into isopropyl acetate (13.5 L) and 5% aq KH_2PO_4 (13.5 L), agitated, and the layers separated. The organic layer was washed with 5% aq KH_2PO_4 solution (13.5 L), satd aq $NaHCO_3$ solution (13.5 L), and satd aq NaCl solution (10 L). The organic solution was concentrated and the product crystallized. Isopropanol (4 L) was added and the mixture was stirred at 45 °C for 30 min, then chilled to 4 °C and stirred at this temperature for 2 h. The product was collected by filtration and dried at 55 °C in a vacuum oven to give 793 g (87%) of **16** as a white crystalline solid: mp = 166.5–168 °C; IR (film, cm^{-1}) 1771.3, 1722, 1453, 1265, 1169, 1107; ^{1}H NMR ($CDCl_3$) δ 9.06 (d, $J=2.1$ Hz, 1H), 8.23 (d, $J=1.9$ Hz, 1H), 8.07–8.03 (m, 5H), 7.81 (d, $J=8.2$ Hz, 1H), 7.62–7.58 (m, 3H), 7.55–7.45 (m, 5H), 6.63 (d, $J=16.2$ Hz, 1H), 6.40 (ddd, $J=6.4$, 7.6, 16.9 Hz, 1H), 5.54 (s, 1H), 5.09 (dd, $J=7.7$, 10.7 Hz, 1H), 5.05 (d, $J=4.9$ Hz, 1H), 4.99 (d, $J=9.7$ Hz, 1H), 4.97 (m, 1H), 4.88 (dd, $J=3.0$, 9.5 Hz, 1H), 4.51 (m, 1H), 4.14 (dd, $J=6.1$, 11.0 Hz, 1H), 3.99 (dd, $J=7.6$, 11.0 Hz, 1H), 3.93 (m, 1H), 3.85 (dd, $J=1.5$, 8.8 Hz, 1H), 3.75 (d, $J=6.1$ Hz, 1H), 3.71 (s,1H), 3.56 (s, 3H), 3.01 (m, 1H), 2.88 (q, $J=7.0$ Hz, 1H), 2.81 (m, 1H), 2.61 (m, 1H), 2.51 (d, $J=15.0$ Hz, 1H), 2.36 (6H, s), 1.86–1.72 (m, 5H), 1.58 (dd, $J=1.5$, 15.0 Hz, 1H), 1.47 (s, 3H), 1.40–1.36 (m, 2H), 1.31 (s, 3H), 1.24–1.21 (m, 9H), 1.14 (d, $J=7.3$ Hz, 3H), 1.08 (d, $J=6.7$ Hz, 3H), 0.95 (d, $J=6.1$ Hz, 3H), 0.78 (d, $J=7.7$ Hz, 3H), 0.72 (t, $J=7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 217.9, 175.8, 166.1, 165.3, 157.9, 149.9, 147.6, 133.4, 132.7, 132.4, 130.7, 129.9, 129.8, 129.7 (3C), 129.6 (2C), 129.1, 129.0, 128.4 (2C), 128.3 (3C), 128.1, 128.0, 126.6, 100.0, 96.0, 83.7, 79.6, 79.4, 78.7, 78.0, 76.0, 73.0, 72.4, 67.5, 64.9, 63.7 (2C), 57.7, 49.6, 45.2, 44.6, 40.8 (2C), 39.2, 38.1, 37.3, 35.2, 31.9, 22.3, 21.2 (2C), 21.0, 18.5, 18.4, 15.5, 13.7, 13.4, 10.6, 9.4. MS (ESI) m/z 1134 (MH+). Anal. Calcd for $C_{64}H_{83}N_3O_{15}+0.5\%\ H_2O$: C, 67.16; H, 7.41; N, 3.67; O, 21.69; Found: C, 67.18; H, 7.24; N, 3.45; O, 21.71.

4.1.8. 6-*O*-3-(3-quinolyl)propenyl-11,12-carbamoyl-3-hydroxy erythromycin A 2′-benzoate (19). Carbamate **16** (750 g, 0.639 mol) was diluted with EtOH (3.64 L) and 2 N HCl (3.64 L) and heated to 45 °C for 16 h. The reaction was monitored by HPLC until starting material was consumed by HPLC. Retention times: desired product 5.2 min, starting carbamate: 9.9 min. The reaction mixture was poured into 10 L of MTBE and 10 L of water, agitated, and the layers separated. The aqueous, product-containing layer was diluted with 6 L of isopropyl acetate and treated with 30% aq K_2CO_3 solution (5 L) with good mixing. The layers were separated. The organic layer was separated and concentrated to give 766 g of crude product. This material was assayed by HPLC at 558 g (94% yield of **19**) and carried on without further purification: mp = 224–226 °C; IR (film, cm^{-1}) 1771.3, 1727, 1456, 1274, 1159, 1119; ^{1}H NMR ($CDCl_3$) δ 9.06 (d, $J=2.1$ Hz, 1H), 8.22 (d, $J=1.8$ Hz, 1H), 8.09 (dd, $J=1.5$, 7.0 Hz, 2H), 8.07 (d, $J=6.7$ Hz, 1H), 7.82 (d, $J=6.7$ Hz, 1H), 7.65 (s, 1H), 7.57 (t, $J=7.0$ Hz, 1H), 7.51 (t, $J=7.0$ Hz, 1H), 7.46–7.44 (m, 2H), 6.65 (d, $J=16.2$ Hz, 1H), 6.37 (dt, $J=16$, 6.1 Hz, 1H), 5.47 (s, 1H), 5.11 (dd, $J=2.7$, 10.4 Hz, 1H), 5.04 (dd, $J=7.6$, 10.4 Hz, 1H), 4.88 (d, $J=7.6$ Hz, 1H), 3.99–3.95 (m, 2H), 3.82 (d, $J=1.8$ Hz, 1H), 3.72 (s, 1H), 3.57–3.53 (m, 2H), 3.41–3.37 (m, 1H), 2.91 (dt, $J=4.0$, 12.0 Hz, 1H), 2.85 (q, $J=6.4$ Hz, 1H), 2.69–2.63 (m, 1H), 2.59–2.53 (m, 1H), 2.29 (s, 6H), 2.01–1.98 (m, 1H), 1.86–1.80 (m, 1H), 1.77–1.71 (m, 2H), 1.46–1.42 (m, 2H), 1.39 (s, 3H), 1.40–1.36 (m, 1H), 1.32 (s, 3H), 1.25 (d, $J=6.7$ Hz, 3H), 1.08 (m, 9H), 0.81–0.75 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 217.5, 175.3, 165.4, 158.1, 149.5, 147.3, 132.8, 132.7, 130.6, 129.8 (3C), 129.3, 129.2, 128.9, 128.7, 128.2 (3C), 128.1, 126.9, 99.3, 83.8, 80.6, 79.0, 77.4, 75.5, 72.1, 68.8, 64.0, 63.2, 58.1, 45.5, 43.9, 40.8 (2C), 38.4, 37.2, 36.0, 32.1, 22.3, 21.0, 20.1, 18.3, 15.3, 13.8, 13.3, 10.4, 7.9. MS (ESI) m/z 872 (MH+). Anal. Calcd for $C_{49}H_{65}N_3O_{11}$: Theory: C, 67.49; H, 7.51; N, 4.82; Found: C, 67.11; H, 7.38; N, 4.60.

4.1.9. 6-*O*-3-(3-quinolyl)propenyl-11,12-carbamoyl-3-keto erythromycin A 2′-benzoate (ABT-773-2′benzoate, 20). Dimethyl sulfide (63.68 g, 1.026 mol) was added to a mixture of *N*-chlorosuccinimide (117.2 g, 880.4 mmol) and CH_2Cl_2 (740 mL) while maintaining the internal temperature at −15 °C. Crude alcohol (**19**, 558 g by assay, 614 mmol) was dissolved in 1.91 L of CH_2Cl_2 and added, followed by triethylamine (70.6 g, 698 mmol). The mixture was stirred at −10 °C for 3 h and poured into 6.7 L EtOAc and 2.7 L of 0.5 N aqueous NaOH. The organic layer was washed with 5% (w/w) aqueous NaCl (3.3 L) and 27% (w/w) aqueous NaCl (3.3 L). The organic solution was concentrated and diluted with 1:1 hexane/MTBE (3 L). After stirring for 30 min at 45 °C, the mixture was cooled to room temperature. The product was filtered and dried to give 537.8 g (97%) of **20** as a white crystalline solid: mp = 150–152 °C; IR (film, cm^{-1}) 1771.3, 1743, 1719, 1697, 1456, 1267.7, 1172, 1104; ^{1}H NMR ($CDCl_3$) δ 9.02 (d, $J=2.1$ Hz, 1H), 8.15 (d, $J=2.1$ Hz, 1H), 8.06 (d, $J=8.4$ Hz, 1H), 8.02 (dd, $J=1.6$, 7.6 Hz, 2H), 7.82 (d, $J=7.6$ Hz, 1H), 7.64 (t, $J=7.6$ Hz, 1H), 7.56 (t, $J=7.6$ Hz, 1H), 7.50 (t, $J=7.6$ Hz, 1H), 7.44 (t, $J=7.6$ Hz, 2H), 6.56 (d, $J=6.56$ Hz, 1H), 6.16 (dt, $J=16$, 6.7 Hz, 1H), 5.49 (s, 1H), 5.03 (dd, $J=7.6$, 10.6 Hz, 1H), 4.93 (d, $J=3.2$, 9.4 Hz, 1H), 4.59 (d, $J=7.6$ Hz, 1H), 4.29 (d, $J=4.3$ Hz, 1H), 3.86–3.80 (m, 3H), 3.69 (dd, $J=6.7$, 12.5 Hz 1H), 3.63 (m, 1H), 3.12–3.04 (m, 1H), 2.89–2.85 (m, 2H), 2.62–2.59 (m, 1H), 2.26 (s, 6H), 1.85 (ddd, $J=3.4$, 7.6, 14.5 Hz, 1H), 1.75–1.82 (m, 1H), 1.63 (dd, $J=11.7$, 14.7 Hz, 1H), 1.54 (dd, $J=2.5$, 14.7 Hz, 1H), 1.48–142 (m, 2H), 1.44 (s, 3H), 1.39 (s, 3H), 1.36 (d, $J=16.9$ Hz, 3H), 1.21 (d, $J=6.1$ Hz, 3H), 1.12 (d, $J=7.0$ Hz, 3H), 1.09 (d, $J=6.7$ Hz, 3H), 1.01 (d, $J=7.9$ Hz, 3H), 0.76 (t, $J=7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 217.3, 205.4, 169.6, 165.2, 157.6, 149.6, 147.6, 132.8, 132.5, 130.5, 129.9, 129.7, 129.6, 129.2, 129.0 (2C), 128.5, 128.3 (2C), 128.0 (2C), 126.7, 100.7, 83.4, 78.8, 77.5, 75.6, 72.0, 69.2, 64.2, 63.5, 58.1, 50.8, 45.7, 45.0, 40.7 (2C), 38.7, 37.2, 31.5, 22.5, 20.9, 20.1, 18.0, 14.4, 13.8, 13.6 (2C), 10.6. MS (ESI) m/z 870 (MH+). Anal. Calcd for $C_{49}H_{63}N_3O_{11}$: Theory: C, 67.64; H, 7.30; N, 4.83; Found: C, 67.37; H, 7.21; N, 4.53.

4.1.10. ABT-773 (1). ABT-773-2′-benzoate **20** (495.0 g, 0.568 mol) was heated in methanol (1.5 L) for 16 h. The reaction was monitored by HPLC. Retention times: desired product 11.1 min, starting material 14.2 min, methyl benzoate 14.6 min. After cooling to room temperature, the reaction mixture was concentrated to approximately 1 L, diluted with 97:3 EtOAc/heptane (3 L), 0.5 N HCl (1.35 L), and agitated. The bottom product-containing layer was separated, diluted with EtOAc (2.5 L), and treated with 15% aq K_2CO_3 solution (1.4 L). The top product-containing layer was separated and concentrated to approximately 1.2 L and allowed to crystallize. The resulting suspension was concentrated and diluted with heptane to achieve a 10:1 mixture of heptane:ethyl acetate. The product was filtered, washed with 10:1 heptane:EtOAc (3×300 mL), and dried to give 402 g (92%) of ABT-773 (**1**) as a white crystalline solid: mp=211–213 °C; IR (film, cm^{-1}) 1769.7, 1746.7, 1714, 1701, 1457, 1108, 1049; ^1H NMR ($CDCl_3$) δ 9.02 (d, $J=2.3$ Hz, 1H), 8.17 (d, $J=2.1$ Hz, 1H), 8.05 (d, $J=8.4$ Hz, 1H), 7.82 (d, $J=8.1$ Hz, 1H), 7.63 (t, $J=6.9$ Hz, 1H), 7.50 (t, $J=6.9$ Hz, 1H), 6.5 (d, $J=16.0$ Hz, 1H), 6.21–6.16 (m, 1H), 5.48 (s, 1H), 4.94 (dd, $J=3.2$, 9.1 Hz, 1H), 4.40 (d, $J=4.7$ Hz, 1H), 4.36 (d, $J=7.3$ Hz, 1H), 3.96 (q, $J=6.7$ Hz, 1H), 3.91 (s, 1H), 3.84 (dd, $J=6.5$, 11.9 Hz, 1H), 3.71 (dd, $J=7.2$, 11.9 Hz, 1H), 3.57–3.53 (m, 1H), 3.50 (bs, 1H), 3.22–3.16 (m, 2H), 2.96 (q, $J=6.5$ Hz, 1H), 2.67–2.61 (m, 1H), 2.52–2.44 (m, 1H), 2.26 (s, 6H), 1.90–1.84 (m, 1H), 1.81 (d, $J=11.9$ Hz, 1H), 1.69 (dd, $J=1.2$, 14.5 Hz, 1H), 1.66 (ddd, $J=1.8$, 2.0, 12.6 Hz, 1H), 1.54–1.51 (m, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.40 (d, $J=8$ Hz, 3H), 1.39 (d, $J=6.9$ Hz, 3H), 1.21 (q, $J=11.0$ Hz, 1H), 1.17 (d, $J=6.1$ Hz, 3H), 1.13 (d, $J=7.5$ Hz, 3H), 1.11 (d, $J=6.9$ Hz, 3H), 0.79 (t, $J=7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 217.3, 205.3, 169.6, 157.6, 149.7, 147.6, 132.4, 129.9, 129.6, 129.1, 129.0, 128.5, 128.0 (2C), 126.7, 102.9, 83.5, 78.7, 77.5, 76.4, 70.2, 69.5, 65.8, 64.3, 58.1, 50.8, 46.2, 45.0, 40.2 (2C), 39.0, 37.3, 28.3, 22.6, 21.1, 20.1, 18.0, 14.4, 14.1, 13.6 (2C), 10.6. MS (ESI) *m/z* 766 (MH+). Anal. Calcd for $C_{42}H_{59}N_3O_{10}$: Theory: C, 65.86; H, 7.76; N, 5.49; Found: C, 65.69; H, 7.60; N, 4.34.

References and notes

1. Omura, S.; Tsuzuki, K.; Sunazuka, T.; Marui, S.; Toyoda, H.; Inatomi, N.; Itoh, Z. *J. Med. Chem.* **1987**, *30*, 1941.
2. Ma, Z.; Nemoto, P. A. *Curr. Med. Chem.-Anti-Infective Agents* **2002**, *1*, 15.
3. Ackermann, G.; Rodloff, A. C. *J. Antimicrob. Chemother.* **2003**, *51*, 497. (b) Zhanel, G. G.; Hisanaga, T.; Nichol, K.; Wierzbowski, A.; Hoban, D. J. *Exp. Opin. Emerg. Drugs* **2003**, *8*, 297.
4. Nilius, A. M.; Ma, Z. *Curr. Opin. Pharmacol.* **2002**, *1*, 493. (b) Bryskier, A.; Denis, A. *Macrolide Antibiot.* **2002**, 97.
5. Agouridas, C.; Denis, A.; Auger, J.-M.; Bennedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; Gouin D'Ambrieres, S.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080. (b) Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V.; Flamm, R.; Mitten, M.; Meulbroek, J.; Ewing, P.; Alder, J.; Or, Y.-S. *J. Med. Chem.* **2001**, *44*, 4137. (c) Or, Y.-S.; Clark, R. F.; Wang, S.; Chu, D. T. W.; Nilius, A. M.; Flamm, R. K.; Mitten, M.; Ewing, P.; Alder, J.; Ma, Z. *J. Med. Chem.* **2000**, *43*, 1045–1049.
6. (a) Or, Y.-S.; Ma, Z.; Clark, R. F.; Chu, D. T.; Plattner, J. J.; Griesgraber, G. US Patent 5,866,549, 1999.(b) Clark, R. F.; Ma, Z.; Wang, S.; Greisgraber, G.; Tufano, M.; Yong, H.; Li, L.; Zhang, X.; Nilius, A. M.; Chu, D. T. W.; Or, Y.-S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 815–819.
7. Lartey, P. A.; Perun, T. J. In *Studies in Natural Products Chemistry*, Atta-ur-Rahman, Ed.; Elsevier Scientific Publishers: Amsterdam, 1993, Vol. 13, p 155.
8. Morimoto, S.; Misawa, Y.; Asaka, T.; Kondoh, H.; Watanabe, Y. *J. Antibiot.* **1990**, *43*, 570.
9. Kawashima, Y.; Morimoto, S.; Matsunaga, J.; Kashimura, M.; Adachi, J.; Watanabe, Y.; Katayama, K.; Hirono, S.; Moriguchi, I. *Chem. Pharm. Bull.* **1990**, *38*, 1485.
10. Massey, E. M.; Kitchell, B.; Martin, L. D.; Gerzon, K.; Murphy, H. W. *Tetrahedron Lett.* **1970**, *11*, 157. (b) Morimoto, S.; Adachi, T.; Asaka, T.; Kashimura, M.; Watanabe, Y. US Patent, 4,670,549, 1987. (c) Watanabe, Y.; Adachi, J.; Asaka, J.; Kashimura, M.; Morimoto, M. *Heterocycles* **1990**, *31*, 2121.(d) Morimoto, S.; Adachi, T.; Matsunaga, T.; Kashimura, M.; Asaka, T.; Watanabe, Y.; Sota, K.; Sekiuchi, K. US Patent, 4,990,602, 1991. (e) Watanabe, Y.; Morimoto, S.; Adachi, T.; Kashimura, M.; Asaka, T. *J. Antibiot.* **1993**, *46*, 647. (f) Omura, S.; Morimoto, S.; Nagate, T.; Adachi, T.; Kohno, Y. *Yakugaku Zasshi* **1992**, *112*, 593. (g) Watanabe, Y.; Adachi, T.; Asaka, T.; Kashimura, M.; Matsunaga, T.; Morimoto, S. *J. Antibiot.* **1993**, *46*, 1163. (h) Watanabe, Y.; Kashimura, M.; Asaka, T.; Adachi, T.; Morimoto, S. *Heterocycles* **1993**, *36*, 243.
11. (a) Watanabe, Y.; Morimoto, S.; Omura, S., US Patent, 4,311,803, 1982. (b) Morimoto, S.; Takahashi, Y.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1984**, *37*, 187. (c) Watanabe, Y.; Morimoto, S.; Goi, M.; Mitsukuchi, M.; Adachi, T.; Nakagami, J.; Asaka, T.; Eguchi, T.; Sota, K. US Patent, 4,672,109, 1987. (d) Morimoto, S.; Adachi, T.; Asaka, T.; Watanabe, Y.; Sota, K. US Patent, 4,680,386, 1987. (e) Morimoto, S.; Adachi, T.; Misawa, Y.; Nagate, T.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1990**, *43*, 544.
12. Stoner, E. J.; Peterson, M. J.; Allen, M. S.; DeMattei, J. A.; Haight, A. R.; Leanna, M. R.; Patel, S. R.; Plata, D. J.; Premchandran, R. H.; Rasmussen, M. W. *J. Org. Chem.* **2003**, *68*, 8847. (b) Stoner, E. J.; Peterson, M. J.; Ku, Y.-Y.; Cink, R. D.; Cooper, A. J.; Deshpande, M. N.; Grieme, T.; Haight, A. R.; Hill, D. R.; Hsu, M. C.-P.; King, S. A.; Leanna, M. R.; Lee, E. C.; McLaughlin, M. A.; Morton, H. E.; Napier, J. J.; Plata, D. J.; Raje, P. S.; Rasmussen, M.; Riley, D.; Tien, J.-H. J.; Wittenberger, S. J. US Patent, 6,437,106, 2002. (c) Lakhmiri, R.; Lhoste, P.; Sinou *Tetrahedron Lett.* **1989**, *30*, 4669.
13. Houlihan, F.; Bouchard, F.; Frechet, M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153. (b) Allen, M. S.; Premchandran, R. H.; Chang, S.-J.; Condon, S.; Dematteі, J. J.; King, S. A.; Kolaczkowski, L.; Manna, S.; Nichols, P. J.; Patel, H. H.; Patel, S. R.; Plata, D. J.; Stoner, E. J.; Tien, J.-H. J.; Wittenberger, S. J. US Patent, 6,417,366, 2002. (c) Allen, M. S.; Premchandran, R. H.; Chang, S.-J.; Condon, S.; Demattei, J. J.; King, S. A.; Kolaczkowski, L.; Manna, S.; Nichols, P. J.; Patel, H. H.; Patel, S. R.; Plata, D. J.; Stoner, E. J.; Tien, J.-H. J.; Wittenberger, S. J. US Patent, 6,579,986, 2003.
14. Curran, D. P.; Brill, J. F.; Rakiewicz, D. M. *J. Org. Chem.*

1984, 49, 1654. (b) Lee, J. G.; Kwak, K. H.; Hwang, J. P. *Tetrahedron Lett.* **1990**, 31, 6677. (c) Greene, T. H.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991. (d) Singh, L.; Ram, R. N. *Synth. Commun.* **1993**, 23, 3139.

15. Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. K. *J. Org. Chem.* **1988**, *53*, 2340.
16. Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Corey, E. J.; Kim, C. U. *J. Org. Chem.* **1973**, *38*, 1233.
17. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
18. Hauske, J. R.; Guadliana, M.; Kostek, G. *J. Org. Chem.* **1987**, *52*, 4622.

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General and systematic synthetic entry to carotenoid natural products

Young Cheol Jeong, Minkoo Ji, Jun Sup Lee, Jae-Deuk Yang, Jingquan Jin, Woonphil Baik and Sangho Koo*

Department of Chemistry, Myong Ji University, San 38-2, Nam-Dong, Yongin, 449-728 Kyunggi-Do, South Korea

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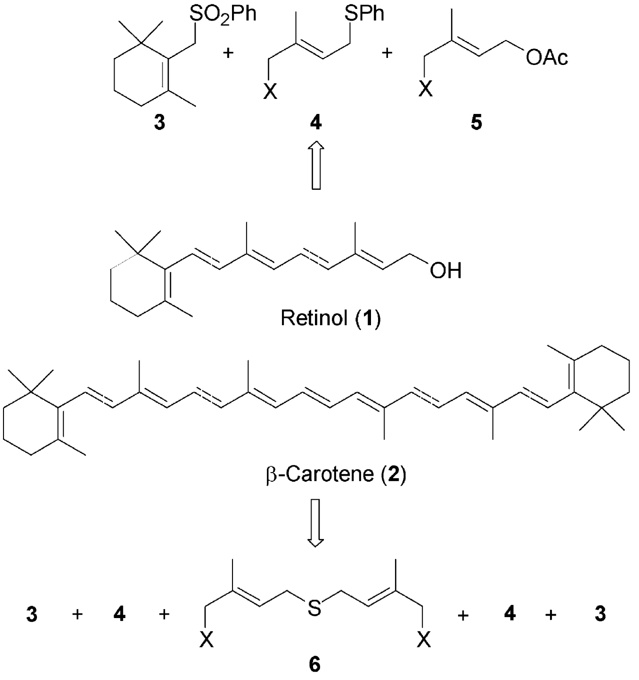
Abstract—A general synthetic method of carotenoid natural products has been developed, in which the systematic chain extension and termination processes were applied. The syntheses of the chain extension and termination units were greatly improved by the use of the common intermediate, 1-bromo-4-chloro-3-methyl-2-butene (**8**), in a short and highly efficient way. The C_{10} chain initiation β-cyclogeranyl sulfone (**3**) was coupled with the C_5 chain extension unit to give the C_{15} chain-extended allylic sulfone after chemoselective sulfide oxidation. This chain-extended C_{15} allylic sulfone underwent the Julia olefination reaction with the C_5 and the C_{10} chain termination units to give retinol (**1**) and β-carotene (**2**), respectively.

1. Introduction

Carotenoids are biologically, medicinally, and commercially important natural products, which include retinol (vitamin A), retinoic acid, β-carotene, canthaxanthin, and astaxanthin etc.[1] Retinol is an essential nutrient for higher animals required for cell growth and differentiation, fertilization, and visual action. Retinoic acid shows broad treatment effects on skin disorders including acne and even on emphysema.[2] β-Carotene and astaxanthin have wide industrial applications especially in animal feeds and the coloration of foodstuffs. These carotenoids belong to the isoprenoid family according to their biogenetic origin, which are enzymatically assembled by repeated uses of isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks.[1] Chemical syntheses of these carotene compounds,[3] therefore, can be generalized in a systematic way by utilizing 'the C_5 building blocks,' as chemical mimics for IPP or DMAP. The Julia sulfone olefination protocol[4] is the best method to construct these highly unstable carotenoid structures through the much more stable allylic sulfone intermediates that can be transformed to the fully conjugated polyene chains in the final stage. Retrosynthetic analyses of the two representative carotenoid compounds, retinol (**1**) and β-carotene (**2**) utilizing the sulfone chemistry disintegrate these carotenoid structures systematically into the chain initiation allylic sulfone **3**, the chain extension C_5 unit **4**, and the chain termination C_5 and C_{10} units, **5** and **6**, respectively (Scheme 1). We herein report the details of our systematic studies on



Scheme 1. Disconnection approaches to retinol (**1**) and β-carotene (**2**).

Keywords: Carotenoid; Olefination; Retinol; β-Carotene; Total synthesis.

* Corresponding author. Tel.: +82 31 330 6185; fax: +82 31 335 7248; e-mail: sangkoo@mju.ac.kr

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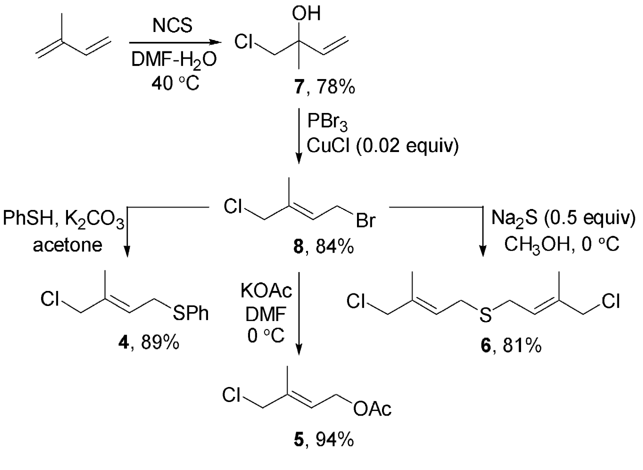
the efficient syntheses of each unit, the chain extension process, and the total syntheses of retinol (**1**) and β-carotene (**2**).

2. Results and discussion

β-Cyclogeranyl sulfone (**3**)[5] which can be readily prepared by the electrophilic cyclization of geranyl sulfone was used as a chain initiation unit for our carotenoid synthesis. The C_5 chain extension unit was so designed as to give the 1,5-arrangement of the methyl substituents, which is the general substitution pattern of the carotenoid compounds, and to give the chain-extended allylic sulfones again after the Julia coupling reaction with the chain-initiating allylic sulfone **3**. 4-Halo-3-methyl-2-butenyl sulfide **4** instead of the corresponding sulfone compound was selected in order to facilitate the Julia coupling reaction with β-cyclogeranyl sulfone **3**, where the undesirable dehydrohalogenation reaction could be prevented.[6] The resulting chain-extended allylic sulfide can be oxidized to the corresponding allylic sulfone. The chain-extended allylic sulfone then undergoes olefination process with the C_5 and the C_{10} chain termination units **5** and **6** to give retinol (**1**) and β-carotene (**2**), respectively. Bis(haloallylic) sulfide **6** has proven to be a stable substitute for highly unstable 1,8-dihalo-2,7-dimethyl-2,4,6-octatriene as the C_{10} chain termination unit for β-carotene and lycopene syntheses.[6,7]

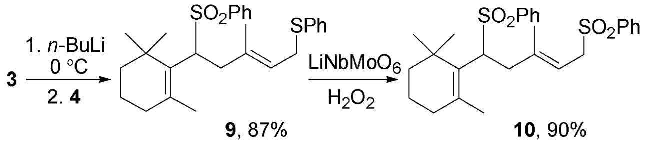
It was envisioned that the chain extension unit **4**[8] and the chain termination units **5**[9] and **6**[6,7] might be obtained in a highly efficient and convenient way from the common intermediate **8** in proviso that the ambidextrous allylic halide **8** could show different electrophilic reactivity (Scheme 2). In fact, the nucleophiles of PhS^- (PhSH, K_2CO_3 in acetone), AcO^- (AcOK in DMF) and S^{2-} (Na_2S in CH_3OH) discriminated allylic bromide from allylic chloride of 1-bromo-4-chloro-3-methyl-2-butene (**8**) to directly give rise to the C_5 chain extension unit, phenyl 4-chloro-3-methyl-2-butenyl sulfide (**4**)[10] in 89% yield and the C_5 and the C_{10} chain termination units, 4-chloro-3-methyl-2-butenyl acetate (**5**)[10] and bis(4-chloro-3-methyl-2-butenyl) sulfide (**6**) in 94 and 81% yields, respectively.



Scheme 2. Syntheses of the chain-extension unit **4** and the chain-termination units **5** and **6**.

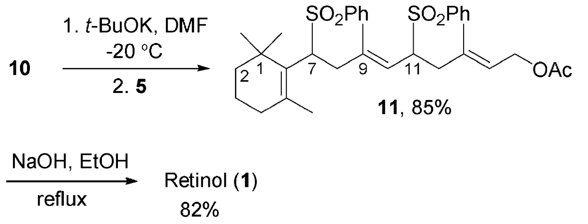
The ambidextrous allylic halide **8** was prepared from readily available isoprene in two steps: chlorohydrin formation using *N*-chlorosuccinimide in H_2O-DMF (78% yield), followed by PBr_3-promoted bromination of the resulting chlorohydrin **7** under CuCl catalyst (84% yield), where the allylic-transposed bromination product **8** was exclusively obtained with a high *E*:*Z* ratio of 10:1.[10]

The chain extension unit **4** that was proposed as a chemical mimic for IPP or DMAP was then utilized in the chain extension process. The Julia coupling reaction of β-cyclogeranyl sulfone (**3**) with the C_5 chain extension unit **4** produced the chain-extended allylic sulfides **9** (Scheme 3).[11] This coupling reaction works well (87% yield) with *n*-BuLi as a base. Chemoselective sulfur oxidation of **9** proceeded smoothly with 2.5 equiv H_2O_2 under $LiNbMoO_6$ catalyst[12] to give the C_{15} disulfone compound **10** (90% yield), where no epoxidation at the tetra-substituted double bond in the cyclohexene ring was observed contrary to the case of the conventional electrophilic oxidant such as MCPBA. The white crystalline disulfone compound **10** was easily purified by washing with diethyl ether.



Scheme 3. Chain extension process to obtain the C_{15} disulfone compound **10**.

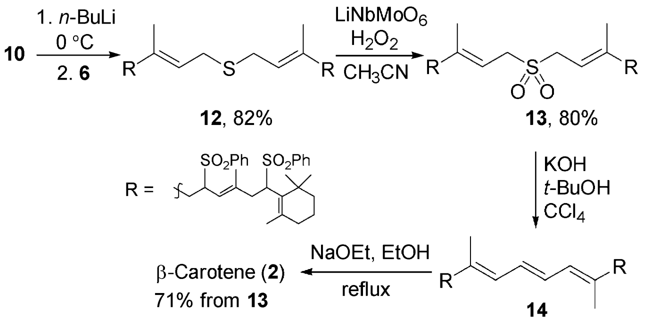
The Julia olefination reaction of the chain-extended allylic sulfone **10** with the C_5 chain termination unit **5** produced retinol (**1**). The coupling reaction of the C_{15} disulfone **10** and the C_5 unit **5** under *t*-BuOK/DMF condition provided the C_{20} compound **11** in 85% yield (Scheme 4). Deprotonation at the α-carbons to the benzenesulfonyl groups of the disulfone **10** can be completed by the use of 2 equiv of a strong base such as *t*-BuOK or *n*-BuLi, where the coupling reaction proceeded only at the less-substituted secondary carbanion. The dehydrosulfonation reaction of the C_{20} coupling product **11** using NaOH as a base in EtOH then produced all-(*E*)-retinol (**1**) in 82% yield after chromatographic separation of a small amount (less than 10%) of 13-(*Z*)-retinol.[13] It is beneficial to use NaOH as a base in EtOH and to operate the reaction initially at room temperature and then at the reflux temperature of EtOH to facilitate the hydrolysis of acetate first, and then promote dehydrosulfonation reaction in order to minimize the possibility of the base-promoted elimination of acetate producing anhydro vitamin A. Base-promoted



Scheme 4. Retinol synthesis.

dehydrosulfonation reaction produces a *E*-double bond in the Julia sulfone olefination.[14] Dehydrosulfonation at C(7,8) in the compound **11** proceeded rapidly even at room temperature presumably due to steric congestion, however, dehydrosulfonation at C(11,12) requires a stronger condition of boiling EtOH.

The Julia olefination reaction of the chain-extended allylic sulfone **10** with the C_{10} chain termination unit **6** in combination with the Ramberg-Bäcklund reaction produced β-carotene (**2**). The coupling reaction of the C_{15} disulfone **10** (2 equiv) with the C_{10} unit **6** (1 equiv) provided the C_{40} compound **12** (Scheme 5). To complete the deprotonation and the coupling reaction at the secondary α-carbon to the benzenesulfonyl group in compound **10**, 2 equiv *n*-BuLi was used as a base to give the optimized yield of 82%. Chemoselective oxidation of the bisallylic sulfide **12** to the corresponding bisallylic sulfone **13** proceeded by H_2O_2 (2.5 equiv) under $LiNbMoO_6$ catalyst (0.05 equiv) in 80% yield,[12] where MeCN was used as a solvent to improve the solubility of the compound **12** containing tetra-benzenesulfonyl groups. The Ramberg-Bäcklund reaction of bisallylic sulfone **13** under Meyers condition[15] produced the C_{40} compound **14** containing the central triene moiety. It was necessary to apply the dehydrosulfonation reaction to the crude product **14** without purification because the C_{40} compound **14** was not stable under air, and furthermore, some of the premature dehydrosulfonation products at C(7) were also observed at the Ramberg-Bäcklund reaction stage. Dehydrosulfonation reaction of the crude product **14** under excess NaOEt in refluxing EtOH, which presumably allowed thermal isomerization of the (*Z*)-isomers, then produced all-(*E*)-β-carotene (**2**) in 71% overall yield after two steps from the bisallylic sulfone **13**.



Scheme 5. β-Carotene synthesis.

3. Conclusion

We have developed a general and systematic synthetic method of carotenoid natural products. This biomimetic approach highlights the use of the C_5 chain extension unit **4** and the C_5 and the C_{10} chain termination units **5** and **6** that are prepared from the common intermediate **8** in a highly efficient way. The usefulness and general applicability of our systematic approach have been demonstrated in the synthesis of retinol (**1**) and β-carotene (**2**). This approach for carotenoid syntheses can be applied to the systematic syntheses of other isoprenoid natural products including terpenoids and steroids, which have the same biogenetic origin as the carotenoid compounds.

4. Experimental

4.1. General information

^1H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded in deuterated chloroform ($CDCl_3$). Solvents for extraction and chromatography were reagent grade and used as received. The column chromatography was performed by the method of Still with silica gel 60, 230–400 mesh ASTM supplied by Merck. Solvents used as reaction media were dried over pre-dried molecular sieve (4 Å) by microwave oven. All reactions were performed under a dry argon atmosphere in oven-dried glassware except for those used H_2O as a reaction medium.

4.2. Bis(4-chloro-3-methyl-2-butenyl) sulfide (6)

To a stirred solution of 1-bromo-4-chloro-3-methyl-2-butene (**8**) (15.6 g, 80.7 mmol) in THF (100 mL) at 0 °C was added Na_2S (6.76 g, 40.3 mmol). The reaction mixture was stirred at that temperature for 6 h, and H_2O was added. The mixture was extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **6** [7.83 g, 32.7 mmol; (*E*,*E*):(*E*,*Z*)=5:1] in 81% yield.

4.2.1. Data for (*E*,*E*)-6.[7] ^1H NMR δ 1.78 (s, 6H), 3.10 (d, $J=7.6$ Hz, 4H), 4.03 (s, 4H), 5.62 (t, $J=7.6$ Hz, 2H) ppm. Data for (*E*,*Z*)-**6**: ^1H NMR δ 1.78 (s, 3H), 1.83 (s, 3H), 3.10 (d, $J=7.6$ Hz, 2H), 3.12 (d, $J=8.1$ Hz, 2H), 4.01 (s, 2H), 4.03 (s, 2H), 5.44 (t, $J=8.1$ Hz, 1H), 5.62 (t, $J=7.6$ Hz, 1H) ppm.

4.3. 3-Methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-1,5-dibenzenesulfonyl-2-pentene (10)

To a stirred solution of **3** (2.78 g, 10.00 mmol) in THF (50 mL) at 0 °C was added 1.6 M solution of *n*-BuLi in hexane (7.5 mL, 12.00 mmol). The mixture was stirred for 1 h, and a solution of **4** (2.55 g, 12.00 mmol) in THF (10 mL) was added. The mixture was stirred at 0 °C for 1.5 h, quenched with 1 M HCl (20 mL), and extracted with ether. The organic layer was washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give **9**[11] (2.96 g, 8.71 mmol) in 87% yield.

To a stirred solution of **9** (2.94 g, 6.50 mmol) in CH_3OH (30 mL) and benzene (10 mL) at 0 °C were added $LiNbMoO_6$ (94 mg, 0.30 mmol) and 30% H_2O_2 solution (1.84 g, 16.25 mmol). The reaction mixture was warmed up and stirred at 25 °C for 6 h, and most of solvent was removed under reduced pressure. The crude material was diluted with $CHCl_3$ (50 mL), washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **10** (2.83 g, 5.80 mmol) in 90% yield. The product was further purified by recrystallization with ether to give the (*E*)-**10** (2.55 g, 5.23 mmol) in 72% yield.

4.3.1. Data for (*E*)-10. ^{1}H NMR δ 0.76 (s, 3H), 0.98 (s, 3H), 1.11 (s, 3H), 1.33–1.60 (m, 4H), 1.95–2.18 (m, 2H), 1.99 (s, 3H), 2.57 (d of ABq, $J_{AB}=14.6$ Hz, $J_d=6.2$ Hz, 1H), 3.10 (d of ABq, $J_{AB}=14.6$ Hz, $J_d=7.1$ Hz, 1H), 3.64 (d of ABq, $J_{AB}=15.4$ Hz, $J_d=7.8$ Hz, 1H), 3.70 (d of ABq, $J_{AB}=15.4$ Hz, $J_d=7.8$ Hz, 1H), 3.87 (dd, $J=7.1$, 6.2 Hz, 1H), 5.23 (dt, $J_d=1.0$ Hz, $J_t=7.8$ Hz, 1H), 7.43–7.70 (m, 6H), 7.76–7.93 (m, 4H) ppm; ^{13}C NMR δ 15.7, 18.9, 23.3, 28.4, 28.9, 34.5, 36.0, 39.6, 41.1, 55.9, 65.2, 114.7, 128.2, 128.5, 128.8, 129.1, 130.5, 133.2, 133.7, 138.2, 138.7, 141.6 ppm; IR (KBr) 1448, 1385, 1144, 1084 cm^{-1}; HRMS (CI$^+$) calcd for $C_{27}H_{35}O_4S_2$ 487.1977, found 487.1990.

4.4. 1-Acetoxy-5,9-dibenzenesulfonyl-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadiene (11)

To a stirred solution of **10** (0.50 g, 1.03 mmol) in DMF (20 mL) at −20 °C was added *t*-BuOK (0.29 g, 2.47 mmol). The mixture was stirred at that temperature for 1 h, and a solution of C_5 chloroacetate **5** (0.25 g, 1.54 mmol) in DMF (5 mL) was added. The resulting mixture was stirred at −20 °C for 3 h, and 2 M HCl solution (10 mL) was added to quench the reaction. The mixture was extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **11** (0.54 g, 0.88 mmol) in 85% yield, which was a 2:1 mixture of diastereomers

4.4.1. Data for the major isomer of 11. ^{1}H NMR δ 0.68 (s, 3H), 0.80 (s, 3H), 1.12 (s, 3H), 1.27–1.68 (m, 4H), 1.57 (s, 3H), 1.95–2.09 (m, 2H), 1.96 (s, 3H), 2.01 (s, 3H), 2.24 (dd, $J=14.3$, 11.3 Hz, 1H), 2.62 (dd, $J=15.0$, 5.9 Hz, 1H), 2.87 (br d, $J=14.3$ Hz, 1H), 3.05 (dd, $J=15.0$, 5.9 Hz, 1H), 3.78 (t, $J=5.9$ Hz, 1H), 3.91 (ddd, $J=11.3$, 10.3, 3.3 Hz, 1H), 4.38–4.55 (m, 2H), 4.95 (d, $J=10.3$ Hz, 1H), 5.28 (t, $J=6.7$ Hz, 1H), 7.47–7.70 (m, 6H), 7.75–7.95 (m, 4H) ppm; ^{13}C NMR δ 15.9, 16.3, 18.9, 20.9, 23.5, 28.7, 28.7, 34.5, 35.6, 38.4, 39.5, 41.6, 60.9, 63.0, 65.6, 120.8, 122.3, 128.8, 129.0, 129.0, 129.4, 131.5, 133.4, 133.8, 136.2, 137.3, 138.0, 140.9, 142.1, 170.9 ppm; IR (KBr) 2934, 1737, 1446, 1304, 1233, 1145 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{22}H_{33}O_2$ ($C_{34}H_{45}O_6S_2-2C_6H_6SO_2$) 329.2481, found 329.2485.

4.5. Retinol (1)[4]

To a stirred solution of **11** (7.53 g, 12.27 mmol) in 99.9% EtOH (100 mL) was added NaOH (4.91 g, 0.12 mol). The mixture was stirred at room temperature for 1 h and then heated to reflux for 15 h. The reaction mixture was cooled to room temperature, and most of the solvent was removed under reduced pressure. The mixture was carefully treated with H_2O and 3 M HCl (40 mL) solution, extracted with $CHCl_3$, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product which contained a small amount (less than 10%) of 13-(*Z*)-retinol was purified by silica gel flash column chromatography to give all-(*E*)-retinol (**1**) (2.88 g, 10.06 mmol) in 82% yield.

4.6. Bis[3,7-dimethyl-5,9-dibenzenesulfonyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadienyl] sulfide (12)

To a stirred solution of **10** (4.00 g, 8.21 mmol) in THF (50 mL) at 0 °C was added 1.6 M solution of *n*-BuLi in hexane (11.3 mL, 18.1 mmol). The mixture was stirred at that temperature for 20 min, and a solution of **6** (1.18 g, 4.11 mmol) in THF (15 mL) was added. The resulting mixture was stirred at 0 °C for 1 h, quenched with 1 M HCl solution, extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **12** (3.85 g, 6.75 mmol) in 82% yield. This coupling product was composed of a mixture of diastereomers, which were not easily separable.

4.6.1. Data for the major diastereomer of 12. ^{1}H NMR δ 0.77 (s, 6H), 0.82 (s, 6H), 1.16 (s, 6H), 1.23–1.43 (m, 4H), 1.43–1.52 (m, 4H), 1.50 (s, 6H), 1.86–2.12 (m, 4H), 1.97 (s, 6H), 2.03–2.32 (m, 2H), 2.44–3.00 (m, 6H), 2.90–3.20 (m, 4H), 3.72–3.99 (m, 4H), 4.83–5.00 (m, 2H), 5.12–5.27 (m, 2H), 7.43–7.68 (m, 12H), 7.74–7.95 (m, 8H) ppm; ^{13}C NMR δ 15.8, 18.7, 23.2, 28.5, 28.7, 34.4, 35.5, 35.7, 38.4, 39.4, 40.9, 41.4, 62.6, 65.4, 120.7, 124.3, 124.9, 128.6, 128.9, 129.0, 129.0, 131.3, 133.4, 133.7, 137.4, 137.7, 140.9, 141.8 ppm; IR (KBr) 2931, 1447, 1304, 1144 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{52}H_{71}S_3O_4$ [$C_{64}H_{83}S_5O_8-2\times(C_6H_6SO_2)$] 855.4514, found 855.4511.

4.7. Bis[3,7-dimethyl-5,9-dibenzenesulfonyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6-nonadienyl] sulfone (13)

To a stirred solution of **12** (1.61 g, 1.41 mmol) in MeCN (20 mL) at 0 °C were added $LiNbMoO_6$ (20 mg, 0.07 mmol) and a 35% aqueous solution of H_2O_2 (0.34 g, 3.53 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 12 h. The mixture was then extracted with CH_2Cl_2, washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give **13** (1.36 g, 1.13 mmol) in 80% yield. This coupled product was composed of a mixture of diastereomers, which were not easily separable.

4.7.1. Data for the major diastereomer of 13. ^{1}H NMR δ 0.67 (s, 6H), 0.79 (s, 6H), 1.28 (s, 6H), 1.23–1.54 (m, 8H), 1.67 (s, 6H), 1.93–2.03 (m, 4H), 2.00 (s, 6H), 2.05–2.66 (m, 4H), 2.71–2.92 (m, 2H), 2.98–3.32 (m, 2H), 3.42–3.70 (m, 4H), 3.74–4.02 (m, 4H), 4.86–5.10 (m, 2H), 5.13–5.40 (m, 2H), 7.45–7.69 (m, 12H), 7.72–7.92 (m, 8H) ppm; ^{13}C NMR δ 15.8, 18.9, 23.4, 28.4, 28.7, 34.6, 35.7, 36.1, 38.4, 39.5, 41.5, 51.7, 62.3, 65.4, 113.8, 114.5, 120.4, 128.6, 129.0, 129.0, 129.2, 131.1, 133.5, 133.8, 137.2, 137.8, 140.8, 142.2 ppm; IR (KBr) 2931, 1447, 1305, 1144 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{46}H_{65}S_2O_4$ [$C_{64}H_{83}S_5O_{10}-3\times(C_6H_6SO_2)$] 745.4324, found 745.4333.

4.8. β-Carotene (2)[3,7]

To a stirred solution of **13** (0.98 g, 0.84 mmol, 1 equiv) in CCl_4 (15 mL) and *t*-BuOH (10 mL) at 0 °C was added pulverized KOH (0.47 g, 8.36 mmol, 10 equiv). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 10 h, and carefully quenched with H_2O. The mixture was then neutralized with 1 M HCl (10 mL), extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product (1.15 g) was not stable and directly used for the next dehydrosulfonation reaction without purification.

A solution of the crude product **14** (1.15 g) in 99.9% EtOH (20 mL) was added to a solution of NaOEt which was prepared by adding Na (1.20 g, 52.14 mmol) to 99.9% EtOH (50 mL). The resulting mixture was heated to reflux for 12 h, and cooled to room temperature. Most of the solvent was removed under reduced pressure. The crude mixture was treated with 1 M HCl solution, extracted with $CHCl_3$, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give all-(*E*)-β-carotene (**2**) (0.32 g, 0.60 mmol) in 71% overall yield from **13**.

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References and notes

1. (a) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, 1993; pp 168–191. (b) Cane, D. E. Comprehensive Natural Products Chemistry; Barton, D., Nakanishi, K., Eds.; Elsevier: Oxford, 1999; Vol. 2, pp 1–13.
2. (a) Orfanos, C. E.; Ehlert, R.; Gollnick, H. *Drugs* **1987**, *34*, 459–503. (b) Leid, M.; Kastner, P.; Chambon, P. *Trends Biochem. Sci.* **1992**, *17*, 427–433.
3. Reviews for carotenoid synthesis, (a) Pommer, H. *Angew. Chem.* **1960**, *72*, 911–915. (b) Isler, O. *Pure Appl. Chem.* **1979**, *51*, 447–462. (c) Widmer, E. *Pure Appl. Chem.* **1985**, *57*, 741–752. (d) Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45–58. (e) Bernhard, K.; Mayer, H. *Pure Appl. Chem.* **1991**, *63*, 35–44.
4. (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836. (b) Julia, M.; Arnould, D. *Bull. Soc. Chim. France* **1973**, 743–746. (c) Julia, M.; Launay, M.; Stacino, J.-P.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2465–2468. (d) Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, *23*, 3265–3266.
5. Torii, S.; Uneyama, K.; Isihara, M. *Chem. Lett.* **1975**, 479–482.
6. Ji, M.; Choi, H.; Park, M.; Kee, M.; Jeong, Y. C.; Koo, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3627–3629.
7. Choi, H.; Ji, M.; Park, M.; Yun, I.-K.; Oh, S.-S.; Baik, W.; Koo, S. *J. Org. Chem.* **1999**, *64*, 8051–8053.
8. Koo, S.; Yang, J.-D.; Kim, J.-S.; Lee, S.; Park, M. WO 037854 A1, 2003.
9. (a) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608–4613. (b) Babler, J. H.; Olsen, D. O. *Tetrahedron Lett.* **1974**, 351–354. (c) Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, 239–242.
10. Lee, J.-S.; Jeong, Y. C.; Ji, M.; Baik, W.; Lee, S.; Koo, S. *Synlett* **2004**, 1937–1940.
11. Ji, M.; Choi, H.; Jeong, Y. C.; Jin, J.; Baik, W.; Lee, S.; Kim, J. S.; Park, M.; Koo, S. *Helv. Chim. Acta* **2003**, *86*, 2620–2628.
12. Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* **2001**, *66*, 8192–8198.
13. Dehydrosulfonation reaction of the C_{20} disulfone compound to produce the ester of retinoic acid had been reported: Uneyama, K.; Torii, S. *Chem. Lett.* **1977**, 39–40.
14. Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387–396.
15. Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512.

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Formal synthesis of (−)-anisomycin based on stereoselective nucleophilic substitution along with 1,2-aryl migration☆

Machiko Ono, Shin Tanikawa, Keiko Suzuki and Hiroyuki Akita*

School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract—The stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** using the $AgNO_3$/MS 4 Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **6** from (4*S*)-**7** based on osmium tetroxide-catalyzed stereoselective hydroxylation was achieved.

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1. Introduction

We previously reported that silica gel promotes the γ-lactonization and the concomitant 1,2-aryl migration of 4-aryl-5-tosyloxy pentanoate **1** to give γ-lactone **2** along with complete inversion in high yield.[2] In the case of this reaction, an intramolecular attack of the ester carbonyl group to the σ-bridged phenonium ion **A** proceeded selectively at the C_4-position to provide the γ-lactone. If the 4-aryl-5-tosyloxy-2(*E*)-pentenoate **3** is subjected to solvolysis in the presence of a nucleophile, 1,2-aryl migration followed by intermolecular nucleophilic substitution along with inversion at the C_4-position should occur to afford the 5-aryl-4-substituted-2(*E*)-pentenoate derivatives **B**. However, this type of reaction has not been reported so far. In this paper, we wish to report both the possibility of the above-mentioned reaction and its stereochemical course. After the reaction was established, we describe the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** and its application to the formal total synthesis of (−)-anisomycin **6** via synthetic intermediate (4*S*)-**7**.

The antibiotic (−)-anisomycin **6**, isolated from the fermentation broth of *Streptomyces* sp., was reported to possess the 2*R*,3*S*,4*S* absolute configuration.[3] (−)-Anisomycin **6** exhibits strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to trichomonas vaginilis and of amoebic dysentery[3] (Scheme 1).

2. 1,2-Aryl migration under solvolysis condition

At first, 1,2-aryl migration along with the intermolecular nucleophilic substitution at the C_4-position using (±)-**4** and (±)-**8** was examined. The reported substrate (±)-**4**[4] was treated with Ts_2O to give the corresponding tosylate (±)-**9** (96% yield) which was subjected to solvolysis in water-saturated $MeNO_2$ to provide an inseparable mixture of (±)-**5** and (±)-**9**. This mixture was subjected to enzymatic hydrolysis using lipase OF-360 from *Candida rugosa* to afford the desired (±)-**5** (51% yield) together with the starting (±)-**9** (34% recovery). The structure of (±)-**5** was determined by NMR analysis and finally confirmed by conversion of (4*R*)-**4** into the synthetic intermediate (4*S*)-**7** for (−)-anisomycin **6** as described later in the text. The second substrate (±)-**8**[4] was also converted to the tosylate (±)-**10** (80% yield) which was subjected to solvolysis under the same conditions as for (±)-**9** to afford the 1,2-migration product (±)-**12** (53% yield). The structure of (±)-**12** was confirmed by NMR analysis and the similar spectrum of (±)-**12** to that of (±)-**5**. In the case of these reactions, the reaction rate was found to be sluggish at 90 °C for 2–4 d. It was apparent that there was no difference in reactivity between the substrates (±)-**9** and (±)-**10** (Scheme 2).

Then, the leaving group in the substrate (±)-**4** was exchanged to a bromo group. Bromination of (±)-**4** gave

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☆ See Ref. 1.

Keywords: (−)-Anisomycin; 1,2-Aryl migration; Phenonium ion.

* Corresponding author. Tel.: +81-474-72-1805; fax: +81-474-76-6195; e-mail: akita@phar.toho-u.ac.jp

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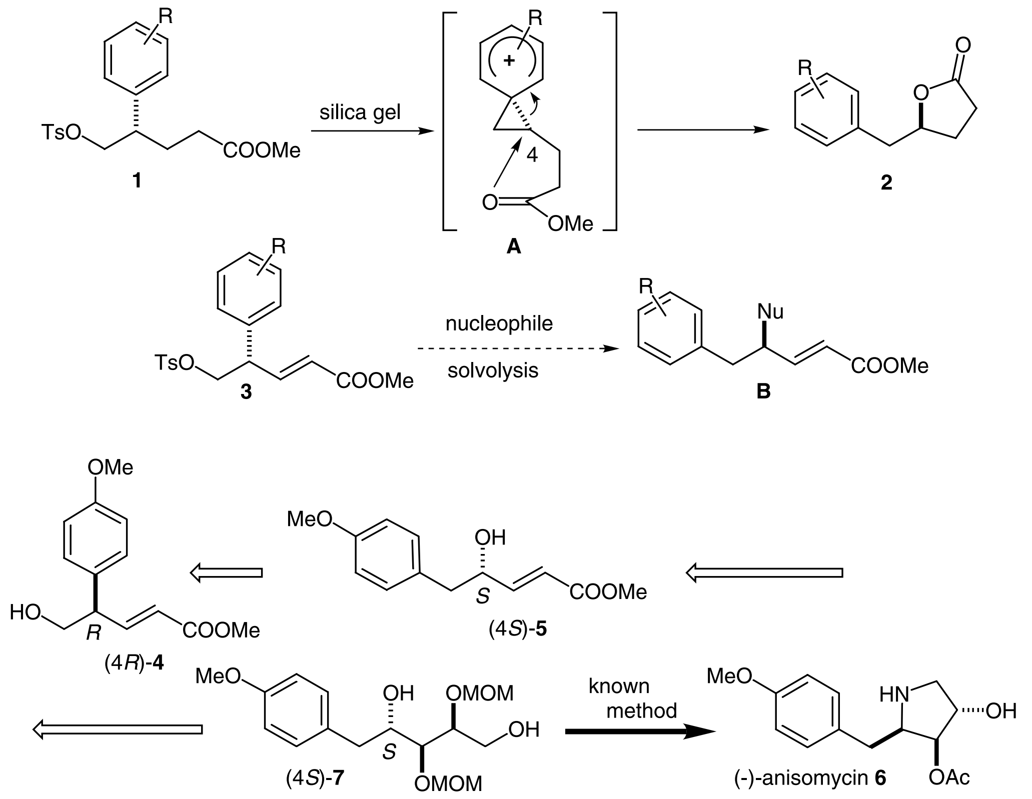
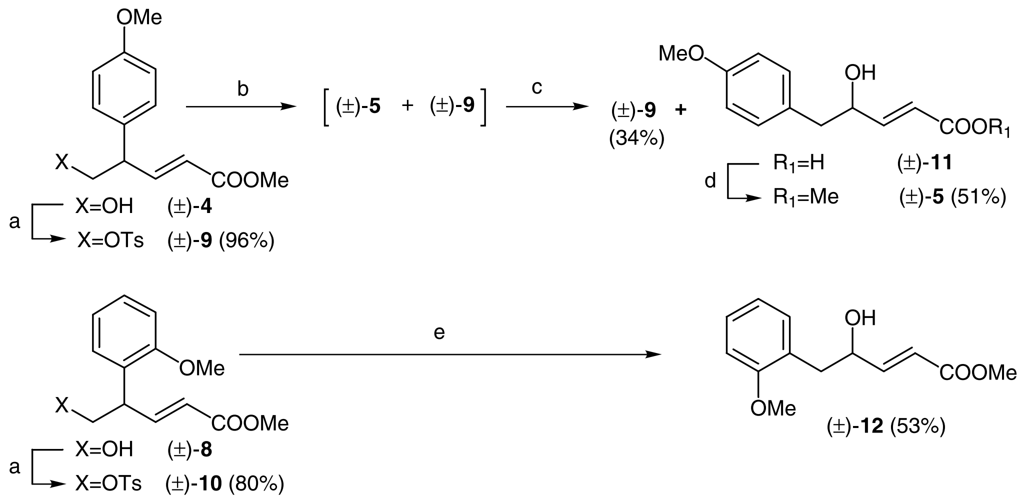


Scheme 1.

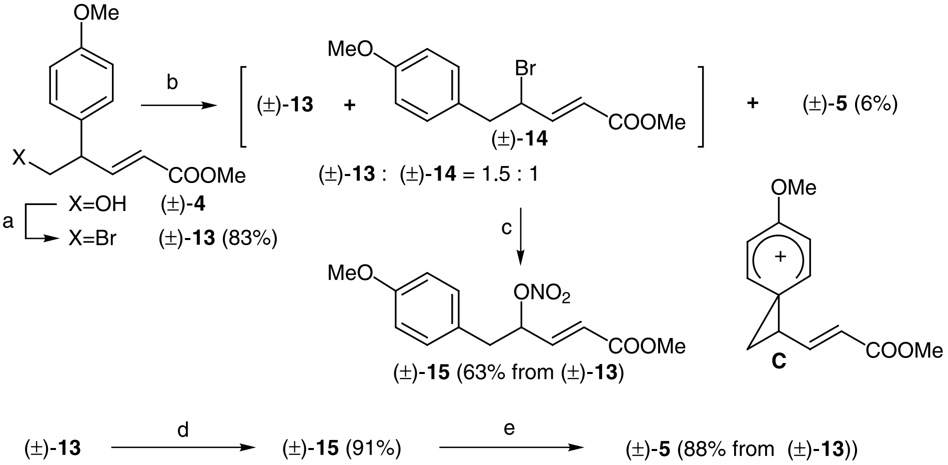
the corresponding bromide (±)-**13**[5] (83% yield) which was subjected to solvolysis in the same manner as in the case of (±)-**9** to afford (±)-**5** (6% yield) and an inseparable mixture (±)-**13**:(±)-**14** = 1.5:1) of the starting (±)-**13** and an aryl migration product (±)-**14** (Scheme 3).

The structure of (±)-**14** could be determined by NMR analysis and the formation of (±)-**14** could be presumed to be attributed to the fact that the liberated bromo ion attacked again at the C(4)-position of the σ-bridged phenonium ion C to provide (±)-**14**. In order to confirm this presumption, conversion of the bromo group in (±)-**14** to an oxygen functional group was carried out. The above-mentioned mixture was treated with $AgNO_3$ in the presence of molecular sieves (MS 4 Å) at room temperature for 12 h to furnish the nitrate (±)-**15** in 63% overall yield from (±)-**13**. In order to check an effect on the silver salt, six kinds of silver salts were examined in H_2O–saturated $MeNO_2$ and the results are shown in Table 1.

In the cases of entries 1, 2, 3, 5 and 6, the desired (±)-**5** was obtained in moderate yield. In the case of using silver trifluoroacetate (entry 4) and silver nitrate (entry 7), trifluoroacetate (±)-**16** and nitrate (±)-**15** were obtained in addition to (±)-**5**, respectively. In terms of the reaction conditions and reagent usefulness, $AgNO_3$ was found to be a suitable reagent to trap the generated bromo ion. This result focuses on the direct formation of (±)-**15** from (±)-**13**.



Scheme 2. (a) Ts_2O/pyridine; (b) $H_2O/MeNO_2$, 90 °C, 2 d; (c) lipase OF-360; (d) CH_2N_2; (e) (1) $H_2O/MeNO_2$, 90 °C, 4 d; (2) CH_2N_2.



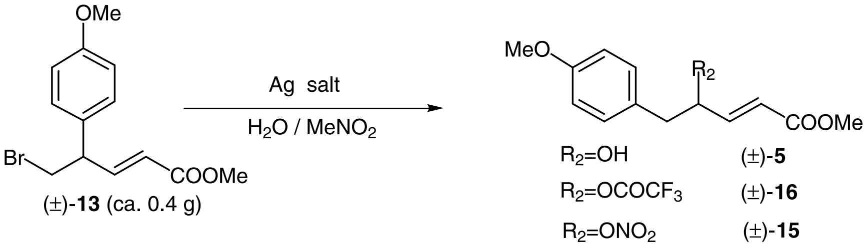
Scheme 3. (a) $CBr_4/Ph_3P/CH_3CN$; (b) $H_2O/MeNO_2$, 80 °C, 1 d; (c) $AgNO_3/MeNO_2$, MS 4 Å, rt, 12 h; (d) $AgNO_3/MeNO_2$, MS 4 Å, rt, 4 h; (e) $Zn/NH_4OAc/MeOH$, 0 °C, 1 h.

(Scheme 3) The reaction of (±)-**13** and $AgNO_3$, MS 4 Å in $MeNO_2$ at room temperature for 4 h yielded (±)-**15** (91% yield) which was treated with Zn and NH_4OAc in MeOH to give the desired (±)-**5** in 88% yield from (±)-**13**. This reaction was explained as follows. When substrates possessing a methoxyl group at least at the *ortho* and/or *para* positions of the phenyl group are applied, this type reaction should occur because electrophilicity of the presumed phenonium ion is adequately high. This presumption should be supported by the fact that tosylate **1** possessing a methoxyl group at least at the $2'$, $4'$ and $6'$ positions of the phenyl ring afforded γ-lactone **2** in good yield.[2] From the above-mentioned experiment of this type reaction, $MeNO_2$ was regarded as the best reaction solvent and the presence of Ag^+ was essential. Oxygen nucleophiles such as the hydroxyl, trifluoroacetoxyl and nitrate groups were considered to be active, while nitrogen nucleophiles such as the azide ion, primary or secondary amines and phthalimide, and AgCN were inactive, to afford the starting (±)-**13**.

3. Confirmation of the stereochemical course and formal synthesis of (−)-anisomycin 6

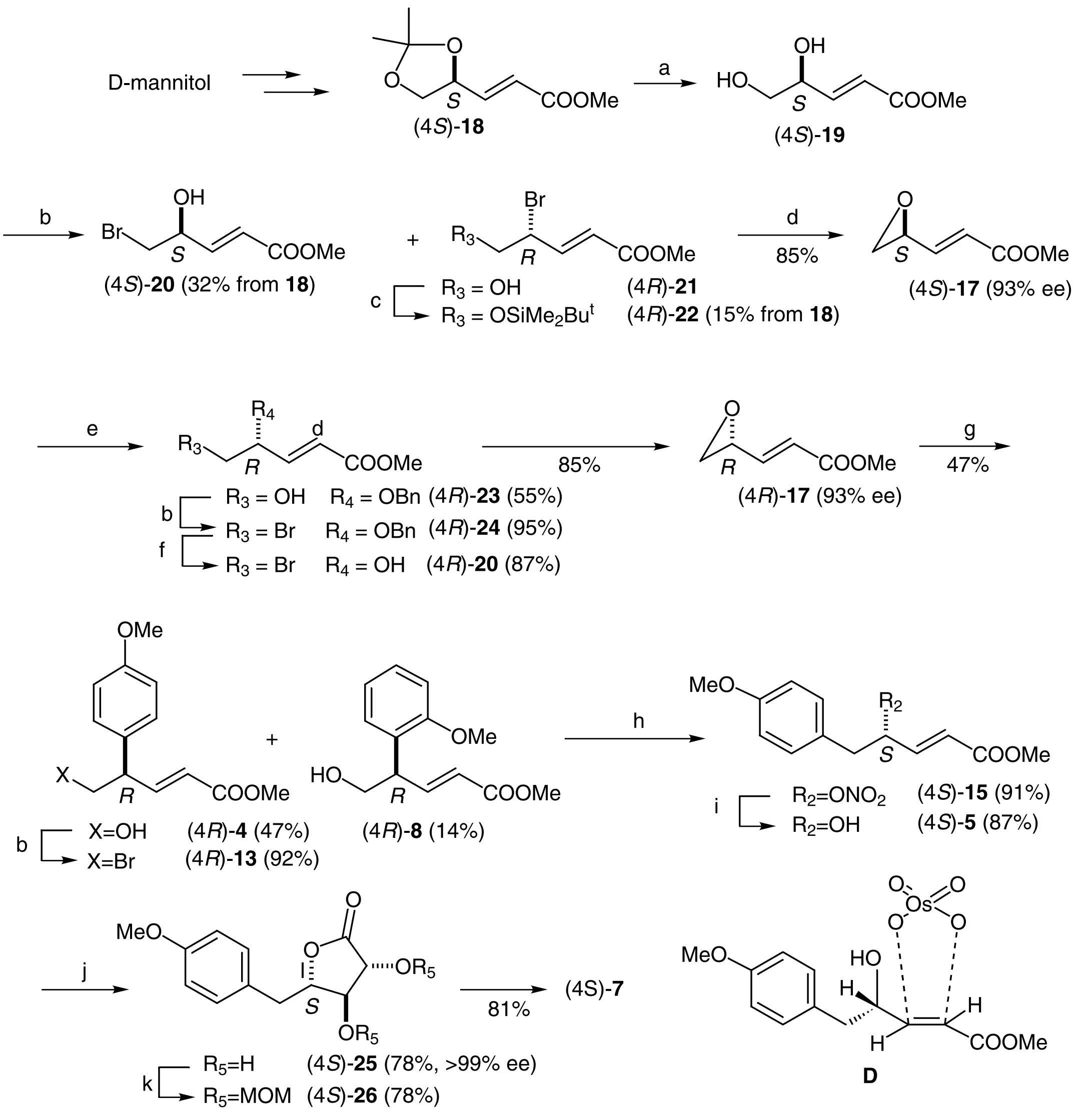
In order to clarify the stereochemical course of the above-mentioned reaction, the synthesis of (4*R*)-**4** from (4*R*)-4,5-epoxy-2(*E*)-pentenoate **17** is required because the reaction of (±)-**17** and anisole in the presence of $BF_3 \cdot Et_2O$ was reported to afford (±)-**4** as a main product.[4] (Scheme 4) The synthesis of (4*R*)-**17** was carried out by way of the following process from the commercially available (*E*)-unsaturated ester (4*S*)-**18**. By applying the reported procedure,[6] subsequent treatment of (4*S*)-**18** with 80% aqueous AcOH at 80 °C afforded the diol (4*S*)-**19** in quantitative yield. Bromination of (4*S*)-**19** with CBr_4 and triphenylphosphine in CH_2Cl_2 at reflux provided a mixture of bromohydrins (4*S*)-**20** and (4*R*)-**21**. This mixture was subjected to silylation followed by chromatographic separation to give the desired (4*S*)-**20** (32% overall yield from (4*S*)-**18**) and (4*R*)-**22** (15% overall yield from (4*S*)-**18**). The bromohydrin (4*S*)-**20** was treated with K_2CO_3 in MeOH to afford the

Table 1.



Entry	Ag salt (equiv)	Temperature	Time (h)	Products (%)
1	$Ag(CF_3SO_3)$ (2.0)	−20 to 0 °C	1	(±)-**5** (42%)
2	$AgClO_4$ (2.0)	0°C–rt	1	(±)-**5** (38%)
3	$AgClO_4$ (0.8)	0°C–rt	1	(±)-**5** (61%)
4	$Ag(CF_3COO)$ (2.0)	rt	1	(±)-**5**+(±)-**16** (59%)[a]
5	Ag_2CO_3 (2.0)	80 °C	15	(±)-**5** (49%)
6	Ag_2SO_4 (2.0)	80 °C	15	(±)-**5** (32%)
7	$AgNO_3$ (2.0)	rt	21	(±)-**5** (28%)+(±)-**15** (47%)

[a] Yield after conversion of a mixture of (±)-**5** and (±)-**16** into (±)-**5**.



Scheme 4. (a) 80% AcOH aq.; (b) $CBr_4/Ph_3P/CH_2Cl_2$; (c) $^tBuMe_2SiCl$/imidazole/DMF; (d) K_2CO_3/MeOH; (e) $PhCH_2OH/BF_3\cdot Et_2O/CH_2Cl_2$; (f) $AlCl_3$/*m*-xylene/CH_2Cl_2; (g) anisole/$BF_3\cdot Et_2O/CH_2Cl_2$; (h) $AgNO_3$/MS 4 Å/$MeNO_2$; (i) Zn/NH_4OAc/MeOH; (j) (1) OsO_4/*N*-methylmorpholine *N*-oxide/acetone–H_2O, (2) recrystallization; (k) MOM-Cl/diisoproethylpylamine/MeCN; (l) Dibal-H/benzene.

desired (4*S*)-4,5-epoxy-2(*E*)-pentenoate **17** in 85% yield. Optical purity of the present (4*S*)-**17** was estimated to be 93% ee by means of HPLC analysis. Conversion of (4*S*)-**17** into (4*R*)-**17** without loss of optical purity was carried out by modification of the reported procedure.[7] The reaction of (4*S*)-**17** with benzyl alcohol in the presence of $BF_3\cdot Et_2O$ gave (4*R*)-**23** ($[\alpha]_D = -57.0$ ($c=0.52$, $CHCl_3$) corresponding to 93% ee) in 55% yield. Bromination of (4*R*)-**23** provided (4*R*)-**24** ($[\alpha]_D = -40.2$ ($c=0.52$, $CHCl_3$) corresponding to 93% ee; 95% yield)) followed by deprotection of the benzyl group using the $AlCl_3$/*m*-xylene system[7] afforded bromohydrin (4*R*)-**20** ($[\alpha]_D$ -2.50 ($c=0.52$, $CHCl_3$) in 87% yield. An alkaline treatment of (4*R*)-**20** yielded the desired (4*R*)-**17** ($[\alpha]_D = -29.1$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee) in 85% yield. The reaction of (4*R*)-**17** and anisole in the presence of $BF_3\cdot Et_2O$ followed by enzymatic separation gave (4*R*)-**4** ($[\alpha]_D = +2.00$ ($c=0.51$, $CHCl_3$) corresponding to 93% ee; 47% yield) and (4*R*)-**8** ($[\alpha]_D = +17.7$ ($c=0.50$, $CHCl_3$) corresponding to 93% ee; 14% yield). The former (4*R*)-**4** was converted into the bromide (4*R*)-**13** ($[\alpha]_D = +3.00$ ($c=0.5$, $CHCl_3$) in 92% yield in the same way as (±)-**13**. Treatment of (4*R*)-**13** with $AgNO_3$ and MS 4 Å in $MeNO_2$ furnished the nitrate (4*S*)-**15** ($[\alpha]_D = +15.9$ ($c=0.51$, $CHCl_3$); 91% yield) which was converted to the desired (4*S*)-**5** ($[\alpha]_D = +1.00$ ($c=0.5$, $CHCl_3$) corresponding to 93% ee) in 87% yield in the same way as in the case of (±)-**15**. Osmium tetroxide-catalyzed dihydroxylation followed by treatment with *N*-methylmorpholine *N*-oxide gave the 3,4-*anti*-γ-lactone (4*S*)-**25** ($[\alpha]_D = -72.2$ ($c=0.41$, MeOH) corresponding to 93% ee; 78% yield) and the 3,4-*syn*-diastereomer ($[\alpha]_D = -86.0$ ($c=0.11$, MeOH); 2% yield). This high diastereoselectivity (3,4-*anti*: 3,4-*syn* = 39:1) was understood by the reported explanation.[8] A transition state D in which the carbon–oxygen bond is near the plane of the conjugated double bond is compatible with the observed stereochemical course of the hydroxylation reaction. Presumably, this conformation results from a favorable interaction between the *p*-orbital of the double bond and an unshared pair on the γ-oxygen. Consequently, osmium tetroxide attacks from the less stereochemically hindered β-side. Recrystallization of the 93% ee of (4*S*)-**25** afforded the enantiomerically pure (4*S*)-**25**. Treatment of (4*S*)-**25** with chloromethyl methyl ether (MOM-Cl) furnished the di-MOM ether (4*S*)-**26** ($[\alpha]_D = -19.7$ ($c = 0.49$, $CHCl_3$); 78% yield). Reduction of (4*S*)-**26** with Dibal-H gave the (4*S*)-diol **7** ($[\alpha]_D = -39.3$ ($c = 0.51$, MeOH)) in 81% yield, whose spectral data were identical with those ($[\alpha]_D = -22.7$ ($c = 16.21$, MeOH) and ^1H NMR) of the reported (4*S*)-**7**.[9] The synthesis of (−)-anisomycin **6** from (4*S*)-**7** is already achieved.[9] From these experiments, conversion of the bromide (4*R*)-**13** into the nitrate (4*S*)-**15** from a stereochemical point of view was found to occur along with complete inversion at the C_4-position. In conclusion, the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxypheny)-2(*E*)-pentenoate **4** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** using the $AgNO_3$/MS 4 Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **6** from (4*S*)-**5** based on osmium tetroxide-catalyzed stereoselective hydroxylation was achieved.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H NMR spectra were recorded by a JEOL EX 400 spectrometer (Tokyo, Japan). Spectra were taken with 5–10% (w/v) solution in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS-DX 303 (matrix; glycerol, *m*-nitrobenzyl alcohol) spectrometer. IR spectra were recorded on a JASCO FT/IR-300 spectrometer. The HPLC system was composed of a detector (UV detector SSC-5200, Senshu), pump (SSC-3210, Senshu) and integrator (chromatocorder SIC 21). HPLC analysis conditions were as follows; column: CHIRALCEL AS, eluent: *n*-hexane/EtOH = 100:1, Detection: UV at 254 nm, Flow rate; 1 mL/min. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.1.1. (±) Methyl 4-(4′-methoxyphenyl)-5-tosyloxy-2(*E*)-pentenoate 9. A mixture of (±)-**4** (2.774 g, 11.7 mmol), *p*-toluenesulfonic anhydride (Ts_2O, 4.60 g, 14.1 mmol), pyridine (1.40 g, 17.7 mmol) in benzene (25 mL) was stirred for 2 d at 50 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was washed with 1 M aqueous HCl and 7% aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**9** (4.393 g, 96%) as a colorless oil. (±)-**9**: IR (neat): 1722 cm^{-1}; ^1H NMR: δ 2.44 (3H, s), 3.71 (3H, s), 3.76 (1H, br.q, $J = 8$ Hz), 3.79 (3H, s), 4.20 (2H, d, $J = 7$ Hz), 5.79 (1H, dd, $J = 2$, 16 Hz), 6.81 (2H, d, $J = 8$ Hz), 6.97 (1H, dd, $J = 8$, 16 Hz), 7.00 (2H, d, $J = 8$ Hz), 7.30 (2H, d, $J = 8$ Hz), 7.70 (2H, d, $J = 8$ Hz). Anal. Calcd for $C_{20}H_{22}SO_6$: C, 61.52; H, 5.68. Found: C, 61.32; H, 5.56. MS (FAB) *m/z*: 391 ($M^+ + 1$).

4.1.2. (±) Methyl 4-(2′-methoxyphenyl)-5-tosyloxy-2(*E*)-pentenoate 10. A mixture of (±)-**8** (1.042 g, 4.41 mmol), *p*-toluenesulfonic anhydride (Ts_2O, 1.73 g, 5.3 mmol), pyridine (2 mL) in benzene (15 mL) was stirred for 3 d at 50 °C. The reaction mixture was worked up in the same way for (±)-**9** to afford (±)-**10** (1.38 g, 80%) as a colorless oil. (±)-**9**: IR (neat): 1722 cm^{-1}; ^1H NMR: δ 2.44 (3H, s), 3.71 (3H, s), 3.73 (3H, s), 4.16 (1H, q, $J = 10$ Hz), 4.26 (1H, dd, $J = 6$, 10 Hz), 4.30 (1H, dd, $J = 7$, 10 Hz), 5.80 (1H, dd, $J = 2$, 16 Hz), 6.81 (1H, d, $J = 8$ Hz), 6.87 (1H, t, $J = 8$ Hz), 7.00 (1H, dd, $J = 2$, 8 Hz), 7.02 (1H, dd, $J = 8$, 16 Hz), 7.23 (1H, dt, $J = 2$, 8 Hz), 7.295 (2H, d, $J = 8$ Hz), 7.69 (2H, d, $J = 9$ Hz). Anal. Calcd for $C_{20}H_{22}SO_6$: C, 61.52; H, 5.68. Found: C, 61.09; H, 5.87. MS (FAB) *m/z*: 391 ($M^+ + 1$).

4.1.3. Solvolysis of (±)-9. A solution of (±)-**9** (0.500 g, 1.28 mmol) in water-saturated nitromethane (50 mL) was stirred for 2 d at 90 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue. A suspension of the above-mentioned residue and lipase OF-360 from Candida rugosa (0.20 g) in phosphate buffer (pH 7.4, 150 mL) was stirred for 3 d at 33 °C. The reaction mixture was extracted with ether and the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**9** (0.170 g, 34% recovery). On the other hand, the water layer was acidified with 1 M aqueous HCl and extracted with ether. Evaporation of the organic solvent gave a residue (±)-**11**, which was treated with CH_2N_2–ether solution to afford an oil. It was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**5** (0.153 g, 51%) as a colorless oil. (±)-**5**: IR (neat): 3456, 1722 cm^{-1}; ^1H NMR: δ 2.12 (1H, br.s), 2.73 (1H, dd, $J = 8$, 14 Hz), 2.88 (1H, dd, $J = 5$, 14 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.47 (1H, dq, $J = 2$, 5 Hz), 6.05 (1H, dd, $J = 2$, 16 Hz), 6.85 (2H, d, $J = 8$ Hz), 6.99 (1H, dd, $J = 5$, 16 Hz), 7.13 (2H, d, $J = 8$ Hz). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.85. MS (FAB) *m/z*: 237 ($M^+ + 1$).

4.1.4. Solvolysis of (±)-10. A solution of (±)-**10** (0.251 g, 0.64 mmol) in water-saturated nitromethane (40 mL) was stirred for 4 d at 90 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was treated with CH_2N_2–ether solution to afford an oil. It was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**12** (0.081 g, 53%) as a colorless oil. (±)-**12**: IR (neat): 3451, 1717 cm^{-1}; ^1H NMR: δ 2.49 (1H, br.s), 2.82 (1H, dd, $J = 8$, 14 Hz), 3.01 (1H, dd, $J = 5$, 14 Hz), 3.73 (3H, s), 3.84 (3H, s), 4.56 (1H, ddt, $J = 2$, 5, 5 Hz), 6.06 (1H, dd, $J = 2$, 16 Hz), 6.88 (1H, br.d, $J = 9$ Hz), 6.92 (1H, t, $J = 8$ Hz), 7.02 (1H, dd, $J = 5$, 16 Hz), 7.13 (1H, dd, $J = 2$, 8 Hz), 7.24 (1H, t, $J = 8$ Hz). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.67; H, 6.80. MS (FAB) *m/z*: 237 ($M^+ + 1$).

4.1.5. (±) Methyl-5-bromo-4-(4′-methoxyphenyl)-2(*E*)-pentenoate 13. To a solution of (±)-**4** (2.012 g, 8.52 mmol) in MeCN (40 mL) were added triphenyl phosphine (Ph_3P; 10.06 g, 38.4 mmol) and *N*-bromosuccinimide (NBS; 6.83 g, 38.3 mmol) at 0 °C and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**13** (2.104 g, 83%) as a colorless oil. (±)-**13**: IR (neat): 1723 cm^{-1}; ^1H NMR: δ 3.60 (2H, dd, $J=2$, 7 Hz), 3.73 (3H, s), 3.79 (3H, s), 3.80 (1H, br.q, $J=7$ Hz), 5.88 (1H, dd, $J=2$, 16 Hz), 6.88 (2H, d, $J=9$ Hz), 7.09 (1H, dd, $J=8$, 16 Hz), 7.11 (2H, d, $J=9$ Hz). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 52.48; H, 4.64. MS (FAB) *m/z*: 299, 301 ($M^+ + 1$).

4.1.6. Solvolysis of (±)-13. A solution of (±)-**13** (0.500 g, 1.67 mmol) in water-saturated nitromethane (20 mL) was stirred for 12 h at 80 °C. The reaction mixture was diluted with water and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g) to afford a mixture (0.382 g) of (±)-**13** and (±)-**14** from *n*-hexane/AcOEt = 10:1eluent and (±)-**5** (0.024 g, 6%) from *n*-hexane/AcOEt = 5:1eluent. To a solution of this mixture (0.382 g) in $MeNO_2$ (10 mL) were added molecular sieves (4 Å; 0.5 g) and silver nitrate ($AgNO_3$; 0.43 g, 2.53 mmol) and the whole mixture was stirred for 12 h at room temperature. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 30:1) to afford (±)-**15** (0.298 g, 63% overall yield) as a colorless oil. (±)-**15**: IR (neat): 1726 cm^{-1}; ^1H NMR: 2.93 (1H, dd, $J=6$, 14 Hz), 3.03 (1H, dd, $J=7$, 15 Hz), 3.75 (3H, s), 3.79 (3H, s), 5.58 (1H, dq, $J=2$, 6 Hz), 6.01 (1H, dd, $J=2$, 16 Hz), 6.84 (1H, dd, $J=6$, 16 Hz), 6.85 (2H, d, $J=8$ Hz), 7.12 (2H, d, $J=8$ Hz). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.77; H, 5.32; N, 5.02. MS (FAB) *m/z*: 281 (M^+).

4.1.7. Solvolysis of (±)-13 (Table 1).

1) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver trifrate ($Ag(CF_3SO_3)$; 0.683 g, 2.66 mmol) and the whole mixture was stirred for 1 h at 0 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 15:1) to afford (±)-**5** (0.132 g, 42%).
2) To a solution of (±)-**13** (0.403 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver perchlorate ($AgClO_4$; 0.555 g, 2.68 mmol) and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.119 g, 38%).
3) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver perchlorate ($AgClO_4$; 0.220 g, 1.06 mmol) and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.193 g, 61%).
4) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver trifluoroacetate ($Ag(CF_3COO)$; 0.592 g, 2.68 mmol) and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was worked up in the same way as 1) to afford a mixture (0.42 g) of (±)-**5** and (±)-**16**. To a solution of the above mixture in MeOH (8 mL) was added K_2CO_3 (90 mg) and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 15:1) to afford (±)-**5** (0.188 g, 59%).
5) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver carbonate (Ag_2CO_3; 0.739 g, 2.68 mmol) and the whole mixture was stirred for 15 h at 80 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.155 g, 49%).
6) To a solution of (±)-**13** (0.401 g, 1.34 mmol) in water-saturated nitromethane (10 mL) was added silver sulfate (Ag_2SO_4; 0.835 g, 2.68 mmol) and the whole mixture was stirred for 15 h at 80 °C. The reaction mixture was worked up in the same way as 1) to afford (±)-**5** (0.100 g, 32%).
7) To a solution of (±)-**13** (0.400 g, 1.33 mmol) in water-saturated nitromethane (10 mL) was added silver nitrate ($AgNO_3$; 0.451 g, 2.66 mmol) and the whole mixture was stirred for 21 h at room temperature. The reaction mixture was worked up in the same way as 1) to afford (±)-**15** (0.175 g, 47%) and (±)-**5** (0.087 g, 28%).

4.1.8. Synthesis of (±) methyl-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate 5 from (±)-13 via (±)-15. To a solution of (±)-**13** (1.43 g, 4.78 mmol) in nitromethane (20 mL) were added molecular sieves (4 Å; 2.0 g) and silver nitrate ($AgNO_3$; 1.62 g, 9.54 mmol) and the whole mixture covered with aluminum foil was stirred for 4 h at room temperature. The reaction mixture was worked up in the same way as the previous (±)-**15** to give (±)-**15** (1.222 g, 91%). To a mixture of Zn-dust (0.7 g) and CH_3COONH_4 (0.5 g) in MeOH (5 mL) was added a solution of (±)-**15** (0.501 g, 1.78 mmol) in MeOH (5 mL) and the whole mixture was stirred for 1 h at 0 °C. After the generated precipitate was filtered off with the aid of celite, the filtrate was diluted with water and ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt = 5:1) to afford (±)-**5** (0.371 g, 88%) as a colorless oil. The NMR data of the present (±)-**5** were identical with those of the previous (±)-**5**.

4.1.9. Methyl (4*S*)-(4,5)-epoxy-2(*E*)-pentenoate 17. (1) A solution of commercially available (4*S*)-**18** (31.19 g, 0.17 mol) in 80% aqueous AcOH (200 mL) was stirred for 30 min at 80 °C. The reaction mixture was diluted with toluene and condensed under reduced pressure to give a crude diol (4*S*)-**19** (25.21 g, quantitative yield). (2) To a solution of (4*S*)-**19** (25.21 g) in CH_2Cl_2 (120 mL) were added Ph_3P (16.92 g, 0.0645 mol) and carbon tetrabromide

(CBr_4; 21.39 g, 0.0645 mol) and the whole mixture was refluxed for 1 h with stirring. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt = 10:1) to provide an inseparable mixture (18.81 g) of (4*S*)-**20** and (4*R*)-**21**. (3) To a solution of the above-mentioned mixture (18.81 g) in DMF (120 mL) were added imidazole (18.38 g, 0.270 mol) and *tert*-butyldimethylsilyl chloride (TBDMSCl; 5.42 g, 0.034 mol) at 0 °C and the whole mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g) to afford an oily (4*R*)-**22** (8.25 g, 15% overall yield from (4*S*)-**18**) from *n*-hexane/AcOEt = 20:1 elute and an oily (4*S*)-**20** (11.11 g, 32% overall yield from (4*S*)-**18**) from *n*-hexane/AcOEt = 5:1 elute, respectively. (4*S*)-**20**: IR (neat): 3451, 1716 cm^{-1}; ^{1}H NMR: δ 2.72 (1H, d, J = 7 Hz), 3.42 (1H, dd, J = 7, 11 Hz), 3.57 (1H, dd, J = 4, 11 Hz), 3.76 (3H, s), 4.51–4.58 (1H, m), 6.16 (1H, dd, J = 2, 16 Hz), 6.88 (1H, dd, J = 5, 16 Hz). MS (FAB) *m*/*z*: 209.211 ($M^+ + 1$). (4*R*)-**22**: IR (neat): 1725 cm^{-1}; ^{1}H NMR: δ 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 3.75 (3H, s), 3.83 (1H, dd, J = 7, 11 Hz), 3.93 (1H, dd, J = 5, 11 Hz),4.47–4.53 (1H, m), 6.02 (1H, dd, J = 1, 15 Hz), 6.93 (1H, dd, J = 9, 15 Hz). MS (FAB) *m*/*z*: 323.325 ($M^+ + 1$). (4) A mixture of molecular sieves (3 Å; 7.5 g) and K_2CO_3 (17.1 g, 0.124 mol) in MeOH (450 mL) was stirred for 30 min at 0 °C, and (4*S*)-**20** (14.42 g, 0.069 mol) in MeOH (50 mL) was slowly added to the above-mentioned mixture. The reaction mixture was stirred for 2.5 h at 0 °C and filtered with the aid of filter paper. The MeOH was distilled under ordinary pressure and the residue was chromatographed on silica gel (200 g, *n*-hexane/AcOEt = 20:1) to afford (4*S*)-**17** (7.51 g, 85%) as a colorless oil. (4*S*)-**17**: $[\alpha]_D^{24} = +22.3$ ($c = 0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis). (4*R*)-**17**: $t_R = 17.1$ min, (4*S*)-**17**: $t_R = 20.0$ min. The NMR data of (4*S*)-**17** were identical with those of the reported (±)-**17**.[4b]

4.1.10. Methyl (4*R*)-(4,5)-epoxy-2(*E*)-pentenoate 17. (1) To a solution of (4*S*)-**17** (7.62 g, 0.0595 mol) in CH_2Cl_2 (80 mL) were added benzyl alcohol ($PhCH_2OH$; 32.12 g, 0.298 mol) and $BF_3 \cdot Et_2O$ (8 mL, 0.064 mol) at −20 °C and the whole mixture was stirred for 1.5 h at 0 °C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt = 5:1) to afford (4*R*)-**23** (7.794 g, 56%) as a colorless oil. (4*R*)-**23**: $[\alpha]_D^{23} = -57.0$ ($c = 0.52$, $CHCl_3$) corresponding to 93% ee): IR (neat): 3433, 1721 cm^{-1}; ^{1}H NMR: δ 3.65 (1H, dd, J = 8, 12 Hz), 3.73 (1H, br.dd, J = 5, 12 Hz), 3.81 (3H, s), 4.16–4.21 (1H, m), 4.49 (1H, d, J = 12 Hz), 4.71 (1H, d, J = 12 Hz), 6.18 (1H, dd, J = 2, 16 Hz), 6.92 (1H, dd, J = 6, 16 Hz), 7.32–7.44 (5H, m). MS (FAB) Calcd For $C_{13}H_{16}O_4$ *m*/*z*: 237.1127 ($M^+ + 1$). Found *m*/*z*: 237.1154. (2) To a solution of (4*R*)-**23** (3.00 g, 12.7 mmol) in CH_2Cl_2 (50 mL) were added Ph_3P (6.66 g, 25.4 mmol) and carbon tetrabromide (CBr_4; 8.42 g, 25.4 mmol) at 0 °C and the whole mixture was stirred for 1 h at room temperature. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (150 g, *n*-hexane/AcOEt = 20:1) to provide (4*R*)-**24** (3.596 g, 95%) as a colorless oil. (4*R*)-**24**: $[\alpha]_D^{24} = -40.2$ ($c = 0.52$, $CHCl_3$) corresponding to 93% ee); IR (neat): 1722 cm^{-1}; ^{1}H NMR: δ 3.41 (1H, dd, J = 7, 12 Hz), 3.46 (1H, dd, J = 7, 12 Hz), 3.77 (3H, s), 4.21 (1H, dq, J = 2, 7 Hz), 4.50 (1H, d, J = 12 Hz), 4.63 (1H, d, J = 12 Hz), 6.13 (1H, dd, J = 2, 15 Hz), 6.86 (1H, dd, J = 7, 15 Hz), 7.28–7.40 (5H, m). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 51.65; H, 4.88. MS (FAB) *m*/*z*: 299.301 ($M^+ + 1$). (3) To a suspension of $AlCl_3$ (8.92 g, 66.9 mmol) in CH_2Cl_2 (120 mL) was added a solution of (4*R*)-**24** (10.167 g, 34 mmol) in *m*-xylene (25 mL) at −20 °C and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (200 g, *n*-hexane/AcOEt = 5:1) to afford (4*R*)-**20** (6.170 g, 87%) as a colorless oil. (4*R*)-**20**: $[\alpha]_D^{23} = -2.50$ ($c = 0.52$, $CHCl_3$) corresponding to 93% ee. The spectral data (IR and NMR) of (4*R*)-**20** were identical with those of (4*S*)-**20**. (4) A mixture of molecular sieves (3 Å; 3.0 g) and K_2CO_3 (8.98 g, 65 mmol) in MeOH (350 mL) was stirred for 30 min at 0 °C, and (4*R*)-**20** (13.59 g, 65 mmol) in MeOH (50 mL) was slowly added to the above-mentioned mixture. The reaction mixture was stirred for 30 min at 0 °C and filtered with the aid of filter paper. The MeOH was distilled under ordinary pressure and the residue was chromatographed on silica gel (200 g, *n*-hexane/AcOEt = 20:1) to afford (4*R*)-**17** (7.101 g, 85%) as a colorless oil. (4*R*)-**17**: $[\alpha]_D^{24} = -29.1$ ($c = 0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), HPLC analysis conditions were the same as for (4*S*)-**17**. The NMR data of (4*R*)-**17** were identical with those of the reported (±)-**17**.[4b]

4.1.11. Methyl (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate 4. (1) To a solution of (4*R*)-**17** (3.71 g, 28.9 mmol) in CH_2Cl_2 (50 mL) were added anisole (PhOMe; 9.39 g, 86.8 mmol) and $BF_3 \cdot Et_2O$ (7 mL, 56 mmol) at −20 °C and the whole mixture was stirred for 1 h at −20 °C. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to provide a residue, which was chromatographed on silica gel (100 g) to afford (4*R*)-**8** (0.375 g, 5% yield) from *n*-hexane/AcOEt = 3:1 elute, and 1:3 mixture (2.620 g) of (4*R*)-**8** and (4*R*)-**4** from *n*-hexane/AcOEt = 3:1 elute, and (4*R*)-**4** (1.504 g, 22% yield) from *n*-hexane/AcOEt = 2:1 elute, respectively. (2) To a solution of a 1:3 mixture (2.620 g) of (4*R*)-**8** and (4*R*)-**4** in pyridine (5 mL) was added Ac_2O (2.26 g, 22.1 mmol) and the whole mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was washed with 2 M aqueous HCl, and 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (60 g, *n*-hexane/AcOEt = 10:1) to afford a mixture of the corresponding acetates (2.81 g). (3) A suspension of the above-mentioned mixture (2.81 g) and lipase Amano P from *Pseudomonas* sp. (0.50 g) in phosphate buffer (pH 7.4; 300 mL) was stirred at 33 °C for 12 h. The reaction mixture was filtered, and the precipitate was washed with ether. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (60 g) to give an acetate

(0.707 g, 9% yield from (4*R*)-**17**)) of (4*R*)-**8** from *n*-hexane/AcOEt = 7:1 elute and (4*R*)-**4** (1.737 g, total; 3.241 g (47% overall yield from (4*R*)-**17**)) as a homogeneous oil from *n*-hexane/AcOEt = 2:1 elute, respectively. (4*R*)-**4**: $[\alpha]_D^{24} = +2.00$ ($c = 0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*R*)-**4** were identical with those of the reported (±)-**4**.[5] Acetate of (4*R*)-**8**: $[\alpha]_D^{26} = +8.98$ ($c = 0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis): IR (neat): 1740 cm^{-1}; ^1H NMR: δ 2.02 (3H, s), 3.72 (3H, s), 3.82 (3H, s), 4.23 (1H, br, q, $J = 7.0$ Hz), 4.33 (1H, dd, $J = 11.0, 5.0$ Hz), 4.40 (1H, dd, $J = 11.0, 9.0$ Hz), 5.87 (1H, dd, $J = 16.0, 2.0$ Hz), 6.88 (1H, dd, $J = 8.0, 2.0$ Hz), 6.92 (1H, dt, $J = 8.0, 2.0$ Hz), 7.11 (1H, dd, $J = 8.0, 2.0$ Hz), 7.16 (1H, dd, $J = 16.0, 7.0$ Hz), 7.25 (1H, dt, $J = 8.0, 2.0$ Hz). FAB MS *m/z*: 279 $(M+1)^{+}$; Anal. Found: C, 64.60; H, 6.50. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%.

4.1.12. Methyl (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate 5.

(1) To a solution of (4*R*)-**4** (2.01 g, 8.51 mmol) in CH_2Cl_2 (40 mL) were added triphenyl phosphine (Ph_3P; 4.46 g, 17 mmol) and carbon tetrabromide (CBr_4; 8.46 g, 25.5 mmol) at 0 °C and the whole mixture was stirred for 1.5 h at room temperature. The reaction mixture was evaporated to afford a residue, which was chromatographed on silica gel (80 g, *n*-hexane/AcOEt = 30:1) to provide (4*R*)-**13** (2.342 g, 92%) as a colorless oil. (4*R*)-**13**: $[\alpha]_D^{27} = +3.00$ ($c = 0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*R*)-**13** were identical with those of the reported (±)-**13**. (2) To a solution of (4*R*)-**13** (1.43 g, 4.8 mmol) in nitromethane (20 mL) were added molecular sieves (4 Å; 2.0 g) and silver nitrate ($AgNO_3$; 1.62 g, 9.54 mmol) and the whole mixture covered with aluminum foil was stirred for 24 h at room temperature. The reaction mixture was worked up in the same way as the previous (±)-**15** to give (4*S*)-**15** (1.22 g, 91%). (4*S*)-**15**: $[\alpha]_D^{27} = +15.9$ ($c = 0.51$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*S*)-**15** were identical with those of the reported (±)-**15**. (3) To a mixture of Zn-dust (1.14 g) and CH_3COONH_4 (1.14 g) in MeOH (5 mL) was added a solution of (4*S*)-**15** (1.140 g, 4.06 mmol) in MeOH (7 mL) and the whole mixture was stirred for 1 h at 0 °C. The generated precipitate was filtered off with the aid of celite and the filtrate was diluted with water and ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (40 g, *n*-hexane/AcOEt = 5:1) to afford (4*S*)-**5** (0.833 g, 87%) as a colorless oil. (4*S*)-**5**: $[\alpha]_D^{26} = +1.00$ ($c = 0.50$, $CHCl_3$) corresponding to 93% ee by means of HPLC analysis), The NMR data of (4*S*)-**5** were identical with those of the previous (±)-**5**.

4.1.13. (2*S*,3*S*,4*S*)-4-Hydroxy-2,3-dimethoxymethyl-5-(4′-methoxyphenyl)-pentanol 7.

(1) To a solution of 50% aqueous *N*-methylmorpholine *N*-oxide (0.58 mL, 2.49 mmol) and 2% aqueous osmium tetraoxide (OsO_4; 3.16 mL, 10 mol%) in acetone (5 mL) was added a solution of (4*S*)-**5** (0.588 g, 2.49 mmol) in acetone (5 mL) at 0 °C and the whole mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with 10% aqueous Na_2SO_3 (5 mL) at 0 °C and the whole mixture was stirred for 30 min. The generated precipitate was filtered with the aid of celite and the filtrate was condensed. The residue was diluted with ether and treated with 10% aqueous HCl. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (30 g, *n*-hexane/AcOEt = 1:1) to afford diastereomeric lactone (2*S*,3*R*,4*S*)-**25** (0.010 g, 2%) and the desired (2*R*,3*S*,4*S*)-**25** (0.463 g, 78%) in elution order. Crystallization of (2*R*,3*S*,4*S*)-**25** from $CHCl_3$ gave a colorless crystal. (2*R*,3*S*,4*S*)-**25**: mp 81–82 °C, $[\alpha]_D^{24} = -72.2$ ($c = 0.41$, MeOH) corresponding to >99% ee by means of HPLC analysis): IR (KBr): 3298, 1756 cm^{-1}; ^1H NMR: δ 2.82 (1H, dd, $J = 8, 15$ Hz), 3.13 (1H, dd, $J = 3, 15$ Hz), 3.74 (3H, s), 3.88 (1H, t, $J = 9$ Hz), 4.25 (1H, dt, $J = 3, 8$ Hz), 4.30 (1H, d, $J = 9$ Hz), 6.84 (2H, d, $J = 9$ Hz), 7.17 (2H, d, $J = 9$ Hz). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 50.90; H, 5.90. MS (FAB) *m/z*: 239 $(M^+ + 1)$. (2*S*,3*R*,4*S*)-**25**: $[\alpha]_D^{22} = -86.0$ ($c = 0.11$, MeOH) corresponding to 93% ee by means of HPLC analysis): IR (KBr): 3429, 1758 cm^{-1}; ^1H NMR: δ 2.90 (1H, dd, $J = 8, 15$ Hz), 3.08 (1H, dd, $J = 5, 15$ Hz), 3.76 (3H, s), 4.03 (1H, d, $J = 5$ Hz), 4.19 (1H, t, $J = 5$ Hz), 4.72 (1H, dt, $J = 5, 8$ Hz), 6.84 (2H, d, $J = 9$ Hz), 7.20 (2H, d, $J = 9$ Hz). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.37; H, 5.91. MS (FAB) *m/z*: 239 $(M^+ + 1)$. (2) To a solution of (2*R*,3*S*,4*S*)-**25** (0.101 g, 0.42 mmol) and *N*,*N*-diisopropylethylamine (1.32 g, 9.29 mmol) in MeCN (1 mL) was added chloromethylmethyl ether (CH_3OCH_2Cl; 0.68 g, 8.45 mmol) at 0 °C and the whole mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with brine and ether at 0 °C, the organic layer was dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 8:1) to afford (2*R*,3*S*,4*S*)-**26** (0.107 g, 78%) as a colorless oil. (2*R*,3*S*,4*S*)-**26**: $[\alpha]_D^{24} = -18.7$ ($c = 0.49$, $CHCl_3$) corresponding to >99% ee by means of HPLC analysis): IR (neat): 1790 cm^{-1}; ^1H NMR: δ 2.94 (1H, dd, $J = 7, 14$ Hz), 3.15 (1H, dd, $J = 4, 14$ Hz), 3.40 (3H, s), 3.44 (3H, s), 3.79 (3H, s), 4.07 (1H, t, $J = 7$ Hz), 4.42 (1H, dt, $J = 4, 7$ Hz), 4.47 (1H, d, $J = 7$ Hz), 4.65 (1H, d, $J = 7$ Hz), 4.73 (1H, d, $J = 7$ Hz), 4.79 (1H, d, $J = 7$ Hz), 5.02 (1H, d, $J = 7$ Hz), 6.85 (2H, d, $J = 8$ Hz), 7.18 (2H, d, $J = 8$ Hz). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.96; H, 6.97. MS (FAB) *m/z*: 326 (M^+). (3) To a solution of (2*R*,3*S*,4*S*)-**26** (0.076 g, 0.23 mmol) in benzene (5 mL) was added 1 M diisobutylaluminum hydride (Dibal-H) in toluene solution (1.41 mL, 1.41 mmol) at 0 °C and the whole mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 1:1) to afford (4*S*)-**7** (0.062 g, 81%) as a colorless oil. (4*S*)-**7**: $[\alpha]_D^{24} = -39.3$ ($c = 0.51$, MeOH) corresponding to >99% ee by means of HPLC analysis): IR (neat): 3439 cm^{-1}; ^1H NMR: δ 2.62 (1H, dd, $J = 10, 14$ Hz), 2.92 (1H, d, $J = 5$ Hz), 3.00 (1H, dd, $J = 3, 14$ Hz), 3.21 (1H, t, $J = 6$ Hz), 3.41 (3H, s), 3.46 (3H, s), 3.65 (1H, dd, $J = 4, 7$ Hz), 3.74–3.78 (2H, m), 3.79 (3H, s), 3.91–3.97 (2H, m), 4.71–4.77 (4H, m), 6.85 (2H, d, $J = 9$ Hz), 7.18 (2H, d, $J = 9$ Hz). Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 57.75; H, 8.06. MS (FAB) *m/z*: 369 $(M^+ + K)$.

References and notes

1. This work was published as a preliminary communication: Ono, M.; Suzuki, K.; Akita, H. *Tetrahedron Lett.* **1999**, *40*, 8223–8226.
2. (a) Nagumo, S.; Furukawa, T.; Ono, M.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 2849–2852. (b) Nagumo, S.; Ono, M.; Kakimoto, Y.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N.; Akita, H. *J. Org. Chem.* **2002**, *67*, 6618–6622.
3. Recent references concerning the structure determination and syntheses of (−)-anisomycin Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383–1386.
4. (a) Ono, M.; Yamamoto, Y.; Todoriki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181–185. (b) Ono, M.; Yamamoto, Y.; Todoriki, R.; Akita, H. *Chem. Pharm. Bull.* **1994**, *42*, 1590–1595. (c) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553–558.
5. Under this condition, an aryl migration product was not obtained because a catalytic reduction of (±)-**13** gave 4-(4′-methoxyphenyl)-pentanoate.
6. Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. *Tetrahedron Lett.* **1997**, *38*, 3419–3422.
7. Ono, M.; Saotome, C.; Akita, H. *Tetrahedron:Asymmetry* **1996**, *7*, 2595–2602.
8. Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951–3954.
9. Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069–1073.

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Facile acid-catalyzed condensation of 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone with phenols, methoxyaromatic systems and enols

Suven Das,[a] Animesh Pramanik,[a,*] Roland Fröhlich[b] and Amarendra Patra[a]

[a] *Department of Chemistry, University of Calcutta, 92, A. P. C. Road, Kolkata 700 009, India*
[b] *Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149 Münster, Germany*

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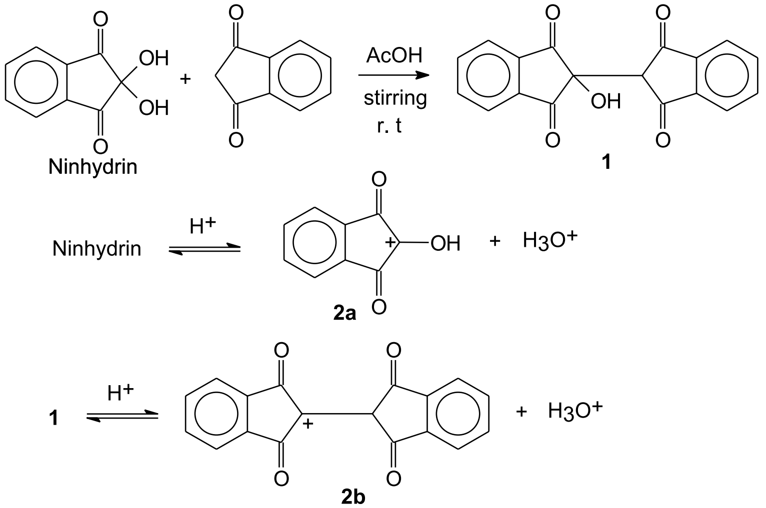
Abstract—Various phenols, methoxy aromatic compounds, 3- and 4-hydroxycoumarins and enols smoothly condense with 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone **1** in an acid medium producing 2-aryl/alkyl-2,2′-biindan-1,1′,3,3′-tetrones in high yields. The adducts of resorcinol, 1,3,5-trihydroxybenzene and α- and β-naphthols of **1** preferably remain in the intramolecular hemi-ketal form, confirmed by X-ray diffraction studies. On the other hand *para* and *meta* substituted phenols condense with **1** in an acid medium to produce 6 or 7 substituted 2′,4-spiro(1′,3′-indanedion)-indeno[3,2-*b*]chromenes in good yields.

1. Introduction

The mechanistic details of the formation of Ruhemann's Purple from the reaction of ninhydrin with amino acids is not fully understood, but it is accepted that the formation of 2,2′-dihydroxy-2,2′-biindan-1,1′,3,3′-tetrone, popularly known as hydrindantin, is a critical step in the whole process.[1] Although hydrindantin is structurally similar to ninhydrin, the instability of the former in acid medium prevents the study of its electrophilic chemistry towards various phenols and enolic substrates.[1d,2] On the other hand, the partially reduced derivative of hydrindantin, viz., 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone **1** (Scheme 1), which can be easily generated by the acid catalyzed condensation of ninhydrin with 1,3-indanedione,[3] is found to be quite stable in acid medium and therefore creates an



Scheme 1.

Keywords: 2-Hydroxy-2,2′-biindan-1,1′,3,3′-tetrone; Phenols; Enols; Electrophilic addition; Chromenes.

* Corresponding author. Tel.: +91 33 2484 1647; fax: +91 33 351 9755; e-mail: animesh_in2001@yahoo.co.in

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Table 1. Preparation of 2-aryl 2,2′-biindan-1,1′,3,3′-tetrones and chromenes by condensation of phenols with **1** in acid medium

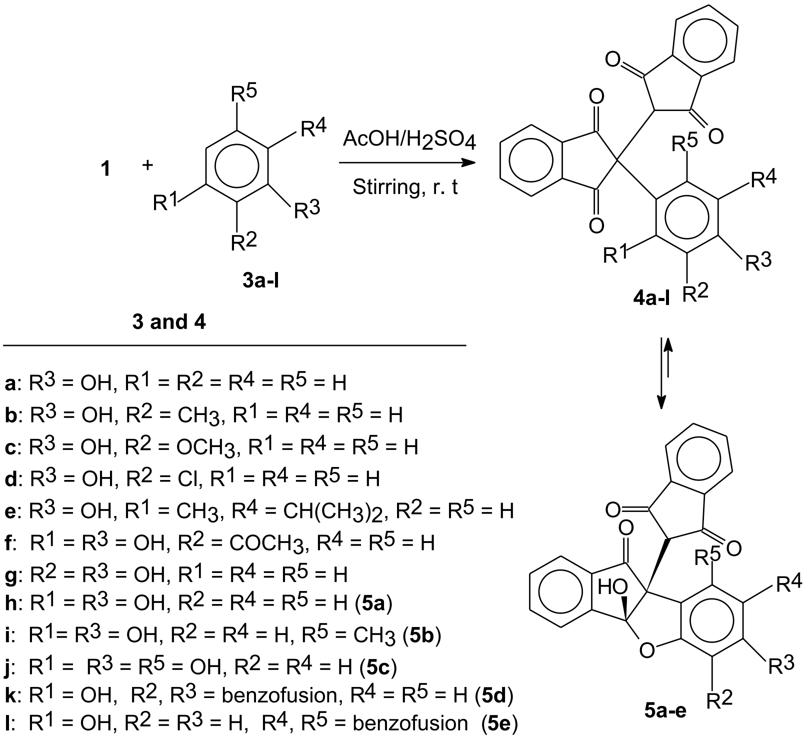
Entry	Substrates	Products	Reaction time (h)	Yields (%)[a]	Mp (°C)[b]
Scheme 2					
1	Phenol	**4a**	6.0	73	272–273
2	*o*-Cresol	**4b**	5.0	69	248–250
3	Guaiacol	**4c**	5.0	62	243–245
4	*o*-Chlorophenol	**4d**	7.0	72	236–237
5	Thymol	**4e**	5.0	68	228–230
6	2,6-Dihydroxyacetophenone	**4f**	4.0	70	320–322
7	Catechol	**4g**	24.0	55	264–265
8	Resorcinol	**5a**	24.0	65	256–258
9	Orcinol	**5b**	24.0	60	268–269
10	1,3,5-Trihydroxybenzene	**5c**	20.0	61	280–281
11	α-Naphthol	**5d**	3.5	70	264–265
12	β-Naphthol	**5e**	3.5	72	255–256
Scheme 3					
13	*p*-Cresol	**9a**	5.0	82	285–286
14	*m*-Cresol	**9b**	6.0	73	254–255
15	*p*-Methoxyphenol	**9c**	6.0	68	298–299
16	*p*-Chlorophenol	**9d**	6.0	72	276–278
17	*p*-Bromophenol	**9e**	8.0	76	304–306
18	*m*-Iodophenol	**9f**	8.0	65	330–332
19	*p*-Chloro-*m*-cresol	**9g**	5.0	70	321–322
20	Ethyl *p*-hydroxybenzoate	**9h**	30.0	62	225–226
21	Methyl *p*-hydroxybenzoate	**9i**	32.0	65	258–259

[a] Yields refer to pure isolated products.

[b] Mps are uncorrected.

opportunity to study its electrophilic chemistry towards phenols, enols and aromatic substrates.

Various reports established that the C-2 position of ninhydrin is reactive to nitrogen-, sulfur-, oxygen-, and carbon-based nucleophiles.[4] Acid catalysed condensation of ninhydrin with various phenols, enols and aromatic substrates has been studied extensively.[5–10] In all these cases the protonation of the hydroxy group of ninhydrin is followed by elimination of water to produce the C-2 carbocation **2a** (Scheme 1) which then undergoes nucleophilic attack from various phenols, enols and aromatic substrates.[9] Likewise **1** can potentially generate a C-2 carbocation **2b** (Scheme 1) in acid medium. So far no efforts have been made to examine the electrophilic chemistry of **1** towards various substrates. In this paper we have carried out an extensive study to explore the electrophilic chemistry of **1**.



a: R^3 = OH, R^1 = R^2 = R^4 = R^5 = H
b: R^3 = OH, R^2 = CH_3, R^1 = R^4 = R^5 = H
c: R^3 = OH, R^2 = OCH_3, R^1 = R^4 = R^5 = H
d: R^3 = OH, R^2 = Cl, R^1 = R^4 = R^5 = H
e: R^3 = OH, R^1 = CH_3, R^4 = $CH(CH_3)_2$, R^2 = R^5 = H
f: R^1 = R^3 = OH, R^2 = $COCH_3$, R^4 = R^5 = H
g: R^2 = R^3 = OH, R^1 = R^4 = R^5 = H
h: R^1 = R^3 = OH, R^2 = R^4 = R^5 = H (**5a**)
i: R^1= R^3 = OH, R^2 = R^4 = H, R^5 = CH_3 (**5b**)
j: R^1 = R^3 = R^5 = OH, R^2 = R^4 = H (**5c**)
k: R^1 = OH, R^2, R^3 = benzofusion, R^4 = R^5 = H (**5d**)
l: R^1 = OH, R^2 = R^3 = H, R^4, R^5 = benzofusion (**5e**)

Scheme 2.

2. Results and discussion

In the present study it has been noted that 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone **1** like ninhydrin, condenses with various phenols (Table 1, entries 1–5), polyhydroxy benzenes (entries 6–10) as well as α- and β-naphthols (entries 11 and 12). This is done simply by stirring in a solution of acetic acid and few drops of conc. H_2SO_4 at room temperature for a period varying from 2.5 to 24 h to produce the adducts 2-aryl-2,2′-biindan-1,1′,3,3′-tetrones **4** in high yield (Scheme 2). In general, **1** is found to be slightly less reactive than ninhydin in acid medium[5] because the carbocation **2b** generated from **1** is comparatively less stable and more sterically crowded than that of the oxonium ion **2a** derived from ninhydrin (Scheme 1).[9a] As a result, **1** needs a few drops of conc. H_2SO_4 as catalyst in the reaction, and longer reaction time for adduct formation. The electrophilic attack to phenols generally takes place at the *para* position with respect to the hydroxy groups, producing the adducts 2-aryl-2,2′-biindan-1,1′,3,3′-tetrones **4a–e**. ^{1}H and ^{13}C NMR spectra for most of the adducts **4a–e** display a symmetrical pattern for two 1,3-dioxoindane moieties indicating tetraketo structures with a plane of symmetry.

In the case of substrates like resorcinol, orcinol, 1,3,5-trihydroxybenzene as well as α- and β-naphthols the electrophilic attack of carbocation **2b** takes place at the *ortho* position with respect to the hydroxy groups. ^{1}H and ^{13}C NMR spectra of these adducts **4h–l** show an unsymmetrical structure formation. This observation indicates that they preferably remain in the intramolecular hemi-ketal form **5** (Scheme 2). Further X-ray studies of the adducts **5c** and **5e** derived by the condensation of **1** with 1,3,5-trihydroxybenzene and β-naphthol, respectively, confirm the hemi-ketal structures with the *cis* geometry of the vicinal –OH and 1,3-indanedionyl moiety at the bridgehead of the bicyclo[3.3.0] system (Figs. 1 and 2).[11] In the case of catechol, the newly formed C–C bond does not have any *ortho* hydroxy group for the formation of a hemi-ketal, and as a result it produces a symmetrical adduct **4g**. 2,6-Dihydroxyacetophenone (entry 6) also undergoes the reaction as with other polyhydroxy benzenes (entries 7–10) to produce adduct **4f**, in contrast to the earlier report[7a] that the acid catalyzed condensation with ninhydrin generally fails if an electron-withdrawing group like –NO$_2$, –CHO, –CO$_2$Et etc. is attached to the benzene ring of the phenolic substrate **3**. It is found by NMR study that in spite of having an *ortho* hydroxy group with respect to the newly formed C–C bond in the adduct **4f**, hemi-ketal formation does not occur, probably due to the electron-withdrawing effect of the acetyl group.

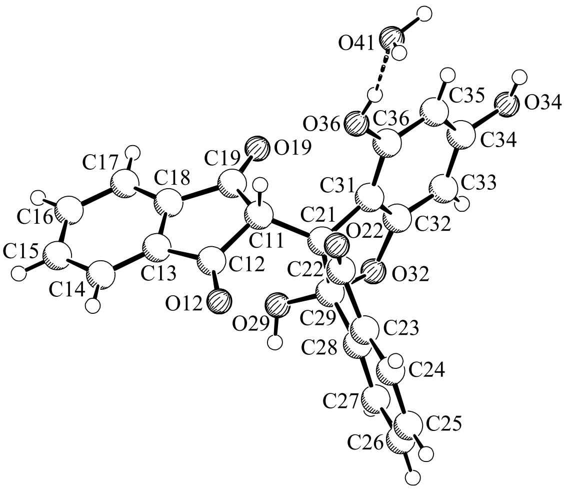


Figure 1. X-ray crystal structure of hemi-ketal **5c**.

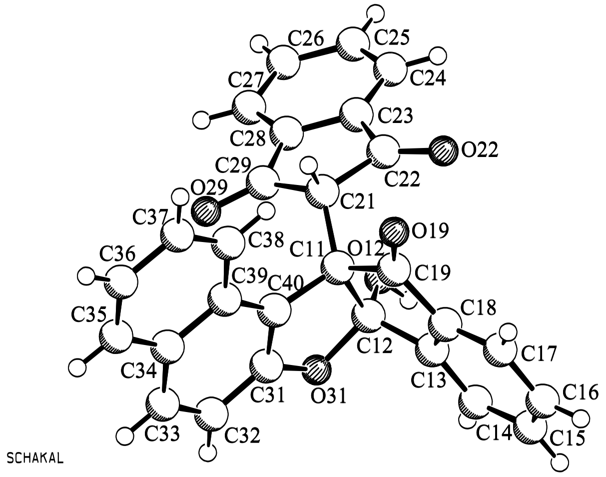
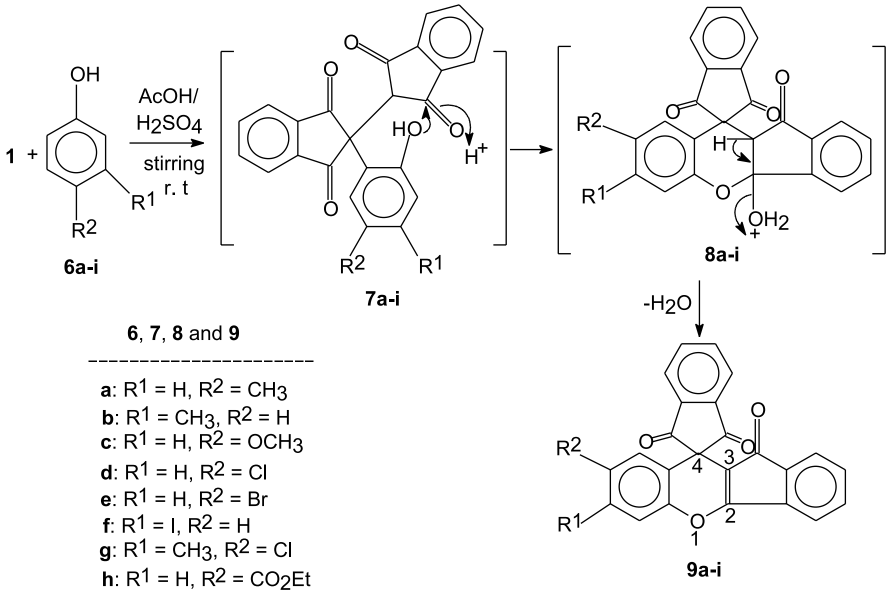


Figure 2. X-ray crystal structure of hemi-ketal **5e**.

Interestingly it was observed that *para* or *meta* substituted phenols **6a–i** such as *p*-cresol, *m*-cresol, *p*-methoxyphenol, *p*-bromophenol, *m*-iodophenol etc. condense with **1** in acid medium to furnish 6 or 7 substituted 2′,4-spiro(1′,3′-indanedion)-indeno[3,2-*b*]chromenes[12] **9a–i** as yellow precipitates in fairly good yields (Table 1, Scheme 3). In these reactions initially the arylated intermediates 2-aryl-2,2′-biindan-1,1′,3,3′-tetrones **7a–i** are formed by the nucleophilic attack of phenols **6a–i** to the carbocation **2b** in the acetic acid and conc. H_2SO_4 mixture (Scheme 3). Subsequently, the arylated intermediates **7a–i** undergo an intramolecular nucleophilic attack by the phenolic hydroxy group to either of the carbonyl groups at $C_{1'}$ or $C_{3'}$, followed by dehydration to furnish chromenes **9a–i**. The *para* or *meta* substituted phenols **6a–i** are required for the reaction which ensure the initial formation of adducts only *ortho* to the phenolic hydroxy group. The intermediates **7a–i** and **8a–i** were not isolated. Ethyl and methyl *p*-hydroxy benzoates **6h**,**i** are found to take a longer time for chromene formation than the phenols **6a–g** due to the electron-withdrawing effect of the ethyl and methyl carboxylate groups (Table 1).

All the chromenes **9a–i** were thoroughly characterized by ^{1}H and ^{13}C NMR studies and confirmed for **9a** by two dimensional ^{13}C–^{1}H correlation studies. The solid state structure of **9b** was determined by single crystal X-ray diffraction study. The result is shown in Figure 3.

It has also been observed that various methoxy aromatic systems such as anisole, veratrole, 1,3-dimethoxy-, 1,4-dimethoxy- and 1,2,3-trimethoxybenzene (Table 2, entries 22–26) react with **1** in acetic acid and few drops of conc. H_2SO_4 at room temperature to furnish the adduct 2-aryl-2,2′-biindan-1,1′,3,3′-tetrones **10a–e** in high yields



6, **7**, **8** and **9**

- **a**: R^1 = H, R^2 = CH_3
- **b**: R^1 = CH_3, R^2 = H
- **c**: R^1 = H, R^2 = OCH_3
- **d**: R^1 = H, R^2 = Cl
- **e**: R^1 = H, R^2 = Br
- **f**: R^1 = I, R^2 = H
- **g**: R^1 = CH_3, R^2 = Cl
- **h**: R^1 = H, R^2 = CO_2Et
- **i**: R^1 = H, R^2 = CO_2Me

Scheme 3.

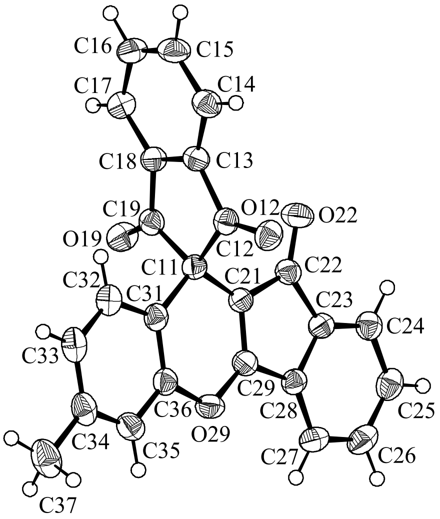
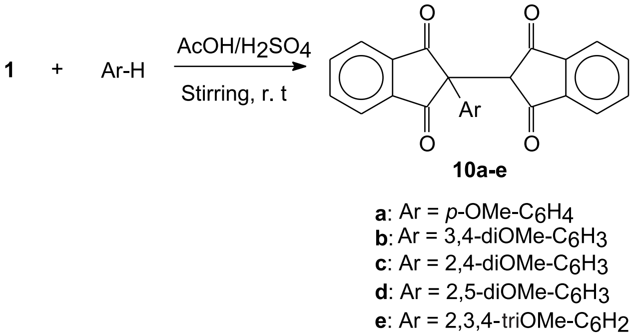


Figure 3. Diamond-plot of chromene **9b** with thermal ellipsoids (50% probability) and atom numbering scheme.



- **a**: Ar = *p*-OMe-C_6H_4
- **b**: Ar = 3,4-diOMe-C_6H_3
- **c**: Ar = 2,4-diOMe-C_6H_3
- **d**: Ar = 2,5-diOMe-C_6H_3
- **e**: Ar = 2,3,4-triOMe-C_6H_2

Scheme 4.

(Scheme 4). In the case of anisole, the preferred electrophilic attack is at the *para* position with respect to the methoxy group. ^1H and ^{13}C NMR spectra of the adducts **10a–e** indicate the formation of symmetrical tetrone structures. X-ray structure of the adduct **10e** derived from **1** and 1,2,3-trimethoxybenzene shows the preferred conformation of the molecule in the solid state (Fig. 4).[11]

Table 2. Preparation of 2-aryl/alkyl 2,2′-biindan-1,1′,3,3′-tetrones by condensation of methoxy aromatic systems and enols with **1** in acid medium

Entry	Substrates	Products	Reaction time (hr)	Yields (%)[a]	Mp (°C)[b]
Scheme 4					
22	Anisole	**10a**	3.0	75	239–240
23	1,2-Dimethoxybenzene	**10b**	4.0	72	225–226
24	1,3-Dimethoxybenzene	**10c**	2.5	75	230–231
25	1,4-Dimethoxybenzene	**10d**	4.0	70	217–218
26	1,2,3-Trimethoxybenzene	**10e**	4.5	67	221–222
Scheme 5					
27	4-Hydroxycoumarin	**11a**	4.0	68	296–298
28	3-Hydroxycoumarin	**11b**	4.0	65	259–260
29	1,3-Indanedione	**11c**	5.0	62	Ref.[13]
30	1,3-Cyclohexadione	**11d**	4.5	60	288–290

[a] Yields refer to pure isolated products.

[b] Mps are uncorrected.

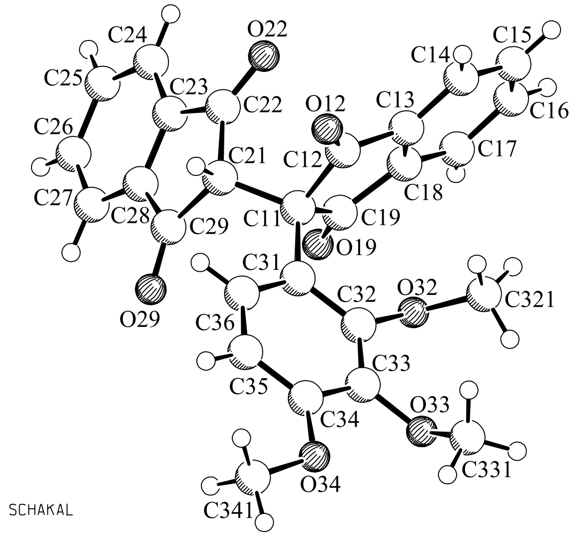
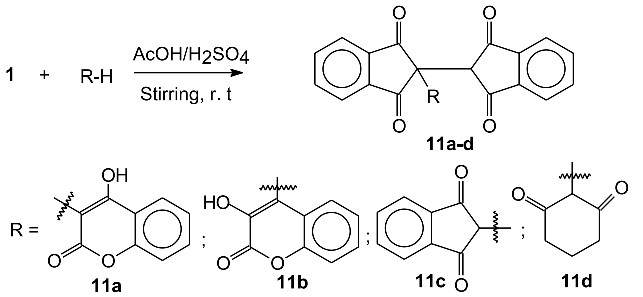


Figure 4. X-ray crystal structure of **10e**.

4- and 3-Hydroxycoumarins (Table 2, entries 27 and 28) behave like enolic compounds and react with **1** in AcOH/H_2SO_4 to produce adducts **11a** and **11b** when stirred for about 4 h at room temperature (Scheme 5). 1,3-Indanedione and 1,3-cyclohexadione, which preferably remain in enolic form, also react with **1** to furnish the products **11c** and **11d**, respectively. The biologically active trisindanedione **11c** was also synthesized previously from ninhydrin.[13] The adducts **11a–d** display somewhat symmetrical ^1H and ^{13}C NMR spectra for the two 1,3-dioxoindane parts, and thus prefer to remain in the tetraketo form in contrast to adducts **4h–l** which stay mainly in the hemi-ketal form **5a–e** (Scheme 2). X-ray study of the adduct **11c** derived from **1** and 1,3-indanedione shows a structure with a C_2 axis of symmetry (Fig. 5).[11]



Scheme 5.

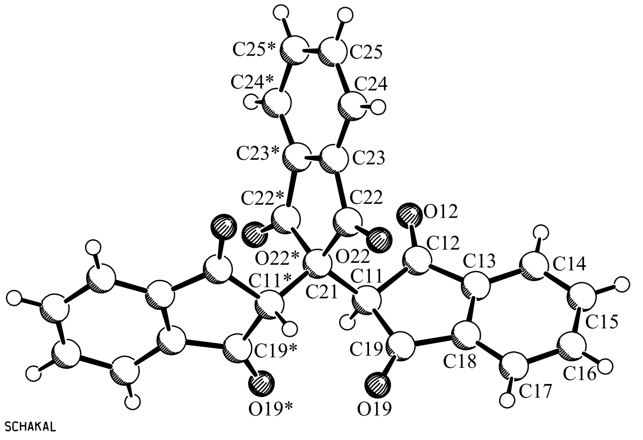


Figure 5. X-ray crystal structure of trisindanedione **11c**.

In summary, efficient routes to 2-aryl/alkyl-2,2′-biindan-1,1′,3,3′-tetrones and some hemi-ketals of the bicyclo-[3.3.0]octano system have been derived through facile condensation of 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone with hydroxy- and methoxy aromatic systems as well as with enols under acid catalysis. The study has also led to the development of a new and facile method for the preparation of 6 or 7 substituted 2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromenes from readily available ninhydrin.

3. Experimental

Melting points were determined in open capillary tubes. IR spectra were examined in KBr disc on a Perkin–Elmer-782 spectrophotometer. Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded on Bruker AM 300L (300 MHz) or a Bruker DRX-500 (500 MHz) spectrometers in the solvents indicated. Chromatography was performed on Merck silica gel 60. TLC analyses were run on Merck silica gel (60F-254) plates (0.25 mm), precoated with a fluorescent indicator.

3.1. Preparation of 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone 1

The substrate 1,3-indanedione (0.61 g, 4.2 mmol) was added to a solution of ninhydrin (0.25 g, 1.4 mmol) in acetic acid (10 mL). The mixture was stirred at room temperature for 2 h. The white solid product **1** was filtered out and washed thoroughly with acetic acid and then with water. The product **1** was purified by silica-gel column chromatography using $CHCl_3$ as the eluent (yield ~ 87%).

3.1.1. 2-Hydroxy-2,2′-biindan-1,1′,3,3′-tetrone 1. White solid, mp 189–191 °C, IR (KBr): (cm^{-1}) 3428, 1704, 1586, 1264; ^1H NMR (300.13 MHz, $CDCl_3$) δ: 8.02–7.83 (8H, m), 5.46 (1H, s), 3.97 (1H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.3 (2C), 196.2 (2C), 142.2 (2C), 141.2 (2C), 136.6 (d, 2C), 136.3 (d, 2C), 124.3 (d, 2C), 123.6 (d, 2C), 76.3, 53.4 (d). Anal. Calcd for $C_{18}H_{10}O_5$: C, 70.59; H, 3.29. Found: C, 70.64; H, 3.35%.

3.2. General procedure for preparation of 2-aryl/alkyl-2,2′-biindan-1,1′,3,3′-tetrones (entries 1–30)

A mixture of 2-hydroxy-2,2′-biindan-1,1′,3,3′-tetrone **1** (0.43 g, 1.4 mmol) in acetic acid (8 mL) was warmed to make a clear solution. The appropriate substrates such as phenols (**3** and **6**), methoxybenzenes (Ar-H), enols (R-H) etc. (4.2 mmol) and 0.5–1.0 mL conc. H_2SO_4 were then added (for catechol, resorcinol, orcinol and 1,3,5-trihydroxybenzene addition of H_2SO_4 is not necessary) at room temperature and stirred for a certain period (Tables 1 and 2). The solid products were filtered out and washed thoroughly with acetic acid and then with water. The products were purified by silica-gel column chromatography using ethyl acetate and pet-ether as eluent. The resulting solids were further purified by crystallization from $CHCl_3$/pet-ether.

3.2.1. 2-(4-Hydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4a. White solid, mp 272–273 °C, IR (KBr): (cm^{-1}) 3482, 1702, 1588, 1263, 771; ^{1}H NMR (300.13 MHz, acetone-d_6) δ: 8.68 (1H, br. s), 7.99–7.85 (8H, m), 7.21 (2H, d, $J=8.8$ Hz), 6.82 (2H, d, $J=8.8$ Hz), 4.56 (1H, s); ^{13}C NMR (75.47 MHz, acetone-d_6) δ: 199.0 (2C), 197.6 (2C), 158.3, 143.2 (2C), 142.5 (2C), 137.1 (d, 2C), 136.6 (d, 2C), 129.8 (d, 2C), 125.1, 124.5 (d, 2C), 123.6 (d, 2C), 116.5 (d, 2C), 65.1, 56.4 (d). Anal. Calcd for $C_{24}H_{14}O_5$: C, 75.39; H, 3.69. Found: C, 75.45; H, 3.74%.

3.2.2. 2-(3-Methyl-4-hydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4b. White solid, mp 248–250 °C, IR (KBr): (cm^{-1}) 3292, 1705, 1592, 1264, 757; ^{1}H NMR (300.13 MHz, acetone-d_6) δ: 8.55 (1H, s), 7.98–7.83 (8H, m), 7.13 (1H, d, $J=2.2$ Hz), 6.98 (1H, dd, $J=8.6$, 2.2 Hz), 6.77 (1H, d, $J=8.6$ Hz), 4.55 (1H, s), 2.08 (3H, s); ^{13}C NMR (75.47 MHz, acetone-d_6) δ: 199.0 (2C), 197.6 (2C), 156.4, 143.2 (2C), 142.5 (2C), 137.1 (d, 2C), 136.6 (d, 2C), 131.0 (d), 127.2 (d), 125.6, 125.1, 124.5 (d, 2C), 123.6 (d, 2C), 115.9 (d), 64.2, 56.5 (d), 16.4 (q). Anal. Calcd for $C_{25}H_{16}O_5$: C, 75.75; H, 4.07. Found: C, 75.81; H, 4.14%.

3.2.3. 2-(3-Methoxy-4-hydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4c. White solid, mp 243–245 °C, IR (KBr): (cm^{-1}) 3528, 1709, 1515, 1263; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.99–7.96 (2H, m), 7.90–7.87 (2H, m), 7.85–7.79 (4H, m), 7.03 (1H, d, $J=1.7$ Hz), 6.88–6.81 (2H, m), 5.66 (1H, s), 4.21 (1H, s), 3.89 (3H, s). Anal. Calcd for $C_{25}H_{16}O_6$: C, 72.81; H, 3.91. Found: C, 72.90; H, 3.85%.

3.2.4. 2-(3-Chloro-4-hydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4d. White solid, mp 236–237 °C, IR (KBr): (cm^{-1}) 3221, 1704, 1589, 1266, 761; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 8.00–7.96 (2H, m), 7.90–7.79 (6H, m), 7.42 (1H, d, $J=2.3$ Hz), 7.27 (1H, dd, $J=8.7$, 2.3 Hz), 6.99 (1H, d, $J=8.7$ Hz), 5.69 (1H, s), 4.18 (1H, s). Anal. Calcd for $C_{24}H_{13}O_5Cl$: C, 69.15; H, 3.14; Cl, 8.52. Found: C, 69.23; H, 3.21; Cl, 8.61%.

3.2.5. 2-(2-Methyl-4-hydroxy-5-isopropylphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4e. Light yellow solid, mp 228–230 °C, IR (KBr): (cm^{-1}) 3310, 1703, 1590, 1259, 758; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.99–7.96 (2H, m), 7.91–7.86 (2H, m), 7.85–7.78 (5H, m), 6.84 (1H, s), 6.53 (1H, s), 4.65 (1H, s), 3.02–2.98 (1H, m), 2.53 (3H, s), 1.05 (6H, d, $J=11.1$ Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 198.5 (2C), 197.0 (2C), 152.3, 142.3 (4C), 137.2, 135.6 (d, 2C), 135.4 (d, 2C), 132.0, 128.1, 123.8 (d, 2C), 123.2 (d, 2C), 120.0, 66.0, 54.6 (d), 27.2 (d), 22.3 (q, 2C), 22.1 (q). Anal. Calcd for $C_{28}H_{22}O_5$: C, 76.70; H, 5.06. Found: C, 76.78; H, 5.13%.

3.2.6. 2-(2,4-Dihydroxy-3-acetylphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4f. White solid, mp 320–322 °C, IR (KBr): (cm^{-1}) 3283, 1713, 1638, 1274, 1219; ^{1}H NMR (300.13 MHz, acetone-d_6) δ: 7.99–7.66 (8H, m), 7.58 (1H, d, $J=8.4$ Hz), 6.57 (1H, d, $J=8.4$ Hz), 4.52 (1H, s), 2.59 (3H, s);^{13}C NMR (125 MHz, acetone-d_6): 204.5, 198.0, 197.1, 165.0, 143.6, 142.1, 137.0, 136.4, 136.2, 132.9, 131.9, 125.5, 124.3, 123.5, 111.2, 65.0, 55.3, 32.3. Anal. Calcd for $C_{26}H_{16}O_7$: C, 70.91; H, 3.66. Found: C, 70.85; H, 3.73%.

3.2.7. 2-(3,4-Dihydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4g. Light greenish solid, mp 264–265 °C, IR (KBr): (cm^{-1}) 3429, 1702, 1589, 1264, 1194, 769; ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.99–7.86 (8H, m), 6.92 (1H, d, $J=2.1$ Hz), 6.76 (1H, d, $J=8.3$ Hz), 6.67 (1H, dd, $J=8.3$, 2.1 Hz), 4.49 (1H, s). Anal. Calcd for $C_{24}H_{14}O_6$: C, 72.36; H, 3.54. Found: C, 72.43; H, 3.61%.

3.2.8. 2-(2,4-Dihydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4h (remains as hemiketal 5a). White solid, mp 256–258 °C, IR (KBr): (cm^{-1}) 3293, 1709, 1603, 1267, 1136, 767; ^{1}H NMR (500 MHz, acetone-d_6) δ:8.40 (1H, s), 7.87–7.76 (7H, m), 7.64–7.61 (1H, m), 7.41 (1H, s), 7.27 (1H, d, $J=8.3$ Hz), 6.50 (1H, dd, $J=8.3$, 2.1 Hz), 6.21 (1H, d, $J=2.1$ Hz), 4.40 (1H, s); ^{13}C NMR (125 MHz, acetone-d_6) δ: 198.3, 197.6, 196.5, 160.1, 158.4, 150.7, 143.1, 141.8, 136.0, 135.9, 135.4, 135.2, 130.9, 125.4, 124.2, 123.7, 122.8, 122.7, 116.0, 113.3, 109.3, 97.6, 65.4, 55.0. Anal.Calcd for $C_{24}H_{14}O_6$: C, 72.36; H, 3.54. Found: C, 72. 45; H, 3.64%.

3.2.9. 2-(2,4-Dihydroxy-6-methylphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4i (remains as hemiketal 5b). White solid, mp 268–269 °C, IR (KBr): (cm^{-1}) 3429, 1704, 1587, 1265, 1214; ^{1}H NMR (500 MHz, acetone-d_6) δ: 8.27 (1H, s), 7.85–7.74 (7H, m), 7.64–7.62 (1H, m), 7.33 (1H, s), 6.30 (1H, d, $J=1.5$ Hz), 6.03 (1H, d, $J=1.9$ Hz), 4.67 (1H, s), 2.58 (3H, s). Anal. Calcd for $C_{25}H_{16}O_6$: C, 72.81; H, 3.91. Found: C, 72.93; H, 4.01%.

3.2.10. 2-(2,4,6-Trihydroxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4j (remains as hemiketal 5c). White solid, mp 280–281 °C, IR (KBr): (cm^{-1}) 3445, 3325, 1710, 1620, 1465, 1269, 1132; ^{1}H NMR (300.13 MHz, acetone-d_6) δ: 8.39 (1H, s), 8.05 (1H, s), 7.89–7.80 (8H, m), 7.47 (1H, s), 6.01 (1H, d, $J=1.8$ Hz), 5.78 (1H, d, $J=1.8$ Hz), 4.67 (1H, s). Anal. Calcd for $C_{24}H_{14}O_7$: C, 69.56; H, 3.41. Found: C, 69.62; H, 3.50%.

3.2.11. 2-(1-Hydroxynaphthyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4k (remains as hemiketal 5d). Light yellow solid, mp 264–265 °C, IR (KBr): (cm^{-1}) 3401, 1704, 1590, 1256, 774; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.85 (1H, d, $J=6.3$ Hz), 8.51 (1H, d, $J=8.1$ Hz), 8.22 (1H, d, $J=8.1$ Hz), 8.15–7.79 (4H, m), 7.56–7.30 (4H, m), 6.94 (1H, dd, $J=7.9$, 1.5 Hz), 6.84 (1H, d, $J=7.8$ Hz), 6.73–6.69 (1H, m), 5.55 (1H, s); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 198.3, 198.0, 197.3, 154.5, 154.0, 141.5, 141.2, 137.6, 137.1, 136.6, 133.8, 129.7, 127.2, 126.6, 126.3, 125.3, 124.7, 124.4, 123.6, 123.5, 121.0, 120.4, 108.2, 108.1, 107.9, 66.8, 63.7, 55.5. Anal. Calcd for $C_{28}H_{16}O_5$: C, 77.77; H, 3.73. Found: C, 77.83; H, 3.65%.

3.2.12. 2-(2-Hydroxynaphthyl)-2,2′-biindan-1,1′,3,3′-tetrone, 4l (remains as hemiketal 5e). White solid, mp 255–256 °C, IR (KBr): (cm^{-1}) 3263, 1704, 1593, 1270, 722; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 8.82 (1H, br. s), 8.47 (1H, d, $J=8.5$ Hz), 7.89–7.70 (6H, m), 7.61–7.50 (4H, m), 7.34 (1H, t, $J=7.8$ Hz), 7.05 (1H, d, $J=8.8$ Hz), 5.10

(1H, s). Anal. Calcd for $C_{28}H_{16}O_5$: C, 77.77; H, 3.73. Found: C, 77.85; H, 3.64%.

3.2.13. 6-Methyl-2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromene, 9a. Yellow solid, mp 285–286 °C, IR (KBr): (cm^{-1}) 1711, 1649, 1396, 1252; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.16–8.13 (2H, m), 8.00–7.96 (2H, m), 7.41–7.25 (5H, m), 7.12 (1H, dd, J=8.4, 1.6 Hz), 6.40 (1H, d, J=1.6 Hz), 2.14 (3H, s); ^{13}C NMR (75.47 MHz, CDCl$_3$) δ: 198.3 (2C), 190.5, 171.3, 149.1, 143.2 (2C), 136.8, 136.1 (d, 2C), 132.5 (d), 132.0, 130.7 (d), 130.5 (d), 127.6 (d), 124.2 (d, 2C), 123.3, 121.9 (d), 119.7, 118.9 (d), 118.6 (d), 105.7, 54.4, 20.6. Anal. Calcd for $C_{25}H_{14}O_4$: C, 79.36; H, 3.73. Found: C, 79.30; H, 3.69%.

3.2.14. 7-Methyl-2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromene, 9b. Yellow solid, mp 254–255 °C, IR (KBr): (cm^{-1}) 3438, 1709, 1650, 1389, 1243; ^{1}H NMR (300.13 MHz, acetone-d_6) δ: 8.16–8.15 (4H, m), 7.61–7.33 (5H, m), 6.99 (1H, d, J=7.9 Hz), 6.66 (1H, d, J=7.9 Hz). 2.36 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.8, 191.1, 171.8, 151.1, 143.5, 140.8, 137.2, 136.6, 133.0, 132.3, 131.2, 127.6, 127.4, 124.7, 122.3, 119.7, 119.3, 117.4, 106.1, 21.5. Anal. Calcd for $C_{25}H_{14}O_4$: C, 79.36; H 3.73. Found: C, 79.42; H, 3.81%.

3.2.15. 6-Methoxy-2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromene, 9c. Yellow solid, mp 298–299 °C, IR (KBr): (cm^{-1}) 3438, 1707, 1645, 1394, 1197; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.16–8.13 (2H, m), 7.99–7.97 (2H, m), 7.40–7.26 (5H, m), 6.87 (1H, dd, J=9.0, 2.9 Hz), 6.12 (1H, d, J=2.9 Hz), 3.63 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.6, 191.0, 171.9, 157.7, 145.5, 143.4, 137.1, 136.7, 133.0, 132.4, 131.2, 124.7, 122.3, 121.1, 120.1, 119.3, 114.9, 113.2, 106.0, 56.0. Anal. Calcd for $C_{25}H_{14}O_5$: C, 76.14; H, 3.58. Found: C, 76.25; H, 3.68%.

3.2.16. 6-Chloro-2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromene, 9d. Yellow solid, mp 276–278 °C, IR (KBr): (cm^{-1}) 1710, 1651, 1394, 1247; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.10–8.07 (2H, m), 7.95–7.91 (2H, m), 7.38–7.24 (6H, m), 6.53 (1H, d, J=1.4 Hz). Anal. Calcd for $C_{24}H_{11}O_4Cl$: C, 72.27; H, 2.78; Cl, 8.90. Found: C, 72.35, H, 2.86; Cl, 8.79%.

3.2.17. 6-Bromo-2′,4-spiro(1′, 3′-indanedion)-indeno-[3,2-*b*]chromene, 9e. Yellow solid, mp 304–306 °C, IR (KBr): (cm^{-1}) 3430, 1708, 1654, 1392, 1256; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.18–8.15 (2H, m), 8.03–7.99 (2H, m), 7.45–7.36 (5H, m), 7.27 (1H, apparent d, J=8.1 Hz), 6.74 (1H, d, J=2.2 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.0, 190.7, 171.3, 150.6, 143.3, 137.0, 136.8, 133.3, 133.2, 132.1, 131.4, 130.6, 125.0, 122.6, 122.3, 120.9, 119.4, 119.3, 105.9, 54.6.

3.2.18. 7-Iodo-2′,4-spiro(1′, 3′-indanedion)-indeno[3,2-*b*]-chromene, 9f. Yellow solid, mp 330–332 °C, IR (KBr): (cm^{-1}) 3436, 1710, 1651, 1383, 1251; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.16–8.13 (2H, m), 8.02–7.98 (2H, m), 7.77 (1H, d, J=1.7 Hz), 7.47–7.33 (5H, m), 6.37 (1H, d, J=8.2 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 197.9, 190.6, 171.2, 151.3, 143.1, 137.0, 136.5, 135.6, 133.3, 131.8, 131.4, 129.0, 128.1, 124.7, 122.4, 120.0, 119.4, 105.8, 94.2.

3.2.19. 6-Chloro-7-methyl-2′,4-spiro(1′, 3′-indanedion)-indeno[3,2-*b*]chromene, 9g. Yellow solid, mp 321–322 °C, IR (KBr): (cm^{-1}) 3438, 1707, 1647, 1377, 1245; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.10–8.07 (2H, m), 7.96–7.92 (2H, m), 7.39–7.21 (4H, m), 7.19 (1H, s), 6.52 (1H, s), 2.30 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.1, 190.7, 171.0, 149.5, 143.1, 138.8, 137.0, 136.7, 133.2, 132.0, 131.4, 127.6, 124.7, 124.6, 122.3, 121.2, 119.4, 119.0, 105.7, 20.3. Anal. Calcd for $C_{25}H_{13}O_4Cl$: C, 72.73; H, 3.17; Cl, 8.60. Found: C, 72.82; H, 3.26; Cl, 8.55%.

3.2.20. 6-Carbethoxy-2′,4-spiro(1′, 3′-indanedion)-indeno[3,2-*b*]chromene, 9h. Yellow solid, mp 225–226 °C, IR (KBr): (cm^{-1}) 3437, 1712, 1652, 1392, 1258; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 8.17–8.15 (2H, m), 8.03 (1H, d, J=1.8 Hz), 8.01–7.99 (2H, m), 7.93 (1H, dd, J=8.6, 1.8 Hz), 7.44–7.34 (4H, m), 6.81 (1H, d, J=8.6 Hz), 4.26 (2H, q, J=7.1 Hz), 1.28 (3H, t, J=7.1 Hz); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.2, 190.8, 171.3, 165.2, 154.4, 143.4, 136.9, 136.7, 133.2, 132.0, 131.6, 131.5, 130.0, 128.9, 124.9, 122.6, 120.6, 119.5, 119.3, 106.3, 61.7, 54.7, 14.6. Anal. Calcd for $C_{27}H_{16}O_6$: C, 74.31; H, 3.70. Found: C, 74.40; H, 3.81%.

3.2.21. 6-Carbomethoxy-2′,4-spiro(1′, 3′-indanedion)-indeno[3,2-*b*]chromene, 9i. Yellow solid, mp 258–259 °C, IR (KBr): (cm^{-1}) 3410, 1711, 1390, 1255; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 8.18–8.15 (2H, m), 8.04 (1H, d, J=1.8 Hz), 8.03–7.99 (2H, m), 7.47–7.34 (6H, m), 3.80 (3H, s); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 198.2, 190.7, 171.2, 165.7, 154.5, 143.4, 136.9, 136.7, 133.3, 131.9, 131.7, 131.5, 130.0, 128.5, 124.9, 122.6, 120.6, 119.5, 119.4, 106.3, 54.7, 52.7. Anal. Calcd for $C_{26}H_{14}O_6$: C, 73.93; H, 3.34. Found: C, 74.01; H, 3.41%.

3.2.22. 2-(4-Methoxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 10a. Light yellow solid, mp 239–240 °C, IR (KBr): (cm^{-1}) 1705, 1594, 1511, 1264, 762; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 7.95–7.80 (8H, m), 7.35 (2H, d, J=8.2 Hz), 6.88 (2H, d, J=8.2 Hz), 4.23 (1H, s), 3.77 (3H, s); ^{13}C NMR (75.47 MHz, CDCl$_3$) δ: 197.9 (2C), 196.5 (2C), 159.8, 142.2 (2C), 141.6 (2C), 135.8 (d, 2C), 135.5 (d, 2C), 128.9 (d, 2C), 124.7, 123.9 (d, 2C), 123.2 (d, 2C), 114.4 (d, 2C), 63.1, 55.9 (q), 55.2 (d). Anal. Calcd for $C_{25}H_{16}O_5$: C, 75.75; H, 4.07. Found: C, 75.82; H, 4.13%.

3.2.23. 2-(3,4-Dimethoxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 10b. Light yellow solid, mp 225–226 °C, IR (KBr): (cm^{-1}) 1703, 1591, 1513, 1255, 764; ^{1}H NMR (300.13 MHz, CDCl$_3$) δ: 7.98–7.78 (8H, m), 7.05 (1H, d, J=2.1 Hz), 6.89 (1H, dd, J=8.5, 2.1 Hz), 6.80 (1H, d, J=8.5 Hz), 4.23 (1H, s), 3.87 (3H, s), 3.76 (3H, s); ^{13}C NMR (75.47 MHz, CDCl$_3$) δ: 197.8 (2C), 196.4 (2C), 149.6, 147.2, 142.2 (2C), 141.6 (2C), 135.8 (d, 2C), 135.5 (d, 2C), 125.0, 123.9 (d, 2C), 123.2 (d, 2C), 120.7 (d), 111.6 (d), 111.0 (d), 63.2, 56.2 (q), 56.0 (q), 55.9 (d). Anal. Calcd for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25. Found: C, 73.31; H, 4.33%.

3.2.24. 2-(2,4-Dimethoxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 10c. Light yellow solid, mp 230–231 °C, IR

(KBr): (cm^{-1}) 1710, 1592, 1264, 791; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.94–7.75 (8H, m), 7.29 (1H, d, $J=8.7$ Hz), 6.54 (1H, dd, $J=8.7$, 2.2 Hz), 6.39 (1H, d, $J=2.2$ Hz), 4.67 (1H, s), 3.76 (3H, s), 3.52 (3H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.5 (2C), 196.8 (2C), 160.9, 158.4, 142.2 (4C), 135.3 (d, 2C), 135.1 (d, 2C), 130.4 (d), 123.3 (d, 2C), 123.0 (d, 2C), 115.7, 106.2 (d), 100.5 (d), 62.1, 55.8 (q), 55.3 (q), 54.6 (d). Anal. Calcd for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25. Found: C, 73.29; H, 4.31%.

3.2.25. 2-(2,5-Dimethoxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 10d. White solid, mp 217–218 °C, IR (KBr): (cm^{-1}) 1707, 1594, 1502, 1266, 1228, 759; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.96–7.77 (8H, m), 7.02 (1H, d, $J=2.1$ Hz), 6.85–6.78 (2H, m), 4.64 (1H, s), 3.77 (3H, s), 3.48 (3H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.1 (2C), 196.5 (2C), 154.6, 151.7, 142.4 (2C), 142.3 (2C), 135.4 (d, 2C), 135.1 (d, 2C), 125.0, 123.4 (d, 2C), 123.2 (d, 2C), 116.0 (d), 115.2 (d), 114.6 (d), 61.2, 57.0 (q), 55.8 (q), 55.2 (d). Anal. Calcd for $C_{26}H_{18}O_6$: C, 73.23; H, 4.25. Found: C, 73.34; H, 4.36%.

3.2.26. 2-(2,3,4-Trimethoxyphenyl)-2,2′-biindan-1,1′,3,3′-tetrone, 10e. White solid, mp 221–222 °C, IR (KBr): (cm^{-1}) 1708, 1594, 1267, 784; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 7.94–7.76 (8H, m), 7.25 (1H, d, $J=9.0$ Hz), 6.75 (1H, d, $J=9.0$ Hz), 4.48 (1H, s),3.84 (3H, s), 3.73 (3H, s), 3.51 (3H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 197.1 (2C), 196.6 (2C), 153.9 (2C), 151.6, 142.3 (2C), 142.2 (2C), 135.4 (d, 2C), 135.1 (d, 2C), 123.8 (d), 123.4 (d, 2C), 123.1 (d, 2C),120.9, 108.1 (d), 61.8, 60.4 (q), 60.1 (q), 56.0 (q), 55.5 (d). Anal. Calcd for $C_{27}H_{20}O_7$: C, 71.05; H, 4.42. Found: C, 71.13; H, 4.51%.

3.2.27. 2-[3-(4-Hydroxy coumarin)]-2,2′-biindan-1,1′,3,3′-tetrone, 11a. White solid, mp 296–298 °C, IR (KBr): (cm^{-1}) 3190, 1739, 1696, 1273, 757; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 7.91–7.80 (8H, m), 7.61 (1H, t, $J=8.5$ Hz), 7.52 (1H, d, $J=7.7$ Hz), 7.41 (1H, d, $J=8.4$ Hz), 7.27 (1H, t, $J=7.5$ Hz), 5.32 (1H, s); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 197.4 (2C), 197.1 (2C), 162.4, 157.8, 154.6, 141.6 (4C), 135.5 (d, 4C), 133.5 (d), 124.5 (d), 124.2 (d), 122.8 (d, 2C), 122.5 (d, 2C), 116.8 (d), 111.6, 100.0, 64.2, 51.0 (d). Anal. Calcd for $C_{27}H_{14}O_7$: C, 72.00; H, 3.13. Found: C, 72.08; H, 3.21%.

3.2.28. 2-[4-(3-Hydroxy coumarin)]-2,2′-biindan-1,1′,3,3′-tetrone, 11b. White solid, mp 259–260 °C, IR (KBr): (cm^{-1}) 3289, 1713, 1274, 758; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.43 (1H, s), 8.18 (1H, d, $J=7.6$ Hz), 7.90–7.76 (8H, m), 7.69–7.67 (1H, m), 7.49–7.36 (2H, m), 5.16 (1H, s); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 196.6 (2C), 196.5 (2C), 153.1, 150.9, 148.9, 141.7 (2C), 141.0 (2C), 135.6 (d, 2C), 135.5 (d, 2C), 131.3 (d), 128.9 (d), 123.7 (d), 122.7 (d, 2C), 122.6 (d, 2C), 117.5, 116.5 (d), 113.1, 67.1, 53.0 (d). Anal. Calcd for $C_{27}H_{14}O_7$: C, 72.00; H, 3.13. Found: C, 72.10; H, 3.19%.

3.2.29. 2-(2,6-Dioxocyclohexanyl)-2,2′-biindan-1,1′,3,3′-tetrone, 11d. White solid, mp 288–290 °C, IR (KBr): (cm^{-1}) 3430, 1709, 1588, 1266; ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 9.00 (1H, s), 7.90–7.60 (8H, m), 4.65 (1H, s), 2.47–2.33 (6H, m). Anal. Calcd for $C_{24}H_{16}O_6$: C, 71.99; H, 4.03. Found: C, 72.12; H, 4.12%.

3.3. X-ray structure analyses.[11]

3.3.1. Compound 5c. Formula $C_{24}H_{14}O_7\cdot H_2O$, $M=432.37$, colourless crystal 0.35×0.30×0.30 mm^3, $a=15.516(1)$ Å, $b=8.764(1)$ Å, $c=15.268(1)$ Å, $\beta=104.49(1)°$, $V=2010.1(3)$ Å^3, $\rho_{calc}=1.429$ g cm^{-3}, $\mu=1.09$ cm^{-1}, empirical absorption correction ($0.963\le T\le 0.968$), $Z=4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda=0.71073$ Å, $T=198$ K, ω and ϕ scans, 11435 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda]=0.66$ Å^{-1}, 4745 independent ($R_{int}=0.036$) and 3691 observed reflections [$I\ge 2\sigma(I)$], 298 refined parameters, $R=0.043$, $wR^2=0.102$, max. residual electron density 0.33 (−0.28) e Å^{-3}, hydrogens at water molecule from difference fourier calculations, other calculated and all refined as riding atoms.

3.3.2. Compound 5e. Formula $C_{28}H_{16}O_5\cdot C_3H_6O$, $M=490.49$, colourless crystal 0.15×0.10×0.05 mm^3, $a=8.525(1)$ Å, $b=17.239(1)$ Å, $c=16.290(1)$ Å, $\beta=93.92(1)°$, $V=2388.4(3)$ Å^3, $\rho_{calc}=1.364$ g cm^{-3}, $\mu=0.95$ cm^{-1}, empirical absorption correction ($0.986\le T\le 0.995$), $Z=4$, monoclinic, space group $P2_1/n$ (No. 14), $\lambda=0.71073$ Å, $T=198$ K, ω and ϕ scans, 15689 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda]=0.66$ Å^{-1}, 5689 independent ($R_{int}=0.059$) and 3234 observed reflections [$I\ge 2\sigma(I)$], 337 refined parameters, $R=0.057$, $wR^2=0.112$, max. residual electron density 0.21 (−0.24) e Å^{-3}, hydrogens calculated and refined as riding atoms.

3.3.3. Compound 9b. Formula $C_{25}H_{14}O_4$, $M=378.36$, yellow crystal 0.20×0.10×0.06 mm^3, $a=7.267(1)$ Å, $b=9.641(1)$ Å, $c=14.351(1)$ Å, $\alpha=103.85(1)°$, $\beta=101.49(1)°$, $\gamma=103.89(1)°$, $V=911.86(2)$ Å^3, $\rho_{calc}=1.378$ g cm^{-3}, $\mu=0.93$ cm^{-1}, empirical absorption correction ($0.982\le T\le 0.994$), $Z=2$, triclinic, space group $P1$bar (No. 2), $\lambda=0.71073$ Å, $T=198$ K, ω and ϕ scans, 7847 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda]=0.62$ Å^{-1}, 3692 independent ($R_{int}=0.050$) and 2306 observed reflections [$I\ge 2\sigma(I)$], 263 refined parameters, $R=0.052$, $wR^2=0.108$, max. residual electron density 0.23 (−0.22) e Å^{-3}, hydrogens calculated and refined as riding atoms.

3.3.4. Compound 10e. Formula $C_{27}H_{20}O_7$, $M=456.43$, colourless crystal 0.30×0.30×0.15 mm^3, $a=7.689(1)$ Å, $b=22.698(1)$ Å, $c=12.166(1)$ Å, $\beta=95.31(1)°$, $V=2114.2(3)$ Å^3, $\rho_{calc}=1.434$ g cm^{-3}, $\mu=1.04$ cm^{-1}, no absorption correction ($0.969\le T\le 0.985$), $Z=4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda=0.71073$ Å, $T=198$ K, ω and ϕ scans, 8798 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda]=0.66$ Å^{-1}, 5003 independent ($R_{int}=0.026$) and 3888 observed reflections [$I\ge 2\sigma(I)$], 310 refined parameters, $R=0.043$, $wR^2=0.108$, max. residual electron density 0.29 (−0.24) e Å^{-3}, hydrogens calculated and refined as riding atoms.

3.3.5. Compound 11c. Formula $C_{27}H_{14}O_6$, $M=434.38$, orange crystal 0.25×0.20×0.20 mm^3, $a=12.511(1)$ Å, $b=10.591(1)$ Å, $c=15.533(1)$ Å, $\beta=95.39(1)°$, $V=2049.1(3)$ Å^3, $\rho_{calc}=1.408$ g cm^{-3}, $\mu=1.0$ cm^{-1}, empirical absorption correction ($0.975\le T\le 0.980$), $Z=4$, monoclinic, space group $C2/c$ (No. 15), $\lambda = 0.71073$ Å, $T = 198$ K, ω and ϕ scans, 6663 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.66$ Å^{-1}, 2435 independent ($R_{\text{int}} = 0.031$) and 2085 observed reflections $[I \geq 2\sigma(I)]$, 150 refined parameters, $R = 0.039$, $wR^2 = 0.094$, max. residual electron density 0.23 (-0.16) e Å^{-3}, hydrogens calculated and refined as riding atoms.

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References and notes

1. (a) Ruhemann, S. *Trans. Chem. Soc.* **1910**, *97*, 1438. (b) MacFadyen, D. A.; Fowler, N. *J. Biol. Chem.* **1950**, *186*, 13. (c) Joullié, M. M.; Thompson, T. R. *Tetrahedron* **1991**, *47*, 8791. (d) Schertz, T. D.; Reiter, R. C.; Stevenson, C. D. *J. Org. Chem.* **2001**, *66*, 7596.
2. Das, S.; Pramanik, A. Unpublished work.
3. (a) Campagna, F.; Carotti, A.; Casini, G.; Ferappi, M. *Gazz. Chim. Ital.* **1983**, *113*, 507. (b) Schoenberg, A.; Singer, E. *Chem. Ber.* **1970**, *103*, 3871.
4. (a) Peet, N. P.; Huber, E. W.; Huffman, J. C. *J. Heterocycl. Chem.* **1995**, *32*, 33. (b) Black, D. St. C.; Bowyer, M. C.; Condie, G. C.; Craig, D. C.; Kumar, N. *Tetrahedron* **1994**, *50*, 10983. (c) Kundu, S. K.; Pramanik, A.; Patra, A. *Synlett* **2002**, *5*, 823. (d) Bullington, J. L.; Dodd, J. H. *J. Org. Chem.* **1993**, *58*, 4833. (e) Usmani, J. N.; Ismail, S. M. *Pak. J. Sci. Ind. Res.* **1987**, *30*, 89.
5. Kundu, S. K.; Patra, A.; Pramanik, A. *Indian J. Chem.* **2004**, *43B*, 604.
6. (a) Poupelin, J.-P.; Saint-Ruf, G.; Perche, J.-C.; Laude, B.; Narcisse, G.; Bakri-Logesis, F.; Hubert, F. *Eur. J. Med. Chem.* **1980**, *15*, 253. (b) Poupelin, J.-P.; Saint-Ruf, G.; Perche, J.-C.; Lacroix, R.; Uchida-Ernouf, G.; Narcisse, G.; Hubert, F. *Eur. J. Med. Chem.* **1979**, *14*, 171.
7. (a) Schmitt, G.; Dinh, A. N.; Poupelin, J.-P.; Vebrel, J.; Laude, B. *Synthesis* **1984**, 758. (b) Yamazaki, T.; Takizawa, T. *Tetrahedron* **1972**, *28*, 4675.
8. Song, H. N.; Seong, M. R.; Son, J. S.; Kim, J. N. *Synth. Commun.* **1998**, *28*, 1865.
9. (a) Klumpp, D. A.; Fredrick, S.; Lau, S.; Jin, K. K.; Bau, R.; Surya Prakash, G. K.; Olah, G. A. *J. Org. Chem.* **1999**, *64*, 5152. (b) Campbell, L. A.; Morrison, B. J.; Musgrave, O. C. *J. Chem. Res. (S)* **2002**, 638.
10. Olah, G. A. In *Friedel–Crafts and Related Reactions*, Wiley: New York, 1964; Vol. 2, pp 597–640.
11. Data set were collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN (Otwinowski, Z.; Minor, W. *Methods in Enzymology* **1997**, *276*, 307–326), absorption correction data SORTAV (Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33–37; Blessing, R. H. *J. Appl. Cryst.* **1997**, *30*, 421–426), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics SCHAKAL (Keller, E. 1997). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-240992, 240993, 233350, 240994, and 240995. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk].
12. Green, G. R.; Evans, J. M.; Vong, A. K. Comprehensive Heterocyclic Chemistry; Katritzky, A. R., Rees, C. W., Seriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 5, pp 469–500.
13. (a) Vanags, G.; Duburs, G. *Zhurnal Obshchei Khimii* **1957**, *27*, 2729. (b) Panashchenko, A. D. *Farmakol. i Toksikol* **1956**, *19*, 17. (c) Vanags, G.; Giller, S.; Geita, L.; Bleksmit, Z. D.; Kovalenko, V. N.; Kotovshchikova, M. A. *Farmakol. i Toksikol* **1956**, *19*, 23.

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Tetrahedron

New bromotyrosine alkaloids from the marine sponge *Psammaplysilla purpurea*

Supriya Tilvi,* Celina Rodrigues, C. G. Naik, P. S. Parameswaran and Solimabi Wahidhulla

National Institute of Oceanography, Dona Paula-Goa, India

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Abstract—Seven new bromotyrosine alkaloids Purpurealidin A, B, C, D, F, G, H and the known compounds Purealidin Q, Purpurealidin E, 16-Debromoaplysamine-4 and Purpuramine I have been isolated from the marine sponge *Psammaplysilla purpurea.* Their structure was elucidated on the basis of detailed 1D, 2D NMR and MS spectroscopic data. Purpurealidin B, 16-Debromoaplysamine-4 and Purpuramine I exhibited in vitro antimicrobial activities against *E. coli*, *S. aureus*, and *V. cholerae.* In addition, Purpurealidin B and 16-Debromoaplysamine-4 were also active against *Shigella flexineri* and *Salmonella typhi* while Purealidin Q was bactericidal only against *Salmonella typhi*.

1. Introduction

Marine sponges of the order Verongida are characterized by their ability to synthesize brominated tyrosine derivatives, many of which possess potent antimicrobial and cytotoxic activities. Chemical modification occurs both in the side chain and the aromatic ring of the brominated tyrosine precursors, giving rise to a broad range of biosynthetically related compounds.[1] Purealin,[2–4] Lipopurealin A–E,[5–6] Purealidin A–S,[6–11] Psammaplysin A–B,[12] Purpuramine A–J,[11,13] Aplysamines 2-5,[14] Macrocyclic peptides Bastadins[15] etc. have been previously reported from the sponge *Psammaplysilla* sp. In our earlier communication we reported the isolation of known compounds 16-Debromoaplysamine-4[9,16] and Purpuramine I.[13,16] The present paper deals with the isolation, structures and in vitro bioactivity of bromotyrosine metabolites Purpurealidin A–D and F–H along with Purealidin Q[10] and Purpurealidin E.[17]

2. Results and discussions

The animals were collected by scuba diving at a depth of 8–10 m from Mandapam, Tamil Nadu, India. A voucher specimen is deposited at the National Institute of Oceanography, Dona Paula Goa, India. The frozen sponge (250 g, dry weight) was extracted with Methanol (1 L×3) and concentrated under vacuo to obtain 10 g of crude extract. Successive chromatography of the crude MeOH extract on Silica gel, Sephadex LH-20 and a reverse phase column yielded 11 compounds (see Fig. 1). The structures and complete assignment of the ^{1}H and ^{13}C NMR spectra for the new compounds was determined based on extensive 1D and 2D NMR spectroscopic studies.

Compound **1**, was obtained as colourless oil. HRMS showed pseudomolecular ion peak at *m/z* 741.8, 743.8, 745.8, 747.8, 749.8 in the ratio 1.07:4.23:6.2:4.0:1.0, which indicated the presence of four bromine atoms in the molecule and established the molecular formula as $C_{23}H_{27}N_3O_4Br_4$. It was identified as Purealidin Q previously described from the Okinawan marine sponge *Psammaplysilla purea*, by comparison with the spectral data (UV, IR, 1D and 2D NMR) reported in the literature (see Table 1).[10] The stereochemistry at C1 and C6 of the spiroisoxazole ring in **1** was deduced to be *trans* from the proton chemical shift (ca. δ 4.05) of H-1 in CD_3OD.[18] The absolute configuration was not assigned. The HRMS of **1** also showed pseudomolecular peaks at *m/z* 755.8, 757.8, 759.8, 761.8, 763.8 for the minor compound Purpurealidin A (**2**) (see Table 1), which is 14 amu higher than Purealidin Q. This can be accounted from the presence of an additional methyl group either as –OMe at C-1 or –NMe at N-9. The position was established as –NMe at N-9 based on the fragmentation ion peaks. The MS/MS at *m/z* 755.8, 759.8 and 763.8 gave the product ions at *m/z* 418.9, 420.9, 422.9 for fragmentation at C8–C9 (Scheme 1) and the absence of mass peaks at *m/z* 404.9, 406.9, 408.9 (Scheme 2) as found in Purealidin Q.

Keywords: Antimicrobial activity; Bromotyrosine alkaloids; Marine sponge; *Psammaplysilla purpurea*; Purpurealidin.

* Corresponding author. Tel.: +91 832 2450394/2450392; fax: +91 832 2450603/2450604; e-mail: supriyat@darya.nio.org

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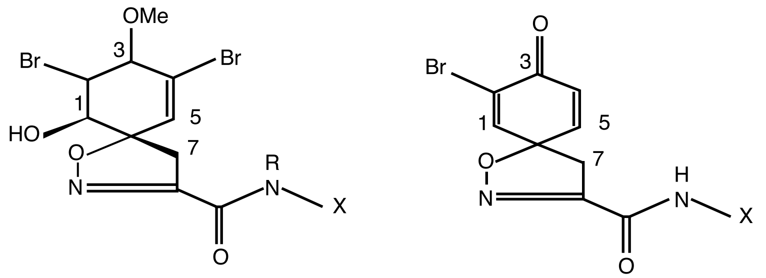
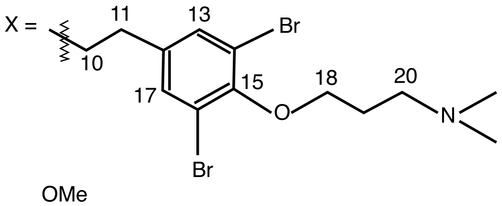
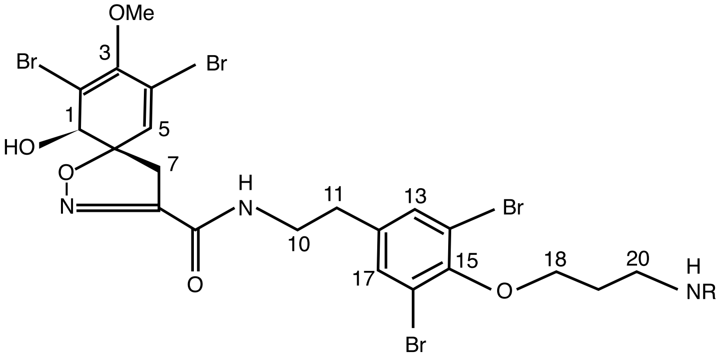


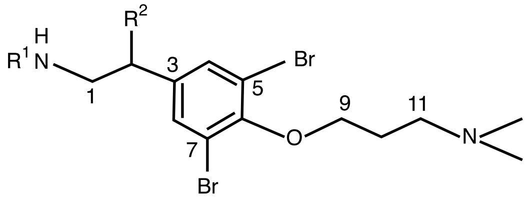
Purealidin Q (1) R=H
Purpurealidin A (2) R=Me

Purpurealidin B (3)

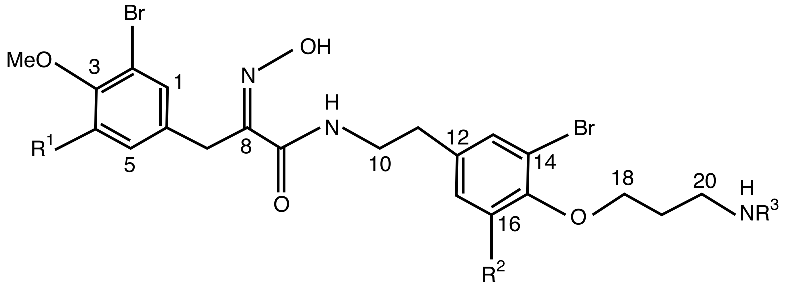




Purpurealidin C (4) R=-CO(CH$_2$)$_{11}$CH(CH$_3$)$_2$
Purpurealidin C (5) R=-CO(CH$_2$)$_{12}$CH$_2$CH$_2$CH$_3$



Purpurealidin E (6) R^1=H, R^2=H
Purpurealidin F (7) R^1=H, R^2=OH
Purpurealidin G (8) R^1=-COCH$_2$CH$_3$, R^2=OH

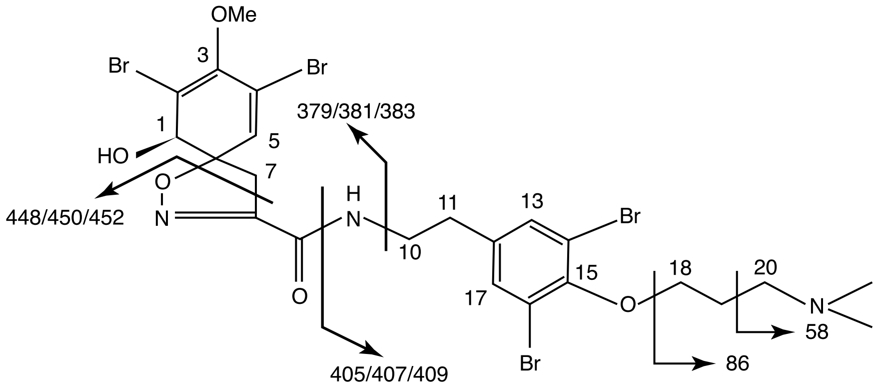


16-Debromoaplysamine-4 (9) R^1=Br, R^2=R^3=H
Purpurealidin H (10) R^1=Br, R^2=H, R^3=Me
Purpurealidin I (11) R^1=H, R^2=Br, R^3=Me

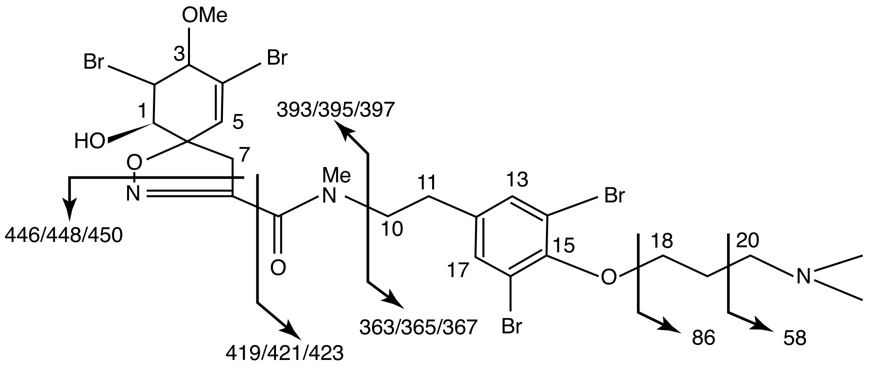
Figure 1. Structures of compounds **1**–**11** from the sponge *Psammaplysilla purpurea*.

Table 1. ^{1}H, ^{13}C NMR of Purealidin Q (**1**) and Purpurealidin A (**2**), in CD_3OD

Carbon Nos.	**1**		**2**	
	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR
1	130.9, d	6.29 (1H, s)	130.9, d	6.29 (1H, s)
2	121.4, s		121.4, s	
3	147.5, s		147.5, s	
4	113.3, s		113.3, s	
5	73.8, d	4.33 (1H, s)	73.8, d	4.33 (1H, s)
6	91.9, s		91.9, s	
7	38.8, t	2.98 (1H, d, *J*=18.3 Hz) 3.92 (1H, d, *J*=18.6 Hz)	38.8, t	2.98 (1H, d, *J*=18.3 Hz) 3.92 (1H, d, *J*=18.6 Hz)
8	153.9, s		153.9, s	
9	159.2, s		159.2, s	
10	40.1, t	3.54 (2H, t, *J*=12.2, 6.6 Hz)	40.1, t	3.54 (2H, t, *J*=12.2, 6.6 Hz)
11	34.2, t	2.77 (2H, t, *J*=12.6, 6.8 Hz)	34.2, t	2.77 (2H, t, *J*=12.6, 6.8 Hz)
12	137.2, s		137.2, s	
13,17	132.9, d	7.35 (2H, s)	132.9, d	7.35 (2H, s)
14,16	118.1, s		118.1, s	
15	151.5, s		151.5, s	
18	71.0, t	4.05 (2H, t, *J*=12.0, 5.6 Hz)	71.0, t	4.05 (2H, t, *J*=12.0, 5.6 Hz)
19	27.0, t	2.19 (2H, m)	27.0, t	2.19 (2H, m)
20	56.0, t	2.92 (2H, t, *J*=5.6 Hz)	56.0, t	2.92 (2H, t, *J*=5.6 Hz)
$-OCH_3$	60.0, q	3.74 (3H,s)	60.0, q	3.74 (3H, s)
$-N(CH_3)_2$	44.5, q	2.89 (6H, s)	44.5, q	2.89 (6H, s)
–NH		7.40 (1H, s)		
$-N-CH_3$			39.3, t	3.4 (3H, s)



Scheme 1. Fragmentation patterns of Purealidin Q (**1**).



Scheme 2. Fragmentation patterns of Purpurealidin A (**2**).

The monoisotopic peaks at *m/z* 58, 86 also help in confirming the side chain to be dimethylpropylamine.

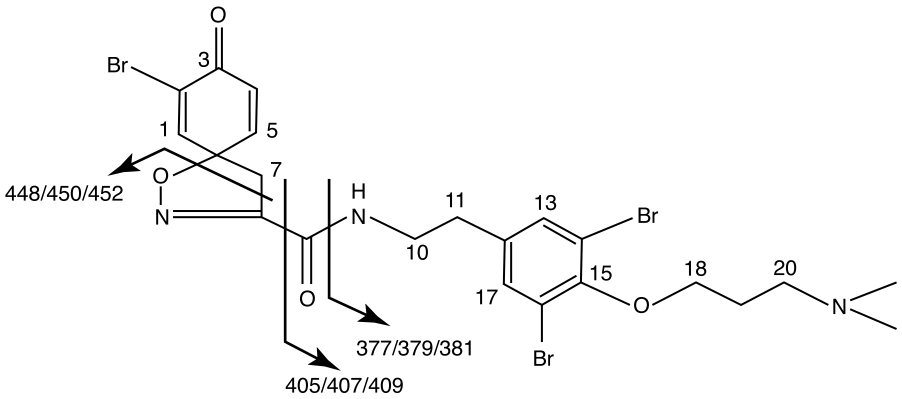
The Purpurealidin B (**3**) contains a dibromospirocyclohexadienonyldihydroisoxazole moiety of the type found in Verongida metabolites but differing in having one bromine atom and dienone ring system.[19,20] The mass spectrum of Purpurealidin B showed a 1.06:3.13:3.06:1.0 quartet for the pseudomolecular ion peak $[M+H]^+$ at *m/z* 631.8, 633.8, 635.8, 637.8, indicative of the presence of three bromine

Table 2. ^{1}H, ^{13}C NMR and COSY of Purpurealidin B (**3**), in $CDCl_3$

Carbon Nos.	^{13}C NMR	^{1}H NMR	COSY	HMBC
1	144.2, d	7.27 (1H, d, J=2.2 Hz)	H5	C2, C3, C5
2	125.8, s			
3	177.9, s			
4	127.7, d	6.34 (1H, d, J=9.8 Hz)	H5	C2, C6
5	144.2, d	6.87 (1H, dd, J=2.2, 9.8 Hz)	H1, H4	C3
6	84.5, s			
7	43.1, t	3.48 (1H, d, J=18.0 Hz)		
		3.90 (1H, d, J=18.0 Hz)		C5, C8
8	153.4, s			
9	158.4, s			
10	40.4, t	3.57 (2H, t, J=7.0 Hz)	H11	C9, C11, C12, C13, 17
11	34.1, t	2.81 (2H, t, J=7.2 Hz)	H10	C10
12	137.3, s			
13,17	132.9, d	7.34 (2H, s)		C11, C13,17, C15, C14,16
14,16	117.9, s			
15	150.8, s			
18	69.5, t	4.04 (2H, t, J=5.6 Hz)	H19	C19, C20
19	25.2, t	2.38 (2H, m)	H20, H18	C18, C20
20	55.7, t	3.42 (2H, t, J=5.6 Hz)	H19	C18, C19
–NH	7.4		C8	
–N $(CH_3)_2$	43.1, q	2.89(6H, s)		

atoms in the molecule, which is appropriate for the molecular formula $C_{22}H_{24}N_3O_4Br_3$. The ^{13}C NMR spectrum had 22 carbon signals, the multiplicities of which were assigned from a DEPT 135 experiment as two methyls, six methylenes, five methines, and nine quarternary carbons. The coupling pattern in proton signals at δ_H 7.27 (1H, d, J=2.2 Hz), 6.87 (1H, dd, J=2.2, 9.8 Hz) and 6.34 (1H, d, J=9.8 Hz) indicated the presence of a 2,3,6-trisubstituted aromatic moiety (see Table 2). Analysis of the proton COSY spectrum showed connectivities for H1–H5, H4–H5 and H5–H1–H4 for the 2, 3, 6-trisubstituted aromatic moieties. The HMBC experiment showed that the proton signal at δ_H 7.27 is connected to C2, C3, C5 and δ_H 6.34 to C2, C6, C5 and δ_H 6.87 to C3. The presence of signal at δ_C 177.18 in the ^{13}C NMR spectrum shows presence of a ketone in the ring system. Thus, the partial structure was confirmed to be monobromospirocyclohexadienoneisoxazole. The structure of the remaining part of the molecule, which is linked to the nitrogen atom of the carboxamide group at C-8, was similar to that of Purealidin Q, which was established by inspection of 1H–1H connectivities. This clearly indicates presence of H10–H11 and also the H18–H19–H20 methylene chain. The HMBC showed a proton signal at δ_H 7.34 (2H, s) connected to C11, C13, 17, C15, C14, 16 for the tetrasubstituted aromatic ring. A 6H singlet at δ_H 2.89 was assigned to be a dimethylamino group. This is also confirmed by pseudomolecular peaks at m/z 405, 407, 409, and 448, 450, 452 (Scheme 3).

Purpurealidin C (**4**) and D (**5**) exhibited the same characteristic features as Purealidin Q (**2**) except for one additional amide proton at δ_H 5.3, the carbonyl signal at δ_C 173.6, and methylene signals at δ_C 27.0–32.7 (δ_H 1.19) indicative of the presence of an additional amide carbonyl group and long straight fatty chain. A doublet at δ_H 0.80 (6H, J=6.8 Hz) was assigned to the isopropyl group. The structure is also confirmed by ^{1}H, ^{13}C, COSY and HMBC spectral data (see Table 3). The molecular weight of Purpurealidin C (**4**) was higher than that of Purealidin Q (**2**). The low resolution mass spectrum showed pseudomolecular ion peaks at m/z 938.0, 940.0, 942.0, 944.0, 946.0. The mass spectrum showed additional pseudomolecular ion peaks at m/z 952.0, 954.0, 956.0, 958.0, 960.0, which are 14 units higher than (**4**) indicative of an extra methylene group. The presence of a signal at δ_H 0.70 (t) and ^{13}C signal at δ_C 14.0 suggested for terminal methyl group in **5** (see Table 4). The



Scheme 3. Fragmentation patterns of Purpurealidin B (**3**).

Table 3. ^{1}H, ^{13}C NMR, COSY and HMBC of Purpurealidin C (**4**), in $CDCl_3$

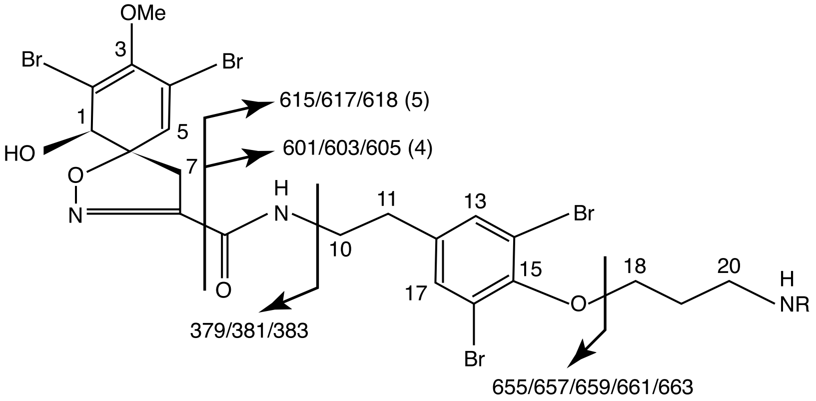
Carbon Nos.	^{13}C NMR	^{1}H NMR	COSY	HMBC
1	74.0, d	4.28 (1H, s)		C3, C2, C5
2	112.7, s			
3	148.0, s			
4	121.4, s			
5	130.0, s	6.24 (1H, s)		C4, C3
6	91.5, s			
7	38.8, t	Ha = 2.93 (1H, d, J = 18.6 Hz)	Hb	C5, C1, C8
		Hb = 3.88 (1H, d, J = 18.3 Hz)	Ha	
8	154.9, s			
9	159.1, s			
10	40.3, t	3.54 (2H, t, J = 13.2, 6.6 Hz)	H11	C11
11	34.4, t	2.67 (2H, t, J = 12.6, 7.8 Hz)	H10	C10, C12, C13
17				
12	138.0, s			
13,17	132.9, d	7.34 (2H, s)		C11, C13,17, C15, C14,16
14,16	118.2, s			
15	151.2, s			
18	71.0, t	4.01 (2H, t, J = 12.0, 6.0 Hz)	H19	C15, C19, C20
19	29.2, t	2.06 (2H, m)	H18, H20	C18, C20
20	37.0, t	3.63 (2H, t)	H19	C18, C19
21	173.6, s			
22	34.4, t	2.67(2H, m)		
23–32	27.0–32.7, t	1.19 (24H, s)		
33	29.0, d	1.53 (2H, m)		C34,35
34,35	22.6, q	0.80 (6H, d, J = 6.8 Hz)	H33	
–N-9		7.43 (1H, d)		
–N-20		5.30 (1H, s)		
–OCH3	60.0, q	3.67 (3H, s)		C3

fragmentation pattern of **4** and **5** (Scheme 4) is different from the Arapplysillin II isolated from the *Psammaplysilla purpurea*[21] and agrees well with the structure assigned.

The mass spectrum of Purpurealidin E (**6**) showed a pseudomolecular ion peak $[M+H]^+$ at *m/z* 378.9768, 380.9757, 382.97 in the ratio 1.05:2.05:1.0, characteristic for the presence of two bromine atoms. Examination of the ^{1}H and ^{13}C and COSY showed that the structure is similar to the part structure of Purealidin Q. In addition, the mass spectrum of (**6**) showed minor pseudomolecular ion peaks at *m/z* 394.9, 396.9, 398.9 and 451.0, 453.0, 455.0 compounds Purpuealidin F (**7**) and G (**8**). The ^{1}H NMR signal at 3.77 (1H, m) and δ_C 59.6 is accounted for the hydroxy methine at

Table 4. ^{1}H, ^{13}C NMR, COSY and HMBC of Purpurealidin D (**5**), in $CDCl_3$

Carbon Nos.	^{13}C NMR	^{1}H NMR	COSY	HMBC
1	74.0, d	4.28 (1H, s)		C3, C2, C5
2	112.7, s			
3	148.0, s			
4	121.4, s			
5	130.0, s	6.24 (1H, s)		C4, C3
6	91.5, s			
7	38.8, t	Ha = 2.93 (1H, d, J = 18.6 Hz)	Hb	C5, C1, C8
		Hb = 3.88 (1H, d, J = 18.3 Hz)	Ha	
8	154.9, s			
9	159.1, s			
10	40.3, t	3.54 (2H, t, J = 13.2, 6.6 Hz)	H11	C11
11	34.4, t	2.67 (2H, t, J = 12.6, 7.8 Hz)	H10	C10, C12, C13, 17
12	138.0, s			
13,17	132.9, d	7.34(2H, s)		C11, C13,17, C15, C14,16
14,16	118.2, s			
15	151.2, s			
18	71.0, t	4.01 (2H, t, J = 12.0, 6.0 Hz)	H19	C15, C19, C20
19	29.2, t	2.06 (2H, m)	H18, H20	C18, C20
20	37.0, t	3.63 (2H, t)	H19	C18, C19
21	173.6, s			
22	34.4, t	2.67 (2H, m)		
23–34	27.0–32.7, t)	1.19 (24H, s)		
35	29.0, d	1.53 (2H, m)		C35
36	14.0, q	0.70 (3H, t)	H35	C34
–N-9		7.43 (1H, s)		
–N-20		5.40 (1H, s)		
–OCH3	60.0, q	3.67 (3H, s)		C3



Scheme 4. Fragmentation patterns of Purpurealidin C (**4**) and D (**5**).

C2 in 7 and 8 (see Table 5). The carbonyl signal at δ_C 173.0, methylene signal at δ_C 29.2 (δ_H 1.20, s) and methyl signal at δ_C 14.0 (δ_H 0.81, t, $J=7.0$ Hz) were indicative of the presence of an additional amide carbonyl group and ethyl groups.

The mass spectrum of the known compound that we have reported earlier, 16-Debromo aplysamine-4 (**9**), revealed characteristic isotope peaks for $[M+H]^+$ pseudo molecular ion at 619.8, 621.8, 623.8 and 625.8 in the ratio 1.05:3.1:3.06:1.0, indicating the presence of three bromine atoms in the molecule. Its ^{13}C NMR spectrum had 21 carbon signals, which were designated as one methyl, six methylenes, five methines, and nine quarternary carbons from a DEPT135 experiment. The signals at 7.52 (1H, s) and 7.40 (1H,s) and 7.33 (1H, d, $J=2.0$ Hz), 6.86 (1H, d, $J=8.4$ Hz) and 7.02 (1H, dd, $J=8.4$, 2.0 Hz) in the ^{1}H NMR spectrum indicated the presence of tetra and 1,2,4-trisubstituted aromatic moieties. The IR absorptions at 3350, 1655, and 1624 cm^{-1} and ^{13}C NMR signals at 163.8 and 152.3 ppm were indicative of amide and oxime groups. The exchangeable proton signals at δ_H 11.40 (2H, br m), 8.70 (1H, br s,) and 7.90 (1H, br s,) in the ^{1}H NMR spectrum indicated the presence of NH_2, NH and OH groups. The presence of a primary amine in the molecule is also confirmed by the positive ninhydrin test. The above results, as well as the assumption that this compound is a derivative of aplysamine/purpuramine, indicated its molecular formula to be $C_{21}H_{24}Br_3N_3O_4$. The upfield ^{13}C NMR chemical shift of C-7 (27.3 ppm) suggested *E* configuration of the oxime as the corresponding value for (*Z*)-oxime is >35 ppm.[1] It also shows additional singly charged $[M+H]^+$ at *m/z* at 633.8, 635.8, 637.8, 639.8 for (**10**), 14 units higher than that of the compound **9**. This is accounted for the methyl group at the terminal *N*-methyl.

Compounds **1**, **3**, **9** and **11** were evaluated for their antimicrobial activity (see Table 6) against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Shigella flexineri*, *Klebsiella* sp and *V. cholerae* bacterial strains and fungal strains of *Aspergillus fumigatus*, *Fusarium* sp, *Cryptococcus neoformans*, *Aspergillus niger*, *Rhodotorula* sp, *Norcardia* sp, and *Candida albicans*. The compounds did not show any activity against bacterial strains *Klebsiella* sp, *Pseudomonas aeruginosa* and all fungal strains. Purealidin Q (**1**) showed good activity against *Salmonella typhi*. It was previously reported to show cytotoxic activity against tumor cell lines and moderate inhibitory against epidermal growth factor (EGF) kinase.[10] Purpurealidin B (**3**) showed good activity against *E. coli*, *S. aureus*, *V. cholerae* and weak activity against *Shigella flexineri*. 16-Debromo aplysamine-4 (**9**) showed moderate activity against *Salmonella typhi* and very weak acivity against *E. coli*, *Staphylococcus aureus* and *V. cholerae*.

Table 5. ^{1}H, ^{13}C NMR and COSY of Purpurealidin E (**6**), F (**7**), G (**8**) in CD_3OD

Carbon Nos.	6		7		8	
	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR
1	40.0, t	2.73 (2H, t, $J=13.2$, 6.6 Hz)	40.0, t	2.73 (2H, t, $J=13.2$, 6.6 Hz)	40.0, t	2.73 (2H, t, $J=13.2$, 6.6 Hz)
2	33.6, t	3.24 (2H, t)	59.6, t	3.77 (1H, m)	59.6, t	3.77 (1H, m)
3	130.3, s		130.3, s		130.3, s	
4,8	133.0, t	7.43 (2H,s)	133.0, t	7.43 (2H, s)	133.0, t	7.43 (2H, s)
5,7	117.3, s		117.3, s		117.32, s	
6	150.7, s		150.7, s		150.72, s	
9	69.8, t	4.05 (2H, t, $J=5.6$ Hz)	69.8, t	4.05 (2H, t, $J=5.6$ Hz)	69.8, t	4.05 (2H, t, $J=5.6$ Hz)
10	25.0, t	2.23 (2H, m)	25.0, t	2.23 (2H, m)	25.0, t	2.23 (2H, m)
11	55.8, t	3.44 (2H, t) $J=5.6$ Hz)	55.8, t	3.44 (2H, t) $J=5.6$ Hz)	55.8, t	3.44 (2H, t, $J=5.6$ Hz) $J=5.6$ Hz)
12,13	42.7, q	2.90 (6H, s)	42.7, q	2.90 (6H, s)	42.7, q	2.90 (6H, s)
NH_2		7.63 (br, s)				
NH				8.10 (br, s)		8.10 (br, s)
CO					173.0	
CH_2					29.2	1.20 (2H, s)
CH_3					14.0	0.81 (3H, t, $J=7.0$ Hz)

Table 6. Effect of compounds **1**, **3**, **9** and **11** on growth of microbial strains (MIC in μg/ml)

Compounds	*E. Coli*	*S. aureus*	*Salmonella typhi*	*Shigella flexineri*	*Vibrio cholarae*
Purealidin Q (**1**)	—	—	>25	—	—
Purpurealidin B (**3**)	>12	10	—	100	25
16-Debromo aplysamine 4 (**9**)	250	200	>50	—	100
Purpuramine I (**11**)	100	50	—	—	100
Streptomycin	10	10	10	10	10

Good activity: 10–25 μg/ml. Moderate activity: 26–100 μg/ml. Weak activity: >100 μg/ml.

Moderate acivity against *S. aureus* was confirmed for Purpuramine I (**11**) according to the previous studies. It also showed moderate activity against *E. coli* and *V. cholerae*.

3. Experimental

3.1. General experimental procedures

Column chromatographies were carried out using Silica gel (60–120 mesh, Qualigens), gel filtrations were carried out using Sephadex LH20 17-0090-01 Pharmacia Biotech). Fractions were monitored on TLC using alumina-backed sheets (Si gel 60 F254, 0.25 mm thick) with visualization under UV (254 nm) and Ninhydrin spray reagent. All analytical reverse phase HPLC (Chromspher 5 C18 column 250×10 mm, MeOH/H2O 85/15) were performed with a P4000 pump (Spectra system) equipped with a UV2000 detector (spectra system).

UV spectra were recorded in MeOH, using a Shimadzu UV–Vis 2401PC Spectrophotometer, and IR spectra were recorded on a Shimadzu FT-IR 8201PC Spectrophotometer. Optical rotations were recorded in MeOH using Optical Polarimeter ADP220 (Bellingham Stanley Ltd).

Mass spectra were recorded on a PE Sciex-QSTAR and QSTAR-TOF MS/MS of Applied Biosystems.

NMR (^{1}H, ^{13}C, COSY, HMQC and HMBC) experiments were obtained on a Bruker (Avance 300) spectrometer with TMS as internal standard.

3.2. Animal material

The animals were collected by scuba diving at a depth of 8–10 m from Mandapam, Tamil Nadu, India, and identified by Dr. P. A. Thomas of Vizhingam Research Center of Central Marine Fisheries Research Institute, Kerala, India. A voucher specimen is deposited at the National Institute of Oceanography, Dona Paula Goa, India.

3.3. Extraction and isolation

The frozen sponge (250 g, dry weight) was extracted with methanol (1 L×3) and concentrated under vacuo to obtain 10 g of crude extract. The extract showed antimicrobial activity against pathological strains, which was chromatographed on silica gel (Qualigens silica gel 60–120 mesh) column using dichloromethane with increasing amounts of methanol as eluent. The fractions eluted with 8, 10 and 20% were purified separately. The fraction eluted with 8% MeOH (1.5 g) was further purified by repeated[1] gel chromatography (Sephadex LH20) columns using chloroform/methanol (1:1) to get Purealidin Q (200 mg), Purpurealidin B (800 mg) and Purpurealidin C and D (400 mg). The fractions eluted with 10% MeOH were purified on reverse phase HPLC using Chromspher 5 C18 column 250×10 mm^2, MeOH/H$_2$O 85/15, flow rate 2 mL/min and UV detection at $\lambda_{\max}$ 254 nm) which afforded 16-Debromo aplysamine-4, Purpurealidin-H (R_t 18.4 min) (20 mg) and Purpuramine I (R_t 27.5 min) (25 mg). The fractions eluted with 20% were subjected to silica gel column eluted with increasing amounts of methanol in dichloromethane to yield mixture of Purpurealidin E, F, G (300 mg).

3.3.1. Purealidin Q (1). Colorless oil, UV (MeOH) $\lambda_{\max}$ 277 nm (ε 1700), 284 nm (ε 1400); $[\alpha]_D^{28}=+9.5$ (*c* 0.2, MeOH); IR (neat) $\nu_{\max}$ 3418, 2922, 1668, 1537, 1458.1, 1254, 1051, 920, 737 cm^{-1}; ^{1}H and ^{13}C recorded in CD$_3$OD see Table 1; HRMS: *m/z* (relative heights) 741.8691(450), 743.8871(1780), 745.8710(2600), 747.8762(1700), 749.7914(420) [1.07:4.23:6.2:4.0:1.0],[†] [M+H]$^+$, found 741.8691 C$_{23}$H$_{27}$N$_3$O$_5$Br$_4$ requires 741.8764; [M+H−Br]$^+$ 662.9, 664.9, 666.9, 668.9; [M+H+Br+CH$_3$]$^+$ 647.8, 649.8, 651.8, 653.8; 404.8, 406.8, 408.8; 378.9, 380.9, 382.9; 348.9, 350.8, 352.8; 58; 86.

3.3.2. Purpurealidin A (2). Colorless oil, UV (MeOH) $\lambda_{\max}$ 277 nm (ε 1700), 284 nm (ε 1400); $[\alpha]_D^{28}=+9.5$ (*c* 0.2, MeOH); IR (neat) $\nu_{\max}$ 3418, 2922, 1668, 1537, 1458.1, 1254, 1051, 920, 737 cm^{-1}; ^{1}H and ^{13}C recorded in CD$_3$OD see Table 1; HRMS: *m/z* (relative heights) 755.8819(55), 757.8799(210), 759.8810(310), 761.8820(200), 763.8(50) [1.1:4.2:6.2:4.0:1.0],[†] [M+H]$^+$, found 755.8819 C$_{24}$H$_{29}$N$_3$O$_5$Br$_4$ requires 755.8920.

3.3.3. Purpurealidin B (3). White amorphous solid, mp 175.8 °C; UV (MeOH) $\lambda_{\max}$ 283 (1320); IR (KBr pellet) $\nu_{\max}$ 3302, 2932, 2689, 1678, 1605, 1541, 1460, 1383, 1259, 910 and 739 cm^{-1}. ^{1}H and ^{13}C recorded in CDCl$_3$ see Table 2; HRMS: *m/z* (relative heights) 631.8403(1600), 633.8185(4700), 635.8118(4600), 637.8226(1500) [1.06:3.13:3.03:1.0],[†] [M+H]$^+$, found 631.8403 C$_{22}$H$_{24}$N$_3$O$_4$Br$_3$ requires 631.8396; 404.9, 406.9, 408.9; 376.9, 378.9, 380.9; 224.9, 226.9.

3.3.4. Purpurealidin C (4). Colorless oil, UV (MeOH) $\lambda_{\max}$ 282(10,000), 218(2500), $[\alpha]_D^{28}=+158.5$ (*c* 0.2, CHCl$_3$); IR (KBr pellet) $\nu_{\max}$ 3319, 2925, 2854, 1660, 1605, 1456, 1257, 739 cm^{-1}, ^{1}H and ^{13}C recorded in CDCl$_3$ see Table 3 ESI-MS: *m/z* (relative heights) 938.0(22), 940.0(85), 942.0(125), 944.0(80), 946.0(20) [1.1:4.2:6.2:4.0:1.0],[†] [M+H]$^+$,

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[†] Real ratios of the pseudomolecular ion peaks.

found 938.05 $C_{36}H_{51}N_3O_6Br_4$ requires 938.0591; 615, 617, 619; 379, 381, 383.

3.3.5. Purpurealidin D (5).[2] Colorless oil, UV (MeOH) λ_{max} 282(10,000), 218(2500); IR (KBr pellet) ν_{max} 3319, 2925, 2854, 1660, 1605, 1456, 1257, 739 cm^{-1}, ^{1}H ($CDCl_3$, 300 MHz) see Table 4 ESI-MS: *m*/*z* (relative heights) 952.0(16), 954.0(65), 956.0(95), 958.0(60), 960.0(15) [1.06:4.3:6.3:4.0:1.0],[†] $[M+H]^+$, found 952.07 $C_{37}H_{53}N_3O_6Br_4$ requires 952.0747; 655, 657, 659, 661, 662; 601, 603, 605; 379, 381, 383.

3.3.6. Purpurealidin E (6). Colourless oil, UV (MeOH) λ_{max} 282 (ε 950), 277 (ε 925); IR (neat) ν_{max} 3302, 2933, 1666, 1545, 1458, 1259, 1039, 739 cm^{-1}, ^{1}H and ^{13}C recorded in $CDCl_3$ see Table 5; HRMS: *m*/*z* (relative heights) 378.9768(37), 380.9757(72), 382.97(35) [1.05:2.05:1.0],[†] $[M+H]^+$, found 378.9768 $C_{13}H_{20}N_2OBr_2$ requires 378.9943.

3.3.7. Purpurealidin F (7). Colourless oil, UV (MeOH) λ_{max} 282 (ε 950), 277 (ε 925); IR (neat) ν_{max} 3302, 2933, 1666, 1545, 1458, 1259, 1039, 739 cm^{-1}, ^{1}H and ^{13}C recorded in $CDCl_3$ see Table 5; HRMS: *m*/*z* (relative heights) 394.9667(16), 396.9661(32), 398.9618(15) [1.06:2.1:1.0],[†] $[M+H]^+$, found 394.9667 $C_{13}H_{20}N_2O_2Br_2$ requires 394.9970.

3.3.8. Purpurealidin G (8). Colorless oil, UV (MeOH) λ_{max} 282 (ε 950), 277 (ε 925); IR (neat) ν_{max} 3302, 2933, 1666, 1545, 1458, 1259, 1039, 739 cm^{-1}, ^{1}H and ^{13}C recorded in $CDCl_3$ see Table 5; HRMS: *m*/*z* (relative heights) 451.0220(10), 453.0210(20), 455.0301(10) [1:2:1], $[M+H]^+$, found 451.0220 $C_{16}H_{24}N_2O_3Br_2$ requires 452.0232.

3.3.9. 16-Debromo aplysamine-4 (9). Colorless amorphous solid (MeOH): mp 124–126 °C; UV (MeOH) λ_{max} 218 nm (ε 12675), 280 nm (ε 2675); IR (KBr pellet) ν_{max} 3350, 3205, 2958, 1655, 1624, 1541, 1497, 1472, 1421, 1256, 1203, 1049, 993 and 739 cm^{-1}; ^{1}H (CD_3OD, 300 MHz) δ_H 11.40 (2H, br m, $-NH_2$), 8.70 (1H, brs, –NH), 7.90 (1H, brs, –OH), 7.4 (2H, s, H-1, 5), 7.33 (1H, d, $J=2.0$ Hz, H-13), 7.02 (1H, dd, $J=2.0$, 8.4 Hz, H-17), 6.86 (1H, d, $J=8.4$ Hz, H-16), 4.06 (2H, t, $J=6.5$ Hz, H-18), 3.75 (3H, s, $-OCH_3$), 3.74 (1H, s, H-7), 3.34 (2H, t, $J=7.0$ Hz, H-10), 3.15 (2H, t, $J=6.8$ Hz, H-20), 2.65 (2H, s, $J=7.0$ Hz, H-11), 2.09 (2H, m, H-19); ^{13}C NMR(CD_3OD, 300 MHz) (165.2 (s, C-9), 154.6 (s, C-3), 153.7 (s, C-8), 151.9 (s, C-15), 137.2 (s, C-12), 134.5 (s, C-6), 134.4 (d, C-1, 5), 134.4 (d, C-13), 130.2 (d, C-17), 118.5 (s, C-2, 4), 114.4 (d, C-16), 112.6 (s, C-14), 67.6 (t, C-18), 61.0 (q, $-OCH_3$), 41.7 (t, C-10), 38.8 (t, C-20), 35.1 (t, C-11), 28.7 (t, C-7), 28.1 (t, C-19); HRMS: *m*/*z* (relative heights) 619.8797 (525), 621.8535 (1550), 623.8444 (1530), 625.8845 (500) [1.05:3.1:3.06:1.0],[†] $[M+H]^+$, found 619.8797 $C_{21}H_{24}N_3O_4Br_3$ requires 619.9396.

3.3.10. Purpurealidin H (10). Colorless amorphous solid (MeOH); UV (MeOH) λ_{max} 218 nm (ε 12675), 280 nm (ε 2675); IR (KBr pellet) ν_{max} 3350, 3205, 2958, 1655, 1624, 1541, 1497, 1472, 1421, 1256, 1203, 1049, 993 and 739 cm^{-1}; ^{1}H (CD_3OD, 300 MHz) δ_H 11.40 (2H, br m, $-NH_2$), 8.70 (1H, brs, –NH), 7.90 (1H, brs, –OH), 7.4 (2H, s, H-1, 5), 7.33 (1H, d, $J=2.0$ Hz, H-13), 7.02 (1H, dd, $J=2.0$, 8.4 Hz, H-17), 6.86 (1H, d, $J=8.4$ Hz, H-16), 4.06 (2H, t, $J=6.5$ Hz, H-18), 3.75 (3H, s, $-OCH_3$), 3.74 (1H, s, H-7), 3.34 (2H, t, $J=7.0$ Hz, H-10), 3.15 (2H, t, $J=6.8$ Hz, H-20), 2.764 (3H, s, $-NCH_3$), 2.65 (2H, s, $J=7.0$ Hz, H-11), 2.09 (2H, m, H-19); ^{13}C NMR (CD_3OD, 300 MHz) δ 165.2 (s, C-9), 154.6 (s, C-3), 153.7 (s, C-8), 151.9 (s, C-15), 137.2 (s, C-12), 134.5 (s, C-6), 134.4 (d, C-1, 5), 134.4 (d, C-13), 130.2 (d, C-17), 118.5 (s, C-2, 4), 114.4 (d, C-16), 112.6 (s, C-14), 67.6 (t, C-18), 61.0 (q, $-OCH_3$), 41.7 (t, C-10), 38.8 (t, C-20), 35.1 (t, C-11), 28.7 (t, C-7), 28.1 (t, C-19), 27.615 (q, $-NCH_3$); HRMS: *m*/*z* (relative heights) 633.9220(420), 635.9091(1250), 637.9021(1220), 639.9104(400) [1.05:3.12:3.05:1.0],[†] $[M+H]^+$, found 633.9220 $C_{22}H_{26}N_3O_4Br_3$ requires 633.9550.

3.4. Antibacterial assays

Antibacterial activity was determined against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Shigella flexineri*, *Klebsiella* sp. and *V. cholerae* using the paper disk assay method. The paper disk impregnated with the sample was placed on agar plate containing bacterium and the plates were incubated for 24 h at 37 °C, and observed for zone of inhibition halos. Streptomycin was used as a positive control.

3.5. Antifungal assays

Antifungal activity was determined against strains of *Aspergillus fumigatus*, *Fusarium* sps, *Cryptococcus neofromans*, *Aspergillus niger*, *Rhodotorula* sp., *Norcardia* sp., and *Candida albicans*. The paper disk impregnated with the sample was placed on agar plate containing fungus and plates were incubated for 18 h at 24 °C. *Nystatin* was used as a positive control.

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References and notes

1. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137–1140.
2. Nakamura, H.; Wu, H.; Kobayashi, J.; Nakamura, Y.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett.* **1985**, *26*, 4517–4520.
3. Takito, J.; Nakamura, H.; Kobayashi, J.; Ohizumi, Y.; Ebisava, K.; Nakamura, Y. *J. Biol. Chem.* **1986**, *261*, 13861–13865.
4. Nakamura, Y.; Kobayashi, M.; Nakamura, H.; Wu, H.; Kobayashi, J.; Ohizumi, Y. *Eur. J. Biochem.* **1987**, *167*, 1–6.

5. Wu, H.; Nakamura, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y. *Experientia* **1986**, *42*, 855–856.
6. Kobayashi, J.; Honma, K.; Tsuda, M.; Kosaka, T. *J. Nat. Prod.* **1995**, *58*, 467–470.
7. Ishibashi, M.; Tsuda, M.; Ohizumi, Y.; Sasaki, T.; Kobayashi, J. *Experientia* **1991**, *47*, 299–300.
8. Tsuda, M.; Shigemori, H.; Ishibashi, H. *Tetrahedron Lett.* **1992**, *33*, 2597–2598.
9. Tsuda, M.; Shigemori, H.; Ishibashi, M.; Kobayashi, J. *J. Nat. Prod.* **1992**, *55*, 1325–1327.
10. Kobayashi, J.; Honma, K.; Sasaki, T.; Tsuda, M. *Chem. Pharma. Bull.* **1995**, *43*, 403–407.
11. Tabudravu, J. N.; Jaspars, M. *J. Nat. Prod.* **2002**, *65*, 1798–1801.
12. Roll, D. M.; Chang, C. W. J.; Scheuer, P. J.; Gray, G. A.; Shoolery, J. N.; Matsumota, G. K.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *107*, 2916–2920.
13. Yagi, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1993**, *49*, 3749–3754.
14. Jurek, J.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1993**, *56*, 1609–1612.
15. Carney, J. R.; Scheuer, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1993**, *56*, 153–157.
16. Tilvi, S.; Parameswaran, P. S.; Naik, C. G. In *Proceedings, National Conference on the utilization of the Bioresources, Bhubaneshwar, Orissa, India*. Sree, A., Rao, Y. R., Nanda, B., Mishra, V. N., Eds.; 2002, 458–463.
17. Venkateshwarlu, Y.; Rama, R.; Venkatesham, U. *J. Nat. Prod.* **1998**, *1388*, 1389.
18. Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn* **1985**, *58*, 3453–3456.
19. Patrizia, C.; Carmela, D. A.; Ernesto, F.; Silvana, M. *Tetrahedron* **1996**, *52*, 9863–9868.
20. Tymiak, A. A.; Rienehart, J. K. L. *J. Am. Chem. Soc.* **1981**, *103*, 6763–6764.
21. Longeon, A.; Guyot, M.; Vacelet, J. *Experientia* **1990**, *46*, 548–550.

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Novel antifungal polyene amides from the myxobacterium *Cystobacter fuscus*: isolation, antifungal activity and absolute structure determination

Bangi A. Kundim,[a] Yu Itou,[a] Youji Sakagami,[a] Ryosuke Fudou,[b] Shigeru Yamanaka[c] and Makoto Ojika[a,*]

[a]*Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa-ku, Nagoya 464-8601, Japan*
[b]*Institute of Life Science, Ajinomoto Co. Inc., Kawasaki-ku, Kawasaki 210-0801, Japan*
[c]*Faculty of Textile Science and Technology, Shinshu University, Tokida, Ueda 386-8567, Japan*

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Abstract—Three new unstable metabolites, (6*E*,10*Z*)-2′-*O*-methylmyxalamide D (**1**), 2′-*O*-methylmyxalamide D (**2**) and (6*E*)-2′-*O*-methylmyxalamide D (**3**) were isolated from the myxobacterium *Cystobacter fuscus*. The planar structures were elucidated by spectroscopic analyses to be geometrical isomers of a polyene amide related to a myxobacterial metabolite, myxalamide D (**4**). Their absolute stereochemistry was determined by synthesis of degradation products. Antifungal activities of **1**–**3** as well as their acetates were evaluated against the phythopathogenic fungus *Phythopthora capsici*.

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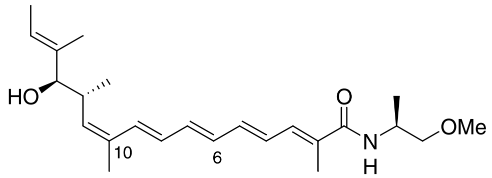
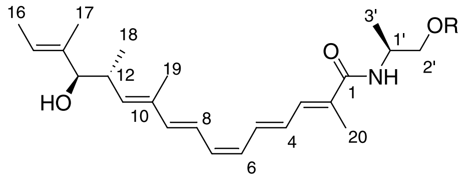
1. Introduction

Myxobacteria are unique gram-negative bacteria characterized by the gliding and fruiting body forming nature. They have recently been well established as a new and potent source for natural products with biological activities because of their potential to produce a considerable variety of metabolites.[1–3] Polyene antibiotics are a group of metabolites characteristic of the myxobacteria. Myxalamides, examples of such antibiotics from myxobacteria, have been discovered from *Myxococcus xanthus* Mx X12.[4,5]

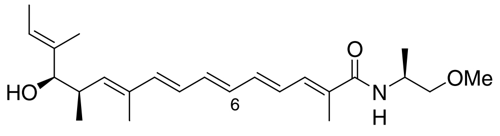
In the course of our screening for bioactive metabolites from myxobacteria, we previously discovered a series of antifungal metabolites named cystothiazoles from a myxobacterium species, *Cystobacter fuscus* AJ-13278.[6–8] On the other hand, a further search for additional antifungal agents from *C. fuscus* has resulted in the isolation of three new polyene amides that are structurally related to myxalamide D (**4**),[5] namely, (6*E*,10*Z*)-2′-*O*-methylmyxalamide D (**1**), 2′-*O*-methylmyxalamide D (**2**) and (6*E*)-2′-*O*-methylmyxalamide D (**3**) (Fig. 1). This paper reports the isolation,



(6*E*,10*Z*)-2′-*O*-methylmyxalamide D (**1**)



R = Me: 2′-*O*-methylmyxalamide D (**2**)
R = H: myxalamide D (**4**)



(6*E*)-2′-*O*-methylmyxalamide D (**3**)

Figure 1. Structures of myxalamide D (**4**) and its new derivatives **1**–**3**.

Keywords: Myxobacteria; *Cystobacter fuscus*; Antifungal; Polyene antibiotics.

* Corresponding author. Tel./fax: +81 52 789 4284;
e-mail: ojika@agr.nagoya-u.ac.jp

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structure elucidation, antifungal activity and absolute stereochemistry for these new metabolites.

2. Results and discussion

Production of the antibiotics was performed as reported previously for the isolation of the cystothiazoles.[6,7] The bacterial cells and adsorbent resin obtained from a 150-L fermentation broth of *C. fuscus* were extracted with acetone and the extract was subjected to solvent partition. The non-polar fraction was chromatographed twice on silica gel to afford less polar fractions containing cystothiazoles[6–8] and a relatively polar fraction containing polyene metabolites. The latter fraction was further subjected to reversed-phase HPLC to give the myxalamide D derivatives **1** (0.6 mg), **2** (0.6 mg) and **3** (2.4 mg). The content of these metabolites should be potentially much higher (more than 10 times) than the isolated amounts, because the more they were purified, the more they decomposed due to their instability.

All three compounds **1–3** showed similar spectroscopic data to each other. The molecular formula of $C_{24}H_{37}NO_3$ for all three compounds were determined by HRMS measurement. The resonances at 168.3 ppm in the ^{13}C NMR spectra indicated the presence of an amide carbonyl carbon in all compounds, which was confirmed by the characteristic IR absorption band at 1653 cm^{-1}. Based on these findings, 2D NMR analysis was then performed to determine the planar structures of the compounds as discussed below.

Many olefinic signals observed between 5 and 7 ppm in the ^1H NMR spectrum of **1** (Table 1) are characteristic of polyenes like the myxalamides.[5,9] The proton–carbon direct connectivities in **1** were first determined by the HMQC spectrum. The chemical shifts are summarized in Tables 1 and 2. The partial structures of H3–H9, H11–H12(H18)–H13, H15–H16 and NH–H1′(H3′)–H2′ were revealed by the DQF-COSY data (Fig. 2). These were then successfully connected to each other by the HMBC spectrum to give the planar structure of **1** (Fig. 2). The singlet signal observed at δ 3.38 (3H) in the ^1H NMR spectrum was easily determined to be the 2′-*O*-methyl group from the HMBC correlation to C2′. The geometry of the double bonds at C4, C6, and C8 were determined from the proton coupling constants of $J_{4,5}=14.6$ Hz, $J_{6,7}=14.5$ Hz, $J_{8,9}=15.0$ Hz as 4*E*, 6*E*, 8*E*, respectively. The geometry of the trisubstituted olefins at C2, C10, and C14 was determined from the NOESY correlations of H4/H20, H9/H12, H11/H19, and H13/H15 as 2*E*, 10*Z*, 14*E*, respectively (Fig. 2). Although the molecular formula of **1** is the same as myxalamide C,[5] which is the C16-methylated homologue of myxalamide D (**4**), these were unambiguously distinguished by the NMR analysis, especially the HMBC correlation of OCH_3/C2′, Thus, the

Table 1. ^1H NMR spectral data for **1–3** in $CDCl_3$ (600 MHz)

Position	1	2	3
	δ_H (m, *J* in Hz)	δ_H (m, *J* in Hz)	δ_H (m, *J* in Hz)
3	6.96 (d, 11.0)	7.00 (d, 11.0)	6.95 (d, 11.3)
4	6.47 (dd, 14.6, 11.0)	6.48 (dd, 14.5, 11.0)	6.45 (dd, 14.6, 11.3)
5	6.54 (dd, 14.6, 10.6)	6.99 (dd, 14.5, 11.0)	6.53 (dd, 14.6, 10.0)
6	6.39 (dd, 14.5, 10.6)	6.10 (dd, 11.0, 11.0)	6.35 (dd, 15.0, 10.0)
7	6.48 (dd, 14.5, 10.8)	6.16 (dd, 11.3, 11.0)	6.40 (dd, 15.0, 10.0)
8	6.36 (dd, 15.0, 10.8)	6.69 (dd, 15.1, 11.3)	6.26 (dd, 15.0, 10.0)
9	6.73 (d, 15.0)	6.36 (d, 15.1)	6.36 (d, 15.0)
11	5.28 (d, 10.0)	5.46 (d, 9.8)	5.43 (d, 9.7)
12	2.83 (m)	2.75 (m)	2.73 (m)
13	3.64 (d, 8.9)	3.69 (d, 8.7)	3.68 (d, 8.8)
15	5.49 (q, 6.5)	5.49 (q, 6.3)	5.49 (q, 6.0)
16	1.64 (d, 6.5)	1.64 (d, 6.3)	1.63 (d, 6.0)
17	1.66 (s)	1.64 (s)	1.64 (s)
18	0.83 (d, 6.7)	0.84 (d, 6.7)	0.83 (d, 6.7)
19	1.91 (s)	1.91 (s)	1.86 (s)
20	1.98 (s)	1.99 (s)	1.97 (s)
1′	4.25 (m)	4.25 (m)	4.25 (m)
2′	3.43 (dd, 9.5, 4.0)	3.43 (dd, 9.5, 4.0)	3.42 (dd, 9.5, 4.0)
	3.39 (dd, 9.5, 4.0)	3.39 (dd, 9.5, 4.0)	3.39 (dd, 9.5, 4.0)
3′	1.23 (d, 6.8)	1.23 (d, 6.8)	1.22 (d, 6.2)
2′-OCH_3	3.38 (s)	3.38 (s)	3.37 (s)
NH	5.96 (d, 7.6)	5.98 (d, 7.6)	5.96 (d, 7.8)

Table 2. ^{13}C NMR chemical shifts for **1–3** in $CDCl_3$ (150 MHz)

Position	1[a]	2[a]	3
1	168.3	168.3	168.3
2	129.8[b]	130.5	129.6
3	133.6	133.5	133.7
4	127.7	128.0	127.3[b]
5	138.1	133.2	138.3
6	132.8	128.4	132.0
7	136.1	132.5	136.0
8	130.0[b]	122.3	127.2[b]
9	131.4	139.8	139.2
10	134.0	136.0	136.1
11	135.2	137.6	137.1
12	36.3	37.3	37.2
13	82.7	82.7	82.8
14	135.6	135.7	135.6
15	123.6	123.4	123.5
16	13.1	13.1	13.1
17	10.7	10.7	10.6
18	17.8	17.3	17.3
19	20.7	13.1	12.9
20	13.1	13.1	13.1
1′	45.0	45.0	45.0
2′	75.6	75.6	75.6
3′	17.8	17.8	17.8
2′-OCH_3	59.1	59.1	59.1

[a] Chemical shifts were partially determined by HMQC and HMBC data.
[b] Interchangeable signals.

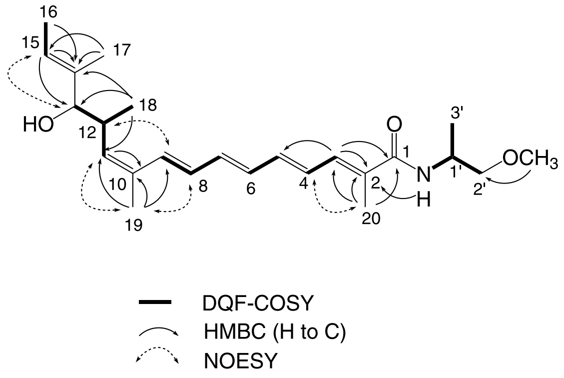


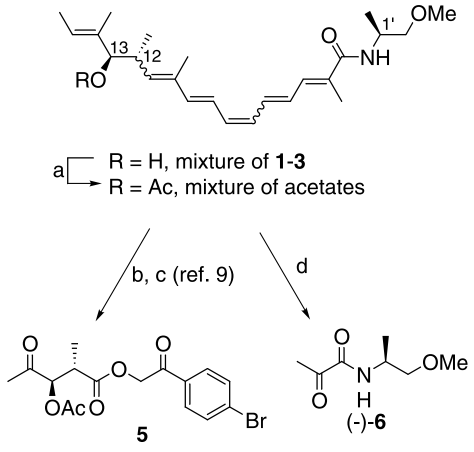
Figure 2. Gross structure of **1** determined by the 2D NMR correlations shown.

compound **1** was determined to be (6*E*,10*Z*)-2′-*O*-methylmyxalamide D.

The NMR data of **2** (Tables 1 and 2) were quite similar to those for **1**, suggesting that it was a stereoisomer of **1**. The planar structure of **2** was determined by 2D NMR in a similar manner to that for **1**. The 4*E*, 6*Z*, 8*E* geometry was determined from the coupling constants of $J_{4,5} = 14.5$ Hz, $J_{6,7} = 11.0$ Hz, $J_{8,9} = 15.1$ Hz, respectively. The 2*E*, 10*E*, 14*E* geometry of the trisubstituted double bonds was determined from the NOESY correlations of H4/H20, H9/H11, H12/H19, and H13/H15. These findings revealed that the compound **2** was 2′-*O*-methylmyxalamide D.

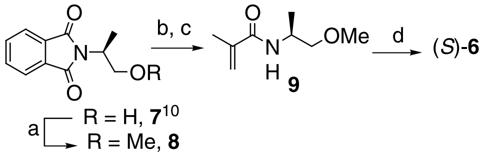
Similarly, the NMR data of **3** (Tables 1 and 2) suggested that this compound was a stereoisomer of **1** and **2**. The same planar structure as those of **1** and **2** was then determined by 2D NMR analysis. The 4*E*, 6*E*, 8*E* geometry were determined from the coupling constants as shown in Table 1, and the 2*E*, 10*E*, 14*E* geometry of the trisubstituted double bonds were determined from the NOESY correlations of H4/H20, H12/H19, and H13/H15. Thus, the compound **3** was determined to be (6*E*)-2′-*O*-methylmyxalamide D. The steric repulsion effect in the ^{13}C NMR data, that is, high-field shifts of the carbons adjacent to a *cis* olefin, also supported the geometry of these polyene metabolites **1**–**3**. Thus, high-field shifts compared to the all *E* compound **3** were observed for the following carbons of **1** and **2**: C9 ($\Delta\delta$ −7.8) in **1**, C5 ($\Delta\delta$ −5.1) and C8 ($\Delta\delta$ −4.9) in **2**.

To determine the absolute stereochemistry of the myxalamide D derivatives **1**–**3**, we followed the methodology described by Jansen et al.[9] with a slight modification. A mixture of **1**–**3** was used for degradation to obtain the fragments that contained asymmetric centers because **1**–**3** easily isomerized to each other under light and decomposed during purification. Acetylation of a mixture of **1**–**3** gave a mixture of the corresponding acetates, which was subjected to oxidative cleavage of the double bonds followed by esterification to yield *p*-bromophenacyl ester **5** (Scheme 1). The spectral data including specific rotation for **5** was identical to those reported,[9] revealing the 12*R*, 13*R* configuration of **1**–**3**. To determine the stereochemistry at C1′ a mixture of the acetates of **1**–**3** was treated with ozone followed by Me_2S to obtain keto amide (−)-**6** (Scheme 1). The configuration of (−)-**6** was determined by the synthesis of (*S*)-**6** from phthalimide **7**[10] in four steps as shown in Scheme 2. Methylation of the hydroxyl group in **7** afforded methyl ether **8**. Deprotection of the phthalimide group of **8** with hydrazine gave the corresponding free amine, which was treated with methacryloyl chloride and triethylamine to give acrylamide **9**. Finally, ozonolysis of **9** gave (*S*)-ketoamide **6**: $[\alpha]_D^{23}$ −13° (*c* 0.3, $CHCl_3$) [natural: −17° (*c* 0.03, $CHCl_3$)]. The NMR spectra and other spectral data including specific rotations of both synthetic and natural **6** were identical, indicating the 1′*S* configuration of **1**–**3**. The stereochemistry of **1**–**3** is therefore the same as that of the known myxalamides.



Reagents and conditions: (a) Ac_2O, pyridine, DMAP, rt; (b) O_3, MeOH, -78 °C, then H_2O_2, 100 °C; (c) *p*-Bromophenacyl bromide, Et_3N, acetone; (d) O_3, MeOH, -78 °C, then Me_2S, -78 °C to rt.

Scheme 1. Degradation routes to determine the absolute stereochemistry of **1**–**3**.



Reagents and conditions: (a) MeI, Ag_2O, CH_3CN, rt; (b) $H_2NNH_2.H_2O$, EtOH, 75 °C; (c) Methacryloyl chloride, Et_3N, -10 to 0 °C; (d) O_3, MeOH, -78 °C.

Scheme 2. Synthetic route to (*S*)-**6**.

The antifungal activities of the compounds **1**–**3** as well as their acetates was evaluated by a paper disc assay method against the phytopathogenic fungus *Phytophthora capsici*. The minimum dose to form a recognizable inhibition zone in the neighborhood of the paper disc was determined to be 2 μg/disc for all three compounds. The acetates of **1**–**3** as a mixture showed antifungal activity at a minimum dose of 5 μg/disc.

Discovery of the myxalamide D derivatives **1**–**3** from the myxobacterium *C. fuscus* suggests that polyene amides such as the myxalamides seem to be fairly common secondary metabolites in the myxobacteria. The myxalamides were also discovered from *Stigmatella aurantiaca*[11] and others[2] after the original discovery from *M. xanthus*,[4,5] although methyl ether-type derivatives such as **1**–**3** were the first examples in the myxalamides. *C. fuscus* seems to possess a metabolic system that is similar to that of the other myxalamide producers but is unique, because myxalamide-related metabolites other than **1**–**3** were not detected in photodiode array HPLC analysis of the extracts. Since all three isomers **1**–**3** showed the same antifungal activity against the fungus *P. capsici*, the olefin geometry plays no crucial role for their antifungal activity. The activity of the acetates (mixture) suggests that the free 13-OH group is not essential. In addition, the free 2′-hydroxyl group of the known myxalamides seems not to be very important, though a direct comparison of the activity was not performed between the myxalamides and our compounds. Based on a structural similarity to the myxalamides the mode of action of our new myxalamide derivatives could be blocking the mitochondrial respiratory chain by inhibition of NADH oxidation at complex I.[4,12] It should be noted that more than one species of the myxobacteria can produce similar polyene amides with stereochemical homogeneity.

3. Experimental

3.1. General

Thin-layer chromatography (TLC) was performed by using pre-coated silica gel 60 F_{254} plates (Art. 5715, Merck) or RP-18 F_{254} plates (Art. 15389, Merck). Open column chromatography was performed using silica gel BW-300 (Fuji Silysia) or Cosmosil $75C_{18}$-OPN (Nacalai Tesque). HPLC was performed on a high-pressure gradient system equipped with PU-980 pumps and UV-970 detector or an MD-915 photodiode array UV detector (JASCO). Specific rotations were obtained by using a DIP-370 digital polarimeter (JASCO). FT-IR spectra were recorded on a FT-IR-7000S spectrometer (JASCO). UV spectra were recorded on a Ubest-50 UV/VIS spectrophotometer (JASCO). Mass spectra (MS) were recorded on a Mariner Biospectrometry Workstation (Applied Biosystems) in the positive ESI mode. Residual phthalic acid anhydride (*m/z* 149.0233) and a peptide mixture (angiotensin I, bradykinin and neurotensin) were used as internal standards for high-resolution MS analysis. NMR spectra were recorded on an ARX 400 (400 MHz) or an AMX2 600 (600 MHz) spectrometer (Bruker). The NMR chemical shifts (ppm) were referenced to the solvent peaks of δ_H 7.26 (residual $CHCl_3$) and δ_C 77.0 for $CDCl_3$ solutions or δ_H 3.30 (residual CHD_2OD) and δ_C 49.0 for CD_3OD solutions. The assay method was the same as the previously reported one for the cystothiazoles.[6,7]

3.2. Isolation of 1–3

A large scale (150 L) fermentation of *C. fuscus* followed by extraction and silica gel chromatography was described previously.[6,7] The first chromatography of the crude hexane/EtOAc (3:1)–soluble material (14.2 g) on silica gel afforded five fractions. The third fraction yielded cystothiazole A as described in our reference (see Ref. 6). A portion (770 mg) of the fourth fraction (2.5 g) eluted with EtOAc was chromatographed on silica gel [Develosil LOP60 (∅ 20× 300 mm), Nomura Chemical; 160 min linear gradient from 2 to 42% acetone in benzene, 5 mL/min]. The sixth fraction (42.8 mg) eluted from 8.25 to 8.5% acetone in benzene was applied to HPLC [TSK gel ODS-120T (∅ 20×250 mm), TOSOH, 72% aq MeOH, 5 mL/min, detected at 380 nm] to obtain (6*E*,10*Z*)-2′-*O*-methylmyxalamide D (**1**) (0.6 mg, $t_R=101.0$ min), 2′-*O*-methylmyxalamide D (**2**) (0.6 mg, $t_R=105.4$ min), and (6*E*)-2′-*O*-methylmyxalamide D (**3**) (2.4 mg, $t_R=114.6$ min) as pale yellow oils. The rest (1.73 g) of the fourth fraction eluted with EtOAc was used for obtaining a crude mixture of **1–3** (287 mg), which was used for degradation without further purification (see Section 3.3.1).

3.2.1. (6*E*,10*Z*)-2′-*O*-Methylmyxalamide D (1). Pale yellow oil; $[\alpha]_D^{21}$ −12° (*c* 0.03, MeOH); IR (film) ν_{max} 3370 (br), 1653, 1522, 1108, 1000 cm^{-1}; UV (MeOH) λ_{max} 260 (ε 6000), 340 (sh), 355 (30,000), 370 (sh) nm; MS (ESI^+) *m/z* 388 $[M+H]^+$, 410 $[M+Na]^+$. HRMS found 388.2794, calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2846. For NMR data refer to Tables 1 and 2.

3.2.2. 2′-*O*-Methylmyxalamide D (2). Pale yellow oil; $[\alpha]_D^{21}$ −27° (*c* 0.04, MeOH); IR (film) ν_{max} 3367 (br), 1653, 1522, 1107, 1000 cm^{-1}; UV (MeOH) λ_{max} 260 (ε 6000), 340 (sh), 355 (30,000), 370 (sh) nm; MS (ESI^+) *m/z* 388 $[M+H]^+$, 410 $[M+Na]^+$. HRMS found 388.2805, calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2846. For NMR data refer to Tables 1 and 2.

3.2.3. (6*E*)-2′-*O*-Methylmyxalamide D (3). Pale yellow oil; $[\alpha]_D^{21}$ −31° (*c* 0.017, MeOH); IR (film) ν_{max} 3365 (br), 1653, 1522, 1106, 998 cm^{-1}; UV (MeOH) λ_{max} 257 (ε 3000), 340 (sh), 356 (30,000), 370 (sh) nm; MS (ESI^+) *m/z* 388 $[M+H]^+$, 410 $[M+Na]^+$. HRMS found 388.2807, calcd for $C_{24}H_{38}NO_3$ $[M+H]^+$ 388.2846. For NMR data refer to Tables 1 and 2.

3.3. Degradation

3.3.1. 13-*O*-Acetyl derivatives of 1–3. A mixture of **1–3** (46.1 mg, 0.12 mmol) was treated with a mixture of pyridine (4 mL), DMAP (22 mg, 0.18 mmol) and Ac_2O (2 mL) at room temperature for 3 h. The mixture was concentrated and the residue was chromatographed on silica gel (hexane/EtOAc 2:1) to obtain a mixture of acetates as a pale yellow oil (20.7 mg, 40%): ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–7.05 (1H, m, H-3), 6.05–6.68 (6H, m, H-4–H-9), 5.90–6.00 (1H, m, NH), 5.50–5.60 (1H, m, H-15), 5.37 (1H, m, H-11), 4.98 (1H, m, H-13), 4.25 (1H, m, H-1′), 3.35–3.45 (2H, m, H-2′), 3.33, 3.37 and 3.38 (total 3H, s each, 2′-OCH_3), 2.83–2.93 (1H, m, H-12), 1.97 and 1.98 (total 3H, s each, H-20), 1.94 and 1.95 (total 3H, s each, acetate), 1.86, 1.81 and 1.72 (total 3H, s each, H-19), 1.65 and 1.58 (total 6H, m, H-16, 17), 1.21, 1.22 and 1.23 (total 3H, d each, $J=6.8$ Hz, H-3′), 0.87 and 0.88 (total 3H, d each, $J=6.8$ Hz, H-18).

3.3.2. *N*-(2-Methoxy-1-methylethyl)-2-oxopropanamide (6). The above acetate mixture (20.7 mg, 0.048 mmol) was dissolved in MeOH (1.5 mL) and cooled to −78 °C. A stream of ozone (8%) in oxygen was passed through this solution for 1 h. The solution was flushed with oxygen, treated with Me_2S (0.5 mL) and then allowed to warm to room temperature with stirring for 3 h. Solvent evaporation gave an oily residue (4.9 mg), which was chromatographed on silica gel (hexane/acetone 10:1) to obtain pure **6** (0.5 mg, 7%) as a colorless oil: $[\alpha]_D^{23}$ −17° (*c* 0.03, $CHCl_3$). The NMR and other spectroscopic data were identical to synthetic (*S*)-**6** (refer to Section 3.4).

3.3.3. 3-Acetoxy-2-methyl-4-oxopentanoic acid *p*-bromophenacyl ester (5). The reaction was carried out in a manner similar to that described in Ref. 6. Briefly, a mixture of the above acetates (24.7 mg, 0.057 mmol) was subjected to ozonolysis followed by oxidative treatment with H_2O_2 and subsequent esterification of the resulting carboxylic acid with *p*-bromophenacyl bromide (26 mg, 0.094 mmol) to give **5** (0.7 mg, 3%): $[\alpha]_D^{23}$ $+10°$ (*c* 0.06, $CHCl_3$) (lit.:[9] $[\alpha]_D^{20}$ $+11°$ (*c* 0.3, $CHCl_3$)). ^1H NMR spectrum was identical to that reported in the literature.[9]

3.4. Synthesis of ketoamide (*S*)-6

3.4.1. (*S*)-2-(2-Methoxy-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (8). To a solution of phthalimide **7**[10] (592 mg, 2.9 mmol) in CH_3CN (7.5 mL) was added Ag_2O (2 g, 8.7 mmol) and the mixture was heated at reflux temperature for 5 h in the dark. Ag_2O was filtered off by using a pad of celite and the filtrate was concentrated to afford **8** (602 mg, 95%) as chromatographically pure material: colorless oil, $[\alpha]_D^{23}$ $+20°$ (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, m), 7.69 (2H, m), 4.61 (1H, m), 3.97 (1H, t, $J=9.8$ Hz), 3.53 (1H, dd, $J=5.4$, 9.8 Hz), 3.32 (3H, s), 1.44 (3H, d, $J=7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 133.8, 132.1, 123.1, 72.9, 58.7, 46.3, 15.0; UV (MeOH) λ_{max} 219 (ε 31,000), 240 (7600, sh), 295 (1600) nm; IR (film) ν_{max} 2984, 2939, 2894, 1775, 1714, 1705, 1468, 1394, 1373, 1337, 1111, 1042, 878, 720, 532 cm^{-1}; HRMS *m/z* 220.0967 $(M+H)^+$, calcd for $C_{12}H_{14}NO_3$ 220.0968.

3.4.2. (*S*)-*N*-(2-Methoxy-1-methylethyl)-2-methyl-2-propenamide (9). Phthalimide **8** (96.4 mg, 0.44 mmol) was dissolved in EtOH (0.1 mL) in a sealed tube. To this solution was added hydrazine monohydrate (25 μL, 0.48 mmol), and the tube was sealed and heated at 75 °C for 5 h. After cooling to room temperature, Et_3N (0.61 mL, 4.4 mmol) was added and stirred for 5 min before cooling to -10 °C. Then methacryloyl chloride (0.43 mL, 4.4 mmol) was added dropwise and the mixture was stirred at 0 °C for 5 h. The reaction mixture was diluted with water and extracted with EtOAc three times. The combined organic layers were dried (anhyd Na_2SO_4) and concentrated to give a crude oil, which was chromatographed on silica gel (hexane/acetone 4:1) to give acrylamide **9** (21.6 mg, 31%): colorless oil, $[\alpha]_D^{23}$ $-10°$ (*c* 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (NH, br s), 5.65 (1H, s), 5.29 (1H, s), 4.19 (1H, m), 3.39 (1H, dd, $J=4.2$, 9.4 Hz), 3.36 (1H, dd, $J=4.1$, 9.4 Hz), 3.35 (3H, s), 1.94 (3H, s), 1.19 (3H, d, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 140.2, 119.2, 75.4, 59.0, 44.8, 18.6, 17.6; UV (MeOH) λ_{max} 203 (ε 8700) and 296 (350, sh) nm; IR (film) ν_{max} 3312, 2981, 2930, 1721, 1678, 1659, 1624, 1530, 1455, 1154, 1111, 1038, 935 cm^{-1}; HRMS *m/z* 180.0991 $(M+Na)^+$, calcd for $C_8H_{15}NO_2Na$ 180.0995.

3.4.3. (*S*)-*N*-(2-Methoxy-1-methylethyl)-2-oxopropanamide [(*S*)-6)]. A stream of ozone (8% in O_2) was passed through a solution of **9** (26.3 mg, 0.17 mmol) in MeOH (1.5 mL) at -78 °C for 1 h. After removal of ozone, the reaction mixture was concentrated to obtain (*S*)-**6** (6.6 mg, 25%): colorless oil, $[\alpha]_D^{23}$ $-13°$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (NH, br s), 4.10 (1H, m), 3.37 (2H, dd, $J=1.0$, 4.4 Hz), 3.35 (3H, s), 2.46 (3H, s), 1.21 (3H, d, $J=6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 159.6, 75.1, 59.1, 45.1, 24.4, 17.2; UV (MeOH) λ_{max} 230 (ε 1440, sh) nm; IR (film) ν_{max} 3400, 1718, 1684, 1522, 1169, 1110, 669 cm^{-1}; HRMS *m/z* 182.0778 $(M+Na)^+$, calcd for $C_7H_{13}NO_3Na$ 182.0788. It must be noted that product (*S*)-**6** (both natural and synthetic) is a very volatile compound and most product was lost mainly during concentration between spectroscopic measurements.

Acknowledgements

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References and notes

1. Reichenbach, H.; Gerth, K.; Irschik, H.; Kunze, B.; Höfle, G. *Trends Biotechnol.* **1998**, *6*, 115–121.
2. Reichenbach, H.; Höfle, G. Production of Bioactive Secondary Metabolites. In *Myxobacteria II*; Dworkin, M., Kaiser, D., Eds.; American Society for Microbiology: Washington, DC, 1993; pp 347–397; Chapter 16.
3. Gerth, K.; Pradella, S.; Perlova, O.; Beyer, S.; Müller, R. *J. Biotechnol.* **2003**, *106*, 233–253.
4. Gerth, K.; Jansen, R.; Reifenstahl, G.; Höfle, G.; Irschik, H.; Kunze, B.; Reichenbach, H.; Thierbach, G. *J. Antibiot.* **1983**, *36*, 1150–1155.
5. Jansen, R.; Reifenstahl, G.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1983**, 1081–1095.
6. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S. *J. Antibiot.* **1998**, *51*, 275–281.
7. Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. *Tetrahedron* **1998**, *54*, 11399–11404.
8. Akita, H.; Sasaki, T.; Kato, K.; Suzuki, Y.; Kondo, K.; Sakagami, Y.; Ojika, M.; Fudou, R.; Yamanaka, S. *Tetrahedron* **2004**, *60*, 4735–4738.
9. Jansen, R.; Sheldrick, W. S.; Höfle, G. *Liebigs Ann. Chem.* **1984**, 78–84.
10. Berardi, F.; Loiodice, F.; Fracchiolla, G.; Colabufo, N. A.; Perrone, R.; Tortorella, V. *J. Med. Chem.* **2003**, *46*, 2117–2124.
11. Höfle, G.; Kunze, B.; Zorzin, C.; Reichenbach, H. *Liebigs Ann. Chem.* **1984**, 1883–1904.
12. Friedrich, T.; Van Heek, P.; Leif, H.; Ohnishi, T.; Forche, E.; Kunze, B.; Jansen, R.; Trowitzsch-Kienast, W.; Höfle, G.; Reichenbach, H. *Eur. J. Biochem.* **1994**, *219*, 691–698.

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Tetrahedron

A versatile approach to 6-substituted-5-methoxy-δ-lactam framework and application to the formal synthesis of (±)-homopumiliotoxin 223G

Bo-Fong Chen, Min-Ruei Tasi, Cheng-Yu Yang, Jung-Kai Chang and Nein-Chen Chang*

Department of Chemistry, National Sun Yat-Sen University, 70 Lien-hai Rd., Kaohsiung 804, Taiwan, ROC

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Abstract—Of the various 6-substituted-5-methoxy-δ-lactams **6** were synthesized from α-sulfonyl acetamide **9** in 4 steps in good yield. The key glutarimides **7** were obtained via facile [3+3] annulation. The method featured regioselective introduction of C-6 substituents in glutarimides **7**. Synthesis of tribenzyl lactam **8** and the formal synthesis of (±)-homopumiliotoxin 223G were also reported.

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1. Introduction

Naturally occurring 3-piperidinols and polyhydroxylated piperidines such as prosopinine (**1**), mannonolactam (**2**), deoxymannojirimycin (**3**) and homopumiliotoxins (**4**) alkaloids (Fig. 1) have received much attention owing to a variety of their biological activities.[1] Numerous syntheses of these classes of compounds have been reported.[2,4] However, it is still desirable to develop a general synthetic strategy that provides a common pivotal intermediate from which 2,6-disubstituted piperidine-3-ol **5** can be derived. 6-Substituted-5-hyrdoxy-δ-lactams **6** have been reported as precursors for the synthesis of 2,6-disubstituted piperidine-3-ol **5**.[2c,k,r,u,3] In this paper, we described a new and versatile approach to 6-substituted-5-methoxy-δ-lactams **6** starting from glutarimides **7** (Scheme 1). The synthesis of tribenzyl lactam **8** was discussed (Fig. 2). Tribenzyl lactam **8** is a key intermediate for the preparation of prosopinine **1**, mannonolactam **2** and deoxymannojirimycin **3**. The formal synthesis of (±)-homopumiliotoxin 223G **4d** was also reported.

2. Results and discussion

2.1. Synthesis of 5-methoxy-3-tolsyl glutarimides 7a and 7b

Glutarimide **7a** was successfully prepared in just one step. It was taken from α-sulfonyl acetamide **9a** and ester **10** via stepwise [3+3] cycloaddition[5] in 80% yield. The stereochemistry of **7a** was established by X-ray analysis (Fig. 3).[6]

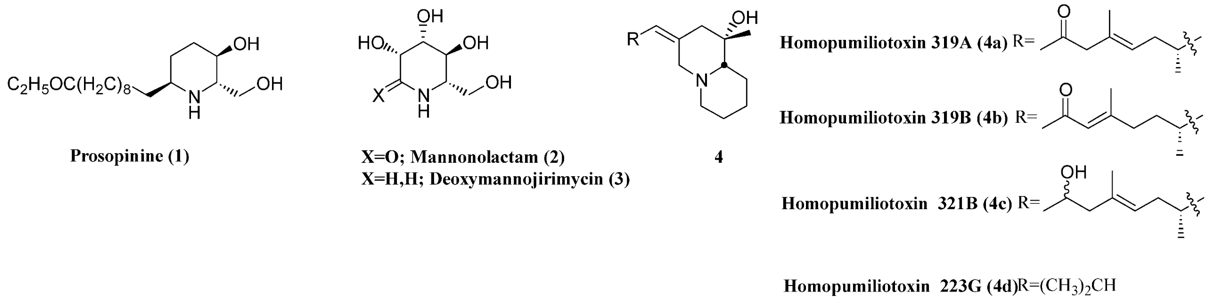

Figure 1.

Keywords: 3-Piperidinol; [3+3] Annulation; Regioselective reduction.

* Corresponding author. Tel.: +886 7 5252000 3914; fax: +886 7 5253913; e-mail: ncchang@mail.nsysu.edu.tw

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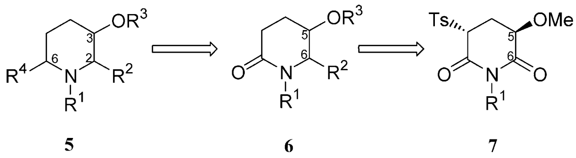
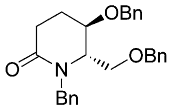


Scheme 1.



tribenzyl lactam (**8**)

Figure 2.

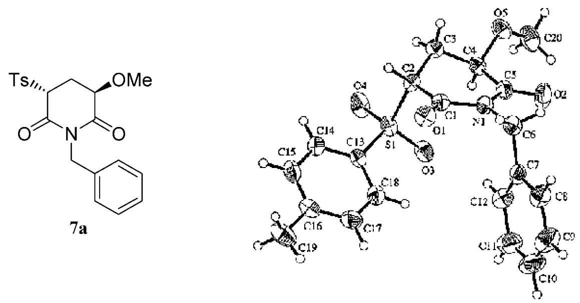
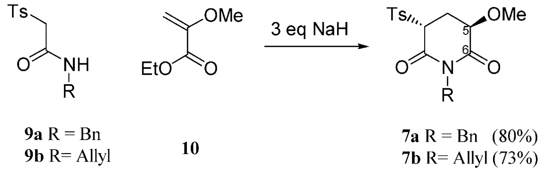


Figure 3. X-ray crystallography of **7a**.

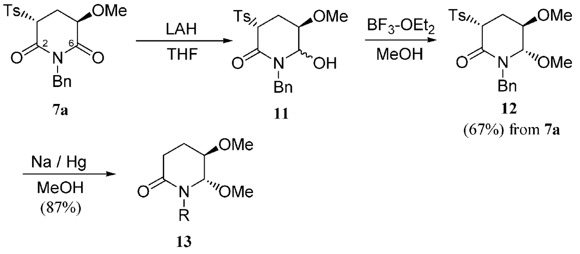


Scheme 2.

Following the same procedure, **7b** was prepared from **9b** in 73% yield (Scheme 2).

2.2. Regioselective introduction of C-6 substituents in 7a

With **7a** in hand, the next step was to introduce substituent regioselectively at C-6 position in **7a**. Such introduction was accomplished by the following procedures. (1) Reduction of **7a** with LiAlH$_4$ afforded hydroxy lactam **11**.[7] Without purification, **11** was converted to 5,6-dimethoxy-δ-lactam **12** in methanol solution in the presence of BF$_3$–OEt$_2$. (2) Lactam **12** was desulfonated with sodium amalgam to produce *trans*-5,6-dimethoxy-δ-lactam **13** as *N*-acyliminium ion precursor (Scheme 3). The stereochemistry of **13** was established by NMR spectra (Fig. 4). (3) Treatment of **13** with various nucleophiles in the presence of BF$_3$–OEt$_2$ furnished the corresponding *N*-benzyl-6-substituted-5-methoxy-δ-lactams **14a**–**14e** as shown in Table 1.[8] Attempts to improve the stereoselectivity of the nucleophilic addition with different substituent group at C-5 oxygen (i.e., Ac, TBS) were failed. The stereochemical assignment of *N*-benzyl-6-substituted-5-methoxy-δ-lactams **14a**–**14e** were established by NOE studies and coupling constants. It is noteworthy that the trans isomer **14b** was obtained as the only product when nucleophilic addition with propargyl trimethylsilane was performed. The reason of not observing *cis*-**14b** is not clear.



Scheme 3.

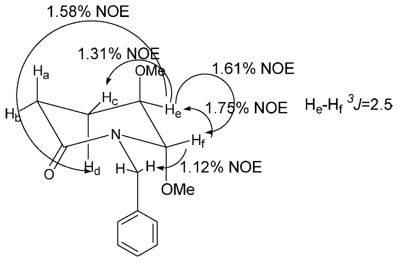


Figure 4. Meaningful NOE and coupling constants for **13**.

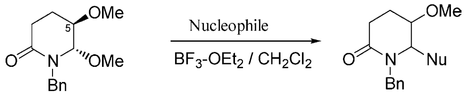
2.3. Preparation of tribenzyl lactam 8, a key intermediate for the synthesis of prosopinine (1), mannonolactam (2) and deoxymannojirimycin (3).[2a,b]

The reaction of propargyl trimethylsilane with dimethoxy δ-lactam **12** in the presence of BF$_3$–OEt$_2$ produced allene **15** as the only product. The stereochemistry of **15** was established by NMR spectra (Fig. 5). Compound **15** was transformed into hydroxymethyl product **16** by ozonolysis followed by the reduction of the corresponding aldehyde with NaBH$_4$ in 76% yield in two steps. Subsequently, the acetylation of primary alcohol with acetic anhydride followed by demethylation of the resulting compound **17** with BBr$_3$ and quenched with NaHCO$_3$ provided alcohol **18**. After removing the sulfonyl group in compound **18** with sodium amalgam, the resulting diol was subsequently treated with sodium hydride and benzyl bromide. δ-Lactam **8** was obtained from **18** in 51% yield (Scheme 4). The spectroscopic data of **8** were identical with those reported in the literature.[2a,b]

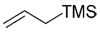
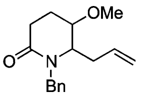
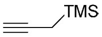
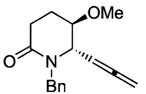
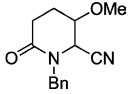
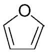
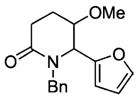
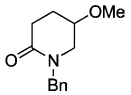
2.4. Formal synthesis of (±)-homopumiliotoxin 223G from 19

For the synthesis of homopumiliotoxin 223G, **7b** was used as starting material. Following the same procedures described in Scheme 3, **19** was obtained in 61% yield from **7b**. In the presence of BF$_3$–OEt$_2$, **19** smoothly reacted with allylsilane to yield the diallyl adduct **20** as a mixture of three diastereomers (ca. 33:33:34 as judged by ^{1}H NMR). This unexpected result might due to part of the C-3 stereocenter epimerized under the reaction condition. Therefore, three diastereoisomers were obtained instead of two. Inasmuch as this mixture would converge to a single compound **24**, the diastereomers were not individually isolated and characterized. The stage was thus set for

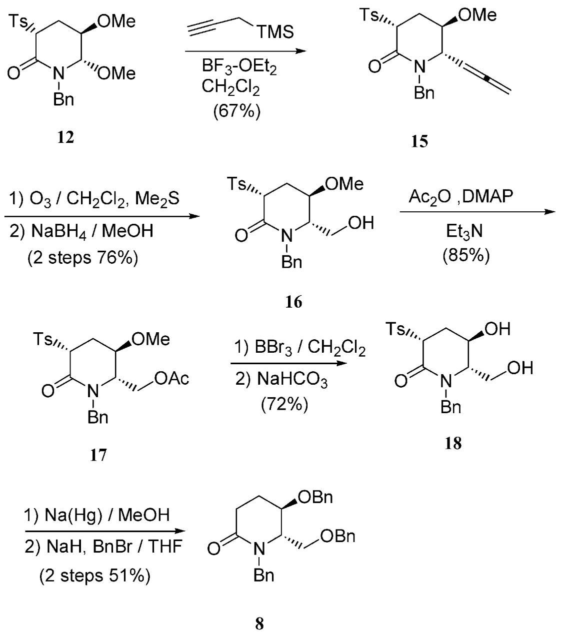
Table 1. Treatment of **13** with various nucleophiles in the presence of BF_3–OEt_2



13 → **14a~14e**

Entry	Nucleophile	Product	(yield)[a]
1		**14a** 	*cis* 62% *trans* 27%
2		**14b** 	71%
3	TMSCN	**14c** 	*cis* 26% *trans* 55%
4		**14d** 	*cis* 41% *trans* 43%
5	Et_3SiH	**14e** 	96%

[a] Isolated yields after column chromatography.



Scheme 4. Preparation of δ-lactam **8**, a key intermediate for the synthesis of prosopinine (**1**), mannonolactam (**2**) and deoxymannojirimycin (**3**).[2a,b]

intramolecular metathesis. Exposure of mixture **20** to the first-generation Grubbs' catalyst at room temperature cleanly provided a mixture of quinolizidinones **21** in 71% yield. Subsequently, the hydrogenation of olefin followed by demethylation of the resulting product with NaI and TMSCl provided mixture **22**. Removal of the sulfonyl function was effected with sodium amalgam to afford hydroxy lactam **23** as a mixture of two isomers (ca. 30:70 as judged by ^{1}H NMR). After oxidation of **23** with Jones reagent, the resulting ketone **24** underwent stereoselectively 1,2-addition with MeMgBr. The desired **25** was obtained as the only product in the 74% yield (Scheme 5). The spectroscopic data for **25** matched those reported in the literature.[4a] The present work constitutes a formal synthesis of (±)-homopumiliotoxin 223G.

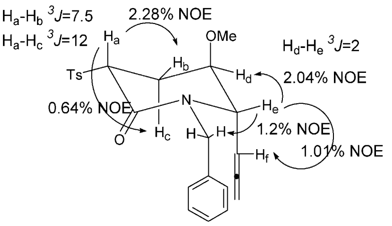
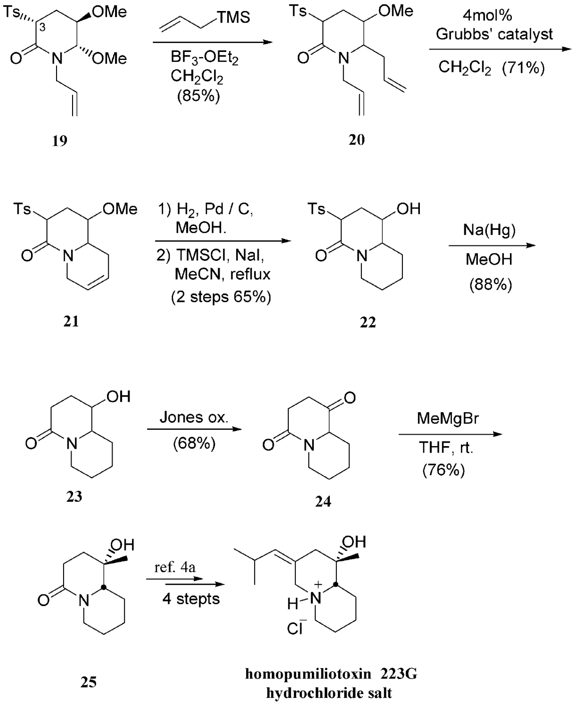


Figure 5. Meaningful NOE and coupling constants for **15**.

3. Conclusion

In conclusion, the *N*-substituted-5-methoxy-3-tolsyl glutarimides **7** were synthesized in good yield. The glutarimides **7** are versatile intermediate for the preparation of 6-substituted-5-methoxy-δ-lactam **6**. These results were applied to the preparation of δ-lactam **8**, which is a key intermediate for the synthesis of prosopinine **1**, mannonolactam **2** and deoxymannojirimycin **3**. Formal synthesis of (±)-homopumiliotoxin 223G was also reported.



Scheme 5. Formal synthesis of (±)-homopumiliotoxin 223G.

4. Experimental

4.1. General

Before use, THF was distilled from a deep blue solution resulting from sodium and benzophenone under nitrogen. All reagents and solvents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) analysis was performed with precoated silica gel (60 f254 plates) and column chromatography was carried out on silica (70–230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.1.1. Preparation of 2-methoxyacrylic acid ethyl ester (10). A mixture of ethyl pyruvate (5 g, 43.06 mmol) and trimethyl orthoformate (10.9 g, 103.34 mmol) was added dropwise concentrated sulfuric acid (0.1 mL) at room temperature. After being stirred for 6 h, the residue was diluted with water (10 mL) and extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Without purification, to a solution of above crude product in dry DMF (5 mL), P_2O_5 (3.05 g, 21.52 mmol) was added under strong stirring. The mixture was heated for 6 h at 100 °C, cooled to room temperature, poured on to saturated aqueous $NaHCO_3$ (15 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with water (30 mL), dried, filtered and evaporated. Distillation gave 4.19 g of **10** (75%) as colorless oil.

4.1.2. Procedure of [3+3] cycloaddition to *N*-substituted-5-methoxy-3-tolsyl glutarimides 7. A solution of *N*-substituted-2-(toluene-4-sulfonyl)acetamide (2.0 mmol) **9a**, **9b** in THF (15 mL) was added to a rapidly stirred suspension of sodium hydride (4.4 mmol, 60%) in THF (10 mL). After the reaction mixture was stirred at room temperature for 15 min, α,β-unsaturated ester **10** (6.0 mmol) was added. The resulting mixture was stirring for 7 h at room temperature, quenched with NH_4Cl (1 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel chromatography (hexane/ethyl acetate = 4/1–2/1) produced products.

For **7a**. Yield 80%; white solid; mp 146.6 °C; IR ($CHCl_3$, cm^{-1}) 1685; FAB-MS: $C_{20}H_{21}NO_5S$ *m/z* (%) = 91 (100), 137 (36), 154 (35), 388 ($M^+ + 1$, 12); HRMS (FAB, $M^+ + 1$) Calcd for $C_{20}H_{22}NO_5S$ 388.1219, found 388.1216; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, $J = 8$ Hz, 2H), 7.32 (d, $J = 8$ Hz, 2H), 7.30–7.23 (m, 5H), 4.95 (d, $J = 14.5$ Hz, 1H), 4.88 (d, $J = 14.5$ Hz, 1H), 4.39 (dd, $J = 4.5$, 8.5 Hz, 1H), 4.31 (t, $J = 6.5$ Hz, 1H), 3.55 (S, 3H), 2.85 (ddd, $J = 4.5$, 6.5, 14.5 Hz, 1H), 2.52 (ddd, $J = 6$, 8.5, 14.5 Hz, 1H), 2.64 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.34, 164.22, 145.73, 136.00, 134.52, 129.77 (2C), 129.25 (2C), 128.52 (2C), 128.39 (2C), 127.61, 74.11, 64.30, 59.30, 43.74, 24.44, 21.77. Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28, found C, 61.98; H, 5.44; N, 3.58; S, 8.28. Compound **7a** was recrystallized from ethyl acetate, and as a colorless prism.

For **7b**. Yield 73%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1738, 1687; FAB-MS: $C_{16}H_{19}NO_5S$ *m/z* (%) = 91 (100), 151 (38), 155 (9), 182 (14), 337 (M^+, 1); HRMS (FAB, $M^+ + 1$) Calcd for $C_{16}H_{20}NO_5S$ 337.0978, found 337.0980; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 5.78–5.70 (m, 1H), 5.18 (dd, $J = 1$, 17.5 Hz, 1H), 5.14 (dd, $J = 1$, 10 Hz, 1H), 4.37–4.30 (m, 4H), 3.85 (s, 3H), 2.83 (ddd, $J = 4$, 7, 15 Hz, 1H), 2.55 (ddd, $J = 6$, 11.5, 15 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.92, 164.00, 145.74, 134.86, 130.95, 129.79 (2C), 129.25 (2C), 117.75, 74.14, 64.02, 59.20, 42.41, 24.42, 21.74.

4.1.3. Preparation of 1-substituted-5,6-dimethoxy-3-(toluene-4-sulfonyl)piperidin-2-one (12), (19). A solution of glutarimide **7** (2.0 mmol) in THF (20 mL) was added lithium aluminum hydride (2.5 mmol) at −10 °C. The resulting mixture was stirred for 3 h, quenched with saturated aqueous NH_4Cl (1 mL) at the same temperature, filtered and then concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Without purification, to a solution of above crude product in MeOH (20 mL) was treated with BF_3–OEt_2 (0.24 mL, 2.0 mmol) at room temperature. After 15 h, the resulting mixture was diluted with saturated aqueous $NaHCO_3$, concentrated under reduce pressure and extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel chromatography (hexane/ethyl acetate = 4/1–2/1) produced products.

For **12**. Yield 67%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1654; FAB-MS: $C_{21}H_{25}NO_5S$ *m/z* (%)=91 (100), 69 (61), 372 (8), 404 ($M^+ + 1$, 9); HRMS (FAB, $M^+ + 1$) Calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1529; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J=8$ Hz, 2H), 7.33 (d, $J=8$ Hz, 2H), 7.27–7.18 (m, 5H), 5.24 (d, $J=15.5$ Hz, 1H), 4.34 (dd, $J=1.5$, 3 Hz, 1H), 4.22 (dd, $J=7$, 11.5 Hz, 1H), 4.06 ((d, $J=15.5$ Hz, 1H), 3.69 (dt, $J=4.5$, 2.5 Hz, 1H), 3.35 (S, 3H), 3.20 (S, 3H), 2.76 (ddd, $J=2.5$, 11.5, 14.5 Hz, 1H), 2.59–2.54 (m, 1H), 2.43 (S, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.51, 144.54, 136.67, 136.17, 129.36 (2C), 129.29 (2C), 128.48 (2C), 127.98 (2C), 127.42, 87.12, 72.52, 62.44, 56.98, 56.72, 48.51, 21.68, 21.42. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47; S, 7.95, found C, 62.52; H, 6.24; N, 3.45; S, 8.00.

For **19**. Yield 61%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1740, 1689; FAB-MS: $C_{17}H_{23}NO_5S$ *m/z* (%)=166 (100%), 91 (12), 168 (7), 354 ($M^+ + 1$, 7); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1374; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, $J=8.5$ Hz, 2H), 7.34 (d, $J=8.5$ Hz, 2H), 5.66–5.58 (m, 1H), 5.12 (dd, $J=17$, 1.5 Hz, 1H), 5.08 (dd, $J=10$, 1 Hz, 1H), 4.39 (dd, $J=15.5$, 4 Hz, 1H), 4.37 (d, $J=1.5$ Hz, 1H), 4.09 (dd, $J=11.5$, 7 Hz, 1H), 3.68–3.66 (m, 1H), 3.51 (dd, $J=15.5$, 7 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.62 (ddd, $J=14$, 12, 2 Hz, 1H), 2.53–2.48 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.82, 144.29, 136.31, 131.96, 129.01 (2C), 128.96 (2C), 171.24, 87.38, 72.31, 61.99, 56.63, 56.53, 48.17, 21.39, 20.96. Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96; S, 9.07, found C, 58.02; H, 6.68; N, 3.93; S, 9.39.

4.1.4. 1-Benzyl-5,6-dimethoxypiperidin-2-one (13).

Sodium amalgam 6% (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of **12** (806 mg, 2.0 mmol) in MeOH (5 mL), and vigorously stirred for 2 h at room temperature The residue was filtered and washed with MeOH (2×10 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate=2/1–1/1) to afford **13** (433 mg, 87%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1654; FAB-MS: $C_{14}H_{19}NO_3$ *m/z* (%)=91 (100), 69 (43), 218 (16), 250 ($M^+ + 1$, 71); HRMS (FAB, $M^+ + 1$) Calcd for $C_{14}H_{20}NO_3$ 250.1443, found 250.1442; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 5.34 (d, $J=15$ Hz, 1H), 4.34 (dd, $J=1.5$, 2.5 Hz, 1H), 4.06 (d, $J=15$ Hz, 1H), 3.52 (dt, $J=4.5$, 2.5 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 2.58 (ddd, $J=7$, 12, 18.5 Hz, 1H), 2.41 (ddd, $J=3$, 9.5, 17.5 Hz, 1H), 2.14–2.09 (m, 1H), 1.97–1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.02, 137.14, 128.66, 128.09, 127.68, 127.15 (2C), 88.19, 73.31, 56.75, 56.27, 47.54, 27.20, 20.34.

4.1.5. Preparation of *N*-benzyl-6-substituted-5-methoxy-δ-lactams 14a–14e.

To a solution of **13** (0.26 mmol) and the nucleophiles (1.0 mmol) in dry CH_2Cl_2 (5 mL), BF_3–OEt_2 (0.12 mL, 1.0 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and was monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1–1/1) produced products.

For cis-*6-allyl-1-benzyl-5-methoxypiperidin-2-one* (*cis*-**14a**). Yield 62%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3071, 1638; FAB-MS: $C_{16}H_{21}NO_2$ *m/z* (%)=91 (100), 117 (42), 218 (18), 260 ($M^+ + 1$, 69); HRMS (FAB, $M^+ + 1$) Calcd for $C_{16}H_{22}NO_2$ 260.1650, found 260.1653; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 5H), 5.87–5.79 (m, 1H), 5.43 (d, $J=15$ Hz, 1H), 5.13 (dd, $J=17.5$, 3 Hz, 1H), 5.09 (d, $J=10$ Hz, 1H), 3.94 (d, $J=15$ Hz, 1H), 3.49–3.42 (m, 2H), 3.25 (s, 3H), 2.65 (dt, $J=18$, 5.5 Hz, 1H), 2.59–2.49 (m, 2H), 2.34–2.28 (m, 1H), 1.98–1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.67, 137.22, 135.38, 128.59 (2C), 127.83 (2C), 127.32, 117.77, 75.72, 57.11, 56.36, 48.55, 33.76, 28.59, 22.12.

For trans-*6-allyl-1-benzyl-5-methoxypiperidin-2-one* (*trans*-**14a**). Yield 27%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3076, 1638; FAB-MS: $C_{16}H_{21}NO_2$ *m/z* (%)=91 (100), 133 (52), 260 ($M^+ + 1$, 34); HRMS (FAB, $M^+ + 1$) Calcd for $C_{16}H_{22}NO_2$ 260.1650, found 260.1651; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 5.70–5.63 (m, 1H), 5.44 (d, $J=15.5$ Hz, 1H), 5.12–5.08 (m, 2H), 3.94 (d, $J=15.5$ Hz, 1H), 3.44–3.43 (m, 2H), 3.12 (s, 3H), 2.64 (ddd, $J=8$, 11, 18 Hz, 1H), 2.54–2.49 (m, 1H), 2.40 (ddd, $J=3$, 6.5, 18 Hz, 1H), 2.19–2.13 (m, 1H), 2.05–1.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.79, 137.14, 133.59, 128.47 (2C), 127.78 (2C), 127.16, 118.43, 74.28, 57.71, 55.58, 47.53, 36.67, 27.01, 21.07.

For trans-*1-benzyl-5-methoxy-6-propa-1,2-dienyl-piperidin-2-one* (*trans*-**14b**). Yield 71%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1960, 1648; FAB-MS: $C_{16}H_{19}NO_2$ *m/z* (%)=91 (100), 133 (43), 258 ($M^+ + 1$, 26); HRMS (FAB, $M^+ + 1$) Calcd for $C_{16}H_{20}NO_2$ 258.1494, found 258.1497; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 5.32 (d, $J=15$ Hz, 1H), 5.03 (dd, $J=6$, 13 Hz, 1H), 4.92–4.90 (m, 2H), 4.00–3.98 (m, 1H), 3.79 (d, $J=15$ Hz, 1H), 3.43 (dt, $J=4.5$, 2 Hz, 1H), 3.15 (s, 3H), 2.61 (ddd, $J=7.5$, 12, 18 Hz, 1H), 2.41 (ddd, $J=2$, 6.5, 18 Hz, 1H), 2.17–2.20 (m, 1H), 2.00–1.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.56, 169.58, 137.07, 128.54 (2C), 127.95 (2C), 127.15, 90.19, 78.18, 76.31, 57.00, 55.91, 47.42, 27.01, 21.33.

For cis-*1-benzyl-3-methoxy-6-oxopiperidine-2-carbonitrile* (*cis*-**14c**). Yield 26%; colorless oil; IR ($CHCl_3$, cm^{-1}) 2391, 1654; FAB-MS: $C_{14}H_{16}N_2O_2$ *m/z* (%)=154 (100), 91 (70), 137 (72), 245 ($M^+ + 1$, 65); HRMS (FAB, $M^+ + 1$) Calcd for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1288; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.56 (d, $J=15$ Hz, 1H), 4.31 (dd, $J=1.5$, 5 Hz, 1H), 3.91 (d, $J=15$ Hz, 1H), 3.57 (dt, $J=11$, 4.5 Hz, 1H), 3.38 (s, 3H), 2.77 (ddd, $J=3.5$, 6.5, 18.5 Hz, 1H), 2.52 (ddd, $J=7$, 11, 18.5 Hz, 1H), 2.21–2.17 (m, 1H), 2.16–2.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.17, 135.00, 129.06 (2C), 128.46 (2C), 128.33, 115.42, 73.63, 57.00, 51.18, 48.53, 29.06, 23.82.

For trans-*1-benzyl-3-methoxy-6-oxopiperidine-2-carbonitrile* (*trans*-**14c**). Yield 55%; colorless oil; IR ($CHCl_3$, cm^{-1}) 2303, 1658; FAB-MS: $C_{14}H_{16}N_2O_2$ *m/z* (%)=91 (100), 136 (85), 145 (87), 245 ($M^+ + 1$, 42); HRMS (FAB,

$M^+ + 1$) Calcd for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1291; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.67 (d, $J = 15$ Hz, 1H), 4.24 (t, $J = 2.5$ Hz, 1H), 3.86 (d, $J = 15$ Hz, 1H), 3.80 (dt, $J = 4.5$, 2.5 Hz, 1H), 3.17 (s, 3H), 2.70 (ddd, $J = 7$, 12, 18.5 Hz, 1H), 2.54 (ddd, $J = 2.5$, 6.5, 18.5 Hz, 1H), 2.30–2.22 (m, 1H), 2.18–2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.48, 134.98, 128.91 (2C), 128.25 (2C), 128.11, 116.36, 74.04, 56.61, 49.54, 47.96, 26.88, 23.23.

For cis-*1-benzyl-6-furan-2-yl-5-methoxypiperidin-2-one* (*cis*-**14d**). Yield 41%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3123, 3045, 1638; FAB-MS: $C_{17}H_{19}NO_3$ *m/z* (%) = 91 (100), 154 (95), 286 ($M^+ + 1$, 60); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1443; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, $J = 1$ Hz, 1H), 7.34–7.18 (m, 5H), 6.39 (dd, $J = 2$, 3 Hz, 1H), 6.26 (d, $J = 3.5$ Hz, 1H), 5.46 (d, $J = 15.5$ Hz, 1H), 4.61 (d, $J = 4.5$ Hz, 1H), 3.61 (dt, $J = 11$, 5 Hz, 1H), 3.51 (d, $J = 15.5$ Hz, 1H), 3.31 (s, 3H), 2.77 (ddd, $J = 3$, 7, 18 Hz, 1H), 2.58 (ddd, $J = 8$, 11, 18 Hz, 1H), 2.05–1.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.41, 150.08, 142.86, 136.74, 128.60 (2C), 128.08 (2C), 127.46, 110.31, 109.76, 76.02, 56.70, 55.29, 48.06, 29.62, 22.81.

For trans-*1-benzyl-6-furan-2-yl-5-methoxypiperidin-2-one* (*trans*-**14d**). Yield 43%; colorless oil; IR ($CHCl_3$, cm^{-1}) 3108, 3040, 1641; FAB-MS: $C_{17}H_{19}NO_3$ *m/z* (%) = 91 (100), 136 (38), 154 (36), 286 ($M^+ + 1$, 32); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1442; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J = 2$ Hz, 1H), 7.32–7.21 (m, 5H), 6.36 (dd, $J = 1.5$, 3 Hz, 1H), 6.22 (d, $J = 3$ Hz, 1H), 5.60 (d, $J = 15.5$ Hz, 1H), 4.58 (s, 1H), 3.64 (dt, $J = 4.5$, 2.5 Hz, 1H), 3.58 (d, $J = 15.5$ Hz, 1H), 3.20 (s, 3H), 2.71 (ddd, $J = 7.5$, 12.5, 18.5 Hz, 1H), 2.50 (ddd, $J = 2.5$, 6.5, 18.5 Hz, 1H), 2.06–2.00 (m, 1H), 1.96–1.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.89, 151.94, 142.58, 136.80, 128.49 (2C), 127.85 (2C), 127.24, 110.47, 108.06, 75.81, 56.86, 56.16, 47.55, 27.10, 21.84.

For 1-benzyl-5-methoxypiperidin-2-one (**14e**). Yield 96%; colorless oil; IR ($CHCl_3$, cm^{-1}) 1638; FAB-MS: $C_{13}H_{17}NO_2$ *m/z* (%) = 91 (59), 220 ($M^+ + 1$, 100); HRMS (FAB, $M^+ + 1$) Calcd for $C_{13}H_{18}NO_2$ 220.1338, found 220.1338; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 4.61 (d, $J = 15$ Hz, 1H), 4.56 (d, $J = 15$ Hz, 1H), 3.59–3.56 (m, 1H), 3.30 (dd, $J = 4$, 13 Hz, 1H), 3.25 (s, 3H), 3.23 (ddd, $J = 1$, 4.5, 13 Hz, 1H), 2.62 (ddd, $J = 6.5$, 16, 17.5 Hz, 1H), 2.40 (dt, $J = 6$, 17.5 Hz, 1H), 2.02–1.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.21, 136.70, 128.40 (2C), 128.77 (2C), 127.17, 72.21, 55.80, 50.19, 49.71, 27.80, 25.08.

4.1.6. 1-Benzyl-5-methoxy-6-propa-1,2-dienyl-3-(toluene-4-sulfonyl)piperidin-2-one (15). To a solution of **12** (564 mg, 1.4 mmol) and the propargyl trimethylsilane (627 mg, 5.6 mmol) in dry CH_2Cl_2 (5 mL), BF_3–OEt_2 (0.7 mL, 5.6 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **15** (386 mg, 67%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1963, 1654; EI-MS: $C_{23}H_{25}NO_4S$ *m/z* (%) = 91 (100), 411 (M^+, 0.59); HRMS (FAB, $M^+ + 1$) Calcd for $C_{23}H_{26}NO_4S$ 412.1583, found 412.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.32–7.18 (m, 5H), 5.39 (d, $J = 15$ Hz, 1H), 5.10 (dd, $J = 6.5$, 13 Hz, 1H), 5.00–4.91 (m, 2H), 4.28 (dd, $J = 7.5$, 12 Hz, 1H), 3.99 (m, 1H), 3.77 (d, $J = 15$ Hz, 1H), 3.58 (dt, $J = 4.5$, 2.5 Hz, 1H), 3.05 (s, 3H), 2.69 (ddd, $J = 2$, 12, 14 Hz, 1H), 2.59–2.54 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.76, 161.98, 144.52, 136.84, 136.10, 129.37 (2C), 129.17 (2C), 128.44 (2C), 128.17 (2C), 127.43, 89.01, 78.51, 75.54, 62.36, 56.66, 56.19, 47.94, 22.67, 21.68.

4.1.7. 1-Benzyl-6-hydroxymethyl-5-methoxy-3-(toluene-4-sulfonyl)piperidin-2-one (16). A stream of ozone was bubbled through a solution of **15** (197 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) at −78 °C until a pale blue color developed (5 min). Nitrogen was bubbled through the solution to remove excess ozone and dimethyl sulfide (0.5 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 5 h. The solution was concentrated under reduce pressure followed diluted with MeOH (10 mL), $NaBH_4$ (22 mg, 0.58 mmol) was added and monitored by TLC. When the reaction was finished, water (10 mL) was added and then concentrated under reduced pressure. The residue was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **16** (147 mg, 76%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3432, 1660; FAB-MS: $C_{21}H_{25}NO_5S$ *m/z* (%) = 117 (100), 91 (43), 219 (12), 404 ($M^+ + 1$, 2); HRMS (FAB, $M^+ + 1$) Calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1532; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.28–7.21 (m, 5H), 5.11 (d, $J = 15.5$ Hz, 1H), 4.27 (dd, $J = 8$, 10.5 Hz, 1H), 4.21 (d, $J = 15.5$ Hz, 1H), 3.80–3.78 (m, 3H), 3.58–3.55 (m, 1H), 3.05 (s, 3H), 2.79 (ddd, $J = 3$, 10.5, 15 Hz, 1H), 2.55–2.49 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.65, 144.76, 136.39, 136.35, 129.46 (2C), 129.10 (2C), 128.57 (2C), 127.94 (2C), 127.54, 73.09, 62.77, 62.00, 59.44, 56.09, 49.16, 23.57, 21.71.

4.1.8. Acetic acid 1-benzyl-3-methoxy-6-oxo-5-(toluene-4-sulfonyl)piperidin-2-ylmethyl ester (17). To a solution of **16** (318 mg, 0.79 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (96 mg, 0.79 mmol) in triethylamine (0.5 mL) was added acetic anhydride (2 mL) at room temperature. The reaction mixture was stirred for 3 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **17** (298 mg, 85%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1747, 1654; FAB-MS: $C_{23}H_{27}NO_6S$ *m/z* (%) = 91 (100), 133 (24), 290 (3), 446 ($M^+ + 1$, 6); HRMS (FAB, $M^+ + 1$) Calcd for $C_{23}H_{28}NO_6S$ 446.1637, found 446.1637; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.30–7.21 (m, 5H), 5.27 (d, $J = 15$ Hz, 1H), 4.28–4.23 (m, 3H), 4.06 (d, $J=15$ Hz, 1H), 3.70 (dd, $J=3$, 6.5 Hz, 1H), 3.66–3.63 (m, 1H), 3.03 (s, 3H), 2.68 (ddd, $J=$ 2.5, 10.5, 15 Hz, 1H), 2.62–2.57 (m, 1H), 2.45 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.43, 162.39, 144.75, 136.45, 136.01, 129.46 (2C), 129.13 (2C), 128.53 (2C), 128.14 (2C), 127.59, 73.02, 62.68, 62.42, 56.42, 56.15, 48.74, 23.19, 21.72, 20.76.

4.1.9. 1-Benzyl-5-hydroxy-6-hydroxymethyl-3-(toluene-4-sulfonyl)piperidin-2-one (18). To a solution of **17** (298 mg, 0.67 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added dropwise a 1.0 M solution of boron tribromide in dichloromethane (4.0 mL, 4.0 mmol). After stirring the solution for 10 h, the reaction contents was quenched with a saturated aqueous $NaHCO_3$ (10 mL) at 0 °C. The resulting mixture was stirred for 20 min and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 1/1–1/2) to afford **18** (188 mg, 72%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 3401, 1640; FAB-MS: $C_{20}H_{23}NO_5S$ *m/z* (%) = 91 (100), 136 (74), 390 ($M^+ + 1$, 30); HRMS (FAB, $M^+ + 1$) Calcd for $C_{20}H_{24}NO_5S$ 390.1375, found 390.1375; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, $J=$ 8.5 Hz, 2H), 7.36 (d, $J=8.5$ Hz, 2H), 7.33–7.22 (m, 5H), 5.10 (d, $J=15$ Hz, 1H), 4.41–4.39 (m, 1H), 4.33 (t, $J=9$ Hz, 1H), 4.25 (d, $J=15$ Hz, 1H), 3.81–3.79 (m, 2H), 3.40 (dd, $J=4$, 9 Hz, 1H), 2.84 (ddd, $J=2.5$, 9, 14.5 Hz, 1H), 2.44 (s, 3H), 2.42–2.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.60, 144.91, 136.33, 136.22, 129.53 (2C), 129.23 (2C), 128.82 (2C), 127.85 (2C), 127.67, 64.31, 63.69, 63.02, 61.90, 49.16, 26.12, 21.73.

4.1.10. 1-Benzyl-5-benzyloxy-6-benzyloxymethylpiperidin-2-one (8). Sodium amalgam 6% (Na/Hg, 3.0 g) and sodium phosphate (40 mg) were added to a stirred solution of lactam **18** (132 mg, 0.34 mmol) in methanol (5 mL), and vigorously stirred for 2 h at room temperature The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude product. Without purification, the solution of above crude product in dry THF (5 mL) was added to a rapidly stirred suspension of NaH (48 mg, 1.2 mmol, 60%) in dry THF (5 mL) at room temperature. The mixture was stirred for 5 min and then benzyl bromide (149 mg, 0.87 mmol) was added. After stirring for 30 min, the reaction was quenched with water (10 mL). The resulting mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **8** (72 mg, 51%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1640; FAB-MS: $C_{27}H_{29}NO_3$ *m/z* (%) = 91 (100), 154 (86), 416 ($M^+ + 1$, 8); HRMS (FAB, $M^+ + 1$) Calcd for $C_{27}H_{30}NO_3$ 416.2226, found 416.2224; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.19 (m, 15), 5.36 (d, $J=15$ Hz, 1H), 4.45 (d, $J=$ 12 Hz, 1H), 4.41 (d, $J=12$ Hz, 1H), 4.38 (d, $J=12$ Hz, 1H), 4.30 (d, $J=12$ Hz, 1H), 3.97 (d, $J=15$ Hz, 1H), 3.86 (dd, $J=2.5$, 6.5 Hz, 1H), 3.68–3.66 (m, 1H), 3.55 (dd, $J=4$, 10 Hz, 1H), 3.45 (dd, $J=7$, 9.5 Hz, 1H), 2.70 (ddd, $J=8$, 10, 18 Hz, 1H), 2.43 (ddd, $J=4$, 6.5, 18 Hz, 1H), 2.04–2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.31, 138.03, 137.52, 137.18, 128.50 (2C), 128.45 (2C), 128.29 (2C), 127.91, 127.78 (2C), 127.61 (2C), 127.54, 127.31 (2C), 127.12, 73.30, 71.98, 70.03, 69.36, 58.59, 47.96, 27.41, 22.38.

4.1.11. 1,6-Diallyl-5-methoxy-3-(toluene-4-sulfonyl) piperidin-2-one (20). To a solution of **19** (1 g, 2.9 mmol) and the allylsilane (1.32 g, 11.6 mmol) in dry CH_2Cl_2 (20 mL), $BF_3 \cdot OEt_2$ (1.46 mL, 11.6 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and monitored by TLC. When the reaction was finished, saturated aqueous $NaHCO_3$ (5 mL) was added and the water layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography to afford **20** (897 mg, 85%) as mixture (ca. 33:33:34) of three diastereomers and as colorless oil. For spectroscopic characterization a mixture of the three isomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (comp, 2H), 7.34–7.32 (comp, 2H), 5.88–5.58 (comp, 2H), 5.24–5.07 (comp, 4H), 4.60–4.12 (comp, 1H), 4.16 (t, $J=10$ Hz, 0.3H), 4.11 (t, $J=10$ Hz, 0.3H), 4.06 (tt, $J=5$, 8 Hz, 0.3H), 3.97 (dt, $J=9.5$, 4 Hz, 0.3H), 3.65 (q, $J=3$ Hz, 0.3H), 3.63 (q, $J=4.5$ Hz, 0.3H), 3.57–3.34 (comp, 2.3H), 3.41 (s, 1H), 3.38 (s, 3H), 3.30 (s, 1H), 2.74 (dt, $J=15$, 4.5 Hz, 0.3H), 2.64–2.23 (comp, 6.3H).

4.1.12. 1-Methoxy-3-(toluene-4-sulfonyl)-1,2,3,6,9,9a-hexa hydroquinolizin-4-one (21). 1st Grubbs' catalyst (82 mg, 0.1 mmol) was added to a solution of mixture **20** (881 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) and stirred for 12 h at room temperature The resulting mixture was concentrated and purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **21** (570 mg, 71%) as a mixture of three diastereomers. For spectroscopic characterization the major isomer was isolated by chromatography; colorless oil; IR ($CHCl_3$, cm^{-1}) 3045, 1639; FAB-MS: $C_{17}H_{21}NO_4S$ *m/z* (%) = 154 (100), 136 (87), 219 (30), 336 ($M^+ + 1$, 28); HRMS (FAB, $M^+ + 1$) Calcd for $C_{17}H_{22}NO_4S$ 336.1270, found 336.1271; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J=$ 8 Hz, 2H), 7.34 (d, $J=8$ Hz, 2H), 5.85–5.81 (m, 1H), 5.66–5.63 (m, 1H), 4.55 (dd, $J=3.5$, 18.5 Hz, 1H), 4.10 (t, $J=$ 7 Hz, 1H), 4.04 (ddd, $J=3$, 5, 8 Hz, 1H), 3.57 (dt, $J=11.5$, 4 Hz, 1H), 3.54 (d, br, $J=19$ Hz, 1H), 3.46 (s, 3H), 2.64 (ddd, $J=3$, 7, 14 Hz, 1H), 2.52 (ddd, $J=6$, 9, 15 Hz, 1H), 2.44 (s, 3H), 2.36–2.32 (m, 1H), 2.12 (d, br, $J=17$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.80, 144.63, 136.70, 129.39, 129.30, 129.20, 129.02, 124.31, 123.33, 72.82, 63.45, 57.19, 55.48, 43.14, 26.12, 22.83, 21.64.

4.1.13. 1-Hydroxy-3-(toluene-4-sulfonyl)octahydroquinolizin-4-one (22). Palladium on activated carbon 10% (10 mg) was added to the solution of **21** (577 mg, 1.7 mmol) in MeOH (20 mL) The hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 3 h at room temperature. The catalyst was filtered through a short plug of celite and washing with MeOH (2×5 mL). The combined organic layers were evaporated. Without purification, sodium iodide (1.27 g, 8.5 mmol) was added to a solution of above crude product in MeCN (10 mL), followed by 8.5 mmol (1.1 mL) of distilled Me_3SiCl added dropwise. The mixture was refluxed for 15 h. After cooling to room temperature, few drops of aqueous 10% NH_4Cl were added, follow by CH_2Cl_2

(2×10 mL) extraction. The organic layer was sequentially washed with aqueous 20% $Na_2S_2O_3$ and brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 2/1–1/1) to afford **22** (65%) as a mixture of three diastereomers. For spectroscopic characterization the major isomer was isolated by chromatography; white solid; mp 184.6 °C; IR ($CHCl_3$, cm^{-1}) 3447, 1640; FAB-MS: $C_{16}H_{21}NO_4S$ *m/z* (%) = 136 (100), 77 (93), 154 (88), 324 ($M^+ + 1$, 23); HRMS (FAB, $M^+ + 1$) Calcd for $C_{16}H_{22}NO_4S$ 324.1269, found 324.1270; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 4.59 (d, br, J = 13.5 Hz, 1H), 4.32–4.29 (m, 2H), 3.35 (d, J = 11.5 Hz, 1H), 2.59 (dt, J = 13, 6.5 Hz, 1H), 2.49–2.40 (m, 5H), 1.91–1.81 (m, 1H), 1.68–1.63 (m, 2H), 1.52 (ddt, J = 13, 3 Hz, 1H), 1.46–1.39 (m, 1H), 1.30 (dtt, J = 13, 4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.22, 144.92, 137.06, 129.31 (2C),128.96 (2C), 64.17, 62.42, 60.50, 43.05, 27.26 (2C), 25.21, 23.73, 21.63. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33; S, 9.92, found C, 59.25; H, 6.58; N, 4.32; S, 9.97.

4.1.14. 1-Hydroxyoctahydroquinolizin-4-one (23). Sodium amalgam 6% (Na/Hg, 3 g) and sodium phosphate (40 mg) were added to a stirred solution of **22** (286 mg, 0.9 mmol) in MeOH (5 mL), and vigorously srirred for 2 h at room temperature The residue was filtered and washed with MeOH (2×10 mL). The combined organic layers were concentrated to obtain the crude product. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 1/1–1/2) to afford **23** (132 mg, 88%) as a mixture of two diastereomers (ca. 70:30) and as colorless oil. For spectroscopic characterization an inseparable mixture of the two isomers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62–4.59 (comp, 1H), 3.95–3.94 (m, 0.7H), 3.65–3.62 (m, 0.3H), 3.22 (ddd, J = 3, 4, 12 Hz, 0.7H), 3.10 (ddd, J = 2.5, 4.5, 12 Hz, 0.3H), 2.58–2.46 (comp, 1H), 2.37–2.31 (comp, 1H) 2.27–2.20 (comp, 1H), 1.91–1.09 (comp, 8H).

4.1.15. Hexahydroquinolizine-1,4-dione (24). To an ice-cold solution of **23** (132 mg, 0.8 mmol) in acetone (10 mL) was added dropwise Jones reagent (0.5 mL). After being stirred for 10 min, isopropanol (1 mL) was added and the mixture was concentrated to a residue that was partitioned in CH_2Cl_2 (20 mL) and water (5 mL). The organic layer was separated, washed with brine, dried, filtered and evaporated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 1/1) to afford **24** (89 mg, 68%) as colorless oil; IR ($CHCl_3$, cm^{-1}) 1731, 1638; EI-MS: $C_9H_{13}NO_2$ *m/z* (%) = 83 (100), 167 (M^+, 21); HRMS (EI, M^+) Calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0943; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (d, br, J = 13 Hz, 1H), 3.69 (dd, J = 12, 3 Hz, 1H), 2.77–2.64 (m, 4H), 2.48 (dt, J = 12.5, 3 Hz, 1H), 2.15 (d, br, J = 13 Hz, 1H), 1.79 (d, br, J = 13 Hz, 1H), 1.74–1.72 (m, 1H), 1.58–1.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.42, 168.06, 64.82, 42.82, 35.37, 30.26, 29.60, 24.55, 24.17.

4.1.16. 1-Hydroxy-1-methyloctahydroquinolizin-4-one (25). To a solution of **24** (89 mg, 0.5 mmol) in THF (5 mL) was added MeMgBr (3 M in THF, 0.27 mL, 0.8 mmol) at room temperature, and the mixture was stirred for 10 min. Water (10 mL) was added to the mixture and the aqueous solution was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 1/1) produced **25** (74 mg, 76%). The ^{1}H, ^{13}C NMR data was in accordance with the reported in the literature.[4a]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.001

References and notes

1. (a) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89–183. (b) Aguinaldo, A. M.; Read, R. W. *Phytochemistry* **1990**, *29*, 2309–2313. (c) Bolzani, V. das; Gunatilaka, A. A. L.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 5929–5934. (d) Astudillo, S. L.; Jurgens, S. K.; Schmeda Hirschmann, G.; Griffith, G. A.; Holt, D. H.; Jenkins, P. R. *Planta Med.* **1999**, *65*, 161. (e) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.(f) Daly, J. W.; Garrafo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, CA, 1993; p 85.
2. (a) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575. (b) Campbell, J. A.; Lee, W. K.; Rapoport *J. Org. Chem.* **1995**, *60*, 4602. (c) Toyooka, N.; Yoshida, Y.; Yotssui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914. (d) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281. (e) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401. (f) Enders, D.; Kirchhoff, J. H. *Synthesis* **2000**, 2099. (g) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (h) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun.* **1999**, 41. (i) Liao, L.-X.; Wang, Z.-M.; Zhang, H.-X.; Zhou, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649. (j) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (k) Folmer, J. J.; Carles Acero, D. L.; Thai, D. L. *J. Org. Chem.* **1998**, *63*, 8170. (l) Agami, C.; County, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783. (m) Agami, C.; County, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505. (n) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776. (o) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 7469. (p) Xu, Y.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 741. (q) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793. (r) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996**, *61*, 4882. (s) Yuasa, Y.; Ando, J.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1525. (t) Johnson, C. R.; Golebiowski, A.; Schoffers, E.; Sundram, H.; Braun, M. P.

Synlett **1995**, 313. (u) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715. (v) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099. (w) Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926.

3. Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
4. (a) Pilli, R. A.; Santo, L. S. *Tetrahedron Lett.* **2001**, *42*, 6999. (b) Aoyagi, S.; Hasegawa, Y.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149. (c) Kibayashi, C.; Aoyagi, S.; Wang, T. C.; Saito, K.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157.
5. (a) Chang, M. Y.; Chang, B. R.; Tai, H. M.; Chang, N. C. *Tetrahedron Lett.* **2000**, *41*, 10273. (b) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Tetrahedron* **2002**, *58*, 5075. (c) Chang, M. Y.; Lin, J. Y. C.; Chen, S. T.; Chang, N. C. *J. Chin. Chem. Soc.* **2002**, *49*, 1015. (d) Chang, M. Y.; Chen, C. Y.; Chen, S. T.; Chang, N. C. *Tetrahedron* **2003**, *59*, 7547.
6. Compound **7a** was recrystallized from ethyl acetate, and the X-ray crystallographic analysis succeeded in confirming the stereochemistry. CCDC 243915 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http:/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).
7. Chang, B. R.; Chen, C. Y.; Chang, N. C. *Tetrahedron Lett.* **2002**, *43*, 3233.
8. (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

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Z/E Stereoselective synthesis of β-bromo Baylis–Hillman ketones using $MgBr_2$ as promoter via a one-pot three-component reaction

Han-Xun Wei,* Richard L. Jasoni, Jiali Hu, Guigen Li and Paul W. Paré*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409, USA

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Abstract—The first time steroselective synthesis of (*Z*)-β-bromo Baylis–Hillman ketones has been achieved using a one-pot three-component reaction. The new system uses $MgBr_2$ as both the Lewis acidic promoter and the bromine source for the Michael-type addition with α,β-acetylenic ketones to form an active β-bromo allenolate intermediate, which in turn attacks various aldehydes to afford β-bromo Baylis–Hillman adducts in good yields and *Z*-selectivity.

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1. Introduction

The synthesis of multifunctionalized alkenes in stereoselective fashions is an important goal in organic chemistry.[1–4] Among these alkenes, the Baylis–Hillman adducts are particularly useful for serving as chemically and biologically important precursors.[5] The β-iodo Baylis–Hillman ketones were first synthesized by Kishi et al.[6] via a $TiCl_4$-promoted conjugative addition of tetrabutylammonium iodide ($(n\text{-Bu})_4NI$) to α,β-acetylenic ketones followed by electrophilic coupling with aldehydes. The *Z*/*E* selectivity of the products in this system is dependant on reaction temperature. At −78 °C, *Z* isomer products were the most abundant; however, at a temperature of 0 °C, the *E* isomer was exclusively produced.

Recently, we have developed several methods for the synthesis of β-halo Baylis–Hillman adducts,[7] which were based on using $TiCl_4$, $TiBr_4$, $TiCl_4/(n\text{-Bu})_4I$, Et_2AlI, MgI_2 and TMSI as halogen sources and promoters. The $TiCl_4$, $TiBr_4$, and $TiCl_4/(n\text{-Bu})_4NI$ systems were reacted at 0 °C and resulted in the *E* isomer being the major product, while the Et_2AlI, MgI_2 and TMSI system produced the *Z* isomer as the major product. Recently, Kataoka[8] and co-workers applied the chalogeno-Baylis–Hillman reaction to the synthesis of (*Z*)-β-halo Baylis–Hillman hydroxy ketones and esters. This reaction was performed at 0 °C in the presence of chalogenides such as 2,6-diphenylselenopyrin-4-one as a catalyst. A fairly large loading of α,β-acetylenic ketones (3 equiv) and electron deficient aldehydes are needed for this reaction. It was worthy to note that for synthesizing β-bromo Baylis–Hillman adducts, the reagent $TiBr_4$ mainly produces the *E*-isomer of the Baylis–Hillman adducts, with very little or no *Z*-isomer products detected in the reaction system.[7d,8,9] Because of these factors, a new methodology for synthesizing the *Z*-isomer of β-bromo Baylis–Hillman adducts is required. In our continuing development of new Baylis–Hillman-type processes, we are pleased to find that MgI_2 is an excellent Lewis acid for the synthesis of (*Z*)-β-iodo Baylis–Hillman hydroxy ketones and esters.[7a] Consequently, we tried to extend the scope of this reaction to determine if MgI_2 can be replaced by $MgBr_2$ as a Lewis acid for the synthesis of (*Z*)-β-bromo Baylis–Hillman hydroxy ketones and esters. Another reason to make this effort is because bromo Baylis–Hillman adducts are normally more easily handled and stable. For example, we have noted that the bromo Baylis–Hillman adducts can be stored at room temperature for as long as 2 months; while, iodo Baylis–Hillman adducts change to a red color at room temperature within 3 days. The present paper describes results that have led to a novel and simple method for the first time synthesis of (*Z*)-β-bromo Baylis–Hillman hydroxy ketones. This new procedure is represented in Scheme 1 with results summarized in Table 1.

The initial reaction was carried out by reacting 3-butyn-2-one (1.3 equiv) with benzaldehyde (1.0 equiv) in the presence of $MgBr_2$ (1.2 equiv) in CH_2Cl_2 at 0 °C as previously described.[7a] Unfortunately, the reaction did not go to completion even after a prolonged reaction time of 24 h, with less than 90% consumption of benzaldehyde.

Keywords: Baylis–Hillman adducts; Magnesium bromine; α,β-Acetylenic ketones; (*Z*)-β-Bromovinyl ketone.

* Corresponding authors. Tel.: +1 8046987291; fax: +1 8046987298 (H.-X.W.); e-mail: hwei@rdg.boehringer-ingelheim.com

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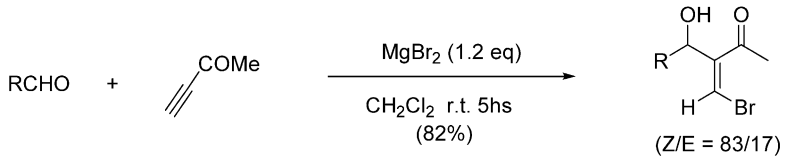
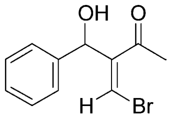
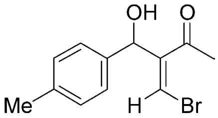
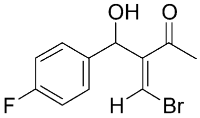
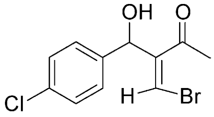
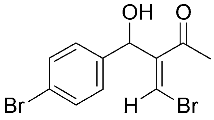
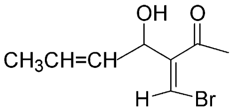
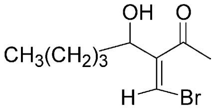
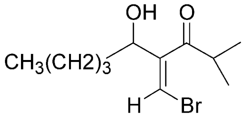
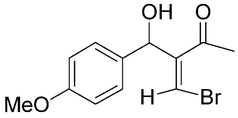
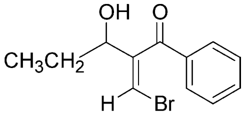


Scheme 1.

Table 1. Results of the $MgBr_2$-mediated reaction for synthesis of β-iodo Baylis–Hillman adducts

Entry	Substrate	Product	*Z/E* selectivity (%)[a]	Yield (%)[b,c]
1	Benzaldehyde	 **1**	87/13	82
2	4-*p*-Tolualdehyde	 **2**	86/14	74
3	4-Fluorobenzaldehyde	 **3**	85/15	86
4	4-Chlorobenzaldehyde	 **4**	82/18	86
5	4-Bromobenzaldehyde	 **5**	82/18	85
6	Crotonaldehyde	 **6**	82/18	84
7	*n*-Valeraldehyde	 **7**	71/29	68[d]
8	*n*-Valeraldehyde	 **8**	63/37	74[d,e]
9	*p*-Anisaldehyde	 **9**	86/14	55[e]
10	Propionaldehyde	 **10**	70/30	67[d,f]

[a] *Z/E* selectivity was estimated by crude ^1H NMR determination.

[b] Yields after purification by column chromatography.

[c] Unless otherwise noted, reactions were carried out at room temperature for 5 h.

[d] Two isomers were inseparable.

[e] Reaction for 20 h.

[f] Reaction for 10 h.

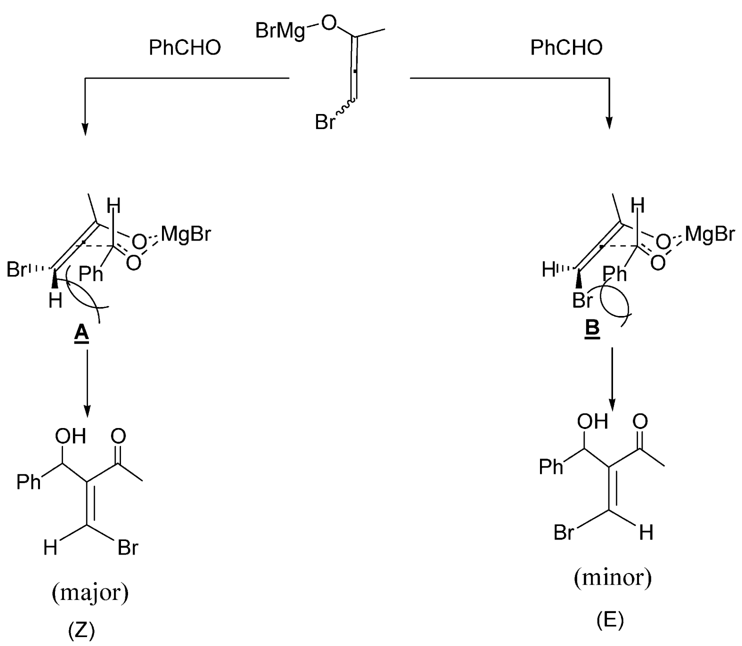
However, after raising the reaction temperature to room temperature, the reaction went to completion within 5 h and gave the desired product of β-bromo Baylis–Hillman ketones in 82% yield with a *Z*/*E* selectivity ratio of 87:13, which was based on crude ^{1}H NMR analysis. Unlike our previous MgI_2-based system,[7a] in which the reaction required mixing benzaldehyde and MgI_2 in CH_2Cl_2 at room temperature for 20 min before adding the 3-butyn-2-one, this new synthesis can be conveniently conducted by mixing three components; $MgBr_2$, aldehydes and α,β-acetylenic ketones together in a dichloromethane solution. Also, the present reaction needs a longer time to proceed to completion than the MgI_2-based process. This is due to the fact that $MgBr_2$ is a relatively weaker Lewis acid and less reactive toward α,β-acetylenic ketone for the Michael-type addition. Competition experiments also demonstrated that only MgI_2 could react with methyl propynoate for the Michael-type addition while $MgBr_2$ cannot do so.

Dichloromethane provided the highest efficiency among the solvents tested in terms of yield and *Z*/*E* selectivity when using benzaldehyde as the electrophilic acceptor. Diethyl ether, benzene and toluene gave rise to a lower yield of 50, 45 and 40% within a 5-h reaction period, respectively. However, all the above solvents gave nearly the same *Z*/*E* selectivity. It is worthy to note that a 50% yield of desired product was obtained when THF was employed as the solvent, which is different from the MgI_2-based process that results in a very low yield (<10%) of desired product when THF is used as the solvent. Both aromatic and aliphatic acetylenic ketones were successfully employed as Michael-type acceptors to generate MgBr-allenolates, although ethynyl phenyl ketone and ethynyl isopropyl ketone need a longer time to proceed to completion than 3-butyn-2-one due to the large steric factor of phenyl and isopropyl groups (entries 8 and 10). In addition, aromatic and aliphatic aldehydes were suitable electrophilic acceptors in the new reaction system and good yields were realized for all examples that were investigated. As shown in Table 1, for aromatic aldehydes having electron-withdrawing groups, as expected, the reaction proceeded at a faster rate and gave higher yields than the aldehydes having a substitution of an electron-donating group. For example, the aldehydes bearing F, Cl and Br as electron-withdrawing groups (entries 3–5, Table 1), the reactions will go to completion within 5 h with high yield; however, the aldehydes having an electron-donating group resulted in a much lower reaction rate (20 h for entry 9, Table 1) and low yield (74% for entry 2, Table 1). With regard to aliphatic aldehydes (entries 6–8 and 10), the products have lower *Z*/*E* selectivity and yields than that of aromatic aldehydes; however, the products were predominantly produced in *Z* configuration.

Table 2. ^{1}H NMR chemical shifts for the terminal olefin proton signals for *Z* and *E* isomers

Products	*Z*-isomer	*E*-isomer
1	6.60	7.74
2	6.59	7.70
3	6.67	7.78
4	6.67	7.75
5	6.67	7.77
6	6.62	7.55
7	6.61	7.54
8	6.61	7.51
9	6.63	7.72
10	6.71	6.83

The *Z*/*E* selectivities listed in Table 1 were measured by ^{1}H NMR analysis of crude products. In all cases, the terminal olefin proton signals for *Z* and *E* isomers were clearly distinguishable with the proton for the *Z* isomer upfield relative to the proton for the *E*-isomer (Table 2). Isomers could be readily separated by flash chromatography and the geometry was determined by the comparison of ^{1}H NMR data of adduct **1** in Table 1 with our previous ^{1}H NMR data of the same product.[7d]



Scheme 2.

To explain the high *Z*/*E* stereoselectivity of this new system, a cyclic transition state model proposed by Kishi can be invoked.[6] In their system, not only was the (n-Bu)$_4$NI/TiCl$_4$ combination employed but they also used Et$_2$AlI and TiI$_4$ for the reaction. The exclusive *Z*-stereoselectivity of β-iodo Baylis–Hillman ketones was obtained at −78 °C, while the high *E*-stereoselectivity was observed at 0 °C. By using a cyclic transition state model, they suggested the *Z*-stereoisomer was the kinetically controlled product, while the *E*-stereoisomer was the thermodynamically controlled product. In the system we report here, the *Z*-isomer was favored under all reaction conditions tested. These results suggest that the kinetic control plays a significant role in determining the geometric selectivity at room temperature (Scheme 2). Also, from Scheme 2, because of the smaller steric effect of bromine in comparison to that of iodine, now we can easily explain why the bromo Baylis–Hillman adducts have a relatively lower *Z*/*E* selectivity than those of β-iodo Baylis–Hillman adducts.

In summary, this new procedure provides the first example of the efficient synthetic method for (*Z*)-β-bromo Baylis–Hillman ketones. Compared to TiBr$_4$-based systems, our new process gives much higher yields of desired products. The new protocol utilizes MgBr$_2$ as the bromine anion sources, and concurrently as a Lewis acid promoter under relatively mild conditions. This new reaction system offers an extensive functionlization of vinyl ketones with good chemical yields and geometric selectivity.

2. Experimental

2.1. General methods

All reactions were conducted at room temperature in a flask (10.0 mL) with magnetic stirring. Dichloromethane was dried and freshly distilled from calcium hydride under a nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometrics were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Infrared spectra (IR) were recorded on a HYPER IR (SHIMADZU) FTIR-8400 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 500 MHz NMR spectrometer. ^{13}C NMR spectra were recorded at 125 MHz using CDCl$_3$ as the solvent and the internal reference. Chemical shifts are given in ppm from tetramethylsilane. Mass spectra were recorded with a JEOL JMS-D300 mass spectrometer using direct inlet electron impact ionization (70 eV). The Mass Spectroscopy Laboratory at the University of Texas at Austin conducted high-resolution mass spectral analysis.

2.2. Typical procedure

Typical procedure: (Table 1, entry 1). A dry standard glass test tube (150×22 mm^2) with a magnetic stirring bar was flushed with nitrogen at room temperature. Magnesium bromide (225 mg, 1.2 mmol), benzaldehyde (0.1 mL, 1.0 mmol, 3-butyn-2-one (1.3 equiv) and freshly distilled dichloromethane (8.0 mL) were added to the glass test tube. The suspension mixture was stirred at room temperature for 5 h before turning to a dark brown homogenous solution. The reaction was quenched by drop-wise addition of 10% aqueous NaHCO$_3$ (3 mL). The resulting two phases were separated, and the aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic layers were then washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 5:1, v/v) to provide products **1***Z* (182.0 mg) and **1***E* (35.5 mg) as colorless oils (82% combined yield).

2.2.1. Compound 1Z. 208 mg, 82%, colorless oil. IR (CHCl$_3$) ν 1671 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.29 (s, 3H), 3.17 (d, J=5.0 Hz, 1H), 5.45 (d, J=5.0 Hz, 1H), 6.60 (d, J=1.5 Hz, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 30.1, 75.6, 109.4, 126.4×2, 128.3, 128.7×2, 139.7, 148.1, 203.1. MS (CI, CH$_4$): m/z (%) 255 [M]$^+$; HRMS calcd for 253.9942; found: 253.9954. **1***E*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.31 (s, 3H), 4.42 (d, J=11.0 Hz, OH), 5.93 (d, J=11.0 Hz, 1H), 7.28–7.40 (m, 5H), 7.74 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 27.3, 73.1, 125.1, 126.7, 127.4, 128.4, 141.2, 145.9, 197.9.

2.2.2. Compound 2Z. 198 mg, 74%, colorless oil. IR (CHCl$_3$) ν 1668 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.29 (s, 3H), 2.33 (s, 3H), 2.99 (d, J=5.0 Hz, OH), 5.42 (d, J=5.0 Hz, 1H), 6.59 (d, J=1.5 Hz), 7.14–7.22 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 21.1, 31.1, 75.4, 109.1, 126.4×2, 129.3, 136.8, 138.1, 148.3, 203.1. MS (CI, CH$_4$): m/z (%) 269 [M]$^+$; HRMS calcd for 268.0099; found: 268.0108. **2***E*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.26 (s, 3H), 2.32 (s, 3H), 4.48 (d, J=11.0 Hz, OH), 5.88 (d, J=11.0 Hz, 1H), 7.08–7.30 (m, 4H), 7.70 (s, 1H).

2.2.3. Compound 3Z. 233 mg, 86%; colorless oil. IR (CHCl$_3$) ν 1666 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.34 (s, 3H), 3.01 (d, J=5.0 Hz, OH), 5.48 (d, J=5.0 Hz, 1H), 6.67 (d, J=1.5 Hz, 1H), 7.05 (m, 2H), 7.29 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 31.2, 75.1, 110.2, 115.5, 115.7, 128.1, 128.2, 135.6, 147.7, 161.6, 202.7. MS (CI, CH$_4$): m/z (%) 273 [M]$^+$; HRMS calcd for 271.9848; found: 271.9851. **3***E*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.35 (s, 3H), 4.57 (d, J=11.0 Hz, OH), 5.87 (d, J=11.0 Hz, 1H), 7.01 (m, 2H), 7.30 (m, 2H), 7.78 (s, 1H).

2.2.4. Compound 4Z. 247 mg, 86%; colorless oil. IR (CHCl$_3$) ν 1666 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.34 (s, 3H), 3.26 (d, J=5.0 Hz, 1H), 5.44 (d, J=5.0 Hz, 1H), 6.67 (d, J=1.5 Hz, 1H), 7.24–7.34 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 31.2, 75.0, 110.6, 127.7×2, 128.8×2, 134.1, 138.4, 147.5, 202.7. MS (CI, CH$_4$): m/z (%) 289 [M]$^+$; HRMS calcd for 287.9553; found: 287.9564. **4***E*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.33 (s, 3H), 4.37 (d, J=11.5 Hz, OH), 5.88 (d, J=11.2 Hz, 1H), 7.28–7.32 (m, 4H), 7.75 (s, 1H).

2.2.5. Compound 5Z. 281 mg, 85%; colorless oil. IR (CHCl$_3$) ν 1667 cm^{-1} (C=O); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.34 (s, 3H), 3.20 (d, J=5.0 Hz, 1H), 5.44 (d, J=5.0 Hz, 1H), 6.67 (d, J=1.5 Hz, 1H), 7.20 (m, 2H), 7.47 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 31.3, 75.1, 110.8, 122.2, 128.1×2, 131.8×2, 138.9, 147.4, 202.7. MS (CI,

CH_4): *m*/*z* (%) 333 $[M]^+$; HRMS calcd for 331.9048; found: 331.9052. **5*E***: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 4.51 (d, $J=11.5$ Hz, OH), 5.82 (d, $J=11.2$ Hz, 1H), 7.22 (m, 2H), 7.42 (m, 2H), 7.77 (s, 1H).

2.2.6. Compound 6*Z*. 183 mg, 84%; yellowish oil. IR ($CHCl_3$) ν 1678 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (d, $J=10.0$ Hz, 3H), 2.47 (s, 3H), 3.12 (d, $J=5.1$ Hz, OH), 4.83 (m, 1H), 5.50 (m, 1H), 5.78 (m, 1H), 6.62 (d, $J=1.5$ Hz, 1H). MS (CI, CH_4): *m*/*z* (%) 219 $[M]^+$; HRMS calcd for 217.9942; found: 217.9948. **6*E***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (d, $J=10.0$ Hz, 3H), 2.42 (s, 3H), 3.86 (d, $J=10.5$ Hz, OH), 5.17 (m, 1H), 5.62 (m, 1H), 5.73 (m, 1H), 7.55 (s, 1H).

2.2.7. Compound 7. 160 mg, 68%; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) for *Z* isomer δ 2.49 (s, 3H), 3.08 (d, $J=5.0$ Hz, OH), 4.32 (m, 1H), 6.61 (s, 1H), other resonances could not be discerned from *E* isomer; ^{1}H NMR (300 MHz, $CDCl_3$) for *E* isomer δ 2.35 (s, 3H), 3.72 (d, $J=11.2$ Hz, OH), 4.69 (m, 1H), 7.54 (s, 1H), other resonances could not be discerned from *Z* isomer.

2.2.8. Compound 8. 195 mg, 74%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) for *Z* isomer δ 2.93 (d, $J=5.1$ Hz, OH), 3.26 (m, 1H), 4.31 (m, 1H), 6.61 (s, 1H), other resonances could not be discerned from *E* isomer; ^{1}H NMR (300 MHz, $CDCl_3$) for *E* isomer δ 3.15 (m, 1H), 3.72 (d, $J=11.0$ Hz, OH), 4.71 (m, 1H), 7.51 (s, 1H), other resonances could not be discerned from *Z* isomer.

2.2.9. Compound 9*Z*. 156 mg, 55%; colorless oil. IR ($CHCl_3$) ν 1680 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.72 (s, 3H), 4.95 (d, $J=5.0$ Hz, 1H), 6.63 (d, $J=1.5$ Hz, 1H), 7.02 (m, 2H), 7.22 (m, 2H). MS (CI, CH_4): *m*/*z* (%) 285 $[M]^+$; HRMS calcd for 284.0048; found: 284.0053.

2.2.10. Compound 10. 180 mg, 67%; yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) for *Z* isomer δ 1.61 (m, 2H), 2.54 (d, $J=5.2$ Hz, OH), 4.38 (m, 1H), 6.71 (s, 1H), other resonances could not be discerned from *E* isomer; ^{1}H NMR (300 MHz, $CDCl_3$) for *E* isomer δ 1.83 (m, 2H), 3.55 (d, $J=11.2$ Hz, OH), 4.79 (m, 1H), 6.83 (s, 1H), other resonances could not be discerned from *Z* isomer.

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References and notes

1. Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 139–168.
2. (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988. (b) Trost, B. M.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 360.
3. Wori, M.; Kuroda, S.; Dekura, F. *J. Am. Chem. Soc.* **1999**, *121*, 5591.
4. Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821.
5. For reviews regarding the Baylis–Hillman reaction see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
6. (a) Taniguchi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *34*, 4763. (b) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *39*, 4767.
7. (a) Wei, H.-X.; Hu, J. L.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949. (b) Deng, G.-H.; Wei, H.-X.; Paré, P. W. *Helv. Chim. Acta* **2003**, *86*, 3510. (c) Wei, H.-X.; Gao, J. J.; Li, G.; Paré, P. W. *Tetrahedron Lett.* **2002**, *43*, 5677. (d) Li, G.; Wei, H.-X.; Gao, J. J.; Johnson, J. *Synth. Commun.* **2002**, *32*, 1765. (e) Wei, H.-X.; Gao, J. J.; Li, G. *Tetrahedron Lett.* **2001**, *42*, 9119. (f) Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823. (g) Wei, H.-X.; Kim, S. H.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397.
8. Kataoka, T.; Kinoshita, S.; Iwamura, T.; Watanable, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358.
9. (a) Shi, M.; Wang, C.-J. *Tetrahedron* **2002**, *58*, 9063. (b) Shi, M.; Wang, C.-J. *Helv. Chim. Acta* **2002**, *85*, 84.

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Sequential alkynylation of ω-bromoalkyl triflates: facile access to unsymmetrical non-conjugated diynes including precursors to diene pheromones

Rosemary J. Armstrong-Chong, Kristopher Matthews and J. Michael Chong*

Department of Chemistry, University of Waterloo, 200 University Ave W, Waterloo, Ont., Canada N2L 3G1

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Abstract—Sequential treatment of ω-bromoalkyl triflates with an alkynyllithium at 0 °C followed by addition of a second alkynyllithium and NaI and heating the reaction mixture provides a simple one-pot access to unsymmetrical diynes in good yields. These diynes may be transformed stereoselectively into diene pheromones such as (*Z*,*Z*)- and (*E*,*Z*)-3,13-octadecadienyl acetate.

1. Introduction

There are many insect pheromones which contain non-conjugated dienes as part of their structures.[1] In principle, the corresponding diynes could serve as synthetic intermediates to many of these compounds by taking advantage of well-established stereoselective reduction methods (e.g., semi-hydrogenation over Lindlar-type catalysts or P-2 Ni to prepare *Z* alkenes[2] or Li/NH_3 reductions to produce *E* alkenes[3]). Chemoselective reductions could be achieved using proximity effects such as hydroaluminations of propargyl and homopropargylic alcohols.[4]

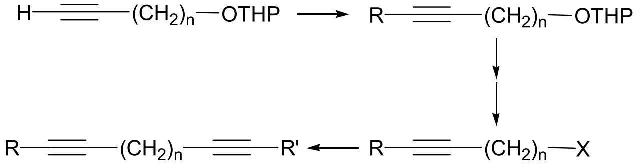
In the past, unsymmetrical diynes have been typically prepared using protecting group chemistry. Thus one might first prepare a THP-protected alkynyl alcohol, alkylate the alkyne, deprotect the alcohol, convert it to a halide, and then alkynylate that alkyl halide (Scheme 1).[5]

A more expeditious route to such diynes would be to sequentially alkynylate difunctional linkers containing leaving groups of widely differing electrofugality (Scheme 2). We now report that this simple approach to unsymmetrical diynes may be implemented in a one-pot procedure using ω-bromotriflates.

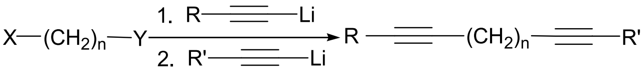
2. Results and discussions

Previous attempts to chemoselectively monoalkynylate chloroiodoalkanes have met with limited success, with variable yields.[6,7] Since iodide is a much better leaving group than chloride, one might expect that selective reaction should be possible. However, the iodide ion formed can participate in Finkelstein reactions generating more reactive alkyl iodides from chlorides. In fact, we have recently shown that bromoalkanes react with alkynyllithiums in THF in the presence of iodide ion but only very slowly in the absence of iodide.[8] This suggests that suppression of Finkelstein reactions is necessary to minimize dialkynylation.

The use of triflates should circumvent any problems with Finkelstein reactions. Alkynylation of alkyl triflates with alkynyllithiums is known to occur under relatively mild



Scheme 1.



Scheme 2.

Keywords: Alkynyllithium; Alkynylation; Diyne; Bromotriflate; Diene pheromone.

* Corresponding author. Tel.: +1-519-888-4567x6643; fax: +1-519-746-0435; e-mail: jmchong@uwaterloo.ca

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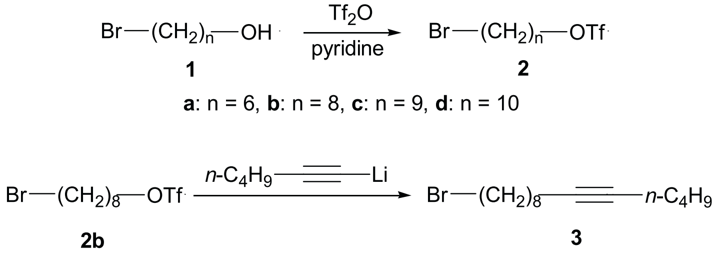


Scheme 3.

conditions.[9] The triflate ion formed, unlike iodide ion, is unlikely to react as a nucleophile. In addition, the selective alkynylation of a primary triflate in the presence of a primary tosylate has previously been demonstrated.[10] As ω-bromoalkanols are readily available,[11] it seemed that the derived ω-bromoalkyl triflates might be good candidates for sequential dialkynylation.

Our initial investigations centered on bromotriflate **2b** which was easily prepared from 8-bromooctanol (Scheme 3; Tf_2O, py, CH_2Cl_2). Treatment of **2b** with 1-hexynyllithium at 0 °C for 1 h in THF lead to the clean formation of the expected alkynyl bromide **3** (91% isolated yield). There was no evidence (GCMS analysis using an authentic sample) of the possible diyne derived from displacement of both the triflate and bromide groups even when 2 equiv of alkynyllithium were used. It was not surprising that there was a large difference in reactivity between the triflate and bromide in **2b** since it is known that triflates can react 10^7 times faster than bromides.[12]

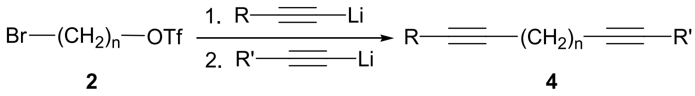
With the monoalkynylation established, we examined the sequential dialkynylation reaction. It has been shown that alkylation of alkynyllithiums with alkyl bromides proceeds well in THF at reflux temperatures if a catalytic amount of NaI or n-Bu_4NI is added.[8] Since the alkynylation of triflates is also run in THF but at 0 °C, development of a sequential reaction was relatively simple. Thus the bromotriflate of interest in THF was treated initially with an alkynyllithium at 0 °C and then a second alkynyllithium was added along with 10 mol% NaI and the reaction mixture was heated to reflux. The desired unsymmetrical diynes were isolated in good yields (Table 1).

The bromotriflates could be isolated and purified but were somewhat unstable and showed some decomposition upon column chromatography. Isolated yields of crude triflates were near quantitative but purified material could only be obtained in ∼70% yields. Thus triflates were prepared immediately before use and not purified before alkynylation. The yields in Table 1 are only modest in some cases but are quite respectable considering that they are based on bromoalcohol precursors and represent the overall purified yields of products after triflation and two alkynylations. Since many ω-bromoalcohols are commercially available or easily prepared in quantity by treatment of diols with HBr in toluene,[11] this sequence represents a very quick and reasonably efficient route to many unsymmetrical diynes.

Control experiments were run to determine whether higher yields could be obtained by carrying out the sequential dialkynylation with isolation of the alkynylbromide intermediate. In the cases examined, similar or only slightly higher overall yields were obtained when the intermediate alkynylbromide was isolated and purified. For example, yields for the production of **4c** by the 2-step procedure were 78 and 79% for an overall yield of 62%. This is comparable to that obtained in the one-pot reaction (Table 1, entry 3). In practice, it is more convenient to prepare the desired diynes without isolation of intermediates. Of course, the intermediate bromides could serve as useful alkylating agents for other transformations as well.

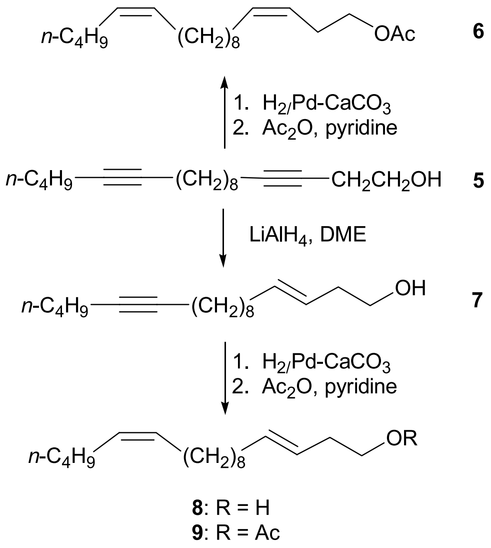
To illustrate a possible use of these diynes, **4d** was converted into (3*E*,13*Z*)-3,13-octadecadienyl acetate and (3*Z*,13*Z*)-3,13-octadecadienyl acetate, both of which are components of the cherrytree borer pheromone[13] (Scheme 4). The *E*,*Z* isomer (or its alcohol) is also a component of many other lepidopteran pheromone blends.[7a] Removal of the THP group in **4d** was readily accomplished (PPTS, EtOH, 99%) to furnish the diynol **5**. Semi-hydrogenation of

Table 1. One-pot preparation of unsymmetrical diynes



Entry	R	R′	*n*	Product (% yield)[a]
1	CH_2OTHP	n-C_6H_{13}	6	**4a** (62)
2	$(CH_2)_2OTHP$	n-C_4H_9	6	**4b** (70)
3	CH_2OTHP	n-C_4H_9	8	**4c** (55)
4	$(CH_2)_2OTHP$	n-C_4H_9	8	**4d** (58)
5	$(CH_2)_2OTHP$	n-C_6H_{13}	8	**4e** (75)
6	$(CH_2)_2OTHP$	n-C_8H_{17}	8	**4f** (78)
7	CH_2OTHP	n-C_4H_9	9	**4g** (67)
8	$(CH_2)_2OTHP$	n-C_4H_9	10	**4h** (73)

[a] Isolated yield of purified **4**.



Scheme 4.

5 (H_2, Pd/$CaCO_3$) followed by acetylation gave the *Z*,*Z*-isomer **6** (90% yield, 2 steps) with no surprises.

In the hydroalumination of **5**, it was expected that the isolated Δ13 triple bond would not be reduced.[4a] However, prolonged heating of **5** with $LiAlH_4$ (diglyme, 120 °C, 40 h), conditions previously used to affect reductions of homopropargylic alcohols,[14] gave mixtures of the desired enyne **7** and a diene (which, based on GCMS and ^{13}C NMR evidence, likely has *E*,*E*-stereochemistry). Fortunately, formation of this diene could be effectively suppressed by carrying out the reaction at lower temperatures (refluxing DME) for shorter times (18 h). This procedure followed by acetylation and semi-hydrogenation furnished the 3*E*,13*Z*-isomer **9** in 88% overall yield, 3 steps.

3. Conclusions

In summary, we have developed a very convenient route to unsymmetrical diynes which takes advantage of the vastly different reactivities of alkyl triflates and bromides with alkynyllithiums. A wide variety of diynes (and hence the corresponding dienes) should be accessible using this chemistry.

4. Experimental

4.1. General

All reactions were carried out under argon using flame-dried glassware. NMR data were recorded on a 300 MHz instrument in $CDCl_3$ unless otherwise noted. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. THF was freshly distilled from Na/benzophenone. Dichloromethane and pyridine were distilled from CaH_2. Reagents were purchased from Aldrich Chemical Co. and used without further purification. *n*-BuLi was titrated using *N*-benzylbenzamide before use.[15] Silica gel 60 (40–63 μm) from EM Science was used for flash chromatography. Bromoalcohols were prepared from the corresponding diols.[11]

4.2. General procedure A: preparation of bromotriflates from bromoalcohols

To a cold (−15 °C), stirred solution of bromoalcohol **1** in CH_2Cl_2 (4 mL/mmol) was added pyridine (1.0 equiv) followed by triflic anhydride (1.2 equiv). The reaction was stirred at 0 °C for 1 h then diluted with hexanes (2× volume of CH_2Cl_2) and filtered through a Celite pad. Concentration of the filtrate and removal of volatiles (0.1 mmHg, 30 min) afforded crude triflates which could be used directly for alkynylations. The crude materials could be further purified by filtration through a short column of silica gel using hexanes as eluent.

4.2.1. 1-Trifluoromethanesulfonyloxy-6-bromohexane (2a). This compound was prepared from 6-bromo-1-hexanol using General procedure A (Section 4.2) in 68% yield after purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (2H, t, $J=6.3$ Hz), 3.40 (2H, t, $J=6.7$ Hz), 1.92–1.77(4H, m), 1.55–1.40 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.58 (q, $J_{C\text{–}F}=320$ Hz), 77.36, 33.30, 32.27, 29.00, 27.31, 24.25; IR (neat) 1413, 1248, 1207, 1146, 936 cm^{-1}; MS (EI) *m/z* 232 (1), 83 (60), 55 (100).

4.2.2. 1-Trifluoromethanesulfonyloxy-8-bromooctane (2b). This compound was prepared from 8-bromo-1-octanol using General procedure A (Section 4.2) in 70% yield after purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (2H, t, $J=6.3$ Hz), 3.39 (2H, t, $J=6.7$ Hz), 1.90–1.77 (4H, m), 1.52–1.28 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.61 (q, $J_{C\text{–}F}=319$ Hz), 77.61, 33.73, 32.60, 29.12, 28.60, 28.39, 27.89, 24.91; IR (neat) 1413, 1247, 1208, 1146, 934 cm^{-1}; MS (EI) *m/z* 260 (1), 69 (100), 55 (55).

4.2.3. 1-Trifluoromethanesulfonyloxy-9-bromononane (2c). This compound was prepared from 9-bromo-1-nonanol using General procedure A (Section 4.2) in 83% yield after purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (2H, t, $J=6.3$ Hz), 3.39 (2H, t, $J=6.7$ Hz), 1.92–1.77 (4H, m), 1.55–1.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.63 (q, $J_{C\text{–}F}=319$ Hz), 77.64, 33.85, 32.69, 29.16, 29.09, 28.68, 28.51, 28.01, 24.97; IR (neat) 1413, 1247, 1210, 1147, 934 cm^{-1}; MS (EI) *m/z* 274 (1), 135 (15), 83 (35), 69 (100).

4.2.4. 1-Trifluoromethanesulfonyloxy-10-bromodecane (2d). This compound was prepared from 10-bromo-1-decanol using General procedure A (Section 4.2) in 70% yield after purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (2H, t, $J=6.3$ Hz), 3.39 (2H, t, $J=6.7$ Hz), 1.92–1.78 (4H, m), 1.50–1.28 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.62 (q, $J_{C\text{–}F}=319$ Hz), 77.68, 33.88, 32.73, 29.16, 29.15, 29.12, 28.73, 28.60, 28.05, 24.97; IR (neat) 1414, 1247, 1208, 1147, 935 cm^{-1}; MS (EI) *m/z* 288 (1), 135 (18), 97 (29), 83 (48), 69 (84), 55 (100).

4.2.5. 1-Bromotetradec-9-yne (3). To a cold (0 °C), stirred solution of 1-hexyne (130 μL, 1.1 mmol) in dry THF (5 mL) was added *n*-BuLi (0.63 mL, 1.60 M in hexanes, 1.0 mmol). The solution was stirred at 0 °C then cooled to −78 °C. Bromotriflate **1a** (338 mg, 0.99 mmol) was slowly added and the reaction mixture was stirred at −78 °C for 5 min then at 0 °C for 1 h. Standard aqueous work-up using ether and satd aqueous NH$_4$Cl provided crude material which was purified by flash chromatography on silica gel (15 g) using hexanes as eluent to provide 250 mg (91%) of the known[16] alkyne **3** as a colorless liquid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.39 (2H, t, J=7 Hz), 2.12 (4H, m), 1.83 (2H, quintet, J=7 Hz), 1.5–1.2 (14H, m), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 80.07, 79.90, 33.77, 32.71, 31.17, 28.98, 28.85, 28.59, 28.58, 28.02, 21.83, 18.61, 18.33, 13.54; MS (EI) m/z 272 (M^{+}, ^{79}Br, 0.1), 215 (3), 95 (59), 81 (100), 67 (84).

4.3. General procedure B: sequential dialkynylation of bromotriflates

To a cold (−78 °C), stirred solution of propargyl alcohol THP ether or 3-butyn-1-ol THP ether in THF (3 mL/mmol) was added *n*-BuLi (1.6 M in hexanes, 1.0 equiv). The solution was stirred at 0 °C for 15 min then cooled to −78 °C and a THF solution (2 mL/mmol) of bromotriflate **2** (1.0 equiv, crude material prepared according to General procedure A (Section 4.2)) was slowly added. The mixture was stirred at 0 °C for 1 h to generate the intermediate bromoalkyne. A THF solution (2 mL/mmol) of an alkynyllithium (freshly prepared from a terminal alkyne and *n*-BuLi, −78 °C→0 °C, 15 min, 2.0 equiv) and NaI (10–20 mol%) were then added and the mixture was heated at reflux for 16–30 h (monitor by TLC). After cooling to rt, standard extractive workup (ether/aq NH$_4$Cl then brine) afforded crude materials which were purified by flash chromatography on silica gel using 3–5% ether in hexanes as eluent to yield the desired diynes as colorless oils.

4.3.1. 1-Tetrahydropyranyloxy-2,10-heptadecadiyne (4a). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1a** in 62% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.77 (1H, t, J=3 Hz), 4.20 (2H, AB of ABX$_2$, $\Delta\nu$=25.6 Hz, J_{AB}=15.2 Hz, J_{AX}=J_{BX}=2 Hz), 3.86–3.74 (1H, m), 3.51–3.41 (1H, m), 2.20–2.07 (6H, m), 1.88–1.25 (22H, m), 0.85 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 96.44, 86.43, 80.19, 79.85, 75.68, 61.79, 54.47, 31.27, 30.18, 29.01, 28.88, 28.42, 28.38, 28.27, 28.19, 25.29, 22.47, 19.01, 18.66, 18.63, 18.58, 13.94; IR (neat) 1480, 1110, 1040, 1020 cm^{-1}; MS (EI) m/z 247 (M^{+}−THP, 11), 85 (100), 67 (40), 55 (38). Anal. Calcd for C$_{22}$H$_{36}$O$_2$: C, 79.46; H, 10.91. Found: C, 79.61; H, 10.97.

4.3.2. 1-Tetrahydropyranyloxy-3,11-octadecadiyne (4b). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1a** in 70% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.62 (1H, t, J=3 Hz), 3.90–3.73 (2H, m), 3.54–3.44 (2H, m), 2.45 (2H, tt, J=7, 3 Hz), 2.12 (6H, br t, J=7 Hz), 1.88–1.36 (18H, m), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 98.52, 81.05, 80.07, 79.87, 76.66, 66.08, 61.95, 31.13, 30.45, 28.90, 28.75, 28.22, 25.35, 21.80, 20.10, 19.28, 18.59, 18.57, 18.30, 13.50; IR (neat) 1137, 1122, 1070, 1034 cm^{-1}; MS (EI) m/z 85 (100), 67 (15), 55 (13). Anal. Calcd for C$_{21}$H$_{34}$O$_2$: C, 79.19; H, 10.76. Found: C, 79.36; H, 10.67.

4.3.3. 1-Tetrahydropyranyloxy-2,12-heptadecadiyne (4c). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1b** in 55% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.78 (1H, t, J=3 Hz), 4.21 (2H, AB of ABX$_2$, $\Delta\nu$=25.9 Hz, J_{AB}=15.2 Hz, J_{AX}=J_{BX}=2 Hz), 3.87–3.77 (1H, m), 3.53–3.46 (1H, m), 2.23–2.10 (6H, m), 1.85–1.20 (22H, m), 0.87 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 96.50, 86.62, 80.09, 80.04, 75,64, 61.86, 54.54, 31.18, 30.21, 29.05, 28.95 (2C), 28.74, 28.71, 28.51, 25.32, 21.85, 19.03, 18.73, 18.65, 18.36, 13.56; IR (neat) 1132, 1118, 1025 cm^{-1}; MS (EI) m/z 247 (M^{+}−THP, 1), 85 (100), 67 (59), 55 (72). Anal. Calcd for C$_{22}$H$_{36}$O$_2$: C, 79.46; H, 10.91. Found: C, 79.60; H, 10.85.

4.3.4. 1-Tetrahydropyranyloxy-3,13-octadecadiyne (4d). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1b** in 58% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.61 (1H, t, J=3 Hz), 3.91–3.72 (2H, m), 3.51–3.42 (2H, m), 2.12–2.05 (6H, m), 1.81–1.23 (22H, m), 0.87 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 98.54. 81.17, 80.03, 80.00, 76.61, 66.11, 61.97, 31.16, 30.47, 29.03, 28.96, 28.93, 28.87, 28.70, 28.68, 25.38, 21.81, 20.12, 19.30, 18.62 (2C), 18.32, 13.52; IR (neat) 1130, 1110, 1070, 1040 cm^{-1}; MS (EI) m/z 85 (100), 67 (20), 55 (20). Anal. Calcd for C$_{23}$H$_{38}$O$_2$: C, 79.71; H, 11.05. Found: C, 79.90; H, 10.86.

4.3.5. 1-Tetrahydropyranyloxy-3,13-icosadiyne (4e). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1b** in 75% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.61 (1H, t, J=3 Hz), 3.90–3.69 (2H, m), 3.51–3.42 (2H, m), 2.46–2.36 (2H, m), 2.10 (6H, br t, J=7 Hz), 1.82–1.22 (26H, m), 0.85 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 98.54, 81.18, 80.11, 80.02, 76.61, 66.12, 61.98, 31.29, 30.48, 29.04, 28.98, 28.96, 28.88, 28.72, 28.70, 28.44, 25.37, 22.49, 20.13, 19.31, 18.65, 18.64, 13.96; IR (neat) 1130, 1110, 1060, 1030 cm^{-1}; MS (EI) m/z 289 (M^{+}−THP, 0.3), 85 (100), 67 (20), 55 (23). Anal. Calcd for C$_{25}$H$_{42}$O$_2$: C, 80.16; H, 11.30. Found: C, 80.18; H, 11.05.

4.3.6. 1-Tetrahydropyranyloxy-3,13-docosadiyne (4f). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1b** in 78% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.61 (1H, t, J=3 Hz), 3.90–3.70 (2H, m), 3.52–3.42 (2H, m), 2.40 (2H, br t, J=7 Hz), 2.09 (6H, br t, J=7 Hz), 1.82–1.23 (30H, m), 0.84 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 98.57, 81.20, 80.14, 80.05, 76.63, 66.14, 62.01, 31.78, 30.50, 29.16, 29.09, 29.07, 29.00, 28.98, 28.90, 28.80, 28.75, 28.73, 25.39, 22.60, 20.15, 19.33, 18.67, 18.65, 14.03; IR (neat) 1130, 1110, 1070, 1030 cm^{-1}; MS (EI) m/z 85 (100), 67 (24), 55 (20). Anal. Calcd for C$_{27}$H$_{46}$O$_2$: C, 80.54; H, 11.51. Found: C, 80.22; H, 11.13.

4.3.7. 1-Tetrahydropyranyloxy-2,13-octadecadiyne (4g). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1c** in 67% yield after purification. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.76 (1H, t, J=3 Hz), 4.18 (2H, AB of ABX$_2$, $\Delta\nu$=24.2 Hz, J_{AB}=15.2 Hz, J_{AX}=J_{BX}=2 Hz), 3.82–3.73 (1H, m), 3.49–3.41 (1H, m), 2.18–2.07 (6H, m), 1.82–1.22 (24H, m), 0.84 (3H, t, J=7 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 96.39, 86.51, 79.97 (2C), 75.60, 61.76, 54.45, 31.14, 30.16, 29.27, 29.01, 28.97, 28.94, 28.72, 28.68, 28.47, 25.28, 21.79, 18.99, 18.67, 18.60, 18.29, 13.49; IR (neat) 1130, 1110, 1060, 1040 cm^{-1}; MS (EI) *m/z* 261 (M^{+} − THP, 1), 85 (100), 67 (50), 55 (50). Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.60; H, 10.92.

4.3.8. 1-Tetrahydropyranyloxy-3,15-icosadiyne (4h). This compound was prepared following General procedure B (Section 4.3) from bromoalcohol **1d** in 73% yield after purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (1H, t, J = 3 Hz), 3.89–3.71 (2H, m), 3.53–3.42 (2H, m), 2.46–2.38 (2H, m), 2.14–2.08 (6H, m), 1.82–1.25 (26H, m), 0.87 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.56, 81.22, 80.06, 80.03, 76.60, 66.13, 62.00, 31.19, 30.49, 29.43, 29.40, 29.08, 29.06, 28.91, 28.76, 25.38, 21.83, 20.14, 19.32, 18.65, 18.35, 13.55; IR (neat) 1130, 1110, 1060, 1030 cm^{-1}; MS (EI) *m/z* 85 (100), 67 (20), 55 (19). Anal. Calcd for $C_{25}H_{42}O_2$: C, 80.16; H, 11.30. Found: C, 79.86; H, 11.17.

4.3.9. 3,13-Octadecadiyn-1-ol (5). A solution of THP ether **4d** (1.53 g, 4.4 mmol) and PPTS (200 mg) in ethanol (25 mL) was heated at 60 °C for 4 h. It was cooled to rt and solid $NaHCO_3$ was added before removal of volatiles by rotoevaporation. Standard extractive workup (ether, satd $NaHCO_3$ then brine) gave crude material which was purified by flash chromatography on silica gel using hexanes/ether, 2:1 to yield the known[17] alcohol **5** (1.15 g, 99%) as a low-melting colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (2H, t, J = 7 Hz), 2.42–2.35 (2H, m), 2.14–2.07 (6H, m), 1.48–1.23 (16H, m), 0.86 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.54, 80.10, 80.06, 76.23, 61.28, 31.17, 29.03, 28.94, 28.88 (2C), 28.75, 28.70, 23.06, 21.84, 18.64 (2C), 18.34, 13.54.

4.3.10. (3*Z*,13*Z*)-3,13-Octadecadien-1-yl acetate (6). A mixture of diyne **5** (135 mg) and 5% Pd/$CaCO_3$ poisoned with lead (28 mg) in hexanes (2 mL) was stirred under an atmosphere of H_2 for 18 h. The mixture was filtered through Celite and volatiles were removed by rotoevaporation. The residue was stirred with pyridine (1.5 mL), Ac_2O (0.5 mL) and DMAP (∼3 mg). Removal of volatiles in vacuo followed by flash chromatography on silica gel using hexanes/ether, 50:1 as eluent provided *Z*,*Z*-diene **6**[12] (141 mg, 90%) as a colorless liquid. Diene **6** co-eluted with its 3*E*,13*Z* and 3*E*,13*E* isomers on GC (DB-5 column) but high stereochemical purity was ascertained by the absence of ^{13}C signals at δ 124.9 and 133.5 (3E olefinic carbons) and 130.2 (13E olefinic carbons). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50–5.25 (4H, m), 4.02 (2H, t, J = 7 Hz), 2.33 (2H, app q, J = 7 Hz), 2.05–1.95 (6H, m), 1.99 (s, 3H), 1.36–1.22 (16H, m), 0.86 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 132.9, 129.8 (2C), 124.2, 63.9, 31.9, 29.7, 29.5, 29.4, 29.2, 27.2, 27.1, 26.8, 26.7, 22.3, 20.9, 13.9.

4.3.11. (*E*)-Octadec-3-en-13-yn-1-ol (7). To a solution of diene **5** (156 mg, 0.6 mmol) in DME (4 mL) was carefully added $LiAlH_4$ (92 mg, 2.4 mmol) and the mixture was heated at reflux for 18 h. The reaction mixture was cooled to 0 °C, diluted with ether and carefully quenched with satd NH_4Cl. Standard aqueous workup with 1 M HCl then brine afforded crude alcohol **7** which was directly acetylated. An analytical sample was purified by flash chromatography on silica gel using hexanes/ether, 2:1 to afford **7** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56–5.25 (2H, m), 3.57 (2H, t, J = 7 Hz), 2.23 (2H, app q, J = 7 Hz), 2.15–2.04 (4H, m), 1.94 (2H, app q, J = 7 Hz), 1.75–1.20 (16H, m), 0.86 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.26, 125.63, 80.14 (2C), 61.98, 35.91, 32.62, 31.21, 29.39, 29.32, 29.09, 29.05, 28.98, 28.78, 21.87, 18.69, 18.38, 13.58; IR (neat) 3351, 1466, 1048 cm^{-1}; MS (EI) *m/z* 233 (M^{+} − CH_2OH, 0.2), 95 (43), 81 (90), 67 (100), 55 (93). Anal. Calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.20. Found: C, 81.81; H, 12.01.

4.3.12. (*E*)-Octadec-3-en-13-yn-1-yl acetate (8). Crude alcohol **7** from the previous reaction was stirred with pyridine (1.5 mL), Ac_2O (0.5 mL) and DMAP (∼3 mg). Removal of volatiles in vacuo followed by flash chromatography on silica gel using hexanes/ether, 50:1 as eluent provided acetate **8** (166 mg, 91%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55–5.25 (2H, m), 4.02 (2H, t, J = 7 Hz), 2.27 (2H, app q, J = 7 Hz), 2.15–2.05 (4H, m), 2.00 (3H, s), 1.95 (2H, app q, J = 7 Hz), 1.50–1.20 (16H, m), 0.87 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.10, 133.53, 124.91, 80.12, 80.11, 64.10, 32.54, 31.89, 31.21, 29.31, 29.09, 29.05, 29.01, 28.78, 21.87, 20.92, 18.68, 18.38, 13.58; IR (neat) 1743, 1238 cm^{-1}; MS (EI) *m/z* 264 (M^{+} − C_2H_2O, 0.2), 93 (48), 81 (69), 79 (62), 67 (100), 55 (55). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.42; H, 11.10.

4.3.13. (3*E*,13*Z*)-3,13-Octadecadien-1-yl acetate (9). A mixture of enyne **8** (150 mg) and 5% Pd/$CaCO_3$ poisoned with lead (15 mg) in hexanes (2 mL) was stirred under an atmosphere of H_2 for 40 h. The mixture was filtered through Celite and volatiles were removed by rotoevaporation. Purification of the residue by flash chromatography on silica gel using hexanes/ether, 50:1 as eluent provided the known[7a] *E*,*Z*-diene **9** (147 mg, 97%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50–5.24 (4H, m), 4.01 (2H, t, J = 7 Hz), 2.25 (2H, app q, J = 7 Hz), 2.02–1.90 (6H, m), 1.99 (s, 3H), 1.34–1.20 (16H, m), 0.85 (3H, t, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 133.5, 129.7 (2C), 124.9, 64.0, 32.5, 31.9, 31.8, 29.7, 29.6, 29.4, 29.3, 29.2, 29.0, 27.1, 26.8, 22.3, 22.1, 20.8, 13.9.

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References and notes

1. Mori, K. The Synthesis of Insect Pheromones, 1979–1989. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 9, pp 1–534.
2. Rylander, P. N. *Hydrogenation Methods*; Academic: San Diego, 1985; pp 53–65.
3. Brandsma, L.; Nieuwenhuizen, W. F.; Zwikker, J. W.; Mäeorg, U. *Eur. J. Org. Chem.* **1999**, 775–779.

4. (a) Bailey, W. J.; Pfeifer, C. R. *J. Org. Chem.* **1955**, *20*, 1337–1341. (b) Kang, M. J.; Jang, J. S.; Lee, S. G. *Tetrahedron Lett.* **1995**, *36*, 8829–8832.
5. Schwarz, M.; Klun, J. A.; Leonhardt, B. A.; Johnson, D. T. *Tetrahedron Lett.* **1983**, *24*, 1007–1010.
6. Alkynylation of I$(CH_2)_7$Cl was reported to give a mixture of chloroalkyne and iodoalkyne: Grimmer, G.; Krqacht, J. *Chemische Berichte* **1963**, *96*, 3370–3373 as quoted in CA 60:22944.
7. For apparently similar reactions, reported yields vary from 33–93%: (a) Capdevila, A.; Prasad, A. R.; Quero, C.; Petschen, I.; Bosch, M. P.; Guerrero, A. *Org. Lett.* **1999**, *1*, 845–848. (b) Crundwell, E.; Cripps, A. L. *J. Med. Chem.* **1972**, *15*, 754–756. (c) Romeril, S. P.; Lee, V.; Claridge, D. W.; Baldwin, J. E. *Tetrahedron Lett.* **2002**, *43*, 327–329. (d) Barrot, M.; Fabriás, G.; Camps, F. *Tetrahedron* **1994**, *50*, 9789–9796. (e) van der Louw, J.; Komen, C. M. D.; Knol, A.; de Kanter, F. J. J.; van der Baan, J. L.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Lett.* **1989**, *30*, 4453–4456.
8. Buck, M.; Chong, J. M. *Tetrahedron Lett.* **2001**, *42*, 5825–5827.
9. (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033–10046. (b) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789–1797. (c) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 3943–3946.
10. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609–4612.
11. Chong, J. M.; Heuft, M. A.; Rabbat, P. *J. Org. Chem.* **2000**, *65*, 5837–5838.
12. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.
13. Uchida, M.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1978**, *42*, 1067–1070.
14. Pop, L.; Oprean, I.; Barabas, A.; Hodosan, F. *J. Prakt. Chem.* **1986**, *328*, 867–878.
15. Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.
16. Svirskaya, P. I.; Leznoff, C. C. *J. Chem. Ecol.* **1984**, *10*, 321–333.
17. Abrams, S. R.; Nucciarone, D. D.; Steck, W. F. *Can. J. Chem.* **1983**, *61*, 1073–1076.

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Microwave-assisted epoxidation of hindered homoallylic alcohols using VO(acac)$_2$: application to polypropionate synthesis

Gerardo Torres, Wildeliz Torres and José A. Prieto*

Department of Chemistry, University of Puerto Rico, Río Piedras Campus, PO Box 23346, San Juan, PR 00931-3346, USA

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Abstract—The VO(acac)$_2$ catalyzed epoxidation of hindered homoallylic alcohols was conducted under microwave irradiation in an open vessel using toluene as solvent. The reaction time for the epoxidation of a series of *cis*- and *trans*-2-methyl-3-alkenols was dramatically reduced from 6 to 10 days to less than 3 h when compared to conventional heating. The *cis* alkenols exhibited very high diastereoselectivity. The more elaborated polypropionate precursors **12**, **14** and **16** were epoxidized in good yield and excellent diastereoselectivities using the microwave-assisted epoxidation technique described here, which is safe and suitable for multi-gram scales.

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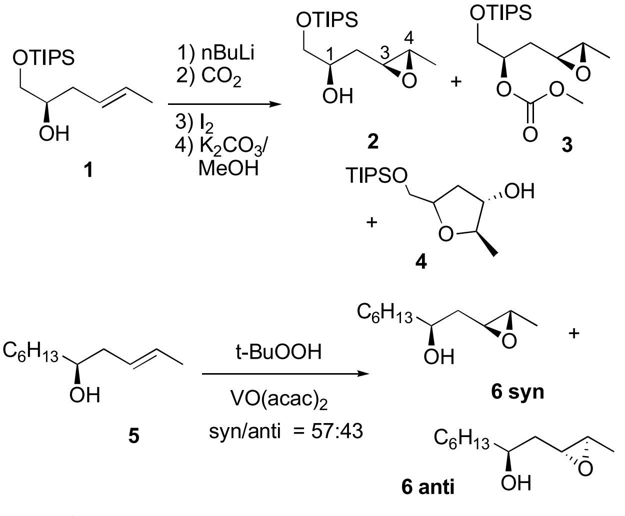
1. Introduction

The 3,4-epoxy alcohol functionality has been widely used in organic synthesis, particularly in the preparation of 1,3-diols.[1] This synthon is usually prepared by the epoxidation of homoallylic alcohols, but unlike their allylic counterparts, there are fewer effective methods for their stereoselective elaboration.[2] Among the available methods, the most frequently used approaches are based on iodocyclizations[3] and on transition metal catalyzed epoxidation reactions.[4] Regarding the area of iodocyclizations, the iodocarbonatation/methanolysis (carbonate extension) reaction is the most useful method for the stereoselective epoxidation of homoallylic alcohols.[3a–c,5] This reaction offers good stereoselectivity for *cis*, as well as *trans*, alkenols, generally favoring the *syn* product. However, the implementation of the iodocarbonatation methodology is somewhat tedious, requiring a strong base, low temperature, gaseous carbon dioxide, and a separate step for the methanolysis of the intermediate iodocarbonate, which can take up to 24 h. This approach has provided us a series of diastereomeric 2-methyl-3,4-epoxy alcohols, but in some instances we have experienced long reaction times, and poor yields.[5] For example, in the case of the *trans* homoallylic alcohol **1**, the reaction produced a mixture of the desired 3,4-epoxy alcohol **2**, the mixed carbonate **3** and the cyclic by-product **4** in variable ratios, depending on the methanolysis conditions (Scheme 1).



Scheme 1. Epoxidation of homoallylic alcohols.

Concerning the area of transition metal-catalyzed epoxidations, the VO(acac)$_2$/*tert*-butyl hydroperoxide procedure has been extensively used for the epoxidation of homoallylic alcohols.[4] This procedure is easy to implement and is usually carried out at refluxing temperature in nonpolar solvents. Similar to the carbonate extension reaction, the stereoselectivity of the VO(acac)$_2$ catalyzed epoxidation reaction is very good for *cis* alkenols, generally favoring the *syn* product. However, this procedure exhibits poor

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Keywords: Epoxidation; Homoallylic alcohols; Microwave synthesis; Polypropinate synthesis.

* Corresponding author. Tel.: +1-787-759-6880; fax: +1-787-759-6885; e-mail: jprieto@upracd.upr.clu.edu

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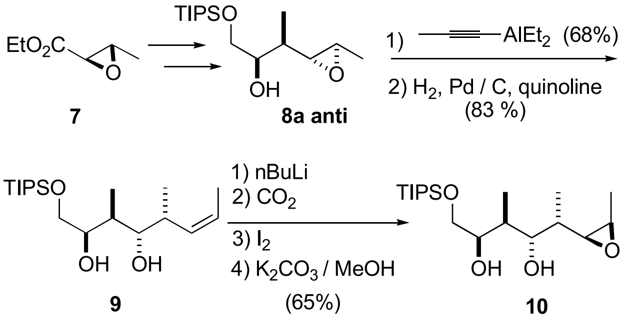
selectivity when applied to *trans* homoallylic alcohols (Scheme 1).[4b] In addition, this reaction requires longer reaction times (16–96 h) as the steric demands of the alkenol system increases.

For some time, our group has been interested in the use of 3,4-epoxy alcohols for the stereoselective construction of polypropionate units (Scheme 2).[5,6] In our epoxide-based approach toward polypropionates, the configuration of the resulting hydroxyl and methyl groups rely on the configuration and the *cis*/*trans* geometry of the epoxide precursors (**7**, **8**, **10**). In this sequence, the crucial stereoselective epoxidations of the hindered homoallylic alcohols were, until now, attained exclusively by the somewhat problematic iodocyclization reactions.[5] When the traditional VO(acac)$_2$ catalyzed epoxidation conditions were applied to these hindered systems, the reaction was too slow to be of practical significance (6 days, 19%).

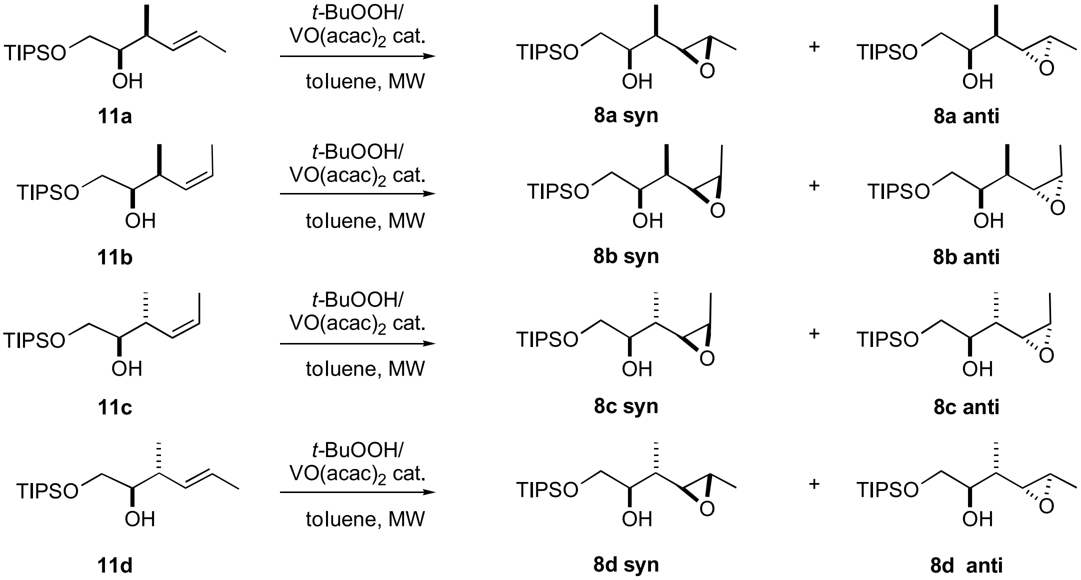


Scheme 2. Epoxide approach for polypropionate construction.

Knowing that the reaction mechanism of the vanadium-catalyzed epoxidation involves charge separation at the oxygen transfer (slow) step,[4d] and that a potential microwave induced rate enhancement is greater for those reactions were the polarity is altered during the reaction progress,[7a,b] we decided to investigate the application of microwave heating. Microwave irradiation has been introduced as a tool to enhance the efficacy of many organic reactions.[7] However, there is a paucity of accounts in the area of applying this technique to epoxide synthesis.[8] Since the vanadium/*tert*-butyl hydroperoxide reaction is a one-pot procedure, it could be adapted to a microwave setup. By applying this technology we expected to reduce the reaction time, and perhaps increase the yield and affect the stereoselectivity. With this in mind, we prepared the four diastereomeric forms of 2-methyl-3-alkenol **11**[9] and subjected them to a microwave-assisted VO(acac)$_2$ epoxidation (Scheme 3).

2. Results and discussion

Initial optimization of the VO(acac)$_2$-catalyzed epoxidation was conducted with the problematic *trans* substrate **11a** (Table 1). A variety of different microwave irradiation conditions (time/temperature) and solvents, including methylene chloride, 1,2-dichloroethane, and toluene were investigated. Further attempted refinements of the experimental set up, such as solvent-free conditions, the addition of an ionic liquid,[10] or microencapsulating the catalyst[11] did not cause notable improvement. Having achieved a set of optimized conditions in terms of time and yield for the VO(acac)$_2$ catalyzed epoxidation of alkenol **11a**, we applied them to alkenols **11b–d** and compared the results with conventional heating (Table 1). The microwave-assisted approach made possible the conversion of alkenols **11a–d** to their corresponding epoxides within 3 h, relative to 6–10 days for conventional heating. As shown, the overall reaction yields improved substantially in the case of alkenols **11a** and **11c** (entries 2 and 7). In relation to the stereoselectivity of the epoxidation reaction, as expected, the *syn* stereoisomer was favored in most cases. The *cis* alkenols provided good diastereoselectivities (entries 4–7) while the *trans* systems did not (entries 1, 2, 8 and 9). Not surprising, the *syn cis* alkenol **11b** produced only the *anti* epoxide **8b** (entries 4 and 5). The present stereoselectivities are in agreement with those obtained by Mihelich in related



Scheme 3. Stereochemical possibilities on the epoxidation of diastereomeric 2-methyl-3-alkenols.

Table 1. Results on the transition metal-catalyzed epoxidation of 2-methyl-3,4-epoxyalcohols

Entry	Alkenol	Method[a]	Time	Major product[b]	% Yield[c]	*syn*/*anti* Selectivity[d]
1	**11a**	$VO(acac)_2$/CH	6 days	**8a** *syn*	19	52:48
2	**11a**	$VO(acac)_2$/MW	3 h	**8a** *syn*	63	62:38
3	**11a**	$Mo(CO)_6$/MW	3 h	**8a** *syn*	85[e]	52:48
4	**11b**	$VO(acac)_2$/CH	6 days	**8b** *anti*	65[e]	<5:95[f]
5	**11b**	$VO(acac)_2$/MW	3 h	**8b** *anti*	65	<5:95[f]
6	**11c**	$VO(acac)_2$/CH	4 days	**8c** *syn*	60[e]	>95:5[f]
7	**11c**	$VO(acac)_2$/MW	45 min	**8d** *syn*	90	>95:5[f]
8	**11d**	$VO(acac)_2$/CH	10 days	**8d** *syn*	88[e]	63:37
9	**11d**	$VO(acac)_2$/MW	3 h	**8d** *syn*	90	63:37
10	**11d**	$Mo(CO)_6$/MW	3 h	**8d** *syn*	82	63:37

[a] All reactions carried out in toluene at reflux using either conventional heating (CH) or microwave-assisted heating (MW) and a 1.4 mol% catalyst loading.
[b] The relative configuration of the 2-methyl-3,4-epoxy alcohols **8** was determined by spectral comparison with reported values.[5]
[c] Isolated yield (for microwave procedure).
[d] Determined by ^{13}C and ^{1}H NMR spectroscopy.
[e] Some starting material was present.
[f] Only one isomer was observed by NMR analysis.

systems using conventional heating.[4b,c] To explain the observed diastereoselectivity, he proposed a tetrahedral vanadate ester transitions-state model that, according to the commonly accepted principles of conformational analysis, minimizes steric interactions among the various substituents. Therefore, *cis* homoallylic alcohols show good selectivities, as they react through the favored chair transition-state. In contrast, and according to this model, stereoselectivities for *trans* are low due to the energetically competitive boat transition states. Although a slight selectivity improvement was observed for alkenol **11a** under microwave irradiation (entry 2), this could not be further improved after various optimization attempts. These results suggest that there are no mechanistic differences between conventional and microwave heating procedures for this reaction, other than the difference in the nature of the heat transfer process and higher temperatures achievable under microwave irradiation.

In order to discard the possibility of an intrinsic diastereoselectivity for the hindered *trans* homoallylic epoxides **11a** and **11d**, control reactions were carried out using $Mo(CO)_6$ as catalyst, which is known to proceed without coordination to the hydroxy group (entries 3 and 10).[4a] As expected, although the yields were slightly better, there was no difference in the diastereoselectivity using $Mo(CO)_6$ for the *trans* systems. Only a small preference favoring the *syn* product was observed in both cases. Other epoxidating reagent, such as MCPBA, afforded similar results.

Given that toluene is not a good microwave-absorbing medium because of its low dielectric constant ($\varepsilon = 2.38$), we studied the individual heating profiles for the solvent, the alkenol, the peroxide, the catalyst, and the reaction mixture in order to assess the microwave energy-transfer process for the system. At constant power (1000 W) and 3 min irradiation, it became evident that the alkenol showed

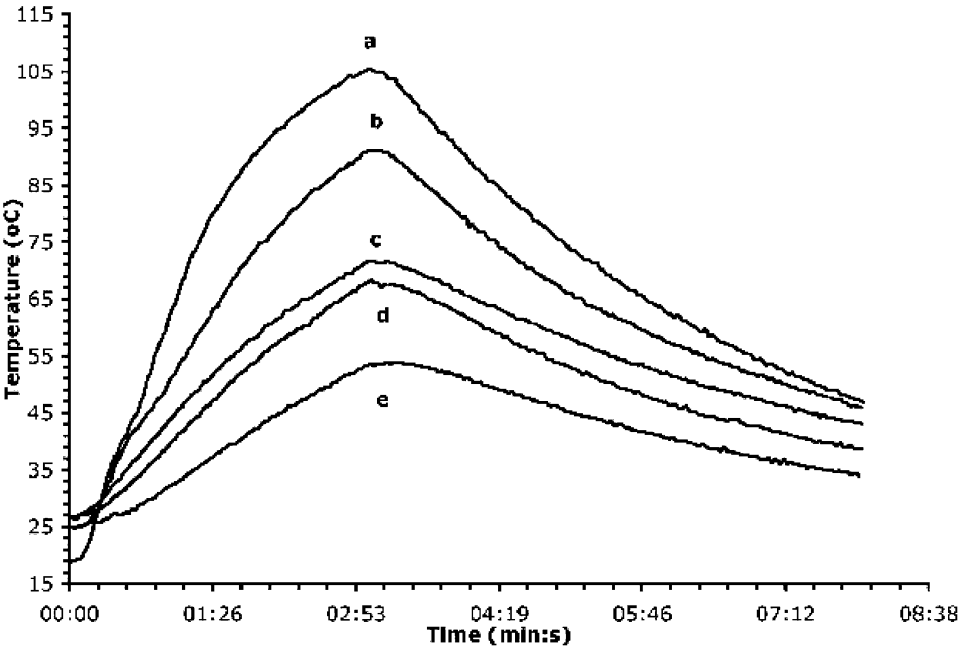
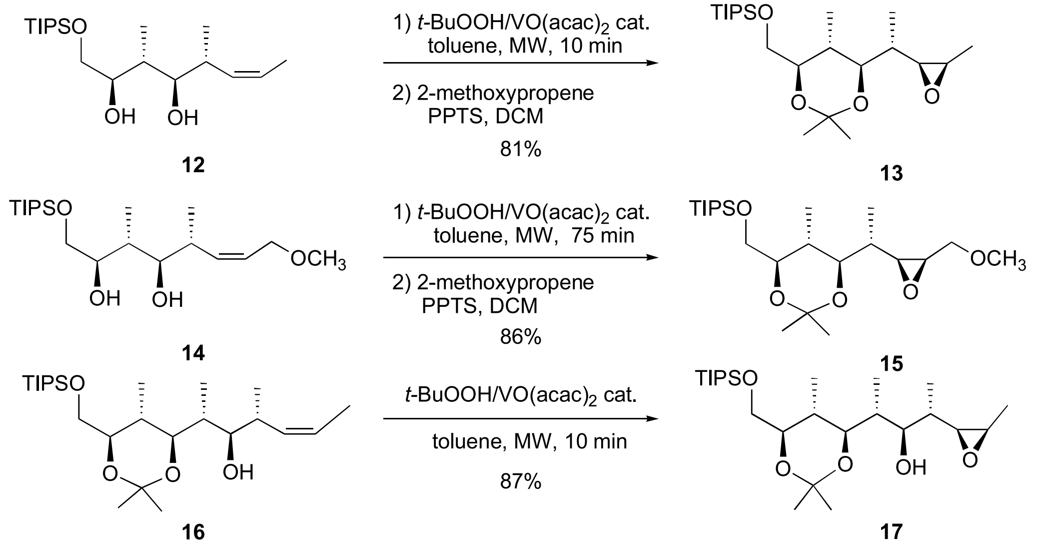


Figure 1. Heating profiles at 1000 W for 3 min in an open-vessel for (a) reaction mixture, (b) 0.083 M solution of homoallylic alcohol **11a** in toluene, (c) 0.091 M TBHP in toluene (1.1 mol equiv), (d) 0.001 M $VO(acac)_2$ in toluene (1.4 mol%), (e) and neat toluene.



Scheme 4. Epoxidation of polypropionate model systems.

significant microwave absorption (Fig. 1). The heating profile for the solvent, the catalyst and the peroxide where much lower, suggesting that the heat transfer agent is the homoallylic alcohol, though when all reagents are mixed, a slightly stronger microwave absorption profile is observed.[12] It is noteworthy that this microwave-assisted approach for the epoxidation of hindered homoallylic alcohols is applicable to gram quantities. In fact, the epoxidation of *cis* alkenol **11c** (entry 7) was conducted in up to a 30 g-scale in comparable reaction times.

To extend the scope of this microwave-assisted epoxidation to polypropionate synthesis and to explore the synthetic potential of this method, the microwave conditions were applied to the more complex homoallylic alcohols **12**, **14** and **16** (Scheme 4).[13] These compounds are precursors for our ongoing synthesis of the polypropionate chains of streptovaricins D and U.[14] When **12** was subjected to the VO(acac)$_2$ epoxidation conditions, the *syn* epoxide **13** was the only stereoisomer observed in 81% yield, after acetonide formation. The acetonide allowed better handling and characterization of the diol product. Similarly, diol **14** was epoxidized in 75 min producing *syn* epoxide **15** in 86% yield for the two synthetic steps. Correspondingly, the more elaborated fragment **16** (prepared from **13**) was transformed to epoxy acetonide **17** in 10 min with excellent diastereoselectivity and 87% yield. Compound **15**, which contains six adjacent stereocenters generated in a highly stereoselective manner, is a potential precursors to the C(5)–C(10) fragment of streptovaricin D. Likewise, compound **17** (which has 8 chirality centers) is a potential precursor to the C(5)–C(12) fragment of streptovaricin U. This demonstrates the applicability of the microwave approach for the efficient stereoselective epoxidation of *cis* alkenols.

The relative configuration of the epoxy alcohol products was established by ^{13}C NMR. (Table 2). As previously reported for *cis*-2-methyl-3,4-epoxy alcohols,[6a] when an *anti* 2-methyl-3-epoxide relationship is present (**8b** *anti* and **8c** *syn*, entries 3 and 4), the epoxide carbons show ^{13}C NMR signals around 51 and 57 ppm ($\Delta\delta \sim 6.5$ ppm relative to higher values for the *syn* relationship). This observation holds for epoxy alcohols **17** and **18**, showing a $\Delta\delta$ of 6.5 and 6.6 ppm, respectively (entries 7 and 8). For the *trans* epoxides, when the relative configuration between the 2-methyl and the 3-epoxide moiety is *syn* (**8a** *syn* and **8d** *anti*, entries 1 and 6), a difference of 7.1–7.5 ppm is observed. For a 2-methyl-3-epoxide *anti* relationship (**8a** *anti* and **8d** *syn*, entries 2 and 4), the difference ranges from 8.0 to 8.2. The characterization of the polypropionate system **13**, **15** and **17** was performed by 1D and 2D NMR analysis. The acetonides were prepared to aid in the determination of their relative configuration. In this way, the characteristic *syn* acetonide dimethyl ^{13}C shifts (around 20 and 30 ppm)[15] and the expected J values of 10.3–10.5 for vicinal axial–axial proton relationship (equatorially

Table 2. Relationship between the ^{13}C NMR chemical shifts for the epoxide (C-3, C-4) carbons and the 2-methyl-3-epoxide relative configuration

Entry	Compound	δ C-3	δ C-4	$\Delta\delta$	Configuration[a]
1	**8a** *syn*	61.5	54.0	7.5	*syn*
2	**8a** *anti*	61.7	53.5	8.2	*anti*
3	**8b** *anti*	58.5	51.9	6.5	*anti*
4	**8c** *syn*	57.7	51.1	6.6	*anti*
5	**8d** *syn*	60.6	52.6	8.0	*anti*
6	**8d** *anti*	62.1	55.0	7.1	*syn*
7	17	56.9	50.3	6.6	*anti*
8	**18**[b]	57.1	50.6	6.5	*anti*

[a] Relative configuration between the C-2 methyl and the epoxide.

[b] Diol resulting from the acetonide hydrolysis of **13**.

substituted acetonide rings) were observed for these products, confirming the relative configuration of the remaining chiral carbons.

3. Conclusions

The VO(acac)$_2$ catalyzed epoxidation of hindered homoallylic alcohols under microwave dielectrical heating dramatically reduced the reaction time and improved the reaction yield. Excellent diastereoselectivities were observed for *cis*-2-methyl-3-alkenols. The scope was extended to more elaborated systems establishing the applicability and utility of this epoxidation approach for homoallylic alkenols.

4. Experimental

4.1. General comments

All reactions were carried out under nitrogen. All solvents were distilled before use. Dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. Toluene was distilled from sodium/benzophenone prior to use. All commercially available compounds were used as received. Compounds **11a**, **11b**, **11c**, and **11d** were prepared by published procedures.[5] Unless otherwise noted, all compounds were purified by silica gel column chromatography and fully characterized by 1D and 2D ^{1}HNMR and ^{13}CNMR (500 or 300 MHz spectrometer) as solutions in deuterochloroform. NMR chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Elemental analysis was done by Atlantic Microlabs, Inc. Norcross, GA.

4.2. Microwave reactor

An Ethos 1660 Labstation (Milestone, Inc.) multimode microwave reactor was used in the standard configuration as delivered for organic synthesis in a open glass vessel. This reactor has dual independent magnetrons (2×800 W, 2.45 GHz) that can deliver a power of up to 1000 W in 10 W increments (variable pulsed irradiation). A rotating diffuser ensures a homogeneous microwave distribution throughout the Teflon plasma coated stainless steel oven compartment (35 cm×35 cm×35 cm). The reaction mixture was stirred using the built-in magnetic stirrer and a Teflon-coated stirring bar. The experiment time, temperature and power were controlled/monitored with the proprietary easyWave software package (version 3.2.1). The temperature was monitored using a shielded thermocouple (ATC 400CE) immersed into the reaction mixture. The reaction temperature was set to 113 °C. This equipment has the capability to regulate the power (1000 W maximum) to achieve and maintain the selected temperature.

Caution. Because of the relatively long reaction times and high microwave irradiation power, this method has been specifically developed for the above hardware. This synthetic microwave system has a series of built-in interlocks and safety features that allow long irradiation times. A built-in exhaust system (for the oven cavity and system electronics) is connected to a fume-hood in case that any fume leaks into the microwave cavity.

4.3. General procedure for the microwave-assisted epoxidation of homoallylic alcohols

VO(acac)$_2$ (0.015 g, 0.014 equiv) was added to a round-bottom flask equipped with a reflux condenser, followed by toluene (3 mL, 0.083 M) and the alkenol **11a–d** (0.60 g, 2.1 mmol). A microwave ramp (1000 W maximum) was applied until a temperature of 113 °C was reached (approx. 15 min). When the reaction mixture started to reflux, the irradiation was paused and 0.65 mL of *t*-butyl hydroperoxide (4.24 M in toluene, 1.1 equiv) was carefully added. Microwave irradiation was continued maintaining the reaction temperature at 113 °C. The reaction mixture changed from red to yellow during the course of reaction. It was refluxed until completion as judged by TLC. After the irradiation period, the reaction was cooled to room temperature (approx. 20 min). The crude product mixture was diluted with saturated $Na_2S_2O_3$, the aqueous phase was extracted with ether. The organic phase was filtered through Celite and silica with the aid of ether and dried over $MgSO_4$ prior to concentration under reduced pressure. The crude product was purified by flash chromatography (9:1 hexane/EtOAc), to yield the pure epoxy alcohol as a clear oil. In the case of the *trans* alkenols, were *syn*/*anti* product mixtures were obtained, the isomers were separated, of which the typically less polar *anti* isomer eluted first.

4.4. Preparation of acetonides

Although the epoxy alcohols prepared from **12**, **14** and **16** could be purified by chromatography (with concomitant decomposition), it was best to carry these compounds through the subsequent protection without purification due to its instability on silica gel. The resulting crude was converted to the acetonide using PPTS (0.06 equiv) and 2-methoxypropene, (5 equiv, 0.105 M CH_2Cl_2 at 0 °C) to produce the protected 3,4-epoxides.

Compounds **8a–d** were spectroscopically identical with those prepared by the iodocarbonatation procedure.[5] The purity was assessed by NMR and elemental analysis.

4.4.1. (±)-(2*R,3*R**,4*S**,5*S**)-4,5-Epoxy-3-methyl-1-[(triisopropylsilyl)oxy]-2-hexanol (8a).** 0.60 g (2.1 mmol) of alkenol **11a** produced 0.38 g (63% yield) of a 62:38 *syn*/*anti* mixture of epoxy alcohols **8a** *syn* and **8a** *anti*. For **8a** *syn*: ^{1}H NMR ($CDCl_3$): δ 3.76 (dd, J=2.18, 8.1 Hz, 1H), 3.67 (mult., 1H), 2.86 (qd, J=5.2, 2.2 Hz, 1H), 2.60 (dd, J=6.6, 2.3 Hz, 1H), 1.65 (s, 1H, O*H*), 1.54 (mult., 1H), 1.29 (d, J=5.2 Hz, 3H), 1.10 (mult., 24H); ^{13}C NMR ($CDCl_3$): δ 73.5, 65.4, 61.5, 54.0, 38.1, 17.9, 17.6, 11.9. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.78; H, 11.51. For the *anti* isomer **8a** *anti*: ^{1}H NMR ($CDCl_3$): δ 3.84 (dd, J=9.7, 3.6 Hz, 1H), 3.71 (mult., 1H), 3.59 (dd, J=9.7, 8.1 Hz, 1H), 2.78 (qd, J=5.2, 2.5 Hz, 1H), 2.65 (s, 1H, O*H*), 2.45 (dd., J=2.2, 7.4 Hz, 1H), 1.35 (mult., 1H), 1.30 (d, J=5.2 Hz, 3H), 1.10 (mult., 24H); ^{13}C NMR ($CDCl_3$): δ 73.8, 65.9, 61.7, 53.5, 38.8, 17.7, 12.36, 11.9, 11.6. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.74; H, 11.47.

4.4.2. ($\pm$)-($2R^*,3R^*,4R^*,5S^*$)-4,5-Epoxy-3-methyl-1-[(triisopropylsilyl)oxy]-2-hexanol (8b *anti*). 0.60 g (2.1 mmol) of alkenol **11b** produced 0.39 g (65% yield) of epoxide **8b** *anti*; ^{1}H NMR (CDCl$_3$): δ 3.91 (dd, J=9.5, 3.3 Hz, 1H), 3.71 (ddd, J=8.3, 6.7, 3.3 Hz, 1H), 3.61 (dd, J=9.5, 8.3 Hz, 1H), 3.05 (qd, J=5.6, 4.4 Hz, 1H), 2.78 (dd, J=9.4, 4.4 Hz, 1H), 1.65 (s, 1H, –O*H*), 1.40 (mult., 1H), 1.27 (d, J=5.6 Hz, 3H), 1.10 (mult., 24H); ^{13}C NMR (CDCl$_3$): δ 74.3, 66.0, 58.5, 51.9, 34.8, 17.8, 12.9, 11.8, 11.6; MS *m/z* (relative intensity) 173.2 (25), 131.2 (67), 119.1 (19), 111.1 (29), 103.1 (100), 75.1 (62), 69.1 (27), 59.0 (18). Anal. Calcd for C$_{16}$H$_{34}$O$_3$Si: C, 63.52; H, 11.33. Found: C, 63.43; H, 11.27.

4.4.3. ($\pm$)-($2R^*,3S^*,4S^*,5R^*$)-4,5-Epoxy-3-methyl-1-[(triisopropylsilyl)oxy]-2-hexanol (8c *syn*). 0.60 g (2.1 mmol) of alkenol **11c** produced 0.56 g (90% yield) of epoxide **8c** *syn*; ^{1}H NMR (CDCl$_3$): δ 3.80 (mult., 3H), 3.04 (mult., 2H), 2.78 (s, 1H, O*H*), 1.51 (mult., 1H), 1.27 (d, J=5.4 Hz, 3H), 1.07 (mult., 21H), 1.03 (d, J=7.3 Hz, 3H); ^{13}C NMR (CDCl$_3$): δ 75.4, 66.0, 57.7, 51.1, 34.5, 17.9, 13.2, 11.9, 11.6. Anal. Calcd for C$_{16}$H$_{34}$O$_3$Si: C, 63.52; H, 11.33. Found: C, 63.38; H, 11.31.

4.4.4. ($\pm$)-($2R^*,3S^*,4S^*,5S^*$)-4,5-Epoxy-3-methyl-1-[(triisopropylsilyl)oxy]-2-hexanol (8d). 0.60 g (2.1 mmol) of alkenol **11d** produced 0.57 g (90% yield) of a 63:37 *syn*/*anti* mixture of epoxy alcohols **8d** *syn* and **8d** *anti*. For **8d** *syn*: ^{1}H NMR (CDCl$_3$): δ 3.9–3.5 mult., 3H), 2.87 (qd, J=5.2, 2.2 Hz, 1H), 2.66 (dd, J=7.4, 2.2 Hz, 1H), 2.70 (s, 1H, O*H*), 1.48 (mult., 1H), 1.30 (d, J=5.2 Hz, 3H), 1.10 (mult., 24H); ^{13}C NMR (CDCl$_3$): δ 74.1, 65.4, 60.6, 52.6, 38.5, 17.9, 12.9, 11.9, 11.8. For **8d** *anti*: ^{1}H NMR (CDCl$_3$): δ 3.9–3.5 mult., 3H), 2.78 (qd, J=5.2, 2.5 Hz, 1H), 2.65 (s, 1H, O*H*), 2.45 (dd, J=7.4, 2.2 Hz, 1H), 1.35 (mult., 1H), 1.30 (d, J=5.2 Hz, 3H), 1.10 (mult., 24H); ^{13}C NMR (CDCl$_3$): δ 74.9, 65.7, 62.1, 55.0, 38.3, 17.9, 17.6, 11.9, 11.3. Anal. Calcd for C$_{16}$H$_{34}$O$_3$Si: C, 63.52; H, 11.33. Found: C, 63.72; H, 11.44.

4.4.5. ($\pm$)-($4R^*,5S^*,S^*$)-4-[($1R^*,2R^*,3S^*$)-(2,3-Epoxy-1-methylbutyl)]-2,2,5-trimethyl-6-[(triisopropylsilyloxy) methyl]-1,3-dioxane (13). 5.34 g (15.52 mmol) of alkenol **12** produced 4.69 g (81% yield) of epoxy acetonide **13**; ^{1}H NMR (CDCl$_3$): δ 3.82 (dd, J=10.8, 3.5 Hz, 1H), 3.71 (dd, J=10.8, 5.1 Hz, 1H), 3.52 (ddd, J=10.3, 5.3, 3.5 Hz, 1H), 3.48 (dd, J=10.5, 2.1 Hz, 1H), 3.09 (dd, J=9.2, 4.5 Hz, 1H), 2.93 (dq, J=5.5, 4.5 Hz, 1H), 1.86 (ddq, J=10.5, 10.3, 6.5 Hz, 1H), 1.70 (ddq, J=9.2, 7.1, 2.1 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.27 (d, J=5.5 Hz, 3H), 1.08 (m, 21H), 0.96 (d, J=7.1 Hz, 3H), 0.85 (d, J=6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$): δ 97.8, 77.4, 76.1, 66.3, 56.4, 50.3, 33.6, 33.0, 29.9, 19.4, 13.9, 13.4, 12.1, 12.0. Anal. Calcd for C$_{22}$H$_{44}$O$_4$Si: C, 65.95; H, 11.07. Found: C, 65.87; H, 11.14.

4.4.6. ($\pm$)-($4R^*,5S^*,6S^*$)-4-[($1R^*,2R^*,3S^*$)-(2,3-Epoxy-4-methoxy-1-methylbutyl)]-2,2,5-trimethyl-6-[(triisopropylsilyloxy) methyl]-1,3-dioxane (15). 0.21 g (0.61 mmol) of alkenol **14** produced 0.203 g (86% yield) of epoxy acetonide **15**; ^{1}H NMR (CDCl$_3$): δ 3.82 (dd, J=10.8, 3.4 Hz, 1H), 3.71 (dd, J=10.8, 5.2 Hz, 1H), 3.66 (dd, J=11.0, 4.0 Hz, 1H), 3.53 (ddd, J=10.3, 5.2, 3.4 Hz, 1H), 3.45 (dd, J=10.5, 2.0 Hz, 1H), 3.43 (s, 3H), 3.37 (dd, J=11.0, 6.7 Hz, 1H), 3.21 (dd, J=9.2, 4.4 Hz, 1H), 3.07 (ddd, J=6.7, 4.4, 4.0 Hz, 1H), 1.87 (ddq, J=10.5, 10.3, 6.5 Hz, 1H), 1.71 (ddq, J=9.2, 7.2, 2.0 Hz, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.06 (m, 21H), 0.96 (d, J=7.2 Hz, 3H), 0.86 (d, J=6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$): δ 97.8, 77.5, 76.1, 70.9, 66.3, 59.1, 55.6, 53.0, 33.5, 33.5, 29.9, 19.4, 18.0, 14.2, 12.1, 12.0. HRMS-FAB (*m/z*): $[\mathrm{M+Li}]^+$ calcd for C$_{23}$H$_{46}$O$_5$SiLi, 437.328; found, 437.326.

4.4.7. ($\pm$)-($4S^*,5S^*,6S^*$)-4-[($1S^*,2S^*,3S^*,4R^*,5S^*$)-1,3-Dimethyl-2-hydroxy-4,5-epoxyhexyl]-6-[(triisopropylsilyloxy)methyl]-2,2,5-trimethyl-1,3-dioxane (17). 0.35 g (0.80 mmol) of alkenol **16** produced 0.390 g (87% yield) of epoxy acetonide 17; ^{1}H NMR (CDCl$_3$): δ 3.78 (dd, J=10.9, 3.3 Hz, 1H), 3.70 (dd, J=10.9, 5.1 Hz, 1H), 3.60 (dd, J=10.5, 2.6 Hz, 1H), 3.51 (ddd, J=10.3, 5.1, 3.3 Hz, 1H), 3.47 (dd, J=10.9, 1.4 Hz, 1H), 3.11 (dd, J=9.2, 4.6 Hz, 1H), 2.98 (dq, J=5.4, 4.6 Hz, 1H), 2.28 (ddq, J=10.9, 7.0, 2.6 Hz, 1H), 1.95 (ddq, J=10.5, 10.3, 6.5 Hz, 1H), 1.69 (s, 1H, OH), 1.61 (ddq, J=9.2, 6.9, 1.4 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.28 (d, J=5.4 Hz, 3H), 1.05 (m, 24H), 0.96 (d, J=7.0 Hz, 3H) 0.91 (d, J=6.5 Hz, 3H). ^{13}C NMR (CDCl$_3$): δ 98.1, 80.2, 78.3, 76.5, 65.8, 56.9, 50.3, 36.6, 35.1, 34.5, 30.2, 18.2, 17.9, 14.7, 13.4, 12.6, 12.0. Anal. Calcd for C$_{25}$H$_{50}$O$_5$Si: C, 65.45; H, 10.99. Found: C, 65.72; H, 11.22.

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References and notes

1. (a) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, *20*, 335. (b) Lipshutz, B. H.; Kozlowski, J. *J. Org. Chem.* **1984**, *49*, 1147. (c) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495. (d) Mohr, P. *Tetrahedron Lett.* **1992**, *33*, 2455. (e) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (f) Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 581. (g) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 312.
2. (a) Okachi, T.; Murai, N.; Onaka, M. *Org. Lett.* **2003**, *5*, 85. (b) Bryant, E. R.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707. (c) Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, 83. (d) Guanti, G.; Bamfi, L.; Narisano, .; Thea, S. *Tetrahedron Lett.* **1991**, *32*, 6943. (e) Karjalainen, J. K.; Hormi, O. E. O.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 3895.
3. (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626. (c) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Junstedt, K. K. *J. Org.*

Chem. **1982**, *47*, 4013. (d) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.

4. (a) Michaelson, R. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690. (c) Mihelich, E. D. *Tetrahedron Lett.* **1979**, *20*, 4729. (d) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.
5. Tirado, R.; Prieto, J. A. *J. Org. Chem.* **1993**, *58*, 5666.
6. (a) Arbelo, D. O.; Castro-Rosario, L.; Prieto, J. A. *Synth. Commun.* **2003**, *33*, 3211. (b) Arbelo, D. O.; Prieto, J. A. *Tetrahedron Lett.* **2002**, *43*, 4111.
7. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161. (c) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, M. P. *Chem. Soc. Rev.* **1998**, *27*, 213. (e) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (f) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petti, A. *Tetrahedron* **1999**, *55*, 10851.
8. (a) dos Santos, A. A.; Wendler, E. P.; Marques, F. de A.; Simonelli, F. *Lett. Org. Chem.* **2004**, *1*, 47. (b) Palombi, L.; Bonadies, F.; Scettri, A. *Tetrahedron* **1997**, *53*, 15867. (c) Pillai, U. R.; Sahle-Demessie, E.; Varma, R. S. *Tetrahedron Lett.* **2002**, *43*, 2909. (d) Fawcett, J.; Griffith, G. A.; Percy, J. M.; Uneyama, E. *Org. Lett.* **2004**, *6*, 1277. (e) Sharifi, A.; Bolourtchian, M.; Mohsenzadeh, F. *J. Chem. Res.* **1998**, 668.
9. The 2-methyl-3,4-epoxy alcohols **11a–d** were prepared by the diethylpropynylalane cleavage of the *cis* or *trans* TIPS-protected 2,3-epoxy-1-butanols followed by a *cis* or *trans* reduction of the homopropargylic alcohols (Ref. 5).
10. (a) Chandrasekhar, S.; Narasihmulu, Ch.; Jagadeshwar, V.; Reddy, K. V. *Tetrahedron Lett.* **2003**, *44*, 3629. (b) Leadbeater, N. E.; Torrenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145. (c) Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dalliger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904.
11. Lattanzi, A.; Leadbeater, N. E. *Org. Lett.* **2002**, *4*, 1519.
12. Corrections for the borosilicate glass vessel, which is known to transfer some microwave energy was not made Garbacia, S.; Desai, B.; Levastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136.
13. *cis* Alkene diols **12** and **14** were prepared from the corresponding diethylalkynylalane cleavage of epoxide **8c** *syn*, followed by the Pd/C, quinoline hydrogenation of the resulting alkynes. Alkenol **16** was similarly prepared from epoxide **13** (Ref. 5).
14. (a) Rinehart, K.; Maheshwari, M. L.; Antosz, F. J.; Mathur, H. H.; Sasaki, K.; Schacht, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 6273. (b) Rinehart, K. L.; Antosz, F. J.; Sasaki, K.; Martin, P. K.; Maheshwari, M. L.; Reussre, F.; Li, H. L.; Moran, D.; Wiley, P. F. *Biochemistry* **1974**, *13*, 861. (c) Miyashita, M.; Shiratani, T.; Kawamine, K.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1996**, 1027.
15. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

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Hydrogen bonding-mediated self-assembly of rigid and planar metallocyclophanes and their recognition for mono- and disaccharides

Ying-Qi Chen,[a,*] Xiao-Zhong Wang,[a] Xue-Bin Shao,[b] Jun-Li Hou,[b] Xin-Zhi Chen,[a] Xi-Kui Jiang[b] and Zhan-Ting Li[b,*]

[a]*Institute of Pharmaceutical Engineering, College of Materials Science and Chemical Engineering, Yuquan Campus, Zhejiang University, Hangzhou, Zhejiang 310027, China*

[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

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Abstract—A hydrogen bonding approach has been developed to facilitate the self-assembly of a new series of rigid and planar metallocyclophanes. Two new anthranilamide derivatives **1** and **2**, which are incorporated with two acetylene units, respectively, have been synthesized and characterized. X-ray analysis (for **1**), 1D and 2D ^{1}H NMR and IR experiments reveal that, due to the formation of intramolecular three-centered hydrogen bonding, both compounds adopt rigid and planar conformations with the two acetylene units located at the same side of the anthranilamide skeleton. Two new metallocyclophanes **17** and **18** have been constructed in moderate yields from the reaction of **1** and **2** with *trans*-$Pt(PEt_3)_2Cl_2$, respectively, in dichloromethane in the presence of diethylamine and cupric chloride. Fluorescent and ^{1}H NMR investigations reveal that both **17** and **18** can efficiently complex mono- and disaccharide derivatives in chloroform, with a binding selectivity for disaccharides, which is driven by intermolecular hydrogen bonding.

1. Introduction

In the past decade, the development of supramolecular macrocyclic architectures has received intensive interest.[1] Among various non-covalent forces, the coordination bonding motif between transition metal ions and organic ligands has proven itself to be a highly useful tool for their preparation.[2] In order to overcome the entropic disadvantage and to achieve high assembling efficiency, rigid aromatic ligands are usually used. Over years a large number of metallosupramolecular assemblies have been constructed from covalently bonded aromatic ligands. Nevertheless, functional metallocyclophanes are still relatively rare despite their perceived advantages over the constituent building blocks.[3]

Following the increasing applications of hydrogen bonding for controlling the folding and unfolding conformations of unnatural organic molecules,[4,5] we had recently initiated a project to develop new hydrogen bonding-mediated building blocks for constructing novel generation of functional supramolecular architectures. Previously, we have reported the self-assembly of a new class of oligoanthranilamides whose straight, rigid, and planar conformations could be stabilized by intramolecular three-centered hydrogen bonding.[6] In this paper, we report that similar approach has been successfully utilized to control the rigid conformation of acetylene precursors for the generation of a new series of rigid and planar metallocyclophanes. We also report the binding behavior of the new metallocyclophanes towards mono- and disaccharides in chloroform.

2. Results and discussion

A number of metallocyclophanes have been constructed from linear bisphenylacetylene ligands and coordinatively unsaturated metal complexes.[7] Previously, Hamilton and Gong have revealed that intramolecular three-centered hydrogen bonding can induce 1,3-substituted anthranilamide derivatives to adopt folding, rigid and planar conformation.[8] Recently, we have also reported that similar hydrogen bonding approach could be used to induce 1,4-substituted anthranilamides to generate unfolding, rigid and

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* Corresponding authors. Tel.: +86 571 87952693 (Y.-Q.C.); tel.: +86 21 64163300; fax: +86 21 64166128 (Z.T.L.);
e-mail addresses: yqchen@zju.edu.cn; ztli@mail.sioc.ac.cn

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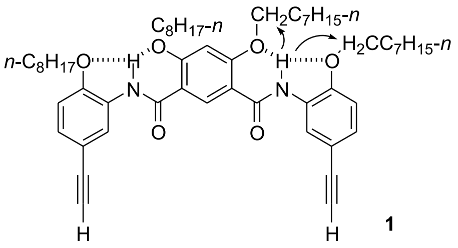
straight conformations.[6] To explore the possibility of the intramolecular three-centered hydrogen bonding to control the rigidity and directionality of new bisphenylacetylene ligands for self-assembly of new kinds of metallocyclophanes, compounds **1** and **2** were designed and synthesized. The two acetylene units of both compounds were expected to be parallel to each other at the same side due to the formation of intramolecular hydrogen bonding. Such an arrangement should remarkably facilitate the formation of corresponding metallocyclophanes.



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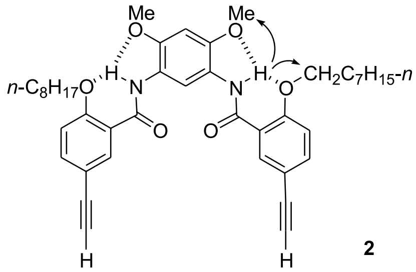
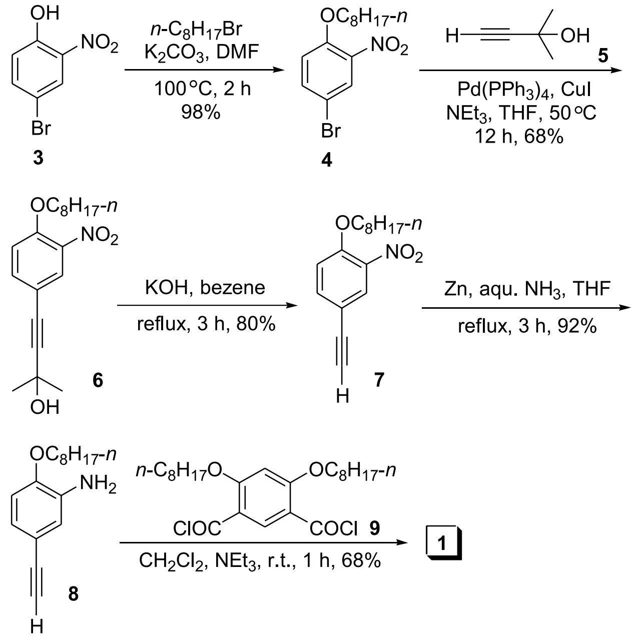


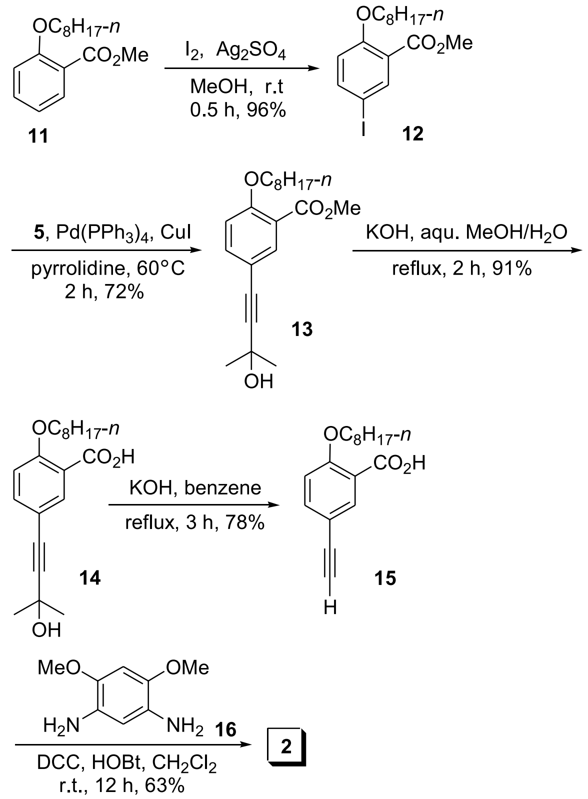
2

The synthetic route of compound **1** is shown in Scheme 1. In brief, compound **3** was first octylated in hot DMF in the presence of potassium carbonate to give bromide **4** in 98% yield. The latter was then coupled with compound **5** in THF with Pd(0) as catalyst to produce compound **6** in 68% yield. Hydrolysis of **6** with potassium hydroxide in refluxing benzene afforded acetylene **7** in 80% yield, which was then selectively reduced to amine **8** in 92% yield by zinc in water and THF solution of ammonia. Treatment of **8** with diacyl chloride **9** in dichloromethane with triethylamine as a base produced compound **1** in 68% yield.



Scheme 1.

For the preparation of compound **2** (Scheme 2), ester **12** was first produced in 96% yield from the reaction of **11** and iodine in the presence of silver sulfate in methanol. The coupling reaction of **12** with **5**, catalyzed by Pd(0), in hot pyrrolidine produced **13** in 72% yield. Compound **13** was then treated with potassium hydroxide in hot aqueous THF to give **14** in 91% yield. The latter was treated with potassium hydroxide again in hot benzene to afford **15** in 78% yield. Compound **15** was then coupled with diamine **16** in the presence of DCC and HOBt in dichloromethane to afford **2** in 63% yield.



Scheme 2.

Compounds **1** and **2** have been identified by ^{1}H NMR and MALDI-TOF mass spectroscopy, and microanalysis. ^{1}H NMR spectrum in chloroform-*d* revealed typical three-centered hydrogen bonding for both compounds (NH: 9.90 and 9.99 ppm, respectively). ^{1}H NMR experiments in chloroform-*d* revealed very small concentration dependence (<0.01 ppm) within the range of 20–0.3 mM and low temperature dependence ($<4.0\times10^{-3}$ ppm/K within the region of 10–55 °C) for the NH and aromatic proton signals of both compounds.[8] These observations are well consistent with the results observed in structurally similar rigid and straight oligoanthranilamides.[6] The observations also exclude any important intermolecular aggregation for both compounds. 2D-NOESY ^{1}H NMR studies in chloroform-*d* (10 mM) also revealed moderate strength of NOE connections between the NH and the neighboring OCH_3 and OCH_2

signals (see the structures). In addition, all the NH stretching frequencies (ν) of their IR spectra, measured in chloroform (4 mM) and with the KBr disk method, are $<3310\ \mathrm{cm}^{-1}$ and independent of concentration changes.[9] All the results support that intramolecular three-centered hydrogen bonding is formed, which induces the rigid and planar conformation as shown in the text.

Single crystals of compound **2** were obtained by slow evaporation of its dichloromethane and methanol solution at room temperature. The X-ray structure of the compound is provided in Figure 1. It can be found that the compound adopts a nearly perfect planar conformation. The two acetylene units are nearly parallel, located at the same side due to the existence of two three-centered hydrogen bonding, which is well consistent with the above spectral observations.

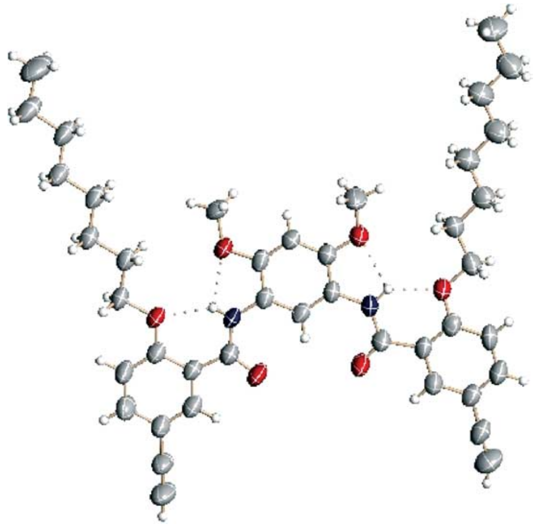
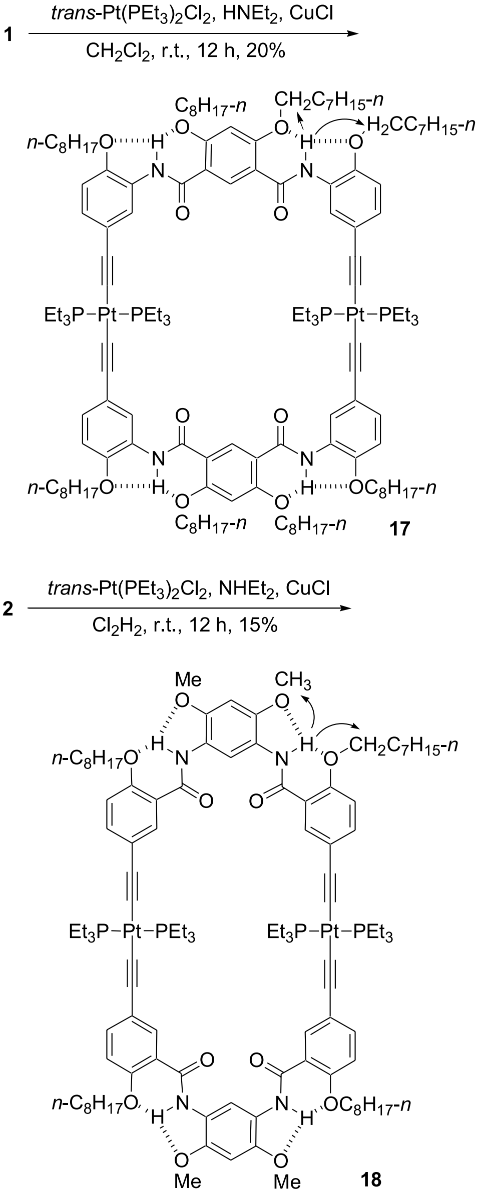


Figure 1. The crystal structure of compound **2**, revealing two typical three-centered NH–O hydrogen bonds and a rigid and planar conformation.

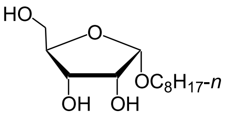
Treatment of compounds **1** and **2** with *trans*-$Pt(PEt_3)_2Cl_2$ in dichloromethane in the presence of diethylamine and cupric chloride produced metallocyclophanes **17** and **18** in 20 and 15% yields, respectively (Scheme 3).[7] Both **17** and **18** are soluble in common organic solvents such as chloroform and dichloromethane.

Compounds **17** and **18** were identified by ^{1}H and ^{13}C NMR and MALDI-TOF mass spectroscopy, and microanalysis. ^{1}H NMR spectrum of **17** and **18** in chloroform-*d* showed the signal of NH in the downfield area (9.80 and 9.97 ppm, respectively), indicating the existence of three-centered hydrogen bonding in the new metallocyclophanes. 2D-NOESY ^{1}H NMR experiments revealed NOEs between the NH and the neighboring OCH_3 and OCH_2 signals, as shown in Scheme 3. The IR spectrum obtained in chloroform showed the NH stretching frequency at 3330 and $3325\ \mathrm{cm}^{-1}$, respectively, which are typically those of amides involved in intramolecular hydrogen bonding.[9] All these results indicate that the metallocyclophanes also possess rigid and planar conformation due to the formation of intramolecular three-centered hydrogen bonding. The maximum absorbance wavelength of **17** (267 nm) and **18** (259 nm), obtained in chloroform, is significantly increased, compared to that of their constituents **1** (258 nm) and **2** (248 nm), respectively.

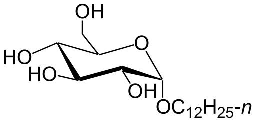


Scheme 3.

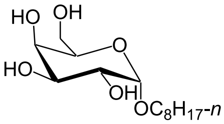
Molecular modeling revealed that both **17** and **18** possess a rigid cavity with all the C=O oxygen located to the center of the cavity. The distances between the two Pt atoms are about 12.3 and 10.6 Å in **17** and **18**, respectively, whereas the distances between the two oxygen atoms of one side are about 12.9 and 13.8 Å, respectively. Such an arrangement of all the carbonyl groups with the oxygen atoms pointing to the inner of the cavity is very favorable for binding multi-hydroxyl molecules. The binding behaviors of metallocyclophanes **17** and **18** towards mono- and disaccharide derivatives **19–25** were then investigated in chloroform.[10] The long aliphatic chains were introduced into the saccharides to provide solubility in less polar solvents like chloroform. Compounds **19–23** and **25** were prepared according to reported methods, while the synthetic route



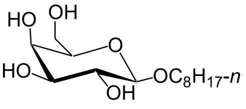
α–D-Ribose (**19**)



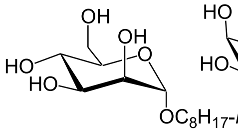
α–D-Glucose (**20**)



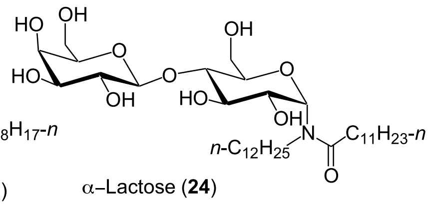
α-D-Galactose (**21**)



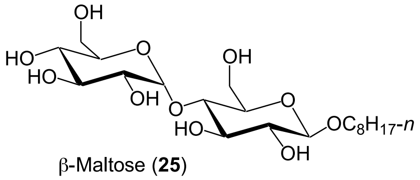
β-D-Galactose (**22**)



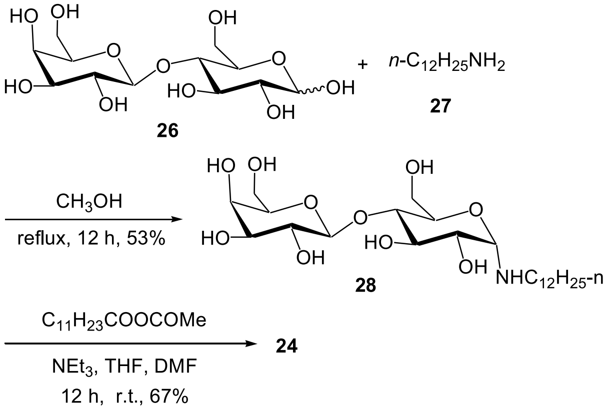
α-D-Mannose (**23**)



α–Lactose (**24**)



β-Maltose (**25**)



Scheme 4.

for compound **24** is provided in Scheme 4. Initially, we had tried to prepare the *n*-dodecyl derivative of lactose similar to other saccharides, which was found to be insoluble in chloroform.

Adding **19–25** to the solution of **17** or **18** in chloroform led to important increase of the fluorescent emission of both compounds. The hydroxyl signals of the saccharides in ^{1}H NMR spectrum in chloroform-*d* also moved downfield remarkably upon addition of **17** or **18**. These observations indicate that the metallocyclophanes are able to complex the saccharides in chloroform. Job' plots for the mixture solution of **17** with **21** in chloroform-*d* revealed largest downfield shifting for the CH_2OH signal in the ^{1}H NMR spectrum when the ratio of **17** and **21** is 1:1,[11] which supported a 1:1 binding stoichiometry between the metallocyclophane and the saccharide. Similar 1:1 stoichiometry was also observed with the fluorescent method for the system of **17** and **24**. Quantitative binding studies were then preformed with both the fluorescent and ^{1}H NMR titration methods,[12] and the corresponding association constants K_{assoc} were derived by fitting the data to a 1:1 binding mode, which are listed in Table 1. As an example, the plot of the emission intensity of **17** vs [**25**] in chloroform is provided in Figure 2.

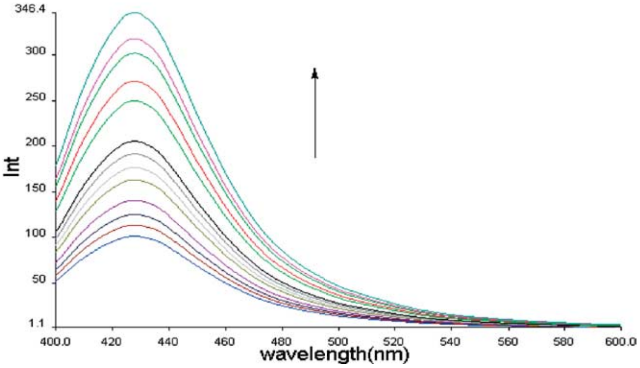


Figure 2. Fluorescent spectra of metallocyclophane **17** (5.5×10^{-5} M, excitation wavelength = 375 nm) in chloroform at 23 °C, increased gradually with the addition of disaccharide **25** (from 0 to 1.2×10^{-3} M).

It can be found that both **17** and **18** exhibit greater binding ability for disaccharides than for monosaccharides. This selectivity might suggest that, in addition to the expected binding between the C=O and OH groups, the OH groups of the longer disaccharides can also bind the ether oxygen or amide nitrogen of **17** and **18**. Table 1 also shows that, for all the saccharide guests, **17** displays greater binding ability than **18**, which may be ascribed to its larger cavity and consequently a reduced hindrance of the PEt_3 units. Since the binding between the metallocyclophanes and the saccharides are a dynamic process, we are not able to establish the exact binding pattern of the complexes at the present stage, but the 1:1 binding mode seems to indicate that the binding takes place in the cavity of the metallocyclophanes. The binding ability of **1** and **2** towards **19** was also investigated in chloroform-*d* with the ^{1}H NMR titration method, which gave a K_{assoc} value of 58 and 32 M^{-1} for complexes **1**·**19** and **2**·**19**, respectively.

Table 1. Association constants K_{assoc} (M^{-1}) of complex between **17** and **18** and mono- and disaccharide derivatives **19–25** in chloroform at 23 °C[a]

	17	**18**		**17**	**18**
19	1.4×10^3	7.4×10^2	**22**	3.0×10^3	9.4×10^2
20	5.6×10^3	2.1×10^3	**23**	6.4×10^3	2.9×10^3
20[b]	5.4×10^3	2.4×10^3	**24**	2.5×10^4	9.4×10^3
21	3.4×10^3	1.1×10^3	**25**	4.3×10^4	7.8×10^3

[a] With error of less than 20%.

[b] Determined by the ^{1}H NMR titration method.

3. Conclusion

In summary, we have demonstrated that intramolecular hydrogen bonding can be utilized to rigidify the conformation of bisphenylacetylene building blocks and consequently facilitate the self-assembly of a new series of rigid and planar metallocyclophanes. The hydrogen bonded metallocyclophanes represent a new series of synthetic receptors for saccharide derivatives albeit in the less polar chloroform. In principle, the spatial separation of the two acetylene units in the assembled building blocks can be increased conveniently by introducing longer oligo-anthranilamide linkers, which would lead to the formation of new metallocyclophanes with extended cavity size. Moreover, replacing the acetylene units with other functional groups such as pyridyl units would also provide new opportunity to construct other kinds of metallocyclophanes. Investigations along these lines are being performed in our laboratory.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures. All reactions were carried out under an atmosphere of nitrogen. Silica gel (1–4 μ) was used for column chromatography. Compounds **19**,[13] **20**,[14] **21**,[15] **22**,[16] **23**,[17] **25**[18] were prepared according to reported methods.

4.1.1. 4-Bromo-2-nitro-phenol (3). A suspension of 4-bromophenol (6.92 g, 40.0 mmol), oxone (24.4 g, 40.0 mmol), wet silica gel (0.40 g) and sodium nitrile (2.76 g, 40.0 mmol) in dichloromethane (120 mL) was stirred at room temperature for 2 h. The solid was filtered and the filtrate was washed with water (30 mL × 3), brine (30 mL), dried over sodium sulfate, and evaporated in vacuo. The resulting residue was recrystallized from ethanol to afford compound **3** as a yellow sheet crystal (7.60 g, 88%). Mp 88–89 °C (87 °C, lit.[19]). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.07–7.10 (d, $J = 6.5$ Hz, 1H), 7.67 (d, d, $J_1 = 6.5$ Hz, $J_2 = 2.2$ Hz, 1H), 8.25 (d, $J = 2.2$ Hz, 1H), 10.5 (s, 1H). MS (EI): *m/z* 219 [M]$^+$.

4.1.2. 4-Bromo-2-nitro-1-*n*-octyloxy-benzene (4). A mixture of compound **2** (5.00 g, 25.0 mmol), 1-bromooctane (6.00 g, 30.0 mmol) and potassium carbonate (4.00 g, 30.0 mmol) in DMF (80 mL) was stirred at 100 °C for 2 h, and then poured into water (250 mL). The mixture was extracted with ethyl acetate (75 mL × 3) and the combined organic phase was washed with water (100 mL), brine (100 mL), and dried over sodium sulfate. After the solvent was removed under reduced pressure, the resulting crude product was purified with column chromatography (petroleum ether/AcOEt 8:1) to give compound **4** as a yellow oil (7.57 g, 98%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.27–1.48 (m, 10H), 1.79–1.84 (m, 2H), 4.06 (t, $J = 6.2$ Hz, 2H), 6.96 (d, $J = 6.6$ Hz, 1H), 7.59 (d, d, $J_1 = 6.6$ Hz, $J_2 = 2.2$ Hz, 1H), 7.93 (d, $J = 2.2$ Hz, 1H). MS (EI): *m/z* 329 [M]$^+$. Anal. Calcd for $C_{14}H_{20}BrNO_3$: C, 50.92; H, 6.10. Found: C, 51.14; H, 6.22.

4.1.3. 2-Methyl-4-(3-nitro-4-octyloxy-phenyl)-but-3-yn-2-ol (6). To a solution of compounds **4** (2.10 g, 6.30 mmol) and **5** (0.87 g, 10.0 mmol) in THF (30 mL) was added [Pd(PPh$_3$)$_4$] (0.24 g, 0.30 mmol, 5%), CuI (60.0 mg, 0.30 mmol) and triethylamine (2.0 mL). The reaction mixture was stirred at 50 °C for 12 h and then poured into concentrated in vacuo. The resulting residue was triturated with ethyl acetate (150 mL) and the organic phase was washed with water (50 mL), brine (50 mL), dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting brown oil was subjected to flash chromatography (CH$_2$Cl$_2$/petroleum ether 1:2) to give compound **6** (1.43 g, 68%) as a yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz):δ 0.86–0.90 (m, 3H), 1.27–1.50 (m, 10H), 1.61 (s, 6H), 1.80–1.85 (m, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 6.99 (d, $J = 6.6$ Hz, 1H), 7.53 (d, d, $J_1 = 6.5$ Hz, $J_2 = 2.2$ Hz, 1H), 7.87 (d, $J = 2.2$ Hz, 1H). MS (EI): *m/z* 333 [M]$^+$. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.12; H, 8.04; N, 4.05.

4.1.4. 4-Ethynyl-2-nitro-1-octyloxy-benzene (7). A suspension of compound **6** (1.20 g, 3.60 mmol) and potassium hydroxide (0.28 g, 5.00 mmol) in benzene (60 mL) was refluxed for 3 h and then concentrated in vacuo. The resulting residue was triturated with dichloromethane (60 mL) and the organic phase was washed with dilute hydrochloric acid (1 N, 20 mL), water (20 mL), brine (20 mL), and dried over sodium sulfate. After removal of the solvent in vacuo, the crude product was purified with column chromatography (CH$_2$Cl$_2$/petroleum ether 1:3) to afford compound **7** as a yellow solid (0.81 g, 80%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.25–1.49 (m, 10H), 1.78–1.88 (m, 2H), 3.07 (s, 1H), 4.10 (t, $J = 6.5$ Hz, 2H), 7.00 (d, $J = 6.6$ Hz, 1H), 7.59–7.62 (d, d, $J_1 = 6.6$ Hz, $J_2 = 2.2$ Hz, 1H), 7.94 (d, $J = 2.2$ Hz, 1H). MS (EI): *m/z* 275 [M]$^+$. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.02; H, 7.81; N, 4.97.

4.1.5. 5-Ethynyl-2-octyloxy-phenylamine (8). To a solution of compound **7** (0.70 g, 2.50 mmol) in THF (20 mL) was added zinc powder (0.65 g, 10.0 mmol) and concentrated ammonia solution (30 mL). The mixture was stirred under reflux 3 h. After the solid was filtered, the filtrate was concentrated in vacuo and the resulting residue triturated with dichloromethane (150 mL). The organic phase was washed with aqueous sodium carbonate (0.5 N, 50 mL), water (50 mL), brine (50 mL), and dried over sodium sulfate. The solvent was then distilled under reduced pressure, the crude product was subjected to flash chromatography (CH$_2$Cl$_2$/petroleum ether 1:2.5) to give compound **8** (5.62 g, 92%) as a pale yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.87–0.91 (m, 3H), 1.26–1.48 (m, 10H), 1.76–1.85 (m, 2H), 2.94 (s, 1H), 3.81 (br, 2H), 3.98 (t, $J = 6.4$ Hz, 2H), 6.68 (d, $J = 6.6$ Hz, 1H), 6.85 (d, d, $J_1 = 6.6$ Hz, $J_2 = 2.2$ Hz, 1H), 6.89 (d, $J = 2.2$ Hz, 1H). MS (EI):

m/*z* 245 $[\mathrm{M}]^+$. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.22; H, 9.43; N, 5.69.

4.1.6. *N*,*N′*-bis-(5-Ethynyl-2-octyloxy-phenyl)-4,6-bis-octyloxy-isophthalamide (1). Compound **9** was prepared from the reaction of oxalyl chloride and the corresponding diacid[20] in the presence of catalytic amount of DMF. After the volatile materials were removed under reduced pressure, the resulting oily compound **9** was used for the next step with further purification. To a solution of compound **9** (0.30 g, 0.29 mmol) in dichloromethane (30 mL) was added a solution of compound **8** (0.15 g, 0.61 mmol) and triethylamine (0.5 mL). After stirring at room temperature for 0.1 h, the mixture was washed with water, brine, dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting brown oil was subjected to flash chromatography (CH_2Cl_2/EtOAc 100:1) to give **1** (0.18 g, 68%) as a light green solid. Mp 201 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 12H), 1.25–1.43 (m, 40H), 1.77–1.82 (m, 4H), 1.89–1.94 (m, 4H), 2.98 (s, 2H), 4.04 (t, $J=6.6$ Hz, 4H), 4.22 (t, $J=6.5$ Hz, 4H), 6.49 (s,1H), 6.78 (d, $J=6.5$ Hz, 2H), 7.17 (d, d, $J_1=6.5$ Hz, $J_2=2.2$ Hz, 2H), 8.80 (d, $J=2.2$ Hz, 2H), 9.07 (s, 1H), 9.80 (s, 2H). IR: ν 3315, 3224, 2955, 2925, 2854, 2103, 1664, 1580, 1537, 1423, 1232, 1021, 799, 676 cm^{-1}. MS (MALDI-TOF): *m*/*z* 877 $[\mathrm{M}]^+$. Anal. Calcd for $C_{56}H_{80}N_2O_6$: C, 76.67; H, 9.19; N, 3.19. Found: C, 76.35; H, 8.98; N, 3.42.

4.1.7. 5-Iodo-2-octyloxy-benzoic acid methyl ester (12). A mixture of compound **11**[20a] (14.0 g, 53.0 mmol), iodine (14.0 g, 55.0 mmol) and silver sulfate (17.0 g, 55.0 mmol) in methanol (200 mL) was stirred at room temperature for 0.5 h and then concentrated in vacuo. The resulting residue was triturated with ethyl acetate (300 mL). The organic phase was washed with water (120 mL×2), brine (120 mL), and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the resulting residue was subjected to flash chromatography (dichloromethane) to give compound **12** (19.9 g, 96%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.25–1.48 (m, 10H), 1.76–1.83 (m, 2H), 3.87 (s, 3H), 3.98 (t, $J=6.4$ Hz, 2H), 6.72 (d, $J=6.6$ Hz, 1H), 7.68 (d, d, $J_1=6.6$ Hz, $J_2=2.2$ Hz, 1H), 8.04 (d, $J=2.2$ Hz, 1H). MS (EI): *m*/*z* 390 $[\mathrm{M}]^+$. Anal. Calcd for $C_{16}H_{23}IO_3$: C, 49.24; H, 5.94. Found: C, 49.11; H, 6.21.

4.1.8. 5-(3-Hydroxy-3-methyl-but-1-ynyl)-2-octyloxy-benzoic acid methyl ester (13). A suspension of compounds **12** (4.00 g, 10.3 mmol), **5** (1.30 g, 15.0 mmol), $Pd(PPh_3)_4$ (0.38 g, 0.50 mmol, 5%), and CuI (0.10 g, 0.50 mmol) in pyrrolidine (30 mL) was stirred at 60 °C for 2 h and then concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate (150 mL) and the organic phase was washed with dilute hydrochloric acid (1 N, 50 mL), water (50 mL), brine (50 mL), and dried over sodium sulfate. After the solvent was distilled under reduced pressure, the resulting crude product was subjected to flash chromatography (CH_2Cl_2) to give compound **13** (2.58 g, 72%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.28–1.50 (m, 10H), 1.60 (s, 6H), 1.77–1.84 (m, 2H), 3.87 (s, 3H), 4.02 (t, $J=6.6$ Hz, 2H), 6.88 (d, $J=6.5$ Hz, 1H), 7.47 (d, d, $J_1=6.5$ Hz, $J_2=2.2$ Hz, 1H), 7.85 (d, $J=2.2$ Hz, 1H). MS (EI): *m*/*z* 346 $[\mathrm{M}]^+$. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.88.

4.1.9. 5-(3-Hydroxy-3-methyl-but-1-ynyl)-2-octyloxy-benzoic acid (14). Compound **13** (2.00 g, 5.80 mmol) and potassium hydroxide (0.56 g, 10.0 mmol) were added to a mixture of methanol (50 mL) and water (20 mL). The mixture was stirred under reflux for 2 h and concentrated to about 20 mL. The solution was neutralized with dilute hydrochloric acid (2 N) and then extracted with dichloromethane (30 mL×2). The combined organic phase was washed with water (20 mL×3), brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting brown residue was subjected to flash chromatography (CH_2Cl_2/EtOAc 10:1) to give intermediate **14** (1.75 g, 91%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85–0.90 (m, 3H), 1.25–1.49 (m, 10H), 1.60 (s, 6H), 1.88–1.93 (m, 2H), 4.22–4.26 (t, $J=6.6$ Hz, 2H), 6.96 (d, $J=6.4$ Hz, 1H), 7.56 (d, d, $J_1=6.4$ Hz, $J_2=2.3$ Hz, 1H), 8.22 (d, $J=2.3$ Hz, 1H). MS (EI): *m*/*z* 332 $[\mathrm{M}]^+$. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.27; H, 8.64.

4.1.10. 5-Ethynyl-2-octyloxy-benzoic acid (15). To a solution of acid **13** in benzene (80 mL) was added potassium hydroxide (0.56 g, 10.0 mmol). The mixture was refluxed for 3 h. After normal workup, the crude product was chromatographed (CH_2Cl_2) to afford compound **15** as a pale yellow solid (1.50 g, 78%). Mp 63–64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86–0.90 (m, 3H), 1.25–1.48 (m, 10H), 1.89–1.94 (m, 2H), 3.06 (s, 1H), 4.26 (t, $J=6.5$ Hz, 2H), 6.99 (d, $J=6.6$ Hz, 1H), 7.64 (d, d, $J_1=6.5$ Hz, $J_2=2.2$ Hz, 1H), 8.32 (d, $J=2.2$ Hz, 1H), 10.84 (br, 1H). MS (EI): *m*/*z* 274 $[\mathrm{M}]^+$. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.30; H, 8.17.

4.1.11. *N*,*N′*-bis-(5-Ethynyl-2-octyloxy-benzoyl)-4,6-bis-methoxy-1,3-phenylenediamine (2). A solution of compounds **15** (0.14 g, 0.50 mmol) and **16**[21] (42.0 mg, 0.25 mmol), in dichloromethane (20 mL) was stirred in ice bath for 30 min. A solution of HOBt (90.0 mg, 0.58 mmol) and DCC (0.12 g, 0.58 mmol) in dichloromethane (10 mL) was added. Stirring was continued for another 12 h and the solid was filtered. The filtrate was evaporated in vacuo and the resulting residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 10:1) to give compound **2** as a yellow solid (0.11 g, 63%). Mp 197 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 6H), 1.25–1.51 (m, 20H), 1.92–2.01 (m, 4H), 3.01 (s, 2H), 3.90 (s, 6H), 4.18 (t, $J=6.6$ Hz, 4H), 6.54 (s, 1H), 6.93 (d, $J=6.5$ Hz, 2H), 7.54 (d, d, $J_1=6.5$ Hz, $J_2=2.2$ Hz, 2H), 8.50 (d, $J=2.2$ Hz, 2H), 9.53 (s, 1H), 9.97 (s, 2H). IR: ν 3351, 3298, 3251, 2106, 1662, 1542, 1470, 1421, 1249, 1201, 1027, 810, 684 cm^{-1}. MS (MALDI-TOF): *m*/*z* 680 $[\mathrm{M}]^+$, 703 $[\mathrm{M+Na}]^+$, 719 $[\mathrm{M+K}]^+$. Anal. Calcd for $C_{42}H_{52}N_2O_6$: C, 74.08; H, 7.70; N, 4.11. Found: C, 74.05; H, 7.73; N. 3.82.

4.1.12. Metallocyclophane 17. To a solution of compounds **1** (0.10 g, 0.11 mmol) and *trans*-$PtCl_2(PEt_3)_2$ (60.0 mg, 0.11 mmol) in dichloromethane (100 mL) was added diethylamine (0.5 mL) and cupric chloride (5 mg) with stirring. The mixture was stirred at room temperature for 12 h and washed with dilute hydrochloric acid (1 N, 20 mL), water (20 mL × 3), brine (30 mL), and dried over sodium sulfate. The solvent was removed in vacuo and the resulting residue purified by column chromatography (CH_2Cl_2/MeOH 200:1) to afford compound **17** as a light yellow solid (58 mg, 20%). Mp 253 °C (decomp.). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 24H), 1.19–1.44 (m, 116H), 1.77–1.82 (m, 8H), 1.93–1.98 (m, 8H), 2.22–2.29 (m, 24H), 4.05 (t, $J=6.5$ Hz, 8H), 4.26 (t, $J=6.6$ Hz, 8H), 6.53 (s, 2H), 6.72 (d, $J=6.5$ Hz, 4H), 6.95 (d, d, $J_1=6.5$ Hz, $J_2=2.2$ Hz, 4H), 8.78 (d, $J=2.2$ Hz, 4H), 9.27 (s, 2H), 9.90 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 8.1, 8.5, 14.2, 16.3, 16.5, 16.7, 22.6, 22.7, 22.71, 25.9, 25.9, 28.9, 29.3, 29.3, 29.4, 29.4, 29.5, 29.8, 31.8, 31.8, 31.9, 68.9, 70.0, 111.0, 116.7, 128.7, 145.5, 159.6, 162.0. IR: ν 3358, 2958, 2928, 2855, 2101, 1666, 1577, 1531, 1481, 1230, 1035, 766, 670 cm^{-1}. MS (MALDI-TOF): *m/z* 2613 $[M+H]^+$. Anal. Calcd for $C_{136}H_{216}N_4O_{12}P_4Pt_2$: C, 62.46; H, 8.37; N, 2.14. Found: C, 62.72; H, 8.53; N, 2.05.

4.1.13. Metallocyclophane 18. A suspension of compounds **2** (0.10 g, 0.16 mmol), *trans*-$PtCl_2(Et_3P)_2$ (83.0 mg, 0.16 mmol), cupric acid (5.0 mg), and diethylamine (0.5 mL) in dichloromethane (150 mL) was stirred at room temperature for 12 h. After workup as described **17**, the resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH 40:1) to afford **18** as a light yellow solid (52 mg, 15%). Mp 250 °C (decomp.). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.84–0.88 (m, 12H), 1.21–1.50 (m, 80H), 1.95–2.00 (m, 8H), 2.20–2.28 (m, 24H), 3.90 (s,12H), 4.14 (t, $J=6.6$ Hz, 8H), 6.54 (s, 2H), 6.82 (d, $J=6.3$ Hz, 4H), 7.29 (d, d, $J_1=6.3$ Hz, $J_2=2.2$ Hz, 4H), 8.38 (d, $J=2.2$ Hz, 4H), 9.99 (s, 2H), 10.15 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 9.7, 15.4, 17.5, 17.7, 18.0, 24.0, 27.2, 30.5, 30.6, 30.7, 33.1, 56.9, 70.8, 96.2, 101.5, 113.2, 122.8, 123.4, 135.6, 137.5, 146.1, 155.7, 163.7. IR: ν 3353, 2960, 2929, 2855, 2101, 1666, 1542, 1469, 1421, 1201, 1036, 768, 733 cm^{-1}. MS (MALDI-TOF): *m/z* 2242 $[M+K]^+$. Anal. Calcd for $C_{108}H_{160}N_4O_{12}P_4Pt_2$: C, 58.42; H, 7.26; N, 2.52. Found: C, 58.76; H, 6.90; N, 2.14.

4.1.14. Compound 28. The method by Stadler et al. was used to prepare this compound.[22] A mixture of lactose **26** (1.70 g, 5.00 mmol) and lauryl amine **27** (1.00 g, 5.50 mmol) in methanol (10 mL) was stirred at 65 °C overnight and then concentrated under reduced pressure. The resulting residue was subject to column chromatography (CH_2Cl_2/MeOH 2:1) to afford compound **28** as a pale yellow solid (1.35 g, 53%). ^1H NMR (CD_3OD, 300 MHz): δ 0.88–0.93 (m, 3H), 1.29–1.37 (m, 18H), 1.509–1.52 (m, 2H), 2.58–2.67 (m, 1H), 2.84–2.91 (m, 1H), 3.10–3.16 (t, $J=4.6$ Hz, 1H), 3.30–3.31 (m, 2H), 3.33–3.37 (m, 1H), 3.49–3.60 (m, 4H), 3.70–3.87 (m, 5H), 4.34–4.37 (d, $J=5.0$ Hz, 1H). MS (ESI): *m/z* 510 $[M+H]^+$. $C_{24}H_{47}NO_{10}$: C, 56.56; H, 9.30; N, 2.75. Found: C, 55.67; H, 9.43; N, 2.62.

4.1.15. Compound 24. To a stirred solution of lauric acid (0.60 g, 3.00 mmol) and methyl chloroformate (0.33 g, 3.00 mmol) in THF (8 mL) was added triethylamine (0.42 mL, 3.00 mmol) dropwise at 0 °C. The mixture was stirred for another 1 h at room temperature and filtered rapidly. The filtrate was then added to a solution of **28** (1.52 g, 3.00 mmol) in DMF. After stirring for another 12 h, the solvent was removed under reduced pressure. The resulting residue was triturated with chloroform (100 mL) and the organic phase was washed with water (20 mL × 3), brine (20 mL) and dried over magnesium sulfate. Upon removal of the solvent with a rotavapor, the resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH 8:1) to give **24** as a white solid (0.14 g, 67%). Mp 134 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88–0.92 (m, 6H), 1.29–1.37 (m, 34H), 1.59–1.63 (m, 4H), 2.45–2.48 (t, $J=5.3$ Hz, 2H), 3.29–3.31 (m, 4H), 3.47–3.60 (m, 8H), 3.71–3.87 (m, 6H), 4.36–4.385 (d, $J=5.7$ Hz, 1H). MS (ESI): *m/z* 692 $[M+H]^+$. Anal. Calcd for $C_{36}H_{69}NO_{11}\cdot H_2O$: C, 60.90; H, 10.08; N, 1.97. Found: C, 60.72; H, 10.02; N. 1.87.

4.1.16. Crystal data for compound 1. $C_{43}H_{54}N_2O_6C_{l2}$, $M=765.78$, triclinic, space group P-1, $a=11.415(4)$ Å, $b=12.505(4)$ Å, $c=15.308(5)$ Å, $\alpha=94.678(7)$, $\beta=99.096(7)$, $\gamma=103.542(6)$, $U=2081.7(12)$ $Å^3$, $Z=2$, calcd density $=1.222$ Mg/m^3, absorption coefficient $=0.204$ mm^{-1}, 12,824 reflections collected (unique 9300), $R_{int}=0.1294$, crystal size: 0.488 × 0.350 × 0.148 mm.

4.1.17. Binding studies. For the fluorescent titration experiments, 2.5 mL of the mixture solution with the fixed concentration of **17** or **18** and the changing concentration of saccharide guests was placed in a cuvette and the fluorescent spectra (usually 15–20 spectra) were sequentially recorded at 23 °C. The values of the emission strength at fixed wavelengths were used. Origin 6.0 software was used to fit the data to a 1:1 binding isotherm: $\Delta I=(\Delta I_{max}/[H])\times\{0.5[G]+0.5([H]+K_d)\text{-}0.5[[G]^2+(2[S](K_d\text{-}[H])+(K_d+[H])^2)^{1/2}]\}$, where $[H]$ is the concentration of metallocyclophane, $[G]$ is the concentration of saccharide, and $K_d=(K_{assoc})^{-1}$. Association constants reported are the average values of two experiments. The ^1H NMR titration followed the same principle.

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References and notes

1. (a) Dietrich, B.; Viout, P.; Lehn, J. M. Macrocyclic Chemistry: Aspects of Organic and Inorganic Supra Molecular Chemistry; VCH: Weinheim, 1993; p 384. (b) Parker, D., Ed.; Oxford University Press: Oxford, 1996; p 252.
2. Blanco, M.-J.; Jimynez, M. C.; Chambron, J.-C.; Heitz, V.; Linke, M.; Sauvage, J.-P. *Chem. Soc. Rev.* **1999**, *28*, 293–306. (b) Baxter, P. N. W.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1999**, *5*, 102–112. (c) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005–2062. (d) Sanders, J. K. M. *Pure Appl. Chem.* **2000**, *72*, 2265–2274. (e) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509–518. (f) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972–983.

(g) Baldini, L.; Hunter, C. A. *Adv. Inorg. Chem.* **2002**, *53*, 213–243. (h) Schalley, C. A.; Lützen, A.; Albrecht, M. *Chem. Eur. J.* **2004**, *10*, 1072–1080.

3. Dinolfo, P. H.; Hupp, J. T. *Chem. Mater.* **2001**, *13*, 3113–3125. (b) Merlau, M. L.; del Pilar, M. M.; Nguyen, S. T.; Hupp, J. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4239–4242. (c) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2001**, *123*, 10454–10459. (d) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347–1349. (e) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948–12949. (f) Gianneschi, N. C.; Bertin, P. A.; Nguyen, S. T.; Mirkin, C. A.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 10508–10509.
4. Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180. (c) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714–723. (d) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012. (e) Sanford, A. R.; Gong, B. *Curr. Org. Chem.* **2003**, *7*, 1649–1659.
5. Delnoye, D. A. P.; Sijbesma, R. P.; Vekemans, J. A. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **1996**, *118*, 8717–8718.
6. Wu, Z.-Q.; Jiang, X.-K.; Zhu, S.-Z.; Li, Z.-T. *Org. Lett.* **2004**, *6*, 229–232.
7. Whiteford, J. A.; Lu, C. V.; Stang, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 2524–2533. (b) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948–12949. (c) Jiang, H.; Hu, A.; Lin, W. *Chem. Commun.* **2003**, 96–97. (d) Jiang, H.; Lin, W. *Org. Lett.* **2004**, *6*, 861–865.
8. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587–10593. (b) Parra, R. D.; Zeng, H.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Eur. J.* **2001**, *7*, 4352–4357.
9. Legon, A. C. *Chem. Soc. Rev.* **1990**, *19*, 197–238.
10. Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev.* **1997**, *97*, 1567–1608. (b) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978–2996. (c) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200. (d) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81–102.
11. Job, P. *Ann. Chim. Ser. 10* **1928**, *9*, 113–134.
12. Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.
13. Pathak, A. K.; Pathak, V.; Maddry, J. A.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 3145–3151.
14. de Goede, A. T. J. W.; Benckhuijsen, W.; van Rantwijk, F.; Maat, L.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 567–576.
15. Konstantinovic, S.; Imitrijevic, B.; Adulovic, V.; Indian *J. Chem. Sect. B* **2002**, *41*, 598–604.
16. Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243–2289.
17. Kikuchi, Y.; Toi, H.; Aoyama, Y. *Bull. Chem. Soc. Jpn* **1993**, *66*, 1856–1862.
18. Turnbull, W. B.; Bruce, W.; Harrison, J. A.; Kartha, K. P. R.; Schenkman, S.; Field, R. A. *Tetrahedron* **2002**, *58*, 3207–3216.
19. Zolfigol, M. A.; Ghaemi, E.; Madrakian, E. *Synlett* **2003**, 191–194.
20. Zeng, H.; Miller, R. S.; Flowers, R. A.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635–2644. (b) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15129–15142.
21. Corbett, J. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 999–1005.
22. Lockhoff, O.; Stadler, P. *Carbohydr. Res.* **1998**, *314*, 13–19.

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Ring-expanded analogues of natural oxetanocin

Vasu Nair,[a,b,*] Byoung-Kwon Chun[b] and Jean John Vadakkan[a]

[a]*Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Room 320A, R. C. Wilson PH, Athens, GA 30602, USA*
[b]*Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA*

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Abstract—Synthesis of ring-expanded analogs of the natural compound, oxetanocin is described. The starting material for the synthesis of the series, **4–7**, was D-glucosamine and introduction of the base moiety was done through the stereochemically appropriate epoxide. For the enantiomeric series, **8–11**, the starting material was D-glucose and preparation of the key intermediate involved a rearrangement reaction. The structures of the target molecules were established by NMR, HRMS, optical rotation and UV data. Single-crystal X-ray data confirmed the enantiomeric structural assignments.

1. Introduction

Oxetanocin (**1**), a natural nucleoside with a surrogate carbohydrate moiety isolated from bacterial sources, exhibits anti-HIV activity.[1] In designing ring-expanded analogs of oxetanocin that would have the potential for antiviral activity, we envisaged that a combination of the structural features of the surrogate carbohydrate moiety of oxetanocin with the sugar component of another antiviral compound, 4(*S*)-(adenin-9-yl)-2(*S*)-hydroxymethyltetrahydrofuran [(*S*,*S*)-isoddA] (**2**) (Fig. 1) would be of interest.[2–5] Earlier work in our laboratory had led to the discovery of (*S*,*S*)-isoddA which exhibits potent anti-HIV activity against HIV-1, HIV-2, and HIV-resistant strains. (*S*,*S*)-IsoddA triphosphate is among the strongest known inhibitors of HIV reverse transcriptase.[2] In addition, another isomeric nucleoside related to oxetanocin, compound **3**, shows antiviral activity against HSV-1 (KOS) and HSV-2 (186).[6] Our design of novel nucleosides included the enantiomeric purine isonucleosides **4** and **8** and the pyrimidine counterparts **5–7** and **9–11** (Fig. 2).

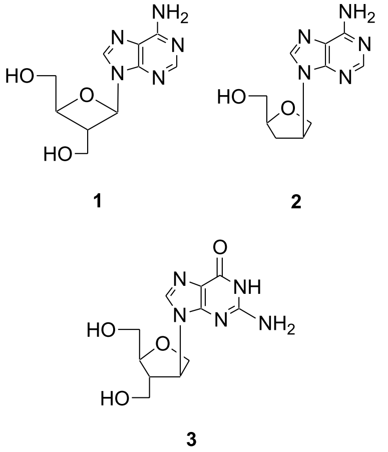

Figure 1. Structures of oxetanocin, (*S*,*S*)-IsoddA and an analog of oxetanocin.

2. Results and discussion

In order to synthesize target compounds (**4–7**), epoxide **13** was prepared from D-glucosamine using a known method.[7,8] The ditrityl derivative, **12**, under Mitsunobu conditions, gave the key precursor **13** in 89% yield (Scheme 1). An S_N2-type condensation of **13** with the sodium salt of adenine in DMF at 120 °C[5] gave an inseparable diastereomeric mixture of **14** and **15** in 49% yield (**14**:**15** ratio = 3:1). The ratio of products reflects the higher steric hindrance to nucleophilic attack that is inherent on one of the two carbon centers of epoxide **13**. This product mixture was converted to the deoxygenated compounds **16** and **17** using the Barton deoxygenation.[9] Separation of the diastereoisomers by preparative silica gel TLC was possible at this stage to give **16** and **17** in 52 and 17% yield, respectively. Deprotection of **16** and **17** using 80% acetic acid gave the target compound **4** (74%) and its diastereoisomer **18** (72%).

Keywords: Oxetanocin; Stereochemical synthesis; Glucosamine; Epoxide; Rearrangement reaction; Enantiomers; NMR; X-ray.

* Corresponding author. Tel.: +1-706-542-6293; fax: +1-706-583-8283; e-mail: vnair@rx.uga.edu

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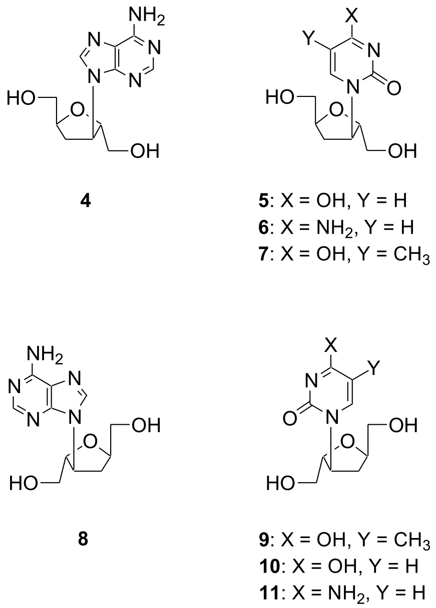
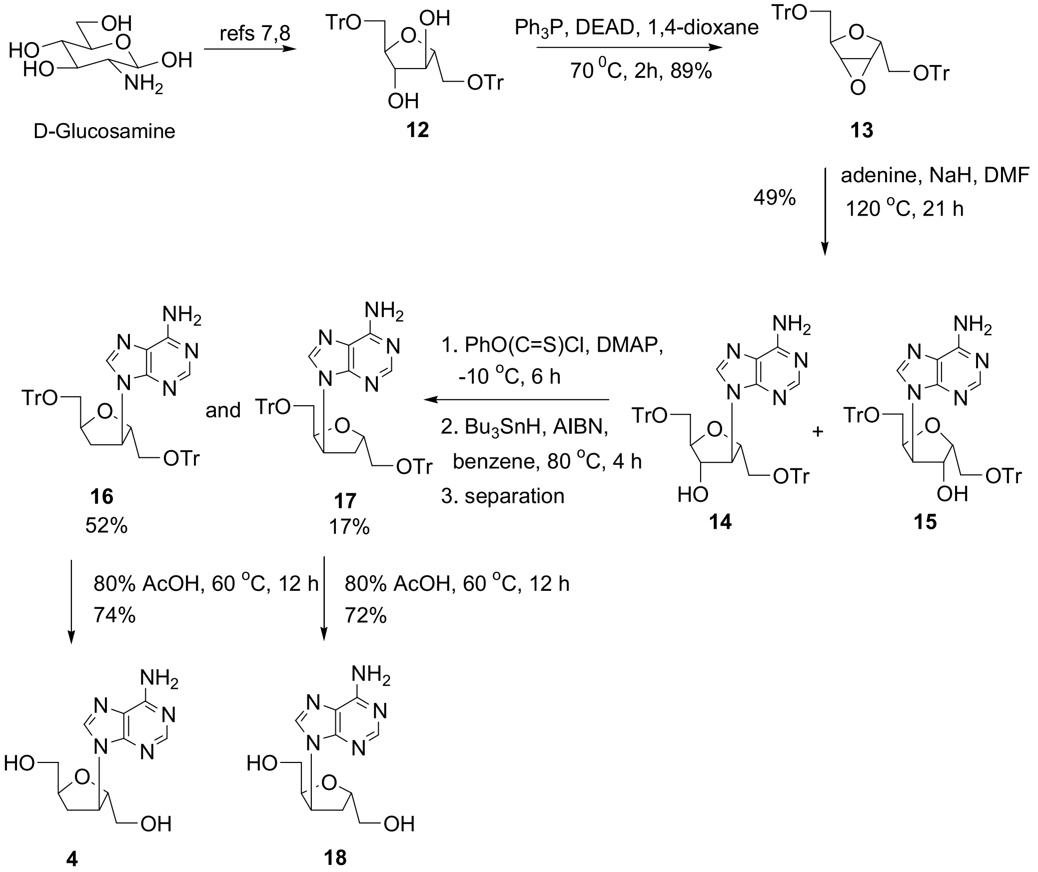


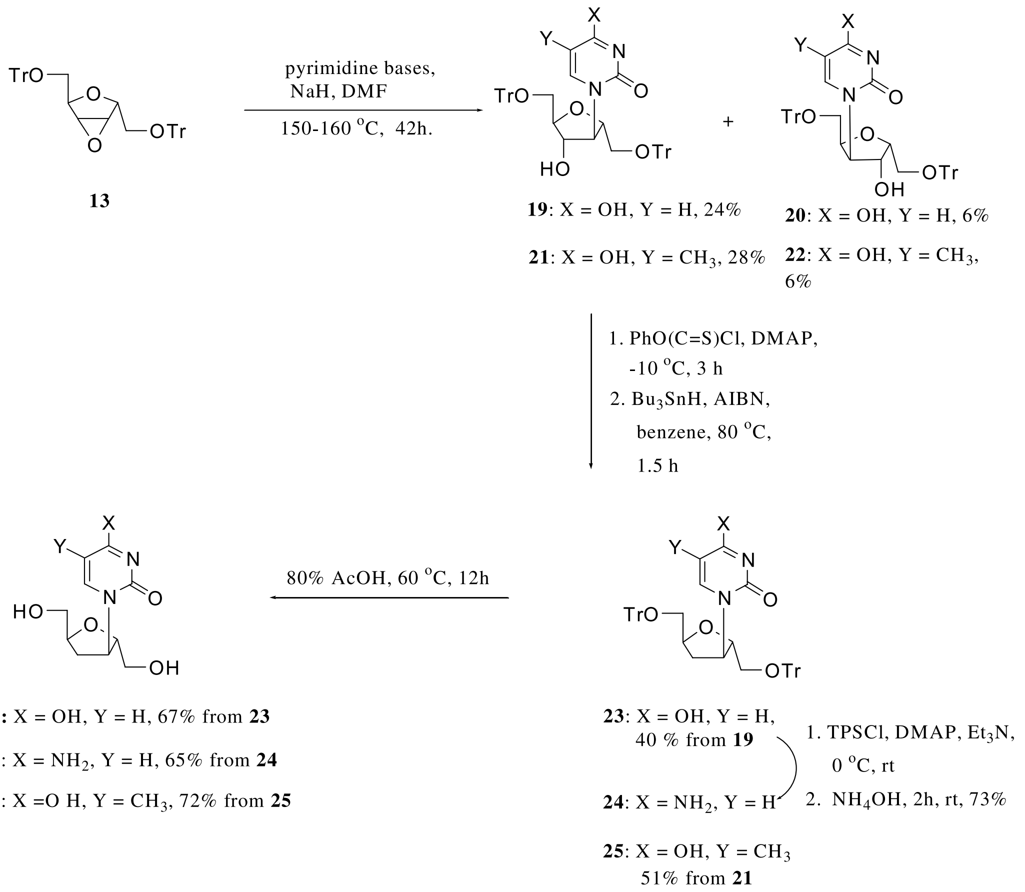
Figure 2. Ring-expanded analogs of oxetanocin.

For the preparation of pyrimidine derivatives, the key intermediate **13** was coupled with the sodium salt of uracil, under conditions similar to the preparation of adenosine analogue **14**, to give two products, **19** and **20** (Scheme 2). The major product **19** was deoxygenated to **23** (40% yield) and then aminated to cytidine analogue **24** (73% yield) by sequential treatment with 2,4,6-triisopropylbenzenesulfonyl chloride and ammonium hydroxide.[10] Finally, uridine and cytidine analogues, **5** and **6**, were prepared from the intermediates **23** and **24**, by deprotection with acetic acid respectively in 67 and 65% yield. Thymidine analogue **7** was similarly obtained from compound **13** via intermediates **21** and **25** (Scheme 2).

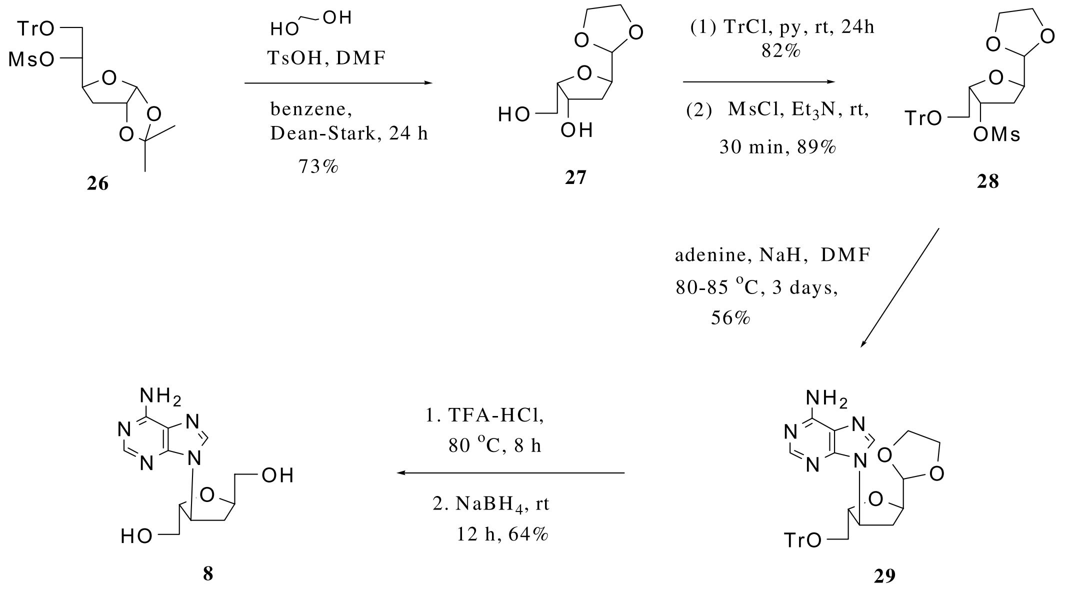
For the synthesis of the corresponding enantiomers (**8**–**11**), a different synthetic strategy was employed where starting material **26** was prepared from diacetone D-glucose using known procedures (Scheme 3).[11,12] To prepare key intermediate **28**, an acid-catalyzed rearrangement of **26**[13] was carried out to produce an aldehyde intermediate which, was under the conditions of the reaction, was transformed to the cyclic acetal **27**. Selective tritylation of the primary hydroxyl functionality (82%) followed by mesylation of the remaining hydroxyl group (89%) of **27** gave intermediate **28**. Coupling of **28** with the sodium salt of adenine in *N*,*N*-dimethylformamide at 80–85 °C gave the protected adenosine analogue **29** in 56% yield. The cyclic acetal of compound **29** was hydrolyzed with trifluoroacetic acid–HCl and the resulting aldehyde was reduced with $NaBH_4$ to the isoadenosine target **8** in 64% yield. Its structure was confirmed by single crystal X-ray data (Fig. 3). While its ^1H and ^{13}C NMR spectra were identical to that of its enantiomer, the dextrorotatory compound **4**, compound **8** was laevorotatory and the magnitude of its optical rotation was close to that for **4**. Thus, the spectroscopic data, the



Scheme 1.



Scheme 2.



Scheme 3.

crystal structure data, and the optical rotation data confirmed the structures of both **4** and **8**.

For the preparation of thymidine analogue **9**, the key intermediate **28** was treated with sodium salt of thymine in *N*,*N*-dimethylformamide at elevated temperatures to give protected thymidine analogue **30** (20%) which was converted to the target thymidine **9** in 67% yield (Scheme 4). Because of the low yield for the direct coupling, the synthesis of uracil and cytosine analogues utilized a base construction methodology from the amino intermediate **31** prepared in high yield from **28** through azide displacement and catalytic reduction. The amine **31** was treated with 3-methoxyacryloyl isocyanate,[14] freshly prepared from

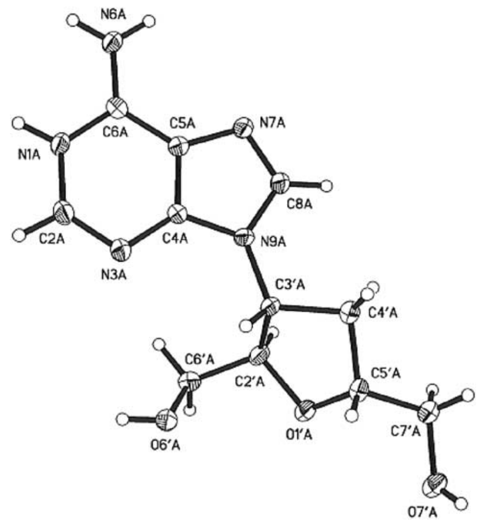


Figure 3. Ortep plot of single-crystal X-ray structure of compound **8**.

3-methoxyacryloyl chloride and silver cyanate, to give an acryloylurea intermediate which was cyclized to **32** (66%) under catalysis with ammonium hydroxide at 100 °C in a steel bomb. The isouridine analogue **10** was obtained from **32** in 67% yield by deprotection with trifluoroacetic acid and HCl followed by reduction with $NaBH_4$. Similarly, the final target cytidine analogue **11** was prepared from **10** in three steps in 36% yield (Scheme 4).

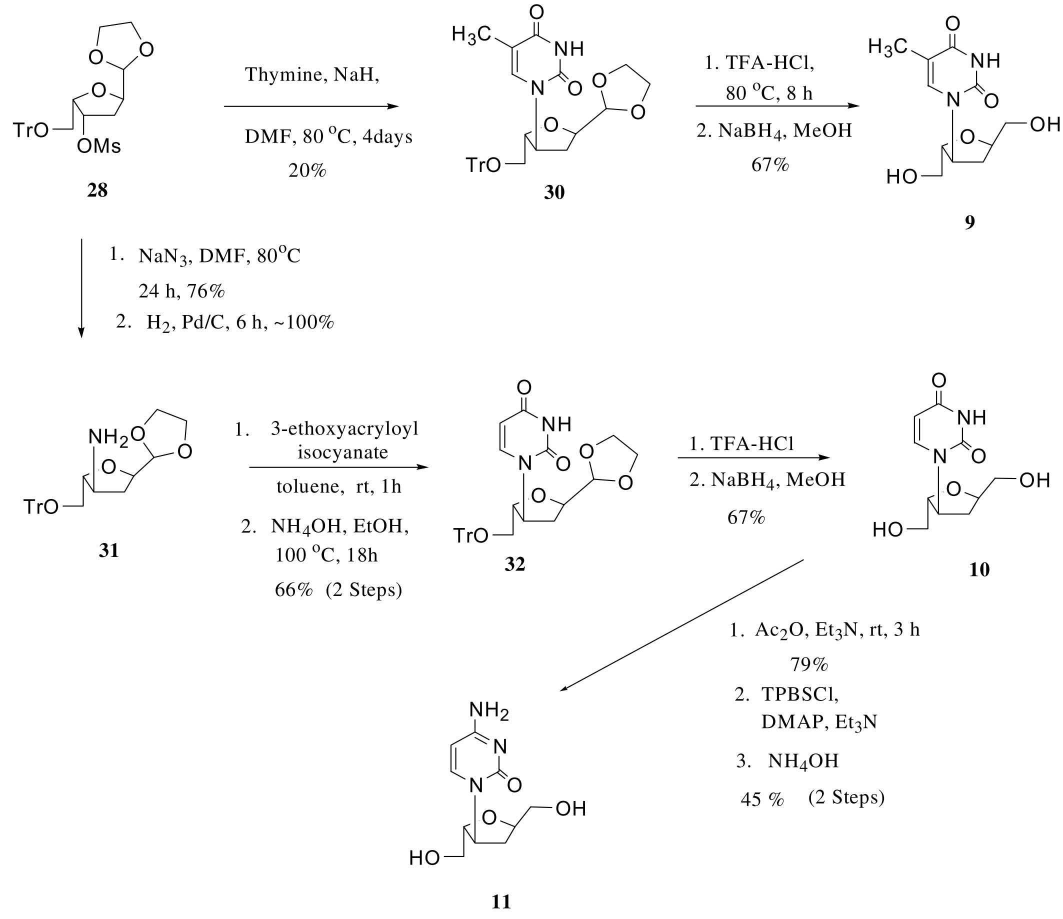
In summary, new enantiomeric isonucleoside analogs related to natural oxetanocin have been synthesized from D-glucose and D-glucosamine. The structures of the target compounds and intermediates were confirmed by NMR, HRMS, UV, single crystal X-ray and optical rotation data. These compounds are undergoing comprehensive antiviral testing against various viral infected cell lines and those results will be reported elsewhere.

3. Experimental

3.1. General

Melting points reported are uncorrected and were determined on an Electrothermal Engineering Ltd. melting point apparatus. Nuclear magnetic resonance spectra were recorded on Bruker Model AC300 and WM 360 systems. High-resolution mass spectral data were determined at the Nebraska Center for Mass Spectrometry. Ultraviolet spectra were recorded on a Varian Cary Model 3 spectrophotometer. Purities of intermediates and final products were determined by a combination of HPLC analyses, ^{13}C NMR spectra, HRMS data and quantitative UV data.

3.1.1. 2,5:3,4-Dianhydro-1,6-di-*O*-trityl-D-altritol (13). To a mixture of compound **12** (9.8 g, 15.11 mmol) and triphenylphosphine (7.9 g, 30.12 mmol) in anhydrous 1,4-dioxane (50 mL) was cooled to 0 °C and DEAD (4.8 mL,



Scheme 4.

30.48 mmol) in 8 mL anhydrous 1,4-dioxane was added with stirring under nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 2 h at 70 °C. The solvent was removed under vacuum and the residue obtained was separated by silica gel column chromatography (chloroform) to give compound **13**[15] as a white solid (8.5 g, 89%). Mp 166–168 °C; ^{1}H NMR (CDCl$_3$) δ (ppm) 7.57–7.23 (m, 30H), 4.35 (t, 1H, $J=6.3$ Hz), 4.24 (t, 1H, $J=4.2$ Hz), 4.02 (d, 1H, $J=3.0$ Hz), 3.75 (d, 1H, $J=3.0$ Hz), 3.45–3.32 (m, 3H), 3.19 (dd, 1H, $J=3.6$, 9.9 Hz); ^{13}C NMR (CDCl$_3$) δ (ppm) 144.0, 143.7, 128.8, 128.7, 128.0, 127.9, 127.2, 127.1, 87.0, 86.9, 77.5, 76.9, 64.2, 62.7, 58.3, 57.5; FABMS: 653 (M+Na)$^+$.

3.1.2. 4(*R*)-(Adenin-9-yl)-2(*R*),5(*S*)-di(trityloxymethyl)-3(*R*)-hydroxytetrahydrofuran (14) and 4(*S*)-(adenin-9-yl)-2(*R*),5(*S*)-di(trityloxymethyl)-3(*S*)-hydroxytetrahydrofuran (15). A mixture of adenine (936 mg, 6.93 mmol) and 60% sodium hydride (277 mg, 6.93 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL) was heated at 110 °C for 2 h and compound **13** (1.46 g, 2.31 mmol) in *N*,*N*-dimethylformamide (5 mL) was added under nitrogen atmosphere. The resulting reaction mixture was heated at 110–120 °C for 21 h. After removal of solvent under reduced pressure, the residue was separated by silica gel column chromatography (chloroform–methanol = 49:1) to give a mixture of compound **14** and **15** (14:15 ratio = 3:1 by ^{1}H NMR) as a white solid (866 mg, 49%). Data given for **14/15** mixture. UV $\lambda_{\max}$ 262 nm (MeOH); HRFABMS: calcd mass 766.3393 for C$_{49}$H$_{44}$N$_5$O$_4$, found 766.3413 (M+H)$^+$.

3.1.3. 3(*R*)-(Adenin-9-yl)-2(*S*),5(*S*)-di(trityloxymethyl) tetrahydrofuran (16) and 3(*S*)-(adenin-9-yl)-2(*S*),5(*S*)-di(trityloxymethyl)tetrahydrofuran (17). To a solution of the mixture of **14** and **15** (760 mg, 0.99 mmol) and 4-dimethyl-aminopyridine (242 mg, 1.98 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) was added phenyl chlorothionoformate (0.22 mL, 1.98 mmol) slowly at −10 °C over 10 min under nitrogen atmosphere. The resulting mixture was stirred at −10 °C for 6 h and the reaction was quenched with water (2 mL). After dilution with EtOAc (200 mL), the reaction mixture was washed with brine (3× 15 mL), dried on sodium sulfate, and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc) to give a xanthate intermediate (640 mg, 0.71 mmol, 71%), which was dried under high vacuum and dissolved in benzene (30 mL). To this solution, Bu$_3$SnH (1.47 mL, 5.46 mmol) and AIBN (70 mg, 0.41 mmol) were added and the resulting mixture was heated under reflux for 1.5 h and cooled to rt. Upon concentration, the residue was separated by preparative silica gel TLC (chloroform–methanol = 40:1) to afford compound **16** (268 mg, 52%) and compound **17** (88 mg, 17%) as oils. Compound **16**. UV $\lambda_{\max}$ 261 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 8.29 (s, 1H), 7.78 (s, 1H), 7.50–7.20 (m, 30H), 5.70 (s, 2H), 5.14 (q, 1H, $J=7.9$ Hz), 4.48 (m, 2H), 3.33 (d, 4H, $J=4.5$ Hz), 2.61 (dt, 1H, $J=7.2$, 13.4 Hz), 2.46 (m, 1H); ^{13}C NMR (CDCl$_3$) δ (ppm) 155.2, 152.7, 150.0, 143.9, 143.6, 138.8, 129.6, 128.7, 128.6, 127.9, 127.8, 127.1, 127.0, 87.0, 86.8, 81.2, 77.7, 65.9, 64.2, 56.7, 35.3; HRFABMS: calcd mass 750.3444 for C$_{49}$H$_{44}$N$_5$O$_3$, found 750.3464 (M+H)$^+$. Compound **17**. UV $\lambda_{\max}$ 261 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 8.23 (s, 1H), 7.68 (s, 1H), 7.51–7.14 (m, 30H), 5.63 (s, 2H), 4.65 (m, 1H), 4.57 (m, 1H), 3.26 (d, 2H, $J=4.8$ Hz), 3.13 (dd, 1H, $J=4.8$, 9.6 Hz), 2.67 (dd,1H, $J=7.4$, 9.6 Hz), 2.48 (dt, 1H, $J=7.4$, 12.1 Hz), 2.35 (dd 2H, $J=8.1$, 12.0 Hz); ^{13}C NMR (CDCl$_3$) δ (ppm) 155.5, 153.1, 150.4, 144.1, 143.5, 139.6, 129.3, 128.8, 128.2, 127.9, 127.4, 127.2, 87.2, 79.9, 77.4, 66.5, 61.9, 55.7, 35.5; HRFABMS: calcd mass 750.3444 for C$_{49}$H$_{44}$N$_5$O$_3$, found 750.3434 (M+H)$^+$.

3.1.4. 3(*R*)-(Adenin-9-yl)-2(*S*),5(*S*)-di(hydroxymethyl) tetrahydrofuran (4). Compound **16** (200 mg, 0.27 mmol) in 80% acetic acid (13 mL) was heated at 60 °C for 12 h and concentrated to give a white solid that was purified by silica gel column chromatography (chloroform–methanol = 10:1) to give compound **4** (53 mg, 74%) as a white solid. Mp 189–191 °C; $[\alpha]_D^{20}=+27.0°$ (c 0.6 MeOH). UV $\lambda_{\max}$ 260 nm (ε 12,695, MeOH); ^{1}H NMR (D$_2$O) δ (ppm) 8.30 (s, 1H), 8.20 (s, 1H), 5.11 (dd, 1H, $J=1.5$, 8.3 Hz), 4.45 (m, 2H), 3.88–3.65 (m, 4H), 2.72 (m, 1H), 2.37 (m, 1H); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 157.08, 154.01, 150.04, 142.13, 120.12, 83.64, 80.39, 64.57, 62.40, 56.91, 34.97; HRFABMS: calcd mass 266.1253 for C$_{11}$H$_{16}$N$_5$O$_3$, found 266.1258 (M+H)$^+$.

3.1.5. 3(*S*)-(Adenin-9-yl)-2(*S*),5(*S*)-di(hydroxymethyl) tetrahydrofuran (18). Using the same procedure for **4**, compound **18** (21 mg, 72%) was obtained as a white solid from compound **17** (80 mg, 0.11 mmol). Mp 189–192 °C; $[\alpha]_D^{20}=+85.0°$ (c 0.5 MeOH). UV $\lambda_{\max}$ 261 nm (ε 12 863, MeOH); ^{1}H NMR (D$_2$O) δ (ppm) 8.21 (s, 1H), 8.12 (s, 1H), 5.31 (m, 1H), 4.71 (m, 1H), 4.36 (m, 1H), 3.71 (m, 2H), 3.35 (dd, 1H, $J=6.0$, 16.0 Hz), 3.15 (dd, 1H, $J=8.8$, 16.0 Hz), 2.54 (m, 2H); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 157.11, 154.25, 150.76, 142.23, 120.24, 81.91, 80.15, 65.00, 61.22, 57.28, 35.02; HRFABMS: calcd mass 266.1253 for C$_{11}$H$_{16}$N$_5$O$_3$, found 266.1257 (M+H)$^+$.

3.1.6. 2(*S*),5(*S*)-Di(hydroxymethyl)-3(*R*)-(uracil-1-yl) tetrahydrofuran (5). A mixture of uracil (1.99 g, 17.75 mmol) and 60% sodium hydride (710 mg, 17.75 mmol) in anhydrous *N*,*N*-dimethylformamide (150 mL) was heated at 110 °C for 2 h and then compound **13** (2.80 g, 4.44 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) was added. The reaction mixture was heated at 150–160 °C for 48 h and concentrated under reduced pressure. The residue was separated by silica gel column, chromatography (chloroform–methanol = 60:1) to give compound **19** (800 mg, 24%) and **20** (200 mg, 6%) as oils. Compound **19**. UV $\lambda_{\max}$ 266 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 9.35 (s, 1H), 7.45–7.15 (m, 31H), 5.52 (d, 1H, $J=8.0$ Hz), 4.84 (t, 1H, $J=6.0$ Hz), 4.37 (t, 1H, $J=6.1$ Hz), 4.20 (dd, 1H, $J=5.2$, 11.1 Hz), 4.07 (m, 1H), 3.44 (dd, 1H, $J=4.7$, 10.3 Hz), 3.38 (dd, 1H, $J=5.3$, 10.2 Hz), 3.32 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 163.2, 151.0, 143.6, 143.5, 142.0, 128.8, 128.6, 128.0, 127.9, 127.2, 103.0, 87.2, 87.2, 82.6, 79.1, 76.9, 66.4, 64.3, 64.1. Compound **20**. UV $\lambda_{\max}$ 266 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 8.63 (s, 1H), 7.59–7.18 (m, 31H), 5.39 (d, 1H, $J=8.1$ Hz), 5.27 (t, 1H, $J=6.7$ Hz), 4.96 (dd, 1H, $J=7.6$, 15.0 Hz), 4.78 (m, 1H), 4.59 (m, 1H), 3.69 (dd, 1H, $J=4.2$, 10.5 Hz), 3.34–3.25 (m, 2H), 2.88 (dd, 1H, $J=2.7$, 10.8 Hz); ^{13}C NMR (CDCl$_3$) δ (ppm) 167.7, 151.0, 143.2, 143.1, 141.8, 128.5, 128.4, 128.2, 128.0, 127.4, 127.3, 101.7, 87.8, 87.7, 77.9, 76.4, 74.6, 64.3, 63.6, 62.4. Compound **23** (234 mg, 40%) was obtained from compound **19** (600 mg, 0.81 mmol) using the same method as described for compound **16**. UV $\lambda_{\max}$ 266 nm (MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 8.76 (s, 1H), 7.46–7.19 (m, 31H), 5.55 (d, 1H, $J=8.1$ Hz), 4.32 (m, 1H), 4.28 (m, 1H), 3.43 (dd, 1H, $J=3.7$, 10.2 Hz), 3.35 (dd, 1H, $J=4.1$, 9.3 Hz), 3.19 (m, 2H), 2.46 (m, 1H), 1.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 162.8, 150.6, 143.6, 141.3, 128.8, 128.6, 127.9, 127.3, 127.2, 103.2, 87.3, 87.2, 81.7, 77.7, 65.4, 64.7, 57.3, 34.2.

Compound **5** (10 mg, 67%) was obtained from compound **23** (45 mg, 0.062 mmol) using the same method for compound **4**. Mp 200–202 °C; $[\alpha]_D^{20}=+32°$; (*c* 0.24, MeOH). UV $\lambda_{\max}$ 266 nm (ε 10 076, MeOH); ^{1}H NMR (D_2O) δ (ppm) 7.81 (d, 1H, $J=8.1$ Hz), 5.92 (d, 1H, $J=8.0$ Hz), 5.08 (dt, 1H, $J=6.3$, 8.6 Hz), 4.34 (m, 1H), 4.23 (dt, 1H, $J=3.9$, 6.0 Hz), 3.83 (dd, 1H, $J=3.1$, 12.4 Hz), 3.75–3.65 (m, 3H), 2.54 (m, 1H), 2.08 (dt, 1H, $J=8.9$, 13.1 Hz); ^{13}C NMR (D_2O+DMSO-d_6) δ (ppm) 167.8, 153.8, 145.4, 104.1, 83.0, 80.3, 64.4, 62.6, 58.4, 33.6; HRFABMS: calcd mass 243.0980 for $C_{10}H_{15}N_2O_5$, found 243.0984 $(M+H)^+$.

3.1.7. 3(*R*)-(Cytosin-1-yl)-2(*S*),5(*S*)-di(hydroxymethyl) tetrahydrofuran (6). To a mixture of compound **23** (230 mg, 0.32 mmol) and 4-dimethylaminopyridine (114 mg, 0.93 mmol) in anhydrous acetonitrile (15 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (282 mg, 0.93 mmol) and triethylamine (1.3 mL) at 0 °C. The resulting reaction mixture was stirred at rt for 3 h. Ammonium hydroxide (29%, 8 mL) was added to the reaction mixture, which was then stirred for additional 2 h. After removal of solvent, the residue was separated by silica gel column chromatography (chloroform–methanol = 30:1) to give compound **24** (170 mg, 76%) as an oil. UV $\lambda_{\max}$ 276 nm (MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.58–7.21 (m, 31H), 5.54 (d, 1H, $J=10.0$ Hz), 5.31 (m, 1H), 4.38 (m, 1H), 4.28 (m, 1H), 3.43–3.22 (m, 4H), 2.55 (m, 1H), 1.89 (m, 1H) 1.76 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 164.7, 156.0, 143.8, 143.7, 142.7, 128.8, 128.7, 127.7, 127.1, 127.0, 94.8, 87.1, 86.9, 82.2, 77.6, 65.6, 64.7, 57.8, 35.1. Compound **6** (20 mg, 65%) was obtained as a hygroscopic white solid from compound **24** (93 mg, 0.128 mmol) using the same method for compound **4**. $[\alpha]_D^{20}=+29°$ (*c* 0.24, MeOH). UV $\lambda_{\max}$ 276 nm (ε 10 405, MeOH); ^{1}H NMR (D_2O) δ (ppm) 7.77 (d, 1H, $J=7.5$ Hz), 6.08 (d, 1H, $J=7.5$ Hz), 5.12 (m, 1H), 4.35 (m, 1H), 4.23 (m, 1H), 3.82 (m, 1H), 3.70 (m, 3H), 2.54 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (D_2O+DMSO-d_6) δ (ppm) 166.0, 158.5, 143.6, 96.9, 82.2, 78.9, 63.1, 61.4, 57.5, 32.8; HRFABMS: calcd mass 242.1140 for $C_{10}H_{16}N_3O_4$, found 242.1141 $(M+H)^+$.

3.1.8. 2(*S*),5(*S*)-Di(hydroxymethyl)-3(*R*)-(thymin-1-yl)-tetrahydrofuran (7). A mixture of thymine (1.90 g, 15.06 mmol) and 60% sodium hydride (608 mg, 15.20 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) was heated at 110 °C for 2 h and then compound **13** (2.40 g, 3.80 mmol) was added. The resulting reaction mixture was heated at 150–160 °C for 48 h and concentrated under reduced pressure. The residue was separated by silica gel column chromatography (chloroform–methanol = 1:1) to give compound **21** (807 mg, 28%) and **22** (168 mg, 6%) as oils. Compound **21**. UV $\lambda_{\max}$ 270 nm (MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.50 (s, 1H), 7.46–7.04 (m, 30H), 7.04 (s, 1H), 4.88 (t, 1H, $J=6.1$ Hz), 4.42 (t, 1H, $J=4.2$ Hz), 4.22 (q, 1H, $J=5.8$ Hz), 4.05 (m, 1H), 3.67 (bs, 1H), 3.42 (m, 2H), 3.30 (m, 2H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 163.7, 151.3, 143.7, 143.6, 137.5, 128.7, 128.6, 127.9, 127.9, 127.2, 127.1, 111.6, 87.2, 87.1, 82.4, 79.0, 77.2, 65.8, 64.2, 64.0, 12.4. Compound **22**. UV $\lambda_{\max}$ 270 nm (MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 8.57 (s, 1H), 7.71–7.09 (m, 30H), 7.08 (s, 1H), 5.23 (t, 1H, $J=6.7$ Hz), 5.00 (q, 1H, $J=7.2$ Hz), 4.79 (m, 1H), 4.60 (dt, 1H, $J=4.0$, 7.2 Hz), 3.68 (dd, 1H, $J=4.3$, 10.5 Hz), 3.35–3.24 (m, 3H), 2.87 (dd, 1H, $J=3.0$, 10.6 Hz), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 163.4, 151.2, 143.2, 138.0, 128.5, 128.4, 128.2, 127.4, 127.3, 109.7, 89.8, 87.5, 78.0, 76.4, 74.5, 64.3, 63.5, 62.7, 12.2. Compound **25** (393 mg, 51%) was obtained from compound **21** (750 mg, 0.99 mmol) using the same method for compound **16**. UV $\lambda_{\max}$ 270 nm (MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 8.65 (s, 1H), 7.48–7.17 (m, 31H), 5.13 (m, 1H), 4.33 (m, 1H), 4.19 (q, 1H, $J=5.2$ Hz), 3.38 (m, 2H), 3.20 (m, 2H), 2.44 (m, 1H), 1.94 (m, 1H), 1.73 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 163.4, 150.7, 143.7, 143.6, 129.0, 128.7, 128.6, 127.9, 127.9, 127.2, 127.1, 111.8, 87.2, 86.9, 81.2, 77.5, 65.6, 64.6, 57.0, 34.1, 12.5.

Compound **7** (50 mg, 72%) was obtained from compound **25** (200 mg, 0.27 mmol) using the same method for compound **4**. Compound **7**. Mp 199–202 °C; $[\alpha]_D^{20}=+30°$ (*c* 0.23, MeOH). UV $\lambda_{\max}$ 270 nm (ε 10 100, MeOH); ^{1}H NMR (D_2O) δ (ppm) 7.64 (s, 1H), 5.08 (dt, 1H, $J=6.5$, 8.6 Hz), 4.32 (m, 1H), 4.23 (dt, 1H, $J=3.8$, 6.0 Hz), 3.84 (dd, 1H, $J=3.0$, 12.3 Hz), 3.73–3.64 (m, 3H), 2.52 (ddd, 1H, $J=6.6$, 8.5, 13.0 Hz), 2.06 (t, 1H, $J=9.1$, 12.9 Hz), 1.92 (s, 3H); ^{13}C NMR (D_2O–DMSO-d_6) δ (ppm) 167.6, 153.1, 140.4, 112.7, 82.7, 79.9, 64.7, 62.5, 57.7, 33.5, 13.1; HRFABMS: calcd mass 279.0957 for $C_{11}H_{16}N_2O_5Na$, found 279.0950 $(M+Na)^+$.

3.1.9. 3(*S*)-(Adenin-9-yl)-2(*R*),5(*R*)-di(hydroxymethyl) tetrahydrofuran (8). A mixture of compound **26** (1.88 g, 3.58 mmol), prepared by known methodology,[11,12] ethylene glycol (1.6 mL, 28.69 mmol), *p*-toluenesulfonic acid (330 mg, 1.73 mmol) in benzene (140 mL) containing *N*,*N*-dimethylformamide (3 mL) was refluxed with (Dean–Stark apparatus, for 24 h), neutralized with saturated aqueous sodium bicarbonate, and concentrated under reduced pressure. The residue obtained was separated by silica gel column chromatography (chloroform–methanol = 30:1) to give 2,5-anhydro-3-deoxy-L-talose ethylene acetal (**27**) (500 mg, 73%) as a syrup; $[\alpha]_D^{20}=+17.11°$ (*c* 0.45, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) 4.87 (d, 1H, $J=4.1$ Hz), 4.53 (m, 1H), 4.29 (dt, 1H, $J=4.1$, 7.8 Hz), 4.04–3.89 (m, 6H), 3.17 (m, 1H), 2.07 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 104.8, 81.8, 78.1, 73.6, 65.5, 65.3, 61.5, 36.8. A solution of compound **27** (1.76 g, 9.25 mmol) in anhydrous pyridine (20 mL) was treated with trityl chloride (3.25 g, 12.02 mmol) at rt. The resulting reaction mixture was stirred for 24 h, quenched with cold water, and concentrated. The residue was separated by silica gel column chromatography (hexanes–ethylacetate = 5:1 to 1:1) to give 2,5-anhydro-3-deoxy-6-*O*-trityl-L-talose ethylene acetal (3.28 g, 82%); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.44–7.21(m, 15H), 4.86 (d, 1H, $J=4.1$ Hz), 4.57 (m, 1H), 4.25 (dt, 1H, $J=4.1$, 7.5 Hz), 4.17

(m, 1H), 3.99–3.97 (m, 2H), 3.90–3.87 (m, 2H), 3.48 (dd, 1H, $J=4.6$, 9.5 Hz), 3.29 (dd, 1H, $J=7.5$, 9.5 Hz), 2.43 (s, 1H), 2.09–2.06 (m, 2H); FABMS: 455 $(M+Na)^+$, 450 $(M+NH_4)^+$. To a solution of the trityl compound (2.45 g, 5.66 mmol) in anhydrous methylene chloride (80 mL) containing triethylamine (6 mL) was added methanesulfonyl chloride (1.75 mL, 22.61 mmol) at 0 °C over 10 min and the resulting reaction mixture was stirred at rt for 1 h and then quenched with cold water. The reaction mixture was diluted with methylene chloride (50 mL), washed with water (30 mL), dried with sodium sulfate, and concentrated to give a residue, which was then purified by silica gel column chromatography (hexanes–ethylacetate = 10:1 to 1:1) to give 2,5-anhydro-3-deoxy-4-*O*-methanesulfonyl-6-*O*-trityl-L-talose ethylene acetal (**28**) (2.57 g, 89%) as an oil; ^{1}H NMR (CDCl$_3$) δ (ppm) 7.43–7.21 (m, 15H), 5.38 (m, 1H), 4.91 (d, 1H, $J=3.5$ Hz), 4.29–4.26 (m, 2H), 4.12–3.88 (m, 4H), 3.52 (dd, 1H, $J=5.2$, 9.3 Hz), 3.19 (dd, 1H, $J=7.8$, 9.2 Hz), 2.72 (s, 3H), 2.47 (m, 1H), 2.25 (m, 1H). A mixture of adenine (1.99 g, 14.72 mmol) and sodium hydride (60% in oil) in anhydrous *N*,*N*-dimethylformamide (120 mL) was heated at 100 °C for 1 h and cooled to 85 °C. Compound **28** (1.88 g, 3.68 mmol) in anhydrous *N*,*N*-dimethylformamide (20 mL) was then added. The resulting reaction mixture was heated at 85 °C for 3 days and concentrated under reduced pressure to give a residue which was separated by silica gel column chromatography (chloroform–methanol = 30:1) to give compound **29** (1.13 g, 56%) as white foam. UV λ_{max} 265 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 8.32 (s, 1H), 8.02 (s, 1H), 7.32–7.17 (m, 15H), 5.60 (s, 2H), 5.21 (m, 1H), 5.07 (d, 1H, $J=3.5$ Hz), 4.46 (m, 1H), 4.34 (t, 1H, $J=3.5$, 7.6 Hz), 4.04–3.95 (m, 4H), 3.34 (dd, 1H, $J=4.7$, 10.0 Hz), 3.27 (dd, 1H, $J=5.6$, 10.0 Hz), 2.71 (dt, 1H, $J=8.9$, 13.3 Hz), 2.40 (dt, 1H, $J=7.4$, 13.4 Hz); ^{13}C NMR (CDCl$_3$) δ (ppm) 155.3, 152.9, 150.1, 143.5, 139.1, 128.6, 127.8, 127.1, 119.6, 104.2, 87.0, 82.2, 78.7, 65.7, 65.3, 64.1, 56.3, 33.5. Compound **29** (550 mg, 1.00 mmol) was dissolved in tetrahydrofuran (4 mL) containing trifluoroacetic acid (2 mL) and conc. HCl (0.3 mL) heated at 80 °C for 8 h, neutralized with saturated aqueous sodium bicarbonate and concentrated. The obtained residue was dissolved in methanol (10 mL) and NaBH$_4$ (100 mg, 2.64 mmol) was added at 0 °C. The resulting reaction mixture was stirred at rt for 8 h and concentrated to give a residue, which was separated by silica gel column chromatography (chloroform–methanol = 10:1) to give compound **8** (170 mg, 64%) as a white solid. Mp 189–190 °C. UV λ_{max} 260 nm (ε 12 286, MeOH); $[\alpha]_D^{20}=-25°$ (c 3.0, MeOH); ^{1}H NMR (D$_2$O) δ (ppm) 8.30 (s, 1H), 8.20 (s, 1H), 5.11 (dd, 1H, $J=1.5$, 8.3 Hz), 4.45 (m, 2H), 3.98–3.65 (m, 4H), 2.72 (m, 1H), 2.37 (m, 1H); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 157.0, 154.0, 150.0, 142.1, 120.1, 83.7, 80.5, 64.7, 63.4, 56.9, 35.0; HRFABMS: calcd mass 288.1072 for $C_{11}H_{15}N_5O_3Na$, found 288.1068 $(M+Na)^+$.

3.1.10. 2(*R*),5(*R*)-Di(hydroxymethyl)-3(*S*)-(thymin-1-yl)-tetrahydrofuran (9). A mixture of 60% sodium hydride (230 mg, 9.20 mmol) and thymine (1.16 g, 9.19 mmol) in anhydrous *N*,*N*-dimethylformamide (15 mL) was heated at 95 °C for 1 h and then compound **28** (1.17 g, 2.29 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) was introduced. The reaction mixture was stirred at 100 °C for 4 days, concentrated in vacuo, and separated by silica gel column chromatography (hexanes–ethylacetate = 2:1) to give compound **30** (248 mg, 20%) as a syrup; ^{1}H NMR (CDCl$_3$) δ (ppm) 8.38 (s 1H), 7.41–7.20 (m, 16H), 5.16 (m, 1H), 5.04 (d, 1H, $J=2.9$ Hz), 4.28 (dt, 1H, $J=2.9$, 7.8 Hz), 4.13 (dd, 1H, $J=5.2$, 10.5 Hz), 4.06–3.96 (m, 4H), 3.35 (dd, 1H, $J=5.0$, 10.0 Hz), 3.19 (dd, 1H, $J=5.5$, 10.0 Hz), 2.55 (dt, 1H, $J=9.2$, 13.7 Hz), 1.98 (dt, 1H, $J=7.1$, 13.6 Hz), 1.95 (s, 3H); ^{13}C NMR (CDCl$_3$) δ (ppm) 163.3, 150.6, 143.6, 137.4, 128.6, 127.9, 127.2, 111.4, 104.0, 87.2, 81.6, 78.4, 65.6, 65.3, 64.6, 57.0, 32.2, 12.6. Using the procedure for **29** to **8**, compound **9** was obtained from compound **30** in 67% yield as a white solid. Mp 197–200 °C; $[\alpha]_D^{20}=-27°$; (c 0.4, MeOH). UV λ_{max} 270 nm (9,100, MeOH); ^{1}H NMR (D$_2$O) δ (ppm) 7.64 (s, 1H), 5.08 (dt, 1H, $J=6.5$, 8.6 Hz), 4.32 (m, 1H), 4.23 (dt, 1H, $J=3.8$, 6.0 Hz), 3.84 (dd, 1H, $J=3.0$, 12.3 Hz), 3.73–3.64 (m, 3H), 2.52 (ddd, 1H, $J=6.6$, 8.5, 13.0 Hz), 2.06 (dt, 1H, $J=9.1$ Hz, 12.9 Hz), 1.92 (s, 3H); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 167.6, 153.1, 140.4, 112.6, 82.7, 79.9, 64.7, 62.5, 57.7, 33.5, 13.1; HRFABMS: calcd mass 279.0957 for $C_{11}H_{16}N_2O_5Na$, found 279.0975 $(M+Na)^+$.

3.1.11. 2(*R*),5(*R*)-Di(hydroxymethyl)-3(*S*)-(uracil-1-yl)-tetrahydrofuran (10). A mixture of compound **28** (710 mg, 1.39 mmol) and sodium azide (452 mg, 6.95 mmol) in anhydrous *N*,*N*-dimethylformamide (15 mL) was heated at 85 °C for 24 h, concentrated in vacuo, and purified by silica gel column chromatography (hexanes–ethylacetate = 5:1) to give an azide as a white foam (502 mg, 79%); ^{1}H NMR (CDCl$_3$) δ (ppm) 7.48–7.22 (m, 15H), 4.94 (d, 1H, $J=5.1$ Hz), 4.16–3.91 (m, 7H), 3.24 (dd, 1H, $J=4.8$, 10.1 Hz), 3.17 (dd, 1H, $J=3.7$, 10.1 Hz), 2.43 (m, 1H), 2.02 (m, 1H); ^{13}C NMR (CDCl$_3$) δ (ppm) 143.7, 128.7, 127.9, 127.1, 104.3, 83.0, 79.2, 77.3, 65.5, 65.3, 63.9, 62.5, 32.4. A mixture of the azide (650 mg, 1.42 mmol) and 10 wt% Pd/C (170 mg) in ethyl acetate–ethanol (1:1, 20 mL) was stirred at 30 psi in the presence of hydrogen gas for 4 h at rt. The catalyst was filtered and the filtrate was concentrated and purified by silica gel column chromatography (hexanes–ethylacetate = 5:1) to give compound **31** as a white foam (600 mg, 98%); ^{1}H NMR (CDCl$_3$) δ (ppm) 7.45–7.20 (m, 15H), 4.93 (d, 1H, $J=3.9$ Hz), 4.08 (dt, 1H, $J=3.9$, 7.5 Hz), 4.02 (m, 2H), 3.90 (m, 2H), 3.80 (dd, 1H, $J=5.9$, 10.5 Hz), 3.39 (dd, 1H, $J=7.4$, 13.4 Hz), 3.29 (dd, 1H, $J=4.5$, 9.6 Hz), 3.12 (dd, 1H, $J=6.1$, 9.6 Hz), 2.31 (dt, 1H, $J=7.5$, 12.7 Hz), 1.69 (dt, 1H, $J=7.4$, 12.7 Hz), 1.60 (bs, 2H); ^{13}C NMR (CDCl$_3$) δ (ppm) 143.9, 128.6, 127.8, 127.0, 104.8, 86.8, 85.9, 78.5, 65.5, 65.2, 65.0, 55.2, 36.1. A mixture of β-methoxyacryloyl chloride (800 mg, 6.64 mmol) and silver cyanate (1.79 g, 11.94 mmol) in anhydrous toluene (40 mL) was heated under reflux for 30 min and cooled, and then the supernatant was added to compound **31** (680 mg, 1.58 mmol) in anhydrous toluene (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min at rt for 1 h. The reaction mixture was poured onto saturated aqueous sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (2×50 mL). After concentration of the organic layer, the residue was purified by silica gel column chromatography (hexanes–ethylacetate = 2:1) and the product (800 mg, 88%) was dissolved in ethanol (40 mL) and 29% ammonium hydroxide solution (5 mL) was added. The resulting reaction mixture was heated at 100 °C for 18 h in a steel bomb. After concentration, the residue was purified by silica gel column chromatography (hexanes–ethylacetate = 1:1) to give compound **32** (546 mg, 66% from 31) as a white foam. UV λ_{max} 266 nm (MeOH); ^{1}H NMR (CDCl$_3$) δ (ppm) 8.31 (s, 1H), 7.54 (d, 1H, $J=8.1$ Hz), 7.40–7.20 (m, 15H), 5.75 (dd, 1H, $J=2.2$, 8.1 Hz), 5.17 (m, 1H), 5.02 (d, 1H, $J=2.7$ Hz), 4.29 (dt, 1H, $J=2.7$, 7.7 Hz), 4.12 (m, 1H), 4.07–3.93 (m, 4H), 3.35 (dd, 1H, $J=4.8$, 10.0 Hz), 3.18 (dd, 1H, $J=5.8$, 9.9 Hz), 2.25 (dt, 1H, $J=8.5$, 13.6 Hz), 1.97 (dt, 1H, $J=6.9$, 13.7 Hz); ^{13}C NMR (CDCl$_3$) δ (ppm) 162.6, 150.5, 143.5, 141.5, 128.6, 127.9, 127.2, 103.9, 102.9, 87.3, 81.5, 78.4, 65.7, 65.3, 64.6, 57.2, 32.2. Compound **10**: (62 mg, 67%) was obtained from compound **32** (200 mg, 0.38 mmol) using the same method for compound **9**. Compound **10**. Mp 200–202 °C; $[\alpha]_D^{20}=-30°$ (c 0.5, MeOH). UV λ_{max} 266 nm (ε 11 200, MeOH); ^{1}H NMR (D$_2$O) δ (ppm) 7.81 (d, 1H, $J=8.1$ Hz), 5.92 (d, 1H, $J=8.0$ Hz), 5.08 (dt, 1H, $J=6.3$, 8.6 Hz), 4.34 (m, 1H), 4.23 (dt, 1H, $J=3.9$, 6.0 Hz), 3.83 (dd, 1H, $J=3.1$, 12.4 Hz), 3.75–3.65 (m, 3H), 2.54 (m, 1H), 2.08 (dt, 1H, $J=8.9$, 13.1 Hz); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 167.8, 153.8, 145.4, 104.1, 83.0, 80.3, 64.4, 62.6, 58.4, 33.6; HRFABMS: calcd mass 243.0980 for $C_{10}H_{15}N_2O_5$, found 243.0983 $(M+H)^+$.

3.1.12. 3(*S*)-(Cytosin-1-yl)-2(*R*),5(*R*)-di(hydroxymethyl) tetrahydrofuran (11). To a solution of compound **10** (460 mg, 1.90 mmol) in anhydrous acetonitrile (20 mL) containing triethylamine (10 mL) was added acetic anhydride (3.6 mL, 38.15 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 3 h, cooled to 0 °C, treated with water (5 mL), stirred for 4 h, diluted with ethylacetate (50 mL), and then washed with water (3 × 10 mL). The organic layer was concentrated and the residue was purified by silica gel chromatography (hexanes–ethylacetate = 1:2) to give a diacetate as a syrup (489 mg, 79%); ^{1}H NMR (CDCl$_3$) δ (ppm) 9.05 (s, 1H), 7.43 (d, 1H, $J=8.1$ Hz), 5.78 (d, 1H, $J=8.1$ Hz), 5.14 (m, 1H), 4.42 (m, 1H), 4.33 (m, 1H), 4.23–4.13 (m, 4H), 2.61 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 1.94 (m, 1H); ^{13}C NMR (CDCl$_3$) δ (ppm) 170.6, 170.6, 162.9, 150.8, 140.7, 103.7, 79.9, 76.2, 65.0, 63.5, 56.8, 33.7, 20.9, 20.8. To a solution of the diacetate (142 mg, 0.44 mmol) in anhydrous acetonitrile (20 mL) containing 4-dimethylaminopyridine (54 mg, 0.44 mmol) and triethylamine (1 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (133 mg, 0.44 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 4 h, treated with ammonium hydroxide (29%, 3.5 mL) for an additional 2 h and then concentrated. The resulting residue was separated by silica gel column chromatography (chloroform–methanol = 10:1 to 5:1) to give compound **11** (23 mg, 45%) as a white solid. Mp 200–201 °C; ^{1}H NMR (D$_2$O) δ (ppm) 7.7 (d, 1H, $J=7.5$ Hz), 6.08 (d, 1H, $J=7.5$ Hz), 5.12 (m, 1H), 4.35 (m, 1H), 4.23 (m, 1H), 3.82 (m, 1H), 3.70 (m, 3H), 2.54 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (D$_2$O + DMSO-d_6) δ (ppm) 166.0, 158.5, 143.6, 96.9, 82.2, 78.9, 63.1, 61.4, 57.5, 37.8; HRFABMS: calcd mass 264.0960 for $C_{10}H_{15}N_3O_4Na$, found 265.0971 $(M+Na)^+$.

3.2. X-ray crystallographic data

Crystallographic data (excluding structure factors) for compound **8** described in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 230719. Copies of the data can be obtained, free of charge, on application to the CCDC (deposit@ccdc.cam.ac.uk).

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References and notes

1. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077–1078.
2. Nair, V.; St. Clair, M.; Reardon, J. E.; Krasny, H. C.; Hazen, R. J.; Paff, M. T.; Boone, L. R.; Tisdale, M.; Najera, I.; Dornsife, R. E.; Everett, D. R.; Borroto-Esoda, K.; Yale, J. L.; Zimmerman, T. P.; Rideout, J. L. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993–1999.
3. Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017–1029.
4. Nair, V. *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier: Amsterdam, Netherlands, 2002; pp 149–166.
5. (a) Nair, V.; Nuesca, Z. M. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953. (b) Bolon, P. S.; Sells, T. B.; Nuesca, Z. M.; Purdy, D. F.; Nair, V. *Tetrahedron* **1994**, *50*, 7747–7764.
6. Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221–1229.
7. Horton, D.; Philips, K. D. *Carbohydr. Res.* **1973**, *30*, 367–374.
8. Guthrie, R.-D.; Jenkins, I.-D.; Walter, J. J.; Wright, M. W.; Yamasaki, R. *Aust. J. Chem.* **1982**, *35*, 2169–2173.
9. Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 8502–8504.
10. Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.-I.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10167–10182.
11. Rokach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis* **1998**, 569–580.
12. Bolon, P. J.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1995**, *51*, 10443–10452.
13. Defaye, J.; Horton, D.; Musser, M. *Carbohydr. Res.* **1971**, *20*, 305–318.
14. Purdy, D. F.; Zintek, L.; Nair, V. *Nucleosides Nucleotides* **1994**, *13*, 109–126.
15. Lei, Z.; Min, J. M.; Zhang, L. H. *Tetrahedron: Asymmetry* **2000**, *11*, 2899–2906.

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Diastereoselective Reformatsky reaction of methyl 4-bromocrotonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose: application to novel bicyclic nucleosides

Mukund K. Gurjar,* Dandepally Srinivasa Reddy, Mohan M. Bhadbhade and Rajesh G. Gonnade

National Chemical Laboratory, Pune 411 008, India

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Abstract—This paper describes an efficient synthetic route for novel bicyclic nucleosides. The stereochemistry of the targeted bicyclic nucleosides was successfully achieved by vinylogous Reformatsky reaction and ring closing metathesis reaction on a carbohydrate backbone.

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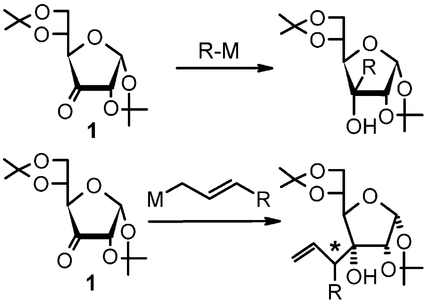
1. Introduction

Due to the inherent structural complexity associated with carbohydrate precursors, many organometallic C–C bond forming reactions occur with impressive stereoselectivity.[1] For instance, the 3-ulose derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) has been particularly targeted with significant successes.[2] The conformationally rigid 1,2-*O*-isopropylidene functionality of **1** dictates[3] the approach of the nucleophile from the β-face giving rise to the 3-*C*-substituted-D-allose derivative. In most C–C bond forming reactions studied so far, only one new chiral center at C-3 has been created.[4] We were interested in exploring the organometallic reaction of **1** with a specific organometallic reagent which is tuned to produce two new chiral centers as shown in Scheme 1. We believe that this study would be of significant interest for synthesizing novel molecules including bicyclic derivatives.

The design of conformationally restricted nucleosides is a very important approach towards potential antiviral agents and monomers in conformationally restricted oligonucleotides, for potential antisense therapeutic and diagnostic purposes.[5] Anticipating better biological activity, many useful strategies for modification of naturally occurring nucleosides have been developed in the recent past, and the quest for more analogues is still in progress. In particular, nucleoside analogues with bicyclic carbohydrate moieties have been designed as potential antiviral agents. Due to the decrease in conformational freedom introduced by the bicyclic nucleosides, these oligonucleotides have displayed very promising results as compounds with improved recognition of complementary RNA and DNA sequences.[6] Leumann and co-workers introduced the concept of bicyclic oligonucleotides by synthesizing the several bicyclic nucleosides (**2** and its analogues) and incorporating them into oligonucleotides.[7] Since then, numerous approaches for a variety of bicyclic sugar nucleosides have appeared in the literature.[8] Recently, Nielson and co-workers have synthesized various bicyclic nucleoside analogues (**3** and **4**) from diacetone-D-glucose and carried out extensive studies on their ability to incorporate into oligonucleotides.[8a,9] In



Scheme 1.

Keywords: Bicyclic nucleosides; Vinylogous Reformatsky reaction; Ring closing metathesis; Grubbs' catalyst; Vorbrüggen-type coupling reaction.

* Corresponding author. Tel.: +91-20-25893614; fax: +91-20-25882456; e-mail: gurjar@dalton.ncl.res.in

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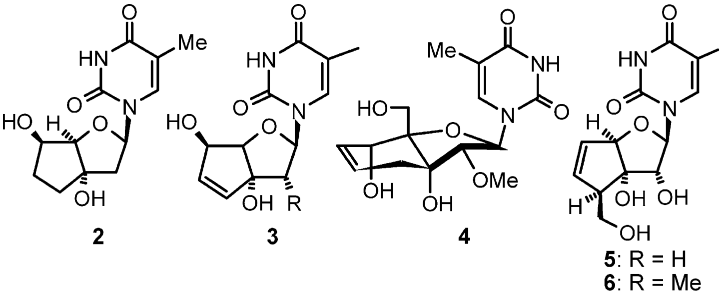


Figure 1.

this report we describe the synthesis of novel bicyclic nucleosides **5**, **6** and their analogues (Fig. 1).[10]

2. Results and discussion

The vinylogous Reformatsky reaction of 3-ulose derivative[11] (**1**) was attempted with methyl 4-bromocrotonate and Zn–Cu couple.[12] This reaction gave two products chromatographically separated on silica gel. The major product obtained in 52% yield was assigned as structure **7** based on the ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. The stereochemical assignment of **7** was confirmed by single crystal X-ray diffraction studies (Fig. 2). The minor product obtained in 26% yield, was given the structure **8** based on spectroscopic and analytical data. The formation of a single diastereomer **7** could be explained by considering the two transition states A and B. The preferred *E*-dienolate of Zn (transition state A) seemed to be more preferred while *Z*-dienolate based transition state B has steric hindrance (Fig. 3).

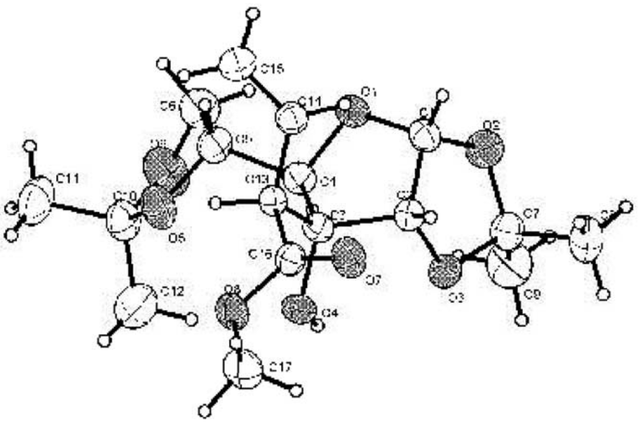


Figure 2. ORTEP diagram of **7**.

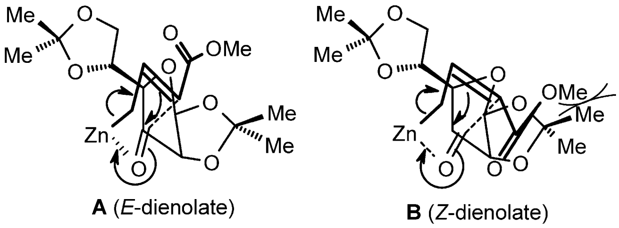
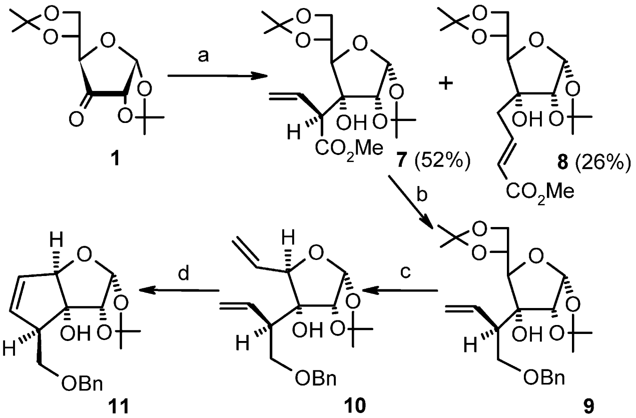


Figure 3. Possible transition states.

The carbomethoxy moiety of **7** was reduced with $LiAlH_4$ and then the resulting hydroxyl group was protected as its benzylic ether (**9**) by using benzyl bromide–Ag_2O. In order to derive the diene **10**, the successive hydrolysis of 5,6-*O*-isopropylidene group with 0.8% H_2SO_4 in methanol, dimesylation of the 5,6-diol derivative with MsCl and ^{i}Pr$_2$EtN, and elimination with NaI in ethyl methyl ketone were carried out. The ring closing metathesis reaction of **10** with 4 mol% of Grubbs' 1st generation catalyst in refluxing benzene provided the bicyclic derivative **11** in 87% yield (Scheme 2).[13] The stereochemistry of **11** was unambiguously assigned by NOE studies (Fig. 4). Strong NOE correlations among bridgehead hydroxyl group and the adjacent allylic protons were noticed.

Our final concern was to introduce pyrimidine bases at the anomeric center. The 1,2-*O*-isopropylidene moiety of **11** was cleaved with 60% AcOH followed by acetylation with Ac_2O and Et_3N to afford the triacetylated derivative **12**. The modified Vorbrüggen-type coupling reaction of **12** with



Scheme 2. Reagents and conditions: (a) methyl 4-bromocrotonate, Zn–Cu couple, ether, reflux, 1 h; (b) (i) $LiAlH_4$, ether, 0 °C–rt, 2 h, 83%; (ii) BnBr, Ag_2O, CH_2Cl_2, rt, 1 h, 95%; (c) (i) 0.8% H_2SO_4, MeOH, rt, 24 h, 80%; (ii) MsCl, ^{i}Pr$_2$EtN, CH_2Cl_2, 0 °C, 5 min, 95%; (iii) NaI, Et–CO–Me, reflux, 4 h, 83%; (d) Grubbs' catalyst, C_6H_6, reflux, 8 h, 87%.

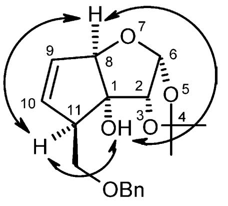
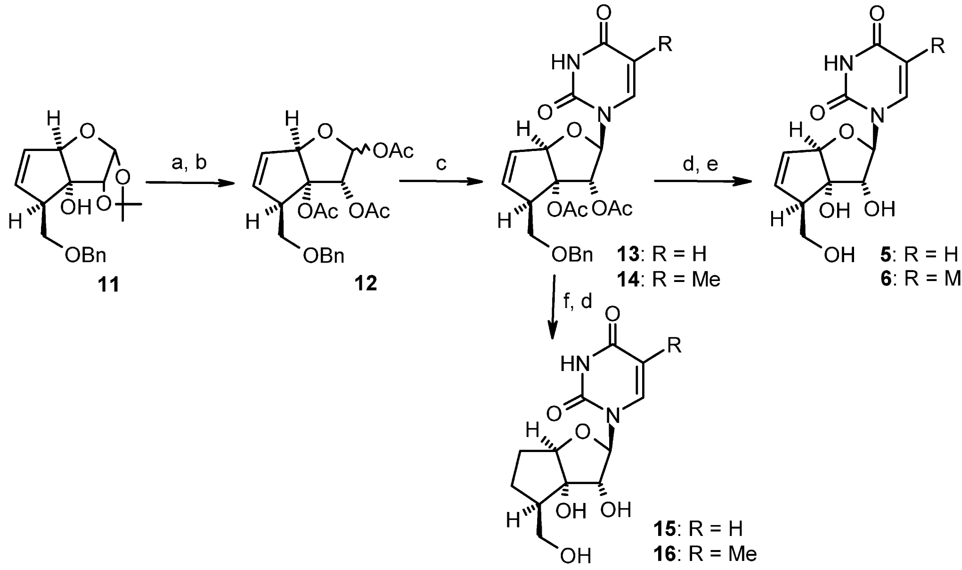


Figure 4. NOE studies on **11**.



Scheme 3. Reagents and conditions: (a) 60% AcOH, reflux, 2 h, 93%; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 96%; (c) uracil/thymine, BSA, TMSOTf, CH_3CN, 50 °C, 2 h, 69%/77%; (d) NaOMe, MeOH, 0 °C, 20 min; (e) BCl_3, CH_2Cl_2, −78 °C, 5 h; (f) 20% $Pd(OH)_2/C$, H_2, MeOH, rt, 12 h.

uracil was achieved in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf to afford exclusively the β-nucleoside **13**, attributed to the anchimeric assistance from 4-*O*-acetyl group.[14]

The de-protection of the two acetyl groups under Zemplén reaction condition[15] and the benzylic ether with BCl_3 of **13** afforded **5**. Simultaneously, compound **13** was hydrogenated in the presence of 20% $Pd(OH)_2/C$, followed by deacetylation using NaOMe (Zemplén conditions) to give compound **15**. Similarly, the triacetate **12** was coupled to thymine using *N*,*O*-bis(trimethylsilyl)acetamide and TMSOTf to obtain **14**. Compound **14** was transformed into **6** and **16** as described above (Scheme 3).

In conclusion, we described an elegant methodology to synthesize the novel bicyclic nucleosides having the structural framework of some carbocyclic nucleosides and bridgehead hydroxyl moiety. The biological activity of these novel bicyclic nucleosides is under study and will be published in due course.

3. Experimental

3.1. General

The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard on AC-200 MHz, MSL-300 MHz, DRX-500 MHz. Optical rotations were measured with a JASCO DIP 370 digital polarimetrometer. EI Mass spectra were recorded on Finngan MAT-1020. Combustion data were recorded on Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were obtained from Perkin–Elmer 68515 PC-FTIR spectrophotometer. Melting points were measured on Buchi 535 melting point apparatus and are uncorrected. Starting materials and reagents were purchased from Aldrich or Lancaster and used as received. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV, I_2 and anisaldehyde in ethanol as development reagents.

3.1.1. 3-*C*-[(*S*)-1-Carbomethoxy-prop-2-enyl]-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (7) and 3-*C*-(3-carbomethoxy-prop-2-enyl]-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (8). To a suspension of activated Zn–Cu couple (40.0 g, 611.7 mmol) and iodine (50 mg) in anhydrous ether (140 mL) were gradually added methyl 4-bromocrotonate (45 g, 251.4 mmol) and the solution of **1** (40.0 g, 155.0 mmol in 50 mL of ether) over a period of 30 min. The reaction mixture was heated under reflux for 30 min, cooled and poured over saturated NH_4Cl. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel by using EtOAc–light petroleum (1:7) as eluent to give **7**[16] (28.9 g, 52%) as a colorless solid, mp 88–90 °C; $[\alpha]_D = -42.5$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3462, 2990, 1737, 1384, 1216, 1167, 1075, 1015, 756; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37, 1.45, 1.58 (3s, 12H), 3.32 (s, 1H), 3.74 (s, 3H), 3.78–3.81 (m, 2H), 3.87 (dd, 1H, $J=5.1$, 8.8 Hz), 4.08–4.12 (m, 1H), 4.21 (dt, 1H, $J=9.1$, 5.6 Hz), 5.04 (d, 1H, $J=3.9$ Hz), 5.28–5.35 (m, 2H), 5.61 (d, 1H, $J=4.1$ Hz), 5.83 (ddd, 1H, $J=8.6$, 10.1, 17.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 26.0, 26.2, 51.3, 51.4, 67.9, 72.2, 79.5, 79.6, 82.9, 103.5, 109.3, 111.6, 119.6, 130.0, 171.0; EIMS (*m*/*z*) 343 $[M^+ - 15]$. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.68; H, 7.52.

Further elution with EtOAc–light petroleum (1:5) gave **8** (14.4 g, 26%) as a colorless solid, mp 106–108 °C; $[\alpha]_D = -25.6$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3440, 3020, 1716, 1376, 1166, 1079, 759; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34, 1.36, 1.45, 1.59 (4s. 12H), 2.30 (dd, 1H, $J=9.1$, 14.7 Hz), 2.78 (s, 1H, OH), 2.80 (ddd, 1H, $J=1.6$, 5.8, 14.7 Hz), 3.75 (s, 3H), 3.78 (m, 1H), 3.87–3.95 (m, 1H), 4.06–4.14 (m, 2H), 4.24 (d, 1H, $J=3.8$ Hz), 5.66 (d, 1H, $J=3.8$ Hz), 5.94 (d, 1H, $J=15.8$ Hz), 7.12 (ddd, 1H, $J=5.4$, 8.8, 15.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 26.4, 26.6, 26.7, 34.9, 51.6, 68.1, 73.2, 78.9, 81.3, 81.9, 103.5, 109.9, 112.8, 124.7, 143.1, 166.3; EIMS (*m/z*) 343 [$M^+ - 15$]. Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.86; H, 7.27.

3.1.2. 3-*C*-[(*R*)-1-Benzyloxymethyl-prop-2-enyl]-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (9). A solution of **7** (28.0 g, 78.0 mmol) and $LiAlH_4$ (4.15 g) in anhydrous ether (150 mL) was stirred for 2 h at rt, quenched with EtOAc and filtered through a plug of Celite. The filtrate was concentrated and purified on silica gel column with EtOAc–light petroleum (1:3) to afford 3-*C*-[(*R*)-1-hydroxymethyl-prop-2-enyl]-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (16.8 g, 83%) as a colorless solid, mp 78–80 °C; $[\alpha]_D = -3.4$ (*c* 1.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3401, 2989, 1384, 1217, 1074, 1010, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 6H), 1.45, 1.59 (2s, 6H), 2.72–2.89 (br s, 1H, OH), 2.91–3.07 (m, 1H), 3.12 (s, 1H, OH), 3.68–3.90 (m, 3H), 3.99–4.17 (m, 2H), 4.24–4.36 (m, 1H), 4.50 (d, 1H, $J = 3.9$ Hz), 5.17–5.32 (m, 2H), 5.60 (d, 1H, $J = 3.9$ Hz), 5.71 (ddd, 1H, $J = 8.7$, 10.7, 17.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3, 26.3, 26.5, 26.6, 47.1, 63.2, 68.4, 72.5, 80.5, 81.0, 84.1, 103.9, 109.7, 112.2, 118.5, 134.3; EIMS (*m/z*) 315 [$M^+ - 15$]. Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 57.87; H, 8.18.

The above product (16.0 g, 48.4 mmol), freshly prepared Ag_2O (33.7 g, 145.3 mmol) and benzyl bromide (6.9 mL, 58.0 mmol) in CH_2Cl_2 (50 mL) were stirred for 1 h at rt, filtered through Celite and concentrated. The residue was purified on silica gel by using EtOAc–light petroleum (1:9) to get **9** (19.35 g, 95%) as a syrup: $[\alpha]_D = +13.7$ (*c* 1.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3402, 2936, 1385, 1275, 1217, 1045, 756; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33, 1.35, 1.44, 1.59 (4s, 12H), 2.85–2.94 (m, 1H), 3.17 (s, 1H, OH), 3.75–3.96 (m, 4H), 4.08–4.16 (m, 1H), 4.25–4.36 (m, 1H), 4.46–4.55 (m, 2H), 4.75 (d, 1H, $J = 7.7$ Hz), 5.18–5.29 (m, 2H), 5.62 (d, 1H, $J = 3.8$ Hz), 5.75–5.94 (m, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.2, 26.2, 26.4, 45.6, 68.2, 70.7, 72.4, 72.9, 79.7, 81.0, 83.9, 103.6, 109.2, 111.5, 117.5, 127.1, 127.8, 135.2, 138.2; EIMS (*m/z*) 405 [$M^+ - 15$]. Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.47; H, 7.58.

3.1.3. 3-*C*-[(*R*)-1-Benzyloxymethyl-prop-2-enyl]-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (10). Compound **9** (16.0 g, 38.0 mmol) and 0.8% H_2SO_4 (20 mL) in MeOH (50 mL) were stirred at rt for 24 h, and then neutralized with solid $NaHCO_3$. The solid was filtered, concentrated and the residue purified on silica gel using EtOAc–light petroleum (1:2) to give 3-*C*-[(*R*)-1-benzyloxymethyl-prop-2-enyl]-1,2-*O*-isopropylidene-α-D-allofuranose (11.6 g, 80%) as a syrup: $[\alpha]_D = -11.4$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3418, 2988, 1385, 1275, 1217, 1087, 1027, 757; ^1H NMR (200 MHz, $CDCl_3$): δ 1.34, 1.58 (2s, 6H), 2.37–2.53 (br s, 1H, OH), 2.90–3.07 (m, 2H), 3.56–3.88 (m, 6H), 3.91–4.03 (m, 1H), 4.46–4.57 (m, 2H), 4.66 (d, 1H, $J = 3.9$ Hz), 5.17–5.27 (m, 2H), 5.57 (d, 1H, $J = 3.9$ Hz), 5.66–5.84 (m, 1H), 7.21–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.1, 44.9, 64.3, 68.9, 70.3, 72.8, 80.0, 80.2, 80.7, 103.7, 111.5, 117.7, 127.1, 127.8, 134.3, 137.8; EIMS (*m/z*) 322 [$M^+ - 58$]. Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 62.88; H, 7.74.

The above compound (10.0 g, 26.3 mmol), $^iPr_2EtN$ (16 mL, 92.0 mmol), and MsCl (5 mL, 65.7 mmol) in CH_2Cl_2 (40 mL) were stirred at 0 °C for 5 min. The reaction mixture was quenched with saturated Na_2CO_3, water, dried (Na_2SO_4), and concentrated. The crude oily compound was purified on silica gel with EtOAc–light petroleum (1:5) to afford the 5,6-dimesylate derivative (13.4 g, 95%), as a clear oil: $[\alpha]_D = -10.1$ (*c* 1.45, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.58 (2s, 6H), 3.00–3.04 (m, 1H), 3.06 (s, 3H), 3.13 (s, 3H), 3.56–3.67 (m, 1H), 3.74 (dd, 1H, $J = 5.4$, 9.4 Hz), 3.94 (dd, 1H, $J = 3.9$, 9.4 Hz), 4.00 (d, 1H, $J = 9.1$ Hz), 4.32 (dd, 1H, $J = 5.7$, 11.5 Hz), 4.45–4.63 (m, 3H), 4.83 (d, 1H, $J = 3.8$ Hz), 5.21–5.41 (m, 2H), 5.55–5.74 (m, 1H), 5.62 (d, 1H, $J = 3.8$ Hz), 7.21–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0, 26.1, 37.0, 39.0, 44.8, 68.3, 70.6, 72.7, 73.6, 78.8, 79.7, 103.4, 111.8, 118.9, 127.1, 127.9, 133.3, 137.6. Anal. Calcd for $C_{22}H_{32}O_{11}S_2$: C, 49.24; H, 6.01; S, 11.95. Found: C, 48.97; H, 5.77; S, 12.14.

The 5,6-dimesylate (12.0 g, 22.4 mmol) and NaI (33.5 g, 223.6 mol) in 2-butanone (100 mL) were heated under reflux for 4 h and concentrated. The residue was partitioned between EtOAc and saturated aq $Na_2S_2O_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel with EtOAc–light petroleum (1:9) to afford **10** (6.43 g, 83%) as a syrup: $[\alpha]_D = -15.2$ (*c* 0.95, $CHCl_3$); ν_{max} ($CHCl_3$) 3402, 2933, 1403, 1276, 1092, 1027, 755; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35, 1.58 (2s, 6H), 2.68 (dt, 1H, $J = 9.2$, 5.1 Hz), 3.46 (s, 1H, OH), 3.75–3.82 (m, 2H), 4.33 (dt, 1H, $J = 1.4$, 2.8 Hz), 4.46–4.53 (m, 2H), 4.59 (d, 1H, $J = 3.9$ Hz), 5.09–5.46 (m, 4H), 5.64 (d, 1H, $J = 3.9$ Hz), 5.70–6.00 (m, 2H), 7.23–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9, 26.0, 44.6, 69.8, 72.6, 79.9, 80.2, 83.8, 103.4, 111.1, 117.1, 117.3, 126.9, 127.7, 131.4, 134.1, 137.7; EIMS (*m/z*) 331 [$M^+ - 15$]. Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.18; H, 7.71.

3.1.4. (1*R*,2*R*,6*R*,8*R*,11*R*)-11-Benzyloxymethyl-1-hydroxy-4,4-dimethyl-3,5,7-trioxatricyclo[6.3.0.0^{2,6}]undec-9-ene (11). Compound **10** (6.0 g, 17.3 mmol) and Grubbs' catalyst (0.57 g, 0.69 mmol) in anhydrous benzene (250 mL) were heated under reflux for 8 h and then evaporated. The residue was purified on silica gel with EtOAc–light petroleum (1:4) to obtain **11** (4.8 g, 87%), as an oil: $[\alpha]_D = +112$ (*c* 1.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3498, 2988, 2935, 2861, 1455, 1383, 1374, 1219, 1166, 1096, 1002, 750, 700; ^1H NMR (500 MHz, $CDCl_3$): δ 1.37, 1.59 (2s, 6H), 3.06–3.10 (m, 1H), 3.29 (s, 1H, OH), 3.40 (dd, 1H, $J = 7.2$, 10.1 Hz), 3.53 (dd, 1H, $J = 4.2$, 10.1 Hz), 4.50 (ABq, 2H, $J = 12.1$ Hz), 4.61 (d, 1H, $J = 3.8$ Hz), 4.75 (d, 1H, $J = 1.9$ Hz), 5.62 (d, 1H, $J = 3.8$ Hz), 5.85 (dt, 1H, $J = 5.9$, 2.7 Hz), 5.89 (dd, 1H, $J = 2.7$, 5.9 Hz), 7.29–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1, 27.4, 54.2, 68.6, 73.2, 80.3, 86.2, 93.1, 106.9, 112.6, 127.9, 128.0, 128.5, 129.8, 136.9, 137.7; EIMS (*m/z*) 318 [M^+]. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.96; H, 7.18.

3.1.5. (3*R*/*S*,1*R*,4*R*,5*R*,6*R*)-3,4,5-Triacetoxy-6-benzyloxymethyl-2-oxa-bicyclo[3.3.0]oct-7-ene (12). Compound **11** (2.0 g, 6.3 mmol) and 60% AcOH (15 mL) were heated under reflux for 2 h. The reaction mixture was neutralized with solid Na_2CO_3 and evaporated. The residue was extracted with EtOAc, dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with EtOAc–light petroleum (1:1) to give (3*R*/*S*,1*R*,4*R*,5*R*,6*R*)-6-benzyloxymethyl-3,4,5-trihydroxy-2-oxa-bicyclo[3.3.0]oct-7-ene (1.63 g, 93%) as a solid: mp 92–94 °C; ν_{max} ($CHCl_3$) 3359, 2936, 1454, 1401, 1366, 1081, 1027, 749, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 3.06–3.19 (m, 1H), 3.35 (d, 1H, $J=4.7$ Hz, OH), 3.44 (s, 1H, OH), 3.60–3.79 (m, 2H), 3.86 (d, 1H, $J=5.8$ Hz, OH) 4.07 (t, 1H, $J=4.0$ Hz), 4.54–4.60 (m, 2H), 5.14 (s, 1H), 5.29–5.33 (m, 1H), 5.57 (d, 1H, $J=6.0$ Hz), 5.79 (dt, 1H, $J=6.0$, 2.1 Hz), 7.28–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.7, 68.8, 72.0, 73.0, 85.6, 92.8, 97.4, 127.5, 128.2, 130.7, 132.8, 137.5. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.39; H, 6.42.

The above product (1.5 g, 5.39 mmol), Ac_2O (3.1 mL, 32.76 mmol), Et_3N (7.5 mL), DMAP (135 mg) in anhydrous CH_2Cl_2 (20 mL) were stirred at rt for 1 h. The reaction mixture was partitioned between water–CH_2Cl_2, the organic layer washed with saturated $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel with EtOAc–light petroleum (1:4) as an eluent to obtain **12** (2.1 g, 96%) as an oil: ν_{max} ($CHCl_3$) 3410, 3018, 2958, 1720, 1452, 1374, 1276, 1084, 1027, 756, 714; ^1H NMR (200 MHz, $CDCl_3$): δ 2.01, 2.09, 2.13 (3s, 9H), 3.39 (t, 1H, $J=5.2$ Hz), 3.69–3.74 (m, 2H), 4.49 (ABq, 2H, $J=11.9$ Hz), 5.50 (s, 1H), 5.58 (d, 1H, $J=4.3$ Hz), 5.80–5.89 (m, 2H), 6.29 (d, 1H, $J=4.3$ Hz), 7.20–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.1, 20.6, 21.2, 51.4, 68.4, 70.9, 72.9, 90.0, 92.6, 95.2, 95.9, 127.4, 128.1, 135.4, 137.8, 168.6, 169.0, 169.6. Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.09; H, 6.12.

3.1.6. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-benzyloxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (13).

Compound **12** (0.36 g, 0.89 mmol), uracil (0.20 g, 1.78 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.1 mL, 4.45 mmol) in anhydrous CH_3CN (8 mL) were heated under reflux for 15 min, cooled to 0 °C and then TMSOTf (0.32 mL, 1.78 mmol) was added. The reaction mixture was stirred at 50 °C for 2 h, quenched with ice-cold saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water, dried (Na_2SO_4), concentrated, and the residue purified on silica gel with EtOAc–light petroleum (1:1) to give **13** (0.28 g, 69%), as a syrup: $[\alpha]_D=+16.8$ (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3022, 1748, 1693, 1455, 1373, 1240, 1048, 755; ^1H NMR (200 MHz, $CDCl_3$): δ 2.02, 2.15 (2s, 6H), 3.26–3.36 (m, 1H), 3.80 (dd, 1H, $J=4.3$, 10.0 Hz), 4.02–4.13 (m, 1H), 4.50 (ABq, 2H, $J=11.2$ Hz), 5.03 (dd, 1H, $J=2.0$, 8.1 Hz), 5.16 (d, 1H, $J=1.6$ Hz), 5.86–6.01 (m, 3H), 6.17 (d, 1H, $J=7.5$ Hz), 7.08 (d, 1H, $J=8.1$ Hz), 7.25–7.37 (m, 5H), 9.62 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.3, 21.2, 53.2, 68.6, 71.8, 73.1, 86.3, 90.8, 92.2, 103.2, 127.1, 127.7, 128.4, 137.4, 137.7, 139.3, 150.8, 162.9, 169.1, 169.9. Anal. Calcd for $C_{23}H_{24}O_8N_2$: C, 60.52; H, 5.30; N, 6.14. Found: C, 60.29; H, 5.00; N, 6.32.

3.1.7. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (5).

To a solution of **13** (0.21 g, 0.46 mmol), 1 M methanolic NaOMe (50 μL) in MeOH (3 mL) were stirred at 0 °C for 20 min. The reaction mixture was neutralized with concd HCl, filtered and concentrated. The residue was purified by silica gel column chromatography with MeOH–CH_2Cl_2 (1:9) to afford (1*R*,3*R*,4*R*,5*R*,6*R*)-6-benzyloxymethyl-4,5-dihydroxy-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (0.145 g, 85%), as a solid: mp 150–152 °C; $[\alpha]_D=-24$ (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (t, 1H, $J=6.5$ Hz), 3.72 (d, 2H, $J=6.5$ Hz), 4.07 (br s, 1H, OH), 4.25 (d, 1H, $J=7.2$ Hz), 4.53 (s, 2H), 4.60 (br s, 1H, OH), 5.05 (s, 1H), 5.66 (d, 1H, $J=8.2$ Hz), 5.82 (dd, 2H, $J=6.4$, 12.3 Hz), 6.13 (d, 1H, $J=7.6$ Hz), 7.25–7.35 (m, 6H), 10.0 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3+MeOD$): δ 52.8, 68.1, 73.1, 74.8, 85.4, 88.3, 92.8, 102.6, 127.5, 128.1, 130.0, 134.5, 137.5, 139.5, 151.1, 163.8. Anal. Calcd for $C_{19}H_{20}O_6N_2$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.09; H, 5.42; N, 7.69.

The above product (0.125 g, 0.34 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred at −78 °C and then a 1 M solution of BCl_3 in CH_2Cl_2 (0.53 mL, 0.67 mmol) was added dropwise. After being stirred for 5 h at −78 °C the mixture was treated with MeOH (3 mL) and water (0.2 mL) and stirred at rt for 1 h. The solvents were removed under vacuum and the residue purified on silica gel using MeOH–CH_2Cl_2 (1:9) to afford **5** (0.09 g, 95%) as a solid: mp 62–64 °C; $[\alpha]_D=-47.4$ (*c* 0.75, MeOH); ν_{max} ($CHCl_3$) 3204, 3019, 1693, 1462, 1400, 1272, 1216, 1105, 757; ^1H NMR (500 MHz, DMSO-d_6): δ 2.67–2.72 (m, 1H), 3.47 (dd, 1H, $J=9.0$, 10.6 Hz), 3.77 (dd, 1H, $J=5.2$, 10.6 Hz), 4.00 (d, 1H, $J=8.4$ Hz), 4.74 (s, 1H), 5.68 (dd, 1H, $J=2.0$, 8.1 Hz), 5.80 (dt, 1H, $J=1.8$, 6.2 Hz), 5.90 (d, 1H, $J=6.2$ Hz), 5.92 (d, 1H, $J=8.1$ Hz), 7.42 (d, 1H, $J=8.1$ Hz), 11.35 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.5, 59.3, 72.6, 84.5, 86.8, 92.2, 102.4, 130.1, 135.0, 140.2, 150.9, 162.9. Anal. Calcd for $C_{12}H_{14}O_6N_2$: C, 51.06; H, 4.99; N, 9.92. Found: C, 51.19; H, 4.81; N, 9.69.

3.1.8. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]octane (15).

Compound **13** (0.11 g, 0.24 mmol) and 20% $Pd(OH)_2$ (0.025 g) in MeOH (4 mL) were stirred under a H_2 atmosphere for 12 h, filtered through a pad of Celite and concentrated. The residue was purified on silica gel with EtOAc–light petroleum (4:1) to give (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-diacetoxy-6-hydroxymethyl-3-(uracil-1-yl)-2-oxa-bicyclo[3.3.0]octane (0.075 g, 84%) as a syrup: $[\alpha]_D=-30.4$ (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.89–1.98 (m, 4H), 2.05, 2.13 (2s, 6H), 2.43–2.53 (m, 1H), 3.79 (dd, 1H, $J=5.7$, 11.2 Hz), 4.06 (dd, 1H, $J=4.0$, 11.2 Hz), 4.77 (d, 1H, $J=2.7$ Hz), 5.74 (d, 1H, $J=7.4$ Hz), 5.77 (dd, 1H, $J=2.2$, 7.4 Hz), 6.07 (d, 1H, $J=7.5$ Hz), 7.52 (d, 1H, $J=7.5$ Hz), 9.45 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 21.2, 26.3, 29.4, 49.9, 60.8, 71.5, 87.2, 87.3, 90.6, 102.9, 140.0, 150.6, 163.3, 169.6, 170.1. Anal. Calcd for $C_{16}H_{20}O_8N_2$: C, 52.17; H, 5.47; N, 7.60. Found: C, 52.29; H, 5.76; N, 7.71.

The above product (0.07 g, 0.19 mmol) 1 M methanolic NaOMe (20 μL) in MeOH (4 mL) were stirred for 20 min and worked up as described above to give **15** (0.04 g, 74%) as a solid: mp 185–187 °C; $[\alpha]_D=-20.2$ (*c* 1, MeOH); ν_{max} (MeOH) 3361, 2945, 2833, 1698, 1451, 1402, 1113, 1029; ^1H NMR (500 MHz, DMSO-d_6): δ 1.54–1.65 (m, 2H), 1.70–1.83 (m, 2H), 1.88–1.94 (m, 1H), 3.41 (dd, 1H, $J=8.7$, 10.5 Hz), 3.72 (dd, 1H, $J=4.7$, 10.5 Hz), 3.88 (d, 1H,

J=8.2 Hz), 4.12 (d, 1H, J=6.7 Hz), 4.90–5.07 (br s, 1H, OH), 5.11–5.27 (br s, 1H, OH), 5.66 (d, 2H, J=8.8 Hz), 7.67 (d, 1H, J=8.8 Hz), 11.34 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.0, 29.3, 51.6, 60.1, 70.9, 83.2, 85.3, 88.5, 102.0, 140.6, 150.8, 162.7. Anal. Calcd for $C_{12}H_{16}O_6N_2$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.49; H, 6.02; N, 9.69.

3.1.9. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Diacetoxy-6-benzyloxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (14). Compound **12** (0.50 g, 1.23 mmol), thymine (0.31 g, 2.47 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.5 mL, 6.18 mmol) in anhydrous CH_3CN (10 mL) were heated under reflux for 15 min, cooled to 0 °C and then TMSOTf (0.45 mL, 2.47 mmol) was added. The reaction mixture was stirred at 50 °C for 2 h, quenched with ice-cold saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water, dried (Na_2SO_4), concentrated, and the residue purified on silica gel with EtOAc–light petroleum (1:1) to give **14** (0.45 g, 77%) as a colorless syrup: $[\alpha]_D = -20.9$ (*c* 1.7, $CHCl_3$); ν_{max} ($CHCl_3$) 3195, 3030, 2929, 1748, 1694, 1466, 1371, 1234, 1097, 753; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (s, 3H), 2.01, 2.15 (2s, 6H), 3.35–3.40 (m, 1H), 3.75 (dd, 1H, J=5.1, 10.2 Hz), 3.96 (dd, 1H, J=3.2, 10.2 Hz), 4.53 (ABq, 2H, J=11.9 Hz), 5.2 (s, 1H), 5.88–5.99 (m, 3H), 6.24 (d, 1H, J=7.7 Hz), 7.08 (d, 1H, J=1.3 Hz), 7.28–7.34 (m, 5H), 9.22 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0, 20.2, 21.2, 52.4, 68.2, 71.9, 72.8, 86.1, 90.9, 91.7, 111.7, 127.3, 127.5, 128.2, 134.5, 136.9, 137.7, 150.9, 163.5, 169.2, 169.9. Anal. Calcd for $C_{24}H_{26}O_8N_2$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.94; H, 5.81; N, 5.83.

3.1.10. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (6). To a solution of **14** (0.16 g, 0.34 mmol), 1 M methanolic NaOMe (46 μL) in MeOH (3 mL) were stirred at 0 °C for 20 min. The reaction mixture was neutralized with concd HCl, filtered and concentrated. The residue was purified by silica gel column chromatography with MeOH–CH_2Cl_2 (1:9) to give (1*R*,3*R*,4*R*,5*R*,6*R*)-6-benzyloxymethyl-4,5-dihydroxy-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]oct-7-ene (0.11 g, 88%) as colorless syrup: $[\alpha]_D = -51.6$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (s, 3H), 3.12 (br s, 1H), 3.73 (d, 2H, J=6.4 Hz), 4.23 (d, 1H, J=7.2 Hz), 4.54 (s, 2H), 5.06 (s, 1H), 5.83 (ABq, 2H, J=5.9 Hz), 6.10 (d, 1H, J=7.4 Hz), 7.12 (s, 1H), 7.27–7.36 (m, 5H), 9.56 (br s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 52.7, 68.5, 73.5, 75.6, 86.6, 89.1, 93.1, 111.4, 127.8, 127.9, 128.5, 130.6, 134.2, 134.9, 137.6, 151.5, 163.7. Anal. Calcd for $C_{20}H_{22}O_6N_2$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.86; N, 7.52.

The above product (0.065 g, 0.168 mmol) in anhydrous CH_2Cl_2 (3 mL) was stirred at −78 °C and then a 1 M solution of BCl_3 in CH_2Cl_2 (0.42 mL, 0.42 mmol) was added dropwise. After being stirred for 5 h at −78 °C the mixture was treated with MeOH (3 mL) and water (0.2 mL) and stirred at rt for 1 h. The solvents were removed under vacuum and the residue purified on silica gel using MeOH–CH_2Cl_2 (1:9) to afford **6** (0.04 g, 80%) as a solid: mp 90–92 °C; $[\alpha]_D = -57.1$ (*c* 0.75, MeOH); ν_{max} ($CHCl_3$) 3391, 2947, 2835, 1675, 1450, 1404, 1111, 1027; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (s, 3H), 2.69–2.73 (m, 1H), 3.50 (dt, 1H, J=9.9, 5.6 Hz), 3.79 (dt, 1H, J=9.9, 4.8 Hz), 4.05 (t, 1H, J=7.7 Hz), 4.58 (t, 1H, J=5.0 Hz), 4.73 (s, 1H, OH), 5.21 (d, 1H, J=6.9 Hz, OH), 5.45 (s, 1H, OH), 5.79–5.81 (m, 1H), 5.90–5.93 (m, 2H), 7.29 (s, 1H), 11.33 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.9, 55.6, 59.3, 72.0, 84.3, 86.5, 92.0, 109.8, 129.8, 134.9, 135.4, 150.9, 163.4. Anal. Calcd for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.52; H, 5.76; N, 9.52.

3.1.11. (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-Dihydroxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]octane (16). Compound **14** (0.20 g, 0.42 mmol) and 20% $Pd(OH)_2$ (0.035 g) in MeOH (6 mL) were stirred under a H_2 atmosphere for 12 h. After the usual work up, (1*R*,3*R*,4*R*,5*R*,6*R*)-4,5-diacetoxy-6-hydroxymethyl-3-(thymin-1-yl)-2-oxa-bicyclo[3.3.0]octane (0.15 g, 92%) was isolated as a colorless syrup: $[\alpha]_D = -28.7$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3462, 3020, 1745, 1694, 1469, 1373, 1241, 1057, 755; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 3H), 1.93–1.96 (m, 4H), 2.07, 2.12 (2s, 6H), 2.45–2.54 (m, 1H), 2.60–2.74 (m, 1H, OH), 3.81 (dd, 1H, J=5.8, 11.3 Hz), 4.01–4.09 (m, 1H), 4.76 (d, 1H, J=2.6 Hz), 5.76 (d, 1H, J=6.8 Hz), 6.05 (d, 1H, J=6.8 Hz), 7.31 (s, 1H), 9.48–9.62 (m, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 20.2, 21.1, 26.3, 29.3, 49.8, 60.7, 71.1, 86.9, 90.5, 111.1, 135.6, 150.7, 163.7, 169.4, 170.0. Anal. Calcd for $C_{17}H_{22}O_8N_2$: C, 53.40; H, 5.80; N, 7.33. Found: C, 53.54; H, 5.52; N, 7.56.

The above compound (0.12 g, 0.31 mmol) and 1 M methanolic NaOMe (0.1 mL) in MeOH (2 mL) were stirred for 20 min and worked up as described above to give **16** (0.075 g, 80%) as a solid: mp 182–184 °C; $[\alpha]_D = -32.9$ (*c* 0.8, MeOH); ν_{max} (MeOH) 3369, 2946, 2834, 1704, 1450, 1404, 1111, 1029, 758; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.56–1.60 (m, 1H), 1.65–1.80 (m, 2H), 1.82 (s, 3H), 1.81–1.85 (m, 1H), 1.89–1.96 (m, 1H), 3.45 (dt, 1H, J=9.6, 5.5 Hz), 3.73 (dt, 1H, J=9.6, 4.4 Hz), 3.92 (t, 1H, J=7.7 Hz), 4.1 (d, 1H, J=6.1 Hz), 4.32 (t, 1H, J=4.9 Hz, OH), 4.97 (s, 1H, OH), 5.13 (d, 1H, J=6.9 Hz, OH), 5.65 (d, 1H, J=8.5 Hz), 7.49 (s, 1H), 11.32 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.7, 27.0, 29.3, 51.7, 60.1, 70.5, 83.2, 85.0, 88.4, 109.7, 135.8, 150.9, 163.4. Anal. Calcd for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.12; H, 6.36; N, 9.37.

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References and notes

1. Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983.
2. Vasella, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Otto salle Verlag GmbH: Frankfurt am Main, 1980; Vol. 2, pp 173–267.
3. (a) Yoshimura, J. In *Carbohydrate Chemistry and*

Biochemistry; Tipson, S., Horton, D., Eds.; Acacemic: New York, 1984; Vol. 42, pp 69–134. (b) Stütz, E. A. In *Topics in Current Chemistry*; Springer: Heidelberg, 2001; pp 1–345.

4. For examples where two new chiral cenres have been generated see: (a) Kishida, M.; Yamauchi, N.; Sawada, K.; Ohashi, Y.; Eguchi, T.; Kakinuma, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 891–895. (b) Bouifraden, S.; Lavergne, J.-P.; Martinez, J.; Viallefont, P.; Riche, C. *Tetrahedron: Asymmetry* **1997**, *8*, 949–955. (c) González, Z.; González, A. *Carbohydr. Res.* **2000**, *329*, 901–906.
5. For reviews see: (a) Kool, E. T. *Chem. Rev.* **1997**, *97*, 1473–1488. (b) Herdewijn, P. *Biochim. Biophys. Acta* **1999**, *1489*, 167–179. (c) Leumann, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 841–854.
6. For a recent review on the use of bicyclic nucleosides in oligonucleotides see: Meldgaard, M.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3539–3554.
7. (a) Tarköy, M.; Bolli, M.; Schweizer, B.; Leumann, C. *Helv. Chim. Acta* **1993**, *76*, 481–510. (b) Bolli, M.; Lubini, P.; Leumann, C. *Helv. Chim. Acta* **1995**, *78*, 2077–2096. (c) Leumann, C.; Bolli, M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 694–696.
8. (a) Freitag, M.; Thomasen, H.; Christensen, N. K.; Petersen, M.; Nielsen, P. *Tetrahedron* **2004**, *60*, 3775–3786 and references therein. (b) Obika, S.; Sekiguchi, M.; Osaki, T.; Shibata, N.; Masaki, M.; Hari, Y.; Imanishi, T. *Tetrahedron Lett.* **2002**, *43*, 4365–4368. (c) Lescop, C.; Huet, F. *Tetrahedron* **2000**, *56*, 2995–3003. (d) Oh, J.; Lee, C. R.; Chun, K. H. *Tetrahedron Lett.* **2001**, *42*, 4879–4881. (e) Kværnø, L.; Wengel, J. *J. Org. Chem.* **2001**, *66*, 5498–5503. (f) Sørensen, M. H.; Nielsen, C.; Nielsen, P. *J. Org. Chem.* **2001**, *66*, 4878–4886. (g) Wang, G.; Gunic, E. *Nucleosides Nucleotides* **1999**, *18*, 531–536. (h) Singh, S. K.; Kumar, R.; Wengel, J. *J. Org. Chem.* **1998**, *63*, 6078–6079. (i) Obika, S.; Nanbu, D.; Hari, Y.; Morio, K.; In, Y.; Ishida, T.; Imanishi, T. *Tetrahedron Lett.* **1997**, *38*, 8735–8738. (j) Steffens, R.; Leumann, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3250–3255. (k) Obika, S.; Morio, K.; Nanbu, D.; Imanishi, T. *Chem. Commun.* **1997**, 1643–1644. (l) Obika, S.; Morio, K.; Hari, Y.; Imanishi, T. *Chem. Commun.* **1999**, 2423–2424.
9. Ravn, J.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 985–993.
10. For our earlier efforts on the synthesis of novel nucleosides see: Gurjar, M. K.; Maheshwar, K. *J. Org. Chem.* **2001**, *66*, 7552–7554.
11. Garegg, P. J.; Samuelsson, B. *Carbohydr. Res.* **1978**, *67*, 267–270.
12. (a) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845–1848. (b) Fürstner, A. *Synthesis* **1989**, 571–590. (c) Rathke, M. W., Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H. Eds.; Pergamon: Oxford, 1991, Vol. 2, pp 277–299.
13. For recent reviews: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (c) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043. (d) Kotha, S.; Sreenivasachary, N. *Ind. J. Chem. B* **2001**, *40*, 763–780.
14. (a) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654–3660. (b) Vorbrüggen, H.; Krolikewiez, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255. (c) Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256–1268.
15. Zemplén, G.; Kunz, A. *Ber.* **1923**, *56B*, 1705.
16. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-233198. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

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Hetero-Diels–Alder and pyroglutamate approaches to (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid

James E. Tarver, Jr.,[†] Kristen M. Terranova[†] and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, USA

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Abstract—The stereoselective syntheses of fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid, a non-coded amino acid of cyclomarin A, and its diastereomer are reported. A pyroglutamate template was employed in the key diastereoselective alkylation used for introducing the 4-methyl stereochemistry. In addition, the first diastereoselective intramolecular hetero-Diels–Alder of a 2-cyano-1-azadiene with an electron deficient dienophile is described.

1. Introduction

Cyclomarin A (**1**, Fig. 1) is a potent anti-inflammatory agent[1] that has been a recent target of interest in several research laboratories,[2,3] including our own.[4–7] The non-coded amino acid constituents of cyclomarin A provide a wealth of structural diversity and challenges which require extension of the scope of existing methods or development of new strategies for synthesizing these compounds. In our continuing efforts to complete both novel and efficient syntheses of these amino acids, we have investigated the use of a hetero-Diels–Alder reaction employing a 2-cyano-1-azadiene to prepare the fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment of cyclomarin A. We also report the completed synthesis of this fragment and its diastereomer (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid, using a pyroglutamate framework for the establishment of stereochemistry.

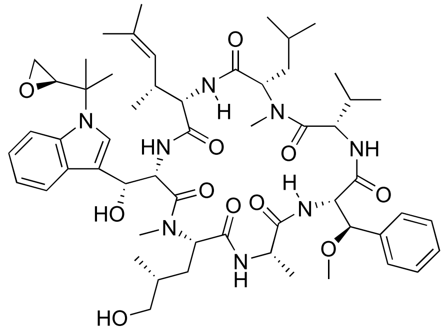

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Figure 1. Cyclomarin A.

2. Results

The initial strategy used for making the (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment utilized a hetero-Diels–Alder reaction that allowed for stereochemical control at both the 2- and 4-positions in one step. The hydroxyl and *N*-methyl functionalities would be introduced by oxidation of the olefin and reduction of the resultant formyl groups. Azadienes have been used previously in Diels–Alder (DA) reactions and their application and scope have been reviewed thoroughly.[8,9] Since the nitrogen of 1-azadienes renders the pi system more electron deficient, its ability to undergo a Type I Diels–Alder reaction is diminished. Most reported examples of hetero-DA reactions with 1-azadienes occur via an inverse electron demand (Type II) mechanism.[8,9] If there are enolizable protons at the 4-position, tautomerization may occur to generate an enamine which can undergo the DA reaction more easily with an electron deficient dienophile[8] (Fig. 2). Other factors contributing to the low yields of hetero-DA reactions using 1-azadienes include competitive imine [2 + 2] cycloadditions and the instability of the enamine products. The low reactivity and product instability may be reduced by the use of substrates with *N*-acyl,[10] *N*,*N*-sulfonyl[8] or *N*,*N*-dialkylamino[11] substitution

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Keywords: Hetero-Diels–Alder; Pyroglutamate; Cyclomarin A.

* Corresponding author. Tel.: +1-215-898-3158; fax: +1-215-573-9711; e-mail: mjoullie@sas.upenn.edu

[†] Lexicon Pharmaceuticals, Medicinal Chemistry, 350 Carter Road, Princeton, New Jersey 08540, USA.

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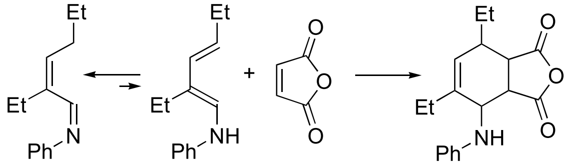


Figure 2. 1-Azadienes can undergo tautomerization to enamides.

on the nitrogen. It is believed that the acyl and sulfonyl substitution stabilize the enamine products; the dialkyl group increases the electron density in the system. It has also been observed that a methoxy or cyano group at the 2-position on the azadiene improves the DA reaction[10,12,13] (Fig. 3).

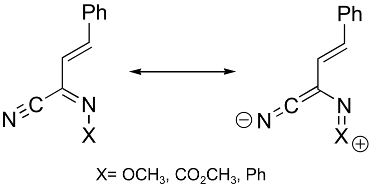


Figure 3. Electronic stabilizing groups for 1-azadienes.

Motorina and Grierson have extensively investigated the use of 2-cyano-1-azadienes in DA or intramolecular DA (IMDA) reactions.[14] The authors observed that 2-cyano-1-azadienes may undergo DA type reactions in a regio-controlled fashion with moderate stereocontrol. We expected that existing chirality in the diene or dienophile in our system would induce asymmetry to the remote methyl center. It was believed that this effect could be enhanced if the reaction was run in an intramolecular fashion. In addition, the regiochemistry of the DA reaction could be controlled by the tether restriction. The most accessible location for the chiral auxiliary would be attached to the nitrogen at the 1-position, though it would reduce the reactivity of the diene itself. It was hoped that this deficiency could be overcome by the addition of a cyano or methoxy group at the 2-position on the diene (Fig. 4). It was predicted that the proposed synthon would lead to the undesired (2*S*,4*S*)-diastereomer (Fig. 5); however, there was reason to believe that the desired compound could be produced by modification of the chiral auxiliary or epimerization.

The synthesis (Scheme 1) began with *S*-phenylglycinol, which is available from Aldrich or from a borohydride reduction of phenylglycine ethyl ester hydrochloride salt.[15,16] The amino alcohol was treated with *trans*-crotonyl chloride and 2 N sodium carbonate under biphasic conditions to give the crotonamide **2** in 97% yield.[17] The subsequent esterification step was achieved by treating the crotonamide with acryloyl chloride under phase transfer conditions in 93% yield.[18] The enamide **3** was then treated with Hunig's base and triflic anhydride at −60 °C, followed by displacement of the vinyl triflate by lithium cyanide and 12-crown-4 complex to provide the 2-cyano-1-azadiene **4** in low yield. This triene was heated to 110 °C in benzene for 48 h, yielding an unstable bicyclic compound **5** the structure and stereochemistry of which were determined by spectroscopic methods to be those of a single diastereomer. Despite the low yield, this reaction represents the first example of remote asymmetric induction with either intermolecular or intramolecular DA reactions of 2-cyano-1-azadienes.[4] It is also the first example of a diastereoselective intramolecular DA reaction of a 2-cyano-1-azadiene with an electron deficient dienophile. Unfortunately, treatment of the unstable cycloadduct with ozone led to decomposition.

Given the difficulties encountered in formation of the cyanoazadiene and its low reactivity, other methods were investigated (Scheme 2). The effect of an electron donating substituent in the diene system was probed by the addition of a 2-alkoxy group, employing imidoesters and an oxazoline. The methyl imido ester was formed by treatment of the enamide **3** with methyl triflate, but heating this unstable compound (**7**) in a sealed tube yielded only decomposition products. Use of a microwave reactor gave the same results.

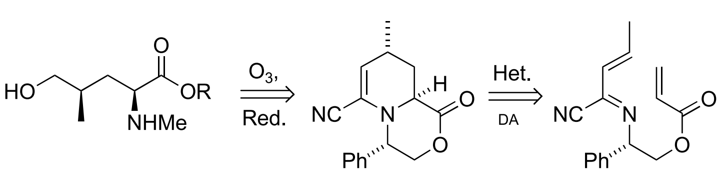


Figure 4. Hetero-Diels–Alder disconnections.

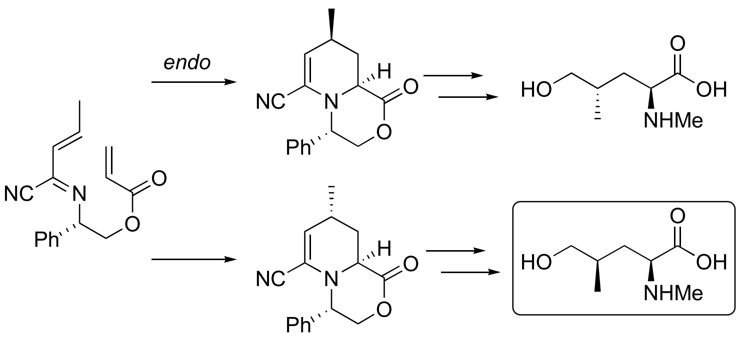
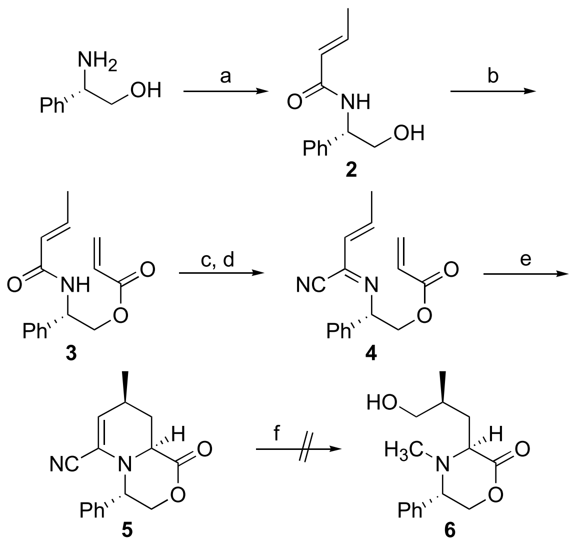
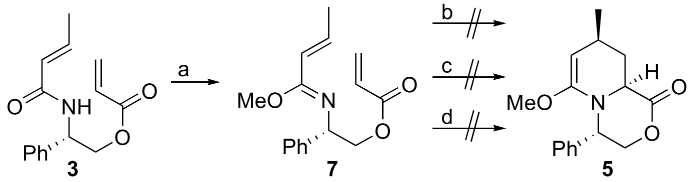


Figure 5. 2-Methylamino-5-hydroxy-4-methylpentanoic acid stereochemistry for both possible Diels–Alder adducts.



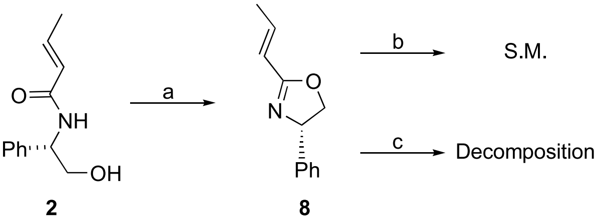
Scheme 1. Reagents and conditions: (a) *trans*-crotonyl chloride, aq Na_2CO_3, CH_2Cl_2, 97%; (b) 30% aq KOH, CH_2Cl_2, acryloyl chloride, TBAI, 0 °C, 93%; (c) DIEA, Tf_2O, CH_2Cl_2, -60 °C; (d) 12-crown-4, LiCN, THF, -60 °C, 24% over 2 steps; (e) toluene, 120 °C, 48 h, 9%; (f) ozone, CH_2Cl_2, -78 °C; $NaBH_4$, MeOH.



Scheme 2. Reagents and conditions: (a) MeOTf, CH_2Cl_2; (b) 150 °C, 12 h, neat; (c) benzene, 110 °C, 4d; (d) 5 M ether–$LiClO_4$, 5 days.

Treatment of alcohol **2** with tosyl chloride and triethylamine produced oxazoline **8** in 63% yield (Scheme 3).[17] This compound was then treated with several conditions including various dienophiles, but no reaction was observed except decomposition in certain instances. The lack of reactivity was attributed to the preferred *s-trans* conformation of the pi system when the diene's 4-position is substituted.

Huang and co-workers reported intramolecular DA reactions with 1-azadiene substrates that were formed in situ for the construction of heterocyclic ring systems.[19] The advantages of these reactions were the mild conditions (trialkylsilyl chlorides and triethylamine) under which they proceeded. Fukomoto and co-workers used the milder trialkylsilyl trifluoromethanesulfonates and triethylamine conditions having previously used TMSCl, $ZnCl_2$ and TEA in toluene at high temperature[20] to effect the DA reaction of enamides with α,β-unsaturated esters.[21] Using TBSOTf or TMSCl/$ZnCl_2$ and TEA, attempts were made to form the azadiene in situ at both ambient and elevated temperature. Both reactions resulted either in recovery of starting material or decomposition. In an effort to improve the electronic alignment, an electron-withdrawing group was installed on the terminus of the acrylate functionality. The expectation was that even if the DA reaction did not occur, maybe a degenerate mechanism, such as a base-mediated tandem conjugate addition would allow generation of the desired product. However, after many variations of the hetero-Diels–Alder route were attempted with no significant improvement, this approach was eventually abandoned for a more favorable one.[5]



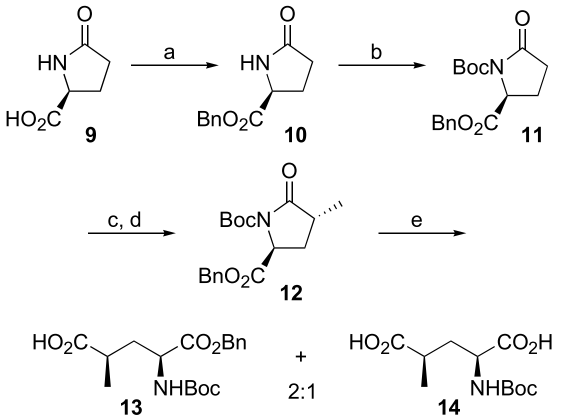
Scheme 3. Reagents and conditions: (a) TsCl, TEA, CH_2Cl_2, 2d, 63%; (b) maleic anhydride, 110–115 °C; (c) diethyl acetylene dicarboxylate.

3. Discussion

The pyroglutamate moiety is a powerful synthetic building block that has been previously used to prepare glutamic acid and leucine derivatives.[22,23] Its versatility and high functional group density allows it to be used for a variety of targets.[24] It was envisioned that using a stereoselective alkylation at the α-position of the amide followed by inversion would afford the product with the desired stereochemistry (Fig. 6). Investigations by several groups[24–28] had validated the feasibility of this approach, but conflicting results were obtained with regard to the *cis*:*trans* selectivity of the alkylation depending on the substrate, base and electrophile.[25,27–30] Young and co-workers found that the major product of alkylation mixtures was the *cis* product.[29,30] Furthermore, they were able to improve both the yield and stereoselectivity of the reaction to 70% and a 17:1 *cis*:*trans* ratio[29] if lithium hexamethyldisilazide was used as the base and methyl triflate as the electrophile.

Figure 6. Pyroglutamic acid disconnection.

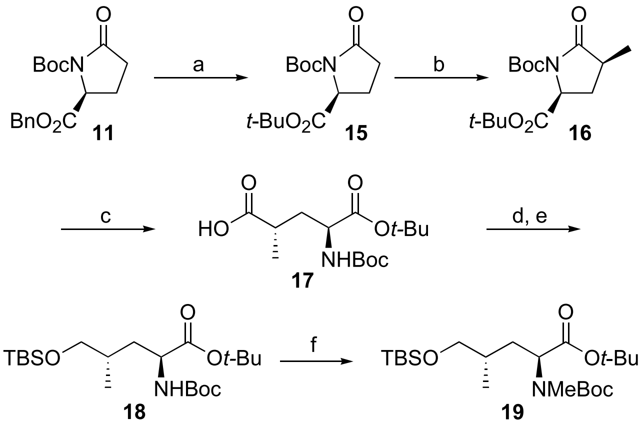
In our system, the original protecting group was a benzyl ester, with the hope that upon lithium hydroxide opening of the lactam ring little or no hydrolysis of the ester would occur. The synthesis (Scheme 4) proceeded in good yield following the procedure of Young and co-workers to afford the fully protected pyroglutamate **11**.[22] The stereoselective alkylation using LiHMDS and methyl triflate followed by



Scheme 4. Reagents and conditions: (a) TEA, benzyl chloride, acetone, 85%; (b) Boc_2O, DMAP, CH_3CN, 73%; (c) LiHMDS, MeOTf, Toluene, −78 °C; (d) LiHMDS, 2,6-di-*t*-butylphenol, Toluene, −78 °C, 34% over 2 steps; (e) 1 M LiOH, THF, 30 min, 0 °C, 54%.

inversion using LiHMDS and ammonium chloride proceeded with a *cis*:*trans* ratio of 1:4 in 34% yield over two steps. The lithium hydroxide ring opening did not proceed as well as planned and generated what was believed to be the desired benzyl ester **13** as well as the free carboxylic acid **14**, but never in isolable yields. A modification of the protecting group scheme was required and we investigated the use of a *tert*-butyl group instead of a benzyl moiety.

The *tert*-butyl ester allowed for opening of the lactam ring without hydrolysis of the ester.[22] Beginning with fully protected pyroglutamate **11**, the ester was deprotected using standard hydrogenation conditions and protected as the *tert*-butyl ester **15** using Boc_2O, TEA, and DMAP in acetonitrile in an 83% yield over 2 steps (Scheme 5). The stereoselective alkylation proceeded in 70% yield with a 7:1 ratio of *cis* **16**:*trans*. The lithium hydroxide opening proceeded in quantitative yield, and subsequent reduction of the mixed anhydride produced the alcohol in 69% yield.[22,31] The resulting alcohol was to be protected as its TBS ether. Standard conditions of TBSCl and imidazole in methylene chloride led to consistently low yields. Variation of the base-catalyst system (imidazole, 2,6-lutidine and TEA/DMAP) did not increase the yield. Eventually, changing the solvent to DMF and using TBSCl with the TEA/DMAP system successfully provided TBS ether **18** in 91% yield.

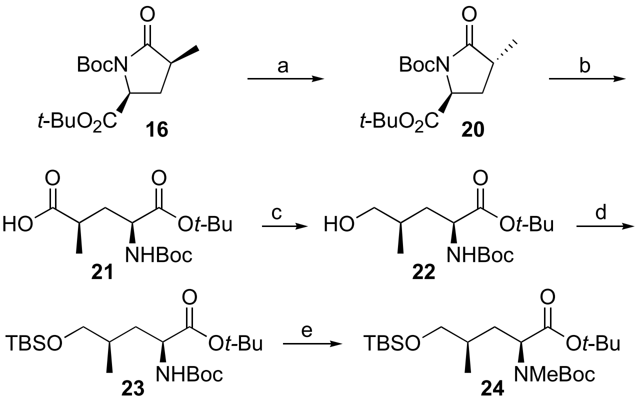


Scheme 5. Reagents and conditions: (a) (i) H_2, Pd/C, EtOAc; (ii) Boc_2O, DMAP, TEA, MeCN, 83%; (b) (i) LiHMDS, THF, −78 °C; (ii) MeOTf, 70% 7:1; (c) LiOH, THF, 0 °C to rt, quant; (d) (i) *i*-BuOCOCl, TEA, THF, −40 °C; (ii) $NaBH_4$, H_2O, 0 °C, 69%; (e) TBSCl, DMAP, TEA, DMF, 91%; (f) (i) NaHMDS, THF, 0 °C to rt; (ii) MeI, 70%.

N-Boc protected nitrogens have been previously methylated using NaH or KH[32] though in this particular case both reagents met with limited success. Using NaHMDS as the base[33] provided methylated product **19** in 36% yield. In an effort to improve the methylation, carbamate **18** was treated with Ag_2O and MeI,[34] which led to a clean product in 50% yield. The nitrogen was methylated in 70% yield using optimized conditions of NaHMDS (2.5 equiv) and MeI (10 equiv), to provide the fully protected unnatural diastereomer of (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid **19** with the same stereochemistry as the product obtained in the hetero-DA reaction.

The stereoselective alkylation of the protected pyroglutamate yielded two diastereomers, the major product being the undesired *cis* product **16**, but the products were separable by column chromatography. The *cis* product had been isomerized previously by Ezquerra and co-workers, using 1 equiv of KCN in DMF over 4 days to give a final ratio of 33:67 of *cis*:*trans* product.[27,26] Conditions which would allow for faster reaction time while maintaining a similar yield and product ratio were desired.

Initial studies with the benzyl ester indicated that use of LiHMDS and a kinetic quench with ammonium chloride would give a *cis*:*trans* ratio of 1:4; however, this result did not translate to the *tert*-butyl ester series. Despite numerous trials with various conditions, products were obtained which consisted primarily of the *cis* isomer. Use of KHMDS and ammonium chloride led to decomposition, while NaHMDS with ammonium chloride led to more successful inversion (1:2 *cis*:*trans*), but in reduced yield. Using acetic acid to quench the isomerization after enolization with NaHMDS[23] led to recovery of starting material. The next bases tried were DABCO and DBU; DABCO produced no reaction and led only to the isolation of starting material. However, the use of 4 equiv of DBU in methylene chloride over 2 days consistently gave primarily inverted product **20** in a 3:1 ratio and in high yields (Scheme 6). With epimerization achieved, the lactam ring was hydrolyzed selectively with



Scheme 6. Reagents and conditions: (a) 4 equiv DBU, CH_2Cl_2, 0 °C to rt, 86%, 3.1:1; (b) LiOH, THF, 0 °C to rt, 78%; (c) (i) *i*-BuOCOCl, TEA, THF, −40 °C; (ii) $NaBH_4$, H_2O, 0 °C, 67%; (d) TBSCl, DMAP, TEA, DMF, 93%; (e) (i) NaHMDS, THF, 0 °C to rt; (ii) MeI, 57%.

lithium hydroxide. Mixed anhydride reduction of the resulting acid **21** proceeded in 67% yield to afford the primary alcohol **22**. The TBS protection and subsequent *N*-methylation proceeded in 93 and 57% yields, respectively, using conditions developed during synthesis of the unnatural diastereomer to give fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid **24**.

4. Conclusions

The synthesis of the fully protected (2*S*,4*R*)-2-methylamino-5-hydroxy-4-methylpentanoic acid fragment of cyclomarin A was accomplished in 8 steps and 14% overall yield. In addition, we have synthesized (2*S*,4*S*)-2-methylamino-5-hydroxy-4-methylpentanoic acid in 7 steps and 26% overall yield. We also have reported the first example of a diastereoselective intramolecular Diels–Alder reaction of a 2-cyano-1-azadiene with an electron deficient dienophile.

5. Experimental

5.1. General

All reactions were performed under argon. THF was distilled over sodium-benzophenone, while CH_2Cl_2 and toluene were distilled over calcium hydride. Flash column chromatography was carried out on E. Merck silica gel 60 (240–400 mesh) using the solvent systems listed under individual experiments. Proton and carbon magnetic resonance spectra were recorded on a Bruker AM-500 Fourier transform spectrometer. Infrared spectra (IR) were obtained on a Perkin–Elmer Model 1600 FT-IT spectrophotometer. Optical rotations were recorded on a Perkin–Elmer Model 341 polarimeter at the sodium D line. Melting points were obtained on a Thomas Hoover Uni-melt apparatus and are uncorrected.

5.1.1. (*S*)-Acrylic acid 2-but-2-enoylamino-2-phenylethyl ester 3. To a cold (0 °C) solution of alcohol **2** (2.29 g, 11.0 mol) in CH_2Cl_2 (20 mL) was added 30:70 KOH solution (20 mL) and tetrabutylammonium iodide (TBAI, 0.406 g, 1.1 mmol). To the reaction mixture was added acryloyl chloride (1.3 mL, 15.6 mmol) in CH_2Cl_2 (3 mL) via an addition funnel at 0 °C. After 20 min, the organic layer was separated. The organic layer was then washed with water (3×10 mL) until the aqueous layer was neutral. The organic phase was dried (Na_2SO_4) and concentrated to yield an orange oil. Column chromatography (20% acetone/hexanes) afforded a clear white glass (2.65 g, 93%). (**3**): R_f 0.25 (30% acetone/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.35 (m, 5H), 6.79–6.89 (m, 1H), 6.55–6.62 (m, 1H), 6.49 (dd, $J=17.4$, 1.2 Hz, 1H), 6.10 (dd, $J=17.3$, 10.4 Hz, 1H), 5.80–5.89 (m, 2H), 5.36–5.45 (m, 1H), 4.51 (dd, $J=11.4$, 7.5 Hz, 1H), 4.37 (dd, $J=11.5$, 6.7 Hz, 1H), 1.83 (dd, $J=6.9$, 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.5, 140.3, 138.4, 131.4, 128.6, 127.8, 127.8, 126.7, 124.8, 66.1, 52.4, 17.6; IR (neat) 3282, 3064, 1726, 1670, 1633, 1541, 1446, 1408, 1294, 1269, 1188, 1060, 968, 810, 700 cm^{-1}; HRMS *m*/*z* calculated for $C_{15}H_{17}NO_3Na$ $(M+Na)^+$ 282.1106, found 282.1093; $[\alpha]_D^{25}+56.4$ (*c* 3.63, $CHCl_3$).

5.1.2. (*S*)-Acrylic acid 2-(1-cyano-but-2-enylidene-amino)-2-phenylethyl ester 4. A cold (−60 °C) solution of acrylate **3** (0.500 g, 1.93 mmol) and diisopropylethyl amine (0.5 mL, 2.89 mmol) in CH_2Cl_2 (6.5 mL) was stirred for 1 h. Triflic anhydride (freshly opened bottle) was added dropwise. The reaction was allowed to stir 2 h during which time it turned to a brown solution. To this reaction mixture was added a suspension of (89 mg, 2.72 mmol) LiCN (dried over P_2O_5 under vacuum at 80 °C for 4 h) and 12-crown-4 (30 μL, 0.19 mmol) in THF (6 mL) at −73 °C via cannula syringe and then warmed to −60 °C for 1.5 h. After that time, the reaction was warmed to −20 °C over 30 min and water (6 mL) was added. The reaction was diluted with ether while warming to room temperature. The layers formed were separated and the aqueous layer was extracted with ether (2×10 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and concentrated to a brown oil. Column chromatography (5% acetone/hexanes to 8% acetone/hexanes) afforded a yellow oil (0.111 g, 21%). (**4**): R_f 0.65 (30% acetone/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.52 (m, 5H), 6.71–6.78 (m, 1H), 6.37–6.41 (m, 2H), 6.09 (dd, $J=17.4$, 10.4 Hz, 1H), 5.83 (dd, $J=10.5$, 1.3 Hz, 1H), 5.08–5.13 (m, 1H), 4.50 (dd, $J=11.1$, 3.9 Hz, 1H), 4.40 (dd, $J=11.1$, 9.2 Hz, 1H), 1.96 (dd, $J=6.9$, 1.6 Hz, 3H); HRMS (CI) *m*/*z* calculated for $C_{16}H_{17}N_2O_2$ $(M+H)^+$ 269.1284, found 269.1284. Product was too unstable for further characterization.

5.1.3. (4*S*,8*S*,10*S*)-8-Methyl-1-oxo-4-phenyl-1,3,4,8,9,9a-hexahydropyrido[2,1-*c*][1,4]oxazine-6-carbonitrile 5. Azadiene **4** (164 mg, 0.61 mmol) was dissolved in toluene (12 mL), placed in a sealed tube and charged with a magnetic stirrer. The reaction was heated to 130 °C for 50 h. The compound was concentrated and purified by column chromatography (2% ethyl acetate/hexanes to 8% ethyl acetate/hexanes) to afford the product as a brown oil, (14 mg, 9%) and starting material, as a yellow oil, (39 mg, 24%). (**5**): R_f 0.54 (30% ethyl acetate/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.45 (m, 5H), 4.93 (t, $J=3.8$ Hz, 1H), 5.33 (s, 1H), 4.66–4.76 (m, 2H), 3.86 (dd, $J=11.2$, 3.1 Hz, 1H), 2.43–2.51 (m, 2H), 1.65 (quartet of doublets, $J=12.1$, 2.5 Hz, 1H), 1.08 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 135.4, 128.7, 127.9, 127.3, 123.2, 115.2, 70.6, 56.2, 54.1, 32.7, 29.7, 28.4, 20.3; HRMS (CI) *m*/*z* calculated for $C_{16}H_{17}N_2O_2$ $(M+H)^+$ 269.1284, found 269.1284. Product was too unstable for further characterization.

5.1.4. (*S*)-Acrylic acid 2-(1-methoxy-but-2-enylidene-amino)-2-phenylethyl ester 7. To a solution of amide **3** (1.67 g, 7.45 mmol) in CH_2Cl_2 (25 mL) was added methyl triflate (1.5 mL, 12.88 mmol) dropwise at room temperature. The reaction was allowed to stir for 96 h then diluted with CH_2Cl_2 (40 mL), washed with saturated sodium bicarbonate (30 mL) and dried (Na_2SO_4). The solution was concentrated in vacuo to a yellow oil. Column chromatography (10% acetone/hexanes to 20% acetone/hexanes) afforded the product as a yellow oil (0.844 g, 48%) as well as starting material (40%). (**7**): R_f 0.61 (30%

acetone/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 (m, 2H), 7.32 (m, 2H), 7.25 (m, 1H), 6.54 (m, 1H), 6.35 (m, 1H), 6.08 (m, 2H), 5.78 (m, 1H), 4.90 (dd, $J=8.1$, 5.0 Hz, 1H), 4.35 (ddd, $J=10.7$, 5.1, 2.8 Hz, 1H), 4.25 (m, 1H), 3.75 (d, $J=2.2$ Hz, 3H), 1.80 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.0, 158.5, 141.5, 137.7, 130.6, 128.5, 128.3, 127.3, 117.9, 117.8, 69.7, 69.5, 59.8, 52.4, 18.2; IR (neat) 3060, 3028, 2944, 2348, 2096, 17,225, 1673, 1621, 1492, 1437, 1406, 1377, 1287, 1265, 1182, 1098, 1044, 986, 963, 839 cm^{-1}; HRMS (CI) *m/z* calcd for C$_{16}$H$_{19}$NO$_2$ (M+H)$^+$: 274.1440, found 274.1435; $[\alpha]^{25}_{\rm D}+5.9°$ (*c* 1.05, CHCl$_3$).

5.1.5. (2*S*,4*R*)-4-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester, *trans*-12, and (2*S*,4*S*)-4-Methyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester, *cis*-12. To a cooled (−78 °C) solution of lactam **11** (1.00 g, 3.13 mmol) in anhydrous toluene (6 mL) was added 1 M LiHMDS solution in THF (3.6 mL, 3.60 mmol). After stirring for 1 h at the same temperature, methyl triflate (0.39 mL, 3.44 mmol) was added via syringe. After stirring for another 2 h at −78 °C, 1 M LiHMDS in THF (4.1 mL, 4.07 mmol) was added to the reaction mixture. Following another 2 h of stirring at −78 °C, the reaction was quenched with saturated ammonium chloride and allowed to warm to room temperature for 10 min before diluting it with ethyl acetate. The reaction was extracted into ethyl acetate (3× 25 mL), dried with sodium sulfate and concentrated to a yellow-tan foam. The crude residue was purified by column chromatography (5% ethyl acetate/hexanes to 30% ethyl acetate/hexanes) to afford 0.280 g (27%) of yellow oil *trans*-**12** and 0.070 g (7%) of yellow oil *cis*-**12**. (*trans*-**12**): $R_{\rm f}$ 0.70 (40% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26–7.41 (m, 5H), 5.25 (d, $J=12.2$ Hz, 1H), 5.20 (d, $J=12.2$ Hz, 1H), 4.62 (dd, $J=9.6$, 1.3 Hz, 1H), 2.55–2.73 (m, 1H), 2.14–2.35 (m, 1H), 1.80–2.00 (m, 1H), 1.46 (s, 9H), 1.23 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.5, 171.1, 149.5, 135.1, 128.7, 128.6, 128.4, 83.5, 67.3, 57.0, 36.5, 30.5, 27.8, 15.1; IR (neat) 3033, 2977, 2934, 2879, 2359, 1792, 1752, 1716, 1498, 1456, 1391, 1368, 1316, 11,284, 1251, 1185, 1153, 1120, 1100, 1061, 973, 014, 854, 776, 750, 699 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{18}$H$_{23}$NO$_5$ (M+Na)$^+$: 356.1576, found 356.1484; $[\alpha]^{25}_{\rm D}-18.0°$ (*c* 1.42, CHCl$_3$).

(*cis*-**12**): $R_{\rm f}$ 0.57 (40% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26–7.41 (m, 5H), 5.20 (d, $J=12.1$ Hz, 1H), 5.14 (d, $J=12.1$ Hz, 1H), 4.47–4.54 (m, 1H), 2.46–2.64 (m, 2H), 1.51–1.64 (m, 1H), 1.47 (s, 9H), 1.19 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.5, 171.2, 149.3, 134.9, 128.5, 128.5, 128.4, 83.4, 67.1, 57.3, 37.3, 29.5, 27.7, 16.1, 14.1; IR (neat) 3033, 2978, 2934, 2878, 2360, 1790, 1751, 1716, 1498, 1456, 1392, 1369, 1318, 1292, 1259, 1176, 1154, 1124, 969, 913, 850, 784, 749, 699 cm^{-1}; HRMS (CI) *m/z* calcd for C$_{18}$H$_{23}$NO$_5$ (M+H)$^+$: 334.1654, found 334, 1656; $[\alpha]^{25}_{\rm D}-43.9°$ (*c* 1.38, CHCl$_3$).

5.1.6. (2*S*,4*S*)-2-(*tert*-Butoxycarbonylmethylamino)-5-(*tert*-butyldimethylsilanyloxy)-4-methylpentanoic acid *tert*-butyl ester 19. To a solution of TBS ether **18** (0.0448 g, 0.107 mmol) in THF (0.8 mL) at 0 °C, NaHMDS (1.0 M in THF, 0.27 mL, 0.268 mmol) was added dropwise. The reaction stirred at 0 °C for 10 min and at room temperature for 30 min before iodomethane (0.07 mL, 1.07 mmol) was added dropwise. After 2 h, the reaction was quenched with the addition of saturated NH$_4$Cl and ether. The aqueous portion was extracted 3 times with ether and the combined organic portions were washed with water and brine, dried over MgSO$_4$, filtered and concentrated. The crude product was purified by flash chromatography using 1% acetone in petroleum ether, which yielded **19** as a yellow oil (0.0326 g, 70%). (**19**): $R_{\rm f}$ 0.64 (5% acetone/petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.75 (dd, $J=11.8$, 2.9 Hz, 0.5H), 4.51 (dd, $J=11.7$, 3.7 Hz, 0.5H), 3.43 (dd, $J=9.7$, 5.1 Hz, 1H), 3.35 (m, 1H), 2.73 (d, $J=15.7$, 3H), 1.90 (m, 1H), 1.51 (m, 1H), 1.47 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 0.87 (m, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 4.82 (m, 1H), 3.43 (m, 2H), 2.85 (s, 3H), 1.98 (m, 1H), 1.69 (m, 2H), 1.44 (s, 9H), 1.35 (s, 9H), 0.96 (d, $J=2.9$ Hz, 3H), 0.93 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.7, 171.4, 156.4, 155.9, 81.1, 81.0, 79.9, 79.6, 68.3, 68.3, 57.2, 56.1, 32.2, 31.9, 30.1, 28.4, 28.0, 25.9, 18.3, 15.6, 15.5, −5.4; ^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 171.6, 156.5, 80.9, 79.7, 69.1, 58.1, 33.8, 33.4, 31.0, 30.8, 28.9, 28.5, 26.5, 18.9, 16.5, −5.0; IR (neat) 2956, 2930, 2857, 1737, 1700, 1472, 1391, 1367, 1324, 1254, 1154, 1093, 1034, 1007, 950, 912, 838, 776, 666 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{22}$H$_{45}$NO$_5$Si (M+Na)$^+$: 454.3051, found 454.2944; $[\alpha]^{25}_{\rm D}-16.8°$ (*c* 1.15, CHCl$_3$).

5.1.7. (2*S*,4*R*)-4-Methyl-5-oxopyrrolidine-1,2-dicarboxylic acid di-*tert*-butyl ester 20.[30] *cis*-Methylpyroglutamate **16** (0.1571 g, 0.525 mmol) was taken up in 4.1 mL CH$_2$Cl$_2$ and cooled to 0 °C. DBU (0.31 mL, 2.10 mmol) was added dropwise and the reaction stirred at 0 °C for 15 min and then at room temperature for 48 h. The reaction was diluted with CH$_2$Cl$_2$, washed twice with 10% HCl, and once each with water and brine. The organic portion was dried over Na$_2$SO$_4$, filtered and concentrated to give the crude product which was purified by flash chromatography using 5–10% ethyl acetate in petroleum ether yielding **20** as a clear colorless oil (0.1351 g, 86% in a 3.1:1 ratio of *trans*/*cis*). (**20**): $R_{\rm f}$ 0.65 (30% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.35 (dd, $J=9.5$, 1.1 Hz, 1H), 2.58 (m, 1H), 2.17 (ddd, $J=13.2$, 8.7, 1 Hz, 1H), 1.83 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.14 (d, $J=7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.7, 170.2, 149.4, 89.9, 82.1, 57.6, 36.4, 30.6, 27.8, 22.5, 15.1; IR (neat) 2977, 2934, 2359, 23,341, 1792, 1739, 1717, 1457, 1368, 1315, 1284, 1249, 1225, 1154, 1099, 973, 917, 884, 846, 813, 775 cm^{-1}; HRMS (ESI) *m/z* calcd for C$_{15}$H$_{25}$NO$_5$ (MH)$^+$: 300.1811, found 300.1805; $[\alpha]^{25}_{\rm D}-12.6°$ (*c* 1.11, CHCl$_3$).

5.1.8. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-4-methylpentanedioic acid 1-*tert*-butyl ester 21. *trans*-Methylpyroglutamate **20** (0.1039 g, 0.347 mmol) was taken up in 1.8 mL THF and cooled to 0 °C. 0.42 mL 1 M LiOH (aqueous, 0.416 mmol) was added dropwise over 15 min, the reaction was stirred for 15 min and was the quenched by addition of a mixture of ethyl acetate (1 mL) and saturated sodium bicarbonate (1 mL). The layers were separated and the organic portion was extracted with saturated sodium bicarbonate. The aqueous portions were combined, cooled to 0 °C and acidified to pH 4 using 10% citric acid and extracted 5 times with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated yielding **21** as a white solid (0.0862 g, 78%). (**21**): mp 72–74 °C; R_f 0.54 (50% ethyl acetate/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 10.42 (bs, 1H), 5.21 (d, $J=$ 6.6 Hz, 1H), 5.01 (d, $J=8.3$ Hz, 1H), 2.56 (m, 1H), 2.17 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H), 1.40 (s, 9H), 1.20 (d, $J=$ 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 171.4, 155.8, 82.4, 80.2, 52.5, 36.8, 36.2, 28.2, 27.9, 17.4; IR (neat) 3330, 2978, 2931, 2359, 2340, 1714, 1508, 1455, 1396, 1368, 1255, 1154, 1061, 847, 669 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}NO_6$ $(M+Na)^+$: 340.1838, found 340.1731; $[\alpha]_D^{25} -23.4°$ (*c* 1.4, MeOH).

5.1.9. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-4-methylpentanoic acid *tert*-butyl ester 22. To a solution of acid **21** (0.1429 g, 0.450 mmol) in 2.3 mL THF at −40 °C, Et_3N (0.08 mL, 0.585 mmol) was added dropwise. Isobutyl chloroformate (0.07 mL, 0.540 mmol) was added dropwise over 10 min, to give a yellow/orange color and the reaction was stirred at −40 °C for 2 h. The reaction was warmed to 0 °C, $NaBH_4$ (0.102 g, 2.70 mmol) in H_2O (2 mL) was added and the reaction stirred at 0 °C for 1 h and then warmed to room temperature. After stirring at room temperature for 3.5 h, the reaction was quenched with the addition of ethyl acetate and brine at 0 °C. The organic portion was washed with ice cold 10% citric acid 3 times, twice with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified using flash chromatography using 25% ethyl acetate/petroleum ether yielding **22** as a clear colorless oil (0.0913 g, 67%). (**22**): R_f 0.48 (30% ethyl acetate/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (d, $J=6.8$ Hz, 1H), 4.24 (d, $J=$ 4.7 Hz, 1H), 3.48 (dd, $J=10.7$, 5.3 Hz, 1H), 3.41 (dd, $J=$ 10.7, 6.3 Hz, 1H), 2.65 (bs, 1H), 1.75 (m, 2H), 1.44–1.35 (m, 1H), 1.40 (s, 9H), 1.38 (s, 9H), 0.90 (d, $J=6.7$, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.6, 81.8, 79.7, 67.7, 52.6, 37.7, 32.3, 28.2, 27.9, 17.4; IR (neat) 3364, 2976, 1712, 1511, 1455, 1390, 1367, 1251, 1154, 1046, 848 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}NO_5$ $(M+Na)^+$: 326.2045, found 326.1941; $[\alpha]_D^{25} +5.16°$ (*c* 1.03, $CHCl_3$).

5.1.10. (2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-5-(*tert*-butyldimethylsilanyloxy)-4-methyl-pentanoic acid *tert*-butyl ester 23. Alcohol **22** (0.0857 g, 0.282 mmol) was dissolved in 0.7 mL DMF and TBS-Cl (0.128 g, 0.846 mmol) was added. The reaction was stirred for 10 min. DMAP (0.0345 g, 0.282 mmol) and Et_3N (0.24 mL, 1.69 mmol) were added and the solution was allowed to stir for 18 h. The reaction was quenched with the addition of brine and was extracted 3 times with ether. The organic portion was washed sequentially with H_2O (3 times), ice cold 10% HCl, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using 10% ethyl acetate in petroleum ether, yielding **23** as a pale yellow oil (0.1093 g, 93%). (**23**): R_f 0.46 (5% acetone/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (d, $J=7.7$ Hz, 1H), 4.13 (m, 1H), 3.49 (dd, $J=9.9$, 5.1 Hz, 1H), 3.36 (dd, $J=9.9$, 5.8 Hz, 1H), 1.81 (m, 2H), 1.70 (m, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.90 (d, $J=6.9$, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.4, 81.4, 79.3, 67.1, 52.6, 36.2, 32.4, 28.3, 28.0, 25.9, 25.6, 17.3, −3.6, −5.5; IR (neat) 3359, 2956, 2930, 2857, 2348, 1718, 1501, 1472, 1392, 1366, 1252, 1154, 1093, 1049, 836, 776 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{43}NO_5Si$ $(M+Na)^+$: 440.2910, found 440.2796; $[\alpha]_D^{25} -0.5°$ (*c* 1.09, $CHCl_3$).

5.1.11. (2*S*,4*R*)-2-(*tert*-Butoxycarbonylmethylamino)-5-(*tert*-butyldimethylsilanyloxy)-4-methylpentanoic acid *tert*-butyl ester 24. The procedure described above for compound **19** was followed, using TBS-ether **23** (0.1250 g, 0.299 mmol). Compound **24** was isolated as a pale yellow oil (0.0739 g, 57%). (**24**): R_f 0.59 (5% acetone/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (dd, $J=10.2$, 5.0 Hz, 0.5H), 4.40 (dd, $J=10.1$, 5.0 Hz, 0.5H), 3.43 (m, 2H), 2.76 (d, $J=20.6$ Hz, 3H), 1.92 (m, 1H), 1.56 (m, 1H), 1.44 (m, 1H), 1.42 (s, 9H), 1.41 (s, 9H), 0.92 (d, $J=6.8$ Hz, 3H), 0.86 (s, 9H), 0.01 (d, $J=4.7$ Hz, 6H); ^1H NMR (500 MHz, d_8-toluene, 363 K) δ 4.77 (m, 1H), 3.51 (d, $J=$ 4.0 Hz, 2H), 2.84 (d, $J=12.8$ Hz, 3H), 1.69 (m, 1H), 1.53 (m, 2H), 1.48 (s, 9H), 1.41 (s, 9H), 0.98–0.94 (m, 3H), 0.97 (s, 9H), 0.08 (d, $J=7.3$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.3, 156.2, 155.9, 81.1, 79.9, 79.6, 66.5, 57.9, 56.6, 32.3, 32.0, 30.5, 29.7, 28.4, 28.0, 25.9, 18.3, 17.7, 17.5, −5.4; ^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 171.5, 156.4, 80.8, 79.7, 67.7, 58.5, 33.7, 33.4, 31.0, 28.9, 28.5, 26.5, 18.9, 17.9, −5.0; IR (neat) 2956, 2930, 2857, 2350, 1737, 1700, 1472, 1391, 1367, 1323, 1254, 1148, 1096, 1045, 1006, 952, 910, 838, 776, 665 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{45}NO_5Si$ $(M+Na)^+$: 454.3051, found 454.2977; $[\alpha]_D^{25} -18.4°$ (*c* 1.06, $CHCl_3$).

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References and notes

1. Renner, M. K.; Shen, Y.-C.; Cheng, X.-C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273–11276.
2. Sugiyama, H.; Shioiri, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, *43*, 3489–3492.
3. Wen, S.-J.; Zhang, H.-W.; Yao, Z.-J. *Tetrahedron Lett.* **2002**, *43*, 5291–5294.
4. Tarver, J. E., Jr.; Joullie, M. M. Abstracts of Papers, 224th ACS National Meeting, Boston, MA 2002, ORGN-499.
5. Tarver, J. E., Jr. PhD, University of Pennsylvania, 2003.
6. Tarver, J. E.; Joullie, M. M. *J. Org. Chem.* **2004**, *69*, 815–820.
7. Hansen, D. B.; Joullie, M. M. Abstracts of Papers, 224th ACS National Meeting, Boston, MA 2002, ORGN-502.
8. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939.
9. Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288.
10. Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075–2080.
11. Tamion, R.; Mineur, C.; Ghosez, L. *Tetrahedron Lett.* **1995**, *36*, 8977–8980.
12. Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093–2097.

13. Sisti, N. J.; Motorina, I. A.; Dau, M.-E. T. H.; Riche, C.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715–3728.
14. Motorina, I. A.; Grierson, D. S. *Tetrahedron Lett.* **1999**, *40*, 7215–7218.
15. Seki, H.; Koga, K.; Matsuo, H.; Ohki, S.; Matsuo, I.; Yamada, S.-i. *Chem. Pharm. Bull.* **1965**, *13*, 995–1000.
16. Pointdexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, *40*, 3527–3528.
17. Elliot, M. C.; Kruiswijk, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3157–3166.
18. Szeja, W. *Synthesis* **1980**, 402–403.
19. Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365–2378.
20. Ihara, M.; Kirihara, T.; Fukumoto, K.; Kametani, T. *Heterocycles* **1985**, *23*, 1097–1100.
21. Ihara, M.; Tsuruta, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1159–1161.
22. August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 507–514.
23. Acevedo, C. M.; Kogut, E. F.; Lipton, M. A. *Tetrahedron* **2001**, *57*, 6353–6359.
24. Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
25. Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459–7468.
26. Coudert, E.; Archer, F.; Azerad, R. *Synthesis* **1997**, 863–865.
27. Ezquerra, J.; Pegregal, C.; Rubio, A.; Yrurtagoyena, B.; Escribano, A.; Sanchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665–8678.
28. Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477–2480.
29. Charrier, J.-D.; Duffy, J. E. S.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1998**, *39*, 2199–2202.
30. Charrier, J.-D.; Duffy, J. E. S.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2367–2371.
31. Moody, C. M.; Starkmann, B. A.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 5485–5488.
32. Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556.
33. Ding, X.; Vera, M. D.; Liang, B.; Zhao, Y.; Leonard, M. S.; Joullie, M. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 231–234.
34. Olsen, R. K. *J. Org. Chem.* **1970**, *35*, 1912–1915.

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Synthesis and electrochemical properties of dendrimers containing *meta*-terphenyl peripheral groups and a 4,4′-bipyridinium core

Perumal Rajakumar* and Kannupal Srinivasan

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600025, Tamil Nadu, India

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Abstract—Fréchet-type poly(arylether) dendrons carrying *m*-terphenyl peripheral groups were synthesized up to second generation by convergent methodology. Simple quarternisation of 4,4′-bipyridine with the dendritic bromides afforded the corresponding dendrimers containing a 4,4′-bipyridine core. The electrochemical parameters were obtained for all the dendrimers and the half-wave potentials of both the first and second redox processes shift to less-negative values as the dendrimer generation increases.

1. Introduction

The peripheral groups of dendrimers act as the primary interface between the dendrimer and the external environment.[1] The properties of dendrimers such as solubility, chemical reactivity and glass transition temperature are strongly influenced by the nature of the peripheral groups. Hence there is a continuing interest in modifying the peripheral groups of dendrimers. The systems end-capped with organoruthenium moieties,[2] naphthalene and pyrene groups,[3] ferrocene units[4] and coumarin 2 (laser dye) units[5] are some examples of peripherally modified Fréchet-type dendrons and dendrimers. We have proven that *meta*-terphenyls are ideal building blocks in cyclophane chemistry.[6] In order to extend their utility to other supramolecular systems, we planned to introduce *m*-terphenyls as peripheral groups in dendrimers. A *m*-terphenyl carrying methoxy groups at 4,4″-positions was chosen to serve this purpose for three reasons: (i) the methoxy groups will provide appropriate solubility to permit dendritic growth through the repetition of coupling and activation steps, (ii) since the outer rings are orthogonal to the central ring in the *m*-terphenyl, there will be electron rich pockets for molecular recognition at the dendrimer surface and (iii) the electron-rich *m*-terphenyl will allow intramolecular charge transfer (CT) to take place from the periphery through the dendrimer backbone to the center of the molecule if the core is electron-deficient. Dendrimers with various types of encapsulated redox active cores have been reported.[7] Among them, dendrimers with a 4,4′-bipyridinium core have attracted significant interest as promising materials for nanoelectronics[8] and light harvesting.[9] Hence the incorporation of this group as the core of dendrimer structure is of interest and importance. Herein we report synthesis and electrochemical properties of dendrimers containing a 4,4′-bipyridinium core and *m*-terphenyl peripheral groups.

2. Results and discussion

2.1. Synthesis

The synthetic strategy for the preparation of the *m*-terphenyl-capped dendrons utilized a convergent method.[10] Hart's tandem aryne sequence reaction[11] between 2,6-dibromo-4-methyliodobenzene (**1**) and 4-anisylmagnesium bromide (**2**) afforded the *m*-terphenyl **3** in 62% yield. Radical bromination of **3** with NBS in CCl_4 gave the zeroth generation *m*-terphenyl bromide **4**, [G-0]-CH_2Br, in 44% yield. The presence of methoxy groups in the *m*-terphenyl significantly lowers the yield of this step. Coupling of 2 equiv of **4** with 1 equiv of the monomer, methyl-3,5-dihydroxy benzoate, in the presence of K_2CO_3 and 18-crown-6 in DMF at 80 °C afforded the first generation ester **5**, [G-1]-CO_2Me, in 72% yield. This ester was converted into the corresponding alcohol **6**, [G-1]-CH_2OH, in 90% yield by reduction with LAH in refluxing THF. Conversion of the alcohol **6** to the corresponding bromide **7** using CBr_4 and Ph_3P in THF was

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Keywords: Dendrimers; *m*-Terphenyl; 4,4′ -Bipyridine; Redox potentials.

* Corresponding author. Tel.: +91-44-22351269-213; fax: +91-44-22352494; e-mail: perumalrajkumar2003@yahoo.co.in

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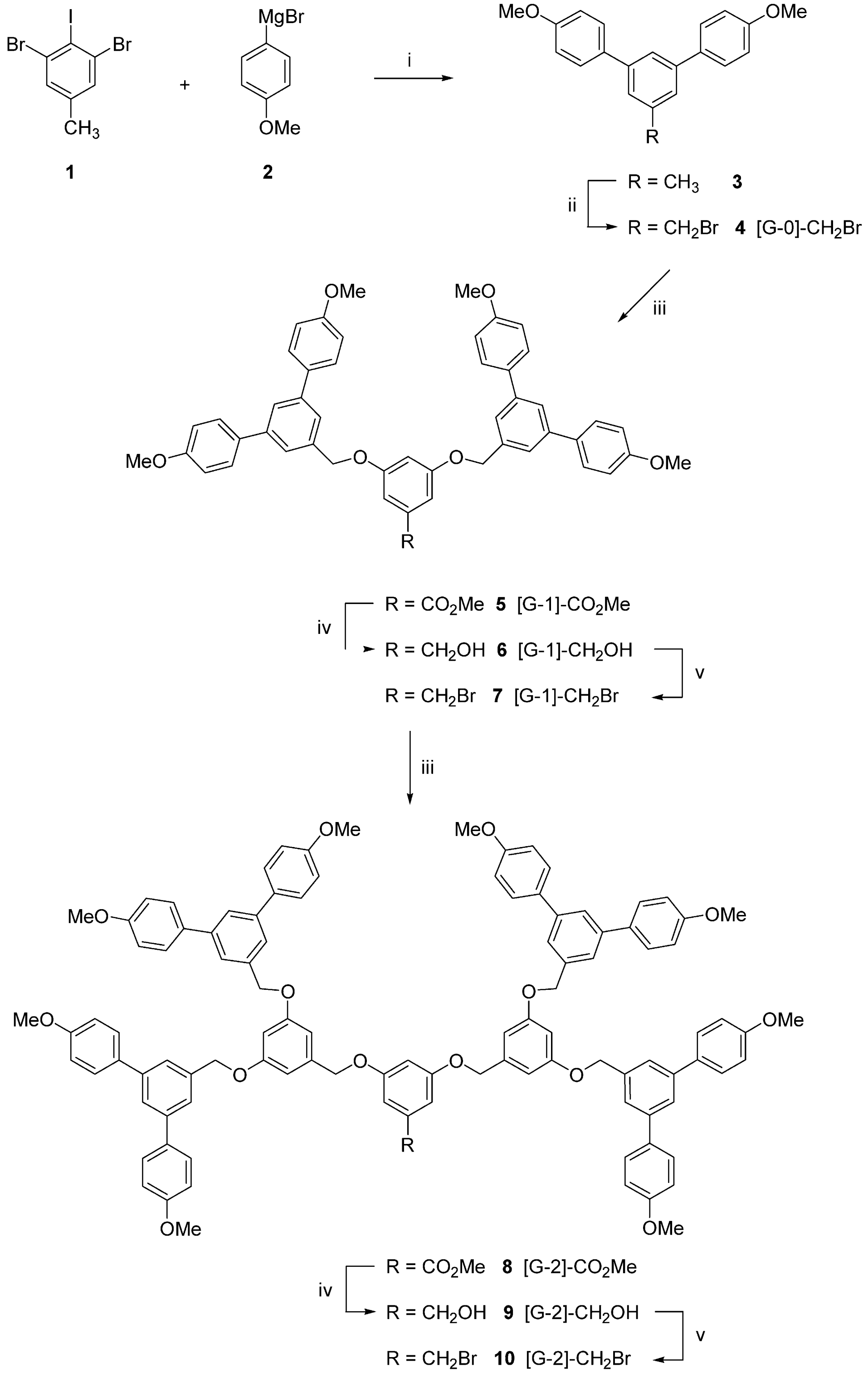
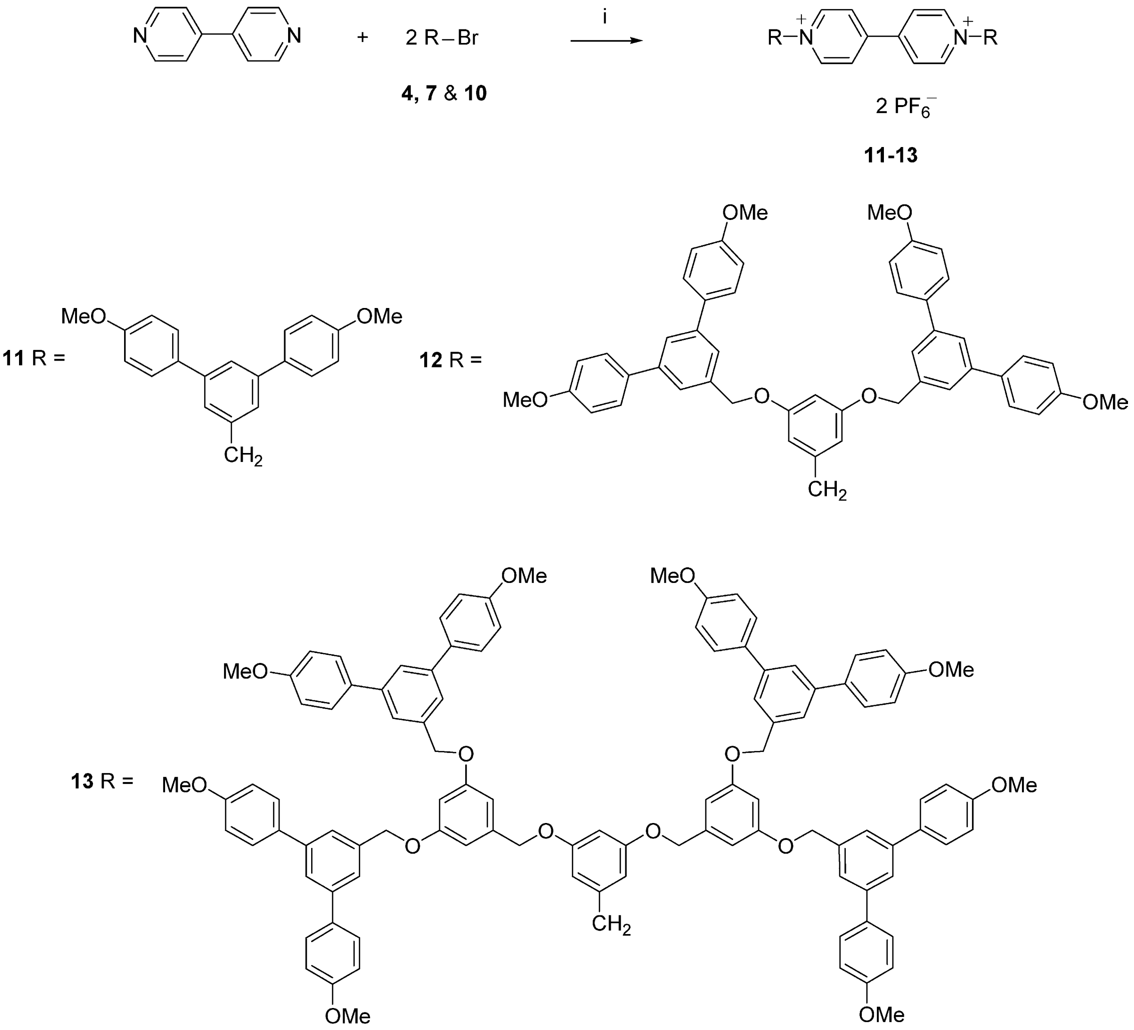
unsuccessful as the removal of triphenylphosphine oxide from the bromide was difficult. Hence the alcohol **6** was treated with PBr_3 in CH_2Cl_2 to afford the bromide **7**, [G-1]-CH_2Br, in 68% yield. The second generation dendritic bromide **10**, [G-2]-CH_2Br, was built in a similar way by the repetition of the above three reactions namely *O*-alkylation, reduction and bromination (Scheme 1).

In the ^1H NMR spectra of the dendrons, the intra-annular *m*-terphenyl protons (proton at 2′-position of the *m*-terphenyl unit) resonate in the region 7.58–7.69 ppm as singlets, the *m*-terphenyl protons *ortho* to methoxy groups resonate at 6.88–6.99 ppm as doublets and the aromatic and methylene protons of each layer of monomer units resonate in separate regions. The resonances of methylene protons of CH_2OH



Scheme 1. Reagents and conditions: (i) THF, reflux, 12 h, 62%; (ii) NBS, CCl_4, Bz_2O_2, reflux, 48 h, 44%; (iii) methyl-3,5-dihydroxy benzoate, K_2CO_3, 18-crown-6, DMF, 80 °C, 48 h; afforded **5** (72%) and **8** (70%); (iv) LAH, THF, reflux, 6 h; afforded **6** (90%) and **9** (86%); (v) PBr_3, CH_2Cl_2, 0 °C to rt, 2 h; afforded **7** (68%) and **10** (54%).



Scheme 2. Reagents and conditions: (i) CH_3CN, reflux, 24 h; then NH_4 PF_6, H_2O; afforded **11** (78%), **12** (63%) and **13** (50%).

group in **6** and **9** occur at 4.61 and 4.57 ppm, respectively, whereas those of the CH_2Br group in **7** and **10** occur at 4.44 and 4.27 ppm, respectively. In the ^{13}C NMR spectra of the dendritic alcohols and their bromides, however, a vast difference in the chemical shifts (about 31.5 ppm) is found between CH_2OH and CH_2Br carbons. All the dendrons show absorption maxima around 268 nm and emission maxima around 348 nm in $CHCl_3$.

Heating 2 equiv of each of the dendritic bromides **4**, **7** and **10** under reflux with 1 equiv of 4,4′-bipyridine in CH_3CN, followed by counterion exchange and purification, afforded the dendrimers **11–13** in 78, 63 and 50% yields, respectively (Scheme 2).

Unlike the lower generation dendrimers **11** and **12**, dendrimer **13** is soluble in CH_2Cl_2 and $CHCl_3$ despite its dicationic nature, which indicates the influence of hydrophobic dendritic framework on solubility. In the ^1H NMR spectra, the bipyridinium protons of the dendrimers resonate in the region 8.12–9.68 ppm as two doublets and the CH_2N protons resonate at 5.78–6.32 ppm as singlets.

2.2. Electrochemical properties

Dendrimers **11–13** exhibited two sets of redox waves corresponding to the formation of a radical cation ($BIPY^{2+} \rightarrow BIPY^{+}$) and a neutral species ($BIPY^{+} \rightarrow BIPY$).[12] Fig. 1 shows the cyclic voltammogram of dendrimer **12** in CH_3CN at 50 mV/s.

The half-wave potentials ($E_{1/2}$) and diffusion co-efficients (D) obtained for the dendrimers are shown in Table 1.

The microenvironment around the 4,4′-bipyridinium core

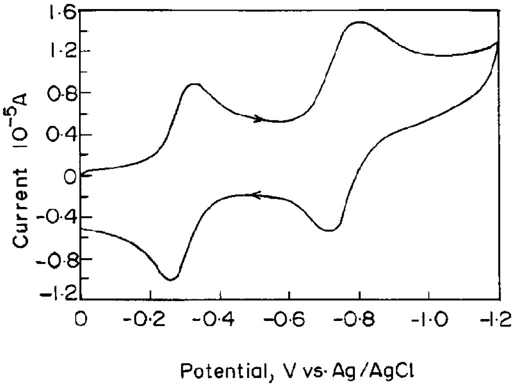


Figure 1. Cyclic voltammogram of dendrimer **12** in CH_3CN at 50 mV/s.

Table 1. The half-wave potentials ($E_{1/2}$) and diffusion co-efficients (D) obtained for the dendrimers in CH_3CN at 25 °C (the reported half-wave potentials were measured at 50 mV/s)

Dendrimer[a]	$E^1_{1/2}$ (mV)	$E^2_{1/2}$ (mV)	D (cm^2/s)
11	−320	−755	2.5619×10^{-7}
12	−291	−751	5.4984×10^{-8}
13	−204	−688	—

[a] $E^1_{1/2}$ and $E^2_{1/2}$ are the averages of the cathodic and anodic peak potentials of the first and second redox processes respectively.

should become more electron-rich with increasing dendrimer generation due to the increasing number of electron-rich *m*-terphenyl units. Hence the reduction should become more difficult and the half-wave potentials should shift to more-negative values as the dendrimer generation increases.[7a] However, the half-wave potentials of both first and second redox processes shift to less-negative values with increasing dendrimer generation. As compared to the half-wave potentials of dibenzyl viologen ($E^1_{1/2} = -320$ mV and $E^2_{1/2} = -758$ mV vs. Ag/AgCl in CH_3CN), the half-wave potentials of the dendrimers (particularly for **12** and **13**) shift to less-negative values. This trend observed in $E_{1/2}$ values is attributable to the increasing hydrophobic character of the dendrimer periphery, which makes it progressively harder to solvate effectively the two positive charges of the bipyridinium core and, therefore, reduction becomes more favourable with increasing dendrimer generation.[8] Thus the hydrophobic character of the dendrimer backbone dominates over its electron-rich character in determining redox potentials.

Diffusion co-efficients (D) obtained for the dendrimers **11** and **12** using Randles–Sevcik equation[13] indicate that the diffusion of **12** is around five times slower than that of **11**. However, we could not able to obtain reliable D value for the second generation dendrimer **13** due to the precipitation of the one-electron reduced species.

The difference between anodic and cathodic potentials (ΔE_p) indicates that all these redox processes are reversible at low scan rates even for the second generation dendrimer **13** (Table 2). This may be attributable to the angular nature of the *m*-terphenyl units, which does not allow complete steric burial of the core within the dendrimer structure.[14] At higher scan rates, however, all the redox processes become quasireversible, particularly in case of **12** and **13**. Some distortion associated with precipitation of the one-electron reduced species on the electrode surface is found in the cyclic voltammogram of **13**.

3. Conclusions

We have synthesized Fréchet-type poly(arylether) dendrimers carrying *m*-terphenyl peripheral groups and a redox active 4,4′-bipyridinium core up to second generation by convergent methodology. The dendrimer **13** is soluble in CH_2Cl_2 and $CHCl_3$ despite its dicationic nature, which indicates the influence of the hydrophobic dendritic framework on solubility. They exhibit two sets of reversible redox waves corresponding to the formation of a radical cation ($BIPY^{2+} \rightarrow BIPY^{+}$) and a neutral species ($BIPY^{+} \rightarrow BIPY$). The half-wave potentials ($E_{1/2}$) of both the first and second redox processes shift to less-negative values as the dendrimer generation increases and this indicates that the hydrophobic character of the dendrimer backbone dominates over its electron-rich character in determining redox potentials.

4. Experimental

4.1. General

Melting points were determined by using a Toshniwal melting point apparatus by open capillary tube method and were uncorrected. Ultraviolet-Visible spectra (UV) were recorded on Shimadzu 260 spectrophotometer and emission spectra on Perkin–Elmer LS-5B spectrophotometer. IR spectra were recorded on Shimadzu FTIR-8300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol 500 MHz, Jeol 400 MHz, Bruker 400 MHz, Bruker 300 MHz and Bruker ARX 200 MHz spectrometers. The FAB-MS spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer using a *m*-nitro benzyl alcohol (NBA) matrix, MALDI-TOF MS spectrum on Voyager-DE PRO mass spectrometer using a α-cyano-4-hydroxy cinnamic acid (CHCA) matrix and EI-MS spectra on Jeol DX-303 mass spectrometer. Elemental analyses were performed on a Perkin–Elmer 240B elemental analyzer. Electrochemical studies were carried out on a CH Instruments electrochemical analyzer.

4.1.1. Synthesis of *m*-terphenyl 3. To a solution of 4-anisylmagnesium bromide (**2**) [prepared from 4-bromoanisole (10.7 mL, 85.46 mmol) and magnesium (2.08 g, 85.46 mmol) in dry THF (150 mL)] heated at reflux under nitrogen atmosphere was added dropwise a solution of 3,5-dibromo-4-iodo toluene (**1**) (10.0 g, 26.61 mmol) in dry THF (100 mL). After 12 h additional heating at reflux, the reaction mixture was cooled to 20 °C and quenched by the

Table 2. The difference between the cathodic and anodic peak potentials (ΔE_p) of the first and second redox processes of the dendrimers at different scan rates in CH_3CN at 25 °C

Scan rate[a] (mV/s)	**11**		**12**		**13**	
	ΔE^1_p (mV)	ΔE^2_p (mV)	ΔE^1_p (mV)	ΔE^2_p (mV)	ΔE^1_p (mV)	ΔE^2_p (mV)
25	66	70	60	70	66	59
50	68	74	60	69	75	65
100	69	68	66	72	88	97
200	68	75	73	82	102	127
500	74	82	92	112	—	—
750	79	87	102	121	—	—

[a] ΔE^1_p and ΔE^2_p are the difference between the cathodic and anodic peak potentials of the first and second redox processes respectively.

addition of dil. HCl (6 M, 50 mL). Most of the solvent was evaporated on a water bath; the reaction mixture was then diluted with H_2O and extracted with $CHCl_3$ (2×200 mL). The combined extracts were washed with water (2×200 mL), satd. $NaHCO_3$ solution (1×200 mL) and dried (anhydrous Na_2SO_4). The crude product obtained after solvent removal was chromatographed (SiO_2; hexane/$CHCl_3$, 7:3, v/v) to give the *m*-terphenyl **3** as a colorless solid. Yield 62%; mp 136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.69 (s, 6H), 6.85 (d, $J=8.5$ Hz, 4H), 7.19 (s, 2H), 7.42–7.46 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2, 55.9, 114.8, 123.2, 126.6, 128.9, 134.5, 139.3, 142.0, 159.8; EI-MS: *m*/*z* (%) 304 (M^+, 100), 289 (47), 273 (11), 261 (34), 215 (30), 152 (31). Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86, H, 6.62. Found: C, 82.78, H, 6.57.

4.1.2. Synthesis of *m*-terphenyl bromide 4 {[G-0]-CH_2Br}. NBS (3.22 g, 18.09 mmol) was added in four equal portions at 4 h intervals to a solution of **3** (5.00 g, 16.43 mmol) in CCl_4 heated at reflux. Each portion was immediately followed by the addition of Bz_2O_2 (a few mg). After heating under reflux for a total of 48 h, the mixture was cooled and the precipitated succinimide was removed by filtration. The residue obtained after evaporation of the solvent was chromotographed (SiO_2; hexane/$CHCl_3$, 7:3, v/v) to give **4** as a colorless solid. Yield 44%; mp 116 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 6H), 4.46 (s, 2H), 6.88 (d, $J=8.7$ Hz, 4H), 7.38–7.53 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.3, 55.9, 114.9, 125.9, 126.3, 128.8, 133.7, 139.2, 142.5, 160.0; EI-MS: *m*/*z* (%) 384 (M^+, 28), 382 (M^+, 28), 304 (43), 303 (100), 258 (14), 217 (17), 192 (13), 152 (45). Anal. Calcd for $C_{21}H_{19}BrO_2$: C, 65.81, H, 5.00. Found: C, 65.52, H, 5.10.

4.2. General procedure for the synthesis of dendritic esters

A mixture of the corresponding dendritic bromide (2.1 equiv), methyl-3,5-dihydroxy benzoate (1.0 equiv), dried potassium carbonate (3.0 equiv) and 18-crown-6 (0.1 equiv) in dry DMF (30 mL) was vigorously stirred at 80 °C for 48 h under nitrogen atmosphere. The reaction mixture was then allowed to cool to room temperature and poured into ice water. The resulting precipitate was filtered, washed thoroughly with water and dissolved in $CHCl_3$ (150 mL). The organic layer was separated, washed with brine (1×150 mL), dried (anhydrous Na_2SO_4) and evaporated to give the crude ester, which was purified by column chromatography (SiO_2) using hexane/$CHCl_3$ (1:1–1:9, v/v) as the eluent.

4.2.1. Dendritic ester 5 {[G-1]-CO_2Me}. The dendritic ester **5** was obtained as a colourless solid from methyl-3,5-dihydroxy benzoate (1.0 g, 5.95 mmol) and **4** (4.79 g, 12.50 mmol). Yield 72%; mp 183 °C; IR (cm^{-1}) 1720 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 12H), 3.92 (s, 3H), 5.17 (s, 4H), 6.89 (distorted t, 1H), 6.99 (d, $J=8.7$ Hz, 8H), 7.37 (d, $J=2.2$ Hz, 2H), 7.25–7.59 (m, 12H), 7.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 70.4, 107.3, 108.4, 114.2, 124.4, 125.1, 128.3, 132.1, 133.4, 137.3, 141.7, 159.3, 159.8, 166.8; FAB-MS: *m*/*z* (%) 772 (M^+, 40). Anal. Calcd for $C_{50}H_{44}O_8$: C, 77.70, H, 5.74. Found: C, 77.58, H, 5.68.

4.2.2. Dendritic ester 8 {[G-2]-CO_2Me}. The dendritic ester **8** was obtained as a colourless solid from methyl-3,5-dihydroxy benzoate (200 mg, 1.19 mmol) and **7** (2.02 g, 2.50 mmol). Yield 70%; mp 105 °C; IR (cm^{-1}) 1720 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 24H), 3.88 (s, 3H), 5.00 (s, 4H), 5.11 (s, 8H), 6.67 (distorted t, 2H), 6.74 (distorted d, 4H), 6.80 (distorted t, 1H), 6.97 (d, $J=8.6$ Hz, 16H), 7.29 (d, $J=2.3$ Hz, 2H), 7.54–7.57 (m, 24H), 7.66 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.4, 55.4, 70.2, 70.4, 101.9, 106.6, 107.2, 108.5, 114.3, 124.5, 125.1, 128.4, 132.1, 133.5, 137.7, 139.0, 141.8, 159.4, 159.8, 160.3, 166.8; FAB-MS: *m*/*z* (%) 1620 (M^+, 28). Anal. Calcd for $C_{106}H_{92}O_{16}$: C, 78.50, H, 5.72. Found: C, 78.68, H, 5.54.

4.3. General procedure for the reduction of the dendritic ester into the corresponding alcohol

To a stirred suspension of LAH (2.5 equiv) in dry THF (20 mL), a solution of the corresponding dendritic ester (1.0 equiv) in dry THF (30 mL) was added dropwise at room temperature under nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h, after which it was cooled to 0–10 °C and the excess LAH was quenched by cautiously adding 10% NaOH solution dropwise. Anhydrous Na_2SO_4 was added to the reaction mixture, stirred and filtered. THF (20 mL) was added to the residue, digested on a steam bath and filtered. The process was repeated for four or five times. The combined THF fractions were evaporated to give the crude alcohol, which was purified by column chromatography (SiO_2).

4.3.1. Dendritic alcohol 6 {[G-1]-CH_2OH}. The dendritic alcohol **6** was obtained as a colourless solid by reducing **5** (2.5 g, 3.23 mmol) with LAH (306 mg, 8.08 mmol) and then eluting the column with $CHCl_3$. Yield 90%; mp 112 °C; IR (cm^{-1}) 3421 (O–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 12H), 4.61 (s, 2H), 5.08 (s, 4H), 6.62 (distorted t, 1H), 6.66 (distorted d, 2H), 6.96 (d, $J=8.8$ Hz, 8H), 7.52–7.56 (m, 12H), 7.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 65.2, 70.2, 101.3, 105.7, 114.2, 124.3, 124.9, 128.2, 133.4, 137.7, 141.6, 143.5, 159.3, 160.2; FAB-MS: *m*/*z* (%) 744 (M^+, 32). Anal. Calcd for $C_{49}H_{44}O_7$: C, 79.01, H, 5.95. Found: C, 79.33, H, 5.79.

4.3.2. Dendritic alcohol 9 {[G-2]-CH_2OH}. The dendritic alcohol **9** was obtained as a colourless solid by reducing **8** (1.0 g, 0.627 mmol) with LAH (60 mg, 1.57 mmol) and then eluting the column with $CHCl_3$/EtOAc (9.5:0.5, v/v). Yield 86%; mp 110 °C; IR (cm^{-1}) 3420 (O–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 24H), 4.57 (s, 2H), 4.96 (s, 4H), 5.10 (s, 8H), 6.54 (distorted t, 1H), 6.59 (distorted d, 2H), 6.65 (distorted t, 2H), 6.73 (distorted d, 4H), 6.96 (d, $J=8.8$ Hz, 16H), 7.53–7.57 (m, 24H), 7.66 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 65.2, 69.1, 70.3, 101.3, 101.8, 105.9, 106.5, 114.2, 124.3, 125.0, 128.3, 133.5, 137.7, 139.4, 141.7, 159.3, 160.1, 160.2; FAB-MS: *m*/*z* (%) 1592 (M^+, 14). Anal. Calcd for $C_{105}H_{92}O_{15}$: C, 79.12, H, 5.82. Found: C, 78.98, H, 5.87.

4.4. General procedure for the conversion of the dendritic alcohol into the corresponding bromide

To a stirred suspension of the corresponding dendritic alcohol (1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise a solution of PBr_3 (3.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then quenched by the addition of ice water. The organic layer was separated, washed with water (2×25 mL), satd. $NaHCO_3$ solution (1×25 mL), dried (anhydrous Na_2SO_4) and evaporated to give the crude dibromide, which was purified by column chromatography (SiO_2) using hexane/CH_2Cl_2 (1:1–1:8 v/v) as the eluent.

4.4.1. Dendritic bromide 7 {[G-1]-CH_2Br}. The dendritic bromide **7** was obtained as a white foam-like solid by the bromination of **6** (2.0 g, 2.68 mmol) with PBr_3 (0.77 mL, 8.10 mmol). Yield 68%; mp 202 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 12H), 4.44 (s, 2H), 5.12 (s, 4H), 6.65 (distorted t, 1H), 6.71 (distorted d, 2H), 6.99 (d, $J=8.6$ Hz, 8H), 7.54–7.59 (m, 12H), 7.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8, 55.5, 70.4, 102.4, 108.3, 114.4, 124.5, 125.2, 128.4, 133.5, 137.6, 140.0, 141.8, 159.4, 160.2; FAB-MS: *m/z* (%) 808 (M^+, 27), 806 (M^+, 27). Anal. Calcd for $C_{49}H_{43}BrO_6$: C, 72.86, H, 5.37. Found: C, 72.66, H, 5.42.

4.4.2. Dendritic bromide 10 {[G-2]-CH_2Br}. The dendritic bromide **10** was obtained as a white foam-like solid by the bromination of **9** (500 mg, 0.314 mmol) with PBr_3 (0.09 mL, 0.948 mmol). Yield 54%; mp 125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 24H), 4.27 (s, 2H), 4.88 (s, 4H), 5.03 (s, 8H), 6.46 (distorted t, 1H), 6.53 (distorted d, 2H), 6.59 (distorted t, 2H), 6.64 (distorted d, 4H), 6.88 (d, $J=8.8$ Hz, 16H), 7.45–7.49 (m, 24H), 7.58 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 55.3, 70.1, 70.3, 101.8, 102.2, 106.5, 108.3, 113.4, 114.2, 124.3, 125.0, 128.3, 133.5, 137.7, 139.2, 141.7, 159.3, 160.0, 160.2; FAB-MS: *m/z* (%) 1656 (M^+, 15), 1654 (M^+, 15). Anal. Calcd for $C_{105}H_{91}BrO_{14}$: C, 76.12, H, 5.54. Found: C, 76.38, H, 5.56.

4.5. General procedures for the synthesis of dendrimers with a 4,4′-bipyridine core

A mixture of the corresponding dendritic bromide (2.0 equiv) and 4,4′-bipyridine (1.0 equiv) in dry CH_3CN (25 mL) was heated at reflux for 24 h under nitrogen. After cooling the reaction mixture to room temperature, the solvent was reduced to one-fifth of its volume under vacuum. The precipitated crude product was filtered and purified by recrystallisation or column chromatography (SiO_2).

4.5.1. Dendrimer 11. The dendrimer **11** was obtained from the dendritic bromide **4** (491 mg, 1.28 mmol) and 4,4′-bipyridine (100 mg, 0.640 mmol). The crude product was purified by column chromatography over SiO_2 using CH_3OH/H_2O/satd. aq. NH_4Cl (6:3:1) as the eluent. The dendrimer-containing fractions were combined and the solvent was evaporated under vacuum. The residue was dissolved in H_2O (25 mL) and solid NH_4PF_6 (0.25 g) was added, then the precipitate was filtered, washed thoroughly with H_2O and dried to give the pure dendrimer **11** as a pale yellow solid. Yield 78%; mp 170 °C (dec.); ^1H NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 12H), 5.99 (s, 4H), 7.03 (d, $J=8.3$ Hz, 8H), 7.71 (d, $J=8.8$ Hz, 8H), 7.84 (s, 2H), 7.89 (s, 4H), 8.71 (d, $J=6.4$ Hz, 4H), 9.68 (d, $J=6.4$ Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.4, 64.0, 114.6, 125.2, 125.6, 127.5, 128.4, 131.9, 135.5, 141.7, 145.8, 149.5, 159.5; FAB-MS: *m/z* (%) 907 (M^+-PF_6, 34), 762 (M^+-2PF_6, 63). Anal. Calcd for $C_{52}H_{46}F_{12}N_2O_4P_2$: C, 59.32, H, 4.40, N, 2.66. Found: C, 59.49, H, 4.34, N, 2.78.

4.5.2. Dendrimer 12. The dendrimer **12** was obtained from the dendritic bromide **7** (259 mg, 0.320 mmol) and 4,4′-bipyridine (25 mg, 0.160 mmol). The precipitated solid was filtered and washed thoroughly with diethyl ether (10 mL) and $CHCl_3$ (10 mL). The residue was suspended in CH_3CN (10 mL), solid NH_4PF_6 (0.1 g) was added, and the mixture was stirred for 30 min and then filtered. The solvent was removed under vacuum; the residue was washed thoroughly with H_2O and then dried. The crude product was recrystallised from CH_3CN to give the pure dendrimer **12** as a pale yellow solid. Yield 63%; mp 134 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 3.74 (s, 24H), 5.20 (s, 8H), 5.78 (s, 4H), 6.90 (distorted t, 2H), 6.93 (distorted d, 4H), 6.97 (d, $J=8.6$ Hz, 16H), 7.55 (distorted d, 8H), 7.62 (d, $J=8.6$ Hz, 16H), 7.71 (s, 4H), 8.50 (d, $J=6.9$ Hz, 4H), 9.68 (d, $J=6.9$ Hz, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.7, 70.1, 108.9, 114.9, 124.3, 124.5, 127.5, 128.5, 132.7, 136.6, 138.4, 141.2, 146.1, 149.6, 149.8, 159.6, 160.6; FAB-MS: *m/z* (%) 1755 (M^+-PF_6, 28), 1610 (M^+-2PF_6, 30). Anal. Calcd for $C_{108}H_{94}F_{12}N_2O_{12}P_2$: C, 68.21, H, 4.98, N, 1.47. Found: C, 68.39, H, 4.76, N, 1.52.

4.5.3. Dendrimer 13. The dendrimer **13** was obtained from the dendritic bromide **10** (106 mg, 0.064 mmol) and 4,4′-bipyridine (5 mg, 0.032 mmol). The crude product was dissolved in DMF (1 mL) and a satd. aq. solution of NH_4PF_6 (1 mL) was added dropwise and stirred for 30 min. The resulting precipitate was filtered, washed thoroughly with H_2O and dried. The product was recrystallised from CH_2Cl_2 to give the dendrimer **13** as a yellow solid. Yield 50%; mp 122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 48H), 5.12 (s, 16H), 5.22 (s, 8H), 6.32 (s, 4H), 6.40 (s, 4H), 6.51–6.56 (m, 14H), 6.83 (d, $J=8.3$ Hz, 32H), 7.39–7.44 (m, 48H), 7.53 (s, 8H), 8.12 (d, $J=6.8$ Hz, 4H), 8.47 (distorted d, 4H); MALDI-TOF-MS: *m/z* (%) 3306 (M^+-2PF_6, 11).

4.6. Electrochemical properties

Electrochemical experiments were carried out in nitrogen-purged CH_3CN solutions at room temperature. The solutions for electrochemistry were held at a concentration of 0.25 mM of the electroactive species. $TBAPF_6$ (0.1 M) was included as a supporting electrolyte. A glassy carbon electrode (0.052 cm^2) was used as the working electrode; its surface was routinely polished with a 0.05 μm alumina–water slurry on a felt surface prior to use. All potentials were recorded against a saturated Ag/AgCl electrode and a platinum wire was used as a counter electrode. Cyclic voltammograms were obtained at scan rates of 25, 50, 75, 100, 200, 300, 400, 500, 600 and 750 mV/s. A plot of cathodic peak currents of first redox processes vs. (scan rate)$^{1/2}$ was linear. From the slope of the plot, the diffusion co-efficients (*D*) were calculated using Randles–Sevcik equation.[13]

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References and notes

1. (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, 101, 3819–3867. (b) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; Wiley: Chichester, 2001.
2. (a) Liao, Y.-H.; Moss, J. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1774–1777. (b) Liao, Y.-H.; Moss, J. R. *Organomettalics* **1996**, *15*, 4307–4316.
3. Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354–4360.
4. Shu, C.-F.; Shen, H.-M. *J. Mater. Chem.* **1997**, *7*, 47–52.
5. Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *J. Org. Chem.* **1999**, *64*, 7474–7484.
6. (a) Kannan, A.; Rajakumar, P.; Kabaleeswaran, V.; Rajan, S. S. *J. Org. Chem.* **1996**, *61*, 5090–5102. (b) Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **1997**, *38*, 5323–5326. (c) Rajakumar, P.; Murali, V. *Tetrahedron* **2000**, *56*, 7995–7999. (d) Rajakumar, P.; Srisailas, M. *Tetrahedron* **2001**, *57*, 9749–9754. (e) Rajakumar, P.; Srinivasan, K. *Eur. J. Org. Chem.* **2003**, 1277–1284.
7. (a) Dandliker, P. J.; Diederich, F.; Gross, M.; Knobler, C. B.; Louati, A.; Sanford, E. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1739–1742. (b) Smith, D. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1563–1565. (c) Weyermann, P.; Gisselbrecht, J.-P.; Bouden, C.; Diederich, F.; Gross, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3215–3219. (d) Wang, Y.; Cardona, C. M.; Kaifer, A. E. *J. Am. Chem. Soc.* **1999**, *121*, 9756–9757.
8. Toba, R.; Quintela, J. M.; Peinador, C.; Román, E.; Kaifer, A. E. *Chem. Commun.* **2001**, 857–858.
9. Ghaddar, T. H.; Wishart, J. F.; Thompson, D. W.; Whitesell, J. K.; Fox, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 8285–8289.
10. Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
11. Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162–3165.
12. Bird, C. L.; Kuhn, A. T. *Chem. Soc. Rev.* **1981**, *10*, 49–82.
13. Bard, A. J.; Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*; Wiley: New York, 1980.
14. Jestin, I.; Levillain, E.; Roncali, J. *Chem. Commun.* **1998**, 2655–2656.

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Highly selective conversion of *N*-aroyl-α-dehydronaphthylalaninamides into 3,4-dihydrobenzoquinolinone derivatives via photoinduced intermolecular electron transfer

Kei Maekawa,* Ayana Shinozuka, Michiko Naito, Tetsutaro Igarashi and Tadamitsu Sakurai*

Department of Applied Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686, Japan

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Abstract—The irradiation of substituted (*Z*)-*N*-aroyl-α-dehydronaphthylalaninamides [(*Z*)-**1**] in methanol containing triethylamine (TEA) with Pyrex-filtered light was found to give 3,4-dihydrobenzoquinolinone derivatives (**2**) in high yields along with minor amounts of 4,5-dihydrooxazole derivatives (**3**). Analysis of the substituent effects on product composition revealed that both the photoreactivity of **1** and the selectivity of **2** are decreased with increasing electron-withdrawing ability of the substituent introduced at the *para*-position on the *N*-benzoyl benzene ring. From the analysis of the dependence of the quantum yield for the formation of **2** on the TEA concentration, it was found that back electron transfer occurs efficiently within an (*E*)-**1** anion radical–TEA cation radical pair intermediate.

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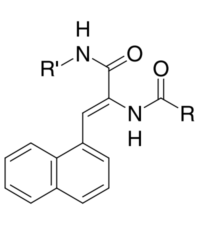
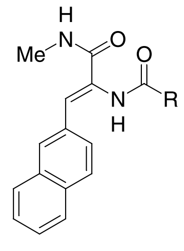
1. Introduction

Organic photochemistry has continued to contribute to the development of efficient and selective transformations for the preparation of complicated molecules which could not have been synthesized by conventional methods. In recent years much attention is being devoted to the synthetic application of photoinduced electron transfer (PET) reactions, owing to the fact that many of these reactions enable the construction of various heterocyclic rings.[1] On the other hand, α-dehydroamino acid derivative is one of the important intermediates for the synthesis of natural and biologically active products. Many useful synthetic methods of substituted α-dehydroamino acid derivatives have been reported but there have been only limited investigations of the photochemistry of these amino acid derivatives.[2,3] Taking into account the fact that aromatic olefins undergo efficient PET reactions in their excited states,[4] it can be expected that α-dehydroamino acids having the aromatic olefin chromophore are subject to PET reactions. Keeping this expectation in mind, we embarked on a systematic study toward the characterization of the excited-state reactivity of substituted α-dehydroamino acids.[5–7] In the course of this study we discovered a novel intermolecular ET-initiated photocyclization reaction of substituted *N*-acetyl-α-dehydronaphthylalaninamides that afford 3,4-dihydrobenzo[*f*]-quinolinones.[6] Because many heterocyclic compounds having a dihydroquinolinone ring exhibit pharmacological and physiological activities, it is of fundamental significance to develop synthetic methods for the construction of the quinolinone ring.[8] If we consider that PET reactions of *N*-aroyl-α-dehydronaphthylalaninamides may afford the corresponding dihydrobenzoquinolinone derivatives in high selectivities, it is possible to extend synthetic utility of the ET-initiated photocyclization reactions described



(*Z*)-**1a–i**



(*Z*)-**1j–l**

1a (R= Ph, R'= Me); **1b** (R= 4-OMeC_6H_4, R'= Me);
1c (R= 4-BrC_6H_4, R'= Me); **1d** (R= 4-$CF_3C_6H_4$, R'= Me);
1e (R= 4-CNC_6H_4, R'= Me); **1f** [R= 2,4-$(OMe)_2C_6H_3$, R'= Me];
1g (R= *t*-Bu, R'= Me); **1h** (R= Ph, R'= H); **1i** (R= Ph, R'= PhCH_2);
1j (R= Ph); **1k** (R= 4-OMeC_6H_4); **1l** [R= 2,4-$(OMe)_2C_6H_3$]

Keywords: Amino acids and derivatives; Photochemistry; Electron transfer; Photocyclization; Dihydrobenzoquinolinones.

* Corresponding authors. Tel.: +81 45 481 5661; fax: +81 45 491 7915; e-mail addresses: maekako2@kanagawa-u.ac.jp; sakurt01@kanagawa-u.ac.jp

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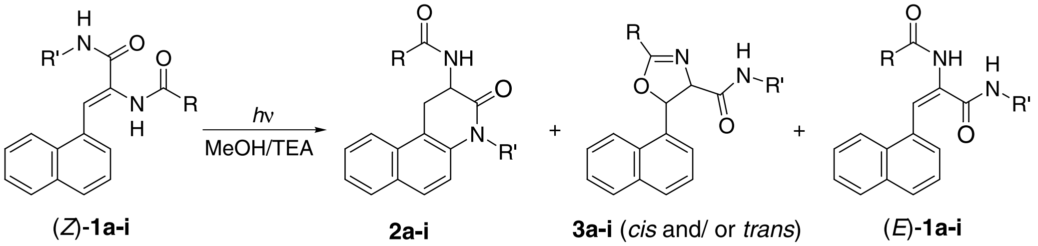
above. For this end we synthesized (*Z*)-*N*-aroyl-α-dehydronaphthylalaninamides [(*Z*)-**1a–l**] and investigated substituent effects on both the reactivity of (*Z*)-**1** and the selectivity of each photoproduct. Additionally, we analyzed quantum yield for the photoisomerization of (*E*)-**1** as well as the effects of TEA concentration on the quantum yield for the formation of dihydrobenzoquinolinone derivative, hoping to shed much light on the mechanism of novel ET-initiated photocyclization reactions.

2. Results and discussion

2.1. Photocyclization of (Z)-1a–l

The starting (*Z*)-isomers (**1a–l**) were prepared in good yields by the ring-opening reactions of (*Z*)-naphthyl-substituted oxazolones with primary amines.[9] After a nitrogen-saturated methanol solution of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high-pressure Hg lamp for 3 h at room temperature, the product mixture obtained was washed with a small amount of EtOH and then with hexane, giving the analytically pure 3,4-dihydrobenzo[*f*]quinolinone derivative (**2a**, 67%; conversion, >99%). Preparative TLC (silica gel) of the residual solid [that was obtained by evaporating the filtrate (EtOH–hexane) to dryness] enabled the isolation of the *cis*-4,5-dihydrooxazole derivative (*cis*-**3a**, 5%). In addition, we succeeded in isolating the (*E*)-isomer from the reaction mixture obtained by the 0.5-h irradiation of (*Z*)-**1a** (conversion, 7%; Scheme 1). The structures of isolated products were determined based on their spectroscopic and physical properties and were confirmed by the ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectra of these products. Careful ^{1}H NMR spectral analysis of the product mixture suggested that there is very little formation of the *trans*-4,5-dihydrooxazole derivative (*trans*-**3a**) whose ring-proton signals with the $J_{4,5}$ value of 6.4 Hz were detected at 4.75 and 6.57 ppm,[7] though attempts to isolate *trans*-**3a** from the mixture were unsuccessful owing to its poor yield. The same product distribution was obtained by the irradiation of other α-dehydro(1-naphthyl)alaninamide derivatives (**1b–i**).

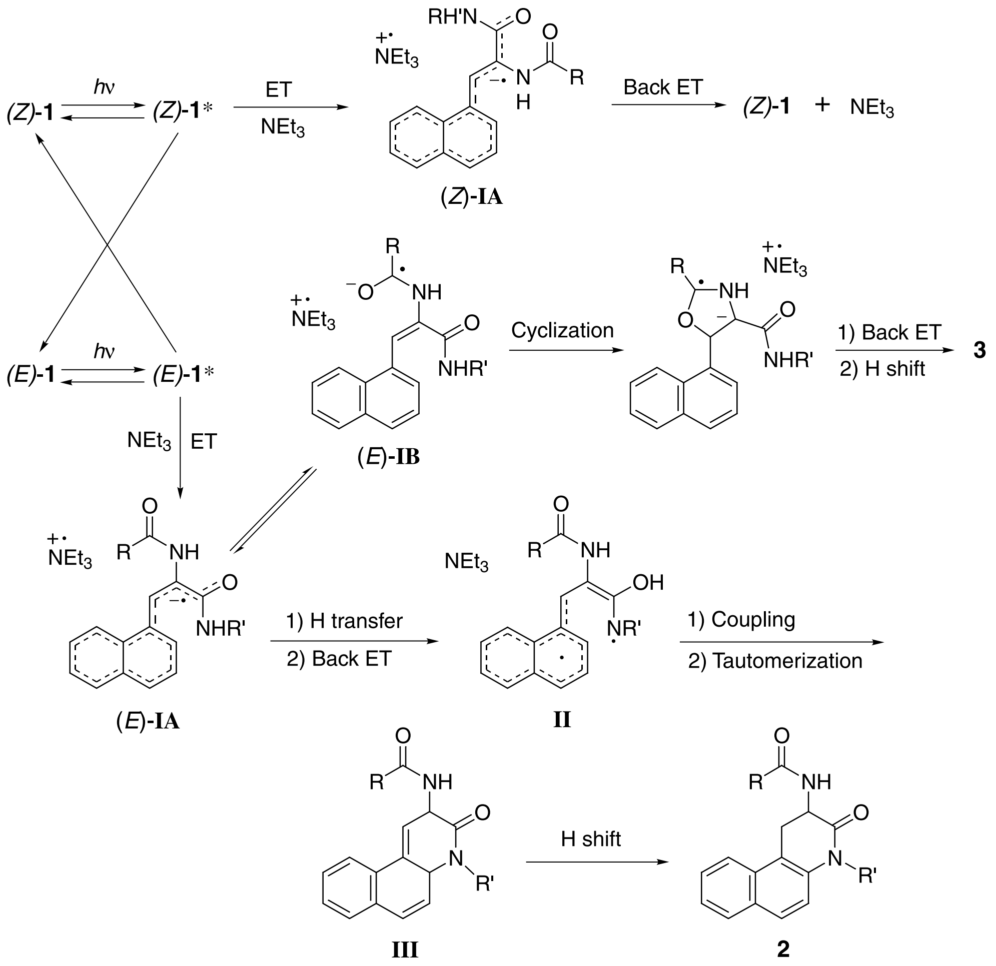
The finding that the photoproducts (**2a** and **3a**) are stable enough such that they undergo only negligible decomposition under the irradiation conditions employed (450 W high-pressure Hg lamp; Pyrex-filtered light; [(*Z*)-**1a**]=3.75×10^{-3} mol dm^{-3}; [TEA]=0.10 mol dm^{-3}) made it possible to monitor the reactions by means of ^{1}H NMR spectroscopy, as typically shown in Table 1. The result obtained for (*Z*)-**1a** demonstrates the rapid production of (*E*)-**1a** and the subsequent increase in compositions for **2a** and **3a** with the decrease of (*E*)- and (*Z*)-isomer compositions, being consistent with the mechanism in which the excited-state (*E*)- and (*Z*)-isomers serve as precursors of these products. Based on our previous findings,[6,7] we are able to propose Scheme 2 as the formation mechanism of dihydrobenzoquinolinone (**2**) and dihydrooxazole derivatives (**3**). The result that at the early stage of the reaction (0.5-h irradiation) the composition ratio of (*Z*)-**1a** to its isomer exhibits a negligible dependence on the TEA concentration (0–0.10 mol dm^{-3}) strongly suggests a minor contribution of the isomerization from (*Z*)-**1a**$^{-\cdot}$ to its isomer anion radical, (*E*)-**1a**$^{-\cdot}$. It is, thus, very likely that the (*Z*)-**1**-derived ion radical pair (*Z*)-**IA** undergoes an exclusive back ET to regenerate (*Z*)-**1** and TEA (Scheme 2). An ET from the ground-state TEA to the singlet excited-state (*E*)-isomer produces the ion radical pair intermediate (*E*)-**IA** which may be in equilibrium with the ion radical pair (*E*)-**IB** formed via intramolecular ET. Hydrogen transfer from the amide nitrogen to the amide carbonyl oxygen in the intermediate (*E*)-**IA** and the subsequent back ET to the TEA cation radical afford TEA and the enol-type biradical intermediate **II**, the coupling and tautomerization of which generate the cyclization product **III**. The process that reaches the dihydrobenzoquinolinone derivative (**2**) is completed by aromatization of **III** via hydrogen shift. In competition with this cyclization process, the nucleophilic attack of the *N*-acyl carbonyl oxygen anion upon the olefinic carbon in (*E*)-**IB** takes place to give the cyclized anion radical. A back ET to the TEA cation radical followed by



Scheme 1.

Table 1. Relation between irradiation time and composition (%) of each compound obtained by the 5-h irradiation of (*Z*)-**1a** in MeOH–TEA at room temperature

Irradiation time (h)	Composition (%)				
	(*Z*)-**1a**	(*E*)-**1a**	**2a**	*cis*-**3a**	*trans*-**3a**
0	100	0	0	0	0
0.5	85.6	12.8	1.4	0.2	0
3.0	52.8	25.3	19.7	1.9	0.3
5.0	36.1	20.5	39.3	3.5	0.6



Scheme 2.

hydrogen shift leads to *cis*- and *trans*-**3** (Scheme 2). Evidence in support of this mechanism comes from the finding that the free energy change (ΔG_{et}) for an ET from TEA to the singlet excited-state (*E*)-**1f** is $-85\ \mathrm{kJ\ mol^{-1}}$. This ΔG_{et} was estimated by using the simplified Weller equation: $\Delta G_{\mathrm{et}}/\mathrm{kJ\ mol^{-1}} = 96.5\ (E_{\mathrm{ox}} - E_{\mathrm{red}}) - E_{\mathrm{S}}$,[10] where E_{ox}, E_{red} and E_{S} refer to the oxidation potential of TEA (0.76 V vs. Ag/AgCl in MeCN), the reduction potential of (*E*)-**1f** (-2.09 V vs. Ag/AgCl in MeCN) and the first singlet excitation energy of (*E*)-**1f** ($360\ \mathrm{kJ\ mol^{-1}}$ in MeCN), respectively. In addition, a methanol solution of **1a** ($3.75 \times 10^{-3}\ \mathrm{mol\ dm^{-3}}$) containing deuteriated TEA ($0.10\ \mathrm{mol\ dm^{-3}}$) was irradiated with Pyrex-filtered light from a 450 W high pressure Hg lamp for 3.0 h at room temperature. ^{1}H NMR spectral analysis of the product mixture in DMSO-d_6, obtained after usual work-up, clearly showed no disappearance of the 4.86 ppm signal which is ascribed to the proton attached to the 3-position of the dihydrobenzoquinolinone ring. This finding substantiates that proton transfer from the TEA cation radical to the (*E*)-**1**-derived anion radical occurs within the intermediate (*E*)-**IA** to, if any, only a small extent and, hence, consistent with the formation mechanism shown in Scheme 2.

In Table 2 is summarized composition of each compound obtained by the 0.5- and 5-h irradiation of methanol solutions of **1a**–**i** ($3.75 \times 10^{-3}\ \mathrm{mol\ dm^{-3}}$) containing TEA ($0.10\ \mathrm{mol\ dm^{-3}}$) at room temperature (450 W high-pressure Hg lamp; Pyrex-filtered light). An inspection of Table 2 demonstrates that the reactivity of **1** has a clear propensity to decrease with increasing the electron-withdrawing ability of the substituent introduced at the *para*-position on the benzoyl benzene ring (**1b** > **1a** ≈ **1c** > **1d** ≫ **1e**). It is likely that anion radical produced by an ET from TEA migrates to the benzoyl moiety in the presence of stronger electron-withdrawing substituent to a more extent. Therefore, we see that the introduction of trifluoromethyl or cyano group promotes a back ET from the anion radical to the TEA cation radical to result in a decrease in the conversion of **1**. Additionally, the observation that the selectivity of **2** is also decreased by introducing these substituents allows us to propose that the shift of equilibrium between (*E*)-**IA** and (*E*)-**IB** to the latter intermediate lowers the relative rate for hydrogen abstraction in the former intermediate (Scheme 2). Taking into account the fact that the irradiation of **1b** having the electron-donating methoxy substituent at the *para*-position on the benzoyl benzene ring gives **2** in higher selectivity than that of **1a**, it can be predicted that the conversion of **1** and the selectivity of **2** is enhanced with decreasing the electron-withdrawing ability of aroyl group. From the data given in Table 2 we can see that the conversion of **1g** having the trimethylacetyl group is higher than that of **1a** having the benzoyl and also that the selectivity of **2g** is greater as compared to that of **2a**.

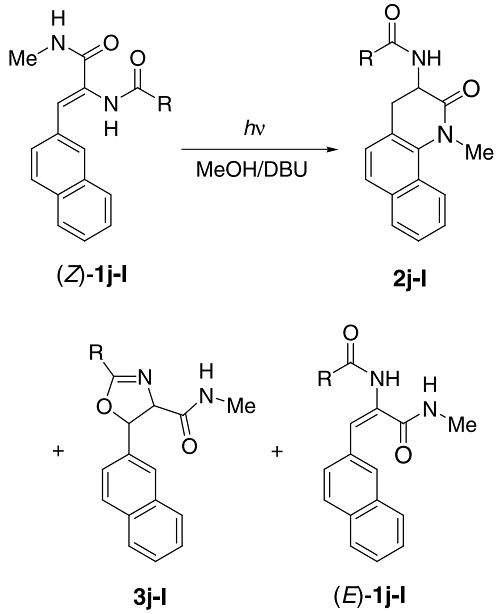
Table 2. Substituent effects on the conversion of **1** and selectivity of each compound, obtained by the irradiation of (*Z*)-**1** in MeOH containing TEA at room temperature

Compound	Irradiation time (h)	Composition (%)				Conversion[a] (%)	Selectivity of **2** (%)[b]
		(*Z*)-**1**	(*E*)-**1**	**2**	**3**[c]		
1a	0.5	85.6	12.8	1.4	0.2		
	5	36.1	20.5	39.3	4.1	43	91
1b	0.5	78.9	16.7	4.4	0		
	5	14.8	7.4	75.6	2.2	78	97
1c	0.5	87.0	11.6	1.3	0.2		
	5	40.0	21.8	34.2	3.9	38	90
1d	0.5	93.2	6.8	0	0		
	5	51.6	25.5	18.8	4.1	23	82
1e	0.5	97.9	2.1	0	0		
	10	60.1	25.0	11.1	3.8	15	74
1f	0.5	86.9	9.4	3.6	0		
	5	48.8	7.4	43.8	0	44	100
1g	0.5	79.3	18.2	2.5	0		
	5	21.6	16.9	59.9	1.6	62	97
1h	0.5	82.4	16.0	1.1	0.5		
	5	37.8	26.2	27.3	8.7	36	76
1i	0.5	82.7	16.0	0.6	0.4		
	5	36.4	28.2	28.6	6.7	35	81

[a] Conversion was estimated by the sum of compostion for **2** and **3**.
[b] Selectivity for **2** was evaluated by dividing the composition for **2** by the sum of compostion for **2** and **3**.
[c] The sum of composition for *cis*-**3** and *trans*-**3**.

Interestingly, ET-initiated photocyclization of **1f** bearing the 2,4-dimethoxybenzoyl group afforded **2f** in quantitative yield without forming **3f**, though the expected high conversion of **1f** was not attained. Because the rate for isomerization of (*Z*)-**1f** is much slower as compared to that of (*Z*)-**1b** (Table 2, 0.5-h irradiation), it is reasonable to explain the decreased photoreactivity of 2,4-dimethoxybenzoyl-substituted **1f** in terms of the enhanced deactivation of the excited-state (*Z*)-**1f**. Electronic effects of the *ortho*-methoxy group in the (*Z*)-isomer may play a role in slowing

Table 3. Composition of each compound, conversion of **1** and selectivity of **2**, obtained by the 5-h irradiation of (*Z*)-**1** in MeOH containing DBU at room temperature



Compound	Composition (%)				Conversion (%)	Selectivity of **2** (%)
	(*Z*)-**1**	(*E*)-**1**	**2**	**3**[a]		
1j	48.1	27.1	17.6	7.2	25	71
1k	53.8	15.2	25.7	5.3	31	83
1l	62.8	19.1	11.4	6.7	18	63

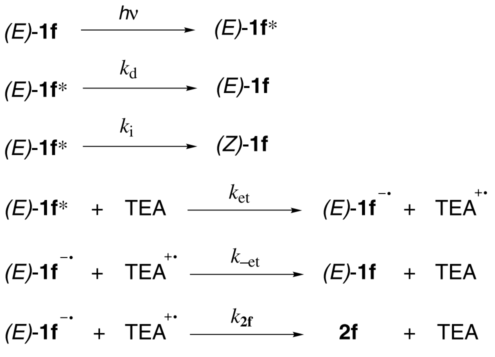
[a] The mixture of *cis*- and *trans*-isomers.

down the isomerization into (*E*)-**1f**. These considerations, therefore, substantiate the mechanism proposed by us.

In order to explore the scope and limitations of the observed ET-initiated photocyclization, we attempted PET reactions of α-dehydronaphthylalaninamides (**1j**–**l**) in which the 2-naphthyl group was introduced instead of the 1-naphthyl. When a methanol solution of **1j** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light from a 450 W high-pressure Hg lamp at room temperature, complicated product mixtures were obtained. However, the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.10 mol dm^{-3}) as an electron donor enabled the estimation of composition for each compound obtained by the 5-h irradiation of **1j**, as shown in Table 3. Because DBU possesses greater electron-donating ability than TEA, the presence of DBU is considered to markedly enhance the relative rate of ET process affording only the products derived from PET reaction. The same product distribution was observed by the irradiation of methanol solutions of **1k** and **1l** (Table 3). A comparison of the selectivity for **2a**,**b**,**f** with that for **2j**–**l** reveals that replacement of the 1-naphthyl group by the 2-naphthyl lowers the selectivity of a given dihydrobenzoquinolinone. The 2-naphthyl substituent in (*E*)-**1j**–**l** is considered to exert less steric hindrance than the 1-naphthyl in (*E*)-**1a**–**i** in the cyclization process from the anion radical in **IB**. This less steric hindrance accelerates the cyclization reaction that proceeds through **IB** to result in a decrease in the selectivity of **2** as observed.

2.2. Effects of TEA concentration on the quantum yield for formation of 2

As described in Section 2.1, the ET-initiated photocyclization of **1f** selectively produces the corresponding dihydrobenzoquinolinone derivative (**2f**). This result allows us to obtain quantitative information concerning the relative rates of ET and related processes (that control the formation efficiency of **2**), through analysis of the TEA concentration dependence of the quantum yield (Φ) for appearance of **2**. We are able to propose Scheme 3 based on the findings that the presence of TEA affects the rate for photoisomerization from (*E*)-**1** into (*Z*)-**1** to a negligible extent and, in addition, the singlet excited-state (*E*)-isomer serves as a precursor of **2**. In order to exclude the contribution of (*Z*)-**1f**-derived ET reaction process, quantum yields for the isomerization into (*Z*)-**1f** as well as for appearance of **2f** were determined at less than 4% conversion of (*E*)-**1f** employed as the starting isomer. By applying the steady-state approximation to Scheme 3, we obtain Eqs. 1 and 2, where $\Phi_{\mathbf{2f}}$ and Φ_{i} refer to the quantum yields for the formation of **2f** and for the isomerization, respectively.



Scheme 3.

$$\Phi_{\mathbf{2f}}^{-1}=\left(1+\frac{k_{-\mathrm{et}}}{k_{\mathbf{2f}}}\right)\left\{1+\frac{k_\mathrm{d}+k_\mathrm{i}}{k_\mathrm{et}[\mathrm{TEA}]}\right\} \tag{1}$$

$$\Phi_\mathrm{i}=\frac{k_\mathrm{i}}{(k_\mathrm{i}+k_\mathrm{d})} \tag{2}$$

As typically depicted in Figure 1, there was a linear relationship between the reciprocals of $\Phi_{\mathbf{2f}}$ ($\Phi_{\mathbf{2f}}^{-1}$) and TEA concentration ([TEA]$^{-1}$). From the intercept and the ratio of slope to the intercept of linear plot obtained, we were able to evaluate the relative rates of ET and back ET processes, that is, the magnitude of $k_\mathrm{et}/(k_\mathrm{d}+k_\mathrm{i})$ and $k_{-\mathrm{et}}/k_{\mathbf{2f}}$, respectively. Furthermore, there was no formation of **2f** when a methanol solution of (*E*)-**1f** containing no TEA was irradiated,[6] so that we were able to determine quantum yield for the isomerization (Φ_i) and then to estimate the relative rates of given processes by the use of Φ_i ($=0.35\pm0.01$) and Eqs. 3–5.

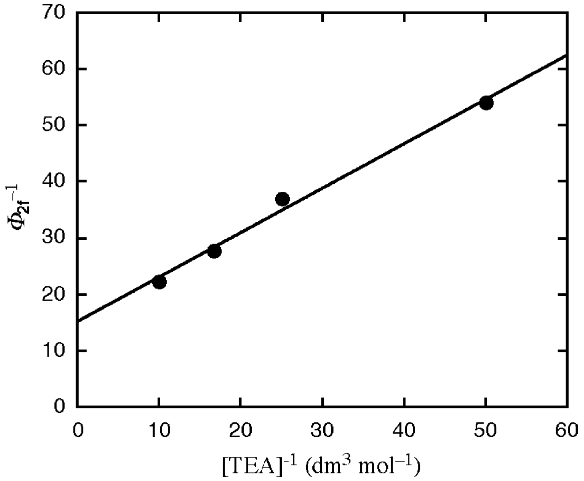


Figure 1. Double reciprocal plot of $\Phi_{\mathbf{2f}}^{-1}$ versus [TEA]$^{-1}$ for the ET-initiated photocyclization of (*E*)-**1f** in methanol at room temperature.

$$\frac{k_\mathrm{et}}{\Phi_\mathrm{i}(k_\mathrm{d}+k_\mathrm{i})}=\frac{k_\mathrm{et}}{k_\mathrm{i}} \tag{3}$$

$$\Phi_\mathrm{i}^{-1}-1=\frac{k_\mathrm{d}}{k_\mathrm{i}} \tag{4}$$

$$\left(\frac{k_\mathrm{et}}{k_\mathrm{i}}\right)\left(\frac{k_\mathrm{i}}{k_\mathrm{d}}\right)=\frac{k_\mathrm{et}}{k_\mathrm{d}} \tag{5}$$

In Table 4 are summarized these relative rates which demonstrate that the ET rate (k_et[TEA], [TEA]$=$ 0.10 mol dm^{-3}) is faster than the rate for deactivation and isomerization ($k_\mathrm{d}+k_\mathrm{i}$) of the excited-state (*E*)-**1f** by a factor of about 2. In addition, the magnitude of $k_\mathrm{i}/k_\mathrm{d}$ confirms that isomerization into (*Z*)-**1f** is the minor deactivation pathway of the excited-state (*E*)-isomer in the absence of TEA. Despite the rapid progress of PET reaction, the $\Phi_{\mathbf{2f}}$ value

Table 4. Relative rates for given processes

k_i/k_d	k_{et}[TEA]/k_d[a]	k_{et}[TEA]/k_i[a]	k_{et}[TEA]/(k_d+k_i)[a]	k_{-et}/k_{2f}
0.54	2.9	5.4	1.9	14

[a] Value estimated at [TEA]$=0.10$ mol dm^{-3}.

was not so large ($\Phi_{2f}=0.045$ at [TEA]$=0.10$ mol dm^{-3}). The fact that the rate for a back ET from the (*E*)-**1** anion radical to the TEA cation radical (k_{-et}) is 14 times as fast as that for the cyclization (k_{2f}), therefore, led us to conclude that the relative rate for this back ET is a major factor that controls the overall efficiency of PET reactions examined.

3. Conclusions

Although there are many synthetic methods for the construction of significant heterocyclic rings,[11] convenient photochemical route to dihydrobenzoquinolinone derivatives is scarcely known.[12] Because it is facile to prepare the starting *N*-aroyl-α-dehydronaphthylalaninamides (**1**) and related α-dehydroarylalaninamides, a wide variety of substituted dihydroquinolinones can be synthesized by the ET-initiated photocyclization of these alaninamide derivatives. The facts that dihydrobenzoquinolinones are extremely stable under irradiation conditions and then obtained in high selectivities render our PET reactions in methanol containing TEA or DBU very useful in constructing the dihydroquinolinone ring. We were also able to obtain quantitative information about the relative rates of ET and related processes, through analysis of the dependence of quantum yield for formation of **2** on the TEA concentration.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a HITACHI 270-30 infrared spectrometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. HPLC analysis was performed on a SHIMADZU LC-10AT high-performance liquid chromatography system equipped with a 4.6×250-mm ODS (Zorbax) column and a SHIMADZU SPD-10A UV detector (detection wavelength=240 nm; mobile phase, MeCN/H_2O=60:40, v/v). UV absorption and fluorescence spectra were measured at room temperature with a HITACHI U-3300 spectrophotometer and a HITACHI F-4500 spectrofluorimeter, respectively. A cell with a 10-mm pathlength was used. Elemental analysis was performed on a PERKIN–ELMER PE2400 series II CHNS/O analyzer. Oxidation and reduction potentials were measured with a YANACO P-1100 polarographic analyzer. Mass spectra were recorded on a JEOL JMS-01SG-2 spectrometer. MeOH was purified according to the standard procedure and freshly distilled prior to use. TEA and DBU were fractionally distilled from sodium hydroxide. All other reagents used were obtained from commercial sources and of the highest grade available.

A potassium tris(oxalato)ferrate(III) actinometer was employed to determine quantum yields for appearance of **2f** and (*Z*)-**1f** at low conversions of the starting (*E*)-**1f** ($<$ 4%).[13] A 450 W high-pressure Hg lamp was used as the light source from which 313 nm light was selected with 1.0 wt% potassium carbonate solution of potassium chromate (2.0×10^{-3} mol dm^{-3}), CORNING 7-54 and TOSHIBA IRA-25S glass filters. Linear calibration curves for **2f** and (*Z*)-**1f**, made under the same analytical conditions, were utilized to quantify the formation of these two compounds. All of the quantum yields are an average of more than three determinations.

4.2. General procedure for the synthesis of (*Z*)-4-(1-naphthylmethylene)-2-(substituted phenyl)-5(4*H*)-oxazolones, (*Z*)-4-(2-naphthylmethylene)-2-(substituted phenyl)-5(4*H*)-oxazolones and (*Z*)-2-(*tert*-butyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone

N-(Substituted benzoyl)glycine or trimethylacetylglycine (0.04 mol), 1-naphthaldehyde or 2-naphthaldehyde (0.05 mol), and sodium acetate (0.02 mol) were added to acetic anhydride (25 mL) and the resulting mixture was heated at 65–75 °C for 1–2 h [*N*-(substituted benzoyl)glycine] or 6 h (*N*-trimethylacetylglycine) with stirring. The mixture was cooled with ice and the solid separated out was collected by filtration with suction and washed with water, a small amount of cold EtOH and then with dry hexane. After the crude product had been air-dried at room temperature, it was recrystallized from hexane–$CHCl_3$ to give yellow crystals (50–70%).

4.2.1. (*Z*)-2-Phenyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 166.0–167.0 °C. IR (KBr): 1797, 1647, 1167 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (2H, dd, $J=7.3$, 7.6 Hz), 7.55 (1H, dd, $J=8.6$, 8.6 Hz), 7.62 (1H, dd, $J=7.3$, 7.3 Hz), 7.63 (1H, dd, $J=8.6$, 8.6 Hz), 7.64 (1H, dd, $J=6.7$, 8.6 Hz), 7.90 (1H, d, $J=8.6$ Hz), 7.97 (1H, d, $J=8.6$ Hz), 8.13 (1H, s), 8.21 (2H, d, $J=7.6$ Hz), 8.31 (1H, d, $J=8.6$ Hz), 9.03 (1H, d, $J=6.7$ Hz).

4.2.2. (*Z*)-2-(4-Methoxyphenyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 207.0–208.0 °C. IR (KBr): 1788, 1644, 1170 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (3H, s), 7.03 (2H, d, $J=8.8$ Hz), 7.54–7.66 (3H, m), 7.90 (1H, d, $J=7.9$ Hz), 7.95 (1H, d, $J=7.9$ Hz), 8.07 (1H, s), 8.16 (2H, d, $J=8.8$ Hz), 8.32 (1H, d, $J=8.5$ Hz), 9.02 (1H, d, $J=7.3$ Hz).

4.2.3. (*Z*)-2-(4-Bromophenyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 201.0–201.5 °C. IR (KBr): 1799, 1650, 1180 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (1H, dd, $J=7.6$, 7.6 Hz), 7.63–7.66 (2H, m), 7.69 (2H, d, $J=8.3$ Hz), 7.92 (1H, d, $J=8.2$ Hz), 7.99 (1H, d, $J=8.3$ Hz), 8.07 (2H, d, $J=8.3$ Hz), 8.17 (1H, s), 8.31 (1H, d, $J=8.2$ Hz), 9.00 (1H, d, $J=7.6$ Hz).

4.2.4. (*Z*)-2-(4-Trifluoromethylphenyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 201.0–202.0 °C. IR

(KBr): 1797, 1641, 1167 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.58 (1H, dd, J=6.7, 7.9 Hz), 7.65–7.69 (2H, m), 7.81 (2H, d, J=8.6 Hz), 7.93 (1H, d, J=8.2 Hz), 8.10 (1H, d, J=8.2 Hz), 8.24 (1H, s), 8.33 (2H, d, J=8.6 Hz), 8.33 (1H, d, J=7.9 Hz), 9.02 (1H, d, J=7.6 Hz).

4.2.5. (*Z*)-2-(4-Cyanophenyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 237.0–238.0 °C. IR (KBr): 2236, 1794, 1641, 1164 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.59 (1H, dd, J=7.3, 7.9 Hz), 7.64–7.68 (2H, m), 7.84 (2H, d, J=8.2 Hz), 7.93 (1H, d, J=7.9 Hz), 8.02 (1H, d, J=7.9 Hz), 8.25 (1H, s), 8.31 (2H, d, J=8.2 Hz), 8.32 (1H, d, J=8.5 Hz), 9.00 (1H, d, J=7.3 Hz).

4.2.6. (*Z*)-2-(2,4-Dimethoxyphenyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 174.0–175.5 °C. IR (KBr): 1768, 1643, 1165 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.91 (3H, s), 4.01 (3H, s), 6.56 (1H, d, J=2.4 Hz), 6.63 (1H, dd, J=2.4, 8.5 Hz), 7.55 (1H, dd, J=7.3, 6.7 Hz), 7.6–7.60 (2H, m), 7.89 (1H, d, J=7.9 Hz), 7.94 (1H, d, J=8.5 Hz), 8.05 (1H, s), 8.08 (1H, d, J=8.5 Hz), 8.33 (1H, d, J=8.5 Hz), 9.07 (1H, d, J=7.3 Hz).

4.2.7. (*Z*)-2-(*tert*-Butyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 89.0–90.0 °C. IR (KBr): 1794, 1652, 1647, 1150 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.41 (9H, s), 7.54 (1H, dd, J=6.9, 8.2 Hz), 7.60 (1H, dd, J=7.6, 8.2 Hz), 7.61 (1H, dd, J=6.9, 8.9 Hz), 7.89 (1H, d, J=8.2 Hz), 7.94 (1H, d, J=8.2 Hz), 8.04 (1H, s), 8.27 (1H, d, J=8.9 Hz), 8.89 (1H, d, J=7.6 Hz).

4.2.8. (*Z*)-4-(2-Naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone. Mp 142.0–143.0 °C. IR (KBr): 1797, 1626, 1167 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.51 (1H, dd, J=7.9, 7.9 Hz), 7.54 (1H, dd, J=7.9, 7.9 Hz), 7.54 (2H, dd, J=7.9, 7.9 Hz), 7.61 (1H, dd, J=7.9, 7.9 Hz), 7.83 (1H, d, J=7.9 Hz), 7.89 (1H, d, J=8.5 Hz), 7.91 (1H, d, J=7.9 Hz), 8.19 (2H, d, J=7.9 Hz), 8.43 (1H, s), 8.49 (1H, d, J=8.5 Hz).

4.2.9. (*Z*)-2-(4-Methoxyphenyl)-4-(2-naphthylmethylene)-5(4*H*)-oxazolone. Mp 198.0–199.0 °C. IR (KBr): 1788, 1653, 1167 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.91 (3H, s), 7.04 (2H, d, J=8.9 Hz), 7.32 (1H, s), 7.49–7.58 (2H, m), 7.83–7.94 (3H, m), 8.17 (2H, d, J=8.9 Hz), 8.46–8.52 (2H, m).

4.2.10. (*Z*)-2-(2,4-Dimethoxyphenyl)-4-(2-naphthylmethylene)-5(4*H*)-oxazolone. Mp 173.5–174.5 °C. IR (KBr): 1775, 1655, 1170 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.92 (3H, s), 4.06 (3H, s), 6.58 (1H, d, J=2.1 Hz), 6.64 (1H, dd, J=2.1, 8.6 Hz), 7.32 (1H, s), 7.51–7.56 (2H, m), 7.84–7.93 (3H, m), 8.08 (1H, d, J=8.6 Hz), 8.47 (1H, d, J=8.9 Hz), 8.56 (1H, s).

4.3. General procedure for the synthesis of (*Z*)-*N*-alkyl-3-(1-naphthyl)-2-(substituted benzoylamino)-2-propenamides [(*Z*)-1a–f,i], (*Z*)-*N*-methyl-3-(1-naphthyl)-2-trimethylacetylamino-2-propenamide [(*Z*)-1g], (*Z*)-3-(1-naphthyl)-2-benzoylamino-2-propenamide [(*Z*)-1h], and (*Z*)-*N*-methyl-3-(2-naphthyl)-2-(substituted benzoylamino)-2-propenamides [(*Z*)-1j–l]

(*Z*)-4-(1-Naphthylmethylene)-2-(substituted phenyl)-5(4*H*)-oxazolone (for **1a**–**f**,**h**,**i**, 0.010 mol), (*Z*)-2-(*tert*-butyl)-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (for **1g**, 0.010 mol) or (*Z*)-4-(2-naphthylmethylene)-2-(substituted phenyl)-5(4*H*)-oxazolone (for **1j**–**l**, 0.010 mol) was added to dry CHCl$_3$ (30 mL) containing primary amine (0.012 mol) and the resulting solution was stirred for 0.5–1 h at room temperature. After removal of the solvent under reduced pressure, the crystalline solid obtained was recrystallized twice from EtOH–hexane affording colorless crystals (50–80%).

4.3.1. (*Z*)-2-Benzoylamino-*N*-methyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1a]. Mp 205.0–206.0 °C. IR (KBr): 1650, 1670, 3080, 3300 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.75 (3H, d, J=4.9 Hz) 7.43 (2H, dd, J=7.3, 7.3 Hz), 7.43 (1H, dd, J=6.7, 7.9 Hz), 7.52 (1H, dd, J=7.3, 7.3 Hz), 7.54 (1H, dd, J=6.7, 7.0 Hz), 7.56 (1H, dd, J=6.7, 7.9 Hz), 7.62 (1H, d, J=6.7 Hz), 7.76 (1H, s), 7.84 (2H, d, J=7.3 Hz), 7.86 (1H, d, J=7.9 Hz), 7.93 (1H, d, J=7.0 Hz), 8.04 (1H, d, J=7.9 Hz), 8.19 (1H, q, J=4.9 Hz), 9.75 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 124.2, 125.3, 125.99, 126.02, 126.03, 126.3, 127.8 (2C), 128.0 (2C), 128.4 (2C), 131.1, 131.5 (2C), 132.4, 133.1, 133.7, 165.2, 166.2. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (75.97); H, 5.49 (5.18); N, 8.48% (8.45%).

4.3.2. (*Z*)-2-(4-Anisoylamino)-*N*-methyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1b]. Mp 226.0–227.0 °C. IR (KBr): 1670, 1650, 3080, 3300 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.74 (3H, d, J=4.3 Hz), 3.79 (3H, s), 6.96 (2H, d, J=8.6 Hz), 7.42 (1H, dd, J=7.3, 7.9 Hz), 7.57–7.53 (2H, m), 7.60 (1H, d, J=7.3 Hz), 7.71 (1H, s), 7.83 (2H, d, J=8.6 Hz), 7.85 (1H, d, J=7.9 Hz), 7.93 (1H, d, J=7.6 Hz), 8.03 (1H, d, J=7.9 Hz), 8.16 (1H, q, J=4.3 Hz), 9.61 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 55.4, 113.3 (2C), 124.3, 125.4, 125.5, 126.0 (2C), 126.03, 126.4, 128.38, 128.40, 129.8 (2C), 131.2 (2C), 131.5, 132.6, 161.9, 165.4, 165.7. Anal. Calcd (found) for $C_{22}H_{20}N_2O_3$: C, 73.32 (73.53); H, 5.59 (5.51); N, 7.77% (7.37%).

4.3.3. (*Z*)-2-(4-Bromobenzoylamino)-*N*-methyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1c]. Mp 220.0–221.0 °C. IR (KBr): 1630, 1650, 3200, 3350 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.74 (3H, d, J=4.9 Hz), 7.43 (1H, dd, J=7.3, 7.9 Hz), 7.56–7.52 (2H, m), 7.58 (1H, d, J=7.3 Hz), 7.66 (2H, d, J=8.6 Hz), 7.76 (1H, s), 7.78 (2H, d, J=8.6 Hz), 7.86 (1H, d, J=7.9 Hz), 7.93 (1H, d, J=9.2 Hz), 8.02 (1H, d, J=7.3 Hz), 8.22 (1H, q, J=4.9 Hz), 9.84 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 124.2, 125.3, 125.4, 125.99, 126.00, 126.3, 126.4, 128.4, 128.5, 130.0 (2C), 131.1, 131.13 (2C), 131.4, 132.1, 132.9, 133.1, 165.0, 165.3. Anal. Calcd (found) for $C_{21}H_{17}Br_1N_2O_2$: C, 61.63 (61.26); H, 4.19 (3.90); N, 6.84% (7.00%).

4.3.4. (*Z*)-*N*-Methyl-3-(1-naphthyl)-2-(4-trifluoromethylbenzoylamino)-2-propenamide [(*Z*)-1d]. Mp 195.0–196.0 °C. IR (KBr): 1650, 1675, 3170, 3290 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.76 (3H, d, J=4.9 Hz), 7.44 (1H, dd, J=6.7, 7.9 Hz), 7.54 (1H, dd, J=6.1, 7.3 Hz), 7.57 (1H, dd, J=6.1, 8.9 Hz), 7.61 (1H, d, J=6.7 Hz), 7.81 (1H, s), 7.83 (2H, d, J=7.9 Hz), 7.87 (1H, d, J=7.9 Hz), 7.94 (1H, d, $J=8.9$ Hz), 8.03 (2H, d, $J=7.9$ Hz), 8.03 (1H, d, $J=7.3$ Hz), 8.26 (1H, q, $J=4.9$ Hz), 10.01 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 123.9 (1C, q, $J=273.1$ Hz), 124.2, 125.1 (2C, q, $J=3.0$ Hz), 125.4, 126.0, 126.1, 126.4, 126.7, 128.5, 128.6, 128.7 (2C), 131.1, 131.3, 131.5 (1C, q, $J=31.0$ Hz), 131.9, 133.2, 137.6, 164.9, 165.1. Anal. Calcd (found) for $C_{22}H_{17}F_3N_2O_2$: C, 66.33 (66.12); H, 4.30 (4.06); N, 7.03% (7.16%).

4.3.5. (*Z*)-2-(4-Cyanobenzoylamino)-*N*-methyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1e]. Mp 210.0–211.0 °C. IR (KBr): 1650, 1670, 2230, 3290, 3400 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.74 (3H, d, $J=4.9$ Hz), 7.42 (1H, dd, $J=7.3$, 8.5 Hz), 7.52–7.55 (2H, m), 7.57 (1H, d, $J=7.3$ Hz), 7.79 (1H, s), 7.85 (1H, d, $J=8.5$ Hz), 7.96–7.91 (5H, m), 8.00 (1H, d, $J=7.3$ Hz), 8.24 (1H, q, $J=4.9$ Hz), 9.99 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 113.8, 118.3, 124.2, 125.4, 126.0, 126.1, 126.4, 126.8, 128.5 (2C), 128.6 (2C), 131.1, 131.3, 131.8, 132.2 (2C), 133.2, 137.8, 164.8, 164.9. Anal. Calcd (found) for $C_{22}H_{17}N_3O_2$: C, 74.35 (73.98); H, 4.82 (4.72); N, 11.82% (12.14%).

4.3.6. (*Z*)-2-(2,4-Dimethoxybenzoylamino)-*N*-methyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1f]. Mp 176.0–176.5 °C. IR (KBr): 1640, 1665, 3348 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.76 (3H, d, $J=4.3$ Hz), 3.59 (3H, s), 3.79 (3H, s), 6.58 (1H, d, $J=2.5$ Hz), 6.62 (1H, dd, $J=2.5$, 8.9 Hz), 7.27 (1H, s), 7.54–7.57 (3H, m), 7.62 (1H, d, $J=7.3$ Hz), 7.77 (1H, d, $J=8.9$ Hz), 7.92 (1H, d, $J=7.9$ Hz), 7.98–7.96 (1H, m), 8.08–8.06 (1H, m), 8.22 (1H, q, $J=4.3$ Hz), 9.47 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.2, 55.6, 56.0, 98.5, 106.1, 113.6, 120.1, 124.5, 125.4, 126.10, 126.15, 126.4, 128.2, 128.4, 130.9, 131.4, 132.7, 133.2, 133.4, 158.6, 162.6, 163.4, 165.4. Anal. Calcd (found) for $C_{23}H_{22}N_2O_4$: C, 70.75 (70.41); H, 5.68 (5.61); N, 7.17% (6.87%).

4.3.7. (*Z*)-*N*-Methyl-3-(1-naphthyl)-2-trimethylacetylamino-2-propenamide [(*Z*)-1g]. Mp 180.0–181.5 °C. IR (KBr): 1630, 1650, 3300, 3350 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.03 (9H, s), 2.75 (3H, d, $J=4.9$ Hz), 7.47 (1H, dd, $J=7.3$, 7.9 Hz), 7.53–7.55 (4H, m), 7.84 (1H, q, $J=4.9$ Hz), 7.88 (1H, d, $J=7.9$ Hz), 7.93–7.95 (1H, m), 7.98–8.00 (1H, m), 8.75 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 26.9 (3C), 38.3, 124.4, 124.8, 125.2, 125.9, 126.2, 126.3, 128.3, 128.4, 131.0, 131.5, 132.8, 133.1, 165.6, 176.9. Anal. Calcd (found) for $C_{19}H_{22}N_2O_2$: C, 73.52 (73.80); H, 7.14 (7.04); N, 9.03% (9.10%).

4.3.8. (*Z*)-2-Benzoylamino-3-(1-naphthyl)-2-propenamide [(*Z*)-1h]. Mp 159.5–160.0 °C. IR (KBr): 1650, 1690, 3190, 3280 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.30 (1H, br s), 7.41 (2H, dd, $J=7.3$, 7.3 Hz), 7.43 (1H, dd, $J=7.3$, 8.5 Hz), 7.50 (1H, dd, $J=7.3$, 7.3 Hz), 7.54 (1H, dd, $J=6.7$, 8.6 Hz), 7.57 (1H, dd, $J=6.7$, 7.9 Hz), 7.62 (1H, d, $J=7.3$ Hz), 7.75 (1H, s), 7.75 (1H, br s), 7.82 (2H, d, $J=7.3$ Hz), 7.85 (1H, d, $J=8.5$ Hz), 7.92 (1H, d, $J=8.6$ Hz), 8.04 (1H, d, $J=7.9$ Hz), 9.71 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 124.3, 125.4, 126.1, 126.2 (2C), 126.4, 127.8 (2C), 128.2 (2C), 128.47, 128.5, 131.2, 131.5, 131.6, 132.5, 133.2, 133.9, 166.2, 166.7. Anal. Calcd (found) for $C_{20}H_{16}N_2O_2$: C, 75.93 (75.61); H, 5.10 (5.13); N, 8.86% (8.96%).

4.3.9. (*Z*)-2-Benzoylamino-*N*-benzyl-3-(1-naphthyl)-2-propenamide [(*Z*)-1i]. Mp 178.0–178.5 °C. IR (KBr): 1610, 1650, 3060, 3250 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.47 (2H, d, $J=6.1$ Hz), 7.25 (1H, dd, $J=7.3$, 7.3 Hz), 7.34 (2H, dd, $J=7.3$, 7.3 Hz), 7.40 (2H, d, $J=7.3$ Hz), 7.42–7.46 (3H, m), 7.52 (1H, dd, $J=7.9$, 7.9 Hz), 7.55 (1H, dd, $J=7.3$, 8.5 Hz), 7.58 (1H, dd, $J=7.3$, 7.9 Hz), 7.66 (1H, d, $J=6.7$ Hz), 7.84 (1H, s), 7.86 (2H, d, $J=7.9$ Hz), 7.86 (1H, d, $J=7.9$ Hz), 7.94 (1H, d, $J=8.5$ Hz), 8.05 (1H, d, $J=7.9$ Hz), 8.84 (1H, t, $J=6.1$ Hz), 9.83 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.6, 124.3, 125.4, 126.0, 126.1, 126.4, 126.6 (2C), 127.2 (2C), 127.9 (2C), 128.1, 128.2, 128.45, 128.53, 131.1, 131.4, 131.5 (2C), 132.4, 133.2 (2C), 133.8, 139.8, 164.9, 166.4. Anal. Calcd (found) for $C_{27}H_{22}N_2O_2$: C, 79.78 (79.51); H, 5.46 (5.87); N, 6.89% (6.70%).

4.3.10. (*Z*)-2-Benzoylamino-*N*-methyl-3-(2-naphthyl)-2-propenamide [(*Z*)-1j]. Mp 189.0–190.0 °C. IR (KBr): 1628, 3052, 3248 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.72 (3H, d, $J=4.9$ Hz) 7.42 (1H, s), 7.49 (1H, dd, $J=6.7$, 7.6 Hz), 7.50 (1H, dd, $J=6.7$, 7.6 Hz), 7.53 (2H, dd, $J=7.3$, 7.9 Hz), 7.60 (1H, dd, $J=7.9$, 7.9 Hz), 7.71 (1H, d, $J=8.5$ Hz), 7.78 (1H, d, $J=6.7$ Hz), 7.83 (1H, d, $J=8.5$ Hz), 7.85 (1H, d, $J=6.7$ Hz), 8.03 (2H, d, $J=7.9$ Hz), 8.08 (1H, s), 8.14 (1H, q, $J=4.9$ Hz), 9.98 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 126.1, 126.5, 126.7, 127.4, 127.7, 127.9 (2C), 128.0, 128.3 (2C), 128.8, 129.3, 130.5, 131.6, 132.0, 132.6, 132.7, 133.8, 165.4, 165.9. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (76.30); H, 5.49 (5.60); N, 8.48% (8.31%).

4.3.11. (*Z*)-2-(4-Anisoylamino)-*N*-methyl-3-(2-naphthyl)-2-propenamide [(*Z*)-1k]. Mp 138.0–139.5 °C. IR (KBr): 1610, 1640, 3090, 3250 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.72 (3H, d, $J=4.6$ Hz), 3.84 (3H, s), 7.07 (2H, d, $J=8.9$ Hz), 7.38 (1H, s), 7.48–7.52 (2H, m), 7.70 (1H, d, $J=8.5$ Hz), 7.78 (1H, d, $J=8.5$ Hz), 7.82 (1H, d, $J=8.5$ Hz), 7.85 (1H, d, $J=7.2$ Hz), 8.02 (2H, d, $J=8.9$ Hz), 8.06 (1H, s), 8.13 (1H, q, $J=4.6$ Hz), 9.85 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.3, 55.4, 113.5 (2C), 126.1, 126.2, 126.5, 126.7, 127.4, 127.7, 128.0, 128.5, 129.3, 129.9 (2C), 130.7, 132.1, 132.6, 132.8, 162.0, 165.5, 165.6. Anal. Calcd (found) for $C_{22}H_{20}N_2O_3$: C, 73.32 (72.98); H, 5.59 (5.93); N, 7.77% (7.43%).

4.3.12. (*Z*)-2-(2,4-Dimethoxybenzoylamino)-*N*-methyl-3-(2-naphthyl)-2-propenamide [(*Z*)-1l]. Mp 173.5–174.5 °C. IR (KBr): 1630, 1643, 3323 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.72 (3H, d, $J=4.6$ Hz), 3.85 (3H, s), 3.89 (3H, s), 6.68 (1H, dd, $J=2.3$, 8.6 Hz), 6.74 (1H, dd, $J=2.3$ Hz), 7.12 (1H, s), 7.51–7.53 (2H, m), 7.74 (1H, d, $J=8.6$ Hz), 7.82–7.90 (4H, m), 8.06 (1H, q, $J=4.6$ Hz), 8.10 (1H, s), 9.63 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.2, 55.6, 56.2, 98.5, 106.0, 114.3, 125.3, 126.3, 126.5, 126.6, 127.5, 127.8, 128.0, 128.8, 130.8, 132.1, 132.5, 132.7, 132.8, 158.9, 163.4 (2C), 165.6. Anal. Calcd (found) for $C_{23}H_{22}N_2O_4$: C, 70.75 (70.93); H, 5.68 (6.01); N, 7.17% (7.08%).

4.4. General procedure for the irradiation of (*Z*)-1a–l

In order to examine the dependence of product distribution and composition on irradiation time, a MeOH solution (45 mL) of (*Z*)-**1** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}, for **1a–i**), or DBU (0.10 mol dm^{-3}, for **1j–l**) placed in a Pyrex vessel, was irradiated under nitrogen at room temperature with Pyrex-filtered light from a 450 W high-pressure Hg lamp (external irradiation). At suitable time intervals, an aliquot (5 mL) of the solution was pipetted off and concentrated to dryness in vacuo. The resulting residue was dissolved in DMSO-d_6 and subjected to ^{1}H NMR spectral analysis. When DBU was used as an electron donor, the resulting residue was at first dissolved in CHCl$_3$ and subsequently washed with 0.2 mol dm^{-3} HCl solution (20 mL). After removal of CHCl$_3$ under reduced pressure, the resulting residue was dissolved in DMSO-d_6 and subjected to ^{1}H NMR spectral analysis. The product composition was estimated from the area ratio of a given ^{1}H NMR signal for each compound.

On the other hand, a MeOH solution (200 mL) of (*Z*)-**1a–l** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}, for **1a–i**) or DBU (0.10 mol dm^{-3}, for **1j–l**), placed in a Pyrex vessel, was irradiated for a given period of time under nitrogen with Pyrex-filtered light from a 400 W high-pressure Hg lamp at room temperature (internal irradiation). After 3-h (**1b**), 6-h (**1a**,**c**,**f–l**), 10-h (**1d**), or 30-h (**1e**) irradiation, an appropriate amount of the solution (5 mL) being irradiated was pipetted off and concentrated to dryness in vacuo giving the residue which was subjected to ^{1}H NMR spectral analysis in DMSO-d_6. DBU was removed according to the same procedure as above. The remaining solutions of **1a–l** were concentrated to dryness under reduced pressure. The resulting residues were washed with a small amount of EtOH, allowing us to obtain analytical-grade **2a–l**. The combined filtrates were concentrated to dryness and subjected to column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc–hexane. For the purpose of isolating and purifying the photoproducts, preparative TLC plate (silica gel) was also used. Physical and spectroscopic properties of the isolated isomers [(*E*)-**1a**,**f**,**h–j**], 3,4-dihydrobenzo[*f*]quinolinones (**2a–i**), 3,4-dihydrobenzo[*h*]quinolinones (**2j–l**) and 4,5-dihydrooxazoles (*cis*-**3a**,**h**,**i**) are as follows. Conversion was estimated by the sum of composition for **2** and **3**.

4.4.1. (*E*)-1a. Yield, 10% (conversion, 7%). Mp 171.0–172.0 °C. IR (KBr): 1678, 1664, 3264, 3320 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.46 (3H, d, $J=4.9$ Hz), 7.33 (1H, s), 7.43–7.47 (2H, m), 7.54 (2H, dd, $J=7.3$, 7.9 Hz), 7.54–7.58 (2H, m), 7.61 (1H, dd, $J=7.3$, 7.3 Hz), 7.83 (1H, d, $J=7.3$ Hz), 7.83 (1H, q, $J=4.9$ Hz), 7.94 (1H, d, $J=6.4$ Hz), 7.98 (2H, d, $J=7.9$ Hz), 8.07 (1H, d, $J=7.9$ Hz), 10.27 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.7, 115.7, 124.4, 125.3, 125.4, 125.8, 126.0, 127.3, 127.7 (2C), 128.2, 128.3 (2C), 131.2, 131.7, 132.0, 133.0, 133.7, 134.8, 164.8, 164.9. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (76.34); H, 5.49 (5.81); N, 8.48% (8.47%).

4.4.2. (*E*)-1f. Yield, 6% (conversion, 12%). Mp 191.0–192.0 °C. IR (KBr): 1608, 1636, 2945, 3347 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.45 (3H, d, $J=4.8$ Hz), 3.87 (3H, s), 4.00 (3H, s), 6.72 (1H, dd, $J=2.1$, 8.6 Hz), 6.74 (1H, d, $J=2.1$ Hz), 7.38 (1H, d, $J=7.6$ Hz), 7.46 (1H, dd, $J=7.6$, 7.9 Hz), 7.54–7.60 (2H, m), 7.65 (1H, q, $J=4.8$ Hz), 7.84 (1H, d, $J=8.6$ Hz), 7.92–7.95 (2H, m), 7.93 (1H, s), 8.08 (1H, d, $J=7.9$ Hz), 9.96 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.9, 55.6, 56.4, 98.7, 106.3, 114.0, 114.1, 124.6, 125.4, 125.7, 125.9, 126.1, 127.4, 128.3, 131.3, 132.4, 132.7, 133.2, 133.8, 158.7, 162.8, 163.5, 165.3. Anal. Calcd (found) for $C_{23}H_{22}N_2O_4$: C, 70.75 (70.62); H, 5.68 (5.77); N, 7.17% (7.32%).

4.4.3. (*E*)-1h. Yield, 12% (conversion, 6%). Mp 160.5–161.5 °C. IR (KBr): 1666, 1690, 3368, 3464 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.14 (1H, br s), 7.30 (1H, s), 7.34 (1H, br s), 7.46 (1H, dd, $J=7.3$, 8.2 Hz), 7.54 (2H, dd, $J=7.3$, 8.5 Hz), 7.54–7.58 (3H, m), 7.61 (1H, dd, $J=7.3$, 7.3 Hz), 7.84 (1H, d, $J=8.2$ Hz), 7.93–7.95 (1H, m), 7.99 (2H, d, $J=8.5$ Hz), 8.05–8.07 (1H, m), 10.24 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 116.2, 124.6, 125.4, 125.9, 126.0, 126.1, 127.4, 127.7 (2C), 128.26 (2C), 128.32 (2C), 131.3, 131.7, 132.3, 133.1, 133.9, 165.0, 166.0. Anal. Calcd (found) for $C_{20}H_{16}N_2O_2$: C, 75.93 (75.72); H, 5.10 (5.35); N, 8.86% (8.75%).

4.4.4. (*E*)-1i. Yield, 10% (conversion, 6%). Mp 155.5–157.0 °C. IR (KBr): 1627, 1644, 3256, 3330 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.19 (2H, d, $J=6.1$ Hz), 6.97–6.99 (2H, m), 7.14–7.16 (3H, m), 7.32 (1H, s), 7.33 (1H, dd, $J=7.3$, 8.5 Hz), 7.42 (1H, d, $J=6.7$ Hz), 7.53–7.57 (2H, m), 7.55 (2H, dd, $J=7.3$, 7.9 Hz), 7.62 (1H, dd, $J=7.9$, 7.9 Hz), 7.84 (1H, d, $J=8.5$ Hz), 7.94 (1H, d, $J=7.9$ Hz), 8.01 (2H, d, $J=7.3$ Hz), 8.07 (2H, d, $J=7.3$ Hz), 8.44 (1H, t, $J=6.1$ Hz), 10.34 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.3, 124.7, 125.4, 125.9, 126.0 (2C), 126.4, 127.3 (2C), 127.4 (2C), 127.8 (2C), 127.9 (2C), 128.3, 128.4 (2C), 131.4, 131.8, 132.1, 133.1, 133.9, 134.9, 138.9, 164.6, 165.0. Anal. Calcd (found) for $C_{27}H_{22}N_2O_2$: C, 79.78 (79.37); H, 5.46 (5.87); N, 6.89% (6.80%).

4.4.5. (*E*)-1j. Yield, 10% (conversion, 4%). Mp 167.0–168.0 °C. IR (KBr): 1643, 3059, 3260 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.60 (3H, d, $J=4.9$ Hz), 6.89 (1H, s), 7.43 (1H, d, $J=8.5$ Hz), 7.47 (1H, dd, $J=7.3$, 7.3 Hz), 7.49 (1H, dd, $J=7.3$, 7.3 Hz), 7.53 (2H, dd, $J=7.3$, 8.3 Hz), 7.60 (1H, dd, $J=7.3$, 7.3 Hz), 7.79 (1H, s), 7.83 (1H, d, $J=7.3$ Hz), 7.85 (1H, d, $J=8.5$ Hz), 7.95 (2H, d, $J=8.3$ Hz), 8.08 (1H, q, $J=4.9$ Hz), 10.20 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.8, 118.0, 125.9, 126.1, 126.2, 126.9, 127.3 (2C), 127.7 (3C), 128.3 (2C), 131.7, 131.9, 132.7, 132.9, 133.8, 133.9, 164.8, 165.1. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (76.18); H, 5.49 (5.32); N, 8.48% (8.40%).

4.4.6. 3-Benzoylamino-3,4-dihydro-1-methyl-2(1*H*)-benzo[*f*]quinolinone (2a). Yield, 67% (conversion, >99%). Mp 167.0–168.0 °C. IR (KBr): 1630, 1690, 3090, 3340 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.28 (1H, dd, $J=15.3$, 15.3 Hz), 3.45 (3H, s), 3.74 (1H, dd, $J=6.7$, 15.3 Hz), 4.86 (1H, ddd, $J=6.7$, 8.5, 15.3 Hz), 7.46 (1H, dd, $J=6.7$, 7.3 Hz), 7.52 (1H, d, $J=8.5$ Hz), 7.53 (2H, dd, $J=6.7$, 7.3 Hz), 7.57 (1H, dd, $J=6.7$, 8.5 Hz), 7.59 (1H, dd, $J=7.3$, 7.3 Hz), 7.93 (1H, d, $J=7.3$ Hz), 7.96 (2H, d, $J=6.7$ Hz), 7.96 (1H, d, $J=8.5$ Hz), 8.06 (1H, d, $J=8.5$ Hz), 8.86 (1H, d, $J=8.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.7, 30.4, 48.5, 116.1, 117.6, 123.0, 124.5, 127.1, 127.3 (2C), 128.1, 128.4 (3C), 129.6, 130.5, 131.5, 134.1, 137.2, 166.2, 168.3. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (76.10); H, 5.49 (5.50); N, 8.48% (8.70%).

4.4.7. 3-(4-Anisoylamino)-3,4-dihydro-1-methyl-2(1*H*)-benzo[*f*]quinolinone (2b). Yield, 80% (conversion, >99%). Mp 172.0–173.0 °C. IR (KBr): 1640, 1690, 3300, 3400 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.25 (1H, dd, $J=14.7$, 15.3 Hz), 3.33 (3H, s), 3.44 (3H, s), 3.72 (1H, dd, $J=6.1$, 15.3 Hz), 4.84 (1H, ddd, $J=6.1$, 7.9, 14.7 Hz), 7.06 (2H, d, $J=9.2$ Hz), 7.45 (1H, dd, $J=7.3$, 7.9 Hz), 7.51 (1H, d, $J=9.2$ Hz), 7.56 (1H, dd, $J=7.9$, 8.5 Hz), 7.96–7.92 (4H, m), 8.06 (1H, d, $J=8.5$ Hz), 8.70 (1H, d, $J=7.9$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.7, 30.3, 48.3, 55.3, 113.5 (2C), 116.0, 117.6, 123.0, 124.4, 126.2, 126.9, 127.9, 128.3, 129.1 (2C), 129.5, 130.5, 137.1, 161.6, 165.5, 168.4. Anal. Calcd (found) for $C_{22}H_{20}N_2O_3$: C, 73.32 (73.69); H, 5.59 (5.63); N, 7.77% (7.78%).

4.4.8. 3-(4-Bromobenzoylamino)-3,4-dihydro-1-methyl-2(1*H*)-benzo[*f*]quinolinone (2c). Yield, 77% (conversion, >99%). Mp 209.0–210.0 °C. IR (KBr): 1640, 1685, 3300, 3350 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.26 (1H, dd, $J=14.7$, 15.3 Hz) 3.44 (3H, s), 3.73 (1H, dd, $J=6.1$, 15.3 Hz), 4.84 (1H, ddd, $J=6.1$, 8.5, 14.7 Hz), 7.46 (1H, dd, $J=6.7$, 7.9 Hz), 7.51 (1H, d, $J=9.2$ Hz), 7.56 (1H, dd, $J=7.3$, 7.9 Hz), 7.75 (2H, d, $J=8.5$ Hz), 7.91 (2H, d, $J=8.5$ Hz), 7.93 (1H, d, $J=9.2$ Hz), 7.95 (1H, d, $J=6.7$ Hz), 8.06 (1H, d, $J=7.3$ Hz), 8.98 (1H, d, $J=8.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.6, 30.4, 48.6, 116.1, 117.5, 123.1, 124.6, 125.3, 127.1, 128.1, 128.4, 129.6 (2C), 129.7, 130.6, 131.5 (2C), 133.2, 137.2, 165.4, 168.2. Anal. Calcd (found) for $C_{21}H_{17}BrN_2O_2$: C, 61.63 (61.47); H, 4.19 (4.20); N, 6.84% (7.08%).

4.4.9. 3,4-Dihydro-1-methyl-3-(4-trifluoromethylbenzoylamino)-2(1*H*)-benzo[*f*]quinolinone (2d). Yield, 75% (conversion, >99%). Mp 213.0–214.0 °C. IR (KBr): 1640, 1690, 3310 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.28 (1H, dd, $J=14.6$, 15.3 Hz), 3.45 (3H, s), 3.77 (1H, dd, $J=6.1$, 15.3 Hz), 4.88 (1H, ddd, $J=6.1$, 8.5, 14.6 Hz), 7.46 (1H, dd, $J=7.3$, 7.9 Hz), 7.52 (1H, d, $J=8.6$ Hz), 7.56 (1H, dd, $J=7.3$, 8.5 Hz), 7.93 (2H, d, $J=8.2$ Hz), 7.94 (1H, d, $J=7.9$ Hz), 7.96 (1H, d, $J=8.6$ Hz), 8.07 (1H, d, $J=8.5$ Hz), 8.16 (2H, d, $J=8.2$ Hz), 9.15 (1H, d, $J=8.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.5, 30.4, 48.6, 116.1, 117.5, 123.1, 123.9 (1C, q, $J=272.1$ Hz), 124.5, 125.4 (2C, q, $J=4.1$ Hz), 127.0, 128.1, 128.3 (2C), 128.34, 129.6, 130.5, 131.3 (1C, q, $J=31.0$ Hz), 137.1, 137.9, 165.1, 168.1. Anal. Calcd (found) for $C_{22}H_{17}F_3N_2O_2$: C, 66.20 (66.20); H, 4.30 (3.97); N, 7.03% (6.87%).

4.4.10. 3-(4-Cyanobenzoylamino)-3,4-dihydro-1-methyl-2(1*H*)-benzo[*f*]quinolinone (2e). Yield, 60% (conversion, >99%). Mp 217.0–218.0 °C. IR (KBr): 1632, 1674, 2230, 3316 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.27 (1H, dd, $J=15.2$, 15.2 Hz), 3.44 (3H, s), 3.76 (1H, dd, $J=6.7$, 15.2 Hz), 4.86 (1H, ddd, $J=6.7$, 8.5, 15.2 Hz), 7.46 (1H, dd, $J=6.7$, 7.3 Hz), 7.52 (1H, d, $J=8.6$ Hz), 7.57 (1H, dd, $J=6.7$, 8.5 Hz), 7.93 (1H, d, $J=7.3$ Hz), 7.95 (1H, d, $J=8.6$ Hz), 8.03 (2H, d, $J=8.6$ Hz), 8.06 (1H, d, $J=8.5$ Hz), 8.11 (2H, d, $J=8.6$ Hz), 9.17 (1H, d, $J=8.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.4, 30.3, 48.6, 113.7, 116.0, 117.4, 118.2, 123.0, 124.5, 127.0, 128.0, 128.1 (2C), 128.3, 129.6, 130.4, 132.4 (2C), 137.0, 138.0, 164.8, 167.9. Anal. Calcd (found) for $C_{22}H_{17}N_3O_2$: C, 74.35 (74.36); H, 4.82 (4.86); N, 11.82% (11.71%).

4.4.11. 3,4-Dihydro-3-(2,4-dimethoxybenzoylamino)-1-methyl-2(1*H*)-benzo[*f*]quinolinone (2f). Yield, 87% (conversion, >99%). Mp 198.0–199.0 °C. IR (KBr): 1610, 1643, 3352 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.05 (1H, dd, $J=15.3$, 14.7 Hz), 3.47 (3H, s), 3.86 (3H, s), 3.99 (3H, s), 4.04 (1H, dd, $J=15.3$, 6.1 Hz), 4.63 (1H, ddd, $J=14.7$, 6.1, 5.5 Hz), 6.69 (1H, dd, $J=8.8$, 2.4 Hz), 6.73 (1H, d, $J=2.4$ Hz), 7.47 (1H, d, $J=7.3$, 6.7 Hz), 7.53 (1H, d, $J=9.2$ Hz), 7.58 (1H, dd, $J=8.5$, 6.7 Hz), 7.94 (1H, d, $J=9.2$ Hz), 7.95 (1H, d, $J=7.3$ Hz), 7.98 (1H, d, $J=8.8$ Hz), 8.03 (1H, d, $J=8.5$ Hz), 8.90 (1H, d, $J=5.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.4, 164.0, 163.3, 159.0, 137.0, 132.8, 130.6, 129.7, 128.4, 128.0, 127.1, 124.6, 123.1, 118.0, 116.2, 113.7, 106.0, 98.7, 56.3, 55.5, 49.2, 30.5, 26.6. Anal. Calcd (found) for $C_{22}H_{22}N_2O_4$: C, 70.75 (70.43); H, 5.68 (5.41); N, 7.17% (7.13%).

4.4.12. 3,4-Dihydro-1-methyl-3-trimethylacetylamino-2(1*H*)-benzo[*f*]quinolinone (2g). Yield, 75% (conversion, >99%). Mp 220.0–221.5 °C. IR (KBr): 1650, 1690, 3360 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (9H, s), 3.15 (1H, dd, $J=14.6$, 15.3 Hz), 3.41 (3H, s), 3.60 (1H, dd, $J=6.7$, 15.3 Hz), 4.59 (1H, ddd, $J=6.7$, 7.3, 14.6 Hz), 7.44 (1H, dd, $J=7.3$, 7.3 Hz), 7.48 (1H, d, $J=8.6$ Hz), 7.56 (1H, dd, $J=7.3$, 8.5 Hz), 7.76 (1H, d, $J=7.3$ Hz), 7.92 (1H, d, $J=7.3$ Hz), 7.93 (1H, d, $J=8.6$ Hz), 8.02 (1H, d, $J=8.5$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.5, 27.4 (3C), 30.3, 38.2, 47.9, 116.1, 117.7, 123.0, 124.5, 127.0, 127.9, 128.3, 129.6, 130.5, 137.1, 168.5, 177.5. Anal. Calcd (found) for $C_{19}H_{22}N_2O_2$: C, 73.52 (73.92); H, 7.14 (7.21); N, 9.03% (9.18%).

4.4.13. 3-Benzoylamino-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone (2h). Yield, 59% (conversion, 94%). Mp 184.0–186.0 °C. IR (KBr): 1650, 1680, 1746, 2944, 3404 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.54 (3H, d, $J=6.7$ Hz), 3.29 (1H, dd, $J=15.2$, 14.6 Hz), 3.62 (3H, s), 3.70 (1H, dd, $J=15.2$, 6.1 Hz), 4.80 (1H, ddd, $J=14.6$, 8.6, 6.1 Hz), 5.35 (1H, q, $J=6.7$ Hz), 7.48 (1H, dd, $J=7.9$, 7.9 Hz), 7.52 (2H, dd, $J=7.3$, 7.9 Hz), 7.58 (1H, d, $J=9.2$ Hz), 7.58–7.60 (2H, m), 7.94 (1H, d, $J=9.2$ Hz), 7.94 (1H, d, $J=7.9$ Hz), 7.95 (2H, d, $J=7.3$ Hz), 8.09 (1H, d, $J=8.5$ Hz), 8.90 (1H, d, $J=8.6$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.1, 26.8, 48.6, 52.1, 53.5, 116.1, 119.1, 123.3, 124.8, 127.2, 127.4 (2C), 128.2, 128.3 (3C), 129.9, 130.6, 131.5, 134.0, 136.3, 166.1, 168.3, 171.0. Anal. Calcd (found) for $C_{24}H_{22}N_2O_4$: C, 71.63 (71.80); H, 5.51 (5.34); N, 6.96% (6.59%).

4.4.14. 3-Benzoylamino-1-benzyl-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone (2i). Yield, 55% (conversion, 96%). Mp 194.0–195.0 °C. IR (KBr): 1640, 1690, 3090, 3340 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.37 (1H, dd, $J=14.3$, 14.3 Hz), 3.82 (1H, dd, $J=6.4$, 14.3 Hz), 5.06 (1H, ddd, $J=6.4$, 8.2, 14.3 Hz), 5.33 (1H, d, $J=16.5$ Hz), 5.37 (1H, d, $J=16.5$ Hz), 7.24–7.20 (1H, m), 7.34–7.28 (4H, m), 7.38 (1H, d, $J=9.2$ Hz), 7.44 (1H, dd, $J=7.0$, 7.0 Hz), 7.54 (2H, dd, $J=7.0$, 7.6 Hz), 7.56 (1H, dd, $J=7.0$, 7.6 Hz), 7.60 (1H, dd, $J=7.6$, 7.6 Hz), 7.80 (1H, d, $J=9.2$ Hz), 7.85 (1H, d, $J=7.0$ Hz), 8.00 (2H, d, $J=7.0$ Hz), 8.07 (1H, d, $J=$

7.6 Hz), 8.96 (1H, d, J=8.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.8, 45.4, 48.5, 116.4, 118.2, 123.2, 124.7, 126.5 (2C), 127.0, 127.1, 127.4 (2C), 128.0, 128.3, 128.4 (2C), 128.6 (2C), 129.7, 130.7, 131.5, 134.1, 136.1, 137.2, 166.3, 168.8. Anal. Calcd (found) for $C_{27}H_{22}N_2O_2$: C, 79.78 (79.95); H, 5.46 (5.55); N, 6.89% (6.99%).

4.4.15. 3-Benzoylamino-3,4-dihydro-1-methyl-2(1*H*)-benzo[*h*]quinolinone (2j). Yield, 35% (conversion, 72%). Mp 153.0–154.0 °C. IR (KBr): 1636, 1690, 3237 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.06–3.10 (1H, m), 3.30–3.36 (1H, m), 3.50 (3H, s), 4.73–4.78 (1H, m), 7.48 (1H, d, J=8.5 Hz), 7.53 (2H, dd, J=7.3, 7.3 Hz), 7.54 (1H, dd, J=7.3, 8.5 Hz), 7.56 (1H, dd, J=7.3, 8.6 Hz), 7.58 (1H, dd, J=7.3, 7.3 Hz), 7.75 (1H, d, J=8.6 Hz), 7.95 (1H, d, J=7.3 Hz), 7.97 (1H, d, J=8.5 Hz), 8.03 (1H, d, J=8.6 Hz), 8.74 (1H, d, J=7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.6, 37.9, 49.2, 123.4, 124.8, 124.9, 125.3, 125.5, 125.7, 125.9, 127.3 (2C), 128.3 (2C), 128.6, 131.4, 133.8, 134.0, 136.5, 166.2, 171.1. Anal. Calcd (found) for $C_{21}H_{18}N_2O_2$: C, 76.34 (76.28); H, 5.49 (5.24); N, 8.48% (8.35%).

4.4.16. 3-(4-Anisoylamino)-3,4-dihydro-1-methyl-2(1*H*)-benzo[*h*]quinolinone (2k). Yield, 40% (conversion, 85%). Mp 224.0–225.0 °C. IR (KBr): 1660, 1680, 3400 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.07 (1H, dd, J=5.5, 15.6 Hz), 3.29–3.38 (1H, m), 3.50 (3H, s), 3.84 (3H, s), 4.75 (1H, ddd, J=5.5, 7.9, 14.2 Hz), 7.05 (2H, d, J=9.2 Hz), 7.47 (1H, d, J=8.5 Hz), 7.53 (1H, dd, J=7.9, 9.2 Hz), 7.57 (1H, dd, J=7.9, 8.5 Hz), 7.75 (1H, d, J=8.5 Hz), 7.94 (2H, d, J=9.2 Hz), 7.97 (1H, d, J=9.2 Hz), 8.02 (1H, d, J=8.5 Hz), 8.60 (1H, d, J=7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.7, 37.8, 49.0, 55.3, 113.5 (2C), 123.3, 124.7, 124.8, 125.3, 125.4, 125.6, 125.8, 126.1, 128.6, 129.2 (2C), 133.7, 136.5, 161.7, 165.6, 171.3. Anal. Calcd (found) for $C_{22}H_{20}N_2O_3$: C, 73.32 (73.14); H, 5.59 (5.63); N, 7.77% (7.74%).

4.4.17. 3,4-Dihydro-3-(2,4-dimethoxybenzoylamino)-1-methyl-2(1*H*)-benzo[*h*]quinolinone (2l). Yield, 30% (conversion, 70%). Mp 198.0–198.5 °C. IR (KBr): 3360, 1672, 1639 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.07 (1H, dd, J=14.4, 15.1 Hz), 3.41 (1H, dd, J=5.5, 15.1 Hz), 3.52 (3H, s), 3.85 (3H, s), 4.00 (3H, s), 4.58 (1H, ddd, J=5.5, 5.5, 14.4 Hz), 6.69 (1H, dd, J=2.1, 8.3 Hz), 6.73 (1H, d, J=2.1 Hz), 7.49 (1H, d, J=8.3 Hz), 7.54 (1H, dd, J=6.9, 7.6 Hz), 7.57 (1H, dd, J=6.9, 8.3 Hz), 7.77 (1H, d, J=8.3 Hz), 7.95 (1H, d, J=8.3 Hz), 7.98 (1H, d, J=7.6 Hz), 8.01 (1H, d, J=8.3 Hz), 8.95 (1H, d, J=5.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 33.6, 39.5, 51.5, 57.2, 57.9, 100.3, 107.7, 115.2, 125.0, 126.5, 126.8, 126.9, 127.2, 127.4, 127.6, 130.3, 134.4, 135.4, 138.1, 160.7, 164.9, 165.3, 172.8. Anal. Calcd (found) for $C_{22}H_{22}N_2O_4$: C, 70.75 (70.76); H, 5.68 (5.95); N, 7.17% (7.22%).

4.4.18. *cis*-4-Methylaminocarbonyl-5-(1-naphthyl)-2-phenyl-4,5-dihydrooxazole (3a). Yield, 5% (conversion, >99%). IR (KBr): 3244, 1651 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.03 (3H, d, J=4.9 Hz), 5.33 (1H, d, J=10.4 Hz), 6.80 (1H, d, J=10.4 Hz), 7.44 (1H, dd, J=7.3, 7.3 Hz), 7.47 (1H, d, J=7.3 Hz), 7.47 (1H, q, J=4.9 Hz), 7.53 (2H, m), 7.57 (2H, dd, J=7.3, 7.3 Hz), 7.65 (1H, dd, J=7.3, 7.3 Hz), 7.85 (1H, d, J=7.3 Hz), 7.92 (1H, d, J=7.3 Hz), 8.07 (2H, d, J=7.3 Hz), 8.07 (1H, d, J=7.3 Hz). ^{13}C NMR (500 MHz, DMSO-d_6): δ 25.0, 73.6, 80.2, 123.3, 123.8, 124.8, 125.5, 125.8, 127.1, 128.0, 128.2, 128.3 (2C), 128.6 (2C), 130.2, 132.0, 132.7, 132.9, 164.8, 167.9. EI-MS (*m*/*z*, %): 330 (M^{+}, 56.91).

4.4.19. *cis*-4-Aminocarbonyl-5-(1-naphthyl)-2-phenyl-4,5-dihydrooxazole (3h). Yield, 3% (conversion, 94%). IR (KBr): 3453, 3321, 1667 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.32 (1H, d, J=10.4 Hz), 6.67 (1H, s), 6.76 (1H, d, J=10.4 Hz), 7.02 (1H, s), 7.45 (1H, dd, J=7.3, 7.9 Hz), 7.53–7.51 (3H, m), 7.56 (2H, dd, J=6.7, 7.9 Hz), 7.63 (1H, dd, J=7.9, 7.9 Hz), 7.84 (1H, d, J=7.9 Hz), 7.91 (1H, d, J=7.3 Hz), 8.05 (2H, d, J=6.7 Hz), 8.05 (1H, d, J=7.9 Hz). ^{13}C NMR (500 MHz, DMSO-d_6): δ 73.2, 80.3, 123.6, 124.1, 125.1, 125.6, 126.0, 127.2, 128.1, 128.3 (3C), 128.7 (2C), 130.3, 132.0, 132.9, 133.0, 164.6, 169.6. EI-MS (*m*/*z*, %): 316 (M^{+}, 48.36).

4.4.20. *cis*-4-Benzylaminocarbonyl-5-(1-naphthyl)-2-phenyl-4,5-dihydrooxazole (3i). Yield, 10% (conversion, 96%). IR (KBr): 3265, 1657, 1645 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.77 (1H, dd, J=5.8, 15.3 Hz), 3.81 (1H, dd, J=6.1, 15.3 Hz), 5.47 (1H, d, J=10.7 Hz), 6.43 (2H, d, J=7.3 Hz), 6.83 (1H, d, J=10.7 Hz), 7.02 (2H, dd, J=7.0, 7.3 Hz), 7.07 (1H, dd, J=7.0, 7.0 Hz), 7.45 (1H, dd, J=7.6, 7.6 Hz), 7.59–7.53 (5H, m), 7.65 (1H, dd, J=7.3, 7.3 Hz), 7.90 (1H, d, J=7.6 Hz), 7.99–7.97 (1H, m), 8.08 (2H, d, J=8.6 Hz), 8.11–8.07 (1H, m), 8.13 (1H, dd, J=5.8, 6.1 Hz). ^{13}C NMR (500 MHz, DMSO-d_6): δ 41.6, 73.3, 80.4, 123.6, 123.9, 125.1, 125.6, 126.0, 126.2, 126.5 (2C), 127.1, 127.8 (2C), 128.1, 128.25 (2C), 128.3, 128.7 (2C), 130.2, 132.0, 132.6, 132.9, 137.6, 138.6, 164.7, 167.6. EI-MS (*m*/*z*, %): 406 (M^{+}, 32.06).

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References and notes

1. Mariano, P. S.; Stavinoha, J. L. *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1984; pp 145–257.
2. (a) Shin, C.; Yonezawa, Y.; Ikeda, M. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3573–3579. (b) Shin, C.; Takahashi, N.; Yonezawa, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2020–2023. (c) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487–490. (d) Effenberger, F.; Kuehlwein, J.; Hopf, M.; Stelzer, U. *Liebigs Ann. Chem.* **1993**, 1303–1311. (e) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1998**, *39*, 9575–9578. (f) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *Tetrahedron Lett.* **2000**, *41*, 7437–7441. (g) Sai, H.; Ogiku, T.; Ohmizu, H. *Synthesis* **2003**, 201–204.
3. (a) Shin, C.; Nakajima, Y.; Haga, T.; Sato, Y. *Bull. Chem. Soc.*

Jpn **1986**, *59*, 3917–3923. (b) Sato, Y.; Nakajima, Y.; Shin, C. *Heterocycles* **1992**, *33*, 589–595.

4. (a) Lewis, F. D.; Reddy, G. D. *J. Am. Chem. Soc.* **1989**, *111*, 6465–6466. (b) Lewis, F. D.; Reddy, G. D.; Bassani, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 6468–6469. (c) Lewis, F. D.; Bassani, D. M.; Reddy, G. D. *J. Org. Chem.* **1993**, *58*, 6390–6393. (d) Lewis, F. D.; Reddy, G. D.; Bassani, D. M.; Schneider, S.; Gahr, M. *J. Am. Chem. Soc.* **1994**, *116*, 597–605. (e) Lewis, F. D.; Bassani, D. M.; Burch, E. L.; Cohen, B. E.; Engleman, J. A.; Reddy, G. D.; Schneider, S.; Jaeger, W.; Gedeck, P.; Gahr, M. *J. Am. Chem. Soc.* **1995**, *117*, 660–669.
5. (a) Kubo, K.; Yaegashi, S.; Sasaki, K.; Sakurai, T.; Inoue, H. *Tetrahedron Lett.* **1996**, *37*, 5917–5920. (b) Kubo, K.; Koshiba, M.; Hoshina, H.; Sakurai, T. *Heterocycles* **1998**, *48*, 25–29. (c) Hoshina, H.; Kubo, K.; Morita, A.; Sakurai, T. *Tetrahedron* **2000**, *56*, 2941–2951. (d) Hoshina, H.; Turu, H.; Kubo, K.; Igarashi, T.; Sakurai, T. *Heterocycles* **2000**, *53*, 2261–2274. (e) Motohashi, T.; Maekawa, K.; Kubo, K.; Igarashi, T.; Sakurai, T. *Heterocycles* **2002**, *57*, 269–292.
6. (a) Sakurai, T.; Morioka, Y.; Maekawa, K.; Kubo, K. *Heterocycles* **2000**, *53*, 271–276. (b) Maekawa, K.; Igarashi, T.; Kubo, K.; Sakurai, T. *Tetrahedron* **2001**, *57*, 5515–5526.
7. Maekawa, K.; Sasaki, T.; Kubo, K.; Igarashi, T.; Sakurai, T. *Tetrahedron Lett.* **2004**, *45*, 3663–3667.
8. (a) Martinez, G. R.; Walker, K. A. M.; Hirschfeld, D. R.; Bruno, J. J.; Yang, D. S.; Maloney, P. J. *J. Med. Chem.* **1992**, *35*, 620–628. (b) Jones, C. D.; Audia, J. E.; Lawhorn, D. E.; McQuaid, L. A.; Neubauer, B. L.; Pike, A. J.; Pennington, P. A.; Stamm, N. B.; Toomey, R. E.; Hirsch, K. S. *J. Med. Chem.* **1993**, *36*, 421–423. (c) Nishikawa, T.; Omura, M.; Iizuka, T.; Saito, I.; Yoshida, S. *Arzneim.-Forsch./Drug Res.* **1996**, *46*, 875–878. (d) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658–667. (e) Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottorii, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177–189. (f) Butenschön, I.; Möller, K.; Hönsel, W. *J. Med. Chem.* **2001**, *44*, 1249–1256.
9. (a) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749–764. (b) Rzeszotarska, B.; Karolak-Wojciechowska, J.; Broda, M. A.; Galdecki, Z.; Trzezwinska, B.; Koziol, A. E. *Int. J. Pept. Protein Res.* **1994**, *44*, 313–319.
10. (a) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259–271. (b) Rehm, D.; Weller, A. Z. *Phys. Chem.* **1970**, *69*, 183–200.
11. (a) Lenz, G. R. *Synthesis* **1978**, 489–518. (b) Naruto, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1980**, *28*, 900–909. (c) Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 941–948. (d) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115–116. (e) Johnson, G. P.; Marples, B. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3399–3406. (f) Beck, A. L.; Mascal, M.; Moody, C. J.; Coates, W. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 813–821. (g) Rezaie, R.; Bremner, J. B.; Blanch, G. K.; Skelton, B. W.; White, A. H. *Heterocycles* **1995**, *41*, 959–972. (h) Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264–4270. (i) Nishio, T.; Asai, H.; Miyazaki, T. *Helv. Chim. Acta* **2000**, *83*, 1475–1483. (j) Zhao, H.; Thurkauf, A.; Braun, J.; Brodbeck, R.; Kieltyka, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2119–2122. (k) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516–7522. (l) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507–2514. (m) Feldman, K. S.; Cutarelli, T. D.; Florio, R. D. *J. Org. Chem.* **2002**, *67*, 8528–8537. (n) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747–2762.
12. (a) Ninomiya, I.; Naito, T. *Heterocycles* **1981**, *15*, 1433–1462. (b) Ninomiya, I.; Hashimoto, C.; Kiguchi, T.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2967–2971. (c) Naito, T.; Tada, Y.; Ninomiya, I. *Heterocycles* **1984**, *22*, 237–240.
13. Hatchard, C. G.; Parker, C. A. *Proc. R. Soc. London, Ser. A* **1956**, *235*, 518–536.

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Stereoselective oxazaborolidine–borane reduction of biphenyl methyl diketones: influence of biphenyl substitution pattern

Giovanna Delogu,[a,*] Maria Antonietta Dettori,[a] Angela Patti[b,*] and Sonia Pedotti[b]

[a] *Istituto di Chimica Biomolecolare del CNR—Sez. di Sassari, Traversa la Crucca 3, regione Baldinca, Li Punti, 07040 Sassari, Italy*
[b] *Istituto di Chimica Biomolecolare del CNR—Sez. di Catania, Via del Santuario 110, I-95028 Valverde CT, Italy*

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Abstract—The stereoselective oxazaborolidine–borane reduction of biphenyl methyl diketones with different substitution patterns on the biaryl unit was investigated, with the aim to better rationalize the factors influencing the diastereo- and enantioselectivity of the reaction for this class of compounds. The observed stereoselectivity in the reduction of diketones **6** and **7**, possessing a methoxy group in the *meta* position with respect to the carbonyl group, is clearly dependent on the experimental conditions. The presence of an asymmetric centre in the intermediate hydroxyketone influences the global stereoselectivity in the reduction of **5** and **6**, as indicated from the different selectivity ratios determined for each step of reaction.

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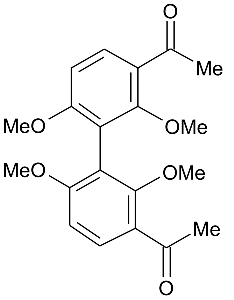
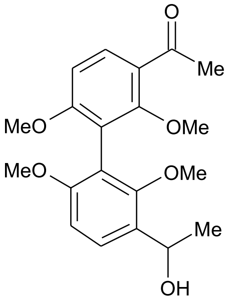
1. Introduction

Enantiopure biphenyl carbinols are valuable intermediates in the preparation of new ligands[1] and useful models for understanding the biosynthesis and stereochemistry of naturally occurring compounds which possess the biphenyl structure.[2] Recently, much progress has been made in the study of conformationally flexible hydroxylated biphenyls including their application in stoichiometric and catalytic asymmetric reactions.[3] It reflects the importance of the biphenyl unit in stereochemical control[4] and the efforts devoted to design new chiral configurationally flexible biphenyls, more available than the configurationally stable *ortho* tetrasubstituted biphenyls. In spite of the importance of biphenyl carbinols, an efficient method to synthesise these compounds in high chemical and optical yields is still required.

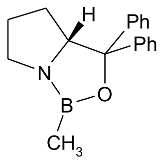
We have previously described the stereoselective reduction of conformationally stable diketone (±)-**1** using 60% mol of (*R*)-oxazaborolidine **2** as chiral catalyst and $BH_3 \cdot Me_2S$ as the hydride source. The reaction, that proceeded with satisfactory diastereoselectivity mainly dictated by the axial chirality of the substrate, allowed us to prepare the corresponding chiral carbinols in high chemical and optical yield according to the stereochemical outcome of the CBS reaction.[5] Selected experiments using diastereoisomeric monoketones (±)-**3** and (±)-**4** indicated a chiral cooperativity effect between the stereogenic axis and the first formed stereogenic centre at the biphenyl structure in the reduction reaction of (±)-**1**.



aR/*aS* **(±)-1**



aR,*S*/*aS*,*R* **(±)-3**
aR,*R*/*aS*,*S* **(±)-4**



(*R*)-**2**

The same procedure was then applied to conformationally flexible diketones **5** and **6**; in both cases enantiopure (*S*,*S*)-diols together with small amounts of *meso*-carbinols were

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Keywords: Diketones; Biphenyls; Oxazaborolidine; Asymmetric reduction.

* Corresponding authors. Tel.: +39-0957212136; fax: +39-0957212141 (A.P.); e-mail addresses: giovanna.delogu@icb.cnr.it; angela.patti@icb.cnr.it

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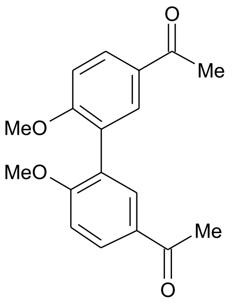
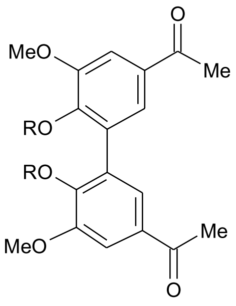
obtained.[6] Despite the different substitution pattern of the biphenyl backbone of **5** and **6**, the CBS-reduction proceeded with the same apparent stereoselectivity observed in the reduction of **1** and thus the developed protocol seemed generally applicable to biphenyldiketones.

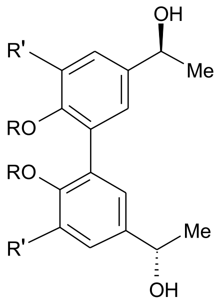
However, when we reduced the amount of the catalyst, we noticed marked differences in the reduction course of **5** and **6**. This finding prompted us to extend our investigation considering different experimental conditions as well as other substrates related to **5** and **6** with the aim to obtain a better understanding of the factors contributing to the global stereoselectivity of the CBS-reduction of the flexible C_2-symmetrical biphenyl methyl diketones.



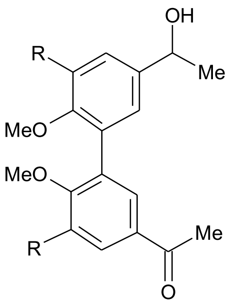
5



6 R = Me
7 R = Ac



R = Me R' = H (*S,S*)-**8**
R = Me R' = OMe (*S,S*)-**9**
R = Ac R' = OMe (*S,S*)-**10**



R = H (±)-**11**
R = OMe (±)-**12**

2. Results and discussion

2.1. Asymmetric reduction of biphenyl methyl diketones

In order to make the reported reduction of **5** and **6** to diols **8** and **9** more economic, we tried to decrease the amount of (*R*)-CBS with respect to the substrate while maintaining the chemical yield, diastereoselectivity and enantioselectivity previously reported.

When we reduced **5** using 20% mol of (*R*)-CBS the corresponding (*S*,*S*)-**8** was obtained in high yield and optical purity; a small increase in the amount of the *meso*-isomer was noted with respect to the reaction with 60% mol catalyst (Table 1, entries 1 and 2). The high stereoselectivity of the reaction was not substantially affected by further decrease in the amount of (*R*)-CBS to 10% mol (entry 3) so that enantiopure diol with a diastereomeric ratio 89:11 was isolated. The observed decrease in diastereoselectivity is in agreement with the generally accepted explanation that a decrease in the catalyst amount implies an increase in the unselective chemical reduction of carbonyl groups by borane itself.[7]

The use of 20% mol catalyst in the reduction of **6** resulted in a dramatic change of the reaction rate, so that after 24 h the starting diketone (20%) and the intermediate monoketone (*S*)-**12** (54%) were also present in the reaction mixture. Furthermore, the obtained diol **9** showed a high content of the *meso*-isomer (entry 6). Using an excess of $BH_3 \cdot Me_2S$ (2.5 equiv) exhaustive conversion of **6** was reached in 4 h, but the diastereomeric ratio was substantially unchanged (entry 7) allowing us to deduce that the uncatalyzed borane reduction of diketone was not responsible for all *meso*-isomer formation.[7a]

A parallel experiment of reduction of the racemic

Table 1. Asymmetric reduction of biphenylmethylketones[a]

Entry	Ketone	% mol (*R*)-CBS	Solvent	Time (h)	Conv. %[b]	Diol % ee[c]	dl/*meso* ratio[c]
1[d]	**5**	60	THF	0.5	100	>99	94:6
2	**5**	20	THF	1	100	>99	92:8
3	**5**	10	THF	3	100	98	89:11
4	**5**	20	Toluene	3	100	92	73:27
5[d]	**6**	60	THF	1	100	>99	96:4
6	**6**	20	THF	24	80[e]	96	79:21
7	**6**	20	THF[f]	4	100	>99	75:25
8	**6**	20	Toluene	3	100	>99	86:14
9	**11**	10	THF	3	100	65	56:44
10	**12**	10	THF	24	41	87	51:49
11	**7**	60	THF	1	100	>99	97:3
12	**7**	20	THF	3	100	98	81:19
13	**7**	20	Toluene	1	100	>99	87:13

[a] See Section 4.
[b] Determined by ^1H NMR of the reaction mixture.
[c] Determined by chiral HPLC analysis.
[d] Ref. 6.
[e] 54% of monoketone **12** was present in the reaction mixture.
[f] 2.5 equiv of borane were used.

hydroxyketone (±)-**12** (entry 10) indicated the resistance of this substrate to be converted into the corresponding diol and, after 24 h, 60% of unchanged (±)-**12** was isolated from the reaction mixture. Due to the racemic nature of the recovered **12**, it is easy to deduce that both enantiomers reacted at the same rate giving a (*S*,*S*)-diol with 87% ee and a 51:49 diastereomeric ratio.

We then considered diketone **7**, related to **6** by substitution of the *para*-methyl ether with an acetoxygroup, as substrate for the CBS-catalyzed asymmetric reduction. In a comparison between the corresponding 'monomers',[8] the asymmetric reduction of 3-methoxy-4-acetylacetophenone proceeded with better selectivity with respect to 3,4-dimethoxyacetophenone.

In agreement with our previous results, using the standard procedure with 60% mol of catalyst, excellent enantio- and diastereoselectivity were obtained in the reduction of **7** and diol (*S*,*S*)-**10** with >99% ee and 97:3 diastereoisomeric ratio was isolated in 90% yield (entry 11). However, as observed for **6**, the reduction of catalyst to 20% mol afforded a marked decrease in diastereoselectivity nevertheless the conversion of diketone **7** was complete in 3 h (entry 12).

From these data it seems clear that the presence of a methoxy group in the *meta*-position with respect to the carbonyl group has an influence on the stereoselective course of the CBS-catalysed reduction,[9] mainly evident when the amount of the catalyst is decreased. This effect could be due to sterical hindrance during the coordination of the substrate to the intermediate oxazaborolidine–borane complex since it is generally observed in substituted biphenyls that the influence of *meta* substituents is mainly related to steric factors.[10]

We then examined the CBS-catalysed (20% mol) reduction of diketones **5**–**7** in a different solvent; changing the reaction solvent from tetrahydrofuran to toluene,[11] the reduction of **6** and **7** in both cases proceeded with better diastereoselectivity and reaction rate (compare entries 6 and 8 for compound **6** and entries 12 and 13 for compound **7**) whereas the solvent effect was opposite for diketone **5** which in toluene afforded the corresponding diol **8** with markedly lower enantiomeric and diastereoisomeric purity (compare entries 2 and 4). As a possible explanation, the two oxygenated functionalities at the 5(5′) and 6(6′) positions (two methoxyl groups for compound **6** and a methoxyl group and an acetyl group for compound **7**) could be involved in coordination with the catalyst. This interaction, most stabilized in the more coordinating solvent THF, could remove the catalyst from the carbonyl group with consequent lowering of reaction rate and stereoselectivity.

2.2. Determination of the selectivity ratios

Although enantiopure dicarbinols are often obtained in the asymmetric reduction of symmetrical diketones, as a consequence of statistical multiplicative effect of the selectivities for each reduction step, the formation of the *meso* diastereomers cannot be overlooked.[7,12] Indeed, the observed diastereoselectivity is usually lower than expected from statistical argument based on the results for the related monoketones and in some instances an intramolecular hydride transfer of the initially formed –OBH_2 group to the vicinal carbonyl group in the intermediate ketoalcohol has been invoked.[13] Other authors suggested that the uncatalysed reduction by free borane has higher significance for the more reactive diketones with respect to simple monoketones.[7c]

However, the asymmetric reduction of a diketone could not be considered merely a sum of two independent steps because the first introduced stereocentre on the intermediate hydroxyketone could influence the stereoselectivity of second carbonyl group reduction, so that the final diastereoselectivity could be intrinsically due to a difference in the selectivities rather than a competing chemical pathway.

A mathematical relationship between the diastereo- and enantiomeric excesses of a diol obtained from the CBS-reduction of a prochiral C_2-symmetrical diketone has been recently described by Kagan[14] under the assumption that the enantioselectivity in the first reduction step and the diastereoselectivities in the second one are the same.

$$\mathrm{Ee_{diol}} = \frac{2\sqrt{\mathrm{De}}}{(1+\mathrm{De})} \tag{1}$$

In a general and complementary approach, the enantiomeric excess and the diastereomeric ratio of the diol obtained from the reduction of a prochiral C_2-symmetrical diketone with a catalyst with *S* stereopreference, can be expressed as a function of the selectivity ratios for each reduction step, defined as

$$A_1 = \frac{[S]}{[R]};\ A_2 = \frac{[SS']}{[SR']} \text{ and } A_3 = \frac{[RS']}{[RR']}$$

where *R* and *S* refer to the configuration of the first carbinolic center and *S′* and *R′* to the second one (see Scheme 1). The enantiomer ratio (Er) and diastereomer ratio (Dr) of the obtained diol are given by the following equations:

$$\mathrm{Er} = \frac{SS'}{RR'} = A_1\frac{A_2}{A_2+1}(A_3+1) \tag{2}$$

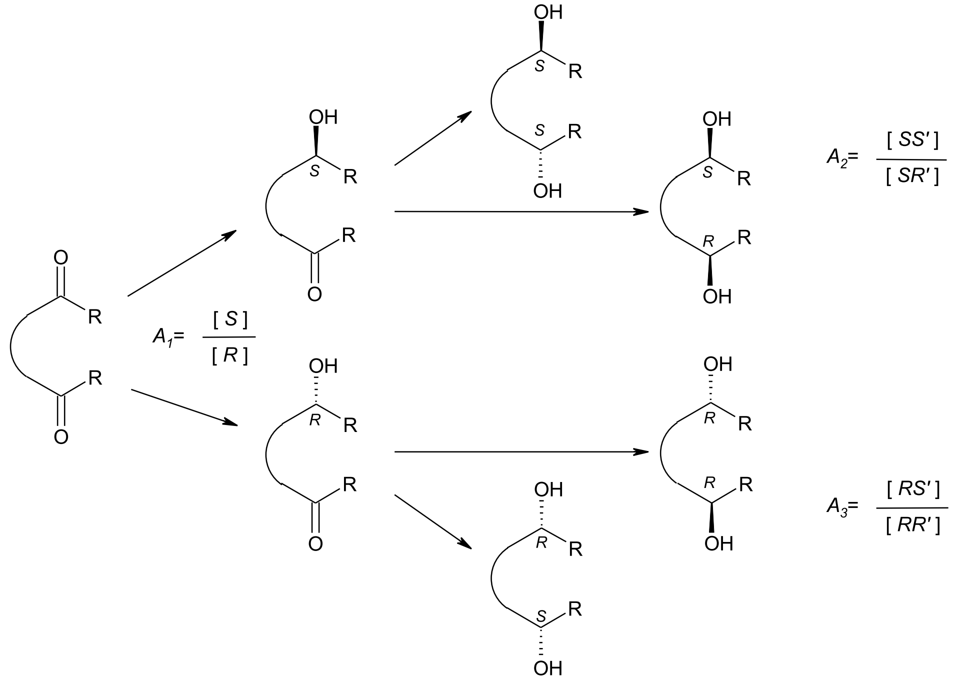
$$\mathrm{Dr} = \frac{SS'+RR'}{RS'+SR'} = \frac{\frac{A_1A_2}{1+A_2}+\frac{1}{1+A_3}}{\frac{A_1}{1+A_2}+\frac{A_3}{1+A_3}} = \frac{A_2(\mathrm{Er}+1)}{(\mathrm{Er}+A_2A_3)} \tag{3}$$

where Er and Dr are easily derived from the experimental data by

$$\mathrm{Er} = \frac{1+\mathrm{Ee}}{1-\mathrm{Ee}};\ \mathrm{Dr} = \frac{1+\mathrm{De}}{1-\mathrm{De}}$$

Since in the Eq. 2 the term A_2/A_2+1 tends to 1 increasing the A_2 value, the final Er value depends linearly on A_1 and A_3, the most influence being due to the selectivity in the first step of reaction.[15]

The optimal value of Dr, compatible with a satisfactory Er, depends on an appropriate balance of A_2 and A_3 and, for a defined A_1 selectivity, the amount of *meso*-isomer is



Scheme 1. Stereochemical distribution of the formed products in the asymmetric reduction of a symmetric prochiral diketone.

minimized for high values of A_2 and low values of A_3; however, too low A_3 selectivity directly affects the optical purity of the chiral diols.

Due to the impossibility to evaluate the individual amounts of RS' and SR' indistinguishable diols in the final reaction mixture the simultaneous determination of the three selectivity ratios is not possible in the asymmetric reduction of C_2-symmetrical diketones, but when the related racemic hydroxyketone is reacted in the same conditions used for a diketone, the determination of diastereo- and enantiomeric composition of the obtained diol could allow calculation of A_2 and A_3.

These A_2 and A_3 ratios describe the stereoselectivity of the reduction of one carbonyl group under the influence of the chirality of a carbinolic function present on the same molecule and it could be assumed that, in the same way, they express the stereoselectivity of the second step of the reduction of a symmetrical diketone. Under this assumption, applying these A_2 and A_3 values and the experimental Er of the diol obtained from the reduction of diketone to Eq. 2, the A_1 ratio can be calculated.

As an example of this approach, we reduced hydroxyketone (±)-**11** in the presence of 10% mol of CBS-catalyst and, from the enantio- and diastereomeric ratios of the obtained (*S*,*S*)-**8** (see entry 9), we calculated

$$A_2 = \frac{[SS']}{[SR']} = 12.1 \text{ and } A_3 = \frac{[RS']}{[RR']} = 4.1$$

When these values were used in Eq. 2 applying the experimental Er for the reaction of entry 2, the A_1 ratio was derived as

$$A_1 = \frac{[S]}{[R]} = >42.2$$

In the same way, the combination of the data obtained in the reduction of hydroxyketone (±)-**12** (entry 10) and diketone **6** (entry 6) using the same amount of catalyst/carbonyl group, allowed us to calculate the selectivity ratios

$$A_1 = 3.4,\ A_2 = 20.6 \text{ and } A_3 = 14.1$$

On the basis of the determined selectivity ratios, some important considerations arise:

(a) although the hydroxyl group of (±)-**11** or (±)-**12** is quite distant from the carbonyl moiety, a long range influence of its stereochemistry could be deduced from the difference in the A_2 and A_3 selectivity ratios;

(b) the high stereoselectivity observed in the reduction of **5** with respect to **6** could be explained taken into account the marked difference (about 10-fold) in the corresponding A_1 values. Due to the multiplicative effect of the selectivity ratios, the enantiomeric excess of the obtained diols is quite satisfactory in both cases, but not the diastereomeric ratio;

(c) in the diketone **6**, the presence of a methoxy group in the *meta* position with respect to the carbonyl group mainly influences the first step of reduction rather the second one, that proceeded with better selectivity ratios. This finding could be in agreement with a faster uncatalyzed reduction of the first carbonyl group by the free borane with respect the second one, as suggested by some authors;[7c]

(d) the significance of this uncatalyzed reduction seems to be minimized in the diketone **5**, where the absence of the *meta*-substituent could promote a more efficient coordination of the diketone with the oxazaborolidine–borane complex and the subsequent asymmetric hydride transfer.

3. Conclusions

We have reviewed the (*R*)-CBS-catalyzed asymmetric reduction of biphenylmethylketones **5** and **6** under different experimental conditions and extended our protocols to the related diketone **7**. The reduction of **5** proceeded with satisfactory stereoselectivity also in the presence of 10% mol (5% equiv) of catalyst. In the reduction of diketones **6** and **7**, possessing a *meta*-substituent with respect to the carbonyl group, the amount of *meso*-isomer contaminating the optically active diols is clearly dependent on the experimental conditions. An interesting improvement in the reactivity, enantioselectivity and diastereoselectivity was observed in the reduction of biphenyls **6** and **7** when the reaction was carried out in toluene with respect to THF.

The quantitative relationship between the experimental enantio- and diastereomeric ratio and the corresponding selectivity ratios for each step of the reduction have been developed and discussed.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance™ 400 spectrometer Chemical shift (δ) are given as ppm relative to the residual solvent peak. Coupling constants (J) are in Hz. Optical rotations were measured on a DIP 135 JASCO instrument. THF and toluene were distilled under argon from sodium benzophenone ketyl. (*R*)-Methyl-CBS–oxazaborolidine, (*R*)-CBS, was purchased from Aldrich as 1 M solution in toluene. All the CBS-catalyzed reactions were carried out under argon using standard Schlenk techniques. Column chromatography was performed on silica gel 60 (70–230 mesh) using the specified eluants. Chiral HPLC analyses were carried out on Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane/*iso*-propanol mixtures as a mobile phase and detection by UV–vis detector at 225 nm.

4.2. General procedure for the asymmetric reduction

In a typical procedure, (*R*)-CBS (0.36 mmol, 0.36 mL of 1 M solution in toluene) was dissolved in THF (8 mL) under argon and cooled to 0 °C. From a syringe charged with $BH_3 \cdot Me_2S$ (2 M in THF, 0.6 mL, 1.2 mmol) dissolved in 8 mL of THF, 20% of the final amount was added to the catalyst solution. After 10 min of stirring, the remaining $BH_3 \cdot Me_2S$ and a solution of diketone (0.6 mmol in 10 mL of THF) were simultaneously added by syringe pump within 20 min. The reaction mixture was then stirred at room temperature and stopped when quantitative conversion of the substrate was observed by TLC analysis. At the completion, the reaction was quenched by careful dropwise addition of MeOH (2 mL), diluted with sat. NH_4Cl (50 mL) and extracted with AcOEt (3×30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum to give a residue that was purified by column chromatography.

4.2.1. 1,1′-[5,5′-Dimethoxy-6,6′-diacetoxy-1,1′-biphenyl-3,3′-diyl]diethanone, 7. To a suspension of 1,1′-[6,6′-dihydroxy-5,5′-dimethoxy-1,1′-biphenyl-3,3′-diyl]diethanone (0.5 g, 1.5 mmol) in dry pyridine (10 mL), acetyl chloride (0.36 g, 4.5 mmol) was added dropwise. The mixture was stirred at rt for 6 h then treated with 10% HCl until pH 3 and extracted with CH_2Cl_2 (3×30 mL). The organic phases were collected, dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash chromatography (pentane:AcOEt 60:40, R_f 0.35) to obtain diketone **7** (0.41 g, 66% yield) as white solid, mp 208–209 °C; IR (KBr) 2941, 1765, 1686, 1591, 1369, 1197 cm^{-1}; ^{1}H NMR: δ 2.12 (6H, s, OAc), 2.58 (6H, s, MeCO), 3.93 (6H, s, OMe–), 7.47 (2H, d, $J=2.0$ Hz, 2×Ar-H), 7.64 (2H, d, $J=2.0$ Hz, 2×Ar-H); ^{13}C NMR: δ 19.5, 25.7, 55.5, 110.2, 122.8, 130.0, 134.5, 140.9, 150.9, 167.2, 195.9. Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.95; H, 5.40%.

4.2.2. (1*S*,1′*S*)-1,1′-[5,5′-Dimethoxy-6,6′-diacetoxy-1,1′-biphenyl-3,3′-diyl]diethanol, (−)-10. Asymmetric reduction of diketone **7** according the general procedure described above (60% mol of catalyst) afforded diol (−)-**10** as a glassy solid in 85% isolated yield, $R_f=0.26$ (CH_2Cl_2/AcOEt 60:40); >99% ee; 97:3 diastereoisomeric ratio; $[\alpha]_D=-22.3$ (*c* 1.42, $CHCl_3$); IR (liquid film) 3414, 2972, 1762, 1591, 1370, 1200 cm^{-1}; ^{1}H NMR: δ 1.53 (6H, d, $J=6.4$ Hz, *Me*CH–), 2.11 (6H, s, OAc–), 3.89 (6H, s, OMe–), 4.91 (2H, q, $J=6.4$ Hz, C*H*OH–), 6.83 (2H, d, $J=1.9$ Hz, 2×Ar-H), 7.07 (2H, d, $J=1.9$ Hz, 2×Ar-H); ^{13}C NMR: δ 21.1, 25.9, 56.7, 70.8, 109.5, 120.1, 131.9, 137.3 144.7, 152.0, 169.4. HPLC: *n*-hexane/2-PrOH 85:15, flow rate 0.5 mL/min, t_R/min=20.9 (1*S*,1′*S*), 23.1 (1*R*, 1′*S*), 28.2 (1*R*,1′*R*) Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.28; H, 6.28%.

4.2.3. 1-[3′-(1-Hydroxyethyl)-6,6′-dimethoxy-1,1′-biphenyl-3-yl]ethanone, (±)-11. Compound **5** (500 mg, 1.65 mmol) was dissolved in THF (10 mL) and a solution of $NaBH_4$ (26 mg, 0.7 mmol) in MeOH (1 mL), was added dropwise. The reaction mixture was stirred at rt and after 2 h diols began to be detected by TLC analysis. The excess of $NaBH_4$ was quenched with MeOH (2 mL) and the reaction mixture diluted with H_2O (15 mL) and extracted with AcOEt (2×20 mL). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a residue that was purified on silica gel column eluting with CH_2Cl_2/AcOEt 80:20 to give (±)-**11** as a viscous oil, (280 mg, 57% yield). Unreacted diketone **5** and diol (±)-**8** were discarded. $R_f=0.34$ (CH_2Cl_2/AcOEt 80:20); IR (liquid film) 3413, 2968, 1672, 1597, 1249 cm^{-1}; ^{1}H NMR: δ 1.27 (3H, d, $J=6.4$ Hz *Me*CH–), 2.58 (3H, s, *Me*CO), 3.78 (3H, s, OMe–), 3.85 (3H, s, OMe–), 4.90 (1H, q, $J=6.4$ Hz, –C*H*OH), 6.97 (1H, d, $J = 8.4$ Hz, Ar-H), 7.02 (1H, d, $J = 8.6$ Hz, Ar-H), 7.26 (1H, d, $J = 2.1$ Hz, Ar-H), 7.39 (1H, dd, $J = 8.4$, 2.1 Hz, Ar-H), 7.88 (1H, d, $J = 2.2$ Hz, Ar-H), 8.00 (1H, dd, $J = 8.6$, 2.2 Hz, Ar-H); ^{13}C NMR: δ 24.8, 26.2, 55.7, 69.7, 110.2, 110.9, 125.0, 126.6, 127.6, 128.5, 129.7, 129.8, 131.0, 137.6, 156.3, 160.9, 196.7. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.09 H, 6.77%.

4.2.4. 1-[3′-(1-Hydroxyethyl)-5,5′,6,6′-tetramethoxy-1,1′-biphenyl-3-yl]ethanone, (±)-12. Reduction of diketone **6** (500 mg 1,38 mmol) with $NaBH_4$ according to the procedure described above afforded a residue that was purified on silica gel column (CH_2Cl_2/AcOEt 80:20) to afford pure (±)-**12** as a viscous oil (300 mg, 60% yield); $R_f = 0.30$ (CH_2Cl_2/AcOEt 80:20); IR (liquid film) 3418, 2966, 2937, 1678, 1580, 1362, 1280, 1146 cm^{-1}; ^{1}H NMR δ 1.54 (3H, d, $J = 6.4$ Hz, *Me*CH–), 2.58 (3H, s, *Me*CO), 3.65 (3H, s, OMe–), 3.77 (3H, s, OMe–), 3.96 (3H, s, OMe–), 3.98 (3H, s, OMe–) 4.91 (1H, q, $J = 6.4$ Hz, –C*H*OH), 6.86 (1H, d, $J = 1.9$ Hz, Ar-H), 7.05 (1H, d, $J = 1.9$ Hz, Ar-H), 7.51 (1H, d, $J = 1.9$ Hz, Ar-H), 7.6 (1H, d, $J = 1.9$ Hz, Ar-H); ^{13}C NMR: δ 25.2, 26.4, 55.9, 55.9, 60.6, 60.8, 109.1, 110.5, 119.8, 125.1, 131.7, 132.0, 132.4, 141.3, 151.2, 152.8, 152.8. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.81; H, 6.76%.

Acknowledgements

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References and notes

1. (a) Weber, E.; Skobridis, K.; Wierig, A.; Stathi, S.; Nassimbeni, L. R.; Niven, M. L. *Angew. Chem. Int., Ed. Engl.* **1993**, *32*, 606–608. (b) Fabris, F.; De Lucchi, O. *J. Org. Chem.* **1997**, *62*, 7156–7164. (c) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem. Int., Ed.* **1997**, *36*, 2768–2771. (d) Longmire, J. M.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 375–378. (e) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *J. Org. Chem.* **2000**, *65*, 3326–3333. (f) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91–94.
2. (a) Elix, J. A.; Jayanthi, V. K.; Jones, A. J.; Lennard, C. J. *Aust. J. Chem.* **1984**, *37*, 1531–1538. (b) Uchida, I.; Shigematsu, N.; Ezaki, M.; Hashimoto, M.; Aoki, H.; Imanaka, I. *J. Antibiot.* **1985**, *38*, 1462–1468. (c) Abe, F.; Yamauchi, T.; Wan, A. S. C. *Phytochemistry* **1989**, *28*, 3473–3476. (d) Hanawa, F.; Shiro, M.; Hayashi, Y. *Phytochemistry* **1997**, *45*, 589–596. (e) Tene, M.; Wabo, H. K.; Kamnaing, P.; Tsopmo, A.; Tane, P.; Ayafor, J. F.; Sterner, O. *Phytochemistry* **2000**, *54*, 975–978. (f) Syrjänen, K.; Sipila, J.; Björk, H.; Brunow, G. *J. Agric. Food Chem.* **2000**, *48*, 5211–5215. (g) Syrjänen, K.; Brunow, G. *Tetrahedron* **2001**, *57*, 365–370.
3. (a) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625–1634. (b) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **1999**, *8*, 1319–1321. (c) Bartels, B.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1999**, 741–742. (d) Superchi, S.; Casarini, D.; Laurita, A.; Bavoso, A.; Rosini, C. *Angew. Chem. Int., Ed.* **2001**, *40*, 451–454. (e) Pàmies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 1097–1108. (f) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91–94.
4. Mikami, K.; Yamanaka, M. *Chem. Rev.* **2003**, *103*, 3369–3400.
5. Delogu, G.; Fabbri, D.; de Candia, C.; Patti, A.; Pedotti, S. *Tetrahedron: Asymmetry* **2002**, *13*, 891–898.
6. Delogu, G.; Dettori, M. A.; Patti, A.; Pedotti, S.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2467–2474.
7. (a) Quallich, G. J.; Keavey, K. N.; Woodall, T. M. *Tetrahedron Lett.* **1995**, *36*, 4729–4732. (b) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Manzanal, J.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1091–1094. (c) Bach, J.; Berenguer, R.; Garcia, J.; Lopez, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**, *54*, 14947–14962. (d) Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883–3886.
8. Ponzo, V. L.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105–9108.
9. The reduction of 4-methoxyacetophenone with CBS catalyst gave 4-methoxy-α-methylbenzenemethanol with >99% ee. Mathre, D. J.; Thompson, A. S.; Douglas, K. H.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880–2888. Using the same procedure 3,4-dimethoxyacetophenone gave the corresponding alcohol with 88% ee (see Ref. 8).
10. Wolf, C.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, 357–363.
11. (a) Corey, E. J.; Cheng, X.-M.; Cimprich, K. A.; Sarshar, S. *Tetrahedron Lett.* **1991**, *32*, 6835–6838. (b) Manju, K.; Trehan, S. *Tetrahedron: Asymmetry* **1998**, *9*, 3365–3369. (c) Ponzo, V. L.; Kaufman, T. S. *Synlett* **2002**, *7*, 1128–1130.
12. (a) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409–418. (b) Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265–10274. (c) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950–968.
13. Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888–3889.
14. Lagasse, F.; Tsukamoto, M.; Welch, C. J.; Kagan, H. B. *J. Am. Chem., Soc.* **2003**, *125*, 7490–7491.
15. Under the assumption of Kagan, i.e. $A_1 = A_2 = A_3$, $\mathrm{Er} = A^2$; $\mathrm{Dr} = (A^2 + 1)/2A$ and the Eq. 1 is satisfied.

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Studies on the catalytic hydrogenation of Baylis–Hillman derivatives of substituted isoxazolecarbaldehydes. Unusual retention of isoxazole ring during Pd–C-promoted hydrogenation of Baylis–Hillman adducts☆,☆☆

R. Saxena, V. Singh and S. Batra*

Medicinal Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226 001, India

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Abstract—Results of the catalytic hydrogenation of Baylis–Hillman adducts obtained from substituted 3-, 4- and 5-isoxazolecarboxaldehydes and their corresponding acetates in the presence of Raney-Ni and Pd–C are presented. The hydrogenation of Baylis–Hillman adducts of substituted 5-isoxazolecarbaldehydes and 3-isoxazolecarbaldehydes in the presence of Raney-Ni furnishes diastereoselectively *syn* enaminones over *anti* and in the presence of boric acid as an additive further enhancement of diastereoselectivity in favor of *syn* isomer is observed. The Pd–C-promoted hydrogenation of these substrates is also diastereoselective in favor of *syn* isomer but occurs without the hydrogenolysis of isoxazole-ring. The presence of boric acid as an additive in this hydrogenation exhibits no pronounced effect on diastereoselectivity. The Raney-Ni-mediated hydrogenation of Baylis–Hillman adducts of substituted 4-isoxazolecarbaldehydes yield pyridone derivatives and Pd–C-promoted hydrogenation of the same substrate is diastereoselective to afford the *anti* isomer of the resulting products. The enaminones derived from Baylis–Hillman adducts of 3- and 5-isoxazolecarbaldehydes serve as versatile precursors for α'-hydroxy-1,3-diketones, which undergo acid-catalyzed ring-closure reaction to afford the furanone derivatives in excellent yields.

1. Introduction

The isoxazole heterocycle represents masked β-enaminone and 1,3-dione systems because of the lability of the N–O bond towards catalytic and chemical reductions under mild conditions.[1–5] This ability of the isoxazole-ring besides making it a useful synthetic intermediate also evokes interest to understand reasons for biological activity because our interest in the Baylis–Hillman chemistry of isoxazolecarbaldehydes has not only led us to generate novel isoxazole-based synthetic intermediates but has also led to identification of bioactive compounds.[6–10]

The hydrogenation studies of the Baylis–Hillman adduct and their corresponding derivatives under heterogeneous catalytic conditions with Pd–C and rhodium have been earlier reported.[11–14] While these detailed studies address the issue of diastereoselectivity in the reduced product under different additives and solvent conditions, the fate of the Baylis–Hillman adducts during hydrogenation in the presence of Raney-Ni remains unreported. Since the isoxazole ring is known to undergo hydrogenolysis in the presence of Raney-Ni and Pd–C,[15–18] it was desired to evaluate the effect of these catalysts on the Baylis–Hillman adducts of substituted isoxazolecarbaldehydes. During the course of this study we have noted some unusual and interesting observations, which prompt us to report our findings.

2. Results and discussion

The hydrogenation of the Baylis–Hillman adducts **2a–c** and **3b**, originating from substituted 5-isoxazolecarbaldehydes **1a–c**, in the presence of Raney-Ni in appropriate solvent led to diastereoisomeric mixtures of the enaminones **4a–c** and **5b**, respectively (Scheme 1). Beside other spectroscopic evidence, the opening of the isoxazole-ring was characterized by the presence of two broad singlets for NH_2 protons and an upfield shift of the isoxazole =CH proton from δ

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☆☆ Presented in portion as poster at IUPAC-BNP-2004, 26th–31st, January, 2004. PN-342.

Keywords: Baylis–Hillman; Isoxazolecarbaldehyde; Hydrogenation; Raney-Ni; Pd–C; Enaminones; Furanone.

* Corresponding author. Tel.: +91-522-2212411-18x4368; fax: +91-522-2223405,2223938; e-mail: batra_san@yahoo.co.uk

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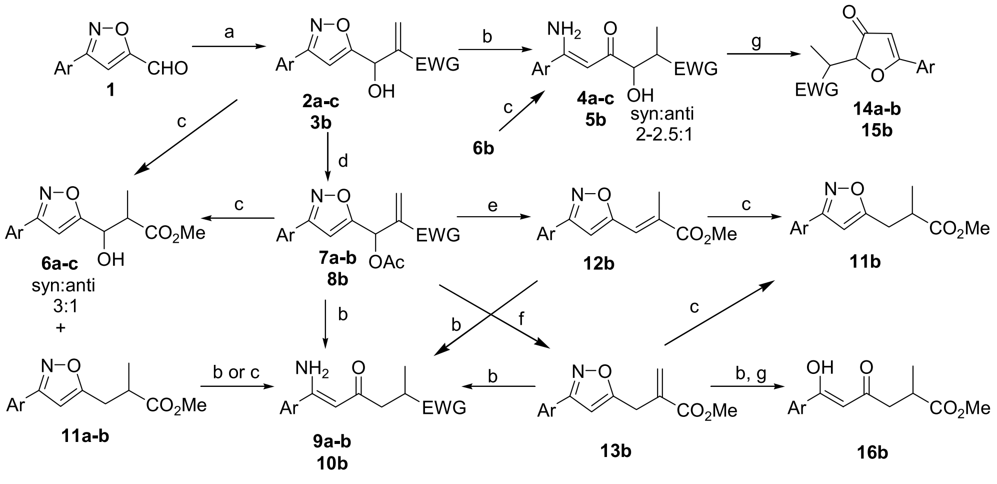


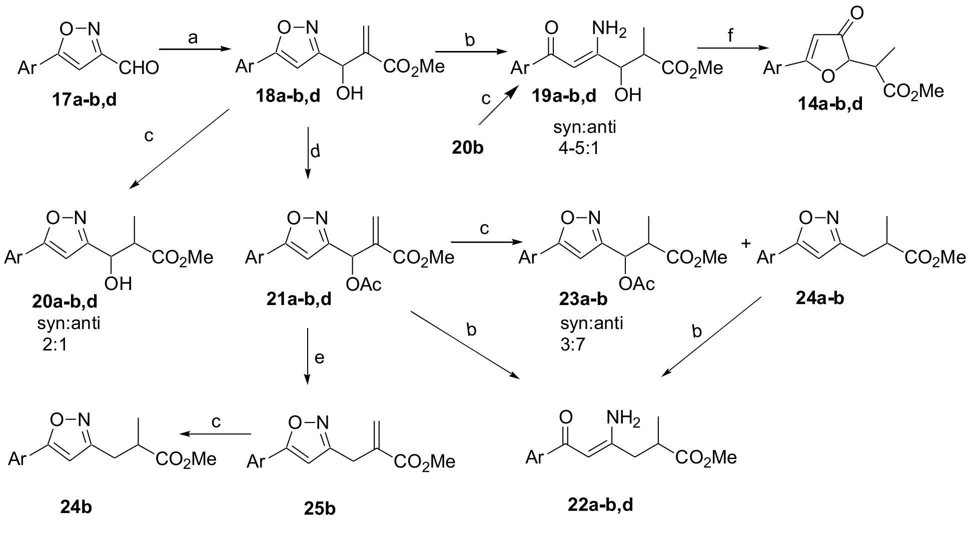
No.	EWG
2, 4, 7, 9, 14	CO_2Me
3, 5, 8, 10, 15	CO_2Et

No.	Ar
a	C_6H_5
b	4-Me-C_6H_4
c	2-Cl-C_6H_4
d	4-Cl-C_6H_4

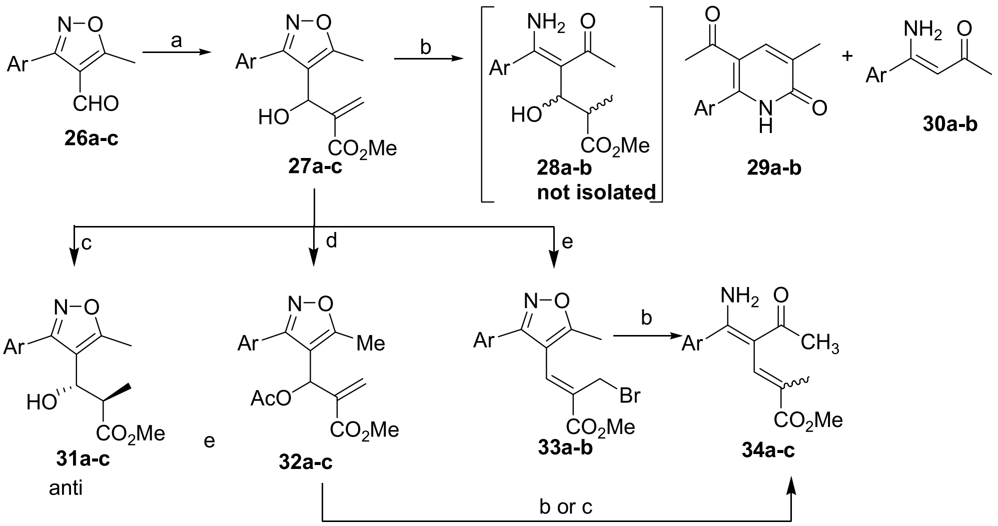
For all schemes

Scheme 1. Reagents and conditions (a) $CH_2{=}CHEWG$, DABCO, 30 min (b) Raney-Ni, H_2 (balloon at rt or Parr assembly at 30 psi), MeOH, 3 h (c) Pd–C, H_2, (balloon at rt or Parr assembly at 30 psi), MeOH or EtOAc, 2–2.5 h (**6b** to **4b**, 10 h) (d) CH_3COCl, pyridine, CH_2Cl_2, rt, 3–5 h (e) $NaBH_4$, MeOH, rt, 2 h (f) DABCO, $NaBH_4$, THF: H_2O (1:1), rt, 15 min (g) H^+ (HCl, H_2SO_4, CH_3CO_2H at rt, or mixture of HCO_2H and CH_3CO_2H at 60 °C), 24 h.

6.5–5.5 of enaminone in the ^{1}H NMR spectrum. The hydrogenation of **3b** in particular aimed to understand the influence of the ester group on the outcome of hydrogenation. The analyses of the stereochemistry of the hydrogenation products were based on their ^{1}H NMR spectra, which revealed *syn* selectivity over the *anti* products in the range of 2–2.5:1. Compared to these observations, the Pd–C promoted catalytic hydrogenation of compounds **2a–c** using methanol or ethyl acetate as solvent gave diastereoisomeric mixture of products **6a–c**. The absence of the signal for the amino group of the enamine and the unchanged chemical shift of the $=$CH proton of the isoxazole-ring in the ^{1}H NMR spectra coupled with mass spectra of these compounds indicated that only the reduction of the methylene group had occurred with retention of isoxazole-ring. This result was contrary to the previous literature reports where hydrogenolysis of the isoxazole ring under similar conditions has been reported.[19–21] In these cases, the reaction was also diastereoselective in favor of *syn* isomer over *anti* (ratio of 3:1). In our attempts to understand this unusual behavior, the Pd–C-mediated hydrogenation was carried out under different conditions. In the first instance in a representative example, the Pd–C promoted hydrogenation of compound **2b** was continued for more than 24 h but no hydrogenolysis was observed and compound **6b** was isolated exclusively. Thereafter, the reaction was carried out with an excess of catalyst (ca. 3–5 fold) without any success. Successively, the compound **6b** was again subjected to hydrogenation in the presence of Pd–C. Interestingly this reaction was completed within 10 h to



Scheme 2. Reagents and conditions (a) $CH_2{=}CHCO_2Me$, DABCO, 30 min (b) Raney-Ni, H_2 (balloon at rt or Parr assembly at 30 psi), MeOH, 3 h (c) Pd–C, H_2, (Balloon at rt or Parr assembly at 30 psi), MeOH or EtOAc, 2–2.5 h, (**20b** to **19b**, 10 h) (d) CH_3COCl, pyridine, CH_2Cl_2, rt, 2–3 h (e) DABCO, $NaBH_4$, THF: H_2O (1:1), rt, 15 min (f) H^+ (HCl, H_2SO_4, CH_3CO_2H at rt, or mixture of HCO_2H and CH_3CO_2H at 60 °C), 24 h.



Scheme 3. Reagents and conditions (a) $CH_2=CHCO_2Me$, DABCO, 2d (b) Raney-Ni, H_2 (balloon at rt or Parr assembly at 30 psi), MeOH, 3 h (c) Pd–C, H_2, (balloon at rt or Parr assembly at 30 psi), MeOH or EtOAc, 2–2.5 h (d) CH_3COCl, pyridine, CH_2Cl_2, rt, 1 h (e) PBr_3, CH_2Cl_2, rt, 45 min.

yield the hydrogenolysis products **4b** exclusively. In view of these results, we next examined the hydrogenation of the Baylis–Hillman adducts of 3- and 4-isoxazolecarbaldehydes. Similar to reactions of the Baylis–Hillman adducts of 5-isoxazolecarbaldehydes, the hydrogenation of the Baylis–Hillman adducts (**18a**–**b**, **d**), derived from substituted 3-isoxazolecarbaldehydes (**17a**–**b**, **d**) in the presence of Raney-Ni led to isolation of envisaged enaminones (**19a**–**b**, **d**) in good yields (Scheme 2). The observed diastereoselectivity in favor of *syn* isomer over the *anti* isomer was slightly better as compared to the enaminones derived from Baylis–Hillman derivatives of 5-isoxazolecarbaldehydes because the ratio ranged from 4 to 5:1. The hydrogenation of adducts **18a**–**b**, **d** in the presence of Pd–C afforded diastereoisomeric mixtures (*syn*:*anti*, 2:1) of products **20a**–**b**, **d** without the hydrogenolysis of the isoxazole ring. However when compound **20b** was again subjected to hydrogenation, the hydrogenolysis of the isoxazole-ring did occur to afford enaminone **19b**. Interestingly when the Baylis–Hillman adducts (**27a**–**b**), derived from substituted 4-isoxazolecarbaldehydes, were subjected to hydrogenation in the presence of Raney-Ni; the envisaged enaminones (**28a**–**b**) could not be isolated. The two products isolated from the reaction were identified as substituted pyridones **29a**–**b** and enaminones **30a**–**b** (Scheme 3). The formation of the minor product namely the pyridone derivative (**29a**–**b**) can be rationalized on the basis of hydrogenolysis of the isoxazole ring followed by ring closure involving the amino and the ester group followed by dehydration.[22] The plausible explanation for the formation of compound **30** is shown in Figure 1. However the hydrogenation of compounds **27a**–**c** in the presence of Pd–C was stereospecific to afford the *anti* isomer of products **31a**–**c** without the cleavage of the isoxazole-ring. Since enaminones **28a**–**b** were not isolated during the hydrogenolysis of compounds **27a**–**b**, no attempts were made to carry out Pd–C-promoted hydrogenolysis of compounds **31a**–**c**.

In the next stage of the study we directed our attention towards evaluating the effect of hydrogenation on the acetates derived from the Baylis–Hillman adducts of substituted isoxazolecarbaldehydes. The Raney-Ni promoted hydrogenolysis of acetates **7a**–**b** and **8b** led to enaminones **9a**–**b** and **10b**, respectively (Scheme 1). Such products may have resulted via hydrogenolysis of the isoxazole-ring with simultaneous loss of acetic acid followed by the reduction of the double bond in the intermediate. In principle, a product similar to compound **9** could be generated from compound **12** or **13**, which in turn can be easily synthesized through reaction of sodium borohydride with the acetate (**7**) under appropriate conditions.[9,10] In order to obtain chemical evidence for the formation of compounds **9**–**10**, compounds **12b** and **13b** were subjected to hydrogenation in the presence of Raney-Ni. As envisaged both reactants led to the product **9b** in good yield. To evaluate the fate of hydrogenation in the presence of Pd–C, acetates **7a**–**b** were subjected to hydrogenation in the presence of this catalyst. Unlike the corresponding Baylis–Hillman adduct (**2a**–**b**), the acetates (**7a**–**b**) invariably furnished a separable mixture of two products. The non-polar products were identified as **11a**–**b** while the polar products were **6a**–**b** (Scheme 1). The formation of compounds **11a**–**b** could be rationalized based on a similar mechanism for compounds **9**–**10** except for the cleavage of the isoxazole-ring. As reported earlier[13] compound **6** may have resulted from simple reduction of

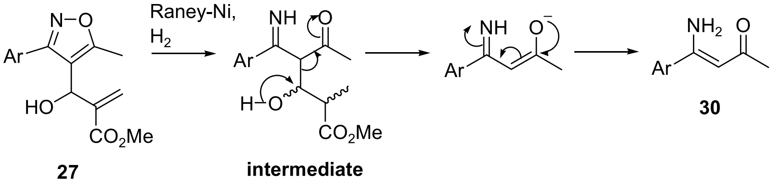


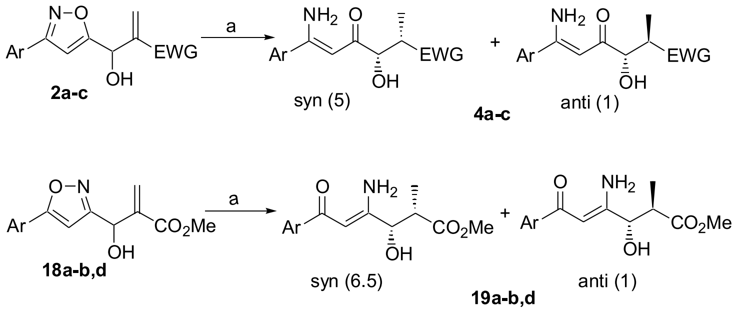
Figure 1.

the double bond with simultaneous deacetylation. In accordance with the literature precedence,[13] we too did not observe diastereoselectivity during the formation of product **6**. The additional chemical evidence for the formation of product **11** was achieved by Pd–C-mediated hydrogenation of compounds **12b** and **13b**, which furnished the product **11b**. Further evidence for the assigned structure to compound **11** came from the Raney-Ni promoted hydrogenolysis of **11b** to furnish compound **9b**. In addition, when compound **11b** was subjected to hydrogenation in the presence of Pd–C the hydrogenolysis of the isoxazole-ring does occur to yield compound **9b**.

The Raney-Ni catalyzed hydrogenation of acetates **21a**–**b**, **d** yielded exclusively the expected enaminones **22a**–**b**, **d** in good yields (Scheme 2). However the Pd–C promoted hydrogenation of these acetates (**21a**–**b**) gave a mixture of two products. Based on the spectroscopic evidence these products were identified as **23a**–**b** and **24a**–**b**. Contrary to the observation with the corresponding derivatives obtained from 5-isoxazolecarbaldehydes (**7**), the deacetylation does not occur during the process and only the reduced products **23** are obtained. Further the stereochemistry of compounds **23** was in favor of the *anti* isomer over *syn* by 7:3. To unambiguously confirm the formation of products **24a**–**b**, hydrogenation of compound **24b** in the presence of Raney-Ni led to isolation of product **22b**. The Pd–C promoted hydrogenation of compound **25b**, that was in turn generated from the sodium borohydride-promoted S_N2' nucleophilic substitution of hydride on the acetate **21b**, yielded the product **24b**.

The hydrogenation of acetates (**32a**–**c**) generated from Baylis–Hillman adducts of substituted 4-isoxazolecarbaldehydes was found to be significantly different. The hydrogenolysis of compounds **32a**–**c** in the presence of Raney-Ni invariably led to isolation of enaminones **34a**–**c** (Scheme 3). Unlike the reaction of other acetates described earlier in this text, the hydrogenolysis of the isoxazole ring here may have proceeded with simultaneous reduction of the methylene group and elimination of acetic acid. However, it seems that further reduction of double bond possibly did not occur because of the steric impedance. On the basis of NOE studies the stereochemistry of the product **34** was assigned as Z. In our efforts to gain further insight into the formation of product **34**, the allylic bromide **33b** was generated and subjected to hydrogenolysis in the presence of Raney-Ni. This reaction also afforded compound **34b**. Similarly, the Pd–C catalyzed hydrogenation of acetates **32a**–**c** also led to the isolation of products **34a**–**c**. The formation of compounds **34a**–**c** was in contrast to other Pd–C mediated reactions carried out during this study where the ring-cleavage did not take place. Thus the extensive hydrogenation studies carried out herein indicate that the behavior of the Baylis–Hillman derivatives of 5- and 3-isoxazolecarbaldehydes is very much similar during the Raney-Ni and the Pd–C-promoted reactions whereas the Baylis–Hillman derivatives obtained from 4-isoxazolecarbaldehydes yields significantly different products. The change in the ester group does not affect the outcome of the hydrogenation reaction. At this point of time the present investigations do not impart any explanation for the stability of the isoxazole ring during Pd–C-promoted hydrogenation of derivatives of Baylis–Hillman reaction of isoxazolecarbaldehydes. Nevertheless, once the double bond present in the side-chain is saturated the hydrogenolysis of the isoxazole-ring does take place in the presence of Pd–C.

It has been reported earlier that the α'-hydroxy-1,3-diketones derived from isoxazoles provide a facile synthetic method to obtain 3(2H)-furanones derivatives.[23–25] In a similar observation Chimichi et al. recently reported the synthesis of substituted 3(2H)-furanones through appropriately substituted α'-hydroxy-1,3-diketones utilizing isoxazoles as the starting substrate. As part of our objectives to demonstrate the synthetic utility of the enaminones synthesized during this study, compounds **4a**–**b**, **5b** and **19a**–**b**, **d** were subjected to acid-promoted cyclization-dehydration reaction. The reaction of compounds **4a**–**c**, **5b** and **19a**–**b**, **d** with HCl or H_2SO_4 led to the furanones **14a**–**d** and **15b** in moderate yields only. However excellent yields of furanones (**14a**–**d** and**15b**) were achieved when the same reaction was carried out in the presence of a mixture of acetic acid and formic acid (Scheme 1 and 2). To provide chemical evidence for the fact that the formation of furanones is via the cyclodehydration of the diketo derivatives afforded by the enaminones in the presence of acid, compound **10b** was treated with acid to yield the diketo-derivative **16b** in quantitative yields. It has been reported[26] earlier that Raney-Ni-promoted hydrogenation of 2-isoxazolines and isoxazoles, in the presence of boric acid leads to diketo-derivatives. To assess the possibility of generating these furanones through one pot reaction we decided to carry out the Raney-Ni-mediated hydrogenation of **2a**–**c** in the presence of boric acid.[27] This hydrogenation though did not yield the desired furanones; there was a dramatic change in the degree of diastereoselectivity (Scheme 4). The *syn* isomer was preferentially obtained over *anti* isomer as shown in Table 1. Encouraged by this observation we also subjected the Baylis–Hillman



Scheme 4. Reagents and conditions (a) Raney-Ni, H_2, H_3BO_3, rt, 6 h.

Table 1. Ratio of *syn* and *anti* enaminones derivative obtained without and with boric acid during Raney-Ni promoted hydrogenation of Baylis–Hillman adducts of 5 and 3-isoxazolecarbaldehydes

Compound No.	Raney-Ni only (*syn*:*anti*)	Raney-Ni + boric acid (*syn*:*anti*)
2a	**4a** (2:1)	**4a** (5:1)
2b	**4b** (5:2)	**4b** (6:1)
2c	**4c** (5:2)	**4c** (5:1)
3b	**5b** (4:1)	**5b** (9:1)
18a	**19a** (4:1)	**19a** (7:1)
18b	**19b** (5:1)	**19b** (13:2)
18d	**19d** (5:1)	**19d** (13:2)

derivatives **2a** and **18a** to Pd–C-promoted hydrogenation in the presence of boric acid. However during the process, we did not observe any significant change in the diastereoselectivity.

3. Conclusions

In summary, we have described some interesting observations made during the Raney-Ni and Pd–C catalyzed hydrogenation of the Baylis–Hillman adducts generated from 3-, 4- and 5-isoxazolecarbaldehydes and their corresponding acetates. For the first time we report here the diastereoselective hydrogenation of the Baylis–Hillman derivatives in the presence of Raney-Ni. During the course of the present study better diastereoselectivity was achieved by carrying out these hydrogenations in the presence of boric acid. Presently, it is difficult to assign reason for preservation of the isoxazole-ring in the Pd–C-promoted hydrogenation of derivatives of Baylis–Hillman reaction during this study. The enaminones generated from the hydrogenation of Baylis–Hillman adducts of isoxazolecarbaldehydes could serve as direct access to substituted α'-hydroxy-1,3-diketones that are scarcely available.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. The spectroscopic data for all products obtained as diastereoisomeric mixtures are presented as such and no attempts were made to separate them. For preparation of compounds **2**, **7**, **18**, **21**, **27** and **32** refer to Refs. 6, 8, 9.

4.2. Hydrogenation in the presence of Raney-Ni-representative procedure

A mixture of compound **2a** (520 mg, 2.0 mmol) and Raney-Ni (100 mg in ethanol) in methanol (10 mL) was subjected to hydrogenation either in the Parr assembly at 35 psi at rt or stirred in a sealed vessel having hydrogen atmosphere maintained by a balloon. The reaction was allowed to continue for 2.5 h. Thereafter, the catalyst was removed by vacuum-filtering the reaction mixture through a celite bed with methanol. The filtrate was evaporated to obtain an oily residue which was taken in ethyl acetate (2×20 mL) and washed with water (20 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo to obtain a crude oily product. Purification of the crude product by column chromatography over silica gel (230–400 mesh) using hexane:ethyl acetate (3:2, v/v) as the eluent furnished compound **4a** as yellow oil.

4.2.1. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-phenyl-hex-5-enoic acid methyl ester (4a). 65% (0.34 g from 0.52 g of **2a**); yellow oil; [found: C, 63.83; H, 6.19; N, 5.04. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32]. ν_{max} (Neat) 1731 (CO_2Me), 3406 (OH and NH_2) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=1.07$ (d, 3H, $J=7.0$ Hz, –CH–CH_{3anti}), 1.26 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 2.90–2.99 (m, 2H, 2×–CH–CH_3), 3.69 (s, 3H, CO_2CH_{3syn}), 3.75 (s, 3H, CO_2CH_{3anti}), 4.34 (brs, 1H, –CH(OH)–CH_{anti}), 4.70 (brs, 1H, –CH(OH)–CH_{syn}), 5.47 (s, 1H, =CH_{syn}), 5.49 (s merged with brs, 3H, =CH_{anti} and 2×1H of NH_2), 7.44–7.58 (m, 10H, ArH), 9.89 (brs, 2H, 2×1H of NH_2); mass (FAB+) m/z 264 ($M^{+}+1$).

4.2.2. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-*p*-tolyl-hex-5-enoic acid methyl ester (4b). 67% (1.34 g from 2.0 g of **2b**); yellow oil; [found: C; 65.23, H, 6.72; N, 4.88. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05]. ν_{max} (Neat) 1730 (CO_2Me), 3402 (OH and NH_2) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=1.07$ (d, 3H, $J=7.2$ Hz, –CH–CH_{3anti}), 1.26 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 2.40 (s, 6H, 2×Ar–CH_3), 2.87–2.97 (m, 2H, 2×–CH–CH_3), 3.69 (s, 3H, CO_2CH_{3syn}), 3.74 (s, 3H, CO_2CH_{3anti}), 4.34 (t, 1H, $J=6.0$ Hz, –CH(OH)–CH_{anti}), 4.68 (d, 1H, $J=3.0$ Hz, –CH(OH)–CH_{syn}), 5.45 (s, 1H, =CH_{syn}), 5.48 (s, 1H, =CH_{anti}), 5.54 (brs, 2H, 2×1H of NH_2), 7.25 (d, 4H, $J=8.0$ Hz, ArH), 7.45 (d, 4H, $J=8.0$ Hz, ArH), 9.86 (brs, 2H, 2×1H of NH_2); mass (ES+) m/z 300.73 ($M^{+}+Na$).

4.2.3. 6-Amino-6-(2-chloro-phenyl)-3-hydroxy-2-methyl-4-oxo-hex-5-enoic acid methyl ester (4c). 63% (0.72 g from 1.14 g of **2c**); yellow solid, mp 124–26°C; [found: C, 56.85; H, 5.40; N, 4.44. $C_{14}H_{16}ClNO_4$ requires C, 56.48; H, 5.42; N, 4.70]. ν_{max} (KBr) 1730 (CO_2Me), 3402 (OH and NH_2) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta=1.07$ (d, 3H, $J=7.0$ Hz, –CH–CH_{3anti}), 1.25 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 2.87–2.98 (m, 2H, 2×–CH–CH_3), 3.67 (s, 3H, CO_2CH_{3syn}), 3.72 (s, 3H, CO_2CH_{3anti}), 4.28 (brs, 1H, –CH(OH)–CH_{anti}), 4.67 (brs, 1H, –CH(OH)–CH_{syn}), 5.23 (s, 1H, =CH_{syn}), 5.25 (s, 1H, =CH_{anti}), 6.18 (s, 2H, 2×1H of NH_2), 7.35–7.47 (m, 8H, ArH), 9.85 (brs, 2H, 2×1H of NH_2); mass (FAB+) m/z 298 ($M^{+}+1$).

4.2.4. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-*p*-tolyl-hex-5-enoic acid ethyl ester (5b). 62% (0.62 g from 1.0 g from **3b**); yellow solid, mp 118–120 °C; [found: C, 66.03; H, 6.98; N, 4.51. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81]. ν_{max} (KBr) 1726 (CO_2Et), 3402 (OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.06$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.19–1.32 (m, 9H, –CH–CH_{3syn}, 2×CH_2CH_3), 2.41 (s, 6H, 2×Ar–CH_3), 2.80–2.91 (m, 2H, 2×–C*H*–CH_3), 4.09–4.29 (m, 2q merged, 4H, 2×CO_2CH_2), 4.35 (d, 1H, $J = 6.6$ Hz, –C*H*(OH)–CH_{anti}), 4.69 (d, 1H, $J = 3.0$ Hz, –C*H*(OH)–CH_{syn}), 5.48 (s, 1H, =CH_{syn}), 5.49 (s, 1H, =CH_{anti}), 5.60 (s, 2H, 2×1H of NH_2), 7.25 (d, 4H, $J = 8.0$ Hz, Ar*H*), 7.45 (d, 4H, $J = 8.0$ Hz, Ar*H*), 9.85 (brs, 2H, 2×1H of NH_2); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 9.8$, 13.5, 14.5, 21.7, 44.4, 44.8, 60.9, 61.2, 75.3, 76.9, 90.0, 91.2, 126.6, 130.1, 133.9, 134.1, 141.9, 142.0, 163.4, 163.8, 174.4, 195.8, 196.0; mass (FAB) *m/z* 292 ($M^+ + 1$).

4.2.5. 6-Amino-2-methyl-4-oxo-6-phenyl-hex-5-enoic acid methyl ester (9a). 65% (0.37 g from 0.57 g of **7a**); yellow oil; [found: C, 67.71; H, 7.01; N, 5.67. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66]. ν_{max} (Neat) 1728 (CO_2Me), 3406 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.22$ (d, 3H, $J = 6.8$ Hz, –CH–CH_3), 2.32–2.55 (m, 1H, –C*H*–CH_3), 2.83–3.06 (m, 2H, –CH–CH_2), 3.69 (s, 3H, CO_2CH_3), 5.38 (brs, 1H, NH_2), 5.42 (s, 1H, =C*H*), 7.42–7.56 (m, 5H, Ar*H*), 9.89 (brs, 1H, NH_2); mass (ES+) *m/z* 270.80 ($M^+ + Na$).

4.2.6. 6-Amino-2-methyl-4-oxo-6-*p*-tolyl-hex-5-enoic acid methyl ester (9b). 67% (0.27 g from 0.40 g of **7b**); white solid; mp 80–82°C; [found: C, 68.54; H, 7.11; N, 5.23. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36]. ν_{max} (KBr) 1720 (CO_2Me), 3394 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.22$ (d, 3H, $J = 6.8$ Hz, –CH–CH_3), 2.39 (s, 3H, Ar–CH_3), 2.44–2.55 (m, 1H, –C*H*–CH_3), 2.82–3.03 (m, 2H, –CH–CH_2), 3.69 (s, 3H, CO_2CH_3), 5.21 (brs, 1H, NH_2), 5.41 (s, 1H, =C*H*), 7.23 (d, 2H, $J = 8.2$ Hz, Ar*H*), 7.46 (d, 2H, $J = 8.2$ Hz, Ar*H*), 9.90 (brs, 1H, NH_2); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 17.6$, 21.7, 36.2, 46.0, 52.1, 94.64, 126.5, 130.0, 134.6, 141.4, 161.5, 177.4, 197.3; mass (ES+) *m/z* 284.80 ($M^+ + Na$).

4.2.7. 6-Amino-2-methyl-4-oxo-6-*p*-tolyl-hex-5-enoic acid ethyl ester (10b). 65% (0.33 g from 0.5 g of **8b**); yellow oil; [found: C, 69.94; H, 7.33; N, 5.32. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09]. ν_{max} (Neat) 1727 (CO_2Et), 3409 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.21$ (d, 3H, $J = 7.2$ Hz, –CH–CH_3), 1.25, (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 2.39 (s, 3H, Ar–CH_3), 2.43–2.53 (m, 1H, –C*H*–CH_3), 2.81–3.01 (m, 2H, –CH–CH_2), 4.15 (q, 2H, $J = 7.0$ Hz, CO_2CH_2), 5.20 (brs, 1H, NH_2), 5.42 (s, 1H, =C*H*), 7.23 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.44 (d, 2H, $J = 8.0$ Hz, Ar*H*), 9.89 (brs, 1H, NH_2); mass (ES+) *m/z* 298.53 ($M^+ + Na$).

4.2.8. 4-Amino-3-hydroxy-2-methyl-6-oxo-6-phenyl-hex-4-enoic acid methyl ester (19a). 70% (0.84 g from 1.20 g of **18a**); white solid, mp 88–90°C; [found: C, 63.57; H, 6.67; N, 4.99. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.36]. ν_{max} (KBr) 1653 (C=O), 1733 (CO_2Me), 3410 (br, OH and NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.22$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.30 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.85–2.90 (m, 2H, 2×–C*H*–CH_3), 3.75 (s, 6H, 2×CO_2CH_3), 4.18 (d, 1H, $J = 6.6$ Hz, –C*H*(OH)–CH_{anti}), 4.36 (d, 1H, $J = 4.6$ Hz, –C*H*(OH)–CH_{syn}), 5.70 (s, 1H, =CH_{syn}), 5.72 (s, 1H, =CH_{anti}), 6.10 (brs, 2H, 2×1H of NH_2), 7.39–7.58 (m, 6H, Ar*H*), 7.85–7.96 (m, 4H, Ar*H*), 10.04 (brs, 2H, 2×1H of NH_2), 11.40 (brs, 2H, 2×O*H*); mass (FAB+) *m/z* 264 ($M^+ + 1$).

4.2.9. 4-Amino-3-hydroxy-2-methyl-6-oxo-6-*p*-tolyl-hex-4-enoic acid methyl ester (19b). 87% (0.35 g from 0.40 g of **18b**); yellow oil; [found: C, 65.08; H, 7.02; N, 4.89. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05]. ν_{max} (Neat) 1652 (C=O), 1734 (CO_2Me), 3402 (br OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.20$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.27 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.38 (s, 3H, Ar–CH_{3syn}), 2.41 (s, 3H, Ar–CH_{3anti}), 2.78–2.89 (m, 2H, 2×–C*H*–CH_3) 3.73 (s, 3H, CO_2CH_{3syn}), 3.76 (s, 3H, CO_2CH_{3anti}), 4.12 (d, 1H, $J = 6.4$ Hz, –C*H*(OH)–CH_{anti}), 4.34 (d, 1H, $J = 2.6$ Hz, –C*H*(OH)–CH_{syn}), 5.56 (s, 1H, =CH_{syn}), 5.70 (s, 1H, =CH_{anti}), 6.10 (brs, 2H, 2×1H of NH_2), 7.21 (d, 2H, $J = 8.0$ Hz, ArH_{anti}), 7.25 (d, 2H, $J = 8.0$ Hz, ArH_{anti}), 7.76 (d, 2H, $J = 8.0$ Hz, ArH_{syn}), 7.84 (d, 2H, $J = 8.0$ Hz, ArH_{syn}), 10.05 (brs, 2H, 2×1H of NH_2), 10.72 (brs, 2H, 2×O*H*); mass (FAB+) *m/z* 278 ($M^+ + 1$).

4.2.10. -Amino-6-(4-chloro-phenyl)-3-hydroxy-2-methyl-6-oxo-hex-4-enoic acid methyl ester (19d). 73% (0.42 g from 0.48 g of **18d**); sticky solid; [found: C, 56.24; H, 5.51; N, 5.01. $C_{14}H_{16}ClNO_4$ requires C, 56.48; H, 5.42; N, 4.70]. ν_{max} (Neat) 1730 (CO_2Me), 3406 (br OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.20$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.29 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.82–2.89 (m, 2H, 2×–C*H*–CH_3), 3.73 (s, 3H, CO_2CH_{3syn}), 3.76 (s, 3H, CO_2CH_{3anti}), 4.36 (d, 1H, $J = 7.4$ Hz, –C*H*(OH)–CH_{anti}), 4.81 (d, 1H, $J = 4.6$ Hz, –C*H*(OH)–CH_{syn}), 5.58 (d, 1H, =CH_{syn}), 5.65 (s, 1H, =CH_{anti}), 6.11 (brs, 1H, 1H of NH_2), 6.52 (brs, 1H, 1H of NH_2), 7.37 (d, 4H, $J = 8.6$ Hz, Ar*H*), 7.78 (d, 4H, $J = 8.6$ Hz, Ar*H*), 10.05 (brs, 1H, 1H of NH_2), 10.32 (brs, 1H, 1H of NH_2); mass (FAB+) *m/z* 298 ($M^+ + 1$).

4.2.11. 4-Amino-2-methyl-6-oxo-6-phenyl-hex-4-enoic acid methyl ester (22a). 83% (0.66 g from 0.80 g of **21a**); yellow oil; [found: C, 68.20; H, 6.79; N, 5.97. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66]. ν_{max} (Neat) 1734 (CO_2Me), 3396 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.27$ (d, 3H, $J = 7.0$ Hz, –CH–CH_3), 2.59–2.82 (m, 3H, –C*H*–CH_2 and –CH–CH_2), 3.71 (s, 3H, CO_2CH_3), 5.50 (brs, 1H, 1H of NH_2), 5.69 (s, 1H, =C*H*), 7.39–7.58 (m, 3H, Ar*H*), 7.85–7.96 (m, 2H, Ar*H*), 10.08 (brs, 1H, 1H of NH_2); mass (FAB+) *m/z* 248 ($M^+ + 1$).

4.2.12. 4-Amino-2-methyl-6-oxo-6-*p*-tolyl-hex-4-enoic acid methyl ester (22b). 85% (0.33 g from 0.35 g of **21a**); yellow oil; [found: C, 69.03; H, 7.17; N, 5.50. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36]. ν_{max} (Neat) 1734 (CO_2Me), 3497 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.27$ (d, 3H, $J = 7.0$ Hz, –CH–CH_3), 2.38 (s, 3H, Ar–CH_3), 2.59–2.82 (m, 3H, –C*H*–CH_2 and –CH–CH_2), 3.71 (s, 3H, CO_2CH_3), 5.50 (brs, 1H, 1H of NH_2), 5.69 (s, 1H, =C*H*), 7.21 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.77 (d, 2H, $J = 8.0$ Hz, Ar*H*), 10.10 (brs, 1H, 1H of NH_2); mass (FAB+) *m/z* 262 ($M^+ + 1$).

4.2.13. 4-Amino-6-(4-chloro-phenyl)-2-methyl-6-oxo-hex-4-enoic acid methyl ester (22d). 85% (0.21 g from

0.25 g of **21d**); yellow oil; [found: C, 59.77; H, 5.99; N, 5.21. $C_{14}H_{16}ClNO_3$ requires C, 59.68; H, 5.72; N, 4.97]. ν_{max} (Neat) 1729 (CO_2Me); 3478 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.27$ (d, 3H, $J = 7.0$ Hz, $-CH-CH_3$), 2.23–2.48 (m, 1H, $-CH-CH_3$), 2.57–2.86 (m, 2H, $-CH-CH_2$), 3.71 (s, 3H, CO_2CH_3), 5.65 (s, 1H, $=CH$), 5.70 (brs, 1H, 1H of NH_2), 7.37 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.80 (d, 2H, $J = 8.0$ Hz, Ar*H*), 10.10 (brs, 1H, 1H of NH_2); mass (ES+) *m/z* 282.47 ($M^+ + 1$).

4.2.14. 5-Acetyl-3-methyl-6-phenyl-1*H*-pyridin-2-one (29a). 15% (0.045 g from 0.30 g of **27a**); yellow solid, mp 163–165 °C; [found: C, 73.24; H, 6.62; N, 5.44 $C_{14}H_{13}NO_2$ requires C, 73.99; H, 6.16; N, 5.77]. ν_{max} (KBr) 1697 (COMe), 1667 (CONH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.82$ (s, 3H, $=C-CH_3$), 2.02 (s, 3H, $COCH_3$), 7.33–7.51 (m, 5H, Ar*H*), 7.70 (s, 1H, $CH{=}C-CH_3$), 10.72 (brs, 1H, N*H*); mass (FAB+) *m/z* 228 ($M^+ + 1$).

4.2.15. 5-Acetyl-3-methyl-6-*p*-tolyl-1*H*-pyridin-2-one (29b). 16% (0.080 g from 0.50 g of **27b**); yellow solid, mp 164–166 °C; [found: C, 74.93; H, 6.45; N, 5.98. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.81]. ν_{max} (KBr) 1699 (COMe), 1668 (CONH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.81$ (s, 3H, $=C-CH_3$), 2.04 (s, 3H, $COCH_3$), 2.41 (s, 3H, $Ar-CH_3$), 7.15 (s, 4H, Ar*H*), 7.72 (s, 1H, $CH{=}C-CH_3$), 10.72 (brs, 1H, N*H*); mass (FAB+) *m/z* 242 ($M^+ + 1$).

4.2.16. 4-Amino-4-phenyl-but-3-en-2-one (30a). 58% (0.17 g from 0.30 g of **27a**); yellow solid, mp 93–95 °C; [found: C, 66.93; H, 7.51; N, 7.58. $C_{10}H_{11}NO \cdot H_2O$ requires C, 67.02; H, 7.31; N, 7.82]. ν_{max} (KBr) 1697 (COMe), 3395 (NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.15$ (s, 3H, $COCH_3$), 5.31 (brs, 1H, NH_2), 5.45 (s, 1H, $=CH$), 7.42–7.45 (m, 3H, Ar*H*), 7.52–7.57 (m, 2H, Ar*H*), 9.98 (brs, 1H, NH_2), ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 30.2$, 95.6, 126.6, 129.3, 137.7, 161.3, 197.9; mass (FAB+) *m/z* 162 ($M^+ + 1$).

4.2.17. 4-Amino-4-*p*-tolyl-but-3-en-2-one (30b). 58% (0.29 g from 0.50 g of **27b**); yellow solid, mp 58–60 °C; [found: C, 71.33; H, 6.79; N, 7.45. $C_{11}H_{13}NO.1/2H_2O$ requires C, 71.71; H, 7.11; N, 7.60]. ν_{max} (KBr) 1694 (COMe), 3402 (NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 2.15$ (s, 3H, $COCH_3$), 2.39 (s, 3H, $Ar-CH_3$), 5.34 (brs, 1H, NH_2), 5.44 (s, 1H, $=CH$), 7.23 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.44 (d, 2H, $J = 8.0$ Hz, Ar*H*), 10.01 (brs, 1H, NH_2); mass (FAB+) *m/z* 176 ($M^+ + 1$).

4.2.18. (*Z*) 4-Acetyl-5-amino-2-methyl-5-phenyl-penta-2,4-dienoic acid methyl ester (34a). 65% (0.45 g from 0.53 g of **32a**); Brown solid, mp 96–98°C; [found: C, 69.77; H, 6.63; N, 5.55. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40]. ν_{max} (KBr) 1699 (COMe and CO_2Me), 3441 (br, NH_2) cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) $\delta = 1.36$ (s, 3H, $=C-CH_3$), 2.18 (s, 3H, $COCH_3$), 3.67 (s, 3H, CO_2CH_3), 5.31 (brs, 1H, NH_2), 7.38 (s, 5H, Ar*H*), 7.44 (d, 1H, $J = 1.2$ Hz, $C-CH{=}C$), 10.67 (brs, 1H, NH_2); mass (ES+) *m/z* 260.60 ($M^+ + 1$).

4.2.19. (*Z*) 4-Acetyl-5-amino-2-methyl-5-*p*-tolyl-penta-2,4-dienoic acid methyl ester (34b). 85% (0.45 g from 0.53 g of **32b**); yellow solid, mp 76–78°C; [found: C, 70.33; H, 6.76; N, 4.99. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12]. ν_{max} (KBr) 1705 (COMe and CO_2Me), 3377 (br, NH_2) cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) $\delta = 1.36$ (s, 3H, $=C-CH_3$), 2.17 (s, 3H, $COCH_3$), 2.35 (s, 3H, $Ar-CH_3$), 3.68 (s, 3H, CO_2CH_3), 5.31 (brs, 1H, NH_2), 7.14 (d, 1H, $J = 8.0$ Hz, Ar*H*), 7.22 (m, 2H, $J = 8.0$ Hz, Ar*H*), 7.46 (d, 1H, $J = 1.2$ Hz, $C-CH{=}C$); mass (FAB+) *m/z* 274 ($M^+ + 1$).

4.2.20. (*Z*) 4-Acetyl-5-amino-5-(2-chloro-phenyl)-2-methyl-penta-2,4-dienoic acid methyl ester (34c). 80% (0.24 g from 0.30 g of **32c**); yellow solid, mp 118–120°C; [found: C, 61.08; H, 5.82; N, 4.97. $C_{15}H_{16}ClNO_3$ requires C, 61.33; H, 5.49; N, 4.77]. ν_{max} (KBr) 1707 (COMe and CO_2Me), 3369 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.58$ (s, 3H, $=C-CH_3$), 2.14 (s, 3H, $COCH_3$), 3.64 (s, 3H, CO_2CH_3), 7.17–7.38 (m, 4H, Ar*H*), 7.49 (d, 1H, $J = 1.2$ Hz, $C-CH{=}C$); mass (FAB+) *m/z* 294 ($M^+ + 1$).

4.3. Hydrogenation in the presence of Pd–C. Representative procedure

To the methanolic solution of compound **2a** (520 mg, 2.0 mmol), 75 mg of 10% Pd–C was added under nitrogen atmosphere. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out either on the Parr assembly at 30 psi at rt or through stirring in a sealed vessel having hydrogen atmosphere maintained by a balloon. After completion, the reaction mixture was filtered over a pad of celite and the solvent was concentrated under reduced pressure to obtain an oily residue. This residue was purified over silica gel (230–400 mesh) column using hexane: ethyl acetate (80:20, v/v) as eluent to yield **6a** as yellow oil.

4.3.1. 3-Hydroxy-2-methyl-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (6a). 78% (0.41 g from 0.52 g of **2a**); yellow oil; [found: C, 64.72; H, 5.98; N, 5.25. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36]. ν_{max} (Neat) 1732 (CO_2Me), 3429 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.22$ (d, 3H, $J = 7.2$ Hz, $-CH-CH_{3anti}$), 1.31 (d, 3H, $J = 7.2$ Hz, $-CH-CH_{3syn}$), 3.07–3.14 (m, 2H, $2\times -CH-CH_3$), 3.67 (s, 3H, CO_2CH_{3syn}), 3.72 (s, 3H, CO_2CH_{3anti}), 4.96 (t, 1H, $J = 6.0$ Hz, $-CH(OH)-CH_{anti}$), 5.34 (d, 1H, $J = 5.6$ Hz, $-CH(OH)-CH_{syn}$), 6.59 (s, 1H, $=CH_{syn}$), 6.62 (s, 1H, $=CH_{anti}$), 7.43–7.46 (m, 6H, Ar*H*), 7.77–7.82 (m, 4H, Ar*H*); mass (FAB+) *m/z* 262 ($M^+ + 1$).

4.3.2. 3-Hydroxy-2-methyl-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid methyl ester (6b). 80% (0.54 g from 0.67 g of **2b**); white solid; mp 68–70 °C; [found: C, 65.68; H, 6.32; N, 4.70. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22, N, 5.09]. ν_{max} (KBr) 1738 (CO_2Me), 3417 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.21$ (d, 3H, $J = 7.2$ Hz, $-CH-CH_{3anti}$), 1.31 (d, 3H, $J = 7.2$ Hz, $-CH-CH_{3syn}$), 2.39 (s, 6H, $2\times Ar-CH_3$), 3.07–3.14 (m, 2H, $2\times -CH-CH_3$), 3.67 (s, 3H, CO_2CH_{3syn}), 3.72 (s, 3H, CO_2CH_{3anti}), 4.94 (t, 1H, $J = 6.8$ Hz, $-CH(OH)-CH_{anti}$), 5.27 (t, 1H, $J = 1.5$ Hz, $-CH(OH)-CH_{syn}$), 6.56 (s, 1H, $=CH_{anti}$), 6.59 (s, 1H, CH_{syn}), 7.24 (d, 4H, $J = 8.0$ Hz, Ar*H*), 7.68 (d, 4H, $J = 8.0$ Hz, Ar*H*); mass (FAB+) *m/z* 276 ($M^+ + 1$).

4.3.3. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (6c). 81% (0.20 g from 0.25 g of **3c**); pale yellow oil; [found: C, 56.66; H, 5.77; N, 5.74. $C_{14}H_{14}ClNO_4$ requires C, 56.36; H, 5.79; N, 5.36]. ν_{max} (Neat) 1734 (CO_2Me), 3401 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.22$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.31 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 3.07–3.14 (m, 2H, 2×–CH–CH_3), 3.73 (s, 3H, CO_2CH_{3syn}), 3.76 (s, 3H, CO_2CH_{3anti}), 4.97 (t, 1H, $J = 6.0$ Hz, –CH(OH)–CH_{anti}), 5.31 (t, 1H, $J = 1.5$ Hz, –CH(OH)–CH_{syn}), 6.59 (s, 1H, =CH_{anti}), 6.73 (s, 1H, =CH_{syn}), 7.33–7.50 (m, 6H, ArH), 7.69–7.82 (m, 2H, ArH); mass (ES+) m/z 296.23 ($M^+ + 1$).

4.3.4. 2-Methyl-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (11a). 38% (0.21 g from 0.55 g of **7a**); white solid; mp 94–96 °C; [found: C, 68.76; H, 5.89; N, 5.36. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71]. ν_{max} (KBr) 1733 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.26$ (d, 3H, $J = 7.2$ Hz, –CH–CH_3), 2.89–2.97 (m, 2H, –CH–CH_2), 3.19–3.24 (m, 1H, –CH–CH_3), 3.76 (s, 3H, CO_2CH_3), 6.35 (s, 1H, =CH), 7.46–7.53 (m, 3H, ArH), 7.81–7.86 (m, 2H, ArH); mass (ES+) m/z 246.47 ($M^+ + 1$).

4.3.5. 2-Methyl-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid methyl ester (11b). 25% (0.16 g from 0.65 g of **7b**); white solid; mp 78–80 °C; [found: C, 69.48; H, 6.61; N, 5.40. $C_{15}H_{17}NO_3$ requires C, 69.64; H, 6.41, N, 5.33]. ν_{max} (KBr) 1726 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.27$ (d, 3H, $J = 7.2$ Hz, –CH–CH_3), 2.39 (s, 3H, Ar–CH_3), 2.89–2.96 (m, 2H, –CH–CH_2), 3.18–3.21 (m, 1H, –CH–CH_2), 3.70 (s, 3H, CO_2CH_3), 6.31 (s, 1H, =CH), 7.24 (d, 2H, $J = 8.0$ Hz, ArH), 7.67 (d, 2H, $J = 8.0$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 17.4$, 21.8, 30.8, 38.6, 52.3, 100.4, 109.94, 126.7, 127.0, 129.9, 140.4, 162.8, 171.4, 175.7; mass (FAB+) m/z 260 ($M^+ + 1$).

4.3.6. 3-Hydroxy-2-methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (20a). *syn*:*anti* 2:1 85% (0.13 g from 0.15 g of **18a**); white solid, mp 74–76 °C; [found: C, 64.11; H, 5.99; N, 4.98. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79, N, 5.36]. ν_{max} (Neat) 1731 (CO_2Me), 3403 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.24$–1.31 (m, 6H, 2×–CH–CH_3), 3.04–3.11 (m, 1H, –CH–CH_{3syn}), 3.33–3.36 (m, 1H, –CH–CH_{3anti}), 3.78 (s, 6H, 2×CO_2CH_3), 4.91, 4.98 (t, 1H, $J = 6.53$ Hz, –CH(OH)–CH_{anti}), 5.28 (t, 1H, $J = 1.5$ Hz, –CH(OH) –CH_{syn}), 6.60 (s, 2H, 2×=CH), 7.44–7.49 (m, 6H, ArH), 7.76–7.80 (m, 2H, ArH); mass (FAB+) m/z 262 ($M^+ + 1$).

4.3.7. 3-Hydroxy-2-methyl-3-(5-*p*-tolyl-isoxazol-3-yl)-propionic acid methyl ester (20b). *syn*:*anti* 2:1 89% (0.18 g from 0.20 g of **18b**); white solid; mp 90–92°C; [found: C, 64.75; H, 6.48; N, 5.24. $C_{15}H_{17}NO_4$ requires C, 64.44; H, 6.22, N, 5.09]. ν_{max} (KBr) 1738 (CO_2Me), 3458 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.26$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.28 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.40 (s, 6H, 2×Ar–CH_3), 3.02–3.09 (m, 1H, –CH–CH_{3syn}), 3.48–3.74 (m, 1H, –CH–CH_{3anti}), 3.74 (s, 6H, 2×CO_2CH_3), 4.93 (t, 1H, $J = 6.2$ Hz, –CH(OH)–CH_{anti}), 5.26 (t, 1H, $J = 1.5$ Hz, –CH(OH)–CH_{syn}), 6.54 (s, 2H, 2×=CH), 7.26 (d, 4H, $J = 8.0$ Hz, ArH), 7.66 (d, 4H, $J = 8.0$ Hz, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 11.5$, 14.6, 21.9, 44.8, 44.9, 52.5, 68.3, 69.5, 97.5, 98.1, 125.0, 126.2, 130.1, 140.9, 165.6, 165.9, 170.9, 175.9, 176.3; mass (FAB+) m/z 276 ($M^+ + 1$).

4.3.8. 3-[5-(4-Chloro-phenyl)-isoxazol-3-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (20d). *syn*:*anti* 2:1 87% (0.58 g from 0.67 g of **18d**); white solid; mp 134–36°C; [found: C, 57.04; H, 4.89; N, 4.77. $C_{14}H_{14}ClNO_4$ requires C, 56.86; H, 4.77, N, 4.74]. ν_{max} (KBr) 1733 (CO_2Me), 3427 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.26$ (d, 3H, $J = 7.0$ Hz, –CH–CH_{3anti}), 1.28 (d, 3H, $J = 7.0$ Hz, –CH–CH_{3syn}), 3.03–3.10 (m, 1H, –CH–CH_{3syn}), 3.42–3.48 (m, 1H, –CH–CH_{3anti}), 3.74 (s, 6H, 2×CO_2CH_3), 4.93 (t, 1H, $J = 3.0$ Hz, –CH(OH)–CH_{anti}), 5.27 (brs, 1H, –CH(OH)–CH_{syn}), 6.61 (s, 1H, 2×=CH), 7.43 (d, 4H, $J = 8.6$ Hz, ArH), 7.70 (d, 4H, $J = 8.6$ Hz, ArH); mass (FAB+) m/z 296 ($M^+ + 1$).

4.3.9. 3-Acetoxy-2-methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (23a). *syn*:*anti* 3:7 17% (0.097 g from 0.58 g of **21a**); yellow oil; [found: C, 63.55; H, 5.76; N, 4.66. $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.65; N, 4.62] ν_{max} (Neat) 1745 (COMe and CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.20$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.32 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.09 (s, 3H, $COCH_{3anti}$), 2.16 (s, 3H, $COCH_{3syn}$), 3.17–3.25 (m, 2H, 2×–CH–CH_3), 3.70 (s, 3H, CO_2CH_{3syn}), 3.75 (s, 3H, CO_2CH_{3anti}), 6.16 (d, 1H, $J = 9.0$ Hz, –CH(OAc)–CH_{anti}), 6.31 (d, 1H, $J = 6.0$ Hz, CH(OAc)–CH_{syn}), 6.49 (s, 1H, =CH_{syn}), 6.52 (s, 1H, =CH_{anti}), 7.44–7.49 (m, 6H, ArH), 7.75–7.79 (m, 4H, ArH); mass (FAB+) m/z 304 ($M^+ + 1$).

4.3.10. 3-Acetoxy-2-methyl-3-(5-*p*-tolyl-isoxazol-3-yl)-propionic acid methyl ester (23b). *syn*:*anti* 2:3 15% (0.038 g from 0.25 g of **21b**); white solid, mp 60–62°C; [found: C, 63.96; H, 5.85; N, 4.49. $C_{17}H_{19}NO_5$ requires C, 64.34; H, 6.03; N, 4.41]. ν_{max} (KBr) 1745 (COMe, CO_2Me), cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.20$ (d, 3H, $J = 7.2$ Hz, –CH–CH_{3anti}), 1.31 (d, 3H, $J = 7.2$ Hz, –CH–CH_{3syn}), 2.09 (s, 3H, $COCH_{3anti}$), 2.15 (s, 3H, CH_{3syn}), 2.39 (s, 6H, 2×CH_3), 3.15–3.23 (m, 2H, 2×–CH–CH_3), 3.70 (s, 3H, CO_2CH_{3syn}), 3.74 (s, 3H, CO_2CH_{3anti}), 6.13 (d, 1H, $J = 8.8$ Hz, –CH(OAc)–CH_{anti}), 6.30 (d, 1H, $J = 6.0$ Hz, –CH(OAc)–CH_{syn}), 6.43 (s, 1H, =CH_{syn}), 6.45 (s, 1H, =CH_{anti}), 7.27 (d, 4H, $J = 8.0$ Hz, ArH), 7.66 (d, 4H, $J = 8.0$ Hz, ArH); mass (ES+) m/z 340.47 ($M^+ + Na$).

4.3.11. 2-Methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (24a). 52% (0.30 g from 0.58 g of **21a**); yellow oil; [found: C, 68.55; H, 5.91; N, 5.83. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16, N, 5.71]. ν_{max} (Neat) 1735 (CO_2Me), 3456 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.28$ (d, 3H, $J = 7.0$ Hz, –CH–CH_3), 2.82–3.12 (m, 3H, –CH–CH_3 and –CH_2–CH), 3.71 (s, 3H, CO_2CH_3), 6.37 (s, 1H, =CH), 7.42–7.48 (m, 3H, ArH), 7.73–7.77 (m, 2H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta = 8.8$, 30.2, 39.1, 52.9, 99.87, 126.2, 127.9, 129.3, 130.5, 162.6, 170.2, 176.2; mass (FAB+) m/z 246 ($M^+ + 1$).

4.3.12. 2-Methyl-3-(5-*p*-tolyl-isoxazol-3-yl)-propionic acid methyl ester (24b). 49% (0.12 g from 0.25 g of **21b**); white solid, mp 83–84°C; [found: C, 69.52; H, 6.60; N, 5.12. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40].

ν_{max} (KBr) 1730 (CO_2Me), 3446 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=1.27$ (d, 3H, $J=6.6$ Hz, –CH–CH_3), 2.39 (s, 3H, Ar–CH_3), 2.81–3.11 (m, 3H, –C*H*–CH_3 and –CH_2–CH), 3.71 (s, 3H, CO_2CH_3), 6.31 (s, 1H, =C*H*), 7.24 (d, 2H, $J=8.0$ Hz, Ar*H*), 7.64 (d, 2H, $J=8.0$ Hz, Ar*H*); mass (ES+) *m/z* 260.36 ($M^+ + 1$).

4.3.13. 3-Hydroxy-2-methyl-3-(5-methyl-3-phenyl-isoxazol-4-yl)-propionic acid methyl ester (31a). *anti* 60% (0.25 g from 0.42 g of **27a**); white solid, mp 84–85°C; [found: C, 65.55; H, 5.91; N, 4.83. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09]. ν_{max} (KBr) 1733 (CO_2Me), 3411 (br, OH) cm^{-1}; ^1H NMR (200 MHz, DMSOd_6) $\delta=0.69$ (d, 3H, $J=7.0$ Hz, –CH–CH_3), 2.52 (s, 3H, =C–CH_3), 2.67–2.85 (m, 1H, –C*H*–CH_3), 3.56 (s, 3H, CO_2CH_3), 4.66–4.71 (m, 1H, –C*H*(OH)–CH), 7.53–7.55 (m, 3H, Ar*H*), 7.73–7.76 (m, 2H, Ar*H*); mass (FAB+) *m/z* 276 ($M^+ + 1$).

4.3.14. 3-Hydroxy-2-methyl-3-(5-methyl-3-*p*-tolyl-isoxazol-4-yl)-propionic acid methyl ester (31b). *anti* 63% (0.26 g from 0.41 g of **27b**); pale yellow solid, mp 100–102°C; [found: C, 66.36; H, 6.88; N, 4.72. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84]. ν_{max} (KBr) 1714 (CO_2Me), 3411 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=0.84$ (d, 3H, $J=7.2$ Hz, –CH–CH_3), 2.40 (s, 3H, Ar–CH_3), 2.55 (s, 3H, =C–CH_3), 2.74–2.83 (m, 1H, –C*H*–CH_3), 3.71 (s, 3H, CO_2CH_3), 4.84, 4.89 (d, 1H, $J=9.8$ Hz, –C*H*(OH)–CH), 7.25 (d, 2H, $J=8.0$ Hz, Ar*H*), 7.60 (d, 2H, $J=8.0$ Hz, Ar*H*); mass (FAB+) *m/z* 290 ($M^+ + 1$).

4.3.15. 3-[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (31c). *anti* 63% (0.32 g from 0.50 g of **18a**); white solid, mp 108–110°C; [found: C, 57.89; H, 5.14; N, 4.27. $C_{15}H_{16}ClNO_4$ requires C, 58.16; H, 5.21; N, 4.52]. ν_{max} (KBr) 1730 (CO_2Me), 3425 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=0.90$ (d, 3H, $J=7.2$ Hz, –CH–CH_3), 2.56 (s, 3H, =C–CH_3), 2.65–2.79 (m, 1H, –C*H*–CH_3), 3.67 (s, 3H, CO_2CH_3), 4.63 (d, 2H, $J=9.8$ Hz, –C*H*(OH)–CH), 7.35–7.52 (m, 4H, Ar*H*); mass (ES+) *m/z* 310.53 ($M^+ + 1$).

4.4. Preparation of allylic bromide-typical procedure

To the stirred solution of compound **27b** (500 mg, 1.74 mmol) in dry dichloromethane (5 mL) was added a solution of PBr_3 (0.17 mL, 1.74 mmol) dropwise at 0 °C. The reaction was allowed to proceed for 30 min at same temperature. Thereafter the reaction mixture was decomposed with ice-cold water and extracted with dichloromethane (2×20 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to furnish a residue that crystallizes on triturating with hexane to yield 0.48 g of bromide.

4.4.1. (*E*) 2-Bromomethyl-3-(5-methyl-3-*p*-tolyl-isoxazol-4-yl)-acrylic acid methyl ester (33b). 95%; yellow solid, mp 128–130 °C; [found: C, 54.52; H, 4.60; N, 4.12. $C_{15}H_{17}NO_3$ requires C, 54.87; H, 4.61; N, 4.00;]. ν_{max} (KBr) 1723 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta=2.37$ (s, 3H, Ar–CH_3), 2.39 (s, 3H, =CH–CH_3), 3.88 (s, 3H, CO_2CH_3), 4.09 (s, 2H, =C–CH_2–Br), 7.25 (d, 2H, $J=8.0$ Hz, Ar*H*), 7.42 (s, 1H, =C*H*–C–), 7.50 (d, 2H, $J=8.0$ Hz, Ar*H*); mass (ES+) *m/z* 350.80 ($M^+ + 1$).

4.5. Reaction of enamine ketones with acetic acid–formic acid mixture. Representative procedure

The compound **4a** (525 mg, 2.0 mmol) was stirred in 4 mL of acetic acid–formic acid (80%) mixture (50:50, v/v) at 60 °C for 24 h. After cooling to room temperature, the mixture was partitioned between ethyl acetate (30 mL) and water (25 mL). The organic layer was separated and successively washed with 10% $NaHCO_3$ aq. solution (until the washing was neutral). The organic layer was finally washed with brine, dried over Na_2SO_4 and evaporated to obtain a residue. This residue upon column chromatography over silica gel using hexane: ethyl acetate (85:15, v/v) furnished the product.

4.5.1. 2-(3-Oxo-5-phenyl-2, 3-dihydro-furan-2-yl)-propionic acid methyl ester (14a). *syn*:*anti* 1:1 88% (0.46 from 0.52 g of **4a**); pale yellow oil; [found: C, 63.23; H, 5.88. $C_{14}H_{14}O_4\cdot H_2O$ requires C, 63.63; H, 6.10] ν_{max} (Neat) 1697 (C=O), 1740 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=1.13$ (d, 3H, $J=7.2$ Hz, –CH–CH_{3anti}), 1.41, 1.44 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 3.12–3.21 (m, 2H, 2×C*H*), 3.69 (s, 3H, CO_2CH_{3syn}), 3.81 (s, 3H, CO_2CH_{3anti}), 4.80 (d, 1H, $J=5.6$ Hz, –CO–C*H*–O–$_{anti}$), 5.13, 5.14 (s, 1H, $J=3.1$ Hz, –CO–C*H*–O–$_{syn}$), 6.07 (s, 1H, =CH_{anti}), 6.08 (s, 1H, CH_{syn}), 7.44–7.58 (m, 6H, Ar*H*), 7.78–7.85 (m, 4H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) $\delta=12.72$, 13.94, 41.35, 43.66, 44.16, 46.10, 47.1, 52.8, 53.0, 86.2, 94.5, 99.7, 102.1, 127.7, 127.9, 128.2, 128.7, 128.8, 129.3, 130.5, 133.5, 134.1, 134.9, 171.2, 174.6, 175.5, 189.4, 195.4; mass (ES+) *m/z* 269.60 ($M^+ +$Na).

4.5.2. 2-(3-Oxo-5-*p*-tolyl-2, 3-dihydro-furan-2-yl)-propionic acid methyl ester (14b). 88% (0.40 from 0.45 g of **4b**); pale yellow solid, mp 108–110 °C; [found: C, 68.91; H, 5.90. $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20]. ν_{max} (KBr) 1694 (C=O), 1740 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=1.12$ (d, 3H, $J=7.2$ Hz, –CH–CH_{3anti}), 1.41 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 2.43 (s, 6H, 2×Ar–CH_3), 3.11–3.20 (m, 2H, 2×C*H*), 3.69 (s, 3H, CO_2CH_{3syn}), 3.80 (s, 3H, CO_2CH_{3anti}), 4.79 (d, 1H, $J=5.6$ Hz, –CO–C*H*–O–$_{anti}$), 5.12, (d, 1H, $J=3.0$ Hz, –CO–C*H*–O–$_{syn}$), 6.03 (s, 1H, =CH_{anti}), 6.04 (s, 1H, =CH_{syn}), 7.29 (d, 4H, $J=8.0$ Hz, Ar*H*), 7.69 (d, 4H, $J=8.0$ Hz, Ar*H*), 7.73 (d, 4H, $J=8.0$ Hz, Ar*H*); ^{13}C NMR (50.32 MHz, $CDCl_3$) $\delta=12.8$, 14.0, 22.2, 31.3, 43.6, 44.6, 46.1, 47.2, 52.9, 53.1, 94.4, 98.9, 104.7, 125.8, 127.9, 128.3, 130.6, 132.4, 145.3, 170.9, 171.4, 174.6, 189.8, 195.5; mass (FAB+) *m/z* 261 ($M^+ + 1$).

4.5.3. 2-[5-(4-Chloro-phenyl)-3-oxo-2,3-dihydro-furan-2-yl]-propionic acid methyl ester (14d). 85% (0.34 from 0.40 g of **4d**); pale yellow sticky solid; [found: C, 60.00; H, 4.91. $C_{14}H_{13}ClO_4$ requires C, 59.90; H, 4.67]. ν_{max} (Neat) 1694 (C=O), 1738 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta=1.13$ (d, 3H, $J=7.2$ Hz, –CH–CH_{3anti}), 1.42 (d, 3H, $J=7.2$ Hz, –CH–CH_{3syn}), 3.16–3.21 (m, 2H, 2×C*H*), 3.69 (s, 3H, –CO_2CH_{3syn}), 3.81 (s, 3H, CO_2CH_{3anti}), 4.79 (d, 1H, $J=5.6$ Hz, –CO–C*H*–O–$_{anti}$), 5.14 (d, 1H, $J=3.0$ Hz, –CO–C*H*–O–$_{syn}$), 6.03 (s, 1H, =CH_{anti}), 6.08 (s, 1H, =CH_{syn}), 7.47 (d, 4H, $J=8.6$ Hz, Ar*H*), 7.74 (d, 4H, $J=8.0$ Hz, Ar*H*), mass (FAB+) *m/z* 281 ($M^+ + 1$).

4.5.4. 2-(3-Oxo-5-*p*-tolyl-2,3-dihydro-furan-2-yl)-propionic acid ethyl ester (15b). 89% (0.89 g from 1.0 g of **5b**);

pale yellow oil; [found: C, 69.87; H, 6.65. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61]. ν_{max} (Neat) 1699 (C=O), 1734 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.10–1.46$ (m, 12H, 4×CH_2CH_3), 2.43 (s, 6H, 2×Ar–CH_3), 3.00–3.20 (m, 2H, 2×–CH–CH_3), 4.13–4.29 (m, 4H, 2×CO_2CH_2–), 4.76, (d, 1H, $J = 5.4$ Hz, –CO–CH–O–$_{anti}$), 5.13 (d, 1H, $J = 3.0$ Hz, –CO–CH–O–$_{syn}$), 6.02 (s, 1H, =CH_{anti}), 6.04 (s, 1H, =CH_{syn}), 7.29 (d, 4H, $J = 8.0$ Hz, ArH), 7.69 (d, 2H, $J = 8.0$ Hz, ArH), 7.73 (d, 2H, $J = 8.0$ Hz, ArH); mass (FAB+) m/z 275 ($M^+ + 1$).

4.5.5. 6-Hydroxy-2-methyl-4-oxo-6-*p*-tolyl-hex-5-enoic acid methyl ester (16b). 89% (0.089 g from 0.1 g of **9b**); yellow oil; [found: C, 68.76; H, 6.77. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92]. ν_{max} (Neat) 1690 (C=O), 1736 (CO_2Me), 3455 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) $\delta = 1.25$ (d, 3H, $J = 7.0$ Hz, –CH–CH_3), 2.40 (s, 3H, Ar–CH_3), 2.41–2.48 (m, 1H, –CH–CH_3), 2.84–3.04 (m, 2H, –CH–CH_2), 3.70 (s, 3H, CO_2CH_3), 6.14 (s, 1H, =CH–CO–), 7.24 (d, 2H, $J = 8.0$ Hz, ArH), 7.77 (d, 2H, $J = 8.0$ Hz, ArH); mass (FAB+) m/z 263 ($M^+ + 1$).

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References and notes

1. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857–869.
2. Li, C. S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565–3568.
3. Jones, R. C. F.; Dunn, S. H.; Duller, K. A. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1319–1321.
4. Kenar, J. A. *J. Am. Oils Chem. Soc.* **2003**, *80*, 1027–1032.
5. (a) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkins Trans. 1* **1994**, 2513–2515. (b) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Vulto, S. I. E. *J. Chem. Soc., Perkins Trans. 1* **1999**, 765–776. (c) Jones, R. C. F.; Dawson, C. E.; O'Mahony, M. J. *Synlett* **1999**, 873–876.
6. (a) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276–281. (b) Roy, A. K.; Batra, S. *Synthesis* **2003**, 1347–1356. (c) Roy, A. K.; Batra, S. *Synthesis* **2003**, 2325–2330.
7. Roy, A. K.; Rajaraman, B.; Batra, S. *Tetrahedron* **2004**, *60*, 2301–2310.
8. (a) Patra, A.; Batra, S.; Bhaduri, A. P. *Synlett* **2003**, 1611–1614. (b) Saxena, R. A.; Patra, A.; Batra, S. *Synlett* **2003**, 1439–1442. (c) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, 1819–1822.
9. Batra, S.; Roy, A. K.; Patra, A.; Bhaduri, A. P.; Surin, W. S.; Raghvan, S. A. V.; Sharma, P.; Kapoor, K.; Dikshit, M. *Bioorg. Med. Chem.* **2004**, *12*, 2059–2077.
10. Patra, A.; Batra, S.; Bhaduri, A. P.; Khanna, A.; Chander, R.; Dikshit, M. *Bioorg. Med. Chem.* **2003**, *11*, 2269–2276.
11. Bouzide, A. *Org. Lett.* **2002**, *4*, 1347–1350.
12. Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901–6908.
13. Mateus, C. R.; Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2000**, *41*, 2533–2536.
14. (a) Brown, J. M.; Cutting, I.; James, A. P. *Bull. Soc. Chim. Fr.* **1988**, 211–217. (b) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578–579.
15. Sainsbury, M. Trost, B. M., Ed.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 8, pp 644–646.
16. Bianchi, G.; DeAmici, M. *J. Chem. Soc., Chem. Commun.* **1978**, 962–963.
17. Amicchio, S.; Morrocchi, S.; Ricca, A. *Tetrahedron Lett.* **1974**, 2793–2796.
18. Stork, G.; Ohashi, M.; Kamachi, H.; Kakisawa, H. *J. Org. Chem.* **1971**, *36*, 2784–2786.
19. Chimichi, S.; Boccalini, M.; Cosimelli, B.; Viola, G.; Vedaldi, D.; Dall' Acqua, F. *Tetrahedron Lett.* **2002**, *43*, 7473–7476.
20. Chimichi, S.; Boccalini, M.; Cosimelli, B.; Dall' Acqua, F.; Viola, G. *Tetrahedron* **2003**, *43*, 5215–5223.
21. Pei, Y.; Wickham, B. O. S. *Tetrahedron Lett.* **1993**, *34*, 7509–7512.
22. Stuyter, M. A. T.; Pandit, U. K.; Speckaamp, W. N.; Huismon, H. O. *Tetrahedron Lett.* **1966**, 87–90.
23. Casnati, G.; Quilico, A.; Vita-Finzi, P. *Gazz. Chim. Ital.* **1966**, *96*, 1073–1083.
24. Casnati, G.; Ricca, A. *Tetrahedron Lett.* **1967**, 327–330.
25. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett.* **1984**, *25*, 4313–4316.
26. (a) Kozikowski, A. P.; Goldstein, S. *J. Org. Chem.* **1983**, *48*, 1139–1141. (b) Jensen, S.; Torssell, K. B. G. *Acta Chem. Scand.* **1995**, *49*, 53–56.
27. (a) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1988**, *B42*(5), 309–313. (b) Ueno, T.; Oikawa, M.; Oikawa, H.; Ichihara, A. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2104–2110.

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Efficient and selective deprotection method for *N*-protected 2(*3H*)-benzoxazolones and 2(*3H*)-benzothiazolones

Pascal Carato,[a,*] Saïd Yous,[a] Didier Sellier,[a] Jacques H. Poupaert,[b] Nicolas Lebegue[a] and Pascal Berthelot[a]

[a]*Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, EA 1043, 3, rue du Professeur Laguesse, BP 83, 59006 Lille cedex, France*
[b]*Laboratory of Medicinal Chemistry, School of Pharmacy, UCL, Avenue Emmanuel Mounier, 73, B-1200 Brussels, Belgium*

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Abstract—Cyclic carbamate flanked with heterocyclic or aliphatic moieties are frequently used in medicinal chemistry. The synthesis of derivatives bearing a free NH often requires the use of a protection method. A literature search reveals very few protection/deprotection methods for cyclic carbamates. In this paper, we described different methods applicable to 2(*3H*)-benzoxazolone and 2(*3H*)-benzothiazolone.

1. Introduction

2(*3H*)-Benzoxazolones and 2(*3H*)-benzothiazolones derivatives have attracted considerable attention as a result of their medicinal properties. Several potentially useful drugs and pharmacological tools based on these pharmacophores have been developed in recent years.[1–6] *N*-methyl-2(*3H*)-benzoxazolones and 2(*3H*)-benzothiazolones have been largely used in medicinal chemistry, but surprisingly their N–H homologues are less accessible although in many cases, a free N(3)–H group is an essential structural requirement for activity and receptor selectivity of these 2(*3H*)-benzazolones derivatives. Moreover, the NH heterocycle can serve as a pivotal structure for the constitution of a library N-derivatized analogues.

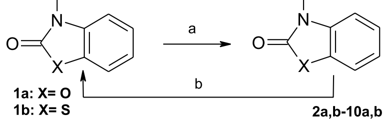
Indeed, in many cases encountered in our own research, reactions that are successful in the N-methyl series cannot be applied in the N–H series: C(6)-formylation,[7,8] C(6)-tributyltin derivatization, photohalogenation,[9] crotonisation, etc.[10,11] Obviously, the use of N-protected 2(*3H*)-benzazolones are in order for the success of these reactions. However, close inspection of the literature reveals very few indications concerning protecting groups of cyclic carbamates that can be easily introduced and subsequently smoothly removed. Indeed, benzyl protecting group[12] was found in this series of heterocycle but reaction of formylation, acylation or the cleavage of N-benzyle derivative with NBS, AIBN could induced secondary products. Therefore, in an effort to fill this gap, we explored various protecting groups and examined their ease of deprotection.

2. Results and discussion

2.1. Protection/deprotection of cyclic carbamate on phenyl ring (1a,b) via different methods

The compounds **2a**,**b**–**10a**,**b**, in Scheme 1, were synthetized by methods A or B, according the reagent desired, with 2(*3H*)-benzoxazolone (**1a**) or 2(*3H*)-benzothiazolinone (**1b**). Various deprotection methods, described in Table 1, were then tested.

As expected, deprotection of derivatives **2a** and **2b** did take place under mild acid (methods C and D), basic (method F)



Scheme 1. Protection and deprotection of 2(*3H*)-benzazolones derivatives (**2a**,**b**–**10a**,**b**) via different methods. (a): method A: ClP (P: COR or SO_2R), Bu_4NBr, K_2CO_3, CH_2Cl_2; method B: ClP (P: MOM or MEM), K_2CO_3, DMF (b) method C: TFA; method D: HCl 12 N (3 équiv), MeOH; method E: $TiCl_4$ (3 équiv), CH_2Cl_2; method F: KOH (3 équiv), MeOH; method G: Bu_4NF (1 M in solution in THF, 3 équiv), THF.

Keywords: 2(*3H*)-Benzoxazolone; 2(*3H*)-Benzothiazolone; Protecting groups.

* Corresponding author. Tel.: +33-3-20964040; fax: +33-3-20-964913; e-mail: pcarato@pharma.univ-lille2.fr

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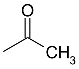
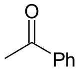
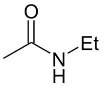
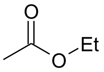
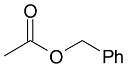
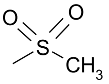
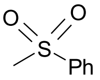
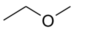
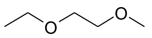
Table 1. results of deprotection attempts of 2(*3H*)-benzazolones derivatives (**2a**,**b**–**10a**,**b**)

Entry	X	Protecting groups	TFA (C)	HCl–MeOH (D)	TiCl$_4$–CH$_2$Cl$_2$ (E)	KOH–MeOH (F)	Bu$_4$NF–THF (G)
2a	O		1 h rt (85%)	2 h rt (79%)	N	0.5 h rt (89%)	1 h rt (91%)
2b	S		1 h rt (81%)	1.5 h rt (89%)	N	0.5 h rt (68%)	1 h rt (95%)
3a	O		N	N	N	0.5 h rt (30%)	1 h rt (95%)
3b	S		N	N	N	0.5 h rt (91%)	1 h rt (97%)
4a	O		N	N	N	0.5 h rt (78%)	0.25 h rt (98%)
4b	S		N	N	N	0.5 h rt (94%)	0.25 h rt (95%)
5a	O		N	N	N	0.5 h rt (39%)	0.25 h rt (89%)
5b	S		N	N	N	0.5 h rt (90%)	0.25 h rt (94%)
6a	O		N	N	2 h rt (90%)	0.5 h rt (20%)	0.5 h rt (96%)
6b	S		N	N	2 h rt (86%)	0.5 h rt (95%)	0.5 h rt (98%)
7a	O		N	N	N	0.5 h rt (10%)	0.5 h rt (96%)
7b	S		N	N	N	0.5 h rt (90%)	0.5 h rt (93%)
8a	O		N	N	N	Ring opening	1 h rt (93%)
8b	S		N	N	N	N	1 h rt (97%)
9a	O		4 h reflux (92%)	N	N	N	N
9b	S		4 h reflux (96%)	N	N	N	N
10a	O		4 h reflux (95%)	N	N	N	N
10b	S		4 h reflux (97%)	N	N	N	N

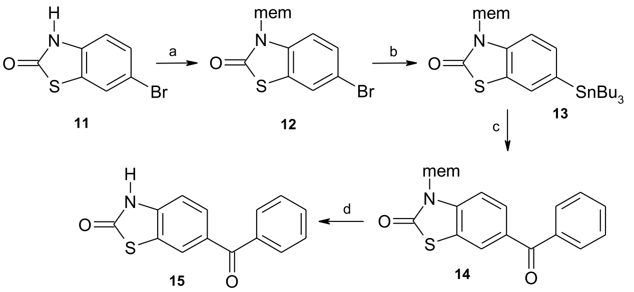
N: unsuccessful test performed 1 day at room temperature and then 1 day at reflux; rt: room temperature.

and neutral (method G) conditions and therefore the *N*-acetyl cannot be considered as a good protecting group. Compounds **3a**,**b**–**5a**,**b** and **7a**,**b**, respectively with COPh, CONHEt, CO$_2$Et and SO$_2$Me, resisted in acid medium (methods C, D and E). Application of the method F, in basic media, to the compounds **3b**–**5b** and **7b** give the desired derivative **1b** with good yield (90–95%), but in the 2(*3H*)-benzoxazolone series (**3a**–**5a** and **7a**) we observed that deprotected compounds were accompanied by important amounts of ring opening products (such as 2-aminophenol) which reduced the yield (10 to 78%). Deprotection method G, for compounds **3a**,**b**–**5a**,**b** and **7a**,**b**, with Bu$_4$NF in THF,[13,14] however gives excellent yields (89–98%).

Compound **6a**,**b** (Cbz protected) was not deprotected in acid media (method C and D) but in mild basic media (X=S: 95% and X=O: 20%) with method F (30 min at rt) and also by methods E and G with excellent yields (86–98%). Another attempt of deprotection of **6a**,**b** was performed by hydrogenolysis in THF using Pd/C (5 h, rt), which gave the deprotected derivatives **1a**,**b** with excellent yields (X=O: 94% and X=S: 97%). Method G with Bu$_4$NF in THF was found to be a very good alternative (**6a**: 96% and **6b**: 98%) specially because we did not observe any ring opening products.

Surprisingly, with compound **8b** we did not observe any deprotection either in acid or basic medium (methods C, D, E and F). In the corresponding 2(*3H*)-benzoxazolone series (**8a**) we observed ring opening, which gave 2-amino-(*N*-phenylsulfonyl) phenol. Compounds **8a**,**b** were successfully cleaved with Bu$_4$NF (THF, rt, 1 h, 93 and 97%). Deprotection of compounds **9a**,**b** and **10a**,**b** was realized only in TFA at reflux for 4 h, nevertheless with very good yields (92 to 97%).

In order to validate the interest of the protecting group for 2(*3H*)-benzazolone, we applied our results to a benchmark, i.e. the synthesis of 6-benzoyl-2(*3H*)-benzothiazolone. In our laboratory we observed indeed that the introduction of tributyltin in the 6-position of the 2(*3H*)-benzothiazolone could be performed only on N-methyl compounds and not on the free NH series. In Scheme 2, we introduced the MEM protecting group on 6-bromo-2(*3H*)-benzothiazolone (**12**) to synthetise the corresponding tributyltin derivative. The benzoyl moiety was then easily introduced and the resulting



Scheme 2. Protection of 2(*3H*)-benzothiazolone. (a): MEM-Cl, K$_2$CO$_3$, DMF (b): (Bu$_3$Sn)$_2$, Pd(PPh$_3$)$_4$, toluene (c): ClCOPh, PdCl$_2$(PPh$_3$)$_2$, toluene (d): TFA.

compound was then deprotected to afford the free NH derivative (**15**).

More specifically, 6-bromobenzothiazolinone[15] (**11**) was protected in DMF with MEM group to afford compound **12**. Tributyltin derivative **13** was obtained from the bromo precursor **12** via Stille's reaction with $(Bu_3Sn)_2$ and $Pd(PPh_3)_4$ in toluene. Compound **13** can then embarked in coupling reactions with various aryl or cycloalkylcarbonyl chlorides. In Scheme 2, to exemplify the validity of our approach, we introduced a benzoyl group in 6-position to give derivative **14**. The MEM protection group was then cleaved in refluxed TFA for 2 h to furnish the expected compound **15**.[16]

3. Conclusion

In conclusion, we found different protecting groups which can be used in acid or basic medium reaction conditions and subsequently removed without major problems. The COPh, CONHEt, CO_2Et, CO_2CH_2Ph, SO_2CH_3 derivatives (**3a**,**b**–**7a**,**b**) resisted in acid conditions and were cleaved in basic medium. MOM and MEM protection (**9a**,**b**–**10a**,**b**) resisted in basic media and were cleaved in TFA. The SO_2Ph protection (**8b**) resisted in acid and basic media and was cleaved with Bu_4NF in THF (method G).

Method G in particular constitutes a mild and selective method of deprotection for *N*-protected-2(*3H*)-benzazolones (derivatives **3a**,**b**–**8a**,**b**) with excellent yields (89–98%) and was compatible both with acid or basic-sensitive groups. To exemplify the validity of our approach, we synthesized compounds **15** via *N*-MEM protection. These deprotection methods could be extended to other cyclic carbamates, such as oxazolo[4,5]pyridin-2(*3H*)-ones, hydantoins, and barbiturates.

4. Experimental

4.1. General methods of protection

Method A (**2a**,**b**–**8a**,**b**). To a solution of 2(*3H*)-benzazolones (22 mmol) in CH_2Cl_2 (30 mL), K_2CO_3 (66 mmol), Bu_4NBr (1 mmol) and the desired acid chloride reagent (66 mmol) were added. The reaction was refluxed for 4 h. The solvent was evaporated under reduce pressure. The solution was hydrolyzed with water (30 mL) and stirred for 1 h. The precipitate was filtered and recrystallized from the appropriate solvent.

Method B (**9a**,**b**–**10a**,**b**). To a solution of 2(*3H*)-benzazolones (22 mmol) in DMF (30 mL), K_2CO_3 (66 mmol) was added. The reaction was stirred at 80 °C for 1 h and the desired chlororeagent (66 mmol) added. The solution was stirred for 3 h at the same temperature. The solvent was evaporated under reduced pressure. The solution was hydrolyzed with water (30 mL) and stirred for 1 h. The precipitate was filtered and recrystallized with the appropriate solvent.

4.1.1. 3-Acetyl-2(*3H*)-benzoxazolone (2a). Yield 90% (cyclohexane). Mp 90–91 °C. IR (KBr) 2870, 1726, 1688, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=2.75$ (s, 3H), 7.15–7.29 (m, 3H), 8.25 (m, 1H).

4.1.2. 3-Acetyl-2(*3H*)-benzothiazolone (2b). Yield 84% (cyclohexane). Mp 103–104 °C. IR (KBr) 2930, 1695, 1676, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=2.80$ (s, 3H), 7.03–7.24 (m, 3H), 8.15 (m, 1H).

4.1.3. 3-Benzoyl-2(*3H*)-benzoxazolone (3a). Yield 70% (cyclohexane). Mp 178–179 °C. IR (KBr) 1805, 1697, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=7.25$–7.38 (m, 3H), 7.48–7.59 (m, 2H), 7.67 (m, 1H), 7.81–7.92 (m, 3H).

4.1.4. 3-Benzoyl-2(*3H*)-benzothiazolone (3b). Yield 81% (cyclohexane). Mp 165–166 °C. IR (KBr) 1702, 1724, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=7.32$–7.48 (m, 3H), 7.65–7.78 (m, 2H), 7.84 (m, 1H), 7.95–8.14 (m, 3H).

4.1.5. 3-Ethylaminocarbonyl-2(*3H*)-benzoxazolone (4a). Yield 80% (cyclohexane). Mp 104–106 °C. IR (KBr) 3350, 2970, 1737, 1658, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=1.30$ (t, $J=7.30$ Hz, 3H), 3.20 (q, $J=7.30$ Hz, 2H), 5.00 (m, 1H), 7.23–7.30 (m, 3H), 8.05 (m, 1H).

4.1.6. 3-Ethylaminocarbonyl-2(*3H*)-benzothiazolone (4b). Yield 88% (cyclohexane). Mp 112–113 °C. IR (KBr) 3340, 2954, 1701, 1665, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=1.35$ (t, $J=7.20$ Hz, 3H), 3.20 (q, $J=7.20$ Hz, 2H), 5.05 (m, 1H), 7.11–7.23 (m, 3H), 8.10 (m, 1H).

4.1.7. 3-Ethoxycarbonyl-2(*3H*)-benzoxazolone (5a). Yield 70% (petroleum ether). Mp 70–71 °C. IR (KBr) 2975, 1852, 1747, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=1.51$ (t, $J=7.34$ Hz, 3H), 4.55 (q, $J=7.34$ Hz, 2H), 7.26–7.38 (m, 3H), 7.80 (m, 1H).

4.1.8. 3-Ethoxycarbonyl-2(*3H*)-benzothiazolone (5b). Yield 90% (petroleum ether). Mp 65–66 °C. IR (KBr) 2971, 1845, 1746, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=1.50$ (t, $J=7.30$ Hz, 3H), 4.50 (q, $J=7.30$ Hz, 2H), 7.31–7.53 (m, 3H), 8.10 (m, 1H).

4.1.9. Benzyloxycarbonyl-2(*3H*)-benzoxazolone (6a). Yield 70% (cyclohexane). Mp 130–131 °C. IR (KBr) 1809, 1749, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=5.50$ (s, 2H), 7.16–7.28 (m, 3H), 7.36–7.46 (m, 3H), 7.50–63–7.24 (m, 2H), 7.75 (m, 1H).

4.1.10. Benzyloxycarbonyl-2(*3H*)-benzothiazolone (6b). Yield 88% (cyclohexane). Mp 62–63 °C. IR (KBr) 1739, 1709, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=5.55$ (s, 2H), 7.26–7.45 (m, 8H), 7.55 (m, 1H).

4.1.11. 3-Methylsulfonyl-2(*3H*)-benzoxazolone (7a). Yield 75% (cyclohexane). Mp 142–143 °C. IR (KBr) 1733, 1600, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=3.50$ (s, 3H), 7.18–7.31 (m, 3H), 7.70 (m, 1H).

4.1.12. 3-Methylsulfonyl-2(*3H*)-benzothiazolone (7b). Yield 79% (cyclohexane). Mp 148–149 °C. IR (KBr) 1697, 1600, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) $\delta=3.60$ (s, 3H), 7.28–7.43 (m, 3H), 8.10 (m, 1H).4.1.

4.1.13. 3-Phenylsulfonyl-2(*3H*)-benzoxazolone (8a). Yield 96% (cyclohexane). Mp 145–146 °C. IR (KBr) 1733, 1600, 1190 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=7.25$ (m, 1H), 7.35–7.48 (m, 2H), 7.60 (m, 2H), 7.70 (m, 1H), 8.10 (m, 2H), 8.25 (m, 1H).

4.1.14. 3-Phenylsulfonyl-2(*3H*)-benzothiazolone (8b). Yield 96% (cyclohexane). Mp 136–137 °C. IR (KBr) 1717, 1620, 1190 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=7.30$ (m, 1H), 7.32–7.45 (m, 2H), 7.60 (m, 2H), 7.70 (m, 1H), 8.10 (m, 2H), 8.25 (m, 1H).

4.1.15. 3-Methoxymethyl-2(*3H*)-benzoxazolone (9a). Yield 90% (cyclohexane). Mp 90–91 °C. IR (KBr) 1762, 1600 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=3.40$ (s, 3H), 5.20 (s, 2H), 7.12–7.29 (m, 4H).

4.1.16. 3-Methoxymethyl-2(*3H*)-benzothiazolone (9b). Yield 95% (cyclohexane). Mp 114–115 °C. IR (KBr) 1695, 1600 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=3.35$ (s, 3H), 5.10 (s, 2H), 7.02–7.24 (m, 4H).

4.1.17. 3-Methoxyethoxymethyl-2(*3H*)-benzoxazolone (10a). Yield 90% (cyclohexane). Mp 28–29 °C. IR (KBr) 2882, 1782, 1600 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=3.30$ (s, 3H), 3.50 (t, $J=7.00$ Hz, 2H), 3.75 (t, $J=7.00$ Hz, 2H), 5.40 (s, 2H), 7.15–7.36 (m, 4H).

4.1.18. 3-Methoxyethoxymethyl-2(*3H*)-benzothiazolone (10b). Yield 93% (cyclohexane). Mp 75–76 °C. IR (KBr) 2898, 1709, 1600 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta=3.30$ (s, 3H), 3.50 (t, $J=7.05$ Hz, 2H), 3.70 (t, $J=7.05$ Hz, 2H), 5.35 (s, 2H), 7.06–7.28 (m, 4H).

4.1.19. 6-Bromo-3-methylethoxymethyl-2(*3H*)-benzothiazolone (12). To a mixture of 6-bromo-2(*3H*)-benzothiazolone (**11**) (5 g, 21.7 mmol) in DMF (50 mL), potassium carbonate (9 g, 65.2 mmol) and MEM-Cl (9.9 mL, 86.8 mmol) were added. The reaction was stirred at 90 °C for 2 h. The solution was evaporated under reduced pressure and 50 mL of water added. The solution was extracted with CH$_2$Cl$_2$, then the organic layer evaporated under reduced pressure. The residue was recrystallized in cyclohexane. Yield 92%. Mp 97–98 °C. IR 1692, 1600. ^{1}H NMR (CDCl$_3$) $\delta=3.30$ (s, 3H), 3.50 (m, 2H), 3.70 (m, 2H), 5.50 (s, 2H), 7.15 (d, 1H, $J=8.30$ Hz), 7.45 (dd, 1H, $J=8.30$ Hz, $J=1.50$ Hz), 7.55 (d, 1H, $J=1.50$ Hz).

4.1.20. 6-Tributyltin-3-methylethoxymethyl-2(*3H*)-benzothiazolinone (13). To a mixture of 6-bromo-3-methylethoxymethyl-2(*3H*)-benzothiazolone (**12**) (5 mmol) in toluene (20 mL) under argon, tetrakis(triphenyl phosphine) palladium (0.5 mmol) and bis(tributyltin) (10 mmol) were added. The reaction was refluxed for 16 h. The solution was evaporated under reduced pressure. The oily residue was purified by flash column chromatography with petroleum ether/EtOAc (9.5/0.5) to give an oily product. Yield 63%. IR 1692, 1605. ^{1}HNMR (CDCl$_3$): $\delta=0.90$ (t, 9H, $J=5.90$ Hz), 1.10 (t, 6H, $J=6.10$ Hz), 1.35 (m, 6H), 1.55 (m, 6H), 3.35 (s, 3H), 3.55 (m, 2H), 3.75 (m, 2H), 5.45 (s, 2H), 7.30 (d, 1H, $J=7.90$ Hz), 7.40 (dd, 1H, $J=7.90$ Hz, $J=1.05$ Hz), 7.50 (s, 1H).

4.1.21. 6-Benzoyl-3-methylethoxymethyl-2(*3H*)-benzothiazolone (14). 6-Tributylstannic-3-methylethoxymethyl-2(*3H*)-benzothia-zolone (**13**) (1.9 mmol) in toluene (10 mL) was placed under argon, dichlorobis(triphenylphosphine) palladium (0.18 mmol) and benzoylchloride (2.8 mmol) were added. The reaction was refluxed for 16 h. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography with CH$_2$Cl$_2$/EtOAc (9/1) and recrystallized in cyclohexane. Yield 86%. Mp 101–102 °C; IR 1696, 1649. ^{1}HNMR (CDCl$_3$): $\delta=3.35$ (s, 3H), 3.50 (m, 2H), 3.75 (m, 2H), 5.50 (s, 2H), 7.40 (d, 1H, $J=8.70$ Hz), 7.50 (m, 2H), 7.60 (m, 1H), 7.80 (m, 2H), 7.85 (dd, 1H, $J=8.70$ Hz, $J=1.10$ Hz), 8.00 (d, 1H, $J=1.10$ Hz).

References and notes

1. Diouf, O.; Carato, P.; Depreux, P.; Bonte, J. P.; Caignard, D. H.; Guardiola-Lemaitre, B.; Rettori, M. C.; Belzung, C.; Lesieur, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2579–2584.
2. Diouf, O.; Carato, P.; Lesieur, I.; Rettori, M. C.; Caignard, D. H. *Eur. J. Med. Chem.* **1999**, *34*, 69–73.
3. Carato, P.; Bonte, J. P.; Lesieur, D.; Depreux, P.; Caignard, D. H.; Millan, M.; Newman-Tancredi, A.; Renard, P.; Rettori, M. C. Eur. Patent Chem. Abstr., 1998, P4662x.
4. Carato, P.; Depreux, P.; Lesieur, D.; Millan, M.; Newman-Tancredi, A.; Rettori, M. C.; Caignard, D. H. *Drug Des. Disc.* **2000**, *17*, 173.
5. Lesieur, D.; Delmas, E.; Yous, S.; Depreux, P.; Guillaumet, G.; Dacquet, C.; Levens, N.; Boutin, J.; Bennejean, C.; Renard, P. French Patent 00-01289, 2000.
6. Lesieur, D.; Blanc-Delmas, E.; Bennejean, C.; Chavatte, P.; Guillaumet, G.; Dacquet, C.; Levens, N.; Boutin, J.; Renard, P. French Patent 01-12205, 2001.
7. Bonte, J. P.; Lesieur, D.; Lespagnol, Ch.; Plat, M.; Cazin, J. C.; Cazin, M. *Eur. J. Med. Chem.* **1974**, *9*, 491–496.
8. Kanyonyo, M. R.; Ucar, H.; Isa, M.; Carato, P.; Lesieur, D.; Renard, P.; Poupaert, J. H. *Bull. Soc. Chim. Belg.* **1996**, *105*, 17–22.
9. Liacha, M.; Yous, S.; Depreux, P.; Poupaert, J. H.; Lesieur, D. *Heterocycles* **1999**, *51*, 1929–1944.
10. Moussavi, Z.; Depreux, P.; Lesieur, I.; Sauzieres, J. *Heterocycles* **1991**, *32*, 2119–2125.
11. Depreux, P.; Moussavi, Z.; Lesieur, D. *Synth. Commun.* **1992**, *22*, 1541–1545.
12. Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331–332.
13. Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595–596.
14. Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J. Y. *Tetrahedron Lett.* **2002**, *43*, 589–591.
15. D'Amico, J. J.; Bollinger, F. G.; Freeman, J. F. *J. Heterocycl. Chem.* **1988**, *25*, 1503–1509.
16. Yous, S.; Poupaert, J. H.; Lesieur, I.; Depreux, P.; Lesieur, D. *J. Org. Chem.* **1994**, *59*, 1574–1576.

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Synthesis and catalytic activities of Pd^{II}–phosphine complexes modified poly(ether imine) dendrimers

Thatavarathy Rama Krishna and Narayanaswamy Jayaraman*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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Abstract—In this paper, we report synthesis of new alkyldiphenyl phosphine ligand modified poly(ether imine) dendrimers up to the third generation. The phosphinated dendrimers were obtained by functional group transformations of the alcohols present at the periphery of the dendrimers to chloride, followed by phosphination using $LiPPh_2$. The modification at the peripheries of the dendrimers was performed successfully to obtain up to 16 alkyl diphenylphosphines in the case of a third generation dendrimer, in good yields for each individual step. After phosphination, dendritic ligands were complexed with $Pd(COD)Cl_2$ to give dendritic phosphine–Pd^{II} complexes. Both the ligands and the metal complexes were characterized by spectroscopic and spectrometric techniques including high-resolution mass spectral analysis for the lower generations. Evaluation of the catalytic efficacies of the dendrimer–Pd^{II} metal complexes in mediating a prototypical C–C bond forming reaction, namely the Heck reaction, was performed using various olefin substrates. While the substrate conversion lowered with catalyst in the order from monomer to third generation dendrimer, the second and third generation dendrimers themselves were found to exhibit significantly better catalytic activities than the monomer and the first generation dendrimer.

1. Introduction

Dendrimers are synthesized in a step-wise iterative fashion, so as to construct them with a controlled architecture which allows their molecular structures to be precise and unique, in contrast to many other types of macromolecules.[1] The controlled architectures of dendrimers make them useful in several areas of research such as host–guest chemistry,[2] drug delivery,[3] self-assembly[4] and catalysis.[5] In these and other areas, amplification of functional groups at the peripheries of the dendritic structures is often targeted. Amplification of functional groups induces occasionally one of the so called 'dendritic effects'.[6]

In the area of organometallic catalysis, ligands with mixed donor atoms receive much attention.[7] Hemilabile ligands with 'soft' (phosphorus) and 'hard' (nitrogen) donor atoms provide flexible coordination modes, so as to maximize the stability of a metal complex and its subsequent use in catalysis.[8] The first synthesis of ligands containing phosphorus–nitrogen–phosphorus donors (PNP ligands) was reported as early as 1970.[9] Even though the coordination chemistry of these ligands with transition metals was reported,[10] applying them in catalysis is fairly recent. In most cases, the nitrogen site in the ligand is involved in tethering the ligand, for example, to carriers such as solid supports[11] and proteins.[12]

Organometallic catalysis using dendrimers was reported first by van Koten[5] and since then a variety of ligands and catalytically active complexes have been incorporated at various locations of dendrimers.[13] Owing to the importance of phosphorus ligands in catalysis, incorporation of both chiral and achiral phosphine ligands has been accomplished.[14] Dendrimers have often been considered as a template or support to perform catalysis, and dendrimers have been idealized as meeting the requirement of both homogeneous and heterogeneous catalysis. The effectiveness of dendritic over polymeric support has also been tested in recycling, nano-filtration and continuous batch reactor process.[15]

In this paper, we describe the synthesis of bidentate PNP ligands, followed by their incorporation at the peripheries of new poly(ether imine) dendrimers, reported by us recently.[16] A strategy in which the phosphine ligand is introduced towards the final step of the synthesis is important, as it overcomes concerns arising from other functional groups present in the preformed dendrimer. Upon synthesis, complexation with $Pd(COD)Cl_2$ (COD = 1,5-cyclooctadiene) followed by evaluation of the catalytic

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Keywords: Catalysis; Dendrimers; Heck coupling; Phosphine ligands; Palladium(II) complexes.

* Corresponding author. Tel.: +91-80-2293-2406/2403; fax: +91-80-2360-0529; e-mail: jayaraman@orgchem.iisc.ernet.in

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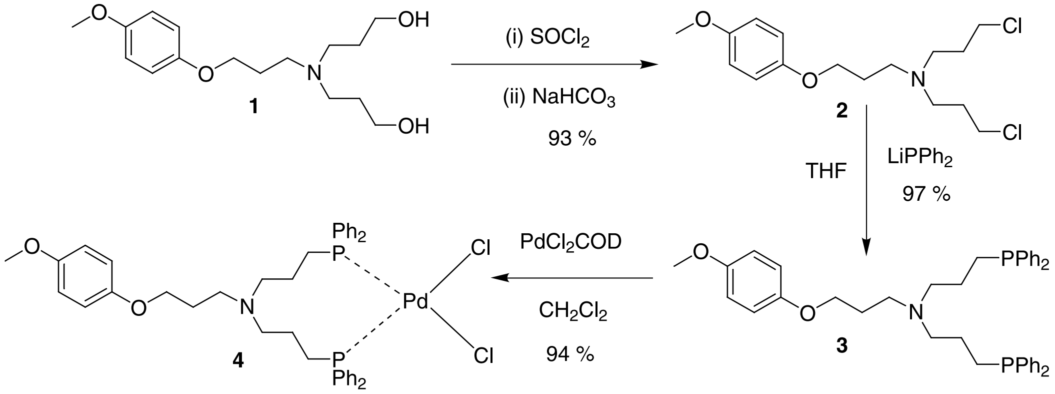


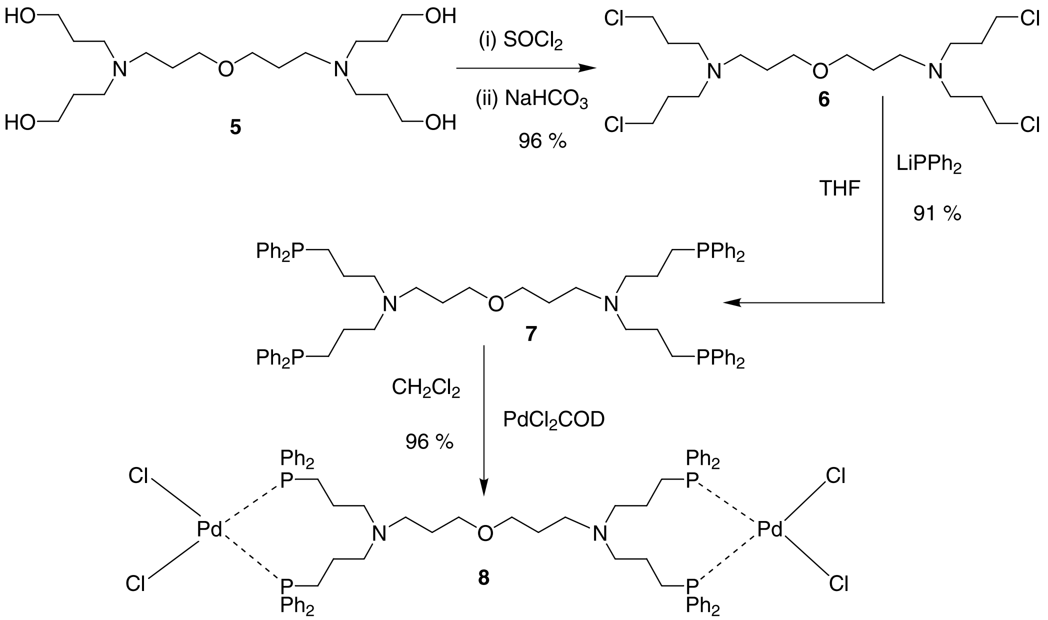
Scheme 1. Synthesis of new alkyl diphenylphosphine ligand and its Pd^{II} complex.

activities of these new phosphine–metal dendritic complexes were performed. Details of synthesis, metal complexation and an assessment of the catalytic activities are described herein.

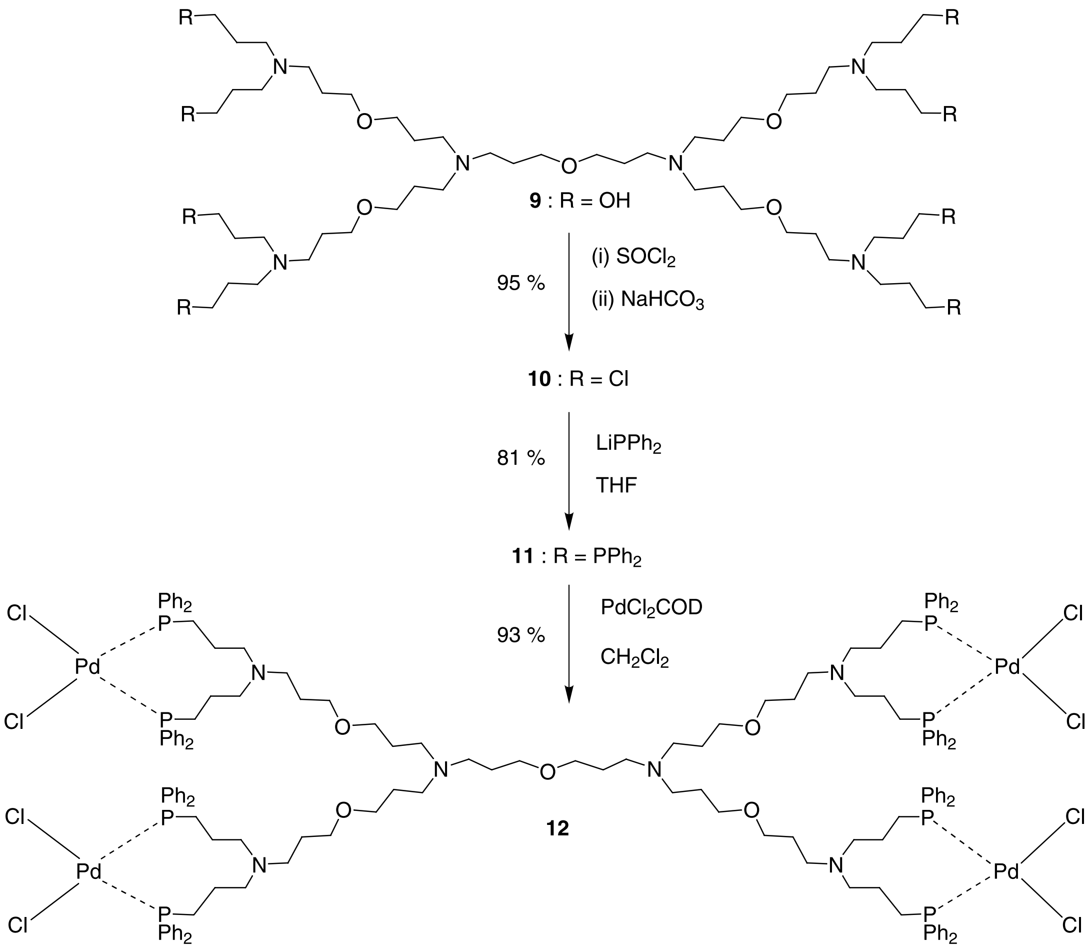
2. Results

Synthesis of new bidentate alkyldiphenylphosphine ligand was accomplished by reaction of a halide with a phosphide of Li or K in THF. In order to modify the poly(ether imine) dendrimers,[16] the free hydroxyl groups at the peripheries of dendrimers were used. Thus, the alcohol functionalities in **1** were transformed to chloride in **2**, using excess $SOCl_2$ as the reagent (Scheme 1). Removal of excess $SOCl_2$, first by co-evaporation with solvent and then by quenching with EtOH, is essential in order to prevent charring of the product under the reaction conditions. The resulting water-soluble hydrochloride salt was neutralized with aq $NaHCO_3$ and chloride **2** was extracted with EtOAc. Treatment of **2** with lithium diphenylphosphide, prepared in situ from lithium and triphenylphosphine, in THF afforded bidentate alkyl diphenylphoshine **3** in a nearly quantitative yield. The alkyl diphenylphosphine **3** is air sensitive and is oxidized when exposed to the atmosphere; however, it appeared to be stable when stored under an argon atmosphere. It remains as a colorless viscous liquid and is readily soluble in various organic solvents. Phosphine–Pd^{II} complex **4** was prepared by mixing 1 molar equiv of $Pd(COD)Cl_2$ to 2 molar equiv of alkyl diphenylphosphine at ambient temperature in CH_2Cl_2. The metal complex **4** was thus obtained in excellent yield, as an orange-yellow solid. Triturating the resulting complex with Et_2O removed the unreacted ligand and by-products. The above synthetic protocol was utilized to prepare first generation poly(ether imine) dendrimer, in order to obtain the metallo-dendrimer with two catalytic sites at the peripheries (Scheme 2).

Modifications of the second and third generation dendrimers were accomplished using the same protocol (Schemes 3 and 4). It was observed that the alkyl diphenylphosphinated third generation dendrimer was less soluble in ether, when compared to the first and second generation phosphinated dendrimers. The Pd^{II} metal complexes of second **12** and third generation **16** dendrimers were moderately soluble in chlorinated solvents.



Scheme 2. Synthesis of G-1 metallo-dendrimer **8** with two catalytic sites.



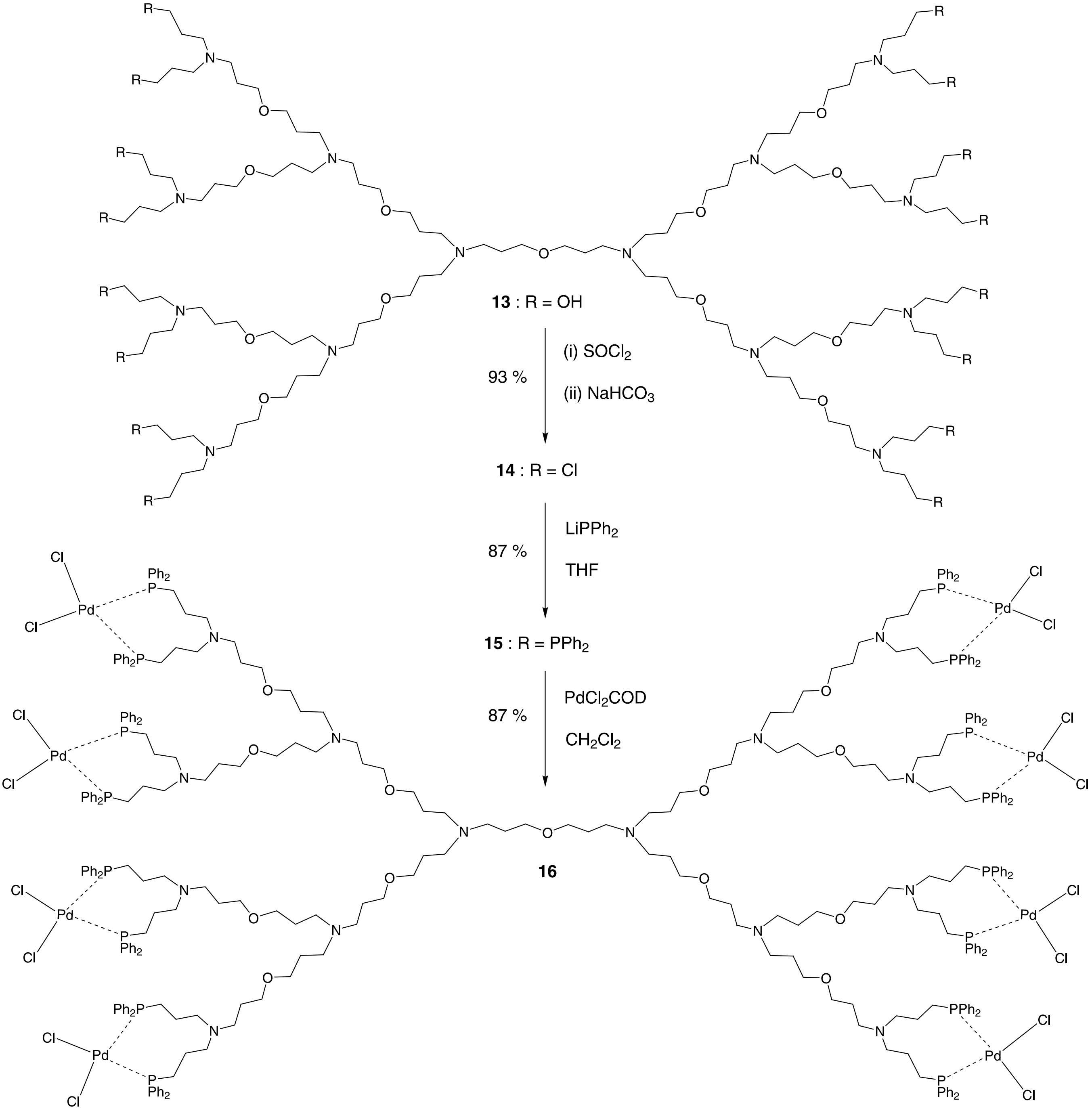
Scheme 3. Synthesis of G-2 metallo-dendrimer **12** with 4 catalytic sites.

In general, all of the phosphine–Pd complexes (**4**, **8**, **12** and **16**) were air stable in the solid state, however they appeared to be sensitive when left in the solution phase for extended periods. Decomposition occurred slowly for complex **4**, whereas G-1 (**8**), G-2 (**12**) and G-3 (**16**) complexes were unstable and decomposed more quickly.

All the compounds were characterized by ^{1}H, ^{13}C NMR, IR spectroscopies and by mass spectrometry. The transformation of alcohols to chlorides was monitored using IR spectroscopy so as to observe disappearance of the alcohol stretching frequency (ν 3390). Characteristics of the ^{1}H NMR spectra were changes in the chemical shifts of the $-CH_2-$ groups at the peripheries that depend on the nature of the functional group attached. The ^{1}H NMR of alcohols and chlorides appeared similar, whereas the difference between them was evident in ^{13}C NMR spectra where the peripheral $-CH_2-$ resonated at 43 ppm for chlorides and 62 ppm for alcohols. Disappearance of the triplet at $\sim$3.57 ppm of $-CH_2Cl$ group and the appearance of resonances at $\sim$2.00 ppm, corresponding to the formation of $-CH_2PPh_2$ was distinct for the alkyl diphenylphosphine ligands.

The ^{1}H NMR spectrum of phosphinated G-3 dendrimer is shown in Figure 1. ^{13}C NMR spectra had shown a multiplet at 128 ppm, doublets at 132 and 139 ppm, with coupling constants of 18 and 13 Hz, respectively, for the phenyl rings of the phosphine moiety of the dendrimers. The characteristic ^{13}C NMR spectroscopic feature was the presence of three doublets at $\delta = 23$ ($^2J = 16.1$ Hz), $\delta = 25$ ($^1J = 11.2$ Hz) and $\delta = 54$ ($^3J = 14.2$ Hz), indicating the presence of alkyl diphenylphosphine on the periphery of the dendrimers. Compounds whose molecular weight was less than 1000 were characterized by high-resolution mass spectrometry. The alkyl diphenylphosphine dendritic ligands (**3**, **7**, **11** and **15**) were characterized further by ^{31}P NMR spectrum, which exhibited a sharp singlet -16.1 ppm, typical for a phosphorus nucleus in alkyldiphenylphosphine environment. We have also observed a trace of phosphine oxide product, formed due to aerial oxidation of phosphine, as evident from a resonance at 32.9 ppm.

The ligand environment around the metal site follows a nearly identical pattern, from monomer to the dendrimer, as observed from the respective ^{31}P NMR spectra. Upon metal complexation, all the dendritic complexes showed a shift in the resonance of ^{31}P NMR spectra by $\sim$33.2 ppm, i.e., from -16.1 ppm for uncomplexed ligand to 17.1 ppm after metal complexation (Fig. 2). Also, the ^{31}P NMR spectra of Pd^{II} complexes (**4**, **8**, **12** and **16**) indicated that all the phosphorus atoms were coordinated to the metal ion in an equivalent environment. All the dendritic metal complexes showed ^{31}P NMR resonances uniformly at 17.1 ppm, indicating that they have a similar bidentate mode of complexation, as in the monomer metal complex **4**.



Scheme 4. Synthesis of G-3 metallo-dendrimer **16** with 8 Pd bidentate complexes at the periphery.

From the ^{31}P NMR spectrum of third generation Pd^{II} complex, which also showed signals at lower fields, it appears that the mode of complexation may be slightly different than suggested for this complex. Alternatively, the lower field resonances in the ^{31}P NMR spectrum of **16** could indicate a decomposition of the complex in solution. The resonances of the ligand **15** at -5.3 and 33.0 ppm correspond to triphenylphosphine and the triphenylphosphine oxide, respectively. When triphenylphosphine is complexed with Pd(COD)Cl$_2$, it forms Pd(PPh$_3$)$_2$Cl$_2$ complex. Pd(PPh$_3$)$_2$Cl$_2$ complex is insoluble in CH$_2$Cl$_2$[17] and thus it could be separated from the dendritic complex **16**. In all the cases, complete metallation was established by elemental analysis. Elemental analysis of the complexes agreed well with the theoretical values, except third generation Pd^{II} complex, which showed a slight deviation in the elemental analysis. Irrespective of this slight deviation, complete metallation was evident from the ^{31}P NMR spectrum, in comparison to the corresponding free ligand. The metal complexation experiments show that the ligand locations are freely accessible at the peripheries of the dendrimers and allow metal complexation at all phosphine ligand sites.

The dendritic alkyldiarylphosphine–Pd^{II} metal complexes were subjected to organometallic catalysis. In this study, we

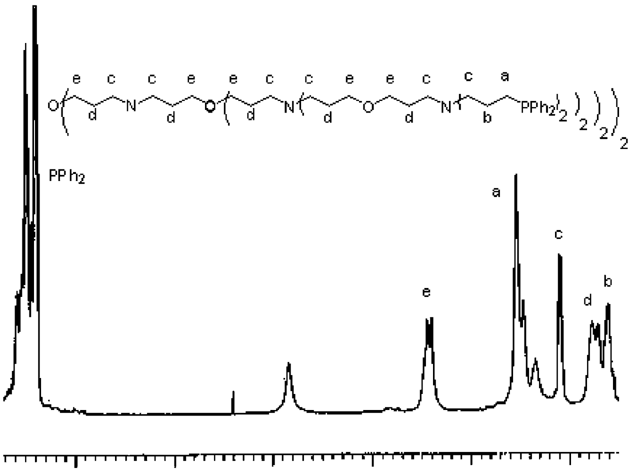
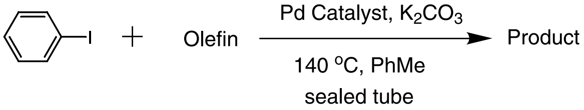


Figure 1. ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of G-3 dendrimer (**15**) with 16 alkyl diphenyl phosphines.

have chosen the C–C bond forming reaction, namely Heck coupling, mediated by the newly formed dendritic catalysts. The catalytic activities were tested for the reaction of iodobenzene with a variety of olefins (Scheme 5).

All the reactions were carried out in a sealed tube at 140 °C, using K_2CO_3 as the base and PhMe as the solvent under argon atmosphere. The products were characterized by ^{1}H and ^{13}C NMR spectroscopies and were also compared with the spectra of authentic samples. The molar ratio of dendritic Pd^{II}–metal complex to substrate was taken initially in the range of 1:100, then gradually increased to 1:1000. The olefin substrate and K_2CO_3 were used in 1.2 molar equiv to that of iodobenzene. The catalytic activity of the reaction is summarized in Table 1. In all the Heck reactions, only a single product, corresponding to the *trans* isomer was obtained, apart from the unreacted starting material. None of the *cis* isomer or any other by-product could be observed, either by tlc or in the ^{1}H NMR spectrum. The reactions were performed at least twice and the percentage of conversion is calculated on the basis of isolated yields, after column chromatographic purification of the product. It was observed that the catalysts in general were more active for acrylates and good conversions could be achieved.



Scheme 5. Reaction of iodobenzene with olefins in the presence of dendritic catalyst.

Complex **4** did not show any evidence of an induction time and the reaction initiated immediately after the temperature of the reaction mixture reached 120 °C, at which point a mild black precipitate appeared in the reaction vessel. It is likely that the required Pd^{0} complexes form in situ as the

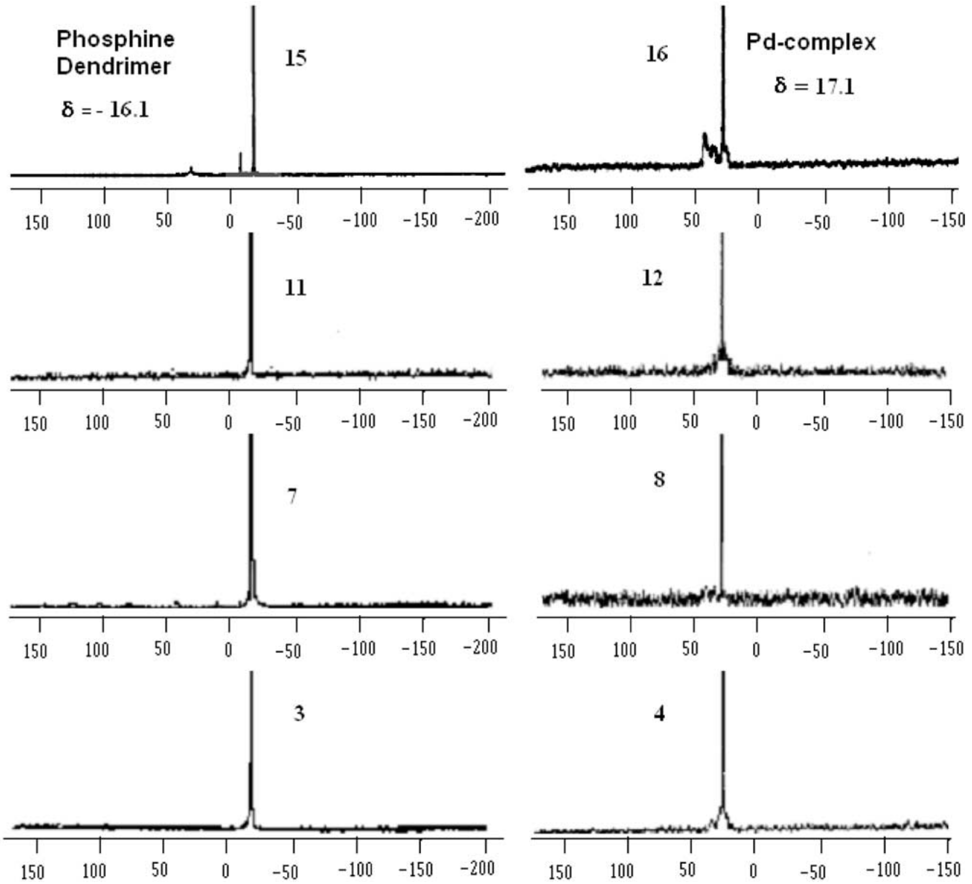
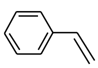
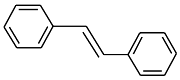
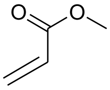
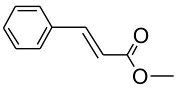
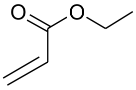
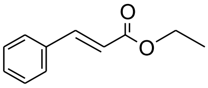
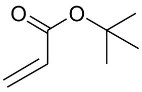
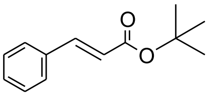
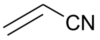
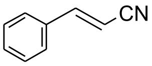
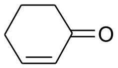
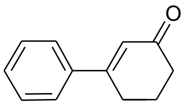
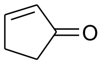
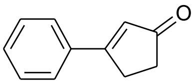
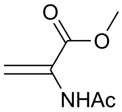
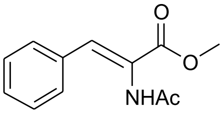
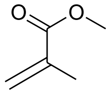
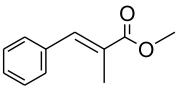
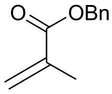
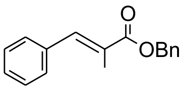
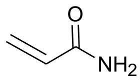
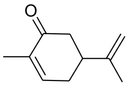
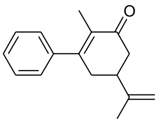
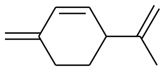


Figure 2. ^{31}P NMR spectra (400 MHz, CDCl$_3$) of phosphinated dendrimers (**3**, **7**, **11** and **15**) and the corresponding Pd^{II} dendrimers (**4**, **8**, **12** and **16**).

Table 1. Olefin substrates and the corresponding products formed by the Heck coupling catalyzed by dendritic metal-complexes **4**, **8**, **12** and **16**

Entry	Substrate	Reaction time (h)	Product	Catalyst	Yield (%)
1		20		**4** **8** **12** **16**	50 65 45 36
2		4		**4** **8** **12** **16**	65 69 56 54
3		4		**4** **8** **12** **16**	75 76 57 59
4		4		**4** **8** **12** **16**	85 81 63 69
5		4		**4** **8** **12** **16**	72 79 56 57
6		4		**4** **8** **12** **16**	63 76 54 43
7		4		**4** **8** **12** **16**	72 62 56 52
8		4		**4** **8** **12** **16**	78 74 54 45
9		4		**4** **8** **12** **16**	Trace conversion
10		4		**4** **8** **12** **16**	Trace conversion
11		16	No reaction	**4**	
12		6		**4**	Trace conversion
13		6	Mixture	**4**	

active catalyst. Owing to the temperature being maintained above the boiling point of the olefinic substrate, the reactions had to be carried out in a sealed tube. For styrene, the reaction was sluggish and took more time than other olefinic substrate. We did not observe any reaction between acrylamide, probably due to its insolubility in PhMe.

3. Discussion

The most studied dendritic structures functionalized with phosphine ligands at their peripheries were those derived from (i) PAMAM[13b,14e–g,18] (ii) poly(propylene imine)[6e,13c,19] (iii) carbosilane[5,6c,20] and (iv) phosphine.[21] Apart from these, phosphines were also incorporated in the interiors of dendritic structure, such as those reported by DuBois,[14a,22] Rengan and Engel[23] and Majoral.[24] Dendritic catalysts are considered as new materials that combine the advantages and disadvantages associated with heterogeneous and homogeneous catalysis. van Koten reported that dendritic catalysts are superior to a polymer support, as the number and the position of catalytic sites can be strictly controlled.[5] The potential advantage arising from nanoscopic properties of dendritic catalyst was also demonstrated.[15] An important enhancement in the catalytic activities due to ‘cooperative effects’ has been reported by Jacobsen and co-workers.[6d] Detty and co-workers[25] have reported increased activity per catalytic group in successive generations in a two-phase oxidation of bromide in the presence of H_2O_2, catalyzed by phenylseleno-containing dendrimers. These authors proposed that the ‘dendritic effect’ observed in these catalysis may be due to presumed micelle-like nature of the oxidized catalyst.

We have observed that the optimum conversion level is highly substrate dependent. Table 1 shows an increase in the substrate conversion could be realized for the G1-Pd catalyst, followed by a mild fall in the conversion of substrates with higher generations. It could also be noticed that catalytic activity of G-1–Pd^{II} complex was greater than the monomer complex **4**, G-2–Pd^{II} (**12**) and G-3–Pd^{II} (**16**) catalyst. G-1–Pd^{II} (**8**) complex appeared to be better among the catalysts and catalyzed reactions faster than the other catalysts.

The results of the molar ratio of substrate to catalyst with various olefins are presented in Figure 3. In this plot, the molar ratio was determined on the basis of the minimum amount of catalyst required to initiate the reaction. There is a general increase in the ratio, starting with monomeric catalyst **4** to higher generation dendritic catalysts.

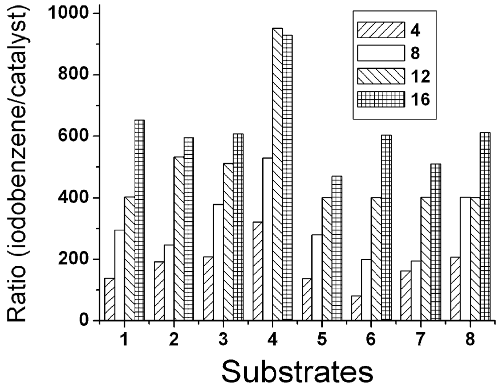


Figure 3. Ratio of substrate to catalyst employed in Heck coupling reaction of iodobenzene with substrates (1 = styrene; 2 = methylacrylate; 3 = ethylacrylate; 4 = *t*-butylacrylate; 5 = acrylonitrile; 6 = 2-cyclohexenone; 7 = 2-cyclopentenone and 8 = 2-acetamidomethylacrylate) employing dendritic catalysts.

From Figure 3, it is clear that higher generation dendritic catalysts are better than monomeric and lower generation catalysts, in terms of the amount of molar catalyst employed for catalytic conversion. Attempts were undertaken to recycle the catalysts. While catalysis was possible with regenerated catalysts, the catalytic activities were diminished, when compared to the corresponding fresh catalyst.

The turn-over-number (TON) calculated after 4 h in the reaction of iodobenzene with the olefinic substrate is shown in Figure 4. The TON for acrylates is substantially higher than other olefinic substrates.

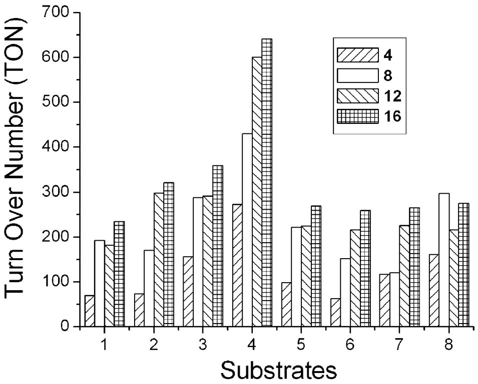


Figure 4. Turn Over Number (TON) of Heck coupling reaction of iodobenzene with substrates (1 = styrene; 2 = methylacrylate; 3 = ethylacrylate; 4 = *t*-butylacrylate; 5 = acrylonitrile; 6 = 2-cyclohexenone; 7 = 2-cyclopentenone and 8 = 2-acetamidomethylacrylate) employing dendritic catalysts.

Within the acrylates, Heck coupling of *t*-butylacrylate was far more efficient than methyl and ethyl acrylates. We also find that when an electron-donating group such as a methyl group is present (entries 9, 10, 12 and 13 in Table 1), the substituents retarded the Heck coupling. On the other hand, when an electron-withdrawing group such as an acetylated amine substituent is present on the double bond of the acrylate (entry 8), moderate TON could be observed and the products were formed in good yields. We also find that the TON increases in general with the higher generation dendrimers, namely, the second and third generation dendritic catalysts, than the monomer and the first generation catalysts. We realize that even though the TONs are not exceptionally high, the modest increase in the TON as the generations advance is clearly observable.

4. Conclusion

We have modified poly(ether imine) dendrimer peripheries with new alkyldiphenylphosphine ligands, followed by their conversion to catalytically active phosphine–Pd^{II} complexes efficiently and in high yields. The dendrimers thereby contain catalytic sites in precise locations. A series of catalysts with 1, 2, 4 and 8 catalytic centers was prepared, corresponding to the monomer, first, second and third generation dendrimers, respectively. In addition, alkyldiphenylphosphine **3** is a useful ligand, which has not been studied so far and thus remains to be explored further for a variety of catalysis. Catalytic reactions involving these new dendritic catalysts were conducted in the case of the C–C bond forming Heck coupling reaction, which showed good conversion for the reaction of an aromatic halide with a variety of alkene substrates. The catalysts were comparatively efficient for Heck coupling of the acrylates compared to other olefinic substrates. The dendritic catalysts reported herein add further to repertoire of catalysts for the well-documented Heck coupling reaction in synthesis. The high catalytic performance of the higher generation metallo-dendrimers, when compared to monomeric complex **4**, could be a useful property for further studies with these dendritic catalysts.

5. Experimental

5.1. General methods

Chemicals were purchased from commercial sources and used as received. Solvents were dried and distilled according literature procedures. Analytical TLC was performed on commercial Merck plates coated with aluminium oxide 60 F_{254} neutral (type E, 0.2 mm) or silica gel GF_{254} (0.25 mm). Silica gel (100–200 mesh) and basic alumina were used for column chromatography. Infrared spectra were recorded as neat or KBr samples. Electrospray mass spectra were recorded as a solution in either $MeCN/H_2O$ (1:1) or $MeOH/H_2O$ (1:1). ^1H and ^{31}P NMR spectral analysis were performed on a spectrometer operating at 400 and 162 MHz, respectively. ^{13}C NMR spectral analyses were performed on a spectrometer operating at 75.5 MHz. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; band, several overlapping signals; b, broad.

5.2. General procedure for transformation of alcohol to chloride

To a solution of alcohol in $CHCl_3$ (25 mL), $SOCl_2$ in $CHCl_3$ was added drop-wise, the reaction mixture was kept at 55 °C for 3 h. Excess $SOCl_2$ and solvent were removed in vacuo and the crude product was diluted with EtOH (5 mL) and warmed for 10 min. Solvents were removed in vacuo, the resulting residue diluted with EtOAC and washed with aq $NaHCO_3$ brine, dried and evaporated. The resulting crude product was purified (alumina) to obtain the desired product as a colorless liquid.

5.3. General procedure for phosphination of chloride

To a solution of chloride in THF (25 mL), $LiPPh_2$ in THF (50 mL) was added drop-wise at 0 °C, for 30 min. The reaction mixture was then refluxed for additional 20 min, cooled and evaporated in vacuo. The residue was dissolved in Et_2O, filtered and concentrated to obtain phosphide as a colorless liquid.

5.4. General procedure for preparation of Pd catalyst

A mixture of phosphine and $Pd(COD)Cl_2$ in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h, solvents were removed, the residue washed with hexane followed by Et_2O and dried to give the desired complex. The catalysts were prepared freshly each time before the catalytic studies were performed.

5.5. General experimental procedure for Heck coupling of olefins with iodobenzene

Iodobenzene (102 mg, 0.5 mmol), olefin (0.6 mmol), K_2CO_3 (81 mg, 0.6 mmol) and monomeric or dendritic Pd^{II} catalyst (5–0.5 μmol) in PhMe (1 mL) were taken in sealed tube (25 mL), fitted with a teflon cap. The tube was evacuated, flushed with argon gas, after which the reaction mixture refluxed with stirring at 140 °C for 4 h. The reaction mixture was then cooled, solvents evaporated and the residue was extracted with Et_2O to give the crude product, which was purified by column chromatography. Heck coupling products were characterized by ^1H NMR spectroscopy and the ^1H NMR resonances were compared with that known previously.[26] Conversion percentage is calculated based on the product obtained. Turn-over-number (TON) is calculated using the formula: (substrate mole/catalyst mole) × conversion%.

5.5.1. Compound 2. To a stirring solution of **1**[16] (2.75 g, 9.1 mmol) in $CHCl_3$ (25 mL), $SOCl_2$ (3.04 g, 25.5 mmol) in $CHCl_3$ (25 mL) was added drop-wise and followed further as described in the general procedure. The resulting crude product was purified (alumina, hexane:EtOAc = 95:5) to obtain **2** (2.85 g, 93%) as a colorless liquid. FT-IR (neat) ν: 1506, 1231, 1039, 825, 652; ^1H NMR ($CDCl_3$) δ: 1.88 (q, 6H, $J = 6.3$ Hz), 2.55 (t, 6H, $J = 6.3$ Hz), 3.57 (t, 4H, $J = 6.3$ Hz), 3.77 (s, 3H), 3.95 (t, 2H, $J = 6.3$ Hz), 6.82 (s, 4H); ^{13}C NMR ($CDCl_3$) δ: 27.2, 30.2, 43.2, 50.3, 50.6, 55.6, 66.1, 114.6, 115.3, 153.1, 153.7; EI-MS: *m/z*: 334 $[M]^+$; HRMS: *m/z*: calcd for $C_{16}H_{25}O_2NCl_2$: 334.1340. Found: 334.1339.

5.5.2. Compound 3. To a stirring solution of **2** (2.85 g, 8.5 mmol) in THF (25 mL), $LiPPh_2$ (3.65 g, 19 mmol) in THF (50 mL) was added drop-wise and followed further as described in the general procedure to obtain **3** (5.22 g, 97%) as a colorless liquid. FT-IR (neat) ν: 1507, 1434, 1231, 1181, 740, 696; ^1H NMR ($CDCl_3$) δ: 1.47–1.57 (m, 4H), 1.81 (q, 2H, $J = 6.8$ Hz), 1.95–2.04 (m, 4H), 2.45 (t, 6H, $J = 6.8$ Hz), 3.75 (s, 3H), 3.87 (t, 2H, $J = 6.8$ Hz), 6.78 (s, 4H), 7.23–7.37 (m, 20H); ^{13}C NMR ($CDCl_3$) δ: 23.5 (d, $J = 16.1$ Hz), 25.6 (d, $J = 11.2$ Hz), 27.1, 50.3, 54.8 (d, $J = 13.6$ Hz), 55.7, 66.7, 114.6, 115.4, 128.4 (m), 132.6 (d, $J = 18.6$ Hz), 138.8 (d, $J = 13.1$ Hz), 153.2, 153.6; ^{31}P NMR ($CDCl_3$) δ: −16.1; EI-MS: *m/z*: 634 $[M+1]^+$; HRMS: *m/z*: calcd for $C_{40}H_{45}O_2NP_2$: 634.3004. Found: 634.2975.

5.5.3. Compound 4. A mixture of **3** (44 mg, 70 μmol) and $Pd(COD)Cl_2$ (20 mg, 70 μmol) in CH_2Cl_2 (5 mL) was stirred for 1 h and processed further as given in the general procedure to afford **4** (53 mg, 94%) as a pale yellow solid. FT-IR (neat) ν: 3425, 1434, 1101, 742; ^{31}P NMR ($CDCl_3$) δ: 17.1; EI-MS: *m/z*: 834 $[M+Na]^+$; HRMS: *m/z*: calcd for $C_{40}H_{45}O_2NP_2PdCl_2$: 834.3259. Found: 834.3288; Elemental analysis: calcd for $C_{40}H_{45}O_2NP_2PdCl_2$: C 59.23, H 5.59, N 1.73. Found: C 60.91, H 5.81, N 1.62.

5.5.4. Compound 6. To a stirring solution of **5**[16] (0.33 g, 0.9 mmol) in $CHCl_3$ (25 mL), $SOCl_2$ (0.56 g, 4.7 mmol) in $CHCl_3$ (25 mL) was added drop-wise and followed further as described in the general procedure. The resulting crude product was purified (alumina, hexane: EtOAc = 85:15) to obtain **6** (0.38 g, 96%) as a colorless liquid. FT-IR (neat) ν:

1463, 1296, 1115, 652; ^{1}H NMR ($CDCl_3$) δ: 1.70 (q, 4H, $J=6.0$, 6.9 Hz), 1.88 (q, 8H, $J=6.6$, 6.3 Hz), 2.46 (t, 4H, $J=6.9$ Hz), 2.53 (t, 8H, $J=6.6$ Hz), 3.42 (t, 4H, $J=6.3$ Hz), 3.60 (t, 8H, $J=6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ: 27.4, 30.3, 43.2, 50.6, 50.7, 68.8; EI-MS: *m/z*: 437, 439 $[M]^+$; HRMS: *m/z*: calcd for $C_{18}H_{36}ON_2Cl_4$: 437.1660. Found: 437.1648.

5.5.5. Compound 7. To a stirring solution of **6** (0.24 g, 0.55 mmol) in THF (25 mL), $LiPPh_2$ (0.44 g, 2.4 mmol) in THF (50 mL) was added drop-wise and followed further as described in the general procedure to obtain **7** (0.52 g, 91%) as a colorless liquid. FT-IR (neat) ν: 1434, 1183, 1118, 739, 696; ^{1}H NMR ($CDCl_3$) δ: 1.47–1.57 (m, 8H), 1.62 (q, 4H, $J=6.4$ Hz), 1.96 (appr. t, 8H), 2.37 (t, 4H, $J=6.8$ Hz), 2.44 (t, 8H, $J=6.8$ Hz), 3.34 (t, 4H, $J=6.8$ Hz), 7.23–7.40 (m, 40H); ^{13}C NMR ($CDCl_3$) δ: 23.1 (d, $J=16.1$ Hz), 25.6 (d, $J=11.7$ Hz), 26.9, 50.6, 54.6 (d, $J=13.1$ Hz), 69.0, 128.4 (m), 132.6 (d, $J=18.0$ Hz), 138.7 (d, $J=13.1$ Hz); ^{31}P NMR ($CDCl_3$) δ: -16.1; EI-MS: *m/z*: 1037 $[M+1]^+$; HRMS: *m/z*: calcd for $C_{60}H_{76}ON_2P_4$: 1037.4986. Found: 1037.4999.

5.5.6. Compound 8. A mixture of **7** (36 mg, 35 μmol) and $Pd(COD)Cl_2$ (20 mg, 70 μmol) in CH_2Cl_2 (5 mL) was stirred for 1 h and processed further as given in the general procedure to afford **6** (46 mg, 96%) give as a pale yellow solid. FT-IR (neat) ν: 3425, 1434, 1101, 742; ^{31}P NMR ($CDCl_3$) δ: 17.1; Elemental analysis: calcd for $C_{66}H_{76}ON_2P_4Pd_2Cl_4$: C 56.95, H 5.50, N 2.01. Found: C 57.37, H 5.88, N 2.33.

5.5.7. Compound 10. To a stirring solution of **9**[16] (0.66 g, 0.63 mmol) in $CHCl_3$ (25 mL), $SOCl_2$ (0.66 g, 5.5 mmol) in $CHCl_3$ (25 mL) was added drop-wise and followed further as described in the general procedure. The resulting crude product was purified (alumina, hexane: $EtOAc=75:25$) to obtain **10** (0.71 g, 95%) as a colorless liquid. FT-IR (neat) ν: 1463, 1368, 1296, 1116, 722, 653; ^{1}H NMR ($CDCl_3$) δ: 1.70 (q, 20H, $J=6.8$, 6.4 Hz), 1.89 (q, 16H, $J=6.8$, 6.4 Hz), 2.47 (t, 20H, $J=6.8$ Hz), 2.54 (t, 16H, $J=6.4$ Hz), 3.43 (m, 20H), 3.61 (t, 16H, $J=6.4$ Hz); ^{13}C NMR ($CDCl_3$) δ: 27.2, 27.3, 27.4, 30.3, 43.2, 50.7, 50.8, 68.7, 69.1; EI-MS: *m/z*: 1201 $[M+1]^+$.

5.5.8. Compound 11. To a stirred solution of **10** (0.40 g, 0.33 mmol) in THF (25 mL), $LiPPh_2$ (0.53 g, 2.9 mmol) in THF (50 mL) was added drop-wise and followed further as described in the general procedure to obtain **11** (0.644 g, 81%) as a colorless liquid. FT-IR (neat) ν: 1434, 1184, 1118, 741, 696; ^{1}H NMR ($CDCl_3$) δ: 1.43–1.51 (m, 16H), 1.59–1.65 (m, 20H), 1.84 (appr. t, 16H), 2.34–2.44 (m, 36H), 3.29–3.36 (m, 20H), 7.25–7.40 (m, 80H); ^{13}C NMR ($CDCl_3$) δ: 23.5 (d, $J=16.1$ Hz), 25.7 (d, $J=11.2$ Hz), 27.3, 27.4, 29.7, 50.7, 50.8, 54.9 (d, $J=14.2$ Hz), 69.3, 128.4 (m), 132.6 (d, $J=18.6$ Hz), 138.9 (d, $J=13.1$ Hz); ^{31}P NMR ($CDCl_3$) δ: -16.1.

5.5.9. Compound 12. A mixture of **11** (42 mg, 18 μmol) and $Pd(COD)Cl_2$ (20 mg, 70 μmol) in CH_2Cl_2 (5 mL) was stirred for 1 h and processed further as given in the general procedure to afford **12** (50 mg, 93%) as a pale yellow solid. FT-IR (neat) ν: 3392, 1435, 1109, 739; ^{31}P NMR ($CDCl_3$) δ: 17.1; Elemental analysis: calcd for $C_{150}H_{188}O_5N_6P_8Pd_4Cl_8$: C 57.89, H 6.09. Found: C 57.52, H 6.03.

5.5.10. Compound 14. To a stirring solution of **13**[16] (0.24 g, 98 μmol) in $CHCl_3$ (25 mL), $SOCl_2$ (0.21 g, 1.74 mmol) in $CHCl_3$ (25 mL) was added drop-wise and followed further as described in the general procedure. The resulting product was purified (alumina, hexane: $EtOAc=55:45$) to obtain **14** (0.25 g, 93%) as a colorless liquid. FT-IR (neat) ν: 1463, 1368, 1296, 1116, 722, 653; ^{1}H NMR ($CDCl_3$) δ: 1.62 (b, 52H), 1.81 (q, 32H, $J=6.3$ Hz), 2.36–2.48 (m, 84H), 3.35 (m, 52H), 3.53 (t, 32H, $J=6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3, 27.5, 30.3, 43.2, 50.6, 50.7, 50.8, 68.7, 69.1.

5.5.11. Compound 15. To a stirring solution of **14** (0.25 g, 91 μmol) in THF (25 mL), $LiPPh_2$ (0.308 g, 2.9 mmol) in THF (50 mL) was added drop-wise and followed further as described in the general procedure to obtain **15** (0.408 g, 87%) as a colorless liquid. FT-IR (neat) ν: 1434, 1184, 1118, 741, 696; ^{1}H NMR ($CDCl_3$) δ: 1.43–1.51 (m, 32H), 1.59–1.65 (m, 52H), 1.99 (appr. t, 84H), 2.35–2.45 (m, 32H), 3.28–3.37 (m, 52H), 7.25–7.40 (m, 160H); ^{13}C NMR ($CDCl_3$) δ: 23.3 (d, $J=16.1$ Hz), 25.6 (d, $J=11.2$ Hz), 26.7, 27.0, 27.7, 29.5, 50.4, 50.6, 50.7, 54.2 (m), 68.7, 69.0, 69.1, 128.4 (m), 132.6 (d, $J=18.6$ Hz), 138.9 (d, $J=13.1$ Hz); ^{31}P NMR ($CDCl_3$) δ: -16.1, -5.3, 33.0.

5.5.12. Compound 16. A mixture of **15** (22 mg, 4.3 μmol) and $Pd(COD)Cl_2$ (20 mg, 70 μmol) in CH_2Cl_2 (5 mL) was stirred for 1 h, filtered and processed further as given in the general procedure to afford **16** (25 mg, 87%) a pale yellow solid. FT-IR (neat) ν: 3388, 1435, 1101, 745; ^{31}P NMR ($CDCl_3$) δ: 17.1, 26.5, 32.5; Elemental analysis: calcd for $C_{318}H_{412}O_{13}N_{14}P_{16}Pd_8Cl_{16}$: C 58.29, H 6.34. Found: C 57.35, H 5.89.

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References and notes

1. For few reviews, see: (a) Newkome, G. R.; Moorefield, C.; Vögtle, F. *Dendritic Macromolecules: Concepts, Synthesis, Perspectives*; VCH: Weinheim, 1996. (b) Smith, D. K.; Diederich, F. *Chem. Rev.* **1998**, 4, 1353–1361. (c) Gorman, C. B. *Adv. Mater.* **1998**, 10, 295–309. (d) Fisher, M.; Vögtle, F. *Angew. Chem. Int. Ed.* **1999**, 38, 884–905. (e) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, 101, 3819–3867. (f) *Top. Curr. Chem.* **2002**, *217* (g) Tomalia, D. A.; Fréchet, J. M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, 40, 2719–2728. (h) Boas, U.; Heegaard, P. M. H. *Chem. Soc. Rev.* **2004**, 33, 43–63.
2. (a) Jansen, J. F. G. A.; de Brabander-van den Berg,

E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226–1229. (b) Brennecke, J. F. *Nature* **1997**, *389*, 333–334. (c) Aulenta, F.; Hayes, W.; Rannard, S. *Eur. Polym. J.* **2003**, *39*, 1741–1771.

3. (a) Twyman, L. J.; Beezer, A. E.; Esfand, R.; Hardy, M. J.; Mitchell, J. C. *Tetrahedron Lett.* **1999**, *40*, 1743–1746. (b) Hawthorne, M. F. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 950–984. (c) Qualmann, B.; Kessels, M. M.; Musiol, H.-J.; Sierralta, W. D.; Jungblut, P. W.; Moroder, L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 909–911.
4. (a) Zimmerman, S. C.; Zeng, F. W.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095–1098. (b) Huck, W. T. S.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1213–1215. (c) Zhou, M.; Bentley, D.; Ghosh, I. *J. Am. Chem. Soc.* **2004**, *126*, 734–735.
5. Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, P. W. N. M.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature* **1994**, *372*, 659–662.
6. For few examples of cooperativity or a dendritic effect, see: (a) Lee, J. J.; Ford, W. T.; Moore, J. A.; Li, Y. *Macromolecules* **1994**, *27*, 4632–4634. (b) Enomoto, M.; Aida, T. *J. Am. Chem. Soc.* **1999**, *121*, 874–875. (c) Kleij, A. W.; Gossage, A.; Jastrzebski, J. T. B. H.; Boersma, J.; van Koten, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 176–178. (d) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 3604–3607. (e) Alonso, E.; Astruc, D. *J. Am. Chem. Soc.* **2000**, *122*, 3222–3223. (f) Nithyanandhan, J.; Davis, R.; Das, S.; Jayaraman, N. *Chem. Eur. J.* **2004**, *10*, 689–698.
7. (a) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688. (b) Hiraoka, M.; Nishikawa, A.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 704.
8. Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663–682.
9. (a) Sacconi, L.; Morassi, R. *J. Chem. Soc. A* **1968**, 2997–3002. (b) Morassi, R.; Sacconi, L. *J. Chem. Soc. A* **1971**, 492–499.
10. For reports of the PNP ligands: (a) Rahmouni, N.; Osborn, J. A.; de Cian, A.; Fischer, J.; Ezzamarty, A. *Organometallics* **1998**, *17*, 2470–2476. (b) Hahn, C.; Vitagliano, A.; Giorgano, F.; Taube, R. *Organometallics* **1998**, *17*, 2060–2066.
11. Aijou, A. N.; Alper, H. *J. Am. Chem. Soc.* **1998**, *120*, 1466–1468.
12. Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 2861–2862.
13. For recent representative reports: (a) Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 12558–12566. (b) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2003**, *125*, 13126–13131. (c) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1526–1528. (d) Chow, H. F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116–5127. (e) Liao, Y.-H.; Moss, J. R. *Organometallics* **1996**, *15*, 4307–4316.
14. (a) Miedaner, A.; Curtis, C. J.; Barkley, R. M.; DuBois, D. L. *Inorg. Chem.* **1994**, *33*, 5482–5490. (b) de Groot, D.; Eggeling, E. B.; de Wilde, J. C.; Kooijman, H.; van Haaren, R. J.; van der Made, A. W.; Spek, A. L.; Vogt, D.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun.* **1999**, 1623–1624. (c) Wijkens, P.; Jastrzebski, J. T. B. H.; van der Schaaf, P. A.; Kolly, R.; Hafner, A.; van Koten, G. *Org. Lett.* **2000**, *2*, 1621–1624. (d) Benito, M.; Rossell, O.; Seco, M.; Segales, G. *Organometallics* **1999**, *18*, 5191–5193. (e) Bourque, S. C.; Maltais, F.; Xiao, W.-J.; Tardif, O.; Alper, H.; Arya, P.; Manzer, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 3035–3038. (f) Bourque, S. C.; Alper, H.; Manzer, L. E.; Arya, P. *J. Am. Chem. Soc.* **2000**, *122*, 956–957. (g) Arya, P.; Ran, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881–1885. (h) Bardaji, M.; Kustos, M.; Caminade, A. M.; Majoral, J.-P.; Chaudret, B. *Organometallics* **1997**, *16*, 403–410. (i) Maraval, V.; Laurent, R.; Caminade, A. M.; Majoral, J.-P. *Organometallics* **2000**, *19*, 4025–4029. (j) Hovestad, N.; Eggeling, E. B.; Heidbuechel, H. J.; Jastrzebski, J. T. B. H.; Kragl, U.; Keim, W.; Vogt, D.; van Koten, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1655–1658.
15. Brinkmann, N.; Giebel, D.; Lohmer, G.; Reetz, M. T.; Kragl, U. *J. Catal.* **1999**, *183*, 163–168.
16. Krishna, T. R.; Jayaraman, N. *J. Org. Chem.* **2003**, *68*, 9694–9704.
17. Kharsh, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882–884.
18. Gong, A.; Fan, Q.; Chen, Y.; Liu, H.; Chen, C.; Xi, F. *J. Mol. Catal. A: Chem.* **2000**, *159*, 225–232.
19. de Groot, D.; de Waal, B. G. M.; Reek, J. N. H.; Schenning, A. P. H. J.; Kamer, P. C. J.; Meijer, E. W.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2001**, *123*, 8453–8458.
20. Findeis, R. A.; Gade, L. H. *Eur. J. Inorg. Chem.* **2003**, 99–110.
21. (a) Slany, M.; Bardaji, M.; Casanove, M. J.; Caminade, A. M.; Majoral, J.-P.; Chaudret, B. *J. Am. Chem. Soc.* **1995**, *117*, 9764–9765. (b) Slany, M.; Bardaji, M.; Caminade, A. M.; Chaudret, B.; Majoral, J.-P. *Inorg. Chem.* **1997**, *36*, 1939–1945.
22. Herring, A. M.; Steffey, B. D.; Miedaner, A.; Wander, S. A.; DuBois, D. L. *Inorg. Chem.* **1995**, *34*, 1100–1109.
23. (a) Rengan, K.; Engel, R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 987–990. (b) Rengan, K.; Engel, R. *J. Chem. Soc. Chem. Commun.* **1990**, 1084.
24. Majoral, J.-P.; Caminade, A. M.; Maraval, V. *Chem. Commun.* **2002**, 2929–2942.
25. Francavilla, C.; Bright, F. V.; Detty, M. R. *Org. Lett.* **1999**, *1*, 1043–1046.
26. Entries 2, 3 and 4 in Table 1: (a) Phillips, W. M.; Currie, D. J. *Can. J. Chem.* **1969**, *47*, 3137–3146. (b) Entry 5: Robinson, C. N.; Horton, J. L.; Foshee, D. O.; Jones, J. W.; Hanissian, S. H.; Slater, C. D. *J. Org. Chem.* **1986**, *51*, 3535–3540. (c) Entry 6: Bedford, G. R.; Taylor, P. J. *Org. Magn. Res.* **1977**, *9*, 49–52. (d) Entry 7: Howell, J. A. S.; O'Leary, P. J.; Yates, P. C.; Goldschmidt, Z.; Gottlieb, H. E.; Hezroni-Langerman, D. *Tetrahedron* **1995**, *51*, 7231–7246. (e) Entry 8: Bunlaksanusons, T.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3941–3943.

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A new and efficient method for conjugate addition of trialkylphosphites to 3-acylsubstituted coumarins

Rositca D. Nikolova,[a] Anka G. Bojilova[a] and Nestor A. Rodios[b,*]

[a]Department of Organic Chemistry, University of Sofia, J. Bourchier Avenue 1, Sofia 1126, Bulgaria
[b]Laboratory of Organic Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, GR-54006 Thessaloniki, Greece

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Abstract—A new and efficient conjugate addition of trialkylphosphites to 3-ω-bromoacetylcoumarin **1** catalysed by *p*-toluenesulfonic acid (TsOH) has been studied. Under the same conditions, an enolphosphate gave the corresponding esters of 3-acetyl-4-phosphono-2-oxochromans in high yields. The use of TsOH in the reaction of 3-acetyl-, 3-benzoyl-, and 3-ethoxycarbonyl coumarins led mainly to 1,4-addition products—the corresponding 3-acyl-4-dialkylphosphono-2-oxochromans—in very good yields.

1. Introduction

In a previous paper[1] we described the reaction of 3-(ω-bromoacetyl)coumarin **1** with trialkylphosphites, from which, depending on the reaction conditions and the phosphite used, the corresponding enolphosphates **2**, for R=CH_3 or C_2H_5, or the 2-oxophosphonate **3**, for R=Ph were the only isolated products. On the other hand, the interaction of the bromoderivative **1** with diethyl and dibutylphosphite under phase transfer conditions gave the corresponding epoxyphosphonates **4** as the main products.

The preparation of dialkyl 2-oxophosphonates **3** (CH_3 or C_2H_5) were realized[1] only when the carbonyl group in the starting ketone **1** was protected by the ethoxycarbonylhydrazono group, followed by Arbuzov reaction.

The experimental findings, concerning the mechanisms of the above transformations, taking into account theoretical considerations and the experimental data available for Perkow, Arbuzov and Michaelis-Becker reactions,[2–16] could be explained as follows:

1. The transformation of bromoderivative **1** to 2-oxophosphonates **3** proceeds as an Arbuzov reaction. According to the proposed mechanism for this reaction[4–9] the most simple and more likely pathway for this transformation involves the S_N2 displacement of the bromine by the phosphite. It should be emphasized that this transformation (**1**→**3**) goes only with the less reactive[2,9,16] triphenylphosphite whereas with trialkylphosphites no such products were isolated. This different behavior of triphenyl- and trialkylphosphites in the reaction with the bromoketone **1** could be explained via the formation of the more stable triphenyl phosphonium salt[7] and its thermal decomposition to the phosphonate **3**.
2. It also seems clear that the formation of epoxyphosphonates **4** proceeds under the Michaelis-Becker reaction conditions.[10–12] The first step is the nucleophilic addition of the deprotonated dialkylphosphite anion to the C=O group of **1**, followed by elimination of the bromine and cyclization to the epoxyphosphonates **4**. In fact, the transformation of **1** into epoxy derivative **4** proceed as another variation of the classic Darzen's reaction[17] and it looks normal that it proceeds with a stronger nucleophile as is the dialkylphosphite anion (Scheme 1).
3. The transformation of the bromoacetyl coumarin **1** into the enolphosphates **2**, realized under various conditions, typical for the Arbuzov/Perkow reaction, took place only with trialkyl phosphites. Surprisingly, when the reaction was performed in acetic acid, it was completed within 5 min giving the enolphosphate **2** in 84% yield.

It has been reported[3,15,16] that the reaction of α-haloketones with trialkylphosphites in the presence of acetic acid favors the formation of enolphosphates and a similar action has been observed[14] when this reaction was performed in the presence of phosphoric acid. The dramatic acceleration observed[1] in our case in the reaction of **1** with

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Keywords: 2-Oxo-2*H*-1-benzopyranes; 3-Acylsubstituted coumarins; Trialkylphosphites; 1,4-Addition/conjugated addition; Phosphonates; *p*-Toluenesulfonic acid.

* Corresponding author. Tel.: +30-2310-99-78-03; fax: +30-2310-99-76-79; e-mail: rodios@chem.auth.gr

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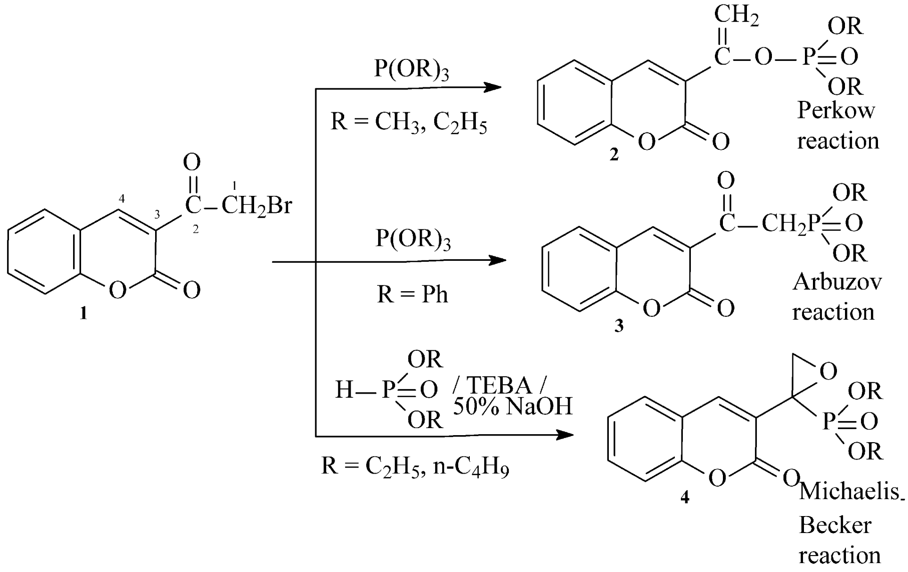


Scheme 1.

trialkylphosphites, prompted us to investigate what would be the result of this reaction in the case of carrying it out in the presence of a stronger acid such as *p*-toluenesulfonic acid (TsOH).

2. Results and discussion

The results of the reaction of **1** with trimethyl and triethylphosphites and in the presence of TsOH, performed

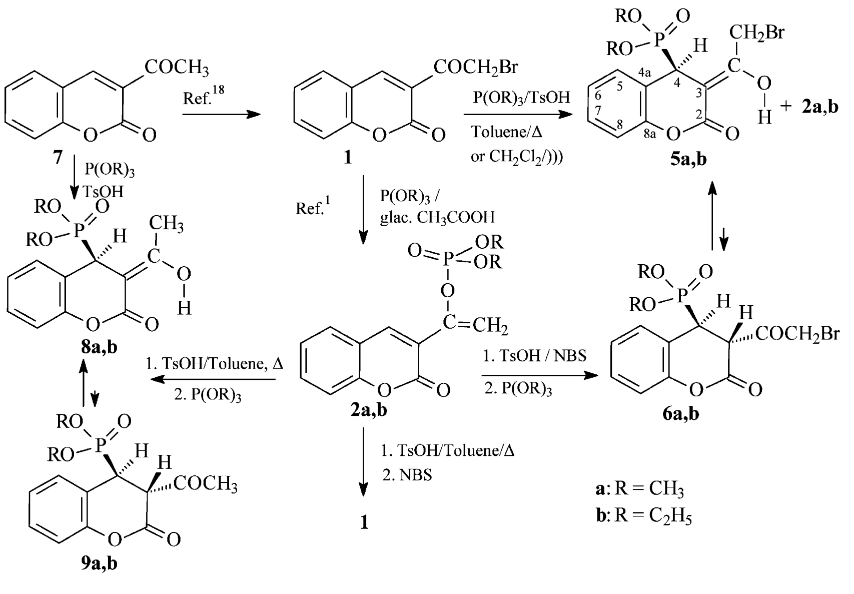
Table 1. Interaction of 3-bromoacetylcoumarin **1** with trialkylphosphites $P(OR)_3$ in the presence of TsOH[a]

Method	Reaction condition	Time [min]	Yields, %			
			2[b]		**5**[b]	
	Ratio **1**:$P(OR)_3$:TsOH		**a**	**b**	**a**	**b**
A	1:2:1/Δ/toluene	150		54		30
A_1	1:5:1/Δ/toluene	90	33		55	
B	1:5:0.1/CH_2Cl_2/)))[c]	20	86	94	8	Trace
C	1:5:1/CH_2Cl_2/)))	20	17	5	76	90
C_1	1:5:2/CH_2Cl_2/)))	20	10	3	82	93

[a] TsOH = *p*-toluenesulfonic acid.

[b] **a**: $R = CH_3$, **b**: $R = C_2H_5$.

[c]))): Reaction carried out under ultrasound irradiation.

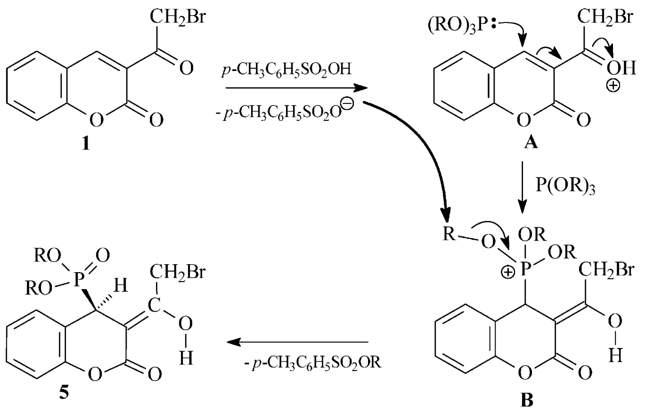


Scheme 2.

in refluxing toluene (Methods A, A_1) or in methylene chloride under ultrasound irradiation (Methods B, C and C_1) and in different bromoketone **1**:trialkylphosphite:toluenesulfonic acid ratios are presented in Table 1.

The course of the reaction of **1** with $P(OR)_3$ in the presence of TsOH was completely different to that with acetic acid,[1] giving, in addition to the expected enolphosphates **2a**,**b**, new 1,4-addition products **5a**,**b** (Table 1, Scheme 2). Thus in refluxing toluene (Methods A, A_1), the reaction of **1** with $P(OR)_3$ gave the enolphosphates **2a** and **2b** in 33, 54% and the 1,4-adducts **5a** and **5b** in 30, 55% yields, respectively.

The results, concerning yields and the **2**:**5** ratios were significantly different when the reaction took place in methylene chloride and under the action of ultrasound irradiation (Methods B, C, C_1). The reaction was completed within 20 min and the yields of the isolated products **2** and **5** depended on the amount of TsOH used to perform the reaction. When TsOH was used in catalytic amounts (Table 1, Method B) the enolphosphates **2a**, **2b** were the main products, with yields of 86 and 94%, respectively. By increasing the bromocoumarin **1**:TsOH ratio to 1:1 (Table 1, Method C) the 1,4-addition products **5a**, **5b** were the main ones, with yields of 76 and 90%, respectively, whereas the corresponding enolphosphates **2a**, **2b** were isolated in yields of 17 and 5%, respectively. A further increase of the **1**:TsOH ratio to 1:2 did not substantially change the yields of the reaction products (Table 1, Method C_1).



Scheme 3.

Table 2. Interaction[a] of 3-bromoacetylcoumarin **1** with dialkylphosphites $(RO)_2PH$

	R	2	7	8
a	CH_3	20	2	7
b	C_2H_5	6	5	17

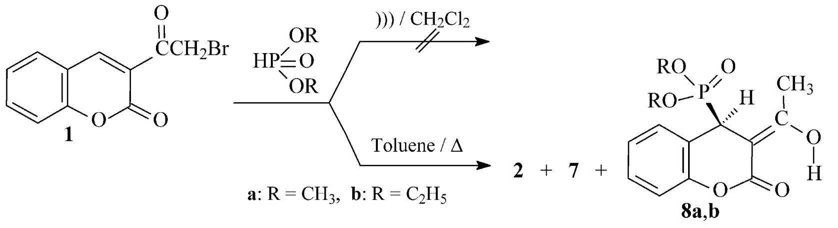
[a] In refluxing toluene, 4 h.

The formation of the 1,4-adducts **5** from the reaction of bromoacetylcoumarin **1** and trialkylphosphites in the presence of TsOH could be explained by initial protonation of the C=O group. The protonated ketone **A** acting as an activated conjugate system reacts easily with trialkylphosphites to form the intermediate 1,4-adduct **B**. The transformation of the latter to the products **5** goes most probably with the participation of the TsOH anion (Scheme 3). The formation of the corresponding esters of *p*-toluenesulfonic acid was proved by their isolation from the reaction mixtures in yields of 70–75% and by comparing their R_f-values and IR spectra with authentic samples.

In the reaction mixture containing $P(OR)_3$ and TsOH, however, the possibility of trialkylphosphite to have been transformed into the corresponding dialkylphosphite[19] should be taken into account. In order therefore to prove the real reagent in the reaction of 1,4-addition of the phosphites to compound **1**, trialkylphosphite or dialkylphosphite, the reaction of **1** with dialkylphosphite under ultrasound irradiation in methylene chloride, without and in the presence of TsOH, was carried out. In both cases the starting coumarin **1** was isolated in quantitative yield.

When the reaction of **1** with dialkylphosphites was, however, carried out in refluxing toluene, a complicated reaction mixture (TLC) was obtained from which 3-acetylcoumarin **7** (at 2–5%), the corresponding enolphosphates **2** (at ~20%) and the products of 1,4-addition of dialkylphosphites to 3-acetylcoumarin (**8a**,**b**) were isolated (Table 2, Scheme 4).

The behavior of the enolphosphate **2a** in the reaction with trialkylphosphites in refluxing toluene and in the presence of TsOH was also studied. From this reaction (Methods A_2 and A_3, Table 3, Schemes 2 and 5) the 1,4-adducts **8a** and **8b** were isolated. When this reaction was performed in two stages, i.e. first the solution of **2a** and TsOH in toluene is refluxed for 5 min and after that addition of $P(OR)_3$ (Method A_3, Table 3), the transformation of **2a** to **8a** was almost quantitative (the enolic forms of the 3-acetyl-4-dialkylphosphono-2-oxochromans **8a** and **8b** were isolated in 87 and 93%, respectively, with no unreacted starting compound). These findings indicate that in the above reaction, the enolphosphate **2** is first hydrolyzed to 3-acetylcoumarin **7** by the strong acid TsOH[2] (and this was proved in a separate experiment, where hydrolysis of **2a** to **7** was completed within 15 min with 90% yield) and in a second step the 1,4 addition of trialkylphosphite is taking place (Scheme 5).

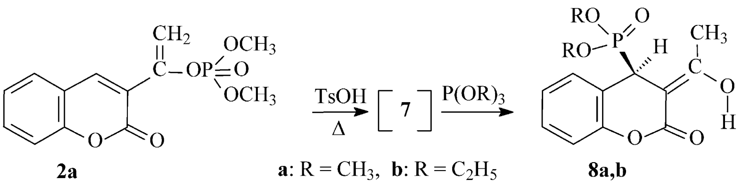


Scheme 4.

Table 3. Interaction of enolphosphates **2a** with trialkylphosphites

Method	Reaction conditions Ratio **2a**:P(OR)$_3$:TsOH	Time, h	Unreacted **2**	Yields, %	
				8a	**8b**
A$_2$	1:5:2.5/Δ/toluene	4	15/26[a]	43	39
A$_3$	1:2:2/Δ/toluene, 2-stage	0.5		87	93

[a] When the reaction was carried out in one stage.

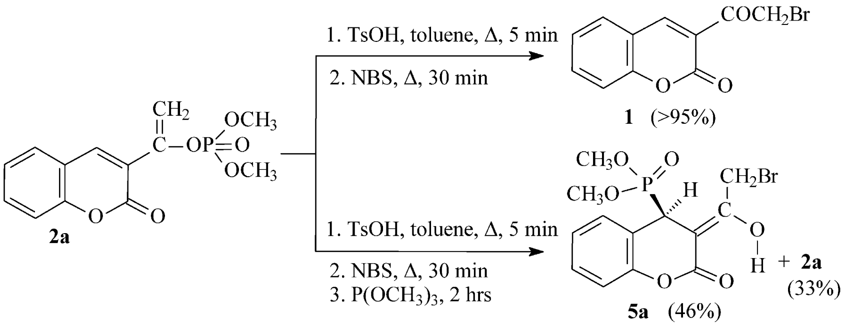


Scheme 5.

The possibility of the enolphosphate **2a** being transformed into 3-ω-bromoacetylcoumarin **1** was also studied. This was achieved in a one pot two-stage reaction by the action of TsOH for the hydrolysis of **2a** and then of NBS for the bromination of the hydrolysis product of 3-acetylcoumarin **7**. Compound **1** was obtained in almost quantitative yield. By repeating the same reaction and, in a third stage, by adding trimethylphosphite to the reaction mixture, compounds **2a** (33%) and **5a** (46%) were isolated (Scheme 6). Almost the same proportion (**2a**/**5a**) were obtained from reaction of **1** with P(OCH$_3$)$_3$, (Table 1, Method A$_1$).

Over the last few years the reaction of 3-acetylcoumarin **7** with dialkyl- and trialkylphosphites, from which the 1,4-addition products **8** were obtained in 40–80% yields on refluxing for 8–10 h, has been reported.[20–23] Since we have found that the use of TsOH favors the 1,4-addition of trialkylphosphites to 3-bromoacetylcoumarin **1** and substantially shortens the reaction time, we investigated the same reactions of trialkylphosphites with 3-acetylcoumarin **7** as well as with 3-benzoyl and 3-ethoxycarbonyl coumarins **10** and **11** respectively, in the presence of TsOH and under ultrasound irradiation. The results (Table 4) show that the corresponding 4-dialkylphosphono-2-oxocromans **8/9**, **12/13** and **14** (Scheme 7) were obtained in yields from 60 to 95% (Table 4, Method C).

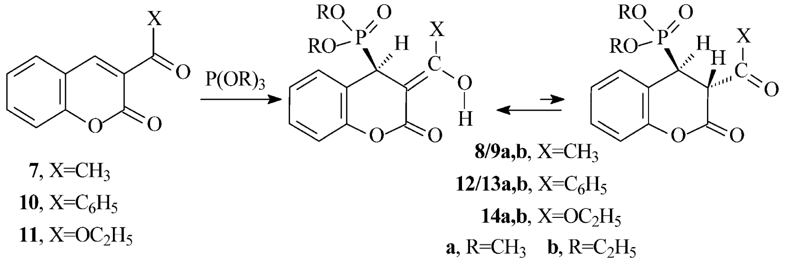
The structures of the isolated compounds were assigned mainly on the basis of their ^{1}H and ^{13}C NMR spectral data. Thus, compounds **5/6a**,**b** and **8/9a**,**b** appeared exclusively in the enol-tautomeric forms **5** and **8** respectively, and this is in agreement with the reported[21,23] structure of compound **8/9a**,**b**. Compounds **12/13b** and **14a**,**b** on the other hand appeared exclusively in the keto-tautomeric form **13** and **14** respectively, whereas compound **12/13a** appeared as a mixture of both tautomers **12a**⇆**13a**, with a **12**:**13** ratio of



Scheme 6.

Table 4. Reaction of trialkylphosphites with 3-acylsubstituted coumarins

Starting Compd.	Method	Reaction conditions (Ratio coumarin: P(OR)$_3$:TsOH)	Time[min]	Reaction product	Yield %	
					a	**b**
7	A$_1$	1:5:1/Δ/toluene	15	**8/9**	90	91
7	C	1:5:1/CH$_2$Cl$_2$/)))	30	**8/9**	95	95
7	D	1:5/CH$_2$Cl$_2$ + ROH/))), without TsOH	30	**8/9**	86	94
7	E	1:5/CH$_3$COOH/))), without TsOH	15	**8/9**	87	93
10	C	1:5:1/CH$_2$Cl$_2$/)))	30	**12/13**	94	69
11	C	1:5:1/CH$_2$Cl$_2$/)))	30	**14**	58	88



Scheme 7.

9:1 (^{1}H NMR), which, on standing the sample in the NMR-tube ($CDCl_3$) for one week, changed to ~1:1.

The ^{1}H NMR spectra of the enol-forms **5a**,**b**, **8a**,**b** and **12a** showed an OH peak at $\delta \sim 13$ ppm, exchangeable with D_2O. The 4-H proton appeared as a doublet at $\delta = 4.19$–4.45 ppm with a $^2J_{HCP} \approx 22$ Hz, and the enolic methyl group of compounds **8a**,**b**, $=C–CH_3$, showed a doublet with a $^5J_{HP} \approx 3$ Hz (homoallylic), whereas the corresponding two methylenic protons of compounds **5a**,**b**, $=C–CH_2Br$ appeared at ~4 and 4.5 ppm as dd ($^2J_{HCH} = 11.2$ Hz, $^5J_{HP} \approx 1$ Hz) and ddd ($^2J_{HCH} = 11.2$ Hz, $^5J_{HP} \approx {}^5J_{HH} \approx 1.5$ Hz) respectively. Of interest is the observed coupling between the hydroxyl proton and one of the two methylenic protons of the CH_AHBr group, $^4J_{H,OH} = 1.5$–1.7 Hz. This indicates a fixed W disposition of these two protons, as a result of a restricted rotation of the CH_2Br group due to the bulky bromine atom, and of the OH group due to hydrogen bonding of the OH proton to the 2-oxochroman carbonyl oxygen. This hydrogen bonding has been also observed[23] in the crystal structure of compounds **7/8**. In their ^{13}C NMR spectra the enolic forms gave a peak for C-4 at ~37.5 ppm coupled with the phosphorus atom with $^1J_{CP} = 141$–144 Hz and a peak for C-3 at ~90 ppm, with a $^2J_{CP} = 8.9$ Hz. The enolic carbon $=C–OH$ appeared as doublet, ($^3J_{CP} \approx 6$–7 Hz) at $\delta = 176$–179 ppm and the carbonyl carbon (C-2) gave a peak at $\delta \approx 169$ ppm. The absence of the keto-form peaks for the 3-H protons in the ^{1}H NMR spectra and for the saturated C-3 in the ^{13}C NMR spectra is characteristic of these tautomeric compounds.

The keto-forms on the other hand, **13a**,**b** and **14a**,**b**, showed a doublet for the 4-H proton at $\delta = 3.8$–3.9 ppm, coupled with the phosphorus atom with $^2J_{HCP} = 23$–24 Hz and a peak for 3-H proton at $\delta = 4.5$–5.2 ppm coupled with the phosphorus atom with $^3J_{HP} = 10.4$–14.5 Hz and with 4-H with a very small $^3J = 0.8$–1 Hz. The very small ^3J value between 4-H and 3-H suggests a dihedral angle of H–C4–C3–H of about 90°, which, as also revealed by inspection of stereomodels, indicates a *trans* disposition of the two protons. In their ^{13}C NMR spectra the most characteristic peaks are those of C-3 at $\delta = 47$–49 ppm and of C-4 at $\delta \sim 39$ ppm, coupled with the phosphorus atom with $^2J_{CP}$ of 2.3–3.5 Hz and $^1J_{CP} \approx 144$ Hz, respectively. The carbonyl carbon of the 3-benzoyl group in **13a**,**b** appeared at $\delta = 192$ ppm and that of the ethoxycarbonyl group in **14a**,**b** at $\delta \approx 166$ ppm. In both cases these carbons were strongly coupled with phosphorous atom with a $^3J_{CP}$ value of ~17–22 Hz.

It is noted that a mixture of the two tautomers from the reaction of **7** with dialkylphosphites **8/9a**,**b**, i.e. **8**$\leftrightarrows$**9**, has been also reported.[22] However, the NMR spectral data provided to support this suggestion are not as complete as they should be to support the proposed appearance of the two tautomers.

3. Conclusions

From the experimental data given above together with the results reported earlier,[1] it is concluded that the 3-bromoacetyl coumarin shows a special behavior in the reaction with phosphites:

1. It reacts with triphenylphosphite giving the 2-oxophosphonate **3** (R = Ph).
2. With trialkylphosphites compound **1** may react in two directions:
   i. To the formation of the enolphosphates **2** (maybe by the initial 1,2 addition of the trialkylphosphites to the conjugated system of the 3-bromoacethylcoumarin) and
   ii. To the formation mainly (about 90%) of the corresponding 3-(ω-bromoacetyl)-4-dialkyphosphono-2-oxochromans **5/6** by the 1,4-addition of the trialkylphosphites to the bromoacetylcoumarin **1**. This direction was realized only when the reaction was carried out in the presence of TsOH.

The use of TsOH in the reaction of 3-acyl-coumarines with trialkylphosphites leads mainly to 1,4-addition products, giving, in good yields and shorter reaction times, the corresponding 3-acyl-4-dialkylphosphono-2-oxochromans.

4. Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a Specord IR 71 or IR 75 spectrophotometers. ^{1}H NMR and ^{13}C NMR spectra, reported in δ units, were obtained with a Bruker WM 250 (at 250 and 62.9 MHz, respectively) or a Bruker AM 300 (at 300 and 75.4 MHz, respectively) instruments. All NMR spectra were obtained by using TMS as internal standard in $CDCl_3$. E.I. mass spectra were obtained at 70 eV a VG TS-250 spectrometer. Elemental analyses of C, H, P and N were carried out in the Laboratory of Elemental Analysis at the Department of Organic Chemistry, University of Sofia.

Column chromatography was carried out on silica gel (Merck or Fluka 0.063–0.2 mm) using as eluent *n*-hexane/EtOAc mixtures with increasing polarity. Sonications were effected with Bransonic 321 (390 W, 50 kHz).

4.1. Preparation of the starting materials

The starting 3-substituted 2-oxo-2*H*-1-benzopyrans were prepared according to the literature procedures[1,18,24–26] and their spectroscopic characteristics (IR, ^{1}H NMR and MS) were in agreement with their structures. Trialkyl phosphites and dialkyl phosphites are commercially available (Fluka).

4.2. Interaction of 3-bromoacetylcoumarin 1 with trialkylphosphites. General procedure

Depending of the reaction conditions (ratio of the reagents, temperature, etc.) the following methods are distinguished:

Method A. A solution of 3-bromoacetylcoumarin **1** (0.27 g, 1 mmol), the corresponding phosphite (2 mmol) and *p*-toluenesulfonic acid (0.19 g, 1 mmol) was refluxed in dry toluene (3 mL) until the starting coumarin was consumed (TLC-monitoring). The solvent was removed under reduced pressure. To the residue methylene chloride (20 mL) was added, washed with water (40 mL), with 10% solution of potassium carbonate (20 mL), again with water (30 mL) and dried (Na_2SO_4). The precipitate obtained after the removal of the solvent was filtered and washed with ethyl acetate (10 mL).

Method A_1. The same as in Method A but the amount of the corresponding phosphite was 5 mmol.

Method B. A solution of 3-bromoacetylcoumarin **1** (0.27 g, 1 mmol), the corresponding phosphite (5 mmol) and *p*-toluenesulfonic acid (catalytic amount) in methylene chloride (3 mL) was irradiated with ultrasound at room temperature until the starting coumarin was consumed (TLC-monitoring). The reaction mixture was poured out into ice water (40 mL) and extracted with methylene chloride (3×30 mL). The organic layer was washed with water (30 mL) and dried (Na_2SO_4). After evaporation of the solvent the obtained crystals were isolated from ethyl acetate (5 mL). The filtrate was chromatographed on a silica gel column with *n*-hexane–ethyl acetate (with increasing polarity) as eluent.

Methods C and C_1. The same as in Method B, but the amount of the *p*-toluenesulfonic acid was 1 and 2 mmol, respectively.

4.2.1. Dimethyl 3-(2-bromo-1-hydroxyaethylidene)-2-oxochroman-4-ylphosphonate (5a). From **1** and trimethyl phosphite. Method B: 0.32 g, 86%, white crystals, mp = 151–153 °C (ethyl acetate); [Found: C, 41.21; H, 3.43. $C_{13}H_{14}O_6PBr$ requires C, 41.40; H, 3.74%]; IR (nujol): ν = 1720, 1630, 1590, 1190, 1080, 1055 cm^{-1}. ^{1}H NMR (300 MHz): δ = 13.15 (s; OH, 1H), 7.31–7.38 (m; 5-, 7-H, 2H), 7.21 (m as t, J = 7.5 Hz; 6-H, 1H), 7.11 (d, J = 8.3 Hz; 8-H, 1H), 4.50 (ddd as dt, $^2J_{HH}$ = 11.2 Hz, $^4J_{H,OH}$ ~ 1.5 Hz, $^5J_{HP}$ ~ 1.3 Hz; CH_AHBr, 1H), 4.30 (d, J = 21.9 Hz; 4-H, 1H), 3.99 (dd, $^2J_{HH}$ = 11.2 Hz, $^5J_{HP}$ = 1.0 Hz; CHH_BBr, 1H), 3.68 (d, $^3J_{HP}$ = 10.4 Hz; $POCH_3$, 3H), 3.66 (d, $^3J_{HP}$ = 10.2 Hz; $POCH_3$, 3H). ^{13}C NMR (75.4 MHz): δ = 173.8 (d, $^3J_{CP}$ = 6.8 Hz; =COH), 168.8 (d, $^3J_{CP}$ = 1.7 Hz; C-2), 150.9 (d, $^3J_{CP}$ = 5.6 Hz; C-8a), 129.6 (d, $^3J_{CP}$ = 2.9 Hz; C-5), 129.6 (d, $^5J_{CP}$ = 1.8 Hz; C-7), 125.1 (d, $^4J_{CP}$ = 3.4 Hz; C-6), 117.2 (d, $^4J_{CP}$ = 3.6 Hz; C-8), 116.5 (d, $^2J_{CP}$ = 8.5 Hz; C-4a), 91.0 (d, $^2J_{CP}$ = 9.9 Hz; C-3), 54.1 (d, $^2J_{COP}$ = 7.7 Hz; $POCH_3$) 54.0 (d, $^2J_{COP}$ = 7.3 Hz; $POCH_3$), 37.3 (d, $^1J_{CP}$ = 142.7 Hz; C-4), 25.5 (CH_2Br).

4.2.2. Diethyl 3-(2-bromo-1-hydroxyaethylidene)-2-oxochroman-4-ylphosphonate (5b). From **1** and triethyl phosphite. Method B: 0.38 g, 94%, white crystals, mp = 147–149 °C (ethyl acetate); [Found: C, 44.61; H, 4.40. $C_{15}H_{18}O_6PBr$ requires C, 44.47; H, 4.48%]; IR (nujol): ν = 1730, 1635, 1500, 1190, 1090, 1050, 1020 cm^{-1}. ^{1}H NMR (300 MHz): δ = 13.17 (s; OH, 1H), 7.32–7.40 (m; 5-, 7-H, 2H), 7.21 (m as t, J = 7.5 Hz; 6-H, 1H), 7.12 (d, J = 8.0 Hz; 8-H, 1H), 4.55 (ddd as dt, $^2J_{HH}$ = 11.1 Hz, $^4J_{H,OH}$ = 1.7 Hz, $^5J_{HP}$ = 1.2 Hz; CH_AHBr, 1H), 4.28 (d, $^2J_{HP}$ = 21.8 Hz; 4-H, 1H), 3.93–4.12 (m; CHH_BBr, $POCH_2$, 5H), 1.26 (t, J = 7.0 Hz; CH_3), 1.24 (t, J = 7.0 Hz; CH_3). ^{13}C NMR (75.4 MHz): δ = 173.6 (d, $^3J_{CP}$ = 7.1 Hz; =COH), 168.9 (d, $^3J_{CP}$ ~ 1.0 Hz; C-2), 150.2 (d, $^3J_{CP}$ = 5.4 Hz; C-8a), 129.7 (d, $^3J_{CP}$ = 4.4 Hz; C-5), 129.5 (d, $^5J_{CP}$ = 3.7 Hz; C-7), 125.0 (d, $^4J_{CP}$ = 3.5 Hz; C-6), 117.1 (d, $^4J_{CP}$ = 3.6 Hz; C-8), 116.8 (d, $^2J_{CP}$ = 8.7 Hz; C-4a), 91.2 (d, $^2J_{CP}$ = 9.9 Hz; C-3), 63.6 (d, $^3J_{CP}$ = 7.0 Hz; $POCH_2$), 63.5 (d, $^3J_{CP}$ = 7.4 Hz; $POCH_2$), 37.7 (d, $^1J_{CP}$ = 142.6 Hz; C-4), 25.6 (CH_2Br), 16.4 (d, $^3J_{CP}$ = 4.8 Hz; CH_3), 16.3 (d, $^3J_{CP}$ = 4.8 Hz; CH_3). MS *m*/*z* (%): 406/404 (M^+) (4), 325 (61), 283 (60), 268/266 (72), 188 (73), 173 (84), 146 (33), 118 (69), 77 (38), 29 (100).

4.3. Interaction of enolphosphate 2a and 3-acetylcoumarin 7 with trialkyl phosphites. General procedure

Depending of the reaction conditions the following methods are distinguished:

Method A_2. The ratio of the reagents **2a**:phosphites:TsOH 1:2:2.5 in refluxing toluene (3 mL). The reaction carried out and worked up as mentioned above for Method A.

Method A_3. To the refluxing solution of the starting coumarin (0.27 g, 1 mmol) in dry toluene (3 mL) was added 4-toluenesulphonic acid (0.38 g, 2 mmol). After 5 min to the reaction mixture the corresponding trialkyl phosphite (2 mmol) was added and refluxed until the starting coumarin was consumed (TLC-monitoring) for about 15 min. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with *n*-hexane–ethyl acetate (with increasing polarity) as an eluent.

Method D. A solution of the starting coumarin (0.27 g, 1 mmol) and the corresponding phosphite (5 mmol) in alcohol (methanol, resp. ethanol (2 mL)) and methylene chloride (1 mL) was irradiated with ultrasound at room temperature until the starting coumarin was consumed (TLC-monitoring). The solvent was distilled under reduced pressure. To the residue was added a small quantity of corresponding alcohol (1 mL) and water (drop wise) for crystallization at low temperature. The obtained crystals were filtrated.

Method E. A solution of the coumarin (0.27 g, 1 mmol) and the corresponding phosphite (5 mmol) in glacial acetic acid (2 mL) was irradiated with ultrasound at low temperature (ice-water-bath) until the starting coumarin was consumed (TLC-monitoring). The reaction mixture was decomposed on ice-water (50 mL). The obtained crystals were filtrated and washed with water to neutral pH.

4.3.1. Dimethyl 3-(1-hydroxyaethylidene)-2-oxochroman-4-ylphosphonate (8a). From **2a** or **7** and trimethyl phosphite. Method C: 0.28 g, 95%, white crystals, mp=127–129 °C (ethyl acetate), (lit.[21,22] 129–130 °C).

4.3.2. Diethyl 3-(1-hydroxyaethylidene)-2-oxochroman-4-ylphosphonate (8b). From **2a** or **7** and triethyl phosphite. Method C: 0.31 g, 95%, white crystals, mp=145–148 °C (ethyl acetate), (lit.[21,22] 147–148 °C).

4.3.3. Dimethyl 3-benzoyl-2-oxochroman-4-ylphosphonate (12/13a). From 3-benzoylcoumarin **10** and trimethyl phosphite. Method D: 0.34 g, 94%, white crystals, mp=120–134 °C (methanol), (mixture of the two tautomers **12a**$\leftrightarrows$**13a**, with a 9:1 ratio (^{1}H NMR), which on staying the sample in the NMR tube for about 1 week ($CDCl_3$) changed to $\sim$1:1); [Found: C, 60.07; H, 4.90. $C_{18}H_{17}O_6P$ requires C, 60.00; H, 4.76%]; IR (CH_3Cl): ν=1780, 1700, 1625, 1060, 1030 cm^{-1}. ^{1}H NMR (300 MHz), enol-form (**12a**): δ=13.29 (s; OH, 1H), 7.58–7.65 (m; 2′-, 6′-H, 2H), 7.46–7.54 (m; 3′-, 5′-, 4′-H, 3H), 7.26–7.37 (m; 5-H, 7-H, 2H), 7.12–7.19 (m; 6-H, 8-H, 2H), 4.45 (d, $^2J_{HP}$=23.9 Hz; 4-H, 1H), 3.49 (d, $^3J_{HP}$=10.6 Hz; OCH_3, 3H), 3.41 (d, $^3J_{HP}$=10.6 Hz; OCH_3, 3H). Keto-form (**13a**): 7.96–7.99 (m, 2′-, 6′-H, 2H), 7.65 (dddd as tt, J=7.4, 1.4 Hz; 4′-H, 1H), 7.48–7.55 (m; 3′-H, 5′-H, 2H), 7.34 (dddd as tt, J=7.7, $\sim$2.0 Hz; 7-H, 1H), 7.22 (ddd as dt, J=8.2, $\sim$2.1 Hz; 5-H, 1H), 7.11–7.17 (m; 6-, 8-H, 2H), 5.19 (dd, $^3J_{HP}$=13.7 Hz, $^3J_{HH}$=0.8 Hz; 3-H, 1H), 3.80 (bd, $^2J_{HP}$=23.4 Hz; 4-H, 1H), 3.81 (d, $^3J_{HP}$=10.8 Hz; OCH_3, 3H), 3.68 (d, $^3J_{HP}$=10.8 Hz; OCH_3, 3H). ^{13}C NMR (75.4 MHz), enol-form (**12a**): δ=175.5 (d, $^3J_{CP}$=6.7 Hz; =COH), 169.1 (d, $^3J_{CP}\sim$1 Hz; C-2), 150.9 (d, $^3J_{CP}$=5.5 Hz; C-8a), 133.6 (d, $^4J_{CP}$=2.2 Hz; C-1′), 130.9 (C-4′), 129.9 (d, $^3J_{CP}$=4.5 Hz; C-5), 129.3 (d, $^5J_{CP}<5$ Hz; C-7), 128.8 (C-3′,-5′), 128.2 (C-2′,-6′), 125.0 (d, $^4J_{CP}$=3.3 Hz; C-6), 117.7 (d, $^2J_{CP}$=7.5 Hz; C-4a), 117.1 (d, $^4J_{CP}$=3.9 Hz; C-8), 89.7 (d, $^2J_{CP}$=9.9 Hz; C-3), 53.6 (d, $^2J_{COP}$=7.6 Hz; $POCH_3$), 53.3 (d, $^2J_{COP}$=7.4 Hz; $POCH_3$), 37.6 (d, $^1J_{CP}$=140.8 Hz; C-4). Keto-form (**13a**): 191.7 (d, $^3J_{CP}$=17.5 Hz; CO), 163.2 (d, $^3J_{CP}$-$\sim$0.5 Hz; C-2), 151.2 (d, $^3J_{CP}$=6.5 Hz; C-8a), 134.5 (C-4′), 133.2 (C-1′), 129.4 (d, $^3J_{CP}$=2.9 Hz, C-5), 129.2 (C-2′,-6′), 129.2 (d, $^5J_{CP}<5.2$ Hz; C-7), 129.2 (C-3′,-5′), 125.0 (d, $^4J_{CP}$=3.3 Hz; C-6), 117.3 (d, $^4J_{CP}$=3.6 Hz; C-8), 114.5 (d, $^2J_{CP}$=7.8 Hz; C4a), 54.1 (d, $^2J_{COP}$=6.7 Hz; $POCH_3$), 53.8 (d, $^2J_{COP}$=7.6 Hz; $POCH_3$), 49.1 (d, $^2J_{CCP}$=3.4 Hz; C-3), 38.5 (d, $^1J_{CP}$=143.9 Hz; C-4). MS *m/z* (%): 361 (MH^+) (51), 360 (M^+) (20), 328 (18), 254 (48), 174 (81), 146 (52), 118 (49), 111 (79), 105 (50), 76 (100).

4.3.4. Diethyl 3-benzoyl-2-oxochroman-4-ylphosphonate (13b). From 3-benzoylcoumarin **10** and triethyl phosphite. Method D: 0.27 g, 69%, white solid, mp=106–108 °C (ethanol); [Found: C, 61.77; H, 5.65. $C_{20}H_{21}O_6P$ requires C, 61.86; H, 5.45%]; IR (CH_3Cl): ν=1780, 1700, 1620, 1500, 1170, 1055, 1030 cm^{-1}. ^{1}H NMR (300 MHz): δ=7.98 (m; 2′, 6′-H, 2H), 7.64 (dddd as tt, J=7.4, 1.3 Hz; 4′-H, 1H), 7.50 (dddd as tt, J=7.4, 1.5 Hz; 3′, 5′-H, 2H), 7.32 (dddd as tt, J=7.7, 2.0 Hz; 7-H, 1H), 7.21 (ddd as dt, J=8.0, 2.0 Hz; 5-H, 1H), 7.08–7.14 (m, 6-, 8-H, 2H), 5.20 (dd, J=14.0, 0.9 Hz; 3-H, 1H), 4.11–4.23 (m; $POCH_2$), 3.88 (dq, J=8.2, 7.1 Hz; $POCH_2$), 3.73 (bd, $^2J_{HCP}$=23.3 Hz; 4-H, 1H), 1.36 (t, J=7.1 Hz; CH_3, 3H), 1.24 (t, J=7.0 Hz; CH_3, 3H). ^{13}C NMR (75.4 MHz): δ=192.0 (d, $^3J_{CP}$=17.1 Hz; CO), 163.3 (d, $^3J_{CP}$=2.2 Hz; C-2), 151.3 (d, $^3J_{CP}$=5.7 Hz; C-8a), 134.4 (C-4′), 133.2 (C-1′), 130.0 (d, $^3J_{CP}$=4.4 Hz; C-5), 129.7 (d, $^5J_{CP}$=4.2 Hz; C-7), 129.2 (C-2′,-6′), 129.1 (C-3′, -5′), 124.8 (d, $^4J_{CP}$=3.2 Hz; C-6), 117.2 (d, $^4J_{CP}$=3.2 Hz; C-8), 114.7 (d, $^2J_{CP}$=7.7 Hz; C-4a), 63.8 (d, $^2J_{COP}$=7.5 Hz; $POCH_2$), 63.4 (d, $^2J_{COP}$=7.2 Hz; $POCH_2$), 49.2 (d, $^2J_{CP}$=3.5 Hz; C-3), 38.9 (d, $^1J_{CP}$=143.5 Hz; C-4), 16.3 (d, $^3J_{CP}$=6.2 Hz; CH_3), 16.2 (d, $^3J_{CP}$=5.5 Hz; CH_3). MS *m/z* (5): 389 (MH^+) (57), 388 (M^+) (21), 282 (74), 250 (58), 228 (92), 173 (41), 146 (52), 118 (43) 105 (100), 78 (92), 77 (79).

4.3.5. Ethyl 4-(dimethoxyphosphoryl)-2-oxo-3-chromanecarboxylate (14a). From ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate **11** and trimethyl phosphite. Method C: 0.19 g, 58%, colorless needles, mp=94–95 °C (methanol); [Found: C, 50.84; H, 5.00. $C_{14}H_{17}O_7P$ requires C, 51.23; H, 5.22%]; IR (CH_3Cl): ν=1795, 1755, 1620, 1160, 1030, 1045 cm^{-1}. ^{1}H NMR (300 MHz): δ=7.30–7.37 (m; 5-, 7-H, 2H), 7.17 (ddd as dt, J=7.5, 1.0 Hz; 6-H, 1H), 7.10 (d, J=8.5 Hz; 8-H, 1H), 4.15 (dd, $^3J_{HH}$=1.3 Hz, $^3J_{HP}$=11.1 Hz; 3-H, 1H), 4.12 (dq, ^3J=7.1 Hz, $^6J_{HP}$=2.6 Hz; OCH_2, 2H), 3.95 (bd, $^2J_{HP}$=22.6 Hz; 4-H, 1H), 3.75 (d, $^3J_{HP}$=10.8 Hz; $POCH_3$, 3H), 3.75 (d, $^3J_{HP}$=10.8 Hz; $POCH_3$, 3H), 1.11 (t, J=7.1 Hz; CH_3, 3H). ^{13}C NMR (75.4 MHz): δ=166.0 (d, $^3J_{CP}$=22.7 Hz; C=O), 162.2 (d, $^3J_{CP}$=2.2 Hz; C-2), 151.2 (d, $^3J_{CP}$=5.3 Hz; C-8a), 130.1 (d, $^3J_{CP}$=5.2 Hz; C-5), 129.9 (d, $^5J_{CP}$=3.4 Hz; C-7), 125.1 (d, $^4J_{CP}$=3.2 Hz; C-6), 117.3 (d, $^4J_{CP}$=3.2 Hz; C-8), 115.4 (d, $^2J_{CCP}$=7.5 Hz; C-4a), 63.0 (OCH_2), 53.9 (d, $^2JC_{COP}$=7.4 Hz; $POCH_3$), 53.7 (d, $^2J_{COP}$=7.4 Hz; $POCH_3$), 46.9 (d, $^2J_{CP}$=2.3 Hz; C-3), 38.7 (d, $^1J_{CP}$=144.5 Hz; C-4), 13.8 (CH_3). MS *m/z* (%): 328 (M^+) (22), 282 (7), 255 (100), 219 (24), 173 (87), 146 (11), 118 (13), 79 (6).

4.3.6. Ethyl 4-(diethoxyphosphoryl)-2-oxo-3-chromanecarboxylate (14b). From ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate **11** and triethyl phosphite. Method C: 0.32 g, 88%, light-yellow oil; [Found: C, 53.59; H, 5.96. $C_{16}H_{21}O_7P$ requires C, 53.93; H, 5.94%]; IR (CH_3Cl): ν=1790, 1750, 1625, 1600, 1170, 1060sh, 1030 cm^{-1}. ^{1}H NMR (250 MHz) δ=7.29–7.36 (m; 5-, 7-H, 2H), 7.16 (dd as t, J=7.2 Hz; 6-H, 1H), 7.09 (d, J=8.2 Hz; 8-H, 1H), 4.15 (d, J=14.4 Hz; 3-H, 1H), 3.92–4.61 (m; CH_2O, 6H), 3.90 (d, $^2J_{HP}$=24.2 Hz; 4-H, 1H), 1.32 (t, J=7.0 Hz; CH_3, 3H), 1.21 (t, J=7.0 Hz; CH_3, 3H), 1.11 (t, J=7.1 Hz; CH_3, 3H). ^{13}C NMR (62.59 MHz) δ=166.1 (d, $^3J_{CP}$=21.5 Hz; CO), 162.3 (d, $^3J_{CP}$=2.0 Hz; C-2), 151.2 (d, $^3J_{CP}$=4.7 Hz; C-8a), 130.0 (d; $^3J_{CP}$=4.8 Hz; C-5), 129.7 (d, $^5J_{CP}$=3.7 Hz; C-7), 124.9 (d, $^4J_{CP}$=3.2 Hz; C-6), 117.1 (d, $^4J_{CP}$=3.2 Hz; C-8), 115.6 (d, $^2J_{CP}$=7.2 Hz; C-4a), 63.5 (d, $^2J_{COP}$=7.1 Hz; $POCH_2$), 63.2 (d, $^2J_{COP}$=7.1 Hz; $POCH_2$), 62.8 ($COOCH_2$), 46.9 (d, $^2J_{CP}$=2.7 Hz; C-3), 39.5 (d, $^1J_{CP}$=144.2 Hz; C-4), 16.2 (d, $^3J_{CP}$=5.7 Hz;

CH_3CH_2OP), 16.0 (d, $^3J_{CP}=5.6$ Hz; CH_3CH_2OP), 13.7 (CH_3). MS *m*/*z* (%): 356 (M^+ 1(1), 284 (11), 218 (6), 211 (8), 183 (18), 173 (18), 146 (25), 118 (16), 77 (9), 28 (100).

4.4. Interaction of 3-bromoacetylcoumarin 1 with dialkyl phosphites

A solution of 3-bromoacetylcoumarin **1** (0.27 g, 1 mmol) and the corresponding dialkyl phosphite (5 mmol) was refluxed in dry toluene (3 mL) for 4 h. The complicated reaction mixtures were worked up as usually (Method A) and after the column chromatography were isolated the compounds **2**, **7** and **8**—for the yields see Table 2.

Transformation of the enolphosphate **2a** into **7**. A solution of enolphosphate **2a** (0.29 g, 1 mmol) and 4-toluenesulfonic acid (0.95 g, 5 mmol) in dry toluene (3 mL) was refluxed until the starting compound was consumed (TLC-monitoring). The reaction mixture was worked up as above and the 3-acetyl coumarin **7** (0.17 g, 90%) was isolated from ethanol.

Transformation of the enolphosphate **2a** into **1**. To the refluxing solution of the starting coumarin **2a** (0.29 g, 1 mmol) in dry toluene (3 mL) 4-toluenesulfonic acid (0.19 g, 1 mmol) was added. After 5 min to the reaction mixture *N*-bromosuccinimide (0.18 g, 1 mmol) was added and refluxed until the starting coumarin was consumed (TLC-monitoring) for about 30 min. The solvent was removed under reduced pressure and the reaction mixture was worked up as pointed above and from ethyl acetate were isolated bromoacetylcoumarin **1** in quantitative yield.

Transformation of the enolphosphate **2a** into **5a**. To the refluxing solution of the starting coumarin **2a** (0.29 g, 1 mmol) in dry toluene (3 mL) 4-toluenesulfonic acid (0.19 g, 1 mmol) was added. After 5 min to the reaction mixture was added *N*-bromosuccinimide (0.18 g, 1 mmol) and after further 45 min the trimethylphosphite (0.25 g, 2 mmol) was added. The reaction mixture was refluxed until the starting coumarin was consumed (TLC-monitoring) for about 2 h. Standard workup and purification by column chromatography gave enolphosphate **2a** (0.09 g, 33%) and the product of 1,4-addition **5a** (0.17 g, 46%).

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References and notes

1. Nikolova, R.; Bojilova, A.; Rodios, N. A. *Tetrahedron* **1998**, *52*, 14407.
2. Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607.
3. Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723.
4. Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.
5. Henning, F. G.; Hilgetag, G. *Zeitschr. Chem.* **1967**, *7*, 169.
6. Marguarding, D.; Ramirez, F.; Ugi, I.; Gillespie, P. *Angew. Chem.* **1973**, *85*, 99.
7. Arbuzov, B. A. *Zeitschr. Chem.* **1974**, *14*, 41.
8. Pudovik, A. N.; Gazizov, T. H. *Izv. Akad. Nauk SSSR* **1977**, 1945.
9. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
10. Kem, K. M.; Nguyen, N. V.; Cross, D. J. *J. Org. Chem.* **1981**, *46*, 5188.
11. Makosza, M.; Wojciechowski, K. *Bull. Pol. Acad. Sci.* **1984**, *32*, 175.
12. Ye, W.; Liao, X. *Synthesis* **1985**, 986.
13. Gaydou, E. M.; Bianchini, J.-P. *J. Chem. Soc., Chem. Commun.* **1975**, 541.
14. Machleid, H.; Strehlke, G. U. *Angew. Chem.* **1964**, *76*, 494.
15. Borowitz, I. J.; Firstenberg, S.; Borowitz, G. B.; Schuessler, D. *J. Am. Chem. Soc.* **1972**, *94*, 1623.
16. Chopard, P. A.; Clark, V. M.; Hudson, R. F.; Kirby, A. J. *Tetrahedron* **1965**, *21*, 1961.
17. Savignac, P.; Iorga, B. *Modern Phosphonate Chemistry*; CRC: Boca Raton, FL, 2003; p 139.
18. Koelsch, C. F. *J. Am. Chem. Soc.* **1950**, *72*, 2294.
19. Barton, D.; Ollis, W. D. *Comprehensive organic chemistry; The Synthesis and Reactions of Organic Compounds*; in Russian translation: Moscow, IZd. 'Khimija', 1983; Vol. 4, p 595.
20. Fahmy, A. A.; Hafez, T. S.; El-Farargy, F. A.; Hamad, M. M. *Phosph. Sulf. Sil.* **1991**, *57*, 211.
21. Osman, F. H.; Abd El-Rahman, N. M.; El-Samahy, F. A. *Phosph. Sulf. Sil.* **1998**, *133*, 151.
22. Abdou, W. M.; Sediek, A. A. *Tetrahedron* **1999**, *55*, 14777.
23. Osman, F. H.; Abd El-Kahman, N. M.; El-Samahy, F. A.; Farag, I. S. A. *Phosph. Sulf. Sil.* **2003**, *178*, 531.
24. Knoevenagel, E. *Chem. Ber.* **1898**, *31*, 730.
25. Knoevenagel, E.; Arnot, R. *Chem. Ber.* **1904**, *37*, 4498.
26. Horning, G. C.; Horning, M. H.; Dimming, D. A. *Organic Preparations and Proceedings* 1955. Collect. Vol. III, p 165.

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Anionic ring opening of norbornenes fused to heterocycles

Antonio R. Hergueta,[†] Carmen López, Xerardo García-Mera and Franco Fernández*

Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela,
E-15782 Santiago de Compostela, Spain

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Dedicated to Professor José L. Soto, on the occasion of his retirement

Abstract—The 2-hydroxy and 2-oxo derivatives of 1,2,3,4-tetrahydro-1,4-methanophenazine were prepared and found to evolve in basic media through the opening of their bicyclo[2.2.1]heptene moiety, affording 2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline derivatives with two-carbon 1-substituents that depend on the starting compound. In the case of 2-hydroxy starting compounds, ring-opening occurs regardless of the orientation of the hydroxyl group, and in methanolic solution is spontaneous, though slow, even in the absence of added base (at least in the case of the *endo* derivative). It is presumably favoured by the steric strain of the heteroaryl-fused bicyclo[2.2.1]heptene moiety, and is hypothesized to involve the base-promoted formation of anionic intermediates that are stabilized by the π-deficient nature of the quinoxaline system.

1. Introduction

Though first reported over 40 years ago, molecules consisting of an aromatic heterocycle fused to norbornene or norbornadiene have only more recently attracted attention. Relatively simple derivatives of compounds of this kind have been proposed for storage of light energy,[1,2] while more complex derivatives have been developed as initiators of photochemical polymerization,[3,4] as components of holographic recording media,[5–8] as ligands forming part of models for the study of long-range electron transfer between chelated metal centres,[9,10] and as the monomers of self-assembling dimeric capsules[11,12] or of molecular cavities and ribbons.[13,14] In the pharmacological field, compounds of this type have been prepared in pursuit of virucidal or virustatic agents,[15] antiulcer agents,[16] brain acetylcholinesterase inhibitors,[17–19] serotonin antagonists,[20] central nervous system stimulants,[21–23] dihydrofolate reductase inhibitors,[24] and mGluR1 antagonists.[25]

Although much of the relevant literature, especially the older papers, merely describes their preparation (sometimes incidental) and/or their spectroscopic properties,[26–42] there have also been studies of their chemistry, including work on electrophilic addition reactions;[43–46] aromatic substitution in the heterocyclic moiety;[47] the regiochemistry of their di-π-methane photorearrangement;[48,49] the relationship between their basicity and internal strain;[50] and their behaviour as dienophiles in Diels–Alder reactions.[51] Of particular interest is the participation of the heterocyclic moiety as neighbouring group in the solvolysis of diverse sulfonates,[52–54] in the acidic opening of an epoxide ring previously formed on the norbornene moiety[55] and in electrophilic additions,[43–46] and the influence of the electronic π-richness or π-deficiency of that moiety on π-facial selectivity in the latter reactions.[56,57]

If the heterocyclic moiety is π-deficient the norbornene moiety can behave quite differently from carbocyclic or non-condensed analogues. For example, subjecting diols **1** to the conditions of Swern's reaction does not afford the corresponding diketones **2**, but instead 63–75% yields of alcohols **3** as the only isolatable products.[58] Here we report that the norbornene moiety of **1a** and of other oxygenated 1,2,3,4-tetrahydro-1,4-methanophenazine derivatives (**4** and **5**) also opens very readily in basic media, a finding that as far as we know has no precedent in the literature except for a preliminary report of ours concerning **1a**.[59]

Keywords: Quinoxaline-fused norbornene; Ring opening; Anionic intermediates; Basic medium.

* Corresponding author. Tel.: +34-981-563-100; fax: +34-981-594-912; e-mail: qofranco@usc.es

[†] Present address: Tripos Receptor Research Ltd, Bude-Stratton Business Park, Bude-Cornwall EX23 8LY, England.

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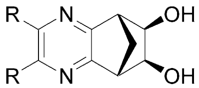

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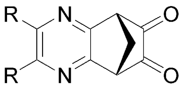
1b R = H



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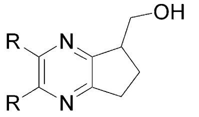

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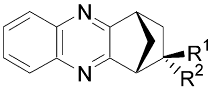
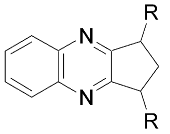
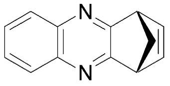


4a R^1 = H, R^2 = OH
4b R^1 = OH, R^2 = H
5 (R^1,R^2) = O



6 R = CO_2H
7 R = CH_2OH
8 R = CHO



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Our interest in **1a** originated from the wish to obtain diacid **6** and diol **7** for the synthesis of carbocyclic analogues of nucleosides with phthalazine-fused carbocycles; after several unsuccessful attempts to obtain **6** and **7** through oxidative cleavage of the double bond in **9**,[60] we hoped that mild treatment of **1a** (e.g., with periodic acid) would result in oxidative cleavage leading to dialdehyde **8**, which would then be oxidized to **6** or reduced to **7** in situ.[61] Since it was planned to use **1a** on more than one occasion in exploring its oxidative cleavage under diverse conditions, the finding that it tended to decompose when stored at rt led us to prepare compound **16** as a stable derivative that could presumably be easily converted to **1a** immediately before use. In the event, we found that the basic conditions used for conversion of **16** into **1a** caused the opening of its norbornene moiety.

2. Results and discussion

Compound **16** was obtained as shown in Scheme 1. A commercially available racemic mixture of *endo* and *exo* norbornenyl acetates (**10**) was dihydroxylated to **11**, and benzoylation followed by selective hydrolysis of the acetate afforded **13**. Since dihydroxylation of bicyclo[2.2.1]heptenes occurs almost exclusively at the *exo* face,[62] **11–13** were virtually monoepimeric at positions 2 and 3, and oxidation of both 5-epimers of **13** took place easily to afford monoketone **14**, which upon treatment with selenium dioxide gave the α-diketone **15**. Finally, condensation of **15** with *ortho*-phenylenediamine yielded the dibenzoate **16**.

Because of the likelihood of rearrangements of Wagner–Meerwein type due to its norbornene moiety, the conversion of **16** to **1a** was attempted by basic rather than acid hydrolysis. Initial attempts gave only intractable mixtures or unaltered starting material, but the mildest conditions compatible with effective saponification of the benzoate groups (0.9 M KOH in MeOH/H_2O, rt, 12 h) afforded a crude product that upon flash chromatography on silica gel gave a 66% yield of a dark green solid. This product underwent alteration when left standing in solution, but IR, MS and ^1H and ^{13}C NMR data obtained immediately after purification were compatible with its being the enediol **17**. This identification was confirmed by single-crystal X-ray crystallography of the stable diacetylated derivative **18** (Fig. 1),[63] which was obtained by acetylation of **17** with Ac_2O/pyridine.

It may be assumed that the first step in the conversion of **16** to **17** is the desired hydrolysis to **1a**; this is supported by the fact that a sample of **1a** prepared by an independent route,[58] was transformed into **17** in very similar yield when subjected to the same basic conditions as **16**. A plausible account of subsequent steps is shown in Scheme 2. Under the basic working conditions, diol **1a** will be in equilibrium with its monoalkoxide, which because of the stress in the bridged ring system must be highly susceptible to ring

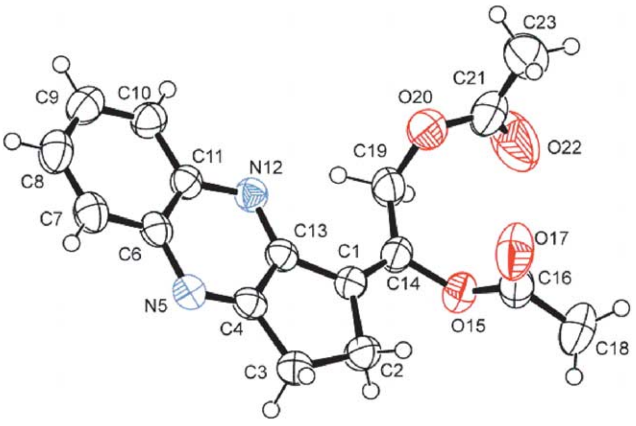
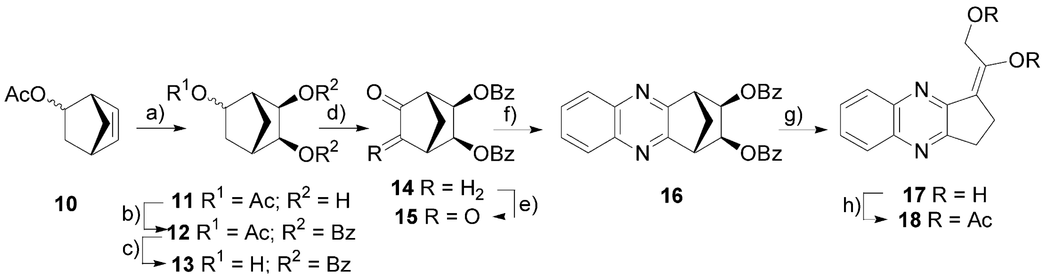
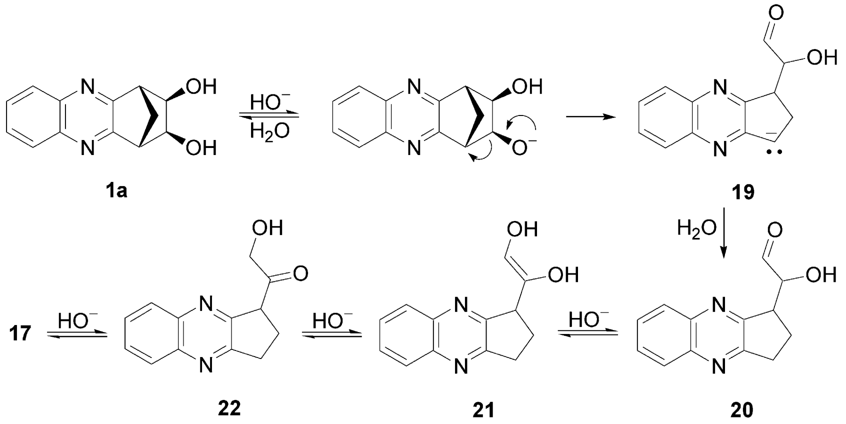


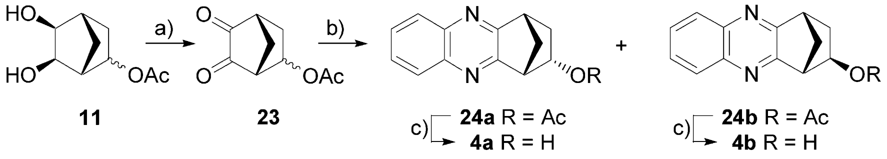
Figure 1. ORTEP plot of the molecular structure of **18** in the solid state.



Scheme 1. Reagents and conditions: (a) OsO_4/NMNO/Me_2CO–H_2O, 40 °C, 18 h; (b) BzCl/Py, rt, 24 h; (c) K_2CO_3/MeOH, rt, 30 min; (d) $CrO_3\cdot Py$/DCM, rt, 6 h; (e) SeO_2/xylene, 140 °C, 24 h; (f) *o*-$(C_6H_4)(NH_2)_2$/$ZnCl_2$/THF, 66 °C, 18 h; (g) 0.9 M KOH/MeOH–H_2O, rt, 12 h; (h) Ac_2O/Py, rt, 14 h.



Scheme 2. Suggested mechanism for the formation of **17** from **1a**.



Scheme 3. Reagents and conditions: (a) DMSO-TFAA/DCM/TEA, −78 °C, 3 h; (b) *o*-$(C_6H_4)(NH_2)_2/ZnCl_2$/THF, 66 °C, 4.5 h; (c) 0.7 M Na_2CO_3/MeOH, rt, 2 h.

opening. The resulting carbanion **19** will be stabilized by its charge being formally located on the carbon α to position 3 of the π-deficient quinoxaline system, and following protonation of this carbon the resulting α-hydroxyaldehyde **20** will be susceptible to base-catalyzed isomerization to the α-hydroxyketone **22** via the enediol **21** (a well-known conversion in sugar chemistry). Finally, isomerization of **22** to the enediol **17** will be favoured by the exocyclic C=C bond of the latter being conjugated with the aromatic quinoxaline system.

As there appear to be no published precedents for the above anionically driven ring-opening of a bicyclo[2.2.1]heptene derivative, we began to explore its scope using the structurally simpler monoalcohols **4a** (*endo*) and **4b** (*exo*), which were prepared as shown in Scheme 3 by Swern oxidation of **11** to the mixture of epimeric diketones **23**, followed by condensation of **23** with *ortho*-phenylenediamine, chromatographic separation of the resulting mixture of diastereomeric methanophenazines **24**, and mild hydrolysis of **24a** and **24b** (0.7 M Na_2CO_3 in methanol, rt, 2 h). The identity of **24a** (the major isomer) was confirmed by X-ray crystallographic analysis of a single crystal (Fig. 2).[63]

Hydrolysis of **24a** or **24b** under more severe conditions (longer reaction times, or use of 1 M KOH instead of 0.7 M Na_2CO_3) afforded a mixture including a product with spectroscopic data compatible with its being aldehyde **25** (in particular, a substituted cycloalkyl acetaldehyde was indicated by a strong IR band at 1722 cm^{-1}, ^1H NMR signal at 9.88 ppm, and ^{13}C NMR signals at 201.03 and 47.52 ppm). Starting from **24a**, the greatest yield of **25** was obtained by simply maintaining the conditions used to obtain **4a** for 6 h instead of 2 h (Scheme 4); this gave an approximately 71% yield of a product shown by ^1H NMR data to be **25**, in a sample enriched to a 90% content, as

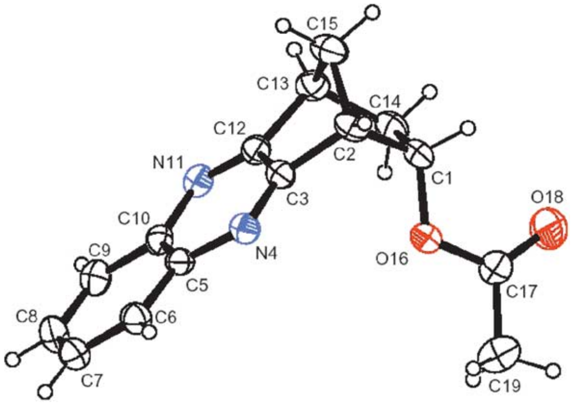
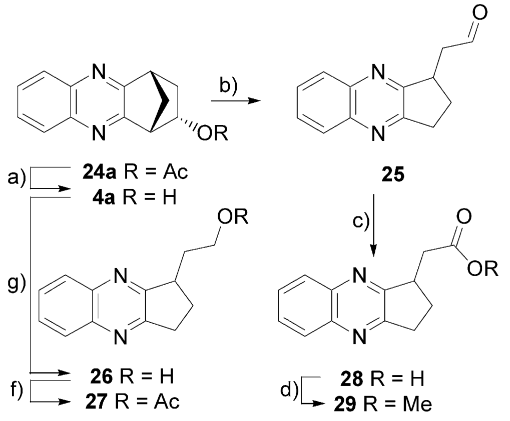


Figure 2. ORTEP plot of the molecular structure of **24a** in the solid state.



Scheme 4. Reagents and conditions: (a) 0.7 M Na_2CO_3/MeOH, rt, 2 h; (b) 0.7 M Na_2CO_3/MeOH, rt, 6 h; (c) $AgNO_3/NH_4OH$, rt, 3 h; (d) MeOH/TsOH, 65 °C, 3.5 h; (e) $NaBH_4$/EtOH, rt, 15 h; (f) Ac_2O/Py, rt, 18 h; (g) 0.5 M $Na_2CO_3/NaBH_4$/EtOH, rt, 18 h.

estimated by ^{1}H NMR. Since this product tended to undergo alteration during work-up,[64] it was converted to more stable forms by Tollens oxidation to acid **28** and $NaBH_4$ reduction to alcohol **26**, which were then further converted into the methyl ester **29** and the acetate **27**, respectively (Scheme 4). Compounds **26–29** all had spectra in keeping with the proposed structures, and that of **26** was confirmed by X-ray crystallography of a single crystal (Fig. 3).[63] If both Na_2CO_3 and $NaBH_4$ are included in the reaction medium, **4a** is transformed into **25** and **25** into **26** in a tandem process with an overall yield of 63%, as against an estimated 54% if **25** is first isolated.

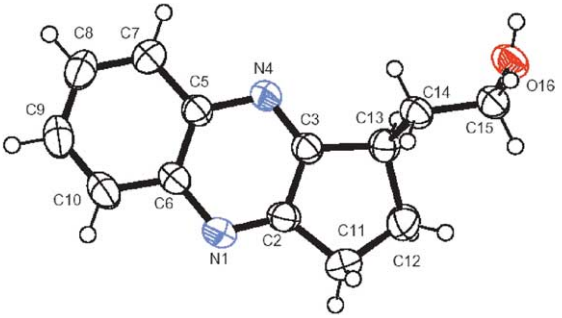
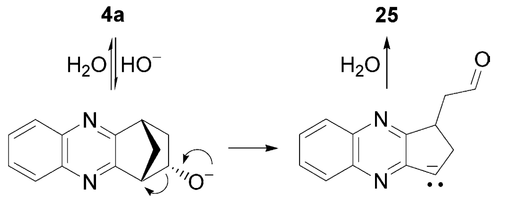


Figure 3. ORTEP plot of the molecular structure of **26** in the solid state.

The formation of **25** from **4a** (or, similarly, from **4b**) may be attributed to the mechanism shown in Scheme 5, which is exactly analogous to the first part of that shown in Scheme 2 for the conversion of **1a** into **17**. At rt it occurs even in methanol without added base (being detectable by ^{1}H NMR after 48 h), possibly being autocatalysed by the basic centres of the tetrahydrophenazine alcohol (although solid **4a** can be stored at 5 °C for several weeks without any alteration detectable by ^{1}H NMR). The acetylated precursors **24** are perfectly stable in methanol at rt.

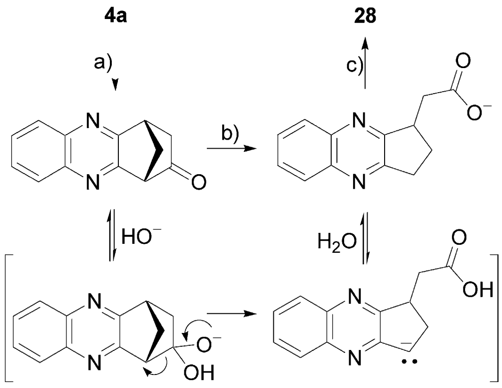


Scheme 5. Suggested mechanism for the formation of **25** from **4a**.

Finally, we also performed the ring-opening reaction on ketone **5**, which was easily obtained by oxidation of **4a** with CrO_3. In basic medium, **5** was converted to the acid **28** by a mechanism hypothesized as starting by the nucleophilic attack of the base to the carbonyl carbon and otherwise being analogous to those proposed above (Scheme 6). Under appropriate conditions, the reaction could be used preparatively, though spontaneous partial transformation of **5** into **28** in chloroform-*d* $CDCl_3$/methanol-d_3 CD_3OD solution was also observed (^{1}H NMR) after 3 days at rt.

3. Conclusion

Basic media promote the opening of the bicyclo[2.2.1]heptene moiety of 2-hydroxy and 2-oxo derivatives of 1,2,3,4-tetrahydro-1,4-methanophenazine, affording 2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline derivatives with two-carbon 1-substituents that depend on the starting compound. Ring-opening occurs regardless of the orientation of the hydroxyl group in the case of 2-hydroxy starting compounds, and in methanolic solution is spontaneous, though slow, even in the absence of added base (at least in the case of the 2-*endo*-hydroxy or 2-oxo derivatives). It is presumably favoured by the steric strain of the heteroaryl-fused bicyclo[2.2.1]heptene moiety, and may involve the base-promoted formation of anionic intermediates that are stabilized by the π-deficient nature of the quinoxaline system. Although there have been several reports of Wagner–Meerwein and ring-opening processes involving cationic intermediates which are undergone by benzene-fused[65–69] or heteroarene-fused[44–46,54,55] bicyclo[2.2.1]heptenes, the reactions described here are as far as we know the first examples of base-promoted ring-opening involving a carbanion intermediate.



Scheme 6. Preparation of **5** from **4a** and suggested mechanism for the rearrangement of **5** to **26** in basic media. Reagents and conditions: (a) $CrO_3\cdot Py$/DCM, 0 °C, 6 h; (b) 1 M NaOH/H_2O, rt, 14 h; (c) H_3O^{+}/pH 4.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi apparatus. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded using TMS as internal reference (chemical shifts in δ values, J in Hz). Microanalyses were performed by the Microanalysis Service of the University of Santiago. Crystallographic data were obtained with a MACH3 Enraf Nonius diffractometer. Flash chromatography was performed on silica gel (230–240 mesh) and analytical TLC on pre-coated silica gel plates (F254, 0.25 mm) and spots were examined with UV light and sulfuric acid/anisaldehyde spray.

4.1.1. (±)-(5-*exo*,6-*exo*)-5,6-Dihydroxybicyclo[2.2.1]-hept-2-yl acetate (mixture of 2-*endo* and 2-*exo*) (11). A solution of commercial (±)-5-norbornen-2-yl acetate (10.0 g, 65.8 mmol) in 4:1 acetone/water (140 mL) was heated to 40 °C, *N*-methylmorpholine *N*-oxide (8.50 g, 72.5 mmol) was added, and 5 min later this mixture was treated with 2 mL of a commercial solution of OsO_4 (4 wt% in water), which caused it to turn brown almost immediately. The stirred, heated mixture was monitored by TLC, and after 18 h the reaction was deemed complete. The acetone was removed under reduced pressure, the remaining aqueous solution was extracted with AcOEt, the resulting organic extract was dried (Na_2SO_4), the solvent was removed, and the crude residue was purified by column chromatography with 1:1 (v/v) hexane/EtOAc as eluent, affording a yellowish oil composed of a mixture of diols **11** (11.6 g, 95%) in approximate *endo*/*exo* ratio 78:22 (as determined by ^{1}H NMR). This oil solidified spontaneously. IR (KBr) ν: 3385 (OH), 1731 (CO), 1377, 1248, 1147, 942 cm^{-1}. EIMS *m*/*z* (%): 168 (4), 126 (79), 79 (100), 70 (79), 67 (55), 58 (81). ^{1}H NMR and ^{13}C NMR for the major isomer (2-*endo*) were in accordance with the literature.[70]

4.1.2. (±)-(5-*exo*,6-*exo*)-5,6-Dibenzoyloxybicyclo[2.2.1]-hept-2-yl acetate (mixture of 2-*endo* and 2-*exo*) (12). Benzoyl chloride (8 mL, 68 mmol) was slowly added to a solution of **11** (5.00 g, 26.8 mmol) in dry pyridine (37 mL) at 0 °C, and the mixture was stirred at rt for 24 h and then placed in an ice-bath, brought to pH 8 with 2 N NaOH, and extracted with EtOAc (2×150 mL). The pooled organic extracts were washed several times with water and dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using 5:1 (v/v) hexane/EtOAc as eluent, which afforded the ester mixture **12** as a low melting solid (8.05 g, 76%) in approximate *endo*/*exo* ratio 4:1 (as determined by ^{1}H NMR). IR (KBr) ν: 1738, 1719, 1708, 1651, 1615, 1558, 1540, 1456, 1239, 1026, 712 cm^{-1}. EIMS *m*/*z* (%): 394 (M^+, 1), 335 (7), 289 (11), 272 (4), 186 (6), 106 (7), 105 (100), 78 (3), 77 (42), 76 (2), 51 (9). Major isomer (2-*endo*): ^{1}H NMR ($CDCl_3$) δ: 7.89–7.81 [4H, m, 2×(2′,6′-H_2)], 7.51–7.43 [2H, m, 2×(4′-H)], 7.31–7.21 [4H, m, 2×(3′,5prime;-H_2)], 5.64 (1H, dd, *J*=5.9, 1.4 Hz, 6-H), 5.26 (1H, dd, *J*=5.9, 1.3 Hz, 5-H), 5.12–5.08 (1H, m, 2-*exo*-H), 2.81 (1H, d, *J*=3.4 Hz, 1-H), 2.52 (1H, d, *J*=4.7 Hz, 4-H), 2.25–2.17 (2H, m, 3-*exo*-H+7-*H*H), 2.13 (3H, s, CH_3), 2.07–2.03 (1H, m, 7-H*H*), 1.28–1.21 (1H, m, 3-*endo*-H). ^{13}C NMR and DEPT ($CDCl_3$) δ: 171.4 (CO), 165.9 (CO), 133.3 (CH), 130.2 (C), 129.98 (CH), 129.97 (C), 128.6 (CH), 128.5 (CH), 76.6 (CH), 72.3 (CH), 72.1 (CH), 45.8 (CH), 42.0 (CH), 33.4 (CH_2), 33.0 (CH_2), 21.5 (CH_3). HRMS calcd for $C_{23}H_{22}O_6$: 394.1416. Found: 394.1409.

4.1.3. (±)-(5-*exo*,6-*exo*)-5,6-Dibenzoyloxybicyclo[2.2.1]-heptan-2-ol (mixture of 2-*endo* and 2-*exo*) (13). Solid K_2CO_3 (1.43 g, 10.3 mmol) was added to a solution of **12** (8.16 g, 20.7 mmol) in MeOH (120 mL), and the mixture was successively stirred at rt for 30 min, diluted with EtOAc (500 mL), washed with saturated NH_4Cl solution followed by water, and dried (Na_2SO_4). The organic solvents were removed under reduced pressure, and the residue was purified by silica gel column chromatography using 1:1 (v/v) hexane/EtOAc as eluent, which afforded the alcohol mixture **13** (6.71 g, 92%) as a waxy solid in approximate *endo*/*exo* ratio 4:1, as determined by ^{1}H NMR. IR (KBr) ν: 3505 (OH), 1720 (CO), 1651, 1540, 1455, 1286, 1123, 1025, 707 cm^{-1}. EIMS *m*/*z* (%): 352 (0.5, M^+), 335 (7), 289 (11), 247 (2), 230 (9), 186 (5), 136 (4), 125 (11), 108 (4), 106 (7), 105 (100), 77 (42), 51 (9). Major isomer (2-*endo*): ^{1}H NMR ($CDCl_3$) δ: 7.89–7.84 [4H, m, 2×(2′,6′-H_2)], 7.49–7.44 [2H, m, 2×(4′-H)], 7.29–7.23 [4H, m, 2×(3′,5′-H_2)], 5.79 (1H, d, *J*=6.0 Hz, 6-H), 5.27 (1H, d, *J*=6.0 Hz, 5-H), 4.39 (1H, dt, *J*=10.3, 4.1 Hz, 2-*exo*-H), 2.62 (1H, d, *J*=3.4 Hz, 1-H), 2.49 (1H, d, *J*=4.1 Hz, 4-H), 2.25–2.12 (2H, m, 3-*exo*-H+7-*H*H), 1.71 (1H, b s, D_2O exchang., OH), 1.47 (1H, d, *J*=10.8 Hz, 7-H*H*), 1.46 (1H, dt, *J*=13.8, 3.4 Hz, 3-*endo*-H). ^{13}C NMR and DEPT ($CDCl_3$) δ: 166.1 (CO), 166.0 (CO), 133.2 (CH), 130.4 (C), 130.0 (CH), 125.6 (CH), 77.1 (CH), 72.3 (CH), 70.3 (CH), 48.2 (CH), 42.6 (CH), 35.1 (CH_2), 33.7 (CH_2). HRMS calcd for $C_{21}H_{20}O_5$: 352.1311. Found: 352.1304.

4.1.4. (±)-(*exo*,*exo*)-5,6-Dibenzoyloxybicyclo[2.2.1]heptan-2-one (14). A solution of **13** (3.86 g, 11.0 mmol) in CH_2Cl_2 (100 mL) was added during 15 min to a stirred mixture of pyridine (11 mL), CH_2Cl_2 (110 mL) and CrO_3 (6.63 g, 66.3 mmol) kept at 0 °C, and stirring was continued for 6 h. The mixture was then filtered through celite and evaporated to dryness under reduced pressure. Purification of the resulting residue by silica gel column chromatography with 7:3 (v/v) hexane/EtOAc as eluent afforded **14** (2.99 g, 78%) as a white solid. An analytical sample was obtained by recrystallization from cyclohexane. Mp 141–142 °C. IR (KBr) ν: 1751 (CO), 1726 (CO), 1651, 1600, 1558, 1548, 1508, 1315, 1287, 708 cm^{-1}. EIMS *m*/*z* (%): 350 (M^+, 0.5), 323 (3), 322 (14), 228 (3), 186 (14), 106 (8), 105 (100), 79 (4), 78 (4), 77 (60), 76 (3), 51 (13). ^{1}H NMR ($CDCl_3$) δ: 7.90–7.82 [4H, m, 2×(2′,6′-H_2)], 7.55–7.45 [2H, m, 2×(4′-H)], 7.33–7.22 [4H, m, 2×(3′,5′-H_2)], 5.37 (2H, virtual s, 5-H+6-H), 3.01 (1H, d, *J*=3.8 Hz, 4-H), 2.96 (1H, s, 1-H), 2.58 (1H, d, *J*=11.1 Hz, 7-*H*H), 2.30 (1H, dd, *J*=18.6, 5.3 Hz, 3-*exo*-H), 2.16 (1H, dd, *J*=18.6, 4.2 Hz, 3-*endo*-H), 1.95 (1H,d, *J*=11.1 Hz, 7-H*H*). ^{13}C NMR and DEPT ($CDCl_3$) δ: 212.4 (CO), 165.8 (CO), 165.5 (CO), 133.62 (CH), 133.56 (CH), 130.1 (CH), 130.0 (CH), 129.8 (C), 129.7 (C), 128.7 (CH), 128.6 (CH), 75.6 (CH), 71.6 (CH), 56.3 (CH), 41.7 (CH_2), 41.2 (CH), 34.0 (CH_2). Anal. Calcd for $C_{21}H_{18}O_5$ (350.36): C, 71.99; H, 5.18. Found: C, 71.72; H, 5.28.

4.1.5. (*exo*,*exo*)-5,6-Dibenzoyloxybicyclo[2.2.1]heptane-2,3-dione (15). A mixture of **14** (1.95 g, 5.56 mmol), SeO_2 (0.61 g, 5.56 mmol) and xylenes (6 mL) was refluxed for 24 h, vacuum-filtered through celite, and condensed to dryness under reduced pressure. Purification of the resulting residue by silica gel column chromatography with 4:1 (v/v) hexane/EtOAc as eluent afforded **15·H₂O** as a white solid (1.59 g, 74%). An analytical sample was obtained by recrystallization from EtOAc–hexane. Mp 109–110 °C. IR (KBr) ν: 3423, 1777, 1723, 1600, 1450, 1279, 1114, 713 cm^{-1}. Anal. Calcd for $C_{21}H_{16}O_6\cdot H_2O$ (382.36): C, 65.96; H, 4.74. Found: C, 66.21; H, 4.57.

4.1.6. (*exo*,*exo*)-1,2,3,4-Tetrahydro-1,4-methanophenazine-2,3-diyl dibenzoate (16). A mixture of **15**·$\mathbf{H_2O}$ (1.45 g, 3.79 mmol), *o*-phenylenediamine (1.10 g, 10.5 mmol) and the zinc catalyst $ZnCl_2[C_6H_5CH(NH_2)CH_3]_2$ (10 mg) in dry THF (33 mL) was refluxed for 18 h. The solvent was then evaporated off, and chromatographic purification of the resulting crude product with 7:3 (v/v) hexane/EtOAc as eluent afforded **16** (1.31 g, 79%) as a white solid. An analytical sample was obtained by recrystallization from EtOAc–hexane. Mp 194–195 °C. IR

(KBr) ν: 1731, 1716, 1600, 1276, 1120, 1072, 971, 760, 708 cm^{-1}. EIMS *m/z* (%): 437 (14, M+1), 436 (47, M^{+}), 331 (16), 209 (11), 181 (8), 169 (11), 105 (100), 77 (24). ^{1}H NMR (CDCl$_3$) δ: 8.06 (2H, dd, *J*=6.3, 3.3 Hz, 6-H+9-H), 7.90 [4H, d, *J*=8.0 Hz, 2×(2′,6′-H$_2$)], 7.73 (2H, dd, *J*=6.2, 3.5 Hz, 7-H+8-H), 7.50 [2H, t, *J*=7.3 Hz, 2×(4′-H)], 7.28 [4H, t, *J*=7.7 Hz, 2×(3′,5′-H$_2$)], 5.48 (2H, s, 2-H+3-H), 3.87 (2H,s, 1-H+4-H), 2.96 (1H, d, *J*=10.3 Hz, 7-*H*H), 2.44 (1H, d, *J*=10.3 Hz, 7-H*H*). ^{13}C NMR and DEPT (CDCl$_3$) δ: 165.6 (CO), 159.9 (C), 142.4 (C), 133.6 (CH), 130.1 (CH), 129.9 (CH), 129.8 (C), 129.6 (CH), 128.7 (CH), 73.3 (CH), 50.1 (CH), 42.0 (CH$_2$). Anal. Calcd for $C_{27}H_{20}N_2O_4$ (436.47): C, 74.30; H, 4.62; N, 6.42. Found: C, 74.11; H, 4.71; N 6.29.

4.1.7. *E*-1-(2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-ylidene)-1,2-ethanediol (17). 1 N KOH (20 mL) was added to a solution of **16** (1.25 g, 2.86 mmol) in MeOH (3 mL), and the mixture was stirred at rt for 12 h, brought to pH 8 with 1 N HCl, concentrated under reduced pressure, and extracted with CH$_2$Cl$_2$ (2×20 mL). The pooled extracts were washed with saturated NaCl solution and dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The purification of the resulting residue by flash chromatography with 10:1 (v/v) EtOAc/MeOH as eluent afforded **17** as a deep green solid (0.43 g, 66%), solutions of which changed with time from fluorescent green to black. The best samples were obtained by rapid recrystallization from EtOAc–hexane. The product obtained by chromatography was used directly to obtain its diacetylated derivative. IR (KBr) ν: 3434, 3318, 1644, 1610, 1580, 1558, 1232, 1068, 901, 770, 600 cm^{-1}. EIMS *m/z* (%): 228 (32, M^{+}), 197 (71), 170 (41), 169 (61), 168 (26), 58 (100), 52 (2). ^{1}H NMR (CDCl$_3$) δ: 10.32 (1H, b s, D$_2$O exchang., 1-OH), 7.55 (1H, dt, *J*=7.9, 1.2 Hz), 7.32 (1H, dt, *J*=7.7, 1.3 Hz), 7.18 (1H, dt, *J*=7.7, 1.3 Hz), 7.04 (1H, dt, *J*=7.9, 1.2 Hz), 4.34 (2H, s, CH$_2$O), 3.49 (1H, b s, D$_2$O exchang., 2-OH), 3.06–3.02 (2H, m), 2.81–2.77 (2H, m). ^{13}C NMR and DEPT (CDCl$_3$) δ: 194.6 (C), 171.1 (C), 143.3 (C), 136.5 (C), 129.6 (CH), 129.3 (C), 128.6 (CH), 124.7 (CH), 115.8 (CH), 105.9 (C), 65.7 (CH$_2$), 30.2 (CH$_2$), 22.7 (CH$_2$).

4.1.8. *E*-1-(2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-ylidene)ethane-1,2-diyl diacetate (18). Acetic anhydride (5 mL) was slowly added to a solution of **17** (0.30 g, 1.31 mmol) in dry pyridine (5 mL), and the mixture was stirred at rt for 14 h. The solvent and excess reagent were removed under reduced pressure, and purification of the residue by silica gel column chromatography with 1:1 (v/v) EtOAc/hexane as eluent afforded **18** as a white solid (0.35 g, 85%). An analytical sample was obtained by recrystallization from EtOAc–hexane. Mp 136–137 °C. IR (KBr) ν: 1758, 1736, 1437, 1375, 1230, 1170, 1102, 1017, 803 cm^{-1}. EIMS *m/z* (%): 312 (7, M^{+}), 253 (35), 213 (23), 211 (29), 195 (12), 61 (100), 59 (12), 43 (82), 42 (82), 42 (29), 41 (39), 33 (17), 28 (87), 19 (49), 17 (76). ^{1}H NMR (CDCl$_3$) δ: 8.07–8.03 (1H, m), 8.00–7.97 (1H, m), 7.73–7.67 (2H, m), 5.76 (2H, s, CH$_2$O), 3.27–3.22 (2H, m), 2.96–2.90 (2H, m), 2.27 (3H, s, CH$_3$), 2.11 (3H, s, CH$_3$). ^{13}C NMR and DEPT (CDCl$_3$) δ: 171.2 (CO), 168.5 (CO), 162.5 (C), 152.6 (C), 145.2 (C), 142.1 (C), 142.0 (C), 131.0 (C), 130.3 (CH), 130.2 (CH), 129.7 (CH), 128.9 (CH), 60.7 (CH$_2$), 29.3 (CH$_2$), 24.6 (CH$_2$), 21.3 (CH$_3$), 21.1 (CH$_3$). Anal. Calcd for $C_{17}H_{16}N_2O_4$ (312.33): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.17; H, 5.23; N 8.84.

4.1.9. (±)-5,6-Dioxobicyclo[2.2.1]hept-2-yl acetate (mixture of *endo* and *exo*) (23). Dry DMSO (7 mL) was added very slowly to a solution of dry trifluoroacetic anhydride (12.3 mL, 88.1 mmol) in dry CH$_2$Cl$_2$ (52 mL) at −78 °C (internal temperature), and the mixture was stirred for 10 min, treated with a solution of the acetate mixture **11** (5.75 g, 30.9 mmol) in CH$_2$Cl$_2$ (15 mL), stirred at −78 °C for 2.5 h, treated with Et$_3$N (23 mL), stirred at −78 °C for a further 3 h, allowed to reach 0 °C, transferred to an ice-bath, acidified with 3 M HCl, and extracted with CH$_2$Cl$_2$ (2×120 mL). The pooled extracts were washed with brine and dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure, leaving the acetate mixture **23** as a dark, viscous oil (4.03 g). Crude product was used directly in the next synthetic step. A small sample (0.53 g) was resolved by silica gel column chromatography with 7:1 (v/v) hexane/EtOAc as eluent into the two epimers of **23**, isolated as clear oils.

Compound endo-**23**. IR (NaCl) ν: 1747 (CO), 1407, 1244, 1046 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 5.39 (1H, ddd, *J*=9.5, 5.5, 3.5 Hz, 2-*exo*-H), 3.37 (1H, dd, *J*=5.1, 1.2 Hz, m, 1-H), 3.06 (1H, d, *J*=5.1 Hz, 4-H), 2.65 (1H ddd, *J*=14.7, 9.9, 5.1 Hz, 3-*exo*-H), 2.30–1.98 (2H, m, 7-H$_2$), 1.97 (3H, s, CH$_3$), 1.72 (1H, dt, *J*=14.7, 3.0 Hz, 3-*endo*-H).

Compound exo-**23**. IR (NaCl) ν: 1740 (CO), 1376, 1230, 1057 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 4.87 (1H, d, *J*=6.9 Hz, 2-*endo*-H), 2.79–2.76 (1H, m, 1-H), 2.09–1.99 (1H, m, 4-H), 2.03 (3H, s, CH$_3$), 1.89–1.70 (2H, m, 7-H$_2$), 1.14–1.04 (1H, m, 3-*exo*-H), 0.89–0.82 (1H, m, 3-*endo*-H).

4.1.10. (±)-*endo*- and (±)-*exo*-1,2,3,4-Tetrahydro-1,4-methanophenazin-2-yl acetates (24a and 24b). *o*-Phenylenediamine (2.70 g, 25.0 mmol) and the zinc catalyst ZnCl$_2$[C$_6$H$_5$CH(NH$_2$)CH$_3$]$_2$ (10 mg) were added to a solution of the crude product of the previous reaction (3.50 g) in dry THF (80 mL), and the mixture was refluxed for 4.5 h. The solvent was then removed under reduced pressure, and fractionation of the residue by column chromatography, first with 7:3 (v/v) hexane/EtOAc as eluent which afforded the minor isomer **24b** (0.37 g) and then with 4:6 (v/v) hexane/EtOAc to isolate the major isomer, **24a** (1.47 g) (joint yield from mixture **11**, 27%). Analytical samples of both isomers were obtained by recrystallization from EtOAc/hexane.

Compound **24a**. White solid, mp 131–132 °C. IR (KBr) ν: 1730 (CO), −339, 1114, 769 cm^{-1}. EIMS *m/z* (%): 254 (47, M^{+}), 212 (64), 184 (76), 183 (100), 181 (29), 169 (31), 168 (69), 76 (9). ^{1}H NMR (CDCl$_3$) δ: 8.07–8.01 (2H, m, 6-H+9-H), 7.71–7.68 (2H, m, 7-H+8-H), 5.62 (1H, ddd, *J*=9.4, 4.5, 3.1 Hz, 2-*exo*-H), 3.86 (1H, dd, *J*=4.5, 1.4 Hz, 1-H), 3.58 (1H, d, *J*=3.3 Hz, 4-H), 2.71 (1H, ddd, *J*=13.6, 9.5, 4.5 Hz, 3-*exo*-H), 2.16 (1H, dm, *J*=10.5 Hz, 11-*H*H), 2.06 (1H, dm, *J*=10.5 Hz, 11-H*H*), 1.82 (3H, s, CH$_3$), 1.43 (1H, dt, *J*=13.6, 3.2 Hz, 3-*endo*-H). ^{13}C NMR and DEPT (CDCl$_3$) δ: 171.2 (CO), 163.4 (C), 159.8 (C), 142.1 (C), 142.0 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.0 (CH), 73.2 (CH), 48.6 (CH), 44.4 (CH$_2$), 43.9 (CH), 35.2 (CH$_2$), 21.2 (CH_3). Anal. Calcd for $C_{15}H_{14}N_2O_2$ (254.29): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.68; H, 5.63; N 10.84.

Compound **24b**. White solid, mp 83–84 °C. IR (KBr) ν: 1731 (CO), 1460, 1033, 762 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.77–7.71 (2H, m, 6-H+9-H), 7.41–7.38 (2H, m, 7-H+8-H), 4.74–4.76 (1H, m, 2-*endo*-H), 3.46 (1H, s, 1-H), 3.37 (1H, d, J=2.8 Hz, 4-H), 2.12 (1H, d, J=10.0 Hz, 11-*H*H), 1.97 (1H, d, J=10.0 Hz, 11-H*H*), 1.88 (3H, s, CH_3), 1.91–1.80 (2H, m, 3-H_2). ^{13}C NMR and DEPT ($CDCl_3$) δ: 170.2 (CO), 163.8 (C), 159.7 (C), 141.4 (C), 141.3 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 73.8 (CH), 50.1 (CH), 43.5 (CH), 42.8 (CH_2), 36.5 (CH_2), 21.2 (CH_3). Anal. Calcd for $C_{15}H_{14}N_2O_2$ (254.29): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.74; H, 5.62; N, 10.87.

4.1.11. (±)-*endo*-1,2,3,4-Tetrahydro-1,4-methanophenazin-2-ol (4a). Na_2CO_3 (2.00 g, 18.86 mmol) was added to a solution of **24a** (1.00 g, 3.93 mmol) in MeOH (25 mL), and the mixture was stirred vigorously for 2 h. The MeOH was then removed under reduced pressure, and the residue was taken into water (50 mL) and extracted with EtOAc (2× 100 mL). The pooled organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure, and purification of the solid residue by silica gel column chromatography with 10:1 (v/v) EtOAc/hexane as eluent afforded **4a** as a white solid (0.77 g, 92%). An analytical sample was obtained by recrystallization from EtOAc/hexane. Mp 171–172 °C. IR (KBr) ν: 3208 (OH), 1510, 1465, 1367, 1343, 1309, 1288, 1235, 1202, 1183, 1134, 1118, 1076, 1054, 941, 767 cm^{-1}. EIMS m/z (%): 212 (41, M^+), 183 (100), 169 (32), 167 (49), 102 (16), 76 (10), 50 (11). ^1H NMR ($CDCl_3$) δ: 8.03–7.99 (2H, m, 6-H+9-H), 7.70–7.63 (2H, m, 7-H+8-H), 5.00 (1H, ddd, J=9.4, 4.3, 3.4 Hz, 2-*exo*-H), 3.96 (1H, b s, D_2O exchang., OH), 3.62–3.54 (2H, m, 1-H+4-H), 2.67 (1H, ddd, J=13.3, 9.2, 4.4 Hz, 3-*exo*-H), 2.09 (1H, dm, J=10.3 Hz, 11-*H*H), 2.00 (1H, d, J=10.3 Hz, 11-H*H*), 1.37 (1H, dt, J=13.3, 3.1 Hz, 3-*endo*-H). ^{13}C NMR and DEPT ($CDCl_3$) δ: 164.2 (C), 160.6 (C), 142.1 (C), 141.5 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 71.3 (CH), 51.3 (CH), 44.5 (CH_2), 44.4 (CH), 37.1 (CH_2). Anal. Calcd for $C_{13}H_{12}N_2O$ (212.25): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.38; H, 5.77; N 13.04.

4.1.12. (±)-*exo*-1,2,3,4-Tetrahydro-1,4-methanophenazin-2-ol (4b). Compound **4b** was obtained from **24b** in the same way as **4a** from **24a**. Yield 93%. Mp 154–155 °C. IR (KBr) ν: 3262, 1541, 1512, 1452, 1440, 1401, 1360, 1329, 1307, 1283, 1241, 1227, 1196, 1166, 1154, 1125, 1082, 1053, 1019, 972, 959, 916, 902, 839, 772, 717, 677 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.99–7.96 (2H, m, 6-H+9-H), 7.69–7.65 (2H, m, 7-H+8-H), 4.34 (1H, d, J=4.9 Hz, 2-*endo*-H), 3.60–3.57 (2H, m, 1-H+4-H), 2.52 (1H, d, J=10.0 Hz, 11-*H*H), 2.20 (1H, d, J=10.0 Hz, 11-H*H*), 2.14–2.00 (2H, m, 3-H_2). Anal. Calcd for $C_{13}H_{12}N_2O$ (212.25): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.31; H, 5.83; N 13.12.

4.1.13. 2-(2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-yl)etanol (26). (a) $NaBH_4$ (17 mg, 0.45 mmol) was added to a solution of **25** (77 mg of the chromatographed material) in EtOH (4 mL), and the mixture was successively stirred at rt for 14 h, treated with 1 N HCl (1 mL), brought to about pH 8 with saturated $NaHCO_3$ solution, and extracted with EtOAc (2×10 mL). The pooled organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure, and purification of the residue by silica gel column chromatography with 7:3 (v/v) EtOAc/hexane as eluent afforded **26** as a clear oil that subsequently crystallized (50 mg; overall yield with regard to **24a**, 51%). An analytical sample was obtained by recrystallization from EtOAc/hexane. Mp 80–81 °C. IR (KBr) ν: 3284 (OH), 1375, 1323, 1145, 1057, 774 cm^{-1}. EIMS m/z (%): 214 (13, M^+), 184 (23), 183 (38), 182 (17), 181 (29), 168 (100), 102 (27), 89 (15), 77 (29), 76 (29), 75 (23), 63 (15), 51 (17), 50 (21), 39 (13), 31 (22). ^1H NMR ($CDCl_3$) δ: 8.04–8.00 (2H, m, 5-H+8-H), 7.72–7.68 (2H, m, 6-H+7-H), 5.12 (1H, b s, D_2O exchang., OH), 3.99 (2H, t, J=6.8 Hz, CH_2O), 3.49–3.43 (1H, m, 1-H), 3.22–3.17 (2H, m, 3-H_2), 2.61–2.54 (1H, m, 1-C*H*H), 2.10–1.90 (3H, m, 1-CH*H*+2-H_2). ^{13}C NMR and DEPT ($CDCl_3$) δ: 162.4 (C), 161.2 (C), 142.1 (C), 140.8 (C), 129.6 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 62.7 (CH_2), 44.6 (CH), 36.5 (CH_2), 31.8 (CH_2), 30.1 (CH_2). Anal. Calcd for $C_{13}H_{14}N_2O$ (214.27): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.69; H, 6.70; N 13.00.

(b) Alternatively, a solution of alcohol **4a** (100 mg, 0.47 mmol), Na_2CO_3 (98 mg, 0.92 mmol) and $NaBH_4$ (35 mg, 0.92 mmol) in EtOH (2 mL) was stirred at rt for 18 h, diluted with water (5 mL) and extracted with EtOAc (2×10 mL). Work-up and purification as in method (a) afforded a product (64 mg, 63%) with characteristics identical to those of **26** prepared as above.

4.1.14. 2-(2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-yl)ethyl acetate (27). Alcohol **26** (25 mg, 0.12 mmol) was dissolved in a mixture of dry pyridine (1 mL) and Ac_2O (1 mL), and this solution was stirred at rt for 18 h, poured over crushed ice (5 g), stirred for 1 h more, and extracted with EtOAc (2×5 mL). The pooled extracts were washed successively with 2 N HCl (5 mL) and brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure then left **27** as a colourless oil (23 mg, 77%). IR (NaCl) ν: 1736 (CO), 1653, 1497, 1459, 1366, 1241, 1120, 764 cm^{-1}. EIMS m/z (%): 256 (19, M^+), 213 (14), 196 (99), 186 (23), 185 (20), 184 (22), 183 (79), 181 (48), 168 (100), 142 (14), 129 (21), 115 (19), 103 (18), 102 (47), 90 (14), 89 (33), 78 (14), 77 (37), 76 (37), 75 (31), 63 (17), 51 (16), 50 (21), 43 (21), 42 (60), 41 (19), 39 (17). ^1H NMR ($CDCl_3$) δ: 8.01–7.95 (2H, m, 5-H+8-H), 7.66–7.61 (2H, m, 6-H+7-H), 4.35 (2H, t, J=6.6 Hz, CH_2O), 3.40–3.31 (1H, m, 1-H), 3.17–3.08 (2H, m, 3-H_2), 2.59–2.43 (2H, m, 1-CH_2), 2.02 (3H, s, CH_3), 1.97–1.84 (2H, m, 2-H_2). ^{13}C NMR and DEPT ($CDCl_3$) δ: 171. 5 (CO), 162.3 (C), 160.6 (C), 142.1 (C), 142.1 (C), 129.4 (CH), 129.3 (CH), 129.14 (CH), 129.10 (CH), 63.0 (CH_2), 41.1 (CH), 32.7 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 21.4 (CH_3). HRMS calcd for $C_{15}H_{16}N_2O_2$: 256.1212. Found: 256.1218.

4.1.15. (2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-yl) acetic acid (28). Acetate **24a** (240 mg, 0.94 mmol) was treated and worked up as in the preparation of **4a** except that reaction was prolonged for 6 h. Chromatography of the crude product with 10:1 (v/v) EtOAc/hexane as eluent, afforded a dark slurry (159 mg) that consisted very predominantly of **25** (90% as determined by ^1H NMR;

estimated yield in **25**, 71%). This material was used directly in subsequent transformations.

Compound **25**. IR (KBr) ν: 1722 (CO) cm^{-1}. EIMS *m/z* (%): 212 (1, M$^+$), 184 (76), 183 (100, M−CHO), 169 (44), 168 (21), 102 (9), 76 (8), 58 (9). ^{1}H NMR (CDCl$_3$) δ: 9.88 (1H, s, CHO). ^{13}C NMR and DEPT (CDCl$_3$) δ: 201.0 (CHO), 161.3 (C), 160.3 (C), 141.93 (C), 141.86 (C), 129.4 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 47.5 (CH$_2$), 38.3 (CH), 31.3 (CH$_2$), 29.3 (CH$_2$).

Minor contaminant: EIMS *m/z* (%): 424 (7), 213 (44), 212 (23), 184 (33), 183 (100), 181 (32), 169 (100), 168 (47), 129 (7), 102 (10), 77 (11).

A solution of the above product (66 mg) in MeOH (2 mL) was treated with 3 drops of Tollens' reagent,[71] left for 3 h at rt (a silver mirror was formed on the wall of the flask), diluted with water (10 mL), extracted with CHCl$_3$ (5 mL), brought to pH 5 with formic acid, and finally extracted with EtOAc (2×5 mL). These last extracts were pooled and dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure, leaving **28** as a yellowish thick paste (40 mg; yield, 45% with regard to starting **24a**). IR (NaCl) ν: 3420, 2508, 1718, 1507, 1329, 1192, 770 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 8.05–8.00 (2H, m, 5-H+8-H), 7.70–7.67 (2H, m, 6-H+7-H), 3.82–3.71 (1H, m, 1-H), 3.27–3.17 (3H, m, 1-C*H*H+3-H$_2$), 2.77–2.63 (2H, m, 1-CH*H*+2-*H*H), 1.98 (1H, dd, J=12.9, 9.2 Hz, 2-H*H*).

4.1.16. Methyl (2,3-dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-yl)acetate (29). *p*-Toluenesulfonic acid (5 mg) was added to a solution of **28** (35 mg, 0.15 mmol) in dry MeOH (3 mL), and the mixture was refluxed under argon for 3.5 h, mixed with saturated NaHCO$_3$ solution (5 mL), and extracted with EtOAc (2×5 mL). The pooled organic extracts were dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure, leaving **29** as a clear oil that solidified spontaneously (25 mg, 67%). An analytical sample was obtained by recrystallization from EtOAc/hexane. Mp 155 °C, dec.). IR (KBr) ν: 1732 (CO), 1560, 1501, 1436, 1369, 1325, 1263, 1196, 1171, 764 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 8.03–7.98 (2H, m, 5-H+8-H), 7.69–7.65 (2H, m, 6-H+7-H), 3.82–3.70 (1H, m, 1-H), 3.74 (3H, s, CH$_3$), 3.28–3.15 (3H, m, 1-C*H*H+3-H$_2$), 2.73–2.58 (2H, m, 1-CH*H*+2-*H*H), 1.95 (1H, m, J=12.9, 9.2 Hz, 2-H*H*). ^{13}C NMR and DEPT (CDCl$_3$) δ: 173.0 (CO), 161.3 (C), 160.5 (C), 142.1 (C), 142.0 (C), 129.4 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 52.2 (CH$_3$), 40.5 (CH), 37.8 (CH$_2$), 31.3 (CH$_2$), 29.2 (CH$_2$). Anal. Calcd for C$_{14}$H$_{14}$N$_2$O$_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.28; H, 5.89; N 11.60.

4.1.17. 1,2,3,4-Tetrahydro-1,4-methanophenazin-2-one (5). To a solution of dry pyridine (0.67 mL, 8.4 mmol) in CH$_2$Cl$_2$ (7.5 mL) at 0 °C was added CrO$_3$ (0.42 g, 4.2 mmol) followed by a solution of **4a** (150 mg, 0.71 mmol) in CH$_2$Cl$_2$ (3.5 mL). The reaction mixture was left stirring overnight at rt, and was then filtered through celite. The celite was washed with EtOAc (10 mL), the pooled filtrates were dried (Na$_2$SO$_4$), and the solvents were removed under reduced pressure. Purification of the residue by silica gel column chromatography with 7:3 (v/v) EtOAc/hexane as eluent afforded **5** as a clear yellowish oil (99 mg, 67%). IR (NaCl) ν: 1751 (CO), 1578, 1510, 1463, 1410, 1361, 1303, 1274, 1254, 1216, 1200, 1158, 1111, 1086, 1059, 957, 834, 762, 732, 700 cm^{-1}. EIMS *m/z* (%): 210 (75, M$^+$), 181 (100), 168 (99), 140 (20), 129 (31), 128 (22), 103 (27), 102 (39), 91 (28), 78 (25), 77 (22), 76 (62), 75 (20), 74 (25), 64 (20), 63 (30), 53 (21), 52 (22), 51 (32), 50 (42), 39 (27). ^{1}H NMR (CDCl$_3$) δ: 7.91–7.86 (2H, m, 6-H+9-H), 7.62–7.56 (2H, m, 7-H+8-H), 3.85–3.82 (2H, m, 1-H+4-H), 2.66–2.54 (2H, m, 3-*exo*-H+11-*H*H), 2.46 (1H, dd, J=10.4, 1.2 Hz, 11-H*H*), 2.16 (1H, dd, J=17.8, 4.3 Hz, 3-*endo*-H). ^{13}C NMR and DEPT (CDCl$_3$) δ: 208.2 (CO), 163.1 (C), 156.3 (C), 142.1 (C), 141.6 (C), 129.9 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 59.9 (CH), 46.7 (CH$_2$), 42.6 (CH), 40.2 (CH$_2$). HRMS calcd for C$_{13}$H$_{10}$N$_2$O: 210.0793. Found: 210.0801.

^{1}H and ^{13}C NMR spectra obtained after **5** had been left in an NMR spectrometry tube for 3 days at rt showed signals of **5** and **28** in approximately 1:1 ratio.

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References and notes

1. Takehara, S.; Shoji, T.; Kurokawa, J. Dainippon Ink and Chemicals, Inc. JP 60152435, 1985; *Chem. Abstr.* **1986**, *104*, 88183m.
2. Takehara, S.; Shoji, T.; Kurokawa, J. Dainippon Ink and Chemicals, Inc. JP 60152473, 1985; *Chem. Abstr.* **1986**, *104*, 88578u.
3. Toba, Y.; Yasuike, M.; Yamaguchi, T. Toyo Inki Seizo K.K. Japan. JP 04113361, 1992; *Chem. Abstr.* **1993**, *118*, 136244v.
4. Toba, Y.; Yasuike, M.; Yamaguchi, T., Toyo Ink Mfg Co, Ltd, Japan. JP 04243261, 1992; *Chem. Abstr.* **1993**, *119*, 17907z.
5. Yamaguchi, T.; Toba, Y.; Yasuike, M. Toyo Ink Mfg Co., Japan. JP 06175564, 1994; *Chem. Abstr.* **1995**, *122*, 147529a.
6. Toba, Y.; Yamaguchi, T.; Yasuike, M., Toyo Ink Mfg Co., Japan. JP 06195015, 1994; *Chem. Abstr.* **1995**, *122*, 147507s.
7. Toba, Y.; Yamaguchi, T.; Yasuike, M., Toyo Ink Mfg Co., Japan. JP 06202544, 1994; *Chem. Abstr.* **1995**, *122*, 147513r.
8. Yamaguchi, T.; Toba, Y.; Yasuike, M., Toyo Ink Mfg Co., Japan. JP 06202546, 1994; *Chem. Abstr.* **1995**, *122*, 147511p.
9. Golka, A.; Keyte, P. J.; Paddon-Row, M. N. *Tetrahedron* **1992**, *48*, 7663–7678.
10. Golka, A.; Craig, D. C.; Paddon-Row, M. N. *Aust. J. Chem.* **1994**, *47*, 101–110.
11. Tokunaga, Y.; Rudkevich, D. M.; Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2656–2659.
12. Tokunaga, Y.; Rudkevich, D. M.; Santamaria, J.; Hilmersson, G.; Rebek, J. *Chem.—Eur. J.* **1998**, *4*, 1449–1457.
13. Warrener, R. N.; Johnston, M. R.; Gunter, M. J. *Synlett* **1998**, 593–595.
14. Johnston, M. R.; Gunter, M. J.; Warrener, R. N. *Tetrahedron* **2002**, *58*, 3445–3451.

15. Esanu, A. Societé de Conseils de Recherches et d'Applications Scientifiques, Fr. BE 902231, 1985; *Chem. Abstr.* **1986**, *104*, 110121p.
16. Tanida, H.; Irie, T.; Tsutsumiuchi, M. Shionogi and Co, Ltd, Japan. JP 61155371, 1986; *Chem. Abstr.* **1986**, *105*, 226391b.
17. Kawakami, H.; Ohuchi, R.; Kitano, M.; Ono, K. Sumitomo Pharmaceuticals Co, Ltd, Japan. EP 268871, 1988; *Chem. Abstr.* **1988**, *109*, 110275v.
18. Desai, M. C. Pfizer Inc., USA WO 8902739, 1989; *Chem. Abstr.* **1989**, *111*, 153657e.
19. Desai, M. C. Pfizer Inc., USA EP 311303, 1989; *Chem. Abstr.* **1989**, *111*, 153658f.
20. Takahashi, A.; Aoki, T.; Shimanuki, E.; Genko, K.; Yamada, S.; Yamaguchi, T.; Manome, Y.; Sato, I.; Kojo, K.; Narita, S. Toa Eiyo Ltd, Japan. JP 08059627, 1996; *Chem. Abstr.* **1996**, *125*, 10839.
21. Nagai, S.-I.; Ueda, T.; Sugiura, S.; Nagatsu, A.; Murakami, N.; Sakakibara, J.; Fujita, M.; Hotta, Y. *J. Heterocycl. Chem.* **1998**, *35*, 325–327.
22. Nagai, S.-I.; Ueda, T.; Nagatsu, A.; Nakaoka, K.; Murakami, N.; Sakakibara, J.; Fujita, M.; Hotta, Y. *J. Heterocycl. Chem.* **1998**, *35*, 329–332.
23. Nagai, S.-I.; Miyachi, T.; Nakane, T.; Ueda, T.; Uozumi, Y. *J. Heterocycl. Chem.* **2001**, *38*, 379–381.
24. Rosowsky, A.; Papoulis, A. T.; Queener, S. F. *J. Heterocycl. Chem.* **1999**, *36*, 723–728.
25. Ambler, S. J.; Baker, S. R.; Clark, B. P.; Coleman, D. S.; Foglesong, R. J.; Goldsworthy, J.; Jagdmann, G. E., Jr.; Johnson, K. W.; Kingston, A. E.; Owton, W. M.; Schoepp, D. D.; Hong, J. E.; Schkeryantz, J. M.; Vannieuwenhze, M. S.; Zia-Ebrahimi, M. S. Eli Lilly and Company, USA WO 0132632, 2001; *Chem. Abstr.* **2001**, *134*, 340517.
26. Archilla, F. M. *Publ. Inst. Quim. 'Alonso Barba' (Madrid)* **1961**, *47*, 56; *Chem. Abstr.* **1963**, *59*, 7561d.
27. Dashkevich, L. B.; Korbelainen, E. S. *Akad. Nauk Latv. SSR* **1965**, *64*, 595–597; *Chem. Abstr.* **1966**, *64*, 19310.
28. Corr, D. H.; Glover, E. E. *J. Chem. Soc.* **1965**, 5816–5819.
29. Sotiropoulos, J.; Lamazouere, A. M.; Bedos, P. C. R. *Hebd. Seances Acad. Sci., Ser. C* **1967**, *265*, 99–102.
30. Sotiropoulos, J.; Lamazouere, A. M. C. R. *Acad. Sci., Ser. C* **1970**, *271*, 1592–1595.
31. Scharf, H. D.; Kuesters, W. *Chem. Ber.* **1972**, *105*, 564–574.
32. Rau, H.; Schuster, O.; Bacher, A. *J. Am. Chem. Soc.* **1974**, *96*, 3955–3959.
33. Skramstad, J.; Midthaug, T. *Acta Chem. Scand. B* **1978**, *B32*, 413–416.
34. Rau, H.; Schuster, O. *Z. Naturforsch.* **1979**, *34B*, 1519–1524.
35. Lamazouere, A. M.; Sotiropoulos, J. *Tetrahedron* **1981**, *37*, 2451–2457.
36. Skramstad, J.; Sletten, T. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 319–322.
37. Takasuka, M.; Irie, T.; Tanida, H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1673–1675.
38. Reinecke, M. G.; Brown, E. S.; Capehart, B. P.; Minter, D. E.; Freeman, R. K. *Tetrahedron* **1988**, *44*, 5675–5680.
39. Kobayashi, T.; Ono, K.; Suda, H.; Yamashita, Y.; Kato, H. *Bull. Chem. Soc. Jpn* **1993**, *66*, 2707–2713.
40. Margetic, D.; Butler, D. N.; Warrener, R. N. *Aust. J. Chem.* **2000**, *53*, 959–963.
41. García Martínez, A.; Teso Vilar, E.; García Fraile, A.; Herrera Fernández, A.; De La Moya Cerero, S.; Moreno Jiménez, F. *Tetrahedron* **1998**, *54*, 4607–4614.
42. Warrener, R. N.; Harrison, P. A. *Molecules* **2001**, *6*, 353–369.
43. Kobayashi, T.; Miki, K. *Bull. Chem. Soc. Jpn* **1998**, *71*, 1443–1449.
44. Kobayashi, T.; Tsuzuki, T.; Saitoh, M. *Bull. Chem. Soc. Jpn* **1999**, *72*, 1597–1605.
45. Kobayashi, T.; Miki, K.; Nikaeen, B.; Baba, H. *Tetrahedron* **1999**, *55*, 13179–13192.
46. Kobayashi, T.; Uchiyama, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2731–2739.
47. Tanida, H.; Irie, T.; Wakisaka, Y. *J. Heterocycl. Chem.* **1986**, *23*, 177–181.
48. Paquette, L. A.; Coghlan, M. J.; Cottrell, C. E.; Irie, T.; Tanida, H. *J. Org. Chem.* **1986**, *51*, 696–699.
49. Paquette, L. A.; Burke, L. D.; Irie, T.; Tanida, H. *J. Org. Chem.* **1987**, *52*, 3246–3250.
50. Markgraf, J. H.; Cort, J. R.; Davis, H. A.; Lindeman, N. I.; Myers, C. R.; Christl, M.; Kraft, A. *J. Org. Chem.* **1991**, *56*, 3755–3756.
51. Kobayashi, T.; Suda, H.; Takase, H.; Iriye, R.; Kato, H. *Bull. Chem. Soc. Jpn* **1995**, *68*, 3269–3275.
52. Tanida, H.; Irie, T.; Hayashi, Y. *J. Org. Chem.* **1984**, *49*, 2527–2533.
53. Tanida, H.; Irie, T.; Hayashi, Y. *J. Org. Chem.* **1985**, *50*, 821–825.
54. Tanida, H.; Irie, T. *J. Org. Chem.* **1987**, *52*, 5218–5224.
55. Kobayashi, T.; Sugawara, H.; Nikaeen, B. *Bull. Chem. Soc. Jpn* **1998**, *71*, 497–502.
56. Kobayashi, T.; Miki, K.; Nikaeen, B.; Ohta, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1372–1385.
57. Kobayashi, T.; Tsuzuki, T.; Tayama, Y.; Uchiyama, Y. *Tetrahedron* **2001**, *57*, 9073–9085.
58. Kobayashi, T.; Kobayashi, S. *Molecules* **2000**, *5*, 1062–1067.
59. A preliminary account of the ring opening of **1a** in basic medium has already been reported: López, C.; Caamaño, O.; Hergueta, A. R.; Fernández, F. *Tetrahedron Lett.* **2002**, *43*, 5311–5313.
60. Successfull work leading to the preparation of the corresponding benzo-fused analogues can be seen at: (a) Fernández, F.; García-Mera, X.; Morales, M.; Rodríguez-Borges, J. E. *Synthesis* **2001**, 239–242. (b) Fernández, F.; García-Mera, X.; Morales, M.; Rodríguez-Borges, J. E.; De Clercq, E. *Synthesis* **2002**, 1084–1090.
61. The formation of **8** was hypothesized by Kobayashi et al. (Ref. 58) to explain their findings, but its isolation has not hitherto been reported in the literature.
62. (a) Mehta, G.; Talukdar, P.; Mohal, N. *Tetrahedron Lett.* **2001**, *42*, 7663–7666. (b) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2001**, *66*, 4941–4944. (c) Wang, G. T.; Wang, S.; Chen, Y.; Gentles, R.; Sowin, T. *J. Org. Chem.* **2001**, *66*, 2052–2056.
63. The crystallographic data of **18**, **24a** and **26** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publications Nos. CCDC 185239, 211486 and 211485, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.
64. The autoaddition product (aldolic dimer) of **25** was detected in the mass spectrum of the concentrate of **25**.
65. Dastan, A.; Demir, U.; Balci, M. *J. Org. Chem.* **2000**, *65*, 6534–6538.
66. Volz, H.; Shin, J. H.; Miess, R. *J. Chem. Soc., Chem. Commun.* **1993**, 543–544.
67. Adam, W.; Carballeira, N.; Scheutzow, D.; Peters, K.; Peters, E. M.; Von Schnering, H. G. *Chem. Ber.* **1984**, *117*, 1139–1152.

68. Goering, H. L.; Chang, C-S.; Masilamani, D. *J. Am. Chem. Soc.* **1978**, *100*, 2506–2510.
69. Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1976**, *98*, 6304–6308.
70. Kapeller, H.; Griengl, H. *Tetrahedron* **1997**, *53*, 14635–14644.
71. Furniss, B. S., Hannaford, A. J., Smith, P. N. G. & Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Wiley: New York, 1989; p 1219.

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Experimental and theoretical DFT study of the reaction of 3-amino-1,2-diols with dichloromethane and paraformaldehyde

A. Hamdach,[a] E. M. El Hadrami,[c] C. Hajji,[a] E. Zaballos-García,[a] J. Sepulveda-Arques[a,*] and R. J. Zaragozá[b,*]

[a]*Departamento de Química Orgánica, Universidad de Valencia, Ave. Vte Andres Estelles, E-46100 Burjassot, Valencia, Spain*
[b]*Instituto de Ciencia Molecular/Dpto. Q. Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain*
[c]*Laboratoire de Chimie Organique, Faculté des Sciences et Techniques, Fes, Morocco*

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Abstract—The reactions of 3-phenyl-3-methylamino-1,2-propanediol **1a** and 3-[(*tert*-butyldimethylsilyl)oxy]-1-methylamino-1-phenyl-2-propanol **1b** with $(CH_2O)n$ and CH_2Cl_2 are appropriate procedures for the preparation of 1,3-oxazines or 1,3-oxazolidines under proper selection of kinetic or thermodynamic reaction conditions. The reaction of **1b** with $(CH_2O)n$ or CH_2Cl_2, affords the oxazolidine **2b** under kinetic conditions and then this compound can be slowly converted into 5-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine **3b** under thermodynamic control. The mechanism proposed for this transformation and the effect of polar solvents on the acceleration of the reaction has been studied theoretically (DFT level).

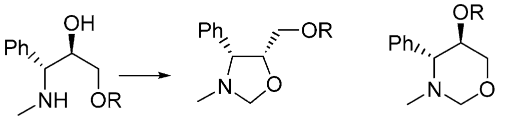
1. Introduction

The reaction of amino alcohols with dihalomethanes or aldehydes leading to cyclic compounds has been extensively studied.[1] The formation of 1,3-heterocycles and the ring-chain tautomeric equilibration of the intermediates in these reactions, has been recently reviewed.[2] In previous works we reported the results observed in the reactions of amino alcohols, with dihalomethanes,[3,4] 2,2-dimethoxypropane[5] and aldehydes.[5] Some of the reactions with these polyfunctionalised systems containing amino and alcohol functions were useful as a preparative procedures for the synthesis of 1,3-oxazines, 1,3-oxazolidines and 1,3-dioxolanes. The most interesting one, was the reaction of 3-phenyl-3-methylamino-1,2-propanediol **1a** with CH_2Cl_2 at 100 °C that afforded 3-methyl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazin-5-ol **3a** (reaction of the primary hydroxyl group), with no traces of oxazolidine derivative **2a** as a result of the reaction of the secondary hydroxyl group.[3] According with these results, we thought that the reaction with dihalomethanes or aldehydes of the aminodiol **1a**, with the primary hydroxyl function protected as silyl derivative **1b**,[6] would be an appropriate procedure for the synthesis of the oxazolidine derivative **2b**. Silyl groups are generally used for protection of hydroxy functions, because they are easy to introduce and may be readily removed,[7] so we prepared the 3-[(*tert*-butyldimethylsilyl)oxy]-1-methylamino-1-phenyl-2-propanol **1b** and studied its reactivity with $(CH_2O)n$ and CH_2Cl_2.

2. Results and discussion

The reaction of the monosilylated aminodiol **1b** with $(CH_2O)n$ in benzene (80 °C 8 h or 100 °C 1 h) afforded, as it was expected, the corresponding oxazolidine **2b** with a high yield (95%). However the reaction of **1b** with CH_2Cl_2 at 100 °C (12 h) gave a mixture of the oxazolidine **2b** (25%), unreacted aminodiol **1b** as a chlorhydrate salt[8] and traces of a secondary product, the oxazine **3b** (Scheme 1).

When the reaction was maintained at this temperature for longer periods, the unreacted aminodiol **1b** remained as a chlorhydrate and increased amounts of the oxazine **3b**



1a R=H
1b R=TBDMS

2a
2b

3a
3b

Scheme 1.

Keywords: Silyl migration; Oxazine; Oxazolidine.

* Corresponding authors. Tel.: +34-963544938; fax: +34-963544939 (J.S.-A.); e-mail addresses: jose.sepulveda@uv.es; ramon.j.zaragoza@uv.es

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appeared in the crude reaction mixture (experiment for 64 h, 71% **1b** as a chlorhydrate salt, 21% **2b**, 8% **3b**). For the removal of the formed hydrochloric acid which protonated the aminodiol **1b** and make more slowly the reaction, several bases were assayed. With $NaHCO_3$ we got the best results. When the reaction was carried out in the presence of $NaHCO_3$ (2 equiv), mixtures of **2b**–**3b** were obtained without traces of the protonated aminodiol.

The structure of the oxazine **3b** was confirmed spectroscopically and it was also synthesised by other route through silylation of the oxazine **3a**. In the ^1H NMR the hydrogens of the methylene at the C2 position appear at δ 4.65 and 3.91 ppm with a geminal coupling constant of 8 Hz. The hydrogens at C6 appear at δ 4.18 and 3.40 ($J=10.6$ Hz). In the ^{13}C NMR the C2 appears at 87.4 ppm.

The formation of the silylated 3,4,5,6-tetrahydro-2*H*-1,3-oxazin-5-ol **3b** suppose the migration of the silyl group from the primary hydroxyl group to the secondary one. The increased amounts of the oxazine **3b** with long reaction times and higher temperatures was indicative that the oxazolidine **2b**, initially formed under kinetic control, rearranged to the oxazine **3b** under thermodynamic conditions.

In order to explain the different observed reactivity of the amino alcohols **1a** and **1b** with CH_2Cl_2, we have made a theoretical study and completed additional chemical experiments.

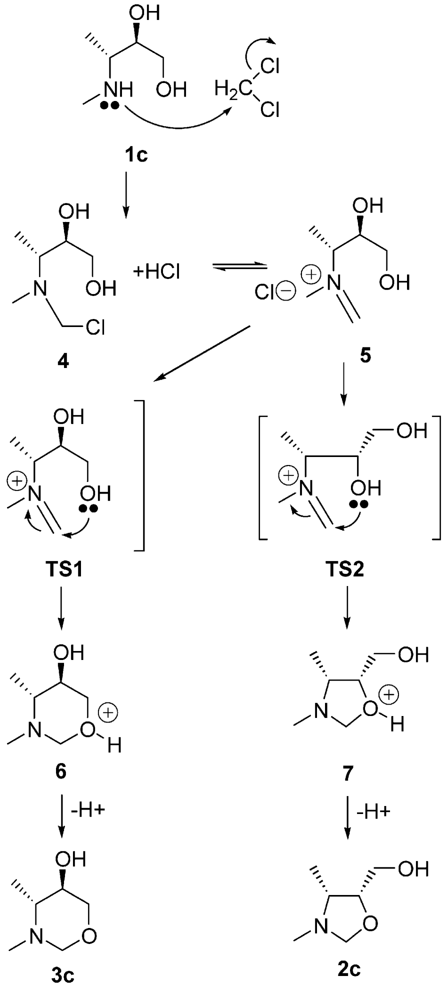
2.1. Theoretical studies and additional experiments

2.1.1. Computational methods. All calculations were carried out with the Gaussian 98 suite of programs[9] using the HF/6-31G*[10] level. Since the mechanism involves ionic species the inclusion of solvent effects was necessary in order to obtain accurate energies. The optimisations were carried out using the Berny analytical gradient optimisation method[11] and the solvent effects, was considered using a relatively simple self-consistent reaction field (SCRF)[12] based on the polarisable continuum model (PCM)[13] of the Tomasi's group. Finally, more accurate results have been obtained using density functional theory (DFT)[14] by means of B3LYP/6-31G*[15] single point energy calculations (B3LYP/6-31G*//HF/6-31G*) in CH_2Cl_2 or methanol.

2.1.2. Transformation of 1a into 3a. For the explanation of the exclusive transformation of amino alcohol **1a** into the oxazine **3a** by reaction with CH_2Cl_2, we have made a theoretical study of this transformation using as a simplified model, the amino alcohol **1c** (Me instead of Ph in **1a**).

The suggested mechanism is presented in Scheme 2, the energies of the relevant species are in Table 1 and Figure 1 shows the geometries of transition states (TS) involved in the mechanism.

The nucleophilic attack of the methylamino group to the dichloromethane gives in a first stage, the α-chloroamine **4**, best represented as the immonium salt **5**.[16] Then, intramolecular attack of the primary hydroxyl function to this immonium salt through a **TS1** would afford **6**, which by deprotonation would give finally the oxazine **3c**. On the other hand, intramolecular attack of the secondary hydroxyl group through a **TS2**, and deprotonation would afford the oxazolidine **2c**.



Scheme 2.

As we can see in the Table 1, the formation of the oxazine **3c** is favoured, both kinetically and thermodynamically. The transition state **TS1** (4.38 kcal mol^{-1}) is 6.18 kcal mol^{-1} lower than **TS2** (10.56 kcal mol^{-1}) and the oxazine **3c** is 1.78 kcal mol^{-1} more stable than the oxazolidine **2c**.

The low activation barrier for **TS1** is not in agreement with the high temperatures and long reaction times required for the transformation of amino alcohol **1a** into the oxazine **3a**.

Table 1. Total (au) and relative energies (kcal mol^{-1}) for some stationary points of the reaction of **1c** and CH_2Cl_2

B3LYP/6-31G*//HF/6-31G* (in CH_2Cl_2)		
	E	E_r[a]
5	−442.05598	0
TS1	−442.04900	4.38
TS2	−442.03915	10.56
3c	−441.63278	0
2c	−441.629939	1.78
MC	−1094.868055	0
TS3	−1094.831199	23.13

[a] Energies relative to **5**, **3c** or **MC**.

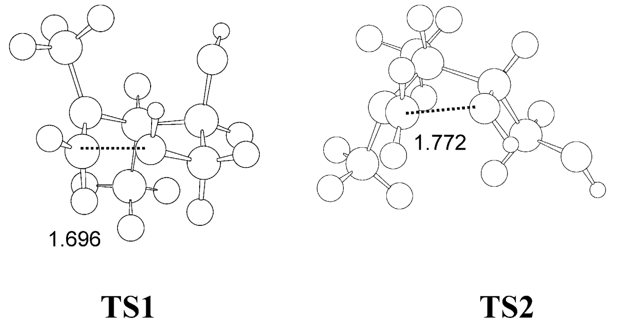
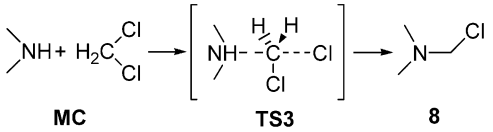


Figure 1. Geometries of the transition structures **TS1** and **TS2** involved in the reaction of N-methyl aminodiol **1c** and CH_2Cl_2. The values given are the bond lengths in angstroms obtained at the HF/6-31G* level in CH_2Cl_2 as solvent.

So, it should be the first step of the reaction, the formation of the immonium salt **5**, the rate determining step of the global process. For an approximate calculation of the energy required for this stage, we studied theoretically the reaction of dimethylamine with dichloromethane as simplified model (Scheme 3) and the data are reported in Table 1. The activation barrier calculated for **TS3**, relative to the energy of the molecular complex (MC) initially formed between dimethylamine and dichloromethane is 23.13 kcal mol^{-1}. This high value confirms that the formation of the immonium salt, is the rate determining step in the transformation of the amino alcohol **1a** into the oxazine **3a**.



Scheme 3.

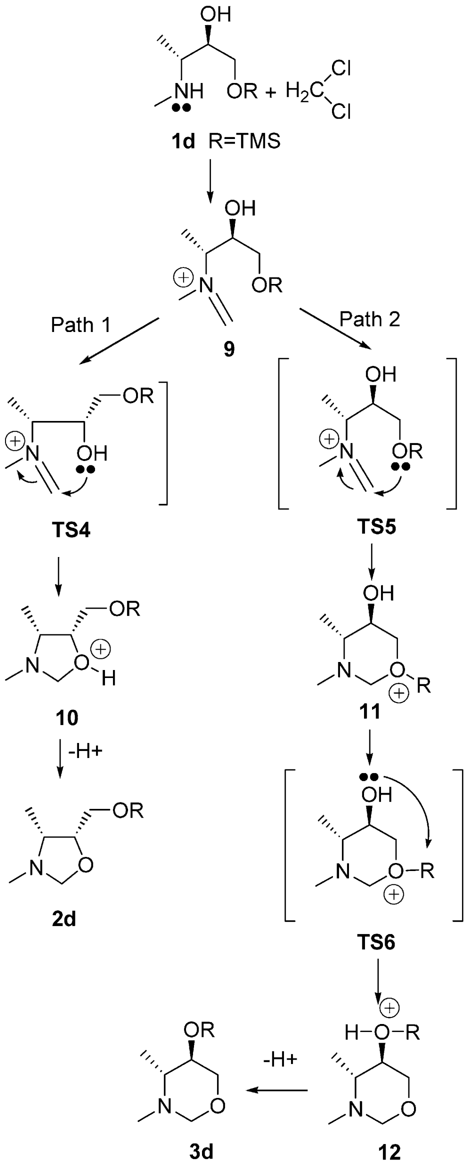
These theoretical results were supported experimentally and when the reaction was carried out in dibromomethane instead of dichloromethane, the reaction took place at 50 °C. The energy of the corresponding **TS** for the reaction with the dibromomethane is lower, because the bromide is a better leaving group.

It was also predictable that the reaction of **1a** with formaldehyde through a similar mechanism would afford **3a**. In fact when aminodiol **1a** was reacted with formaldehyde in benzene at 100 °C (1 h), at reflux (8 h), or at room temperature (18 h), the oxazine **3a** was formed exclusively as a result of a lower activation barrier for the formation of the corresponding immonium salt.

2.1.3. Transformation of 1b into 2b and 3b.

For the theoretical study of this transformation we have used the amino alcohol **1d** as a simplified model (Me instead of Ph and trimethylsilyl instead of *tert*-butyldimethylsilyl in **1b**).

The suggested mechanism is presented in Scheme 4, the energies of the species are in Table 2. Figure 2 shows the geometries of the transition states involved in the mechanism.



Scheme 4.

The oxazolidine **2d** comes from the immonium salt **9**, through **TS4** (path 1, Scheme 4), according to a mechanism similar to the one proposed for the formation of the oxazolidine **2c** (Scheme 2). However for the formation of the oxazine **3d**, path 2, the proposed mechanism supposes the attack of the silylated primary hydroxy function to the immonium salt with formation of the oxonium salt **11**. The intramolecular silyl migration of TMS (**TS6**) to the secondary hydroxy function would give the oxonium ion **12**, which by deprotonation would afford the oxazine **3d**.

The results of the theoretical study in CH_2Cl_2 confirm that the formation of the oxazolidine **2d** is favoured kinetically. **TS4** is 8.73 kcal mol^{-1} and **TS6** is 25.33 kcal mol^{-1}. However the oxazine **3d** is 2.26 kcal mol^{-1} more stable than the oxazolidine **2d** and would predominate in the equilibrium under thermodynamic control. According to the theoretical studies, the initially formed oxazolidine **2d** would be in equilibrium with the immonium salt **9** which through a **TS5**, **11**, **TS6** and **12** would afford the oxazine **3d** under high temperatures and long reaction times. The rate determining step of this equilibration would be determined

Table 2. Total (au) and relative energies (kcal mol^{-1}) for the stationary points of the reaction of **1d** and CH_2Cl_2 in CH_2Cl_2 or CH_3OH as solvent

B3LYP/6-31G*//HF/6−31G*	In CH_2Cl_2		In CH_3OH		ΔE[b]
	E	E_r[a]	E	E_r[a]	
1d	−812.241496		−812.249031		−4.73
9	−850.772201	0.00	−850.791476	0.00	−12.10
TS4	−850.758283	8.73	−850.784678	4.27	−16.56
10	−850.763705	5.33	−850.800813	−5.86	−23.29
TS5	−850.759395	8.04	−850.779216	7.69	−12.44
11	−850.761914	6.46	−850.779143	7.74	−10.81
TS6	−850.731834	25.33	−850.752093	24.71	−12.71
12	−850.764639	4.75	−850.780914	6.63	−10.21
3d	−850.349989	0.00	−850.356701	0.00	−4.21
2d	−850.346386	2.26	−850.353512	2.00	−4.47

[a] Energies relative to **9** or **3d**.

[b] E(in CH_3OH) − E(in CH_2Cl_2) in kcal mol^{-1}.

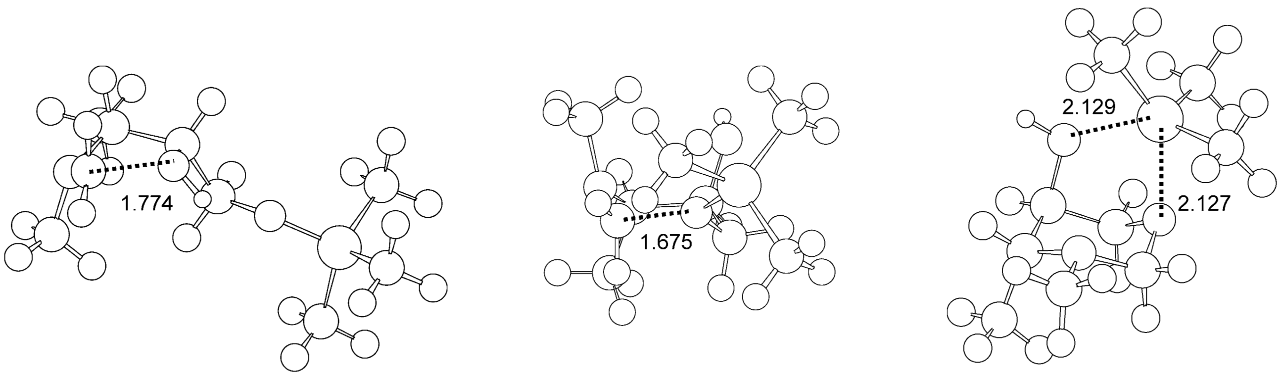
by the silyl migration from the primary hydroxy group to the secondary one through **TS6**.

This assertion was supported with additional experiments. When the oxazolidine **2b** was heated in CH_2Cl_2 at 100 °C it was observed a very slow equilibration of the oxazolidine **2b** into the oxazine **3b** (48 h, 7/1, **2b**/**3b**). In this equilibration the dichloromethane would play the role of a solvent. According to this, other solvents could afford the same results. In fact when **2b** was heated in methanol at 100 °C the same equilibration **2b**–**3b** took place quickly (**2b**/**3b** 1/1 after 9 h). In experiments with long reaction times (64 h) the equilibration reaction reached the values expected thermodynamically and only 5% of the compound **2b** appeared in the crude reaction mixture.[17]

In order to explain the observed rate increase of the **2b**–**3b** equilibration in methanol, theoretical calculations were carried out using methanol as solvent. As it can see (Table 2), the reaction in methanol does not produce significant changes in the activation barrier of **TS6**, relative to the immonium salt **9** (24.71 kcal mol^{-1} in methanol; 25.33 kcal mol^{-1} in CH_2Cl_2). The changes in the relative stability of the final products **2d** and **3d** in methanol and CH_2Cl_2 is also very similar (2.00 kcal mol^{-1} in methanol and 2.26 kcal mol^{-1} in CH_2Cl_2). However the energy differences between the charged species in dichloromethane and in methanol are important (10–23 kcal mol^{-1}, see last column in Table 2) meanwhile the neutral species (initial product **1d** and final products **2d** and **3d**) have only a small increase stabilisation in methanol (4 kcal mol^{-1}). According to these values, the activation barrier for the equilibration of the oxazolidine **2d** into the oxazine **3d** is lowered about 8 kcal mol^{-1} in methanol.

3. Conclusions

The reaction of 3-phenyl-3-methylamino-1,2-propanediol **1a** with $(CH_2O)n$ affords the corresponding 1,3-oxazine **3a** and is completed at room temperature in 20 h or at 100 °C in 1 h. However with CH_2Cl_2 the formation of the 1,3-oxazine **3a** required 100 °C and 64 h for completion of the reaction, because the higher activation barrier in the formation of the intermediate immonium salt. By the other hand, the reaction with $(CH_2O)n$ and CH_2Cl_2, of the same aminodiol partially protected as TBDMS in the primary hydroxyl group **1b** affords the oxazolidine **2b** under kinetic conditions and this compound can be slowly converted into the silylated oxazine **3b** under thermodynamic control. This reaction suppose the migration of the silyl group from the primary hydroxyl group to a secondary one and it is accelerated in



TS4 **TS5** **TS6**

Figure 2. Geometries of the transition structures **TS4**, **TS5** and **TS6** involved in the reaction of N-methyl aminodiol **1d** and CH_2Cl_2. The values given are the bond lengths in angstroms obtained at the HF/6-31G* level in CH_2Cl_2 as solvent.

polar solvents as methanol. The mechanism suggested for this transformation has been supported chemically and theoretically.

4. Experimental

4.1. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use. Analytical thin layer chromatography was performed on Merck silica gel (60 F_{254}) plates and column chromatography was accomplished on Merck Kieselgel 60 (230–240 mesh). IR spectra were recorded on a FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured for $CDCl_3$ solutions at 300 or 400 MHz and 75.4 or 100 MHz respectively; using a Bruker AC-300 and a Varian Unity 400 MHz spectrometers and chemical shifts are recorded relative to Me_4Si. High-resolution mass spectral data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionisation mode used in mass spectra were FAB, or chemical ionisation (CI) at 70 eV.

4.1.1. General procedure for the reactions of amino alcohols (1a or 1b) with dichloromethane or paraformaldehyde. **4.1.1.1. Reaction with dichlorometane.** *Method A*. The aminodiol 3-[(*tert*-butyldimethylsilyl)oxy]-1-methylamino-1-phenyl-2-propanol **1b** (6 mmol) in CH_2Cl_2 (50 mL) was heated in a pressure reactor at 100 °C for 64 h. The solvent was concentrated under reduced pressure to dryness and the residue was analysed by ^{1}H and ^{13}C NMR showed an 8/2.3/1 mixture of **1b** as chlorhydrate/**2b**/**3b**.

Method B. A solution of 3-methylamino-3-phenyl-1,2-propanediol **1a** or 3-[(*tert*-butyldimethylsilyl)oxy]-1-methylamino-1-phenyl-2-propanol **1b** (0.6 mmol) in the solvent indicated (5 mL) was added $NaHCO_3$ (1.2 mmol) and water (1 mL). The mixture was heated in a pressure reactor at 100 °C for the time indicated. After cooling the organic layer was separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate mixtures).

Compound **1a** in CH_2Cl_2 for 24 h afforded **3a** (90%).

Compound **1b** in CH_2Cl_2 for 64 h afforded 7/1 mixture of **2b**/**3b** (84%).

Compound **1b** in a 3/1 mixture of CH_2Cl_2/methanol for 64 h afforded a 1/1 mixture of **2b**/**3b** (85%).

4.1.1.2. Reaction with paraformaldehyde. The compounds **1a** or **1b** (0.24 mmol) in the solvent indicated (6 mL) and paraformaldehyde (11 mg, 0.37 mmol) were heated for the time indicated. The solvent was concentrated in vacuum. The residue was analysed by ^{1}H and ^{13}C NMR. The products were purified by column chromatography (silica gel, hexane/ethyl acetate mixtures).

Compound **1a** in benzene at room temperature for 20 h or reflux temperature for 8 h afforded **3a** (92%).

Compound **1b** in benzene reflux for 8 h or heated at 100 °C in a pressure reactor for 1 h afforded **2b** (95%).

Compound **1b** in methanol at 100 °C in a pressure reactor for 1 h afforded a 4.5/1 mixture of **2b**/**3b** (95%).

Compound **1b** in methanol at 100 °C in a pressure reactor for 20 h afforded a 2.5/1 mixture of **2b**/**3b** (95%).

4.1.2. Equilibration assays 2b–3b. A solution of 1,3-oxazolidine **2b** (35 mg, 0.12 mmol) in the solvent indicated (3 mL) was heated in the pressure reactor at 100 °C for the time indicated The solvent was evaporated in vacuum and the residue was analysed by ^{1}H and ^{13}C NMR spectroscopy.

In dichloromethane for 48 h afforded a 7/1 mixture of **2b**/**3b**.

In methanol for 64 h afforded a 5/75/20 mixture of **2b**/**3b**/**3a**.[17]

4.1.3. Synthesis of the chlorhydrate of 1b. To a solution of amino alcohol **2b** (50 mg, 0.17 mmol) in THF (1 mL) was added a solution of HCl 0.0012 M in THF (3 mL). The mixture was stirred at room temperature for 3 h and concentrated in vacuum to obtain the corresponding chlorhydrate.

4.1.4. Synthesis of 3b from 3a. To a solution of 3-methyl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazin-5-ol[3] **3a** (0.21 g, 1.2 mmol) in CH_2Cl_2 (10 mL) stirred under argon in an ice bath, were added triethylamine (0.2 mL, 1.42 mmol) and dimethylaminopyridine (0.01 g, 0.08 mmol). The reaction mixture was stirred for 15 mn and then *tert*-butyldimethylsilyl chloride (0.22 g, 1.46 mmol) was added. The mixture was stirred at room temperature for 96 h and then water (20 mL) and dichloromethane (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with saturated NH_4Cl aqueous solution (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, 9/1 hexane/ethyl acetate mixture) to afford 5-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine **3b** (76%).

4.1.5. Characterisation date of the new compounds. **4.1.5.1. 5-[(*tert*-Butyldimethylsilyl)oxymethyl]-3-methyl-4-phenyl-1,3-oxazolidine (2b).** Colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$) δ -0.24 (s, 3H), -0.14 (s, 3H), 0.92 (s, 9H), 2.35 (s, 3H), 3.23 (dd, $J=10.9$, 4.9 Hz, 1H, H-6), 3.45 (dd, $J=10.9$, 7.3 Hz, 1H, H-6), 3.81 (d, $J=7.7$ Hz, 1H, H-4), 4.15 (d, $J=2.4$ Hz, 1H, H-2), 4.51 (ddd, $J=7.7$, 7.3, 4.9 Hz, 1H, H-5), 4.91 (d, $J=2.4$ Hz, 1H, H-2), 7.4 (m, 5H) ppm; ^{13}C NMR (75.4 MHz; $CDCl_3$) δ -5.5 (q), -5.3 (q), 18.5 (s), 25.9 (q), 37.1 (q), 64.1 (t), 70.7 (d), 82.1 (d), 88.24 (t), 127.7 (d), 128.2 (d), 128.6 (d), 137.1 (s) ppm; IR (mineral oil) 3439, 2930, 1672, 1458, 1254, 1096 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{30}NO_2Si$: 308.2045. Found: 308.2056 $[M+1]^+$.

4.1.5.2. 5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine (3b). Colourless oil. ^{1}H NMR (300 MHz; CDCl$_3$) δ -0.65 (s, 3H), -0.15 (s, 3H), 0.81 (s, 9H), 2.05 (s, 3H), 2.89 (d, $J=8.7$ Hz, 1H, H-4), 3.40 (t, $J=10.6$ Hz, 1H, H-6), 3.91 (m, 2H, H-2 + H-5), 4.18 (dd, $J=10.6$, 5.1 Hz, 1H, H-6′), 4.65 (d, $J=8$ Hz, 1H, H-2′), 7.49 (m, 5H); ^{13}C NMR (62.9 MHz; CDCl$_3$) δ -5.3 (q), -4.8 (q), 18.0 (s), 25.8 (q), 37.3 (q), 69.9 (d), 73.0 (t), 76.1 (d), 87.4 (t), 127.7 (d), 128.6 (d), 129.3 (d), 139.9 (s) ppm; IR (film) 3449, 2955, 1667, 1473, 1254, 1101 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{30}NO_2Si$: 308.2046. Found: 308.2049 $[M+1]^+$.

4.1.5.3. Chlorhydrate of 1b. ^{1}H NMR: (300 MHz; CDCl$_3$) δ -0.04 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 2.47 (s, 3H), 3.23 (m, 1H), 3.55 (m, 1H), 3.9 (d, $J=3$ Hz, 1H), 4.19 (m, 1H), 7.4–7.6 (m, 5H) ppm; ^{13}C NMR: (75.4 MHz; CDCl$_3$) δ 18.5 (s), 26.3 (c), 33.5 (c), 64.1 (t), 66.7 (d), 72.3 (d), 128.5 (d), 128.7 (d), 129.12 (d), 135.9 (s) ppm.

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References and notes

1. (a) Dai, W. M.; Zhu, H. J.; Hao, X. J. *Tetrahedron: Asymmetry* **1996**, *7*, 1245. (b) Kuma, G. B.; Patel, H. V.; Shah, A. C.; Trenkle, M.; Cardin, C. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3391. (c) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *85*, 5736. (d) Martinek, T.; Lázár, L.; Fúlop, F.; Riddell, F. G. *Tetrahedron* **1998**, *54*, 12887. (e) Darabantu, M.; Plé, G.; Manger, S.; Gaina, L.; Cotora, E.; Mates, A.; Costas, L. *Tetrahedron* **1997**, *53*, 1891. (f) Star, A.; Goldberg, I.; Fuchs, B. *Angew. Chem.* **2000**, *39*, 2685. (g) Star, A.; Goldberg, I.; Fuchs, B. *Eur. J. Org. Chem.* **2001**, 729.
2. Lázár, L.; Fúlop, F. *Eur. J. Org. Chem.* **2003**, 3025.
3. Hajji, C.; Testa, M. L.; Salud-Bea, R.; Zaballos-García, E.; Server-Carrio, J.; Sepúlveda-Arques, J. *Tetrahedron* **2000**, *56*, 8173.
4. Hajji, C.; Testa, M. L.; Zaballos-García, E.; Zaragozá, R. J.; Server-Carrió, J.; Sepúlveda-Arques, J. *Tetrahedron* **2002**, *58*, 3281.
5. Hajji, C.; Zaballos-García, E.; Sepúlveda-Arques, J. *Synth. Commun.* **2003**, *33*, 4347.
6. Testa, M. L.; Hajji, C.; Zaballos-García, E.; García-Segovia, A. B.; Sepúlveda-Arques, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1369.
7. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
8. In our previous work[2] we reported that the reaction of the aminodiol **1a** with CH_2Cl_2 afforded the oxazine **3a**, without any traces of the five membered oxazolidine **2a**. In these experiments variable amounts of the chlorhydrate salt of the starting aminodiol **1a** (5–20%) also appeared in the crude reactions mixtures
9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; 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.
10. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.
11. (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 Publishing: Singapore, Singapore, 1994.
12. (a) Tapia, O. *J. Math. Chem.* **1992**, 10, 139. (b) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, 94, 2027. (c) Simkin, B. Y.; Sheikhet, I. *Quantum Chemical and Statistical Theory of Solutions-A Computational Approach*; Ellis Horwood: London, 1995.
13. (a) Cances, M. T.; Mennunci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.
14. (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Ziegler, T. *Chem. Rev.* **1991**, 91, 651–667.
15. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
16. Böhme, H.; Mundlos, E.; Herboth, O. E. *Chem. Ber.* **1957**, *90*, 2003.
17. When the oxazolidine **2b** was heated for 64 h furthermore of the oxazine **3b** the desilylated oxazine **3a** were obtained (**2b/3b/3a**, 5/75/20).

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Tetrahedron

New access to 1,3-diketones from aldehydes

Valérie Fargeas,[a,*] Myriam Baalouch,[a] Estelle Metay,[a] Jerôme Baffreau,[a] Delphine Ménard,[b] Pascal Gosselin,[b] Jean-Pascal Bergé,[c] Chantal Barthomeuf[d] and Jacques Lebreton[a,*]

[a]*Laboratoire de Synthèse Organique, CNRS UMR 6513, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France*
[b]*Laboratoire de Synthèse Organique, CNRS UMR 6511, Faculté des Sciences, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France*
[c]*IFREMER, Département Valorisation des Produits de la Mer, rue de l'Île d'Yeu, B.P. 21105, 44311 Nantes Cedex 3, France*
[d]*UMR-INSERM U-484, Laboratoire de Pharmacognosie et Biotechnologies, Faculté de Pharmacie, Université d'Auvergne, pl. H. Dunant, 63001 Clermont-Fd Cedex, France*

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Abstract—A simple and efficient methodology to introduce an 1,3-diketone motif from various aldehyde precursors in three steps with good overall yields is described using β-ketosulphone **7** as masked equivalent of acetone.

Ifremer reported in 1999 the isolation of carotenoid metabolite **1** from the cultured marine micro-algae *Skeletonema costatum*.[1] This natural product, for which neither the absolute nor the relative configuration were elucidated, exhibited potent cytotoxicity against a variety of human carcinoma cell lines.[2] As a part of our interest in the total synthesis of biologically active molecules, especially antitumor agents, we drawn our attention towards the synthesis of the metabolite **1**, and we have established the retrosynthetic plan depicted in Figure 1. Our strategy was centered on introduction of a 1,3-diketone unit from aldehyde **2** at the final stage.

1,3-Diketones are important building blocks, and their usefulness in heterocyclic preparations, e.g. pyrazole,[3] isoxazole,[4] triazole[5] and benzopyran-4-ones[6] has been largely illustrated. Also, 1,3-diketones are key structural units in many chelating ligands for lanthanide and transition metals.[7] As a consequence, a number of methods have been developed over the years to introduce this moiety which met various degrees of success. One of the most popular approaches to introduce the 1,3-diketone motif from the ketone precursor, is based on the C-acylation of the corresponding enolates (or silyl enol ethers) with acylating agents, e.g. acid chlorides,[8] acyl cyanides[9] or 1-acylbenzotriazoles,[10] and some improvements[11] have been recently done to minimize side reactions such as *O*-acylation. However, to our knowledge less attention has been devoted to aldehydes.[12]

Also, in order to attach the diketone side chain from **2** to reach our target molecule **1**, we became interested in developing a good and reliable method compatible with sterically hindered aldehydes. As a model of hindered aldehyde, we retained cyclohexylcarboxaldehyde **3**.

Our initial efforts have been to prepare 1,3-diketone from dithiane in an umpolung fashion. Though unprecedented, we tried to condense the lithiated dithiane **4** of the corresponding cyclohexylcarboxaldehyde **3** with 3-chloro-2-(trimethylsiloxy)-1-propene[13] **5** as electrophile acetonylating reagent (see Scheme 1). Unfortunately, all attempts to carry out this reaction in various conditions (bases and additives) were unsuccessful: no reaction takes place. By contrast, the addition of more reactive electrophiles such as allybromide[14] to lithiated dithiane **4** led to the formation of the desired product in reasonable yield (60% yield non-optimized).

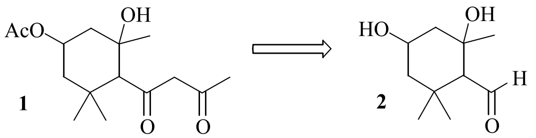

Figure 1. Retrosynthetic analysis of marine natural carotenoid metabolite **1**.

Keywords: Aldehydes; Sulfones; Alkylation; 1,3-Diketones.

* Corresponding authors. Tel.: +33-251125403; fax: +33-25112552 (J.L.); e-mail addresses: fargeas@chimie.univ-nantes.fr; lebreton@chimie.univ-nantes.fr

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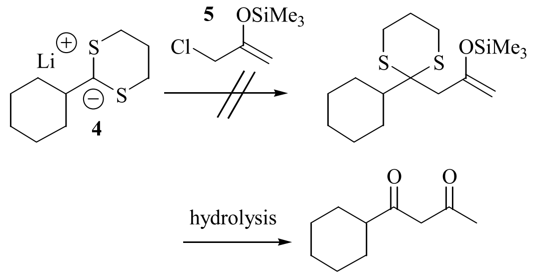
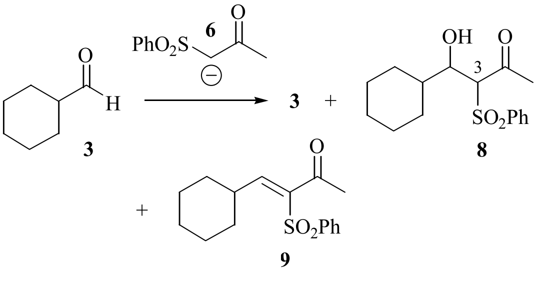


Scheme 1.

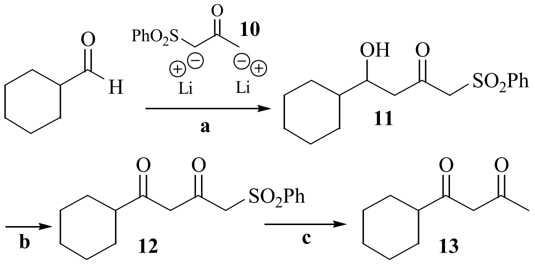
Next, it was considered that the monoanion **6**[15] of the 1-phenylsulfonylpropanone **7**, a masked nucleophilic acetonyl equivalent, could be condensed on the cyclohexylcarboxaldehyde **3** to afford the corresponding adduct **8** (see Scheme 2). Although, many conditions (NaH/THF, NaH/DMSO, LDA/THF, or DBU/PhH) to generate the stabilized carbanion **6** were screened, we always obtained a mixture (vide supra) of starting material, desired adduct **8** and unsaturated condensation compound **9**. The formation of this latter could be attributed to the acidity of the hydrogen on C-3. Also, quenching conditions were carefully investigated, however, the amounts of the byproduct **9** could be only slightly lowered by addition of saturated aqueous ammonium chloride at low temperature.

At this point, we turned our attention to an alternative strategy involving the condensation of the dianion **10** of the 1-phenylsulfonylpropanone **7** on aldehyde **3** (see Scheme 3). According to the work of Belletire,[16] the sulfone **7** was treated with 2.5 equimolar amounts of LDA in THF at low temperature to afford the colored dianion **10** which was then reacted with aldehyde **3** to give exclusively after work up the expected aldol **11** in high yield. In this condensation, no unsaturated compound was detected in the crude mixture (see vide supra). This aldol **11** was converted by oxidation with the Dess–Martin periodinane[17] (DMP) into the 1,3-diketone intermediate **12** in good yield. This method was found to be more efficient compared to PCC and Jones oxidation. Finally, the cleavage of the sulfonyl group of **12** was achieved with sodium-amalgam[18] to afford the diketone **13** in 77% yield (45% overall yield in 3 steps from aldehyde **3**).

To investigate the potential utility of this methodology, various aldehydes were readily converted to the corresponding diketones as summarized in Table 1. The different intermediates and final products were thus obtained in good to high yields for all steps, except for the removal of the sulfone group for cinnamaldehyde (entry 2). We were unable to suppress the competitive reduction of the conjugate double bond on intermediate **17**, even using sodium-amalgam with NaH_2PO_4 to control pH of the medium.[19] All attempts to use samarium(II) iodide to cleave the sulfone group of **17**, with HMPA or DMPU as additives failed, leading to complete decomposition of the starting material.[20] It is especially noteworthy that sodium-amalgam mediated cleavage of sulfones can be applied to substrates containing isolated double bond, such as **25**, in this case no over reduction occurs.



Scheme 2.



Scheme 3. Reagents and conditions: condensation: (a) 1.6 equiv of **10**, THF/HMPA (7/1), 4 h at 0 °C, then overnight at rt, 86%. Oxidation: (b) 1.0 equiv DMP, CH_2Cl_2, 6 h, rt, 76%. Desulfonation; (c) 5% Na(Hg), MeOH, −50 °C, then 2 h at −20 °C, 77%.

In conclusion, we have developed a simple and efficient methodology to introduce an 1,3-diketone motif from aldehyde precursors in three steps with good overall yields. To evaluate the scope and the efficiency of the present methodology, various aldehydes have been used. We are now extending this methodology to the total synthesis of marine natural carotenoid metabolite **1** and the results will be published in due course.

1. Physical data and spectroscopic measurements

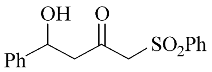
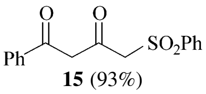
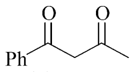
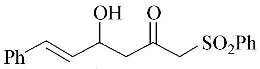
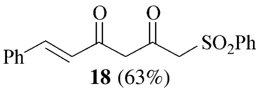
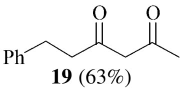
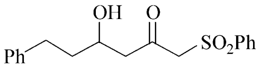
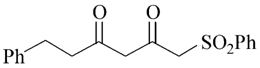
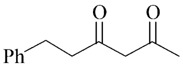
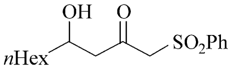
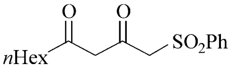
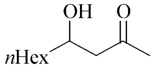
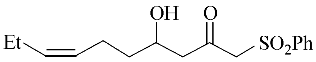
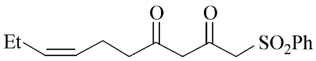
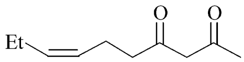
^1H NMR spectra were recorded on a Bruker AC 300 instrument at 300 MHz. The chemical shifts are expressed (ppm), referenced to residual chloroform (7.26 ppm). Data are reported as follows: δ, chemical shift; multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quintet and m, multiplet), coupling constants (J in Hertz, Hz), integration and assigment (aromatic, ar). H,H-COSY experiments were routinely carried out to ascertain H–H connectivities.

^{13}C NMR spectra were recorded on a Bruker AC 300 instrument at 75 MHz. The chemical shifts are expressed (ppm), reported from the central peak of deuterochloroform (76.9 ppm). DEPT (DEPT) experiments were used for evaluating CH multiplicities. When necessary, ^{13}C spectra were assigned with the aid of HETCOR experiments.

Mass spectra (MS) were obtained on a HP 5889 quadrupolar spectrometer in electronic impact (70 eV) or in chemical ionization (500 eV) with NH_3 gas. HMRS spectra were obtained on a JEOL AX500. Mass spectral data are reported as m/z.

IR spectra were recorded neat in KBr cells with a Bruker IFS 45 WHR Fourier transform spectrometer. The wave numbers (ν) are given in cm^{-1}.

Table 1

Entry	Aldehyde	Condensation[a] (yield)	Oxidation[a] (yield)	Desulfonation[a] (yield)
1	PhCHO	 **14** (92%)	 **15** (93%)	 **16** (77%)
2	(*E*)-PhCH=CHCHO	 **17** (77%)	 **18** (63%)	 **19** (63%)
3	$PhCH_2CH_2CHO$	 **20** (76%)	 **21** (94%)	 **19** (71%)
4	*n*-HexCHO	 **22** (85%)	 **23** (80%)	 **24** (90%)
5	(*Z*)-$EtCH=CH(CH_2)_2CHO$	 **25** (85%)	 **26** (80%)	 **27** (90%)

[a] See condition (a) in Scheme 3.

1.1. Chromatography

All reactions were monitored by thin-layer chromatography (TLC) carried out on precoated plate of silica gel 60F 254 (Merk, Art. 5735 alumina sheet).

Flash chromatography was performed on silica gel Merk 60, 230–400 mesh.

1.2. Solvents distillation

Tetrahydrofuran (THF) was distilled from sodium–benzophenone. Methanol (MeOH) was distilled from the corresponding magnesium derivative. Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure.

1.3. Usual procedures

All air and/or water sensitive reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents using standard syringe/septa techniques.

Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise stated.

1.3.1. 1-Phenylsulfonyl-2-propanone 6.[16b] To a solution of chloroacetone (9.2 mL; 114.65 mmol) in 150 mL of freshly distilled DMF was added at rt sodium sulfinate (18.8 g; 114.65 mmol; 1 equiv). After stirring 24 h at rt, the reaction mixture was diluted with 20 mL of Et_2O and 20 mL of water. The aqueous phase was extracted with 3×15 mL Et_2O before washing with an aqueous NaCl solution and drying on $MgSO_4$. After evaporation of the solvent, the crude residue was purified on silica gel (eluant: petroleum ether/ethyl acetate: 7/3) to furnish 20 g of the desired product as pale yellow crystals (yield=88%). ^1H NMR ($CDCl_3$): $\delta=2.24$ (s, 3H, H_3); 4.09 (s, 2H, H_1); 7.54–7.67 (m, 3H, H_{ar}); 7.80–7.94 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$): $\delta=32.4$ (C_3); 68.7 (C_1); 129.1 (C_6 and $C_{6'}$); 130.3 (C_5 et $C_{5'}$); 135.3 (C_7); 139.5 (C_4); 197.0 (C_2). SM (CI/NH_3): $M+1=199$. IR: $\nu=1725$; 1322; 1151.

1.4. General procedure for aldolization

To a solution of diisopropylamine (8.8 mL; 62.5 mmol; 2.5 equiv) in 13 mL of anhydrous THF at 0 °C was added dropwise a solution of *n*-butyllithium 1.6 M in hexanes (39 mL; 62.5 mmol; 2.5 equiv) and the solution was stirred during 45 mn before cooling at −78 °C. At this temperature, 6 mL of HMPA were added followed by a solution of 1-phenylsulfonyl-2-propanone (5 g; 25 mmol) in 30 mL of THF. After 4 h at 0 °C, aldehyde (32.5 mmol; 1.3 equiv) was added to the resulting orange heterogenous solution and the reaction mixture was allowed to warm to rt overnight. Hydrolysis was achieved at 0 °C with a saturated aqueous solution of NH_4Cl (30 mL), subsequent treatments (Et_2O extraction, drying on $MgSO_4$, concentration and flash chromatography) afforded the desired compound.

1.4.1. 4-Cyclohexyl-4-hydroxy-1-phenylsulfonyl-2-butanone 11. (Eluant: CH_2Cl_2) 7 g of **11** were obtained as a yellow oil (yield=86%). ^1H NMR ($CDCl_3$): $\delta=1.00$–1.84 (m, 11H, $H_{cyclohexyl}$); 2.86 (d, $J=7.3$ Hz, 2H, H_3); 2.90 (s, 1H, OH); 3.77–3.86 (m, 1H, H_4); 4.22 (s, 2H, H_1); 7.26–7.91 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$): $\delta=26.0$; 26.1; 26.3; 28.1; 28.8 ($C_{cyclohexyl}$); 43.2 ($C_{cyclohexyl}$); 48.6 (C_3); 67.5 (C_1); 71.7 (C_4); 128.3 (2C, C_{ar}); 129.4 (2C, C_{ar}); 134.4 (C_{ar}); 138.7 (C_{ar}); 199.3 (C_2). SM (CI/NH_3): $M+1=311$. SM (EI) *m/z* (%): 227 (78); 199 (66); 183 (15); 141 (79); 77 (100); 55 (65); 41 (36). IR: 3520; 1715; 1310, 1152.

1.4.2. 4-Hydroxy-4-phenyl-1-phenylsulfonyl-2-butanone 14. (Eluants: petroleum ether/ethyl acetate: 6/4) 7 g of **14** were obtained as a yellow oil (Yield=92%). ^1H NMR ($CDCl_3$): $\delta=2.96$ and 3.08 (part AB of an ABX system, 2H, $J=17.2$, 9.2, 3.4 Hz, H_3); 4.18 (s, 2H, H_1); 5.07 (m, part X of the ABX system, 1H, H_4); 7.30–7.80 (m, 10H, H_{ar}). ^{13}C NMR ($CDCl_3$): $\delta=52.7$ (C_3); 66.8 (C_1); 69.5 (C_4); 125.7; 127.72; 128.2; 128.3; 129.8; 134.2; 138.5; 142.7

(C_{ar}); 197.7 (C_2). MS (CI/NH_3): M+18=332; M+1=305. MS (EI) *m/z* (%): 163 (5); 141 (18); 105 (44); 77 (100). IR: ν=3521; 1716; 1310; 1152.

1.4.3. (5*E*)-4-Hydroxy-6-phenyl-1-phenylsulfonyl-hex-5-en-2-one 17. (Eluants: petroleum ether/ethyl acetate: 5/5) 6.3 g of **17** were obtained as a yellow oil (yield=77%). ^{1}H NMR δ (ppm): 4.23 (s, 2H, H_1); 3.05 (m, 2H, H_3); 4.75 (qu., 1H, H_4); 6.20 (dd, 1H, H_5, *J*=6.2, 16 Hz); 6.64 (d, 1H, H_6, *J*=16 Hz). ^{13}C NMR δ (ppm): 50.9 (C_3); 67.5 (C_1); 68.4 (C_4); 126.6 (C_{ar}); 134.4 (C_{ar}); 136.2 (C_7); 138.5 (C_{ar}); 197.8 (C_2). MS (CI/NH_3): M−(H_2O)+18=330. MS (EI) *m/z* (%): 312 (5); 171 (93); 157 (35); 128 (87); 105 (100); 77 (48); 51 (30); 18 (25). IR: 3515; 3060; 3026; 2927; 1721; 1447; 1320; 1151; 969; 744.

1.4.4. 4-Hydroxy-6-phenyl-1-phenylsulfonyl-2-hexanone 20. (Eluants: petroleum ether/ethyl acetate: 6/4) 6.3 g of **20** were obtained as a yellow oil (yield=76%). ^{1}H NMR δ (ppm): 1.75 (m, 2H, H_5); 2.66 (m, 2H, H_6); 2.82 (d, 2H, H_3, *J*=5.8 Hz); 4.10 (m, 1H, H_4); 4.28 (s, 2H, H_1); 7.18–7.88 (m, 10H, H_{ar}). ^{13}C NMR δ (ppm): 31.6 (C_6); 38.2 (C_5); 51.1 (C_3); 66.7 (C_4); 66.9 (C_1); 125.9; 128.2; 128.4; 129.3; 134.3; 138.7; 141.6 (C_{ar}); 198.6 (C_2). MS (CI/NH_3): M+18=350. MS (EI) *m/z* (%): 172 (35); 141 (21); 91 (100); 77 (64). IR: 3526; 3026; 2927; 1716; 1602; 1584; 1447; 1309; 1151; 1083; 742.

1.4.5. 4-Hydroxy-1-phenylsulfonyl-2-decanone 22. (Eluants: petroleum ether/ethyl acetate: 6/4) 6.6 g of **22** were obtained as a yellow oil (yield=85%). ^{1}H NMR δ (ppm): 0.87 (m, 3H, H_{10}); 1.26 (m, 10H, H_5, H_6, H_7, H_8, H_9); 2.81 (m, 2H, H_3); 4.03 (m, 1H, H_4); 4.21 (s, 2H, H_1); 7.52–7.90 (m, 5H, H_{ar}). ^{13}C NMR δ (ppm): 14.3 (C_{10}); 22.8 (C_9); 25.6 (C_5); 29.5 (C_7); 32.0 (C_6); 36.9 (C_8); 51.4 (C_3); 67.7 (C_4); 67.9 (C_1); 128. 6 (2C, C_{ar}); 129.7 (2C, C_{ar}); 134.7 (C_{ar}); 138.9 (C_{ar}); 199.2 (C_2). MS (CI/NH_3): M+18=330. MS (EI) *m/z* (%): 227 (32); 199 (41); 141 (61); 77 (100); 43 (99). IR: 3521; 3063; 2925; 1716; 1585; 1494; 1447; 1310; 1152; 1083; 743.

1.4.6. (7*Z*)-4-Hydroxy-1-phenylsulfonyl-7-decen-2-one 25. (Eluants: petroleum ether/ethyl acetate: 6/4) 6.6 g of **25** were obtained as a yellow oil (yield=85%). ^{1}H NMR δ (ppm): 0.99 (m, 3H, H_{10}); 1.52 (m, 2H, H_6); 2.10 (m, 4H, H_6, H_9); 2.84 (m, 2H, H_3); 4.06 (m, 1H, H_4); 4.22 (s, 2H, H_1); 4.06 (m, 2H, H_7, H_8); 7.55–7.92 (m, 5H, H_{ar}). ^{13}C NMR δ (ppm): 14.3 (C_{10}); 20.5 (C_{11}); 23.1 (C_6); 36.4 (C_5); 51.1 (C_3); 67.2 (C_4); 67.5 (C_1); 127.8 (C_7 or C_8); 128.3 (C_{ar}); 129.4 (C_{ar}); 132.7 (C_7 or C_8); 134.4 (C_{ar}); 138.6 (C_{ar}); 198.7 (C_2). MS (CI/NH_3): M−(H_2O)+18=310. MS (EI) *m/z* (%): 224 (24); 141 (12); 83 (100); 77 (55); 69 (36); 55 (31); 41 (71). IR: 3518; 3061; 1715; 1483; 1310; 1152; 744.

1.5. General procedure for oxydation

To a solution of Dess–Martin periodinane (0.41 g; 1.0 mmol; 1.6 equiv) in 4.4 mL of CH_2Cl_2 was added at rt a solution of compound to oxidize (0.6 mmol) in 3 mL of CH_2Cl_2. The reaction mixture was stirred 6 h at rt then diluted with 15 mL of Et_2O. 10 mL of a 10% aqueous solution of $Na_2S_2O_3$ and 10 mL of a 10% aqueous solution of $NaHCO_3$ were successively added. Subsequent extraction with Et_2O (3×10 mL) afforded an organic phase which was submitted to usual treatments (drying on $MgSO_4$, concentration and a short flash chromatography) affording the desired compound.

1.5.1. 1-Cyclohexyl-4-phenylsulfonyl-1,3-butadione 12. (Eluant: CH_2Cl_2) 150 mg of **12** were obtained as a yellow oil (yield=76%). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.25–1.80 (m, 11H, $H_{cyclohexyl}$); 4.02 (s, 2H, H_3); 5.67 (s, 2H, H_1); 7.44–7.59 (m, 3H, H_{ar}); 7.88–7.98 (m, 2H, H_{ar}). ^{13}C NMR ($CDCl_3$) δ (ppm): 25.7; 26.1; 28.1; 28.2; 29.4 (5C, $C_{cyclohexyl}$); 48.6 ($C_{cyclohexyl}$); 64.8 (C_1); 51.7 (C_3); 128.5 (2C, C_{ar}); 129.4 (2C, C_{ar}); 134.3 (C_{ar}); 138.7 (C_{ar}); 210.5 (C_4); 215.3 (C_2). MS (CI/NH_3): M+1=309. SM (EI) *m/z* (%): 308 (3); 225 (100); 183 (97); 141 (100); 111 (23); 77 (56); 55 (46). IR: 2995; 2935; 1602; 1322; 1151.

1.5.2. 1-Phenyl-4-phenylsulfonyl-1,3-butanedione 15. (Eluants: petroleum ether/ethyl acetate: 6/4) 0.17 g of **15** were obtained as a yellow solid (yield=93%). ^{1}H NMR δ (ppm): 4.17 (s, 2H, H_1); 6.38 (s, 1H, H_3); 7.40–7.80 (m, 10H, H_{ar}). ^{13}C NMR δ (ppm): 31.2 (C_1); 65.4 (C_3); 127.7; 128.5; 129.1; 129.6; 130.4; 133.5; 134.6; 138.8 (C_{ar}); 184.7 (C_4); 208.2 (C_2). MS (CI/NH_3): M+18=320; M+1=303. MS (EI) *m/z* (%): 160 (18); 147 (37); 118 (35); 105 (100); 77 (59). IR: 2995; 2936; 1603; 1573; 1451; 1308; 1159; 1085; 694.

1.5.3. (5*E*)-6-Phenyl-1-phenylsulfonyl-hexene-2,4-dione 18. (Eluants: petroleum ether/ethyl acetate: 3/7) 0.63 g of **17** were obtained as a red oil (yield=63%). ^{1}H NMR δ (ppm): 4.13 (s, 2H, H_1); 5.92 (s, 1H, H_3); 6.51 (d, 1H, H_6, *J*=15.8 Hz); 7.29–7.68 (m, 11H, H_{ar} and H_5). ^{13}C NMR δ (ppm): 65.9 (C_1); 102.4 (C_6); 121.8–141.9 (14C, 12C_{ar}, C_5, C_3); 178.5 (C_4); 185.8 (C_2). MS (CI/NH_3): M+18=346; M+1=329. MS (EI) *m/z* (%): 312 (12); 171 (100); 157 (33); 128 (61); 105 (65); 77 (35); 51 (15). IR: 3439; 3060; 3028; 2925; 1633; 1578; 1446; 1313; 1307; 1156; 1084.

1.5.4. 6-Phenyl-1-phenylsulfonyl-hexane-2,4-dione 19. (Eluants: petroleum ether/ethyl acetate: 6/4) 0.186 g of **18** were obtained as a brown oil (yield=94%). ^{1}H NMR δ (ppm): 2.78 (m, 4H, H_5 and H_6); 4.00 (s, 2H, H_1); 5.69 (s, 1H, H_3); 7.16–8.00 (m, 10H, H_{ar}). ^{13}C NMR δ (ppm): 31.5 (C_6); 40.3 (C_5); 64.7 (C_1); 102.6 (C_3); 126.7; 128.6; 128.7; 128.9; 129.5; 134.6; 138.8; 140.4 (C_{ar}); 179.4 (C_2); 195.1 (C_4). MS (CI/NH_3): M+18=348; M+1=331. MS (EI) *m/z* (%): 188 (27); 141 (30); 131 (54); 104 (62); 91 (100); 77 (81). IR: 3062; 3027; 2927; 1721; 1602; 1496; 1447; 1323; 1310; 1153; 1083; 700.

1.5.5. 1-Phenylsulfonyl-decane-2,4-dione 23. (Eluants: petroleum ether/ethyl acetate: 6/4) 0.15 g of **23** were obtained as a yellow oil (yield=80%). ^{1}H NMR δ (ppm): 0.86 (m, 3H, *J*=7 Hz, H_{10}); 1.27 (m, 8H, H_6, H_7, H_8, H_9); 1.55 (m, 2H, H_5); 4.00 (s, 2H, H_1); 5.65 (s, 1H, H_3); 7.49–7.90 (m, 5H, H_{ar}). ^{13}C NMR δ (ppm): 14.3 (C_{10}); 22.7 (C_9); 25.7 (C_5); 29.0 (C_7); 31.7 (C_6); 38.6 (C_8); 64.7 (C_1); 102.2 (C_3); 128.7 (2C, C_{ar}); 129.5 (2C, C_{ar}); 134.5 (C_{ar}); 138.9 (C_{ar}); 179.9 (C_4); 196.2 (C_2). MS (CI/NH_3): M+18=328; M+1=311. MS (EI) *m/z* (%): 240 (38); 225 (16); 183 (49); 169 (33); 141 (98); 125 (29); 113 (40); 99 (41); 85 (75); 77

(100); 69 (24); 55 (36); 43 (91). IR: 2995; 2936; 1602; 1445; 1317; 1308; 1159; 1085; 694.

1.5.6. (7Z)-1-Phenylsulfonyl-decene-2,4-dione 26. (Eluants: petroleum ether/ethyl acetate: 6/4) 0.15 g of **26** were obtained as a yellow oil (yield = 80%). ^{1}H NMR δ (ppm): 0.93 (t, 3H, $J=7$ Hz, H_{10}); 1.90–2.15 (m, 2H, H_9); 2.19–2.45 (m, 4H, H_5 and H_6); 4.02 (s, 2H, H_1); 5.15–5.62 (m, 2H, H_3 and H_4); 5.70 (s, 1H, H_3); 7.49–7.99 (m, 5H, H_{ar}). ^{13}C NMR δ (ppm): 14.2 (C_{10}); 20.5 (C_9); 23.0 (C_5 or C_6); 38.4 (C_5 or C_6); 64.5 (C_1); 102.2 (C_7 and C_8); 126.3, 128.4, 129.4, 134.3, 138.5 (5C, C_{ar}), 179.8 (C_4); 195.1 (C_2). MS (CI/NH_3): M + 18 = 326; M + 1 = 309. MS (EI) *m/z* (%): 240 (56); 225 (12); 199 (15); 183 (29); 167 (26); 141 (77); 125 (31); 109 (53); 77 (100); 67 (48); 55 (46); 41 (75). IR: 2957; 2930; 1615; 1506; 1446; 1320; 1309; 1156; 1085.

1.6. General procedure for desulfonation

Turnings of sodium (0.46 g; 20 mmol; 12.2 equiv) were added to mercury (7.3 g; 36.4 mmol; 22 equiv) at rt. 8.3 mL of dry MeOH were then added to the corresponding amalgam and the temperature was cooled to −50 °C. A solution of 1,3-dione (1.7 mmol; 1 equiv) in 12 mL of MeOH was added and the reaction mixture was stirred 2 h at −20 °C before the hydrolysis was achieved with a saturated aquous solution of NH_4Cl (40 mL) at 0 °C. After filtration, the aqueous phase was extracted with 3 × 10 mL Et_2O before drying on $MgSO_4$. After evaporation of the solvent, the crude residue was purified by a short flash chromatography to afford the desired compound. All compounds were obtained under their enolic form.

1.6.1. 1-Cyclohexyl-butane-1,3-dione 13. (Eluants: CH_2Cl_2) 0.22 mg of **13** were obtained as a pale orange oil (yield = 77%). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.69–1.89 (m, 10H, $H_{cyclohexyl}$); 2.06 (s, 3H, H_4); 2.22 (m, 1H, $H_{cyclohexyl}$); 3.60 (s, 2H, $H_{2'}$); 5.48 (s, 1H, H_2); 12.06 (s, 1H, OH). ^{13}C NMR δ (ppm): 24.0; 25.9; 27.8; 29.6 (4C, $C_{cyclohexyl}$); 28.5 (C_4); 46.4 (C_5); 98.1 (C_2); 192.6 (C_1 and C_3). MS (CI/NH_3): M + 1 = 169. MS (EI) *m/z* (%): 168 (18); 113 (12); 85 (100); 55 (24); 43 (35). HR MS: 168.1167 ($C_{10}H_{16}O_2$; calcd 168.1150). IR: 2966; 1612; 1492; 1364.

1.6.2. 1-Phenyl-butan-1,3-dione 16. (Eluants: petroleum ether/ethyl acetate: 7/3) 140 mg of **16** were obtained as a pale yellow oil (yield = 76%). ^{1}H NMR δ (ppm): 2.06 (s, 3H, H_1); 5.03 (m, 1H, H_3); 7.15–7.24 (m, 5H, H_{ar}) [10% of the 1–3 diketone form is detected: 2.18 (s, 3H, H_1); 6.20 (s, 2H, H_3); 7.43–7.84 (m, 5H, H_{ar})[21]]. ^{13}C NMR δ (ppm): 24.1 (C_1); 47.0 (C_3); 68.8 (C_2); 75.2 (C_4); 125.7 (2C, C_{ar}); 127.5 (Car); 128.5 (2C, C_{ar}); 144.5 (C_{ar}). MS (CI/NH_3): M + 1 = 163; M + 18 = 180. MS (EI) *m/z* (%): 146 (28); 105 (53); 77 (67); 43 (98). IR: 3436; 3062; 3030; 2925; 1713; 1603; 1494; 1449; 1360; 1323; 1158; 1083; 756; 701.

1.6.3. 6-Phenyl-hexan-2,4-dione 19. (Eluants: petroleum ether/ethyl acetate: 7/3) 224 mg of **19** were obtained as a brown oil (yield = 71%). ^{1}H NMR δ (ppm): 2.04 (s, 3H, H_1); 2.65 (m, 2H, H_5); 2.92 (m, 2H, H_6); 5.48 (s, 1H, H_3); 7.17–7.29 (m, 5H, H_{ar}). ^{13}C NMR δ (ppm): 25.1 (C_5); 31.8 (C_1); 40.3 (C_3); 100.3 (C_6); 126.5 (C_{ar}); 128.6 (2C, C_{ar}); 128.8 (2C, C_{ar}); 140.9 (C_{ar}); 191.3 (C_4); 193.5 (C_2). MS (CI/NH_3): M + 1 = 191; M + 18 = 208. SM (EI) *m/z* (%): 190 (21); 104 (67); 91 (100); 77 (30); 43 (100). HR MS: 190.0996 ($C_{12}H_{14}O_2$; calcd 190.0994). IR: 3027; 2928; 1706; 1603; 1496; 1454; 1361; 1134; 785; 750; 699.

1.6.4. Decane-2,4-dione 24. (Eluants: petroleum ether/ethyl acetate: 7/3) 265 mg of **24** were obtained as a yellow oil (yield = 90%). ^{1}H NMR δ (ppm): 0.86 (m, 3H, H_{10}); 1.26 (m, 16H, H_6–H_9); 2.02 (m, 3H, H_1); 2.22 (m, 2H, H_5); 5.47 (s, 1H, H_3). ^{13}C NMR δ (ppm): 14.2; 22.7; 25.2; 25.9; 29.1 (5C, C_{alk}); 31.8 (C_1); 38.5 (C_{alk}); 99.9 (C_3); 191.7 (C_4); 194.5 (C_2). MS (CI/NH_3): M + 1 = 171; M + 18 = 188. MS (EI) *m/z* (%): 170 (2); 113 (18); 100 (55); 85 (100); 72 (16); 43 (100). HR MS: 170.1304 ($C_{10}H_{18}O_2$; calcd 170.130). IR: 2956; 2929; 2858; 1613; 1460; 1364.

1.6.5. (7Z)-Decene-2,4-dione 27. (Eluants: petroleum ether/ethyl acetate: 7/3) 265 mg of **27** were obtained as a yellow oil (yield = 90%). ^{1}H NMR δ (ppm): 0.88 (t, 3H, $J=7$ Hz, H_{10}); 1.95 (s, 3H, H_1); 1.95 (m, 2H, H_9); 2.25 (m, 4H, H_5–H_6); 5.15–5.41 (m, 2H, H_7–H_8); 5.42 (s, 1H, H_3). ^{13}C NMR δ (ppm): 13 (C_{10}); 20 (C_9); 22 (C_6); 24 (C_1); 37 (C_5); 99 (C_3); 126 and 132 (C_7 and C_8); 190 and 192 (C_2 and C_4). MS (CI/NH_3): M + 1 = 169; M + 18 = 186. MS (EI) *m/z* (%): 168 (2); 110 (11); 100 (30); 85 (100); 67 (27); 55 (14); 43 (71). HR MS: 168.1154 ($C_{10}H_{16}O_2$; calcd 168.1150). IR: 2956; 2863; 1713; 1620; 1454; 1360; 1142.

Acknowledgements

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References and notes

1. WO 0044718 A1 20000803 or *Chem. Abstr. 133*, 134246.
2. Bergé, J. P.; Bourgougnon, N.; Carbonnelle, D.; Le Bert, V.; Tomasoni, C.; Durand, P.; Roussakis, C. *Anticancer Res.* **1997**, *17*, 2115–2120.
3. Nagpal, A.; Unny, R.; Joshi, Y. C. *Heterocycl. Commun.* **2001**, *32*, 589–592.
4. Simoni, D.; Invidiata, F. P.; Rondanin, R.; Grimaudo, S.; Cannizzo, G.; Barbusca, E.; Porretto, F.; D'Alessandro, N.; Tolomeo, M. *J. Med. Chem.* **1999**, *42*, 4961–4969.
5. Alekseev, V. V.; Zelinin, K. N.; Yakimovich, S. I. *Russ. J. Org. Chem.* **1995**, *31*, 705–727.
6. Ellis, G. P. The Chemistry of Heteroclic Compounds. In *Chromanones and Chromones*; Ellis, G. P. Ed.; Interscience: USA, Vol. 33, pp 495–555. (b) Raston, C. L.; Salem, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1702–1703.
7. Garnovskii, A. D.; Kharixov, B. I.; Blanco, L. M.; Garnovskii, D. A.; Burlov, A. S.; Vasilchenko, I. S.; Bondarenko, G. I. *J. Coord. Chem.* **1999**, *46*, 365–375.
8. Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, *18*, 1187–1190.
9. Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249–2252.
10. Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679–3682.
11. (a) Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**,

61, 3885–3887 and references cited herein. For recent reference, see: (b) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948. (c) Kel'in, A. V. *Curr. Org. Chem.* **2003**, *7*, 1–21.

12. Ballini, R.; Bartoli, G. *Synthesis* **1993**, 965–967.
13. Hosomi, H.; Shirahata, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1981**, *46*, 4631–4633.
14. For similar examples, see: (a) Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *Tetrahedron* **1998**, *54*, 14581–14596. (b) Jia, Y. X.; Li, X.; Wu, B.; Zhao, X. Z.; Tu, Y. Q. *Tetrahedron* **2002**, *58*, 1697–1708.
15. Giblin, G. M. P.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1987**, 207–208. For a good preparation of 1-phenylsulfonylpropanone **7**, see: Tavares, D. F.; O'Sullivan, W. I.; Hauser, C. R. *J. Org. Chem.* **1962**, *27*, 1251–1254.
16. (a) Belletire, J. L.; Spletzer, E. G. *Synth. Commun.* **1987**, *17*, 1701–1707. (b) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205–1220.
17. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.
18. See: Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkins Trans. 1* **1978**, 829–834.
19. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477–3478.
20. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135–1138. For more recent examples, see: Colucci, J.; Lee, D.; Wilson, M.-C. *Org. Lett.* **2002**, *4*, 4705–4706.
21. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948.

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Efficient method for the synthesis of diphosphine ligands with a heteroaryl–aryl bridge

Nataliya V. Artemova,[a] Marina N. Chevykalova,[a,b] Yuri N. Luzikov,[b] Ilya E. Nifant'ev[b,*] and Eduard E. Nifant'ev[a]

[a] *Department of Chemistry, Moscow State Pedagogical University, Nesvizhskii per. 3, Moscow 119021, Russian Federation*
[b] *Department of Chemistry, Moscow State University, Moscow 119992, Russian Federation*

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Abstract—A new efficient method for the synthesis of heteroaryl–aryl diphosphine ligands by direct double metallation of heteroaryl–aryls followed by phosphorylation of the resulting *o*,*o*′-dilithium salts is described. A number of new C_1-symmetric diphosphine ligands based on 3-arylheteroaryls, X-heteroaryls (X=N), and diphosphine ligands with a heterocyclic bridge with *o*-tolyl as the aryl fragment have been synthesized.

1. Introduction

Currently, complexes derived from 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) are among the most efficient and versatile homogeneous metal complex catalysts. The successful use of BINAP in enantioselective catalysis both in the laboratory and on an industrial scale[1] initiated the development of the synthesis of BINAP analogues.

The synthesis of C_2-symmetric diphosphine ligands has long received primary attention.[2,3] However, studies showed that C_2 symmetry is not a necessary condition for attaining high results in catalysis.[4,5] Thus, a group of C_1-symmetric diphosphine ligands based on biphenyl[6] and binaphthyl[7] have been synthesized by step-by-step introduction of two nonequivalent phosphine groups. It was found that the BINAPP′ ligand can be even more efficient than the C_2-symmetric BINAP, for example, in the Rh-catalyzed hydrogenation of acrylic acid derivatives and in the Pd-catalyzed allylic alkylation.[7]

Several years ago, Benincori's research group reported the synthesis of a new class of C_1-symmetric diphosphine ligands with heteroaryl–aryl type bridges in which the phosphorus-bearing phenyl is located in position 3 of the heterocycle[8–10] (Fig. 1).

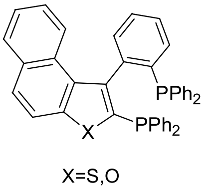

Figure 1.

Previously, it has been shown that the introduction of a heterocycle into a diphosphine molecule provides easy variation of the steric and electronic properties, which is favorable for fine tuning of the catalyst towards a particular substrate.[11] Experiments carried out with enantiomerically pure diphosphines of the heteroaryl–aryl type have shown that these compounds can actually serve as effective catalysts of Diels–Alder and hydrogenation reactions.[8–10]

In connection with solution of the topical problem of the design and synthesis of inexpensive, readily available and efficient ligands, we decided to develop an efficient and general method for the synthesis of C_1-symmetric bidentate diphosphine ligands, both chiral and achiral, and to prepare a number of diphosphines based on 3-arylheteroaryls, X-heteroaryls (X=N), and diphosphine ligands with a heterocyclic bridge with *o*-tolyl as the aryl fragment.

Keywords: Heterocycles; Phosphorylation; Diphosphines; Indole; Thiophene.

* Corresponding author. Tel./fax: +7-095-939-4098;
e-mail: inif@org.chem.msu.ru

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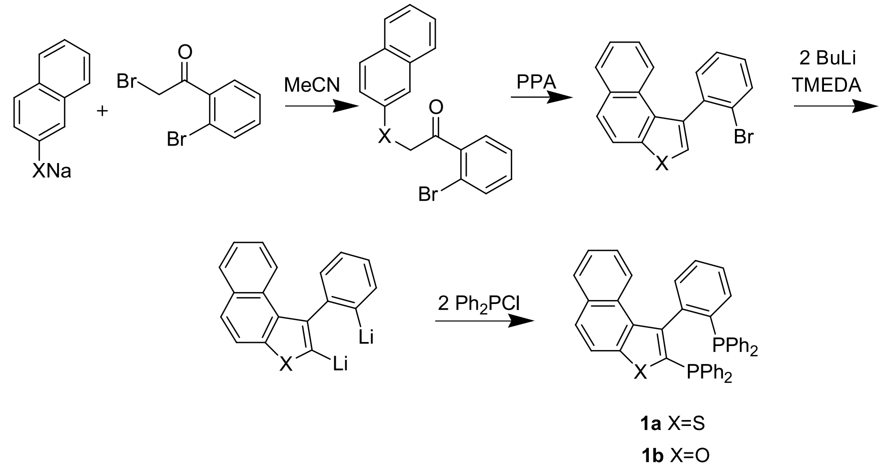


Scheme 1.

2. Results and discussion

The heteroaryl type diphosphine ligands described previously were synthesized by the reaction of the *o*-bromophenyl derivatives of the corresponding heterocycles with butyllithium followed by treatment of the intermediate dilithium salts with chlorodiphenylphosphine (Scheme 1).[8–10] It is worthy of note that further extension of the class of new C_1-symmetric diphosphine ligands is held up by low synthetic accessibility of the starting *o*-bromophenyl derivatives.

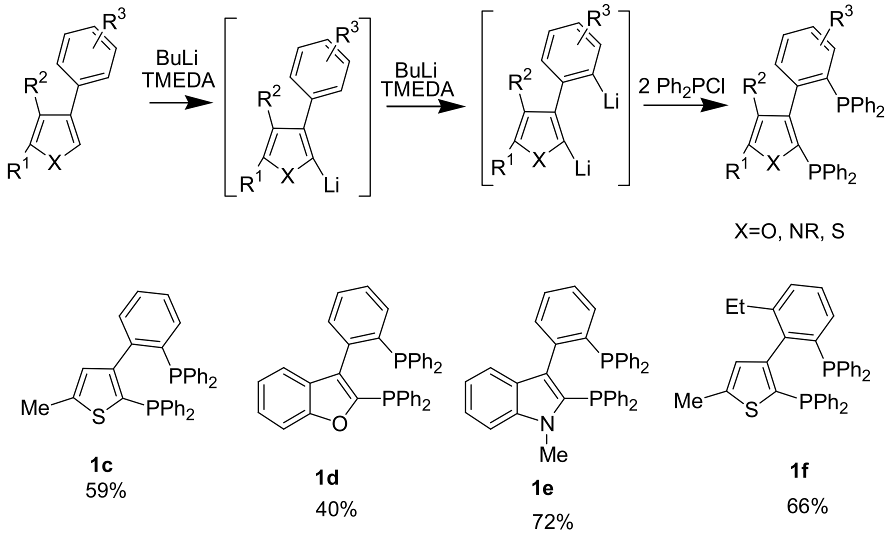
We have developed a much more efficient and general method for the synthesis of heteroaryl–aryl diphosphines (Scheme 2). As the starting compounds, we used synthetically more accessible heteroarylaryls.

The method represents direct double metallation of a 3-arylheterocycle with butyllithium in the presence of TMEDA (as described for biphenyl[12]) followed by treatment of the resulting dilithium derivative with dichlorophenylphosphine. Since the rate-determining step in the preparation of the dilithium derivative of biphenyl is apparently monometallation, because the heterocycle is metallated much more easily than benzene,[13] the yields of the dilithium derivatives were expected to be higher in the case of heteroaryl–aryl derivatives.

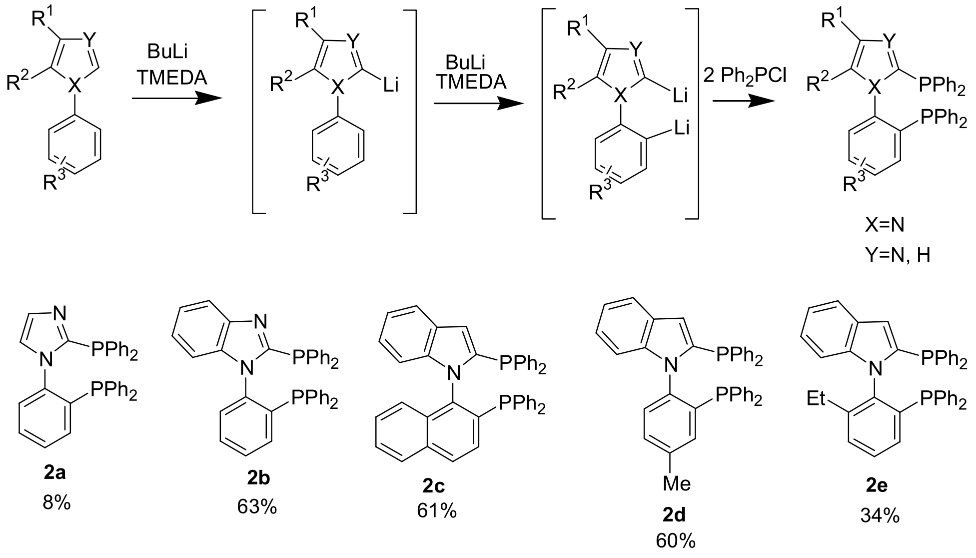
The method we proposed proved to provide a versatile and an efficient pathway to almost any heteroaryl–aryl bridged diphosphine **1**. For example, we employed this method to prepare compound **1a** directly from the readily available 1-phenylnaphtho[2,1-*b*]thiophene.

Using this method, we markedly extended the range of heteroaryl–aryl bridged diphosphines of type **1**. First, we synthesized heteroaryl–aryl diphosphines containing only one heteroatom in the ring: sulfur, oxygen or nitrogen. The phenyl rings in diphosphines **1c**–**1e** contain no substituents. The ethyl group in the *o*-position of 4-(2-ethylphenyl)-2-methylthiophene directs the metallation of the phenyl group to the free *o*-position (diphosphine **1f**).

We showed that *o*,*o*′-dimetallation can be performed not



Scheme 2.



Scheme 3.

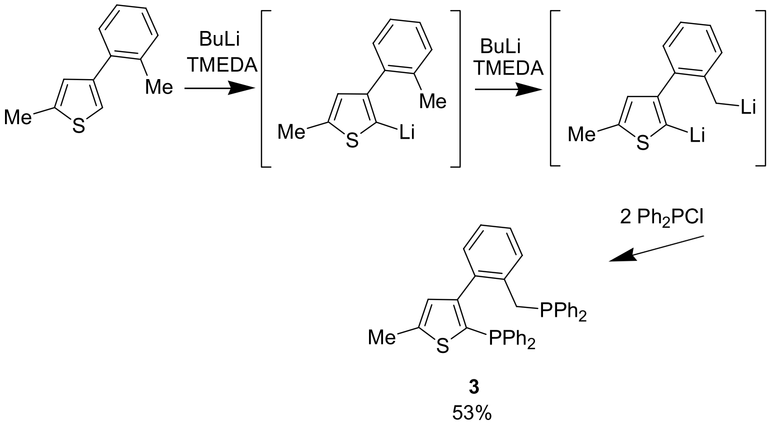
only in a 3-phenylsubstituted heterocycle but also in systems in which phenyl is located at the pyrrole, imidazole and indole nitrogen atom; this gives diphosphines **2a**, **2b** and **2c**–**2e**, respectively (Scheme 3).

The replacement of the phenyl group by the naphthyl group did not result in crucial changes. *N*-naphthylindole, like *N*-phenylimidazole and *N*-phenylbenzimidazole underwent selective double deprotonation at the *o*,*o*′-positions. When *N*-*p*-tolylindole was treated with butyllithium in the presence of TMEDA, deprotonation, as expected, involved the *o*,*o*′-position (diphosphine **2d**). The introduction of the ethyl substituent into the *o*-position of the phenyl group, as in the case of diphosphine **1f**, directed deprotonation to the free *o*-position; this gave diphosphine ligand **2e**.

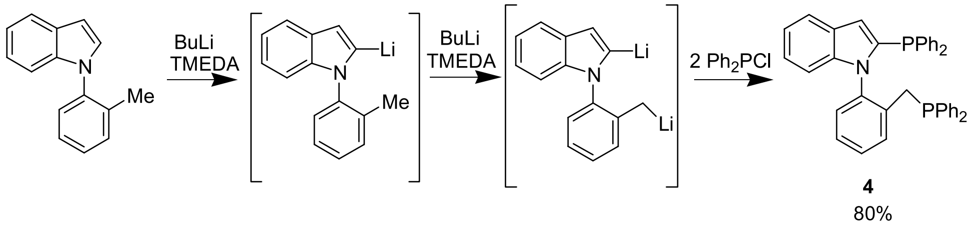
In the case where the heterocycle is bound to the *o*-tolyl group, metallation follows an unusual route to give diphosphine **3** in which phosphorus is bound to phenyl through a methylene bridge (Scheme 4).

Metallation of 1-(2-methylphenyl)-1*H*-indole proceeds in a similar way giving rise to diphosphine **4** (Scheme 5).

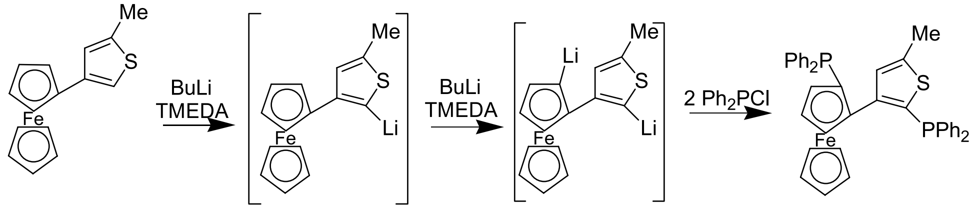
In view of the interest in the chelate derivatives of ferrocene,



Scheme 4.



Scheme 5.



5
22%

Scheme 6.

which are highly enantioselective in hydrogenation and cross-coupling reactions, we considered it expedient to synthesize bidentate phosphines in which the phenyl ring has been replaced by ferrocene; in doing this, we were aware of the substantial ferrocene acidity. The reaction gave diphosphine **5** based on 2-methylthienylferrocene (Scheme 6).

Thus, in this study, we developed a new general method for the synthesis of diphosphine ligands of the heteroaryl–aryl type. A number of diphosphines obtained are racemates. The resolution of racemates allows efficient preparation of pure diphosphine enantiomers, which display high efficiency in enantioselective catalysis. The data on enantioselective catalysis will be published elsewhere.

3. Experimental

All experiments were carried out in argon. Et_2O was purified as follows:[14] it was stored and distilled over KOH and then over sodium benzophenone ketyl. Commercial reagents available from Lancaster, Merck, and Fluka were used. Column chromatography was carried out using silica gel from Merck (0.063–0.200 mm). ^{1}H, ^{13}C, ^{31}P NMR spectra were recorded on a Varian VXR-400 instrument. 2-methyl-4-phenylthiophene,[15] 4-(2-ethylphenyl)-2-methylthiophene,[15] 2-methyl-4-(2-methylphenyl)thiophene,[15] 3-phenyl-1-benzofuran,[16] 1-methyl-3-phenyl-1*H*-indole,[17] 1-phenyl-1*H*-benzimidazole,[18] 1-(1-naphthyl)-1*H*-indole,[18] 1-(4-methylphenyl)-1*H*-indole,[18] 1-(2-ethylphenyl)-1*H*-indole,[18] 1-(2-methylphenyl)-1*H*-indole[18] were synthesized using known procedures.

3.1. Typical procedure for 1c–1f, 2a–2e, 3, 4, 5

A 1.6 M solution of BuLi in hexane (2.2 mmol) was added with stirring and cooling to -70 °C to a solution of heteroaryl–aryl (1 mmol) in Et_2O (15 mL) and TMEDA (2.2 mmol). The reaction mixture was stirred at room temperature for 4 h and cooled to -40 °C, and a solution of Ph_2PCl (2.3 mmol) in Et_2O (15 mL) was added. The cooling bath was removed and the mixture was stirred for 12 h. A 10% solution of NH_4Cl (20 mL) was added and the precipitate was filtered off and washed with water and hexane. The product was dried in a high vacuum and purified by column chromatography (silica gel 40, benzene for **1c**, **1d**, **1e**, **2c**, **2d**, **3**; benzene–EtOAc, 4:1 for **2a**, **2b**; hexane–CH_2Cl_2, 4:1 for **1f**, **4**, **5**; hexane–CH_2Cl_2, 7:1 for **2e**). The solvent was evaporated to give white-colored finely crystalline solids (except for compound **5**, which was yellow).

3.1.1. {3-[2-(Diphenylphosphino)phenyl]-5-methyl-2-thienyl}(diphenyl)phosphine (1c). ^{1}H NMR ($CDCl_3$), δ: 2.45 (s, 3H, Me); 6.70 (s, 1H, –CH=thiophene ring); 7.15–7.50 (group of multiplets, 24H, –CH=, Ar). ^{13}C NMR ($CDCl_3$), δ: 15.4 (–CH_3); 127.3, 127.6–128.1 (group of signals), 130.0 (t, $J=5.3$ Hz), 130.9 (t, $J=4.6$ Hz) (–CH=); 131.9 (d, $J=19.1$ Hz) (=C<); 132.9 (d, $J=22.9$ Hz), 133.6 (d, $J=22.8$ Hz) (–CH=); 136.7 (d, $J=13$ Hz), 137.4 (d, $J=12.8$ Hz), 138.5 (d, $J=9.5$ Hz), 142.8 (d, $J=3.9$ Hz), 143.1 (d, $J=4$ Hz), 144.4, 150.4 (d, $J=6.4$ Hz), 150.7 (d, $J=6.4$ Hz) (=C<). ^{31}P NMR ($CDCl_3$), δ: -16.60 (d, $J=9.7$ Hz), -29.03 (d, $J=9.7$ Hz). Anal. calcd for $C_{35}H_{28}P_2S$ (%): C, 77.47; H, 5.20. Found (%): C, 77.54; H, 5.32. Mp 156–158 °C.

3.1.2. {3-[2-(Diphenylphosphino)phenyl]-1-benzofuran-2-yl}(diphenyl)phosphine (1d). ^{1}H NMR ($CDCl_3$), δ: 7.21–7.65 (group of multiplets, 28H, –CH=, Ar). ^{13}C NMR ($CDCl_3$), δ: 111.4, 121.2 (d, $J=3.4$ Hz), 122.3, 125,2, 127.8, 127.8, 127.9, 128.0–128.1 (group of signals), 128.2, 128.3, 128.4, 128.6, 128.8 (–CH=); 128.8–128.9 (m) (=C<); 131.7 (dd, $J_1=2.1$ Hz, $J_2=5.6$ Hz), 132.9, 133.1 (d, $J=6.9$ Hz), 133.3, 133.4, 133.5 (d, $J=8.7$ Hz), 133.6 (d, $J=13.8$ Hz) (–CH=); 134.1 (d, $J=7.4$ Hz) (=C<); 134.2 (d, $J=1.5$ Hz) (–CH=); 135.3 (d, $J=5$ Hz), 136.2 (d, $J=7.2$ Hz), 136.8 (d, $J=13$ Hz), 137.5 (d, $J=13.3$ Hz), 137.7, 137.8 (d, $J=15.5$ Hz), 151.8 (d, $J=33.9$ Hz), 156.9 (=C<). ^{31}P NMR ($CDCl_3$), δ: -16.98 (d, $J=16.4$ Hz), -34.20 (d, $J=16.4$ Hz). Anal. calcd for $C_{38}H_{28}P_2O$ (%): C, 81.13; H, 5.02. Found (%): C, 81.24; H, 5.12. Mp 183–184 °C.

3.1.3. 2-(Diphenylphosphino)-3-[2-(diphenylphosphino)-phenyl]-1-methyl-1*H*-indole (1e). ^{1}H NMR ($CDCl_3$), δ: 3.27 (s, 3H, Me); 7.09–7.46 (group of multiplets, 28H, –CH=, Ar). ^{13}C NMR ($CDCl_3$), δ: 32.3 (–CH_3); 109.2, 119.4, 120.9, 123.3, 127.3, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0–128.1 (m), 128.2, 128.4 (–CH=); 130.2 (d, $J=28.3$ Hz), 130.7 (d, $J=7.6$ Hz) (=C<); 131.2 (dd, $J_1=2$ Hz, $J_2=17$ Hz), 131.7 (d, $J=17.6$ Hz), 132.7–132.7 (group of signals), 133.0 (dd, $J_1=1.5$ Hz, $J_2=19.8$ Hz), 133.5 (d, $J=19.9$ Hz), 134.3 (d, $J=2$ Hz) (–CH=); 135.3 (d, $J=10.9$ Hz), 135.7 (d, $J=11.9$ Hz), 137.6 (d, $J=13.9$ Hz), 138.2 (d, $J=10.9$ Hz), 138.4 (d, $J=14.5$ Hz), 139.2, 141.5 (d, $J=4.8$ Hz), 141.9 (d, $J=4.6$ Hz) (=C<). ^{31}P NMR ($CDCl_3$), δ: -18.13 (d, $J=9.7$ Hz), -34.50 (d, $J=9.7$ Hz). Anal. calcd for $C_{39}H^{31}P_2N$ (%): C, 81.38; H, 5.43; N, 2.43. Found (%): C, 81.29; H, 5.55; N, 2.53. Mp 202–203 °C.

3.1.4. {3-[2-(Diphenylphosphino)-6-ethylphenyl]-5-methyl-2-thienyl}(diphenyl)phosphine(1f). ^{1}H NMR

(CDCl$_3$), δ: 0.97 (t, $J=7.7$ Hz, 3H, Me); 2.31 (d, $J=1.1$ Hz, 3H, Me); 2.33–2.42 (m, 2H, –CH$_2$–); 6.10 (s, 1H, –CH=thiophene ring); 6.89–6.91 (m, 1H), 7.10–7.15 (m, 2H); 7.21–7.36 (group of multiplets, 16H); 7.42–7.48 (m, 4H). ^{31}P NMR (CDCl$_3$), δ: -15.83 (d, $J=19.3$ Hz), -29.57 (d, $J=19.3$ Hz). Anal. calcd for $C_{37}H_{32}P_2S$ (%): C, 77.87; H, 5.65. Found (%): C, 77.85; H, 5.62. Mp 169–170 °C.

3.1.5. 2-(Diphenylphosphino)-1-[2-(diphenylphosphino)-phenyl]-1*H*-imidazole (2a). ^{1}H NMR (CDCl$_3$), δ: 6.89–6.91 (m, 1H), 7.10–7.14 (m, 1H) (imidazole ring –CH=); 7.17–7.58 (group of multiplets, 24H, –CH=, Ar). ^{13}C NMR (CDCl$_3$), δ: 124.6, 127.9 (d, $J=7.2$ Hz), 128.3–128.6 (group of signals), 128.8, 129.2 (d, $J=6.2$ Hz), 130.6, 133.2 (dd, $J_1=12.9$ Hz, $J_2=20$ Hz)), 133.9 (dd, $J_1=8.1$ Hz, $J_2=21$ Hz), 134.5 (–CH=); 135.6 (t, $J=3.6$ Hz), 136.8 (d, $J=12$ Hz), 136.0, 136.8 (d, $J=17.3$ Hz), 141.6 (d, $J=2$ Hz), 141.9 (d, $J=2$ Hz), 147.2 (d, $J=4.2$ Hz) (=C<). ^{31}P NMR (CDCl$_3$), δ: -20.89 (d, $J=24.0$ Hz), -33.09 (d, $J=24.0$ Hz). Anal. calcd for $C_{32}H_{26}P_2N_2$ (%): C, 77.33; H, 5.11; N, 5.47. Found (%): C, 77.50; H, 5.25; N, 5.50. Mp 135–136 °C.

3.1.6. 2-(Diphenylphosphino)-1-[2-(diphenylphosphino)-phenyl]-1*H*-benzimidazole (2b). ^{1}H NMR (CDCl$_3$), δ: 6.61 (d, $J=7.9$ Hz, 1H), 6.96 (t, $J=7.8$ Hz, 2H), 7.08 (t, $J=7.9$ Hz, 2H), 7.19–7.40 (group of multiplets, 17H), 7.46–7.52 (group of multiplets, 5H), 7.88 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (CDCl$_3$), δ: 110.4, 120.0, 121.8, 122.9, 128.0, 128.1 (dd, $J_1=2.5$ Hz, $J_2=8$ Hz), 128.2, 128.4 (dd, $J_1=3.9$ Hz, $J_2=11.6$ Hz), 128.8, 129.2, 129.4–129.5 (group of signals), 129.7, 133.1 (d, $J=1.7$ Hz), 133.3 (dd, $J_1=1.7$ Hz, $J_2=6.1$ Hz), 133.4 (d, $J=1.8$ Hz), 133.9, 134.1, 134.4, 134.6 (–CH=); 134.7 (d, $J=4.6$ Hz) (=C<); 135.0 (d, $J=2.2$ Hz) (–CH=); 135.4 (dd, $J_1=1.57$ Hz, $J_2=12.16$ Hz), 136.1 (d, $J=12.1$ Hz), 137.6 (t, $J=1.9$ Hz), 139.1 (d, $J=16.1$ Hz), 140.0 (d, $J=1.9$ Hz), 140.3 (d, $J=1.7$ Hz), 143.9, 155.1 (d, $J=8.7$ Hz) (=C<). ^{31}P NMR (CDCl$_3$), δ: -21.07 (d, $J=39.7$ Hz), -28.03 (d, $J=39.7$ Hz). Anal. calcd for $C_{36}H_{28}P_2N_2$ (%): C, 78.99; H, 5.02; N, 4.98. Found (%): C, 78.89; H, 5.13; N, 5.01. Mp 193–194 °C.

3.1.7. 2-(Diphenylphosphino)-1-[2-(diphenylphosphino)-1-naphthyl]-1*H*-indole (2c). ^{1}H NMR (CDCl$_3$), δ: 6.50 (d, $J=8.0$ Hz, 1H), 6.80 (s, 1H), 6.86 (d, $J=7.9$ Hz, 1H), 6.90 (t, $J=8.1$ Hz, 1H), 7.10 (t, $J=8.0$ Hz, 1H), 7.14 (t, $J=7.9$ Hz, 1H), 7.22–7.40 (group of multiplets, 17H), 7.42–7.50 (group of multiplets, 4H), 7.54 (dd, $J_1=2.6$ Hz, $J_2=8.1$ Hz, 1H), 7.74 (d, $J=7.9$ Hz, 1H), 7.90 (d, $J=8.0$ Hz, 1H), 7.98 (d, $J=7.8$ Hz, 1H). ^{13}C NMR (CDCl$_3$), δ: 111.0, 112.0, 119.8, 120.3, 122.3, 123.9, 126.6, 126.9, 127.4, 127.8 (–CH=); 127.9 (=C<); 128.0–128.2 (group of signals), 128.6 (d, $J=9.8$ Hz), 129.0, 130.1 (–CH=); 131.9 (d, $J=3.8$ Hz) (=C<); 132.7, 132.9, 133.0, 134.0 (d, $J=9.2$ Hz) (–CH=); 134.1 (=C<); 134.2 (d, $J=9.1$ Hz) (–CH=); 135.7 (d, $J=9.2$ Hz), 136.6, 136.7 (d, $J=21.9$ Hz), 137.2 (d, $J=15.3$ Hz), 137.5 (d, $J=13.1$ Hz), 140.1 (d, $J=26.7$ Hz), 140.2, 141.4 (d, $J=3$ Hz) (=C<). ^{31}P NMR (CDCl$_3$), δ: -20.5 (d, $J=27.5$ Hz), -32.8 (d, $J=27.5$ Hz). Anal. calcd for $C_{42}H_{31}NP$ (%): C, 82.47; H, 5.11 Found (%): C, 82.45; H, 5.08. Mp 207–208 °C.

3.1.8. 2-(Diphenylphosphino)-1-[2-(diphenylphosphino)-4-methylphenyl]-1*H*-indole (2d). ^{1}H NMR (CDCl$_3$), δ: 2.40 (s, 3H, Me); 6.51 (s, 1H, indole ring –CH=); 6.71 (d, $J=8.0$ Hz, 1H), 6.95–7.00 (m, 2H), 7.10–7.47 (group of multiplets, 23H), 7.64 (d, $J=8.1$ Hz, 1H). ^{13}C NMR (CDCl$_3$), δ: 21.2 (–CH$_3$); 110.8, 111.5, 119.56, 120.1, 121.9 (–CH=); 127.6 (=C<); 127.9–128.2 (group of signals), 128.5 (d, $J=19.7$ Hz), 129.8, 130.4, 133.1, 133.3, 133.79 (d, $J=11.8$ Hz), 134.0 (d, $J=12.6$ Hz), 135.4 (d, $J=2.3$ Hz) (–CH=); 136.2 (d, $J=10.8$ Hz), 136.5 (d, $J=13.1$ Hz), 136.8 (d, $J=6.9$ Hz), 137.2 (d, $J=13.1$ Hz), 138.7, 138.9, 139.1, 139.7, 139.8 (d, $J=25.2$ Hz), 141.0 (=C<). ^{31}P NMR (CDCl$_3$), δ: -20.46 (d, $J=32.3$ Hz), -31.51 (d, $J=32.3$ Hz). Anal. calcd for $C_{39}H_{31}P_2N$ (%): C, 81.38; H, 5.43; N, 2.43. Found (%): C, 81.44; H, 5.32; N, 2.55. Mp 219–220 °C.

3.1.9. 2-(Diphenylphosphino)-1-[2-(diphenylphosphino)-6-ethylphenyl]-1*H*-indole (2e). ^{1}H NMR (CDCl$_3$), δ: 0.73 (t, $J=7.8$ Hz, 3H), 1.68–1.80 (m, 1H), 1.88–2.00 (m, 1H), 6.36 (d, $J=8.0$ Hz, 1H), 6.64 (s, 1H), 6.78 (t, $J=7.9$ Hz, 1H), 7.02 (t, $J=7.8$ Hz, 1H), 7.08 (t, $J=8.0$ Hz, 2H), 7.12–7.54 (group of multiplets, 21H), 7.59 (dd, $J_1=2.7$ Hz, $J_2=8.0$ Hz, 1H). ^{13}C NMR (CDCl$_3$), δ: 13.4 (–CH$_3$); 22.9 (–CH$_2$–); 110.7, 111.8, 119.4, 120.1, 122.0 (–CH=); 127.7 (=C<); 127.8, 127.9 (d, $J=3.1$ Hz), 128.0, 128.1, 128.2 (d, $J=7.98$ Hz), 128.5, 128.9, 129.1, 132.3, 132.8 (d, $J=11.4$ Hz), 133.0 (d, $J=11.3$ Hz), 134.1, 134.3, 134.4, 134.6 (–CH=); 135.5 (d, $J=9.8$ Hz), 136.4 (d, $J=13.3$ Hz), 137.0 (d, $J=6.6$ Hz), 137.8 (d, $J=13.4$ Hz), 138.8, 140.1–140.3 (group of signals), 143.8(=C<). ^{31}P NMR (CDCl$_3$), δ: -19.6 (d, $J=37.4$ Hz), -32.8 (d, $J=37.4$ Hz). Anal. calcd for $C_{40}H_{33}P_2N$ (%): C, 81.49; H, 5.60; N, 2.37. Found (%): C, 81.47; H, 5.55; N, 2.33. Mp 149–150 °C.

3.1.10. (3-{2-[(Diphenylphosphino)methyl]phenyl}-5-methyl-2-thienyl)(diphenyl)phosphine (3). ^{1}H NMR (CDCl$_3$), δ: 2.5 (s, 3H, Me); 3.45 (s, 2H, –CH$_2$–); 6.55 (s, 1H, thiophene ring –CH=); 7.10–7.55 (group of multiplets, 24H, –CH=, Ar). ^{13}C NMR (CDCl$_3$), δ: 15.4 (–CH$_3$); 33.5 (d, $J=16.8$ Hz) (–CH$_2$–); 125.2, 127.3, 128.0 (d, $J=6.5$ Hz), 128.2, 129.3, 129.7 (d, $J=10$ Hz), 130.4 (–CH=); 131.3 (=C<); 133.2–132.7 (group of signals) (–CH=); 135.8 (d, $J=8.8$ Hz), 137.0, 138.5–138.4 (group of signals), 145.4, 150.2, 150.5 (=C<). ^{31}P NMR (CDCl$_3$), δ: -13.66 (s), -28.86 (s). Anal. calcd for $C_{36}H_{30}P_2S$ (%): C, 77.68; H, 5.43. Found (%): C, 77.75; H, 5.54. Mp 145–146 °C.

3.1.11. 2-(Diphenylphosphino)-1-{2-[(diphenylphosphino)methyl]phenyl}-1*H*-indole (4). ^{1}H NMR (CDCl$_3$), δ: 3.05–3.25 (m, 2H), 6.50 (s, 1H), 6.91 (d, $J=7.9$ Hz, 2H), 7.08–7.13 (m, 2H), 7.14–7.20 (group of multiplets, 4H), 7.22–7.30 (group of multiplets, 6H), 7.35–7.40 (group of multiplets, 10H), 7.42 (s, 1H), 7.43–7.49 (m, 2H), 7.62–7.66 (m, 1H). ^{13}C NMR (CDCl$_3$), δ: 31.0 (dd, $J_1=4.5$ Hz, $J_2=17.3$ Hz) (–CH$_2$–); 110.5, 111.3, 119.5, 119.9, 122.1, 126.1 (d, $J=2.4$ Hz) (–CH=); 127.6 (=C<); 127.7–127.9 (group of signals), 128.1, 128.3, 129.6, 130.0, 130.1, 132.1, 132.2, 132.4, 133.1, 133.2 (d, $J=5.7$ Hz), 133.4 (–CH=); 135.4 (d, $J=8.7$ Hz) 135.8 (d, $J=6.7$ Hz), 136.3–136.4 (group of signals), 136.8 (d, $J=9.5$ Hz), 137.5 (d, $J=16.4$ Hz), 138.0 (d, $J=15.6$ Hz), 138.6 (d, $J=3.1$ Hz), 140.0 (d, $J=3.1$ Hz) (=C<). ^{31}P NMR ($CDCl_3$), δ: -17.10 (d, $J=12.2$ Hz), -30.97 (d, $J=12.2$ Hz). Anal. calcd for $C_{39}H^{31}P_2N$ (%): C, 81.38; H, 5.43; N, 2.43. Found (%): C, 81.31; H, 5.54; N, 2.50. Mp 170–171 °C.

3.1.12. 1-(Diphenylphosphino)-2-[2-(diphenylphosphino)-5-methyl-3-thienyl]ferrocene (5). ^{1}H NMR ($CDCl_3$), δ: 2.49 (s, 3H, Me); 3.75 (m, 1H), 4.1 (s, 5H), 4.39 (m, 1H), 4.59 (m, 1H) (ferrocenyl fragment); 7.06 (t, $J=6.3$ Hz, 2H), 7.12–7.28 (group of multiplets, 8H), 7.42–7.47 (group of multiplets, 6H), 7.50–7.56 (m, 2H), 7.59–7.64 (group of multiplets, 3H). ^{13}C NMR ($CDCl_3$), δ: 15.6 ($-CH_3$); 69.3, 70.1, 71.3 (d, $J=3.8$ Hz), 73.6 (dd, $J_1=3$ Hz, $J_2=13.66$ Hz) (–CH=); 76.4, 88.3 (dd, $J_1=5.4$ Hz, $J_2=23$ Hz) (=C<); 127.3, 127.8–127.7 (group of signals), 127.9, 128.0 (d, $J=5.4$ Hz), 128.3 (d, $J=6.9$ Hz), 128.5, 128.9 (–CH=); 130.9–130.8 (group of signals), 131.2(=C<); 131.9 (d, $J=17.6$ Hz), 132.6, 132.8, 133.0, 133.2, 135.0 (d, $J=21.2$ Hz) (–CH=); 138.0 (d, $J=10.5$ Hz), 138.5 (dd, $J_1=9.2$ Hz, $J_2=21$ Hz), 139.2 (d, $J=11.4$ Hz), 144.1, 146.5 (d, $J=27.1$ Hz) (=C<). ^{31}P NMR ($CDCl_3$), δ: -23.4 (s), -29.11 (s). Anal. calcd for $C_{39}H_{32}P_2FeS$ (%): C, 72.00; H, 4.92. Found (%): C, 71.98; H, 4.94. Mp 155–156 °C.

References and notes

1. Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.
2. (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 2228.
3. (a) Kagan, H. B.; Morrison, J. D., Ed.; *Asymmetric Synthesis*; Vol. 5. Academic: Orlando FL; 1985, p 1. (b) Brunner, H.; Zettlmeir, W.; *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; Vol. II. VCH: Weinheim, 1993. (c) Noyori, R. Asymmetric Catalysis in Organic Synthesis. Wiley: New York, 1994.
4. Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169.
5. (a) Francio, g.; Faraone, F.; Leitner, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 1428. (b) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (c) Yoshikawa, K.; Yamamoto, N.; Murata, M.; Awano, K.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1996**, *37*, 5347. (d) Cereghetti, M.; Arnold, W.; Broger, E.; Rageot, A. *Tetrahedron Lett.* **1996**, *37*, 5347–5350.
6. Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoette, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.
7. Gladiali, S.; Dore, A.; Fabbri, D.; Medici, S.; Pirri, G.; Pulacchini, S. *Eur. J. Org. Chem.* **2000**, 2861.
8. Benincori, T.; Gladiali, S.; Rizzo, S.; Sanncolo, F. *J. Org. Chem.* **2001**, *66*, 5940–5942.
9. Sannicolo, f.; Benincori, T.; Rizzo, S.; Gladiali, S.; Pulacchini, S.; Zotti, G. *Synthesis* **2001**, *15*, 2327–2336.
10. Antognazza, P.; Benincori, T.; Gladiali, S.; Sannicolo F. WO98/22484.
11. (a) Benincori, T.; Sannicolo, F.; Rizzo, S.; Piccolo, O. *J. Org. Chem.* **2000**, *65*, 8340–8347. (b) Benincori, T.; Brenna, E.; Sannicolo, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartine, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244–6251. (c) Benincori, T.; Sannicolo, F.; Cesarotti, E.; Piccolo, O. *J. Org. Chem.* **2000**, *65*, 2043–2047.
12. Neugebauer, W.; Kos, A. J.; Schleyer, P. R. *J. Organomet. Chem.,* **1982**, *228*, 107–118.
13. Talalaeva, T. V.; Kocheshkov, K. A. Nesmeyanov, A. N., Kocheshkov, K. A., Eds.; *Metody Elementorganicheskoi Khimii. Litii, Natrii, Kalii, Rubidii, Tsezii [Methods of Organoelement Chemistry. Lithium, Sodium, Potassium, Rubidium, Cesium].* Nauka: Moscow, 1971. Book one, p 475.
14. Weissberger, A. *Organic Solvents. Physical Properties and Methods of Purification*; Interscience: New York, 1955, p 475.
15. Nifant'ev, I. E.; Kashulin, I. A.; Ivchenko, P. V.; Klusener, P. A.; Korndorffer, F. M.; deKloe, K. P.; Rijsemus, J. J. H. WO 02/092564 A2.
16. Davies, W.; Middleton, S. *J. Chem. Soc.* **1958**, 822.
17. Bergman, J. *Acta Chem. Scand.* **1971**, *25*, 1277–1280.
18. Pozharskii, A. F.; Martsokha, B. K.; Simonov, A. M. *Zh. Obshch. Khim.* **1963**, *33*, 1005. *J. Gen. Chem. USSR*, **1963**, *33* (Engl. Transl.) .